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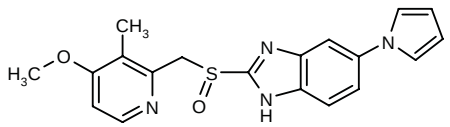
CCC: 0377-8282/99

IY-81149

Antiulcerative
H^+/K^+-ATPase Inhibitor

2-[(4-Methoxy-3-methylpyridin-2-yl)methylsulfinyl]-5-(1-pyrrolyl)-1*H*-benzimidazole



$C_{19}H_{18}N_4O_2S$ Mol wt: 366.4432

CAS: 172152-36-2

EN: 228755

Synthesis

The synthesis of IY-81149 can be obtained according to Scheme 1. (1) The oxidation of 2,3-lutidine (I) with hydrogen peroxide in acetic acid affords 2,3-dimethylpyridine-*N*-oxide (II), which is treated with sulfuric acid and nitric acid to give the corresponding nitro compound (III). The treatment of (III) with NaOH in methanol gives 2,3-dimethyl-4-methoxypyridine-*N*-oxide (IV), which is reacted with acetic acid and acetic anhydride and oxidated in refluxing NaOH, yielding 3-methyl-4-methoxypyridine-2-methanol (V). The chlorination of (V) with thionylchloride in CH_2Cl_2 affords 3-methyl-4-methoxy-2-chloromethylpyridine (VI). The reaction of 2-mercapto-5-nitrobenzimidazole (VII) with iron and concentrated HCl in refluxing ethanol and water gives monoamine (VIII), which by condensation with 2,5-dimethoxytetrahydrofuran (IX) in acetic acid yields 2-mercapto-5-(1-pyrrolyl)benzimidazole (X). The condensation of (VI) with (X) by means of NaOH in methanol gives 2-[(4-methoxy-3-methyl-2-pyridinyl)-methylsulfanyl]-5-(1*H*-pyrrol-1-yl)-1*H*-benzimidazole (XI), which is finally treated with *m*-chloroperoxybenzoic acid (*m*-CPBA) in chloroform.

Description

Pale yellow crystalline powder, m.p. 152-5 °C, $[\alpha]_D^{23}$ 0.0° (c 1%, chloroform).

Introduction

The use of [(2-pyridinyl)methylsulfinyl]benzimidazoles, such as omeprazole, for the treatment of acid-related gastrointestinal disorders, duodenal and gastric ulcers and gastroesophageal reflux disease is now well established (2, 3). These compounds, as shown in Table I, produce moderate suppression of gastric acid secretion through specific inhibition of H^+/K^+-ATPase (the proton pump) (4). Most of these enzyme inhibitors, however, have long-lasting antisecretory effects which can lead to elevation of plasma gastrin levels and potentially serious side effects (*e.g.*, gastric carcinoids) as a result of increased plasma gastrin levels (5). Based on the need for new, irreversible antiulcerative compounds with a stronger antisecretory effect than omeprazole, a longer-lasting inhibition of gastric H^+/K^+-ATPase (6) and antibacterial activity against *Helicobacter pylori*-induced gastric ulcer (7), we synthesized a novel series of substituted benzimidazoles showing fewer side effects.

A series of 5-*N*-substituted aminobenzimidazoles with substituted alkyl or alkoxy groups at position 3 or 4 on the pyridine ring of omeprazole was synthesized at Il-Yang Pharmaceutical Co. and subjected to pharmacological efficacy studies (8, 9). The nature of the substituted alkyl or alkoxy groups at position 3 or 4 was found to be critical for attaining high potency. IY-81149 is a structural analog of omeprazole which is more potent than omeprazole in terms of antisecretory and anti-*Helicobactor pylori* activity *in vitro*. It also has a shorter half-life, thus avoiding the induction of gastrin, which makes it a most attractive candidate for further evaluation.

Pharmacological studies of IY-81149 carried out in various rat models of ulcer have demonstrated that after oral administration, the compound exhibits potent inhibitory effects on the formation of stress-induced gastric and chronic ulcers. Results of phase I/II clinical studies indicate that IY-81149, as compared to omeprazole, is at least as safe, is more potent and has a longer duration of action, with a once-daily dose providing 24 h of protection against gastric acid secretion.

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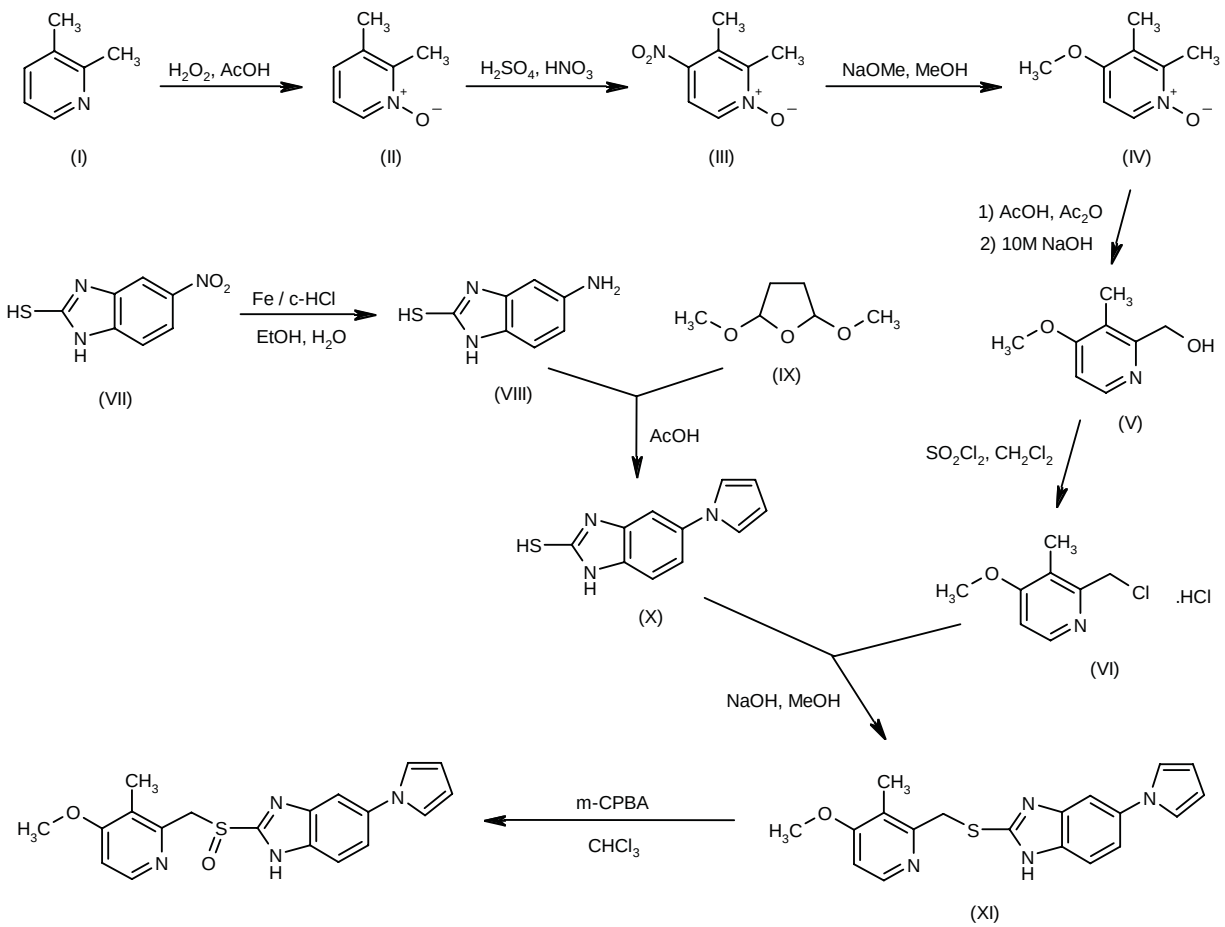
Scheme 1: Synthesis of IY-81149



Pharmacological Actions

IY-81149 dose-dependently inhibited H^+/K^+-ATPase activity in isolated rabbit parietal cells (IC_{50} = 6.0 μM) and was more potent than omeprazole (IC_{50} = 100 μM). Title compound also inhibited histamine-stimulated accumulation of [^{14}C]-aminopyrine in isolated rabbit parietal cells (IC_{50} = 9.0 nM); the IC_{50} for omeprazole in this experiment was 19 nM. In human parietal cells, both IY-81149 and omeprazole inhibited histamine-stimulated accumulation of [^{14}C]-aminopyrine by a ratio of about 2:1. The above results suggest that IY-81149 is more potent than omeprazole.

In fistula rat model, IY-81149 dose-dependently inhibited histamine-stimulated gastric acid secretion following both intravenous and intraduodenal administration (ED_{50}s = 0.24 and 0.43 mg/kg, respectively). The ED_{50}s for omeprazole were 0.3 and 0.68 mg/kg for intravenous and intraduodenal administration, respectively. In this case, IY-81149 was 3 times more effective than omeprazole in inhibiting gastric acid secretion. The effects of IY-81149 on basal gastric secretion were evaluated in several rat models. In pylorus-ligated rats, IY-81149 administered intraduodenally decreased basal gastric secretion in a dose-dependent manner (ED_{50} = 1.94 mg/kg) and was about 3-fold more potent than omeprazole (ED_{50} = 5.64 mg/kg). In rat models of gastric ulcer, IY-81149 dose-dependently prevented the formation of stress- and ethanol-induced gastric lesions, with ED_{50}s of 3.5 and 14.2 mg/kg, respectively. In other experiments, both IY-81149 and omeprazole dose-dependently inhibited indomethacin- and acetic acid-induced gastric lesions. The ED_{50} values were 1.6 and 5.5 mg/kg for IY-81149 and 3.6 and 20.0 mg/kg for omeprazole, with IY-81149 being approximately 3-fold more potent than omeprazole (Fig. 1).

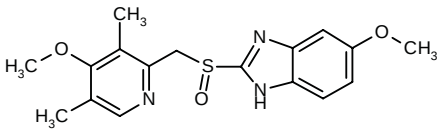
The effects of IY-81149 on mucus secretion in rats were also investigated. IY-81149 significantly inhibited ethanol-induced ulcers in a dose-dependent manner. The rates of Alcian blue staining were increased by 24.7, 55.0 and 86.7 % in rats administered IY-81149 doses of 10, 30 and 50 mg/kg, respectively, as compared with the control animals. These rates were similar to those for

Table I: Irreversible proton pump inhibitors launched, preregistered and in clinical trials.

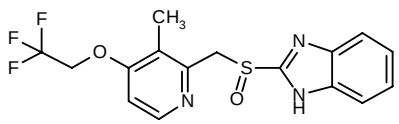
Launched
1. Omeprazole
   AstraZeneca (1989)
2. Lansoprazole
   Takeda (1995)
3. Pantoprazole
   Byk Gulden (1994)
4. Rabeprazole sodium
   Eisai (1999)

Preregistered
5. Leminoprazole
   Nippon Chemiphar

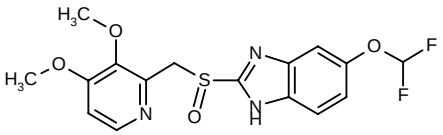
Clinical Trials
6. Esomeprazole
   AstraZeneca
7. Tenatoprazole
   Tokyo Tanabe
8. IY-81149
   Il-Tang Pharma.



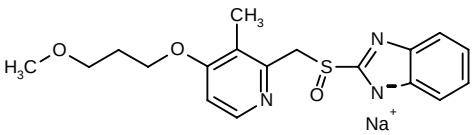
(1)



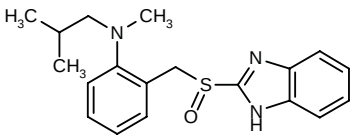
(2)



(3)



(4)



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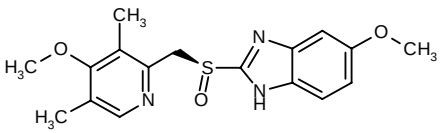

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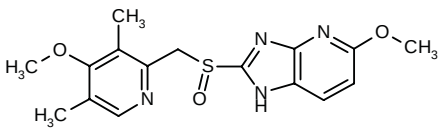

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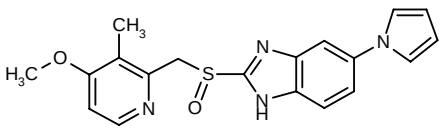

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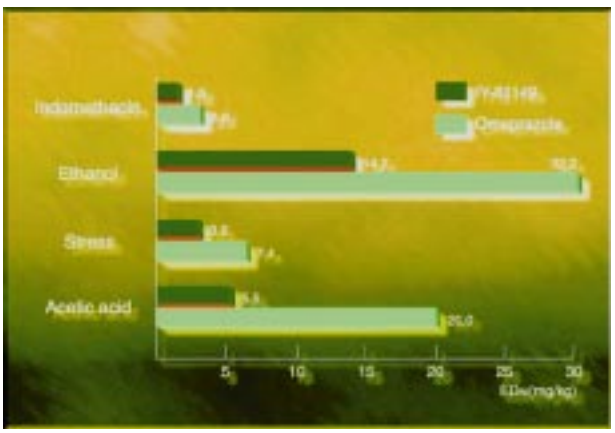

Fig. 1. The effect of IY-81149 on chemically induced gastric ulcer in rats.

omeprazole and much lower than those for rebamipide, indicating a positive effect on mucus secretion. It appeared that IY-81149 did not directly increase mucus but rather decreased gastric ulcer formation.

In pylorus-ligated rats, both IY-81149 and omeprazole decreased gastric acid secretion after single and repeated doses (ED_{50}s = 1.94 and 1.39, respectively, for IY-81149 *vs.* 5.64 and 4.30 mg/kg, respectively, for omeprazole). These results suggest that IY-81149 would not cause drug tolerance.

In *in vitro* studies, IY-81149 in combination with amoxicillin and clarithromycin exhibited potent antibacterial effects against Helicobacter pylori and was twice as effective as omeprazole in eradicating bacteria, especially in combination with amoxicillin.

Pharmacokinetics and Metabolism

[^{14}C]-labeled IY-81149 was used for absorption, distribution, metabolism and excretion studies in male and female Sprague-Dawley rats. Plasma concentration profiles of [^{14}C]-IY-81149 were obtained after rats were dosed intravenously with 5 mg/kg or orally with 20 or 100 mg/kg. After i.v. administration, the terminal plasma half-lives of IY-81149 were 17.4 and 7.3 h for male and female rats, respectively. Orally administered [^{14}C]-IY-81149 was rapidly absorbed, with secondary peaks occurring around 1 and 4 h postdose. Unmetabolized IY-81149 was observed in the plasma at these time points. Studies performed in bile duct-cannulated rats

indicated that the uptake of orally administered [^{14}C]-IY-81149 was fairly even over the 24-h period. Approximately 34% of the oral dose was recovered in the bile over 24 h. The excretion of orally administered [^{14}C]-IY-81149 (100 mg/kg) was predominantly through the feces. The tissue levels of radioactivity 2 days postdose were approximately 8 μg-eq/g for the liver and 5 μg-eq/g for the kidney. Whole-body autoradiographic studies conducted 15 min after an oral dose of 100 mg/kg showed that concentrations (nCi/g) were highest in the liver, followed by kidney, lung, blood and adipose tissues. Tissue concentrations decreased after 24 h to about 30% or less than those at 15 min.

Toxicity

In single-dose toxicity studies in rats, the LD_{50}s of IY-81149 after oral and intraperitoneal administration were > 5000 and > 2500 mg/kg, respectively. In single-dose toxicity studies in dogs, no effects were observed on any of the parameters measured at 1000 and 2000 mg/kg. Therefore, the no observed effect level (NOEL) in beagle dogs was considered to be ≥ 2000 mg/kg. In a 28-day oral toxicity study in dogs, the no-effect dose was 10 mg/kg. The effects observed microscopically in dogs administered 33 mg/kg/day were minimal to slight and the dogs were asymptomatic. In a 13-week, repeated oral toxicity study in rats, the NOEL of IY-81149 was 80 mg/kg in both male and female rats. The toxic dose was above 320 mg/kg. IY-81149 had no effects on the cardiovascular or autonomic nervous systems except for slight effects on the CNS when administered at high doses. Thus it appears that the clinical dose of IY-81149 has no effect on general pharmacological actions.

In fertility and developmental studies in rats, orally administered IY-81149 (320 mg/kg/day) to male rats during a 63-day premating period and throughout mating elicited minimal toxicity, characterized by a decrease in body weight during days 1-4 of treatment.

Clinical Studies

The usual adverse effects of proton pump inhibitors, such as vomiting and nausea, were not observed during phase I clinical trials with IY-81149, and thus the drug was considered to be very safe.

As demonstrated by the AUCs and C_{max}, IY-81149 exhibited linear pharmacokinetics, where 2-fold increases in dose levels (5, 10, 20 and 40 mg) resulted in 2-fold increases in AUCs and C_{max}. There were no significant changes in t_{max}, K_{el} and half-life among doses. Based on safety and tolerance endpoints, single ascending doses of 5, 10, 20 and 40 mg of IY-81149 appeared to be safe, with little or no changes observed in laboratory tests or vital signs such as blood pressure, pulse rate, respiratory rate and ECG. No adverse events were reported.

In multiple-dose studies, IY-81149 also showed linear pharmacokinetics, in which a 2-fold increase in the dose (from 20 to 40 mg) resulted in an approximately 2-fold increase in AUCs and C_{max}. There was no indication of drug accumulation during the 5-day treatment period, since there were no significant changes in the drug's half-life. The safety and tolerance results showed that IY-81149 at doses of 20 and 40 mg/day, adminstered for 5 days, was safe, with little or no changes observed in laboratory tests or vital signs such as blood pressure, pulse rate and ECG. As in the single-dose studies, no significant adverse events were reported.

In an early double-blind phase II clinical trial in patients with gastroesophageal reflux disease, IY-81149 was more potent than omeprazole even when administered at low doses. These preliminary findings indicate that IY-81149 is more effective than omeprazole.

Manufacturer

Il-Yang Pharmaceutical Co. Ltd. (KO).

References

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