Discovery and Structure−Activity Relationship of (1*R*)-8-Chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (Lorcaserin), a Selective Serotonin 5-HT_{2C} Receptor Agonist for the Treatment of Obesity

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The synthesis and SAR of a novel 3-benzazepine series of 5-HT_{2C} agonists is described. Compound **7d** (lorcaserin, APD356) was identified as one of the more potent and selective compounds in vitro (pEC_{50} values in functional assays measuring [^{3}H]phosphoinositol turnover: 5-HT_{2C} = 8.1; 5-HT_{2A} = 6.8; 5-HT_{2B} = 6.1) and was potent in an acute in vivo rat food intake model upon oral administration (ED_{50} at 6 h = 18 mg/kg). Lorcaserin was further characterized in a single-dose pharmacokinetic study in rat ($t_{1/2}$ = 3.7 h; F = 86%) and a 28-day model of weight gain in growing Sprague-Dawley rat (8.5% decrease in weight gain observed at 36 mg/kg b.i.d.). Lorcaserin was selected for further evaluation in clinical trials for the treatment of obesity.

Introduction

Despite an increased understanding of the causes and adverse consequences of obesity, the incidence of this disease continues to rise. In the U.S., the incidence of obesity has risen from 13% in 1960 to 32% in 2004, a trend that is mirrored worldwide in both developed and developing countries. The obvious primary cause is an excess of energy intake relative to energy expenditure, but less certain are the contributions of genetics, diet, lifestyle, and other factors related to modern life. The consequences of obesity include an increased risk of cardiovascular disease, diabetes, cancer, and stroke, which result in a significant economic burden on society. The current yearly cost of obesity in the U.S. is estimated at $117 billion in medical expenses and lost productivity. Although studies have shown that as little as 5% weight loss results in improved health as measured by improvements in cardiovascular risk factors such as diabetes, hypertension, and dyslipidemia, weight loss and maintenance of weight loss are difficult to achieve.[1]

Pharmacotherapy is one of several strategies, including diet, exercise, behavioral therapy, and surgery, that are used for weight loss and long-term weight management. Currently, sibutramine and orlistat, Figure 1, are the only two drugs approved in the U.S. for the long-term treatment of obesity. Sibutramine is a centrally acting serotonin and norepinephrine reuptake inhibitor that exerts a beneficial effect on satiety and metabolism. The use of sibutramine is limited by side effects, the most serious of which is increased blood pressure but also insomnia, headache, constipation, and dry mouth. Orlistat is a lipase inhibitor that reduces the intestinal absorption of fats. Gastrointestinal side effects are common and, though not usually a health concern, can be unpleasant. A number of amphetamine-like drugs, including phentermine and diethylpropion, remain approved for short-term use. These drugs, which are releasers of neuronal dopamine and norepinephrine, cause a decrease in hunger and an increase in metabolism but result in several serious side effects including increased heart rate and blood pressure and the potential for abuse. A newer drug, rimonabant, which acts by blocking the cannabinoid 1 (CB_1) receptor, was approved in Europe in June of 2006. Whether or not this drug represents a significant improvement over existing drugs remains to be seen. Two drugs that are no longer approved, fenfluramine and the (*S*)-enantiomer dexfenfluramine, exert their effects by activating central serotonergic pathways, resulting in increased satiety and weight loss. Fenfluramine is an older drug approved in the 1970s for short-term use only. In 1996, dexfenfluramine was approved by the FDA as the first drug for the long-term treatment of obesity. Reports of greater weight loss from fenfluramine or dexfenfluramine in combination with phentermine led to the widespread use of the "fen−phen" combination.

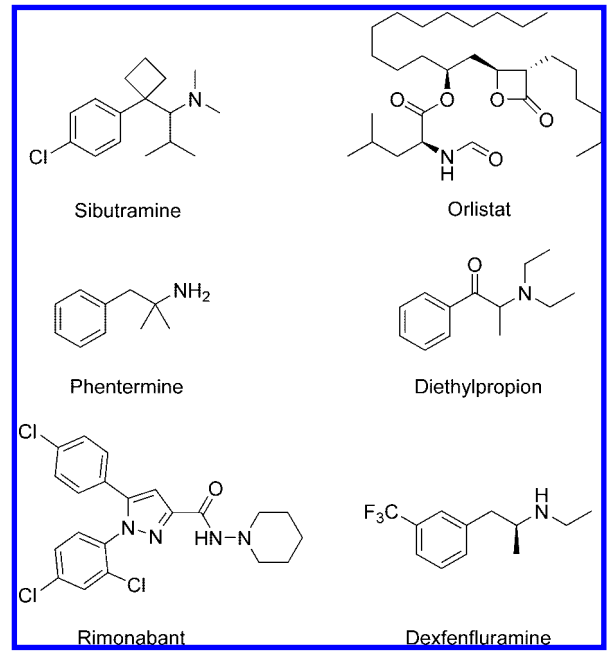

Figure 1. Weight loss drugs, past and present.

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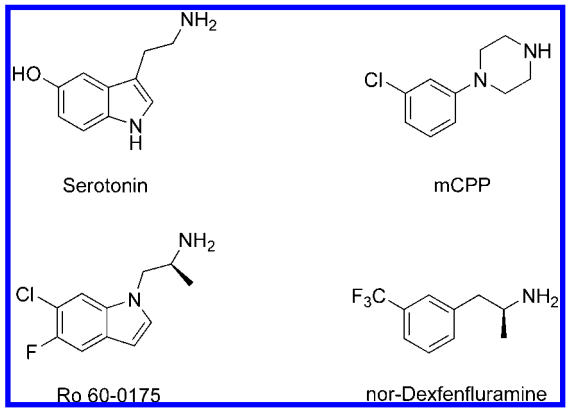


Figure 2. Some known 5-HT_{2C} agonists.

As the number of patients using fenfluramine and dexfenfluramine increased in conjunction with a longer duration of use, a rare but serious defect of the cardiac valves was reported. As more cases were reported, the available evidence linking these cases of cardiac valvulopathy to the use of fenfluramine and dexfenfluramine led to the withdrawal of these drugs in September of 1997.[2]

Animal pharmacology and genetic experiments identify the 5-HT_{2C} receptor as an important mediator of satiety and the likely target through which fenfluramine acts to cause weight loss. For example, a number of nonselective $5HT_{2C}$ receptor agonists (Figure 2), including mCPP, Ro 60-0175, fenfluramine, and its active metabolite norfenfluramine, are known to reduce food intake and lead to weight loss in rodents. These effects are reversed upon preadministration of a selective 5-HT_{2C} receptor antagonist. Mice lacking the 5-HT_{2C} receptor are hyperphagic and mildly obese. Additionally, the food intake and weight loss effects of nonselective 5-HT_{2C} agonists are absent or blunted in 5-HT_{2C} receptor knockout mice. The receptor itself is localized in the hypothalamus, an area of the brain known to be important in the regulation of appetite and feeding. For these reasons, the search for selective $5HT_{2C}$ agonists for the treatment of obesity has become an industry-wide effort.[3]

The 5-HT_{2C} receptor is one of 14 distinct serotonin receptor subtypes. Two receptors that are closely related to the $5HT_{2C}$ receptor are the $5HT_{2A}$ and $5HT_{2B}$ receptors, which share considerable sequence homology. It is believed that activation of central $5HT_{2A}$ receptors is a cause for a number of adverse central nervous system effects of nonselective serotonergic drugs including changes in perception and hallucination. Activation of $5HT_{2B}$ receptors located in the cardiovascular system is hypothesized to result in the heart valve disease and pulmonary hypertension associated with the use of fenfluramine and a number of other drugs that act via serotonergic mechanisms. In fact, it is these safety issues surrounding the use of fenfluramine that largely define the challenges awaiting the discovery and development of $5HT_{2C}$ receptor agonists.[4]

A starting point for the Arena medicinal chemistry program was the arylethylamine motif, which is present in a number of nonselective $5HT_{2C}$ agonists, including serotonin (5-HT), norfenfluramine, and Ro 60-0175. We reasoned that constraining the arylethylamine motif into a bicyclic system, which would reduce the number of available conformations, could lead to compounds with improved $5HT_{2C}$ receptor selectivity versus the closely related $5HT_{2A}$ and $5HT_{2B}$ receptors. The design, synthesis, and characterization of one such series, the 3-benzazepines described herein, led to compounds with good receptor potency and selectivity and, in addition, excellent efficacy, safety, and pharmaceutical properties.[5]

Chemistry

Several methods are known for making 3-benzazepines. These include reductive cyclization[6] to form the azepine carbon−nitrogen bonds, ring expansions such as the Beckmann rearrangement of a β-tetralone oxime,[7] and cyclization via aromatic substitution such as the Friedel–Crafts reaction[8] or the intramolecular Heck reaction.[9] The Heck reaction seemed particularly attractive because of the availability of variously substituted phenethylamines as starting materials, the ease of synthesis to the cyclization intermediate, and the mild conditions for cyclization.

A general synthesis of 3-benzazepines via the Heck route is outlined in Scheme 1, beginning with various phenethylamines **1**. Protection as the trifluoroacetamide, iodination with bis(pyridine)iodonium(I) tetrafluoroborate,[10] and then allylation led to the Heck precursor **4**. Milder variations on the iodination reaction, such as treatment with *N*-iodosuccinimide, worked well on electron-rich aromatic rings but were less successful on halogenated aromatics. Treatment of the Heck precursor **4** with $Pd(OAc)_2$, PPh_3, KOAc, and *n*-Bu_4NBr in DMF at 105 °C overnight led to the desired cyclized product **5** in 50–80% yield. Hydrogenation produced the protected 3-benzazepine intermediate **6**, which was deprotected under basic conditions to give the desired 1-methyl-3-benzazepine **7** as a racemic mixture. Racemic compounds that showed reasonable 5-HT_{2C} receptor potency were further separated into their enantiomers by chiral HPLC, either as the final amine compounds or as the trifluoroacetamide precursors. In some cases, the trifluoroacetamide intermediates **6** were further substituted prior to deprotection. An example is shown in Scheme 2, whereby the protected (*S*)-8-chloro-1-methylbenzazepine **6e** was chlorinated with *N*-chlorosuccinimide (NCS), resulting in a regioisomeric mixture of the protected (*S*)-7,8-dichloro-1-methyl-3-benzazepine **6p** and (*S*)-8,9-dichloro-1-methyl-3-benzazepine **6x**. These were separated by HPLC and then deprotected to the desired final products **7p** and **7x**, respectively.

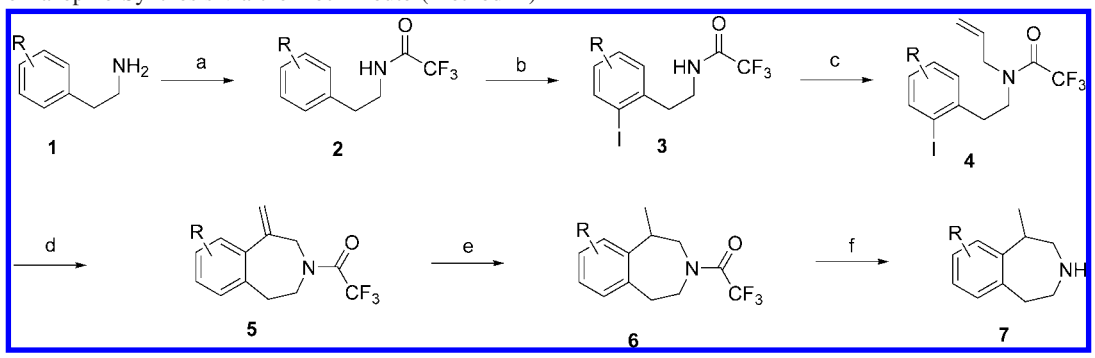
In cases where it was not possible to iodinate selectively ortho to the phenethylamine side chain, the Friedel–Crafts cyclization was employed. Two general syntheses of 3-benzazepines that were used are shown in Scheme 3. Treatment of a phenethylamine **1** with 2-chloropropionyl chloride led to amide derivative **8** in near-quantitative yield. Reduction of the chloroamide with LAH in ether gave the chloroamine derivative **9**, which was then treated with 3 equiv of $AlCl_3$ as a solventless melt for several hours to give the 3-benzazepine **7**. Alternatively, the order of reaction could be reversed, Friedel–Crafts reaction first, to benzazepinone **10**, followed by borane reduction to **7**. Analysis of the purity and yield from a number of these Friedel–Crafts reactions showed cyclization of the amine to be the preferred route.

Biological Evaluations

Functional Assays To Measure Receptor Potency and Selectivity. The functional activity of the compounds at the h5-HT_{2C} (INI isoform), h5-HT_{2A}, and h5-HT_{2B} receptors was determined by measurement of [^{3}H]phosphoinositol turnover in transiently transfected HEK-293 cells.

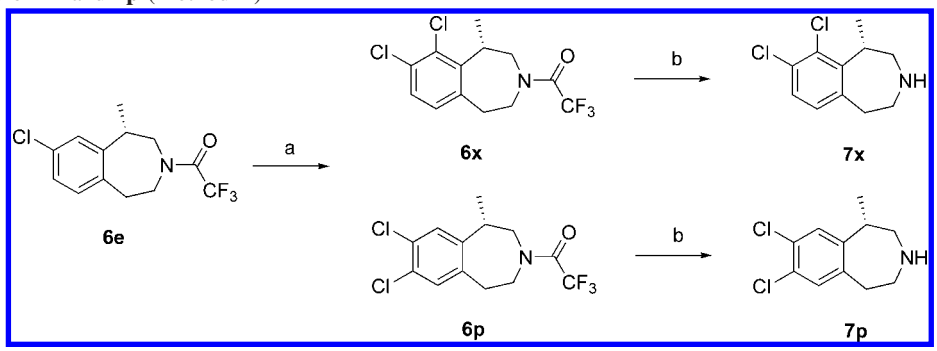
Acute in Vivo Assays To Measure Effects on Rat Food Intake. Compounds were screened for the ability to reduce food intake in male Sprague-Dawley rats. Rats were caged separately and spent 2 weeks on reverse light cycle. On the day of the experiment, freely fed rats (eight per group) were injected po

Scheme 1. Benzazepine Synthesis via the Heck Route (Method A)[a]



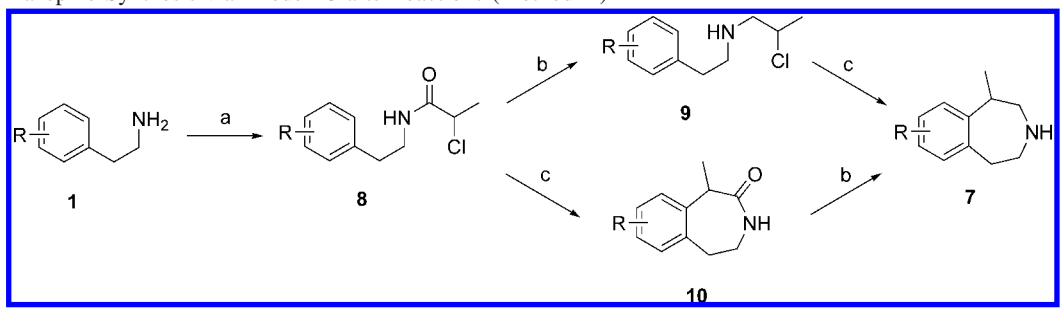
[a] Reagents: (a) $(CF_3CO)_2O$, pyridine, CH_2Cl_2; (b) ICl, MeOH or bispyridine iodonium tetrafluoroborate, CF_3SO_3H, CH_2Cl_2; (c) allyl bromide, NaOH, K_2CO_3, *n*-Bu_4NBr, toluene; (d) $Pd(OAc)_2$, various conditions; (e) 10% Pd/C, H_2, MeOH; (f) NaOH, MeOH/H_2O.

Scheme 2. Synthesis of **7x** and **7p** (Method B)[a]



[a] Reagents: (a) NCS, CH_3CN; (b) NaOH, MeOH/H_2O.

Scheme 3. Benzazepine Synthesis via Friedel–Crafts Reactions (Method D)[a]



[a] Reagents: (a) $CH_3CHClCOCl$, pyridine, CH_2Cl_2; (b) BH_3, ether; (c) $AlCl_3$, 150–200 °C.

(oral gavage) with vehicle, 12.5, 25, 50, and 100 mg/kg 1 h before the dark cycle. Food intake was measured 2 h postdose and compared to vehicle control. In addition, the effect on food intake for lorcaserin was measured at 6 h postdose and compared to vehicle.

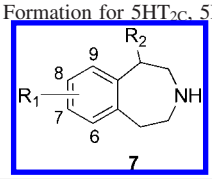
Chronic in Vivo Assays To Measure Effects on Rat Body Weight. Lorcaserin **7d** was tested for the ability to decrease food intake and body weight over a 28-day period in male Sprague-Dawley rats. Adult male rats weighing 250–400 g were caged separately and provided free access to water and food. Treatment groups included vehicle control, lorcaserin at 9, 18, and 36 mg/kg twice daily, and 18 mg/kg once daily. Rats were injected po (oral gavage) with vehicle or drug twice daily for 28 days and their food intake and body weight recorded.

Results

The in vitro screening results measuring IP accumulation at the 5-HT_{2C}, 5-HT_{2A}, and 5-HT_{2B} receptors for new compounds, mCPP, nordexfenfluramine, Ro 60-0175, serotonin, and two older benzazepines **7a**[11] and **7dd**[12] are displayed in Table 1. Substitution of chlorine, bromine, or trifluoromethyl at the 8-position or chlorine at the 7-position led to compounds with good 5-HT_{2C} potency. Substitution of methoxy, fluorine, or hydrogen at only the 7 and 8 postions led to compounds with reduced potency. Substitution of chlorine at either the 6- or 9-position only also led to compounds of lower potency. Addition of a second substituent to the 8-chlorobenzazepine, regardless of the substituent (Cl, F, or OMe) or position, generally resulted in potent compounds with the exception of the (*R*)-1-methyl-8,9-dichlorobenzazepine **7y**, which is about 1.5 log units less active. For the series of 8-chlorobenzazepines with variable substitution at the 1-position, either unsubstituted, methyl, or ethyl, all show good 5-HT_{2C} potency except the 1,1-dimethyl-8-chlorobenzazepine, which is an order of magnitude less potent.

All compounds appear to show some selectivity for the 5-HT_{2C} receptor. Selectivities range between 0.6 and 2.4 log units versus the 5-HT_{2A} recptor and between 0.5 and 2.6 log units versus the 5-HT_{2B} receptor. The most selective compounds are the (*S*)-1-methyl-8,9-disubstituted benzazepines **7z** and **7bb**,

Table 1. Substituents, Functional Activity As Measured by IP3 Formation for $5HT_{2C}$, $5HT_{2A}$, and $5HT_{2B}$ Receptors



			pEC$_{50}$ (n)				
compd	R_1	R_2	$5HT_{2C}$	$5HT_{2A}$	$5HT_{2B}$	log 2A/2C	log 2B/2C
7a	H	H	5.5 ± 0.2 (4)	<5 (1)	<5 (3)		
7b (*R,S*)	H	Me	6.5 ± 0.3 (2)	5.8 ± 0.3 (3)	5.4 ± 0.3 (2)		
7c (*R,S*)	8-Cl	Me	7.9 ± 0.3 (7)	6.7 ± 0.3 (6)	6.0 ± 0.1 (5)	1.2	1.9
7d (*R*)[a]	8-Cl	Me	8.1 ± 0.2 (40)	6.8 ± 0.2 (34)	6.1 ± 0.2 (34)	1.3	2.0
7e (*S*)	8-Cl	Me	7.8 ± 0.2 (7)	6.6 ± 0.2 (10)	5.9 ± 0.2 (7)	1.2	1.9
7f (*R,S*)	8-CF_3	Me	8.2 ± 0.1 (2)	7.0 ± 0.0 (2)	6.1 ± 0.4 (3)	1.2	2.1
7g (*R*)[b]	8-CF_3	Me	8.1 ± 0.0 (3)	6.9 ± 0.4 (4)	6.3 ± 0.3 (2)	1.2	1.8
7h (*S*)[b]	8-CF_3	Me	8.0 ± 0.1 (2)	7.0 ± 0.1 (3)	6.1 ± 0.2 (2)	1.0	1.9
7i (*R,S*)	8-Br	Me	8.0 ± 0.3 (3)	6.3 ± 0.0 (2)	5.7 ± 0.2 (2)	1.7	2.3
7j (*R,S*)	8-F	Me	6.4 ± 0.1 (3)	5.8 ± 0.1 (2)	<5 (2)		
7k (*R,S*)	8-OMe	Me	6.7 ± 0.4 (2)	6.6 ± 0.4 (2)	5.3 ± 0.1 (2)		
7l (*R,S*)	7-Cl	Me	7.6 ± 0.4 (7)	6.8 ± 0.1 (3)	6.3 ± 0.2 (5)	0.8	1.3
7m (*R,S*)	7-OMe	Me	5.9 ± 0.5 (4)	<5 (2)	<5 (1)		
7n (*R,S*)	9-Cl	Me	6.1 ± 0.2 (3)	<5 (1)	<5 (1)		
7o (*R,S*)	6-Cl	Me	6.1 ± 0.1 (3)	<5 (2)	<5 (2)		
7p (*R,S*)	7,8-diCl	Me	8.4 ± 0.1 (3)	7.7 ± 0.1 (4)	7.3 ± 0.2 (4)	0.7	1.1
7q (*R*)[c]	7,8-diCl	Me	8.4 ± 0.2 (2)	8.0 ± 0.1 (3)	7.4 ± 0.1 (2)	0.4	1.0
7r (*S*)[c]	7,8-diCl	Me	8.1 ± 0.0 (2)	7.0 ± 0.1 (3)	6.6 ± 0.0 (2)	1.1	1.5
7s (*R,S*)	7-Cl, 8-OMe	Me	7.3 ± 0.1 (2)	7.0 ± 0.4 (4)	6.7 ± 0.0 (2)	0.3	0.6
7t (*R,S*)	8-Cl, 7-OMe	Me	8.1 ± 0.3 (9)	7.2 ± 0.2 (7)	7.2 ± 0.3 (9)	0.9	0.9
7u (*R*)[c]	8-Cl, 7-OMe	Me	8.1 ± 0.2 (3)	6.7 ± 0.0 (2)	6.4 ± 0.1 (3)	1.4	1.7
7v (*S*)[c]	8-Cl, 7-OMe	Me	8.2 ± 0.2 (2)	7.5 ± 0.1 (4)	7.4 ± 0.3 (5)	0.7	0.8
7w (*R,S*)	8-Cl, 7-F	Me	8.2 ± 0.1 (2)	7.2 ± 0.1 (2)	6.5 ± 0.0 (2)	1.0	1.7
7x (*R,S*)	8,9-diCl	Me	8.1 ± 0.1 (2)	6.7 ± 0.0 (2)	5.8 ± 0.1 (2)	1.4	2.3
7y (*R*)[c]	8,9-diCl	Me	6.5 ± 0.4 (7)	5.6 ± 0.1 (2)	<5 (3)		
7z (*S*)[c]	8,9-diCl	Me	8.5 ± 0.1 (6)	6.9 ± 0.3 (4)	5.9 ± 0.1 (2)	1.6	2.6
7aa (*R,S*)	8-Cl, 9-F	Me	7.7 ± 0.1 (2)	6.1 ± 0.1 (2)	5.6 ± 0.1 (2)	1.6	2.1
7bb (*S*)[c]	8-Cl, 9-F	Me	8.4 ± 0.2 (2)	6.0 ± 0.5 (2)	<5 (2)	2.4	>3.4
7cc (*R,S*)	6,8-diCl	Me	7.7 ± 0.2 (3)	6.9 ± 0.2 (3)	6.1 ± 0.1 (3)	0.8	1.6
7dd	8-Cl	H	7.9 ± 0.1 (3)	7.0 ± 0.1 (4)	6.0 ± 0.1 (3)	0.9	1.9
7ee (*R*)[b]	8-Cl	Et	7.4 ± 0.2 (3)	6.6 ± 0.2 (3)	6.6 ± 0.3 (2)	0.8	0.8
7ff (*S*)[b]	8-Cl	Et	7.7 ± 0.1 (3)	6.5 ± 0.1 (2)	6.2 ± 0.2 (2)	1.2	1.5
7gg	8-Cl	Me, Me	6.7 ± 0.0 (3)	5.8 ± 0.2 (2)	<5 (1)		
mCPP			8.1 ± 0.2 (12)	7.2 ± 0.1 (17)	7.4 ± 0.3 (6)	0.9	0.7
nordexfenfluramine			7.6 ± 0.2 (6)	6.7 ± 0.2 (10)	7.8 ± 0.3 (7)	0.9	−0.2
Ro 60-0175			8.4 ± 0.1 (5)	7.3 ± 0.2 (7)	8.8 ± 0.3 (6)	1.1	−0.4
serotonin			7.6 ± 0.2 (294)	6.9 ± 0.2 (106)	7.6 ± 0.3 (84)	0.7	0.0

[a] Stereochemical assignment confirmed by X-ray crystallography. [b] Assigned by analogy to **7d**: first eluting enantiomer is (*R*)-configuration. [c] Prepared from compound of known configuration, either **7d** or **7e**.

with selectivities of 1.5–2.4 and 2.3–2.6 log units versus the 5-HT_{2A} and 5-HT_{2B} receptors, respectively. The 8-halobenzazepines **7c**−**i**, regardless of stereochemistry, also show good selectivities versus the 5-HT_{2A} and 5-HT_{2B} receptors in the ranges 1.0–1.7 and 1.8–2.3 log units, respectively. For the 7,8-dichloro-1-methylbenzazepine and the 7-chloro-8-methoxy-1-methylbenzazepine, one enantiomer of each pair also shows selectivities of 1.1 and 1.3, respectively, versus the 5-HT_{2A} receptor and 1.5 and 1.6, respectively, at the 5-HT_{2B} receptor. Also in this range is one enantiomer of the 8-chloro-1-ethylbenzazepine with selectivities of 1.2 and 1.5 log units versus the 5-HT_{2A} and 5-HT_{2B} receptors, respectively. All other compounds, excluding racemates for some of the selective enantiomers, have selectivities for the 5-HT_{2C} receptor below 1 log unit versus either or both of the 5-HT_{2A} and 5-HT_{2B} receptors.

The results of rat acute food intake studies for several compounds are displayed in Table 2. The effects on food intake were dose-dependent, and most compounds were able to inhibit food intake by 50% in the dose range of 25–100 μmol/kg. Several behavioral effects that have been previously reported for 5-HT_{2C} agonists, such as reduced locomotor activity, hunched posture, and penile erection, were also observed over a similar dose range as that of the hypophagic response. Additionally, the acute effects of lorcaserin **7d** on rat food intake were reversed by preadministration of the selective 5-HT_{2C} receptor antagonist SB242086, demonstrating that the food

Table 2. Acute Food Intake in Rat

	% inhibition at 2 h postdose			
compd	12.5 μmol/kg	25 μmol/kg	50 μmol/kg	100 μmol/kg
7c		52 ± 5	62 ± 6	81 ± 5
7d	34 ± 3	58 ± 4	77 ± 5	82 ± 6
7e	7 ± 4	26 ± 7	41 ± 4	73 ± 5
7g	14 ± 5	22 ± 7	41 ± 8	
7h	16 ± 7	18 ± 7	45 ± 7	
7p		33 ± 8	44 ± 7	60 ± 6
7q		16 ± 6	40 ± 4	66 ± 4
7r		54 ± 5	58 ± 5	74 ± 6
7t		38 ± 6	52 ± 6	71 ± 6
7u		32 ± 6	36 ± 6	43 ± 3
7v		60 ± 8	66 ± 7	77 ± 8
7w		30 ± 6	41 ± 7	58 ± 7
7z		19 ± 13	41 ± 14	69 ± 10
7dd		63 ± 5	68 ± 3	85 ± 4

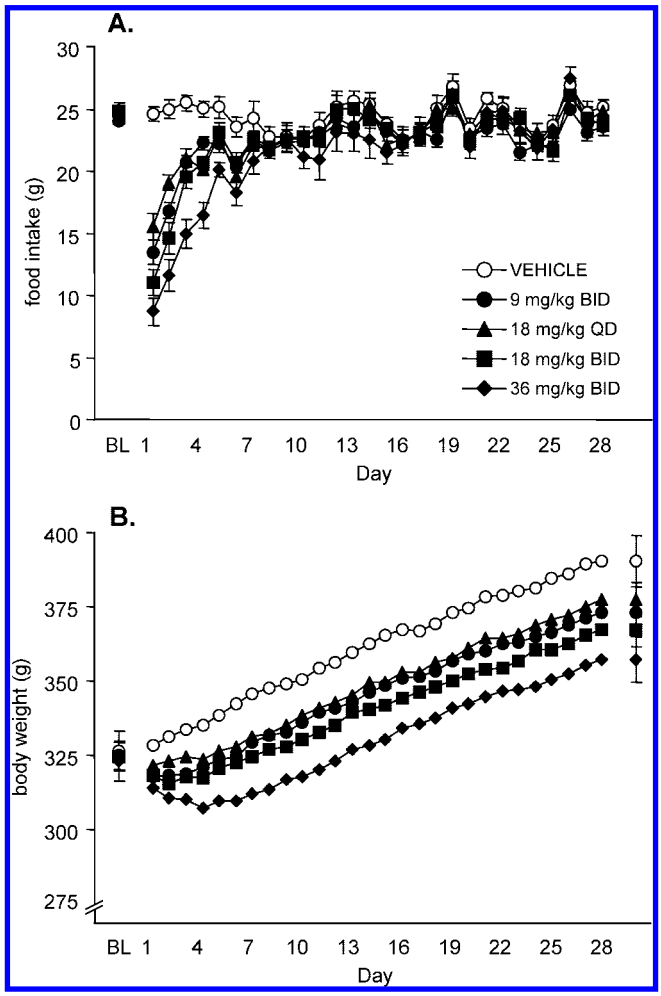


Figure 3. Effects on food intake and body weight of chronic administration of lorcaserin in rat (eight per group), showing percent body weight change, from day 0 to day 28: vehicle, 20.35 ± 0.96; 18 mg/kg q.d., 17.02 ± 0.93; 9 mg/kg b.i.d., 15.75 ± 0.78; 18 mg/kg b.i.d., 14.03 ± 0.96; 36 mg/kg b.i.d., 11.84 ± 0.73.

intake effects are 5-HT_{2C} receptor mediated. For the purposes of determining suitable doses for chronic studies, percent inhibition at 6 h was determined for lorcaserin at doses of 6.25, 12.5, 25, 50, and 100 μmol/kg relative to vehicle control, and the results were then used to calculate an ED_{50} value of 18 mg/kg.

Lorcaserin **7d** was evaluated in a 28-day chronic study measuring the effect on food intake and body weight in male Sprague-Dawley rats, the results of which are displayed in Figure 3. As can be seen from the plots, there is a dose-dependent decrease in food intake and body weight gain out to day 7, followed by maintenance of the day 7 weight differences between each dose group and vehicle control throughout the remainder of the 28-day experiment. At day 28, the 36 mg/kg b.i.d. dose group weighed an average of 8.5% less than the control group. Although the decrease in food intake and body weight gain appears to last for only 7 days, the effect on body weight is maintained throughout the dosing period, as other experiments with lorcaserin have shown that body weight gradually returns to match that of the vehicle control group after dosing is discontinued (data not shown).

Other in vitro and in vivo experiments confirmed the suitability of lorcaserin as a lead candidate for the Arena program. Screening of a panel of 75 other receptors and ion channels revealed no significant activity at 1 μM. The pharmacokinetic profile of lorcaserin in rat is characterized by rapid absorption, high oral bioavailability, and moderate half-life as shown in Table 3. Purkinje fiber and hERG assays revealed no liability for cardiac QT prolongation at therapeutic doses. The potential for drug−drug interactions was considered low on the basis of results from cyp450 inhibition assays using human liver microsomes.

Discussion

The decision to move forward with lorcaserin was made on the basis of the synthetic chemical accessibility, results from in vitro screening assays, and results from the acute in vivo food intake experiments in rats. Other contenders, on the basis of receptor potency and selectivity (vide infra), were considerably more difficult to prepare. The 8,9-disubstituted compounds **7z** and **7bb** were prepared by chlorination or fluorination of a protected **7e** and then separated from the major 7,8-regioisomer. Other methods, such as the Friedel–Crafts cyclization directly to the 8,9-disubstituted benzazepines, led to difficulty in separating mixtures. An enantiomer of **7i** would suffer from the questionable suitability of bromine in a drug candidate, as well as the lability of bromine under either Friedel–Crafts conditions or the hydrogenation conditions required for the Heck route. The trifluoromethyl analogues of lorcaserin, **7g** and **7 h**, posed challenges related to the electron-withdrawing characteristics of the trifluoromethyl substituent and poor yields obtained during the required electrophilic aromatic substitutions reactions, either Friedel–Crafts alkylation or aromatic iodination. In contrast, an efficient three-step synthesis of lorcaserin in high overall yield and amenable to large-scale synthesis was developed and will be the subject of a future publication. Although most compounds of interest were quite potent in the acute rat food intake experiments, lorcaserin was one of the more potent compounds and appeared to be more potent than the equally selective enantiomer **7e**, as shown in Table 2. Other experiments, including chronic rat food intake and reduction in weight gain studies and single-dose pharmacokinetic studies in rats, confirmed the suitability of lorcaserin as a development candidate. Lorcaserin was subsequently selected for evaluation in clinical trials for the treatment of obesity.

Experimental Section

Chemistry. All reagents were commercially available and used without further purification. Spectra were recorded with the following instruments: ^{1}H NMR [chemical shifts (δ) reported in ppm relative to trimethylsilane as an internal standard, coupling constants J in hertz], Varian 400 (400 MHz) or Bruker 400 (400 MHz); MS, PE Sciex API 150 EX. All target compounds were analyzed by reverse-phase HPLC (acetonitrile/water) and found to be greater than 98% pure. In addition, single enantiomers were analyzed by chiral HPLC (isopropanol/hexane) and found to be greater than 96% enantiomeric excess.

Method A. Preparation of (1*R,S*)-8-Chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7c) from 4-Chlorophenethylamine via the Heck Reaction Route. *N*-Trifluoroacetyl-4-chlorophenethylamine (2c). A solution of 4-chlorophenethylamine (1.0 g, 6.4 mmol) in dichloromethane (20 mL) was cooled to 0 °C, treated with pyridine (1.0 mL, 12.8 mmol), and trifluoroacetic anhydride (1.6 g, 7.7 mmol) and then stirred for 1 h while warming to 20 °C. The product mixture was diluted with EtOAc (100 mL), washed sequentially with 10% aqueous HCl (50 mL), water (50 mL), and brine (50 mL), dried with Na_2SO_4, and concentrated to give 1.6 g of a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 12 Hz, 2 H), 7.12 (d, J = 12 Hz, 2 H), 6.39 (bs, 1 H), 3.60 (dd, J = 4, 8 Hz, 2 H), 2.87 (dd, J = 4, 8 Hz, 2 H). MS calculated for $C_{10}H_9ClF_3NO$ + H, 252; observed, 252.

Table 3. Pharmacokinetic Parameters of Lorcaserin (7d) in Male Sprague-Dawley Rats[a]

route	dose (mg/kg)	$t_{1/2}$ (h)	Cl ((L/h)/kg)	V_{ss} (L/kg)	t_{max} (h)	C_{max} (μg/mL)	AUC0-inf (h·μg/mL)	F (%)
intravenous	5	3.1 ± 0.9	6.1 ± 1.1	18.0 ± 3.8	NA	NA	0.8 ± 0.2	NA
oral	10	3.7 ± 1.8	NA	NA	0.5 ± 0.0	0.26 ± 0.13	1.4 ± 0.7	86 ± 42

[a] Data are the mean ± SD, n = 4–7.

***N*-Trifluoroacetyl-2-iodo-4-chlorophenethylamine (3c).** A solution of *N*-trifluoroacetyl-4-chlorophenethylamine (1.6 g, 6.4 mmol) in dichloromethane (20 mL) was treated with bis(pyridine)iodonium(I) tetrafluoroborate (2.6 g, 7.0 mmol) and CF_3SO_3H (2.1 g, 14.1 mmol) and stirred overnight at 20 °C. The product mixture was concentrated, dissolved in EtOAc (100 mL), washed twice with 5% aqueous sodium bisulfite (50 mL), twice with saturated aqueous $NaHCO_3$ (50 mL), and once with brine (50 mL), dried with Na_2SO_4, and concentrated to give 0.94 g of a clear oil. MS calculated for $C_{10}H_8ClF_3INO$ + H, 378; observed, 378.

***N*-Allyl-*N*-trifluoroacetyl-2-iodo-4-chlorophenethylamine (4c).** A solution of *N*-trifluoroacetyl-2-iodo-4-chlorophenethylamine (0.94 g, 2.4 mmol) in toluene (25 mL) was treated with K_2CO_3 (0.43 g, 3.12 mmol), KOH (0.40 g, 7.2 mmol), *n*-Bu_4NBr (0.077 g, 0.24 mmol), and allyl bromide (0.43 g, 3.6 mmol) sequentially. The mixture was stirred at 80 °C for 3.5 h, cooled to 20 °C, and acidified with 10% aqueous HCl. The phases were separated, the aqueous phase extracted with ether (100 mL), the combined organic phases were washed with brine (50 mL), dried with Na_2SO_4, and concentrated to give 0.76 g of a clear oil. MS calculated for $C_{13}H_{12}ClF_3INO$ + H, 418; observed, 418.

***N*-Trifluoroacetyl-8-chloro-2,3,4,5-tetrahydro-1-methylene-1*H*-3-benzazepine (5c).** A solution of *N*-allyl-*N*-trifluoroacetyl-2-iodo-4-chlorophenethylamine (0.76 g, 1.8 mmol) in dimethylformamide (20 mL) was treated with KOAc (0.53 g, 5.4 mmol), *n*-Bu_4NBr (0.58 g, 1.8 mmol), PPh_3 (0.047 g, 0.18 mmol), and $Pd(OAc)_2$ (0.041 g, 0.18 mmol) and stirred overnight at 105 °C. The product mixture was cooled to 20 °C, filtered, diluted with water (100 mL), and extracted with ether (3 × 100 mL), and the combined organic phases were washed with water (100 mL) and brine (100 mL), dried with Na_2SO_4, and concentrated. Flash chromatography (10% EtOAc in hexane, silica) resulted in 0.228 g of a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (s, 1 H), 7.18 (m, 1 H), 7.04 (m, 1 H), 5.38 (m, 2 H), 5.40 (d, J = 16 Hz, 2 H), 3.80 (m, 2 H), 3.00 (m, 2 H). MS calculated for $C_{13}H_{11}ClF_3NO$ + H, 290; observed, 290.

(1*R,S*)-*N*-Trifluoroacetyl-8-chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (6c). A solution of *N*-trifluoroacetyl-8-chloro-2,3,4,5-trihydro-1-methylene-1*H*-3-benzazepine (0.16 g, 0.55 mmol) in methanol (10 mL) was treated with 10% Pd/C (0.02 g) and stirred 30 min under an atmosphere of hydrogen. The product mixture was filtered, concentrated, and purified by flash chromatography (5% EtOAc in hexane, silica), resulting in 0.057 g of a white solid. MS calculated for $C_{13}H_{13}ClF_3NO$ + H, 292; observed, 292.

(1*R,S*)-8-Chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7c). A solution of *N*-trifluoroacetyl-8-chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (65 mg, 0.22 mmol) in methanol (2 mL) was treated with 15% aqueous NaOH (2 mL) and stirred for 3.5 h at 60 °C. The product mixture was concentrated, extracted three times with CH_2Cl_2 (5 mL), dried with Na_2SO_4, and concentrated to give 35 mg of a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 1 H), 7.05 (d, J = 8 Hz, 1 H), 6.98 (d, J = 8 Hz, 1 H), 3.1–2.9 (m, 6 H), 2.71 (m, 1 H), 2.68 (bs, 1 H), 1.32 (d, J = 8 Hz, 3 H). MS calculated for $C_{11}H_{14}ClN$ + H, 196; observed, 196.

(1*R*)-8-Chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7d). (1*R,S*)-*N*-Trifluoroacetyl-8-chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (**6c**) was separated by chiral chromatography (t_R = 23.8 min, 5% isopropanol in hexane with 0.2% diethylamine at a flow rate of 7 mL/min on a 20 mm × 250 mm Chiracel OD chiral column) and then deprotected under standard conditions. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 1 H), 7.05 (d, J = 8 Hz, 1 H), 6.98 (d, J = 8 Hz, 1 H), 3.1–2.9 (m, 6 H), 2.71 (m, 1 H), 2.68 (bs, 1 H), 1.32 (d, J = 8 Hz, 3 H). MS calculated for $C_{11}H_{14}ClN$ + H, 196; observed, 196. The (*R*)-configuration was confirmed by X-ray crystallography.

(1*S*)-8-Chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7e). (1*R,S*)-*N*-Trifluoroacetyl-8-chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (**6c**) was separated by chiral chromatography (t_R = 29.2 min, 5% isopropanol in hexane with 0.2% diethylamine at a flow rate of 7 mL/min on a 20 mm × 250 mm Chiracel OD chiral column) and then deprotected under standard conditions. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 1 H), 7.05 (d, J = 8 Hz, 1 H), 6.98 (d, J = 8 Hz, 1 H), 3.1–2.9 (m, 6 H), 2.71 (m, 1 H), 2.68 (bs, 1 H), 1.32 (d, J = 8 Hz, 3 H). MS calculated for $C_{11}H_{14}ClN$ + H, 196; observed, 196.

(1*R,S*)-8-Trifluoromethyl-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7f). 7f was obtained from 4-trifluoromethylphenethylamine via method A as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 (d, J = 8 Hz, 1 H), 7.49 (s, 1 H), 7.43 (d, J = 8 Hz, 1 H), 3.55–3.50 (m, 1H), 3.43–3.23 (m, 7 H), 3.13 (dd, J = 16, 7 Hz, 1H), 3.0–2.91 (m, 2H), 1.36 (d, J = 7 Hz, 3 H). MS calculated for $C_{12}H_{14}F_3N$ + H, 230; observed, 230.

(1*R*)-8-Trifluoromethyl-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7g). (1*R,S*)-*N*-Trifluoroacetyl-8-trifluoromethyl-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (**6f**) was separated by chiral chromatography (t_R = 18.6 min, 1% isopropanol in hexane with 0.2% diethylamine at a flow rate of 9 mL/min on a 20 mm × 250 mm Chiracel OD chiral column) and then deprotected under the standard conditions. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 (d, J = 8 Hz, 1 H), 7.49 (s, 1 H), 7.43 (d, J = 8 Hz, 1 H), 3.55–3.50 (m, 1H) 3.43–3.23 (m, 7 H), 3.13 (dd, J = 16, 7 Hz, 1H), 3.0–2.91 (m, 2H), 1.36 (d, J = 7 Hz, 3 H). MS calculated for $C_{12}H_{14}F_3N$ + H, 230; observed, 230.

(1*S*)-8-Trifluoromethyl-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7h). (1*R,S*)-*N*-Trifluoroacetyl-8-trifluoromethyl-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (**6f**) was separated by chiral chromatography (t_R = 21.4 min, 1% isopropanol in hexane with 0.2% diethylamine at a flow rate of 9 mL/min on a 20 mm × 250 mm Chiracel OD chiral column) and then deprotected under standard conditions. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 (d, J = 8 Hz, 1 H), 7.49 (s, 1 H), 7.43 (d, J = 8 Hz, 1 H), 3.55–3.50 (m, 1H) 3.43–3.23 (m, 7 H), 3.13 (dd, J = 16, 7 Hz, 1H), 3.0–2.91 (m, 2H), 1.36 (d, J = 7 Hz, 3 H). MS calculated for $C_{12}H_{14}F_3N$ + H, 230; observed, 230.

(1*R,S*)-8-Fluoro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7j). 7j was obtained from 4-fluorophenethylamine as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (dd, J = 8, 10 Hz, 1 H), 6.86 (d, J = 10 Hz, 1 H), 6.76 (d, J = 8 Hz, 1 H), 3.08–2.56 (m, 7 H), 1.85 (bs, 1 H), 1.31 (d, J = 7 Hz, 3 H). MS calculated for $C_{11}H_{14}FN$ + H, 180; observed, 180.

(1*R,S*)-7-Chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7l). 7l was obtained from 3-chlorophenethylamine as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, J = 8 Hz, 1 H), 7.06 (m, 2 H), 3.1–2.9 (m, 6 H), 2.70 (dd, J = 13, 7 Hz, 1 H), 1.89 (bs, 1 H), 1.31 (d, J = 7 Hz, 3 H). MS calculated for $C_{11}H_{14}ClN$ + H, 196; observed, 196.

(1*R,S*)-8-Chloro-2,3,4,5-tetrahydro-1-ethyl-1*H*-3-benzazepine. The product was obtained from 4-chlorophenethylamine and crotyl bromide as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.2 (m, 3 H), 3.3–3.0 (m, 7 H), 1.9–1.6 (m, 2 H), 0.91 (t, J = 7 Hz, 3 H). MS calculated for $C_{12}H_{16}ClN$ + H, 210; observed, 210.

(1*R*)-8-Chloro-2,3,4,5-tetrahydro-1-ethyl-1*H*-3-benzazepine (7ee). (1*R,S*)-*N*-Trifluoroacetyl-8-chloro-2,3,4,5-tetrahydro-1-ethyl-1*H*-3-benzazepine (**6y** and **6z**) was separated by chiral chromatog-

raphy (t_R = 13.7 min, 5% isopropanol in hexane with 0.2% diethylamine at a flow rate of 10 mL/min on a 20 mm × 250 mm Chiracel OD chiral column) and then deprotected under standard conditions. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.2 (m, 3 H), 3.3–3.0 (m, 7 H), 1.9–1.6 (m, 2 H), 0.91 (t, J = 7 Hz, 3 H). MS calculated for $C_{12}H_{16}ClN$ + H, 210; observed, 210.

(1*S*)-8-Chloro-2,3,4,5-tetrahydro-1-ethyl-1*H*-3-benzazepine (7ff). (1*R,S*)-*N*-Trifluoroacetyl-8-chloro-2,3,4,5-tetrahydro-1-ethyl-1*H*-3-benzazepine (**6y** and **6z**) was separated by chiral chromatography (t_R = 20.2 min, 5% isopropanol in hexane with 0.2% diethylamine at a flow rate of 10 mL/min on a 20 mm × 250 mm Chiracel OD chiral column) and then deprotected under standard conditions. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.2 (m, 3 H), 3.3–3.0 (m, 7 H), 1.9–1.6 (m, 2 H), 0.91 (t, J = 7 Hz, 3 H). MS calculated for $C_{12}H_{16}ClN$ + H, 210; observed, 210.

Method B. Preparation of (1*R,S*)-7,8-Dichloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7p). (1*R,S*)-*N*-Trifluoroacetyl-8-chloro-2,3,4,5-tetrahydro-1-methyl-1 *H*-3-benzazepine (0.900 g, 2.67 mmol) was dissolved in acetonitrile (30 mL), treated with *N*-chlorosuccinimide (0.357 g, 2.67 mmol), and stirred overnight at 70 °C. The product mixture was diluted with water (100 mL) and extracted twice with EtOAc (100 mL), and the combined organic phases were washed with brine (100 mL), dried with Na_2SO_4, and concentrated. Flash chromatography (20% EtOAc in hexane, silica) resulted in 0.399 g of a clear oil. The trifluoroacetyl-protected intermediate was dissolved in methanol (20 mL), treated with 15% aqueous NaOH (20 mL), and stirred overnight at 20 °C. The product mixture was diluted with water (100 mL) and extracted twice with EtOAc (100 mL), and the combined organic phases were washed with brine (100 mL), dried with Na_2SO_4, and concentrated to give 0.306 g of a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 1 H), 7.16 (s, 1 H), 3.05–2.86 (m, 6 H), 2.71 (dd, J = 7, 13 Hz, 1 H), 1.83 (bs, 1 H), 1.33 (d, J = 7 Hz, 3 H). MS calculated for $C_{11}H_{13}Cl_2N$ + H, 230; observed, 230.

(1*R*)-7,8-Dichloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7q). 7q was obtained from (1*R*)-*N*-trifluoroacetyl-8-chloro-2,3,4,5-tetrahydro-1-methyl-1 *H*-3-benzazepine via method B as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 1 H), 7.16 (s, 1 H), 3.05–2.86 (m, 6 H), 2.71 (dd, J = 7, 13 Hz, 1 H), 1.83 (bs, 1 H), 1.33 (d, J = 7 Hz, 3 H). MS calculated for $C_{11}H_{13}Cl_2N$ + H, 230; observed, 230.

(1*S*)-7,8-Dichloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7r). 7r was obtained from (1*S*)-*N*-trifluoroacetyl-8-chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine via method B as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 1 H), 7.16 (s, 1 H), 3.05–2.86 (m, 6 H), 2.71 (dd, J = 7, 13 Hz, 1 H), 1.83 (bs, 1 H), 1.33 (d, J = 7 Hz, 3 H). MS calculated for $C_{11}H_{13}Cl_2N$ + H, 230; observed, 230.

(1*R,S*)-8,9-Dichloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7x). The minor regioisomer was obtained from (1*R,S*)-*N*-trifluoroacetyl-8-chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine via method B as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8 Hz, 1 H), 7.16 (d, J = 8 Hz, 1 H), 4.17 (m, 1 H), 3.55 (m, 2 H), 3.5–3.3 (m, 2 H), 3.2–3.0 (m, 2 H), 1.43 (d, J = 7 Hz, 3 H). MS calculated for $C_{11}H_{13}Cl_2N$ + H, 230; observed, 230.

(1*R*)-8,9-Dichloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7y). The minor regioisomer was obtained from (1*R*)-*N*-trifluoroacetyl-8-chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine via method B as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8 Hz, 1 H), 7.16 (d, J = 8 Hz, 1 H), 4.17 (m, 1 H), 3.55 (m, 2 H), 3.5–3.3 (m, 2 H), 3.2–3.0 (m, 2 H), 1.43 (d, J = 7 Hz, 3 H). MS calculated for $C_{11}H_{13}Cl_2N$ + H, 230; observed, 230.

(1*S*)-8,9-Dichloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7z). The minor regioisomer was obtained from (1*S*)-*N*-trifluoroacetyl-8-chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine via method B as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8 Hz, 1 H), 7.16 (d, J = 8 Hz, 1 H), 4.17 (m, 1 H), 3.55 (m, 2 H), 3.5–3.3 (m, 2 H), 3.2–3.0 (m, 2 H), 1.43 (d, J = 7 Hz, 3 H). MS calculated for $C_{11}H_{13}Cl_2N$ + H, 230; observed, 230.

(1*R,S*)-8-Chloro-7-methoxy-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7t). 7t was obtained from (1*R,S*)-*N*-trifluoroacetyl-7-methoxy-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine via method C as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 1 H), 6.59 (s, 1 H), 3.80 (s, 3 H), 3.0–2.8 (m, 6 H), 2.62 (m, 1 H), 2.16 (bs, 1 H), 1.24 (d, J = 7 Hz, 3 H). MS calculated for $C_{12}H_{16}ClNO$ + H, 226; observed, 226.

(1*R*)-8-Chloro-7-methoxy-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7v). (1*R,S*)-8-Chloro-7-methoxy-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (**7t**) was separated by chiral chromatography (t_R = 42 min, 5% isopropanol in hexane with 0.2% diethylamine at a flow rate of 9 mL/min on a 20 mm × 250 mm Chiracel OD chiral column). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 1 H), 6.59 (s, 1 H), 3.80 (s, 3 H), 3.0–2.8 (m, 6 H), 2.62 (m, 1 H), 2.16 (bs, 1 H), 1.24 (d, J = 7 Hz, 3 H). MS calculated for $C_{12}H_{16}ClNO$ + H, 226; observed, 226.

(1*S*)-8-Chloro-7-methoxy-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7u). (1*R,S*)-8-Chloro-7-methoxy-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (**7t**) was separated by chiral chromatography (t_R = 47 min, 5% isopropanol in hexane with 0.2% diethylamine at a flow rate of 9 mL/min on a 20 mm × 250 mm Chiracel OD chiral column). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 1 H), 6.59 (s, 1 H), 3.80 (s, 3 H), 3.0–2.8 (m, 6 H), 2.62 (m, 1 H), 2.16 (bs, 1 H), 1.24 (d, J = 7 Hz, 3 H). MS calculated for $C_{12}H_{16}ClNO$ + H, 226; observed, 226.

Method C. Preparation of (1*R,S*)-8-Chloro-7-fluoro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7w). A solution of (1*R,S*)-*N*-trifluoroacetyl-8-chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (2.5 g, 8.5 mmol) in 1,2-dichloroethane (15 mL) was treated with Selectfluor (3.9 g, 11 mmol) and trifluoromethanesulfonic acid (8 mL, 90 mmol) and stirred 60 h at 75 °C. The product mixture was poured into water (200 mL) and extracted with EtOAc (200 mL), and the organic phase was washed with saturated aqueous $NaHCO_3$ (2 × 100 mL) and brine (100 mL), dried with Na_2SO_4, and concentrated. The crude product was purified by flash chromatography (6% EtOAc in hexane, silica), resulting in 1.6 g of a white solid. MS calculated for $C_{13}H_{12}ClF_4NO$ + H, 310; observed, 310. A solution of the trifluoroacetyl-protected intermediate (160 mg, 0.22 mmol) was dissolved in methanol (3 mL), treated with 15% aqueous NaOH (2 mL), and stirred for 3.5 h at 25 °C. The product mixture was concentrated, extracted three times with CH_2Cl_2 (5 mL), dried with Na_2SO_4, and concentrated to give 93 mg of a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (m, 1 H), 6.85 (m, 1 H), 3.05–2.95 (m, 3 H), 2.95–2.80 (m, 3H), 2.68 (m, 1 H), 2.38 (bm, 1 H), 1.31 (m, 3 H). MS calculated for $C_{11}H_{13}ClFN$ + H, 214; observed, 214.

(1*R,S*)-8-Chloro-9-fluoro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7aa). The minor regioisomer was obtained from (1*R,S*)-*N*-trifluoroacetyl-8-chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine via method C as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (dd, J = 8, 8 Hz, 1 H), 6.75 (d, J = 8 Hz, 1 H), 3.58 (m, 1 H), 3.25–3.15 (m, 3 H), 2.93 (d, J = 13 Hz, 1 H), 2.75–2.60 (m, 3H), 1.96 (bs, 1 H), 1.33 (d, J = 8 Hz, 3 H). MS calculated for $C_{11}H_{13}ClFN$ + H, 214; observed, 214.

(1*S*)-8-Chloro-9-fluoro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7bb). The minor regioisomer was obtained from (1*S*)-*N*-trifluoroacetyl-8-chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine via method C as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (dd, J = 8, 8 Hz, 1 H), 6.75 (d, J = 8 Hz, 1 H), 3.58 (m, 1 H), 3.25–3.15 (m, 3 H), 2.93 (d, J = 13 Hz, 1 H) 2.75–2.60 (m, 3H), 1.96 (bs, 1 H), 1.33 (d, J = 8 Hz, 3 H). MS calculated for $C_{11}H_{13}ClFN$ + H, 214; observed, 214.

Method D. Preparation of (1*R,S*)-6,8-Dichloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7cc) from 2,4-Dichlorophenethylamine via the Friedel–Crafts Route. (2*R,S*)-2-Chloro-*N*-(2,4-dichlorophenethyl)propanamide (8cc). A solution of 2-(2,3-dichlorophenethylamine (2.0 g, 10.5 mmol) in dichloromethane (50 mL) was treated with diisopropylethylamine (1.63 g, 12.6 mmol) and 2-chloropropionyl chloride (1.12 mL, 11.6 mmol) sequentially, and the mixture was stirred at 20 °C for 1 h. The mixture was diluted with dichloromethane (50 mL), washed with 10% aqueous HCl and brine (20 mL), dried with $MgSO_4$, and concentrated. Flash chromatography (30% ethyl acetate in hexanes)

resulted in 2.7 g of a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 2.0 Hz, 1 H), 7.21 (dd, J = 8.0, 2.0 Hz, 1 H), 7.16 (d, J = 8.0 Hz, 1 H), 6.64 (bs, 1 H), 4.39 (q, J = 7.1 Hz, 1 H), 3.55 (q, J = 6.7 Hz, 2 H), 2.97 (t, J = 7.0 Hz, 2 H), 1.71 (d, J = 6.8 Hz, 3 H). MS calculated for $C_{11}H_{12}Cl_3NO$ + H, 280; observed, 280.

(2*R,S*)-2-Chloro-*N*-(2,4-dichlorophenethyl)propan-1-amine (9cc). A solution of 2-chloro-*N*-(2,3-dichlorophenethyl)propanamide (1.0 g, 3.8 mmol) in tetrahydrofuran (10 mL) was treated with 1.0 M borane in THF (10.0 mL, 10.0 mmol) and stirred at 65 °C for 4 h. The mixture was quenched with methanol (10 mL), acidified with concentrated HCl (0.2 mL), azeotroped with methanol (3 × 100 mL), and concentrated. Preparative HPLC (10–95% gradient, acetonitrile in water with 0.5% TFA) resulted in 0.89 g of a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 2.0 Hz, 1 H), 7.39 (d, J = 8.0 Hz, 1 H), 7.35 (dd, J = 8.0, 2.0 Hz, 1 H), 4.02 (sextet, J = 5.8 Hz, 1 H), 2.86–2.73 (m, 6 H), 1.42 (d, J = 6.4 Hz, 3 H). MS calculated for $C_{11}H_{14}Cl_3N$ + H, 266; observed, 266.

(1*R,S*)-6,8-Dichloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7cc). Neat 2-chloro-*N*-(2,3-dichlorophenethyl)propan-1-amine (2.0 g, 7.5 mmol) and $AlCl_3$ (2.0 g, 15 mmol) were heated at 140 °C for 4 h while stirring. The product mixture was quenched with water (10 mL) and diluted with chloroform (100 mL), and the organic phase was separated, washed with 1 M aqueous NaOH (3 × 50 mL), dried with $MgSO_4$, and concentrated. Preparative HPLC (10–95% gradient, acetonitrile in water with 0.5% TFA) and conversion to the HCl salt resulted in 430 mg of a yellow solid. ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 7.56 (d, J = 2.0 Hz, 1 H), 7.26 (d, J = 2.0 Hz, 1 H), 3.57 (quintet, J = 7.4 Hz, 1 H), 3.45–3.37 (m, 2 H), 3.31–3.22 (m, 2 H), 2.91–2.84 (m, 2 H, 1.36 (d, J = 7.2 Hz, 3 H). MS calculated for $C_{11}H_{13}Cl_2N$ + H, 230; observed, 230.

(1*R,S*)-8-Methoxy-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7k). 7k was obtained from 4-methoxyphenethylamine via method D as a colorless oil. ^{1}H NMR (400 MHz, CD_3OD) δ 7.20 (d, J = 9 Hz, 1 H), 6.83 (s, 1 H), 6.82 (d, J = 9 Hz, 1H), 3.79 (s, 3 H), 3.48–3.24 (m, 4 H), 3.10 (m, 2 H), 2.96 (m, 1 H), 1.46 (d, J = 7 Hz, 3 H). MS calculated for $C_{12}H_{17}NO$ + H, 191; observed, 191.

(1*R,S*)-9-Chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7n). 7n was obtained from 3-chlorophenethylamine via method D as a colorless oil. ^{1}H NMR (400 MHz, CD_3OD) δ 7.40 (m, 1 H), 7.21 (m, 2 H), 4.18 (m, 1 H), 3.59 (m, 2 H), 3.50–3.35 (m, 2 H), 3.12 (m, 2 H), 1.46 (d, J = 7 Hz, 3 H). MS calculated for $C_{11}H_{14}ClN$ + H, 196; observed, 196.

(1*R,S*)-6-Chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (7o). 7o was obtained from 2-chlorophenethylamine via method D as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 8 Hz, 1 H), 6.93 (m, 2 H), 3.97 (bs, 1 H), 3.79 (m, 1 H), 3.3–3.1 (m, 3 H), 2.95 (d, J = 11 Hz, 1 H), 2.8–2.6 (m, 2 H), 1.3 (d, J = 8 Hz, 3 H). MS calculated for $C_{11}H_{14}ClN$ + H, 196; observed, 196.

Method E. Preparation of 8-Chloro-2,3,4,5-tetrahydro-1,1-dimethyl-1*H*-3-benzazepine (7gg). Preparation of Ethyl *N*-[2-(4-Chlorophenyl)ethyl]glycinate. A solution of 4-chlorophenethylamine (1.1 g, 7.1 mmol) in tetrahydrofuran (5 mL) was treated with diisopropylethylamine (1.5 mL, 8.5 mmol) and ethyl bromoacetate (0.87 mL, 7.8 mmol) sequentially, and the mixture was stirred at 50 °C for 2 h and then cooled to 20 °C. The mixture was diluted with EtOAc (50 mL), washed with brine (20 mL), dried with Na_2SO_4, and concentrated. Flash chromatography (5% methanol in dichloromethane) resulted in 1.0 g of a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 2 H), 7.18 (m, 2 H), 4.19 (q, J = 4 Hz, 2 H), 3.59 (bs, 1 H), 3.42 (s, 1 H), 2.88 (m, 2 H), 2.81 (m, 2 H), 1.29 (t, J = 4 Hz, 3 H). MS calculated for $C_{12}H_{16}ClNO_2$ + H, 242; observed, 242.

Preparation of *N*-[2-(4-Chlorophenyl)ethyl]-1-amino-2-methylpropanol. A solution of ethyl *N*-[2-(4-chlorophenyl)ethyl]glycinate (1.0 g, 4.1 mmol) in tetrahydrofuran (10 mL) was treated with 3.0 M methylmagnesium chloride in tetrahydrofuran (6.1 mL, 18.4 mmol) and stirred for 1 h at 20 °C. The product mixture was quenched and diluted with saturated aqueous ammonium chloride (50 mL) and extracted with EtOAc (3 × 500 mL), and the combined organic phases were washed with brine (50 mL), dried with Na_2SO_4, and concentrated. Flash chromatography (10–20% methanol in methylene chloride, silica) resulted in 0.12 g of a brown viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (m, 2 H), 7.06 (m, 2 H), 2.85 (t, J = 7 Hz, 2 H), 2.70 (t, J = 7 Hz, 2 H), 2.48 (s, 2 H), 1.08 (s, 6 H). MS calculated for $C_{12}H_{18}ClNO$ + H, 228; observed, 228.

Preparation of *N*-[2-(4-Chlorophenyl)ethyl]-*N,O*-ditrifluoroacetyl-1-amino-2-methylpropanol. A solution of *N*-[2-(4-chlorophenyl)ethyl]-1-amino-2-methylpropanol (0.12 g, 0.53 mmol) in dichloromethane (5 mL) was treated with pyridine (0.09 mL, 1.2 mmol) and trifluoroacetic anhydride (0.17 mL, 1.2 mmol) and stirred for 2 h at 20 °C. The product mixture was diluted with EtOAc (50 mL), washed with 5% aqueous HCl (20 mL) and then brine (20 mL), dried with Na_2SO_4, and concentrated to give 0.17 g of a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (m, 2 H), 7.01 (m, 2 H), 3.76 (s, 2 H), 3.64 (t, J = 8 Hz, 2 H), 2.81 (t, J = 8 Hz, 2 H), 1.53 (s, 6 H). MS calculated for $C_{16}H_{16}ClF_6NO_3$ + H, 420; observed, 420.

Preparation of *N*-Trifluoroacetyl-8-chloro-2,3,4,5-tetrahydro-1,1-dimethyl-1*H*-3-benzazepine. Neat *N*-[2-(4-chlorophenyl)ethyl]-*N,O*-ditrifluoroacetyl-1-amino-2-methylpropanol (0.15 g, 0.37 mmol) and $AlCl_3$ (0.15 g, 1.1 mmol) were heated at 150 °C for 2.5 h while stirring. The product mixture was quenched with water (10 mL) and diluted with EtOAc (50 mL), and the organic phase was separated, washed with brine (20 mL), dried with Na_2SO_4, and concentrated. Flash chromatography (10% EtOAc in hexane, silica) resulted in 26 mg of a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 1 H), 7.13 (d, J = 8 Hz, 1 H), 7.03 (d, J = 8 Hz, 2 H), 3.74 (bm, 4 H), 3.13 (m, 2 H), 1.37 (s, 6 H). MS calculated for $C_{14}H_{15}ClF_3NO$ + H, 306; observed, 306.

Preparation of 8-Chloro-2,3,4,5-tetrahydro-1,1-dimethyl-1*H*-3-benzazepine (7gg). A solution of *N*-trifluoroacetyl-8-chloro-2,3,4,5-tetrahydro-1,1-dimethyl-1*H*-3-benzazepine (26 mg, 0.085 mmol) in methanol (5 mL) was treated with 15% aqueous NaOH (0.5 mL) and stirred at 20 °C for 16 h. The product mixture was concentrated, washed with EtOAc (2 × 10 mL), dried with Na_2SO_4, and concentrated to give 15 mg of a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 1 H), 6.98 (d, J = 8 Hz, 1 H), 6.90 (d, J = 8 Hz, 2 H), 2.93 (m, 4 H), 2.79 (m, 2 H), 2.28 (bm, 1 H), 1.26 (s, 6 H). MS calculated for $C_{12}H_{16}ClN$ + H, 210; observed, 210.

Biology. Intracellular IP_3 Accumulation Assay. HEK293 cells were transfected in 15 cm sterile dishes with or without (control) 16 μg of human $5HT_{2A}$, $5HT_{2B}$, or $5HT_{2C}$ receptor cDNA using 25 μL of lipofectamine. Cells were then incubated for 3–4 h at 37 °C and 5% CO_2, and then transfection media were removed and replaced with 100 μL of Dulbecco's modified Eagle medium (DMEM). Cells were then plated onto 100 cm sterile dishes. The next day cells were plated into 96-well poly-D-lysine microtiter plates at a density of 55K/0.2 mL. Six hours later, the medium was exchanged with [^{3}H]inositol (0.25 μCi/well) in inositol-free DMEM and plates were incubated at 37 °C and 5% CO_2 overnight. The next day, wells were aspirated and 200 μL of DMEM containing test compound, 10 μM pargyline, and 10 mM LiCl was added to appropriate wells. Plates were then incubated at 37 °C and 5% CO_2 for 3 h followed aspiration and by addition of fresh ice-cold stop solution (1 M KOH, 19 mM Na borate, 3.8 mM EDTA) to each well. Plates were kept on ice for 5–10 min, and the wells were neutralized by addition of 200 μL of fresh ice-cold neutralization solution (7.5% HCl). Plates were then frozen until further processing is desired. The lysate was then transferred into 1.5 mL Eppendorf tubes, and 1 mL of chloroform/methanol (1:2) was added per tube. The solution was vortexed for 15 s, and the upper phase was applied to a Biorad AG1-X8 anion exchange resin (100–200 mesh). First, the resin was washed with water at 1:1.25 w/v and 0.9 mL of upper phase was loaded onto the column. The column was then washed with 10 mL of 5 mM myoinositol and 10 mL of 5 mM Na borate/60 mM Na formate. The inositol trisphosphates were eluted into scintillation vials containing 10 mL of scintillation cocktail with 2 mL of 0.1 M formic acid/1 M ammonium formate. The columns were regenerated by washing

with 10 mL of 0.1 M formic acid/3 M ammonium formate and rinsed twice with deionized water and stored at 4 °C in water. Plates were then counted in a Packard TopCount scintillation counter, and EC_{50} values were obtained by fitting the data to a nonlinear curve-fitting program (Prism, San Diego, CA).

Animals and Housing. Male Sprague-Dawley rats (Harlan, San Diego, CA) weighing 250–400 g were used throughout the in vivo studies. Upon arrival at the test facility, animals were housed separately within a holding room controlled for temperature and light (lights off from 10:30 to 18:30). All food intake studies were conducted during the dark phase. Rats received food and water ad libitum unless stated otherwise.

Inhibition of Basal Food Intake Rats. On the test day, the animals were weighed and placed into individual cages (no bedding) at 9:00 a.m. At 10:00 a.m., animals were injected with 12.5, 25, 50, or 100 μmol/kg of test compound or vehicle (2 mL/kg, p.o.), with treatment groups counter-balanced according to Animal weights. Immediately upon lights out at 10:30 a.m., each animal was presented with a preweighed amount of food in a dish. Food consumption was then determined by weighing the food cup 2 h after the food was presented. Food intake (g) was subjected to one-way analyses of variance (ANOVA) and reported as percent inhibition of food intake at each dose relative to vehicle.

Effect of Lorcaserin on Body Weight, Food Intake, and Water Intake in Rats during Chronic (28 Days) Administration. For the repeated administration study, doses of lorcaserin were based on the ED_{50} at 6 h as determined in an acute dark-induced food intake study (study not shown). This was calculated to be 18 mg/kg. Four dose groups, eight per group, were included in the repeated administration study (in addition to a vehicle-treated group): 9, 18, and 36 mg/kg b.i.d. and 18 mg/kg q.d. Vehicle-treated animals were injected b.i.d. The b.i.d. injections occurred at 10:00 (30 min prior to lights off) and at 18:30 (immediately after lights on). Animals in the 18 mg/kg q.d. group were injected with lorcaserin at 10:00 and vehicle at 18:30. For the duration of the study, body weight, food intake, and water intake were measured daily at 09:00. Body weight on each day was used to dose the appropriate volume for both morning (10:00) and evening (18:30) injections. During the seven days immediately preceding compound administration, baseline body weight, food intake, and water intake were measured as described above, with b.i.d. injection of vehicle to acclimatize the animals to oral gavage. After these 7 baseline days, compound administration began and continued for 28 days.

Rat Pharmacokinetics. Male Sprague-Dawley rats were dosed intravenously and orally at 5 and 10 mg/kg, respectively, in water or phosphate buffered saline. Animals were fasted overnight prior to oral dose administration. Whole blood samples were collected from the jugular vein over a 24 h period postdose. Plasma was prepared from sodium heparin-treated whole blood and separated by centrifugation. Plasma samples were frozen and stored at −70 °C until assayed using a specific and sensitive HPLC/MS/MS method. The method provided a lower limit of quantitation of 1 ng/mL and an upper limit of quantitation of 2000 ng/mL. Serial sampling was used to define the plasma concentration vs time profile ($n = 4$–7 animals/administration route). Noncompartmental pharmacokinetic analysis was performed with a commercial software package (WinNonlin Professional, version 4.1.b., Pharsight, Mountain View, CA).

Supporting Information Available: Results from elemental analysis of target compounds; crystallographic data, positional parameters, and ORTEP diagram for lorcaserin hydrochloride hemihydrate. This material is available free of charge via the Internet at http://pubs.acs.org.

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