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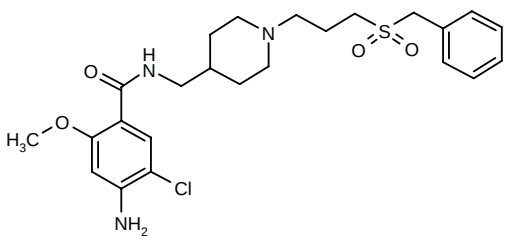
CCC: 0377-8282/99

Y-36912

Gastroprokinetic
5-HT$_4$ Receptor Agonist

4-Amino-*N*-[1-[3-(benzylsulfonyl)propyl]piperidin-4-ylmethyl]-5-chloro-2-methoxybenzamide



$C_{24}H_{32}ClN_3O_4S$ Mol wt: 494.05

CAS: 213600-06-7

EN: 261788

Synthesis

The synthesis of Y-36912 is performed as illustrated in Scheme 1. The condensation of 4-(aminomethyl)piperidine with benzaldehyde in toluene gives 4-(benzylideneaminomethyl)piperidine (II). The reaction of benzylmercaptol (III) with 1-bromo-3-chloropropane in methanol, followed by oxidation with hydrogen peroxide in formic acid, gives 3-(benzylsulfonyl)propylchloride (IV). The alkylation of (II) with (IV) in the presence of potassium carbonate and potassium iodide in acetonitrile, followed by treatment with hydrochloric acid, affords 1-[3-(benzylsulfonyl)propyl]-4-piperidylmethylamine (V). The coupling reaction between (V) and 4-amino-5-chloro-2-methoxybenzoic acid (VI) by means of isobutyl chloroformate and triethylamine in $CHCl_3$ gives the target compound, Y-36912 (1). Scheme 1.

Description

White to pale yellowish white crystalline powder, m.p. 169-74 °C.

Introduction

Benzamides (cisapride, metoclopramide, zacopride, *etc.*) are used clinically as gastrointestinal motility stimulants and the gastroprokinetic effect of these compounds is thought to be mediated by serotonin4 (5-HT$_4$) receptor agonism (2). However, these compounds possess not only 5-HT$_4$ receptor agonism but also 5-HT$_3$, 5-HT$_2$, dopamine D$_2$ and adrenergic α_1 receptor antagonism (3-6). The antagonism against these receptors should reduce gastrointestinal motility stimulated by 5-HT$_4$ agonism and/or cause central nervous system adverse reactions such as depression and extrapyramidal syndrome (7).

In order to develop a selective 5-HT$_4$ receptor agonist as a novel gastrointestinal motility stimulant which would enhance both upper and lower gastrointestinal motility and have few adverse reactions, we synthesized a series of novel benzamides (8, 9) and pharmacologically evaluated them *in vitro* and *in vivo* (10). Among them, Y-36912 was found to be a selective and potent 5-HT$_4$ receptor agonist which enhanced both upper and lower gastrointestinal motility (11).

Pharmacological Actions

Y-36912 showed a high affinity for the 5-HT$_4$ receptor in the rat striatum, with a K_i value of 1.5 nmol/L. The affinities of cisapride and mosapride were 70 and 300 nmol/L, respectively (12). In contrast, Y-36912 showed little specific affinity for the other receptors (dopamine D$_1$, dopamine D$_2$, adrenergic α_1, muscarinic, histamine H$_1$, 5-HT$_{1A}$, 5-HT$_2$, 5-HT$_3$) (Table I). Hence, Y-36912 was confirmed to have selective affinity for the 5-HT$_4$ receptor.

In the presence of methysergide and granisetron, Y-36912 produced concentration-dependent contractions of the guinea pig ascending colon, with an EC_{50} value of 10.8 nmol/L. The maximal contractile response of Y-36912 was 12.7% of that elicited by methacholine (30 μmol/L). The concentration-effect curve for Y-36912 was shifted rightward by GR-113808, a selective 5-HT$_4$ receptor antagonist, with a pK_B value of 8.8. On the other hand, cisapride had an EC_{50} of 45.1 nmol/L (maximal contractile response: 28.2%) and mosapride was not effective (13).

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Scheme 1: Synthesis of Y-36912

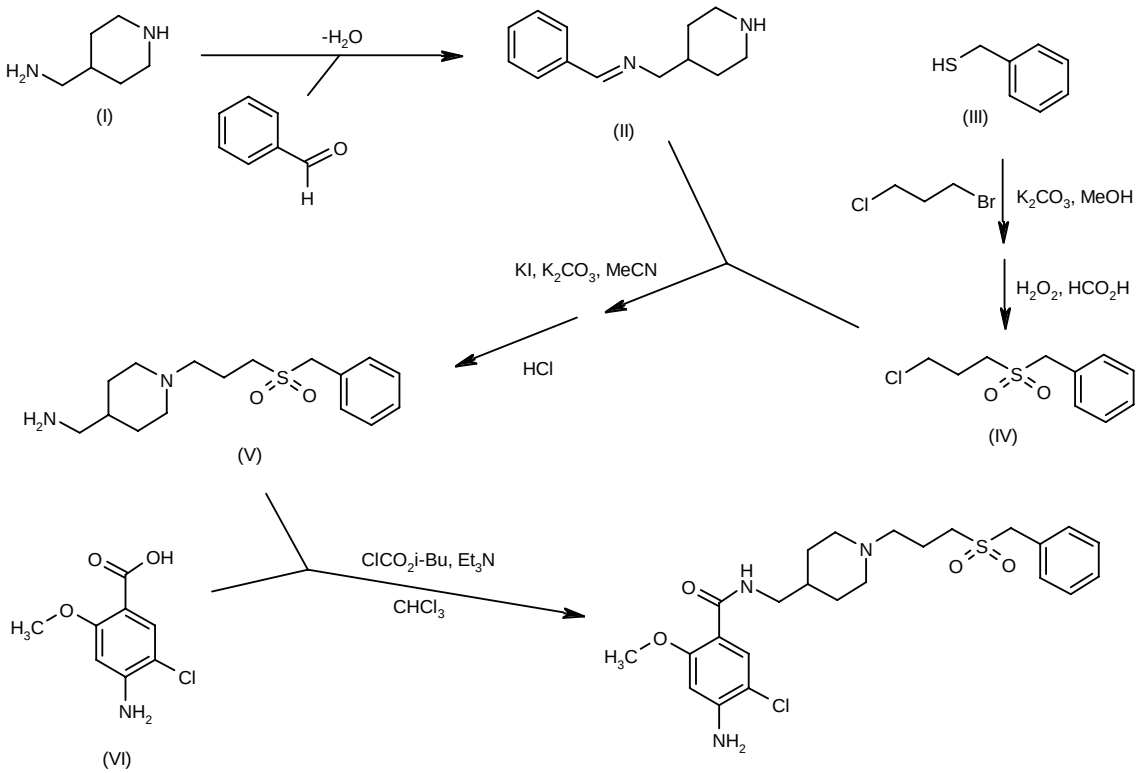

Table I: Receptor profiles and 5-HT$_4$ receptor activity of Y-36912.

Binding assay (K_i, nmol/L)[a]									5-HT$_4$ receptor activity	
Dopamine D_1	Dopamine D_2	Adrenergic α_1	Muscarinic	Histamine H_1	5-HT$_{1A}$	5-HT$_2$	5-HT$_3$	5-HT$_4$	EC_{50}[c] (nmol/L)	Maximal response[d] (%)
[^{3}H]SCH23390	[^{3}H]spiperone	[^{3}H]prazosin	[^{3}H]QNB	[^{3}H]mepyramine	[^{3}H]8-OH-DPAT	[^{3}H]ketanserin	[^{3}H]granisetron	[^{3}H]GR-113808		
>1000[b]	>1000[b]	>1000[b]	>1000[b]	>1000[b]	>1000[b]	430	>1000[b]	1.5	10.8 (5.73-18.1)	12.7 ± 1.56

[a]Each value is mean from triplicate assays in a single experiment. [b]IC_{50} value. [c]The EC_{50} value and 95% confidence limit were determined by linear regression analysis (n = 6). [d]A percentage (mean ± SE) of the contraction caused by methacoline 30 μM.

These results indicate that Y-36912 possesses selective and potent 5-HT$_4$ receptor agonism.

Regarding effects on the upper gastrointestinal system, Y-36912 significantly accelerated gastric emptying of liquid meal (phenol red solution) at doses of 3 and 10 mg/kg p.o. in mice and solid meal (barium pellets) at doses of 0.3 and 3 mg/kg p.o. in rats. These findings indicate that Y-36912 should enhance upper gastrointestinal motility.

Additionally, the effects of Y-36912 on lower gastrointestinal system were studied. Y-36912 significantly increased defecation at a dose of 0.3 mg/kg p.o. in mice and accelerated colonic transit rate at doses of 1 and 3 mg/kg p.o. in guinea pigs. Furthermore, these effects of Y-36912 on defecation and colonic transit were inhibited by GR-113808. These results demonstrate that the gastroprokinetic effects of Y-36912 are mediated by 5-HT$_4$ receptor agonism.

The effects of Y-36912 on gastrointestinal motility in conscious dogs in the postprandial state were measured by strain gauge transducers sutured on the serosa of the gastric antrum, duodenum, jejunum, ileum and ascending colon. Y-36912 significantly increased antral motor activity at doses of 0.03 and 0.1 mg/kg i.v., jejunal motor activity at 0.03 mg/kg i.v. and ileal and colonic motor activity at 0.1 mg/kg i.v. The gastroprokinetic effects of title compound were superior or equal to those of cisapride in *in vivo* studies.

Pharmacokinetics

In rats, the maximum plasma concentration (C_{max}) and the area under the plasma concentration-time curve (AUC) values of unchanged drug were not proportional to the dose, suggesting saturation of first-pass metabolism at high doses. The C_{max} and AUC in dogs were greater than those in rats, due to the drug's higher bioavailability. Dogs were administered Y-36912 at intravenous and oral doses of 3 mg/kg. After i.v. administration, the elimination half life ($t_{1/2}$) of unchanged drug in plasma was 7.9 h and the $AUC_{(0\text{-}24\ h)}$ was 16.4 μg.h/mL. After oral administration of Y-36912, the unchanged drug concentrations reached a C_{max} of 1.6 μg/mL at 3.3 h and the $t_{1/2}$ was 9.5 h. The $AUC_{(0\text{-}24\ h)}$ was 12.3 μg.h/mL and the bioavailability was 75.1%.

Conclusions

Y-36912 showed selective and potent 5-HT_4 receptor agonism. In *in vivo* studies, Y-36912 accelerated gastric emptying in mice and rats, defecation in mice and colonic transit in guinea pigs. In conscious dogs, Y-36912 significantly enhanced motor activity of both the upper and lower gastrointestinal tracts in the postprandial state.

These findings indicate that Y-36912 should be clinically effective in improving the gastrointestinal symptoms (*e.g.*, heartburn, upper abdominal pain, abdominal bloating) caused by chronic gastritis, postoperative digestive function failure, non-ulcer dyspepsia and gastroesophageal reflux, as well as in the treatment of gastrointestinal motility disorders such as irritable bowel syndrome and atonic constipation.

Manufacturer

Yoshitomi Pharm. Ind., Ltd. (JP).

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