New 5-HT_3 (Serotonin-3) Receptor Antagonists. IV. Synthesis and Structure–Activity Relationships of Azabicycloalkaneacetamide Derivatives

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The synthesis and structure–activity relationships of a series of new azabicycloalkanes as 5-HT_3 (serotonin-3) receptor antagonists are described. Our study on the azabicycloalkaneacetamide derivatives showed that 2,3-dihydroindole as the aromatic ring moiety afforded potent 5-HT_3 receptor antagonist activity, as judged by blockade of bradycardia induced by i.v. injection of 2-methylserotonin in anesthetized rats. 7-Azaindole as the aromatic moiety afforded weak 5-HT_3 receptor antagonists activity. The best 5-HT_3 antagonists in this study were *endo*-3,3-diethyl- (9k) and 3,3-dimethyl-2,3-dihydro-1-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)acetyl-1*H*-indole (9d), being approximately 10-fold more potent than ondansetron (1). This study shows that the azabicycloalkaneacetyl group is a new pharmacophoric element as a basic nitrogen and a linking carbonyl moiety.

Key words azabicycloalkaneacetamide; 2,3-dihydro-1*H*-indole; 5-HT_3 receptor antagonist; structure–activity relationship; von Benzold–Jarisch reflex

The 5-hydroxytryptamine (5-HT) receptor has been classified into several subtypes on the basis of pharmacological responses.[1] In recent years, there has been intensive effort aimed at the preparation of ligands with selective subtype specificity. In particular, several promising 5-HT_3 receptor antagonists have been reported and developed for the treatment of nausea and emesis associated with cancer chemotherapy.[2] The structures of representative 5-HT_3 receptor antagonists are shown in Chart 1.[3]

Most of these antagonists can be categorized into two general structural classes. One is the imidazole derivatives, such as ondansetron (**1**). The other is a group of aliphatic amine derivatives typified by metoclopramide (**2**), zacopride (**3**), tropisetron (**4**), and granisetron (**5**). In earlier publications, we reported that pyrido[1,2-*a*]indole and pyrimido[1,6-*a*]indole derivatives having an imidazole ring possess potent 5-HT_3 receptor antagonist activity.[4] In particular, compound **6** (FK 1052) is a candidate drug for the treatment of gastrointestinal disorder.[5] As part of our program aimed at finding new 5-HT_3 receptor antagonists, we next attempted to synthesize "aliphatic amine" type 5-HT_3 receptor antagonists. The pharmacophoric elements of the 5-HT_3 receptor antagonists are regarded as an aromatic moiety, a linking acyl group, and a basic nitrogen.[6] The majority of the 5-HT_3 receptor antagonists of "aliphatic amine" type so far reported have the amide or ester linkage joining the amine group and the aromatic ring moiety (compound **7** in Chart 2). Some conformational restraints derived from these functional groups were assumed to be important for defining the appropriate spatial relationships between the aromatic ring and the amine group for binding to the receptor. It is of interest to synthesize 5-HT_3 receptor antagonists with a carbon linkage in place of a nitrogen or an oxygen in order to evaluate the contribution of the amide or ester function to the potency (compound **8** in Chart 2). We have designed and prepared compounds of general structure **9**, which correspond to the bioisosters of tropisetron (**4**). As an alternative pathway to the new "aliphatic amine" 5-HT_3 receptor antagonists, the aromatic ring part was modified

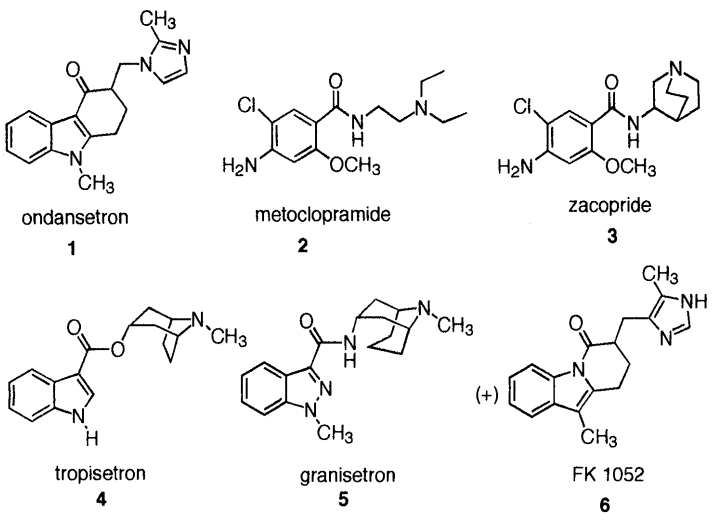

Chart 1

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to an azaindole ring (**10**), which is an isomer of the indazole ring of granisetron (**5**). During the course of this study, BRL46470A (**11**), the nitrogen bioisoster of compound **9**, was reported to be a potent 5-HT_3 receptor antagonist.[7] In this paper, we describe the synthesis and structure–activity relationships of azabicycloalkaneacetamide derivatives (**9**) and 7-azaindole derivatives (**10**).

Chemistry

Compound **9** was prepared by coupling of the 2,3-dihydroindole (**12**) with the corresponding carboxylic acid (**13**) in the presence of dicyclohexylcarbodiimide (DCC) or 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (WSCD) and 1-hydroxybenzotriazole (HOBT) (Chart 3). The 2-methoxyaniline derivative (**9a**) was prepared by the same method. 3-Methyl-2,3-dihydroindole (**9c**) was dehydrogenated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to give the indole (**9b**). The *N*-oxide (**9i**) was prepared from **9d** by oxidation using 3-chloroperbenzoic acid.

2,3-Dihydroindoles (**12**) were prepared by the procedure described in the literature.[8] The general route for the synthesis of the azabicycloalkaneacetic acids (**13**) is exemplified by the preparation of 8-methyl-8-azabicyclo[3.2.1]-octane-3-acetic acid (**13b**) in Chart 4. Horner–Emmons olefination of 8-methyl-8-azabicyclo[3.2.1]octan-3-one (**14**) with diethylphosphonoacetic acid ethyl ester in tetrahydrofuran (THF) gave the *exo*-olefin (**15**) and a small amount of the *endo*-olefin (**16a**). 9-Methyl-9-azabicyclo-[3.3.1]nonan-3-one also gave a mixture of **18** and **16b**. 1-Azabicyclo[2.2.2]octan-3-one exclusively gave the *exo*-olefin (**19**), whose stereochemistry was assumed on the basis of the NMR spectra. The presence of a long-range coupling between the olefin proton at δ 6.26 (triplet, $J=2.3$ Hz) and the methylene proton at the 2-position suggested that these protons have a *trans* relationship to each other. Hydrogenation of **15** and **16a** with palladium on carbon (Pd–C) in ethanol gave the *endo*-ethyl ester (**17**),[9] which had already been prepared by a similar procedure and whose stereochemistry at the 3-position had been assigned as *endo*.[9] Compound **21** similarly prepared was also assumed to be a kinetic *endo*-product. The acids **13a** and **13b** were respectively prepared by alkaline hydrolysis of **15** and **17** with aqueous sodium hydroxide. Other azabicycloalkane acids **13c—e** were prepared in a manner similar to that used for **13a**.

The synthesis of 7-azaindole derivatives (**10**) is shown in Chart 5. 7-Azaindole (**22**), prepared by the literature procedure,[10] was alkylated with various alkylating agents and sodium hydride in *N*,*N*-dimethylformamide (DMF) to give alkylated compounds (**23**). The 8-azabicyclo-[3.2.1]octane-3-acetyl derivative (**10a**) was prepared by the Friedel–Crafts reaction of **23a** with the corresponding acid chloride and aluminum chloride. Vilsmeier reaction of **23** with phosphorus oxychloride and DMF gave the aldehyde (**24**), which was converted to the acid (**26**) by two methods. One was the oxidation with potassium permanganate in aqueous acetone. The other consisted of oxidation to the methyl ester (**25**) with manganese dioxide and sodium cyanide, followed by alkaline hydrolysis to **26c** (R^3 = allyl). Coupling of **26** with *endo*-8-methyl-8-azabicyclo[3.2.1]octan-3-amine or *endo*-9-methyl-9-azabicyclo[3.3.1]nonan-3-amine by the DCC–HOBT method

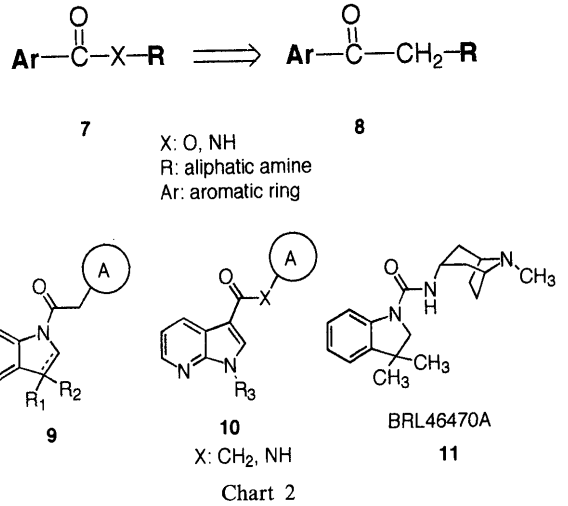


Chart 2

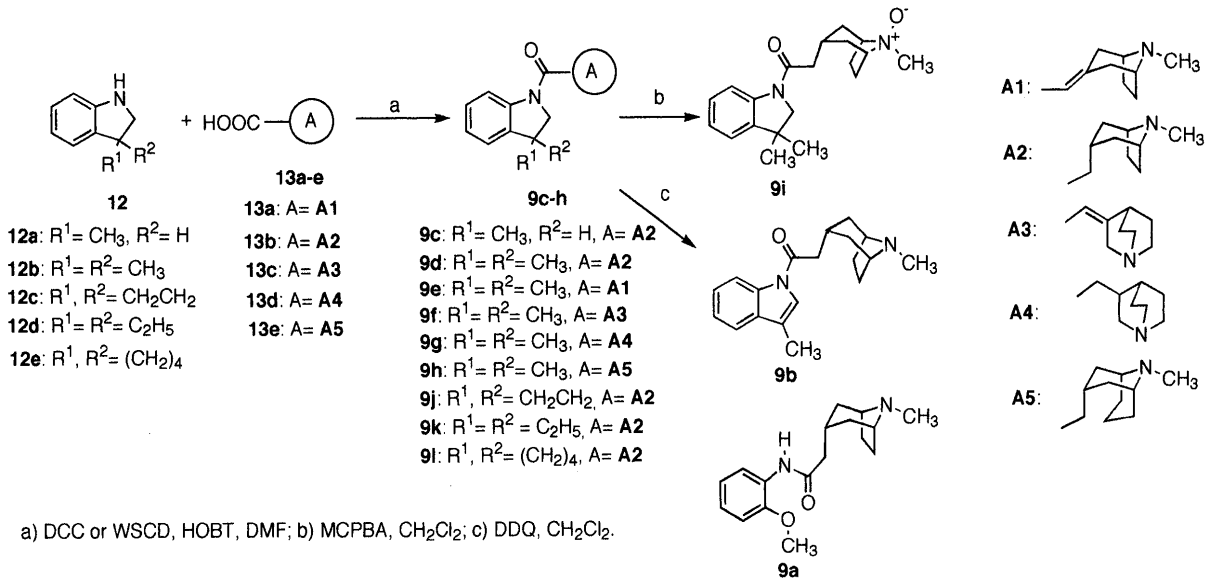
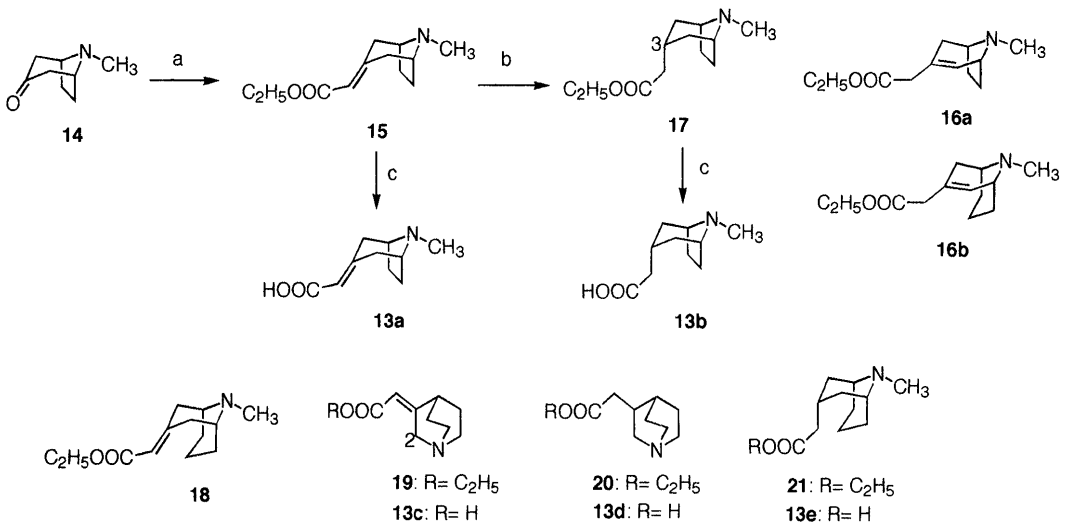
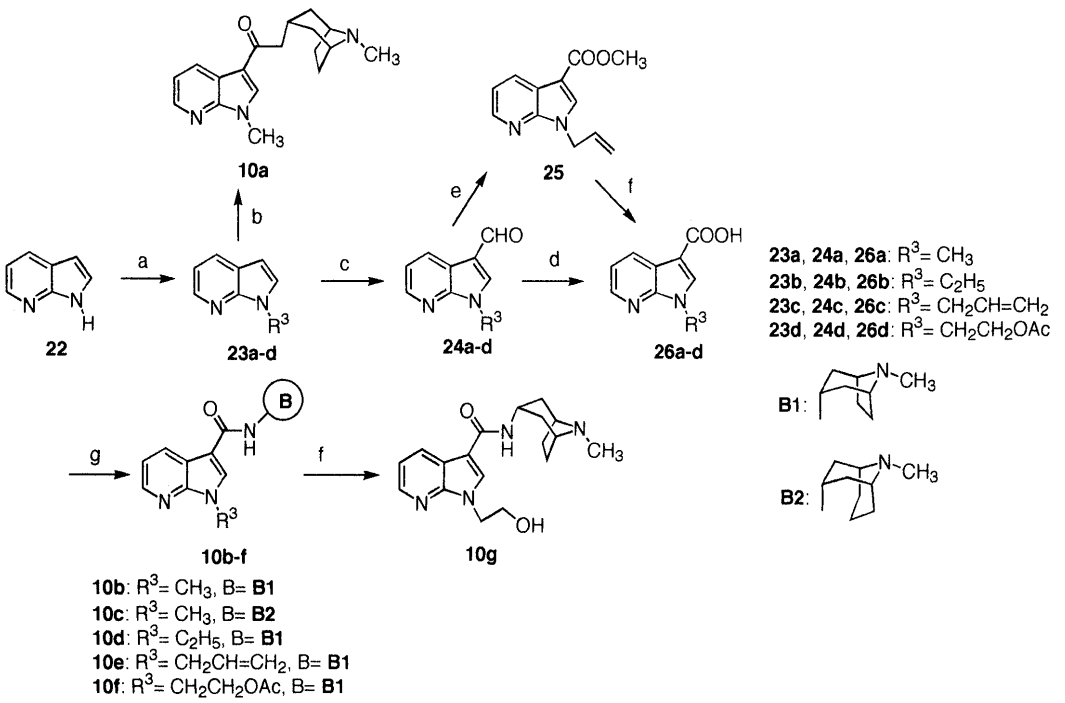


Chart 3



a) $(C_2H_5O)_2P(O)CH_2COOC_2H_5$, NaH, THF; b) H_2, 10% Pd–C, EtOH; c) NaOH, H_2O, EtOH.

Chart 4



a) R^3X, NaH, DMF; b) i: **13b**, $SOCl_2$; ii: $AlCl_3$, CS_2; c) $POCl_3$, DMF; d) $KMnO_4$, acetone, H_2O; e) MnO_2, NaCN, MeOH, AcOH; f) NaOH, H_2O, EtOH; g) DCC, HOBT.

Chart 5

gave compounds **10b**—**f**. The hydroxyethyl compound **10g** was prepared by alkaline hydrolysis of the acetoxyethyl (**10f**).

Biological Results and Discussion

The activity of the compounds 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. The 5-HT induced activation of the BJ reflex is mediated *via* 5-HT_3 receptors in the right ventricle. 2-Me-5-HT was reported to be a selective 5-HT_3 receptor agonist.[11] Compounds were screened after intravenous administration. The results are listed in Tables 1 and 2, together with the data for ondansetron (**1**) and BRL46470A (**11**) as reference compounds.

In order to identify the preferred aromatic ring moiety in the general structure **8** for binding to the 5-HT_3 receptor, we introduced 3-methylindole (**9b**) and 7-azaindole rings (**10a**), which are bioisosters of the aromatic ring moiety of tropisetron (**4**) and granisetron (**5**), respectively (Table 1). The 8-methyl-8-azabicyclo[3.2.1]octane-3-acetyl group was retained as the amine part because it is a common amine component in many 5-HT_3 receptor antagonists.

Table 1. Inhibition of von BJ Reflex: Modification of Aromatic Ring Part of Azabicycloalkaneacetamides

Compd. No.[a]	% inhibition of 2-Me-5-HT-induced bradycardia (μg/kg i.v.)[b]							ED_{50} (μg/kg i.v.)
	100	32	10	3.2	1.0	0.32	0.10	
9a	29.0							
9b	71.4	67.5	45.0	53.0	8.3			9.9
10a	38.0			6.0				
9c	68.2	54.9		36.3				15.2
9d	73.6	74.1	69.1	60.0	29.0			2.3
9e	43.0							
9f	67.7		50.2	28.0				17.0
9g	71.5		48.0		−3.0			12.6
9h	6.7			0.2				
9i	58.0			0.9				
9j			71.3	65.6	10.7			3.2
9k				68.2	29.1	10.3		1.7
9l			71.4	62.0	1.0			3.3
1 (Ondansetron)	79.5	72.1	43.3					17.5
11 (BRL46470A)					74.7	36.0	11.4	0.5

a) Compounds were tested as racemates when a chiral center was present in the molecule. *b*) Each compound was tested in groups of three animals and data represent mean values of peak inhibition.

Table 2. Inhibition of von BJ Reflex: Pyrrolo[2,3-*b*]pyridine Derivatives

Compd. No.	% inhibition of 2-Me-5-HT-induced bradycardia (μg/kg i.v.)[a]			ED_{50} (μg/kg i.v.)
	100	32	3.2	
10a	38.0		6.0	
10b	60.8	47.1	23.0	40.2
10c	49.4		−6.0	
10d	64.0		−20.0	
10e	38.0		−3.0	
10f	60.2		−3.0	
10g	55.4		21.3	

a) See footnote *b*) in Table 1.

The activity of the 2-methoxyaniline (**9a**), a monocyclic compound, was marginal. This result could be attributed to the absence of coplanarity between the aromatic ring and the amine part. In contrast, the 3-methylindole (**9b**) showed a high potency (ED_{50} 9.9 μg/kg). But the activity of the 7-azaindole counterpart (**10a**) was low. We next introduced a 2,3-dihydroindole ring for the purpose of investigating the effect of the double bond. Saturation of the 2,3-double bond of **9b** caused a small decrease in potency (**9c**, ED_{50} 15.2 μg/kg) to a level similar to that of ondansetron (**1**) (ED_{50} 17.5 μg/kg). Next, several substituents were incorporated at the 3-position of 2,3-dihydroindole in order to investigate the steric tolerance at the 3-position. The 3,3-dimethyl compound (**9d**) had improved potency (ED_{50} 2.3 μg/kg). All 3,3-disubstituted compounds, cyclopropyl (**9j**), 3,3-diethyl (**9k**), and cyclopentyl (**9l**), retained high potency, suggesting that there is large steric tolerance at the 3-position. Because of the results obtained above, the 3,3-dimethyl substituents were maintained, and the amine part was modified further. The 1-azabicyclo[2.2.2]octane-3-acetyl derivative (**9g**) showed a small decrease in potency (ED_{50} 12.6 μg/kg), whereas the 9-methyl-9-azabicyclo[3.3.1]nonane (**9h**) showed dramatically decreased activity, in marked contrast to the high potency of granisetron (**5**). The decrease in potency of **9h** might be attributed to an unfavorable interaction between the hydrogen atoms at the 2-position of the 2,3-dihydroindole ring and the hydrogen atom at the 7-position of the 9-methyl-9-azabicyclo[3.3.1]nonane-3-acetyl group, disfavoring the active conformation of the molecule. This result parallels the structure–activity relationships of the pyrazolo[1,5-*b*]pyridine derivatives in the literature.[12] Comparison of the saturated compound (**9d**) with the unsaturated congener (**9e**) revealed that unsaturation at the amine part is deleterious, presumably because of the unfavorable steric constraint due to the unsaturation, whereas in the 1-azabicyclo[2.2.2]octane derivatives, the unsaturation had essentially no effect on the activity of compounds **9f** and **9g**. Oxidation of the amine (**9d**) to produce the amine oxide **9i** resulted in a reduction in potency. In this series, compounds **9d** and **9k**, having a 3,3-dimethyl or 3,3-diethyl substituent in the 2,3-dihydroindole ring and 8-methyl-8-azabicyclo[3.2.1]-octane-3-acetyl as an amine part, are the most potent, being approximately 10-fold more potent than ondansetron (**1**), but 4-fold less active than BRL46470A (**11**).

As described above, the 7-azaindole (**10a**) having a 8-methyl-8-azabicyclo[3.2.1]octane-3-acetyl group as an amine part was significantly less active. This result prompted us to prepare the amide counterpart (**10b**) in order to compare the ketone function of **10a** with the amide of **10b** (Table 2). Compound **10b** showed increased potency (ED_{50} 40.2 μg/kg), though it was still less active than ondansetron (**1**). Comparison of **10a** with **10b** revealed the importance of coplanarity of the aromatic ring portion and the amine group. 9-Methyl-9-azabicyclo[3.3.1]nonan-3-amine (**10c**) showed decreased activity, a similar result to that observed with **9h**. Several substituents were introduced at the 1-position of the 7-azaindole ring in an effort to increase the activity of **10b**, but all the compounds tested (**10d—g**) showed a small decrease in potency. The low activity of 7-azaindole derivatives (**10**) may have been a consequence of the loss of favorable interactions between the aromatic ring moie-

ty and the 5-HT_3 receptor due to the electron-deficient property of the 7-azaindole ring.

In this paper, we described the azabicycloalkaneacetic acid derivatives as new 5-HT_3 receptor antagonists. Although numerous publications have appeared on 5-HT_3 receptor antagonists derived from azabicycloalkanamine and azabicycloalkanol, there has been only one report on azabicycloalkaneacetic acid derivatives and their biological activities were not shown.[13] We found that 2,3-dihydroindole derivatives (**9d** and **9k**) having a *gem*-dimethyl or *gem*-diethyl substituent at the 3-position and a 8-methyl-8-azabicyclo[3.2.1]octane-3-acetyl group as the amine part still retained high ptency, being approximately 10-fold more potent than ondansetron (**1**) in the inhibition of BJ reflex after i.v. administration. A comparison of ED_{50} values of **9k** (1.7 μg/kg) and BRL46470a (**11**) (0.5 μg/kg) suggests that an amide or ester function in the carbonyl part is not essential for high potency, though steric constraint by an amide or ester function is beneficial. These azabicycloalkaneacetic acid derivatives represent a new type of 5-HT_3 receptor antagonists.

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 with a Shimadzu IR-480 spectrometer. Mass spectra were recorded on a JEOL D-300 mass spectrometer. Column chromatography on silica gel was performed with Kieselgel 60 (E. Merck, No. 7734). 2,3-Dihydro-3-methyl-1*H*-indole (**12a**),[8a] 2,3-dihydro-3,3-dimethyl-1*H*-indole (**12b**),[8b] 1′,2′-dihydrospiro[cyclopropane-1,3′-[3*H*]indole] (**12c**),[8c] and 1′,2′-dihydrospiro[cyclopentane-1,3′-[3*H*]indole] (**12e**)[8c] were prepared by the literature procedures. 3,3-Diethyl-2,3-dihydro-1*H*-indole (**12d**) was prepared by a procedure similar to that described in the literature.[8b]

***endo*-3,3-Diethyl-2,3-dihydro-1-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)acetyl]-1*H*-indole Maleate (9k)** A mixture of *endo*-8-methyl-8-azabicyclo[3.2.1]octane-3-acetic acid (**13b**) (1.28 g, 7.0 mmol), DCC (1.44 g, 7.0 mmol), and HOBT·H_2O (1.07 g, 7.0 mmol) in DMF (15 ml) was stirred at room temperature for 1.5 h. A solution of **12d** (1.28 g, 7.3 mmol) in DMF (5 ml) was added and the mixture was stirred at room temperature for 72 h. The reaction mixture was diluted with H_2O, made basic with 3 N aqueous NaOH, and extracted with $CHCl_3$. 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 (20% MeOH–$CHCl_3$) to give an oil (0.61 g), which was treated with a solution of maleic acid (0.208 g, 1.8 mmol) in MeOH. After evaporation of the solvent, the residue was crystallized from 2-propanol–ether to give **9k** (0.627 g, 19%), mp 160—162 °C. IR (Nujol): 2000—2400, 1690, 1650, 1605, 1590 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.71 (6H, t, J=7 Hz), 1.55—1.80 (6H, m), 2.10—2.60 (7H, m), 2.68 (3H, s), 2.78 (2H, m), 3.81 (2H, br s), 3.86 (2H, s), 6.03 (2H, s), 6.99—7.20 (3H, m), 8.06 (1H, d, J=8 Hz).

Compounds **9a**, **9c—h**, **9j**, and **9l** were prepared *via* the procedure described for **9k**. Compounds **10b—f** were also prepared from the acids **26a—d** and the corresponding amines by means of the procedure described for **9k**.

***endo*-3,3-Dimethyl-2,3-dihydro-1-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)acetyl]-1*H*-indole *N*-Oxide Hydrochloride (9i)** A solution of **9d** (1.1 g, 3.8 mmol) and 3-chloroperbenzoic acid (911 mg, 5.3 mmol) in CH_2Cl_2 (30 ml) was stirred at room temperature for 2 h. The reaction mixture was diluted with H_2O and washed with aqueous $NaHCO_3$. After evaporation of the solvent, the residue was dissolved in a mixture of EtOAc–THF. The solution was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. Purification of the residue by column chromatography on silica gel (13% MeOH–$CHCl_3$), followed by treatment with 6 N HCl and ether, gave **9i** (0.42 g, 29%), mp 225—231 °C (H_2O). IR (Nujol): 1650, 1590, 1540 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.31 (6H, s), 1.70—2.81 (11H, m), 3.56 (3H, s), 3.88 (2H, s), 4.17 (2H, s), 6.90—7.20 (2H, m), 7.35 (1H, dd, J=7 Hz), 8.06 (1H, d, J=7 Hz). MS m/z: 328 (M^+).

***endo*-3-Methyl-1-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)acetyl]-1*H*-indole Hydrochloride (9b)** A solution of **9c** (0.7 g, 2.3 mmol) and DDQ (0.64 g, 2.8 mmol) in CH_2Cl_2 (10 ml) was refluxed for 8 h. After cooling, the reaction mixture was washed with 1 N NaOH and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (15% MeOH–$CHCl_3$) to give an oil (0.35 g), which was converted to the hydrochloride by HCl–EtOH. Crystallization from 2-propanol gave **9b** (0.101 g, 13%), mp 191—193 °C. IR (Nujol): 1690, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.50—2.80 (12H, m), 3.10—3.40 (3H, m), 3.50—3.90 (3H, m), 4.31 (1H, d, J=4 Hz), 7.23—7.37 (2H, m), 7.55 (1H, dd, J=1, 7 Hz), 7.82 (1H, s), 8.33 (1H, d, J=6 Hz).

The physical data of compounds **9** are listed in Table 3.

Table 3. Physical Data for Compounds in Tables 1 and 2

Compd. No.	Yield (%)	mp (°C) (Recryst. solvent)[a]	Formula	Analysis (%) Calcd			Found		
				C	H	N	C	H	N
9a	71	116—117 (H)	$C_{17}H_{24}N_2O_2$	70.80	8.39	9.71	70.61	8.45	9.66
9b	13	191—193 (P)	$C_{19}H_{24}N_2O\cdot HCl\cdot 1.3H_2O$	64.05	7.81	7.86	63.79	7.52	7.77
9c	44	76—80 (W)	$C_{19}H_{26}N_2O\cdot 0.5H_2O$	74.23	8.85	9.11	74.51	9.09	9.17
9d	69	83—89 (D–H)	$C_{20}H_{28}N_2O\cdot 0.5H_2O$	74.72	9.09	8.71	74.61	9.14	8.74
9e	40	74—78 (A–H)	$C_{20}H_{26}N_2O\cdot 0.5C_4H_8O_2$[b]$\cdot 3H_2O$	64.88	8.88	6.86	64.72	8.55	7.19
9f	73	267—268 (I)	$C_{19}H_{24}N_2O\cdot HCl\cdot 0.3H_2O$	67.45	7.63	8.28	67.19	7.87	8.04
9g	35	245—250 (B–D)	$C_{19}H_{26}N_2O\cdot HCl\cdot 0.3CH_2Cl_2$	64.32	7.72	7.78	64.13	7.98	7.98
9h	22	117—118 (A–D)	$C_{21}H_{30}N_2O\cdot 0.5H_2O$	75.18	9.31	8.35	75.23	9.08	8.42
9i	29	225—231 (W)	$C_{20}H_{28}N_2O_2\cdot HCl$	65.83	8.01	7.68	65.59	8.11	7.65
9j	58	178—180 (M–D)	$C_{20}H_{26}N_2O\cdot C_4H_4O_4$[c]	67.59	7.09	6.57	67.30	7.01	6.47
9k	19	160—162 (P–D)	$C_{22}H_{32}N_2O\cdot C_4H_4O_4$[c]	68.40	7.95	6.14	68.08	7.91	6.13
9l	42	74—80 (E–D)	$C_{22}H_{30}N_2O\cdot C_4H_4O_4\cdot H_2O$[c]	66.08	7.68	5.93	66.28	7.84	5.60
10a	31	212—213 (M–D)	$C_{18}H_{23}N_3O\cdot 2HCl\cdot 1.5H_2O$	54.41	7.10	10.58	54.47	7.18	10.39
10b	76	207—215 (E–D)	$C_{17}H_{22}N_4O\cdot 2HCl\cdot 1.7H_2O$	50.80	6.87	13.94	50.62	6.74	13.88
10c	45	>280 (M–A)	$C_{18}H_{24}N_4O\cdot HCl\cdot 0.25H_2O$	61.19	7.27	15.87	61.00	7.35	15.75
10d	26	124—127 (E–A)	$C_{18}H_{24}N_4O\cdot 2HCl\cdot 2H_2O$	51.31	7.18	13.30	50.99	6.90	13.30
10e	33	142—143 (A–D)	$C_{19}H_{24}N_4O\cdot 0.5H_2O$	68.44	7.56	16.80	68.61	7.46	16.94
10f	62	145—146 (A–D)	$C_{20}H_{26}N_4O_3$	64.85	7.07	15.12	64.55	7.11	15.03
10g	38	77—79 (A–D)	$C_{18}H_{24}N_4O_2\cdot 1.5H_2O$	60.82	7.66	15.76	60.82	7.38	15.52

a) The symbols are as follows; A, ethyl acetate; B, dichloromethane; D, diethyl ether; E, ethanol; H, hexane; I, isopropyl ether; M, methanol; P, 2-propanol; W, H_2O. *b*) Ethyl acetate. *c*) Maleate.

***endo*-1-Methyl-3-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)acetyl]-1*H*-pyrrolo[2,3-*b*]pyridine Dihydrochloride (10a)** Compound **13b**·HCl, prepared from **13b** (366 mg, 2 mmol) by treatment with HCl–ether, was added to a mixture of $SOCl_2$ (2 ml) and benzene (10 ml) at room temperature. After 1 h of strring, the mixture was evaporated *in vacuo* to give the crude acid chloride, which was suspended in CS_2 (3 ml) at room temperature. The suspension of the acid chloride prepared above was slowly added to a mixture of 1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (**23a**) (270 mg, 2 mmol) and $AlCl_3$ (2 g, 15 mmol) in CS_2 (10 ml) at room temperature. After having been stirred for 4 h at room temperature, the reaction mixture was evaporated *in vacuo*. The residue was diluted with H_2O, made basic with aqueous $NaHCO_3$, and extracted with 10% MeOH–CH_2Cl_2. The organic layer was dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography of the residue (15% MeOH–$CHCl_3$), followed by treatment with HCl–ether and crystallization from MeOH–ether, gave **10a** (115 mg, 31%), mp 212—213 °C. IR (Nujol): 3550, 1640, 1590, 1560, 1540 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.63 (2H, m), 2.08—2.75 (9H, m), 2.63 (3H, s), 3.14 (2H, m), 3.76 (2H, s), 3.90 (3H, s), 7.30 (1H, dd, J=5, 8 Hz), 8.38 (1H, dd, J=2, 5 Hz), 8.48 (1H, dd, J=2, 8 Hz), 8.71 (1H, s).

***endo*-1-(2-Hydroxyethyl)-*N*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxamide (10g)** A solution of **10f** (560 mg, 1.51 mmol) in 1 N NaOH (3.5 ml) and EtOH (3 ml) was stirred at room temperature for 2 h. The solution was neutralized with 1 N HCl and evaporated *in vacuo*. The residue was dissolved in aqueous $NaHCO_3$ and extracted with 10% MeOH–$CHCl_3$. Column chromatography of the residue (20% MeOH–$CHCl_3$), followed by crystallization from EtOAc–ether, gave **10g** (167 mg, 38%). mp 77—79 °C. IR (Nujol): 3270, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.60—2.20 (8H, m), 2.17 (3H, s), 3.05 (2H, m), 3.79 (2H, t, J=5 Hz), 3.90—4.10 (1H, m), 4.33 (2H, t, J=5 Hz), 5.00 (1H, br s), 7.20 (1H, dd, J=5, 8 Hz), 7.46 (1H, d, J=5 Hz), 8.26 (1H, s), 8.29 (1H, dd, J=2, 5 Hz), 8.40 (1H, dd, J=2, 8 Hz). MS m/z: 328 (M^+).

The physical data of compounds **10** are listed in Table 3.

Ethyl (8-Methyl-8-azabicyclo[3.2.1]oct-3-ylidene)acetate (15) and Ethyl 8-Methyl-8-azabicyclo[3.2.1]oct-2-en-3-ylacetate (16a) NaH (60% in mineral oil, 2.2 g, 0.055 mol) was added to a solution of diethylphosphonoacetic acid ethyl ester (12.33 g, 0.055 mol) in THF (100 ml) at 10 °C under nitrogen. The solution was stirred for 30 min at 10 °C, then a solution of 8-methyl-8-azabicyclo[3.2.1]octan-3-one (6.96 g, 0.05 mol) in THF (25 ml) was added to it. The mixture was stirred at room temperature for 3 h and at 60 °C for 4 h, then diluted with H_2O, and extracted with EtOAc. The organic layer was extracted twice with 1 N HCl. The aqueous layer was made basic with 10 N NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 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–CH_2Cl_2) gave **15** (5.71 g, 66%) as an oil. IR (film): 1705, 1635 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.19 (3H, t, J=7 Hz), 1.30—1.50 (2H, m), 1.86—2.60 (4H, m), 2.26 (3H, s), 3.19—3.43 (4H, m), 4.05 (2H, q, J=7 Hz), 5.70 (1H, t, J=2 Hz). MS m/z: 209 (M^+). Further elution gave **16a** (2.39 g, 23%) as an oil. IR (film): 1710, 1625 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.18 (3H, t, J=7 Hz), 1.35—2.10 (5H, m), 2.21 (3H, s), 2.35—2.45 (1H, m), 2.90 (2H, s), 3.11 (2H, t, J=5 Hz), 4.04 (2H, q, J=7 Hz), 5.60 (1H, d, J=5 Hz). MS m/z: 209 (M^+).

Compounds **18**, **16b** and **19** were prepared by the same procedure as described for compounds **15**. Compounds **18** and **16b** could not be isolated and were used in the next reaction without separation.

Ethyl (9-Methyl-9-azabicyclo[3.3.1]non-3-ylidene)acetate (18) and Ethyl 9-Methyl-9-azabicyclo[3.3.1]non-2-en-3-ylacetate (16b) Yield 41%. An oil. IR (film): 1730, 1560, 1250 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz), 1.30—1.90 (7H, m), 2.38 and 2.60 (3H, each s), 2.30—3.20 (5H, m), 4.10—4.30 (2H, m), 5.49 and 5.64 (1H, each m). MS m/z: 223 (M^+).

Ethyl (1-Azabicyclo[2.2.2]oct-3-ylidene)acetate (19) Yield 65%. An oil. ^{1}H-NMR (DMSO-d_6) δ: 1.20 (3H, t, J=7 Hz), 1.57—1.76 (4H, m), 2.62—2.88 (4H, m), 3.39 (1H, s), 3.74 (2H, s), 4.06 (2H, q, J=7 Hz), 5.68 (1H, t, J=2 Hz). MS m/z: 195 (M^+).

Ethyl *endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-ylacetate (17) A solution of **15** (32.0 g, 0.153 mol) in EtOH (320 ml) was hydrogenated under H_2 at 14 atm pressure with 10% Pd–C (4 g) as the catalyst for 14 h at room temperature. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo*. The residue was purified by column chromatography on neutral alumina (CH_2Cl_2) to give **17** (19.4 g, 60%) as an oil. IR (film): 1730 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.10—1.20 (2H, m), 1.17 (3H, t, J=7 Hz), 1.50 (2H, m), 1.80—2.10 (5H, m), 2.11 (3H, s), 2.38 (2H, d, J=8 Hz), 2.98 (2H, m), 4.05 (2H, q, J=7 Hz). MS m/z: 211 (M^+).

Compounds **20** and **21** were prepared by the same procedure as described for **17**.

Ethyl 1-Azabicyclo[2.2.2]oct-3-ylacetate Hydrochloride (20) Yield 84%. mp 127—131 °C (ether). IR (film): 1720 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (3H, d, J=7 Hz), 1.60—1.85 (4H, m), 2.34—2.80 (5H, m), 3.10—3.25 (4H, m), 3.33 (1H, t, J=11 Hz), 4.07 (2H, q, J=7 Hz). *Anal.* Calcd for $C_{11}H_{19}NO_2 \cdot HCl \cdot 0.2H_2O$: C, 55.67; H, 8.66; N, 5.90. Found: C, 55.64; H, 8.93; N, 5.86. MS m/z: 197 (M^+).

Ethyl *endo*-9-Methyl-9-azabicyclo[3.3.1]non-3-ylacetate (21) Yield 90%. An oil. IR (film): 1725, 1430 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90—2.40 (13H, m), 1.27 (3H, t, J=7 Hz), 2.51 (3H, s), 2.90—3.20 (2H, m), 4.12 (2H, q, J=7 Hz). MS m/z: 225 (M^+).

(8-Methyl-8-azabicyclo[3.2.1]oct-3-ylidene)acetic Acid (13a) A mixture of **15** (3.0 g, 14.3 mmol), 1 N NaOH (20 ml), and EtOH (10 ml) was stirred at room temperature for 14 h, then neutralized with 1 N HCl, and evaporated *in vacuo*. The residue was dissolved in EtOH and the insoluble material was filtered off. Evaporation of the filtrate, followed by trituration of the residue with ether, gave **13a** (2.5 g, 96%) as a hygroscopic powder. mp 173—183 °C. IR (film): 3300—2200, 1640, 1560 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.41—1.61 (2H, m), 1.90—2.21 (3H, m), 2.40—2.80 (2H, m), 2.44 (3H, s), 3.37—3.50 (3H, m), 5.75 (1H, s). MS m/z: 181 (M^+).

Compounds **13b—e** were prepared by the same procedure as described for **13a**.

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-ylacetic Acid (13b)** Yield 75%. An amorphous powder. mp 140—150 °C. IR (Nujol): 3400, 2600—2000, 1650, 1565 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.28—1.35 (2H, m), 1.45—1.65 (2H, m), 2.00—2.30 (5H, m), 2.28 (3H, s), 2.50 (2H, m), 3.22 (2H, m). MS m/z: 183 (M^+).

(1-Azabicyclo[2.2.2]oct-3-ylidene)acetic Acid (13c) Yield 65%. An amorphous powder. IR (Nujol): 3300, 1650 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.40—1.80 (4H, m), 2.50—2.90 (5H, m), 2.60—2.80 (2H, m), 5.68 (1H, m).

1-Azabicyclo[2.2.2]oct-3-ylacetic Acid (13d) Yield 90%. An amorphous powder. IR (Nujol): 3300, 1650, 1550 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.50—1.90 (4H, m), 2.22—2.50 (4H, m), 2.70 (1H, dd, J=7, 13 Hz), 2.95—3.10 (4H, m), 3.35 (1H, t, J=11 Hz). MS m/z: 169 (M^+).

***endo*-9-Methyl-9-azabicyclo[3.3.1]non-3-ylacetic Acid (13e)** Yield 80%. An amorphous powder. IR (Nujol): 3250, 1570, 1450 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20—3.10 (13H, m), 2.84 (3H, s), 3.50 (2H, d, J=10 Hz), 11.95 (1H, br s). MS m/z: 197 (M^+).

1-Substituted 1*H*-pyrrolo[2,3-*b*]pyridines (**23a—d**) were prepared by a procedure similar to that described for 1-*p*-chlorobenzyl-1*H*-pyrrolo-[2,3-*b*]pyridine in the literature.[14]

1-Ethyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (24b) $POCl_3$ (2.36 g, 15.4 mmol) was added to DMF (10 ml) at 0 °C with stirring. After 10 min at room temperature, a solution of 1-ethyl-1*H*-pyrrolo[2,3-*b*]pyridine (**23b**) (2.0 g, 14 mmol) in DMF (10 ml) was added over 5 min to the above solution cooled to 0 °C. The mixture was stirred at 0 °C for 1.5 h and at 60 °C for 0.5 h, then diluted with ice and H_2O, made basic with aqueous $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried ($MgSO_4$), and evaporated *in vacuo*. The residue obtained was washed with diisopropyl ether to give **24b** (1.6 g, 66%), mp 56—58 °C. IR (film): 1670, 1640, 1595, 1565 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.57 (3H, t, J=7 Hz), 4.42 (2H, q, J=7 Hz), 7.26 (1H, dd, J=5, 8 Hz), 7.90 (1H, s), 8.43 (1H, dd, J=2, 5 Hz), 8.55 (1H, dd, J=2, 8 Hz), 9.98 (1H, s).

Compounds **24a**, **24c**, and **24d** were prepared by the same procedure as described for **24b**.

1-Methyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (24a) Yield 74%. mp 84—86 °C ($CHCl_3$–hexane). IR (Nujol): 2780, 1650, 1600, 1570, 1530 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.93 (3H, s), 7.20 (1H, m), 7.70 (1H, s), 8.30—8.60 (2H, m), 9.90 (1H, s). MS m/z: 160 (M^+).

1-Allyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (24c) Yield 62%. mp 49—53 °C. IR (film): 1670, 1590, 1565 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.90—5.40 (4H, m), 5.90—6.20 (1H, m), 7.27 (1H, dd, J=5, 7 Hz), 7.89 (1H, s), 8.43 (1H, dd, J=2, 5 Hz), 8.56 (1H, dd, J=2, 7 Hz), 9.98 (1H, s).

1-(2-Acetoxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (24d) Yield 85%. An oil. IR (film): 1735, 1660, 1595, 1575 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.04 (3H, s), 4.50 (2H, t, J=5 Hz), 4.64 (2H, t, J=5 Hz), 7.28 (1H, dd, J=5, 8 Hz), 7.92 (1H, s), 8.42 (1H, dd, J=2, 5 Hz), 8.56

(1H, dd, $J=2$, 8 Hz), 10.00 (1H, s).

1-Ethyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylic Acid (26b) A solution of $KMnO_4$ (2.52 g, 16 mmol) in H_2O (40 ml) was added dropwise to a solution of **24b** (1.4 g, 8 mmol) in acetone (50 ml) at room temperature. The mixture was stirred at room temperature for 1 h, then filtered, and the filtrate was evaporated *in vacuo*. The residue was washed with CH_2Cl_2 and neutralized with AcOH. The precipitate formed was washed with H_2O and dried to give **26b** (0.94 g, 62%), mp 209—210 °C. IR (Nujol): 1680, 1590, 1520 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.43 (3H, t, $J=7$ Hz), 4.37 (2H, q, $J=7$ Hz), 7.28 (1H, dd, $J=5$, 8 Hz), 8.30—8.40 (3H, m), 12.30 (1H, br s). MS *m/z*: 190 (M^+). Compounds **26a** and **26d** were prepared by the same procedure as described for **26b**.

1-Methyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylic Acid (26a) Yield 58%. mp >260 °C. 2500, 1665, 1595, 1530 cm^{-1}. ^{1}H-NMR (1 N NaOD in D_2O) δ: 3.60 (3H, s), 7.10 (1H, dd, $J=4$, 8 Hz), 7.65 (1H, s), 8.00 (1H, d, $J=4$ Hz), 8.30 (1H, d, $J=8$ Hz). MS *m/z*: 176 (M^+).

1-(2-Acetoxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylic Acid (26d) Yield 40%. mp 183—185 °C. IR (Nujol): 2500, 1730, 1690, 1590 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.91 (3H, s), 4.44 (2H, t, $J=5$ Hz), 4.59 (2H, t, $J=5$ Hz), 7.29 (1H, dd, $J=5$, 8 Hz), 8.30—8.40 (3H, m), 12.30 (1H, br s).

1-Allyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylic Acid (26c) A mixture of **24c** (1.3 g, 7.0 mmol), NaCN (1.36 g, 27.8 mmol), AcOH (660 mg) and MnO_2 (13 g) in MeOH (35 ml) was stirred at room temperature for 3 h. After filtration of the mixture, the filtrate was evaporated *in vacuo*. The residue was dissolved in $CHCl_3$. This solution was washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo* to give the crude methyl ester (**25**) as an oil, which was used in the next reaction without purification. The oil thus prepared (1.51 g) was dissolved in a mixture of EtOH (15 ml) and 1 N NaOH (8.7 ml). The solution was stirred at room temperature for 2 h and then at 60°C for 3 h. After evaporation of the solvent, the residue was neutralized with 1 N HCl. The precipitate formed was collected and washed with H_2O to give **26c** (1.1 g, 78%), mp 169—171 °C. IR (Nujol): 1690, 1635, 1595, 1570 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ: 4.90—5.30 (4H, m), 6.00—6.20 (1H, m), 7.20—7.40 (1H, m), 8.23 (1H, s), 8.30—8.40 (2H, m), 12.32 (1H, s). MS *m/z*: 202 (M^+).

Pharmacology von BJ Reflux 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.[15] 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 the 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.

Acknowledgement We thank the staff of the Analytical Research Laboratories for their help in the physical characterization of the compounds in this study. We also thank Dr. K. Sakane for his helpful comments and discussions.

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