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Ibodutant

Prop INN

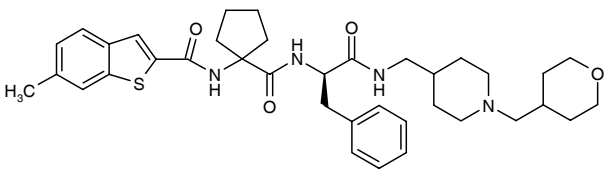
Tachykinin NK_2 Receptor Antagonist
Treatment of Irritable Bowel Syndrome

MEN-15596

6-Methylbenzo[*b*]thiophene-2-carboxylic acid [1-[2-phenyl-1*R*-[[[1-(tetrahydropyran-4-yl)methyl]piperidin-4-ylmethyl]carbamoyl]ethylcarbamoyl]cyclopentyl]amide

N^2-[1-(6-Methyl-1-benzothien-2-ylcarboxamido)cyclopentylcarbonyl]-N^1-[1-(tetrahydropyran-4-ylmethyl)piperidin-4-ylmethyl]-D-phenylalaninamide

InChI=1/C37H48N4O4S/c1-26-9-10-30-23-33(46-32(30)21-26)35(43)40-37(15-5-6-16-37)36(44)39-31(22-27-7-3-2-4-8-27)34(42)38-24-28-11-17-41(18-12-28)25-29-13-19-45-20-14-29/h2-4,7-10,21,23,28-29,31H,5-6,11-20,22,24-25H2,1H3,(H,38,42)(H,39,44)(H,40,43)/t31-/m1/s1



$C_{37}H_{48}N_4O_4S$
Mol wt: 644.8676

CAS: 522664-63-7

EN: 435218

Abstract

Tachykinins are widely expressed endogenous peptides in mammals endowed with physiological and pathophysiological effects. The potent effects of tachykinins on smooth muscle, local inflammatory effects and visceral hypersensitivity observed in human intestine are mainly mediated by NK_2 receptors. Ibodutant (MEN-15596) is a potent and selective tachykinin NK_2 receptor antagonist with a simple chemical structure and one chiral center. It competitively and selectively antagonizes the NK_2 receptor with subnanomolar affinity, both in animal and human tissues, and blocks NK_2 receptor-mediated effects, with a good oral bioavailability and long duration of action. Ibodutant inhibited visceral hyperalgesia evoked by colorectal distension in inflamed unanesthetized guinea pigs, whereas it was without effect on rectal distension-induced abdominal contractions in control animals. Ibodutant showed a very good safety profile in a series of studies, including *in vivo* cardiovascular safety evaluation using telemetry in dogs. It has successfully completed phase I clinical studies and is currently in phase II clinical development for the oral treatment of irritable bowel syndrome (IBS).

Synthesis

Ibodutant is synthesized (1) starting from commercially available methyl tetrahydro-2*H*-pyran-4-carboxylate (I), which is hydrolyzed to the corresponding carboxylic acid by treatment with sodium hydroxide (1 M) and immediately transformed to the acyl chloride (II) with oxalyl chloride and catalytic DMF in dichloromethane. Reaction of (II) with isonipecotamide (III) in DMF/dichloromethane in the presence of triethylamine gives the diamide (IV), which is successfully reduced to the corresponding diamine (V) using lithium aluminum hydride in refluxing THF. Coupling of (V) with *tert*-butyloxycarbonyl-(*R*)-phenylalanine *N*-hydroxysuccinimide ester (Boc-D-Phe-OSu) in THF and Boc deprotection with HCl/dioxane gives (VI). Further coupling of (VI) with the *N*-Boc derivative of aminocyclopentanecarboxylic acid (VII) in the presence of EDC.HCl and HOBT, and deprotection of the Boc group with HCl/dioxane, provides 1-aminocyclopentanecarboxylic acid [2-phenyl-1-(*R*)-[[1-(tetrahydropyran-4-ylmethyl)piperidin-4-ylmethyl]carbamoyl]ethyl]amide (VIII). The free amine compound (VIII) is in turn coupled with 6-methylbenzo[*b*]thiophene-2-carbonyl chloride (IX), obtained from the corresponding carboxylic acid by reaction with oxalyl chloride under the usual conditions, finally giving ibodutant. Scheme 1.

Background

Tachykinin NK_2 receptors are widely expressed in peripheral tissues of mammals and their stimulation induces marked effects in human airways, urinary bladder and gastrointestinal smooth muscle (2, 3). An NK_2 receptor-mediated component of cellular inflammation has also been described (4). Preclinical data indicate that

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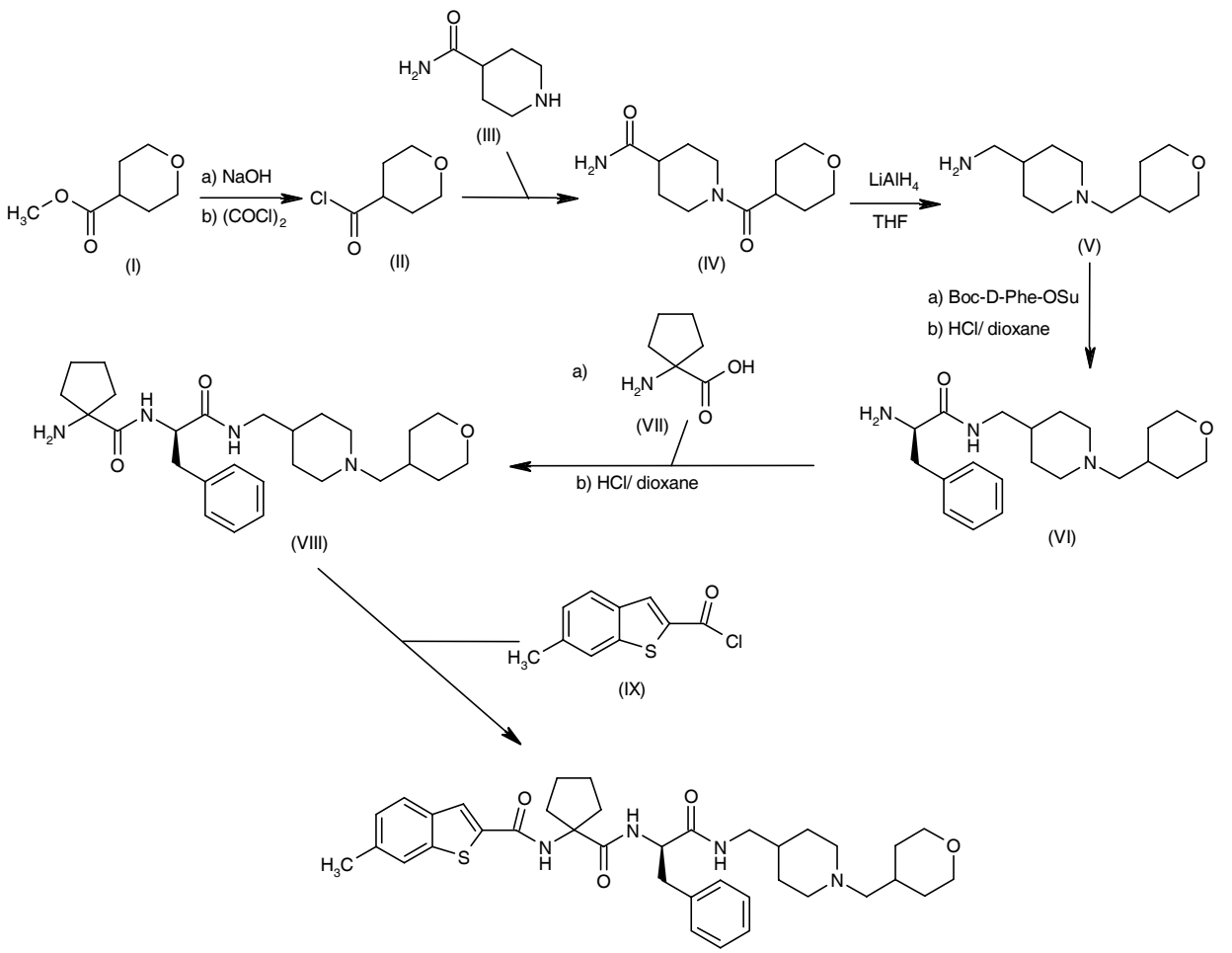
Scheme 1: Synthesis of Ibodutant



tachykinins, particularly NKA through the NK_2 receptor, play a role in modulating visceral nociception in pharmacologically or pathologically altered conditions (5). In addition, tachykinins (TKs) are expressed in extrinsic sensory fibers, intrinsic primary afferent neurons and interneurons in the human intestine, where the pronociceptive effect of TKs mainly involves NK_2 receptor stimulation, as evidenced in *in vivo* in studies in humans (6). Therefore, NK_2 receptor antagonists can reduce hyperalgesia/allodynia associated with inflammation or stress (7). This aspect of tachykinin pharmacology may be revealed to be of utmost importance in the development of effective drugs for irritable bowel syndrome (IBS). In fact, in patients suffering from this diffuse pathology, visceral hypersensitivity, manifested as abdominal pain, is often associated with other symptoms such as altered gut motility (8).

IBS is a quite common pathology in the world population and patients perceive as noxious stimuli that do not induce pain in normal subjects. According to epidemiological data, between 15% and 20% of the population is estimated to suffer from this disorder. There is no current therapy able to control IBS symptoms with a satisfactory balance between benefits and side effects (9). At present, tricyclic antidepressants, in low doses, are considered the most useful medications to reduce symptoms.

Interestingly, the blockade of visceral hyperalgesia/allodynia by NK_2 receptor antagonists can be associated either with the inhibition of exaggerated intestinal motility or with the recovery of an inhibited motility (7). In both cases, administration of NK_2 receptor antagonists can lead to restoration of basal intestinal parameters. Proof of concept that these effects can also occur in humans has been obtained in clinical studies in healthy volunteers. In fact, i.v. infusion of NKA in healthy subjects changed the pattern of intestinal motility from the fasted to the fed state and precipitated a series of intestinal adverse events: all these effects were prevented by the tachykinin NK_2 receptor antagonist nepadutant, whereas in the same study nepadutant alone had no effect on basal intestinal motility (6).

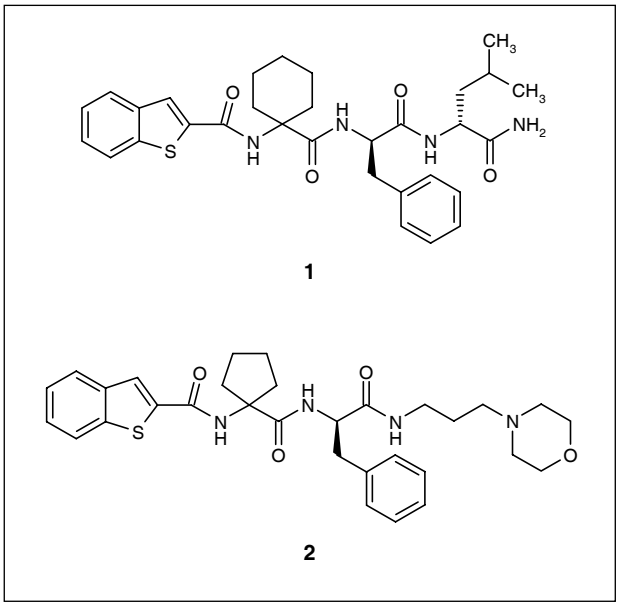


Fig. 1. Discovery of ibodutant: Leads from library screening and further optimization.

Ibodutant (MEN-15596) is the result of a research project aimed at identifying a potent, selective and orally acting NK_2 receptor antagonist to be developed as a new therapeutic option for the treatment of IBS. Ibodutant maintains some of the chemical features, such as aromatic groups and a basic moiety, which in the past yielded a series of compounds with high affinity for the tachykinin NK_2 receptor (1, 10). Ibodutant is a small molecule rationally derived from previous peptide antagonists at Menarini through an extensive process of chemical modifications guided by computer-assisted drug design. Initially, a library of tripeptide amides was screened for affinity for the human NK_2 receptor (11). Tripeptides were characterized by the presence of an α,α-cycloalkyl amino acid, capped on the amine with different acyl groups, as the amino acid in the first position of the peptide sequence. The *S*- and *R*-forms of all the natural amino acids, except cysteine, were inserted in positions 2 and 3 of the sequence. A number of hits emerged from library screening, compound **1** (Fig. 1) being the best in terms of affinity for the human NK_2 receptor (pK_i = 7.3) (11). Further structural modifications led to compound **2**, with subnanomolar binding affinity for the human NK_2 receptor (pK_i = 9.2), although this compound was devoid of significant *in vivo* activity.

A lead optimization process focused on iterated structural modifications was thus started (1). The effects of the introduction of a wide variety of substituents on the lipophilic aromatic part of the molecule, and the modulation of the structural constraint through the insertion of different achiral α,α-dialkyl amino acids, were investigated. In addition, the length and the rigidity of the hydrophilic pseudo-*C*-terminal pendant were evaluated through the insertion of different amines. This process finally led to the selection of ibodutant as the best compound.

Preclinical Pharmacology

Ibodutant is a potent and selective antagonist at the human tachykinin NK_2 receptor, as demonstrated in binding and *in vitro* functional studies (12). Ibodutant showed subnanomolar affinity for the human NK_2 receptor expressed in CHO cells (pK_i = 10.1 ± 0.2). In functional tests in these cells, ibodutant inhibited intracellular calcium release produced by receptor stimulation with a pK_B of 9.10 ± 0.05. It also inhibited NK_2 receptor-mediated inositol phosphate (IP) accumulation in CHO cells with a pK_B of 10.6 ± 0.1. The compound was characterized by high *in vitro* selectivity, with at least 3 orders of magnitude lower potency *versus* 28 other common receptors (including tachykinin NK_1 and NK_3 receptors), 5 ion channels and 3 transporters, most of them of the human type.

In isolated guinea pig colon, ibodutant competitively inhibited NK_2 receptor-mediated contractions at subnanomolar concentrations, with a pK_B of 9.3 ± 0.1. In other functional tests in isolated animal tissues, it showed high species selectivity, with pK_B values of 8.8 ± 0.1 in minipig urinary bladder, 7.5 ± 0.1 in rabbit pulmonary artery, 6.3 ± 0.1 in rat urinary bladder and 5.8 ± 0.2 in mouse urinary bladder. In functional tests in isolated human tissues (urinary bladder, ileum, colon), ibodutant behaved as an antagonist at subnanomolar concentrations, with a pK_B of 9.2 ± 0.2. No residual agonist activity was detected in any of the *in vitro* studies performed.

The ability of ibodutant to block NKA-induced functional responses (IP accumulation in CHO cells expressing human NK_2 receptors) was long lasting and binding to the receptor was slowly reversible. In fact, the compound (2 nM) inhibited the response to NKA (30 nM) by 88 ± 3%, and after washing with drug-free medium every 15 min for 3 h (12 washing periods), a residual inhibition of 28 ± 4% was still present. Ibodutant showed a slower recovery time as compared to the nonpeptide NK_2 receptor antagonist saredutant, although maintaining full competitive behavior.

The *in vitro* intestinal absorption properties of ibodutant were evaluated using a cell culture of human colon carcinoma (Caco-2 cell permeability test) differentiated in mature enterocytes. At pH 7.4 and a concentration of 100 μM, it showed intermediate permeability, with a P_{app} of 5.1 ± 1.3 x 10^{-6} cm/s.

Ibodutant also exhibited potent NK_2 receptor-antagonist activity in *in vivo* experiments (12). When administered by either the i.v. (ED_{50} = 0.12 mg/kg) or the intraduodenal (ED_{50} = 2.04 mg/kg) route, it fully inhibited colon contractions induced by the selective NK_2 agonist [βAla^8]-NKA(4-10) (3 nmol/kg i.v.) in anesthetized guinea pigs. The compound showed a long duration of action (over 4 h), and following single and repeated (5 days) oral administration (20 mg/kg), complete and long-lasting (over 9 h) inhibition of the NK_2-mediated colonic motor response was obtained. The selectivity of ibodutant for the NK_2 *versus* the NK_1 receptor was confirmed in *in vivo* experiments: at 1.9 mg/kg i.v. the compound completely antagonized guinea pig colon contractions induced by the selective NK_2 receptor agonist [βAla^8]-NKA(4-10), without

affecting contractions of similar amplitude induced by the NK_1 agonist [Sar^9]-SP sulfone.

Following i.v. administration, ibodutant produced dose-dependent inhibition of the bronchoconstriction evoked by [βAla^8]-NKA(4-10) in guinea pigs. At 0.6 and 1.9 μmol/kg, it blocked the response by 77 ± 4% and 99 ± 1%, respectively, and at the higher dose the response was still markedly inhibited (about 80%) for up to 4 h.

In other *in vivo* studies, ibodutant at a dose of 20 mg/kg p.o. fully prevented the increase in intestinal transit induced by the selective NK_2 agonist in guinea pigs, without affecting basal intestinal propulsion. At a dose of 1.9 mg/kg i.v., it blocked the distension-induced atropine-resistant proximal colon reflex contractions mediated by endogenous tachykinin release, with a long duration of action. Under basal conditions, ibodutant at doses up to 6.5 mg/kg s.c. did not modify the colorectal sensitivity to distension in noninflamed anesthetized guinea pigs. In contrast, under inflammatory conditions (TNBS-induced colitis), at doses of 1.9 and 6.5 mg/kg s.c. it exhibited an antinociceptive effect against visceral pain in guinea pigs, significantly reducing the number of abdominal cramps in animals with experimental colonic inflammation.

These results provide a background for speculating that ibodutant could have a beneficial effect in a variety of human diseases in which peripheral tachykinin NK_2 receptors play a pathogenic role, such as IBS, asthma and urinary bladder dysfunction (13).

Safety

Ibodutant has shown an excellent tolerability profile in a series of preclinical safety pharmacology studies performed *in vivo* in mice and rats. When administered to mice and rats at doses up to 1000 mg/kg p.o., ibodutant did not exert any significant effect on spontaneous locomotor activity or motor coordination, nor was it associated with a proconvulsant effect in mice. A marked analgesic effect was seen in a model of pain induced by i.p. injection of acetic acid in the mouse (writhing test): the number of recorded abdominal contractions was reduced by 49% at 100 mg/kg and by 73% at 1000 mg/kg. This effect can likely be ascribed to the expected pharmacological antagonism of visceral pain.

The effects of ibodutant were evaluated on various cardiovascular (systolic and diastolic blood pressure, heart rate, left ventricular systolic pressure, femoral blood flow, ECG) and respiratory (rate, minute volume and tidal volume) parameters after a single intraduodenal administration in anesthetized rats (n=4) at doses of 10, 100 and 1000 mg/kg. No relevant effects were observed on heart rate or diastolic and systolic arterial blood pressure at any of the doses tested. Normal ECG (lead II) wave forms were obtained from all treated animals throughout the experiment. No changes in respiratory rate, tidal volume and minute volume considered to be related to treatment were recorded.

The cardiac safety of ibodutant in animals was confirmed by the results of a telemetry study in conscious male beagle dogs. Ibodutant administered orally at 30, 90 and 120 mg/animal had no substantial effect on arterial blood pressure, heart rate and the P-R and Q-T intervals. No lengthening of the $Q\text{-}T_c$ interval, arrhythmia or other changes in the morphology of the ECG were observed at any dose of ibodutant.

Clinical Studies

Ibodutant has successfully completed phase I clinical studies. Two studies have been performed aimed at evaluating the pharmacokinetics, safety and tolerability of ibodutant after single doses and repeated oral administration for 7 days in healthy volunteers. Kinetic results indicate good oral absorption and a half-life long enough to allow once-daily dosing. Ibodutant was safe and well tolerated in humans even at the maximal doses of 240 mg as a single dose or 120 mg/day for 7 days.

A multinational, double-blind, placebo-controlled, dose-finding phase II study is ongoing in order to evaluate the effect of a 4-week oral treatment with three doses of ibodutant in male and female IBS patients, including diarrhea-prevalent, constipation-prevalent, mixed and unsubtyped IBS.

Source

The Menarini Group (IT).

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