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Design and synthesis of 6-fluoro-2-naphthyl derivatives as novel CCR3 antagonists with reduced CYP2D6 inhibition

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ABSTRACT

In our previous study on discovering novel types of CCR3 antagonists, we found a fluoronaphthalene derivative (**1**) that exhibited potent CCR3 inhibitory activity with an IC_{50} value of 20 nM. However, compound **1** also inhibited human cytochrome P450 2D6 (CYP2D6) with an IC_{50} value of 400 nM. In order to reduce its CYP2D6 inhibitory activity, we performed further systematic structural modifications on **1**. In particular, we focused on reducing the number of lipophilic moieties in the biphenyl part of **1**, using $Clog D_{7.4}$ values as the reference index of lipophilicity. This research led to the identification of *N*-{(3-*exo*)-8-[(6-fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl}-3-(piperidin-1-ylcarbonyl)isonicotinamide 1-oxide (**30**) which showed comparable CCR3 inhibitory activity (IC_{50} = 23 nM) with much reduced CYP2D6 inhibitory activity (IC_{50} = 29,000 nM) compared with **1**.

1. Introduction

Infiltration of eosinophils into the airways and the mucosal tissues is one of the pathological features of various inflammatory diseases, such as allergic asthma, allergic rhinitis, and atopic dermatitis. In particular, asthma is a chronic inflammatory disease accompanied by airway obstruction and hyper-responsiveness caused by cytotoxic proteins, chemical mediators, and inflammatory mediators released from activated eosinophils.[1a,1b] Therefore, eosinophils are thought to play a critical role in the induction and progression of these allergic diseases.

Chemokines are a family of small (8–12 kDa), heparin-binding, basic proteins that induce the migration and activation of leukocytes, such as monocytes, lymphocytes, eosinophils, and basophils. They are classified into four sub-families, CC chemokines, CXC chemokines, C chemokines, and CX_3C chemokines, based on the positions of the first two of their conserved N-terminal cysteine residues. CCR3, which is one of the CC chemokine receptor, is prominently expressed on eosinophils, and is responsible for eosinophil chemotaxis.[2a–e] The specific antibody against eotaxin-1, a selective CCR3 ligand, reduces the lung eosinophilia and airway hyper-responsiveness in mice that occurs in response to ovalbumin.[3]

Thus, novel type CCR3 antagonists may have potential as therapeutic agents for eosinophil-related allergic diseases, such as allergic asthma, allergic rhinitis, and atopic dermatitis.

In our previous research aimed at discovery of a novel type of CCR3 antagonist, a 6-fluoro-2-naphthyl derivative, compound **1**, was found to have potent CCR3 inhibitory activity with an IC_{50} value of 20 nM. However, further biological studies revealed that **1** also had potent inhibitory activity against human cytochrome P450 2D6 (CYP2D6), which is a polymorphic member of the P450 superfamily (IC_{50}: 400 nM), but weak inhibitory activity against other CYP enzymes, such as CYP1A2, 2C9, 2C19, and 3A4 (IC_{50} > 20,000 nM) (Fig. 1). Since CYP2D6 is important to the metabolism of about 20% of clinically used drugs, its inhibition can cause unfavorable drug–drug metabolizing interaction.[4] Therefore, a program to further reduce the CYP2D6 inhibitory activity of **1** was designed as described below.

Recently, we reported that both the 6-fluoro-2-naphthyl moiety and the nortropane ring of **1** were essential for potent inhibitory activity against CCR3.[5] Therefore, we attempted to modify the biphenyl moiety of compound **1** by dividing into Part A and Part B (Fig. 1). This study focused on compound lipophilicity since some groups have already reported that it is an important contributor to CYP inhibition.[6a–c] Reduction of the molecular lipophilicity was speculated to be an effective way to reduce inhibitory activity against CYP2D6, despite the fact that it is preferable to have bulky and/or lipophilic moieties on Part A of **1**.[5] Therefore, in order to

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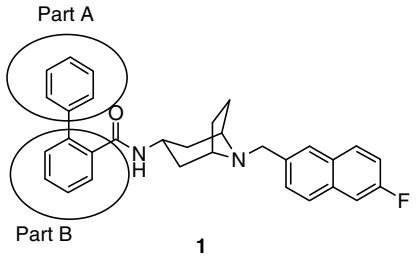


1

inhibitory activity
CCR3:IC_{50} = 20 nM
CYP2D6: IC_{50} = 400 nM
CYP1A2: IC_{50} > 20,000 nM
CYP2C9: IC_{50} > 20,000 nM
CYP2C19: IC_{50} > 20,000 nM
CYP3A4: IC_{50} > 20,000 nM

Figure 1. The structure of compound **1**.

obtain less lipophilic compounds with potent CCR3 inhibitory activity, attempts were made to replace the phenyl ring with other heteroaromatic rings or non-aromatic heterocyclic rings and optimize their linkages. The *n*-octanol/water distribution coefficient of designed compounds calculated at pH 7.4 ($C\log D_{7.4}$) was used as an index of lipophilicity. The $C\log D_{7.4}$ values were calculated using ACD/log*D* software, and the lead compound **1** was determined to have a $C\log D_{7.4}$ value of 3.79.[7] Thus, the attenuation of CYP2D6 inhibitory activity was assumed to be achieved by designing and synthesizing derivatives with $C\log D_{7.4}$ values lower than those of **1**.

In this paper, we describe the successful development of a novel type of CCR3 antagonist with reduced CYP2D6 inhibitory activity.

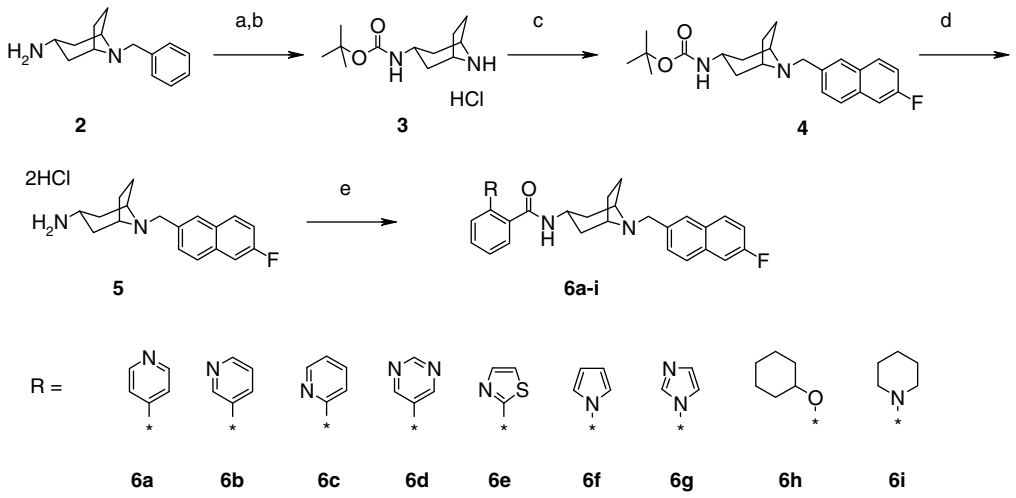
2. Chemistry

The synthetic routes of compounds **6a–i** are shown in Scheme 1. The protection of amine **2**[8] with the Boc group and subsequent deprotection of the benzyl group yielded the amine **3**. Alkylation of **3** with 2-(bromomethyl)-6-fluoronaphthalene,[9] followed by removal of the Boc group by creating an acidic condition yielded the key intermediate, amine **5**. Condensation of **5** with a commercially available (in the cases of **6f** and **6g**) or synthesized (**9a–c**, **12a**, **12b**, **15**, and **17**) carboxylic acids afforded compounds **6a–i**.

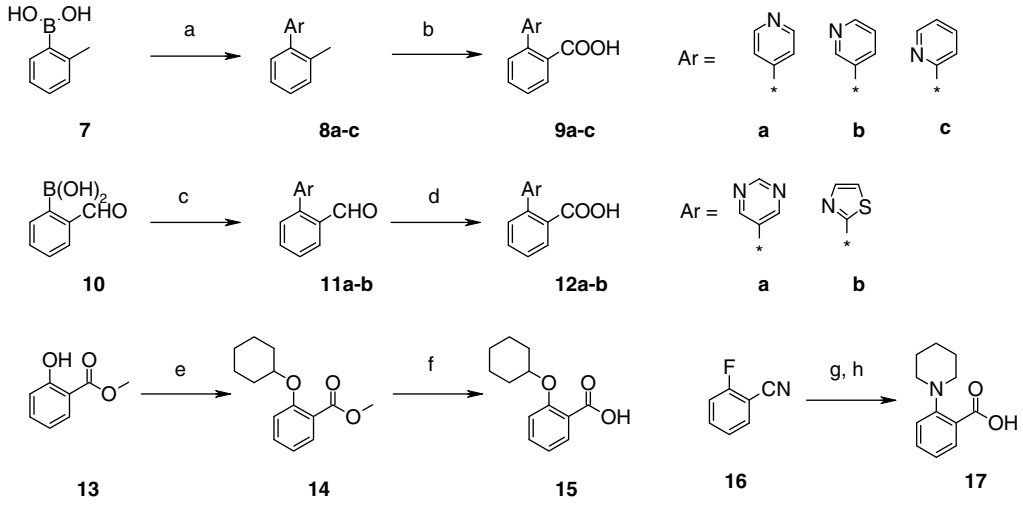
Scheme 2 summarizes the synthesis of the carboxylic acids **9a–c**, **12a**, **12b**, **15**, and **17**. Compounds **9a–c** were obtained by Suzuki coupling of 2-methylphenyl boronic acid (**7**) and appropriate bromopyridines, followed by oxidation of the methyl moiety using $KMnO_4$.[10] The carboxylic acids **12a–b** were prepared from 2-formylphenylboronic acid (**10**) and appropriate arylbromides by Suzuki coupling, followed by oxidation of the formyl group. The Mitsunobu reaction was performed using methyl salicylate (**13**) and cyclohexanol to yield the ester **14**,[11] and subsequent hydrolysis of the ester group afforded the carboxylic acid **15**. The carboxylic acid **17** was obtained from 2-fluorobenzonitrile (**16**) via a substitution reaction with a piperidine, followed by hydrolysis of the nitrile group.

Compounds **20a–g** were synthesized by condensation of the amine **5** with appropriate carboxylic acids (**19a–g**) which were prepared from phthalic anhydride (**18**) and the corresponding amines (Scheme 3).

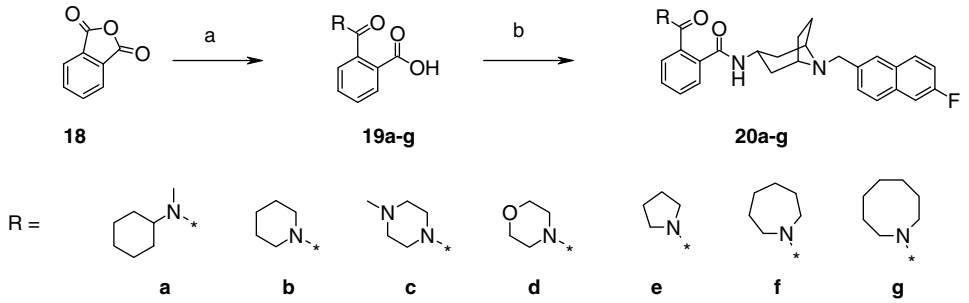
Scheme 4 shows the syntheses of several carboxylic acids (**23**, **26**, **29**, **27**, and **35**) required for generation of the corresponding compounds (**24**, **28**, **30**, **32**, and **36**). The carboxylic acid **23**, which corresponded to compound **24**, was synthesized according to the method reported by Zhenrong Guo et al., as described below.[12] Dimethyl pyridine-2,3-dicarboxylate (**21**) was regioselectively converted to the amide (**22**) by treatment with piperidine in the presence of $MgCl_2$. The amide (**22**) was then hydrolyzed to yield compound **23**. The carboxylic acid **26** was prepared from pyridine-3,4-dicarboxylic acid (**25**) in three steps. Compound **25** was treated with acetic anhydride to yield pyridine-3,4-dicarboxylic anhydride, and then a ring-opening reaction by piperidine afforded the 1:1 mixture of carboxylic acids **26** and **27**. Compound **27** could be easily removed by recrystallization from EtOH–EtOAc to yield the pure carboxylic acid **26**. The carboxylic acid **29** was synthesized by oxidation of the 1:1 mixture of above-obtained carboxylic acids **26** and **27**, followed by purification via silica gel column chromatography. Pure Compound **27** was obtained by the regioselective ring-opening reaction of pyridine-3,4-dicarboxylic anhydride with MeOH,[13] followed by direct conversion of the ester group to the amide group by piperidine under neat conditions. The condensation of **33**[14] with piperidine using WSC as the coupling reagent yielded the amide **34**, and subsequent hydrolysis of **34** yielded the carboxylic acid **35**. Condensation of the carboxylic acids **23**, **26**, **29**, **27**, and **35** with the amine **5** yielded compound **24**, **28**, **30**, **32**, and **36**, respectively.



Scheme 1. Synthesis of compounds **6a–i**. Reagents and conditions: (a) Boc_2O, THF, rt, 11 h; (b) H_2, 10 wt% $Pd(OH)_2/C$, 4 M HCl/EtOAc, EtOH–MeOH, rt, 3 h, 96% for two steps; (c) 2-(bromomethyl)-6-fluoronaphthalene,[9] K_2CO_3, DMF, rt, 21 h, quant.; (e) ArCOOH, WSC, HOBt, Et_3N, CH_2Cl_2, rt.



Scheme 2. Synthesis of compounds **9a–c**, **12a–b**, **15**, and **17**. Reagents and conditions: (a) bromopyridine, $Pd(PPh_3)_4$, CsF, DME, reflux; (b) $KMnO_4$, H_2O, reflux; (c) ArBr, $Pd(PPh_3)_4$, Na_2CO_3, DME–H_2O, reflux; (d) $NaClO_2$, 31% H_2O_2 aq, NaH_2PO_4, H_2O–MeCN; (e) cyclohexanol, PPh_3, DEAD, THF, rt, 4 d, 57%; (f) 1 M NaOH, MeOH, rt, 3.5 d, quant.; (g) piperidine, K_2CO_3, DMF, 70 °C, over night; (h) KOH, 2-ethoxyethanol–H_2O, reflux, 4 h, 58% for two steps.



Scheme 3. Synthesis of compounds **20a–g**. Reagents and conditions: (a) amine, THF, rt; (b) **5**, WSC, HOBt, Et_3N, CH_2Cl_2, rt.

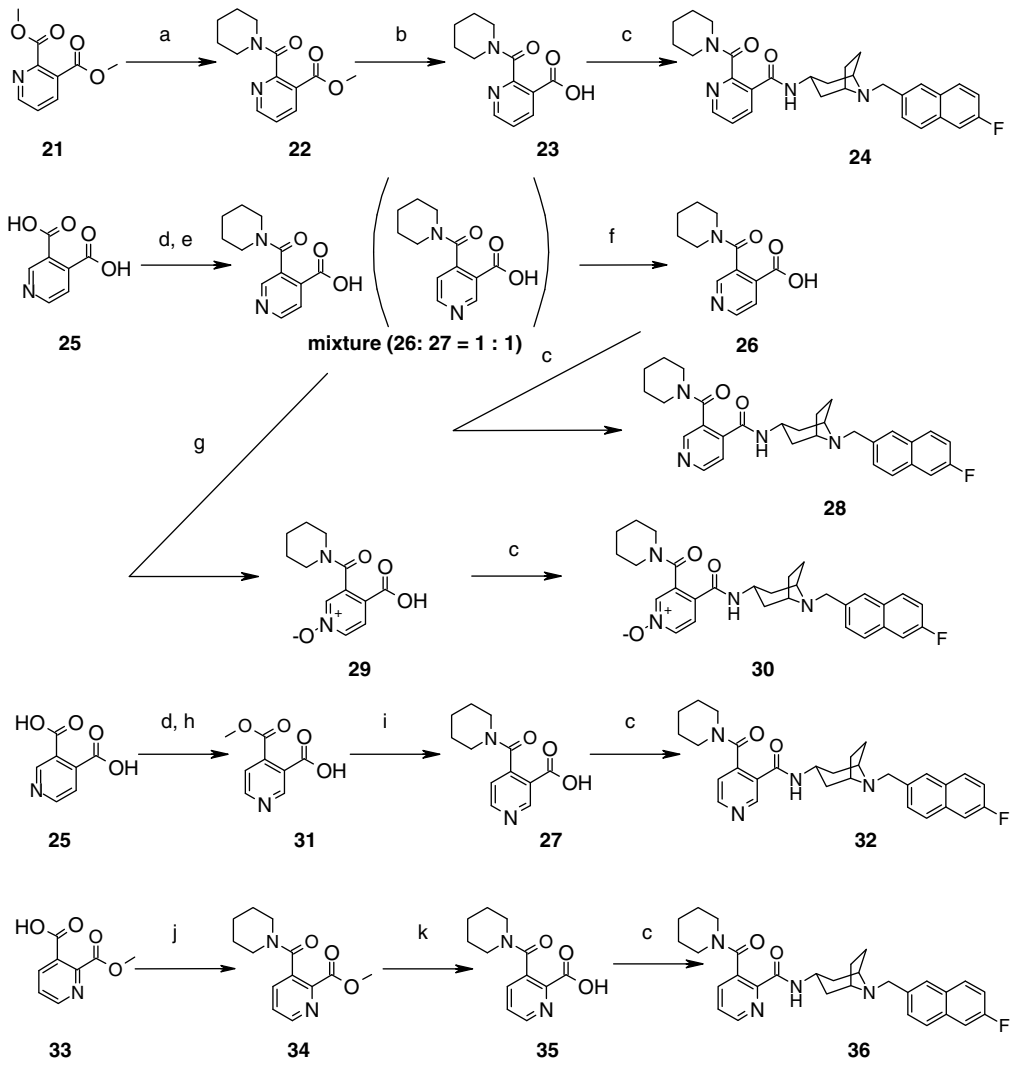
3. Results and discussion

The synthesized compounds were evaluated for their CCR3 inhibitory activity (IC_{50}) on eotaxin-induced Ca^{2+} influx using CCR3-expressing preB cells. The lead compound (**1**) displayed potent CCR3 inhibitory activity with an IC_{50} value of 20 nM. The CYP2D6 inhibitory activity (IC_{50}) of the selected compounds was also evaluated according to the reported procedure.[15] The lead compound (**1**) displayed potent CYP2D6 inhibitory activity with an IC_{50} value of 400 nM. The $C\log D_{7.4}$ values were calculated using the ACD/logD software, and that for the lead compound (**1**) was determined to be 3.79.[7]

First, the effects of replacing the Part A of **1** with other aromatic rings were explored (Table 1). While the CCR3 inhibitory activities of both the 4-pyridyl derivative (**6a**) and the 2-pyridyl derivative (**6c**) were about 30-fold less and threefold less, respectively, than that of **1**, the activity of the 3-pyridyl derivative (**6b**) was similar to that of **1** (IC_{50} = 29 nM). However, the pyrimidyl derivative (**6d**) exhibited about fivefold less activity than that of **1**. It seemed that only one nitrogen atom may be tolerated at the 3-positon of Part A of **1** since other substituted patterns were not. As we expected, compounds **6b**, **6c**, and **6d** showed reduced inhibitory activity against CYP2D6 (IC_{50} = 1600, 4000, and 2900 nM, respectively) probably due to the fall in their $C\log D_{7.4}$ values. The CCR3 inhibitory activity of all 5-membered aromatic ring derivatives (**6e**, **6f**, and **6g**) was lower than that of **1**. It seemed that, in terms of CCR3 inhibitory activity, Part A of **1** may prefer a larger molecule than 5-membered aromatic ring system. Similar to the above, compound **6e** also showed reduced CYP2D6 inhibitory activity, as indicated by the reduction in $C\log D_{7.4}$ values.

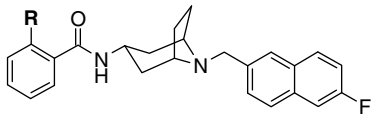
Next, the effect induced by replacing Part A of **1** with other hetero non-aromatic rings connected by hetero-atoms-containing linkages was investigated (Tables 2 and 3). When Part A was replaced with a cyclohexyl ether moiety (**6h**), a decrease in CCR3 inhibitory activity of about sixfold occurred, and the activity of the cyclohexyl amide derivative (**20a**) was moderate (IC_{50} = 44 nM). The same tendency was observed in the pair of the piperidine derivative (**6i**) and the piperidinocarbonyl derivative (**20b**). These results indicated that the carbonyl group of Part A could play a significant role in the interaction with the CCR3 receptor. Thus, some potent inhibitors with hetero non-aromatic rings at Part A of **1** were found by introducing a carbonyl group there. With respect to CYP2D6 inhibition, **6h**, which had a similar $C\log D_{7.4}$ value to that of **1**, showed comparable activity to **1**. And, **20a** and **20b**, which both had lower $C\log D_{7.4}$ values than **1**, showed weaker activity (IC_{50} = 2900 and 6500 nM, respectively).

These results therefore prompted us to investigate the effects of replacing the piperidine ring in **20b** with other cyclic amines. The piperazine and morpholine derivatives (**20c** and **20d**), which had lower $C\log D_{7.4}$ values than that of **20b**, showed significantly less potent CCR3 inhibitory activity, although their CYP2D6 inhibitory activity was similar to that of **20b**. These results suggest that the presence of hetero-atoms in this position would not be suitable for CCR3 inhibitory activity, but they would be effective for the attenuation of CYP2D6 inhibition. Among compounds **20e**, **20f**, and **20g**, in which the piperidine ring in **20b** was converted to 5-,



Scheme 4. Synthesis of compounds **24**, **28**, **30**, **32**, and **36**. Reagents and conditions: (a) piperidine, $MgCl_2$, THF, rt, 1 d, 37%; (b) 1 M NaOH, EtOH, rt, over night, quant.; (c) **5**, WSC, HOBt, Et_3N; (d) Ac_2O, reflux; (e) piperidine, THF, rt, 17 h; (f) recrystallization from EtOAc–EtOH, 23% from **25**; (g) *m*CPBA, CH_2Cl_2, rt, 21 h, 34% from 1:1 mixture of **26** and **27**; (h) MeOH, reflux, 4.5 h, 45%; (i) piperidine, neat, 70 °C, 1 d, 58%; (j) piperidine, WSC·HCl, HOBt, CH_2Cl_2, rt, 3 h, 74%; (k) 1 M NaOH, MeOH, rt, 1 d, quant.

Table 1
CCR3 and CYP2D6 inhibitory activities of 6-fluoronaphthalene derivatives (**6a**–**6g**)



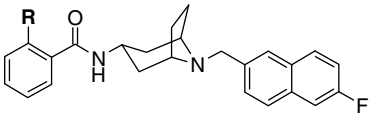
Compound	R	CCR3, IC_{50}[a] (nM)	CYP2D6, IC_{50}[b] (nM)	$Clog D_{7.4}$[c]
1	Phenyl	20 ± 3.9	400 ± 0	3.59
6a	Pyridin-4-yl	613 ± 100	NT[d]	2.23
6b	Pyridin-3-yl	29 ± 7.8	1600 ± 130	2.30
6c	Pyridin-2-yl	57 ± 16	4000 ± 150	2.27
6d	Pyrimidin-5-yl	93 ± 22	2900[e]	1.27
6e	1,3-Thiazol-2-yl	89 ± 27	2400[e]	2.64
6f	1H-pyrrol-1-yl	221 ± 49	NT[d]	3.07
6g	1H-imidazol-1-yl	217 ± 73	NT[d]	1.91

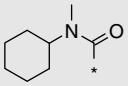
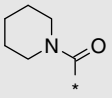
[a] The IC_{50} values are shown as means ± SEM for at least three determinations.
[b] The IC_{50} values are shown as means ± SEM for at least four determinations.
[c] See Ref. 7.
[d] Not tested.
[e] Mean of two experiments.

7-, and 8-membered rings, respectively, compound **20f** had the most potent CCR3 inhibitory activity (IC_{50} = 12 nM). These results indicated that the molecular size of the 6 or 7 member ring systems in Part A would be favorable for potent inhibitory activity against the CCR3 receptor. The larger $Clog D_{7.4}$ values the compounds **20e**, **20b**, **20f**, and **20g** had, the stronger the CYP2D6 inhibitory activity was observed.

Correlation analyses were performed based on the results obtained above and using the IC_{50} values of CYP2D6 inhibitory activity and the $Clog D_{7.4}$ values of the synthesized compounds. The pIC_{50} ($-\log IC_{50}$) values were plotted against the $Clog D_{7.4}$ values in a scatter diagram. As shown in Figure 2, the coefficient of determination obtained from this diagram showed that the value of R^2 was 0.8241, which would explain the positive correlation between the pIC_{50} values of CYP2D6 inhibitory activity and the $Clog D_{7.4}$ values. Since the results of this analysis supported our hypothesis, we assumed that the further attenuation of CYP2D6 inhibitory activity could be accomplished by further lowering the $Clog D_{7.4}$ values. To accomplish this, we planned to replace the phenyl ring of **20b**, the position of which corresponded to the Part B of **1**, with pyridine rings.

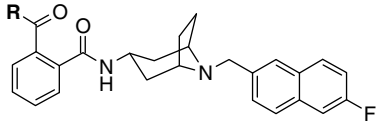
Table 2
CCR3 and CYP2D6 inhibitory activities of 6-fluoronaphthalene derivatives (**6h**, **6i**, **20a**, and **20b**)



Compound	R	CCR3, IC_{50}[a] (nM)	CYP2D6, IC_{50}[b] (nM)	$C\log D_{7.4}$[c]
1		20 ± 3.9	400 ± 0	3.59
6h		118 ± 38	580[e]	3.98
20a		44 ± 0.6	2900 ± 120	1.89
6i		279 ± 64	NT[d]	2.7
20b		23 ± 5.0	6500[e]	0.84

[a] The IC_{50} values are shown as means ± SEM for at least three determinations.
[b] The IC_{50} values are shown as means ± SEM for at least four determinations.
[c] See Ref. 7.
[d] Not tested.
[e] Mean of two experiments.

Table 3
CCR3 and CYP2D6 inhibitory activities of 6-fluoronaphthalene derivatives (**20c**–**20g**)



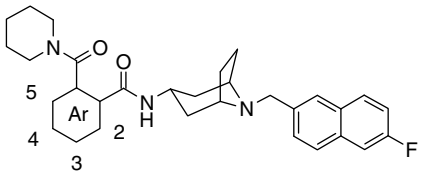
Compound	R	CCR3, IC_{50}[a] (nM)	CYP2D6, IC_{50}[b](nM)	$C\log D_{7.4}$[c]
20b	Piperidin-1-yl	23 ± 5.0	6500[d]	0.84
20c	4-Methylpiperazin-1-yl	482 ± 201	7100[d]	−0.35
20d	Morpholin-4-yl	679 ± 129	8200 ± 570	−0.7
20e	Pyrrolidin-1-yl	225 ± 82	7300[d]	0.29
20f	Azepan-1-yl	12 ± 5.0	3000 ± 200	1.41
20g	Azocan-1-yl	62 ± 7.9	2700[d]	1.97

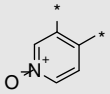
[a] The IC_{50} values are shown as means ± SEM for at least three determinations.
[b] The IC_{50} values are shown as means ± SEM for at least four determinations.
[c] See Ref. 7.
[d] Mean of two experiments.

The results are shown in Table 4. As for CCR3 inhibitory activity, the potency of 4-pyridyl derivative **28** was twofold compared to that of **1** (IC_{50} = 13 nM), whereas other substituted patterns (**24**, **32**, and **36**) led to four- to sixfold decreases in activity. This observation suggests that, for CCR3 inhibition, the nitrogen atom is tolerated only at the 4-position of Part B.

Unfortunately, the CYP2D6 inhibition of compound **28**, which was the most potent inhibitor in this study, showed an activity equal to that of **20b**. In contrast, activity of **24**, **32**, and **36** was

Table 4
CCR3 and CYP2D6 inhibitory activities of 6-fluoronaphthalene derivatives (**24**, **28**, **30**, **32**, and **36**)



Compound	Ar	CCR3, IC_{50}[a] (nM)	CYP2D6, IC_{50}[b] (nM)	$C\log D_{7.4}$[c]
20b		23 ± 5.0	6500[d]	0.84
24		98 ± 8.1	18,300 ± 1630	0.72
28		13 ± 3.4	6800 ± 510	0.17
32		85 ± 12	26,700[d]	0.34
36		131 ± 6.0	23,500[d]	0.13
30		23 ± 4.7	29,000[d]	−2.36

[a] The IC_{50} values are shown as means ± SEM for at least three determinations.
[b] The IC_{50} values are shown as means ± SEM for at least four determinations.
[c] See Ref. 7.
[d] Mean of two experiments.

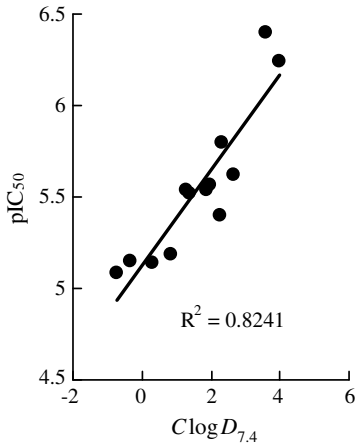


Figure 2. Scatter plot of pIC_{50} of CYP2D6 against $C\log D_{7.4}$ values.

significantly improved because their $C\log D_{7.4}$ values were lower than that of **20b**.

In order to reduce the CYP2D6 inhibitory activity of **28**, we designed and synthesized the pyridine *N*-oxide derivative **30**, which had much lower $C\log D_{7.4}$ value (−2.36) than **28**. Predictably, compound **30**'s inhibitory activity against CCR3 was equal to that of **1**, with reduced activity against CYP2D6 (IC_{50} = 29,000 nM). This

value was the least potent among this series. Thus, compound **30** was identified as having satisfactory selectivity for CCR3 inhibition over CYP2D6 inhibition. In addition, compound **30** showed no inhibitory effects against other CC chemokines (CCR1, CCR2, and CCR5) at the concentration of 10 μM, and had weak inhibitory activity against other CYP enzymes (CYP1A2, 2C9, 2C19, and 3A4) with IC_{50} values of more than 40,000 nM.

Further biological, pharmacokinetic and pharmacotoxic evaluations are now being carried out for **30**.

4. Conclusions

Over the course of our discovery research for a novel type of CCR3 antagonist to attenuate the CYP2D6 inhibition of lead compound **1**, novel compounds with relatively low $C\log D_{7.4}$ values were synthesized and their inhibitory activities against CCR3 and CYP2D6 were evaluated. These SAR studies revealed that the carbonyl group at Part A of **1** effectively inhibited CCR3 activity, and it allowed the incorporation of hetero non-aromatic rings into Part A. In addition, it could also lower the $C\log D_{7.4}$ value accompanying reduced CYP2D6 inhibition. Furthermore, replacements of the phenyl ring at Part B with a pyridine ring lowered $C\log D_{7.4}$ value, and could cause further reduction of CYP2D6 inhibitory activity. In this study, good correlation was observed in the $C\log D_{7.4}$ values and CYP2D6 inhibition, and we could confirm that the $C\log D_{7.4}$ values was an important contributor for CYP2D6 inhibition. These results indicate the successful identification of **30** as a potent CCR3 inhibitor with reduced CYP2D6 activity. For our series of synthesized compounds, the strategic synthesis of compounds that would attenuate CYP2D6 inhibitory activity was accomplished by referring to the $C\log D_{7.4}$ values.

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. High resolution (HR)-mass spectra were recorded using a Waters QTOF Premier 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 those theoretical values.

5.1.1. *tert*-Butyl (3-*exo*)-8-azabicyclo[3.2.1]oct-3-ylcarbamate hydrochloride (3)

To a solution of 3-*exo*-8-benzyl-8-azabicyclo[3.2.1]octan-3-amine (**2**)[8] (31.32 g, 145 mmol) in THF (600 mL) was added di-*tert*-butyl carbonate (34.76 g, 159 mmol), and the mixture was stirred at room temperature for 11 h. The mixture was concentrated in vacuo. The crude solid was washed with Et_2O, and the precipitate was collected by filtration, washed with Et_2O, and dried in vacuo to yield *tert*-butyl (3-*exo*-8-benzyl-8-azabicyclo[3.2.1]oct-3-yl)carbamate (36.54 g, 79%) as a colorless powder. To an ice-cooled solution of above-obtained compound (36.54 g, 115 mmol) in EtOH (500 mL) and MeOH (250 mL) were added 4 M HCl (g)/EtOAc (27 mL), and $Pd(OH)_2$ (20 wt%, 11.5 g), and the mixture was stirred in a hydrogen atmosphere at room temperature for 3 h. The catalyst was removed by filtration on Celite and the filtrate was concentrated in vacuo to yield **3** (29.12 g, 96%) as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.38 (s, 9H), 1.61 (dd, J = 12.0, 11.6 Hz, 2H), 1.77–1.86 (m, 4H), 1.89–1.94 (m, 2H), 3.58–3.70 (m, 1H), 3.82–3.88 (m, 2H), 6.94–6.99 (m, 1H); MS (FAB) m/z = 227 $[M+H]^+$.

5.1.2. *tert*-Butyl {(3-*exo*)-8-[(6-fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl}carbamate (4)

To a solution of **3** (29.11 g, 111 mmol) in DMF (400 mL) were added K_2CO_3 (45.93 g, 332 mmol) and 2-(bromomethyl)-6-fluoronaphthalene[9] (29.13 g, 122 mmol), and the mixture was stirred at room temperature for 21 h. The mixture was concentrated in vacuo. The residue 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 residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 100:0–98:2) to yield **4** (42.62 g, quant.) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.44 (s, 9H), 1.45–1.56 (m, 2H), 1.69–1.77 (m, 2H), 1.79–1.86 (m, 2H), 2.03–2.08 (m, 2H), 3.21–3.26 (m, 1H), 3.67(s, 2H), 3.78–3.88 (m, 1H), 4.30–4.39 (m, 1H), 7.22 (dd, J = 8.6, 2.6 Hz, 1H), 7.43 (dd, J = 9.9, 2.4 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.70–7.81 (m, 3H). MS (FAB) m/z = 385 $[M+H]^+$.

5.1.3. (3-*exo*)-8-[(6-Fluoro-2-naphthyl)methyl]-8-azabicyclo-[3.2.1]octan-3-amine dihydrochloride (5)

To a solution of **4** (42.62 g, 111 mmol) in EtOAc (300 mL) was added 4 M HCl (g)/EtOAc (300 mL), and the mixture was stirred at room temperature for 5.5 h. The mixture was concentrated in vacuo to yield **5** (39.66 g, quant.) as a slightly brown foam. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.89–2.09 (m, 7H), 2.18–2.27 (m, 2H), 2.36–2.42 (m, 1H), 3.78, 3.87(m, 2H), 4.32, 4.89 (m, 2H), 7.45–7.56 (m, 1H), 7.75–7.81 (m, 1H), 7.95–8.05 (m, 3H), 8.33–8.39 (m, 2H), 8.64–8.70 (m, 1H), 11.21 (br, 1H); MS (FAB) m/z = 285 $[M+H]^+$.

5.1.4. 4-(2-Methylphenyl)pyridine (8a)

To a solution of 4-bromopyridine hydrochloride (1.94 g, 10.0 mmol) in DME (15 mL) were added 2-methylphenyl boronic acid (**7**) (1.50 g, 11.0 mmol), CsF (3.34 g, 22.0 mmol), and $Pd(PPh_3)_4$ (0.35 g, 0.30 mmol), and the mixture was stirred at reflux for 14.5 h. The mixture was cooled to room temperature and 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 (hexane/EtOAc = 20:1–10:1) to yield **8a** (0.918 g, 54%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.28 (s, 3H), 7.18–7.36 (m, 6H), 8.65 (dd, J = 4.9, 1.7 Hz, 2H); MS (FAB) m/z = 170 $[M+H]^+$.

5.1.5. 2-Pyridin-4-ylbenzoic acid (9a)

To a solution of **8a** (918 mg, 5.42 mmol) in H_2O (10 mL) was added $KMnO_4$ (3.24 g, 16.3 mmol) and the mixture was stirred at reflux for 2 h. To the mixture was then added EtOH (4 mL) and the mixture was stirred at reflux for 1 h. The mixture was cooled to room temperature and filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was dissolved in H_2O, and the mixture was acidified with 1 M HCl (pH 6). The precipitate was collected by filtration, washed with H_2O, and dried in vacuo to yield **9a** (374 mg, 35%) as a colorless solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.34 (dd, J = 4.5, 1.7 Hz, 2H), 7.41 (dd, J = 7.6, 1.1 Hz, 2H), 7.55 (ddd, J = 7.6, 7.6, 1.1 Hz, 2H), 7.55 (ddd, J = 7.6, 7.6, 1.4 Hz, 2H), 7.85 (dd, J = 7.6, 1.4 Hz, 2H), 8.59 (dd, J = 4.5, 1.7 Hz, 2H); MS (FAB) m/z = 200 $[M+H]^+$.

5.1.6. *N*-{(3-*exo*)-8-[(6-Fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-pyridin-4-ylbenzamide (6a)

To a solution of **5** (324 mg, 0.75 mmol) in CH_2Cl_2 (3 mL) were added **9a** (166 mg, 0.83 mmol), HOBt (123 mg, 0.91 mmol), WSC (175 mg, 1.13 mmol), and Et_3N (0.33 mL, 2.37 mmol), and this mixture was stirred at room temperature over night. The mixture was then partitioned between $CHCl_3$ and satd $NaHCO_3$ aq, 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 = 99:1–98:2). The crude solid was recrystallized from MeCN to yield **6a** (172 mg, 49%) as a colorless crystal. Mp: 103–107 °C (MeCN). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17–1.26 (m, 2H), 1.59–1.66 (m, 2H), 1.68–1.76 (m, 2H), 2.02–2.08 (m, 2H), 3.14–3.20 (m, 2H), 3.58 (s, 2H), 4.10–4.23 (m, 1H), 5.10 (d, J = 8.3 Hz, 1H), 7.21–7.27 (m, 1H), 7.34–7.38 (m, 3H), 7.39–7.43 (m, 1H), 7.44–7.54 (m, 4H), 7.62 (dd, J = 7.3, 1.5 Hz, 1H), 7.67–7.68 (m, 1H), 7.72 (d, J = 8.3 Hz, 1H), 7.78 (dd, J = 8.8, 5.9 Hz, 1H), 8.63 (dd, J = 4.7, 1.8 Hz, 1H); MS (FAB) m/z = 466 $[M+H]^+$. Anal. Calcd for $C_{30}H_{28}FN_3O$: C, 77.39; H, 6.06; N, 9.03; F, 4.08. Found: C, 77.21; H, 6.04; N, 9.02; F, 3.98.

5.1.7. 3-(2-Methylphenyl)pyridine (8b)

Compound **8b** was prepared from **7** and 3-bromopyridine in a manner similar to that described for compound **8a**, with a yield of 97% as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.28 (s, 3H), 7.19–7.38 (m, 5H), 7.63–7.68 (m, 1H), 8.57–8.62 (m, 2H); MS (FAB) m/z = 170 $[M+H]^+$.

5.1.8. 2-Pyridin-3-ylbenzoic acid (9b)

Compound **9b** was prepared from **8b** in a manner similar to that described for compound **9a**, with a yield of 28% as a colorless solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.40–7.47 (m, 2H), 7.53 (ddd, J = 7.5, 7.5, 1.4 Hz, 1H), 7.64 (ddd, J = 7.5, 7.5, 1.7 Hz, 1H), 7.75 (ddd, J = 7.7, 2.2, 1.7 Hz, 2H), 7.84–7.88 (m, 1H), 8.51 (dd, J = 2.4, 0.7 Hz, 1H), 8.55 (dd, J = 4.7, 1.7 Hz, 1H); MS (FAB) m/z = 200 $[M+H]^+$.

5.1.9. *N*-{(3-*exo*)-8-[(6-Fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-pyridin-3-ylbenzamide dihydrochloride (6b)

Compound **6b** was prepared from **5** and **9b** in a manner similar to that described for compound **6a**, with a yield of 55% as a colorless solid. Mp: 174–177 °C (MeCN). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.64–2.00 (m, 6H), 2.15–2.45 (m, 2H), 4.02–4.25 (m, 1H), 4.25–4.32 (m, 2H), 4.74 (d, J = 5.8 Hz, 1H), 7.48–7.74 (m, 5H), 7.78 (dd, J = 10.3, 2.5 Hz, 1H), 7.81–7.95 (m, 1H), 7.96–8.05 (m, 3H), 8.23–8.30 (m, 2H), 8.56 (d, J = 7.8 Hz, 1H), 8.77–8.85 (m, 3H), 10.75–11.00 (m, 1H); MS (FAB) m/z = 466 $[M+H]^+$. Anal. Calcd for $C_{30}H_{28}FN_3O{\cdot}2HCl{\cdot}2H_2O$: C, 61.75; H, 6.05; N, 7.20; Cl, 12.15; F, 3.76. Found: C, 61.78; H, 6.03; N, 7.38; Cl, 11.99; F, 3.05.

5.1.10. 2-(2-Methylphenyl)pyridine (8c)

Compound **8c** was prepared from **7** and 2-bromopyridine in a manner similar to that described for compound **8a**, with a yield of 81% as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.37 (s, 3H), 7.21–7.32 (m, 4H), 7.37–7.42 (m, 2H), 7.71–7.78 (m, 1H), 8.68–8.74 (m, 1H); MS (FAB) m/z = 170 $[M+H]^+$.

5.1.11. 2-Pyridin-2-ylbenzoic acid (9c)

Compound **9c** was prepared from **8c** in a manner similar to that described for compound **9a**, with a yield of 55% as a colorless solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.35 (ddd, J = 7.5, 4.8, 1.0 Hz, 2H), 7.48–7.62 (m, 4H), 7.69–7.73 (m, 1H), 7.86 (ddd, J = 7.7, 7.7, 1.8 Hz, 2H); MS (FAB) m/z = 200 $[M+H]^+$.

5.1.12. *N*-{(3-*exo*)-8-[(6-Fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-pyridin-2-ylbenzamide (6c)

Compound **6c** was prepared from **5** and **9c** in a manner similar to that described for compound **6a**, with a yield of 77% as a colorless crystal. Mp: 187–189 °C (EtOAc–EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.24–1.33 (m, 2H), 1.63–1.68 (m, 2H), 1.69–1.74 (m, 2H), 2.02–2.07 (m, 2H), 3.14–3.20 (m, 2H), 3.62 (s, 2H), 4.11–4.23 (m, 1H), 5.78 (d, J = 8.8 Hz, 1H), 7.21–7.30 (m, 2H), 7.40–7.55 (m, 6H), 7.62–7.65 (m, 1H), 7.68–7.79 (m, 4H), 8.64–8.68 (m, 1H); MS (FAB) m/z = 466 $[M+H]^+$. Anal. Calcd for $C_{30}H_{28}FN_3O$: C, 77.39; H, 6.06; N, 9.03; F, 4.08. Found: C, 77.42; H, 6.05; N, 9.11; F, 4.07.

5.1.13. *N*-{(3-*exo*)-8-[(6-Fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-pyrimidin-5-ylbenzamide fumarate (6d)

To a solution of 5-bromopyrimidine (1.79 g, 11.0 mmol) in DME (60 mL) were added $Pd(PPh_3)_4$ (347 mg, 0.30 mmol), Na_2CO_3 (1.07 g, 10.0 mmol) in H_2O (15 mL), and *o*-formylphenylboronic acid (**10**) (1.55 g, 10.0 mmol), and the mixture was stirred at reflux over night. The 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 = 100:0–98:2) to yield **11a** (1.84 g, quant.) as a pale yellow solid. To a solution of above-obtained residual compound (920 mg, 5.00 mmol) in CH_3CN (20 mL) and H_2O (8 mL) were added NaH_2PO_4 (0.16 g, 1.33 mmol), and 35% H_2O_2 aq (0.5 mL, 5.15 mmol), was added $NaClO_2$ (792 mg, 8.76 mmol) in H_2O (7 mL) dropwise over 2 h and the mixture was stirred under 15 °C for 4 h. The resulting precipitate was collected by filtration, and washed with cold-H_2O, and dried in vacuo to yield **12a** (420 mg, 40%, 90% purity) as a cream-colored solid. To a solution of **5** (324 mg, 0.75 mmol) in CH_2Cl_2 (3 mL) were added **12a** (164 mg, 0.75 mmol, 90% purity), HOBt (123 mg, 0.91 mmol), WSC (175 mg, 1.13 mmol), and Et_3N (0.33 mL, 2.37 mmol), and this mixture was stirred at room temperature over night. The mixture was then partitioned between $CHCl_3$ and satd $NaHCO_3$ aq, 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 = 99:1–96:4). The crude amorphous solid was converted to its fumaric acid salt by treating it with fumaric acid (70 mg, 0.60 mmol). The crude solid was recrystallized from EtOH–EtOAc to yield **6d** (270 mg, 62%) as a colorless crystal. Mp: 193–196 °C (EtOAc–EtOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.51–1.57 (m, 4H), 1.63–1.70 (m, 2H), 2.05–2.12 (m, 2H), 3.25–3.33 (m, 2H), 3.79 (s, 2H), 3.98–4.09 (m, 1H), 6.61 (s, 2H), 7.40–7.46 (m, 1H), 7.50–7.63 (m, 5H), 7.70 (dd, J = 10.2, 2.4 Hz, 1H), 7.82–7.92 (m, 2H), 7.97 (dd, J = 9.3, 5.8 Hz, 1H) , 8.24 (d, J = 8.3 Hz, 1H), 8.76 (s, 2H) , 9.16 (s, 1H); MS (FAB) m/z = 467 $[M+H]^+$. Anal. Calcd for $C_{29}H_{27}FN_4O{\cdot}C_4H_4O_4$: C, 68.03; H, 5.36; N, 9.62; F, 3.26. Found: C, 67.98; H, 5.43; N, 9.62; F, 3.28.

5.1.14. 2-(1,3-Thiazol-2-yl)benzoic acid (12b)

Compound **12b** was prepared from **10** and 2-bromothiazole in a manner similar to that described for compound **12a**, with a yield of 39% from **10** as a cream-colored solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.55–7.64 (m, 2H), 7.68–7.73 (m, 2H), 7.84 (d, J = 3.2 Hz, 1H), 7.92 (d, J = 3.2 Hz, 1H), 12.96 (s, H); MS (ESI$^+$) m/z = 206.1 $[M+H]^+$.

5.1.15. *N*-{(3-*exo*)-8-[(6-Fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-(1,3-thiazol-2-yl)benzamide (6e)

Compound **6e** was prepared from **5** and **12b** in a manner similar to that described for compound **6a**, with a yield of 73% as a colorless crystal. Mp: 163–165 °C (MeCN). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40–1.48 (m, 2H), 1.74–1.82 (m, 4H), 2.04–2.09 (m, 2H), 3.20–3.35

(m, 2H), 3.65 (s, 2H), 4.20–4.34 (m, 1H), 6.14 (d, J = 8.3 Hz, 1H), 7.21–7.27 (m, 1H), 7.41–7.50 (m, 4H), 7.56 (d, J = 8.8 Hz, 1H), 7.61–7.67 (m, 2H), 7.73–7.74 (m, 2H) , 7.78 (dd, J = 8.8, 5.9 Hz, 1H), 7.88 (d, J = 3.0 Hz, 1H); MS (FAB) m/z = 472 $[M+H]^+$. Anal. Calcd for $C_{28}H_{26}FN_3O_2S$: C, 71.31; H, 5.56; N, 8.91; S, 6.80; F, 4.03. Found: C, 71.29; H, 5.53; N, 8.92; S, 6.79; F, 4.04.

5.1.16. *N*-{(3-*exo*)-8-[(6-Fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-(1H-pyrrol-1-yl)benzamide (6f)

Compound **6f** was prepared from **5** and 2-(1H-pyrrol-1-yl)benzoic acid in a manner similar to that described for compound **6a**, with a yield of 55% as a colorless crystal. Mp: 144–146 °C (iPr$_2$O–MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.22–1.30 (m, 2H), 1.63–1.75 (m, 4H), 2.02–2.07 (m, 2H), 3.15–3.20 (m, 2H), 3.64 (s, 2H), 4.08–4.20 (m, 1H), 5.03 (d, J = 8.3 Hz, 1H), 6.38 (dd, J = 2.3, 1.9 Hz, 1H), 6.84 (dd, J = 2.3, 1.9 Hz, 1H), 7.21–7.28 (m, 1H), 7.34 (dd, J = 8.8, 1.5 Hz, 1H), 7.41–7.46 (m, 2H), 7.49 (ddd, J = 7.8, 7.3, 1.8 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H) , 7.71–7.75 (m, 2H), 7.78 (dd, J = 8.8, 5.9 Hz, 1H), 7.84 (dd, J = 7.8, 2.2 Hz, 1H); MS (FAB) m/z = 454 $[M+H]^+$. Anal. Calcd for $C_{29}H_{28}FN_3O$: C, 76.80; H, 6.22; N, 9.26; F, 4.19. Found: C, 76.71; H, 5.95; N, 9.33; F, 4.10.

5.1.17. *N*-{(3-*exo*)-8-[(6-Fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-(1H-imidazol-1-yl)benzamide difumarate (6g)

Compound **6g** was prepared from **5** and 2-(1H-imidazol-1-yl)benzoic acid in a manner similar to that described for compound **6a**, with a yield of 16% as a colorless crystal. Mp: 202–204 °C (MeCN–MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.48–1.70 (m, 6H), 2.05–2.15 (m, 2H), 3.23–3.31 (m, 2H), 3.77 (s, 2H), 3.96–4.08 (m, 1H), 6.61 (d, 4H), 7.01 (s, 1H), 7.28 (s, 1H), 7.38–7.53 (m, 4H), 7.54–7.63 (m, 2H), 7.69 (dd, J = 10.3, 2.4 Hz, 1H), 7.74 (s, 1H), 7.86–7.92 (m, 2H) , 7.96 (dd, J = 8.8, 5.8 Hz, 1H), 8.20 (d, J = 7.9 Hz, 1H); MS (FAB) m/z = 455 $[M+H]^+$. Anal. calcd for $C_{28}H_{27}FN_4O{\cdot}2C_4H_4O_4$: C, 62.97; H, 5.14; N, 8.16; F, 2.77. Found: C, 63.10; H, 5.19; N, 8.46; F, 2.70.

5.1.18. Methyl 2-(cyclohexyloxy)benzoate (14)

To a solution of methyl salicylate (**13**) (3.38 g, 22.0 mmol) in THF (4 mL) was added cyclohexanol (2.02 g, 20.0 mmol), PPh_3 (5.77 g, 22.0 mmol), and DEAD (3.31 mL, 21.0 mmol), and the mixture was stirred at room temperature for 4 d. The mixture was concentrated in vacuo, and the solid was then diluted with Et_2O and insoluble matter was removed by filtration, and the filtrate was concentrated in vacuo The residue was purified by silica gel column chromatography (hexane/Et_2O = 95:5–90:10) to yield **14** (2.67 g, 57%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.32–1.45 (m, 3H), 1.47–1.58 (m, 1H), 1.62–1.72 (m, 2H), 1.76–1.87 (m, 2H), 1.88–1.97 (m, 2H), 3.88 (s, 3H), 4.32–4.39 (m, 1H), 6.78 (dd, J = 8.3, 7.3 Hz, 1H), 6.99 (d, J = 8.3 Hz, 1H), 7.40 (ddd, J = 7.8, 7.3, 2.0 Hz, 1H), 7.75 (dd, J = 7.8, 2.0 Hz, 1H); MS (FAB) m/z = 235 $[M+H]^+$.

5.1.19. 2-(Cyclohexyloxy)benzoic acid (15)

To a solution of **14** (1.17 g, 5.00 mmol) in MeOH (10 mL) was added 1 M NaOH aq (6.5 mL), and the mixture was stirred at room temperature for 3.5 d. The mixture was concentrated in vacuo, and the residue was then partitioned between $CHCl_3$ and 1 M HCl aq, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. to yield **15** (1.10 g, quant.) as a pale yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.28–1.41 (m, 3H), 1.42–1.56 (m, 3H), 1.66–1.78 (m, 2H), 1.80–1.88 (m, 2H), 4.41–4.49 (m, 1H), 6.96 (dd, J = 7.8, 7.3 Hz, 1H), 7.13 (d, J = 8.3 Hz, 1H), 7.44 (ddd, J = 8.3, 7.3, 2.0 Hz, 1H), 7.59 (dd, J = 7.8, 2.0 Hz, 1H 1H), 12.48 (s, 1H); MS (FAB) m/z = 219 $[M-H]^+$.

5.1.20. 2-(Cyclohexyloxy)-*N*-{(3-*exo*)-8-[(6-fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl}benzamide fumarate (6h)

Compound **6h** was prepared from **5** and **15** in a manner similar to that described for compound **6a**, with a yield of 77% as a colorless crystal. Mp: 211–214 °C (EtOAc–EtOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.26–1.59 (m, 6H), 1.67–1.87 (m, 8H), 1.92–1.99 (m, 2H), 2.10–2.18 (m, 2H), 3.32–3.39 (m, 2H), 3.85 (s, 2H), 4.16–4.29 (m, 1H), 4.50–4.58 (m, 1H), 6.61 (s, 2H), 7.00 (dd, J = 7.9, 7.3 Hz, 1H), 7.16 (d, J = 8.3 Hz, 1H), 7.39–7.46 (m, 2H), 7.64 (d, J = 8.3 Hz, 1H) , 7.70 (dd, J = 10.8, 2.7 Hz, 1H), 7.73 (dd, J = 7.8, 2.0 Hz, 1H), 7.90 (d, J = 8.8 Hz, 1H) , 7.92–7.98 (m, 2H), 8.01 (d, J = 7.9 Hz, 1H); MS (FAB) m/z = 487 $[M+H]^+$. Anal. Calcd for $C_{31}H_{35}FN_2O_2{\cdot}C_4H_4O_4$: C, 69.75; H, 6.52; N, 4.65; F, 3.15. Found: C, 69.69; H, 6.59; N, 4.67; F, 3.18.

5.1.21. 2-Piperidin-1-ylbenzoic acid (17)

To a solution of 2-fluorobenzonitrile (**16**) (2.47 g, 20.0 mmol) in DMF (20 mL) were added piperidine (3.61 g, 42.0 mmol) and K_2CO_3 (2.77 g, 20.0 mmol), and the mixture was stirred at 70 °C over night. The 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 to yield 2-piperidin-1-ylbenzonitrile (3.18 g, 85%) as a brown oil. To a solution of above-obtained residual compound (1.00 g, 5.37 mmol) in 2-ethoxyethanol (4 mL) and H_2O (0.5 mL) was added KOH (2.23 g, 39.8 mmol), and the mixture was stirred at reflux for 4 h. The mixture was then cooled to 0 °C, and neutralized with concd HCl (2.8 mL), and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 98:2) to yield **17** (0.64 g, 58%) as a brown solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.59–1.68 (m, 2H), 1.70–1.81 (m, 4H), 3.01–3.08 (m, 4H), 3.30–3.34 (m, 2H), 7.40–7.47 (m, 1H), 7.67 (dt, J = 8.1, 1.7 Hz, 1H), 7.70–7.75 (m, 1H), 8.05 (dd, J = 7.8, 1.6 Hz, 1H); MS (FAB) m/z = 206 $[M+H]^+$.

5.1.22. *N*-{(3-*exo*)-8-[(6-Fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-piperidin-1-ylbenzamide (6i)

Compound **6i** was prepared from **5** and **17** in a manner similar to that described for compound **6a**, with a yield of 25% as a pale yellow crystal. Mp: 157–159 °C (MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.63–1.75 (m, 4H), 1.78–1.86 (m, 6H), 1.96–2.03 (m, 2H), 2.08–2.15 (m, 2H), 2.89–2.96 (m, 4H), 3.27–3.33 (m, 2H), 3.73 (s, 2H), 4.32–4.44 (m, 1H), 7.18–7.27 (m, 3H), 7.38–7.46 (m, 2H), 7.61 (d, J = 8.3 Hz, 1H), 7.74–7.80 (m, 3H), 8.19 (dd, J = 8.0, 1.5 Hz, 1H) , 10.13 (d, J = 8.3 Hz, 1H); MS (FAB) m/z = 472 $[M+H]^+$. Anal. Calcd for $C_{30}H_{34}FN_3O$: C, 76.40; H, 7.27; N, 8.91; F, 4.03. Found: C, 76.31; H, 7.40; N, 8.85; F, 3.87.

5.1.23. 2-[Cyclohexyl(methyl)carbamoyl]benzoic acid (19a)

To a solution of cyclohexylmethylamine (1.55 g, 13.7 mmol) in THF (30 mL) was added phthalic anhydride (**18**) (2.04 g, 13.7 mmol), and the mixture was stirred at room temperature for 15.5 h. The mixture was then concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 98:2–90:10) to yield **19a** (2.72 g, 76%) as a colorless amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.85–1.02 (m, 2H), 1.25–1.84 (m, 8H), 1.94–2.12 (m, 6H), 2.32–2.50 (m, 2H), 2.56–2.59, 2.78–2.84 (each m, 3H), 3.05–3.14 (m, 1H), 3.76–3.92, 4.31–4.36 (each m, 2H), 4.10–4.30 (m, 1H), 4.79–4.84 (m, 1H), 7.18–7.29 (m, 2H), 7.39–7.56 (m, 4H), 7.76–7.82 (m, 2H), 7.90–8.08 (m, 2H), 8.23–8.27 (m, 1H), 8.29–8.33, 8.39–8.43 (each m, 1H), 10.40–10.66 (m,1H); MS (FAB) m/z = 260 $[M+H]^+$.

5.1.24. *N*-Cyclohexyl-*N'*-{(3-*exo*)-8-[(6-fluoro-2-naphthyl)-methyl]-8-azabicyclo[3.2.1]oct-3-yl}-*N*-methylphthalamide hydrochloride (20a)

Compound **20a** was prepared from **5** and **19a** in a manner similar to that described for compound **6a**, with a yield of 59% as a colorless crystal. Mp: 270–272 °C (MeCN–Et_2O). ^1H NMR (400 MHz, DMSO-d_6) δ: 0.85–1.02 (m, 2H), 1.25–1.84 (m, 8H), 1.94–2.12 (m, 6H), 2.32–2.50 (m, 2H), 2.56–2.59, 2.78–2.84 (each m, 3H), 3.05–3.14 (m, 1H), 3.76–3.92, 4.31–4.36 (each m, 2H), 4.10–4.30 (m, 1H), 4.79–4.84 (m, 1H), 7.18–7.29 (m, 2H), 7.39–7.56 (m, 4H), 7.76–7.82 (m, 2H), 7.90–8.08 (m, 2H), 8.23–8.27 (m, 1H), 8.29–8.33, 8.39–8.43 (each m, 1H), 10.40–10.66 (m,1H); MS (FAB) *m/z* = 528 $[M+H]^+$. Anal. Calcd for $C_{33}H_{38}FN_3O_2$·HCl: C, 70.26; H, 6.97; N, 7.45; Cl, 6.28; F, 3.37. Found: C, 69.93; H, 7.14; N, 7.38; Cl, 6.21; F, 3.42.

5.1.25. 2-(Piperidin-1-ylcarbonyl)benzoic acid (19b)

Compound **19b** was prepared from piperidine and phthalic anhydride (**18**) in a manner similar to that described for compound **19a**, with a yield of 73% as a pale brown amorphous solid. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.78–1.84 (m, 2H), 3.08–3.20 (m, 8H), 7.23–7.28 (m, 1H), 7.41–7.47 (m, 1H), 7.54–7.58 (m, 1H), 8.08(*J* = 7.9 Hz, 1H), 9.98 (br, 1H); MS (FAB) *m/z* = 234 $[M+H]^+$.

5.1.26. *N*-{(3-*exo*)-8-[(6-Fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-(piperidin-1-ylcarbonyl)benzamide (20b)

Compound **20b** was prepared from **5** and **19b** in a manner similar to that described for compound **6a**, with a yield of 45% as a pale yellow amorphous solid. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.37–1.46 (m, 2H), 1.60–1.83 (m, 10H), 2.08–2.12 (m, 2H), 3.10 (t, *J* = 5.4 Hz, 2H), 3.24–3.29 (m, 2H), 3.68–3.72 (m, 2H), 4.24–4.36 (m, 1H), 6.73 (d, *J* = 8.3 Hz, 1H), 7.18–7.27 (m, 2H), 7.41–7.49 (m, 3H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.73–7.82 (m, 4H); MS (FAB) *m/z* = 500 $[M+H]^+$. Anal. Calcd for $C_{31}H_{34}FN_3O_2$·0.5H_2O: C, 73.20; H, 6.94; N, 8.26; F, 3.74. Found: C, 73.08; H, 7.01; N, 8.57; F, 3.80.

5.1.27. 2-[(4-Methylpiperazin-1-yl)carbonyl]benzoic acid (19c)

Compound **19c** was prepared from 1-methylpiperazine and phthalic anhydride (**18**) in a manner similar to that described for compound **19a**, with a yield of 96% as a colorless powder. ^1H NMR (400 MHz, D_2O) δ: 2.94 (s, 3H), 3.05–3.80 (m, 8H), 7.28–7.35 (m, 1H), 7.55–7.62 (m, 2H), 7.82–7.89 (m, 1H); MS (FAB) *m/z* = 249 $[M+H]^+$.

5.1.28. *N*-{(3-*exo*)-8-[(6-Fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-[(4-methylpiperazin-1-yl)carbonyl]benzamide (20c)

Compound **20c** was prepared from **5** and **19c** in a manner similar to that described for compound **6a**, with a yield of 36% as a slightly brown amorphous solid. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.56–1.68 (m, 2H), 1.78–1.88 (m, 4H), 2.06–2.14 (m, 2H), 2.23–2.32 (m, 2H), 2.28 (s, 3H), 2.47 (t, *J* = 4.9 Hz, 2H), 3.17 (t, *J* = 4.9 Hz, 2H), 3.24–3.30 (m, 2H), 3.70 (s, 2H), 3.77–3.86 (m, 2H), 4.24–4.37 (m, 1H), 6.57 (d, *J* = 8.8 Hz, 1H), 7.21–7.25 (m, 2H), 7.41–7.50 (m, 3H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.73–7.82 (m, 4H); MS (FAB) *m/z* = 515 $[M+H]^+$. Anal. Calcd for $C_{31}H_{35}FN_4O_2$·0.25H_2O: C, 71.72; H, 6.89; N, 10.79; F, 3.66. Found: C, 71.57; H, 6.96; N, 10.57; F, 3.75.

5.1.29. *N*-{(3-*exo*)-8-[(6-Fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-(morpholin-4-ylcarbonyl)benzamide (20d)

To a solution of morpholine (880 mg, 10.0 mmol) in THF (50 mL) was added phthalic anhydride (**18**) (1.48 g, 10.0 mmol), and the mixture was stirred at reflux for 4 h. The mixture was cooled to room temperature and then concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 98:2–90:10) to yield crude **19d** (1.59 g) as a pale yellow solid. To a solution of **5** (501 mg, 1.40 mmol) in 1,2-dichloroethane (14 mL) were added crude **19d** (330 mg, 1.40 mmol), HOBt (189 mg, 1.14 mmol), WSC (219 mg, 1.41 mmol), and Et_3N (0.42 mL, 3.05 mmol), and this mixture was stirred at room temperature over night. The mixture was then partitioned between $CHCl_3$ and satd $NaHCO_3$ aq, 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 = 99:1–98:2) to yield **20d** (343 mg, 48%) as a pale yellow amorphous solid. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.60–1.70 (m, 2H), 1.75–1.92 (m, 4H), 2.06–2.18 (m, 2H), 3.16–3.21 (m, 2H), 3.25–3.30 (m, 2H), 3.53–3.60 (m, 2H), 3.73–3.82 (m, 4H), 4.25–4.38 (m, 1H), 6.43 (d, *J* = 8.3 Hz, 1H), 7.22–7.26 (m, 1H), 7.41–7.51 (m, 3H), 7.59 (d, *J* = 8.3 Hz, 1H), 7.68–7.72 (m, 1H), 7.73–7.82 (m, 4H); MS (FAB) *m/z* = 501 $[M+H]^+$. Anal. Calcd for $C_{30}H_{32}FN_3O_3$·0.5H_2O: C, 70.57; H, 6.51; N, 8.23; F, 3.72. Found: C, 70.80; H, 6.50; N, 8.37; F, 3.78.

5.1.30. 2-(Pyrrolidin-1-ylcarbonyl)benzoic acid (19e)

Compound **19e** was prepared from pyrrolidine and phthalic anhydride (**18**) in a manner similar to that described for compound **19a**, with a yield of 75% as a pale brown amorphous solid. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.82–1.99 (m, 4H), 3.10–3.17 (m, 2H), 3.62–3.89 (m, 2H), 7.32 (d, *J* = 7.4 Hz, 1H), 7.45 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.55 (dd, *J* = 7.8, 7.4 Hz, 1H), 8.08 (d, *J* = 7.8 Hz, 1H); MS (FAB) *m/z* = 220 $[M+H]^+$.

5.1.31. *N*-{(3-*exo*)-8-[(6-Fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-(pyrrolidin-1-ylcarbonyl)benzamide (20e)

Compound **20e** was prepared from **5** and **19e** in a manner similar to that described for compound **6a**, with a yield of 33% as a cream-colored amorphous solid. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.74–1.89 (m, 6H), 1.89–1.98 (m, 2H), 2.10–2.18 (m, 2H), 3.12 (t, *J* = 6.8 Hz, 2H), 3.30–3.36 (m, 2H), 3.63 (t, *J* = 6.8 Hz, 1H), 3.78 (s, 2H), 4.26–4.39 (m, 1H), 6.80 (d, *J* = 7.3 Hz, 1H), 7.23–7.29 (m, 2H), 7.41–7.50 (m, 3H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.73–7.84 (m, 4H); MS (FAB) *m/z* = 486 $[M+H]^+$. HR-MS calcd for $C_{30}H_{32}FN_3O_2$ *m/z* = 486.2557 $[M+H]^+$. Found: 486.2539.

5.1.32. 2-(Azepan-1-ylcarbonyl)benzoic acid (19f)

Compound **19f** was prepared from azepane and phthalic anhydride (**18**) in a manner similar to that described for compound **19a**, with a quantitative yield as a pale brown amorphous solid. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.50–1.68 (m, 6H), 1.75–1.86 (m, 2H), 3.13–3.22 (m, 2H), 3.62–3.77 (m, 2H), 7.27 (d, *J* = 7.4 Hz, 1H), 7.42 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.55 (dd, *J* = 7.4, 7.4 Hz, 1H), 8.06 (d, *J* = 7.4 Hz, 1H), 10.16 (br, 1H); MS (FAB) *m/z* = 248 $[M+H]^+$.

5.1.33. 2-(Azepan-1-ylcarbonyl)-*N*-{(3-*exo*)-8-[(6-fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl}benzamide (20f)

Compound **20f** was prepared from **5** and **19f** in a manner similar to that described for compound **6a**, with a yield of 48% as a pale yellow amorphous solid. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.47–1.58 (m, 4H), 1.59–1.70 (m, 4H), 1.75–1.89 (m, 6H), 2.05–2.23 (m, 2H), 3.14–3.21 (m, 2H), 3.22–3.29 (m, 2H), 3.65–3.75 (m, 2H), 3.70 (s, 2H), 4.21–4.32 (m, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 7.19–7.25 (m, 2H), 7.42–7.49 (m, 3H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.72–7.82 (m, 4H); MS (FAB) *m/z* = 514 $[M+H]^+$. Anal. Calcd for $C_{32}H_{36}FN_3O_2$·0.5H_2O: C,73.54; H, 7.14; N, 8.04; F, 3.63. Found: C, 73.43; H, 7.08; N, 8.19; F, 3.65.

5.1.34. 2-(Azocan-1-ylcarbonyl)-*N*-{(3-*exo*)-8-[(6-fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl}benzamide (20g)

Compound **20g** was prepared from **5** and **19g** in a manner similar to that described for compound **20d**, with a yield of 56% as a colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40–1.70 (m, 10H), 1.74–1.98 (m, 8H), 2.05–2.14 (m, 2H), 3.08–3.20 (m, 2H), 3.23–3.29 (m, 2H), 3.70 (s, 2H), 4.22–4.35 (m, 1H), 6.80 (d, J = 7.8 Hz, 1H), 7.20–7.27 (m, 2H), 7.41–7.50 (m, 3H), 7.60 (d, J = 8.3 Hz, 1H), 7.73–7.82 (m, 4H); MS (FAB) m/z = 528 $[M+H]^+$. Anal. Calcd for $C_{33}H_{38}FN_3O_2{\cdot}0.25H_2O$: C, 74.48; H, 7.29; N, 7.90; F, 3.57. Found: C, 74.63; H, 7.47; N, 8.11; F, 3.59.

5.1.35. Methyl 2-(piperidin-1-ylcarbonyl)nicotinate (22)

To a solution of dimethyl pyridine-2,3-dicarboxylate (**21**) (1.02 g, 5.12 mmol) and $MgCl_2$ (249 mg, 2.56 mmol) in THF (20 mL) was added piperidine (1.33 g, 15.56 mmol) in THF (9 mL) dropwise and the mixture was stirred at room temperature over night. The mixture was then partitioned between EtOAc and 1 M HCl 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 = 99:1–98:2) to yield **22** (444 mg, 37%) as a pale brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.50–1.58(m, 2H), 1.66–1.77 (m, 4H), 3.14–3.18 (m, 2H), 3.75–3.80 (m, 2H), 3.92 (s, 2H), 7.39 (dd, J = 8.3, 4.9 Hz, 1H), 8.31 (dd, J = 8.3, 1.4 Hz, 1H), 8.73 (dd, J = 4.9, 1.4 Hz, 1H); MS (FAB) m/z = 249 $[M+H]^+$.

5.1.36. *N*-{(3-*exo*)-8-[(6-Fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-(piperidin-1-ylcarbonyl)nicotinamide (24)

To a solution of **22** (464 mg, 1.87 mmol) in EtOH (4 mL) was added 1 M NaOH aq (3.8 mL), and the mixture was stirred at room temperature over night. 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 **23** (440 mg, quant.) as a pale brown solid. To a solution of **5** (669 mg, 1.87 mmol) in DMF (18 mL) were added **23** (440 mg, 1.87 mmol), HOBt (206 mg, 1.52 mmol), WSC (293 mg, 1.88 mmol), and Et_3N (0.57 mL, 4.09 mmol), and this mixture was stirred at room temperature over night. The mixture was then partitioned between EtOAc and satd $NaHCO_3$ aq, and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 99:1–98:2) to yield **24** (575 mg, 61%) as a colorless amorphous soild. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.44–1.53 (m, 2H), 1.60–1.88 (m, 10H), 2.07–2.15 (m, 2H), 3.04–3.08 (m, 2H), 3.25–3.29 (m, 2H), 3.61 (s, 2H), 3.75–3.79 (m, 2H), 4.23–4.32 (m, 1H), 7.23 (dd, J = 8.8, 2.4 Hz, 1H), 7.35–7.48 (m, 3H), 7.60 (d, J = 8.3 Hz, 1H), 7.73–7.82 (m, 3H), 8.18 (dd, J = 8.1, 1.5 Hz, 1H), 8.65 (dd, J = 4.9, 1.5 Hz, 1H); MS (FAB) m/z = 501 $[M+H]^+$. Anal. Calcd for $C_{30}H_{33}FN_4O_2{\cdot}0.25H_2O$: C, 71.34; H, 6.68; N, 11.09; F, 3.76. Found: C, 71.24; H, 6.59; N, 11.27; F, 3.78.

5.1.37. 3-(Piperidin-1-ylcarbonyl)isonicotinic acid (26)

A solution of pyridine-3,4-dicarboxylic acid (**25**) (3.00 g, 18.0 mmol) in Ac_2O (12 mL) was stirred at reflux for 1.5 h. The mixture was filtered and the filtrate was concentrated in vacuo to yield pyridine-3,4-dicarboxylic anhydride. To an ice-cooled solution of above-obtained compound in THF (60 mL) was added piperidine (3.9 mL, 39 mmol), and the mixture was stirred at room temperature for 17 h. The mixture was concentrated in vacuo. The residue was then diluted with satd $NaHCO_3$ aq and extracted with $CHCl_3$ three times. The organic layer was acidified by 6 M HCl aq and concentrated in vacuo, and the solid was diluted with hot EtOH, and insoluble matter was removed by filtration, and the filtrate was concentrated in vacuo. The residue was crystallized from hexane–EtOAc to yield the mixture of compounds **26**, **27**, and piperidine hydrochloride (5.42 g). The above-obtained residual compound (959 mg) was diluted with $CHCl_3$ and washed with NaCl–saturated 5% citric acid aq twice, and the organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to give the 1:1 mixture of **26** and **27**. The residue was recrystallized from EtOAc–EtOH to yield pure compound **26** (173 mg, 23% from **25**) as a colorless powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.38–1.47 (m, 2H), 1.52–1.65 (m, 4H), 3.05–3.10 (m, 2H), 3.55–3.61 (m, 2H), 7.78 (d, J = 4.8 Hz,1H), 8.57 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 13.80 (s, 1H); MS (FAB) m/z = 233 $[M+H]^+$.

5.1.38. *N*-{(3-*exo*)-8-[(6-Fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl}-3-(piperidin-1-ylcarbonyl)isonicotinamide (28)

Compound **28** was prepared from **5** and **26** in a manner similar to that described for compound **6a**, with a yield of 51% as a slightly brown amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.44–1.50 (m, 2H), 1.64–1.70 (m, 6H), 1.74–1.87 (m, 4H), 2.08–2.13 (m, 2H), 3.12–3.17 (m, 2H), 3.25–3.30 (m, 2H), 3.70 (s, 2H), 3.73–3.78 (m, 2H), 4.23–4.35 (m, 1H), 6.95 (d, J = 8.1 Hz, 1H), 7.21–7.28 (m, 1H), 7.44 (dd, J = 9.8, 2.5 Hz, 1H), 7.59 (d, J = 9.1 Hz, 1H), 7.64–7.66 (m, 1H), 7.73–7.78 (m, 3H), 8.52 (s, 1H), 7.59 (d, J = 5.4 Hz, 1H); MS (FAB) m/z = 501 $[M+H]^+$. Anal. Calcd for $C_{30}H_{33}FN_4O_2{\cdot}0.25H_2O$: C, 71.34; H, 6.68; N, 11.09; F, 3.76. Found: C, 71.24; H, 6.69; N, 10.93; F, 3.63.

5.1.39. 3-(Piperidin-1-ylcarbonyl)isonicotinic acid 1-oxide (29)

To a solution of the 1:1 mixture of **26** and **27** (269 mg, 1.15 mmol) obtained by the same manner described for compound **26** in CH_2Cl_2 (3 mL) was added *m*CPBA (238 mg, 1.38 mmol), and the mixture was stirred at room temperature for 21 h. The mixture was directly purified by silica gel column chromatography ($CHCl_3$/MeOH/AcOH = 97:3:1–94:6:1) to yield **29** (98 mg, 34%) as a slightly yellow amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.39–1.50 (m, 2H), 1.51–1.63 (m, 4H), 3.05–3.20 (m, 2H), 3.45–3.62 (m, 2H), 7.82 (d, J = 6.9 Hz, 1H), 8.23–8.29 (m, 2H); MS (FAB) m/z = 251 $[M+H]^+$.

5.1.40. *N*-{(3-*exo*)-8-[(6-Fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl}-3-(piperidin-1-ylcarbonyl)isonicotinamide 1-oxide (30)

Compound **30** was prepared from **5** and **29** in a manner similar to that described for compound **6a**, with a yield of 58% as a slightly yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.45–1.55 (m, 2H), 1.57–1.72 (m, 6H), 1.74–1.87 (m, 4H), 2.08–2.13 (m, 2H), 3.15–3.21 (m, 2H), 3.25–3.30 (m, 2H), 3.69 (s, 2H), 3.70–3.75 (m, 2H), 4.20–4.32 (m, 1H), 6.87 (d, J = 7.8 Hz, 1H), 7.21–7.29 (m, 1H), 7.44 (dd, J = 9.8, 2.4 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.71 (d, J = 6.9 Hz, 1H), 7.73–7.82 (m, 3H), 8.02 (d, J = 1.4 Hz, 1H), 8.19 (dd, J = 6.9, 1.4 Hz, 1H); MS (FAB) m/z = 517 $[M+H]^+$. Anal. Calcd for $C_{30}H_{33}FN_4O_3{\cdot}0.2CHCl_3{\cdot}0.25H2O$: C, 66.56; H, 6.23; N, 10.28; F, 3.49; Cl, 3.90. Found: C, 66.40; H, 6.47; N, 9.99; F, 3.29; Cl, 3.53.

5.1.41. 4-(Piperidin-1-ylcarbonyl)nicotinic acid (27)

A mixture of **31**[13] (500 mg, 2.76 mmol) and piperidine (1.64 mL, 16.6 mmol) was stirred at 70 °C for 1 d. The mixture was diluted with NaCl–saturated 5% citric acid aq, extracted with $CHCl_3$, and the organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to yield **27** (382 mg, 59%) as a brown foam. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.35–1.47 (m, 2H), 1.50–1.63 (m, 4H), 2.97–3.04 (m, 4H), 7.29 (d, J = 5.1 Hz, 1H), 8.72 (d, J = 5.1 Hz, 1H), 9.02 (s, 1H); MS (FAB) m/z = 233 $[M+H]^+$.

5.1.42. *N*-{(3-*exo*)-8-[(6-Fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl}-4-(piperidin-1-ylcarbonyl)nicotinamide (32)

Compound **32** was prepared from **5** and **27** in a manner similar to that described for compound **6a**, with a yield of 6% as a colorless amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.38–1.75 (m, 12H), 2.01–2.09 (m, 2H), 3.00–3.09 (m, 2H), 3.19–3.24 (m, 2H), 3.45–6.59 (m, 2H), 3.71 (s, 2H), 4.05–4.15 (m, 1H), 7.31 (d, J = 5.4 Hz, 1H), 7.41 (ddd, J = 9.3, 8.8, 2.6 Hz, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.68 (dd, J = 10.3, 2.5 Hz, 1H), 7.85–7.90 (m, 2H), 7.96 (dd, J = 8.8, 5.9 Hz, 1H), 8.35 (d, J = 7.8 Hz, 1H), 8.66 (d, J = 5.9 Hz, 1H), 8.79 (s, 1H); HR-MS calcd for $C_{30}H_{33}FN_4O_2$ m/z = 501.2666 $[M+H]^+$. Found: 501.2663.

5.1.43. Methyl 3-(piperidin-1-ylcarbonyl)pyridine-2-carboxylate (34)

To a solution of **33**[14] (414 mg, 2.29 mmol) in CH_2Cl_2 (5 mL) were added piperidine (0.25 mL, 2.50 mmol), HOBt (340 mg, 2.51 mmol), and WSC·HCl (570 mg, 2.97 mmol), and the mixture was stirred at room temperature for 3 h. The 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 residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 200:1) to yield **34** (423 mg, 74%) as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.46–1.55 (m, 2H), 1.65–1.74 (m, 4H), 3.12–3.16 (m, 2H), 3.75–3.79 (m, 2H), 3.99 (s, 3H), 7.52 (dd, J = 8.0, 4.8 Hz, 1H), 7.68 (dd, J = 8.0, 1.6 Hz, 1H), 8.75 (dd, J = 4.8, 1.6 Hz, 1H); MS (FAB) m/z = 249 $[M+H]^+$.

5.1.44. 3-(Piperidin-1-ylcarbonyl)pyridine-2-carboxylic acid (35)

To a solution of **34** (396 mg, 1.59 mmol) in MeOH (4 mL) was added 1 M NaOH aq (2.5 mL, 2.50 mmol), and the mixture was stirred at room temperature for 1 d. The mixture was then concentrated in vacuo, and the residue was partitioned between Et_2O and H_2O, and the aqueous layer was acidified with 1 M HCl aq (pH 5), and concentrated in vacuo. The solid was diluted with EtOH, and insoluble matter was removed by filtration, and the filtrate was concentrated in vacuo to yield **35** (373 mg, quant.) as a slightly brown amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.32–1.60 (m, 6H), 2.95–3.03 (m, 2H), 3.40–3.60 (m, 2H), 7.31–7.39 (m, 1H), 7.51–7.56 (m, 1H), 8.46 (m, 1H); MS (FAB) m/z = 233 $[M+H]^+$.

5.1.45. *N*-{(3-*exo*)-8-[(6-Fluoro-2-naphthyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl}-3-(piperidin-1-ylcarbonyl)pyridine-2-carboxamide (36)

Compound **36** was prepared from **5** and **35** in a manner similar to that described for compound **6a**, with a yield of 52% as a slightly brown amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.25–1.75 (m, 10H), 1.79–1.88 (m, 2H), 2.00–2.08 (m, 2H), 2.91–3.05 (m, 2H), 3.18–3.23 (m, 2H), 3.25–3.41 (m, 2H), 3.78 (s, 2H), 4.10–4.21 (m, 1H), 7.40 (ddd, J = 8.8, 8.8, 2.5 Hz, 1H), 7.59–7.64 (m, 2H), 7.67 (dd, J = 10.2, 2.5 Hz, 1H), 7.75 (dd, J = 7.8, 1.5 Hz, 1H), 7.85–7.92 (m, 2H), 7.96 (dd, J = 8.3, 5.8 Hz, 1H), 8.50 (d, J = 8.8 Hz, 1H), 8.64 (dd, J = 4.6, 1.7 Hz, 1H); MS (FAB) m/z = 501 $(M+H)^+$. Anal. Calcd for $C_{30}H_{33}FN_4O_2 \cdot 0.5H_2O$: C, 70.70; H, 6.72; N, 10.99; F, 3.73. Found: C, 70.82; H, 6.71; N, 11.04; F, 3.70.

5.2. Biology

5.2.1. Measurement of intracellular Ca^{2+} concentrations

CCR3-transfected B300-19 cells[16] 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 concentration 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 wavelengths of 340 nM and 380 nM and at an emission wavelength of 510 nM. Calculation of Ca^{2+} concentration was performed using the Kd 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.

5.2.2. CYP2D6 inhibition

This test was carried out in accordance with the method of Crespi et al.[15] Using a 96-well plate, 3-[2-(*N*,*N*-diethyl-*N*-methylamino)ethyl]-7-methoxy-4-methylcoumarin (1.5 μM), each test compound (from 0.031 to 50 μM), and the enzyme (5 nmol) were incubated at 37 °C for 20 min in 200 μL in total volume of 100 mM phosphate buffer (pH 7.4) containing 8.2 μM $NADP^+$, 0.41 mM glucose-6-phosphate, 0.41 mM $MgCl_2$ and 0.4 U/mL glucose-6-phosphate dehydrogenase. Thereafter, the reaction was stopped by adding 0.5 M 2-amino-2-hydroxymethyl-1,3-propanediol aqueous solution containing 80% acetonitrile, and the fluorescence intensity (excitation wavelength; 390 nM, fluorescence wavelength; 460 nM) was measured using a fluorescence plate reader. The inhibition ratio was calculated based on the following formula, and concentration of each test compound by which the inhibition ratio becomes 50% (IC_{50}) was obtained.

$$\text{The inhibition ratio } (\%) = 100 - (C_1 - B_1)/(C_0 - B_1) \times 100$$

C_1: Fluorescence intensity in the presence of test compound having known concentration, enzyme, and substrate.
C_0: Fluorescence intensity in the absence of test compound and in the presence of enzyme and substrate.
B_1: Fluorescence intensity of blank well.

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