Articles

Discovery of a Potent, Peripherally Selective *trans*-3,4-Dimethyl-4-(3-hydroxyphenyl)piperidine Opioid Antagonist for the Treatment of Gastrointestinal Motility Disorders

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Structure–activity relationship studies were pursued within *N*-substituted-*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines in an effort to discover a peripherally selective opioid antagonist with high activity following systemic administration. Altering the size and the polarity of the N-substituent led to the discovery of **3** (LY246736). Compound **3** has high affinity for opioid receptors (K_i = 0.77, 40, and 4.4 nM for μ, κ, and δ receptors, respectively). It is a potent μ receptor antagonist following parenteral and oral administration and distributes selectively (>200-fold selectivity) to peripheral receptors. Thus, **3** has properties suitable for the clinical investigation of μ opioid receptor involvement in GI motility disorders.

Introduction

A large body of evidence indicates an important role for endogenous opioids in the physiological control of gastrointestinal (GI) motility.[1–4] High concentrations of opioids have been found along the GI track, and opioid peptides and opiates have potent effects on GI motility. Clinical studies with the opioid antagonist naloxone have provided additional evidence for a role of endogenous opioids in the regulation of GI motility and have further implicated their involvement in dysfunctional GI transit.[5–8] In addition, the constipating activity of opiates is well-known and is often a distressing side effect of opiate analgesic therapy.[9,10]

The site(s) of action of various opioid-induced GI motility changes have not been conclusively determined,[11] and exogenously administered opioids can affect GI motility, acting at both peripheral and central receptors. However, a substantial amount of evidence suggests a predominant involvement of peripheral opioid receptors in the control of GI motility. Of the three well-characterized opioid receptors (μ, κ, δ), μ receptor activity appears to be most importantly involved. Thus it may be possible to use a μ opioid receptor antagonist to treat various GI motility disorders (IBS, opiate-induced constipation, and idiopathic constipation). A suitable antagonist should have selectivity for the μ receptor, good activity following oral administration, and distribute selectivity to peripheral receptors following *in vivo* administration.

Previous efforts to develop peripherally selective opioid antagonists have primarily focused on the quaternization of known opioid antagonists through addition of alkyl substitutents on the tertiary nitrogen atom.[12–14] These quaternary opioid antagonists (i.e., naloxone methiodide; **1**, Figure 1) have served as important pharmacological probes for characterizing peripherally and centrally mediated opioid effects; however, their usefulness is limited because of low selectivity for peripheral versus central receptors (parent molecule or metabolite) and their limited potency. Their use as therapeutic agents has also been precluded because of inadequate oral bioavailability.

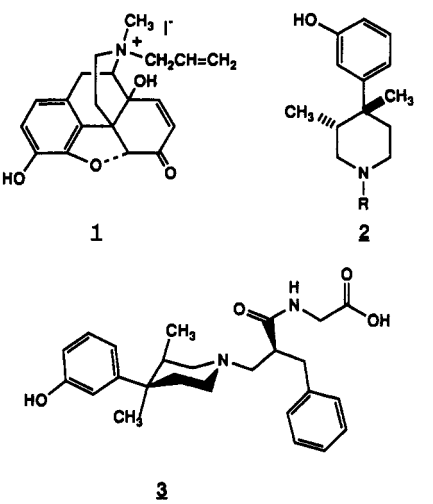

Figure 1.

Accordingly, we sought to discover a peripherally selective μ opioid antagonist suitable for use in the treatment of GI motility disorders. Structure–activity relationship (SAR) studies were pursued within a unique series of opioid antagonists, *N*-substituted-*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines (**2**, Figure 1). Previous SAR studies within this series involving alteration of the substituent on nitrogen led to the discovery of many highly potent opioid antagonists.[15–18] In this study the N-substituent was systemically altered to increase μ opioid receptor antagonist activity and to prevent passage through the blood–brain barrier into the central nervous system following systemic administration. The strategy involved increasing both the size and polarity of the N-substitutent in the arylpiperidine **2**. Previous SAR findings provided direction in the

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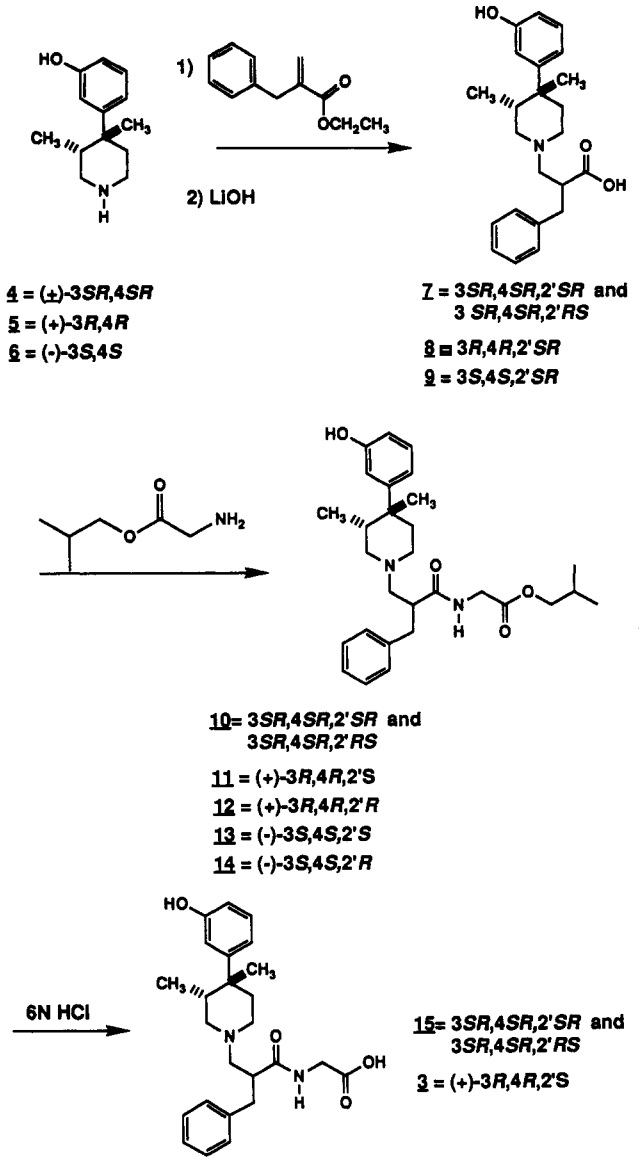
Scheme 1



choice of new analog synthesis.[15-17] From these efforts, we report the discovery of **3** (Figure 1).

Compound **3** was originally evaluated as the racemic, diastereomeric mixture **15** (Scheme 1). In an attempt to increase oral activity several esters of **15** were prepared. Of these, **10** showed the most promise. The four isomers of **10** were synthesized, and the highest *in vitro* activity was found with (+)-3*R*,4*R*,2'*S* isomer **11**. A thorough comparison of the activities of **11** and **3** revealed no significant differences in their μ antagonist activities following oral administration.

Chemistry

The synthesis of these *N*-substituted-4-phenylpiperidines is shown in Scheme 1. Compounds **10** and **15** were synthesized from racemic **4**, while compounds **11** and **12** and **13** and **14** were synthesized from **5** and **6**, respectively. The diastereomers **11** and **12** as well as **13** and **14** were separated by preparative HPLC. Acidic hydrolysis of **11** gave **3**. Synthesis and determination of the absolute configurations of **5** and **6** have been previously reported.[19] The absolute configuration of the third asymmetric center of **3** (designed 2') was established through X-ray crystallography.[20]

Table 1. Affinities of the 4-Phenylpiperidine Antagonists for μ and κ Opioid Receptors

	[^{3}H]NAL[a] binding assay (μ receptor) % displacement[c]			[^{3}H]EKC[b] binding assay (κ receptor) % displacement[c]		
compound	K_i (nM)[d]	10 nM	100 nM	K_i (nM)[d]	10 nM	100 nM
7	2.6				0	15
15	0.89				23	53
10	4.0				7	16
11	5.5			23		
12		11	70		0	0
13	19.2				4	55
14		57	92		0	34
3[e]	0.77			40		
naloxone	3.7			66		
naltrexone	0.56			6.0		
WIN 44,441-3	0.73			0.54		

[a] Naloxone. [b] Ethylketocyclazocine. [c] Percent specific displacement of either ^{3}H-Nal or ^{3}H-EKC run in triplicate at the concentration indicated. The triplicate values generally differed by less than 10%. [d] Derived from six different concentrations each run in triplicate. The correlation coefficient for calculating the K_i values were >0.9. [e] The K_i value for [^{3}H]-D-Ala^2-D-Leu^3-enkephalin (δ receptor) displacement for **3** is 4.4 nM (see ref 17 for method description).

Table 2. Opioid Antagonist Effects of the 4-Phenylpiperidine Antagonists in the Isolated Guinea Pig Ileum and Mouse vas Deferens[21]

	opioid antagonist activity (pA_2)[a]		
	GPI[b]		MVD[c]
compound	DAMGO[d] (μ)	U69593 (κ)	DPDPE[e] (δ)
3	9.7 ± 0.11	7.8 ± 0.05	8.7 ± 0.09
naloxone	8.5 ± 0.10	7.7 ± 0.11	7.3 ± 0.10

[a] Negative log of the equilibrium dissociation constant ± standard error of the mean (K_e), K_e = [antagonist]/(dose ratio − 1) (see ref 21 for methods description). [b] Guinea pig ileum. [c] Mouse vas deferens. [d] Tyr-D-Ala-Gly-MePhe-NH(CH$_2$)$_2$OH. [e] D-Pen^2-D-Pen^5-enkephalin.

Pharmacology

Affinities for opioid receptors were determined using radioligand binding assays by previously described methods.[16,17] For compound **3**, opioid receptor affinities were also determined in the isolated guinea pig ileum and mouse vas deferens by measuring its ability to block the effects of receptor-selective agonists.[21]

μ receptor-mediated opioid antagonist activity within the central nervous system was determined using the mouse abdominal stretching assay. The ability of the test compound to reverse a fully efficacious dose of morphine (1.25 mg/kg sc) was measured. These methods have been described previously.[16]

Peripheral μ antagonist activity was assessed in morphine-dependent mice by measuring the precipitation of diarrhea. This assay was developed specifically for this research project, and details are provided in the Experimental Section.

Results and Discussion

In radioligand binding assays (Table 1), **3** has high affinity for the μ receptor and lower affinity for κ and δ receptors. It has good selectivity for μ versus κ receptors. Opioid receptor antagonist potencies were obtained using the guinea pig ileum (μ and κ) and mouse vas deferens (δ), Table 2. In the guinea pig ileum, **3** also has high affinity for μ receptors and markedly lower affinity for κ receptors. Its affinity for δ receptors is

Table 3. Peripherally and Centrally Mediated μ Opioid Antagonist Effects of the 4-Phenylpiperidine Antagonists

compound	precipitation of diarrhea in morphine-dependent mice ED_{50} (mg/kg ± sem)[a] (sc)	(po)	antagonism of morphine analgesia AD_{50} (mg/kg ± sem)[b] (sc)
7	0.028 ± 0.001	–	note[c]
15	0.028 ± 0.006	2.0 ± 1.10	>40
10	0.150 ± 0.000	1.1 ± 0.2	>40
11	0.044 ± 0.009	1.3 ± 0.1	11.6 ± 1.3
12	0.50 ± 0.035	>10	29.6 ± 1.9
13	0.020 ± 0.010	1.7 ± 0.4	16.8 ± 0.4
14	0.37 ± 0.035	>10	>40
3	0.040 ± 0.029[d]	0.84 ± 0.28	9.0 ± 1.3[d]
naloxone	0.050 ± 0.004	1.5 ± 0.1	0.08 ± 0.01
naloxone methiodide	0.31 ± 0.000	–	1.5 ± 0.2

[a] Dose (± standard error of the mean) calculated to produce diarrhea in 50% of the mice treated. [b] Dose calculated for 50% reduction in the analgesic response to morphine (1.25 mg/kg sc) in the abdominal stretching assay. [c] Flat dose response, significant antagonist activities were observed at 1.25 mg/kg but reduction was only 50% at 40 mg/kg. [d] Following iv administration.

less than that for μ receptors and greater than that for κ receptors. Importantly, these values compare favorably with those obtained in ligand binding assays. No opioid agonist activity was detected for **3** in the isolated tissue assays, indicating it to be a pure opioid antagonist.

As shown in Table 1, esterification of **3** to the isobutyrate **11** slightly decreases affinity for the μ receptor. Comparison of the isobutyrates **11-14** show that opioid receptor affinity is maximized with the 3*R*,4*R*,2′*S* isomer. This is in accord with previous findings of the phenylpiperidine portion of **1**, where opioid receptor affinities were highest for the 3*R*,4*R* isomer. *In vivo* (Table 3), **3** is a potent antagonist of peripheral μ receptors. Only at relatively high doses it is able to antagonize centrally mediated morphine-induced analgesia. Following intravenous administration it is approximately 200-fold more potent (following iv administration) at blocking peripheral μ receptors than central μ receptors. Thus, it takes very high serum concentrations for **3** to cross the blood–brain barrier. This degree of selectivity is striking when compared to that achieved with naloxone methiodide in these assays. Table 3 also provides the *in vivo* μ antagonist potencies of the isobutyrates **11-14**. In general the activities in morphine-dependent mice *in vivo* parallel their relative affinities for the μ receptor. As shown in Table 3, **3** has good activity following oral administration.

In summary, SAR studies with the 4-phenylpiperidine opioid antagonists have led to the discovery of **3**. Compound **3** is a potent μ receptor antagonist which, following *in vivo* administration, distributes selectivity to peripheral μ receptors. Compound **3** differs from previously characterized peripherally selective opioid antagonists by its potency and degree of peripheral receptor selectivity. Furthermore, in contrast to the quaternary opioid antagonists, metabolism is unlikely to convert **3** to a potent opioid antagonist which readily crosses the blood–brain barrier. Thus, **3** is an important new pharmacological probe to characterize peripheral vs central opioid (particularly μ receptor) mediated effects. Compound **3** also has high activity following oral administration. With these properties, **3** can be used to investigate the involvement of endogenous opioids in GI motility disorders. These studies have also further characterized the SAR of the *N*-substituted-*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine antagonists. As found previously, all newly synthesized *N*-substituted derivatives were without opioid agonist activities and thus further confirm the pure opioid antagonist nature of this phenylpiperidine nucleus.

Experimental Section

Melting points were determined for all solids on a Thomas-Hoover apparatus and are unconnected. NMR spectra were recorded on either a Brucker WM-270 or GE QE-300 spectrometer and were consistent with assigned structures. Mass spectra and microanalyses were determiend by the Physical Chemistry Department of the Lilly Research Laboratories. Mass spectra were consistent with assigned structures for all compounds. All compounds were elementally analyzed within 0.4% of theoretical value unless otherwise indicated. Column chromatography was performed by gravitational flow with use of Allied Fisher silica (70–150 mesh).

4-(3-Hydroxyphenyl)-3(*R*),4(*R*)-dimethyl-2′(*SR*)-(phenylmethyl)-1-piperidinepropanoic Acid (8). A solution of **5** (4.4 g, 0.022 mol), 3-phenyl-2-(ethoxycarbonyl)-1-propene[22] (4.5 g, 0.024 mol), and 225 mL of methanol was stirred at room temperature under nitrogen for 10 days. The reaction mixture was evaporated to dryness to give 8.8 g of a viscous oil. This material was passed through a Prep-500 liquid chromatography system eluting with a gradient of hexane to 10% ethyl acetate/hexane to yield **8** ethyl ester, 8.0 g, as a white foam.

Without further purification **8** ethyl ester (6.0 g, 0.015 mol) and lithium hydroxide (1.9 g) were combined in a mixture of THF/methanol/water (192 mL/64 mL/64 mL) and stirred at room temperature for 3 h. The mixture was poured into 1 N HCl. The pH of the aqueus solution was adjusted to 9.8 with triethylamine and extracted with 1-butanol/toluene (3:1). The organic layer was dried over $MgSO_4$ and evaporated to give 7.14 g of a white foam. This material was purified by column chromatography over silca gel, eluting with a gradient of ethyl acetate/methanol (9:1) to ethyl acetate/methanol (1:1), yielding **8** as a white powder. This was triturated in ethyl acetate: mp 146.5–149 °C. Anal. ($C_{23}H_{29}NO_3$) C, H, N.

4-(3-Hydroxyphenyl)-3(*SR*),4(*SR*)-dimethyl-2′(*SR* and *RS*)-(phenylmethyl)-1-piperidinepropanoic Acid (7). Prepared from **4** as described for **8**, only the ethyl ester was hydrolyzed in dioxane and 6 N HCl (2:1), refluxing for 2 h. Following silica gel column chromatography the residue was triturated in ethyl ether to give **7** as the monohydrate: mp 120–131 °C. Anal. ($C_{23}H_{31}NO_4$) C, H, N.

4-(3-Hydroxyphenyl)-3(*S*),4(*S*)-dimethyl-2′(*SR*)-(phenylmethyl)-1-piperidinepropanoic Acid (9). Prepared as described for **7**. The free-base mixture was triturated in ethyl acetate: mp 142–145 °C. Anal. ($C_{23}H_{29}NO_3$) C, H, N.

(+)-[[2′(*S*)-[[4(*R*)-(3-Hydroxyphenyl)-3(*R*),4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic Acid 2-Methylpropyl Ester (11) and (+)-[[2′(*R*)-[[4(*R*)-(3-Hydroxyphenyl)-3(*R*),4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic Acid 2-Methylpropyl Ester (12). Compound **8** (2.45 g, 0.0067 mol), *sec*-butyl 2-aminoacetate *p*-tosylate (1.82 g, 0.0060 mol), triethylamine (0.60 g), 1-hydroxybenzotriazole hydrate (0.81 g), and 1,3-dicyclohexylcarbodiimide (1.23 g) were combined in dry DMF (180 mL) and stirred at room temperature under nitrogen for 72 h. The mixture was filtered and the filtrate evaporated to dryness. The residue was partitioned between ethyl acetate and water, and the pH of the aqueous layer was adjusted to 9.8 with 1 N NaOH. The organic layer was dried over K_2CO_3 and evaporated to give 3.21 g of material. This was further purified by silica gel column chromatography, eluting with a gradient of hexane/ethyl acetate (9:1) to ethyl acetate providing 2.31 g of a mixture of **11** and **12**. These compounds were separated with a Prep-500 liquid chromatography system, eluting with a gradient of hexane/triethylamine (99:1) to hexane/ethyl acetate/triethylamine (75:24:1). Compound **11** separated as a first peak: $[\alpha]^{25}_{365} = +172.7°$ (c = 1.0, MeOH).

Anal. ($C_{29}H_{40}N_2O_4$) C, H, N. This was converted to its HCl salt: mp 91–95 °C. Compound **12** separated as the second peak and was recrystallized from isopropyl ether: mp 136–136.5 °C; $[\alpha]^{25}_{365}$ = +153.0° (*c* = 0.76, MeOH). Anal. ($C_{29}H_{40}N_2O_4$) C, H, N.

(−)-[[2′(*S*)-[[4(S)-(3-Hydroxyphenyl)-3(*S*),4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic Acid 2-Methylpropyl Ester (13) and (−)-[[2′(*R*)-[[4(*S*)-(3-Hydroxyphenyl)-3(*S*),4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic Acid 2-Methylpropyl Ester (14). Compound **14** was characterized as the free base amorphous solid: $[\alpha]^{25}_{365}$ = −172.1° (*c* = 1.0, MeOH). Anal. ($C_{29}H_{40}N_2O_4$) C, H, N. Compound **13** was recrystallized from isopropyl ether: mp 130–133 °C; $[\alpha]^{25}_{365}$ = −154.0° (*c* = 0.75, MeOH). Anal. ($C_{29}H_{40}N_2O_4$) C, H, N.

[[2′(*SR* and *RS*)-[[4(*SR*)-(3-Hydroxyphenyl)-3(*SR*),4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]-amino]acetic Acid 2-Methylpropyl Ester (10). The mixture **10** was characterized as a HCl salt: mp 97–102 °C. Anal. ($C_{29}H_{41}ClN_2O_4$) C, H, N.

(+)-[[2′(*S*)-[[4(*R*)-(3-Hydroxyphenyl)-3(*R*),4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic Acid (3, LY246736). Compound **11** (0.30 g, 0.00058 mol), dioxane (15 mL), and 6 N HCl (15 mL) were combined and refluxed for 6 h. After cooling to room temperature the mixture was evaporated to dryness and the resulting solid was partitioned between water and butanol/toluene (3:1). The water layer was adjusted to a pH of 9.8 using triethylamine. The layers were separated, and the organic layer was dried over $MgSO_4$ and evaporated to dryness. The residue was purified using silica gel column chromatography, eluting with a gradient of ethyl acetate/methanol (9:1) to methanol providing 0.13 g of **3** as the monohydrate: mp 135–138 °C; $[\alpha]^{25}_{365}$ = +51.8° (*c* = 1.0, DMSO). Anal. ($C_{25}H_{34}N_2O_5$) C, H, N.

[[2′(*SR* and *RS*)-[[4(*SR*)-(3-Hydroxyphenyl)-3(*SR*),4-dimethyl-1-piperidinyl]methyl]-1-oxo-3-phenylpropyl]-amino]acetic Acid (15). The mixture **15** was characterized as the free base monohydrate: mp 161–165 °C. Anal. ($C_{25}H_{34}N_2O_5$) C, H, N.

Measurement of Peripheral Opioid Antagonist Activity: Precipitation of Diarrhea in Morphine-Dependent Mice. A colony of approximately 50 CF-1 male mice (Charles River, Portage, MI) were maintained with access to a morphine (1 mg/mL) in 0.01 M Na saccharin water solution as their sole source of fluid. In these experiments, the mice were maintained for a minimum of 10 days on the morphine solution, and the average consumption had to be 3 g of solution per mouse per day for 3 days consecutively before the animals were used for testing purposes. Under such conditions, mice become physically dependent on morphine. To test for the peripheral opioid antagonist activity, five morphine-dependent mice were removed from access to the morphine solution for 45 min, injected with test compound, and placed in cylindrical observation chambers. At a half hour after injection, the mice were scored for the presence or absence of diarrhea. In general, testing began with a fairly high dose, and then lower doses were tested until no diarrhea occurred. After testing, the mice were returned to their colony cages with access to the morphine solution. They could be retested after 3 days on the morphine solution. The data was calculated as the "percent of mice at each dose with diarrhea", and at least five mice were tested at each dose of compound. The ED_{50} was defined as the dose of antagonist that precipitated diarrhea in 50% of the mice tested. The ED_{50}'s and standard error of the means were calculated using a method developed at Eli Lilly which uses nonlinear curve fitting with JMP software.

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