A Potent, Long-Acting, Orally Active (2*R*)-2-[(1*R*)-3,3-Difluorocyclopentyl]-2-hydroxy-2-phenylacetamide: A Novel Muscarinic M_3 Receptor Antagonist with High Selectivity for M_3 over M_2 Receptors

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Received July 24, 2000

A novel series of (2*R*)-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamides was designed and synthesized based on the structure and biological profiles of an active metabolite **2** of our prototype muscarinic M_3 receptor selective antagonist **1**, to develop a potent, long-acting, orally active M_3 antagonist for the treatment of urinary tract disorders, irritable bowel syndrome, and respiratory disorders. Investigation of (2*R*)-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamides containing a phenyl or heterocyclic ring as the piperidinyl side chain in place of the 4-methyl-3-pentenyl moiety of **15a** revealed that this acid moiety was a versatile template for improving the selectivity for M_3 over M_2 receptors in comparison with the corresponding cyclopentylphenylacetic acid group. However, since the in vitro metabolic stability of these analogues was insufficient compared with that of **2**, further derivatization was performed by introducing an appropriate hydrophilic group into the phenyl or 2-pyridyl ring. Thus, the 1-(6-aminopyridin-2-ylmethyl)piperidine analogue **15y** exhibiting 190-fold selectivity for M_3 receptors (K_i = 2.8 nM) over M_2 receptors (K_i = 530 nM) in a human binding assay and good in vitro metabolic stability in dog and human hepatic microsomes was identified. This compound has excellent oral activity at 4 h after oral dosing (1 mg/kg), inhibiting methacholine-induced bronchoconstriction in dogs, and may be useful in clinical situations in which M_3 over M_2 selectivity is desirable.

Introduction

Classical anti-cholinergic drugs such as atropine have been used for the treatment of obstructive airway diseases; however, their clinical utility is restricted due to unfavorable peripheral and central adverse effects such as tachycardia, mydriasis, and dementia. To circumvent these side effects, aerosol muscarinic antagonists represented by ipratropium bromide[1] were developed and are widely used as anti-cholinergic bronchodilators. However, these aerosols may be not ideal because of their short duration of action and nonselective profiles for muscarinic receptor subtypes.

To date, five distinct but homologous gene sequences coding for muscarinic receptors (m1−m5) have been identified and cloned.[2−6] Pharmacologically, four receptor subtypes (M_1, M_2, M_3, and M_4) have been defined; the physiological roles of m5 gene products remain to be determined.[7,8]

In the airways of several species, at least three receptor subtypes (M_1, M_2, and M_3) are expressed and differentially distributed.[9,10] M_1 receptors are found in parasympathetic ganglia, where they facilitate neurotransmission. M_2 receptors are localized to the post ganglionic cholinergic nerve terminals and provide a functional negative feedback modulation of acetylcholine (ACh) release. M_3 receptors, localized in airway smooth muscle and mucosal glands, mediate bronchoconstriction and mucus secretion, respectively.

The bladders of various species contain a mixed population of M_2 and M_3 receptors. Although M_2 receptors predominate, it is generally believed that the contractile response is mediated through M_3 receptors.[11]

A number of reports have indicated that nonselective muscarinic antagonists increase ACh release from isolated human and guinea pig bronchial tissues and potentiate bronchoconstriction in certain animals by blocking the airway neuronal M_2 receptors when both are vagally stimulated.[12−15] Furthermore, we have recently demonstrated that the blockade of airway neuronal M_2 receptors stimulates SO_2-induced mucus hypersecretion in a rat bronchitis model.[16] Therefore, M_3 antagonists with far greater selectivity for M_3 over neuronal M_2 receptors may provide more ideal anticholinergic therapy for clinical situations in which muscarinic receptor subtype selectivity is desirable.

Thus, pharmaceutical research into therapeutic agents selective for muscarinic receptor subtypes has recently focused on the development of an M_3 selective antagonist for the treatment of urinary tract disorders such as urinary incontinence (UI), gastrointestinal diseases such as irritable bowel syndrome (IBS), and respiratory disorders such as chronic obstructive pulmonary disease (COPD).[17] Several orally active M_3 selective antagonists

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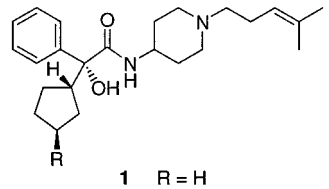
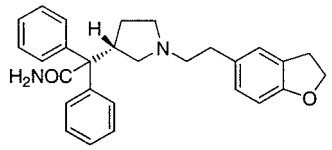
10.1021/jm0003135 CCC: $19.00
Published on Web 11/28/2000

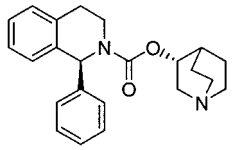
Chart 1



1 R = H
2 R = OH



Darifenacin



YM-905

such as darifenacin[18] and YM-905[19] have been disclosed so far, and some of them are being developed for the treatment of the urinary tract disorders and IBS.

Previously, we described a prototype M_3 antagonist **1** (Chart 1) with 120-fold selectivity for M_3 over M_2 receptors.[20] Compound **1** is a potent bronchodilator with a duration of action of 10 h after oral administration (10 mg/kg) in rats despite its short plasma half-life ($T_{1/2}$ = 2 h).[21] Further investigation to solve the discrepancy led to the identification of an active metabolite **2** possessing comparable selectivity for M_3 over M_2 receptors and better metabolic stability than **1**.[22] We supposed that improvement of the metabolic stability of an M_3 antagonist may result in long duration of action.

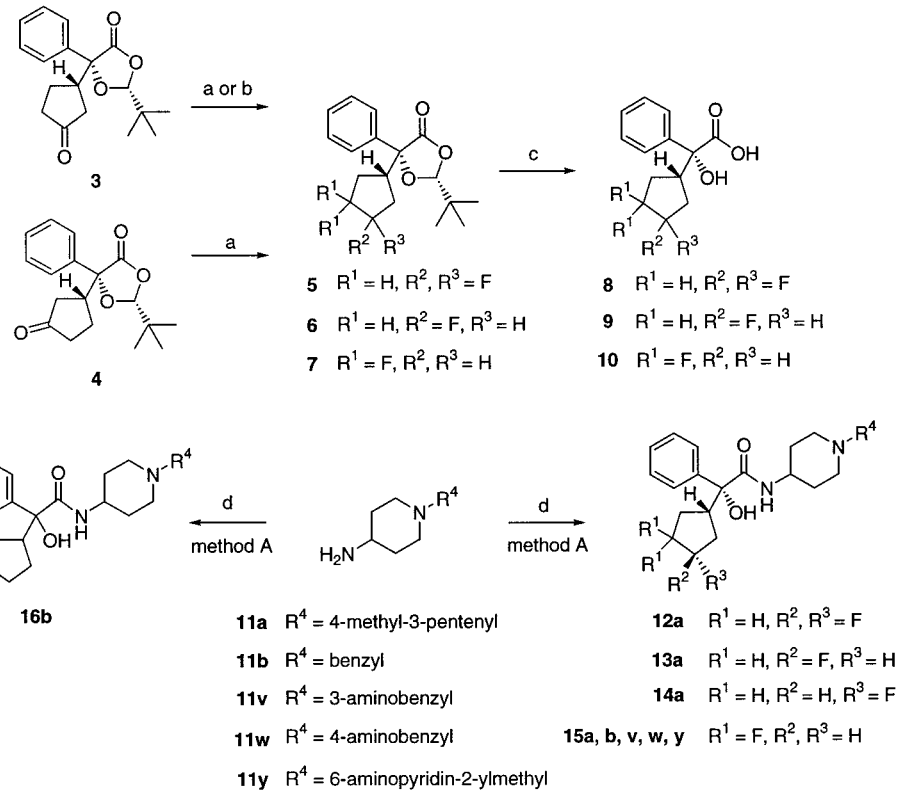
Derivatization of **2** revealed that substitution on the cyclopentane ring was effective in improving the M_3 subtype selectivity and metabolic stability.[22] In our continuing efforts to substitute hydrogen(s) on the cyclopentane ring of **1** with fluorine atom(s) to protect the metabolically soft spots, 3-monofluorinated analogues (**13a** and **14a**) and geminal-difluorocyclopentyl analogues (**12a** and **15a**) were designed and synthesized. Among them, the (1*R*)-3,3-difluorocyclopentyl analogue (**15a**) showed not only better metabolic stability against dog and human hepatic microsomes but also higher selectivity for M_3 over M_2 receptors than did **1**.

We report here that a (2*R*)-2-[(1*R*)-3,3-difuluorocyclopentyl]-2-hydroxy-2-phenylacetic acid provided a versatile template for improving selectivity for M_3 over M_2 receptors, and that the structure−activity relationship (SAR) of the substituents on the piperidine nitrogen of the difluorinated cyclopentyl derivatives led to the discovery of the 1-(6-aminopyridin-2-ylmethyl)piperidine analogue **15y**.

Chemistry

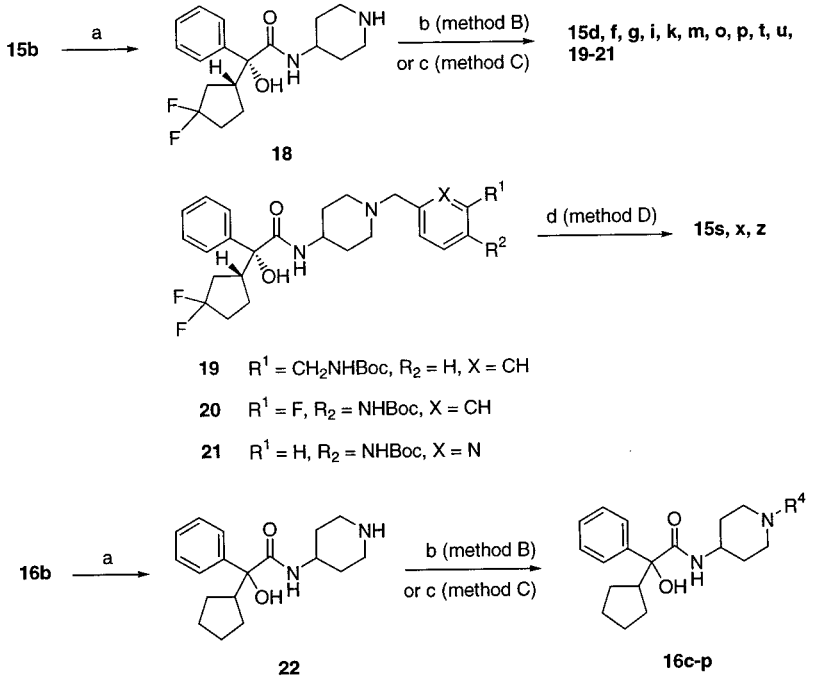
General synthetic methods of the compounds **12**−**16** listed in Tables 1−3 are summarized in Schemes 1 and 2. Synthesis of the fluorinated cylopentyl analogues **12a**, **13a**, **14a**, and **15a**−**z** was initiated from optically active ketone **3** or **4**.[22] Difluorination of **3** or **4** by treatment with diethylaminosulfur trifluoride (DAST) followed by alkaline hydrolysis provided difluorocyclopentane acids

Scheme 1[a]



[a] Reagents: (a) DAST, $CHCl_3$; (b) (1) $NaBH_4$, MeOH, (2) DAST, $CHCl_3$; (c) NaOH, H_2O−MeOH; (d) acid (**8**−**10**, **17**), WSC·HCl, HOBt, $CHCl_3$.

Scheme 2[a]



[a] Reagents: (a) H_2, $Pd(OH)_2$, EtOH; (b) aldehyde, AcOH, $NaB(OAc)_3H$, THF; (c) mesylate or bromide, K_2CO_3, CH_3CN; (d) 10% HCl−MeOH.

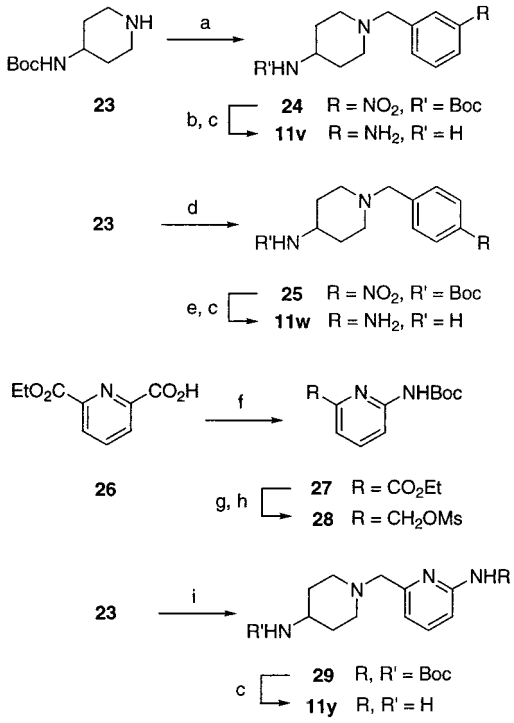
8 and **10** in good yields. Monofluorocyclopentane acid **9** was obtained as a mixture of two diastereomers using the following method. Reduction of **4** with L-selectride and the subsequent treatment of the resulting secondary alcohols with DAST yielded monofluorinated cyclopentane **6**, which was hydrolyzed under a basic condition to afford the desired acid **9**.

Coupling reaction of acids **8**, **9**, and **10** with 1-substituted 4-aminopiperidine **11a**[20] produced **12a**, **13a**, **14a**, and **15a**, respectively (method A). According to this method, compounds **15b**, **15v**, **15w**, and **15y** were prepared from the amines **11b**, **11v**, **11w**, and **11y** (see Scheme 3) and the difluorocyclopentane acid **10**.

Other difluorocyclopentyl analogues **15d**, **15f**, **15g**, **15i**, **15k**, **15m**, **15o**, **15p**, **15q**, **15t**, and **15u** and *N*-Boc-intermediates **19**−**21** were synthesized as follows. The benzyl analogue **15b** was hydrogenated with a catalytic amount of $Pd(OH)_2$ to provide a secondary amine **18**. The amine **18** was subjected to reductive alkylation (method B) with the appropriate aldehydes or alkylation (method C) with bromides or mesylates (see Scheme 4) to produce the desired compounds. Compounds **15s**, **15x**, and **15z** were obtained by deprotection of **19**−**21** under acidic condition (method D).

Cyclopentyl analogues **16b**−**q** were synthesized as racemates starting from a racemic 2-cyclopentyl-2-hydroxy-2-phenylacetic acid **17**[23] in manners similar to that described for the preparation of the difluorocyclopentane analogues.

Scheme 3[a]



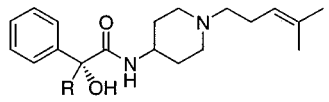
[a] Reagents: (a) 3-nitrobenzyl chloride, K_2CO_3, CH_3CN; (b) H_2, Pd-C, MeOH; (c) 10% HCl−MeOH; (d) 4-nitrobenzaldehyde, AcOH, $NaB(OAc)_3H$, THF; (e) Fe, aqueous HCl−MeOH; (f) DPPA, Et_3N, *t*-BuOH, toluene; (g) $CaCl_2$, $NaBH_4$, EtOH; (h) MsCl, Et_3N, AcOEt; (i) **28**, K_2CO_3, CH_3CN.

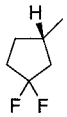
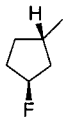
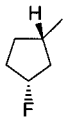
Results and Discussion

The compounds were tested in initial screens for binding affinity against human muscarinic receptor subtypes (hm1, hm2, and hm3) in transfected CHO cells and selectivity for M_3 over M_2 receptors.[20] Subsequently, optically active compounds were examined for their in vitro metabolic stability in dog and human hepatic microsomes.[22] The in vivo efficacy of representative compounds was evaluated in dogs by methacholine provocation test (MPT).[24]

First, the fluorinated analogues **12a**, **13a**, **14a**, and **15a** were characterized by binding affinity, selectivity for M_3 over M_2 receptors, and metabolic stability and

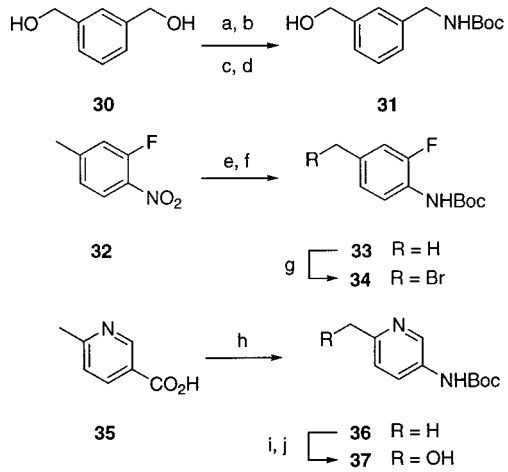
Table 1. Binding Affinity to Muscarinic Receptors and Metabolic Stability of Fluorinated Analogues



No.	R	% Yield (method)	Binding Affinity[a] (Ki, nM) m3	m1	m2	Selectivity m2/m3	Metabolic stability[b] % (dog, human)
12a		73 (A)	16	57	1400	89	77, 75
13a		17 (A)	19	75	1300	66	60, 66
14a		25 (A)	11	61	2300	220	64, 75
15a		71 (A)	6.2	22	2000	330	70, 68
1			4.2	19	490	120	31, 54
2			18	88	2300	130	75, 76

[a] The affinities were determined by inhibition of specific binding of [^{3}H-NMS] using membranes from CHO cells expressing cloned human m1−m3 receptors (ref 20). Values are the mean of two or more independent assays. [b] Percent remaining after 30 min of incubation in hepatic microsomes ($n > 2$) (ref 22).

Scheme 4[a]

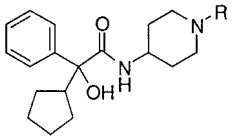


[a] Reagents: (a) MsCl, Et_3N, AcOEt; (b) NaN_3, DMF; (c) Ph_3P, H_2O−THF; (d) Boc_2O, aqueous $NaHCO_3$, THF; (e) H_2, Pd-C, EtOH; (f) Boc_2O, dioxane; (g) NBS, benzoyl peroxide, CCl_4; (h) DPPA, Et_3N, *t*-BuOH, toluene; (i) mCPBA, $CHCl_3$; (j) Ac_2O then K_2CO_3, MeOH.

were compared with the original compound **1** and its active metabolite **2** (Table 1). As expected, the metabolic stability of these compounds was improved by introducing fluorine atom(s), while the binding affinity and M_3 selectivity depended on the number and position of the fluorine atom(s) introduced. Among them, compound **15a** with a (1*R*)-3,3-difluorocyclopentyl moiety was optimal in terms of binding affinity (K_i = 6.2 nM) and selectivity for M_3 (330-fold) over M_2 receptors. In fact, the (1*R*)-3,3-difluorocyclopentyl moiety of **15a** was associated with approximately 3-fold improvement in M_3 subtype selectivity without loss of binding affinity and with considerable enhancement in metabolic stability in dog microsomes as compared with **1**. These results prompted us to further investigate alternatives to the 4-methyl-3-pentenyl moiety on the piperidinyl side chain.

Previously, we reported that a 4-methyl-3-pentenyl moiety on the piperidinyl side chain in the cyclopentyl class of compounds was the optimal alkyl substituent for both binding affinity and M_3 selectivity, while a benzyl group did not contribute to the enhancement of M_3 selectivity.[20] In parallel with the modification of the cyclopentane moiety, the detailed SAR of cyclic side chains on the piperidine ring of the cyclopentyl derivatives was also investigated and transferred to the 3,3-difluorocyclopentyl derivatives. Specifically, replace-

Table 2. Binding Affinity of **16** to Muscarinic Receptors



no.	R	% yield (method)	binding affinity[a] (K_i, nM) m3	m1	m2	selectivity m2/m3
16b	benzyl	94 (A)	2.5	2.6	30	13
16c	2-Me-benzyl	50 (B)	220	1200	37000	170
16d	3-Me-benzyl	73 (B)	2.3	1.4	70	30
16e	4-Me-benzyl	43 (B)	6.4	3.5	22	3.4
16f	3-MeO-benzyl	49 (B)	5.9	8.5	270	45
16g	2-pyridylmethyl	53 (B)	14	26	320	23
16h	3-pyridylmethyl	68 (B)	100	470	4600	46
16i	4-pyridylmethyl	60 (B)	190	660	6400	34
16j	6-Me-2-pyridylmethyl	87 (B)	11	36	2400	220
16k	3-thienylmethyl	52 (B)	3.6	9.0	79	22
16l	5-Me-3-thienylmethyl	89 (B)	3.5	2.1	24	7.0
16m	3-furylmethyl	79 (B)	50	140	1800	36
16n	cyclopentylmethyl	71 (C)	270	4300	14000	52
16o	cyclohexylmethyl	14 (B)	17	200	3300	190
16p	cycloheptylmethyl	27 (B)	12	200	3100	260
16q	cyclooctylmethyl	65 (B)	93	70	9400	100

[a] See footnote *a* in Table 1.

ment of the phenyl ring (**16b**) with heterocyclic rings and cycloalkyl rings was studied (Table 2). Substitution with a 2-, 3-, or 4-pyridinyl (**16g**, **16h,** or **16i**), 3-thienyl (**16k**), and 3-furyl group (**16m**) led to approximately 2-fold improvement in M_3 selectivity compared with that of **16a**. By contrast, substitution with a cyclohexyl (**16o**) or cycloheptyl group (**16p**) resulted in greater than 15-fold improvement in M_3 selectivity, while substitution with a cyclopentyl (**16n**) or cyclooctyl group (**16q**) reduced M_3 binding affinity and selectivity, compared with **16o** and **16p**, suggesting that stringent bulkiness of the side chain was required for M_3 affinity and selectivity.

To examine the effects of a substituent on the phenyl ring on M_3 affinity and selectivity, a methyl group was introduced into the *ortho*- (**16c**), *meta*- (**16d**), or *para*-position (**16e**) on the phenyl ring. Incorporation of a methyl group into the *ortho*- and *para*-position resulted in loss of affinity or M_3 selectivity, respectively. By contrast, methylation at the *meta*-position improved M_3 selectivity without loss of affinity. Replacement of the methyl group of **16d** with methoxy (**16f**) was also tolerated. On the basis of these findings, we tried to introduce a methyl group into the *meta*-position of the 2-pyridinyl (**16g**) and 3-thienyl (**16k**) analogues. The resultant 6-methyl-2-pyridinyl analogue **16j** showed approximately 10-fold higher M_3 selectivity than the original compound **16g**, while the 5-methyl-3-thienyl analogue **16l** lost M_3 selectivity.

Following up on the SAR of the above cyclopentyl class of compounds, we first synthesized nine compounds **15b**−**p**. As expected, all compounds showed dramatically improved M_3 selectivity in comparison with the corresponding racemic cyclopentyl analogues. Except for **15b**, these compounds displayed 2 or 3 orders of magnitude selectivity for M_3 over M_2 receptors without loss of binding affinity. In particular, the 6-methyl-2-pyridinyl analogue **15j** showed 2000-fold M_3 selectivity, suggesting that a synergistic effect was achieved by incorporating the difluorocyclopentyl moiety and the methyl group at the 6-position.

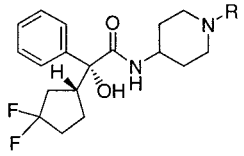
As described above, the difluorocyclopentyl moiety of **15a** contributed to improve metabolic stability in dog and human hepatic microsomes. Therefore, we examined the metabolic stability of compounds **15b**−**p**. Except for the cyclohexyl analogue **15o**, these compounds showed lower metabolic stability than **15a**, suggesting that these piperidinyl side chains were more labile than the 4-methyl-3-pentenyl group. We hypothesized that increasing the hydrophilicity on the piperidinyl side chain improves the metabolic stability of the whole molecules.

Based on this hypothesis, incorporation of a hydrophilic substituent such as a hydroxyl or an amino group to the phenyl ring was investigated. Introduction of a hydroxyl group into the methyl moiety (**15r**) on the 3-methylphenyl ring or into the *meta*-position of the phenyl ring (**15u**) led to significant improvement in metabolic stability only in the dog hepatic microsomes. By contrast, introduction of an amino group (**15s** and **15v**) significantly improved metabolic stability in both dog and human hepatic microsomes. Compound **15s** showed an approximate 10-fold loss in binding affinity compared with that of **15d**, but maintained high M_3 selectivity. Unlike compound **15u** with decreased M_3 selectivity, compound **15v** retained both M_3 binding affinity and selectivity to some extent in comparison with **15b**, suggesting that an amino group is an optimal hydrophilic substituent.

Introduction of an amino group into the 5- (**15z**) or 6-position (**15y**) of the pyridine ring led to the identification of compound **15y** showing 190-fold M_3 selectivity with high binding affinity and good metabolic stability in dog and human microsomes.

To select the best M_3 antagonist from the difluorocyclopentyl class of compounds, the in vivo activity of the representative compounds **15a**, **15d**, **15j**, **15o**, **15r**, **15v**, and **15y**, and their duration of action were simultaneously evaluated by methacholine provocation test (MPT)[24] in anesthetized dogs (Table 4). All of the compounds tested shifted the methacholine concentration response curve to the right at 4 h after oral dosing (1 mg/kg). Compound **15a** showed bronchodilatory effects comparable to those of the original compound **1** despite significantly improved metabolic stability. We assume that compounds **15a** and **1** were not distinguished in this test due to their inherent short duration or low oral bioavailability. The low oral bronchodilatory activity of the cyclohexylmethyl (**15o**) and hydroxymethyl (**15r**) analogues with higher metabolic stability than that of **1** may be due to relatively low binding affinity. Compound **15j** with 2000-fold selectivity for M_3 over M_2 receptors showed low in vivo efficacy in this test, probably due to low metabolic stability as seen in the dog hepatic microsomes. By contrast, compound **15d** caused 25-fold shifts of the methacholine concentration response curve, while having relatively low metabolic stability comparable to that of **1** in dog microsomes. The 3-aminophenyl (**15v**) and 6-amino-2-pyridyl (**15y**) analogues with higher metabolic stability than that of **15d** respectively caused 42- and greater than 64-fold shifts in this test, as expected. These compounds were also expected to show longer duration of action than **15d**.

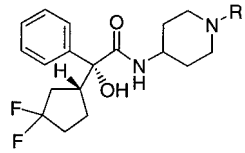
Table 3. Binding Affinity to Muscarinic Receptors and Metabolic Stability of **15**



no.	R	% yield (method)	binding affinity[a] (K_i, nM) m3	m1	m2	selectivity m2/m3	metabolic stability[b] %(dog, human)
15b	benzyl	97 (A)	3.8	2.4	260	69	45, 47
15d	3-Me-benzyl	21 (B)	2.0	0.88	310	150	32, 55
15f	3-MeO-benzyl	26 (B)	3.5	4.4	1000	290	53, 46
15g	2-pyridylmethyl	61 (B)	13	15	2400	190	45, 60
15j	6-Me-2-pyridylmethyl	91 (B)	8.9	26	17000	2000	24, 52
15k	3-thienylmethyl	53 (B)	3.2	5.3	460	140	37, 35
15m	3-furylmethyl	36 (B)	30	72	8600	290	NT[c]
15o	cyclohexylmethyl	29 (B)	18	140	21000	1200	70, 86
15p	cycloheptylmethyl	89 (C)	28	170	17000	610	NT[c]
15r	3-$HOCH_2$-benzyl	*d*	17	17	6900	420	73, 34
15s	3-H_2NCH_2-benzyl	99 (C), 50 (D)	21	340	3400	160	77, 80
15t	3-F-benzyl	49 (B)	3.1	2.5	480	160	23, 52
15u	3-HO-benzyl	65 (B)	5.4	1.2	37	6.8	73, 56
15v	3-H_2N-benzyl	63 (A)	6.9	3.2	330	48	88, 90
15w	4-H_2N-benzyl	48 (A)	7.8	3.5	220	28	89, 88
15x	4-H_2N-3-F-benzyl	58 (C), 78 (D)	6.1	2.5	310	51	78, 78
15y	6-H_2N-2-pyridylmethyl	75 (A)	2.8	1.5	530	190	84, 80
15z	5-H_2N-2-pyridylmethyl	59 (C), 60 (D)	15	14	930	62	NT[c]

[a,b] See footnotes *a*, *b* in Table 1. [c] Not tested. [d] See Experimental Section.

Table 4. Methacoline Provocation Test (MPT) in Dogs



no.	R	MPT[a] shifts (folds)
15a	4-methyl-3-pentenyl	4.2
15d	3-Me-benzyl	25
15i	6-Me-2-pyridylmethyl	3.0
15o	cyclohexylmethyl	2.3
15r	3-$HOCH_2$-benzyl	3.1
15w	3-H_2N-benzyl	43
15y	6-H_2N-2-pyridylmethyl	>64
1		5.2
2		2.9

[a] The MPT was conducted 4 h after oral administration of the drugs (1 mg/kg) in anesthesized dogs. The bronchodilatory activity of the drugs was expressed as shifts in the following equation: Shifts (folds) = [the methacholine provocative dose after drug administration]/[the methacholine provocative dose without drug administration].

As a result of its binding affinity, M_3 selectivity, metabolic stability, and in vivo bronchodilatory activity, compound **15y** with a 6-amino-2-pyridylmethyl moiety was selected for further examination.[25,26]

Conclusion

Our continuing derivatization of the prototype antagonist **1**, focusing on substitution at the cyclopentyl moiety of the acid fragment, led to the discovery of a (2*R*)-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid that was a versatile template for enhancement of selectivity for M_3 over M_2 receptors. Further derivatization of the difluorocyclopentyl class of compounds, considering binding affinity, M_3 selectivity, metabolic stability, and in vivo bronchodilatory activity, led us to the identification of **15y** as a potent, long-acting, orally active muscarinic M_3 antagonist.

Experimental Section

General. All reagents and solvents were of commercial quality and used without further purification unless otherwise noted. Melting points were determined with a Yanaco MP micromelting point apparatus and were not corrected. ^{1}H NMR spectra were obtained on a Varian Gemini-300 with tetramethylsilane as an internal standard. Mass spectrometry were performed with JEOL JMS-SX 102A. Optical rotations were measured with Jasco DIP-370 polarimeter. TLC was done with Merck Kieselgel F_{254} precoated plates. Silica gel column chromatography was carried out on Wako gel C-300.

(2*R*,5*R*)-2-*tert*-Butyl-5-[(1*S*)-3,3-difluorocyclopentyl]-5-phenyl-1,3-dioxolan-4-one (5). To a solution of **3**[22] (320 mg, 1.06 mmol) in $CHCl_3$ (15 mL) was added DAST (0.35 mL, 2.65 mmol) at room temperature, and the mixture was refluxed for 2.5 days. After being cooled to 0 °C, the reaction was quenched by carefully adding H_2O. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography (hexane−EtOAc, 100:1 elution) to give **5** (151 mg, 44%) as an oil: ^{1}H NMR ($CDCl_3$) δ 0.91 (9H, m), 1.52 (1H, m), 1.71 (1H, m), 1.85−2.31 (4H, m), 2.79 (1H, m), 5.43 (1H, s), 7.28−7.42 (3H, m), 7.67 (2H, brd, J = 6.8 Hz). HRMS calcd for $C_{18}H_{23}O_3F_2$ $(M + H)^+$: 325.1615, found 325.1593. $[\alpha]_D^{20}$ +16.0 (*c* 1.0, $CHCl_3$).

(2*R*)-[(1*S*)-3,3-Difluorocyclopentyl]-2-hydroxy-2-phenylacetic Acid (8). To a solution of **5** (138 mg, 0.426 mmol) in MeOH (3 mL) was added 3 N NaOH (0.4 mL, 1.2 mmol), and the mixture was stirred for 16 h at room temperature. After evaporation, the residue was diluted with H_2O and washed with Et_2O. The aqueous layer was acidified with 1 N HCl and extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$) and evaporated to give **9** (100 mg, ca. 92%) which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 1.47 (1H, m), 1.53 (1H, m), 1.87−2.30 (4H, m), 3.18 (1H, m), 7.28−7.41 (3H, m), 7.64 (2H, brd, J = 8.1 Hz); MS *m*/*z* 257 $(M + H)^+$.

(2*R*,5*R*)-2-*tert*-Butyl-5-[(1*R*,3*RS*)-3-fluorocyclopentyl]-5-phenyl-1,3-dioxolan-4-one (6). To a solution of **3**[22] (490

mg, 1.62 mmol) in THF (14 mL) was added 1.0 M L-Selectride in THF solution (2.0 mL, 2.00 mmol) at −78 °C, and the mixture was stirred at the same temperature for 1.5 h. The reaction was quenched by adding 30% H_2O_2 (2 mL), and the mixture was warmed to room temperature. The mixture was poured into a mixture of EtOAc and saturated aqueous $NaHCO_3$. The separated organic layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated. To a solution of the residue in $CHCl_3$ (4 mL) was added DAST (0.32 mL, 2.42 mmol) at −60 °C, and the mixture was stirred at the same temperature for 1.5 h. The reaction was quenched by adding H_2O, and the mixture was warmed to room temperature. The mixture was poured into a mixture of EtOAc and saturated aqueous $NaHCO_3$. The separated organic layer was washed with H_2O and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (hexane−EtOAc, 8:1 elution) to give **6** (375 mg, ca. 1:1 diastereomer mixture, 76%) as an oil: ^{1}H NMR ($CDCl_3$) δ 0.91 (9H, m), 1.28−2.35 (6H, m), 2.58 (1H×1/2, m), 2.89 (1H×1/2, m), 4.93−5.30 (1H, m), 5.39 (1H×1/2, s), 5.49 (1H×1/2, s), 7.28−7.42 (3H, m), 7.62−7.73 (2H, m); MS *m*/*z* 307 $(M + H)^+$.

(2*R*)-[(1*R*, 3*RS*)-3-Fluorocyclopentyl]-2-hydroxy-2-phenylacetic Acid (9). Compound **9** was prepared from **6** by a method similar to that described for **8** (95%): ^{1}H NMR ($CDCl_3$) δ 1.35−2.39 (6H, m), 3.10−3.40 (1H, m), 5.02−5.41 (1H, m), 7.24−7.44 (3H, m), 7.60−7.76 (2H, m); MS *m*/*z* 239 $(M + H)^+$.

(2*R*,5*R*)-2-*tert*-Butyl-5-[(1*R*)-3,3-difluorocyclopentyl]-5-phenyl-1,3-dioxolan-4-one (7). To a solution of **4**[22] (32.2 g, 107 mmol) in $CHCl_3$ (500 mL) was added DAST (31.0 mL, 235 mmol) at room temperature, and the mixture was heated at 70 °C for 2.5 days. After being cooled to 0 °C, the reaction was quenched by carefully adding H_2O. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography (hexane−EtOAc, 50:1 elution) to give **7** (31.6 g, 92%) as an oil: ^{1}H NMR ($CDCl_3$) δ 0.92 (9H, s), 1.70−2.30 (6H, m), 2.81 (1H, m), 5.42 (1H, s), 7.29−7.43 (3H, m), 7.60−7.70 (2H, m). HRMS calcd for $C_{18}H_{22}O_3F_2Na$ $(M + Na)^+$: 347.1435, found 347.1443. $[\alpha]_D^{20}$ +3.4 (*c* 1.0, $CHCl_3$).

(2*R*)-[(1*R*)-3,3-Difluorocyclopentyl]-2-hydroxy-2-phenylacetic Acid (10). To a solution of **7** (24.9 g, 78.2 mmol) in MeOH (270 mL) was added 4 N NaOH (50 mL, 200 mmol), and the mixture was stirred at room temperature for 15 h. After evaporation, the residue was diluted with H_2O and washed with Et_2O. The aqueous layer was acidified with 4 N HCl and extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$) and evaporated, and the residual solid was recrystallized from hexane−$CHCl_3$ to afford **10** (16.9 g, 84%) as a colorless crystal: mp 145−148 °C; ^{1}H NMR ($CDCl_3$) δ 1.69−2.35 (6H, m), 3.25 (1H, m), 7.28−7.42 (3H, m), 7.62 (2H, brd, J = 8.3 Hz); MS *m*/*z* 257 $(M + H)^+$; $[\alpha]_D^{20}$ −14.8 (*c* 1.0, $CHCl_3$). Anal. ($C_{13}H_{14}O_3F_2$) C, H.

General Procedure for Method A. (2*R*)-*N*-(1-Benzylpiperidin-4-yl)-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (15b). To a solution of **9** (1.28 g, 5.29 mmol) and 4-amino-1-benzylpiperidine **11b** (1.32 g, 6.94 mmol) in $CHCl_3$ (100 mL) were added 1-hydroxybenzotriazole (1.20 g, 8.88 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.30 g, 6.78 mmol), and the mixture was stirred at room temperature for 14 h. After the reaction mixture was evaporated, the residue was diluted with Et_2O. The organic layer was washed with saturated aqueous $NaHCO_3$, H_2O, and brine, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography ($CHCl_3$−MeOH, 50:1 elution) to give **15b** (2.13 g, 97%) as a white solid: mp 182−183 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.32−1.52 (2H, m), 1.68−2.27 (10H, m), 2.70−2.82 (2H, m), 3.30 (1H, m), 3.41 (1H, brs, OH), 3.48 (2H, s), 3.70 (1H, m), 6.27 (1H, brd, J = 8.0 Hz, NH), 7.20−7.40 (8H, m), 7.54 (2H, brd, J = 7.2 Hz); MS *m*/*z* 429 $(M + H)^+$; $[\alpha]_D^{20}$ −17.2 (*c* 1.0, $CHCl_3$). Anal. ($C_{25}H_{30}N_2O_2F_2$) C, H, N.

The following compounds (**12a**, **13a**, **14a**, **15a**, **15v**, **15w**, and **15y**) were prepared from the appropriate acids (**8**, **9,** and **10**) and amines (**11a**, **11b**, **11v**, **11w**, and **11y**) by a method similar to that described for **15b** (method A). For the preparation of **15v**, **15w**, and **15y**, Et_3N was used as a base for neutralization of the hydrochloride salts (**11v**, **11w**, and **11y**).

(2*R*)-*N*-[1-(4-Methyl-3-pentenyl)piperidin-4-yl]-2-[(1*S*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (12a). Compound **12a** was prepared as an oil from **8** and **11a**[20] (73%): ^{1}H NMR ($CDCl_3$) δ 1.38−2.21 (14H, m), 1.60 (3H, s), 1.68 (3H, s), 2.31−2.41 (2H, m), 2.80−2.93 (2H, m), 3.30 (1H, m), 3.41 (1H, brs, OH), 3.71 (1H, m), 5.05 (1H, m), 6.27 (1H, brd, J = 7.2 Hz, NH), 7.25−7.40 (3H, m), 7.56 (2H, brd, J = 8.3 Hz); MS *m*/*z* 421 $(M + H)^+$; $[\alpha]_D^{20}$ −7.8 (*c* 1.0, $CHCl_3$); **12a**·fumarate: mp 208−211 °C (EtOH). Anal. ($C_{24}H_{34}N_2O_2F_2 \cdot C_4H_4O_4$) C, H, N.

(2*R*)-*N*-[1-(4-Methyl-3-pentenyl)piperidin-4-yl]-2-[(1*S*,3*S*)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide (13a) and (2*R*)-*N*-[1-(4-Methyl-3-pentenyl)piperidin-4-yl]-2-[(1*S*,3*R*)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide (14a). Compounds **13a** (17%) and **14a** (25%) were prepared as oils from **11** and **11a**[20] and were separated by silica gel column chromatography ($CHCl_3$−MeOH, 40:1). The stereochemical structure of the cyclopentane moiety in **14a** was determined by conversion of **2**[22] to **14a** by a method similar to that described for **6** (50%). **13a**: ^{1}H NMR ($CDCl_3$) δ 1.28−2.20 (14H, m), 1.60 (3H, s), 1.68 (3H, s), 2.26−2.39 (2H, m), 2.66−2.86 (2H, m), 3.24 (1H, m), 3.70 (1H, m), 3.89 (1H, brs, OH), 5.00−5.31 (2H, m), 5.90 (1H, brd, J = 6.9 Hz, NH), 7.25−7.41 (3H, m), 7.52−7.61 (2H, m); MS *m*/*z* 403 $(M + H)^+$; $[\alpha]_D^{20}$ −19.1 (*c* 1.0, $CHCl_3$). **13a**·fumarate: mp 200−202 °C (*i*-PrOH). Anal. ($C_{24}H_{35}N_2O_2F \cdot C_4H_4O_4$) C, H, N. **14a** (25%): ^{1}H NMR ($CDCl_3$) δ 1.32−2.39 (16H, m), 1.60 (3H, s), 1.68 (3H, s), 2.71−2.90 (2H, m), 3.50 (1H, m), 3.69 (1H, m), 5.07 (1H, m), 5.20 (1H, brd, J = 55.2 Hz), 6.91 (1H, brd, J = 7.2 Hz, NH), 7.24−7.40 (3H, m), 7.64−7.77 (2H, m); MS *m*/*z* 403 $(M + H)^+$; $[\alpha]_D^{20}$ +25.6 (*c* 1.0, $CHCl_3$). **14a**·fumarate: mp 213−215 °C (*i*-PrOH). Anal. ($C_{24}H_{35}N_2O_2F \cdot C_4H_4O_4$) C, H, N.

(2*R*)-*N*-[1-(4-Methyl-3-pentenyl)piperidin-4-yl]-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (15a). Compound **15a** was prepared as a white solid from **9** and **11a**[20] (73%): mp 163−165 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.32−1.50 (2H, m), 1.60 (3H, s), 1.68 (3H, s), 1.70−2.38 (12H, m), 2.41−2.50 (2H, m), 2.71−2.96 (2H, m), 3.30 (1H, m), 3.46 (1H, brs, OH), 3.70 (1H, m), 5.05 (1H, m), 6.31 (1H, m, NH), 7.23−7.41 (3H, m), 7.55 (2H, brd, J = 7.8 Hz); MS *m*/*z* 421 $(M + H)^+$; $[\alpha]_D^{20}$ −14.4 (*c* 1.0, $CHCl_3$). Anal. ($C_{24}H_{34}N_2O_2F_2$) C, H, N.

(2*R*)-*N*-[1-(3-Aminobenzyl)piperidin-4-yl]-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (15v). Compound **15v** was prepared from **10** and **11v** (63%): mp 193−195 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.30−1.50 (2H, m), 1.55−2.28 (10H, m), 2.65−2.80 (2H, m), 3.30 (1H, m), 3.38 (2H, s), 3.43 (1H, brs, OH), 3.45−3.80 (3H, m, including NH_2), 6.26 (1H, brd, J = 7.9 Hz, NH), 6.57 (1H, dd, J = 7.8, 1.5 Hz), 6.60−6.70 (2H, m), 7.08 (1H, dd, J = 7.8, 7.8 Hz), 7.21−7.41 (3H, m), 7.54 (2H, brd, J = 7.2 Hz); MS *m*/*z* 444 $(M + H)^+$; $[\alpha]_D^{20}$ −12.4 (*c* 1.0, $CHCl_3$). Anal. ($C_{25}H_{31}N_3O_2F_2$) C, H, N.

(2*R*)-*N*-[1-(4-Aminobenzyl)piperidin-4-yl]-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (15w). Compound **15w** was prepared from **10** and **11w** (48%): mp 207−208 °C (hexane−$CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.32−1.52 (2H, m), 1.60−2.27 (10H, m), 2.66−2.84 (2H, m), 3.30 (1H, m), 3.35−3.80 (4H, m, including OH and NH_2), 3.41 (2H, s), 6.29 (1H, brd, J = 7.4 Hz, NH), 6.63 (2H, d, J = 8.5 Hz), 7.06 (2H, d, J = 8.5 Hz), 7.23−7.41 (3H, m), 7.54 (2H, brd, J = 7.1 Hz); MS *m*/*z* 444 $(M + H)^+$; $[\alpha]_D^{20}$ −17.1 (*c* 1.0, $CHCl_3$). Anal. ($C_{25}H_{31}N_3O_2F_2$) C, H, N.

(2*R*)-*N*-[1-(6-Aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (15y). Compound **15y** was prepared from **10** and **11y** (75%): mp 169−170 °C (hexane−$CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.35−1.51 (2H, m), 1.68−2.29 (10H, m), 2.68−2.80 (2H, m),

3.30 (1H, m), 3.41 (2H, s), 3.52 (1H, brs, OH), 3.70 (1H, m), 4.40 (2H, brs, NH_2), 6.28 (1H, brd, J = 8.1 Hz, NH), 6.36 (1H, d, J = 8.2 Hz), 6.67 (1H, d, J = 7.3 Hz), 7.25−7.40 (4H, m), 7.55 (2H, brd, J = 7.2 Hz); MS m/z 445 $(M + H)^+$; $[\alpha]_D^{20}$ +1.8 (*c* 1.0, EtOH). Anal. ($C_{24}H_{30}N_4O_2F_2$) C, H, N.

***N*-(1-Benzylpiperidin-4-yl)-2-cyclopentyl-2-hydroxy-2-phenylacetamide (16b).** Compound **16b** was prepared from **17**[23] and **11b** (94%): mp 191−193 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.10−1.90 (12H, m), 2.00−2.18 (2H, m), 2.61−2.80 (2H, m), 3.01 (1H, m), 3.14 (1H, brs, OH), 3.46 (2H, s), 3.70 (1H, m), 6.28 (1H, brd, J = 7.8 Hz, NH), 7.15−7.49 (8H, m), 7.59 (2H, brd, J = 7.1 Hz); MS m/z 393 $(M + H)^+$. Anal. ($C_{25}H_{32}N_2O_2$) C, H, N.

(2*R*)-*N*-(Piperidin-4-yl)-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (18). A mixture of **15b** (1.91 g, 4.61 mmol) and 20% $Pd(OH)_2$ (Degussa type, 900 mg) in EtOH (150 mL) was hydrogenated for 8 h under atmospheric pressure. The catalyst was filtered off, and the filtrate was evaporated. The residue was poured into a mixture of Et_2O and 1 N HCl, and the separated aqueous layer was basified with 3 N NaOH and extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$) and evaporated. The resulting solid was crystallized from hexane−EtOAc to yield **18** (1.29 g, 83%) as a white solid: mp 153−155 °C; ^{1}H NMR ($CDCl_3$) δ 1.16−1.32 (2H, m), 1.70−2.30 (8H, m), 2.65−2.70 (2H, m), 2.91−3.04 (2H, m), 3.31 (1H, m), 3.75 (1H, m), 6.35 (1H, brd, J = 7.8 Hz, NH), 7.21−7.40 (3H, m), 7.55 (2H, brd, J = 8.1 Hz); MS m/z 339 $(M + H)^+$; $[\alpha]_D^{20}$ −19.4 (*c* 1.0, $CHCl_3$). Anal. ($C_{18}H_{24}N_2O_2F_2$) C, H, N.

***N*-(Piperidin-4-yl)-2-cyclopentyl-2-hydroxy-2-phenylacetamide (22).** Compound **22** was prepared from **16b** by a method similar to that described for **18** (74%): mp 186−187 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.12−1.37 (2H, m), 1.40−1.92 (10H, m), 2.57−2.65 (2H, m), 2.93−3.12 (3H, m), 3.79 (1H, m), 6.38 (1H, brd, J = 7.8 Hz, NH), 7.20−7.40 (3H, m), 7.60 (2H, brd, J = 7.8 Hz); MS m/z 303 $(M + H)^+$. Anal. ($C_{18}H_{26}N_2O_2 \cdot 0.2H_2O$) C, H, N.

General Procedure for Method B. (2*R*)-*N*-[1-(6-Methylpyridin-2-ylmethyl)piperidin-4-yl]-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (15j). To a solution of **18** (75 mg, 0.22 mmol), 6-methyl-2-pyridinecarboxaldehyde (70 mg, 0.58 mmol), and acetic acid (40 mg, 0.83 mmol) in THF (3 mL) was added sodium triacetoxyborohydride (110 mg, 0.71 mmol), and the mixture was stirred at room temperature for 18 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$), evaporated, and purified by preparative TLC ($CHCl_3$-MeOH, 10:1) to give **15j** (90 mg, 91%) as a white solid: mp 191−193 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.35−1.52 (2H, m), 1.70−2.30 (10H, m), 2.53 (3H, s), 2.67−2.80 (2H, m), 3.30 (1H, m), 3.59 (2H, s), 3.71 (1H, m), 6.30 (1H, brd, J = 7.8 Hz, NH), 7.01 (1H, d, J = 7.5 Hz), 7.18 (1H, d, J = 8.1 Hz), 7.25−7.40 (4H, m), 7.48−7.60 (3H, m); MS m/z 444 $(M + H)^+$; $[\alpha]_D^{20}$ −18.6 (*c* 1.0, $CHCl_3$). Anal. ($C_{25}H_{31}N_3O_2F_2$) C, H, N.

The following compounds (**15d**, **15f**, **15g**, **15k**, **15m**, **15o**, **15t**, **15u, 16c**−**m**, and **16o**−**q**) were prepared from the amines (**18** and **22**) and appropriate aldehydes by a method similar to that described for **15j** (method B).

(2*R*)-*N*-[1-(3-Methylbenzyl)piperidin-4-yl]-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (15d). Compound **15d** was prepared from **18** and 3-methylbenzaldehyde (21%): mp 164−165 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.30−1.50 (2H, m), 1.68−2.25 (10H, m), 2.33 (3H, m), 2.65−2.79 (2H, m), 3.29 (1H, m), 3.42 (2H, s), 3.45 (1H, brs, OH), 3.69 (1H, m), 6.23 (1H, brd, J = 8.1 Hz, NH), 7.00−7.14 (3H, m), 7.19 (1H, dd, J = 7.4, 7.4 Hz) 7.23−7.40 (3H, m), 7.54 (2H, brd, J = 7.2 Hz); MS m/z 443 $(M + H)^+$; $[\alpha]_D^{20}$ −13.8 (*c* 1.0, $CHCl_3$). Anal. ($C_{26}H_{32}N_2O_2F_2$) C, H, N.

(2*R*)-*N*-[1-(3-Methoxylbenzyl)piperidin-4-yl]-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (15f). Compound **15f** was prepared from **18** and 3-methoxybenzaldehyde (26%): mp 171−173 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.35−1.52 (2H, m), 1.66−2.27 (10H, m), 2.69−2.81 (2H, m), 3.30 (1H, m), 3.42 (1H, brs, OH), 3.45 (2H, s), 3.70 (1H, m), 3.80 (3H, m), 6.27 (1H, brd, J = 8.0 Hz, NH), 6.79 (1H, m), 6.83−6.90 (2H, m), 7.18−7.40 (4H, m), 7.54 (2H, brd, J = 7.2 Hz); MS m/z 459 $(M + H)^+$; $[\alpha]_D^{20}$ −18.2 (*c* 1.0, $CHCl_3$). Anal. ($C_{26}H_{32}N_2O_3F_2$) C, H, N.

(2*R*)-*N*-[1-(2-Pyridylmethyl)piperidin-4-yl]-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (15g). Compound **15g** was prepared from **18** and 2-pyridinecarboxaldehyde (61%): mp 168−169 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.38−1.52 (2H, m), 1.70−2.30 (10H, m), 2.69−2.81 (2H, m), 3.30 (1H, m), 3.58 (1H, brs, OH), 3.61 (2H, s), 3.71 (1H, m), 6.32 (1H, brd, J = 7.8 Hz, NH), 7.15 (1H, ddd, J = 7.6, 4.8, 1.2 Hz), 7.25−7.42 (4H, m), 7.52−7.60 (2H, m), 7.63 (1H, ddd, J = 7.6, 7.6, 1.8 Hz), 8.52 (1H, m); MS m/z 430 $(M + H)^+$; $[\alpha]_D^{20}$ −12.6 (*c* 1.0, $CHCl_3$). Anal. ($C_{24}H_{29}N_3O_2F_2$) C, H, N.

(2*R*)-*N*-[1-(3-Thienylmethyl)piperidin-4-yl]-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (15k). Compound **15k** was prepared from **18** and 3-thiophenecarboxaldehyde (53%): mp 185−186 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.31−1.49 (2H, m), 1.60−2.29 (10H, m), 2.68−2.81 (2H, m), 3.29 (1H, m), 3.40 (1H, brs, OH), 3.49 (2H, s), 3.69 (1H, m), 6.25 (1H, brd, J = 8.2 Hz, NH), 7.02 (1H, dd, J = 4.9, 1.1 Hz), 7.08 (1H, m), 7.22−7.41 (4H, m), 7.54 (2H, brd, J = 7.5 Hz); MS m/z 435 $(M + H)^+$; $[\alpha]_D^{20}$ −16.6 (*c* 1.0, $CHCl_3$). Anal. ($C_{23}H_{28}N_2O_2F_2S$) C, H, N, S.

(2*R*)-*N*-[1-(3-Furylmethyl)piperidin-4-yl]-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (15m). Compound **15m** was prepared from **18** and 3-furaldehyde (36%): mp 176−178 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.30−1.49 (2H, m), 1.64−2.29 (10H, m), 2.67−2.82 (2H, m), 3.30 (1H, m), 3.33 (2H, s), 3.41 (1H, brs, OH), 3.69 (1H, m), 6.26 (1H, brd, J = 7.2 Hz, NH), 6.35 (1H, s), 7.25−7.44 (5H, m), 7.50−7.60 (2H, m); MS m/z 419 $(M + H)^+$; $[\alpha]_D^{20}$ −13.0 (*c* 1.0, $CHCl_3$). Anal. ($C_{23}H_{28}N_2O_3F_2$) C, H, N.

(2*R*)-*N*-(1-Cyclohexylmethylpiperidin-4-yl)-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (15o). Compound **15o** was prepared from **18** and cyclohexanecarboxaldehyde (29%): mp 198−200 °C (hexane−$CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.78−0.92 (2H, m), 1.10−2.28 (21H, m), 2.08 (2H, d, J = 7.2 Hz), 2.61−2.76 (2H, m), 3.29 (1H, m), 3.49 (1H, brs, OH), 3.68 (1H, m), 6.25 (1H, brd, J = 7.8 Hz, NH), 7.24−7.40 (3H, m), 7.50−7.58 (2H, m); MS m/z 435 $(M + H)^+$; $[\alpha]_D^{20}$ −15.2 (*c* 1.0, $CHCl_3$). Anal. ($C_{25}H_{36}N_2O_2F_2$) C, H, N.

(2*R*)-*N*-[1-(3-Fluorobenzyl)piperidin-4-yl]-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (15t). Compound **15t** was prepared from **18** and 3-fluorobenzaldehyde (49%): mp 169−171 °C (hexane−$CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.33−1.52 (2H, m), 1.65−2.29 (10H, m), 2.65−2.80 (2H, m), 3.30 (1H, m), 3.40 (1H, brs, OH), 3.46 (2H, s), 3.71 (1H, m), 6.28 (1H, brd, J = 7.7 Hz, NH), 6.93 (1H, m), 7.00−7.10 (2H, m), 7.20−7.41 (4H, m), 7.50−7.61 (2H, m); MS m/z 447 $(M + H)^+$; $[\alpha]_D^{20}$ −17.0 (*c* 1.0, $CHCl_3$). Anal. ($C_{25}H_{29}N_2O_2F_3$) C, H, N.

(2*R*)-*N*-[1-(3-Hydroxybenzyl)piperidin-4-yl]-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (15u). Compound **15u** was prepared as a white foam from **18** and 3-hydroxybenzaldehyde (65%): ^{1}H NMR ($CDCl_3$) δ 1.47−1.66 (2H, m), 1.70−2.29 (10H, m), 2.84−2.98 (2H, m), 3.31 (1H, m), 3.55 (2H, s), 3.74 (1H, m), 6.58 (1H, brd, J = 7.9 Hz, NH), 6.71−6.82 (2H, m), 6.91 (1H, brs), 7.16 (1H, dd, J = 7.8, 7.8 Hz), 7.24−7.40 (3H, m), 7.52−7.60 (2H, m); MS m/z 445 $(M + H)^+$; $[\alpha]_D^{20}$ −15.5 (*c* 1.0, $CHCl_3$). Anal. ($C_{25}H_{30}N_2O_3F_2$) C, H, N.

***N*-[1-(2-Methylbenzyl)piperidin-4-yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide (16c).** Compound **16c** was prepared from **22** and 2-methylbenzaldehyde (50%): mp 163−165 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.10−1.86 (12H, m), 2.04−2.18 (2H, m), 2.33 (3H, s), 2.67−2.78 (2H, m), 3.02 (1H, m), 3.18 (1H, brs, OH), 3.41 (2H, s), 3.71 (1H, m), 6.31 (1H, brd, J = 7.7 Hz, NH), 7.08−7.38 (7H, m), 7.60 (2H, brd, J = 7.8 Hz); MS m/z 407 $(M + H)^+$. Anal. ($C_{26}H_{34}N_2O_2$) C, H, N.

***N*-[1-(3-Methylbenzyl)piperidin-4-yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide (16d).** Compound **16d** was prepared from **22** and 3-methylbenzaldehyde (73%): mp 176−178 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.10−2.20 (14H, m), 2.33 (3H, s), 2.65−2.81 (2H, m), 3.01 (1H, m), 3.15 (1H, brs, OH), 3.43 (2H, s), 3.70 (1H, m), 6.32 (1H, brd, J = 8.0 Hz, NH), 7.00−7.40 (7H, m), 7.58 (2H, brd, J = 8.0 Hz); MS m/z 407 (M + H)$^+$. Anal. ($C_{26}H_{34}N_2O_2$) C, H, N.

***N*-[1-(4-Methylbenzyl)piperidin-4-yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide (16e).** Compound **16e** was prepared from **22** and 4-methylbenzaldehyde (43%): mp 200−202 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.04−1.88 (12H, m), 2.01−2.15 (2H, m), 2.32 (3H, s), 2.68−2.79 (2H, m), 3.01 (1H, m), 3.13 (1H, brs, OH), 3.42 (2H, s), 3.69 (1H, m), 6.28 (1H, brd, J = 7.9 Hz, NH), 7.10 (2H, d, J = 8.0 Hz), 7.16 (2H, d, J = 8.0 Hz), 7.22−7.36 (3H, m), 7.59 (2H, brd, J = 8.1 Hz); MS m/z 407 (M + H)$^+$. Anal. ($C_{26}H_{34}N_2O_2$) C, H, N.

***N*-[1-(3-Methoxybenzyl)piperidin-4-yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide (16f).** Compound **16f** was prepared from **22** and 3-methoxybenzaldehyde (49%): mp 164−165 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.08−1.89 (12H, m), 2.02−2.15 (2H, m), 2.67−2.79 (2H, m), 3.01 (1H, m), 3.13 (1H, brs, OH), 3.45 (2H, s), 3.70 (1H, m), 3.80 (3H, s), 6.31 (1H, brd, J = 8.2 Hz, NH), 6.79 (1H, m), 6.84−6.88 (2H, m), 7.18−7.36 (4H, m), 7.57−7.62 (2H, m); MS m/z 423 (M + H)$^+$. Anal. ($C_{26}H_{34}N_2O_3$) C, H, N.

***N*-[1-(2-Pyridylmethyl)piperidin-4-yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide (16g).** Compound **16g** was prepared from **22** and 2-pyridinecarboxaldehyde (53%): mp 181−182 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.18−1.84 (12H, m), 2.13−2.28 (2H, m), 2.68−2.81 (2H, m), 3.12 (1H, m), 3.21 (1H, brs, OH), 3.61 (2H, s), 3.73 (1H, m), 6.35 (1H, brd, J = 8.3 Hz, NH), 7.12−7.37 (5H, m), 7.56−7.68 (3H, m), 8.53 (1H, m); MS m/z 394 (M + H)$^+$. Anal. ($C_{24}H_{31}N_3O_2$) C, H, N.

***N*-[1-(3-Pyridylmethyl)piperidin-4-yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide (16h).** Compound **16h** was prepared from **22** and 3-pyridinecarboxaldehyde (68%): mp 171−172 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.16−2.20 (14H, m), 2.63−2.80 (2H, m), 3.03 (1H, m), 3.30 (1H, brs, OH), 3.47 (2H, s), 3.72 (1H, m), 6.40 (1H, brd, J = 7.6 Hz, NH), 7.20−7.40 (4H, m), 7.55−7.68 (3H, m), 8.46−8.55 (2H, m); MS m/z 394 (M + H)$^+$. Anal. ($C_{24}H_{31}N_3O_2$) C, H, N.

***N*-[1-(4-Pyridylmethyl)piperidin-4-yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide (16i).** Compound **16i** was prepared from **22** and 4-pyridinecarboxaldehyde (60%): mp 154−155 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.14−1.98 (12H, m), 2.08−2.18 (2H, m), 2.64−2.75 (2H, m), 3.04 (1H, m), 3.23 (1H, brs, OH), 3.46 (2H, s), 3.70 (1H, m), 6.41 (1H, brd, J = 7.8 Hz, NH), 7.20−7.38 (5H, m), 7.58−7.64 (2H, m), 8.50 (2H, brd, J = 9.0 Hz); MS m/z 394 (M + H)$^+$. Anal. ($C_{24}H_{31}N_3O_2$) C, H, N.

***N*-[1-(6-Methylpyridin-2-ylmethyl)piperidin-4-yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide (16j).** Compound **16j** was prepared from **22** and 6-methyl-2-pyridinecarboxaldehyde (87%): mp 178−179 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.20 (1H, m), 1.36−1.90 (11H, m), 2.11−2.28 (2H, m), 2.53 (3H, m), 2.68−2.81 (2H, m), 3.11 (1H, m), 3.15 (1H, brs, OH), 3.59 (2H, s), 3.72 (1H, m), 6.31 (1H, brd, J = 8.1 Hz, NH), 7.00 (1H, d, J = 7.6 Hz), 7.18 (1H, d, J = 7.6 Hz), 7.22−7.39 (3H, m), 7.52 (1H, dd, J = 7.6, 7.6 Hz), 7.59 (2H, brd, J = 7.1 Hz); MS m/z 408 (M + H)$^+$. Anal. ($C_{25}H_{33}N_3O_2$) C, H, N.

***N*-[1-(3-Thieylmethyl)piperidin-4-yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide (16k).** Compound **16k** was prepared from **22** and 3-thiophenecarboxaldehyde (52%): mp 163−164 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.13−1.90 (12H, m), 2.03−2.18 (2H, m), 2.68−2.82 (2H, m), 3.02 (1H, m), 3.11 (1H, brs, OH), 3.50 (2H, s), 3.70 (1H, m), 6.31 (1H, brd, J = 7.8 Hz, NH), 7.02 (1H, dd, J = 4.9, 1.2 Hz), 7.09 (1H, m), 7.22−7.38 (4H, m), 7.56−7.64 (2H, m); MS m/z 399 (M + H)$^+$. Anal. ($C_{23}H_{30}N_2O_2S$) C, H, N, S.

***N*-[1-(5-Methylthien-3-ylmethyl)piperidin-4-yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide (16l).** Compound **16l** was prepared from **22** and 5-methyl-3-thiophenecarboxaldehyde (89%): mp 187−189 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.12−1.89 (12H, m), 1.98−2.12 (2H, m), 2.44 (3H, s), 2.64−2.80 (2H, m), 3.02 (1H, m), 3.14 (1H, brs, OH), 3.38 (2H, s), 3.69 (1H, m), 6.29 (1H, brd, J = 7.8 Hz, NH), 6.67 (1H, s), 6.80 (1H, s), 7.22−7.38 (3H, m), 7.55−7.62 (2H, m); MS m/z 413 (M + H)$^+$. Anal. ($C_{24}H_{32}N_2O_2S$) C, H, N, S.

***N*-[1-(3-Furylmethyl)piperidin-4-yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide (16m).** Compound **16m** was prepared from **22** and 3-furaldehyde (79%): mp 157−158 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.13−1.90 (12H, m), 2.00−2.14 (2H, m), 2.69−2.82 (2H, m), 3.02 (1H, m), 3.11 (1H, brs, OH), 3.33 (2H, s), 3.69 (1H, m), 6.29 (1H, brd, J = 8.1 Hz, NH), 6.35 (1H, d, J = 1.0 Hz), 7.22−7.39 (5H, m), 7.56−7.62 (2H, m); MS m/z 383 (M + H)$^+$. Anal. ($C_{23}H_{30}N_2O_3$) C, H, N.

***N*-(1-Cyclohexylmethylpiperidin-4-yl)-2-cyclopentyl-2-hydroxy-2-phenylacetamide (16o).** Compound **16o** was prepared as an oil from **22** and cyclohexanecarboxaldehyde (14%): ^{1}H NMR ($CDCl_3$) δ 0.73−0.92 (2H, m), 1.03−1.90 (21H, m), 1.92−2.20 (2H, m), 2.12 (2H, d, J = 6.9 Hz), 2.66−2.81 (2H, m), 3.01 (1H, m), 3.18 (1H, brs, OH), 3.70 (1H, m), 6.32 (1H, brd, J = 8.1 Hz, NH), 7.21−7.40 (3H, m), 7.59 (2H, brd, J = 7.5 Hz); MS m/z 399 (M + H)$^+$. **16o**·HCl: mp 215−216 °C (*i*-Pr_2O/*i*-PrOH). Anal. ($C_{25}H_{38}N_2O_2$·HCl·0.6H_2O) C, H, N.

***N*-(1-Cycloheptylmethylpiperidin-4-yl)-2-cyclopentyl-2-hydroxy-2-phenylacetamide (16p).** Compound **16p** was prepared as an oil from **22** and cycloheptanecarboxaldehyde (27%): ^{1}H NMR ($CDCl_3$) δ 1.00−1.91 (25H, m), 1.96−2.19 (4H, m), 2.61−2.84 (2H, m), 3.02 (1H, m), 3.20 (1H, brs, OH), 3.72 (1H, m), 6.31 (1H, brd, J = 7.2 Hz, NH), 7.21−7.41 (3H, m), 7.56−7.68 (2H, m); MS m/z 413 (M + H)$^+$. **16p**·HCl: mp 211−212 °C (*i*-Pr_2O-*i*-PrOH). Anal. ($C_{26}H_{40}N_2O_2$·HCl·0.8H_2O) C, H, N.

***N*-(1-Cyclooctylmethylpiperidin-4-yl)-2-cyclopentyl-2-hydroxy-2-phenylacetamide (16q).** Compound **16q** was prepared as an oil from **22** and cyclooctanecarboxaldehyde (65%): ^{1}H NMR ($CDCl_3$) δ 1.10−1.89 (27H, m), 1.95−2.11 (4H, m), 2.62−2.77 (2H, m), 3.02 (1H, m), 3.19 (1H, brs, OH), 3.69 (1H, m), 6.26 (1H, brd, J = 7.5 Hz, NH), 7.20−7.39 (3H, m), 7.59 (2H, brd, J = 8.4 Hz); MS m/z 427 (M + H)$^+$. **16q**·HCl: mp 196−197 °C (*i*-Pr_2O-EtOH). Anal. ($C_{27}H_{42}N_2O_2$·HCl) C, H, N.

General Procedure for Method C. (2*R*)-*N*-(1-Cycloheptylmethylpiperidin-4-yl)-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (15p). To a solution of cycloheptanemethanol (60 mg, 0.47 mmol) in EtOAc (3 mL) were added Et_3N (0.13 mL, 0.9 mmol) and MsCl (0.06 mL, 0.7 mmol), and the mixture was stirred at 0 °C for 1 h. The reaction was quenched by adding saturated aqueous $NaHCO_3$. The separated organic layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated to give the crude mesylate. To a suspension of **18** (90 mg, 0.28 mmol), K_2CO_3 (100 mg, 0.73 mmol), and potassium iodide (5 mg, 0.03 mmol) in CH_3CN (3 mL) was added the crude mesylate, and the mixture was heated at 70 °C for 17 h. After being cooled to room temperature, the reaction mixture was poured into H_2O and extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography ($CHCl_3$−MeOH, 100:1 elution) to yield **15p** (106 mg, 89%) as a white solid: mp 190−191 °C (hexane−$CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.00−1.15 (2H, m), 1.28−2.28 (23H, m), 2.05 (2H, d, J = 7.2 Hz), 2.60−2.73 (2H, m), 3.29 (1H, m), 3.49 (1H, brs, OH), 3.68 (1H, m), 6.23 (1H, brd, J = 8.1 Hz, NH), 7.23−7.40 (3H, m), 7.50−7.58 (2H, m); MS m/z 449 (M + H)$^+$; $[\alpha]_D^{20}$ −16.8 (c 1.0, $CHCl_3$). Anal. ($C_{26}H_{38}N_2O_2F_2$) C, H, N.

The following compounds (**16n** and **19**−**21**) were prepared from the amines (**18** and **22**) and appropriate alcohols or bromide by a method similar to that described for **15p** (method C).

***N*-(1-Cyclopentylmethylpiperidin-4-yl)-2-cyclopentyl-2-hydroxy-2-phenylacetamide (16n).** Compound **16n** was prepared from **22** and cyclopentanemethanol (71%): mp 169.5−171 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.04−2.23 (23H, m), 2.25 (2H, d, J = 7.2 Hz), 2.68−2.90 (2H, m), 3.01 (1H, m), 3.29 (1H, brs, OH), 3.69 (1H, m), 6.36 (1H, brd, J =

8.4 Hz, NH), 7.20−7.42 (3H, m), 7.59 (2H, brd, J = 7.0 Hz); MS m/z 385 $(M + H)^+$. Anal. ($C_{24}H_{36}N_2O_2$) C, H, N.

(2*R*)-*N*-[1-(3-*tert*-Butoxycarbonylaminomethylbenzyl)-piperidin-4-yl]-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (19). Compound **19** was prepared as an oil from **18** and 3-*tert*-butoxycarbonylaminomethylbenzyl alcohol **31** (99%): ^{1}H NMR ($CDCl_3$) δ 1.32−1.53 (2H, m), 1.47 (9H, s), 1.65−2.28 (10H, m), 2.64−2.80 (2H, m), 3.30 (1H, m), 3.45 (2H, s), 3.48 (1H, brs, OH), 3.71 (1H, m), 4.30 (2H, brd, J = 5.7 Hz), 4.82 (1H, m, NH), 6.28 (1H, brd, J = 7.8 Hz, NH), 7.12−7.41 (7H, m), 7.51−7.61 (2H, m). HRMS calcd for $C_{31}H_{42}O_4N_3F_2$ $(M + H)^+$: 558.3143, found 558.3160. $[\alpha]_D^{20}$ −13.2 (c 1.0, $CHCl_3$).

(2*R*)-*N*-[1-(4-*tert*-Butoxycarbonylamino-3-fluorobenzyl)-piperidin-4-yl]-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (20). Compound **20** was prepared as an oil from **18** and 4-*tert*-butoxycarbonylamino-3-fluorobenzyl bromide **34** (58%): ^{1}H NMR ($CDCl_3$) δ 1.30−1.51 (2H, m), 1.52 (9H, s), 1.70−2.25 (10H, m), 2.60−2.80 (2H, m), 3.30 (1H, m), 3.38 (2H, s), 3.42 (1H, brs, OH), 3.70 (1H, m), 6.24 (1H, brd, J = 7.5 Hz, NH), 6.63 (1H, m), 6.96−7.16 (2H, m), 7.24−7.41 (2H, m), 7.51−7.60 (2H, m), 7.97 (1H, m). HRMS calcd for $C_{30}H_{39}O_4N_3F_3$ $(M + H)^+$: 562.2893, found 562.2889. $[\alpha]_D^{20}$ −9.3 (c 1.0, $CHCl_3$).

(2*R*)-*N*-[1-(5-*tert*-Butoxycarbonylamino-2-pyridylmethyl)piperidin-4-yl]-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (21). Compound **21** was prepared as a foam from **18** and 5-*tert*-butoxycarbonylamino-2-pyridinemethanol **37** (59%): ^{1}H NMR ($CDCl_3$) δ 1.35−1.54 (2H, m), 1.52 (9H, s), 1.71−2.26 (10H, m), 2.61−2.79 (2H, m), 3.30 (1H, m), 3.48 (1H, brs, OH), 3.55 (2H, s), 3.71 (1H, m), 6.27 (1H, brd, J = 7.8 Hz, NH), 6.51 (1H, brs), 7.20−7.41 (4H, m), 7.51−7.59 (2H, m), 7.93 (1H, m), 8.32 (1H, d, J = 2.7 Hz). HRMS calcd for $C_{29}H_{39}O_4N_4F_2$ $(M + H)^+$: 545.2939, found 545.2933. $[\alpha]_D^{20}$ −12.4 (c 1.0, $CHCl_3$).

General Procedure for Method D. (2*R*)-*N*-[1-(3-Aminomethylbenzyl)piperidin-4-yl]-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (15s). A solution of **19** (200 mg, 0.36 mmol) in 10% HCl−MeOH (3 mL) was stirred at room temperature for 15 h. After the reaction mixture was evaporated, the resulting residue was poured into a mixture of $CHCl_3$ and saturated aqueous $NaHCO_3$. The separated organic layer was dried ($MgSO_4$) and evaporated to give the residue, which was crystallized from i-Pr_2O-EtOH yielding **15s** (82 mg, 50%) as a white crystalline solid: mp 126−129 °C; ^{1}H NMR ($CDCl_3$) δ 1.31−1.50 (2H, m), 1.70−2.29 (10H, m), 2.64−2.80 (2H, m), 3.30 (1H, m), 3.46 (2H, s), 3.70 (1H, m), 3.84 (2H, s), 6.36 (1H, brd, J = 8.4 Hz, NH), 7.11−7.40 (7H, m), 7.51−7.61 (2H, m); MS m/z 458 $(M + H)^+$; $[\alpha]_D^{20}$ −15.3 (c 1.0, $CHCl_3$). Anal. ($C_{26}H_{33}N_3O_2F_2$) C, H, N.

The following compounds (**15x** and **15z**) were prepared from **20** and **21** by a method similar to that described for **15s** (method D).

(2*R*)-*N*-[1-(4-Amino-3-fluorobenzyl)piperidin-4-yl]-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (15x). Compound **15x** was prepared from **20** (78%): mp 190−191 °C (hexane−$CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.29−1.49 (2H, m), 1.65−2.30 (10H, m), 2.62−2.77 (2H, m), 3.30 (1H, m), 3.33 (2H, s), 3.45 (1H, brs, OH), 3.51−3.78 (3H, m, including NH_2), 6.25 (1H, brd, J = 8.1 Hz, NH), 6.69 (1H, dd, J = 8.9, 8.1 Hz), 6.82 (1H, dd, J = 8.1, 1.6 Hz), 6.93 (1H, dd, J = 12.0, 1.6 Hz), 7.24−7.40 (3H, m), 7.50−7.58 (2H, m); MS m/z 462 $(M + H)^+$. $[\alpha]_D^{20}$ −15.5 (c 1.0, $CHCl_3$). Anal. ($C_{25}H_{30}N_3O_2F_3$) C, H, N.

(2*R*)-*N*-[1-(5-Aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (15z). Compound **15z** was prepared from **21** (60%): mp 197−200 °C (i-Pr_2O-EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.35−1.54 (2H, m), 1.68−2.28 (10H, m), 2.68−2.81 (2H, m), 3.30 (1H, m), 3.52 (2H, s), 3.62 (1H, brs, OH), 3.71 (1H, m), 6.27 (1H, brd, J = 7.8 Hz, NH), 6.95 (1H, dd, J = 8.4, 2.6 Hz), 7.11 (1H, d, J = 8.4 Hz), 7.21−7.41 (3H, m), 7.50−7.60 (2H, m), 8.03 (1H, d, J = 2.6 Hz); MS m/z 445 $(M + H)^+$; $[\alpha]_D^{20}$ −12.5 (c 1.0, $CHCl_3$). Anal. ($C_{24}H_{30}N_4O_2F_2$) C, H, N.

(2*R*)-*N*-[1-(3-Hydroxymethylbenzyl)piperidin-4-yl]-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (15r). To a solution of **18** (90 mg, 0.27 mmol), methyl 3-formylbenzoate (100 mg, 0.61 mmol), and acetic acid (20 mg, 0.42 mmol) in THF (3 mL) was added sodium triacetoxyborohydride (220 mg, 1.4 mmol), and the mixture was stirred at room temperature for 15 h. The reaction mixture was poured into a mixture of saturated aqueous $NaHCO_3$ and $CHCl_3$. The separated organic layer was dried ($MgSO_4$) and evaporated. To a solution of the residue in THF (3 mL) was added LAH (20 mg, 0.52 mmol) at 0 °C, and the mixture was stirred for 1.5 h. After the reaction was quenched by adding $Na_2SO_4 \cdot 10H_2O$, the resulting mixture was further stirred at room temperature for 3 h. The insoluble materials were filtered off and washed with THF. Evaporation of the filtrate gave the residue, which was purified by preparative TLC ($CHCl_3$−MeOH, 10:1) to give **15r** (66 mg, 54%) as a white solid: mp 140−143 °C (i-Pr_2O-EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.32−1.50 (2H, m), 1.59−2.28 (10H, m), 2.67−2.88 (2H, m), 3.30 (1H, m), 3.41 (1H, brs, OH), 3.55 (2H, s), 3.72 (1H, m), 4.69 (2H, s), 6.35 (1H, brd, J = 7.8 Hz, NH), 7.20−7.41 (7H, m), 7.54 (2H, brd, J = 7.5 Hz); MS m/z 459 $(M + H)^+$; $[\alpha]_D^{20}$ −15.6 (c 1.0, $CHCl_3$). Anal. ($C_{26}H_{32}N_2O_3F_2$) C, H, N.

4-Amino-1-(3-aminobenzyl)piperidine (11v). To a suspension of 4-*tert*-butoxycarbonylaminopiperidine **23**[27] (350 mg, 1.75 mmol) and K_2CO_3 (580 mg, 4.20 mmol) in DMF (12 mL) was added 3-nitrobenzyl chloride (330 mg, 1.91 mmol), and the mixture was stirred at room temperature for 3 h. The reaction mixture was poured into a mixture of Et_2O and H_2O, and the separated organic layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography ($CHCl_3$−MeOH, 100:1 elution) to yield 4-*tert*-butoxycarbonylamino-1-(3-nitrobenzyl)-piperidine **24** (510 mg, 87%) as a white solid: mp 124−125 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.44 (9H, s), 1.48 (2H, m), 1.93 (2H, m), 2.14 (2H, m), 2.79 (2H, m), 3.50 (1H, m), 3.56 (2H, s), 4.42 (1H, m, NH), 7.47 (1H, dd, J = 8.1, 7.5 Hz), 7.64 (1H, brd, J = 7.5 Hz), 8.09 (1H, brd, J = 8.1 Hz), 8.20 (1H, brs); MS m/z 336 $(M + H)^+$. Anal. ($C_{17}H_{25}N_3O_4$) C, H, N.

A mixture of **24** (300 mg, 0.89 mmol) and 10% palladium on carbon (30 mg) in MeOH (10 mL) was hydrogenated for 1 h under atmospheric pressure. The catalyst was filtered off, and the filtrate was evaporated and purified by silica gel column chromatography ($CHCl_3$−MeOH, 50:1 elution) to give 4-*tert*-butoxycarbonylamino-1-(3-aminobenzyl)piperidine (240 mg, 88%) as a white solid: mp 148−149 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.44 (2H, m), 1.46 (9H, s), 1.92 (2H, m), 2.10 (2H, m), 2.81 (2H, m), 3.40 (2H, s), 3.49 (1H, m), 3.64 (2H, brs, NH_2), 4.41 (1H, m, NH), 6.59 (1H, brd, J = 8.1 Hz), 6.65−6.75 (2H, m), 7.10 (1H, dd, J = 8.1, 8.1 Hz); MS m/z 306 $(M + H)^+$. Anal. ($C_{17}H_{27}N_3O_2$) C, H, N.

A solution of 4-*tert*-butoxycarbonylamino-1-(3-aminobenzyl)-piperidine (240 mg, 0.80 mmol) in 10% HCl−MeOH (10 mL) was stirred at room temperature for 17 h. Evaporation of the reaction mixture gave the crude **11v**·hydrochloride (160 mg, ca. 97%), which was used without further purification: ^{1}H NMR (CD_3OD) δ 2.12 (2H, m), 2.28 (2H, m), 3.29 (2H, m), 3.45−3.65 (3H, m), 4.44 (2H, s), 7.51 (1H, brd, J = 8.1 Hz), 7.61−7.78 (3H, m); MS m/z 206 $(M + H)^+$.

4-Amino-1-(4-aminobenzyl)piperidine (11w). To a solution of **23**[27] (100 mg, 0.50 mmol), 4-nitrobenzaldehyde (100 mg, 0.66 mmol), and acetic acid (30 mg, 0.63 mmol) in THF (6 mL) was added sodium triacetoxyborohydride (270 mg, 1.70 mmol), and the mixture was stirred at room temperature for 20 h. The reaction mixture was poured into a mixture of saturated aqueous $NaHCO_3$ and $CHCl_3$. The separated organic layer was dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography ($CHCl_3$−MeOH, 100:1 elution) to yield 4-*tert*-butoxycarbonylamino-1-(4-nitrobenzyl)piperidine **25** (130 mg, 78%) as a white solid: mp 143−144 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.45 (2H, m), 1.47 (9H, s), 1.95 (2H, m), 2.17 (2H, m), 2.79 (2H, m), 3.51 (1H, m), 3.59 (2H, s), 4.44 (1H, m, NH), 7.51 (2H, d, J = 8.7 Hz), 8.19 (2H, d, J = 8.7 Hz); MS m/z 336 $(M + H)^+$. Anal. ($C_{17}H_{25}N_3O_4$) C, H, N.

To a solution of **25** (130 mg, 0.39 mmol) in a mixture of MeOH (5 mL) and 1 N HCl (0.5 mL) was added Fe (75 mg, 1.34 mmol) in one portion, and the mixture was stirred at room temperature for 14 h. The reaction mixture was basified with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography ($CHCl_3$−MeOH, 50:1 elution) to give 4-*tert*-butoxycarbonylamino-1-(4-aminobenzyl)-piperidine (75 mg, 75%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.42 (2H, m), 1.44 (9H, s), 1.88 (2H, m), 2.05 (2H, m), 2.78 (2H, m), 3.39 (2H, s), 3.47 (1H, m), 3.62 (2H, m, NH_2), 4.42 (1H, m, NH), 6.64 (2H, d, J = 8.4 Hz), 7.08 (2H, d, J = 8.4 Hz). HRMS calcd for $C_{17}H_{28}N_3O_2$ $(M + H)^+$: 306.2182, found 306.2173.

A solution of 4-*tert*-butoxycarbonylamino-1-(4-aminobenzyl)-piperidine (67 mg, 0.22 mmol) in 10% HCl−MeOH (2 mL) was stirred at room temperature for 20 h. Evaporation of the reaction mixture gave the crude **11w**·hydrochloride (68 mg, ca. 98%), which was used without further purification: ^{1}H NMR (CD_3OD) δ 2.13 (2H, m), 2.24 (2H, m), 3.22 (2H, m), 3.51 (1H, m), 3.67 (2H, m), 4.40 (2H, s), 7.47 (2H, d, J = 8.7 Hz), 7.77 (2H, d, J = 8.7 Hz); MS m/z 206 $(M + H)^+$.

4-Amino-1-(6-aminopyridin-2-ylmethyl)piperidine (11y). To a solution of 6-ethoxycarbonyl-2-pyridinecarboxylic acid **26**[28] (500 mg, 2.54 mmol) and Et_3N (0.70 mL, 5.04 mmol) in a mixture of toluene (15 mL) and *t*-BuOH (1.5 mL) was added diphenylphosphoryl azide (0.75 mL, 3.48 mmol) at room temperature, and the mixture was heated at 100 °C for 20 h. After being cooled to room temperature, the reaction mixture was diluted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. The resulting residue was purified by silica gel column chromatography (hexane−EtOAc, 4:1 elution) to give ethyl 6-*tert*-butoxycarbonylamino-2-pyridinecarboxylate **27** (600 mg, 89%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.42 (3H, t, J = 7.2 Hz), 1.52 (9H, s), 4.45 (1H, q, J = 7.2 Hz), 7.50 (1H, brs, NH), 7.71−7.82 (2H, m), 8.13 (1H, dd, J = 6.8, 3.2 Hz). HRMS calcd for $C_{13}H_{19}O_4N_2$ $(M + H)^+$: 267.1345, found 267.1332.

To a mixture of **27** (370 mg, 1.39 mmol) and $CaCl_2$ (310 mg, 2.82 mmol) in EtOH (15 mL) was added $NaBH_4$ (270 mg, 7.14 mmol), and the mixture was stirred at 0 °C for 2 h. The reaction mixture was poured into H_2O and extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (hexane−EtOAc, 2:1 elution) to give 6-*tert*-butoxycarbonylamino-2-pyridinemethanol (277 mg, 89%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.54 (9H, s), 3.39 (1H, m, OH), 4.66 (2H, d, J = 4.2 Hz), 6.89 (1H, d, J = 8.1 Hz), 7.24 (1H, brs, NH), 7.66 (1H, dd, J = 8.1, 8.1 Hz), 7.82 (1H, d, J = 8.1 Hz). HRMS calcd for $C_{11}H_{17}O_3N_2$ $(M + H)^+$: 225.1239, found 225.1228.

To a solution of 6-*tert*-butoxycarbonylamino-2-pyridinemethanol (235 mg, 1.04 mmol) and Et_3N (0.45 mL, 3.24 mmol) in EtOAc (6 mL) was added MsCl (0.24 mL, 3.10 mmol), and the mixture was stirred at 0 °C for 15 min. After the reaction was quenched by adding saturated aqueous $NaHCO_3$, the separated organic layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated. To a solution of the crude mesylate **28** (320 mg) in CH_3CN (7 mL) were added K_2CO_3 (450 mg, 3.26 mmol) and **23**[27] (187 mg, 0.94 mmol), and the mixture was stirred at room temperature for 15 h. The reaction mixture was poured into H_2O and extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography ($CHCl_3$-MeOH, 100:1 elution) to give 4-*tert*-butoxycarbonylamino-1-(6-*tert*-butoxycarbonylaminopyridin-2-ylmethyl)piperidine **29** (360 mg, 95%) as a foam: ^{1}H NMR ($CDCl_3$) δ 1.44 (9H, s), 1.51 (9H, s), 1.55 (2H, m), 1.91 (2H, m), 2.12 (2H, m), 2.82 (2H, m), 3.48 (2H, s), 4.41 (1H, m), 6.99 (1H, d, J = 7.4 Hz), 7.60 (1H, dd, J = 8.2, 7.4 Hz), 7.78 (1H, d, J = 8.2 Hz). HRMS calcd for $C_{21}H_{35}O_4N_4$ $(M + H)^+$: 407.2658, found 407.2663.

A solution of **29** (360 mg, 0.89 mmol) in 10% HCl−MeOH (10 mL) was stirred at room temperature for 45 h. Evaporation of the reaction mixture gave the crude **11y**·hydrochloride (271 mg, ca. 97%), which was used for without further purification: ^{1}H NMR (CD_3OD) δ 1.98−2.40 (4H, m), 3.21−3.62 (3H, m), 3.69 (2H, m), 4.50 (2H, s), 7.11 (1H, dd, J = 9.2, 1.0 Hz), 7.15 (1H, dd, J = 7.2, 1.0 Hz), 7.93 (1H, dd, J = 9.2, 7.2 Hz); MS m/z 207 $(M + H)^+$.

3-*tert*-Butoxycarbonylaminomethylbenzyl Alcohol (31). To a solution of 3-hydroxymethylbenzyl alcohol **30** (2.65 g, 19.2 mmol) and Et_3N (3.00 mL, 21.6 mmol) in EtOAc (60 mL) was added MsCl (1.50 mL, 19.4 mmol), and the mixture was stirred at 0 °C for 45 min. After the reaction was quenched by adding saturated aqueous $NaHCO_3$, the separated organic layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated. To a solution of the residue (4.40 g) in DMF (60 mL) was added NaN_3 (2.10 g, 32.3 mmol), and the mixture was heated at 90 °C for 1 h. After being cooled to room temperature, the reaction mixture was diluted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and evaporated. To a solution of the residue (3.30 g) in a mixture of THF (100 mL) and H_2O (10 mL) was added Ph_3P (4.80 g, 18.3 mmol), and the mixture was heated at 70 °C for 4 h. After the reaction mixture was cooled to room temperature, saturated aqueous $NaHCO_3$ (5 mL) and di-*tert*-butyl dicarbonate (4.00 g, 18.3 mmol) were added, and the mixture was stirred for 8 h. The reaction mixture was evaporated and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The resulting residue was purified by silica gel column chromatography (*n*-hexane−EtOAc, 4:1 elution) to give **31** (410 mg, 10%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.46 (9H, s), 4.32 (2H, brd, J = 5.7 Hz), 4.69 (2H, s), 4.83 (1H, m), 7.18−7.38 (4H, m). HRMS calcd for $C_{13}H_{20}O_3N$ $(M + H)^+$: 238.1443, found 238.1440.

4-*tert*-Butoxycarbonylamino-3-fluorobenzyl Bromide (34). A mixture of 3-fluoro-4-nitrotoluene **32** (1.01 g, 6.52 mmol) and 10% Pd-C (210 mg) in EtOH (20 mL) was hydrogenated under atmospheric pressure for 3 h. The catalyst was filtered off, and the filtrate was evaporated to give the crude 4-amino-3-fluorotoluene (790 mg): ^{1}H NMR ($CDCl_3$) δ 2.23 (3H, s), 3.57 (2H, brs, NH_2), 6.64−6.87 (3H, m); MS m/z 126 $(M + H)^+$.

To a solution of the crude 4-amino-3-fluorotoluene (790 mg, 6.32 mmol) in dioxane (20 mL) was added di-*tert*-butyl dicarbonate (2.18 g, 9.99 mmol) at room temperature, and the mixture was heated at 100 °C for 48 h. After being cooled to room temperature, the reaction mixture was poured into H_2O and extracted with Et_2O. The organic layer was washed with brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (hexane−EtOAc, 5:1 elution) to give 4-*tert*-butoxycarbonylamino-3-fluorotoluene **33** (1.17 g, 80%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.52 (9H, s), 2.29 (3H, s), 6.59 (1H, brs, NH), 6.81−6.92 (2H, m), 7.89 (1H, m). HRMS calcd for $C_{12}H_{16}O_2NF$ $(M)^+$: 225.1165, found 225.1154.

A mixture of **33** (100 mg, 0.44 mmol), *N*-bromosuccinimide (90 mg, 0.51 mmol) and benzoyl peroxide (3 mg, 0.01 mmol) in CCl_4 (3 mL) was heated at 85 °C for 4 h. The insoluble materials were filtered off, and the filtrate was evaporated to give **34** (160 mg) which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 1.52 (9H, s), 4.54 (2H, s), 6.72 (1H, brs, NH), 7.07−7.20 (2H, m), 8.08 (1H, m).

5-*tert*-Butoxycarbonylamino-2-pyridinemethanol (37). To a solution of 6-methyl-3-pyridinecarboxylic acid **35** (2.00 g, 14.6 mmol) and Et_3N (7.0 mL, 50.0 mmol) in a mixture of toluene (100 mL) and *t*-BuOH (15 mL) was added diphenylphosphoryl azide (4.0 mL, 18.6 mmol), and the mixture was heated at 100 °C for 22 h. After being cooled to room temperature, the reaction mixture was diluted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, H_2O and brine, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography (hexane−EtOAc, 2:1 elution) to give 3-*tert*-butoxycarbonylamino-6-methylpyridine **36** (2.04 g, 67%) as a white solid: mp 114−115 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.51 (9H, s), 2.49 (2H, s), 6.59 (1H, brs, NH), 7.08 (1H, d, J = 8.1 Hz), 7.85 (1H, m), 8.30 (1H, d, J = 2.7 Hz). HRMS calcd for $C_{11}H_{17}O_2N_2$ $(M + H)^+$: 209.1290, found 209.1287. Anal. ($C_{11}H_{16}N_2O_2$) C, H, N.

To a solution of **36** (2.04 g, 9.81 mmol) in $CHCl_3$ (100 mL) was added 3-chloroperbenzoic acid (2.80 g, 16.2 mmol), and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. A solution of the residue in acetic anhydride (15 mL) was heated at 100 °C for 30 min. After being cooled to room temperature, the reaction mixture was poured into EtOAc, washed with saturated aqueous $NaHCO_3$ and brine, and evaporated. A mixture of the resulting residue and K_2CO_3 (5.00 g, 36.2 mmol) in MeOH (100 mL) was stirred at room temperature for 15 h. The reaction mixture was poured into H_2O, and the organic solvent was evaporated. The aqueous layer was extracted with EtOAc, and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated. Purification of the residue by silica gel column chromatography (hexane−EtOAc, 1:2 elution) afforded **37** (1.01 g, 46%) as a white solid: mp 139−140 °C (hexane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.54 (9H, s), 4.72 (2H, s), 6.56 (1H, brs, NH), 7.21 (1H, d, J = 8.4 Hz), 7.97 (1H, m), 8.41 (1H, d, J = 2.1 Hz). HRMS calcd for $C_{11}H_{17}O_3N_2$ $(M + H)^+$: 225.1239, found 225.1248. Anal. ($C_{11}H_{16}N_2O_3$) C, H, N.

Receptor Binding Assay. According to the reported method,[20] the binding affinities were determined by inhibition of specific binding of [^{3}H]-NMS using membranes from CHO cells expressing cloned human m1−m3 receptors.

Metabolic Stability in Hepatic Microsomes. According to the reported method,[22] the remaining percentage of the test compound (10 μM) was measured after 30 min of incubation at 37 °C in hepatic microsomes (1 mg protein/mL).

Methacholine Provocation Test in Dogs. Beagle dogs, weighing 10 to 15 kg, were anesthetized with sodium pentobarbital (30 mg/kg, i.v.). Respiration was spontaneous. A cuffed endotracheal tube (7.5 mm ID) was inserted into the trachea and connected to the Astogragh (TCK-6100H, Chest M.I. Tokyo, Japan), an apparatus for a measurement of airway hyperresponsiveness with a system for delivering serially increasing doses of methacholine consisting of 12 identical nebulizers. Each nebulizer was connected to the main tube between the mouthpiece and the flowmeter. The air compressor could be switched in turn from one nebulizer to the next one at constant intervals of time. In this way, 12 kinds of aerosol could be sequentially delivered. Using this apparatus, the direct-writing dose−response curve of respiratory resistance (Rrs, $cmH_2O/L/s$) was obtained by the forced 3 Hz oscillation method. After baseline recording of Rrs, normal saline (0.9% NaCl) was inhaled through the first nebulizer for 1 min and followed by 1 min inhalations of methacholine through the next nebulizer in doubling dose from 5×10^{-7} M (0.078 mg/mL) to 2.5×10^{-4} M (40 mg/mL) without any intervals. When Rrs had become twice the initial one, salbutamol aerosol (1 mg/mL) was given for 2 min through the nebulizer in order to achieve bronchodilation. Airway responsiveness was calculated by interpolation, as the dose of methacholine causing 2-fold increases in basal Rrs. The dose of methacholine causing a doubling of Rrs was termed the methacholine provocative dose.

Compounds tested (1 mg/kg) were administered orally through a gavage tube in a conscious state. The methacholine provocation test was conducted at 4 h after dosing; the animal was anesthetized as previously described 15 min before methacholine challenge, and the cumulative methacholine provocation was started after baseline recording of Rrs. Bronchodilatory activity for each compound was expressed as shifts of the methacholine dose response curves between nontreatment and treatment with a compound. Nontreatment control responses in dogs were obtained in advance. Shifts were calculated by the following equation: Shifts = [the methacholine provocative dose after drug administration]/[the methacholine provocative dose without drug administration (nontreatment control response)].

Acknowledgment. We are grateful to Ms. A. Dobbins, Merck & Co., for critical reading of this manuscript.

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(25) The PK data of **15y** in dogs showed the good oral bioavailability [49.4−68.0% (0.03−0.3 mg/kg, p.o.)] and favorable terminal half-life [8.8−10.4 h (0.01−0.1 mg/kg, i.v.)]: Banyu Development Research Laboratories, unpublished results.

(26) Compound **15y** showed more than 1000-fold selectivities against other representative GPCRs including serotonergic (5-HT_1, 5-HT_{1A}, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_6, and 5-HT_7) and dopaminergic (D_1, D_{2S}, D_3, $D_{4.4}$, and D_5) receptors. Compound **15y** was not a potent inhibitor for P450 isozymes (CYP3A4, 2C9, and 2D6). As a result of these studies, it was decided to take **15y** forward in clinical development for the treatment of COPD as well as UI.

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JM0003135