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A short synthesis of cisapride: a gastrointestinal stimulant derived from *cis*-4-amino-3-methoxypiperidine

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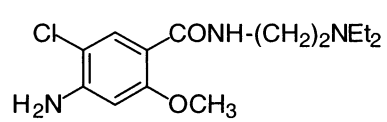
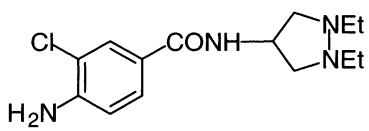
Abstract—Cisapride was synthesized in seven steps from piperidin-4-one by using a diastereoselective reduction of an α-oximino ether with the complex BH_3·THF.

Metoclopramide is used clinically as a stimulant of upper gastrointestinal motility and as an antiemetic.[1] The gastric prokinetic action of metoclopramide is ascribed to stimulation of the gut motility by an increase in acetylcholine release from the cholinergic nerves of the gut.[2] Acetylcholine release is due to either blockade of the serotonin ($5\text{-}HT_3$)[3] receptors[4–6] or activation of particular 5-HT-like receptors which have not yet been characterized in enteric nervous systems.[7] This mechanism of action, however, remains to be determined. On the other hand, metoclopramide has a dopamine D_2 receptor antagonistic property, which is not related to its gastric prokinetic activity.[8,9] Blockade of dopamine D_2 receptors in metaclopramide is reported to reduce several unfavorable effects such as central nervous system depression and extrapyramidal syndrome in man,[10,11] which limits its clinical use. Recently, several benzamide compounds such as diazopride **2**,[12] BRL-24924 **3**[13–15] and cisapride **4**,[16,17] showing potent gastric prokinetic action and reduced dopamine D_2 receptor antagonistic activity, were derived from a modification of the side chain of metoclopramide (Scheme 1).

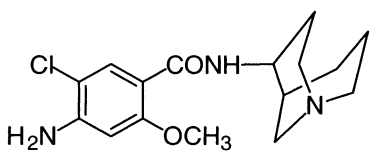
Cisapride has been previously synthesized from piperidin-4-one in 13 steps[18] or 11 steps.[17] A shorter synthesis has been reported in nine steps with an overall yield of 3%.[19] Here, we report a more efficient synthesis of cisapride from piperidin-4-one in seven steps with an overall yield of 4.5%.



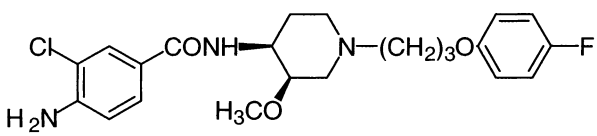
1 Metoclopramide



2 Diazopride



3 BRL-24924



4 Cisapride

Scheme 1. Benzamide compounds with potent gastric prokinetic action.

Keywords: cisapride; piperidin-4-one; oximino ether; reduction; borane.
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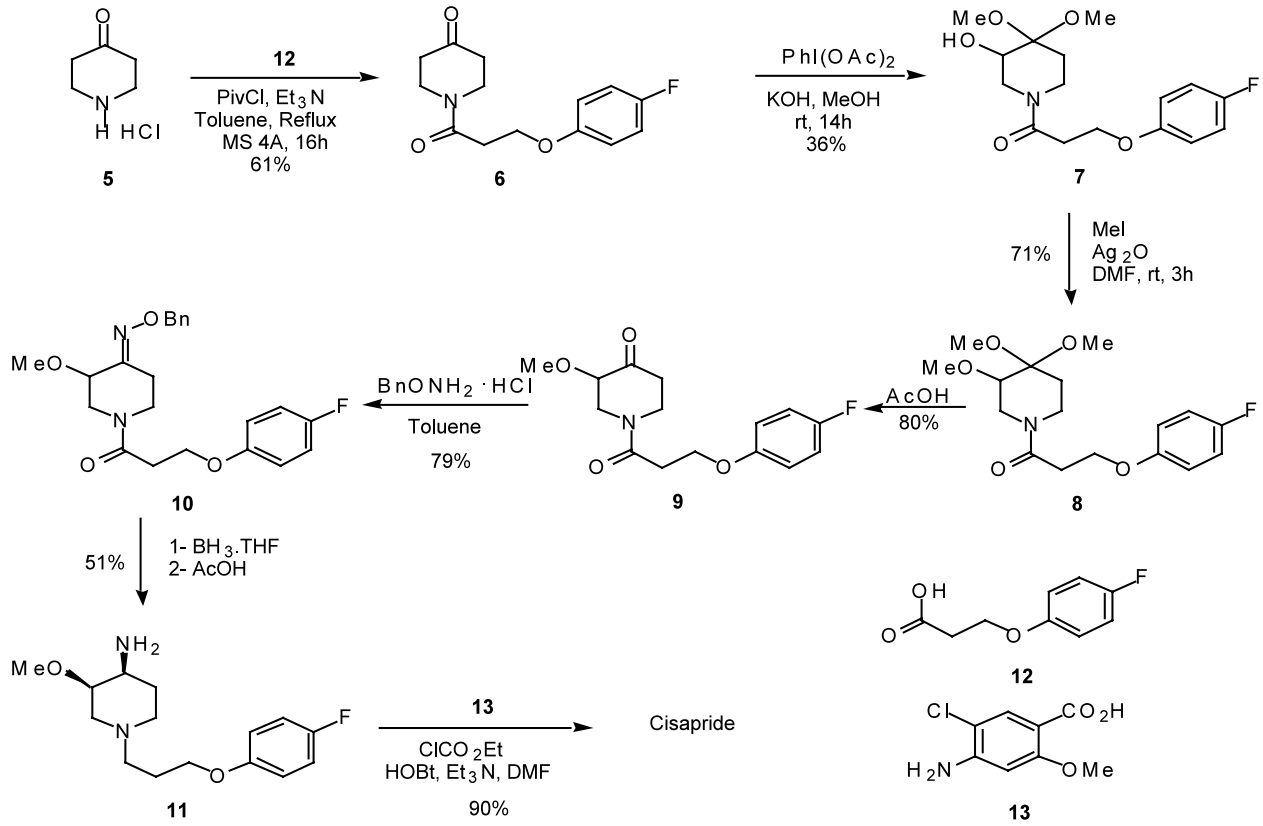

Scheme 2. Synthesis of cisapride.

Piperidin-4-one hydrochloride **5** was transformed into amide **6** by treatment with carboxylic acid **12** in the presence of pivaloyl chloride and triethylamine in refluxing toluene for 16 h (yield 61%). The introduction of the methoxy group at the C-3 position of the piperidine was achieved in two steps. The first step involved oxidation of the amido ketone **6** by using diacetoxyiodobenzene[20] in the presence of KOH (methanol, rt, 14 h), which afforded the hydroxy methoxy ketal **7** (36%). Compound **7** was then transformed into α-methoxy ketone **8** in 71% yield by treatment with MeI in the presence of Ag_2O (DMF, 3 h, 0°C→rt). Deprotection of the ketone by using acetic acid gave the 3-methoxy amido ketone **9** (80% yield), which was condensed with *O*-benzylhydroxylamine hydrochloride in the presence of pyridine in refluxing toluene (Dean–Stark, 3 h) to yield the corresponding oximino ether **10**. The oxime was then reduced diastereoselectively by using BH_3·THF (THF, 0°C→rt, 18 h). After treatment of the amine borane with acetic acid (50°C, 1 h), the *cis*-amino ether **11** was isolated in 51% yield, with a diastereomeric excess of 96%. Treatment of amine **11** with the carboxylic acid **13** (EtO-COCl, 1-hydroxybenzotriazole, Et_3N, DMF) gave cisapride in 90% yield (Scheme 2).

The synthesis of cisapride requires only seven steps and proceeds in 4.5% overall yield. A key feature is the highly stereoselective reduction of oximino ether **10** with BH_3·THF.

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