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# Novel *N*-[1-(1-Substituted 4-Piperidinylmethyl)-4-piperidinyl]benzamides as Potent Colonic Prokinetic Agents

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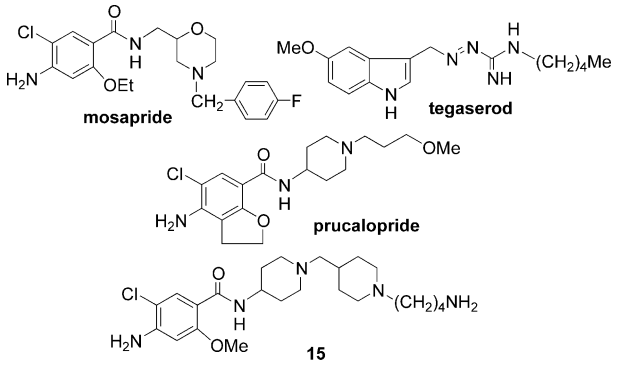
**Abstract**—A series of novel *N*-[1-(1-substituted 4-piperidinylmethyl)-4-piperidinyl]benzamides was prepared and its compounds were evaluated for their binding to 5-$HT_4$ receptors and effects on gastrointestinal motility in conscious dogs. 4-Amino-*N*-[1-[1-(4-aminobutyl)-4-piperidinylmethyl]-4-piperidinyl]-5-chloro-2-methoxybenzamide (**15**) was found to have a potent binding affinity for 5-$HT_4$ receptors ($IC_{50}$: 6.47 nM) and showed excellent colonic prokinetic activity. © 2002 Published by Elsevier Science Ltd.

## Introduction

The serotonin 4 (5-$HT_4$) receptors are located in the gastrointestinal tract,[1–3] heart,[4] urinary bladder,[5] and brain.[6] In the gastrointestinal system, in particular, 5-$HT_4$ receptors are distributed from the esophagus to the colon and are especially involved in the regulation of gastrointestinal motility.[7,8] Mosapride,[9] a 5-$HT_4$ receptor partial agonist developed in our laboratories, is used clinically as a gastroprokinetic agent in Japan. Other novel and potent 5-$HT_4$ receptor agonists such as the indole carbazimidamide tegaserod[10,11] and the 2,3-dihydrobenzo[*b*]furan-7-carboxamide prucalopride[12] are currently advanced in clinical development for the treatment of various forms of constipation. As the colonic motility enhancement of mosapride is weaker than the gastric antral motility in conscious dogs implanted with force transducers,[13] we were interested in identifying a potent and selective 5-$HT_4$ receptor agonist which enhances lower gastrointestinal motility. Colonic motility in dogs consists of rhythmically occurring contractile states that have migrating and non-migrating motor complexes. The main propulsive force in the canine colon appears to be a function of large-amplitude giant migrating contractions (GMCs). It is well known that GMCs occur during defecation and are associated with mass movement.[14,15] We designed the structurally novel 4-amino-1-[1-(3-amino-2-hydroxypropyl)-4-piperidinylmethyl]piperidine (**2**) from 2-aminomethyl-4-(4-fluorobenzyl)morpholine, which is the amine moiety of mosapride, via 1-(3-amino-2-hydroxypropyl)-4-benzylpiperidine (**1**, Scheme 1). On the basis of the results of structure–activity relationships (SARs), we found that 4-amino-*N*-[1-[1-(4-aminobutyl)-4-piperidinylmethyl]-4-piperidinyl]-5-chloro-2-methoxybenzamide (**15**) is a potent colonic motility enhancer. Here, the synthesis and SARs concerning the binding affinity for 5-$HT_4$ receptors and gastric antral and colonic motility in dogs of a series of *N*-[1-(1-substituted 4-piperidinylmethyl)-4-piperidinyl]benzamides are described.

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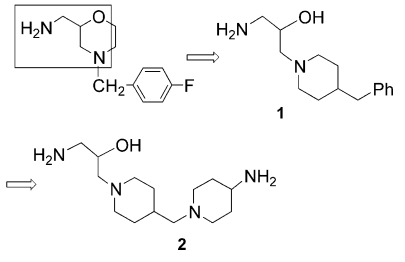
## Chemistry

Isonipecotic acid was treated with benzyl chloroformate in aqueous NaOH–$CH_2Cl_2$ mixture to give 1-benzyloxycarbonyl (Cbz) piperidine-4-carboxylic acid (**3**) in 94% yield. Treatment of **3** with $SOCl_2$, followed by reaction of the resulting 4-piperidinecarbonyl chloride with commercially available 4-[*tert*-butoxycarbonyl (Boc)]-aminopiperidine (**4**) in the presence of $Et_3N$ in $CH_2Cl_2$ afforded the piperidinylamide **5** in 83% yield. Reduction of the amide moiety of **5** with borane–THF complex gave the corresponding 1-(4-piperidinylmethyl)piperidine **6** in 96% yield. After deprotection of the Cbz group using hydrogenolysis, the resulting 4-(*tert*-butoxycarbonyl)amino-1-(4-piperidinylmethyl)piperidine was treated with *N*-(2,3-epoxypropyl)phthalimide (EPP) to produce the epoxy ring opened product **7**. Reaction of **7** with hydrazine monohydrate, followed by condensation of the aminoethanol **8** with 4-amino-5-chloro-2-methoxybenzoic acid (ACMB) using 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDC) as a coupling agent and successive deprotection of the Boc group gave the benzamide **9** in 67% overall yield (Scheme 2).

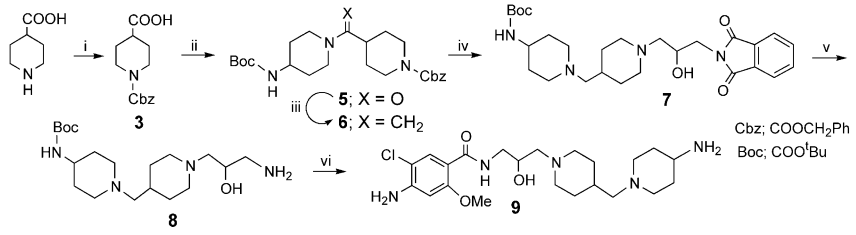
Treatment of the key intermediates **5** and **6** with aqueous HCl, following by condensation of the resulting 4-aminopiperidines with ACMB provided **10a**,**b** in good yield. In order to avoid the elimination of 5-chloro group of **10a**,**b** by hydrogenolysis, the other deprotection of the Cbz group was carried out. Thus, reaction of **10a**,**b** with $MeSO_3H$ in the presence of anisole in refluxing $CHCl_3$ afforded the deprotected piperidines **11a**,**b**, which were treated with *N*-protected amino acid derivatives, followed by deprotection to give **19**–**28**. Reduction of the several *N*-protected amides with borane and reaction of **11a** with EPP, following by deprotection afforded **12**–**17**. Methanesulfonylation of **14** in the presence of $Et_3N$ gave **18** in ca. 50% yield (Scheme 3).



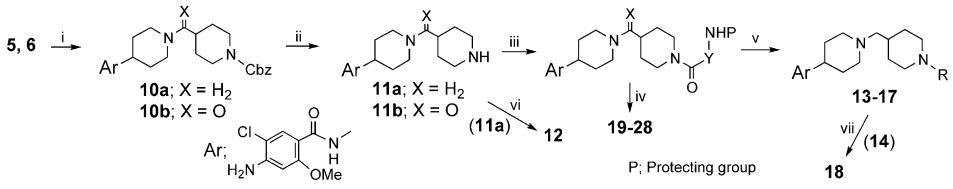

**Scheme 1.**

## Results and Discussion

Gastric and colonic motility enhancing activities in conscious dogs implanted with force transducers were measured as follows. The compounds prepared (1.0 mg/kg, iv) were administered to dogs in a postprandial state (2–3 h after feeding). The signals from the force transducers implanted in the gastric antrum and ascending colon were analyzed using our own system controlled by a computer. The motor index given by the processing system corresponded to the measurements of the area surrounded by the contraction wave and base line, that is, the product of the amplitude (voltage) and the time in min over a fixed period. The motor index for the 30 min period after administration of each compound is expressed as a percentage of that for the 30 min period before administration. The colonic motility was expressed by the induction number of GMCs. Mosapride at 1.0 mg/kg, iv did not induce any GMCs associated with defecation and all other compounds except **16** produced a less potent gastric motility enhancement than mosapride. The binding affinity for 5-$HT_4$ receptors was assayed using [$^3$H]GR1138038, a specific 5-$HT_4$ receptor ligand in guinea-pig striatum. All compounds exhibited much more potent affinity for 5-$HT_4$ receptors than mosapride. The pharmacological results are given in Table 1.



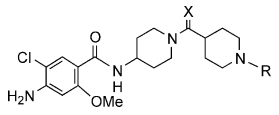

**Scheme 2.** Reagents and conditions: (i) (1) $ClCO_2Bn$, rt, 15 h; (ii) (1) $SOCl_2$, $CH_2Cl_2$, reflux, 1 h; (2) **4**, $Et_3N$, rt, 4 h; (iii) $BH_3$, THF, rt, 13 h; (iv) (1) 5% Pd/C, $H_2$, EtOH, 30 °C; (2) EPP, MeCN, reflux, 15 h; (v) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux, 0.5 h; (vi) (1) ACMB, EDC, $CH_2Cl_2$, rt, 3 h; (2) 30% aq HCl–EtOH, rt, 2 h.




**Scheme 3.** Reagent and conditions: (i) (1) 30% aq HCl–EtOH, rt, 1 h; (2) ACMB, EDC, $CH_2Cl_2$, rt, 3 h; (ii) $MeSO_3H$, PhOMe, 3 h; (iii) HOOC-Y-NHP, EDC; (iv) deprotection; (v) (1) $BH_3$, THF, rt, 15 h; (2) deprotection; (vi) (1) EPP, MeCN, reflux, 15 h; (2) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux, 0.5 h; (vii) $MeSO_2Cl$, $Et_3N$, rt, 3 h.

The binding affinity for 5-$HT_4$ receptors of the *N*-[1-(4-piperidinylmethyl)-4-piperidinyl]benzamide **12** was more potent than that of the *N*-[3-(1-piperidinyl)-2-hydroxypropyl]benzamide **9** ($IC_{50}$: 14.4 nM vs $IC_{50}$: 40.6 nM). In addition, **9** showed a moderate toxicity. Thus, **12** was selected and we examined a series of *N*-[1-(1-substituted 4-piperidinylmethyl)-4-piperidinyl]benzamides. The benzamide **13** with a 2-aminoethyl substituent showed the same binding affinity for 5-$HT_4$ receptors as **12**. Compounds **12** and **13** as well as mosapride did not produce any GMCs. On the other hand, elongation of the methylene chain of **13** (yielding **14**–**16**) led to an increase in colonic motility enhancement as GMCs were observed several times. The binding affinity for 5-$HT_4$ receptors of **15** was ca. 2 times more potent than that of **14** and **16**. Compound **15** having a straight alkylene group showed more potent colonic motility enhancement and 5-$HT_4$ receptor affinity than **17** having the corresponding branched alkylene group. Introduction of methanesufonyl group (giving **18**) into the amino group of **14** produced a moderate colonic motility enhancement independent of the potency of affinity for 5-$HT_4$ receptors. This result suggested that the binding affinity for 5-$HT_4$ receptors and the induction number of GMCs are not remarkably influenced by the basicity of amine moiety. Next, we addressed compounds with a carbonyl group. Exchange of a methylene group of **13** into a carbonyl group (giving **19**) was found to cause an increase in gastrointestinal motility and affinity for 5-$HT_4$ receptors. Introduction of methylene and ethylene groups (giving **20** and **21**, respectively) in **19** yielded a colonic motility enhancement identical to that of **19**. Compound **21** showed a much potent affinity for 5-$HT_4$ receptors ($IC_{50}$; 3.99 nM). Replacement of a methylene group between two piperidine rings of **21** by a carbonyl group (yielding **22**) caused a drastic decrease in 5-$HT_4$ receptor affinity, indicating that the basic nitrogen atom in the piperidine ring would be an important factor for a potent 5-$HT_4$ receptor affinity. Compound **23**, which is the *n*-butylene analogue of **19**, did not induce GMCs although it showed a potent affinity for 5-$HT_4$ receptors. Introduction of methyl and propyl groups (giving **24**–**28**) in **19** or **20** led to a decrease in colonic motility enhancement. These compounds exhibited a potent affinity for 5-$HT_4$ receptors. As a whole, the clear relationship between the binding affinity for 5-$HT_4$ receptors

**Table 1.** Pharmacological results of benzamide derivatives **12**–**28**




| Compd | R | X | Gastrointestinal motility (1.0 mg/kg, iv) | | 5-$HT_4$ binding $IC_{50}$ (nM) |
|---|---|---|---|---|---|
| | | | Stomach (%) | GMCs (number) | |
| **12** | $CH_2CH(OH)CH_2NH_2$ | $H_2$ | 121 | — | 14.4 |
| **13** | $(CH_2)_2NH_2$ | $H_2$ | 127 | — | 14.3 |
| **14** | $(CH_2)_3NH_2$ | $H_2$ | 151 | 7 | 13.4 |
| **15** | $(CH_2)_4NH_2$ | $H_2$ | 148 | 6 | 6.47 |
| **16** | $(CH_2)_5NH_2$ | $H_2$ | 194 | 4 | 11.2 |
| **17** | $CH_2CH(Me)CH_2NH_2$ | $H_2$ | 177 | 1 | 14.3 |
| **18** | $(CH_2)_3NHSO_2Me$ | $H_2$ | 151 | 2 | 21.1 |
| **19** | $COCH_2NH_2$ | $H_2$ | 165 | 5 | 9.30 |
| **20** | $CO(CH_2)_2NH_2$ | $H_2$ | 107 | 3 | 9.50 |
| **21** | $CO(CH_2)_3NH_2$ | $H_2$ | 130 | 5 | 3.99 |
| **22** | $CO(CH_2)_3NH_2$ | O | 132 | 2 | 425.4 |
| **23** | $CO(CH_2)_4NH_2$ | $H_2$ | 112 | — | 3.91 |
| **24** | $COCH(Me)NH_2$ | $H_2$ | 127 | — | 5.06 |
| **25** | $COCH(Me)CH_2NH_2$ | $H_2$ | 121 | — | 5.08 |
| **26** | $COCH(Pr)NH_2$ | $H_2$ | 117 | 1 | 2.57 |
| **27** | $COCH(^{iso}Pr)NH_2$ | $H_2$ | 147 | — | 2.53 |
| **28** | $COCMe_2NH_2$ | $H_2$ | 112 | — | 2.60 |
| | Mosapride | | 188 | — | 113.0 |

— no GMCs.

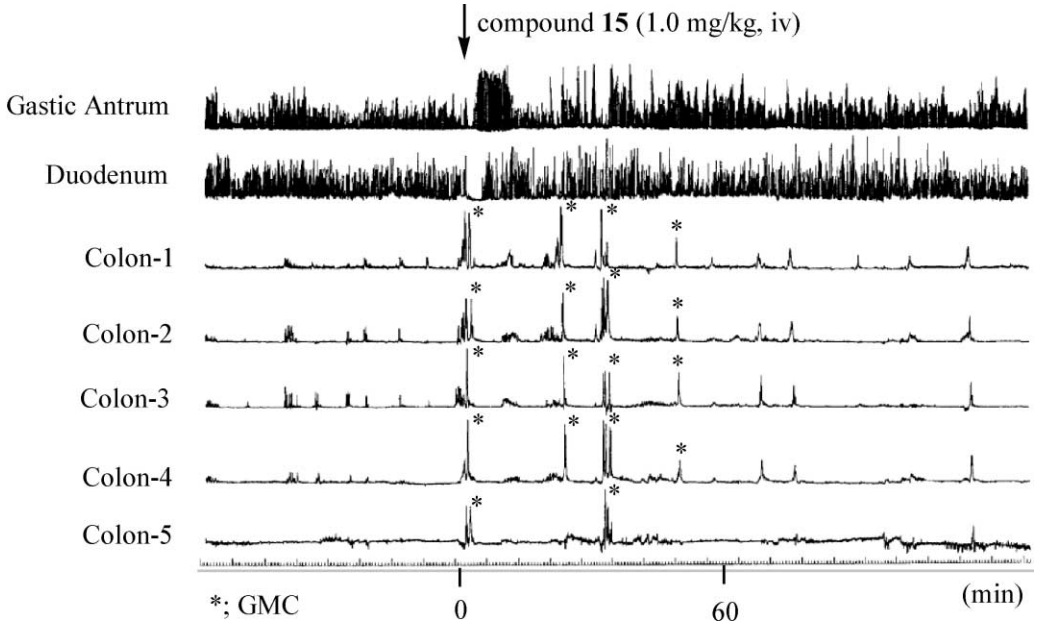



**Figure 1.** Effects of **15** on gastrointestinal motility in postprandial state in a conscious dog.

and the induction number of GMCs was not observed; it was considered that other mechanisms contributed to the colonic motility enhancement. On the basis of the above screening results, **15** with a 4-aminobutyl substituent was found to be optimal as novel colonic prokinetic agent. Finally, we examined the effects of **15** on the gastrointestinal motility in postprandial state in a conscious dog. When **15** was given as an intravenous bolus dose of 1.0 mg/kg, the motility of the gastric antrum, duodenum, and colons 1–5 (4, 8, 16, 24, and 32 cm from the ileocolonic junction, respectively) was rapidly enhanced as shown in Figure 1. Compound **15** induced several times GMCs associated with defecation without causing diarrhea and vomit in comparison with mosapride. Furthermore, **15** was effective in fecal excretion in unfasted mice at doses $>1$ mg/kg, sc.

Next, we tested the influence of GR 1138038,[16] a selective and potent 5-$HT_4$ receptor antagonist, on the stimulated gastrointestinal motility by **15**. GR 1138038 inhibited the stimulation of antral motility and GMCs caused by **15**. It is, therefore, suggested that **15** is 5-$HT_4$ receptor agonist. Unfortunately, **15** produced weak gastrointestinal motility stimulation when administered orally; no induction of GMCs was observed at a dose of 1.0 mg/kg, po. On the other hand, 5 times GMCs were induced at 10 mg/kg, po. However, prucalopride induced GMCs and defecation at 0.3 mg/kg, po. In order to improve oral bioavailability of **15**, further modification in the series of *N*-[1-(1-substituted 4-piperidinylmethyl)-4-piperidinyl]benzamides is now in progress at our laboratories.

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