Discovery of (*R*)-9-Ethyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one, a Selective, Orally Active Agonist of the 5-HT_{2C} Receptor

Dean A. Wacker,* Jeffrey G. Varnes, Sarah E. Malmstrom, Xueying Cao, Chen-Pin Hung, Thao Ung, Ginger Wu, Ge Zhang, Eva Zuvich, Michael A. Thomas, William J. Keim, Mary Jane Cullen, Kenneth W. Rohrbach, Qinling Qu, Rangaraj Narayanan, Karen Rossi, Evan Janovitz, Lois Lehman-McKeeman, Mary F. Malley, James Devenny, Mary Ann Pelleymounter, Keith J. Miller, and Jeffrey A. Robl

Departments of Discovery Chemistry, Metabolic Diseases, Lead Evaluation, Computer-Assisted Drug Design, Discovery Toxicology, and Pharmaceutical Candidate Optimization, Bristol-Myers Squibb, Pharmaceutical Research Institute, P.O. Box 5400, Princeton, New Jersey 08543-5400

Received November 7, 2006

Robust pharmaceutical treatment of obesity has been limited by the undesirable side-effect profile of currently marketed therapies. This paper describes the synthesis and optimization of a new class of pyrazinoisoindolone-containing, selective 5-HT_{2C} agonists as antiobesity agents. Key to optimization of the pyrazinoisoindolone core was the identification of the appropriate substitution pattern and functional groups which led to the discovery of (*R*)-9-ethyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one (**58**), a 5-HT_{2C} agonist with >300-fold functional selectivity over 5-HT_{2B} and >70-fold functional selectivity over 5-HT_{2A}. Oral dosing of **58** reduced food intake in an acute rat feeding model, which could be completely reversed by a selective 5-HT_{2C} antagonist and caused a reduction in body weight gain in a 4-day rat model.

Introduction

Obesity is recognized as a major global public health issue. In the U.S., greater than 66% of the adult population are considered overweight with a body-mass index (BMI) of >25, and 32% are classified as obese with a BMI > 30.[1] Furthermore, obesity rates are climbing every year, and, if this trend continues, obesity will overtake smoking as the leading cause of preventable deaths in the U.S. The issue is not limited to the U.S. or developed countries, as studies indicate that obesity rates are rising in every part of the world.[2] The increasing prevalence of obesity is seen across all age groups, and the rate of morbid obesity is increasing at an even faster rate than obesity.

Obesity negatively affects both the physical and psychological health of patients. The prevalence of serious, chronic health problems such as coronary heart disease, hypertension, stroke, diabetes, arthritis, and some cancers have been correlated to the severity of obesity.[3] For example, it has been estimated that controlling obesity would reduce the incidence of hypertension by 48% in Caucasians and 28% in African Americans.[4] Also, evidence from numerous studies indicate that a causal relationship exists between obesity and reduced self-esteem and a lower quality of life, especially in children.[5] Given the widespread nature of this disease, there is an increasing importance in finding new treatments for obesity.

Historically, antiobesity pharmacotherapy has focused on modulation of neurotransmitter receptor activity. The elevation of monoaminergic neurotransmitter levels by inhibition of reuptake mechanisms, stimulation of release mechanisms, or direct activation of the neurotransmitter receptors has provided several antiobesity drugs such as sibutramine, phentermine, and dexfenfluramine. However, these drugs have had limited success because of several undesirable side effects presumably arising from a lack of receptor selectivity, such as valvular hypertrophy, pulmonary hypertension, and abuse potential. To overcome these issues, more recent research has focused on the selective regulation of the neurotransmitter receptors and, specifically, serotonin receptors.

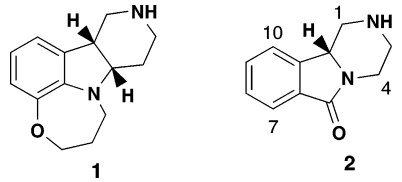


Figure 1. Published and proposed 5-HT_{2C} agonists.

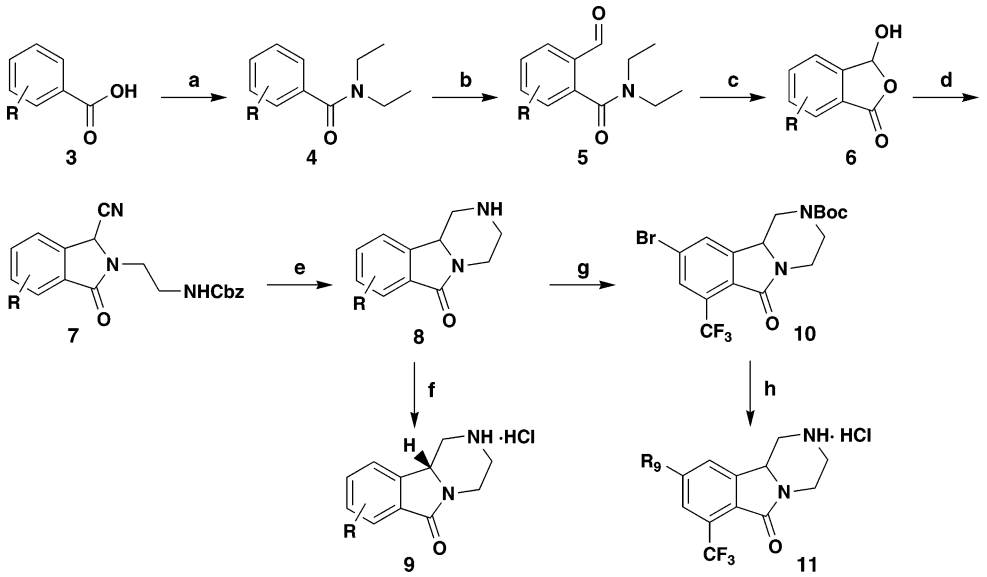
Several serotonin receptors have been implicated in the regulation of appetite, however, a growing body of evidence implicates 5-HT_{2C} as a primary contributor. In preclinical models, the nonselective 5-$HT_{2B/2C}$ agonist *m*-chlorophenylpiperazine (mCPP) reduces food intake in rats.[6] This effect is attenuated by the selective 5-HT_{2C} antagonist SB-242086[7] and is absent in 5-HT_{2C} receptor knock-out mice.[8] In clinical settings, mCPP reduces appetite and body weight of both normal and obese human subjects.[9] In light of these results, our efforts have focused on discovering new structural motifs with potent 5-HT_{2C} agonist activity. The challenge has been to identify compounds[10] that are also selective over the homologous 5-HT_{2A} receptor, to eliminate the unwanted side-effect of hallucinogenesis, and 5-HT_{2B} receptor, to reduce the possibility of valvular hypertrophy.[11]

A series of tetracyclic indolines, exemplified by **1** (Figure 1), were reported by Bristol-Myers Squibb to be potent and selective 5-HT_{2C} agonists.[12] Selected compounds from the series exhibited excellent sustained efficacy in in vivo models out to 14 weeks in duration. Unfortunately, the tetracyclic indolines had unwanted toxicities believed to be associated with the amphiphilic nature of the molecules, such as parietal cell necrosis. This toxicity has been observed with multiple 5-HT_{2C} agonist structural motifs.[13] To overcome these issues, we have focused on retaining the three-dimensional orientation of the basic amine in relation to the core phenyl ring, while reducing the size and more evenly distributing the polarity of the molecule. The pyrazinoisoindolone core structure **2** offered the

* To whom correspondence should be addressed. Phone: 609-818-5381. Fax: 609-818-3331. E-mail: dean.wacker@bms.com.

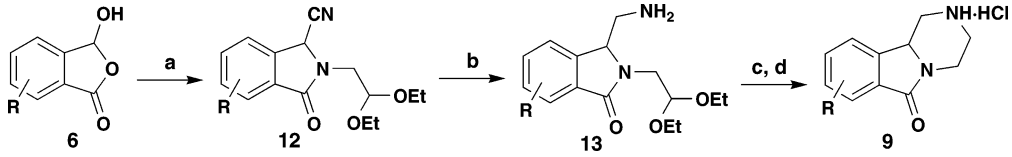
10.1021/jm0612968 CCC: $37.00 © 2007 American Chemical Society
Published on Web 02/23/2007

Scheme 1. Synthesis of Pyrazinoisoindolones (Method A)[a]



[a] Reagents: (a) (1) Oxalyl chloride, 0.1 equiv of DMF, CH_2Cl_2, (2) 2.2 equiv of diethylamine, CH_2Cl_2; (b) (1) *s*-BuLi, TMEDA, THF, −78 °C, 15 min, then DMF, −78 °C to rt, 1 h; (c) 6 M aq HCl, reflux, 16 h; (d) NaOAc, NaCN, *N*-Cbz-ethylenediamine hydrochloride, 2:1 EtOH:AcOH; (e) 60 psi H_2, 10% Pd/C, concd HCl, MeOH; (f) (1) Boc_2O, CH_2Cl_2, (2) chiral separation, (3) 12 M HCl; (g) (1) NBS, concd H_2SO_4, (2) Boc_2O, Na_2CO_3, THF; (h) (1) R_9-$B(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, DME, H_2O, reflux or R_9-$Sn(n\text{-}Bu)_3$, $Pd(PPh_3)_4$, Tol, reflux, (2) 12 M HCl.

Scheme 2. Alternative Synthesis of Pyrazinoisoindolones (Method B)[a]



[a] Reagents: (a) NaOAc, NaCN, 2,2-diethoxyethylamine, 2:1 EtOH:AcOH; (b) 1 atm H_2, Raney Ni, EtOH; (c) (1) 12 M HCl, (2) $NaBH(OAc)_3$, MeOH, $ClCH_2CH_2Cl$, (3) Boc_2O, Na_2CO_3, EtOAc; (d) 12 M HCl.

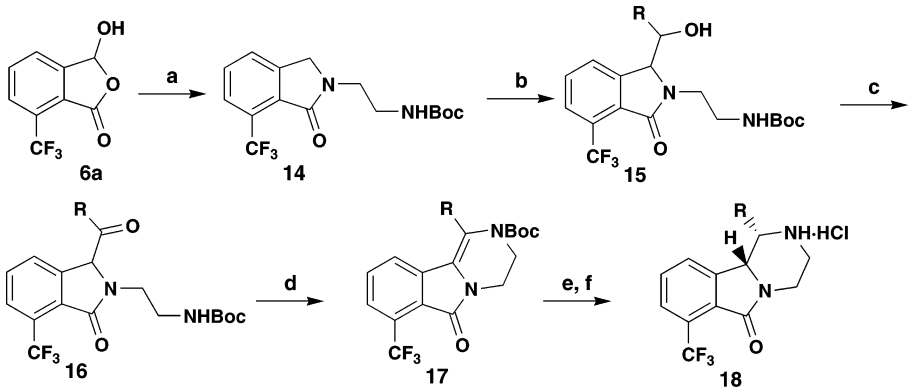
potential to accomplish these goals. A puckered shape is retained at the piperazine ring fusion, while a polar amide is centrally located in the structure. This paper reports the optimization of the pyrazinoisoindolone core and identification of (*R*)-9-ethyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one (**58**), a potent and selective orally bioavailable $5HT_{2C}$ agonist.

Chemistry. Two general synthetic routes, based on the work of Welch,[14] were developed for the synthesis of the pyrazinoisoindolone core structures (Schemes 1 and 2). The first route began with readily available benzoic acids **3**, which were converted to the corresponding diethyl amides **4** with oxalyl chloride and diethylamine in excellent yield. Benzamides **4** were then deprotonated with *sec*-butyllithium and TMEDA, and the resulting anions were quenched with DMF to provide intermediates **5**. Isobenzofurans **6** were formed by refluxing **5** with 6 M aq HCl overnight. Utilizing the procedures of Welch,[14] **6** was reacted with sodium cyanide and *N*-Cbz-ethylenediamine hydrochloride to produce compounds **7**. The cyanoisoindolones **7** were cyclized in the presence of palladium on carbon and hydrogen to yield final products **8**. To obtain the chiral products, compounds **8** were reacted with di-*tert*-butyl dicarbonate and the resulting *N*-Boc carbamates were separated by chiral HPLC. Deprotection with 12 M HCl afforded the chiral final products **9**. Derivatives of the 7-CF_3-substituted pyrazinoisoindolone core were synthesized by reacting **8** with concd H_2SO_4 and *N*-bromosuccinimide to yield intermediate bromide **10**. Alkylation of **10** under Suzuki or Stille conditions, followed by enantiomeric resolution by chiral HPLC and subsequent deprotection with 12 M HCl, afforded final alkyl products **11**. Absolute configuration was determined by X-ray crystallography.[15]

Alternatively, when the starting benzoic acids had substituents that were sensitive to hydrogenation conditions with palladium on carbon, a slightly modified synthetic scheme was used relying on a Raney nickel-catalyzed reduction (Scheme 2). Isobenzofurans **6** were treated with sodium cyanide and 2,2-diethoxyethylamine to provide nitriles **12** in good yield. The cyano group of **12** was reduced with Raney nickel and hydrogen to yield intermediates **13**. Treatment of **13** with 12 M HCl for 30 min and then reaction with $NaBH(OAc)_3$ gave the cyclized products which were protected with di-*tert*-butyl dicarbonate to facilitate purification and chiral separation if desired. The final products **9** were obtained by removal of the protecting group with 12 M HCl.

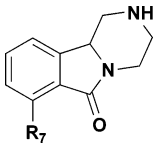
Compounds with alkyl substitutuents at C1 of the pyrazinoisoindolone core were synthesized from isobenzofuran **6a** (Scheme 3). Treatment of **6a** with *N*-Boc-ethylenediamine hydrochloride and $NaBH(OAc)_3$ yielded isoindolone **14**. Intermediate **14** was deprotonated with *sec*-butyllithium, and the resulting anion was then quenched with the desired aldehyde. Alcohols **15** were then oxidized to the corresponding ketones **16** under Dess−Martin conditions. Intermediates **16** were cyclized to the corresponding enamines with 12 M HCl and protected with di-*tert*-butyl dicarbonate and DMAP to yield **17**. This protection was necessary for optimal reduction of the enamines in the next step. The final products **18** were then synthesized by reduction of **17** with palladium on carbon and

Scheme 3. Synthesis of 1-Substituted Pyrazinoisoindolone Core[a]



[a] Reagents: (a) NaBH(OAc)$_3$, *N*-Boc-ethylenediamine hydrochloride, AcOH, ClCH$_2$CH$_2$Cl; (b) (1) *s*-BuLi, THF, −78 °C, 15 min, (2) RCOH, −78 °C − 0 °C, 5 min; (c) Dess−Martin periodinane, CH$_2$Cl$_2$; (d) (1) 12 M aq HCl, Et$_2$O, (2) Boc$_2$O, 2 equiv of DMAP; (e) (1) 60 psi H$_2$, 10% Pd/C, MeOH, (2) chiral separation; (f) 12 M HCl.

Table 1. In Vitro Activity of the Pyrazinoisoindolone Core



	chirality	R7	5-HT$_{2C}$ K_i, nM[a]	5-HT$_{2B}$ K_i, nM[a]	5-HT$_{2A}$ K_i, nM[a]	5-HT$_{2C}$ EC$_{50}$, nM[a, b]	5-HT$_{2B}$ EC$_{50}$, nM[a, b]	5-HT$_{2A}$ EC$_{50}$, nM[a,b]
19	*rac*	H	630 ± 130	4540 ± 220	8540 ± 250	1500 ± 30	>10000	>10000
20	*rac*	CF$_3$	19 ± 10	249 ± 87	110 ± 2	24 ± 11	192 ± 6	131 ± 17
21	*rac*	OMe	133 ± 62	192 ± 26	3280 ± 410	136 ± 46	207 ± 29	>10000
22	*rac*	OCF$_3$	20 ± 7	550 ± 300	67 ± 4	26 ± 7	498 ± 31	87 ± 14
23	*rac*	F	1030 ± 350	3690 ± 400	>10000	1730 ± 57	>10000	>10000
24	*rac*	Cl	31 ± 20	309 ± 79	586 ± 36	37 ± 2	501 ± 29	1780 ± 140
25	*rac*	CN	300 ± 100	3930 ± 270	>10000	281 ± 35	>10000	>10000
26	*rac*	SMe	40 ± 12	84 ± 6	216 ± 78	42 ± 15	87 ± 32	111 ± 10
27	*rac*	OH	980 ± 520	3740 ± 490	1670 ± 320	514 ± 26	>10000	>10000
28	*rac*	OiPr	115 ± 48	1600 ± 500	250 ± 100	107 ± 28	825 ± 49	449 ± 69
29	*R*	CF$_3$	7 ± 1	74 ± 10	59 ± 5	7 ± 2	180 ± 26	176 ± 38
30	*S*	CF$_3$	1100 ± 330	3430 ± 620	>10000	1840 ± 100	>10000	>10000

[a] K_i and EC$_{50}$ values were calculated from dose−response curves. Positive control was mCPP which gave 5-HT$_{2C}$ K_i = 17 ± 2 nM, EC$_{50}$ = 15 ± 4 nM; 5-HT$_{2B}$ K_i = 24 ± 1 nM, EC$_{50}$ = 287 ± 94 nM; 5-HT$_{2A}$ K_i = 48 ± 4 nM, EC$_{50}$ = 290 ± 110 nM. [b] Intrinsic activity for all compounds = 1 as compared to serotonin at 3 μM unless noted in parentheses.

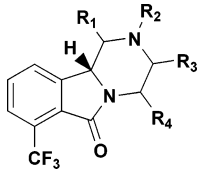
hydrogen followed by chiral HPLC resolution and deprotection with 12 M HCl.

Results and Discussion

Lead Identification and Optimization. Our initial operating assumption was that the core structure of an agonist needed to have some functional preference for 5-HT$_{2C}$ over 5-HT$_{2B}$ and 5-HT$_{2A}$ if we were to achieve our desired selectivity profile. The goal of our research was to design a 5-HT$_{2C}$ agonist with a K_i and EC$_{50}$ of less than 25 nM and greater than 100-fold functional selectivity over the 5-HT$_{2B}$ and 5-HT$_{2A}$ receptors. When we tested the unsubstituted, racemic pyrazinoisoindolone core (**19**),[14] we were very encouraged by the preliminary binding and functional assay results (Table 1). Although not extremely potent, compound **19** was >9-fold functionally selective for 5-HT$_{2C}$ over 5-HT$_{2B}$ and >14-fold over 5-HT$_{2A}$.

In order to increase the potency and selectivity of the pyrazinoisoindolone core, our efforts focused on substituting the 7-position, which, according to our modeling efforts, was analogous to the lower ring of the tetracyclic indoline core previously described. Incorporation of the nonpolar electron-withdrawing CF$_3$ group (**20**) provided a compound with a ~30-fold increase in potency and similar selectivity as compared to **19**. However, not all electron-withdrawing groups provided a large potency increase when compared to the unsubstituted core. The fluoro group (**23**) reduced potency, and the cyano functionality (**25**) provided little potency advantage. Electron-donating groups also provided mixed results. While the hydroxyl moiety (**27**) decreased potency, the methoxy substituent (**21**) provided a modest ~4-fold increase in potency. Large improvements in both binding and function were obtained with the trifluoromethoxy (**22**) and methylthiol (**26**) functionalities when compared to **19**. The greater potency obtained with **22** and **26** is most likely due to the reduced electron-donating ability of these functional groups when compared to that of a methoxy group rather than any hydrophobic contribution. This is supported by compound **28**, which is roughly equipotent with **21**, despite the added methyl groups. To evaluate the potential potency and selectivity differences between enantiomers, all racemic compounds were separated into their enantiomerically pure components. As exemplified by the CF$_3$ analogs (**29** and **30**), the *R*-enantiomers in all cases proved to be significantly more potent than the *S*-enantiomers. The selectivity differences between the enantiomers could not be meaningfully addressed due to the low potency of the S-configured compounds. As a result, all further optimization studies utilized the *R*-enantiomeric configuration. This initial exploration of the pyrazinoisoindolone

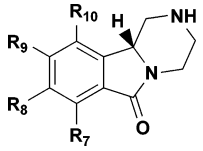
Table 2. In Vitro Activity of Substituted Piperazine Ring Analogs



	R1	R2	R3	R4	5-HT$_{2C}$ K_i, nM[a]	5-HT$_{2B}$ K_i, nM[a]	5-HT$_{2A}$ K_i, nM[a]	5-HT$_{2C}$ EC$_{50}$, nM[a,b]	5-HT$_{2B}$ EC$_{50}$, nM[a,b]	5-HT$_{2A}$ EC$_{50}$, nM[a,b]
31	H	Me	H	H	430 ± 200	1580 ± 230	4120 ± 100	296 ± 68	417 ± 35	994 ± 8
32	H	H	Me, Me	H	1450 ± 61	3190 ± 390	>10000	1580 ± 250	>10000	>10000
33	H	H	*S*-Me	H	369 ± 236	3010 ± 580	>10000	478 ± 87	>10000	>10000
34	H	H	*R*-Me	H	321 ± 211	2350 ± 870	>10000	>10000	>10000	>10000
35	H	H	H	*R*-Me	74 ± 24	116 ± 16	360 ± 180	82 ± 26	100 ± 19	370 ± 62
36	H	H	H	*S*-Me	22 ± 14	29 ± 13	117 ± 10	18 ± 9	40 ± 10	91 ± 2
37	H	H	H	*S*-i Pr	13 ± 3	7 ± 1	38 ± 19	10 ± 7	14 ± 5	56 ± 10
38	*S*-Me	H	H	H	29 ± 8	24 ± 1	122 ± 25	28 ± 8	22 ± 6	78 ± 16
39	*S*-Et	H	H	H	335 ± 7	235 ± 32	91 ± 25	480 ± 94	293 ± 36	126 ± 28

[a] K_i and EC$_{50}$ values were calculated from dose−response curves. Positive control was mCPP which gave 5-HT$_{2C}$ K_i = 17 ± 2 nM, EC$_{50}$ = 15 ± 4 nM; 5-HT$_{2B}$ K_i = 24 ± 1 nM, EC$_{50}$ = 287 ± 94 nM; 5-HT$_{2A}$ K_i = 48 ± 4 nM, EC$_{50}$ = 290 ± 110 nM. [b] Intrinsic activity for all compounds = 1 as compared to serotonin at 3 μM unless noted in parentheses.

Table 3. In Vitro Activity of Phenyl Ring Analogs



	R7	R8	R9	R10	5-HT$_{2C}$ K_i, nM[a]	5-HT$_{2B}$ K_i, nM[a]	5-HT$_{2A}$ K_i, nM[a]	5-HT$_{2C}$ EC$_{50}$, nM[a,b]	5-HT$_{2B}$ EC$_{50}$, nM[a,b]	5-HT$_{2A}$ EC$_{50}$, nM[a,b]
40	OMe	H	H	Cl	5060 ± 780	>10000	>10000	NT	NT	NT
41	Cl	H	H	Me	927 ± 11	730 ± 170	4010 ± 740	54 ± 12	290 ± 51	>3000
42	Cl	H	H	Et	425 ± 41	547 ± 170	2420 ± 130	46 ± 21	274 ± 51	3280 ± 640
43	Cl	H	H	OMe	59 ± 42	1420 ± 610	86 ± 1	5 ± 1	>1000	220 ± 120
44	CF$_3$	H	H	Cl	1084 ± 43	4030 ± 680	1473 ± 61	35 ± 4	>1000	>3000
45	Cl	Cl	H	H	107 ± 5	70 ± 11	383 ± 37	20 ± 5	57 ± 16	>1000
46	OMe	Cl	H	H	176 ± 15	86 ± 15	813 ± 69	12 ± 1	28 ± 3	872 ± 74
47	OMe	Et	H	H	37 ± 15	18 ± 3	43 ± 6	1.4 ± 0.5	8 ± 1	123 ± 22
48	H	OMe	Cl	H	2330 ± 780	471 ± 92	1780 ± 180	246 ± 84	>1000	>1000
49	H	OMe	Et	H	36 ± 14	75 ± 1	589 ± 55	17 ± 3	33 ± 7	374 ± 47
50	Cl	H	OMe	H	209 ± 88	890 ± 140	4500 ± 380	86 ± 44	>10000	>10000
51	Cl	H	Et	H	124 ± 1	248 ± 82	4960 ± 510	49 ± 13	>10000	>10000

[a] K_i and EC$_{50}$ values were calculated from dose−response curves. Positive control was mCPP which gave 5-HT$_{2C}$ K_i = 17 ± 2 nM, EC$_{50}$ = 15 ± 4 nM; 5-HT$_{2B}$ K_i = 24 ± 1 nM, EC$_{50}$ = 287 ± 94 nM; 5-HT$_{2A}$ K_i = 48 ± 4 nM, EC$_{50}$ = 290 ± 110 nM. [b] Intrinsic activity for all compounds = 1 as compared to serotonin at 3 μM unless noted in parentheses.

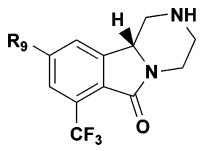
core provided a very potent compound (**29**); however, further efforts were needed to achieve the desired functional selectivity.

To increase the selectivity of compound **29**, a variety of substitution patterns were investigated. The modification of the piperazine ring by alkylation of the amino group (**31**) or alpha to the nitrogen at C3 (**32**−**34**) dramatically reduced the binding and functional potency at all three of the serotonin receptor subtypes (Table 2). In contrast, substitution of C4 with alkyl groups (**35**−**37**) provided very potent 5-HT$_{2C}$ compounds, however, functional selectivity versus 5-HT$_{2A}$ and 5-HT$_{2B}$ was lost. Substitution at C1 with a methyl group (**38**) also provided a potent 5-HT$_{2C}$ compound, but again selectivity over 5-HT$_{2A}$ and 5-HT$_{2B}$ was dramatically reduced. Additionally, any further increase in steric bulk at C1, as exemplified by compound **39**, decreased both 5-HT$_{2C}$ binding and functional potency.

Similar results were obtained when the substitution pattern of the aryl ring was investigated (Table 3). Compounds were either dramatically less potent, as seen with the 7,10-disubstituted compounds **40**−**42** and **44**, or very potent but with little to no selectivity over 5-HT$_{2A}$ and 5-HT$_{2B}$, e.g. 7,8-disubstituted **45**−**47** and 8,9-disubstituted **49**. An exception was compound **43**, which was both functionally potent and selective for 5-HT$_{2C}$ but lacked the desired receptor binding affinity. The most intriguing results from this work were obtained from 7,9-disubstituted compounds **50** and **51**. Although **50** and **51** were not extremely potent 5-HT$_{2C}$ agonists, the compounds had >100-fold functional selectivity for 5-HT$_{2C}$ over 5-HT$_{2A}$ and 5-HT$_{2B}$. This substitution pattern provided the desired selectivity profile and suggested additional modification of the substituents would provide selective 5-HT$_{2C}$ compounds with better potency to test in our in vivo models.

Due to the desirable combination of potency and selectivity imparted by the trifluoromethyl group, investigation of the 7,9-disubstituted pyrazinoisoindolone analogs focused on compounds with this moiety at C7 (Table 4). Diversification of C9 with a wide variety of functional groups was investigated. A number of these groups, such as halogens (**52**) and polar functionalities (**53**, **54**), dramatically decreased binding potency compared to **29**. Methoxy and ethoxy analogs **55** and **56**, respectively, did afford a comparative improvement in both binding and functional potency at 5-HT$_{2C}$, but neither compound met our criteria for 5-HT$_{2C}$ potency. However, a simple methyl group at C9 provided a very potent 5-HT$_{2C}$ agonist that was 27- and 47-fold functionally selective over 5-HT$_{2A}$ and 5-HT$_{2B}$,

Table 4. In Vitro Activity of 7,9-Disubstituted Phenyl Analogs



	R9	5-HT$_{2C}$ K_i, nM[a]	5-HT$_{2B}$ K_i, nM[a]	5-HT$_{2A}$ K_i, nM[a]	5-HT$_{2C}$ EC_{50}, nM[a,b]	5-HT$_{2B}$ EC_{50}, nM[a,b]	5-HT$_{2A}$ EC_{50}, nM[a,b]
52	Cl	900 ± 260	>10000	1040 ± 120	NT	NT	NT
53	Ac	1610 ± 27	>10000	5200 ± 800	NT	NT	NT
54	CH_2OH	460 ± 210	470 ± 290	3050 ± 890	NT	NT	NT
55	OMe	40 ± 4	1090 ± 220	1400 ± 170	11 ± 2	175 ± 27	289 ± 22
56	OEt	158 ± 51	1300 ± 460	3820 ± 59	63 ± 10	>10000	>10000
57	Me	9 ± 3	336 ± 85	560 ± 130	6 ± 4	282 ± 62	167 ± 41
58	Et	20 ± 6	153 ± 42	431 ± 41	16 ± 4	4926 ± 498 (0.5)	1170 ± 200 (0.5)
59	Pr	48 ± 1	380 ± 130	1070 ± 130	94 ± 4	>10000	>10000
60	Bu	57 ± 13	220 ± 120	627 ± 66	363 ± 13	>10000	>10000
61	*i*-Pr	51 ± 9	190 ± 100	2620 ± 410	72 ± 28	>10000	>10000
62	CH_2CH	43 ± 16	648 ± 270	829 ± 52	43 ± 21	1610 ± 520	1620 ± 83
63	HCC	332 ± 61	2099 ± 710	6560 ± 200	NT	NT	NT
64	*c*-Pr	35 ± 3	209 ± 84	579 ± 94	14 ± 6	2980 ± 260	513 ± 240
65	1-Me-*c*-Pr	34 ± 3	29 ± 7	2310 ± 89	54 ± 17	>10000	>10000

[a] K_i and EC_{50} values were calculated from dose−response curves. Positive control was mCPP which gave 5-HT$_{2C}$ K_i = 17 ± 2 nM, EC_{50} = 15 ± 4 nM; 5-HT$_{2B}$ K_i = 24 ± 1 nM, EC_{50} = 287 ± 94 nM; 5-HT$_{2A}$ K_i = 48 ± 4 nM, EC_{50} = 290 ± 110 nM. [b] Intrinsic activity for all compounds = 1 as compared to serotonin at 3 μM unless noted in parentheses.

Table 5. Single Dose Plasma Pharmacokinetic Parameters of **58** in Male Sprague−Dawley Rats

dose iv/po (mg/kg)	4.4/8.8
po T_{max} (h)	0.7 ± 0.3
po C_{max} (nM)	4050 ± 910
po $T_{1/2}$ (h)	1.6 ± 0.2
po AUC_{tot} (nM*h)	11000 ± 1100
po *F*%	77
iv Cl (mL/min/kg)	37.4 ± 6.9
iv V_{ss} (L/kg)	4.8 ± 0.6
Caco-2 (nm/s)	212
protein binding (% bound)	83

respectively. Encouraged by this result, we increased the steric bulk of the alkyl chain at C9. The structure−activity relationship was extremely narrow with respect to 5-HT$_{2C}$ potency and selectivity over 5-HT$_{2B}$ and 5-HT$_{2A}$. Increasing the size of the C9 substituent resulted in a decease in 5-HT$_{2C}$ potency; the propyl **59**, butyl **60**, and isopropyl **61** compounds no longer exhibited robust 5-HT$_{2C}$ functional efficacy but in turn had excellent functional selectivity. In contrast, the ethyl substituent (**58**) provided the desired 5-HT$_{2C}$ binding and functional potency and was >300-fold functionally selective over 5-HT$_{2B}$ and 73-fold selective over 5-HT$_{2A}$. Interestingly, **58** was also the first compound from the series that exhibited partial agonism at both 5-HT$_{2B}$ and 5-HT$_{2A}$. To further optimize the potency and selectivity of this molecule, the steric size of the ethyl group was attenuated by replacement with a vinyl (**62**) or an acetylene (**63**) functionality, but these substitutions only reduced 5-HT$_{2C}$ potency. Cyclopropyl **64** and 1-methylcyclopropyl **65** were also investigated and had good 5-HT$_{2C}$ potency and selectivity profiles. While **58**, **64**, and **65** were viable candidates for in vivo experiments, we opted to focus on **58** due to its better overall potency profile.

Pharmacokinetics and Metabolism of 58. A summary of the pharmacokinetic characteristics of **58** are detailed in Table 5. In Sprague−Dawley rats, **58** had a moderate systemic clearance with a relatively high volume of distribution and a brain-to-plasma concentration ratio slightly above 1 when measured at 2, 4, 8, and 24 h postdose. The absorption parameters were excellent, with a high Caco-2 value, rapid absorption in vivo, as seen by the short T_{max}, and good oral bioavailability. Free fraction in rat and human serum was 17%. Compound **58** modestly inhibited the cytochrome P-450 3A4 isoform with an IC_{50} of 8.7 μM, while all other isoforms tested had IC_{50}s over 40 μM.

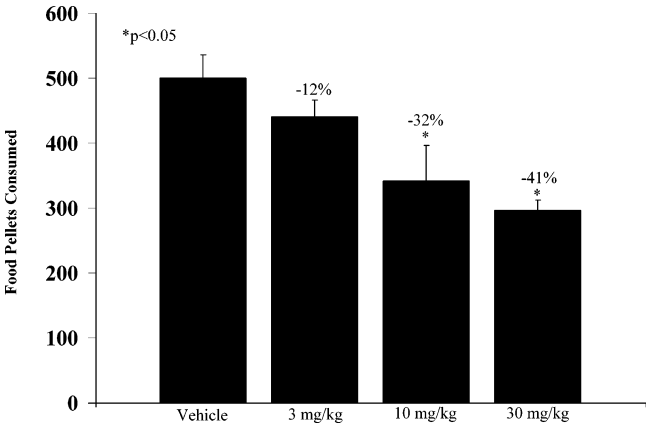


Figure 2. 20-h rat operant feeding model with compound **58**. Values indicate percent reduction in consumed pellets from vehicle dosed animals.

In Vivo Pharmacology. The in vivo efficacy of **58** was tested in an acute food intake model in Sprague−Dawley rats (Figure 2). In this 20 h operant feeding model, 250 g rats were dosed orally with compound 1 h prior to onset of the dark cycle and food availability. Compound **58** caused a dose-dependent reduction in food pellet consumption, with a statistically significant 32% reduction at 10 mg/kg and 41% at 30 mg/kg. During the experiment, water consumption and locomotor activity were within normal ranges and no overt physical or behavior abnormalities were observed. A reversal experiment was conducted to confirm that the observed food intake reduction was mediated by the 5-HT$_{2C}$ receptor (Figure 3). In the same operant feeding model, **58** was coadminstered with SB-243213, a selective 5-HT$_{2C}$ antagonist.[16] The 5-HT$_{2C}$ antagonist caused a complete reversal in the food intake in a dose-dependent manner, indicating that 5-HT$_{2C}$ receptor activation was the mechanism that mediated food reduction by **58**.

The ability of **58** to cause body weight reduction was tested by subchronic administration to lean Sprague−Dawley rats fed

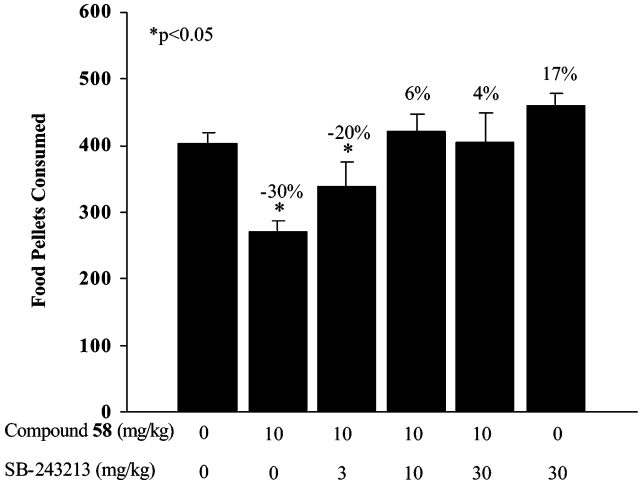


Figure 3. Antagonist reversal in the 20-h rat operant feeding model.

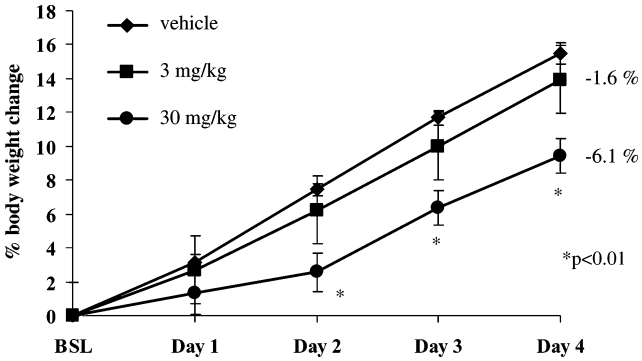


Figure 4. 4-Day rat weight loss model with compound **58**. Values indicate percent reduction in weight gain from vehicle dosed animals.

ad libitum on a choice diet consisting of standard rat chow and a highly palatable high fat chow (Figure 4). The compound was administered orally once daily 1 h prior to onset of the dark cycle for 4 days. Compound **58** reduced the body weight increase of the rats in a dose-dependent manner with a statistically significant reduction seen as early as day 2 at the 30 mg/kg dose. The overall reduction in body weight over control at day 4 at 30 mg/kg was 6%.

The compelling results from the feeding models encouraged us to evaluate compound **58** for gastric parietal cell necrosis to determine if this previously observed toxicity had been circumvented. Compound **58** was dosed orally to mice at doses up to 300 mg/kg. After 24 h the stomachs were evaluated for lesions by histopathological analysis, and no effects were observed.

Conclusion

Pyrazinoisoindolones were identified as a new class of 5-HT_{2C} agonists for the treatment of obesity. SAR studies found that 7,9-disubstitution of the aromatic ring presented the best balance between potency and selectivity, especially over 5-HT_{2B}. After surveying a wide variety of functional groups at both positions, **58** proved to have the best overall characteristics for advancement. In an acute feeding model, oral dosing of the compound produced a statistically significant reduction in food intake in a dose-dependent manner. The effect was reversed with a selective 5-HT_{2C} antagonist, indicating a 5-HT_{2C} mechanism-based reduction in food intake. In a 4-day model, oral dosing of **58** caused a robust reduction in body weight gain by young rats, and no overt physical or behavioral abnormalities were seen in any of the in vivo models. On the basis of its efficacy and selectivity profile, compound **58** was selected for further evaluation for the treatment of obesity, the results of which will be disclosed in the future.

Experimental Section

Chemistry. All nonaqueous reactions were carried out under an argon or nitrogen atmosphere at room temperature, unless otherwise noted. All reagents and solvents were purchased from commercial sources and were used without further purification or distillation, unless otherwise stated. Analytical thin-layer chromatography (TLC) was performed on EM Science silica gel 60 F_{254} (0.25 mm). Compounds were visualized by UV light and/or stained with either iodine or cerium molybdate followed by heating. Flash column chromatography was performed on EM Science silica gel 60 (particle size of 40−63 μm). Radial chromatography was performed on a Harrison Research Chromatotron. Radial silica gel plates of 1, 2, 4, or 8 mm thickness were obtained from Analtech Research. Analytical high-pressure liquid chromatography (HPLC) and LC-MS analyses were conducted using Shimadzu LC-10AS pumps and a SPD-10AV UV−vis detector set at 220 nm with the MS detection performed with a Micromass Platform LC spectrometer. NMR (^{1}H and ^{13}C) spectra were recorded on JEOL 400 MHz spectrometer and calibrated using an internal reference. Elemental analyses were performed by Robertson Microlit Laboratories, and the results obtained are within ±0.4% of the theoretical values.

General Procedure A for the Synthesis of Pyrazino[2,1-*a*]-isoindol-6(2*H*)-ones. Preparation of (±)-1,3,4,10b-Tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (20). Step A. To a stirring solution of 2-trifluoromethylbenzoic acid (3.6 g, 18.9 mmol) in dry CH_2Cl_2 (150 mL) with DMF (0.5 mL) was added a 2 M solution of oxalyl chloride in CH_2Cl_2 (17.5 mL) dropwise over 30 min. The reaction was stirred for 2 h and then concentrated *in vacuo* to a white solid. The solid was dissolved in CH_2Cl_2 (150 mL), and diethylamine (3.2 g, 43.8 mmol) was added. The reaction was stirred for 16 h and then concentrated *in vacuo* to a yellow solid. The solid was purified by radial chromatography (SiO_2, 1:5, EtOAc:hexanes) to yield 4.3 g (93%) of *N*,*N*-diethyl-2-trifluoromethylbenzamide as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 7.9 Hz, 1 H), 7.57 (t, J = 7.5 Hz, 1 H), 7.48 (t, J = 7.7 Hz, 1 H), 7.32 (d, J = 7.5 Hz, 1 H), 3.81−3.90 (m, 1 H), 3.21−3.30 (m, 1 H), 3.07 (ddd, J = 19.0, 14.2, 7.3 Hz, 2 H), 1.22 (t, J = 7.3 Hz, 3 H), 1.03 (t, J = 7.0 Hz, 3 H). MS (ESI) 246.2 (M + H).

Step B. To a stirring solution of *N*,*N*-diethyl-2-trifluoromethylbenzamide (2260 mg, 9.2 mmol) and *N*,*N*,*N*′,N′-tetramethylethylenediamine (1410 mg) in dry THF (20 mL) at −78 °C was added 0.93 M *sec*-butyllithium in hexanes (10.2 mL) dropwise. The reaction was stirred for 30 min and then DMF (2.0 mL) was added. The reaction was stirred for 1 h and then quenched with 1 M HCl (15 mL). The reaction was extracted with EtOAc (3 × 15 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to a yellow oil. The oil was purified by radial chromatography (SiO_2, 1:4, EtOAc:hexanes) to yield 2213 mg (88%) of *N*,*N*-diethyl-2-carboxaldehyde-6-trifluoromethylbenzamide as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1 H), 8.16 (d, J = 7.9 Hz, 1 H), 7.92 (d, J = 7.9 Hz, 1 H), 7.66 (t, J = 7.9 Hz, 1 H), 3.85 (dq, J = 7.0, 6.9 Hz, 1 H), 3.43 (dq, J = 7.0, 6.9 Hz, 1 H), 3.02−3.13 (m, 2 H), 1.28 (t, J = 7.0 Hz, 3 H), 1.01 (t, J = 7.3 Hz, 3 H). MS (ESI) 274.2 (M + H).

Step C. A stirring solution of *N*,*N*-diethyl-2-carboxaldehyde-6-trifluoromethylbenzamide (1378 mg, 5.3 mmol) in 6 M HCl (70 mL) was heated to 100 °C and stirred for 12 h. The reaction was cooled to room temperature and extracted with EtOAc (3 × 70 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to a brown oil. The oil was purified by flash column chromatography (SiO_2, 20−50% EtOAc in hexanes) to provide 3-hydroxy-7-trifluoromethyl-3*H*-isobenzofuran-1-one as an off-white solid (1365 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88−7.93 (m, 1 H), 7.84−7.87 (m, 2 H), 6.64 (s, 1 H), 3.97 (s, 1 H). MS (ESI) 201.2 (M − OH).

Step D. The 3-hydroxy-7-trifluoromethyl-3*H*-isobenzofuran-1-one (1365 mg, 5.0 mmol) from Step C was added to a stirring

solution of 1-(benzyloxycarbonylamino)-2-aminoethane hydrochloride (1156 mg, 5.0 mmol) and sodium acetate (411 mg, 5.0 mmol) in ethanol (13.5 mL) and acetic acid (6.5 mL), followed by sodium cyanide (245 mg, 5.0 mmol). The reaction was stirred overnight and then concentrated *in vacuo* to a yellow solid. The solid was partitioned between water (10 mL) and EtOAc (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to a yellow oil. The oil was purified by radial chromatography (SiO_2, 1:3, EtOAc:hexanes) to yield 1331 mg (66%) of (±)-2-[2-[(benzyloxycarbonyl)amino]ethyl]-1-carbonitrile-1,3-dihydro-4-trifluoromethyl-isoindol-3(1*H*)-one as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 7.5 Hz, 1 H), 7.77−7.85 (m, 2 H), 7.16−7.24 (m, 5 H), 5.76 (s, 1 H), 5.09 (s, 1 H), 4.89 (s, 2 H), 4.25 (ddd, J = 14.6, 10.4, 3.9 Hz, 1 H), 3.70−3.81 (m, 1 H) 3.47(dt, J = 14.5, 3.5 Hz, 1 H), 3.33−3.42 (m, 1 H). MS (ESI) 404.3 (M + H).

Step E. A stirring solution of (±)-2-[2-[(benzyloxycarbonyl)-amino]ethyl]-1-carbonitrile-1,3-dihydro-4-trifluoromethylisoindol-3(1*H*)-one (1331 mg, 3.3 mmol) and 10% palladium on carbon (440 mg) in EtOH (9 mL) and HCl (1 mL) was placed under 80 psi of hydrogen. The reaction was stirred for 96 h. The reaction was filtered and the filtrate was concentrated *in vacuo* to yield a white solid. The solid was partioned between 1 M aq NaOH (10 mL) and EtOAc (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to a pale yellow oil. The oil was purified by radial chromatography (SiO_2, 98:2, CH_2Cl_2:MeOH with NH_4OH) to yield 432 mg of the product as a colorless oil. The oil was treated with 1.0 N HCl in ether, dried *in vacuo*, and lyophilized from water to give **20** as a white solid (493 mg, 51%). ^{1}H NMR (400 MHz, CD_3-OD) δ 7.90−7.97 (m, 2 H), 7.85 (t, J = 7.5 Hz, 1 H), 4.92 (dd, J = 12.1, 4.2 Hz, 1 H), 4.52−4.60 (m, 1 H), 4.11−4.15 (m, 1H), 3.46−3.57 (m, 2H), 3.01−3.12 (m, 1 H), 2.83 (t, J = 12.1 Hz, 1 H). MS (ESI) 257.3 (M − Cl). Anal. ($C_{12}H_{11}F_3N_2O$·HCl·1.3H_2O), C, H, N.

(±)-7-Methoxy-1,3,4,10b-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (21). Prepared according to General Procedure A with substitution of 2-methoxybenzoic acid for 2-trifluoromethoxybenzoic acid at Step A. ^{1}H NMR (400 MHz, D_2O) δ 7.57 (t, J = 7.9 Hz, 1 H), 7.11 (d, J = 7.5 Hz, 1 H), 7.05 (d, J = 8.4 Hz, 1 H), 4.76−4.79 (m, 1 H), 4.38 (dd, J = 14.7, 4.2 Hz, 1 H), 4.01 (dd, J = 12.7, 3.9 Hz, 1 H), 3.85 (s, 3 H), 3.54 (dd, J = 12.7, 3.5 Hz, 1 H), 3.40−3.49 (m, 1 H), 3.01 (dt, J = 12.6, 4.6 Hz, 1 H), 2.74 (t, J = 12.30 Hz, 1 H). MS (ESI) 219.3 (M − Cl). Anal. ($C_{12}H_{14}N_2O_2$·HCl·0.4H_2O), C, H, N.

(±)-1,3,4,10b-Tetrahydro-7-trifluoromethoxypyrazino[2,1-*a*]-isoindol-6(2*H*)-one (22). Prepared according to General Procedure A with substitution of 2-trifluoromethoxybenzoic acid for 2-trifluoromethylbenzoic acid at Step A. This sample was not treated with 1.0 N HCl or lyophilized from water. ^{1}H NMR (400 MHz, CD_3OD) δ 7.46 (t, J = 7.9 Hz, 1 H), 7.26 (d, J = 7.5 Hz, 1 H), 7.18−7.23 (m, 1 H), 4.33 (dd, J = 10.8, 4.2 Hz, 1 H), 4.25−4.30 (m, 1 H), 3.53 (dd, J = 12.1, 4.2 Hz, 1 H), 2.99−3.08 (m, 2 H), 2.47−2.56 (m, 1 H), 2.22 (t, J = 11.4 Hz, 1 H). MS (ESI) 273 (M + H). Anal. ($C_{12}H_{11}F_3N_2O_2$ · 0.35 CH_2Cl_2), C, H, N.

(±)-7-Fluoro-1,3,4,10b-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one Trifluoroacetic Acid Salt (23). Prepared according to General Procedure A with substitution of 2-fluorobenzoic acid for 2-trifluoromethylbenzoic acid at Step A. Final purification was accomplished by reverse phase high performance liquid chromatography (C_{18}, 20−100% CH_3CN/H_2O w/0.05% TFA). ^{1}H NMR (400 MHz, CD_3CN) δ 7.63 (dt, J = 7.9, 4.8 Hz, 1 H) 7.41 (d, J = 7.5 Hz, 1 H) 7.22 (t, J = 9.0 Hz, 1 H) 4.98 (dd, J = 11.7, 3.7 Hz, 1 H) 4.34−4.41 (m, 1 H) 3.98 (dd, J = 12.3, 3.9 Hz, 1 H) 3.45−3.56 (m, 2 H) 2.87−2.96 (m, 1 H) 2.66 (t, J = 12.1 Hz, 1 H). MS (ESI) 207.2 (M − CF_3CO_2). Anal. ($C_{11}H_{11}FN_2O$·2.2$C_2HF_3O_2$·0.5CH_3-CN), C, H, N.

General Procedure B for the Synthesis of Pyrazino[2,1-*a*]-isoindol-6(2*H*)-one Hydrochloric Acid Salts. Preparation of (±)-7-Chloro-1,3,4,10b-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (24). Step A. To (±)-1-carbonitrile-2-(2,2-diethoxyethyl)-1,3-dihydro-4-chloro-isoindol-3(1*H*)-one (1.0 g, 3.25 mmol) [prepared according to General Procedure A, Steps A−D, using aminoacetaldehyde diethyl acetal] in ethanol (30 mL) was added Raney 2400 Nickel (1 mL; slurry in water). The mixture was degassed and the reaction vessel was fitted with a hydrogen balloon. After 4 h, the mixture was filtered (with a water wash), concentrated *in vacuo*, and purified by radial chromatography (SiO_2, 2% ammonium hydroxide in 4% methanol in dichloromethane) to give (±)-1-(aminomethyl)-2-(2,2-diethoxyethyl)-1,3-dihydro-4-chloroisoindol-3(1*H*)-one as a yellow oil (640 mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) 7.47 (t, J = 7.5 Hz, 1 H), 7.40 (d, J = 7.9 Hz, 1 H), 7.34 (d, J = 7.5 Hz, 1 H), 4.81 (t, J = 5.1 Hz, 1 H), 4.63−4.68 (m, 1 H), 3.90 (dd, J = 14.3, 4.6 Hz, 1 H), 3.71−3.81 (m, 2 H), 3.51−3.63 (m, 2 H), 3.31−3.38 (m, 2 H), 3.15−3.21 (m, 1 H), 1.22 (t, J = 7.0 Hz, 3 H), 1.17 (t, J = 7.0 Hz, 3 H). MS (ESI) 267.3, 269.2 (M + H).

Step B. To (±)-1-(aminomethyl)-2-(2,2-diethoxyethyl)-1,3-dihydro-4-chloroisoindol-3(1*H*)-one (200 mg, 0.65 mmol) was added concentrated aqueous HCl (5 mL, 12N). The resulting mixture was stirred for 30 min before being concentrated *in vacuo*. The resulting residue was concentrated from toluene and treated with 1,2-dichloroethane (5 mL). To this yellow mixture were added sodium triacetoxyborohydride (270 mg, 1.3 mmol) and methanol (0.5 mL), and the resulting mixture was stirred for 1 h before being quenched with aqueous HCl (5 mL, 1N). The mixture was then basified with sodium carbonate, diluted with EtOAc (6 mL), and treated with excess di-*tert*-butyl dicarbonate (400 mg). After 1 h, the reaction was extracted with EtOAc (×3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting yellow residue was purified by radial chromatography (SiO_2, 30−50% EtOAc in hexanes) to give (±)-*N*-(*tert*-butoxycarbonyl)-7-chloro-1,3,4,10b-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one as a white solid (87 mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.48 (m, 2 H), 7.33 (d, J = 7.0 Hz, 1 H), 4.72 (s, 1 H), 4.34−4.42 (m, 2 H), 4.17 (s, 1 H), 3.07−3.17 (m, 1 H), 2.74 (s, 1 H), 2.32 (s, 1 H), 1.48−1.54 (m, 9 H). MS (ESI) 323.3, 325.3 (M + H).

Step C. To (±)-*N*-(*tert*-butoxycarbonyl)-1,3,4,10b-tetrahydro-7-chloropyrazino[2,1-*a*]isoindol-6(2*H*)-one (15 mg, 0.05 mmol) was added concentrated HCl (1 mL). After 15 min, the resulting solution was concentrated *in vacuo*, diluted with water, and lyophilized to give **24** as an off-white solid (12 mg, 100%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.60−7.65 (m, 2 H), 7.51−7.57 (m, 1 H), 4.85−4.88 (m, 1 H), 4.53 (d, J = 14.5 Hz, 1 H), 4.08 (dd, J = 12.1, 3.7 Hz, 1 H), 3.46−3.57 (m, 2 H), 3.00−3.10 (m, 1 H), 2.80 (t, J = 11.9 Hz, 1 H). MS (ESI) 223.2, 225.2 (M − Cl). Anal. ($C_{11}H_{12}Cl_2N_2O$·1.15HCl·0.5H_2O), C, H, N.

(±)-7-Methylthio-1,3,4,10b-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (26). Prepared according to General Procedure B with the substitution of 2-(methylthio)benzoic acid for 2-chlorobenzoic acid in step A. ^{1}H NMR (400 MHz, CD_3-OD) δ 7.59 (t, J = 7.5 Hz, 1 H), 7.33−7.40 (m, 2 H), 4.81 (dd, J = 11.9, 3.9 Hz, 1 H), 4.50 (dd, J = 14.5, 3.9 Hz, 1 H), 4.03 (dd, J = 12.1, 3.7 Hz, 1 H), 3.34−3.55 (m, 2 H), 3.41 (d, J = 3.5 Hz, 1 H), 3.02 (dt, J = 12.4, 4.2 Hz, 1 H), 2.76 (t, J = 12.1 Hz, 1 H), 2.50 (s, 3 H). MS (ESI) 235.2 (M − Cl). Anal. ($C_{12}H_{14}N_2OS$·1.7HCl·H_2O), C, H, N.

(±)-7-Nitrile-1,3,4,10b-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (25). To *N*-(*tert*-butoxycarbonyl)-(±)-7-chloro-1,3,4,10b-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one (25 mg, 0.08 mmol) in a round-bottom flask were added zinc cyanide (5 mg, 0.05 mmol), tris(dibenzylideneacetone)dipalladium(0) (1.4 mg, 0.002 mmol), and 1,1′-bis(diphenylphosphino)ferrocene (1.7 mg, 0.003 mmol). To these reagents was added *N*, *N*-dimethylacetamide (1 mL), and the resulting mixture was degassed. The reaction was then subjected to microwave conditions (130 °C, 30 min; 300 W). The reaction was then cooled, and additional zinc cyanide (0.05 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.002 mmol), and 1,1′-bis(diphenylphosphino)ferrocene (0.003

mmol) were added. The reaction was again subjected to microwave conditions (160 °C, 60 min; 300 W). The resulting black mixture was then subjected to microwave conditions for a final time (220 °C, 60 min; 300 W) before being cooled and diluted with tetrahydrofuran (2 mL) and treated with excess di-*tert*-butyl dicarbonate. After 1 h, the reaction was diluted with EtOAc, and the mixture was washed with saturated aq ammonium hydroxide and brine. The organic layer was then dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified by radial chromatography (SiO_2, 30−50% EtOAc in hexanes) to give a clear residue. To the clear residue was added concentrated aqueous HCl (1 mL). After 1 min, the solution was concentrated *in vacuo*, diluted with water, and lyophilized to yield 25 as a white residue (1.0 mg, 18%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (t, J = 7.3 Hz, 2 H), 7.85 (t, J = 7.7 Hz, 1 H), 4.90−4.96 (m, 1 H), 4.57 (d, J = 14.5 Hz, 1 H), 4.13 (dd, J = 12.3, 3.5 Hz, 1 H), 3.48−3.60 (m, 2 H), 3.03−3.13 (m, 1 H), 2.85 (t, J = 12.1 Hz, 1 H). MS (ESI) 214.3 (M − Cl). Anal. ($C_{12}H_{11}N_2O_2$·HCl·0.5H_2O), C, H, N.

(±)-7-Hydroxy-1,3,4,10b-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (27). Step A. To a solution of (±)-7-methoxy-1,3,4,10b-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one (1.7 g, 0.008 mmol) prepared according General Procedure A (substituting 2-methoxybenzoic acid for 2-trifluoromethylbenzoic acid at Step A) in tetrahydrofuran (20 mL) was added di-*tert*-butyl dicarbonate (2.5 g, 0.012 mmol). After 2 h, the solution was concentrated and purified by flash column chromatography (SiO_2, 50−100% EtOAc in hexanes) to give *N*-(*tert*-butoxycarbonyl)-(±)-7-methoxy-1,3,4,10b-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one as a white solid (2.4 g, quant). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (app. t, J = 8.4, 7.5 Hz, 1H), 7.00 (d, J = 7.5 Hz, 1 H), 6.93 (d, J = 8.4 Hz, 1 H), 4.63−4.74 (m, 1H), 4.32−4.40 (m, 2 H), 4.11 (s, 1 H), 3.96 (s, 3 H), 3.09 (dt, J = 12.6, 3.3 Hz, 1 H), 2.65−2.76 (m, 1 H), 2.31 (s, 1 H), 1.50 (s, 9 H). MS (ESI) 319.3 (M + H).

Step B. To a solution of *N*-(*tert*-butoxycarbonyl)-(±)-7-methoxy-1,3,4,10b-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one (100 mg, 0.31 mmol) in dichloromethane (3 mL) at −78 °C was added dropwise boron tribromide (0.79 mL, 0.79 mmol; 1.0 M in CH_2Cl_2). After 5 min, the reaction was warmed to 0 °C and an additional 0.2 mL of boron tribromide (1.0 M in CH_2Cl_2) was added. After 2 h, the yellow mixture was cooled to −78 °C and quenched with water. The reaction was warmed to room temperature and stirred for 14 h. The mixture was then concentrated *in vacuo* and quenched again with aq HCl (3 M), and the resulting yellow solution was concentrated *in vacuo* to dryness. The residue was diluted with tetrahydrofuran (10 mL) and saturated aqueous sodium bicarbonate (1 mL). Di-*tert*-butyl dicarbonate (69 mg, 0.31 mmol) was added, and the mixture was stirred for 1 h. The reaction was then diluted with EtOAc, and the layers were separated. The organic layer was then dried over sodium sulfate, fitered, and concentrated *in vacuo*. The resulting residue was purified by radial chromatography (SiO_2, 20% EtOAc in hexanes) to give an off-white solid. To the solid was added 12 N aq HCl (1 mL). After 5 min, the solution was concentrated *in vacuo*, diluted with water, and lyophilized to give **27** as an off-white solid (8 mg, 42%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.45−7.51 (m, 1 H), 7.08 (d, J = 7.5 Hz, 1 H), 6.91 (d, J = 8.4 Hz, 1 H), 4.80 (dd, J = 11.9, 3.9 Hz, 1 H), 4.49 (dd, J = 14.3, 4.2 Hz, 1 H), 4.01 (dd, J = 12.3, 3.9 Hz, 1 H), 3.49−3.54 (m, 1 H), 3.40−3.49 (m, 1 H), 3.03 (dt, J = 12.4, 4.2 Hz, 1 H), 2.76 (t, J = 11.9 Hz, 1 H). MS (ESI) 205.2 (M − Cl). Anal. ($C_{11}H_{12}N_2O_2$·HCl·1.1H_2O), C, H, N.

(±)-7-Isopropoxy-1,3,4,10b-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (28). To a stirring solution of *N*,*N*-dimethylformamide (1.5 mL), *N*-(*tert*-butoxycarbonyl)-(±)-7-hydroxy-1,3,4,10b-tetrahydropyrazino[2,1-*a*]isoindol-6 (2*H*)-one (25 mg, 0.083 mmol), and anhydrous potassium carbonate (34 mg, 0.25 mmol) was added 2-iodopropane (0.012 mL, 0.125 mmol). The mixture was warmed to 80 °C and stirred for 12 h. The reaction was cooled, diluted with EtOAc, and washed with 50% saturated aqueous sodium chloride. The organic layer was then dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified by radial chromatography (SiO_2, 30% EtOAc in hexanes) to afford a clear residue. To the residue was added concentrated aqueous HCl (1 mL). After 5 min, the solution was concentrated *in vacuo*, diluted with water, and lyophilized to give **28** as a white solid (4 mg, 18%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.55−7.62 (m, 1 H), 7.12−7.18 (m, 2 H), 4.74−4.84 (m, 2 H), 4.51 (dd, J = 14.5, 3.9 Hz, 1 H), 4.02 (dd, J = 12.3, 3.9 Hz, 1 H), 3.52 (dd, J = 12.5, 3.3 Hz, 1 H), 3.38−3.47 (m, 1 H), 3.01 (dt, J = 12.6, 4.2 Hz, 1 H), 2.69−2.77 (m, 1 H), 1.35−1.41 (m, 6 H). MS (ESI) 247.3 (M − Cl). Anal. ($C_{14}H_{18}N_2O_2$·HCl·1.7 H_2O), C, H, N.

General Procedure for the Preparation of Chiral Pyrazino-[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salts. (*R*)-1,3,4,10b-Tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (29). Step A. To a stirring solution of (±)-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one (432 mg, 1.1 mmol) in dry CH_2Cl_2 (10 mL) was added di-*tert*-butyl dicarbonate (383 mg, 1.8 mmol). The reaction was stirred for 4 h and then concentrated *in vacuo* to a white solid. The solid was purified by radial chromatography (SiO_2, 1:10, EtOAc:hexanes). The compound was then separated by chiral HPLC (Chiracell OD column with 80% heptane with 0.1% diethylamine and 20% 1:1 MeOH:EtOH with 0.1% diethylamine) to yield 181 mg of *N*-(*tert*-butoxycarbonyl)-(*R*)-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one and 217 mg of the *N*-(*tert*-butoxycarbonyl)-(*S*)-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one as white solids. *R* enantiomer: Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77−7.82 (m, 1 H), 7.64−7.68 (m, 2 H), 4.79 (s, 1 H), 4.46 (dd, J = 11.0, 4.4 Hz, 1 H), 4.40 (dd, J = 13.6, 3.5 Hz, 1 H), 4.20 (s, 1 H), 3.11−3.20 (m, 1 H), 2.72−2.84 (m, 1 H), 2.36 (s, 1 H), 1.51 (s, 9 H). MS (ESI) 357.3 (M + H); *S* enantiomer: Enantiomeric excess >99:1 based on chiral HPLC. NMR (400 MHz, $CDCl_3$) δ 7.77−7.82 (m, 1 H), 7.64−7.68 (m, 2 H), 4.79 (s, 1 H), 4.46 (dd, J = 11.0, 4.4 Hz, 1 H), 4.40 (dd, J = 13.6, 3.5 Hz, 1 H), 4.20 (s, 1 H), 3.11−3.20 (m, 1 H), 2.72−2.84 (m, 1 H), 2.36 (s, 1 H), 1.51 (s, 9 H). MS (ESI) 357.3 (M + H).

Step B. To a stirring solution of *N*-(*tert*-butoxycarbonyl)-(*R*)-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one (181 mg, 0.51 mmol) in dry ether (5 mL) was added concentrated HCl (1 mL). The reaction was stirred for 1 h and then concentrated *in vacuo* to a white solid. The solid was dissolved in water and lyophilized to 147 mg of **29** a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.90−7.97 (m, 2 H), 7.85 (t, J = 7.5 Hz, 1 H), 4.92 (dd, J = 12.1, 4.2 Hz, 1 H), 4.52−4.60 (m, 1 H), 4.11−4.15 (m, 1H), 3.46−3.57 (m, 2H), 3.01−3.12 (m, 1 H), 2.83 (t, J = 12.1 Hz, 1 H). MS (ESI) 257.3 (M − Cl). $[\alpha]_D$ −8.4 (0.238 g/dL, MeOH). Anal. ($C_{12}H_{11}F_3N_2O$·HCl·1.4 H_2O), C, H, N.

(*S*)-1,3,4,10b-Tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]-isoindol-6(2*H*)-one Hydrochloric Acid Salt (30). Prepared according to procedures described for compound **29** with substitution of *N*-(*tert*-butoxycarbonyl)-(*S*)-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one for *N*-(*tert*-butoxycarbonyl)-(*R*)-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one at Step B. ^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (d, J = 7.9 Hz, 1 H), 7.92 (d, J = 7.5 Hz, 1 H), 7.84 (t, J = 7.5 Hz, 1 H), 4.96 (dd, J = 11.7, 3.7 Hz, 1 H), 4.52−4.59 (m, 1 H), 4.15 (dd, J = 12.1, 3.7 Hz, 1 H), 3.48−3.60 (m, 2 H), 3.02−3.11 (m, 1 H), 2.82 (t, J = 12.1 Hz, 1 H). MS (ESI) 257.3 (M − Cl). $[\alpha]_D$ +8.5 (0.212 g/dL, MeOH). Anal. ($C_{12}H_{11}F_3N_2O$·HCl·H_2O), C, H, N.

(±)-2-Methyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino-[2,1-*a*]isoindol-6(2*H*)-one (31). To a stirring solution of (±)-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one (60 mg, 0.23 mmol) in water (1 mL) were added formic acid (0.22 mL, 5.9 mmol) and formaldehyde (190 mg, 2.3 mmol; 37% soln in water). The reaction flask was sealed with a rubber septum (no nitrogen inlet) and warmed to 60 °C. After 24 h, the reaction was cooled to room temperature and then diluted with saturated aqueous sodium bicarbonate and extracted with EtOAc (3 × 50 mL), and the combined organic layers were dried over sodium

sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified by radial chromatography (SiO_2, 2% ammonium hydroxide in 8% methanol in dichloromethane) to afford **31** (33 mg, 52%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 6.2 Hz, 1 H) 7.57−7.65 (m, 2 H), 4.54 (dd, J = 11.0, 3.9 Hz, 1 H), 4.37 (dd, J = 13.2, 3.1 Hz, 1 H), 3.36 (dd, J = 10.8, 4.2 Hz, 1 H), 3.25 (dt, J = 12.7, 3.9 Hz, 1 H), 2.87 (dd, J = 11.4, 3.9 Hz, 1 H), 2.38 (s, 3 H), 1.98 (dt, J = 11.9, 4.2 Hz, 1 H), 1.64 (t, J = 10.8 Hz, 1 H). MS (ESI) 271.6 (M + H). Anal. ($C_{13}H_{13}F_3N_2O\cdot0.7H_2O$), C, H, N.

(±)-3,3-Dimethyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (32). Prepared according to General Procedure A with the substitution of 1-amino-2-(benzyloxycarbonylamino)-2-methylpropane hydrochloride[17] for 1-(benzyloxycarbonylamino)-2-aminoethane hydrochloride. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 6.6 Hz, 1 H), 7.59−7.65 (m, 2 H), 4.34 (dd, J = 10.8, 4.6 Hz, 1 H), 4.15 (d, J = 12.7 Hz, 1 H), 3.45 (dd, J = 12.7, 4.4 Hz, 1 H), 2.85 (d, J = 12.7 Hz, 1 H,) 2.64 (dd, J = 12.7, 11.0 Hz, 1 H), 1.24 (s, 3 H), 1.06 (s, 3 H). MS (ESI) 285 (M + H). Anal. ($C_{14}H_{15}F_3N_2O_2\cdot$HCl$\cdot$0.7 H_2O), C, H, N.

(3*S*,10b*R*)-3-Methyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (33). Prepared according to General Procedure A with the substitution of (*S*)-1-amino-2-(benzyloxycarbonylamino)propane hydrochloride for 1-(benzyloxycarbonylamino)-2-aminoethane hydrochloride. Separation of the diastereomers was carried out at the last step during purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74−7.78 (m, 1 H), 7.59−7.64 (m, 2 H), 4.38−4.43 (m, 2 H), 3.63 (dd, J = 11.9, 4.2 Hz, 1 H), 2.67−2.76 (m, 2 H), 2.38 (app t, J = 11.7, 10.6 Hz, 1 H), 1.17 (d, J = 5.9 Hz, 3 H). MS (ESI) 271 (M − Cl). Anal. ($C_{13}H_{13}F_3N_2O\cdot$HCl$\cdot$3.2H_2O), C, H, N.

(3*R*,10b*R*)-3-Methyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (34). Prepared according to General Procedure A with the substitution of (*R*)-1-amino-2-(benzyloxycarbonylamino)propane hydrochloride for 1-(benzyloxycarbonylamino)-2-aminoethane hydrochloride. Separation of the diastereomers was carried out at the last step during purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 6.6, 1 H), 7.52−7.58 (m, 2 H), 4.34 (dd, J = 11.0, 4.4, 1 H), 3.28 − 3.37 (m, 2H), 3.23 (dd, J = 4.4, 13.2 Hz, 1 H), 2.59 (app t, J = 11.0, 12.2 Hz, 1 H), 1.60 (br s, 2H), 1.04 (d, J = 6.6 Hz, 3 H). MS (ESI) 271 (M − Cl). Anal. ($C_{13}H_{13}F_3N_2O\cdot$HCl), C, H, N.

(4*R*,10b*R*)-4-Methyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (35). Prepared according to General Procedure A with the substitution of (*R*)-2-amino-1-(benzyloxycarbonylamino)propane hydrochloride[18] for 1-(benzyloxycarbonylamino)-2-aminoethane hydrochloride. Separation of the diastereomers was carried out at the last step during purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1 H), 9.54 (s, 1 H), 8.08 (d, J = 7.5 Hz, 1 H), 7.91 (d, J = 7.9 Hz, 1 H), 7.85 (t, J = 7.7 Hz, 1 H), 4.96 (dd, J = 11.4, 3.9 Hz, 1 H), 4.62−4.69 (m, 1 H), 3.98−4.05 (m, 1 H), 3.31 (d, J = 12.7 Hz, 1 H), 3.04−3.13 (m, 1 H), 2.65−2.76 (m, 1 H), 1.41 (d, J = 7.0 Hz, 3 H). MS (ESI) 271 (M − Cl). ($C_{13}H_{13}F_3N_2O\cdot$HCl$\cdot$0.7 H_2O), C, H, N.

(4*S*,10b*R*)-4-Methyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (36). Prepared according to General Procedure A with the substitution of (*S*)-2-amino-1-(benzyloxycarbonylamino)propane hydrochloride[17] for 1-(benzyloxycarbonylamino)-2-aminoethane hydrochloride. Separation of the diastereomers was carried out at the last step during purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (d, J = 7.5 Hz, 1 H), 7.89 (d, J = 7.9 Hz, 1 H), 7.82 (t, J = 7.7 Hz, 1 H,) 4.82 (dd, J = 11.4, 3.5 Hz, 1 H), 3.98−4.07 (m, 2 H), 3.34 (d, J = 12.7 Hz, 1 H), 2.83−2.93 (m, 1 H), 2.73−2.83 (m, 1 H), 1.72 (d, J = 6.6 Hz, 3 H). MS (ESI) 271 (M − Cl). ($C_{13}H_{13}F_3N_2O\cdot$1.1HCl$\cdot$ H_2O), C, H, N.

(4*S*,10b*R*)-4-Isopropyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (37). Prepared according to General Procedure A with the substitution of (*S*)-2-amino-1-(benzyloxycarbonylamino)-3-methyl-butane[15] hydrochloride for 1-(benzyloxycarbonylamino)-2-aminoethane hydrochloride. Separation of the diastereomers was carried out at the last step during purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (d, J = 7.5 Hz, 1 H), 7.89 (d, J = 7.9 Hz, 1 H), 7.82 (t, J = 7.7 Hz, 1 H), 4.83 (dd, J = 11.6, 3.7 Hz, 1 H), 4.00 (dd, J = 11.9, 3.5 Hz, 1 H), 3.59−3.71 (m, 1 H), 3.45 (d, J = 11.9 Hz, 1 H), 3.15−3.26 (m, 1 H), 2.91 (s, 1 H), 2.75 (s, 1 H), 1.08 (d, J = 6.6 Hz, 3 H), 0.99 (d, J = 6.6 Hz, 3 H). MS (ESI) 299 (M − Cl). Anal. ($C_{15}H_{17}F_3N_2O\cdot$HCl$\cdot$1.8H_2O), C, H, N.

(1*S*,10b*R*)-1-Methyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (38). Step A. To 3-hydroxy-7-(trifluoromethyl)isobenzofuran-1(3*H*)-one (5.6 g, 25.7 mmol; General Procedure A, Step C) in 10% acetic acid in 1,2-dichloroethane (250 mL) were added *N*-(*tert*-butoxycarbonyl)ethylenediamine (3.7 mL, 23.4 mmol) and sodium triacetoxyborohydride (7.4 g, 35.1 mmol). The resulting mixture was warmed to 50 °C and maintained at this temperature for 14 h. The reaction was cooled to 23 °C, diluted with brine, and extracted with EtOAc (×3). The combined organic layers were dried over sodium sulfate and filtered, and the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, 0−80% EtOAc in hexanes) to afford 2-[2-[(*tert*-butoxycarbonyl)amino]ethyl]-1,3-dihydro-4-trifluoromethylisoindol-3(1 *H*)-one (7.9 g, 89%) as an off-white oily solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 7.9 Hz, 1 H), 7.59−7.65 (m, 2 H), 4.81 (s, 1 H), 4.52 (s, 2 H), 3.74 (t, J = 6.2 Hz, 2 H), 3.45 (q, J = 5.9 Hz, 2 H), 1.25 (s, 9 H). MS (ESI) 345 (M + H).

Step B. To 2-[2-[(*tert*-butoxycarbonyl)amino]ethyl]-1,3-dihydro-4-trifluoromethylisoindol-3(1*H*)-one (2.31 g, 6.71 mmol) in tetrahydrofuran at −78 °C was added *sec*-butyllithium (12.3 mL, 14.8 mmol; titrated with diphenylacetic acid, 1.2 M) in cyclohexane/hexane (92/8) in one portion. After stirring the reaction at −78 °C for 15 min, acetaldehyde (1.88 mL, 33.6 mmol) was added in one portion. The brown-green solution was warmed to 0 °C over 5 min and was then quenched with aq HCl (1 N) and brine. The mixture was extracted with EtOAc (×3), the combined organic layers were dried over sodium sulfate and filtered, and the filtrate was concentrated. The resulting residue was purified by flash column chromatography (SiO_2, 0−50% EtOAc in hexanes) to afford (±)-2-[2-[(*tert*-butoxycarbonyl)amino]ethyl]-1,3-dihydro-1-(1-hydroxyethyl)-4-trifluoromethylisoindol-3(1*H*)-one (2.2 g, 84%) as a white foam-like solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.0 Hz, 0.33H), 7.68 (m, 1 H), 7.52−7.61 (m, 1.66 H), 4.93−5.02 (s, 0.65 H), 4.87−4.93 (s, 0.35 H), 4.73 (s, 1 H), 4.48−4.38 (1 H), 3.97−4.80 (m, 1 H), 3.86−3.96 (m, 0.55 H), 3.70−3.85 (m, 2.45 H), 1.98 (s, 3 H), 1.19 (s, 9 H). MS (ESI) 389 (M + H).

Step C. To (±)-2-[2-[(*tert*-butoxycarbonyl)amino]ethyl]-1,3-dihydro-1-(1-hydroxyethyl)-4-trifluoromethylisoindol-3(1*H*)-one (2.2 g, 5.7 mmol) in dichloromethane at 23 °C was added Dess−Martin periodinane (3.4 g, 7.9 mmol) in one portion. After 20 min, the reaction was quenched with methanol (10 mL) and concentrated *in vacuo*. The resulting white mixture was purified by flash column chromatography (SiO_2, 0−50% EtOAc in hexanes) to afford (±)-2-[2-[(*tert*-butoxycarbonyl)amino]ethyl]-1,3-dihydro-1-(1-oxoethyl)-4-trifluoromethylisoindol-3(1*H*)-one (1.9 g, 86%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78−7.88 (m, 1 H), 7.64−7.73 (m, 2 H), 5.30 (s, 1 H), 4.77 (s, 1 H), 4.17−4.27 (m, 1 H), 3.58 (s, 1 H), 3.17−3.29 (m, 2 H), 1.99 (s, 3 H), 1.22 (s, 9 H). MS (ESI) 387 (M + H).

Step D. Concentrated aqueous HCl (5 mL) was added to a mixture of diethyl ether (20 mL) and (±)-2-[2-[(*tert*-butoxycarbonyl)amino]ethyl]-1,3-dihydro-1-(1-oxoethyl)-4-trifluoromethylisoindol-3(1*H*)-one (1.9 g, 4.9 mmol). The resulting mixture was stirred for 5 min and became a yellow solution. The solution was concentrated *in vacuo* to dryness and azeotroped three times with toluene (5 mL). Finally, the residue was treated with dichloromethane (5 mL) and concentrated *in vacuo* to a yellow orange solid. Di-*tert*-butyl dicarbonate (4.8 g, 22 mmol) was added to the residue, and the mixture was warmed to 55 °C. To this mixture was added 4-(dimethylamino)pyridine (1.2 g, 9.8 mmol). After 5

min, the orange brown solution was directly purified by flash column chromatography (SiO_2, 0−30% EtOAc in hexanes) to afford *N*-(*tert*-butoxycarbonyl)-3,4-dihydro-1-methyl-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one (1.5 g, 83%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.9 Hz, 1 H), 7.71 (d, J = 7.5 Hz, 1 H), 7.63 (t, J = 7.7 Hz, 1 H), 3.88 (s, 2 H), 2.53 (s, 2 H), 1.54 (s, 12 H). MS (ESI) 369 (M + H).

Step E. To a solution of *N*-(*tert*-butoxycarbonyl)-3,4-dihydro-1-methyl-7-trifluoromethylpyrazino[2,1-*a*]isoind ol-6(2*H*)-one (0.20 g, 0.54 mmol) in methanol (10 mL) was added palladium on carbon (20 mg, 10 wt %). The resulting mixture was degassed (vacuum then argon, ×3) and subjected to a hydrogen atmosphere (60 psi) for 12 h. The mixture was then filtered, and the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, 0−50% EtOAc in hexanes) to afford *N*-(*tert*-butoxycarbonyl)-(±)-1-methyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one (0.19 g, 94%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 7.5 Hz, 1 H), 7.59−7.68 (m, 2 H), 5.03−5.10 (m, 0.66 H), 4.78−4.85 (s, 0.33H), 4.63 (d, J = 4.4 Hz, 1 H), 4.35 (d, J = 9.7 Hz, 1 H), 4.10−4.20 (s, 0.33 H), 3.99−4.06 (m, 0.66 H), 2.97−3.21 (m, 2H), 1.51 (s, 12 H). MS (ESI) 371 (M + H).

Step F. The mixture of enantiomers contained in *N*-(*tert*-butoxycarbonyl)-(±)-1-methyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one (81 mg, 0.22 mmol) was separated by chiral HPLC (Chiracell AD column with 90% heptane containing 0.1% diethylamine and 10% 1:1 MeOH:EtOH containing 0.1% diethylamine). The resulting solids were individually repurified by flash column chromatography (SiO_2, 0−50% EtOAc in hexanes) to yield 35 mg of the (1*S*,10b*R*) enantiomer and 36 mg of the (1*R*,10b*S*) enantiomer as white solids. The solids were individually dissolved in dry ether (1 mL)and the treated with HCl (1 mL). The reactions were stirred for 5 min and then concentrated *in vacuo* to a white solid. The solids were dissolved in water and lyophilized to yield 28 mg (quant) of the (1*S*,10b*R*) enantiomer and 28 mg (93%) of the (1*R*,10b*S*) enantiomer as white solids. Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, D_2O) δ 7.88−7.93 (m, 1 H), 7.80−7.84 (m, 2 H), 5.11 (d, J = 4.4 Hz, 1 H), 4.52−4.57 (m, 1 H), 4.49 (dd, J=14.9, 4.4 Hz, 1 H), 3.41−3.55 (m, 2 H), 3.33 (dt, J = 12.9, 4.4 Hz, 1 H), 0.80 (d, J = 6.6 Hz, 3 H). MS (ESI) 271 (M − Cl). Anal. ($C_{13}H_{13}F_3N_2O\cdot HCl\cdot 0.4H_2O$), C, H, N.

(1*S*,10b*R*)-1-Ethyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (39). Prepared according to the procedures described in Example **38** with substitution of propionaldehyde for acetaldehyde at step B. Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, CD_3OD) 7.98 (d, J = 7.5 Hz, 1 H), 7.92 (d, J = 7.5 Hz, 1 H), 7.85 (t, J = 7.7 Hz, 1 H), 5.14 (d, J = 3.9 Hz, 1 H), 4.52 (dd, J = 14.3, 4.6 Hz, 1 H), 4.32 (ddd, J = 9.0, 4.8, 4.6 Hz, 1 H), 3.54 (dt, J = 13.4, 4.4 Hz, 1 H), 3.38−3.44 (m, 1 H), 3.26−3.34 (m, 1 H), 1.28−1.40 (m, 1 H), 0.99−1.10 (m, 1 H), 0.83 (t, J = 7.7 Hz, 3 H). MS (ESI) 285 (M − Cl) Anal. ($C_{14}H_{15}F_3N_2O\cdot HCl\cdot H_2O$), C, H, N.

((*R*)-10-Chloro-7-methoxy-1,3,4,10b-tetrahydropyrazino[2,1-*a*]isoindol-6(2 H)-one Hydrochloric Acid Salt (40). Prepared according to General Procedure B with substitution of 5-chloro-2-methoxybenzoic acid for 2-chlorobenzoic acid. Chiral resolution and deprotection were carried out according to the General Procedure for the preparation of chiral pyrazino[2,1-*a*]isoindol-6(2*H*)-one hydrochloric acid salts (Chiracell OJ chiral column and 10% (1:1) methanol/ethanol in heptane containing 0.1% diethylamine. Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, D_2O) δ 7.58 (d, J = 8.8 Hz, 1 H), 7.12 (d, J = 9.2 Hz, 1 H), 4.92 (dd, J = 11.9, 3.9 Hz, 1 H), 4.44 (dd, J=14.5, 3.9 Hz, 1 H), 4.36 (dd, J=12.3, 3.9 Hz, 1 H), 3.89 (s, 3 H), 3.47−3.58 (m, 2 H) 3.03 (dt, J=12.5, 4.4 Hz, 1 H), 2.82 (t, J=12.1 Hz, 1 H). MS (ESI) 253, 255 (M − Cl). Anal. ($C_{12}H_{13}ClN_2O_2\cdot HCl\cdot 0.8H_2O$), C, H, N.

(*R*)-7-Chloro-10-methyl-1,3,4,10b-tetrahydropyrazino[2,1-*a*]-isoindol-6(2*H*)-one Hydrochloric Acid Salt (41). Step A. To *N*-(*tert*-butoxycarbonyl)-(±)-7-chloro-10-hydroxy-1,3,4,10b-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one (1.0 g, 2.96 mmol) [prepared from (a) 2-chloro-5-methylbenzoic acid according to General Procedure B and (b) the demethylation procedure used for compound **27** followed by reprotection with di-*tert*-butyl dicarbonate (1.0 equiv)] were added dichloromethane (30 mL), 2,6-lutidine (1.37 mL, 11.8 mmol), and trifluoromethanesulfonic anhydride (0.60 mL, 3.55 mmol) at 0 °C. After 40 min, the reaction was concentrated to a red mixture and purified by flash column chromatography (SiO_2, 0−50% EtOAc in hexanes) to afford *N*-(*tert*-butoxycarbonyl)-(±)-7-chloro-1,3,4,10b-tetrahydro-10-trifluoromethanesulfonyl-pyrazino[2,1-*a*]isoindol-6(2*H*)-one (1.11 g, 80%) as a beige solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.8 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1 H), 4.90 (br s, 1 H), 4.58 (dd, J = 10.8, 4.2 Hz, 1 H), 4.39 (dd, J = 13.4, 3.3 Hz, 1 H), 4.29 (br s, 1 H), 3.13−3.22 (m, 1 H), 2.65−2.76 (m, 1 H), 2.45 (br s, 1 H), 1.51 (s, 9 H). MS (ESI) 471.2, 473.2 (M − Cl).

Step B. *N*-(*tert*-Butoxycarbonyl)-(*R*)-7-chloro-10-methyl-1,3,4,10b-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one was prepared according to the procedure described for **57** (substituting cesium carbonate for potassium carbonate and [1,1′-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) for tetrakis(triphenylphospine)palladium(0)) followed by chiral chromatography (Chiracell OJ column and 15% (1:1) methanol/ethanol in heptane containing 0.1% diethylamine). The carbamate was then treated with concentrated aqueous hydrogen chloride, concentrated *in vacuo*, and lyophilized from water to afford **41** as a white solid. Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, D_2O) δ 7.33−7.38 (m, 2 H), 4.83 (dd, J = 11.9, 3.9 Hz, 1 H), 4.50 (dd, J = 14.3, 4.2 Hz, 1 H), 4.15 (dd, J = 12.3, 3.95 Hz, 1 H), 3.49−3.59 (m, 2 H), 3.02 (dt, J = 12.5, 4.4 Hz, 1 H), 2.75 (t, J=12.1 Hz, 1 H), 2.30 (s, 3 H). MS (ESI) 237.3, 239.3 (M − Cl). Anal. ($C_{12}H_{13}ClN_2O\cdot 1.7HCl$), C, H, N.

(*R*)-7-Chloro-10-ethyl-1,3,4,10b-tetrahydropyrazino[2,1-*a*]-isoindol-6(2*H*)-one Hydrochloric Acid Salt (42). Prepared from *N*-(*tert*-butoxycarbonyl)-(±)-7-chloro-1,3,4,10b-tetrahydro-10-trifluoromethanesulfonylpyrazino[2,1-*a*]isoindol-6(2*H*)-one according to the procedures described for compounds **58** and **62**. Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, D_2O) δ 7.35−7.41 (m, 2 H), 4.85 (dd, J = 11.6, 3.7 Hz, 1 H), 4.47 (dd, J = 14.3, 4.2 Hz, 1 H), 4.09 (dd, J = 12.3, 3.9 Hz, 1 H), 3.45−3.55 (m, 2 H), 2.99 (dt, J = 12.5, 4.4 Hz, 1 H),2.75 (t, J = 12.3 Hz, 1 H), 2.52−2.64 (m, 2 H), 1.15 (t, J = 7.5 Hz, 3 H). MS (ESI) 251.3, 253.3 (M − Cl). Anal. ($C_{13}H_{15}ClN_2O\cdot HCl\cdot 1.3H_2O$), C, H, N.

(*R*)-7-Chloro-10-methoxy-1,3,4,10b-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (43). Prepared according to General Procedure B with substitution of 2-chloro-5-methoxybenzoic acid for 2-chlorobenzoic acid. Chiral resolution and deprotection were carried out according to the General Procedure for the preparation of chiral pyrazino[2,1-*a*]isoindol-6(2*H*)-one hydrochloric acid salts (Chiracell OJ chiral column and 15% (1:1) methanol/ethanol in heptane containing 0.1% diethylamine). Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, D_2O) δ 7.43 (d, J = 8.8 Hz, 1 H), 7.14 (d, J = 8.8 Hz, 1 H), 4.80 (dd, J = 11.9, 3.9 Hz, 1 H), 4.44 (dd, J = 14.3, 4.2 Hz, 1 H), 4.15 (dd, J = 12.5, 4.2 Hz, 1 H), 3.84 (s, 3 H), 3.51−3.56 (m, 1 H), 3.42−3.51 (m, 1 H), 3.00 (dt, J = 12.7, 4.4 Hz, 1 H), 2.72 (t, J = 12.1 Hz, 1 H). MS (ESI) 253.3, 255.3 (M − Cl). Anal. ($C_{12}H_{13}ClN_2O_2\cdot HCl\cdot 1.7H_2O$), C, H, N.

(*R*)-10-Chloro-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino-[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (44). Prepared according to General Procedure B and the General Procedure for the preparation of chiral pyrazino[2,1-*a*]isoindol-6(2*H*)-one hydrochloric acid salts (Chiracell OJ chiral column and 20% (1:1) methanol/ethanol in heptane containing 0.1% diethylamine) from 5-chloro-2-trifluoromethylbenzoic acid. Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, D_2O) δ 7.88 (d, J = 8.4 Hz, 1 H), 7.79 (d, J = 8.34 Hz, 1 H), 5.04 (dd, J = 11.9, 3.9 Hz, 1 H), 4.53 (dd, J = 13.2, 3.1 Hz, 1 H), 4.41 (dd, J = 12.5, 4.2 Hz, 1 H), 2.99−3.07 (m, 1 H) 3.49−3.61 (m, 2 H), 2.83 (t, J = 12.1 Hz, 1 H). MS (ESI) 291.3, 293.3 (M − Cl). Anal. ($C_{12}H_{10}ClF_3N_2O\cdot HCl\cdot 0.7H_2O$), C, H, N.

(*R*)-7,8-Dichloro-1,3,4,10b-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (45). Prepared according to General Procedure B with substitution of 2,3-dichlorobenzoic acid for 2-chlorobenzoic acid with chiral resolution and deprotection carried out according to the General Procedure described for compound **29**. Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, D_2O) δ 7.80 (d, J = 8.4 Hz, 1 H), 7.51 (d, J = 8.4 Hz, 1H), 4.88 (dd, J = 11.9, 3.9 Hz, 1H), 4.51 (dd, J = 14.7, 4.2 Hz, 1H), 4.08 (dd, J = 12.3, 3.9 Hz, 1H), 3.51−3.61 (m, 1H), 3.51−3.56 (m, 1H), 3.04 (dt, J = 12.5, 4.4 Hz, 1H), 2.82 (t, J = 12.3 Hz, 1H). MS (ESI) 257 (M − Cl). Anal. ($C_{11}H_{10}Cl_2N_2O\cdot 1.3HCl\cdot 0.5H_2O$), C, H, N.

(*R*)-8-Chloro-7-methoxy-1,3,4,10b-tetrahydropyrazino[2,1-*a*]-isoindol-6(2*H*)-one Hydrochloric Acid Salt (46). Prepared according to General Procedure B with substitution of 3-chloro-2-methoxybenzoic acid[19] for 2-chlorobenzoic acid with chiral resolution and deprotection carried out according to the General Procedure described for compound **29**. Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, D_2O) δ 7.72 (d, J = 7.9 Hz, 1 H), 7.33 (d, J = 8.8 Hz, 1 H), 4.86 (dd, J = 11.9, 3.9 Hz, 1 H), 4.46 (dd, J = 14.5, 3.9 Hz, 1 H), 4.05 (dd, J = 12.5, 4.2 Hz, 1 H), 3.95 (s, 3 H), 3.57 (dd, J = 12.7, 3.5 Hz, 1 H), 3.45−3.53 (m, 1 H), 3.03 (dt, J = 12.6, 4.6 Hz, 1 H), 2.79 (t, J = 12.1 Hz, 1 H). MS (ESI) 253 (M − Cl). Anal. ($C_{12}H_{13}ClN_2O_2\cdot HCl\cdot 0.90H_2O$).

(*R*)-8-Ethyl-7-methoxy-1,3,4,10b-tetrahydropyrazino[2,1-*a*]-isoindol-6(2*H*)-one Hydrochloric Acid Salt (47). Step A. To *N*-(*tert*-butoxycarbonyl)-(±)-8-chloro-7-methoxy-1,3,4,10b-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one (0.55 mg, 1.56 mmoL) prepared from 3-chloro-2-methoxybenzoic acid[18] using General Procedure B was added bis(tri-*tert*-butylphosphine)palladium(0) (32 mg, 0.06 mmol), 2,4,6-trivinylcyclotriboroxane pyridine complex (653 mg, 1.72 mmol), potassium fluoride (633 mg, 11 mmol), and dioxane (16 mL). The mixture was degassed and warmed to reflux. After 6 h, an additional portion of catalyst (32 mg) was added. The reaction was maintained at reflux for another 8 h and was then cooled to room temperature. The mixture was diluted with saturated aqueous sodium hydrogen carbonate and brine before being extracted with EtOAc (×3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, 0−50% EtOAc in hexanes) to afford *N*-(*tert*-butoxycarbonyl)-(±)-8-ethenyl-7-methoxy-1,3,4,10b-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one as a yellow solid (475 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 7.9 Hz, 1 H), 7.04−7.13 (m, 2 H), 5.76 (d, J = 18.9 Hz, 1 H), 5.33 (d, J = 11.0 Hz, 1 H), 4.67 (s, 1 H), 4.29−4.40 (m, 2 H), 4.10 (s, 1 H), 4.04 (s, 3 H), 3.05−3.14 (m, 1 H), 2.72 (s, 1 H), 2.33 (s, 1 H), 1.50 (s, 9 H). MS (ESI) 345.3 (M + H).

Step B. Final product was prepared according to the procedures of compound **58** substituting *N*-(*tert*-butoxycarbonyl)-(±)-8-ethenyl-7-methoxy-1,3,4,10b-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one for *N*-(*tert*-butoxycarbonyl)-(*R*)-9-ethyl-1,3,4,10b-tetrahydro-7-trifluoromethyl-pyrazino[2,1-*a*]isoindol-6(2*H*)-one to yield **47**. Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, D_2O) δ 7.57 (d, J = 7.9 Hz, 1 H), 7.30 (d, J = 7.9 Hz, 1 H), 4.83 (dd, J = 11.8, 4.4 Hz, 1 H), 4.46 (dd, J = 14.7, 4.2 Hz, 1 H), 4.05 (dd, J = 12.3, 3.9 Hz, 1 H), 3.89 (s, 3 H), 3.57 (dd, J = 12.7, 3.9 Hz, 1 H), 3.45−3.53 (m, 1 H), 3.03 (dt, J = 12.6, 4.6 Hz, 1 H), 2.65−2.75 (m, 3 H), 1.15 (t, J = 7.5 Hz, 3 H). MS (ESI) 247 (M − Cl). Anal. ($C_{14}H_{18}N_2O_2\cdot HCl\cdot 1.1H_2O$), C, H, N.

(*R*)-9-Chloro-8-methoxy-1,3,4,10b-tetrahydropyrazino[2,1-*a*]-isoindol-6(2*H*)-one Hydrochloric Acid Salt (48). Prepared according to General Procedure B with substitution of 4-chloro-3-methoxybenzoic acid for 2-chlorobenzoic acid. Chiral resolution and deprotection were carried out according to the General Procedure for the preparation of chiral pyrazino[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric acid salts. Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, D_2O) δ 7.70 (s, 1 H), 7.47 (s, 1 H), 4.86 (dd, J = 11.9, 4.4 Hz, 1 H), 4.44−4.50 (m, 1 H), 4.05 (dd, J = 12.7, 3.9 Hz, 1 H), 3.96 (s, 3 H), 3.53−3.61 (m, 2 H), 3.00−3.08 (m, 1 H), 2.78 (t, J = 12.3 Hz, 1 H). MS (ESI) 253.3, 255.3 (M − Cl). Anal. ($C_{12}H_{13}ClN_2O_2\cdot HCl$), C, H, N.

(*R*)-9-Ethyl-8-methoxy-1,3,4,10b-tetrahydropyrazino[2,1-*a*]-isoindol-6(2*H*)-one Hydrochloric Acid Salt (49). Prepared according to the procedure of compound **47** from *N*-(*tert*-butoxycarbonyl)-(±)-9-chloro-8-methoxy-1,3,4,10b-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one. Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, D_2O) δ 7.44 (s, 1 H), 7.30 (s, 1 H), 4.81 (dd, J = 11.9, 3.9 Hz, 1 H), 4.47 (dd, J = 13.6, 3.5 Hz, 1 H), 4.07 (dd, J = 12.3, 3.9 Hz, 1 H), 3.88 (s, 3 H), 3.50−3.61 (m, 2 H), 3.00−3.09 (m, 1 H), 2.64−2.73 (m, 2 H), 1.15 (t, J = 7.7 Hz, 3 H). MS (ESI) 247.3 (M − Cl). Anal. ($C_{14}H_{18}N_2O_2\cdot HCl$), C, H, N.

(*R*)-7-Chloro-9-methoxy-1,3,4,10b-tetrahydropyrazino[2,1-*a*]-isoindol-6(2*H*)-one Hydrochloric Acid Salt (50). Step A. To a solution of 2-chloro-4-hydroxybenzoic acid hydrate (2.0 g, 12 mmol), iodomethane (2.9 mL, 46 mmol) and *N*,*N*-dimethylformamide (50 mL) was added sodium hydride (1.9 g, 46 mmol; 60% dispersion in mineral oil) in one portion. After the mixture was vigorously stirred for 16 h, the reaction was quenched with water and washed with EtOAc. The aqueous layer was then acidified with aqueous HCl (6 N) to give a white precipitate. The mixture was filtered and washed with water, and the filter cake was dried in a vacuum oven to give the desired acid as an off-white solid (1.4 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.8 Hz, 1H), 6.98 (d, J = 2.6 Hz, 1H), 6.83 (dd, J = 8.8, 2.6 Hz, 1H), 3.85 (s, 3H). MS (ESI) 187.1, 189.1 (M + H).

Step B. Final compound was prepared according to General Procedure B, substituting 2-chloro-4-methoxybenzoic acid for 2-chlorobenzoic acid at Step A with chiral separation according to General Procedures to yield **50**. Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.18 (s, 1 H), 7.12 (d, J = 2.20 Hz, 1 H), 4.76 (dd, J = 11.9, 3.9 Hz, 1 H), 4.52 (dd, J = 14.7, 4.2 Hz, 1 H), 4.03 (dd, J = 12.1, 3.7 Hz, 1 H), 3.90 (s, 3 H), 3.51 (dd, J = 12.5, 3.7 Hz, 1 H), 3.37−3.46 (m, 1 H), 3.02 (dt, J = 12.5, 4.4 Hz, 1 H), 2.79 (t, J = 12.1 Hz, 1 H). MS (ESI) 253.2, 255.2 (M − Cl). Anal. ($C_{12}H_{13}ClN_2O_2\cdot HCl\cdot H_2O$), C, H, N.

(*R*)-7-Chloro-9-ethyl-1,3,4,10b-tetrahydropyrazino[2,1-*a*]-isoindol-6(2*H*)-one HCl (51). Step A. To a stirring solution of 4-bromo-2-chlorobenzoic acid (5.0 g, 21.2 mmol) in dry CH_2Cl_2 (150 mL) was added a 2 M solution of oxalyl chloride in CH_2Cl_2 (21.2 mL). Dry DMF (0.1 mL) was added and the reaction was stirred for 4 h and then concentrated *in vacuo* to a white solid. The solid was dissolved in CH_2Cl_2 (150 mL), and diethylamine (4.8 mL, 46.6 mmol) was added dropwise over 15 min. The reaction was washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (SiO_2, 1:5, EtOAc:hexanes) to yield *N*,*N*-diethyl-4-bromo-2-chlorobenzamide (6.2 g, 100%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 1.8 Hz, 1 H), 7.43 (dd, J = 8.4, 1.8 Hz, 1 H), 7.14 (d, J = 7.9 Hz, 1 H), 3.71−3.82 (m, 1 H), 3.30−3.41 (m, 1 H), 3.07−3.18 (m, 2 H), 1.25 (t, J = 7.0 Hz, 3 H). 1.05 (t, J = 7.5 Hz, 3 H). MS (ESI) 290 (M + H).

Step B. Tetrakis(triphenylphospine)palladium(0) (30 mg, 0.026 mmol) was added in one portion to a degassed mixture of *N*,*N*-diethyl-4-bromo-2-chlorobenzamide (0.6 g, 2.1 mmol), potassium carbonate (0.29 g, 2.1 mmol), and 2,4,6-trivinylcyclotriboroxane pyridine complex (0.78 g, 2.1 mmol) in 1,2-dimethoxyethane (16 mL) and water (5 mL). The mixture was warmed to 100 °C. After 14 h, the reaction was cooled to room temperature, diluted with brine, and extracted with EtOAc (×3), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, 0−50% ethylacetate/hexanes) to give *N*,*N*-diethyl-2-chloro-4-ethenylbenzamide as a off-white solid (0.47 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 1.3 Hz, 1 H), 7.31 (dd, J = 7.9, 1.3 Hz, 1 H), 7.21 (d, J = 7.9 Hz, 1 H), 6.64 (dd, J = 17.6, 11.0 Hz, 1 H), 5.78 (d, J = 17.6 Hz, 1 H), 5.34 (d, J = 11.0 Hz, 1 H), 3.73−3.83 (m, 1 H), 3.35 (dd, J = 13.2, 6.2

Hz, 1 H), 3.15 (dt, J = 11.4, 7.0 Hz, 2 H), 1.25 (t, J = 7.3 Hz, 3 H) 1.05 (t, J = 7.0 Hz, 3 H). MS (ESI) 238 (M + H).

Step C. To *N*,*N*-diethyl-2-chloro-4-ethenylbenzamide (0.15 g, 0.62mmol) was added ethanol (5 mL), and the resulting solution was degassed via alternating exposure to vacuum and argon. To this mixture was added Raney nickel and the black suspension was subjected a hydrogen atmosphere (1 atm). After 3 h, the reaction was filtered and concentrated *in vacuo*, and the resulting yellow residue was purified by radial chromatography (SiO_2, 0−50% EtOAc/hexanes) to afford *N*,*N*-diethyl-2-chloro-4-ethylbenzamide (0.11 g, 70%) as a clear residue. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 1.3 Hz, 1 H), 7.16 (d, J = 7.9 Hz, 1 H), 7.10 (dd, J= 7.9, 1.3 Hz, 1 H), 3.77 (s, 1 H), 3.36 (s, 1 H), 3.15 (qd, J = 7.0, 2.2 Hz, 2 H), 2.63 (q, J = 7.6 Hz, 2 H), 1.20−1.27 (m, 6 H), 1.05 (t, J = 7.0 Hz, 3 H). MS (ESI) 240 (M − Cl).

Step D. (*R*)-7-Chloro-9-ethyl-1,3,4,10b-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one HCl was prepared from *N*,*N*-diethyl-2-chloro-4-ethylbenzamide according to General Procedure B and the General Procedure for the synthesis of chiral pyrazino[2,1-*a*]isoindol-6(2*H*)-one hydrochloric acid salts. Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.47 (s, 1 H), 7.41 (s, 1 H), 4.83 (dd, J = 11.9, 3.9 Hz, 1 H), 4.53 (dd, J = 14.1, 4.4 Hz, 1 H), 4.07 (dd, J = 12.3, 3.94 Hz, 1 H), 3.47−3.56 (m, 2 H), 3.05 (dt, J = 12.2, 4.6 Hz, 1 H), 2.74−2.82 (m, 3 H), 1.29 (t, J = 7.5 Hz, 3 H), MS (ESI) 251 (M − Cl). Anal. ($C_{13}H_{15}ClN_2O\cdot HCl\cdot H_2O$), C, H, N.

(*R*)-9-Acetyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino-[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (53). Step A. To a stirring solution of (*R*)-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one hydrochloric acid salt (688 mg, 2.4 mmol) were added concentrated sulfuric acid (2.4 mL) [conc. sulfuric acid is neat, not aqueous] and *N*-bromosuccinimide (420 mg, 2.4 mmol). The resulting brown solution was covered with aluminum foil and stirred in the dark for 24 h. The reaction was then diluted with ice−water and basified with saturated aqueous sodium bicarbonate. The resulting mixture was diluted with tetrahydrofuran (30 mL) and treated with di-*tert*-butyl dicarbonate (567 mg, 2.6 mmol). After 4 h, the reaction was extracted with EtOAc (3 × 50 mL), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified by radial chromatography (SiO_2, 25% EtOAc in hexanes) to afford *N*-(*tert*-butoxycarbonyl)-(*R*)-9-bromo-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one (878 mg, 85%) as a white foam-like solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1 H), 7.80 (s, 1 H), 4.75 (s, 1H), 4.44 (dd, J = 11.0, 4.4 Hz, 1 H), 4.38 (dd, J = 13.6, 3.1 Hz, 1 H), 4.20 (s, 1 H), 3.10−3.18 (m, 1 H), 2.77 (s, 1 H), 2.37 (s, 1 H), 1.51 (s, 9 H). MS (ESI) 435.2, 437.2 (M + H).

Step B. To a degassed solution of tetrakis(triphenylphospine)-palladium(0) (3 mg, 0.002 mmol) in toluene (2 mL) was added *N*-(*tert*-butoxycarbonyl)-(*R*)-9-bromo-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one (50 mg, 0.12 mmol). The resulting solution was degassed by exposure to vacuum and then an argon atmosphere (×3). To this solution was added tributyl-(1-ethoxyvinyl)tin (0.041 mL, 0.12 mmol). The resulting solution was degassed a final time and was then warmed to reflux. The light yellow solution was maintained at reflux conditions for 14 h and became gray in color. The reaction was cooled and diluted with EtOAc, aqueous HCl (1 N), and saturated aqueous sodium chloride. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified by radial chromatography (SiO_2, 10−30% EtOAc in hexanes) to give a clear residue. To the residue was added concentrated aqueous HCl (1 mL). After 5 min, the solution was concentrated *in vacuo*, diluted with water, and lyophilized to give **53** as a white solid (33 mg, 62%). Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.57 (s, 1 H), 8.41 (s, 1 H), 5.02 (dd, J = 11.6, 3.7 Hz, 1 H), 4.53−4.63 (m, 1 H), 4.23 (dd, J = 12.3, 3.9 Hz, 1 H), 3.51−3.62 (m, 2 H), 3.03−3.13 (m, 1 H), 2.88 (t, J = 12.1 Hz, 1 H), 2.73 (s, 3 H). MS (ESI) 299.3 (M − Cl). Anal. ($C_{14}H_{13}F_3N_2O_2\cdot HCl\cdot 1.3H_2O$), C, H, N.

(*R*)-9-Chloro-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino-[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (52). Step A. To a stirring degassed solution of *N*-(*tert*-butoxycarbonyl)-(*R*)-9-bromo-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one (464 mg, 1.1 mmol) in dry DMF (5 mL) was added copper(I) chloride (211 mg, 2.1 mmol). The reaction was heated to reflux for 4 h and then cooled to room temperature. The reaction was treated with di-*tert*-butyl dicarbonate (350 mg, 1.6 mmol). The reaction was stirred for 1 h and then quenched with 9:1 saturated NH_4Cl:NH_4OH. After 15 min, the reaction was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to a brown oil. The oil was purified by flash chromatography (SiO_2, 0−50% EtOAc in hexanes) to yield 140 mg of a colorless oil. To the oil was added concentrated aqueous HCl (1 mL). After 5 min, the solution was concentrated *in vacuo*, diluted with water, and lyophilized to give **52** as a white solid (114 mg, 36%). Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, D_2O) δ 7.95 (s, 1 H), 7.90 (s, 1 H), 4.97 (dd, J = 11.9, 3.9 Hz, 1 H), 4.50 (dd, J = 14.3, 4.2 Hz, 1 H), 4.10 (dd, J = 12.5, 4.2 Hz, 1 H), 3.60 (dd, J = 12.7, 3.5 Hz, 1 H), 3.48−3.57 (m, 1 H), 3.03 (dt, J = 12.7, 4.4 Hz, 1 H), 2.82 (t, J = 12.3 Hz, 1 H), MS (ESI) 291 (M − Cl). Anal. ($C_{12}H_{10}ClF_3N_2O_2\cdot HCl\cdot 1.5H_2O$), C, H, N.

(*R*)-9-Hydroxymethyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (54). To a stirring solution of *N*-(*tert*-butoxycarbonyl)-(*R*)-9-(*cis*-1-propenyl)-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one (182 mg, 0.46 mmol) in MeOH (5.0 mL) at −78 °C was bubbled ozone for 5 min until the reaction turned a light blue color. After 5 min, sodium borohydride (23 mg, 0.6 mmol) was added. The reaction was stir for 1 h and then warmed to room temperature. The reaction was concentrated *in vacuo* to a white solid and then dissolved in 1 M aq HCl. After 15 min, the reaction was diluted with EtOAc, basified with $NaHCO_3$, and treated with di-*tert*-butyl dicarbonate (125 mg, 0.58 mmol). After 1 h, the reaction was extracted with EtOAc (3 × 5 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to a colorless oil. The oil was purified by flash chromatography (silica gel, 0−50% EtOAc in hexanes) to give 141 mg of a white solid. To 14 mg of the white solid was added concentrated aqueous HCl (1 mL). After 5 min, the solution was concentrated *in vacuo*, diluted with water, and lyophilized to give **54** as a white solid (11 mg). Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, D_2O) δ 7.90 (s, 1 H), 7.84 (s, 1 H), 4.99 (dd, J = 11.9, 3.9 Hz, 1 H), 4.79 (s, 2 H), 4.53 (dd, J = 14.5, 4.4 Hz, 1 H), 4.15 (dd, J = 12.3, 3.9 Hz, 1 H), 3.50−3.65 (m, 2 H), 3.06 (dt, J = 12.3, 4.4 Hz, 1 H,) 2.83 (t, J = 12.1 Hz, 1 H). MS (ESI) 287 (M − Cl). ($C_{13}H_{13}F_3N_2O_2\cdot 1.25HCl\cdot 0.5H_2O$), C, H, N.

(*R*)-9-Methoxy-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino-[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (55). Step A. To a stirring degassed solution of *N*-(*tert*-butoxycarbonyl)-(*R*)-9-bromo-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one (435 mg, 1.0 mmol), bis(pinacolato)diboron (279 mg, 1.1 mmol), and potassium acetate (294 mg, 3.0 mmol) in dry DMF (5.0 mL) was added palladium(II) acetate (6.7 mg, 0.03 mmol). The reaction was heated to 80 °C for 2 h and then cooled to room temperature. The reaction was quenched with water and extracted with EtOAc (3 × 5 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to a brown oil. The oil was dissolved in THF (5 mL) and acetic acid (0.05 mL) and treated with hydrogen peroxide (0.25 mL). The reaction was stirred for 15 min and then quenched with saturated aqueous $NaHSO_3$. The reaction was extracted with EtOAc (3 × 5 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to a brown oil. The oil was purified by flash chromatography (SiO_2, 0−70% EtOAc in hexanes) to give 347 mg of *N*-(*tert*-butoxycarbonyl)-(*R*)-9-methoxy-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.86 (s, 1 H), 7.28 (s, 2 H), 7.17

(s, 2 H), 4.56 (s, 1 H), 4.48 (dd, J = 10.6, 3.9 Hz, 1 H), 4.08 (dd, J = 12.7, 3.5 Hz, 1 H), 4.01 (d, J = 7.0 Hz, 1 H), 3.03 (dt, J = 12.7, 3.9 Hz, 1 H), 2.64−2.76 (m, 1 H), 2.38 (s, 1 H), 1.44 (s, 9 H). MS (ESI) 373 (M + H).

Step B. To a stirring degassed solution of *N*-(*tert*-butoxycarbonyl)-(*R*)-9-methoxy-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino-[2,1-*a*]isoindol-6(2*H*)-one (58 mg, 0.16 mmol), and potassium carbonate (33 mg, 0.24 mmol) in dry DMF (1.0 mL) was added methyl iodide (24 mg, 0.17 mmol). The reaction was stirred for 2 h and then quenched with brine. The reaction was extracted with EtOAc (3 × 5 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to a pale yellow oil. The oil was purified by flash chromatography (SiO_2, 0−50% EtOAc in hexanes) to give 41 mg of a colorless oil. To the oil was added concd aq HCl (1 mL). After 5 min, the solution was concentrated *in vacuo*, diluted with water, and lyophilized to give **54** as a white solid (30 mg, 50%). Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, D_2O) δ ppm 7.44 (s, 1 H), 7.38 (s, 1 H), 4.93 (d, J = 11.9 Hz, 1 H), 4.49 (dd, J = 14.7, 4.2 Hz, 1 H), 4.09 (dd, J = 12.7, 3.9 Hz, 1 H), 3.92 (s, 3 H), 3.60 (dd, J = 12.7, 3.5 Hz, 1 H), 3.48−3.56 (m, 2 H), 3.04 (dt, J = 12.6, 4.2 Hz, 1 H), 2.82 (t, J = 12.1 Hz, 1 H). MS (ESI) 287 (M − Cl). Anal. ($C_{13}H_{13}F_3N_2O_2$·HCl·H_2O), C, H, N.

(*R*)-9-Ethoxy-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino-[2,1-*a*]isoindol -6(2*H*)-one Hydrochloric Acid Salt (56). Prepared according to procedures described for compound **55** with substitution of ethyl iodide for methyl iodide in Step B. Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, D_2O) δ 7.43 (s, 1 H), 7.35 (s, 1 H), 4.91 (dd, J = 11.9, 3.9 Hz, 1 H), 4.49 (dd, J = 14.7, 4.2 Hz, 1 H), 4.20 (q, J = 7.0 Hz, 2 H), 4.08 (dd, J = 12.5, 4.2 Hz, 1 H), 3.59 (dd, J = 12.7, 3.5 Hz, 1 H), 3.47−3.55 (m, 1 H), 3.03 (dt, J = 12.6, 4.6 Hz, 1 H), 2.81 (t, J = 12.3 Hz, 1 H), 1.38 (t, J = 7.0 Hz, 3 H). MS (ESI) 301 (M − Cl). Anal. ($C_{14}H_{15}F_3N_2O_2$·HCl·1.2H_2O), C, H, N.

(*R*)-9-Ethenyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino-[2,1-*a*]isoindo l-6(2*H*)-one Hydrochloric Acid Salt (62). Tetrakis-(triphenylphospine)palladium(0) (305 mg, 0.26 mmol) was added in one portion to a degassed mixture of *N*-(*tert*-butoxycarbonyl)-(*R*)-9-bromo-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]-isoindol-6(2*H*)-one (4.6 g, 11 mmol), potassium carbonate (1.8 g, 13 mmol), and 2,4,6-trivinylcyclotriboroxane pyridine complex (4.2 g, 11 mmol) in 1,2-dimethoxyethane (80 mL) and water (25 mL). The mixture was warmed to 100 °C. After 1 h, the reaction was cooled to room temperature, diluted with brine, and extracted with EtOAc (×3), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, 0−50% ethyl acetate/hexanes) to as a off-white solid (3.53 g, 87%). To 15 mg of white solid was added concentrated aqueous HCl (1 mL). After 5 min, the solution was concentrated *in vacuo*, diluted with water, and lyophilized to give **62** as a white solid (11 mg). Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (s, 1 H), 7.94 (s, 1 H), 6.94 (dd, J = 17.6, 11.0 Hz, 1 H), 6.11 (d, J = 17.6 Hz, 1 H), 5.56 (d, J = 11.0 Hz, 1 H), 4.88−4.93 (m, 1 H), 4.55 (dd, J = 14.3, 4.2 Hz, 1 H,) 4.14 (dd, J = 12.3, 3.9 Hz, 1 H), 3.52−3.58 (m, 1 H), 3.45−3.50 (m, 1 H), 3.06 (dt, J = 12.2, 4.2 Hz, 1 H), 2.85 (t, J = 12.1 Hz, 1 H). MS (ESI) 283 (M − Cl). Anal. ($C_{14}H_{13}F_3N_2O$·1.3HCl·2H_2O), C, H, N.

(*R*)-9-Ethyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino-[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (58). To *N*-(*tert*-butoxycarbonyl)-(*R*)-9-ethenyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one (3.53 mg, 9.22) was added methanol (50 mL), and the resulting solution was degassed via alternating exposure to vacuum and argon. To this solution was added 10% palladium on carbon (300 mg, 10 wt %), and the black suspension was subjected a hydrogen atmosphere (1 atm). After 1 h, the reaction was filtered and concentrated *in vacuo*, and the resulting yellow residue was purified by flash column chromatography (SiO_2, 0−50% EtOAc/hexanes) to afford a white foam solid (3.1 g, 87%). To the 21 mg of white solid was added concentrated aqueous HCl (1 mL). After 5 min, the solution was concentrated *in vacuo*, diluted with water, and lyophilized to give **58** as a white solid (17 mg). Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (500 MHz, CD_3OD) δ 7.80 (s, 1 H), 7.75 (s, 1 H), 4.87−4.90 (m, 1 H), 4.53 (dd, J = 14.1, 4.4 Hz, 1 H), 4.11 (dd, J = 12.3, 3.9 Hz, 1 H), 3.51−3.56 (m, 1 H), 3.44−3.49 (m, 1 H), 2.99−3.08 (m, 1 H), 2.87 (q, J = 7.5 Hz, 2 H), 2.80 (t, J = 12.1 Hz, 1 H), 1.31 (t, J = 7.7 Hz, 3 H). ^{13}C (100 MHz, d_6-DMSO) δ 162.0 (s, 1H), 148.8 (s, 1H), 144.8 (s, 1H), 126.6 (s, 1H), 126.1 (s, 1H), 126.0 (s, 1H), 125.0 (q, J = 33.6 Hz, 1H), 122.9 (q, J = 271.0 Hz, 1H), 53.0 (s, 1H), 45.8 (s, 1H), 41.8 (s, 1H), 35.6 (s, 1H), 28.1 (s, 1H), 15.1 (s, 1H). MS (ESI) 271.3 (M + H). $[\alpha]_D$ −23.3 (0.660 g/dL, MeOH). Anal. ($C_{14}H_{15}F_3N_2O$·HCl), C, H, N.

(*R*)-9-Methyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino-[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (57). Prepared according to procedures described for compound **62** with substitution of trimethylboroxine for 2,4,6-trivinylcyclotriboroxane pyridine complex. Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, CD_3OD) 7.76 (s, 1 H), 7.66 (s, 1 H), 4.92 (dd, J = 11.9, 3.9 Hz, 1 H), 4.51 (dd, J = 14.7, 4.2 Hz, 1 H), 4.10 (dd, J = 12.3, 4.4 Hz, 1 H), 3.60 (dd, J = 12.7, 3.9 Hz, 1 H), 3.48−3.57 (m, 1 H), 3.04 (dt, J = 12.6, 4.2 Hz, 1 H), 2.79 (t, J = 12.3 Hz, 1 H), 2.48 (s, 3 H). MS (ESI) 271 (M − Cl). Anal. ($C_{13}H_{13}F_3N_2O$·HCl·0.7H_2O), C, H, N.

(*R*)-9-Propyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino-[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (59). Prepared according to the procedures of compound **62** and **58** with the substitution of *cis*-1-propenylboronic acid for 2,4,6-trivinylcyclotriboroxane pyridine complex. Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.79 (s, 1 H), 7.73 (s, 1 H), 4.88−4.92 (m, 1 H), 4.54 (dd, J = 13.8, 4.2 Hz, 1 H), 4.13 (dd, J = 12.3, 3.9 Hz, 1 H), 3.46−3.58 (m, 2 H), 3.00−3.09 (m, 1 H), 2.77−2.85 (m, 3 H), 1.68−1.77 (m, 2 H), 0.98 (t, J = 7.5 Hz, 3 H). MS (ESI) 299.3 (M − Cl). Anal. ($C_{15}H_{17}F_3N_2O$·HCl·0.4H_2O), C, H, N.

(*R*)-9-Butyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino-[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (60). Prepared according to procedures described in Example **62** with substitution of n-butylboronic acid for *cis*-1-propenylboronic acid and 1,1′-bis-(diphenylphosphino)ferrocene palladium(II) dichloride dichloromethane complex for tetrakis(triphenylphosphine)-palladium(0). Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, D_2O) δ 7.76 (s, 1 H), 7.67 (s, 1 H), 4.91 (dd, J = 11.9, 3.9 Hz, 1 H), 4.50 (dd, J = 14.5, 3.9 Hz, 1 H), 4.09 (dd, J = 12.5, 4.2 Hz, 1 H), 3.59 (dd, J = 12.7, 3.9 Hz, 1 H), 3.47−3.56 (m, 1 H), 3.03 (dt, J = 12.5, 4.4 Hz, 1 H), 2.72−2.82 (m, 3 H), 1.55−1.64 (m, 2 H), 1.25 (dq, J = 14.9, 7.5 Hz, 2 H), 0.84 (t, J = 7.0 Hz, 3 H). MS (ESI) 313 (M − Cl). Anal. ($C_{16}H_{19}F_3N_2O$·HCl·1.1H_2O), C, H, N.

(*R*)-9-Isopropyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino-[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (61). Prepared according to procedures described for compound **62** and **58** with substitution of isopropenylboronic acid for 2,4,6-trivinylcyclotriboroxane pyridine complex. Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, D_2O) δ 7.82 (s, 1 H), 7.74 (s, 1 H), 4.93 (dd, J = 11.9, 3.9 Hz, 1 H), 4.51 (dd, J = 14.9, 3.9 Hz, 1 H), 4.11 (dd, J = 12.3, 3.5 Hz, 1 H), 3.62 (d, J = 2.6 Hz, 1 H), 3.54−3.64 (m, 1 H), 3.47−3.53 (m, 1 H), 3.00−3.13 (m, 1 H), 2.78 (t, J = 12.1 Hz, 1 H), 1.24 (d, J = 7.0 Hz, 6 H). MS (ESI) 299 (M − Cl). Anal. ($C_{15}H_{18}F_3N_2O$·1.6HCl·H_2O), C, H, N.

(*R*)-9-Ethynyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino-[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (63). To a stirring solution of *N*-(*tert*-butoxycarbonyl)-(*R*)-1,3,4,10b-tetrahydro-9-trimethylsilylethynyl-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one (44 mg, 0.1 mmol) [prepared according to procedures described for compound **52** with substitution of tributyl(trimethylsilylethynyl)tin for tributyl(1-ethoxyvinyl)tin] in MeOH (1.0 mL) was added potassium carbonate (13 mg, 0.1 mmol). The reaction was stirred for 5 min and then quenched with brine. The reaction was extracted with EtOAc (2 × 5 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to a pale

yellow oil. The oil was purified by radial chromatography (SiO_2, 30% EtOAc in hexanes) to give 27 mg of a pale yellow oil. To the oil was added concentrated aqueous HCl (1 mL). After 5 min, the solution was concentrated *in vacuo*, diluted with water, and lyophilized to give **59** as a white solid (21 mg). Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.05 (s, 1 H), 7.96 (s, 1 H), 4.90 (dd, J = 11.6, 4.2 Hz, 1 H), 4.55 (dd, J = 14.1, 3.9 Hz, 1 H), 4.11 (dd, J = 12.3, 3.9 Hz, 1 H), 4.00 (s, 1 H), 3.51−3.57 (m, 1 H), 3.44−3.49 (m, 1 H), 3.05 (dt, J = 12.4, 4.6 Hz, 1 H), 2.85 (t, J=12.1 Hz, 1 H). MS (ESI) 281 (M − Cl). Anal. ($C_{14}H_{11}F_3N_2O$·HCl·1.1H_2O), C, H, N.

(*R*)-9-Cyclopropyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (64). Prepared according to procedures described for compound **62** with substitution of 2-cyclopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane for 2,4,6-trivinylcyclotriboroxane pyridine complex and 1,1′-bis(diphenylphosphino)ferrocene palladium(II) dichloride dichloromethane complex for tetrakis(triphenylphosphine)palladium(0). Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, D_2O) δ 7.62 (s, 1 H), 7.52 (s, 1 H), 4.90 (dd, J = 12.1, 4.2 Hz, 1 H), 4.50 (dd, J = 14.7, 4.2 Hz, 1 H), 4.08 (dd, J = 12.3, 4.4 Hz, 1 H), 3.56−3.62 (m, 1 H), 3.47−3.56 (m, 1 H), 3.03 (dt, J = 12.6, 4.6 Hz, 1 H), 2.77 (t, J = 14.0 Hz, 1H), 2.07−2.13 (m, 1 H), 1.09−1.14 (m, 2 H), 0.81−0.85 (m, 2 H). MS (ESI) 297 (M − Cl). Anal. ($C_{15}H_{15}F_3N_2O$·HCl·0.9H_2O), C, H, N.

(*R*)-9-(1-Methylcyclopropyl)-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino[2,1-*a*]isoindol-6(2*H*)-one Hydrochloric Acid Salt (65). To a stirring degassed solution of *N*-(*tert*-butoxycarbonyl)-(*R*)-9-isopropenyl-1,3,4,10b-tetrahydro-7-trifluoromethylpyrazino-[2,1-*a*]isoindol-6(2*H*)-one (185 mg, 0.47 mmol) and palladium(II) acetate (1 mg, 0.004 mmol) in CH_2Cl_2 (1 mL) under Ar was added a 0.5 M solution of diazomethane in ether (2.6 mL). After 1 h, the reaction was warmed to room temperature for 16 h. The addition of diazomethane was repeated twice more. The reaction was filtered and then concentrated *in vacuo* to a pale yellow oil. The oil was dissolved in acetone (2 mL) and treated with 4-methylmorpholine *N*-oxide (55 mg, 0.47 mmole) and osmium tetraoxide in water (1.0 mg in 0.16 mL). The reaction was stirred for 1 h and then quenched with sat. aq Na_2SO_3. The reaction was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo* to a pale yellow oil. The oil was purified by flash chromatography (SiO_2, 0−50% EtOAc in hexanes) to yield a colorless oil (83 mg, 43%). To the oil was added concentrated aqueous HCl (1 mL). After 5 min, the solution was concentrated *in vacuo*, diluted with water, and lyophilized to give **65** as a white solid (63 mg). Enantiomeric excess >99:1 based on chiral HPLC. ^{1}H NMR (400 MHz, D_2O) δ 7.75 (s, 1 H), 7.71 (s, 1 H), 4.89 (dd, J = 11.9, 3.9 Hz, 1 H), 4.49 (dd, J = 14.5, 4.4 Hz, 1 H), 4.08 (dd, J = 12.3, 3.9 Hz, 1 H), 3.49−3.60 (m, 2 H), 3.01 (dt, J = 12.5, 3.9 Hz, 1 H), 2.75 (t, J = 12.3 Hz, 1 H), 1.40 (s, 3 H), 0.92−0.98 (m, 2 H), 0.87−0.91 (m, 2 H). MS (ESI) 311 (M − Cl). Anal. ($C_{16}H_{17}F_3N_2O$·HCl·1.6H_2O), C, H, N.

Binding Assays for the 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$ Receptors. Radioligand binding studies were conducted to determine the binding affinities (K_i values) of compounds for the human recombinant 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$ receptors stably expressed in HEK293E cell line.[20] Assays were conducted in disposable polypropylene 96-well plates (Costar Corp., Cambridge, MA) and were initiated by the addition of 5-HT$_{2A}$,5-HT$_{2B}$, or 5-HT$_{2C}$ membrane homogenate in tissue buffer (10−30 μg/well) to assay buffer (50 mM Tris HCl, 0.5 mM EDTA, 10 mM pargyline, 10 mM $MgSO_4$, 0.05% ascorbic acid, pH 7.5) containing [^{125}I]DOI for the 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors (0.3−0.5 nM, final) or [^{3}H]-LSD (1−2.0 nM, final) for the 5-HT$_{2B}$ receptor, with or without competing drug. For a typical competition experiment, a fixed concentration of radioligand was competed with duplicate concentrations of compound (12 concentrations ranging from 10 pM to 10 μM). The reaction mixtures were incubated to equilibrium for 45 min at 37 °C and terminated by rapid filtration (Packard cell harvester; Perkin-Elmer) over GFF glass-fiber filters that had been presoaked in 0.3% polyethyleneimine. Filters were washed in ice-cold 50 mM Tris HCl buffer (pH 7.5) prior to determining radioactivity content on a Top Count (Packard).

Functional Assays for the 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$ Receptors. HEK293E cells stably expressing the human 5-HT$_{2A}$, 5-HT$_{2C}$, or 5-HT$_{2B}$ receptors were maintained Dulbecco's modified Eagle's media with high glucose (DMEM; Gibco BRL) containing 10% dialyzed fetal bovine serum (FBS) and 500 μg/mL G418 (Gibco BRL). The cells was lifted with 2 mL Cellstripper (Mediatech/Cellgro) and plated at a density of 20 000 cells/25 μL/well onto poly-D-lysine-coated 384-well plates (Biocoat; Becton Dickinson, Bedford, MA) in phenol red free Dulbecco's modified Eagle's media (DMEM; Gibco BRL) containing a high concentration of glucose without FBS. Following an overnight (~15−18 h) incubation at 37 °C, the cell plates were removed from the incubator and dye loading buffer (25 μL of 1x Hanks BSS without calcium and magnesium with 25 mM HEPES) containing 5 μM of the calcium dye reagent Fluo-4 was added to each well. Following the dye loading of the cells for 1 h at room temperature, the cell plates were transferred to the FLIPR^{384} (Molecular Devices, Sunnyvale, CA). Eleven concentrations of test compounds in 25 μL loading buffer were added to the cell plate on the FLIPR^{384} to determine a concentration−response curve, and the changes in fluorescence units due to the elevation of intracellular calcium were monitored for a period of 90 s. The raw data from time sequence recording was normalized to the percentage response obtained from the positive control (Serotonin 3 μM) on the same plate and analyzed to fit the four-parameter logistic equation in order to assess the compound's potency (EC_{50}) and efficacy (intrinsic activity) from the 384-FLIPR agonist assay.

Rat Pharmacokinetic Study. Male Sprague Dawley rats (Charles River, MA) weighing between 200 and 250 g were used. Animals were allowed free access to a standard laboratory chow and water. They were housed in a constant temperature−humidity environment. Three rats were used in each of the iv and oral (po) arms of the studies. Doses of 4.4 mg/kg and 8.86 mg/kg were administered via iv and po routes, respectively. The vehicle consisted of polyethylene glycol 400:Tween 80:water (15:1:84, v/v). Blood was sampled from the jugular vein at 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 24 h postdose. Plasma was obtained after centrifugation of the blood samples. Following protein precipitation using acetonitrile and subsequent centrifugation, samples were analyzed using LC/MS−MS.

Rat 20 h Operant Feeding Assay. Compounds were assessed for their ability to reduce food consumption during a 20 h period, which began at the onset of the dark cycle. Male Sprague−Dawley rats, obtained from Charles River Laboratories, were trained in operant chambers (Coulbourn Instruments, Allentown, Pa) equipped with a lever, a food hopper, a water bottle with photocells, and an infrared activity monitor. Rats were trained on a fixed ratio three (FR3) response paradigm which required three consecutive bar presses in order to obtain a food pellet (Research Diets purified food pellet). The number of bar presses and pellets consumed serve as the measure of food intake by the animal. Rats (n = 6) were administered (po) test compound or vehicle (14% PPG, 1% Tween, 85% water, v/v) 60 min prior to the onset of the dark cycle. Treated animals were then placed in individual operant boxes for 20 h period (12 h of dark cycle and the first 8 h of the light cycle). Percent reduction in food intake was calculated as the ratio of total food intake of drug-treated animals divided to the total food intake of vehicle-treated counterparts. Simultaneous measurements of water intake and locomotor activity are also measured during the period to evaluate potential adverse effects.

Rat 4-Day Body Weight Loss Model. Male Sprague Dawley (Charles River Breeding Laboratory) rats weighing approximately 240 g were placed in individual plastic cages with AlphaDri bedding. There were eight rats per treatment group. The room was maintained at 72 °F and 50% humidity, and a 12/12 light-dark cycle with lights out at 1600 h. The rats were conditioned for 5 days prior to the start of the study to have a choice of two diets: (1) standard chow (Harlan Teklad, 2018) containing 18% protein, 5% fat, and 73% carbohydrate and (2) a high fat, high sugar diet

(Research Diets (D2327) containing 20% protein, 40% fat, and 40% carbohydrate where the carbohydrate is entirely sucrose and the fat is soybean and coconut oil. Drug treatment was po at 2.0 mL/kg as a solution in 15% propylene glycol, 1% Tween 80 in water at 1500 h beginning on day 0, and continuing daily through day 4. Body weight and consumption of both diets and water were measured daily. Water was available ad libitum throughout the study. Body weight data was converted to percent change from baseline where baseline body weight was measured prior to drug treatment on day 0 of the study. Differences between dose groups at specified time points were analyzed using ANOVA followed by Fisher's PLSD as the posthoc measure for dose differences.

Gastric Parietal Cell Necrosis Assay. Male CD-1 mice, obtained from Charles River Laboratories, received a single oral dose (by gavage) of 0, 30, 100, 200, or 300 mg/kg ($n = 5$/group) of an experimental compound or an internal tetracyclic indoline, as a positive control. Control animals were dosed with vehicle (aqueous 1% Tween 80/14% propylene glycol; 5 mL/kg). Mice were euthanized 24-h after dosing, and a blood sample was collected to determine plasma concentrations. Stomachs were removed, cleaned, and fixed in formalin prior to routine processing for histopathology evaluation following staining with hematoxylin and eosin (H&E).

Acknowledgment. The authors thank Cindy Li for assistance in structural elucidations.

Supporting Information Available: Table of combustion analysis and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) National Center for Health Statistics. http://www.cdc.gov/nchs/fastats/overwt.htm (accessed Sept 2006).
(2) Eckel, R. H.; York, D. A.; Rossner, S.; Hubbard, V.; Caterson, I.; St. Joer, S. T.; Hayman. L. L.; Mullis, R. M.; Blair, S. N. Prevention conference VII: Obesity, a worldwide epidemic related to heart disease and stroke: executive summary. *Circulation* **2004**, *110*, e463−e470.
(3) Ogden, C. L.; Carroll, M. D.; Flegal, K. M. Epidemiologic trends in overweight and obesity. *Endocrinol. Metab. Clin. North Am.* **2003**, *32*, 741−760.
(4) El-Atat, F.; Aneja, A.; McFarlane, S.; Sowers, J. Obesity and hypertension. *Endocrinol. Metab. Clin. North Am.* **2003**, *32*, 823−854.
(5) Tuthill, A.; Slawik, H.; O'Rahilly, S.; Finer, N. Psychiatric comorbidities in patients attending specialist obesity services in the UK. *Q. J. Med.: Monthly J. Assoc. Physicians* **2006**, *99*, 317−325.
(6) Vickers, S. P; Benwell, K. R.; Porter, R. H.; Bickerdike, M. J.; Kennett, G. A.; Dourish, C. T. Comparative effects of continuous infusion of mCPP, Ro 60-0175. and d-fenfluramine on food intake, water intake, body weight and locomotor activity in rats. *Br. J. Pharmacol.* **2000**, *130*, 1305−1314.
(7) Kennett, G. A.; Wood, M. D.; Bright, F.; Trail, B.; Riley, G.; Holland, V.; Avenell, K. Y.; Stean, T.; Upton, N.; Bromidge, S.; Forbes, I. T.; Brown, A. M.; Middlemiss, D. N.; Blackburn, T. P. SB 242084, a selective and brain penetrant 5-HT$_{2C}$ receptor antagonist. *Neuropharmacology* **1997**, *36*, 609−620.
(8) Tecott, L. H.; Sun, L. M.; Akana, S. F.; Strack, A. M.; Lowenstein, D. H.; Dallman, M. F.; Julius, D. Eating disorder and epilepsy in mice lacking 5-HT$_{2C}$ serotonin receptors. *Nature* **1995**, *374*, 542−546.
(9) (a) Walsh, A. E.; Smith, K. A.; Oldman, A. D.; Williams, C.; Goodall, E. M.; Cowen, P. J. m-Chlorophenylpiperazine decreases food intake in a test meal. *Psychopharmacology* **1994**, *116* (1), 120−122. (b) Sargent, P. A.; Sharpley, A. L.; Williams, C.; Goodall, E. M.; Cowen, P. J. 5-HT$_{2C}$ receptor activation decreases appetite and body weight in obese subjects. *Psychopharmacology* **1997**, *133*, 309−312.
(10) (a) Lacivita, E.; Leopoldo, M. Selective agents for serotonin2C (5-HT$_{2C}$) receptor. *Curr. Topics in Med. Chem.* **2006**, *6* (18), 1927−1970. (b) Nilsson, B. M. 5 -Hydroxytryptamine 2C (5-HT$_{2C}$) receptor agonists as potential antiobesity agents. *J. Med. Chem.* **2006**, *49*, 4023−4034. (c) Fitzgerald, L. W.; Ennis, M. D. 5-HT$_{2C}$ receptor modulators: progress in development of new CNS medicines. *Annu. Rep. Med. Chem.* **2002**, *37*, 21−30.
(11) (a) Fitzgerald, L. W.; Burn, T. C.; Brown, B. S.; Patterson, J. P.; Corjay, M. H.; Valentine, P. A.; Sun, J.-H.; Link, J. R.; Abbaszade, I.; Hollis, J. M.; Largent, B. L.; Hartig, P. R.; Hollis, G. F.; Meunier, P. C.; Robichaud, A. J.; Robertson, D. W. Possible role of valvular serotonin 5-HT2B receptors in the cardiopathy associated with fenfluramine. *Mol. Pharmacol.* **2000**, *57*, 75−81. (b) Rothman, R. B.; Baumann, M. H.; Savage, J. E.; Rauser, L.; McBride, A.; Hufeisen, S. J.; Roth, B. L. Evidence for possible involvement of 5-HT$_{2B}$ receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. *Circulation* **2000**, *102*, 2836−2841. (c) Xu, J.; Jian, B.; Chu, R.; Lu, Z.; Li, Q.; Dunlop, J.; Rosenzweig-Lipson, S.; McGonigle, P.; Levy, R. J.; Liang, B. Serotonin mechanisms in heart valve disease II: The 5-HT2 receptor and its signaling pathway in aortic valve interstitial cells. *Am. J. Pathol.* **2002**, *161*, 2209−2218.
(12) (a) Robichaud, A. J.; Chen, W.; McClung, C.; McClung, C.; Clark, D.; Deng, W.; Brondyke-Calvello, E.; Mitchell, I. S.; Lee, T.; Rajagopalan, P.; Fitzgerald, L. W.; Conklin, D. S.; McElroy, J. F.; Rohrbach, K. W.; Miller, K. J.; Largent, B. L.; Robertson, D. W. Synthesis and biological evaluation of novel, selective 5-HT2C receptor agonists for the treatment of obesity. *Abstracts of Papers*; 221st American Chemical Society National Meeting, San Diego, CA, American Chemical Society: Washington, DC, 2001, MEDI-105. (b) Lee, T.; Robichaud, A. J.; Chen, W.; Lu, Y.; Dowdell, S.; Boyle, K. E.; Mitchell, I. S.; Fevig, J. M.; Wexler, R. R.; Miller, K. J.; Largent, B. L.; Rohrbach, K. W.; Devenny, J. J.; McElroy, J. F. Synthesis and biological evaluation of novel, selective 5-HT$_{2C}$ receptor agonists for obesity. *Abstracts of Papers*; 229th American Chemical Society National Meeting, San Diego, CA; American Chemical Society: Washington, DC, 2005; MEDI-283.
(13) Richter, H. G. F.; Adams, D. R.; Benardeau, A.; Bickerdike, M. J.; Bentley, J. M.; Blench, T. J.; Cliffe, I. A.; Dourish, C.; Hebeisen, P.; Kennett, G. A.; Knight, A. R.; Malcolm, C. S.; Mattei, P.; Misra, A.; Mizrahi, J.; Monck, N. J. T.; Plancher, J.-M.; Roever, S.; Roffey, J. R. A.; Taylor, S.; Vickers, S. P. Synthesis and biological evaluation of novel hexahydro-pyrido[3′,2′:4,5]pyrrolo[1,2-a]pyrazines as potent and selective 5-HT$_{2C}$ receptor agonists. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1207−1211.
(14) Welch, W. M. Synthesis of the 1,2,3,4-tetrahydropyrazino[2,1-*a*]-isoindol-6(2*H*)-one ring system. *J. Org. Chem.* **1982**, *47*, 886−888.
(15) Absolute stereochemistry was determined from the (*S*)-10-camphorsulfamide of compound **30** and correlated to all other compounds by chiral HPLC retention times. Crystallographic data (excluding structure factors) for compound **30** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 632659. Copies of the data can be obtained free of charge upon application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (Fax: (+44)1223-336-033. E-mail: deposit@ccdc.cam.ac.uk).
(16) Bromidge, S. M.; Dabbs, S.; Davies, D. T.; Davies, S.; Duckworth, D. M.; Forbes, I. T.; Gaster, L. M.; Ham, P.; Jones, G. E.; King, F. D.; Mulholland, K. R.; Saunders, D. V.; Wyman, P. A.; Blaney, F. E.; Clarke, S. E.; Blackburn, T. P.; Holland, V.; Kennett, G. A.; Lightowler, S.; Middlemiss, D. N.; Trail, B.; Riley, G. J.; Wood, M. D. Biarylcarbamoylindolines Are Novel and Selective 5-HT2C Receptor Inverse Agonists: Identification of 5-Methyl-1-[[2-[(2-methyl-3-pyridyl)oxy]-5-pyridyl]carbamoyl]-6-trifluoromethylindoline (SB-243213) as a Potential Antidepressant/Anxiolytic Agent. *J. Med. Chem.* **2000**, *43*, 1123−1134.
(17) Alongi, M.; Minetto, G.; Taddei, M. New pyrrole-based amino acids for the synthesis of peptidomimetic constrained scaffolds. *Tetrahedron Lett.* **2005**, *46*, 7069−7072.
(18) Pittelkow, M.; Lewinsky, R.; Christensen, J. B. Selective synthesis of carbamate protected polyamines using alkyl phenyl carbonates. *Synthesis* **2002**, 2195−2202.
(19) Short, J. H. Antiemetic and antipsychotic agents. U.S. Patent 4 470 977, 1984.
(20) Fitzgerald, L. W.; Conklin, D. S.; Krause, C. M.; Marshall, A. P.; Patterson, J. P.; Tran, D. P.; Iyer, G.; Kostich, W. A.; Largent, B. L.; Hartig, P. R. High-affinity agonist binding correlates with efficacy (intrinsic activity) at the human serotonin 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors: evidence favoring the ternary complex and two-state models of agonist action. *J. Neurochem.* **1999**, *72*, 2127−2134.

JM0612968