Regular Article

Discovery of 3-Chloro-*N*-{(*S*)-[3-(1-ethyl-1*H*-pyrazol-4-yl)phenyl][(2*S*)-piperidine-2-yl]methyl}-4-(trifluoromethyl)pyridine-2-carboxamide as a Potent Glycine Transporter 1 Inhibitor

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A novel glycine transporter 1 (GlyT1) inhibitor was designed by the superposition of different chemotypes to enhance its inhibitory activity. Starting from 2-chloro-*N*-{(*S*)-phenyl[(2*S*)-piperidin-2-yl]methyl}-3-(trifluoromethyl)benzamide (2, SSR504734), the introduction of heteroaromatic rings enabled an increase in the GlyT1 inhibitory activity. Subsequent optimization led to the identification of 3-chloro-*N*-{(*S*)-[3-(1-ethyl-1*H*-pyrazol-4-yl)phenyl][(2*S*)-piperidine-2-yl]methyl}-4-(trifluoromethyl)pyridine-2-carboxamide (7w), which showed a powerful GlyT1 inhibitory activity (IC_{50}=1.8 nM), good plasma exposure and a plasma to brain penetration in rats that was sufficient to evaluate the compound's pharmacological properties. Compound 7w showed significant effects in several rodent models for schizophrenia without causing any undesirable central nervous system side effects.

Key words glycine transporter 1 inhibitor; ligand based drug design; schizophrenia; structure–activity relationship

N-Methyl-D-aspartate (NMDA) receptor hypofunction is thought to be involved in the pathophysiology of schizophrenia.[1,2] This NMDA hypofunction hypothesis is based on the observation that NMDA receptor antagonists mimic the positive, negative, and cognitive symptoms of schizophrenia.[3,4] Thus enhancing NMDA function may improve the symptoms of schizophrenia, but excess activation of the glutamate binding site is considered to induce neurotoxicity.[5] Elevating the levels of glycine, which is an important coagonist of the NMDA receptor, is an alternative approach. In fact, the co-administration of glycine or the glycine site agonist D-serine with atypical antipsychotics helps to improve schizophrenia.[6]

Levels of glycine are controlled by the glycine transporter, which consist of two subunits, glycine transporter 1 (GlyT1) and GlyT2. GlyT1 is widely expressed in forebrain areas such as cortex and hippocampus, where it might be co-localized with strychnine-insensitive glycine regulatory sites on NMDA receptors. In contrast, the expression of GlyT2 is limited to the brain stem, spinal cord, and cerebellum, and GlyT2 is known to be co-localized with strychnine-sensitive glycine receptors. Thus increasing NMDA receptor activity by inhibiting GlyT1 is an attractive drug discovery target for schizophrenia.[7,8]

Most effort has been focused on the development of GlyT1 inhibitors.[9] Early inhibitors were designed based on sarcosine (methylglycine) structure, a weak GlyT1 inhibitor, like **1**[10] (ALX-5407, Fig. 1). Reported sarcosine-based inhibitors have suffered from poor pharmacokinetics (PK) profiles, including low brain penetration. Thus, recent development has focused on non-sarcosine type inhibitors, and several structurally diverse inhibitors have been reported from many groups. *N*-[Phenyl(piperidin-2-yl)methyl]benzamide derivatives, represented by **2** (SSR504734), are one type of non-sarcosine type inhibitor.[11] The reported IC_{50} values of **2** were 18 and 15 nM in *in vitro* human and rat glycine uptake inhibitory assays. Merck's researchers have reported a sulfone based chemical class, represented by **3** (DCCCyB),[12] as well as sulfonamide class inhibitors, represented by **4**.[13–16] At present, many other chemical classes, such as **5** (PF-0346275)[17] and **6** (RG1678),[18] have been reported. Among them, **6** showed a significant improvement in the negative symptoms of patients with schizophrenia in phase 2 clinical trial.[19]

Recently, we reported the pharmacological profiles of **7w** (TP0439150), which showed a potent *in vitro* glycine uptake inhibitory activity in rats (IC_{50}=1.5 nM) and exhibited significant effects in a rodent model of negative symptoms and cognitive impairment associated with schizophrenia.[20] In the present article, we describe the medicinal chemistry efforts that resulted in the potent inhibitor **7w**.

To discover a novel GlyT1 inhibitor with a strong *in vitro* potency and *in vivo* efficacy at low doses, we selected a ligand based drug design (LBDD) approach using known GlyT1 inhibitors. Among the reported chemotypes, we focused on the *N*-[phenyl(piperidin-2-yl)methyl]benzamide derivatives represented by **2** (scaffold A, Fig. 2) and the sulfonamide derivatives represented by **4** (scaffold B, Fig. 2). Both of these chemotypes have a secondary benzamide with ortho substituent as a similar substructure, and we supposed that these two different chemotypes inhibit GlyT1 by binding at the same site and have similar pharmacophore.

Compound **4** (scaffold B) has been reported to have a potent GlyT1 inhibitory activity (IC_{50}=3 nM),[15] and we thought that the structurally characteristic SO_2 group likely played a key role as a hydrogen bond acceptor (HBA) in increasing potency. On the other hand, corresponding HBAs are absent

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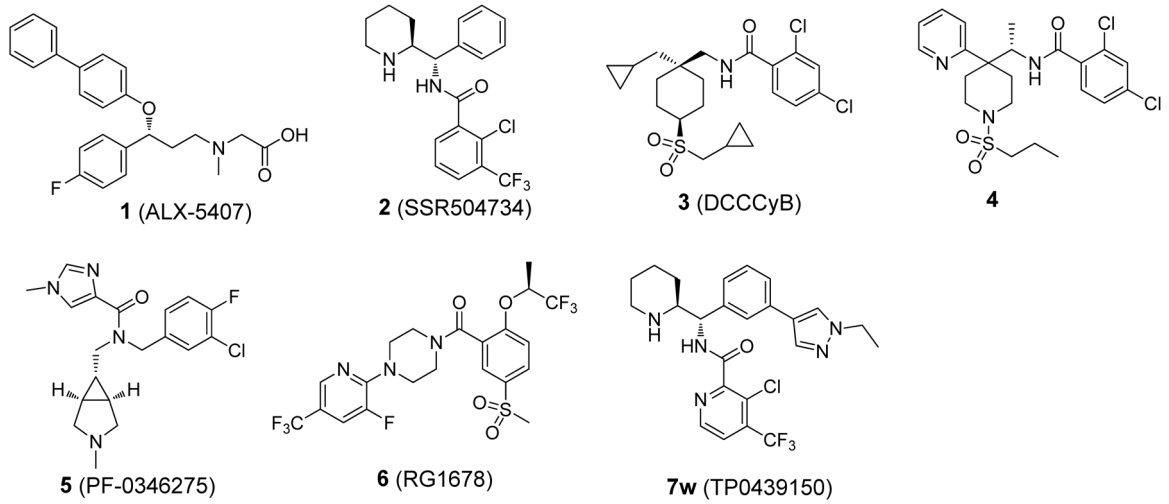


Fig. 1. Structures of GlyT1 Inhibitors

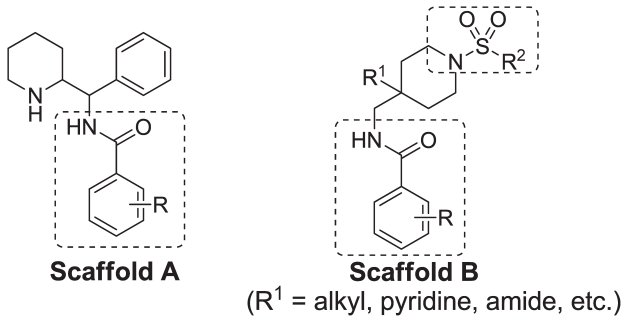


Fig. 2. Comparison of *N*-[Phenyl(piperidin-2-yl)]benzamide Derivative (Scaffold A) and Sulfonamide Derivative (Scaffold B)

in scaffold A; therefore, we presumed that the introduction of suitable HBAs to scaffold A would enhance the inhibitory activity. According to this hypothesis, the superposition of the two chemotypes was performed to explore suitable positions for introducing HBAs to scaffold A. Firstly, a pharmacophore model for scaffold B was generated from known sulfonamide derivatives described in the literature[13–16] by applying the "Common Feature Pharmacophore Generation" protocol in the BIOVIA Discovery Studio[21] (Fig. 3(a)). Secondly, compound **2**, which represents a typical compound of scaffold A, was superposed onto the obtained pharmacophore model (Fig. 3(b)). The result clearly showed that the characteristic HBAs of scaffold B were missing in scaffold A and were placed over the outer space of the phenyl or piperidine moiety of **2**.

Based on this model, we decided to introduce HBAs around the phenyl moiety of scaffold A in consideration of the synthetic accessibility (Fig. 3(c)). For the HBAs, heteroaromatic rings were selected because of their size and the ease at which the heteroatom positions can be adjusted.

Chemistry

The compounds described in this work were prepared as shown in Charts 1–5. All the final compounds were formed from a hydrochloric acid salt. Chart 1 describes the synthesis of the reference biphenyl derivatives **7a**, **b**, and intermediate **14c**. The reaction of Grignard reagent with Weinreb amide **8** prepared from (*S*)-pipecolinic acid provided ketone (**9a**–**c**), which was reduced diastereoselectively by L-Selectride to yield an alcohol (**10a**–**c**). After the exchange of the protective group from a *tert*-butoxycarbonyl (Boc) to an allyl group, the mesylation of the hydroxyl group and the subsequent reaction with ammonia provided a benzylamine intermediate (**13a**–**c**). In this amination step, the configuration of the benzylic position was retained, since the aziridine intermediate was firstly formed by the intramolecular reaction of an allyl amine moiety with a methansulfonyloxy group. Condensation with 2-chloro-3-(trifluoromethyl)benzoic acid provided **14a**–**c**, which was then converted to **7a** and **b** by the removal of an allyl group.

Intermediate **14c** was used for the introduction of heteroaromatic rings (Chart 2). The removal of a methyl group by boran tribromide and the subsequent triflation led to **16**. Then, the introduction of an Ar^l group by Suzuki coupling and the removal of an allyl group yielded **7f**, **h**, and **i**.

An alternative route is shown in Chart 3. Compounds **17a** and **b**, which were prepared in the same way as **9c**, were hydrogenated, followed by triflation to yield **18a** and **b**, respectively. Compounds **18a** and **b** were reduced by L-Selectride followed by coupling with the desired boronic acid or its pinacol ester to yield **20a**–**g**, which were converted to **21a**–**g** using the same way as that shown in Charts 1(c)–(e). Subsequent condensation with desired carboxylic acid and deprotection provided **7c**–**e** and **k**–**y**, respectively.

Compounds **7g** and **j** were prepared according to Chart 4. The coupling reaction of **19b** with bis(pinacolato)diboron provided **22**. A subsequent Suzuki-coupling reaction with aryl halide provided **23a** and **b**, which were converted to **7g** and **j** using the same method as that shown in Charts 1(c)–(g).

An improved synthetic route for **7w** is shown in Chart 5. In this scheme, we aimed to reduce the number of synthetic steps. Mono lithiation of 1,3-dibromobenzene and a subsequent reaction with Weinreb amide **8** provided ketone **25**, which was converted to hydroxyimine **26** (mixture of *cis* and *trans* isomers) by reaction with hydroxylamine hydrochloride under reflux condition in ethanol. The Boc group was removed in this step; thus, re-protecion was needed. A Suzuki coupling reaction of *N*-hydroxyimine **26** using [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)-palladium(II) dichloride (PEPPSI-IPR) as a palladium catalyst yielded **27**,[22] which was reduced diastereoselectively by cata-

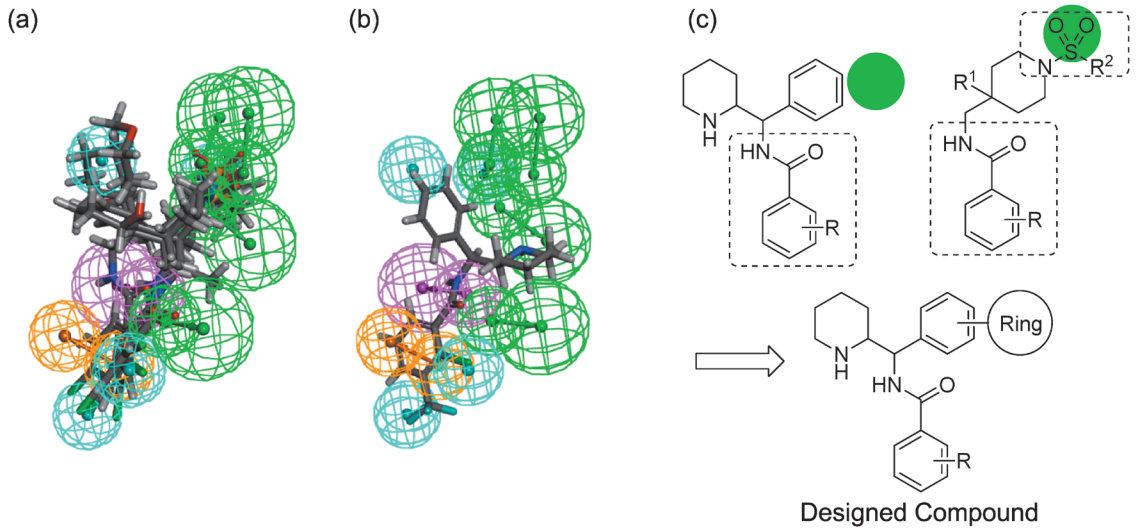
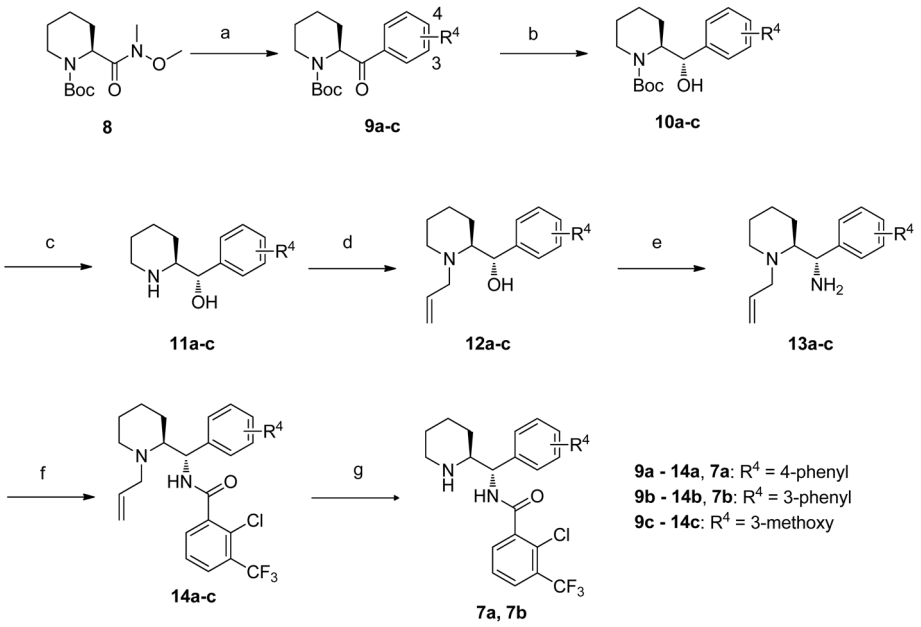


Fig. 3. (a) A Pharmacophore Model of Sulfonamide Derivatives; (b) Superposition of **2** on the Pharmacophore Model; (c) Schematic Representation of Compounds of the Scaffold A and B, and the Designed Compounds in This Study

The green arrow and the associated spheres show a hydrogen bond acceptor, the purple ones show a hydrogen bond donor, the blue sphere shows a hydrophobic site, and the orange arrow and the spheres show an aromatic ring.



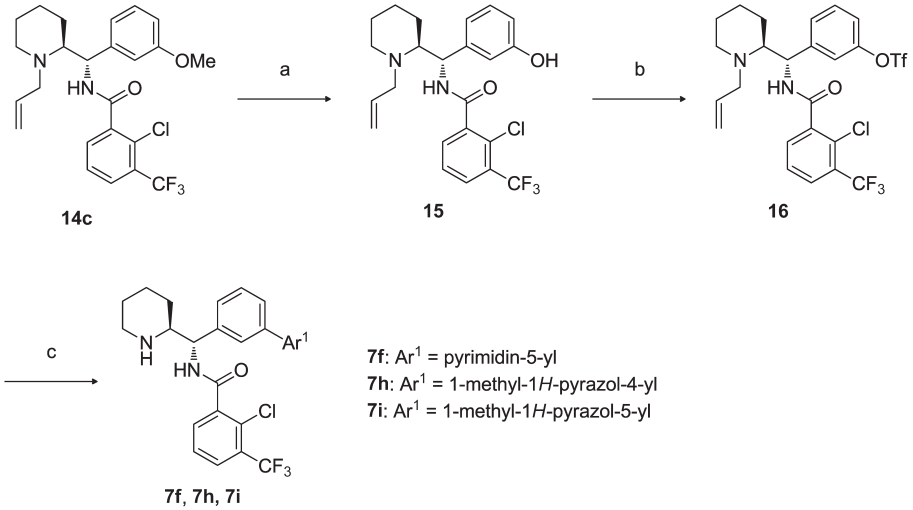
Reagents and conditions: (a) 4-Biphenylmagnesium bromide (for **9a**) or 3-biphenylmagnesium bromide (for **9b**) or 3-methoxyphenylmagnesium bromide (for **9c**), THF, 0°C; (b) L-Selectride, THF, −78°C; (c) KOH, MeOH, H_2O, reflux; (d) allyl bromide, K_2CO_3, DMF, 80°C; (e) (1) MsCl, Et_3N, $CHCl_3$; (2) ammonia, MeOH; (f) 2-Cl–3-CF_3-benzoic acid, HOBt–H_2O, WSC–HCl, DMF; (g) $Pd(PPh_3)_4$, 1,3-dimethylbarbituric acid, $CHCl_3$.

Chart 1

lytic hydrogenation in a methanol solvent containing ammonia to yield amine **28**. Racemization was not observed in any of steps. Subsequent condensation and deprotection yielded **7w**. In this matter, **7w** was prepared from Weinreb amide **8** in seven steps, compared with the eleven steps that were required in Chart 4.

Results and Discussion

Introduction of Heteroaromatic Rings to Improve Activity The glycine uptake inhibitory activity was evaluated according to reported methods utilizing glioma T98G cells expressing human GlyT1.[23] The investigation of optimal Ar^1 groups is described in Table 1. As a reference, we introduced phenyl group with the same size as the heteroaromatic rings that we intended to introduce. The biphenyl derivatives **7a** and **b** showed reduced inhibitory activities (**7a**: IC_{50}=0.42 μM, **7b**: 0.52 μM), compared with the literature value for **2**, suggesting that the introduction of bulkiness without HBA at this position had a negative effect on the activity. According to our initial synthetic plan, several heteroaromatic rings were introduced. The introduction of a 3-pyridine group to the *para* and *meta* positions led to increased activities (**7c**: 0.037 μM, **7d**: 0.014 μM), compared with those of the biphenyl derivatives. For the 5-pyrimidine derivatives, a *meta*-substituted derivative had a higher activity (**7f**: 0.0063 μM) than the corresponding 3-pyridine derivative **7d** and the literature value for **2**



Reagents and conditions: (a) BBr_3, $CHCl_3$; (b) Tf_2O, pyridine, $CHCl_3$; (c) (1) $Ar^1B(OH)_2$ or pinacolester, $Pd(PPh_3)_4$, K_2CO_3, DMF, EtOH, 80°C; (2) $Pd(PPh_3)_4$, 1,3-dimethylbarbituric acid, $CHCl_3$.

Chart 2

(0.018 μM), while the *para*-substitution led to a reduced activity (**7e**: 0.093 μM). We thought that the increased activity of **7f** was obtained through the introduction of a suitable HBA, as per our initial hypothesis.

A comparison between *para*-substituted derivatives (**7c**, **e**) and *meta*-substituted derivatives (**7d**, **f**) suggested that the *meta*-position was suitable for modification. Since the 5-pyrimidine derivative **7f** had a higher activity than the 3-pyridine derivative **7d**, we further explored rings that included two nitrogen atoms. The introduction of pyrazine resulted in an intermediate activity between that of 3-pyridine **7d** and that of 5-pyrimidine **7f**, while the 1-methylpyrazol-4-yl derivative **7h** had a greater inhibitory activity (**7h**: 0.0025 μM). The introduction of the 1-methylpyrazol-5-yl group as a regioisomer of the pyrazole derivative **7h** proved to decrease the activity by more than 10 times (**7i**: 0.042 μM). The 1-methylimidazol-5-yl derivative **7j**, which was a nitrogen atom transferred analog of **7i**, had a better IC_{50} value (**7j**: 0.0036 μM) than that of **7i** and was equal or slightly inferior to that of **7h**. Based on these modifications of the Ar^1 moiety, the two nitrogen atoms of the 1-methylpyrazol-4-yl group were thought to be suitable for interaction with GlyT1.

Modification of Substituents on Benzamide and Pyrazole Moieties The influence of substituents on the benzamide moiety of scaffold A has not been reported until now. The results of modification of the benzamide moiety (Ar^2) of **7h** are shown in Table 2. We synthesized the 2,4-dichlorobenzamide derivative **7k**, the substituents of which were often used in the derivatization of scaffold B; however, only weak inhibitory activity was observed (Table 2, **7k**: 0.20 μM). We thought that the suitable substituents might differ depending on the scaffold, and further structure–activity relationships were studied to confirm the optimum substituents on Ar^2.

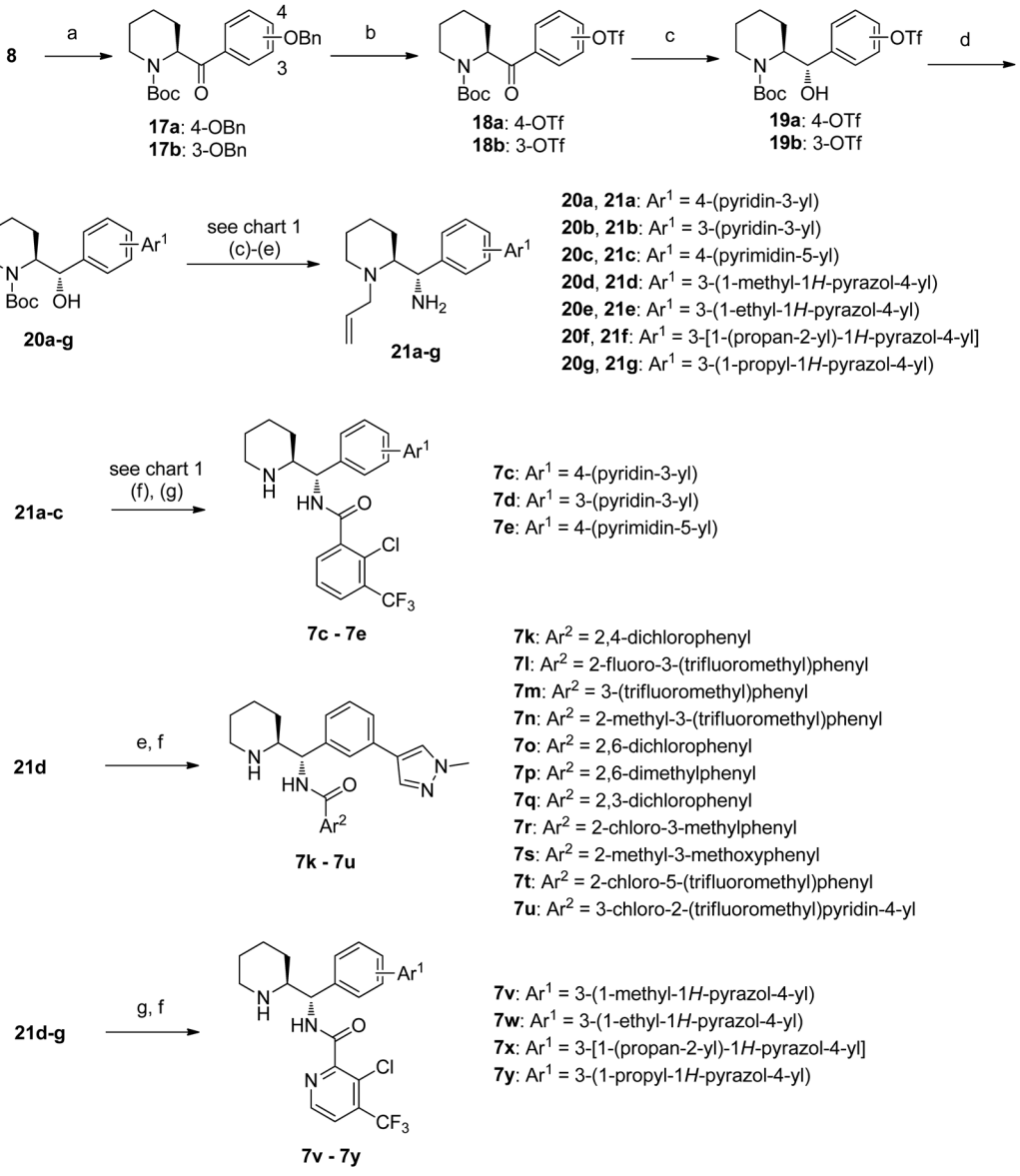
The replacement of a chlorine atom of **7h** with a fluorine atom led to a decrease in activity (**7l**: 0.068 μM), as did the removal of 2-chlorine atom (**7m**: 0.22 μM). Replacement with a methyl group also produced a 5-fold decrease in activity (**7n**: 0.012 μM), compared with the chlorine substituent. These results indicated that substituents at the *ortho*-position had a considerable effect on the GlyT1 inhibitory activity. To increase the potency, we examined 2,6-disubstitution, but both the dichloro derivative **7o** and the dimethyl derivative **7p** showed moderate activities (**7o**: 0.021 μM, **7p**: 0.042 μM). We thought that these reductions in activity were caused by the removal of the *meta*-substituent.

The replacement of the trifluoromethyl group of **7h** with chlorine, methyl, or a methoxy group each reduced the activity; in particular, the methoxy group had a detrimental effect on the activity (**7s**: 0.21 μM). We considered that electron-withdrawing substituents at the *meta*-position might be important for potent inhibitory activity. The 2-chloro-5-(trifluoromethyl)-benzamide derivative **7t** also exhibited a reduced activity (**7t**: 0.0097 μM). A comparison of **7k**, **o**, and **q** suggested that 2,3-disubstitution was the best pattern for higher activity.

Pyridinecarboxamide derivatives were also examined in an attempt to reduce the lipophilicity of **7h** (**7h**: $C\log P$=4.56).[24] The 3-chloro-2-(trifluoromethyl)pyridine-4-carboxamide derivative **7u** ($C\log P$=3.52) and the 3-chloro-4-(trifluoromethyl)-pyridine-2-carboxamide derivative **7v** ($C\log P$=3.87) were synthesized, and both analogs showed favorable inhibitory activities (**7u**: 0.0049 μM, **7v**: 0.0015 μM). In particular, the 2-pyridine derivative **7v** showed an equipotent or slightly higher activity than **7h**.

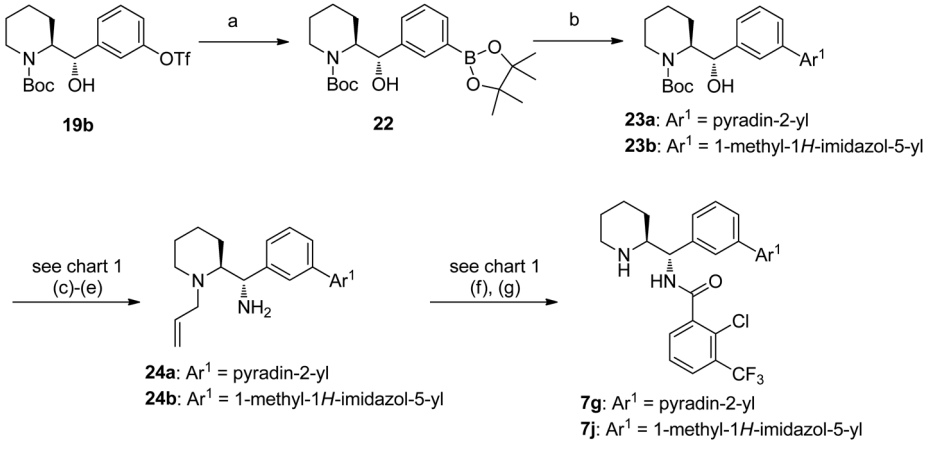
Regarding drug-likeness properties, the reduction in lipophilicity provided an opportunity for another derivatization. As shown in Table 3, the elongation of the alkyl group on the pyrazole moiety was investigated as a final fine tuning. The ethyl pyrazole derivative **7w** showed almost the same inhibitory activity (**7w**: 0.0018 μM), although isopropyl and normal-propyl substitution showed slightly reduced activities (**7x**: 0.0024 μM, **7y**: 0.0039 μM). These results indicated that the modification of the alkyl substituent of the pyrazole moiety was unlikely to increase the activity.

Results of Metabolism, Pharmacokinetics, and Pharmacological Studies Among the synthetic derivatives, we selected the most potent compounds **7v** and **w** for further evaluation. Both compounds had low metabolism rates in human liver microsomes (**7v**: 13.8%, **7w**: 16.4%),[25] and did not significantly inhibit the major CYP450 enzymes (3A4, 2D6, 2C9, 2C19, 1A2) at a concentration of 10 μM. As shown



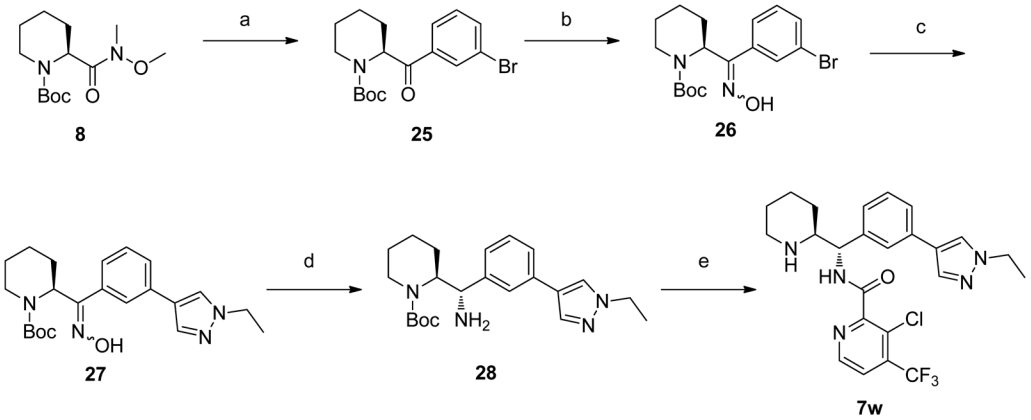
Reagents and conditions: (a) 4-Benzyloxyphenylmagnesium bromide or 3-benzyloxyphenylmagnesium bromide, THF, 0°C; (b) (1) H_2, Pd–C, EtOH; (2) Tf_2O, pyridine, $CHCl_3$, 0°C; (c) L-Selectride, THF, −78°C; (d) $Ar^1B(OH)_2$ or pinacol ester, $Pd(PPh_3)_4$, K_2CO_3, DMF, EtOH, 80°C; (e) Ar^2–CO_2H, HOBt–H_2O, WSC–HCl, DMF; (f) $Pd(PPh_3)_4$, 1,3-dimethylbarbituric acid, $CHCl_3$; (g) 3-chloro-4-(trifluoromethyl)pyridine-2-carboxylic acid, HOBt–H_2O, WSC–HCl, DMF.

Chart 3



Reagents and conditions: (a) Bis(pinacolato)diboron, $Pd(dppf)Cl_2$, dppf, KOAc, DMSO, 80°C; (b) Ar^1–Cl, $Pd(PPh_3)_4$, K_2CO_3, DMF, EtOH, 80°C.

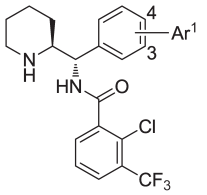
Chart 4

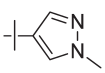
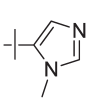


Reagents and conditions: (a) 1,3-Dibromobenzene, *n*-BuLi, THF, −78°C; (b) (1) NH_2OH–HCl, EtOH, reflux; (2) Boc_2O, $CHCl_3$; (c) 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole, PEPPSI–IPR, K_2CO_3, toluene, EtOH, H_2O, 110°C; (d) H_2, Pd–C, NH_3/MeOH; (e) (1) 3-chloro-4-(trifluoromethyl)pyridine-2-carboxylic acid, WSC–HCl, HOBt–H_2O, DMF; (2) HCl, EtOAc.

Chart 5

Table 1. *In Vitro* GlyT1 Inhibitory Activity of Compounds **7a–j**



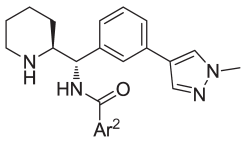
Compound	Position	Ar^1	hGlyT1 IC_{50} (μM)
2 (SSR504734)	—	—	0.018
7a	4		0.42
7b	3		0.52
7c	4		0.037
7d	3		0.014
7e	4		0.093
7f	3		0.0063
7g	3		0.010
7h	3		0.0025
7i	3		0.042
7j	3		0.0036

in Table 4, both compounds showed acceptable plasma exposure and brain/plasma concentration ratios after oral administration in rats. Since the pharmacokinetics properties of **7w** were more favorable, we selected **7w** for further *in vivo* evaluation studies. The detailed pharmacological properties of **7w** have already been reported.[20] Compound **7w** significantly improved MK-801-impaired cognition in social recognition tests performed in rats at a dose of 0.1 mg/kg orally and also significantly reversed the phencyclidine-induced reduction in the social interaction of paired mice at a dose of 0.3 mg/kg orally. These studies may reflect the cognitive dysfunction and negative symptom of schizophrenia, respectively. Moreover, compound **7w** did not affect spontaneous locomotor activity or rotarod performance when administered 10 mg/kg orally. These results suggest that **7w** may be useful for the treatment of cognitive dysfunction and the negative symptom associated with schizophrenia without any undesirable side effects in patients.

Conclusion

In this article, we have described the identification and efficient synthetic route of **7w**, which showed a potent GlyT1 uptake inhibitory activity. To create a novel GlyT1 inhibitor with a strong *in vitro* potency and an *in vivo* efficacy when administered at low doses, we selected a ligand based drug design (LBDD) approach using known GlyT1 inhibitors. We added HBAs to **2** as a novel interactive structure, which was designed by superposition with different known chemotype like sulfonamide-based GlyT1 inhibitors. After reviewing several heteroaromatic rings as HBA, the introduction of a 1-methylpyrazol-4-yl group led to an increased inhibitory activity. Through optimization of the benzamide and pyrazole moieties, we successfully achieved **7w**. Compound **7w** exhibited an inhibitory activity that was about 10 times higher than the reference value of **2** and showed good plasma exposure and a plasma-to-brain penetration sufficient to evaluate its pharmacological properties. The results of *in vivo* pharmacological evaluations showed significant effects in several rodent models for schizophrenia, suggesting that **7w** may be useful for the treatment of cognitive dysfunction and the negative symptoms associated with schizophrenia without causing any

Table 2. *In Vitro* GlyT1 Inhibitory Activity of Compounds **7h** and **k–v**



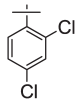
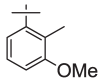
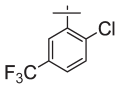
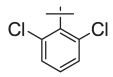
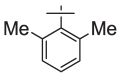
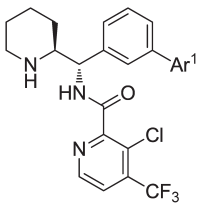
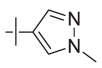
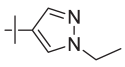
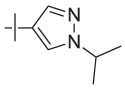
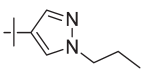
Compound	Ar^2	hGlyT1IC$_{50}$ (μM)	Compound	Ar^2	hGlyT1IC$_{50}$ (μM)
7h		0.0025	**7q**		0.025
7k		0.20	**7r**		0.036
7l		0.068	**7s**		0.21
7m		0.22	**7t**		0.0097
7n		0.012	**7u**		0.0049
7o		0.021	**7v**		0.0015
7p		0.042			

Table 3. *In Vitro* GlyT1 Inhibitory Activity of Compounds **7v–y**



Compound	Ar^1	hGlyT1 IC$_{50}$ (μM)	*C*log*P*
7v		0.0015	3.87
7w		0.0018	4.40
7x		0.0024	4.71
7y		0.0039	4.93

undesirable side effects.

Experimental

^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM-ECA600, JEOL JNM-ECA500, Varian UNITYNOVA300, or Varian GEMINI2000/200, and the chemical shifts were expressed in δ (ppm) values with trimethylsilane as an internal reference (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad peak). Mass spectra (MS) were recorded on a micromass Platform LC or Shimadzu LCMS-2010EV. High resolution (HR) mass spectral data were acquired using a Shimadzu LCMS-IT-TOF equipped with an electrospray ionization (ESI)/atmospheric pressure chemical ionization (APCI) dual ion source. The purities of the final compounds were confirmed using LC-MS on an Agilent instrument with electrospray ionization. The LC-MS conditions were as follows: Agilent 1290 infinity and Agilent 6150; column Waters Acquity CSH C18, 1.7 μm, 2.1×50 mm; eluent A, water+0.1% formic acid; eluent B, acetonitrile+0.1% formic acid; 20–99% B for 1.2 min, 99% B for 0.2 min; flow rate 0.8 mL/min; UV detection, λ=254 nm. Optical rotations were measured on a Rudolph Research Analytical AUTOPOL V.

Table 4. Pharmacokinetics Profiles of **7v** and **w** after Oral Administration in Rats

Compound	**7v**	**7w**
Dose (mg/kg)	10	10
T_{max} (h)	3.0±1.73	4.0±0.0
C_{max} (ng/mL)	49.3±12.4	117±15.4
B/P ratio	0.69 (4 h)	0.52 (4 h)
AUC (ng·h/mL)	235±53.7	661±42.2

Each value represents the mean±S.D. of three animals.

***tert*-Butyl (2*S*)-2-(3-Methoxybenzoyl)piperidine-1-carboxylate (9c)** Under a nitrogen gas atmosphere, 3-bromoanisole (35 mL, 277 mmol) was added dropwise to a mixture of magnesium (7.1 g, 292 mmol) and a catalytic amount of iodine in tetrahydrofuran (THF) (270 mL), and the mixture was stirred for 2 h. This reaction solution was added dropwise to a solution of *tert*-butyl (2*S*)-2-{[methoxy(methyl)amino]-carbonyl}piperidine-1-carboxylate (**8**, 50.0 g, 184 mmol) in THF (300 mL) under ice cooling, and the mixture was stirred at room temperature for 2 h. Ten percent aqueous NH_4Cl solution was added, followed by extraction with EtOAc. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified using silica gel column chromatography (11% EtOAc in hexane) to yield **9c** (32.7 g, 56%) as a pale yellow oil. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.29–1.53 (m, 11H), 1.53–1.88 (m, 3H), 1.99–2.22 (m, 1H), 3.07–3.29 (m, 1H), 3.85 (s, 3H), 3.88–4.05 (m, 1H), 5.41–5.69 (m, 1H), 7.05–7.15 (m, 1H), 7.30–7.57 (m, 3H); MS (ESI): *m*/*z* 342 $[M+Na]^+$.

***tert*-Butyl (2*S*)-2-([1,1′-Biphenyl]-4-carbonyl)piperidine-1-carboxylate (9a)** Compound **9a** (55%) was obtained in a manner similar to that described for **9c**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.37–1.52 (m, 12H), 1.59–1.74 (m, 1H), 1.77–1.95 (m, 1H), 2.06–2.22 (m, 1H), 3.11–3.29 (m, 1H), 3.88–4.05 (m, 1H), 5.47–5.78 (m, 1H), 7.35–7.49 (m, 3H), 7.62 (br d, *J*=7.4 Hz, 2H), 7.64–7.71 (m, 2H), 7.94–8.05 (m, 2H); MS (ESI): *m*/*z* 266 $[M-Boc+H]^+$.

***tert*-Butyl (2*S*)-2-([1,1′-Biphenyl]-3-carbonyl)piperidine-1-carboxylate (9b)** Compound **9b** (55%) was obtained in a manner similar to that described for **9c**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.33–1.51 (m, 11H), 1.57–1.73 (m, 2H), 1.76–1.89 (m, 1H), 2.04–2.22 (m, 1H), 3.08–3.25 (m, 1H), 3.87–4.05 (m, 1H), 5.49–5.78 (m, 1H), 7.34–7.41 (m, 1H), 7.42–7.56 (m, 3H), 7.61 (br d, *J*=7.4 Hz, 2H), 7.78 (br d, *J*=7.4 Hz, 1H), 7.82–7.96 (m, 1H), 8.06–8.20 (m, 1H); MS (ESI): *m*/*z* 266 $[M-Boc+H]^+$.

***tert*-Butyl (2*S*)-{(*S*)-Hydroxy(3-methoxyphenyl)methyl}-piperidine-1-carboxylate (10c)** Under a nitrogen gas atmosphere, lithium tri-*sec*-butylborohydride (L-Selectride, 1 mol/L solution in THF, 200 mL, 200 mmol) was added dropwise to a solution of **9c** (32.7 g, 103 mmol) in THF (300 mL) cooled with a dryice–acetone bath, and the mixture was stirred for 3 h. The reaction was quenched with 15% aqueous H_2O_2 solution (200 mL) and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was suspended in 10% EtOAc in hexane, and the precipitate was filtered to yield **10c** (22.0 g, 67%) as a colorless powder. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.26–1.34 (m, 1H), 1.35–1.75 (m, 5H), 1.51 (s, 9H), 2.84–3.15 (m, 1H), 3.82 (s, 3H), 3.95–4.46 (m, 2H), 4.83–4.88 (m, 1H), 6.81–6.87 (m, 1H), 6.90–7.00 (m, 2H), 7.22–7.31 (m, 1H); MS (ESI): *m*/*z* 344 $[M+Na]^+$.

***tert*-Butyl (2*S*)-2-[(*S*)-([1,1′-Biphenyl]-4-yl)(hydroxy)methyl]piperidine-1-carboxylate (10a)** Compound **10a** (96%) was obtained in a manner similar to that described for **10c**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.32–1.38 (m, 1H), 1.38–1.65 (m, 4H), 1.52 (s, 9H), 1.66–1.74 (m, 1H), 2.89–3.17 (m, 1H), 3.98–4.55 (m, 2H), 4.93 (d, *J*=10.5 Hz, 1H), 7.32–7.37 (m, 1H), 7.40–7.49 (m, 4H), 7.54–7.64 (m, 4H); MS (ESI): *m*/*z* 390 $[M+Na]^+$.

***tert*-Butyl (2*S*)-2-[(*S*)-([1,1′-Biphenyl]-3-yl)(hydroxy)methyl]piperidine-1-carboxylate (10b)** Compound **10b** (81%) was obtained in a manner similar to that described for **10c**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.30–1.37 (m, 1H), 1.37–1.65 (m, 4H), 1.52 (s, 9H), 1.65–1.74 (m, 1H), 2.87–3.18 (m, 1H), 3.97–4.54 (m, 2H), 4.95 (d, *J*=10.1 Hz, 1H), 7.31–7.40 (m, 2H), 7.39–7.49 (m, 3H), 7.50–7.65 (m, 4H); MS (ESI): *m*/*z* 368 $[M+H]^+$.

(*S*)-{(2*S*)-1-Allylpiperidin-2-yl}(3-methoxyphenyl)methanol (12c) KOH (39.2 g, 699 mmol) in water (350 mL) was added to a solution of **10c** (28.1 g, 87.4 mmol) in MeOH (400 mL), and the mixture was stirred under reflux condition for 16 h. The organic solvent was distilled off, followed by extraction with $CHCl_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was suspended in 5% EtOAc in hexane, and precipitate was filtered to yield **11c** (19.0 g, 98%) as a colorless powder. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.20–1.32 (m, 2H), 1.34–1.44 (m, 2H), 1.54–1.61 (m, 1H), 1.73–1.79 (m, 1H), 2.56–2.63 (m, 1H), 2.63–2.68 (m, 1H), 3.06–3.11 (m, 1H), 3.82 (s, 3H), 4.37 (d, *J*=6.9 Hz, 1H), 6.79–6.85 (m, 1H), 6.88–6.94 (m, 2H), 7.23–7.28 (m, 1H); MS (ESI): *m*/*z* 222 $[M+H]^+$.

K_2CO_3 (15.9 g, 116 mmol) and allyl bromide (7.3 mL, 84.4 mmol) were added to a solution of **11c** (17.0 g, 76.8 mmol) in *N*,*N*-dimethylformamide (DMF) (200 mL), and the mixture was stirred at 50°C for 2 h. The reaction mixture was partitioned between water and EtOAc, and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified using NH-silica gel column chromatography (5% EtOAc in hexane) to yield **12c** (16.8 g, 84%) as a colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.12–1.77 (m, 6H), 2.56–2.81 (m, 2H), 2.93–3.11 (m, 1H), 3.27–3.51 (m, 2H), 3.81 (s, 3H), 4.72 (d, *J*=9.7 Hz, 1H), 5.11–5.26 (m, 2H), 5.76–5.99 (m, 1H), 6.76–6.85 (m, 1H), 6.89–6.97 (m, 2H), 7.18–7.28 (m, 1H); MS (ESI): *m*/*z* 262 $[M+H]^+$.

(*S*)-([1,1′-Biphenyl]-4-yl)[(2*S*)-1-(prop-2-en-1-yl)piperidin-2-yl]methanol (12a) Compound **12a** (33% in 2 steps) was obtained in a manner similar to that described for **12c**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.20–1.31 (m, 1H), 1.32–1.40 (m, 1H), 1.49–1.66 (m, 3H), 1.68–1.78 (m, 1H), 2.64–2.74 (m, 1H), 2.74–2.81 (m, 1H), 3.00–3.12 (m, 1H), 3.34–3.41 (m, 1H), 3.43–3.51 (m, 1H), 4.80 (br d, *J*=9.9 Hz, 1H), 5.15–5.26 (m, 2H), 5.90 (ddt, *J*=17.0, 10.4, 6.3, 6.3 Hz, 1H), 7.30–7.36 (m, 1H), 7.40–7.45 (m, 4H), 7.54–7.61 (m, 4H); MS (ESI): *m*/*z* 308 $[M+H]^+$.

(*S*)-([1,1′-Biphenyl]-3-yl)[(2*S*)-1-(prop-2-en-1-yl)piperidin-2-yl]methanol (12b) Compound **12b** (44% in 2 steps) was obtained in a manner similar to that described for **12c**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.21–1.29 (m, 1H), 1.32–1.40 (m, 1H), 1.48–1.66 (m, 3H), 1.68–1.77 (m, 1H), 2.66–2.73 (m, 1H), 2.73–2.80 (m, 1H), 3.01–3.11 (m, 1H), 3.37 (br dd, *J*=13.6, 6.6 Hz, 1H), 3.43–3.51 (m, 1H), 4.82 (d, *J*=9.9 Hz, 1H), 5.15–5.25 (m, 2H), 5.84–5.94 (m, 1H), 7.32–7.37 (m, 2H), 7.38–7.47 (m, 3H), 7.47–7.53 (m, 1H), 7.57–7.62 (m, 3H); MS (ESI): *m*/*z* 308 $[M+H]^+$.

(*S*)-1-{(2*S*)-1-Allylpiperidin-2-yl}-1-(3-methoxyphenyl)-methanamine (13c) Methanesulfonyl chloride (6.9 mL, 89.1 mmol) was added to an ice-cooled solution of **12c** (16.6 g, 63.5 mmol) and triethylamine (15 mL, 108 mmol) in $CHCl_3$ (160 mL), and the mixture was stirred under cooling for 1.5 h and at room temperature for an additional 1 h. The reaction mixture was concentrated *in vacuo* and the residue was dis-

solved in 8 mol/L NH_3 solution in MeOH (150 mL). After stirring at 40°C for 1 h, the reaction mixture was concentrated *in vacuo*. The residue was purified using silica gel column chromatography ($CHCl_3$–MeOH–28% NH_3 in water=50 : 1 : 0.5) to yield **13c** (12.9 g, 78%) as a yellow oil. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.01–1.07 (m, 1H), 1.29–1.54 (m, 4H), 1.59–1.69 (m, 1H), 2.62–2.71 (m, 2H), 3.01–3.08 (m, 1H), 3.32–3.42 (m, 2H), 3.81 (s, 3H), 4.17 (d, J=9.6 Hz, 1H), 5.10–5.15 (m, 1H), 5.18–5.24 (m, 1H), 5.84–5.93 (m, 1H), 6.76–6.80 (m, 1H), 6.91–6.96 (m, 2H), 7.19–7.25 (m, 1H); MS (ESI): m/z 261 $[M+H]^+$.

(*S*)-1-([1,1′-Biphenyl]-4-yl)-1-[(2*S*)-1-(prop-2-en-1-yl)piperidin-2-yl]methanamine (13a) Compound **13a** (83% in 2 steps) was obtained in a manner similar to that described for **13c**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.04–1.16 (m, 1H), 1.28–1.57 (m, 4H), 1.60–1.71 (m, 1H), 2.66–2.73 (m, 2H), 3.07 (ddd, J=13.8, 9.9, 3.4 Hz, 1H), 3.35–3.43 (m, 2H), 4.25 (d, J=9.6 Hz, 1H), 5.09–5.26 (m, 2H), 5.87–5.96 (m, 1H), 7.29–7.35 (m, 1H), 7.39–7.47 (m, 4H), 7.52–7.62 (m, 4 H); MS (ESI): m/z 307 $[M+H]^+$.

(*S*)-1-([1,1′-Biphenyl]-3-yl)-1-[(2*S*)-1-(prop-2-en-1-yl)piperidin-2-yl]methanamine (13b) Compound **13b** (74% in 2 steps) was obtained in a manner similar to that described for **13c**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.02–1.12 (m, 1H), 1.29–1.46 (m, 3H), 1.46–1.56 (m, 1H), 1.60–1.74 (m, 1H), 2.66–2.75 (m, 2H), 3.02–3.10 (m, 1H), 3.33–3.45 (m, 2H), 4.27 (d, J=9.6 Hz, 1H), 5.09–5.27 (m, 2H), 5.86–5.95 (m, 1H), 7.28–7.52 (m, 6H), 7.54–7.66 (m, 3H); MS (ESI): m/z 307 $[M+H]^+$.

***N*-[(*S*)-{(2*S*)-1-Allylpiperidin-2-yl}(3-methoxyphenyl)methyl]-2-chloro-3-(trifluoromethyl)benzamide (14c)** 1-Hydroxybenzotriazole monohydrate (2.18 g, 16.1 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.54 g, 13.2 mmol) were added to a solution of 2-chloro-3-(trifluoromethyl)benzoic acid (2.58 g, 11.5 mmol) in DMF (15 mL), and the mixture was stirred for 30 min. A solution of **13c** (3.00 g, 11.5 mmol) was added to the reaction mixture, and the mixture was stirred for 3 h. The reaction was quenched with saturated $NaHCO_3$ aqueous solution and extracted with EtOAc. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified using silica gel column chromatography (2% MeOH in $CHCl_3$) to yield **14c** (3.42 g, 64%) as a colorless powder. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.25–1.88 (m, 6H), 2.45–2.64 (m, 1H), 2.75–3.03 (m, 2H), 3.10–3.38 (m, 2H), 3.81 (s, 3H), 4.88–4.98 (m, 1H), 5.02–5.17 (m, 2H), 5.61–5.83 (m, 1H), 6.75–6.84 (m, 1H), 6.90–7.01 (m, 2H), 7.19–7.32 (m, 1H), 7.36–7.48 (m, 1H), 7.64–7.81 (m, 3H); MS (ESI): m/z 467 $[M+H]^+$.

***N*-{(*S*)-([1,1′-Biphenyl]-4-yl)[(2*S*)-1-(prop-2-en-1-yl)-piperidin-2-yl]methyl}-2-chloro-3-(trifluoromethyl)benzamide (14a)** Compound **14a** (67%) was obtained in a manner similar to that described for **14c**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.35–1.62 (m, 5H), 1.77–1.90 (m, 1H), 2.54–2.62 (m, 1H), 2.85–2.91 (m, 1H), 2.94–3.01 (m, 1H), 3.21–3.27 (m, 1H), 3.33 (br dd, J=13.8, 6.4 Hz, 1 H), 4.97–5.04 (m, 1H), 5.08–5.18 (m, 2H), 5.70–5.80 (m, 1H), 7.26 (s, 1H), 7.31–7.36 (m, 1H), 7.41–7.49 (m, 5H), 7.56–7.61 (m, 4H), 7.71–7.79 (m, 2H); MS (ESI): m/z 513 $[M+H]^+$.

***N*-{(*S*)-([1,1′-Biphenyl]-3-yl)[(2*S*)-1-(prop-2-en-1-yl)piperidin-2-yl]methyl}-2-chloro-3-(trifluoromethyl)benzamide (14b)** Compound **14b** (84%) was obtained in a manner similar to that described for **14c**. ^{1}H-NMR (600 MHz, dimethyl sulfoxide (DMSO)-d_6) δ: 1.08–1.14 (m, 1H), 1.27–1.45 (m, 4H), 1.66–1.72 (m, 1H), 1.99 (s, 1H), 2.45–2.49 (m, 1H), 2.73 (s, 1H), 2.90–2.95 (m, 1H), 2.96–3.01 (m, 1H), 3.34–3.41 (m, 1H), 3.46 (br dd, J=14.2, 6.4 Hz, 1H), 5.11–5.15 (m, 1H), 5.21–5.26 (m, 1H), 5.43–5.48 (m, 1H), 5.88 (ddt, J=17.0, 10.4, 6.2, 6.2 Hz, 1H), 7.35–7.40 (m, 1H), 7.42–7.51 (m, 4H), 7.53–7.61 (m, 1H), 7.62–7.69 (m, 4H), 7.76–7.79 (m, 1H), 7.93 (dd, J=7.1, 2.5 Hz, 1H), 9.04–9.10 (m, 1H); MS (ESI): m/z 513 $[M+H]^+$.

***N*-{(*S*)-([1,1′-Biphenyl]-4-yl)[(2*S*)-piperidin-2-yl]-methyl}-2-chloro-3-(trifluoromethyl)benzamide Hydrochloride (7a)** 1,3-Dimethylbarbituric acid (299 mg, 1.9 mmol) and tetrakis(triphenylphosphine)palladium(0) (7.4 mg, 0.0064 mmol) were added to a solution of **14a** (328 mg, 0.64 mmol) in $CHCl_3$ (5 mL), and the mixture was stirred for 2 h. The reaction mixture was partitioned between $CHCl_3$ and saturated $NaHCO_3$ aqueous solution, and the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified using silica gel column chromatography (2% MeOH in $CHCl_3$) to yield the free form of **7a** (212 mg). 4 mol/L HCl in EtOAc solution (0.2 mL) was added to a solution of the free form of **7a** in EtOAc (1 mL), and the precipitate was filtered to yield **7a** (202 mg, 62%) as a colorless powder. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 1.35–1.51 (m, 3H), 1.56–1.67 (m, 1H), 1.68–1.78 (m, 2H), 2.79–2.92 (m, 1H), 3.27–3.41 (m, 1H), 3.50–3.60 (m, 1H), 5.20–5.26 (m, 1H), 7.35–7.41 (m, 1H), 7.45–7.57 (m, 4H), 7.65–7.76 (m, 5H), 7.93–8.05 (m, 2H), 8.73–8.85 (m, 1H), 8.99–9.16 (m, 1H), 9.63 (d, J=8.7 Hz, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 165.3, 139.8, 139.5, 138.7, 137.0, 133.4, 129.0, 128.7, 128.4, 128.0, 127.7, 127.6, 127.2 (q, J=31 Hz), 126.9, 126.7, 122.7 (q, J=273 Hz), 58.2, 55.6, 44.8, 25.8, 21.6, 21.4; HR-MS: Calcd for $C_{26}H_{24}ClF_3N_2O$ $[M+H]^+$ 473.1602. Found 473.1590; $[\alpha]_D$=+72 (c=0.50, MeOH).

***N*-{(*S*)-([1,1′-Biphenyl]-3-yl)[(2*S*)-piperidin-2-yl]-methyl}-2-chloro-3-(trifluoromethyl)benzamide (7b)** Compound **7b** (38%) was obtained from **14b** in a manner similar to that described for **7a**. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 1.36–1.45 (m, 1H), 1.45–1.52 (m, 2H), 1.57–1.67 (m, 1H), 1.68–1.77 (m, 2H), 2.80–2.90 (m, 1H), 3.31–3.38 (m, 1H), 3.56–3.65 (m, 1H), 5.25–5.32 (m, 1H), 7.36–7.46 (m, 2H), 7.47–7.54 (m, 3H), 7.63–7.69 (m, 2H), 7.69–7.73 (m, 2H), 7.79 (s, 1H), 7.92–7.97 (m, 1H), 8.01–8.07 (m, 1H), 8.81–8.99 (m, 1H), 9.05–9.19 (m, 1H), 9.69 (d, J=8.3 Hz, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 165.4, 140.5, 139.7, 138.7, 138.5, 133.4, 129.3, 128.9, 128.6, 127.7, 127.7, 127.6 (q, J=82 Hz), 127.1, 127.0, 126.8, 126.4, 126.0, 122.7 (q, J=274 Hz), 58.2, 55.8, 44.8, 25.7, 21.6, 21.3; HR-MS: Calcd for $C_{26}H_{24}ClF_3N_2O$ $[M+H]^+$ 473.1602. Found 473.1596; $[\alpha]_D$=+76 (c=0.52, MeOH).

3-{(*S*)-{[2-Chloro-3-(trifluoromethyl)benzoyl]amino}-[(2*S*)-piperidin-2-yl]methyl}phenyl Trifluoromethanesulfonate (16) Boran tribromide (2.0 mL, 21.2 mmol) was added to an ice cooled solution of **14c** (3.29 g, 7.05 mmol) in $CHCl_3$ (30 mL), and the mixture was stirred under ice cooling for 1.5 h. The reaction was quenched with saturated $NaHCO_3$ aqueous solution and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified using silica gel column chromatography (0–12% MeOH in $CHCl_3$) to yield **15** (3.15 g,

98%) as a colorless amorphous. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.28–1.63 (m, 5H), 1.70–1.86 (m, 1H), 2.51–2.65 (m, 1H), 2.74–3.03 (m, 2H), 3.16–3.37 (m, 2H), 4.90 (d, J=9.2 Hz, 1H), 5.04–5.20 (m, 2H), 5.62–5.82 (m, 1H), 6.59–6.67 (m, 1H), 6.78–6.93 (m, 2H), 7.10–7.20 (m, 1H), 7.37–7.45 (m, 1H), 7.65–7.93 (m, 3H); MS (ESI): m/z 453 $[M+H]^+$.

Trifluoromethanesulfonic anhydride (1.3 mL, 7.74 mmol) was added to an ice cooled solution of **15** (2.97 g, 6.56 mmol) and pyridine (2.6 mL, 32.2 mmol) in $CHCl_3$ (20 mL), and the mixture was stirred under ice cooling for 30 min and at room temperature for an additional 1.5 h. The reaction was quenched with saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified using silica gel column chromatography (0–3% MeOH in $CHCl_3$) to yield **16** (3.39 g, 88%) as a brown oil. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.22–1.91 (m, 6H), 2.49–2.70 (m, 1H), 2.71–3.03 (m, 2H), 3.12–3.38 (m, 2H), 4.92–5.03 (m, 1H), 5.05–5.20 (m, 2H), 5.61–5.84 (m, 1H), 7.12–7.34 (m, 2H), 7.37–7.50 (m, 3H), 7.65–7.85 (m, 3H); MS (ESI): m/z 585 $[M+H]^+$.

2-Chloro-*N*-{(*S*)-(2*S*)-piperidin-2-yl[3-(pyrimidin-5-yl)-phenyl]methyl}-3-(trifluoromethyl)benzamide Hydrochloride (7f) Pyrimidine-5-boronic acid (212 mg, 1.71 mmol), potassium carbonate (236 mg, 1.71 mmol), and tetrakis(triphenylphosphine)palladium(0) (40 mg, 0.035 mmol) were added to a solution of **16** (657 mg, 1.12 mmol) in a mixed solvent of DMF–EtOH (2 : 1, 10 mL), and the mixture was stirred at 90°C for 4 h. The reaction mixture was partitioned between saturated $NaHCO_3$ aqueous solution and EtOAc, and the organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified using NH-silica gel column chromatography (20% EtOAc in hexane) to yield a colorless amorphous solid (237 mg). 1,3-Dimethylbarbituric acid (215 mg, 1.38 mmol) and tetrakis(triphenylphosphine)palladium(0) (5.3 mg, 0.0046 mmol) were added to a solution of the amorphous solid in $CHCl_3$ (4 mL), and the mixture was stirred for 3 h. The reaction mixture was partitioned between saturated $NaHCO_3$ aqueous solution and $CHCl_3$, and the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified using silica gel column chromatography (5% MeOH in $CHCl_3$) and NH-silica gel column chromatography (100% EtOAc) to yield the free form of **7f** (70 mg). 2 mol/L HCl in isopropanol solution (1.0 mL) was added to an ice-cooled solution of the free form of **7f** in EtOH (1.0 mL). After concentration *in vacuo*, the residue was solidified with EtOAc to yield **7f** (59 mg, 10% in 2 steps from **16**) as a colorless powder. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 1.37–1.54 (m, 3H), 1.54–1.66 (m, 1H), 1.66–1.78 (m, 2H), 2.81–2.91 (m, 1H), 3.31–3.39 (m, 1H), 3.56–3.64 (m, 1H), 5.26–5.33 (m, 1H), 7.51–7.57 (m, 1H), 7.60 (t, J=7.8 Hz, 1H), 7.67 (t, J=7.8 Hz, 1H), 7.81–7.86 (m, 1H), 7.92–7.97 (m, 2H), 7.98–8.02 (m, 1H), 8.73–8.80 (m, 1H), 8.88–8.97 (m, 1H), 9.20 (s, 2H), 9.23 (s, 1H), 9.55 (d, J=8.7 Hz, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 165.4, 157.5, 154.8, 138.9, 138.6, 134.1, 133.4, 132.8, 129.6, 128.6, 128.5, 128.0, 127.7, 127.2 (q, J=30 Hz), 126.6, 126.2, 122.7 (q, J=274 Hz), 58.2, 55.6, 44.8, 25.7, 21.6, 21.3; HR-MS: Calcd for $C_{24}H_{22}ClF_3N_4O$ $[M+H]^+$ 475.1507. Found 475.1493; $[\alpha]_D$=+72 (c=0.48, MeOH).

2-Chloro-*N*-{(*S*)-[3-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-[(2*S*)-piperidin-2-yl]methyl}-3-(trifluoromethyl)benzamide Hydrochloride (7h) Compound **7h** (44% in 2 steps) was obtained from **16** in a manner similar to that described for **7f**. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 1.34–1.49 (m, 3H), 1.56–1.65 (m, 1H), 1.68–1.77 (m, 2H), 2.80–2.90 (m, 1H), 3.33–3.38 (m, 1H), 3.48–3.55 (m, 1H), 3.88 (s, 3H), 5.15–5.19 (m, 1H), 7.24–7.27 (m, 1H), 7.39 (t, J=7.8 Hz, 1H), 7.52–7.55 (m, 1H), 7.63–7.69 (m, 2H), 7.86 (s, 1H), 7.93–7.97 (m, 1H), 7.97–8.02 (m, 1H), 8.14 (s, 1H), 8.68–8.81 (m, 1H), 8.90–9.02 (m, 1H), 9.51 (d, J=8.7 Hz, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 165.3, 138.7, 138.4, 136.0, 133.5, 132.9, 129.2, 128.6, 128.0, 127.9, 127.7, 127.2 (q, J=31 Hz), 125.2, 124.6, 124.4, 122.7 (q, J=274 Hz), 121.6, 58.2, 55.8, 44.8, 38.7, 25.7, 21.6, 21.3; HR-MS: Calcd for $C_{24}H_{24}ClF_3N_4O$ $[M+H]^+$ 477.1664. Found 477.1663; $[\alpha]_D$=+74 (c=1.05, MeOH).

2-Chloro-*N*-{(*S*)-[3-(1-methyl-1*H*-pyrazol-5-yl)phenyl]-[(2*S*)-piperidin-2-yl]methyl}-3-(trifluoromethyl)benzamide Hydrochloride (7i) Compound **7i** (21% in 2 steps) was obtained from **16** in a manner similar to that described for **7f**. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 1.37–1.51 (m, 3H), 1.54–1.64 (m, 1H), 1.69–1.77 (m, 2H), 2.82–2.90 (m, 1H), 3.33–3.39 (m, 1H), 3.51–3.60 (m, 1H), 3.88 (s, 3H), 5.22–5.27 (m, 1H), 6.44 (d, J=1.8 Hz, 1H), 7.47–7.58 (m, 4H), 7.61 (s, 1H), 7.68 (t, J=7.8 Hz, 1H), 7.95 (s, 1H), 7.97 (s, 1H), 8.63–8.77 (m, 1H), 8.83–8.99 (m, 1H), 9.54 (d, J=8.7 Hz, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 165.3, 142.3, 138.6, 138.5, 137.9, 133.4, 130.5, 129.2, 128.6, 128.1, 127.9, 127.9, 127.7, 127.6, 127.2 (q, J=31 Hz), 122.7 (q, J=274 Hz), 105.9, 58.1, 55.6, 44.8, 37.6, 25.7, 21.6, 21.3; HR-MS: Calcd for $C_{24}H_{24}ClF_3N_4O$ $[M+H]^+$ 477.1664. Found 477.1662; $[\alpha]_D$=+66 (c=0.50, MeOH).

***tert*-Butyl (2*S*)-2-[4-(Benzyloxy)benzoyl]piperidine-1-carboxylate (17a)** Compound **17a** (53%) was obtained in a manner similar to that described for **9c**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.31–1.72 (m, 13H), 1.74–1.90 (m, 1H), 1.98–2.18 (m, 1H), 3.10–3.29 (m, 1H), 3.84–4.02 (m, 1H), 5.12 (s, 2H), 5.38–5.69 (m, 1H), 6.96–7.05 (m, 2H), 7.31–7.46 (m, 5H), 7.86–7.96 (m, 2H); MS (ESI): m/z 418 $[M+Na]^+$.

***tert*-Butyl (2*S*)-2-[3-(Benzyloxy)benzoyl]piperidine-1-carboxylate (17b)** Compound **17b** (60%) was obtained in a manner similar to that described for **9c**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.30–1.50 (m, 11H), 1.52–1.73 (m, 2H), 1.74–1.85 (m, 1H), 1.98–2.16 (m, 1H), 3.07–3.28 (m, 1H), 3.86–4.03 (m, 1H), 5.10 (s, 2H), 5.39–5.70 (m, 1H), 7.13–7.20 (m, 1H), 7.30–7.41 (m, 4H), 7.41–7.45 (m, 2H), 7.46–7.58 (m, 2H); MS (ESI): m/z 418 $[M+Na]^+$.

***tert*-Butyl (2*S*)-2-(4-{[(Trifluoromethyl)sulfonyl]oxy}benzoyl)piperidine-1-carboxylate (18a)** 5% Pd/C (1.0 g) was added to a solution of **17a** (9.90 g, 25 mmol) in MeOH (120 mL), and the mixture was stirred overnight under a hydrogen gas atmosphere. After filtration, the filtrate was concentrated *in vacuo*. The residue was solidified with 33% EtOAc in hexane to yield a colorless powder (4.94 g), which was converted to **18a** (6.82 g, 62% in 2 steps from **17a**, pale yellow powder) in a manner similar to that described for **16**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.30–2.16 (m, 15H), 2.96–3.26 (m, 1H), 3.83–4.05 (m, 1H), 5.35–5.65 (m, 1H), 7.32–7.43 (m, 2H), 7.99–8.11 (m, 2H); MS (ESI): m/z 438 $[M+H]^+$, m/z 460 $[M+Na]^+$.

***tert*-Butyl (2*S*)-2-{3-[(Trifluoromethanesulfonyl)oxy]benzoyl}piperidine-1-carboxylate (18b)** Compound **18b** (66%

in 2 steps) was obtained from **17b** in a manner similar to that described for **18a**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.29–2.16 (m, 15H), 2.96–3.25 (m, 1H), 3.80–4.00 (m, 1H), 5.29–5.61 (m, 1H), 7.40–7.62 (m, 2H), 7.75–8.02 (m, 2H); MS (ESI): *m/z* 438 $[M+H]^+$.

***tert*-Butyl (2*S*)-2-[(*S*)-Hydroxy(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)methyl]piperidine-1-carboxylate (19a)** Compound **19a** (6.3 g, 94%) was obtained from **18a** (6.70 g) in a manner similar to that described for **10c**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.21–1.32 (m, 1H), 1.37–1.76 (m, 14H), 2.85–3.17 (m, 1H), 3.96–4.50 (m, 2H), 4.87–5.00 (m, 1H), 7.26–7.37 (m, 2H), 7.44–7.55 (m, 2H); MS (ESI): *m/z* 440 $[M+H]^+$.

***tert*-Butyl (2*S*)-2-[(*S*)-Hydroxy{3-[(trifluoromethanesulfonyl)oxy]phenyl}methyl]piperidine-1-carboxylate (19b)** Compound **19b** (96%) was obtained from **18a** in a manner similar to that described for **10c**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.22–1.29 (m, 1H), 1.38–1.73 (m, 5H), 1.51 (s, 9H), 2.93–3.11 (m, 1H), 3.99–4.36 (m, 2H), 4.92 (brd, *J*=10.3 Hz, 1H), 7.20–7.24 (m, 1H), 7.29 (s, 1H), 7.41–7.48 (m, 2H); MS (ESI): *m/z* 462 $[M+Na]^+$.

***tert*-Butyl (2*S*)-2-{(*S*)-Hydroxy[4-(pyridin-3-yl)phenyl]methyl}piperidine-1-carboxylate (20a)** 3-Pyridineboronic acid (2.50 g, 20.3 mmol), potassium carbonate (2.84 g, 20.5 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.47 g, 0.41 mmol) were added to a solution of **19a** (6.00 g, 13.7 mmol) in a mixed solvent of DMF–EtOH (2 : 1, 135 mL) were added, and the mixture was stirred at 90°C for 1.5 h. The reaction mixture was partitioned between water and EtOAc, and the organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified using NH-silica gel column chromatography (33–50% EtOAc in hexane) to yield **20a** (4.40 g, 87%) as a pale yellow powder. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.31–1.38 (m, 1H), 1.40–1.55 (m, 2H), 1.52 (s, 9H), 1.56–1.84 (m, 3H), 2.97–3.16 (m, 1H), 3.99–4.50 (m, 2H), 4.89–5.01 (m, 1H), 7.35–7.39 (m, 1H), 7.45–7.62 (m, 4H), 7.85–7.90 (m, 1H), 8.56–8.61 (m, 1H), 8.82–8.86 (m, 1H); MS (ESI): *m/z* 369 $[M+H]^+$.

***tert*-Butyl (2*S*)-2-{(*S*)-Hydroxy[3-(pyridin-3-yl)phenyl]methyl}piperidine-1-carboxylate (20b)** Compound **20b** (quant.) was obtained from **19b** in a manner similar to that described for **20a**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.32–1.37 (m, 1H), 1.39–1.81 (m, 5H), 1.51 (s, 9H), 2.93–3.18 (m, 1H), 3.98–4.48 (m, 2H), 4.97 (brd, *J*=9.9 Hz, 1H), 7.37 (dd, *J*=7.6, 4.7 Hz, 1H), 7.39–7.54 (m, 3H), 7.59 (brs, 1H), 7.88–7.91 (m, 1H), 8.60 (dd, *J*=4.7, 1.4 Hz, 1H), 8.85 (d, *J*=2.1 Hz, 1H); MS (ESI): *m/z* 369 $[M+H]^+$.

***tert*-Butyl (2*S*)-2-{(*S*)-Hydroxy[4-(pyrimidin-5-yl)phenyl]methyl}piperidine-1-carboxylate (20c)** Compound **20c** (97%) was obtained from **19a** in a manner similar to that described for **20a**. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 1.20–1.39 (m, 3H), 1.40 (s, 9H), 1.43–1.49 (m, 1H), 1.59–1.82 (m, 2H), 2.85–3.02 (m, 1H), 3.86–3.96 (m, 1H), 4.07–4.23 (m, 1H), 4.89 (brdd, *J*=8.9, 4.1 Hz, 1H), 5.33 (brs, 1H), 7.51 (d, *J*=8.2 Hz, 2H), 7.80 (d, *J*=8.3 Hz, 2H), 9.15 (s, 2H), 9.18 (s, 1H); MS (ESI): *m/z* 370 $[M+H]^+$.

***tert*-Butyl (2*S*)-2-{(*S*)-Hydroxy[3-(1-methyl-1*H*-pyrazol-4-yl)phenyl]methyl}piperidine-1-carboxylate (20d)** Compound **20d** (quant.) was obtained from **19b** in a manner similar to that described for **20a**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.31–1.75 (m, 6H), 1.52 (s, 9H), 2.85–3.19 (m, 1H), 3.95 (s, 3H), 3.97–4.50 (m, 2H), 4.90 (d, *J*=10.1 Hz, 1H), 7.21 (brd, *J*=7.3 Hz, 1H), 7.32–7.36 (m, 1H), 7.39–7.43 (m, 1H), 7.48 (brs, 1H), 7.63 (brs, 1H), 7.76 (s, 1H); MS (ESI): *m/z* 372 $[M+H]^+$.

***tert*-Butyl (2*S*)-2-[(*S*)-[3-(1-Ethyl-1*H*-pyrazol-4-yl)phenyl](hydroxy)methyl]piperidine-1-carboxylate (20e)** Compound **20e** (80%) was obtained from **19b** in a manner similar to that described for **20a**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.29–1.72 (m, 6H), 1.52 (s, 9H), 1.54 (t, *J*=7.3 Hz, 3H), 2.86–3.17 (m, 1H), 3.97–4.47 (m, 2H), 4.21 (q, *J*=7.3 Hz, 2H), 4.90 (dd, *J*=10.5, 5.0 Hz, 1H), 7.21 (d, *J*=7.3 Hz, 1H), 7.32–7.36 (m, 1H), 7.39–7.44 (m, 1H), 7.50 (brs, 1H), 7.68 (brs, 1H), 7.78 (s, 1H); MS (ESI): *m/z* 386 $[M+H]^+$.

***tert*-Butyl (2*S*)-2-[(*S*)-Hydroxy{3-[1-(propan-2-yl)-1*H*-pyrazol-4-yl]phenyl}methyl]piperidine-1-carboxylate (20f)** Compound **20f** (quant.) was obtained from **19b** in a manner similar to that described for **20a**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.27–1.77 (m, 15H), 1.53 (d, *J*=6.9 Hz, 3H), 1.56 (d, *J*=6.9 Hz, 3H), 2.86–3.15 (m, 1H), 3.99–4.47 (m, 2H), 4.48–4.57 (m, 1H), 4.91 (dd, *J*=10.3, 4.4 Hz, 1H), 7.20 (d, *J*=7.3 Hz, 1H), 7.32–7.36 (m, 1H), 7.40–7.45 (m, 1H), 7.51 (brs, 1H), 7.71 (brs, 1H), 7.78 (s, 1H); MS (ESI): *m/z* 400 $[M+H]^+$.

***tert*-Butyl (2*S*)-2-{(*S*)-Hydroxy[3-(1-propyl-1*H*-pyrazol-4-yl)phenyl]methyl}piperidine-1-carboxylate (20g)** Compound **20g** (78%) was obtained from **19b** in a manner similar to that described for **20a**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 0.91–0.98 (m, 3H), 1.29–1.73 (m, 6H), 1.52 (s, 9H), 1.87–1.96 (m, 2H), 2.90–3.17 (m, 1H), 3.98–4.52 (m, 4H), 4.90 (brdd, *J*=10.1, 4.1 Hz, 1H), 7.20 (brd, *J*=7.8 Hz, 1H), 7.32–7.36 (m, 1H), 7.39–7.44 (m, 1H), 7.50 (brs, 1H), 7.66 (brs, 1H), 7.78 (s, 1H); MS (ESI): *m/z* 400 $[M+H]^+$.

(*S*)-1-[(2*S*)-1-(Prop-2-en-1-yl)piperidin-2-yl]-1-[4-(pyridin-3-yl)phenyl]methanamine (21a) Compound **21a** (33% in 4 steps) was obtained from **20a** in a manner smilar to that described for the synthesis of **13c** from **10c**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.04–1.12 (m, 1H), 1.23–1.56 (m, 4H), 1.62–1.72 (m, 1H), 2.67–2.74 (m, 2H), 3.03–3.11 (m, 1H), 3.36–3.42 (m, 2H), 4.28 (d, *J*=10.1 Hz, 1H), 5.12–5.16 (m, 1H), 5.20–5.25 (m, 1H), 5.87–5.95 (m, 1H), 7.33–7.37 (m, 1H), 7.47–7.50 (m, 2H), 7.52–7.56 (m, 2H), 7.85–7.89 (m, 1H), 8.57–8.59 (m, 1H), 8.85 (d, *J*=2.3 Hz, 1H); MS (ESI): *m/z* 308 $[M+H]^+$.

(*S*)-1-[(2*S*)-1-(Prop-2-en-1-yl)piperidin-2-yl]-1-[3-(pyridin-3-yl)phenyl]methanamine (21b) Compound **21b** (43% in 4 steps) was obtained from **20b** in a manner similar to that described for **21a**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.03–1.11 (m, 1H), 1.31–1.57 (m, 4H), 1.63–1.71 (m, 1H), 2.66–2.76 (m, 2H), 3.03–3.11 (m, 1H), 3.35–3.44 (m, 2H), 4.29 (d, *J*=10.1 Hz, 1H), 5.12–5.17 (m, 1H), 5.20–5.25 (m, 1H), 5.86–5.95 (m, 1H), 7.34–7.38 (m, 1H), 7.39–7.52 (m, 3H), 7.58–7.61 (m, 1H), 7.87–7.91 (m, 1H), 8.57–8.60 (m, 1H), 8.85–8.86 (m, 1H); MS (ESI): *m/z* 308 $[M+H]^+$.

(*S*)-1-[(2*S*)-1-(Prop-2-en-1-yl)piperidin-2-yl]-1-[4-(pyrimidin-5-yl)phenyl]methanamine (21c) Compound **21c** (99% in 4 steps) was obtained from **20c** in a manner similar to that described for **21a**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.31–4.44 (m, 12H), 5.46 (d, *J*=11.0 Hz, 2H), 6.05–6.19 (m, 1H), 7.49–7.72 (m, 4H), 8.89–8.92 (m, 2H), 9.20 (s, 1H); MS (ESI): *m/z* 309 $[M+H]^+$.

(*S*)-1-[3-(1-Methyl-1*H*-pyrazol-4-yl)phenyl]-1-[(2*S*)-1-(prop-2-en-1-yl)piperidin-2-yl]methanamine (21d) Compound **21d** (17% in 4 steps) was obtained from **20d** in a manner similar to that described for **21a**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.01–1.09 (m, 1H), 1.29–1.55 (m, 4H), 1.60–1.89 (m, 1H), 2.65–2.72 (m, 2H), 3.02–3.08 (m, 1H), 3.33–3.43 (m, 2H), 3.94 (s, 3H), 4.22 (d, J=10.1 Hz, 1H), 5.13 (dd, J=10.1, 1.8 Hz, 1H), 5.19–5.24 (m, 1H), 5.86–5.94 (m, 1H), 7.18–7.21 (m, 1H), 7.30 (t, J=7.8 Hz, 1H), 7.34–7.37 (m, 1H), 7.46–7.50 (m, 1H), 7.64 (s, 1H), 7.77 (s, 1H); MS (ESI): m/z 311 $[M+H]^+$.

(*S*)-1-[3-(1-Ethyl-1*H*-pyrazol-4-yl)phenyl]-1-[(2*S*)-1-(prop-2-en-1-yl)piperidin-2-yl]methanamine (21e) Compound **21e** (48% in 4 steps) was obtained from **20e** in a manner similar to that described for **21a**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.02–1.10 (m, 1H), 1.30–1.57 (m, 4H), 1.53 (t, J=7.3 Hz, 3H), 1.58–1.84 (m, 1H), 2.67–2.73 (m, 2H), 3.03–3.09 (m, lH), 3.34–3.44 (m, 2H), 4.18–4.24 (m, 3H), 5.11–5.16 (m, 1H), 5.18–5.26 (m, 1H), 5.85–5.95 (m, 1H), 7.19 (d, J=7.8 Hz, 1H), 7.30 (t, J=7.8 Hz, 1H), 7.35–7.38 (m, 1H), 7.50 (brs, 1H), 7.68 (s, 1H), 7.78 (s, 1H); MS (ESI): m/z 325 $[M+H]^+$.

(*S*)-1-{3-[1-(Propan-2-yl)-1*H*-pyrazol-4-yl]phenyl}-1-[(2*S*)-1-(prop-2-en-1-yl)piperidin-2-yl]methanamine (21f) Compound **21f** (39% in 4 steps) was obtained from **20f** in a manner similar to that described for **21a**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.02–1.09 (m, 1H), 1.30–1.59 (m, 4H), 1.55 (d, J=6.9 Hz, 6H), 1.61–1.85 (m, 1H), 2.67–2.73 (m, 2H), 3.03–3.09 (m, 1H), 3.34–3.43 (m, 2H), 4.23 (d, J=9.6 Hz, 1H), 4.50–4.56 (m, 1H), 5.11–5.15 (m, 1H), 5.19–5.25 (m, 1H), 5.86–5.95 (m, 1H), 7.16–7.19 (m, 1H), 7.29 (t, J=7.6 Hz, 1H), 7.36–7.39 (m, 1H), 7.50–7.52 (m, 1H), 7.71 (s, 1H), 7.79 (s, 1H); MS (ESI): m/z 339 $[M+H]^+$.

(*S*)-1-[(2*S*)-1-(Prop-2-en-1-yl)piperidin-2-yl]-1-[3-(1-propyl-1*H*-pyrazol-4-yl)phenyl]methanamine (21g) Compound **21g** (33% in 4 steps) was obtained from **20g** in a manner similar to that described for **21a**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 0.95 (t, J=7.3 Hz, 3H), 1.03–1.11 (m, 1H), 1.29–1.73 (m, 5H), 1.89–1.96 (m, 2H), 2.67–2.73 (m, 2H), 3.02–3.10 (m, 1H), 3.33–3.44 (m, 2H), 4.11 (t, J=7.1 Hz, 2H), 4.22 (d, J=9.6 Hz, 1H), 5.10–5.16 (m, 1H), 5.19–5.25 (m, 1H), 5.85–5.96 (m, 1H), 7.17–7.20 (m, 1H), 7.30 (t, J=7.6 Hz, 1H), 7.35–7.39 (m, 1H), 7.49–7.52 (m, 1H), 7.66 (s, 1H), 7.79 (s, 1H); MS (ESI): m/z 339 $[M+H]^+$.

2-Chloro-*N*-{(*S*)-(2*S*)-piperidin-2-yl[4-(pyridin-3-yl)-phenyl]methyl}-3-(trifluoromethyl)benzamide Dihydrochloride (7c) Compound **7c** (42% in 2 steps) was obtained from **21a** in a manner similar to that described for the synthesis of **14c** and **7a**. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 1.35–1.52 (m, 3H), 1.59–1.68 (m, 1H), 1.70–1.77 (m, 2H), 2.80–2.89 (m, 1H), 3.34–3.40 (m, 1H), 3.54–3.63 (m, 1H), 5.23–5.28 (m, 1H), 7.63–7.65 (m, 2H), 7.67 (t, J=8.0 Hz, 1H), 7.90–7.97 (m, 4H), 8.04 (dd, J=7.8, 1.4 Hz, 1H), 8.64–8.69 (m, 1H), 8.81 (dd, J=5.5, 1.4 Hz, 1H), 8.85–8.90 (m, 1H), 9.16–9.23 (m, 2H), 9.76 (d, J=8.3 Hz, 1H); ^{13}C-NMR (126 MHz, DMSO- d_6) δ: 165.3, 143.7, 143.0, 139.6, 139.1, 138.6, 136.9, 134.7, 133.5, 128.7, 128.6, 128.0, 127.7, 127.5, 127.2 (q, J=32 Hz), 125.9, 122.8 (q, J=274 Hz), 58.0, 55.6, 44.7, 25.8, 21.6, 21.3; HR-MS: Calcd for $C_{25}H_{23}ClF_3N_3O$ $[M+H]^+$ 474.1555. Found 474.1547; $[\alpha]_D$=+71 (c=0.52, MeOH).

2-Chloro-*N*-{(*S*)-(2*S*)-piperidin-2-yl[3-(pyridin-3-yl)-phenyl]methyl}-3-(trifluoromethyl)benzamide Hydrochloride (7d) Compound **7d** (65% in 2 steps) was obtained from **21b** in a manner similar to that described for **7c**. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 1.36–1.46 (m, 1H), 1.46–1.52 (m, 2H), 1.58–1.67 (m, 1H), 1.69–1.77 (m, 2H), 2.80–2.90 (m, 1H), 3.32–3.39 (m, 1H), 3.59–3.70 (m, 1H), 5.29–5.33 (m, 1H), 7.58–7.64 (m, 2H), 7.66 (t, J=7.8 Hz, 1H), 7.84–7.86 (m, 1H), 7.93–8.00 (m, 3H), 8.05 (dd, J=7.8, 1.4 Hz, 1H), 8.65–8.71 (m, 1H), 8.83 (dd, J=5.5, 1.4 Hz, 1H), 8.92–8.98 (m, 1H), 9.10–9.18 (m, 1H), 9.21 (d, J=2.3 Hz, 1H), 9.73 (d, J=8.7 Hz, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 165.4, 144.1, 143.3, 139.3, 139.1, 138.6, 137.0, 135.4, 133.5, 129.7, 128.6, 128.6, 128.0, 127.7, 127.2 (q, J=30 Hz), 126.9, 126.6, 125.8, 122.7 (q, J=273 Hz), 58.1, 55.7, 44.8, 25.7, 21.6, 21.3; HR-MS: Calcd for $C_{25}H_{23}ClF_3N_3O$ $[M+H]^+$ 474.1555. Found 474.1552; $[\alpha]_D$=+76 (c=0.60, MeOH).

2-Chloro-*N*-{(*S*)-(2*S*)-piperidin-2-yl[4-(pyrimidin-5-yl)phenyl]methyl}-3-(trifluoromethyl)benzamide Hydrochloride (7e) Compound **7e** (24% in 2 steps) was obtained from **21c** in a manner similar to that described for **7c**. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 1.34–1.51 (m, 3H), 1.56–1.69 (m, 1H), 1.69–1.79 (m, 2H), 2.81–2.93 (m, 1H), 3.32–3.43 (m, 1H), 3.50–3.63 (m, 1H), 5.21–5.33 (m, 1H), 7.63 (d, J=8.3 Hz, 2H), 7.68 (t, J=7.8 Hz, 1H), 7.91 (d, J=8.3 Hz, 2H), 7.97 (d, J=7.8 Hz, 1H), 8.02 (d, J=7.3 Hz, 1H), 8.75–8.82 (m, 1H), 9.03–9.11 (m, 1H), 9.17–9.24 (m, 3H), 9.67 (d, J=8.7 Hz, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 165.3, 157.4, 154.7, 138.7, 138.6, 133.5, 133.4, 132.6, 128.7, 128.6, 128.0, 127.7, 127.2, 127.2 (q, J=30 Hz), 122.7 (q, J=274 Hz), 58.1, 55.5, 44.8, 25.7, 21.6, 21.3; HR-MS: Calcd for $C_{24}H_{22}ClF_3N_4O$ $[M+H]^+$ 475.1507. Found 475.1498; $[\alpha]_D$=+71 (c=0.53, MeOH).

2,4-Dichloro-*N*-{(*S*)-[3-(1-methyl-1*H*-pyrazol-4-yl)-phenyl][(2*S*)-piperidin-2-yl]methyl}benzamide Hydrochloride (7k) Compound **7k** (62% in 2 steps) was obtained from **21d** in a manner similar to that described for **7c**. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 1.33–1.45 (m, 3H), 1.55–1.64 (m, 1H), 1.67–1.76 (m, 2H), 2.79–2.88 (m, 1H), 3.31–3.37 (m, 1H), 3.48–3.55 (m, 1H), 3.87 (s, 3H), 5.12–5.16 (m, 1H), 7.24 (d, J=7.8 Hz, 1H), 7.38 (t, J=7.6 Hz, 1H), 7.52 (d, J=7.8 Hz, 1H), 7.56 (dd, J=8.3, 2.3 Hz, 1H), 7.65 (brs, 1H), 7.67 (d, J=2.3 Hz, 1H), 7.74–7.77 (m, 1H), 7.86 (s, 1H), 8.13 (s, 1H), 8.63–8.76 (m, 1H), 8.94–9.08 (m, 1H), 9.42 (d, J=8.7 Hz, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 165.3, 138.7, 136.0, 134.9, 134.6, 132.9, 131.5, 131.0, 129.2, 129.1, 127.9, 127.1, 125.2, 124.6, 124.3, 121.6, 58.2, 55.7, 44.7, 38.7, 25.8, 21.6, 21.3; HR-MS: Calcd for $C_{23}H_{24}Cl_2N_4O$ $[M+H]^+$ 443.1400. Found 443.1397; $[\alpha]_D$=+66 (c=0.55, MeOH).

2-Fluoro-*N*-{(*S*)-[3-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-[(2*S*)-piperidin-2-yl]methyl}-3-(trifluoromethyl)benzamide Hydrochloride (7l) Compound **7l** (55% in 2 steps) was obtained from **21d** in a manner similar to that described for **7c**. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 1.32–1.48 (m, 3H), 1.57–1.67 (m, 1H), 1.68–1.76 (m, 2H), 2.77–2.86 (m, 1H), 3.30–3.37 (m, 1H), 3.55–3.63 (m, 1H), 3.88 (s, 3H), 5.15–5.21 (m, 1H), 7.25–7.30 (m, 1H), 7.40 (t, J=7.8 Hz, 1H), 7.50–7.56 (m, 2H), 7.66–7.70 (m, 1H), 7.88 (s, 1H), 7.91–7.96 (m, 1H), 8.09–8.14 (m, 1H), 8.16 (s, 1H), 8.67–8.81 (m, 1H), 8.98–9.17 (m, 1H), 9.55 (d, J=8.7 Hz, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 162.5, 156.3 (d, J=258 Hz), 139.0, 136.0, 135.2, 133.0, 129.3, 128.0, 125.4 (q, J=13 Hz), 125.1, 124.9, 124.8, 124.7, 124.3, 122.5 (q, J=272 Hz), 121.6, 116.9–117.4 (m), 58.2, 55.8, 44.6, 38.7, 25.9, 21.6, 21.3; HR-MS: Calcd for $C_{24}H_{24}F_4N_4O$ $[M+H]^+$ 461.1959. Found 461.1948; $[\alpha]_D$=+56 (c=0.51,

MeOH).

***N*-{(*S*)-[3-(1-Methyl-1*H*-pyrazol-4-yl)phenyl][(2*S*)-piperidin-2-yl]methyl}-3-(trifluoromethyl)benzamide Hydrochloride (7m)** Compound **7m** (58% in 2 steps) was obtained from **21d** in a manner similar to that described for **7c**. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 1.34–1.48 (m, 3H), 1.57–1.68 (m, 1H), 1.68–1.79 (m, 2H), 2.80–2.89 (m, 1H), 3.32–3.38 (m, 1H), 3.67–3.76 (m, 1H), 3.87 (s, 3H), 5.19–5.26 (m, 1H), 7.28–7.32 (m, 1H), 7.36 (t, J=7.6 Hz, 1H), 7.48–7.53 (m, 1H), 7.71–7.77 (m, 2H), 7.87 (s, 1H), 7.94 (d, J=7.8 Hz, 1H), 8.14 (s, 1H), 8.33 (s, 1H), 8.38 (d, J=7.8 Hz, 1H), 8.63–8.80 (m, 1H), 9.07–9.21 (m, 1H), 9.71 (d, J=9.2 Hz, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 165.0, 139.5, 136.1, 134.8, 133.0, 132.0, 129.5, 129.3, 129.0 (q, J=32 Hz), 128.1, 127.9, 125.2, 124.5, 124.4, 124.4, 124.0 (q, J=273 Hz), 121.5, 58.0, 56.0, 44.6, 38.7, 26.0, 21.6, 21.3; HR-MS: Calcd for $C_{24}H_{25}F_3N_4O$ [M+H]$^+$ 443.2053. Found 443.2053; $[\alpha]_D$=+22 (c=0.66, MeOH).

2-Methyl-*N*-{(*S*)-[3-(1-methyl-1*H*-pyrazol-4-yl)phenyl][(2*S*)-piperidin-2-yl]methyl}-3-(trifluoromethyl)benzamide Hydrochloride (7n) Compound **7n** (59% in 2 steps) was obtained from **21d** in a manner similar to that described for **7c**. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 1.34–1.44 (m, 3H), 1.55–1.65 (m, 1H), 1.67–1.77 (m, 2H), 2.26 (s, 3H), 2.78–2.90 (m, 1H), 3.33–3.40 (m, 1H), 3.48–3.55 (m, 1H), 3.88 (s, 3H), 5.13–5.18 (m, 1H), 7.24–7.27 (m, 1H), 7.40 (t, J=7.6 Hz, 1H), 7.48–7.55 (m, 2H), 7.64–7.67 (m, 1H), 7.75–7.81 (m, 2H), 7.87 (s, 1H), 8.15 (s, 1H), 8.61–8.73 (m, 1H), 8.89–9.08 (m, 1H), 9.37 (d, J=8.7 Hz, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 168.1, 139.2, 139.2, 136.0, 133.9, 133.0, 131.5, 129.3, 128.0 (q, J=28 Hz), 127.9, 126.6, 126.1, 125.1, 124.6, 124.3, 124.3 (q, J=275 Hz), 121.6, 58.0, 55.8, 44.7, 38.7, 25.9, 21.6, 21.3, 15.5; HR-MS: Calcd for $C_{25}H_{27}F_3N_4O$ [M+H]$^+$ 457.2210. Found 457.2199; $[\alpha]_D$=+53 (c=0.60, MeOH).

2,6-Dichloro-*N*-{(*S*)-[3-(1-methyl-1*H*-pyrazol-4-yl)phenyl][(2*S*)-piperidin-2-yl]methyl}benzamide Hydrochloride (7o) Compound **7o** (30% in 2 steps) was obtained from **21d** in a manner similar to that described for **7c**. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 1.38–1.61 (m, 3H), 1.65–1.72 (m, 1H), 1.73–1.82 (m, 2H), 2.86–2.95 (m, 1H), 3.23–3.58 (m, 2H), 3.88 (s, 3H), 5.27–5.33 (m, 1H), 7.27 (d, J=7.3 Hz, 1H), 7.39 (t, J=7.8 Hz, 1H), 7.45–7.49 (m, 1H), 7.51–7.56 (m, 3H), 7.66–7.69 (m, 1H), 7.85 (s, 1H), 8.11 (s, 1H), 8.52–8.80 (m, 2H), 9.58 (d, J=8.3 Hz, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 163.4, 137.3, 136.0, 135.7, 132.8, 131.3, 131.2, 129.0, 128.2, 127.8, 125.6, 124.6, 121.7, 58.6, 55.1, 45.1, 38.7, 25.0, 21.6, 21.4; HR-MS: Calcd for $C_{23}H_{24}Cl_2N_4O$ [M+H]$^+$ 443.1400. Found 443.1392; $[\alpha]_D$=+79 (c=0.54, MeOH).

2,6-Dimethyl-*N*-{(*S*)-[3-(1-methyl-1*H*-pyrazol-4-yl)phenyl][(2*S*)-piperidin-2-yl]methyl}benzamide Hydrochloride (7p) Compound **7p** (33% in 2 steps) was obtained from **21d** in a manner similar to that described for **7c**. ^{1}H-NMR (600 MHz, DMSO-d_6): δ1.32–1.44 (m, 2H), 1.50–1.62 (m, 2H), 1.68–1.77 (m, 2H), 2.12 (brs, 6H), 2.80–2.90 (m, 1H), 3.27–3.54 (m, 2H), 3.88 (s, 3H), 5.16–5.22 (m, 1H), 7.02 (s, 1H), 7.03 (s, 1H), 7.17 (t, J=7.6 Hz, 1H), 7.24 (d, J=7.3 Hz, 1H), 7.38 (t, J=7.6 Hz, 1H), 7.53 (d, J=7.8 Hz, 1H), 7.67 (brs, 1H), 7.85 (s, 1H), 8.12 (s, 1H), 8.37–8.56 (m, 1H), 8.67–8.84 (m, 1H), 8.95 (d, J=8.3 Hz, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6): δ169.2, 138.8, 137.5, 136.0, 133.9, 132.8, 129.0, 128.2, 127.8, 127.1, 125.6, 124.5, 121.7, 58.0, 55.5, 44.9, 38.7, 25.6, 21.6, 21.4, 19.0; HR-MS: Calcd for $C_{25}H_{30}N_4O$ [M+H]$^+$ 403.2492. Found 403.2499; $[\alpha]_D$=+82 (c=0.54, MeOH).

2,3-Dichloro-*N*-{(*S*)-[3-(1-methyl-1*H*-pyrazol-4-yl)phenyl][(2*S*)-piperidin-2-yl]methyl}benzamide Hydrochloride (7q) Compound **7q** (39% in 2 steps) was obtained from **21d** in a manner similar to that described for **7c**. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 1.35–1.47 (m, 3H), 1.54–1.64 (m, 1H), 1.68–1.77 (m, 2H), 2.79–2.89 (m, 1H), 3.30–3.38 (m, 1H), 3.46–3.53 (m, 1H), 3.88 (s, 3H), 5.11–5.17 (m, 1H), 7.23–7.25 (m, 1H), 7.39 (t, J=7.6 Hz, 1H), 7.48 (t, J=7.8 Hz, 1H), 7.52–7.55 (m, 1H), 7.63–7.67 (m, 2H), 7.72–7.76 (m, 1H), 7.85–7.88 (m, 1H), 8.14 (s, 1H), 8.57–8.68 (m, 1H), 8.85–8.96 (m, 1H), 9.40 (d, J=8.7 Hz, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 165.5, 138.6, 138.2, 136.0, 132.9, 132.0, 131.4, 129.1, 128.3, 128.0, 127.9, 125.3, 124.6, 124.3, 121.6, 58.2, 55.7, 44.8, 38.7, 25.7, 21.6, 21.3; HR-MS: Calcd for $C_{23}H_{24}Cl_2N_4O$ [M+H]$^+$ 443.1400. Found 443.1394; $[\alpha]_D$=+86 (c=0.63, MeOH).

2-Chloro-3-methyl-*N*-{(*S*)-[3-(1-methyl-1*H*-pyrazol-4-yl)phenyl][(2*S*)-piperidin-2-yl]methyl}benzamide Hydrochloride (7r) Compound **7r** (44% in 2 steps) was obtained from **21d** in a manner similar to that described for **7c**. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 1.33–1.49 (m, 3H), 1.54–1.63 (m, 1H), 1.67–1.76 (m, 2H), 2.34 (s, 3H), 2.79–2.89 (m, 1H), 3.31–3.37 (m, 1H), 3.41–3.63 (m, 1H), 3.88 (s, 3H), 5.12–5.17 (m, 1H), 7.24 (d, J=7.3 Hz, 1H), 7.33 (t, J=7.6 Hz, 1H), 7.38 (t, J=7.6 Hz, 1H), 7.42–7.45 (m, 1H), 7.45–7.49 (m, 1H), 7.53 (d, J=7.8 Hz, 1H), 7.64 (brs, 1H), 7.84–7.87 (m, 1H), 8.13 (s, 1H), 8.46–8.61 (m, 1H), 8.84–8.99 (m, 1H), 9.19 (d, J=8.7 Hz, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 166.7, 138.7, 136.5, 136.3, 136.0, 132.9, 131.9, 130.1, 129.1, 127.9, 126.9, 126.6, 125.3, 124.6, 124.4, 121.6, 58.3, 55.6, 44.8, 38.7, 25.7, 21.6, 21.3, 19.9; HR-MS: Calcd for $C_{24}H_{27}ClN_4O$ [M+H]$^+$ 423.1946. Found 423.1934; $[\alpha]_D$=+85 (c=0.50, MeOH).

3-Methoxy-2-methyl-*N*-{(*S*)-[3-(1-methyl-1*H*-pyrazol-4-yl)phenyl][(2*S*)-piperidin-2-yl]methyl}benzamide Hydrochloride (7s) Compound **7s** (67% in 2 steps) was obtained from **21d** in a manner similar to that described for **7c**. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 1.31–1.46 (m, 3H), 1.53–1.64 (m, 1H), 1.66–1.77 (m, 2H), 2.01 (s, 3H), 2.77–2.86 (m, 1H), 3.30–3.37 (m, 1H), 3.42–3.60 (m, 1H), 3.78 (s, 3H), 3.88 (s, 3H), 5.11–5.16 (m, 1H), 7.04 (d, J=8.3 Hz, 1H), 7.10 (d, J=7.8 Hz, 1H), 7.22–7.27 (m, 2H), 7.38 (t, J=7.8 Hz, 1H), 7.50–7.53 (m, 1H), 7.65 (brs, 1H), 7.86 (s, 1H), 8.13 (s, 1H), 8.46–8.58 (m, 1H), 8.92–9.01 (m, 1H), 9.04 (d, J=8.7 Hz, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 168.9, 157.3, 139.4, 137.7, 136.0, 132.9, 129.2, 127.9, 126.3, 125.1, 124.5, 124.3, 123.7, 121.6, 119.4, 111.6, 58.1, 55.6, 44.7, 38.7, 25.9, 21.6, 21.4, 12.4; HR-MS: Calcd for $C_{25}H_{30}N_4O_2$ [M+H]$^+$ 419.2442. Found 419.2429; $[\alpha]_D$=+59 (c=0.51, MeOH).

2-Chloro-*N*-{(*S*)-[3-(1-methyl-1*H*-pyrazol-4-yl)phenyl][(2*S*)-piperidin-2-yl]methyl}-5-(trifluoromethyl)benzamide Hydrochloride (7t) Compound **7t** (55% in 2 steps) was obtained from **21d** in a manner similar to that described for **7c**. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 1.34–1.45 (m, 3H), 1.58–1.68 (m, 1H), 1.68–1.78 (m, 2H), 2.82–2.92 (m, 1H), 3.35–3.40 (m, 1H), 3.47–3.56 (m, 1H), 3.87 (s, 3H), 5.15–5.20 (m, 1H), 7.22–7.25 (m, 1H), 7.38 (t, J=7.6 Hz, 1H), 7.52–7.55 (m, 1H), 7.66 (brs, 1H), 7.74 (d, J=8.3 Hz, 1H), 7.82–7.88 (m, 2H), 8.10–8.13 (m, 1H), 8.13 (s, 1H), 8.78–8.91 (m, 1H), 8.92–9.08 (m, 1H), 9.49 (d, J=8.7 Hz, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 165.1, 138.4, 136.8, 136.0, 134.7,

132.9, 130.9, 129.2, 127.9, 127.8, 127.6 (q, J=34 Hz), 126.3, 125.3, 124.7, 124.3, 123.6 (q, J=270 Hz), 121.6, 58.3, 55.8, 44.7, 38.7, 25.8, 21.6, 21.2; HR-MS: Calcd for $C_{24}H_{24}ClF_3N_4O$ $[M+H]^+$ 477.1664. Found 477.1658; $[\alpha]_D$=+68 (c=0.52, MeOH).

3-Chloro-*N*-{(*S*)-[3-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-[(2*S*)-piperidin-2-yl]methyl}-2-(trifluoromethyl)pyridine-4-carboxamide Hydrochloride (7u) Compound **7u** (43% in 2 steps) was obtained from **21d** in a manner similar to that described for **7c**. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 1.33–1.49 (m, 3H), 1.55–1.66 (m, 1H), 1.67–1.77 (m, 2H), 2.81–2.91 (m, 1H), 3.34–3.39 (m, 1H), 3.48–3.58 (m, 1H), 3.87 (s, 3H), 5.11–5.24 (m, 1H), 7.25 (d, J=7.8 Hz, 1H), 7.39 (t, J=7.6 Hz, 1H), 7.54 (d, J=7.3 Hz, 1H), 7.65 (s, 1H), 7.87 (s, 1H), 8.07–8.21 (m, 2H), 8.82 (d, J=4.6 Hz, 1H), 8.89–9.10 (m, 2H), 9.78–9.86 (m, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 163.5, 147.7, 146.2, 143.3 (q, J=34 Hz), 138.1, 136.1, 133.0, 129.2, 127.9, 127.4, 126.2, 125.2, 124.8, 124.3, 121.6, 120.9 (q, J=277 Hz), 58.2, 55.8, 44.8, 38.7, 25.7, 21.6, 21.2; HR-MS: Calcd for $C_{23}H_{23}ClF_3N_5O$ $[M+H]^+$ 478.1616. Found 478.1605; $[\alpha]_D$=+69 (c=0.53, MeOH).

3-Chloro-*N*-{(*S*)-[3-(1-methyl-1*H*-pyrazol-4-yl)phenyl]-[(2*S*)-piperidin-2-yl]methyl}-4-(trifluoromethyl)pyridine-2-carboxamide Hydrochloride (7v) Compound **7v** (43% in 2 steps) was obtained from **21d** in a manner similar to that described for **7c**. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 1.33–1.52 (m, 3H), 1.53–1.63 (m, 1H), 1.66–1.77 (m, 2H), 2.77–2.86 (m, 1H), 3.25–3.36 (m, 1H), 3.55–3.64 (m, 1H), 3.88 (s, 3H), 5.12–5.21 (m, 1H), 7.25–7.30 (m, 1H), 7.41 (t, J=7.8 Hz, 1H), 7.52–7.57 (m, 1H), 7.65 (s, 1H), 7.87 (s, 1H), 8.07 (d, J=5.0 Hz, 1H), 8.15 (s, 1H), 8.46–8.60 (m, 1H), 8.75–8.86 (m, 1H), 8.88 (d, J=5.0 Hz, 1H), 9.60 (d, J=8.7 Hz, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 163.6, 152.6, 148.5, 138.4, 136.1, 135.8 (q, J=32 Hz), 133.0, 129.3, 127.9, 125.7, 125.2, 124.7, 124.4, 123.1, 121.8 (q, J=275 Hz), 121.6, 58.1, 55.5, 44.7, 38.7, 25.6, 21.6, 21.4; HR-MS: Calcd for $C_{23}H_{23}ClF_3N_5O$ $[M+H]^+$ 478.1616. Found 478.1603; $[\alpha]_D$=+71 (c=0.50, MeOH).

3-Chloro-*N*-{(*S*)-[3-(1-ethyl-1*H*-pyrazol-4-yl)phenyl]-[(2*S*)-piperidin-2-yl]methyl}-4-(trifluoromethyl)pyridine-2-carboxamide Hydrochloride (7w) Compound **7w** (71% in 2 steps) was obtained from **21e** in a manner similar to that described for **7c**. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 1.35–1.52 (m, 3H), 1.41 (t, J=7.3 Hz, 3H), 1.54–1.65 (m, 1H), 1.68–1.77 (m, 2H), 2.78–2.87 (m, 1H), 3.27–3.34 (m, 1H), 3.57–3.64 (m, 1H), 4.17 (q, J=7.3 Hz, 2H), 5.16–5.21 (m, 1H), 7.26–7.29 (m, 1H), 7.41 (t, J=7.8 Hz, 1H), 7.53–7.57 (m, 1H), 7.66–7.68 (m, 1H), 7.88 (s, 1H), 8.06 (d, J=4.6 Hz, 1H), 8.20 (s, 1H), 8.52–8.65 (m, 1H), 8.81–9.00 (m, 1H), 8.87 (d, J=5.0 Hz, 1H), 9.65 (d, J=9.2 Hz, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 163.6, 152.7, 148.5, 138.5, 135.9, 135.8 (q, J=37 Hz), 133.1, 129.3, 126.5, 125.7, 125.1, 124.7, 124.5, 123.0, 121.7 (q, J=275 Hz), 121.4, 58.1, 55.5, 46.4, 44.6, 25.5, 21.6, 21.4, 15.5; HR-MS: Calcd for $C_{24}H_{25}ClF_3N_5O$ $[M+H]^+$ 492.1772. Found 492.1763; $[\alpha]_D$=+68 (c=0.52, MeOH).

3-Chloro-*N*-[(*S*)-[(2*S*)-piperidin-2-yl]{3-[1-(propan-2-yl)-1*H*-pyrazol-4-yl]phenyl}methyl]-4-(trifluoromethyl)-pyridine-2-carboxamide Hydrochloride (7x) Compound **7x** (58% in 2 steps) was obtained from **21f** in a manner similar to that described for **7c**. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 1.32–1.52 (m, 3H), 1.46 (d, J=6.9 Hz, 6H), 1.52–1.65 (m, 1H), 1.67–1.78 (m, 2H), 2.77–2.87 (m, 1H), 3.27–3.35 (m, 1H), 3.56–3.65 (m, 1H), 4.49–4.56 (m, 1H), 5.15–5.20 (m, 1H), 7.27 (d, J=7.3 Hz, 1H), 7.41 (t, J=7.6 Hz, 1H), 7.56 (d, J=7.8 Hz, 1H), 7.67 (br s, 1H), 7.87 (s, 1H), 8.07 (d, J=5.0 Hz, 1H), 8.23 (s, 1H), 8.50–8.58 (m, 1H), 8.83–8.92 (m, 2H), 9.63 (d, J=9.2 Hz, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 163.5, 152.5, 148.4, 138.4, 135.8 (q, J=31 Hz), 135.6, 133.2, 129.2, 125.7, 125.1, 124.8, 124.7, 124.4, 123.1, 121.7 (q, J=275 Hz), 121.1, 58.1, 55.5, 53.1, 44.6, 25.6, 22.7, 21.6, 21.3; HR-MS: Calcd for $C_{25}H_{27}ClF_3N_5O$ $[M+H]^+$ 506.1929. Found 506.1917; $[\alpha]_D$=+70 (c=0.49, MeOH).

3-Chloro-*N*-{(*S*)-(2*S*)-piperidin-2-yl[3-(1-propyl-1*H*-pyrazol-4-yl)phenyl]methyl}-4-(trifluoromethyl)pyridine-2-carboxamide Hydrochloride (7y) Compound **7y** (61% in 2 steps) was obtained from **21g** in a manner similar to that described for **7c**. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 0.85 (t, J=7.3 Hz, 3H), 1.34–1.52 (m, 3H), 1.54–1.65 (m, 1H), 1.67–1.76 (m, 2H), 1.82 (tq, J=7.3, 7.2 Hz, 2H), 2.77–2.87 (m, 1H), 3.25–3.34 (m, 1H), 3.56–3.65 (m, 1H), 4.09 (t, J=6.9 Hz, 2H), 5.16–5.21 (m, 1H), 7.28 (d, J=7.8 Hz, 1H), 7.41 (t, J=7.8 Hz, 1H), 7.53–7.57 (m, 1H), 7.66–7.68 (m, 1H), 7.89 (s, 1H), 8.06 (d, J=5.0 Hz, 1H), 8.19 (s, 1H), 8.51–8.62 (m, 1H), 8.83–8.94 (m, 2H), 9.65 (d, J=8.7 Hz, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 163.5, 152.5, 148.5, 138.4, 136.0, 135.8 (q, J=32 Hz), 133.1, 129.3, 127.2, 125.7, 125.1, 124.7, 124.4, 123.1, 121.7 (q, J=275 Hz), 121.2, 58.1, 55.5, 53.0, 44.7, 25.6, 23.2, 21.6, 21.3, 10.9; HR-MS: Calcd for $C_{25}H_{27}ClF_3N_5O$ $[M+H]^+$ 506.1929. Found 506.1916; $[\alpha]_D$=+84 (c=0.41, MeOH).

***tert*-Butyl (2*S*)-2-{(*S*)-Hydroxy[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl}piperidine-1-carboxylate (22)** Potassium acetate (5.27 g, 53.7 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (1.46 g, 1.79 mmol), 1,1′-bis(diphenylphosphino)ferrocene (1.19 g, 2.51 mmol), and bis(pinacolato)diboron (5.00 g, 19.7 mmol) were added to a solution of **19b** (7.86 g, 17.9 mmol) in 1,4-dioxane (150 mL), and the mixture was stirred at 80°C for 3 h. The reaction solution was partitioned between water and EtOAc, and the organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified using silica gel column chromatography (33–50% EtOAc in hexane) to yield **22** (6.82 g, 91%) as a pale yellow amorphous. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.83 (br s, 1H), 7.74 (d, J=7.3 Hz, 1H), 7.44–7.49 (m, 1H), 7.33–7.40 (m, 1H), 4.89 (d, J=10.1 Hz, 1H), 3.98–4.50 (m, 2H), 2.87–3.41 (m, 1H), 1.52 (s, 9H), 1.34 (s, 12H), 1.25–1.73 (m, 6H); MS (ESI): m/z 418 $[M+H]^+$.

***tert*-Butyl (2*S*)-2-{(*S*)-Hydroxy[3-(pyrazin-2-yl)phenyl]-methyl}piperidine-1-carboxylate (23a)** 2-Chloropyrazine (0.64 g, 5.56 mmol), tetrakis(triphenylphosphine)palladium(0) (96 mg, 0.083 mmol), and potassium carbonate (0.77 g, 5.56 mmol) were added to a solution of **22** (1.16 g, 2.78 mmol) in a mixed solvent of DMF–EtOH (2 : 1, 18 mL), and the mixture was stirred at 90°C for 2 h. The reaction solution was partitioned between water and EtOAc, and the organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified using silica gel column chromatography (33–67% EtOAc in hexane) to yield **23a** (0.79 g, 77%) as a colorless amorphous. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.32–1.86 (m, 6H), 1.52 (s, 9H), 2.91–3.18 (m, 1H), 3.99–4.25 (m, 1H), 4.35–4.54 (m, 1H), 5.00 (d, J=10.5 Hz, 1H), 7.48–7.57 (m, 2H), 7.92–7.99 (m, 1H), 8.03–8.08 (m, 1H), 8.52 (d, J=2.6 Hz, 1H), 8.62–8.66 (m, 1H),

9.04 (d, J=1.3 Hz, 1H); MS (ESI): m/z 370 $[M+H]^+$.

***tert*-Butyl (2*S*)-2-{(*S*)-Hydroxy[3-(1-methyl-1*H*-imidazol-5-yl)phenyl]methyl}piperidine-1-carboxylate (23b)** Compound **23b** (74%) was prepared from **22** in a manner similar to that described for **23a**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.30–1.74 (m, 6H), 1.51 (s, 9H), 2.89–4.47 (m, 3H), 3.67 (s, 3H), 4.93 (br d, J=9.1 Hz, 1H), 7.11 (s, 1H), 7.31–7.35 (m, 1H), 7.36–7.47 (m, 3H), 7.52 (s, 1H); MS (ESI): m/z 372 $[M+H]^+$.

(*S*)-1-[(2*S*)-1-(Prop-2-en-1-yl)piperidin-2-yl]-1-[3-(pyrazin-2-yl)phenyl]methanamine (24a) Compound **24a** (49% in 4 steps) was prepared from **23a** in a manner similar to that described for the synthesis of **13c** from **10c**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.04–1.11 (m, 1H), 1.31–1.77 (m, 5H), 2.67–2.77 (m, 2H), 3.04–3.11 (m, 1H), 3.34–3.46 (m, 2H), 4.32 (d, J=10.1 Hz, 1H), 5.13–5.16 (m, 1H), 5.20–5.25 (m, 1H), 5.87–5.96 (m, 1H), 7.45–7.52 (m, 2H), 7.88–7.91 (m, 1H), 8.02–8.04 (m, 1H), 8.50–8.52 (m, 1H), 8.63–8.65 (m, 1H), 9.04–9.06 (m, 1H); MS (ESI): m/z 309 $[M+H]^+$.

(*S*)-1-[3-(1-Methyl-1*H*-imidazol-5-yl)phenyl]-1-[(2*S*)-1-(prop-2-en-1-yl)piperidin-2-yl]methanamine (24b) Compound **24b** (20% in 4 steps) was prepared from **23b** in a manner similar to that described for the synthesis of **13c** from **10c**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.02–1.09 (m, 1H), 1.31–1.68 (m, 5H), 2.65–2.72 (m, 2H), 3.02–3.09 (m, 1H), 3.36–3.41 (m, 2H), 3.67 (s, 3H), 4.25 (d, J=10.1 Hz, 1H), 5.11–5.16 (m, 1H), 5.19–5.26 (m, 1H), 5.85–5.95 (m, 1H), 7.10–7.11 (m, 1H), 7.27–7.29 (m, 1H), 7.36–7.41 (m, 3H), 7.51 (s, 1H); MS (ESI): m/z 311 $[M+H]^+$.

2-Chloro-*N*-{(*S*)-(2*S*)-piperidin-2-yl[3-(pyrazin-2-yl)-phenyl]methyl}-3-(trifluoromethyl)benzamide Hydrochloride (7g) Compound **7g** (37% in 2 steps) was prepared from **24a** in a manner similar to that described for **7c**. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 1.34–1.49 (m, 3H), 1.55–1.66 (m, 1H), 1.68–1.77 (m, 2H), 2.82–2.91 (m, 1H), 3.33–3.39 (m, 1H), 3.54–3.63 (m, 1H), 5.25–5.31 (m, 1H), 7.57–7.62 (m, 2H), 7.68 (t, J=7.8 Hz, 1H), 7.94–7.97 (m, 1H), 7.98–8.02 (m, 1H), 8.13–8.15 (m, 1H), 8.24–8.27 (m, 1H), 8.66 (d, J=2.8 Hz, 1H), 8.72–8.87 (m, 2H), 8.95–9.10 (m, 1H), 9.29–9.35 (m, 1H), 9.62 (d, J=8.7 Hz, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 165.4, 151.1, 144.3, 143.7, 142.2, 138.8, 138.6, 136.2, 133.4, 129.4, 128.7, 128.0, 127.7, 127.2 (q, J=31 Hz), 126.4, 126.1, 126.0, 122.7 (q, J=273 Hz), 58.1, 55.8, 44.8, 25.7, 21.6, 21.3; HR-MS: Calcd for $C_{24}H_{22}ClF_3N_4O$ $[M+H]^+$ 475.1507. Found 475.1498; $[\alpha]_D$=+77 (c=0.55, MeOH).

2-Chloro-*N*-{(*S*)-[3-(1-methyl-1*H*-imidazol-5-yl)phenyl]-[(2*S*)-piperidin-2-yl]methyl}-3-(trifluoromethyl)benzamide Hydrochloride (7j) Compound **7j** (40% in 2 steps) was prepared from **24b** in a manner similar to that described for **7c**. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 1.34–1.51 (m, 3H), 1.56–1.65 (m, 1H), 1.69–1.77 (m, 2H), 2.79–2.88 (m, 1H), 3.29–3.43 (m, 1H), 3.57–3.66 (m, 1H), 3.88 (s, 3H), 5.24–5.29 (m, 1H), 7.57–7.64 (m, 3H), 7.66 (t, J=7.8 Hz, 1H), 7.72 (s, 1H), 7.88 (s, 1H), 7.93–7.97 (m, 1H), 7.98–8.04 (m, 1H), 8.77–8.92 (m, 1H), 9.07–9.22 (m, 2H), 9.72–9.77 (m, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ: 165.3, 139.1, 138.6, 136.8, 133.8, 133.5, 129.5, 129.1, 128.8, 128.6, 128.3, 128.0, 127.7, 127.2 (q, J=30 Hz), 126.3, 122.8 (q, J=274 Hz), 118.2, 57.9, 55.5, 44.7, 34.5, 25.7, 21.5, 21.4; HR-MS: Calcd for $C_{24}H_{24}ClF_3N_4O$ $[M+H]^+$ 477.1664. Found 477.1662; $[\alpha]_D$=+54 (c=0.59, MeOH).

***tert*-Butyl (2*S*)-2-(3-Bromobenzoyl)piperidine-1-carboxylate (25)** Under a nitrogen gas atmosphere, *n*-BuLi (2.64 mol/L hexane solution, 175 mL) was added dropwise to a solution of 1,3-dibromobenzene (148 g, 629 mmol) in THF (680 mL) cooled with a dry ice-acetone bath, and the mixture was stirred at a temperature below −70°C for 30 min. A solution of **8** (114 g, 419 mmol) in THF (230 mL) was added in a dropwise manner, and the reaction mixture was stirred for 2 h. The reaction was quenched with saturated NH_4Cl aqueous solution and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified using silica gel column chromatography (11% EtOAc in hexane) to yield **25** (71.2 g, 46%) as a pale yellow powder. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.28–1.88 (m, 14H), 1.96–2.20 (m, 1H), 2.98–3.17 (m, 1H), 3.82–4.06 (m, 1H), 5.33–5.64 (m, 1H), 7.29–7.37 (m, 1H), 7.63–7.72 (m, 1H), 7.76–7.89 (m, 1H), 8.00–8.09 (m, 1H); MS (ESI): m/z 368 $[M+H]^+$.

***tert*-Butyl (2*S*)-2-[(3-Bromophenyl)(hydroxyimino)methyl]piperidine-1-carboxylate (26)** Hydroxylamine hydrochloride (1.92 g, 27.6 mol) was added to a solution of **26** (5.10 g, 13.8 mmol) in EtOH (50 mL), and the mixture was stirred for 5 h under reflux condition. After cooling with an ice bath, 4 mol/L HCl solution in EtOAc was added to the reaction mixture and the mixture was stirred overnight at room temperature. A mixed solvent of hexane–EtOAc (1 : 1, 50 mL) was added to the solution, and the precipitate was filtered to yield colorless solid (4.97 g). This solid was suspended in MeOH (50 mL), and triethylamine (5.8 mL, 41.6 mmol) and di-*t*-butyl dicarbonate (9.5 mL, 41.4 mmol) were added under ice cooling. The mixture was stirred for 3 h at rom temperature and then concentrated *in vacuo*. The residue was partitioned between EtOAc and 5% aqueous potassium bisulfate solution, and the organic layer was washed with saturated $NaHCO_3$ aqueous solution, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified using silica gel column chromatography (10–33% EtOAc in hexane) to yield **26** (4.18 g, 79%) as a pale yellow oil. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.37–1.96 (m, 14H), 2.15–2.24 (m, 1H), 2.28–2.94 (m, 1H), 3.66–3.75 (m, 1H), 5.49–5.54 (m, 1H), 7.18–7.52 (m, 4H), 8.27 (s, 1H); MS (ESI): m/z 383 $[M+H]^+$.

***tert*-Butyl (2*S*)-2-{[3-(1-Ethyl-1*H*-pyrazol-4-yl)phenyl]-(hydroxyimino)methyl}piperidine-1-carboxylate (27)** A solution of potassium carbonate (117 g, 850 mmol) in water (1 L) and a solution of 1-ethyl-1*H*-pyrazole-4-boronic acid pinacol ester (163 g, 736 mmol) in EtOH (1 L) and [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)-palladium(II) dichloride (7.70 g, 11.4 mmol) were added to a solution of **26** (217 g, 566 mmol) in toluene (1 L), and the mixture was stirred for 2 h at 72°C. After the reaction mixture was cooled to room temperature, brine (400 mL) was added, followed by extraction with EtOAc (400 mL×2). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified using silica gel column chromatography (20–60% EtOAc in hexane) to yield **27** (174 g, 77%) as a pale yellow amorphous. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.23–1.39 (m, 9H), 1.40–2.26 (m, 9H), 2.28–3.03 (m, 1H), 3.67–3.77 (m, 1H), 4.16–4.24 (m, 2H), 5.59–5.65 (m, 1H), 7.12–7.19 (m, 1H), 7.30–7.48 (m, 3H), 7.65 (s, 1H), 7.74–7.76 (m, 1H), 8.01–8.53 (m, 1H); MS (ESI): m/z 399 $[M+H]^+$.

***tert*-Butyl (2*S*)-2-{(*S*)-Amino[3-(1-ethyl-1*H*-pyrazol-4-yl)-phenyl]methyl}piperidine-1-carboxylate (28)** Compound

27 (50.1 g, 126 mmol) and 10% Pd/C (5.0 g) were added to an 8 mol/L NH_3 solution in MeOH (300 mL), and the mixture was stirred under a hydrogen gas atmosphere for 20 h at room temperature. 8 mol/L NH_3 solution in MeOH (140 mL) and 10% Pd/C (5.0 g) were added, and the mixture was stirred for an additional 7.5 h at 45°C. After filtration, the solvent was removed *in vacuo*. The residue was purified using silica gel column chromatography (5% MeOH in $CHCl_3$) to yield **28** (37.7 g, 78%) as a colorless syrup. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.28–1.32 (m, 1H), 1.34–1.73 (m, 14H), 1.54 (t, J=7.3 Hz, 3H), 2.80–3.04 (m, 1H), 4.01–4.51 (m, 3H), 4.21 (q, J=7.3 Hz, 2H), 7.14–7.21 (m, 1H), 7.28–7.35 (m, 1H), 7.37–7.41 (m, 1H), 7.42–7.50 (m, 1H), 7.62–7.71 (m, 1H), 7.77 (s, 1H); MS (ESI): m/z 385 $[M+H]^+$.

Synthesis of 3-Chloro-*N*-{(*S*)-[3-(1-ethyl-1*H*-pyrazol-4-yl)phenyl][(2*S*)-piperidin-2-yl]methyl}-4-(trifluoromethyl)pyridine-2-carboxamide (7w) from 28 1-Hydroxybenzotriazole monohydrate (63.8 g, 417 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (68.5 g, 357 mmol) were added to an ice-cooled solution of 3-chloro-4-(trifluoromethyl)pyridine-2-carboxylic acid (67.2 g, 298 mmol) in DMF (500 mL), and the mixture was stirred under ice cooling for 10 min. A solution of **28** (114.5 g, 298 mmol) in DMF (400 mL) was added dropwise to the reaction mixture, and the mixture was stirred at room temperature for 4 h. The reaction was quenched with saturated $NaHCO_3$ aqueous solution and extracted with a mixed solvent of hexane–EtOAc (1 : 1). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified using silica gel column chromatography (40–60% EtOAc in hexane) to yield a colorless amorphous. The amorphous solid was dissolved in EtOAc (1100 mL), and 4 mol/L HCl in EtOAc (280 mL) was then added under ice cooling. The mixture was stirred at room temperature for 3 h, and the reaction solution was concentrated *in vacuo*. The residue was suspended in $CHCl_3$, and 2 mol/L aqueous sodium hydroxide solution was added under ice cooling. The mixture was partitioned, and the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified using silica gel column chromatography (3–7% MeOH in $CHCl_3$) to yield free form of **7w** (96.2 g, 66% in 2 steps) as a colorless amorphous. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.31–1.59 (m, 4H), 1.53 (t, J=7.2 Hz, 3H), 1.74–1.80 (m, 1H), 1.81–1.86 (m, 1H), 2.46–2.54 (m, 1H), 2.94–3.03 (m, 2H), 4.20 (q, J=7.2 Hz, 2H), 5.11 (dd, J=8.1, 3.1 Hz, 1H), 7.20 (d, J=7.8 Hz, 1H), 7.33–7.41 (m, 2H), 7.45–7.48 (m, 1H), 7.65 (s, 1H), 7.73 (d, J=4.5 Hz, 1H), 7.76–7.78 (m, 1H), 8.35 (br d, J=7.8 Hz, 1H), 8.72 (d, J=4.5 Hz, 1H); MS (ESI): m/z 492 $[M+H]^+$.

Biological Assay Glioma T98G cells expressing human GlyT1 were used. The T98G cells were seeded at a density of 2.0×10^4 cells/well onto a 96-well plate and cultured overnight in a carbon dioxide incubator. The test compound was dissolved in 100% DMSO and then dissolved in 10 mM 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid (HEPES) buffer solution (pH 7.4) containing 150 mM sodium chloride, 1 mM calcium chloride, 5 mM potassium chloride, 1 mM magnesium chloride, 10 mM glucose, and 0.2% bovine serum albumin. After the medium for the cell culture was removed, the test compound and [^{3}H] glycine (final concentration, 250 nM) were added to the cells and reacted at room temperature for 15 min. After the completion of the reaction, the labeled glycine solution was aspirated with a manifold. The cells were then lysed with 0.5 mol/L sodium hydroxide solution. The amount of intracellular glycine was determined by measuring the radio activity in the cell lysate using a liquid scintillation counter. The quantity of glycine uptake in the presence of 10 μM ALX5407 was defined as nonspecific uptake, and the specific uptake amount was determined by subtracting the nonspecific uptake amount from the total uptake amount in the absence of 10 μM ALX5407. The glycine uptake inhibitory activity (IC_{50} value) was calculated from an inhibition curve for test compound concentrations of 10^{-10} to 10^{-6}.

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Conflict of Interest All authors are employees of Taisho Pharmaceutical Co., Ltd.

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