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Lorcaserin Hydrochloride

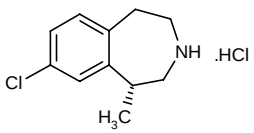
USAN

5-HT$_{2C}$ Receptor Agonist
Antiobesity Drug

APD-356

8-Chloro-1(*R*)-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride

InChI=1/C11H14ClN.ClH/c1-8-7-13-5-4-9-2-3-10(12)6-11(8)9;/h2-3,6,8,13H,4-5,7H2,1H3;1H/t8-;/m0./s1



$C_{11}H_{15}Cl_2N$
Mol wt: 232.1489

CAS: 846589-98-8

CAS: 616202-92-7 (free base)

EN: 355197

Abstract

Obesity affects millions of people worldwide and the socio-economic cost of the condition is substantial. Despite lifestyle changes, pharmacotherapy is needed for the treatment of obesity. Lorcaserin is a highly selective 5-HT$_{2C}$ receptor agonist developed for the treatment of obesity. In rats, lorcaserin led to dose-dependent weight loss. Lorcaserin proved safe and well tolerated in healthy volunteers and obese patients. In a phase II clinical study, patients administered 20 mg/day lorcaserin achieved an average weight loss of 3.6 kg (7.9 lbs), which was significantly greater than the average weight loss of 0.3 kg (0.7 lbs) in the placebo group. A phase III clinical trial is ongoing to evaluate the long-term safety and efficacy of lorcaserin in patients with obesity.

Synthesis

Lorcaserin hydrochloride can be prepared by several different procedures. 4-Chlorophenethylamine (I) is acylated with 2-chloropropionyl chloride (II) in the presence of pyridine in CH_2Cl_2 to give the chloropropionamide (III), which is cyclized to the benzazepinone (IV) upon heating with $AlCl_3$. Subsequent reduction of (IV) with either BH_3 or $LiAlH_4$ in Et_2O affords the racemic lorcaserin (V) (1-3). In a related method, chloropropionamide (III) is reduced with borane in THF to yield the chloro amine (VIa), which is then cyclized to benzazepine (V) in the presence of $AlCl_3$ (3). Alternatively, condensation of 4-chlorophenethyl bromide (VII) with 1-amino-2-propanol (VIII) provides the aminoalcohol (IX), which is converted to either the chloro amine (VIa) or the analogous bromo amine (VIb) by treatment with $SOCl_2$ or $SOBr_2$, respectively (3). Optical resolution of tetrahydrobenzazepine (V) either employing chiral HPLC or by crystallization with D-tartaric acid furnishes the target (*R*)-enantiomer (X) (1-3). This is finally converted to the title hydrochloride salt by treatment with HCl in different solvent systems (4). In a further procedure, after protection of 4-chlorophenethylamine (I) as the corresponding trifluoroacetamide (XI) by means of trifluoroacetic anhydride and pyridine in CH_2Cl_2, iodination with bis(pyridine)iodonium tetrafluoroborate in the presence of trifluoromethanesulfonic acid furnishes (XII). Subsequent alkylation of trifluoroacetamide (XII) with allyl bromide under phase transfer conditions leads to the iodo olefin (XIII), which undergoes intramolecular Heck cyclization in the presence of $Pd(OAc)_2$ and PPh_3 to furnish the methylene benzazepine (XIV). After reduction of (XIV) to the methyl analogue (XV) by catalytic hydrogenation over Pd/C, the *N*-trifluoroacetyl group is hydrolyzed with NaOH in aqueous MeOH to give 8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (V) (5). Scheme 1.

Background

Obesity affects millions of people worldwide. According to the Centers for Disease Control and Prevention at the U.S. Department of Health and Human Services, more than 30% of Americans are obese and the prevalence of overweight and obesity is increasing dramatically (6). Obesity is closely associated with numerous health risks, including diabetes, coronary heart disease and hypertension. It is a leading cause of diabetes and it

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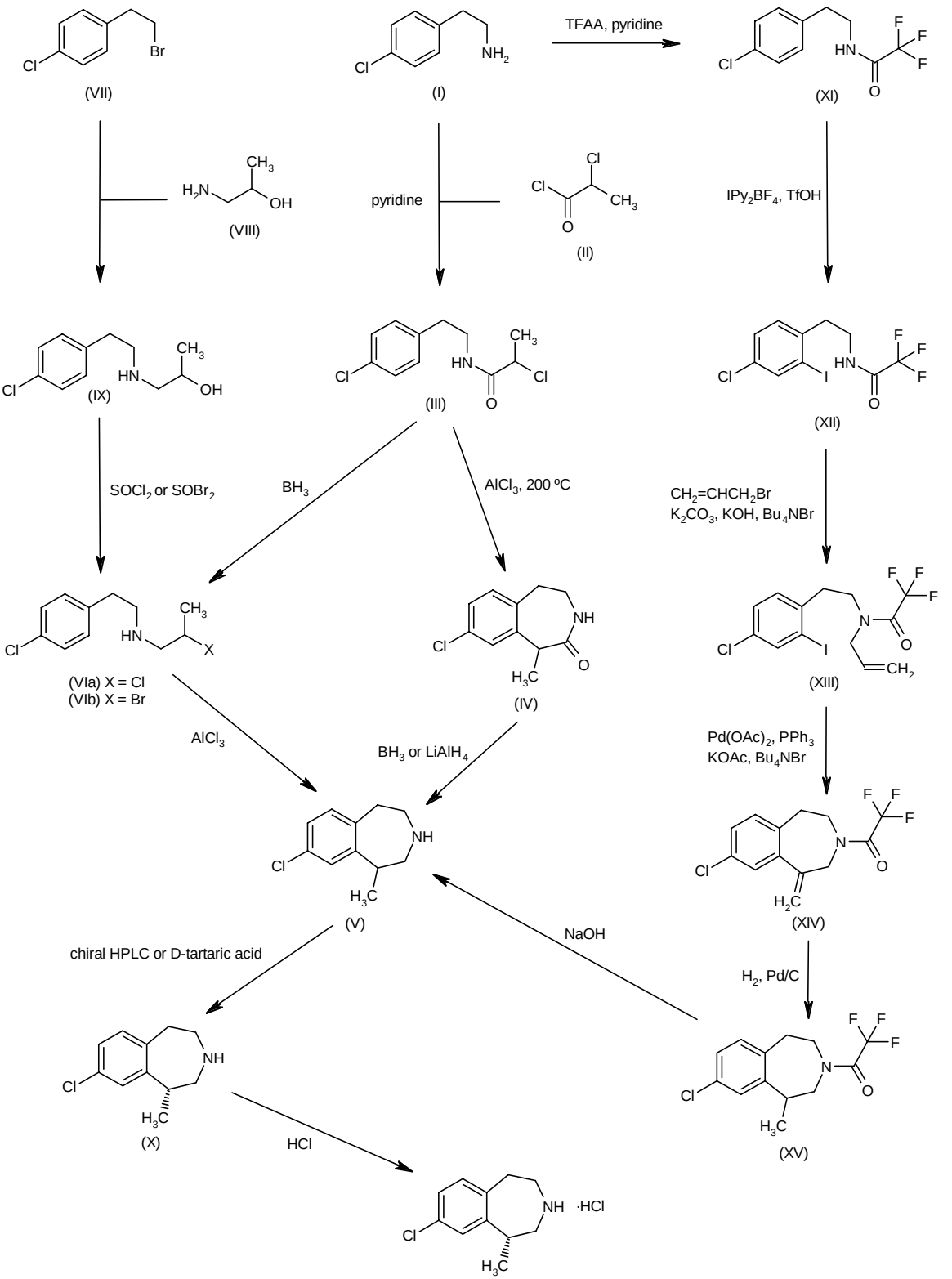
Scheme 1: Synthesis of Lorcaserin Hydrochloride



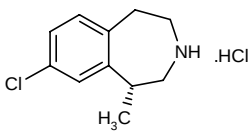
accounts for approximately 2.6 million deaths annually. According to the U.S. Surgeon General, direct and indirect economic costs of obesity and being overweight approached approximately USD 117 billion in 2000 (7). In addition to lifestyle changes, pharmacotherapy is therefore needed for the treatment of overweight and obese individuals.

However, finding a safe and effective agent for the treatment of obesity has not been easy. Two widely used antiobesity agents, fenfluramine and dexfenfluramine, were withdrawn from the market due to serious side effects, including cardiac valvular fibrosis and pulmonary hypertension. Orlistat (Xenical®; Roche) and sibutramine (Meridia®; Abbott) are currently approved in the U.S. for the treatment of obesity. Orlistat inhibits the absorption of dietary fat by blocking the activity of gastrointestinal lipases, whereas sibutramine acts within the CNS to suppress appetite and increase energy expenditure. However, both orlistat and sibutramine have limited long-term efficacy and side effects (8-11). Treatment options with high efficacy and a good safety profile are therefore needed.

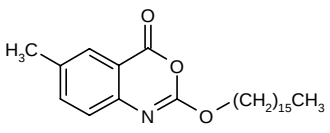
Rimonabant (Acomplia®; sanofi-aventis), the first selective cannabinoid CB_1 antagonist, was approved in Europe in 2006 for the treatment of obesity. Treatment with rimonabant led to significant weight loss and improvement in cardiovascular risk factors. For patients with obese-associated type 2 diabetes, treatment with rimonabant also led to reduction in hemoglobin A1c (HbA1c) and improvement in insulin sensitivity. The drug was well tolerated in clinical trials, with the most common side effects including depression, nausea, dizziness and anxiety. However, the long-term side effects of the drug are not yet known (9, 12). Selected products currently under clinical development for the treatment of obesity include lorcaserin (Arena Pharmaceuticals), cetilistat (ATL-962; Alizyme, Takeda), CP-945598 (Pfizer), PYY3-36 (Nastech, Amylin), SLV-319 (Solvay, Bristol-Myers Squibb), phentermine/topiramate (Qnexa™; Vivus), bupropion/naltrexone (Contrave™; Orexigen), bupropion/zonisamide (Empatic™, formerly Excalia™; Orexigen) and pramlintide (Amylin) (8-10, 12) (Table I).

Table I: Selected products under clinical development for obesity.

Drug	Source	Phase
1. Bupropion/naltrexone (Contrave™)	Orexigen	III
2. CP-945598*	Pfizer	III
3. Lorcaserin hydrochloride	Arena	III
4. Bupropion/zonisamide (Empatic™)	Orexigen	II
5. Cetilistat	Alizyme/Takeda	II
6. Phentermine/topiramate (Qnexa™)	Vivus	II
7. Pramlintide acetate**	Amylin	II
8. PYY3-36 (AC-162352)	Nastech/Amylin	II
9. SLV-319	Solvay/Bristol-Myers Squibb	II



(**3**)



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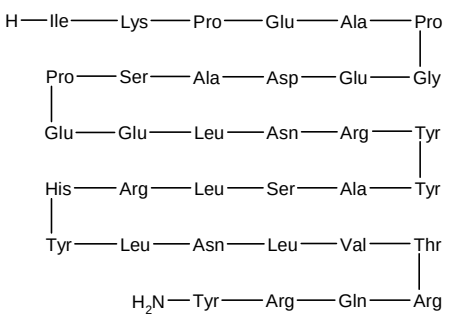

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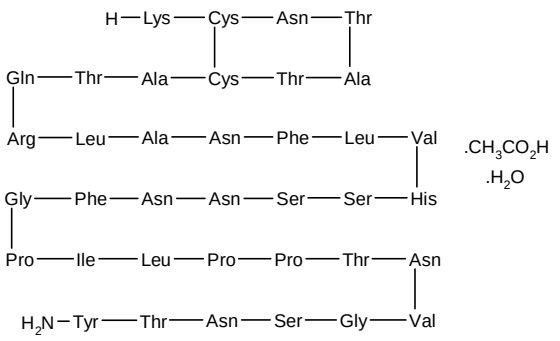

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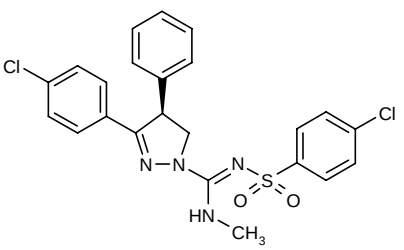

(**9**)

*Structure not available. **Launched in 2005 for the treatment of diabetes.

The benzazepine lorcaserin hydrochloride (formerly APD-356) is a selective 5-HT_{2C} receptor agonist developed at Arena Pharmaceuticals and selected for clinical evaluation for the treatment of obesity. Lorcaserin helps patients with obesity lose weight by selectively stimulating the 5-HT_{2C} receptor, located in the hypothalamus, which is involved in regulating satiety and influences metabolism (2, 11, 13-15).

Preclinical Pharmacology

In vitro, lorcaserin hydrochloride demonstrated approximately 15- and 100-fold selectivity for the 5-HT_{2C} receptor over 5-HT_{2A} and 5-HT_{2B} receptors, respectively, with respective EC_{50} values in a functional assay in HEK-293 cells of 11, 260 and 1100 nM. It has been suggested that the 5-HT_{2B} receptor is primarily implicated in the cardiac valvulopathy associated with nonselective serotonergic agents, and that the 5-HT_{2A} receptor is responsible for many of the central nervous system-associated adverse events of nonselective serotonergic agents. With its high selectivity for 5-HT_{2C} receptors, lorcaserin is therefore expected to be safe and effective for the treatment of obesity (2, 13). In an acute feeding model in male rats, it reduced food intake for at least 6 h when administered p.o. (12.5-50 mg/kg) 1 h before the dark cycle (2).

The potential use of lorcaserin in the treatment of obesity was then evaluated in male and female diet-induced obesity-prone rats. In the study, the rats were first fed with a high-fat diet for 8 weeks and then treated with either lorcaserin or sibutramine for 28 days. Lorcaserin demonstrated promising efficacy comparable to sibutramine. The agent significantly and dose-dependently reduced food intake and body weight, primarily due to a reduction in fat mass. Rats that received 18 mg/kg b.i.d lorcaserin consumed an average of 25% less food and had a 10% weight loss. In addition, lorcaserin significantly improved dyslipidemia (13, 16).

Pharmacokinetics and Metabolism

In a phase Ia study conducted in healthy volunteers, oral lorcaserin demonstrated a good pharmacokinetic profile. Following single oral doses of up to 40 mg, the terminal plasma elimination half-life ($t_{1/2}$) was approximately 11 h, indicating its suitability for once-daily dosing. The study also indicated that the absorption of lorcaserin was not affected by food. Lorcaserin at the dose of 40 mg produced serum drug concentrations well above concentrations required to activate 5-HT_{2C} receptors *in vitro* (17).

The pharmacokinetics of lorcaserin were further evaluated in a phase Ib trial in which healthy volunteers received doses of 3, 10 and 20 mg/day for 14 days. Pharmacokinetics increased in a dose-proportional manner and no gender differences were observed. The time to peak plasma concentrations (t_{max}) was approximately 2 h after administration and the plasma $t_{1/2}$ was approximately 10 h, similar to in the phase Ia study. Patients achieved steady-state plasma levels by day 5 (18).

Safety

The safety of lorcaserin was also assessed in the phase Ib study. Lorcaserin proved to be safe and well tolerated. As expected, side effects, which were generally mild, occurred more frequently on the highest dose, whereas adverse events in the two lower dose groups were similar to those seen on placebo. The most commonly reported adverse events included headache, nausea and vomiting. No patients withdrew from the study because of adverse events (18).

Lorcaserin again proved safe and well tolerated in a subsequent multicenter, randomized, double-blind, placebo-controlled phase IIa trial evaluating doses of 1, 5 and 15 mg in 352 obese subjects. Adverse events that occurred in more than 5% of the patients in any group included headache, nausea, diarrhea, cough and nasopharyngitis. No apparent effect on heart valves or pulmonary artery pressure was detected on electrocardiograms (19).

In a randomized, double-blind, placebo-controlled phase IIb study conducted in 469 obese patients, no drug-related effects on heart valve function or pulmonary artery pressure were reported following doses of lorcaserin of 10 and 15 mg/day and 10 mg b.i.d. Adverse events were mostly mild or moderate, with the most common including headache, nausea and dizziness. Four cases of serious adverse events occurred, including 1 case of kidney stone and 1 case of pneumonia in the placebo group, 1 case of clinical depression in the 10 mg/day group and 1 case of new-onset seizures in the 20 mg/day group. Four patients in the placebo group and 2, 9 and 6 patients in the 10 mg once daily, 15 mg once daily and 10 mg b.i.d lorcaserin groups, respectively, discontinued treatment due to adverse events (20, 21).

Clinical Studies

The acute effects of lorcaserin on food intake were evaluated in part C of the phase Ia study, a double-blind, randomized, placebo-controlled, crossover trial. Subjects received 0.1, 1 or 10 mg lorcaserin or placebo at weekly intervals over a period of 4 weeks. Compared with placebo, lorcaserin at the dose of 10 mg, approximately 10 times the *in vitro* EC_{50} for 5-HT_{2C} receptor activation, led to a 6.5% mean reduction in meal size (17).

The efficacy of lorcaserin in terms of weight loss was evaluated in the randomized, double-blind, multiple-dose phase IIa trial in 352 obese volunteers with an average body mass index (BMI) of 36 kg/m^2 and an average weight of 223 lbs, who were divided into 4 groups to receive 1, 5 or 15 mg lorcaserin or placebo once daily for 28 days. Patients in the highest dose group achieved a significantly greater average weight loss of 1.3 kg (2.9 lbs) compared to patients in the placebo group (0.4 kg, or 0.7 lbs). However, no statistically significant weight loss was reported in the other dose groups (19).

Lorcaserin was also tested for its efficacy in the 12-week phase IIb study conducted in 469 obese patients who

had an average baseline weight of 100 kg (220 lbs) and a mean BMI of 36.4 kg/m^2. During the 12-week study, the patients maintained their lifestyle in terms of diet and exercise habits, abstained from alcohol, and continued on antihypertensive or dyslipidemic therapy if required. Compared with patients in the placebo group who achieved an average weight loss of only 0.3 kg (0.7 lbs), patients taking higher doses of lorcaserin achieved a statistically significant weight loss, with an average weight loss of 1.8 kg (4.0 lbs) on 10 mg, 2.6 kg (5.7 lbs) on 15 mg and 3.6 kg (7.9 lbs) on 20 mg. Compared with patients in the placebo group, significantly more patients in the lorcaserin groups lost at least 5% of their initial body weight: 31.2% in the 20-mg group, 19.5% in the 15-mg group, 12.8% in the 10-mg group and 2.3% in the placebo group (20, 21).

To further evaluate the safety and efficacy of lorcaserin in obese patients, Arena initiated a phase III trial in September 2006. This multicenter, double-blind, randomized, placebo-controlled study, known as BLOOM (Behavioral modification and Lorcaserin for Overweight and Obesity Management), is the first of three overlapping pivotal trials and will enroll approximately 3,000 overweight and obsese patients (22).

Source

Arena Pharmaceuticals, Inc. (US).

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