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Article

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Discovery of *N*-Substituted 2-Phenylcyclopropylmethylamines as Functionally Selective Serotonin 2C (5-HT_{2C}) Receptor Agonists for Potential Use as Antipsychotic Medications

Guiping Zhang,[†] Jianjun Cheng,[†, #] John D. McCorvy,[‡] Paul J. Lorello,[§] Barbara J. Caldarone,[§] Bryan L. Roth, [‡] and Alan P. Kozikowski[*,†]

[†]Drug Discovery Program, Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois 60612, USA

[‡]National Institute of Mental Health Psychoactive Drug Screening Program, and Department of Pharmacology and Division of Chemical Biology and Medicinal Chemistry, University of North Carolina Chapel Hill Medical School, Chapel Hill, North Carolina 27599, USA

[§]Department of Neurology, Brigham and Women's Hospital, Harvard NeuroDiscovery Center, and Harvard Medical School, Boston, Massachusetts 02115, USA

ABSTRACT

A series of *N*-substituted 2-phenylcyclopropylmethylamines were designed and synthesized, with the aim of finding 5-HT_{2C}-selective agonists with preference for G_q signaling. A number of these compounds exhibit 5-HT_{2C} selectivity with preference for G_q-mediated signaling compared with β-arrestin recruitment. Furthermore, the *N*-methyl compound (+)-**15a**, which displayed an EC_{50} of 23 nM in the calcium flux assay while showing no β-arrestin recruitment activity, is the most functionally-selective 5-HT_{2C} agonist reported to date. The *N*-benzyl compound (+)-**19**, which showed an EC_{50} of 24 nM at the 5-HT_{2C} receptor, is fully selective over the 5-HT_{2B} receptor. In an amphetamine-induced hyperactivity model, compound (+)-**19** showed significant antipsychotic drug-like activity. These novel compounds shed light on the role of functional selectivity at the 5-HT_{2C} receptor with respect to antipsychotic activity.

INTRODUCTION

The serotonin 2C ($5\text{-}HT_{2C}$) receptor, a serotonin (5-HT, **1,** Figure 1), G protein-coupled receptor (GPCR), has been identified as a promising drug target for obesity and other central nervous system (CNS) disorders, such as schizophrenia and drug addiction.[1-6] The $5\text{-}HT_{2C}$ receptor shares approximately 50% homology similarity with the other two $5\text{-}HT_2$ subtypes, namely the $5\text{-}HT_{2A}$ and $5\text{-}HT_{2B}$ receptors, where agonists respectively mediate hallucinogenic activity[7] and cardiac valvulopathy.[8, 9]

Furthermore, the classical understanding of GPCR signaling has undergone important changes in recent years with the recognition of the phenomenon of "functional selectivity", namely the ability of a specific agonist to differentially mediate multiple receptor signaling events (i.e., G_q-linked calcium flux vs. β-arrestin recruitment in the case of $5\text{-}HT_{2C}$ receptors).[10] β-Arrestin was named after its initially discovered ability to arrest (turn off) GPCR signaling, and is an important downstream signaling and regulatory factor. β-Arrestin recruitment is responsible for desensitization, internalization, and eventual degradation of GPCRs.[11] It has furthermore been demonstrated that the β-arrestin mediated signaling pathway functions can provide signaling independent of G-protein pathways.[12] Thus, a GPCR agonist that has minimal capability to activate the β-arrestin signaling pathway could display long-term efficacy in regard to tolerance mediated by receptor desensitization and downregulation. Recently, biased GPCR ligands have been suggested to offer great therapeutic benefits as new generation drugs with enhanced efficacy and functional selectivity, resulting in reduced side effects.[13, 14]

Thus, to develop $5\text{-}HT_{2C}$ agonists as potential antipsychotic medications, it is essential to explore ligands that are both G protein-biased and highly selective over $5\text{-}HT_{2B}$ and $5\text{-}HT_{2A}$. Most importantly, the high selectivity for $5\text{-}HT_{2C}$ over $5\text{-}HT_{2B}$ has emerged as paramount due to the fact that chronic $5\text{-}HT_{2B}$ agonism leads to irreversible cardiac valvulopathy, as illustrated by the withdrawal of fenfluramine and pergolide and the

restriction of sales of cabergoline owing to their off-target activities at the 5-HT_{2B} receptor.[9] To date, a number of selective 5-HT_{2C} ligands have been disclosed (Figure 1). In particular, lorcaserin (**2**) was approved by the FDA for the treatment of obesity in 2012. It shows excellent 5-HT_{2C} agonist activity (EC_{50} = 9 nM, E_{max} = 99%), but only moderate (100-fold) selectivity over 5-HT_{2B} (EC_{50} = 943 ± 90 nM, E_{max} = 100%), which is relevant to understanding the higher incidence of cardiac valve disorders compared to placebo in clinical trails.[15] Vabicaserin (**3**) with partial agonism (E_{max} = 50%, EC_{50} = 12 or 102 nM depending on receptor expression level) at the 5-HT_{2B} receptor has failed to achieve its primary endpoints in clinical trails, although a proof-of-concept has been achieved for the use of 5-HT_{2C} agonists in treating schizophrenia.[16, 17] The pyrimido[3,4-*d*]azepine, PF-4479745 (**5**), a hybrid of lorcaserin and CP-809101 (**4**),[18] displays high potency (EC_{50} = 10 nM) and moderate efficacy (E_{max} = 67%) at 5-HT_{2C} while possessing no measurable agonism at either the 5-HT_{2A} or 5-HT_{2B} receptor.[19] The pyrido[3,4-*d*]azepine, PF-04781340 (**6**), is a potent 5-HT_{2C} ligand (EC_{50} = 9 nM, E_{max} = 99%), with about 160-fold selectivity over 5-HT_{2B}.[20] Both compounds **5** and **6** were reported to have excellent ADME properties commensurate with an orally bioavailable and CNS penetrant profile. However, to the best of our knowledge, few biased 5-HT_{2c} agonists have been reported to date.[21]

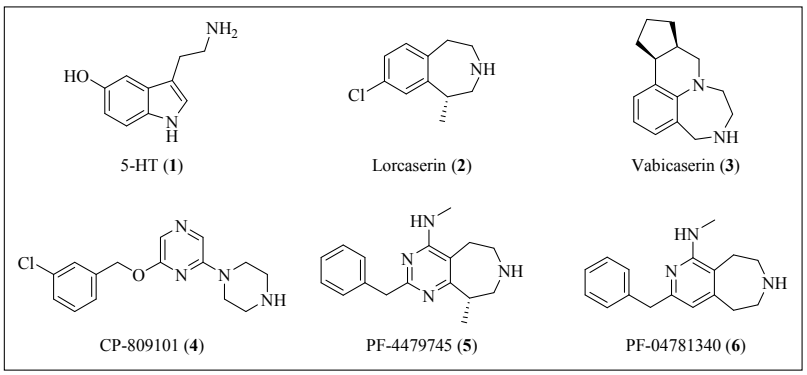


Figure 1. Selected 5-HT_{2C} agonists.

In our prior work, tranylcypromine was identified as a hit compound in an initial high-throughput screening (HTS) assay using a library containing 800 compounds. We developed our first-generation potent 5-HT_{2C} agonists by homologation of the side chain of tranylcypromine to 2-phenylcyclopropylmethylamine (2-PCPMA).[22]

Subsequent structure-activity relationship (SAR) studies indicated that a 2-alkoxy substituent is a beneficial functional group for maintaining potency and selectivity (Figure 2). Further fine-tuning of the 2-alkoxy and the halogen substituents led to the identification of **11** and **12**,[23, 24] which showed excellent pharmacological profiles with regard to 5-HT_{2C} potency and selectivity over 5-HT_{2A} and 5-HT_{2B}. In addition, compounds **11** and **12** showed only weak β-arrestin recruitment efficacy (E_{max} = 23% and 26%, respectively; unpublished data) similar to a series of structurally similar benzofuran-based compounds reported recently.[21]

The achievement of optimal brain exposure, which is a critical and challenging task in CNS drug discovery, requires a more restrictive selection of physicochemical properties compared to orally active, peripheral drugs (Rule of 5).[25-27] Due to the relatively low molecular weights (MW) of the 2-phenylcyclopropylmethylamines (for example, MW < 230 for **11** and **12**), the addition of halogen atoms to the phenyl ring has previously been demonstrated to improve brain penetrance.[23, 24] To further optimize drug-like properties, alkylation at the basic primary amino group of the 2-PCPMA scaffold was envisioned to provide opportunities for additional non-covalent interactions with the 5-HT_{2C} receptor while also increasing the ligands' lipophilicity. In earlier studies we found that *N*-methylation of 2-(2-methoxyphenyl)cyclopropylmethylamine (**8**, cLogP = 1.59, LogBB = –0.04) gave a fully G_q-biased 5-HT_{2c} agonist with good potency (EC_{50} = 23 nM, E_{max} = 71%; cLogP = 2.07, LogBB = 0.26), while *N*-methylation of our first-generation 2-phenylcyclopropylmethylamine (**7**) led to a dramatic loss in activity.[22] Moreover, it has been reported that *N*-benzylation of phenethylamines and 5-methoxytryptamines leads to improved agonism at 5-HT_2 receptors.[28, 29] Given that the additional *N*-substitution could improve the physicochemical properties in terms of further enhancing brain penetration, a new series of *N*-substituted 2-(2-alkoxyphenyl)cyclopropylmethylamines (Figure 2) was developed and evaluated for their potency and bias profiles in continuation of our previous SAR studies, along with behavioral tests and *in vitro* ADMET studies of a promising 5-HT_{2C} receptor agonist which showed no activity at the 5-HT_{2B} receptor.

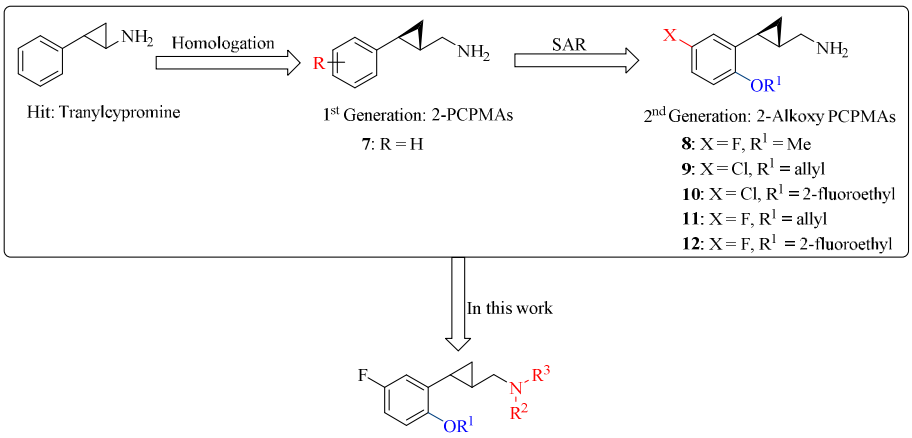


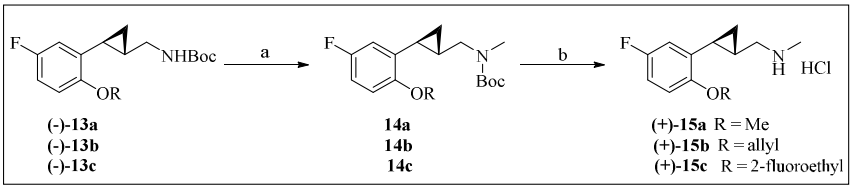
Figure 2. Selected 5-HT_{2C} agonists based on the 2-phenylcyclopropylmethylamine scaffold, and new *N*-substituted derivatives.

RESULTS AND DISCUSSION

Chemistry

N-Monomethylation of compounds **8**, **11**, and **12** was carried out starting from Boc-protected 2-(2-alkoxyphenyl)cyclopropylmethylamines (–)-**13a-c** reported previously by our group as synthetic intermediates.[23] As shown in Scheme 1, introduction of an *N*-methyl group with NaH and iodomethane followed by deprotection under acidic condition (2M HCl/Et_2O) afforded the *N*-methylamines (+)-**15a-c**. Since the *N*-methylamine (+)-**15a** possessing a methoxy group at the 2-position of the phenyl ring maintained potency at 5-HT_{2C}, the present work was focused on *N*-substituted analogs of compound **8**.

Scheme 1. Synthesis of *N*-Methyl Analogs (+)-15a-c[a]

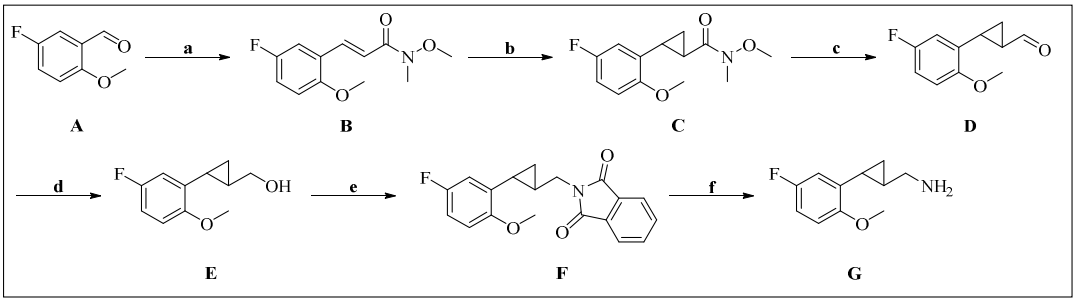


[a]Reagents and conditions: (a) MeI, NaH, THF, rt; (b) 2M HCl/Et_2O, rt.

The synthesis of these compounds was accomplished from the cyclopropane-bearing aldehyde **D** and primary amine **G** (Scheme 2)[30] by reductive amination or *N*-substitution reactions (Scheme 3). For example, the *N*-alkyl derivatives **16-18** and *N*-arylmethyl/heteroarylmethyl derivatives **19-22**, **26-32**, and **34-35** were synthesized starting from the aldehyde **D** and amines by treatment with $NaBH_4$ or $NaBH(OAc)_3$. The tertiary amine **23** was prepared from the phenol **22** using a Mitsunobu reaction with 2-fluoroethanol. The *N*-arylmethyl/heteroarylmethyl derivatives **24**, **33**, and **36-39** were synthesized from the primary amine **G** and appropriate aldehydes following the same approach, while the derivative **24** was prepared from the intermediate tosylate **24b** (Scheme 4) via a nucleophile substitution reaction. Hydrolysis of **24** under basic condition ($NaOH/H_2O_2$) smoothly afforded the amide **25**.

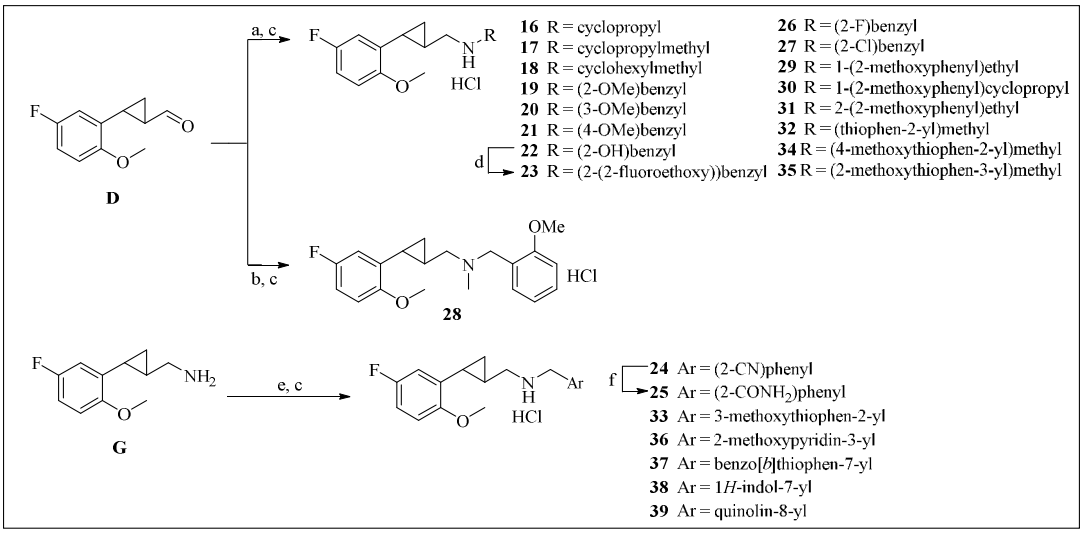
The intermediate cyclopropylamine **30b** for the synthesis of compound **30** was obtained from 2-methoxybenzonitrile **30a** using EtMgBr and $Ti(O^iPr)_4$, followed by treatment with a Lewis acid (BF_3•Et_2O) (Scheme 4).[31] The intermediate thiophenylmethanamines **34e** and **35e** required for the synthesis of compounds **34** and **35** were prepared in four steps as illustrated in Scheme 5. The commercial thiophenes **34a** and **35a** were brominated with NBS followed by replacement of bromide with tritylamine to provide **34c** and **35c** in high yield. The bromides **34c** and **35c** were reacted with CH_3ONa/CuBr to afford **34d** and **35d**,[32] followed by the removal of the Trt group under acidic conditions to give **34e** and **35e** as acetic acid salts (Scheme 5).

Scheme 2. Synthesis of Intermediates D and G[a]



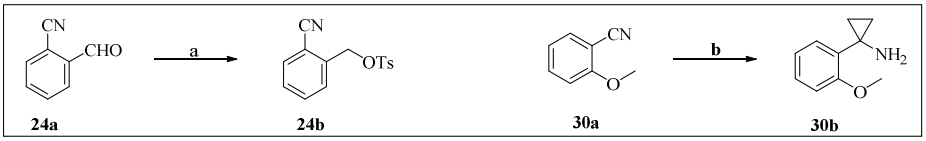
[a]Reagents and conditions: (a) Ph_3P=CHC(O)N(OMe)Me, CH_2Cl_2, rt; (b) $Me_3S^+(O)I^-$, NaH, DMSO, rt; (c) DIBAL-H, THF, -78 ^oC; (d) $NaBH_4$, MeOH, 0 ^oC to rt; (e) phthalimide, PPh_3, DEAD, THF, rt; (f) N_2H_4•H_2O, EtOH, reflux.

Scheme 3. Synthesis of Target Compounds 16-39[a]



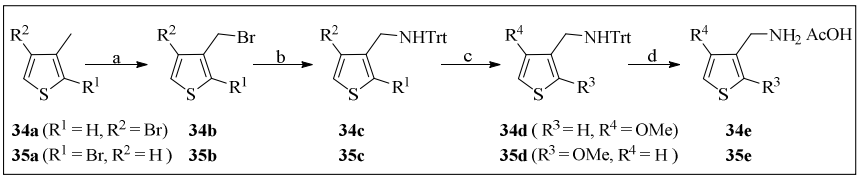
[a]Reagents and conditions: (a) RNH_2, $NaBH_4$, MeOH; (b) 2-methoxy-*N*-methylbenzylamine, $NaBH_4$, MeOH; (c) 2M HCl/Et_2O, rt; (d) Ph_3P, DEAD, 2-fluoroethanol, THF; (e) $ArCH_2OTs$, K_2CO_3, CH_3CN for **24**; ArCHO, $NaBH(OAc)_3$, DCE for **33**, **37**-**39**; ArCHO, $NaBH_4$, MeOH for **36**; (f) NaOH, H_2O_2, MeOH.

Scheme 4. Synthesis of Intermediates 24b and 30b for Analogs 24 and 30[a]



[a]Reagents and conditions: (a) i. $NaBH_4$, MeOH; ii. TsCl, TEA, DCM; (b) i. EtMgBr, $Ti(O^iPr)_4$, Et_2O, -78 ^oC; ii. BF_3•Et_2O, Et_2O.

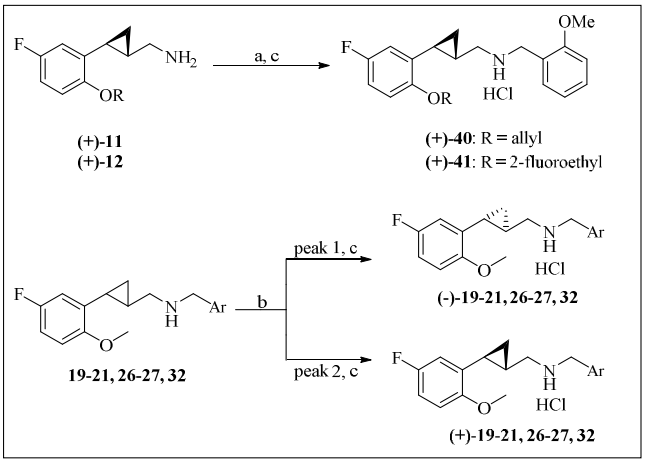
Scheme 5. Synthesis of Intermediates 34e-35e for Analogs 34-35[a]



[a]Reagents and conditions: (a) NBS, AIBN, CCl_4, 60 ^oC; (b) $TrtNH_2$, DCM, rt; (c) CH_3ONa, CH_3OH, CuBr, 100 ^oC; (d) AcOH, 50 ^oC.

Unless otherwise noted, the *N*-substituted derivatives were tested as racemic mixtures. The *N*-benzyl derivatives of (+)-**11** and (+)-**12**, namely **40** and **41**, respectively, were directly prepared from the enantiomers (+)-(*S*,*S*)-**11** and (+)-(*S*,*S*)-**12** via reductive alkylation with 2-methoxybenzaldehyde, while the pure (–)- and (+)-isomers of **19-21**, **26-27**, and **32** were obtained by preparative HPLC on a chiral stationary phase (Scheme 6). Compounds **40** and **41** were found to show the same sign of optical rotation as their parent compounds (+)-**11** and (+)-**12**. Moreover, our finding that the (+)-enantiomers of all new *N*-arylmethyl/thiophenylmethyl compounds are more potent than their (–)-enantiomers is consistent with that previously observed for similar scaffolds.[22-24] Thus, the absolute configuration of the (+)-enantiomers was assigned as 1*S*, 2*S* and that of the (–)-enantiomers as 1*R*, 2*R*.

Scheme 6. Preparation of Enantiomers 19-21, 26-27, 32, and 40-41[a]



[a]Reagents and conditions: (a) 2-methoxybenzaldehyde, $NaBH_4$, MeOH; (b) chiral preparative HPLC separation; (c) 2M HCl/Et_2O, rt.

In vitro Pharmacology

Activity at 5-HT_2 Receptors

Preliminary studies demonstrated that 2-phenylcyclopropylmethylamines with the phenyl ring bearing 2-alkoxy and 5-fluoro substituents provided excellent 5-HT_{2C} potency and selectivity over 5-HT_{2A} and 5-HT_{2B} receptors. Moreover, the initial *N*-methylation of 2-(2-methoxyphenyl)cyclopropylmethylamine (**8**) maintained

potency at 5-HT_{2C} (compound (+)-**15a**: EC_{50} = 23 nM, E_{max} = 71%, Table 1), which was not the case with the best ligands **11** and **12** (resulting in compounds (+)-**15b** and (+)-**15c**). Further binding studies showed that (+)-**15a** had high affinity for 5-HT_{2C} (K_i = 81 nM, see Supporting Information Table S3). Thus, the parent compound **8** was taken as a lead to develop *N*-substituted derivatives. Physicochemical properties such as cLogP and LogBB were calculated to predict blood-brain barrier (BBB) permeability.

Substitution with larger alkyl groups, such as cyclopropyl (compound **16**) and cyclopropylmethyl (compound **17**), led to decreased potency at 5-HT_{2C} (EC_{50} > 300 nM; Table 1). However, in view of the lack of activity for the cyclopropylmethyl derivative **17**, it was intriguing that the even bulkier cyclohexylmethyl derivative **18** showed moderate potency (EC_{50} = 95 nM) and superior selectivity over 5-HT_{2B} and 5-HT_{2A}, but with extremely low efficacy (E_{max} = 15%). We therefore saw an opportunity for the introduction of an aromatic ring (Table 1), which could possibly engage in a π-π stacking interaction with the receptor.

Furthermore, Nichols *et al*. have demonstrated that *N*-(2-methoxybenzyl)-substituted 2, 5-dimethoxyphenethylamines exhibited enhanced agonism at 5-HT_2 receptors.[28, 29] We therefore first prepared the *N*-(2-methoxybenzyl) analog **19**. The compound (+)-**19** proved to have high potency at 5-HT_{2C} (EC_{50} = 24 nM, E_{max} = 92%) and full selectivity against 5-HT_{2B}. In addition, it was hypothesized that a hydrogen bond acceptor (HBA) at the ortho position of the benzyl moiety was beneficial to improve the potency of *N*-benzylated 2,5-dimethoxyphenethylamines.[29] Movement of the *o*-methoxy group to the meta and para positions as in compounds (+)-**20** and (+)-**21**, respectively, led to decreased potency (EC_{50} = 231 nM and 1200 nM). Furthermore, substituents with different electronic and steric properties acting as HBA groups at the 2-position of the benzyl group were investigated. The phenol **22** gave modest activity at 5-HT_{2C} (EC_{50} = 304 nM, E_{max} = 63%) but poor selectivity (0.25-fold) against 5-HT_{2A}, although it showed full selectivity over 5-HT_{2B}. The slightly bulkier 2-fluoroethyl[33] derivative **23** showed good potency at 5-HT_{2C} (EC_{50} = 28 nM), but only 2-fold selectivity against 5-HT_{2B} (EC_{50} = 56 nM). The cyano and carbamoyl

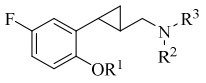
derivatives **24** and **25** displayed attenuated activity (EC_{50} > 200 nM, E_{max} < 35%). Moreover, introduction of other electron-withdrawing substituents (EWG) such as F (compound (+)**-26**) and Cl (compound (+)**-27**) resulted in significant loss of potency at 5-HT_{2C} (EC_{50} > 500 nM), which suggested that an EWG attached to the phenyl ring of the benzyl group was disadvantageous for 5-HT_{2C} activity. Additional *N*-methylation of the benzylamine moiety as in analog **28** resulted in a 15-fold reduction of 5-HT_{2C} potency (EC_{50} = 670 nM for the racemate) compared to the parent compound (+)**-19**. Additional substitution at the benzylic position of the 2-methoxybenzyl moiety with a methyl and ethylene group led to the sterically hindered analogs **29** and **30**, respectively, with predicted increase in BBB penetration based on the calculated LogBB values. Their potency at 5-HT_{2C} was, however, reduced. Moreover, homologation of the *N*-(2-methoxybenzyl) moiety as in compound **31** led to reduced potency at 5-HT_{2C} (EC_{50} = 615 nM) and increased potency at 5-HT_{2B} (EC_{50} = 96 nM).

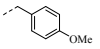
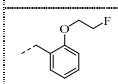
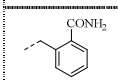
To explore further structural diversity, *N*-heteroarylmethyl derivatives with altered electron densities in the aromatic ring that might result in different pharmacokinetic properties were investigated as depicted in Table 1. The isosteric thiophene derivative (+)**-32** showed 120 nM potency at 5-HT_{2C} and full selectivity against 5-HT_{2B}. In line with the *N*-benzyl derivatives above, (+)**-32** was more potent at 5-HT_{2C} than its (–)-enantiomer (EC_{50} = 308 nM). Upon introduction of an additional methoxy group at the 3-position of the thiophene ring (compound **33**), a 2-fold increased potency at 5-HT_{2C} (EC_{50} = 121 nM for the racemate) and good selectivity against 5-HT_{2B} were obtained. The regioisomers **34** and **35** displayed weaker potency at 5-HT_{2C}. In contrast, the electron-deficient pyridine derivative **36** was less potent at 5-HT_{2C} (EC_{50} = 433 nM) compared to (+)**-32**. Moreover, several benzene-fused heterocyclic derivatives (**37-39**) with various heteroatoms (N and S) at the 2-position of the benzene ring were also investigated. Intriguingly, in contrast with the modest potency at 5-HT_{2C} of the benzo[*b*]thiophene derivative **37** (EC_{50} = 777 nM) and quinoline derivative **39** (EC_{50} = 530 nM), the indole derivative **38** was entirely inactive at

5-HT_{2C}, which possibly resulted from the absence of a hydrogen bond acceptor at the ortho position of the aryl ring.

In an effort to discover potent and selective 5-HT_{2C} agonists in a series of *N*-substituted 2-(2-methoxyphenyl)cyclopropylmethylamines, the *N*-(2-methoxybenzyl) derivative (+)**-19** has been established as the best ligand in terms of selectivity for 5-HT_{2C}. Introduction of the *N*-(2-methoxybenzyl) group onto the previously reported 5-HT_{2C}-selective ligands **11** and **12** also gave very high 5-HT_{2C} potency (**40**, EC_{50} = 9.2 nM, E_{max} = 97%; **41**, EC_{50} = 2.4 nM, E_{max} = 93%), but poor selectivity against 5-HT_{2B} (**40**, EC_{50} = 113 nM; **41**, EC_{50} = 24 nM) and 5-HT_{2A} (**40**, EC_{50} = 28 nM; **41**, EC_{50} = 24 nM). Furthermore, to identify potential off-target activity, compound (+)**-19** was profiled against a panel of serotonin receptors, dopamine receptors, monoamine transporters, and other selected CNS targets (see Supporting Information Table S2). Compound (+)**-19** showed good selectivity with much higher binding affinity for 5-HT_{2C} (K_i = 78 nM) than 5-HT_{2B} (K_i = 411 nM) and 5-HT_{2A} (K_i = 492 nM). None of the other screened targets were found to display any significant off-target affinity for compound (+)**-19**. Taken together, compound (+)**-19** represents a good candidate for further studies in terms of both its 5-HT_{2C} and selectivity.

Table 1. Functional Activity and Selectivity of *N*-substituted Derivatives 15a-c and 16-41 at 5-HT_2 Receptors in the Calcium Flux Assay[a]



Compd.	R^1	R^2	R^3	cLogP	LogBB	5-HT_{2C}		5-HT_{2B}		5-HT_{2A}	
						pEC_{50} (EC_{50}, nM)	E_{max} (%)	pEC_{50} (EC_{50}, nM)	E_{max} (%)	pEC_{50} (EC_{50}, nM)	E_{max} (%)
serotonin	-					9.78 ± 0.02 (0.17)	100 ±0.5	8.84 ± 0.03 (1.46)	100 ±1.1	8.63 ± 0.02 (2.35)	100 ±0.7
lorcaserin	-					8.58 ± 0.01 (2.64)	100 ±0.7	6.36 ± 0.03 (433)	80 ± 1.6	6.61 ± 0.01 (248)	68 ± 0.5
(+)-**15a**	Me	H	Me	2.07	0.26	7.65 ± 0.05 (23)	71 ± 1.5	7.05 ± 0.04 (89)	54 ± 1.1	6.57 ± 0.02 (271)	79 ± 1.0
(+)-**15b**	allyl	H	Me	2.63	0.40	7.89 ± 0.25 (13)	15 ± 1.4	NA	NA	6.55 ± 0.25 (284)	19 ± 2.5
(+)-**15c**	2-fluoroethyl	H	Me	2.16	0.31	NA	NA	NA	NA	NA	NA
(±)-**16**	Me	H		2.42	0.37	6.10 ± 1.40 (399)	70 ± 0.7	6.19 ± 0.52 (641)	14 ± 0.2	5.96 ± 1.22 (1090)	69 ± 0.4
(±)-**17**				2.84	0.56	NA	NA	NA	NA	5.37 ± 4.33 (4260)	43 ± 0.9
(±)-**18**				4.35	1.07	7.02 ± 0.25 (95)	15 ± 1.8	NA	NA	NA	NA
(–)-**19**				3.86	0.72	6.99 ± 0.05 (103)	104 ±2.1	6.24 ± 0.06 (570)	72 ± 2.3	7.15 ± 0.04 (72)	94 ± 1.4
(+)-**19**						7.63 ± 0.04 (23.5)	92 ± 1.3	NA	NA	6.86 ± 0.07 (139)	63 ± 2.1
(–)-**20**				3.86	0.72	5.58 ± 0.11 (2600)	85 ± 6.5	NA	NA	5.17 ± 0.08 (6840)	97 ± 6.8
(+)-**20**						6.64 ± 0.08 (231)	83 ± 2.9	NA	NA	5.43 ± 0.06 (3700)	70 ± 4.2
(–)-**21**				3.86	0.72	NA	NA	NA	NA	NA	NA
(+)-**21**						5.92 ± 0.09 (1200)	71 ± 3.4	NA	NA	NA	NA
(±)-**22**				3.06	0.90	6.52 ± 0.06 (304)	63 ± 2.2	NA	NA	7.11 ± 0.06 (77)	76 ± 2.0
(±)-**23**				3.91	0.79	7.55 ± 0.17 (28)	16 ± 1.1	7.25 ± 0.15 (56)	11 ± 0.7	6.40 ± 0.03 (398)	80 ± 1.2
(±)-**24**				3.30	0.81	6.61 ± 0.11 (245)	30 ± 2.7	6.62 ± 0.04 (238)	82 ± 1.7	6.14 ± 0.06 (721)	63 ± 2.3
(±)-**25**				2.24	0.16	6.39 ± 0.25 (409)	31 ± 0.5	6.48 ± 0.30 (335)	82 ± 0.8	5.88 ± 0.02 (1310)	67 ± 0.8
(–)-**26**				3.82	0.80	5.79 ± 0.07 (1640)	90 ± 4.1	NA	NA	5.73 ± 0.06 (1880)	78 ± 2.9
(+)-**26**						6.30 ± 0.06 (502)	78 ± 2.5	NA	NA	5.73 ± 0.07 (1880)	63 ± 3.0

(–)-**27**				4.57	0.90	5.73 ± 0.1 (1860)	72 ± 4.4	NA	NA	5.53 ± 0.06 (2990)	84 ± 3.9
(+)-**27**						6.28 ± 0.06 (529)	94 ± 2.7	NA	NA	5.45 ± 0.07 (3530)	64 ± 3.5
(±)-**28**	Me	Me		4.17	0.94	6.17 ± 0.10 (670)	49 ± 2.6	NA	NA	5.60 ± 0.08 (2540)	24 ± 1.4
(±)-**29**				4.12	0.83	5.59 ± 0.05 (2550)	81 ± 2.6	NA	NA	6.62 ± 0.06 (238)	106 ±2.9
(±)-**30**				4.07	1.07	6.06 ± 0.05 (874)	77 ± 2.2	NA	NA	6.18 ± 0.05 (655)	102 ±2.9
(±)-**31**				4.06	0.78	6.21 ± 0.1 (615)	51 ± 3.1	7.02 ± 0.14 (96)	17 ± 1.1	6.51 ± 0.06 (307)	59 ± 1.8
(–)-**32**				3.31	0.66	6.51 ± 0.03 (308)	81 ± 1.5	NA	NA	6.17 ± 0.04 (674)	59 ± 1.6
(+)-**32**						6.92 ± 0.06 (120)	60 ± 1.7	NA	NA	6.36 ± 0.08 (438)	34 ± 1.5
(±)-**33**				3.30	0.68	6.92 ± 0.06 (121)	66 ± 1.8	NA	NA	6.83 ± 0.06 (148)	102 ±2.7
(±)-**34**	Me	H		3.30	0.68	6.64 ± 0.03 (228)	65 ± 1.0	NA	NA	6.84 ± 0.04 (145)	89 ± 1.5
(±)-**35**				3.30	0.68	6.26 ± 0.04 (556)	65 ± 1..3	NA	NA	6.33 ± 0.03 (463)	100 1.5
(±)-**36**				2.83	0.44	6.36 ± 0.07 (433)	65 ± 2.5	6.56 ± 0.20 (274)	32 ± 3.3	5.89 ± 0.06 (1290)	66 ± 2.9
(±)-**37**				5.00	0.94	6.11 ± 0.06 (777)	94 ± 3.0	6.09 ± 0.04 (807)	79 ± 1.7	5.65 ± 0.06 (2220)	70 ± 2.8
(±)-**38**				3.81	0.55	NA	NA	NA	NA	NA	NA
(±)-**39**				3.75	0.31	6.28 ± 0.07 (530)	84 ± 3.1	7.06 ± 0.04 (87)	73 ± 1.4	6.34 ± 0.03 (460)	69 ± 1.3
(+)-**40**	allyl	H		4.48	0.91	8.05 ± 0.04 (9.2)	97 ± 1.3	6.95 ± 0.17 (113)	28 ± 2.2	7.56 ± 0.05 (28)	80 ± 1.7
(+)-**41**	2-fluoroethyl	H		3.91	0.79	8.65 ± 0.03 (2.4)	93 ± 1.1	7.61 ± 0.22 (24)	22 ± 2.0	7.62 ± 0.03 (24)	78 ± 1.1

[a]All new compounds were tested as HCl salts except compound **36**, which was tested as the free base. Pharmacological data were acquired with recombinant, stably expressed human 5-HT receptors in the HEK-293 cell line, using a fluorescence imaging plate reader (FLIPR) assay. pEC_{50} and E_{max} values are shown as the mean ± SEM (n = 3). EC_{50} values were calculated from averaged pEC_{50} values. "NA" indicates no activity up to 10 μM. "–" indicates structures of 5-HT

and lorcaserin are not shown. cLogP and LogBB values were calculated for the free bases using the ACD Percepta program.

5-HT_{2C} Functional Selectivity

Recently, we have discovered benzofuran-based compounds as functionally selective 5-HT_{2C} agonists with weak β-arrestin recruitment activities.[21] However, no fully biased 5-HT_{2C} agonist has been disclosed to date. The functional selectivity of the above 5-HT_{2C}-selective *N*-substituted 2-phenylcyclopropylmethylamines was investigated and compared to lorcaserin and 5-HT. β-Arrestin recruitment activity was tested using reported methods[21, 34] in parallel with a G_q-mediated calcium flux assay using the same drug dilutions. The relative activities (log E_{max}/EC_{50}) were calculated to account for partial agonist differences. As shown in Table 2 and Figure 3, compounds (+)-**15a** and (+)-**32** showed no β-arrestin recruitment activity, which indicates that these compounds exclusively signal via G_q-mediated calcium flux. The *N*-(2-methoxybenzyl) derivative (–)-**19** also displayed preference for G_q-mediated calcium flux with weak potency (> 1 μM) for β-arrestin recruitment activity, whereas its (+)-enantiomer showed stronger potency for β-arrestin recruitment (EC_{50} = 70 nM) albeit with much reduced efficacy (E_{max} = 43%) compared to the reference ligand, lorcaserin (EC_{50} = 40 nM, E_{max} = 97%). The *N*-(2-methoxybenzyl) derivatives of **11** and **12**, namely (+)-**40** and (+)-**41**, respectively, had a preference for G_q signaling driven mainly by their weaker β-arrestin recruitment efficacy (E_{max} = 56 and 54%, respectively) compared to lorcaserin (E_{max} = 97%).

Table 2. Functional Selectivity for 5-HT_{2C}-Selective Agonists[a]

Compd.	G_q calcium flux			*β*-arrestin-2		
	pEC_{50} (EC_{50}, nM)	E_{max} (%)	Log(E_{max} / EC_{50})	pEC_{50} (EC_{50}, nM)	E_{max} (%)	Log(E_{max} / EC_{50})
5-HT	9.74 ± 0.02 (0.18)	100 ± 0.9	9.85	7.82 ± 0.03 (15)	100 ± 1.0	7.82
Lorcaserin	8.68 ± 0.04 (2.1)	101 ± 1.4	8.68	7.40 ± 0.05 (40)	97 ± 2.1	7.38

(+)-15a	7.64 ± 0.05 (23)	71 ± 1.4	7.49	NA	NA	-
(+)-19	7.62 ± 0.04 (24)	92 ± 1.3	7.58	7.16 ± 0.04 (70)	43 ± 0.9	6.79
(–)-19	6.99 ± 0.05 (103)	104 ± 2.1	7.00	> 1,000	ND	-
(+)-32	6.92 ± 0.06 (120)	60 ± 0.7	6.70	NA	NA	-
(+)-40	8.04 ± 0.04 (9.2)	97 ± 1.3	8.02	7.64 ± 0.05 (22.7)	56 ± 1.0	7.39
(+)-41	8.62 ± 0.03 (2.4)	93 ± 1.1	8.59	7.96 ± 0.05 (11)	54 ± 1.0	7.69

[a]Data were acquired with the human 5-HT_{2C}-INI receptor isoform measuring G_q calcium flux (FLIPR) and β-arrestin-2 recruitment (Tango). E_{max} values are shown as the mean ± SEM (n = 3), and assays were conducted in parallel with the same drug dilutions. "NA" indicates no activity up to 10 μM. "ND" indicates not determined because of no saturable E_{max}.

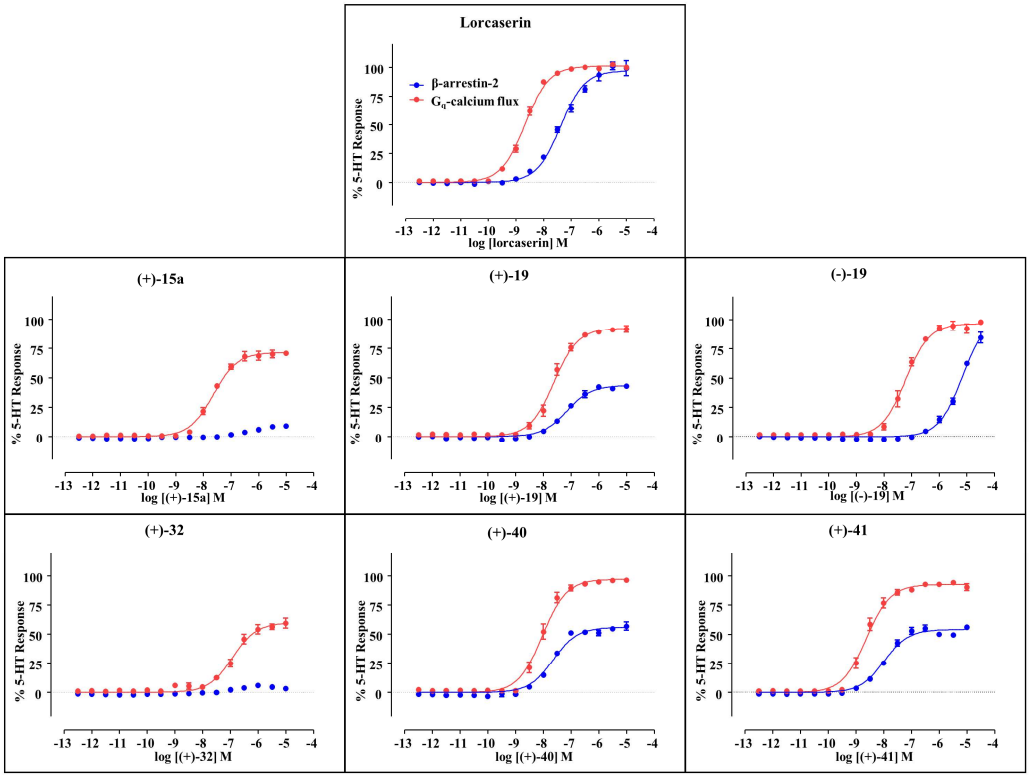


Figure 3. Profiling of 5-HT_{2C} functional selectivity measuring G_q-calcium flux (FLIPR, red) and β-arrestin-2 recruitment (Tango, blue). Data were acquired with the human 5-HT_{2C}-INI receptor isoform. E_{max} values are shown as the mean (n = 3), and assays were conducted in parallel with the same drug dilutions.

Evaluation in Animal Models of Antipsychotic Drug-like Activity.

In vitro pharmacology profiles identified the *N*-(2-methoxybenzyl) compound (+)**-19** as the most potent 5-HT_{2C} agonist (EC_{50} = 24 nM, E_{max} = 92%) with full selectivity over 5-HT_{2B} in the present series of compounds. As the absence of 5-HT_{2B} agonism is necessary to avoid potential cardiovascular side effects, compound (+)**-19** was selected for further *in vivo* studies in the amphetamine (AMPH)-induced and phencyclidine (PCP)-induced hyperactivity models (details of the behavioral studies are provided in the Experimental Section), which are both well-recognized models to evaluate the possible antipsychotic activities of compounds.

Amphetamine (AMPH)-induced Hyperactivity Model. In this model, adult male C57BL/6J mice were administered saline (vehicle), lorcaserin (as the positive control, 3 mg/kg), or the test compound (+)**-19** (10 and 20 mg/kg), and locomotor activity was monitored for 15 min (baseline). As shown in Figure 4A, lorcaserin decreased baseline locomotion while the compound (+)**-19** (10 and 20 mg/kg) had no effect. Next the mice were given saline or amphetamine (3 mg/kg), and activity was measured for an additional 90 min. The results showed that lorcaserin reduced amphetamine-induced hyperactivity consistent with other 5-HT_{2C} agonists,[35, 36] whereas responses to 10 and 20 mg/kg of (+)**-19** were differentiated by dose (Figure

4A and 4B). Although the low dose (10 mg/kg) of (+)-**19** had no significant effect, the higher dose (20 mg/kg) decreased the hyperlocomotion such that its effects were similar to those of lorcaserin. Thus, compound (+)-**19** (20 mg/kg) showed an antipsychotic action by blocking amphetamine-induced hyperactivity with no effect on spontaneous motor activity.

Phencyclidine (PCP)-induced hyperactivity model. In contrast to amphetamine-induced hyperactivity, lorcaserin showed a tendency to suppress PCP-induced hyperactivity at the beginning of the test session, but there was no overall reduction in activity that was statistically significant. While the low dose (10 mg/kg) of (+)-**19** increased locomotion, the higher dose (20 mg/kg) had no effect on PCP-induced hyperlocomotion (Figure 4C and 4D). In general, it has been demonstrated that 5-HT_{2C} agonists decrease PCP-induced hyperactivity.[37, 38] The locomotion enhancement observed with the lower dose of (+)-**19** could result from other off-target effects on PCP. For example, from our *in vitro* ADMET results (Table 3), (+)-**19** exhibits strong inhibition (85.6%, Table 3) of human cytochrome P450 (CYP) 3A4 (in the mouse mainly its highly homologous 3A11)[39] which is the same enzyme that has been reported to metabolize PCP.[40] Alternatively, the 5-HT_{2A} agonism of (+)-**19** (EC_{50} = 139 nM, E_{max} = 63%, Table 1) might also explain its effect on PCP-induced locomotor activity. The 5-$HT_{2A/2C}$ agonist DOI (5-HT_{2A}, EC_{50} = 57 nM, E_{max} = 46%; 5-HT_{2C}, EC_{50} = 178 nM, E_{max} = 90%)[41] has been shown to potentiate the locomotor effects of PCP.[42] These results indicate that (+)-**19** at doses

of either 10 or 20 mg/kg does not possess an antipsychotic-like profile in the PCP-induced locomotion model.

In summary, (+)-**19** has superiority over lorcaserin based on its behavioral profile in decreasing amphetamine-induced hyperactivity without having an effect on spontaneous activity. Further studies are required to determine the precise mechanism of the enhancement of PCP using the lower dose (+)-**19**.

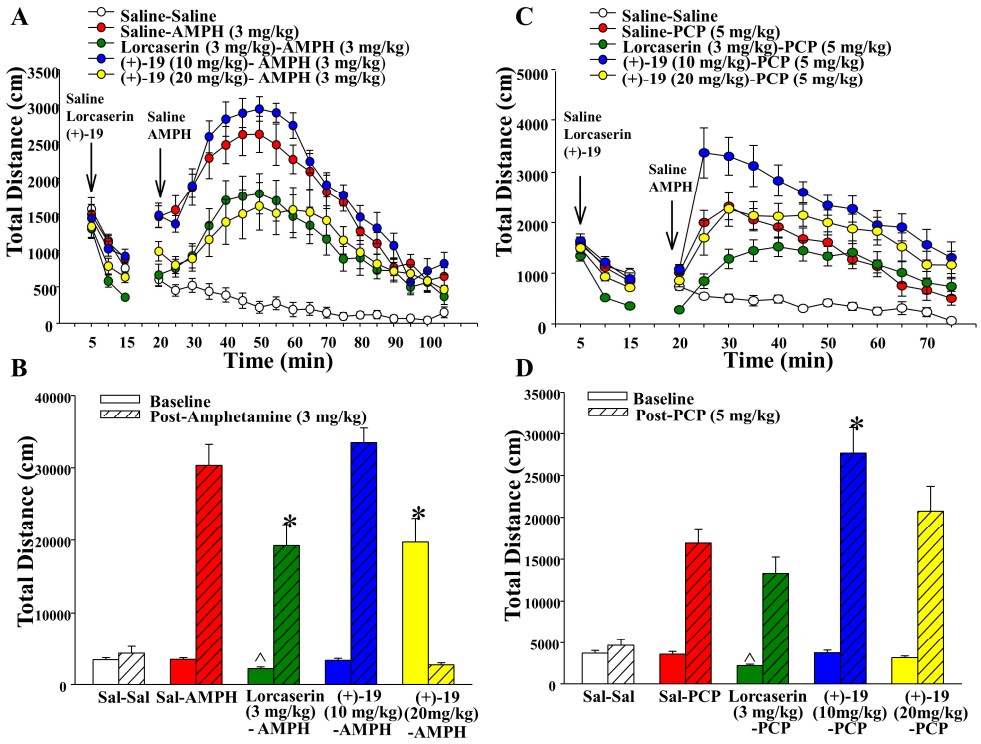


Figure 4. Evaluation of compound (+)-**19** in animal models of antipsychotic drug-like activity. (A) Locomotor activity reflecting baseline responses (0-15 min) and AMPH-induced hyperactivity with reductions by lorcaserin and (+)-**19** (20-105 min). (B) Cumulative baseline locomotor activities (0-15 min), AMPH-induced hyperactivities, and reductions by lorcaserin and (+)-**19** (20-105 min); ^ $p < 0.05$, compared to Sal-Sal group, baseline; * $p < 0.05$ compared to Sal-AMPH,

Post-AMPH. (C) Locomotor activity reflecting baseline responses (0-15 min) and PCP-induced hyperactivity with effects by lorcaserin and (+)-**19** (20-75 min). (B) Cumulative baseline locomotor activities (0-15 min), PCP-induced hyperactivities, and effects by lorcaserin and (+)-**19** (20-75 min); ^ $p < 0.05$, compared to Sal-Sal group, baseline; * $p < 0.05$ compared to Sal-PCP, Post-PCP. N = 8-10 mice/group.

ADMET Studies (*In vitro*).

Due to its efficacy in the amphetamine-induced hyperactivity model, compound (+)-**19** was evaluated for selected *in vitro* ADMET properties (Table 3) to qualify it as a possible candidate for further development. Compared with the structurally similar parent 2-(5-chlorophenyl)cyclopropylmethylamines (+)-**9** and (+)-**10** previously reported by us, the *N*-benzylated derivative (+)-**19** displayed higher human plasma protein binding (82%, (+)-**19**; 75%, (+)-**9**; 57%, (+)-**10**)[23] as a result of its enhanced lipophilicity, as the cLogP is a highly correlated indicator that determines protein binding properties. In the recombinant CYP inhibition assay, (+)-**19** showed low inhibition of CYP 1A2 and CYP 2C9, and relatively higher inhibition of CYP 2D6 and CYP 3A4 at 10 μM (> 50%). Compound (+)-**19** was found to have a half-life of 43 min in the human hepatocyte stability assay, which may be a consequence of the presence of the electron-rich *N*-benzyl group.[43] Moreover, moderate hERG inhibition (IC_{50} = 1.4 μM) was detected.

Table 3. *In Vitro* ADMET Data for Compound (+)-19

Assay	(+)-19

PPB at 10 μM (%)	human	82.0
	mouse	92.0
CYP inhibition at 10 μM (%)[a]	1A2	20.5
	2C9	9.3
	2D6	68.9
	3A4	85.6
$T_{1/2}$ (min) [b]	human	43.0
	mouse	7.8
hERG IC_{50} (μM)[c]		1.4

[a]The CYP inhibition test was performed using human liver microsomes. Phenacetin, tolbutamide, dextromethorphan, and midazolam were used as test substrates for the 1A2, 2C9, 2D6, and 3A4 isoforms, respectively. [b]The concentration of hepatocytes was 0.5×10^6 cells/mL, and (+)**-19** was tested at 1 μM. [c]hERG inhibition was tested on CHO cells using the automated patch-clamp method.

Conclusions

New *N*-substituted 2-phenylcyclopropylmethylamines have been characterized as reasonably selective 5-HT_{2C} receptor agonists with novel patterns of functional selectivity. The *N*-methyl compound (+)-**15a**, which displayed an EC_{50} of 23 nM at 5-HT_{2C} with no β-arrestin recruitment activity, is the first potent and at the same time fully G_q-biased 5-HT_{2C} agonist reported to date, while the *N*-benzyl compound (+)-**19** with an EC_{50} of 24 nM at 5-HT_{2C} is fully selective over 5-HT_{2B}. The potency and lack of detectable arrestin recruitment of (+)-**15a** make it a valuable chemical probe to better understand biased 5-HT_{2C} signaling. Moreover, although (+)-**19** had a relatively short half-life in the hepatocyte stability assay, preliminary *in vivo* studies in an amphetamine-induced hyperactivity model indicate that (+)-**19** shows potential antipsychotic effects. Further compound optimization to develop better drug-like analogs is in progress.

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 on 230−400 mesh silica gel using a Teledyne CombiFlash R_f flash chromatograph. ^{1}H 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 are reported in δ (ppm) using residual solvent peaks as standards ($CDCl_3$–7.26 (H), 77.16 (C); CD_3OD–3.31 (H), 49.00 (C)). Mass spectra were measured using an LCMS-IT-TOF (Shimadzu) mass spectrometer in ESI mode. Preparative HPLC purification of synthetic intermediates was performed on a Shimadzu LC-8A instrument with an ACE 5AQ column (150 × 21.2 mm, particle size 5 μm; eluent: 8 – 100% MeOH (0.05% TFA)/ H_2O (0.05% TFA) gradient, 30 min; flow rate: 17 mL/min; UV detection at 254 and 280 nm). Chiral separation of racemic intermediates was conducted by preparative HPLC on RegisPack (25 cm × 21.1 mm, particle size 10 μm) or ChromegaChiral CCJ (25 cm × 20 mm, particle size 10 μm) chiral columns with isopropanol (0.05% diethylamine, DEA)/ *n*-hexane (0.05% DEA) as the eluent. The purity of all final compounds (greater than 95% in all cases) was determined by analytical HPLC on an ACE 3AQ C_{18} column (150 × 4.6 mm, particle size 3 μm; eluent: MeOH (0.05% TFA)/ H_2O (0.05% TFA) gradient, 25 min; flow rate: 1.0 mL/min). Specific rotations were recorded on a Rudolph Research Autopol IV automatic polarimeter.

The synthetic procedures, chiral separation methods, and characterization data of all intermediates can be found in the Supporting Information. All intermediates subjected to chiral preparative HPLC separation were prepared with an optical purity of > 90% ee (determined by analytical HPLC using a RegisPack (25 cm × 4.6 mm, 10 μm) or ChromegaChiral CCJ (25 cm × 4.6 mm, 10 μm) chiral column and isopropanol (0.05% DEA)/ *n*-hexane (0.05% DEA) as the eluent).

General Method A: Preparation of HCl Salts 15a-c. The *N*-Boc-amines **14a-c** were dissolved in 2M HCl (g) in diethyl ether (5 equiv.) 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 the HCl salts as white solids.

General Method B: Preparation of HCl Salts 16-22, 26-32, and 34-35 from the Intermediate Aldehyde D. The aldehyde **D** was prepared according to the reported procedure.[24] Aldehyde **D** (1.0 equiv.) and amines (1.2 equiv.) were reacted under reductive amination condition ($NaBH_4$ (1.5 equiv.)/MeOH). The reaction mixtures were quenched with water and extracted with DCM. The organic phases were washed with brine, dried over sodium sulfate, concentrated, and purified by preparative HPLC to give the trifluoroacetate salts. The salts were neutralized with aq. $NaHCO_3$, and the resulting solutions were extracted with DCM. The organic layers were dried over sodium sulfate and concentrated to provide the desired compounds as free bases. For **19-21**, **26-27**, and **32**, the obtained racemic free bases were separated by chiral preparative HPLC to afford their enantiomers (see Supporting Information). The racemic or enantiopure free bases were dissolved in 2M HCl (g) in diethyl ether (3

equiv.) and stirred at room temperature for 1-2 h. The white solids formed were collected by filtration, washed with diethyl ether, and dried under vacuum to give the HCl salts as white solids in high yields (80-95%).

General Method C: Preparation of HCl Salts 24-25, 33, and 36-39 from the Intermediate Cyclopropylmethylamine G. The cyclopropylmethylamine **G** was prepared according to the reported procedure.[24] The listed compounds were prepared from the cyclopropylmethylamine **G** (1.0 equiv.) and ArCHO (1.0 equiv.) or $ArCH_2OTs$ (1.0 equiv.) via reductive amination ($NaBH_4$ (1.5 equiv.)/MeOH or $NaBH(OAc)_3$ (2.0 equiv.)/DCE) or nucleophile substitution reactions (base/CH_3CN), respectively. The crude products were purified by preparative LC and reacted with 2M HCl/Et_2O to afford the HCl salts as white solids according to the similar procedure described in General Method B.

(+)-1-[(1*S*,2*S*)-2-(5-Fluoro-2-methoxyphenyl)cyclopropyl]-*N*-methylmethanamine Hydrochloride (15a). Obtained from the intermediate **14a** (56 mg, 0.18 mmol) employing General Method A (40 mg, 90% yield). ^{1}H NMR ($CDCl_3$) δ 9.61 (s, 2H), 6.88 – 6.82 (m, 1H), 6.76 (dd, J = 9.0, 4.6 Hz, 1H), 6.66 (dd, J = 9.3, 3.0 Hz, 1H), 3.85 (s, 3H), 3.10 (dd, J = 13.1, 7.1 Hz, 1H), 3.02 (dd, J = 13.0, 7.6 Hz, 1H), 2.75 (s, 3H), 2.25 – 2.07 (m, 1H), 1.52 – 1.37 (m, 1H), 1.21 – 1.09 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 157.2 (d, J = 238.2 Hz), 154.5 (s), 130.6 (d, J = 7.4 Hz), 113.3 (d, J = 23.9 Hz), 113.1 (d, J = 22.5 Hz), 111.2 (d, J = 8.5 Hz), 56.2 (s), 52.9 (s), 32.1 (s), 17.8 (s), 16.9 (s), 13.0 (s); HRMS (ESI) calculated for $C_{12}H_{17}FNO$ ($[M+H]^+$), 210.1289; found, 210.1269. $[\alpha]_D^{20}$ +18.0 (*c* 0.1, $CHCl_3$).

(+)-1-[(1*S*,2*S*)-2-[2-(Allyloxy)-5-fluorophenyl]cyclopropyl]-*N*-methylmethanamine Hydrochloride (15b). Obtained from the intermediate **14b** (188 mg, 0.56 mmol) employing General Method A (140 mg, 93% yield). ^{1}H NMR ($CDCl_3$) δ 9.62 (s, 2H), 6.82 (td, J = 8.4, 3.0 Hz, 1H), 6.75 (dd, J = 8.9, 4.6 Hz, 1H), 6.65 (dd, J = 9.3, 3.0 Hz, 1H), 6.14 – 6.02 (m, 1H), 5.41 (dd, J = 17.2, 1.4 Hz, 1H), 5.30 (dd, J = 10.5, 1.4 Hz, 1H), 4.54 (d, J = 5.3 Hz, 2H), 3.21 – 3.06 (m, 1H), 3.05 – 2.92 (m, 1H), 2.73 (s, 3H), 2.25 – 2.17 (m, 1H), 1.53 – 1.41 (m, 1H), 1.15 (t, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 157.3 (d, J = 238.7 Hz), 153.4 (s), 133.4 (s), 131.0 (d, J = 7.3 Hz), 118.0 (s), 113.2 (d, J = 23.8 Hz), 113.1 (d, J = 22.6 Hz), 112.7 (d, J = 8.4 Hz), 69.9 (s), 52.8 (s), 32.2 (s), 17.9 (s), 17.0 (s), 13.0 (s); HRMS (ESI) calculated for $C_{14}H_{19}FNO$ ($[M+H]^+$), 236.1445; found, 236.1408. $[\alpha]_D^{20}$ +20.3 (*c* 0.1, $CHCl_3$).

(+)-1-[(1*S*,2*S*)-2-[5-Fluoro-2-(2-fluoroethoxy)phenyl]cyclopropyl]-*N*-methylmethanamine Hydrochloride (15c). Obtained from the intermediate **14c** (70 mg, 0.20 mmol) employing General Method A (52 mg, 95% yield). ^{1}H NMR ($CDCl_3$) δ 9.53 (s, 2H), 6.86 (td, J = 8.5, 2.7 Hz, 1H), 6.77 (dd, J = 8.9, 4.5 Hz, 1H), 6.68 (dd, J = 9.2, 2.8 Hz, 1H), 5.02 – 4.68 (m, 2H), 4.36 – 4.12 (m, 2H), 3.19 – 2.99 (m, 2H), 2.74 (s, 3H), 2.29 – 2.17 (m, 1H), 1.52 – 1.36 (m, 1H), 1.26 – 1.07 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 157.7 (d, J = 239.6 Hz), 153.3 (s), 131.4 (d, J = 7.4 Hz), 113.7 (d, J = 23.8 Hz), 113.3 (d, J = 22.9 Hz), 112.8 (d, J = 8.5 Hz), 82.4 (d, J = 169.9 Hz), 68.5 (d, J = 19.4 Hz), 53.0 (s), 32.5 (s), 17.8 (s), 17.3 (s), 12.8 (s). HRMS (ESI) calculated for $C_{13}H_{18}F_2NO$ ($[M+H]^+$), 242.1351; found, 242.1328. $[\alpha]_D^{20}$ +8.2 (*c* 0.1, $CHCl_3$).

***N*-[[2-(5-Fluoro-2-methoxyphenyl)cyclopropyl]methyl]cyclopropanamine Hydrochloride (16).** Prepared from cyclopropanamine employing Method B. ^{1}H NMR ($CDCl_3$) δ 9.72 (s, 2H), 6.87 – 6.80 (m, 1H), 6.75 (dd, J = 8.9, 4.6 Hz, 1H), 6.63 (dd, J = 9.3, 3.0 Hz, 1H), 3.83 (s, 3H), 3.20 (dd, J = 13.0, 6.9 Hz, 1H), 3.03 (dd, J = 13.0, 7.8 Hz, 1H), 2.78 – 2.66 (m, 1H), 2.28 – 2.15 (m, 1H), 1.59 – 1.46 (m, 1H), 1.36 – 1.07 (m, 4H), 0.91 – 0.75 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 157.2 (d, J = 238.2 Hz), 154.4 (s), 130.9 (d, J = 7.3 Hz), 113.0 (d, J = 24.8 Hz), 112.9 (d, J = 21.2 Hz), 111.1 (d, J = 8.4 Hz), 56.1 (s), 52.2 (s), 29.5 (s), 17.8 (s), 17.0 (s), 13.5 (s), 4.1 (s), 3.8 (s); HRMS (ESI) calculated for $C_{14}H_{19}FNO$ ($[M+H]^+$), 236.1445; found, 236.1405.

1-Cyclopropyl-*N*-[[2-(5-fluoro-2-methoxyphenyl)cyclopropyl]methyl]methanamine Hydrochloride (17). Prepared from cyclopropylmethanamine employing Method B. ^{1}H NMR ($CDCl_3$) δ 9.65 (s, 2H), 6.84 (td, J = 8.5, 2.9 Hz, 1H), 6.75 (dd, J = 8.9, 4.5 Hz, 1H), 6.62 (dd, J = 9.3, 2.9 Hz, 1H), 3.84 (s, 3H), 3.26 – 3.01 (m, 2H), 3.00 – 2.88 (m, 2H), 2.23 – 2.09 (m, 1H), 1.56 – 1.40 (m, 1H), 1.39 – 1.22 (m, 1H), 1.19 – 1.07 (m, 2H), 0.76 – 0.64 (m, 2H), 0.55 – 0.40 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 157.3 (d, J = 238.3 Hz), 154.4 (s), 130.8 (d, J = 7.4 Hz), 113.1 (d, J = 24.0 Hz), 113.0 (d, J = 24.4 Hz), 111.2 (d, J = 8.4 Hz), 56.2 (s), 51.3 (s), 50.7 (s), 17.8 (s), 17.2 (s), 13.2 (s), 7.2 (s), 4.9 (s), 4.7 (s); HRMS (ESI) calculated for $C_{15}H_{21}FNO$ ($[M+H]^+$), 250.1602; found, 250.1545.

1-Cyclohexyl-*N*-[[2-(5-fluoro-2-methoxyphenyl)cyclopropyl]methyl]methanamine Hydrochloride (18). Prepared from cyclohexylmethylamine employing Method B. ^{1}H NMR ($CDCl_3$) δ 9.52 (s, 1H), 9.43 (s, 1H), 6.88 – 6.80 (m, 1H), 6.76 (dd, J = 9.0,

4.6 Hz, 1H), 6.59 (dd, *J* = 9.3, 3.0 Hz, 1H), 3.83 (s, 3H), 3.17 – 3.03 (m, 2H), 2.98 – 2.81 (m, 2H), 2.22 – 2.11 (m, 1H), 2.04 – 1.85 (m, 3H), 1.81 – 1.62 (m, 3H), 1.50 – 1.38 (m, 1H), 1.36 – 1.09 (m, 5H), 1.08 – 0.94 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 157.3 (d, *J* = 238.3 Hz), 154.3 (s), 130.8 (d, *J* = 7.3 Hz), 113.0 (d, *J* = 22.8 Hz), 112.8 (d, *J* = 23.8 Hz), 111.1 (d, *J* = 8.4 Hz), 56.2 (s), 52.5 (s), 51. 6 (s), 34.8 (s), 31.1 (s), 31.0 (s), 26.0 (s), 25.5 (s), 25.4 (s), 17.8 (s), 17.3 (s), 13.0 (s); HRMS (ESI) calculated for $C_{18}H_{27}FNO$ ($[M+H]^+$), 292.2071; found, 292.2073.

(+)-1-[(1*S*,2*S*)-2-(5-Fluoro-2-methoxyphenyl)cyclopropyl]-*N*-(2-methoxybenzyl)methanamine Hydrochloride ((+)-19). Prepared from 2-methoxybenzylamine employing Method B including chiral separation. ^{1}H NMR ($CDCl_3$) δ 10.02 (s, 1H), 9.15 (s, 1H), 7.48 (d, *J* = 6.7 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 6.95 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 6.81 (td, *J* = 8.6, 2.9 Hz, 1H), 6.72 (dd, *J* = 8.9, 4.5 Hz, 1H), 6.59 (dd, *J* = 9.2, 2.9 Hz, 1H), 4.19 (m, 2H), 3.84 (s, 3H), 3.78 (s, 3H), 3.08 – 2.72 (m, 2H), 1.99 – 1.83 (m, 1H), 1.47 – 1.37 (m, 1H), 1.09 – 0.88 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 157.9 (s), 157.2 (d, *J* = 238.3 Hz), 154.4 (d, *J* = 2.0 Hz), 132.2 (s), 131.2 (s), 130.7 (d, *J* = 7.4 Hz), 121.2 (s), 119.0 (s), 113.5 (d, *J* = 23.8 Hz), 113.1 (d, *J* = 22.7 Hz), 111.1 (d, *J* = 8.4 Hz), 110.7 (s), 56.2 (s), 55.7 (s), 50.3 (s), 45.8 (s), 17.9 (s), 17.3 (s), 13.2 (s); HRMS (ESI) calculated for $C_{19}H_{23}FNO_2$ ($[M+H]^+$), 316.1707; found, 316.1703; $[\alpha]_D^{20}$ +34.0 (*c* 0.6, $CHCl_3$).

(–)-1-[(1*R*,2*R*)-2-(5-Fluoro-2-methoxyphenyl)cyclopropyl]-*N*-(2-methoxybenzyl)methanamine Hydrochloride ((–)-19). Prepared from 2-methoxybenzylamine employing General Method B including chiral separation. ^{1}H NMR ($CDCl_3$) δ 10.02

(s, 1H), 9.15 (s, 1H), 7.48 (d, J = 6.7 Hz, 1H), 7.33 (t, J = 7.8 Hz, 1H), 6.95 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 6.81 (td, J = 8.6, 2.9 Hz, 1H), 6.72 (dd, J = 8.9, 4.5 Hz, 1H), 6.59 (dd, J = 9.2, 2.9 Hz, 1H), 4.19 (m, 2H), 3.84 (s, 3H), 3.78 (s, 3H), 3.07 – 2.72 (m, 2H), 1.99 – 1.83 (m, 1H), 1.47 – 1.37 (m, 1H), 1.09 – 0.87 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 157.9 (s), 157.2 (d, J = 238.3 Hz), 154.4 (d, J = 2.0 Hz), 132.2 (s), 131.2 (s), 130.7 (d, J = 7.4 Hz), 121.2 (s), 119.0 (s), 113.5 (d, J = 23.8 Hz), 113.1 (d, J = 22.7 Hz), 111.1 (d, J = 8.4 Hz), 110.7 (s), 56.2 (s), 55.7 (s), 50.3 (s), 45.8 (s), 17.9 (s), 17.3 (s), 13.2 (s); HRMS (ESI) calculated for $C_{19}H_{23}FNO_2$ ($[M+H]^+$), 316.1707; found, 316.1710; $[\alpha]_D^{20}$ –39.0 (*c* 0.2, $CHCl_3$).

(+)-1-[(1*S*,2*S*)-2-(5-Fluoro-2-methoxyphenyl)cyclopropyl]-*N*-(3-methoxybenzyl)methanamine Hydrochloride ((+)-20). Prepared from 3-methoxybenzylamine employing General Method B including chiral separation. ^{1}H NMR ($CDCl_3$) δ 10.00 (s, 2H), 7.42 – 7.23 (m, 2H), 7.19 – 7.06 (m, 1H), 6.89 (d, J = 8.1 Hz, 1H), 6.82 (td, J = 8.6, 2.3 Hz, 1H), 6.73 (dd, J = 8.8, 4.4 Hz, 1H), 6.63 (dd, J = 9.1, 2.4 Hz, 1H), 4.12 (s, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 3.08 – 2.75 (m, 2H), 2.20 – 2.03 (m, 1H), 1.57 – 1.36 (m, 1H), 1.15 – 0.96 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 160.3 (s), 157.3 (d, J = 238.5 Hz), 154.4 (s), 132.0 (s), 130.7 (d, J = 7.2 Hz), 130.3 (s), 122.3 (s), 115.8 (s), 115.1 (s), 113.2 (d, J = 23.4 Hz), 113.0 (d, J = 22.2 Hz), 111.2 (d, J = 8.3 Hz), 56.2 (s), 55.7 (s), 49.9 (s, 2C), 18.0 (s), 17.0 (s), 13.4 (s); HRMS (ESI) calculated for $C_{19}H_{23}FNO_2$ ($[M+H]^+$), 316.1707; found, 316.1706; $[\alpha]_D^{20}$ +13.6 (*c* 0.3, MeOH).

(–)-1-[(1*R*,2*R*)-2-(5-Fluoro-2-methoxyphenyl)cyclopropyl]-*N*-(3-methoxybenzyl)methanamine Hydrochloride ((–)-20). Prepared from 3-methoxybenzylamine

employing General Method B including chiral separation. ^{1}H NMR ($CDCl_3$) δ 10.01 (s, 2H), 7.42 – 7.23 (m, 2H), 7.19 – 7.06 (m, 1H), 6.89 (d, J = 8.1 Hz, 1H), 6.82 (td, J = 8.6, 2.3 Hz, 1H), 6.73 (dd, J = 8.8, 4.4 Hz, 1H), 6.63 (dd, J = 9.1, 2.4 Hz, 1H), 4.12 (s, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 3.08 – 2.75 (m, 2H), 2.20 – 2.03 (m, 1H), 1.57 – 1.36 (m, 1H), 1.15 – 0.96 (m, 2H).; ^{13}C NMR ($CDCl_3$) δ 160.3 (s), 157.3 (d, J = 238.5 Hz), 154.4 (s), 132.0 (s), 130.7 (d, J = 7.2 Hz), 130.3 (s), 122.3 (s), 115.8 (s), 115.1 (s), 113.2 (d, J = 23.4 Hz), 113.0 (d, J = 22.2 Hz), 111.2 (d, J = 8.3 Hz), 56.2 (s), 55.7 (s), 49.9 (s, 2C), 18.0 (s), 17.1 (s), 13.4 (s); HRMS (ESI) calculated for $C_{19}H_{23}FNO_2$ ($[M+H]^+$), 316.1707; found, 316.1703; $[\alpha]_D^{20}$ –15.0 (*c* 0.3, MeOH).

(+)-1-[(1*S*,2*S*)-2-(5-Fluoro-2-methoxyphenyl)cyclopropyl]-*N*-(4-methoxybenzyl)methanamine Hydrochloride ((+)-21). Prepared from 4-methoxybenzylamine employing General Method B including chiral separation. ^{1}H NMR ($CDCl_3$) δ 9.90 (s, 2H), 7.54 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 8.5 Hz, 2H), 6.81 (td, J = 8.4, 3.0 Hz, 1H), 6.72 (dd, J = 8.9, 4.5 Hz, 1H), 6.62 (dd, J = 9.3, 3.0 Hz, 1H), 4.09 – 4.01 (m, 2H), 3.78 (s, 3H), 3.74 (s, 3H), 3.00 – 2.74 (m, 2H), 2.10 – 2.06 (m, 1H), 1.49 – 1.46 (m, 1H), 1.06 – 1.00 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 160.4 (s), 157.2 (d, J = 238.1 Hz), 154.3 (s), 131.9 (s, 2C), 130.8 (d, J = 7.2 Hz), 122.5 (s), 114.5 (s, 2C), 113.2 (d, J = 24.1 Hz), 112.9 (d, J = 23.0 Hz), 111.1 (d, J = 8.4 Hz), 56.1 (s), 55.3 (s), 49.6 (s), 49.3 (s), 17.9 (s), 17.0 (s), 13.4 (s); HRMS (ESI) calculated for $C_{19}H_{23}FNO_2$ ($[M+H]^+$), 316.1707; found, 316.1700; $[\alpha]_D^{20}$ +20.6 (*c* 1.0, MeOH).

(–)-1-[(1*R*,2*R*)-2-(5-Fluoro-2-methoxyphenyl)cyclopropyl]-*N*-(4-methoxybenzyl)methanamine Hydrochloride ((–)-21). Prepared from 4-methoxybenzylamine

employing General Method B including chiral separation. ^{1}H NMR ($CDCl_3$) δ 9.90 (s, 2H), 7.54 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 8.5 Hz, 2H), 6.81 (td, J = 8.4, 3.0 Hz, 1H), 6.72 (dd, J = 8.9, 4.5 Hz, 1H), 6.62 (dd, J = 9.3, 3.0 Hz, 1H), 4.09 – 4.01 (m, 2H), 3.78 (s, 3H), 3.74 (s, 3H), 3.00 – 2.74 (m, 2H), 2.10 – 2.05 (m, 1H), 1.49 – 1.46 (m, 1H), 1.06 – 1.02 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 160.4 (s), 157.2 (d, J = 238.1 Hz), 154.3 (s), 131.9 (s, 2C), 130.8 (d, J = 7.2 Hz), 122.5 (s), 114.5 (s, 2C), 113.2 (d, J = 24.1 Hz), 112.9 (d, J = 23.0 Hz), 111.1 (d, J = 8.4 Hz), 56.1 (s), 55.3 (s), 49.6 (s), 49.3 (s), 17.9 (s), 17.0 (s), 13.4 (s); HRMS (ESI) calculated for $C_{19}H_{23}FNO_2$ ($[M+H]^+$), 316.1707; found, 316.1702; $[\alpha]_D^{20}$ –22.3 (*c* 1.0, MeOH).

2-[[[[2-(5-Fluoro-2-methoxyphenyl)cyclopropyl]methyl]amino]methyl]phenol Hydrochloride (22). Prepared from 2-hydroxybenzylamine employing General Method B. ^{1}H NMR ($CDCl_3$) δ 9.52 (s, 1H), 9.07 (s, 1H), 8.75 (s, 1H), 7.27 – 7.10 (m, 3H), 6.88 – 6.75 (m, 2H), 6.69 (dd, J = 8.8, 4.3 Hz, 1H), 6.52 (dd, J = 9.1, 2.4 Hz, 1H), 4.32 – 4.01 (m, 2H), 3.76 (s, 3H), 3.14 – 2.79 (m, 2H), 2.09 – 1.90 (m, 1H), 1.42 – 1.28 (m, 1H), 1.10 – 0.76 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 157.1 (d, J = 238.2 Hz), 155.8 (s), 154.4 (s), 131.5 (s), 131.4 (s), 130.3 (d, J = 7.3 Hz), 120.5 (s), 117.1 (s, 2C), 113.4 (d, J = 23.7 Hz), 113.1 (d, J = 22.3 Hz), 111.1 (d, J = 8.2 Hz), 56.2 (s), 50.7 (s), 47.5 (s), 17.8 (s), 17.4 (s), 12.7 (s); HRMS (ESI) calculated for $C_{18}H_{21}FNO_2$ ($[M+H]^+$), 302.1551; found, 302.1554.

***N*-[2-(2-Fluoroethoxy)benzyl]-1-[2-(5-fluoro-2-methoxyphenyl)cyclopropyl] methanamine Hydrochloride (23).** To a solution of the free base **22** (30 mg, 0.1 mmol), 2-fluoroethanol (10 mg, 0.15 mmol), and triphenylphosphine (52 mg, 0.2

mmol) in anhydrous THF (5 mL) at 0 °C was slowly added diethyl azodicarboxylate (35 mg, 0.2 mmol), and the solution was then heated in a microwave reactor at 60 ºC for 45 min. The mixture was concentrated, and the residue was purified by flash chromatography to give the free base, which was further treated with 2M HCl in ether to afford the title compound as a white solid (25 mg, 63% yield). ^{1}H NMR ($CDCl_3$) δ 9.86 (s, 1H), 9.23 (s, 1H), 7.58 (dd, J = 7.5, 1.4 Hz, 1H), 7.40 – 7.31 (m, 1H), 7.02 (t, J = 7.3 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 6.87 – 6.81 (m, 1H), 6.74 (dd, J = 8.9, 4.5 Hz, 1H), 6.61 (dd, J = 9.2, 3.0 Hz, 1H), 4.93 – 4.82 (m, 1H), 4.82 – 4.68 (m, 1H), 4.42 – 4.26 (m, 2H), 4.26 – 4.11 (m, 2H), 3.77 (s, 3H), 3.04 – 2.83 (m, 2H), 2.07 – 1.95 (m, 1H), 1.49 – 1.36 (m, 1H), 1.04 (t, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 157.3 (d, J = 238.2 Hz), 156.8 (s), 154.4 (s), 132.6 (s), 131.3 (s), 130.8 (d, J = 7.4 Hz), 121.9 (s), 119.6 (s), 113.4 (d, J = 23.9 Hz), 113.0 (d, J = 22.7 Hz), 111.6 (s), 111.1 (d, J = 8.4 Hz), 82.0 (d, J = 170.5 Hz), 67.6 (d, J = 19.6 Hz), 56.1 (s), 50.8 (s), 45.7 (s), 17.7 (s), 17.3 (s), 13.2 (s); HRMS (ESI) calculated for $C_{20}H_{24}F_2NO_2$ ($[M+H]^+$), 348.1770; found, 348.1754.

2-[[[[2-(5-Fluoro-2-methoxyphenyl)cyclopropyl]methyl]amino]methyl]benzonitrile Hydrochloride (24). Prepared from the tosylate **24b** employing General Method C (K_2CO_3 (3.0 equiv.)/CH_3CN, 60 ^{o}C). ^{1}H NMR ($CDCl_3$) δ 14.79 (s, 1H), 9.36 (t, J = 7.8 Hz, 1H), 7.84 (m, 1H), 7.71 (t, J = 7.6 Hz, 1H), 7.63 (d, J = 7.7 Hz, 1H), 7.28 (m, 1H), 6.80 (td, J = 8.8, 2.9 Hz, 1H), 6.70 (dd, J = 8.9, 4.6 Hz, 1H), 6.58 (dd, J = 9.4, 2.9 Hz, 1H), 5.85 (s, 2H), 3.96 – 3.84 (m, 1H), 3.75 – 3.63 (m, 1H), 3.67 (s, 3H), 2.29 – 2.18 (m, 1H), 1.64 – 1.50 (m, 1H), 1.23 – 1.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 158.4

(s, J = 237.6 Hz), 154.5 (s), 136.5 (s), 131.4 (s, J = 7.7 Hz), 130.8 (s), 128.8 (s), 126.5 (s), 124.0 (s), 121.6 (s), 113.1 (d, J = 23.7 Hz), 112.9 (s), 112.8 (s, J = 22.9 Hz), 111.2 (d, J = 8.4 Hz), 56.2 (s), 48.3 (s), 48.2 (s), 20.4 (s), 17.4 (s), 13.3 (s); HRMS (ESI) calculated for $C_{19}H_{20}FN_2O$ ($[M+H]^+$), 311.1554; found, 312.1563.

2-[[[[2-(5-Fluoro-2-methoxyphenyl)cyclopropyl]methyl]amino]methyl]benzamide Hydrochloride (25). To a solution of the free base **24** (35 mg, 0.1 mmol) and 5N sodium hydroxide (30 μL) in methanol (5 mL) was added 30% hydrogen peroxide (0.2 mL). The mixture was heated to reflux for 1 h. The reaction mixture was cooled, treated with water, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography to give the free base, which was further treated with 2M HCl in ether to afford the title compound as a white solid (30 mg, 73% yield). ^{1}H NMR ($CDCl_3$) δ 14.54 (s, 1H), 9.32 (s, 1H), 7.90 – 7.84 (m, 1H), 7.77 – 7.68 (m, 1H), 7.68 – 7.58 (m, 1H), 7.35 – 7.30 (m, 1H), 6.81 (td, J = 8.7, 2.0 Hz, 1H), 6.71 (dd, J = 8.7, 4.4 Hz, 1H), 6.59 (dd, J = 9.1, 2.1 Hz, 1H), 5.85 (s, 2H), 5.20 (s, 2H), 4.02 – 3.83 (m, 1H), 3.80 – 3.60 (m, 1H), 3.68 (s, 3H), 2.31 – 2.18 (m, 1H), 1.67 – 1.51 (m, 1H), 1.24 – 1.03 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 172.5 (s), 157.2 (d, J = 238.0 Hz), 154.5 (s), 143.5 (s), 139.4 (s), 136.5 (s), 131.5 (d, J = 7.3 Hz), 130.9 (s), 128.8 (s), 121.7 (s), 113.1 (d, J = 23.8 Hz), 112.7 (d, J = 22.7 Hz), 111.2 (d, J = 8.4 Hz), 56.3 (s), 48.5 (s), 48.3 (s), 20.4 (s), 17.4 (s), 13.4 (s); HRMS (ESI) calculated for $C_{19}H_{22}FN_2O_2$ ($[M+H]^+$), 329.1660; found, 329.1660.

(+)-*N*-(2-Fluorobenzyl)-1-[(1*S*,2*S*)-(+)-2-(5-fluoro-2-methoxyphenyl)cyclopropyl] methanamine Hydrochloride ((+)-26). Prepared from 2-fluorobenzylamine employing General Method B including chiral separation. ^{1}H NMR ($CDCl_3$) δ 10.18 (s, 1H), 9.98 (s, 1H), 7.89 (t, J = 7.2 Hz, 1H), 7.37 (m, 1H), 7.21 (t, J = 7.3 Hz, 1H), 7.11 (t, J = 9.0 Hz, 1H), 6.81 (td, J = 8.5, 3.0 Hz, 1H), 6.72 (dd, J = 8.9, 4.5 Hz, 1H), 6.63 (dd, J = 9.3, 3.0 Hz, 1H), 4.25 (s, 2H), 3.79 (s, 3H), 3.12 – 2.80 (m, 2H), 2.16 – 2.04 (m, 1H), 1.56 – 1.40 (m, 1H), 1.13 – 0.98 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 161.3 (d, J = 248.6 Hz), 157.2 (d, J = 238.1 Hz), 154.4 (s), 132.7 (s), 131.7 (d, J = 8.2 Hz), 130.7 (d, J = 7.3 Hz), 125.2 (d, J = 3.0 Hz), 118.0 (d, J = 14.0 Hz), 115.9 (d, J = 21.5 Hz), 113.3 (d, J = 28.5 Hz), 113.0 (d, J = 27.1 Hz), 111.1 (d, J = 8.3 Hz), 56.2 (s), 50.2 (s), 42.6 (s), 17.9 (s), 16.9 (s), 13.5 (s); HRMS (ESI) calculated for $C_{18}H_{20}F_2NO$ ($[M+H]^+$), 304.1507; found, 304.1508; $[\alpha]_D^{20}$ +12.6 (*c* 0.6, MeOH).

(–)-*N*-(2-Fluorobenzyl)-1-[(1*R*,2*R*)-2-(5-fluoro-2-methoxyphenyl)cyclopropyl] methanamine Hydrochloride ((–)-26). Prepared from 2-fluorobenzylamine employing General Method B including chiral separation. ^{1}H NMR ($CDCl_3$) δ 10.18 (s, 1H), 9.98 (s, 1H), 7.89 (t, J = 7.2 Hz, 1H), 7.37 (m, 1H), 7.21 (t, J = 7.3 Hz, 1H), 7.11 (t, J = 9.0 Hz, 1H), 6.81 (td, J = 8.5, 3.0 Hz, 1H), 6.72 (dd, J = 8.9, 4.5 Hz, 1H), 6.63 (dd, J = 9.3, 3.0 Hz, 1H), 4.25 (s, 2H), 3.79 (s, 3H), 3.11 – 2.81 (m, 2H), 2.16 – 2.04 (m, 1H), 1.56 – 1.41 (m, 1H), 1.13 – 0.98 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 161.3 (d, J = 248.6 Hz), 157.2 (d, J = 238.1 Hz), 154.4 (s), 132.7 (s), 131.7 (d, J = 8.2 Hz), 130.7 (d, J = 7.3 Hz), 125.2 (d, J = 3.0 Hz), 118.0 (d, J = 14.0 Hz), 115.9 (d, J = 21.5 Hz), 113.3 (d, J = 28.5 Hz), 113.0 (d, J = 27.1 Hz), 111.1 (d, J = 8.3 Hz), 56.2 (s),

50.2 (s), 42.6 (s), 17.9 (s), 16.9 (s), 13.5 (s); HRMS (ESI) calculated for $C_{18}H_{20}F_2NO$ ($[M+H]^+$), 304.1507; found, 304.1508; $[\alpha]_D^{20}$ –11.7 (*c* 0.6, MeOH).

(+)-*N*-(2-Chlorobenzyl)-1-[(1*S*,2*S*)-2-(5-fluoro-2-methoxyphenyl)cyclopropyl]methanamine Hydrochloride ((+)-27). Prepared from 2-chlorobenzylamine employing General Method B including chiral separation. ^{1}H NMR ($CDCl_3$) δ 10.25 (s, 1H), 9.84 (s, 1H), 7.97 (dd, *J* = 7.0, 1.8 Hz, 1H), 7.42 (dd, *J* = 7.0, 2.2 Hz, 1H), 7.37 – 7.29 (m, 2H), 6.85 – 6.77 (m, 1H), 6.71 (dd, *J* = 8.9, 4.5 Hz, 1H), 6.60 (dd, *J* = 9.2, 3.0 Hz, 1H), 4.35 (s, 2H), 3.76 (s, 3H), 3.10 – 2.90 (m, 2H), 2.14 – 2.02 (m, 1H), 1.55 – 1.39 (m, 1H), 1.08 (t, *J* = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 157.1 (d, *J* = 238.2 Hz), 154.2 (s), 134.7 (s), 132.4 (s), 130.9 (s), 130.5 (d, *J* = 7.2 Hz), 129.9 (s), 128.8 (s), 127.8 (s), 113.2 (d, *J* = 24.4 Hz), 112.9 (d, *J* = 23.4 Hz), 111.0 (d, *J* = 8.3 Hz), 56.0 (s), 50.4 (s), 46.5 (s), 17.8 (s), 17.0 (s), 13.3 (s); HRMS (ESI) calculated for $C_{18}H_{20}ClFNO$ ($[M+H]^+$), 320.1212; found, 320.1166; $[\alpha]_D^{20}$ +4.2 (*c* 1.4, MeOH).

(–)-*N*-(2-Chlorobenzyl)-1-[(1*R*,2*R*)-2-(5-fluoro-2-methoxyphenyl)cyclopropyl]methanamine Hydrochloride ((–)-27). Prepared from 2-chlorobenzylamine employing General Method B including chiral separation. ^{1}H NMR ($CDCl_3$) δ 10.25 (s, 1H), 9.84 (s, 1H), 7.97 (dd, *J* = 7.0, 1.8 Hz, 1H), 7.42 (dd, *J* = 7.0, 2.2 Hz, 1H), 7.37 – 7.29 (m, 2H), 6.85 – 6.77 (m, 1H), 6.71 (dd, *J* = 8.9, 4.5 Hz, 1H), 6.61 (dd, *J* = 9.2, 3.0 Hz, 1H), 4.35 (s, 2H), 3.76 (s, 3H), 3.11 – 2.90 (m, 2H), 2.14 – 2.02 (m, 1H), 1.55 – 1.39 (m, 1H), 1.07 (t, *J* = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 157.1 (d, *J* = 238.2 Hz), 154.2 (s), 134.7 (s), 132.4 (s), 130.9 (s), 130.5 (d, *J* = 7.2 Hz), 129.9 (s), 128.8 (s), 127.8 (s), 113.2 (d, *J* = 24.4 Hz), 112.9 (d, *J* = 23.4 Hz), 111.0 (d, *J* = 8.3 Hz), 56.0 (s), 50.4 (s),

46.5 (s), 17.8 (s), 17.0 (s), 13.3 (s); HRMS (ESI) calculated for $C_{18}H_{20}ClFNO$ ($[M+H]^+$), 320.1212; found, 320.1206; $[\alpha]_D^{20}$ –3.6 (*c* 1.4, MeOH).

1-[2-(5-Fluoro-2-methoxyphenyl)cyclopropyl]-*N*-(2-methoxybenzyl)-*N*-methylmethanamine Hydrochloride (28). Prepared from 2-methoxy-*N*-methylbenzylamine employing General Method B. ^{1}H NMR ($CDCl_3$, racemic mixture of two pairs of enantiomeric salts) δ 11.62 (s, 1H), 11.43 (s, 1H), 7.48 – 7.34 (m, 4H), 7.02 (t, J = 7.5 Hz, 2H), 6.96 (d, J = 8.3 Hz, 2H), 6.91 – 6.82 (m, 2H), 6.77 (dd, J = 8.9, 4.5 Hz, 2H), 6.65 – 6.54 (m, 2H), 4.53, 4.44 (ABq, J = 12.9 Hz, 2H), 4.30, 4.22 (ABq, J = 12.9 Hz, 2H), 3.84 (s, 6H), 3.81 (s, 6H), 3.39 (dd, J = 13.3, 6.5 Hz, 1H), 3.29 – 3.15 (m, 2H), 3.00 (dd, J = 13.3, 7.7 Hz, 1H), 2.82 (s, 6H), 2.29 – 2.15 (m, 2H), 1.43 – 1.32 (m, 2H), 1.25 – 1.13 (m, 2H), 1.07 – 0.97 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 158.29 (s), 158.24 (s), 157.28 (d, J = 238.3 Hz, 2C), 154.35 (s), 158.31 (s), 133.04 (s), 132.92 (s), 132.07 (s, 2C), 130.28 (d, J = 7.3 Hz, 2C), 121.36 (s, 2C), 117.26 (s, 2C), 113.22 (d, J = 22.7 Hz, 2C), 112.83 (d, J = 24.0 Hz), 112.80 (d, J = 23.9 Hz), 111.46 (s, 2C), 111.19 (d, J = 8.5 Hz, 2C), 59.43 (s), 59.23 (s), 56.00 (s, 2C), 55.52 (s, 2C), 53.81 (s), 53.43 (s), 39.34 (s), 38.82 (s), 17.98 (s), 17.74 (s), 15.95 (s), 15.90 (s), 12.90 (s), 12.77 (s); HRMS (ESI) calculated for $C_{20}H_{25}FNO_2$ ($[M+H]^+$), 330.1864; found, 330.1817.

***N*-[[2-(5-Fluoro-2-methoxyphenyl)cyclopropyl]methyl]-1-(2-methoxyphenyl)ethan-1-amine Hydrochloride (29).** Prepared from 1-(2-methoxyphenyl)ethylamine employing General Method B. ^{1}H NMR (CD_3OD, racemic mixture of two pairs of enantiomers) δ 7.45 (t, J = 7.9 Hz, 2H), 7.40 – 7.32 (m, 2H), 7.14 (dd, J = 8.1, 3.6 Hz,

2H), 7.08 (t, *J* = 7.6 Hz, 2H), 6.99 – 6.84 (m, 4H), 6.75 – 6.64 (m, 2H), 4.75 (m, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.20 (dd, *J* = 13.0, 5.7 Hz, 1H), 3.01 (dd, *J* = 13.2, 7.4 Hz, 1H), 2.92 (dd, *J* = 13.2, 7.4 Hz, 1H), 2.82 (dd, *J* = 13.0, 7.9 Hz, 1H), 2.15 – 2.06 (m, 2H), 1.71 (d, *J* = 7.0 Hz, 3H), 1.68 (d, *J* = 7.0 Hz, 3H), 1.34 – 0.91 (m, 6H); ^{13}C NMR (CD_3OD) δ 158.61 (d, *J* = 237.0 Hz), 158.57 (d, *J* = 235.3 Hz), 158.43 (s), 158.32 (s), 155.76 (s, 2C), 132.22 (d, *J* = 9.7 Hz), 132.15 (s, 2C), 132.06 (d, *J* = 7.8 Hz), 129.76 (s, 2C), 124.97 (s), 124.90 (s), 122.56 (s), 122.52 (s), 114.05 (d, *J* = 19.8 Hz), 113.97 (d, *J* = 24.1 Hz), 113.91 (d, *J* = 22.7 Hz), 113.83 (d, *J* = 23.8 Hz), 112.71 (s, 2C), 112.44 (d, *J* = 8.3 Hz), 112.40 (d, *J* = 8.3 Hz), 56.51 (s), 56.46 (s), 56.10 (s, 2C), 55.35 (s), 55.26 (s), 51.01 (s), 50.92 (s), 18.74 (s), 18.32 (s), 18.28 (s, 2C), 18.14 (s), 18.01 (s), 13.75 (s), 13.05 (s); HRMS (ESI) calculated for $C_{20}H_{25}FNO_2$ ($[M+H]^+$), 330.1864; found, 330.1802.

***N*-[[2-(5-Fluoro-2-methoxyphenyl)cyclopropyl]methyl]-1-(2-methoxyphenyl)cyclopropan-1-amine Hydrochloride (30).** Prepared from **30b** employing General Method B. ^{1}H NMR (CD_3OD) δ 7.49 – 7.45 (m, 1H), 7.42 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.04 (td, *J* = 7.6, 0.9 Hz, 1H), 6.92 – 6.89 (m, 2H), 6.64 (dd, *J* = 8.0, 2.8 Hz, 1H), 3.97 (s, 3H), 3.86 (s, 3H), 3.02 (dd, *J* = 13.2, 7.3 Hz, 1H), 2.89 (dd, *J* = 13.1, 7.6 Hz, 1H), 2.02 – 1.97 (m, 1H), 1.46 – 1.39 (m, 1H), 1.33 – 0.89 (m, 4H), 1.09 – 1.02 (m, 1H), 0.95 – 0.88 (m, 1H); ^{13}C NMR (CD_3OD) δ 160.2, 159.8 (d, *J* = 235.5 Hz), 155.7 (d, *J* = 2.0 Hz), 132.8, 132.2 (d, *J* = 7.4 Hz), 132.0, 122.7, 122.2, 114.1 (d, *J* = 22.8 Hz), 113.9 (d, *J* = 24.2 Hz), 112.5 (d, *J* = 8.4 Hz), 112.4, 56.5, 56.3,

51.6, 41.6, 18.5, 18.4, 14.2, 12.4, 11.8; HRMS (ESI) calculated for $C_{21}H_{25}FNO_2$: $[M+H]^+$, *m*/*z* 342.1864; found: 342.1833.

***N*-[[2-(5-Fluoro-2-methoxyphenyl)cyclopropyl]methyl]-2-(2-methoxyphenyl)etha n-1-amine Hydrochloride (31).** Prepared from 2-(2-methoxyphenyl)ethylamine employing General Method B. ^{1}H NMR ($CDCl_3$) δ 9.79 (s, 1H), 9.67 (s, 1H), 7.27 – 7.16 (m, 2H), 6.91 – 6.85 (m, 1H), 6.85 – 6.77 (m, 2H), 6.70 (dd, *J* = 9.0, 4.5 Hz, 1H), 6.60 (dd, *J* = 9.3, 3.0 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.42 – 3.21 (m, 4H), 3.21 – 3.02 (m, 2H), 2.19 – 2.09 (m, 1H), 1.53 – 1.40 (m, 1H), 1.18 – 1.07 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 157.5 (s), 157.2 (d, *J* = 238.2 Hz), 154.4 (d, *J* = 2.0 Hz), 130.8 (s), 130.7 (d, *J* = 7.2 Hz), 128.7 (s), 125.0 (s), 120.9 (s), 113.0 (d, *J* = 24.0 Hz), 112.9 (d, *J* = 24.5 Hz), 111.0 (d, *J* = 8.4 Hz), 110.4 (s), 56.0 (s), 55.3 (s), 51.0 (s), 46.1 (s), 27.8 (s), 17.8 (s), 17.2 (s), 13.0 (s); HRMS (ESI) calculated for $C_{20}H_{25}FNO_2$ ($[M+H]^+$), 330.1864; found, 330.1822.

(+)-1-[(1*S*,2*S*)-2-(5-Fluoro-2-methoxyphenyl)cyclopropyl]-*N*-(thiophen-2-ylmethy l)methanamine Hydrochloride ((+)-32). Prepared from 2-thiophenylmethylamine employing General Method B including chiral separation. ^{1}H NMR ($CDCl_3$) δ 10.10 (s, 2H), 7.48 (d, *J* = 2.9 Hz, 1H), 7.34 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.04 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.86 – 6.79 (m, 1H), 6.74 (dd, *J* = 9.0, 4.6 Hz, 1H), 6.63 (dd, *J* = 9.3, 3.0 Hz, 1H), 4.40 (s, 2H), 3.81 (s, 3H), 3.02 (dd, *J* = 13.1, 7.2 Hz, 1H), 2.93 (dd, *J* = 13.1, 7.5 Hz, 1H), 2.19 – 2.09 (m, 1H), 1.55 – 1.42 (m, 1H), 1.13 – 1.02 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 157.2 (d, *J* = 238.4 Hz), 154.4 (d, *J* = 2.0 Hz), 131.4 (s), 131.3 (s), 130.7 (d, *J* = 7.4 Hz), 128.0 (s), 127.9 (s), 113.3 (d, *J* = 22.3 Hz), 113.0 (d, *J* = 21.2 Hz),

111.2 (d, *J* = 8.3 Hz), 56.2 (s), 49.4 (s), 43.5 (s), 18.0 (s), 17.0 (s), 13.2 (s); HRMS (ESI) calculated for $C_{16}H_{19}FNOS$ ($[M+H]^+$), 292.1166; found, 292.1160; $[\alpha]_D^{20}$ +30.6 (*c* 1.0, MeOH).

(–)-1-[(1*R*,2*R*)-2-(5-Fluoro-2-methoxyphenyl)cyclopropyl]-*N*-(thiophen-2-ylmeth yl)methanamine Hydrochloride ((–)-32). Prepared from 2-thiophenylmethylamine employing General Method B including chiral separation. ^{1}H NMR ($CDCl_3$) δ 10.10 (s, 2H), 7.48 (d, *J* = 2.9 Hz, 1H), 7.34 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.04 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.86 – 6.79 (m, 1H), 6.74 (dd, *J* = 9.0, 4.6 Hz, 1H), 6.63 (dd, *J* = 9.3, 3.0 Hz, 1H), 4.40 (s, 2H), 3.81 (s, 3H), 3.02 (dd, *J* = 13.1, 7.2 Hz, 1H), 2.93 (dd, *J* = 13.1, 7.5 Hz, 1H), 2.19 – 2.09 (m, 1H), 1.55 – 1.42 (m, 1H), 1.13 – 1.03 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 157.2 (d, *J* = 238.4 Hz), 154.4 (d, *J* = 2.0 Hz), 131.4 (s), 131.3 (s), 130.7 (d, *J* = 7.4 Hz), 128.0 (s), 127.9 (s), 113.3 (d, *J* = 22.3 Hz), 113.0 (d, *J* = 21.2 Hz), 111.2 (d, *J* = 8.3 Hz), 56.2 (s), 49.5 (s), 43.5 (s), 18.0 (s), 17.0 (s), 13.2 (s); HRMS (ESI) calculated for $C_{16}H_{19}FNOS$ ($[M+H]^+$), 292.1166; found, 292.1160; $[\alpha]_D^{20}$ –28.5 (*c* 1.0, MeOH).

1-[2-(5-Fluoro-2-methoxyphenyl)cyclopropyl]-*N*-[(3-methoxythiophen-2-yl)meth yl]methanamine Hydrochloride (33). Prepared from 3-methoxythiophene-2-carboxaldehyde employing General Method C ($NaBH(OAc)_3$ (2.0 equiv.)/DCE). ^{1}H NMR (CD_3OD) δ 7.53 (d, *J* = 5.6 Hz, 1H), 7.08 (d, *J* = 5.6 Hz, 1H), 6.95 – 6.90 (m, 2H), 6.75 (dd, *J* = 9.6, 2.4 Hz, 1H), 4.40, 4.36 (ABq, *J* = 14.2 Hz, 2H), 3.92 (s, 3H), 3.84 (s, 3H), 3.19 (dd, *J* = 13.1, 6.9 Hz, 1H), 3.05 (dd, *J* = 13.1, 7.9 Hz, 1H), 2.23 – 2.18 (m, 1H), 1.34 – 1.28 (m, 1H), 1.19 – 1.14 (m, 1H), 1.07 –

1.02 (m, 1H); ^{13}C NMR (CD_3OD) δ 159.5 (s), 158.6 (d, J = 236.8 Hz), 155.9 (d, J = 2.0 Hz), 132.2 (d, J = 7.5 Hz), 127.8 (s), 117.1 (s), 114.1 (d, J = 24.2 Hz), 114.0 (d, J = 22.8 Hz), 112.4 (d, J = 8.5 Hz), 108.3 (s), 59.4 (s), 56.5 (s), 51.8 (s), 42.2 (s), 18.4 (s), 18.3 (s), 13.2 (s); HRMS (ESI) calculated for $C_{17}H_{21}FNO_2S$ ($[M+H]^+$), m/z 322.1272; found: 322.1225.

1-[2-(5-Fluoro-2-methoxyphenyl)cyclopropyl]-*N*-[(4-methoxythiophen-3-yl)methyl]methanamine Hydrochloride (34). Prepared from **34e** employing General Method B. ^{1}H NMR (CD_3OD) δ 7.60 (d, J = 3.2 Hz, 1H), 6.93 – 6.90 (m, 2H), 6.75 (dd, J = 9.6, 2.4 Hz, 1H), 6.61 (d, J = 3.2 Hz, 1H), 4.24, 4.19 (ABq, J = 13.6 Hz, 2H), 3.89 (s, 3H), 3.83 (s, 3H), 3.20 (dd, J = 13.1, 7.0 Hz, 1H), 3.08 (dd, J = 13.0, 7.9 Hz, 1H), 2.23 – 2.16 (m, 1H), 1.38 – 1.30 (m, 1H), 1.19 – 1.14 (m, 1H), 1.07 – 1.03 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 157.2 (d, J = 237.6 Hz), 156.2 (s), 154.4 (s), 130.7 (d, J = 7.4 Hz), 127.6 (s), 121.9 (s), 113.5 (d, J = 23.9 Hz), 113.1 (d, J = 22.7 Hz), 111.1 (d, J = 8.4 Hz), 97.7 (s), 57.8 (s), 56.2 (s), 50.0 (s), 41.7 (s), 17.9 (s), 17.1 (s), 13.2 (s); HRMS (ESI) calculated for $C_{17}H_{21}FNO_2S$ ($[M+H]^+$), m/z 322.1272; found: 322.1241.

1-[2-(5-Fluoro-2-methoxyphenyl)cyclopropyl]-*N*-[(2-methoxythiophen-3-yl)methyl]methanamine Hydrochloride (35). Prepared from **35e** employing General Method B. ^{1}H NMR (CD_3OD) δ 6.95 – 6.90 (m, 3H), 6.83 (d, J = 6.0 Hz, 1H), 6.74 (dd, J = 9.6, 2.4 Hz, 1H), 4.19, 4.14 (ABq, J = 13.5 Hz, 2H), 4.00 (s, 3H), 3.83 (s, 3H), 3.16 (dd, J = 13.0, 7.0 Hz, 1H), 3.05 (dd, J = 13.1, 7.8 Hz, 1H), 2.23 – 2.18 (m, 1H), 1.31 – 1.28 (m, 1H), 1.19 – 1.14 (m, 1H), 1.07 – 1.03 (m, 1H); ^{13}C NMR (CD_3OD) δ 166.7 (s), 158.6 (d, J = 235.3 Hz), 155.8 (d, J = 2.0 Hz), 132.2 (d, J = 7.5

Hz), 127.3 (s), 114.0 (d, J = 23.0 Hz), 113.9 (d, J = 24.1 Hz), 113.1 (s), 112.4 (d, J = 8.5 Hz), 111.2 (s), 62.4 (s), 56.4 (s), 52.1 (s), 42.7 (s), 18.3 (s), 18.2 (s), 13.3 (s); HRMS (ESI) calculated for $C_{17}H_{21}FNO_2S$ ($[M+H]^+$), m/z 322.1272; found: 322.1193.

1-[2-(5-Fluoro-2-methoxyphenyl)cyclopropyl]-*N*-[(2-methoxypyridin-3-yl]methyl)methanamine (36). The free base **36** was obtained from 2-methoxynicotinaldehyde according to the similar procedure described in General Method C ($NaBH_4$ (1.5 equiv.)/MeOH) as a colorless oil. ^{1}H NMR (CD_3OD) δ 8.10 (dd, J = 5.0, 1.8 Hz, 1H), 7.59 (dd, J = 7.2, 1.8 Hz, 1H), 6.88 (dd, J = 7.1, 5.1 Hz, 1H), 6.86 – 6.78 (m, 1H), 6.75 (dd, J = 8.9, 4.6 Hz, 1H), 6.58 (dd, J = 9.5, 3.0 Hz, 1H), 3.98 (s, 3H), 3.89, 3.84 (ABq, J = 14.0 Hz, 2H), 3.81 (s, 3H), 3.08 (br s, 1H), 2.86 (dd, J = 12.1, 6.0 Hz, 1H), 2.55 (dd, J = 12.1, 7.8 Hz, 1H), 1.97 – 1.88 (m, 1H), 1.31 – 1.20 (m, 1H), 0.99 – 0.91 (m, 1H), 0.88 – 0.80 (m, 1H); ^{13}C NMR (CD_3OD) δ 162.1 (s), 157.4 (d, J = 237.6 Hz), 154.4 (s), 145.7 (s), 138.0 (s), 132.7 (d, J = 6.6 Hz), 127.2 (s), 116.9 (s), 112.7 (d, J = 23.7 Hz), 112.3 (d, J = 22.7 Hz), 111.0 (d, J = 8.6 Hz), 56.1 (s), 53.6 (s), 53.5 (s), 48.3 (s), 22.0 (s), 16.8 (s), 12.8 (s); HRMS (ESI) calculated for $C_{18}H_{22}FN_2O_2$ ($[M+H]^+$), 317.1660; found, 317.1626.

1-(Benzo[b]thiophen-7-yl)-*N*-[(2-(5-fluoro-2-methoxyphenyl)cyclopropyl)methyl] methanamine Hydrochloride (37). Prepared from benzo[b]thiophene-7-carboxaldehyde employing General Method C ($NaBH(OAc)_3$ (2.0 equiv.)/DCE). ^{1}H NMR ($CDCl_3$) δ 10.34 (s, 1H), 10.05 (s, 1H), 7.94 (d, J = 7.3 Hz, 1H), 7.84 (d, J = 7.9 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.41 (d, J = 5.4 Hz, 1H), 6.83 – 6.76 (m, 1H), 6.67 (dd, J = 9.0, 4.5 Hz, 1H), 6.62 (dd, J = 9.2, 3.0 Hz, 1H), 4.46 (s,

2H), 3.64 (s, 3H), 3.12 – 2.94 (m, 2H), 2.08 – 1.97 (m, 1H), 1.53 – 1.42 (m, 1H), 1.15 – 1.01 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 157.2 (d, J = 238.4 Hz), 154.3 (s), 140.5 (s), 140.4 (s), 130.5 (d, J = 7.3 Hz), 126.3 (s), 126.2 (s), 125.6 (s), 125.1 (s), 125.0 (s), 124.9 (s), 113.5 (d, J = 23.9 Hz), 113.1 (d, J = 22.6 Hz), 111.1 (d, J = 8.3 Hz), 56.0 (s), 50.6 (s), 48.5 (s), 18.0 (s), 17.3 (s), 13.2 (s); HRMS (ESI) calculated for $C_{20}H_{21}FNOS$ ($[M+H]^+$), 342.1322; found, 342.1288.

1-[2-(5-Fluoro-2-methoxyphenyl)cyclopropyl)-*N*-[(1*H*-indol-7-yl)methyl]methanamine Hydrochloride (38). Prepared from indole-7-carboxaldehyde employing General Method C ($NaBH(OAc)_3$ (2.0 equiv.)/DCE). ^{1}H NMR ($CDCl_3$) δ 11.25 (s, 1H), 9.65 (s, 1H), 9.22 (s, 1H), 7.73 (dd, J = 7.4, 1.3 Hz, 1H), 7.40 (t, J = 6.9 Hz, 1H), 7.13 – 7.03 (m, 2H), 6.80 – 6.72 (m, 1H), 6.64 – 6.56 (m, 3H), 4.61 – 4.38 (m, 2H), 3.49 (s, 3H), 3.19 – 3.06 (m, 1H), 2.87 – 2.75 (m, 1H), 1.98 – 1.90 (m, 1H), 1.44 – 1.33 (m, 1H), 1.16 – 1.06 (m, 1H), 1.03 – 0.92 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 157.2 (d, J = 238.7 Hz), 154.2 (s), 134.5 (s), 123.0 (d, J = 7.3 Hz), 129.5 (s), 126.3 (s), 124.8 (s), 123.1 (s), 119.4 (s), 113.6 (d, J = 24.1 Hz), 113.3 (d, J = 23.0 Hz), 112.8 (s), 111.1 (d, J = 8.3 Hz), 102.7 (s), 55.8 (s), 50.8 (s), 48.9 (s), 18.1 (s), 17.8 (s), 12.7 (s); HRMS (ESI) calculated for $C_{20}H_{22}FN_2O$ ($[M+H]^+$), 325.1711; found, 325.1664.

1-[2-(5-Fluoro-2-methoxyphenyl)cyclopropyl]-*N*-(quinolin-8-ylmethyl)methanamine Hydrochloride (39). Prepared from 8-quinolinecarboxaldehyde employing General Method C ($NaBH(OAc)_3$ (2.0 equiv.)/DCE). ^{1}H NMR (CD_3OD) δ 9.01 (dd, J = 4.8, 1.5 Hz, 1H), 8.69 (d, J = 7.8 Hz, 1H), 8.27 (d, J = 7.0 Hz, 1H), 8.12 (d, J = 8.1 Hz, 1H), 7.85 – 7.73 (m, 2H), 6.84 – 6.75 (m, 1H), 6.72 (dd, J = 8.9, 4.5 Hz, 1H),

6.59 (dd, *J* = 9.2, 3.0 Hz, 1H), 4.96, 4.87 (ABq, *J* = 13.7 Hz, 2H), 3.71 (s, 3H), 3.38 (dd, *J* = 12.5, 7.1 Hz, 1H), 3.18 – 3.09 (m, 1H), 2.11 – 1.99 (m, 1H), 1.47 – 1.33 (m, 1H), 1.13 – 0.96 (m, 2H); ^{13}C NMR (CD_3OD) δ 158.3 (s), 157.3 (d, *J* = 238.5 Hz), 154.5 (s), 147.6 (s), 142.9 (s), 136.7 (s), 130.9 (s), 130.6 (d, *J* = 7.5 Hz), 129.3 (s), 128.9 (s), 125.5 (s), 122.3 (s), 113.6 (d, *J* = 24.0 Hz), 113.2 (d, *J* = 22.5 Hz), 111.2 (d, *J* = 8.4 Hz), 55.9 (s), 52.0 (s), 47.8 (s), 17.6 (s), 17.5 (s), 12.7 (s); HRMS (ESI) calculated for $C_{21}H_{22}FN_2O$ ($[M+H]^+$), 337.1711; found, 337.1689.

(+)-1-[(1*S*,2*S*)-2-[2-(Allyloxy)-5-fluorophenyl]cyclopropyl]-*N*-(2-methoxybenzyl) methanamine Hydrochloride ((+)-40). Prepared from (+)-**10** employing General Method C ($NaBH_4$ (1.5 equiv.)/MeOH). ^{1}H NMR (CD_3OD) δ 7.52 – 7.44 (m, 1H), 7.41 (d, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 8.3 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.98 – 6.83 (m, 2H), 6.74 (dd, *J* = 9.5, 2.8 Hz, 1H), 6.11 – 6.07 (m, 1H), 5.38 (dd, *J* = 17.3, 1.5 Hz, 1H), 5.24 (dd, *J* = 10.5, 1.2 Hz, 1H), 4.63 – 4.49 (m, 2H), 4.36, 4.26 (ABq, *J* = 12.9 Hz, 2H), 3.36 (s, 3H), 3.16 (d, *J* = 7.3 Hz, 2H), 2.39 – 2.21 (m, 1H), 1.50 – 1.34 (m, 1H), 1.25 – 0.99 (m, 2H); ^{13}C NMR (CD_3OD) δ 159.3 (s), 158.7 (d, *J* = 237.2 Hz), 154.7 (d, *J* = 2.1 Hz), 134.7 (s), 132.8 (s), 132.7 (s), 132.6 (d, *J* = 7.4 Hz), 122.0 (s), 120.5 (s), 118.0 (s), 114.1 (d, *J* = 8.4 Hz), 113.9 (d, *J* = 23.0 Hz), 113.7 (d, *J* = 24.2 Hz), 112.0 (s), 70.8 (s), 56.1 (s), 52.4 (s), 49.8 (s), 47.6 (s), 18.5 (s), 13.4 (s); HRMS (ESI) calculated for $C_{21}H_{25}FNO_2$ ($[M+H]^+$), 342.1864; found, 342.1829; $[\alpha]_D^{20}$ +10.0 (*c* 0.1, MeOH).

(+)-1-[(1*S*,2*S*)-2-[5-Fluoro-2-(2-fluoroethoxy)phenyl]cyclopropyl]-*N*-(2-methoxybenzyl)methanamine Hydrochloride ((+)-41). Prepared from (+)-**11** employing

General Method C ($NaBH_4$ (1.5 equiv.)/MeOH). ^{1}H NMR (CD_3OD) δ 7.46 (t, J = 7.9 Hz, 1H), 7.40 (d, J = 7.4 Hz, 1H), 7.11 (d, J = 8.3 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 6.96 (dd, J = 8.9, 4.7 Hz, 1H), 6.91 (td, J = 8.6, 2.9 Hz, 1H), 6.76 (dd, J = 9.5, 2.9 Hz, 1H), 4.85 – 4.61 (m, 2H), 4.36 – 4.21 (m, 4H), 3.89 (s, 3H), 3.20 (dd, J = 13.1, 7.2 Hz, 1H), 3.12 (dd, J = 13.1, 7.4 Hz, 1H), 2.34 – 2.22 (m, 1H), 1.45 – 1.30 (m, 1H), 1.28 – 1.17 (m, 1H), 1.14 – 1.03 (m, 1H); ^{13}C NMR (CD_3OD) δ 159.36 (s), 158.94 (d, J = 237.6 Hz), 154.76 (d, J = 2.1 Hz), 132.98 (d, J = 7.6 Hz), 132.71 (s), 132.70 (s), 122.03 (s), 120.44 (s), 114.26 (d, J = 8.5 Hz), 114.03 (d, J = 23.0 Hz), 113.98 (d, J = 24.1 Hz), 112.08 (s), 83.34 (d, J = 168.4 Hz), 69.78 (d, J = 19.3 Hz), 56.12 (s), 52.28 (s), 47.58 (s), 18.56 (s), 18.42 (d, J = 1.2 Hz), 13.35 (s); HRMS (ESI) calculated for $C_{20}H_{24}F_2NO_2$ ($[M+H]^+$), 348.1770; found, 348.1764; $[\alpha]_D^{20}$ +9.4 (*c* 0.5, MeOH).

Calcium Flux Assay. Calcium flux assays were performed on a FLIPR^{TETRA} fluorescence imaging plate reader (Molecular Dynamics) with Flp-In-293 cells stably expressing the human 5-HT_{2A}, 5-HT_{2B}, or 5-$HT_{2C\text{-}INI}$ receptors as previously described.[21] Cells were preincubated in 384-well poly-L-lysine plates at a density of 10,000 cells/well. Next day, cells were loaded with Fluo-4 Direct dye (Invitrogen, (20 µL/well) for 1 h at 37 °C in drug buffer (pH 7.4, 1× HBSS, 2.5 mM probenecid, and 20 mM HEPES). Dilutions of each tested drug were prepared at 3× final concentration in drug buffer (pH 7.4, 1× HBSS, 20 mM HEPES, 0.1% BSA, 0.01% ascorbic acid). The tested drugs in 10 µL assay buffer were added, and calcium flux was measured every second for 5 min. For assessment of functional selectivity, drug solutions for FLIPR assay were exactly the same as used for the Tango assay (below).

Fluorescence in each well was normalized to the average of the first 10 reads (i.e., baseline fluorescence), then the maximum-fold increase was determined and fold over baseline was plotted as a function of drug concentration. Data were normalized to % 5-HT stimulation and analyzed using log(agonist) vs. response in Graphpad Prism 5.0.

Tango Arrestin Recruitment Assay. The HEK cell line expressing TEV-fused β-Arrestin-2 (HTLA cells, kindly provided by Dr. Richard Axel) and a tetracycline transactivator (tTA)-driven luciferase were utilized for Tango assay testing β-arrestin-2 recruitment.[24] HTLA cells were transfected with the 5-HT_{2C} INI receptor fused to tTA containing a TEV cleavage site. Cells were incubated as for the FLIPR assay in 40 μL except into white 384-well plates, and stimulated with the same drugs used for FLIPR (3×, 20 μL per well in HBSS, 20 mM HEPES, 0.1% BSA, 0.01% ascorbic acid, pH 7.4). After incubation for 20 hours at 37° C and 5% CO_2, medium containing drugs was decanted, and 20 μL of Bright-Glo reagent (Promega) was added per well. The plate was incubated for 20 min at room temperature for complete cell lysis before being counted using a Wallac MicroBeta Trilux luminescence counter (Perkin Elmer). Results (relative luminescence units) were plotted as a function of drug concentration, normalized to % 5-HT, and subjected to non-linear least-squares regression analysis using the sigmoidal dose-response function in GraphPad Prism 5.0.

Animal Behavioral Studies. *Materials and Methods.* Male C57BL/6J mice (approximately 9-10 week of age at the start of testing) were obtained from Jackson Laboratories (Bar Harbor, ME). Mice were group-housed in Tecniplast ventilated

cages and were maintained on a 12/12 hour light/dark cycle (lights on 7 am). The room temperature was maintained at 20-23 ℃ with relative humidity at approximately 50%. Food and water were available *ad libitum* for the duration of the study, except during testing, and all testing was conducted during the light phase of the light/dark cycle. The behavioral tests were conducted according to established protocols approved by the Harvard Center for Comparative Medicine (HCCM) IACUC committee in AALAC-accredited facilities, and in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health 2011).

Drugs. *d*-Amphetamine (Tocris Bioscience, Bristol, UK), PCP (Sigma-Aldrich, St. Louis, MO), lorcaserin (HCl salt, Carbosynth, San Diego CA), and compound (+)-**19** were dissolved in physiological saline and administered by intraperitoneal injection (IP) at a concentration of 10 mL/kg.

Procedures. Locomotor activity was measured in Plexiglas square chambers (27.3 × 27.3 × 20.3 cm; Med Associates Inc., St Albans, VT) surrounded by infrared photobeam sources and detectors. Mice were tested under ambient light, and data were collected by Med Associates software (Activity Monitor, version 5.9). Mice were injected with saline vehicle, lorcaserin (3 mg/kg), or (+)-**19** (10 or 20 mg/kg), and locomotor activity was monitored for 15 min (baseline total distance). Mice were then administered saline or *d*-amphetamine (AMPH) (3 mg/kg), and activity was measured for an additional 90 min. In a second experiment mice were administered phencyclidine (PCP) (5 mg/kg), and activity was measured for an additional 60 min.

Statistics. Locomotor activity was measured as total distance traveled (cm), assessed via infrared beam breaks. Locomotion prior to AMPH or PCP administration (baseline, 0-15 min) was analyzed by one-way analysis of variance (ANOVA) with drug treatment (doses of test compounds) as the independent variable. The effect of test compounds on AMPH- and PCP-induced hyperactivity was analyzed by one-way ANOVA with drug treatment after AMPH (Post Amphetamine, 15-105 min) or PCP (Post PCP, 15-75 min) as the independent variable. All significant effects were followed up with the Student Newman-Keuls post hoc test. An effect was considered significant if $p<0.05$ (Statview for Windows, Version 5.0).

Supporting information

Synthetic procedures, chiral separation methods, and characterization data of all intermediates; Molecular formula strings and related data.

Author information

Corresponding author

*A.P.K.: e-mail, kozikowa@uic.edu; telephone, +1 312 996-7577; fax, 312-996-7107.

Present Addresses

[#]J.C.: iHuman Institute, Shanghai Tech University, 99 Haike Road, Pudong New District, Shanghai 201210, China.

Notes

The authors declare no competing financial interest.

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Abbreviations

5-HT, serotonin; GPCR, G protein-coupled receptor; CNS, central nervous system; FDA, U.S. Food and Drug Administration; ADMET, absorption, distribution, metabolism, excretion, and toxicity; HTS, high throughput screening; 2-PCMPA, 2-phenylcyclopropylmethylamine; SAR, structure-activity relationship; MW, molecular weight; HPLC, high-performance liquid chromatography; BBB,

blood-brain barrier; FLIPR, fluorescence imaging plate reader; HEK-293, human embryonic kidney-293 cell; CYP, cytochrome P450; AMPH, amphetamine; PCP, phencyclidine; PPB, plasma protein binding; hERG, human ether-a-go-go-related gene.

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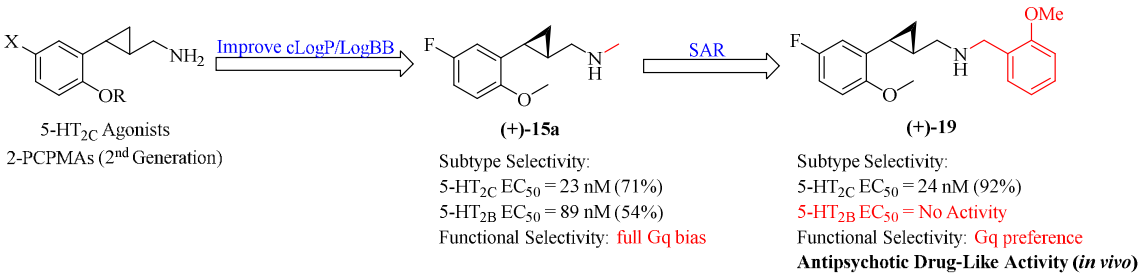

5-HT_{2C} Agonists
2-PCPMAs (2nd Generation)

(+)-15a

Subtype Selectivity:
5-HT_{2C} EC_{50} = 23 nM (71%)
5-HT_{2B} EC_{50} = 89 nM (54%)
Functional Selectivity: full Gq bias

(+)-19

Subtype Selectivity:
5-HT_{2C} EC_{50} = 24 nM (92%)
5-HT_{2B} EC_{50} = No Activity
Functional Selectivity: Gq preference
Antipsychotic Drug-Like Activity (*in vivo*)

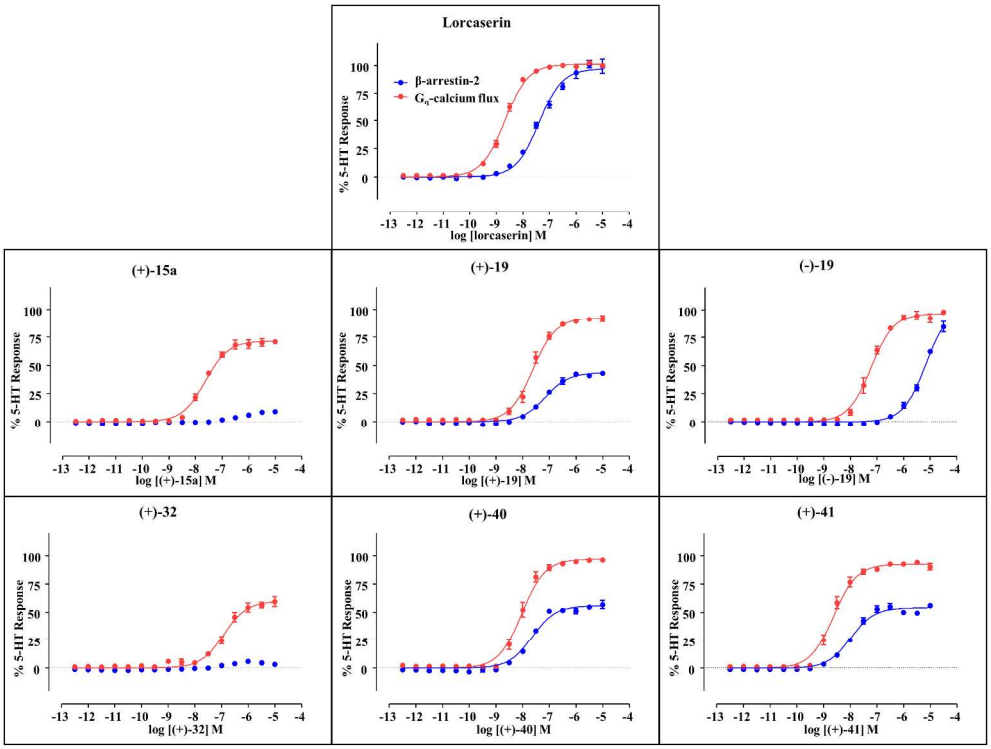

Figure 3_Profiling of 5-HT2C functional selectivity measuring Gq-calcium flux (FLIPR, red) and β-arrestin-2 recruitment (Tango, blue)

254x190mm (300 x 300 DPI)

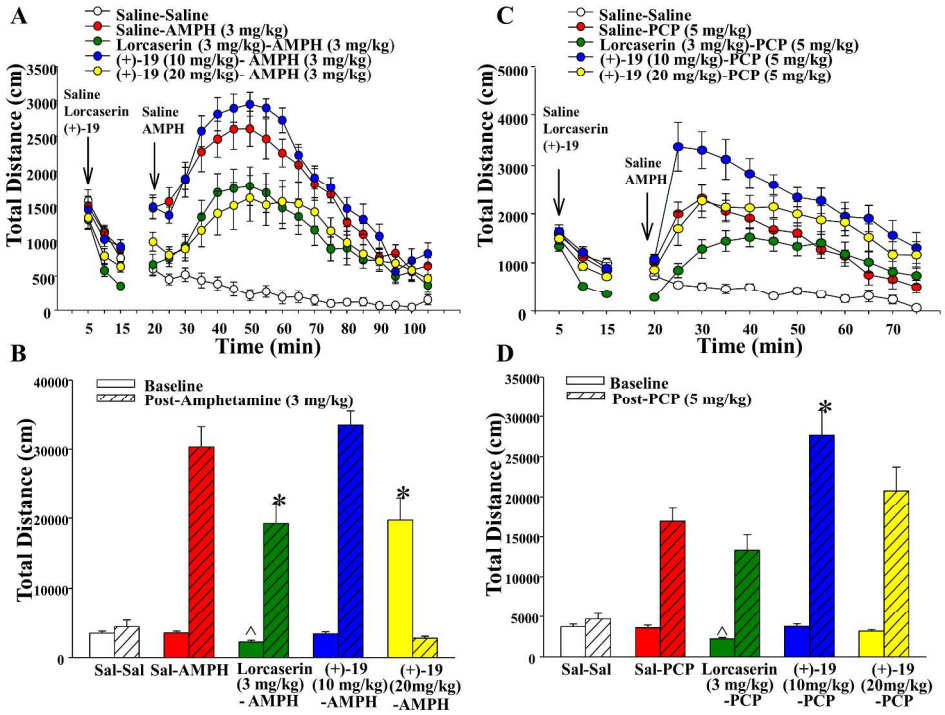

Figure 4. Evaluation of compound (+)-19 in animal models of antipsychotic drug-like activity.

254x190mm (300 x 300 DPI)