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Further Advances in Optimizing (2-Phenylcyclopropyl)methylamines as Novel Serotonin 2C Agonists: Effects in Open Field, Prepulse Inhibition, and Cognition Models

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Abstract

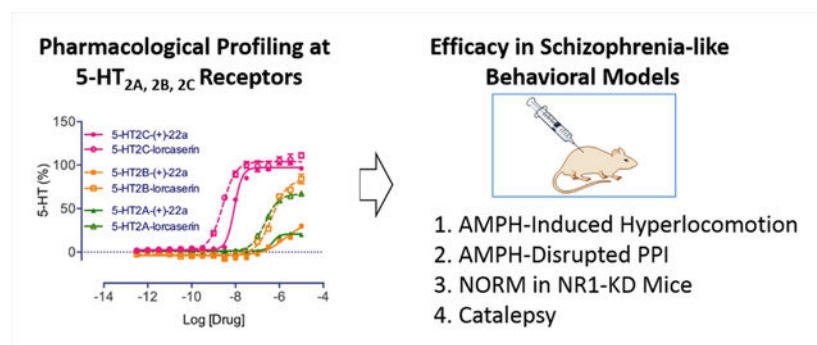
A series of novel compounds with two halogen substituents have been designed and synthesized to further optimize the 2-phenylcyclopropylmethylamine scaffold in the quest for drug-like 5-HT_{2C} agonists. Compound (+)-**22a** was identified as a potent 5-HT_{2C} receptor agonist, with good selectivity against the 5-HT_{2B} and the 5-HT_{2A} receptors. ADMET assays showed that compound (+)-**22a** possessed desirable properties in terms of its microsomal stability, and CYP and hERG inhibition, along with an excellent brain penetration profile. Evaluation of (+)-**22a** in animal models of schizophrenia-related behaviors revealed that it had a desirable activity profile, as it reduced locomotor activity in *d*-amphetamine-stimulated hyperlocomotion in the open field test, it restored *d*-amphetamine-disrupted prepulse inhibition, it induced cognitive improvements in NR1-KD animals in the novel object recognition memory test, and it produced very little catalepsy relative to haloperidol. These data support the further development of (+)-**22a** as drug candidate for the treatment of schizophrenia.

Graphical Abstract

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Supporting Information

Synthetic procedures for compounds **16a–g**, **18a–g**, and **19a–g**, and characterization data of all chemical intermediates can be found in this section. This material is available free of charge on the ACS Publications website at <http://pubs.acs.org>.



Introduction

Schizophrenia is a severe mental disease that affects 1% of the population in the US and more than 21 million people worldwide.¹ It is a disease of complex etiology with likely more than 100 genetic loci and unspecified non-genetic contributing factors.^{2, 3} At least three types of symptoms exemplify schizophrenia: positive, negative and cognitive. The available antipsychotic drugs are effective against positive symptoms while having minimal effects at cognitive and negative symptoms.^{4, 5}

The 5-HT_{2C} serotonin receptor has recently been identified as a promising drug target for the treatment of a variety of central nervous system (CNS) disorders, including obesity, schizophrenia, and substance abuse.^{6, 7} Lorcaserin (**1**, Fig. 1) and vabicaserin (**2**) are two representative 5-HT_{2C} agonists that have been developed. Lorcaserin has been approved as an anti-obesity drug, vabicaserin was studied in clinical trials for the treatment of acute schizophrenia.^{8, 9} However, development of vabicaserin was discontinued for unknown reasons. For many years it has been appreciated that 5-HT_{2C} receptor function might be altered in schizophrenia and that the 5-HT_{2C} antagonist activity of certain atypical antipsychotic drugs might be associated with weight gain and adverse metabolic consequences.^{10–13} The 5-HT_{2C} receptor is a promising target for treating schizophrenia and related disorders because: (1) activation of 5-HT_{2C} receptors specifically decreases mesolimbic dopamine release without affecting nigrostriatal dopamine,¹⁴ thus it is predicted to have antipsychotic efficacy while causing few extrapyramidal side effects (EPS); and (2) 5-HT_{2C} agonists are known to induce weight loss, and thus such drugs should lack the undesired side effects of weight gain and associated metabolic disorders, which have been associated with most current antipsychotic drugs.^{13, 15} Additionally, activation of the 5-HT_{2C} receptor has been demonstrated to counter cognitive deficits induced by NMDA antagonism,¹⁶ as well as to overcome cognitive deficits in animals bearing the human tryptophan hydroxylase 2 loss of function mutation.¹⁷ Therefore, developing safe 5-HT_{2C} agonists for the treatment of schizophrenia could potentially address the cognitive deficits associated with this disease with fewer EPS and a lower risk of causing weight gain.

The greatest challenge for developing 5-HT_{2C} receptor agonists is their selectivity against the other two related receptors of the 5-HT₂ subfamily, namely 5-HT_{2A} and 5-HT_{2B}. Activation of 5-HT_{2A} receptors has been reported to be associated with hallucinogenic effects,¹⁸ while activation of 5-HT_{2B} receptors, which are mainly expressed in the periphery,

produces valvulopathy and pulmonary hypertension as has been observed with the use of dexfenfluramine.^{7, 19} The FDA-approved drug lorcaserin was reported to have 100-fold selectivity for 5-HT_{2C} relative to the 5-HT_{2B} subtype, however it possesses full agonist activity at 5-HT_{2B} with moderate potency (EC₅₀ = 943 ± 90 nM, E_{max} = 100%),²⁰ and lorcaserin was reported to cause a higher incidence of cardiac valve disorders in clinical trials compared to the placebo group.²¹ We previously reported on a series of novel compounds that have excellent selectivity for 5-HT_{2C} receptors which are comprised of a 2-phenylcyclopropylmethylamine scaffold.^{22–25} Among the reported compounds, analogs **3–6** (Fig. 1) were identified to possess moderate to excellent pharmacological profiles, and they are now undergoing further evaluation in preclinical models.²²

Due to the relatively small structural scaffold of the 2-phenylcyclopropylmethylamines and the very strict steric limitations applying to these compounds as revealed by previous structure-activity relationships (SARs) studies, adding a second halogen atom to the benzene ring appeared to offer a practical approach to further enhancing ligand potency and possibly metabolic stability. Decoration of the aromatic ring of a drug candidate with halogen atoms, especially fluorine and chlorine, has been used extensively in medicinal chemistry.²⁶ The role of halogen substituents in enhancing ligand potency as well as in optimizing pharmacokinetic properties is well known. The incorporation of multi-halogen atoms is exemplified by drugs not only for peripheral diseases such as sitagliptin (**7**)²⁷ and crizotinib (**8**)²⁸, but also for CNS drugs such as aripiprazole (**9**)²⁹ (Fig. 2). Moreover, the role of halogen binding in protein–ligand interactions has been studied recently,³⁰ and halogen bonds have been proposed to provide orthogonal molecular interactions to hydrogen bonds.³¹ The lipophilicity of halogen atoms, which enhances the LogP values of small molecules, might also help to improve the blood-brain barrier (BBB) permeability of compounds designed for CNS indications.

Encouraged by the promising results that had been achieved for the mono halogenated compounds,²² and the possible beneficial effect of a second halogen, we synthesized a new series of compounds containing two halogen substituents on the benzene ring, as depicted by the general structure **10** (Fig. 2). The synthesis and SAR results are described herein, along with the ADMET evaluation and efficacy study of a key compound in four different schizophrenia-related animal behavioral models.

Chemical Synthesis and Pharmacological Profiling.

The synthesis of the di-halogenated compounds was achieved employing methods similar to those reported by us previously, starting from the appropriate benzaldehydes. Thus, various di-halogenated benzaldehydes **11a–g** were purchased or prepared according to literature methods (for details, see Supporting Information). As shown in Scheme 1, the benzaldehydes **11a–g** were converted to the corresponding acrylamides **12a–g**, with the double bond in *E* configuration, using the commercially available Wittig reagent *N*-methoxy-*N*-methyl(triphenylphosphoranylidene)acetamide. This reagent was preferred over ethyl 2-(triphenylphosphoranylidene)acetate due to the facts that better or complete *E* selectivity was observed for the newly formed double bond, and that the subsequent cyclopropanation step proceeds more efficiently with α,β -unsaturated Weinreb amides than

with esters.^{32, 33} The acrylamides **12a–g** were then subjected to the Corey-Chaykovsky cyclopropanation reaction to generate the cyclopropanes **13a–g** as their *trans* isomers, using the sulfur ylide generated from trimethylsulfoxonium iodide by treatment with sodium hydride. Next sequential reduction using DIBAL-H followed by sodium borohydride provided alcohols **14a–g** in good yields. Mitsunobu reaction of **14a–g** with phthalimide produced the phthal imides **15a–g** in excellent yields. De-protection of these imides with hydrazine hydrate afforded the primary amines, which were protected as their Boc intermediates **16a–g**. De-methylation of intermediates **16a–g** with BBr₃ in dichloromethane afforded the phenol intermediates **17a–g**. In our previous SAR studies,²² the analogs containing 2-fluoroethyl and allyl ether moieties were found to provide compounds with the best pharmacological profiles. Thus, the phenols **17a–g** were converted to the 2-fluoroethyl ethers **18a–g** using Mitsunobu conditions while alkylation of **17a–g** with allyl bromide afforded allyl ethers **19a–g**. The racemic compounds **16a–g**, **18a–g** and **19a–g** were then resolved by chiral preparative-HPLC to provide both the (–)- and (+)-enantiomers, which were then de-protected with HCl in ether to afford both enantiomers of compounds **20a–g**, **21a–g** and **22a–g** as their HCl salts.

All compounds were screened in functional assays at the 5-HT_{2C}, 5-HT_{2B} and 5-HT_{2A} receptors. Data were acquired using recombinant, stably expressed human serotonin receptors in the HEK-293 cell line, using a fluorescence imaging plate reader (FLIPR) assay as described previously.²²

As shown in Table 1, a 2-methoxy substituent provides analogs with good potency but low selectivity for 5-HT_{2C}, while the 2-fluoroethoxy and allyloxy substituents afford compounds with sometimes reduced but in other cases still good 5-HT_{2C} potency and improved selectivity.

Compared to compounds bearing a single fluorine or chlorine group at position 5,²² those with an additional fluorine atom at position 4 or 6 exhibited slightly modified pharmacological profiles. In comparison to the 5, 6-difluorinated compounds, the 4, 5-difluoro substitution pattern led to better potency, as shown by the pairs (+)-**20a** vs (+)-**20b**, (+)-**21a** vs (+)-**21b**, and (+)-**22a** vs (+)-**22b**, wherein an ~ 3-fold difference can be observed within each pair. The 2-fluoroethyl and allyl ethers provided improved subtype selectivity. Thus, compounds (+)-**21a**, (+)-**22a**, (+)-**21b**, and (+)-**22b** showed good to excellent profiles as selective 5-HT_{2C} agonists. Notably, compound (+)-**22a** represents the best of this series, exhibiting an EC₅₀ value of 8.7 nM at the 5-HT_{2C} receptors, with > 200-fold selectivity over 5-HT_{2B} and > 50-fold selectivity over 5-HT_{2A}. Given the fact that this compound displayed very weak activation of both the 5-HT_{2B} receptors (E_{max} = 35%) and 5-HT_{2A} receptors (E_{max} = 21%), (+)-**22a** is a good candidate for further studies. The superiority of compound (+)-**22a** over its 5-monofluoro analog relies on its very weak 5-HT_{2A} activity, as the latter showed greater activation of the same receptor (EC₅₀ = 374 nM, E_{max} = 56%).²²

Similarly, the 4-fluoro-5-chloro substituted analogs provided an advantage in respect to potency compared to the 5-chloro-6-fluoro scaffold, which is illustrated by comparisons of (+)-**20c** vs (+)-**20d**, (+)-**21c** vs (+)-**21d**, and (+)-**22c** vs (+)-**22d**. Compound (+)-**22c**

displayed an EC₅₀ of 42 nM at 5-HT_{2C}, no activity at 5-HT_{2A}, and good selectivity over 5-HT_{2B} (EC₅₀ = 1001 nM, E_{max} = 44%).

The introduction of a second chlorine atom which is significantly larger than fluorine, into the 5-monochloro compound, led to a notable change in potency and selectivity. Compound (–)-**20e**, bearing a 4, 5-dichloro substitution pattern, showed good potency at the 5-HT_{2C} receptor (EC₅₀ = 14 nM), and good selectivity over 5-HT_{2B} (EC₅₀ = 696 nM, E_{max} = 16%). However, only moderate selectivity over 5-HT_{2A} (EC₅₀ = 84 nM) was found. Compound (+)-**21e**, with 2-fluoroethoxy group at position 2, displayed an EC₅₀ of 18 nM and excellent selectivity against 5-HT_{2B}, but only moderate selectivity against 5-HT_{2A}.

Most of the compounds above displayed the same enantiomer preference as we had described previously,²² with (+)-enantiomer showing the better potency. However, the introduction of a chlorine atom at position 6, as in the compound **20f**, led to the reversal of this preference. (–)-**20f** showed excellent 5-HT_{2C} potency (EC₅₀ = 0.95 nM), 50-fold selectivity over 5-HT_{2B} and 40-fold selectivity over 5-HT_{2A}, while its enantiomer (+)-**20f** is 20-fold weaker at the 5-HT_{2C} receptors. The introduction of slightly larger 2-alkoxy group led to a decrease in potency, as shown by compounds **21f** and **22f**. With the combination of a 5-fluoro and 6-chloro group, similar enantiomer preference was observed for compound **20g**, with the (–)-enantiomer showing higher potency (EC₅₀ = 3.2 nM). Although (+)-**20g** is 7.5-fold weaker (EC₅₀ = 24 nM) compared to (–)-**20g**, it showed good selectivity against 5-HT_{2B} (EC₅₀ = 2176 nM, 91-fold) and 5-HT_{2A} (EC₅₀ = 769 nM, 32-fold). Compounds (–)-**21g** and (–)-**22g** showed only mid-nanomolar potency at 5-HT_{2C} but good selectivity against both 5-HT_{2A} and 5-HT_{2B} receptors. In earlier work, based on the support of good internal consistency of our potency data, we tacitly assumed that enantiomers with the same sign of optical rotation as their parents devoid of substituents on the benzene ring had the same absolute configuration as those parents.²⁵ An independent determination of the any of the new compounds' absolute configuration has not yet been carried out, but the observed switch of the eutomer from the (+)- to the (–)-isomer in the two compounds mentioned above may result from the sign of optical rotation for a given absolute configuration having changed in response to the change in the substitution pattern, as from the eutomer possessing the opposite absolute configuration in those cases.

The SAR results of the above di-halogenated ligands further demonstrate the strict steric limitations applying to these cyclopropylmethylamine-based 5-HT_{2C} ligands. (+)-**22a** is the best compound in this series with respect to its 5-HT_{2C} potency and selectivity against the 5-HT_{2B} (> 200-fold) and 5-HT_{2A} receptors (> 50-fold). The low E_{max} values of this compound at the other two receptors make it unlikely to cause side-effects associated with their activation of those receptors. We thus selected (+)-**22a** for further studies of its ADMET properties and *in vivo* efficacy in animal behavioral models.

ADMET Study of Compound (+)-**22a**

The liver microsomal stability of (+)-**22a** using both human and mouse microsomes was assayed, and the data are shown in Table 2. Better stability was observed in the mouse liver microsomes in the absence of NADPH, indicating that oxidative mechanisms are likely

involved in the metabolism of this compound. In the presence of NADPH, only 32.4% of (+)-**22a** remained after 2 h. In contrast, the compound's stability in the presence of human liver microsomes is much better, with 70.5% of the parent compound remaining under the same conditions. Thus, good metabolic stability is anticipated in humans.

A frequently confronted challenge in developing CNS targeted drugs is insufficient blood-brain barrier (BBB) penetration. Thus compound (+)-**22a** was tested in mice to verify its CNS exposure. The compound was administered intraperitoneally (ip) to CD1 mice at a dose of 10 mg/kg, and both brain and plasma concentrations were assayed at the 0.5 and 2 h time-points (Table 3). Excellent brain penetration was observed for compound (+)-**22a**, with brain/plasma concentration ratios of 29.9 and 45.0 at 0.5 and 2.0 h, respectively. The high brain penetration of this compound should thus maximize its exposure in the CNS allowing for robust activation of central 5-HT_{2C} receptors, while at the same time minimizing possible side effects due to compound interactions with peripheral systems.

The inhibition of the cytochrome P450 enzymes by (+)-**22a** was tested at five different isoforms, and the data are shown in Table 4. Although a high inhibition of CYP 1A2 (86%) was observed with (+)-**22a** when it was tested at a concentration of 10 μ M, low inhibition was observed for the other, more abundant isoforms, especially CYP 3A4 (3.4% inhibition at 10 μ M). Furthermore, inhibition of the human Ether-à-go-go related gene (hERG) channel was also tested, and (+)-**22a** displayed a dose-dependent inhibition of hERG, with an IC₅₀ value of 9.1 μ M. This is not unexpected as the structure of (+)-**22a** falls into the common templates which are known to cause hERG inhibition.³⁴ However, the high brain concentrations found for this compound should minimize the possible cardiac toxicity associated with hERG inhibition.

Efficacy Study of Compound (+)-**22a** in Animal Models of Schizophrenia-like Behaviors

To explore the possible use of (+)-**22a** in the treatment of schizophrenia, this compound was tested in four different animal behavioral paradigms. The open field test was used to evaluate the ability of the compound to decrease hyperlocomotion using *d*-amphetamine (AMPH) as the stimulant, whereas the AMPH-disrupted prepulse inhibition (PPI) test was used to analyze possible compound effects on abnormalities in sensorimotor gating.^{35, 36} The well-known novel object recognition memory (NORM) test using transgenic *N*-methyl-D-aspartate (NMDA) receptor NR1-knockdown (KD) mice was conducted to assess the ability of the compound to improve cognition.³⁷ Lastly, the ability of (+)-**22a** to induce catalepsy was evaluated and compared to haloperidol. These data are detailed below.

Open Field Activity.

Baseline activity of the mice was tested for 15 min before the administration of AMPH. During this period, only those mice from the 30 mg/kg (+)-**22a** + AMPH group showed a small, albeit significant ($p < 0.040$) reduction in locomotion compared to the Veh + AMPH group; all other groups had similar levels of baseline activities (Fig. 3A–B). Administration of AMPH induced a significant increase in locomotor activity, as shown by the comparison

of the Veh + AMPH group with the Veh + Veh group (Fig. 3A, C). Animals given (+)-**22a** showed a dose-dependent suppression of AMPH-stimulated hyperlocomotion; the 2 mg/kg dose showed no significant efficacy while 5, 10, 20, and 30 mg/kg significantly reduced the hyperactivity compared to the Veh + AMPH group. Notably, locomotor activities of mice treated with 20 or 30 mg/kg (+)-**22a** + AMPH did not significantly differ from animals in the 20 mg/kg (+)-**22a** + Veh or the Veh + Veh control groups which had similar activity levels. Thus a dose of 20 or 30 mg/kg of (+)-**22a** reduced the animal activity to normal levels.

Prepulse Inhibition (PPI).

The Veh + AMPH group showed a marked suppression of PPI compared to Veh + Veh controls ($p < 0.007$) and a loss of prepulse dependency at the 8 and 12 dB prepulse intensities (Fig. 4A). The 0.5 ($p < 0.01$) and 1 mg/kg ($p < 0.05$) doses of (+)-**22a** restored this AMPH-disrupted PPI. Mice treated with the 1 mg/kg dose + AMPH showed full prepulse dependency of the PPI response, where the percentages of the PPI at 4, 8, and 12 dB were significantly distinguished from each other ($p < 0.010$). Although 2 mg/kg (+)-**22a** increased AMPH-disrupted PPI, this was not significantly different from the Veh + AMPH group. Mice in the 4 mg/kg (+)-**22a** + Veh group showed similarly high levels of PPI with the Veh + Veh group. However, the 4 mg/kg dose failed to increase AMPH-disrupted PPI.

The startle or “pulse-only” responses to the 120 dB acoustic stimulus (Fig. 4B) were similar among the Veh + Veh, 4 mg/kg (+)-**22a** + Veh, Veh + AMPH, and 4 mg/kg (+)-**22a** + AMPH groups. In contrast, the 0.5, 1, and 2 mg/kg doses of this compound decreased startle activities with the 0.5 mg/kg dose significantly reducing this response relative to the Veh + Veh, 4 mg/kg (+)-**22a** + Veh, Veh + AMPH, and 4 mg/kg (+)-**22a** + AMPH groups ($ps < 0.035$). Null activities were not distinguished across treatment conditions, with activities of 10.60 ± 0.53 AU across all animals, which accounted for less than 4% of the average pulse-only response. Together, these data show that (+)-**22a** can normalize AMPH-disrupted PPI and restore prepulse dependency of the response, with 1 mg/kg showed the best response.

Novel Object Recognition Memory (NORM).

This task in rodents is considered similar to testing declarative memory in humans, and individuals with schizophrenia are deficient on declarative memory tasks.^{38, 39} We used the transgenic NR1-KD mice since these mice represent a hypoglutamatergic model of schizophrenia and are deficient on the novel object recognition memory test.³⁷

As expected, vehicle-treated wild type (WT) mice displayed a preference for the novel object at testing, whereas the NR1-KD animals showed no preference for either object ($p < 0.001$; Fig. 5A). Administration of (+)-**22a** produced an attenuation in NORM in WT animals with 1 mg/kg ($p < 0.010$). By comparison, these same doses increased novel object preference in NR1-KD mice, and 1 mg/kg (+)-**22a** significantly enhanced this preference relative to the vehicle-treated NR1-KD animals ($p < 0.002$) to a level that was indistinguishable from the WT vehicle control. Hence, the 1 mg/kg dose decreased NORM in WT mice, but augmented it in the hypoglutamatergic NR1-KD animals.

To determine whether the differences in responses between the genotypes or among the doses of (+)-**22a** could be attributed to neophobia, total object exploration times were examined both at training and at testing for long-term memory (LTM). The vehicle-treated NR1-KD mice were observed to spend more time exploring objects than WT controls at both training ($p < 0.006$; Fig. 5B) and testing ($p < 0.032$; Fig. 5C). By contrast, following administration of 0.5 or 1 mg/kg (+)-**22a**, object exploration was similar between genotypes during training and testing. Hence, the rescue of NORM in NR1-KD mice cannot be attributed to neophobia in these mutants.

Catalepsy.

We next determined whether compound (+)-**22a** had any cataleptic activity as compared with the vehicle and haloperidol responses. Catalepsy at baseline prior to injection (time 0) was similar for all groups with time in catalepsy = 1 second (data not shown). One hour after injection, catalepsy was very low in all groups given 0.01 to 30 mg/kg (+)-**22a** and this result was not different from that of the vehicle control (Fig. 6). In contrast, catalepsy was observed to increase in a dose-dependent fashion with haloperidol such that responses at the 1 and 10 mg/kg doses were significantly higher than those for all groups given (+)-**22a** as well as that for the vehicle control ($p < 0.001$). These findings demonstrate that the cataleptic potential of (+)-**22a** is extremely low.

CONCLUSION

A new series of cyclopropylmethylamine-based 5-HT_{2C} ligands bearing two halogen substituents on the phenyl ring have been designed and synthesized in order to further optimize this class of molecules. Compound (+)-**22a** was identified as a potent 5-HT_{2C} receptor agonist ($EC_{50} = 8.7$ nM, $E_{max} = 97\%$), with good selectivity against the 5-HT_{2B} ($EC_{50} = 1745$ nM, $E_{max} = 35\%$) and 5-HT_{2A} receptors ($EC_{50} = 491$ nM, $E_{max} = 21\%$). Improved selectivity over the 5-HT_{2A} receptor has been achieved in comparison to the analog containing a single fluorine substituent, which showed moderate potency at the 5-HT_{2A} receptor as well as higher efficacy ($EC_{50} = 374$ nM, $E_{max} = 56\%$).²² In ADMET tests, compound (+)-**22a** displayed good stability in the liver microsome assays and low inhibition of the most abundant CYP isoforms. It inhibits the hERG channel with moderate potency ($IC_{50} = 9.1$ μ M). However, a brain penetration study in mice indicated high brain concentration/plasma concentration ratios at 0.5 h (29.9) and 2.0 h (45.0), respectively.

Compound (+)-**22a** showed efficacy in two schizophrenia-related behavioral models. It suppressed AMPH-induced hyperlocomotion in the open field in a dose-dependent manner, and it normalized the AMPH-disrupted PPI. Furthermore, it rescued NORM of mice in the NR1-KD hypoglutamatergic animal model. Catalepsy was very low with compound (+)-**22a** as it was similar to that of the vehicle control and it was significantly lower than that for haloperidol. Taken together, these data support the further development of compound (+)-**22a** as a potential drug candidate for the treatment of schizophrenia. This agent may cause fewer side effects while improving cognition and avoiding weight gain in schizophrenia patients based upon its 5-HT_{2C}-directed mechanism of action.

EXPERIMENTAL SECTION

General.

All chemicals and solvents were purchased from Sigma-Aldrich or Fisher Scientific, and were used as obtained without further purification. Microwave reactions were run in a Biotage Initiator microwave reactor. Synthetic intermediates were purified by CombiFlash flash chromatography on 230–400 mesh silica gel. ^1H and ^{13}C NMR spectra were recorded on Bruker DPX-400 or AVANCE-400 spectrometers; at 400 MHz and 100 MHz respectively. NMR chemical shifts were reported in δ (ppm) using residual solvent peaks as standard (CDCl_3 –7.26 (H), 77.23 (C); CD_3OD –3.31 (H), 49.15 (C); DMSO-d_6 –2.50 (H), 39.52 (C)). Mass spectra were measured in the ESI mode at an ionization potential of 70 eV with an LC-MS MSD (Hewlett-Packard). Purity of all final compounds (greater than 95%) was determined by analytical HPLC (ACE 3AQ C_{18} column (150 \times 4.6 mm, particle size 3 μM), 0.05% TFA in H_2O /0.05% TFA in MeOH gradient eluting system). Optical rotation values were recorded on a Rudolph Research Autopol IV automatic polarimeter.

Compounds **16a–g**, **18a–g** and **19a–g** were prepared according to the methods depicted in Scheme 1. The synthetic procedures and characterization data of all intermediates can be found in the Supporting Information.

General Methods.

(1) Chiral HPLC separation of racemic **16a–g**, **18a–g**, and **19a–g**. Analytical conditions: RegisCell chiral column (25 cm \times 4.6 mm, 10 μm particle size), 1.5–15% EtOH in *n*-hexane as the mobile phase; preparative conditions: RegisPack chiral column (25 cm \times 21.1 mm, 10 μm particle size), 3.0–7.5% EtOH in *n*-hexane as the eluting system (isocratic eluent, stacked injections, flow rate = 18 mL/min, λ = 254 and 280 nm). Optical purity of both enantiomers were determined on analysis HPLC after the separation, and a second separation was done when necessary to guarantee an enantiomeric excess of > 90%. (2) Both enantiomers of compounds **16a–g**, **19a–g**, and **21a–g** were dissolved in 2M HCl in diethyl ether and stirred at room temperature for 24–48 h. The white solids formed were collected by filtration, washed with diethyl ether, and dried under vacuum to give compounds (–)-**20a–g**, (+)-**20a–g**, (–)-**21a–g**, (+)-**21a–g**, (–)-**22a–g**, and (+)-**22a–g** as HCl salts.

(–)-[2-(4,5-Difluoro-2-methoxyphenyl)cyclopropyl]methanamine Hydrochloride ((–)-20a).

White solid. HPLC: 99.8%; ^1H NMR (CD_3OD) δ 6.94–6.88 (m, 2H), 3.87 (s, 3H), 3.08 (dd, J = 13.2, 7.2 Hz, 1H), 2.93 (dd, J = 13.2, 8.0 Hz, 1H), 2.09–2.03 (m, 1H), 1.27–1.23 (m, 1H), 1.13–1.08 (m, 1H), 1.04–1.00 (m, 1H); ^{13}C NMR (CD_3OD) δ 156.2 (d, J_{CF} = 7.4 Hz), 150.2 (dd, J_{CF} = 242.7, 13.5 Hz), 145.5 (dd, J_{CF} = 236.5, 12.6 Hz), 127.1, 116.4 (d, J_{CF} = 19.2 Hz), 101.6 (d, J_{CF} = 21.4 Hz), 56.9, 45.1, 19.5, 17.8, 13.1; HRMS calcd for $\text{C}_{11}\text{H}_{14}\text{F}_2\text{NO}^+$ ($[\text{M}+\text{H}]^+$): 214.1038, found: 214.1035; $[\alpha]_{\text{D}}^{20}$ –7.9 (*c* 0.7, MeOH).

(+)-[2-(4,5-Difluoro-2-methoxyphenyl)cyclopropyl]methanamine Hydrochloride ((+)-20a).

White solid. HPLC: 99.8%; ^1H NMR (CD_3OD) δ 6.94–6.88 (m, 2H), 3.87 (s, 3H), 3.08 (dd, J = 13.2, 7.2 Hz, 1H), 2.93 (dd, J = 13.2, 8.0 Hz, 1H), 2.08–2.03 (m, 1H), 1.26–1.22 (m,

1H), 1.14–1.08 (m, 1H), 1.04–0.98 (m, 1H); HRMS calcd for C₁₁H₁₄F₂NO⁺ ([M+H]⁺): 214.1038, found: 214.1030; [α]_D²⁰ +6.0 (c 0.2, MeOH).

(–)-[2-(2,3-Difluoro-6-methoxyphenyl)cyclopropyl]methanamine Hydrochloride ((–)-20b).

White solid. HPLC: 99.6%; ¹H NMR (CD₃OD) δ 7.08 (q, *J* = 9.6 Hz, 1H), 6.74–6.71 (m, 1H), 3.86 (s, 3H), 3.13 (dd, *J* = 13.2, 6.8 Hz, 1H), 2.92 (dd, *J* = 13.2, 8.4 Hz, 1H), 1.85–1.79 (m, 1H), 1.54–1.47 (m, 1H), 1.27–1.21 (m, 1H), 1.11–1.05 (m, 1H); ¹³C NMR (CD₃OD) δ 156.7 (dd, *J*_{CF} = 5.8, 2.0 Hz), 151.3 (dd, *J*_{CF} = 243.3, 13.8 Hz), 146.7 (dd, *J*_{CF} = 237.2, 13.9 Hz), 119.3 (d, *J*_{CF} = 11.4 Hz), 115.6 (d, *J*_{CF} = 18.3 Hz), 106.8 (dd, *J*_{CF} = 6.4, 3.5 Hz), 56.8, 45.4, 18.3, 13.6, 12.9; HRMS calcd for C₁₁H₁₄F₂NO⁺ ([M+H]⁺): 214.1038, found: 214.1044; [α]_D²⁰ –36.9 (c 0.7, MeOH).

(+)-[2-(2,3-Difluoro-6-methoxyphenyl)cyclopropyl]methanamine Hydrochloride ((+)-20b).

White solid. HPLC: 99.8%; ¹H NMR (CD₃OD) δ 7.08 (q, *J* = 9.6 Hz, 1H), 6.75–6.71 (m, 1H), 3.86 (s, 3H), 3.13 (dd, *J* = 12.8, 6.8 Hz, 1H), 2.91 (dd, *J* = 12.8, 8.4 Hz, 1H), 1.85–1.79 (m, 1H), 1.51–1.46 (m, 1H), 1.27–1.22 (m, 1H), 1.10–1.05 (m, 1H); HRMS calcd for C₁₁H₁₄F₂NO⁺ ([M+H]⁺): 214.1038, found: 214.1041; [α]_D²⁰ +38.0 (c 0.2, MeOH).

(–)-[2-(5-Chloro-4-fluoro-2-methoxyphenyl)cyclopropyl]methanamine Hydrochloride ((–)-20c).

White solid. HPLC: 99.2%; ¹H NMR (CD₃OD) δ 7.06 (d, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 11.2 Hz, 1H), 3.89 (s, 3H), 3.08 (dd, *J* = 13.2, 7.2 Hz, 1H), 2.93 (dd, *J* = 13.2, 8.0 Hz, 1H), 2.06–2.00 (m, 1H), 1.29–1.21 (m, 1H), 1.13–1.08 (m, 1H), 1.04–0.98 (m, 1H); ¹³C NMR (CD₃OD) δ 159.8, 158.6 (d, *J*_{CF} = 235.0 Hz), 129.2, 128.0, 112.0 (d, *J*_{CF} = 17.9 Hz), 101.2 (d, *J*_{CF} = 25.4 Hz), 56.8, 45.1, 19.3, 17.7, 12.9; HRMS (ESI) *m/z* calcd for C₁₁H₁₄ClFNO⁺ ([M+H]⁺): 230.0742, found: 230.0719; [α]_D²⁰ –37.4 (c 0.5, MeOH).

(+)-[2-(5-Chloro-4-fluoro-2-methoxyphenyl)cyclopropyl]methanamine Hydrochloride ((+)-20c).

White solid. HPLC: 99.7%; ¹H NMR (CD₃OD) δ 7.06 (d, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 11.2 Hz, 1H), 3.89 (s, 3H), 3.08 (dd, *J* = 13.2, 7.2 Hz, 1H), 2.92 (dd, *J* = 13.2, 8.0 Hz, 1H), 2.06–2.00 (m, 1H), 1.28–1.21 (m, 1H), 1.14–1.08 (m, 1H), 1.04–0.98 (m, 1H); ¹³C NMR (CD₃OD) δ 159.8, 158.6 (d, *J*_{CF} = 234.8 Hz), 129.2, 128.0, 112.1 (d, *J*_{CF} = 17.8 Hz), 101.2 (d, *J*_{CF} = 25.7 Hz), 56.8, 45.1, 19.3, 17.7, 12.9; HRMS (ESI) *m/z* calcd for C₁₁H₁₄ClFNO⁺ ([M+H]⁺): 230.0742, found: 230.0724; [α]_D²⁰ +35.6 (c 0.5, MeOH).

(–)-[2-(3-Chloro-2-fluoro-6-methoxyphenyl)cyclopropyl]methanamine Hydrochloride ((–)-20d).

White solid. HPLC: 98.9%; ¹H NMR (CD₃OD) δ 7.28 (t, *J* = 8.8 Hz, 1H), 6.79 (dd, *J* = 9.2, 1.6 Hz, 1H), 3.87 (s, 3H), 3.11 (dd, *J* = 13.2, 6.8 Hz, 1H), 2.90 (dd, *J* = 13.2, 8.0 Hz, 1H), 1.82–1.76 (m, 1H), 1.48–1.43 (m, 1H), 1.23–1.18 (m, 1H), 1.09–1.03 (m, 1H); ¹³C NMR (CD₃OD) δ 160.1 (d, *J*_{CF} = 6.6 Hz), 158.7 (d, *J*_{CF} = 243.8 Hz), 129.6, 118.9 (d, *J*_{CF} = 20.1 Hz), 113.9 (d, *J*_{CF} = 19.3 Hz), 108.5, 56.8, 45.4, 18.4, 13.7, 13.1; HRMS (ESI) *m/z* calcd for C₁₁H₁₄ClFNO⁺ ([M+H]⁺): 230.0742, found: 230.0740; [α]_D²⁰ –54.0 (c 0.15, MeOH).

(+)-[2-(3-Chloro-2-fluoro-6-methoxyphenyl)cyclopropyl]methanamine Hydrochloride ((+)-20d).

White solid. HPLC: 99.4%; ^1H NMR (CD_3OD) δ 7.29 (t, J = 8.8 Hz, 1H), 6.79 (dd, J = 8.8, 1.6 Hz, 1H), 3.88 (s, 3H), 3.11 (dd, J = 12.8, 6.4 Hz, 1H), 2.90 (dd, J = 12.8, 8.4 Hz, 1H), 1.82–1.77 (m, 1H), 1.48–1.44 (m, 1H), 1.24–1.18 (m, 1H), 1.09–1.04 (m, 1H); ^{13}C NMR (CD_3OD) δ 160.1 (d, J_{CF} = 6.6 Hz), 158.7 (d, J_{CF} = 243.8 Hz), 129.6, 118.9 (d, J_{CF} = 20.1 Hz), 113.8 (d, J_{CF} = 19.3 Hz), 108.4, 56.8, 45.4, 18.4, 13.7, 13.0; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{14}\text{ClFNO}^+$ ($[\text{M}+\text{H}]^+$): 230.0742, found: 230.0744; $[\alpha]_{\text{D}}^{20}$ +50.0 (c 0.1, MeOH).

(-)-[2-(4,5-Dichloro-2-methoxyphenyl)cyclopropyl]methanamine Hydrochloride ((-)-20e).

White solid. HPLC: 99.6%; ^1H NMR (CD_3OD) δ 7.11 (s, 2H), 3.88 (s, 3H), 3.08 (dd, J = 13.2, 7.2 Hz, 1H), 2.92 (dd, J = 13.2, 8.0 Hz, 1H), 2.09–2.04 (m, 1H), 1.28–1.26 (m, 1H), 1.16–1.10 (m, 1H), 1.06–1.00 (m, 1H); ^{13}C NMR (CD_3OD) δ 159.1, 131.6, 131.5, 129.2, 124.5, 113.7, 56.8, 45.0, 19.5, 17.8, 13.2; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{14}\text{Cl}_2\text{NO}^+$ ($[\text{M}+\text{H}]^+$): 246.0447, found: 246.0438; $[\alpha]_{\text{D}}^{20}$ -37.4 (c 0.3, MeOH).

(+)-[2-(4,5-Dichloro-2-methoxyphenyl)cyclopropyl]methanamine Hydrochloride ((+)-20e).

White solid. HPLC: 99.7%; ^1H NMR (CD_3OD) δ 7.11 (s, 2H), 3.89 (s, 3H), 3.08 (dd, J = 13.2, 7.6 Hz, 1H), 2.93 (dd, J = 12.8, 8.0 Hz, 1H), 2.09–2.04 (m, 1H), 1.29–1.26 (m, 1H), 1.15–1.10 (m, 1H), 1.06–1.02 (m, 1H); ^{13}C NMR (CD_3OD) δ 159.1, 131.6, 131.5, 129.2, 124.5, 113.7, 56.8, 45.0, 19.5, 17.8, 13.2; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{14}\text{Cl}_2\text{NO}^+$ ($[\text{M}+\text{H}]^+$): 246.0447, found: 246.0441; $[\alpha]_{\text{D}}^{20}$ +37.7 (c 0.4, MeOH).

(-)-[2-(2,3-Dichloro-6-methoxyphenyl)cyclopropyl]methanamine Hydrochloride ((-)-20f).

White solid. HPLC: 99.9%; ^1H NMR (CD_3OD) δ 7.40 (d, J = 8.8 Hz, 1H), 6.96 (d, J = 8.8 Hz, 1H), 3.88 (s, 3H), 3.06 (d, J = 7.2 Hz, 2H), 1.78–1.73 (m, 1H), 1.44–1.40 (m, 1H), 1.21–1.15 (m, 1H), 1.11–1.06 (m, 1H); ^{13}C NMR (CD_3OD) δ 159.9, 135.9, 130.2, 129.6, 125.7, 111.7, 56.7, 45.4, 20.1, 18.3, 15.2; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{14}\text{Cl}_2\text{NO}^+$ ($[\text{M}+\text{H}]^+$): 246.0447, found: 246.0449; $[\alpha]_{\text{D}}^{20}$ -62.0 (c 0.1, MeOH).

(+)-[2-(2,3-Dichloro-6-methoxyphenyl)cyclopropyl]methanamine Hydrochloride ((+)-20f).

White solid. HPLC: 99.8%; ^1H NMR (CD_3OD) δ 7.40 (d, J = 9.2 Hz, 1H), 6.96 (d, J = 9.2 Hz, 1H), 3.88 (s, 3H), 3.06 (d, J = 7.2 Hz, 2H), 1.77–1.74 (m, 1H), 1.44–1.42 (m, 1H), 1.21–1.15 (m, 1H), 1.09–1.05 (m, 1H); ^{13}C NMR (CD_3OD) δ 159.9, 135.9, 130.2, 129.6, 125.7, 111.7, 56.7, 45.4, 20.1, 18.3, 15.2; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{14}\text{Cl}_2\text{NO}^+$ ($[\text{M}+\text{H}]^+$): 246.0447, found: 246.0448; $[\alpha]_{\text{D}}^{20}$ +69.0 (c 0.2, MeOH).

(-)-[2-(2-Chloro-3-fluoro-6-methoxyphenyl)cyclopropyl]methanamine Hydrochloride ((-)-20g).

White solid. HPLC: 99.7%; ^1H NMR (CD_3OD) δ 7.10 (t, J = 8.8 Hz, 1H), 6.92 (dd, J = 9.2, 4.4 Hz, 1H), 3.86 (s, 3H), 3.10–3.00 (m, 2H), 1.76–1.73 (m, 1H), 1.47–1.42 (m, 1H), 1.19–1.08 (m, 2H); ^{13}C NMR (CD_3OD) δ 157.1, 154.2 (d, J_{CF} = 237.8 Hz), 129.1, 124.6 (d, J_{CF} = 18.2 Hz), 115.5 (d, J_{CF} = 22.9 Hz), 111.1 (d, J_{CF} = 8.5 Hz), 56.8, 45.4, 19.6, 17.5, 14.7;

HRMS (ESI) m/z calcd for $C_{11}H_{14}ClFNO^+$ ($[M+H]^+$): 230.0742, found: 230.0723; $[\alpha]_D^{20}$ -66.4 (c 0.3, MeOH).

**(+)-[2-(2-Chloro-3-fluoro-6-methoxyphenyl)cyclopropyl]methanamine Hydrochloride
(+)-20g).**

White solid. HPLC: 99.6%; 1H NMR (CD_3OD) δ 7.10 (t, J = 8.8 Hz, 1H), 6.92 (dd, J = 9.2, 4.4 Hz, 1H), 3.86 (s, 3H), 3.10–3.00 (m, 2H), 1.76–1.73 (m, 1H), 1.47–1.43 (m, 1H), 1.19–1.07 (m, 2H); ^{13}C NMR (CD_3OD) δ 157.1, 154.2 (d, J_{CF} = 237.9 Hz), 129.1, 124.6 (d, J_{CF} = 18.1 Hz), 115.5 (d, J_{CF} = 22.9 Hz), 111.1 (d, J_{CF} = 8.4 Hz), 56.8, 45.4, 19.6, 17.5, 14.7; HRMS (ESI) m/z calcd for $C_{11}H_{14}ClFNO^+$ ($[M+H]^+$): 230.0742, found: 230.0758; $[\alpha]_D^{20}$ $+69.4$ (c 0.3, MeOH).

**(-)-[2-[4,5-Difluoro-2-(2-fluoroethoxy)phenyl]cyclopropyl]methanamine Hydrochloride
(-)-21a).**

White solid. HPLC: 99.7%; 1H NMR (CD_3OD) δ 6.99–6.93 (m, 2H), 4.88–4.74 (m, 2H), 4.32–4.22 (m, 2H), 3.03–3.00 (m, 2H), 2.11–2.08 (m, 1H), 1.25–1.15 (m, 2H), 1.05–1.01 (m, 1H); ^{13}C NMR (CD_3OD) δ 155.0 (dd, J_{CF} = 7.4, 2.0 Hz), 150.1 (dd, J_{CF} = 243.0, 13.5 Hz), 145.8 (dd, J_{CF} = 237.3, 12.6 Hz), 127.6, 116.6 (d, J_{CF} = 19.5 Hz), 102.9 (d, J_{CF} = 21.4 Hz), 83.4 (d, J_{CF} = 166.9 Hz), 69.9 (d, J_{CF} = 18.8 Hz), 44.9, 19.7, 17.8, 12.8; HRMS calcd for $C_{12}H_{15}F_3NO^+$ ($[M+H]^+$): 246.1100, found: 246.1106; $[\alpha]_D^{20}$ -1.5 (c 0.4, MeOH).

**(+)-[2-[4,5-Difluoro-2-(2-fluoroethoxy)phenyl]cyclopropyl]methanamine Hydrochloride
(+)-21a).**

White solid. HPLC: 99.5%; 1H NMR (CD_3OD) δ 6.99–6.93 (m, 2H), 4.88–4.74 (m, 2H), 4.32–4.22 (m, 2H), 3.03–3.00 (m, 2H), 2.11–2.07 (m, 1H), 1.24–1.15 (m, 2H), 1.05–1.00 (m, 1H); HRMS calcd for $C_{12}H_{15}F_3NO^+$ ($[M+H]^+$): 246.1100, found: 246.1086; $[\alpha]_D^{20}$ $+1.4$ (c 0.1, MeOH).

**(-)-[2-[2,3-Difluoro-6-(2-fluoroethoxy)phenyl]cyclopropyl]methanamine Hydrochloride
(-)-21b).**

White solid. HPLC: 99.6%; 1H NMR (CD_3OD) δ 7.09 (q, J = 9.6 Hz, 1H), 6.77–6.73 (m, 1H), 4.88–4.86 (m, 1H), 4.77–4.74 (m, 1H), 4.31–4.20 (m, 2H), 3.10 (dd, J = 13.2, 7.6 Hz, 1H), 2.99 (dd, J = 13.2, 7.6 Hz, 1H), 1.89–1.84 (m, 1H), 1.56–1.53 (m, 1H), 1.35–1.31 (m, 1H), 1.12–1.07 (m, 1H); ^{13}C NMR (CD_3OD) δ 155.6 (dd, J_{CF} = 5.6, 2.1 Hz), 151.4 (dd, J_{CF} = 243.7, 13.9 Hz), 147.0 (dd, J_{CF} = 238.0, 13.8 Hz), 119.9 (d, J_{CF} = 11.5 Hz), 115.6 (d, J_{CF} = 18.3 Hz), 108.2 (dd, J_{CF} = 3.6 Hz), 83.4 (d, J_{CF} = 167.1 Hz), 69.7 (d, J_{CF} = 18.9 Hz), 45.2, 18.4, 13.8, 12.9; HRMS calcd for $C_{12}H_{15}F_3NO^+$ ($[M+H]^+$): 246.1100, found: 246.1099; $[\alpha]_D^{20}$ -36.0 (c 0.5, MeOH).

**(+)-[2-[2,3-Difluoro-6-(2-fluoroethoxy)phenyl]cyclopropyl]methanamine Hydrochloride
(+)-21b).**

White solid. HPLC: 99.3%; 1H NMR (CD_3OD) δ 7.09 (q, J = 9.6 Hz, 1H), 6.77–6.73 (m, 1H), 4.88–4.85 (m, 1H), 4.76–4.74 (m, 1H), 4.31–4.20 (m, 2H), 3.09 (dd, J = 13.2, 7.6 Hz, 1H), 2.99 (dd, J = 12.8, 7.6 Hz, 1H), 1.89–1.84 (m, 1H), 1.56–1.53 (m, 1H), 1.35–1.31 (m,

1H), 1.12–1.07 (m, 1H); HRMS calcd for C₁₂H₁₅F₃NO⁺ ([M+H]⁺): 246.1100, found: 246.1088; [α]_D²⁰ +30.2 (c 0.2, MeOH).

(–)-[2-[5-Chloro-4-fluoro-2-(2-fluoroethoxy)phenyl]cyclopropyl]methanamine Hydrochloride ((–)-21c).

White solid. HPLC: 99.2%; ¹H NMR (CD₃OD) δ 7.10 (d, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 11.2 Hz, 1H), 4.86–4.76 (m, 2H), 4.35–4.24 (m, 2H), 3.05–2.97 (m, 2H), 2.10–2.04 (m, 1H), 1.26–1.15 (m, 2H), 1.05–1.00 (m, 1H); ¹³C NMR (CD₃OD) δ 158.6, 158.5 (d, *J*_{CF} = 244.2 Hz), 129.5, 128.3, 112.7 (d, *J*_{CF} = 17.8 Hz), 102.3 (d, *J*_{CF} = 25.4 Hz), 83.3 (d, *J*_{CF} = 167.0 Hz), 69.7 (d, *J*_{CF} = 18.8 Hz), 45.0, 19.5, 17.8, 12.6; HRMS calcd for C₁₂H₁₅ClF₂NO⁺ ([M+H]⁺): 262.0805, found: 262.0782; [α]_D²⁰ –26.4 (c 0.5, MeOH).

(+)-[2-[5-Chloro-4-fluoro-2-(2-fluoroethoxy)phenyl]cyclopropyl]methanamine Hydrochloride ((+)-21c).

White solid. HPLC: 99.3%; ¹H NMR (CD₃OD) δ 7.10 (d, *J* = 8.4 Hz, 1H), 6.96 (d, *J* = 10.8 Hz, 1H), 4.86–4.75 (m, 2H), 4.34–4.24 (m, 2H), 3.04–2.98 (m, 2H), 2.09–2.04 (m, 1H), 1.25–1.15 (m, 2H), 1.05–1.00 (m, 1H); ¹³C NMR (CD₃OD) δ 158.6, 158.5 (d, *J*_{CF} = 243.9 Hz), 129.5, 128.3, 112.7 (d, *J*_{CF} = 17.5 Hz), 102.3 (d, *J*_{CF} = 25.5 Hz), 83.3 (d, *J*_{CF} = 167.1 Hz), 69.7 (d, *J*_{CF} = 19.0 Hz), 45.0, 19.5, 17.8, 12.6; HRMS calcd for C₁₂H₁₅ClF₂NO⁺ ([M+H]⁺): 262.0805, found: 262.0788; [α]_D²⁰ +28.4 (c 0.5, MeOH).

(–)-[2-[3-Chloro-2-fluoro-6-(2-fluoroethoxy)phenyl]cyclopropyl]methanamine Hydrochloride ((–)-21d).

White solid. HPLC: 98.8%; ¹H NMR (CD₃OD) δ 7.29 (t, *J* = 8.8 Hz, 1H), 6.81 (d, *J* = 9.2 Hz, 1H), 4.88–4.83 (m, 1H), 4.77–4.75 (m, 1H), 4.35–4.21 (m, 2H), 3.09 (dd, *J* = 13.2, 7.2 Hz, 1H), 2.98 (dd, *J* = 13.2, 7.6 Hz, 1H), 1.88–1.83 (m, 1H), 1.55–1.51 (m, 1H), 1.32–1.28 (m, 1H), 1.12–1.06 (m, 1H); ¹³C NMR (CD₃OD) δ 159.0 (d, *J*_{CF} = 6.4 Hz), 158.7 (d, *J*_{CF} = 244.0 Hz), 129.5, 119.4 (d, *J*_{CF} = 14.7 Hz), 114.4 (d, *J*_{CF} = 19.2 Hz), 109.5, 83.3 (d, *J*_{CF} = 167.4 Hz), 69.6 (d, *J*_{CF} = 19.0 Hz), 45.3, 18.5, 13.9, 13.1; HRMS calcd for C₁₂H₁₅ClF₂NO⁺ ([M+H]⁺): 262.0805, found: 262.0791; [α]_D²⁰ –53.0 (c 0.3, MeOH).

(+)-[2-[3-Chloro-2-fluoro-6-(2-fluoroethoxy)phenyl]cyclopropyl]methanamine Hydrochloride ((+)-21d).

White solid. HPLC: 99.3%; ¹H NMR (CD₃OD) δ 7.29 (t, *J* = 8.8 Hz, 1H), 6.81 (dd, *J* = 8.8, 1.4 Hz, 1H), 4.88–4.83 (m, 1H), 4.77–4.74 (m, 1H), 4.33–4.23 (m, 2H), 3.10 (dd, *J* = 12.8, 7.2 Hz, 1H), 2.98 (dd, *J* = 13.2, 7.6 Hz, 1H), 1.88–1.83 (m, 1H), 1.55–1.51 (m, 1H), 1.32–1.28 (m, 1H), 1.12–1.06 (m, 1H); ¹³C NMR (CD₃OD) δ 159.0 (d, *J*_{CF} = 6.5 Hz), 158.7 (d, *J*_{CF} = 244.4 Hz), 129.5, 119.4 (d, *J*_{CF} = 14.7 Hz), 114.4 (d, *J*_{CF} = 19.3 Hz), 109.5, 83.3 (d, *J*_{CF} = 167.3 Hz), 69.6 (d, *J*_{CF} = 19.0 Hz), 45.3, 18.5, 13.9, 13.1; HRMS calcd for C₁₂H₁₅ClF₂NO⁺ ([M+H]⁺): 262.0805, found: 246.0793; [α]_D²⁰ +53.5 (c 0.4, MeOH).

(-)-[2-[4,5-Dichloro-2-(2-fluoroethoxy)phenyl]cyclopropyl]methanamine Hydrochloride ((-)-21e).

White solid. HPLC: 99.6%; ^1H NMR (CD_3OD) δ 7.16 (s, 1H), 7.15 (s, 1H), 4.88–4.74 (m, 2H), 4.37–4.25 (m, 2H), 3.04–3.02 (m, 2H), 2.13–2.08 (m, 1H), 1.29–1.25 (m, 1H), 1.23–1.18 (m, 1H), 1.08–1.01 (m, 1H); HRMS calcd for $\text{C}_{12}\text{H}_{15}\text{Cl}_2\text{FNO}^+$ ($[\text{M}+\text{H}]^+$): 278.0509, found: 278.0496; $[\alpha]_{\text{D}}^{20}$ -32.4 (c 0.25, MeOH).

(+)-[2-[4,5-Dichloro-2-(2-fluoroethoxy)phenyl]cyclopropyl]methanamine Hydrochloride ((+)-21e).

White solid. HPLC: 99.4%; ^1H NMR (CD_3OD) δ 7.16 (s, 1H), 7.15 (s, 1H), 4.88–4.75 (m, 2H), 4.36–4.24 (m, 2H), 3.04–3.01 (m, 2H), 2.13–2.08 (m, 1H), 1.29–1.26 (m, 1H), 1.23–1.19 (m, 1H), 1.08–1.03 (m, 1H); ^{13}C NMR (CD_3OD) δ 158.1, 131.9, 131.6, 129.5, 125.1, 114.8, 83.3 (d, $J_{\text{CF}} = 167.1$ Hz), 69.7 (d, $J_{\text{CF}} = 18.9$ Hz), 44.9, 19.7, 17.9, 12.9; HRMS calcd for $\text{C}_{12}\text{H}_{15}\text{Cl}_2\text{FNO}^+$ ($[\text{M}+\text{H}]^+$): 278.0509, found: 278.0508; $[\alpha]_{\text{D}}^{20}$ $+30.2$ (c 0.5, MeOH).

(-)-[2-[2,3-Dichloro-6-(2-fluoroethoxy)phenyl]cyclopropyl]methanamine Hydrochloride ((-)-21f).

White solid. HPLC: 99.3%; ^1H NMR ($\text{DMSO}-d_6$) δ 8.09 (br, 3H), 7.48 (d, $J = 8.8$ Hz, 1H), 7.03 (d, $J = 8.8$ Hz, 1H), 4.90–4.73 (m, 2H), 4.32–4.22 (m, 2H), 3.26–3.22 (m, 1H), 2.64–2.59 (m, 1H), 1.78–1.73 (m, 1H), 1.45–1.41 (m, 1H), 1.18–1.12 (m, 1H), 1.04–1.00 (m, 1H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 157.1, 133.8, 128.8, 128.6, 123.5, 112.4, 82.2 (d, $J_{\text{CF}} = 165.6$ Hz), 68.1 (d, $J_{\text{CF}} = 18.6$ Hz), 42.7, 18.7, 16.9, 14.0; HRMS calcd for $\text{C}_{12}\text{H}_{15}\text{Cl}_2\text{FNO}^+$ ($[\text{M}+\text{H}]^+$): 278.0509, found: 278.0494; $[\alpha]_{\text{D}}^{20}$ -96.0 (c 0.1, MeOH).

(+)-[2-[2,3-Dichloro-6-(2-fluoroethoxy)phenyl]cyclopropyl]methanamine Hydrochloride ((+)-21f).

White solid. HPLC: 99.0%; ^1H NMR ($\text{DMSO}-d_6$) δ 8.11 (br, 3H), 7.47 (d, $J = 8.8$ Hz, 1H), 7.03 (d, $J = 8.8$ Hz, 1H), 4.89–4.73 (m, 2H), 4.32–4.22 (m, 2H), 3.24 (dd, $J = 12.4, 5.2$ Hz, 1H), 2.64–2.59 (m, 1H), 1.78–1.73 (m, 1H), 1.45–1.41 (m, 1H), 1.18–1.13 (m, 1H), 1.04–1.00 (m, 1H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 157.0, 133.7, 128.8, 128.6, 123.5, 112.4, 82.2 (d, $J_{\text{CF}} = 165.6$ Hz), 68.1 (d, $J_{\text{CF}} = 18.6$ Hz), 42.7, 18.6, 16.9, 13.9; HRMS calcd for $\text{C}_{12}\text{H}_{15}\text{Cl}_2\text{FNO}^+$ ($[\text{M}+\text{H}]^+$): 278.0509, found: 278.0493; $[\alpha]_{\text{D}}^{20}$ $+70.0$ (c 0.1, MeOH).

(-)-[2-[2-Chloro-3-fluoro-6-(2-fluoroethoxy)phenyl]cyclopropyl]methanamine Hydrochloride ((-)-21g).

White solid. HPLC: 99.1%; ^1H NMR (CD_3OD) δ 7.11 (t, $J = 8.8$ Hz, 1H), 6.94 (dd, $J = 9.0, 4.2$ Hz, 1H), 4.88–4.85 (m, 1H), 4.77–4.74 (m, 1H), 4.32–4.20 (m, 2H), 3.34 (dd, $J = 13.2, 6.4$ Hz, 1H), 2.85 (dd, $J = 13.2, 8.8$ Hz, 1H), 1.85–1.79 (m, 1H), 1.56–1.50 (m, 1H), 1.23–1.18 (m, 2H); ^{13}C NMR (CD_3OD) δ 156.0, 154.5 (d, $J_{\text{CF}} = 238.6$ Hz), 129.7, 124.7 (d, $J_{\text{CF}} = 18.2$ Hz), 115.5 (d, $J_{\text{CF}} = 22.9$ Hz), 112.6 (d, $J_{\text{CF}} = 7.6$ Hz), 83.4 (d, $J_{\text{CF}} = 167.3$ Hz), 69.8 (d, $J_{\text{CF}} = 18.9$ Hz), 45.3, 19.7, 17.7, 14.7; HRMS calcd for $\text{C}_{12}\text{H}_{15}\text{ClF}_2\text{NO}^+$ ($[\text{M}+\text{H}]^+$): 262.0805, found: 262.0801; $[\alpha]_{\text{D}}^{20}$ -54.5 (c 0.2, MeOH).

(+)-[2-[2-Chloro-3-fluoro-6-(2-fluoroethoxy)phenyl]cyclopropyl]methanamine Hydrochloride ((+)-21g).

White solid. HPLC: 99.2%; ^1H NMR (CD_3OD) δ 7.11 (t, J = 8.8 Hz, 1H), 6.94 (dd, J = 9.0, 4.2 Hz, 1H), 4.88–4.85 (m, 1H), 4.78–4.74 (m, 1H), 4.33–4.20 (m, 2H), 3.34 (dd, J = 13.2, 8.8 Hz, 1H), 2.85 (dd, J = 13.2, 8.8 Hz, 1H), 1.85–1.79 (m, 1H), 1.56–1.52 (m, 1H), 1.24–1.17 (m, 2H); ^{13}C NMR (CD_3OD) δ 156.0, 154.5 (d, J_{CF} = 238.6 Hz), 129.7, 124.7 (d, J_{CF} = 18.2 Hz), 115.5 (d, J_{CF} = 22.8 Hz), 112.6 (d, J_{CF} = 7.7 Hz), 83.4 (d, J_{CF} = 167.3 Hz), 69.8 (d, J_{CF} = 19.0 Hz), 45.3, 19.7, 17.7, 14.7; HRMS calcd for $\text{C}_{12}\text{H}_{15}\text{ClF}_2\text{NO}^+$ ($[\text{M}+\text{H}]^+$): 262.0805, found: 262.0807; $[\alpha]_{\text{D}}^{20}$ +61.4 (c 0.3, MeOH).

(-)-[2-[2-(Allyloxy)-4,5-difluorophenyl]cyclopropyl]methanamine Hydrochloride ((-)-22a).

White solid. HPLC: 99.3%; ^1H NMR (CD_3OD) δ 6.95–6.88 (m, 2H), 6.18–6.08 (m, 1H), 5.47 (dd, J = 17.2, 1.6 Hz, 1H), 5.33 (dd, J = 10.4, 1.6 Hz, 1H), 4.60 (d, J = 5.2 Hz, 2H), 3.07 (dd, J = 12.8, 7.2 Hz, 1H), 2.98 (dd, J = 13.2, 8.0 Hz, 1H), 2.17–2.09 (m, 1H), 1.33–1.29 (m, 1H), 1.13–1.02 (m, 2H); ^{13}C NMR (CD_3OD) δ 155.0 (dd, J_{CF} = 7.6, 2.0 Hz), 150.0 (dd, J_{CF} = 242.8, 13.5 Hz), 145.7 (dd, J_{CF} = 236.9, 12.7 Hz), 134.5, 127.5, 118.6, 116.2 (d, J_{CF} = 19.2 Hz), 103.1 (d, J_{CF} = 21.3 Hz), 71.1, 45.1, 19.4, 18.0, 13.4; HRMS calcd for $\text{C}_{13}\text{H}_{16}\text{F}_2\text{NO}^+$ ($[\text{M}+\text{H}]^+$): 240.1194, found: 240.1189; $[\alpha]_{\text{D}}^{20}$ -14.0 (c 0.4, MeOH).

(+)-[2-[2-(Allyloxy)-4,5-difluorophenyl]cyclopropyl]methanamine Hydrochloride ((+)-22a).

White solid. HPLC: 99.4%; ^1H NMR (CD_3OD) δ 6.94–6.89 (m, 2H), 6.18–6.08 (m, 1H), 5.47 (dd, J = 17.2, 1.6 Hz, 1H), 5.33 (dd, J = 10.8, 1.6 Hz, 1H), 4.60 (d, J = 5.2 Hz, 2H), 3.06 (dd, J = 13.2, 7.2 Hz, 1H), 2.97 (dd, J = 13.2, 7.6 Hz, 1H), 2.17–2.08 (m, 1H), 1.33–1.28 (m, 1H), 1.13–1.02 (m, 2H); HRMS calcd for $\text{C}_{13}\text{H}_{16}\text{F}_2\text{NO}^+$ ($[\text{M}+\text{H}]^+$): 240.1194, found: 246.1192; $[\alpha]_{\text{D}}^{20}$ +12.0 (c 0.1, MeOH).

(-)-[2-[6-(Allyloxy)-2,3-difluorophenyl]cyclopropyl]methanamine hydrochloride ((-)-22b).

White solid. HPLC: 97.0%; ^1H NMR (CD_3OD) δ 7.06 (q, J = 9.6 Hz, 1H), 6.75–6.71 (m, 1H), 6.16–6.09 (m, 1H), 5.46 (dd, J = 17.2, 1.6 Hz, 1H), 5.32 (dd, J = 10.8, 1.6 Hz, 1H), 4.59 (d, J = 5.6 Hz, 2H), 3.08 (dd, J = 13.2, 7.6 Hz, 1H), 3.01 (dd, J = 13.2, 7.6 Hz, 1H), 1.91–1.86 (m, 1H), 1.61–1.56 (m, 1H), 1.31–1.27 (m, 1H), 1.12–1.08 (m, 1H); ^{13}C NMR (CD_3OD) δ 155.7 (d, J_{CF} = 5.6 Hz), 151.3 (dd, J_{CF} = 243.3, 14.0 Hz), 146.8 (dd, J_{CF} = 237.6, 13.8 Hz), 134.6, 119.7 (d, J_{CF} = 11.2 Hz), 118.6, 115.5 (d, J_{CF} = 18.3 Hz), 108.5, 71.1, 45.3, 18.3, 13.9, 13.0; HRMS calcd for $\text{C}_{13}\text{H}_{16}\text{F}_2\text{NO}^+$ ($[\text{M}+\text{H}]^+$): 240.1194, found: 240.1188; $[\alpha]_{\text{D}}^{20}$ -46.8 (c 0.5, MeOH).

(+)-[2-[6-(Allyloxy)-2,3-difluorophenyl]cyclopropyl]methanamine hydrochloride ((+)-22b).

White solid. HPLC: 99.7%; ^1H NMR (CD_3OD) δ 7.06 (q, J = 9.6 Hz, 1H), 6.75–6.71 (m, 1H), 6.16–6.08 (m, 1H), 5.46 (dd, J = 17.2, 1.6 Hz, 1H), 5.32 (dd, J = 10.4, 1.6 Hz, 1H), 4.59 (d, J = 5.6 Hz, 2H), 3.07 (dd, J = 13.2, 7.6 Hz, 1H), 3.00 (dd, J = 13.2, 7.6 Hz, 1H), 1.91–1.85 (m, 1H), 1.60–1.56 (m, 1H), 1.31–1.26 (m, 1H), 1.11–1.06 (m, 1H); HRMS calcd for $\text{C}_{13}\text{H}_{16}\text{F}_2\text{NO}^+$ ($[\text{M}+\text{H}]^+$): 240.1194, found: 240.1191; $[\alpha]_{\text{D}}^{20}$ +41.6 (c 0.2, MeOH).

(-)-[2-[2-(Allyloxy)-5-chloro-4-fluorophenyl]cyclopropyl]methanamine Hydrochloride ((-)-22c).

White solid. HPLC: 99.8%; ^1H NMR (CD_3OD) δ 7.07 (d, $J = 8.4$ Hz, 1H), 6.90 (d, $J = 11.2$ Hz, 1H), 6.18–6.08 (m, 1H), 5.47 (dd, $J = 13.6, 1.6$ Hz, 1H), 5.34 (dd, $J = 10.4, 1.6$ Hz, 1H), 4.62 (d, $J = 5.2$ Hz, 2H), 3.06 (dd, $J = 12.8, 7.2$ Hz, 1H), 2.98 (dd, $J = 12.8, 8.0$ Hz, 1H), 2.11–2.05 (m, 1H), 1.32–1.28 (m, 1H), 1.13–1.01 (m, 2H); ^{13}C NMR (CD_3OD) δ 158.5, 158.4 (d, $J_{\text{CF}} = 243.8$ Hz), 134.3, 129.2, 128.3, 118.8, 112.3 (d, $J_{\text{CF}} = 17.6$ Hz), 102.4 (d, $J_{\text{CF}} = 25.4$ Hz), 70.9, 45.0, 19.2, 17.9, 13.2; HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{16}\text{ClFNO}^+$ ($[\text{M}+\text{H}]^+$): 256.0899, found: 256.0875; $[\alpha]_{\text{D}}^{20} -36.2$ (c 0.5, MeOH).

(+)-[2-[2-(Allyloxy)-5-chloro-4-fluorophenyl]cyclopropyl]methanamine Hydrochloride ((+)-22c).

White solid. HPLC: 99.3%; ^1H NMR (CD_3OD) δ 7.07 (d, $J = 8.4$ Hz, 1H), 6.91 (d, $J = 11.2$ Hz, 1H), 6.17–6.08 (m, 1H), 5.47 (dd, $J = 13.6, 1.6$ Hz, 1H), 5.34 (dd, $J = 11.2, 1.2$ Hz, 1H), 4.62 (d, $J = 5.2$ Hz, 2H), 3.06 (dd, $J = 11.2, 7.2$ Hz, 1H), 2.99 (dd, $J = 12.8, 5.6$ Hz, 1H), 2.11–2.05 (m, 1H), 1.32–1.28 (m, 1H), 1.13–1.01 (m, 2H); ^{13}C NMR (CD_3OD) δ 158.5, 158.4 (d, $J_{\text{CF}} = 243.7$ Hz), 134.3, 129.2, 128.3, 118.8, 112.3 (d, $J_{\text{CF}} = 17.6$ Hz), 102.4 (d, $J_{\text{CF}} = 25.4$ Hz), 70.9, 45.0, 19.2, 17.9, 13.2; HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{16}\text{ClFNO}^+$ ($[\text{M}+\text{H}]^+$): 256.0899, found: 256.0880; $[\alpha]_{\text{D}}^{20} +34.6$ (c 0.5, MeOH).

(-)-[2-[6-(Allyloxy)-3-chloro-2-fluorophenyl]cyclopropyl]methanamine Hydrochloride ((-)-22d).

White solid. HPLC: 98.5%; ^1H NMR (CD_3OD) δ 7.26 (t, $J = 8.4$ Hz, 1H), 6.79 (d, $J = 9.2$ Hz, 1H), 6.17–6.07 (m, 1H), 5.46 (d, $J = 17.2$ Hz, 1H), 5.33 (d, $J = 10.4$ Hz, 1H), 4.61 (d, $J = 5.2$ Hz, 2H), 3.08–2.97 (m, 2H), 1.88–1.83 (m, 1H), 1.59–1.52 (m, 1H), 1.28–1.22 (m, 1H), 1.11–1.06 (m, 1H); ^{13}C NMR (CD_3OD) δ 159.0 (d, $J_{\text{CF}} = 6.4$ Hz), 158.7 (d, $J_{\text{CF}} = 243.9$ Hz), 134.4, 129.4, 119.2 (d, $J_{\text{CF}} = 14.6$ Hz), 118.7, 113.9 (d, $J_{\text{CF}} = 19.3$ Hz), 109.7, 70.9, 45.3, 18.4, 13.9, 13.1; HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{16}\text{ClFNO}^+$ ($[\text{M}+\text{H}]^+$): 256.0899, found: 256.0900; $[\alpha]_{\text{D}}^{20} -54.0$ (c 0.3, MeOH).

(+)-[2-[6-(Allyloxy)-3-chloro-2-fluorophenyl]cyclopropyl]methanamine Hydrochloride ((+)-22d).

White solid. HPLC: 99.6%; ^1H NMR (CD_3OD) δ 7.26 (t, $J = 8.6$ Hz, 1H), 6.79 (dd, $J = 9.2, 1.6$ Hz, 1H), 6.17–6.07 (m, 1H), 5.46 (dd, $J = 17.2, 1.4$ Hz, 1H), 5.33 (dd, $J = 10.4, 1.2$ Hz, 1H), 4.61 (d, $J = 5.6$ Hz, 2H), 3.08–2.97 (m, 2H), 1.88–1.83 (m, 1H), 1.57–1.52 (m, 1H), 1.28–1.22 (m, 1H), 1.11–1.06 (m, 1H); ^{13}C NMR (CD_3OD) δ 159.0 (d, $J_{\text{CF}} = 6.6$ Hz), 158.7 (d, $J_{\text{CF}} = 243.8$ Hz), 134.4, 129.4, 119.2 (d, $J_{\text{CF}} = 14.5$ Hz), 118.7, 113.9 (d, $J_{\text{CF}} = 19.2$ Hz), 109.7, 70.9, 45.3, 18.4, 13.9, 13.1; HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{16}\text{ClFNO}^+$ ($[\text{M}+\text{H}]^+$): 256.0899, found: 256.0901; $[\alpha]_{\text{D}}^{20} +55.0$ (c 0.2, MeOH).

(-)-[2-[2-(Allyloxy)-4,5-dichlorophenyl]cyclopropyl]methanamine Hydrochloride ((-)-22e).

White solid. HPLC: 99.1%; ^1H NMR (CD_3OD) δ 7.12 (s, 1H), 7.10 (s, 1H), 6.17–6.07 (m, 1H), 5.47 (dd, $J = 17.6, 1.6$ Hz, 1H), 5.34 (dd, $J = 10.4, 1.6$ Hz, 1H), 4.63 (d, $J = 5.2$ Hz, 2H), 3.08–2.97 (m, 2H), 2.14–2.09 (m, 1H), 1.37–1.32 (m, 1H), 1.15–1.03 (m, 2H); ^{13}C

NMR (CD₃OD) δ 157.9, 134.3, 131.9, 131.4, 129.2, 124.7, 118.7, 115.0, 70.9, 44.9, 19.4, 17.9, 13.5; HRMS (ESI) m/z calcd for C₁₃H₁₆Cl₂NO⁺ ([M+H]⁺): 272.0603, found: 272.0596; [α]_D²⁰ -35.0 (*c* 0.4, MeOH).

(+)-[2-[2-(Allyloxy)-4,5-dichlorophenyl]cyclopropyl]methanamine Hydrochloride ((+)-22e).

White solid. HPLC: 99.2%; ¹H NMR (CD₃OD) δ 7.12 (s, 1H), 7.10 (s, 1H), 6.17–6.07 (m, 1H), 5.47 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.34 (d, *J* = 10.4 Hz, 1H), 4.63 (d, *J* = 5.2 Hz, 2H), 3.08–2.96 (m, 2H), 2.14–2.09 (m, 1H), 1.39–1.32 (m, 1H), 1.15–1.03 (m, 2H); ¹³C NMR (CD₃OD) δ 157.9, 134.3, 131.9, 131.4, 129.2, 124.7, 118.7, 115.0, 70.9, 44.9, 19.4, 17.9, 13.5; HRMS (ESI) m/z calcd for C₁₃H₁₆Cl₂NO⁺ ([M+H]⁺): 272.0603, found: 272.0597; [α]_D²⁰ +37.6 (*c* 0.3, MeOH).

(-)-[2-[6-(Allyloxy)-2,3-dichlorophenyl]cyclopropyl]methanamine Hydrochloride ((-)-22f).

White solid. HPLC: 98.3%; ¹H NMR (CD₃OD) δ 7.37 (d, *J* = 9.2 Hz, 1H), 6.94 (d, *J* = 9.2 Hz, 1H), 6.18–6.08 (m, 1H), 5.46 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.34 (dd, *J* = 10.8, 1.2 Hz, 1H), 4.62 (d, *J* = 5.2 Hz, 2H), 3.30 (dd, *J* = 13.2, 8.8 Hz, 1H), 2.86 (dd, *J* = 13.2, 8.8 Hz, 1H), 1.83–1.77 (m, 1H), 1.48–1.45 (m, 1H), 1.23–1.12 (m, 2H); ¹³C NMR (CD₃OD) δ 158.8, 135.9, 134.4, 130.0, 129.9, 125.8, 118.9, 113.3, 70.9, 45.3, 20.2, 18.5, 15.3; HRMS (ESI) m/z calcd for C₁₃H₁₆Cl₂NO⁺ ([M+H]⁺): 272.0603, found: 272.0611; [α]_D²⁰ -68.0 (*c* 0.1, MeOH).

(+)-[2-[6-(Allyloxy)-2,3-dichlorophenyl]cyclopropyl]methanamine Hydrochloride ((+)-22f).

White solid. HPLC: 99.1%; ¹H NMR (CD₃OD) δ 7.37 (d, *J* = 8.8 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 6.18–6.08 (m, 1H), 5.47 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.34 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.63 (d, *J* = 5.2 Hz, 2H), 3.30 (dd, *J* = 12.8, 8.8 Hz, 1H), 2.86 (dd, *J* = 12.8, 8.8 Hz, 1H), 1.83–1.79 (m, 1H), 1.48–1.46 (m, 1H), 1.23–1.15 (m, 2H); ¹³C NMR (CD₃OD) δ 158.8, 135.9, 134.5, 130.0, 129.9, 125.8, 118.8, 113.3, 71.0, 45.4, 20.2, 18.6, 15.3; HRMS (ESI) m/z calcd for C₁₃H₁₆Cl₂NO⁺ ([M+H]⁺): 272.0603, found: 272.0596; [α]_D²⁰ +64.0 (*c* 0.1, MeOH).

(-)-[2-[6-(Allyloxy)-2-chloro-3-fluorophenyl]cyclopropyl]methanamine Hydrochloride ((-)-22g).

White solid. HPLC: 99.7%; ¹H NMR (CD₃OD) δ 7.09 (t, *J* = 8.8 Hz, 1H), 6.92 (dd, *J* = 9.2, 4.4 Hz, 1H), 6.16–6.07 (m, 1H), 5.46 (dd, *J* = 17.6, 1.6 Hz, 1H), 5.33 (dd, *J* = 10.6, 1.4 Hz, 1H), 4.60 (d, *J* = 5.6 Hz, 2H), 3.29 (dd, *J* = 13.2, 6.4 Hz, 1H), 2.87 (dd, *J* = 12.8, 8.6 Hz, 1H), 1.84–1.77 (m, 1H), 1.53–1.47 (m, 1H), 1.22–1.17 (m, 2H); ¹³C NMR (CD₃OD) δ 156.1, 154.3 (d, *J*_{CF} = 238.3 Hz), 134.7, 129.5, 124.5 (d, *J*_{CF} = 18.2 Hz), 118.7, 115.4 (d, *J*_{CF} = 22.7 Hz), 112.8 (d, *J*_{CF} = 7.5 Hz), 71.1, 45.4, 19.7, 17.7, 14.8; HRMS (ESI) m/z calcd for C₁₃H₁₆ClFNO⁺ ([M+H]⁺): 256.0899, found: 256.0895; [α]_D²⁰ -52.0 (*c* 0.2, MeOH).

(+)-[2-[6-(Allyloxy)-2-chloro-3-fluorophenyl]cyclopropyl]methanamine Hydrochloride ((+)-22g).

White solid. HPLC: 99.7%; ¹H NMR (CD₃OD) δ 7.09 (t, *J* = 8.8 Hz, 1H), 6.92 (dd, *J* = 9.2, 4.4 Hz, 1H), 6.17–6.08 (m, 1H), 5.46 (dd, *J* = 17.6, 1.6 Hz, 1H), 5.33 (dd, *J* = 10.4, 1.2 Hz,

1H), 4.60 (d, $J = 4.8$ Hz, 2H), 3.29 (dd, $J = 13.6, 6.0$ Hz, 1H), 2.87 (dd, $J = 12.8, 8.8$ Hz, 1H), 1.84–1.78 (m, 1H), 1.53–1.47 (m, 1H), 1.21–1.17 (m, 2H); ^{13}C NMR (CD_3OD) δ 156.1, 154.3 (d, $J_{\text{CF}} = 238.0$ Hz), 134.7, 129.5, 124.5 (d, $J_{\text{CF}} = 18.1$ Hz), 118.7, 115.4 (d, $J_{\text{CF}} = 22.7$ Hz), 112.8 (d, $J_{\text{CF}} = 6.6$ Hz), 71.1, 45.3, 19.7, 17.7, 14.8; HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{16}\text{ClFNO}^+$ ($[\text{M}+\text{H}]^+$): 256.0899, found: 256.0906; $[\alpha]_{\text{D}}^{20} +61.8$ (c 0.4, MeOH).

Calcium Flux Assay.

Calcium flux assay was recorded on a FLIPR^{TETRA} fluorescence imaging plate reader (Molecular Dynamics) on Flp-In-293 cells stably expressing the human 5-HT_{2A}, 5-HT_{2B}, or 5-HT_{2C-INI} as previously described.²²

Animal Behavioral Studies Methods

Animals.

Adult male and female C57BL/6 and NR1 mice were used for behavioral testing. Mice were maintained on a 14 h light/10 h dark light-dark cycle with the onset of that dark cycle at 2000 h. Testing was conducted during the light cycle between 1000–1600 h. All animals were housed by genotype and sex. Forty-eight h before testing mice were weighed and moved into the appropriate test room. Mice remained in the test room for the duration of testing and had *ad libitum* access to food and water. All studies were conducted with an approved protocol from the Duke University Institutional Animal Care and Use Committee.

Drugs.

Haloperidol (Sigma-Aldrich, St. Louis MO) and compound (+)-**22a** were dissolved in 0.5% *N, N*-dimethylacetamide and 10% (2-hydroxypropyl)- β -cyclodextrin in sterile saline. *d*-Amphetamine (Tocris Bioscience, Bristol, UK) was dissolved in sterile saline. All treatments were delivered in a 4 mL/kg volume (ip).

Open Field Activity.

Activity in the open field was assessed as distance traveled in a novel environment (20 \times 20 \times 20 cm) using a Versamax Analyzer system (Omnitech Electronics, Columbus, OH). Locomotor activity was monitored by infrared diodes interfaced to a computer running Fusion software (Omnitech Electronics). Mice ($n = 7$ –10 mice/treatment) were injected with vehicle (Veh) or 2, 5, 10, 20, or 30 mg/kg compound (+)-**22a** and placed into the open field. After 15 min each animal was removed and given Veh or 3 mg/kg *d*-amphetamine (AMPH) and returned immediately to the open field for an additional 105 min. Controls consisted of separate groups of mice administered Veh-Veh or 20 mg/kg compound (+)-**22a** + Veh. The results are depicted as total distance traveled in 5-min intervals over testing or cumulative distance traveled over the 15 min of baseline and 75 min following injection of AMPH or the vehicle.

Prepulse Inhibition.

Prepulse inhibition (PPI) was assessed using the SR Startle Lab Response system for mice (San Diego Instruments, San Diego, CA). Adult C57BL/6 males ($n = 8$ –11 mice/treatment

group) were administered the vehicle or 0.5, 1, 2, or 4 mg/kg compound (+)-**22a** followed 10 min later with vehicle or 3 mg/kg AMPH. Mice were placed into a Plexiglas holder which was positioned into the test chamber that was interfaced to a computer running SR Lab Startle Reflex software.⁴⁰ After a 10 min acclimatization period, mice were exposed to 42 test trials composed of 18 pulse-only trials, 18 prepulse-pulse trials, and 6 null trials. A 62 dB white noise background was present during testing. Pulse-only trials consisted of a single 40 ms 120 dB burst of white noise. Prepulse-Pulse trials consisted of a 20 dB prepulse of white noise that was 4, 8, or 12 dB above the 62 dB background, followed 100 ms later with the 120 dB pulse. The white noise background was the only stimulus present during the null only trials. Testing began and ended with a block of 5 pulse-only trials; the remaining pulse-only trials were randomized with the null trials and the prepulse-pulse trials between these two blocks of pulse-only trials. The percent PPI for each prepulse intensity was calculated as the ratio of the average response during the prepulse-pulse trials to the average pulse-only responses, subtracted from 1, and expressed as a percentage. Null activity and pulse-only responses are reported in arbitrary units (AU) as measured by the SR Startle Lab Response system. The peak measure of the startle response (AU) was measured within a 65 ms window following onset of the pulse-only stimulus.⁴¹

Novel Object Recognition Memory.

Wild type (WT) and NR1-KD mice (n = 9–10 mice/genotype/treatment) were randomly assigned to three treatment groups that received Veh or 0.5 or 1 mg/kg compound (+)-**22a**. Testing was conducted over three days with a single trial (5 min) on each day.⁴⁰ Mice were acclimated to the empty test chambers (38 × 22 × 20 cm) on day 1 and exposed to two identical objects on day 2. Twenty-four h later mice were presented with one of the same objects from day 2 which was paired with a novel object to evaluate long-term memory (LTM). Mice were administered Veh or compound (+)-**22a** 30 min prior to the trials on days 2 and 3. All trials were video-recorded using the Noldus Media Recorder (Noldus Technologies, Wageningen, Netherlands) and behavioral data were analyzed using Noldus Ethovision 10. Duration of time spent investigating the objects was scored. The results are presented as preference scores; Object Preference = (time spent with novel object – time spent with familiar object) / total time with both objects. Positive scores denote preference for the novel object, negative scores signify preference for the familiar object, and scores approaching zero indicate no preference for either object.

Catalepsy.

Male C57BL/6J mice (Jackson Laboratories; n = 8–10 mice/treatment/time-point) were assessed for cataleptic responses. Baseline cataleptic responses were assessed following removal from the home-cage by placing both front paws on a 60 cm horizontal bar (2.5 mm diameter) elevated above the bench with both rear paws in direct contact with the bench. Immediately following the baseline assessment, each animal was injected with vehicle, haloperidol, or compound (+)-**22a** and returned to its home cage. Catalepsy was evaluated in separate groups of mice at 60 min. The time spent in catalepsy was measured as the time following placement to removal of the front paws from the bar, with a maximum cut-off time of 60 seconds.

Statistics.

All data were analyzed using SPSS 22 (IBM SPSS, Chicago, IL) and are presented as means and standard errors of the mean (SEM). Distance traveled in the open field was assessed with RMANOVA with time as the within subject effect and treatment condition as the between subject effect. For PPI, null and startle activities were assessed using ANOVA with treatment as the between subject variable. Differences in PPI were examined with RMANOVA with prepulse intensity as the within subject variable and treatment condition as the between subject variable. Responses in NORM were evaluated using ANOVA for preference scores in the LTM test with genotype and treatment as independent variables. Duration of contact with the objects during the training session and the LTM test were analyzed with RMANOVA using test-session as the within subject variable and genotype and treatment as the between subject variables. For time spent in catalepsy, a one-way ANOVA was performed examining the effects of treatment. *Post-hoc* comparisons were performed with Bonferroni corrected pair-wise comparisons for all analyses. In all cases, a $p < 0.05$ was considered significant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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ABBREVIATIONS USED

5-HT	serotonin
ADMET	absorption, distribution, metabolism, excretion and toxicity
AMPH	<i>d</i> -amphetamine
BBB	blood–brain barrier
CNS	central nervous system
CYP	cytochrome
FDA	US Food and Drug Administration
GPCR	G-protein coupled receptor
HEK-293	Human Embryonic Kidney 293 cells
hERG	human ether-à-go-go-related gene
HPLC	high-performance liquid chromatography
KD	knockdown

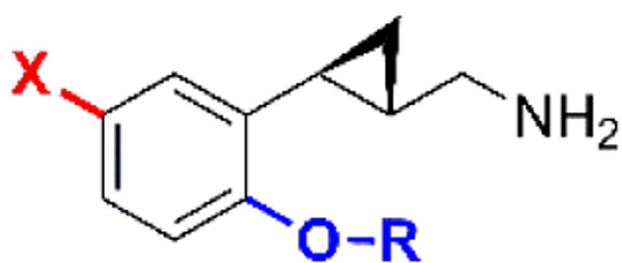
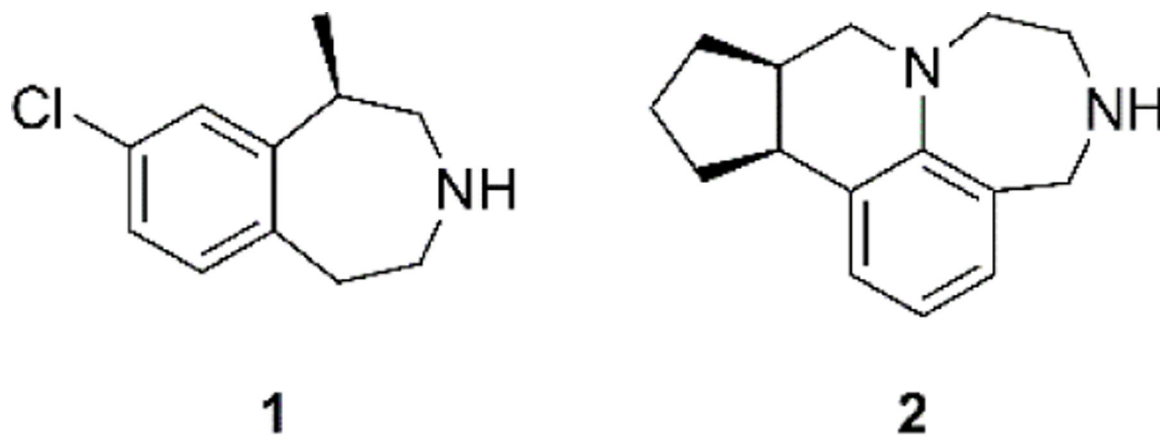
LTM	long-term memory
NMDA	<i>N</i> -methyl-D-aspartate
NORM	novel object recognition memory
SAR	structure–activity relationship
Veh	vehicle
WT	wild type

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- 3:** X = Cl, R = 2-fluoroallyl
4: X = Cl, R = 2-fluoroethyl
5: X = F, R = allyl
6: X = F, R = 2-fluoroethyl

Figure 1.
Structures of lorcaserin (1), vabicaserin (2) and compounds 3–6.

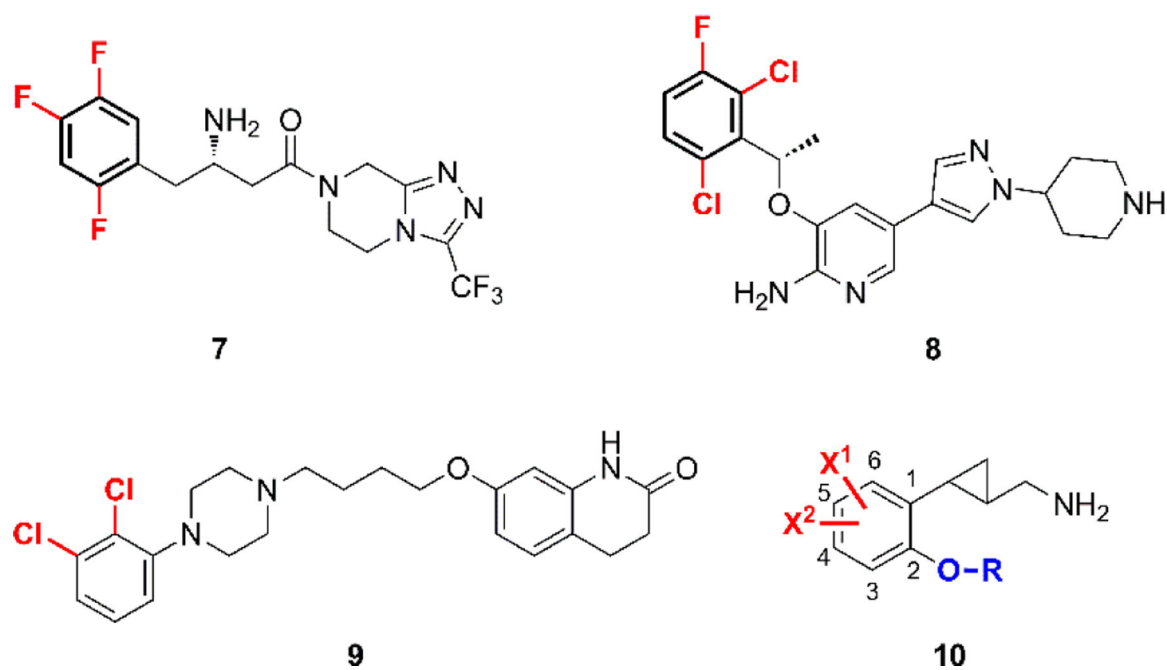


Figure 2. Representative drugs having a multi-halogen substitution pattern and the general structure of new 2-phenylcyclopropylmethylamines.

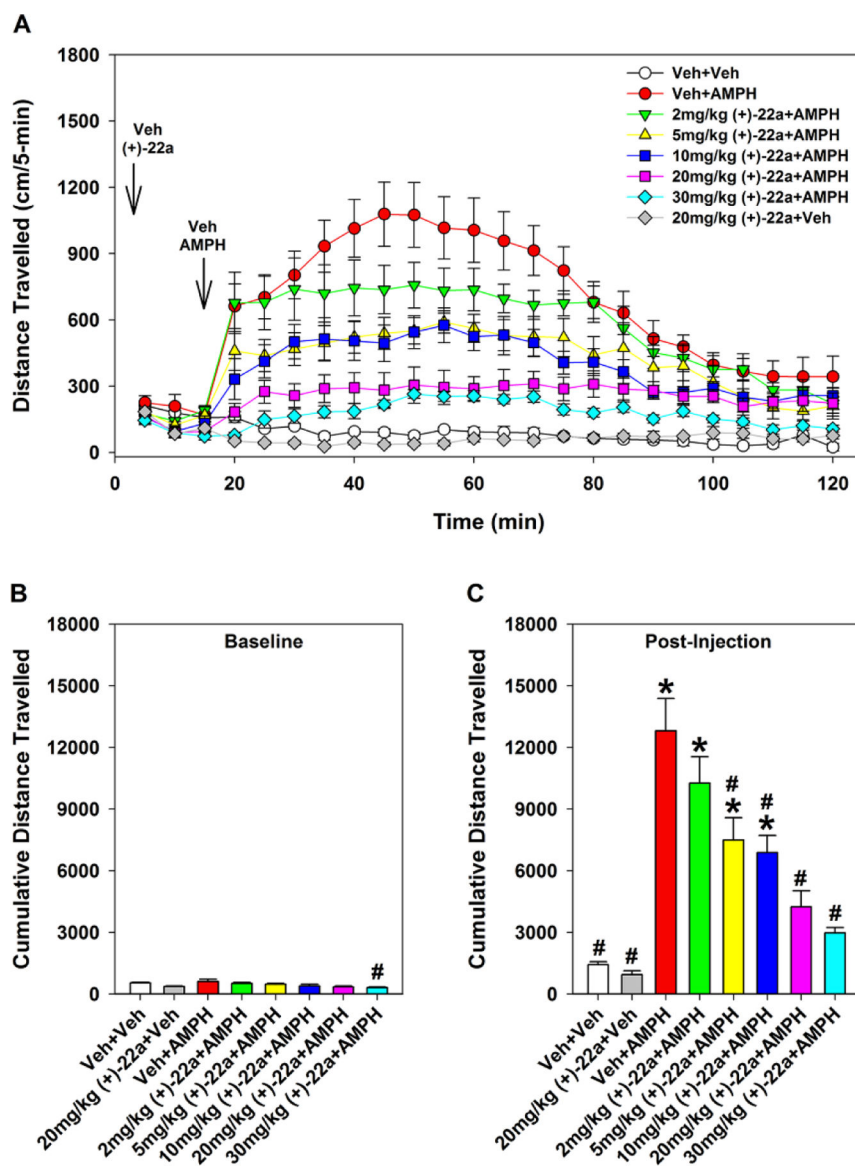


Figure 3. Effects of compound (+)-22a on *d*-amphetamine (AMPH)-stimulated hyperlocomotion in the open field. (A) Locomotor activity in the open field in 5-min blocks reflecting baseline responses (0–15 min) and AMPH stimulated activity with its reduction by (+)-22a (15–120 min). (B) Cumulative baseline locomotor activities (0–15 min). (C) Cumulative AMPH-stimulated activities and reductions in activity with (+)-22a (16–90 min). $N = 7–10$ mice/treatment; *, $p < 0.05$, compared to the Veh + Veh group; #, $p < 0.05$, compared to the Veh + AMPH group.

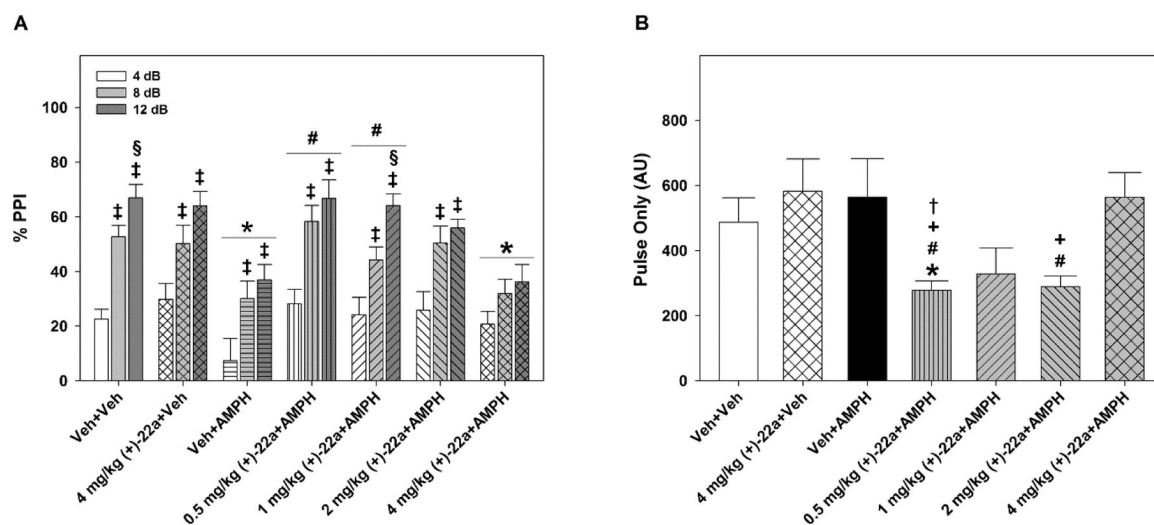


Figure 4.

Compound (+)-**22a** restores *d*-amphetamine (AMPH)-disrupted PPI in C57BL/6 mice. (A) Mice treated with vehicle-vehicle (Veh + Veh) showed prepulse dependency in the PPI response. Four mg/kg (+)-**22a** alone did not affect PPI relative to the Veh + Veh controls. Mice administered Veh + AMPH had a marked reduction in PPI. Treatment with 0.5, 1, or 2 mg/kg (+)-**22a** restored overall AMPH-disrupted PPI to the levels of the Veh + Veh group; with 1 mg/kg fully rescuing prepulse dependency of the response. Mice given the 4 mg/kg dose + AMPH showed a reduction in PPI similar to that found in Veh + AMPH animals. $N = 8-11$ mice/treatment; *, $p < 0.05$, compared to the Veh + Veh control; #, $p < 0.05$, compared to the Veh + AMPH group; ‡, $p < 0.05$, within treatment 8 or 12 dB compared to the 4 dB response; §, $p < 0.05$, within treatment 12 dB compared to the 8 dB response. (B) Pulse-only responses during PPI testing were not affected by treatment in the (+)-**22a**+Veh or the Veh + AMPH groups but when (+)-**22a** was given before AMPH the startle-only response was attenuated in dose-dependent manner. $N = 8-11$ mice/treatment; *, $p < 0.05$, compared to the Veh + Veh control; #, $p < 0.05$, compared to the Veh + AMPH group; +, $p < 0.05$ compared to 4 mg/kg (+)-**22a** + Veh treatment; †, $p < 0.05$, compared to the 4 mg/kg (+)-**22a** + AMPH treatment.

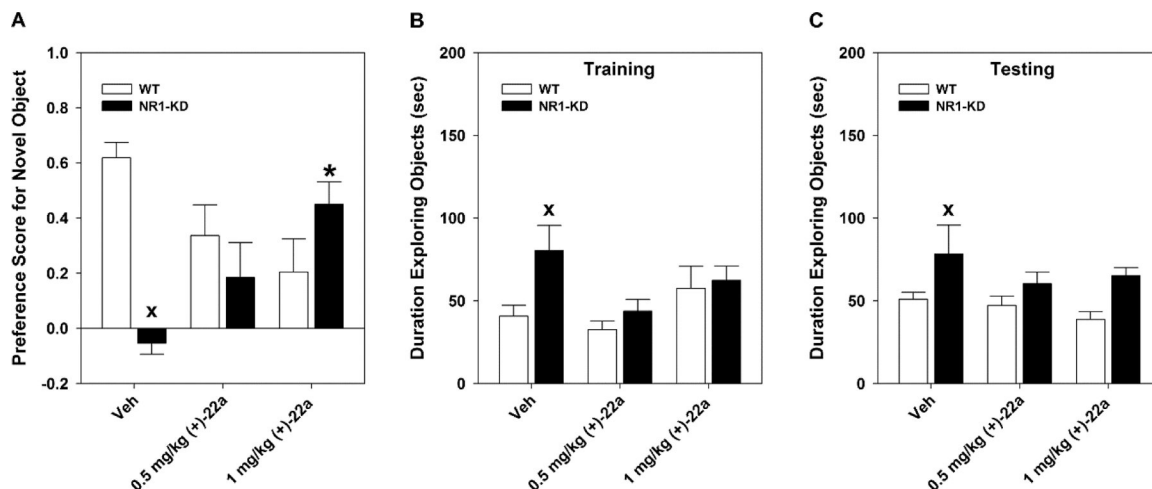


Figure 5.

Compound (+)-22a rescues novel object recognition memory in NR1-KD mice. Mice were given vehicle (Veh) or 0.5 or 1 mg/kg (+)-22a 30 min before training or at testing for long-term memory (LTM). (A) At testing for LTM, Veh-treated wild-type (WT) controls displayed a preference for the novel object, whereas NR1-KD mice showed no preference for either object. In contrast, 1 mg/kg (+)-22a rescued this deficit in the mutants while producing some impairment in the WT animals. (B–C) As a control, the duration of object exploration was examined during (B) training and (C) LTM testing. At training and at testing Veh-treated NR1-KD mice spent more time exploring the objects than WT mice, while (+)-22a reduced this exploration time to levels that were not significantly different from the WT controls. N = 9–10 mice/genotype/treatment; *, $p < 0.05$, (+)-22a compared to the Veh within genotype; ^x, $p < 0.05$, NR1-KD compared to the WT vehicle.

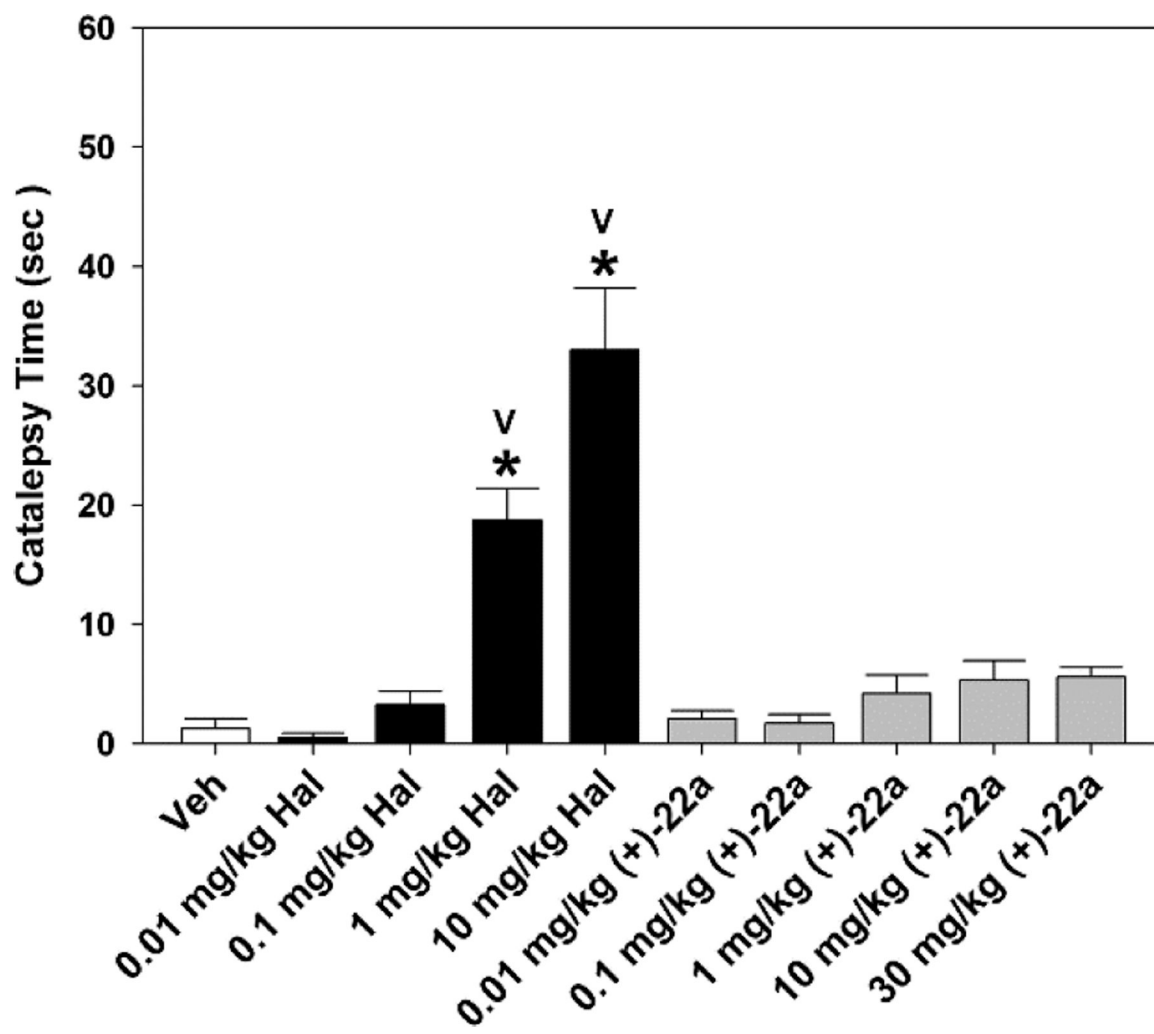
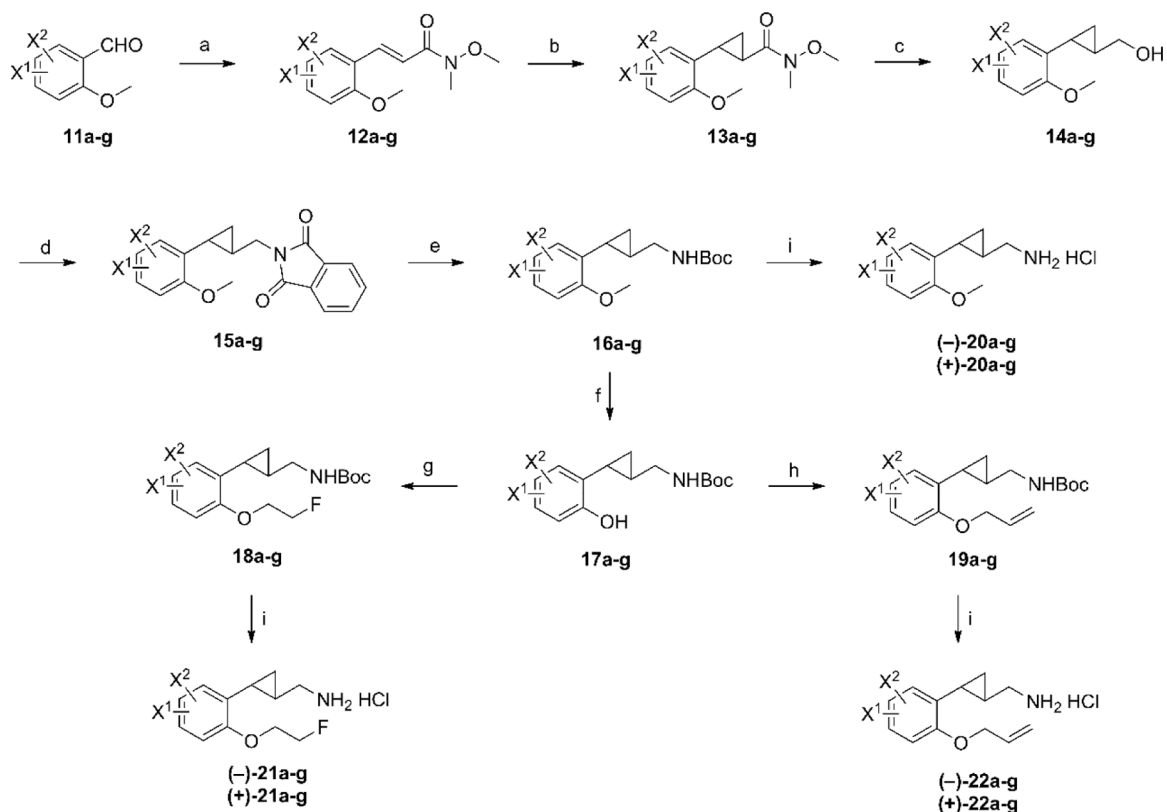


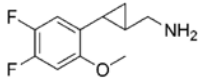
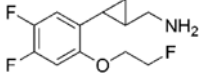
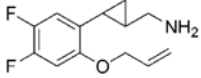
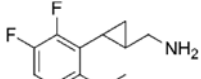
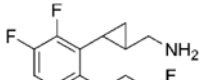
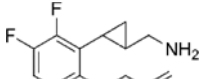
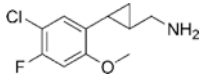
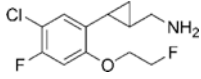
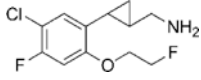
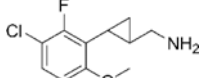
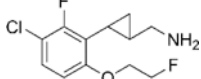
Figure 6. Comparison of catalepsy induced by haloperidol and (+)-22a in C57BL/6 mice with the horizontal bar test. Separate groups of mice were injected with vehicle (Veh), or 0.01, 0.1, 1, or 10 mg/kg haloperidol (Hal), or 0.01, 0.1, 1, 10, or 30 mg/kg compound (+)-22a and evaluated for catalepsy 60 min later. N = 8–10 mice/treatment; *, $p < 0.05$, compared to the Veh control; V, $p < 0.05$, compared to all other groups.

**Scheme 1.**

Synthesis of target compounds **20a-g**, **21a-g**, and **22a-g**.^{a a} Reagents and conditions: (a) $\text{Ph}_3\text{P}=\text{CHC}(\text{O})\text{N}(\text{OMe})\text{Me}$, CH_2Cl_2 , rt, overnight; (b) $\text{Me}_3\text{S}^+(\text{O})\text{I}^-$, NaH, DMSO, rt, overnight; (c) DIBAL-H, THF, -78°C , 2 h; then NaBH_4 , MeOH, 0°C to rt, 0.5 h; (d) phthalimide, PPh_3 , DEAD, THF, rt, overnight; (e) $\text{N}_2\text{H}_4\text{-H}_2\text{O}$, EtOH, reflux, 3 h; then Boc_2O , Et_3N , CH_2Cl_2 , rt, 0.5 h; (f) BBr_3 , CH_2Cl_2 , -78°C to rt; then Boc_2O , Et_3N , CH_2Cl_2 ; (g) 2-fluoroethanol, Ph_3P , DEAD, THF, 0°C to 60°C , 1 h; (h) allyl bromide, Cs_2CO_3 , DMF; (i) (1) chiral preparative-HPLC; (2) 2M HCl in Et_2O , rt, 24 h. **11-22a**: 4, 5-diF; **11-22b**: 5, 6-diF; **11-22c**: 4-F, 5-Cl; **11-22d**: 5-Cl, 6-F; **11-22e**: 4, 5-diCl; **11-22f**: 5, 6-diCl; **11-22g**: 5-F, 6-Cl.

Table 1.

Pharmacological Profiles of Di-halogenated Compounds at 5-HT₂ Receptors.^a

Structure (HCl salt)	Compound	EC ₅₀ , nM (E _{max})		
		5-HT _{2C}	5-HT _{2B}	5-HT _{2A}
-	5-HT	0.18 (100%)	1.0 (100%)	1.9 (100%)
-	lorcaserin	2.7 (98%)	328 (80%)	258 (67%)
	(-)-20a	30 (104%)	400 (59%)	511 (76%)
	(+)-20a	3.4 (108%)	27 (69%)	81 (81%)
	(-)-21a	772 (73%)	NA	NA
	(+)-21a	7.3 (95%)	453 (32%)	361 (51%)
	(-)-22a	116 (94%)	NA	831 (17%)
	(+)-22a	8.7 (97%)	1745 (35%)	491 (21%)
	(-)-20b	16 (108%)	462 (62%)	461 (72%)
	(+)-20b	9.5 (108%)	209 (64%)	437 (79%)
	(-)-21b	509 (78%)	9871 (29%)	NA
	(+)-21b	25 (95%)	2182 (36%)	2332 (30%)
	(-)-22b	151 (89%)	4464 (26%)	NA
	(+)-22b	36 (100%)	3339 (35%)	NA
	(-)-20c	16 (99%)	329 (44%)	235 (88%)
	(+)-20c	7.6 (97%)	25 (59%)	81 (93%)
	(-)-21c	776 (70%)	2521 (26%)	NA
	(+)-21c	24 (87%)	506 (39%)	654 (41%)
	(-)-22c	308 (77%)	1957 (22%)	NA
	(+)-22c	42 (87%)	1001 (44%)	NA
	(-)-20d	3.8 (93%)	165 (64%)	68 (86%)
	(+)-20d	13 (92%)	354 (52%)	212 (85%)
	(-)-21d	386 (80%)	NA	NA
	(+)-21d	71 (86%)	NA	934 (40%)

Structure (HCl salt)	Compound	EC ₅₀ , nM (E _{max})		
		5-HT _{2C}	5-HT _{2B}	5-HT _{2A}
	(-)-22d	165 (87%)	NA	1081 (16%)
	(+)-22d	116 (90%)	6983 (69%)	NA
	(-)-20e	14 (89%)	696 (16%)	84 (75%)
	(+)-20e	9.7 (95%)	31 (45%)	21 (85%)
	(-)-21e	435 (75%)	NA	NA
	(+)-21e	18 (87%)	>10000 (26%)	92 (58%)
	(-)-22e	278 (84%)	NA	NA
	(+)-22e	61 (88%)	714 (26%)	167 (37%)
	(-)-20f	0.95 (104%)	51 (62%)	38 (88%)
	(+)-20f	21 (98%)	534 (46%)	203 (76%)
	(-)-21f	224 (85%)	>10,000 (62%)	NA
	(+)-21f	232 (90%)	5523 (99%)	949 (22%)
	(-)-22f	108 (93%)	3962 (99%)	426 (32%)
	(+)-22f	165 (70%)	NA	NA
	(-)-20g	3.2 (96%)	101 (91%)	119 (72%)
	(+)-20g	24 (89%)	2176 (60%)	769 (77%)
	(-)-21g	135 (80%)	3486 (29%)	NA
	(+)-21g	49 (86%)	961 (55%)	798 (39%)
	(-)-22g	104 (89%)	5176 (57%)	NA
	(+)-22g	96 (92%)	927 (55%)	NA

^aData were acquired with recombinant, stably expressed human serotonin receptors in the HEK-293 cell line, using a fluorescence imaging plate reader (FLIPR) assay. "NA", no activity (E_{max} < 15%) at 10 μM.

Table 2.Liver Microsomal Stability of Compound (+)-**22a**.^a

Assay Format	Remaining Percentage (%)					
	HLM			MLM		
	0 min	30 min	120 min	0 min	30 min	120 min
+ NADPH	100.0	91.9	70.5	100.0	68.1	32.4
- NADPH	100.0	94.7	81.9	100.0	97.8	79.6

^a Concentration of liver microsomes was 0.5 mg/mL and (+)-**22a** was tested at a concentration of 2 μ M; HLM = human liver microsomes; MLM = mouse liver microsomes.

Table 3.Brain Penetration Study of Compound (+)-**22a**.

Route	Time (h)	Animal ID	Brain (ng/g)	Plasma (ng/mL)	Ratio (Brain Plasma) ^a	Mean
ip 10 mg/kg	0.5	1	10120	321	31.5	29.9
		2	8480	300	28.3	
	2.0	1	3948	96.4	41.0	45.0
		2	2228	45.4	49.1	

^aDensity of brain tissue is calculated as 1.0 g/mL.

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Table 4.Cytochrome P450 Inhibition by Compound (+)-**22a**.^a

CYP Isoform (Substrate)	Inhibition (%) \pm SEM
1A2 (Phenacetin)	86.0 \pm 0.25
2C9 (Tolbutamide)	29.2 \pm 2.2
2C19 (Mephenytoin)	32.0 \pm 5.3
2D6 (Dextromethorphan)	43.5 \pm 3.0
3A4 (Midazolam)	3.4 \pm 1.6

^aCompound (+)-20a was tested at 10 μ M; concentration of human liver microsomes was 0.2 mg/mL; concentration of phenacetin, tolbutamide, mephenytoin, dextromethorphan, and midazolam was 40, 200, 50, 10, and 5 μ M respectively.

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