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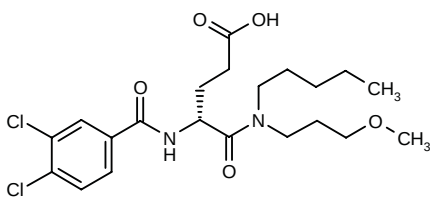
Dexloxiglumide

Rec INN

CCK_1 (CCK_A) Receptor Antagonist
Treatment of Irritable Bowel Syndrome

CR-2017

(*R*)-4-(3,4-Dichlorobenzamido)-5-[*N*-(3-methoxypropyl)-*N*-pentylamino]-5-oxopentanoic acid



$C_{21}H_{30}Cl_2N_2O_5$ Mol wt: 461.3900

CAS: 119817-90-2

EN: 180635

Synthesis*

The condensation of the *N*-(benzyloxycarbonyl)-D-glutamic acid 5-benzyl ester (I) with *N*-(3-methoxypropyl)-*N*-pentylamine (II) by means of ethyl chloroformate and triethylamine in THF gives the corresponding amide (III), which is debenzylated by hydrogenation over Pd/C in methanol, yielding compound (IV). Finally, the free amino group of (IV) is acylated with 3,4-dichlorobenzoyl chloride (V) by means of NaOH in water to give dexloxiglumide (1). Scheme 1.

Description

Crystals m.p. 97-100 °C; [α] +9.5°.

Introduction

Cholecystokinin (CCK) is an important peptide hormone widely distributed in the small intestine (duodenal I cells and enteric nerves). It is secreted in response to meals (2) and plays an important role in regulating gallbladder contraction (3, 4) and pancreatic enzyme secretion (5). CCK is also able to produce both hypertrophy and hyperplasia of the exocrine pancreas (6) by increasing pancreatic weight without affecting endocrine components of the gland (7). Moreover, at present there is considerable evidence that regulation of the motor and sensory functions at various levels of the alimentary tract represents one of the most important physiological roles of CCK (8). The peptide delays gastric emptying rate in both humans and animals (9), decreases small bowel and increases colonic transit time (10) and causes lower esophageal sphincter relaxation (11). The biological action of CCK on exocrine pancreas, gallbladder and gastrointestinal smooth muscle is mediated by CCK_1-subtype receptors (12-14) located on the target organs, in neurons in the myenteric plexus and in vagal afferents from the gastrointestinal tract (15). CCK_1 receptors are also located in certain brain nuclei, including the interpeduncular nucleus, the area postrema and the nucleus tractus solitarius (16).

The availability of potent and selective CCK_1 receptor antagonists has allowed the elucidation of the physiological role of CCK. Among the different classes of CCK_1 receptor antagonists developed to date, the amino acid derivatives lorglumide and loxiglumide represent potent and specific CCK_1 receptor antagonists which are orally active and antagonize the effects of both exogenous and endogenous CCK (17). Dexloxiglumide, the dextro isomeric form of the racemic mixture loxiglumide, was selected for further development because of its potency and selectivity (1).

Pharmacological Actions

Dexloxiglumide is a potent CCK_1 receptor antagonist. The compound inhibited [^{125}I]-CCK-8 binding to pancreatic CCK_1 receptors with an IC_{50} of 130 nM (18) and had more than 150-fold selectivity over CCK_2 receptors in rat cerebral cortex (Table I).

In a functional study in *in vitro* perfused rat pancreas, dexloxiglumide antagonized in a surmountable manner the amylase secretion induced by CCK-8. In fact, the

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Scheme 1: Synthesis of Dexloxiglumide

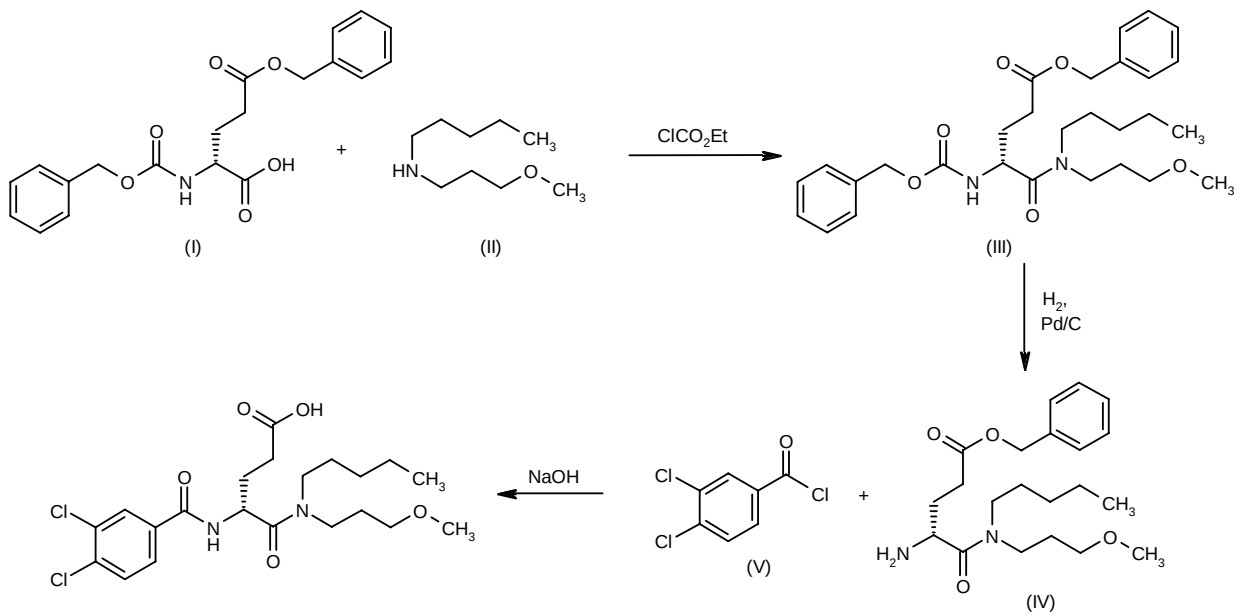

Table I: Affinities of dexloxiglumide, CCK-8 and selected CCK_1 antagonists. Values are IC_{50} (nM) (Prous Science MFLine® database).

Compound	CCK_1 Rat pancreas[1]	CCK_2 Rat cerebral cortex[1]	Selectivity CCK_2/CCK_1	Ref.
CCK-8	0.5	2.4	4.8	29
Dexloxiglumide	130	22.0 µM	169	18
Loxiglumide	195	18.8 µM	96	30, 31
Devazepide	0.1	320	3200	31, 32

[1]displacement of [^{125}I]-CCK-8.

Table II: Effect of dexloxiglumide on CCK-8-stimulated pancreatic amylase secretion in anesthetized rat (Prous Science MFLine® database).

Compound	ID_{50}	Ref.
Dexloxiglumide	0.76 mg/kg i.v.	19
Loxiglumide	6.0 µmol/kg i.v.	33
Devazepide	0.025 µmol/kg.i.v.	33

dose-response curve of CCK-8 was shifted to the right by dexloxiglumide, without reduction of the maximum response to agonist; the pA_2 calculated from Schild-plot analysis was 6.41 (19). In a rat model of pancreatic secretion, CCK-8 intravenously infused at a dose of 0.5 µmol/kg/h caused a 5-and 10-fold increase in the volume of pancreatic juice and amylase content, respectively. Dexloxiglumide dose-dependently antagonized CCK-induced amylase secretion with a calculated ED_{50} of 0.76 mg/kg i.v. (Table II). Moreover, even in this model, dexloxiglumide was able to produce a rightward shift of the dose-response curve of CCK-8, with no effect on the maximum, suggesting a competitive antagonism.

In rat experiments where caerulein (an amphibian CCK peptide analog retaining full CCK-like agonist activity) or camostate (a synthetic protease inhibitor used to release endogenous CCK) were administered for 7 consecutive days, a significant increase of pancreatic hypertrophia and hyperplasia were observed. Dexloxiglumide administered alone at a dose of 25 mg/kg s.c. 3 times daily for 7 days almost completely reduced the trophic effect of both caerulein and camostate (20) without affecting pancreatic size and composition. These results suggest an important role of CCK in the pathogenesis of different kinds of acute pancreatitis and demonstrate the ability of dexloxiglumide to reverse these effects.

As mentioned above, CCK also plays a physiological role in the regulation of intestinal motility. Pharmacological investigations have demonstrated the presence of specific CCK receptors, distinct from those of gastrin, on gastric smooth muscle cells (21). These receptors have been shown to mediate relaxation of the proximal stomach and contraction of the antropyloric region with a consequent delay in gastric emptying. In a model of CCK-8-induced delay of gastric emptying in gastric fistula con-

Table III: Effect of dexloxiglumide on CCK-8-stimulated gastric emptying in the conscious rat (Prous Science MFLine® database).

Compound	ID_{50} (mg/kg)	Route	Ref.
Dexloxiglumide	1.14[1]	i.v.	22
Loxiglumide	0.9	i.p.	34
Devazepide	0.14	p.o.	35

[1]gastric fistula rat

scious rats, dexloxiglumide administered i.v. dose-dependently antagonized the effect of CCK-8, with an ID_{50} of 1.14 mg/kg (Table III) (22).

When food enters the duodenum, CCK is promptly released and induces gallbladder contraction, pancreas secretion and inhibits gastric emptying. There is experimental evidence in both humans and dogs that the distension of the colon or the rectum could delay gastric emptying. In humans, gastric motor disturbances associated with a delay in gastric emptying have been described in irritable bowel syndrome (IBS). To evaluate the efficacy of dexloxiglumide in reversing the inhibition of gastric emptying induced by colonic distension, adult Beagle dogs chronically fitted with a Thomas gastric cannula and a cecostomy were used. Dexloxiglumide given 10 min before the meal at doses of 0.2 and 1 mg/kg significantly and dose-dependently accelerated both liquid and solid basal gastric emptying and reduced the inhibition induced by distension of the proximal colon (23). These results provide a rationale for the use of CCK_1 receptor antagonists in the clinical management of delayed gastric emptying and IBS.

Gastroesophageal reflux has been found to be associated with transient lower esophageal sphincter relaxation (TLESR) that is triggered by gastric mechanoreceptors and CCK seems to be involved in this mechanism (11, 24). In dogs chronically fitted with a cervical esophagostomy and provided with catheters introduced into esophageal body, lower esophageal sphincter and gastric fundus, the gastric distension induced by air insufflation into the stomach was shown to produce TLESR. Dexloxiglumide given at doses of 1 and 5 mg/kg i.v., 10 min before the onset of distension, significantly reduced the number of TLESRs induced by gastric distension and completely abolished the increase in TLESR frequency induced by CCK-8 infusion (25). These results indicated that CCK_1 receptor antagonists might be of therapeutic value in gastroesophageal reflux disease, not only because they prevent the prostprandial decrease of lower esophageal pressure and reduce the occurrence of TLESR but also because they accelerate gastric emptying.

Clinical Studies

At present, dexloxiglumide and loxiglumide are the CCK_1 receptor antagonists at the most advanced stage of clinical research in gastroenterology. Dexloxiglumide is currently being evaluated in phase III trails for IBS and functional dyspepsia.

In a phase I trial in 20 healthy male volunteers, oral dexloxiglumide 200 mg (b.i.d. or t.i.d.) was administered in a randomized, placebo-controlled, double-blind, 3-arm crossover fashion for 3 consecutive 7-day periods. A liquid formula fiber diet was given during each experimental period to induce a delay in colonic transit time (CTT). Both dexloxiglumide regimens accelerated CTT without impairing postprandial gallbladder kinetics, despite an increase in fasting gallbladder volume (26).

In a double-blind study in 12 functional dyspepsia patients, placebo or dexloxiglumide were infused intravenously together with an intraduodenal infusion of a lipid emulsion. Dexloxiglumide (5 mg/kg/h) was shown to completely abolish the increase in intragastric volume, secondary to a decrease in gastric basal tone, induced by lipid emulsion infusion, and to decrease the intensity of dyspeptic symptoms such as fullness, bloating, nausea and discomfort (27).

In a randomized, placebo-controlled, double-blind, parallel-group, multicenter study involving 469 patients with all the bowel habit subgroups of IBS, nondiarrhea-predominant and diarrhea-predominant subjects were prospectively stratified and randomized to receive either dexloxiglumide (200 mg p.o. tid) or placebo for 12 weeks. Dexloxiglumide was more effective than placebo in relieving IBS symptoms and both treatments were equally well tolerated. With regard to efficacy, the proportion of responders was higher with dexloxiglumide than with placebo, reaching statistical significance in all patients regardless of bowel habit predominance (59% and 45% for dexloxiglumide and placebo, respectively), and in non-diarrhea-predominant patients (60% and 42% for dexloxiglumide and placebo, respectively). In this latter group, dexloxiglumide was also significantly effective in terms of the number of pain- and bloating-free days, reductions in straining and incomplete evacuation and improved global well being (28).

Manufacturer

Rotta Research Laboratorium SpA (IT).

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