New 5-HT_3 (Serotonin-3) Receptor Antagonists. I. Synthesis and Structure–Activity Relationships of Pyrido[1,2-*a*]indoles

Masayuki KATO,* Kiyotaka ITO, Shigetaka NISHINO, Hisashi YAMAKUNI, and Hisashi TAKASUGI

New Drug Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 1–6, 2-chome, Kashima, Yodogawa-ku, Osaka 532, Japan. Received June 7, 1994; accepted August 18, 1994

A series of pyrido[1,2-*a*]indol-6(7*H*)-ones was prepared and evaluated for 5-HT_3 receptor antagonist activity. The structural requirements for the 5-HT_3 receptor antagonist have been defined as an aromatic moiety, a basic nitrogen, and a linking acyl group. The (5-methylimidazol-4-yl)methyl group as a basic nitrogen moiety was an important element for high potency. The highest potency was observed for compounds which have 7- and 10-methyl substituents on the pyrido[1,2-*a*]indol-6(7*H*)-one ring. From this series, (+)-11b (FK 1052) was selected for further evaluation. FK 1052 was a potent 5-HT_3 receptor antagonist in the Bezold–Jarisch reflex test in rats (ED_{50} 0.9 μg/kg, i.v.) and a very effective antiemetic agent against cisplatin-induced emesis in dogs (ED_{50} 1.1 × 2 μg/kg, i.v. and 2.7 × 2 μg/kg, *p.o.*).

Keywords pyrido[1,2-*a*]indol-6(7*H*)-one; 5-HT_3 receptor antagonist; Bezold–Jarisch reflex; structure–activity relationship; cisplatin-induced emesis

5-Hydroxytryptamine (5-HT) receptors have been broadly grouped into four subclasses (5-HT_1, 5-HT_2, 5-HT_3, and 5-HT_4) on the basis of their pharmacological responses.[1] Because 5-HT was considered to be a neurotransmitter involved in a wide range of pharmacological effects, intensive efforts have been made toward the discovery of selective ligands for these subtypes. In particular the understanding of the 5-HT_3 receptor has been greatly improved by the discovery of selective 5-HT_3 receptor antagonists. Metoclopramide (**1**), ondansetron (GR 38032F) (**2**), tropisetron (ICS 205-930) (**3**), and granisetron (BRL 43694) (**4**) are representatives of 5-HT_3 receptor antagonists (Chart 1). 5-HT_3 receptor antagonists are effective in the control of nausea and emesis evoked by anticancer drugs such as cisplatin.[2] Ondansetron (**2**) and granisetron (**4**) have already been marketed for this indication. Moreover, 5-HT_3 receptors have been identified in the central nervous system (CNS).[3] Animal studies have suggested that 5-HT_3 receptor antagonists may be effective in the treatment of migraine, schizophrenia, anxiety, and dementia.[4]

On the basis of the structures of known ligands, several studies have been conducted to define the structural requirements of the 5-HT_3 receptor antagonists.[5] Three structural features were shown to contribute to binding to 5-HT_3 receptors: an aromatic ring, a basic nitrogen, and a linking acyl functional group. We started our studies with the aim of identifying compounds which possess more potent activity than ondansetron (**2**), because **2** is one of the compounds that have been well characterized pharmacologically and clinically.[6] In the course of our study, the pyrido[1,2-*a*]indol-6(7*H*)-one (**5**) was found to possess potent 5-HT_3 receptor antagonist activity (Chart 1). In this paper, we report the synthesis and structure–activity relationships of a series of pyrido[1,2-*a*]indol-6(7*H*)-ones having a basic heteroaromatic ring at the 7-position.

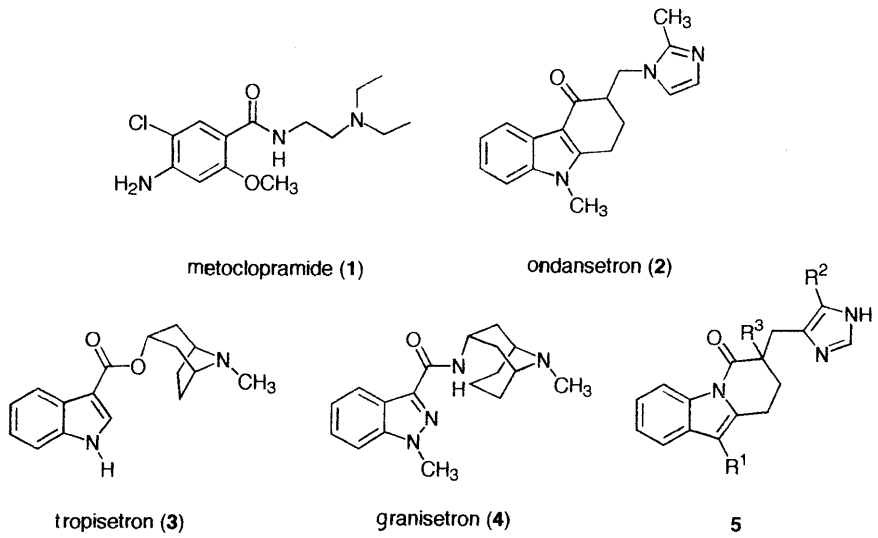
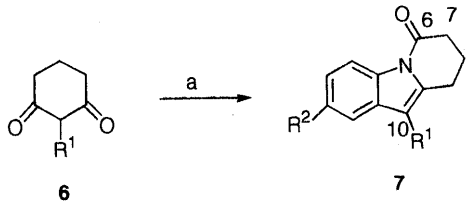


Chart 1

Chemistry

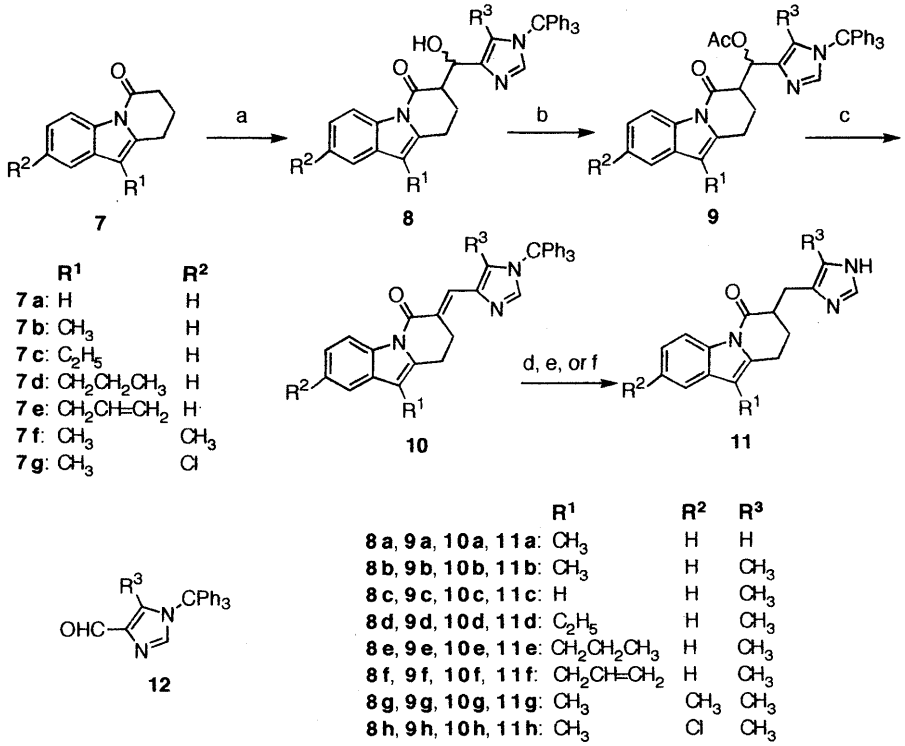
The important intermediate in this work was pyrido[1,2-*a*]indol-6(7*H*)-one (**7**), which was prepared in one step by heating a 2-substituted cyclohexane-1,3-dione (**6**) and an appropriate phenylhydrazine in a mixture of toluene and 40% aqueous H_2SO_4 (Chart 2).[7] The unsubstituted **7a** was prepared by intramolecular Wittig reaction according to the literature procedure.[8] General synthetic procedures for the (imidazol-4-yl)methyl compounds (**11**) are shown in Chart 3. The pyrido[1,2-*a*]indole (**7**) was condensed with the imidazole-4-carbaldehyde (**12**) after deprotonation with lithium diisopropylamide (LDA), giving the alcohol (**8**) as a diastereomeric mixture. Acetylation of **8** with acetic anhydride and pyridine afforded the acetate (**9**). Treatment of **9** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene provided the olefin (**10**) as a single isomer of *E*-configuration at the double bond. The stereochemistry at the double bond of **10** was inferred from the nuclear Overhauser and exchange spectroscopy (NOESY) spectrum. The compounds **11** were prepared by one of three methods. a) Refluxing a solution of **10**, ammonium formate, and palladium on carbon in acetic acid directly gave **11** (method A). b) Hydrogenation of **10** with palladium on carbon in acetic acid, followed by treatment with aqueous acetic acid at 60 °C, gave **11** (method B). c) The 10-allyl (**11f**) and 2-chloro compounds (**11h**), whose substituents were sensitive to the conditions employed above, were obtained by treatment with zinc powder in refluxing acetic acid (method C).



a) p-R^2-C_6H_4-$NHNH_2$, aq. H_2SO_4, toluene

Chart 2

Detritylation of the alcohol (**8b**) and olefin (**10b**) with aqueous acetic acid gave diastereomers of the alcohol (**13a, b**) and the olefin (**14**), respectively (Chart 4). The stereochemistry of the hydroxy group of **13** was not determined. The 1- and 3-methylimidazoles (**15a—d**) were prepared by methylation of **11a** and **11b** with methyl iodide and sodium hydride, followed by separation of the isomers. The position of methylation was assumed on the basis of nuclear Overhauser effects (NOE) in the NOESY spectrum. In compound **15c** with a high *Rf* value on thin layer chromatography (TLC), NOE was observed between the new methyl resonance (δ 3.50) and the resonance of the methyl hydrogen at the 5-position of the imidazole (δ 2.13). But no NOE was observed in **15d** with a low *Rf* value on TLC. These data suggested that the new methyl substituent of **15c** was located at the N1-position of the imidazole and that of **15d** at N3. The structures of **15a** and **15b** were also confirmed by examination of NOE in the NOESY spectrum. The synthesis of the (imidazol-1-yl)methyl compound (**18**) is outlined in Chart 5. Compound **7b** was



	R^1	R^2
7a:	H	H
7b:	CH_3	H
7c:	C_2H_5	H
7d:	$CH_2CH_2CH_3$	H
7e:	$CH_2CH{=}CH_2$	H
7f:	CH_3	CH_3
7g:	CH_3	Cl

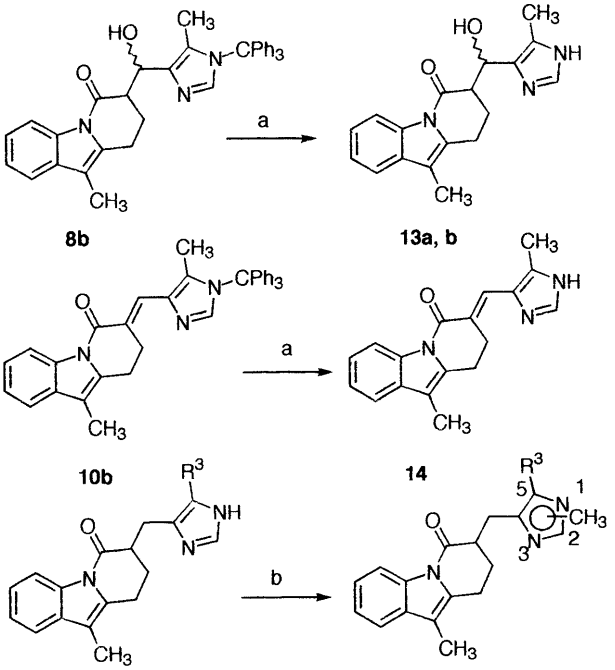
	R^1	R^2	R^3
8a, 9a, 10a, 11a:	CH_3	H	H
8b, 9b, 10b, 11b:	CH_3	H	CH_3
8c, 9c, 10c, 11c:	H	H	CH_3
8d, 9d, 10d, 11d:	C_2H_5	H	CH_3
8e, 9e, 10e, 11e:	$CH_2CH_2CH_3$	H	CH_3
8f, 9f, 10f, 11f:	$CH_2CH{=}CH_2$	H	CH_3
8g, 9g, 10g, 11g:	CH_3	CH_3	CH_3
8h, 9h, 10h, 11h:	CH_3	Cl	CH_3

a) LDA, **12**, THF; b) Ac_2O, Py; c) DBU, toluene; d) 10% Pd–C, $HCOONH_4$, AcOH (method A); e) i: 10% Pd–C, AcOH; ii: aq. AcOH (method B); f) Zn, AcOH (method C)

Chart 3

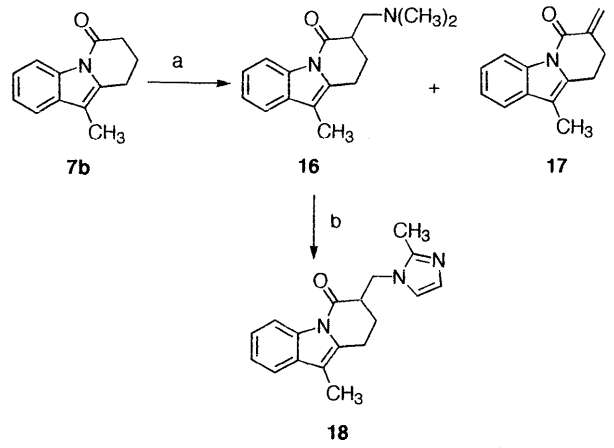
treated with LDA and then *N*,*N*-dimethylmethyleneammonium iodide (Eschenmoser's salt) to give the dimethylaminomethyl compound (**16**) and a small amount of the 7-methylene compound (**17**). Compound **16** was heated with a mixture of 2-methylimidazole, 2-propanol, and 2 N hydrochloric acid to give **18**. The 7-substituted compounds (**21**) were prepared from the trityl compound (**19**) as illustrated in Chart 6. Treatment of **19** with LDA and subsequent reaction with alkyl halides, allyl bromide, or paraformaldehyde afforded **20**. The trityl group of **20** was removed with aqueous acetic acid to give **21**. The 7-propyl compound (**21d**) was obtained by hydrogenation of the 7-allyl compound (**21e**) with palladium on carbon in acetic acid and methanol. The (pyridin-3-yl)methyl compounds (**25a, b**) were prepared by a similar route to that used for the imidazole derivatives (**11**) (Chart 7). Synthesis of the spiro compound (**27**) is shown in Chart 8. The hydroxymethyl compound (**20c**) was treated with thionyl chloride in dichloromethane to give a polar product, which was assumed to be the cyclized quarternary salt (**26**). Compound **27** was obtained by removal of the trityl group of **26** with aqueous acetic acid.

Optical isomers of **11b** were prepared by fractional crystallization of the salt of **11b** and di-*p*-toluoyltartaric acid in a mixture of chloroform and methanol. (+)-Di-*p*-toluoyl-D-tartaric acid gave (+)-**11b** after neutralization of the salt and conversion to the hydrochloride salt. Similar treatment with (−)-di-*p*-toluoyl-L-tartaric acid gave (−)-**11b**. Racemic **21a** could not be resolved by fractional crystallization of the diastereomeric salt with various chiral acids. Therefore we attempted a new route for the synthesis of optically active **21a** (Chart 9). The lactam ring of **20a** was hydrolyzed by heating with aqueous sodium hydroxide to give the acid (**28**). Compound **28** was converted to the diastereomeric (*S*)-pyrrolidinemethanol derivative (**29**) by a mixed anhydride method (ethyl chloroformate and (*S*)-pyrrolidinemethanol). Diastereomers of **29** were separat-



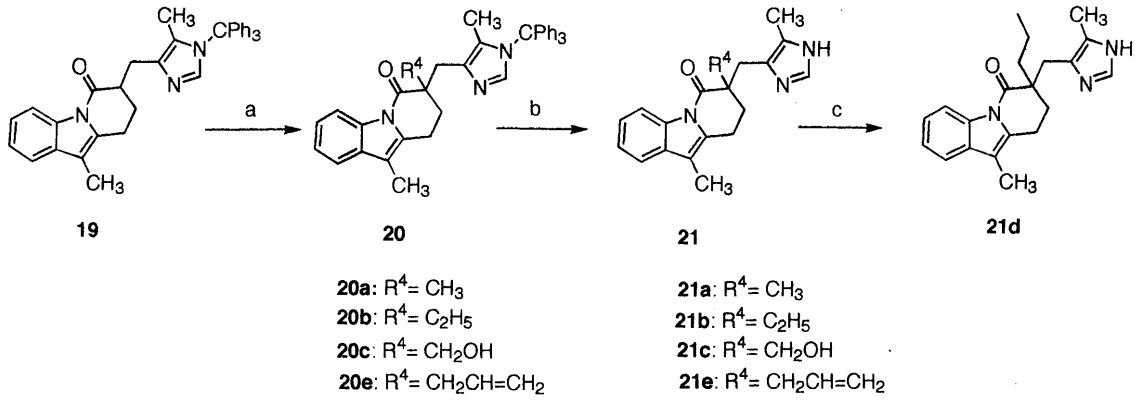
a) aq. AcOH; b) NaH, CH_3I, DMF

Chart 4



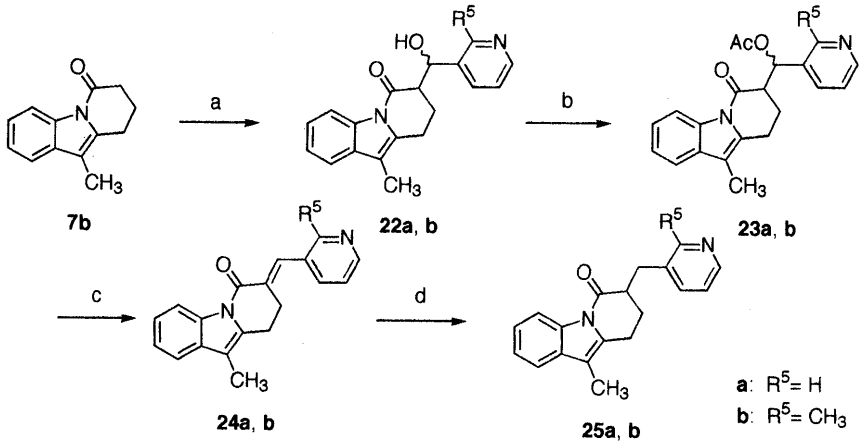
a) LDA, $CH_2{=}N^+(CH_3)_2{\cdot}I^-$, THF; b) 2-methylimidazole, iso-PrOH, 2 N HCl

Chart 5



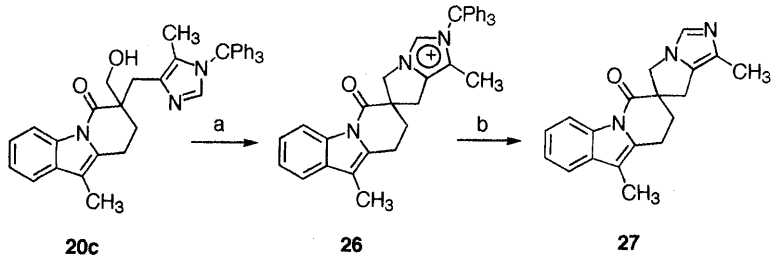
a) LDA, R^4X or $(HCHO)_n$, THF; b) aq. AcOH; c) **21e**, 10% Pd–C, AcOH, MeOH

Chart 6



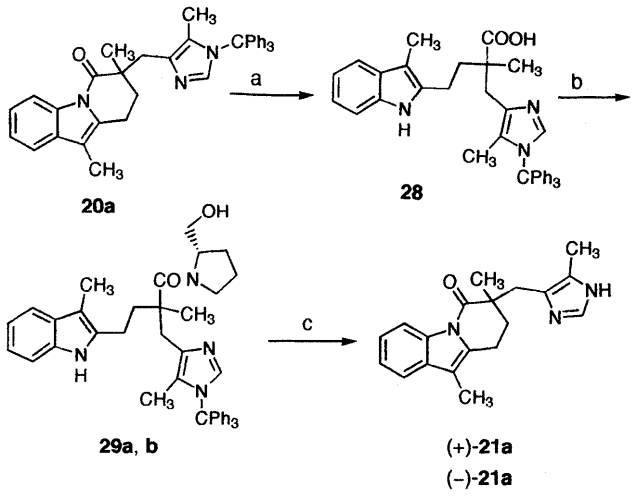
a) LDA, 3-Py-CHO, THF; b) Ac_2O, Py; c) DBU, toluene; d) 10% Pd–C, $HCOONH_4$, AcOH

Chart 7



a) $SOCl_2$, CH_2Cl_2; b) aq. AcOH

Chart 8



a) aq. NaOH; b) i: ClCOOEt, *N*-methylmorpholine, THF, (*S*)-prolinol; ii: silica gel chromatography; c) 3 N HCl, toluene

Chart 9

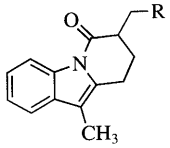
ed by column chromatography on silica gel. Refluxing a solution of each isomer of **29** in a mixture of 3 N hydrochloric acid and toluene caused cyclization and detritylation simultaneously to afford (+)-**21a** or (−)-**21a** in one step. One isomer of **29** with the higher *Rf* value gave (−)-**21a** and the other one with the lower *Rf* value gave (+)-**21a**.

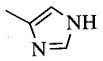
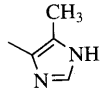
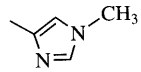
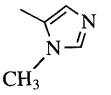
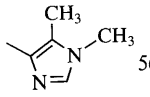
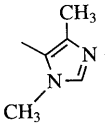
Biological Results and Discussion

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 urethan-anesthetized rats. 2-Me-5-HT was reported to be a selective 5-HT_3 receptor agonist.[9] The 5-HT-induced activation of the BJ reflex is mediated *via* the 5-HT receptors in the right ventricle.[10] Test results are listed in Tables I and II together with the data for ondansetron (**2**) as the reference compound.

We first attempted to optimize the basic heteroaromatic ring in the 7-position of the pyrido[1,2-*a*]indole ring (Table I). Similar activity was observed with compounds **18** and **2**, whose side chains are the same, *i.e.*, the (2-methylimidazol-1-yl)methyl group (ED_{50} 29.2 and 17.5 μg/kg i.v., respectively). On the other hand, the imidazol-4-yl compound (**11a**) showed a remarkable increase in potency. Replacement of the imidazole ring with a pyridine yielded compounds of reduced activity (**25a, b**). The significant increase in potency of **11a**, compared with **18**, might reflect the importance of a hydrogen atom on the imidazole ring nitrogen. Because of the high potency of **11a**, the (imidazol-4-yl)methyl group at the 7-position was retained and a methyl group was introduced into the imidazole ring to examine the structure–activity relationships on the imidazole ring (Table I). The methyl group at the 5-position slightly increased the potency (**11a** *vs.* **11b**). Methylation at the nitrogens on the imidazole ring retained

TABLE I. Inhibition of Bezold–Jarisch Reflex: Effect of Modification of the Heteroaromatic Ring in Pyrido[1,2-*a*]indoles[a]



Compd. No.	R	% 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	
18		70.5	62.4	23.5	−6.5		29.2
25a		54.1			−23.1		
25b		50.1			−15.2		
11a		81.1		59.9	58.4	44.3	1.4
11b		66.9		67.9		64.2	
15a		18.0			−53.4		
15b		53.0			25.4		
15c		56.6		62.5	35.3	6.3	18.7
15d		67.3		55.4	43.0	0.3	7.9
2 (ondansetron)		79.5	72.1	43.3			17.5

a) All compounds tested were racemates. *b*) Each compound was tested in groups of three animals and data represent mean values of peak inhibition.

TABLE II. Inhibition of Bezold–Jarisch Reflex: Effect of Modifications of Pyrido[1,2-*a*]indole and Methylene Side Chain

Compd.[a] No.	% inhibition of 2-Me-5-HT-induced bradycardia (μg/kg i.v.)[d]					ED_{50} (μg/kg i.v.)
	100	10	3.2	1.0	0.32	
11c	62.6	65.8	50.1	47.1		1.4
11b	66.9	67.9		64.2		
11d			75.4	32.5	11.3	1.5
11e	32.5					
11f		76.1	70.4	50.0	25.0	1.2
11g	20.6		6.0			
11h	43.5		9.3			
21a			62.8	47.1	44.5	1.1
21b	58.8		25.0			
21c			67.5	27.6	−1.9	1.9
21d	67.8		−20.9			
21e	59.2		−43.8			
13a[b]	62.7					
13b[c]	75.4	69.7	51.8	12.0		5.9
14	64.1	26.5	−5.4			22.2
27	70.9	62.6	26.6			12.4
2 (ondansetron)	79.5	43.3				17.5

a) Compounds were tested as racemates when a chiral center was present in the molecule. *b*) One isomer with the high *Rf* value on silica gel TLC. *c*) The other isomer with the low *Rf* value. *d*) See footnote *b*) in Table I.

TABLE III. Inhibition of Bezold–Jarisch Reflex and Antiemetic Activity of Optically Active **11b** and **21a**

Compd. No.	Inhibition of BJ reflex ED_{50}, (μg/kg i.v.)	Inhibition of cisplatin induced emesis in dogs[a] ED_{50}, (μg/kg i.v.)		% inhibition 100 μg/kg i.v. 4 h before cisplatin
		i.v. (×2)	*p.o.* (×2)	
(+)-**11b**	0.9	1.1	2.7	65.1
(−)-**11b**	6.3	9.7	34.1	
(+)-**21a**	0.8	0.8	3.4	97.3
(−)-**21a**	−22.5[b]	>100		
Ondansetron	17.5	12.6	30.6	

a) Test compounds were given as a divided dose 10 min before and 90 min after cisplatin. *b*) % inhibition at 3.2 μg/kg.

considerable activity in the case of the 5-methyl derivatives (**15c, d**), whereas in the 5-unsubstituted compounds (**15a, b**) methylation at the nitrogens resulted in reduction in potency. This result confirmed the beneficial effect of the 5-methyl substituent. The decrease in potency by methylation on the nitrogens could be attributed to an unfavorable steric interaction with the receptor, rendering the active conformation disfavored. The potency order of 1- and 3-methylated compounds (**15b** > **15a**, **15d** > **15c**) suggested that the nitrogen at the 1-position interacted with the receptor, because a methyl group at the 1-position caused a greater decrease in potency than a 3-methyl substituent did.

Next, the methyl group at the 10-position of the most active **11b** was systematically varied (Table II). The hydrogen (**11c**), methyl (**11b**), ethyl (**11d**), and allyl (**11f**) compounds were all potent 5-HT_3 receptor antagonists, but the increased steric demand of the propyl group (**11e**) reduced the potency. The most potent compound in this series is the 10-methyl compound (**11b**), which suggests that lipophilic interactions at the 10-position with the receptor may play some role in increasing activity, although there is no bulk tolerance at the 10-position. Substitution in the benzene ring with methyl (**11g**) and chloro (**11h**) resulted in a marked reduction in potency. Further modification of the benzene ring was not attempted.

Several substituents were incorporated into the 7-position of **11b** (Table II). The methyl (**21a**) and hydroxymethyl (**21c**) compounds retained high potency, but the ethyl (**21b**), propyl (**21d**), and allyl (**21e**) compounds showed considerably decreased potency. This lack of steric tolerance at the 7-position might reflect the interaction of the carbonyl group at the 6-position with the receptor, such as hydrogen bonding, which would be interfered with by the presence of a large substituent at the 7-position. Modification of the methylene part at the 7-position of **11b** resulted in some loss of activity compared with

11b (**13b**, **14**). Finally, in order to identify the active conformation of the most potent compound **11b**, we prepared the spiro compound (**27**). Compound **27**, however, can be regarded as a conformationally restricted analogue of **18** rather than **11b**, because **27** and **18** do not have a hydrogen atom on the imidazole nitrogen but **11b** does. Because **27** has no rotatable bond, unlike other representative 5-HT_3 receptor antagonists, **27** was expected to possess higher potency than **11b** or **18** if the constrained conformation of **27** matched the active conformation. Indeed, compound **27** retained considerable potency, being more potent than ondansetron (**2**) and **18** and less active than **11b**. This result suggests that the active conformation of **11b** and **18** is similar to that of **27**, that is, the nitrogen at the 1-position of the imidazole ring of **11b** is in the same plane as the pyrido[1,2-*a*]indole ring or only slightly derviates from coplanarity, because the nitrogen at the 1-position of **27** was assumed to be in the plane of the pyrido[1,2-*a*]indole ring and the imidazole ring of **27** is placed perpendicular to the plane of the aromatic ring. Further support for this conclusion comes from the olefin compound (**14**). Compound **14** has a single rotatable bond and the rotation of the imidazole ring is restricted by conjugation with the *exo*-methylene double bond, whereby the nitrogen at the 1-position is supposed to be coplanar with the aromatic ring. Activity was still retained in compound **14**, though it was less active than **27** (EC_{50} 22.2 and 12.4 μg/kg, i.v., respectively), suggesting that the aromatic ring and the nitrogen at the 1-position of the imidazole ring are approaching coplanarity in the active conformation.

Optimal activity was observed for compounds **11b** and **21a**, both of which were selected for further evaluation. The potencies of enantiomers of **11b** and **21a** were assessed by means of the BJ reflex assay in rats and by measuring antiemetic activity against cisplatin-induced emesis in dogs (Table III). In the BJ reflex assay, the ED_{50} values of (+)-**11b**, (−)-**11b**, (+)-**21a**, and (−)-**21a** were 0.9, 6.3, 0.8, and >3.2 μg/kg respectively, showing that the (+)-isomer is the more active enantiomer in this series. Both (+)-isomers were approximately 20-fold more active than ondansetron (**2**). Both (+)-**11b** and (+)-**21a** were very potent in reducing emetic episodes produced by cisplatin in dogs following either intravenous or oral administration. After i.v. administration, the ED_{50} values of (+)-**11b**, (+)-**21a**, and ondansetron (**2**) were 1.1, 0.8, and 12.6 μg/kg, respectively. Following oral administration, the ED_{50} values of (+)-**11b** (+)-**21a**, and ondansetron (**2**) were 2.7, 3.4, and 30.6 μg/kg, respectively. A comparison of the *p.o.*/i.v. ratios of ED_{50} values of these compounds showed that (+)-**11b** (2.5) is well absorbed orally compared to (+)-**21a** (4.3). Finally, the duration of action after oral administration was investigated. Following pretreatment with 100 μg/kg i.v. at 4 h before cisplatin administration, (+)-**21a** and (+)-**11b** showed 97% and 65% inhibition, respectively. Of these two compounds, **11b** was selected for further pharmacological evaluation. Recently, several studies have suggested that 5-HT_3 receptor antagonists are effective in the treatment of gastrointestinal dysfunction, such as irritable bowel syndrome (IBS).[11] Compound **11b** (FK 1052) is currently undergoing clinical trials for the treatment of IBS.

We have described here the synthesis and structure–activity studies of the pyrido[1,2-*a*]indoles that led to the discovery of **11b** (FK 1052), a potent 5-HT_3 receptor antagonist. Pharmacological details have been reported elsewhere.[12]

Experimental

Melting points are uncorrected. ^{1}H-NMR spectra were recorded on a Varian EM-390 spectrometer (90 MHz) and a Bruker AC-200p (200 MHz) 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. Optical rotations were measured on a JASCO DIP-360 polarimeter. Column chromatography on silica gel was performed with Kiesel gel 60 (E. Merck, No. 7734).

The following 8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-ones (**7**) were prepared according to the procedures described in the literature: 8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one (**7a**),[8] 8,9-dihydro-10-methylpyrido[1,2-*a*]indol-6(7*H*)-one (**7b**),[7] 8,9-dihydro-10-ethylpyrido[1,2-*a*]indol-6(7*H*)-one (**7c**),[13] 8,9-dihydro-10-propylpyrido[1,2-*a*]indol-6(7*H*)-one (**7d**),[13] and 10-allyl-8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one (**7e**).[13] 5-Methyl-1-(triphenylmethyl)-1*H*-imidazole-4-carbaldehyde and 1-(triphenylmethyl)-1*H*-imidazole-4-carbaldehyde were prepared by the literature method.[14]

Preparation of 8,9-Dihydro-10-substituted-pyrido[1,2-*a*]indol-6(7*H*)-one (7) According to the conditions of the literature,[7] the following pyrido[1,2-*a*]indoles (**7**) were prepared from the corresponding cyclohexane-1,3-dione (**6**) and phenylhydrazines.

8,9-Dihydro-2,10-dimethylpyrido[1,2-*a*]indol-6(7*H*)-one (7f) Yield 52%, mp 106—109 °C (MeOH). IR (Nujol): 1705, 1675, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.06 (2H, m), 2.15 (3H, s), 2.45 (3H, s), 2.74 (2H, t, J=6 Hz), 2.88 (2H, t, J=6 Hz), 7.10 (1H, d, J=9 Hz), 7.20 (1H, s), 8.29 (1H, d, J=9 Hz). *Anal.* Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 79.02; H, 7.19; N, 6.61.

2-Chloro-8,9-dihydro-10-methylpyrido[1,2-*a*]indol-6(7*H*)-one (7g) Yield 50%, mp 102—103 °C (MeOH). IR (Nujol): 1690, 1675, 1625 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.08 (2H, m), 2.12 (3H, s), 2.75 (2H, t, J=6 Hz), 2.88 (2H, t, J=6 Hz), 7.21 (1H, dd, J=2, 9 Hz), 7.35 (1H, d, J=2 Hz), 8.32 (1H, d, J=9 Hz). *Anal.* Calcd for $C_{13}H_{12}ClNO$: C, 66.81; H, 5.18; N, 5.99. Found: C, 66.51; H, 5.16; N, 5.97.

8,9-Dihydro-7-[(hydroxy)[5-methyl-1-(triphenylmethyl)-1*H*-imidazol-4-yl]methyl]-10-methylpyrido[1,2-*a*]indol-6(7*H*)-one (8b) A solution of 8,9-dihydro-10-methylpyrido[1,2-*a*]indol-6(7*H*)-one (**7b**) (3.39 g, 17 mmol) in tetrahydrofuran (THF) (39 ml) was added over 15 min to a stirred solution of LDA (19 mmol, prepared from 1.89 g of diisopropylamine and 11.5 ml of 1.64 M *n*-butyllithium in hexane) in THF (30 ml) at −70 °C under nitrogen. The mixture was stirred at −70 °C for 30 min, and a solution of 5-methyl-1-(triphenylmethyl)-1*H*-imidazole-4-carbaldehyde[14] (6.0 g, 17 mmol) in THF (75 ml) was added dropwise over 20 min. After 1 h at −70 °C, the 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 chromatography on silica gel (1% MeOH–CH_2Cl_2) to give **8b** (5.1 g, 54%) as a mixture of two diastereomers, an amorphous powder. MS *m/z*: 552 (M^+). Compounds **8** and **22** were prepared similarly. ^{1}H-NMR and IR spectral data for **8** and **22** and yields obtained are listed in Table IV.

7-[(Acetoxy)[5-methyl-1-(triphenylmethyl)-1*H*-imidazol-4-yl]methyl]-8,9-dihydro-10-methylpyrido[1,2-*a*]indol-6(7*H*)-one (9b) A solution of **8b** (4.0 g, 7.3 mmol) and acetic anhydride (5 ml) in pyridine (50 ml) was stirred at room temperature for 20 h. After evaporation of the solvent, the residue was chromatographed on silica gel (1% MeOH–CH_2Cl_2) to give **9b** (4.3 g, 100%) as a mixture of two diastereomers, an amorphous powder. IR (Nujol): 1730, 1685, 1625, 1235 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.40 and 1.46 (3H, each s), 1.93 and 2.00 (3H, each s), 2.13 (3H, s), 1.90—2.30 (2H, m), 2.70—3.50 (3H, m), 6.63 (1H, d, J=6 Hz), 6.90—7.50 (19H, m), 8.20 (1H, m). MS *m/z*: 598 (M^+). Compounds **9** and **23** prepared similarly were used in the next reaction without purification.

8,9-Dihydro-10-methyl-7-[[5-methyl-1-(triphenylmethyl)-1*H*-imidazol-4-yl]methylene]pyrid[1,2-*a*]indol-6(7*H*)-one (10b) A solution of **9b** (4.3 g, 7.3 mmol) and DBU (5 ml) in toluene (60 ml) was stirred at 55 °C

TABLE IV. 8,9-Dihydro-7-[(hydroxy)[1-(triphenylmethyl)-1*H*-imidazol-4-yl]methyl]pyrido[1,2-*a*]indol-6(7*H*)-one (**8**) and 8,9-Dihydro-7-[(hydroxy)(pyridin-3-yl)methyl]pyrido[1,2-*a*]indol-6(7*H*)-one (**22**)

Compd. No.	Yield[a] (%)	IR ν_{max}^{Nujol} cm^{-1}	^{1}H-NMR δ, ppm
8a	73	1710, 1685, 1660	($CDCl_3$) 1.40—2.00 (2H, m), 2.07 (3H, s), 2.40—3.30 (3H, m), 3.51 (0.5H, m), 4.60 (0.5H, m), 5.20 (0.5H, m), 5.53 (0.5H, m), 6.70 (1H, s), 6.90—7.40 (20H, m), 8.30 (1H, m)
8b	54	1680, 1620	(DMSO-d_6) 1.40 (3H, s), 2.00—2.20 (2H, m), 2.10 (3H, s), 2.50—3.30 (3H, m), 5.10 (1H, m), 5.33 (1H, m), 6.90—7.50 (19H, m), 8.20 (1H, m)
8c	63	1690, 1590	($CDCl_3$) 1.46 (3H, s), 1.60—2.40 (2H, m), 2.80—3.50 (3H, m), 4.80—5.20 (1H, m), 6.29 (1H, s), 7.00—7.40 (19H, m), 8.30—8.50 (1H, m)
8d	80	1685, 1615	(DMSO-d_6) 1.15 (3H, m), 1.44 (3H, s), 2.15 (2H, m), 2.61—3.25 (5H, m), 5.14—5.45 (2H, m), 6.95—7.54 (19H, m), 8.35 (1H, m)
8e	85	1705, 1610	(DMSO-d_6) 0.87 (3H, t, J=7 Hz), 1.44 (3H, s), 1.57 (2H, m), 2.16 (2H, m), 2.55—3.30 (5H, m), 5.16—5.46 (2H, m), 6.96—7.54 (19H, m), 8.32 (1H, m)
8f	95	1685, 1615	(DMSO-d_6) 1.43 (3H, s), 2.16 (2H, m), 2.80–3.40 (5H, m), 4.96—5.44 (4H, m), 5.83—5.99 (1H, m), 6.95—7.53 (19H, m), 8.35 (1H, m)
8g	74	1680, 1620	($CDCl_3$) 1.48 (3H, s), 1.60—2.00 (2H, m), 2.13 (3H, s), 2.45 (3H, s), 2.60—3.40 (4H, m), 5.09 (0.8H, d, J=8 Hz), 5.25 (0.2H, d, J=6 Hz), 7.00—7.40 (18H, m), 8.26 (1H, d, J=8 Hz)
8h	45	1675, 1615, 1590	($CDCl_3$) 1.48 (3H, s), 1.60—2.00 (2H, m), 2.11 (3H, s), 2.60—3.40 (3H, m), 5.13 (0.7H, d, J=8 Hz), 5.27 (0.3H, d, J=7 Hz), 7.00—7.40 (18H, m), 8.29 (1H, d, J=9 Hz)
22a	47	1685, 1615	(DMSO-d_6) 1.60—2.10 (2H, m), 2.14 (3H, m), 2.50—3.10 (3H, m), 3.76 (0.5H, s), 5.10 (0.5H, d, J=9 Hz), 5.44 (0.5H, s), 5.80 (0.5H, s), 7.20—7.40 (4H, m), 7.70—7.90 (1H, m), 8.40—8.70 (3H, m)
22b	13	1690, 1610	(DMSO-d_6) 2.15 (3H, s), 2.23 (2H, t, J=6 Hz), 2.85 (3H, s), 2.70—3.00 (1H, m), 3.10—3.40 (2H, m), 5.30 (1H, d, J=2 Hz), 7.10—7.50 (3H, m), 7.94 (1H, dd, J=6, 7 Hz), 8.10—8.30 (1H, m), 8.60—8.80 (2H, m)

a) Compounds except **22b** were amorphous. **22b** was isolated as the hydrochloride, mp 232—233 °C (EtOAc–$CHCl_3$–ether). *Anal.* Calcd for $C_{20}H_{20}N_2O_2 \cdot HCl \cdot 0.2H_2O$: C, 66.66; H, 5.98; N, 7.77. Found: C, 66.68; H, 6.04; N, 7.83.

TABLE V. 8,9-Dihydro-7-[[1-(triphenylmethyl)-1*H*-imidazol-4-yl]-methylene]pyrido[1,2-*a*]indol-6(7*H*)-ones (**10**)

Compd. No.	Yield (%)	mp (°C)[a] (Recryst. solvent)	Formula	Analysis (%) Calcd (Found)		
				C	H	N
10a	92	179—181 (C–M)	$C_{36}H_{29}N_3O \cdot 0.25H_2O$	82.49 (82.60)	5.67 5.49	8.02 8.04)
10b	93	223—226 (T–H)	$C_{37}H_{31}N_3O$	83.27 (83.12)	5.85 5.88	7.87 7.79)
10c	94	165—170 (M–B)	$C_{36}H_{29}N_3O \cdot 0.25H_2O$	82.49 (82.68)	5.67 5.71	8.02 8.07)
10d	22	220—222 (M–C)	$C_{38}H_{33}N_3O \cdot 0.8CHCl_3$	72.45 (72.33)	5.30 5.18	6.53 6.50)
10e	83	180—185 (D–H)	$C_{39}H_{35}N_3O \cdot 0.5H_2O$	82.16 (82.25)	6.35 6.78	7.36 6.96)
10f	79	211—214 (M–B)	$C_{39}H_{33}N_3O$	83.68 (83.71)	5.94 6.03	7.51 7.54)
10g	77	234—238 (T–H)	$C_{38}H_{33}N_3O$	83.33 (83.50)	6.07 6.28	7.67 7.48)
10h	88	224—227 (I)	$C_{37}H_{30}ClN_3O \cdot 0.25H_2O$	77.61 (77.68)	5.37 5.40	7.34 7.21)

a) The symbols are as follows; A, ethyl acetate; B, dichloromethane; C, chloroform; D, diethyl ether; H, hexane; I, isopropyl ether; M, methanol; T, toluene.

for 6 h. The solution was washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. Purification of the oil by column chromatography on silica gel (0.5% MeOH–CH_2Cl_2) gave **10b** (3.6 g, 93%) as an amorphous powder. Crystallization from toluene–hexane gave an analytical sample, mp 223—226 °C. IR (Nujol): 1657, 1625, 1610 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.60 (3H, s), 2.17 (3H, s), 2.93 (2H, m), 3.60 (2H, m), 6.90—7.70 (20H, m), 8.40 (1H, m). Compounds **10** were prepared similarly. Their physical data are given in Table V.

10-Ethyl-8,9-dihydro-7-[(5-methyl-1*H*-imidazol-4-yl)methyl]pyrido-[1,2-*a*]indol-6(7*H*)-one Hydrochloride (11d) (Method A) A mixture of **10d** (1.0 g, 1.8 mmol), 10% Pd–C (0.25 g), and ammonium formate (0.5 g) in AcOH (14 ml) was heated at 90 °C for 2 h. The reaction mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was partitioned between 0.5 N HCl and toluene. The aqueous layer was made basic with aqueous $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo* to give crystals. This product was converted to the hydrochloride (**11d**) (273 mg, 44%) by treatment with HCl in MeOH followed by recrystallization from MeOH and ether, mp >260 °C. IR (Nujol): 1702, 1640, 1625 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.16 (3H, t, J=7 Hz), 1.70—2.10 (2H, m), 2.26 (3H, s), 2.63 (2H, q, J=7 Hz), 2.60—3.40 (5H, m), 7.27 (2H, m), 7.54 (1H, m), 8.33 (1H, m), 8.96 (1H, s), 14.46 (2H, br s).

8,9-Dihydro-10-methyl-7-[(5-methyl-1*H*-imidazol-4-yl)methyl]pyrido-[1,2-*a*]indol-6(7*H*)-one Hydrochloride (11b) (Method B) A mixture of **10b** (2.0 g, 3.8 mmol) and 10% Pd–C (0.4 g) in *N*,*N*-dimethylformamide (DMF)–EtOH (6 : 1, 49 ml) was hydrogenated at atmospheric pressure for 6 h. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo* to give an oil. A solution of the oil in AcOH–H_2O (10 : 3, 65 ml) was stirred at 45 °C for 2 h. After evaporation of the solvent, the residue was diluted with aqueous $NaHCO_3$ 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 (10% MeOH–CH_2Cl_2) to give crystals (1.0 g). This product was converted to the hydrochloride salt **11b** (1.1 g, 85%) by treatment with HCl in EtOH, followed by recrystallization from H_2O–EtOH, mp >250 °C. IR (Nujol): 1695, 1635, 1520 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.66—2.10 (2H, m), 2.13 (3H, s), 2.23 (3H, s), 2.60—3.40 (5H, m), 7.27 (2H, m), 7.43 (1H, m), 8.23 (1H, m), 8.90 (1H, s).

2-Chloro-8,9-dihydro-10-methyl-7-[(5-methyl-1*H*-imidazol-4-yl)-methyl]pyrido[1,2-*a*]indol-6(7*H*)-one (11h) (Method C) A mixture of **10h** (0.95 g, 1.7 mmol) and Zn powder (1.09 g) in AcOH (48 ml) was refluxed for 2.5 h. The precipitate was filtered off, and the filtrate was evaporated *in vacuo*. The residue was partitioned between $CHCl_3$ and aqueous $NaHCO_3$. The $CHCl_3$ layer was washed with H_2O and brine, dried (Na_2SO_4), and evaporated *in vacuo*. Chromatography of the residue (silica gel, 3% MeOH–$CHCl_3$) followed by trituration with isopropyl ether gave **11h** (0.50 g, 91%), mp 244—246 °C. IR (Nujol): 1683, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.70—2.10 (2H, m), 2.10 (3H, s), 2.12 (3H, s), 2.60—3.50 (5H, m), 7.28 (1H, dd, J=2, 9 Hz), 7.41 (1H, s), 7.55 (1H, d, J=2 Hz), 8.30 (1H, d, J=9 Hz), 11.60 (1H, br s).

8,9-Dihydro-7-[(hydroxy)(5-methyl-1*H*-imidazol-4-yl)methyl]-10-methylpyrido[1,2-*a*]indol-6(7*H*)-one Maleate (13a, b) Two diastereomers of **8b** prepared from 2 mmol of 8,9-dihydro-10-methylpyrido[1,2-*a*]indol-6(7*H*)-one (**7b**) were separated by column chromatography on silica gel (0.8% MeOH–CH_2Cl_2) to give two fractions. The first-eluted fraction, being a mixture of two products, was crystallized from $CHCl_3$–AcOEt–hexane to give one isomer of **8b** with a high *Rf* value (3.8 g). The second-eluted fraction and the filtrate of the first-eluted one were

TABLE VI. Physical Data for Compounds Listed in Tables I, II, and III

Compd. No.	Method	Yield (%)	mp (°C)[a] (Recryst. solvent)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
11a	B	93	156—157 (I–D)	$C_{17}H_{17}N_3O \cdot 0.75H_2O$	69.72	6.37	14.35	69.31	5.97	14.13
11b	B	85	>250 (W–E)	$C_{18}H_{19}N_3O \cdot HCl$	65.55	6.11	12.74	65.75	6.19	12.78
11c	A	29	262—264 (C–A)	$C_{17}H_{17}N_3O \cdot HCl$	64.65	5.43	13.31	64.44	5.75	13.12
11d	A	44	>260 (M–D)	$C_{19}H_{21}N_3O \cdot HCl \cdot 0.1H_2O$	66.02	6.47	12.16	65.95	6.33	12.05
11e	B	63	193—199 (M–D)	$C_{20}H_{23}N_3O \cdot HCl \cdot H_2O$	63.90	6.97	11.18	63.53	6.44	11.13
11f	C	50	208—216 (M–D)	$C_{20}H_{21}N_3O \cdot HCl \cdot 0.1H_2O$	67.16	6.28	11.75	67.08	6.14	11.72
11g	A	80	255—258 (E)	$C_{19}H_{21}N_3O \cdot 0.25H_2O$	73.17	6.95	13.47	73.25	6.79	13.40
11h	C	91	244—246 (I)	$C_{18}H_{18}ClN_3O \cdot 0.1H_2O$	65.59	5.57	12.75	65.52	5.45	12.66
13a		65	189—190 (M–D)	$C_{18}H_{19}N_3O_2 \cdot C_4H_4O_4$[b] $\cdot 0.2H_2O$	61.59	5.50	9.79	61.85	5.91	9.78
13b		65	155—161 (M–D)	$C_{18}H_{19}N_3O_2 \cdot C_4H_4O_4$[b] $\cdot 0.2H_2O$	61.59	5.50	9.79	61.81	5.68	9.80
14		84	252—255 (C–M–H)	$C_{18}H_{17}N_3O \cdot 0.2H_2O$	73.30	5.94	14.24	73.41	6.13	14.25
15a		27	99—100 (A–D)	$C_{18}H_{19}N_3O \cdot 0.5H_2O$	71.50	6.67	13.90	71.49	6.77	13.92
15b		2	117—118 (C–H)	$C_{18}H_{19}N_3O \cdot 0.25H_2O$	72.72	6.61	14.14	72.84	6.45	13.99
15c		35	180—182 (A–H)	$C_{19}H_{21}N_3O$	74.24	6.89	13.67	74.22	7.14	13.67
15d		7	193—194 (A–H)	$C_{19}H_{21}N_3O \cdot 0.2H_2O$	73.37	6.94	13.51	73.46	6.92	13.51
18		54	120—121 (A–H)	$C_{18}H_{19}N_3O$	73.70	6.53	14.32	73.49	6.58	14.21
21a		46	163—164 (A–D)	$C_{19}H_{21}N_3O \cdot 0.25H_2O$	73.17	6.95	13.47	73.32	6.94	13.25
21b		79	202—204 (D–I)	$C_{20}H_{23}N_3O \cdot 0.25H_2O$	73.70	7.27	12.89	73.84	7.25	12.58
21c		46	245—260 (A–D)	$C_{19}H_{21}N_3O_2 \cdot HCl \cdot 0.5H_2O$	61.89	6.28	11.39	61.94	6.22	11.36
21d		75	>270 (W)	$C_{21}H_{25}N_3O \cdot HCl \cdot 0.1H_2O$	67.62	7.07	11.24	67.68	7.18	11.19
21e		81	209—210 (A–H)	$C_{21}H_{23}N_3O \cdot 0.1H_2O$	75.24	6.98	12.54	75.27	7.04	12.48
25a	A	54	158—160 (A–D)	$C_{19}H_{19}N_2O \cdot 0.25H_2O$	77.39	6.33	9.50	77.55	6.27	9.42
25b	A	47	237—239 (A–C–D)	$C_{20}H_{20}N_2O \cdot HCl \cdot 0.5H_2O$	68.66	6.34	8.01	68.81	6.32	8.02
27		40	>260 (E)	$C_{19}H_{19}N_3O \cdot HCl$	66.76	5.90	12.29	66.34	5.86	12.13
(+)-**11b**		19	>260 (M–D)	$C_{18}H_{19}N_3O \cdot HCl$	65.55	6.11	12.74	65.60	6.16	12.84
(−)-**11b**		17	>260 (M–D)	$C_{18}H_{19}N_3O \cdot HCl$	65.55	6.11	12.74	65.52	6.11	12.82
(+)-**21a**		33	>260 (M–D)	$C_{19}H_{21}N_3O \cdot HCl$	66.37	6.45	12.22	66.10	6.53	12.02
(−)-**21a**		40	>260 (M–D)	$C_{19}H_{21}N_3O \cdot HCl$	66.37	6.45	12.22	66.57	6.51	12.15

a) See footnote a) in Table V. E, ethanol; W, H_2O. b) Maleate.

combined and evaporated *in vacuo* to give a residue (1.9 g), which consisted mainly of the other isomer of **8b** with a low *Rf* value.

A solution of the isomer of **8b** with a high *Rf* value (0.9 g, 1.6 mmol) in AcOH–H_2O (3.5 : 1, 45 ml) was heated at 55 °C for 2.5 h. After evaporation of the solvent, the residue was partitioned between CH_2Cl_2 and H_2O and the solution was neutralized with aqueous $NaHCO_3$ to give a precipitate. Collection of the precipitate, followed by washing with H_2O and CH_2Cl_2, gave crystals (0.363 g), which were treated with maleic acid (0.136 g) in hot MeOH (20 ml). Evaporation of the solvent followed by crystallization from MeOH–ether gave the maleate (**13a**) (0.45 g, 65%), mp 189—190 °C. IR (Nujol): 1685, 1635, 1615, 1575 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.60—2.10 (2H, m), 2.10 (3H, s), 2.27 (3H, s), 2.66—3.40 (3H, m), 5.40 (1H, d, J=5 Hz), 6.00 (2H, s), 7.10—7.50 (3H, m), 8.20 (1H, m), 8.73 (1H, s). Compound **13b** was prepared in a similar manner to that described for **13a**, 65%, mp 155—161 °C. IR (Nujol): 1715, 1690, 1650, 1620, 1530 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.10 (3H, s), 1.70—2.30 (3H, m), 2.23 (3H, s), 2.70—3.30 (3H, m), 5.57 (1H, d, J=3 Hz), 6.00 (2H, s), 7.10—7.50 (3H, m), 8.27 (1H, m), 8.80 (1H, s), 12.50—14.50 (2H, br s).

8,9-Dihydro-10-methyl-7-[(5-methyl-1*H*-imidazol-4-yl)methylene]pyrido[1,2-*a*]indol-6(7*H*)-one (14) A solution of **10b** (0.9 g, 1.7 mmol) in AcOH–H_2O (4 : 1, 50 ml) was heated at 60 °C for 2.5 h. After evaporation of the solvent, the residue was partitioned between aqueous $NaHCO_3$ and CH_2Cl_2. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. Purification of the residue by column chromatography on silica gel (2% MeOH–$CHCl_3$), followed by recrystallization from MeOH–$CHCl_3$–hexane, gave **14** (0.41 g, 84%), mp 252—255 °C. IR (Nujol): 1665, 1625, 1595, 1555 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.16 (3H, s), 2.33 (3H, s), 2.96 (2H, t, J=6 Hz), 3.53 (2H, t, J=6 Hz), 7.10—7.60 (3H, m), 7.63 (1H, s), 7.70 (1H, s), 8.40 (1H, m).

8,9-Dihydro-10-methyl-7-[(1-methyl-1*H*-imidazol-4-yl)methyl]pyrido-[1,2-*a*]indol-6(7*H*)-one (15a) and 8,9-Dihydro-10-methyl-7-[(1-methyl-1*H*-imidazol-5-yl)methyl]pyrido[1,2-*a*]indol-6(7*H*)-one (15b) A mixture of **11a** (1.4 g, 5.0 mmol), NaH (60% in mineral oil, 220 mg, 5.5 mmol), and DMF (14 ml) was stirred at 0 °C for 1 h. Then a solution of methyl iodide (850 mg, 6.0 mmol) in DMF (5 ml) was added, and the resulting mixture was stirred at 0 °C for 1 h and at room temperature for 2 h. After evaporation of the solvent, the residue was dissolved in 5% MeOH–$CHCl_3$. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. Silica gel chromatography of the residue (5% MeOH–$CHCl_3$) first afforded crystals, which were recrystallized from EtOAc to yield **15a** (0.4 g, 27%), mp 99—100 °C. IR (Nujol): 1685, 1675, 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.80—2.30 (2H, m), 2.15 (3H, s), 2.60—3.20 (4H, m), 3.33 (1H, dd, J=4, 14 Hz), 3.62 (3H, s), 6.73 (1H, s), 7.20—7.50 (4H, m). Further elution yielded **15b** (0.03 g, 2%), mp 117—118 °C ($CHCl_3$–hexane). IR (Nujol): 1688, 1668, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.70—2.20 (2H, m), 2.14 (3H, s), 2.70—2.90 (2H, m), 3.00—3.30 (3H, m), 3.33 (3H, s), 6.72 (1H, s), 7.20—7.30 (2H, m), 7.40 (1H, m), 7.52 (1H, s), 8.30—8.40 (1H, m).

8,9-Dihydro-7-[(1,5-dimethyl-1*H*-imidazol-4-yl)methyl]-10-methylpyrido[1,2-*a*]indol-6(7*H*)-one (**15c**) and 8,9-dihydro-7-[(1,4-dimethyl-1*H*-imidazol-5-yl)methyl]-10-methylpyrido[1,2-*a*]indol-6(7*H*)-one (**15d**) were prepared in a similar manner to that described for **15a** and **15b**.

8,9-Dihydro-10-methyl-7-(dimethylaminomethyl)pyrido[1,2-*a*]indol-6(7*H*)-one (16) and 8,9-Dihydro-10-methyl-7-methylenepyrido[1,2-*a*]-indol-6(7*H*)-one (17) A solution of **7b** (1.99 g, 10 mmol) in THF (20 ml) was added over 5 min to a stirred solution of LDA (12 mmol, prepared from 1.21 g of diisopropylamine and 7.3 ml of 1.64 M *n*-butyllithium in hexane) in THF (15 ml) at −70 °C under nitrogen. The mixture was stirred at −70 °C for 30 min and *N*,*N*-dimethylmethyleneammonium iodide (2.41 g, 13.5 mmol) was added in one portion. The resulting mixture was stirred at −70 °C for 30 min and at −40 °C for 1.5 h. The 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*. Silica gel column chromatography of the residue (3% MeOH–CH_2Cl_2) yielded first **17** (0.16 g, 7.6%) as an oil. IR (Nujol): 1680, 1615, 1185 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.13 (3H, s), 2.60—3.10 (4H, m), 5.60 (1H, s), 6.36 (1H, s), 7.30 (3H, s), 8.43 (1H, m). MS *m/z*: 211 (M^+). Further elution yielded **16** (1.15 g, 45%), mp 70—76 °C. IR (Nujol): 1685, 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.70—2.10 (2H, m),

2.13 (3H, s), 2.23 (6H, s), 2.70—3.10 (5H, m), 7.30 (3H, m), 8.40 (1H, m). MS *m/z*: 257 (M^+).

8,9-Dihydro-10-methyl-7-[(2-methyl-1*H*-imidazol-1-yl)methyl]pyrido[1,2-*a*]indol-6(7*H*)-one (18) A mixture of **16** (0.65 g, 2.53 mmol), 2-methylimidazole (0.76 g, 9.3 mmol), 2 N HCl (1.27 ml), and 2-propanol (4 ml) was heated at 100 °C for 3 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2. The CH_2Cl_2 layer was washed with aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated *in vacuo*. Purification by column chromatography on neutral alumina (0.5% MeOH–CH_2Cl_2), followed by recrystallization from EtOAc–hexane, gave **18** (0.40 g, 54%), mp 120—121 °C. IR (Nujol): 1665, 1615, 1520, 1280 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.60—1.90 (2H, m), 2.10 (3H, s), 2.30 (3H, s), 2.66—3.40 (3H, m), 4.13 (1H, dd, J=8, 15 Hz), 4.50 (1H, dd, J=5, 15 Hz), 6.73 (1H, s), 7.03 (1H, s), 7.10—7.50 (3H, m), 8.30 (1H, m).

8,9-Dihydro-7,10-dimethyl-7-[[5-methyl-1-(triphenylmethyl)-1*H*-imidazol-4-yl]methyl]pyrido[1,2-*a*]indol-6(7*H*)-one (20a) A solution of **19** (1.09 g, 2.0 mmol) in THF (5 ml) was added over 15 min to a solution of LDA (2.9 mmol, prepared from 263 mg of diisopropylamine and 1.75 ml of 1.64 M *n*-butyllithium in hexane) in THF (3 ml) at −70 °C under nitrogen. The mixture was stirred at −70 °C for 30 min and −20 °C for 40 min and then a solution of methyl iodide (282 mg, 2.0 mmol) in THF (3 ml) was added dropwise at −70 °C over 10 min. Stirring was continued at −70 °C for 30 min and at −20 °C for 1 h, then the mixture was diluted with H_2O and neutralized with aqueous oxalic acid. The whole was extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. Purification of the residue by column chromatography on silica gel (5% EtOAc–$CHCl_3$) gave **20a** (0.73 g, 66%) as an amorphous powder. Crystallization from hexane gave an analytical sample, mp 116—118 °C. IR (Nujol): 1680, 1625, 1580 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, s), 1.36 (3H, s), 1.90—2.10 (1H, m), 2.17 (3H, s), 2.30—2.50 (1H, m), 2.85 (1H, d, J=14 Hz), 2.80—3.30 (2H, m), 3.00 (1H, d, J=14 Hz), 7.00—7.40 (19H, m), 8.42 (1H, m). *Anal.* Calcd for $C_{38}H_{35}N_3O$: C, 81.43; H, 6.51; N, 7.50. Found: C, 81.53; H, 6.57; N, 7.39. The following compounds were prepared by the same procedure as described for **20a**.

7-Ethyl-8,9-dihydro-10-methyl-7-[[5-methyl-1-(triphenylmethyl)-1*H*-imidazol-4-yl]methyl]pyrido[1,2-*a*]indol-6(7*H*)-one (20b) Yield 30%, mp 144—149 °C (EtOAc–hexane). IR (Nujol): 1680, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, t, J=7 Hz), 1.33 (3H, s), 1.53—1.70 (1H, m), 1.90—2.40 (3H, m), 2.20 (3H, s), 2.83 (1H, d, J=14 Hz), 3.04 (1H, d, J=14 Hz), 2.80—3.10 (2H, m), 7.00—7.50 (19H, m), 8.45 (1H, m). MS *m/z*: 563 (M^+). *Anal.* Calcd for $C_{39}H_{37}N_3O$: C, 83.09; H, 6.62; N, 7.45. Found: C, 83.12; H, 6.82; N, 7.31.

8,9-Dihydro-7-hydroxymethyl-10-methyl-7-[[5-methyl-1-(triphenylmethyl)-1*H*-imidazol-4-yl]methyl]pyrido[1,2-*a*]indol-6(7*H*)-one (20c) Yield 43%. An amorphous powder. IR (Nujol): 1680, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, s), 2.00—2.10 (2H, m), 2.16 (3H, s), 2.85 (1H, d, J=15 Hz), 3.00 (2H, t, J=6 Hz), 3.19 (1H, d, J=15 Hz), 3.71 (1H, d, J=12 Hz), 4.07 (1H, d, J=12 Hz), 7.10—7.50 (19H, m), 8.35 (1H, m). MS *m/z*: 565 (M^+).

7-Allyl-8,9-dihydro-10-methyl-7-[[5-methyl-1-(triphenylmethyl)-1*H*-imidazol-4-yl]methyl]pyrido[1,2-*a*]indol-6(7*H*)-one (20e) Yield 90%, mp 89—95 °C (MeOH). IR (Nujol): 1670, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, s), 2.22 (3H, s), 2.00—2.40 (4H, m), 2.70—3.20 (4H, m), 5.00—5.20 (2H, m), 5.70—6.00 (1H, m), 7.00—7.50 (19H, m), 8.35 (1H, m). MS *m/z*: 575 (M^+). *Anal.* Calcd for $C_{40}H_{37}N_3O \cdot 0.1H_2O$: C, 83.18; H, 6.49; N, 7.28. Found: C, 83.14; H, 6.80; N, 6.91.

Compounds **21a—c**, and **e** were prepared by the procedure described for **14**.

8,9-Dihydro-10-methyl-7-[(5-methyl-1*H*-imidazol-4-yl)methyl]-7-propylpyrido[1,2-*a*]indol-6(7*H*)-one Hydrochloride (21d) A solution of **21e** (250 mg, 0.75 mmol) in AcOH–MeOH (1 : 1, 20 ml) was hydrogenated at atmospheric pressure over 10% Pd–C (50 mg) for 2 h. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The residue was dissolved in a mixture of EtOAc and 2 N HCl. After stirring for 30 min, the precipitate formed was collected and washed with EtOAc to give **21d**, mp >270 °C. IR (Nujol): 1675, 1635, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.87 (3H, t, J=7 Hz), 1.20—2.20 (6H, m), 2.14 (3H, s), 2.17 (3H, s), 2.90—3.10 (2H, m), 3.03 (1H, d, J=15 Hz), 3.21 (1H, d, J=15 Hz), 7.20—7.30 (2H, m), 7.40—7.50 (1H, m), 8.30 (1H, m), 8.95 (1H, s).

Compounds **24a** and **24b** were prepared in a similar manner to that described for **10b**.

8,9-Dihydro-10-methyl-7-[(pyridin-3-yl)methylene]pyrido[1,2-*a*]indol-6(7*H*)-one (24a) Yield 80%, mp 102—103 °C (EtOAc). IR (Nujol): 1670, 1630, 1615 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.20 (3H, s), 2.90—3.10 (4H, m), 7.20—7.50 (4H, m), 7.70—7.80 (1H, m), 7.96 (1H, s), 8.50 (1H, m), 8.60 (1H, dd, J=2, 5 Hz), 8.69 (1H, d, J=2 Hz). MS *m/z*: 288 (M^+).

8,9-Dihydro-10-methyl-7-[(2-methylpyridin-3-yl)methylene]pyrido[1,2-*a*]indol-6(7*H*)-one (24b) Yield 72%, mp 182—183 °C (EtOAc). IR (Nujol): 1675, 1630, 1610 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.17 (3H, s), 2.51 (3H, s), 2.60—3.00 (4H, m), 7.20—7.40 (1H, m), 7.70 (1H, d, J=7 Hz), 7.88 (1H, s), 8.30—8.60 (2H, m). MS *m/z*: 302 (M^+).

Compounds **25a** and **25b** were prepared by the procedure described for **11d**.

8,9-Dihydro-10-methyl-7-[(pyridin-3-yl)methyl]pyrido[1,2-*a*]indol-6(7*H*)-one (25a) IR (Nujol): 1690, 1675, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.90—2.00 (2H, m), 2.13 (3H, s), 2.40—3.60 (5H, m), 7.00—7.70 (5H, m), 8.30—8.60 (3H, m).

8,9-Dihydro-10-methyl-7-[(2-methylpyridin-3-yl)methyl]pyrido[1,2-*a*]-indol-6(7*H*)-one Hydrochloride (25b) IR (Nujol): 1690, 1615, 1545 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.80—2.10 (2H, m), 2.15 (3H, s), 2.82 (3H, s), 2.90—3.70 (5H, m), 7.20—7.30 (2H, m), 7.40—7.60 (1H, m), 7.87 (1H, dd, J=6, 7 Hz), 8.20—8.40 (1H, m), 8.46 (1H, d, J=7 Hz), 8.68 (1H, dd, J=1, 7 Hz). The physical data are listed in Table VI.

8,9-Dihydro-10-methylpyrido[1,2-*a*]indol-6(7*H*)-one-7-spiro-6′-6′,7′-dihydro-1′-methyl-5′*H*-pyrrolo[1,2-*c*]imidazole Hydrochloride (27) A solution of **20c** (0.36 g, 0.64 mmol) and $SOCl_2$ (0.14 g, 1.18 mmol) in CH_2Cl_2 (6 ml) was stirred at 0 °C for 1 h and at room temperature for 1.5 h. After being cooled to 0 °C, the solution was treated with pyridine (0.5 ml). Stirring was continued for 1.5 h at room temperature. The reaction mixture was partitioned between H_2O and $CHCl_3$. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The oil obtained was dissolved in a mixture of AcOH–H_2O (7 : 2, 9 ml), and the solution was heated at 65 °C for 1.5 h. After evaporation of the solvent, the residue was neutralized with aqueous $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. Chromatography of the residue (3% MeOH–$CHCl_3$) gave 160 mg of an oil. The oil was converted to the hydrochloride salt and recrystallized from EtOH to give **27** (87 mg, 40%), mp >260 °C. IR (Nujol): 2650, 2580, 1685, 1625, 1535 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.18 (3H, s), 2.21 (3H, s), 2.35 (2H, m), 2.90—3.40 (4H, m), 4.28 (1H, d, J=12 Hz), 4.80 (1H, d, J=12 Hz), 7.28 (2H, m), 7.50 (1H, m), 8.21 (1H, m), 8.88 (1H, s). MS *m/z*: 305 (M^+).

(+)-8,9-Dihydro-10-methyl-7-[(5-methyl-1*H*-imidazol-4-yl)methyl]-pyrido[1,2-*a*]indol-6(7*H*)-one Hydrochloride [(+)-11b] The free base of compound **11b** (34.6 g, 0.118 mol) and (+)-di-*p*-toluoyl-D-tartaric acid (45.5 g, 0.118 mol) were dissolved in a mixture of $CHCl_3$–MeOH (3 : 7, 2.35 l) at 70 °C. The solution was allowed to stand at 5 °C for 7 d to give crystals (31.0 g). The crystals (30.8 g) were dissolved in DMF (69 ml) at 80 °C. The resulting solution was diluted with $CHCl_3$ (69 ml) and MeOH (323 ml) and then allowed to stand at 5 °C for 5 d to give 17.8 g of crystals. A stirred suspension of the crystals in a mixture of $CHCl_3$ and H_2O was treated with 2 N NaOH (14 ml). The organic layer was washed with H_2O, dried ($MgSO_4$), and evaporated *in vacuo* to give (+)-8,9-dihydro-10-methyl-7-[(5-methyl-1*H*-imidazol-4-yl)methyl]-pyrido[1,2-*a*]indol-6(7*H*)-one (7.1 g) with $[\alpha]_D^{25}$ +63° (*c*=1.0, 10% MeOH–$CHCl_3$). The crystals were converted to the hydrochloride, (+)-**11b** (7.3 g, 19%), by treatment with HCl in EtOH followed by recrystallization from MeOH–ether, mp >250 °C. IR (Nujol): 1700, 1635, 1520, 1310 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.75—2.20 (2H, m), 2.14 (3H, s), 2.26 (3H, s), 2.73—3.40 (5H, m), 7.26 (2H, m), 7.49 (1H, m), 8.32 (1H, m), 8.98 (1H, s), 14.55 (2H, br s). $[\alpha]_D^{25}$ +14.1° (*c*=2.0, MeOH).

Compound (−)-**11b** was prepared in a similar manner to that described for (+)-**11b**. The free base of (−)-**11b**: $[\alpha]_D^{25}$ −62° (*c*=1.0, 10% MeOH–$CHCl_3$). (−)-**11b**: $[\alpha]_D^{25}$ −13.8° (*c*=1.1, MeOH).

2-Methyl-4-(3-methylindol-2-yl)-2-[[5-methyl-1-(triphenylmethyl)-1*H*-imidazol-4-yl]methyl]butanoic Acid (28) A mixture of **20a** (3.78 g, 6.9 mmol), aqueous 3 N NaOH (10 ml), EtOH (10 ml), and dioxane (5 ml) was heated at 90 °C for 30 h. After evaporation of the solvent, the residue was neutralized with aqueous oxalic acid and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo* to give **28** (3.3 g, 85%) as an amorphous powder, which was used in the next reaction without purification. IR (Nujol): 3300—2100, 1680, 1490 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.17 (3H, s), 1.35 (3H, s), 1.71 (1H, m), 1.94 (1H, m), 2.14 (3H, s), 2.66 (2H, m), 2.84

(2H, dd, $J=15$, 23 Hz), 6.89—7.44 (19H, m), 7.88 (1H, br s), 10.73 (1H, s). MS m/z: 307 ($M^+ - CPh_3 - OH$).

1-[2-Methyl-4-(3-methylindol-2-yl)-2-[[5-methyl-1-(triphenylmethyl)-1*H*-imidazol-4-yl]methyl]butanoyl]-2(*S*)-hydroxymethylpyrrolidine (29) A Solution of ethyl chloroformate (0.54 g, 5.0 mmol) in THF (2 ml) was added to a solution of **28** (2.55 g, 4.5 mmol) and Et_3N (0.71 ml, 5.1 mmol) in THF (30 ml) at −20 °C. After 17 min at the same temperature, a solution of (*S*)-pyrrolidinemethanol (1.14 g, 11.3 mmol) in THF (3 ml) was added to the above solution. The mixture was stirred at −10 °C for 2 h and at room temperature for 1 h, then diluted with H_2O, neutralized with aqueous oxalic acid, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O and brine, dried (Na_2SO_4), and evaporated *in vacuo*. Column chromatography of the residue on silica gel (EtOAc–hexane) first afforded an amorphous powder, which was crystallized from MeOH to give **29a** (0.48 g, 16%), mp 145—155 °C. IR (Nujol): 3200, 1600, 1230 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, s), 1.10—1.50 (4H, m), 1.45 (3H, s), 1.70—2.10 (3H, m), 2.17 (3H, s), 2.52 (1H, d, $J=15$ Hz), 2.75 (2H, t, $J=8$ Hz), 3.12 (1H, d, $J=15$ Hz), 3.32 (1H, d, $J=12$ Hz), 3.75 (1H, m), 3.89 (1H, m), 4.24 (1H, m), 4.38 (1H, d, $J=12$ Hz), 6.99—7.46 (20H, m). $[\alpha]_D^{25}$ −10.7° ($c=1.03$, MeOH). *Anal.* Calcd for $C_{43}H_{46}N_4O_2 \cdot H_2O$: C, 77.21; H, 7.23; N, 8.38. Found: C, 77.63; H, 7.42; N, 8.21. Further elution followed by crystallization of the product from MeOH yielded **29b** (0.54 g, 18.5%), mp 133—145 °C. IR (Nujol): 3250, 1600, 1240 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ: 1.08 (3H, s), 1.20—1.50 (4H, m), 1.38 (3H, s), 1.70—2.00 (2H, m), 2.22 (3H, s), 2.10—2.40 (2H, m), 2.70—2.88 (2H, m), 3.16—3.27 (2H, m), 3.60—3.83 (2H, m), 4.17 (1H, m), 4.32 (1H, d, $J=11$ Hz). 7.00—7.48 (20H, m). $[\alpha]_D^{25}$ −55.3° ($c=1.03$, MeOH). *Anal.* Calcd for $C_{43}H_{46}N_4O_2 \cdot H_2O$: C, 77.21; H, 7.23; N, 8.38. Found: C, 77.09; H, 7.09; N, 8.31.

(+)-8,9-Dihydro-7,10-dimethyl-7-[(5-methyl-1*H*-imidazol-4-yl)methyl]pyrido[1,2-*a*]indol-6(7*H*)-one Hydrochloride [(+)-21a] A mixture of **29b** (0.52 g, 0.80 mmol), 3 N HCl (20 ml), and toluene (10 ml) was refluxed for 4 h. After evaporation of the solvent, the residue was made basic with aqueous $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed on silica gel (5% MeOH–$CHCl_3$) to give the free base of (+)-**21a** (175 mg) with $[\alpha]_D^{25}$ +204° ($c=1.0$, 10% MeOH–$CHCl_3$). The product was treated with HCl in MeOH and recrystallized from MeOH–ether to give (+)-**21a** (90 mg, 33%), mp >260 °C. IR (Nujol): 1700, 1640, 1625 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.29 (3H, s), 1.94 (2H, m), 2.15 (3H, s), 2.18 (3H, s), 3.00 (2H, m), 7.26 (2H, m), 7.50 (1H, m), 8.30 (1H, m), 8.92 (1H, s), 14.16 (1H, s). $[\alpha]_D^{25}$ +15.1° ($c=1.0$, MeOH).

(−)-8,9-Dihydro-7,10-dimethyl-7-[(5-methyl-1*H*-imidazol-4-yl)-methyl]pyrido[1,2-*a*]indol-6(7*H*)-one hydrochloride [(−)-**21a**] was prepared from **29a** in a similar manner to that described for (+)-**21a**. Yield 40%. The free base of (−)-**21a**: $[\alpha]_D^{25}$ −202.5° ($c=0.98$, $CHCl_3$). (−)-**21a**: $[\alpha]_D^{25}$ −15.0° ($c=1.0$, MeOH).

Pharmacology BJ Reflex in Urethane-Anesthetized Rats 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 the 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 agonist-induced bradycardia.

Cisplatin-Induced Emesis in Dogs Emesis was induced by i.v. injection of cisplatin (3.2 mg). Cisplatin was dissolved in 0.9% warm saline to a final concentration of 3 mg/ml and used immediately. Test compounds or saline (i.v.) were given as a divided dose 10 min before and 90 min after cisplatin. For *p.o.* studies, compounds were given 30 min before and 90 min after cisplatin. The latency period for the onset of emesis and the number of emetic episodes were compared with those of saline-based controls for up to 5 h. In the duration-of-action studies, compounds (100 μg/kg i.v.) were administered 4 h before cisplatin.

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 discussion, and Dr. A. Sato and Dr. T. Azuma for measurement of NOESY spectra.

References

1) B. P. Richardson, G. Engel, *Trends Neurosci.*, **9**, 424 (1986); S. J. Peroutka, *Trends Neurosci.*, **11**, 496 (1988); D. E. Clarke, D. A. Craig, J. R. Fozard, *Trends Pharmacol. Sci.*, **10**, 385 (1989).
2) K.Bunce, M. Tyers, P. Beranek, *Trends Pharmacol. Sci.*, **12**, 46 (1991); P. L. R. Andrews, W. G. Rapeport, G. J. Sanger, *ibid.*, **9**, 334 (1988).
3) G. J. Kilpatrick, B. J. Jones, M. B. Tyers, *Nature* (London), **330**, 746 (1987).
4) E. Acquas, E. Carboni, L. Garau, G. Di Chiara, *Psychopharmacology* (Berlin), **100**, 459 (1990); M. G. Cutler, *Neuropharmacology*, **29**, 515 (1990); J. M. Barnes, B. Costall, J. Coughlan, A. M. Domeney, P. A. Gerrard, M. E. Kelly, R. J. Naylor, E. S. Onaivi, D. M. Tomkins, M. B. Tyers, *Pharmacol. Biochem. Behav.*, **35**, 955 (1990).
5) M. F. Hibert, R. Hoffman, R. C. Miller, A. A. Carr. *J. Med. Chem.*, **33**, 1594 (1990); A. W. Schmidt, S. J. Peroutka, *Mol. Pharmacol.*, **36**, 505 (1989); C. J. Swain, R. Baker, C. Kneen, R. Herbert, J. Moseley, J. Saunders, E. M. Seward, G. I. Stevenson, M. Beer, J. Stanton, K. Watling, R. G. Ball, *J. Med. Chem.*, **35**, 1019 (1992).
6) A. Butler, J. M. Hill, S. J. Ireland, C. C. Jordan, M. B. Tyers, *Br. J. Pharmacol.*, **94**, 397 (1988); M. B. Tyers, K. T. Bunce, P. P. A. Humphrey, *Eur. J. Cancer Clin. Oncol.*, **25** (suppl. 1), s15 (1989); C. P. Blackwell, S. M. Harding, *ibid.*, **25** (suppl. 1), s21 (1989); T. J. Priestman, *ibid.*, **25** (suppl. 1), s29 (1989).
7) E. Schlittler, N. Weber, *J. Prakt. Chem.*, **314**, 669 (1972).
8) M. D. Grenshaw, H. Zimmer, *J. Heterocycl. Chem.*, **21**, 623 (1984).
9) A. J. Fox, I. K. M. Morton, *Brit. J. Pharmacol.*, **101**, 553 (1990).
10) J. R. Fozard, M. Host, *Br. J. Pharmacol.*, **77**, 520 p (1982).
11) C. J. Steadman, N. J. Talley, S. F. Phillips, C. Mulvihill, *Gastroenterology*, **98**, A394 (1990); D. G. Maxton, C. G. Haigh, P. J. Whorwell, *ibid.*, **100**, A468 (1991); A. Prior, N. W. Read, *Gut*, **31**, A1174 (1990).
12) Y. Nagakura, M. Kadowaki, K. Tokoro, M. Tomoi, J. Mori, M. Kohsaka, *J. Pharmacol. Exp. Ther.*, **265**, 752 (1993); M. Kadowaki, Y. Nagakura, M. Tomoi, J. Mori, M. Kohsaka, *ibid.*, **266**, 74 (1993).
13) H. J. Teuber, E. Worbs, D. Cornelius, *Arch. Pharm.* (Weinheim), **315**, 388 (1982).
14) I. H. Coats, J. Bradshaw, J. A. Bell, D. C. Humber, G. B. Ewan, W. L. Mitchell, Ger. Offen. DE 3740352 (1988) [*Chem. Abstr.*, **109**, 231018*x* (1988)].