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# Selective 5-Hydroxytrytamine 2C Receptor Agonists Derived from the Lead Compound Tranylcypromine – Identification of Drugs with Antidepressant-Like Action

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## Abstract

We report here the design, synthesis, and pharmacological properties of a series of compounds related to tranylcypromine (**9**), which itself was discovered as a lead compound in a high-throughput screening campaign. Starting from **9**, which shows modest activity as a 5-$HT_{2C}$ agonist, a series of 1-aminomethyl-2-phenylcyclopropanes was investigated as 5-$HT_{2C}$ agonists through iterative structural modifications. Key pharmacophore feature of this new class of ligands is a 2-aminomethyl-*trans*-cyclopropyl side chain attached to a substituted benzene ring. Among the tested compounds, several were potent and efficacious 5-$HT_{2C}$ receptor agonists with selectivity over both 5-$HT_{2A}$ and 5-$HT_{2B}$ receptors in functional assays. The most promising compound is **37** with 120- and 14-fold selectivity over 5-$HT_{2A}$ and 5-$HT_{2B}$, respectively ($EC_{50}$ = 585, 65, and 4.8 nM at the 2A, 2B, and 2C subtypes, respectively). In animal studies, compound **37** (10–60 mg/kg) decreased immobility time in the mouse forced swim test.

## Introduction

Serotonin (5-HT[a]) (**1**) mediates or regulates a wide variety of behaviors including cognition, emotion, attention, and appetite among others.[1,2] The diverse effects of this neurotransmitter are related to the extensive projections of serotonergic neurons throughout the brain and to the presence of at least 14 different receptor subtypes in humans.[3–5] The 5-$HT_2$ subtype family includes the 5-$HT_{2A}$, 5-$HT_{2B}$, and 5-$HT_{2C}$ receptors. The 5-$HT_{2A}$ receptor mediates the hallucinogenic activity of drugs such as lysergic acid diethylamide (LSD) and is a major target for treating schizophrenia as well as insomnia.[6] The 5-$HT_{2B}$ receptor mediates the potentially lethal valvulopathic side effects of several compounds that were used as prescription drugs.

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[a]Abbreviations: 5-HT, 5-hydroxytrytamine (serotonin); LSD, lysergic acid diethylamide; CNS, central nervous system; MAO, monoamine oxidase; SAR, structure activity relationship; SERT, serotonin 5-HT transporter; NET, norepinephrine transporter; DAT, dopamine transporter.

[7–9] Two decades after its initial identification, the 5-$HT_{2C}$ receptor has only recently emerged as a promising target in the treatment of depression, anxiety, eating disorders, obsessive-compulsive disorder, chronic pain conditions, obesity, epilepsy, and erectile dysfunction.[10–19] The 5-$HT_{2C}$ receptor is abundantly expressed throughout the central nervous system (CNS) and displays high-affinity interactions with a wide variety of psychiatric medications.[20–23] Due to the serious side effects caused by the activation of the pharmacologically and structurally closely related subtypes,24 it is essential that 5-$HT_{2C}$ agonists developed for clinical use have a high specificity and subtype selectivity. To date, a number of designed synthetic compounds have been identified that show 5-$HT_{2C}$ receptor agonistic activity (Figure 1).[18,25–31] Several compounds have shown efficacy in preclinical animal models and are currently being tested in clinical trials.[32]

Despite recent progress in obtaining crystal structures of G protein-coupled receptors,[33–35] information about the structure and function of 5-HT receptors is still restricted to homology modeling using rhodopsin or beta-adrenergic receptors as a starting template. However, it is well known that there are inherent limitations in the use of such homology models for drug design purposes[36] and they still lack sufficient predictive power for drug discovery.[37] Therefore, we based our search for selective 5-$HT_{2C}$ receptor agonists on high-throughput chemical library screening to identify a suitable lead structure followed by stepwise activity-guided chemical modification. Using this approach, we have identified the reversible monoamine oxidase (MAO) inhibitor tranylcypromine **9**[38,39] as a lead compound from screening the Prestwick drug library of 800 compounds (Figure 2).[40]

In initial experiments, we then examined the effects of side chain homologation, stereochemistry, and amine substitution in 5-$HT_{2A}$, 5-$HT_{2B}$, and 5-$HT_{2C}$ functional calcium flux assays (Figure 2). The *trans*-2-phenylcyclopropylmethylamine hydrochloride **14a** turned out to be a potent ($EC_{50}$ = 13 nM), moderately selective and fully efficacious ($E_{max}$ = 96%) agonist at the 5-$HT_{2C}$ receptor. Thus, this core structure was selected for substitution screening in all of the subsequent SAR studies. Several ring-unsubstituted *N*-alkyl derivatives of *trans*-aminomethyl-2-phenylcyclopropane (**14a**) have previously been found to have sympathomimetic activity in animal tests, but these effects were probably mediated by a 5-$HT_{2C}$ independent mechanism.[41,42]

## Chemistry

Both the *trans*- and cis-(2-phenylcyclopropyl)methylamine hydrochlorides were prepared as structurally more flexible analogs of the lead compound **9** starting from styrene **10** (Scheme 1). Cyclopropanation was carried out using ethyl diazoacetate in the presence of $Cu(acac)_2$ as a catalyst.[43] The ester product was obtained as a 2:1 racemic mixture of the *trans* and *cis* isomers. After separation of the configurational isomers on silica gel, the resulting ester isomers *trans*-**11a** and *cis*-**11b** were converted to the corresponding amine hydrochlorides **14a** and **14b**, respectively, employing a standard sequence of reactions involving amide formation, followed by borane reduction.

*N*-Monomethylation of the amino group in compound **9** (Figure 2, n = 0) and of the elongated cyclopropylmethylamine derivative (Figure 2, n = 1) was carried out by reduction of the corresponding *N*-formyl derivatives. Formylation of the amine with acetic formic anhydride followed by *in situ* borane-dimethyl sulfide reduction afforded the corresponding *N*-methylamines.[44] The products **15** and **16** obtained in this way were free of any contamination by the dialkylation product. The *N,N*-dimethylamine derivative **17** of compound **9** was prepared by reductive *N*-alkylation using an excess of 37% aqueous formaldehyde and $NaBH_3CN$ according to a literature procedure.[45,46] The mono-isopropyl and mono-benzylamine analogs **18–20** were prepared by similar reductive *N*-alkylation protocols[47,48] (Scheme 2).

Next, we explored the activity of derivatives bearing various substituents on the aromatic ring, or having the aromatic ring replaced by the larger naphthyl ring or by a biphenyl structure (Figure 3). The substituted phenyl and naphthyl derivatives **26–61** were synthesized from the corresponding styrenes **22**, followed by application of the same chemistry used in the preparation of **14a** and **14b**. Some of styrenes were prepared from the corresponding aldehydes **21** by Wittig chemistry (Scheme 3).

The *N*-Boc protected aminomethylcyclopropane derivatives **62–64** were very useful intermediates for the preparation of other analogs. The bromophenyl derivatives **29, 36**, or **43** were thus used as convenient starting materials to generate a limited number of biphenyl and heteroarylphenyl derivatives **66–74** by means of the Suzuki coupling reaction.[49] Some of amide and amine substituted phenyl derivatives **78** and **80–84** were prepared through Pd catalyzed conversion of the bromo group to an amine. These amines were reacted in turn with acid chlorides or aryl- and alkylisocyanates to afford the corresponding amides and urethanes. An alkynyl group was also successfully introduced as a side chain appendage into the arylcyclopropane by the Sonogashira coupling reaction (**86–90**)[50] (Scheme 4).

In order to prepare the pure enantiomers of **14a** (Scheme 5), we first converted the intermediate carboxylic acid formed in the cyclopropanation step into its diastereomeric amides. This was brought about by coupling the racemic carboxylic acid **12a** with (*R*)-phenylglycinol.[46] The resulting diastereomeric pair was then separated by silica gel column chromatography. The choice of (*R*)-phenylglycinol as the alcohol component was based on its successful use in the resolution of other racemic carboxylic acids and the ease of cleavage of the resulting diastereomers under acidic conditions that involves an *N*,*O*-acyl transfer. The carboxylic acids (+)-**12a** and (−)-**12a**, whose optical rotations were compared with the known compounds in the literature,[51] were then converted individually to (+)-and (−)-*trans*-(2-phenylcyclopropyl) methylamine hydrochloride ((+)-**14a** and (−)-**14a**) using the same method as described above.[52]

## Biological Results and Discussion

### *In vitro* SAR studies

The functional activity of the compounds was determined by measuring $G_q$ mediated transient intracellular calcium mobilization in HEK-293 cells stably expressing the human 5-$HT_{2A}$, human 5-$HT_{2B}$, and human 5-$HT_{2C\ (INI)}$ receptors.[53] The results are summarized in Table 1, 2, and 3. Throughout the course of the project, different batches of cell lines or passages were used. In contrast to binding affinities, the potencies in functional assays can vary strongly depending on cell type, receptor expression level, and passage number. Direct comparisons of the potencies and efficacies are only valid within the bounds of each particular table section. In over-expressing cell lines such as those utilized in the current screening it is common to observe $EC_{50}$ potency concentrations much lower than the $K_i$ binding constant, particularly when $^3$H-antagonist radioligands are used for competition binding studies.[54]

The *trans* isomer **14a** with its side chain elongated by one methylene group was much more potent ($EC_{50}$ = 13 nM) at the 5-$HT_{2C}$ receptor as compared to its parent compound **9** and the *cis* isomer **14b** was much less active than the *trans* isomer **14a** (Table 1). The *trans*-aminomethyl-2-phenylcyclopropane **14a** and several of its *N*-mono- and *N*-dialkyl analogs have previously been described as centrally active sympathomimetic compounds that cause hyperlocomotion, reverse reserpine-induced depressant effects in a model of antidepressant activity, and cause anorexia similar to compound **9**[41] while the fully unsubstituted compound **14a** was devoid of MAO inhibitory activity in a tryptamine potentiation model.[42] This behavioral and biochemical profile and the different structure-activity relationships suggest a

non-5-$HT_{2C}$-mediated mechanism for these early ring-unsubstituted compounds, perhaps through inhibition of monoamine reuptake.

Assay of the two enantiomers revealed that the (*S*,*S*)-stereoisomer (+)-**14a** was significantly more potent than its (*R*,*R*)-isomer (−)-**14a**. We have observed the same stereochemical preference for the corresponding 2-bromo-substituted enantiomeric pair (+)-**29** and (−)-**29** (Table 2).

Alkylation of the amine nitrogen in analogs **15–20** led to sharply decreased 5-$HT_{2C}$ receptor potency in comparison to the parent compounds **9** or **14a**. Compound **9** and its potent analogs **14a** (racemic) and (+)-**14a** were full agonists at the 5-$HT_{2C}$ receptor and displayed a high selectivity over the 5-$HT_{2A}$ receptor and a three to seven-fold selectivity over the 5-$HT_{2B}$ receptor.

As a preliminary summary, the initial SAR studies established the following essential features responsible for high 5-$HT_{2C}$ receptor potency: a cyclopropyl ring attached to a phenyl group carrying a primary aminomethyl group in *trans* orientation. Based upon these preliminary observations, our further work focused on variations in the phenyl ring of this core structure.

In the following four rounds of structural exploration and functional screening, we systematically tested the effects of mono- and disubstitutions at the phenyl ring (Table 2). Selected compounds from previous optimization rounds, the known 5-$HT_{2C}$ agonist WAY 629 (1,2,3,4,8,9,10,11-octahydro-[1,4]diazepino[6,7,1-jk]carbazole) (**6**)[29] and lorcaserin ((1*R*)-8-chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine) (**7**)[30] as well as **1** were included as reference compounds for comparison purposes.

All tested compounds were highly efficacious 5-$HT_{2C}$ agonists. Mono- and disubstituted analogs carrying chloro and bromo substitutions in the 2-position were consistently more potent than their respective fluoro, trifluoromethyl, methyl, methoxy, or hydroxy analogs.

In the 3-position, potency was less strongly influenced by the tested substituents and tended to decrease with molecular size from fluoro, methyl, and hydroxy over chloro to bromo and trifluoromethyl.

In the 4-position, the optimal substitution was a fluoro group. Any replacement by other halogens, methyl, trifluoromethyl, methoxy, or hydroxy groups resulted in a sharp decrease in 5-$HT_{2C}$ potency and selectivity over 5-$HT_{2B}$ activity.

Qualitatively similar trends of these substituent effects on potency and selectivity were observed between mono- and disubstituted compounds. However, the tested disubstitutions did not result in additive effects on potency or selectivity.

At the 5-$HT_{2B}$ receptor, the 3-hydroxy analog **40** has about a ten-fold higher potency than the corresponding 3-methyl analog **37** while both compounds were essentially equipotent at the 5-$HT_{2C}$ receptor. This made compound **37** one of the most selective compounds and might indicate a hydrogen bond interaction between compound **40** and the 5-$HT_{2B}$ receptor that is absent in the 5-$HT_{2C}$-**40**-complex.

5-$HT_{2A}$ potencies of most tested compounds were above or around 0.5 μM, resulting in a generally good 5-$HT_{2A}$ over 5-$HT_{2C}$ selectivity. Additionally, most compounds were partial agonists at the 5-$HT_{2A}$ receptor, but full agonists at the 5-$HT_{2C}$ receptor. 2-Chloro and 2-bromo substitutions resulted in increased 5-$HT_{2A}$ potency, a trend also seen at the other two receptors.

We also prepared and tested the biphenyl and heteroaryl-phenyl derivatives **66–74**, the 2- and 3-acetamido, 2- and 3-benzamido, 2-benzylamino, and 2-(4-chlorophenyl)urea analogs **78, 80–84**, and a series of extended alkynyl derivatives **86–90** (Table S1). Most of these compounds were inactive or had potencies above 1 μM at all tested receptors. None of these compounds had a 5-$HT_{2C}$ potency below 100 nM.

The basic ring-monosubstituted derivatives presented in this publication do not reach the same level of selectivity as the 5-$HT_{2C}$ agonists that are currently in clinical trials; in our hands the potent compound (+)-**29** displayed about five-fold less 5-$HT_{2C}$ over 5-$HT_{2B}$ selectivity as compared to 7.

A molecular overlay of several of the new selective 5-$HT_{2C}$ agonists prepared by other research groups with one of our more selective compounds **37** reveals the molecular features common to all these compounds, which include a similarly aligned positively charged nitrogen atom (blue) positioned above the plane of an aromatic ring which is substituted with hydrophobic group(s), such as chloro, methyl, ethyl, or trifluoromethyl (Figure 4).

A selection of compounds was then subjected to binding experiments together with **7** as a reference compound (Table 3). **37** (3-Me), **41** (4-F), and **53** (2-Cl, 4-F) had comparable 5-$HT_{2C}$ binding affinities. Compound **41** was as 5-$HT_{2C}$-selective as **7** while **29**, (+)-**29**, and **37** where less selective. Since earlier data suggested sympathomimetic effects for the unsubstituted parent compound **14a**,41,[42] we also tested these compounds on all three monoamine reuptake transporters. None of the compounds had sub-micromolar binding affinities at SERT (5-HT transporter), NET (norepinephrine transporter), and DAT (dopamine transporter).

### *In vivo* studies: evaluation of a 5-$HT_{2C}$ agonist for antidepressant potential

5-$HT_{2C}$ agonists have been reported to have antidepressant-like properties in multiple animal models, indicating that the 5$HT_{2C}$ receptor may be a desired target for CNS therapeutic effects. Compound **37** is one of the most potent and selective ligands for the 5$HT_{2C}$ receptor in the current series (120-fold selectivity over 2A and 14-fold selectivity over 2B, $EC_{50}$ = 585, 65, and 4.8 nM at the 2A, 2B, and 2C subtypes, respectively, see Table 2). Based on this *in-vitro* profile, compound **37** was chosen for an initial *in vivo* profiling in the mouse forced swim test, which is a commonly used assay to validate antidepressant-like properties of compounds.

In the mouse forced swim test, compound **37** (10–60 mg/kg) produced a dose-dependent decrease in immobility time compared to vehicle ($F(4,45) = 8.865$, $p < 0.001$). Post-hoc analysis indicated that compound **37** produced a significant decrease in immobility at all 3 doses tested (28%, 38%, and 38% decrease in the 10, 30, and 60 mg/kg groups, respectively, ($p < 0.05$). In comparison, the reference selective serotonin reuptake inhibitor sertraline (**92**) (10 mg/kg) was used as a positive control in the same study. Both **92** ($p < 0.001$) and compound **37** significantly reduced the immobility time, indicative of an antidepressant-like effect (Figure 5). The results also demonstrate that compound **37** possesses drug-like properties *in-vivo* and that it is centrally active. The antidepressant-like effects together with the absence of monoamine reuptake transporter binding are in agreement with previous studies which demonstrated that 5$HT_{2C}$ agonists have antidepressant-like properties in both acute and chronic preclinical models used to predict antidepressant efficacy.[20,22]

## Conclusions

5-$HT_{2C}$ agonists have demonstrated efficacy in preclinical models of depression, obesity, and psychosis.[23,55] The present work reports the chemical synthesis of 67 new side-chain analogs of the monoamine oxidase inhibitor **9**, which were identified as a new class of 5-$HT_{2C}$ agonists.

Starting from compound **9**, a selective but only moderately potent 5-$HT_{2C}$ agonist, we have undertaken a structural optimization campaign that has led to a potent and moderately selective agonist that demonstrates antidepressant-like effects in a commonly used behavioral assay. Moreover, preliminary results based on the work presented in this article suggest the possibility of compounds with improved selectivity profiles comparable to drugs currently in clinical trials. This study therefore presents a new scaffold for 5-$HT_{2C}$ drug discovery, which may in turn lead to novel therapeutics for use in a variety of CNS related disorders.

## Experimental Section

### Chemistry

$^1H$ and $^{13}C$ NMR spectra were obtained with a Bruker Avance spectrometer at 300 and **75** MHz, or a Bruker Avance spectrometer at 400 and 100 MHz, respectively. $^1H$ chemical shifts (δ) were reported in ppm downfield from internal $Me_4Si$. Mass spectra were measured in positive mode electrospray ionization (ESI). The HRMS data were obtained on a Micromass Q-TOF-2TM, ThermoFinnigan LTQFT and Shimadzu LCMSITTOF instruments. Optical rotations were measured with an AUTOPOL IV (Rudolph Research Analytical) instrument. TLC was performed on silica gel $60F_{254}$ glass plates; column chromatography was performed using Merck silica gel (230–400 mesh). Analytical HPLC was performed using a Shimadzu LC-10AD system equipped with the following columns: Column 1: ACE 5 AQ $C_{18}$ UltraInert column (4.6 × 250 mm; 5 μm). Column 2: Waters μ-Bondapak $C_{18}$ column (3.9 × 300 mm; 5 μm). Column 3: ACE 3 AQ $C_{18}$ UltraInert column (4.6 × 100 mm; 3.5 μm). Chiralcel OJ (4.6 × 250 mm, DAICEL) and Chiralpak AD (10.0 × 250 mm, DAICEL) were used for Chiral HPLC analysis. HPLC data were recorded using following methods. Method A: $H_2O$/MeCN (0.1% TFA), 90/10 → 0/100 in 18 min, + 2 min isocratic, flow rate of 1.6 mL/min, λ = 254, 280 nm. Method B: $H_2O$/MeCN (0.1% TFA), 100/0 → 0/100 in 20 min, + 2 min isocratic, flow rate of 1.6 mL/min, λ = 254, 280 nm. Method C: $H_2O$/MeCN (0.1% TFA), 70/30 → 0/100 in 21 min, + 7 min isocratic, flow rate of 1.3 mL/min, λ = 254, 280 nm. Method D: $H_2O$/MeCN (0.1% TFA), 90/10 → 0/100 in 20 min, + 7 min isocratic, flow rate of 1mL/min, λ = 254, 280 nm. Method E: $H_2O$/MeCN (0.1% TFA), 100/0 → 0/100 in 30 min, + 3 min isocratic, flow rate of 1.3 mL/min, λ = 254, 280 nm. Starting materials were obtained from Aldrich, Alfa Aesar, or Acros. Solvents were obtained from Fisher Scientific or Aldrich and were used without further purification unless noted otherwise.

### General Procedure for the Synthesis of *trans*- and *cis*-(2-Phenylcyclopropyl)methylamine Hydrochloride (14a and 14b). Step A. *trans*- and *cis*-2-Phenylcyclopropanecarboxylic Acid Ethyl Ester (11a and 11b)

Under dry conditions, $Cu(acac)_2$ (78 mg, 0.3 mmol) was dissolved in anhydrous $CH_2Cl_2$ (20 mL). After the solution was stirred for 5 min, a few drops of phenylhydrazine were added and stirring was continued. To this solution was added styrene (1.15 mL, 10 mmol). The mixture was stirred at 40 °C for 5 min, and a solution of ethyl diazoacetate (1.56 mL, 15 mmol) in $CH_2Cl_2$ (20 mL) was added via syringe pump over 5 h at 40 °C. After stirring for one more hour followed by the addition of $CH_2Cl_2$ (50 mL), the mixture was washed successively with satd. aq. $NaHCO_3$ (×2) and $H_2O$ (×2). The organic portion was dried over $Na_2SO_4$ and all volatiles were removed *in vacuo*. The isomers were separated by silica gel chromatography (hexane/$Et_2O$ 20:1) to afford the title compounds as colorless oils (*trans*-isomer **11a**: 1.19 g, 67% yield) and (*cis*-isomer **11b**: 490 mg, 27% yield). **11a**: $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 2 H), 7.24 (m, 1 H), 7.13 (d, *J* = 7.1 Hz, 2 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 2.54 (m, 1 H), 1.93 (m, 1 H), 1.63 (m, 1 H), 1.37-1.29 (m, 4 H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 173.3, 140.0, 128.4, 126.4, 126.1, 60.6, 26.1, 24.1, 17.0, 14.2. **11b**: $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.29-7.21 (m, 5 H), 3.90 (q, *J* = 7.1 Hz, 2 H), 2.60 (m, 1 H), 2.10 (m, 1 H), 1.74 (m, 1 H), 1.35 (m, 1 H), 0.99

(t, $J$ = 7.1 Hz, 3 H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.1, 136.5, 129.2, 127.8, 126.6, 60.1, 25.4, 21.7, 14.0, 11.0.

### Step B. *trans*-2-Phenylcyclopropanecarboxylic Acid (12a)

A solution of **11a** (128 mg, 0.726 mmol) in MeOH (1 mL) was added to KOH (406 mg, 7.26 mmol) in MeOH (3 mL) at 0 °C. The mixture was stirred at rt overnight, and then poured into water and extracted with $CH_2Cl_2$. The organic layer was discarded, and the aqueous phase was acidified with 10% HCl and extracted with $CH_2Cl_2$ (×2). The combined organic phases were dried over $Na_2SO_4$ and all volatiles were removed *in vacuo*. The acid was isolated as white powders and further purified by recrystallization from hexane (80 mg, 68% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 10.3 (br s, 1 H), 7.34-7.22 (m, 3 H), 7.14 (d, $J$ = 7.0 Hz, 2 H), 2.64 (m, 1 H), 1.93 (m, 1 H), 1.70 (m, 1 H), 1.44 (m, 1 H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 180.2, 139.9, 128.9, 127.1, 126.7, 27.5, 24.4, 17.9.

### *cis*-2-Phenylcyclopropanecarboxylic Acid (12b)

Prepared by the same procedure as described for **12a** (233 mg, 77% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.29-7.20 (m, 5 H), 2.65 (m, 1 H), 2.05 (m, 1 H), 1.68 (m, 1 H), 1.40 (m, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 177.2, 135.8, 129.2, 127.9, 126.8, 26.6, 21.4, 12.0.

### Step C. *trans*-2-Phenylcyclopropanecarboxylic Acid Amide (13a)

Several drops of dimethylformamide and thionyl chloride (13.5 mL, 185 mmol) were added dropwise to a solution of **12a** (2.0 g, 12.3 mmol) in toluene (40 mL). After stirring at 80 °C for 3 h, the reaction mixture was concentrated under vacuum. The resulting residue was dissolved in toluene (10 mL), and the resulting solution was added to liquid ammonia at -78 °C. After stirring at -78 °C for 30 min and then at rt for 30 min, $CH_2Cl_2$ (25 ml) was added to the mixture at -78 °C and the resulting mixture was stirred at rt overnight. After addition of EtOAc, the mixture was washed with satd. aqueous $NH_4Cl$ (×2), dried over $Na_2SO_4$, and all volatiles were removed *in vacuo*. The title compound was isolated as a pearly yellow powder and further purified by recrystallization from hexane/EtOAc (1.72 g, 87% yield). $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7.60 (br s, 1 H), 7.29-7.10 (m, 5 H), 6.91 (br s, 1 H), 2.21 (m, 1 H), 1.82 (m, 1 H), 1.32 (m, 1 H), 1.18 (m, 1 H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 173.8, 142.1, 129.2, 126.8, 126.6, 26.4, 24.8, 16.1.

### *cis*-2-Phenylcyclopropanecarboxylic Acid Amide (13b)

Prepared by the same procedure as described for **13a** (128 mg, 56% yield). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.40 (br s, 1 H), 7.21-7.20 (m, 4 H), 7.13 (m, 1 H), 6.59 (br s, 1 H), 2.36 (m, 1 H), 1.97 (m, 1 H), 1.45 (m, 1 H), 1.13 (m, 1 H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 170.9, 138.2, 129.4, 127.9, 126.2, 24.3, 23.4, 9.9.

### Step D. *trans*-(2-Phenylcyclopropyl)methylamine Hydrochloride (14a)

To a solution of **13a** (1.6 g, 9.93 mmol) in anhydrous THF (40 mL) was added dropwise 1 M borane/THF solution (39.7 mL) at 0 °C. The mixture was heated under reflux at 70 °C overnight, then was quenched by the careful addition of 10% aqueous HCl. After stirring at rt for 1 h, the THF was removed by evaporation and the residual aqueous solution was washed with $Et_2O$ (×2), neutralized with 10% NaOH, and then extracted with $Et_2O$ (×4). The combined organic layers were dried over $Na_2SO_4$ and concentrated until the volume was reduced to about 20 mL. To the solution was added 1 M HCl in $Et_2O$ (20 mL, 20 mmol) at 0 °C. After stirring at 0 °C for 15 min and at rt for 1 h, the mixture was concentrated under vacuum. The resulting residue was purified by recrystallization from ethanol/$Et_2O$ to afford the title compound as a white solid (1.54 g, 86% yield). HPLC purity: 11.9 min, 95.4% (column 1, method C). $^1$H NMR (300 MHz, MeOD-$d_4$) δ 7.29-7.24 (m, 2 H), 7.18-7.13 (m, 3 H), 3.01 (d, $J$ = 7.4 Hz, 2

H), 2.03 (m, 1 H), 1.41 (m, 1 H), 1.14-1.05 (m, 2 H). $^{13}$C NMR (75 MHz, MeOD-$d_4$) δ 141.6, 128.4, 126.0, 125.9, 43.9, 22.2, 19.8, 14.0. MS (ESI) *m/z* 148.1 [$MH^+$]. HRMS (ESI) calculated for $C_{10}H_{14}N^+$ [$MH^+$] 148.1126, found 148.1127.

### *cis*-(2-Phenylcyclopropyl)methylamine Hydrochloride (14b)

Prepared by the same procedure as described for **14a** (26.8 mg, 47% yield). HPLC purity: 12.4 min, 95.5% (column 1, method C). $^1$H NMR (300 MHz, MeOD-$d_4$) δ 7.35-7.24 (m, 5 H), 2.99-2.94 (m, 1 H), 2.20 (m, 1 H), 1.49 (m, 1 H), 1.25-1.18 (m, 1 H), 1.08 (m, 1 H). $^{13}$C NMR (75 MHz, MeOD-$d_4$) δ 137.3, 129.1, 128.5, 126.8, 40.5, 21.1, 15.5, 8.3. MS (ESI) *m/z* 148.1 [$MH^+$]. HRMS (ESI) calculated for $C_{10}H_{14}N^+$ [$MH^+$] 148.1126, found 148.1123.

### General Procedure for the Preparation of Optically Pure Ligand ((+)- and (−)-14a). Step A. (+)- and (−)-*trans*-2-Phenylcyclopropanecarboxylic Acid (2-Hydroxy-1-phenylethyl)amide ((+)- and (−)-91)

To a stirred solution of **12a** (1.62 g, 10.0 mmol) in $CH_2Cl_2$ (20 mL) were added (*R*)-(−)-**2**-phenylglycinol (2.06 g, 15.0 mmol), HOBT (1.35 g, 10.0 mmol) and EDC·HCl (2.88 g, 15.0 mmol). The mixture was stirred at 0 °C for 1 h followed at rt overnight. The reaction mixture was washed with 5% aqueous citric acid, satd. aqueous $NaHCO_3$ and satd. NaCl. The organic layer was dried over $Na_2SO_4$, filtered, and concentrated. The crude residue was purified by silica gel column chromatography (EtOAc/$Et_2O$ 1:2) to afford the (−)-isomer with a higher Rf value (650 mg, 23% yield) and the (+)-isomer with a lower $R_f$ value (703 mg, 25% yield) as colorless solids. (+)-**91**: $^1$H NMR (300 MHz, MeOD-$d_4$) δ 7.35-7.10 (m, 9 H), 5.02 (t, *J* = 6.3 Hz, 1 H), 3.75 (m, 2 H), 2.34 (m, 1 H), 2.03 (m, 1 H), 1.53 (m, 1 H), 1.27 (m, 1 H). $^{13}$C NMR (75 MHz, MeOD-$d_4$) δ 173.6, 141.2, 140.4, 128.5, 128.4, 127.4, 127.0, 126.3, 126.1, 65.3, 56.4, 25.8, 24.8, 15.2. (−)-**91**: $^1$H NMR (300 MHz, MeOD-$d_4$) δ 7.36-7.13 (m, 9 H), 5.03 (t, *J* = 6.3 Hz, 1 H), 3.75 (m, 2 H), 2.42 (m, 1 H), 2.03 (m, 1 H), 1.46 (m, 1 H), 1.24 (m, 1 H). $^{13}$C NMR (75 MHz, MeOD-$d_4$) δ 173.6, 141.2, 140.4, 128.5, 128.4, 127.4, 127.0, 126.2, 126.0, 65.2, 56.3, 25.7, 24.8, 15.4.

### Step B. (+)-*trans*-2-Phenylcyclopropanecarboxylic Acid ((+)-12a)

A solution of (+)-**91** (150 mg, 0.534 mmol) in dioxane (5 mL) was added to 3 N $H_2SO_4$ (5 mL). The mixture was stirred at 100 °C for 24 h and then poured into water and extracted with $CH_2Cl_2$ (×3). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica gel column chromatography (EtOAc/hexane 1:2) to afford the title compound as a colorless solid (73 mg, 84% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 10.3 (br s, 1 H), 7.34-7.22 (m, 3 H), 7.14 (d, *J* = 7.0 Hz, 2 H), 2.64 (m, 1 H), 1.93 (m, 1 H), 1.70 (m, 1 H), 1.44 (m, 1 H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 180.2, 139.9, 128.9, 127.1, 126.7, 27.5, 24.4, 17.9. $[\alpha]_D$ +389° (c 0.61, $CHCl_3$) [lit. 405° (c 1.0, $CHCl_3$), Macromolecules, 1971, 4, 718-722]

### (−)-*trans*-2-Phenylcyclopropanecarboxylic Acid ((−)-12a)

Prepared by the same procedure as described for (+)-**12a**. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.76 (br s, 1 H), 7.34-7.22 (m, 3 H), 7.14 (d, *J* = 7.0 Hz, 2 H), 2.64 (m, 1 H), 1.93 (m, 1 H), 1.70 (m, 1 H), 1.44 (m, 1 H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 180.2, 139.9, 128.9, 127.1, 126.7, 27.5, 24.4, 17.9, $[\alpha]_D$ -396° (c 0.72, $CHCl_3$) [lit. -410° (c 1.0, $CHCl_3$), Macromolecules, 1971, 4, 718-722]

### Step C. (+)-*trans*-(*S,S*)-(2-Phenylcyclopropyl)methylamine Hydrochloride ((+)-14a)

Refer to the general procedure for the synthesis of **14a** described above with substituting (+)-*trans*-2-phenyl-cyclopropanecarboxylic acid (+)-**12a** for (±)-**12a** in Step C. HPLC purity: 12.8 min, 97.9% (column 1, method C). $^1$H NMR (MeOD-$d_4$) δ 7.29-7.24 (m, 2 H), 7.18-7.13 (m,

3 H), 3.01 (d, $J$ = 7.4 Hz, 2 H), 2.02 (m, 1 H), 1.41 (m, 1 H), 1.14-1.06 (m, 2 H). $^{13}$C NMR (MeOD-$d_4$) δ 141.6, 128.4, 126.0, 125.9, 43.9, 22.2, 19.8, 14.0. MS (ESI) *m/z* 148.2 [$MH^+$]. HRMS (ESI) calculated for $C_{10}H_{14}N^+$ [$MH^+$] 148.1126, found 148.11202. $[\alpha]_D$ +72.9° (c 0.45, MeOH).

### (−)-*trans*-(*R,R*)-(2-Phenylcyclopropyl)methylamine Hydrochloride ((−)-14a)

Prepared by the same procedure as described for (+)-**14a**. HPLC purity: 12.6 min, 98.1% (column 1, method C). $^1$H NMR (300 MHz, MeOD-$d_4$) δ 7.29-7.24 (m, 2 H), 7.18-7.13 (m, 3 H), 3.01 (d, $J$ = 7.4 Hz, 2 H), 2.06-2.02 (m, 1 H), 1.42 (m, 1 H), 1.13-1.05 (m, 2 H). $^{13}$C NMR (75 MHz, MeOD-$d_4$) δ 141.6, 128.4, 126.0, 125.9, 43.9, 22.2, 19.8, 14.0. MS (ESI) *m/z* 148.2 [$MH^+$]. HRMS (ESI) calculated for $C_{10}H_{14}N^+$ [$MH^+$] 148.1126, found 148.11200. $[\alpha]_D$ -71.3° (c 0.45, MeOH).

### *trans*-*N*-Methyl-(2-phenylcyclopropyl)amine (15)

Acetic formic anhydride was generated by dropwise addition of formic acid (0.36 mL, 9.6 mmol) to acetic anhydride (0.73 mL, 7.8 mmol). The mixture was kept on ice and then heated at 50 °C for 2 h. The mixture was cooled to rt, and THF (5 mL) was added. This mixture (0.6 mL, 0.3 mmol) was added to a solution of *9* (50 mg, 0.3 mmol) in THF (1 mL) at -15 °C followed by addition of *N*-methylmorpholine (45 μL, 0.3 mmol). The resulting mixture was stirred at -15 °C for 30 min and at rt for 1 h, insoluble materials were filtered out, and the solution was concentrated *in vacuo*. The crude residue (65 mg) was dissolved in THF (1.2 mL), and to the solution was added 1.0 M solution of borane dimethylsulfide complex in THF (0.75 mL). After the mixture was stirred at 65 °C overnight, the reaction was quenched by 10% aqueous HCl. The mixture was concentrated under reduced pressure to remove THF, and the residual aqueous solution was washed with $Et_2O$ (×1), neutralized with 10% aqueous NaOH, and then extracted with $Et_2O$ (×3). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by preparative TLC (EtOAc/$Et_3N$/MeOH 8:1:1) to afford the title compound as a colorless oil (21 mg, 47% yield). HPLC purity: 24.8 min, 95.2% (column 2, method C). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.30-7.25 (m, 2 H), 7.20-7.16 (m, 1 H), 7.09-7.06 (m, 2 H), 2.54 (br s, 3 H), 2.34 (m, 1 H), 1.92 (m, 1 H), 1.76 (br s, 1 H), 1.12-1.06 (m, 1 H), 1.02-0.98 (m, 1 H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 142.8, 128.6, 126.3, 125.9, 43.7, 36.2, 25.3, 17.5. MS (ESI) *m/z* 148.1 [$MH^+$]. HRMS (ESI) calculated for $C_{10}H_{14}N^+$ [$MH^+$] 148.1126, found 148.1124.

### *trans*-*N*-Methyl-(2-phenylcyclopropylmethyl)amine (16)

Acetic formic anhydride was generated as described above for **15** from formic acid (0.18 mL, 4.8 mmol) and acetic anhydride (0.365 mL, 3.9 mmol), and THF (4.5 mL). This mixture (0.53 mL, 0.408 mmol) was added to a solution of **14a** (30 mg, 0.163 mmol) in THF (1 mL) at -15 °C followed by addition of *N*-methylmorpholine (17.9 μL, 0.163 mmol). The resulting mixture was stirred at -15 °C for 30 min and at rt for 1 h, insoluble materials were filtered out, and the mixture was concentrated *in vacuo*. The crude residue (42 mg) was dissolved in THF (1.2 mL), and to the solution was added 1.0 M borane dimethylsulfide complex in THF (0.41 mL). After the mixture was stirred at 65 °C overnight, the reaction was quenched by 10% aqueous HCl. The mixture was concentrated *in vacuo* to remove THF, and the residual aqueous solution was washed with $Et_2O$ (×1), neutralized with 10% aqueous NaOH, and then extracted with $Et_2O$ (×3). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by preparative TLC (EtOAc/$Et_3N$/MeOH 8:1:1) to afford the title compound as a colorless oil (14.0 mg, 53% yield). HPLC purity: 21.0 min, 96.8% (column 2, method C). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.29-7.24 (m, 2 H), 7.18-7.15 (m, 1 H), 7.10-7.07 (m, 2 H), 2.66 (br d, 2 H), 2.49 (br s, 3 H), 2.37 (br s, 1 H), 1.77 (m, 1 H), 1.38-1.32 (m, 1 H), 0.99-0.85 (m, 2 H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 143.3, 128.7, 126.2, 125.9, 56.5, 36.5, 23.3,

22.5, 15.1. MS (ESI) *m/z* 162.1 [$MH^+$]. HRMS (ESI) calculated for $C_{11}H_{16}N^+$ [$MH^+$] 162.1283, found 162.1285.

### *trans*-*N*,*N*-Dimethyl-(2-phenylcyclopropyl)amine (17)

To a stirred solution of **9** (34 mg, 0.2 mmol) in acetonitril/$H_2O$ (1:1, v/v) (5 mL) were added *N*-methylmorpholine (45 μL, 0.4 mmol), 37% aqueous formaldehyde (0.16 mL, 2.0 mmol), and sodium cyanoborohydride (40 mg, 0.6 mmol). Glacial acetic acid (40 μL) was added to the mixture over 10 min and the reaction was stirred at rt for 30 min. To the reaction mixture was added crushed ice, and the acetonitrile was removed *in vacuo*. The aqueous residue was extracted with $CH_2Cl_2$. The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by preparative TLC (EtOAc/$Et_3N$ 95:5) to afford the title compound as a colorless oil (19.7 mg, 61% yield). HPLC purity: 19.8 min, 94.8% (column 1, method C). $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.34-7.26 (m, 2 H), 7.18 (t, *J* = 7.3 Hz, 1 H), 7.09 (d, *J* = 7.2 Hz, 2 H), 2.74 (d, *J* = 3.6 Hz, 2 H), 2.42 (s, 6 H), 2.00 (m, 1 H), 1.83 (m, 1 H), 1.13 (m, 1 H), 0.99 (m, 1 H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 142.5, 128.6, 126.5, 126.0, 50.6, 45.4, 25.7, 17.6. MS (ESI) *m/z* 162.1 [$MH^+$]. HRMS (ESI) calculated for $C_{11}H_{16}N^+$ [$MH^+$] 162.1283, found 162.1279.

### *trans*-*N*-Isopropyl-(2-phenylcyclopropyl)amine (18)

To a stirred solution of **9** (50 mg, 0.295 mmol) in MeOH (1 mL) were added acetone (21.7 μL, 0.295 mmol) and sodium cyanoborohydride (22 mg, 0.354 mmol). The mixture was stirred at 0 °C for 1 h and at rt overnight. Crushed ice was added to the reaction mixture and the MeOH was removed *in vacuo*. The aqueous residue was extracted with $CH_2Cl_2$. The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by preparative TLC (EtOAc/$Et_3N$ 95:5) to afford the title compound as a colorless oil (16.7 mg, 32% yield). HPLC purity: 8.6 min, 97.4% (column 1, method C). $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.30-7.25 (m, 2 H), 7.19-7.14 (m, 1 H), 7.06 (d, *J* = 7.3 Hz, 2 H), 3.01 (m, 1 H), 2.31 (m, 1 H), 1.90 (m, 1 H), 1.87 (br s, 1 H), 1.12 (d, *J* = 6.3 Hz, 6 H), 1.07 (m, 2 H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 142.8, 128.6, 126.1, 125.8, 49.7, 40.7, 25.9, 23.7, 23.6, 17.2. MS (ESI) *m/z* 176.1 [$MH^+$]. HRMS (ESI) calculated for $C_{12}H_{18}N^+$ [$MH^+$] 176.1439, found 176.1437.

### *trans*-*N*-Benzyl-(2-phenylcyclopropyl)amine (19)

Prepared by the same procedure as described for **18** with benzaldehyde (27 μL, 0.266 mmol) as the starting material (15.4 mg, 23% yield). HPLC purity: 14.6 min, 96.8% (column 1, method C). $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.40-7.25 (m, 9 H), 7.18 (m, 1 H), 7.03 (d, *J* = 7.3 Hz, 2 H), 3.92 (s, 2 H), 2.42 (m, 1 H), 2.25 (m, br s, 1 H), 1.97 (m, 1 H), 1.14 (m, 1 H), 1.01 (m, 1 H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 142.7, 140.7, 128.8, 128.7, 128.6, 127.4, 126.3, 125.9, 54.0, 41.6, 25.8, 17.5. MS (ESI) *m/z* 224.1 [$MH^+$]. HRMS, (ESI) calculated for $C_{16}H_{18}N^+$ [$MH^+$] 224.1439, found 224.1440.

### *trans*-*N*-Benzyl-(2-phenylcyclopropylmethyl)amine (20)

Prepared by the same procedure as described for **18** with **14a** (30 mg, 0.163 mmol) and benzaldehyde (14.9 μL, 0.147 mmol) as the starting materials (20.8 mg, 54% yield). HPLC purity: 15.7 min, 95.1% (column 1, method C). $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.36-7.25 (m, 7 H), 7.19-7.16 (m, 1 H), 7.10-7.07 (m, 2 H), 3.87 (s, 2 H), 2.71 (m, 1 H), 1.73 (m, 1 H), 1.69 (br s, 1 H), 0.95 (m, 1 H), 0.85 (m, 1 H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 143.4, 140.8, 128.8, 128.7, 128.5, 127.4, 126.1, 125.9, 54.1, 54.0, 23.8, 22.5, 15.3. MS (ESI) *m/z* 238.1 [$MH^+$]. HRMS (ESI) calculated for $C_{17}H_{20}N^+$ [$MH^+$] 238.1596, found 238.1589.

### General Procedure for the Synthesis of Substituted Styrene (22)

To a stirred suspension of benzaldehyde **21** (10 mmol) and methyltriphenylphosphonium bromide (4.28 g, 12 mmol) in THF (50 mL) was added sodium hydride (1.08 g, 45.10 mmol) under argon purge at 0 °C. After the mixture was stirred at rt overnight, the organic layer was washed three times with brine, dried over $Na_2SO_4$, filtered, and concentrated. The crude product was purified by silica gel column chromatography (hexane/$Et_2O$ 20:1) to afford the title compound as a colorless oil (90-99% yield).

### *trans*-(2-Naphthalen-2-ylcyclopropyl)methylamine Hydrochloride (26)

Refer to the general procedure for the synthesis of **14a** described above by using 2-vinylnaphthalene as the starting material. HPLC purity: 14.8 min, 97.7% (column 1, method C). $^1$H NMR (300 MHz, MeOD-$d_4$) δ 7.81-7.77 (m, 3 H), 7.63 (s, 1 H), 7.48-7.38 (m, 2 H), 7.28 (m, 1 H), 3.06 (d, $J$ = 7.4 Hz, 2 H), 2.20 (m, 1 H), 1.55 (m, 1 H), 1.24 (m, 1 H), 1.15 (m, 1 H). $^{13}$C NMR (75 MHz, MeOD-$d_4$) δ 139.1, 134.0, 132.7, 128.1, 127.6, 127.4, 126.2, 125.3, 124.7, 124.3, 43.9, 22.4, 19.9, 14.1. MS (ESI) *m/z* 198.1 [$MH^+$]. HRMS (ESI) calculated for $C_{14}H_{16}N^+$ [$MH^+$] 198.1283, found 198.1290.

### *trans*-[2-(2-Fluorophenyl)cyclopropyl]methylamine Hydrochloride (27)

Refer to the general procedure for the synthesis of **14a** described above by using 2-fluorostyrene as the starting material. HPLC purity: 12.3 min, 95.8% (column 1, method C). $^1$H NMR (300 MHz, MeOD-$d_4$) δ 7.21 (m, 1 H), 7.13-7.02 (m, 3 H), 3.07-3.03 (m, 2 H), 2.16 (m, 1 H), 1.49 (m, 1 H), 1.17-1.09 (m, 2 H). $^{13}$C NMR (75 MHz, MeOD-$d_4$) δ 162.1 (d, $^1J_{CF}$ = 243.9 Hz), 128.3 (d, $^2J_{CF}$ = 14.2 Hz), 127.81 (d, $^3J_{CF}$ = 8.3 Hz), 127.2 (d, $^3J_{CF}$ = 3.9 Hz), 124.4 (d, $^4J_{CF}$ = 3.5 Hz), 115.0 (d, $^2J_{CF}$ = 22.1 Hz), 43.8, 18.3, 15.7, 12.7. MS (ESI) *m/z* 166.1 [$MH^+$]. HRMS (ESI) calculated for $C_{10}H_{13}NF^+$ [$MH^+$] 166.1032, found 166.1029.

### *trans*-[2-(2-Chlorophenyl)cyclopropyl]methylamine Hydrochloride (28)

Refer to the general procedure for the synthesis of **14a** described above by using 2-chlorostyrene as the starting material. HPLC purity: 6.8 min, 96.2% (column 3, method A). $^1$H NMR (300 MHz, MeOD-$d_4$) δ 7.38 (dd, $J$ = 7.4, 1.2 Hz, 1 H), 7.26-7.11 (m, 3 H), 3.25 (m, 1 H), 2.93 (m, 1 H), 2.22 (m, 1 H), 1.37 (m, 1 H), 1.12 (t, $J$ = 6.8 Hz, 2 H). $^{13}$C NMR (75 MHz, MeOD-$d_4$) δ 139.8, 136.4, 130.4, 129.0, 128.7, 128.4, 44.9, 21.6, 19.7, 14.9. MS (ESI) *m/z* 182.1 [$MH^+$]. HRMS (ESI) calculated for $C_{10}H_{13}NCl^+$ [$MH^+$] 182.0731, found 182.0738.

### *trans*-[2-(2-Bromophenyl)cyclopropyl]methylamine Hydrochloride (29)

Refer to the general procedure for the synthesis of **14a** described above by using 2-bromostyrene as the starting material. HPLC purity: 14.8 min, 96.1% (column 1, method C). $^1$H NMR (300 MHz, MeOD-$d_4$) δ 7.57 (d, $J$ = 8.1 Hz, 1 H), 7.29 (t, $J$ = 7.0 Hz, 1 H), 7.13 (m, 2 H), 3.33 (m, 1 H), 2.89 (m, 1 H), 2.17 (m, 1 H), 1.39 (m, 1 H), 1.13 (m, 2 H). $^{13}$C NMR (75 MHz, MeOD-$d_4$) δ 140.3, 132.5, 128.2, 127.9, 127.8, 125.8, 43.8, 23.3, 18.7, 12.9. MS (ESI) *m/z* 226.0 [$MH^+$]. HRMS (ESI) calculated for $C_{10}H_{13}NBr^+$ [$MH^+$] 226.0231, found 226.0228.

### *trans*-[2-(2-Methylphenyl)cyclopropyl]methylamine Hydrochloride (30)

Refer to the general procedure for the synthesis of **14a** described above by using 2-methylstyrene as the starting material. HPLC purity: 9.4 min, 98.5% (column 1, method E). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.13 (t, $J$ = 7.8 Hz, 1 H), 6.96-6.91 (m, 3 H), 7.13 (m, 2 H), 3.00 (m, 1 H), 2.28 (s, 3 H), 2.89 (m, 1 H), 2.01-1.96 (m, 1 H), 1.44 (m, 1 H), 1.05 (t, $J$ = 6.7 Hz, 1 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 142.6, 139.0, 129.4, 127.8, 127.7, 124.1, 45.1,

23.2, 21.6, 20.8, 15.2. MS (ESI) *m/z* 162.1 [$MH^+$]. HRMS (ESI) calculated for $C_{11}H_{16}N^+$ [$MH^+$] 161.1277, found 162.1270.

### *trans*-[2-(2-Trifluoromethylphenyl)cyclopropyl]methylamine Hydrochloride (31)

Refer to the general procedure for the synthesis of **14a** described above by using 2-trifluoromethylstyrene as the starting material. HPLC purity: 7.9 min, 99.3% (column 3, method A). $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.20 (s, 3 H), 7.67 (d, $J$ = 6.4 Hz, 1 H), 7.58 (m, 1 H), 7.40 (m, 1 H), 7.29 (d, $J$ = 5.8 Hz, 1 H), 3.00 (m, 1 H), 2.75 (m, 1 H), 2.15 (m, 1 H), 1.50 (m, 1 H), 1.09 (m, 2 H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 140.0, 133.2, 128.6 (q, $^2J_{CF}$ = 30.0 Hz), 128.0, 127.0, 126.1 (q, $^3J_{CF}$ = 5.5 Hz), 125.1 (q, $^1J_{CF}$ = 273.7 Hz), 42.7, 19.3, 19.2, 14.3. MS (ESI) *m/z* 216.1 [$MH^+$]. HRMS (ESI) calculated for $C_{11}H_{13}NF_3^+$ [$MH^+$] 216.0995, found 216.0990.

### *trans*-[2-(2-Methoxyphenyl)cyclopropyl]methylamine Hydrochloride (32)

Refer to the general procedure for the synthesis of **14a** described above by using 2-methoxystyrene as the starting material. HPLC purity: 7.3 min, 97.7% (column 3, method A). $^1$H NMR (300 MHz, MeOD-$d_4$) δ 7.17-7.13 (m, 1 H), 6.94-6.82 (m, 3 H), 3.86 (s, 3 H), 2.79 (m, 2 H), 2.07-2.02 (m, 1 H), 1.29-1.25 (m, 1 H), 1.09-1.02 (m, 1 H), 0.97-0.90 (m, 1 H). $^{13}$C NMR (75 MHz, MeOD-$d_4$) δ 159.8, 130.7, 128.5, 127.3, 121.7, 111.4, 56.1, 45.8, 20.8, 18.2, 13.3. MS (ESI) *m/z* 178.1 [$MH^+$]. HRMS (ESI) calculated for $C_{11}H_{16}NO^+$ [$MH^+$] 178.1226, found 178.1228.

### *trans*-[2-(2-Hydroxyphenyl)cyclopropyl]methylamine Hydrochloride (33)

To a solution of **32** (80 mg, 0.451 mmol) in dry $CH_2Cl_2$ (2 mL) under a nitrogen atmosphere at -78 °C was slowly added a solution of boron tribromide (1.0 M in $CH_2Cl_2$, 1 mL). The reaction mixture was allowed to warm to rt and stirred for 4 h. The brown solution was cooled with an ice bath, and to the solution was slowly added water (2 mL). The organic layer was separated, and the water layer was extracted with EtOAc (×4). The combined organic layers were dried over $Na_2SO_4$ and concentrated until the volume was reduced to about 1 mL. To the solution was added 1 M HCl in $Et_2O$ (1 mL, 1 mmol) at 0 °C. After stirring at 0 °C for 15 min and at rt for 1 h, the mixture was concentrated *in vacuo*. The resulting residue was purified by recrystallization from ethanol/$Et_2O$ to afford the title compound as a white solid (50 mg, 68% yield). HPLC purity: 7.7 min, 97.7% (column 3, method B). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.03-6.99 (m, 1 H), 6.91 (d, $J$ = 7.5 Hz, 1 H), 6.79-6.73 (m, 2 H), 3.15-3.10 (m, 1 H), 2.91-2.86 (m, 1 H), 2.07-2.02 (m, 1 H), 1.24-1.20 (m, 1 H), 1.75-1.11 (m, 1 H), 1.00-0.95 (m, 1 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 157.3, 128.4, 128.4, 127.8, 120.8, 115.7, 45.5, 19.5, 18.4, 12.6. MS (ESI) *m/z* 164.1 [$MH^+$]. HRMS (ESI) calculated for $C_{10}H_{14}NO^+$ [$MH^+$] 164.1070, found 164.1068.

### *trans*-[2-(3-Fluorophenyl)cyclopropyl]methylamine Hydrochloride (34)

Refer to the general procedure for the synthesis of **14a** described above by using 3-fluorostyrene as the starting material. HPLC purity: 12.6 min, 95.9% (column 1, method C). $^1$H NMR (300 MHz, MeOD-$d_4$) δ 7.27 (m, 1 H), 6.98 (d, $J$ = 7.7 Hz, 1 H), 6.90 (m, 2 H), 3.01 (m, 2 H), 2.06 (m, 1 H), 1.44 (m, 1 H), 1.12 (m, 2 H). $^{13}$C NMR (75 MHz, MeOD-$d_4$) δ 163.5 (d, $^1J_{CF}$ = 243.0 Hz), 144.8 (d, $^3J_{CF}$ = 6.0 Hz), 130.1 (d, $^3J_{CF}$ = 8.8 Hz), 122.0, 112.7 (d, $^2J_{CF}$ = 22.0 Hz), 43.7, 22.0, 20.3, 14.4. MS (ESI) *m/z* 166.0 [$MH^+$]. HRMS (ESI) calculated for $C_{10}H_{13}NF^+$ [$MH^+$] 166.1032, found 166.1032.

### *trans*-[2-(3-Chlorophenyl)cyclopropyl]methylamine Hydrochloride (35)

Refer to the general procedure for the synthesis of **14a** described above by using 3-chlorostyrene as the starting material. HPLC purity: 7.4 min, 98.6% (column 3, method

A). $^{1}$H NMR (300 MHz, MeOD-$d_4$) δ 7.27-7.05 (m, 4 H), 3.00 (d, $J$ = 4.1 Hz, 2 H), 2.03 (m, 1 H), 1.43 (m, 1 H), 1.11 (m, 2 H). $^{13}$C NMR (75 MHz, MeOD-$d_4$) δ 145.4, 135.4, 131.1, 127.3, 127.2, 125.6, 44.9, 23.0, 21.3, 15.4. MS (ESI) *m/z* 182.1 [$MH^+$]. HRMS (ESI) calculated for $C_{10}H_{13}NCl^+$ [$MH^+$] 182.0731, found 182.0732.

### *trans*-[2-(3-Bromophenyl)cyclopropyl]methylamine Hydrochloride (36)

Refer to the general procedure for the synthesis of **14a** described above by using 3-bromostyrene as the starting material. HPLC purity: 16.3 min, 95.9% (column 1, method C). $^{1}$H NMR (300 MHz, MeOD-$d_4$) δ 7.33 (d, $J$ = 7.8 Hz, 2 H), 7.26-7.11 (m, 2 H), 3.08-2.95 (m, 2 H), 2.07-2.01 (m, 1 H), 1.50-1.39 (m, 1 H), 1.17-1.07 (m, 2 H). $^{13}$C NMR (75 MHz, MeOD-$d_4$) δ 144.5, 130.2, 129.2, 129.1, 124.8, 122.4, 43.7, 21.8, 20.2, 14.2. MS (ESI) *m/z* 226.0 [$MH^+$]. HRMS (ESI) calculated for $C_{10}H_{13}NBr^+$ [$MH^+$] 226.0231, found 226.0235.

### *trans*-[2-(3-Methylphenyl)cyclopropyl]methylamine Hydrochloride (37)

Refer to the general procedure for the synthesis of **14a** described above by using 3-methylstyrene as the starting material. HPLC purity: 9.5 min, 99.2% (column 1, method E). $^{1}$H NMR (400 MHz, MeOD-$d_4$) δ 7.13-7.05 (m, 3 H), 7.02-7.00 (m, 1 H), 3.25-3.21 (m, 1 H), 2.94-2.88 (m, 1 H), 2.40 (s, 3 H), 2.04-1.99 (m, 1 H), 1.46-1.41 (m, 1 H), 1.09-1.04 (m, 1 H), 0.97-0.93 (m, 1 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 140.2, 138.8, 130.8, 127.5, 127.1, 126.8, 45.1, 21.6, 20.0, 18.7, 13.9. MS (ESI) *m/z* 162.1 [$MH^+$]. HRMS (ESI) calculated for $C_{11}H_{16}N^+$ [$MH^+$] 161.1277, found 162.1270.

### *trans*-[2-(3-Trifluoromethylphenyl)cyclopropyl]methylamine Hydrochloride (38)

Refer to the general procedure for the synthesis of **14a** described above by using 3-trifluorostyrene as the starting material. HPLC purity: 8.4 min, 98.3% (column 3, method A). $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 7.94 (s, 3 H), 7.50-7.39 (m, 4 H), 2.96 (m, 1 H), 2.74 (m, 1 H), 2.12 (m, 1 H), 1.34 (m, 1 H), 1.15-1.05 (m, 2 H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 143.2, 129.6, 129.3, 129.0 (q, $^{2}J_{CF}$ = 31.0 Hz), 124.2 (q, $^{1}J_{CF}$ = 272.6 Hz), 122.6 (q, $^{3}J_{CF}$ = 3.5 Hz), 122.4 (q, $^{3}J_{CF}$ = 3.5 Hz), 42.7, 21.3, 20.4, 14.4. MS (ESI) *m/z* 216.1 [$MH^+$]. HRMS (ESI) calculated for $C_{11}H_{13}NF_3{}^+$ [$MH^+$] 216.0995, found 216.0991.

### *trans*-[2-(3-Methoxyphenyl)cyclopropyl]methylamine Hydrochloride (39)

Refer to the general procedure for the synthesis of **14a** described above by using 3-methoxystyrene as the starting material. HPLC purity: 6.9 min, 98.5% (column 3, method A). $^{1}$H NMR (300 MHz, MeOD-$d_4$) δ 7.18-7.13 (m, 1 H), 6.72-6.69 (m, 3 H), 3.76 (s, 3 H), 2.99 (d, $J$ = 7.3 Hz, 2 H), 2.03-1.97 (m, 1 H), 1.44-1.39 (m, 1 H), 1.11-1.01 (m, 2 H). $^{13}$C NMR (75 MHz, MeOD-$d_4$) δ 161.4, 144.5, 130.5, 119.3, 113.1, 112.5, 55.8, 45.0, 23.4, 21.0, 15.2. MS (ESI) *m/z* 178.1 [$MH^+$]. HRMS (ESI) calculated for $C_{11}H_{16}NO^+$ [$MH^+$] 178.1226, found 178.1226.

### *trans*-[2-(3-Hydroxyphenyl)cyclopropyl]methylamine Hydrochloride (40)

Prepared by the same procedure as described for **33** with **39** as the starting material (45 mg, 70% yield). HPLC purity: 7.5 min, 97.2% (column 1, method E). $^{1}$H NMR (400 MHz, MeOD-$d_4$) δ 6.95 (t, $J$ = 7.7 Hz, 1 H), 6.51-6.45 (m, 3 H), 2.87 (m, 2 H), 1.83 (m, 1 H), 1.28 (m, 1 H), 0.96-0.91 (m, 2 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 158.6, 144.4, 130.5, 118.4, 114.1, 113.8, 45.1, 23.3, 20.9, 15.2. MS (ESI) *m/z* 164.1 [$MH^+$]. HRMS (ESI) calculated for $C_{10}H_{14}NO^+$ [$MH^+$] 164.1070, found 164.1073.

### *trans*-[2-(4-Fluorophenyl)cyclopropyl]methylamine Hydrochloride (41)

Refer to the general procedure for the synthesis of **14a** described above by using 4-fluorostyrene as the starting material. HPLC purity: 12.7 min, 95.4% (column 1, method C). $^{1}$H NMR (300 MHz, MeOD-$d_4$) δ 7.16 (m, 2 H), 7.00 (m, 2 H), 3.01 (d, $J$ = 7.4 Hz, 2 H), 2.04 (m, 1 H), 1.39 (m, 1 H), 1.08 (m, 2 H). $^{13}$C NMR (75 MHz, MeOD-$d_4$) δ 161.8 (d, $^{1}J_{CF}$ = 243.0 Hz), 137.6, 127.8 (d, $^{3}J_{CF}$ = 7.9 Hz), 115.0 (d, $^{2}J_{CF}$ = 21.7 Hz), 43.8, 21.5, 19.7, 13.9. MS (ESI) *m/z* 166.1 [MH$^+$]. HRMS (ESI) calculated for $C_{10}H_{13}NF^+$ [MH$^+$] 166.1032, found 166.1034.

### *trans*-[2-(4-Chlorophenyl)cyclopropyl]methylamine Hydrochloride (42)

Refer to the general procedure for the synthesis of **14a** described above by using 4-chlorostyrene as the starting material. HPLC purity: 7.4 min, 98.2% (column 3, method A). $^{1}$H NMR (300 MHz, MeOD-$d_4$) δ 7.25 (d, $J$ = 8.4 Hz, 2 H), 7.12 (d, $J$ = 8.5 Hz, 2 H), 3.00 (d, $J$ = 7.2 Hz, 2 H), 2.05-1.99 (m, 1 H), 1.44-1.38 (m, 1 H), 1.09 (t, $J$ = 6.9 Hz, 2 H). $^{13}$C NMR (75 MHz, MeOD-$d_4$) δ 141.7, 132.8, 129.6, 128.8, 44.9, 22.8, 21.2, 15.3. MS (ESI) *m/z* 182.1 [MH$^+$]. HRMS (ESI) calculated for $C_{10}H_{13}NCl^+$ [MH$^+$] 182.0731, found 182.0736.

### *trans*-[2-(4-Bromophenyl)cyclopropyl]methylamine Hydrochloride (43)

Refer to the general procedure for the synthesis of **14a** described above by using 4-bromostyrene as the starting material. HPLC purity: 14.3 min, 97.4% (column 1, method C). $^{1}$H NMR (400 MHz, MeOD-$d_4$) δ 7.41 (d, $J$ = 8.5 Hz, 2 H), 7.08 (d, $J$ = 8.4 Hz, 2 H), 3.05-2.96 (m, 2 H), 2.04-1.99 (m, 1 H), 1.44-1.39 (m, 1 H), 1.14-1.07 (m, 2 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 140.6, 131.0, 127.6, 119.1, 21.3, 19.6, 13.7. MS (ESI) *m/z* 225.9 [MH$^+$]. HRMS (ESI) calculated for $C_{10}H_{13}NBr^+$ [MH$^+$] 226.0231, found 226.0233.

### *trans*-[2-(4-Methylphenyl)cyclopropyl]methylamine Hydrochloride (44)

Refer to the general procedure for the synthesis of **14a** described above by using 4-methylstyrene as the starting material. HPLC purity: 6.5 min, 98.8% (column 1, method D). $^{1}$H NMR (400 MHz, MeOD-$d_4$) δ 6.92 (d, $J$ = 7.9 Hz, 2 H), 6.86 (d, $J$ = 7.9 Hz, 2 H), 2.78 (d, $J$ = 7.4 Hz, 2 H), 2.13 (s, 3 H), 1.81-1.76 (m, 1 H), 1.22-1.18 (m, 1 H), 0.90-0.82 (m, 2 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 139.9, 136.6, 130.1, 127.0, 45.4, 23.0, 21.7, 21.1, 15.0. MS (ESI) *m/z* 162.1 [MH$^+$]. HRMS (ESI) calculated for $C_{11}H_{16}N^+$ [MH$^+$] 161.1277, found 162.1272.

### *trans*-[2-(4-Trifluoromethylphenyl)cyclopropyl]methylamine Hydrochloride (45)

Refer to the general procedure for the synthesis of **14a** described above by using 4-trifluorostyrene as the starting material. HPLC purity: 8.4 min, 99.3% (column 3, method A). $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 8.17 (s, 3 H), 7.61 (d, $J$ = 8.0 Hz, 2 H), 7.33 (d, $J$ = 8.0 Hz, 2 H), 2.96 (m, 1 H), 2.75 (m, 1 H), 2.14 (m, 1 H), 1.40 (m, 1 H), 1.12 (t, $J$ = 7.0 Hz, 2 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 147.6, 129.0 (q, $^{2}J_{CF}$ = 32.3 Hz), 127.7, 126.2 (q, $^{3}J_{CF}$ = 3.3 Hz), 125.7 (q, $^{1}J_{CF}$ = 270.8 Hz), 45.1, 23.2, 21.7, 16.1. MS (ESI) *m/z* 216.1 [MH$^+$]. HRMS (ESI) calculated for $C_{11}H_{13}NF_3^+$ [MH$^+$] 216.0995, found 216.0989.

### *trans*-[2-(4-Methoxyphenyl)cyclopropyl]methylamine Hydrochloride (46)

Refer to the general procedure for the synthesis of **14a** described above by using 4-methoxystyrene as the starting material. HPLC purity: 5.7 min, 99.1% (column 3, method A). $^{1}$H NMR (300 MHz, MeOD-$d_4$) δ 7.05 (d, $J$ = 8.3 Hz, 2 H), 6.81 (d, $J$ = 8.3 Hz, 2 H), 3.74 (s, 3 H), 2.98 (d, $J$ = 6.8 Hz, 2 H), 1.95 (m, 1 H), 1.31 (m, 1 H), 1.01 (m, 2 H). $^{13}$C NMR (75 MHz, MeOD-$d_4$) δ 159.7, 134.6, 128.3, 115.0, 55.8, 45.1, 22.7, 20.5, 14.7. MS (ESI) *m/z* 178.1 [MH$^+$]. HRMS (ESI) calculated for $C_{11}H_{16}NO^+$ [MH$^+$] 178.1226, found 178.1226.

### *trans*-[2-(4-Hydroxyphenyl)cyclopropyl]methylamine Hydrochloride (47)

Prepared by the same procedure as described for **33** with **46** as the starting material (38 mg, 72% yield). HPLC purity: 6.1 min, 99.2% (column 3, method B). $^{1}$H NMR (300 MHz, MeOD-$d_4$) δ 6.96 (d, $J$ = 8.4 Hz, 2 H), 6.68 (d, $J$ = 8.4 Hz, 2 H), 2.96 (d, $J$ = 7.3 Hz, 2 H), 1.95-1.89 (m, 1 H), 1.29 (m, 1 H), 1.03-0.92 (m, 2 H). $^{13}$C NMR (75 MHz, MeOD-$d_4$) δ 157.0, 133.3, 128.4, 116.3, 45.2, 22.7, 20.4, 14.5. MS (ESI) *m/z* 164.1 [MH$^+$]. HRMS (ESI) calculated for $C_{10}H_{14}NO^+$ [MH$^+$] 164.1070, found 164.1069.

### *trans*-[2-(2,3-Difluorophenyl)cyclopropyl]methylamine Hydrochloride (48)

Refer to the general procedure for the synthesis of substituted styrene **14a** described above by using 2,3-difluorobenzaldehyde as the starting material. HPLC purity: 8.7 min, 95.1% (column 1, method C). $^{1}$H NMR (400 MHz, MeOD-$d_4$) δ 7.08-7.05 (m, 2 H), 6.87-6.86 (m, 1 H), 3.08-3.02 (m, 2 H), 2.21-2.16 (m, 1 H), 1.58-1.51 (m, 1 H), 1.16 (t, $J$ = 6.9 Hz, 2 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 151.9 (dd, $^{1}J_{CF}$ = 246.0, $^{2}J_{CF}$ = 13.0 Hz), 150.9 (dd, $^{1}J_{CF}$ = 245.4, $^{2}J_{CF}$ = 13.0 Hz), 132.3 (d, $^{2}J_{CF}$ = 10.9 Hz), 125.6 (dd, $^{2}J_{CF}$ = 7.2, $^{3}J_{CF}$ = 4.8 Hz), 123.2 (m), 116.0 (d, $^{2}J_{CF}$ = 17.3 Hz), 44.7, 19.8, 16.7, 14.3. MS (ESI) *m/z* 184.1 [MH$^+$]. HRMS (ESI) calculated for $C_{10}H_{12}NF_2^+$ [MH$^+$] 184.0932, found 184.0931.

### *trans*-[2-(2,4-Difluorophenyl)cyclopropyl]methylamine Hydrochloride (49)

Refer to the general procedure for the synthesis of substituted styrene and **14a** described above by using 2,4-difluorobenzaldehyde as the starting material. HPLC purity: 8.5 min, 95.5% (column 1, method C). $^{1}$H NMR (400 MHz, MeOD-$d_4$) δ 7.11 (dd, $J$ = 15.4, 8.4 Hz, 1 H), 6.93-6.86 (m, 2 H), 3.02 (m, 2 H), 2.11-2.06 (m, 1 H), 1.43-1.40 (m, 1 H), 1.14-1.05 (m, 2 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 163.1 (d, $^{1}J_{CF}$ = 258 Hz), 163.0 (d, $^{1}J_{CF}$ = 258 Hz), 129.7 (dd, $^{3}J_{CF}$ = 9.5, $^{3}J_{CF}$ = 5.4 Hz), 112.3 (dd, $^{2}J_{CF}$ = 21.4, $^{3}J_{CF}$ = 3.7 Hz), 104.5 (dd, $^{2}J_{CF}$ = 26.1, $^{2}J_{CF}$ = 26.1 Hz), 44.8, 19.3, 16.5, 13.5. MS (ESI) *m/z* 184.1 [MH$^+$]. HRMS (ESI) calculated for $C_{10}H_{12}NF_2^+$ [MH$^+$] 184.0932, found 184.0930.

### *trans*-[2-(2,6-Difluorophenyl)cyclopropyl]methylamine Hydrochloride (50)

Refer to the general procedure for the synthesis of substituted styrene **14a** described above by using 2,6-difluorobenzaldehyde as the starting material. HPLC purity: 5.4 min, 96.5% (column 3, method A). $^{1}$H NMR (300 MHz, MeOD-$d_4$) δ 7.31-7.21 (m, 1 H), 6.98-6.89 (m, 2 H), 3.06-3.03 (m, 2 H), 1.93 (m, 1 H), 1.64 (m, 1 H), 1.26 (m, 1 H), 1.13 (m, 1 H). $^{13}$C NMR (75 MHz, MeOD-$d_4$) δ 162.5 (d, $^{1}J_{CF}$ = 246.5 Hz), 128.5 (d, $^{3}J_{CF}$ = 10.7 Hz), 116.5, 111.4 (d, $^{2}J_{CF}$ = 26.1 Hz), 43.9, 17.0, 11.7, 11.6. MS (ESI) *m/z* 184.1 [MH$^+$]. HRMS (ESI) calculated for $C_{10}H_{12}NF_2^+$ [MH$^+$] 184.09323; found 184.09316.

### *trans*-[2-(3,4-Difluorophenyl)cyclopropyl]methylamine Hydrochloride (51)

Refer to the general procedure for the synthesis of substituted styrene and **14a** described above by using 3,4-difluorobenzaldehyde as the starting material. HPLC purity: 8.6 min, 96.4% (column 1, method C). $^{1}$H NMR (400 MHz, MeOD-$d_4$) δ 7.17-7.05 (m, 2 H), 6.98-5.97 (m, 1 H), 2.98 (m, 2 H), 2.10-2.06 (m, 1 H), 1.44 (m, 1 H), 1.12-1.09 (m, 2 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 151.6 (dd, $^{1}J_{CF}$ = 245.7, $^{2}J_{CF}$ = 12.8 Hz), 150.0 (dd, $^{1}J_{CF}$ = 244.1, $^{2}J_{CF}$ = 12.7 Hz), 140.6 (dd, $^{3}J_{CF}$ = 5.9, $^{4}J_{CF}$ = 3.6 Hz), 123.7 (dd, $^{3}J_{CF}$ = 6.1, $^{4}J_{CF}$ = 3.3 Hz), 118.2 (d, $^{2}J_{CF}$ = 17.3 Hz), 116.1 (d, $^{2}J_{CF}$ = 17.9 Hz), 44.9, 22.6, 21.3, 15.3. MS (ESI) *m/z* 184.1 [MH$^+$]. HRMS (ESI) calculated for $C_{10}H_{12}NF_2^+$ [MH$^+$] 184.0932, found 184.0930.

### *trans*-[2-(4-Chloro-2-fluorophenyl)cyclopropyl]methylamine Hydrochloride (52)

Refer to the general procedure for the synthesis of substituted styrene and **14a** described above by using 4-chloro-2-fluorobenzaldehyde as the starting material. HPLC purity: 7.4 min, 94.4%

(column 3, method A). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.13-7.07 (m, 3 H), 3.13-3.00 (m, 2 H), 2.16-2.12 (m, 1 H), 1.57-1.52 (m, 1 H), 1.17-1.11 (m, 2 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 162.8 (d, $^1J_{CF}$ = 247.9 Hz), 133.4 (d, $^3J_{CF}$ = 10.4 Hz), 129.6 (d, $^3J_{CF}$ = 4.9 Hz), 128.6 (d, $^2J_{CF}$ = 14.4 Hz), 125.7 (d, $^4J_{CF}$ = 3.6 Hz), 116.7 (d, $^2J_{CF}$ = 25.9 Hz), 44.7, 19.5, 16.6, 14.1. MS (ESI) *m/z* 200.1 [MH$^+$]. HRMS (ESI) calculated for $C_{10}H_{12}NFCl^+$ [MH$^+$] 200.0637, found 200.0639.

### *trans*-[2-(2-Chloro-4-fluorophenyl)cyclopropyl]methylamine Hydrochloride (53)

Refer to the general procedure for the synthesis of substituted styrene and **14a** described above by using 2-chloro-4-fluorobenzaldehyde as the starting material. HPLC purity: 7.2 min, 98.2% (column 3, method A). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.20-7.17 (m, 2 H), 7.03-6.99 (m, 1 H), 3.27-3.22 (m, 1 H), 2.96-2.91 (m, 1 H), 2.19-2.14 (m, 1 H), 1.44-1.39 (m, 1 H), 1.17-1.07 (m, 2 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 162.6 (d, $^1J_{CF}$ = 247.0 Hz), 137.0 (d, $^3J_{CF}$ = 10.3 Hz), 136.0, 130.3 (d, $^3J_{CF}$ = 8.8 Hz), 117.4 (d, $^2J_{CF}$ = 25.2 Hz), 115.2 (d, $^2J_{CF}$ = 21.2 Hz), 44.8, 21.1, 19.5, 13.8. MS (ESI) *m/z* 200.1 [MH$^+$]. HRMS (ESI) calculated for $C_{10}H_{12}NFCl^+$ [MH$^+$] 200.0637, found 200.0633.

### *trans*-[2-(2,3-Dichlorophenyl)cyclopropyl]methylamine Hydrochloride (54)

Refer to the general procedure for the synthesis of substituted styrene and **14a** described above by using 2,3-dichlorobenzaldehyde as the starting material. HPLC purity: 8.7 min, 98.7% (column 3, method A). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.37 (d, *J* = 6.9 Hz, 1 H), 7.22 (dd, *J* = 7.9, 7.9 Hz, 1 H), 7.10 (d, *J* = 7.8 Hz, 1 H), 3.32-3.25 (m, 1 H), 2.98-2.93 (m, 1 H), 2.29-2.24 (m, 1 H), 1.49-1.45 (m, 1 H), 1.21-1.10 (m, 2 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 142.4, 134.5, 133.9, 129.7, 128.9, 127.2, 44.8, 22.5, 19.8, 14.2. MS (ESI) *m/z* 216.0 [MH$^+$]. HRMS (ESI) calculated for $C_{10}H_{12}NCl_2^+$ [MH$^+$] 216.0341, found 216.0338.

### *trans*-[2-(2,4-Dichlorophenyl)cyclopropyl]methylamine Hydrochloride (55)

Refer to the general procedure for the synthesis of substituted styrene and **14a** described above by using 2,4-dichlorobenzaldehyde as the starting material. HPLC purity: 8.3 min, 93.7% (column 3, method A). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.43 (d, *J* = 1.9 Hz, 1 H), 7.26 (dd, *J* = 8.3, 1.9 Hz, 1 H), 7.12 (d, *J* = 8.4 Hz, 1 H), 3.25-3.20 (m, 1 H), 2.96-2.91 (m, 1 H), 2.22-2.17 (m, 1 H), 1.45-1.40 (m, 1 H), 1.18-1.09 (m, 2 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 138.9, 137.1, 133.8, 130.0, 129.9, 128.5, 44.7, 21.1, 19.7, 14.0. MS (ESI) *m/z* 216.0 [MH$^+$]. HRMS (ESI) calculated for $C_{10}H_{12}NCl_2^+$ [MH$^+$] 216.0341, found 216.0338.

### *trans*-[2-(4-Fluoro-3-methylphenyl)cyclopropyl]methylamine Hydrochloride (56)

Refer to the general procedure for the synthesis of **14a** described above by using 1-fluoro-2-methyl-4-vinylbenzene as the starting material. HPLC purity: 11.69 min, 99.6% (column 1, method E). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.08-6.84 (m, 3 H), 3.07-2.91 (m, 1 H), 2.22 (s, 3 H), 2.04-1.92 (m, 1 H), 1.42-1.28 (m, 1 H), 1.12-0.96 (m, 2 H).$^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 161.0 (d, $^1J_{CF}$ = 241.4 Hz), 136.7 , 128.8, 124.6 (d, $^3J_{CF}$ = 7.9 Hz), 124.2, 114.2 (d, $^2J_{CF}$ = 25.5 Hz), 43.4, 21.1, 19.2, 13.3, 13.0. MS (ESI) *m/z* 163.0 [MH$^+$]. HRMS (ESI) calculated for $C_{11}H_{15}NF^+$ [MH$^+$] 180.1183, found 180.1187.

### *trans*-[2-(2-Chloro-6-methylphenyl)cyclopropyl]methylamine Hydrochloride (57)

Refer to the general procedure for the synthesis of **14a** described above by using 1-chloro-3-methyl-2-vinylbenzene as the starting material. HPLC purity: 13.76 min, 96.7% (column 1, method E). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.24-7.18 (m, 1 H), 7.14-7.09 (m, 2 H), 3.56-3.45 (m, 1H), 2.81-2.70 (m, 1H), 2.44 (s, 3H), 1.86-1.77 (m, 1H), 1.48-1.35 (m, 1 H), 1.27-1.17 (m, 1 H), 1.02-0.92 (m, 1H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 140.8, 135.7, 135.6, 128.7, 127.5,

127.0, 43.6, 19.3, 18.9, 18.8, 14.2. MS (ESI) *m/z* 179.1 [$MH^+$]. HRMS (ESI) calculated for $C_{11}H_{15}NCl^+$ [$MH^+$] 196.0888, found 196.0892.

### *trans*-[2-(2-Bromo-4-methylphenyl)cyclopropyl]methylamine Hydrochloride (58)

Refer to the general procedure for the synthesis of **14a** described above by using 2-bromo-4-methyl-1-vinylbenzene as the starting material. HPLC purity: 16.41 min, 96.8% (column 1, method E). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.41 (s, 1 H), 7.09 (d, $J$ = 7.9 Hz, 1 H), 7.0 (d, $J$ = 7.9 Hz, 1 H), 3.37-3.24 (m, 1 H), 2.92-2.81 (m, 1 H), 2.29 (s, 3 H), 2.17-2.06 (m, 1 H), 1.40-1.26 (m, 1 H), 1.13-1.02 (m, 2H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 136.5, 135.1, 130.9, 126.5, 125.3, 123.6, 41.9, 20.9, 17.6, 16.6, 10.8. MS (ESI) *m/z* 224.0 [$MH^+$]. HRMS (ESI) calculated for $C_{11}H_{15}NBr^+$ [$MH^+$] 240.0382, found 240.0388.

### *trans*-[2-(2,3-Dimethylphenyl)cyclopropyl]methylamine Hydrochloride (59)

Refer to the general procedure for the synthesis of **14a** described above by using 1,2-dimethyl-3-vinylbenzene as the starting material. HPLC purity: 12.92 min, 98.4% (column 1, method E). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.03-6.80 (m, 3 H), 3.27-3.15 (m, 1H), 2.97-2.83 (m, 1 H), 2.33 (s, 3H), 2.27 (s, 3 H), 2.08-1.94 (m, 1H), 1.46-1.32 (m, 1 H), 1.11-1.0 (m, 1H), 0.95-0.88 (m, 1 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 138.4, 136.0, 135.7, 127.7, 125.0, 123.9, 43.6, 20.8, 19.1, 17.1, 14.0, 12.2. MS (ESI) *m/z* 159.1 [$MH^+$]. HRMS (ESI) calculated for $C_{12}H_{18}N^+$ [$MH^+$] 176.1434, found 176.1436.

### *trans*-[2-(3,4-Dimethylphenyl)cyclopropyl]methylamine Hydrochloride (60)

Refer to the general procedure for the synthesis of **14a** described above by using 1,2-dimethyl-4-vinylbenzene as the starting material. HPLC purity: 13.03 min, 99.2% (column 1, method E). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.0 (d, $J$ = 7.8 Hz, 1 H), 6.89 (s, 1 H), 6.82 (d, $J$ = 7.8 Hz, 1 H), 3.02 (m, 2 H), 2.25 (s, 3 H), 2.21 (s, 3 H), 1.97-1.89 (m, 1 H), 1.40-1.29 (m, 1H), 1.08-0.95 (m, 2 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 138.4, 136.0, 133.7, 129.11, 126.8, 122.8, 43.5, 21.4, 19.1, 18.3, 17.9, 13.2. MS (ESI) *m/z* 159.1[$MH^+$]. HRMS (ESI) calculated for $C_{12}H_{18}N^+$ [$MH^+$] 176.1434, found 176.1433.

### *trans*-[2-(6-Chloro-2-fluoro-3-methylphenyl)cyclopropyl]methylamine Hydrochloride (61)

Refer to the general procedure for the synthesis of **14a** described above by using 1-chloro-3-fluoro-4-methyl-2-vinylbenzene (1g, 5.8 mmol) as the starting material. HPLC purity: 13.03 min, 95.6% (column 1, method D). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.16-7.04 (m, 2 H), 3.22-3.11 (m, 1 H), 3.0-2.91 (m, 1 H), 2.22 (s, 3 H), 1.88-181 (m, 1 H), 1.56-1.45 (m, 1 H), 1.21-1.11 (m, 2 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 161.6 (d, $^1J_{CF}$ = 245.4 Hz), 133.5, 129.8, 125.8 (d, $^2J_{CF}$ = 16.4 Hz), 125.2, 123.8, 43.5, 17.5, 15.2, 12.9, 12.5. MS (ESI) *m/z* 214.1 [$MH^+$]. HRMS (ESI) calculated for $C_{11}H_{14}NFCl^+$ [$MH^+$] 214.0793, found 214.0786.

### *trans*-[2-(2-Bromophenyl)cyclopropylmethyl]carbamic Acid *tert*-Butyl Ester (62)

To a solution of **29** (1.63 g, 6.21 mmol) and $Boc_2O$ (1.35 g, 8.07 mmol) in $Et_2O$ (75 mL) was added 10% aqueous NaOH (14.9 mL, 37.2 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min and then at rt for 7 h. To the resulting mixture were added crushed ice and $Et_2O$. The organic layer was further washed with water (×1), dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane/EtOAc 10:1) to afford the title compounds as colorless oils (1.71 g, 84% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, $J$ = 8.5 Hz, 2 H), 7.40 (d, $J$ = 8.5 Hz, 2 H), 7.30-7.19 (m, 3 H), 7.00 (d, $J$ = 7.2 H, 1 Hz), 4.45 (br s, 1 H), 3.05-2.95 (m, 2 H), 1.76 (m, 1 H), 1.46 (s, 9 H), 1.26 (m, 1 H), 0.94 (m, 1 H), 0.77 (m, 1 H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 156.2, 141.6, 140.5, 139.6, 133.4, 131.2, 130.0, 128.8, 128.2, 126.1, 125.3, 79.6, 44.9, 28.8, 23.3, 20.6, 14.3.

### *trans*-[2-(3-Bromophenyl)cyclopropylmethyl]carbamic Acid *tert*-Butyl Ester (63)

Prepared by the same procedure as described for **62** (1.59 g, 99% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, $J$ = 6.8 Hz, 1 H), 7.20 (s, 1 H), 7.12 (t, $J$ = 7.8 Hz, 1 H), 6.99 (d, $J$ = 7.6 Hz, 1 H), 4.70 (br s, 1 H), 3.22-3.11 (m, 2 H), 1.80-1.76 (m, 1 H), 1.47 (s, 9 H), 1.33-1.27 (m, 1 H), 0.94 (t, $J$ = 6.9 Hz, 2 H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 156.5, 145.5, 130.2, 129.3, 129.1, 124.9, 122.9, 28.8, 23.8, 22.0, 14.8.

### *trans*-[2-(4-Bromophenyl)cyclopropylmethyl]carbamic Acid *tert*-Butyl Ester (64)

Prepared by the same procedure as described for **62** (356 mg, 82% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, $J$ = 8.3 Hz, 2 H), 6.93 (d, $J$ = 8.3 Hz, 2 H), 4.69 (br s, 1 H), 3.18-3.11 (m, 2 H), 1.79-1.76 (m, 2 H), 1.47 (s, 9 H), 1.28 (m, 2 H), 0.94-0.90 (m, 2 H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 156.0, 142.0, 131.7, 128.0, 127.0, 79.9, 45.0, 28.8, 23.7, 21.9, 14.8.

### *trans*-[2-(4'-Fluorobiphenyl-2-yl)cyclopropyl]methylamine Hydrochloride (66). Step A

**62** (30 mg, 0.092 mmol), $Pd(PPh_3)_4$ (10.4 mg, 0.009 mmol), and 4-fluorophenylboronic acid (32.2 mg, 0.23 mmol) were dissolved in dimethoxyethane (DME) (4 mL), and the mixture was degassed for 1 min and stirred for 10 min at rt. To the mixture was added 2 M aqueous $K_2CO_3$ (0.115 mL, 0.23 mmol). The mixture was degassed again for 1 min, and stirred at 85 °C overnight. The resulting mixture was cooled to ambient temperature and poured into a mixture of 0.1 N HCl/EtOAc (15 mL/15 mL). After partition, the organic layer was washed with water, filtered, and concentrated. The residue was purified by preparative TLC (hexane/EtOAc 4:1) to afford the title compound as a colorless oil (31 mg, 99% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.38 (dd, $J$ = 8.6, 5.5 Hz, 2 H), 7.32-7.12 (m, 5 H), 7.01 (d, $J$ = 7.7 Hz, 1 H), 4.38 (br s, 1 H), 3.07 (m, 1 H), 2.92 (m, 1 H), 1.77 (m, 1 H), 1.46 (s, 9 H), 1.20 (m, 1 H), 0.95 (m, 1 H), 0.76 (m, 1 H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 162.4 (d, $^1J_{CF}$ = 246 Hz), 156.2, 142.0, 139.7, 138.0 (d, $^4J_{CF}$ = 3.3 Hz), 131.4 (d, $^3J_{CF}$ = 7.9 Hz), 130.2, 128.1, 126.1, 125.6, 115.6 (d, $^2J_{CF}$ = 21.3 Hz), 79.6, 45.0, 28.8, 23.1, 20.8, 14.0.

### Step B

To a solution of *trans*-[2-(4'-fluorobiphenyl-4-yl)cyclopropylmethyl]carbamic acid *tert*-butyl ester (30 mg) in $CH_2Cl_2$ (1 mL) was added TFA (0.1 mL) at 0 °C. After standing at 0 °C for 30 min and at rt for 1 h, the mixture was concentrated. The residue was dissolved in $CH_2Cl_2$ (1 mL), and 1 M HCl in $Et_2O$ (0.3 mL) was added to the solution. The mixture was let stand at 0 °C for 30 min, and concentrated. The resulting white solid was purified by recrystallization from ethanol/$Et_2O$ to afford the title compound as a white solid (16 mg, 66% yield). HPLC purity: 7.8 min, 97.7% (column 3, method A). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.43-7.39 (m, 2 H), 7.33-7.24 (m, 2 H), 7.22-7.13 (m, 4 H), 2.96 (m, 1 H), 2.54 (m, 1 H), 1.96 (m, 1 H), 1.31 (m, 1 H), 1.00 (m, 1 H), 0.93 (m, 1 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 163.6 (d, $^1J_{CF}$ = 245 Hz), 143.3, 139.6, 139.3 (d, $^4J_{CF}$ = 3.4 Hz), 132.4 (d, $^3J_{CF}$ = 8.0 Hz), 130.9, 129.0, 127.5, 127.2, 116.1 (d, $^2J_{CF}$ = 21.5 Hz), 44.8, 22.3, 20.3, 15.2. MS (ESI) *m/z* 242.2 [$MH^+$]. HRMS (ESI) calculated for $C_{16}H_{17}NF^+$ [$MH^+$] 242.13395, found 242.13373.

### *trans*-*C*-[2-(2-Benzofuran-2-ylphenyl)cyclopropyl]methylamine Hydrochloride (67)

Prepared by the same procedure as described for **66** with 2-benzofuranboronic acid (37.3 mg, 0.23 mmol) as the starting material (22 mg, 111% and 76% yields). HPLC purity: 10.5 min, 98.9% (column 3, method A). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.77 (d, $J$ = 7.2 Hz, 1 H), 7.66 (d, $J$ = 7.5 H, 1 Hz), 7.55 (d, $J$ = 8.0 Hz, 1 H), 7.39-7.25 (m, 5 H), 7.14 (s, 1 H), 3.21 (m, 1 H), 2.84 (m, 1 H), 2.42 (m, 1 H), 1.50 (m, 1 H), 1.15 (m, 1 H), 1.05 (m, 1 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 157.0, 156.2, 139.9, 132.5, 130.6, 130.2, 129.8, 128.7, 127.9, 125.7, 124.2, 122.3, 112.0, 106.8, 45.1, 23.1, 19.8, 14.8. MS (ESI) *m/z* 264.1 [$MH^+$]. HRMS (ESI) calculated for $C_{18}H_{18}NO^+$ [$MH^+$] 264.13829, found 264.13814.

### *trans*-[2-(4'-Fluorobiphenyl-3-yl)cyclopropyl]methylamine Hydrochloride (68)

Prepared by the same procedure as described for **66** with **63** (30 mg, 0.092 mmol) and 4-fluorophenylboronic acid (32.2 mg, 0.23 mmol) as the starting materials (18 mg, 115% and 63% yields). HPLC purity: 18.2 min, 97.3% (column 3, method A). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.63-7.60 (m, 1 H), 7.40-7.33 (m, 3 H), 7.17 (t, $J$ = 8.8 Hz, 1 H), 7.11 (d, $J$ = 7.5 Hz, 1 H), 3.09-3.00 (m, 2 H), 2.14-2.09 (m, 1 H), 1.52-1.47 (m, 1 H), 1.21-1.16 (m, 1 H), 1.14-1.09 (m, 1 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 164.0 (d, $^1J_{CF}$ = 245 Hz), 143.5, 141.7, 138.8 (d, $^4J_{CF}$ = 3.2 Hz), 130.2, 130.0 (d, $^3J_{CF}$ = 8.1 Hz), 126.0, 125.9, 125.8, 116.6 (d, $^2J_{CF}$ = 21.7 Hz), 45.0, 23.4, 21.1, 15.2. MS (ESI) *m/z* 242.1 [MH$^+$]. HRMS (ESI) calculated for $C_{16}H_{17}NF^+$ [MH$^+$] 242.13395, found 242.13373.

### *trans*-[2-(4'-Chlorobiphenyl-3-yl)cyclopropyl]methylamine Hydrochloride (69)

Prepared by the same procedure as described for **68** with 4-chlorophenylboronic acid (36.0 mg, 0.23 mmol) as the starting material (17 mg, 82% and 83% yields). HPLC purity: 17.9 min, 97.7% (column 1, method C). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.58 (d, $J$ = 8.4 Hz, 2 H), 7.43 (d, $J$ = 8.1 Hz, 2 H), 7.40-7.33 (m, 3 H), 7.12 (d, $J$ = 7.5 Hz, 2 H), 3.02 (m, 2 H), 2.09 (m, 2 H), 1.46 (m, 1 H), 1.18 (m, 1 H), 1.10 (m, 1 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 143.6, 141.5, 141.2, 134.6, 130.3, 130.1, 129.7, 126.3, 126.0, 125.9, 45.0, 23.4, 21.1, 15.2. MS (ESI) *m/z* 258.2 [MH$^+$]. HRMS (ESI) calculated for $C_{16}H_{17}NCl^+$ [MH$^+$] 258.10440, found 258.10422.

### *trans*-[2-(4'-Trifluoromethybiphenyl-3-yl)cyclopropyl]methylamine Hydrochloride (70)

Prepared by the same procedure as described for **68** with 4-trifluoromethylphenylboronic acid (43.7 mg, 0.23 mmol) as the starting material (15 mg, 66% and 81% yields). HPLC purity: 17.6 min, 95.6% (column 1, method C). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.81 (d, $J$ = 8.2 Hz, 2 H), 7.75 (d, $J$ = 8.4 Hz, 2 H), 7.51-7.47 (m, 2 H), 7.41 (t, $J$ = 7.7 Hz, 1 H), 7.19 (d, $J$ = 7.7 Hz, 1 H), 3.07-3.00 (m, 2 H), 2.16-2.11 (m, 1 H), 1.52-1.48 (m, 1 H), 1.24-1.20 (m, 1 H), 1.16-1.11 (m, 1 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 144.4, 141.8, 139.2, 128.4, 126.8, 125.0, 124.9, 124.9, 124.4, 124.3, 43.1, 21.5, 19.2, 13.3. MS (ESI) *m/z* 292.2 [MH$^+$]. HRMS (ESI) calculated for $C_{17}H_{17}NF_3^+$ [MH$^+$] 292.13076, found 292.13050.

### *trans*-[2-(4'-Cyanobiphenyl-3-yl)cyclopropyl]methylamine Hydrochloride (71)

Prepared by the same procedure as described for **68** with 4-cyanophenylboronic acid (33.8 mg, 0.23 mmol) as the starting material (20 mg, 94% and 75% yields). HPLC purity: 13.6 min, 97.9% (column 3, method A). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.81 (s, 4 H), 7.49 (m, 1 H), 7.48 (s, 1 H), 7.41 (t, $J$ = 7.6 Hz, 1 H), 7.21 (d, $J$ = 7.6 Hz, 1 H), 3.10-3.01 (m, 2 H), 2.17-2.12 (m, 1 H), 1.55-1.47 (m, 1 H), 1.24-1.19 (m, 1 H), 1.16-1.11 (m, 1 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 147.2, 144.0, 140.7, 133.9, 130.5, 129.1, 127.3, 126.3, 126.2, 119.9, 112.0, 45.0, 23.4, 21.2, 15.3. MS (ESI) *m/z* 249.2 [MH$^+$]. HRMS (ESI) calculated for $C_{17}H_{17}N_2^+$ [MH$^+$] 249.13863, found 249.13861.

### *trans*-*C*-[2-(3-Benzofuran-2-ylphenyl)cyclopropyl]methylamine Hydrochloride (72)

Prepared by the same procedure as described for **68** with 2-benzofuranboronic acid (37.3 mg, 0.23 mmol) as the starting material (21 mg, 101% and 85% yields). HPLC purity: 12.5 min, 98.4% (column 3, method A). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.71 (d, $J$ = 6.5 Hz, 2 H), 7.61 (d, $J$ = 7.5 Hz, 1 H), 7.52 (d, $J$ = 7.8 Hz, 1 H), 7.37 (t, $J$ = 8.0 Hz, 1 H), 7.29 (d, $J$ = 7.3 Hz, 1 H), 7.23 (t, $J$ = 7.6 Hz, 1 H), 7.19 (br s, 1 H), 7.15 (d, $J$ = 7.8 Hz, 1 H), 3.05 (m, 2 H), 2.13 (m, 1 H), 1.51 (m, 1 H), 1.21 (m, 1 H), 1.14 (m, 1 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 157.2, 156.4, 143.6, 132.0, 130.7, 130.2, 127.4, 125.7, 124.3, 123.8, 123.7, 122.2, 112.0, 102.7, 79.3, 45.0, 23.4, 21.1, 15.2. MS (ESI) *m/z* 264.2 [MH$^+$]. HRMS (ESI) calculated for $C_{18}H_{18}NO^+$ [MH$^+$] 264.13829, found 264.13811.

### *trans*-[2-(4'-Fluorobiphenyl-4-yl)cyclopropyl]methylamine Hydrochloride (73)

Prepared by the same procedure as described for **66** with **64** (34 mg, 0.104 mmol) and 4-fluorophenylboronic acid (36.5 mg, 0.261 mmol) as the starting materials (14 mg, 62% and 86% yields). HPLC purity: 18.0 min, 96.4% (column 1, method C). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.70 (m, 2 H), 7.51 (d, J = 8.1 Hz, 2 H), 7.22 (d, J = 8.1 Hz, 2 H), 7.16 (m, 2 H), 3.03 (d, J = 7.4 Hz, 2 H), 2.06 (m, 1 H), 1.49 (m, 1 H), 1.13 (m, 2 H) (ppm). $^{13}$C NMR δ 157.0, 140.9, 138.2, 137.5, 128.6, 128.5, 126.9, 126.5, 115.6, 115.3, 43.9, 21.9, 20.0, 14.1. MS (ESI) *m/z* 242.1 [$MH^+$]. HRMS (ESI) calculated for $C_{16}H_{17}NF^+$ [$MH^+$] 242.1345, found 242.1344.

### *trans*-[2-(4-Furan-2-ylphenyl)cyclopropyl]methylamine Hydrochloride (74)

Prepared by the same procedure as described for **66** with **64** (30 mg, 0.092 mmol) and 2-furanboronic acid (25.7 mg, 0.23 mmol) as the starting materials (18 mg, 98% and 82% yields). HPLC purity: 13.6 min, 96.5% (column 3, method A). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.60 (d, *J* = 8.2 Hz, 2 H), 7.53 (s, 1 H), 7.17 (d, *J* = 8.1 Hz, 2 H), 6.70 (m, 1 H), 6.50 (s, 1 H), 3.02 (d, *J* = 7.4 Hz, 2 H), 2.07-2.01 (m, 1 H), 1.44 (m, 1 H), 1.18-1.08 (m, 2 H). $^{13}$C NMR δ 154.2, 142.1, 140.9, 129.3, 126.3, 123.8, 111.7, 104.6, 43.8, 22.0, 20.0, 14.1. MS (ESI) *m/z* 214.1 [$MH^+$]. HRMS (ESI) calculated for $C_{14}H_{16}NO^+$ [$MH^+$] 214.1232, found 214.1228.

### *trans*-[2-(2-Aminophenyl)cyclopropylmethyl]carbamic Acid *tert*-Butyl Ester (75). Step A

To a mixture of $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), BINAP (19.1 mg, 0.031 mmol), and **62** (50 mg, 0.153 mmol) in toluene (3 mL) were added benzophenone imine (0.051 mL, 0.306 mmol) and $Cs_2CO_3$ (125 mg, 0.383 mmol) under nitrogen. The resulting mixture was stirred at 100 °C overnight, diluted with EtOAc, filtered, and concentrated. The residue was purified by preparative TLC (hexane/EtOAc 3:1) to afford the corresponding diphenyl ketimine compound as a colorless oil (51.9 mg, a mixture of starting material and the product). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 6.9 Hz, 2 H), 7.46 (m, 3 H), 7.28 (m, 3 H), 7.16 (m ,2 H), 6.86 (m, 2 H), 6.79 (m, 1 H), 6.39 (m, 1 H), 4.88 (br s, 1 H), 3.34-3.23 (m, 2 H), 1.87 (m, 1 H), 1.45 (s, 9 H), 1.28 (m, 1 H), 0.93 (m, 1 H), 0.85 (m, 1 H). $^{13}$C NMR (75MHz, $CDCl_3$) δ 168.3, 156.2, 150.9, 139.9, 136.7, 131.1, 129.8, 129.5, 129.1, 128.7, 128.3, 127.8, 126.1, 123.8, 119.8, 79.4, 45.4, 28.9, 22.9, 18.8, 12.9.

### Step B

To a solution of the ketimine adduct (35 mg, 0.188 mmol) in MeOH (0.8 mL) at rt were added NaOAc (16.2 mg, 0.197 mmol) and $NH_2OH{\cdot}HCl$ (10.3 mg, 0.148 mmol). The mixture was stirred at rt for 2 h, diluted with $CH_2Cl_2$, and purified by preparative TLC (hexane/EtOAc 2:1) to afford the title compound as a colorless oil (20.5 mg, 95% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.05 (m, 1 H), 6.98 (d, *J* = 7.3 Hz, 1 H), 6.69 (m, 2 H), 4.89 (br s, 1 H), 3.42-3.36 (m, 1 H), 3.16-3.11 (m, 1 H), 1.65 (m, 1 H), 1.48 (s, 9 H), 1.14 (m, 1 H), 0.94 (m, 1 H), 0.80 (m, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 156.3, 146.3, 127.8, 127.2, 125.5, 117.9, 114.6, 79.4, 44.2, 28.4, 20.2, 14.1, 9.7.

### *trans*-[2-(3-Aminophenyl)cyclopropylmethyl]carbamic Acid *tert*-Butyl Ester (76)

Prepared by the same procedure as described for **75** with **63** (120 mg, 0.368 mmol) as the starting material (33 mg, 67% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.07 (t, *J* = 7.8 Hz, 1 H), 6.56 (dd, *J* = 1.4Hz, 7.9 Hz, 1 H), 6.52 (d, *J* = 7.6 Hz, 1 H), 6.46 (s, 1 H), 4.70 (br s, 1 H), 3.22 (m, 1 H), 3.10 (m, 1 H), 1.73 (m, 1 H), 1.47 (s, 9 H), 1.28 (m, 1 H), 0.91 (m, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 155.5, 144.9, 143.6, 128.9, 116.4, 112.7, 44.4, 28.0, 22.4, 21.5, 13.8.

### *trans*-[3-(2-Aminomethylcyclopropyl)phenyl]benzylamine Hydrochloride (78). Step A

**76** (15 mg, 0.0572 mmol) was dissolved in MeOH (0.5 mL) containing benzaldehyde (0.0052 mL, 0.0512 mmol) at 0 °C. To the mixture was added $NaCNBH_3$ (4.3 mg, 0.0686 mmol). The resulting mixture was stirred at 0 °C for 1 h and at rt overnight and directly purified by preparative TLC (hexane/EtOAc 1:1) to afford the title compound as a colorless oil (9.9 mg, 49% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.38-7.35 (m, 4 H), 7.32-7.28 (m, 1 H), 7.08 (t, *J* = 7.8 Hz, 1 H), 6.47-6.42 (m, 2 H), 6.37 (s, 1 H), 4.68 (br s, 1 H), 4.33 (s, 2 H), 4.07 (br s, 1 H), 3.26-3.23 (m, 1 H), 3.12-3.05 (m, 1 H), 1.72 (m, 1 H), 1.47 (s, 9 H), 1.28 (m, 1 H), 0.89 (m, 2 H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 155.8, 148.2, 143.7, 139.4, 129.2, 128.6, 127.5, 127.2, 114.9, 110.4, 110.2, 79.1, 48.3, 44.8, 28.4, 22.7, 22.1, 14.2.

### Step B

Prepared by the same deprotection procedure as described for **66** (5.6 mg, 76% yield). HPLC purity: 4.4 min, 94.4% (column 3, method A). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.45-7.41 (m, 6 H), 7.28 (d, *J* = 8.0 Hz, 1 H), 7.20-7.18 (m, 2 H), 4.60 (s, 2 H), 3.03 (m, 2 H), 2.11 (m, 1 H), 1.48 (m, 1 H), 1.17-1.12 (m, 2 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 146.0, 132.4, 131.6, 131.4, 130.9, 130.3, 128.3, 121.7, 121.5, 56.8, 44.7, 23.1, 21.6, 15.6. MS (ESI) *m/z* 253.2 [$MH^+$]. HRMS (ESI) calculated for $C_{17}H_{21}N_2^+$ [$MH^+$] 253.16993, found 253.16979.

### *trans*-*N*-[2-(2-Aminomethylcyclopropyl)phenyl]acetamide Hydrochloride (80). Step A

**75** (7.0 mg, 0.0267 mmol) and DMAP (3.3 mg, 0.0267 mmol) in $CH_2Cl_2$ (0.3 mL) was added acetic anhydride (0.004 mL, 0.0423 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h and rt overnight, and directly purified by preparative TLC (hexane/EtOAc 1:1) to afford the title compound as a colorless oil (7.2 mg, 89% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.63 (br. s, 1 H), 8.09 (d, *J* = 7.9 Hz, 1 H), 7.21 (t, *J* = 7.6 Hz, 1 H), 7.06-6.96 (m, 2 H), 4.89 (br s, 1 H), 3.58 (m, 1 H), 3.05 (m, 1 H), 1.84 (m, 1 H), 1.46 (s, 9 H), 1.27 (m, 1 H), 1.24 (m, 1 H), 0.83 (m, 1 H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 169.7, 157.4, 138.0, 131.5, 127.1, 126.5, 124.4, 122.5, 80.4, 43.7, 30.1, 28.8, 24.8, 22.4, 18.1.

### Step B

Prepared by the same deprotection procedure as described for **66** (3.6 mg, 77% yield). HPLC purity: 4.8 min, 97.0% (column 3, method A). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.22-7.20 (m, 3 H), 6.99 ((m, 3 H), 3.08 (m, 1 H), 2.94 (m, 1 H), 1.96 (m, 1 H), 1.32 (m, 1 H), 1.16 (m, 1 H), 1.08 (m, 1 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 172.6, 138.1, 137.2, 128.1, 127.6, 127.2, 126.0, 45.0, 23.1, 21.2, 19.8, 14.0. MS (ESI) *m/z* 205.2 [$MH^+$]. HRMS (ESI) calculated for $C_{12}H_{17}N_2O^+$ [$MH^+$] 205.13354, found 205.13345.

### *trans*-*N*-[2-(2-Aminomethylcyclopropyl)phenyl]benzamide Hydrochloride (81)

Prepared by the same procedure as described for **80** with **75** (5.8 mg, 0.0221 mmol) and benzoyl chloride (0.0039 mL, 0.0332 mmol) as the starting materials (3.5 mg, 100% and 53% yields). HPLC purity: 6.48 min, 99.2% (column 3, method A). $^1$H NMR (300 MHz, MeOD-$d_4$) δ 8.05 (d, *J* = 7.3 Hz, 2 H), 7.64 (t, *J* = 7.3 Hz, 1 H), 7.56 (t, *J* = 7.4 Hz, 2 H), 7.33-7.27 (m, 3 H), 7.07 (m, 1 H), 3.01 (m, 1 H), 2.86 (m, 1 H), 2.01 (m, 1 H), 1.38 (m, 1 H), 1.21 (m, 1 H), 1.05 (m, 1 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 169.4, 138.7, 137.5, 135.3, 133.3, 129.8, 128.8, 128.4, 127.7, 127.6, 126.3, 45.0, 21.2, 20.2, 13.7. MS (ESI) *m/z* 267.1 [$MH^+$]. HRMS (ESI) calculated for $C_{17}H_{19}N_2O^+$ [$MH^+$] 267.14919, found 267.14900.

### *trans*-1-[2-(2-Aminomethylcyclopropyl)phenyl]-3-(4-chlorophenyl)urea Hydrochloride (82). Step A

To a solution of **75** (30.0 mg, 0.114 mmol) in THF (5 mL) were added DMAP (2.8 mg, 0.023 mmol) and 4-chlorophenyl isocyanate (0.022 mL, 0.172 mmol) at rt. The mixture was stirred at 50 °C overnight and directly purified by preparative TLC (hexane/EtOAc 1:1) to afford the title compound as a colorless oil (29.1 mg, 61% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.42 (br s, 1 H), 8.32 (d, *J* = 8.2 Hz, 1 H), 8.08 (br s, 1 H), 7.53 (d, *J* = 8.8 Hz, 2 H), 7.29-7.22 (m, 3 H), 7.04 (t, *J* = 6.9 Hz, 1 H), 6.90 (d, *J* = 6.9 Hz, 1 H), 6.95 (t, *J* = 7.2 Hz, 1 H), 4.98 (br t, *J* = 6.2 Hz, 1 H), 3.93 (m, 1 H), 3.23 (m, 1 H), 1.61 (m, 1 H), 1.50 (s, 9 H), 1.19 (m, 1 H), 0.83-0.72 (m, 2 H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 158.5, 153.3, 139.7, 138.8, 129.2, 128.9, 127.6, 127.4, 127.1, 122.3, 120.2, 119.3, 81.5, 40.6, 28.8, 21.2, 16.2, 6.5.

### Step B

Prepared by the same deprotection procedure as described for **66** (18 mg, 79% yield). HPLC purity: 8.1 min, 99.5% (column 3, method A). $^1$H NMR (300 MHz, MeOD-$d_4$) δ 7.48 (d, *J* = 8.8 Hz, 2 H), 7.29 (d, *J* = 8.9 Hz, 2 H), 7.24-7.12 (m, 2 H), 7.03 (d, *J* = 7.6 Hz, 1 H), 3.11-2.95 (m, 2 H), 2.12-2.05 (m, 1 H), 1.44-1.38 (m, 1 H), 1.14-1.09 (m, 2 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 155.1, 138.5, 137.1, 135.0, 128.8, 127.6, 126.7, 125.6, 125.5, 124.8, 120.5, 44.0, 19.3, 18.7, 13.0. MS (ESI) *m/z* 316.2 [$MH^+$]. HRMS (ESI) calculated for $C_{17}H_{19}N_3OCl^+$ [$MH^+$] 316.12112, found 316.12080.

### *trans*-*N*-[3-(2-Aminomethylcyclopropyl)phenyl]acetamide Hydrochloride (83)

Prepared by the same procedure as described for **80** with **75** (5.8 mg, 0.0221 mmol) and benzoyl chloride (0.0039 mL, 0.0332 mmol) as the starting materials (3.3 mg, 94% and 60% yields). $^1$H NMR (300 MHz, MeOD-$d_4$) δ 7.47 (s, 1 H), 7.25-7.19 (m, 2 H), 6.90 (d, *J* = 6.4 Hz, 1 H), 3.01 (d, *J* = 7.4 Hz, 2 H), 2.13 (s, 3 H), 2.01 (m, 1 H), 1.42 (m, 1 H), 1.10 (m, 2 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 171.9, 143.6, 140.2, 130.0, 123.0, 119.0, 118.9, 45.0, 24.0, 23.4, 21.1, 15.2. MS (ESI) *m/z* 205.2 [$MH^+$]. HRMS (ESI) calculated for $C_{12}H_{17}N_2O^+$ [$MH^+$] 205.13354, found 205.13341.

### *trans*-*N*-[3-(2-Aminomethylcyclopropyl)phenyl]benzamide Hydrochloride (84)

Prepared by the same procedure as described for **80** with **76** (7.0 mg, 0.0234 mmol) and benzoyl chloride (0.0047 mL, 0.040 mmol) as the starting materials (4.3 mg, 97% and 74% yields). HPLC purity: 4.8 min, 99.6% (column 3, method A). $^1$H NMR (300 MHz, MeOD-$d_4$) δ 7.94 (d, *J* = 7.2 Hz, 2 H), 7.62-7.51 (m, 4 H), 7.13-7.09 (m, 2 H), 7.41 (d, *J* = 8.1 Hz, 1 H), 7.28 (t, *J* = 7.8 Hz, 1 H), 6.97 (d, *J* = 7.6 Hz, 1 H), 3.02 (d, *J* = 7.4 Hz, 2 H), 2.06 (m, 1 H), 1.46 (m, 1 H), 1.17 (m, 1 H), 1.10 (m, 1 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 169.1, 143.6, 140.1, 136.4, 133.1, 130.0, 129.8, 128.7, 123.6, 120.2, 120.0, 45.0, 23.4, 21.1, 15.2. MS (ESI) *m/z* 267.1 [$MH^+$]. HRMS (ESI) calculated for $C_{17}H_{19}N_2O^+$ [$MH^+$] 267.14919, found 267.14899.

### General Procedure for *t*-Boc Deprotection

The protected amine was dissolved in a 2 N HCl solution in diethyl ether, and the reaction mixture was stirred at ambient temperature for 12-24 h. A white precipitate formed after several minutes to hours. The mixture was stirred until the reaction was complete by TLC and worked up as described below.

### *trans*-{2-[2-(6-Hydroxyhex-1-ynyl)phenyl]cyclopropyl}methylamine Hydrochloride (86). Step A

**62** (50 mg, 0.153 mmol), $Pd(PPh_3)_2Cl_2$ (8.6 mg, 0.012 mmol), $PPh_3$ (6.4 mg, 0.024 mmol), CuI (4.7 mg, 0.024 mmol), and 5-hexyn-1-ol (0.037 ml, 0.337 mmol) were dissolved in

triethylamine (TEA) (1.4 mL), and the mixture was degassed for 1 min and stirred at 85 °C overnight. The resulting mixture was cooled to ambient temperature and poured into a mixture of 0.1 N HCl/EtOAc (3 mL/3 mL). After partition, the organic layer was washed with water, filtered, and concentrated. The residue was purified by silica gel chromatography (hexane/$Et_2O$ 4:1) to afford the title compound as colorless oil (30 mg, 57% yield).

### Step B

Refer to the general procedure for *t*-Boc deprotection described above. The mixture was concentrated, and washed with ethanol/$Et_2O$ to afford the title compound as a brown oil (22 mg, 90% yield). HPLC purity: 7.9 min, 94.7% (column 3, method A). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.24-7.08 (m, 3 H), 6.94 (d, $J$ = 7.6 Hz, 1 H), 5.74 (t, $J$ = 7.1 Hz, 1 H), 3.52 (t, $J$ = 6.1 Hz, 2 H), 2.62 (m, 1 H), 2.38-2.33 (m, 1 H), 2.09-2.06 (m, 1 H), 1.57-1.50 (m, 4 H), 1.29 (m, 1 H), 1.02-0.95 (m, 3 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 143.3, 140.8, 132.3, 130.8, 127.5, 126.7, 90.5, 81.2, 62.8, 45.1, 33.4, 30.0, 26.1, 21.7, 20.3, 12.3. MS (ESI) *m/z* 244.2 [$MH^+$]. HRMS (ESI) calculated for $C_{16}H_{22}NO^+$ [$MH^+$] 244.1696, found 244.1688.

### *trans*-[2-(3-Ethynylphenyl)cyclopropyl]methylamine Hydrochloride (87)

$Pd(PhCN)_2Cl_2$ (1.8 mg, 0.0045 mmol) and CuI (0.6 mg, 0.003 mmol) were added to a dry vial, which was then sparged with argon and charged with dioxane (0.3 mL). P(*t*-Bu)$_3$ (1.0 M in dioxane, 9.2 μL, 0.009 mmol), HN(*i*-Pr)$_2$ (13.3 μL, 0.184 mol), **63** (50 mg, 0.153 mmol), and ethynyltrimethylsilane (26 μL, 0.184 mmol) were added to the stirred reaction mixture. During the reaction, precipitation of [$H_2N$(*i*-Pr)$_2$]Br was observed. After stirring at 50 °C overnight, the reaction mixture was diluted with EtOAc (5 mL), filtered through a small pad of silica gel, concentrated, and purified by silica gel chromatography (hexane/$Et_2O$ 4:1) to afford the title compound as brown powder (58 mg, 57% yield). To a stirred solution of *trans*-[2-(3-trimethylsilanylethynylphenyl)cyclopropylmethyl]carbamic acid tert-butyl ester (58 mg, 0.17 mmol) in THF (1.5 mL) was added TBAF solution (1.0 M in THF, 0.255 mL, 0.255 mmol) slowly under argon purge to give a deep dark solution. After 1 h, the reaction mixture was diluted with EtOAc (5 mL). The organic layer was washed with water, filtered and concentrated, and purified by silica gel chromatography (hexane/$Et_2O$ 4:1) to afford the title compound as brown powder (58 mg, 57% yield). Refer to the general procedure for *t*-Boc deprotection described above. The crude precipitate was filtered and purified by recrystallization from ethanol/$Et_2O$ to afford the title compound as a white solid (22 mg, 90% yield). HPLC purity: 9.3 min, 99.4% (column 1, method D). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.28-7.22 (m, 3 H), -7.13 (d, $J$ = 6.8 Hz, 1 H), 3.45 (s, 1 H), 3.04-2.93 (m, 2 H), 2.02-1.97 (m, 1 H), 1.42-1.38 (m, 1 H), 1.33-1.04 (m, 2 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 143.3, 130.8, 130.7, 129.7, 127.6, 124.0, 78.7, 44.9, 23.0, 21.1, 15.2. MS (ESI) *m/z* 272.1 [$MH^+$]. HRMS (ESI) calculated for $C_{12}H_{14}N^+$ [$MH^+$] 172.1121, found 172.1122.

### *trans*-{2-[3-(6-Hydroxyhex-1-ynyl)phenyl]cyclopropyl}methylamine Hydrochloride (88)

Refer to the general procedure for the synthesis of **86** described above with substitution of **63** for **62**. The crude precipitate was filtered and purified by recrystallization from ethanol/$Et_2O$ to afford the title compound as a white solid (21 mg, 86% yield). HPLC purity: 5.8 min, 94.8% (column 1, method C). $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.19-7.05 (m, 3 H), 6.97 (d, $J$ = 7.2 Hz, 1 H), 3.51 (t, $J$ = 5.9 Hz, 2 H), 2.90 (m, 2 H), 2.34 (t, $J$ = 6.7 Hz, 2 H), 1.93-1.88 (m, 1 H), 1.63-1.55 (m, 4 H), 1.34-1.29 (m, 1 H), 1.02-0.96 (m, 2 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 143.1, 130.3, 130.1, 129.5, 126.6, 125.6, 90.7, 81.9, 62.6, 44.9, 32.9, 26.4, 23.1, 21.7, 19.9, 15.2. MS (ESI) *m/z* 244.2 [$MH^+$]. HRMS (ESI) calculated for $C_{16}H_{22}NO^+$ [$MH^+$] 244.1696, found 244.1688.

### *trans*-{2-[3-(3-Hydroxy-3-methylbut-1-ynyl)phenyl]cyclopropyl}methylamine Hydrochloride (89)

Refer to the general procedure for the synthesis of **86** described above with substitution of **63** for **62** and 2-methylbut-3-yn-2-ol for 5-hexyn-1-ol (17 mg, 98% and 85% yields). HPLC purity: 8.5 min, 95.4% (column 3, method A). $^{1}$H NMR (400 MHz, MeOD-$d_4$) δ 7.26-7.16 (m, 3 H), 7.12-7.10 (m, 1 H), 3.04-2.95 (m, 2 H), 2.01-1.98 (m, 1 H), 1.51-1.38 (m, 7 H), 1.13-1.05 (m, 2 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 143.3, 130.4, 130.3, 129.7, 127.4, 124.2, 91.6, 85.6, 65.9, 44.9, 31.5, 28.9, 23.0, 21.1, 15.1. MS (ESI) *m/z* 230.1 [$MH^+$]. HRMS (ESI) calculated for $C_{15}H_{20}NO^+$ [$MH^+$] 230.1539, found 230.1537.

### *trans*-{2-[4-(6-Hydroxyhex-1-ynyl)phenyl]cyclopropyl}methylamine Hydrochloride (90)

Refer to the general procedure for the synthesis of **76** described above with substitution of **64** for **62**. The crude precipitate was filtered and purified by recrystallization from ethanol/$Et_2O$ to afford the title compound as a white solid (21 mg, 86% yield). HPLC purity: 7.7 min, 99.0% (column 3, method A). $^{1}$H NMR (300 MHz, MeOD-$d_4$) δ 7.25 (d, $J$ = 8.2 Hz, 2 H), 7.04 (d, $J$ = 8.2 Hz, 2 H), 3.60 (t, $J$ = 6.1 Hz, 2 H), 2.98 (m, 2 H), 2.47-2.40 (m, 2 H), 2.00-1.95 (m, 1 H), 1.71-1.63 (m, 4 H), 1.39 (m, 1 H), 1.11-1.04 (m, 2 H). $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 142.5, 132.7, 127.0, 123.2, 90.5, 81.8, 62.6, 44.9, 33.0, 26.5, 23.2, 21.3, 19.9, 15.4. MS (ESI) *m/z* 244.2 [$MH^+$]. HRMS (ESI) calculated for $C_{16}H_{22}NO^+$ [$MH^+$] 244.1696, found 244.1689.

## Biological Methods. Calcium Flux Assays

Calcium flux assays were performed essentially as described earlier.[44] HEK 293 cells stably expressing the human 5-$HT_{2A}$, 5-$HT_{2B}$, or 5-$HT_{2C\ (INI)}$ receptor were seeded and incubated for 20 h in serum-free DMEM containing 50 U/mL penicillin and 50 μg/mL streptomycin sulfate in tissue culture-treated black clear-bottom 384-well plates (Greiner, Germany); plates were coated with 20 μL/well of 50 mg/L poly-l-lysine (Sigma, P-1524) in PBS. The cells were preincubated for 75 min at 37 °C in a humidified incubator with 20 μL of reconstituted fura-4 based calcium dye (Calcium Plus Assay Kit, Molecular Devices) in assay buffer (Hanks' balanced salt solution containing calcium and magnesium (Invitrogen, 14065-056), 50 mM HEPES, 2.5 mM probenecid, 100 mg/L ascorbic acid, pH 7.4). The plates were allowed to cool to rt over 10 min and were transferred to a FLIPR Tetra fluorescence image plate reader (Molecular Devices). The test compounds in 15 μL assay buffer were automatically added and fluorescence (excitation: 470–495 nm, emission: 515–575 nm) was measured every second for 3 min. The baseline was averaged from ten data points immediately before the additions and results were exported as the maximal response over baseline during 60 s after addition. Compounds were measured at seven concentrations from 10 μM to 10 pM in triplicate. $EC_{50}$ values and $E_{max}$ values were obtained from nonlinear curve fitting against a sigmoidal dose-response model using Prism (Graphpad).

## Behavior. Animals

C57BL/6J male mice (9 weeks of age at testing) were obtained from Jackson Laboratory (Bar Harbor, ME). Mice were housed 4 to a cage in a colony room maintained at 22 °C on a 12 h light-dark cycle. All animal experiments were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals and the PsychoGenics Animal Care and Use Committee.

## Mouse Forced Swim Test

Procedures were based on those previously described.[48] Mice were individually placed into clear glass cylinders (i.e., 15 cm tall × 10 cm wide, 1 L beakers) containing 23 ± 1 °C water 12 cm deep (approximately 800 mL). The time the animal spent immobile was recorded every

1 min over a 6 min trial. Immobility was described as the postural position of floating in the water. After testing, mice were dried and returned to their home cage.

### Drugs

Sertraline was purchased from a commercial vendor (Sigma, St. Louis, MO). All compounds were dissolved in 10% DMSO vehicle in saline, 30 minutes prior to testing. All compounds were administered i.p., 1 ml/kg dosing volume.

### Statistics

ANOVA was performed to determine the effects of test treatment, followed by post-hoc analysis using Fisher's PLSC.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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McKeeman L, Malley MF, Devenny J, Pelleymounter MA, Miller KJ, Robl JA. Discovery of (*R*)-9-ethyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-a]isoindol- 6(2*H*)-one, a selective, orally active agonist of the 5-$HT_{2C}$ receptor. J. Med. Chem 2007;50:1365–1379. [PubMed: 17315987]

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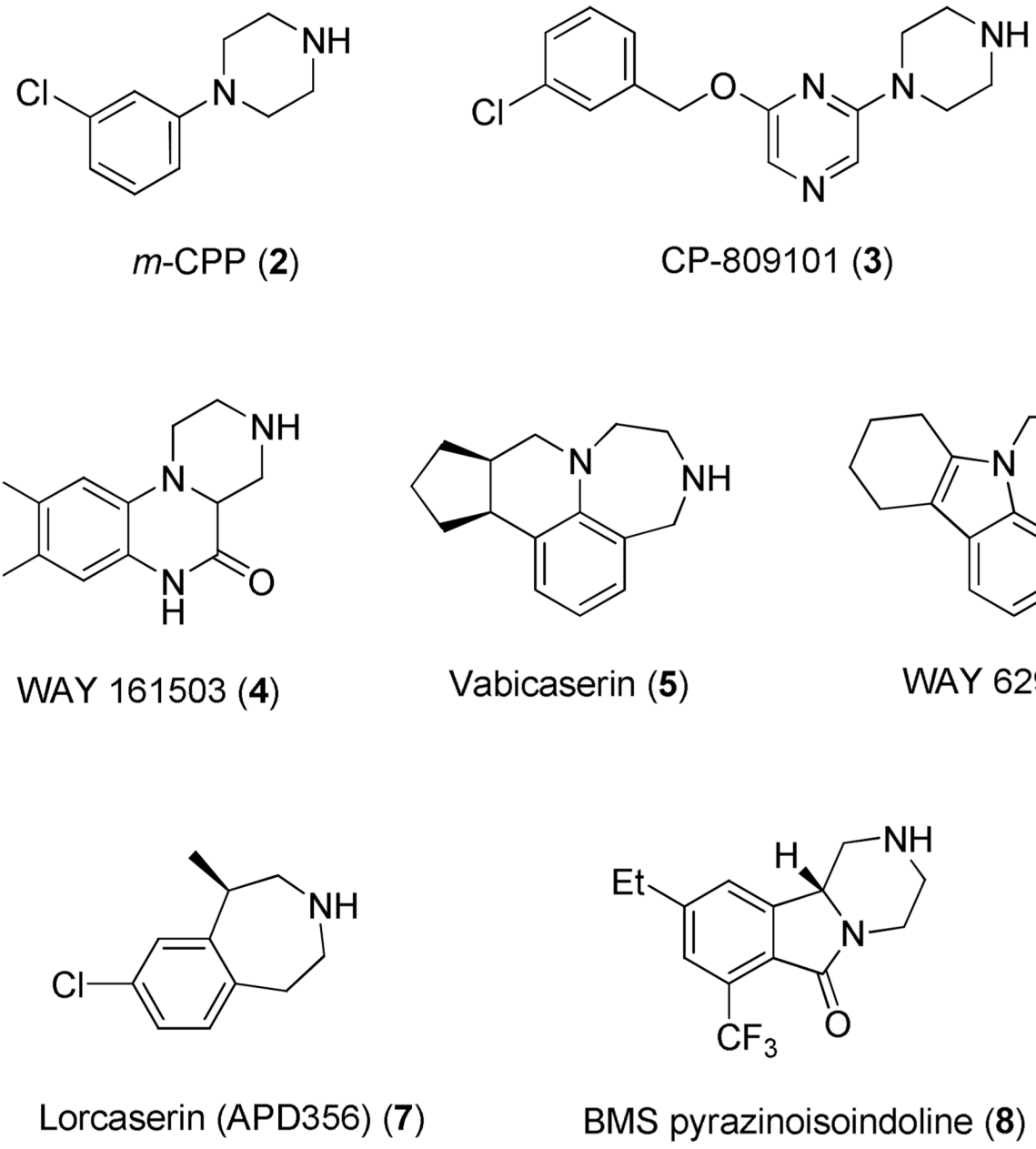



**Figure 1.**
The classical 5-$HT_{2C}$ receptor agonist *m*-CPP and several more recently developed 5-$HT_{2C}$ ligands.

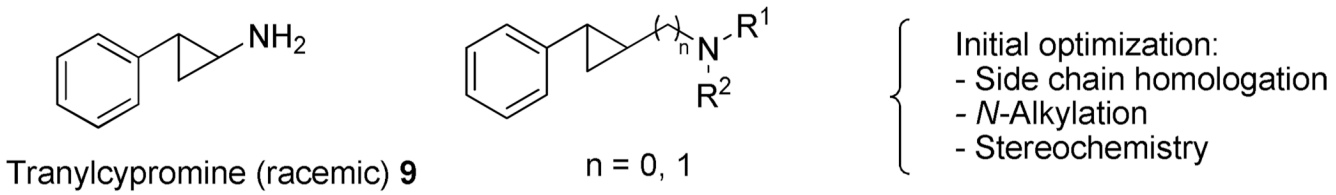



**Figure 2.**
Structures of **9** and its analogs.

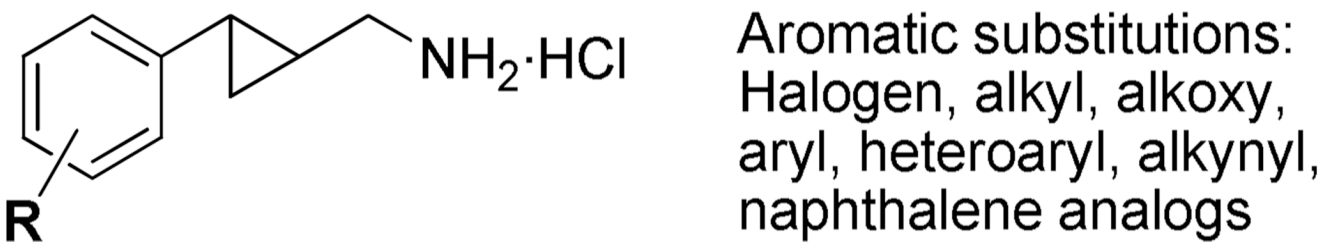



**Figure 3.**
Aromatic substitution screening of *trans*-(2-phenylcyclopropyl)methylamine hydrochloride analogs.

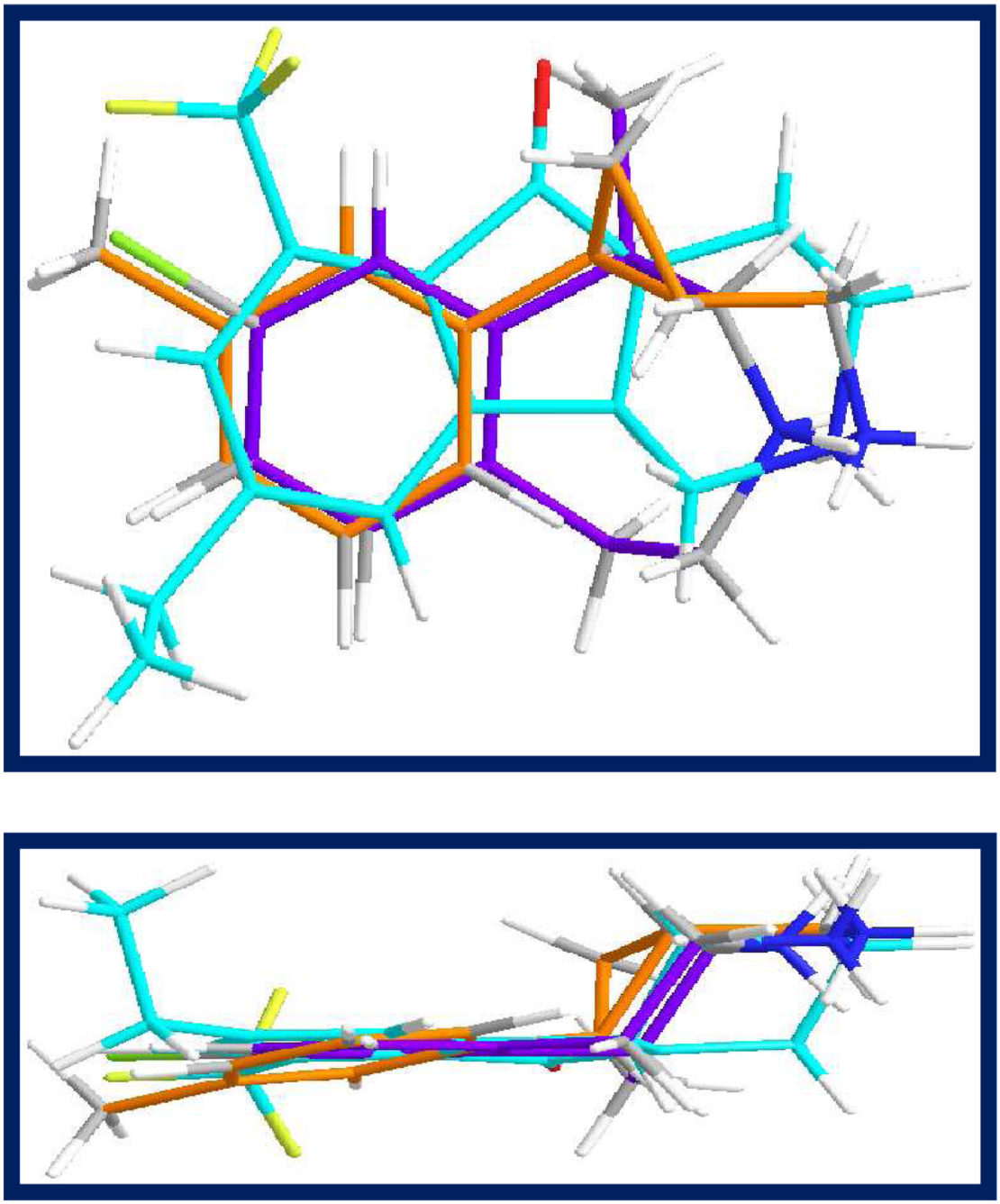


**Figure 4.**
Overlay of the 3-methyl bearing analog **37** (orange) with **7** (purple) and the BMS pyrazinoisoindoline (**8**)[31] (light blue) show the expected similarities in structure. See Figure 1 for structures.

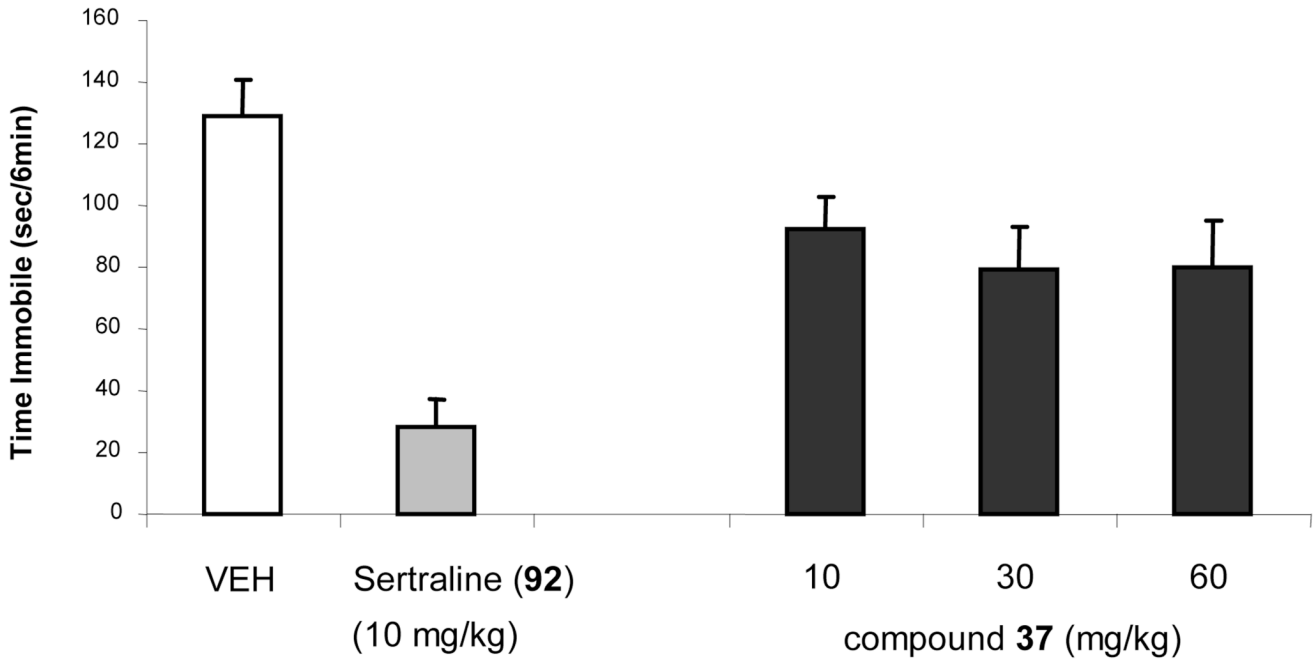
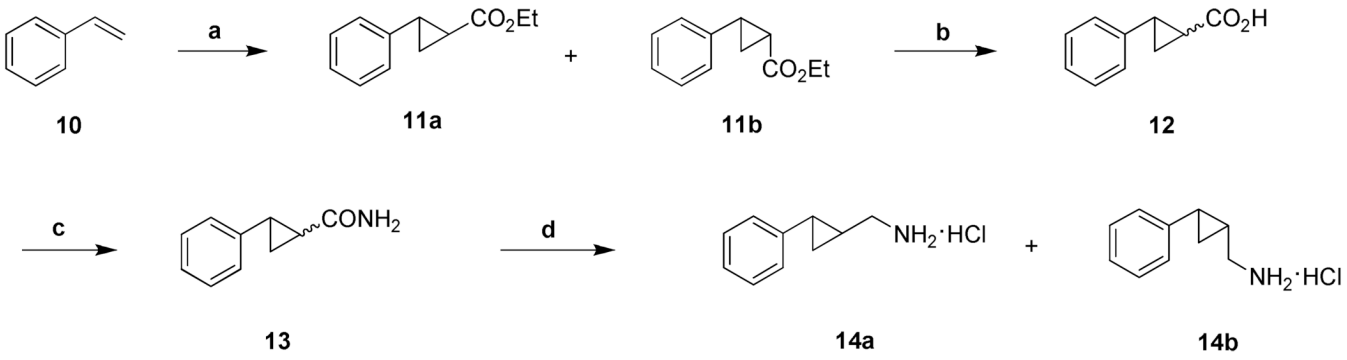


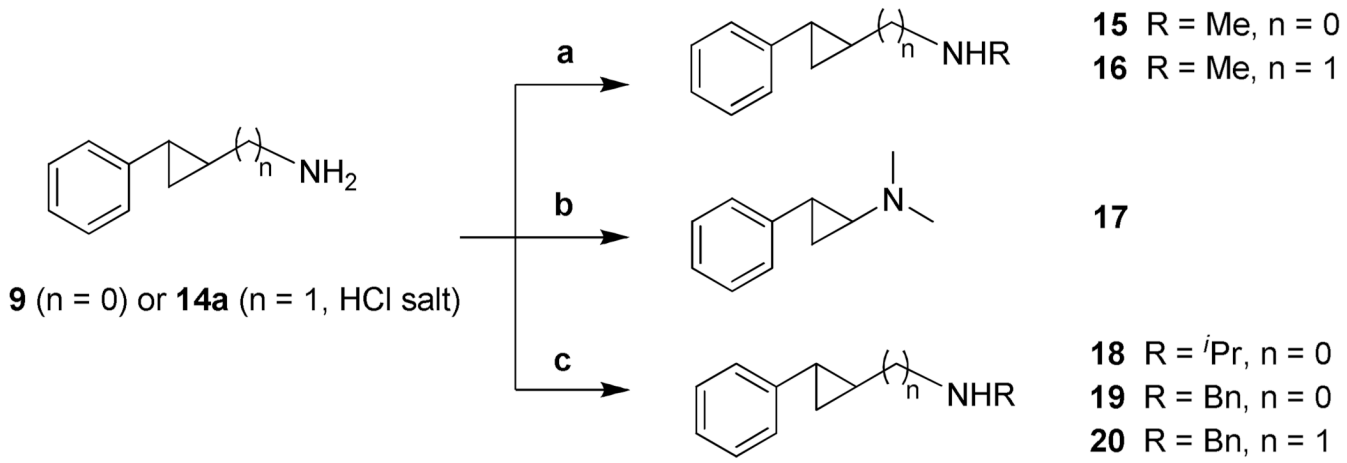

**Figure 5.**

The effects of compound **37** or **92** in the mouse forced swim test. Compound **37** (10–60 mg/kg, ip) or the reference compound **92** (10 mg/kg, ip) was administered 30 minute prior to testing. Both compounds **92** and **37** produced a significant decrease in immobility, which reached significance at all doses tested. These data are indicative of an antidepressant-like effect and *in-vivo* drug-like central activity.



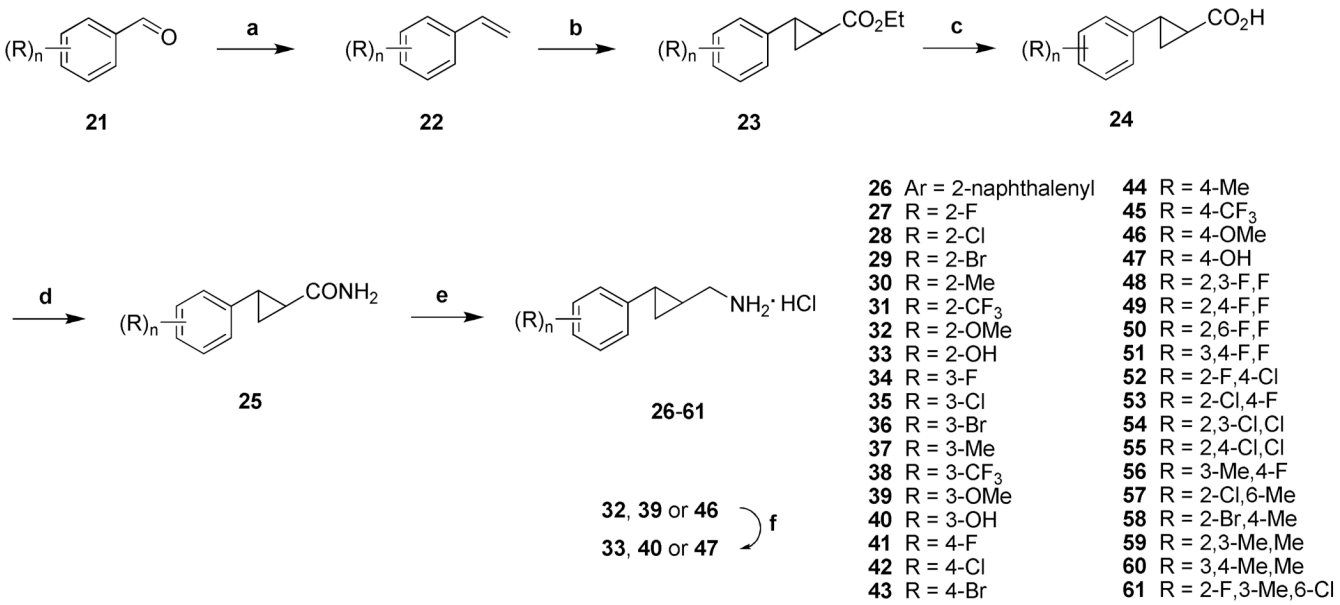

**Scheme 1a.**

[a] Reagents and conditions: (a) $N_2CHCO_2Et$, $Cu(acac)_2$, $CH_2Cl_2$, reflux, 5 h; (b) 2 N KOH, MeOH; (c) (i) $SOCl_2$, toluene, 80 °C, 3 h; (ii) $NH_3$ (liquid), toluene/$CH_2Cl_2$; (d) (i) $BH_3$/THF, reflux, 20 h; (ii) 1 M HCl, 0 °C.



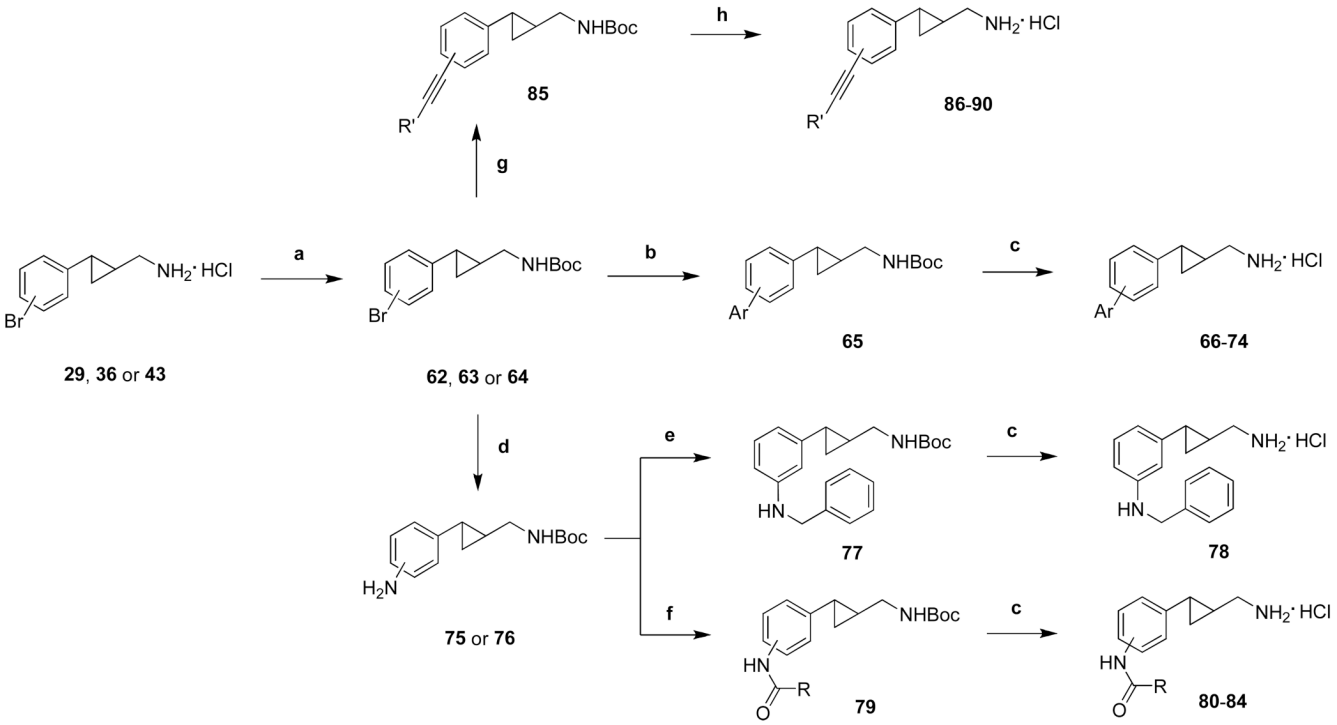

**Scheme 2a.**

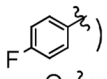
[a] Reagents and conditions: (a) acetic formic anhydride, $BH_3 \cdot SMe_2$/THF; (b) HCHO (excess), $NaBH_3CN$, acetonitrile/$H_2O$; (c) acetone or benzaldehyde, $NaBH_3CN$, MeOH.

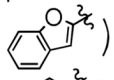


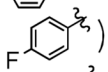

**Scheme 3a.**

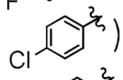
[a] Reagents and conditions: (a) methyltriphenylphosphonium bromide, NaH, THF, 20 h; (b) $N_2CHCO_2Et$, $Cu(acac)_2$, $CH_2Cl_2$, reflux, 5 h; (c) 2 N KOH, MeOH; (d) (i) $SOCl_2$, toluene, 80 °C, 3 h; (ii) $NH_3$ (liquid), toluene/$CH_2Cl_2$; (e) (i) $BH_3$/THF, reflux, 20 h; (ii) 1 M HCl, 0 °C; (f) $BBr_3$, $CH_2Cl_2$, -78 °C.

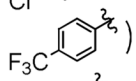


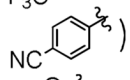

**66** Ar = 2-(  )

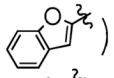
**67** Ar = 2-(  )

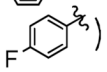
**68** Ar = 3-(  )

**69** Ar = 3-(  )

**70** Ar = 3-(  )

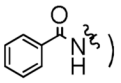
**71** Ar = 3-(  )

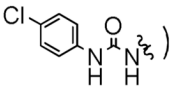
**72** Ar = 3-(  )

**73** Ar = 4-(  )

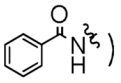
**74** Ar = 4-(  )

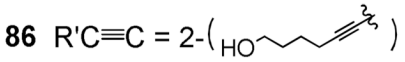
**80** RCONH = 2-(  )

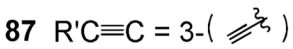
**81** RCONH = 2-(  )

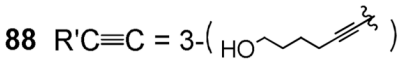
**82** RCONH = 2-(  )

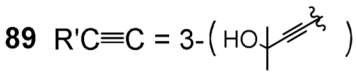
**83** RCONH = 3-(  )

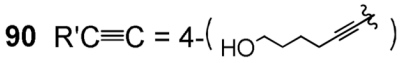
**84** RCONH = 3-(  )

**86** R'C≡C = 2-(  )

**87** R'C≡C = 3-(  )

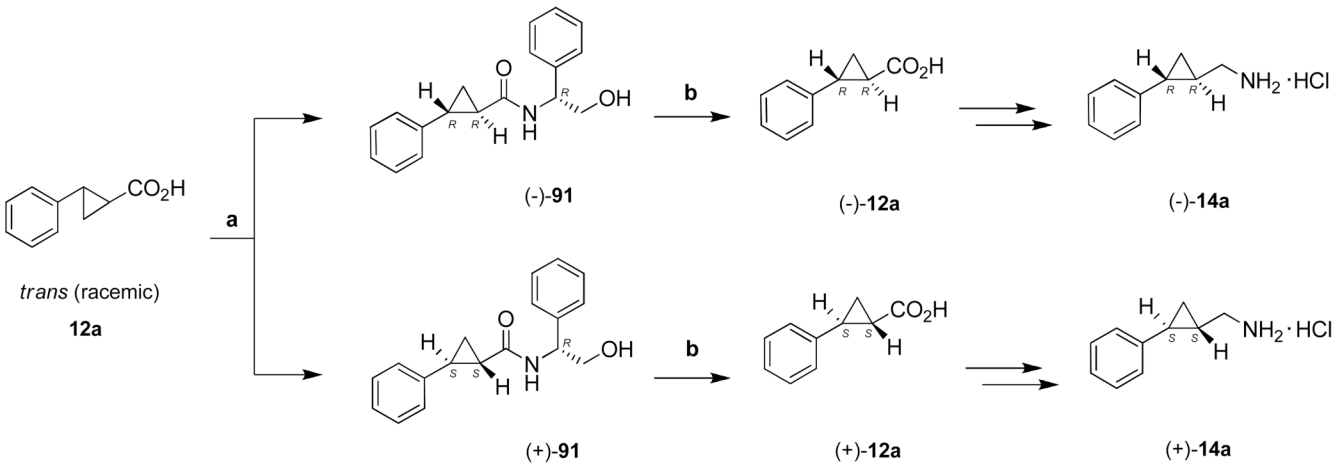
**88** R'C≡C = 3-(  )

**89** R'C≡C = 3-(  )

**90** R'C≡C = 4-(  )

**Scheme 4a.**

[a] Reagents and conditions: (a) $Boc_2O$, triethylamine, $CH_2Cl_2$; (b) Ar-$B(OH)_2$, $Pd(PPh_3)_4$, $K_2CO_3$, dimethoxyethane, 80 °C, 20 h; (c) TFA, $CH_2Cl_2$, rt; (d) (i) benzophenone imine, $Pd(OAc)_2$, BINAP, $Cs_2CO_3$, toluene, 80 °C; (ii) NaOAc, $NH_2OH{\cdot}HCl$, MeOH, rt, 2 h; (e) RCHO, $NaBH_3CN$, MeOH; (f) various anhydrides, DMAP, $CH_2Cl_2$; (g) R'C≡CH, $Pd(PPh_3)_2Cl_2$, $PPh_3$, CuI, triethylamine, reflux; (h) 2 M HCl, rt.

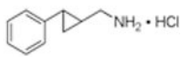
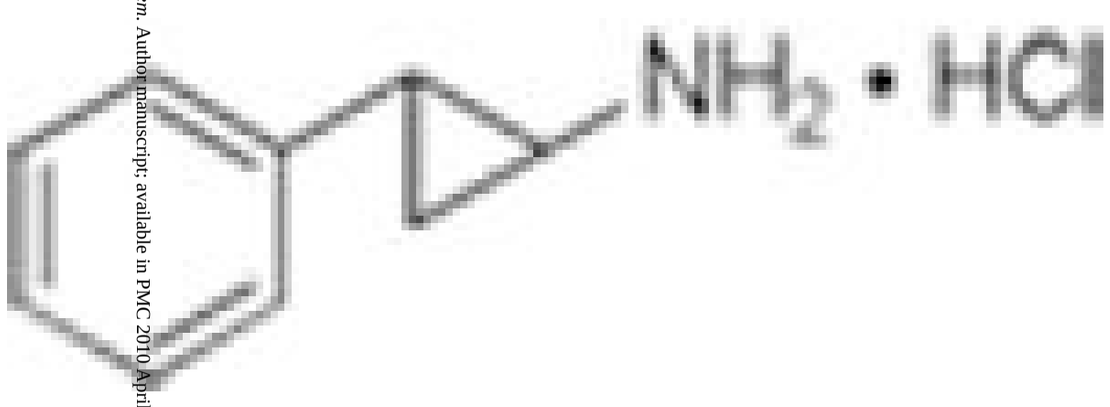
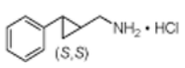
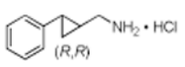



**Scheme 5a.**

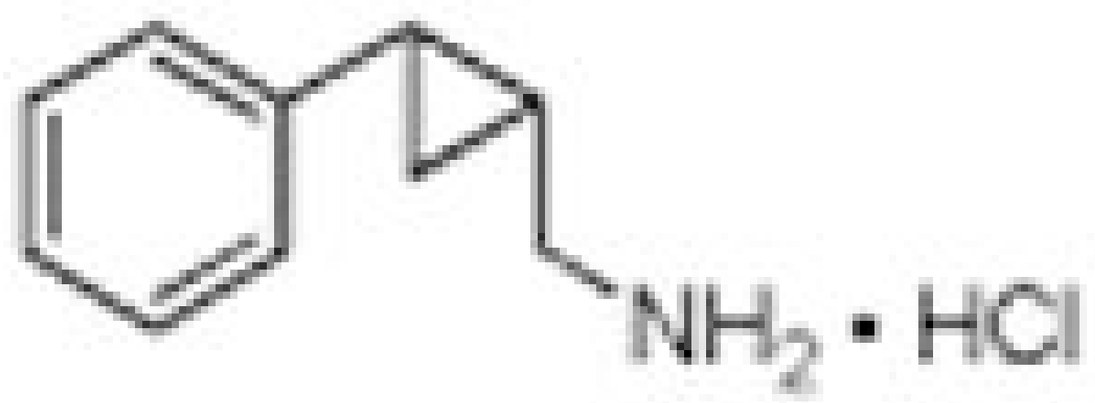
[a] Reagents and conditions: (a) (*R*)-phenylglycinol, EDCI, HOBT, $CH_2Cl_2$; (b) $H_2SO_4$, 100 °C.

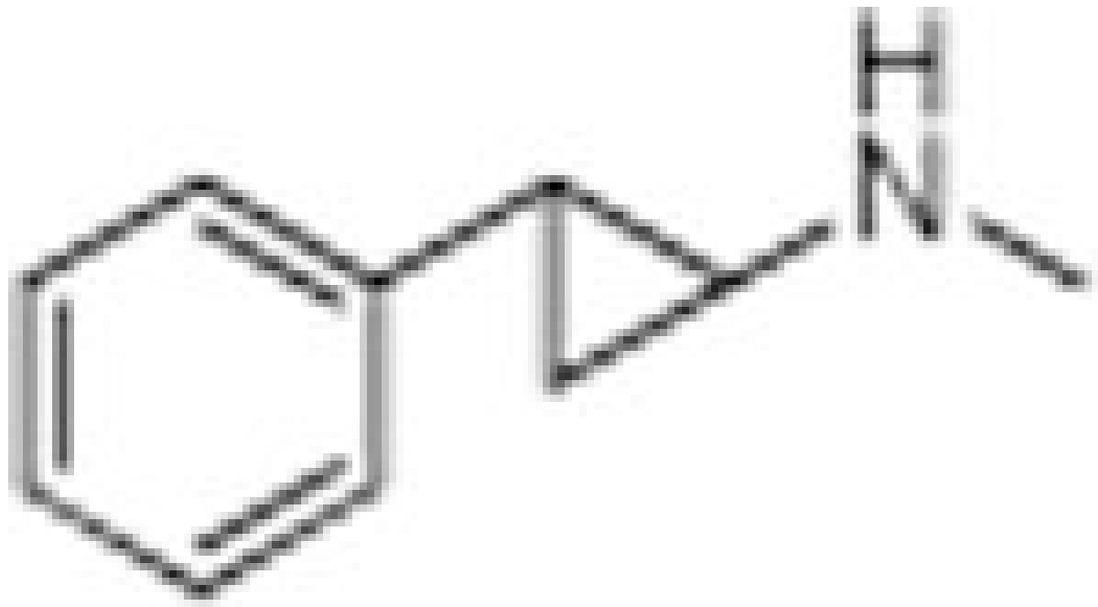
**Table 1**

ional activity and selectivity of the lead compound **9** and its initial analogs **14–20**, and **26** at human 5-$HT_{2A}$, 5-$HT_{2B}$, and 5-$HT_{2C}$ receptors in a calcium flux assays using stably transfected HEK-293 cells.

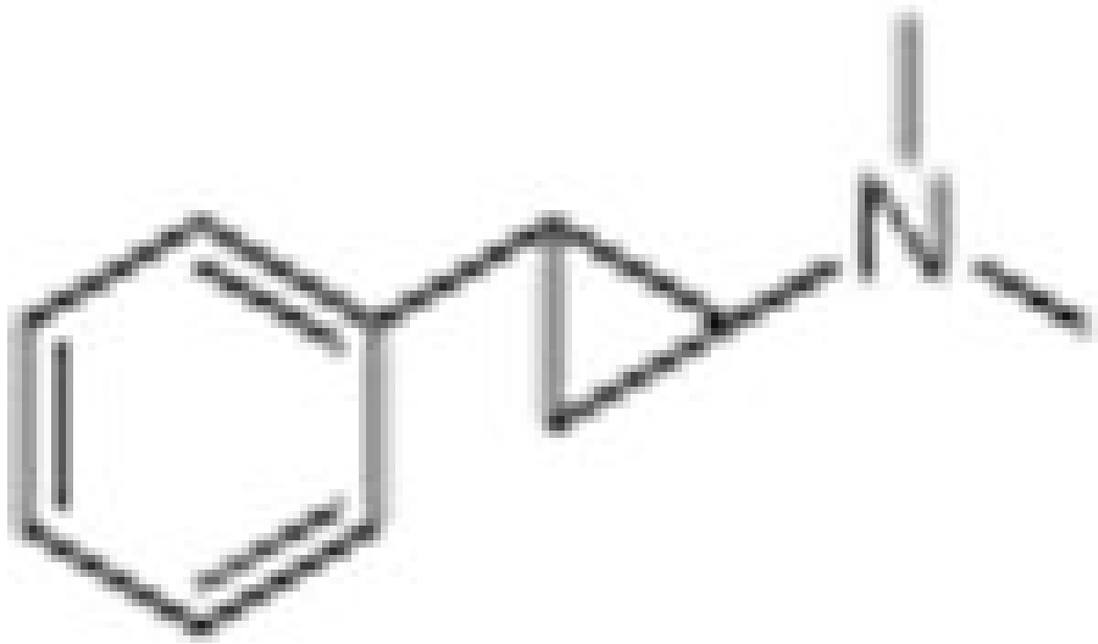
| | | 5-$HT_{2A}$ | | | | | 5-$HT_{2B}$ | | | | | 5-$HT_{2C}$ | | | | | Selectivity | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| d[a] | | $EC_{50}$ ±SEM(nM) | | $E_{max}$ ±SEM[b] | | n[c] | $EC_{50}$ ±SEM(nM) | | $E_{max}$ ±SEM[b] | | n[c] | $EC_{50}$ ±SEM(nM) | | $E_{max}$ ±SEM[b] | | n[c] | 2A/2C | 2B/2C |
| | | 10 | ±1.7 | 100% | | 15 | 1.0 | ±0.10 | 100% | | 15 | 0.09 | ±0.01 | 100% | | 11 | 111 | 11 |
| 4a |  | 1399 | ±169 | 74% | ±8% | 2 | 85 | ±10 | 93% | ±0.7% | 3 | 13 | ±4.6 | 96% | ±3% | 3 | 106 | 6.4 |
| |  | 27 | ±7.2 | 100% | | 11 | 1.4 | ±0.30 | 100% | | 9 | 0.25 | ±0.05 | 100% | | 7 | 108 | 5.8 |
| | | NA | | | | 3 | > 5 μM | | 29% | ±12% | 3 | 2697 | ±451 | 109% | ±12% | 5 | - | - |
| 4a |  | 1396 | ±271 | 79% | ±15% | 4 | 37 | ±10 | 111% | ±3% | 3 | 5.2 | ±0.84 | 108% | ±7% | 4 | 268 | 7.2 |
| 4a |  | NA | | | | 4 | 3092 | ±1156 | 72% | ±4% | 3 | 909 | ±204 | 102% | ±7% | 4 | > 10 | 3.4 |

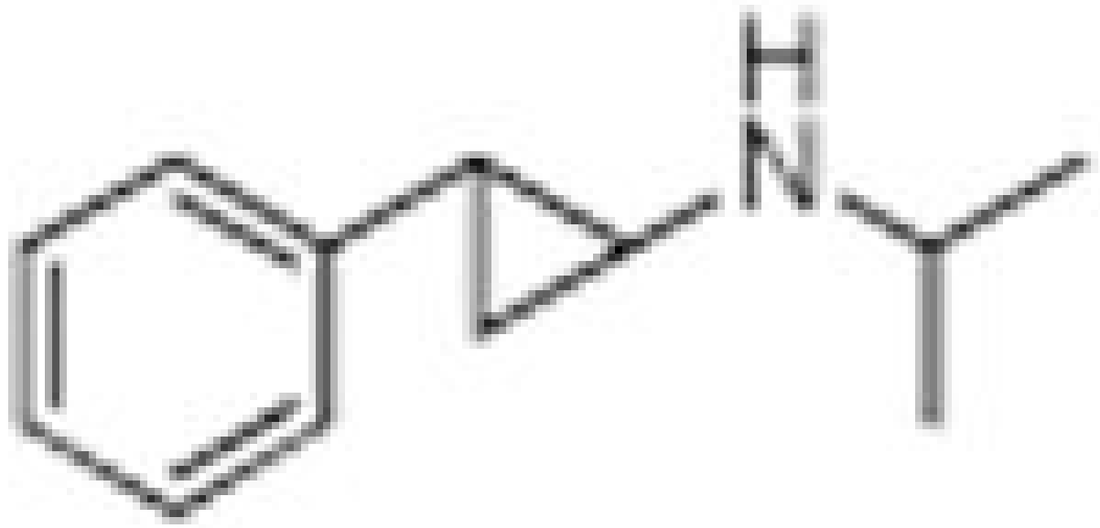
*J Med Chem*. Author manuscript; available in PMC 2010 April 9.

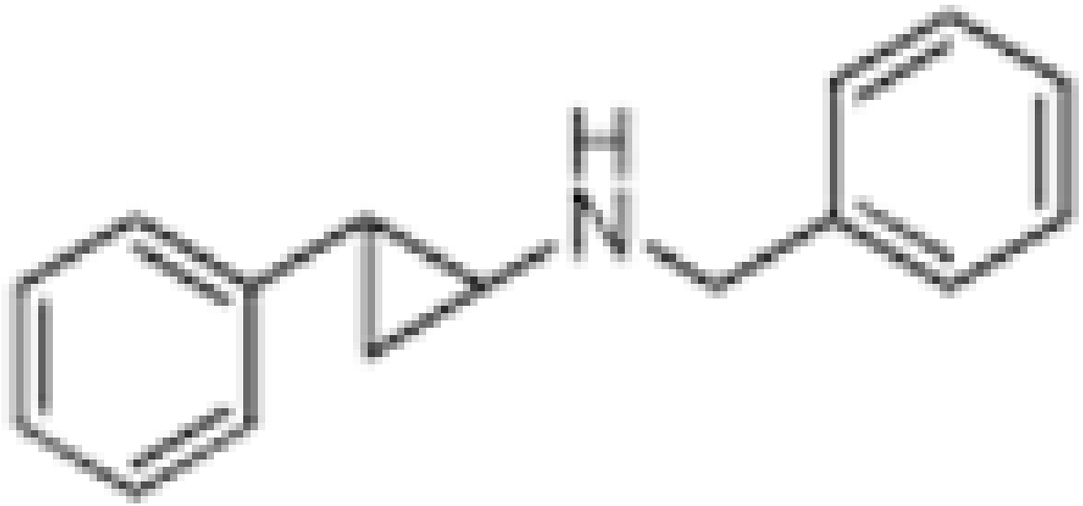
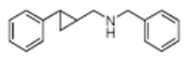
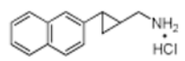
| compd[a] | | 5-HT$_{2A}$ | | | 5-HT$_{2B}$ | |
|---|---|---|---|---|---|---|
| | | EC$_{50}$ ±SEM(nM) | E$_{max}$ ±SEM[b] | n[c] | EC$_{50}$ ±SEM(nM) | E$_{max}$ ± |
| (±)-**14b** |  | NA | | 5 | > 10 μM | 20% |

| compd[a] | | 5-HT$_{2A}$ | | | 5-HT$_{2B}$ | |
|---|---|---|---|---|---|---|
| | | EC$_{50}$ ±SEM(nM) | E$_{max}$ ±SEM[b] | n[c] | EC$_{50}$ ±SEM(nM) | E$_{max}$ ± |
| **15** |  | NA | | 5 | NA | 6% |

| compd[a] | | 5-HT$_{2A}$ | | | 5-HT$_{2B}$ | |
|---|---|---|---|---|---|---|
| | | EC$_{50}$ ±SEM(nM) | E$_{max}$ ±SEM[b] | n[c] | EC$_{50}$ ±SEM(nM) | E$_{max}$ ± |
| **16** |  | NA | | 5 | > 10 μM | 26% |

| compd[a] | | 5-HT$_{2A}$ | | | 5-HT$_{2B}$ | |
|---|---|---|---|---|---|---|
| | | EC$_{50}$ ±SEM(nM) | E$_{max}$ ±SEM[b] | n[c] | EC$_{50}$ ±SEM(nM) | E$_{max}$ ± |
| 17 |  | NA | | 4 | NA | -2% |

| compd[a] | | 5-HT$_{2A}$ | | | 5-HT$_{2B}$ | |
|---|---|---|---|---|---|---|
| | | EC$_{50}$ ±SEM(nM) | E$_{max}$ ±SEM[b] | n[c] | EC$_{50}$ ±SEM(nM) | E$_{max}$ ± |
| **18** |  | NA | | 4 | NA | -1% |

| compd[a] | | 5-HT$_{2A}$ | | | 5-HT$_{2B}$ | | | 5-HT$_{2C}$ | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | EC$_{50}$ ±SEM(nM) | E$_{max}$ ±SEM[b] | n[c] | EC$_{50}$ ±SEM(nM) | E$_{max}$ ±SEM[b] | n[c] | EC$_{50}$ ±SEM(nM) | E$_{max}$ ±SEM[b] | | |
| **19** |  | NA | | 4 | NA | -1% ±1% | 3 | NA | | | |
| **20** |  | NA | | 5 | NA | 10% ±3% | 4 | 5697 | ±2352 | 97% | ±7% |
| **26** |  | NA | | 4 | 510 | ±292 21% ±5% | 3 | 2902 | ±1314 | 60% | ±7% |

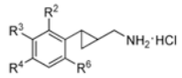
[a] Tested in independent screening campaigns using different cell lines / passages

[b] Percent of maximal activation by 5-HT; activation at 10 μM for compounds without EC$_{50}$ value

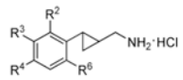
[c] n: Number of concentration curves from ≥ 2 (typically ≥ 3)independent experiments NA: E$_{max}$ ≤ 12%

**Table 2**

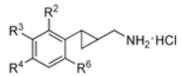
Functional activity of compounds **27–61** in calcium flux assays using HEK-293 cells stably expressing the human 5-$HT_{2A}$, 5-$HT_{2B}$, or 5-$HT_{2C}$ receptor.




| | | | | | 5-$HT_{2A}$ | | | | | 5-$HT_{2B}$ | | | | | 5-$HT_{2C}$ | | | | | Selectivity | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **compd**[a] | **$R^2$** | **$R^3$** | **$R^4$** | **$R^6$** | **$EC_{50}$ ±SEM(nM)** | | **$E_{max}$ ±SEM**[b] | | **n**[c] | **$EC_{50}$ ±SEM(nM)** | | **$E_{max}$ ±SEM**[b] | | **n**[c] | **$EC_{50}$ ±SEM(nM)** | | **$E_{max}$ ±SEM**[b] | | **n**[c] | **2A/2C** | **2B/2C** |
| **1** | | | | | 17 | ±7.1 | 100% | | 14 | 3.0 | ±1.5 | 100% | | 12 | 0.12 | ±0.08 | 100% | | 17 | 134 | 24 |
| **27** | F | | | | > 1000 | | 52% | ±10% | 3 | 1549 | ±821 | 65% | ±16% | 4 | 37 | ±19 | 94% | ±5% | 4 | > 27 | 42 |
| **28** | Cl | | | | 403 | ±53 | 54% | ±33% | 3 | 84 | ±13 | 82% | ±4% | 3 | 5.1 | ±4.2 | 98% | ±14% | 3 | 79 | 16 |
| **29** | Br | | | | 585 | ±178 | 73% | ±13% | 3 | 154 | ±131 | 86% | ±19% | 4 | 2.8 | ±2.2 | 93% | ±8% | 3 | 206 | 54 |
| **31** | $CF_3$ | | | | NA | | | | 2 | 350 | ±7.1 | 102% | ±27% | 2 | 49 | ±11 | 101% | ±8% | 2 | - | 7.2 |
| **34** | | F | | | 1769 | ±2110 | 71% | ±7% | 2 | 51 | ±16 | 106% | ±9% | 3 | 3.9 | ±3.9 | 92% | ±6% | 3 | 450 | 13 |
| **35** | | Cl | | | 1886 | ±540 | 42% | ±9% | 2 | 59 | ±3.8 | 78% | ±7% | 2 | 10.0 | ±0.20 | 98% | ±4% | 2 | 189 | 5.9 |
| **36** | | Br | | | 1680 | ±1368 | 55% | ±13% | 4 | 141 | ±143 | 74% | ±14% | 5 | 14 | ±11 | 90% | ±10% | 5 | 123 | 10 |
| **38** | | $CF_3$ | | | 1485 | ±195 | 35% | ±1% | 2 | 77 | ±16 | 78% | ±16% | 2 | 30 | ±8.8 | 94% | ±4% | 2 | 50 | 2.6 |
| **41** | | | F | | 1098 | ±971 | 67% | ±5% | 4 | 312 | ±150 | 95% | ±6% | 3 | 5.4 | ±2.1 | 93% | ±4% | 2 | 202 | 57 |
| **42** | | | Cl | | 4482 | ±2026 | 64% | ±15% | 2 | 404 | ±28 | 80% | ±11% | 2 | 76 | ±22 | 106% | ±21% | 2 | 59 | 5.3 |
| **43** | | | Br | | > 1000 | | 26% | ±5% | 2 | 2737 | ±1540 | 51% | ±16% | 3 | 138 | ±82 | 87% | ±4% | 5 | > 7 | 20 |
| **45** | | | $CF_3$ | | NA | | | | 3 | > 1000 | | 56% | ±10% | 3 | 779 | ±286 | 91% | ±4% | 3 | - | > 1 |
| **46** | | | OMe | | NA | | | | 2 | NA | | | | 2 | 902 | ±442 | 86% | ±6% | 2 | - | - |
| **47** | | | OH | | NA | | | | 2 | NA | | | | 2 | NA | | | | 2 | - | - |
| **50** | F | | | F | > 1000 | | 38% | ±22% | 4 | 3342 | ±2622 | 58% | ±9% | 5 | 87 | ±76 | 85% | ±14% | 5 | > 11 | 39 |
| **1** | | | | | 10 | ±1.7 | 100% | | 15 | 1.0 | ±0.10 | 100% | | 15 | 0.09 | ±0.01 | 100% | | 11 | 111 | 11 |
| **14a** | | | | | 1399 | ±169 | 74% | ±8% | 2 | 85 | ±10 | 93% | ±0.7% | 3 | 13 | ±4.6 | 96% | ±3% | 3 | 106 | 6 |
| **27** | F | | | | 942 | ±30 | 79% | ±8% | 2 | 199 | ±34 | 89% | ±3% | 3 | 29 | ±6.4 | 91% | ±0.6% | 3 | 32 | 6.8 |
| **28** | Cl | | | | 168 | ±21 | 87% | ±8% | 2 | 32 | ±3.8 | 95% | ±3% | 3 | 5.5 | ±2.0 | 94% | ±4% | 3 | 31 | 5.8 |
| **30** | Me | | | | 1606 | ±940 | 69% | ±4% | 2 | 53 | ±19 | 86% | ±2% | 2 | 23 | ±8.3 | 99% | ±6% | 2 | 71 | 2.3 |
| **32** | OMe | | | | 2166 | ±773 | 61% | ±7% | 4 | 199 | ±26 | 83% | ±6% | 4 | 26 | ±7.0 | 93% | ±2% | 4 | 84 | 7.7 |
| 33 | OH | | | | 513 | ±177 | 81% | ±8% | 3 | 492 | ±28 | 74% | ±8% | 3 | 161 | ±62 | 94% | ±5% | 3 | 3.2 | 3.1 |




| | | | | | 5-HT$_{2A}$ | | | | | 5-HT$_{2B}$ | | | | | 5-HT$_{2C}$ | | | | | Selectivity | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| compd[a] | R$^2$ | R$^3$ | R$^4$ | R$^6$ | EC$_{50}$ ±SEM(nM) | | E$_{max}$ ±SEM[b] | | n[c] | EC$_{50}$ ±SEM(nM) | | E$_{max}$ ±SEM[b] | | n[c] | EC$_{50}$ ±SEM(nM) | | E$_{max}$ ±SEM[b] | | n[c] | 2A/2C | 2B/2C |
| **34** | | F | | | 733 | ±59 | 86% | ±3% | 2 | 13 | ±2.5 | 96% | ±3% | 3 | 3.3 | ±1.0 | 97% | ±3% | 3 | 225 | 4.0 |
| **37** | | Me | | | 585 | ±148 | 86% | ±4% | 4 | 65 | ±15 | 93% | ±2% | 5 | 4.8 | ±1.3 | 95% | ±2% | 4 | 123 | 14 |
| **39** | | OMe | | | 613 | ±157 | 90% | ±3% | 4 | 75 | ±13 | 96% | ±4% | 4 | 16 | ±5.9 | 97% | ±2% | 4 | 39 | 4.8 |
| **40** | | OH | | | 247 | ±138 | 92% | ±3% | 3 | 5.5 | ±1.3 | 98% | ±1% | 3 | 3.3 | ±1.6 | 94% | ±0.7% | 3 | 75 | 1.7 |
| **41** | | | F | | 646 | ±34 | 80% | ±2% | 2 | 57 | ±4.8 | 94% | ±2% | 3 | 8.4 | ±2.5 | 94% | ±1% | 3 | 77 | 6.8 |
| **48** | F | F | | | > 5 μM | | 45% | ±9% | 2 | 366 | ±88 | 93% | ±2% | 2 | 99 | ±37 | 101% | ±6% | 2 | > 50 | 3.7 |
| **49** | F | | F | | 547 | ±296 | 85% | ±2% | 2 | 415 | ±151 | 88% | ±1% | 2 | 42 | ±18 | 98% | ±0.5% | 2 | 13 | 9.9 |
| **51** | | F | F | | 578 | ±219 | 96% | ±4% | 2 | 28 | ±7.2 | 96% | ±0.1% | 2 | 9.0 | ±3.3 | 103% | ±6% | 2 | 64 | 3.2 |
| **52** | F | | Cl | | 774 | ±229 | 83% | ±6% | 3 | 459 | ±154 | 86% | ±2% | 3 | 128 | ±66 | 94% | ±4% | 3 | 6.1 | 3.6 |
| **53** | Cl | | F | | 91 | ±33 | 91% | ±6% | 4 | 22 | ±8.6 | 97% | ±4% | 4 | 3.0 | ±1.2 | 100% | ±2% | 4 | 30 | 7.3 |
| **54** | Cl | Cl | | | 349 | ±54 | 77% | ±2% | 4 | 14 | ±1.9 | 89% | ±2% | 5 | 11 | ±4.1 | 96% | ±3% | 4 | 33 | 1.4 |
| **55** | Cl | | Cl | | 51 | ±18 | 88% | ±3% | 4 | 83 | ±21 | 89% | ±6% | 4 | 18 | ±10 | 98% | ±1% | 4 | 2.9 | 4.7 |
| **1** | | | | | 27 | ±7.2 | 100% | | 11 | 1.4 | ±0.30 | 99% | | 9 | 0.25 | ±0.05 | 100% | | 7 | 108 | 5.8 |
| **59** | Me | Me | | | 360 | ±65 | 59% | ±7% | 4 | 8.4 | ±0.81 | 90% | ±4% | 3 | 7.0 | ±1.2 | 107% | ±8% | 5 | 52 | 1.2 |
| **60** | | Me | Me | | 2392 | ±692 | 40% | ±6% | 4 | 12 | ±2.4 | 78% | ±5% | 3 | 35 | ±8.4 | 97% | ±7% | 4 | 68 | 0.33 |
| **61** | F | Me | | Cl | 330 | ±116 | 65% | ±9% | 3 | 116 | ±51 | 74% | ±11% | 3 | 13 | ±2.7 | 117% | ±11% | 4 | 26 | 9.2 |
| (+)-**29** | Br | | | | 67 | ±12 | 76% | ±17% | 4 | 13 | ±4.8 | 102% | ±4% | 3 | 0.78 | ±0.18 | 116% | ±5% | 4 | 86 | 17 |
| (−)-**29** | Br | | | | NA | | | | 4 | 224 | ±103 | 96% | ±4% | 3 | 78 | ±11 | 113% | ±4% | 4 | > 128 | 2.9 |
| **7** | | 5-HT$_{2C}$ agonist | | | 616 | ±270 | 26% | ±8% | 3 | 219 | ±107 | 92% | ±0.7% | 3 | 2.7 | ±0.90 | 124% | ±13% | 4 | 232 | 82 |
| **1** | | | | | 5.8 | ±0.63 | 100% | | 11 | 0.50 | ±0.04 | 100% | | 8 | 0.16 | ±0.02 | 100% | | 9 | 37 | 3.2 |
| **27** | F | | | | 681 | ±116 | 62% | ±3% | 5 | 69 | ±7.8 | 84% | ±4% | 4 | 33 | ±2.3 | 91% | ±2% | 5 | 20 | 2.1 |
| **29** | Br | | | | 94 | ±9.5 | 71% | ±2% | 5 | 4.8 | ±1.7 | 87% | ±6% | 4 | 1.3 | ±0.54 | 76% | ±19% | 5 | 73 | 3.7 |
| **34** | | F | | | 437 | ±28 | 73% | ±4% | 5 | 3.6 | ±0.41 | 87% | ±5% | 4 | 3.3 | ±0.49 | 96% | ±2% | 5 | 131 | 1.1 |
| **41** | | | F | | 508 | ±35 | 68% | ±3% | 5 | 21 | ±0.90 | 89% | ±4% | 4 | 11 | ±1.2 | 96% | ±2% | 5 | 47 | 1.9 |
| **44** | | | Me | | 1929 | ±300 | 18% | ±3% | 4 | 37 | ±3.2 | 79% | ±4% | 4 | 135 | ±51 | 69% | ±17% | 5 | 14 | 0.28 |




| | | | | | 5-HT$_{2A}$ | | | | | 5-HT$_{2B}$ | | | | | 5-HT$_{2C}$ | | | | | Selectivity | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **compd**[a] | **R$^2$** | **R$^3$** | **R$^4$** | **R$^6$** | **EC$_{50}$ ±SEM(nM)** | | **E$_{max}$ ±SEM**[b] | | **n**[c] | **EC$_{50}$ ±SEM(nM)** | | **E$_{max}$ ±SEM**[b] | | **n**[c] | **EC$_{50}$ ±SEM(nM)** | | **E$_{max}$ ±SEM**[b] | | **n**[c] | **2A/2C** | **2B/2C** |
| **56** | | Me | F | | 235 | ±47 | 73% | ±5% | 4 | 4.9 | ±0.35 | 83% | ±5% | 4 | 6.0 | ±1.4 | 91% | ±4% | 4 | 39 | 0.83 |
| **57** | Cl | | | Me | 726 | ±62 | 56% | ±6% | 5 | 7.0 | ±0.49 | 90% | ±4% | 4 | 3.5 | ±1.0 | 97% | ±3% | 4 | 207 | 2.0 |
| **58** | Br | | Me | | 465 | ±95 | 62% | ±6% | 5 | 116 | ±10 | 68% | ±4% | 4 | 97 | ±20 | 84% | ±5% | 4 | 4.8 | 1.2 |
| **6** | | 5-HT$_{2C}$ agonist | | | NA | | | | 6 | NA | | | | 4 | 261 | ±41 | 69% | ±3% | 5 | - | - |
| **7** | | 5-HT$_{2C}$ agonist | | | 151 | ±16 | 33% | ±3% | 11 | 39 | ±3 | 92% | ±1.7% | 8 | 3.0 | ±0.54 | 96% | ±2% | 9 | 51 | 13 |

[a] Tested in four independent screening campaigns using different cell lines / passages

[b] Percent of maximal activation by 5-HT; activation at 10 μM for compounds without EC$_{50}$ value

[c] n: Number of concentration curves from ≥ 2 (typically ≥ 3) independent experiments NA: Emax ≤ 12%

**Table 3**

Radioligand binding data of selected compounds at the human 5-$HT_{2A}$, human 5-$HT_{2B}$, and 5-$HT_{2C}$ receptors as well as the neurotransmitter reuptake transporters for 5-HT (SERT), norepinephrine (NET), and dopamine (DAT). For 5-$HT_{2B}$ the agonist radioligand [$^3$H]-LSD was used, possibly resulting in higher binding affinities for agonist compounds.

| | 5-$HT_{2A}$ [$^3$H]-Ketanserin | | | 5-$HT_{2B}$ [$^3$H]-LSD[a] | | | 5-$HT_{2C}$ [$^3$H]-Mesulergine | | | SERT [$^3$H]-Citalopram | | | NET [$^3$H]-Nisoxetine | | | DAT [$^3$H]-WIN35428[b] | | | Selectivity | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **compd** | **$K_i$ (nM)** | **SEM (nM)** | **n** | **$K_i$ (nM)** | **SEM (nM)** | **n** | **$K_i$ (nM)** | **SEM (nM)** | **n** | **$K_i$ (nM)** | **SEM (nM)** | **n** | **$K_i$ (nM)** | **SEM (nM)** | **n** | **$K_i$ (nM)** | **SEM (nM)** | **n** | **2A/2C** | **2B/2C** |
| **7** | 2782 | ±35.5 | 2 | 189 | ±37.2 | 3 | 257 | ±63.8 | 3 | 2606 | ±494 | 3 | >10 μM | | 1 | >10 μM | | 3 | 10.8 | 0.73 |
| **29** | 655 | ±154 | 2 | 22 | ±1.16 | 3 | 124 | ±22.0 | 3 | 2716 | ±876 | 3 | 2733 | | 1 | >10 μM | | 3 | 5.3 | 0.18 |
| **37** | 1846 | ±221 | 2 | 85 | ±13.8 | 3 | 268 | ±32.4 | 3 | 5441 | ±1352 | 3 | >10 μM | | 1 | 5400 | ±2366 | 3 | 6.9 | 0.32 |
| **41** | 2778 | ±1292 | 2 | 89 | ±26.1 | 3 | 242 | ±54.7 | 3 | 2710 | ±979 | 3 | 6780 | | 1 | 3261 | ±1251 | 3 | 11.5 | 0.37 |
| **53** | 254 | ±36.7 | 2 | 16 | ±5.39 | 3 | 203 | ±50.4 | 3 | 1042 | ±332 | 3 | >10 μM | | 1 | >10 μM | | 3 | 1.2 | 0.08 |
| (+)-**29** | 246 | ±72.1 | 2 | 16 | ±3.73 | 3 | 66 | ±11.2 | 3 | 3834 | ±559 | 3 | 3404 | | 1 | 2115 | ±862 | 3 | 3.7 | 0.24 |

[a] Agonist radioligand, $K_i$ values are ~30-fold lower than for antagonist radioligands

[b] (−)-2β -Carbomethoxy-3β -(4-fluorophenyl)tropane (IN35428)