Syntheses of Monocyclic and Bicyclic 2,4(1*H*,3*H*)-Pyrimidinediones and Their Serotonin 2 Antagonist Activities

Yoshifumi WATANABE,* Hiroyuki USUI, Toshiro SHIBANO, Tsuyoshi TANAKA, and Munefumi KANAO

Daiichi Pharmaceutical Co., Ltd., Research Institute, 13 Kitakasai 1–16, Edogawa-ku, Tokyo 134, Japan. *Received March 27, 1990*

New serotonine 2 (5-HT_2) antagonists with a monocyclic or bicyclic 2,4(1*H*,3*H*)-pyrimidinedione have been prepared and their activities evaluated. In a series of monocyclic compounds, 1-substituted 5-phenyl-2,4(1*H*,3*H*)-pyrimidinedione 14 showed potent *in vitro* activity, and the corresponding 3-substituted 5-phenyl and 6-phenyl derivatives 3, 8 and 20a also showed moderate activity. In the bicyclic compounds, 3-substituted 5,6,7,8-tetrahydro-2,4(1*H*,3*H*)-quinazolinedione 33 exhibited the most potent activity among the compounds prepared in this paper. The *in vivo* antagonist activity of 33 was comparable to that of ketanserin, a typical peripheral 5-HT_2 antagonist.

Keywords serotonin; 5-HT_2 antagonist; 2,4(1*H*,3*H*)-pyrimidinedione; 2,4(1*H*,3*H*)-quinazolinedione; 4-(4-fluorobenzoyl)piperidine; ketanserin

Serotonin acts as a neurotransmitter in the central nervous system and it has been linked with numerous functions such as thermoregulation, sleep, anxiety, memory, depression, *etc.* On the other hand, serotonin shows potent vasoconstriction activity and platelet aggregation in the cardiovascular system.[1] Serotonin is released from platelets activated by collagen, adenosine diphosphate (ADP), thromboxane A_2 (TXA_2), norepinephrine and other endogenous products. The released serotonin amplifies the effects of the above vasoactive and platelet aggregative substances in a synergistic manner.[2] These properties suggest that serotonin (5-HT) may induce or accelerate circulatory disorders in pathological conditions such as atherosclerosis.[3] Since 5-HT receptors were classified into 5-HT_1, 5-HT_2 and 5-HT_3 subtypes, the 5-HT-induced vasoconstrictions in most vascular beds and platelet aggregation have been demonstrated to be mediated by the 5-HT_2 receptor.[4] Ketanserin, a selective peripheral 5-HT_2 antagonist, has been shown to be useful in the treatment of some kinds of circulatory diseases.[5]

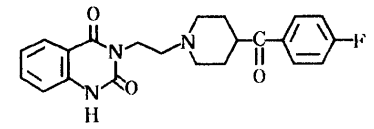
The structure of ketanserin is composed of two parts. One is 4-(4-fluorobenzoyl)piperidine, known as a typical component in neuroleptic agents and essential for binding to the 5-HT_2 receptor. The other is a characteristic 2,4(1*H*,3*H*)-quinazolinedione-3-ethyl group that is an auxiliary part necessary to increase ketanserin's antagonist property. It is noteworthy that the introduction of the hydrophilic 2,4(1*H*,3*H*)-quinazolinedione-3-ethyl group into the neuroleptic element, 4-(4-fluorobenzoyl)piperidine moiety, produced a peripheral 5-HT_2 antagonist. In fact, it has been shown that the concentration of ketanserin in the brain tissues of experimental animals were not very high.[6] We focused on this hydrophilic 2,4(1*H*,3*H*)-quinazolinedione part and tried to modify the component without changing the pyrimidine moiety by replacing the 2,4(1*H*,3*H*)-quinazolinedione-3-ethyl group of ketanserin with several kinds of 2,4(1*H*,3*H*)-pyrimidinedione-3(or 1)-alkyl groups. The general structure is shown in Fig. 1. In this paper we describe the syntheses and pharmacological evaluations of the compounds (I—IV).

Chemistry

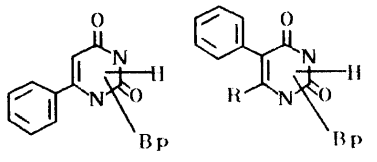
The 2,4(1*H*,3*H*)-pyrimidinedione derivatives prepared in this paper are shown in Table I. The synthetic pathways employed are outlined in Charts 1—6. The position substituted with the 2(or 3)-[4-(4-fluorobenzoyl)piperidin-1-yl]alkyl group on the pyrimidine ring was determined by ultraviolet (UV) spectra.

Condensation of 6-phenyl-1,3-oxazoline-2,4(3*H*)-dione (**1**)[7] with 2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethanol by Mitsunobu reaction[8] produced the 3-substituted compound (**2**), which was treated with ethanolic ammonia to produce 3-substituted 6-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (**3**). The corresponding 1-substituted derivative (**4**) was prepared from **1** with 2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethylamine.

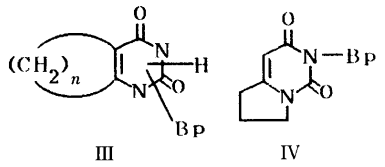
Silylation of 5-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (**5**),[9] followed by acetylation, afforded 1-acetyl-5-phenyl-2,4(1*H*,-3*H*)-pyrimidinedione (**6**) in a moderate yield. Alkylation of **6** by Mitsunobu reaction produced the 3-substituted



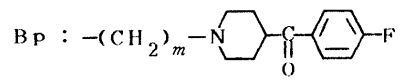
ketanserin



I II



III IV



Bp : $-(CH_2)_m-N$

$n = 3 \cdot 4$, $m = 2 \cdot 3$

R = Me , iso-Pr

Fig. 1

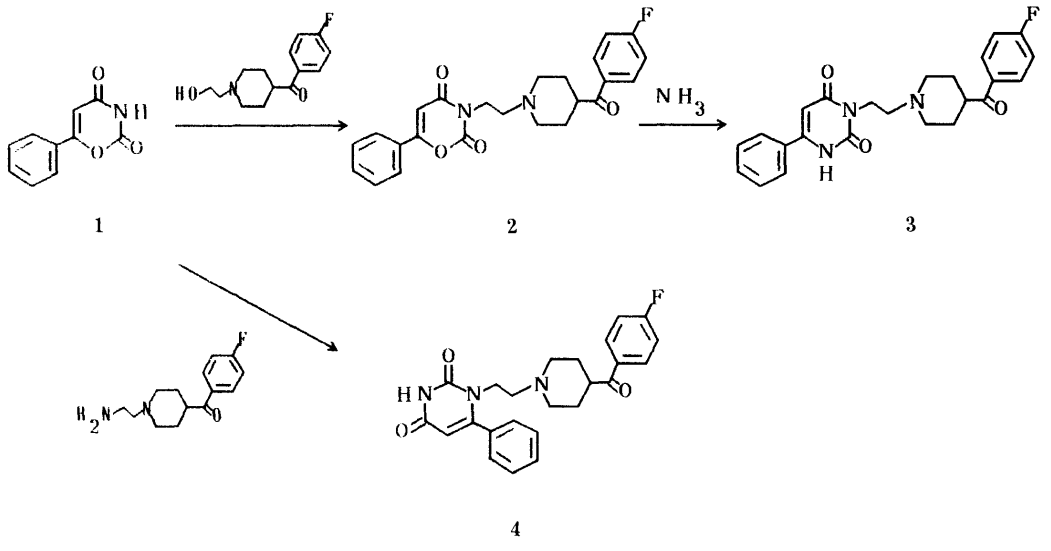


Chart 1

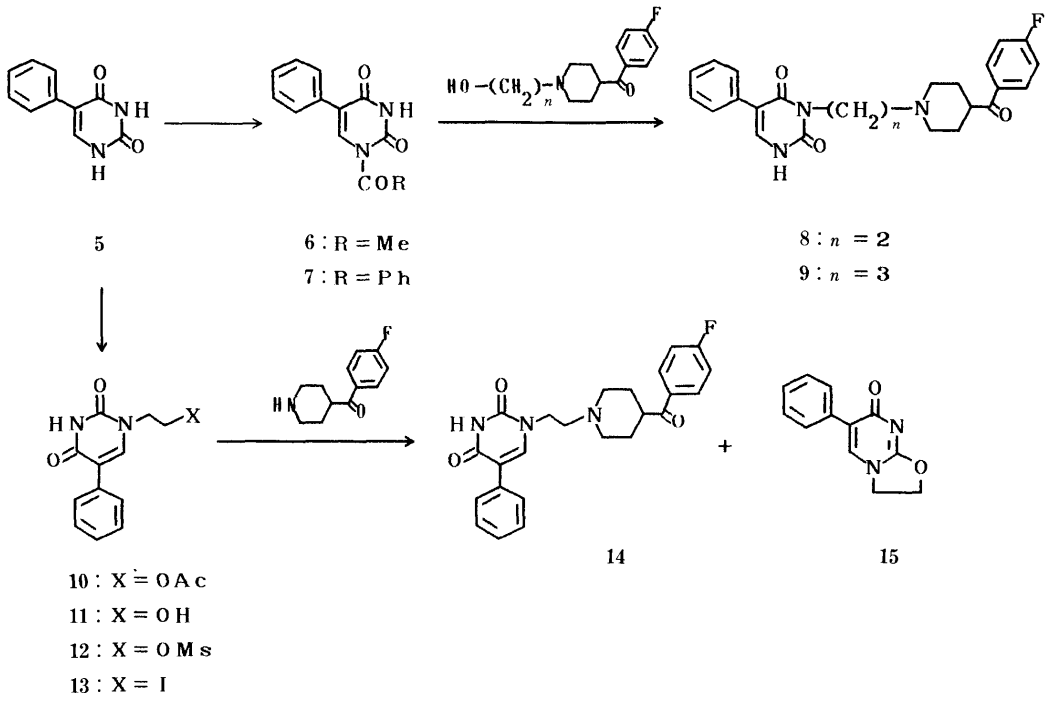


Chart 2

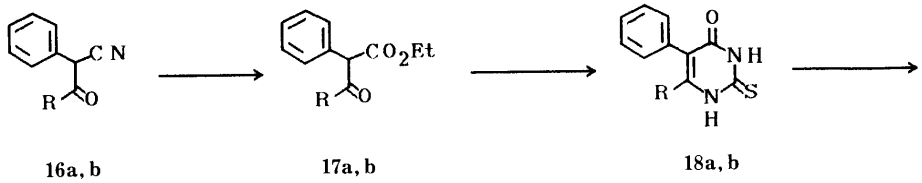
5-phenyl derivative (**8**) in a low yield (12%) because of the lability of the 1-acetyl group of **6**. A more stable 1-benzoyl derivative (**7**) could be converted into **9** in a good yield (53%).

The direct alkylation of **5** with 2-acetoxyethyl bromide yielded 1-(2-acetoxyethyl)-2,4(1*H*,3*H*)-pyrimidinedione (**10**), which was converted successively by hydrolysis, mesylation and substitution with an iodide anion to the iodide (**13**). The reaction of **13** with 4-(4-fluorobenzoyl)piperidine afforded the 1-substituted 5-phenyl derivative (**14**) and an oxazolo[3,2-*a*]pyrimidinone derivative (**15**).

Syntheses of 6-alkyl-5-phenyl-2,4(1*H*,3*H*)-pyrimidinediones have not been reported. 2-Phenylacetonitriles (**16**) were treated with ethanolic hydrogen chloride to produce 2-phenylacetates (**17**). Heating of **17** with thiourea afforded 2,3-dihydro-2-thioxo-4(1*H*)-pyrimidinones (**18**), which were converted into 2,4(1*H*,3*H*)-pyrimidinediones (**19**) by reaction with chloroacetic acid. Condensation of **19** with corresponding alcohols produced the desired products (**20** and **21**).

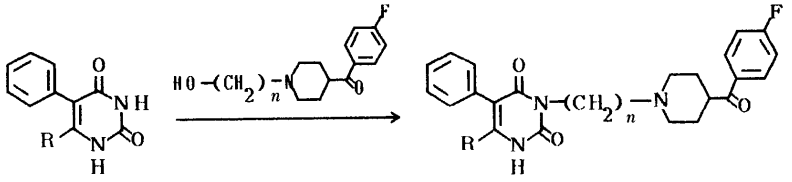
Chlorination of 1-(3-hydroxypropyl)-2,4(1*H*,3*H*)-pyrimidinedione (**22**)[10] produced a 5-chloro derivative (**23**), which was converted into 5-chloro-1-(3-iodopropyl)-2,4(1*H*,3*H*)-pyrimidinedione (**25**). Compound **25** was treated with tributyltin hydride and then with sodium methoxide to give 6,7-dihydropyrrolo[1,2-*c*]-1,3(2*H*,5*H*)-pyrimidinedione (**27**). Condensation of **27** with alcohols produced the desired compounds (**28** and **29**).

It has been reported that the reaction of 2,4(1*H*,3*H*)-pyrimidinedione with 2-bromo-1,1-diethoxyethane affords a 1-alkylated product, but not a 3-substituted product.[11] Similarly, alkylation of 6,7-dihydro-1*H*-cyclopenta-2,4(3*H*,



16a, b 17a, b 18a, b

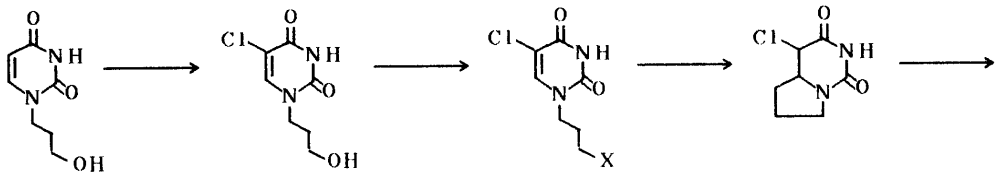
a series : R = Me
b series : R = iso-Pr



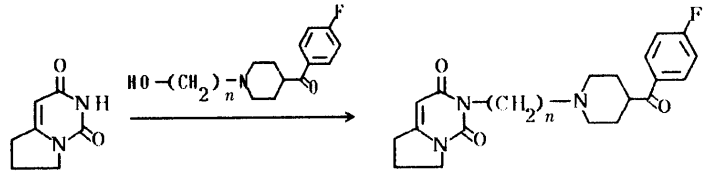
19a, b

20a, b : n = 2
21a : n = 3

Chart 3



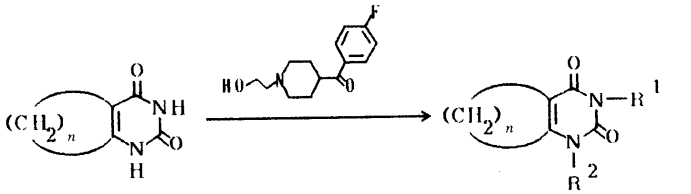
22 23 24 : X = OMs 26
25 : X = I



27

28 : n = 2
29 : n = 3

Chart 4



30 : n = 3
31 : n = 4

32 : n = 3
R^1 = H
R^2 =

33 : n = 4
R^1 =
R^2 = H

Chart 5

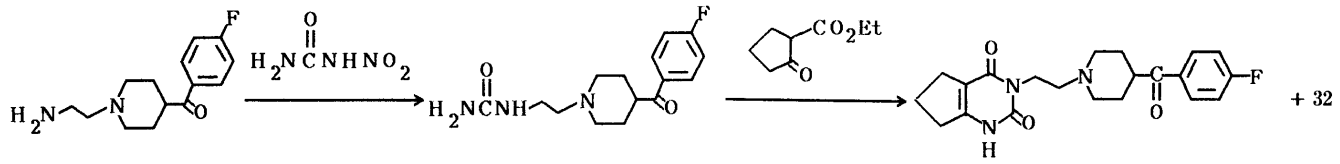
5*H*)-pyrimidinedione (**30**)[12] by Mitsunobu reaction yielded 1-substituted product (**32**). In contrast to that, alkylation of 5,6,7,8-tetrahydro-2,4(1*H*,3*H*)-quinazolinedione (**31**)[12] produced a 3-substituted product (**33**). The methylene group at 8-position of **31** would sterically hinder the 1-position from alkylating.

Heating of ethyl 2-oxocyclopentanecarboxylate and urea (**35**), which was prepared from amine (**34**), yielded **32** and the 3-substituted isomer (**36**).

Pharmacological Results

The *in vitro* 5-HT_2 antagonist activities of the compounds were expressed as the pA_2 values for isolated rat thoracic aorta (Table I). pA_2 values were determined according to the method of Arunlakshana *et al.*[13]

Most compounds showed competitive 5-HT_2 antagonist activities. The activities of a series of compounds having



34 35 36

Chart 6

TABLE I. 5-HT_2 Antagonist Activity

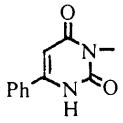
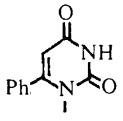
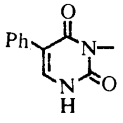
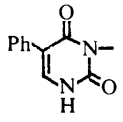
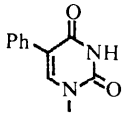
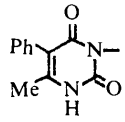
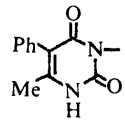
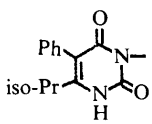
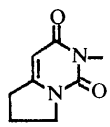
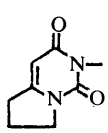
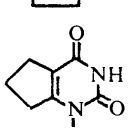
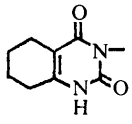
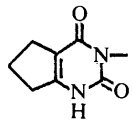
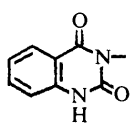
No.	Pm	n	Activity (pA_2)[a]
3		2	7.9
4		2	7.1
8		2	7.9
9		3	7.6
14		2	8.1
20a		2	7.9
21a		3	7.7
20b		2	7.1
28		2	7.3
29		3	7.1
32		2	7.8

TABLE I. (continued)

No.	Pm	n	Activity (pA_2)[a]
33		2	9.0
36		2	Non-competitive
Ketanserin		2	8.6

a) 5-HT_2 antagonist activity in an isolated rat thoracic aorta.

TABLE II. *In Vivo* 5-HT_2 Antagonist Activity of **33**

Time (h)	Dose (mg/kg *p.o.*)	% inhibition[a]	
		Compd. **33**	Ketanserin
1	10	84±8	96±4
3	1	78±9	78±8
	3	85±6	84±9
	10	100±0	100±0

a) Inhibitory activity in rat against elevation of blood pressure caused by 5-HT (300 μM/kg, i.v.) after 1 or 3 h of oral administration of the compound.

an ethylene group between the pyrimidine and piperidine ring were more potent than those of the corresponding trimethylene compounds (**8**>**9**; **20a**>**21a**; **28**>**29**). In a series of 3-substituted 5- or 6-phenylpyrimidines, the activity of 5-phenylpyrimidine (**9**) was similar to that of 6-phenylpyrimidine (**3**). In the corresponding 1-substituted compounds, 6-phenylpyrimidine (**4**) exhibited a tenth of the activity of 5-phenylpyrimidine (**14**). The compound **14** showed the most potent activity (pA_2 8.1) occured in the 5- or 6-phenylpyrimidine derivatives, and the magnitude was one-third as strong as the activity of ketanserin[14] (pA_2 8.6). Although the introduction of a methyl group at 6-position of 3-substituted 5-phenylpyrimidine did not alter the activity (**8**=**20a** and **9**≒**21a**), the introduction of an isopropyl group at the same position decreased the activity (**8**, **20a**>**20b**). In a series of bicyclic pyrimidine derivatives, 3-substituted 5,6,7,8-tetrahydro-2,4(1*H*,3*H*)-quinazolinedione (**33**) showed stronger activity (pA_2 9.0) than ketanserin (pA_2 8.6). The activity of the analogous cyclopentapy-

TABLE III. 2,4(1*H*,3*H*)-Pyrimidinediones

No.	mp (°C) (Recryst. solv.)	Formula	Analysis (%) Calcd (Found) C	H	N	UV Spectra (Solv.)	λ_{max}	NMR Spectra (Solv.)	δ
3	262—267 (EtOH–Et_2O)	$C_{24}H_{24}FN_3O_3$ ·HCl	62.95 (63.16	5.50 5.52	9.18 9.01)	(H_2O) (+OH^-)[a]	245, 280 240, 305	(CD_3OD): 1.80—2.34 (4H, m), 3.1—4.1 (7H, m), 4.38 (2H, t, J=5.7 Hz), 5.99 (1H, s), 7.26 (2H, t, J=8.8 Hz), 7.50—7.76 (5H, m), 8.11 (2H, dd, J=8.8, 5.3 Hz)	
4	225—227 (EtOH–iso-PrOH)	$C_{24}H_{24}FN_3O_3$ ·HCl·1/2H_2O	61.73 (61.55	5.61 5.59	9.00 8.90)	(H_2O) (+OH^-)[a]	254 249, 267 (sh)	(DMSO-d_6): 1.65—2.0 (4H, m), 2.65—4.04 (9H, m), 5.49 (1H, d, J=2.2 Hz), 7.37 (2H, t, J=8.8 Hz) 7.55 (5H, s), 8.07 (2H, dd, J=8.8, 5.5 Hz), 10.53 (1H, br), 11.55 (1H, br s)	
8	197—199 (MeOH–iso-PrOH)	$C_{24}H_{24}FN_3O_3$ ·HCl	62.95 (62.74	5.50 5.49	9.18 9.15)	(EtOH)[b] (+OH^-)[a,b]	241, 275 250, 306	($CDCl_3$)[b]: 1.7—2.0 (4H, m), 2.0—2.4 (2H, m), 2.73 (2H, t-like), 3.04—3.32 (2H, m), 4.18 (2H, t-like), 7.11 (3H, t, J=8.8 Hz), 7.27 (6H, m), 7.93 (2H, dd, J=8.8, 5.3 Hz)	
9	186—188 (EtOH–iso-PrOH)	$C_{25}H_{26}FN_3O_3$ ·HCl·1/2H_2O	62.43 (62.09	5.87 5.90	8.74 8.65)			(DMSO-d_6)[b]: 1.5—2.1 (8H, m), 2.37 (2H, t-like), 2.89 (2H, m), 3.33 (1H, m), 3.92 (2H, t-like), 7.23—7.6 (7H, m), 7.61 (1H, s), 8.04 (2H, dd, J=8.8, 5.5 Hz)	
14	165—168 (EtOH–H_2O)	$C_{24}H_{24}FN_3O_3$ ·HCl·1/2H_2O	61.73 (61.61	5.61 5.34	9.00 9.01)			($CDCl_3$)[b]: 1.8—2.0 (4H, m), 2.1—2.5 (2H, m), 2.71 (2H, t, J=5.7 Hz), 3.0—3.4 (3H, m), 3.91 (2H, t, J=6.1 Hz), 7.1—7.6 (8H, m), 7.79 (2H, dd, J=8.7, 5.7 Hz), 9.18 (1H, br s)	
20a	237—240 (iso-PrOH)	$C_{25}H_{26}FN_3O_3$ ·HCl·1/2H_2O	62.43 (62.72	5.87 6.02	8.74 8.43)	(MeOH)[b] (+OH^-)[a,b]	242, 263 (sh) 243, 293	($CDCl_3$)[b]: 1.8—2.0 (4H, m), 2.08 (3H, s), 2.1—2.4 (2H, m), 2.69 (2H, t-like), 3.0—3.3 (3H, m), 4.15 (2H, t-like), 7.0—7.5 (7H, m), 7.95 (2H, dd, J=8.8, 5.5 Hz), 10.25 (1H, br s)	
21a	222—236 (MeOH–EtOH)	$C_{26}H_{28}FN_3O_3$ ·HCl·H_2O	61.96 (61.77	6.20 6.16	8.34 8.17)	(MeOH) (+OH^-)[a]	242, 264 (sh) 244, 292	($CDCl_3$)[b]: 1.6—2.2 (8H, m), 2.10 (3H, s), 2.49 (2H, t, J=7.2 Hz), 2.8—3.4 (3H, m), 4.05 (2H, t, J=7.0 Hz), 7.0—7.5 (7H, m), 7.94 (2H, dd, J=8.8, 5.5 Hz)	
20b	167—170 (EtOH–iso-PrOH)	$C_{27}H_{30}FN_3O_3$ ·HCl·H_2O	62.60 (62.82	6.42 6.74	8.11 7.86)	(MeOH) (+OH^-)[a]	245, 265 (sh) 245, 295	(DMSO-d_6): 1.12 (6H, d, J=7.0 Hz), 1.6—1.9 (4H, m), 2.2 (2H, m), 2.5—2.7 (3H, m), 3.0 (2H, m), 3.4 (1H, m), 3.9 (2H, t-like), 7.2—7.5 (7H, m), 8.09 (2H, dd, J=8.7, 5.7 Hz), 10.9 (1H, br s)	
28	237—240 (MeOH–EtOH)	$C_{21}H_{24}FN_3O_3$ ·HCl	59.78 (59.62	5.97 5.80	9.96 9.90)			(DMSO-d_6): 1.8—2.2 (6H, m), 2.94 (2H, t, J=7.4 Hz), 3.0—3.4 (5H, m), 3.5—3.8 (2H, m), 3.85 (2H, t, J=7.0 Hz), 4.18 (2H, t-like), 5.68 (1H, s), 7.39 (2H, t, J=8.8 Hz), 8.10 (2H, dd, J=5.3, 8.8 Hz), 10.49 (1H, br s)	
29	229—232 (H_2O–iso-PrOH)	$C_{22}H_{26}FN_3O_3$ ·HCl	60.62 (60.33	6.24 6.17	9.64 9.63)			(DMSO-d_6): 1.7—2.2 (8H, m), 2.8—3.7 (9H, m), 3.84 (4H, t, J=7.0 Hz), 5.64 (1H, s), 7.38 (2H, t, J=8.9 Hz), 8.06 (2H, dd, J=5.7, 8.7 Hz)	
32	255—265 (EtOH)	$C_{21}H_{24}FN_3O_3$ ·HCl·1/2H_2O	58.53 (58.81	6.08 6.06	9.75 9.71)	(MeOH)	255, 267 (sh)	(DMSO-d_6): 2.0 (6H, m), 2.5 (2H, m), 2.8—3.3 (6H, m), 3.5—3.8 (3H, m), 4.16 (2H, t-like), 7.48 (2H, t, J=8.9 Hz), 8.09 (2H, dd, J=5.7, 8.9 Hz), 11.0 (1H, br s), 11.16 (1H, br s)	
33	234—245 (EtOH)	$C_{22}H_{26}FN_3O_3$ ·HCl·1/2H_2O	59.39 (59.57	6.34 6.10	9.44 9.39)	(MeOH) (+OH^-)[a]	244, 264 (sh) 240 (sh), 286	(DMSO-d_6): 1.5—1.8 (4H, m), 1.9—2.5 (8H, m), 3.0—3.5 (4H, m), 3.6—3.9 (3H, m), 4.18 (2H, t-like), 7.39 (2H, t, J=8.7 Hz), 8.11 (2H, dd, J=5.7, 8.7 Hz), 10.30 (1H, br s), 11.11 (1H, br s)	
36	260—263 (EtOH–acetone)	$C_{21}H_{24}FN_3O_3$ ·HCl·1/2H_2O	58.53 (58.32	6.08 6.20	9.75 9.78)	(MeOH) (+OH^-)[a]	244, 262 (sh) 237, 286	(DMSO-d_6): 1.8—2.2 (6H, m), 2.5—2.8 (4H, m), 3.0—3.4 (4H, m), 3.6—3.9 (3H, m), 4.17 (2H, t-like), 7.38 (2H, t, J=8.8 Hz), 8.18 (2H, dd, J=5.7, 8.3 Hz)	

a) Solutions were adjusted to about pH 11 by the addition of 2 drops of 1 N NaOH. *b*) Spectral data of the free base.

rimidine (**36**) could not be determined because **36** did not show competitive activity, but the 1-substituted isomer (**32**) exhibited moderate activity. An isomeric pyrrolo[1,2-*c*]pyrimidine derivatives (**28** and **29**) showed low activities.

We selected the most potent compound (**33**), and compared the *in vivo* 5-HT_2 antagonist activity of **33** with that of ketanserin. The hypertensive phase caused by 5-HT injection, immediately after a transient hypotensive phase, has been considered to be mediated *via* the 5-HT_2 receptor. Then, the *in vivo* 5-HT_2 antagonist activity was determined by the inhibition activity against 5-HT-induced elevation of blood pressure after oral administration of the compound. The value was expressed as a percent inhibition (Table II). The results showed that the activity of **33** was comparable to that of ketanserin.

In conclusion, replacement of the 2,4(1*H*,3*H*)-quinazolinedione part of ketanserin with a 5- or 6-phenyl-2,4(1*H*,3*H*)-pyrimidinedione group decreased 5-HT_2 antagonist activity, but the potency was high enough (**3**, **8**, **14** and **20a**; pA_2 7.9—8.1). Introduction of the 2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethyl group at 1-position of the pyrimidine ring was acceptable to show 5-HT_2 antagonist activity the same as at the 3-position. Finally, 2,4(1*H*,3*H*)-quinazolinedione could be replaceable with 5,6,7,8-tetrahydro-2,4(1*H*,3*H*)-quinazolinedione.

Experimental

The physical data of the final compounds are listed in Table III. Melting points were determined by the Yanagimoto micro melting point apparatus, and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded with JEOL JNM-FX-90Q spectrometers (Me_4Si as an internal standard). Signal multiplicities are represented by s (singlet), d (doublet), dd (doublet doublet), t (triplet), q (quartet), br (broad), br s (broad singlet), s-like (triplet-like) and m (multiplet). Chemical shifts are expressed in δ values and the coupling constants are expressed in hertz (Hz). Ultraviolet (UV) spectra were recorded with Shimazu UV-260 spectrometers, and $\lambda_{max}^{OH^-}$ nm means the spectral data in solutions adjusted to about pH 11 by the addition of 2 drops of 1 N NaOH. For column chromatography, silica gel (Merck, Kieselgel 60, 0.05—0.2 mm) was used.

3-[2-[4-(4-Fluorobenzoyl)piperidin-1-yl)ethyl]-6-phenyl-1,3-oxazine-2,4(3*H*)-dione (2) A solution of 2-[4-(4-fluorobenzoyl)piperidin-1-yl]-ethanol (1.45 g, 6.16 mmol) in dioxane (10 ml) was added by drops to an ice-cooled solution of **1** (1.06 g, 5.6 mmol), triphenylphosphine (1.76 g, 6.72 mol) and diethyl azodicarboxylate (1.1 g, 6.72 mol) in dioxane (40 ml). After being stirred at room temperature for 40 min, the reaction mixture was concentrated *in vacuo*. The residue was crystallized from AcOEt–hexane to produce **2** (0.94 g, 40%) as colorless crystals; mp 159—164 °C (AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 1.7—1.9 (4H, m), 2.0—2.3 (2H, m), 2.70 (2H, t, J=6.5 Hz), 2.9—3.2 (3H, m), 4.10 (2H, t, J=6.5 Hz), 6.36 (1H, s), 7.12 (2H, t, J=8.7 Hz), 7.47—7.55 (3H, m), 7.77—8.03 (4H, m). *Anal.* Calcd for $C_{24}H_{23}FN_2O_4$: C, 68.23; H, 5.49; N, 6.63. Found: C, 68.28; H, 5.53; N, 6.74.

3-[2-[4-(4-Fluorobenzoyl)piperidin-1-yl]ethyl]-6-phenyl-2,4(1*H*,3*H*)-pyrimidinedione Hydrochloride (3) A mixture of **2** (1.80 g, 4.26 mmol) and 15% NH_3–EtOH (50 ml) was refluxed for 15 min. After cooling, the precipitate was collected by filtration and dissolved in 1 N HCl (10 ml) and EtOH (20 ml). The solution was warmed at 50 °C for 1 h with stirring, and

concentrated *in vacuo*. The residue was crystallized from aqueous EtOH to produce **3** (1.60 g, 82%) as a colorless powder.

1-[2-[4-(4-Fluorobenzoyl)piperidin-1-yl]ethyl]-6-phenyl-2,4(1*H*,3*H*)-pyrimidinedione Hydrochloride Hemihydrate (4) A solution of **1** (4.0 g, 21 mmol) and 2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethylamine (2.97 g, 11.9 mmol) in a mixture of water (10 ml) and dioxane (60 ml) was refluxed for 20 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by column chromatography to produce the free base of **4** (0.73 g, 15%, mp 207—211 °C (EtOH)) as colorless crystals, which was treated with concentrated HCl to produce the hydrochloride **4** (0.56 g, 10%) as a colorless powder.

1-Acetyl-5-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (6) A mixture of **5** (4.70 g, 25 mmol), hexamethyldisilazane (60 ml) and $(NH_4)_2SO_4$ (5 mg) was refluxed for 2 h. The reaction mixture was concentrated *in vacuo*. The residual oil was dissolved in MeCN (100 ml), and acetyl chloride (6 ml, 83 mmol) was added. After the reaction mixture was stirred at room temperature for 5.5 h, the insoluble material was filtered to recover **5** (1.90 g, 40%). The filtrate was concentrated *in vacuo* to produce **6** (3.06 g, 57%) as colorless crystals, which was used for the next reaction without further purification. mp 183—185 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.80 (3H, s), 7.36—7.6 (5H, m), 8.36 (1H, s), 8.87 (1H, br s).

Compound **7** was similarly prepared from **5**. Yield, 80%, colorless crystals; mp 212—214 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.4—7.7 (8H, m), 7.67 (2H, dd, J=7.9, 1.8 Hz), 8.03 (1H, s), 11.75 (1H, br s). *Anal.* Calcd for $C_{17}H_{12}N_2O_3$: C, 69.86; H, 4.14; N, 9.58. Found: C, 70.01; H, 4.29; N, 9.56.

Compounds **8** and **9** were prepared from **6** and **7** in 12 and 53% yields, respectively, by a method similar to that described in the synthesis of compound **2**. Free base of **8**: mp 190—191 °C (EtOH). Free base of **9**: mp 175—177 °C (EtOH).

1-(2-Acetoxyethyl)-5-phenylpyrimidine-2,4(1*H*,3*H*)-dione (10) A mixture of **5** (10.0 g, 53.1 mmol), hexamethyldisilazane (100 ml) and $(NH_4)_2SO_4$ (5 mg) was refluxed for 2.5 h. The reaction mixture was concentrated *in vacuo*. The residual oil was heated at 190—200 °C under a nitrogen atmosphere, and 2-acetoxyethyl bromide (9.02 g, 54 mmol) was added by drops over a period of 35 min. After 1 h, the reaction was quenched by addition of 95% EtOH (100 ml). The mixture was concentrated *in vacuo*, and a small portion of $CHCl_3$ was added. After removal of the insoluble material by filtration, the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography to produce **10** (5.85 g, 40%) as colorless crystals; mp 147—148 °C (MeOH–$CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.07 (3H, s), 4.05 (2H, t, J=5.3 Hz), 4.37 (2H, t, J=5.3 Hz), 7.32 (1H, s), 7.3—7.6 (5H, m), 9.06 (1H, br s). UV λ_{max}^{MeOH} nm: 235, 282. *Anal.* Calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.15; H, 5.00; N, 10.25.

1-(2-Hydroxyethyl)-5-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (11) A mixture of **10** (5.84 g, 21.3 mmol) and 90% NaOMe (1.66 g, 27.7 mmol) in MeOH (80 ml) was refluxed for 1 h. The solution was diluted with MeOH (50 ml), and then neutralized with Dowex 50W (H^+ form). After removal of the resin by filtration, the filtrate was concentrated, and the precipitate was collected by filtration to produce **11** (4.43 g, 90%) as needles; mp 217—218 °C (EtOH). ^{1}H-NMR (DMSO-d_6) δ: 3.66 (2H, m), 3.83 (2H, t-like), 4.9 (1H, br s), 7.2—7.7 (5H, m), 7.82 (1H, s), 11.40 (1H, br s). *Anal.* Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.81; H, 5.24; N, 11.98.

1-(2-Methanesulfonyloxyethyl)-5-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (12) Methanesulfonyl chloride (1.6 g, 14 mmol) was added to a stirred solution of **11** (2.5 g, 10.8 mmol) in pyridine (20 ml) with ice-cooling. After being stirred at the same temperature for 2.5 h, the mixture was concentrated *in vacuo*. The residue was crystallized from aqueous EtOH to produce **12** (3.12 g, 94%) as brownish crystals; mp 185—186 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.09 (3H, s), 4.15 (2H, t, J=4.8 Hz), 4.52 (2H, t, J=4.8 Hz), 7.3—7.7 (5H, m), 7.64 (1H, s), 11.44 (1H, br s). *Anal.* Calcd for $C_{13}H_{14}N_2O_5S$: C, 50.32; H, 4.55; N, 9.03. Found: C, 50.01; H, 4.67; N, 8.84.

1-(2-Iodoethyl)-5-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (13) A mixture of sodium iodide (1.5 g, 10.0 mmol) and **12** (2.40 g, 7.73 mmol) in methyl ethyl ketone (50 ml) was refluxed for 70 min. After the insoluble material was filtered off, the filtrate was concentrated *in vacuo*. The residue was treated with a small amount of water to produce **13** (1.86 g, 67%) as yellowish crystals; mp 175—177 °C (EtOH). ^{1}H-NMR ($CDCl_3$) δ: 3.49 (2H, t, J=6.6 Hz), 4.15 (2H, t, J=6.6 Hz), 7.33—7.60 (6H, m), 8.86 (1H, br s). *Anal.* Calcd for $C_{12}H_{11}IN_2O_2$: C, 42.13; H, 3.24; N, 8.19. Found: C, 42.26; H, 3.15; N, 8.09.

1-[2-[4-(4-Fluorobenzoyl)piperidin-1-yl]ethyl]-5-phenyl-2,4(1*H*,3*H*)-pyrimidinedione Hydrochloride Hemihydrate (14) A solution of **13** (1.86 g, 5.2 mmol) in dimethylformamide (DMF) (10 ml) was added by drops to a mixture of 4-(4-fluorobenzoyl)piperidine hydrochloride (1.32 g, 5.4 mmol) and anhydrous K_2CO_3 (0.75 g, 5.4 mmol) in DMF (20 ml) at 70 °C with stirring over 1 h. After the mixture was stirred at the same temperature for 4 h, the solvent was evaporated under reduced pressure. The residue was extracted with $CHCl_3$. The extract was concentrated *in vacuo*, and the precipitate was collected by filtration to produce 2,3-dihydro-6-phenyl-7*H*-oxazolo[3,2-*a*]pyrimidin-7-one (**15**) (0.42 g, 38%) as colorless crystals; mp 218—220 °C (EtOH). ^{1}H-NMR (DMSO-d_6) δ: 4.29 (2H, t, J=7.4 Hz), 4.72 (2H, t, J=7.9 Hz), 7.3—7.7 (5H, m), 8.00 (1H, s). *Anal.* Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.17; H, 4.70; N, 13.17.

The above filtrate was concentrated *in vacuo*. The residue was purified by column chromatography to produce an oil, which was treated with concentrated HCl to afford **14** (0.56 g, 23%) as colorless crystals.

Ethyl 2-Phenylacetoacetate (17a) Hydrogen chloride gas was introduced into a stirred, ice-cooled suspension of **16a** (26 g, 163 mmol) in EtOH (65 ml) for 5 h. The reaction mixture stood overnight at room temperature. After the reaction mixture was concentrated *in vacuo*, the residue was poured into a mixture of Na_2CO_3 (32 g), ice (300 ml) and water (200 ml) with stirring. The mixture was extracted with Et_2O. After the extract was concentrated *in vacuo*, the residue was purified by column chromatography to produce an iminoether intermediate (15.7 g, 47%) as colorless crystals; mp 84—85 °C (hexane–AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7.0 Hz), 1.89 (3H, s), 3.98 (2H, q, J=7.0 Hz), 7.1—7.5 (5H, m), 8.5 (2H, br). *Anal.* Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.19; H, 7.43; N, 6.81.

A solution of the above iminoether (15.0 g, 73 mmol) in a mixture of concentrated HCl (6 ml) and EtOH (100 ml) was warmed at 40 °C for 1.5 h. After the solvent was evaporated *in vacuo*, the residue was extracted with AcOEt (150 ml). The extract was washed with water and concentrated *in vacuo* to produce an oil (15 g), which was purified by column chromatography to produce **17a** (14.7 g, 97%) as a slightly yellowish oil. ^{1}H-NMR ($CDCl_3$) δ: 1.17 and 1.27 (3H, each t), 1.85 and 2.18 (3H, each s), 4.17 and 4.22 (2H, each q), 4.68 (0.7H, s), 7.1—7.5 and 7.35 (5H, m and s).

Compound **17b** was similarly prepared from **16b**. Yield, 56%, a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.02 and 1.13 (6H, each d), 1.26 (3H, t), 2.75 (1H, m), 4.18 (2H, q), 4.89 (1H, s), 7.34 (5H, s).

2,3-Dihydro-6-methyl-5-phenyl-2-thioxo-4(1*H*)-pyrimidinone (18a) A mixture of **17a** (21.0 g, 100 mmol) and thiourea (9.0 g, 118 mmol) was heated at 180 °C for 2.5 h. After cooling, MeOH (40 ml) was added to the mixture, and the insoluble material (**18a**) was collected by filtration. The filtrate was concentrated to dryness, and the residue was purified by column chromatography to produce another crop. The two crops were combined to produce **18a** (4.48 g, 21%) as a brownish powder; mp 302—304 °C (MeOH). ^{1}H-NMR (DMSO-d_6) δ: 1.99 (3H, s), 7.2—7.5 (5H, m). *Anal.* Calcd for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83; S, 14.69. Found: C, 60.66; H, 4.58; N, 12.87; S, 14.57. UV λ_{max}^{MeOH} nm: 280; $\lambda_{max}^{OH^-}$ nm: 265, 320.

Compound **18b** was similarly prepared from **17b**. Yield, 27%, a brownish powder; mp 271—274 °C (MeOH). ^{1}H-NMR (DMSO-d_6) δ: 1.15 (6H, d, J=7.0 Hz), 2.66 (1H, m), 7.1—7.5 (5H, m). *Anal.* Calcd for $C_{13}H_{14}N_2OS$: C, 63.39; H, 5.73; N, 11.37; S, 13.02. Found: C, 63.11; H, 5.85; N, 11.72; S, 12.46. UV λ_{max}^{MeOH} nm: 276; $\lambda_{max}^{OH^-}$ nm: 260, 321.

6-Methyl-5-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (19a) A mixture of **18a** (3.41 g, 15.6 mmol) and chloroacetic acid (5.2 g, 55 mmol) in 40% MeOH (200 ml) was refluxed for 16 h. After the reaction mixture was concentrated, the resulting precipitate was collected by filtration to produce **19a** (2.96 g, 94%) as colorless crystals; mp >300 °C (MeOH). ^{1}H-NMR (DMSO-d_6) δ: 1.94 (3H, s), 7.2—7.5 (5H, m). *Anal.* Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.32; H, 5.00; N, 13.88. UV λ_{max}^{MeOH} nm: 269; $\lambda_{max}^{OH^-}$ nm: 293.

Compound **19b** was similarly prepared from **18b**. Yield, 86%, colorless crystals; mp >300 °C (MeOH). *Anal.* Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.16. Found: C, 67.40; H, 6.10; N, 12.12. UV λ_{max}^{MeOH} nm: 267; $\lambda_{max}^{OH^-}$ nm: 294.

Compounds **20a**, **20b**, **21a**, **28**, **29**, **32** and **33** were prepared by a method similar to that described in the preparation of compound **2** from the corresponding starting materials in 12, 4, 17, 60, 27, 26 and 12% yields, respectively.

5-Chloro-1-(3-hydroxypropyl)-2,4(1*H*,3*H*)-pyrimidinedione (23) Chlorine gas was introduced into an ice-cooled suspension of **22** (4.90 g, 28 mmol) in water (100 ml) for 1 h. The reaction mixture concentrated *in vacuo*. The residue was dissolved in EtOH (100 ml), and refluxed for 0.5 h. After removal of the solvent, the residue was crystallized from

EtOH to produce **23** (3.93 g, 69%) as colorless crystals; mp 178—180 °C (EtOH). ^{1}H-NMR (DMSO-d_6) δ: 1.73 (2H, m), 3.4 (2H, m), 3.75 (2H, t, J=7.0 Hz), 4.62 (1H, br s), 8.12 (1H, s). *Anal.* Calcd for $C_7H_9ClN_2O_3$: C, 41.09; H, 4.43; N, 13.69. Found: C, 41.23; H, 4.52; N, 13.41.

Compound **25** was prepared from **23** *via* the methanesulfonate **24** according to the procedure described in the synthesis of **13** from **11**.

24: Yield, 71% colorless crystals; mp 152—153 °C (EtOH). ^{1}H-NMR (DMSO-d_6) δ: 2.03 (2H, m), 3.17 (3H, s), 3.79 (2H, t, J=6.8 Hz), 4.24 (2H, t, J=6.1 Hz), 8.12 (1H, s), 11.75 (1H, br s).

25: Yield, 88% colorless crystals; mp 180—183 °C (EtOH). ^{1}H-NMR (DMSO-d_6) δ: 2.14 (2H, m), 3.23 (2H, t, J=7.0 Hz), 3.73 (2H, t, J=6.8 Hz), 8.10 (1H, s), 11.74 (1H, br s). *Anal.* Calcd for $C_7H_8ClIN_2O_2$: C, 26.73; H, 2.56; N, 8.91. Found: C, 27.01; H, 2.61; N, 8.98.

4-Chloro-4a,5,6,7-tetrahydropyrrolo[1,2-*c*]-1,3(2*H*,5*H*)-pyrimidinedione (26) A solution of tributyltin hydride (1.93 g, 6.63 mmol) and α,α′-azobis(isobutyronitrile) (10 mg) in benzene (5 ml) was added by drops to a refluxed suspension of **25** (1.60 g, 5.09 mmol) in benzene (50 ml) over 45 min under a nitrogen atmosphere. The reaction mixture was concentrated *in vacuo*, and the residue was crystallized from EtOH to produce **26** (0.68 g, 71%) as a colorless powder; mp 166—169 °C (EtOH). ^{1}H-NMR (DMSO-d_6) δ: 1.6—2.1 (4H, m), 3.4 (2H, m), 3.6—4.0 (1H, m), 4.87 (1H, d, J=11.8 Hz), 10.53 (1H, br s). *Anal.* Calcd for $C_7H_9ClN_2O_2$: C, 44.58; H, 4.81; N, 14.85. Found: C, 44.66; H, 5.11; N, 14.80.

6,7-Dihydropyrrolo[1,2-*c*]-1,3(2*H*,5*H*)-pyrimidinedione (27) A suspension of **26** (1.53 g, 8.11 mmol) and MeONa (0.88 g, 16.3 mmol) in MeOH (25 ml) was refluxed for 1.5 h. The reaction mixture was diluted with MeOH (70 ml) and neutralized with Dowex 50W (H^+ form). After removal of the resin by filtration, the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography to produce **27** (0.71 g, 58%) as colorless crystals; mp 258—259 °C (MeOH). ^{1}H-NMR (DMSO-d_6) δ: 2.03 (2H, m), 2.89 (2H, t, J=7.4 Hz), 3.76 (2H, t, J=7.2 Hz), 5.44 (1H, s), 10.95 (1H, br s). *Anal.* Calcd for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.29; H, 5.34; N, 18.61.

***N*-[2-[4-(4-Fluorobenzoyl)piperidin-1-yl]ethyl]urea (35)** Nitrourea (3.91 g, 37 mmol) was added portionwise to a stirred, ice-cooled solution of 2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethylamine (**34**) (7.80 g, 31 mmol) in a mixture of water (10 ml) and EtOH (2 ml). The reaction mixture was stirred at room temperature for 16 h. After the solvent was removed *in vacuo*, the residue was crystallized from benzene to produce **35** (7.49 g, 82%) as a colorless powder, which was used for the next reaction wtihout further purification. mp 119—122 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.6—1.9 (4H, m), 1.9—2.2 (2H, m), 2.34 (2H, t, J=6.1 Hz), 2.8—3.3 (5H, m), 5.45 (2H, br s), 5.8 (1H, t-like), 7.34 (2H, t, J=8.8 Hz), 8.05 (2H, dd, J=5.7, 8.8 Hz).

3-[2-[4-(4-Fluorobenzoyl)piperidin-1-yl]ethyl]-6,7-dihydro-1*H*-cyclopentapyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride Hemihydrate (36) A mixture of **35** (2.35 g, 8 mmol) and ethyl 2-oxocyclopentanecarboxylate (1.56 g, 10 mmol) was heated at 140—150 °C for 3 h. After cooling, the mixture was purified by column chromatography (silica gel, 80 g; eluent, 4% MeOH–$CHCl_3$) to give the free base of 1-substituted derivative **32** (0.42 g, 14%). Further elution with 5% MeOH–$CHCl_3$ produced the free base of **36** (0.34 g, 11%) as colorless crystals; mp 224—229 °C (EtOH). The free base was converted into the hydrochloride hemihydrate **36** in the usual way. Yield, 75%. Colorless crystals.

5-HT$_2$ Antagonist Activity in Rat Thoracic Aortic Strips The thoracic aorta was removed from a male SD rat weighing 220—250 g (Japan SLC Inc.) and cut into vascular rings of 4—5 mm in length. Preparations were suspended under a tension of 1 g in a modified Krebs-Henseleit solution at 37 °C and aerated by a gas mixture of 95% O_2 and 5% CO_2. The composition of the solution was as follows (mM): NaCl 112, KCl 5, $CaCl_2$ 1.5, $MgSO_4$ 1.2, NaH_2PO_4 1.2, $NaHCO_3$ 25 and glucose 11. Isometric tension was recorded using a TB-652T (Nihon Kohden) transducer connected to a polygraph (Nihon Kohden). After an equilibration period of 120 min, aortic strips were contracted with 60 mM KCl.

To test the anti 5-HT$_2$ activities, the preparations were contracted with 5-HT (0.1—100 μM) cumulatively. Then the preparations were washed, and 1 h later, the second cumulative contractions of aortic strips by 5-HT were observed in the presence of test drugs. The anti 5-HT$_2$ activities of the drugs were calculated from dose-response curves and expressed as pA_2 values if their blockades were competitive.

5-HT$_2$ Antagonist Activity in Rat *in Vivo* An male SD rat was anesthetized with urethane (1 g/kg, i.p.) and alphachloralose (80 mg/kg, i.p.). A catheter, connected to a pressure transducer, was inserted into the carotid artery to measure blood pressure, and a venous catheter was cannulated for drug injection. After 1 or 3 h of orally administrations of a test drug or vehicle, 5-HT (300 μg/kg, i.v.) was injected, and the change of the hypertensive phase, immediately after a transient hypotensive phase, was measured. The anti 5-HT$_2$ activity was expressed as an inhibition percentage.

References and Notes

1) R. A. Glennon, *J. Med. Chem.*, **30**, 1 (1987).
2) J. M. Van Nueten, *Fed. Proc.*, **42**, 223 (1983); F. De. Clerck, J. L. David and P. A. J. Janssen, *Agents and Actions*, **12**, 388 (1982).
3) F. De. Clerck, J. M. Van Nueten and R. S. Reneman, *Agents and Actions*, **15**, 612 (1984); J. D. Cree, J. Leempoels, B. Demoen, V. Roels and H. Verhaegen, *ibid.*, **16**, 313 (1985).
4) P. A. J. Janssen, *J. Cardiovasc. Pharmacol.*, **1985**, 7 (Suppl. 7), S2; J. E. Leysen, F. Awouters, L. Kennis, P. M. Laduron, J. Vandenberk and P. A. J. Janssen, *Life Sci.*, **28**, 1015 (1981).
5) L. R. Bush, *J. Pharmacol. Exp. Ther.*, **240**, 674 (1987); P. M. Vanhoutte, *Fed. Proc.*, **42**, 233 (1983).
6) M. Michiels, J. Monbaliu, W. Meuldermans, R. Hendriks, R. Geerts, R. Woestenborghs and J. Heykants, *Arzneim.-Forsch./Drug Res.* **38**, 775 (1988).
7) S. Ahmed, R. Lofthouse and G. Shaw, *J. Chem. Soc., Perkin Trans. 1*, **1976**, 1969.
8) O. Mitsunobu, *Synthesis*, **1981**, 1.
9) B. R. Baker and J. L. Kelley, *J. Med. Chem.*, **11**, 686 (1968).
10) S. N. Mikhailov, L. I. Kolobushkina, A. M. Kritsyn, N. S. Radyukova and V. L. Florent'ev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1974**, 2582 [*Chem. Abstr.*, **82**, 140078*z* (1975)].
11) A. P. Martinez and W. W. Lee, *J. Org. Chem.*, **30**, 317 (1965).
12) E. Frass, M. Draminski and B. Fiszer, *Rocz. Chem.*, **48**, 971 (1974) [*Chem. Abstr.*, **81**, 169505*b* (1974)].
13) O. Arunlakshana and H. O. Schild, *Brit. J. Pharmacol.*, **14**, 48 (1959).
14) This compound was prepared in our institute for experimental use.