2556 *Chem. Pharm. Bull.* **42**(12) 2556—2564 (1994) Vol. 42, No. 12

New 5-HT$_3$ (Serotonin-3) Receptor Antagonists. II. Synthesis and Structure–Activity Relationships of Pyrimido[1,6-*a*]indoles

Masayuki KATO,* Shigetaka NISHINO, Kiyotaka ITO, 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

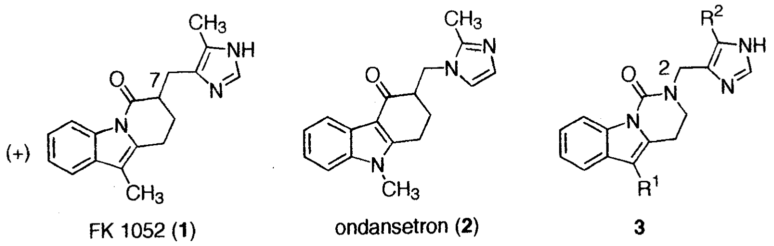
A series of pyrimido[1,6-*a*]indol-1(2*H*)-ones was prepared and evaluated for 5-HT$_3$ receptor antagonist activity. The compounds in this series were regarded as bioisosters of the pyrido[1,2-*a*]indol-6(7*H*)-ones previously reported. High potency was found for compounds having 5-methyl substituents on both the pyrimido[1,6-*a*]indole ring and the imidazole ring. Optimized members of this series, 8b and (+)-26a, were potent 5-HT$_3$ receptor antagonists as determined by measuring inhibition of the Bezold–Jarisch reflex in anesthetized rats (ED$_{50}$ 0.6 and 0.8 μg/kg i.v., respectively), being equipotent to or more potent than FK 1052 (1) in the previous paper and 20- to 30-fold more potent than ondansetron (2).

Keywords pyrimido[1,6-*a*]indol-1(2*H*)-one; 5-HT$_3$ receptor antagonist; Bezold–Jarisch reflex; structure–activity relationship

The first paper in this series described the synthesis and structure–activity relationships of a series of pyrido[1,2-*a*]indole derivatives as 5-HT$_3$ receptor antagonists.[1] Compound **1** (FK 1052), identified as the most active antagonist (ED$_{50}$ 0.9 μg/kg i.v. in rats for inhibition of Bezold–Jarisch reflex), was 20-fold more potent than ondansetron (**2**). In that paper, we suggested that, in the active conformation of a 5-HT$_3$ receptor antagonist such as **1**, the nitrogen atom at the 1-position of the imidazole ring was in the same plane as the aromatic ring moiety or only slightly deviated from coplanarity. This assumption prompted us to synthesize a series of 3,4-dihydropyrimido[1,6-*a*]indoles (**3**), in which the nitrogen at the 2-position of the aromatic ring moiety has an sp^2-like character in contrast to the sp^3 hybridized carbon at the 7-position of pyrido[1,2-*a*]indoles. We speculated that compound **3** would have an optimal conformation for binding to the 5-HT$_3$ receptor, because the side chain of compound **3** was expected to lie in the plane of the pyrimido[1,6-*a*]indole ring. The present paper describes the synthesis and 5-HT$_3$ receptor antagonist activity of a series of 3,4-dihydropyrimido[1,6-*a*]indol-1(2*H*)-ones, together with the corresponding 3,4,4a,5-tetrahydro derivatives.

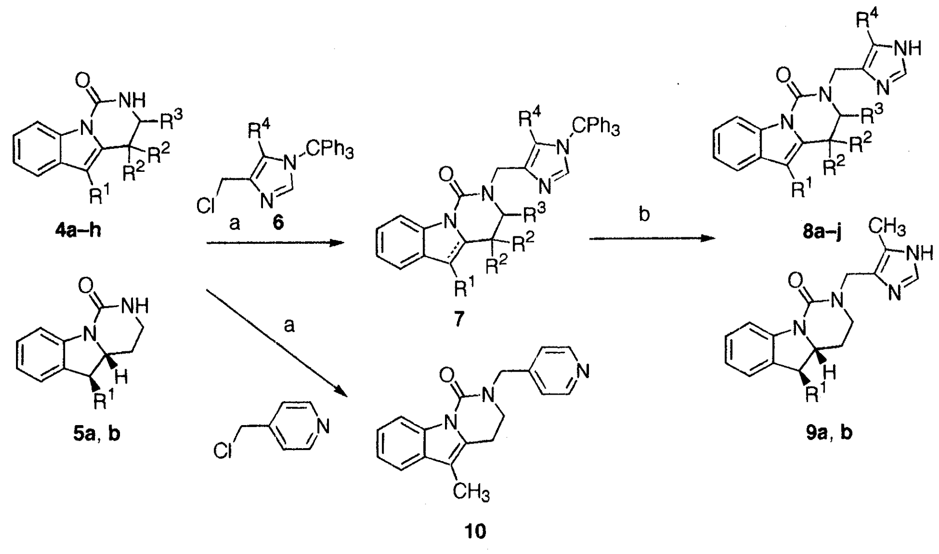
Chemistry

Compounds **8** and **9**, which have an (imidazol-4-yl)methyl group as a basic nitrogen, were prepared by the route shown in Chart 2. Alkylations of 3,4-dihydro- (**4**) and 3,4,4a,5-tetrahydropyrimido[1,6-*a*]indol-1(2*H*)-ones (**5**) with a 4-chloromethylimidazole derivative (**6**) in the presence of sodium hydride gave compounds **7**, which were detritylated with hot aqueous acetic acid to give the 3,4-dihydro- (**8**) and 3,4,4a,5-tetrahydropyrimido[1,6-*a*]indol-1(2*H*)-ones (**9**), respectively. Similar treatment of the 3,4-dihydro-5-methyl compound **4b** with 4-chloromethylpyridine gave **10**. The key 3,4-dihydro- (**4**) and 3,4,4a,5-tetrahydropyrimido[1,6-*a*]indol-1(2*H*)-one (**5**) were prepared according to the procedure shown in Chart 3. Base-catalyzed condensation of the appropriate indole-2-carbaldehyde (**11**) with the nitroalkane gave the nitrovinyl compound **12**, which was reduced with lithium aluminum hydride to the corresponding amine (**13**). Treatment of **13** with 1,1′-carbonyldiimidazole, followed by heating the imidazolecarboxamide (**14**) formed, afforded **4** (method A). The 4,4-dimethyl derivative (**4h**) was prepared from indol-2-ylacetonitrile (**15**) (method B). Treatment of **15** with lithium diisopropylamide (LDA) and subsequent reaction with methyl iodide gave the dimethyl compound (**16**) along with the monomethyl compound (**18**). Catalytic hydrogenation of **16** with rhodium-on-alumina followed by treatment with 1,1′-carbonyldiimidazole afforded **4h**. The 3,4,4a,5-tetrahydro compounds (**5a** and **5b**) were prepared by reduction of **13a** and **13b** with sodium cyanoborohydride to **17a** and **17b**, followed by cyclization with 1,1′-carbonyldiimidazole (method C). The relative stereochemistry of the 5-methyl substituent of **5b** was determined by nuclear Overhauser effect (NOE) experiments in the nuclear Overhauser and exchange spectroscopy (NOESY) spectrum of compound **9b** (Chart



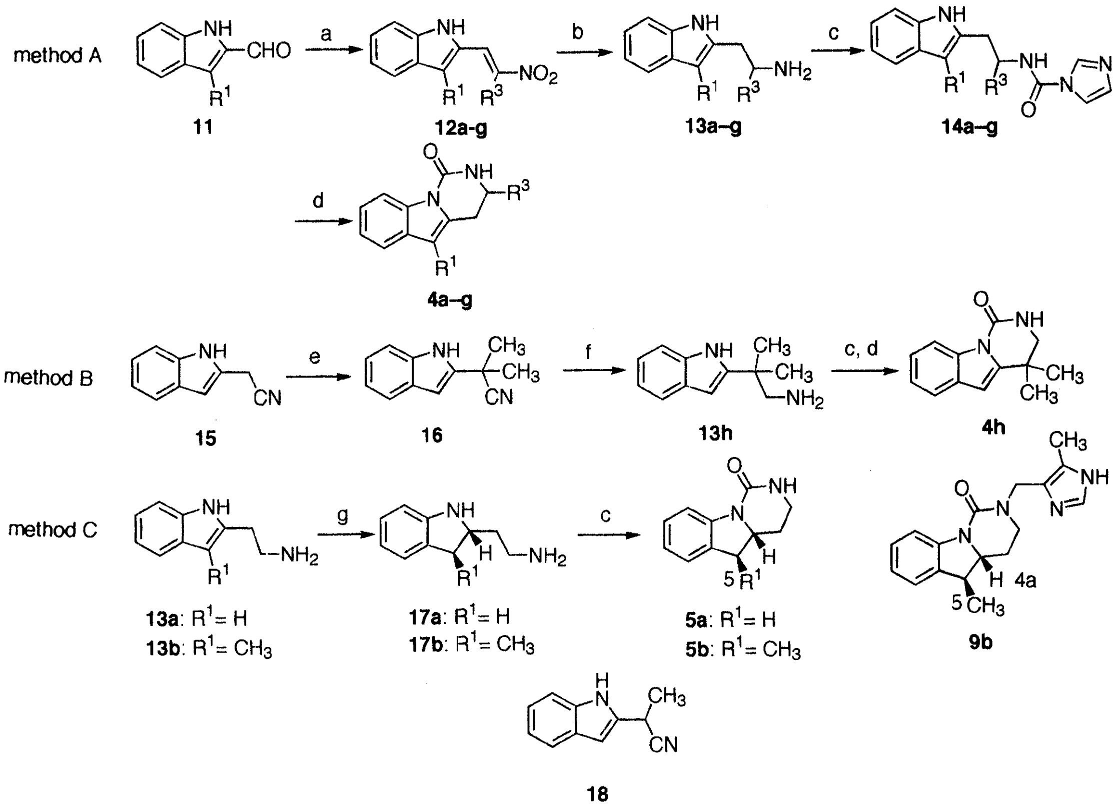
FK 1052 (**1**) ondansetron (**2**) **3**

Chart 1



a) NaH, DMF; b) AcOH-H_2O

Chart 2



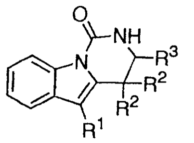
a) $R^3CH_2NO_2$, MeOH, $AcONH_4$; b) $LiAlH_4$, THF; c) 1,1′-carbonyldiimidazole; d) toluene or xylene; e) LDA, MeI, THF; f) 5% Rh-Al_2O_3, H_2, NH_3, MeOH; g) $NaBH_3CN$, AcOH

Chart 3

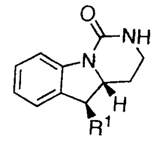
3). A strong NOE was observed between the methyl protons at the 5-position (δ 1.32) and 4a-H (δ 3.78), whereas a weak NOE was observed between 5-H (δ 3.13) and 4a-H. These data supported the assigned structures of **9b** and **5b**.

Preparation of compounds **26** having an alkyl group on the methylene side chain is outlined in Chart 4. Treatment of **19** with LDA resulted in lithiation at the 2-position. Subsequent reaction with ethylene oxide afforded the 2-(indol-2-yl)ethanol (**20**). The mesylate (**21**) was prepared by the reaction of **20** with methanesulfonyl chloride and triethylamine. Compound **21** was treated with the imidazolylmethanamines (**28b, c**) in the presence of potassium carbonate and sodium iodide to give com-

Table I. 3,4-Dihydro- (4) and 3,4,4a,5-Tetrahydropyrimido[1,6-*a*]indol-1(2*H*)-one (5)



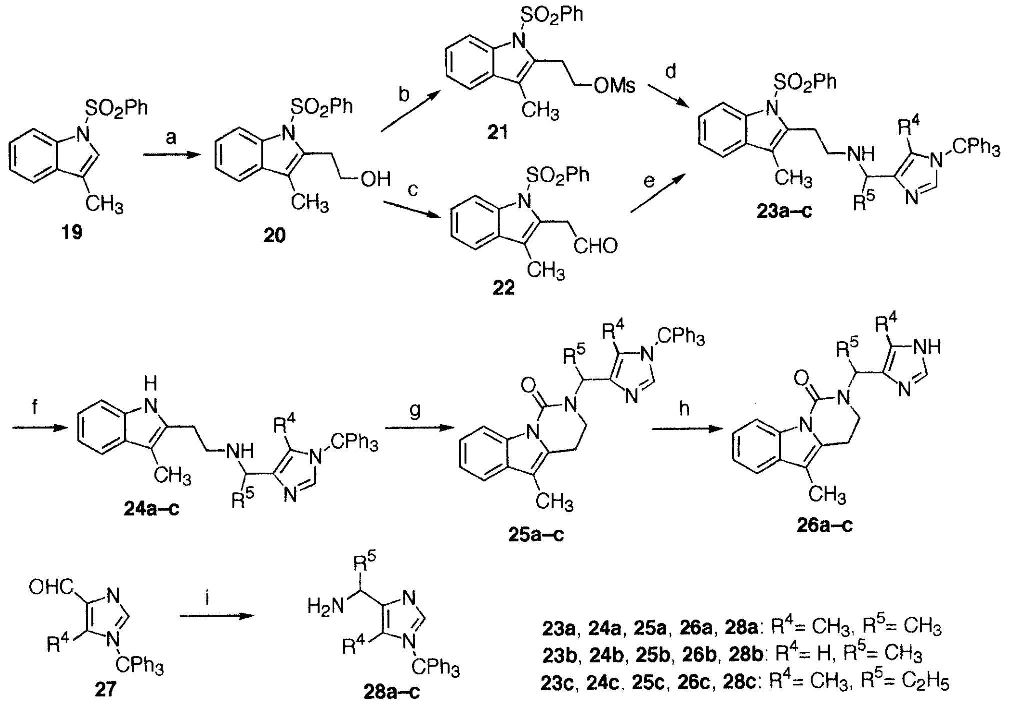
4



5

Compd. No.	R^1	R^2	R^3	Yield (%)	mp (°C)[a] (Recryst. solvent)	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
4a	H	H	H	55[b]	155—157 (C–H)	$C_{11}H_{10}N_2O$	70.95	5.41	15.05	71.08	5.45	15.12
4b	CH_3	H	H	40[c]	187—193 (M)	$C_{12}H_{12}N_2O$	71.97	6.04	13.99	71.80	6.10	13.75
4c	C_2H_5	H	H	9[b]	165—171 (M)	$C_{13}H_{14}N_2O$	72.87	6.59	13.08	72.84	6.91	13.09
4d	$(CH_3)_2CH$	H	H	34[b]	148—152 (M)	$C_{14}H_{16}N_2O$	73.65	7.06	12.27	73.37	7.21	12.21
4e	C_6H_5	H	H	70[c]	237—240 (A–H)	$C_{17}H_{14}N_2O \cdot 0.4H_2O$	75.76	5.54	10.40	75.67	5.41	10.29
4f	$C_6H_5CH_2$	H	H	63[b]	190—192 (C–H)	$C_{18}H_{16}N_2O$	78.23	5.84	10.14	78.14	5.95	10.11
4g	CH_3	H	CH_3	27[b]	146—149 (C–H)	$C_{13}H_{14}N_2O \cdot 0.2H_2O$	71.66	6.66	12.86	71.58	6.69	12.70
4h	H	CH_3	H	56[b]	144—147 (C–H)	$C_{13}H_{14}N_2O \cdot 0.1H_2O$	72.26	6.66	12.97	72.43	6.66	13.02
5a	H			41[c]	192—195 (C–H)	$C_{11}H_{12}N_2O \cdot 0.1H_2O$	69.52	6.47	14.74	69.57	6.47	14.82
5b	CH_3			22[c]	204—207 (A–C–H)	$C_{12}H_{14}N_2O$	71.26	6.98	13.85	71.28	6.97	13.78

a) The symbols are as follows: A, ethyl acetate; B, dichloromethane; C, chloroform; H, hexane; M, methanol; T, toluene. *b*) Yields from the corresponding imidazolecarboxamides (**14**). *c*) Yields from the corresponding amines (**13**).

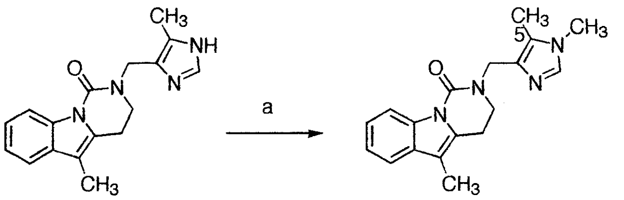


a) LDA, ethylene oxide, THF; b) MsCl, Et_3N; c) CrO_3, Py, CH_2Cl_2; d) **28b** or **28c**, K_2CO_3, NaI, benzene; e) **28a**, $NaBH_3CN$, MeOH; f) KOH, DMSO; g) DBU, 1,1′-carbonyldiimidazole, THF; h) aq. AcOH; i) i: $(Me_3Si)_2NLi$; ii: MeLi or EtMgBr, THF

Chart 4

pounds **23b** and **23c**. Compound **23a** was prepared by an alternative route. Oxidation of **20** with chromium trioxide and pyridine afforded the aldehyde **22**. Reductive amination of **22** with **28a** and sodium cyanoborohydride in methanol gave **23a**. Imidazolylmethanamines **28** were prepared from the imidazole-4-carbaldehyde (**27**). Treatment of **27** with lithium bis(trimethylsilyl)amide gave the trimethylsilylimine and subsequent reaction with methyl lithium or ethyl magnesium bromide gave **28**.[2] Hydrolysis of the benzenesulfonyl group of **23** was conducted with powdered potassium hydroxide in dimethylsulfoxide at 70 °C to give **24**. Refluxing of a solution of **24**, 1,1′-carbonyldiimidazole, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in tetrahydrofuran afforded **25** in one step. Compound **26** was prepared by heating **25** in aqueous acetic acid. Methylation of **8b** with sodium hydride and methyl iodide gave **29**, whose methyl group was located on the less hindered nitrogen at the 1-position of the imidazole ring (Chart 5). The position of the introduced methyl group was supported by NOE in the NOESY spectrum. NOE was observed between the new methyl resonance (δ 3.74) and the resonance of the methyl at the 5-position of the imidazole (δ 2.36).

Two enantiomers of **26a** were prepared from the optically active **28a**. The racemic **28a** was resolved by fractional recrystallization of the salt formed with di-*p*-toluoyltartaric acid. The (+)-di-*p*-toluoyl-D-tartaric

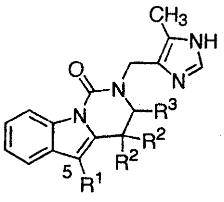


8b **29**

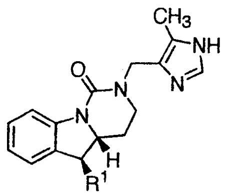
a) NaH, MeI, DMF

Chart 5

Table II. Inhibition of Bezold–Jarisch Reflex: Effect of Modification of the Pyrimido[1,6-*a*]indole Part



8

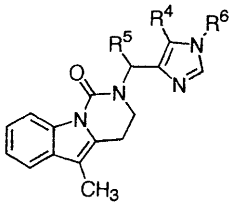


9

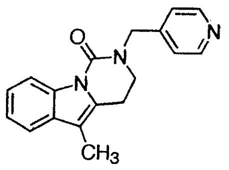
Compd. No.	R^1	R^2	R^3	% inhibition of 2-Me-5-HT induced bradycardia (μg/kg i.v.)[a] 100	32	10	3.2	1.0	0.32	ED_{50} (μg/kg i.v.)
8a	H	H	H				66.6	45.0	21.0	1.4
8b	CH_3	H	H				74.2	61.4	48.7	0.6
8c	C_2H_5	H	H	74.7			65.6	20.5	22.1	2.1
8d	$(CH_3)_2CH$	H	H	59.5			31.0			
8e	C_6H_5	H	H	70.0			42.1			
8f	$C_6H_5CH_2$	H	H	64.4			8.6			
8g[b]	CH_3	H	CH_3	66.2			20.6			
8h	H	CH_3	H				19.2			
9a[b]	H			68.0		67.2	42.7	22.4		7.8
9b[b]	CH_3						78.1	39.3	14.8	1.3
2 (ondansetron)				79.5	72.1	43.3				17.5
1 (FK 1052)				75.4		69.7		53.5	48.4	0.9

a) Each compound was tested in groups of three animals and data represent mean values of peak inhibition. *b*) The compound was tested as a racemate.

Table III. Inhibition of Bezold–Jarisch Reflex: Effect of Alterations of the Imidazole Ring Part



8, 26, 29



10

Compd. No.	R^4	R^5	R^6	% inhibition of 2-Me-5-HT induced bradycardia (μg/kg i.v.)[a] 100	3.2	1.0	0.32	ED_{50} (μg/kg i.v.)
8i	H	H	H	47.0	20.6			
8b	CH_3	H	H		74.3	61.4	48.7	0.6
8j	C_2H_5	H	H		72.1	50.4	43.0	0.7
26a[b]	CH_3	CH_3	H		81.5	32.9		1.5
26b[b]	H	CH_3	H	64.9	5.3			
26c[b]	CH_3	C_2H_5	H		11.3			
29	CH_3	H	CH_3		76.3	59.8	19.8	0.9
10					54.3	−2.0		
(+)-**26a**					75.5	70.1	21.9	0.8
(−)-**26a**				47.6	−16.1			

(*a*) Each compound was tested in groups of three animals and data represent mean values of peak inhibition. *b*) The compound was tested as a racemate.

acid salt gave (−)-**28a** after liberation of the free base. Compound (−)-**28a** was converted to (+)-**26a** according to the procedure described for **26b** and **c** in Chart 4. The (−)-di-*p*-toluoyl-L-tartaric acid salt gave (+)-**28a**, which was converted to (−)-**26a** in a manner similar to that described for (−)-**28a**.

Biological Results and Discussion

The 5-HT$_3$ receptor antagonist potency of the compounds prepared was assessed in terms of their ability to antagonize the 2-methylserotonin (2-Me-5-HT)-induced reflex bradycardia (the Bezold–Jarisch (BJ) reflex) in urethan-anesthetized rats. 2-Me-5-HT was reported to be a selective 5-HT$_3$ receptor agonist.[3] This effect is mediated by activation of 5-HT$_3$ receptors in the right ventricle.[4] Compounds were screened after intravenous administration. The results are presented in Tables II and III together with values for FK 1052 (**1**) and ondansetron (**2**).

The pharmacophore for 5-HT$_3$ receptor antagonists is regarded as an aromatic moiety, a linking acyl group, and a basic nitrogen.[5] We initially introduced various substituents on the pyrimido[1,6-*a*]indole ring in order to identify the optimal substitution in the aromatic ring moiety and linking acyl group portion (Table II). In the series bearing substituents at the 5-position (**8a**—**f**), the hydrogen (**8a**), methyl (**8b**), and ethyl (**8c**) substituents showed high potency. However, introduction of larger substituents, the isopropyl (**8d**), phenyl (**8e**), and benzyl (**8f**) resulted in reduction of potency. A methyl group at the 3- or 4-position caused a marked decrease in potency (**8g, h**). The decrease in potency of **8g** was ascribed to an unfavorable interaction between the methyl group and the imidazole ring. Although 3,4,4a,5-tetrahydro compounds (**9**) were less potent than the corresponding 3,4-dihydro compounds (**8a, b**), **9a** and **9b** still retained high potency. This result suggested that aromaticity in the 5-membered ring of pyrimido[1,6-*a*]indol-1(2*H*)-one is important but not essential for high potency. The beneficial effect of the 5-methyl group seen with the 3,4-dihydro compounds (**8a** *vs*. **8b**) was even more marked with the 3,4,4a,5-tetrahydro compounds (**9a** *vs*. **9b**). The methyl group (**9b**) increased the potency by a factor of 6. From these results, it is suggested that there is a small lipophilic pocket in the receptor near the 5-position of the pyrimido[1,6-*a*]indole ring of the bound ligands.

On the basis of the results described above, we next modified the basic amine part, while keeping the 3,4-dihydro-5-methylpyrimido[1,6-*a*]indole ring constant (Table III). Introduction of an alkyl group at the 5-position of the imidazole ring resulted in a marked increase in potency. The 5-methyl (**8b**) and 5-ethyl (**8j**) compounds showed the same order of potency (ED$_{50}$ 0.6 and 0.7 μg/kg i.v., respectively), whereas the unsubstituted compound (**8i**) was significantly less potent. This result is in marked contrast to that in the pyrido[1,2-*a*]indol-6(7*H*)-one series, in which the unsubstituted compound showed high potency and the methyl group at the 5-position of the imidazole ring resulted in a marginal increase in potency.[1] Furthermore, methylation at the 1-position of the imidazole ring retained a high potency (**29**). This result is also interesting, as a similar modification of the pyrido[1,2-*a*]indoles, reported in our previous paper, caused a drastic decrease in potency. The 4-pyridylmethyl group as a basic nitrogen resulted in a significant reduction in potency (**10**).

The high potency of **8b** prompted us to modify the methylene side chain portion of **8b**. Introduction of a methyl group (**26a**) retained high potency. However, the larger ethyl group (**26c**) resulted in considerable loss of activity, suggesting that large substituents interfere with the interaction between the carbonyl group and the 5-HT$_3$ receptor. The combination of methyl substitution on the methylene side chain and lack of substitution at the 5-position of the imidazole ring caused a further decrease

Table IV. Physical Data for Compounds Listed in Tables I and II

Compd. No.	Yield (%)	mp (°C)[a] (Recryst. solvent)	Formula	Analysis (%) Calcd			Found		
				C	H	N	C	H	N
8a	52	228—230 (D)	$C_{16}H_{16}N_4O\cdot 0.25H_2O$	67.47	5.84	19.67	67.67	5.64	19.49
8b	70	>250 (M–D)	$C_{17}H_{18}N_4O\cdot HCl$	61.72	5.79	16.94	61.52	5.82	16.79
8c	45	264—266 (M–D)	$C_{18}H_{20}N_4O\cdot HCl$	62.69	6.14	16.25	62.54	6.30	16.19
8d	73	258—260 (W)	$C_{19}H_{22}N_4O\cdot HCl$	63.59	6.18	15.61	63.60	6.64	15.39
8e	63	257—260 (W)	$C_{22}H_{20}N_4O\cdot HCl\cdot 1.5H_2O$	62.93	5.76	13.34	62.92	5.70	13.28
8f	55	246—248 (C–M–H)	$C_{23}H_{22}N_4O\cdot 0.25CHCl_3$	69.76	5.60	14.00	69.72	5.98	14.09
8g	36	262—264 (F)	$C_{18}H_{20}N_4O\cdot HCl\cdot 0.75H_2O$	60.33	6.33	15.64	60.88	6.22	15.19
8h	54	255—262 (D)	$C_{18}H_{20}N_4O\cdot HCl\cdot 0.5H_2O$	61.09	6.27	15.83	61.02	6.16	15.56
8i	36	266—269 (F)	$C_{16}H_{16}N_4O\cdot HCl\cdot 1.5H_2O$	55.89	5.86	16.30	55.86	5.54	16.21
8j	64	241—244 (A)	$C_{18}H_{20}N_4O\cdot HCl$	62.70	6.14	16.25	62.46	6.20	16.19
9a	71	225—227 (A–D)	$C_{16}H_{18}N_4O\cdot 1.2H_2O$	63.22	6.76	18.43	63.47	6.76	18.15
9b	44	>250 (M–D)	$C_{17}H_{20}N_4O\cdot HCl\cdot 0.6H_2O$	59.54	6.32	16.34	59.56	6.46	16.31
10	49	198—203 (F)	$C_{18}H_{17}N_3O\cdot HCl\cdot 1.5H_2O$	60.93	5.97	11.84	60.75	5.83	11.78
26a	79	239—241 (E–D)	$C_{18}H_{20}N_4O\cdot HCl\cdot 0.5H_2O$	61.09	6.27	15.83	60.98	6.32	15.74
26b	58	267—269 (A–E)	$C_{17}H_{18}N_4O\cdot HCl$	61.72	5.79	16.94	61.62	5.94	16.79
26c	77	227—229 (E–D)	$C_{19}H_{22}N_4O\cdot HCl$	63.59	6.46	15.61	63.58	6.49	15.43
29	50	221—225 (F)	$C_{18}H_{20}N_4O\cdot HCl\cdot H_2O$	59.58	6.39	15.44	59.75	6.41	15.15
(+)-**26a**[b]	70	238—239 (E–D)	$C_{18}H_{20}N_4O\cdot HCl$	62.70	6.14	16.25	62.60	6.20	16.11
(−)-**26b**[c]	64	237—238 (E–D)	$C_{18}H_{20}N_4O\cdot HCl$	62.70	6.14	16.25	62.54	6.17	16.38

a) See footnote *a*) in Table I. D, diethyl ether; E, ethanol; F, acetone; W, H_2O. *b*) $[\alpha]_D^{25}$ +119.5° ($c=1.0$, MeOH). *c*) $[\alpha]_D^{25}$ −116.5° ($c=1.0$, MeOH).

in potency (**26b**).

From this series, **8b** and **26a** were selected for further evaluation. Since **26a** was racemic, the enantiomers were prepared and their potencies were compared. In the BJ reflex assay, ED_{50} of (+)-**26a** was 0.8 μg/kg i.v. and that of (−)-**26a** was >100 μg/kg i.v. Compound (+)-**26a** was equipotent with FK 1052 (**1**) (ED_{50} 0.9 μg/kg i.v.) and 22-fold more potent than ondansetron (ED_{50} 17.5 μg/kg i.v.). Compound **8b**, which has no asymmetric center, was 1.5-fold more potent than FK 1052 and 30-fold more potent than ondansetron.

In conclusion, a novel series of pyrimido[1,6-*a*]indol-1(2*H*)-ones has been discovered to possess potent $5\text{-}HT_3$ receptor antagonist activity. These compounds can be considered to be bioisosters of pyrido[1,2-*a*]indol-6(7*H*)-ones, described in the first paper.[1] However, structure–activity relationships in this series are different from those of pyrido[1,2-*a*]indole series, suggesting that the conformations of the imidazole ring in the two series are significantly different from each other. The sp^2-hybridized nitrogen at the 2-position in this series and the sp^3-hybridized carbon at the 7-position in the first series may yield different low energy conformations for the basic nitrogen side chain. From this series, **8b** and (+)-**26a** were selected as highly potent $5\text{-}HT_3$ receptor antagonists and are currently being evaluated as drugs for gastrointestinal dysfunction.

Experimental

Melting points are uncorrected. ^1H-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 on 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 Kieselgel 60 (E. Merck, No. 7734). The optical purity of (−)-**28a** was determined by HPLC using a 4.0 × 250 mm Chiracel OD (Daicel) column with hexane–2-propanol (19 : 1) as the mobile phase.

1*H*-Indole-2-ethanamine (**13a**),[6] 3-phenyl-1*H*-indole-2-ethanamine (**13e**),[7] 3-methyl-2-(2-nitrovinyl)indole (**12b**),[8] 3-ethyl-2-(2-nitrovinyl)indole (**12c**),[8] 3-isopropyl-2-(2-nitrovinyl)indole (**12d**),[8] 1*H*-indole-2-acetonitrile (**15**),[9] 3-methyl-1-phenylsulfonylindole (**19**),[10] 4-chloromethyl-5-methyl-1-(triphenylmethyl)-1*H*-imidazole[11] and 4-chloromethyl-1-(triphenylmethyl)-1*H*-imidazole[11] were prepared by the cited methods. 4-Chloromethyl-5-ethyl-1-(triphenylmethyl)-1*H*-imidazole was prepared in a similar manner to that described for 4-chloromethyl-5-methyl-1-(triphenylmethyl)-1*H*-imidazole.

Preparation of the Pyrimido[1,6-*a*]indole-1(2*H*)-ones (4) (Method A). a) 3-Methyl-2-(2-nitro-1-propenyl)indole (12g) A mixture of 3-methylindole-2-carbaldehyde[12] (7.0 g, 44 mmol), $AcONH_4$ (1.4 g, 18 mmol), and nitroethane (10.5 ml) in MeOH (35 ml) was refluxed for 1 h. After evaporation of the solvent, the residue was dissolved in EtOAc. The solution was washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was triturated with isopropyl ether to give **12g** (4.3 g, 45%), mp 181—184 °C. IR (Nujol): 3420, 1630, 1610 cm^{-1}. ^1H-NMR (DMSO-d_6) δ: 2.40 (3H, s), 2.57 (3H, s), 7.10—7.40 (2H, m), 7.49 (1H, d, J=8 Hz), 7.61 (1H, d, J=8 Hz), 8.16 (1H, s), 10.97 (1H, s). MS *m/z*: 216 (M^+).

Compound **12f** was prepared by the procedure described for **12g**.

3-Benzyl-2-(2-nitrovinyl)indole (12f) Yield 61%, mp 171—174 °C (MeOH). IR (Nujol): 1630, 1610 cm^{-1}. ^1H-NMR (DMSO-d_6) δ: 4.33 (2H, s), 6.90—7.30 (7H, m), 7.41 (1H, d, J=8 Hz), 7.59 (1H, d, J=8 Hz), 8.06 (1H, d, J=13 Hz), 8.26 (1H, d, J=13 Hz), 11.64 (1H, s). MS *m/z*: 278 (M^+).

b) 3-Methyl-1*H*-indole-2-ethanamine (13b) A solution of **12b** (7.3 g, 0.036 mol) in tetrahydrofuran (THF) (100 ml) was added to a suspension of $LiAlH_4$ (6.0 g, 0.16 mol) in THF (50 ml) under nitrogen at room temperature over a period of 1 h. After stirring for 1 h at room temperature, the mixture was heated at 60 °C for 5 h. The reaction mixture was cooled to 0 °C and excess $LiAlH_4$ was decomposed by the sequential addition of MeOH and saturated aqueous potassium sodium tartrate. After filtration of the reaction mixture, the filtrate was dried (Na_2SO_4) and evaporated *in vacuo* to give **13b** as an oil (6.3 g, 100%), which was used in the next reaction without purification. IR (film): 3400, 1585 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.04 (2H, br s), 2.18 (3H, s), 2.82 (2H, t, J=6 Hz), 3.00 (2H, t, J=6 Hz), 7.10 (2H, m), 7.28 (1H, m), 7.50 (1H, m). MS *m/z*: 174 (M^+). 3-Ethyl-1*H*-indole-2-ethanamine (**13c**), 3-isopropyl-1*H*-indole-2-ethanamine (**13d**), 3-benzyl-1*H*-indole-2-ethanamine (**13f**), and α,3-dimethyl-1*H*-indole-2-ethanamine (**13g**) were prepared by the same procedure as described for **13b** and used in the next reaction without purification.

Compound 13f Yield 100%. An oil. IR (film): 3400, 3200, 1600 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.70—3.00 (4H, m), 4.07 (2H, s), 7.00—7.50 (9H, m), 9.22 (1H, s). MS *m/z*: 250 (M^+).

c) *N*-[2-(3-Benzyl-1*H*-indol-2-yl)ethyl]-1*H*-imidazole-1-carboxamide (14f) 1,1′-Carbonyldiimidazole (2.6 g, 16 mmol) was added to a solution of crude **13f** (4.1 g, 16 mmol) in AcOEt (80 ml) at room temperature. After 12 h at room temperature, the reaction mixture was washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by chromatography on silica gel (10% EtOAc–$CHCl_3$) to give **14f** (2.64 g, 48%), mp 71—74 °C. IR (Nujol): 3350, 1690 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 3.04 (2H, t, J=7 Hz), 3.55 (2H, t, J=7 Hz), 4.06 (2H, s), 6.67 (1H, t, J=6 Hz), 6.90—7.50 (11H, m), 7.19 (1H, s), 8.68 (1H, s). Compounds **14a**, **14c**, **14d**, and **14g** were prepared by the same procedure as described for **14f**. Compounds **14b** and **14e** were prepared similarly and used in the next reaction without purification.

***N*-[2-(1*H*-Indol-2-yl)ethyl-1*H*-imidazole-1-carboxamide (14a)** Yield 41%. An amorphous powder. IR (Nujol): 3350, 1600 cm^{-1}. ^1H-NMR (DMSO-d_6) δ: 3.01 (2H, t, J=7 Hz), 3.64 (2H, m), 6.21 (1H, s), 6.96 (3H, m), 7.29 (1H, d, J=8 Hz), 7.36 (1H, d, J=8 Hz), 7.66 (1H, s), 8.23 (1H, s), 8.65 (1H, t, J=5 Hz), 11.02 (1H, s). MS *m/z*: 254 (M^+).

***N*-[2-(3-Ethyl-1*H*-indol-2-yl)ethyl]-1*H*-imidazole-1-carboxamide (14c)** Yield 82%, mp 68—73 °C. IR ($CHCl_3$): 3300, 1720, 1710, 1660 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz), 2.69 (2H, q, J=7 Hz), 3.07 (2H, t, J=7 Hz), 3.50—3.80 (2H, m), 6.70—8.70 (8H, m).

***N*-[2-(3-Isopropyl-1*H*-indol-2-yl)ethyl-1*H*-imidazole-1-carboxamide (14d)** Yield 56%, mp 60—63 °C. IR (Nujol): 3350, 3250, 1705, 1650 cm^{-1}. ^1H-NMR (DMSO-d_6) δ: 1.29 (6H, d, J=7 Hz), 2.98 (2H, t, J=7 Hz), 3.00—3.20 (1H, m), 3.40—3.60 (2H, m), 6.80—7.00 (3H, m), 7.26 (1H, d, J=8 Hz), 7.55 (1H, d, J=8 Hz), 7.60 (1H, s), 8.23 (1H, s), 8.65 (1H, t, J=6 Hz), 10.75 (1H, s).

***N*-[1-Methyl-2-(3-methyl-1*H*-indol-2-yl)ethyl]-1*H*-imidazole-1-carboxamide (14g)** Yield 16%, mp 115—118 °C. IR (Nujol): 3300, 1700, 1655 cm^{-1}. ^1H-NMR (DMSO-d_6) δ: 1.20 (3H, d, J=7 Hz), 2.18 (3H, s), 2.80—3.20 (2H, m), 2.37 (1H, br s), 4.10—4.30 (1H, m), 6.60—6.70 (5H, m), 8.20—8.40 (2H, m), 10.70 (1H, s).

d) 5-Benzyl-3,4-dihydropyrimido[1,6-*a*]indol-1(2*H*)-one (4f) A solution of **14f** (2.4 g, 7.0 mmol) in xylene (50 ml) was refluxed for 3 h. After cooling, the mixture was washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by chromatography on silica gel (5% MeOH–$CHCl_3$) to give **4f** (1.2 g, 63%). Recrystallization from $CHCl_3$–hexane gave an analytical sample, mp 190—192 °C. IR (Nujol): 3200, 1690, 1630 cm^{-1}. ^1H-NMR (DMSO-d_6) δ: 3.06 (2H, t, J=6 Hz), 3.39 (2H, t, J=6 Hz), 4.00 (2H, s), 7.00—7.30 (7H, m), 7.39 (1H, dd, J=1, 6 Hz), 7.86 (1H, s), 8.19 (1H, d, J=8 Hz). MS *m/z*: 276 (M^+). Compounds **4a**—**e** and **4g** were prepared by the same procedure as described for **4f**. Physical data for **4** are given in Table I.

Preparation of 3,4-Dihydro-4,4-dimethylpyrimido[1,6-*a*]indol-1(2*H*)-one (4h) (Method B). a) 2-(1*H*-Indol-2-yl)-2-methylpropionitrile (16) A solution of 1*H*-indole-2-ylacetonitrile (**15**) (1.25 g, 8.0 mmol) in THF (10 ml) was added to a stirred solution of LDA (8.7 mmol; prepared from 0.81 g of diisopropylamine and 5.3 ml of 1.64 M *n*-BuLi in hexane) in THF (10 ml) at −30 °C under nitrogen. The mixture was stirred at the same temperature for 1 h, and a solution of methyl iodide (1.14 g, 8.0 mmol) in THF (10 ml) was added over 1 h. The mixture was held for 1 h at −60 °C and 2 h at room temperature, then diluted with H_2O and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. Chromatography of the residue on neutral alumina (10% EtOAc–toluene) first afforded **16** (354 mg, 24%), mp 79—82 °C (EtOAc–hexane). IR (Nujol): 3320, 2240, 1620, 1580 cm^{-1}. ^1H-NMR (DMSO-d_6) δ: 1.78 (6H, s), 6.42 (1H, m), 6.96—7.15 (2H, m), 7.36 (1H, d, J=8 Hz), 7.51 (1H, d, J=8 Hz), 11.42 (1H, s). MS m/z: 184 (M$^+$). *Anal.* Calcd for $C_{12}H_{12}N_2\cdot 0.1H_2O$: 77.47; H, 6.61; N, 15.06. Found: C, 77.56; H, 6.62; N, 15.03. Further elution afforded 2-(1*H*-indol-2-yl)propionitrile (**18**) (599 mg, 44%), mp 72—78 °C (EtOAc–hexane). IR (Nujol): 3320, 2240, 1610 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.66 (3H, d, J=7 Hz), 4.48 (1H, q, J=7 Hz), 6.41 (1H, s), 6.94—7.13 (2H, m), 7.36 (1H, d, J=7 Hz), 7.50 (1H, d, J=8 Hz), 11.36 (1H, s). MS m/z: 170 (M$^+$). *Anal.* Calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.29; H, 5.95; N, 16.50.

b) 2-(1*H*-Indol-2-yl)-2-methylpropylamine (13h) A mixture of **16** (300 mg, 1.6 mmol) and 5% Rh-on-alumina (500 mg) in 10 N NH_3 in MeOH (20 ml) was hydrogenated at 3 atm for 8 h. After removal of the catalysts by filtration, the filtrate was evaporated *in vacuo* to give **13h** (306 mg, 100%), mp 178—182 °C. IR (Nujol): 3250, 1580, 1540 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 1.34 (6H, s), 2.10—3.10 (4H, m), 6.24 (1H, s), 7.00—7.60 (4H, m), 9.54 (1H, br s). MS m/z: 188 (M$^+$).

c) *N*-[2-(1*H*-Indol-2-yl)-2-methylpropyl]-1*H*-imidazole-1-carboxamide (14h) Compound **14h** was prepared from **13h** according to subsection c under method A. Yield 72%, mp 133—136 °C. IR (Nujol): 3300, 3200, 1720, 1615 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 1.46 (6H, s), 3.60 (2H, d, J=6 Hz), 6.29 (1H, d, J=2 Hz), 6.90—7.60 (7H, m), 8.17 (1H, s), 9.95 (1H, s).

d) Compound 4h was prepared from **14h** according to subsection d under method A. Yield 56%, mp 144—147 °C (CHCl$_3$–hexane). IR (Nujol): 3250, 1700, 1590 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 1.47 (6H, s), 3.27 (2H, d, J=3 Hz), 5.68 (1H, s), 6.33 (1H, s), 7.10—7.60 (3H, m), 8.36 (1H, d, J=8 Hz). MS m/z: 214 (M$^+$).

Preparation of the 3,4,4a,5-Tetrahydropyrimido[1,6-*a*]indol-1(2*H*)-ones (5) (Method C). 3,4,4a,5-Tetrahydropyrimido[1,6-*a*]indol-1(2*H*)-one (5a) $NaBH_3CN$ (1.1 g, 17.5 mmol) was added in small portions to a solution of 1*H*-indole-2-ethanamine (**13a**) (1.1 g, 7.1 mmol) in AcOH (10 ml) at 15 °C over a period of 0.5 h. The mixture was stirred at room temperature for 15 h. After dilution with H_2O, the reaction mixture was made basic with NaOH pellets and extracted with ether. The ether layer was washed with H_2O and brine, dried (Na_2SO_4), and evaporated *in vacuo* to give crude 2,3-dihydro-1*H*-indole-2-ethanamine (**17a**) as an oil. IR (film): 3340, 3250, 1600, 1480 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.60 (2H, m), 2.50—2.80 (2H, m), 2.84 (2H, br s), 3.01 (2H, m), 3.80 (1H, m), 6.45 (2H, m), 6.95 (2H, m). MS m/z: 162 (M$^+$).

1,1′-Carbonyldiimidazole (1.1 g, 6.8 mmol) was added in small portions to a solution of crude **17a** in THF (20 ml) at room temperature. After 2 h, the reaction mixture was evaporated *in vacuo*. The residual oil was dissolved in toluene (25 ml) and the solution was heated at 100 °C for 2 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (1% MeOH–CHCl$_3$) to give **5a** (550 mg, 41%). Recrystallization from CHCl$_3$–hexane gave an analytical sample, mp 192—195 °C. IR (Nujol): 3250, 1650, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.60—1.80 (1H, m), 2.20 (1H, dd, J=3, 12 Hz), 2.85 (1H, dd, J=11, 16 Hz), 3.10—3.30 (3H, m), 4.24 (1H, m), 6.66 (1H, br s), 6.84 (1H, t, J=7 Hz), 7.12 (2H, m), 7.71 (1H, d, J=8 Hz). MS m/z: 188 (M$^+$). 5-Methyl-3,4,4a,5-tetrahydropyrimido[1,6-*a*]indol-1(2*H*)-one (**5b**) was prepared by the same procedure as described for **5a**.

3,4-Dihydro-5-methyl-2-[(5-methyl-1*H*-imidazol-4-yl)methyl]pyrimido[1,6-*a*]indol-1(2*H*)-one (8b) a) A solution of **4b** (0.67 g, 3.4 mmol) in DMF (8 ml) at 0 °C was treated with NaH (60% in mineral oil, 0.16 g, 4.0 mmol). After 1 h at 0 °C, 4-chloromethyl-5-methyl-1-(triphenylmethyl)-1*H*-imidazole (1.50 g, 4.0 mmol) was added to the solution in small portions. After 2 h at 0 °C, the reaction mixture was diluted with H_2O to give a precipitate. The precipitate collected was dissolved in CH_2Cl_2. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. Column chromatography (silica gel, 0.5% MeOH–CHCl$_3$) of the residue, followed by recrystallization from toluene–hexane, gave 3,4-dihydro-5-methyl-2-[[5-methyl-1-(triphenylmethyl)-1*H*-imidazol-4-yl]methyl]pyrimido[1,6-*a*]indol-1(2*H*)-one (**7b**) (1.16 g, 66%), mp 210—220 °C. IR (Nujol): 1680, 1620, 1330 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 1.52 (3H, s), 2.17 (3H, s), 2.94 (2H, t, J=6 Hz), 3.64 (2H, t, J=6 Hz), 4.67 (2H, s), 7.10—7.52 (19H, m), 8.33 (1H, d, J=7 Hz). *Anal.* Calcd for $C_{36}H_{32}N_4O\cdot 0.25H_2O$: C, 79.90; H, 6.05; N, 10.35. Found: C, 80.03; H, 6.18; N, 10.18.

b) A solution of **7b** (0.9 g, 1.7 mmol) in AcOH–H_2O (4 : 1, 30 ml) was heated at 65 °C for 3.5 h. After evaporation of the solvent, the residue was neutralized with aqueous $NaHCO_3$ 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 (5% MeOH–CHCl$_3$) to give a crystalline residue. The crystals were treated with HCl in MeOH and recrystallized from MeOH–ether to give **8b** (387 mg, 70%), mp > 250 °C. IR (Nujol): 1685, 1630, 1345 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.15 (3H, s), 2.37 (3H, s), 3.06 (2H, t, J=6 Hz), 3.63 (2H, t, J=6 Hz), 4.72 (2H, s), 7.22 (2H, m), 7.47 (1H, m), 8.19 (1H, m), 9.00 (1H, s). Compounds **8** and **9** were prepared by the same procedure as described for **8b** and the intermediates **7** were used in the next reaction without purification. 3,4-Dihydro-5-methyl-2-(4-pyridylmethyl)pyrimido[1,6-*a*]indol-1(2*H*)-one (**10**) was prepared by the same procedure as described for **7b**. The physical data of compounds **8**, **9**, and **10** are listed in Table IV.

2-[3-Methyl-1-(phenylsulfonyl)-1*H*-indol-2-yl]ethanol (20) A solution of 3-methyl-1-(phenylsulfonyl)-1*H*-indole (**19**) (2.71 g, 10 mmol) in THF (20 ml) was added over 20 min to a solution of LDA (11 mmol prepared from 1.11 g of diisopropylamine and 7.0 ml of 1.61 M *n*-BuLi in hexane) in THF (10 ml) at −70 °C. The solution was stirred for 1 h at −70 °C and allowed to come to 0 °C over 1 h. The mixture was again cooled to −70 °C and treated with a solution of ethylene oxide (484 mg, 11 mmol) in THF (5 ml). The mixture was stirred at −70 °C for 1 h and at room temperature overnight, then diluted with H_2O and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by chromatography on silica gel (5% EtOAc–hexane) to give **20** (1.19 g, 38%) as an oil. IR (film): 3300, 1450, 1230, 1170 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 2.19 (3H, s), 2.76 (1H, br s), 3.27 (2H, t, J=6 Hz), 3.94 (2H, m), 7.10—7.50 (6H, m), 7.60—7.70 (2H, m), 8.10—8.20 (1H, m). MS m/z: 315 (M$^+$).

2-[2-(Methanesulfonyloxy)ethyl]-3-methyl-1-(phenylsulfonyl)-1*H*-indole (21) A solution of methanesulfonyl chloride (2.84 g, 24.8 mmol) in CH_2Cl_2 (57 ml) was added dropwise to a solution of **20** (7.1 g, 22.5 mmol) and Et_3N (2.96 g, 29.3 mmol) in CH_2Cl_2 (70 ml) at −40 °C. After stirring at −40 °C for 30 min, the reaction mixture was diluted with H_2O and neutralized with 1 N HCl. The organic layer was washed with H_2O, dried ($MgSO_4$), and evaporated *in vacuo* to give crude **21** (8.8 g) as an amorphous powder, which was used in the next reaction without purification. IR (Nujol): 3020, 1605 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.18 (3H, s), 3.15 (3H, s), 3.47 (2H, t, J=6 Hz), 4.50 (2H, t, J=6 Hz), 7.00—7.80 (8H, m), 8.06 (1H, d, J=7 Hz).

3-Methyl-1-(phenylsulfonyl)-1*H*-indol-2-acetaldehyde (22) A solution of **20** (630 mg, 2.0 mmol) in CH_2Cl_2 (2 ml) was added to a mixture of chromium trioxide (1.2 g, 12 mmol) and pyridine (1.9 g) in CH_2Cl_2 (40 ml) at room temperature. The mixture was stirred at room temperature for 15 min. The organic layer was separated, washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (5% EtOAc–toluene) to give **22** (423 mg, 68%), mp 81—84 °C. IR (film): 1725, 1670, 1450 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 2.16 (3H, s), 4.10 (2H, s), 7.10—8.10 (9H, m), 9.77 (1H, s). MS m/z: 313 (M$^+$).

3-Methyl-*N*-[1-[5-methyl-1-(triphenylmethyl)-1*H*-imidazol-4-yl]ethyl]-1-(phenylsulfonyl)-1*H*-indole-2-ethanamine (23a) A mixture of **28a** (735 mg, 2.0 mmol), **22** (626 mg, 2.0 mmol), and molecular sieves 3A (100 mg) in MeOH (30 ml) was stirred at room temperature for 30 min. AcOH (0.35 ml) and $NaBH_3CN$ (126 mg, 2.0 mmol) were added and the mixture was stirred at room temperature for 2 h, then diluted with H_2O and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (3% MeOH–CHCl$_3$) to give **23a** (947 mg, 71%) as an amorphous powder. IR (Nujol): 1630, 1590, 1230 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 1.42 (3H, s), 1.61 (3H, d, J=7 Hz), 2.18 (2.90—3.10 (2H, m), 3.20—3.50 (2H, m), 4.11 (1H, q, J=7 Hz), 7.00—7.80 (24H, m), 8.10—8.20 (1H, m).

3-Methyl-*N*-[1-[5-methyl-1-(triphenylmethyl)-1*H*-imidazol-4-yl]propyl]-1-(phenylsulfonyl)-1*H*-indole-2-ethanamine (23c) A mixture of **21** (6.8 g, 17.3 mmol), **28c** (6.0 g, 15.7 mmol), NaI (716 mg, 4.7 mmol), and K_2CO_3 (2.16 g, 15.6 mmol) in benzene (60 ml) was stirred at reflux for 24 h. The reaction mixture was diluted with H_2O and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (3% MeOH–CHCl$_3$) to give **23c** (6.32 g, 59%) as an amorphous powder. IR (Nujol): 2900, 1400, 1370 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.28 (3H, d, J=7 Hz), 1.31 (3H, s), 2.09 (3H, s), 2.40—2.60 (2H, m), 2.90—3.30 (2H, m), 3.69 (1H, q, J=7 Hz), 6.90—7.80 (24H, m), 8.00—8.20 (1H, m). MS m/z: 538 (M$^+$ − SO_2Ph). Compound **23b** was prepared by the same procedure as described for **23c**.

3-Methyl-*N*-[1-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]ethyl]-1-(phe-

nylsulfonyl)-1*H*-indole-2-ethanamine (23b) Yield 41%. An amorphous powder. IR (Nujol): 3250, 1590 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.26 (3H, d, $J=7$ Hz), 2.05 (3H, s), 2.60—3.20 (4H, m), 3.72 (1H, q, $J=7$ Hz), 6.72 (1H, s), 7.00—7.80 (24H, m), 8.00—8.20 (1H, m).

3-Methyl-*N*-[1-[5-methyl-1-(triphenylmethyl)-1*H*-imidazol-4-yl]ethyl]-1*H*-indole-2-ethanamine (24a) A mixture of **23a** (970 mg, 1.46 mmol) and KOH powder (819 mg, 14.6 mmol) in DMSO (10 ml) was stirred at 70 °C for 1 h. The mixture was diluted with H_2O and extracted with a mixture of THF and EtOAc (3 : 7). The extracts were washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (5% MeOH–$CHCl_3$) to give **24a** (611 mg, 80%) as an amorphous powder. IR (Nujol): 2940, 1460, 1370, 1230 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.20—1.40 (6H, m), 2.12 (3H, s), 2.40—2.80 (4H, m), 3.40 (2H, br s), 3.77 (1H, q, $J=7$ Hz), 6.80—7.40 (20H, m). Compounds **24b** and **24c** were prepared by the same procedure as described for **24a**.

3-Methyl-*N*-[1-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]ethyl]-1*H*-indole-2-ethanamine (24b) Yield 64%. An amorphous powder. IR (Nujol) 3250, 1590 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.27 (3H, d, $J=7$ Hz), 2.10 (3H, s), 2.60—3.00 (4H, m), 3.72 (1H, q, $J=7$ Hz), 6.70 (1H, d, $J=1$ Hz), 6.80—7.60 (20H, m), 10.65 (1H, s).

3-Methyl-*N*-[1-[5-methyl-1-(triphenylmethyl)-1*H*-imidazol-4-yl]propyl]-1*H*-indole-2-ethanamine (24c) Yield 72%. An amorphous powder. IR (Nujol): 2900, 1460 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.71 (3H, t, $J=7$ Hz), 1.30 (3H, s), 1.50—1.80 (2H, m), 2.12 (3H, s), 2.50—2.90 (4H, m), 3.30—3.50 (1H, m), 6.90—7.40 (20H, m).

3,4-Dihydro-5-methyl-2-[1-[5-methyl-1-(triphenylmethyl)-1*H*-imidazol-4-yl]ethyl]pyrimido[1,6-*a*]indol-1(2*H*)-one (25a) A mixture of **24a** (262 mg, 0.50 mmol), 1,1′-carbonyldiimidazole (210 mg, 1.3 mmol), DBU (84 mg), and molecular sieves 3A (100 mg) in THF (3 ml) was stirred at reflux for 2 h. The reaction mixture was diluted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (5% MeOH–$CHCl_3$) to give **25a** (208 mg, 76%), mp 103—110 °C (ether–hexane). IR ($CHCl_3$): 1670, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.39 (3H, s), 1.52 (3H, d, $J=7$ Hz), 2.15 (3H, s), 2.50—3.50 (4H, m), 5.68 (1H, q, $J=7$ Hz), 7.00—7.50 (19H, m), 8.10—8.20 (1H, m). MS *m/z*: 550 (M^+). *Anal.* Calcd for $C_{37}H_{34}N_4O \cdot 0.4H_2O$: C, 79.66; H, 6.29; N, 10.03. Found: C, 79.43; H, 6.16; N, 10.07. Compounds **25b** and **25c** were prepared by the same procedure as described for **25a**.

3,4-Dihydro-5-methyl-2-[1-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]ethyl]pyrimido[1,6-*a*]indol-1(2*H*)-one (25b) Yield 82%. An amorphous powder. IR (Nujol): 1680, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.42 (3H, d, $J=7$ Hz), 2.14 (3H, s), 2.50—3.50 (4H, m), 5.66 (1H, q, $J=7$ Hz), 6.90 (1H, s), 7.10—7.70 (19H, m), 8.10—8.30 (1H, m). MS *m/z*: 536 (M^+).

3,4-Dihydro-5-methyl-2-[1-[5-methyl-1-(triphenylmethyl)-1*H*-imidazol-4-yl]propyl]pyrimido[1,6-*a*]indol-1(2*H*)-one (25c) Yield 72%. An amorphous powder. IR (Nujol): 1675, 1620, 1500 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.90 (3H, t, $J=7$ Hz), 1.36 (3H, s), 1.90—2.10 (2H, m), 2.15 (3H, s), 2.50—2.70 (1H, m), 2.90—3.10 (1H, m), 3.30—3.50 (2H, m), 5.44 (1H, t, $J=8$ Hz), 7.00—7.50 (19H, m), 8.10—8.20 (1H, m). MS *m/z*: 564 (M^+).

3,4-Dihydro-5-methyl-2-[1-(5-methyl-1*H*-imidazol-4-yl)ethyl]pyrimido[1,6-*a*]indol-1(2*H*)-one Hydrochloride (26a) A solution of **25a** (60 mg, 0.11 mmol) in AcOH–H_2O (7 : 3, 2.6 ml) was stirred at 60 °C for 2 h. After evaporation of the solvent, the residue was dissolved in 10% MeOH–$CHCl_3$. The solution was washed with aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (10% MeOH–$CHCl_3$). The solid obtained was converted to the hydrochloride (**26a**) (30 mg, 79%) by treatment with HCl in MeOH followed by recrystallization from EtOH–ether, mp 239—241 °C. IR (Nujol): 1675, 1640, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.66 (3H, d, $J=7$ Hz), 2.14 (3H, s), 2.35 (3H, s), 2.90—3.10 (2H, m), 3.30—3.70 (2H, m), 5.82 (1H, q, $J=7$ Hz), 7.10—7.30 (2H, m), 7.40—7.50 (1H, m), 8.10—8.20 (1H, m), 9.04 (1H, s), 14.60 (2H, br s). Compounds **26b** and **26c** were prepared by the same procedure as described for **26a**. Physical data are listed in Table IV.

α,5-Dimethyl-1-(triphenylmethyl)-1*H*-imidazole-4-methanamine (28a) A solution of lithium bis(trimethylsilyl)amide (44 mmol prepared from 7.1 g of 1,1,1,3,3,3-hexamethyldisilazane and 28 ml of 1.56 M *n*-BuLi in hexane) in THF (30 ml) was added over 8 min to a solution of 5-methyl-1-(triphenylmethyl)-1*H*-imidazole-4-carbaldehyde (14.1 g, 40 mmol) in THF (140 ml) at −70 °C under nitrogen. After 25 min at −70 °C, 1.05 M methyllithium in ether (52 ml) was added to the mixture. The whole was stirred at −70 °C for 2.5 h, then diluted with H_2O and extracted twice with ether. The combined extracts were washed with H_2O and brine, dried (Na_2SO_4), and evaporated *in vacuo*. The oil obtained was purified by column chromatography on silica gel (20% MeOH–$CHCl_3$) to give **28a** (9.7 g, 66%). Recrystallization from ether–hexane gave an analytical sample, mp 160—162 °C. IR (film): 3300, 1590, 1485, 1440 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.24 (3H, d, $J=7$ Hz), 1.37 (3H, s), 3.15 (2H, br s), 3.86 (1H, q, $J=7$ Hz), 7.05—7.78 (16H, m). MS *m/z*: 367 (M^+). *Anal.* Calcd for $C_{25}H_{25}N_3$: C, 81.71; H, 6.86; N, 11.43. Found: C, 81.44; H, 7.02; N, 11.12. Compounds **28b** and **28c** were prepared by the same procedure as described for **28a**.

α-Methyl-1-(triphenylmethyl)-1*H*-imidazole-4-methanamine (28b) Yield 44%. An oil. IR (film): 3400, 1480 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (3H, d, $J=5$ Hz), 3.20 (2H, br s), 3.87 (1H, q, $J=5$ Hz), 6.71 (1H, s), 7.00—7.50 (16H, m). MS *m/z*: 353 (M^+).

α-Ethyl-5-methyl-1-(triphenylmethyl)-1*H*-imidazole-4-methanamine (28c) Yield 60%. An oil. IR (film): 3300, 1595, 1440 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.68 (3H, t, $J=7$ Hz), 1.34 (3H, s), 1.40—1.70 (2H, m), 2.90 (2H, br s), 3.45 (1H, t, $J=8$ Hz), 7.00—7.50 (16H, m). MS *m/z*: 381 (M^+).

3,4-Dihydro-5-methyl-2-[(1,5-dimethylimidazol-4-yl)methyl]pyrimido[1,6-*a*]indol-1(2*H*)-one Hydrochloride (29) A solution of the free base of **8b** (343 mg, 1.2 mmol) in DMF (20 ml) at 0 °C was treated with NaH (60% in mineral oil, 51 mg, 1.3 mmol). The mixture was stirred at 0 °C for 30 min, and a solution of methyl iodide (182 mg, 1.3 mmol) in DMF (10 ml) was added to it. After 2 h at 0 °C, the reaction mixture was evaporated *in vacuo*. The residue was dissolved in a mixture of THF and EtOAc (1 : 3, 20 ml) and the solution was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (3% MeOH–$CHCl_3$). The product was dissolved in 2 N HCl (2 ml) and evaporated *in vacuo*. The crystals obtained were washed with acetone to give **29** (200 mg, 50%), mp 221—225 °C. IR (Nujol): 1670, 1625 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.15 (3H, s), 2.36 (3H, s), 3.06 (2H, t, $J=6$ Hz), 3.63 (2H, t, $J=6$ Hz), 3.74 (3H, s), 4.72 (2H, m), 7.22 (2H, m), 7.47 (1H, m), 8.19 (1H, m), 9.04 (1H, s).

(−)-α,5-Dimethyl-1-(triphenylmethyl)-1*H*-imidazole-4-methanamine [(−)-28a] (+)-Di-*p*-toluoyl-D-tartaric acid (91.3 g, 0.236 mol) and **28a** (86.8 g, 0.236 mol) were dissolved in a mixture of MeOH and 2-propanol (1 : 1, 860 ml) at 70 °C. The solution was allowed to stand at 0 °C for 24 h to give 88.0 g of crystals. Two recrystallizations from a mixture of MeOH and 2-propanol (1 : 1) gave crystals with mp 160—164 °C (56 g). The crystals were suspended in H_2O, neutralized with 2 N NaOH, and extracted with ether. The organic layer was washed with H_2O and brine, dried (Na_2SO_4), and evaporated *in vacuo*. The oil obtained was crystallized from ether–hexane to give (−)-**28a** (21.6 g, 25%), mp 148—150 °C, $[\alpha]_D^{25}$ −6.0° ($c=1.0$, MeOH). Optical purity determined by chiral HPLC was 98.3% ee. IR (Nujol): 3330, 1690 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.24 (3H, d, $J=7$ Hz), 1.37 (3H, s), 2.75 (2H, br s), 3.84 (1H, q, $J=7$ Hz), 7.01—7.45 (16H, m). MS *m/z*: 367 (M^+).

(−)-3-Methyl-*N*-[1-[5-methyl-1-(triphenylmethyl)-1*H*-imidazol-4-yl)-ethyl]-1-(phenylsulfonyl)-1*H*-indole-2-ethanamine [(−)-23a] (−)-**23a** was prepared by the same procedure as described for **23c**. Yield 73%. An amorphous powder, $[\alpha]_D^{25}$ −26.6° ($c=1.0$, MeOH). IR (Nujol): 2900, 1400, 1370 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.28 (3H, d, $J=7$ Hz), 1.31 (3H, s), 2.09 (3H, s), 2.40—2.60 (2H, m), 2.90—3.30 (2H, m), 3.69 (1H, q, $J=7$ Hz), 6.90—7.80 (24H, m), 8.00—8.20 (1H, m).

(−)-3-Methyl-*N*-[1-[5-methyl-1-(triphenylmethyl)-1*H*-imidazol-4-yl]-ethyl]-1*H*-indole-2-ethanamine [(−)-24a] (−)-**24a** was prepared by the same method as described for **24a**, Yield 81%. An amorphous powder, $[\alpha]_D^{25}$ −14.4° ($c=1.0$, MeOH). IR (Nujol): 3450, 1590 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.20—1.40 (6H, m), 2.12 (3H, s), 2.40—2.90 (4H, m), 3.75 (1H, q, $J=7$ Hz), 6.80—7.50 (20H, m), 10.66 (1H, s).

(+)-3,4-Dihydro-5-methyl-2-[1-[5-methyl-1-(triphenylmethyl)-1*H*-imidazol-4-yl]ethyl]pyrimido[1,6-*a*]indol-1(2*H*)-one [(+)-25a] (+)-**25a** was prepared from (−)-**24a** by the same method as described for **25a**. Yield 74%. An amorphous powder, $[\alpha]_D^{25}$ +76.4° ($c=1.0$, MeOH). IR (Nujol): 1670, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.34 (3H, s), 1.52 (3H, d, $J=7$ Hz), 2.15 (3H, s), 2.50—2.70 (1H, m), 2.90—3.10 (1H, m), 3.20—3.60 (2H, m), 5.70 (1H, q, $J=7$ Hz), 7.00—7.50 (19H, m), 8.10—8.30 (1H, m). MS *m/z*: 550 (M^+).

(+)-3,4-Dihydro-5-methyl-2-[1-(5-methyl-1*H*-imidazol-4-yl)ethyl]pyrimido[1,6-*a*]indol-1(2*H*)-one Hydrochloride [(+)-26a] (+)-**26a** was prepared by the same method as described for **26a**. Yield 70%, mp

238—239 °C, $[\alpha]_D^{25}$ +119.5° ($c=1.0$, MeOH). IR (Nujol): 1675, 1625 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.67 (3H, d, $J=7$ Hz), 2.14 (3H, s), 2.34 (3H, s), 2.90—3.20 (2H, m), 3.30—3.80 (2H, m), 5.82 (1H, q, $J=7$ Hz), 7.10—7.30 (2H, m), 7.40—7.50 (1H, m), 8.10—8.30 (1H, m), 9.04 (1H, s), 14.71 (1H, s).

Compound (−)-**26a** was prepared from (+)-**28a** by a similar procedure to that described for (+)-**26a**.

Pharmacology BJ Reflex in Urethane-Anesthetized Rats The compounds were evaluated for antagonism of the BJ reflex evoked by 2-Me-5-HT in the anesthetized rat by the method of Fozard and Host.[13] 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 vein was cannulated for the intravenous injection of the drugs. The trachea was also cannulated to ease respiration. The BJ reflex was evoked by rapid bolus injection of 2-Me-5-HT (32 μg/kg, i.v.). When agonist-induced bradycardia returned to the steady state, the test compound (i.v.) was administered, and agonist-induced bradycardia was elicited again 5 min after the test compound administration. Percent inhibition was calculated as the percent difference between the first and second 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 and Dr. A. Sato and Dr. T. Azuma for the measurement of NOESY spectra.

References and Notes

1) M. Kato, K. Ito, S. Nishino, H. Yamakuni, H. Takasugi, *Chem. Pharm. Bull.*, **42**, 2546 (1994).
2) D. J. Hart, K. Kanai, D. G. Thomas, T. K. Yang, *J. Org. Chem.*, **48**, 289 (1983).
3) A. J. Fox, I. K. M. Morton, *Brit. J. Pharmacol.*, **101**, 553 (1990).
4) A. S. Paintal, *Physiol. Rev.*, **53**, 159 (1973).
5) M. F. Hibert, R. Hoffmann, 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. L. Stevenson, M. Beer, J. Stanton, K. Watling, R. G. Ball, *J. Med. Chem.*, **35**, 1019 (1992); J. P. Rizzi, A. A. Nagel, T. Rosen, S. McLean, T. Seeger, *ibid.*, **33**, 2721 (1990).
6) J. Harley-Mason, E. H. Pavri, *J. Chem. Soc.*, **1963**, 2565.
7) F. Gardient, Ger. Offen. DE 3505017 (1985) [*Chem. Abstr.*, **105**, 6523*f* (1985)].
8) T. Itahara, H. Ouya, K. Kozono, *Bull. Chem. Soc. Jpn.*, **55**, 3861 (1982).
9) M. Ikeda, S. Matsugashita, Y. Tamura, *J. Chem. Soc., Perkin Trans. 1*, **1976**, 2587.
10) Compound **18** was prepared in a similar manner to that used for 1-(phenylsulfonyl)-1*H*-indole, described by M. G. Saulnier, G. W. Gribble, *J. Org. Chem.*, **47**, 757 (1982).
11) I. H. Coates, P. C. North, A. W. Oxford, Eur. Pat. Appl. EP 306323 (1989) [*Chem. Abstr.*, **111**, 153800*w* (1989)].
12) W. I. Taylor, *Helv. Chim. Acta*, **33**, 165 (1950).
13) J. R. Fozard, M. Host, *Brit. J. Pharmacol.*, **77**, 520 p (1982).