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Article

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Design and Synthesis of Bitopic 2-Phenylcyclopropylmethylamine (PCPMA) Derivatives as Selective Dopamine D3 Receptor Ligands

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ABSTRACT

2-Phenylcyclopropylmethylamine (PCPMA) analogs have been reported as selective serotonin 2C agonists. Based on the same scaffold, we designed and synthesized a series of bitopic derivatives as dopamine D3R ligands. A number of these new compounds show a high binding affinity for D3R with excellent selectivity. Compound (1*R*,2*R*)-**22e** and its enantiomer (1*S*,2*S*)-**22e** show comparable binding affinity for the D3R, but the former is a potent D3R agonist while the latter acts as an antagonist. Molecular docking studies revealed different binding poses of the PCPMA moiety within the orthosteric binding pocket of the D3R, which might explain the different functional profiles of the enantiomers. Compound (1*R*,2*R*)-**30q** shows a high binding affinity for the D3R (K_i = 2.2 nM) along with good selectivity, as well as good bioavailability and brain penetration properties in mice. These results reveal that the PCPMA scaffold may serve as a privileged scaffold for the design of aminergic GPCR ligands.

INTRODUCTION

G protein-coupled receptors (GPCRs) constitute the largest family of membrane proteins with more than 800 members.[1] GPCRs are the dominant drug targets of over 30% of US FDA-approved small molecule drugs.[2] The aminergic subfamily of GPCRs is particularly rewarding drug targets that have led to the development of many widely prescribed drugs, and they remain the most actively pursued GPCR drug targets.[3] Endogenous ligands of aminergic GPCRs are monoamines (i.e. dopamine, serotonin, and histamine) which share a chemotype that features a basic nitrogen atom attached to an aromatic moiety via a linker. Most drugs targeting aminergic GPCRs are small molecules of a similar chemotype or their structural derivatives. As a result, many drugs that target aminergic GPCRs are polypharmacological drugs that show limited selectivity across receptor subtypes.[3] On the other hand, the shared chemotype among different aminergic GPCR ligands also offers an opportunity for scaffold repurposing of a drug targeting a specific GPCR to compounds that show selectivity for another receptor.

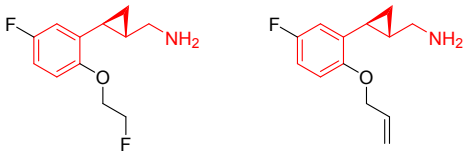


Figure 1. PCPMA-based serotonin 2C agonists and their binding activity at D3R.

2-Phenylcyclopropylmethylamines (PCPMAs) are a class of compounds that have been reported to act as selective serotonin 2C (5-HT_{2C}) agonists,[4-7] which may have potential

value in treating neurological diseases such as schizophrenia and drug addiction.[8, 9] Compounds **1** and **2** (Figure 1), for example, are highly selective 5-HT_{2C} agonists that show in vivo efficacy in schizophrenia-like behavioral models.[4, 9] In our previous screening data of compounds **1** and **2**, we noticed that they showed moderate binding affinities for the dopamine D_3 receptor (D3R) (K_i = 1712 and 811 nM respectively).[4] The D3R is another potential drug target that is involved in central nervous system (CNS) diseases such as drug addiction.[10] Many highly selective D3R ligands have been reported in the literature, and BP-897 (**3**, Figure 2) was the first compound to enter clinical trials.[11] Shown in Figure 2 are representative D3R antagonists that share a well-known scaffold with a primary pharmacophore that binds to the orthosteric binding pocket (OBP) and a secondary pharmacophore binding to the extended binding pocket (EBP), both of which are connected with a proper linker. GPCR ligands with such a scaffold have been depicted as "bitopic" binders.[12] Interestingly, the 2-fluoroethoxyl substitution as in compound **1** has been used in the D3R antagonist **4**,[13] and a cyclopropane can be found in compounds such as **5**[14], **6**[15] and **7**[16], which share structural similarity with the PCPMA scaffold of compounds **1** and **2**. Also, a cyclopropane was recently introduced into the linker of a reported D3R bitopic agonist **8**.[17]

Although several highly selective D3R ligands have been reported in the literature, most compounds suffer from poor bioavailability, low brain penetration or unwanted side effects in clinical trials.[18, 19] Therefore, there is still a need for novel D3R selective ligands. Based on the co-crystal structures of both the 5-HT_{2C} and the D3R receptors,[20, 21] we envisioned that the small PCPMA scaffold of compounds **1** and **2** binds to the

orthosteric pockets of both receptors, with the primary amine group interacts with the conserved Asp3.32 residue through a conserved salt bridge among aminergic GPCRs.[3] By attaching a D3R-preferring spacer and an EBP binding motif to the nitrogen atom of PCPMA, we expect to obtain bitopic PCPMA derivatives as D3R selective ligands (Figure 2). Therefore, we started a campaign to design and synthesize derivatives of compound **1** to discover novel D3R ligands, and these results are reported herein. Our research shows that in addition to its action at the 5-HT_{2C} receptor, PCPMA may serve as a privileged scaffold that can be repurposed for other aminergic GPCRs.

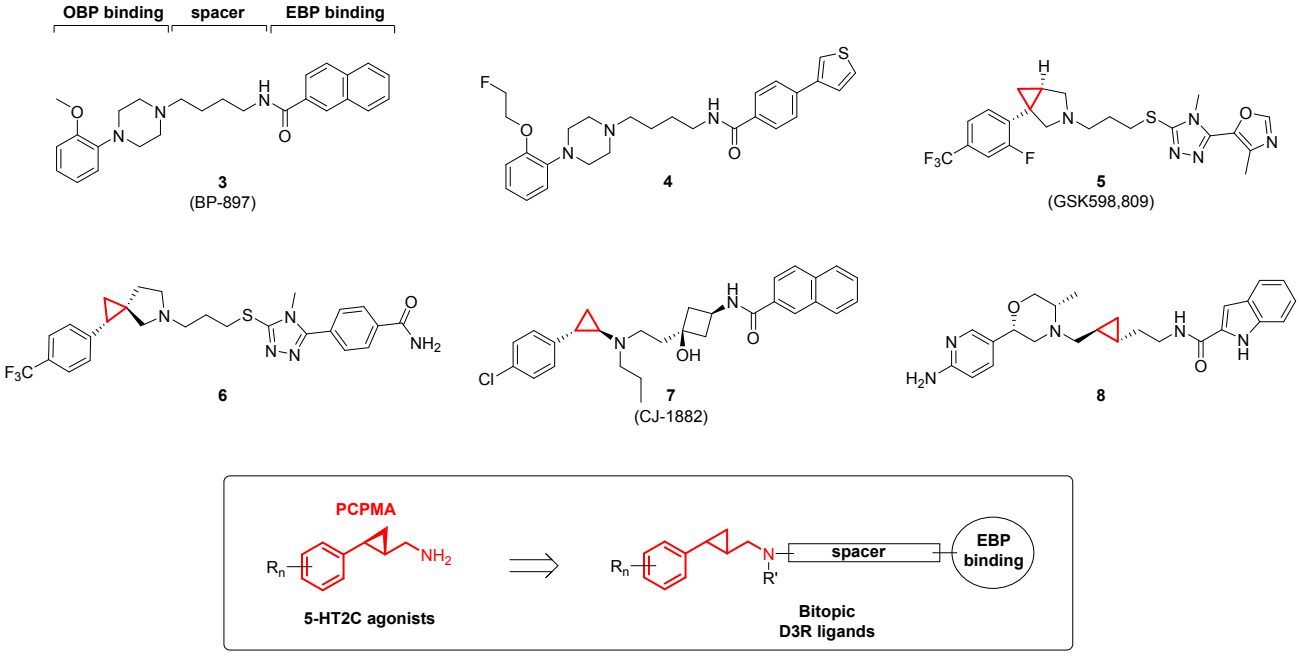


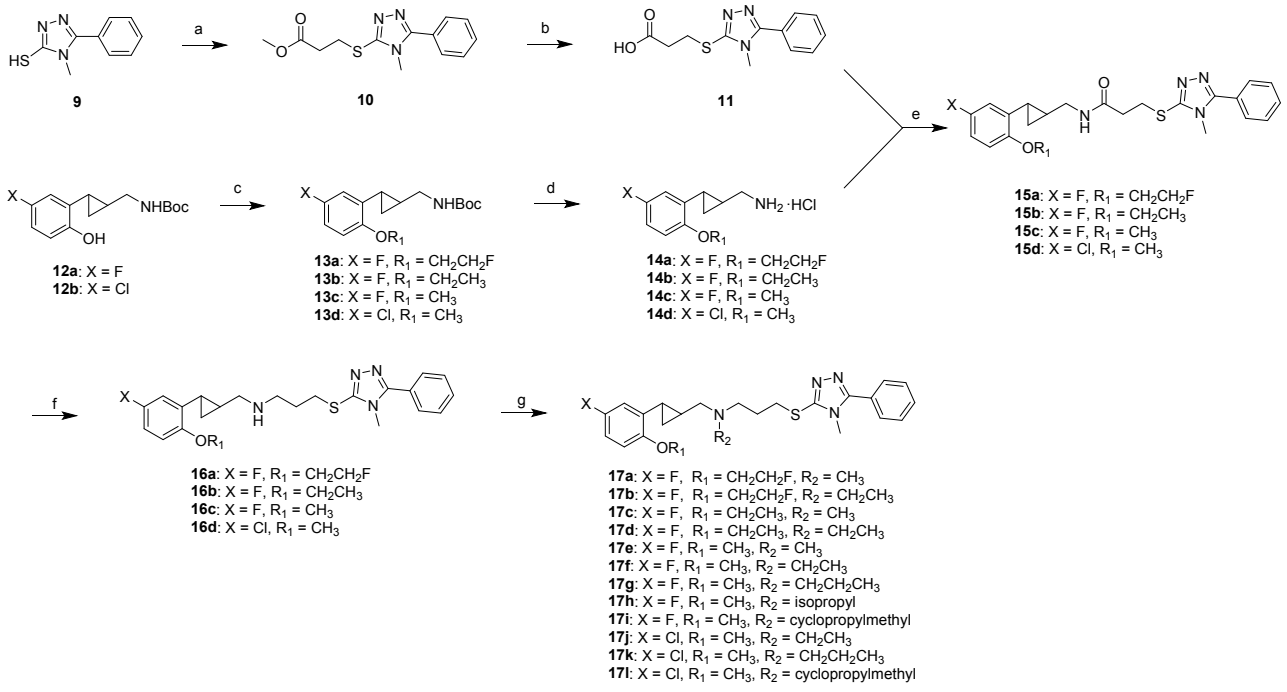
Figure 2. Representative D3R antagonists and the design of PCPMA derivatives.

RESULTS AND DISCUSSION

Chemistry. Based on the structural similarity of the PCPMA with D3R ligands **5** and **6**, we first set out to synthesize PCPMA derivatives with the triazole-thiol ether as the secondary pharmacophore. 4-Methyl-5-phenyl-4H-1,2,4-triazole-3-thiol (**9**) was

synthesized according to reported procedures and used as the starting material.[22] A Michael addition reaction of **9** with methyl acrylate, followed by a saponification afforded the carboxylic acid **11**. For the PCPMA part, Boc-protected intermediates **12a** and **12b** were synthesized according to our published procedures,[4] and both were alkylated to give **13a-d** via Mitsunobu reactions with 2-fluoroethanol or direct alkylations with iodomethane or iodoethane, as we previously reported.[4, 5] After the de-protection of the Boc, the primary amines **14a-d** were coupled with **11** to provide amides **15a-d**, which were subsequently reduced using borane-tetrahydrofuran complex to provide target compounds **16a-d**. These secondary amines could be further alkylated under reductive amination conditions with simple aldehydes to afford compounds **17a-l** as tertiary amines (for details, see Experimental Section).

Scheme 1. Synthesis of triazole-thiol ether derivatives.[a]

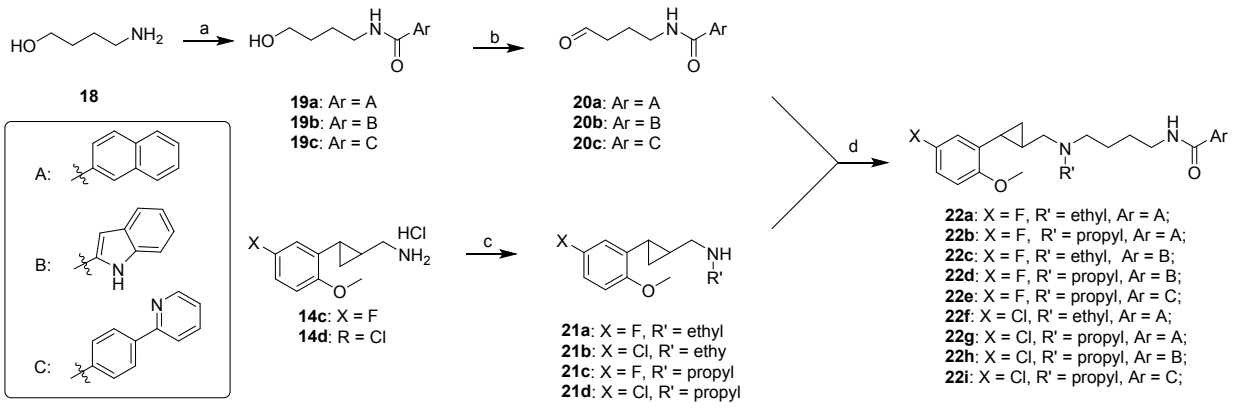


[a]Reagents and conditions: (a) methyl acrylate, Cs_2CO_3, MeOH, microwave, 100 °C, 30

min, 69%; (b) LiOH-H_2O, THF, H_2O, rt, overnight, 60%; (c) for **13a**: 2-fluoroethanol, PPh_3, DEAD, THF, microwave, 60 °C, 30 min, 95%; for **13b**: EtI, K_2CO_3, DMF, microwave, 110 °C, 30 min, 83%; for **13c** and **13d**: MeI, K_2CO_3, DMF, microwave, 110 °C, 30 min, 96%; (d) 2 M HCl in diethyl ether, rt, overnight, 99%; or 4 M HCl in dioxane, rt, 4–5 h, 82–94%; (e) HATU, $NaHCO_3$, DMF, rt, 3 h, 72–90%; (f) BH_3-THF in THF, reflux, 4 h, 58–92%; (g) aldehydes, $NaHB(OAc)_3$, THF, rt, 1 h, 24–89%.

Compounds with an amide connection between the linker and the secondary pharmacophore, similar to those in reported D3R ligands **3** and **4**, were also designed and synthesized. As shown in Scheme 2, 4-aminobutan-1-ol (**18**) was acylated with either acid chloride or coupled with aromatic acids to give amides **19a-c**, and the primary alcohol group was subsequently oxidized to give aldehydes **20a-c**. PCPMAs **14c** and **14d** from Scheme 1 were alkylated under reductive amination conditions to attach ethyl or propyl substituents thereby affording intermediates **21a-d**, which were then reacted with the former aldehydes under reductive amination conditions to yield compounds **22a-i** (for details, see Experimental Section).

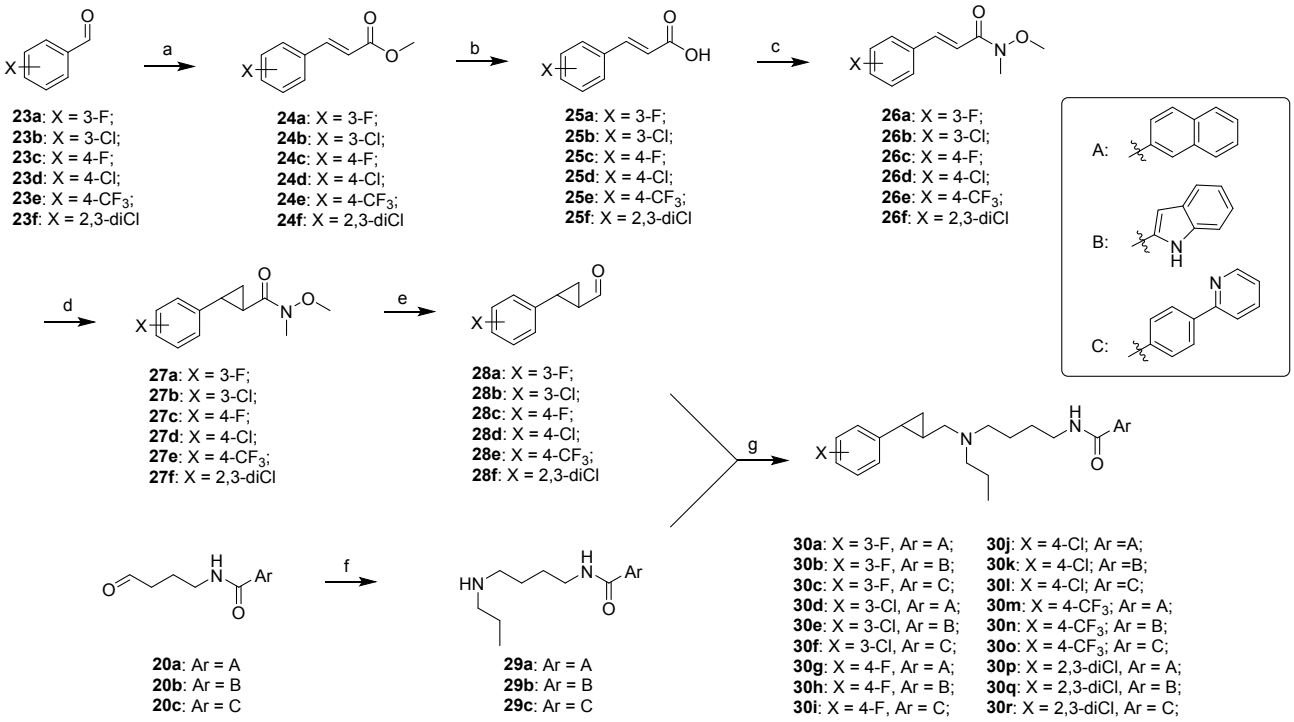
Scheme 2. Synthesis of amide analogs.[a]



[a]Reagents and conditions: (a) for **19a**: 2-naphthoyl chloride, NEt_3, CH_2Cl_2, rt, 2 h, 87%; for **19b**: 1*H*-indole-2-carboxylic acid, HATU, $NaHCO_3$, DMF, rt, 2 h, 80%; for **19c**: 4-(2-pyridyl)benzoic acid, HATU, $NaHCO_3$, DMF, rt, 2 h, 93%; (b) SO_3-Py, DMSO, NEt_3; CH_2Cl_2; (c) for **21a** and **21b**: $NaBH_4$, NEt_3, acetaldehyde, rt, 20 min, 33–34%; for **21c** and **21d**: $NaBH_4$, NEt_3, propionaldehyde, rt, 20 min, 23–31%; (d) $NaHB(OAc)_3$, THF, rt, overnight, 37–68% for steps b and d.

An alternative route for similar amides is shown in Scheme 3. Briefly, starting from phenyl aldehydes **23a-f**, a sequence of Wittig reaction, ester to Weinreb amide conversion, Corey-Chaykowsky cyclopropanation and Weinreb amide to aldehyde reduction provided aldehydes **28a-f**.[4, 5] Next, the abovementioned aldehydes **20a-c** were converted to propyl amines **29a-c** through reductive amination reactions. Further reductive amination reactions of **28a-f** with **29a-c** produced compounds **30a-r** (for details, see Experimental Section).

Scheme 3. Synthesis of amide analogs.[a]

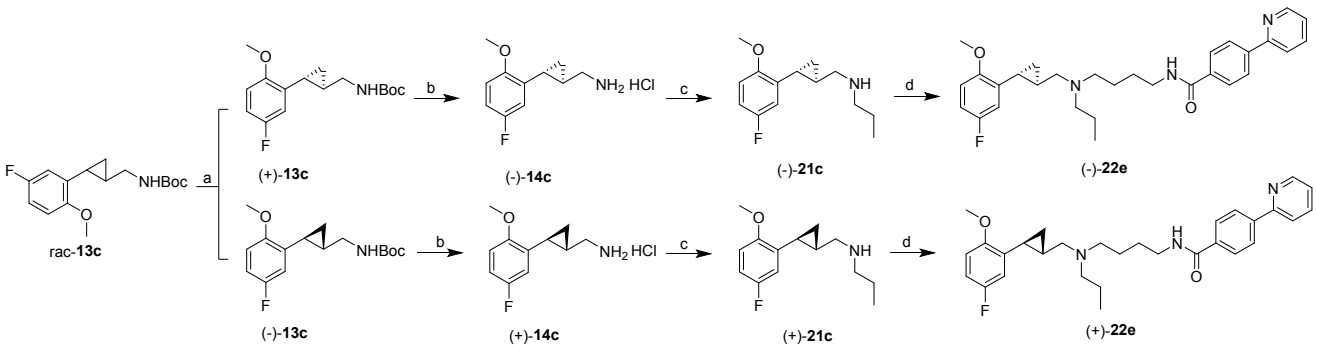


[a]Reagents and conditions: (a) $Ph_3P{=}CHC(=O)OMe$, CH_2Cl_2, rt, overnight, 67–98%; (b) LiOH-H_2O, THF, H_2O, rt, 2 h, 75–100%; (c) N,O-dimethylhydroxylamine hydrochloride, HATU, $NaHCO_3$, DMF, rt, overnight, 81–97%; (d) $Me_3S^+(O)I^-$, NaH, DMSO, rt, overnight, 71–82%; (e) DIBAL-H, THF, −78 °C, 2 h; (f) $NaHB(AcO)_3$, propylamine, AcOH, rt, 44–64%; (g) $NaHB(OAc)_3$, AcOH, THF, rt, overnight, 11–68% for steps e and g.

For the PCPMA moiety of all the new compounds, we obtained only the *trans* isomers through using *E* olefins as the cyclopropanation precursors, the same as our previous 5-HT_{2C} ligands. Of course, the racemic, *trans* compound is composed of a pair of (1*R*, 2*R*)- and (1*S*, 2*S*)-enantiomers. In this research, the racemic compounds **22e**, **30p**, **30q**, and **30r** were separated by chiral HPLC to give optically pure (−)- and (+)-enantiomers for further pharmacological profiling. To determine the absolute configurations of these enantiomers, we re-synthesized the enantiomers of **22e** using a method shown in

Scheme 4 (for details, see Experimental Section). Thus, the Boc-protected intermediate **13c** from Scheme 1 was separated using chiral HPLC to give both isomers (+)-**13c** and (−)-**13c**, which were de-protected subsequently to give HCl salts (−)-**14c** and (+)-**14c** respectively. We had previously determined that the (−)-isomer has the (1*R*, 2*R*) configuration and the (+)-isomer the (1*S*, 2*S*) configuration for very similar compounds.[4, 23] Therefore, the configuration of (−)-**14c** was assigned as (1*R*, 2*R*) and that of (+)-**14c** as (1*S*, 2*S*). Both (−)-**14c** and (+)-**14c** were next converted to (−)-**21c** and (+)-**21c**, and then to (−)-**22e** and (+)-**22e**. Thus, the configuration of (−)-**22e** was assigned as (1*R*,2*R*), and (+)-**22e** as (1*S*,2*S*). As will be discussed below, based on structural similarities and the consistency observed in the 5-HT_{2C} binding data for compounds **30p**, **30q** and **30r**, namely that the (+)-isomer shows better 5-HT_{2C} activity, which is in agreement with both the results from the enantiomers of **22e** and our previous results, the absolute configurations of the (−)-isomers of **30p**, **30q** and **30r** were assigned as (1*R*,2*R*) and the (+)-isomers as (1*S*,2*S*).

Scheme 4. Synthesis of compounds (1*R*,2*R*)- **22e** and (1*S*,2*S*)-**22e**.



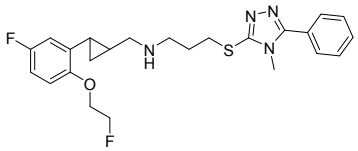
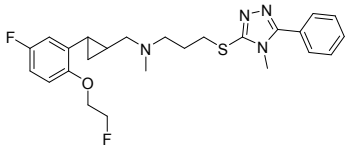
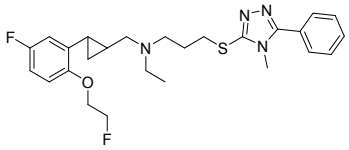
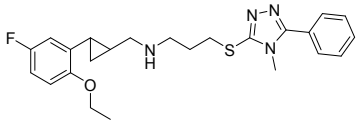
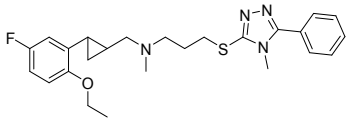
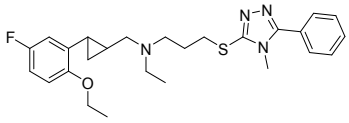
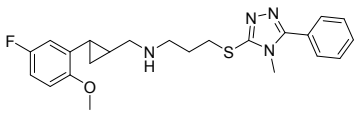
Reagents and conditions: (a) chiral prep-HPLC separation; (b) 4 M HCl in dioxane, rt, overnight, 98%; (c) propionaldehyde, $NaBH_4$, NEt_3, dioxane, rt, 10 min, 34–63%; (d)

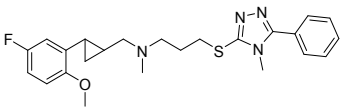
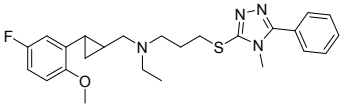
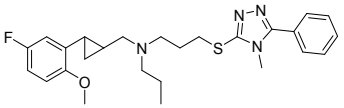
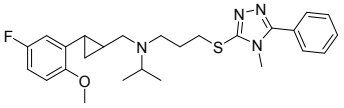
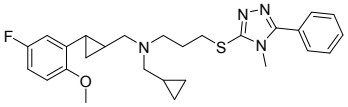
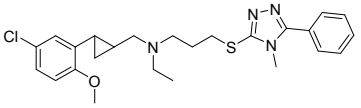
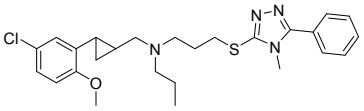
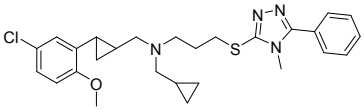
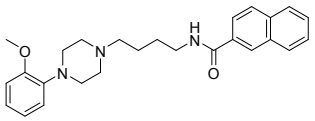
20c, $NaHB(AcO)_3$, THF, rt, overnight, 32–33%.

Structure-Activity Relationships (SARs). Based on the structural similarity between the PCPMA scaffold and the cyclopropane-containing substructures in compounds **5** and **6**, we introduced the 1,2,4-triazolylthiol ether moiety as the EBP binding motif, connected to the *N* atom of PCPMA via a three-carbon spacer. As shown in Table 1, the binding affinity of compounds **16a** and **17a** at D3R increased slightly compared to PCPMA compound **1** (K_i = 1712 nM),[4] but none of them showed significant binding selectivity among five dopamine receptors and the 5-HT_{2C} receptor. The *N*-ethyl compound **17b** showed more than a 10-fold increase in binding affinity compared to the PCPMA compound **1** (113.1 nM *versus* 1712 nM). The 2-fluoroethoxy substituent on the PCPMA part was reduced to an ethoxy group in compounds **16b**, **17c** and **17d**, which resulted in slight increases in binding affinities, as can be seen by comparing **17d** versus **17b**, **17c** versus **17a** and **16b** versus **16a**. When the ethoxy substituent on the benzene ring was further truncated to a methoxy group, binding affinities were further increased, as can be seen from compounds **16c**, **17e** and **17f**, with the last showing a K_i value of 44.0 nM at D3R. The *N*-ethyl group was changed to a propyl (**17g**), an isopropyl (**17h**) or a cyclopropylmethyl group (**17i**), but none of these compounds showed increased affinity for D3R compared to the *N*-ethyl compound **17f**. The fluorine atom on the left-hand benzene ring was changed to a Cl atom in compounds **17j**, **17k** and **17l**, with various *N* substitutions, and these compounds showed comparable binding affinities for D3R and moderate selectivity against D2R, D4R and 5-HT_{2C}, while possessing a lower affinity for the D1R and D5R. Taken together, the introduction

of the 1,2,4-triazolylthiol ether significantly enhanced compound affinity for D3R and reduced their affinity to 5-HT_{2C}, but compared to compound BP-897, their affinity and selectivity still required further improvement. In our assays, BP-897 showed a binding affinity of 3.1 nM at D3R, and 365-, 80-, 205-, 395-, and 70-fold selectivity against D1R (1132 nM), D2R (247.0 nM), D4R (634.0 nM), D5R (1223 nM), and 5-HT_{2C} (218.0 nM) receptors, respectively.

Table 1. Binding affinities of thiol ethers at $D_{1\text{-}5}$ and 5-HT_{2C} receptors.[a]

Compd	Structure[b]	K_i (nM)					
		D_1	D_2	D_3	D_4	D_5	5-HT_{2C}
16a		368.7	1502.0	524.8	962.3	1079.8	NT[c]
17a		1467.8	2435.9	562.3	977.2	2154.4	NT
17b		584.3	844.6	113.1	179.2	1995.3	NT
16b		295.1	660.7	218.8	501.2	588.8	NT
17c		1122.0	>5000	549.6	988.6	>5000	NT
17d		1148.2	380.2	55.0	100.8	1584.9	NT
16c		631.0	253.1	89.8	132.8	926.1	NT

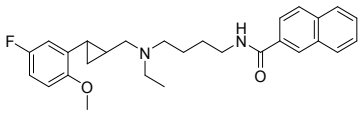
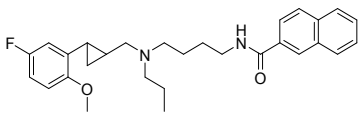
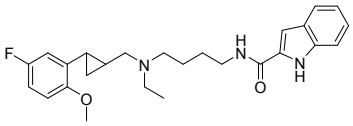
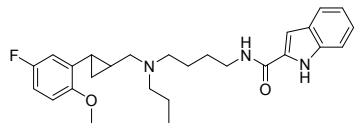
17e		794.3	323.6	84.5	85.1	1000.0	NT
17f		1724.6	275.4	44.0	30.0	1847.9	NT
17g		1668	1161.4	87.1	85.8	>5000	412.1
17h		>5000	512.9	104.7	326.1	>5000	495.4
17i		1078.0	>5000	64.6	291.7	1204.0	125.9
17j		1509	238.0	31.6	241.0	>5000	203.0
17k		1918	233.0	36.7	130.0	>5000	535.0
17l		636	216.0	23.7	163.0	>5000	274.0
BP-897		1132	247.0	3.1	634.0	1223	218.0

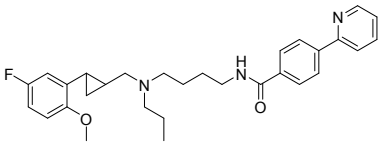
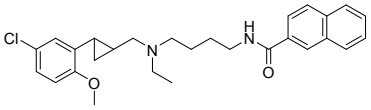
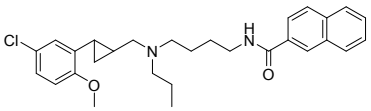
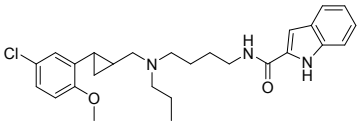
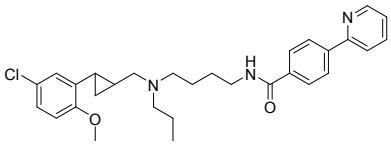
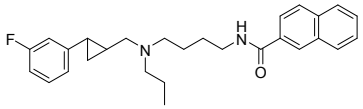
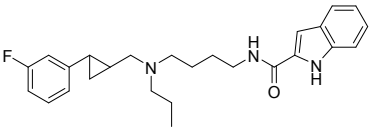
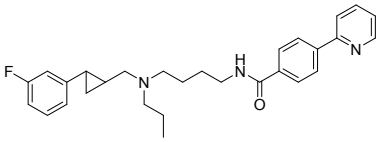
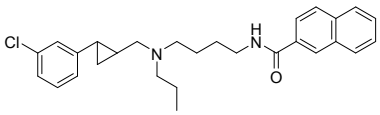
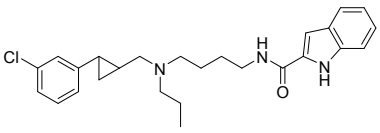
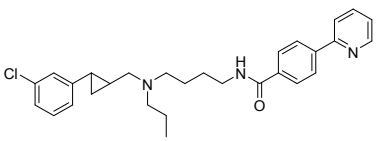
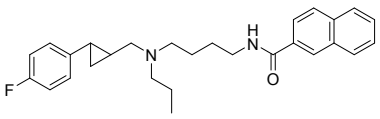
[a]K_i values were calculated from mean pK_i values (mean pK_i ± SEM values from at least three individual experiments are provided in the Supporting Information, Table S1). [b]All compounds were tested as HCl salts. [c]NT, not tested.

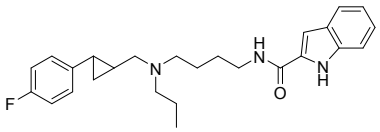
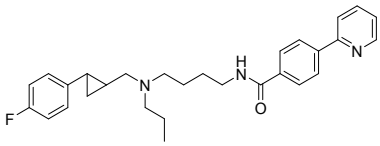
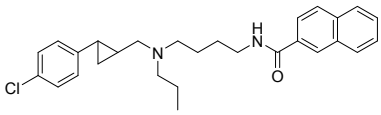
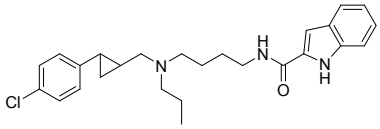
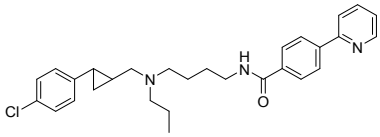
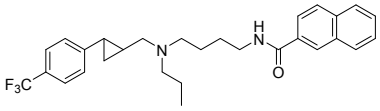
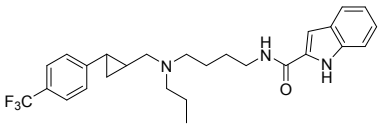
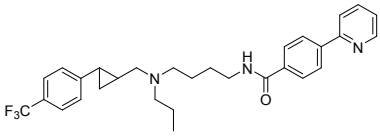
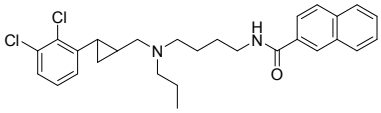
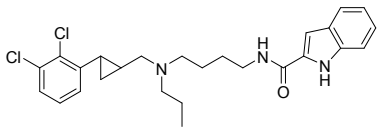
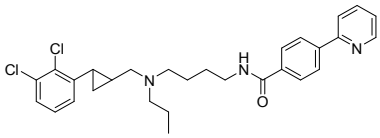
We then turned to a longer spacer group comprised of four carbon atoms, coupled with an amide connection to the EBP-binding aromatic moiety. The results for these analogs are summarized in Table 2. For the aromatic moiety, naphthyl, indolyl and 4-pyridylphenyl were used as they have been reported in numerous D3R selective compounds. Comparing compounds **22a** and **22b**, it can be seen that although they

show identical binding affinities to D3R, the *N*-propyl substitution led to a higher selectivity profile for **22b** versus the *N*-ethyl substitution present in **22a**, especially against D2R and D4R. Also in compound **22d**, the *N*-propyl substituent resulted in a 2-fold increase in binding affinity compared to that of **22c** which has an ethyl substituent. The introduction of a 4-pyridylphenylgroup led to a further increase in binding affinity as in compound **22e**, showing a K_i value of 4.0 nM for D3R. Moreover, compound **22e** showed excellent selectivity against all the other dopamine receptors (439-fold against D1R (1758 nM), 786-fold against D2R (3144 nM), 285-fold against D4R (1142 nM) and >5,000 nM for D5R). However, it showed only moderate selectivity as the racemic mixture over 5-HT_{2C} (53.0 nM *versus* 4.0 nM, or 13-fold). When the fluorine atom was replaced by a chlorine, compound affinity was maintained within the low nM range, but none of these analogs were more potent, as shown for compounds **22f-i**.

Table 2. Binding affinities of amide analogs at $D_{1\text{-}5}$ and 5-HT_{2C} receptors.[a]

Compd	Structure[b]	K_i (nM)					
		D_1	D_2	D_3	D_4	D_5	5-HT_{2C}
22a		986	407.4	15.0	384.6	1721	57.5
22b		967	1083.9	14.5	844.0	2203	63.1
22c		1084	380	23.4	220.0	>5000	49.0
22d		871	507	11.2	376.0	789	68.0

22e		1758	3144	4.0	1142	>5000	53.0
22f		1981	408	23.4	553.0	571	49.0
22g		930	1116	26.9	945.0	1104	85.0
22h		818	1421	11.5	575	4227	85.1
22i		>5000	2105	39.4	1833	>5000	136.0
30a		1308	4823	26.7	1298	>5000	165
30b		1105	3494	18.8	671	>5000	106
30c		2906	>5000	45.4	2222	>5000	1339
30d		940	4012	15.5	1318	8670	136
30e		992	3494	11.1	878	>5000	132
30f		832	>5000	26.5	2326	5580	898
30g		992	5623	55.8	2171	>5000	238

30h		1457	5934	45.7	1609	10532	219
30i		3631	>5000	106.3	2884	>5000	2171
30j		509	4606	32.6	1585	6109	179
30k		649	3162	25.7	510	9290	137
30l		1308	>5000	17.6	1413	8844	284
30m		1711	>5000	43.0	215	5799	1259
30n		1278	>5000	33.1	2073	8191	1308
30o		1423	>5000	23.4	2171	7703	2362
30p		891	2105	2.0	1339	4018	123
30q		891	1502	2.6	1131	3500	105
30r		1647	2362	1.2	2011	>5000	97.7

[a] K_i values were calculated from mean pK_i values (mean pK_i ± SEM values from at least three individual experiments are provided in the Supporting Information, Table S2).

[b]All compounds were tested as HCl salts.

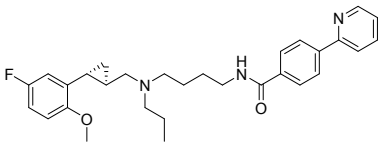
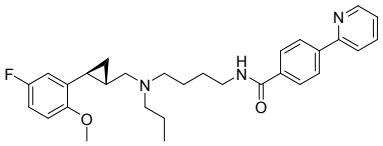
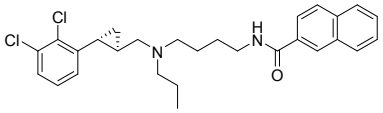
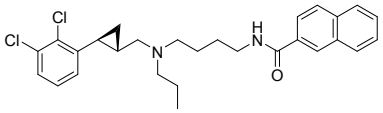
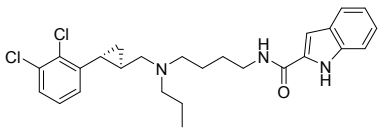
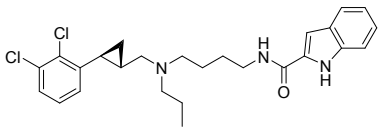
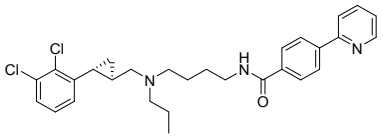
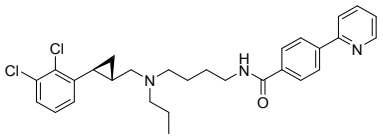
Next, we removed the 2-methoxy group in the PCPMA moiety. Compounds **30a-c**, which retain only the *meta* fluorine substitution, showed good affinities for D3R and excellent selectivity against D2R (Table 2). For example, compound **30c**, with a 4-pyridylphenyl EBP-binding group, showed 45.4 nM binding affinity for D3R, but >5,000 nM binding affinity for D2R and only micromolar affinities for all other tested receptors. When a *meta* chorine was introduced to replace the fluorine atom (compounds **30d-f**), similar results were observed. Compound **30f** showed 26.5 nM binding affinity for D3R, with excellent selectivity against D2R, D4R and D5R and good selectivity over D1R (832 nM) and 5-HT_{2C} (898 nM). We then moved the halogen substitution to the *para* position. As can be seen with compounds **30g-i** (4-F) and **30j-l** (4-Cl), these compounds showed good binding profiles and in particular, compound **30l** represents the best of them, with a K_i value of 17.6 nM for the D3R and good selectivity against the other four dopamine receptors (1308 nM at D1R, no affinity at D2R, 1413 nM at D4R and 8844 nM at D5R, respectively), and moderate selectivity over 5-HT_{2C} (284 nM). The substitution of a *para*-CF_3 group, as present in compounds **5** and **6**, was also introduced. As can be seen from an examination of the data obtained for compounds **30m-o**, although their binding affinities were not improved compared to the *para*-F or *para*-Cl substitution, all three compounds fail to bind to D2R while showing very good selectivity against the other tested receptors. Notably, the presence of a di-chloro substitution pattern, like that present in the drugs aripiprazole and cariprazine, provided compounds **30p-r** which show significantly enhanced binding

affinities for D3R (1.2-2.6 nM). Compound **30r**, which has a K_i of 1.2 nM, showed over 1000-fold selectivity against all other dopamine receptors, and an 81-fold selectivity against 5-HT_{2C} (K_i = 97.7 nM). The overall profiles of **30p** and **30q** were also very encouraging. Based on these results, we selected compounds **22e**, **30p**, **30q** and **30r** for further studies.

Influence of chirality on binding affinity and functional activity. The significance of chirality is a critical consideration in medicinal chemistry and has also been showcased in previous D3R ligand discovery.[17] With respect to the chiral centers on the PCPMA skeleton, although all compounds were synthesized as the *trans* isomers, they were tested as a mixture of (1*R*,2*R*) and (1*S*,2*S*) isomers in our primary screening. We thus selected the four best compounds **22e**, **30p**, **30q** and **30r** for chiral separations and further pharmacological profiling. Chiral separations were conducted using chiral HPLC columns and the absolute configurations of all the isomers were assigned as discussed above. All four pairs of enantiomers were profiled in the same binding assays against the dopamine receptors and the 5-HT_{2C} receptor. As can be seen in Table 3, the (1*R*,2*R*) enantiomers showed slightly better binding affinities for D3R than the (1*S*,2*S*) for compounds **30p**, **30q** and **30r** (4.4 *versus* 20.8 nM, 2.2 *versus* 12.8 nM and 1.5 *versus* 5.3 nM, respectively). For compound **22e**, the enantiomers displayed equal affinities for D3R (4.1 *versus* 3.8 nM). Interestingly, the enantiomers of all four compounds showed comparable affinities for all dopamine receptors within each pair, but their affinities for 5-HT_{2C} were different. The (1*R*,2*R*) enantiomers showed 3-22× weaker 5-HT_{2C} binding affinity than their (1*S*,2*S*) isomers, consistent with the results

of our previous PCPMA analogs.[4] It would appear that the D3R has little binding preference for the chiral conformations of the PCPMA unit, while the 5-HT_{2C} is more sensitive.

Table 3. Enantiomer activity of selected compounds.[a]

Compd	Structure[b]	K_i (nM)					
		D_1	D_2	D_3	D_4	D_5	5-HT_{2C}
(1*R*,2*R*)-**22e**		4898	1349	4.1	575	>5000	1122
(1*S*,2*S*)-**22e**		1071	1230	3.8	851	>5000	50.1
(1*R*,2*R*)-**30p**		1288	676	4.4	813	>5000	427
(1*S*,2*S*)-**30p**		1047	1148	20.8	776	>5000	138
(1*R*,2*R*)-**30q**		1380	537	2.2	1047	>5000	513
(1*S*,2*S*)-**30q**		1122	992	12.8	676	>5000	61.7
(1*R*,2*R*)-**30r**		1349	550	1.5	676	>5000	417
(1*S*,2*S*)-**30r**		2344	1023	5.3	912	>5000	44.7

[a]K_i values were calculated from mean pK_i values (mean pK_i ± SEM values from at least

three individual experiments are provided in the Supporting Information, Table S3). [b]All compounds were tested as HCl salts.

These enantiomers were further profiled for their functional activity at the D_3 and 5-HT_{2C} receptors. As shown in Table 4 and Figure 3A, for compounds **30p-r**, both enantiomers showed full or partial agonist activity at D3R with comparable potency between each pair of enantiomers. Interestingly, (1*R*,2*R*)-**22e** showed very potent agonist activity (EC_{50} = 3.6 nM, E_{max} = 77.9%), while (1*S*,2*S*)-**22e** showed no activity in the agonist mode but behaved as a potent antagonist of D3R (K_i = 16.7 nM). At 5-HT_{2C} (Figure 3C-D), both **22e** enantiomers were weak antagonists with micromolar activity. For compounds **30p-r**, (1*S*,2*S*) isomers were partial agonists with low potency while the (1*R*,2*R*) isomers showed very weak antagonist activity at 5-HT_{2C} receptors. These results reveal that the selected compounds show better selectivity for D3R versus 5-HT_{2C} in the functional assays compared to their selectivity as determined from their binding affinities. Furthermore, these enantiomers were tested at 5-HT_{2A} and 5-HT_{2B} receptors for their agonist activity to exclude potential hallucinogenic or valvulopathic side effects related to these receptors respectively. All enantiomers showed very weak and only partial 5-HT_{2A} agonist activity, and no 5-HT_{2B} agonism was observed (see Supporting Information, Table S1).

The Tango assay was also performed at D3R to evaluate compound activity for β-arrestin2 recruitment (Table 4 and Figure 3B). Compared to their $G_{i/o}$ activity, most compounds showed very weak β-arrestin2 recruitment at D3R. In particular, compounds (1*S*,2*S*)-**22e**, (1*R*,2*R*)-**30p**, (1*R*,2*R*)-**30q** and (1*R*,2*R*)-**30r** showed no

measurable activity in the Tango assay, indicating their preference for the G protein signaling.[24]

Table 4. Functional data of selected compounds at D3R and 5-HT_{2C}.

Compound	D3R G_i	D3R Tango	5-HT_{2C} G_q (Ca^{2+})
(1*R*,2*R*)-**22e**	EC_{50} = 3.58 nM (77.9%[b])	EC_{50} = 126.4 nM (50.2%)	Antagonist: IC_{50} = 14.5 μM
(1*S*,2*S*)-**22e**	No agonism; Antagonist: K_i = 16.7 nM	NT[c]	Antagonist IC_{50} = 0.86 μM
(1*R*,2*R*)-**30p**	EC_{50} = 177.5 nM (71.7%)	9.2% at 3 μM	Antagonist: IC_{50} = 16.1 μM
(1*S*,2*S*)-**30p**	EC_{50} = 99.2 nM (83.4%)	44.4% at 3 μM	Agonist EC_{50} = 3538 nM (30.3 %)
(1*R*,2*R*)-**30q**	EC_{50} = 87.0 nM (40.7%)	<5% at 3 μM	Antagonist: IC_{50} > 30 μM
(1*S*,2*S*)-**30q**	EC_{50} = 142.8 nM (63.4%)	EC_{50} = 1000.2 nM (27.1%)	Agonist EC_{50} = 2549 nM (44.2 %)
(1*R*,2*R*)-**30r**	EC_{50} = 12.5 nM (68.1 %)	3.1% at 3 μM	Antagonist IC_{50} = 10.1 μM
(1*S*,2*S*)-**30r**	EC_{50} = 29.6 nM (96.2%)	EC_{50} = 11086 nM (119.1%)	Agonist EC_{50} = 738.3 nM (51.9%)
Quinpirole	EC_{50} = 0.42 nM (95.4%)	EC_{50} = 35.0 nM (95.2%)	NT
Dopamine	EC_{50} = 0.11 nM (100%)	NT	NT
5-HT	NT	NT	EC_{50} = 0.41 nM (99.0%)

[a]All compounds were tested as HCl salts. [b]For agonist activity, E_{max} values are shown in brackets. [c]NT, not tested.

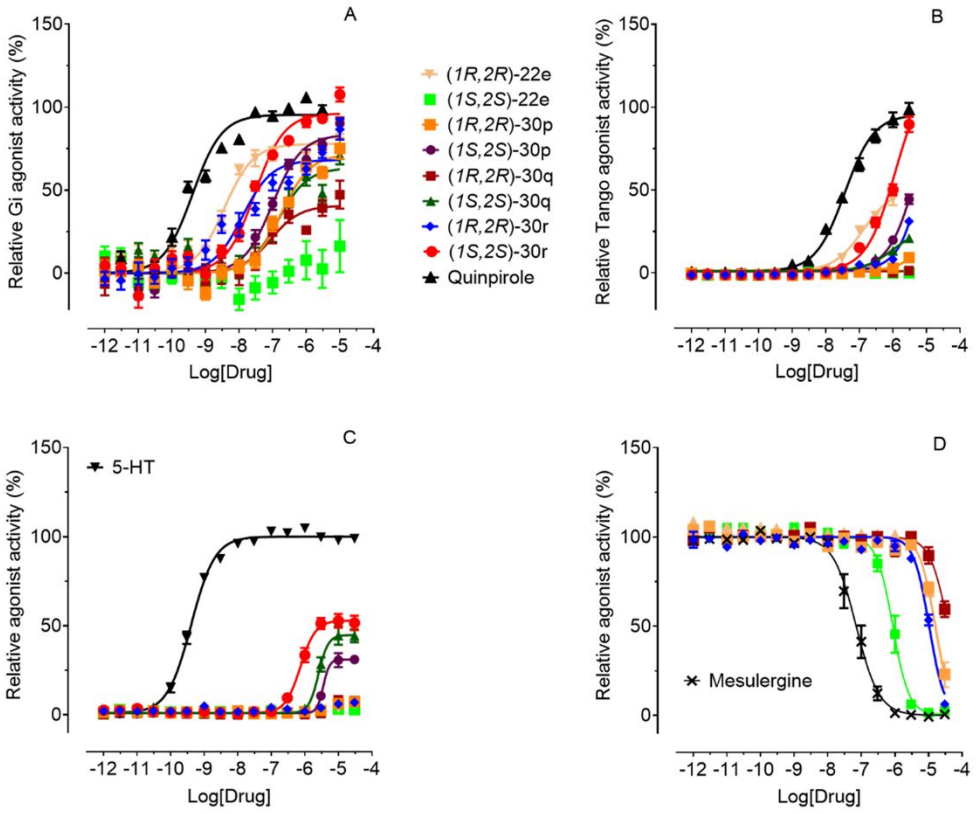


Figure 3. Functional characterization of lead compounds at D_3 dopamine receptors (**A**, **B**) and 5-HT_{2C} receptors (**C**, **D**). (**A**) Inhibition of cAMP production at D_3 (G_i-agonist activity), (**B**) β-arrestin2 recruitment (Tango agonist activity), and calcium mobilization at 5-HT_{2C} (G_q agonist activity in **C** and antagonist activity in **D**) represented means ± SEM from a minimum of 3 independent assays, each in triplicate or quadruplicate. Reference agonist (5-HT) was used at 1 nM final concentration in antagonist assays (**D**), in which mesulergine served as a reference antagonist.

Molecular Docking Studies. To understand the molecular basis of the binding profiles of these new compounds, especially compounds (1*R*,2*R*)- and (1*S*,2*S*)-**22e**, we carried out molecular docking studies on them using Schrödinger's Maestro program. (1*R*,2*R*)- and (1*S*,2*S*)-**22e**, as well as eticlopride, were docked to the antagonist-bound structure of D3R (PDB code: 3PBL).[21] The salt bridge between the positive charged tertiary amine and the carboxylate of D110$^{3.32}$ was observed for all three ligands (Figure 4A), which has been reported as highly conserved for most aminergic receptors.[3] Consistent with previous research[21, 25, 26] and our expectations, the PCPMA moiety of both (1*R*,2*R*)- and (1*S*,2*S*)-**22e** occupies the OBP of D3R, in good alignment with eticlopride, while the attachment to the PCPMA extends into the EBP. Notably, although both (1*R*,2*R*)- and (1*S*,2*S*)-**22e** fit nicely in the OBP with the substituted benzene rings forming π-π stacking and hydrophobic interactions, the orientations of the substituted phenyl ring of (1*R*,2*R*)- and (1*S*,2*S*)-**22e** are quite different. For (1*R*,2*R*)-**22e**, the 2-methoxy substituent on the benzene ring is deeply buried within the OBP, forming hydrophobic contacts with C114$^{3.36}$, S196$^{5.46}$ and F346$^{6.52}$; while the 2-methoxy group of the antagonist (1*S*,2*S*)-**22e** flips up towards the extracellular side. As a result, for antagonist (1*S*,2*S*)-**22e**, the cyclopropane linker between the benzene ring and the protonated *N* overlays perfectly with amide linker of eticlopride, while for the agonist (1*R*,2*R*)-**22e** the cyclopropane points to another direction due to the flip of the benzene ring. Since a structure of the active state of D3R is currently unavailable, the docking of agonist (1*R*,2*R*)-**22e** to the active state of D3R has not been conducted. This flip of the benzene ring in the inactive conformation of D3R might explain the different

functional results observed for these enantiomers.

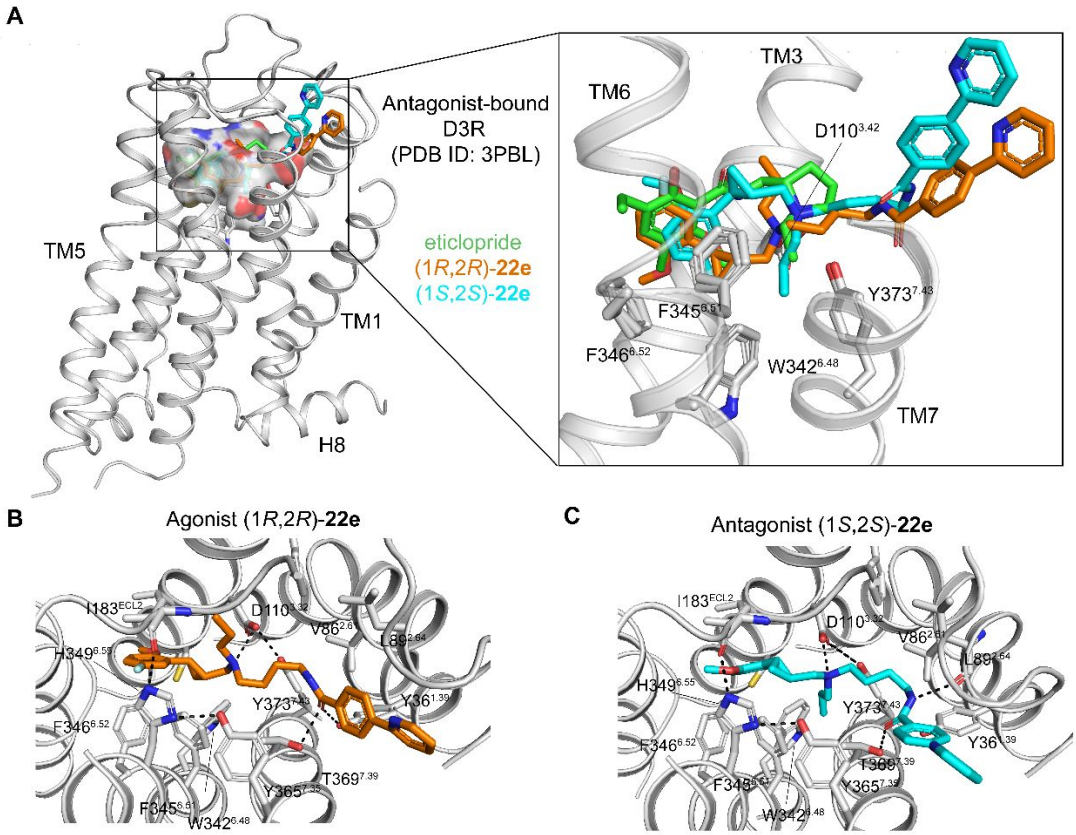


Figure 4. Comparison of binding poses of D3R antagonist eticlopride, (1*R*,2*R*)-**22e** and (1*S*,2*S*)-**22e**. The receptor structure employed for the molecular docking study was extracted from the crystal structure of the eticlopride-D3R complex (PDB code: 3PBL). Carbon atoms of eticlopride, (1*R*,2*R*)-**22e** and (1*S*,2*S*)-**22e** are colored in green, orange and cyan, respectively.

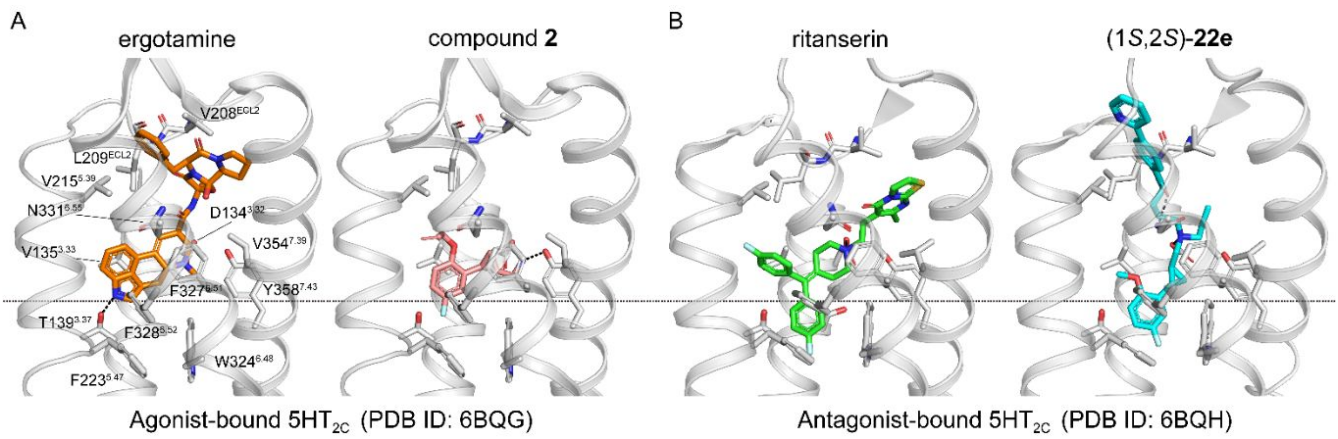


Figure 5. Comparison of binding poses of $5HT_{2C}$ representative agonists (A) and antagonists (B). The receptor structures used in the molecular docking studies were extracted from the crystal structures of the ergotamine-$5HT_{2C}$ complex (PDB code: 6BQG) and the ritanserin-$5HT_{2C}$ complex (PDB code: 6BQH). Carbon atoms of ergotamine, compound **2**, ritanserin, and (1*S*,2*S*)-**22e** are colored in orange, pink, green and cyan, respectively.

A further observation from the functional data is that while the PCPMA compound **2** is a potent agonist of 5-HT_{2C}, the bitopic derivative (1*S*,2*S*)-**22e** turned out to be a moderate antagonist (IC_{50} = 858.5 nM). For the di-Cl substituted compounds **30p**, **30q** and **30r**, although the (*1S,2S*) eutomers showed partial agonist activity, their efficacy was very low (E_{max} = 30.3%, 44.2% and 51.9% respectively). To explore the molecular basis for this conversion from PCPMA-based 5-HT_{2C} agonists to bitopic antagonists/weak partial agonists, we also performed molecular docking of compounds **2** and (1*S*,2*S*)-**22e** to the crystal structures of 5-HT_{2C}. Thus, compound **2** was docked to the ergotamine-bound active structure of 5-HT_{2C} (PDB code: 6BQG), while compound (1*S*,2*S*)-**22e** was docked to the ritanserin-bound inactive structure of 5-HT_{2C} (PDB code:

6BQH).[20] As shown in Figure 5, all of these ligands form salt bridges between the protonated nitrogen atoms of the ligands and D134$^{3.32}$, a key interaction for aminergic GPCR ligands. In the co-crystal structures, the deep binding pose of ritanserin, with the phenyl ring inserted more deeply than the ergoline scaffold of ergotamine, was proposed as a possible explanation for its antagonistic activity.[20] In our docking poses, in comparison to the PCPMA compound **2**, the bitopic derivative (1*S*,2*S*)-**22e** inserts approximately one helical turn deeper into the TM bundle, which likely explains its antagonistic action at the 5-HT$_{2C}$ receptor. The fluorophenyl groups form halogen-aromatic interactions with F223$^{5.47}$and F320$^{6.44}$, aromatic edge-to-face π-π stacking with F328$^{6.52}$ and W324$^{6.48}$, and hydrophobic interactions with T139$^{3.37}$, S138$^{3.36}$ and I142$^{3.40}$. Similar to ritanserin, the deep binding pose of (1*S*,2*S*)-**22e** likely prevents the conformational changes of the toggle switch in TM6 (W324$^{6.48}$) and rotamer switches in the conserved P-I-F motif,[20] thus stabilizing the inactive state of 5-HT$_{2C}$. It may thus be postulated that the attachment of the four carbon linker and the EBP-binding motifs to the PCPMA scaffold results in a deeper binding mode for compound (1*S*,2*S*)-**22e** thus leading to its antagonism of the receptor.

Pharmacokinetic and brain penetration properties. Based on their good binding affinity and selectivity for D3R, we selected compounds (1*R*,2*R*)-**22e**, (1*R*,2*R*)-**30p**, (1*R*,2*R*)-**30q** and (1*R*,2*R*)-**30r** for further PK profiling in male ICR mice. As shown in Table 5, intravenous (iv) administration (5 mg/kg) of these compounds showed moderate exposure in plasma, with high clearance. Oral administration (10 mg/kg)of compounds (1*R*,2*R*)-**22e**, (1*R*,2*R*)-**30p** and (1*R*,2*R*)-**30r** gave very low bioavailability

(3.8%, 6.6% and 13.0% respectively), but compound (1*R*,2*R*)-**30q** showed a reasonably good oral bioavailability of 34.1%. Furthermore, this compound showed an oral half-life of 4.1 h and an MRT of 6 h.

Table 5. PK and brain penetration properties of selected compounds in ICR mice.[a]

Parameters	(1*R*,2*R*)-**22e**		(1*R*,2*R*)-**30p**		(1*R*,2*R*)-**30q**		(1*R*,2*R*)-**30r**	
	iv	**po**	**iv**	**po**	**iv**	**po**	**iv**	**po**
C_{max} (ng/mL)	-	43.2	-	37.3	-	63.9	-	118
t_{max} (h)	-	0.25	-	0.25	-	1.00	-	0.50
$t_{1/2}$ (h)	0.437	2.64	1.51	2.08	3.12	4.11	0.576	2.12
$AUC_{0\text{-}t}$ (h·ng/mL)	660	49.5	616	81.1	629	428	976	254
CL (mL/min/kg)	126	-	134	-	117	-	84.8	-
MRT(h)	0.415	3.72	2.58	2.59	3.40	6.00	0.808	2.77
V_{dSS} (L/kg)	3.13	-	20.8	-	23.8	-	4.11	-
F	-	3.8%	-	6.6%	-	34.1%	-	13.0%
brain concentration at 0.5 h (ng/mL)	530±37	8.21±2	3424±286	23.2±4.0	833±187	51.3±21	980±164	26.7±9.0
plasma concentration at 0.5 h (ng/mL)	446±15	16.8±5.0	270±22	28.4±15	215±13	35.5±7.0	511±67	118±7.0
brain/plasma ratio at 0.5 h	1.19	0.49	12.7	0.82	3.88	1.45	1.92	0.23
brain concentration at 2.0 h (ng/mL)	19.4±11	6.57	913±97	23.2±4.0	543±99	160±45	227±17.0	9.1±5.3
plasma concentration at 2.0 h (ng/mL)	12.7±3.1	8.4±2.4	82.6±9.7	16.4±3.5	94.8±19.3	67.7±20	118±16.5	44.1±7.6
brain/plasma ratio at 2.0 h	1.53	0.79	11.1	1.61	5.72	2.36	1.93	0.207

[a]For all four compounds, iv dose is 5 mg/kg and po dose 10 mg/kg; "-", no applicable.

In our previous studies, PCPMA analogs showed very high brain penetration as 5-HT_{2C} agonists.[4, 5] Accordingly, these four selected compounds were further tested for their brain penetration properties in ICR mice. Brain and plasma drug concentrations after both iv and oral dosing were measured at 0.5 and 2.0 h time points, and brain/plasma ratios were calculated. As shown in Table 5, all four compounds showed good brain

penetration, although significant differences were observed for their brain concentrations following oral dosing, which can be attributed to their different overall PK profiles. Thus, the brain exposures of compounds (1*R*,2*R*)-**22e**, **30p** and **30r** were very low following oral dosing, despite good brain/plasma ratios. As for compound (1*R*,2*R*)-**30q**, high brain/plasma ratios were observed for both iv and oral dosing, at both time points. Calculated concentrations of 108.6 (51.3 ng/mL) and 338.6 nM (160 ng/mL) were observed at 0.5 and 2.0 h, respectively. Moderate but long-lasting brain exposure could be expected for compound (1*R*,2*R*)-**30q**, given the relatively long half-life and MRT observed in PK studies. The overall PK and brain penetration profiles of (1*R*,2*R*)-**30q** support it as a good candidate for further in vivo studies in disease models.

Polypharmacological profiling at other aminergic GPCRs. As mentioned above, polypharmacology is a common feature of many aminergic GPCR ligands. To further profile the binding selectivity of our bitopic D3R ligands, we selected compounds (1*R*,2*R*)-**22e** and (1*R*,2*R*)-**30q** and screened them against 29 other aminergic GPCRs, including serotonin, adrenaline, histamine, and muscarinic receptors. Compounds (1*R*,2*R*)-**22e** and (1*R*,2*R*)-**30q** show weak binding affinity for most receptors ($pK_i < 6$), and modest binding for 5-HT_{1A}, 5-HT_{2B}, α_{2A}, α_{2C}, and H1R (see Supporting Information, Table S4). These data show that compounds (1*R*,2*R*)-**22e** and (1*R*,2*R*)-**30q** have good selectivity for the D3R against most other aminergic GPCRs.

Conclusions

In the past decade, co-crystal structures of aminergic GPCRs have greatly facilitated

our understanding of ligand-receptor interactions at these receptors as well as the structure-based drug design of novel GPCR ligands. Starting from the PCPMA scaffold, we have designed and synthesized a series of bitopic derivatives that possess excellent binding affinities for the D3R with good selectivity against other dopamine receptors. Among the optimized compounds, (1*R*,2*R*)-**22e** showed a binding affinity of 4.1 nM for D3R, with 1195-, 329- and 140-fold selectivity over D1R (4898 nM), D2R (1349 nM) and D4R (575 nM), while possessing weak 5-HT_{2C} affinity (1122 nM) and no affinity for the D5R. Its enantiomer, (1*S*,2*S*)-**22e**, displayed a comparable affinity for D3R (K_i = 3.8 nM), with 282-, 324- and 224-fold selectivity against D1R (1071 nM), D2R (1230 nM) and D4R (851 nM), no affinity for D5R, and moderate selectivity over 5-HT_{2C} (K_i = 50.1 nM). Notably, although the enantiomers showed almost identical binding affinity for D3R, (1*R*,2*R*)-**22e** behaved as a potent agonist (EC_{50} = 3.6 nM), while (1*S*,2*S*)-**22e** showed potent antagonist activity (K_i = 16.7 nM) in the G_i-cAMP assays. Molecular docking results revealed that these enantiomers adopt different binding poses in the D3R OBP, which emphasizes the importance of compound chirality in medicinal chemistry.

Due to high lipophilicity and large molecular weight, most bitopic ligands suffer from poor PK properties and low brain penetration. In this study, we determined that compound (1*R*,2*R*)-**30q**, which shows a high binding affinity for the D3R (K_i = 2.2 nM) with excellent selectivity against all other dopamine receptors (627-, 244- and 476-fold against D1R, D2R and D4R, no binding affinity for D5R) and most other aminergic GPCRs, is a bioavailable (F = 34.1%) and brain penetrant D3R partial agonist (EC_{50} =

87.0 nM, E_{max} = 40.7%). The overall profile of (1*R*,2*R*)-**30q** supports a further evaluation in animal studies.

Experimental Section

General. All commercial chemicals and solvents were used as obtained without further purification. Microwave reactions were run in a Biotage Initiator microwave reactor. Synthetic intermediates were purified on 230−400 mesh silica gel on a Teledyne CombiFlash R_f flash chromatography. ^{1}H NMR spectra were recorded on Bruker AVANCE-II or AVANCE-III spectrometers at 500, 600 or 800 MHz. ^{13}C NMR spectra were recorded on AVANCE-III spectrometer at 201 MHz. NMR chemical shifts were reported in δ (ppm) using residual solvent peaks as standards ($CDCl_3$–7.26 (H), 77.16 (C); CD_3OD–3.31 (H), 49.00 (C); DMSO-d_6–2.50 (H), 39.52 (C)). Mass spectra were measured using an LCMS-IT-TOF (Shimadzu) mass spectrometer in ESI mode. The purity of all final compounds was determined by analytical HPLC (Shim-pack GIST C_{18} column (250 × 4.6 mm, particle size 5 μM); 0.05% TFA in H_2O/0.05% TFA in MeOH gradient eluting system; flow rate = 1.0 mL/min). The purity of all final compounds is over 95%. Optical rotation values were recorded on Rudolph Autopol VI automatic polarimeter (λ = 589 nm, temperature = 20 ^{o}C).

Methyl 3-((4-Methyl-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio)propanoate (10). A mixture of **9** (1.0 g, 5.26 mmol), methyl acrylate (6.0 mL) and Cs_2CO_3 (3.43 g, 10.52 mmol) was heated at 100 ^{o}C for 30 min under microwave radiation. After being cooled to room temperature, the mixture was taken up in ethyl acetate and washed with water.

The organic layer was separated, dried and concentrated. The resulting residue was purified by flash chromatography (0–20% ethyl acetate in petroleum ether) to give the title product as a white solid (4.0 g, 69%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.59 – 7.51 (m, 5H), 4.58 (t, *J* = 7.4 Hz, 2H), 3.72 (s, 3H), 3.66 (s, 3H), 2.96 (t, *J* = 7.4 Hz, 2H). HRMS (ESI) *m/z* calculated for $C_{13}H_{16}N_3O_2S^+$ ($[M + H]^+$): 278.0958, found: 278.0953.

3-((4-Methyl-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio)propanoic Acid (11). Compound **10** (4.0 g, 21.0 mmol) was dissolved in a mixture of THF (50 mL)/H_2O (20 mL), and LiOH-H_2O (4.2 g, 100 mmol) was then added. The mixture was stirred at room temperature overnight. A solution of 3 M HCl (aq) was added to acidify the mixture, and ethyl acetate was then added. The organic layer was separated, washed with water, dried and concentrated. The residue was purified by flash chromatography (0–10% methanol in dichloromethane) to give the title compound as a white solid (2.26 g, 60%). ^{1}H NMR (800 MHz, CD_3OD) *δ* 7.68 – 7.66 (m, 2H), 7.58 – 7.52 (m, 3H), 4.47 (t, *J* = 7.3 Hz, 2H), 3.60 (s, 3H), 2.89 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR (201 MHz, CD_3OD) *δ* 174.21, 168.33, 152.21, 132.06, 130.10 (2C), 129.81 (2C), 127.08, 46.09, 33.47, 33.06. HRMS (ESI) *m/z* calculated for $C_{12}H_{14}N_3O_2S^+$ ($[M + H]^+$): 264.0801, found: 264.0830.

***tert*-Butyl ((2-(5-Fluoro-2-(2-fluoroethoxy)phenyl)cyclopropyl)methyl)carbamate (13a).** A mixture of *tert*-butyl ((2-(5-fluoro-2-hydroxyphenyl)cyclopropyl) methyl)carbamate (100 mg, 0.36 mmol), 2-fluoroethanol (52 μL, 0.89 mmol), and PPh_3 (233 mg, 0.89 mmol) in dry THF (8 mL) was cooled to 0 °C. Diethyl azodicarboxylate (140 μL, 0.89 mmol) was added dropwise. The reaction mixture was irradiated under microwave at 60 °C for 30 min. The mixture was evaporated to dryness to give a crude

product, which was purified by flash chromatography (0–10% ethyl acetate in petroleum ether) to give the title compound as a colorless oil (110 mg, 95%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 6.82 (td, J = 8.4, 3.1 Hz, 1H), 6.77 (dd, J = 8.9, 4.6 Hz, 1H), 6.62 (dd, J = 9.3, 3.1 Hz, 1H), 5.00 (s, 1H), 4.90 – 4.74 (m, 2H), 4.31 – 4.18 (m, 2H), 3.51 (d, J = 13.3 Hz, 1H), 2.81 (dd, J = 13.4, 8.5 Hz, 1H), 1.96 – 1.92 (m, 1H), 1.46 (s, 9H), 1.11 – 1.04 (m, 1H), 1.02 – 0.99 (m, 1H), 0.87 – 0.83 (m, 1H). HRMS (ESI) *m/z* calculated for $C_{17}H_{23}F_2NO_3Na^+$ ($[M + Na]^+$): 350.1538, found: 350.1548.

***tert*-Butyl ((2-(2-Ethoxy-5-fluorophenyl)cyclopropyl)methyl)carbamate (13b).** A mixture of *tert*-butyl ((2-(5-fluoro-2-hydroxyphenyl)cyclopropyl)methyl)carbamate (300 mg, 1.07 mmol), EtI (256 μL, 3.21 mmol) and K_2CO_3 (442 mg, 3.21 mmol) in DMF (10 mL) was irradiated under microwave at 110 ^{o}C for 30 min. The mixture was diluted with ethyl acetate and washed with water. The organic layers were then combined and washed with brine. The volatiles were removed to give a crude product which was purified by flash chromatography (0–10% ethyl acetate in petroleum ether) to give the title compound as a colorless oil (275 mg, 83%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 6.81 (td, J = 8.4, 3.1 Hz, 1H), 6.75 (dd, J = 8.9, 4.5 Hz, 1H), 6.63 (dd, J = 9.3, 3.1 Hz, 1H), 5.15 (s, 1H), 4.15 – 4.02 (m, 2H), 3.62 – 3.55 (m, 1H), 2.75 – 2.68 (m, 1H), 1.88 – 1.84 (m, 1H), 1.51 (t, J = 7.0 Hz, 3H), 1.46 (s, 9H), 1.04 – 0.99 (m, 2H), 0.84 – 0.80 (m, 1H). HRMS (ESI) *m/z* calculated for $C_{17}H_{24}FNO_3Na^+$ ($[M + Na]^+$): 332.1632, found: 332.1629.

***tert*-Butyl ((2-(5-Fluoro-2-methoxyphenyl)cyclopropyl)methyl)carbamate (13c).** A mixture of *tert*-butyl ((2-(5-fluoro-2-hydroxyphenyl)cyclopropyl)-methyl)carbamate

(281 mg, 1.0 mmol), MeI (213 mg, 1.5 mmol) and K_2CO_3 (828 mg, 6.0 mmol) in DMF (8 mL) was irradiated under microwave at 110 °C for 30 min. The mixture was diluted with ethyl acetate and washed with water. The organic layer was separated, dried and concentrated. The resulting residue was purified by flash chromatography (0–10% ethyl acetate in petroleum ether) to give the title compound as a colorless oil (284 mg, 96%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 6.84 (td, J = 8.5, 3.1 Hz, 1H), 6.75 (dd, J = 9.0, 4.5 Hz, 1H), 6.64 (dd, J = 9.3, 3.1 Hz, 1H), 5.28 (s, 1H), 3.88 (s, 3H), 3.56 (s, 1H), 2.76 – 2.66 (m, 1H), 1.87 – 1.81 (m, 1H), 1.47 (s, 9H), 1.05 – 0.97 (m, 2H), 0.88 – 0.81 (m, 1H). HRMS (ESI) *m/z* calculated for $C_{16}H_{22}FNO_3Na^+$ ([M + Na]$^+$): 318.1476, found: 318.1484.

(2-(5-Fluoro-2-(2-fluoroethoxy)phenyl)cyclopropyl)methanamine Hydrochloride (14a). A solution of **13a** (203 mg, 0.62 mmol) in 4 M HCl (*g*) in dioxane (8 mL) and stirred at room temperature for 5 h. The solvent was evaporated and the residue was suspended in a mixture of ethyl acetate and petroleum ether (v/v = 1/2, 5.0 mL) and stirred for 15 min. The precipitate was collected by filtration, washed with ethyl acetate (3 mL) and dried under vacuum to give the title compound as a white solid (134 mg, 82%). ^{1}H NMR (500 MHz, CD_3OD) δ 6.96 – 6.87 (m, 2H), 6.76 (dd, J = 9.4, 3.0 Hz, 1H), 4.87 – 4.70 (m, 2H), 4.34 – 4.18 (m, 2H), 3.05 – 2.97 (m, 2H), 2.19 – 2.13 (m, 1H), 1.27 – 1.22 (m, 1H), 1.21 – 1.15 (m, 1H), 1.05 – 1.00 (m, 1H). HRMS (ESI) *m/z* calculated for $C_{12}H_{16}F_2NO^+$ ([M + H]$^+$): 228.1194, found: 228.1220.

(2-(2-Ethoxy-5-fluorophenyl)cyclopropyl)methanamine Hydrochloride (14b). The title compound was prepared from **13b** using a similar method as described for **14a**.

White solid. ^{1}H NMR (500 MHz, CD_3OD) δ 6.91 – 6.82 (m, 2H), 6.70 (dd, J = 9.5, 2.8 Hz, 1H), 4.11 – 4.02 (m, 2H), 3.08 – 2.93 (m, 2H), 2.17 – 2.12 (m, 1H), 1.43 (t, J = 7.0 Hz, 3H), 1.34 – 1.27 (m, 1H), 1.12 – 1.08 (m, 1H), 1.05 – 1.00 (m, 1H). HRMS (ESI) *m/z* calculated for $C_{12}H_{17}FNO^+$ ($[M + H]^+$): 210.1289, found: 210.1285.

(2-(5-Fluoro-2-methoxyphenyl)cyclopropyl)methanamine Hydrochloride (14c). To a solution of **13c** (196 mg, 0.66 mmol) in THF (4 mL) was added 2 M HCl (*g*) in Et_2O (4 mL) and stirred at room temperature overnight. The volatiles were removed to give a white solid (153 mg, 99%) which was used directly in the next step. ^{1}H NMR (800 MHz, CD_3OD) δ 6.92 – 6.87 (m, 2H), 6.72 (dd, J = 9.3, 2.9 Hz, 1H), 3.86 (s, 3H), 3.07 (dd, J = 13.0, 7.1 Hz, 1H), 2.93 (dd, J = 13.1, 8.0 Hz, 1H), 2.14 – 2.10 (m, 1H), 1.28 – 1.22 (m, 1H), 1.14 – 1.09 (m, 1H), 1.04 – 1.00 (m, 1H). HRMS (ESI) *m/z* calculated for $C_{11}H_{15}FNO^+$ ($[M + H]^+$): 196.1132, found: 196.1135.

(2-(5-Chloro-2-methoxyphenyl)cyclopropyl)methanamine Hydrochloride (14d). The title compound was prepared using **13d** at the starting material, in the same manner as described for **14c**. White solid (yield 99%). ^{1}H NMR (800 MHz, CD_3OD) δ 7.17 (dd, J = 8.7, 2.6 Hz, 1H), 6.97 (d, J = 2.6 Hz, 1H), 6.93 (d, J = 8.7 Hz, 1H), 3.88 (s, 3H), 3.09 (m, 1H), 2.94 (m, 1H), 2.10 (m, 1H), 1.30 – 1.24 (m, 1H), 1.12 (m, 1H), 1.03 (m, 1H). HRMS (ESI) *m/z* calculated for $C_{11}H_{15}ClNO^+$ ($[M + H]^+$): 212.0837; found: 212.0834.

***N*-((2-(5-Fluoro-2-(2-fluoroethoxy)phenyl)cyclopropyl)methyl)-3-((4-methyl-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio)propanamide (15a).** To a mixture of **14a** (120 mg,

0.46 mmol), **11** (132 mg, 0.50 mmol) and HATU (260 mg, 0.68 mmol) in DMF (10 mL) was added $NaHCO_3$ (115 mg, 1.37 mmol). The mixture was stirred at room temperature for 3 h. The mixture was then diluted with ethyl acetate and washed with water and brine. The organic layer was dried and concentrated to give a crude product which was purified by flash chromatography (0–3% methanol in dichloromethane) to give the title compound as a white solid (194 mg, 90%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.67 – 7.63 (m, 2H), 7.59 – 7.50 (m, 3H), 6.87 (dd, *J* = 8.9, 4.7 Hz, 1H), 6.80 (td, *J* = 8.5, 3.1 Hz, 1H), 6.54 (dd, *J* = 9.7, 3.0 Hz, 1H), 4.79 (t, *J* = 4.0 Hz, 1H), 4.69 (t, *J* = 4.0 Hz, 1H), 4.52 (t, *J* = 6.9 Hz, 2H), 4.26 – 4.16 (m, 2H), 3.60 (s, 3H), 3.22 (ddd, *J* = 20.8, 12.8, 6.8 Hz, 2H), 2.79 (t, *J* = 6.9 Hz, 2H), 2.05 – 1.99 (m, 1H), 1.19 – 1.12 (m, 1H), 0.87 – 0.80 (m, 2H). HRMS (ESI) *m/z* calculated for $C_{24}H_{27}F_2N_4O_2S^+$ ($[M + H]^+$): 473.1817, found: 473.1815.

***N*-((2-(2-Ethoxy-5-fluorophenyl)cyclopropyl)methyl)-3-((4-methyl-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio)propanamide (15b).** The title compound was prepared from **14b** using a similar method as described for **15a** as a white solid (yield 72%). ^{1}H NMR (800 MHz, CD_3OD) δ 7.68 (d, *J* = 7.9 Hz, 2H), 7.59 (t, *J* = 7.3 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 2H), 6.85 (dd, *J* = 8.9, 4.7 Hz, 1H), 6.80 (td, *J* = 8.5, 3.0 Hz, 1H), 6.53 (dd, *J* = 9.6, 3.0 Hz, 1H), 4.55 (t, *J* = 7.0 Hz, 2H), 4.07 – 4.00 (m, 2H), 3.62 (s, 3H), 3.35 (dd, *J* = 13.5, 6.2 Hz, 1H), 3.14 (dd, *J* = 13.8, 7.2 Hz, 1H), 2.82 (t, *J* = 7.0 Hz, 2H), 2.06 – 2.01 (m, 1H), 1.42 (t, *J* = 7.0 Hz, 3H), 1.22 – 1.16 (m, 1H), 0.88 – 0.84 (m, 1H), 0.83 – 0.79 (m, 1H). HRMS (ESI) *m/z* calculated for $C_{24}H_{28}FN_4O_2S^+$ ($[M + H]^+$): 455.1912, found: 455.1906.

***N*-((2-(5-Fluoro-2-methoxyphenyl)cyclopropyl)methyl)-3-((4-methyl-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio)propanamide (15c).** The title compound was prepared from **14c** using a similar method as described for **15a** as a white solid (yield 72%). ^{1}H NMR (800 MHz, CD_3OD) δ 7.67 – 7.49 (m, 5H), 6.86 – 6.78 (m, 2H), 6.53 (dd, J = 9.5, 3.1 Hz, 1H), 4.53 (t, J = 7.0 Hz, 2H), 3.82 (s, 3H), 3.60 (s, 3H), 3.21 (d, J = 6.9 Hz, 2H), 2.86 – 2.74 (m, 2H), 2.00 – 1.96 (m, 1H), 1.19 – 1.11 (m, 1H), 0.86 – 0.76 (m, 2H). HRMS (ESI) *m/z* calculated for $C_{23}H_{26}FN_4O_2S^+$ ([M + H]$^+$): 441.1755; found: 441.1749.

***N*-((2-(5-Chloro-2-methoxyphenyl)cyclopropyl)methyl)-3-((4-methyl-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio)propanamide (15d).** The title compound was prepared from **14d** using a similar method as described for **15a** as a yellow solid (yield 88%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.58 – 7.52 (m, 3H), 7.51 (m, 2H), 7.12 (dd, J = 8.7, 2.6 Hz, 1H), 6.84 (d, J = 2.6 Hz, 1H), 6.76 (d, J = 8.7 Hz, 1H), 6.43 (s, 1H), 4.67 – 4.58 (m, 2H), 3.89 (s, 3H), 3.68 – 3.62 (m, 1H), 3.64 (s, 3H), 2.96 – 2.83 (m, 3H), 1.85 (m, 1H), 1.05 – 0.95 (m, 2H), 0.85 (m, 1H). HRMS (ESI) *m/z* calculated for $C_{23}H_{26}ClN_4O_2S^+$ ([M + H]$^+$): 457.1460; found: 457.1457.

***N*-((2-(5-Fluoro-2-(2-fluoroethoxy)phenyl)cyclopropyl)methyl)-3-((4-methyl-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio)propan-1-amine Hydrochloride (16a).** To a solution of **15a** (168 mg, 0.36 mmol) in anhydrous THF (10 mL), a solution of BH_3-THF complex in THF (1 M, 1.4 mL, 1.4 mmol) was added dropwise at 0 ^{o}C under argon. The solution was then heated to reflux and stirred for 4 h. The reaction was quenched by slowly adding MeOH (1 mL) and then 3 M aqueous HCl (1 mL), followed

by refluxing for 30 min. The reaction mixture was cooled to room temperature and then saturated aqueous $NaHCO_3$ was added slowly to adjust to pH 8 ~10. The mixture was extracted with ethyl acetate. The extracts were combined, washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (0–5% methanol in dichloromethane) to give a colorless oil (112 mg, 69%). The oil was then dissolved in dichloromethane and 2 M HCl in diethyl ether (2 mL) was added, and the mixture was stirred at room temperature for 15 min. Volatiles were removed by evaporation to give the title compound as a white solid. HPLC: 99.3% (λ = 254 nm, t_R = 14.7 min); ^{1}H NMR (500 MHz, CD_3OD) δ 7.72 (d, J = 7.0 Hz, 2H), 7.66 – 7.57 (m, 3H), 6.97 – 6.87 (m, 2H), 6.75 (dd, J = 9.4, 2.5 Hz, 1H), 4.88 – 4.69 (m, 2H), 4.45 (t, J = 6.4 Hz, 2H), 4.33 – 4.19 (m, 2H), 3.66 (s, 3H), 3.24 – 3.14 (m, 4H), 2.36 – 2.28 (m, 2H), 2.28 – 2.21 (m, 1H), 1.37 – 1.29 (m, 1H), 1.24 – 1.17 (m, 1H), 1.10 – 1.04 (m, 1H). ^{13}C NMR (201 MHz, CD_3OD) δ 168.83, 158.86 (d, J_{CF} = 237.6 Hz), 154.78, 152.82, 132.83 (d, J_{CF} = 7.5 Hz), 132.27, 130.20 (2C), 129.84 (2C), 126.93, 114.18 (d, J_{CF} = 24.2 Hz), 114.15, 114.06 (d, J_{CF} = 23.0 Hz), 83.48 (d, J_{CF} = 168.0 Hz), 69.70 (d, J_{CF} = 19.0 Hz), 52.96, 46.83, 45.73, 33.65, 26.39, 18.53, 18.34, 13.34. HRMS (ESI) *m/z* calculated for $C_{24}H_{29}F_2N_4OS^+$ ($[M + H]^+$): 459.2025, found: 459.2022.

***N*-((2-(2-Ethoxy-5-fluorophenyl)cyclopropyl)methyl)-3-((4-methyl-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio)propan-1-amine Hydrochloride (16b).** The title compound was prepared from **15b** in the same manner as described for **16a**. White solid (yield 92%). HPLC: 99.6% (λ = 254 nm, t_R = 19.6 min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70

(d, J = 7.3 Hz, 2H), 7.64 – 7.55 (m, 3H), 6.91 – 6.82 (m, 2H), 6.68 (d, J = 9.4 Hz, 1H), 4.44 (t, J = 6.1 Hz, 2H), 4.11 – 4.00 (m, 2H), 3.65 (s, 3H), 3.22 – 3.07 (m, 4H), 2.34 – 2.28 (m, 2H), 2.24 – 2.18 (m, 1H), 1.42 (t, J = 6.8 Hz, 3H), 1.38 – 1.31 (m, 1H), 1.15 – 1.09 (m, 1H), 1.08 – 1.03 (m, 1H). ^{13}C NMR (201 MHz, CD_3OD) δ 168.86, 158.50 (d, J_{CF} = 236.7 Hz), 155.05, 152.84, 132.46 (d, J_{CF} = 7.4 Hz), 132.27, 130.20 (2C), 129.84 (2C), 126.92, 113.86 (d, J_{CF} = 22.9 Hz), 113.72 (d, J_{CF} = 24.1 Hz), 113.71, 65.61, 52.96, 46.82, 45.63, 33.66, 26.45, 18.32, 18.30, 15.33, 13.86. HRMS (ESI) *m/z* calculated for $C_{24}H_{30}FN_4OS^+$ ($[M + H]^+$): 441.2119, found: 441.2112.

***N*-((2-(5-Fluoro-2-methoxyphenyl)cyclopropyl)methyl)-3-((4-methyl-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio)propan-1-amine Hydrochloride (16c).** The title compound was prepared from **15c** in the same manner as described for **16a**. White solid (yield 62%). HPLC: 98.1% (λ = 254 nm, t_R = 13.9 min); ^{1}H NMR (500 MHz, CD_3OD) δ 7.69 (d, J = 7.3 Hz, 2H), 7.64 – 7.54 (m, 3H), 6.93 – 6.86 (m, 2H), 6.71 (d, J = 9.4 Hz, 1H), 4.44 (t, J = 6.6 Hz, 2H), 3.85 (s, 3H), 3.64 (s, 3H), 3.24 – 3.15 (m, 3H), 3.10 – 3.01 (m, 1H), 2.37 – 2.26 (m, 2H), 2.22 – 2.15 (m, 1H), 1.32 – 1.23 (m, 1H), 1.18 – 1.13 (m, 1H), 1.08 – 1.01 (m, 1H). ^{13}C NMR (201 MHz, CD_3OD) δ 168.85, 158.51 (d, J_{CF} = 237.0 Hz), 155.84, 152.83, 132.26, 132.09 (d, J_{CF} = 7.5 Hz), 130.19 (2C), 129.83 (2C), 126.91, 114.04 (d, J_{CF} = 24.2 Hz), 113.97 (d, J_{CF} = 23.0 Hz), 112.38 (d, J_{CF} = 9.0 Hz), 56.58, 52.94, 46.85, 45.59, 33.66, 26.45, 18.38, 18.25, 13.29. HRMS (ESI) *m/z* calculated for $C_{23}H_{28}FN_4OS^+$ ($[M+H]^+$): 427.1962; found: 427.1966.

***N*-((2-(5-Chloro-2-methoxyphenyl)cyclopropyl)methyl)-3-((4-methyl-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio)propan-1-amine (16d).** The title compound was prepared

from **15d** in the same manner as described for **16a**. Colorless semisolid (yield 58%). ^{1}H NMR (800 MHz, CD_3OD) δ 7.70 – 7.65 (m, 2H), 7.62 – 7.53 (m, 3H), 7.10 (dd, J = 8.7, 2.6 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 6.86 (d, J = 2.7 Hz, 1H), 4.41 – 4.35 (m, 2H), 3.85 (s, 3H), 3.62 (s, 3H), 2.85 (dd, J = 12.4, 6.3 Hz, 1H), 2.79 (t, J = 7.1 Hz, 2H), 2.62 (dd, J = 12.4, 7.8 Hz, 1H), 2.20 – 2.12 (m, 2H), 2.02 – 1.98 (m, 1H), 1.20 – 1.15 (m, 1H), 0.99 – 0.96 (m, 1H), 0.89 – 0.85 (m, 1H). HRMS (ESI) *m/z* calculated for $C_{23}H_{28}ClN_4OS^+$ ($[M + H]^+$): 443.1667; found: 443.1675.

***N*-((2-(5-Fluoro-2-(2-fluoroethoxy)phenyl)cyclopropyl)methyl)-*N*-methyl-3-((4-methyl-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio)propan-1-amine Hydrochloride (17a).** To a mixture of **16a** (40 mg, 0.087 mmol) and formaldehyde solution (37 wt% in water, 0.195 mL, 2.62 mmol) in acetonitrile (8 mL), $NaHB(AcO)_3$ (46 mg, 0.22 mmol) was added. The mixture was stirred at room temperature for 1 h. The reaction was quenched with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (0–3% methanol in dichloromethane) to give a colorless oil (24 mg, 58%). The oil was taken up in dichloromethane, 2 M HCl (*g*) in diethyl ether (2 mL) was added, and the mixture was stirred at room temperature for 15 min. Volatiles were removed by evaporation to give the title compound as a white solid. HPLC: 95.7% (λ = 254 nm, t_R = 14.5 min); ^{1}H NMR (500 MHz, CD_3OD) δ 7.68 (d, J = 7.1 Hz, 2H), 7.63 – 7.53 (m, 3H), 6.95 – 6.84 (m, 2H), 6.71 (dd, J = 9.4, 2.4 Hz, 1H), 4.85 – 4.67 (m, 2H), 4.40 (s, 2H), 4.33 – 4.15 (m, 2H), 3.62 (s, 3H), 3.42 – 3.22 (m, 4H), 2.97 (s, 3H), 2.41 – 2.34 (m, 2H), 2.32 – 2.23 (m, 1H), 1.35 – 1.29 (m, 1H), 1.28 – 1.22 (m,

1H), 1.10 – 1.03 (m, 1H). ^{13}C NMR (201 MHz, CD_3OD) δ 168.89, 158.93 (d, J_{CF} = 237.6 Hz), 154.68, 152.77, 132.54 (d, J_{CF} = 7.5 Hz), 132.27, 130.20 (2C), 129.83 (2C), 126.91, 114.25 (d, J_{CF} = 7.6 Hz), 114.13 (d, J_{CF} = 23.0 Hz), 113.80 (d, J_{CF} = 24.5 Hz), 83.41 (d, J_{CF} = 168.3 Hz), 69.76 (d, J_{CF} = 19.3 Hz), 61.18, 54.41, 46.91, 40.56, 33.63, 24.43, 18.50, 18.42, 17.69. HRMS (ESI) *m/z* calculated for $C_{25}H_{31}F_2N_4OS^+$ ($[M + H]^+$): 473.2181, found: 473.2182.

***N*-Ethyl-*N*-((2-(5-fluoro-2-(2-fluoroethoxy)phenyl)cyclopropyl)methyl)-3-((4-methyl-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio)propan-1-amine Hydrochloride (17b).** The title compound was prepared from **16a** and acetaldehyde in the same manner as described for **17a**. White solid (yield 42%). HPLC: 97.3% (λ = 254 nm, t_R = 14.9 min); ^{1}H NMR (500 MHz, CD_3OD) δ 7.66 (d, J = 6.7 Hz, 2H), 7.63 – 7.53 (m, 3H), 6.95 – 6.84 (m, 2H), 6.71 (dd, J = 9.3, 2.4 Hz, 1H), 4.84 – 4.66 (m, 2H), 4.40 (s, 2H), 4.32 – 4.14 (m, 2H), 3.61 (s, 3H), 3.42 – 3.32 (m, 6H), 2.40 – 2.32 (m, 2H), 2.30 – 2.23 (m, 1H), 1.33 (t, J = 7.2 Hz, 3H), 1.30 – 1.26 (m, 1H), 1.23 – 1.20 (m, 1H), 1.10 – 1.00 (m, 1H). ^{13}C NMR (201 MHz, CD_3OD) δ 168.94, 158.92 (d, J_{CF} = 237.9 Hz), 154.71, 152.75, 132.56 (d, J_{CF} = 7.6 Hz), 132.28, 130.21 (2C), 129.79 (2C), 126.90, 114.27 (d, J_{CF} = 8.0 Hz), 114.17 (d, J_{CF} = 23.1 Hz), 113.91 (d, J_{CF} = 24.0 Hz), 83.43 (d, J_{CF} = 168.3 Hz), 69.77 (d, J_{CF} = 19.4 Hz), 57.45, 50.39, 47.00, 33.62, 24.01, 18.45, 17.30, 13.44, 9.20. HRMS (ESI) *m/z* calculated for $C_{26}H_{33}F_2N_4OS^+$ ($[M + H]^+$): 487.2338, found: 487.2333.

***N*-((2-(2-Ethoxy-5-fluorophenyl)cyclopropyl)methyl)-*N*-methyl-3-((4-methyl-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio)propan-1-amine Hydrochloride (17c).** The title

compound was prepared from **16b** and formaldehyde in the same manner as described for **17a** as a light yellow solid (yield 72%). HPLC: 96.5% (λ = 254 nm, t_R = 16.8 min); ^{1}H NMR (500 MHz, CD_3OD) δ 7.68 (d, J = 7.1 Hz, 2H), 7.63 – 7.54 (m, 3H), 6.91 – 6.81 (m, 2H), 6.66 (dd, J = 9.5, 2.4 Hz, 1H), 4.41 (t, J = 5.9 Hz, 2H), 4.12 – 4.00 (m, 2H), 3.62 (s, 3H), 3.37 – 3.30 (m, 4H), 2.99 (s, 3H), 2.41 – 2.34 (m, 2H), 2.32 – 2.25 (m, 1H), 1.40 (t, J = 7.0 Hz, 3H), 1.35 – 1.30 (m, 1H), 1.21 – 1.16 (m, 1H), 1.10 – 1.02 (m, 1H). ^{13}C NMR (201 MHz, CD_3OD) δ 168.60, 158.58 (d, J_{CF} = 236.4 Hz), 154.94 (d, J_{CF} = 2.1 Hz), 152.40, 133.42 (d, J_{CF} = 7.4 Hz), 132.13, 130.15 (2C), 129.77 (2C), 127.00, 113.72 (d, J_{CF} = 8.6 Hz), 113.39 (d, J_{CF} = 22.9 Hz), 112.95 (d, J_{CF} = 24.1 Hz), 65.61, 61.89, 54.60, 47.77, 41.52, 33.57, 25.49, 19.29, 18.20, 15.36, 14.01. HRMS (ESI) *m/z* calculated for $C_{25}H_{32}FN_4OS^+$ ($[M + H]^+$): 455.2275, found: 455.2275.

***N*-((2-(2-Ethoxy-5-fluorophenyl)cyclopropyl)methyl)-*N*-ethyl-3-((4-methyl-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio)propan-1-amine Hydrochloride (17d).** The title compound was prepared from **16b** and acetaldehyde in the same manner as described for **17a**. White solid (yield 47%). HPLC: 96.4% (λ = 254 nm, t_R = 15.2 min); ^{1}H NMR (500 MHz, CD_3OD) δ 7.70 – 7.53 (m, 5H), 6.91 – 6.81 (m, 2H), 6.66 (dd, J = 9.4, 2.4 Hz, 1H), 4.41 (t, J = 6.6 Hz, 2H), 4.14 – 3.98 (m, 2H), 3.62 (s, 3H), 3.43 – 3.34 (m, 6H), 2.41 – 2.33 (m, 2H), 2.32 – 2.26 (m, 1H), 1.41 (t, J = 6.9 Hz, 3H), 1.35 (t, J = 7.2 Hz, 3H), 1.32 – 1.27 (m, 1H), 1.20 – 1.14 (m, 1H), 1.10 – 1.03 (m, 1H). ^{13}C NMR (201 MHz, CD_3OD) δ 168.88, 158.53 (d, J_{CF} = 238.4 Hz), 154.99, 152.67, 132.24, 132.19 (d, J_{CF} = 7.8 Hz), 130.19 and 130.18 (2C), 129.81 and 129.77 (2C), 126.90 and 126.84, 113.96 (d, J_{CF} = 22.8 Hz), 113.77 (d, J_{CF} = 7.2 Hz), 113.46 (d, J_{CF} = 25.0 Hz),65.66 and

65.62, 57.41, 50.50 and 50.13, 49.40, 47.07, 33.63, 24.09 and 23.91, 18.55 and 18.35, 17.23 and 17.07, 15.37, 13.92 and 13.73, 9.41 and 9.14. HRMS (ESI) *m/z* calculated for $C_{26}H_{34}FN_4OS^+$ ($[M + H]^+$): 469.2432, found: 469.2439.

***N*-((2-(5-Fluoro-2-methoxyphenyl)cyclopropyl)methyl)-*N*-methyl-3-((4-methyl-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio)propan-1-amine Hydrochloride (17e).** The title compound was prepared from **16c** and formaldehyde in the same manner as described for **17a**. White solid (yield 89%). HPLC: 98.9% (λ = 254 nm, t_R = 13.7 min); ^{1}H NMR (500 MHz, CD_3OD) δ 7.71 – 7.65 (m, 2H), 7.60 (m, 3H), 6.90 (m, 2H), 6.74 – 6.67 (m, 1H), 4.43 (m, 2H), 3.85 (s, 3H), 3.63 (s, 3H), 3.49 – 3.39 (m, 2H), 3.20 (m, 1H), 3.00 (s, 3H), 2.44 – 2.36 (m, 2H), 2.30 – 2.24 (m, 1H), 1.31 (m, 2H), 1.25 – 1.17 (m, 1H), 1.06 (m, 1H). ^{13}C NMR (201 MHz, CD_3OD) δ 168.94, 158.56 (d, J_{CF} = 236.6 Hz), 155.77, 152.73, 132.24, 131.79 (d, J_{CF} = 6.9 Hz), 130.17 (2C), 129.80 (2C), 126.89, 114.07 (d, J_{CF} = 22.8 Hz), 113.78 (d, J_{CF} = 24.3 Hz), 112.51 (d, J_{CF} = 8.3 Hz), 61.17 and 61.03, 56.59, 54.06 and 53.65, 46.93, 40.52 and 40.44, 33.64, 24.37, 18.74 and 18.40, 17.41 and 17.13, 13.45 and 12.85. HRMS (ESI) *m/z* calculated for $C_{24}H_{30}FN_4OS^+$ ($[M + H]^+$): 441.2119; found: 441.2117.

***N*-Ethyl-*N*-((2-(5-fluoro-2-methoxyphenyl)cyclopropyl)methyl)-3-((4-methyl-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio)propan-1-amine Hydrochloride (17f).** The title compound was prepared from **16c** and acetaldehyde in the same manner as described for **17a**. White solid (yield 60%). HPLC: 98.0% (λ = 254 nm, t_R = 13.9 min); ^{1}H NMR (500 MHz, CD_3OD) δ 7.67 – 7.53 (m, 5H), 6.93 – 6.85 (m, 2H), 6.68 (dd, J = 9.6, 2.6 Hz, 1H), 4.46 – 4.35 (m, 2H), 3.84 (s, 3H), 3.61 (s, 3H), 3.46 – 3.33 (m, 5H), 3.28 –

3.19 (m, 1H), 2.37 (p, J = 7.1 Hz, 2H), 2.28 – 2.18 (m, 1H), 1.35 (t, J = 7.3 Hz, 3H), 1.29 – 1.22 (m, 1H), 1.20 – 1.14 (m, 1H), 1.07 – 1.00 (m, 1H). ^{13}C NMR (201 MHz, CD_3OD) δ 169.01, 158.57 (d, J_{CF} = 237.1 Hz), 155.78, 152.72, 132.25, 131.80 (d, J_{CF} = 6.1 Hz), 130.19 (2C), 129.77 (2C), 126.87, 114.09 (d, J_{CF} = 22.7 Hz), 113.90 (d, J_{CF} = 21.2 Hz), 112.55 (d, J_{CF} = 9.0 Hz), 57.40 and 57.24, 56.63, 50.22 and 50.02, 49.50 and 49.39, 47.01, 33.62, 24.01 and 23.85, 18.63 and 18.51, 17.07, 13.07 and 13.01, 9.31 and 9.19. HRMS (ESI) *m/z* calculated for $C_{25}H_{32}FN_4OS^+$ ($[M + H]^+$): 455.2275; found: 455.2270.

***N*-((2-(5-Fluoro-2-methoxyphenyl)cyclopropyl)methyl)-3-((4-methyl-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio)-*N*-propylpropan-1-amine Hydrochloride (17g).** The title compound was prepared from **16c** and propyl aldehyde in the same manner as described for **17a**. White solid (yield 42%). HPLC: 98.2% (λ = 254 nm, t_R = 16.0 min); ^{1}H NMR (800 MHz, CD_3OD) δ 7.66 – 7.59 (m, 3H), 7.58 – 7.54 (m, 2H), 6.91 – 6.85 (m, 2H), 6.67 (dd, J = 9.4, 2.9 Hz, 1H), 4.44 – 4.38 (m, 2H), 3.84 and 3.83 (s, 3H), 3.61 and 3.60 (s, 3H), 3.49 – 3.36 (m, 3H), 3.28 – 3.18 (m, 3H), 2.43 – 2.35 (m, 2H), 2.30 – 2.23 (m, 1H), 1.82 – 1.72 (m, 2H), 1.29 – 1.25 (m, 1H), 1.20 – 1.16 (m, 1H), 1.07 – 0.98 (m, 4H). ^{13}C NMR (201 MHz, CD_3OD) δ 168.98, 158.57 (d, J_{CF} = 236.8 Hz), 155.73, 152.70, 132.25, 131.83 (d, J_{CF} = 8.2 Hz), 130.19 (2C), 129.77 (2C), 126.84 (d, J_{CF} = 4.3 Hz), 114.07 (d, J_{CF} = 23.2 Hz), 113.80 (d, J_{CF} = 24.3 Hz), 112.55, 57.90 and 57.84, 56.68 and 56.63, 55.79 and 55.45, 50.82 and 50.55, 47.04, 33.63, 23.95 and 23.79, 18.60, 18.46 and 18.36, 17.15 and 17.06, 13.24 and 13.26, 11.21. HRMS (ESI) *m/z* calculated for $C_{26}H_{34}FN_4OS^+$ ($[M + H]^+$): 469.2432, found: 469.2434.

***N*-((2-(5-Fluoro-2-methoxyphenyl)cyclopropyl)methyl)-*N*-isopropyl-3-((4-methyl-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio)propan-1-amine Hydrochloride (17h).** The title compound was prepared from **16c** and acetone in the same manner as described for **17a**. White solid (yield 24%). HPLC: 97.9% (λ = 254 nm, t_R = 14.2 min); ^{1}H NMR (800 MHz, CD_3OD) δ 7.67 – 7.64 (m, 2H), 7.60 – 7.54 (m, 3H), 6.83 (dd, J = 8.9, 4.6 Hz, 1H), 6.77 (td, J = 8.5, 3.1 Hz, 1H), 6.54 (dd, J = 9.8, 3.1 Hz, 1H), 4.30 – 4.23 (m, 2H), 3.81 (s, 3H), 3.61 (s, 3H), 3.18 – 3.10 (m, 1H), 2.74 – 2.50 (m, 4H), 2.12 – 2.01 (m, 3H), 1.13 – 1.07 (m, 1H), 1.06 – 1.01 (m, 6H), 0.93 – 0.88 (m, 1H), 0.85 – 0.79 (m, 1H). ^{13}C NMR (201 MHz, CD_3OD) δ 168.29, 158.72 (d, J = 237.0 Hz), 155.59, 152.11 (d, J_{CF} = 3.3 Hz), 134.62 (d, J_{CF} = 7.3 Hz), 132.04, 130.14 (2C), 129.75 (2C), 127.14, 112.79 (d, J_{CF} = 23.0 Hz), 112.46 (d, J_{CF} = 23.9 Hz), 112.38 (d, J_{CF} = 6.5 Hz), 56.67, 55.40, 51.87, 48.59, 47.70, 33.50, 27.71, 22.74, 18.78, 17.97, 17.87, 14.51. HRMS (ESI) *m/z* calculated for $C_{26}H_{34}FN_4OS^+$ ($[M + H]^+$): 469.2432, found: 469.2438.

***N*-(Cyclopropylmethyl)-*N*-((2-(5-fluoro-2-methoxyphenyl)cyclopropyl)methyl)-3-((4-methyl-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio)propan-1-amine Hydrochloride (17i).** The title compound was prepared from **16c** and cyclopropanecarbaldehyde in the same manner as described for **17a**. White solid (yield 68%). HPLC: 98.8% (λ = 254 nm, t_R = 14.6 min); ^{1}H NMR (800 MHz, CD_3OD) δ 7.66 – 7.63 (m, 2H), 7.62 – 7.59 (m, 1H), 7.58 – 7.55 (m, 2H), 6.92 – 6.85 (m, 2H), 6.68 (dd, J = 9.4, 2.3 Hz, 1H), 4.43 and 4.41 (t, J = 6.4 Hz, 2H), 3.84 (s, 3H), 3.62 and 3.60 (s, 3H), 3.53 – 3.42 (m, 3H), 3.34 – 3.24 (m, 2H), 3.19 – 3.15 (m, 1H), 2.41 – 2.34 (m, 2H), 2.30 – 2.24 (m, 1H), 1.31 – 1.26 (m, 1H), 1.21 – 1.18 (m, 1H), 1.18 – 1.11 (m, 1H), 1.09 – 1.02 (m, 1H),

0.79 – 0.72 (m, 2H), 0.48 – 0.39 (m, 2H). ^{13}C NMR (201 MHz, CD_3OD) δ 168.98 and 168.91, 158.55 (d, J_{CF} = 236.9 Hz), 155.72, 152.64, 132.24, 131.87 (d, J_{CF} = 7.3 Hz), 130.18 (2C), 129.75 (2C), 126.84 (d, J_{CF} = 6.1 Hz), 114.04 (d, J_{CF} = 22.7 Hz), 113.78 and 113.68 (d, J_{CF} = 24.0 Hz), 112.52 (d, J_{CF} = 9.4 Hz), 59.21 and 58.86, 57.78 and 57.75, 56.69 and 56.65, 50.80 and 50.43, 47.11, 33.64, 24.12 and 23.94, 18.63 and 18.53, 17.20 and 17.14, 13.24 and 13.22, 6.71 and 6.63, 5.26 and 5.11, 5.08 and 4.91. HRMS (ESI) *m/z* calculated for $C_{27}H_{34}FN_4OS^+$ ($[M + H]^+$): 481.2432, found: 481.2436.

***N*-((2-(5-Chloro-2-methoxyphenyl)cyclopropyl)methyl)-*N*-ethyl-3-((4-methyl-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio)propan-1-amine Hydrochloride (17j).** The title compound was prepared from **16d** and acetaldehyde in the same manner as described for **17a**. White solid (yield 58%). HPLC: 97.8% (λ = 254 nm, t_R = 14.8 min); ^{1}H NMR (800 MHz, CD_3OD) δ 7.64 – 7.59 (m, 3H), 7.58 – 7.54 (m, 2H), 7.15 (t, *J* = 7.0 Hz, 1H), 6.92 – 6.90 (m, 2H), 4.47 – 4.37 (m, 2H), 3.85 (s, 3H), 3.60 and 3.59 (s, 3H), 3.46 – 3.34 (m, 5H), 3.28 – 3.21 (m, 1H), 2.40 – 2.34 (m, 2H), 2.25 – 2.17 (m, 1H), 1.35 (t, *J* = 7.3 Hz, 3H), 1.27 – 1.21 (m, 1H), 1.19 – 1.15 (m, 1H), 1.05 – 0.99 (m, 1H). ^{13}C NMR (201 MHz, CD_3OD) δ 158.31, 152.74, 132.27, 131.83, 130.20 (2C), 129.73 (2C), 128.28, 127.22, 127.08, 126.82, 126.63, 112.88, 57.40 and 57.21, 56.42 and 56.39, 50.11 and 49.97, 46.96 and 46.94, 33.62, 28.10, 23.94 and 23.80, 18.55 and 18.39, 16.93 and 16.81, 12.85 and 12.76, 9.27 and 9.18. HRMS (ESI) *m/z* calculated for $C_{25}H_{32}ClN_4OS^+$ ($[M + H]^+$): 471.1980, found: 471.1977.

***N*-((2-(5-Chloro-2-methoxyphenyl)cyclopropyl)methyl)-3-((4-methyl-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio)-*N*-propylpropan-1-amine Hydrochloride (17k).** The

title compound was prepared from **16d** and propyl aldehyde in the same manner as described for **17a**. White solid (yield 85%). HPLC: 95.6% (λ = 254 nm, t_R = 15.1 min); ^{1}H NMR (800 MHz, CD_3OD) δ 7.64 – 7.58 (m, 3H), 7.57 – 7.53 (m, 2H), 7.14 (t, J = 7.0 Hz, 1H), 6.92 – 6.87 (m, 2H), 4.45 – 4.36 (m, 2H), 3.84 (s, 3H), 3.60 and 3.59 (s, 3H), 3.48 – 3.35 (m, 3H), 3.27 – 3.17 (m, 3H), 2.41 – 2.33 (m, 2H), 2.24 – 2.17 (m, 1H), 1.81 – 1.71 (m, 2H), 1.27 – 1.22 (m, 1H), 1.18 – 1.14 (m, 1H), 1.05 – 0.98 (m, 4H). ^{13}C NMR (201 MHz, CD_3OD) δ 158.28, 152.71, 132.26, 131.84, 130.20 (2C), 129.72 (2C), 128.24, 127.14, 126.99, 126.82, 126.64, 112.88, 57.87 and 57.76, 56.42 and 56.40, 55.78 and 55.51, 50.68 and 50.49, 46.96, 33.62, 23.89 and 23.74, 18.51 and 18.45, 18.37 and 18.33, 16.95 and 16.80, 12.98 and 12.91, 11.16. HRMS (ESI) *m/z* calculated for $C_{26}H_{34}ClN_4OS^+$ ($[M + H]^+$): 485.2136, found: 485.2131.

***N*-((2-(5-Chloro-2-methoxyphenyl)cyclopropyl)methyl)-*N*-(cyclopropylmethyl)-3-((4-methyl-5-phenyl-4*H*-1,2,4-triazol-3-yl)thio)propan-1-amine Hydrochloride (17l).** The title compound was prepared from **16d** and cyclopropanecarbaldehyde in the same manner as described for **17a**. White solid (yield 77%). HPLC: 99.3% (λ = 254 nm, t_R = 15.2 min); ^{1}H NMR (800 MHz, CD_3OD) δ 7.66 – 7.56 (m, 5H), 7.19 – 7.14 (m, 1H), 6.95 – 6.90 (m, 2H), 4.46 – 4.40 (m, 2H), 3.86 (s, 3H), 3.62 and 3.60 (s, 3H), 3.55 – 3.49 (m, 2H), 3.49 – 3.39 (m, 1H), 3.35 – 3.30 (m, 1H), 3.30 – 3.24 (m, 1H), 3.20 – 3.15 (m, 1H), 2.43 – 2.35 (m, 2H), 2.28 – 2.20 (m, 1H), 1.29 – 1.24 (m, 1H), 1.22 – 1.17 (m, 1H), 1.17 – 1.13 (m, 1H), 1.08 – 1.02 (m, 1H), 0.80 – 0.73 (m, 2H), 0.48 – 0.41 (m, 2H). ^{13}C NMR (201 MHz, CD_3OD) δ 158.29, 152.72, 132.28, 131.80, 130.22 (2C), 129.72 (2C), 128.24, 127.13, 126.97, 126.80, 126.64, 112.89, 59.25 and

58.95, 57.72, 56.41, 50.69 and 50.38, 47.03, 33.63, 24.05 and 23.88, 18.53 and 18.40, 16.93, 12.94, 6.68 and 6.62, 5.15 and 5.10, 5.01 and 4.84. HRMS (ESI) *m/z* calculated for $C_{27}H_{34}ClN_4OS^+$ ($[M + H]^+$): 497.2136, found: 497.2133.

***N*-(4-Hydroxybutyl)-2-naphthamide (19a).** 2-Naphthoyl chloride (218 mg, 1.14 mmol) was dissolved in dichloromethane (10 mL), then trimethylamine (174 mg, 1.72 mmol) and 4-aminobutanol (112 mg, 1.26 mmol) were added successively. The mixture was stirred at room temperature for 2 h. The solvent was evaporated under vacuum to give a residue which was then taken up in ethyl acetate, washed with saturated aqueous $NaHCO_3$, and then brine. The organic layer was separated and concentrated to give the crude product, which was purified by flash chromatography (0–5% methanol in dichloromethane) to give the title compound as a white solid (243 mg, 87%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.84 (dd, J = 8.5, 1.6 Hz, 1H), 7.59 – 7.53 (m, 2H), 3.77 (t, J = 6.1 Hz, 2H), 3.59 (t, J = 6.9 Hz, 2H), 1.82 – 1.77 (m, 2H), 1.75 – 1.71 (m, 2H). HRMS (ESI) *m/z* calculated for $C_{15}H_{18}NO_2^+$ ($[M + H]^+$): 244.1332, found: 244.1329.

***N*-(4-Hydroxybutyl)-1*H*-indole-2-carboxamide (19b).** A mixture of 1*H*-indole-2-carboxylic acid (200 mg, 1.24 mmol), 4-aminobutanol (132 mg, 1.49 mmol), HATU (708 mg, 1.88 mmol) and $NaHCO_3$ (313 mg, 3.72 mmol) in DMF (10 mL) was stirred at room temperature for 2 h. The mixture was diluted with ethyl acetate, washed with water, and then brine. The organic layer was separated and concentrated to give a crude product, which was purified by flash chromatography (0–5% methanol in dichloromethane) to give the title compound as a white solid (231 mg, 80%). ^{1}H NMR

(800 MHz, CD_3OD) δ 7.61 (d, J = 8.0 Hz, 1H), 7.45 (dd, J = 8.3, 0.7 Hz, 1H), 7.24 – 7.20 (m, 1H), 7.08 – 7.05 (m, 2H), 3.63 (t, J = 6.5 Hz, 2H), 3.44 (t, J = 7.1 Hz, 2H), 1.75 – 1.69 (m, 2H), 1.68 – 1.63 (m, 2H). HRMS (ESI) *m/z* calculated for $C_{13}H_{17}N_2O_2^+$ ($[M + H]^+$): 233.1285, found: 233.1280.

***N*-(4-Hydroxybutyl)-4-(pyridin-2-yl)benzamide (19c).** The title compound was prepared from 4-(pyridin-2-yl)benzoic acid using the same method as described for compound **19b**. White solid (yield 93%). ^1H NMR (800 MHz, CD_3OD) δ 8.66 (d, J = 4.8 Hz, 1H), 8.07 (d, J = 8.3 Hz, 2H), 7.96 – 7.92 (m, 4H), 7.44 – 7.40 (m, 1H), 3.63 (t, J = 6.5 Hz, 2H), 3.45 (t, J = 7.1 Hz, 2H), 1.76 – 1.70 (m, 2H), 1.68 – 1.61 (m, 2H). HRMS (ESI) *m/z* calculated for $C_{16}H_{19}N_2O_2^+$ ($[M + H]^+$): 271.1441, found: 271.1434.

General Procedures for the Preparation of 20a–c. A mixture of SO_3-pyridine complex (5.0 eq) in dichloromethane (0.25 mol/L) and DMSO (0.25 mol/L) was cooled to 0 °C. Then a mixture of amides **19a–c** (1.0 eq) and trimethylamine (5.0 eq) in DMSO (0.12 mol/L) was added dropwise. The mixture was stirred at room temperature for 1.5 h. Water was added, and the mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to give an oil, which was used in next step without further purification.

***N*-((2-(5-Fluoro-2-methoxyphenyl)cyclopropyl)methyl)ethanamine (21a).** A mixture of **14c** (162 mg, 0.70 mmol), acetaldehyde (31 mg, 0.70 mmol) and trimethylamine (71 mg, 0.70 mmol) in THF (20 mL) was stirred at room temperature for 1 h. $NaBH_4$ (79 mg, 2.10 mmol) was then added, and the reaction mixture was

stirred at room temperature for 20 min. MeOH (5 mL) was added to quench the reaction. Water was added, and the mixture was extracted with ethyl acetate. The combined extracts were washed with brine and concentrated. The residue was purified by flash chromatography (0–8% methanol in dichloromethane) to give the title compound as a yellow oil (53 mg, 34%). ^{1}H NMR (800 MHz, CD_3OD) δ 6.92 – 6.87 (m, 2H), 6.71 (dd, J = 9.4, 3.0 Hz, 1H), 3.85 (s, 3H), 3.12 – 2.94 (m, 4H), 2.16 – 2.13 (m, 1H), 1.31 (t, J = 7.3 Hz, 3H), 1.28 – 1.22 (m, 1H), 1.14 – 1.11 (m, 1H), 1.03 – 0.99 (m, 1H). HRMS (ESI) *m/z* calculated for $C_{13}H_{19}FNO^+$ ($[M + H]^+$): 224.1445, found: 224.1453.

***N*-((2-(5-Chloro-2-methoxyphenyl)cyclopropyl)methyl)ethanamine (21b).** Using a similar method as described for **21a**, the title compound was prepared as a brown oil (yield 33%). ^{1}H NMR (800 MHz, CD_3OD) δ 7.17 (dd, J = 8.7, 2.5 Hz, 1H), 6.96 (d, J = 2.6 Hz, 1H), 6.93 (d, J = 8.7 Hz, 1H), 3.87 (s, 3H), 3.16 – 3.08 (m, 3H), 3.03 (dd, J = 13.3, 8.3 Hz, 1H), 2.18 – 2.11 (m, 1H), 1.35 (t, J = 7.3 Hz, 3H), 1.30 – 1.23 (m, 1H), 1.18 – 1.12 (m, 1H), 1.07 – 1.00 (m, 1H). HRMS (ESI) *m/z* calculated for $C_{13}H_{19}ClNO^+$ ($[M + H]^+$): 240.1150, found: 240.1156.

***N*-((2-(5-Fluoro-2-methoxyphenyl)cyclopropyl)methyl)propan-1-amine (21c).** Using a similar method as described for **21a**, the title compound was prepared as a colorless oil (yield 23%). ^{1}H NMR (800 MHz, CD_3OD) δ 6.89 (dd, J = 8.9, 4.6 Hz, 1H), 6.87 – 6.84 (m, 1H), 6.67 (dd, J = 9.5, 3.0 Hz, 1H), 3.84 (s, 3H), 2.93 (dd, J = 12.5, 6.5 Hz, 1H), 2.82 – 2.76 (m, 2H), 2.73 (dd, J = 12.5, 7.8 Hz, 1H), 2.07 – 2.03 (m, 1H), 1.67 – 1.60 (m, 2H), 1.22 – 1.16 (m, 1H), 1.08 – 1.04 (m, 1H), 0.99 (t, J = 7.4 Hz, 3H), 0.95 – 0.91 (m, 1H). HRMS (ESI) *m/z* calculated for $C_{14}H_{21}FNO^+$ ($[M + H]^+$):

238.1602, found: 238.1603.

***N*-((2-(5-Chloro-2-methoxyphenyl)cyclopropyl)methyl)propan-1-amine (21d).** Using a similar method as described for **21a**, the title compound was prepared as a colorless oil (yield 31%). ^{1}H NMR (800 MHz, CD_3OD) δ 7.16 (dd, J = 8.7, 2.6 Hz, 1H), 6.95 (d, J = 2.6 Hz, 1H), 6.93 (d, J = 8.7 Hz, 1H), 3.86 (s, 3H), 3.13 (dd, J = 12.9, 7.1 Hz, 1H), 3.05 – 2.96 (m, 3H), 2.17 – 2.13 (m, 1H), 1.77 – 1.71 (m, 2H), 1.31 – 1.24 (m, 1H), 1.17 – 1.12 (m, 1H), 1.06 – 1.01 (m, 4H). HRMS (ESI) *m/z* calculated for $C_{14}H_{21}ClNO^+$ ($[M + H]^+$): 254.1306, found: 254.1310.

General Procedures for the Preparation of 22a–i. To a solution of amines **21a–d** (1.0 eq) in THF was added aldehydes **20a–c** (1.0 eq) and $NaHB(AcO)_3$ (2.0 eq), and the reaction mixture was stirred at room temperature overnight. Methanol was added to afford a clear solution, which was stirred at room temperature for 15–30 min. The solution was concentrated and the residue was purified by flash chromatography (0–6% methanol in dichloromethane) to give colorless oil (**22a-i** free bases). These free bases were converted into their HCl salts using 2 M HCl (g) in diethyl ether in the same manner as described for **17a**.

***N*-(4-(Ethyl((2-(5-fluoro-2-methoxyphenyl)cyclopropyl)methyl)amino)butyl)-2-naphthamide Hydrochloride (22a).** White solid (yield 37%). HPLC: 99.3% (λ = 254 nm, t_R = 15.4 min); ^{1}H NMR (800 MHz, CD_3OD) δ 8.38 (d, J = 7.6 Hz, 1H), 7.97 (t, J = 8.1 Hz, 1H), 7.95 – 7.91 (m, 2H), 7.91 – 7.87 (m, 1H), 7.61 – 7.56 (m, 2H), 6.91 – 6.85 (m, 2H), 6.71 – 6.69 (m, 1H), 3.83 and 3.82 (s, 3H), 3.54 – 3.48 (m, 2H), 3.42 –

3.32 (m, 4H), 3.30 – 3.21 (m, 2H), 2.32 – 2.28 (m, 1H), 1.90 – 1.80 (m, 2H), 1.79 – 1.71 (m, 2H), 1.38 – 1.35 (m, 3H), 1.34 – 1.29 (m, 1H), 1.24 – 1.19 (m, 1H), 1.08 – 1.04 (m, 1H). ^{13}C NMR (201 MHz, CD_3OD) δ 170.38, 158.66 (d, J_{CF} = 237.0 Hz), 155.70, 136.29, 134.05, 132.71, 131.95 (d, J_{CF} = 7.1 Hz), 130.00, 129.39, 128.91, 128.78 (2C), 127.91, 124.80, 113.96 (d, J_{CF} = 22.9 Hz), 113.42 and 113.40 (d, J_{CF} = 24.1 Hz), 112.55 (d, J_{CF} = 8.6 Hz), 57.53 and 57.43, 56.56, 55.34 and 55.06, 53.23 and 52.96, 39.94 and 39.91, 27.83, 22.49 and 22.34, 18.44, 17.46 and 17.39, 13.36 and 13.19, 9.31 and 9.10. HRMS (ESI) *m/z* calculated for $C_{28}H_{34}FN_2O_2^+$ ($[M + H]^+$): 449.2599, found: 449.2604.

***N*-(4-(((2-(5-Fluoro-2-methoxyphenyl)cyclopropyl)methyl)(propyl)amino)butyl)-2-naphthamide Hydrochloride (22b).** White solid (yield 68%). HPLC: 99.4% (λ = 254 nm, t_R = 21.7 min); ^{1}H NMR (800 MHz, CD_3OD) δ 8.39 (d, J = 7.4 Hz, 1H), 7.97 (t, J = 7.6 Hz, 1H), 7.95 – 7.88 (m, 3H), 7.62 – 7.53 (m, 2H), 6.92 – 6.84 (m, 2H), 6.71 – 6.66 (m, 1H), 3.82 (s, 3H), 3.54 – 3.48 (m, 2H), 3.40 – 3.28 (m, 3H), 3.28 – 3.16 (m, 3H), 2.32 – 2.27 (m, 1H), 1.90 – 1.82 (m, 2H), 1.81 – 1.72 (m, 4H), 1.36 – 1.32 (m, 1H), 1.23 – 1.19 (m, 1H), 1.09 – 1.04 (m, 1H), 1.02 – 0.97 (m, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 170.36, 158.68 (d, J_{CF} = 236.7 Hz), 155.66 (d, J_{CF} = 2.8 Hz), 136.29, 134.05, 132.71, 131.97 (d, J_{CF} = 7.4 Hz), 130.00, 129.39, 128.91, 128.79 (2C), 127.91, 124.80, 114.00 and 113.89 (d, J_{CF} = 22.9 Hz), 113.37 and 113.25 (d, J_{CF} = 24.2 Hz), 112.58 and 112.54 (d, J_{CF} = 8.5 Hz), 58.07, 56.58, 55.76 and 55.34, 53.90 and 53.52, 39.91 and 39.88, 27.81, 22.42 and 22.27, 18.46 and 18.31, 18.41, 17.52 and 17.45, 13.44, 11.22 and 11.21. HRMS (ESI) *m/z* calculated for $C_{29}H_{36}FN_2O_2^+$ ($[M + H]^+$):

463.2755, found: 463.2764.

***N*-(4-(Ethyl((2-(5-fluoro-2-methoxyphenyl)cyclopropyl)methyl)amino)butyl)-*H*-indole-2-carboxamide Hydrochloride (22c).** White solid (yield 44%). HPLC: 98.9% (λ = 280 nm, t_R = 14.0 min); ^{1}H NMR (800 MHz, CD_3OD) δ 7.60 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.23 – 7.19 (m, 1H), 7.07 – 7.04 (m, 2H), 6.91 – 6.85 (m, 2H), 6.69 (dd, J = 9.5, 2.9 Hz, 1H), 3.82 (s, 3H), 3.46 (t, J = 6.8 Hz, 2H), 3.37 – 3.20 (m, 6H), 2.30 – 2.26 (m, 1H), 1.84 – 1.76 (m, 2H), 1.75 – 1.69 (m, 2H), 1.34 (t, J = 7.3 Hz, 3H), 1.30 – 1.26 (m, 1H), 1.23 – 1.20 (m, 1H), 1.06 – 1.01 (m, 1H). ^{13}C NMR (201 MHz, CD_3OD) δ 164.33, 158.63 (d, J_{CF} = 236.7 Hz), 155.69, 138.29, 132.09, 131.95 (d, J_{CF} = 7.3 Hz), 128.96, 125.11, 122.75, 121.22, 113.94 (d, J_{CF} = 22.8 Hz), 113.40 (d, J_{CF} = 24.3 Hz), 113.07, 112.54 (d, J_{CF} = 7.2 Hz), 104.51, 57.50 and 57.41, 56.56, 53.19 and 52.91, 48.62, 39.40, 27.88, 22.45 and 22.31, 18.43 and 18.42, 17.46 and 17.40, 13.34 and 13.15, 9.30 and 9.09. HRMS (ESI) *m/z* calculated for $C_{26}H_{33}FN_3O_2^+$ ([M + H]$^+$): 438.2551, found: 438.2550.

***N*-(4-(((2-(5-Fluoro-2-methoxyphenyl)cyclopropyl)methyl)(propyl)amino)butyl)-1*H*-indole-2-carboxamide Hydrochloride (22d).** White solid (yield 65%). HPLC: 98.5% (λ = 280 nm, t_R = 14.7 min); ^{1}H NMR (800 MHz, CD_3OD) δ 7.61 – 7.58 (m, 1H), 7.45 – 7.43 (m, 1H), 7.23 – 7.19 (m, 1H), 7.09 – 7.05 (m, 2H), 6.91 – 6.85 (m, 2H), 6.70 – 6.67 (m, 1H), 3.82 (s, 3H), 3.49 – 3.44 (m, 2H), 3.35 – 3.25 (m, 3H), 3.25 – 3.14 (m, 3H), 2.31 – 2.26 (m, 1H), 1.86 – 1.69 (m, 6H), 1.34 – 1.28 (m, 1H), 1.23 – 1.19 (m, 1H), 1.07 – 1.03 (m, 1H), 1.03 – 0.97 (m, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 164.33, 158.65 (d, J_{CF} = 236.8 Hz), 155.65, 138.30, 132.08, 131.96 (d, J_{CF} = 7.6 Hz),

128.96, 125.12, 122.75, 121.23, 113.93 and 113.92 (d, J_{CF} = 23.3 Hz), 113.31 and 113.28 (d, J_{CF} = 24.3 Hz), 113.08, 112.56 and 112.54 (d, J_{CF} = 7.5 Hz), 104.51, 58.05, 56.58, 55.71 and 55.30, 53.86 and 53.48, 39.38, 27.85, 22.38 and 22.27, 18.44 and 18.39, 18.29, 17.52 and 17.45, 13.41 and 13.39, 11.20. HRMS (ESI) *m/z* calculated for $C_{27}H_{35}FN_3O_2^+$ ([M + H]$^+$): 452.2708, found: 452.2714.

***N*-(4-(((2-(5-Fluoro-2-methoxyphenyl)cyclopropyl)methyl)(propyl)amino)butyl)-4-(pyridin-2-yl)benzamide Hydrochloride (22e).** White solid (yield 57%). HPLC: 98.5% (λ = 254 nm, t_R = 13.6 min); ^{1}H NMR (800 MHz, CD_3OD) δ 8.90 (d, J = 5.6 Hz, 1H), 8.71 (t, J = 8.1 Hz, 1H), 8.45 (d, J = 8.2 Hz, 1H), 8.17 – 8.13 (m, 2H), 8.11 – 8.06 (m, 3H), 6.93 – 6.91 (m, 1H), 6.89 – 6.86 (m, 1H), 6.72 – 6.69 (m, 1H), 3.85 (s, 3H), 3.52 – 3.47 (m, 2H), 3.40 – 3.32 (m, 2H), 3.31 – 3.18 (m, 4H), 2.34 – 2.30 (m, 1H), 1.91 – 1.84 (m, 2H), 1.82 – 1.72 (m, 4H), 1.40 – 1.34 (m, 1H), 1.25 – 1.20 (m, 1H), 1.11 – 1.07 (m, 1H), 1.05 – 1.00 (m, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 168.77, 158.68 (d, J_{CF} = 237.2 Hz), 155.69, 153.21 (d, J_{CF} = 4.2 Hz), 148.23, 143.61, 138.88, 135.19, 132.04 (d, J_{CF} = 7.3 Hz), 129.73 (2C), 129.60 (2C), 127.56, 127.19, 113.93 (d, J_{CF} = 22.9 Hz), 113.30 (d, J_{CF} = 24.5 Hz), 112.60 (d, J_{CF} = 8.2 Hz), 58.06, 56.62, 55.79 and 55.35, 53.88 and 53.49, 40.10 and 40.07, 27.67, 22.50 and 22.37, 18.48 and 18.32, 18.43 and 18.41, 17.54 and 17.45, 13.50, 11.26 and 11.24. HRMS (ESI) *m/z* calculated for $C_{30}H_{37}FN_3O_2^+$ ([M + H]$^+$): 490.2864, found: 490.2863.

***N*-(4-(((2-(5-Chloro-2-methoxyphenyl)cyclopropyl)methyl)(ethyl)amino)butyl)-2-naphthamide Hydrochloride (22f).** White solid (yield 86%). HPLC: 98.8% (λ = 254 nm, t_R = 17.5 min); ^{1}H NMR (600 MHz, CD_3OD) δ 8.37 (d, J = 3.9 Hz, 1H), 7.99 –

7.91 (m, 3H), 7.89 – 7.85 (m, 1H), 7.62 – 7.54 (m, 2H), 7.15 (dd, J = 8.7, 2.6 Hz, 1H), 6.95 – 6.86 (m, 2H), 3.84 and 3.83 (s, 3H), 3.53 – 3.49 (m, 2H), 3.42 – 3.32 (m, 4H), 3.29 – 3.22 (m, 2H), 2.29 – 2.24 (m, 1H), 1.88 – 1.80 (m, 2H), 1.79 – 1.72 (m, 2H), 1.35 (t, J = 7.2 Hz, 3H), 1.33 – 1.29 (m, 1H), 1.26 – 1.20 (m, 1H), 1.08 – 1.02 (m, 1H). ^{13}C NMR (201 MHz, CD_3OD) δ 170.40, 158.23, 136.28, 134.04, 132.71, 131.95, 129.98, 129.39, 128.91, 128.79, 128.74, 128.11, 127.92, 126.67, 126.65, 124.76, 112.83, 57.52 and 57.44, 56.31(2C), 53.18 and 52.93, 39.93 and 39.89, 27.84, 22.44 and 22.27, 18.29, 17.23 and 17.17, 13.21 and 13.07, 9.25 and 9.06. HRMS (ESI) *m/z* calculated for $C_{28}H_{34}ClN_2O_2^+$ ($[M + H]^+$): 465.2303, found: 465.2309.

***N*-(4-(((2-(5-Chloro-2-methoxyphenyl)cyclopropyl)methyl)(propyl)amino)butyl)-2-naphthamide Hydrochloride (22g).** Colorless oil (yield 63%). HPLC: 95.4% (λ = 280 nm, t_R = 24.7 min); ^{1}H NMR (800 MHz, CD_3OD) δ 8.38 (d, J = 5.8 Hz, 1H), 7.99 – 7.93 (m, 3H), 7.91 – 7.88 (m, 1H), 7.62 – 7.57 (m, 2H), 7.15 (dd, J = 8.7, 2.6 Hz, 1H), 6.94 – 6.91 (m, 2H), 3.85 and 3.84 (s, 3H), 3.55 – 3.50 (m, 2H), 3.40 – 3.33 (m, 2H), 3.30 – 3.17 (m, 4H), 2.29 – 2.26 (m, 1H), 1.88 – 1.81 (m, 2H), 1.81 – 1.73 (m, 4H), 1.37 – 1.32 (m, 1H), 1.26 – 1.21 (m, 1H), 1.09 – 1.05 (m, 1H), 1.04 – 1.00 (m, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 170.37, 158.19, 136.27, 134.03, 132.71, 131.98, 129.98, 129.39, 128.90, 128.78, 128.75, 128.07, 127.91, 126.69, 126.58 and 126.55, 124.77, 112.83, 58.03, 56.31, 55.71 and 55.35, 53.81 and 53.46, 39.88, 27.80, 22.36 and 22.20, 18.42 and 18.28, 18.28 and 18.24, 17.26 and 17.20, 13.31 and 13.29, 11.18. HRMS (ESI) *m/z* calculated for $C_{29}H_{36}ClN_2O_2^+$ ($[M + H]^+$): 479.2460, found: 479.2458.

***N*-(4-(((2-(5-Chloro-2-methoxyphenyl)cyclopropyl)methyl)(propyl)amino)butyl)-**

1*H*-indole-2-carboxamide Hydrochloride (22h). White solid (yield 49%). HPLC: 97.2% (λ = 280 nm, t_R = 12.6 min); ^{1}H NMR (800 MHz, CD_3OD) δ 7.60 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 9.0 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.13 (dd, J = 8.7, 2.5 Hz, 1H), 7.10 – 7.08 (m, 1H), 7.06 (t, J = 7.5 Hz, 1H), 6.91 – 6.90 (m, 1H), 6.89 (d, J = 8.7 Hz, 1H), 3.82 (s, 3H), 3.49 – 3.44 (m, 2H), 3.35 – 3.13 (m, 6H), 2.28 – 2.22 (m, 1H), 1.87 – 1.80 (m, 2H), 1.79 – 1.68 (m, 4H), 1.35 – 1.30 (m, 1H), 1.23 – 1.19 (m, 1H), 1.07 – 1.03 (m, 1H), 1.01 – 0.96 (m, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 164.36, 158.20 and 158.19, 138.31, 132.07, 132.00, 128.97, 128.08, 126.69, 126.57 and 126.55, 125.11, 122.75, 121.23, 113.07, 112.85 and 112.84, 104.45, 58.07, 56.34, 55.73 and 55.35, 53.86 and 53.51, 39.37, 27.88, 22.38 and 22.26, 18.45 and 18.31, 18.27, 17.33 and 17.27, 13.31, 11.21 and 11.20. HRMS (ESI) *m/z* calculated for $C_{27}H_{35}ClN_3O_2^+$ ([M + H]$^+$): 468.2412, found: 468.2410.

***N*-(4-(((2-(5-Chloro-2-methoxyphenyl)cyclopropyl)methyl)(propyl)amino)butyl)-4-(pyridin-2-yl)benzamide Hydrochloride (22i).** White solid (yield 64%). HPLC: 98.5% (λ = 254 nm, t_R = 15.3 min); ^{1}H NMR (800 MHz, CD_3OD) δ 8.87 (d, J = 5.5 Hz, 1H), 8.69 (t, J = 7.9 Hz, 1H), 8.42 (d, J = 8.1 Hz, 1H), 8.13 – 8.10 (m, 2H), 8.09 – 8.04 (m, 3H), 7.15 – 7.13(m, 1H), 6.93 – 6.91 (m, 2H), 3.85 (s, 3H), 3.52 – 3.48 (m, 2H), 3.39 – 3.14 (m, 5H), 3.08 – 2.98 (m, 1H), 2.30 – 2.25 (m, 1H), 1.89 – 1.72 (m, 6H), 1.37 – 1.31 (m, 1H), 1.24 – 1.21 (m, 1H), 1.09 – 1.06 (m, 1H), 1.05 – 0.99 (m, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 168.82, 158.25, 148.24, 143.57, 138.83, 132.06, 129.66 (2C), 129.59 (2C), 128.12, 128.07, 127.58, 127.25, 127.18, 126.66 and 126.61, 126.57, 112.90 and 112.89, 58.11, 56.38, 55.77 and 55.40, 53.86 and 53.51, 40.11 and 40.08,

27.6, 22.44 and 22.29, 18.47 and 18.33, 18.30 and 18.27, 17.40 and 17.31, 13.29, 11.19. HRMS (ESI) *m/z* calculated for $C_{30}H_{37}ClN_3O_2^+$ ([M + H]$^+$): 506.2569, found: 506.2566.

General Procedures for the Preparation of 24a–f. To a solution of benzaldehydes **23a–f** (1.0 eq) in anhydrous dichloromethane (0.1–0.2 mol/L) was added methyl (triphenylphosphoranylidene)acetate (1.3 eq), and the solution was stirred at room temperature overnight. The mixture was then concentrated, and the residue was purified by flash chromatography (0–15% ethyl acetate in petroleum ether) to give intermediates **24a–f**.

Methyl (*E*)-3-(3-fluorophenyl)acrylate (24a). Colorless oil (yield 67%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, J = 16.0 Hz, 1H), 7.41 – 7.35 (m, 1H), 7.31 (d, J = 7.7 Hz, 1H), 7.24 (d, J = 9.7 Hz, 1H), 7.11 (td, J = 8.3, 1.9 Hz, 1H), 6.46 (d, J = 16.0 Hz, 1H), 3.84 (s, 3H). HRMS (ESI) *m/z* calculated for $C_{10}H_{10}FO_2^+$ ([M + H]$^+$): 181.0659, found: 181.0657.

Methyl (*E*)-3-(3-chlorophenyl)acrylate (24b). White solid (yield 96%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.62 (d, J = 16.0 Hz, 1H), 7.50 (t, J = 1.7 Hz, 1H), 7.39 (d, J = 7.5 Hz, 1H), 7.37 – 7.34 (m, 1H), 7.32 (t, J = 7.7 Hz, 1H), 6.43 (d, J = 16.0 Hz, 1H), 3.81 (s, 3H). HRMS (ESI) *m/z* calculated for $C_{10}H_{10}ClO_2^+$ ([M + H]$^+$): 197.0364, found: 197.0356.

Methyl (*E*)-3-(4-fluorophenyl)acrylate (24c). White solid (yield 93%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.65 (d, J = 16.0 Hz, 1H), 7.52 – 7.50 (m, 2H), 7.09 – 7.05 (m, 2H), 6.36 (d, J = 16.0 Hz, 1H), 3.80 (s, 3H). HRMS (ESI) *m/z* calculated for $C_{10}H_{10}FO_2^+$ ([M

+ H]$^+$): 181.0659, found: 181.0653.

Methyl (*E*)-3-(4-chlorophenyl)acrylate (24d). White solid (yield 89%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.63 (d, J = 16.0 Hz, 1H), 7.44 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.3 Hz, 2H), 6.40 (d, J = 16.0 Hz, 1H), 3.80 (s, 3H). HRMS (ESI) *m/z* calculated for $C_{10}H_{10}ClO_2^+$ ([M + H]$^+$): 197.0364, found: 197.0359.

Methyl (*E*)-3-(4-(trifluoromethyl)phenyl)acrylate (24e). White solid (yield 97%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.70 (d, J = 16.0 Hz, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 6.51 (d, J = 16.0 Hz, 1H), 3.83 (s, 3H). HRMS (ESI) *m/z* calculated for $C_{11}H_{10}F_3O_2^+$ ([M + H]$^+$): 231.0627, found: 231.0625.

Methyl (*E*)-3-(2,3-dichlorophenyl)acrylate (24f). White solid (yield 98%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 8.09 (d, J = 16.0 Hz, 1H), 7.51 (dd, J = 7.8, 1.3 Hz, 1H), 7.49 (dd, J = 8.0, 1.5 Hz, 1H), 7.23 (t, J = 7.9 Hz, 1H), 6.41 (d, J = 16.0 Hz, 1H), 3.83 (s, 3H). HRMS (ESI) *m/z* calculated for $C_{11}H_9Cl_2O_2^+$ ([M + H]$^+$): 230.9974, found: 230.9970.

General Method for the Preparation of 25a–f. To a solution of esters **24a–f** (1.0 eq) in THF/H_2O (v/v = 5/2, 0.1 mol/L) was added LiOH-H_2O (5.0 eq), and the solution was stirred at room temperature for 2 h. Water was added, and 4 M HCl (aq) was added to adjust the pH to 5. The mixture was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4 and concentrated to give acid intermediates **25a–f** as white solids.

(*E*)-3-(3-Fluorophenyl)acrylic acid (25a). White solid (yield 75%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.75 (d, J = 15.9 Hz, 1H), 7.40 – 7.37 (m, 1H), 7.33 (d, J = 7.7 Hz, 1H), 7.26 – 7.24 (m, 1H), 7.12 (td, J = 8.2, 1.9 Hz, 1H), 6.45 (d, J = 16.0 Hz, 1H).

(*E*)-3-(3-Chlorophenyl)acrylic acid (25b). White solid (yield 100%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.72 (d, J = 16.0 Hz, 1H), 7.54 (t, J = 1.6 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.40 – 7.38 (m, 1H), 7.35 (t, J = 7.8 Hz, 1H), 6.46 (d, J = 16.0 Hz, 1H).

(*E*)-3-(4-Fluorophenyl)acrylic acid (25c). White solid (yield 97%). ^{1}H NMR (800 MHz, CD_3OD) δ 7.67 – 7.63 (m, 3H), 7.17 – 7.12 (m, 2H), 6.43 (d, J = 15.9 Hz, 1H).

(*E*)-3-(4-Chlorophenyl)acrylic acid (25d). White solid (yield 98%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.51 (s, 1H), 7.78 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 16.1 Hz, 1H), 7.53 (d, J = 8.5 Hz, 2H), 6.61 (d, J = 16.0 Hz, 1H).

(*E*)-3-(4-(Trifluoromethyl)phenyl)acrylic acid (25e). White solid (yield 97%). ^{1}H NMR (800 MHz, DMSO-d_6) δ 12.61 (s, 1H), 7.92 (d, J = 8.1 Hz, 2H), 7.76 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 16.0 Hz, 1H), 6.68 (d, J = 16.0 Hz, 1H).

(*E*)-3-(2,3-Dichlorophenyl)acrylic acid (25f). White solid (yield 94%). ^{1}H NMR (800 MHz, DMSO-d_6) δ 12.72 (br, 1H), 7.89 (dd, J = 7.9, 1.4 Hz, 1H), 7.87 (d, J = 15.9 Hz, 1H), 7.70 (dd, J = 8.0, 1.4 Hz, 1H), 7.41 (t, J = 7.9 Hz, 1H), 6.63 (d, J = 15.9 Hz, 1H).

General Method for the Preparation of Acrylamides 26a–f: To a solution of acrylacids **25a–f** in DMF (0.1 mol/L) was added *N*,*O*-dimethylhydroxylamine hydrochloride (1.2 eq), HATU (1.5 eq) and $NaHCO_3$ (3.0 eq), and the mixture was stirred at room temperature overnight. The mixture was diluted with ethyl acetate, washed with water and brine. The organic layer was separated, concentrated and purified by flash chromatography (0 – 30% EtOAc in petroleum ether) to give the acrylamides **26a–f**.

(*E*)-3-(3-Fluorophenyl)-*N*-methoxy-*N*-methylacrylamide (26a). Colorless oil **(**yield 94%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.68 (d, J = 15.8 Hz, 1H), 7.36 – 7.31 (m, 2H), 7.28 – 7.25 (m, 1H), 7.07 – 7.04 (m, 1H), 7.02 (d, J = 15.8 Hz, 1H), 3.77 (s, 3H), 3.31 (s, 3H). HRMS (ESI) *m/z* calculated for $C_{11}H_{13}FNO_2^+$ ([M + H]$^+$): 210.0925, found: 210.0921.

(*E*)-3-(3-Chlorophenyl)-*N*-methoxy-*N*-methylacrylamide (26b). Colorless oil **(**yield 97%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.66 (d, J = 15.8 Hz, 1H), 7.55 (t, J = 1.8 Hz, 1H), 7.42 (dt, J = 7.1, 1.7 Hz, 1H), 7.35 – 7.30 (m, 2H), 7.02 (d, J = 15.8 Hz, 1H), 3.77 (s, 3H), 3.31 (s, 3H). HRMS (ESI) *m/z* calculated for $C_{11}H_{13}ClNO_2^+$ ([M + H]$^+$): 226.0629, found: 226.0623.

(*E*)-3-(4-Fluorophenyl)-*N*-methoxy-*N*-methylacrylamide (26c). Colorless oil **(**yield 92%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.69 (d, J = 15.8 Hz, 1H), 7.57 – 7.53 (m, 2H), 7.09 – 7.05 (m, 2H), 6.96 (d, J = 15.8 Hz, 1H), 3.76 (s, 3H), 3.31 (s, 3H). HRMS (ESI) *m/z* calculated for $C_{11}H_{13}FNO_2^+$ ([M + H]$^+$): 210.0925, found: 210.0918.

(*E*)-3-(4-Chlorophenyl)-N-methoxy-N-methylacrylamide (26d). Colorless oil (yield 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 15.8 Hz, 1H), 7.50 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 7.01 (d, J = 15.8 Hz, 1H), 3.77 (s, 3H), 3.31 (s, 3H). HRMS (ESI) *m/z* calculated for $C_{11}H_{13}ClNO_2^+$ ([M + H]$^+$): 226.0629, found: 226.0625.

(*E*)-*N*-Methoxy-*N*-methyl-3-(4-(trifluoromethyl)phenyl)acrylamide (26e). Colorless oil (yield 81%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.74 (d, J = 15.8 Hz, 1H), 7.66 (d, J = 8.2 Hz, 2H), 7.64 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 15.8 Hz, 1H), 3.78 (s,

3H), 3.32 (s, 3H). HRMS (ESI) *m/z* calculated for $C_{12}H_{13}F_3NO_2^+$ ([M + H]$^+$): 260.0893, found: 260.0889.

(*E*)-3-(2,3-Dichlorophenyl)-*N*-methoxy-*N*-methylacrylamide (26f). Colorless oil (yield 90%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 8.11 (d, J = 15.7 Hz, 1H), 7.55 (dd, J = 7.8, 1.5 Hz, 1H), 7.47 (dd, J = 8.0, 1.5 Hz, 1H), 7.22 (t, J = 7.9 Hz, 1H), 7.00 (d, J = 15.8 Hz, 1H), 3.76 (s, 3H), 3.32 (s, 3H). HRMS (ESI) *m/z* calculated for $C_{11}H_{12}Cl_2NO_2^+$ ([M + H]$^+$): 260.0240, found: 260.0237.

General Method for the Preparation of 27a–f: Trimethylsulfoxonium iodide (1.5–2.0 eq) was suspended in anhydrous DMSO (~2 mol/L), and sodium hydride (1.5–2.0 eq) was added in small portions. The mixture was stirred at room temperature for 0.5 to 1 h to afford a clear solution. A solution of acrylamides **26a–f** (1.0 eq) in anhydrous DMSO (2 mol/L) was then slowly added and the solution was stirred at room temperature overnight. The mixture was diluted with ethyl acetate, washed with water and brine. The organic layer was separated, concentrated and purified by flash chromatography (0–30% ethyl acetate in petroleum ether) to give **27a–f**.

2-(3-Fluorophenyl)-*N*-methoxy-*N*-methylcyclopropane-1-carboxamide (27a). Colorless oil (yield 71%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.26 – 7.22 (m, 1H), 6.94 (d, J = 7.7 Hz, 1H), 6.89 (td, J = 8.4, 2.5 Hz, 1H), 6.82 – 6.79 (m, 1H), 3.71 (s, 3H), 3.25 (s, 3H), 2.52 – 2.47 (m, 1H), 2.42 (s, 1H), 1.67 – 1.62 (m, 1H), 1.32 – 1.28 (m, 1H). HRMS (ESI) *m/z* calculated for $C_{12}H_{15}FNO_2^+$ ([M + H]$^+$): 224.1081, found: 224.1076.

2-(3-Chlorophenyl)-*N*-methoxy-*N*-methylcyclopropane-1-carboxamide (27b).

Colorless oil (yield 77%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.22 – 7.18 (m, 1H), 7.18 – 7.15 (m, 1H), 7.08 (t, J = 1.8 Hz, 1H), 7.03 – 7.01 (m, 1H), 3.70 (s, 3H), 3.23 (s, 3H), 2.48 – 2.45 (m, 1H), 2.41 (s, 1H), 1.65 – 1.60 (m, 1H), 1.31 – 1.26 (m, 1H). HRMS (ESI) *m/z* calculated for $C_{12}H_{15}ClNO_2^+$ ($[M + H]^+$): 240.0786, found: 240.0786.

2-(4-Fluorophenyl)-*N*-methoxy-*N*-methylcyclopropane-1-carboxamide (27c). Colorless oil (yield 73%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.10 – 7.07 (m, 2H), 6.99 – 6.94 (m, 2H), 3.69 (s, 3H), 3.23 (s, 3H), 2.52 – 2.45 (m, 1H), 2.35 (s, 1H), 1.62 – 1.58 (m, 1H), 1.28 – 1.21 (m, 1H). HRMS (ESI) *m/z* calculated for $C_{12}H_{15}FNO_2^+$ ($[M + H]^+$): 224.1081, found: 224.1076.

2-(4-Chlorophenyl)-*N*-methoxy-*N*-methylcyclopropane-1-carboxamide (27d). Colorless oil (yield 82%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.24 (d, J = 8.5 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 3.69 (s, 3H), 3.23 (s, 3H), 2.48 – 2.45 (m, 1H), 2.40 – 2.34 (m, 1H), 1.65 – 1.61 (m, 1H), 1.29 – 1.25 (m, 1H). HRMS (ESI) *m/z* calculated for $C_{12}H_{15}ClNO_2^+$ ($[M + H]^+$): 240.0786, found: 240.0780.

***N*-Methoxy-*N*-methyl-2-(4-(trifluoromethyl)phenyl)cyclopropane-1-carboxamide (27e).** White solid (yield 76%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.53 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 3.70 (s, 3H), 3.24 (s, 3H), 2.57 – 2.53 (m, 1H), 2.46 (s, 1H), 1.71 – 1.67 (m, 1H), 1.36 – 1.32 (m, 1H). HRMS (ESI) *m/z* calculated for $C_{13}H_{15}F_3NO_2^+$ ($[M + H]^+$): 274.1049, found: 274.1045.

2-(2,3-Dichlorophenyl)-*N*-methoxy-*N*-methylcyclopropane-1-carboxamide (27f). Colorless oil (yield 77%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.34 (dd, J = 8.0, 1.5 Hz, 1H),

7.14 (t, J = 7.9 Hz, 1H), 7.00 (d, J = 7.5 Hz, 1H), 3.73 (s, 3H), 3.26 (s, 3H), 2.78 – 2.73 (m, 1H), 2.32 (s, 1H), 1.66 – 1.63 (m, 1H), 1.35 – 1.31 (m, 1H). HRMS (ESI) *m/z* calculated for $C_{12}H_{14}Cl_2NO_2^+$ ($[M + H]^+$): 274.0396, found: 274.0389.

General Method for the Preparation of Aldehydes 28a–f. A solution of **27a–f** (1.0 eq) in anhydrous THF (0.1−0.2 mmol/mL) was cooled to −78 °C under argon. To this solution was added slowly DIBAL-H (1.0 M solution in THF, 2.0 eq) and the solution was stirred at −78 °C for 2−3 h. Saturated aqueous solution of Rochelle's salt was added to quench the reaction and the mixture was warmed to room temperature, stirred for 1 h and filtered. The solid was washed with ethyl acetate and the filtrate was extracted with the same solvent. The combined organic phases were washed with brine, dried and concentrated to give the aldehydes **28a–f** as colorless oil, which were used in the next step without further purification.

General Method for the Preparation of Amines 29a–c. To a solution of crude aldehydes **20a–c** (1.0 eq) in THF (0.25 mol/L) was added propylamine (5.0 eq), $NaHB(AcO)_3$ (2.0–2.5 eq) and AcOH (1.0 eq) successively. The mixture was stirred at room temperature overnight. Methanol was added to quench the reaction, and the mixture was stirred at room temperature for 15 min. The solvent was evaporated under vacuum and the residue formed was purified by flash chromatography (0–10% methanol in dichloromethane) to give propyl amines **29a–c**.

***N*-(4-(Propylamino)butyl)-2-naphthamide (29a).** White solid (yield 44%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.83 – 8.74 (m, 2H), 8.49 (s, 1H), 8.04 – 7.94 (m, 4H), 7.65 –

7.57 (m, 2H), 3.36 – 3.33 (m, 2H), 2.94 – 2.89 (m, 2H), 2.84 – 2.79 (m, 2H), 1.74 – 1.68 (m, 2H), 1.66 – 1.59 (m, 4H), 0.91 (t, J = 7.4 Hz, 3H). HRMS (ESI) *m/z* calculated for $C_{18}H_{25}N_2O^+$ ([M + H]$^+$): 285.1961, found: 285.1958.

***N*-(4-(Propylamino)butyl)-1*H*-indole-2-carboxamide (29b).** White solid (yield 64%). ^{1}H NMR (800 MHz, CD_3OD) δ 7.59 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.08 – 7.05 (m, 2H), 3.45 (t, J = 6.6 Hz, 2H), 3.05 – 3.01 (m, 2H), 2.94 – 2.91 (m, 2H), 1.79 – 1.74 (m, 2H), 1.74 – 1.65 (m, 4H), 1.00 (t, J = 7.3 Hz, 3H). HRMS (ESI) *m/z* calculated for $C_{16}H_{24}N_3O^+$ ([M + H]$^+$): 274.1914, found: 274.1910.

***N*-(4-(Propylamino)butyl)-4-(pyridin-2-yl)benzamide (29c).** Yellow oil (yield 46%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.65 (dt, J = 4.9, 1.3 Hz, 1H), 8.08 – 8.05 (m, 2H), 7.97 – 7.92 (m, 4H), 7.43 – 7.39 (m, 1H), 3.46 (t, J = 6.5 Hz, 2H), 3.05 – 2.99 (m, 2H), 2.94 – 2.90 (m, 2H), 1.78 – 1.66 (m, 6H), 1.01 (t, J = 7.5 Hz, 3H). HRMS (ESI) *m/z* calculated for $C_{19}H_{26}N_3O^+$ ([M + H]$^+$): 312.2070, found: 312.2067.

General Method for the Preparation of 30a–r: To a solution of crude aldehydes **28a–f** (1.0 eq) in CH_3CN (0.03−0.05 mol/L) was added amine **29a–c** (1.0 eq), $NaHB(AcO)_3$ (2.0 eq) and AcOH (1.0 eq), and the reaction mixture was stirred at room temperature overnight. Methanol was added to afford a clear solution, which was stirred at room temperature for 15–30 min. The solution was concentrated and purified by flash chromatography (0–6% methanol in dichloromethane) to give title products as colorless oil. The free amines **30a–r** were converted to corresponding HCl salts using a similar method as depicted for **17a**.

***N*-(4-(((2-(3-Fluorophenyl)cyclopropyl)methyl)(propyl)amino)butyl)-2-naphthamide Hydrochloride (30a).** White solid (yield 68%). HPLC: 98.1% (λ = 254 nm, t_R = 20.2 min); ^{1}H NMR (800 MHz, CD_3OD) δ 8.39 (s, 1H), 7.99 – 7.92 (m, 3H), 7.91 – 7.87 (m, 1H), 7.62 – 7.56 (m, 2H), 7.27 – 7.23 (m, 1H), 6.96 (t, J = 7.7 Hz, 1H), 6.91 – 6.85 (m, 2H), 3.52 – 3.49 (m, 2H), 3.34 – 3.25 (m, 4H), 3.24 – 3.14 (m, 2H), 2.10 – 2.06 (m, 1H), 1.89 – 1.82 (m, 2H), 1.81 – 1.72 (m, 4H), 1.51 – 1.45 (m, 1H), 1.25 – 1.21 (m, 1H), 1.17 – 1.14 (m, 1H), 1.00 (t, J = 7.4 Hz, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 170.37, 164.52 (d, J_{CF} = 244.0 Hz), 145.68 (d, J_{CF} = 7.0 Hz), 136.29, 134.06, 132.79, 131.19 (d, J_{CF} = 8.5 Hz), 129.99, 129.38, 128.89, 128.79, 128.77, 127.91, 124.82, 122.80, 113.73 (d, J_{CF} = 21.8 Hz), 113.37 (d, J_{CF} = 22.1 Hz), 58.22, 55.93, 53.96, 40.07, 28.00, 23.61, 22.80, 19.42, 18.75, 15.60, 11.44. HRMS (ESI) *m/z* calculated for $C_{28}H_{34}FN_2O^+$ ($[M + H]^+$): 433.2650, found: 433.2645.

***N*-(4-(((2-(3-Fluorophenyl)cyclopropyl)methyl)(propyl)amino)butyl)-1*H*-indole-2-carboxamide Hydrochloride (30b).** White solid (yield 36%). HPLC: 98.8% (λ = 280 nm, t_R = 16.3 min); ^{1}H NMR (800 MHz, CD_3OD) δ 7.60 (dd, J = 8.0, 2.5 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.25 – 7.20 (m, 2H), 7.11 (d, J = 3.3 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 6.93 (t, J = 8.7 Hz, 1H), 6.89 – 6.85 (m, 2H), 3.47 – 3.43 (m, 2H), 3.29 – 3.21 (m, 4H), 3.20 – 3.09 (m, 2H), 2.09 – 2.03 (m, 1H), 1.87 – 1.79 (m, 2H), 1.78 – 1.65 (m, 4H), 1.47 – 1.42 (m, 1H), 1.22 – 1.19 (m, 1H), 1.16 – 1.11 (m, 1H), 0.97 (t, J = 7.3 Hz, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 164.35, 164.50 (d, J_{CF} = 243.8 Hz), 145.19 (d, J_{CF} = 7.7 Hz), 138.31, 132.09, 131.26 (d, J_{CF} = 8.6 Hz), 128.97, 125.13, 122.87 and 122.83 (d, J_{CF} = 2.7 Hz), 122.76, 121.24, 113.88 (d, J_{CF} = 21.4 Hz), 113.45 (d, J_{CF} =

22.2 Hz), 113.08, 104.51 and 104.50, 58.05 and 58.01, 55.69 and 55.60, 53.87 and 53.72, 39.33, 27.86 and 27.84, 23.55 and 23.51, 22.27 and 22.21, 18.67 and 18.62, 18.32 and 18.27, 15.62 and 15.60, 11.21 and 11.19. HRMS (ESI) *m/z* calculated for $C_{26}H_{33}FN_3O^+$ ($[M + H]^+$): 422.2602, found: 422.2609.

***N*-(4-(((2-(3-Fluorophenyl)cyclopropyl)methyl)(propyl)amino)butyl)-4-(pyridin-2-yl)benzamide Hydrochloride (30c).** White solid (yield 55%). HPLC: 99.4% (λ = 254 nm, t_R = 12.7 min); ^{1}H NMR (800 MHz, CD_3OD) δ 8.90 (d, J = 5.3 Hz, 1H), 8.72 (t, J = 7.9 Hz, 1H), 8.45 (d, J = 8.2 Hz, 1H), 8.15 (d, J = 8.1 Hz, 2H), 8.12 – 8.05 (m, 3H), 7.30 – 7.23 (m, 1H), 7.02 – 6.96 (m, 1H), 6.92 – 6.86 (m, 2H), 3.52 – 3.46 (m, 2H), 3.36 – 3.28 (m, 4H), 3.25 – 3.17 (m, 2H), 2.14 – 2.11 (m, 1H), 1.90 – 1.84 (m, 2H), 1.83 – 1.78 (m, 2H), 1.77 – 1.69 (m, 2H), 1.53 – 1.48 (m, 1H), 1.26 – 1.22 (m, 1H), 1.21 – 1.16 (m, 1H), 1.01 (t, J = 7.4 Hz, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 168.76, 164.52 (d, J_{CF} = 244.1 Hz), 153.15, 148.32, 145.30, 143.54, 138.92, 135.10, 131.29 and 131.25, 129.75 (2C), 129.61 (2C), 127.60, 127.21, 122.92, 113.88 (d, J_{CF} = 21.4 Hz), 113.48 (d, J_{CF} = 22.2 Hz), 58.02, 55.72 and 55.61, 53.85and 53.71, 40.06 and 40.04, 27.68 and 27.65, 23.56, 22.39 and 22.29, 18.69, 18.33 and 18.30, 15.66 and 15.65, 11.26 and 11.24. HRMS (ESI) *m/z* calculated for $C_{29}H_{35}FN_3O^+$ ($[M + H]^+$): 460.2759, found: 460.2769.

***N*-(4-(((2-(3-Chlorophenyl)cyclopropyl)methyl)(propyl)amino)butyl)-2-naphthamide Hydrochloride (30d).** White solid (yield 46%). HPLC: 99.8% (λ = 254 nm, t_R = 25.3 min); ^{1}H NMR (800 MHz, CD_3OD) δ 8.41 (s, 1H), 7.97 (t, J = 7.3 Hz, 1H), 7.95 – 7.89 (m, 3H), 7.60 – 7.55 (m, 2H), 7.23 – 7.20 (m, 1H), 7.17 – 7.14 (m,

2H), 7.06 – 7.04 (m, 1H), 3.52 – 3.49 (m, 2H), 3.34 – 3.12 (m, 6H), 2.09 – 2.05 (m, 1H), 1.89 – 1.82 (m, 2H), 1.81 – 1.72 (m, 4H), 1.51 – 1.45 (m, 1H), 1.24 – 1.19 (m, 1H), 1.17 – 1.13 (m, 1H), 0.99 (t, J = 7.3 Hz, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 170.34, 144.67, 136.28, 135.46, 134.04, 132.70, 131.05, 130.01, 129.39, 128.90, 128.81, 128.78, 127.91, 127.31, 126.96, 125.35 and 125.30, 124.83, 58.03, 55.72 and 55.60, 53.88 and 53.74, 39.87 and 39.85, 27.82 and 27.79, 23.43, 22.31 and 22.21, 18.62 and 18.60, 18.33 and 18.29, 15.54, 11.24 and 11.22. HRMS (ESI) *m/z* calculated for $C_{28}H_{34}ClN_2O^+$ ($[M + H]^+$): 449.2354, found: 449.2361.

***N*-(4-(((2-(3-Chlorophenyl)cyclopropyl)methyl)(propyl)amino)butyl)-1*H*-indole-2-carboxamide Hydrochloride (30e).** White solid (yield 8%). HPLC: 97.2% (λ = 280 nm, t_R = 20.5 min); ^{1}H NMR (800 MHz, CD_3OD) δ 7.60 (dd, J = 8.0, 2.8 Hz, 1H), 7.47 – 7.44 (m, 1H), 7.23 – 7.19 (m, 2H), 7.16 – 7.13 (m, 2H), 7.12 – 7.11 (m, 1H), 7.06 (t, J = 7.5 Hz, 1H), 7.05 – 7.01 (m, 1H), 3.47 – 3.43 (m, 2H), 3.30 – 3.19 (m, 4H), 3.19 – 3.09 (m, 2H), 2.07 – 2.01 (m, 1H), 1.87 – 1.79 (m, 2H), 1.78 – 1.68 (m, 4H), 1.48 – 1.42 (m, 1H), 1.23 – 1.18 (m, 1H), 1.15 – 1.10 (m, 1H), 0.99 – 0.95 (m, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 164.34, 144.65, 138.31, 135.45, 132.09, 131.06, 128.97, 127.30, 126.95, 125.33 and 125.27, 125.13, 122.77 and 122.76, 121.24, 113.09, 104.55, 58.06 and 58.02, 55.69 and 55.62, 53.87 and 53.73, 39.33, 27.86 and 27.83, 23.43 and 23.41, 22.27 and 22.22, 18.64 and 18.59, 18.32 and 18.28, 15.53, 11.22 and 11.21. HRMS (ESI) *m/z* calculated for $C_{26}H_{33}ClN_3O^+$ ($[M + H]^+$): 438.2307, found: 438.2317.

***N*-(4-(((2-(3-Chlorophenyl)cyclopropyl)methyl)(propyl)amino)butyl)-4-(pyridin-2-yl)benzamide Hydrochloride (30f).** White solid (yield 46%). HPLC: 99.9% (λ =

254 nm, t_R = 14.2 min); ^{1}H NMR (800 MHz, CD_3OD) δ 8.91 (d, J = 5.7 Hz, 1H), 8.75 – 8.71 (m, 1H), 8.46 (d, J = 8.1 Hz, 1H), 8.16 (d, J = 8.1 Hz, 2H), 8.12 – 8.07 (m, 3H), 7.26 – 7.23 (m, 1H), 7.19 – 7.16 (m, 2H), 7.11 – 7.08 (m, 1H), 3.51 – 3.47 (m, 2H), 3.36 – 3.27 (m, 4H), 3.25 – 3.16 (m, 2H), 2.13 – 2.09 (m, 1H), 1.91 – 1.84 (m, 2H), 1.84 – 1.78 (m, 2H), 1.77 – 1.72 (m, 2H), 1.54 – 1.49 (m, 1H), 1.26 – 1.22 (m, 1H), 1.20 – 1.16 (m, 1H), 1.01 (t, J = 7.3 Hz, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 168.72, 153.08, 148.42, 144.76, 143.46, 138.94, 135.45, 134.99, 131.08, 129.77 (2C), 129.62 (2C), 127.65, 127.30, 127.24, 126.98, 125.39 and 125.36, 58.02, 55.72 and 55.61, 53.83 and 53.71, 40.06 and 40.04, 27.67 and 27.65, 23.45, 22.38 and 22.29, 18.67 and 18.66, 18.33 and 18.30, 15.58, 11.27 and 11.25. HRMS (ESI) *m/z* calculated for $C_{29}H_{35}ClN_3O^+$ ($[M + H]^+$): 476.2463, found: 476.2468.

***N*-(4-(((2-(4-Fluorophenyl)cyclopropyl)methyl)(propyl)amino)butyl)-2-naphthamide Hydrochloride (30g).** White solid (yield 38%). HPLC: 99.5% (λ = 254 nm, t_R = 20.6 min); ^{1}H NMR (800 MHz, CD_3OD) δ 8.40 (s, 1H), 7.97 (t, J = 7.3 Hz, 1H), 7.95 – 7.89 (m, 3H), 7.61 – 7.55 (m, 2H), 7.15 – 7.11 (m, 2H), 6.99 – 6.95 (m, 2H), 3.53 – 3.48 (m, 2H), 3.33 – 3.24 (m, 4H), 3.23 – 3.14 (m, 2H), 2.08 – 2.04 (m, 1H), 1.90 – 1.82 (m, 2H), 1.81 – 1.72 (m, 4H), 1.44 – 1.38 (m, 1H), 1.18 – 1.15 (m, 1H), 1.13 – 1.09 (m, 1H), 0.99 (t, J = 7.3 Hz, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 170.35, 162.88 (d, J_{CF} = 243.0 Hz), 137.95 and 137.93, 136.29, 134.05, 132.70, 130.00, 129.40, 128.92, 128.80 (d, J_{CF} = 2.7 Hz), 128.62, 128.61 (d, J_{CF} = 7.9Hz), 128.58, 127.92, 124.82, 116.16 (d, J_{CF} = 21.6 Hz, 2C), 58.15, 55.74 and 55.61, 53.89 and 53.71, 39.87 and 39.85, 27.82 and 27.80, 23.12 and 23.10, 22.33 and 22.20, 18.35 and 18.29,

18.22 and 18.20, 15.21 and 15.19, 11.24 and 11.22. HRMS (ESI) *m/z* calculated for $C_{28}H_{34}FN_2O^+$ ([M + H]$^+$): 433.2650, found: 433.2645.

***N*-(4-(((2-(4-Fluorophenyl)cyclopropyl)methyl)(propyl)amino)butyl)-1*H*-indole-2-carboxamide Hydrochloride (30h).** White solid (yield 16%). HPLC: 98.0% (λ = 280 nm, t_R = 16.9 min); ^{1}H NMR (800 MHz, CD_3OD) δ 7.60 (dd, J = 8.0, 2.5 Hz, 1H), 7.47 – 7.44 (m, 1H), 7.23 – 7.20 (m, 1H), 7.14 – 7.05 (m, 4H), 6.97 – 6.92 (m, 2H), 3.47 – 3.43 (m, 2H), 3.28 – 3.21 (m, 4H), 3.18 – 3.11 (m, 2H), 2.05 – 1.99 (m, 1H), 1.86 – 1.80 (m, 2H), 1.77 – 1.67 (m, 4H), 1.40 – 1.35 (m, 1H), 1.16 – 1.12 (m, 1H), 1.10 – 1.06 (m, 1H), 1.00 – 0.93 (m, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 164.32, 162.86 (d, J_{CF} = 242.5 Hz), 138.31, 137.92 (d, J_{CF} = 2.8 Hz), 132.11 and 132.09, 128.97, 128.59 and 128.57 (d, J_{CF} = 7.9 Hz, 2C), 125.14, 122.78 and 122.76, 121.25, 116.15 (d, J_{CF} = 21.7 Hz, 2C), 113.09, 104.55 and 104.51, 58.17 and 58.14, 55.72 and 55.64, 53.86 and 53.68, 39.34, 27.84 and 27.83, 23.11 and 23.08, 22.30 and 22.20, 18.33 and 18.28, 18.22 and 18.21, 15.23 and 15.21, 11.22 and 11.21. HRMS (ESI) *m/z* calculated for $C_{26}H_{33}FN_3O^+$ ([M + H]$^+$): 422.2602, found: 422.2611.

***N*-(4-(((2-(4-Fluorophenyl)cyclopropyl)methyl)(propyl)amino)butyl)-4-(pyridin-2-yl)benzamide Hydrochloride (30i).** White solid (yield 36%). HPLC: 96.2% (λ = 254 nm, t_R = 12.5 min); ^{1}H NMR (800 MHz, CD_3OD) δ 8.90 – 8.86 (m, 1H), 8.67 – 8.62 (m, 1H), 8.42 – 8.38 (m, 1H), 8.14 – 8.11 (m, 2H), 8.08 – 8.06 (m, 2H), 8.05 – 8.01 (m, 1H), 7.18 – 7.14 (m, 2H), 7.02 – 6.98 (m, 2H), 3.50 – 3.47 (m, 2H), 3.33 – 3.26 (m, 4H), 3.24 – 3.16 (m, 2H), 2.11 – 2.06 (m, 1H), 1.89 – 1.82 (m, 2H), 1.81 – 1.71 (m, 4H), 1.46 – 1.41 (m, 1H), 1.21 – 1.18 (m, 1H), 1.15 – 1.11 (m, 1H), 1.02 (t, J = 7.4 Hz,

3H). ^{13}C NMR (201 MHz, CD_3OD) δ 168.76, 162.85 (d, J_{CF} = 242.4 Hz), 153.23, 148.03, 143.75, 138.80, 138.03, 135.31, 129.72 (2C), 129.56 (2C), 128.65 (d, J_{CF} = 7.6 Hz, 2C), 127.44, 127.13, 116.15 (d, J_{CF} = 21.6 Hz, 2C), 58.14 and 58.13, 55.70 and 55.60, 53.82 and 53.67, 40.07 and 40.05, 27.66 and 27.64 23.13 and 23.11, 22.40 and 22.27, 18.34 and 18.29, 18.27 and 18.25, 15.26 and 15.24, 11.28 and 11.27. HRMS (ESI) *m/z* calculated for $C_{29}H_{35}FN_3O^+$ ([M + H]$^+$): 460.2759, found: 460.2754.

***N*-(4-(((2-(4-Chlorophenyl)cyclopropyl)methyl)(propyl)amino)butyl)-2-naphthamide Hydrochloride (30j).** White solid (yield 46%). HPLC: 98.9% (λ = 254 nm, t_R = 25.4 min); ^{1}H NMR (800 MHz, CD_3OD) δ 8.40 (d, J = 4.1 Hz, 1H), 7.97 (t, J = 7.7 Hz, 1H), 7.95 – 7.88 (m, 3H), 7.60 – 7.55 (m, 2H), 7.24 – 7.21 (m, 2H), 7.11 – 7.08 (m, 2H), 3.53 – 3.47 (m, 2H), 3.34 – 3.24 (m, 4H), 3.22 – 3.12 (m, 2H), 2.08 – 2.03 (m, 1H), 1.89 – 1.82 (m, 2H), 1.81 – 1.72 (m, 4H), 1.47 – 1.42 (m, 1H), 1.20 – 1.16 (m, 1H), 1.15 – 1.11 (m, 1H), 0.99 (t, J = 7.4 Hz, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 170.36, 140.97, 136.29, 134.05, 132.89, 132.70, 130.01, 129.58 and 129.57 (2C), 129.40, 128.92, 128.80 and 128.79 (2C), 128.48 and 128.46 (2C), 127.92, 124.82, 58.08, 55.76 and 55.65, 53.88 and 53.71, 39.86 and 39.84, 27.82 and 27.79, 23.25 and 23.21, 22.32 and 22.17, 18.49 and 18.45, 18.34 and 18.29, 15.47 and 15.43, 11.24 and 11.22. HRMS (ESI) *m/z* calculated for $C_{28}H_{34}ClN_2O^+$ ([M + H]$^+$): 449.2354, found: 449.2356.

***N*-(4-(((2-(4-Chlorophenyl)cyclopropyl)methyl)(propyl)amino)butyl)-1*H*-indole-2-carboxamide Hydrochloride (30k).** White solid (yield 36%). HPLC: 97.1% (λ = 280 nm, t_R = 20.7 min); ^{1}H NMR (800 MHz, CD_3OD) δ 7.60 (dd, J = 8.1, 2.8 Hz, 1H),

7.45 (d, J = 8.2 Hz, 1H), 7.23 – 7.20 (m, 3H), 7.11 – 7.09 (m, 1H), 7.09 – 7.05 (m, 3H), 3.48 – 3.43 (m, 2H), 3.30 – 3.21 (m, 4H), 3.19 – 3.10 (m, 2H), 2.05 – 2.00 (m, 1H), 1.87 – 1.79 (m, 2H), 1.79 – 1.68 (m, 4H), 1.44 – 1.38 (m, 1H), 1.19 – 1.15 (m, 1H), 1.13 – 1.09 (m, 1H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 164.36, 140.94, 138.32, 132.88, 132.08, 129.58 and 129.56 (2C), 128.98, 128.45 and 128.43 (2C), 125.14, 122.77, 121.25, 113.09, 104.49, 58.10 and 58.07, 55.76 and 55.69, 53.88 and 53.70, 39.31 and 39.29, 27.86 and 27.84, 23.25 and 23.20, 22.29 and 22.18, 18.47, 18.34 and 18.29, 15.46 and 15.41, 11.21 and 11.20. HRMS (ESI) *m/z* calculated for $C_{26}H_{33}ClN_3O^+$ ([M + H]$^+$): 438.2307, found: 423.2307.

***N*-(4-(((2-(4-Chlorophenyl)cyclopropyl)methyl)(propyl)amino)butyl)-4-(pyridin-2-yl)benzamide Hydrochloride (30l).** White solid (yield 47%). HPLC: 99.5% (λ = 254 nm, t_R = 14.0 min); ^{1}H NMR (800 MHz, CD_3OD) δ 8.91 (d, J = 5.5 Hz, 1H), 8.72 (t, J = 7.9 Hz, 1H), 8.46 (d, J = 8.1 Hz, 1H), 8.16 – 8.14 (m, 2H), 8.12 – 8.06 (m, 3H), 7.26 – 7.23 (m, 2H), 7.16 – 7.12 (m, 2H), 3.52 – 3.45 (m, 2H), 3.35 – 3.27 (m, 4H), 3.24 – 3.15 (m, 2H), 2.12 – 2.07 (m, 1H), 1.90 – 1.84 (m, 2H), 1.82 – 1.77 (m, 2H), 1.76 – 1.72 (m, 2H), 1.50 – 1.45 (m, 1H), 1.23 – 1.19 (m, 1H), 1.18 – 1.14 (m, 1H), 1.01 (t, J = 7.4 Hz, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 168.74, 153.10, 148.39, 143.48, 141.07, 138.94, 135.02, 132.85, 129.76 (2C), 129.62 (2C), 129.57 (2C), 128.53 and 128.52 (2C), 127.64, 127.24, 58.07 and 58.04, 55.76 and 55.65, 53.83 and 53.67, 40.0 and, 40.04, 27.67 and 27.65, 23.27 and 23.22, 22.40 and 22.25, 18.56 and 18.48, 18.35 and 18.31, 15.50 and 15.46, 11.27 and 11.25. HRMS (ESI) *m/z* calculated for $C_{29}H_{35}ClN_3O^+$ ([M + H]$^+$): 476.2463, found: 476.2473.

_N_-(4-(Propyl((2-(4-(trifluoromethyl)phenyl)cyclopropyl)methyl)amino)butyl)-2-naphthamide Hydrochloride (30m). White solid (yield 44%). HPLC: 98.0% (λ = 254 nm, t_R = 25.1 min); ^{1}H NMR (800 MHz, CD_3OD) δ 8.42 (d, J = 3.3 Hz, 1H), 7.99 (t, J = 7.9 Hz, 1H), 7.97 – 7.90 (m, 3H), 7.62 – 7.56 (m, 2H), 7.54 (d, J = 7.9 Hz, 2H), 7.33 – 7.29 (m, 2H), 3.56 – 3.49 (m, 2H), 3.37 – 3.27 (m, 4H), 3.24 – 3.15 (m, 2H), 2.19 – 2.14 (m, 1H), 1.90 – 1.84 (m, 2H), 1.82 – 1.74 (m, 4H), 1.59 – 1.53 (m, 1H), 1.31 – 1.28 (m, 1H), 1.25 – 1.19 (m, 1H), 1.01 (t, J = 7.3 Hz, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 170.27, 147.01, 136.24, 134.02, 132.69, 130.00, 129.37, 129.22, 128.89, 128.82, 128.77, 127.89, 127.42 (2C), 126.35 (q, J_{CF} = 3.3 Hz, 2C), 125.75 (q, J_{CF} = 270.7 Hz), 124.85, 57.92, 55.69 and 55.62, 53.85 and 53.72, 39.88 and 39.86, 27.77 and 27.74, 23.59 and 23.56, 22.30 and 22.17, 19.01 and 18.99, 18.30 and 18.27, 16.04, 11.25 and 11.23. HRMS (ESI) *m/z* calculated for $C_{29}H_{34}F_3N_2O^+$ ($[M + H]^+$): 483.2618, found: 483.2617.

_N_-(4-(Propyl((2-(4-(trifluoromethyl)phenyl)cyclopropyl)methyl)amino)butyl)-1_H_-indole-2-carboxamide Hydrochloride (30n). Yellow oil (yield 11%). HPLC: 99.0% (λ = 280 nm, t_R = 16.5 min); ^{1}H NMR (800 MHz, CD_3OD) δ 7.60 (dd, J = 8.0, 3.1 Hz, 1H), 7.53 – 7.50 (m, 2H), 7.45 (dd, J = 8.2, 3.3 Hz, 1H), 7.28 – 7.25 (m, 2H), 7.23 – 7.21 (m, 1H), 7.10 (s, 1H), 7.08 – 7.05 (m, 1H), 3.48 – 3.44 (m, 2H), 3.30 – 3.22 (m, 4H), 3.20 – 3.11 (m, 2H), 2.16 – 2.11 (m, 1H), 1.88 – 1.80 (m, 2H), 1.79 – 1.68 (m, 4H), 1.55 – 1.49 (m, 1H), 1.28 – 1.24 (m, 1H), 1.21 – 1.17 (m, 1H), 0.98 (t, J = 7.3 Hz, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 164.36, 146.97, 138.32, 132.07, 129.35 (q, J_{CF} = 32.8 Hz), 128.97, 127.39 (2C), 126.38 (2C), 125.76 (q, J_{CF} = 270.9 Hz), 125.15, 122.76,

121.25, 113.09, 104.52, 58.00 and 57.95, 55.77 and 55.73, 53.90 and 53.74, 39.31 and 39.30, 27.84 and 27.82, 23.60 and 23.56, 22.28 and 22.18, 19.00 and 18.98, 18.33 and 18.29, 16.03 and 16.00, 11.21 and 11.19. HRMS (ESI) *m/z* calculated for $C_{27}H_{33}F_3N_3O^+$ ($[M + H]^+$): 472.2570, found: 472.2572.

***N*-(4-(Propyl((2-(4-(trifluoromethyl)phenyl)cyclopropyl)methyl)amino)butyl)-4-(pyridin-2-yl)benzamide Hydrochloride (30o).** White solid (yield 43%). HPLC: 97.0% (λ = 254 nm, t_R = 15.7 min); ^{1}H NMR (800 MHz, CD_3OD) δ 8.91 (d, J = 5.8 Hz, 1H), 8.74 (t, J = 7.9 Hz, 1H), 8.51 – 8.42 (m, 1H), 8.17 – 8.15 (m, 2H), 8.14 – 8.11 (m, 1H), 8.10 – 8.07 (m, 2H), 7.56 (d, J = 7.8 Hz, 2H), 7.35 (dd, J = 8.1, 3.6 Hz, 2H), 3.51 – 3.46 (m, 2H), 3.37 – 3.32 (m, 3H), 3.30 – 3.16 (m, 3H), 2.23 – 2.17 (m, 1H), 1.92 – 1.85 (m, 2H), 1.83 – 1.79 (m, 2H), 1.78 – 1.70 (m, 2H), 1.63 – 1.57 (m, 1H), 1.34 – 1.28 (m, 1H), 1.27 – 1.22 (m, 1H), 1.01 (t, J = 7.3 Hz, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 168.72, 153.17, 147.95, 147.14, 143.77, 138.73, 135.29, 129.71 (2C), 129.54 (2C), 129.20 (q, J_{CF} = 32.3 Hz), 127.47 (2C), 127.36, 127.10, 126.34 (q, J_{CF} = 3.8 Hz, 2C), 125.75 (q, J_{CF} = 270.8 Hz), 57.92, 55.64 and 55.59, 53.78 and 53.67, 40.06, 27.61 and 27.59, 23.59, 22.34 and 22.24, 19.13 and 19.08, 18.30 and 18.29, 16.09, 11.30 and 11.28. HRMS (ESI) *m/z* calculated for $C_{30}H_{35}F_3N_3O^+$ ($[M + H]^+$): 510.2727, found: 510.2731.

***N*-(4-(((2-(2,3-Dichlorophenyl)cyclopropyl)methyl)(propyl)amino)butyl)-2-naphthamide Hydrochloride (30p).** White solid (yield 43%). HPLC: 98.0% (λ = 254 nm, t_R = 25.9 min); ^{1}H NMR (800 MHz, CD_3OD) δ 8.39 (d, J = 11.4 Hz, 1H), 8.00 – 7.92 (m, 3H), 7.91 – 7.87 (m, 1H), 7.63 – 7.56 (m, 2H), 7.38 (d, J = 8.0 Hz, 1H), 7.22

– 7.19 (m, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 3.62 – 3.58 (m, 1H), 3.56 – 3.51 (m, 2H), 3.41 – 3.34 (m, 2H), 3.28 – 3.17 (m, 3H), 2.37 – 2.33 (m, 1H), 1.93 – 1.84 (m, 2H), 1.83 – 1.72 (m, 4H), 1.50 – 1.45 (m, 1H), 1.31 – 1.28 (m, 1H), 1.27 – 1.23 (m, 1H), 1.05 – 1.01 (m, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 170.34, 141.88, 136.27, 134.18 and 134.16, 134.04 and 134.03, 133.92, 132.67 and 132.65, 130.01, 129.67, 129.39, 128.92, 128.90, 128.81, 128.78, 127.90, 126.60 and 126.56, 124.80, 57.87 and 57.82, 55.88 and 55.61, 53.96 and 53.66, 39.88 and 39.81, 27.77, 22.41 and 22.37, 22.28 and 22.14, 18.44 and 18.30, 17.34 and 17.31, 14.81 and 14.73, 11.23. HRMS (ESI) *m/z* calculated for $C_{28}H_{33}Cl_2N_2O^+$ ([M + H]$^+$): 483.1964, found: 483.1970.

***N*-(4-(((2-(2,3-Dichlorophenyl)cyclopropyl)methyl)(propyl)amino)butyl)-1*H*-indole-2-carboxamide Hydrochloride (30q).** White solid (yield 16%). HPLC: 98.2% (λ = 280 nm, t_R = 24.8 min); ^{1}H NMR (800 MHz, CD_3OD) δ 7.60 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.38 – 7.35 (m, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.17 (td, *J* = 7.9, 3.6 Hz, 1H), 7.08 – 7.05 (m, 2H), 7.04 – 7.01 (m, 1H), 3.60 – 3.56 (m, 1H), 3.51 – 3.46 (m, 2H), 3.37 – 3.32 (m, 2H), 3.26 – 3.15 (m, 3H), 2.35 – 2.31 (m, 1H), 1.89 – 1.70 (m, 6H), 1.46 – 1.40 (m, 1H), 1.27 – 1.24 (m, 1H), 1.23 – 1.20 (m, 1H), 1.03 – 0.99 (m, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 164.38, 141.88, 138.32, 134.18, 133.94, 132.06, 129.67, 128.97, 128.93, 126.57 and 126.54, 125.12, 122.76, 121.23, 113.08, 104.49, 57.88, 55.88 and 55.66, 53.97 and 53.68, 39.33 and 39.30, 27.84 and 27.82, 22.40 and 22.34, 22.25 and 22.20, 18.45 and 18.30, 17.35 and 17.32, 14.78 and 14.71, 11.20 and 11.19. HRMS (ESI) *m/z* calculated for $C_{26}H_{32}Cl_2N_3O^+$ ([M + H]$^+$): 472.1917, found: 472.1916.

***N*-(4-(((2-(2,3-Dichlorophenyl)cyclopropyl)methyl)(propyl)amino)butyl)-4-(pyridin-2-yl)benzamide Hydrochloride (30r).** White solid (yield 43%). HPLC: 97.9% (λ = 254 nm, t_R = 16.3 min); ^{1}H NMR (800 MHz, CD_3OD) δ 8.90 – 8.87 (m, 1H), 8.72 – 8.67 (m, 1H), 8.45 – 8.42 (m, 1H), 8.16 – 8.11 (m, 2H), 8.10 – 8.05 (m, 3H), 7.40 (d, J = 7.9 Hz, 1H), 7.24 (t, J = 7.9 Hz, 1H), 7.12 – 7.09 (m, 1H), 3.62 – 3.57 (m, 1H), 3.52 – 3.47 (m, 2H), 3.40 – 3.32 (m, 2H), 3.28 – 3.18 (m, 3H), 2.39 – 2.34 (m, 1H), 1.91 – 1.84 (m, 2H), 1.83 – 1.73 (m, 4H), 1.51 – 1.45 (m, 1H), 1.32 – 1.25 (m, 2H), 1.06 – 1.01 (m, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 168.75, 153.10, 148.38, 143.49, 141.98, 138.92, 135.02, 134.18, 133.93, 129.75 and 129.74 (2C), 129.68, 129.61 (2C), 128.98, 127.63, 127.23, 126.66 and 126.61, 57.83 and 57.80, 55.87 and 55.58, 53.92 and 53.63, 40.06 and 40.01, 27.65, 22.46 and 22.22, 22.37 and 22.33, 18.45 and 18.32, 17.38 and 17.34, 14.83 and 14.79, 11.25 and 11.24. HRMS (ESI) *m/z* calculated for $C_{29}H_{34}Cl_2N_3O^+$ ($[M + H]^+$): 510.2073, found: 510.2082.

Chiral Separation of Racemic 22e. Analytical conditions: Chiralpak AY-3 column (15 cm × 4.6 mm), 30% isopropanol and 0.1% diethylamine in *n*-hexane as the fluent phase, flow rate = 1.0 mL/min, λ = 254 nm; preparative conditions: Chiralcel AY-5 column (25 cm × 50 mm, 10 μM), 30% isopropanol and 0.1% diethylamine in *n*-hexane as the eluting system, flow rate = 60 mL/min, λ = 254 nm. (1*R*,2*R*)-**22e** was isolated as the first eluting peaks (*ee* = 100%), and (1*S*,2*S*)-**22e** as the second eluting peaks (*ee* = 100%), both of which appeared as a colorless oil after evaporation. The oil was dissolved in dichloromethane and stirred with 2 M HCl in diethyl ether (20 mL/mmol

substrate) at room temperature for 15 min, which was then condensed to dryness to give HCl salts respectively.

***N*-(4-((((1*R*,2*R*)-2-(5-Fluoro-2-methoxyphenyl)cyclopropyl)methyl)(propyl)amino)butyl)-4-(pyridin-2-yl)benzamide Hydrochloride ((1*R*,2*R*)-22e).** White solid. HPLC: 99.1% (λ = 254 nm, t_R = 15.5 min); ^{1}H NMR (800 MHz, CD_3OD) δ 8.87 (d, J = 5.7 Hz, 1H), 8.65 (t, J = 7.9 Hz, 1H), 8.40 (d, J = 8.1 Hz, 1H), 8.12 (t, J = 8.1 Hz, 2H), 8.09 – 8.00 (m, 3H), 6.94 – 6.91 (m, 1H), 6.90 – 6.86 (m, 1H), 6.72 – 6.68 (m, 1H), 3.85 (s, 3H), 3.52 – 3.47 (m, 2H), 3.39 – 3.32 (m, 2H), 3.29 – 3.25 (m, 1H), 3.24 – 3.17 (m, 2H), 2.34 – 2.29 (m, 1H), 1.90 – 1.83 (m, 2H), 1.82 – 1.71 (m, 4H), 1.38 – 1.34 (m, 1H), 1.25 – 1.20 (m, 1H), 1.11 – 1.06 (m, 1H), 1.04 – 1.00 (m, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 168.80, 158.65 (d, J_{CF} = 236.7 Hz), 155.67, 153.39, 147.71, 143.99, 138.69, 135.60, 132.04 (d, J_{CF} = 7.4 Hz), 129.68 (2C), 129.51 (2C), 127.27, 127.03, 113.91 (d, J_{CF} = 23.1 Hz),113.31 and 113.28 (d, J_{CF} = 24.5 Hz), 112.60 (d, J_{CF} = 8.7 Hz), 58.05, 56.63, 55.77 and 55.33, 53.87 and 53.48, 40.09 and 40.06, 27.65, 22.50 and 22.36, 18.47 and 18.31, 18.43 and 18.41, 17.55 and 17.46, 13.51, 11.27 and 11.26. HRMS (ESI) *m/z* calculated for $C_{30}H_{37}FN_3O_2^+$ ($[M + H]^+$): 490.2864; found, 490.2863. $[\alpha]_D^{20}$ –13.00 (*c* 0.4, MeOH).

***N*-(4-((((1*S*,2*S*)-2-(5-Fluoro-2-methoxyphenyl)cyclopropyl)methyl)(propyl)amino)butyl)-4-(pyridin-2-yl)benzamide Hydrochloride ((1*S*,2*S*)-22e).** White solid. HPLC: 98.7% (λ = 254 nm, t_R = 15.4 min); ^{1}H NMR (800 MHz, CD_3OD) δ 8.88 (d, J = 5.7 Hz, 1H), 8.67 (t, J = 8.0 Hz, 1H), 8.42 (d, J = 8.1 Hz, 1H), 8.15 – 8.11 (m, 2H), 8.09 – 8.04 (m, 3H), 6.94 – 6.91

(m, 1H), 6.90 – 6.87 (m, 1H), 6.72 – 6.69 (m, 1H), 3.85 (s, 3H), 3.52 – 3.47 (m, 2H), 3.39 – 3.32 (m, 2H), 3.29 – 3.24 (m, 2H), 3.24 – 3.18 (m, 2H), 2.35 – 2.29 (m, 1H), 1.90 – 1.83 (m, 2H), 1.82 – 1.71 (m, 4H), 1.38 – 1.34 (m, 1H), 1.24 – 1.21 (m, 1H), 1.10 – 1.07 (m, 1H), 1.05 – 1.00 (m, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 168.75, 158.66 (d, J_{CF} = 236.7 Hz), 155.67, 153.19, 148.12, 143.68, 138.82, 135.23, 132.05 (d, J_{CF} = 7.6 Hz), 129.73 (2C), 129.57 (2C), 127.48, 127.15, 113.91 (d, J_{CF} = 23.1 Hz), 113.31 and 113.28 (d, J_{CF} = 23.9 Hz), 112.59 (d, J_{CF} = 7.5 Hz), 58.04, 56.63, 55.77 and 55.32, 53.87 and 53.48, 40.10 and 40.07, 27.64, 22.50 and 22.37, 18.47 and 18.31, 18.43 and 18.41, 17.55 and 17.46, 13.51, 11.27 and 11.26. HRMS (ESI) *m/z* calculated for $C_{30}H_{37}FN_3O_2^+$ ($[M + H]^+$): 490.2864; found, 490.2867. $[\alpha]_D^{20}$ +11.67 (*c* 0.6, MeOH).

Chiral Separation of Racemic 30p. Analytical conditions: Chiralpak AY-3 column (15 cm × 4.6 mm), 10% EtOH and 0.1% diethylamine in *n*-hexane as the fluent phase, flow rate = 1.0 mL/min, λ = 254 nm; preparative conditions: Chiralcel AY-5 column (25 cm × 50 mm, 10 μM), 15% EtOH in *n*-hexane as the eluting system, flow rate = 60 mL/min, λ = 254 nm. (1*R*,2*R*)-**30p** was isolated as the first-eluting peaks (*ee* = 95.1%), and (1*S*,2*S*)-**30p** as the second-eluting peaks (*ee* = 97.3%), both of which appeared as colorless oil after evaporation. The oil was dissolved in dichloromethane and stirred with 2 M HCl in diethyl ether (20 mL/mmol substrate) at room temperature for 15 min, which was then condensed to dryness to give HCl salts respectively.

***N*-(4-((((1*R*,2*R*)-2-(2,3-Dichlorophenyl)cyclopropyl)methyl)(propyl)amino)butyl)-2-naphthamide Hydrochloride ((1*R*,2*R*)-30p).** White solid. HPLC: 98.1% (λ = 254 nm, t_R = 27.1 min); ^{1}H NMR (800 MHz, CD_3OD) δ 8.38 (d, *J* = 11.3 Hz, 1H), 7.98 –

7.91 (m, 3H), 7.90 – 7.86 (m, 1H), 7.62 – 7.56 (m, 2H), 7.37 (d, J = 8.0 Hz, 1H), 7.21 – 7.18 (m, 1H), 7.05 (d, J = 7.8 Hz, 1H), 3.62 – 3.57 (m, 1H), 3.55 – 3.50 (m, 2H), 3.41 – 3.33 (m, 2H), 3.27 – 3.16 (m, 3H), 2.35 – 2.31 (m, 1H), 1.92 – 1.83 (m, 2H), 1.82 – 1.73 (m, 4H), 1.47 – 1.43 (m, 1H), 1.29 – 1.25 (m, 1H), 1.25 – 1.21 (m, 1H), 1.04 – 1.00 (m, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 170.36, 141.89, 136.28, 134.19 and 134.17, 134.04, 133.93, 132.67 and 136.66, 130.01, 129.68, 129.39, 128.92, 128.91, 128.80, 128.78, 127.90, 126.60 and 126.56, 124.79, 57.88 and 57.84, 55.90 and 55.64, 53.98 and 53.67, 39.87 and 39.80, 27.78, 22.41 and 22.37, 22.27 and 22.14, 18.46 and 18.31, 17.35 and 17.32, 14.80 and 14.72, 11.22 and 11.21. HRMS (ESI) *m/z* calculated for $C_{28}H_{33}Cl_2N_2O^+$ ($[M + H]^+$): 483.1964; found, 483.1957. $[\alpha]_D^{20}$ –2.50 (*c* 0.4, MeOH).

***N*-(4-((((1*S*,2*S*)-2-(2,3-Dichlorophenyl)cyclopropyl)methyl)(propyl)amino)butyl)-2-naphthamide Hydrochloride ((1*S*,2*S*)-30p).** White solid. HPLC: 96.0% (λ = 254 nm, t_R = 27.0 min); ^{1}H NMR (800 MHz, CD_3OD) δ 8.38 (d, J = 11.4 Hz, 1H), 7.99 – 7.91 (m, 3H), 7.90 – 7.86 (m, 1H), 7.61 – 7.56 (m, 2H), 7.37 (d, J = 8.0 Hz, 1H), 7.21 – 7.17 (m, 1H), 7.05 (d, J = 7.9 Hz, 1H), 3.62 – 3.56 (m, 1H), 3.55 – 3.48 (m, 2H), 3.39 – 3.31 (m, 2H), 3.26 – 3.16 (m, 3H), 2.37 – 2.31 (m, 1H), 1.92 – 1.84 (m, 2H), 1.82 – 1.74 (m, 4H), 1.49 – 1.44 (m, 1H), 1.28 – 1.25 (m, 1H), 1.24 – 1.22 (m, 1H), 1.05 – 1.00 (m, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 170.33, 141.87, 136.27, 134.18 and 134.16, 134.03, 133.92, 132.67 and 132.66, 130.01, 129.66, 129.38, 128.91, 128.89, 128.79, 128.78, 127.89, 126.60 and 126.55, 124.80, 57.87 and 57.83, 55.88 and 55.62, 53.97 and 53.66, 39.88 and 39.81, 27.76, 22.41 and 22.36, 22.27 and 22.15, 18.44 and 18.30, 17.34 and 17.31, 14.81 and 14.73, 11.22. HRMS (ESI) *m/z* calculated for

$C_{28}H_{33}Cl_2N_2O^+$ ([M + H]$^+$): 483.1964; found, 483.1961. $[\alpha]_D^{20}$ +1.94 (*c* 0.6, MeOH).

Chiral separation of racemic 30q. Analytical conditions: Chiralcel OJ-H column (25 cm × 4.6 mm), 10% isopropanol and 0.1% diethylamine in *n*-hexane as the fluent phase, flow rate = 1.0 mL/min, λ = 214 nm; preparative conditions: Chiralcel OJ-5A column (25 cm × 50 mm, 10 μM), 1% isopropanol and 0.1% diethylamine in *n*-hexane as the eluting system, flow rate = 60 mL/min, λ = 220 nm. (1*R*,2*R*)-**30q** was isolated as the first-eluting peaks (*ee* = 98.6%), and (1*S*,2*S*)-**30q** as the second-eluting peaks (*ee* = 97.4%), both of which appeared as colorless oil after evaporation. The oil was dissolved in dichloromethane and stirred with 2 M HCl in diethyl ether (20 mL/mmol substrate) at room temperature for 15 min, which was then condensed to dryness to give HCl salts respectively.

***N*-(4-((((1*R*,2*R*)-2-(2,3-Dichlorophenyl)cyclopropyl)methyl)(propyl)amino)butyl)-1*H*-indole-2-carboxamide Hydrochloride ((1*R*,2*R*)-30q).** White solid. HPLC: 97.5% (λ = 280 nm, t_R = 22.5 min); ^{1}H NMR (800 MHz, CD_3OD) δ 7.60 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 1H), 7.36 (dt, *J* = 8.0, 1.5 Hz, 1H), 7.23 – 7.21 (m, 1H), 7.17 (td, *J* = 7.9, 3.5 Hz, 1H), 7.09 – 7.05 (m, 2H), 7.02 (dt, *J* = 7.8, 1.8 Hz, 1H), 3.59 – 3.54 (m, 1H), 3.50 – 3.45 (m, 2H), 3.37 – 3.28 (m, 2H), 3.23 – 3.15 (m, 3H), 2.34 – 2.30 (m, 1H), 1.89 – 1.82 (m, 2H), 1.81 – 1.71 (m, 4H), 1.47 – 1.41 (m, 1H), 1.26 – 1.23 (m, 1H), 1.23 – 1.20 (m, 1H), 1.02 – 0.99 (m, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 164.33, 141.86, 138.29, 134.15, 133.91, 132.06, 129.65 and 129.64, 128.96, 128.91, 126.56 and 126.53, 125.12, 122.77, 121.23, 113.09, 104.54, 57.85, 55.84 and 55.62, 53.94 and 53.66, 39.34 and 39.31, 27.81 and 27.79, 22.39 and 22.32, 22.24 and 22.19, 18.43 and

18.28, 17.34 and 17.30, 14.79 and 14.73, 11.21 and 11.20. HRMS (ESI) *m/z* calculated for $C_{26}H_{32}Cl_2N_3O^+$ ([M + H]$^+$): 472.1917; found, 472.1921. $[\alpha]_D^{20}$ –0.25 (*c* 0.4, MeOH).

***N*-(4-((((1*S*,2*S*)-2-(2,3-Dichlorophenyl)cyclopropyl)methyl)(propyl)amino)butyl)-1*H*-indole-2-carboxamide Hydrochloride ((1*S*,2*S*)-30q).** White solid. HPLC: 97.8% (λ = 280 nm, t_R = 22.8 min); ^{1}H NMR (800 MHz, CD_3OD) δ 7.60 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 1H), 7.38 – 7.35 (m, 1H), 7.23 – 7.20 (m, 1H), 7.17 (td, *J* = 7.9, 3.6 Hz, 1H), 7.08 – 7.05 (m, 2H), 7.04 – 7.02 (m, 1H), 3.59 – 3.55 (m, 1H), 3.50 – 3.46 (m, 2H), 3.37 – 3.29 (m, 2H), 3.25 – 3.15 (m, 3H), 2.34 – 2.30 (m, 1H), 1.90 – 1.82 (m, 2H), 1.81 – 1.70 (m, 4H), 1.47 – 1.41 (m, 1H), 1.26 – 1.23 (m, 1H), 1.23 – 1.20 (m, 1H), 1.02 – 0.98 (m, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 164.35, 141.87, 138.30, 134.16, 133.92, 132.06, 129.65, 128.97, 128.92, 126.56 and 126.54, 125.12, 122.76, 121.22, 113.09, 104.52, 57.86, 55.85 and 55.64, 53.95 and 55.66, 39.34 and 39.31, 27.82 and 27.81, 22.39 and 22.33, 22.25 and 22.20, 18.44 and 18.29, 17.35 and 17.31, 14.79 and 14.72, 11.20 and 11.19. HRMS (ESI) *m/z* calculated for $C_{26}H_{32}Cl_2N_3O^+$ ([M + H]$^+$): 472.1917; found, 472.1926. $[\alpha]_D^{20}$ +0.17 (*c* 0.6, MeOH).

Chiral Separation of Racemic 30r. Analytical conditions: Chiralcel OD-H column (15 cm × 4.6 mm), 15% isopropanol and 0.1% diethylamine in *n*-hexane as the fluent phase, flow rate = 1.0 mL/min, λ = 254 nm; preparative conditions: Chiralcel OD-5 column (25 cm × 50 mm, 10 μM), 20% isopropanol and 0.1% diethylamine in *n*-hexane as the eluting system, flow rate = 60 mL/min, λ = 254 nm. (1*R*,2*R*)-**30r** was isolated as the first-eluting peaks *(ee* = 99.4%) and (1*S*,2*S*)-**30r** as the second-eluting peaks (*ee* = 99.4%), both of which appeared as colorless oil after evaporation. Both enantiomers

were dissolved in dichloromethane and stirred with 2 M HCl in diethyl ether (20 mL/mmol substrate) at room temperature for 15 min and then condensed to dryness to give corresponding HCl salts.

***N*-(4-((((1*R*,2*R*)-2-(2,3-Dichlorophenyl)cyclopropyl)methyl)(propyl)amino)butyl)-4-(pyridin-2-yl)benzamide Hydrochloride ((1*R*,2*R*)-30r).** White solid. HPLC: 98.4% (λ = 254 nm, t_R = 18.28 min); ^{1}H NMR (800 MHz, CD_3OD) δ 8.88 (d, J = 5.8 Hz, 1H), 8.68 (t, J = 7.9 Hz, 1H), 8.43 (d, J = 8.1 Hz, 1H), 8.15 – 8.11 (m, 2H), 8.09 – 8.05 (m, 3H), 7.42 – 7.38 (m, 1H), 7.24 (t, J = 7.9 Hz, 1H), 7.11 – 7.09 (m, 1H), 3.61 – 3.56 (m, 1H), 3.53 – 3.47 (m, 2H), 3.40 – 3.32 (m, 2H), 3.29 – 3.18 (m, 3H), 2.39 – 2.33 (m, 1H), 1.93 – 1.84 (m, 2H), 1.83 – 1.72 (m, 4H), 1.53 – 1.46 (m, 1H), 1.30 – 1.25 (m, 2H), 1.06 – 1.02 (m, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 168.72, 153.07, 148.32, 143.53, 141.98, 138.87, 135.04, 134.15, 133.87, 129.75 and 129.74 (2C), 129.66 and 129.64, 129.60 and 129.59 (2C), 128.97 and 128.87, 127.57, 127.21 and 126.94, 126.66 and 126.61, 57.83 and 57.79, 55.85 and 55.56, 53.92 and 53.62, 40.06 and 40.01, 27.62, 22.45 and 22.22, 22.36 and 22.33, 18.44 and 18.31, 17.39 and 17.35, 14.87 and 14.83, 11.27. HRMS (ESI) *m/z* calculated for $C_{29}H_{34}Cl_2N_3O^+$ ($[M + H]^+$): 510.2073; found, 510.2070. $[\alpha]_D^{20}$ –1.58 (*c* 0.4, MeOH).

***N*-(4-((((1*S*,2*S*)-2-(2,3-Dichlorophenyl)cyclopropyl)methyl)(propyl)amino)butyl)-4-(pyridin-2-yl)benzamide Hydrochloride ((1*S*,2*S*)-30r).** White solid. HPLC: 97.3% (λ = 254 nm, t_R = 18.4 min); ^{1}H NMR (800 MHz, CD_3OD) δ 8.88 (d, J = 5.8 Hz, 1H), 8.68 (t, J = 7.9 Hz, 1H), 8.42 (d, J = 8.1 Hz, 1H), 8.15 – 8.11 (m, 2H), 8.09 – 8.04 (m, 3H), 7.39 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 7.9 Hz, 1H), 7.11 – 7.08 (m, 1H), 3.62 – 3.57

(m, 1H), 3.54 – 3.48 (m, 2H), 3.40 – 3.32 (m, 2H), 3.29 – 3.18 (m, 3H), 2.38 – 2.34 (m, 1H), 1.91 – 1.84 (m, 2H), 1.83 – 1.74 (m, 4H), 1.52 – 1.47 (m, 1H), 1.32 – 1.24 (m, 2H), 1.07 – 1.00 (m, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 168.77, 153.20, 148.13, 143.68, 141.98, 138.82, 135.23, 134.16, 133.91, 129.73 and 129.72 (2C), 129.67, 129.58 and 129.57 (2C), 128.98, 127.49, 127.16, 126.66 and 126.61, 57.85 and 57.80, 55.87 and 55.58, 53.94 and 53.64, 40.05 and 40.00, 27.64, 22.46 and 22.22, 22.37 and 22.33, 18.45 and 18.32, 17.40 and 17.34, 14.85 and 14.81, 11.26 and 11.25. HRMS (ESI) *m/z* calculated for $C_{29}H_{34}Cl_2N_3O^+$ ($[M + H]^+$): 510.2073; found, 510.2081. $[\alpha]_D^{20}$ +2.87 (*c* 0.5, MeOH).

Chiral Separation of Racemic 13c. Analytical conditions: Chiralcel OJ-H column (25 cm × 4.6 mm), 1% EtOH in *n*-hexane as the fluent phase, flow rate = 1.0 mL/min, λ = 280 nm. Preparative conditions: Chiralcel OJ-5A column (25 cm × 50 mm, 10 μM), 1% EtOH in *n*-hexane as the eluting system, flow rate = 60 mL/min, λ = 214 nm). (+)-**13c** was isolated as the first-eluting peaks, and (−)-**13c** as the second-eluting peaks, both after evaporation appeared as colorless oil, and *ee* > 95%.

(+)-*tert*-Butyl (((1*R*,2*R*)-2-(5-fluoro-2-methoxyphenyl)cyclopropyl)methyl)-carbamate ((+)-13c). *ee*: 98.5%; ^{1}H NMR (800 MHz, $CDCl_3$) δ 6.84 (td, *J* = 8.4, 3.1 Hz, 1H), 6.75 (dd, *J* = 8.9, 4.5 Hz, 1H), 6.64 (dd, *J* = 9.2, 3.1 Hz, 1H), 3.88 (s, 3H), 3.55 (d, *J* = 13.0 Hz, 1H), 2.72 (dd, *J* = 13.1, 8.7 Hz, 1H), 1.85 – 1.81 (m, 1H), 1.47 (s, 9H), 1.05 – 0.98 (m, 2H), 0.88 – 0.83 (m, 1H). $[\alpha]_D^{20}$ +10.93 (*c* 0.5, $CHCl_3$).

(–)-*tert*-Butyl(((1S,2S)-2-(5-fluoro-2-methoxyphenyl)cyclopropyl)methyl)-

carbamate ((–)-13c). *ee*: 96.4%; ^{1}H NMR (800 MHz, $CDCl_3$) δ 6.84 (td, J = 8.5, 3.1 Hz, 1H), 6.75 (dd, J = 8.9, 4.5 Hz, 1H), 6.64 (dd, J = 9.2, 3.1 Hz, 1H), 3.89 (s, 3H), 3.55 (d, J = 12.8 Hz, 1H), 2.72 (dd, J = 13.1, 8.6 Hz, 1H), 1.85 – 1.81 (m, 1H), 1.47 (s, 9H), 1.05 – 0.98 (m, 2H), 0.88 – 0.83 (m, 1H). $[\alpha]_D^{20}$ –11.13 (*c* 0.5, $CHCl_3$).

(–)-((1*R*,2*R*)-2-(5-Fluoro-2-methoxyphenyl)cyclopropyl)methanamine Hydrochloride ((–)-14c). Compound **(+)-13c** (378 mg, 1.28 mmol) was dissolved in 4 M HCl (*g*) in dioxane (20 mL) and stirred at room temperature overnight. The solvent was evaporated and the residue was suspended in a mixture of ethyl acetate and petroleum ether (v/v = 1/2, 10 mL) for 10 min. The precipitate was collected by filtration, washed with ethyl acetate (3 mL), and dried under vacuum to give the title compound as a yellow solid (290 mg, 98%). ^{1}H NMR (800 MHz, CD_3OD) δ 6.93 – 6.86 (m, 2H), 6.72 (dd, J = 9.4, 2.9 Hz, 1H), 3.86 (s, 3H), 3.07 (dd, J = 13.1, 7.1 Hz, 1H), 2.93 (dd, J = 13.1, 8.0 Hz, 1H), 2.14 – 2.10 (m, 1H), 1.28 – 1.23 (m, 1H), 1.14 – 1.10 (m, 1H), 1.04 – 0.99 (m, 1H). HRMS (ESI) *m/z* calculated for $C_{11}H_{15}FNO^+$ ([M + H]$^+$): 196.1132, found: 196.1128. $[\alpha]_D^{20}$ –14.80 (*c* 0.5, MeOH).

(+)-((1*S*,2*S*)-2-(5-Fluoro-2-methoxyphenyl)cyclopropyl)methanamine Hydrochloride ((+)-14c). The title compound was prepared from **(–)-13c** as described for **(–)-14c** as a yellow solid. ^{1}H NMR (800 MHz, CD_3OD) δ 6.92 – 6.87 (m, 2H), 6.72 (dd, J = 9.4, 2.9 Hz, 1H), 3.86 (s, 3H), 3.07 (dd, J = 13.0, 7.1 Hz, 1H), 2.93 (dd, J = 13.0, 8.0 Hz, 1H), 2.14 – 2.08 (m, 1H), 1.28 – 1.23 (m, 1H), 1.14 – 1.08 (m, 1H), 1.05 – 0.99 (m, 1H). HRMS (ESI) *m/z* calculated for $C_{11}H_{15}FNO^+$ ([M + H]$^+$): 196.1132, found: 196.1129. $[\alpha]_D^{20}$ +14.20 (*c* 0.5, MeOH).

(–)-*N*-(((1*R*,2*R*)-2-(5-Fluoro-2-methoxyphenyl)cyclopropyl)methyl)propan-1-amine ((–)-21c). The title compound was prepared from **(–)-14c** as described for **21a** as a colorless oil. HRMS (ESI) *m/z* calculated for $C_{14}H_{21}FNO^+$ ([M + H]$^+$): 238.1602, found: 238.1603. $[\alpha]_D^{20}$ –14.60 (*c* 0.5, MeOH).

(+)-*N*-(((1*S*,2*S*)-2-(5-Fluoro-2-methoxyphenyl)cyclopropyl)methyl)propan-1-amine ((+)-21c). The title compound was prepared from **(+)-14c** as described for **21a** as a colorless oil. HRMS (ESI) *m/z* calculated for $C_{14}H_{21}FNO^+$ ([M + H]$^+$): 238.1602, found: 238.1605. $[\alpha]_D^{20}$ +16.13 (*c* 0.5, MeOH).

(–)-*N*-(4-((((1*R*,2*R*)-2-(5-Fluoro-2-methoxyphenyl)cyclopropyl)methyl)(propyl)amino)butyl)-4-(pyridin-2-yl)benzamide Hydrochloride ((–)-22e). A mixture of **(–)-21c** (41 mg, 0.17 mmol) and **20c** (46 mg, 0.17 mmol) in THF (15 mL) was stirred at room temperature for 15 min. $NaHB(AcO)_3$ (73 mg, 0.35 mmol) was added, and the reaction mixture was stirred at room temperature overnight. Water was added and the mixture was extracted with ethyl acetate. The combined extracts were washed with brine, concentrated and the residue was purified by flash chromatography (0–5% methanol in dichloromethane) to give a colorless oil (28 mg, 33%), which was converted into the HCl salt using a similar method as depicted for **17a**. ^{1}H NMR (800 MHz, CD_3OD) δ 8.86 (d, J = 5.8 Hz, 1H), 8.62 (t, J = 7.9 Hz, 1H), 8.38 (d, J = 8.1 Hz, 1H), 8.14 – 8.10 (m, 2H), 8.09 – 8.06 (m, 2H), 8.03 – 8.00 (m, 1H), 6.93 – 6.91 (m, 1H), 6.90 – 6.86 (m, 1H), 6.72 – 6.68 (m, 1H), 3.85 (s, 3H), 3.52 – 3.47 (m, 2H), 3.41 – 3.32 (m, 2H), 3.30 – 3.16 (m, 4H), 2.35 – 2.29 (m, 1H), 1.90 – 1.83 (m, 2H), 1.83 – 1.72 (m, 4H), 1.39 – 1.33 (m, 1H), 1.25 –

1.21 (m, 1H), 1.10 – 1.07 (m, 1H), 1.05 – 1.00 (m, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 168.80, 158.65 (d, J_{CF} = 236.9 Hz), 155.67, 153.45, 147.55, 144.11, 138.63, 135.72, 132.05 (d, J_{CF} = 7.5 Hz), 129.67 and 129.66 (2C), 129.48 (2C), 127.18, 126.97, 113.90 (d, J_{CF} = 22.8 Hz), 113.31 and 113.28 (d, J_{CF} = 24.3 Hz), 112.58 (d, J_{CF} = 8.6 Hz), 58.04, 56.64, 55.76 and 55.32, 53.87 and 53.47, 40.09 and 40.05, 27.65, 22.49 and 22.36, 18.46 and 18.31, 18.43 and 18.41, 17.55 and 17.46, 13.52, 11.27 and 11.26. HRMS (ESI) *m/z* calculated for $C_{30}H_{37}FN_3O_2^+$ ($[M + H]^+$): 490.2864, found: 490.2863. $[\alpha]_D^{20}$ –13.00 (*c* 0.5, MeOH).

(+)-*N*-(4-((((1*S*,2*S*)-2-(5-Fluoro-2-methoxyphenyl)cyclopropyl)methyl)(propyl)amino)butyl)-4-(pyridin-2-yl)benzamide Hydrochloride ((+)-22e). The title compound was prepared from **(+)-21c** using the same method as described for **(–)-22e**. ^{1}H NMR (800 MHz, CD_3OD) δ 8.88 (d, *J* = 5.8 Hz, 1H), 8.66 (t, *J* = 7.9 Hz, 1H), 8.41 (d, *J* = 8.1 Hz, 1H), 8.14 – 8.11 (m, 2H), 8.09 – 8.03 (m, 3H), 6.94 – 6.91 (m, 1H), 6.90 – 6.86 (m, 1H), 6.72 – 6.69 (m, 1H), 3.85 (s, 3H), 3.53 – 3.47 (m, 2H), 3.41 – 3.32 (m, 2H), 3.30 – 3.18 (m, 4H), 2.34 – 2.30 (m, 1H), 1.89 – 1.83 (m, 2H), 1.83 – 1.72 (m, 4H), 1.39 – 1.32 (m, 1H), 1.25 – 1.21 (m, 1H), 1.10 – 1.06 (m, 1H), 1.05 – 0.99 (m, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 168.75, 158.65 (d, J_{CF} = 237.0 Hz), 155.67, 153.18, 148.14, 143.66, 138.83, 135.21, 132.05 (d, J_{CF} = 7.3 Hz), 129.73 and 129.72 (2C), 129.58 (2C), 127.50, 127.16, 113.91 (d, J_{CF} = 22.7 Hz), 113.31 and 113.28 (d, J_{CF} = 24.2 Hz), 112.60 (d, J_{CF} = 8.4 Hz), 58.05, 56.64, 55.77 and 55.33, 53.87 and 53.48, 40.10 and 40.07, 27.65, 22.50 and 22.37, 18.47 and 18.31, 18.43 and 18.41, 17.55 and 17.46, 13.52, 11.27 and 11.26.

HRMS (ESI) *m/z* calculated for $C_{30}H_{37}FN_3O_2^+$ ($[M + H]^+$): 490.2864, found: 490.2859. $[\alpha]_D^{20}$ +11.80 (*c* 0.5, MeOH).

Radioligand Binding Assays. Radioligand binding affinities were determined by the National Institute of Mental Health Psychoactive Drug Screening Program (NIMH PDSP), directed by Bryan L Roth, M.D., Ph.D., the University of North Carolina at Chapel Hill, North Carolina, and Program Officer Jamie Driscoll at NIMH, Bethesda, MD. Detail binding protocols and assay conditions are also available at https://pdspdb.unc.edu/pdspWeb/?site=assays.

D_3 GloSensor cAMP Assays. Human D_3 and GloSensor cAMP plasmids (Promega) were co-transfected (4 μg receptor DNA and 4 μg GloSensor cAMP reporter DNA for a 10-cm dish, increased proportional if using a larger size of dishes) in HEK293 T cells overnight in full growth medium (DMEM + 10% FBS) and plated in poly-L-Lys coated 384-well white assay plates using DMEM containing 1% dialyzed FBS at a density of 15,000 – 20,000 cells per 40 μL/well. After a minimum of 6 h recovery (up to 24 h), cells were removed of the medium, stimulated with 25 μL/well drug solutions prepared in assay buffer (1× HBSS, 20 mM HEPES, pH 7.4, 0.1% BSA) for 15 min, followed by addition of 10 μL/well of the mixture of 2 mM luciferin and 100 nM isoproterenol (final), all at room temperature. For antagonist assays, 10 nM dopamine (final) was added at 10 min after test compounds. Luminescence was counted after 20 min incubation. Agonist EC_{50} or antagonist K_i values were shown as the mean from at least three individual experiments.

GPCR Tango (β-Arrestin2 Recruitment) Assays. GPCR Tango assays are conducted as described previously.[25] In brief, HTLA cells, stably expressing a β-arrestin2-TEV fusion protein and a tTA-dependent luciferase reporter, were transiently transfected (8 μg receptor DNA per 10-cm dish) in full growth medium (DMEM with 10% FBS) and plated in poly-L-Lys coated 384-well white assay plates in DMEM with 1% dialyzed FBS at a density of 10,000-15,000 cells/well in a total of 40 μL. After a minimum of 3 h recovery, drug dilutions were made in DMEM with 1% dFBS at 5× of the final concentrations for agonist assays and added to cells at 10 μL/well for incubation (around 16 h). Medium and drugs were removed and Bright-Glo reagents (Promega) were added. Luminescence was counted on a luminescence counter after 20 min incubation at room temperature. Results (relative luminescence counts) were analyzed in Prism 7.0. EC_{50} or % activation values were shown as the mean from at least three individual experiments.

5-HT_{2C} Calcium Mobilization Assays. HEK293 cells stably expressing 5-HT_{2C} receptors were plated in poly-L-Lys coated 384-well black assay plates in DMEM containing 1% dialyzed FBS overnight at a density of 15,000 cells/well/40 μL and incubated overnight. Cells were removed of medium and loaded with Calcium dye (Fluo-4 Direct, Invitrogen), 20 μL/well, prepared in assay buffer (1× HBSS, 20 mM HEPES, pH 7.4, 2.5 mM probenecid), for 50 min in the cell culture incubator (37°C), followed by 10 min incubation at the room temperature in the dark (to equilibrate to room temperature). Drug solutions (at 3× of the final concentrations) were prepared in assay buffer and aliquoted in a matching 384-well plate. Both cell plate and drug plate

were then loaded into the FLIPR^{TETRA} (Molecular Devices). A FLIPR protocol was designed to transfer 10 μL/well drug solutions into cell plate and fluorescence was read for a total of 2 min at a rate of 1 read per second, including 10 seconds before drug addition. The initial 10 readings served as the background for each well and the average background was subtracted from the maximum reading within 60 seconds after drug addition. Fluorescence intensity (fold of basal) upon drug stimulation was exported and analyzed in Prism 7.0. For antagonist assays, additional 10 μL of 5-HT (final of 1 nM) was added 15 min after the first drug addition, and fluorescence intensity (fold of basal) was exported and analyzed as above. EC_{50} or IC_{50} values were shown as the mean from at least three individual experiments.

Computational Methods. Molecular dockings were performed using modules (Maestro, Ligprep, Protein Preparation Wizard and Glide) in the Schrödinger software package (Release 2017-4). The crystal structure of antagonist-bound D3R (PDB code: 3PBL),[21] agonist- and antagonist-bound $5HT_{2C}$ (PDB codes: 6BQG and 6BQH)[20] were retrieved from the Protein Data Bank. The missing side chains and hydrogen bonds were fixed and optimized using the Protein Preparation Wizard.[28] All ligands were prepared using LigPrep with default settings. The docking grid was prepared with Glide defining the binding site by crystal ligands and setting the ligand diameter midpoint box to 10Å on all three axes, while the hydroxyl groups in Ser, Thr and Tyr and the thiol group in Cys around the pocket were allowed to rotate through "Rotatable Groups" option. Finally, all these ligands were docked into the calculated receptor grid using the XP scoring function and enhanced sampling. The docked results were visualized and

analyzed in Maestro and the best scoring poses were selected. All residues within 5 Å of the docked ligands were subjected to relax with sampling method "Minimize" in Prime MM-GBSA module,[29] which were then rescored by Glide XP. Finally, by visual inspection of the optimized docking pose and considering the XP docking scores, the predicted binding poses of these ligands were obtained.

PK and Brain Penetration Studies. Studies were performed by Suzhou Kangrun Pharmaceutical Testing Service, Inc. (Suzhou, China). Male ICR mice (age 6-8 weeks, ~25 g body weight) were purchased from JOINN Laboratories, Inc. (Suzhou). For PK studies, compounds were dissolved in saline, and administered at doses of 5 mg/kg (iv) and 10 mg/kg (po) respectively, with nine animals in each group. Blood samples (0.1 mL) were collected from mouse orbit at 0, 0.083, 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h, which were then centrifuged at 5000 rpm at 4 °C for 10 min to collect plasma samples. Brain tissues were collected at 0.5 and 2.0 h, which were washed with saline, weighted and homogenated in 50% cold methanol (brain weight(g)/50% methanol (mL) = 1/3) to obtain drug solutions. All samples were stored at –80 °C before analysis. Drug concentrations in the samples were determined using liquid chromatography–mass spectrometry (LC-MS/MS). All studies were performed with approved animal use protocols from the institutional animal care and use committees.

ASSOCIATED CONTENT

Supporting Information

Table S1-S4, Figure S1 and HPLC traces of all final compounds (PDF).

SMILES strings of compounds in Table 1-3 (CSV).

This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes.

The authors declare no competing financial interest.

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ABBREVIATIONS USED

cAMP, cyclic adenosine monophosphate; CNS, central nervous system; EBP, extended binding pocket; FDA, Food and Drug Administration; G protein-coupled receptors (GPCRs); HPLC, high performance liquid chromatography; OBP, orthosteric binding pocket; PCPMA, 2-phenylcyclopropylmethylamine; PDB, Protein Data Bank; PK, pharmacokinetic; SAR, structure-activity relationship.

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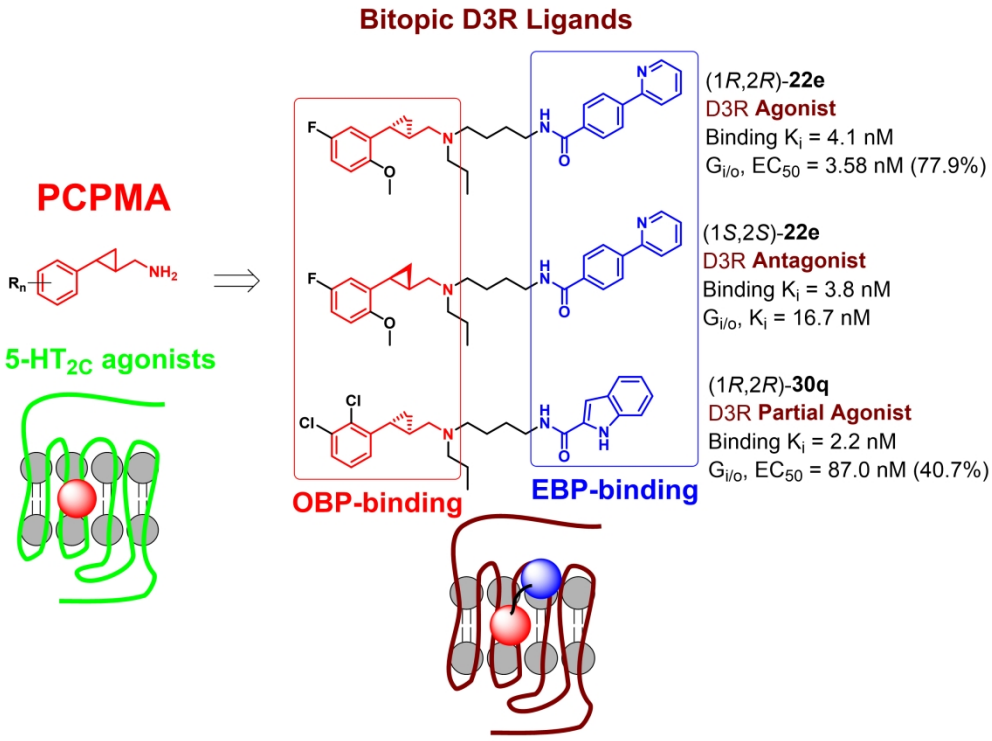

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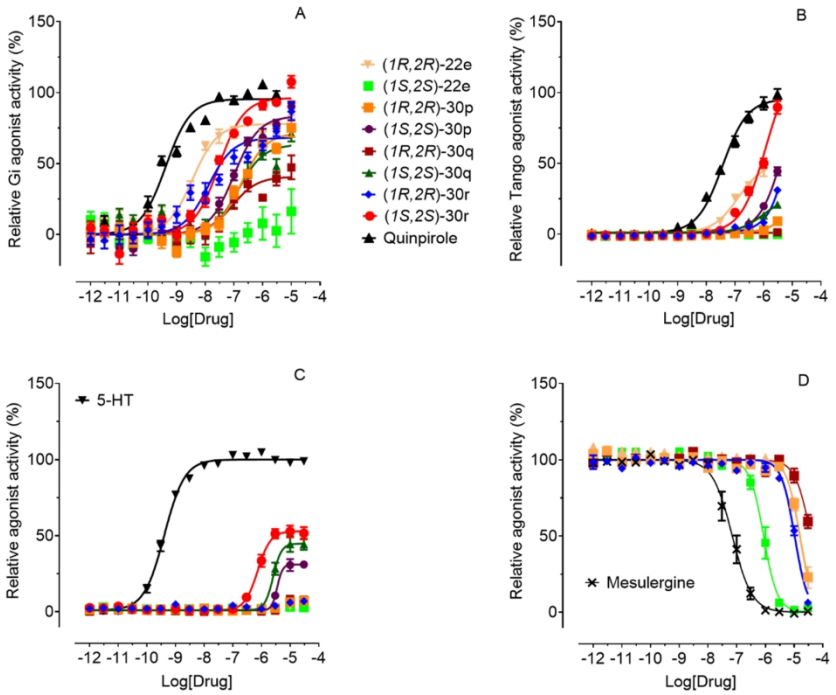

Figure 3. Functional characterization of lead compounds at D3 dopamine receptors (A, B) and 5-HT2C receptors (C, D).

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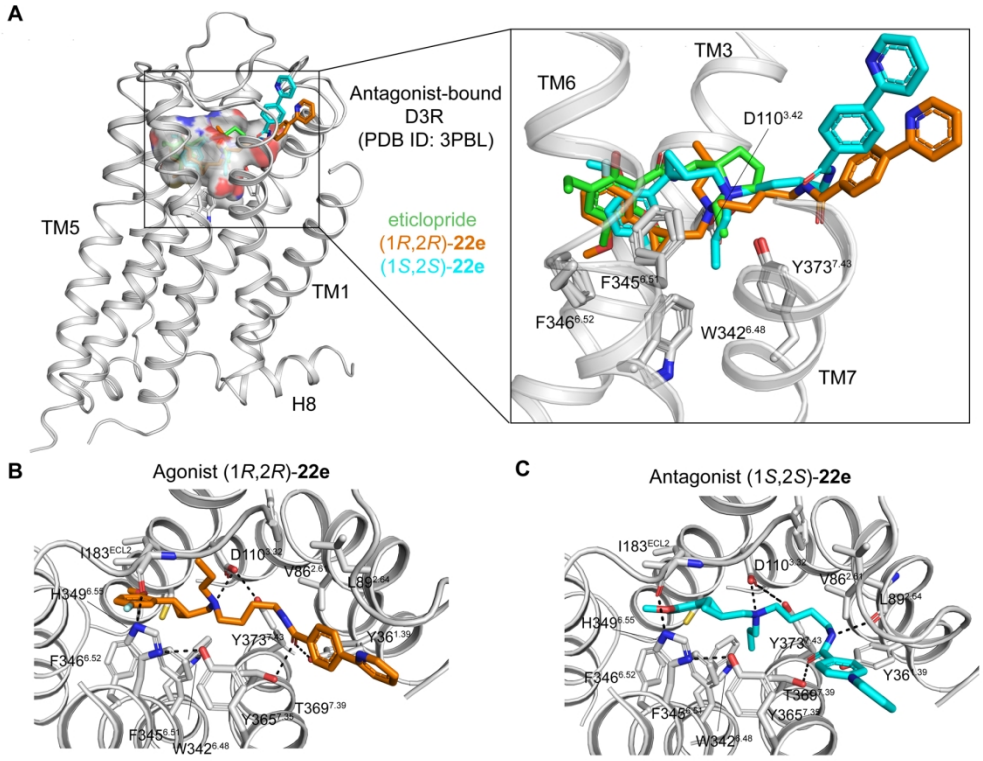

Figure 4. Comparison of binding poses of D3R antagonist eticlopride, (1R,2R)-22e and (1S,2S)-22e.

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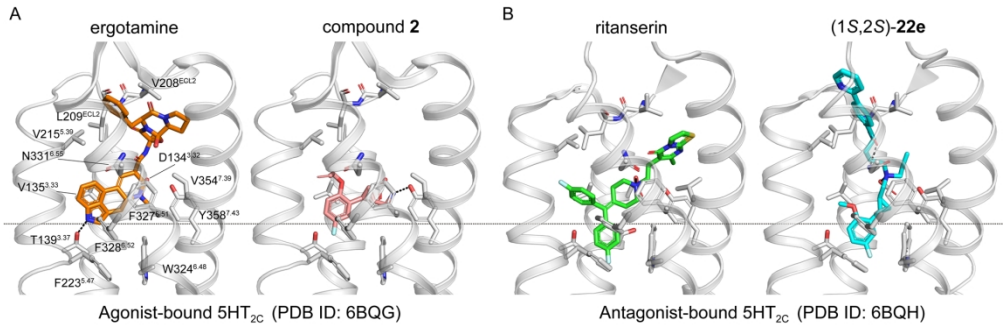

Figure 5. Comparison of binding poses of 5-HT2C representative agonists (A) and antagonists (B).

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