New 5-HT_3 (Serotonin-3) Receptor Antagonists. V. Synthesis and Structure–Activity Relationships of Pyrrolo[2,1-*c*][1,4]benzoxazine-6-carboxamides

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This paper describes the discovery of structurally novel heterocyclic carboxamides which are highly potent 5-HT_3 (serotonin-3) receptor antagonists. Pyrrolo[2,1-*c*][1,4]benzoxazine-6-carboxamides (12 and 20) were found to possess potent 5-HT_3 receptor antagonist activity on the von Bezold–Jarisch reflex in anesthetized rats. Structure–activity studies showed that compounds with small and lipophilic substituents such as chloro and methyl at the 8-position of the aromatic ring portion retained high potency, whereas those with bulky substituents showed essentially no activity. A dimethyl group at the 4-position slightly decreased the potency. 1-Azabicyclo[2.2.2]octan-3-amine as the amine part afforded the most potent activity. From this series, 20a was found to be the most potent 5-HT_3 receptor antagonist, being 40-fold more potent than ondansetron (1).

Key words pyrrolo[2,1-*c*][1,4]benzoxazine; 5-HT_3 receptor antagonist; von Bezold–Jarisch reflex; structure–activity relationship

During recent years, intensive efforts have been made to find potent and selective 5-HT_3 (serotonin-3) receptor antagonists because of their effectiveness in preventing emesis induced by cytotoxic drugs.[1] The 5-HT_3 receptor is present in both the peripheral and central nervous systems.[2] Based on studies in various animal models, these antagonists are expected to be effective in the treatment of gastrointestinal disorders, migraine, psychosis, anxiety, and pain.[3] Some representative 5-HT_3 receptor antagonists are shown in Chart 1. Several studies have suggested that there are three structural requirements for 5-HT_3 receptor antagonists: an aromatic ring, a linking acyl functional group, and a basic nitrogen group.[4] On the basis of the species of the basic nitrogen moiety, the structures of these antagonists can be categorized into two subclasses: (1) imidazole derivatives, as typified by ondansetron (**1**); (2) azabicycloalkane derivatives, *e.g.*, tropisetron (**2**), granisetron (**3**), and BRL46470A (**4**). The latter type also includes a variety of benzamide derivatives (*e.g.*, metoclopramide (**5**) and zacopride (**6**)). Introduction of an alkoxy group at the 2-position of benzamide derivatives was reported to impose a conformational restraint owing to a strong intramolecular hydrogen bonding with the amide group, increasing the affinity for the 5-HT_3 receptor.[5] Furthermore, cyclic ether derivatives, benzofuran- and benzopyrancarboxamides, have been reported to possess potent 5-HT_3 receptor antagonist activity.[6] In previous papers, we described the synthesis and 5-HT_3 receptor antagonist activity of imidazole derivatives[7] and azabicycloalkaneacetamide derivatives.[8] As part of our search for new 5-HT_3 receptor antagonists, we attempted to identify new benzamide derivatives having a novel heterocycle as an aromatic ring moiety and found that structurally novel pyrrolo[2,1-*c*][1,4]benzoxazine-6-carboxamides were potent 5-HT_3 receptor antagonists. In this paper, we describe the synthesis and structure–activity relationships of a series of pyrrolo[2,1-*c*][1,4]benzoxazine-6-carboxamide derivatives.

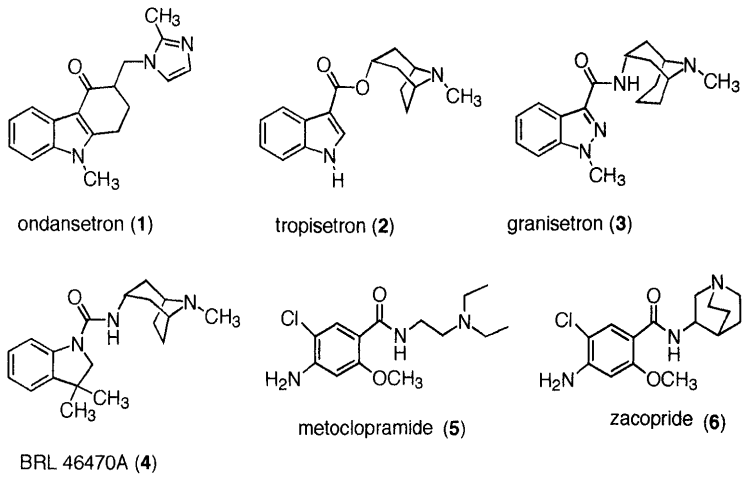

Chart 1

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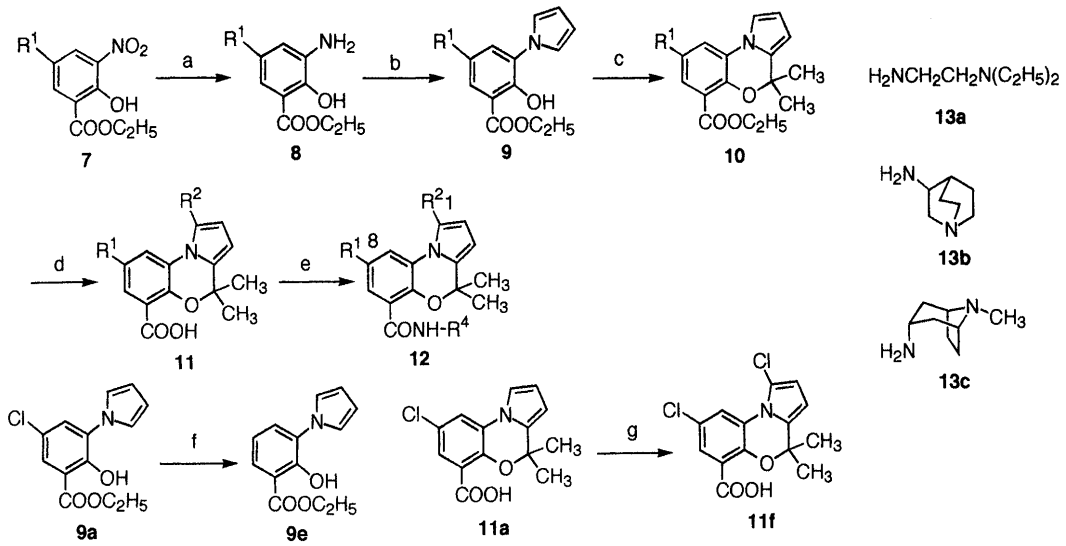
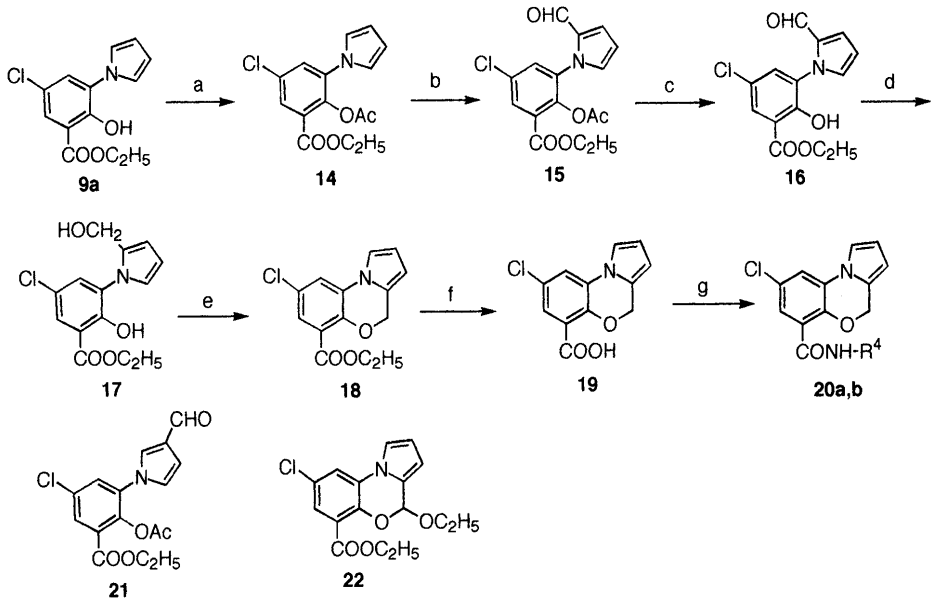


a) Rh-Al_2O_3, H_2, EtOH; b) 2,5-dimethoxytetrahydrofuran, dioxane, AcOH; c) acetone, *p*-TsOH·H_2O, benzene; d) NaOH, H_2O, EtOH; e) **13**, DCC or WSCD, HOBT, DMF; f) H_2, Pd–C, Et_3N, EtOH; g) NCS, DMF.

Chart 2



a) Ac_2O, Py, CH_2Cl_2; b) $POCl_3$, DMF, CH_2ClCH_2Cl; c) NaOMe, EtOH, THF; d) $NaBH_4$, EtOH, THF; e) Ph_3P, $EtO_2CN{=}NCO_2Et$, THF; f) NaOH, EtOH, H_2O; g) **13b** or **13c**, DCC, HOBT, DMF.

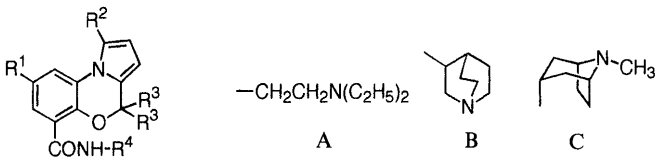
Chart 3

Chemistry

4,4-Dimethylpyrrolo[2,1-*c*][1,4]benzoxazine derivatives were prepared as shown in Chart 2. Catalytic hydrogenation of ethyl 2-hydroxy-3-nitrobenzoate (**7**) with rhodium on alumina gave the corresponding amine (**8**). Compound **8** was heated with 2,5-dimethoxytetrahydrofuran in dioxane–acetic acid to give the pyrrole (**9**). The 8-unsubstituted pyrrole (**9e**) was prepared by hydrogenolysis of the 8-chloro compound (**9a**) with palladium on carbon (Pd–C) in the presence of triethylamine. Condensation of the pyrrole (**9**) with acetone in the presence of *p*-toluenesulfonic acid (*p*-TsOH) gave the pyrrolo[2,1-*c*][1,4]benzoxazine derivatives (**10**) in one step.[9] Hydrolysis of the ethyl ester (**10**) with aqueous sodium hydroxide gave the acid (**11**), which was coupled with the amines (**13a—c**) by using dicyclohexylcarbodiimide (DCC) or 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (WSCD) and 1-hydroxybenzotriazole (HOBT) to give the amides (**12**). The 1-chloro compound (**11f**) was prepared by treatment of **11a** with *N*-chlorosuccinimide (NCS) in *N*,*N*-dimethylformamide (DMF). Compounds (**12**) prepared are listed in Table 1.

An attempt to prepare the 4-unsubstituted pyrrolo[2,1-*c*][1,4]benzoxazine (**18**) from **9a** by a similar procedure to that described for **10** was unsuccessful. Upon treatment with formaldehyde and *p*-TsOH, **9a** decomposed to give an intractable mixture. Compound **20** was prepared as shown in Chart 3. The phenol **9a** was acetylated with

Table 1. Inhibition of von BJ Reflex



Compd. No.	R^1	R^2	R^3	R^4	% inhibition of 2-Me-5-HT-induced bradycardia (μg/kg)[a]				ED_{50} (μg/kg i.v.)
					100	3.2	1.0	0.32	
12a	Cl	H	CH_3	A	4.2				
12b	Cl	H	CH_3	B		68.1	55.9	30.0	0.9
12c	Cl	H	CH_3	C		76.3	22.9	20.4	1.5
12d	H	H	CH_3	B		71.7	53.6	11.5	1.2
12e	H	H	CH_3	C	83.3	8.9			
12f	CH_3	H	CH_3	B		77.6	61.5	8.4	1.0
12g	CH_3	H	CH_3	C		41.2			
12h	CH_3SO_2	H	CH_3	B		−46.8			
12i	CH_3SO_2	H	CH_3	C	3.6	−14.2			
12j	CH_3CONH	H	CH_3	C	64.0	−13.1			
12k	Cl	Cl	CH_3	B	80.5	44.5		−24.4	
20a	Cl	H	H	B		81.8	68.7	44.8	0.4
20b	Cl	H	H	C		70.8	18.3	15.3	1.8
1 (Ondansetron)					79.5	43.3[b]			17.5
4 (BRL46470A)							74.7	36.0	0.5

a) Each compound was tested in a group of three animals and data represent mean values of peak inhibition. *b*) Percent inhibition at 10 μg/kg.

acetic anhydride and pyridine to give the acetate (**14**). Vilsmeier reaction of **14** with phosphorus oxychloride and DMF gave a mixture of the aldehyde (**15**) and the 3-substituted isomer (**21**). Compound **15** was deacetylated with sodium ethoxide to give the phenol (**16**), accompanied with a small amount of the ethyl ether (**22**). Reduction of **16** with sodium borohydride gave the unstable diol (**17**). Mitsunobu reaction of **17** afforded the cyclized compound **18**. Alkaline hydrolysis of the ester (**18**), followed by coupling with the amines (**13b** and **c**) in the presence of DCC and HOBT, yielded the amides (**20**).

Biological Results and Discussion

The activity of the compounds prepared as 5-HT_3 receptor antagonists was evaluated in terms of their ability to inhibit the 2-methylserotonin (2-Me-5-HT)-evoked reflex bradycardia [von Bezold–Jarisch (BJ) reflex] in urethane-anesthetized rats. 2-Me-5-HT was reported to be a selective 5-HT_3 receptor agonist.[10] Compounds were screened after intravenous administration. Test results are listed in Table 1 together with the data for ondansetron (**1**) and BRL46470A (**4**) as reference compounds.

Because of the documented 5-HT_3 receptor antagonist activity of 4-amino-5-chloro-2-methoxybenzamide derivatives such as metoclopramide (**5**) and zacopride (**6**), we selected the 8-chloro group as a constant substituent on the pyrrolo[2,1-*c*][1,4]benzoxazine ring and attempted to identify an optimal amine part (**12a—c**). 1-Azabicyclo[2.2.2]octan-3-amine (**12b**) and *endo*-8-methyl-8-azabicyclo[3.2.1]octan-3-amine (**12c**) showed high potency (ED_{50} 0.9 and 1.5 μg/kg i.v., respectively). The diethylaminoethyl group (**12a**), a structural feature of metoclopramide (**5**), dramatically reduced the activity.

The effect of substitution at the 8-position on the pyrrolo[2,1-*c*][1,4]benzoxazine ring was investigated while employing 1-azabicyclo[2.2.2]octan-3-amine (**13b**) or *endo*-8-methyl-8-azabicyclo[3.2.1]octan-3-amine (**13c**) as the amine moiety. In the 8-unsubstituted compounds (**12d** and **12e**), compound **12d** having the amine **13b** showed high potency, but compound **12e** with the amine **13c** was significantly less potent. 8-Methyl derivatives (**12f** and **12g**) still retained potency. On the other hand, large substituents, methanesulfonyl (**12h** and **12i**) and acetylamino (**12j**) groups, essentially eliminated the activity, which might be ascribed to an unfavorable steric interaction with the 5-HT_3 receptor. A chloro substitution at the 1-position of the pyrrole ring (**12k**) decreased the potency.

Next, we turned our attention to the substituent effect in the 4-position and prepared the 4-unsubstituted compounds (**20a** and **20b**). Compound **20b** with the amine **13c** (ED_{50} 1.8 μg/kg) retained the same order of potency as the corresponding **12c** (ED_{50} 1.5 μg/kg), while compound **20a** having the amine **13b** (ED_{50} 0.4 μg/kg) showed two-fold higher potency than compound **12b** (ED_{50} 0.9 μg/kg).

Among these pyrrolo[2,1-*c*][1,4]benzoxazine derivatives, the 1-azabicyclo[2.2.2]octan-3-amines (**12b**, **12d**, **12f**, and **20a**) were more potent than the 8-methyl-8-azabicyclo[3.2.1]octan-3-amines (**12c**, **12e**, **12g**, and **20b**). Substituents on the aromatic ring have a substantial influence on the potency. A small substituent at the 8-position (H, Cl, or CH_3) was tolerated, but large substituents (methanesulfonyl and acetylamino) were deleterious. A chloro substituent at the 8-position seemed to be the best. Substitution at the 1-position (**12k**) drastically attenuated the activity, while the introduction of dimethyl substituents at the 4-position retained high

potency (**12b** *vs.* **20a** and **12c** *vs.* **20b**). The most active compound in this study was compound **20a** (0.4 μg/kg), which was approximately 40-fold more potent than ondansetron (**1**) (ED_{50} 17.5 μg/kg) and equipotent with BRL46470A (**4**) (ED_{50} 0.5 μg/kg).

In the present paper, we have demonstrated that structurally novel pyrrolo[2,1-*c*][1,4]benzoxazine-6-carboxamides are potent 5-HT_3 receptor antagonists. This study led to the identification of compound **20a** as a highly potent 5-HT_3 receptor antagonist, which was selected for further evaluation.

Experimental

Melting points are uncorrected. ^{1}H-NMR spectra were recorded on Varian EM-390 (90 MHz) and Bruker AC-200p (200 MHz) spectrometers with tetramethylsilane as an internal standard. IR spectra were recorded on a Shimadzu IR-408 spectrophotometer. Mass spectra were obtained with a JEOL JMS D-300 mass spectrometer. Column chromatography on silica gel was performed with Kieselgel 60 (E. Merck, No. 7734). Ethyl 2-hydroxy-3-nitrobenzoate derivatives (**7**) were prepared by nitration of the corresponding ethyl 2-hydroxybenzoate according to the procedure described in the literature.[11]

Ethyl 5-Chloro-2-hydroxy-3-(pyrrol-1-yl)benzoate (9a) A mixture of ethyl 5-chloro-2-hydroxy-3-nitrobenzoate (**7a**) (8.0 g, 32.6 mmol) and 5% Rh on alumina (0.8 g) in EtOH (100 ml) was hydrogenated at atmospheric pressure for 2.5 h. After filtration to remove the catalyst, the filtrate was evaporated *in vacuo* to give crude ethyl 3-amino-5-chloro-2-hydroxybenzoate (**8a**) as an unstable oil. A solution of crude **8a** and 2,5-dimethoxytetrahydrofuran (6.5 g, 49 mmol) in AcOH (25 ml) was heated at 100 °C for 3.5 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2. The organic layer was washed successively with aqueous $NaHCO_3$, H_2O, and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$–hexane, 1 : 1) to give **9a** (7.5 g, 86%), mp 106—107 °C (toluene–hexane). IR (Nujol): 1675, 1585 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (3H, t, J=7 Hz), 4.45 (2H, q, J=7 Hz), 6.34 (2H, m), 7.05 (2H, m), 7.46 (1H, d, J=3 Hz), 7.77 (1H, d, J=3 Hz), 11.40 (1H, s). *Anal.* Calcd for $C_{13}H_{12}ClNO_3$: C, 58.77; H, 4.55; N, 5.27. Found: C, 58.79; H, 4.48; N, 5.22. Compounds **9b—d** were prepared by the same procedure as described for **9a**.

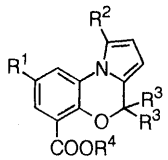
Ethyl 2-Hydroxy-5-methyl-3-(pyrrol-1-yl)benzoate (9b) Yield 82%. mp 67—68 °C. IR (Nujol): 1670, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (3H, t, J=7 Hz), 2.32 (3H, s), 4.43 (2H, q, J=7 Hz), 6.30—6.40 (2H, m), 7.00—7.10 (2H, m), 7.29 (1H, s), 7.60 (1H, s), 11.20 (1H, s). MS *m/z*: 245 (M^+).

Ethyl 2-Hydroxy-5-methanesulfonyl-3-(pyrrol-1-yl)benzoate (9c) Yield 63%. mp 185—188 °C (isopropyl ether–hexane). IR (Nujol): 1695, 1590 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.40 (3H, t, J=7 Hz), 3.31 (3H, s), 4.48 (2H, q, J=7 Hz), 6.29 (2H, m), 7.24 (2H, m), 8.07 (1H, d, J=2 Hz), 8.22 (1H, d, J=2 Hz). *Anal.* Calcd for $C_{14}H_{15}NO_5S$: C, 54.36; H, 4.89; N, 4.53. Found: C, 54.99; H, 4.87; N, 4.33.

Ethyl 5-Acetylamino-2-hydroxy-3-(pyrrol-1-yl)benzoate (9d) Yield 65%. mp 154—155 °C (AcOEt–isopropyl ether). IR (Nujol): 3350, 1660, 1610, 1565 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.38 (3H, t, J=7 Hz), 2.04 (3H, s), 4.41 (2H, q, J=7 Hz), 6.24 (2H, m), 7.08 (2H, m), 8.00 (1H, d, J=3 Hz), 8.12 (1H, d, J=3 Hz), 10.08 (1H, s), 10.96 (1H, s). *Anal.* Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.86; H, 5.72; N, 9.72.

Ethyl 2-Hydroxy-3-(pyrrol-1-yl)benzoate (9e) A mixture of **9a** (7.0 g, 26 mmol), Et_3N (13.3 g, 0.13 mol), H_2O (5 ml), and EtOH (80 ml) was hydrogenated over 10% Pd–C (0.7 g) at atmospheric pressure and room temperature for 5 h. After filtration to remove the catalyst, the filtrate was evaporated *in vacuo*. Crystallization of the residue from MeOH afforded **9e** (2.86 g). The filtrate was evaporated and the residue obtained was chromatographed on silica gel (CH_2Cl_2–hexane, 3 : 2) to give another crop of **9e** (1.29 g, total yield 68%) after recrystallization from MeOH, mp 56—58 °C. IR (Nujol): 1670, 1605, 1585, 1495 cm^{-1}. ^{1}H-NMR

Table 2. 4*H*-Pyrrolo[2,1-*c*][1,4]benzoxazine-6-carboxylic Acids (**11** and **19**) and Their Esters (**10** and **18**)



Compd. No.	R^1	R^2	R^3	R^4	Yield (%)	mp (°C) (Recryst. solvent)[a]	Formula	Analysis (%) Calcd (Found) C	H	N
10a	Cl	H	CH_3	C_2H_5	71	Oil[b]	$C_{16}H_{16}ClNO_3$			
10b	CH_3	H	CH_3	C_2H_5	84	Oil[c]	$C_{17}H_{19}NO_3$			
10c	CH_3SO_2	H	CH_3	C_2H_5	65	Oil[d]	$C_{17}H_{19}NO_5S$			
10d	CH_3CONH	H	CH_3	C_2H_5	21	139—140 (A–I)	$C_{18}H_{20}N_2O_4$	65.84 (65.76)	6.14 6.30	8.53 8.38)
10e	H	H	CH_3	C_2H_5	78	Oil[e]	$C_{16}H_{17}NO_3$			
18	Cl	H	H	C_2H_5	45[f]	90—95 (B–H)	$C_{14}H_{12}ClNO_3$	60.55 (60.72	4.36 4.31	5.04 5.03)
11a	Cl	H	CH_3	H	71	184–185 (A–H)	$C_{14}H_{12}ClNO_3$	60.55 (60.86	4.36 4.39	5.04 5.00)
11b	CH_3	H	CH_3	H	92	168—170 (A–H)	$C_{15}H_{15}NO_3$	70.02 (70.38	5.88 6.05	5.44 5.46)
11c	CH_3SO_2	H	CH_3	H	74	197—198 (A–I)	$C_{15}H_{15}NO_5S \cdot 0.25H_2O$	55.29 (55.53	4.79 4.91	4.30 4.17)
11d	CH_3CONH	H	CH_3	H	91	243—245 (A–I)	$C_{16}H_{16}N_2O_4$	63.99 (63.79	5.37 5.44	9.33 9.18)
11e	H	H	CH_3	H	64	162—167 (A–H)	$C_{14}H_{13}NO_3$	69.12 (68.94	5.39 5.35	5.76 5.66)
11f	Cl	Cl	CH_3	H	68	130—135 (T–H)	$C_{14}H_{11}Cl_2NO_3$	53.87 (53.54	3.55 3.49	4.49 4.42)
19	Cl	H	H	H	95	200—210 (T–B)	$C_{12}H_8ClNO_3$	57.53 (57.75	3.23 3.06	5.61 5.57)

a) The symbols are as follows: A, ethyl acetate; B, dichloromethane; H, hexane; I, isopropyl ether; T, toluene. *b*) MS *m/z*: 305 (M^+). *c*) MS *m/z*: 285 (M^+). *d*) MS *m/z*: 349 (M^+). *e*) MS *m/z*: 271 (M^+). *f*) The yield of two steps. See Experimental.

Table 3. Physical Data for Compounds **12** and **20** of Table 1

Compd. No.	Yield (%)	mp (°C) (Recryst. solvent)[a]	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
12a	69	203—205 (E–D)	$C_{20}H_{26}ClN_3O_2 \cdot HCl$	58.25	6.60	10.19	57.92	6.95	10.12
12b	67	157—165 (E–D)	$C_{21}H_{24}ClN_3O_2 \cdot HCl \cdot 0.5H_2O \cdot 0.5EtOH$	58.15	6.43	9.25	58.22	6.52	9.37
12c	39	164—165 (E–D)	$C_{22}H_{26}ClN_3O_2 \cdot HCl \cdot EtOH$	59.75	6.89	8.71	59.72	6.85	8.77
12d	74	235—238 (M–D)	$C_{21}H_{25}N_3O_2 \cdot HCl \cdot 0.5H_2O$	63.55	6.86	10.58	63.79	7.11	10.51
12e	74	>250 (M–D)	$C_{22}H_{27}N_3O_2 \cdot HCl \cdot H_2O$	62.91	7.20	10.01	62.71	7.25	9.85
12f	55	>250 (A–D)	$C_{22}H_{27}N_3O_2 \cdot HCl \cdot 0.5H_2O$	64.35	7.12	10.23	63.99	7.13	10.06
12g	59	214—216 (M–D)	$C_{23}H_{29}N_3O_2 \cdot HCl \cdot H_2O$	63.65	7.43	9.68	63.45	7.58	9.58
12h	60	>260 (M–D)	$C_{22}H_{27}N_3O_4S \cdot HCl \cdot 0.75H_2O$	55.10	6.20	8.76	55.22	6.48	8.43
12i	37	173—174 (A–I)	$C_{23}H_{29}N_3O_4S \cdot H_2O$	59.85	6.77	9.10	59.84	6.88	9.06
12j	45	215—216 (A–I)	$C_{24}H_{30}N_4O_3 \cdot 0.25H_2O$	67.64	7.19	13.14	67.54	7.39	13.06
12k	48	232—237 (E–D)	$C_{21}H_{23}Cl_2N_3O_2 \cdot HCl$	55.22	5.30	9.20	55.54	5.52	9.09
20a	81	>250 (M–D)	$C_{19}H_{20}ClN_3O_2 \cdot HCl \cdot 0.5H_2O$	56.58	5.49	10.42	56.66	5.41	10.26
20b	54	213—218 (M–D)	$C_{20}H_{22}ClN_3O_2 \cdot HCl \cdot 1.4H_2O$	55.41	5.99	9.69	55.48	5.96	9.59

a) See footnote a) in Table 2. D, diethyl ether; E, ethanol; M, methanol.

(DMSO-d_6) δ: 1.37 (3H, t, J=7 Hz), 4.42 (2H, q, J=7 Hz), 6.23 (2H, t, J=2 Hz), 7.04 (1H, t, J=8 Hz), 7.13 (2H, t, J=2 Hz), 7.64 (1H, dd, J=2, 8 Hz), 7.80 (1H, dd, J=2, 8 Hz). *Anal.* Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.16; H, 5.70; N, 6.04.

Ethyl 8-Chloro-4,4-dimethyl-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-6-carboxylate (10a) A mixture of **9a** (18 g, 68 mmol), *p*-TsOH·H_2O (1.7 g, 8.9 mmol), acetone (150 ml), and benzene (950 ml) was heated at 70 °C for 72 h. After cooling, the reaction mixture was washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (CH_2Cl_2–hexane, 1 : 1) to give **10a** (14.6 g, 71%) as an oil. IR (film): 1725, 1710, 1675, 1590, 1555 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7 Hz), 1.64 (6H, s), 4.37 (2H, q, J=7 Hz), 6.02 (1H, m), 6.33 (1H, t, J=3 Hz), 7.05 (1H, m), 7.42 (1H, d, J=2 Hz), 7.52 (1H, d, J=2 Hz). MS m/z: 305 (M^+). Compounds **10b—e** were prepared by the same procedure as described for **10a** and their physical data are listed in Table 2.

8-Chloro-4,4-dimethyl-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-6-carboxylic Acid (11a) A mixture of **10a** (640 mg, 2.1 mmol), 3 N NaOH (4 ml), and EtOH (5 ml) was stirred at room temperature for 3 h. After evaporation of the solvent, the residue was dissolved in H_2O and washed with CH_2Cl_2. The aqueous layer was made acidic with 3 N HCl and extracted with CH_2Cl_2. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was crystallized from EtOAc–hexane to give **11a** (413 mg, 71%), mp 184—185 °C. IR (Nujol): 3230, 1742, 1595, 1490 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.57 (6H, s), 6.12 (1H, m), 6.30 (1H, m), 7.43 (1H, m), 7.58 (1H, m), 8.01 (1H, m), 13.16 (1H, br s). Compounds **11b—e** were prepared by the same procedure as described for **11a** and their physical data are listed in Table 2.

1,8-Dichloro-4,4-dimethyl-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-6-carboxylic Acid (11f) A solution of **11a** (3.0 g, 10.8 mmol) and NCS (1.44 g, 10.8 mmol) in DMF (30 ml) was stirred at 0 °C for 4 h and at room temperature for 14 h, then diluted with H_2O, and extracted with CH_2Cl_2. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. Recrystallization of the residue from toluene–hexane gave **11f** (2.28 g, 68%), mp 130—135 °C. IR (Nujol): 2800—2400, 1700, 1675, 1595, 1570 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.55 (6H, s), 6.22 (1H, d, J=4 Hz), 6.41 (1H, d, J=4 Hz), 7.54 (1H, d, J=2 Hz), 8.22 (1H, d, J=2 Hz), 13.23 (1H, s).

***N*-(1-Azabicyclo[2.2.2]oct-3-yl)-8-chloro-4,4-dimethyl-4*H*-pyrrolo-[2,1-*c*][1,4]benzoxazine-6-carboxamide Hydrochloride (12b)** A mixture of **11a** (1.0 g, 3.6 mmol), DCC (743 mg, 3.6 mmol), HOBT·H_2O (551 mg, 3.6 mmol), and DMF (15 ml) was stirred at room temperature for 1 h. A solution of 1-azabicyclo[2.2.2]octan-3-amine (500 mg, 4.0 mmol) and Et_3N (0.5 ml, 3.6 mmol) in DMF (5 ml) was added to it. After 14 h, the precipitate formed was removed by filtration and the filtrate was evaporated *in vacuo*. The residue was dissolved in H_2O, made basic with 3 N NaOH, and extracted with CH_2Cl_2. The organic layer was washed with H_2O and brine, dried (Na_2SO_4), and evaporated *in vacuo*. Column chromatography of the residue on silica gel (10% MeOH–$CHCl_3$) gave an oil, which was treated with HCl in EtOH and crystallized from EtOH–ether to give **12b** (1.0 g, 67%), mp 157—165 °C. IR (Nujol): 3360, 2550, 1650,1585, 1530 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.55 (3H, s), 1.60 (3H, s), 1.65—2.20 (5H, m), 3.00—3.80 (6H, m), 4.29 (1H, m), 6.15 (1H, m), 6.31 (1H, m), 7.32 (1H, d, J=2 Hz), 7.60 (1H, m), 7.97 (1H, d, J=2 Hz), 8.59 (1H, d, J=6 Hz). Compounds **12a** and **12c—k** were prepared by the same procedure as described for **12b** and their physical data are listed in Table 3.

Ethyl 2-Acetoxy-5-chloro-3-(pyrrol-1-yl)benzoate (14) A mixture of **9a** (1.0 g, 3.8 mmol), Ac_2O (1 ml), pyridine (1 ml), and CH_2Cl_2 (5 ml) was stirred at room temperature for 40 h. After evaporation of the solvent, the residue was dissolved in toluene and this solution was evaporated *in vacuo*. This operation was repeated three times in order to remove pyridine and Ac_2O to give **14** (1.16 g) as an oil, which was used in the next reaction without further purification. IR (film): 1775, 1725, 1585, 1490 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, J=7 Hz), 2.21 (3H, s), 4.35 (2H, q, J=7 Hz), 6.32 (2H, m), 6.85 (2H, m), 7.54 (1H, d, J=2 Hz), 7.94 (1H, d, J=2 Hz). MS m/z: 307 (M^+).

Ethyl 2-Acetoxy-5-chloro-3-(2-formylpyrrol-1-yl)benzoate (15) $POCl_3$ (0.42 ml) was added dropwise to DMF (0.357 g) cooled to 0 °C. The mixture was stirred at 0 °C for 10 min and then at room temperature for 15 min. A solution of **14** (1.1 g, 3.6 mmol) in 1,2-dichloroethane (14 ml) was added at 0 °C. The mixture was stirred at room temperature for 20 min and at 70 °C for 1 h, then a solution of NaOAc·$3H_2O$ (4.3 g) in H_2O (20 ml) was added and the mixture was stirred at 60 °C for 20 min. After cooling, the reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. Column chromatography of the residue on silica gel (1% MeOH–CH_2Cl_2) first afforded **15** (0.82 g, 65%). Crystallization from EtOAc–hexane gave an analytical sample. mp 125—128 °C. IR (Nujol): 1765, 1725, 1660, 1585, 1525 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, J=7 Hz), 2.06 (3H, s), 4.34 (2H, q, J=7 Hz), 6.41 (1H, m), 6.92 (1H, m), 7.10 (1H, m), 7.55 (1H, d, J=2 Hz), 8.09 (1H, d, J=2 Hz), 9.52 (1H, s). *Anal.* Calcd for $C_{16}H_{14}ClNO_5$: C, 57.24; H, 4.20; N, 4.17. Found: C, 57.44; H, 4.15; N, 4.12. Further elution afforded the 3-formylpyrrole (**21**) (0.31 g, 24%), which was crystallized from CH_2Cl_2–hexane to give an analytical sample. mp 97—98 °C. IR (Nujol): 1760, 1720, 1675, 1585, 1545 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.29 (3H, t, J=7 Hz), 2.19 (3H, s), 4.30 (2H, q, J=7 Hz), 6.67 (1H, m), 7.20 (1H, m), 7.95 (1H, m), 8.01 (1H, m), 8.13 (1H, m), 8.79 (1H, s). *Anal.* Calcd for $C_{16}H_{14}ClNO_5$: C, 57.24; H, 4.20; N, 4.17. Found: C, 56.97; H, 3.91; N, 4.09.

Ethyl 5-Chloro-3-(2-formylpyrrol-1-yl)-2-hydroxybenzoate (16) A solution of 28% NaOMe in MeOH (0.6 ml) was added to a mixture of **15** (0.79 g, 2.4 mmol), EtOH (10 ml), and tetrahydrofuran (THF, 8 ml) at room temperature. After having been stirred for 30 min, the reaction mixture was treated with a mixture of AcOH–H_2O (1 : 1) and evaporated *in vacuo*. The residue was diluted with H_2O and extracted with CH_2Cl_2. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. Column chromatography of the residue on silica gel (CH_2Cl_2–hexane, 1 : 1) yielded first ethyl 8-chloro-4-ethoxy-4*H*-

pyrrolo[2,1-*c*][1,4]benzoxazine-6-carboxylate (**22**) (230 mg, 30%), which was crystallized from CH_2Cl_2–hexane to give an analytical sample, mp 105—112 °C. IR (Nujol): 1725, 1590, 1570 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, t, J=7 Hz), 1.41 (3H, t, J=7 Hz), 3.80 (1H, m), 4.05 (1H, m), 4.42 (2H, q, J=7 Hz), 6.25 (1H, s), 6.30 (1H, m), 6.45 (1H, m), 7.12 (1H, m), 7.50 (1H, d, J=2 Hz), 7.92 (1H, d, J=2 Hz). *Anal.* Calcd for $C_{16}H_{16}ClNO_4$: C, 59.84; H, 5.02; N, 4.36. Found: C, 59.41; H, 5.06; N, 4.36. Further elution yielded **16** (357 mg, 52%), which was crystallized from EtOAc–hexane to give an analytical sample, mp 87—88 °C. IR (Nujol): 3100, 2720, 1675, 1590, 1530 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (3H, t, J=7 Hz), 4.43 (2H, q, J=7 Hz), 6.45 (1H, m), 6.99 (1H, s), 7.14 (1H, m), 7.46 (1H, m), 7.91 (1H, d, J=2 Hz), 9.54 (1H, s), 11.20 (1H, s). *Anal.* Calcd for $C_{14}H_{12}ClNO_4$: C, 57.25; H, 4.12; N, 4.77. Found: C, 57.32; H, 3.92; N, 4.65.

Ethyl 5-Chloro-2-hydroxy-3-(2-hydroxymethylpyrrol-1-yl)benzoate (17) $NaBH_4$ (0.70 g, 18.5 mmol) was added in small portions to a mixture of **16** (2.75 g, 9.4 mmol), THF (15 ml), and EtOH (15 ml) at 0 °C over a period of 1 h. The reaction mixture was stirred at 0 °C for 30 min, then evaporated *in vacuo*. The residue was diluted with H_2O, made acidic with aqueous oxalic acid, and extracted with $CHCl_3$. The organic layer was washed with aqueous $NaHCO_3$, H_2O, and brine, dried (Na_2SO_4), and evaporated *in vacuo*. The unstable oil (2.8 g) obtained was used in the next reaction without further purification. IR (film): 3350, 1680, 1610, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (3H, t, J=7 Hz), 1.87 (1H, t, J=6 Hz), 4.44 (2H, d, J=6 Hz), 4.46 (2H, q, J=7 Hz), 6.30 (1H, m), 6.36 (1H, m), 6.73 (1H, m), 7.55 (1H, d, J=2 Hz), 7.91 (1H, d, J=2 Hz), 11.39 (1H, s).

Ethyl 8-Chloro-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-6-carboxylate (18) A solution of diethyl azodicarboxylate (2.45 g, 14 mmol) in THF (10 ml) was added to a mixture of **17** (2.8 g), Ph_3P (3.68 g, 14 mmol), and THF (10 ml) at 0 °C. After having been stirred at room temperature for 14 h under a nitrogen atmosphere, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (CH_2Cl_2–hexane, 2 : 1) to give **18** (1.16 g, 45%). Recrystallization from CH_2Cl_2–hexane gave an analytical sample, mp 90—95 °C. IR (Nujol): 1725, 1600, 1565 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, t, J=7 Hz), 4.35 (2H, q, J=7 Hz), 5.22 (2H, s), 6.10 (1H, m), 6.35 (1H, m), 7.08 (1H, m), 7.44 (1H, d, J=2 Hz), 7.52 (1H, d, J=2 Hz). Analytical data for **18** are shown in Table 2.

Compound **19** was prepared by the same procedure as described for **11a** and its physical data are listed in Table 2.

Compounds **20a** and **b** were preapred by the same procedure as described for **12b** and their physical data are listed in Table 3.

Pharmacology von BJ Reflex in Urethane-Anesthetized Rats The compounds were evaluated for antagonism of the BJ reflex evoked by 2-Me-5-HT in the anesthetized rat by the method of Fozard and Host.[12] Male Sprague–Dawley rats (260—350 g) were anesthetized with urethane (1.25 g/kg i.p.). Blood pressure and heart rate were monitored continuously from the left common carotid artery with a pressure transducer. A right femoral vein was cannulated for the intravenous injection of drugs. The trachea was also cannulated to ease respiration. The BJ reflex was evoked by rapid bolus injection of 2-Me-5-HT (32 μg/kg, i.v.). When agonist-induced bradycardia returned to the steady state, the test compound (i.v.) was administered, and agonist-induced bradycardia was elicited again 5 min after the test compound administration. Percent inhibition was calculated as the percent difference between the first and second episodes of agonist-induced bradycardia.

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