Synthesis and Preliminary In vitro Investigation of Bivalent Ligands Containing Homo- and Heterodimeric Pharmacophores at μ, δ, and κ Opioid Receptors

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A series of homo- and heterodimeric ligands containing κ agonist and μ agonist/antagonist pharmacophores joined by a linker chain of varying lengths was synthesized and evaluated in vitro by their binding affinity at μ, δ, and κ opioid receptors. The functional activities of these compounds were measured in the [^{35}S]-GTPγS binding assay. The data suggest that the stereochemistry of the pharmacophores, the N-substituents of the pharmacophore, ester linkages, and the spacer length were crucial factors for optimum interactions of such ligands at opioid receptor binding sites. These novel ligands as well as their pharmacological properties will serve as the basis for our continuing investigation of such bivalent ligands as probes of the opioid receptor oligomerization phenomena and for in vivo studies as analgesics.

Introduction

Previous reports from our laboratories indicated that morphinans connected by linking spacers of varying lengths containing identical morphinan pharmacophores such as cyclorphan (**1c**) or butorphan (**1b**) were sensitive to the site of attachment on the morphinan and the length of the linking chain.[1] It was observed that the affinity of these ligands was sensitive to the character and length of the spacer. We have previously reported that a compound linked by a 4-carbon chain ester (**17**), a conformationally constrained fumaryl ester (**19**), and a compound with a 10-carbon chain ester (**18**) were the most potent ligands in this series.[1] The fumaryl ester **19** was further characterized and was shown to be a κ opioid receptor agonist and a μ opioid receptor agonist/antagonist when evaluated in vivo.[2] The structures and affinities are shown in Table 1. Ligands having two pharmacophores connected by a spacer can be termed bivalent ligands and have the potential for binding vicinal receptors.[3,4] Such bridging should be manifested by a substantial increase in potency due to the high concentration of the pharmacophore in the vicinity of the recognition site when the ligand is bound in a monovalent mode.

Portoghese et al.[5] has reported a range of homo- and heterodimeric ligands with varying linker lengths designed to investigate pharmacodynamic and organizational features of opioid receptors. For example, recently reported heterodimeric ligands containing δ antagonist (naltrindole) and κ_1 agonist (ICI-199,441) pharmacophores joined by variable length oligoglycyl-based linkers were demonstrated to possess significantly greater potency and selectivity compared to their monomer congeners, providing further evidence for the opioid receptor hetero-oligomerization phenomena.[6] It is of interest to note that most of the cleavable ligands reported in the literature contain ester linkers, which are designed to be cleaved by plasma esterase to release individual pharmacophores which then can presumably act independently on the specific opioid receptor.

To further investigate such opioid bivalent ligands containing pharmacophores that have established κ/μ affinity, we prepared a series of compounds containing varying length spacers linked by either ester or amide moieties. The monovalent ligands **8** and **12** (Scheme 2 and Table 1) were also synthesized and their μ, δ and κ affinities established for comparison with their bivalent counterparts.

Chemistry

The dextrorotatory morphinans (**2b**,**c**) were prepared from commercially available (+)-3-hydroxy-*N*-methylmorphinan tartrate (dextrorphan) **2a**, which was converted to the free base and N-demethylated[7−9] to yield the normorphinan, followed by alkylation with cyclobutylmethyl (or cyclopropylmethyl) bromide and characterization as their dextrorotatory crystalline mandelate salts (**2b** and **2c**), respectively. The (+),(+)-homodimeric ligand **3** was prepared from **2b** with sebacoyl chloride in the presence of triethylamine. The homodimeric ligands **4**, **5**, and **6** containing only the levorotatory pharmacophores **1d**, **1e** and **1b** were similarly prepared. The homodiester **6** was prepared by condensing **1b** with muconyl chloride, which was made from muconic acid with thionyl chloride (Scheme 1).[10a−c]

The heterodimeric ligand **9** containing (−)-**1b** and the (+)-**2b** pharmacophores was prepared from sebacoyl monobenzyl ester[11] to yield the intermediate **7**, which, after catalytic hydrogenolysis, gave the corresponding acid **8**.[12] Treatment of **8** with the corresponding (+)-isomer (**2b**) in the presence of DCC and DMAP[13] yielded the heterodimeric ligand **9** (Scheme 2).

Similarly prepared were the heterodimeric ligands (**10** and **11**) by condensing the acid **8** with either cyclorphan (**1c**) or morphine (**1g**). The ligand **12** was synthesized to evaluate the effect of the spacer moiety on the binding affinity of these compounds. Compound **13** with an ester linkage at one end of the linking chain and an amide linkage at the other end was obtained by coupling acid **8** with the 3-aminomorphinan **1f**, which was prepared from levorphanol (**1a**) by a previously described procedure.[14] The homodiamides **14**, **15**, and **16** were prepared from 3-aminomorphinan (**1f**) in the presence of succinyl chloride, sebacoyl chloride, or fumaryl chloride in the presence of triethylamine respectively (Scheme 3).

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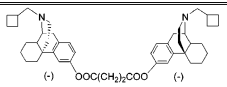
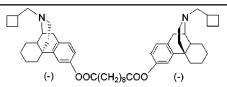
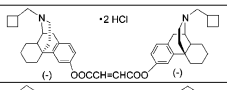
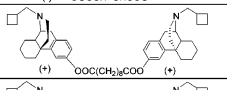
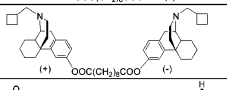
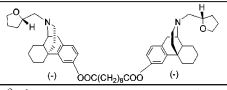
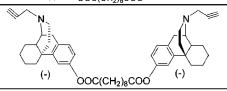
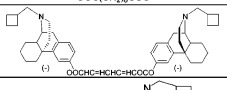
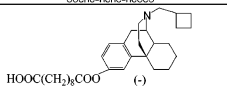
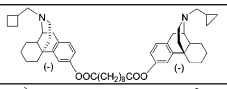
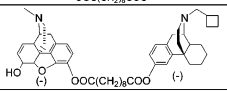
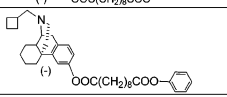
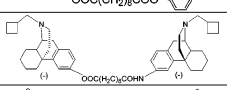
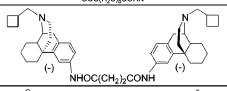
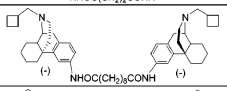
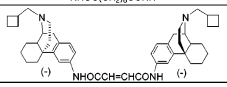
Table 1. K_i Values for the Inhibition of μ, δ, and κ Opioid Binding to CHO Membranes by Mono- and Bivalent Ligands

		Ki(nM) ±SE			Selectivity	
Compound	**Structures/sterochemistry**	**[^{3}H]DAMGO (μ)**	**[^{3}H]Naltrindole (δ)**	**[^{3}H]U69,593 (κ)**	**κ/μ**	**κ/δ**
1a (levorphanol)	**(-)**	**0.21±0.017**	**4.2±0.45**	**2.3±0.26**	**0.09**	**2**
1b (butorphan[a])	**(-)**	**0.23 ± 0.01**	**5.9 ± 0.55**	**0.079 ± 0.003**	**2**	**18**
1c (cyclorphan[a])	**(-)**	**0.062±0.003**	**1.9±0.1**	**0.034±0.002**	**2**	**4**
1d[d]	**(-)**	**0.01±0.002**	**0.27±0.02**	**0.15±0.01**	**0.06**	**1.8**
1e (MCL-117[b])	**(-)**	**0.003±0.001**	**0.62±0.19**	**0.0030±0.0005**	**1**	**210**
1f (MCL-182)	**(-)**	**3.7 ± 0.26**	**180 ± 85**	**1.8 ± 0.06**	**2**	**100**
1g (Morphine)	**(-)**	**0.88±0.14**	**140±18**	**24±2**	**0.04**	**5.8**
2c (MCL-190)	**(+)**	**1100± 69**	**13± 2.2**	**480± 13**	**2**	**0.03**
2b (MCL-191)	**(+)**	**60 ± 4**	**> 10μM**	**55 ±2.9**	**1**	**-**
17(MCL-139)[c]		**0.16 ± 0.01**	**9.4 ± 0.4**	**0.076 ± 0.002**	**2**	**120**
18(MCL-144)[c]		**0.090 ± 0.004**	**4.2 ± 0.4**	**0.049 ± 0.001**	**2**	**90**
19(MCL-145)[c]		**0.20±0.03**	**9.4±0.5**	**0.08±0.01**	**3**	**120**
3 (MCL-192)		**130 ± 7.9**	**700 ± 54**	**130 ± 10**	**1**	**5**
9 (MCL-193)		**2.2 ± 0.1**	**23 ± 1.2**	**1.2 ± 0.32**	**2**	**19**
4 (MCL-406)		**0.67 ± 0.01**	**8.3 ± 0.74**	**1.2 ± 0.04**	**0.6**	**7**
5 (MCL-407)		**14 ± 1.3**	**190 ± 18**	**10 ± 0.5**	**1.4**	**19**
6 (MCL-415)		**2.8 ± 0.2**	**28 ±0.6**	**0.62 ± 0.04**	**4.5**	**45**
8 (MCL-416)		**0.71 ± 0.02**	**18 ± 0.6**	**0.29 ± 0.02**	**2.4**	**62**
10 (MCL-195)		**0.34 ± 0.04**	**4.4 ± 0.08**	**0.23 ± 0.03**	**1.5**	**19**
11 (MCL-196)		**0.22 ± 0.03**	**3.9 ± 0.2**	**0.11 ± 0.01**	**2**	**35**
12 (MCL-197)		**0.44 ± 0.02**	**11 ± 1.4**	**0.30 ± 0.03**	**1.5**	**25**
13 (MCL-414)		**0.65 ± 0.06**	**12 ± 1.3**	**0.38 ± 0.01**	**1.7**	**31.6**
14 (MCL-198)		**3.3 ± 0.3**	**-**	**3.8 ± 0.4**	**0.9**	**-**
15 (MCL-194)		**5.7±0.1**	**38±3.7**	**7.5±1.0**	**0.8**	**5**
16 (MCL-199)		**13 ± 0.4**	**160 ± 8.3**	**7.3 ± 0.1**	**1.8**	**21.9**

[a] Reference 8. [b] Reference 9. [c] Reference 1. [d] Reference 14.

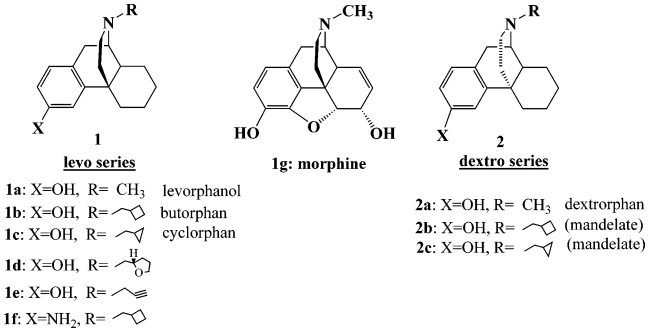
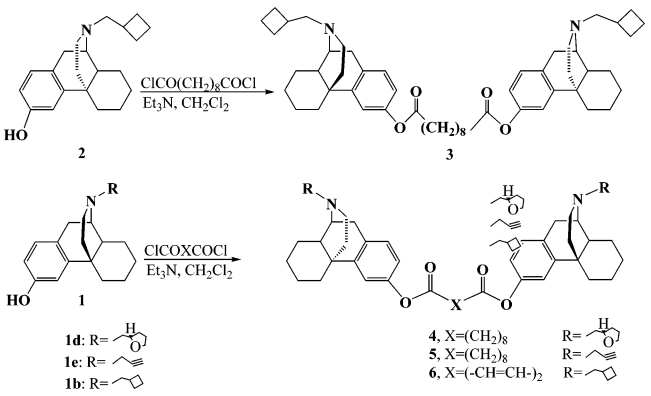


Figure 1. Morphinan monomer pharmacophores.

Scheme 1



Pharmacological Results and Discussion

Affinity and Selectivity of the Synthesized Ligands. The dimeric and bivalent ligands that were investigated contain levo pharmacophores (see Figure 1) that confer good agonist activities or their less active dextro enantiomers (**2b** and **2c**). The spacer length for these compounds was dictated by the peak potency that was observed when a sebacoyl ester (10 carbon) unit was incorporated into the molecule. All the novel dimeric morphinan ligands were evaluated for their affinity at and selectivity for μ, δ, and κ opioid receptors with Chinese hamster ovary (CHO) cell membranes stably expressing the human opioid receptors. The data are summarized in Table 1. For comparison purposes, opioid binding affinity data for **1a**−**f** and the enantiomers of **1b** and **1c** (i.e., **2b** and **2c**) are included in Table 1.

Initially, the monovalent ligands were synthesized as controls in order to evaluate the contribution of the spacer itself to binding. The structures of compound **12** and **8** are similar, both contain **1b** (butorphan) as a pharmacophore with a C-10 ester linking chain. They both have lower affinity than **1b**. Since the interaction between the 3-phenolic hydroxyl group and opioid receptor proteins was historically recognized as crucial for high affinity, it is reasonable that these ligands with a 3-position ester spacer possess lower affinity than butorphan.

In our earlier report,[1] a bivalent ligand containing two identical (−)-morphinan pharmacophores with a 10-carbon spacer (**18**) was the most potent ligand in the series, displaying excellent affinities at μ and κ receptors. However, since it is not known whether such enhancements reflected bridging of opioid recognition sites on a receptor dimer, binding to an accessory site, or results from the hydrolysis of the dimer, we have attempted to distinguish between these possibilities by the synthesis and evaluation of the affinities of dimers with other pharmacophores.

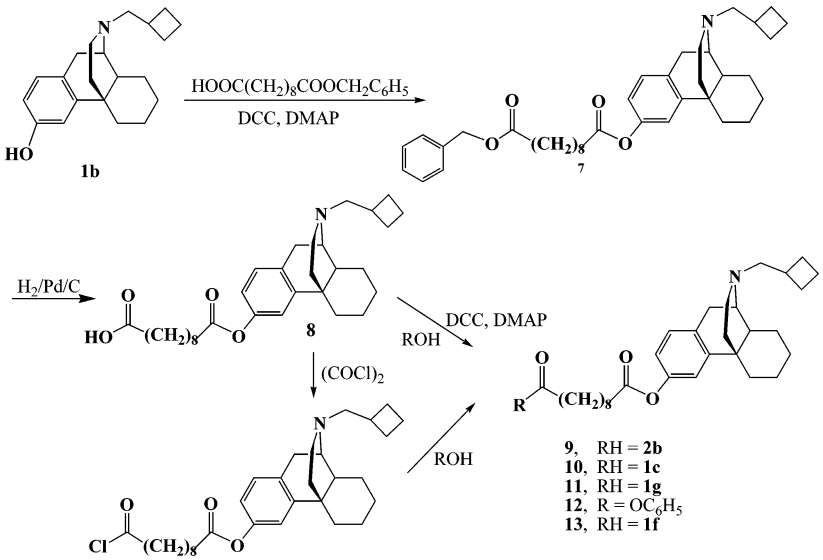
Assuming that such dimeric ligands bridge vicinal opioid receptors, replacement of one of the (−)-morphinan pharmacophores with its (+)-enantiomer as in **9** should lead to a potency decrease due to the lower affinity of the (+)-enantiomer at the neighboring opioid receptor. The affinity of the (+)-enantiomer **2b** is around 700 times lower than that of the corresponding (−)-isomer (butorphan, **1b**) at the κ receptor and around 260 times lower at the μ receptor. Thus, if the (+)-enantiomer interacts nonspecifically with the vicinal opioid site or other membrane sites, the affinity of the (+),(−)-ligand **9** should be lower than that of the homoligand containing only levo pharmacophores but more than that of the monovalent ligands (**8** or **12**). The (+),(−)-ligand **9** contained the same spacer length as the (−),(−)-bivalent ligand **18** that afforded peak activity at the κ receptor. It was observed that the heteroisomer possess 108-fold greater affinity as the (+),(+)-ligand **3**, but 24 times less than that of the (−),(−)-ligand **18** (Table 1). The finding that the (+),(−)-ligand **9** possesses lower affinity at the κ receptor than the monomers **8** and **12** is possibly due to the occupation of a neighboring site by (+)-morphinan, which precludes access by another pharmacophore. Similarly, because the (−),(−)-ligand **18** exhibits a potency that is greater than that derived from the sum of its two monovalent pharmacophors, it can be considered a bivalent ligand that could bridge two opioid receptors.

At this point, we still could not establish if the second pharmacophore itself or a specific moiety in the second pharmacophore is responsible for the affinity. We thus continued our investigation by synthesizing the butorphan-derived ligands containing other pharmacophores. Initially, amide linkages were introduced, as in **13**, with an ester linkage at one end and an amide at the other, and ligand **15**, with amide linkage at both ends. Both ligands (**13** and **15**) were found to have lower affinities than the diester of butorphan **18** (by 7.7- and 153-fold, respectively, for κ). It can thus be assumed that an ester linkage is important for affinity. Heterodimeric compounds such as **10** (**1b** combined with cyclorphan) and **11** (**1b** combined with morphine) with a C-10 linking ester chain have similar high affinitities (K_i = 0.23−0.11 nM for κ and 0.34−0.22 nM for μ receptor) to the monovalent ligand (**8** or **12**) but have lower affinity than the (−),(−)-ligand **18**. Compared to the (−),(−)-ligand **18**, compounds **4** [with *N*-[(*S*)-tetrahydrofurfuryl]morphinan as a pharmacophore] and **5** (with *N*-propargylmorphinan as a pharmacophore), differing only in their N-substituents on the morphinan moiety, decrease the affinity by 24- and 204-fold at the κ receptor. If hydrolysis of such esters in compound **18** had occurred, compound **4**, **5**, and **10** would have higher affinity at μ and κ receptors than **18** because their monomeric forms are more potent than butorphan (**1b**). We thus concluded that the affinities of the (−),(−)-ligand **18** was not due to the hydrolysis of the ester moieties resulting in two monomeric ligands producing butorphan (**1b**) but rather can be ascribed to the interaction of the dimeric ligand **18** to a ligand that could bridge two opioid receptor sites.

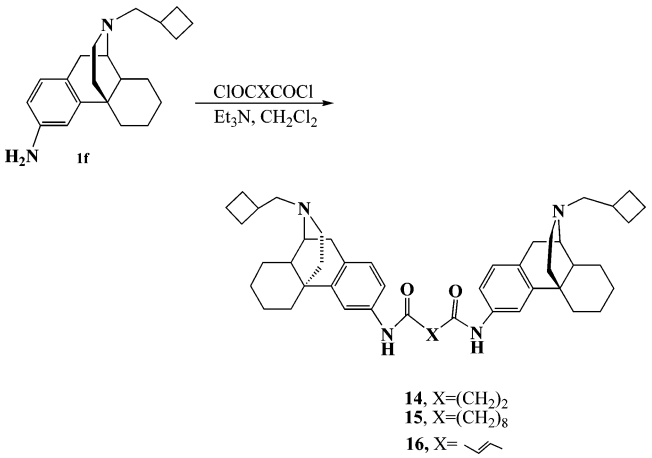
When comparisons are made with the (−),(−)-ligand **18** (**1b** with a 10-carbon chain linker), it is the second pharmacophore itself, not a specific substituent in the second pharmacophore, that is responsible for the κ affinity. Other structural modifications, such as an amide linkage (i.e., **13** and **15**), (+)-enantiomer (**9**), morphine (**11**), and N-substituent other than cyclobutyl methyl (**10**, **4**, **5**), all reduce the κ affinity.

The dimeric diamides **14** and **16** were made to be compared with the conformationally constrained fumaryl ester **19**,[1,2] which is among the most potent ligands synthesized, displaying excellent affinities at μ and κ receptors. When two amide linkages were introduced with a fumaryl linkage as in **16**, the

Scheme 2



Scheme 3



affinity decreased by 100-fold. Similarly, compound **14** with a succinyl amide linkage decreased the affinity by 50-fold compared to the compound with the succinyl ester linking butorphan **17**. It is obvious that ester linkages are preferred to amide linkages, as in **13** and **15**. Compound **6** with the conformationally constrained muconyl spacer was synthesized and its affinity decreased by 7.9-fold at κ and 14-fold at μ. Spacer length is thus a critical factor with respect to the ability of the bivalent ligands to bridge neighboring receptors. A spacer of insufficient length would not permit bridging, and an excessively long spacer would tend to reduce bridging by increasing the confinement volume of the free pharmacophore so that it would spend less time in the vicinity of the unoccupied, neighboring recognition site.

Efficacy Assay of Selected Ligands. To characterize the relative efficacy of these morphinan ligands, compounds **4**, **6**, and **8**−**13**, together with cyclorphan (**1c**) and butorphan (**1b**), were selected for the [^{35}S]GTPγS assay. Table 2 shows the agonist and antagonist properties of these ligands in stimulating [^{35}S]GTPγS binding mediated by the κ opioid receptor. Ligands **4**, **10**, **11**, and **12** produced high maximal stimulation of [^{35}S]-GTPγS binding (E_{max}) comparable to that of selective agonist U50,488, while ligands **6**, **8**, and **9** produced similar maximal stimulation comparable to that of the monomers cylorphan (**1c**) and butorphan (**1b**) but less than that of selective agonist U50,-488. The EC_{50} values of these ligands are similar, which is

Table 2. Agonist and Antagonist Properties of Compounds in Stimulating [^{35}S]GTPγS Binding Mediated by the κ Opioid Receptor[a]

compound	pharmacological properties	E_{max} (%)	EC_{50} (nM)	I_{max} (%)
(-)-U50,488	agonist	110 ± 2.0	46 ± 16	−
1c (cyclorphan)	agonist	90 ± 10	0.19 ± 0.04	−
1b (butorphan)	agonist	80 ± 6.8	1.3 ± 0.4	−
4	agonist	140 ± 4.1	8.8 ± 2.1	no effect
6	agonist	91 ± 8.5	17 ± 7.6	no effect
8	agonist	75 ± 1.1	2.8 ± 0.4	no effect
9	agonist	77 ± 2.4	7.9 ± 0.3	no effect
10	agonist	110 ± 13	2.5 ± 0.5	no effect
11	agonist	150 ± 3.3	2.3 ± 0.3	no effect
12	agonist	170 ± 5.9	3.8 ± 0.2	no effect
13	partial agonist	55 ± 5.0	8.8 ± 2.6	65 ± 5.5 (at 10 μM)

[a] Membranes from CHO cells that stably expressed only the κ opioid receptor were incubated with varying concentrations of the compounds. The stimulation of [^{35}S]GTPγS binding was measured as described in the Experimental Section. To determine the antagonist properties of a compound, membranes were incubated with 100 nM of the κ agonist U50,488 in the presence of varying concentrations of the compound. The E_{max} value is the maximal percent stimulation obtained with the compound. The EC_{50} value is the concentration of compound needed to produce 50% of the E_{max} value. The I_{max} value is the maximal percent inhibition obtained with the compound. The IC_{50} value is the concentration of compound needed to produce half-maximal inhibition. Dashed lines indicate that the compound was not tested for antagonist properties because of its high E_{max} value.

substantially correlated with the K_i values obtained for the compounds in the binding assays with [^{3}H]U69,593, except ligand **6** had a somewhat higher EC_{50} value. Similar to the parent compound butorphan (**1b**), most of these ligands except compound **13** did not inhibit U50,488-stimulated [^{35}S]GTPγS, which suggested that most of these ligands were fully selective κ agonists. Ligand **13** produced modest maximal stimulation of [^{35}S]GTPγS binding and also had a sound maximal inhibition (I_{max}) of the U50,488-stimulated [^{35}S]GTPγS binding. These data indicated that ligand **13** was a partial κ agonist.The agonist and antagonist properties of these ligands in stimulating [^{35}S]-GTPγS binding mediated by the μ opioid receptor are shown in Table 3. Ligands **6**, **8**, **11**, and **12** produced high maximal stimulation of [^{35}S]GTPγS binding mediated by the μ receptor comparable to that of the full opioid agonist DAMGO. Ligands **4**, **10**, and **13** not only produced modest maximal stimulation of [^{35}S]GTPγS binding (E_{max}) but also produced sound maximal inhibition (I_{max}) of the DAMGO-stimulated [^{35}S]GTPγS binding. These data indicated that ligands **4**, **10**, and **13** were μ agonists

Table 3. Agonist and Antagonist Properties of Compounds in Stimulating [^{35}S]GTPγS Binding Mediated by the μ Opioid Receptor[a]

compound	pharmacological properties	E_{max} (%)	EC_{50} (nM)	I_{max} (%)	IC_{50} (nM)
DAMGO	agonist	120 ± 12	110 ± 9.0	–	–
1c (cyclorphan)	partial agonist	40 ± 2.9	0.80 ± 0.06	50 ± 1	1.7 ± 0.4
1b (butorphan)	partial agonist	50 ± 2.5	1.6 ± 0.2	50 ± 3	20 ± 3
4	agonist/antagonist	69 ± 3	12 ± 1	48 ± 4	360 ± 86
6	agonist	96 ± 13	19 ± 2	no effect	no effect
8	agonist	110 ± 8	3.0 ± 0.6	no effect	no effect
9	agonist/antagonist	28	NA	71 ± 2	460 ± 43
10	partial agonist	41 ± 2	2.9 ± 0.8	64 ± 2	96 ± 21
11	agonist	110 ± 11	2.5 ± 0.4	no effect	no effect
12	agonist	93 ± 9	5.1 ± 1.3	no effect	no effect
13	partial agonist	56 ± 6	4.4 ± 2.0	61 ± 1	150 ± 76

[a] Membranes from CHO cells that stably expressed only the μ opioid receptor were incubated with varying concentrations of the compounds. The stimulation of [^{35}S]GTPγS binding was measured as described in the Experimental Section. The E_{max} value is the maximal percent stimulation obtained with the compound. The EC_{50} value is the concentration of compound needed to produce 50% of the E_{max} value. When the E_{max} value was 30% or lower, it was not possible to calculate an EC_{50} value. To determine the antagonist properties of a compound, membranes were incubated with 200 nM of the μ agonist DAMGO in the presence of varying concentrations of the compound. The I_{max} value is the maximal percent inhibition obtained with the compound. The IC_{50} value is the concentration of compound needed to produce half-maximal inhibition. Dashed lines indicate that the compound was not tested.

and antagonists. Ligand **9** had lowest maximal stimulation of [^{35}S]GTPγS binding and highest maximal inhibition (I_{max}) of the DAMGO-stimulated [^{35}S]GTPγS binding, indicating that ligand **9** is a μ antagonist and weak agonist.

The preliminary assay for agonist and antagonist properties of these ligands in stimulating [^{35}S]GTPγS binding mediated by the κ opioid receptor illustrated that most of these ligands were κ agonists or partial agonists. But for the μ receptor, compounds **6**, **8**, **11**, and **12** were agonists, while compounds **4**, **9**, **10**, and **13** were μ agonist/antagonist or partial agonists.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary tube apparatus and are reported uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC300 spectrometer using tetramethylsilane as an internal reference. Element analyses, performed by Atlantic Microlabs, Atlanta, GA, were within 0.4% of theoretical values. Analytical thin-layer chromatography (TLC) was carried out on 0.2 mm Kieselgel 60F 254 silica gel plastic sheets (EM Science, Newark). Flash chromatography was used for the routine purification of reaction products. The column output was monitored by TLC.

(+)-3-Hydroxy-*N*-cyclopropylmethylmorphinan Mandelate (2c). (+)-3-Hydroxy-*N*-cyclobutylmethylmorphinan free base was made from commercially available dextrorphan (Sigma), which was converted to the *S*-(+)-mandelate salt and recrystallized from isopropyl ether/EtOH. The product is obtained as a white solid, mp 204−205 °C. Anal. ($C_{20}H_{27}NO\cdot C_8H_8O_3$) C, H, N

(+)-3-Hydroxy-*N*-cyclobutylmethylmorphinan mandelate (2b) was similarly prepared from dextrophan and converted to the (*S*)-(+)-mandelate salt to yield a light brown solid, mp 208−210 °C. Anal. ($C_{21}H_{29}NO\cdot C_8H_8O_3\cdot 0.2H_2O$) C, H, N

Sebacic Acid 10-((−)-*N*-cyclobutylmethylmorphinan-3-yl) ester sebacic acid (8). The monobenzyl ester of sebacic acid (1.7 mmol) was dissolved in anhydrous dichloromethane (25 mL) and cooled to 0 °C, and oxalyl chloride (500 μL) and 2 drops of DMF were added. The mixture was stirred at 0 °C to room temperature for 2 h and then evaporated to dryness, and the excess of oxalyl chloride was removed under high vacuum. The acid chloride was dissolved in dichloromethane (25 mL) and cooled to 0 °C, and butorphan **1b** (361 mg, 1.1 mmol) was added. Then triethylamine (0.74 mL) was added dropwise. The reaction mixture was stirred at 0 °C to room temperature overnight, saturated aqueous $NaHCO_3$ solution (30 mL) was added, and the reaction mixture was extracted with EtOAc (3 × 30 mL) and washed with brine. The EtOAc extract was evaporated to dryness under high vacuum. The residual oil was purified by flash chromatography (SiO_2, EtOAc:TEA, 100:5) to afford a colorless, oily compound (671.0 mg, 90.7%). The 3-(10-benzyl ester) sebacic acid ester *N*-(cyclobutylmethyl)morphinan **7** (621 mg) was dissolved in ethyl acetate (20 mL), and 10% Pd/C (550 mg) was added. The air in the reaction bottle was flushed with H_2 three times. The solution was then hydrogenated at room temperature overnight with Pd/C after which the catalyst was removed by filtration. The solvent was evaporated to yield 450 mg (85.6%) of a colorless oil, **8**. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.10 (d, J = 8.8 Hz, 1H), 6.92 (d, J = 1.6 Hz, 1H), 6.85 (dd, J = 8.4, 1.2 Hz, 1H), 3.47 (s, 1H), 3.01 (d, J = 18.4 Hz, 1H), 2.81 (s, 1H), 2.62−1.04 (m, 39H). ^{13}C NMR ($CDCl_3$, 75 MHz): 178.5, 172.3, 150.2, 139.8, 130.9, 128.9, 119.9, 118.6, 58.7, 56.2, 45.9, 40.6, 38.4, 36.5, 35.4, 35.2, 34.3, 31.1, 29.2, 29.2, 29.1, 29.0, 27.9, 27.7, 25.9, 25.6, 25.4, 24.8, 24.5, 21.6, 18.6. Anal. ($C_{31}H_{45}NO_4\cdot 0.5H_2O\cdot 1.5HCl$) C, H, N.

General Procedure for the Preparation of Ligands 9−13. Method A. The acid **8** (0.6 mmol) and an appropriate opioid (0.5 mmol) was dissolved in anhydrous dichloromethane (15 mL) under nitrogen. A catalytic amount of 4-(dimethylamino)pyridine was added, followed by N,N′-dicyclohexylcarbodiimide (0.6 mmol). The solution mixture was stirred at room temperature overnight, the solid was filtered off, and the crude product was purified by column chromatography on silica gel (EtOAc:Et_3N, 100:1) to afford the corresponding bivalent ligands.

Method B. The acid **8** (0.5 mmol) was dissolved in anhydrous dichloromethane (25 mL), cooled to 0°C, and oxalyl chloride (2 mmol) and 2 drops of DMF were added. The mixture was stirred at 0 °C to room temperature for 2 h and then evaporated to dryness, and excess of oxalyl chloride was removed under high vacuum. The acid chloride formed was dissolved in dichloromethane (25 mL) and cooled, to which the appropriate opioid (0.5 mmol) was added, followed by triethylamine (4 mmol). The reaction mixture was stirred at 0 °C−25 °C overnight. Then saturated aqueous $NaHCO_3$ solution (20 mL) was added, and the mixture was extracted with EtOAc (3 × 20 mL) and washed with brine. The extract was evaporated to dryness under high vacuum. The crude product was purified by column chromatography on silica gel (EtOAc:Et_3N, 100:1) to afford the corresponding bivalent ligands.

1-((−)-*N*-Cyclobutylmethylmorphinan-3-yl) 10-((+)-*N*-cyclobutylmethylmorphinan-3-yl) sebacoylate (9): light yellow oil (73.1%). ^{1}H NMR (300 MHz): 7.10 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 2.4 Hz, 2H), 6.85 (dd, J = 8.1, 2.1 Hz, 2H), 3.01 (d, J = 18.6 Hz, 2H), 2.82−2.79 (m, 2H), 2.62−1.23 (m, 62H). ^{13}C NMR (75 MHz):172.3, 149.2, 142.0, 135.2, 128.4, 118.4, 118.0, 61.4, 55.8, 45.6, 44.9, 41.7, 37.7, 36.5, 34.9, 34.3, 29.0, 28.9, 27.7, 27.7, 26.7, 26.5, 24.8, 24.3, 22.0, 18.8. Anal. ($C_{52}H_{72}N_2O_5\cdot 1.5H_2O$) C, H, N

1-((−)-*N*-Cyclopropylmethylmorphinan-3-yl) 10-(*N*-cyclobutylmethylmorphinan-3-yl) sebacoylate (10): light yellow oil (80.9%). ^{1}H NMR (300 MHz): 7.10 (d, J = 8.1 Hz, 2H), 6.93 (d, J = 2.1 Hz, 2H), 6.85 (dd, J = 8.1, 2.1 Hz, 2H), 3.102−3.017 (d, J = 18.6 Hz, 2H), 2.956−2.895 (d, J = 18.3 Hz, 2H), 2.82−1.00 (m, 60H). ^{13}C NMR (75 MHz): 172.4, 149.1,149.2, 142.0, 135.2,

135.2, 128.4, 118.4, 118.0, 61.5, 60.0, 55.8, 55.6, 46.2, 45.6, 45.6, 44.9, 41.7, 37.9, 37.7, 36.5, 34.9, 34.4, 32.7, 30.8, 29.0, 29.0, 27.8, 26.7, 26.5, 26.4, 24.8, 24.7, 24.3, 24.2, 22.1, 18.8, 11.5, 9.4, 4.03, 3.4. Anal. ($C_{51}H_{70}N_2O_4 \cdot 0.25Et_3N \cdot 0.25H_2O$) C, H, N.

1-((−)-*N*-Cyclobutylmethylmorphinan-3-yl) 10-(3,6-diol-7,8-didehydro-4,5-epoxy-17-methyl-(5α,6α)morphinan-3-yl) sebacoylate (11): light yellow oil (62.2%). ^{1}H NMR ($CDCl_3$, 300 MHz): 7.10 (d, J = 8.1 Hz, 1H), 6.92 (d, J = 2.4 Hz, 1H), 6.85 (dd, J = 8.1, 2.4 Hz, 1H), 6.74 (d, J = 8.1 Hz, 1H), 6.61 (d, J = 8.1 Hz, 1H), 5.77 (d, J = 9.9 Hz, 1H), 5.30 (dt, J = 9.9, 2.7 Hz, 1H), 4.93 (dd, J = 6.9, 0.9 Hz, 1H), 4.16−1.24 (m, 56H). ^{13}C NMR ($CDCl_3$, 75 MHz): 172.4, 171.5, 149.2, 148.7, 142.0, 135.2, 134.1, 132.7, 132.2, 131.8, 128.4, 127.7, 121.0, 119.9, 118.4, 118.1, 92.2, 65.7, 61.4, 58.8, 55.7, 46.3, 44.9, 43.0, 42.5, 41.7, 40.4, 37.7, 36.5, 35.2, 34.9, 34.4, 33.9, 29.0, 28.8, 27.8, 26.7, 26.5, 24.8, 24.3, 22.1, 20.6, 18.8. Anal. ($C_{48}H_{64}Cl_2N_2O_6 \cdot 0.5H_2O$) C, H, N.

1-Phenyl 10-((−)-*N*-cyclobutylmethylmorphinan-3-yl) sebacoylate (12): light yellow oil (72.2%); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.39 (s, 5H), 7.10 (d, J = 8.4 Hz, 1H), 6.92 (d, J = 1.6 Hz, 1H), 6.85 (dd, J = 8.0, 2.4 Hz, 1H), 5.12 (s, 2H), 3.01 (d, J = 18.4 Hz, 1H), 2.86 (s, 1H), 2.65−1.06 (m, 37H). ^{13}C NMR ($CDCl_3$, 100 MHz): 172.3, 172.2, 150.7, 149.2, 142.0, 135.1, 129.3, 128.4, 125.6, 121.5, 118.5, 118.1, 61.4, 55.8, 45.6, 44.8, 41.6, 37.7, 36.5, 34.8, 34.3, 34.3, 29.0, 29.0, 27.8, 26.7, 26.4, 24.8, 24.4. Anal. ($C_{37}H_{49}NO_4 \cdot 0.2H_2O$) C, H, N.

1-((−)-*N*-Cyclobutylmethylmorphinan-3-yl) 10-((−)-*N*-cyclobutylmethylmorphinan-3-yl) sebacoylate (13): light yellow oil (42.7%); ^{1}H NMR (300 MHz): 7.35−7.28 (m, 3H), 7.06 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 2.4 Hz, 1H), 6.81 (dd, J = 8.0, 2.0 Hz, 1H), 2.97 (dd, J = 18.8, 10.4 Hz, 2H), 2.77 (d, J = 2.8 Hz, 2H), 2.57−1.02 (m, 62H). ^{13}C NMR (75 MHz): 172.4, 171.2, 149.2, 142.0, 141.3, 136.2, 135.3, 133.9, 128.4, 128.0, 118.4, 118.0, 117.4, 116.6, 61.5, 60.3, 55.8, 55.7, 45.7, 45.6, 45.1, 44.9, 41.9, 41.7, 37.7, 37.6, 36.5, 34.9, 34.3, 33.9, 29.14, 29.09, 28.99, 28.98, 27.79, 26.8, 26.7, 26.5, 26.5, 25.6, 25.5, 24.9, 24.8, 24.4, 22.2, 22.1, 18.8, 14.1. Anal. ($C_{52}H_{73}N_3O_3 \cdot 0.25H_2O$) C, H, N.

General Procedure for the Preparation of Ligands 3−6, 14−16. To a cooled solution of the appropriate morphinan (1 mmol) and Et_3N (0.5 mL) in anhydrous CH_2Cl_2 (10 mL), the appropriate acid dichloride (90.6 mmol) was added dropwise at 0 °C. The solution was stirred at room temperature for 48 h and then diluted with dichloromethane. The organic layer was separated, washed with 10% $NaHCO_3$ and brine, dried with Na_2SO_4, and then concentrated to yield a dark oil. The crude product was purified by column chromatography on silica gel (EtOAc:Et_3N, 100:1) to afford the corresponding bivalent ligands.

Bis((+)-*N*-cyclobutylmethylmorphinan-3-yl) sebacoylate (3): colorless oil (69.7%). ^{1}H NMR ($CDCl_3$, 300 MHz): 7.10 (d, J = 8.1 Hz, 2H), 6.92 (d, J = 2.1 Hz, 2H), 6.85 (dd, J = 8.1, 2.1 Hz, 2H), 3.01 (d, J = 18.6 Hz, 2H), 2.82−1.23 (m, 64H). ^{13}C NMR ($CDCl_3$, 75 MHz): 172.4, 149.2, 142.1, 135.3, 128.4, 118.4, 118.1, 61.5, 55.8, 45.6, 44.9, 41.8, 37.8, 36.6, 34.9, 34.4, 29.1, 29.0, 27.8, 26.8, 26.5, 24.8, 24.4, 22.1, 18.8. Anal. ($C_{52}H_{72}N_2O_4 \cdot H_2O$) C, H, N.

Bis((−)-*N*-[(*S*)-tetrahydrofurfuryl]morphinan-3-yl) sebacoylate (4): light yellow oil (81.4%). ^{1}H NMR ($CDCl_3$, 300 MHz): 7.10 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 2.4 Hz, 2H), 6.85 (dd, J = 8.4, 2.4 Hz, 2H), 4.00 (m, 2H), 3.92 (m, 2H), 3.78 (m, 2H), 3.01−1.05 (m, 60H). ^{13}C NMR ($CDCl_3$, 75 MHz): 172.3, 149.1, 142.0, 135.3, 128.4, 118.4, 118.0, 77.6, 68.0, 60.1, 56.8, 45.8, 44.7, 41.7, 37.6, 36.4, 34.3, 30.2, 29.0, 29.0, 26.6, 26.5, 25.4, 24.9, 24.8, 22.1. Anal. ($C_{52}H_{72}N_2O_6$) C, H, N.

Bis((−)-*N*-propargylmorphinan-3-yl) sebacoylate (5): colorless oil (63.2%). ^{1}H NMR ($CDCl_3$, 300 MHz): 7.10 (d, J = 8.4 Hz, 2H), 6.94 (d, J = 2.4 Hz, 2H), 6.86 (dd, J = 8.4, 2.4 Hz, 2H), 3.41 (dt, J = 9.9, 2.7 Hz, 4H), 3.14 (m, 2H), 3.02 (d, J = 18.4 Hz, 2H), 2.70−2.62 (dt, J = 9.9, 2.7 Hz, 4H), 2.56−2.52 (t, J = 2.8 Hz, 4H), 2.32−1.07 (m, 38H). ^{13}C NMR ($CDCl_3$, 75 MHz): 172.3, 149.3, 141.7, 134.7, 128.5, 118.6, 118.1, 80.6, 72.3, 55.6, 45.2, 44.8, 43.9, 41.6, 37.5, 36.4, 34.3, 29.0, 28.9, 26.5, 26.4, 24.8, 24.3, 22.0. Anal. ($C_{48}H_{60}N_2O_4$) C, H, N.

Bis((−)-*N*-cyclobutylmethylmorphinan-3-yl) muconate (6): yellow solid (70.6%). Mp: 79−81 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.59 (dd, J = 11.6, 3.2 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 2.4 Hz, 2H), 6.92 (dd, J = 8.0, 2.4 Hz, 2H), 6.46 (dd, J = 11.6, 3.2 Hz, 2H), 3.03 (d, J = 18.4 Hz, 2H), 2.83 (m, 2H), 2.63−0.88 (m, 46H). ^{13}C NMR ($CDCl_3$, 75 MHz): 164.3, 148.9, 142.3, 141.9, 135.7, 128.6, 128.4, 118.3, 117.9, 61.4, 55.8, 45.6, 44.8, 41.7, 37.8, 36.5, 34.9, 27.8, 26.7, 26.5, 24.4, 22.1, 18.8. Anal. ($C_{48}H_{60}N_2O_4 \cdot H_2O$) C, H, N.

Bis(3-amino-(−)-*N*-cyclobutylmethylmorphinan) succinamide (14): off-white solid (61.2%). Mp: 165−167 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.47 (d, J = 2.0 Hz, 2H), 7.34 (dd, J = 8.4, 2.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 4.90 (s, 2H), 3.31−3.29 (m, 2H), 3.04 (d, J = 19.2 Hz, 2H), 2.94 (s, 2H), 2.72−1.06 (m, 48H). ^{13}C NMR ($CDCl_3$, 75 MHz): 172.9, 141.3, 138.5, 133.8, 129.2, 119.2, 118.2, 62.0, 57.4, 47.2, 45.3, 42.0, 38.5, 37.4, 35.2, 32.7, 29.0, 28.8, 27.9, 27.6, 25.2, 23.3, 19.6. Anal. ($C_{46}H_{62}N_4O_2 \cdot 1.5H_2O$) C, H, N.

Bis(3-amino-(−)-*N*-cyclobutylmethylmorphinan) sebacamide (15): white solid (58.8%). Mp: 165−167 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.61 (s, 2H), 7.36 (d, J = 6.3 Hz, 4H), 7.03 (d, J = 8.4 Hz, 2H), 2.98 (d, J = 18.6 Hz, 2H), 2.79 (s, 2H), 2.59−1.24 (m, 62H). ^{13}C NMR ($CDCl_3$, 75 MHz): 171.4, 141.2, 136.3, 133.8, 128.0, 117.4, 116.6, 61.5, 55.8, 45.7, 45.04, 41.8, 37.6, 37.6, 36.5, 34.8, 29.0, 28.9, 27.8, 26.8, 26.6, 25.4, 24.4, 22.2, 18.8. Anal. ($C_{52}H_{74}N_4O_2 \cdot 0.5H_2O$) C, H, N.

Bis((−)-*N*-cyclobutylmethylmorphinan-3-amino) fumaramide (16): light-brown solid (50.5%). Anal. ($C_{46}H_{60}N_4O_2 \cdot 0.75H_2O$) C, H, N.

Opioid Binding to the Human μ, δ, and κ Opioid Receptors. Chinese hamster ovary (CHO) cells stably transfected with the human κ opioid receptor (hKOR-CHO), δ opioid receptor (hDOR-CHO), and the μ opioid receptor (hMOR-CHO) were obtained from Drs. Larry Toll (SRI International, Palo Alto, CA) and George Uhl (NIDA Intramural Program, Bethesda, MD). The cells were grown in 100 mm dishes in Dulbecco's modified Eagle's media (DMEM) supplemented with 10% fetal bovine serum (FBS) and penicillin-streptomycin (10 000 units/mL) at 37 °C in a 5% CO_2 atmosphere. The affinity and selectivity of the compounds for the multiple opioid receptors were determined by incubating the membranes with radiolabeled ligands and 12 different concentrations of the compounds at 25 °C in a final volume of 1 mL of 50 mM Tris-HCl, pH 7.5. Incubation times of 60 min were used for the μ-selective peptide [^{3}H]DAMGO and the κ-selective ligand [^{3}H]U69,593. A 3-h incubation was used with the δ-selective antagonist [^{3}H]-naltrindole.

[^{35}S]GTPγS Binding Studies To Measure Coupling to G Proteins. Membranes from CHO cells stably expressing either the human κ or μ opioid receptor were used in the experiments. Cells were scraped from tissue culture plates and then centrifuged at 1000*g* for 10 min at 4 °C. The cells were resuspended in phosphate-buffered saline, pH 7.4, containing 0.04% EDTA. After centrifugation at 1000*g* for 10 min at 4 °C, the cell pellet was resuspended in membrane buffer, which consisted of 50 mM Tris-HCl, 3 mM $MgCl_2$, and 1 mM EGTA, pH 7.4. The membranes were homogenized by with a Dounce homogenizer, followed by centrifugation at 40000*g* for 20 min at 4 °C. The membrane pellet was resuspended in membrane buffer, and the centrifugation step was repeated. The membranes were then resuspended in assay buffer, which consisted of 50 mM Tris-HCl, 3 mM $MgCl_2$, 100 mM NaCl, and 0.2 mM EGTA, pH 7.4. The protein concentration was determined by the Bradford assay using bovine serum albumin as the standard. The membranes were frozen at −80 °C until use.

CHO cell membranes expressing either the human κ opioid receptor (15 μg of protein per tube) or μ opioid receptor (7.5μg of protein per tube) were incubated with 12 different concentrations of the agonist in assay buffer for 60 min at 30 °C in a final volume of 0.5 mL. The reaction mixture contained 3 μM GDP and 80 pmol of [^{35}S]GTPγS. Basal activity was determined in the presence of 3 μM GDP and in the absence of an agonist, and nonspecific binding was determined in the presence of 10 μM unlabeled GTPγS. Then, the membranes were filtered onto glass-fiber filters by vacuum

filtration, followed by three washes with 3 mL of ice-cold 50 mM Tris-HCl, pH 7.5. Samples were counted in 2 mL of Ecoscint A scintillation fluid. Data represent the percent of agonist-stimulation [^{35}S]GTPγS binding over the basal activity, defined as [(specific binding/basal binding) × 100] − 100. All experiments were repeated at least three times and were performed in triplicate. To determine antagonist activity of a compound at the μ opioid receptors, CHO membranes expressing the μ opioid receptor were incubated with the compound in the presence of 200 nM of the agonist DAMGO. To determine antagonist activity of a compound at the κ opioid receptors, CHO membranes expressing the κ opioid receptor were incubated with the compound in the presence of 100 nM of the κ agonist U50,488.

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Supporting Information Available: Elemental analyses for all final compounds listed in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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