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Synthesis and structure–activity relationships of *N*-{1-[(6-fluoro-2-naphthyl)methyl]piperidin-4-yl}benzamide derivatives as novel CCR3 antagonists

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Abstract—A novel class of potent CCR3 receptor antagonists were designed and synthesized starting from *N*-{1-[(6-fluoro-2-naphthyl)methyl]piperidin-4-yl}benzamide (**1**),which was found by subjecting our chemical library to high throughput screening (HTS). The CCR3 inhibitory activity of the synthesized compounds against eotaxin-induced Ca^{2+} influx was evaluated using CCR3-expressing preB cells. Systematic chemical modifications of **1** revealed that the 6-fluoro-2-naphthylmethyl moiety was essential for CCR3 inhibitory activity in this new series of CCR3 antagonists. Further structural modifications of the benzamide and piperidine moieties of **1** led to the identification of *N*-{8-[(6-fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3- yl}biphenyl-2-carboxamide (**31**) as a potent CCR3 antagonist with an IC_{50} value of 0.020 μM.

1. Introduction

One of the pathological features of various inflammatory diseases, such as allergic asthma and atopic dermatitis, is infiltration of eosinophils to the sites of inflammation. In particular, asthma is a reversible inflammatory disease that repeatedly caused airway obstruction and enhances airway hyper-responsiveness caused by an injury to the airway epithelium, which is induced by injurious proteins, chemical mediators, and inflammatory mediator released from activated eosinophils.[1a,b]

'Chemokine' is a generic term for small (8–12 kDa), heparin-binding, basic proteins that induce the migration and activation of leukocytes and macrophages, respectively. They are classified into four sub-families, CC chemokines, CXC chemokines, C chemokines, and CX_3C chemokines, based on their structure. Their biological activity is mediated through seven-transmembrane G-protein coupled receptors (GPCRs) on the surface of immune and inflammatory cells. These receptors (CCR1-11, CXC1-6, XCR1, CX_3C1) have been cloned and characterized. Among them, CCR3, a CC chemokine receptor subtype, is thought to play an important role in the migration, activation, and degranulation of inflammatory cells, such as eosinophils, mast cells, basophils, and Th-2 cells.[2a–e]

Studies on CCR3 gene KO mice as animal models of allergic asthma and atopic dermatitis demonstrated that the infiltration of eosinophils into lung and dermal tissues and the enhancement of airway hyper-responsiveness are less than those of wild type mice.[3] Furthermore, the antibody against eotaxin, a selective CCR3 ligand, in vivo reduces the accumulation of eosinophils in the lung that occurs in response to ovalbumin.[4]

These factors suggest that CCR3 antagonists, which selectively suppress the activation of inflammatory cells,

Keywords: Allergic diseases; CCR3 antagonists; 6-fluoro-2-naphthylmethyl moiety; Nortropane derivatives.
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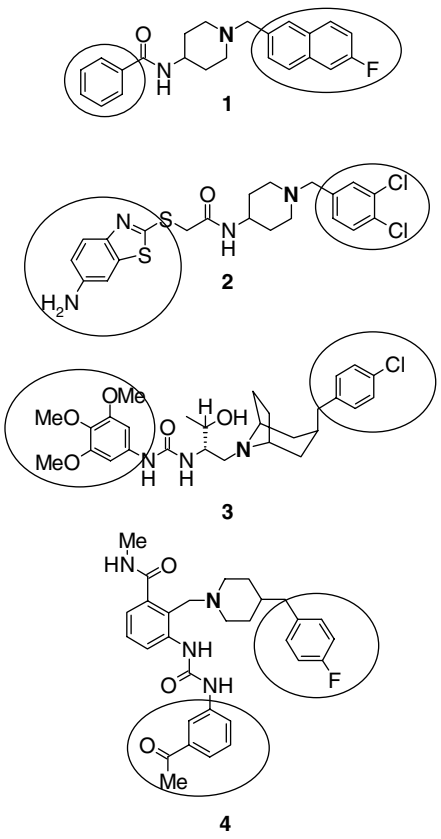
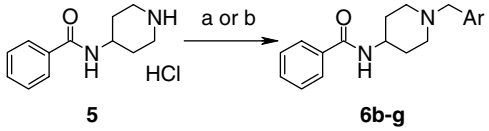


Figure 1. Structure of compound **1** and previously reported CCR3 antagonists (**2**,[8a,b] **3**,[8c] and **4**[8d]).



Scheme 1. Synthesis of compounds **6b–g**. Reagents and conditions: (a) aldehyde, $NaBH(OAc)_3$, AcOH, THF/CH_2Cl_2, rt; (b) in the case of **6f** and **6g**: alkyl halide, K_2CO_3, EtOH, reflux.

may have therapeutic potentials for treating diseases, such as allergic asthma and atopic dermatitis.

To develop a new therapeutic drug for the treatment of the inflammatory diseases described above, a research program was started in an attempt to discover a novel type of CCR3 antagonist. First, our chemical library was subjected to HTS, which resulted in the discovery of a lead compound with moderate activity (IC_{50} = 1.3 μM), *N*-{1-[(6-fluoro-2-naphthyl)methyl]piperidin-4-yl}benzamide (**1**). (Fig. 1). The results of the work on synthesis, the structure–activity relationship (SAR), and the biological activity of each of the *N*-{1-[(6-fluoro-2-naphthyl)methyl]piperidin-4-yl}benzamide derivatives are described herein.

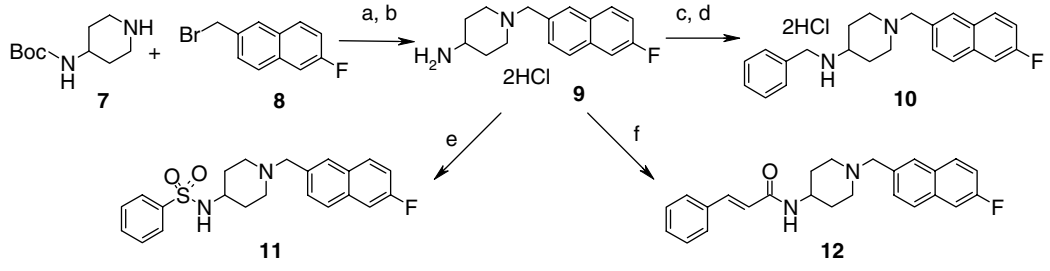
2. Chemistry

The syntheses of the compounds are summarized in Schemes 1–7.

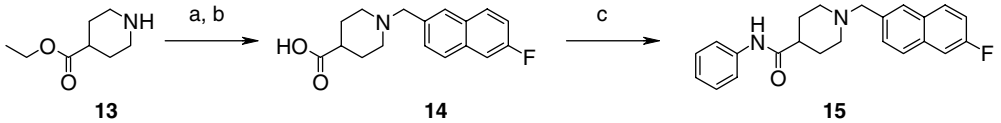
The *N*-(1-alkylpiperidin-4-yl)benzamide derivatives (**6b–e**) were prepared from the amine (**5**) by reductive alkylation with appropriate aldehydes. In the case of **6f** and **6g**, compound **5** was alkylated with 2-(bromomethyl)-6-fluoroquinoline[5] and 3-chloro-4′-fluoropropiophenone, respectively (Scheme 1).

Alkylation of the amine (**7**) with the bromide (**8**)[6] in the presence of K_2CO_3, followed by removal of the Boc group, yielded the intermediate amine (**9**). The benzyl amine (**10**) was obtained by reductive alkylation of **9** with the benzaldehyde. Condensation of **9** with the benzenesulfonyl chloride and the (2*E*)-3-phenylacryloyl chloride yielded compounds **11** and **12**, respectively (Scheme 2).

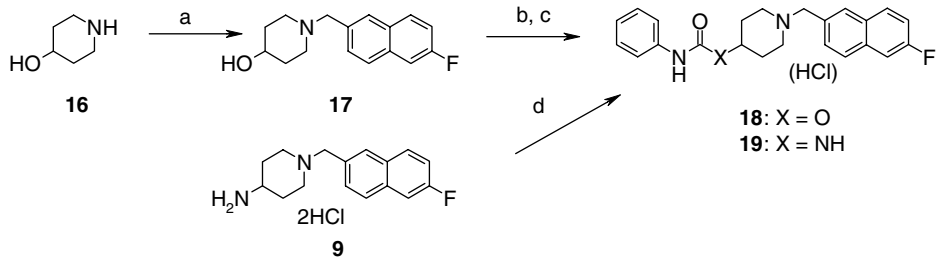
The synthesis of compound **15** is shown in Scheme 3. Alkylation of the amine (**13**) with **8**, followed by hydrolysis with NaOH in EtOH, yielded the carboxylic acid



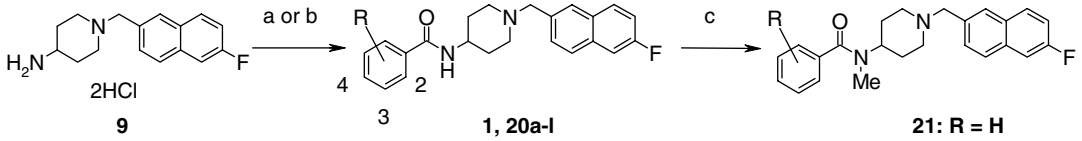
Scheme 2. Synthesis of compounds **10–12**. Reagents and conditions: (a) K_2CO_3, MeCN, rt, 20 h, 76%; (b) 4 M HCl/EtOAc, EtOAc, rt, 90%; (c) PhCHO, $NaBH(OAc)_3$, CH_2Cl_2, rt, 8 h; (d) 4 M HCl/EtOAc, 57% for two steps; (e) $PhSO_2Cl$, DIPEA, CH_2Cl_2, rt, overnight, 41% (f) cinnamoyl chloride, Et_3N, CH_2Cl_2, rt, overnight, 56%.



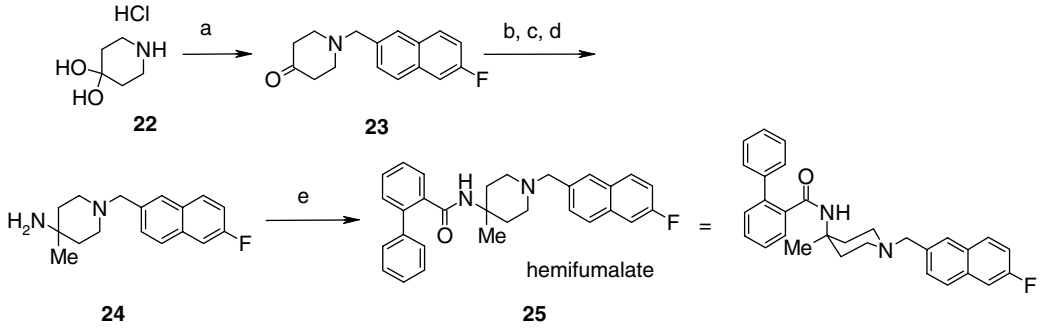
Scheme 3. Synthesis of compounds **15**. Reagents and conditions: (a) **8**, K_2CO_3, EtOH, rt, overnight, 72%; (b) 1 N NaOH, EtOH, rt, 4h, 50%; (c) aniline, WSC·HCl, HOBt, Et_3N, CH_2Cl_2, rt, overnight, 68%.



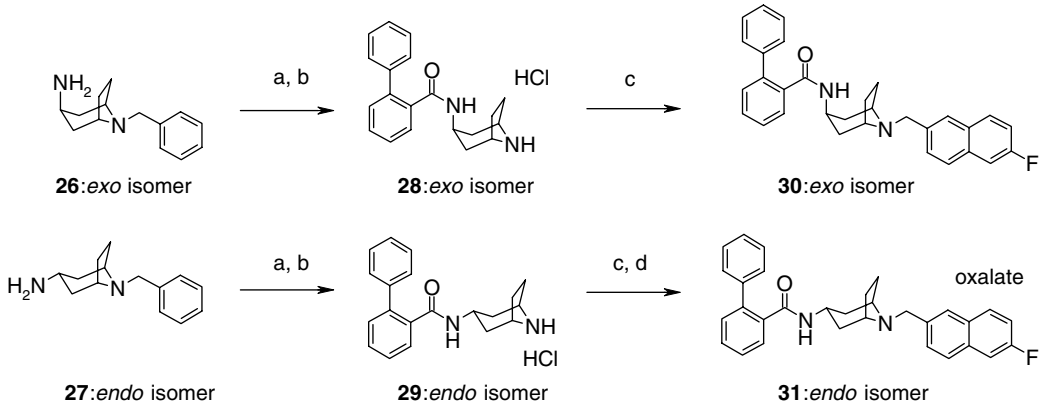
Scheme 4. Synthesis of compounds **18** and **19**. Reagents and conditions: (a) **8**, Et_3N, $CHCl_3$, rt, 4 h, 84%; (b) PhNCO, toluene, reflux, 11 h; (c) 4 M HCl/EtOAc, 40% for two steps; (d) PhNCO, DIPEA, CH_2Cl_2, rt, overnight, 68%.



Scheme 5. Synthesis of compounds **20a–l** and **21**. Reagents and conditions: (a) ArCOCl, base; (b) ArCOOH, WSC·HCl, HOBt, CH_2Cl_2; (c) NaH, DMF, rt, 1.5 h, then MeI, rt, 5 h, 47%.



Scheme 6. Synthesis of compounds **25**. Reagents and conditions: (a) **8**, K_2CO_3, DMF, rt, 78%; (b) MeLi, Et_2O, −70 °C, 90%; (c) MeCN, H_2SO_4, rt, 93%; (d) 3 M HCl, 100 °C, quant; (e) biphenyl-2-carboxylic acid, WSC·HCl, HOBt, 1,2-dichloroethane, rt; (f) fumaric, acid, 31% for two steps.



Scheme 7. Synthesis of compounds **30** and **31**. Reagents and conditions: (a) biphenyl-2-carboxylic acid, WSC·HCl, HOBt, DMF; (b) H_2, 10 wt% $Pd(OH)_2$/C, 4 M HCl/EtOAc, rt; (c) **8**, K_2CO_3, rt; (d) oxalate, MeOH.

(**14**). Compound **14** was transformed into the target compound (**15**) by condensation with aniline.

Scheme 4 illustrates the synthesis of the carbamate (**18**) and the urea (**19**). Compound **16** was alkylated with **8** and the subsequent reaction with the phenylisocyanate afforded the carbamate (**18**). The urea (**19**) was synthesized with **18** from **9** in the same manner.

The condensation of **9** with acids or acid chlorides yielded the 6-fluoro-2-naphthylmethyl derivatives (**20a–l**). Compound **21** was prepared by methylating **1** using MeI (Scheme 5).

Compound **25** was prepared from **22** in five steps, as follows: alkylation with **8**, methylation by MeLi, the Ritter reaction with MeCN and H_2SO_4, condensation with biphenyl-2-carboxylic acid, and then crystallization as a hemifumarate.

Amines **26**[7] and **27**[7] were reacted with the biphenyl-2-carboxylic acid followed by deprotection of the benzyl group to yield the amines **28** and **29**, respectively. Compounds **28** and **29** were converted into the *exo*-derivative (**30**) and the *endo*-derivative (**31**), respectively, by alkylation with **8** (Scheme 7).

The conformation analyses of **20j**, **25**, **30**, and **31** using NMR were performed as described below (Fig. 2). Since the methylene protons of the piperidine ring (Ha and Hb) of **20j** had a vicinal coupling constant (J_{ab}) of more than 12 Hz, the piperidine ring seemed to adopt the chair form as the most stable conformation. As for **25**, nuclear Overhauser effects (NOEs) between the methyl group of the piperidine ring and the methylene protons at the 3-position of the piperidine ring (Hc) were observed; however, no NOEs were observed between the methyl group and the methylene protons at the 2-position of the piperidine ring (Hd). And for the same reason as **20j**, the piperidine ring seemed to adopt the chair form as the most stable conformation. These indicated that the methyl group of **25** should occupy the equatorial position at the 4-position of the piperidine ring, and its benzamide group should occupy the axial position. With respect to the conformation of **30**, the NOEs were observed between the amide proton at **30** and the methylene protons at the bridge of the 8-azabicyclo[3.2.1]octane ring (He). Furthermore, the methine proton at the 3-position of the 8-azabicyclo[3.2.1]octane ring (Hf) did not adopt the axial conformation, since the coupling constant of this methine proton (J_f) was less than 6 Hz. As a result of these NMR analyses, the most stable conformation of **30** was thought to be as shown in Figure 2. The most stable conformation of **31** is believed to be as shown in Figure 2, since NOEs were observed between the methine proton at the 3-position of the 8-azabicyclo[3.2.1]octane ring (Hg) and the methylene protons at the bridge of the 8-azabicyclo[3.2.1]octane ring (Hi).

The crystal of **31** suitable for X-ray analysis was prepared by recrystallization as an oxalate from *i*-PrOH. In addition, it was confirmed that the structure of **31** corresponded to the desired *endo*-isomer (Fig. 3).

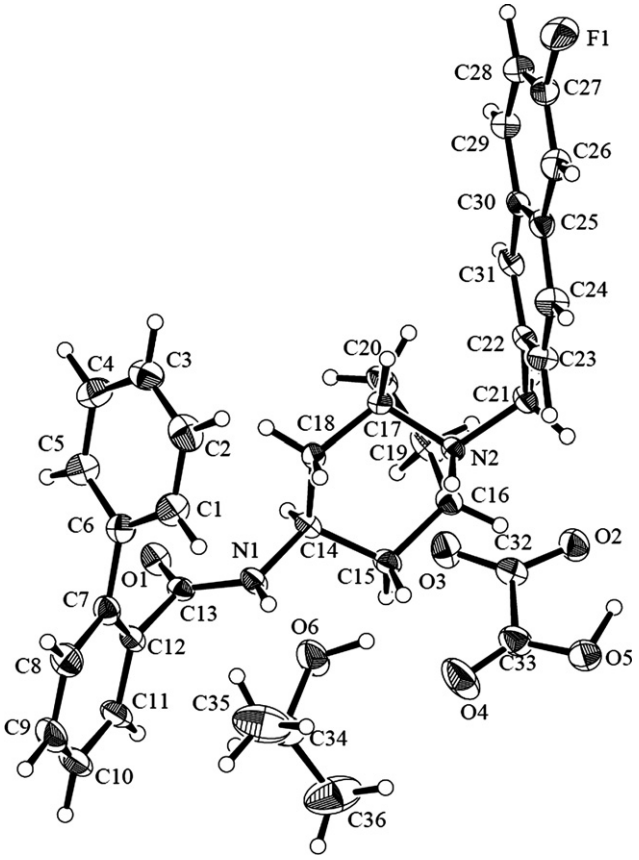


Figure 3. Displacement ellipsoid plot of **31** drawn at the 30% probability level.

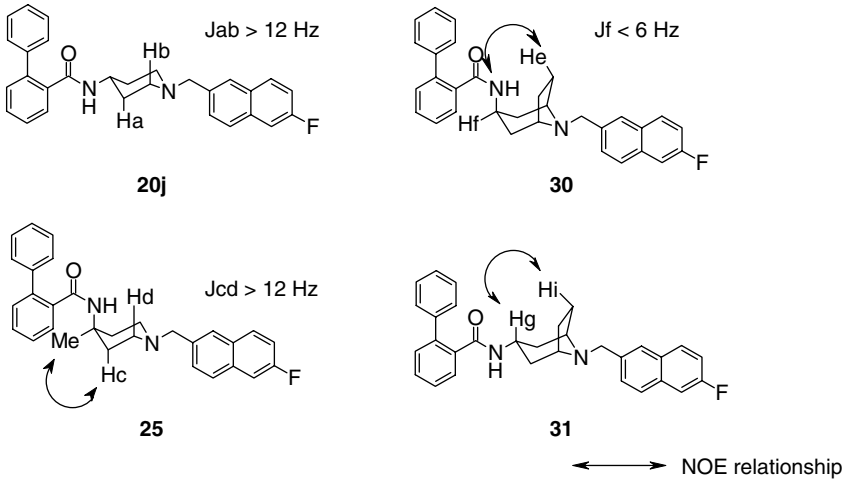


Figure 2. Conformation of **20j**, **25**, **30**, and **31**.

3. Results and discussion

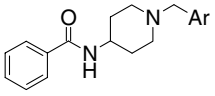
The synthesized compounds were evaluated for their inhibitory activity (IC_{50}) on eotaxin-induced Ca^{2+} influx by using CCR3-expressing preB cells. The lead compound (**1**) displayed moderate CCR3 inhibitory activity with an IC_{50} value of 1.3 μM.

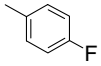
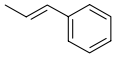
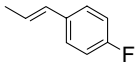
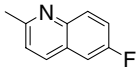
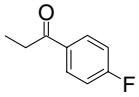
Many of the CCR3 antagonists that have been reported recently have one of two structural features in common with the lead compound (**1**). One is having a basic nitrogen atom in the center of the molecule, and the other is having aryl rings at each terminal of the molecule (Fig. 1).[8a–d] This common structural feature seems to be the key pharmacophore for CCR3 inhibitory activity, therefore a strategy for structural optimization was planned as follows: (1) replace the 6-fluoro-2-naphthylmethyl moiety at the terminal of **1** with the other aryl ring, (2) structural modification of the linker moieties at the center of **1**, (3) introduction of substituents onto the benzamide moiety at another terminal.

First, the effects of replacing the 6-fluoro-2-naphthylmethyl moiety of **1** with another aryl ring were explored (Table 1). The naphthalene (**6a**),[9] which removed a fluorine atom from **1**, had no inhibitory effect at the concentration of 10 μM. The 2-MeO-naphthalene (**6b**) and the 4-fluorobenzyl derivative (**6c**) also had no inhibitory effect at that concentration. Furthermore, introduction of the cinnamoyl (**6d**), the fluoroquinoline (**6f**), and the ketone (**6g**) caused severe losses of activity. In Table 1, only compound **6e**, which introduced a fluorine atom into the cinnamoyl moiety of **6d**, showed moderate activity (IC_{50} value = 3.4 μM). These results suggest that the existence of a heteroatom between the nitrogen atom in the piperidine ring and the terminal fluorine atom would not be tolerated (**6f** and **6g**), and that the terminal fluorine atom would play an important and significant role in CCR3 inhibitory activity (**6a** vs. **1** and **6d** vs. **6e**). The 6-fluoro-2-naphthylmethyl group shows the strongest CCR3 inhibitory activity in this table.

Next, the influence of the linker between the basic nitrogen atom in the piperidine and the phenyl ring of **1** was investigated (Table 2). All compounds with linker lengths of two atoms, such as benzylamine (**10**), sulfonamide (**11**), reverse amide (**15**), and *N*-methyl amide (**21**), inhibited the CCR3 receptor to a degree comparable to **1**. In contrast, all derivatives with linkages of three atoms or more (**12**, **18,** and **19**) were weak inhibitors. These observations indicate that the distance between the terminal phenyl ring and the basic nitrogen atom

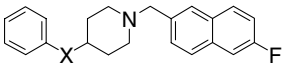
Table 1. CCR3 inhibitory activities of benzamide derivatives (**1**, **6a**–**g**)



Compound	Ar	IC_{50}[a] (μM)
1	6-F-2-Naphthyl	1.3 ± 0.034
6a	2-Naphthyl	N.E[b]
6b	6-MeO-2-naphthyl	N.E[b]
6c		N.E[b]
6d		N.E[b]
6e		3.4 ± 0.30
6f		N.E[b]
6g		N.E[b]

[a] IC_{50} values are shown with ± SE (number of determinations) when more than three determinations were made.
[b] No effect at 10 μM.

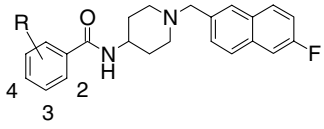
Table 2. CCR3 inhibitory activities of 6-fluoro-2-naphthylmethyl derivatives (**10**–**12**, **15**, **18**, **19**, **21**)



Compound	X	IC_{50}[a] (μM)
1	–CONH–	1.3 ± 0.034
10	–CH2NH–	0.60 ± 0.11
11	–SO2NH–	0.83 ± 0.071
15	–NHCO–	1.7 ± 0.088
21	–CONMe–	0.81 ± 0.19
12	–(*E*)–CH=CH–CONH–	9.7 ± 3.7
18	–NHCOO–	4.8 ± 1.1
19	–NHCONH–	31%[b]

[a] IC_{50} values are shown with ± SE (number of determinations) when more than three determinations were made.
[b] % inhibition at 10 μM.

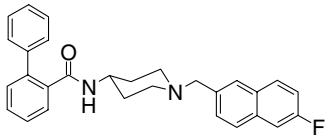
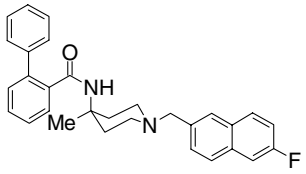
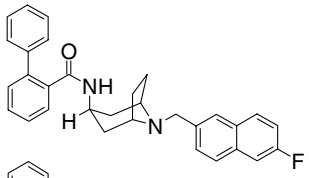
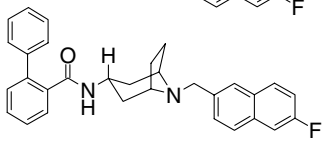
Table 3. CCR3 inhibitory activities of substituted benzamide derivatives (**20a**–**l**)



Compound	R	IC_{50}[a] (μM)
1	H	1.3 ± 0.034
20a	2-F	2.9 ± 0.67
20b	3-F	0.67 ± 0.20
20c	4-F	0.64 ± 0.27
20d	2-MeO	0.72 ± 0.34
20e	3-MeO	3.5 ± 1.0
20f	4-MeO	2.4 ± 0.63
20g	2-PhO	0.095 ± 0.026
20h	3-PhO	1.1 ± 0.37
20i	4-PhO	40%[b]
20j	2-Ph	0.038 ± 0.0054
20k	3-Ph	N.E.[c]
20l	4-Ph	27%[b]

[a] IC_{50} values are shown with ± SE (number of determinations) when more than three determinations were made.
[b] % inhibition at 10 μM.
[c] No effect at 10 μM.

Table 4. CCR3 inhibitory activities of 6-fluoronaphthalene derivatives (**25**, **30,** and **31**)

Compound	Structure	IC_{50}[a] (μM)
20j		0.038 ± 0.0054
25		2.8 ± 0.97
30		2.7 ± 1.4
31		0.020 ± 0.0039

[a] IC_{50} values are shown with ± SE (number of determinations) when more than three determinations were made.

is the important factor determining the inhibitory potency, not which atoms are present in the linker moiety.

In Table 3, the effects of various substituents around the phenyl moiety of **1** were examined. The introduction of a fluorine atom at the 3- or 4-position on the phenyl ring of **1** (**20b** and **20c**) slightly enhanced the inhibitory activity, whereas the introduction of a fluorine atom at the 2-position (**20a**) slightly reduced it. In contrast to these results, the incorporation of the methoxy group at the 3- or 4-position on the phenyl ring of **1** (**20e** and **20f**) slightly reduced inhibitory activity, while at the 2-position (**20d**) inhibitory activity was slightly enhanced. The phenoxy and phenyl groups around the phenyl ring of **1** displayed the same tendency as the methoxy group. The 2-phenoxy and the 2-phenyl derivatives (**20g** and **20j**) led to about 14-fold and 34-fold increases in activity, respectively, compared to **1**. These results indicated that the hydrophobic and bulky groups would be suitable substituents at the 2-position, but there might be steric limitations around the 3- and 4-position.

Finally, we focused on the conformation of **20j** (shown in Fig. 2). Compound **25** was designed and synthesized to have a conformation different from that of **20j**, specifically, the most stable conformation. The piperidine ring should have adopted to the chair form, and the benzamide moiety should have occupied the axial position of the piperidine ring. However, compound **25**, which is a two-atom-linkage derivative, was a weaker CCR3 receptor inhibitor than **20j** (IC_{50} value = 2.8 μM) (Table 4). These observations indicated that the most stable conformation of **20j** is actually the active conformation. Therefore, the expectation was that activity would improve if the conformation was constrained like that of **20j**. To that end, nortropane derivatives **30** and **31** were designed and synthesized. As expected, the *endo*-isomer (**30**), which should have had the same conformation as **25** and been the most stable, had an inhibitory activity equal to that of **25**, and the *exo*-isomer (**31**), which should have the same inhibitory activity as **20j**, was the most potent against the CCR3 receptor among this series, with an IC_{50} value of 0.020 μM. Since it was easier for **31** to adopt the active conformation, the CCR3 inhibitory activity of **31** was approximately two times more potent than that of **20j** (Fig. 3).

Inhibitory activity against other CC chemokines, CCR1, CCR2, and CCR5, of **31** was also evaluated. The results showed that compound **31** had a 40% inhibition rate against CCR1 at the concentration of 10 μM, but had no effect on CCR2 or CCR5 at that concentration. Thus, **31** proved to be a selective and potent CCR3 antagonist.

Further biological, pharmacokinetic and pharmacotoxic evaluation for **31** are now being carried out.

4. Conclusions

In an attempt to discover new potent CCR3 antagonists, a series of *N*-{1-[(6-fluoro-2-naphthyl)methyl]piperidin-4-yl}benzamide derivatives were synthesized and evaluated. The results of the SAR studies in this series indicated that 6-fluoronaphthalene-2-ylmethyl moiety was essential for potent CCR3 inhibitory activity. Furthermore, hydrophobic and bulky groups proved to be appropriate substituents at the 2-position of the benzamide moiety, and the nortropane ring was shown to be more suitable for the cyclic amine moiety than the flexible piperidine ring. Consequently, *exo*-*N*-{8-[(6-fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl} biphenyl-2-carboxamide (**31**) was determined to be a novel lead compound in search for more potent CCR3 antagonists to be used as therapeutic agents for allergic diseases.

5. Experimental

5.1. Chemistry

In general, reagents and solvents were used as purchased without further purification. Melting points were determined with a Yanaco MP-500D melting point apparatus and left uncorrected. ^{1}H NMR spectra were recorded on a JEOL JNM-LA300 or a JEOL JNM-EX400 spectrometer. Chemical shifts were expressed in δ (ppm) values with tetramethylsilane as an internal standard (NMR descriptions; s, singlet; d, doublet; t, triplet; dt, double triplet; m, multiplet, and br, broad peak). Mass spectra were recorded on a JEOL JMS-LX2000 spectrometer. The elemental analyses were performed with a Yanaco MT-5 microanalyzer (C, H, N) and Yokogawa IC-7000S ion chromatographic analyzer (halogens) and were within ±0.4% of theoretical values.

5.1.1. *N*-{1-[(6-Methoxy-2-naphthyl)methyl]piperidin-4-yl}benzamide (6b). To a solution of **5** (300 mg, 1.25 mmol) in CH_2Cl_2 (3 mL), and THF (1 mL) were added 6-methoxy-2-naphthaldehyde (255 mg 1.37 mmol), sodiumtriacetoxyborohydride (362 mg, 1.62 mmol) and AcOH (1 drop), and the mixture was stirred at room temperature for 16 h. The mixture was partitioned between $CHCl_3$ and satd $NaHCO_3$ aq and then the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude solid was recrystallized from MeCN–$CHCl_3$ to yield **6b** (308 mg, 66%) as a colorless powder: mp: 197–199 °C (MeCN–CHCl3); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.53–1.63 (m, 2H), 1.99–2.07 (m, 2H), 2.18–2.27 (m, 2H), 2.86–2.93 (m, 2H), 2.80–2.88 (m, 2H), 3.63 (s, 2H), 3.92 (s, 3H), 3.99–4.09 (m, 1H), 5.94–6.02 (m, 1H), 7.10–7.16 (m, 2H), 7.39–7.52 (m, 4H), 7.65–7.78 (m, 5H); MS (FAB) m/z = 375 $[M+H]^+$. Anal. Calcd for $C_{24}H_{26}N_2O_2$: C, 76.98; H, 7.00; N, 7.48. Found: C, 77.02; H, 7.12; N, 7.54.

5.1.2. *N*-[1-(4-Fluorobenzyl)piperidin-4-yl]benzamide (6c). Compound **6c** was prepared from **5** and 4-fluorobenzaldehyde in a manner similar to that described for compound **6b**, with a yield of 40% as a colorless powder. mp: 145–147 °C (EtOH–MeCN); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.51 (dd, J = 11.4, 3.9 Hz, 1H), 1.59 (dd, J = 11.1, 3.6 Hz, 1H), 1.98–2.08 (m, 2H), 2.17 (dt, J = 11.7, 2.4 Hz, 2H), 2.78–2.88 (m, 2H), 3.48 (s, 2H), 3.95–4.08 (m, 1H), 5.93–6.03 (m, 1H), 6.96–7.05 (m, 2H), 7.24–7.32 (m, 1H), 7.39–7.53 (m, 3H), 7.72–7.77 (m, 2H); MS (FAB) m/z = 313 $[M+H]^+$. Anal. Calcd for $C_{19}H_{21}FN_2O$: C, 73.05; H, 6.78; N, 8.97; F, 6.08. Found: C, 72.95; H, 6.94; N, 9.02, F, 6.08.

5.1.3. *N*-{1-[(2*E*)-3-Phenylprop-2-en-1-yl]piperidin-4-yl}benzamide (6d). Compound **6d** was prepared from **5** and (2*E*)-3-phenylacrylaldehyde in a manner similar to that described for compound **6b**, with a yield of 67% as a colorless powder. mp: 165–168 °C (MeCN–$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.54 (ddd, J = 13.9, 11.2, 3.4 Hz, 2H), 2.04–2.11 (m, 2H), 2.15–2.24 (m, 2H), 2.92–3.00 (m, 2H), 3.17 (dd, J = 6.9, 1.0 Hz, 2H), 3.97–4.09 (m, 1H), 5.99 (d, J = 7.4 Hz, 1H), 6.28 (dt, J = 15.6, 6.9 Hz, 1H), 6.53 (d, J = 15.6 Hz, 1H), 7.21–7.25 (m, 1H), 7.28–7.35 (m, 2H), 7.36–7.46 (m, 4H), 7.47–7.53 (m, 1H), 7.73–7.78 (m, 2H); MS (FAB) m/z = 321 $[M+H]^+$. Anal. Calcd for $C_{21}H_{20}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 78.75; H, 7.67; N, 8.74.

5.1.4. *N*-{1-[(2*E*)-3-(4-Fluorophenyl)prop-2-en-1-yl]piperidin-4-yl}benzamide (6e). Compound **6e** was prepared from **5** and (2*E*)-3-(4-fluorophenyl) acrylaldehyde[10] in a manner similar to that described for compound **6b**, with a yield of 71% as a colorless solid. mp: 181–183 °C (MeCN–$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.58 (ddd, J = 13.7, 11.2, 3.7 Hz, 2H), 2.03–2.11 (m, 2H), 2.15–2.24 (m, 2H), 2.95–3.00 (m, 2H), 3.16 (dd, J = 6.8, 1.0 Hz, 2H), 3.97–4.09 (m, 1H), 5.99 (d, J = 7.3 Hz, 1H), 6.20 (dt, J = 15.6, 6.8 Hz, 1H), 6.54 (d, J = 15.6 Hz, 1H), 6.97–7.03 (m, 2H), 7.31–7.38 (m, 2H), 7.40–7.47 (m, 2H), 7.48–7.53 (m, 1H), 7.73–7.78 (m, 2H); MS (FAB) m/z = 339 $[M+H]^+$. Anal. Calcd for $C_{21}H_{23}FN_2O$: C, 74.53; H, 6.85; N, 8.28; F, 5.61. Found: C, 74.70; H, 6.91; N, 8.31; F 5.58.

5.1.5. *N*-{1-[(6-Fluoroquinolin-2-yl)methyl]piperidin-4-yl}benzamide (6f). To a solution of **5** (300 mg, 1.25 mmol) in EtOH (10 mL) were added 2-(bromomethyl)-6-fluoroquinoline[5] (300 mg 1.25 mmol) and K_2CO_3 (517 mg, 3.74 mmol), and the mixture was stirred at reflux for 3 h. The mixture was cooled to rt and partitioned between EtOAc and brine, and then the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude solid was recrystallized from MeCN to yield **6f** (288 mg, 63%) as a colorless powder. mp: 198–201 °C; ^{1}H NMR (400 MHz, DMSO-d_6 δ: 1.55–1.70 (m, 2H), 1.75–1.84 (m, 2H), 2.13–2.23 (m, 2H), 2.82–2.90 (m, 2H), 3.74–3.86 (m, 3H), 7.45 (dd, J = 7.8, 7.4 Hz, 2H), 7.48–7.54 (m, 1H), 7.63 (dd, J = 9.2, 2.4 Hz, 1H), 7.68 (d, J = 7.6 Hz, 2H), 7.77 (dd, J = 9.2, 2.4 Hz, 1H), 7.83 (d, J = 7.8 Hz, 2H), 8.04 (dd, J = 6.0, 7.2 Hz, 1H), 8.25 (d, J = 7.6 Hz, 1H), 8.34 (d, J = 8.8 Hz, 1H); MS (FAB) m/z = 364 $[M+H]^+$. Anal. Calcd for $C_{22}H_{22}FN_3O$: C, 72.71; H, 6.10; N, 11.56; F, 5.23. Found: C, 72.45; H, 6.12; N, 11.56; F, 5.25.

5.1.6. *N*-{1-[3-(4-Fluorophenyl)-3-oxopropyl]piperidin-4-yl}benzamide (6g). Compound **6g** was prepared from **5** and 3-chloro-4′-fluoropropiophenone in a manner similar to that described for compound **6f**, with a yield of 11% as a colorless solid. mp: 150–156 °C (MeCN); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.62–1.77 (m, 2H), 2.04–2.14 (m, 2H), 2.33–2.44 (m, 2H), 2.95 (t, J = 7.2 Hz, 2H), 2.98–3.07 (m, 2H), 3.26 (t, J = 7.2 Hz, 2H), 4.00–4.14 (m, 1H), 6.06 (d, J = 7.2 Hz, 1H), 7.10–7.17 (m, 2H), 7.39–7.54 (m, 3H), 7.72–7.78 (m, 2H), 7.96–8.04 (m, 2H); MS (FAB) m/z = 355 $[M+H]^+$. Anal. Calcd for $C_{21}H_{23}FN_2O_2{\cdot}0.5H_2O$: C, 69.40; H, 6.66; N, 7.71; F, 5.23. Found: C, 69.08; H, 6.47; N, 7.60; F 5.22.

5.1.7. 1-[(6-Fluoro-2-naphthyl)methyl]piperidin-4-amine dihydrochloride (9). To a solution of *tert*-butyl piperidin-4-ylcarbamate·HCl (14.2 g, 59.3 mmol) in MeCN (200 mL) were added **8** (14.2 g 59.3 mmol) and K_2CO_3 (24.6 g, 178 mmol), and the mixture was stirred at room temperature for 20 h. This mixture was concentrated in vacuo. The residue was then partitioned between EtOAc and H_2O, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH = 100/0–95/5) to yield *tert*-butyl {1-[(6-fluoro-2-naphthyl)methyl]piperidin-4-yl} carbamate (16.2 g, 76%) as a colorless solid. To a solution of compound obtained above in EtOAc (200 mL) were added 4 M HCl (g)/EtOAc (200 mL), and the mixture was stirred at room temperature for 17.5 h. The precipitate was collected by filtration, washed with EtOAc and Et_2O, and dried in vacuo to yield **9** (13.5 g, 90%) as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.94–2.19 (m, 4H), 2.50–3.50 (m, 5H), 4.40, 4.50 (each d, J = 5.2 Hz, 2H), 7.45–7.54. (m, 1H), 7.76–7.89 (m, 2H), 7.98–8.06 (m, 2H), 8.16, 8.18 (each s, 1H), 8.35–8.64 (m, 3H), 11.20–11.46 (m, 1H); MS (FAB) m/z = 259 $[M+H]^+$.

5.1.8. *N*-Benzyl-1-[(6-fluoro-2-naphthyl)methyl]piperidin-4-amine (10). A solution of **9** (600 mg, 1.81 mmol) in EtOAc (50 mL) were washed with satd $NaHCO_3$ aq and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. To a solution of the crude product in CH_2Cl_2 (18 mL) were added benzaldehyde (1.81 mL 1.81 mmol) and sodiumtriacetoxyborohydride (422 mg, 1.99 mmol), and the mixture was stirred at room temperature for 8 h. This mixture was partitioned between EtOAc and satd $NaHCO_3$ aq and the organic layer was washed with brine. The organic layer was then dried over $MgSO_4$, filtered, and concentrated in vacuo. To a solution of compound obtained above in EtOAc (15 mL) were added 4 M HCl (g)/EtOAc (1.5 mL), and the mixture was stirred at room temperature. The precipitate was collected by filtration, washed with EtOAc, and dried in vacuo to yield **10** (435 mg, 57%) as a colorless crystal. mp: 316–318 °C (EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.03–2.16 (m, 2H), 2.26–2.36 (m, 2H), 2.96–3.04 (m, 2H), 3.42–3.52 (m, 2H), 4.22 (d, J = 4.4 Hz, 1H), 4.41 (d, J = 4.4 Hz, 1H), 7.39–7.60 (m, 6H), 7.75–7.86 (m, 2H), 7.96–8.07 (m, 2H), 8.14 (s, 1H), 9.57 (s, 1H), 11.02 (s, 1H); MS (FAB) m/z = 349 $[M+H]^+$. Anal. Calcd for $C_{23}H_{24}FN_2{\cdot}2HCl$: C, 65.56; H, 6.46; N, 6.65; F, 4.51. Found: C, 64.47; H, 6.58; N, 6.66; F, 4.45.

5.1.9. *N*-{1-[(6-Fluoro-2-naphthyl)methyl]piperidin-4-yl}benzenesulfonamide (11). Compound **11** was prepared from **9** and benzenesulfonyl chloride in a manner similar to that described for compound **20c**, with a yield of 41% as a colorless solid. mp: 118–119 °C (MeCN);^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.42–1.53 (m, 2H), 1.70–1.79 (m, 2H), 2.03–2.12 (m, 2H), 2.69–2.78 (m, 2H), 3.16–3.27 (m, 1H), 3.58 (s, 2H), 4.58 (d, J = 7.3 Hz, 1H), 7.21–7.28 (m, 1H), 7.39–7.58 (m, 5H), 7.66 (s, 1H), 7.71 (d, J = 8.3 Hz, 1H), 7.76 (dd, J = 9.0, 5.6 Hz, 1H), 7.86–7.91 (m, 2H); MS (FAB) m/z = 399 $[M+H]^+$. Anal. Calcd for $C_{22}H_{23}FN_2O_2S$: C, 66.31; H, 5.82; N, 7.03; S, 8.05; F, 4.77. Found: C, 66.12; H, 5.82; N, 6.98; S, 8.10; F, 4.74.

5.1.10. (2*E*)-*N*-{1-[(6-Fluoro-2-naphthyl)methyl]piperidin-4-yl}-3-phenylacrylamide (12). Compound **12** was prepared from **9** and cinnamoyl chloride in a manner similar to that described for compound **20c**, with a yield of 56% as a colorless solid. mp: 184–186 °C (MeCN–$CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.48–1.59 (m, 2H), 1.95–2.02 (m, 2H), 2.16–2.26 (m, 2H), 2.83–2.92 (m, 2H), 3.64 (s, 2H), 3.91–4.03 (m, 1H), 5.52 (d, J = 7.8 Hz, 1H), 6.37 (d, J = 15.7 Hz, 1H) 7.23–7.28 (m, 1H), 7.33–7.39 (m, 3H), 7.43 (dd, J = 10.0, 2.8 Hz, 1H), 7.47–7.54 (m, 3H), 7.61 (d, J = 15.7 Hz, 1H), 7.72–7.77 (m, 2H), 7.79 (dd, J = 9.0, 5.6 Hz, 1H); MS (FAB) m/z = 389 $[M+H]^+$. Anal. Calcd for $C_{25}H_{25}FN_2O$: C, 77.29; H, 6.49; N, 7.21; F, 4.89. Found: C, 77.43; H, 6.53; N, 7.21; F, 4.73.

5.1.11. 1-[(6-Fluoro-2-naphthyl)methyl]piperidine-4-carboxylic acid (14). To a solution of Ethyl isonipecotate (406 mg, 2.50 mmol) in EtOH (6 mL) was added **8** (598 mg 2.50 mmol), and K_2CO_3 (433 mg, 3.13 mmol) and the mixture was stirred overnight at room temperature. This mixture was then partitioned between EtOAc and H_2O, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH = 100/0–95/5) to yield Ethyl 1-[(6-fluoro-2-naphthyl)methyl]piperidine-4-carboxylate (569 mg, 72%) as a colorless oil. To a solution of the compound obtained above in EtOH (6 mL) were added 1 M NaOH aq (2.0 mL), and the mixture was stirred at room temperature for 4 h. This mixture was acidified with 1 M HCl aq and the precipitate was collected by filtration, washed with H_2O, and dried in vacuo to yield **14** (259 mg, 50%) as a pale brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.52–1.63 (m, 2H), 1.73–1.83 (m, 2H), 1.97–2.08 (m, 2H), 2.16–2.25. (m, 1H), 2.74–2.82 (m, 2H), 3.59 (s, 2H), 7.40 (ddd, J = 8.8, 7.2, 2.4 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.67 (dd, J = 10.4, 2.4 Hz, 1H), 7.82 (s, 1H), 7.86 (d, J = 8.4 Hz 1H), 7.98 (dd, J = 7.2, 6.0 Hz 1H), 11.90–12.29 (m, 1H); MS (FAB) m/z = 288 $[M+H]^+$.

5.1.12. 1-[(6-Fluoro-2-naphthyl)methyl]-*N*-phenylpiperidine-4-carboxamide (15). Compound **15** was prepared from **14** and aniline in a manner similar to that described for compound **20g**, with a yield of 68% as a colorless solid. mp: 209–211 °C (MeCN–EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.84–1.96 (m, 4H), 2.05–2.13 (m, 2H), 2.20–2.31 (m, 1H), 2.94–3.04 (m, 2H), 3.66 (s, 2H), 7.06–7.16 (m, 2H), 7.22–7.34 (m, 5H), 7.43 (dd, J = 9.8, 2.5 Hz, 1H), 7.49–7.54 (m, 3H), 7.73–7.82 (m, 3H); MS (FAB) m/z = 363 $[M+H]^+$. Anal. Calcd for $C_{23}H_{23}FN_2O$: C, 76.22; H, 6.40; N, 7.73; F, 5.24. Found: C, 76.16; H, 6.42; N,7.74; F, 5.36.

5.1.13. 1-[(6-Fluoro-2-naphthyl)methyl]piperidin-4-ol (17). To a solution of 4-hydroxypiperidine (**16**) (346 mg, 8.37 mmol) in $CHCl_3$ (15 mL) were added **8** (1.00 g 4.18 mmol) and Et_3N (0.58 mL, 4.18 mmol), and the mixture was stirred at room temperature for 4 h. This mixture was partitioned between $CHCl_3$ and satd $NaHCO_3$ aq and the organic layer was then washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH = 95/5) to yield **17** (910 mg, 84%) as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.34–1.47 (m, 2H), 1.66–1.76 (m, 2H), 2.00–2.14 (t, J = 10.0 Hz, 2H), 2.65–2.74 (m, 2H), 3.42–3.52 (m,1H), 3.57 (s, 2H),4.52 (d, J = 3.9 Hz, 1H), 7.35–7.44 (m, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.66 (d, J = 9.3 Hz, 1H), 7.81 (s,1H), 7.86 (d, J = 8.3 Hz, 1H), 7.97 (dd, J = 8.8, 5.9 Hz, 1H); MS (FAB) m/z = 260 $[M+H]^+$.

5.1.14. 1-[(6-Fluoro-2-naphthyl)methyl]piperidin-4-yl phenylcarbamate hydrochloride (18). To a solution of **17** (490 mg, 1.89 mmol) in toluene (15 mL) were added phenylisocyanate (225 mg, 1.89 mmol), and the mixture was stirred at reflux for 11 h. The mixture was cooled to rt and concentrated in vacuo. To a solution of the crude product in EtOAc(10 mL) were added 4 M HCl (g)/EtOAc (0.5 mL), and this mixture was then stirred at room temperature for 0.5 h. The precipitate was collected by filtration, washed with EtOAc, and dried

in vacuo to yield **18** (308 mg, 40%) as a colorless solid. mp: 202–204 °C (EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.97–2.12 (m, 2H), 2.13–2.28 (m, 2H), 3.07–3.22 (m, 2H), 3.30–3.45 (m, 2H), 4.40–4.54 (m, 2H), 4.78–4.99 (m, 1H), 6.99 (t, J = 7.3 Hz, 1H), 7.27 (t, J = 7.5 Hz, 2H), 7.40–7.56 (m, 3H), 7.79 (d, J = 9.7 Hz, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.97–8.09 (m, 2H), 8.15–8.23 (m, 1H), 9.70 (bars, 1H), 11.08–11.32 (m, 1H); MS (FAB) m/z = 379 $[M+H]^+$. Anal. Calcd for $C_{23}H_{23}FN_2O_2$·HCl: C, 66.58; H, 5.83; N, 6.75; F, 4.58; Cl, 8.54. Found: C, 66.32; H, 5.74; N, 6.78; F, 4.37; Cl, 8.42.

5.1.15. *N*-{1-[(6-Fluoro-2-naphthyl)methyl]piperidin-4-yl}-*N*′-phenylurea (19). To a solution of **9** (200 mg, 0.60 mmol) in CH_2Cl_2 (6 mL) were added *N*,*N*-diisopropylethylamine (0.43 mL, 2.42 mmol) and phenylisocyanate (77 mg, 0.64 mmol), and the mixture was stirred at room temperature for over night. This mixture was then partitioned between $CHCl_3$ and H_2O, and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH = 100/0–98/2). The crude solid was recrystallized from MeCN–EtOH to yield **19** (155 mg, 68%) as a colorless crystal. mp: 214–216 °C (MeCN–EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40–1.52 (m, 2H), 1.93–2.01 (m, 2H), 2.13–2.24 (m, 2H), 2.78–2.87 (m, 2H), 3.62 (s, 2H), 3.69–3.79 (m, 1H), 4.56 (d, J = 7.8 Hz, 1H), 6.16 (s, 1H), 7.07–7.13 (m, 1H), 7.21–7.34 (m, 5H), 7.43 (dd, J = 9.8, 2.5 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.70 (s, 1H), 7.73 (d, J = 9.8 Hz, 1H), 7.78 (dd, J = 9.1, 5.7 Hz, 1H); MS (FAB) m/z = 378 $[M+H]^+$. Anal. Calcd for $C_{23}H_{24}FN_3O$: C, 73.19; H, 6.41; N, 11.13; F, 5.03. Found: C, 72.99; H, 6.39; N, 11.10; F, 4.77.

5.1.16. 2-Fluoro-*N*-{1-[(6-fluoro-2-naphthyl)methyl]piperidin-4-yl}benzamide (20a). To an ice-cold solution of **9** (200 mg, 0.60 mmol) in pyridine (2 mL) were added 2-fluorobenzoylchloride (130 mg, 0.79 mmol) in THF (2 mL), and the mixture was stirred overnight at room temperature. This mixture was concentrated in vacuo, and the residue was partitioned between $CHCl_3$ and H_2O. The organic layer was then dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH = 100/0–98/2). The crude solid was recrystallized from MeCN–$CHCl_3$ to yield **20a** (170 mg, 74%) as a colorless crystal. mp: 171–173 °C;- ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.56–1.67 (m, 2H), 2.01–2.09 (m, 2H), 2.20–2.30 (m, 2H), 2.84–2.93 (m, 2H), 3.65 (s, 2H), 4.02–4.14 (m, 1H), 6.64 (dd, J = 12.2, 7.8 Hz, 1H), 7.10 (ddd, J = 12.2, 8.3, 1.0 Hz, 1H), 7.22–7.29 (m, 2H), 7.41–7.49 (m, 2H), 7.53 (d, J = 8.8 Hz, 1H), 7.72–7.77 (m, 2H), 7.79 (dd, J = 9.0, 5.7 Hz, 1H), 8.08 (dt, J = 8.3, 1.9 Hz, 1H); MS (FAB) m/z = 381 $[M+H]^+$. Anal. Calcd for $C_{23}H_{22}FN_2O$: C, 72.61; H, 5.83; N, 7.36; F, 9.99; Found: C, 72.86; H, 5.78; N, 7.40; F, 9.80.

5.1.17. 3-Fluoro-*N*-{1-[(6-fluoro-2-naphthyl)methyl]piperidin-4-yl}benzamide (20b). To an ice-cold solution of **9** (200 mg, 0.60 mmol) in CH_2Cl_2 (2 mL) and 1 M $NaHCO_3$ aq (2.2mL) were added 3-fluorobenzoylchloride (104 mg, 0.64 mmol) in CH_2Cl_2 (2 mL), and the mixture was stirred overnight at room temperature. This mixture was partitioned between CH_2Cl_2 and H_2O, and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH = 100/0–98/2). The crude solid was recrystallized from MeCN–$CHCl_3$ to yield **20b** (166 mg, 72%) as a colorless crystal. mp: 183–185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52–1.64 (m, 2H), 1.98–2.07 (m, 2H), 2.18–2.27 (m, 2H), 2.85–2.94 (m, 2H), 3.65 (s, 2H), 3.96–4.08 (m, 1H), 5.97 (d, J = 7.3 Hz, 1H), 7.15–7.23 (m, 1H), 7.22–7.29 (m, 1H), 7.36–7.55 (m, 5H), 7.66–7.77 (m, 2H), 7.79 (dd, J = 8.8, 5.5 Hz, 1H); MS (FAB) m/z = 381 $[M+H]^+$. Anal. Calcd for $C_{23}H_{22}FN_2O$: C, 72.61; H, 5.83; N, 7.36; F, 9.99; Found: C, 72.77; H, 5.86; N, 7.37; F, 9.89.

5.1.18. 4-Fluoro-*N*-{1-[(6-fluoro-2-naphthyl)methyl]piperidin-4-yl}benzamide (20c). To an ice-cold solution of **9** (250 mg, 0.76 mmol) in CH_2Cl_2 (2 mL) and THF (1 mL) were added Et_3N (0.38 mL, 2.72 mmol) and 2-fluorobenzoylchloride (130 mg, 0.79 mmol), and this mixture was stirred overnight at room temperature. The mixture was poured into H_2O, and the precipitate was collected by filtration, washed with H_2O, and dried in vacuo. The crude solid was recrystallized from MeCN–EtOH–$CHCl_3$ to yield **20c** (176 mg, 61%) as a colorless crystal. mp: 203–206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52–1.64 (m, 2H), 1.98–2.07 (m, 2H), 2.18–2.28 (m, 2H), 2.86–2.94 (m, 2H), 3.65 (s, 2H), 3.96–4.08 (m, 1H), 5.91 (d, J = 7.4 Hz, 1H), 7.07–7.13 (m, 2H), 7.22–7.28 (m, 2H), 7.43 (dd, J = 9.8, 2.5 Hz, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.72–7.78 (m, 4H), 7.79 (dd, J = 8.8, 5.4 Hz, 1H); MS (FAB) m/z = 381 $[M+H]^+$. Anal. Calcd for $C_{23}H_{22}FN_2O$: C, 72.61; H, 5.83; N, 7.36; F, 9.99; Found: C, 72.54; H, 5.68; N, 7.34; F, 10.06.

5.1.19. *N*-{1-[(6-Fluoro-2-naphthyl)methyl]piperidin-4-yl}-2-methoxybenzamide (20d). Compound **20d** 1.5fumarate was prepared from **9** and 2-methoxybenzoylchloride in a manner similar to that described for compound **20c**, with a yield of 45% as a pale pink crystal. mp: 210–213 °C (MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.54–1.66 (m, 2H), 1.81–1.89 (m, 2H), 2.28 (t, J = 10.2 Hz, 2H), 2.80–2.88 (m, 2H), 3.73 (s, 2H), 3.80–3.89 (m, 4H), 6.64 (s, 3H), 7.23 (t, J = 7.4 Hz, 1H), 7.14 (d, J = 8.3 Hz, 1H), 7.39–7.48 (m, 2H), 7.56 (d, J = 8.8 Hz, 1H), 7.65–7.72 (m, 2H), 7.86–7.91 (m, 2H), 7.97-8.05 (m, 2H); MS (FAB) m/z = 393 $[M+H]^+$. Anal. Calcd for $C_{24}H_{29}FN_2O_2$·1.5$C_4H_4O_4$: C, 63.60; H, 5.51; N, 4.94; F, 3.35. Found: C, 63.55; H, 5.49; N, 4.92; F, 3.14.

5.1.20. *N*-{1-[(6-Fluoro-2-naphthyl)methyl]piperidin-4-yl}-3-methoxybenzamide (20e). Compound **20d** was prepared from **9** and 3-methoxybenzoylchloride in a manner similar to that described for compound **20c**, with a yield of 62% as a colorless crystal. mp: 186–188 °C (MeCN); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52–1.63 (m, 2H), 1.99–2.08 (m, 2H), 2.18–2.28 (m, 2H), 2.84–2.93 (m, 2H), 3.65 (s, 2H), 3.84 (s, 3H), 3.96–4.08 (m,

1H), 5.97 (d, J = 7.8 Hz, 1H), 7.03 (ddd, J = 8.3, 2.7, 1.0 Hz, 1H), 7.22–7.28 (m, 3H), 7.30–7.35 (m, 2H), 7.43 (dd, J = 9.8, 2.4 Hz, 1H), 7.52 (d, J = 8.3 Hz, 1H), 7.72–7.76 (m, 2H), 7.79 (dd, J = 9.0, 5.7 Hz, 1H); MS (FAB) m/z = 393 $[M+H]^+$. Anal. Calcd for $C_{24}H_{25}FN_2O_2$: C, 73.45; H, 6.42; N, 7.14; F, 4.84; Found: C, 73.67; H, 6.39; N, 7.16; F, 4.61.

5.1.21. *N*-{1-[(6-Fluoro-2-naphthyl)methyl]piperidin-4-yl}-2-methoxybenzamide (20f). Compound **20f** was prepared from **9** and 4-methoxybenzoylchloride in a manner similar to that described for compound **20c**, with a yield of 62% as a colorless crystal. mp: 216–218 °C (EtOH–$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52–1.63 (m, 2H), 1.98–2.07 (m, 2H), 2.18–2.28 (m, 2H), 2.84–2.93 (m, 2H), 3.65 (s, 2H), 3.84 (s, 3H), 3.96–4.07 (m, 1H), 5.89 (d, J = 7.8 Hz, 1H), 6.89–6.94 (m, 2H), 7.24 (dt, J = 8.7, 2.4 Hz, 1H), 7.43 (dd, J = 9.8, 2.4 Hz, 1H), 7.69–7.81 (m, 5H), 7.79 (dd, J = 8.7, 5.7 Hz, 1H); MS (FAB) m/z = 393 $[M+H]^+$. Anal. Calcd for $C_{24}H_{25}FN_2O_2$: C, 73.45; H, 6.42; N, 7.14; F, 4.84; Found: C, 73.45; H, 6.45; N, 7.14; F, 4.86.

5.1.22. *N*-{1-[(6-Fluoro-2-naphthyl)methyl]piperidin-4-yl}-2-phenoxybenzamide (20g). To a solution of **9** (200 mg, 0.60 mmol) in CH_2Cl_2 (3 mL) were added 2-phenoxybenzoic acid (129 mg, 0.60 mmol), HOBt (98 mg, 0.73 mmol), WSC·HCl (140 mg, 0.725 mmol) and Et_3N (0.20 mL), and this mixture was stirred at room temperature for 3 days. The mixture was then partitioned between CH_2Cl_2 and satd $NaHCO_3$ aq and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude solid was recrystallized from EtOAc to yield **20g** (106 mg, 39%) as a colorless solid. mp: 142–144 °C (EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.38–1.52 (m, 2H), 1.61–1.72 (m, 2H), 2.00–2.12 (m, 2H), 2.65–2.75 (m, 2H), 3.54 (s, 2H), 3.64–3.76 (m, 1H), 6.93–7.02 (m, 3H), 7.11 (t, J = 7.6 Hz, 1H), 7.23 (t, J = 7.2 Hz, 1H), 7.33–7.54 (m, 5H), 7.60 (d, J = 6.8 Hz, 1H), 7.67 (d, J = 10.0 Hz, 1H), 7.79 (br, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.98 (dd, J = 8.4, 5.6 Hz, 1H), 8.05 (d, J = 7.2 Hz, 1H); MS (FAB) m/z = 455 $[M+H]^+$. Anal. Calcd for $C_{29}H_{27}FN_2O_2$: C, 76.63; H, 5.99; N, 6.16; F, 4.18. Found: C, 76.26; H, 6.15; N, 6.02; F, 4.00.

5.1.23. *N*-{1-[(6-Fluoro-2-naphthyl)methyl]piperidin-4-yl}-3-phenoxybenzamide (20h). Compound **20h** was prepared from **9** and 3-phenoxybenzoic acid in a manner similar to that described for compound **20g**, with a yield of 55% as a colorless crystal. mp: 165–168 °C (i-Pr_2O–MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51–1.62 (m, 2H), 1.9–2.06 (m, 2H), 2.17–2.28 (m, 2H), 2.84–2.96 (m, 2H), 3.65 (s, 2H), 3.95–4.06 (m, 1H), 5.93 (d, J = 7.8 Hz, 1H), 6.98–7.05 (m, 2H), 7.08–7.18 (m, 2H), 7.22–7.28 (m, 1H), 7.33–7.48 (m, 6H), 7.51 (d, J = 8.3 Hz, 1H), 7.70–7.76 (m, 2H), 7.99 (dd, J = 8.85.8 Hz, 1H); MS (FAB) m/z = 455 $[M+H]^+$. Anal. calcd for $C_{29}H_{27}FN_2O_2$: C, 76.63; H, 5.99; N, 6.16; F, 4.18. Found: C, 76.71; H, 5.93; N, 6.17; F, 4.34.

5.1.24. *N*-{1-[(6-Fluoro-2-naphthyl)methyl]piperidin-4-yl}-4-phenoxybenzamide (20i). Compound **20i** was prepared from **9** and 3-phenoxybenzoic acid in a manner similar to that described for compound **20g**, with a yield of 67% as a colorless crystal. mp: 173–175 °C (MeCN); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52–1.64 (m, 2H), 1.99–2.09 (m, 2H), 2.18–2.27 (m, 2H), 2.85–2.94 (m, 2H), 3.65 (s, 2H), 3.97–4.08 (m, 1H), 5.90 (d, J = 7.3 Hz, 1H), 6.98–7.06 (m, 4H), 7.14–7.19 (m, 1H), 7.22–7.28 (m, 1H), 7.35–7.40 (m, 2H), 7.43 (dd, J = 9.8, 2.4 Hz, 1H), 7.52 (d, J = 8.3 Hz, 1H), 7.70–7.77 (m, 4H), 7.79 (dd, J = 9.1, 5.7 Hz, 1H); MS (FAB) m/z = 455 $[M+H]^+$. Anal. Calcd for $C_{29}H_{27}FN_2O_2$: C, 76.63; H, 5.99; N, 6.16; F, 4.18. Found: C, 76.75; H, 5.94; N, 6.24; F, 3.97.

5.1.25. *N*-{1-[(6-Fluoro-2-naphthyl)methyl]piperidin-4-yl}biphenyl-2-carboxamide (20j). Compound **20j** was prepared from **9** and biphenyl-2-carboxylic acid in a manner similar to that described for compound **20g**, with a yield of 62% as a colorless solid. mp: 205–207 °C (MeCN); ^{1}H NMR (400 MHz, DMSO-d_6 δ: 1.20–1.38 (m, J > 12 Hz, 2H), 1.50–1.64 (m, 2H), 1.90–2.06 (m, J > 12 Hz, 2H), 2.63–2.77 (m, 2H), 3.54 (br, 2H), 7.28–7.45 (m, 9H), 7.46–7.53 (m, 2H), 7.68 (d, J = 9.3 Hz, 1H), 7.7.76–7.90 (m, 2H), 7.94–8.03 (m, 2H); MS (FAB) m/z = 439 $[M+H]^+$. Anal. Calcd for $C_{29}H_{27}FN_2O{\cdot}0.2H_2O$: C, 78.78; H, 6.25; N, 6.34; F, 4.30. Found: C, 78.76; H, 6.27; N, 6.48; F, 4.46.

5.1.26. *N*-{1-[(6-Fluoro-2-naphthyl)methyl]piperidin-4-yl}biphenyl-3-carboxamide (20k). Compound **20k** hydrochloride was prepared from **9** and biphenyl-3-carboxylic acid in a manner similar to that described for compound **20g**, with a yield of 41% as a colorless solid. mp: 246–248 °C (MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.98–2.17 (m, 4H), 3.08–3.21 (m, 2H), 3.21–3.43 (m, 2H), 3.98–4.24 (m, 1H), 4.40–4.54 (m, 2H), 7.38–7.46 (m, 1H), 7.48–7.61 (m, 4H), 7.70–7.95 (m, 6H), 7.99–8.18 (m, 2H), 8.12–8.24 (m, 2H), 8.52–8.76 (m, 1H), 10.88–11.28 (m, 1H); MS (FAB) m/z = 439 $[M+H]^+$. Anal. Calcd for $C_{29}H_{27}FN_2O{\cdot}HCl{\cdot}0.2H_2O$: C, 72.78; H, 5.98; N, 5.85; F, 3.97; Cl, 7.41. Found: C, 72.65; H, 5.83; N, 5.87; F, 4.14; Cl, 7.35.

5.1.27. *N*-{1-[(6-Fluoro-2-naphthyl)methyl]piperidin-4-yl}biphenyl-4-carboxamide (20l). Compound **20l** was prepared from **9** and biphenyl-4-carboxylic acid in a manner similar to that described for compound **20g**, with a yield of 27% as a colorless solid. mp: 214–218 °C (MeCN); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.54–1.66 (m, 2H), 2.02–2.10 (m, 2H), 2.19–2.29 (m, 2H), 2.86–2.94 (m, 2H), 3.66 (s, 2H), 4.00–4.12 (m, 1H), 6.03 (d, J = 7.8 Hz, 1H), 7.23–7.28 (m, 1H), 7.36–7.50 (m, 4H), 7.53 (d, J = 8.7 Hz, 1H), 7.58–7.68 (m, 4H), 7.72–7.85 (m, 5H); MS (FAB) m/z = 439 $[M+H]^+$. Anal. Calcd for $C_{29}H_{27}FN_2O$: C, 79.43; H, 6.21; N, 6.39; F, 4.33. Found: C, 79.65; H, 6.37; N, 6.47; F, 4.45.

5.1.28. *N*-{1-[(6-Fluoro-2-naphthyl)methyl]piperidin-4-yl}-*N*-methylbenzamide (21). To a solution of **1** (300 mg, 0.83 mmol) in DMF (5 mL) were added NaH (60% oil dispersion, 43 mg 1.08 mmol), and the mixture was stirred at room temperature for 1.5 h. The mixture was

added MeI (58 μl 0.91 mmol), which was then stirred at room temperature for 5 h. This mixture was then partitioned between EtOAc and satd $NaHCO_3$ aq and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude solid was recrystallized from MeCN–*i*-Pr_2O to yield **21** (145 mg, 47%) as a colorless crystal. mp: 124–126 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.50–1.93 (m, 5H), 2.00–2.22 (m, 1H), 2.69–3.00 (m, 5H), 3.49–3.70 (m, 3H), 7.30–7.56 (m, 7H), 7.67 (d, J = 10.3 Hz, 1H), 7.73–7.91 (m, 2H), 7.97 (br, 1H); MS (FAB) m/z = 377 $[M+H]^+$. Anal. Calcd for $C_{24}H_{25}FN_2O$: C, 76.57; H, 6.69; N, 7.44; F, 5.05. Found: C, 76.19; H, 6.80; N, 7.31, F, 4.69.

5.1.29. 1-[(6-Fluoro-2-naphthyl)methyl]-piperidin-4-one (23). To a solution of 4-piperidone monohydrate monohydrochloride (4.11 g, 26.2 mmol) in DMF (80 ml) were added **8** (5.05 g, 21.1 mmol) and K_2CO_3 (7.30 g, 52.4 mmol), and the mixture was stirred at room temperature for 1 week. The mixture was concentrated in vacuo. The residue was partitioned between $CHCl_3$ and H_2O, and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (Hexane–EtOAc = 2/1–1/2) to give **23** (4.22 g, 78%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.47 (dd, J = 6.3, 5.9 Hz, 4H), 2.79 (dd, J = 6.3, 5.9 Hz, 4H), 3.76 (s,2H), 7.23–7.39 (m, 1H), 7.44 (dd, J = 10.0, 2.7 Hz, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.74–7.83 (m, 3H); MS (GC) m/z = 257 $(M)^+$.

5.1.30. 1-[(6-Fluoro-2-naphthyl)methyl]-4-methylpiperidin-4-amine (24). To a cooled (−78 °C) solution of **23** (1.54 g, 6.00 mmol) in Et_2O (80 ml) were added 1.14 M solution of MeLi (14.8 ml, 16.8 mmol,) in Et_2O, and the mixture was stirred at −78 °C for 2 h. The mixture was partitioned between EtOAc and H_2O, and the organic layer was washed with brine, dried over Mg_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH = 100/0–98/2) to give 1-[(6-fluoro-2-naphthyl) methyl]-4-methylpiperidin-4-ol (1.48 g, 90%) as pale yellow solid. To a solution of residual compound obtained above (684 mg, 2.50 mmol) in MeCN (308 mg, 7.5 mmol) were added CH_2SO_4 (1.12 mL, 20.0 mmol), and the mixture was stirred at room temperature for overnight. The mixture was poured onto ice and neutralized with satd $NaHCO_3$ aq and extracted with EtOAc. The organic layer was washed with brine, dried over Mg_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH = 100/0–98/2) to give *N*-{1-[(6-fluoro-2-naphthyl)methyl]-4-methylpiperidin-4-yl}acetamide (734 mg, 93%) as pale brown solid. A solution of residual compound obtained above (350 mg, 1.11 mmol) in 3 M HCl (4.5 ml) were stirred at 100 °C for overnight. The mixture was cooled on ice-bath and neutralized with 3 M NaOH, and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give **25** (315 mg, quant.) as brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.12 (s, 3H), 1.40–1.52 (m, 4H), 1.58–1.67 (m, 2H), 2.40–2.55 (m, 4H), 3.65 (s, 2H), 7.23 (dd, J = 8.8, 2.8 Hz, 1H), 7.43 (dd, J = 9.8, 2.5 Hz, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.72–7.75 (m, 3H), 7.78 (dd, J = 9.0, 5.6 Hz, 1H); MS (FAB) m/z = 273 $[M+H]^+$.

5.1.31. *N*-{1-[(6-Fluoro-2-naphthyl)methyl]-4-methylpiperidin-4-yl}biphenyl-2-carboxamide hemifumarate (25). Compound **25** was prepared from **24** and biphenyl-2-carboxylic acid in a manner similar to that described for compound **20g** with a yield of 31% as a colorless crystal. mp: 168–171 °C (MeOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.21 (s, 3H), 1.38–1.45 (m, J > 12 Hz, 2H), 2.05–2.16 (m, J > 12 Hz, 4H), 2.43–2.49 (m, 2H), 3.60 (s, 2H), 6.60 (s, 1H), 7.30–7.48 (m, 10H), 7.51–7.54 (m, 2H), 7.68 (dd, J = 10.3, 2.6 Hz, 1H), 7.83–7.88 (m, 2H), 8.00 (dd, J = 9.2, 5.8 Hz, 1H); MS (FAB) m/z = 453 $[M+H]^+$. Anal. Calcd for $C_{30}H_{29}FN_2O\cdot 0.5C_4H_4O_4\cdot 0.75H_2O$: C, 73.33; H, 6.25; N, 5.34; F, 3.62. Found: C, 73.23; H, 6.35; N, 5.30; F, 3.66.

5.1.32. *endo-N*-8-Azabicyclo[3.2.1]oct-3-ylbiphenyl-2-carboxamide hydrochloride (28). To a solution of *endo*-8-benzyl-8-azabicyclo[3.2.1]octan-3-amine (**26**)[7] (573 mg, 2.65 mmol) in DMF (10 mL) were added biphenyl-2-carboxylic acid (525 mg, 2.65 mmol), HOBt (430 mg, 3.18 mmol) and WSC·HCl (613 mg, 3.18 mmol), and the mixture was stirred at room temperature for 40 h. This mixture was partitioned between EtOAc and satd $NaHCO_3$ aq and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH = 97.5/2.5) to yield *endo-N*-(8-benzyl-8-azabicyclo[3.2.1]oct-3-yl)biphenyl-2-carboxamide (850 mg, 81%) as a colorless oil. To a solution of the compound obtained above in EtOH (15 mL) and MeOH (5mL) were added 4 M HCl (g)/EtOAc (1 mL), and $Pd(OH)_2$ (10 wt%, 300 mg), and the mixture was stirred in a hydrogen atmosphere at room temperature for 23 h. The catalyst was removed by filtration on celite and the filtrate was concentrated in vacuo to yield **28** (570 mg, quant.) as a colorless amorphous solid.; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.55–1.69 (m, 4H), 1.75–1.83 (m, 2H), 2.16 (ddd, J = 15.6, 6.4, 3.5 Hz, 2H), 3.33 (br, 2H), 3.39–3.48 (m, 1H), 7.33–7.46 (m, 8H), 7.52 (dt,J = 7.5, 1.6 Hz, 1H), 8.16 (d, J = 3.6 Hz, 1H), 8.64–9.20 (m, 1H); MS (FAB) m/z = 307 $[M+H]^+$.

5.1.33. *endo-N*-8-Azabicyclo[3.2.1]oct-3-ylbiphenyl-2-carboxamide hydrochloride (29). Compound **29** was prepared from **27**[7] in a manner similar to that described for compound **28**, with a quantitative yield over two steps as a colorless amorphous solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.55–1.65 (m, 2H), 1.68–1.78 (m, 2H),1.79–1.83 (m, 2H), 1.92–2.03 (m, 2H), 3.85–3.95 (m, 2H), 3.96–4.08 (m, 1H), 7.31–7.50 (m, 8H), 7.48–7.53 (m, 1H), 8.30 (d, J = 7.3 Hz, 1H), 8.74–8.95 (m, 1H), 9.14–9.38 (m, 1H); MS (FAB) m/z = 307 $[M+H]^+$.

5.1.34. *endo-N*-{8-[(6-Fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl}biphenyl-2-carboxamide (30). Compound **30** was prepared from **28** and **8** in a manner similar to that described for compound **6f**, with a yield of 21% as a colorless crystal. mp: 90–92 °C (MeOH);

^{1}H NMR (400 MHz,DMSO-d_6) δ: 1.47–1.54 (m, 4H), 1.72–1.83 (m, 2H), 1.92–2.02 (m, 2H), 2.93–2.99 (m, 2H), 3.55 (s, 2H), 3.82–3.91 (m, $J < 6.0$ Hz, 1H), 7.30–7.45 (m, 8H), 7.49 (dt, $J = 7.3$, 2.0 Hz, 1H), 7.56 (d, $J = 8.8$ Hz, 1H), 7.66 (dd, $J = 10.3$, 2.5 Hz, 1H), 7.78 (d, $J = 5.4$ Hz, 1H), 7.82–7.86 (m, 2H), 7.96 (dd, $J = 5.8$, 8.8 Hz, 1H); MS (FAB) $m/z = 465$ $[M+H]^+$. Anal. Calcd for $C_{31}H_{29}FN_2O{\cdot}0.7H_2O$: C, 78.03; H, 6.42; N, 5.87; F, 3.98. Found: C, 77.90; H, 6.62; N, 5.71; F, 3.83.

5.1.35. *exo*-*N*-{8-[(6-Fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl}biphenyl-2-carboxamide oxalate (31). Compound **31** was prepared from **29** and **8** in a manner similar to that described for compound **6f**, with a yield of 53% as a colorless crystal. mp: 159–161 °C (MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.64–1.76 (m, 4H), 1.84–1.97 (m, 2H), 2.20–2.24 (m, 2H), 3.60–3.73 (m, 2H), 4.02–4.24 (m, 3H), 7.28–7.45 (m, 8H), 7.46–7.53 (m, 2H), 7.68 (d, $J = 8.8$ Hz, 1H), 7.76 (dd, $J = 10.3$, 2.5 Hz, 1H), 7.97 (d, $J = 8.3$ Hz, 1H), 8.02 (dd, $J = 9.3$, 5.8 Hz, 1H), 8.08 (s, 1H), 8.13 (d, $J = 7.9$ Hz, 1H); MS (FAB) $m/z = 465$ $[M+H]^+$. Anal. Calcd for $C_{31}H_{29}FN_2O{\cdot}C_2H_2O_4{\cdot}H_2O$: C, 69.22; H, 5.81; N, 4.89; F, 3.32. Found: C, 69.41; H, 5.94; N, 4.82; F, 3.28.

5.2. Biology

5.2.1. Measurement of intracellular Ca^{2+} concentrations. CCR3-transfected B300-19 cells[11] were loaded with 5 μM Fura-2 acetoxymethyl ester in RPMI 1640 media containing 1% fetal bovine serum for 30 min at 37 °C. After two washes, the cells were resuspended at a density of 2×10^6 cells/mL in 20 mM HEPES buffer containing 0.1% BSA, 130 mM NaCl, 5.4 mM KCl, 1 mM, $MgCl_2$ 2.5 mM, $CaCl_2$, and 5.5 mM glucose. The cell suspension (490 μl) was transferred into cuvettes and placed under constant agitation. Changes in fluorescence were monitored at 25 °C using a spectrophotometer at excitation wavelength of 340 nm and 380 nm and an emission wavelengths of 510 nm. Calculation of Ca^{2+} concentration was performed using the K_d for the Ca^{2+} binding of 224 nm. The antagonist was dissolved in 100% DMSO solution (1 μl) and added to the cuvette 1 min prior to the addition of eotaxin (final concentration of 50 ng/mL). Linear regression analysis using EXSAS-STAT was used to calculate the IC_{50} values. Values are reported as means ± SEM of triplicate experiments.

5.3. X-ray crystallographic data for 31[12]

$C_{31}H_{29}FN_2O{\cdot}C_2H_2O_4{\cdot}C_3H_8O$, $M_w = 614.69$, monoclinic, space group: $P2_1/c$, $a = 16.060(4)$ Å, $b = 13.621(3)$ Å, $c = 14.652(3)$ Å, $\beta = 95.65(2)°$, $V = 3189(1)$ Å^3, $D_x = 1.28$ g/cm^3, and $Z = 4$. A single crystal was used for X-ray diffraction data collection on a Rigaku AFC-7R diffractometer employing graphitemonochromated MoKα radiation. A total of 15582 independent reflection intensities up to $2\theta = 70.0°$ were collected in the ω-2θ scan mode and were corrected for the Lorenz and polarization factors. The structure was solved using the direct method and the SIR92 program.[13] The non-hydrogen atoms were refined using a full-matrix least-squares method with anisotropic thermal parameters and the SIR92 programs. Hydrogen atoms were calculated assuming idealized geometries but were not refined. The discrepancy indices R and wR were 0.115 and 0.183 for 5515 [$I > 0.00\sigma(I)$] reflections. All calculations were performed using the teXan crystallographic software package from Molecular Structure Corporation.[14] Lists of the atomic coordinates, anisotropic thermal parameters, and bond lengths and angles are stored at the Cambridge Crystal Crystallographic Data Centre, UK, CCDC-630758.

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