Synthesis and Biological Evaluation of α- and β-6-Amido Derivatives of 17-Cyclopropylmethyl-3, 14β-dihydroxy-4, 5α-epoxymorphinan: Potential Alcohol-Cessation Agents

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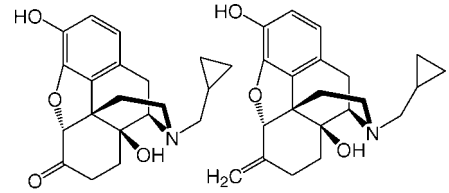
Substituted aryl and aliphatic amide analogues of 6-naltrexamine were synthesized and used to characterize the binding to and functional activity of human μ-, δ-, and κ-opioid receptors. Competition binding assays showed **11**–**25** and **27**–**31** bound to the μ (K_i = 0.05–1.2 nM) and κ (K_i = 0.06–2.4 nM) opioid receptors. Compounds **11**–**18** possessed significant binding affinity for the δ receptor (K_i = 0.8–12.4 nM). Functional assays showed several compounds acted as partial or full agonists of δ or κ receptors while retaining an antagonist profile at the μ receptor. Structure–activity relationship for aryl amides showed that potent compounds possessed lipophilic groups or substituents capable of hydrogen bonding. Metabolic stability studies showed that **11**, **12**, and **14** possessed considerable stability in the presence of rat, mouse, or human liver preparations. The ED_{50} of inhibition of 10% ethanol self-administration in trained rats, using operant techniques for **11**, was 0.5 mg/kg.

Introduction

Alcoholism is a serious disorder with significant social and economic consequences. Numerous studies suggest that alcohol interacts with endogenous opioid systems.[1,2] In 1994, naltrexone (Figure 1) was approved by the United States Food and Drug Administration (FDA) for treatment of alcoholism. Naltrexone is a pure μ-opioid receptor antagonist with no agonist activity and no abuse potential. Blocking the opioid receptor inhibits the effects of pleasure-inducing endogenous opioids released by alcohol, resulting in an attenuation of the positive reinforcing effects of alcohol consumption. In a laboratory study of nonproblem drinkers, naltrexone was found to decrease the reinforcing (i.e., stimulant) effects and increase the unpleasant (i.e., sedative) properties of initial alcohol consumption.[3] Studies using rodent and monkey animal models have shown that the opioid antagonists naloxone and naltrexone decrease the voluntary consumption and stress-induced increase in alcohol self-administration, suggesting that these agents may prevent the reinforcing effects of alcohol consumption.[4] Naltrexone may be most beneficial among alcoholics with higher levels of craving and poorer cognitive functioning.[5] However, in one study, 15% of patients undergoing naltrexone treatment terminated treatment early because of adverse effects including intolerable nausea.[6] Naltrexone is also associated with dose-dependent hepatotoxic side effects that complicate use and confound treatment of alcoholic patients with liver disease.[7] Additional shortcomings include a less than desirable duration of action, relatively low bioavailability,[8] and possibly, a relatively low affinity for δ and κ receptors thought to be involved in diminishing the reinforcing effects of drinking alcohol.[9] Beneficial effects of naltrexone diminish gradually over time, and an extended-release injectable suspension of naltrexone has shown promise.[10] In some cases, the effects of naltrexone have been quite robust, but in other cases, evidence of its efficacy has been less consistent. The naltrexone analogue, nalmefene (Figure 1), an opioid antagonist with superior pharmaceutical properties to naltrexone may hold greater promise as an alcohol treatment medication.



4 **5**

Figure 1. Structure of naltrexone **4** and nalmefene **5**.

Opioid receptor antagonists have direct effects on alcohol-seeking behavior.[4] For example, direct perfusion of naloxone via microdialysis into the nucleus accumbens neurons inhibited alcohol-mediated dopamine release.[11,12] A decrease in alcohol consumption by blockade of opioid receptors suggests direct effects of naloxone in this reinforcement system.[3,4] Animal studies have provided evidence that μ-, δ-, and κ-opioid receptors contribute to alcohol-induced reinforcement.[13,14]

Previously, reports of *N*-acyl-β-naltrexamine derivatives have been reported in the literature. For example, a naphthalene dialdehyde amide of naltrexamine was reported as a μ-receptor affinity label.[15] Others have reported on morphinan amide derivatives as analgesic and diuretic agents.[16] TRX-820[17] and funaltrexamine[18] represent two other examples of antagonists and agonists, respectively, of opioid receptors. The work herein presents a description of a class of compounds that has potency and efficacy against μ-, δ-, and κ-opioid receptors as alcohol self-administration cessation agents and may help determine the

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[a] Abbreviations: DETAPAC, diethylenetriaminepentaacetic acid; BOP, benzotriazol-1-yl-oxy-tris-(dimethylamino)phosphonium hexa-fluorophosphate; ESI, electrospray ionization; GTP, guanosine 5′-triphosphate; FBS, fetal bovine serum; CHO, Chinese hamster ovary; DMEM, Dulbecco's minimal essential medium; BAL, blood alcohol level.

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key opioid receptor(s) required for alcohol self-administration cessation. The objective of our work was to develop metabolically stable analogues of **4** and **5**. Because of the possibility that the C-6 epoxide of nalmefene or other reactive metabolites of naltrexone produced by metabolism contributes to hepatatoxicity, by replacing the metabolically labile 6-keto or 6-methylene groups of **4** and **5**, respectively, with an amide moiety, this may lead to more long-lived agents with potentially less hepatatoxicity but still retain great pharmacological efficacy.

Results and Discussion

The chemical synthesis of a series of substituted aryl and aliphatic amide derivatives of 6-naltrexamine (Table 1) was efficiently accomplished and used to characterize the structural requirements for binding to and functional activity of human μ-, δ-, and κ-opioid receptors.

The naltrexamides **8**–**33** were prepared in good yields according to the synthetic method outlined in Scheme 1. Naltrexone **4** was converted to its oxime **6**[19] in quantitative yield using hydroxylamine hydrochloride in the presence of sodium acetate in refluxing ethanol. Reduction of the oxime functional group in **6** to the corresponding amine **7**[19b] was accomplished by heating **6** with B_2H_6/tetrahydrofuran (THF) for 2 days, and subsequent aqueous workup afforded the amine **7** as a 1:9 (α/β) mixture of diastereomers. The diastereomers were separated by chromatography on silica gel, and the stereochemistry at C-6 was determined by the size of the coupling constant, $J_{5,6}$. The amine **7** was coupled either with a carboxylic acid in the presence of benzotriazol-1-yl-oxy-tris-(dimethylamino)phosphonium hexa-fluorophosphate (BOP)[a] and diisopropylethylamine or, alternatively, with an acid chloride in triethylamine. The product was treated with K_2CO_3 in methanol to remove the side product resulting from esterification of the 3-position hydroxyl group, giving amides **8**−**33** in moderate to high yields. While the BOP coupling procedure resulted in less esterification of the 3 position than the acid chloride method, some esterification at the 3 position could not be avoided. Thus, it was found to be more convenient to run the reaction with an excess of the acid derivative to aid in the purification of the intermediate amide ester. The benzyl groups in compound **8** were removed by hydrogenolysis in the presence of Pd−C and hydrogen gas to give the glucose conjugate diastereomers **9** and **10**. The structure of the naltrexamides **8**–**33** and their respective stereochemistry are depicted in Table 1. The amides were fully characterized by nuclear magnetic resonance (NMR) and high-resolution mass spectrometry (HRMS).

The IC_{50} values for compounds **4**, **5**, and **8**–**33** were obtained from competition binding assays from full dose–response curves in the presence of the μ-, δ-, and κ-opioid receptors. The IC_{50} values for the test compounds and reference materials were determined using the binding assays with the following radioligands: [^{3}H]DAMGO (μ-opioid receptor agonist), [^{3}H]DPDPE (δ-opioid receptor agonist), and [^{3}H]U69593 (κ-opioid receptor agonist). The IC_{50} values determined by measuring the inhibition of binding of the radioligands to the receptors by the test compounds **4**, **5**, and **8**–**33** were converted into K_i values as described in the Experimental Section and listed in Table 2.

In comparison to naltrexone or nalmefene, compounds **4** and **5** as well as saccharide-containing compounds **9** and **10**, generally possessed lower potency than naltrexone for the δ and κ receptors but equal to or greater potency for the μ-opioid receptor. The selectivity of compounds **9** and **10** for the μ versus δ and μ versus κ receptors were greater than 50- and 3-fold, respectively. In comparison to naltrexone but not nalmefene, saccharides **9** and **10** were relatively selective for the μ receptor. A 3- and 2-fold stereoselectivity for binding to the δ- and κ-opioid receptors was observed between the α and β saccharide isomers (i.e., **9** and **10**). The benzyl derivative of saccharide **9** (i.e., compound **8**) was about 4.5- and 1.6-fold less potent than naltrexone and nalmefene, respectively, for the μ-opioid receptor but was more potent against the κ-opioid receptor. This suggested that lipophilic amides could retain potency for μ and δ receptors and possibly have increased potency for the κ receptor. Because our goal was to design agents with increased activity for κ receptors, we synthesized lipophilic aryl amide derivatives of **7**.

In comparison to nalmefene, with the exception of compounds **8**, **25**, and **26**, each of the test compounds examined possessing a C-6 aromatic amide group showed higher affinity (K_i = 0.05–0.9 nM) for the μ-opioid receptor. Compounds **11**–**23** possessed 1.2−7- and 1.5−8-fold higher affinity for the μ receptor compared to naltrexone and nalmefene, respectively. Compound **26** contained a benzoic acid moiety and was the least potent agent tested against the μ receptor. Compounds **27**−**31** showed 2–15-fold greater potency for the μ receptor compared to nalmefene. The rank order of affinity for the most potent aryl amides at the μ receptor was **11** > **27** > **23** = **28** > **12**–**17** > **18** = **19** > **20** > **21** > **33** > **22**. In general, compounds with substitutions on the aromatic portion of the amide (i.e., **11**–**25**) showed significantly more μ versus δ receptor selectivity than μ versus κ receptor selectivity as indicated by the ratio of δ/μ and κ/μ values (Table 2). With the exception of **27**, for compounds examined with aliphatic amide groups (i.e., **27**–**31**), the affinity for the μ receptor was about 1–2-fold greater compared to naltrexone and 3–8-fold greater compared to nalmefene. Compound **27** showed 5.5–15-fold greater potency for the μ receptor compared to naltrexone and nalmefene, respectively. Aliphatic amides **27**–**31** had considerable potency and selectivity for the κ receptor. The values for the ratio of κ/μ receptors for **27**–**31** were 15.2, 0.8, 3.5, 2.7, and 1.6, respectively, but the ratio of δ/μ for these same compounds was 137, 102, 122, 175, and 74, respectively. Compounds **27**–**31** thus possessed considerable potency and selectivity for the κ but not the δ-opioid receptor. Of the amides examined, the thiophene analogue (i.e., compounds **32** and **33**) showed significant stereoselectivity for binding to the δ-opioid receptor. Thus, the α isomer **33** had 15.7-fold greater potency than the β isomer, compound **32**, for binding to the δ-opioid receptor. Compound **33** possessed similar potency as naltrexone and nalmefene for the μ- and κ-opioid receptor and showed higher potency for the δ receptor compared to naltrexone or nalmefene.

Most of the aryl and aliphatic amide compounds examined (i.e., **8**–**10**, **19**–**22**, **24**, and **30**–**32**) had considerably less affinity for the δ receptor compared to naltrexone and nalmefene and, with the exception of a few compounds, had K_i values for the δ receptor greater than 6 nM. The lipophilic compounds **11** and **12** had K_i values of 1.4 and 0.8 nM, respectively, and along with **33** (i.e., K_i = 2.1 nM) showed the greatest potency for the δ receptor. Of the compounds tested, the polar saccharide **10** and carboxyl-containing compound **26** possessed the lowest potency for the δ-opioid receptor.

In keeping with our initial observations for lipophilic derivatives (e.g., compound **8**), numerous lipophilic aryl and aliphatic amides showed considerable potency for the κ receptor. The compounds with the greatest potency against the κ-opioid receptor were lipophilic (i.e., **28**, K_i = 0.09 nM; **12**, K_i = 0.1 nM; or **15**, K_i = 0.16 nM) or possessed hydrogen-bonding capability in the *meta* or *para* position (i.e., **13**, K_i = 0.06 nM; **20**, K_i = 0.29 nM; **22**, K_i

Table 1. Chemical Structures of Amides **8–33** and Their C-6 Diastereomeric Assignment

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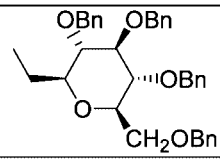
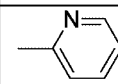
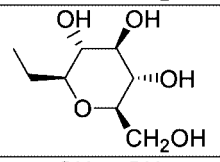
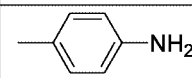
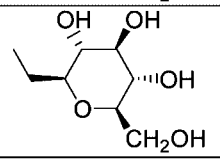
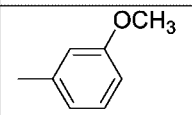
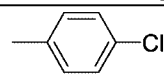
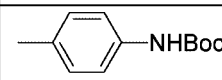
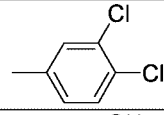
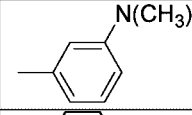
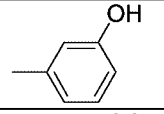
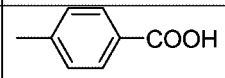
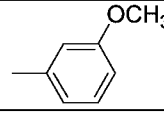
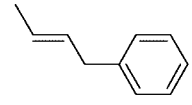
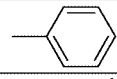
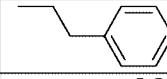
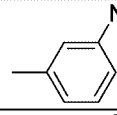
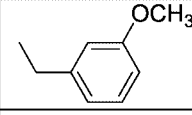
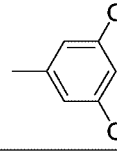
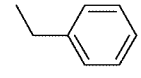
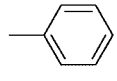
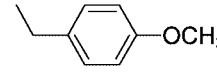
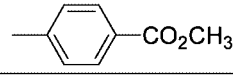
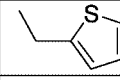
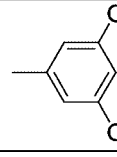
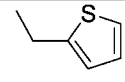
8		α	**21**		β
9		α	**22**		β
10		β	**23**		β
11		β	**24**		β
12		β	**25**		α/β[a]
13		β	**26**		β
14		α	**27**		β
15		β	**28**		β
16		β	**29**		β
17		α	**30**		β
18		α	**31**		β
19		β	**32**		β
20		β	**33**		α

[a] Diastereomeric mixture containing α and β isomers (1:9).

= 0.4 nM; or **31**, K_i = 0.42 nM). In agreement with a previous report,[20] related negatively charged compounds (i.e., **26**, K_i = 151 nM) had considerably less affinity for the κ receptor.

To evaluate the opioid-receptor-mediated activation of its associated G protein, test compounds were evaluated using the [^{35}S]GTPγS assay.[21] In this assay, the potency or affinity of a compound for the receptor is associated with its EC_{50} value for stimulating [^{35}S]GTPγS binding. Agonist activity is determined using a selective full agonist (i.e., DAMGO for μ, DPDPE for δ, and U69,593 for κ) as standards, compounds that are capable

Scheme 1. Synthesis of Naltrexamide Derivatives **8–33**

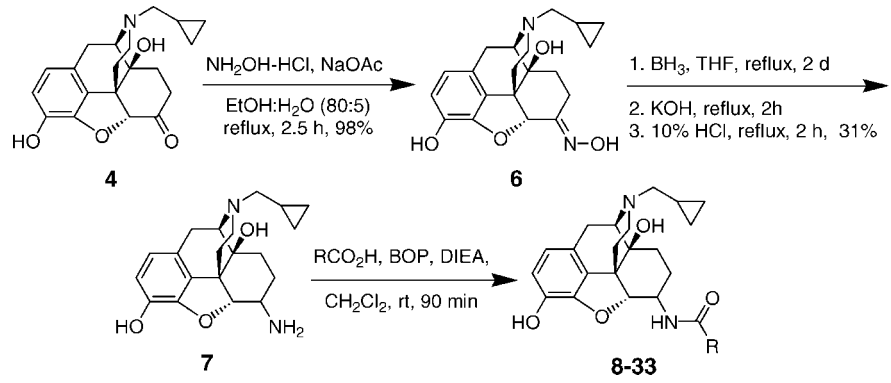


Table 2. K_i Inhibition Values and Selectivity of μ-, δ-, and κ-Opioid Binding to CHO Membranes

	K_i (nM) ± SEM				
compound	μ	δ	κ	δ/μ	κ/μ
naltrexone, **4**	0.30 ± 0	16.31 ± 1.10	0.81 ± 0.02	49	2.5
nalmefene, **5**	0.91 ± 0.10	13.26 ± 0.75	1.03 ± 0.19	15	1.1
8	1.49 ± 0.07	24.52 ± 4.20	0.51 ± 0.09	16.5	0.34
9	0.67 ± 0.12	36.94 ± 6.20	2.03 ± 0.16	55	3.0
10	0.64 ± 0.01	99.00 ± 1.50	4.50 ± 0.07	150	7.0
11	0.05 ± 0.01	1.40 ± 0.10	0.37 ± 0.11	30	7
12	0.10 ± 0.03	0.79 ± 0.10	0.10 ± 0.01	7.9	1.0
13	0.13 ± 0.04	2.73 ± 0.50	0.06 ± 0.02	21	0.5
14	0.16 ± 0	5.82 ± 0.90	0.72 ± 0.05	36	4.5
15	0.18 ± 0.04	9.72 ± 1.40	0.16 ± 0.02	54	0. 89
16	0.19 ± 0.05	4.23 ± 0.20	0.28 ± 0.09	22	1.5
17	0.19 ± 0.02	6.83 ± 1.00	2.41 ± 1.00	36	13
18	0.21 ± 0	12.40 ± 0.90	0.78 ± 0.16	59	3.7
19	0.21 ± 0	27.18 ± 5.40	0.73 ± 0.06	130	3.5
20	0.26 ± 0.12	17.59 ± 2.60	0.29 ± 0.06	68	1.1
21	0.31 ± 0.05	56.30 ± 12.50	0.39 ± 0.07	180	1.3
22	0.43 ± 0.17	36.52 ± 6.10	0.40 ± 0.03	85	0.93
23	0.12 ± 0	3.80 ± 0.40	0.24 ± 0.03	32	2.0
24	0.92 ± 0.05	25.29 ± 5.60	0.79 ± 0.19	28	0.86
25	1.20 ± 0.10	8.50 ± 1.00	1.70 ± 0.40	7.08	1.42
26	10.08 ± 2.50	79.23 ± 3.30	150.61 ± 17.00	7.860	14.94
27	0.06 ± 0.05	8.22 ± 0.70	0.91 ± 0.01	100	20
28	0.12 ± 0.01	12.20 ± 1.40	0.09 ± 0.02	100	0.8
29	0.13 ± 0.03	15.80 ± 2.00	0.45 ± 0.09	120	3.5
30	0.16 ± 0.02	28.00 ± 0.40	0.43 ± 0.03	180	2.7
31	0.27 ± 0.05	19.91 ± 0.60	0.42 ± 0.05	74	1.6
32	0.43 ± 0.10	32.40 ± 0.20	1.20 ± 0.03	75	2.8
33	0.38 ± 0.07	2.07 ± 0.20	2.74 ± 0.93	5.5	7.2

Table 3. Stimulation of [^{32}S]-GTP-γ-S Binding by the μ-, δ-, and κ-Opioid Receptors

	μ		δ		κ	
compound	EC_{50}	E_{max}	EC_{50}	E_{max}	EC_{50}	E_{max}
naltrexone, **4**	>10 000		230.00 ± 0	20.40 ± 0	2.10 ± 0	5.30 ± 0
nalmefene, **5**	>10 000		31.60 ± 0	11.80 ± 0	2.86 ± 0. 70	12.60 ± 4.50
8[a]	9.70 ± 0.50	21.40 ± 0.50	182.20 ± 53.30	15.40 ± 3.60	7.30 ± 2.45	49.00 ± 2.50
10	42.30 ± 5.40	15.80 ± 1.60	56.00 ± 25.00	34.20 ± 6.30	18.00 ± 5.00	11.60 ± 0.40
11	3.90 ± 2.50	45.80 ± 3.80	22.20 ± 7.60	28.70 ± 7.60	7.10 ± 2.70	30.60 ± 2.60
12	2.30 ± 1.40	84.80 ± 7.40	1.40 ± 1.40	84.90 ± 34.60	0.80 ± 0.20	91.40 ± 4.10
23[a]	1.16 ± 0.60	20.60 ± 1.50	10.40 ± 0.60	92.50 ± 4.40	1.53 ± 0.10	93.00 ± 11.00
25[a]	4.64 ± 0.90	19.30 ± 0.10	8.51 ± 0.90	100.20 ± 2.70	1.09 ± 0	104.30 ± 15.70
28	24.80 ± 0	14.50 ± 3.30	18.00 ± 1.00	24.40 ± 2.60	1.55 ± 0.10	74.00 ± 0.80
32[a]	5.20 ± 1.60	16.10 ± 1.90	17.58 ± 4.90	81.80 ± 4.80	94.86 ± 3.70	46.30 ± 5.10

[a] Diastereomeric mixture containing α and β isomers in a 1:9 ratio.

of maximally stimulating [^{35}S]GTPγS binding in the human cloned cell line. Table 3 shows the E_{max} and EC_{50} values for stimulation of [^{35}S]GTPγS binding of standards and test compounds in the cloned human cell membranes containing the μ-, δ-, or κ-opioid receptor. With the exception of compounds **12** and **25** that showed significant agonist activity, compounds **8**, **10**, **23**, and **28** showed significant antagonism of the μ receptor. The [^{35}S]GTPγS-binding data showed that compounds **23** and **25** were full δ agonists and compounds **8**, **10**, **11**, and **28** were found to be partial δ agonists similar to naltrexone and nalmefene. Compounds **12**, **23**, and **25** were observed to be full κ agonists, whereas compounds **8**, **11**, **28**, and **32** were partial κ agonists. Compound **10** showed noncompetitive antagonist activity against the κ-opioid receptor similar to

nalmefene. The overall rank order of the EC_{50} values for the functional assay correlated well with the K_i values derived from the binding experiments. As described below, further kinetic analysis was performed to characterize the properties of these latter compounds.

High-affinity compounds (i.e., compounds possessing low K_i values) that showed no or low agonist activity (20% stimulation or less in the GTPγS-binding experiment) were tested as antagonists. A Schild analysis was conducted, using a full dose−response curve in the presence of at least three concentrations of the putative antagonist.[22] If the Schild slope was significantly different from −1.0, the antagonist activity was judged to be noncompetitive; and in such cases, the pA_2 values were not reported, only the equilibrium dissociation constant (K_e). Compounds **8**, **10**, **23**, **28**, and **32** were found to be full antagonists for the μ-opioid receptor, while compound **10** was also found to be a noncompetitive antagonist at the κ receptor.

Structure–Activity Studies. The structure–activity relationship (SAR) of the aromatic amide portion of the opioid antagonists was examined. In general, *meta*- or *para*-monosubstituted or *meta*, *para*-disubstituted aromatic groups showed quite potent affinity for the μ receptor (Table 1). Thus, compounds **12**–**24** and **27**–**33** all had K_i values in the 0.1−0.9 nM range. The 4-chloro- and 3,4-dichloro-substituted aromatic amides showed the greatest affinity for the μ receptor (i.e., K_i = 0.05 and 0.1 nM, respectively). In contrast, of the compounds tested, compounds **25** and **26** with a *para*-carboxylic acid group or *meta*-*N*,*N*-dimethylamino group that should be charged at neutral pH showed the lowest affinity for the μ receptor (i.e., K_i = 1.2 and 10 nM, respectively). Compound **26** also possessed very low potency against the δ receptor (i.e., K_i = 79 nM) and the κ receptor (K_i = 151 nM). As described above, there was some evidence that, in a few cases, compared to the β isomer, the α diastereomer possessed greater potency for the μ and δ receptors (i.e., **9** > **10**, **17** > **20**, or **33** > **32**) but the stereoselectivity was not large. In the cases examined, the β diastereomer had greater potency than the α diastereomer for the κ receptor (i.e., **20** > **17**, **23** > **14**, and **32** > **33**). Because of the modest diastereoselectivity observed and the paucity of α diastereomer available by chemical synthesis, this aspect was not pursued further.

Metabolic Stability. As a prelude to studying the test compounds *in vivo*, high-performance liquid chromatography (HPLC)-based analytical methods (see the Supporting Information) and biochemical assays were used to assess the metabolic stability of selected compounds in the presence of rat, mouse, and human liver preparations and the appropriate NADPH-generating system. These studies were performed to ascertain the stability of the compounds toward oxidative metabolism in advance of more detailed studies with highly purified CYPs as well as to determine if the compounds possessed sufficient metabolic stability for *in vivo* studies. In comparison to nalmefene, the candidate compounds **11**, **12**, and **14** were metabolically quite stable (Table 4). With the exception of compound **14**, compounds **11** and **12** possessed half-life values in excess of 255 min in the hepatic preparations used. Generally, compounds that were metabolically stable in the presence of mouse or human liver microsomal preparations did not afford evidence of significant amounts of metabolite formation based on inspection of the HPLC profiles (data not shown). It may be that, for this class of compounds, the cyclopropyl methyl moiety inhibited hepatic CYPs. This point is considered in greater detail below. Rat and mouse liver microsomes are known to possess high amounts of amidase activity, and in comparison to human liver S-9 (that represents both cytosolic and microsomal enzymes), similar metabolic stability was observed. This suggests that hepatic cytosolic or microsomal amidases do not contribute in a dominant way to the metabolism of the target compounds.

Table 4. Metabolic Stability of Selected Compounds in Hepatic Preparations[a]

compound	half-life (in min)		
	rat liver microsomes	mouse liver microsomes	human S-9
nalmefene, **5**	100	20	20
11	no change[b]	255	no change
12	no change	no change	346
14	no change	49	no change

[a] Incubations were carried out as described in the Experimental Section. The values are an average of two determinations, and each time point was run in duplicate. The range of variation was less than 10%. [b] During the incubation with the hepatic preparation and the NADPH-generating system, no detectable loss of parent compound was observed.

CYP Inhibition. As reported previously, cyclopropylmethyl-containing amines can inhibit CYP.[23,24] To understand the metabolic stability data described above and to examine the possible extent and selectivity of CYP inhibition, selected compounds (i.e., **11**, **12**, **23**, and **25**) were examined for their ability to inhibit selective functional activities of human CYP enzymes. The observed percent inhibition for selective functional inhibition of CYP-3A4, -2E1, -2B6, −-C9, -2C19, and -2D6 were reported in Table 5. The enzyme assays were performed using standard conditions as previously described.[25] In comparison to nalmefene, generally, the compounds examined (i.e., **11**, **12**, **23**, and **25**) possessed less inhibitory potency against the CYPs examined. A possible exception was CYP2C19 that appeared to be more sensitive to inhibition by **11**, **12**, **23**, and **25** than nalmefene. In addition, compound **23** inhibited CYP2B6 with greater potency than nalmefene. The results suggest that replacement of the C-6 *exo*-methylene group of nalmefene with an amide substituent in this series attenuated the inhibitory potency toward CYP. This suggests a significant contribution of the C-6 moiety in the interaction of nalmefene with CYP and for the C-6 substituted amides examined; it suggests a decreased interaction with CYP. This may in part explain some of the metabolic stability observed for the compounds in this and related series.[26] On the basis of the data from the *in vitro* metabolism studies, the compounds were sufficiently stable and of low CYP inhibitory potency and were judged to be good candidates to study them *in vivo* in an animal model of alcohol self-administration.

***In Vivo* Studies.** We evaluated selected compounds for their effect on baseline ethanol (EtOH) intake in rats trained to self-administer a 10% (w/v) ethanol solution, using operant techniques. A control group consisting of rats administered nalmefene hydrochloride was also examined. The operant procedure provided an animal model system to examine the effect of test compounds on the acute positive reinforcing effects of EtOH self-administration.[27–34] Initially, dose range studies were performed, and if active compounds were observed, more detailed studies were performed. After administration of 0.5 mg/kg of **10** or **28**, a slight increase in alcohol consumption was observed, and consequently, further studies were not pursued with these compounds. Dose range studies of **23** and **25** were attempted; however, a decrease in alcohol self-consumption only at an elevated dose (i.e., 75% decrease at 2 mg/kg and 17% decrease at 1.5 mg/kg for **23** and **25**, respectively) was observed, and the lack of efficacy observed precluded further study. Compound **12** showed potent inhibition of alcohol self-

Table 5. Percent Inhibition of CYP3A4, CYP2B6, CYP2C9, CYP2C19, and CYP2D6 by Selected Naltrexamides and Nalmefene

	percent inhibition[a]				
compound	CYP3A4	CYP2B6	CYP2C9	CYP2C19	CYP2D6
nalmefene, **5**	60.0 ± 8.7	5.2 ± 0.5	35.5 ± 1.7	17.1 ± 1.9	30.9 ± 1.9
11	30.8 ± 3.3	7.0 ± 0.3	28.1 ± 2.8	39.1 ± 1.9	4.7 ± 0.3
12	35.5 ± 0.8	4.7 ± 0.1	32.3 ± 1.7	48.3 ± 2.2	9.8 ± 0.4
23	44.9 ± 7.8	49.3 ± 1.9	ND[b]	47.1 ± 5.4	31.2 ± 2.1
25	39.9 ± 3.7	ND[b]	23.1 ± 2.5	70.0 ± 3.1	23.5 ± 1.7

[a] Percent inhibition in the presence of 10 μM opioid antagonist ± standard deviation. Incubations were carried out as described in the Experimental Section. The test compound was preincubated for 2–5 min with the enzyme and cofactor Then, the appropriate substrate (5 μM) was added, and the rate of product was monitored and compared to the complete system without the test compound present. [b] ND = no detectable inhibition was observed at the concentration of the test compound examined.

administration at a dose of 0.025 mg/kg (i.e., 77% inhibition), but **12** also showed potent analgesic activity and was not studied further. Compound **11** was administered in a dose range study and showed significant efficacy. A more detailed study employing **11** from 0.1 to 2 mg/kg showed efficacy at inhibiting alcohol self-administration with an ED_{50} value of 0.5 mg/kg. This is about the same ED_{50} value observed for naltrexone hydrochloride in similar experiments. In comparison, the ED_{50} value for inhibition of alcohol self-administration by nalmefene was approximately 0.04 mg/kg. We surmised that the potency of **11** for all three μ-, δ-, and κ-opioid receptors coupled with its metabolic stability contributed to the functional activity as an alcohol self-administration cessation agent observed *in vivo*.

Conclusion

A series of C-6-substituted amides of naltrexamine where the amide was appended with substituted aromatic or aliphatic groups was prepared by the reaction of 6-naltrexamine, **7**, with aryl and aliphatic acid chlorides or carboxylic acids. Although this is not the first report of the pharmacological properties of *N*-acyl-β-naltrexamines, to our knowledge, this is the first study examining a number of naltrexamides as alcohol-cessation agents. The target compounds were evaluated as ligands for the human μ-, δ-, and κ-opioid receptors, with the goal of identifying a potent and selective alcohol self-administration cessation agent. Originally, metabolically stable saccharide derivatives of opioids were studied as pain medication candidates.[35] It was noted that glucuronides were less potent than glucose derivatives.[35] In the present study, we initially examined glucose derivatives as alcohol-cessation agents but the compounds examined (e.g., **10**) did not possess significant potency *in vitro* against the δ and κ receptors and was not efficacious *in vivo*. Consequently, **10** was not studied further, *in vivo*. Next, we synthesized analogues of saccharides, such as **13**, **14**, **17**, and **20**, where the substituent mimicked the polar functionalities of a saccharide and they retained significant potency. On that basis, we made a number of analogues to explore SAR. In general, *meta*- or *para*- or *meta*, *para*-disubstituted aromatic groups showed quite potent affinity for the μ receptor. There was not a marked difference in potency between *meta* or *para*-substituted aryl amides. Generally, the aliphatic amides examined all showed significant potency for the μ receptor. With the exception of **11**, generally, *meta*-substituted aryl amides were somewhat more potent than *para*-substituted aryl amides against the δ receptor. Similar to the μ receptor, both *meta*- and *para*-substituted aryl amides possessed considerable potency against the κ receptor. However, some aryl substituents abrogated potency. For example, as described previously,[36] negatively charged carboxyl-containing compounds, such as **26**, had poor affinity for the μ and κ receptors. As shown in Table 3, not all of the compounds stimulated full [^{32}S]GTP-γ-S binding at the μ, δ, and κ receptors. Compounds **8**, **10**, **23**, **25**, **28**, and **32** showed considerable apparent antagonism of the μ receptor. Compound **11** showed partial agonism at all three opioid receptors. The addition of a *meta*-chloro substituent to **11** provided a compound (i.e., **12**) that elicited considerable agonistic potency across all three receptors. Thus, introduction of small substituent changes resulted in dramatic biological effects in this series. The antagonism of the κ receptor by **10** was confirmed by a Schild plot (Table 6). The finding in the *in vivo* studies that **11** was much more potent as an alcohol-cessation agent than **10** suggests that the partial agonist activity at all three opioid receptors might be necessary for alcohol-cessation activity. This will be further evaluated using other partial agonist compounds.

Hepatotoxicity of naltrexone[5] and nalmefene is a concern because, generally, the liver of individuals that abuse alcohol is severely compromised. Although the mechanism of hepatoxicity of naltrexone and nalmefene is unknown, it is likely to involve metabolic bioactivation to a reactive intermediate (i.e., possibly to an epoxide in the case of nalmefene or radical intermediates in the case of naltrexone), and because a relationship between metabolic bioactivation and hepatotoxicity has been established,[37] the original design in our studies was to decrease the metabolic lability of nalmefene by synthesizing analogues with increased bioavailability as a result of modification of the C-6 position. As shown in Tables 4 and 5, compounds **11**, **12**, **14**, **23**, and **25** possessed greater metabolic stability and generally less propensity to interact with hepatic CYP than nalmefene. It may be that by decreasing the affinity of the opioid analogues described herein for metabolic enzymes including CYP and increasing the metabolic stability results in a class of compounds with less potential for hepatotoxicity.

On the basis of the results of the functional assay and K_i values and metabolic stability studies shown herein, selected compounds were evaluated for their effects in an animal model of alcohol self-administration. One objective was to try to determine which opioid receptor contributed to alcohol self-administration cessation. Compound **10** showed little agonistic activity at all three receptors and was not effective *in vivo* and, at 0.5 mg/kg, actually stimulated a modest amount of alcohol consumption in rats. On the other hand, compounds with significant agonist activity at the δ and/or κ receptor (i.e., **12**, **23**, **25**, and **32**) either possessed low potency as alcohol-cessation agents or stimulated alcohol self-administration *in vivo*. Compound **28** possessed significant agonistic activity against the κ but not the μ or δ receptors. However, at 0.5 mg/kg, **28** stimulated alcohol self-administration. Of the compounds examined, compound **11** (that was a weak agonist against all three receptors) showed the greatest efficacy *in vivo* (i.e., approximately ED_{50} of 0.5 mg/kg). On the basis of limited data presented above, it appears that individual antagonism of the μ, δ, or κ receptor alone is not sufficient for alcohol self-administration cessation. It may be that potent κ antagonism can compensate for weak δ antagonism, but what is more likely

Table 6. pA_2 Data for Selected Naltrexamide Analogues

compound	receptor	K_e (nM) ± SEM	pA_2 ± SEM	slope ± SEM
naltrexone, **4**	μ	0.05 ± 0	10.30 ± 0.03	−1.06 ± 0.03
	δ	2.10 ± 0.30	8.80 ± 0.10	−0.91 ± 0.04
	κ	0.23 ± 0.02	9.68 ± 0.03	−0.96 ± 0.02
nalmefene, **5**	μ	0.34 ± 0.02	9.53 ± 0.03	−0.93 ± 0.02
	δ	1.02 ± 0.13	9.04 ± 0.06	−0.95 ± 0.03
	κ[a]	0.15 ± 0.03		
8[b]	μ	0.16 ± 0.02	9.68 ± 0.07	−1.07 ± 0.04
	δ[a]	10.35 ± 2.00		
	κ	PA[c]		
10	μ	0.37 ± 0.03	9.33 ± 0.05	−1.08 ± 0.04
	δ	PA[c]		
	κ[a]	13.40 ± 1.50		
23[b]	μ	0.17 ± 0.01	9.78 ± 0.04	−0.99 ± 0.02
	δ	FA[d]		
	κ	FA[d]		
25	μ	0.14 ± 0.01	9.98 ± 0.04	−0.92 ± 0.02
	δ	FA[d]		
	κ	FA[d]		
28	μ[a]	0.15 ± 0.02		
	δ	PA[c]		
	κ	PA[c]		
32[b]	μ	0.41 ± 0.02	9.34 ± 0.02	−1.05 ± 0.02
	δ	PA[c]		
	κ	PA[c]		

[a] Noncompetitive antagonist. [b] Diastereomeric mixture containing α and β isomers (1:9). [c] PA = partial agonist. [d] FA = full agonist.

is that alcohol self-administration efficacy requires antagonism of all three opioid receptors. Such an agent (i.e., **11**) showed good *in vivo* activity in an animal model of ethanol self-administration in rats trained to self-administer a 10% (w/v) ethanol solution. Another interpretation of the data is the possibility that the compounds with μ partial agonist activity are sufficiently rewarding in themselves that they effectively substitute for the rewarding effects of ethanol. Compound **11** and related agents may represent an exciting lead for developing the next generation of opioid compounds useful in the treatment of alcohol abuse.

Experimental Section

Chemicals. Nalmefene hydrochloride and naltrexone hydrochloride were obtained from Tyco Mallinckrodt (St. Louis, MO). $NADP^+$, glucose-6-phosphate, glucose-6-phosphate dehydrogenase, diethylenetriaminepentaacetic acid (DETAPAC), and $MgCl_2$ were all obtained from Sigma-Aldrich Chemical Co. (St. Louis, MO) and were used as received. All of the solvents and buffers were obtained in the highest grade commercially available from VWR (San Diego, CA).

General Procedures. All reactions were run under a positive pressure of nitrogen with magnetic stirring at ambient temperature using oven-dried glassware unless otherwise indicated. Air- and moisture-sensitive liquids were transferred via syringe through rubber septa. Silica gel (230–400 mesh) was used for column chromatography. *N*,*N*-Dimethylformamide (DMF) was dried by filtration through a column of neutral alumina and stored over activated 4 Å molecular sieves under nitrogen prior to use. All other solvents and reagents were used as received. ^1H and ^{13}C NMR were recorded at 300.0 and 75.4 MHz, respectively, on a Varian Mercury 300 instrument. Chemical shifts were reported in parts per million (δ) relative to $CDCl_3$ at 7.26 and 77 ppm, respectively. NMR spectra were recorded in $CDCl_3$ unless stated otherwise. Melting points were reported uncorrected. High-resolution mass spectra were obtained with a VG 7070 spectrometer with an Opus V3.1 and DEC 3000 Alpha Station data system at the University of California, Riverside, or a Waters LCT Premier instrument operating in the ESI mode at the University of California, Irvine. Analytical purities were determined by straight and reverse-phase HPLC using a Hitachi D2500 Hitachi Chromato-integrator, a L-6000 Hitachi pump, and a L-4200 UV–vis Hitachi detector (285 nM). When an AXXI-chrom silica column (5 μm i.d. × 4.6 mm o.d. × 250 mm) was used (condition A), the mobile phase was MeOH/2-propanol/$HClO_4$ (55:45:0.01, v/v/v) at a flow rate of 1 mL/min. When a reverse-phase system was used (condition B), HPLC was performed with a L-7100 Hitachi pump, a L-7400 UV–vis Hitachi detector (285 nM), a L-7200 Hitachi autosampler, and a D-7000 Hitachi chromato-integrator employing a Supleco reverse-phase column (5 μm × 4.6 mm × 250 mm). The mobile phase was 20% 0.05 M tetrabutylammonium hydroxide and 80% methanol using isocratic elution at a flow rate of 1 mL/min.

Microsomes from rat, mouse, and human liver expressing functional human cytochrome P-450s were purchased from BD Gentest (Woburn, MA) or made in house, and microsomes from baculovirus-infected cells co-expressing cytochrome P-450s (3A4, 2B6, 2C9, 2C19, and 2D6), NADPH-cytochrome P-450 reductase, and cytochrome b_5 (BACULOSOMES) were purchased from PanVera LLC (Madison, WI).

Naltrexone Oxime (6).[19] Naltrexone (500 mg, 1.46 mmol), NH_2OH-HCl (147 mg), and NaOAc (294 mg) were dissolved in absolute ethanol (8 mL), and the mixture was heated at reflux for 2.5 h and then concentrated to dryness. Water (20 mL) was added, and the mixture was made basic with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated to give a white solid (463 mg, 89%). ESI−MS *m*/*z*: 357 (MH^+). ^1H NMR ($CDCl_3$) δ: 6.75 (d, J = 8.2 Hz, 1H), 6.61 (d, J = 8.2 Hz, 1H), 5.00 (s, 1H), 3.15 (m, 2H), 2.65–1.30 (m, 10H), 0.86 (m, 1H), 0.56 (m, 2H), 0.20 (m, 2H).

6-β-Naltrexamine (7a) and 6-α-Naltrexamine (7b). Naltrexone oxime (5.83 g, 16.3 mmol) was dissolved in THF (40 mL) and transferred by cannula over 10 min to a solution of BH_3/THF (300 mL, 300 mmol, 1 M solution in THF) held at 10 °C. A white precipitate formed and then slowly dissolved as the reaction was heated at reflux for 48 h. The solution was cooled to room temperature, and water (10 mL) and 1 N KOH (200 mL) were added slowly. The solution was then reheated at reflux for 2 h. The pH was reduced to 2.5 with 10% HCl (225 mL), and the solution was heated at reflux for 2 h, concentrated to remove THF, and then made basic (pH 8–9) with K_2CO_3. The mixture was extracted with $CHCl_3$ (4 × 150 mL), and the extract was dried over Na_2SO_4, filtered, and concentrated. The resulting oil was purified by chromatography on SiO_2 [26 × 60 cm, elution with 25:5:1 CH_3CN/MeOH/NH_4OH (v/v/v)] providing **7a** (2.14 g, 38%) as a white-yellow solid. R_f = 0.2. ^1H NMR (300 MHz, $CDCl_3$ with 2 drops of CD_3OD) δ: 6.61 (d, J = 8.1 Hz, 1H), 6.49 (d, J = 8.1 Hz, 1H),

4.17 (d, J = 7.5 Hz, 1H), 3.39–0.45 (20 H). ESI−MS m/z: 343 (MH^+). An additional 0.64 g (12%) of material consisting of a mixture of the α and β diastereomers was isolated. Repeated chromatography gave an analytical sample of the α diastereomer, compound **7b**. R_f = 0.16. ^{1}H NMR δ: 6.65 (d, J = 8.1 Hz, 1H), 6.46 (d, J = 8.1 Hz, 1H), 4.50 (d, J = 3.0 Hz, 1H), 3.34 (dt, J = 3.9, 12.6 Hz, 1H), 3.04 (t, J = 6.6 Hz, 1H), 2.95 (s, 1H), 2.63–0.29 (17H). ESI−MS m/z: 343 (MH^+).

General Procedure for the Amidation of Naltrexamine with an Acid Chloride. Naltrexamine (104 mg, 0.3 mmol) was dissolved in CH_2Cl_2 (4 mL) and NEt_3 (0.13 mL, 0.93 mmol), and substituted benzoyl chlorides (0.73 mmol) were added. The solution was stirred for 2 h at room temperature and concentrated to dryness. The residue was filtered through a column of SiO_2 [20:1 CH_2Cl_2/MeOH (v/v)]. The resulting solid was dissolved in anhydrous methanol (3 mL), and K_2CO_3 (300 mg) was added. The mixture was stirred at room temperature for 12 h, concentrated, and purified by SiO_2 chromatography.

General Procedure for the Amidation of Naltrexamine with a Carboxylic Acid. Naltrexamine (100 mg, 0.29 mmol), substituted benzoic acid (0.58 mmol), and BOP (258 mg, 0.58 mmol) were dissolved in CH_2Cl_2 (3 mL). To this solution, i-Pr_2EtN (0.15 mL, 0.88 mmol) was added and the mixture was stirred at room temperature for 2 h. The solution was concentrated and filtered through a short column of SiO_2 (eluted with EtOAc) providing a white material. This product was dissolved in MeOH (3 mL), and K_2CO_3 (300 mg) was then added. The mixture was stirred at room temperature for 3 h and concentrated to dryness. The residue was purified by SiO_2 chromatography [20:1 CH_2Cl_2/MeOH (v/v)] to provide the target compound.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6α-[(2′,3′,4′,6′-tetra-*O*-benzyl-D-glucopyranosyl)acetamido]morphinan (8). The tetra-*O*-benzyl amide was prepare according to the general procedure described above; α-naltrexamine (110 mg, 0.32 mmol), 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl-1-β-1-acetic acid (283 mg, 0.49 mmol), BOP (215 mg, 0.49 mmol), and i-Pr_2EtN (0.17 mL, 0.98 mmol) were combined to produce the target compound, and this was followed by basic hydrolysis with K_2CO_3 (278 mg, 2 mmol) to give the intermediate tetra-*O*-benzyl amide, compound **8**, as a white solid (254 mg, 87%). R_f = 0.11 [30:1 $CHCl_3$/MeOH (v/v)]. ^{1}H NMR ($CDCl_3$) δ: 7.31–7.06 (m, 2H), 6.76 (d, J = 8.2 Hz, 1H), 6.71 (d, J = 8.2 Hz, 1H), 4.94–4.38 (m, 10H), 3.86–3.79 (m, 3H), 3.25–1.40 (m, 20H), 1.08 (m, 1H), 0.81 (m, 2H), 0.45 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 170.4, 143.6, 138.1, 137.6, 128.4, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 118.9, 93.8, 86.8, 81.0, 78.4, 75.8, 75.7, 75.2, 75.0, 73.2, 70.1, 59.2, 50.9, 30.2, 4.1, 3.9. ESI−MS m/z 907 (MH^+). HRMS Calcd for $C_{56}H_{62}N_2O_9$, 907.4534; found, 907.4548.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6α-[(D-glucopyranosyl)acetamido]morphinan (9). The tetra-*O*-benzyl amide, **8** (100 mg, 0.11 mmol), was stirred under an atmosphere of hydrogen gas in the presence of 10% Pd−C (100 mg) and concentrated HCl (0.01 mL) for 12 h, filtered through a pad of celite (eluted with MeOH, 100 mL), and concentrated to dryness. The resulting residue was triturated with ether (3 × 2 mL), providing a white solid (37 mg, 62%) of compound **9**. R_f = 0.06 [25:5:1 CH_3CN/MeOH/NH_4OH (v/v/v)]. mp > 300 °C (dec). ^{1}H NMR (CD_3OD) δ: 6.75 (d, J = 8.2 Hz, 1H), 6.67 (d, J = 8.2 Hz, 1H), 4.68 (d, J = 3.8 Hz, 1H), 3.91–3.55 (m, 5H), 3.28–2.38 (m, 7H), 1.89–1.53 (m, 4H), 1.08 (m, 1H), 0.81 (m, 2H), 0.47 (m, 2H). HRMS Calcd for $C_{28}H_{38}N_2O_9$, 547.2656; found, 547.2646.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-(D-glucopyranosyl)acetamido]morphinan (10). Compound **10** was prepared according to the general procedure described above; combining β-naltrexamine (66 mg, 0.19 mmol), 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl-1-β-1-acetic acid (170 mg, 0.29 mmol), BOP (129 mg, 0.29 mmol), and i-Pr_2EtN (0.1 mL, 0.58 mmol) as above for 2 h gave the phenolic amide as a white solid (104 mg, 59%). The phenolic ester C-6 amide side product was not observed by MS or TLC analysis of this sample. R_f = 0.14 [30:1 $CHCl_3$/MeOH (v/v)]. ESI−MS m/z: 907 (MH^+). A solution of the phenolic amide (100 mg, 0.11 mmol) in anhydrous methanol (4 mL) was stirred under an atmosphere of hydrogen gas in the presence of 10% activated Pd−C (100 mg) and concentrated HCl (10 μL) for 12 h. The mixture was filtered through a pad of celite (eluted with MeOH), and the filtrate was concentrated to dryness. The resulting residue was triturated with ether, and this afforded a white solid (49 mg, 82%). mp = 250 °C. R_f = 0.80 [5:4:0.5:0.5 $CHCl_3$/MeOH/NH_4OH/H_2O (v/v/v/v)]. ^{1}H NMR (CD_3OD) δ: 6.73 (d, J = 8.2 Hz, 1H), 6.65 (d, J = 8.2 Hz, 1H), 4.60 (d, J = 7.8 Hz, 1H), 3.92–3.53 (m, 5H), 3.28–1.53 (m, 11H), 1.08 (m, 1H), 0.81 (m, 2H), 0.47 (m, 2H). ^{13}C NMR (CD_3OD) δ: 173.6, 143.4, 142.7, 130.5, 121.7, 120.9, 119.5, 92.2, 81.5, 79.4, 77.9, 75.0, 71.9, 71.2, 64.2, 63.0, 58.8, 52.6, 47.5, 40.2, 31.1, 28.9, 24.6 (2C), 7.0, 6.4, 3.6. ESI−MS m/z: 547 (MH^+). HRMS Calcd for $C_{28}H_{38}N_2O_9$, 547.2656; found, 547.2650.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[(4′-chloro)benzamido]morphinan (11). Compound **11** was synthesized according to the general procedure described above; combining β-naltrexamine (100 mg, 0.29 mmol), 4-chlorobenzoic acid (68 mg, 0.44 mmol), BOP (190 mg, 0.44 mmmol), and i-Pr_2EtN (0.16 mL, 0.87 mmol) followed by basic hydrolysis with K_2CO_3 gave the title compound as a white solid (28 mg, 20%). mp = 188.8 °C. R_f = 0.06 [30:1 $CHCl_3$/MeOH (v/v)]. ^{1}H NMR [9:1 $CDCl_3$/CD_3OD (v/v)] δ: 7.77 (d, J = 7.8 Hz, 2H), 7.40 (d, J = 7.8 Hz, 2H), 6.70 (d, J = 8.4 Hz,, 2H), 6.51 (d, J = 8.4 Hz, 1H), 4.40 (d, J = 6.6 Hz, 1H), 4.15–4.05 (m, 1H), 3.10–1.35 (m, 11H), 0.50 (m, 2H), 0.10 (m, 2H). ^{13}C NMR [9:1 $CDCl_3$/CD_3OD (v/v)] δ: 166.8, 142.6, 139.7, 137.6, 132.3, 130.2, 128.5, 128.4, 123.7, 118.9, 118.3, 92.7, 70.5, 62.1, 59.0, 50.8, 47.3, 43.8, 31.2, 29.4, 23.9, 22.5, 9.3, 3.9, 3.7. ESI−MS m/z: 481 (MH^+). HRMS Calcd for $C_{27}H_{29}ClN_2O_4$, 481.1894; found, 481.1879.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[(3′,4′-dichloro)benzamido]morphinan (12). Compound **12** was prepared according to the general procedure described above; combining β-naltrexamine (100 mg, 0.29 mmol), 3,4-dichlorobenzoyl chloride (153 mg, 0.73 mmol), and Et_3N (0.15 mL, 0.1 mmol) for 2 h followed by basic hydrolysis with K_2CO_3 (1 g) gave the title compound as a white solid (138 mg, 92%). mp = 108.6 °C. R_f = 0.36 [10:1 CH_2Cl_2/MeOH (v/v)]. ^{1}H NMR ($CDCl_3$) δ: 7.93 (d, J = 1.8 Hz, 1H), 7.67–7.64 (m, 2H), 7.42 (d, J = 8.4 Hz, 1H), 6.60 (d, J = 8.1 Hz, 1H), 6.51 (d, J = 8.1 Hz, 1H), 4.71 (d, J = 6.3 Hz, 1H), 3.99–3.93 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 164.7, 142.2, 139.1, 135.6, 133.8, 132.6, 130.4, 130.2, 129.2, 126.2, 124.5, 119.3, 117.5, 92.3, 70.3, 62.2, 59.3, 51.2, 47.4, 43.9, 31.6, 29.4, 23.5, 22.7, 9.5, 4.1, 4.0. ESI−MS m/z: 516 (MH^+). HRMS Calcd for $C_{27}H_{28}Cl_2N_2O_4$, 515.1505; found, 515.1498.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[(3′-hydroxy)benzamido]morphinan (13). Compound **13** was synthesized according to the general procedure described above; combining β-naltrexamine (100 mg, 0.29 mmol), 3-hydroxybenzoic acid (105 mg, 0.58 mmol), BOP (258 mg, 0.58 mmol), and i-Pr_2EtN (0.15 mL, 0.88 mmol) followed by basic hydrolysis with K_2CO_3 gave the title compound as a white solid (90 mg, 67%). mp = 194.7 °C. R_f = 0.11 [15:1 $CHCl_3$/MeOH (v/v)]. ^{1}H NMR ($CDCl_3$) δ: 7.59 (d, J = 9.0 Hz, 1H), 7.26–7.23 (m, 3H), 6.97–6.94 (m, 1H), 6.70 (d, J = 8.1 Hz, 1H); 6.54 (d, J = 8.1 Hz, 1H), 4.40 (d, J = 6.3 Hz, 1H), 4.15–4.10 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 167.6, 156.5, 142.6, 139.6, 134.7, 130.5, 129.6, 124.1, 119.4, 119.1, 118.1, 117.8, 115.3, 93.5, 70.4, 62.2, 59.2, 51.4, 47.6, 44.0, 31.2, 29.8, 24.3, 22.7, 9.5, 4.2, 3.9. ESI−MS m/z: 463 (MH^+). HRMS Calcd for $C_{27}H_{30}N_2O_5$, 463.2233; found, 463.2225.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6α-[(3′-methoxy)benzamido]morphinan (14). Compound **14** was prepared according to the general procedure described above; combining α-naltrexamine (104 mg, 0.3 mmol), 3-methoxybenzoyl chloride (0.1 mL, 0.73 mmol), and Et_3N (0.13 mL, 0.93 mmol) for 2 h followed by basic hydrolysis with K_2CO_3 (300 mg) gave the title compound as a white solid (134 mg, 92%). mp = 249 °C. R_f = 0.20 [20:1 CH_2Cl_2/MeOH (v/v)]. ^{1}H NMR ($CDCl_3$) δ: 7.40–7.28 (m, 4H), 6.70 (d, J = 8.2 Hz, 1H), 6.54 (d, J = 8.2 Hz, 1H), 4.52 (d, J = 5.7 Hz, 1H), 4.18 (m, 1H), 3.81 (s, 3H). ^{13}C NMR δ: 166.1,

159.6, 143.0, 139.1, 135.8, 130.6, 129.3, 124.6, 119.0, 118.8, 117.6, 117.5, 112.3, 92.8, 70.0, 62.2, 59.3, 55.4, 50.3, 47.3, 43.9, 31.8, 29.1, 23.3, 22.7, 9.5, 4.1, 3.9. ESI−MS *m/z*: 477 (MH^+). HRMS Calcd for $C_{28}H_{32}N_2O_5$, 477.2390; found, 477.2392.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-(benzamido)morphinan (15). Compound **15** was synthesized according to the general procedure described above; β-naltrexamine (100 mg, 0.29 mmol), benzoic acid (71 mg, 0.58 mmol), BOP (258 mg, 0.58 mmol), and *i*-Pr_2EtN (0.15 mL, 0.88 mmol) were combined, and basic hydrolysis with K_2CO_3 (1 g) provided the title compound as a white solid (55 mg, 42%). mp = 139.2 °C. R_f = 0.12 [20:1 CH_2Cl_2/MeOH (v/v)]. ^{1}H NMR ($CDCl_3$) δ: 7.77–7.74 (m, 2H), 7.42–7.32 (m, 3H), 6.62 (d, *J* = 8.1 Hz, 1H), 6.47 (d, *J* = 8.1 Hz, 1H), 4.37 (d, *J* = 6.6 Hz, 1H), 4.05 (m, 1H). ^{13}C ($CDCl_3$) δ: 166.9, 143.1, 139.6, 134.2, 131.4, 130.3, 128.4, 127.0, 123.8, 119.1, 117.9, 92.8, 70.1, 62.2, 59.2, 50.2, 47.1, 44.4, 31.2, 29.3, 23.3, 22.9, 8.9, 4.3, 3.9. ESI−MS *m/z*: 447 (MH^+). HRMS Calcd for $C_{27}H_{30}N_2O_4$, 447.2284; found, 447.2284.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[(3′-nitro)benzamido]morphinan (16). Compound **16** was synthesized according to the general procedure described above; combining β-naltrexamine (100 mg, 0.29 mmol), 3-nitrobenzoyl chloride (135 mg, 0.73 mmol), and Et_3N (0.15 mL, 1.1 mmol) for 2 h followed by basic hydrolysis with K_2CO_3 (1 g) gave the title compound as a white solid (72 mg, 50%). mp = 291 °C. R_f = 0.36 [10:1 CH_2Cl_2/MeOH (v/v)]. ^{1}H NMR ($CDCl_3$) δ: 8.67 (m, 1H), 8.30–8.24 (m, 2H), 7.94 (d, *J* = 8.7 Hz, 1H), 7.59 (d, *J* = 9 Hz, 1H), 6.52 (d, *J* = 8.1 Hz, 1H), 6.46 (d, *J* = 8.1 Hz, 1H), 4.81 (d, *J* = 6 Hz, 1H), 4.06–3.97 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 164.4, 148.0, 142.0, 139.0, 135.7, 133.4, 130.5, 129.4, 125.8, 124.7, 121.9, 119.3, 117.2, 92.3, 70.3, 62.1, 59.4, 51.3, 47.4, 43.8, 31.6, 29.4, 23.4, 22.7, 9.5, 4.1, 4.0. ESI−MS *m/z*: 492 (MH^+). HRMS Calcd for $C_{27}H_{29}N_3O_6$, 492.2135; found, 492.2124.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6α-[(3′, 5′-dimethoxy)benzamido]morphinan (17). Compound **17** was synthesized according to the general procedure described above; combining α-naltrexamine (75 mg, 0.22 mmol), 3,5-dimethoxybenzoic acid (76 mg, 0.42 mmol), BOP (193 mg, 0.43 mmol), and *i*-Pr_2EtN (0.11 mL, 0.63 mmol) for 2 h followed by hydrolysis with K_2CO_3 (300 mg) gave the title compound as a white solid (101 mg, 91%). R_f = 0.20 [10:1 CH_2Cl_2/MeOH (v/v)]. mp = 221 °C. ^{1}H NMR ($CDCl_3$) δ: 6.84 (s, 1H), 6.83 (s, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.55–6.53 (m, 1H), 6.46 (d, *J* = 8.4 Hz, 1H), 4.77–4.70 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 166.7, 160.5, 144.9, 137.0, 136.8, 130.9, 126.0, 119.2, 117.0, 104.9, 103.3, 90.3, 69.5, 62.1, 59.7, 55.6, 47.3, 46.7, 43.2, 33.6, 29.1, 22.9, 21.1, 9.5, 4.1, 4.0. ESI−MS *m/z*: 507 (MH^+). HRMS Calcd for $C_{29}H_{34}N_2O_6$, 507.2495; found, 507.2481.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6α-(benzamido)morphinan (18). Compound **18** was synthesized according to the general procedure described above; combining α-naltrexamine (30 mg, 0.09 mmol), benzoic acid (21 mg, 0.18 mmol), BOP (77 mg, 0.18 mmol), and *i*-Pr_2EtN (0.05 mL, 0.26 mmol) for 2 h followed by basic hydrolysis with K_2CO_3 (300 mg) gave the title compound as a white solid (17 mg, 43%). mp = 121.5 °C. R_f = 0.17 [10:1 CH_2Cl_2/MeOH (v/v)]. ^{1}H NMR ($CDCl_3$) δ: 7.77–7.74 (m, 2H), 7.48–7.34 (m, 3H), 6.64 (d, *J* = 8.4 Hz, 1H), 6.50 (d, *J* = 8.4 Hz, 1H), 4.71–4.63 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 167.6, 145.2, 137.5, 134.0, 131.2, 130.5, 128.1, 127.0, 125.0, 119.0, 117.0, 89.6, 69.5, 61.9, 59.4, 47.0, 46.5, 43.1, 33.3, 29.1, 22.7, 20.7, 9.1, 4.0, 3.6. HRMS Calcd for $C_{27}H_{30}N_2O_4$, 447.2284; found, 447.2276.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[(4′-carbomethoxy)benzamido]morphinan (19). Compound **19** was synthesized according to the general procedure described above; combining β-naltrexamine (100 mg, 0.29 mmol), 4-carbomethoxybenzoic acid (105 mg, 0.58 mmol), BOP (258 mg, 0.58 mmol), and *i*-Pr_2EtN (0.15 mL, 0.88 mmol) for 2 h followed by basic hydrolysis with K_2CO_3 (1 g) gave the title compound as a white solid (118 mg, 80%). R_f = 0.12 [10:1 CH_2Cl_2/MeOH (v/v)]. mp = 156.2 °C. ^{1}H NMR ($CDCl_3$/CD_3OD, 9:1) δ: 7.96 (d, *J* = 8.8 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 1H), 6.57 (d, *J* = 7.8 Hz, 1H), 6.44 (d, *J* = 7.8 Hz, 1H), 4.37 (d, *J* = 7.2 Hz, 1H), 3.92 (m, 1H), 3.81 (s, 3H). ^{13}C NMR (9:1 $CDCl_3$/CD_3OD) δ: 166.9, 166.3, 142.5, 139.7, 138.0, 132.4, 130.2, 129.4, 127.1, 123.7, 118.9, 118.2, 92.6, 70.5, 62.0, 59.0, 52.3, 50.9, 47.3, 43.8, 31.1, 29.4, 23.9, 22.5, 9.3, 3.9, 3.7. ESI−MS *m/z*: 505 (MH^+). HRMS Calcd for $C_{29}H_{32}N_2O_6$, 505.2339; found, 505.2330.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[(3′,5′-dimethoxy)benzamido]morphinan (20). Compound **20** was synthesized according to the general procedure described above; β-naltrexamine (100 mg, 0.29 mmol), 3,5-dimethoxybenzoic acid (106 mg, 0.58 mmol), BOP (258 mg, 0.58 mmol), and *i*-Pr_2EtN (0.15 mL, 0.88 mmol) were combined and basic hydrolysis with K_2CO_3 (1 g) provided the title compound (140 mg, 95%) as a white solid. mp = 146.7 °C. R_f = 0.27 [20:1 CH_2Cl_2/MeOH (v/v)]. ^{1}H NMR ($CDCl_3$) δ: 6.95 (s, 1H), 6.94 (s, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 6.55–6.53 (m, 2H), 4.53 (d, *J* = 5.4 Hz, 1H), 4.20–4.11 (m, 1H), 3.80 (s, 6H). ^{13}C NMR ($CDCl_3$) δ: 166.7, 160.6, 142.9, 139.1, 136.5, 130.6, 124.6, 119.1, 117.5, 104.9, 103.5, 92.9, 70.1, 62.2, 59.3, 55.6, 50.4, 47.3, 43.9, 31.7, 29.1, 23.4, 22.7, 9.5, 4.1, 3.9. ESI−MS *m/z*: 507 (MH^+). HRMS Calcd for $C_{29}H_{34}N_2O_6$, 507.2495; found, 507.2485.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[(2′-pyridyl)acetamido]morphinan (21). Compound **21** was synthesized according to the general procedure described above; combining β-naltrexamine (100 mg, 0.29 mmol), nicotinoyl chloride hydrochloride (130 mg, 0.73 mmol), and Et_3N (0.15 mL, 1.1 mmol) for 2 h followed by basic hydrolysis with K_2CO_3 (1 g) gave the title compound as a white solid (81 mg, 61%). mp = 197.7 °C. R_f = 0.23 [15:1 CH_2Cl_2/MeOH (v/v)]. ^{1}H NMR ($CDCl_3$) δ: 9.01 (d, *J* = 1.5 Hz, 1H), 8.65 (dd, *J* = 1.5, 5.1 Hz, 1H), 8.09–8.05 (m, 1H), 7.80 (d, *J* = 5.1 Hz, 1H), 7.32–7.28 (m, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.56 (d, *J* = 8.1 Hz, 1H), 4.59 (d, *J* = 5.7 Hz, 1H), 4.14 (m, 1H). ^{13}C ($CDCl_3$) δ: 164.9, 151.5, 147.7, 143.0, 139.5, 135.5, 130.5, 130.1, 124.3, 123.4, 119.2, 117.9, 92.3, 70.2, 62.2, 59.3, 50.7, 47.4, 44.0, 31.7, 29.2, 23.5, 22.7, 9.5, 4.2, 3.9. ESI−MS *m/z*: 448 (MH^+). HRMS Calcd for $C_{26}H_{29}N_3O_4$, 448.2236; found, 448.2233.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[(4′-amino)benzamido]morphinan (22). 17-Cyclopropylmethyl-3, 14β-dihydroxy-4, 5α-epoxy-6β-[(4′-tert-butoxycarbonylamino)benzamido]morphinan (**24**) (71 mg, 0.13 mmol) was dissolved in CH_2Cl_2 (2 mL), and TFA (2 mL) was added. The solution was stirred at room temperature for 1 h before the liquids were removed under a stream of nitrogen. The residue was filtered through a pipet column of SiO_2 [10:1:0.2 $CHCl_3$/MeOH/NH_4OH (v/v/v)] and concentrated. The residue was triturated with ether to provide the title compound as a white solid (30 mg, 52%). mp = 215.8 °C. R_f = 0.24 [10:1 $CHCl_3$/MeOH (v/v)]. ^{1}H NMR (9:1 $CDCl_3$/MeOH) δ: 8.05 (d, *J* = 8.7 Hz, 1H); 7.72 (d, *J* = 6.9 Hz, 2H), 6.82–6.63 (m, 4H), 4.59 (d, *J* = 7.2 Hz, 1H), 4.10 (m, 1H). ^{13}C NMR (CD_3OD) δ: 170.0, 153.2, 143.7, 142.8, 130.7, 129.9, 122.7, 121.7, 120.7, 119.6, 114.5, 92.2, 79.4, 71.3, 64.3, 58.7, 53.0, 52.9, 31.2, 28.9, 24.9, 24.5, 6.9, 6.2, 3.4. ESI−MS *m/z*: 461 (MH^+). HRMS Calcd for $C_{27}H_{31}N_3O_4$, 461.2440; found, 461.2439.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[(3′-methoxy)benzamido]morphinan (23). Compound **23** was synthesized according to the procedure described above; combining β-naltrexamine (104 mg, 0.3 mmol), NEt_3 (0.13 mL, 0.93 mmol), and 3-methoxybenzoyl chloride (0.1 mL, 0.73 mmol) for 2 h followed by basic hydrolysis with K_2CO_3 afforded a white solid (134 mg, 92%). mp = 249 °C. R_f = 0.20 [20:1 CH_2Cl_2/MeOH (v/v)]. ^{1}H NMR ($CDCl_3$) δ: 7.40–7.28 (m, 4H), 6.70 (d, *J* = 8.2 Hz, 1H), 6.54 (d, *J* = 8.2 Hz, 1H), 4.52 (d, *J* = 5.7 Hz, 1H), 4.18 (m, 1H), 3.81 (s, 3H). ^{13}C NMR δ: 166.1, 159.6, 143.0, 139.1, 135.8, 130.6, 129.3, 124.6, 119.0, 118.8, 117.6, 117.5, 112.3, 92.8, 70.0, 62.2, 59.3, 55.4, 50.3, 47.3, 43.9, 31.8, 29.1, 23.3, 22.7, 9.5, 4.1, 3.9. ESI−MS *m/z*: 477 (MH^+). HRMS Calcd for $C_{28}H_{32}N_2O_5$, 477.2390; found, 477.2385.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[(4′-*tert*-butoxycarbonylamino)benzamido]morphinan (24). Compound **24** was prepared according to the general procedure described

above; combining β-naltrexamine (100 mg, 0.29 mmol), 4-(tert-butoxycarbonylamino)benzoic acid (138 mg, 0.58 mmol), BOP (258 mg, 0.58 mmol), and *i*-Pr_2EtN (0.15 mL, 0.88 mmol) for 2 h followed by basic hydrolysis with K_2CO_3 (1 g) gave the title compound as a white foam (154 mg, 94%). mp = 193.5 °C. R_f = 0.10 [20:1 CH_2Cl_2/MeOH (v/v)]. ^{1}H NMR ($CDCl_3$) δ: 7.76 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.29 (d, *J* = 9 Hz, 1H), 6.89 (s, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 6.55 (d, *J* = 8.2 Hz, 1H), 4.53 (d, *J* = 6 Hz, 1H), 4.20 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 166.3, 152.1, 143.1, 141.3, 139.1, 137.2, 130.5, 128.4, 128.1, 124.6, 119.0, 117.6, 92.9, 81.0, 70.2, 62.2, 59.3, 50.2, 47.2, 44.0, 31.8, 29.1, 28.4, 23.4, 22.7, 9.5, 4.2, 3.9. ESI−MS *m*/*z*: 562 (MH^+). HRMS Calcd for $C_{32}H_{39}N_3O_6$, 562.2917; found, 562.2900.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6-[(3′-dimethylamino)benzamido]morphinan (25). Compound **25** was synthesized according to the general procedure described above; combining β-naltrexamine (50 mg, 0.15 mmol), 3-(dimethylamino)benzoic acid (27 mg, 0.16 mmol), BOP (71 mg, 0.16 mmol), and *i*-Pr_2EtN (0.09 mL, 0.51 mmol) followed by basic hydrolysis with K_2CO_3 provided the desired product as a white solid (57 mg, 80%) after flash chromatography [10:1 $CHCl_3$/MeOH (v/v)]. R_f = 0.16. ESI−MS *m*/*z* 490 (MH^+). ^{1}H NMR (D_2O) δ: 7.99 (s, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.74 (m, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 4.10 (d, *J* = 5.7 Hz, 1H), 3.94–2.76 (m, 9H), 2.61 (d, *J* = 9.5, 6H), 2.00–1.67 (m, 5H), 1.11 (m, 2H), 0.75 (m, 2H), 0.47 (m, 2H). HRMS Calcd for $C_{29}H_{36}N_3O_4$, 490.2706; found, 490.2694.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[(4′-carboxy)benzamido]morphinan (26). The methyl ester **19** (74 mg, 0.15 mmol) was dissolved in 1:1 THF/H_2O (4 mL), and LiOH (62 mg, 1.47 mmol) was added. The solution was stirred at room temperature for 18 h. The pH was reduced to 5 with 10% HCl, and the solution was concentrated. The residue was purified by SiO_2 chromatography providing the title compound as a white solid (49 mg, 72%). R_f = 0.28 [2:1 $CHCl_3$/MeOH (v/v)]. mp >300 °C (dec). ^{1}H NMR (CD_3OD) δ: 8.00 (d, *J* = 8.1 Hz, 2H), 7.82 (d, *J* = 8.1 Hz, 2H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.59 (d, *J* = 8.1 Hz, 1H), 4.65 (d, *J* = 7.5 Hz, 1H), 4.60 (m, 1H). ESI−MS *m*/*z*: 491 (MH^+). HRMS Calcd for $C_{28}H_{31}N_2O_6$, 491.2182; found, 491.2178.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-(cinnamoylacetamido)morphinan (27). Compound **27** was synthesized according to the general procedure described above; β-naltrexamine (100 mg, 0.29 mmol), *trans*-cinnamoyl chloride (124 mg, 0.73 mmol), and Et_3N (0.15 mL, 1.1 mmol) were combined for 2 h followed by basic hydrolysis with K_2CO_3 (1 g) gave the title compound as a white solid (91 mg, 66%). mp = 248 °C (dec). R_f = 0.33 [15:1 CH_2Cl_2/MeOH (v/v)]. ^{1}H NMR ($CDCl_3$) δ: 7.60 (d, *J* = 15.6 Hz, 1H), 7.47–7.31 (5H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.53 (d, *J* = 8.1 Hz, 1H), 6.41 (d, *J* = 15.6 Hz, 1H), 4.54 (d, *J* = 6.6 Hz, 1H), 4.06 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 165.6, 142.7, 140.9, 139.4, 134.7, 130.7, 129.5, 128.6, 127.7, 124.6, 120.9, 119.1, 117.5, 93.0, 70.2, 62.2, 59.3, 50.6, 47.5, 44.0, 31.4, 29.5, 23.7, 22.7, 9.5, 4.1, 3.9. ESI−MS *m*/*z*: 473 (MH^+). HRMS Calcd for $C_{29}H_{32}N_2O_4$, 473.2440; found, 473.2433.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-(hydroxycinnamoylacetamido)morphinan (28). Compound **28** was synthesized according to the general procedure described above; combination of β-naltrexamine (100 mg, 0.29 mmol), hydrocinnamoyl chloride (0.11 mL, 0.73 mmol), and Et_3N (0.15 mL, 1.1 mmol) for 2 h followed by basic hydrolysis with K_2CO_3 (1 g) provided the title compound as a white solid (36 mg, 26%). mp = 120.2 °C. R_f = 0.36 [10:1 CH_2Cl_2/MeOH (v/v)]. ^{1}H NMR ($CDCl_3$) δ: 7.31–7.17 (m, 5H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 1H), 6.08 (d, *J* = 9.0 Hz, 1H), 4.28 (d, *J* = 6.6 Hz, 1H), 3.95–3.85 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 172.0, 142.7, 140.6, 139.5, 130.7, 128.4, 128.3, 126.1, 124.4, 119.0, 117.7, 93.3, 70.1, 62.2, 59.2, 50.3, 47.4, 44.0, 38.8, 31.8, 31.2, 29.5, 23.9, 22.7, 9.5, 4.1, 3.9. ESI−MS *m*/*z*: 475 (MH^+). HRMS Calcd for $C_{29}H_{34}N_2O_4$, 475.2597; found, 475.2589.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[(3′-methoxy)phenylacetamido]morphinan (29). Compound **29** was synthesized according to the general procedure described above; combining β-naltrexamine (100 mg, 0.29 mmol), 3-methoxyphenylacetyl chloride (0.11 mL, 0.29 mmol), and Et_3N (0.15 mL, 1.1 mmol) for 2 h followed by basic hydrolysis with K_2CO_3 (1 g) gave the title compound as a white solid (82 mg, 57%). mp = 118.1 °C. R_f = 0.38 [10:1 CH_2Cl_2/MeOH (v/v)]. ^{1}H NMR ($CDCl_3$) δ: 7.29–7.24 (m, 1H), 6.86–6.83 (m, 2H), 6.71 (d, *J* = 8.1 Hz, 1H), 6.54 (d, *J* = 8.1 Hz, 1H), 6.06 (d, *J* = 9.3, 1H), 4.25 (d, *J* = 6.9 Hz, 1H), 3.90 (m, 1H), 3.88 (s, 3H), 3.55 (s, 2H). ^{13}C NMR ($CDCl_3$) δ: 170.8, 159.8, 142.5, 139.6, 136.2, 130.7, 129.9, 124.4, 121.7, 119.0, 117.5, 115.1, 112.6, 93.2, 70.1, 62.2, 59.2, 55.3, 50.8, 47.5, 44.0, 31.0, 29.7, 24.0, 22.7, 9.5, 4.1, 3.9. ESI−MS *m*/*z*: 491 (MH^+). HRMS Calcd for $C_{29}H_{34}N_2O_5$, 491.2546; found, 491.2531.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-(benzylacetamido)morphinan (30). Compound **30** was synthesized according to the general procedure described above; combining β-naltrexamine (100 mg, 0.29 mmol), phenylacetyl chloride (0.98 mL, 0.73 mmol), and Et_3N (0.15 mL, 1.1 mmol) for 2 h followed by basic hydrolysis with K_2CO_3 (1 g) gave the title compound as a white solid (48 mg, 36%). mp = 154.3 °C. R_f = 0.33 [10:1 CH_2Cl_2/MeOH (v/v)]. ^{1}H NMR δ: 7.39–7.25 (m, 5H), 6.72 (d, *J* = 8.1 Hz, 1H), 6.55 (d, *J* = 8.1 Hz, 1H), 6.06 (d, *J* = 9.0 Hz, 1H), 4.25 (d, *J* = 6.9 Hz, 1H), 3.93–3.86 (m, 1H), 3.59 (s, 2H). ^{13}C NMR ($CDCl_3$) δ: 171.0, 142.6, 139.6, 134.7, 130.7, 129.4, 128.9, 127.2, 124.3, 119.0, 117.6, 93.2, 70.1, 62.2, 59.2, 50.7, 47.5, 44.0, 43.9, 31.0, 29.6, 23.9, 22.7, 9.4, 4.1, 3.9. ESI−MS *m*/*z*: 461 (MH^+). HRMS Calcd for $C_{28}H_{33}N_2O_4$, 461.2440; found, 461.2433.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[(4′-methoxy)benzylacetamido]morphinan (31). Compound **31** was synthesized according to the general procedure described above; combining β-naltrexamine (100 mg, 0.29 mmol), 4-methoxyphenylacetyl chloride (0.11 mL, 0.73 mmol), and Et_3N (0.15 mL, 1.1 mmol) for 2 h followed by basic hydrolysis with K_2CO_3 (500 mg) gave the title compound as a white solid (22 mg, 15%). mp = 189 °C. R_f = 0.45 [10:1 CH_2Cl_2/MeOH (v/v)]. ^{1}H NMR ($CDCl_3$) δ: 7.17 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 6.71 (d, *J* = 8.1 Hz, 1H), 6.54 (d, *J* = 8.1 Hz, 1H), 6.02 (d, *J* = 9.3 Hz, 1H), 4.23 (d, *J* = 6.9 Hz, 1H), 3.90 (m, 1H), 3.82 (s, 3H), 3.52 (s, 2H). ^{13}C NMR ($CDCl_3$) δ: 171.3, 158.7, 142.5, 139.6, 130.5, 126.5, 124.5, 119.1, 117.6, 114.4, 93.6, 70.0, 62.2, 59.2, 55.3, 50.7, 47.6, 44.0, 43.1, 30.9, 29.8, 24.2, 22.7, 9.5, 4.1, 3.9. ESI−MS (ESI) *m*/*z*: 491 (MH^+). HRMS Calcd for $C_{29}H_{34}N_2O_5$, 491.2546; found, 491.2547.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[(thiophen-2′-yl)acetamido]morphinan (32). Compound **32** was synthesized according to the general procedure described above; combining β-naltrexamine (100 mg, 0.29 mmol), 2-thiopheneactyl chloride (0.07 mL, 0.58 mmol), and Et_3N (0.12 mL, 0.88 mmol) for 2 h followed by basic hydrolysis with K_2CO_3 (1 g) gave the title compound as a white solid (30 mg, 22%). mp = 188.8 °C. R_f = 0.35 [20:1 CH_2Cl_2/MeOH (v/v)]. ^{1}H NMR ($CDCl_3$) δ: 7.25–7.21 (m, 1H), 6.99–6.92 (m, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.53 (d, *J* = 8.5 Hz, 1H), 6.40 (d, *J* = 8.5 Hz, 1H), 4.30 (d, *J* = 6.6 Hz, 1H), 3.93–3.82 (m, 1H), 3.77 (s, 2H). ^{13}C NMR ($CDCl_3$) δ: 169.7, 142.5, 139.6, 135.9, 130.7, 127.4, 127.3, 125.6, 124.5, 119.1, 117.5, 93.2, 70.0, 62.2, 59.2, 50.7, 47.5, 44.0, 37.8, 31.0, 29.7, 24.0, 22.7, 9.5, 4.1, 3.9. ESI−MS *m*/*z*: 467 (MH^+). HRMS Calcd for $C_{26}H_{30}N_2O_4S$, 467.2004; found, 467.1994.

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6α-[(thiophen-2′-yl)acetamido]morphinan (33). Compound **33** was synthesized according to the general procedure described above; combining α-naltrexamine (40 mg, 0.18 mmol), 2-thiopheneacetyl chloride (0.03 mL, 0.23 mmol), and Et_3N (0.05 mL, 0.35 mmol) for 2 h followed by basic hydrolysis with K_2CO_3 (300 mg) gave the title compound as a white-yellow solid (30 mg, 55%). mp = 79.8 °C; R_f = 0.17 [20:1 CH_2Cl_2/MeOH (v/v)]. ^{1}H NMR δ: 7.29–7.25 (m, 1H), 7.00 (dd, *J* = 3.6, 5.1 Hz, 1H), 6.93 (d, *J* = 3.6 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 6.52 (d, *J* = 8.4 Hz, 1H), 4.61 (d, *J* = 3.9 Hz, 1H), 4.60–4.47 (m, 1H), 3.78 (s, 2H). ^{13}C

NMR ($CDCl_3$) δ: 169.1, 144.8, 137.0, 136.4, 130.8, 127.2, 127.1, 125.9, 125.4, 119.2, 116.9, 90.1, 69.4, 62.1, 59.6, 47.2, 46.2, 43.2, 37.7, 33.4, 29.0, 22.9, 21.1, 9.4, 4.1, 3.9. ESI−MS *m/z*: 467 (MH^+). HRMS Calcd for $C_{26}H_{30}N_2O_4S$, 467.2004; found, 467.1991.

Receptor Binding and Functional Experiments. Receptor-binding studies were conducted on human opioid receptors transfected into Chinese hamster ovary (CHO) cells. The μ cell line was maintained in Ham's F-12 medium supplemented with 10% fetal bovine serum (FBS) and 400 μg/mL Geneticin (G418). The δ and the κ cell lines were maintained in Dulbecco's minimal essential medium (DMEM) supplemented with 10% FBS, 400 μg/mL G418, and 0.1% penicillin/streptomycin. All cell lines were grown to confluence and then harvested for membrane preparation. The membranes for functional assays were prepared in buffer A (20 mM HEPES, 10 mM $MgCl_2$, and 100 mM NaCl at pH 7.4), and the membranes for binding assays were prepared in 50 mM Tris buffer (pH 7.7). Cells were scraped from the plates and centrifuged at 500*g* for 10 min. The cell pellet was homogenized in buffer with a polytron, centrifuged at 20000*g* for 20 min, washed, recentrifuged, and finally resuspended at 3 mg of protein/mL in buffer to determine the protein content. The homogenate was then stored at −70 °C in 1 mL aliquots.

Binding assays were conducted using [^{3}H]DAMGO, [^{3}H]C1-DPDPE, and [^{3}H]U69,593 at the μ, δ, and κ receptors, respectively. The assay was performed in triplicate in a 96-well plate. Nonspecific binding was determined with 1.0 μM of the unlabeled counterpart of each radioligand. Cell membranes were incubated with the appropriate radioligand and test compound at 25 °C for 60 min. The incubation was terminated by rapid filtration through glass fiber filter paper on a Tomtec cell harvester. The filters were dried overnight and bagged with 10 mL scintillation cocktail before counting for 2 min on a Wallac Betaplate 1205 liquid scintillation counter. Full characterization of compounds included analysis of the data for IC_{50} values and Hill coefficients using PRISM. K_i values were calculated using the Cheng Prusoff transformation

$$K_i = \frac{IC_{50}}{1 + L/K_d}$$

where L is the radioligand concentration and K_d is the binding affinity of the radioligand, as determined previously by saturation analysis.

[^{35}S]GTPγS Binding for Functional (Agonist/Antagonist) Determinations. Membranes prepared as described above were incubated with [^{35}S]GTPγS (50 pM), GDP (usually 10 μM), and the test compound, in a total volume of 1 mL, for 60 min at 25 °C.[21] Samples were filtered over glass fiber filters and counted as described for the binding assays. A dose−response curve with a prototypical full agonist (DAMGO, DPDPE, and U69,593 for μ, δ, and κ receptors, respectively) was conducted in each experiment to identify full and partial agonist compounds.

High-affinity compounds (K_i value is 100 nM or less) that showed no agonist activity were tested as antagonists. A Schild analysis[22] was conducted using a full agonist dose−response curve in the presence of at least three concentrations of the antagonist. pA_2 values and Schild slopes were determined using a statistical program designed for these experiments. If the Schild slope was significantly different from −1.00, the antagonist activity was noncompetitive; in such cases, the pA_2 value was not reported. Equilibrium dissociation constants (K_e values) were calculated as follows:

$$K_e = \frac{a}{DR - 1}$$

where a was the nanomolar concentration of the antagonist and DR was the shift of the agonist concentration–response curve to the right in the presence of a given concentration of antagonist.

Rat and Mouse Liver Microsome and Human Liver S-9 Stability Assays. A typical assay mixture contained rat or mouse liver microsomes or human liver S-9 (0.4–0.5 mg of protein), 100 μM potassium phosphate buffer (pH 7.4), 40 μM test compound oxalate salt, an NADPH-generating system consisting of 0.5 mM $NADP^+$, 0.5 mM glucose-6-phosphate, 5 IU/mL glucose-6-phosphate dehydrogenase, 1 mg/mL diethylenetriaminepentaacetic acid (DETAPAC), and 7 mM $MgCl_2$ for a final incubation volume of 0.1 mL. Incubations were run for 0, 10, 25, 40, and 60 min in air with shaking at 37 °C in a water bath and were terminated by the addition of 1 mL CH_2Cl_2/2-propanol (3:1, v/v). After centrifugation at 13 000 rpm for 5 min, the organic fraction was collected and the solvent was removed with a stream of argon. The residue was reconstituted in methanol (200 μL) and centrifuged at 13 000 rpm for 5 min, and the supernatant was analyzed by HPLC with an Axxi-chrom (straight-phase) silica column (4.6 × 250 mm, 5 μm) or with a Supelco (reverse-phase) HS F5 pentafluorophenyl column (4.6 × 250 mm, 5 μm) as described above. Standard conditions used an isocratic, ternary-solvent system consisting of solvents A (methanol), B (isopropanol), and C (aqueous 70% $HClO_4$) set at a flow rate of 1.5 mL/min (straight phase) or A and D (water) and E (HCO_2H) set at a flow rate of 1.0 mL/min (reverse phase), $\lambda = 254$ nm with retention times (t_R) evaluated in minutes. The specific conditions and retention times of each individual compound are specified in the Supporting Information.

CYP Inhibition Assays. To measure CYP3A4 activity, testosterone 6-hydroxylation, was determined by a HPLC method as previously described.[25] To measure CYP2C9, diclofenac hydroxylase activity was measured by a HPLC method.[38] For determination of CYP2B6, CYP2C19, and CYP2D6 activity, isozyme-specific Vivid Blue substrate *O*-dealkylation was determined via a modified Panvera Vivid Assay Protocol as previously described.[25] Briefly, for CYP2B6, -2C19, and -2D6, microsomes containing 1 pmol of CYP were added to 0.05 mM Tris buffer (pH 7.4) containing a NADPH-generating system (i.e., 0.5 mM $NADP^+$, 0.5 mM glucose-6-phosphate dehydrogenase, 1 mg/mL DETAPAC, and 7 mM $MgCl_2$) in a total volume of 100 μL. Test compounds (10 μM) were added, and the substrate (5 μM PanVera Vivid Assay substrate) was added to initiate the incubation after a brief but thorough mixing. Incubations were run in a 96-well plate (BD Falcon Microtest, Black Flat Bottom) for up to 60 min and monitored continuously to follow the linear portion of the fluorescent product versus the time profile using a Wallac Victor^2 Multilabel Counter. The inhibition of the amount of product formed was determined by interpolation from a standard curve and a comparison of the complete system without inhibitor. The average percent inhibition ± standard deviation was calculated from three separate experiments.

***In Vivo* Studies.** Briefly, animals ($n = 5$) were trained to voluntarily self-administer EtOH by the oral route using the saccharin fadeout method[39] and were tested for their response for 10% (w/v) EtOH solution in a two-lever free-choice situation. Once baseline EtOH intake was achieved, blood alcohol levels (BALs) were measured to ensure animals were consuming pharmacologically relevant amounts of EtOH during operant sessions. After positive verification of BALs and an indication of potency with an initial screen, a dose−response profile for each compound was established. To allow for a complete dissipation of any carryover effects, a 1 week washout period, where rats were rebaselined during daily 30 min operant sessions, occurred between testing of each compound.

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Supporting Information Available: Table listing the HPLC retention times and the mobile phase and method for analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Grisel, J. E.; Grahame, N. J.; Mogil, J. S.; Belknap, J. K.; Low, M. J. Decreased voluntary ethanol consumption in transgenic mice lacking β-endorphin. *Soc. Neurosci. Abstr.* **1995**, *21*, 1699.

(2) Gianoulakis, C.; Krishnan, B.; Thavundayil, J. Enhanced sensitivity of pituitary β-endophin to ethanol in subjects at high risk of alcoholism. *Arch. Gen. Psychiatry* **1996**, *53*, 250–257.

(3) Roozen, H. G.; deWaele, R.; van der Windt, D. A.; van der Brink, W.; de Jong, C. A.; Kerkhof, A. J. A systematic review of the effectiveness of naltrexone in the maintenance treatment of opioid and alcohol dependence. *Eur. Neuropsychopharmacol.* **2006**, *16*, 311–323.

(4) Pastor, R.; Aragon, C. M. The role of opioid receptor subtypes in the development of behavioral sensitization to ethanol. *Neuropsychopharmacology* **2006**, *31*, 1489–1499.

(5) Bouza, C.; Angeles, M.; Munoz, A.; Amate, J. M. Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: A systematic review. *Addiction* **2004**, *99*, 811–828.

(6) Croop, R. S.; Faulkner, E. B.; Labriola, D. F. The safety profile of naltrexone in the treatment of alcoholism. Result from a multicenter usage study. The naltrexone usage study group. *Arch. Gen. Psychiatry* **1997**, *54*, 1130–1135.

(7) Mason, B. J.; Salvato, F. R.; Williams, L. D.; Ritvo, E. C.; Cutler, R. B. A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence. *Arch. Gen. Psychiatry* **1999**, *56*, 719–724.

(8) Anton, R. F.; Moak, D. H.; Waid, L. R.; Latham, P. K.; Malcolm, R. J.; Dias, J. K. Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: Results of a placebo-controlled trial. *Am. J. Psychiatry* **1999**, *156*, 1758–1764.

(9) Tabakoff, B.; Hoffman, P. L. Alcohol interactions with brain opiate receptors. *Life Sci.* **1983**, *32*, 197–204.

(10) Garbutt, J. C.; Krantzler, H. R.; O'Malley, S. S.; Gastfriend, D. R.; Pettinati, H. M.; Silverman, B. L.; Loewy, J. W.; Ehrich, E. W. Vivitrex study group. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: A randomized controlled trial. *J. Am. Med. Assoc.* **2005**, *293*, 1617–1625.

(11) Benjamin, D.; Grant, E. R.; Pohorecky, L. A. Naltrexone reverses ethanol-induced dopamine release in the nucleus accumbens in awake freely moving rats. *Brain Res.* **1993**, *621*, 137–140.

(12) Widdowson, P. S.; Holman, R. B. Ethanol-induced increase in endogenous dopamine release may involve endogenous opiates. *J. Neurochem.* **1992**, *59*, 157–163.

(13) Herz, A. Endogenous opioid systems and alcohol addiction. *Psychopharmacology* **1997**, *129*, 99–111.

(14) Ulm, R. R.; Volpicelli, J. R.; Volpicelli, L. A. Opiates and alcohol self-administration in animals. *J. Clin. Psychiatry* **1995**, *56*, 5–14.

(15) Zhang, Y.; McCurdy, C. R.; Metzger, T. G.; Potoghese, P. S. Specific cross-linking of Lys233 and Cys235 in the μ opioid receptor by a reporter affinity label. *Biochemistry* **2005**, *44*, 2271–2275.

(16) Hiroshi, N.; Kuniaki, K.; Takashi, E. Morphinan derivatives and its phramaceutical applications. U.S. Patent 20000541793.

(17) Nagase, H.; Hayakawa, J.; Kawamura, K.; Kawal, K.; Takezawa, Y.; Matsuura, H.; Tajima, C.; Endo, T. Discovery of a structurally novel opioid κ-agonist derived from 4,5-epoxymorphinan. *Chem. Pharm. Bull.* **1998**, *46*, 366–369.

(18) Mohamed, M. S.; Larson, D. L.; Takemori, A. E.; Portoghese, P. S. Activity of *N*-methyl-α- and β-funaltrexamine at opioid receptors. *J. Med. Chem.* **1986**, *29*, 1551–1553.

(19) Ko, R. P.; Gupte, S. M.; Nelson, W. L. Opioid agonists and antagonists. 6,6-Hydrazi and 6-oximino derivatives of 14-hydroxydihydromorphinones. *J. Med. Chem.* **1984**, *27*, 1727–1729. (b) Mohamed, M. S.; Portoghese, P. S. Stereoselectivity of the reduction of naltrexone oxime with borane. *J. Org. Chem.* **1986**, *51*, 105–106.

(20) MacDougall, J. M.; Zhang, X. D.; Polgar, W. E.; Khroyan, T. V.; Toll, L.; Cashman, J. R. Synthesis and biological evaluation of some 6-arylamidomorphines as analogues of morphine-6-glucuronide. *Bioorg. Med. Chem.* **2004**, *12*, 5983–5990.

(21) Traynor, J. R.; Nahorski, S. R. Modulation by μ-opioid agonists of guanosine-5′-*O*-(3-^{35} S]thio)triphosphate binding to membranes from human neuroblastoma SH-SY5Y cells. *Mol. Pharmacol.* **1995**, *47*, 848–854.

(22) Schild, H. O. pA_x and competitive drug antagonism. *Br. J. Pharmacol. Chemother.* **1949**, *4*, 277.

(23) Tullman, R. H.; Hanzlik, R. P. Inactivation of cytochrome P-450 and monoamine oxidase by cyclopropylamines. *Drug Metab. Rev.* **1984**, *15*, 1163–1182.

(24) Bondon, A.; Macdonald, T. L.; Harris, T. M.; Guengerich, F. P. Oxidation of cycloalkylamines by cytochrome P-450. *J. Biol. Chem.* **1989**, *264*, 1988–1997.

(25) Denton, T. T.; Zhang, X. D.; Cashman, J. R. Nicotine-related alkaloids and metabolites as inhibitors of human cytochrome P-450 2A6. *Biochem. Pharmacol.* **2004**, *67*, 751–756.

(26) Cashman, J. R.; MacDougall, J. M. Dynamic medicinal chemistry in the elaboration of morphine-6-glucuronide analogs. *Curr. Top. Med. Chem.* **2005**, *5*, 585–594.

(27) Heyser, C. J.; Schulteis, G.; Koob, G. F. Increased ethanol self-administration after a period of imposed ethanol deprivation in rats trained in a limited access paradigm. *Alcohol.: Clin. Exp. Res.* **1997**, *21*, 784–791.

(28) Heyser, C. J.; Roberts, A. J.; Shulteis, G.; Koob, G. F. Central administration of an opiate antagonist decreases oral ethanol self-administration in rats. *Alcohol.: Clin. Exp. Res.* **1999**, *23*, 1468–1476.

(29) Heyser, C. J.; Moc, K.; Koob, G. F. Effects of natrexone alone and in combination with acamprosate on the alcohol deprivation effect in rats. *Neuropsychopharmacology* **2003**, *28*, 1463–1473.

(30) June, H. L.; Grey, C.; Warren-Reese, C.; Durr, L. F.; Ricks-cord, A.; Johnson, A.; McCane, S.; Williams, L. S.; Mason, D.; Cummings, R.; Lawrence, A. *Alcohol.: Clin. Exp. Res.* **1998**, *22*, 2174–2185.

(31) Roberts, A. J.; Smith, A. D.; Weiss, F.; Rivier, C.; Koob, G. F. Estrous cycle effects on operant responding for ethanol in female rats. *Alcohol.: Clin. Exp. Res.* **1998**, *22*, 1564–1569.

(32) Roberts, A. J.; McDonald, J. S.; Heyser, C. J.; Kieffer, B. L.; Matthes, H. W.; Koob, G. F.; Gold, L. H. μ-Opioid receptor knockout mice do not self-administer alcohol. *J. Pharmacol. Exp. Ther.* **2000**, *293*, 1002–1008.

(33) Holter, S. M.; Spanagel, R. Effects of opiate antagonist treatment on the alcohol deprivation effect in long-term ethanol-experienced rats. *Psychopharmacology* **1999**, *145*, 360–369.

(34) Spanagel, R.; Holter, S. M. Long-term alcohol self-administration with repeated alcohol deprivation phases: An animal model of alcoholism. *Alcohol Alcohol.* **1999**, *34*, 231–243.

(35) MacDougall, J. M.; Zhang, X. D.; Polgar, W. E.; Khroyan, T. V.; Toll, L.; Cashman, J. R. Design, chemical synthesis, and biological evaluation of thiosaccharide analogues of morphine- and codeine-6-glucuronide. *J. Med. Chem.* **2004**, *47*, 5809–5815.

(36) Stevens, W. C.; Jones, R. M.; Subramanian, G.; Metzger, T.; Ferguson, D. M.; Portoghese, P. S. Potent and selective indolomorphinan antagonists of the κ-opioid receptor. *J. Med. Chem.* **2000**, *43*, 2759–2769.

(37) Doss, G. A.; Baillie, T. A. Addressing metabolic activation as an integral component of drug design. *Drug Metab. Rev.* **2006**, *38*, 641–649.

(38) Yano, J. K.; Denton, T. T.; Cerny, M. A.; Zhang, X.; Johnson, E. F.; Cashman, J. R. Synthetic inhibitors of cytochrome P-450 2A6: Inhibitory activity, difference spectra, mechanism of inhibition and protein cocrystalization. *J. Med. Chem.* **2006**, *49*, 6987–7001.

(39) Rassnick, S.; Pulvirenti, L.; Koob, G. F. SDZ-205,152, a novel dopamine receptor agonist, reduces oral ethanol self-administration in rats. *Alcohol* **1993**, *10*, 127–132.

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