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A NOVEL SERIES OF 6-METHOXY-1*H*-BENZOTRIAZOLE-5-CARBOXAMIDE DERIVATIVES WITH DUAL ANTIEMETIC AND GASTROPROKINETIC ACTIVITIES

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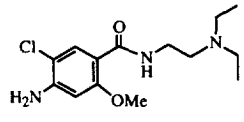
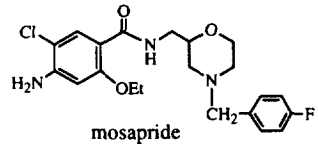
Abstract: A novel series of 6-methoxy-1*H*-benzotriazole-5-carboxamide derivatives with a medium perhydroazacycle ring in the amine moiety were prepared, and their antiemetic and gastroprokinetic activities were evaluated. Among them, *N*-(1-ethylhexahydroazepin-3-yl)-, *N*-(1-ethyloctahydroazocin-3-yl)- and *N*-(1-ethyloctahydroazonin-3-yl)-6-methoxy-1*H*-benzotriazole-5-carboxamides (**24**, **36**, **37**) showed a potent antiemetic activity (inhibition of apomorphine-induced emesis in dogs) along with gastroprokinetic activity (gastric emptying in rats).

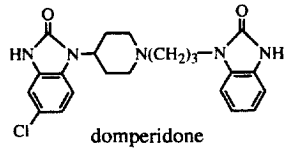
Metoclopramide[1] is used clinically as a gastroprokinetic agent. The mechanism of gastroprokinetic agents is accepted to be correlated with agonistic activity at a serotonin receptor subtype (5-HT_4).[2] Metoclopramide, however, has unfavorable side effects such as extrapyramidal symptoms arising from its dopamine D_2 receptor antagonistic property.[3] Mosapride, a novel gastroprokinetic agent developed in our laboratory, is recognized as a selective 5-HT_4 receptor agonist without dopamine D_2 receptor antagonistic activity.[4] On the other hand, the traditional antiemetic domperidone, a peripheral dopamine D_2 receptor antagonist, has been shown to be effective for treatment of some symptoms of chronic upper gastrointestinal distress and for prevention of nausea and vomiting resulting from a variety of causes.[5] To obtain a novel gastroprokinetic agent with a peripheral dopamine D_2 receptor antagonistic activity, we carried out several modifications of 5-chloro-*N*-(1-ethylhexahydroazepin-3-yl)-2-methoxy-4-methylaminobenzamide[6] (**1**), which



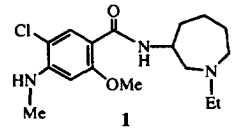
metoclopramide



mosapride



domperidone



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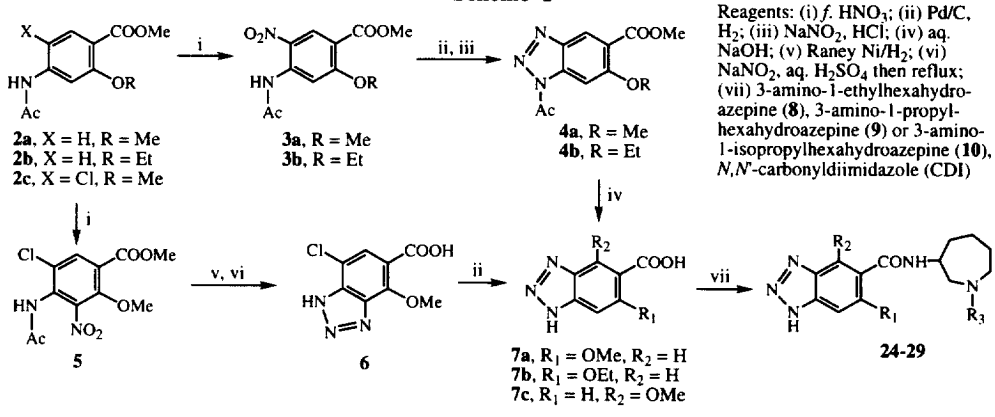
is a dual antagonist for dopamine D_2 and 5-HT_3 receptors. On the basis of the results of screening for antiemetic and gastroprokinetic activities, we found that the structurally novel *N*-(1-ethylhexahydroazepin-3-yl)-6-methoxy-1*H*-benzotriazole-5-carboxamide (**24**) showed a potent antiemetic activity, a moderate gastroprokinetic activity and a weak central nervous system depression. Here, we describe the synthesis and structure-activity relationships (SARs) concerning the antiemetic and gastroprokinetic activities of a series of 6-methoxy-1*H*-benzotriazole-5-carboxamide derivatives with a medium perhydroazacycle ring in the amine moiety.

Chemistry

6-Methoxy- and 6-ethoxy-1*H*-benzotriazole-5-carboxylic acids (**7a,b**) were prepared from the 2-methoxy- and 2-ethoxybenzoic esters[4a] **2a,b**, respectively, according to a previous method.[7] Treatment of **2a,b** with fuming HNO_3 gave the corresponding 5-nitrobenzoic esters **3a,b**. Catalytic hydrogenation of **3a,b** followed by treatment of the resulting 5-aminobenzoic esters with sodium nitrite in aqueous HCl solution afforded the 1-acetyl-6-alkoxy-1*H*-benzotriazole-5-carboxylic esters **4a,b**. Alkaline hydrolysis of **4a,b** produced the desired 1*H*-benzotriazole-5-carboxylic acids **7a,b**. On the other hand, the regioisomer of **7a**, 4-methoxy-1*H*-benzotriazole-5-carboxylic acid (**7c**), was prepared as follows. Nitration of methyl 4-acetylamino-5-chloro-2-methoxybenzoate (**2c**) gave the 3-nitrobenzoic ester **5** in 63% yield. After hydrogenation of **5** using Raney-Ni followed by treatment of the 3-aminobenzoic ester with sodium nitrite in aqueous H_2SO_4 solution at 0 °C, the solution including methyl 1-acetyl-4-methoxy-7-chloro-1*H*-benzotriazole-5-carboxylate was successively heated to reflux to afford the corresponding carboxylic acid **6** in 61% yield. Finally, catalytic hydrogenation of **6** gave the dechlorinated product **7c**. The 1*H*-benzotriazole-5-carboxylic acids **7a-c** thus obtained were treated with 3-amino-1-ethylhexahydroazepine[6] (**8**), 3-amino-1-propylhexahydroazepine[6] (**9**), or 3-amino-1-isopropylhexahydroazepine[6] (**10**) in the presence of *N,N'*-carbonyldiimidazole (CDI) to produce the 1*H*-benzotriazole-5-carboxamides **24**—**29** in good yields (Scheme 1).

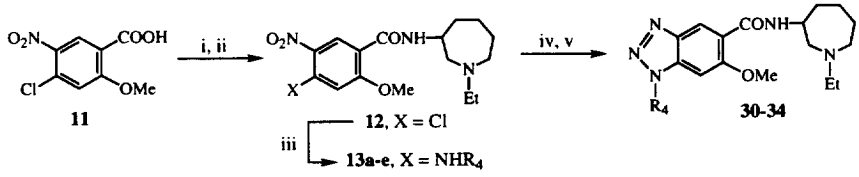
Scheme 1



The 1-substituted 1*H*-benzotriazole-5-carboxamides **30**—**34** were prepared from 4-chloro-2-methoxy-5-nitrobenzoic acid[8] (**11**). Reaction of **11** with thionyl chloride followed by reaction of the resultant acid

chloride with the amine **8** gave the hexahydroazepinyl benzamide **12**, which was treated with the several *N*-substituted amines to produce the 4-substituted amino-5-nitrobenzamides **13a-e** in good yields. After catalytic hydrogenation of **13a-e**, reaction of the 4,5-diaminobenzamides with sodium nitrite in acid solution gave the 1-substituted 1*H*-benzotriazoles **30—34** (Scheme 2).

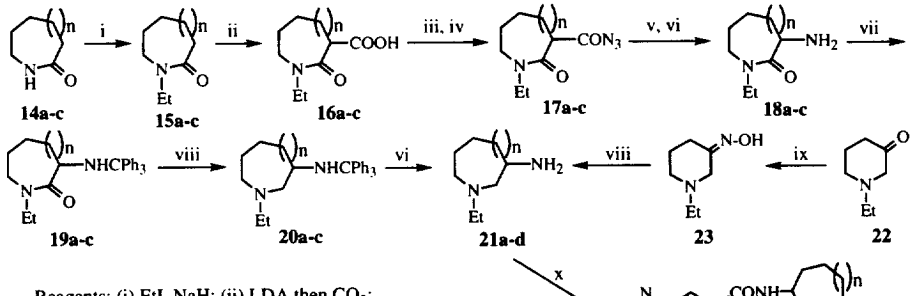
Scheme 2



Reagents: (i) $SOCl_2$; (ii) 3-amino-1-ethylhexahydroazepine (**8**); (iii) R_4-NH_2; (iv) Pd/C, H_2; (v) $NaNO_2$, HCl or AcOH

The amines **21a-d** with a medium perhydroazacycle ring were prepared from the available 2-azacycloalkanones **14a-c** and 1-ethyl-3-piperidone (**22**) as shown in Scheme 3. Reaction of **14a-c** with ethyl iodide in the presence of sodium hydride gave the 1-ethyl derivatives **15a-c**, which were treated with LDA and then solid carbon dioxide to afford the carboxylic acids **16a-c**. The Curtius rearrengement[9] of **16a-c** were carried out; the acyl azides **17a-c** obtained from the mixed anhydrides of **16a-c** and sodium azide were heated to reflux in toluene to give the thermal decomposition isocyanates. Successive acid hydrolysis of the isocyanates furnished the final 3-amino-2-azacycloalkanones **18a-c** in good yields. The lactams **18a-c** were transformed into the desired amines **21a-c** *via* the 3-triphenylmethylamino derivatives **19a-c** and **20a-c** in a similar manner to that described previously.[6] Reaction of **22** with hydroxylamine followed by reduction of the resultant oxime **23** with sodium bis(2-methoxyethoxy)aluminum hydride (Vitride®) gave the 3-amino-1-ethylpiperidine (**21d**). Condensation of the amines **21a-d** thus prepared with 6-methoxy-1*H*-benzotriazole-5-carboxylic acid (**7a**) using CDI produced the desired carboxamides **35–38** in good yields.

Scheme 3



Reagents: (i) EtI, NaH; (ii) LDA then CO_2; (iii) ClCOOEt, Et_3N; (iv) NaN_3; (v) heat; (vi) aq. HCl; (vii) Ph_3CCl, Et_3N; (viii) Vitride®; (ix) NH_2OH; (x) **7a**, CDI

a, n = 2
b, n = 3
c, n = 4
d, n = 0

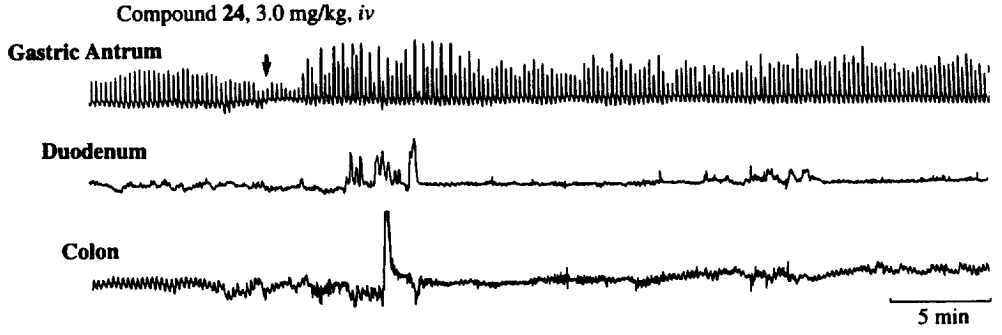
Results and discussion

The antiemetic and gastroprokinetic activities of **24—38** were determined by the suppression of

apomorphine-induced emesis at an oral dose of 1.0 mg/kg in dogs[10] and evaluated by determining their effects on the gastric emptying rates of phenol red semisolid meal through the stomach at an oral dose of 3.0 mg/kg in rats,[4c] respectively (Table 1). For comparison, data for metoclopramide, the selective 5-HT_4 receptor agonist mosapride and the selective dopamine D_2 receptor antagonist domperidone were included in Table 1.

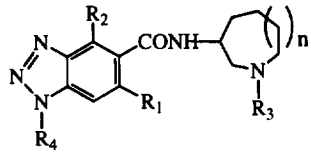
Metoclopramide exhibited both antiemetic and gastroprokinetic activities. Mosapride and domperidone showed only potent gastroprokinetic and antiemetic activities, respectively. In order to find out compounds with antiemetic and gastroprokinetic activities like metoclopramide, random screening of *N*-(1-ethylhexahydroazepin-3-yl)benzamides including **1** and the corresponding carboxamides was performed. As a result, the novel 6-methoxy-1*H*-benzotriazole-5-carboxamide **24** was found to exhibit a strong antiemetic activity (ED_{50} = 0.08 mg/kg, po) without 5-HT_3 receptor antagonistic activity.[11] The suppression of apomorphine-induced emesis correlated with antagonism for dopamine D_2 receptors.[10] Its activity was slightly less than that of domperidone. In addition, **24** showed moderate gastroprokinetic activity. When **24** was given as an intravenous bolus dose of 3.0 mg/kg to a conscious dog, the motor activity of gastric antrum, duodenum and colon was rapidly stimulated as shown in Figure 1. Compound **24** had no affinity for 5-HT_4 receptors; clearly, another mechanism of gastroprokinetic activity must be involved.[11] Moreover, like domperidone, **24** did not produce locomotor suppression at 300 mg/kg, po, which have been observed with metoclopramide. Compound **24**, on the whole, was found to possess the favorable profile and thus selected as a lead compound for further studies.

Figure 1. Effect of compound **24** on Gastrointestrinal Motor Activity in Postprandial State in a Conscious Dog



The SARs associated with modification of the *N*-substituent (R_3) of the hexahydroazepine ring of **24** were first examined. Replacement of the ethyl group of **24** by methyl and propyl groups (giving **25** and **26**, respectively) tended to decrease both activities, whereas the *N*-isopropyl analogue **27** resulted in retention of gastric emptying activity in spite of weak antiemetic activity. The optimum substituent in the hexahydroazepine ring was found to be an ethyl group. The regioisomer of **24**, the 4-methoxy-1*H*-benzotriazole-5-carboxamide **28**, and the 5-ethoxy analogue **25** of **24** were found to be less potent than the parent **24** in both activities. The next discussion concerns the SARs of 1-substituted 1*H*-benzotriazole-5-carboxamide derivatives (**30**—**34**). Introduction of a methyl group (giving **30**) caused a remarkable increase in gastric emptying activity, while

Table 1. Antiemetic and Gastroprokinetic Activities of 1*H*-Benzotriazole-5-carboxamide Derivatives



Compd.[a]	R_1	R_2	R_3	R_4	n	Antiemetic Activity[b] 1.0 mg/kg, po (%) [ED_{50}; mg/kg, po]	Gastric Emptying[c] 3.0 mg/kg, po (%)
24	OMe	H	Et	H	1	100 [0.08]	28*
25	OMe	H	Me	H	1	46	20
26	OMe	H	Pr	H	1	63	17
27	OMe	H	*iso*-Pr	H	1	15	31
28	H	OMe	Et	H	1	50	11
29	OEt	H	Et	H	1	15	18
30	OMe	H	Et	Me	1	77	49**
31	OMe	H	Et	Et	1	89	31**
32	OMe	H	Et	Pr	1	89	29
33	OMe	H	Et	*iso*-Pr	1	94	16
34	OMe	H	Et	$CH_2{}^cPr$	1	74	34*
35	OMe	H	Et	H	0	31	N.T.[d]
36	OMe	H	Et	H	2	100 [0.19]	21*
37	OMe	H	Et	H	3	100 [0.10]	46**
38	OMe	H	Et	H	4	22	31
metoclopramide						86 [0.45]	39**
mosapride						8 [>10]	70**
domperidone						100 [0.02]	0

a) All compounds gave satisfactory results on IR, ^{1}H-NMR, MS and elemental analysis. *b*) Tested for suppression of apomorphine-induced emesis in dogs. *c*) Evaluated for gastoprokinetic activity by determining their effects on the gastric emptying rate of a phenol red semisolid meal in rats. Gastric emptying was expressed as the enhancing percentage which was based on comparion with mean value for control groups (0.5% tragacanth). The asterisk indicates a statistically significant difference from the control group; *, $p<0.05$; **, $p<0.01$ (Duncan's multiple range test). *d*) N.T.; not tested.

keeping a potent antiemetic activity. The gastric emptying activity was more potent than that of metoclopramide. The 1-ethyl and 1-propyl analogous **31** and **32**, respectively, displayed strong antiemetic activity along with moderate gastric emptying activity. Compound **33** with 1-isopropyl group showed weak gastric emptying activity, while keeping a potent antiemetic activity. Introduction of a cyclopropylmethyl group (yielding **34**) caused an increase in gastric emptying activity.

In order to know the influence of the hexahydroazepine ring of **24** on the antiemetic and gastric emptying activities, 1*H*-benzotriazole-5-carboxamide derivatives having a six-, eight-, nine- and ten-membered rings were prepared. Substitution by piperidine (**35**) and decaazecine (ten-membered ring; **38**) rings caused a significant decrease in antiemetic activity. On the other hand, octahydroazocine (eight-membered ring; **36**) and octahydroazonine (nine-membered ring; **37**) derivatives showed a potent antiemetic activity and ED_{50} = 0.19 mg/kg, po and 0.10 mg/kg, po, respectively. In particular, the antiemetic activity of **37** with an octahydroazonine ring was much more potent than that of metoclopramide and has a comparable activity to that of **24**. In addition, **37** showed more potent gastric emptying activity than the hexahydroazepine **24**. As a result, the octahydroazonine derivative **37** exhibited a potent antiemetic and gastric emptying activities.

In conclusion, the 6-methoxy-1*H*-benzotriazole-5-carboxamide derivatives containing a medium perhydroazacycle ring in the amine moiety showed a potent antiemetic activity along with gastric emptying activity. Among them, the 1-ethyloctahydroazonine derivative **37** was found to be more potent than metoclopramide in both activities.

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11. The both binding affinities for 5-HT_3 and 5-HT_4 receptors of **24** showed IC_{50}; >10000 nM.