Drugs of the Future 1999, 24(5): 475-482

CCC: 0377-8282/99

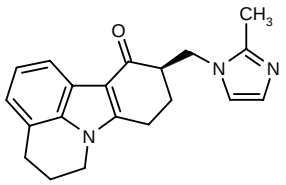
Cilansetron

Rec INN

Treatment of IBS
5-HT$_3$ Antagonist

KC-9946

(–)-(*R*)-10-(2-Methyl-1*H*-imidazol-1-ylmethyl)-4,5,6,8,9,10-hexahydro-11*H*-pyrido[3,2,1-*jk*]carbazol-11-one



$C_{20}H_{21}N_3O$ Mol wt: 319.4059

CAS: 120635-74-7
CAS: 209859-87-0 (as monohydrochloride monohydrate)
CAS: 120635-72-5 (as monohydrochloride)

EN: 149826

Synthesis

The reaction of 1-indanone (I) with sodium azide in acetic acid/sulfuric acid gives the tetrahydroquinolone (II), which is reduced with $LiAlH_4$ in THF, yielding the tetrahydroquinoline (III). The reaction of (III) with $NaNO_2$ and sulfuric acid afords the *N*-nitroso derivative (IV), which is reduced wiith $LiAlH_4$ in THF to the *N*-amino compound (V) (1). The reaction of (V) with cyclohexane-1,3-dione (VI) gives the monohydrazone (VII), which is cyclized by means of HCl in refluxing acetic acid, yielding the tetracyclic compound (VIII). The reaction of (VIII) with dimethylamine and paraformaldehyde in hot acetic acid provides compound (IX), wich is treated with 2-methylimidazole (X) in refluxing water to afford racemic cilansetron (XI) (1, 2). Finally, this racemate is submitted to optical resolution with di-*p*-toluyl-D-tartaric acid (1, 2) or D-pyroglutamic acid (3). Scheme 1.

Description

Hydrochloride: crystals, m.p. 226-8 °C, $[\alpha]_D^{25}$ –6.9° (c 1.8, MeOH) (3).

Introduction

Irritable bowel syndrome (IBS) is a functional digestive disorder in the pathophysiology of which visceral sensitivity plays an important role. Patients commonly present alterations of the visceral sensitivity, including hypersensitivity to mechanical visceral stimuli (rectal distension) associated with motor disturbances (colonic contractions). Therefore, the sensitive pathways innervating the colon have arisen as possible pharmacological targets to relieve pain or modify altered reflexes in patients.

A range of endogenous substances can stimulate the nociceptive afferent pathways in the gut wall. Some act directly on receptors located in the nerve endings, especially serotonin but also adenosine, bradykinin and ATP. Other substances can enhance hyperalgesia either by increasing the permeability of ion channels or by activating G-proteins, thus leading to intracellular phenomena that decrease pain threshold. These include prostaglandin E_2, histamine and neural growth factor (NGF), *etc.* Finally, several substances can modulate the inflammatory responses, either by activating cell mediators or by recruiting more inflammatory cells, eventually worsening the initial pain and maintaining an inflammatory focus. Agents acting indirectly via other cell types include noradrenaline, interleukin (IL)-1, IL-6 and IL-8, tumor necrosis factor (TNF)-α, leukotriene B_4, complement components, substance P, vasointestinal peptide (VIP), *etc.* (4) (Fig. 1).

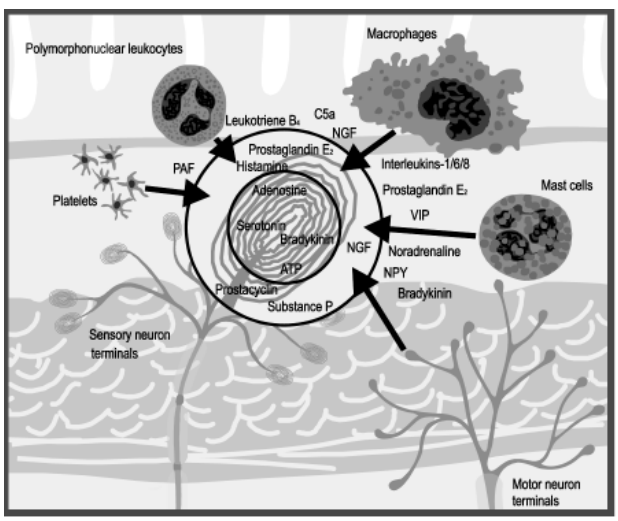


Fig. 1. Stimulation of nociceptive afferent pathways in the gut wall by endogenous mediators.

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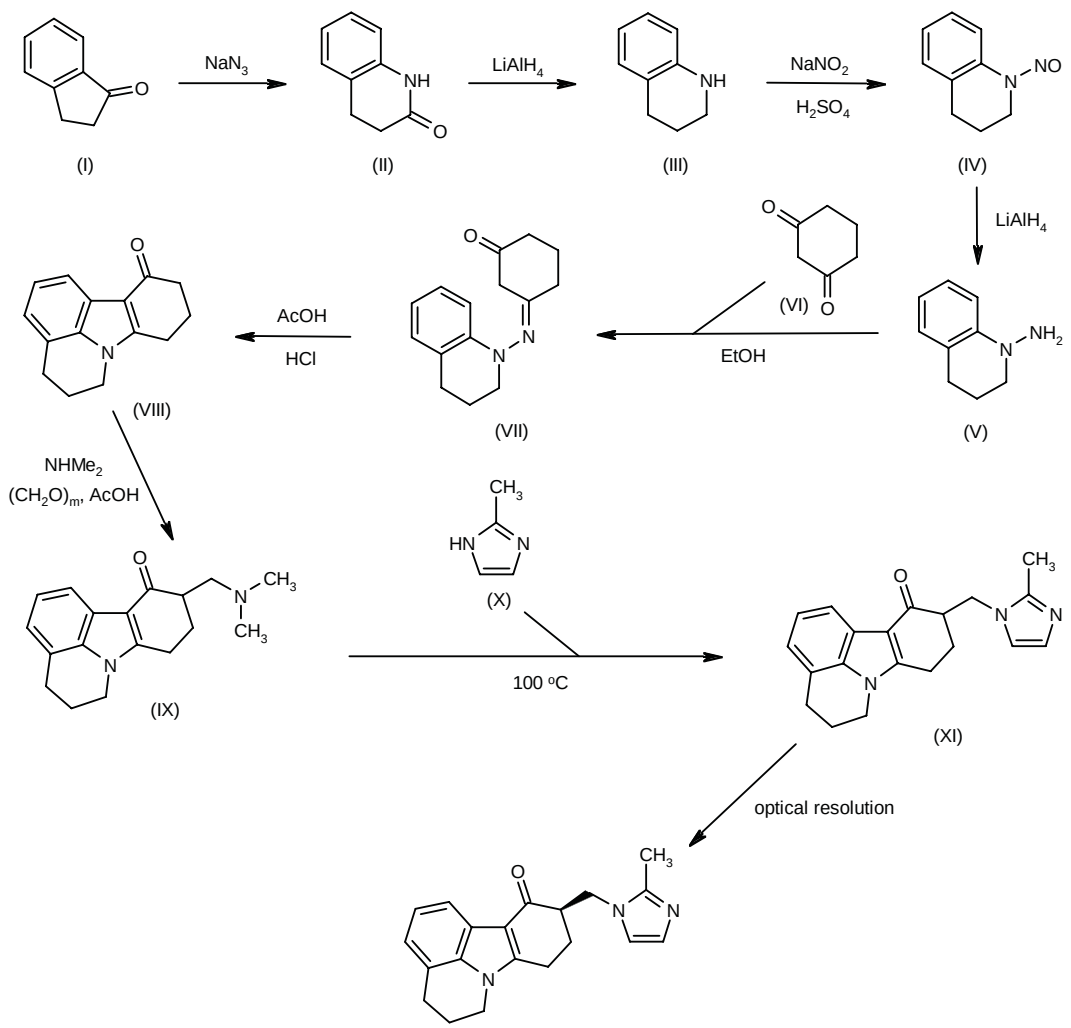
Scheme 1: Synthesis of Cilansetron



Pharmacologically, the most important pain mediator in irritable bowel syndrome is serotonin, which acts on sensory endings through 5-HT_3 receptors. 5-HT_3 receptors are distributed in the striatum, hippocampus (CA1 area), substantia nigra, globus pallidus, postganglionic sympathetic neurons and sensory neurons, and mediate a number of important functions such as sympathetic and parasympathetic neuroexcitation, vagal neuroexcitation and emesis. They are coupled to an intrinsic transmitter-gated sodium channel that promotes increased intracellular calcium concentration via depolarization-induced calcium mobilization mechanisms. Other receptor types involved in pain generation in the intestinal sensory terminals include bradykinin B_2, purinergic P_2X, prostanoid EP_2 and adenosine receptors. Opioid receptors have the opposite effect, inhibiting potassium release (OP_1 and OP_3 receptors) or directly inhibiting calcium entry (OP_2 receptors).

In the enteric nervous system, 5-HT_3 receptors not only transmit nociceptive input to the central nervous system, but also modulate the release of neurotransmitters such as substance P, which induces contraction of the gut wall smooth muscle cells. Activation of these receptors may result from rectal distension and other stimuli. Thus, 5-HT_3 receptor antagonists are currently being used for a variety of conditions, including nausea/vomiting and IBS (Table I).

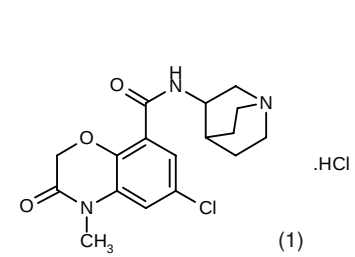
Cilansetron is a potent and selective 5-HT_3 receptor antagonist which is being studied as a prokinetic agent in IBS.

Pharmacological Actions

Cilansetron has a longer duration of action and lower toxicity than similar known compounds, including

Table I: Selected 5-HT$_3$ receptor antagonists launched and under investigation (from Prous Science Ensemble database).

Drug Name	Mechanism of action	Indication
Launched		
1. Azasetron HCl (Yoshitomi)	5-HT$_3$ antagonist	Nausea/vomiting
2. Dolasetron mesilate (Hoechst Marion Roussel)	5-HT$_3$ antagonist	Nausea/vomiting
3. Granisetron (SmithKline Beecham)	5-HT$_3$-antagonist	Nausea/vomiting
4. Ondansetron HCl (Glaxo Wellcome)	5-HT$_3$-antagonist	Nausea/vomiting
5. Ramosetron HCl (Yamanouchi)	5-HT$_3$-antagonist	Nausea/vomiting
6. Tropisetron (Novartis)	5-HT$_3$-antagonist	Nausea/vomiting
Clinical Trials		
7. Alosetron HCl (Glaxo Wellcome) - NDA filed	5-HT$_3$-antagonist	IBS
8. Itasetron (Boehringer Ingelheim) - Phase III	5-HT$_3$-antagonist/5-HT$_4$ agonist	Nausea/vomiting
9. Palonosetron HCl (Roche Bioscience) - Phase III	5-HT$_3$-antagonist	Nausea/vomiting
10. Cilansetron (Solvay) - Phase II	5-HT$_3$-antagonist	IBS
11. E-3620 (Eisai) - Phase II	5-HT$_3$-antagonist/5-HT$_4$ agonist	IBS
12. Indisetron HCl (Nisshin Flour Milling) - Phase II	5-HT$_3$-antagonist/5-HT$_4$ antagonist	Nausea/vomiting
13. Lerisetron (FAES) - Phase II	5-HT$_3$-antagonist	Nausea/vomiting
14. Fabesetron HCl (Fujisawa) - Phase II	5-HT$_3$-antagonist5-HT$_4$ antagonist	IBS
15. Renzapride HCl (Alizyme) - Phase II	5-HT$_3$-antagonist/5-HT$_4$ agonist	IBS



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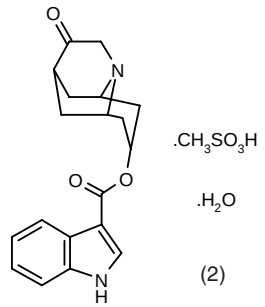

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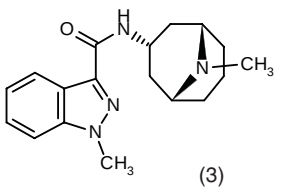

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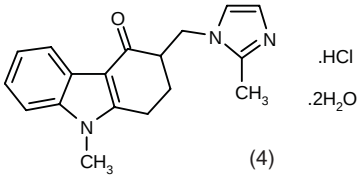

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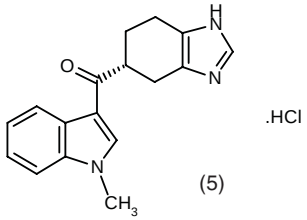

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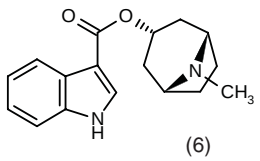

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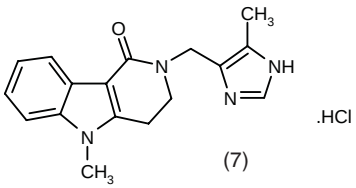

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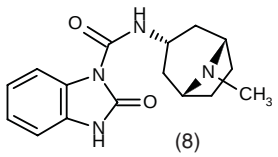

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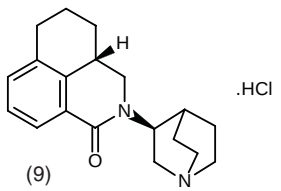

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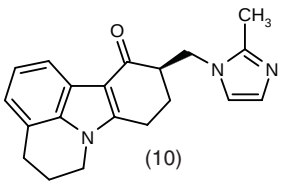

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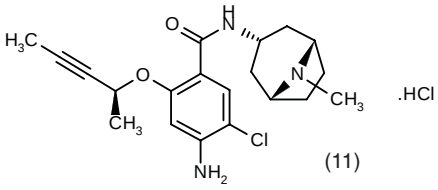

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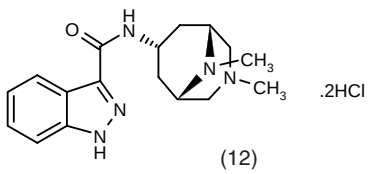

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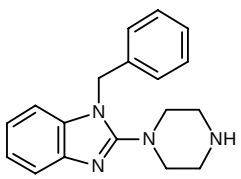

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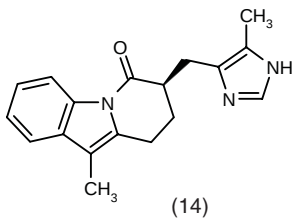

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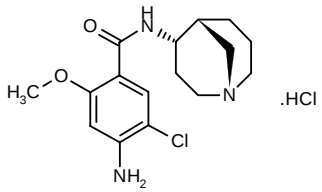

(15)

Table II: Affinities of selected 5-HT$_3$ receptor antagonists for 5-HT$_3$ and 5-HT$_4$ receptors (from Prous Science MFLine database).

Compound	Receptor	[^{3}H]-ligand	Tissue	K_i (nM)	Ref.
Alosetron	5-HT$_3$	GR-65630	Rat entorhinal cortex	0.40	13
Azasetron	5-HT$_3$	Granisetron	Rat cortex	0.54	14
Cilansetron	5-HT$_3$	GR-65630	Rat cortex	0.19	1
	5-HT$_4$	GR-113808	———	960	15
Dolasetron	5-HT$_3$	GR-65630	NG108-15 cells	28.2[a]	16
E-3620	5-HT$_3$	Granisetron	Rat entorhinal cortex	0.40	17
	5-HT$_4$	GR-113808	Rat striatum	2.00	17
Granisetron	5-HT$_3$	Granisetron	Rat cortex	0.38[b]	14,18
	5-HT$_3$	Granisetron	Rat entorhinal cortex	1.26	19
	5-HT$_3$	GR-65630	NIE-115 cells	2.00	20
Indisetron	5-HT$_3$	GR-65630	Rat cortex	1.70	21
Itasetron	5-HT$_3$	Tropisetron	Rat cortex	3.75	22
	5-HT$_4$	GR-113808	Human striatum	48.4	23
Lerisetron	5-HT$_3$	LY-278584	Rat entorhinal cortex	0.63	24
	5-HT$_4$	GR-113808	Rat striatum	>1000	24
Ondansetron	5-HT$_3$	GR-65630	Rat cortex	1.60	1
	5-HT$_3$	GR-65630	NIE-115 cells	7.00	20
	5-HT$_4$	GR-113808	——-	1200	1
Palonosetron	5-HT$_3$	Quipazine	Rat cortex	0.039	25
	5-HT$_3$	Quipazine	NG108-15 cells	0.035	26
	5-HT$_3$	Palonosetron	NG108-15 cells	0.087	26
Ramosetron	5-HT$_3$	GR-65630	N1E-115 cells	0.091	20
Renzapride	5-HT$_4$	GR-113808	Mouse SCE cells	97.7	27
Tropisetron	5-HT$_3$	Tropisetron	Rat cortex	1.71	22
	5-HT$_4$	GR-113808	Mouse SCE cells	158	27

[a]IC_{50}, nM; [b]Calculated as the mean of distinct values from different studies using the same experimental method. NG108-15 cells and N1E-115 cells = mouse neuroblastoma cells; SCE = superior culliculus embryonic cells.

ondansetron, granisetron and tropisetron. In cell membranes from rat cortex, cilansetron displaced [^{3}H]-GR-65630, a radioligand for 5-HT$_3$ receptors, with a K_i value of 0.19 nM, compared to 1.6 nM for ondansetron. Other 5-HT$_3$ receptor antagonists (tropisetron, granisetron, renzapride) had K_i values of 0.6-0.8 (1) (Table II).

Like ondansetron, cilansetron shows very little affinity for other receptor types such as α_1-adrenergic (K_i = 4.9 μM), 5-HT$_4$ (K_i = 1 μM), muscarinic M_2 (K_i = 0.9 μM), opioid OP_2 (K_i = 8.5 μM), σ (K_i = 0.3 μM) and veratridine-sensitive calcium channels (K_i = 5.4 μM), and no affinity for other receptors or channels (1).

The antagonist effect of cilansetron on peripheral 5-HT$_3$ receptors was shown in isolated rat vagus nerve and guinea pig ileum against agonist-induced depolarization or contraction, with pA_2 values of 9.9 and 7.8, respectively. A good level of peripheral activity was also shown against serotonin-induced bradycardia in the Bezold-Jarish reflex test in rats, with an ED_{10} value of 26 μg/kg p.o. In these tests, cilansetron was significantly more active than ondansetron (1) (Tables III and IV).

When given to rats before an intracolonic infusion of the irritants and proinflammatory agents glycerol and trinitrobenzene sulfonic acid/ethanol, cilansetron prevented pain as measured by the number of abdominal spike bursts in the electromyograph, with similar efficacy as ondansetron and granisetron. The three drugs were effective when given by i.p., i.v. and i.c. routes, but cilansetron was more effective when administered i.c., which suggests a local action on colonic 5-HT$_3$ receptors (5). Similar results were found in another study in which abdominal pain was mechanically induced in rats by means of inflatable balloon-mediated rectal distension (6).

Since the frequently used laxative glycerol has been shown to result in abdominal pain with decreased colonic tone in patients with IBS, cilansetron might represent a new therapeutic option for this particularly treatment-refractory disease.

Cilansetron, like ondansetron and granisetron, also prevented the slowing of gastric emptying in dogs after a lipid-rich meal. The three drugs were equipotent when given i.v., although cilansetron was more potent than ondansetron, which in turn was much more potent than granisetron, when given i.d. Surprisingly, however, all three drugs were more effective after i.d. than i.v. administration, suggesting that the prokinetic effects of the 5-HT$_3$ antagonists are indirect rather than local. Cilansetron and ondansetron apper to act, at least partially, on the duodenal mucosa sensory afferents (7).

Clinical Studies

Cilansetron's oral antagonist activity on 5-HT$_3$ receptors makes it potentially useful for the treatment of symptoms caused by overstimulation of peripheral receptors, especially in the gastrointestinal tract. The effects of the drug on esophageal distension volume required to elicit a sensation of pain were evaluated in 12 healthy volunteers

Table III: Pharmacology of selected 5-HT_3 receptor antagonists evaluated by inhibition of muscle contraction (from Prous Science MFLine database).

Compound	Parameter	Material/Agonist	Value	Ref.
Azasetron	pA_2	Guinea pig ileum/Serotonin	7.04	15
Cilansetron	pA_2	Guinea pig ileum/Serotonin	7.80	1
Dolasetron	pA_2	Guinea pig ileum/Carbachol	4.50	16
E-3620	pA_2	Guinea pig ileum/5-Me-5-HT	8.60	17
	pIC_{50}	Rat esophagus/Carbachol	6.82	17
Fabesetron	pA_2	Guinea pig ileum/5-Me-5-HT	8.36	29
Granisetron	pA_2	Guinea pig ileum/5-Me-5-HT	7.86	29
	pK_b	Guinea pig ileum/Carbachol	7.89	30
Indisetron	pIC_{50}	Guinea pig ileum/5-Me-5-HT	7.56[c]	21,37
Itasetron	pA_2	Guinea pig ileum/Serotonin	7.50[a]	38
Ondansetron	pA_2	Guinea pig ileum/5-Me-5-HT	6.79	29
	pA_2	Guinea pig ileum/Serotonin	7.40[c]	39,40
Palonosetron	pKb	Guinea pig ileum/Serotonin	8.80[b]	26
Ramosetron	pIC_{50}	Guinea pig colon/Serotonin	7.94[c]	20,34
Renzapride	pA_2	Guinea pig ileum/Serotonin	6.60	41
	pIC_{50}	Rat esophagus/Carbachol	7.60	42
Tropisetron	pK_b	Guinea pig ileum/Carbachol	8.03	30

[a]In the presence of methysergide; [b]in the presence of methysergide and 5-methoxytryptamine; [c]calculated as the mean of distinct values from different studies using the same experimental method.

Table IV: 5-HT_3 receptor antagonism as assessed by inhibition of bradycardia in the Bezold-Jarisch reflex test (from Prous Science MFLine database).

Compound	Parameter	Material/Agonist	Value[+]	Ref.
Alosetron	ED range	Cat/Serotonin	0.1-1.0	13
Azasetron	ED_{50}	Rat/Serotonin	0.89[a]	14,28
Cilansetron	ED_{10}	Rat/2-Me-5-HT	26.0[b]	1
Dolasetron	ED_{50}	Rat/Serotonin	3.10	16
Fabesetron	ED_{50}	Rat/2-Me-5-HT	0.28	29
Granisetron	ED_{50}	Rat/2-Me-5-HT	0.70	29
	ED_{50}	Rat/Serotonin	0.30[a]	14,24,25,28,30,31
Indisetron	ED_{50}	Rat/2-Me-5-HT	0.73	21
Itasetron	ED_{50}	Rat/Serotonin	0.30	22
Lerisetron	ED_{50}	Rat/Serotonin	2.00	23
Ondansetron	ED_{50}	Rat/2-Me-5-HT	5.23	29
	ED_{50}	Rat/Serotonin	1.75[a]	25,28,30-32
Palonosetron	ED_{50}	Rat/2-Me-5-HT	0.03[a]	25,33
Ramosetron	ED_{50}	Rat/Serotonin	0.03[a]	20,28,31,34
Renzapride	ED_{50}	Rat/Serotonin	3.70	35
Tropisetron	ED_{50}	Rat/Serotonin	0.63[a]	25,30,31

[+]In μg/kg i.v.; [a]calculated as the mean of distinct values from different studies using the same experimental method; [b]administered p.o.

who were administered placebo or cilansetron (4 or 8 mg t.i.d.) for 7 days in a double-blind, crossover study. The results showed a tendency to increase the esophageal pain threshold with cilansetron. Treatment was well tolerated, although 7 and 8 patients on low- and high-dose cilansetron, respectively, experienced constipation (8) (Box 1).

Another double-blind, randomized, crossover study assessed the effects of cilansetron on colonic motility in 12 healthy volunteers administered cilansetron (4 or 8 mg t.i.d.) or placebo during 1 week for 3 weeks. Each treatment was separated by a 1-week washout period. Meal- and neostigmine-stimulated phasic colonic motility increased in both active treatment groups to a similar extent. Cilansetron was well tolerated in this trial (9) (Box 2).

Enteric 5-HT_3 receptors have been involved in the control of gastrointestinal motor functions. Three placebo-controlled, crossover studies compared the effects of 4- and 8-mg doses of cilansetron administered t.i.d. for 14 days on colonic transit time, gastric emptying and postprandial gallbladder contraction. One study was

Box 1: The effects of cilansetron on esophageal perception (8) [from Prous Science CSLine database].

Design	Double-blind, crossover, placebo-controlled clinical study
Population	Healthy male volunteers (n = 12)
Treatments	Cilansetron (C), 4 mg t.i.d. x 7 d C, 8 mg t.i.d. x 7 d Placebo (P)
Adverse events	Constipation in 1 (P), 7 (C4) and 8 (C8) patients
Results	Esophageal distension dilatation (ml) inducing pain: C4 (14.6) = C8 (13.9) = P (13.2) Esophageal contraction propagation was not significantly affected in any group
Conclusions	Cilansetron tended to increase the distension-induced pain threshold and was well tolerated in healthy male volunteers

Box 2: The effects of cilansetron on colonic motor activity (9) [from Prous Science CSLine database).

Design	Placebo-controlled, double-blind, crossover clinical study
Population	Healthy volunteers (n = 12)
Treatments	Cilansetron (C), 4 mg t.i.d./wk x 3 C, 8 mg t.i.d./wk x 3 Placebo (P)
Adverse events	Constipation in 1 (P), 7 (C4) and 8 (C8) patients
Results	Colonic contractions and pressure increased significantly with C; no differences were observed between doses. Stools tended to become firmer with C
Conclusions	Cilansetron increased phasic colonic motility after a meal or after taking a muscle relaxant with no adverse effects

Box 3: The effects of cilansetron on gastrointestinal motility (10) [from Prous Science CSLine database].

Design	Randomized, double-blind, placebo-controlled, crossover clinical study
Population	Healthy male volunteers (n = 12)
Treatments	Cilansetron (C), 4 mg t.i.d. x 1 wk C, 8 mg t.i.d. x 1 wk Placebo (P)
Results	Gastric emptying time: C = P Gallbladder volume/emptying: C = P Colonic transit time was prolonged by 28% after C8
Conclusions	Cilansetron did not affect general gastrointestinal motility but its effects on colonic transit may be useful for certain clinical conditions

conducted in 12 young healthy volunteers, and the other two in elderly healthy volunteers. Both doses of cilansetron increased colon transit time with good tolerability, although constipation was more likely to occur on cilansetron than on placebo in the elderly. However, the trial in young subjects failed to demonstrate any effect of cilansetron on gastric emptying or postprandial gallbladder contraction (10, 11) (Boxes 3 and 4).

In a placebo-controlled, double-blind clinical study in 44 healthy adults, cilansetron (8 mg t.i.d.) increased the

Box 4: The effects of cilansetron on colonic transit time and gastric emptying (11)+ [from Prous Science CSLine database].

Design	Crossover, placebo-controlled clinical study
Population	Healthy young male and elderly volunteers (n = 44)
Treatments	Cilansetron (C), 4 mg t.i.d. x 14 d C, 8 mg t.i.d. x 14 d Placebo (P)
Adverse events	Constipation in 1 (P), 7 (C4) and 8 (C8) patients
Results	Colon transit time (h): young subjects, P (42.2) ≤ C4 (49.4) ≤ C8 (53.8); elderly subjects, P (49.8-56.1) ≤ C4 (55.5) ≤ C8 (79.8) Gastric emptying half-life (h): young subjects, P (2.3) ≤ C4 (2.5) = C8 (2.4); elderly subjects, P (2.4-2.8) ≤ C4 (3.1) = C8 (2.8)
Conclusions	Cilansetron tended to increase colonic transit time and gastric emptying; no significant results were obtained due to large interindividual variability

+Results are summarized from 3 similar studies, one in 12 healthy young men receiving both doses of cilansetron and two in 16 healthy elderly subjects receiving only one of the doses in each study.

threshold of gastric nociception. The drug increased distending pressure/volume eliciting pain or discomfort in comparison to placebo. Cilansetron was well tolerated, the most frequent adverse event being abdominal pain in 5/22 patients on cilansetron and 2/22 on placebo (12).

Manufacturer

Solvay, S.A. (BE).

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