3,4-Dimethyl-4-(3-hydroxyphenyl)piperidines: Opioid Antagonists with Potent Anorectant Activity

Charles H. Mitch,* J. David Leander, Laurane G. Mendelsohn, Walter N. Shaw, David T. Wong, Buddy E. Cantrell, Bryan G. Johnson, Jon K. Reel, John D. Snoddy, A. E. Takemori,† and Dennis M. Zimmerman*

Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285, and Department of Pharmacology, Medical School, University of Minnesota, Minneapolis, Minnesota 55455

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A series of (3*R**,4*R**)-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine opioid antagonists with varying substituents on the nitrogen were evaluated for their effect on food consumption in obese Zucker rats. Opioid affinity (μ, κ, and δ for selected compounds) and opioid antagonist activity (μ and κ) were characterized and compared to effects on food consumption. No compounds with high selectivity for either μ or κ receptors were discovered. However, compounds in the series had exceptional potency as opioid antagonists and in reducing food consumption in the obese Zucker rat. In contrast, a few compounds with high potency as opioid antagonists had much weaker potency for inhibiting food consumption. (3*R*,4*R*)-3,4-Dimethyl-1-[(3*S*)-3-hydroxy-3-cyclohexylpropyl]-4-(3-hydroxyphenyl)piperidine (11, LY255582) emerged as having the best activity profile, both in reducing food consumption and as an opioid antagonist. Compound 11 is a highly potent μ, κ-, and δ-opioid antagonist with possible clinical utility as an appetite suppressant for weight loss.

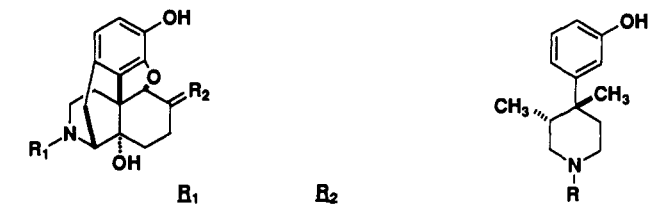
Introduction

Approximately 10% of the adult population of the United States are considered obese under the formal definition of a body mass index greater than 30, defined as weight (in kilograms) divided by height (in meters) squared.[1] While the implications of obesity to health are not fully understood, the frequent association of obesity with serious clinical conditions such as diabetes and cardiovascular disease warrants the use of pharmacological agents to promote weight loss in obese subjects.[2-4]

Endogenous opioids appear to play a significant role in regulation of appetite. Both μ- and κ-opioid agonists, including the endogenous endorphins and dynorphins have been reported to increase food consumption, although not all investigators have found this effect.[5-7] Furthermore opioid antagonists reduce food consumption in a variety of animal species.[7-9]

The relative safety of opioid antagonists makes them attractive candidates as potential drug therapy for the treatment of obesity. However, studies in humans with available antagonists have produced mixed results. Naloxone was found to significantly reduce food consumption, but its poor oral bioavailability and relatively short half-life, prevent its use for weight loss.[10,11] In contrast, naltrexone or nalmefene, potent opioid antagonists following oral administration, had only marginal effects on food consumption and weight loss in humans following acute and chronic administration.[12-15] These apparent differences between naloxone and naltrexone and nalmefene remain unexplained.

In the present work we have sought to find new opioid antagonists that would be more effective than naloxone, naltrexone, or nalmefene as anorectant agents. The preceding paper describes initial findings in the discovery of new phenylpiperidine-based opioid antagonists.[16] Compared to other opioid antagonists, structure–activity studies of 3(*R**),4(*R**)-dimethyl-4-(3-hydoxyphenyl)piperidines (1) are unusual in that a wide range of nitrogen substituents retain potent pure opioid antagonist activity. On the basis of these findings, we decided to explore this series of opioid antagonists for the development of improved anorectants. The effect of different nitrogen substituents on anorectant activity was examined and this activity was compared to the effect of varying nitrogen substituents on antagonist activities at μ- and κ-opioid receptors.



	R_1	R_2
Naloxone	CH_2–allyl	O
Naltrexone	CH_2–cyclopropyl	O
Nalmefene	CH_2–cyclopropyl	CH_2

1

In developing structure–activity studies for this series of opioid antagonists we initially sought antagonists with good selectivity between μ and κ receptors. At that time, evidence favored either a μ- or κ-receptor involvement in mediating feeding behavior; however, more evidence appeared to point to the importance of κ receptors.[17] In this paper we report the results of our structure–activity studies with N-substituted phenylpiperidines as opioid antagonists and as anorectants.

Chemistry

The 3(*R**),4(*R**)-dimethyl-4-(3-hydroxyphenyl)piperidine nucleus (2) was prepared via the metalated enamine (Scheme I) as described in the preceding publication.[16] Carbon–nitrogen bond formation for N-substitution was carried out by one of three methods. In the first method

† University of Minnesota.

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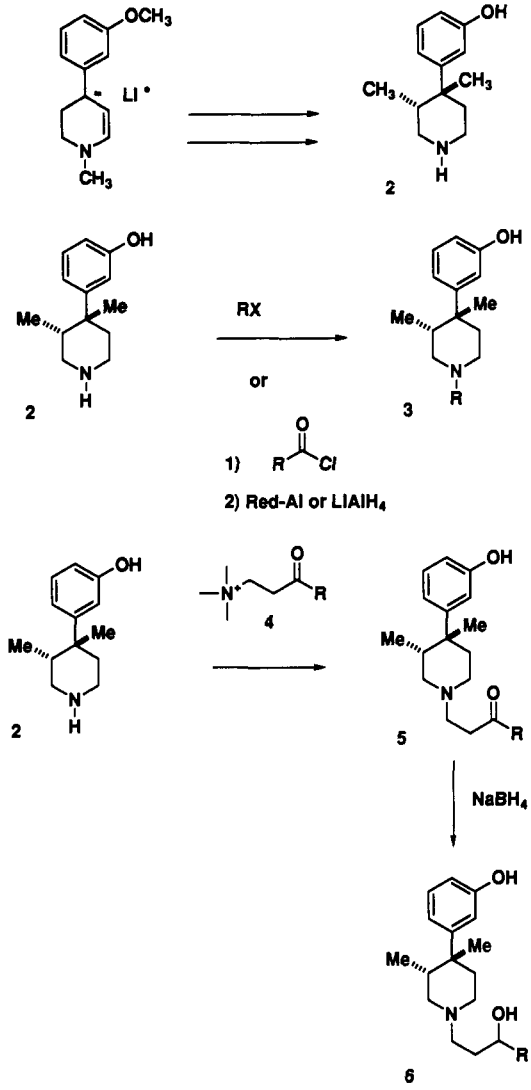
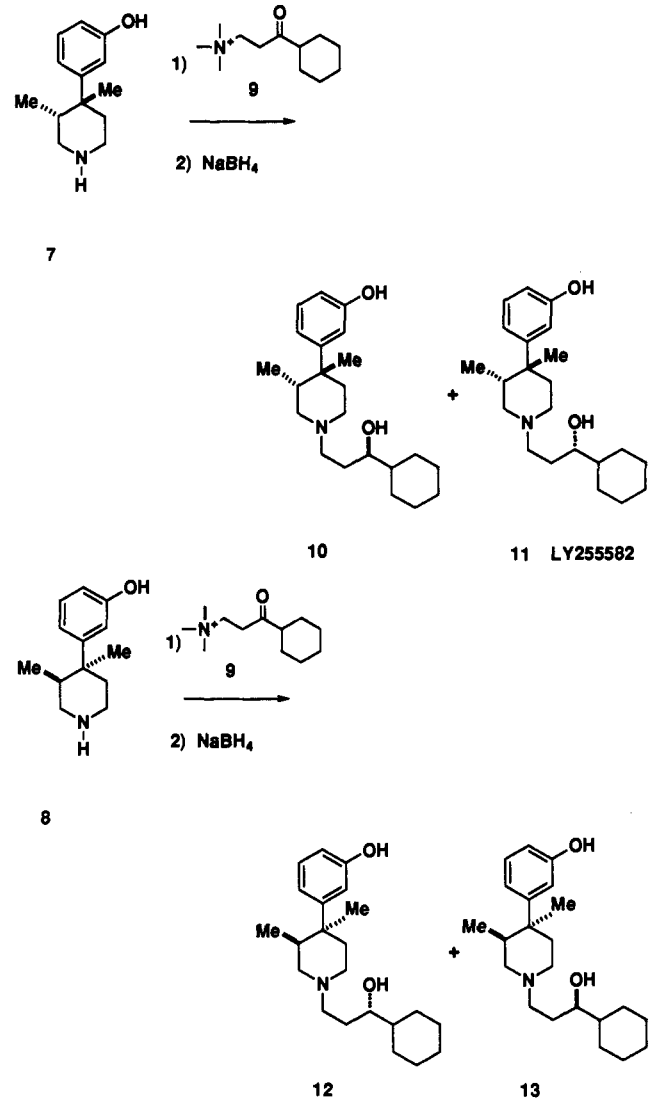
Scheme I



Scheme II



amine **2** was directly alkylated with alkyl halides. Alternatively, **2** was acylated with acid chlorides or anhydrides, followed by hydride reduction to the tertiary amine with either Red-Al or $LiAlH_4$. A third approach was based on Michael reactions between **2** and vinyl ketones, or a quaternized Mannich ketone **4** as vinyl ketone precursor. The resulting ketones, **5**, from the Mannich coupling were then reduced with $NaBH_4$ affording the alcohol **6** as a mixture of hydroxy diastereomers. Pharmacological evaluation of compounds of the type represented by **6** were generally carried out on the mixture of diastereomers unless specifically noted otherwise.

Compounds (+)-(3*R*,4*R*)-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (**7**) and (−)-(3*S*,4*S*)-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (**8**) were resolved by fractional crystallization of the dibenzoyl tartrate salts by previously described methodology.[19] For preparation of each of the four isomers found in compound **36**, the resolved phenylpiperidines **7** and **8** were independently reacted with Mannich ketone **9**, and in each case, the resulting pair of diastereomers was separated chromatographically to afford compounds **10** and **11**, as well as **12** and **13**, respectively (Scheme II).

The relative configuration of the three stereocenters of **11** was determined by X-ray crystallography and an ORTEP representation is shown in Figure 1.[18] An alternative synthesis utilizing resolved (−)-(1*S*)-1-cyclohexyl-1,3-dihydroxypropane for specific formation of **11** has been reported previously.[19] In that work, the resolved cyclohexylpropanol fragment was established to have *S* absolute configuration based on the use of Sharpless asymmetric epoxidation for kinetic resolution of the material.[20,21] It then follows from the relative configuration established by X-ray crystallography that the absolute configuration for **11** is as shown (3′*S*,3*R*,4*R*).

Pharmacology

Compounds were evaluated for their effect on food consumption in genetically obese Zucker rats. The Zucker rats were trained to a meal feeding paradigm in which food was consumed during an 8-h period each day. We have previously described the use of this assay in relating food consumption to weight gain in obese Zucker rats for opioid antagonists including a limited number of the phenylpiperidine type.[22] Opioid antagonists tested in the Zucker rat paradigm differed not only in potency but also in the maximum effect achieved. Because of this, a 20% reduction in food consumption was used as the criterion for summarizing anorectant activity in this study. An ED_{20} value is the dose calculated to reduce food consumption by 20% in comparison with saline-treated control animals, over the first 4 h of the meal feeding period.

Opioid antagonist activity *in vivo* was measured in the mouse writhing analgesia assay. Antagonist activity

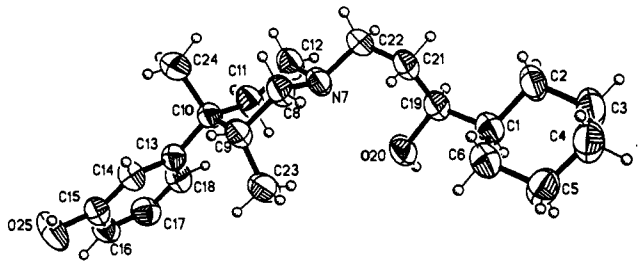


Figure 1.

against μ or κ agonists was evaluated by reversal of the analgesia produced by a fully efficacious dose of morphine (1.25 mg/kg, sc) or U50,488 (2.5 mg/kg, sc), respectively. AD_{50} values for antagonizing μ or κ analgesia were determined as the dose of test compound that reduced the agonist-induced inhibition of writhing to 50% of the control group.

κ-opioid agonists are well known to produce diuresis that can be quantified as a measure of κ-opioid agonist activity.[2,3] Reversal of κ-agonist-induced diuresis in the rat was used as an additional measure of κ-opioid antagonism. AD_{50} values were determined for the dose of test compound that reduced by 50% the cumulative urination induced by bremazocine (0.08 mg/kg, sc) over a 5-h period. Details of these *in vivo* opioid antagonist assays are given in the preceding paper as well as in previous publications.[16,23]

Affinity for μ-opioid receptors was determined in rat brain homogenates using [^{3}H]naloxone as a radioligand. Affinity for κ-opioid receptors was determined in guinea pig cortical tissue using [^{3}H]ethylketocyclazocine (EKC) as a radioligand. Fentanyl and D-Ala^2-D-Leu^5-enkephalin (DADL) were added to inhibit binding of [^{3}H]EKC to μ and δ receptors in the κ-receptor binding assay. A select number of compounds were evaluated for affinity for delta opioid receptors using [^{3}H]DADL as the radioligand with rat brain homogenates.

Results and Discussion

The preceding paper established the importance of the nitrogen substituent for optimizing opioid antagonist potency in a series of phenylpiperidines.[16] In this paper we have extended the structure–activity studies to delineate structural features of the nitrogen substituent maximizing anorectant activity and to compare this activity to receptor affinities and antagonist potencies at μ and κ receptors.

Results are shown in Table I. For the simple straight-chain aliphatic substitutions—methyl **14**, pentyl **15**, hexyl **16**, and heptyl **17**—anorectant activity increased with increasing chain length. Opioid antagonist potency and receptor affinity also increased along a similar trend, with maximum opioid effects found for the *n*-hexyl derivative **16**. Increasing the chain length produced a marked increase in κ-opioid antagonist activity. However with the *n*-heptyl derivative **17**, κ-antagonist activity decreased.

Addition of carbon branching at the end of *n*-alkyl substituents further increased anorectant potency. Maximal activity again occurred at a chain length of 6 carbons, as in 5-methylhexyl **21**. With an ED_{20} of 0.06 mg/kg (sc), compound **21** was one of the most potent anorectants discovered in this series. In general, as the separation of the branched carbon from the nitrogen is increased, opioid antagonist activities and receptor affinities also increased. In contrast to the anorectant activity, the greatest opioid antagonist potency occurred at a carbon atom length of 5, as in **19** and **20**. Interestingly, the order of anorectant potency found between **20** and **21** is the reverse of the order of potency of these two compounds as antagonists of μ and κ analgesia.

Terminating the chain with cyclic aliphatic functionality resulted in some noteworthy structure–activity changes. With the ethylcyclopentyl **22** and propylcyclopentyl derivative **24**, increasing chain length resulted in a decrease in anorectant potency, even though both of the compounds are potent as μ- and κ-opioid antagonists. With the cyclohexyl derivatives (methylcyclohexyl **25**, ethylcyclohexyl **26**, and propylcyclohexyl **27**), increasing chain length produced a marked increase in anorectant potency. However, the 30-fold increase in activity for propylcyclohexyl **27** over ethylcyclohexyl **26** contrasts sharply with their potencies as opioid antagonists. Compound **27** was only 1.5–3-fold less potent than **26** in blocking morphing-, U50,488-, or bremazocine-induced effects.

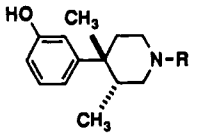
Aromatic substitution at the distal end of the carbon chain produced mixed results. Propylphenyl derivative **28** was considerably less active than the corresponding propylcyclohexyl derivative **27** in anorectant and opioid antagonist assays. On the other hand, 3-(2-thienyl)propyl **29** and 3-(3-thienyl)propyl **30**, were very potent both at inhibiting food consumption and at antagonizing μ- and κ-opioid activity.

Incorporation of a hydroxyl group in a position α to the branched or substituted carbon on the nitrogen substituent generally enhanced both anorectant and opioid antagonist potencies, as found for 3-hydroxy-4-methylpentyl **31**, 3-hydroxy-3-phenyl **32**, 3-hydroxy-3-thienylpropyl **33**, 3-hydroxy-3-cyclopentyl **34** and 3-hydroxy-3-cyclohexyl **36**. Compound **36**, with an ED_{20} of 0.05 mg/kg, was among the most potent anorectant agents of all the opioid antagonists tested. The effect was clearly dose related, and it was highly efficacious with regard to maximum effect achieved (data not shown). This compound is also a very potent antagonist of μ- and κ-opioid activity and has very high affinity for μ- and κ-opioid receptors.

It is important to note that the structure–activity conclusions described above were based on the evaluation of racemic mixtures. To examine the possibility that resolution could reveal enantiomers with substantially different receptor selectivities, four of the more potent compounds at inhibiting food consumption were resolved into their component isomers. The biological activity of the isomers is shown in Table II, along with data for naloxone, naltrexone, and nalmefene as standard comparators. In general, the (+)-isomers tend to be more potent both in their effect on food consumption and as opioid antagonists. Some of the (+)-isomers are as much as 10-fold μ selective when comparing antagonist potencies in the mouse writhing assay. The (−)-isomers showed much less selectivity between μ and κ antagonism in the writhing assay. Compound (+)-**37** is 6-fold more potent than (−)-**38** in anorectant activity even though they are equipotent as antagonists of μ and κ analgesia. On the other hand, (+)-**39** and (−)-**40** are equal in anorectant potency even though (+)-**39** is 4-fold more potent than (−)-**40** as a μ- and κ-opioid antagonist. All four isomers (+)-**10**, (+)-**11**, (−)-**12** and (−)-**13** are potent μ- and κ-opioid antagonists and have relatively high affinity for μ and κ receptors.[24]

Thus with the derivatives examined, only a limited stereochemical effect on opioid receptor selectivity was

Table I



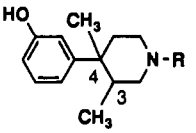
no.	R	food: inhibition feeding, ED_{20}[a] (mg/kg, sc)	opioid antagonist activity, AD_{50} (mg/kg, sc) mouse writhing assay[b] μ, morphine	mouse writhing assay[b] κ, U50,488	Rat Diuresis:[c] κ, bremazocine	receptor binding data, K_i (nM) μ, [^{3}H]Nal	receptor binding data, K_i (nM) κ, [^{3}H]EKC
14	CH_3	4.1	0.74	>5.0	>5.0	80	833
15	$(CH_2)_4CH_3$	3.8	0.37	0.60	0.69	4.3	(44% and 78%)[d]
16	$(CH_2)_5CH_3$	0.51	0.052	0.11	0.70	0.29	9.6
17	$(CH_2)_6CH_3$	0.40	0.21	>0.64	3.3	0.62	(57% and 87%)[d]
18	$(CH_2)_2$– 	>20	0.87	0.62	4.5	32	70
19	$(CH_2)_3$– 	2.1	0.11	0.073	0.39	0.29	9.6
20	$(CH_2)_3$– 	0.29	0.077	0.095	0.39	0.17	21
21	$(CH_2)_4$– 	0.06	0.58	0.24	0.39	0.46	5.9
22	$(CH_2)_2$–	0.34	0.14	0.22	0.67	2.3	7.2
23	$(CH_2)_2$– 	0.44	0.11	0.12	1.4	12	1.0
24	$(CH_2)_3$– 	1.2	0.12	0.13	0.79	0.37	3.4
25	CH_2– 	>20	1.1	0.47	4.6	17	29
26	$(CH_2)_2$– 	3.6	0.10	0.12	0.69	0.65	2.3
27	$(CH_2)_3$– 	0.12	0.35	0.19	1.0	0.49	2.3
28	$(CH_2)_3$–	1.3	2.4	5.3	1.1	0.69	15
29	$(CH_2)_3$– 	0.07	0.22	0.30	1.0	0.56	6.1
30	$(CH_2)_3$– 	0.06	0.12	0.24	1.9	0.26	10
31		0.65	0.14	0.35	0.17	2.6	6.9
32		0.50	0.05	0.92	2.5	1.00	12.5
33		0.07	0.07	0.14	1.4	0.5	11.7
34		0.09	0.04	0.08	0.99	0.41	5.5
35		0.13	0.12	0.26		0.34	3.9
36		0.05	0.07	0.14	0.49	0.29	4.8

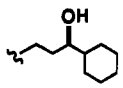
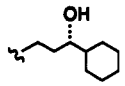
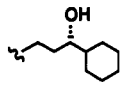
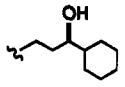
[a] Dose required to reduce food consumption by 20%. [b] Dose required for 50% reduction in the analgesic response to either morphine (1.25 mg/kg, sc) or U50,488 (2.5 mg/kg, sc). [c] Dose required to decreased 5-h bremazocine (0.08 mg/kg, sc)-induced urination. [d] Percent displacement at concentrations of 10 and 100 nM, respectively, run in triplicate.

observed. The possibility that resolution of other compounds in this series could reveal enantiomers with substantially different receptor selectivity from the corresponding racemates cannot be ruled out. However, in no case did the receptor selectivity of a racemate mask a crucial difference in receptor selectivity for any of the enantiomers tested.

Compound 11, the most potent of the isomers of **36**, has activity that surpasses that found for naloxone, naltrexone, and nalmefene (Table II). The greater potency of 11 is most pronounced for its activity as a κ antagonist in the rat diuresis assay. Compound 11 is also 30–40 times more potent than the standard antagonists at inhibiting food consumption. This large difference in anorectant activity

Table II



no.	config.	R	food: inhibition feeding, ED_{20}[a] (mg/kg, sc)	opioid antagonist activity, AD_{50} (mg/kg, sc): mouse writhing assay[b] μ, morphine	κ, U50,488	κ, bremazocine	recentor binding data, K_i (nM): μ, [^{3}H]NaI	κ, [^{3}H]EKC nM	δ, [^{3}H]DADL
37	(+)-3*R*,4*R*	$(CH_2)_5CH_3$	0.19	0.26	0.22	0.86	1.10	5.20	
38	(−)-3*S*,4*S*	$(CH_2)_5CH_3$	1.17	0.21	0.29	1.34	5.61	5.79	
39	(+)-3*R*,4*R*	$(CH_2)_4$- 	0.14	0.08	0.22	1.31	0.89	1.91	
40	(−)-3*S*,4*S*	$(CH_2)_4$- 	0.14	0.35	0.89	4.75	1.36	3.04	
41	(+)-3*R*,4*R*	$(CH_2)_3$- 	0.11	0.03	0.25	1.18	0.2	3.29	10.27
42	(−)-3*S*,4*S*	$(CH_2)_3$- 	0.4	0.24	0.65	1.66	1.8	12.5	
10	(+)-3*R*,4*R*		0.16	0.03	0.36	1.1	2.4	11.4	
11	(+)-3*R*,4*R*		0.04	0.015	0.05	0.38	0.41	2.0	5.2
12	(−)-3*S*,4*S*		0.11	0.13	0.24	1.6	1.4	6.5	
13	(−)-3*S*,4*S*		>1.25[d]	0.52	0.52	5.2	2.2	14.3	
naloxone			1.2[e]	0.08	1.1	3.5	6.3	66	32
naltrexone			1.7[f]	0.05	0.06	2.5	0.56	6.0	6.0
nalmefene			1.5	0.02	0.14	0.99	0.29	2.0	3.4

[a] Dose required to reduce food consumption by 20%. [b] Dose required for 50% reduction in the analgesic response to either morphine (1.25 mg/kg, sc) or U50,488 (2.5 mg/kg, sc). [c] Dose required to decrease 5-h bremazocine (0.08 mg/kg, sc)-induced urination by 50%. [d] Effect on feeding was minimal and not dose related. [e] Measured over 2 h time period due to short duration of action. [f] The maximum effect achieved was approximately 20% and not dose related.

stands in contrast to the relative equivalency in opioid antagonist potency and receptor affinity between 11 and the standard antagonists, especially naltrexone and nalmefene. The lack of anorectant activity for naloxone could be accounted for in terms of it having less κ activity. However, this does not explain the lack of anorectant activity for naltrexone and nalmefene even though both are quite potent at antagonizing κ analgesia and have high affinity for κ receptors. Also shown in Table II are the affinities of 11, naloxone, naltrexone, and nalmefene for the δ-opioid receptor. Differences in affinity for the δ receptor varies much less between these compounds than does their anorectant activity.

Compound 11 was also examined for activity at opioid receptors in smooth muscle preparations. In both the guinea pig ileum[25] and mouse vas deferens,[26] 11 showed no agonist effect up to a concentration of 1 μmol. Opioid antagonist activity for 11 at μ- and κ-opioid receptors (guinea pig ileum) and δ-opioid receptors (mouse vas deferens) is shown in Table III. Compared to naloxone, 11 is a highly potent antagonist at all three opioid receptors. It has highest potency for μ and κ receptors.

The affinity of 11 for a variety of other neuronal receptors were assayed to test if 11 had significant affinity for nonopioid receptors. The results, shown in Table IV, indicate that 11 was devoid of affinity for the 10 different nonopioid receptors tested.

Table III. Opioid Antagonist Effects of Compound 11 and Naloxone At μ, κ, and δ Opioid Receptors in Isolated Tissues

compd	K_e (nM)[a]: guinea pig ileum μ, morphine	guinea pig ileum κ, EKC[b]	mouse vas deferens: δ, DADL[c]
11[d]	0.24 ± 0.12	0.31 ± 0.05	1.64 ± 0.61
naloxone[e]	2.2	16	40

[a] The K_e is the estimated concentration of 11 necessary to produce a 2-fold shift of the agonist dose–response curve and is derived from the Schild relationship (Schild, H. O. *Pharmacol. Rev.* **1957**, *9*, 242) and calculated from an average of at least three IC_{50} determinations using the formula K_e = [antagonist]/(IC_{50} ratio − 1). [b] Ethylketocyclazocine (EKC). [c] D-Ala^2-D-Leu^5-enkephalin. [d] Tested at a concentration of 2 nM. [e] Tested at a concentration of 20 nM.

In summary, this structure–activity study led to the discovery of several highly potent μ- and κ-opioid receptor antagonists and to a few specific antagonists that have exceptional potency as anorectants. The compounds with the greatest anorectant potency were generally also highly potent antagonists of μ- and κ-opioid activity. However, a few compounds (such as compounds **19**, **24**, and **26**) were relatively lacking in anorectant activity even though they had high affinities for opioid receptors and were highly potent in blocking opioid agonists. The reasons for this are unclear. It could indicate that the anorectant activity is mediated by an opioid receptor not differentiated by the assays employed. In accord, with this, compound 11

Table IV. Affinity of Compound 11 for Other Receptor Sites in Rat Brain

receptor	radioligand	IC_{50} (nM)
serotonin 5-HT_1	[^{3}H]5HT	>1000
serotonin 5-HT_2	[^{3}H]spiperone (frontal cortex)	>1000
dopamine D_1	[^{3}H]SCH23390	>1000
dopamine D_2	[^{3}H]spiperone (striatum)	>1000
dopamine autoreceptor	[^{3}H]apomorphine	>1000
muscarinic acetylcholine	[^{3}H]quinuclidinyl benzylate	>10000
α-Adrenergic	[^{3}H]WB4101	>5000
α_2-adrenergic	[^{3}H]clonidine	>5000
β-adrenergic	[^{3}H]dihydroalprenolol	>5000
phencyclidine	[^{3}H]phencyclidine	>1000

has been recently reported to have high affinity for a κ-receptor subtype.[27] Another possibility is that the anorectant activity is mediated through nonopiodergic mechanisms; however, only compounds in this series that were potent opioid antagonists were also potent anorectants. In addition, compound 11 was shown to have highly selective affinity for opioid receptors when compared to a variety of nonopioid receptors.

Compound 11 has exceptional potency as an anorectant in the obese Zucker rat when compared to standard opioid antagonists, naloxone, naltrexone, and nalmefene. Full-dose response comparisons of these antagonists in this assay have been previously reported.[22,24] These studies have shown that 11 is not only more potent, but also produces a greater maximum effect on food consumption than the standard antagonists. In another study, the effects of centrally administered 11 and naloxone on food consumption were studied in Sprague-Dawley rats. In this paradigm, compound 11 was approximately 100 times more potent than naloxone in reducing food consumption.[28] Because the clinical results reported for naloxone, naltrexone, and nalmefene for appetite suppression have been equivocal at best, it is hoped that the differences observed between 11 and these standard antagonists will be predictive of utility for 11 in reducing food consumption and ultimately, body weight loss in man.

Experimental Section

All compounds were prepared as racemates except where specifically indicated otherwise.

Melting points were determined with a Melt-temp apparatus and are uncorrected. Proton and carbon magnetic resonance spectra were recorded on a GE QE-300 spectrometer at 300 and 75 MHz, respectively, and are reported in ppm on a δ scale from internal tetramethylsilane. Microanalyses, mass spectral measurements, and X-ray crystal structures were determined by the Structural and Organic Chemistry Research Department of the Lilly Research Laboratories. Optical rotations were obtained on a Perkin-Elmer Model 248 automatic polarimeter. Gas chromatography was performed on a Hewlett-Packard 5890 instrument with an HP-1 megabore capillary GC column and flame-ionization detection. HPLC analyses were run on a Waters 501 system using a Dupont Zorbax silica column and 280-nm UV detection. Preparative chromatography was performed on a Waters Prep 500 system.

When necessary, solvents and reagents were dried prior to use. Diethyl ether and tetrahydrofuran were distilled from sodium metal/benzophenone ketyl. All other reagents were used as received from Aldrich Chemical Co., Milwaukee, WI.

General Procedure A. Alkylation of 3(*R),4(*R**)-Dimethyl-4-(3-hydroxyphenyl)piperidine (2) with Alkyl Halides.** To a solution of 3(*R**),4(*R**)-dimethyl-4-(3-hydroxyphenyl)-piperidine (2) dissolved in DMF was added 1.1 equiv of $NaHCO_3$ and 1.1 equiv of alkyl halide. The reaction mixture was heated at reflux for 1 h and then cooled to room temperature. The mixture was poured into water and the pH of the solution was adjusted to approximately 9.8 by addition of 1 N NaOH. The mixture was extracted with Et_2O, and the combined organic extracts were dried over anhydrous K_2CO_3. The solvent was evaporated under vacuum followed by preparative chromatography (1:1 EtOAC/hexane, 0.5% Et_3N as eluent) of the resulting oil. Hydrochloride salts were prepared as noted and recrystallized from EtOH/EtOAC.

General Procedure B. Acylation of 3(*R),4(*R**)-Dimethyl-4-(3-hydroxyphenyl)piperidine (2) Followed by Reduction with Either $LiAlH_4$ or Red-Al.** Acyl chloride was prepared by treating a solution of carboxylic acid in CH_2Cl_2, cooled in an ice bath, with 10 equiv of oxalyl chloride and several drops of DMF. After 2 h, the reaction mixture was concentrated under vacuum and hexane was added to the residue. The resulting mixture was filtered and concentrated under vacuum. The residue was then used directly in the acylation procedure.

Acylation. To a solution of 3(*R**),4(*R**)-dimethyl-4-(3-hydroxyphenyl)piperidine (2) and 2.5 equiv of 1,8-bis(dimethylamino)naphthalene (proton sponge) dissolved in DMF was added a solution of 2.5 equiv of acyl chloride in DMF. The reaction mixture was stirred at room temperature for 1 h and poured into water. The mixture was extracted with EtOAc. The combined extracts were washed with 1 N HCl followed by saturated aqueous $NaHCO_3$, then dried over $NaCl/Na_2SO_4$, and evaporated under vacuum.

Reduction with $LiAlH_4$. The above residue was taken up in EtO_2 and cooled in an ice bath and 3 equiv of $LiAlH_4$ was added. After 1 h, reaction workup was carried out by the successive addition of n mL of water, n mL of 15% sodium hydroxide and 3 n mL of water for each n g of $LiAlH_4$ used. The solution was filtered and the filtrate dried over $NaCl/Na_2SO_4$ and evaporated under vacuum. The residue was chromatographed (1:1 EtOAc/hexane, 0.5% Et_3N as eluent) and hydrochloride salts were prepared as noted and recrystallized from EtOH/EtOAc.

Reduction with Red-Al. The residue from the acylation procedure was taken up in THF and cooled in an ice bath, and 2.5 equiv of Red-Al was added. The cooling bath was then removed. After 1 h, pH 10 buffer was added. The mixture was extracted with EtOAc. The organic extracts were combined and washed with brine, then dried over $NaCl/Na_2SO_4$, and evaporated under vacuum. The residue was dissolved in EtOAc and extracted with 1 N HCl, and the combined acidic extracts were washed with Et_2O. The pH of the aqueous mixture was adjusted to approximately 9.8 with 50% NaOH, and the mixture was extracted with EtOAc. The extracts were dried over $NaCl/Na_2SO_4$ and evaporated under vacuum. The residue was chromatographed (1:1 EtOAc/hexane, 0.5% Et_3N as eluent) and hydrochloride salts were prepared as noted and recrystallized from EtOH/EtOAc.

General Procedure C. Michael Reaction of 3(*R),4(*R**)-Dimethyl-4-(3-hydroxyphenyl)piperidine (2) with Quaternary Mannich Ketones.** Mannich ketones were prepared by adding methyl ketones to a solution of 1.3 equiv of paraformaldehyde, 1.3 equiv of dimethylamine hydrochloride, and 0.025 equiv of concentrated hydrochloric acid in ethanol and refluxing the resulting mixture for 16 h.[29] After cooling to room temperature, the solution was evaporated under vacuum. The residue was washed with Et_2O and then partitioned between 1 N NaOH and Et_2O. The Et_2O extracts were dried over $NaCl/Na_2SO_4$ and evaporated under vacuum. The resulting Mannich ketone was taken up in ethanol; 1.1 equiv of MeI was added; and the mixture was stirred for 16 h at room temperature. The resulting white precipitate was collected by filtration and used directly for Michael reactions.

To a solution of 3(*R**),4(*R**)-dimethyl-4-(3-hydroxyphenyl)-piperidine (2) and 2 equiv of Na_2CO_3 in DMF was added 1.1 equiv of the quaternary Mannich ketone. Nitrogen gas was bubbled through the solution with a gas dispersion tube, and the mixture was stirred at room temperature for 3 h. The mixture was then poured into water and extracted with EtOAc. The extracts were dried over $NaCl/Na_2SO_4$ and evaporated under vacuum. The residue was purified by chromatography (1:1 EtOAc/hexane, 0.5% TEA as eluent) and hydrochloride salts were prepared as noted and recrystallized from EtOH/EtOAc.

In some cases ketonic products were reduced with $NaBH_4$ to the corresponding alcohol.

To a 0 °C solution of ketone in 2-propanol was added 1.1 equiv of $NaBH_4$. After 1 h, the reaction was quenched by careful addition of 1 N HCl (50 mL for 500 mg $NaBH_4$), and the mixture was stirred for 30 min. The mixture was concentrated under vacuum. Water was added and the pH of the solution adjusted to approximately 9.8 with 50% NaOH. The solution was extracted with EtOAc, and the combined extracts were dried over $NaCl/Na_2SO_4$ and evaporated under vacuum. The residue was chromatographed (1:1 EtOAc/hexane, 0.5% TEA as eluent), and hydrochloride salts were prepared as noted and recrystallized from EtOH/EtOAC.

(−)-1-[3(*S*)-3-Hydroxy-3-cyclohexylpropyl]-3(*S*),4(*S*)-dimethyl-4-(3-hydroxyphenyl)piperidine [(−)-12]) and (−)-1-[3(*R*)-3-Hydroxy-3-cyclohexylpropyl]-3(*S*),4(*S*)-dimethyl-4-(3-hydroxyphenyl)piperidine [(−)-13]. General procedure C, Michael reaction between (−)-3(*S*),4(*S*)-dimethyl-4-(3-hydroxyphenyl)piperidine [(−)-8][19] and *N,N,N*-trimethyl-3-cyclohexyl-3-oxopropanaminium iodide (**9**) followed by $NaBH_4$ reduction afforded a mixture of (−)-**12** and (−)-**13** which were separated by chromatography (1:1 EtOAc/hexane, 0.5% TEA as eluent). For (−)-**12**: free base; mp 149–151 °C; $[\alpha]^{25}_D$ = −65.0° (c = 0.97, DMSO). Anal. ($C_{22}H_{35}NO_2$) C, H, N. For (−)-**13**: free base; mp 150–151 °C; $[\alpha]^{25}_D$ = −68.8° (c = 1.1, MeOH). Anal. ($C_{22}H_{35}NO_2$) C, H, N.

(+)-1-[3(*R*)-3-Hydroxy-3-cyclohexylpropyl]-3(*R*),4(*R*)-dimethyl-4-(3-hydroxyphenyl)piperidine [(+)-10] and (+)-1-[3(*S*)-3-Hydroxy-3-cyclohexylpropyl]-3(*R*),4(*R*)-dimethyl-4-(3-hydroxyphenyl)piperidine [(+)-11]. General procedure C, Michael reaction between 3(*R*),4(*R*)-dimethyl-4-(3-hydroxyphenyl)piperidine [(+)-7][19] and N,N,N-trimethyl-3-cyclohexyl-3-oxopropanaminium idodide (**9**) followed by $NaBH_4$ reduction afforded a mixture of (+)-**10** and (+)-**11** which were separated by chromatography (1:1 EtOAc/hexane, 0.5% TEA as eluent). For (+)-**10**: free base; mp 150–151 °C; $[\alpha]^{25}_D$ = +73.6° (c = 0.77, DMSO). Anal. ($C_{22}H_{35}NO_2$) C, H, N. For (+)-**11**: free base; mp 150–151 °C; $[\alpha]^{25}_D$ = +70.2 (c = 1.0, MeOH). Anal. ($C_{22}H_{35}NO_2$) C, H, N.

1-(1-Heptyl)-3(*R),4(*R**)-dimethyl-4-(3-hydroxyphenyl)piperidine (17).** General procedure B, acylation with heptanoyl chloride followed by reduction with $LiAlH_4$ afforded **17**: HCl salt; mp 155–157 °C. Anal. ($C_{20}H_{33}NO$·HCl) C, H, N.

1-(3-Methylbutyl)-3(*R),4(*R**)-dimethyl-4-(3-hydroxyphenyl)piperidine (18).** Geneal procedure A, alkylation with 1-bromo-3-methylbutane afforded **18**: HCl salt; mp 155–158 °C. Anal. ($C_{18}H_{29}NO$·HCl) C, H, N.

1-(4-Methylpentyl)-3(*R),4(*R**)-dimethyl-4-(3-hydroxyphenyl)piperidine (19).** General procedure A, alkylation with 1-bromo-4-methylpentane afforded **19**: HCl salt; mp 163–165 °C. Anal. ($C_{19}H_{31}NO$·HCl) C, H, N.

1-[4-Methyl-1-pent-4-enyl]-3(*R),4(*R**)-dimethyl-4-(3-hydroxyphenyl)piperidine (20).** General procedure B, acylation with 1-oxo-4-methyl-4-pentenyl chloride followed by reduction with Red-Al afforded **20**: HCl salt; mp 103–105 °C. Anal. ($C_{18}H_{29}NO$·HCl) C, H, N.

1-(5-Methylhex-1-yl)-3(*R),4(*R**)-dimethyl-4-(3-hydroxyphenyl)piperidine (21).** General procedure B, acylation with 1-oxo-5-methylhexanyl chloride followed by reduction with Red-Al afforded **21**: HCl salt; mp 175–177 °C. Anal. ($C_{20}H_{33}NO$·HCl) C, H, N.

1-(2-Cyclopentylethyl)-3(*R),4(*R**)-dimethyl-4-(3-hydroxyphenyl)piperidine (22).** General procedure B, acylation with 2-cyclopentylacetyl chloride followed by reduction with Red-Al afforded **22**: HCl salt; mp 176–178 °C. Anal. ($C_{20}H_{31}NO$·HCl) C, H, N.

1-(2-Cyclopent-2-enylethyl)-3(*R),4(*R**)-dimethyl-4-(3-hydroxyphenyl)piperidine (23).** General procedure B, acylation with 2-(2-cyclopentenyl)acetyl chloride followed by reduction with Red-Al afforded **23**: HCl salt; mp 128–130 °C. Anal. ($C_{20}H_{29}NO$·HCl) C, H, N.

1-(3-Cyclopentylpropyl)-3(*R),4(*R**)-dimethyl-4-(3-hydroxyphenyl)piperidine (24).** Geneal procedure B, acylation with 3-cyclopentylpropionyl chloride followed by reduction with $LiAlH_4$ afforded **24**: HCl salt; mp 171–174 °C. Anal. ($C_{21}H_{33}NO$·HCl) C, H, N.

1-(Cyclohexylmethyl)-3(*R),4(*R**)-dimethyl-4-(3-hydroxyphenyl)piperidine (25).** General procedure B, acylation with cyclohexanecarbonyl chloride followed by reduction with Red-Al afforded **25**: HCl salt; mp 80–82 °C. Anal. ($C_{20}H_{31}NO$·HCl) C, H, N.

1-(2-Cyclohexylethyl)-3(*R),4(*R**)-dimethyl-4-(3-hydroxyphenyl)piperidine (26).** General procedure A, alkylation with 2-cyclohexylethyl bromide afforded **26**: HCl salt, mp 178–180 °C. Anal. ($C_{21}H_{33}NO$·HCl) C, H, N.

1-(3-Cyclohexylpropyl)-3(*R),4(*R**)-dimethyl-4-(3-hydroxyphenyl)piperidine (27).** General procedure B, acylation with 3-cyclohexylpropionyl chloride followed by reduction with $LiAlH_4$ afforded **27**: HCl salt; mp 195–197 °C. Anal. ($C_{22}H_{35}NO$·HCl) C, H, N.

1-[3-(2-Thienyl)propyl]-3(*R),4(*R**)-dimethyl-4-(3-hydroxyphenyl)piperidine (29).** General procedure B, acylation with 3-(2-thienyl)propionyl chloride followed by reduction with Red-Al afforded **29**: HCl salt; mp 101–103 °C. Anal. ($C_{20}H_{27}NOS$·HCl) C, H, N.

1-[3-(3-Thienyl)propyl]-3(*R),4(*R**)-dimethyl-4-(3-hydroxyphenyl)piperidine (30).** General procedure B, acylation with 3-(3-thienyl)propionyl chloride followed by reduction with Red-Al afforded **30**: HCl salt; mp 96–98 °C. Anal. ($C_{20}H_{27}NOS$·HCl) C, H, N.

1-(3-Hydroxy-4-methylpentyl)-3(*R),4(*R**)-dimethyl-4-(3-hydroxyphenyl)piperidine (31).** General procedure C, Michael reaction with *N,N,N*-trimethyl-4-methyl-3-oxopentanaminium iodide followed by $NaBH_4$ reduction afforded **31** as a mixture of alcohol diastereomers: HCl salt; mp 75–77 °C. Anal. ($C_{19}H_{31}NO_2$·HCl) C, H, N.

1-[3-Hydroxy-3-(2-thienyl)propyl-3(*R),4(*R**)-dimethyl-4-(3-hydroxyphenyl)piperidine (33).** General procedure C, Michael reaction with *N,N,N*-trimethyl-3-thienyl-3-oxopropanaminium iodide followed by $NaBH_4$ reduction afforded **33** as a mixture of alcohol diastereomers: HCl salt; mp 90–92 °C. Anal. ($C_{20}H_{27}NO_2S$·HCl) C, H, N.

1-(3-Hydroxy-3-cyclopentylpropyl)-3(*R),4(*R**)-dimethyl-4-(3-hydroxyphenyl)piperidine (34).** General procedure C, Michael reaction with *N,N,N*-trimethyl-3-cyclopentyl-3-oxopropanaminium iodide followed by $NaBH_4$ reduction afforded **34** as a mixture of alcohol diastereomers: HCl salt; mp 108–110 °C. Anal. ($C_{21}H_{33}NO_2$·HCl) C, H, N.

1-(3-Cyclohexyl-3-oxopropyl)-3(*R),4(*R**)-dimethyl-4-(3-hydroxyphenyl)piperidine (35).** General procedure C, Michael reaction with *N,N,N*-trimethyl-3-cyclohexyl-3-oxopropanaminium iodide afforded **35**: HCl salt; mp 170–173 °C. Anal. ($C_{22}H_{33}NO_2$·HCl) C, H, N.

1-(3-Hydroxy-3-cyclohexylpropyl)-3(*R),4(*R**)-dimethyl-4-(3-hydroxyphenyl)piperidine (36).** General procedure C, Michael reaction with *N,N,N*-trimethyl-3-cyclohexyl-3-oxopropanaminium iodide followed by $NaBH_4$ reduction afforded **36** as a mixture of alcohol diastereomers: HCl salt, mp 113–115 °C. Anal. ($C_{22}H_{35}NO_2$·HCl) C, H, N.

(+)-1-Hexyl-3(*R*),4(*R*)-dimethyl-4-(3-hydroxyphenyl)piperidine [(+)-37]. General procedure B, acylation with heptanoyl chloride and (+)-3(*R*),4(*R*)-dimethyl-4-(3-hydroxyphenyl)-piperidine [(+)-7][19] followed by reduction with $LiAlH_4$ afforded (+)-**37**: HCl salt; $[\alpha]^{25}_D$ = +63.75 (c = 1.0, MeOH). Anal. ($C_{19}H_{31}NO$·HCl) C, H, N.

(−)-1-Hexyl-3(*S*),4(*S*)-dimethyl-4-(3-hydroxyphenyl)piperidine [(−)-38]. General procedure B, acylation with heptanoyl chloride and (−)-3(*S*),4(*S*)-dimethyl-4-(3-hydroxyphenyl)piperidine (−)-8[19] followed by reduction with $LiAlH_4$ afforded (−)-**38**: HCl salt; $[\alpha]^{25}_D$ = −58.81 (c = 1.0, MeOH). Anal. ($C_{19}H_{31}NO$·HCl) C, H, N.

(+)-1-(5-Methylhexyl)-3(*R*),4(*R*)-dimethyl-4-(3-hydroxyphenyl)piperidine [(+)-39]. General procedure B, acylation with 1-oxo-5-methylhexanyl chloride and (+)-3(*R*),4(*R*)-dimethyl-4-(3-hydroxyphenyl)piperidine [(+)-7][19] followed by reduction with $LiAlH_4$ afforded (+)-**39**: HCl salt; $[\alpha]^{25}_D$ = +57.52 (c = 1.0, MeOH). Anal. ($C_{20}H_{33}NO$·HCl) C, H, N.

(−)-1-(5-Methylhexyl)-3(*S*),4(*S*)-dimethyl-4-(3-hydroxyphenyl)piperidine [(−)-40]. General procedure B, acylation with 1-oxo-5-methylhexanyl chloride and (−)-3(*S*),4(*S*)-dimethyl-4-(3-hydroxyphenyl)piperidine [(−)-8][19] followed by

reduction with $LiAlH_4$ afforded (−)-40: HCl salt; $[\alpha]^{25}_D = -62.50$ (c = 1.0, MeOH). Anal. ($C_{20}H_{33}NO$·HCl) C, H, N.

(+)-1-[3-(2-Thienyl)propyl]-3(*R*),4(*R*)-dimethyl-4-(3-hydroxyphenyl)piperidine [(+)-41]. General procedure B, acylation with 3-(2-thienyl)propionyl chloride and (+)-3(*R*),4(*R*)-dimethyl-4-(3-hydroxyphenyl)piperidine (+)-7[19] followed by reduction with Red-Al afforded (+)-41: HCl salt; mp 110–112 °C; $[\alpha]^{25}_D = +54.9$ (c = 1.0, MeOH). Anal. ($C_{20}H_{27}NOS$·HCl) C, H, N.

(−)-1-[3-(2-Thienyl)propyl)-3(*S*),4(*S*)-dimethyl-4-(3-hydroxyphenyl)piperidine ((−)-42). General procedure B, acylation with 3-(2-thienyl)propyl chloride and (−)-3(*S*),4(*S*)-dimethyl-4-(3-hydroxyphenyl)piperidine [(−)-8][19] followed by reduction with Red-Al afforded (−)-42: HCl salt; mp 110–112 °C; $[\alpha]^{25}_D = 55.2$ (c = 1.0, MeOH). Anal. ($C_{20}H_{27}NOS$·HCl) C, H, N.

Mouse Writhing Analgesic and Opioid Antagonist Assay. Five CF-1 male mice (Charles River, Portage, MI), weighing approximately 20 g after being fasted overnight, were observed simultaneously for the writhing response. The writhing response was induced by the intraperitoneal administration of 0.6% acetic acid in a volume of 1 mL/100 g body weight. The observation period was 10 min in duration, beginning 5 min. after injection of acetic acid. The percent inhibition of writhing was calculated from the average number of writhes in the control (nondrug) group. Each data point is the mean (+standard error) for five mice. Dose–response effects were measured by varying the antagonist 2-fold, until minimum and maximum doses were determined. A minimum of five different doses were used. The response for each dose had a standard error <25%. The AD_{50} was defined as the dose of antagonist that reduced the inhibition of writhing produced by a standard dose of the agonist (1.25.mg/kg for morphine or 2.5 mg/kg for U50,488H) to 50%. Each mouse was used only once. All drugs were administered subcutaneously (1 mL/100 g of body weight) 20 min before the injection of acetic acid. The drugs used and the forms in which the doses were calculated are as follows: morphine sulfate, and U-50,488J methane sulfonate (The Upjohn Co., Kalamazoo, MI).

Antagonism of κ (Bremazocine-Induced) Diuresis in Rats. The animals used were a pool of 50 male Long-Evans hooded rats (Charles River, Portage, MI) weighing 350–500 g. They were individually housed in a colony room (23 °C) illuminated between 0600 and 1800 h. Rodent chow and tap water were freely available except during the measurement of urinary output. The animals were used repeatedly, but no more frequently than twice (separated by two days) during a week. To measure urinary output, the animals were removed from their home cages at about 1000 h, weighed, injected, and placed individually in metabolism cages for the next 5 h. Excreted urine was funneled into graduated cylinders, and the volume was recorded at 2 and 5 h after injection. Bremazocine hydrochloride (Sandoz Ltd., Basle, Switzerland) was used as the κ agonist to induce urination. Bremazocine hydrochloride was injected subcutaneously in a dose of 0.08 mg/kg, and without delay doses of the potential antagonists were injected subcutaneously on the opposite side of the rat. For each test compound, three rats per dose were used. The response for each dose had a standard error < 25 %. Test doses were varied 2-fold until minimum and maximum effect doses were identified.

Opioid Receptor Binding Assays. The affinities of test compounds for μ-, κ-, and δ-opioid receptors were determined by a modification of the method of Werling et al.[30] Mu-receptor binding was determined using [^{3}H]naloxone with rat brain homogenates. [^{3}H]Ethylketocyclazocine in the presence of fentanyl and D-Ala^2-D-Leu^5-enkephalin with guinea pig cortical tissue was used for κ-opioid receptor binding. Affinity for δ-opioid receptors was determined using [^{3}H]-D-Ala^2-D-Leu^5-enkephalin with rat brain homogenates. More details of these assays are given in the preceding paper. For all opioid receptor binding assays K_i's were derived from at least six different concentrations, each run in triplicate. The standard errors for the extrapolated K_i's from the regression lines were less than 50% of the K_i. The correlation coefficient for calculating the K_i values were > 0.9 and the triplicate values generally differed by less than 10%.

Nonopioid Receptor Binding Assays. Male Sprague-Dawley rats weighing 110–150 g were decapitated. Brains were immediately removed and cerebral cortice were dissected. Calf brains and choroid plexus were shipped from Pel Freeze (Rogers, AR) on wet ice and striata were dissected over ice. Radioligand binding was conducted as previously described.[31] Respective ^{3}H ligands and tissue used were binding of [^{3}H]serotonin to 5-HT_1 receptors, [^{3}H]spiperone to 5-HT_2 receptors, [^{3}H]quinuclidinyl benzylate to muscarinic receptors, and [^{3}H]WB4101, [^{3}H]-clonidine, and [^{3}H]dihydroalprenolol to α_1-, α_2- and β-adrenergic receptors, all in rat cortical membranes. Binding of [^{3}H]-Sch23390, [^{3}H]spiperone, and [^{3}H]apomorphine to dopamine D_1 and D_2 receptors was conducted using bovine striatal membranes. Specific conditions for binding ^{3}H ligands were similar to those previously described.[31]

Food Consumption. Obese Zucker rats, 3–4 months old, were trained to eat food daily from 8:00 a.m. to 4:00 p.m. only, such that the body weight gain approximates that if the rats were fed ad libitum. These rats were allowed water at all times. Four groups of rats with four rats in each group, two female and two male, were formed. One group served as control for the other three groups each day. Each of the other groups were given one of three subcutaneous doses of the compound to be evaluated for three days consecutively. Animals remained drug free for 4 days before the next test. Food consumption of each rat was measured for the first four hours. The test compound was formulated in physiological saline containing 10% dimethyl sulfoxide by volume. Representative test doses used were 5.0, 1.25, 0.32 mg/kg, respectively, or 1.25, 0.32, 0.08 mg/kg, respectively. Additional testing with a dose of 0.02 mg/kg was carried out in some cases if the response to the 0.08 mg/kg dose was significantly different from control. Likewise, testing with a dose of 20 and/or 5 mg/kg, respectively, was carried out in some cases if the response to lower doses was not significantly different from control. The response for each dose had a standard error < 35%. Due to variation in the maximum effect on food consumption between different compounds, an ED_{20} value, for the dose that reduced food consumption by 20% of control, was calculated from regression analysis of the linear portion of the dose–response curves.

Supplementary Material Available: Details of the X-ray crystal structure determination for compound (+)-11, including tables of atomic coordinates, bond lengths and angles, anisotropic displacement parameters and an ORTEP drawing of structure showing the numbering scheme used in the tables (13 pages). Ordering information is given on any current masthead page.

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