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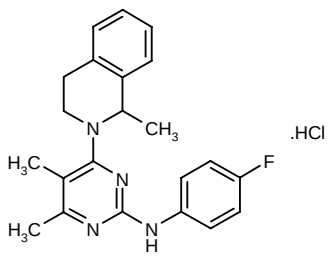
CCC: 0377-8282/2004

Revaprazan Hydrochloride

Treatment of GERD
H^+/K^+-ATPase Inhibitor
Antiulcer Drug

YH-1885
SB-641257A

N-(4-Fluorophenyl)-4,5-dimethyl-6-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidin-2-amine hydrochloride
N-[4,5-Dimethyl-6-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidin-2-yl]-*N*-(4-fluorophenyl)amine hydrochloride



$C_{22}H_{23}FN_4.HCl$
Mol wt: 398,9106
CAS: 178307-42-1
CAS: 199463-33-7 (as free base)
EN: 272502

Abstract

The prevalence of acid-related diseases such as gastroesophageal reflux disease (GERD) and peptic ulcer has increased significantly over the years and the incidence continues to rise. Although the etiology of these diseases remains unclear, acid suppression or antisecretory therapy has emerged as the treatment of choice for both. Of the two main classes of antisecretory agents (histamine H_2 receptor antagonists and proton pump inhibitors [PPIs]), PPIs, which block H^+/K^+-ATPase in gastric parietal cells, exhibit more potent and longer lasting inhibition of gastric acid secretion and have become the preferred treatment option. Revaprazan hydrochloride (YH-1885) is a novel, reversible PPI with potent, long-lasting acid-suppressive effects and improved safety and pharmacokinetic profiles as compared to irreversible PPIs such as omeprazole. Revaprazan was chosen for further development as an antisecretory agent and was shown to be safe, effective and well tolerated in healthy subjects, where it significantly inhibited gastric acid secretion. Revaprazan is currently undergoing phase III development as a treatment for peptic ulcer.

Synthesis

Revaprazan hydrochloride can be obtained by two different ways:

1) Chlorination of 5,6-dimethyl-2,4-dihydroxypyrimidine (I) with phosphorus oxychloride and *N,N*-dimethylaniline under reflux provides the dichloropyrimidine (II), which by selective displacement of its 4-chloro group with 1-methyl-1,2,3,4-tetrahydroisoquinoline (III) by means of Et_3N in DMF affords the 2-chloropyrimidine derivative (IV). Finally, this adduct (IV) is condensed with 4-fluoroaniline (V) in DMF and treated with aquous hydrochloric acid (1). Scheme 1.

2) Condensation of 4-fluoroaniline (V) with cyanamide under acidic conditions affords *N*-(4-fluorophenyl)guanidine (VI), which is cyclized with ethyl 2-methylacetoacetate (VII) in hot DMF to produce 2-(4-fluorophenylamino)-4-hydroxy-5,6-dimethylpyrimidine (VIII). Chlorination of compound (VIII) with $POCl_3$ in DMF gives the chloropyrimidine derivative (IX) (2, 3), which is finally condensed with 1-methyl-1,2,3,4-tetrahydroisoquinoline (III) by means of KOAc in refluxing hexanol or Et_3N in either 1,2-propylene glycol, a refluxing mixture butanol/ethylene glycol (2, 3) or ethylene glycol (4) and treated with conc. hydrochloric acid (2-4). Scheme 2.

Intermediate 1-methyl-1,2,3,4-tetrahydroisoquinoline (III) can be prepared by two different synthetic strategies:

i) Acetylation of phenethylamine (X) with acetyl chloride (XI) by means of Et_3N in dichloromethane provides *N*-(2-phenylethyl)acetamide (XII), which is cyclized with hot polyphosphoric acid to afford 1-methyl-3,4-dihydroisoquinoline (XIII). Finally, compound (XIII) is reduced with sodium borohydride in EtOH (5). Scheme 3.

ii) Alkylation of α-methylbenzylamine (XIV) with 2-bromoethanol (XV) in dichloromethane gives *N*-(2-hydroxyethyl)-α-methylbenzylamine (XVI), which is treated with conc. aqueous HBr under reflux to provide the 2-bromoethylamine derivative (XVII) (2, 3). Finally, amine (XVII) is

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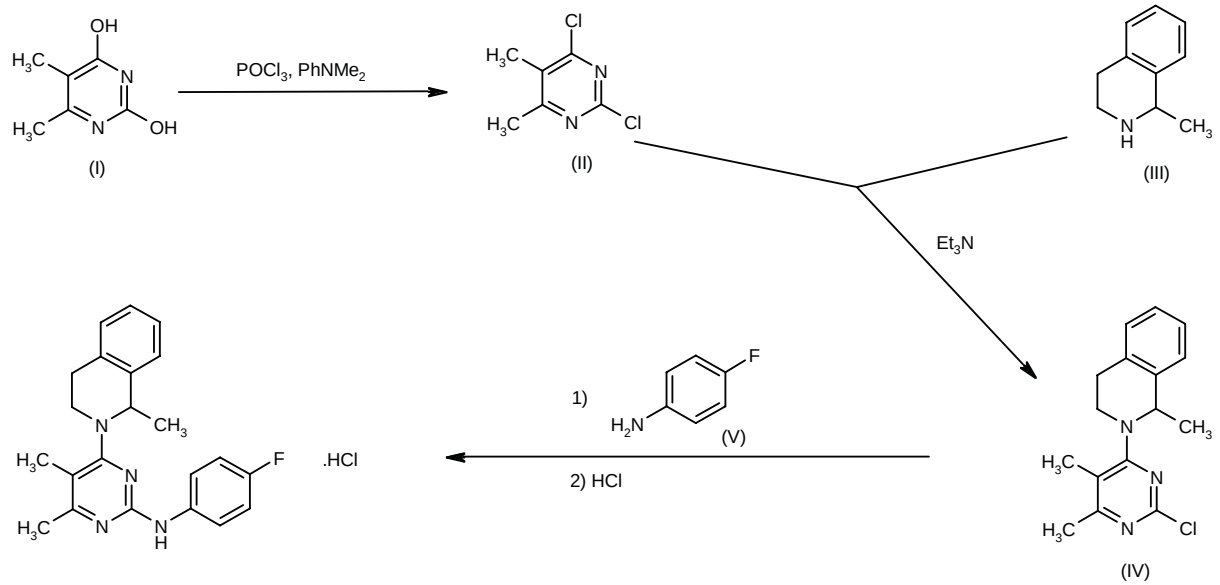
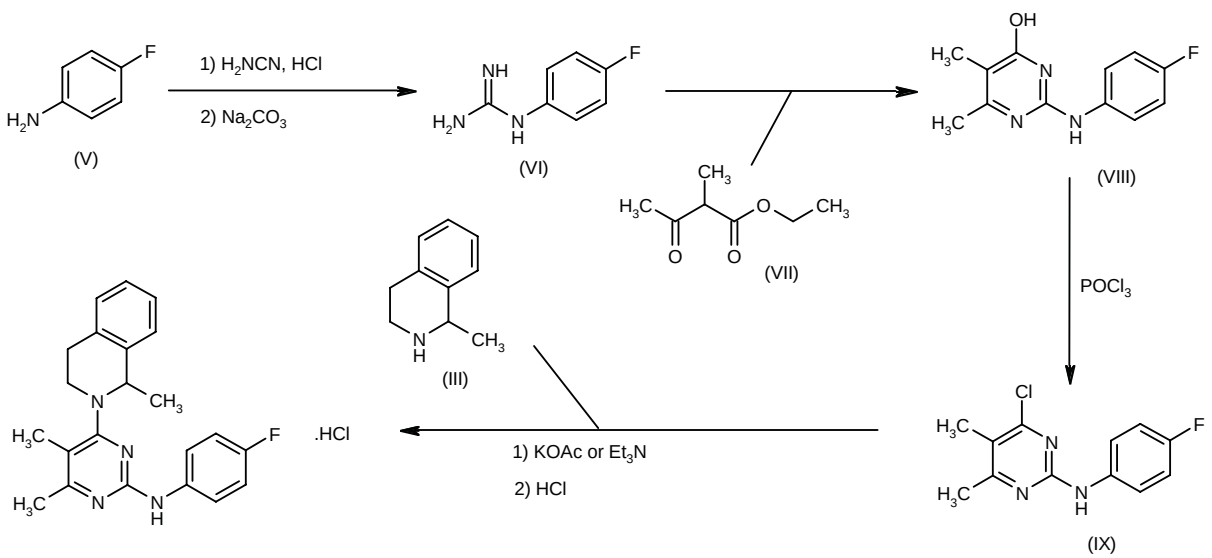
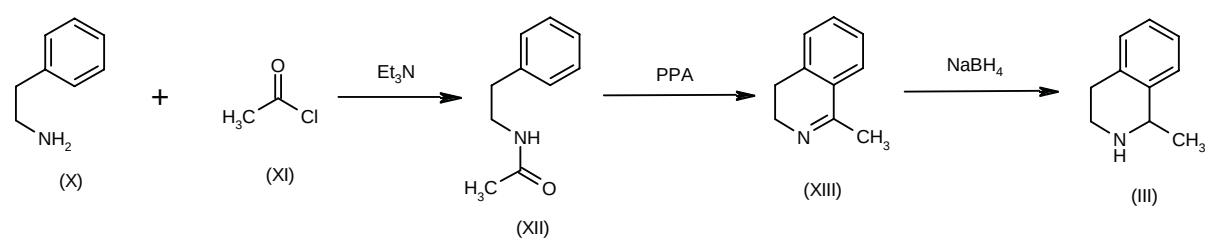
Scheme 1: Synthesis of Revaprazan Hydrochloride



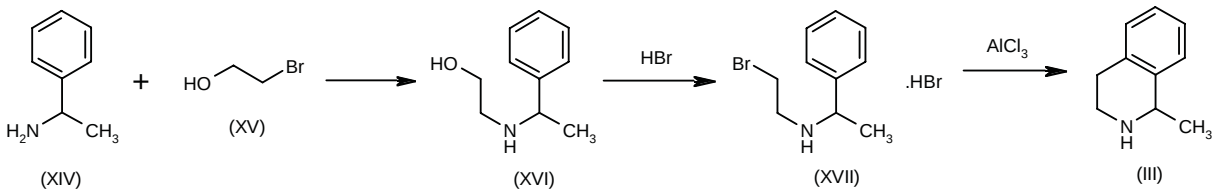
Scheme 2: Synthesis of Revaprazan Hydrochloride



Scheme 3: Synthesis of Intermediate (III)



Scheme 4: Synthesis of Intermediate (III)



submitted to a Friedel-Crafts cyclization by heating with $AlCl_3$ in either decalin or 1,2-dichlorobenzene (2-4). Scheme 4.

Introduction

The prevalence of acid-related diseases such as gastroesophageal reflux disease (GERD) and peptic ulcer disease has increased significantly over the years and the incidence continues to rise, possibly due to changes in diet and lifestyle. According to the American College of Gastroenterology, an estimated 60 million Americans suffer from heartburn, the predominant symptom of GERD, at least once a month and it has been reported that 25 million Americans suffer from peptic ulcer (gastric and duodenal ulcer combined) (6, 7).

The etiology of GERD and gastric ulcer remains controversial. Researchers have speculated that increased gastric acid production, the presence of *Helicobacter pylori* and/or the use of nonsteroidal antiinflammatory drugs (NSAIDs) may contribute significantly to the pathogenesis of the diseases. However, it is clear that the goal of therapy is to relieve and maintain relief from symptoms, to heal mucosal injury and to prevent complications. Acid suppression or antisecretory therapy has emerged as the treatment of choice for both GERD and gastric ulcer. Antisecretory therapy consists of two main classes of agents: histamine H_2 receptor antagonists and proton pump inhibitors (PPIs). The PPIs exhibit more potent and longer lasting inhibition of gastric acid secretion as compared to H_2 antagonists and are the preferred treatment option (6-8).

Proton pump inhibitors are membrane-permeable weak bases that block H^+/K^+-ATPase in gastric parietal cells. These agents can block 70% or more of active pumps by accumulating in the acid spaces of active gastric parietal cells, where they undergo acid-catalyzed conversion to active sulfenamide derivatives. These derivatives in turn covalently bind to H^+/K^+-ATPase through disulfide bridges and inhibit acid production. In contrast to H_2 receptor antagonists which can only block histamine H_2-mediated acid secretion, PPIs block H_2-, gastrin- and cholinergic-mediated sources of acid production (6-10).

The first PPI – omeprazole (Losec; AstraZeneca) – was introduced to the market in 1988. Since then, several PPIs have followed, including lansoprazole (Ogast®; Takeda), pantoprazole sodium (Pantazol®; Byk Gulden), rabeprazole sodium (Aciphex®; Eisai/Janssen-Cilag) and esomeprazole magnesium (Nexium®; AstraZeneca), the (*S*)-isomer of omeprazole. The first-generation compounds such as omeprazole exhibited limitations in terms of pharmacokinetic, pharmacodynamic and efficacy profiles, while newer agents such as rabeprazole and esomeprazole show distinct advantages such as rapid onset and more potent suppression compared to the older agents (11, 12). Thus, researchers continue to search for novel, fast-acting PPIs with improved abilities to suppress gastric acid secretion. Revaprazan hydrochloride (YH-1885) is one such novel, reversible PPI that has been shown to have potent acid-suppressive effects and an excellent safety profile compared to omeprazole. In contrast to irreversible PPIs such as omeprazole and lansoprazole, revaprazan reversibly inhibits H^+/K^+-ATPase via binding to the K^+-binding site of the pump. This reversibility results in fewer adverse events compared to irreversible PPIs. Revaprazan was therefore chosen for further development as an antisecretory agent (13).

Pharmacological Actions

An *in vitro* study using human colonic Caco-2 cell monolayers examined the transepithelial flux of revaprazan. The flux of the agent from the apical to the basolateral side was 3-5 times greater than from the basolateral to the apical side. The uptake of revaprazan into monolayers was saturable and possibly mediated by a high-affinity, energy-dependent transporter (apparent K_m = 1.47 ± 0.21 μM; V_{max} = 25.14 ± 1.16 pmol/cm^2/40 s). Further experiments showed that the transport of revaprazan was inhibited by addition of structural analogues of the agent (*e.g.*, YH-957, YH-1070, YH-1041), uracil and 5-methyluracil, and nucleobase transport inhibitors (*e.g.*, papaverine, dipyridamole, phloridzin), indicating that the flux of revaprazan was partially mediated via a nucleo-base transport system (14).

Pharmacokinetics

The development of an HPLC method to determine concentrations of revaprazan in human plasma and urine and rat blood and tissue homogenates was reported. The detection limits for human plasma and urine and rat tissue homogenates (including blood) were 50, 100 and 100 ng/ml, respectively, and the coefficients of variation (within-day and between-day) for all sample types were generally below 8.84% (15).

Blood partition and protein binding of revaprazan were examined in an *in vitro* study using rabbit and human blood. The agent rapidly reached equilibrium between rabbit plasma and blood cells. Plasma concentrations were constant up to 120 min of incubation, suggesting that metabolism of the agent in blood is not significant. Extensive binding to human serum albumin was observed (16).

The pharmacokinetics of revaprazan (50-200 mg/kg p.o. and 5-20 mmg/kg i.v.) were examined in rats and dogs. The pharmacokinetic parameters for both i.v. and p.o. dosing in these species appeared to be dose-independent. Following p.o. dosing at 50-100 mg/kg in rats, $AUC_{0\text{-}12\ h}$ and $AUC_{0\text{-}24\ h}$ values were proportional to dose. However, $AUC_{0\text{-}24\ h}$ values after p.o. dosing at 200 mg/kg were less than proportional to dose (324, 689 and 815 μg.min/ml for 50, 100 and 200 mg/kg p.o., respectively). This was suggested to be due to poor water solubility, since the percentage of unchanged drug remaining in the gastrointestinal (GI) tract at 24 h increased with dose (11.8%, 15.3% and 42.8% for 50, 100 and 200 mg/kg p.o., respectively). Oral bioavailability was about 40% in rats following dosing with 50 and 100 mg/kg. This relatively low oral bioavailability was speculated to be due to first-pass metabolism in the liver since approximately 30% of the oral dose disappeared after intraportal administration of 5 mg/kg to rats. It was speculated that about 15% of the dose could also disappear via a first-pass effect in the small intestine and/or degradation in the GI tract. When instilled into rat stomach and large intestine, revaprazan was found to be absorbed from the ileum, duodenum and jejunum, but levels were under the detection limit in plasma. $AUC_{0\text{-}10\ h}$ values were not significantly different following p.o. dosing of 0.5 and 2 g to dogs (96.8 and 98.2 μg·min/ml, respectively) also possibly due to poor water solubility. Revaprazan was not detected in the urine of rats or dogs following p.o. or i.v. administration (17).

The pharmacokinetics and pharmacodynamics of revaprazan (60, 100, 150 and 300 mg once daily p.o. for 7 days) were examined in a randomized, single-blind, parallel-group study in 46 healthy volunteers. The agent was safe and well tolerated, with no serious or dose-limiting adverse events reported. After single dosing, C_{max} was reached at 1.3-2.5 h and plasma levels then decreased monoexponentially with a $t_{1/2}$ value of 2.2-2.4 h in subjects receiving doses up to 200 mg. Linear pharmacokinetics were observed with little accumulation after multiple dosing. The parent drug was not detected in urine. A significant increase in mean intragastric pH and the percentage of time at pH > 4 was observed in subjects receiving a single dose of 150 mg or greater. The onset of these effects was rapid, with maximum effects observed on the first day of multiple dosing. Serum gastrin levels also increased rapidly during dosing, although these effects were weakly dose-related (18, 19).

Clinical Studies

A randomized, double-blind, 3-way crossover study involving 25 healthy male volunteers examined the pharmacodynamics of revaprazan (100, 150 and 200 mg once daily p.o. for three 7-day periods separated by a 7-day washout period) and demonstrated significant inhibition of gastric acid secretion. Median intragastric pH on day 7 was 3.2, 3.9 and 4.2 for the respective dose groups and the mean intragastric pH of subjects receiving 200 mg at baseline, day 1 and day 7 was 1.9, 3.5 and 4.2, respectively. The fasting plasma gastrin levels in the 200-mg dose group at baseline, day 1 and day 7 were 40.9, 47.1 and 51.7 ng/l, respectively. The presence of *H. pylori* infection was found to significantly affect the ability of revaprazan to suppress gastric acid secretion. Intragastric pH values of *H. pylori*-positive subjects in the 200-mg dose group at baseline, day 1 and day 7 were 2.3, 4.7 and 6.0, respectively, *versus* 1.6, 2.5 and 2.8, respectively, in *H. pylori*-negative subjects (20).

A phase II clinical trial simulation was performed using pharmacokinetic data from 52 subjects receiving 5 different doses of revaprazan, and intragastric pH data obtained from 46 of these subjects at about 48-72 h postdosing. The simulation indicated that oral doses of 200 and 300 mg taken once daily before breakfast could maintain intragastric pH above 3 for 19.7 ± 4.4 and 21.3 ± 3.7 h, respectively. These times corresponded to therapeutic rates of 94.9 ± 3.1 and 97 ± 2.4%, respectively, which are comparable or superior to available antiulcer therapies (21).

Revaprazan is currently undergoing phase III development for the treatment of peptic ulcer (22).

Source

Yuhan Corp. (KR).

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