(9*S*)-9-(2-Hydroxy-4,4-dimethyl-6-oxo-1-cyclohexen-1-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one, a Selective and Orally Active Neuropeptide Y Y5 Receptor Antagonist

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Received March 31, 2008

(9*S*)-9-(2-Hydroxy-4,4-dimethyl-6-oxo-1-cyclohexen-1-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one ((*S*)-**1**) was identified as a selective and orally active neuropeptide Y Y5 receptor antagonist. The structure−activity relationship for this structural class was investigated and showed that limited substitution on the phenyl ring was tolerated and that modification of the 4,4-dimethyl group of the cyclohexenone and the 3,3-dimethyl group of the xanthenone parts slightly improved potency. The plasma concentration−time profile after oral administration of (*S*)-**1** in Sprague−Dawley (SD) rats showed significant in vivo racemization of (*S*)-**1** and that (*S*)-**1** is cleared much more quickly than (*R*)-**1**. The duration of (*S*)-**1** in SD rats after oral administration of (*RS*)-**1** racemate was twice as long as that following oral administration of (*S*)-**1**. The C_{max} values of (*S*)-**1** after administration of (*S*)-**1** and (*RS*)-**1** were comparable, and the brain to plasma ratio for (*S*)-**1** was 0.34 in SD rats. In our acute D-Trp^{34}NPY-induced food intake model, both (*S*)-**1** and (*RS*)-**1** showed potent and dose-dependent efficacy. Therefore, the use of (*RS*)-**1** is suitable for studies that require sustained plasma exposure of (*S*)-**1**.

Introduction

NPY[a] is a highly conserved 36 amino acid peptide with potent, centrally mediated orexigenic effects.[1–4] Chronic administration of NPY into the brain induces hyperphagia and body weight gain.[5,6] Concentrations of NPY and its mRNA in the hypothalamus are markedly increased during food deprivation and in some genetic models of obesity in rodents.[7–11] In addition, NPY-deficient ob/ob mice are less obese and have reduced food intake when compared with ob/ob mice.[12] These data suggest that NPY may be a major regulator of physiological feeding behavior. Five distinct types of G-protein-coupled NPY receptors (Y1, Y2, Y4, Y5, and y6) have been cloned.[13] Correlations between the in vitro function and the binding activity of different peptide agonists and their potent stimulation of food intake in rodent models resulted in the identification of the Y5 receptor as a major feeding receptor.[14] In addition, a reduction in food intake induced by NPY and related peptides in Y5 receptor deficient (Y5 −/−) mice was observed,[15–17] thereby supporting the role of the Y5 receptor in food intake. On the basis of these findings, the antagonism of the Y5 receptor may have considerable therapeutic benefits in treating obesity. A number of research groups have been interested in the Y5 receptor and have reported diverse structural classes of compounds that target the Y5 receptor.[18–26] Our laboratory has demonstrated the potential for Y5 antagonism with the orally active and selective Y5 antagonist, (*RS*)-9-(2-hydroxy-4,4-dimethyl-6-oxo-1-cyclohexen-1-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one ((*RS*)-**1**) (Figure 1),[27–29] by showing that chronic administration of (*RS*)-**1** ameliorated diet-induced obesity in mice by suppressing weight gain and adiposity while (*RS*)-**1** did not affect diet-induced obesity of Y5 deficient mice.

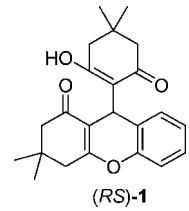
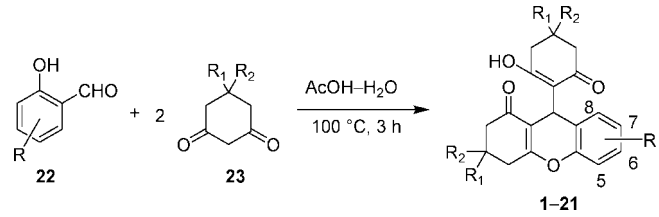


Figure 1. Structure of (*RS*)-**1**.

Scheme 1



Herein, we further elucidate the medicinal chemistry aspects of this novel xanthene class of Y5 antagonists.

Chemistry

Scheme 1 illustrates the general method for the preparation of the xanthene derivatives **1**−**21**.[30,31] A mixture of a 1:2 ratio of the salicylaldehyde **22** to the 1,3-cyclohexanedione **23** was heated in aqueous acetic acid to give the desired xanthene derivatives. The crystalline xanthene derivatives usually precipitated after cooling and dilution of the reaction mixture. 1,3-Hexanediones **23** employed in the present study were either commercially available or reported in the literature. Optical resolution of (*RS*)-**1** was initially performed by preparative HPLC. Subsequently, the active isomer (*S*)-**1** was resolved by fractional crystallization. Fractional crystallization of the diastereomeric salt of (*RS*)-**1** with cinchonidine yielded >99.5% ee of the active isomer (*S*)-**1**. The absolute stereochemistry of

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[a] Abbreviations: NPY, neuropeptide Y; P-gp, P-glycoprotein; SD rat, Sprague−Dawley rat; SAR, structure−activity relationship; CHO, Chinese hamster ovary; icv, intracerebroventricular.

10.1021/jm8003587 CCC: $40.75
Published on Web 07/19/2008

Table 1. Racemization of (*S*)-**1** in Various Media[a]

media	temp, °C	time 1 h	2 h	4 h	8 h	24 h
anhydrous acetnitrile	25	>99.5	>99.5	>99.5	>99.5	>99.5
50% aqueous acetonitrile	25	97.0	88.4	74.1	53.5	10.5
H_2O (suspension)	25	99.1	98.3	98.0	94.9	83.5
anhydrous methanol	25	81.7	65.0	47.5	27.9	2.8

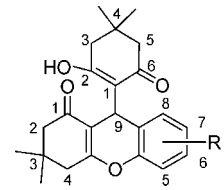
[a] The values represent % enantioexcess.

(*S*)-**1** was unequivocally determined by means of X-ray crystallography of the chinconidine salt of (*S*)-**1**. We tested (*S*)-**1** for its solution stability in terms of racemization. (*S*)-**1** has an indefinite shelf life in the solid state at −20 °C but is susceptible to racemization in aqueous media (Table 1). (*S*)-**1** was stable in an anhydrous aprotic solvent such as acetonitrile at 25 °C for up to 24 h, while fast racemization was observed in 50% aqueous acetonitrile (10.5% ee after 24 h). Suspension of (*S*)-**1** in H_2O also induced racemization. The racemization in H_2O was much slower than that in 50% aqueous acetonitrile. The racemization of (*S*)-**1** was even faster in a protic organic solvent such as anhydrous methanol. Thus, protic media are clearly responsible for the racemization of (*S*)-**1**.

Results and Discussion

Structure−Activity Relationships. We screened our in-house chemical collections for structurally diverse novel NPY Y5 leads and identified 9-(2-hydroxy-4,4-dimethyl-6-oxo-1-cyclohexen-1-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one ((*RS*)-**1**), which has a K_i value of 33 nM at the human Y5 receptor and is selective over NPY receptor subtypes (IC_{50} > 10 μM for human Y1, Y2, and Y4). After resolution and evaluation of the pure enantiomers, (*S*)-**1** was identified as the active isomer. Although racemization during the binding assay was a concern, the binding affinity (K_i = 14 nM) and antagonistic activity (K_i = 34 nM) of (*S*)-**1** was about 2-fold higher than that of (*RS*)-**1** and therefore acceptable (Table 2). The SAR turned out to be rather specific, and we were able to achieve only slight improvement in binding affinity. Substitution effects on the phenyl ring were examined initially (Table 2). Substitution with a methoxy group (**2**−**5**) did not enhance binding affinity; only the 6-methoxy derivative **4** was tolerated, whereas a dramatic decrease in activity was observed for the 5- and 8-methoxy derivatives **2** and **5**. Regarding the chloro derivatives **6**−**8**, both the 5- and 6-chloro derivatives **7** and **8** were tolerated. The fluoro derivatives **10**−**12** showed the same trend as the chloro derivatives. These results clearly suggest that substitution at the 7 and 8 positions should be avoided. The 5-position seems also to be sensitive to the size of the substituent, based on the markedly decreased potency of the 5-methoxy derivative **5**. Variations of the 6-substituent were therefore examined (**12**−**15**) but provided no clues for improving binding affinity. The significantly decreased potency of the ethoxy derivative **14** indicates that this phenyl site is extremely sensitive to the steric bulkiness of the substituents. We then focused on the 4,4-dimethyl group of the cyclohexenone and the 3,3-dimethyl group of the xanthenone parts (Table 3). Removing the methyl groups, as in **16** and **17**, resulted in a decrease in binding affinity. The diethyl derivative **18** was equiactive to (*RS*)-**1**. The cyclobutyl derivative **19** showed a slightly higher affinity than (*RS*)-**1**, whereas enlargement of the ring size, as in **20** and **21**, did not enhance binding affinity. The antagonistic activities of selected potent derivatives were determined by measuring the ability of the antagonists to inhibit

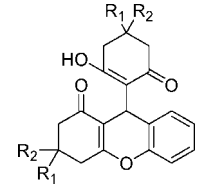
Table 2. In Vitro Potency of Compounds **1**−**15** (Variation of the Substituents on the Phenyl Ring)[a]



compd	R	binding affinity (K_i, nM)[b]	$[Ca^{2+}]_i$ response (IC_{50}, nM)[c]
(*RS*)-**1**	H	33 ± 6	61 ± 8
(*R*)-**1**	H	343 ± 78	>1000
(*S*)-**1**	H	14 ± 4	34 ± 5
2	8-OMe	>1000	[d]
3	7-OMe	590 ± 190	[d]
4	6-OMe	93 ± 19	[d]
5	5-OMe	2167 ± 203	[d]
6	7-Cl	197 ± 7	[d]
7	6-Cl	34 ± 0.3	82 ± 15
8	5-Cl	71 ± 9	[d]
9	7-F	81 ± 20	[d]
10	6-F	29 ± 7	63 ± 6
11	5-F	34 ± 2	73 ± 25
12	6-Me	36 ± 7	111 ± 16
13	6-Et	41 ± 2	[d]
14	6-OEt	833 ± 187	[d]
15	6-Br	36 ± 1	81 ± 6

[a] The values represent the mean ± SE for $n = 3$. [b] Human recombinant Y5 receptors in LMtk$^-$ cells; [^{125}I]PYY. See ref 27. [c] Antagonistic activities (human recombinant Y5 receptors/Gqi5 in CHO cells) at 100 nM NPY stimulation. [d] Not determined.

Table 3. In Vitro Potency of Compounds **16**−**21**[a]



compds	R_1, R_2	binding affinity (K_i, nM)[b]	$[Ca^{2+}]_i$ response (IC_{50}, nM)[c]
(*RS*)-**1**	$R_1 = R_2 =$ Me	33 ± 6	61 ± 8
16	$R_1 = R_2 =$ H	>1000	[d]
17	R_1 = Me, R_2 = H	193 ± 20	[d]
18	$R_1 = R_2 =$ Et	20 ± 2	90 ± 16
19	$-(CH_2)_3-$	14 ± 3	45 ± 7
20	$-(CH_2)_4-$	17 ± 2	58 ± 2
21	$-(CH_2)_5-$	24 ± 4	109 ± 7

[a] The values represent the mean ± SE for $n = 3$. [b] Human recombinant Y5 receptors in LMtk$^-$ cells; [^{125}I]PYY. See ref 27. [c] Antagonistic activities (human recombinant Y5 receptors/Gqi5 in CHO cells) at 100 nM NPY stimulation. [d] Not determined.

NPY-induced $[Ca^{2+}]_i$ increase in LMtk$^-$ cells expressing the recombinant human Y5 receptor. In this $[Ca^{2+}]_i$ functional assay, all the tested compounds showed potent antagonistic activities (Tables 2 and 3). We decided to employ **1** for in vivo concept studies on the basis of its potent functional activity. (*RS*)-**1** had excellent selectivity with respect to other NPY receptors and to 130 diverse selection of unrelated binding sites (IC_{50} > 10 μM for all the binding sites tested).

Pharmacokinetics and Brain Penetration of 1. Plasma concentration−time profiles after oral administration of (*S*)-**1** in SD rats were evaluated. Plasma levels of both enantiomers were monitored because in vivo racemization was speculated on the basis of the in vitro racemization study. In vivo racemization of (*S*)-**1** was indeed observed (Figure 2). It was subsequently found that the duration of (*S*)-**1** was extended when

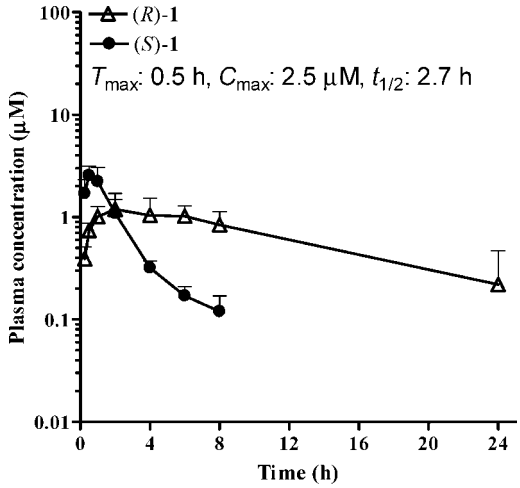


Figure 2. Plasma concentration−time profiles of (*S*)-**1** and (*R*)-**1** after oral dosing of 10 mg/kg of (*S*)-**1** in SD rats. The reported data are generated after 10 mg/kg po doses in $n = 3$ animals/dose.

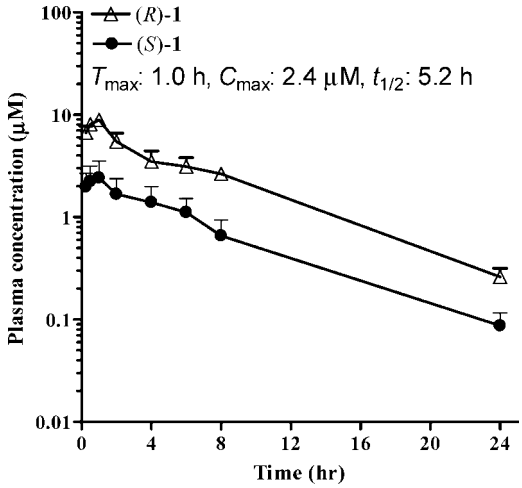


Figure 3. Plasma concentration−time profiles of (*S*)-**1** and (*R*)-**1** after oral dosing of 10 mg/kg of (*RS*)-**1** in SD rats. The reported data are generated after 10 mg/kg po doses in $n = 3$ animals/dose.

(*RS*)-**1** was administered (Figure 3). After oral administration of 10 mg/kg (*RS*)-**1** in SD rats, the initial concentration of (*S*)-**1** was lower than that of (*R*)-**1**, reflecting the first-pass clearance of each enantiomer; nevertheless, the half-life of (*S*)-**1** ($t_{1/2}$ = 5.2 h) was 2 times longer than that after administration of (*S*)-**1** ($t_{1/2}$ = 2.7 h), probably because of the steady supply of (*S*)-**1** from the abundant levels of (*R*)-**1**. This difference in clearance might be partly due to the binding of the enantiomers to plasma proteins. Indeed, rapidly cleared (*S*)-**1** has a higher free fraction (27% free) than (*R*)-**1** (10% free) in rat plasma.[32] Additional experiments are needed to fully understand this observation, and a detailed account will be reported in due course. The brain to plasma ratio of (*S*)-**1** in SD rats 1 h following oral dosing of 10 mg/kg (*S*)-**1** was determined to be 0.34. Interestingly, the brain to plasma ratio for (*R*)-**1** was 0.10, which is one-third of the ratio for (*S*)-**1**. It is noted that (*RS*)-**1** is not a substrate for P-gp (the transcellular transport ratio (B-to-A/A-to-B ratio) for (*RS*)-**1** was 1.0), suggesting that P-gp mediated transport is not involved in the brain penetration of **1**.[32] Hence, this 3-fold difference in the brain to plasma ratio between (*R*)-**1** and (*S*)-**1** is considered to be a consequence of the 3-fold difference in the free fraction in rat plasma between (*R*)-**1** and (*S*)-**1**.

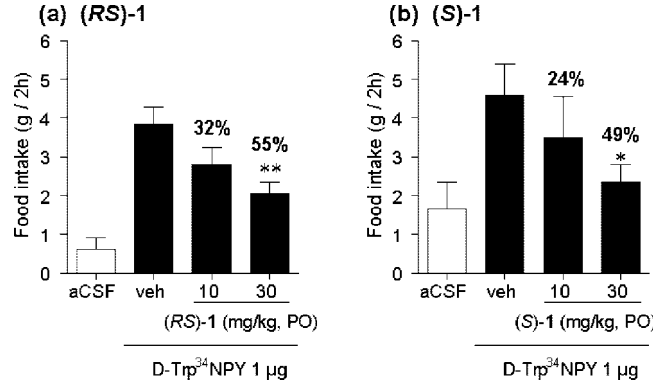


Figure 4. Effect of (*RS*)-**1** (a) and (*S*)-**1** (b) on D-Trp^{34}NPY-induced food intake in SD rats. Significant differences with respect to controls are indicated by an asterisk (∗, $P < 0.05$). The data shown are expressed as the mean ± SE. The graphs show the cumulative food intake in SD rats for 2 h after icv injection of D-Trp^{34}NPY. $n = 8$ rats/group.

Food Intake Inhibition of (*S*)-1 and (*RS*)-1. Prior to evaluation of in vivo efficacy, the effect of (*RS*)-**1** on gross behavior in mice was investigated. Oral administration of (*RS*)-**1** at a dose of 150 mg/kg caused no treatment-related changes in psychomotor activities, motor activities, muscle tone, central nerves system excitation, autonomic responses, and reflexes. No deaths occurred at any time after the administration. Thus, this agent was proven not to cause adverse effects at least up to 150 mg/kg oral dosing. In our D-Trp^{34}NPY-induced food intake model, Y5 antagonists are typically dosed 2 h prior to icv dosing of D-Trp^{34}NPY in SD rats to ensure sufficient distribution of the antagonists, and food intake of the rats is measured subsequently for 2 h. Since the T_{max} value of (*S*)-**1** after the administration of (*S*)-**1** is short (T_{max} = 0.5 h), (*S*)-**1** was instead dosed 1 h prior to icv dosing of D-Trp^{34}NPY. In the event, the differences in the duration of (S)-**1** were not critical in this acute model, and (*RS*)-**1** and (*S*)-**1** showed almost identical potent and dose-dependent food intake inhibition (Figure 4). We recently reported the antiobese effects of chronic treatment with (*RS*)-**1** on diet-induced obese mice.[29] In this chronic study, we employed racemate (*RS*)-**1**, since sustained plasma exposure was required to obtain sustained receptor occupancy and maximum efficacy in this chronic model.

Summary

(9*S*)-9-(2-Hydroxy-4,4-dimethyl-6-oxo-1-cyclohexen-1-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one ((*S*)-**1**) was identified as a selective and orally active neuropeptide Y5 receptor antagonist. The plasma concentration−time profile after oral administration of (*S*)-**1** in SD rats showed significant in vivo racemization of (*S*)-**1** and that (*S*)-**1** is cleared much more quickly than (*R*)-**1**. The duration of (*S*)-**1** in SD rats after oral administration of racemate (*RS*)-**1** was found to be about 2 times longer than that after administration of (*S*)-**1**. In our acute D-Trp^{34}NPY-induced food intake model, both (*S*)-**1** and (*RS*)-**1** showed potent and dose-dependent efficacy. The use of (*RS*)-**1** is suitable for studies that require sustained plasma exposure and receptor occupancy of (*S*)-**1**.

Experimental Section

General. Nuclear magnetic resonance spectra were recorded on Varian Gemini 200, 300, and JEOL JNM-A500 spectrometers in the indicated solvents. Chemical shifts are reported in parts per million (δ unit) relative to tetramethylsilane. Melting points were recorded on a Yanaco MP-S3 model melting point apparatus and are uncorrected. Electrospray ionization (ESI) mass spectra were

recorded on micromass Quattro II and Q-Toff-2 instruments. Elemental analyses were performed on CE instruments EA 1108 automatic elemental analyzer and are within 0.4% of theoretical values otherwise noted. Flash chromatography was performed with Merck silica gel 60 (230−400 mesh). Air- and/or moisture-sensitive reactions were carried out in commercially available anhydrous solvents under an atmosphere of nitrogen. All reagents were obtained from commercial suppliers and were used without further purification.

(*RS*)-9-(2-Hydroxy-4,4-dimethyl-6-oxo-1-cyclohexen-1-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one ((*RS*)-1). A mixture of salicylaldehyde (7.56 mL, 0.07 mol) and dimedone (20.0 g, 0.14 mol) in 140 mL of acetic acid and 140 mL of H_2O were heated to reflux for 1.5 h. The mixture was cooled to room temperature, and the resulting precipitate was collected, washed with ethanol, and vacuum-dried to give 23.2 g (89%) of the title compound: White solid, mp 208−210 °C; ^{1}H NMR ($CDCl_3$) δ 0.99 (6H, s), 1.03 (3H, s), 1.12 (3H, s), 1.92 (1H, d, J = 16.6 Hz), 1.99 (1H, d, J = 16.6 Hz), 2.33 (2H, s), 2.37 (2H, s), 2.47 (1H, d, J = 17.7 Hz), 2.57 (1H, d, J = 17.7 Hz), 4.66 (1H, s), 7.00−7.04 (3H, m), 7.13−7.18 (1H, m), 10.46 (1H, brs); MS (ESI+) m/z $[M + H]^+$ 367; HRMS (ESI+) m/z $[M + H]^+$ 367.1934 ($C_{23}H_{27}O_4$ requires 367.1909). Anal. ($C_{23}H_{26}O_4$) C, H, N.

(*S*)-9-(2-Hydroxy-4,4-dimethyl-6-oxo-1-cyclohexen-1-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one ((*S*)-1). A mixture of (*RS*)-**1** (7 g, 19.1 mmol) and cinchonidine (5.62 g, 19.1 mmol) in 490 mL of acetonitrile was heated to reflux until the mixture became clear. The mixture was cooled and gently stirred at room temperature for 3 days. The precipitate was collected to give 8.34 g of the *S* isomer rich cinchonidine salt. The salt was recrystallized from 490 mL of hot acetonitrile to give 6.85 g of (*S*)-**1** cinchonidine salt. The optically pure salt was suspended in a mixture of 300 mL of ethyl acetate and 200 mL of 10% citric acid, and the mixture was stirred until the layers became clear. The layers were separated, and the organic layer was washed with 10% citric acid and brine, dried over sodium sulfate, and concentrated. The residue was crystallized from hot ethyl acetate and heptane to give 2.23 g of the title compound. The ee was determined to be >99.9% by chiral HPLC analysis (DAICEL CHIRALCEL OD-RH, 150 mm × 4.6 mm i.d., 50:50 H_2O/CH_3CN; 1.0 mL/min, 230 nm; (*S*)-**1**, t_R = 4.69 min, (*R*)-**1**, t_R = 7.07 min): White solid, mp 213−215 °C; $[\alpha]_D^{25}$ +185° (*c* 1.0, $CHCl_3$).

9-(2-Hydroxy-4,4-dimethyl-6-oxocyclohexyl)-8-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (2). 2-Hydroxy-6-methoxybenzaldehyde (447 mg, 2.94 mmol) and dimedone (824 mmol, 5.88 mmol) in 3 mL of acetic acid and 6 mL of H_2O were heated to 100 °C for 1 h and cooled to room temperature. The mixture was diluted with H_2O and the resulting precipitate was collected to give 607 mg (52%) of the title compound: White solid, mp 189−193 °C; ^{1}H NMR ($CDCl_3$) δ 0.94 (3H, s), 0.98 (3H, s), 1.02 (3H, s), 1.11 (3H, s), 1.91 (1H, d, J = 16.7 Hz), 2.00 (1H, d, J = 16.7 Hz), 2.32 (2H, s), 2.34 (2H, s), 2.45 (1H, dd, J = 1.1, 17.5 Hz), 2.59 (1H, d, J = 17.5 Hz), 3.74 (3H, s), 4.74 (1H, s), 6.55 (1H, dd, J = 0.9, 8.3 Hz), 6.69 (1H, dd, J = 0.9, 8.3 Hz), 7.13 (1H, t, J = 8.3 Hz), 10.25 (1H, brs); MS (ESI+) m/z $[M + H]^+$ 397. Anal. ($C_{24}H_{28}O_5$) C, H, N.

9-(2-Hydroxy-4,4-dimethyl-6-oxocyclohexyl)-7-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3). White solid, mp 217−221 °C; ^{1}H NMR ($CDCl_3$) δ 1.00 (3H, s), 1.02 (6H, s), 1.12 (3H, s), 1.94 (1H, d, J = 17.0 Hz), 2.01 (1H, d, J = 17.0 Hz), 2.32 (2H, s), 2.38 (2H, s), 2.46 (1H, d, J = 17.8 Hz), 2.59 (1H, d, J = 17.8 Hz), 3.70 (3H, s), 4.64 (1H, s), 6.50 (1H, d, J = 3.0 Hz), 6.69 (1H, dd, J = 3.0, 8.9 Hz), 6.95 (1H, d, J = 8.9 Hz), 10.57 (1H, brs); MS (ESI+) m/z $[M + H]^+$ 397. Anal. ($C_{24}H_{28}O_5$) C, H, N.

9-(2-Hydroxy-4,4-dimethyl-6-oxocyclohexyl)-6-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (4). White solid, mp 177−181 °C; ^{1}H NMR ($CDCl_3$) δ 0.98 (3H, s), 0.99 (3H, s), 1.02 (3H, s), 1.12 (3H, s), 1.92 (1H, d, J = 16.0 Hz), 1.99 (1H, d, J = 16.0 Hz), 2.33 (2H, s), 2.36 (2H, s), 2.46 (1H, d, J = 17.5 Hz), 2.59 (1H, d, J = 17.5 Hz), 3.77 (3H, s), 4.61 (1H, s), 6.56−6.62 (2H, m), 6.89 (1H, m), 10.41 (1H, brs); MS (ESI+) m/z $[M + H]^+$ 397. Anal. ($C_{24}H_{28}O_5$) C, H, N.

9-(2-Hydroxy-4,4-dimethyl-6-oxocyclohexyl)-5-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (5). White solid, mp 217−222 °C; ^{1}H NMR ($CDCl_3$) δ 0.99 (3H, s), 1.00 (3H, s), 1.03 (3H, s), 1.12 (3H, s), 1.93 (1H, d, J = 16.2 Hz), 2.00 (1H, d, J = 16.2 Hz), 2.33 (2H, s), 2.37 (2H, s), 2.55 (1H, d, J = 17.7 Hz), 2.68 (1H, d, J = 17.7 Hz), 3.89 (3H, s), 4.66 (1H, s), 6.59 (1H, dd, J = 1.2, 7.5 Hz), 6.76 (1H, dd, J = 1.2, 7.5 Hz), 6.94 (1H, t, J = 7.5 Hz), 10.42 (1H, brs); MS (ESI+) m/z $[M + H]^+$ 397. Anal. ($C_{24}H_{28}O_5$) C, H, N.

7-Chloro-9-(2-hydroxy-4,4-dimethyl-6-oxocyclohexyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (6). White solid, 237−238 °C; ^{1}H NMR ($CDCl_3$) δ 1.02 (9H, s), 1.13 (3H, s), 1.98 (2H, s), 2.30−2.65 (6H, m), 4.60 (1H, s), 6.92−7.01 (2H, m), 7.09−7.14 (1H, m), 10.41 (1H, brs); MS (ESI+) m/z $[M + H]^+$ 401. Anal. ($C_{23}H_{25}ClO_4$) C, H, N.

6-Chloro-9-(2-hydroxy-4,4-dimethyl-6-oxocyclohexyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (7). White solid, mp 198−199 °C; ^{1}H NMR ($CDCl_3$) δ 0.98 (6H, s), 1.01 (3H, s), 1.12 (3H, s), 1.93 (1H, d, J = 16.5 Hz), 2.00 (1H, d, J = 16.5 Hz), 2.33 (2H, s), 2.37 (2H, s), 2.46 (1H, d, J = 17.8 Hz), 2.58 (1H, d, J = 17.8 Hz), 4.60 (1H, s), 6.91 (1H, d, J = 8.2 Hz), 6.98 (1H, dd, J = 2.0, 8.2 Hz), 7.03 (1H, d, J = 2.0 Hz), 10.39 (1H, brs); MS (ESI+) m/z $[M + H]^+$ 401. Anal. ($C_{23}H_{25}ClO_4$) C, H, N.

5-Chloro-9-(2-hydroxy-4,4-dimethyl-6-oxocyclohexyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (8). White solid, mp 217−222 °C; ^{1}H NMR ($CDCl_3$) δ 0.99 (6H, s), 1.04 (3H, s), 1.15 (3H, s), 1.95 (1H, d, J = 18.0 Hz), 2.01 (1H, d, J = 18.0 Hz), 2.35 (2H, s), 2.38 (2H, s), 2.67 (1H, d, J = 18.0 Hz), 2.70 (1H, d, J = 18.0 Hz), 4.66 (1H, s), 6.89−6.95 (2H, m), 7.21 (1H, d, J = 7.3 Hz), 10.38 (1H, brs); MS (ESI+) m/z $[M + H]^+$ 401. Anal. ($C_{23}H_{25}ClO_4$) C, H, N.

7-Fluoro-9-(2-hydroxy-4,4-dimethyl-6-oxocyclohexyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (9). White solid, mp 201−206 °C; ^{1}H NMR ($CDCl_3$) δ 1.00 (3H, s), 1.01 (3H, s), 1.02 (3H, s), 1.13 (3H, s), 1.98 (2H, s), 2.33 (2H, s), 2.35 (1H, d, J = 12.8 Hz), 2.41 (1H, d, J = 12.8 Hz), 2.47 (1H, d, J = 17.1 Hz), 2.57 (1H, d, J = 17.1 Hz), 4.63 (1H, s), 6.70 (1H, m), 6.83 (1H, m), 6.95 (1H, m), 10.38 (1H, brs); MS (ESI+) m/z $[M + H]^+$ 385. Anal. ($C_{23}H_{25}FO_4$) C, H, N.

6-Fluoro-9-(2-hydroxy-4,4-dimethyl-6-oxocyclohexyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (10). White solid, mp 238−239 °C; ^{1}H NMR ($CDCl_3$) δ 0.99 (6H, s), 1.02 (3H, s), 1.28 (3H, s), 1.92 (1H, d, J = 17.0 Hz), 2.02 (1H, d, J = 17.0 Hz), 2.33 (2H, s), 2.37 (2H, s), 2.47 (1H, d, J = 17.5 Hz), 2.59 (1H, d, J = 17.5 Hz), 4.61 (1H, s), 6.71 (1H, dd, J = 2.7, 8.2 Hz), 6.75 (1H, dt, J = 2.2, 9.2 Hz), 6.92 (1H, dd, J = 5.9, 7.7 Hz), 10.39 (1H, brs); MS (ESI+) m/z $[M + H]^+$ 385. Anal. ($C_{23}H_{25}FO_4 \cdot 0.3H_2O$) C, H, N.

5-Fluoro-9-(2-hydroxy-4,4-dimethyl-6-oxocyclohexyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (11). White solid, mp 205−209 °C; ^{1}H NMR ($CDCl_3$) δ 0.99 (6H, s), 1.03 (3H, s), 1.13 (3H, s), 1.93 (1H, d, J = 17.1 Hz), 2.01 (1H, d, J = 17.1 Hz), 2.34 (2H, s), 2.38 (2H, s), 2.53 (1H, d, J = 17.8 Hz), 2.66 (1H, d, J = 17.8 Hz), 4.66 (1H, s), 6.76 (1H, m), 6.95 (2H, m), 10.36 (1H, brs); MS (ESI+) m/z $[M + H]^+$ 385. Anal. ($C_{23}H_{25}FO_4$) C, H, N.

9-(2-Hydroxy-4,4-dimethyl-6-oxocyclohexyl)-3,3,6-trimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (12). White solid, mp 192−195 °C; ^{1}H NMR ($CDCl_3$) δ 0.99 (6H, s), 1.03 (3H, s), 1.12 (3H, s), 1.92 (1H, d, J = 17.1 Hz), 2.00 (1H, d, J = 17.1 Hz), 2.29 (3H, s), 2.32 (2H, s), 2.37 (2H, s), 2.45 (1H, d, J = 17.0 Hz), 2.60 (1H, d, J = 17.0 Hz), 4.63 (1H, s), 6.80−6.90 (3H, m), 10.35 (1H, brs); MS (ESI+) m/z $[M + H]^+$ 381. Anal. ($C_{24}H_{28}O_4$) C, H, N.

6-Ethyl-9-(2-hydroxy-4,4-dimethyl-6-oxocyclohexyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (13). White solid, mp 167−171 °C; ^{1}H NMR ($CDCl_3$) δ 0.99 (3H, s), 1.00 (3H, s), 1.03 (3H, s), 1.12 (3H, s), 1.22 (3H, t, J = 7.6 Hz), 1.92 (1H, d, J = 17.1 Hz), 1.99 (1H, d, J = 17.1 Hz), 2.32 (2H, s), 2.37 (2H, s), 2.45 (1H, d, J = 17.0 Hz), 2.59 (1H, d, J = 17.0 Hz), 2.60 (2H, q, J = 7.6 Hz), 4.63 (1H, s), 6.82−6.92 (3H, m), 10.38 (1H, brs); MS (ESI+) m/z $[M + H]^+$ 395. Anal. ($C_{25}H_{30}O_4$) C, H, N.

6-Ethoxy-9-(2-hydroxy-4,4-dimethyl-6-oxocyclohexyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (14). White solid, mp 176.0−176.2 °C; ^{1}H NMR ($CDCl_3$) δ 0.99 (6H, s), 1.02 (3H, s), 1.12 (3H, s), 1.39 (3H, t, J = 6.9 Hz), 1.92 (1H, d, J = 17.0 Hz), 1.99 (1H, d, J = 17.0 Hz), 2.32 (2H, s), 2.36 (2H, s), 2.46 (1H, d, J = 18.0 Hz), 2.59 (1H, d, J = 18.0 Hz), 3.98 (2H, q, J = 6.9 Hz), 4.60 (1H, s), 6.52−6.60 (2H, m), 6.87 (1H, d, J = 9.3 Hz), 10.38 (1H, brs); MS (ESI+) m/z $[M + H]^+$ 411. Anal. ($C_{25}H_{30}O_5$) C, H, N.

6-Bromo-9-(2-hydroxy-4,4-dimethyl-6-oxocyclohexyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (15). White solid, mp 205−208 °C; ^{1}H NMR ($CDCl_3$) δ 0.99 (6H, s), 1.02 (3H, s), 1.12 (3H, s), 1.93 (1H, d, J = 16.5 Hz), 2.00 (1H, d, J = 16.5 Hz), 2.33 (2H, s), 2.37 (2H, s), 2.46 (1H, d, J = 17.7 Hz), 2.59 (1H, d, J = 17.7 Hz), 4.59 (1H, s), 6.87 (1H, d, J = 9.0 Hz), 7.13 (1H, d, J = 9.0 Hz), 7.19 (1H, s), 10.38 (1H, brs); MS (ESI+) m/z $[M + H]^+$ 445. Anal. ($C_{23}H_{25}BrO_4$) C, H, N.

9-(2-Hydroxy-6-oxocyclohexyl)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (16). White solid, mp 215−219 °C; ^{1}H NMR ($CDCl_3$) δ 1.50−2.20 (7H, m), 2.36−2.68 (4H, s), 2.71−2.84 (1H, m), 4.64 (1H, s), 6.98−7.09 (3H, m), 7.10−7.20 (1H, m), 10.80 (1H, brs); MS (ESI+) m/z $[M + H]^+$ 311. Anal. ($C_{19}H_{18}O_4$) C, H, N.

9-(2-Hydroxy-4-methyl-6-oxocyclohexyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (17). White solid, mp 166−171 °C; ^{1}H NMR ($CDCl_3$) δ 1.01 (0.9H, d, J = 5.7 Hz), 1.02 (2.1H, d, J = 5.8 Hz), 1.13 (3H, d, J = 6.3 Hz), 1.87−2.52 (8H, m), 2.60−2.74 (2H, m), 4.50 (0.3H, d, J = 2.6 Hz), 4.52 (0.7H, d, J = 2.6 Hz), 6.75 (1H, m), 6,87 (1H, m), 7.03 (1H, m), 10.35 (1H, brs); MS (ESI+) m/z $[M + H]^+$ 339. Anal. ($C_{21}H_{22}O_4$) C, H, N.

9-(4,4-Diethyl-2-hydroxy-6-oxocyclohexyl)-3,3-diethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (18).[33] White solid, mp 165−168 °C; ^{1}H NMR ($CDCl_3$) δ 0.70−0.90 (12H, m), 1.23−1.49 (4H, m), 1.93 (1H, d, J = 15.0 Hz), 2.01 (1H, d, J = 15.0 Hz), 2.33−2.67 (6H, m), 4.63 (1H, s), 6.99 (2H, m), 7.14 (1H, m), 10.43 (1H, brs); MS (ESI+) m/z $[M + H]^+$ 423. Anal. ($C_{27}H_{34}O_4$) C, H, N.

9′-(6-Hydroxy-8-oxospiro[3.5]non-7-yl)-4′,9′-dihydrospiro[cyclobutane-1,3′-xanthen]-1′(2′*H*)-one (19).[34] White solid, mp 181−184 °C; ^{1}H NMR ($CDCl_3$) δ 1.66−1.96 (12H, m), 2.04 (1H, d, J = 12.0 Hz), 2.29 (1H, d, J = 12.0 Hz), 2.43−2.71 (5H, m), 2.89 (1H, d, J = 12.0 Hz), 4.59 (1H, s), 6.90 (1H, d, J = 6.0 Hz), 6.98 (1H, t, J = 6.0 Hz), 7.02 (1H, d, J = 6.0 Hz), 7.15 (1H, t, J = 6.0 Hz), 10.60 (1H, brs); MS (ESI+) m/z $[M + H]^+$ 391. Anal. ($C_{25}H_{26}O_4$) C, H, N.

9′-(7-Hydroxy-9-oxospiro[4.5]dec-8-yl)-4′,9′-dihydrospiro[cyclopentane-1,3′-xanthen]-1′(2′*H*)-one (20). White solid, mp 203−205 °C; ^{1}H NMR ($CDCl_3$) δ 1.32−1.67 (16H, m), 2.00 (1H, d, J = 16.5 Hz), 2.09 (1H, d, J = 16.5 Hz), 2.44 (2H, s), 2.47 (2H, s), 2.56 (1H, d, J = 17.8 Hz), 2.62 (1H, d, J = 17.8 Hz), 4.63 (1H, s), 6.97−7.04 (3H, m), 7.15 (1H, m), 10.56 (1H, brs); MS (ESI+) m/z $[M + H]^+$ 419. Anal. ($C_{27}H_{30}O_4$) C, H, N.

9′-(2-Hydroxy-4-oxospiro[5.5]undec-3-yl)-4′,9′-dihydrospiro[cyclohexane-1,3′-xanthen]-1′(2′*H*)-one (21). White solid (recrystallized from methanol), mp 185−188 °C; ^{1}H NMR ($CDCl_3$) δ 1.20−1.60 (20H, m), 1.92−2.09 (2H, m), 2.32−2.73 (6H, m), 4.63 (1H, s), 6.96−7.03 (3H, m), 7.15 (1H, m), 10.48 (1H, brs); MS (ESI+) m/z $[M + H]^+$ 447. Anal. ($C_{29}H_{34}O_4 \cdot 0.1MeOH$) C, H, N.

Acknowledgment. We thank Drs. Keiko Miura and Hisaki Kojima for all the X-ray crystallography work.

Supporting Information Available: Procedures for pharmacokinetic and D-Trp^{34}NPY induced food intake studies, X-ray crystallography data, and a table of elemental analysis data for the target compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Tatemoto, K.; Carlquist, M.; Mutt, V. Neuropeptide Y. A Novel Brain Peptide with Structural Similarities to Peptide YY and Pancreatic Polypeptide. *Nature* **1982**, *296*, 659–660.

(2) Clark, J. T.; Kalra, P. S.; Crowley, W. R.; Kalra, S. P. Neuropeptide Y and Human Pancreatic Polypeptide Stimulate Feeding Behavior in Rats. *Endocrinology* **1984**, *115*, 427–429.

(3) Stanley, B. G.; Leibowitz, S. F. Neuropeptide Y: Stimulation of Feeding and Drinking by Injection into the Paraventricular Nucleus. *Life Sci.* **1984**, *35*, 2635–2642.

(4) Tatemoto, K.; Mutt, V. Isolation of Two Novel Candidate Hormones Using a Chemical Method for Finding Naturally Occurring Polypeptides. *Nature* **1984**, *285*, 417–418.

(5) Stanley, B. G.; Kyrkoulim, S. E.; Lampert, S.; Leibowitz, S. F. Neuropeptide Y Chronically Injected into the Hypothalamus: A Powerful Neurochemical Inducer of Hyperphagia and Obesity. *Peptides* **1986**, *7*, 1189–1192.

(6) Zarjevski, N.; Cusin, I.; Vettor, R.; Rohner-Jeanrenaud, F.; Jeanrenaud, B. Chronic Intracerebroventricular Neuropeptide-Y Administration to Normal Rats Mimics Hormonal and Metabolic Changes of Obesity. *Endocrinology* **1993**, *133*, 1753–1758.

(7) Kalra, S. P.; Dube, M. G.; Sahu, A.; Phelps, C. P.; Kalra, P. S. Neuropeptide Y Secretion Increases in the Paraventricular Nucleus in Association with Increased Appetite for Food. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 10931–10935.

(8) White, J. D.; Olchovsky, D.; Kershaw, M.; Berelowitz, M. Increased Hypothalamic Contents of Preproneuropeptide-Y Messenger Ribonucleic Acid in Streptozotocin-Diabetic Rats. *Endocrinology* **1990**, *126*, 765–772.

(9) Sanacora, G.; Kershaw, M.; Finkelstein, J. A.; White, J. D. Increased Hypothalamic Content of Preproneuropeptide Y Messenger Ribonucleic Acid in Genetically Obese Zucker Rats and Its Regulation by Food Deprivation. *Endocrinology* **1990**, *127*, 730–737.

(10) Kesterson, R. A.; Huszar, D.; Lynch, A. A.; Simerly, R. B.; Cone, R. D. Induction of Neuropeptide Y Gene Expression in the Dorsal Medial Hypothalamic Nucleus in Two Models of the Agouti Obesity Syndrome. *Mol. Endocrinol.* **1997**, *11*, 630–637.

(11) Guan, X.-M.; Yu, H.; Van der Ploeg, L. H. T. Evidence of Altered Hypothalamic Pro-opiomelanocortin/neuropeptide Y mRNA Expression in Tubby Mice. *Mol. Brain Res.* **1998**, *59*, 273–279.

(12) Erikson, J. C.; Hollopeter, G.; Palmiter, R. D. Attenuation of the Obesity Syndrome of ob/ob Mice by the Loss of Neuropeptide Y. *Science* **1996**, *274*, 1704–1707.

(13) Blomqvist, A. G.; Herzog, H. Y-Receptor Subtypes. How Many More? *Trends. Neurosci.* **1997**, *20*, 294–298.

(14) Gerald, C.; Walker, M. W.; Criscione, L.; Gustafson, E. L.; Batzl-Hartmann, C.; Smith, K. E.; Vaysse, P.; Durkin, M. M.; Laz, T. M.; Linemeyer, D. L.; Schaffhauser, A. O.; Whitebread, S.; Hofbauer, K. G.; Taber, R. I.; Branchek, T. A.; Weinshank, R. L. A Receptor Subtype Involved in Neuropeptide-Y-Induced Food Intake. *Nature* **1996**, *382*, 168–171.

(15) Marsh, D. J.; Hollopeter, G.; Kafer, K. E.; Palmiter, R. D. Role of the Y5 Neuropeptide Y Receptor in Feeding and Obesity. *Nat. Med.* **1998**, *4*, 718–721.

(16) Pedrazzini, T.; Seydoux, J.; Kunstner, P.; Aubert, J. F.; Grouzmann, E.; Beermann, F.; Brunner, H. R. Cardiovascular Response, Feeding Behavior and Locomotor Activity in Mice Lacking the NPY Y1 Receptor. *Nat. Med.* **1998**, *4*, 722–726.

(17) Kanatani, A.; Mashiko, S.; Murai, N.; Sugimoto, N.; Ito, J.; Fukuroda, T.; Fukami, T.; Morin, N.; MacNeil, D. J.; Van der Ploeg, L. H. T.; Saga, Y.; Nishimura, S.; Ihara, M. Role of Y1 Receptor in the Regulation of Neuropeptide Y-Mediated Feeding Regulation: Comparison of Wild-Type, Y1 Receptor-Deficient, and Y5 Receptor-Deficient Mice. *Endocrinology* **2000**, *141*, 1011–1016.

(18) (a) Galiano, S.; Erviti, O.; Pérez, S.; Moreno, A.; Juanenea, L.; Aldana, I.; Monge, A. Synthesis of New Thiophene and Benzo[*b*-]thiophene Hydrazide Derivatives As Human NPY Y_5 aAntagonists. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 597–599. (b) Juanenea, L.; Galiano, S.; Erviti, O.; Moreno, A.; Pérez, S.; Aldana, I.; Monge, A. Synthesis and Evaluation of New Hydrazide Derivatives as Neuropeptide Y Y_5 Receptor Antagonists for the Treatment of Obesity. *Bioorg. Med. Chem.* **2004**, *12*, 4717–4723.

(19) Rueeger, H.; Gerspacher, M.; Buehlmayer, P.; Rigollier, P.; Yamaguchi, Y.; Schmidlin, T.; Whitebread, S.; Nuesslein-Hildesheim, B.; Nick, H.; Cricione, L. Discovery and SAR of Potent, Orally Available and Brain-Penetrable 5,6-Dihydro-4*H*-3-thia-1-aza-benzo[*e*]azulen- and 4,5-dihydro-6-oxa-3-thia-1-aza-benzo[*e*]azulen Derivatives as Neuropeptide Y Y5 Receptor Antagonists. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2451–2457.

(20) Aquino, C. J.; Ramanjulu, J. M.; Heyer, D.; Daniels, A. J.; Palazzo, F.; Dezube, M. Synthesis and Structure Activity Relationship of Guanidines as NPY Y5 Antagonists. *Bioorg. Med. Chem.* **2004**, *12*, 2691–2708.

(21) Hammond, M.; Elliott, R. L.; Gillaspy, M. L.; Hager, D. C.; Hank, R. F.; LaFlamme, J. A.; Oliver, R. M.; DaSilva-Jardine, P. A.; Stevenson, R. W.; Mack, C. M.; Cassella, J. V. Structure−Activity Relationships in a Series of NPY Y5 Antagonists: 3-Amido-9-ethylcarbazoles, Core-Modified Analogues and Amide Isosteres. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1989–1992.

(22) (a) Islam, I.; Dhanoa, D.; Finn, J.; Du, P.; Walker, M. W.; Salon, J. A.; Zhang, J.; Gluchowski, C. Discovery of Potent and Selective Small Molecule NPY Y5 Receptor Antagonists. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1767–1769. (b) Finn, J.; Pelham, D.; Walker, M. W.; Gluchowski, C. High-Throughput Synthesis Optimization of Sulfonamide NPY Y5 Antagonists. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1771–1774.

(23) Tabuchi, S.; Itani, H.; Sakata, Y.; Oohashi, H.; Satoh, Y. Novel Potent Antagonists of Human Neuropeptide Y Y5 Receptor. Part 1: 2-Oxobenzothiazolin-3-acetic Acid Derivatives. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1171–1175.

(24) Satoh, Y.; Hatori, C.; Ito, H. Novel Potent Antagonists of Human Neuropeptide Y-Y5 Receptor. Part 4: Tetrahydrodiazabenzazulene Derivatives. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1009–1011.

(25) (a) Itani, H.; Ito, H.; Sakata, Y.; Hatakeyama, Y.; Oohashi, H.; Satoh, Y. Novel Potent Antagonists of Human Neuropeptide Y Y5 Receptors. Part 2: Substituted Benzo[*a*]cycloheptene Derivatives. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 757–761. (b) Itani, H.; Ito, H.; Sakata, Y.; Hatakeyama, Y.; Oohashi, H.; Satoh, Y. Novel Potent Antagonists of Human Neuropeptide Y Y5 Receptors. Part 3: 7-Methoxy-1-hydroxy-1-substituted Tetraline Derivatives. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 799–802.

(26) Sato, N.; Takahashi, T.; Shibata, T.; Haga, Y.; Sakuraba, A.; Hirose, M.; Sato, M.; Nonoshita, K.; Koike, Y.; Kitazawa, H.; Fujino, N.; Ishii, Y.; Ishihara, A.; Kanatani, A.; Fukami, T. Design and Synthesis of the Potent, Orally Available, Brain-Penetrable Arylpyrazole Class of Neuropeptide Y5 Receptor Antagonists. *J. Med. Chem.* **2003**, *46*, 666–669.

(27) Kanatani, A.; Ishihara, A.; Iwaasa, H.; Nakamura, K.; Okamoto, O.; Hidaka, M.; Ito, J.; Fukuroda, T.; MacNeil, D. J.; Van der Ploeg, L. H. T.; Ishii, Y.; Okabe, T.; Fukami, T.; Ihara, M. L-152,804: Orally Active and Selective Neuropeptide Y Y5 Receptor Antagonist. *Biochem. Biophys. Res. Commun.* **2000**, *272*, 169–173.

(28) D-Trp^{34} NPY action in rodents: Mashiko, S.; Ishihara, A.; Iwaasa, H.; Sano, H.; Oda, Z.; Ito, J.; Yumoto, M.; Okawa, M.; Suzuki, J.; Fukuroda, T.; Jitsuoka, M.; Morin, N. R.; MacNeil, D. J.; Van der Ploeg, L. H. T.; Ihara, M.; Fukami, T.; Kanatani, A. Characterization of Neuropeptide Y (NPY) Y5 Receptor-Mediated Obesity in Mice: Chronic Intracerebroventricular Infusion of D-Trp(34)NPY. *Endocrinology* **2003**, *144*, 1793–1801.

(29) Ishihara, A.; Kanatani, A.; Mashiko, S.; Tanaka, T.; Hidaka, M.; Gomori, A.; Iwaasa, H.; Murai, N.; Egashira, S.; Murai, T.; Mitobe, Y.; Matsushita, H.; Okamoto, O.; Sato, N.; Jitsuoka, M.; Fukuroda, T.; Ohe, T.; Guan, X.; MacNeil, D. J.; Van der Ploeg, L. H. T.; Nishikibe, M.; Ishii, Y.; Ihara, M.; Fukami, T. A Neuropeptide Y Y5 Antagonist Selectively Ameliorates Body Weight Gain and Associated Parameters in Diet-Induced Obese Mice. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 7154–7158.

(30) Horning, E. C.; Horning, M. G. Methone Derivatives of Aldehydes. *J. Org. Chem.* **1946**, *11*, 95–99.

(31) Jurd, L. Anthocyanidins and Related Compounds. IX. The Synthesis of 9-Phenacyl-5-oxototetrahydroxanthenes. *J. Org. Chem.* **1966**, *31*, 1639–1941.

(32) For the experimental conditions for determination of plasma protein binding and P-gp effluxc index, see the following: Ohe, T.; Sato, M.; Tanaka, S.; Fujino, N.; Hata, M.; Shibata, Y.; Kanatani, A.; Fukami, T.; Yamazaki, M.; Chiba, M.; Ishii, Y. Effect of P-Glycoprotein-Mediated Efflux on Cerebrospinal Fluid/Plasma Concentration Ratio. *Drug Metab. Dispos.* **2003**, *31*, 1251–1254.

(33) For the preparation of 5,5-diethyl-1,3-hexanedione, see the following: Kon, G. A. R.; Linstead, R. P. The Chemistry of the 3-Carbon System. Prat IV. A Case of Retarded Mobility. *J. Chem. Soc.* **1925**, *127*, 815–821.

(34) For the preparation of spiro[3.5]nonane-6,8-dione, see the following: Paulsen, H.; Antons, S.; Brandes, A.; Logers, M.; Muller, S. N.; Naab, P.; Schmeck, C.; Schneider, S.; Stoltefuss, J. Stereoselective Mukaiyama−Michael/Michael/Aldol Domino Cyclization as the Key Step in the Synthesis of Pentasubstituted Arenes: An Efficient Access to Highly Active Inhibitors of Cholesteryl Ester Transfer Protein (CETP). *Angew. Chem., Int. Ed.* **1999**, *38*, 3373–3375.

JM8003587