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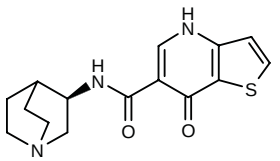
CCC: 0377-8282/99

MKC-733

Treatment of GERD
Treatment of Constipation
5-HT$_3$ Receptor Agonist

7-Oxo-*N*-[3(*R*)-quinuclidinyl]-4,7-dihydrothieno[3,2-*b*]pyridine-6-carboxamide hydrochloride



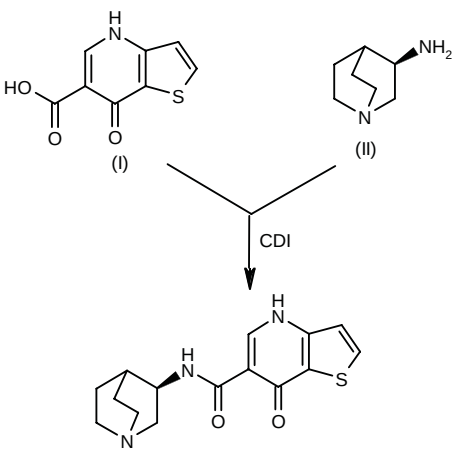
.HCl

$C_{15}H_{17}N_3O_2S.HCl$ Mol wt: 339.8470

CAS: 194093-42-0
CAS: 153062-94-3 (as free base)
CAS: 152995-74-9 (as racemic free base)

EN: 219330
EN: 201554 (as free base)
EN: 203368 (as racemic free base)

Scheme 1: Synthesis of MKC-733



Synthesis

MKC-733 is synthesized by condensation of 7-oxo-4,7-dihydrothieno[3,2-*b*]pyridine-6-carboxylic acid (I) with quinuclidin-3(*R*)-amine (II) by means of carbonyldimidazole in DMF (1). Scheme 1.

Description

Crystals, m.p. >300 °C, $[\alpha]_D^{20}$ +17.6° (c 1, water).

Introduction

Alterations in the absorptive, secretory and motor functions of the gastrointestinal tract are widespread and can undermine human well-being. An imbalance of salt and water absorption can lead to constipation or diarrhea, to dehydration and malnutrition. Constipation can be described as a change in the pattern of normal defecation, a reduction in the frequency of defecation, a hardening of the stools, a reduction in stool volume or a feeling of incomplete evacuation. According to the 1991 National Health Interview Survey, approximately 4.5 million people in the U.S. (mainly women, children and adults age 65 and over) claim to be constipated most or all of the time (2). Constipation is not a disease but rather a symptom that may result from a variety of underlying causes, including subjective factors such as stress or diet, may be congenital, or may be due to endocrine disorders, diseases of the nervous system, diseases of the large intestine or the actions of drugs and toxins.

Although treatment of constipation depends on the cause, severity and duration, in most cases dietary and lifestyle changes will help to relieve symptoms and prevent constipation. When lifestyle changes are not sufficient, the use of laxatives (bulk-forming laxatives, stimulants, stool softeners, saline laxatives) may be beneficial. Pharmacological treatment is only recommended in cases of severe constipation or constipation-predominant irritable bowel syndrome (IBS), where the symptoms are associated with a decrease in colonic motility (3). Patients with constipation-prone IBS may comprise up to 80% of IBS patients in the U.K. and the U.S., indicating the need

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for specific pharmacological treatment for this condition (4).

Pharmacological approaches for the treatment of constipation include the use of prokinetics and compounds with novel mechanisms to stimulate GI motility and transit, such as the CCK-A receptor antagonists, motilin agonists and colonic serotonin 5-HT_4 agonists.

Scientists at Mitsubishi synthesized a series of thieno[3,2-*b*]pyridine derivatives with 5-HT_3-receptor agonist activity. From this series, MKC-733 was selected as a prokinetic agent for further evaluation for the treatment of gastrointestinal motor disorders such as chronic constipation and gastroesophageal reflux disease.

Pharmacological Actions

MKC-733 has been characterized *in vitro* and *in vivo*. The compound exhibited high affinity for the 5-HT_3 receptor in canine intestinal smooth muscle (IC_{50} = 1.3 nM) (5). Species differences were found when the Bezold-Jarish reflex and contraction in isolated colon were studied in guinea pigs, rats and mice, where the intrinsic activity of the drug for 5-HT_3 receptors was higher in mice and guinea pigs (6). In isolated guinea pig colon, MKC-733 induced contractions were concentration-dependent (30 nM to 3 μM). The drug also dose-dependently increased basal short-circuit current (a measure of net ion transport) in isolated guinea pig distal colon, being similar to serotonin, 2-methylserotonin and other 5-HT_3 receptor agonists. The effects of MKC-733 on colon contraction and ion transport were inhibited by the selective 5-HT_3 receptor antagonist ondansetron but not by the 5-HT_4 receptor antagonist SB-204070 (5, 7).

In vivo, MKC-733 restored delayed gastric emptying in cisplatin- and dopamine-treated rats at doses of 0.3-1 mg/kg p.o., being approximately 10-fold more potent than cisapride. It also restored delayed colonic propulsion induced by clonidine in mice at doses of 0.1-10 mg/kg p.o., effects that were again inhibited by ondansetron. In conscious mongrel dogs MKC-733 also markedly stimulated colonic contractile activity at doses of 0.01-0.1 mg/kg p.o. In animals with chronically implanted force transducers, MKC-733 shortened the IMC cycle in both the antrum and the small intestine, with a contractile effect that was inhibited by atropine, hexamethonium and granisetron but not phentolamine or propranolol. This profile of activity suggests that MKC-733 may be useful in the treatment of disorders of gastrointestinal motility such as nonulcer dyspepsia, gastroesophageal reflux disease and chronic constipation (5, 8).

Clinical Studies

The efficacy of MKC-733 was compared to placebo in a single-blind trial in 14 patients with constipation. Subjects received placebo during the first week, followed by 0.2 mg b.i.d. of MKC-733 for 2 weeks, and 0.5 mg b.i.d. of MKC-733 for the last 2 weeks of the study. Compared to placebo, both doses of MKC-733 induced increases in the frequency of defecation, eliminated difficulties in stool passage, improved sensations of incomplete evacuation and improved general gastrointestinal symptoms without changes in stool consistency. Symptomatic improvement appeared to be due to improvement in gastrointestinal transit (9) (Box 1).

According to a spokesperson from Mitsubishi, MKC-733 is in phase II clinical trials.

Manufacturer

Mitsubishi Chemical Corp. (JP).

Box 1: Efficacy of MKC-733 in chronic constipation (9).

Design	Single-blind, randomized, crossover[1] clinical study
Population	Subjects with difficulties in stool passage defecating 2.4 times/wk (n = 14)
Treatments	MKC-733, 0.2 mg p.o. b.i.d. x 2 wks MKC-733, 0.5 mg p.o. b.i.d. x 2 wks Placebo H 1 wk
Results	Defecation frequency (times/wk), change: M0.5 (4.6) > M0.2 (4.0) > P (3.2) Improvement rate, incomplete evacuation: M0.2 (30-40%) < M0.5 (55-64%) Evacuation rate: M0.5 (70.4) > P (47.1) [$p < 0.05$] Gastrointestinal transit: M0.5 (7.4) ≥ M0.3 7.1) ≥ P (6.9) General gastrointestinal symptoms improved 75% in subjects on active treatment Difficulties in stool passage disappeared in treated subjects No changes in stool consistency
Conclusions	MKC-733 improved symptoms of constipation by stimulating intestinal motility

[1]Patients received placebo for 1 week and a low and high dose of MKC-733 for 2 consecutive 2-week periods

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