Novel 5-Hydroxytryptamine (5-HT_3) Receptor Antagonists. I. Synthesis and Structure–Activity Relationships of Conformationally Restricted Fused Imidazole Derivatives

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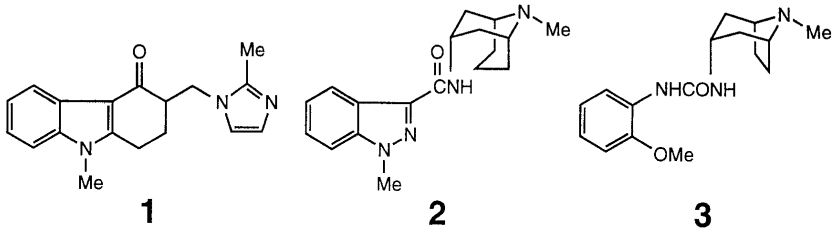
We prepared a novel series of conformationally restricted fused imidazole derivatives 4b, 4c and 4d (possessing 4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridine and substituted 4,5,6,7-tetrahydro-1*H*-benzimidazole for 4b, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine for 4c and 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine for 4d as a basic amine part and (2-methoxyphenyl)aminocarbonyl group as an aromatic-carbonyl part). Their activities were then evaluated as an 5-hydroxytryptamine (5-HT_3) receptor antagonist which may be useful for the treatment of irritable bowel syndrome (IBS) as well as for nausea and vomiting associated with cancer chemotherapy. The most potent compound was *N*-(2-methoxyphenyl)-4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxamide 14 in this series with an ID_{50} value of 0.32 μg/kg on the von Bezold-Jarisch reflex in rats and an IC_{50} value of 0.43 μM on the isolated colonic contraction in guinea pig, approximately ten and two times more potent than ondansetron 1, respectively. The structure–activity relationships (SAR) study suggested that the high potency of 14 may be attributed to the suitable position and direction of the N–C–N centroid in the conformationally restricted imidazole ring against the planar (2-methoxyphenyl)aminocarbonyl part in the binding of 14 to the receptor.

Key words tetrahydrobenzimidazole; 5-HT_3 receptor antagonist; irritable bowel syndrome; vomiting; structure–activity relationship

5-Hydroxytryptamine (5-HT) is a biogenic amine that mediates a variety of physiological actions. 5-HT receptors have been pharmacologically classified into at least four subtypes, 5-HT_1, 5-HT_2, 5-HT_3 and 5-HT_4,[1] among which, the 5-HT_3 receptor has been shown to be a ligand-gated ion channel which causes fast, depolarizing responses in neuronal cells,[2] and to be located in both the central and peripheral nervous systems.[3] In the last decade, research on antagonists for the 5-HT_3 receptor has been accelerated, and pre-clinical and clinical pharmacology has indicated possible roles of these antagonists as therapeutic agents for the treatment of nausea and vomiting associated with cancer chemotherapy, pain of vascular origin, disorders of the central nervous system, and gastrointestinal disorders.[4] Among the 5-HT_3 receptor antagonists, ondansetron **1**[5] and granisetron **2**[6] have already been used clinically as effective agents suppressing vomiting associated with cancer chemotherapy.

Endogenous 5-HT is located in the blood, the nervous system and the gut, and approximately 90% of that is estimated to be within the gastrointestinal tract. The role of 5-HT_3 receptors in controlling gastrointestinal contractivity *in vitro* (isolated guinea pig ileum[5,7] or colon[8]) is well established. Furthermore, our group has demonstrated that 5-HT may mediate bowel dysfunction related with stress *via* 5-HT_3 receptors, based on the results of *in vivo* tests in rodents.[9] In humans stress commonly results in gastrointestinal disorders such as irritable bowel syndrome (IBS).[10,11] The bowel of IBS patients is hypersensitive to many different types of stimulation.[10] This information has prompted us to produce a novel 5-HT_3 receptor antagonist as a therapeutic agent for the treatment of IBS[12] as well as for nausea and vomiting associated with cancer chemotherapy.

A computer-based three-dimensional steric molecular model of the 5-HT_3 receptor pharmacophore has been discussed on the basis of radio-ligand binding data using potent agents, including **1** and **2**. The pharmacophore was demonstrated to consist essentially of a carbonyl group coplanar to an aromatic ring and a basic center with relative positions and dimensions.[13] Beginning with the aromatic component, various allowable modifications have been achieved, namely, substitution with phenyl, indolyl and indazolyl, *etc.*[13] Concerning the basic amine component, a number of sterically hindered and conformationally rigid aliphatic azabicycloamines have been recognized as useful as in, *e.g.*, **2**[14] and BRL44687 **3**,[15] while **1** possessing a single imidazole ring instead of an



1 **2** **3**

Chart 1

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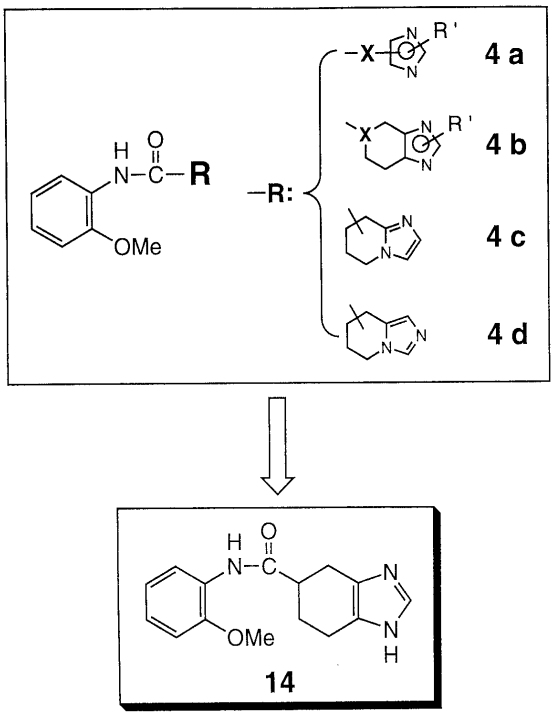


Chart 2

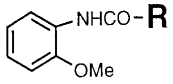
azabicycloamine has also been reported.[16]

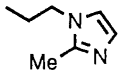
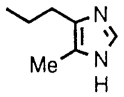
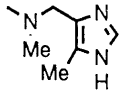
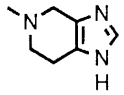
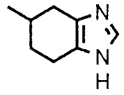
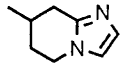
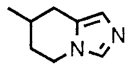
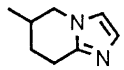
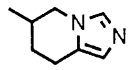
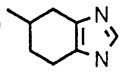
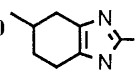
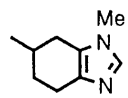
In search of a new type of 5-HT_3 receptor antagonist, we have focused on the preparation of a variety of imidazole derivatives such as **4a—d** which consist of (2-methoxyphenyl)aminocarbonyl group as the aromatic-carbonyl part, a component of **3**. In particular, compounds **4b—d** have conformationally restricted fused imidazole groups (4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]-pyridine and substituted 4,5,6,7-tetrahydro-1*H*-benzimidazole for **4b**, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine for **4c** and 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine for **4d**, respectively) as the basic amine part. We found *N*-(2-methoxyphenyl)-4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxamide **14** to be the most potent 5-HT_3 receptor antagonist in this series. We report the synthesis and structure–activity relationships (SAR) of novel imidazole derivatives **4a—d**.

Chemistry

The syntheses of the compounds **6**, **9**, **11**, **12** and **14—21** (Table 1) are outlined in Chart 3 (method A—D). The *N*-(2-methoxyphenyl)-3-(1-imidazolyl)propanamide **6** was obtained by the reaction of 2-anisidine **5** with 3-bromopropanoyl chloride, followed by the *N*-alkylation of 2-methylimidazole (method A). The reaction of 5-methyl-1-tritylimidazole-4-carboxaldehyde **7**[17] with methyl (triphenylphosphoranilidene)acetate, followed by the saponification, afforded exclusively *E*-isomer of α,β-unsaturated carboxylic acid **8**. The treatment of **8** with thionyl chloride gave the acyl chloride, which was reacted with 2-anisidine **5** to afford an α,β-unsaturated amide, followed by the reduction of the olefin and the removal of the protecting group by catalytic hydrogenation to give the *N*-(2-methoxyphenyl)-3-(5-methyl-4-imidazolyl)propanamide **9** (method B). The *N*-(2-methoxyphenyl)ureas **11** and **12** were prepared by the addition of 4-(*N*-methylamino)methyl-5-methylimidazole[18] or 4,5,6,7-tetrahydroimidazo[4,5-*c*]-pyridine[19] to 2-methoxyphenylisocyanate **10**, respectively (method C). The carboxamide derivatives **14—21** were prepared by the amidation of anisidine **5** with the acyl chlorides, which were obtained from 4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxylic acid **13a**,[20] 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-7-carboxylic acid **13b**, 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine-7-carboxylic acid **13c**, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-6-carbox-

Table 1. 5-HT_3 Receptor Antagonistic Activities



No.	–R	Synth. method[a]	ID_{50} (μg/kg) of B.J. reflex[b] [95% confidence limits]	IC_{50} (μM) of Colonic contraction[c] [95% confidence limits]
6		A	(5%)[d]	>10
9		B	1.9 [1.0—3.4]	>10
11		C	2.7 [2.5—3.1]	1.6 [0.80—3.4]
12		C	(30%)[d]	6.5 [1.9—22]
14		D	0.32 [0.19—0.54]	0.43 [0.27—0.69]
15		D	(30%)[d]	>10
16		D	(36%)[d]	>10
17		D	(11%)[d]	>10
18		D	(26%)[d]	3.1 [1.9—5.1]
19		D	1.1 [0.70—1.6]	0.47 [0.23—0.96]
20		D	(0%)[d]	>10
21		D	(20%)[d]	>10
1			3.8 [1.5—7.9]	0.78 [0.43—1.4]
2			0.88 [0.71—0.96]	0.069 [0.062—0.078]

a) See Chart 3. Synthetic methods A—D. *b*) i.v., vagally mediated bradycardia induced by 5-HT (10 μg/kg, i.v.) in rats. *c*) Contraction of isolated guinea pig colon induced by 5-HT (5×10^{-5} M). *d*) % inhibition at 30 μg/kg.

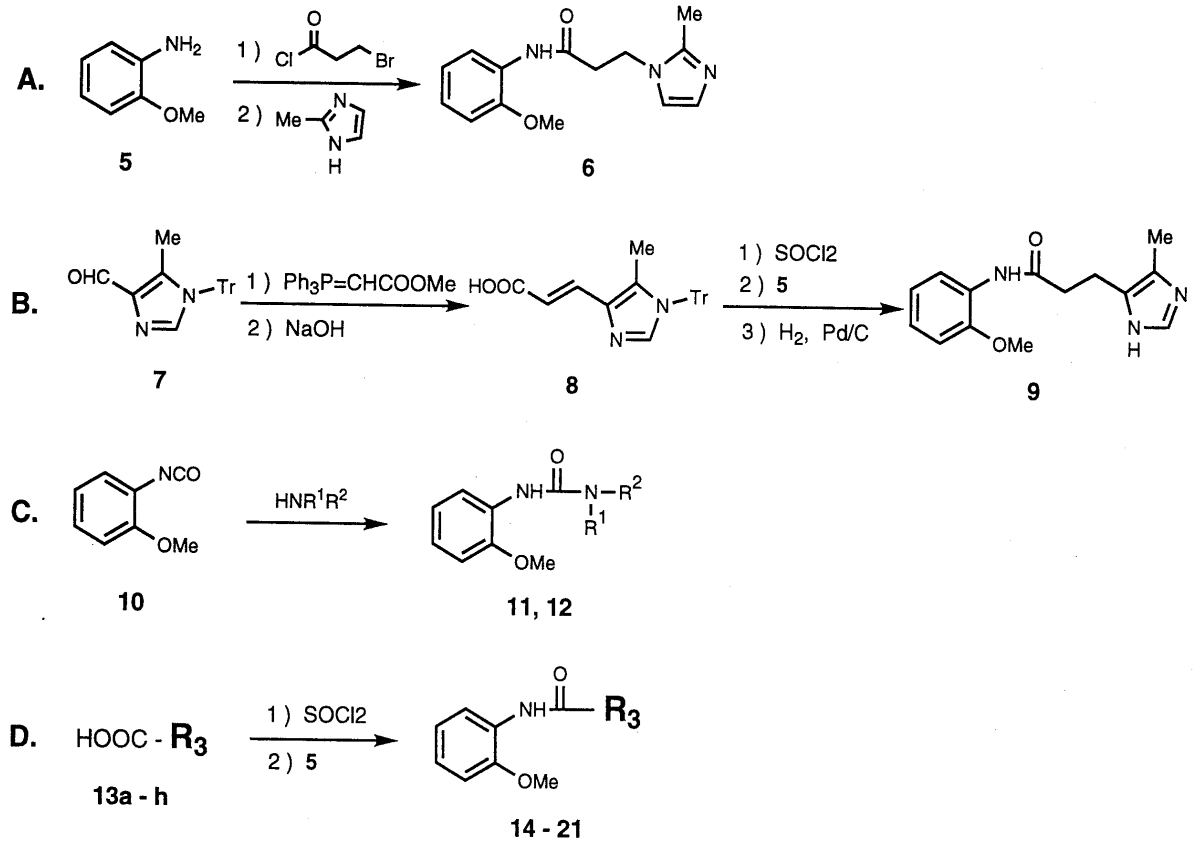


Chart 3. Synthetic Methods A—D

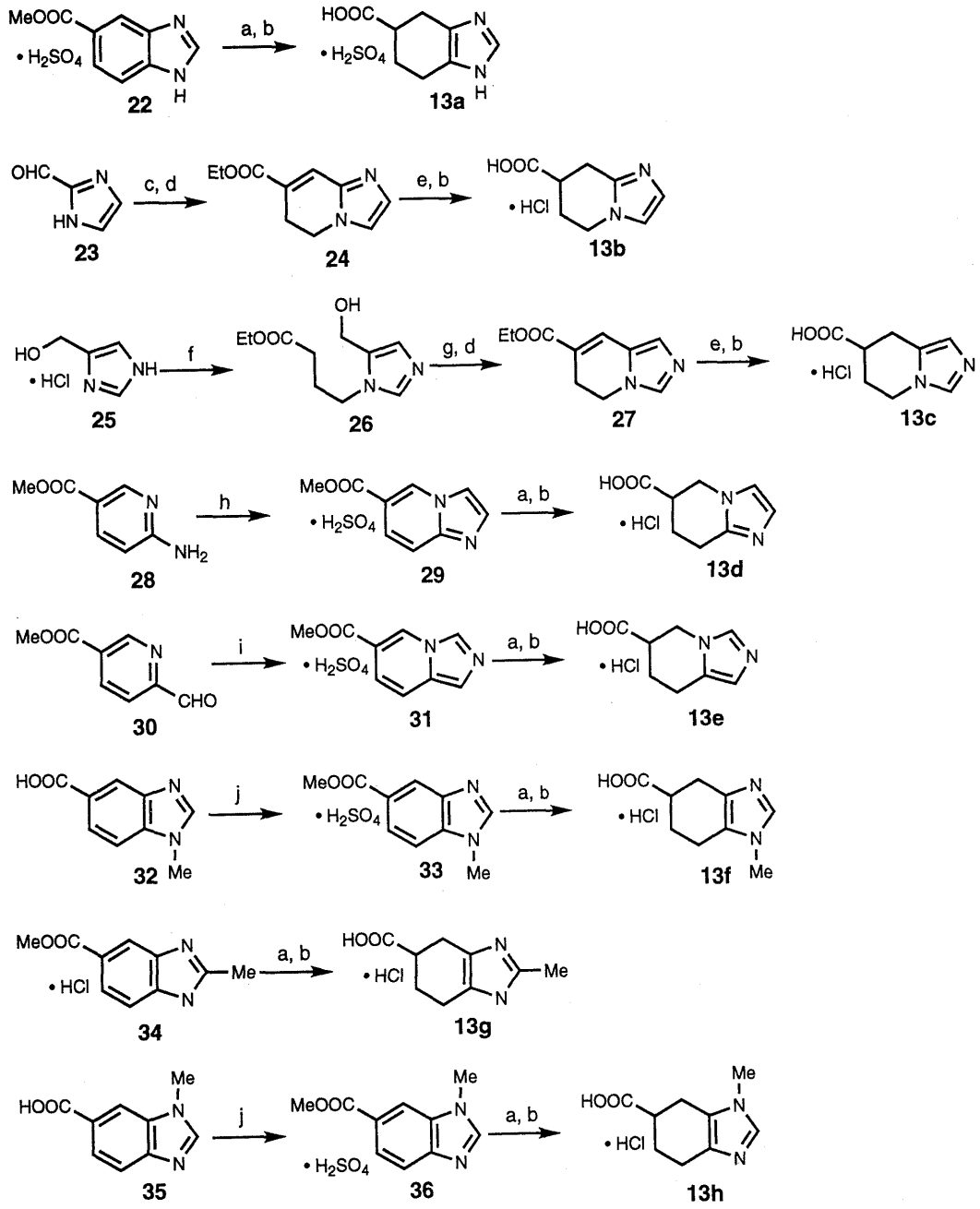
ylic acid **13d**, 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine-6-carboxylic acid **13e**, 1-methyl-4,5,6,7-tetrahydrobenzimidazole-5-carboxylic acid **13f**, 2-methyl-4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxylic acid **13g** or 1-methyl-4,5,6,7-tetrahydrobenzimidazole-6-carboxylic acid **13h**, respectively (method D).

The key intermediates **13a—h** were prepared as shown in Chart 4. The ester **22** was readily hydrogenated (60 atm of H_2 on Pd–C at 80 °C for 5 h) to afford methyl 4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxylate, which was easily converted to **13a** by hydrolysis in 77% total yield in two steps. The novel carboxylic acids **13b—h** were prepared from **23**, **25**, **28**, **30**, **32**, **34** or **35**, respectively (Chart 4). Compound **13b** was prepared by the hydrogenation of 7,8-double bond and the hydrolysis of the ester of ethyl 5,6-dihydroimidazo[1,2-*a*]pyridine-7-carboxylate **24**. Compound **24** was obtained from imidazole-2-carboxaldehyde **23** by 1-alkylation and base catalyzed cyclization. Compound **13c** was also prepared by the hydrogenation of 7,8-double bond and the hydrolysis of the ester of ethyl 5,6-dihydroimidazo[1,5-*a*]pyridine-7-carboxylate **27**. Compound **27** was obtained from 4-hydroxymethylimidazole **25** by regioselective 3-alkylation,[21] oxidation of alcohol to aldehyde and base catalyzed cyclization (*via* ethyl 4-(5-hydroxymethyl-1-imidazolyl)butyrate **26**). Compounds **13d—h** were prepared by the same procedures as for preparation of **13a** from corresponding methyl imidazo[1,2-*a*]pyridine-6-carboxylate **29**, methyl imidazo[1,5-*a*]pyridine-6-carboxylate **31**, methyl 1-methylbenzimidazole-5-carboxylate **33**, methyl 2-methylbenzimidazole-5-carboxylate **34**[22] or methyl 1-methylbenzimidazole-6-carboxylate **36**, respectively. Compound **29** was obtained from methyl 6-aminonicotinate **28** by the reaction with bromoacetaldehyde and the subsequent cyclization. Compound **31** was obtained from methyl 6-formylnicotinate **30**[23] by the formation of oxime, reduction to amine, formylation and intramolecular Vilsmeyer type reaction. The esterification of 1-methylbenzimidazole-5-carboxylic acid **32**[24] and 1-methylbenzimidazole-6-carboxylic acid **35**[24] afforded **33** and **36**, respectively.

The 2-methoxyphenylanilide moiety **37** (Chart 5) is known to adopt a planar conformation by intramolecular hydrogen bonding.[14,25] In the ^{1}H-NMR spectrum the δ value of the hydrogen atom at the 6-position of the benzene ring in **14** was observed to be shifted downfield at 7.86 (dimethyl sulfoxide (DMSO)-d_6), as expected, which might have been caused by the influence of the carbonyl group. Similar results were obtained for all of the other target compounds. The X-ray analysis of the single crystals of *S*-isomer of **14** also supported the planarity of the formation of the 2-methoxyphenylanilide moiety.[26]

Pharmacological Results and Discussion

We evaluated the 5-HT_3 receptor antagonistic activities of compounds **6**, **9**, **11**, **12** and **14—21** (Table 1). We studied the 5-HT induced vagally mediated bradycardia known as the von Bezold–Jarisch reflex (B. J. reflex)[27] (rats) and the contractile responses to 5-HT in the isolated distal colon (guinea pig).[8b] These effects are known to be mediated by the activation of the neuronal 5-HT_3 receptors.[8b,27b] Data are presented as the percent inhibition with intravenous (i.v.) administration of the compounds (30 μg/kg) or ID_{50} values (μg/kg) against the B. J. reflex



a) H_2 (60 atm), Pd/C, 80 °C; b) aq. HCl, 100 °C; c) NaH, Cl-$(CH_2)_3$COOEt; d) NaH, Molecular Sieves; e) H_2 (1 atm), Pd/C;

f) 1) Me_2NCOCl, Et_3N, 2) TMSCl, Et_3N, 3) Br-$(CH_2)_3$COOEt, 4) NH_3, 5) aq. HCl; g) MnO2;

h) 1) $BrCH_2CHO$, 2) c.H_2SO_4; i) 1) H_2NOH, 2) Zn, AcOH, 3) HCOOH, 4) $POCl_3$, 5) c.H_2SO_4; j) MeOH - c.H_2SO_4.

Chart 4. Synthetic Methods of **13a**—**13h**

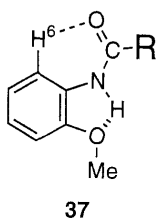


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Chart 5

induced by 5-HT (10 μg/kg, i.v.) in anesthetized rats and IC_{50} values (μM) against the contraction of the isolated guinea pig colon by 5-HT (50 μM).

The inhibitory effect of the compounds on the B. J. reflex was examined. Among the non-cyclic imidazole derivatives, the (2-methyl-1-imidazolyl)ethyl derivative **6** possessing the same amine part as in **1** was inactive. However, the (5-methyl-4-imidazolyl)ethyl derivative **9** was found to be more potent than **1** and the *N*-methyl-*N*-[(5-methyl-4-imidazolyl)methyl]amino derivative **11**

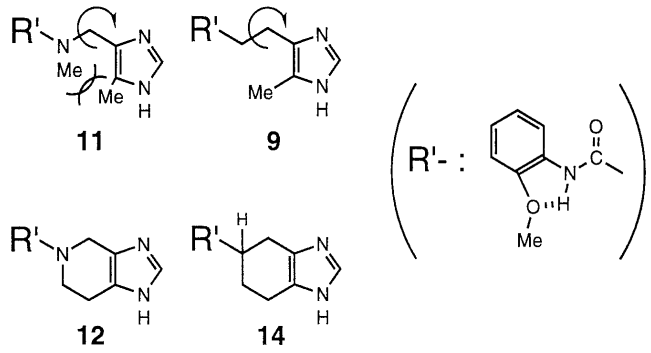

Chart 6

exhibited similar activity to **9**.[28] The C-linked imidazole derivative replacing the 2-methyl-1-imidazolyl group in **1** by 5-methyl-4-imidazolyl group has recently been reported to be more potent than **1**.[16] Our result observed between **6** and **9** is consistent with that report.

Regarding the fused imidazole derivatives, in contrast to **11**, the potency of the 4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridyl derivative **12** was significantly reduced. However, the 4,5,6,7-tetrahydro-1*H*-5-benzimidazolyl derivative **14** showed potent 5-HT_3 receptor antagonistic activity ($ID_{50}=0.32\,\mu g/kg$), approximately ten and two times more potent than **1** and **2**, respectively. The *N*-methylurea derivative **11** cannot adopt a rigid conformation like the cyclic compound **12**, because of the steric repulsion between the methyl groups substituted in the urea part and at the 5-position of the imidazole ring (Chart 6). This indicates that the appropriate orientation of the imidazole ring against the planar benzanilide moiety may be important to exhibit the activity. On the contrary, compound **14** may preferentially adopt the conformation accompanied by a suitable orientation similar to that of the active form of **9** and **11** in the binding. It is further supposed that **14** is more potent than **9** and **11** because of its more restricted conformation in comparison with **9** and **11** which possess rotatable bonds between the imidazole ring and the carbonyl carbon atom (Chart 6).

The 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine derivatives (**15** and **17**) and 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine derivatives (**16** and **18**) showed markedly decreased activities, in which an imidazole ring is supposed to rotate around another toward **14**. Each of **15** or **17** has a nitrogen atom located at a position corresponding to one of the nitrogen atoms at the 1- or 3-position in the tetrahydro-1*H*-benzimidazole part of **14**, respectively. It has been suggested that the imidazole ring is protonated and the positive charge in the imidazole ring centered on the N–C–N centroid would be essentially in the binding to the receptor.[13b,16] Therefore, it may be considered that the N–C–N centroids in the imidazole ring of **15**—**18** are not located at the suitable position compared with that of **14**.

Although 1-methyl-4,5,6,7-tetrahydro-5-benzimidazolyl derivative **19** retained its activity, 2- and 3-methyl-substituted derivatives **20** and **21** lost theirs. Each methyl group substituted at the 2- or 3-position in **20** or **21** is assumed to interfere with binding to the receptor and this may be the reason the activities of **20** and **21** are reduced.

The inhibitory effect of the compounds on the colonic contraction induced by 5-HT was evaluated *in vitro*. Although compounds **6** and **9** were found to be inactive, compound **11** possessed moderate activity. Contrary to the case of **9**, compound **12** exhibited slight activity. Compound **14** was shown to be a potent antagonist ($IC_{50}=0.43\,\mu M$), approximately two times more potent and six times less potent than **1** and **2**, respectively. Each of **15**, **16** and **17** was inactive, however, compound **18** was found to be moderately active. Compound **19** showed potent activity ($IC_{50}=0.47\,mM$) as did **14**, but both **20** and **21** were inactive.

At present it is difficult to completely explain the discrepancy in the SAR in the above two experiments, although postulated the following: (1) species difference or different methods used in *in vivo* or *in vitro* tests could account for this; (2) different subtypes of 5-HT_3 receptors might exist in the heart and the colon; (3) the combination of (2-methoxyphenyl)anilide moiety as the aromatic-carbonyl part and imidazole moieties as the amine part was a mismatch. The first and second possibilities have also been suggested in other reports.[29] The third possibility will be discussed in our subsequent paper including modifications of the aromatic-carbonyl part of compound **14** retaining the 4,5,6,7-tetrahydro-1*H*-benzimidazole moiety unchanged as the amine part.

Conclusion

In our evaluation of the inhibitory effects of various imidazole derivatives **4a**—**d**, *N*-(2-methoxyphenyl)-4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxamide **14** was found to be the most potent 5-HT_3 receptor antagonist in this series: approximately ten (B. J. reflex test) and two times (colonic contraction test) more potent than **1**. SAR study suggested that the great potency of **14** could be attributable to the good position and direction of the N–C–N centroid in the conformationally restricted imidazole ring against the planar (2-methoxyphenyl)aminocarbonyl part in the binding of **14** to the receptor.

Experimental

All melting points were determined on a Yanaco MP-500D melting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured with a JEOL FX90Q, a FX100, a FX270 or FX400 spectrometer; chemical shifts are recorded in δ units using tetramethylsilane as an internal standard and the following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad, dd=double doublet, dt=double triplet. Mass spectra were recorded with a Hitachi M-80 electron impact (EI) or a JEOL JMS-DX300 (FAB) spectrometer. Elemental analyses were performed with a Yanaco MT-5. All organic solvent extracts were dried over anhydrous magnesium sulfate and concentrated with a rotary evaporator under reduced pressure.

***N*-(2-Methoxyphenyl)-3-(2-methyl-1-imidazolyl)propanamide Fumarate (6) [Method A]** (i) A solution of 2-anisidine **5** (8.05 ml, 71.4 mmol) in CH_2Cl_2 (40 ml) was added dropwise to a solution of 3-bromopropionyl chloride (3.6 ml, 35.7 mmol) in CH_2Cl_2 (36 ml) for 1 h at 5 °C. The mixture was allowed to warm to room temperature over 1 h, then was washed with 1 N HCl, H_2O and saturated aqueous sodium bicarbonate. After drying and concentration, the residue was purified by silica gel column chromatography ($CHCl_3$) to give 7.8 g (85% yield) of *N*-(2-methoxyphenyl)-3-bromopropanamide. ^{1}H-NMR ($CDCl_3$) δ: 2.95 (2H, t, J=7 Hz), 3.70 (2H, t, J=7 Hz), 3.85 (3H, s), 6.70—7.10 (3H, m), 7.70—7.90 (1H, m), 8.20—8.45 (1H, m). EI-MS *m/z*: 257, 259 (M^+).

(ii) 2-Methylimidazole (0.17 g, 2.1 mmol) was added to a solution of *N*-(2-methoxyphenyl)-3-brompropanamide (0.26 g, 1.0 mmol) in 2-

propanol (3 ml) at room temperature. The solution was heated at 80 °C for 3 h. Following concentration, H_2O was added to the residue, the mixture was extracted with AcOEt, and then the organic layer was washed with aqueous saturated sodium bicarbonate and dried. After concentration the residue was purified by silica gel column chromatography ($CHCl_3$–MeOH) to give a viscous liquid, which was treated with one equivalent of fumaric acid in MeOH–CH_3CN to give 0.15 g (40% yield) of **6**, mp 123—125 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.38 (3H, s), 2.85 (2H, t, J=7 Hz), 3.76 (3H, s), 4.16 (2H, d, J=7 Hz), 6.54 (2H, s), 6.76—7.12 (5H, m), 7.86 (1H, br d, J=8 Hz), 9.18 (1H, br s). EI-MS m/z: 259 (M^+, as a free base). *Anal.* Calcd for $C_{14}H_{17}N_3O_2 \cdot C_4H_4O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.60; H, 5.70; N, 11.16.

***N*-(2-Methoxyphenyl)-3-(5-methyl-4-imidazolyl)propanamide Fumarate (9) [Method B]** (i) A mixture of 5-methyl-1-tritylimidazole-4-carboxaldehyde[17] **7** (0.70 g, 2.0 mmol) and methyl (triphenylphosphoranilidene) acetate (0.87 g, 2.6 mmol) in toluene (20 ml) was heated under reflux for 15 h. The solution was concentrated, and the residue was purified by silica gel column chromatography to give 0.71 g (87% yield) of methyl 3-(5-methyl-1-trityl-4-imidazolyl)propenilate, which was saponified to give 0.62 g (91% yield) of 3-(5-methyl-1-trityl-4-imidazolyl)propenic acid **8**. ^{1}H-NMR ($CDCl_3$) δ: 2.63 (3H, s), 6.89 (1H, d, J=16 Hz), 6.92—7.60 (15H, m), 7.50 (1H, d, J=16 Hz), 7.89 (1H, s).

(ii) A mixture of **8** (0.57 g, 1.4 mmol) and thionyl chloride (3 ml, 41 mmol) was heated under reflux for 30 min, then concentrated. The residue was diluted with CH_2Cl_2 (5 ml), followed by the addition of 2-anisidine **5** (0.50 g, 4.1 mmol) at 5 °C. The reaction mixture was then stirred at room temperature. The solution was washed with 1 N NaOH and saline, then dried and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$) to give 0.31 g (88% yield) of *N*-(2-methoxyphenyl)-3-(5-methyl-4-imidazolyl)propenamide. This was hydrogenated in EtOH (6 ml) over 10% palladium-on-carbon. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH) to give a viscous liquid, which was treated with one equivalent of fumaric acid in MeOH–MeCN to give 0.17 g (55% yield) of **9**, mp 124—125 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.13 (3H, s), 2.56—2.92 (4H, m), 3.80 (3H, s), 6.60 (2H, s), 6.76—7.17 (3H, m), 7.76—8.04 (1H, m), 9.11 (1H, s), 9.76 (3H, m). EI-MS m/z: 259 (M^+, as a free base). *Anal.* Calcd for $C_{14}H_{17}N_3O_2 \cdot C_4H_4O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.34; H, 5.63; N, 11.46.

1-(2-Methoxyphenyl)-3-methyl-[(5-methyl-4-imidazolyl)methyl]urea (11) [Method C] 2-Methoxyphenylisocyanate **10** (0.3 ml, 2.3 mmol) was added to a solution of 4-(*N*-methylamino)methyl-5-methylimidazole[18] (0.21 g, 1.7 mmol) in dry *N*,*N*-dimethylformamide (DMF) (1 ml) at room temperature. After stirring for 10 min, the mixture was concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH) and recrystallized from MeOH–AcOEt to give 0.36 g (78% yield) of **11**, mp 150—152 °C. ^{1}H-NMR (CD_3OD) δ: 2.27 (3H, s), 3.02 (3H, s), 3.86 (3H, s), 4.49 (2H, s), 6.78—7.08 (3H, m), 7.53 (1H, s), 7.68—7.85 (1H, m). EI-MS m/z: 274 (M^+). *Anal.* Calcd for $C_{14}H_{18}N_4O_2$: C, 61.30; H, 6.61; N, 20.42. Found: C, 61.32; H, 6.69; N, 20.21.

***N*-(2-Methylphenyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-3-carboxamide · 0.5 Fumarate (12)** Compound **12** was prepared by method C using 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine[19] instead of 4-(*N*-methylamino)methyl-5-methylimidazole in 77% yield, mp 103—105 °C (MeOH). EI-MS m/z: 272 (M^+, as a free base). *Anal.* Calcd for $C_{14}H_{16}N_4O_2 \cdot 0.5C_4H_4O_4 \cdot$MeOH: C, 56.34; H, 6.11; N, 15.46. Found: C, 56.00; H, 5.69; N, 15.55. For a free base, ^{1}H-NMR (DMSO-d_6) δ: 2.47—2.86 (2H, m), 3.64—3.99 (2H, m), 3.84 (3H, s), 4.46 (2H, s), 6.76—7.12 (3H, m), 7.51 (1H, s), 7.48—7.86 (1H, m), 11.80 (1H, m).

4,5,6,7-Tetrahydro-1*H*-benzimidazole-5-carboxylic Acid[20] Hydrogensulfate (13a) In an autoclave (1000 ml) a solution of methyl benzimidazole-5-carboxylate hydrogensulfate **22** (40.0 g, 146 mmol) in acetic acid (600 ml) was hydrogenated over 10% Pd–C (11 g) at 60 atm of hydrogen for 5 h at 80 °C. After the calculated amount of hydrogen was absorbed, the catalyst was removed by filtration. The filtrate was concentrated to dryness to give 41.0 g of crude methyl 4,5,6,7-tetrahydrobenzimidazole-5-carboxylate hydrogensulfate as an oil, which was dissolved in H_2O (350 ml) and conc. HCl (340 ml) and heated under reflux for 3 h. The solution was concentrated to give a solid, which was washed with acetone to give 29.6 g (77% yield) of **13a**, mp 145—148 °C (lit. 137 °C[20]). ^{1}H-NMR (DMSO-d_6) δ: 1.60—3.00 (7H, m), 8.84 (1H, S). FAB-MS (Pos.) m/z: 167 ($M^+ + 1$, as a free base).

5,6,7,8-Tetrahydroimidazo[1,2-*a*]pyridine-7-carboxylic Acid Hydrochloride (13b) (i) Imidazole-2-carboxaldehyde **23** (1.51 g, 15.7 mmol) was added by portions to a suspension of 60 w/w% oily sodium hydride (0.79 g, 20 mmol) in DMF (30 ml) at 0 °C and stirred for 1 h at 50 °C. Ethyl 4-chlorobutyrate (3.59 g, 23.8 mmol) was added to the solution at room temperature, then the solution was heated to 70 °C for 4 h. The solvent was removed *in vacuo* and H_2O was added to the residue. After extraction with AcOEt, the organic layer was washed with H_2O and a saline solution, then dried and concentrated. The residue was purified by silica gel column chromatography (AcOEt) to give 2.19 g (66% yield) of 1-(3-ethoxycarbonylpropyl)imidazole-2-carboxaldehyde as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 1.85—2.60 (4H, m), 4.15 (2H, q, J=7 Hz), 4.48 (2H, t, J=6 Hz), 7.17 (1H, s), 7.28 (1H, s), 9.79 (1H, s). EI-MS m/z: 210 (M^+). 1-(3-Ethoxycarbonylpropyl)imidazole-2-carboxaldehyde (2.16 g, 10.3 mmol) was dissolved in toluene (30 ml), molecular sieves 4A (3.0 g) followed by 60 w/w% sodium hydride (0.42 g, 10.5 mmol) were added to the solution at 110 °C and heating was continued under reflux for 6 h. The mixture was cooled, poured into H_2O, extracted with AcOEt, washed with brine, dried and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH) to give 0.21 g (11% yield) of ethyl 5,6-dihydroimidazo[1,2-*a*]pyridine-7-carboxylate **24** as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, t, J=7 Hz), 2.86 (2H, br t, J=7 Hz), 3.80—4.55 (4H, m), 6.95 (1H, s), 7.14 (1H, s), 7.47 (1H, s). EI-MS m/z: 192 (M^+).

(ii) A solution of **24** (0.21 g, 1.1 mmol) in MeOH (10 ml) was hydrogenated over 5% Pd–C (0.02 g) at 1 atm of hydrogen for 10 h at room temperature. After the catalyst was removed by filtration, the filtrate was concentrated and AcOEt was added, followed by extraction with 0.5 N HCl. The aqueous layer was basified by the addition of potassium carbonate and extracted with CH_2Cl_2. The organic layer was washed with saline solution, dried, and concentrated to give 0.18 g (85% yield) of ethyl 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-7-carboxylate as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7 Hz), 1.80—2.60 (2H, m), 2.62—3.30 (3H, m), 3.80—4.55 (4H, m), 6.65—7.15 (2H, m). EI-MS m/z: 194 (M^+). A solution of ethyl 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-7-carboxylate (0.18 g, 0.9 mmol) in 3 N HCl (10 ml) was heated overnight under reflux, then concentrated to give 0.18 g (96% yield) of **13b** as a solid. EI-MS m/z: 166 (M^+, as a free base). This material was used for preparation of **15** without further purification.

5,6,7,8-Tetrahydroimidazo[1,5-*a*]pyridine-7-carboxylic Acid Hydrochloride (13c) (i) Dimethylcarbamyl chloride (1.4 ml, 15 mmol) was added dropwise to a solution of 4-hydroxymethylimidazole hydrochloride **25** (2.0 g, 15 mmol) and Et_3N (4.6 ml, 33 mmol) in MeCN (20 ml) at 0 °C. The solution was heated under reflux for 2.5 h and cooled to 0 °C. Et_3N (2.3 ml, 16.5 mmol) and then chlorotrimethylsilane (2.1 ml, 16.5 mmol) were added to the solution. After stirring for 20 h at room temperature, Et_2O (20 ml) was added to the solution. After the precipitate was removed by filtration, the filtrate was concentrated and Et_2O (30 ml) was added to the residue. Insoluble material was filtered off and the filtrate was concentrated. The residue (1-dimethylcarbamyl-4-trimethylsilyloxymethylimidazole[21]) was dissolved in MeCN (20 ml) and ethyl 4-bromobutyrate (1.45 ml, 10.1 mmol) was added to the solution. The mixture was heated under reflux for 48 h, cooled to 0 °C, bubbled with NH_3 gas for 30 min and concentrated. Et_2O (50 ml) and 1 N HCl (20 ml) were added to the residue, and the mixture was stirred for 30 min at room temperature. The aqueous layer was basified by K_2CO_3 and extracted with AcOEt. After the organic layer was dried and concentrated, the residue was purified by silica gel column chromatography ($CHCl_3$–MeOH) to give 0.87 g (41% yield) of ethyl 4-(5-hydroxymethyl-1-imidazolyl)butyrate **26** as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 1.95—2.45 (4H, m), 4.07 (2H, t, J=7 Hz), 4.12 (2H, q, J=7 Hz), 4.58 (3H, s), 6.81 (1H, s), 7.39 (1H, s). EI-MS m/z: 212 (M^+).

(ii) A suspension of manganese dioxide (8.4 g, 97 mmol) in a solution of **26** (0.84 g, 4.0 mmol) in 1.4-dioxane (84 ml) was heated under reflux for 6 h. The mixture was filtered, and the oxide was washed with three 50 ml portions of 1,4-dioxane. The combined filtrate and the washings were concentrated to give 0.62 g (74% yield) of ethyl 4-(5-formyl-1-imidazolyl)butyrate. ^{1}H-NMR ($CDCl_3$) δ: 1.62 (3H, t, J=7 Hz), 1.95—2.40 (4H, m), 4.14 (2H, q, J=7 Hz), 4.38 (2H, t, J=7 Hz), 7.71 (1H, s), 7.82 (1H, s), 9.76 (1H, s). EI-MS m/z: 210 (M^+). Ethyl 4-(5-formyl-1-imidazolyl)butyrate (0.60 g, 2.85 mmol) was dissolved in toluene (10 ml). Molecular sieves 4A (2 g) and then 60 w/w% sodium hydride (0.17 g, 4.3 mmol) were added to the solution, and the mixture

was heated under reflux for 4 h. After insoluble material was filtered out, the filtrate was concentrated and purified by silica gel column chromatography ($CHCl_3$–MeOH) to give 0.34 g (63% yield) of ethyl 5,6-dihydroimidazo[1,5-*a*]pyridine-7-carboxylate **27**. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, t, J=7 Hz), 2.84 (2H, dt, J=1, 7 Hz), 4.11 (2H, t, J=7 Hz), 4.27 (2H, q, J=7 Hz), 7.21 (1H, s), 7.52 (2H, br s). EI-MS m/z: 192 (M^+).

(iii) **27** (0.24 g, 1.25 mmol) in MeOH (15 ml) and 4 N HCl in 1,4-dioxane (0.4 ml) was hydrogenated over 10% Pd–C (0.01 g) at 1 atm of hydrogen for 3 h at room temperature. After the catalyst was removed by filtration, the filtrate was concentrated and the residue was dissolved in H_2O (7.5 ml) and conc. HCl (2.5 ml). The solution was concentrated for 2 h to dryness, the residual solid was washed with acetone and dried to give 0.22 g (86% yield) of **13c** as a solid. ^{1}H-NMR (DMSO-d_6) δ: 1.97—2.09 (1H, m), 2.28—2.33 (1H, m), 2.83—2.96 (2H, m), 3.09 (1H, dd, J=4, 15 Hz), 4.14—4.21 (1H, m), 4.29—4.35 (1H, m), 7.45 (1H, s), 9.03 (1H, s). FAB-MS (Pos.) m/z: 167 (M^++1, as a free base).

5,6,7,8-Tetrahydroimidazo[1,2-*a*]pyridine-6-carboxylic Acid Hydrochloride (13d) (i) A mixture of bromoacetaldehyde diethylacetal (12.5 g, 63 mmol), conc. HCl (1.5 ml) and H_2O (70 ml) was heated to 90 °C for 1.5 h. Methyl 6-aminonicotinate **28** (3.30 g, 21.7 mmol) and sodium bicarbonate (5.0 g, 60 mmol) were added to the solution at room temperature, followed by heating to 60 °C for 30 min. After cooling to room temperature, the solution was basified by the addition of potassium carbonate and extracted with AcOEt. The organic layer was washed with saline solution, dried, and concentrated. The residue was dissolved in EtOH, and a slightly excess amount of conc. H_2SO_4 was added to this solution. The precipitate was filtered and washed with EtOH to give 4.45 g (75% yield) of methyl imidazo[1,2-*a*]pyridine-6-carboxylate hydrogensulfate **29** as a solid. ^{1}H-NMR (DMSO-d_6) δ: 3.98 (3H, s), 8.09—8.44 (3H, m), 8.50 (1H, d, J=2 Hz), 9.66 (1H, d, J=1 Hz). EI-MS m/z: 176 (M^+, as a free base).

(ii) **29** was hydrogenated in the same manner as described for **13e**-(ii) to give methyl 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxylate in 46% yield as a solid. ^{1}H-NMR ($CDCl_3$) δ: 1.80—2.65 (2H, m), 2.76—3.35 (3H, m), 3.77 (3H, s), 4.18 (2H, d, J=7 Hz), 6.80 (1H, d, J=1 Hz), 6.98 (1H, d, J=1 Hz). EI-MS m/z: 180 (M^+). Methyl 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxylate was hydrolyzed in the same manner as described for **13e**-(ii) to give **13d** in 98% yield as a solid. ^{1}H-NMR (DMSO-d_6) δ: 1.75—2.60 (2H, m), 2.80—3.45 (3H, m), 3.95—4.65 (2H, m), 7.58 (1H, d, J=2 Hz), 7.64 (1H, d, J=2 Hz). EI-MS m/z: 166 (M^+, as a free base).

5,6,7,8-Tetrahydroimidazo[1,5-*a*]pyridine-6-carboxylic Acid Hydrochloride (13e) (i) A mixture of sodium acetate (4.77 g, 58.1 mmol) and hydroxylamine hydrochloride (4.04 g, 58.1 mmol) in MeOH (30 ml) was stirred at room temperature for 30 min. After the salt was removed by filtration, methyl 6-formylnicotinate **30**[23] (3.20 g, 19.4 mmol) was added to the filtrate and the mixture was stirred overnight at room temperature. The solvent was removed, saturated aqueous potassium carbonate was added to the residue and extracted with a mixture of $CHCl_3$ and iso-PrOH. The organic layer was dried and concentrated to give methyl 6-hydroxyiminomethylnicotinate 3.21 g (92% yield) as a solid. ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 4.00 (3H, S), 7.95 (1H, d, J=9 Hz), 8.20 (1H, s), 8.35 (1H, dd, J=3, 9 Hz), 9.15 (1H, d, J=3 Hz). EI-MS m/z: 180 (M^+). Zinc dust (5.73 g, 87.7 mmol) was slowly added to a chilled mixture of methyl 6-hydroxyiminonicotinate (3.16 g, 17.5 mmol), H_2O (34 ml) and acetic acid (51 ml). After insoluble material was removed by filtration, the filtrate was concentrated and aqueous saturated sodium carbonate was added to the residue, followed by extraction with $CHCl_3$. The organic layer was dried and concentrated to give 2.90 g (100% yield) of methyl 6-aminomethylnicotinate as an oil. ^{1}H-NMR ($CDCl_3$) δ: 3.95 (3H, s), 4.05 (2H, s), 7.35 (1H, d, J=9 Hz), 8.25 (1H, dd, J=3, 9 Hz), 9.15 (1H, d, J=3 Hz). EI-MS m/z: 166 (M^+). A solution of methyl 6-aminomethylnicotinate (2.80 g, 17.5 mmol) in formic acid (20 ml) was heated under reflux overnight. After the solution was concentrated, saturated aqueous sodium bicarbonate was added to the residue and extracted with $CHCl_3$. The organic layer was dried and concentrated. The residual solid was washed with Et_2O to give 2.07 g (60% yield) of methyl 6-formylaminomethylnicotinate as a solid. ^{1}H-NMR ($CDCl_3$) δ: 3.95 (3H, s), 4.65 (2H, d, J=5 Hz), 7.30 (1H, d, J=9 Hz), 8.25 (1H, dd, J=3, 9 Hz), 8.35 (1H, s), 9.15 (1H, d, J=3 Hz). EI-MS m/z: 194 (M^+). Phosphorus oxychloride (2.0 ml, 21.3 mmol) was added to a solution of methyl 6-formylaminomethylnicotinate (2.05 g, 10.6 mmol) in CH_2Cl_2 (15 ml), then heated under reflux for 1 h. After the solution was concentrated, saturated aqueous sodium bicarbonate was added to the residue and extracted with $CHCl_3$. The organic layer was dried and concentrated. The residual solid was washed with Et_2O to give 1.79 g (94% yield) of methyl imidazo[1,5-*a*]pyridine-6-carboxylate as a solid. ^{1}H-NMR ($CDCl_3$) δ: 3.94 (3H, s), 7.20 (1H, dd, J=2, 10 Hz), 7.45 (1H, d, J=10 Hz), 7.46 (1H, s), 8.22 (1H, s), 8.74 (1H, d, J=2 Hz). EI-MS m/z: 176 (M^+). The solid was treated with an equal amount of conc. H_2SO_4 in EtOH (20 ml) to give 2.51 g (91% yield) of hydrogensulfate **31** as a solid. ^{1}H-NMR (DMSO-d_6) δ: 3.90 (3H, s), 7.45 (1H, dd, J=2, 10 Hz), 7.90 (1H, d, J=10 Hz), 8.05 (1H, s), 9.30 (1H, d, J=2 Hz), 9.55 (1H, s). EI-MS m/z: 176 (M^+, as a free base).

(ii) In an autoclave (100 ml) a solution of **31** (2.19 g, 8.0 mmol) in acetic acid (30 ml) was hydrogenated over 10% palladium-on-carbon (0.7 g) at 65 atm of hydrogen for 15 h at 70 °C. After the catalyst was removed by filtration, the filtrate was concentrated to dryness. Saturated aqueous sodium carbonate was added to the residue and extracted with $CHCl_3$. The organic layer was dried and concentrated to give 1.4 g (100% yield) of methyl 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine-6-carboxylate as a solid. ^{1}H-NMR ($CDCl_3$) δ: 1.70—2.10 (1H, m), 2.10—2.40 (1H, m), 2.50—3.10 (3H, m), 3.70 (3H, s), 3.95—4.40 (2H, m), 6.75 (1H, br s), 7.40 (1H, br s). EI-MS m/z: 180 (M^+). A solution of methyl 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine-6-carboxylate (1.40 g, 8.0 mmol) in H_2O (15 ml) and conc. HCl (5 ml) was heated under reflux overnight. The solution was concentrated to dryness, and the residual solid was washed with acetone to give 1.35 g (83% yield) of **13e** as a solid. ^{1}H-NMR (DMSO-d_6) δ: 1.9—2.3 (2H, m), 2.75—3.0 (2H, m), 3.0—3.3 (1H, m), 4.1—4.6 (2H, m), 7.4 (1H, s), 9.1 (1H, s). EI-MS m/z: 166 (M^+, as a free base).

1-Methyl-4,5,6,7-tetrahydrobenzimidazole-5-carboxylic Acid Hydrochloride (13f) (i) 1-Methylbenzimidazole-5-carboxylic acid **32**[24] (4.7 g, 27 mmol) was dissolved in MeOH (300 ml) and conc. H_2SO_4 (5 ml), and the solution was heated under reflux for 7 h. Following concentration, H_2O (200 ml) was added to the residue and the solution was adjusted to pH 9 by the addition of 1 N NaOH. After extraction with AcOEt, the organic layer was dried and concentrated to give a solid, which was washed with Et_2O to give 4.8 g (94% yield) of methyl 1-methylbenzimidazole-5-carboxylate as a solid. ^{1}H-NMR (DMSO-d_6) δ: 3.86 (6H, br s), 7.65 (1H, d, J=10 Hz), 7.94 (1H, dd, J=1, 10 Hz), 8.24 (1H, d, J=1 Hz), 8.32 (1H, s). EI-MS m/z: 190 (M^+). The solid (4.8 g, 53 mmol) was dissolved in 2 N H_2SO_4 (26.6 ml) and the solution was concentrated to dryness to give 7.2 g (100% yield) of methyl 1-methylbenzimidazole-5-carboxylate hydrogensulfate **33**, which was used without further purification in the next reaction.

(ii) **33** (6.6 g, 22.9 mmol) was converted to methyl 1-methyl-4,5,6,7-tetrahydrobenzimidazole-5-carboxylate (3.45 g, 78% yield) as an oil in the same manner as described for **13e**-(ii). ^{1}H-NMR ($CDCl_3$) δ: 1.70—3.00 (7H, m), 3.50 (3H, s), 3.70 (3H, s), 7.30 (1H, s). EI-MS m/z: 194 (M^+). Methyl 1-methyl-4,5,6,7-tetrahydrobenzimidazole-5-carboxylate was converted to **13f** as a solid in the same manner as described for **13e**-(ii). ^{1}H-NMR (CD_3OD) δ: 2.00—3.10 (7H, m), 3.80 (3H, s), 8.75 (1H, s). EI-MS m/z: 180 (M^+, as a free base).

2-Methyl-4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxylic Acid Hydrochloride (13g) (i) Methyl 2-methylbenzimidazole-5-carboxylate[22] (5.7 g, 30 mmol) was dissolved in 1 N HCl (30 ml) and concentrated to dryness to give 6.8 g (100% yield) of HCl salt **34** as a solid, which was used without further purification in the next reaction.

(ii) **34** (6.8 g, 30 mmol) was converted to methyl 2-methyl-4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxylate (0.70 g, 12% yield) as an oil in the same manner as described for **13e**-(ii). ^{1}H-NMR ($CDCl_3$) δ: 1.80—3.00 (7H, m), 2.35 (3H, s), 3.70 (3H, s), 9.90 (1H, s). FAB-MS (Pos.) m/z: 195 (M^++1). Methyl 2-methyl-4,5,6,7-tetrahydrobenzimidazole-5-carboxylate was converted to **13g** as a solid in the same manner as described for **13e**-(ii). ^{1}H-NMR (CD_3OD) δ: 2.00—3.00 (7H, m), 2.60 (3H, s). EI-MS m/z: 180 (M^+, as a free base).

1-Methyl-4,5,6,7-tetrahydrobenzimidazole-6-carboxylic Acid Hydrochloride (13h) (i) 1-Methylbenzimidazole-6-carboxylic acid[24] (2.60 g, 14.8 mmol) was dissolved in EtOH (40 ml) and conc. H_2SO_4 (1 ml) was added to the solution. The precipitate was collected to give 3.78 g (89% yield) of hydrogensulfate **35** as a solid.

(ii) **35** (3.39 g, 11.8 mmol) was converted in the same manner as described for **13e**-(ii) to methyl 1-methyl-4,5,6,7-tetrahydrobenzimidazole-6-carboxylate **36** (2.10 g, 92% yield), and then to **13h** (2.19 g, 88% yield). ^{1}H-NMR (DMSO-d_6–CD_3OD) δ: 1.70—2.51 (2H, m), 2.57—3.20 (5H, m), 3.82 (3H, s), 8.75 (1H, s). FAB-MS (Pos.) m/z: 180 (M^+, as

a free base).

***N*-(2-Methoxyphenyl)-4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxamide Hydrochloride (14) [Method D]** Thionyl chloride (3 ml, 41.4 mmol) was added to a solution of 4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxylic acid hydrogensulfate **13a** (5.42 g, 20.5 mmol) in 1,2-dichloroethane (50 ml). The solution was heated at 55—60 °C for 1 h, then concentrated. 1,2-Dichloroethane (50 ml) was added to the residue, and 2-anisidine **5** (6.25 g, 50.7 mmol) at less than 30 °C was added dropwise to the solution. After the addition was complete, the solution was stirred for 2 h at room temperature. The reaction mixture was poured into a mixture of H_2O (60 ml) and MeOH (30 ml), and the pH of the aqueous layer was adjusted to 4.8 by the addition of 10% aqueous NaOH. After separation, MeOH (15 ml) was added to the aqueous layer. Ten percent aqueous NaOH was then slowly added at 5 °C until the pH of the aqueous layer became 11.0. The resulting precipitate was collected and washed with a mixture of H_2O and MeOH (3 : 1) to give 5.62 g (100% yield) of a free base of **14** as a solid, mp 100—101.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.84—2.42 (2H, m), 2.55—3.12 (5H, m), 3.84 (3H, s), 6.76—7.16 (3H, m), 7.49 (1H, s), 7.96 (1H, s), 8.25—8.53 (1H, br s). EI-MS *m/z*: 271 (M^+). The solid (5.07 g, 18.7 mmol) was treated with one equivalent of dry hydrogen chloride in EtOH to give 5.66 g (98% yield) of **14**, mp > 250 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.78—2.28 (2H, m), 2.56—2.88 (4H, m), 2.90—3.14 (1H, m), 3.80 (3H, s), 6.78—7.16 (3H, m), 7.86 (1H, br d, J = 8 Hz), 8,86 (1H, s), 9.28 (1H, br s). EI-MS *m/z*: 271 (M^+, as a free base). *Anal.* Calcd for $C_{15}H_{17}N_3O_2 \cdot HCl$: C, 58.54; H, 5.89; Cl, 11.52; N, 13.65. Found: C, 58.24; H, 5.98; Cl, 11.68; N, 13.48.

***N*-(2-Methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-7-carboxamide Fumarate (15) 15** was prepared by method D using **13b** instead of **13a** in 45% yield, mp 151—153 °C (MeOH–MeCN). ^{1}H-NMR (DMSO-d_6) δ: 1.80—2.40 (2H, m), 2.60—3.22 (3H, m), 3.55—4.15 (2H, m), 3.82 (3H, s), 6.52 (2H, m), 6.65—7.20 (5H, m), 7.84 (1H, br d, J = 9 Hz), 9.20 (1H, br s). EI-MS *m/z*: 271 (M^+, as a free base). *Anal.* Calcd for $C_{15}H_{17}N_3O_2 \cdot C_4H_4O_4$: C, 58.91; H, 5.46; N, 10.85. Found: C, 59.01; H, 5.47; N, 11.21.

***N*-(2-Methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine-7-carboxamide 1.5 Fumarate (16) 16** was prepared by method D using **13c** instead of **13a** in 70% yield, mp 162—164 °C (MeOH–MeCN). ^{1}H-NMR (DMSO-d_6) δ: 1.78—2.02 (1H, m), 2.14—2.20 (1H, m), 2.74—2.84 (1H, m), 2.94—3.08 (2H, m), 3.84 (3H, s), 3.88—3.96 (1H, m), 4.21—4.25 (1H, m), 6.62 (3H, s), 6.75 (1H, s), 6.88—6.93 (1H, m), 7.02—7.11 (2H, m), 7.68 (1H, br s), 7.92—7.95 (1H, m), 9.29 (1H, s). EI-MS *m/z*: 271 (M^+, as a free base). *Anal.* Calcd for $C_{15}H_{17}N_3O_2 \cdot 1.5C_4H_4O_4 \cdot 0.3H_2O$: C, 55.95; H, 5.28; N, 9.32. Found: C, 56.01; H, 5.19; N, 9.64.

***N*-(2-Methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxamide 1.5 Fumarate (17) 17** was prepared by method D using **13d** instead of **13a** in 96% yield, mp 181—183 °C (MeOH–MeCN). ^{1}H-NMR (DMSO-d_6) δ: 1.85—2.32 (2H, m), 2.76—3.02 (2H, m), 3.08—3.42 (1H, m), 3.08 (3H, s), 3.94—4.36 (2H, m), 6.62 (3H, s), 6.76—7.16 (4H, m), 7.18 (1H, d, J = 2 Hz), 7.88 (1H, br d, J = 8 Hz), 9.40 (1H, br s). EI-MS *m/z*: 271 (M^+, as a free base). *Anal.* Calcd for $C_{15}H_{17}N_3O_2 \cdot 1.5C_4H_4O_4$: C, 56.63; H, 5.20; N, 9.43. Found: C, 56.60; H, 5.23; N, 9.52.

***N*-(2-Methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine-6-carboxamide Fumarate (18) 18** was prepared by method D using **13e** instead of **13a** in 86% yield, mp 188—189 °C (MeOH). ^{1}H-NMR (DMSO-d_6) δ: 1.78—1.92 (1H, m), 2.10—2.24 (1H, m), 2.64—2.76 (1H, m), 2.86—2.94 (1H, m), 3.12—3.24 (1H, m), 3.84 (3H, s), 4.00 (1H, dd, J = 9, 9 Hz), 4.30 (1H, dd, J = 5, 9 Hz), 6.62 (2H, s), 6.71 (1H, s), 6.89—6.93 (1H, m), 7.04—7.11 (2H, m), 7.67 (1H, s), 7.91 (1H, d, J = 7 Hz), 9.39 (1H, s). EI-MS *m/z*: 271 (M^+, as a free base). *Anal.* Calcd for $C_{15}H_{17}N_3O_2 \cdot C_4H_4O_4 \cdot 0.1MeOH \cdot 0.45H_2O$: C, 57.54; H, 5.64; N, 10.54. Found: C, 57.82; H, 5.47; N, 10.24.

***N*-(2-Methoxyphenyl)-1-methyl-4,5,6,7-tetrahydrobenzimidazole-5-carboxamide (19) 19** was prepared by method D using **13f** instead of **13a** in 22% yield, mp 94—96 °C (AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 1.84—2.48 (2H, m), 2.50—3.12 (5H, m), 3.50 (3H, s), 6.76—7.16 (3H, m), 7.32 (1H, s), 7.95 (1H, br s), 8.08—8.52 (1H, m). EI-MS *m/z*: 285 (M^+). *Anal.* Calcd for $C_{16}H_{19}N_3O_2 \cdot H_2O$: C, 63.34; H, 6.97; N, 13.85. Found: C, 63.02; H, 6.92; N, 17.74.

***N*-(2-Methoxyphenyl)-2-methyl-4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxamide (20) 20** was prepared by method D using **13g** instead of **13a** in 37% yield, mp 108—110 °C (AcOEt). ^{1}H-NMR (DMSO-d_6) δ: 1.56—2.38 (2H, m), 2.19 (3H, s), 2.38—3.04 (5H, m), 3.84 (3H, s), 6.76—7.13 (4H, m), 7.95 (1H, d, J = 8 Hz), 9.09 (1H, s). FAB-MS (Pos.) *m/z*: 286 (M^+). *Anal.* Calcd for $C_{16}H_{19}N_3O_2 \cdot 1.05H_2O$: C, 63.16; H, 6.98; N, 13.81. Found: C, 62.76; H, 6.98; N, 13.64.

***N*-(2-Methoxyphenyl)-1-methyl-4,5,6,7-tetrahydrobenzimidazole-6-carboxamide Fumarate (21) 21** was prepared by method D using **13h** instead of **13a** in 95% yield, mp 188—190 °C (MeOH–MeCN). ^{1}H-NMR (DMSO-d_6) δ: 1.48—2.16 (2H, m), 2.34—3.13 (5H, m), 3.50 (3H, s), 3.79 (3H, s), 6.56 (2H, s), 6.72—7.13 (3H, m), 7.68 (1H, s), 7.88 (1H, d, J = 8 Hz), 9.16 (1H, s). EI-MS *m/z*: 285 (M^+, as a free base). *Anal.* Calcd for $C_{16}H_{19}N_3O_2 \cdot C_4H_4O_4 \cdot H_2O$: C, 57.27; H, 6.01; N, 10.02. Found: C, 57.56; H, 5.65; N, 10.12.

Biological Methods Doses are expressed in terms of free base. 5-HT was purchased from E. Merck (Darmstadt, FRG) as creatinine sulfate.

Von Bezold–Jarisch Reflex Test[27] Male Wistar rats weighing 200 to 250 g were anesthetized with urethane (1.25 g/kg, i.p.), and then tracheas were cannulated. Arterial blood pressure and heart rate were recorded on a polygraph through a pressure transducer and cardiotachometer, respectively, connected to a catheter placed in the carotid artery. The femoral vein was also cannulated for drug injection. 5-HT at a dose of 10 μg/kg was intravenously administered to rats at intervals of 15 min. After a stable response to 5-HT was obtained, drugs were intravenously administered to rats 10 min before 5-HT injection.

Contraction of Isolated Guinea Pig Colon[8b] The distal portion of the colon was removed from Hartley guinea pigs (300 to 500 g), cleaned in fresh Krebs-bicarbonate buffer at room temperature and then divided into approximately 20 mm segments. Isomeric contraction under a loading tension of 1 g was recorded. Submaximal contraction was first elicited by repeated concentrations of 10^{-6} M 5-HT until a constant response was obtained. Test compounds were added to the bath after a concentration-response curve for 5-HT had been obtained. The tissue was exposed to the test compound for 30 min before rechallenge with 5-HT (control). Each test compound was examined at one or two different concentrations in the same preparation.

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