10-Ketomorphinan and 3-Substituted-3-desoxymorphinan Analogues as Mixed κ and μ Opioid Ligands: Synthesis and Biological Evaluation of Their Binding Affinity at Opioid Receptors

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Received August 28, 2003

A series of 10-ketomorphinan analogues were synthesized, and their binding affinity at all three opioid receptors was investigated. In most cases, high affinity at μ and κ receptors, and lower affinity at δ receptor was observed, resulting in good selectivity for μ and κ receptors. A wide range of substituents can be accommodated on the nitrogen position. The *N*-(*S*)-tetrahydrofurfuryl analogue **11** displayed the highest affinity at all three receptors. The *N*-cyclobutylmethyl analogue **13** gave both high affinity and selectivity at κ receptor, and *N*-2-phenylethyl analogue **18** exhibited good affinity and selectivity at μ receptor. Further modifications of the 3-substituent indicated that one H-bond donor was an essential requirement for good affinity at μ and κ receptors. Similar modifications were investigated at the 3-OH group of morphinans: levorphanol (**2a)**, cyclorphan (**2b**), and MCL-101 (**2c**) lacking the 10-keto group. The 3-amino bioisosteric analogues (**40** and **41**) displayed reasonably good affinity at μ and κ receptors. The 3-carboxamido replacement (compounds **46**−**48**) in the morphinan subseries resulted in similar affinities comparable to their corresponding 3-OH congeners. The high affinity of these carboxamido analogues, along with their greater lipophilicity and metabolic stability, make them promising candidates for further pharmacological investigation.

Introduction

Opioid receptors (μ, κ, and δ) are distributed throughout the central and peripheral nervous system and are involved in a variety of physiological processes, especially analgesia.[1] Mu (μ) opioid receptor agonists such as morphine are used extensively for the treatment of severe pain, but serious side effects, including respiratory depression, tolerance, withdrawal symptoms, decreased gastric motility, and emesis, are frequently present.[2] Studies with kappa (κ) receptor agonists and antagonists demonstrated that κ receptor ligands can also produce analgesia in animals and humans, but lack respiratory depressant, constipating, and strong addictive (euphoria and physical dependence) properties.[2,3] Self-reward response investigations suggested that μ agonists work upstream in the reward neuronal system by exerting an inhibitory action on GABAergic neurons, thus initiating the self-reward response and causing euphoric stimuli, while κ agonists work at a site more downstream in the system and cause an aversive and dysphoric stimulus.[2,4] These findings led to extensive interests in compounds with combined μ and κ agonist/antagonist properties, which may be effective analgesics and have therapeutic potential for drug abuse and dependence. In fact, the nucleus accumbens, a brain region implicated in the dopaminergic actions of cocaine, contains high level of both κ opioid receptors and highly potent κ opioid endogenous peptides, thus an interaction between dopamine neurons and κ receptors may exist.[5−9] It was suggested that agonists at κ opioid receptors may modulate the activity of dopaminergic neurons and alter the neurochemical and behavioral effects of cocaine.[10−19] Recent studies on the effects of benzomorphan and arylacetamide κ agonists on cocaine self-administration in rhesus monkeys demonstrated that most of these κ agonists with relatively higher efficacy at κ receptors produced a dose-dependent decrease in cocaine self-administration, while a low-efficacy κ agonist or κ antagonist were ineffective.[20,21] Further, nonselective κ agonists such as ethylketocyclazocine **1** (EKC), which produce μ receptor-mediated effects in addition to their κ agonist properties, decreased cocaine self-administration more effectively and with fewer unwanted side effects than highly selective κ agonists.[20−22] All these findings indicated that κ agonists with additional properties at μ receptors may provide a novel approach for the treatment of cocaine abuse and dependence.

In our continuing studies on the development of effective analgesics, and the development of pharmaceutical agents for cocaine abuse, we focused our interests on the structural modification and pharmacological evaluation of analogues of benzomorphans and morphinans (Chart 1), which were known to possess mixed κ agonist and μ agonist/antagonist pharmacological profiles.[20−24] We have recently developed a series of N-substituted benzomorphan and morphinan derivatives, with varying *N*-alkyl substituents, a number of

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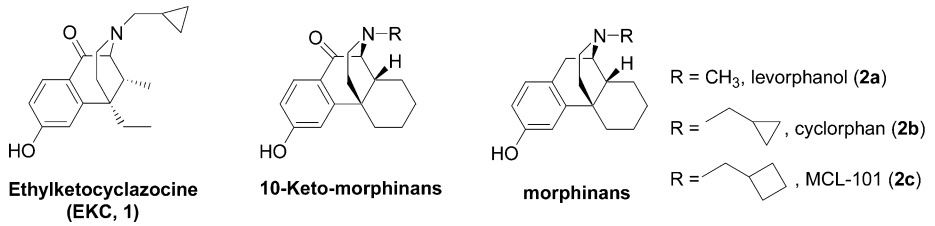
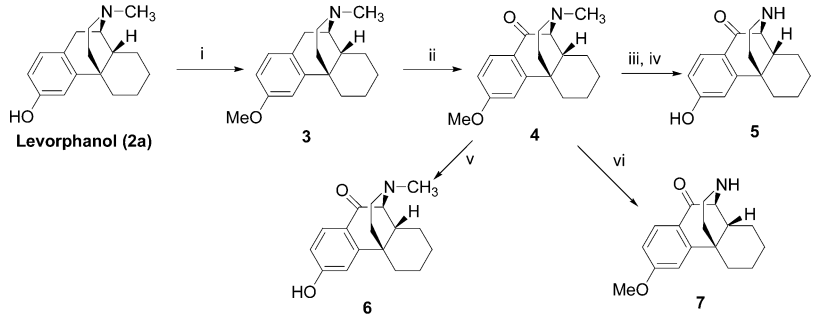
10.1021/jm0304156 CCC: $27.50
Published on Web 12/09/2003

Chart 1



Scheme 1[a]



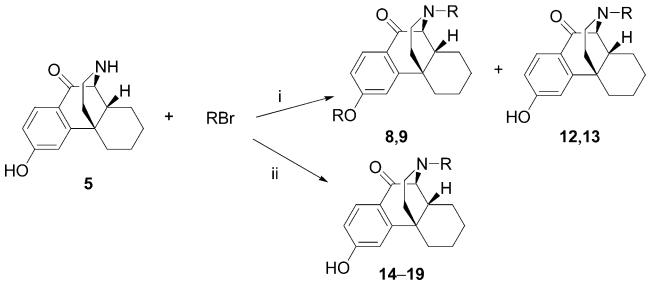
[a] Reagents and conditions: (i) CH_2N_2, Et_2O; (ii) CrO_3, H_2SO_4, 100 °C; (iii) $CH_3CHClOCOCl$, Na_2CO_3, $ClCH_2CH_2Cl$; (iv) HBr (48%), HOAc, 110 °C; (v) BBr_3 (1 M in CH_2Cl_2); (vi) $CH_3CHClOCOCl$, Na_2CO_3, $ClCH_2CH_2Cl$, then MeOH

which were found to be highly potent at both μ/κ receptors, and only moderate affinity at δ receptor.[23,24] These compounds are potentially useful candidates as chemotherapeutic agents for cocaine abuse and are currently under further evaluation. In the present report, we described the synthesis and preliminary pharmacological examination of *N*-alkyl-3-hydroxy (or 3-desoxy-3-substituted)-10-ketomorphinan and morphinan analogues. We speculated that the introduction of a 10-keto group in morphinans would improve the pharmacological properties at κ receptor, similar to **1**.[21] Our previous study[23,24] suggested that the activities of this class of compounds were sensitive to *N*-alkyl substituents, thus a systematic examination of the *N*-alkyl groups, as well as the bioisosteric replacement of the phenolic hydroxyl moiety (with both morphinan and ketomorphinan templates) will be reported. The purpose of this study was to identify novel morphinan ligands which have good binding affinity at both μ/κ receptors but lower affinity at δ receptor.

Synthesis

The synthesis of the 10-ketomorphinans was initiated from commercially available (−)-3-hydroxy-*N*-methylmorphinan (levorphanol, **2a**) as shown in Scheme 1. Thus, **2a** was treated with diazomethane (prepared in situ from diazald) to yield the methyl ether **3**. Oxidation of **3** with CrO_3/H_2SO_4 produced the 10-ketomorphinan **4** in 80% yield.[25] Treatment of **4** with α-chloroethyl chloroformate followed by reflux in HBr/HOAc yielded the 3-hydroxy-normorphinan **5**.[23] O-Demethylation of **4** with BBr_3/CH_2Cl_2 gave the *N*-methyl-10-ketomorphinan **6**. 3-Methoxy normorphinan **7** was obtained by using the standard procedure reported by Olfoson et al.[26] The alkylation of **5** was carried out initially by using $NaHCO_3$/DMF system (Scheme 2), which gave N-alkylated products **12** and **13**, along with the N,O-bisalkylated morphinans **8** and **9** as the minor products. *N*-alkyl 10-ketomorphinans **14**−**19** were obtained as the only products by using Et_3N/EtOH system.

Scheme 2[a]

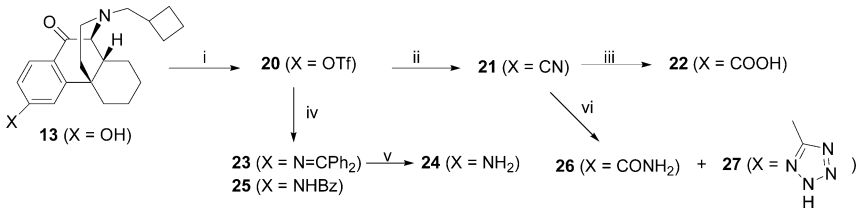


[a] Reagents and conditions: (i) $NaHCO_3$, DMF, 75−80°C; (ii) Et_3N, EtOH, reflux.

3-Desoxy-3-substituted 10-ketomorphinans **21**, **22**, **24**−**27** were prepared as described in Scheme 3. *N*-Cyclobutylmethyl-10-ketomorphinan **13** was treated with $PhNTf_2$/ Et_3N/CH_2Cl_2 to give triflate **20** in 78% yield.[27a] The reaction of **20** with 2 equiv of $Zn(CN)_2$ and a catalytic amount of $Pd(PPh_3)_4$ in DMF at 120 °C for 2 h afforded the corresponding nitrile **21** in moderate yield (less than 60%), while carrying out the cyanation under microwave irradiation (200 °C, 15 min) produced the product in 89% yield.[27a] Amination of the triflate **13** with benzophenone imine or benzylamine using the catalytic system of $Pd(OAc)_2$/BINAP/Cs_2CO_3 gave the corresponding products **23** and **2**5 in 45−52% yields.[28] Treatment of **23** with $NH_2OH{\cdot}HCl$/NaOAc in MeOH provided the primary amine **24**.[29] Hydrolysis of the nitrile **21** in $KOH/H_2O_2/{}^t$BuOH gave the acid **22** rather than the expected amide **26** in 20% yield.[30,31] Treatment of **21** with NaN_3/Bu_3SnCl produced the tetrazole **27** in 46.9% yield, and a small amount of amide **26** was isolated as the byproduct (10.6%).[32]

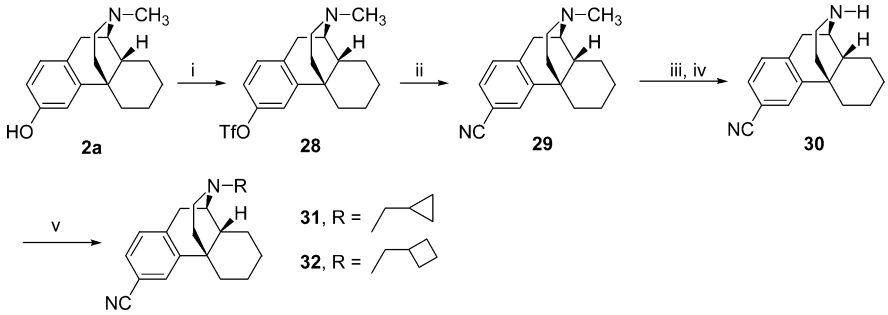
Using similar procedures described above, **2a** was triflated and then converted to the nitrile **29** in 72% yield. In this case, microwave heating failed to give an improved yield over the previously reported procedure.[27b] After removal of the *N*-methyl group, realkylation of norlevorphanol **30** provided nitriles **31** and **32** (Scheme 4). Triflates **34** and **35** were prepared using similar

Scheme 3[a]



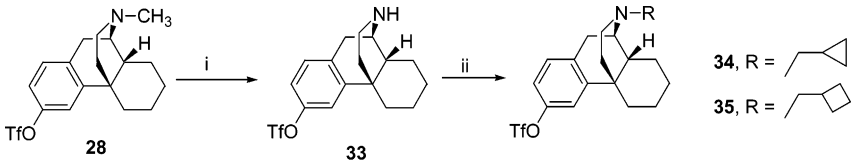
[a] Reagents and conditions: (i) $PhNTf_2$, Et_3N, CH_2Cl_2; (ii) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF; (iii) 25% KOH, ^tBuOH, H_2O_2; (iv) $Ph_2C{=}NH$ or $BzNH_2$, BINAP, $Pd(OAc)_2$, Cs_2CO_3, THF; (v) $NH_2OH{\cdot}HCl$, NaOAc; (vi) NaN_3, Bu_3SnCl, DMF.

Scheme 4[a]



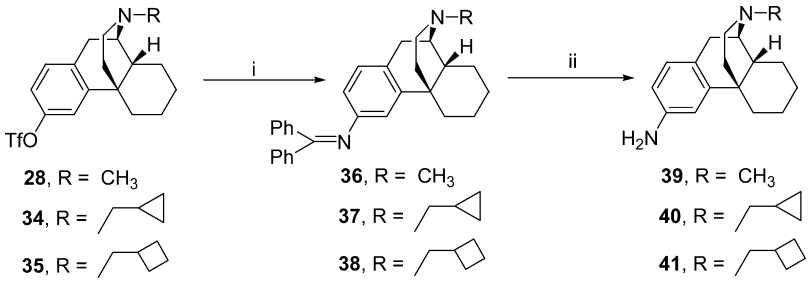
[a] Reagents and conditions: (i) $PhNTf_2$, Et_3N, CH_2Cl_2; (ii) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF; (iii) $CH_3CHClOCOCl$, Na_2CO_3, $ClCH_2CH_2Cl$; (iv) MeOH, 10% NaOH; (v) RBr, Na_2CO_3, DMF.

Scheme 5[a]



[a] Reagents and conditions: (ii) $CH_3CHClOCOCl$, Na_2CO_3, $ClCH_2CH_2Cl$; then MeOH, 10% NaOH; (ii) RBr, Na_2CO_3, DMF.

Scheme 6[a]



[a] Reagents and conditions: (i) $Ph_2C{=}NH$, BINAP, $Pd(OAc)_2$, Cs_2CO_3, THF, reflux; (ii) $NH_2OH{\cdot}HCl$, NaOAc.

methods in which triflate **28** was first demethylated and then realkylated (Scheme 5). The Pd-catalyzed amination of the triflates **28**, **34**, and **35** was conducted under the same condition used for the preparation of **24** producing the corresponding primary amines **39**−**41** in 57−68% yield (Scheme 6).

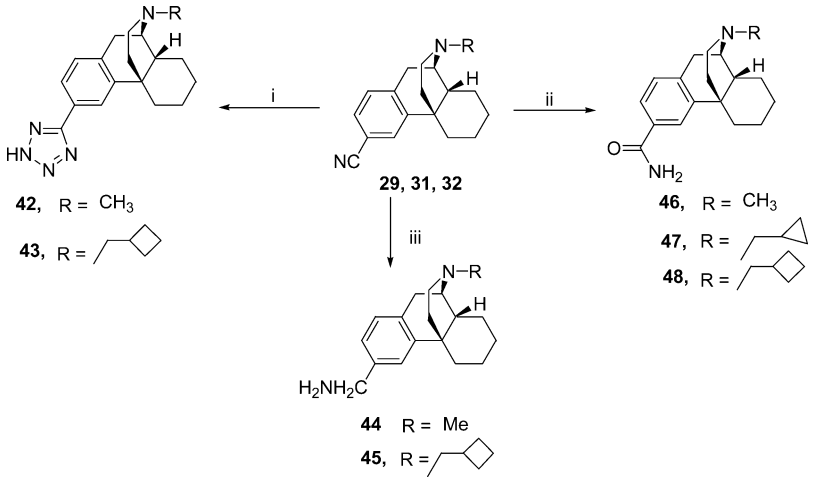
The tetrazoles **42** and **43** were prepared from the corresponding nitriles using the same procedure as for the preparation of **27**. Reduction of nitriles **29**, **32** with $LiAlH_4$ afforded 3-aminomethyl morphinans **44** and **45** (Scheme 7). Hydrolysis of the nitriles **29**, **31**, and **32** with 25% KOH and H_2O_2 in MeOH provided 3-carboxamido analogues **46**−**48**.

Results and Discussion

All new compounds were evaluated for their binding affinity at all three opioid receptors (*μ*, *κ*, and *δ*) (Tables 1 and 2) using a previously reported procedure.[23,24] For comparison purposes, opioid binding affinity data for compounds **1**, **2a**−**c**, and the 10-ketomorphinans **10** and **11** were also included.[23]

Structurally, the phenol moiety, the basic nitrogen, and the keto group are the functional sites in the 10-ketomorphinan template that interact with opioid receptor peptides. They constitute an important pharmacophore of 10-ketomorphinan analogues. The conformational analysis of compound **10** revealed that in this rigid structure (Figure 1), both the keto group and the basic nitrogen moiety are above and much closer to the center of the aromatic ring in the phenol moiety, which results in extensive interaction (electrostatic) between the three functional groups. This analysis[33] can be further supported by the distance map calculated from the conformation which indicates that the distance values (3−5 Å) between the three functional groups are optimal for good activity (Figure 1). The strong electro-

Scheme 7[a]



[a] Reagents and conditions: (i) NaN_3, Bu_3SnCl, DMF; (ii) 25% KOH, MeOH, H_2O_2; (iii) $LiAlH_4$, THF.

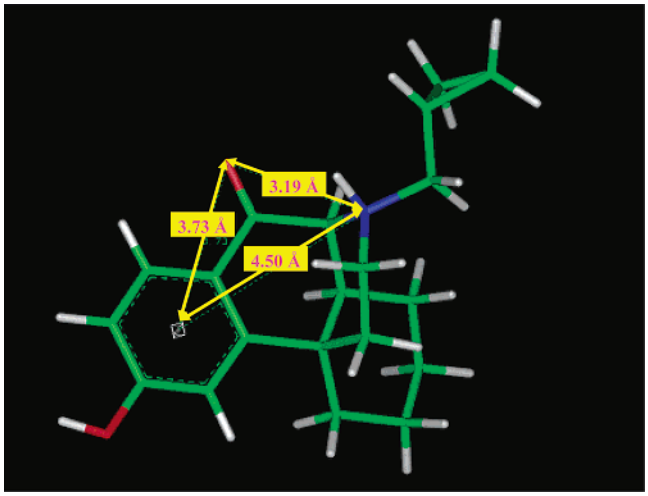
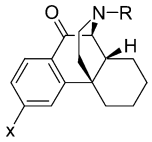


Figure 1. Conformational analysis and distance map of ligand **10**.

philicity of the keto group may partly impact the interaction between the pharmacophore and receptors, which may explain our previous observation that introduction of a 10-keto group decreased the affinity of morphinans (e.g. **2b**→**10**)[23] at all three opioid receptors. But, optimization of the N-substituent and modifications at the phenolic hydroxyl group may compensate this interaction and potentiate the effect of the 10-ketomorphinan pharmacophore with the binding sites at the opioid receptors.

Our initial effort was focused on the elaboration of the N-substituent. It is of note that the 10-ketonormorphinan **5** exhibited the desired pharmacological profile giving good binding affinity (K_i = approximately 20 nM) at both κ and μ receptors and nearly no affinity at δ receptor, the selectivity for κ and μ versus δ was greater than 400. Masking of the 3-hydroxy with a methyl group (compound **7**) resulted in 5- and 15-fold decrease of the affinity at μ and κ receptors, respectively, but the affinity at δ receptor was increased at least 600-fold (K_i = 16 nM). A remarkable decrease of affinity at all the three receptors was observed in compounds **8** and **9**, where the 3-OH was protected by propargyl and cyclobutylmethyl groups, respectively. It is apparent that there is a binding pocket at the 3-hydroxy position for both μ and κ receptors. Thus with the 3-hydroxy group intact, we investigated a variety of N-substituents in compounds **10**−**19**. Compared to compound **5**, cyclopropylmethyl at the nitrogen position (compound **10**) resulted in an appreciable increase in binding affinity at the δ receptor, but a 12-fold decrease at μ receptor and a retained affinity at κ receptor. As reported previously,[23] 3-(*S*)-tetrahydrofurfuryl group in compound **11** greatly improved the affinity at all three opioid receptors (0.38 nM for μ, 1.0 nM for δ, and 0.18 nM for κ receptors). It was suggested that extensive interactions between the tetrahydrofurfuryl group and all three opioid receptors existed, but it was not clear that the stereochemistry, the steric bulk, or both in the (*S*)-tetrahydrofurfuryl moiety were responsible for this significant improvement. Compound **12** with a propargyl group as the N-substituent gave similar results at μ and κ receptors as compound **10**, but the affinity at δ receptor fell into the micromolar range. It is noteworthy that the cyclobutylmethyl group as the N-substituent in compound **13** produced a pronounced improvement in affinity with a K_i value of 3.3 nM for μ receptor, 260 nM for δ receptor, and 0.48 nM for κ receptor. The selectivity for κ over δ is 540, and κ over μ is 7. Compared to compound **5**, 3,3-dimethylallyl and 3-fluoropropyl groups on the N-position (compounds **14** and **15**) retained the affinity at μ receptor, but a 3−7-fold increase in affinity at κ receptor was observed. Interestingly, replacement of 3-fluoropropyl group in compound **15** by 2-fluoroethyl group in compound **16** produced 100-fold and 28-fold decrease in affinity at κ and μ receptors, respectively. This would indicate that there is a remote binding site for both κ and μ receptors approximately three carbons extended from the nitrogen. Introduction of 2-methoxyethyl group at the N-position in compound **17** gave a similar binding profile, compared to compound **5**, but a 4.5-fold decrease of binding affinity at μ receptor, 1.5-fold increase of affinity at κ receptor, and a high selectivity of 590 for κ versus δ receptors were observed. With a 2-phenylethyl group as the N-substituent, compound **18** displayed remarkable increase in affinity at all three receptors (0.63 nM for μ, 9.7 nM for δ, and 7.7 nM for κ receptors). This was the only example in this series where the selectivity of κ over μ was significantly reversed. Apparently, there is a bind-

Table 1. K_i Values Inhibition of μ, δ, and κ Opioid Binding to CHO Membranes by 10-Ketomorphinan Series[a]



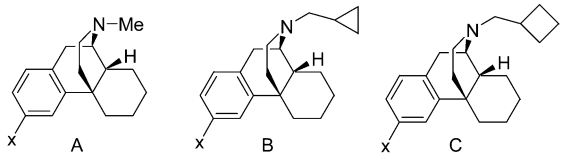
Compound	R	X	K_i (nM) ± SE			Selectivity	
			[^{3}H]DAMGO (μ)	[^{3}H]Naltrindole (δ)	[^{3}H]U69,593 (κ)	δ:μ	δ:κ
5	H	OH	20 ± 1	>10 uM	25 ± 1	>500	>400
6	Me	OH	21 ± 3	1200 ± 74	47 ± 3	57	26
7	H	OMe	110 ± 3	16 ± 3	390 ± 52	0.14	0.04
8			710 ± 28	> 10 uM	500 ± 19	>14	>20
9			800 ± 41	>10 uM	290 ± 27	>12	35
10[23]		OH	240 ± 89	150 ± 71	24 ± 2	0.6	6
11[23]		OH	0.38 ± 0.00	1.0 ± 0.2	0.18 ±0.02	2.6	5.6
12		OH	190 ± 4	2300 ± 190	60 ± 2	12	38
13		OH	3.3 ± 0.3	260 ± 55	0.48 ± 0.03	79	540
14		OH	19 ± 4	1100 ± 98	7.4 ± 1.3	58	150
15		OH	20 ± 5	690 ± 171	2.5 ± 0.4	35	280
16		OH	560 ± 99	> 10 uM	250 ± 32	>18	>40
17		OH	90 ± 10	>10 uM	17 ± 1	>110	>590
18		OH	0.63 ± 0.07	9.7 ± 0.3	7.7 ± 0.2	15	1.3
19		OH	2200 ± 60	> 10 uM	780 ± 44	>4.5	>13
21		CN	2200 ± 136	>10 uM	400 ± 35	>4.5	>25
22		COOH	28 ± 9	800 ± 48	59 ± 3	29	14
24		NH_2	23 ± 2	600 ± 79	4.7 ± 0.5	26	130
25		NHBz	4.4 ± 0.7	380 ± 32	7.7 ± 0.1	86	49
26		$CONH_2$	2.5 ± 0.1	50 ± 2	2.7 ± 0.1	20	19
27			230 ± 20	1800 ± 46	360 ± 50	7.8	5
EKC (1)			0.78 ± 0.10	3.4 ± 0.4	0.62 ± 0.11	4.4	5.4

[a] Guinea pig brain membranes, 0.5 mg of protein/sample, were incubated with 12 different concentrations of the compounds in the presence of receptor-specific radioligands at 25 °C, in a final volume of 1 mL of 50 mM Tris-HCl, pH 7.5. Nonspecific binding was determined using 1 μM naloxone. Data are the mean values SEM from three experiments, performed in triplicate. The statistics and the standard chemicals were the same as used in ref 23.

ing site for the aromatic ring approximately two carbons beyond the N-atom for all the three opioid receptors.

The second series of compounds focused on the 3-desoxy-3-substituted 10-ketomorphinans in which the binding ability of the compounds to hydrogen bond at the 3-position was evaluated. Since compound **13** with a cyclobutylmethyl group as the N-substituent displayed high affinity at κ and μ receptors, but low affinity at δ receptor, it was selected as the lead for the evaluation of the effect of 3-substituent on the opioid receptor binding affinity. Replacement of the 3-hydroxy group, a strong H-bond donor, by a cyano group, a moderate H-bond acceptor (compound **21**), almost abolished the affinity at all three opioid receptors. While a carboxyl group which contains both H-bond donating and accepting properties (compound **22**) retained good affinity at and selectivity for both κ and μ receptors. This extensive structure/activity relationship suggested that a H-bond-donating function at the C-3 position was essential for the κ and μ receptor-selective profile for this class of 10-ketomorphinan ligands. Thus, an amino group that can be considered as a bioisosteric replacement of the 3-OH was introduced into this position.[34] Compared to acid **22**, the affinity at μ receptor for the 3-amino analogue **24** that possesses two H-bond donors was similar, but a 12-fold increase at κ receptor was observed. Compared to the primary amine **24**, the amino analogue **25** exhibited a 5-fold increase in binding affinity at μ receptor but a slight decrease at κ receptor, and the selectivity of κ over μ was reversed. These

Table 2. K_i Values Inhibition of μ, δ, and κ Opioid Binding to CHO Membranes by 3-Substituted Morphinans[a]



Compound		K_i (nM) ± SE			Selectivity	
		[^{3}H]DAMGO (μ)	[^{3}H]Naltrindole (δ)	[^{3}H]U69,593 (κ)	δ:μ	δ:κ
2a	A: X = OH	0.21 ± 0.02	4.2 ± 0.5	2.3 ± 0.3	20	1.8
2b	B: X = OH	0.062 ± 0.003	1.9 ± 0.1	0.034 ± 0.002	31	56
2c	C: X = OH	0.23 ± 0.01	5.9 ± 0.6	0.079 ± 0.003	26	75
29	A: X = CN	20 ± 8	> 1 μM	200 ± 39	>500	>5.0
32	C: X = CN	37 ± 6	1900 ± 220	6.0 ± 0.4	51	320
39	A: X = NH_2	7.9 ± 1.0	1500 ± 770	110 ± 11	190	14
40	B: X = NH_2	1.3 ± 0.0	150 ± 2	0.18 ± 0.00	120	830
41	C: X = NH_2	3.7 ± 0.3	180 ± 85	1.8 ± 0.1	49	100
42	A: X = 	380 ± 4	> 10 μM	380 ± 18	>26	>26
43	C: X = 	1100 ± 145	> 10 μM	850 ± 22	>9	>12
44	A: X = CH_2NH_2	66 ± 4.3	2500 ± 91	120 ± 8	38	21
45	C: X = CH_2NH_2	8.5 ± 0.1	410 ± 12	8.6 ± 1.0	48	48
46	A: X = $CONH_2$	0.073 ± 0.005	13 ± 0	3.9 ± 0.5	180	3.3
47	B: X = $CONH_2$	0.059 ± 0.015	1.0 ± 0.0	0.18 ± 0.01	17	5.6
48	C: X = $CONH_2$	0.10 ± 0.00	4.0 ± 0.7	0.087 ± 0.002	40	46

[a] Same methods were used as in Table 1.

findings indicated that only one N−H bond was required for reasonable affinity at μ receptor, and the stronger H-bond donating ability of the 3-OH than the 3-NHBz was, at least partially, responsible for the high affinity at κ receptor in compound **13**. A pronounced increase of affinity at all the three receptors was observed in the carboxamido analogue **26** which gave similar affinity at both κ and μ receptors (K_i = approximately 2.5 nM). The carboxamido moiety, containing one H-bonding acceptor and two H-bonding donors, was more favorable than the 3-amino replacement pattern for both μ and κ receptors. The SAR observed for compounds **24**−**26** roughly paralleled that observed in the cyclazocine series.[29a,31a] The tetrazolo moiety containing both weak H-bonding donor and H-bonding acceptor in compound **27** displayed remarkably lower affinity at both κ and μ receptors.

Our recent findings[21−23] indicated that the morphinans (**2b** and **2c**) (Chart 1) displayed high affinity at κ and μ receptors and had longer durations of action than compound **1**. They act as full κ agonists and have approximately 2-fold selectivity for κ/μ receptors. These findings suggested that we focus on the synthesis of a series of 3-desoxy-3-substituted morphinans **29**, **32**, **39**−**48**. We envisaged that the further functional transformation at the C-3 position may produce a series of compounds with different pharmacological properties. Thus, with **2a**−**c** as the lead compounds, we investigated the effect of a series of 3-desoxy-3-substituents on the binding affinity at the three opioid receptors.

Replacement of the 3-OH in **2a** and **2b** with a 3-CN, a moderate H-bond acceptor, gave compounds **29** and **32**. Compared to the parent compounds **2a** and **2b**, a loss of affinity at δ receptor, and a 76−160-fold decrease of affinity at both μ and κ receptors were observed. Interestingly, compound **29** was μ-selective, while **32** was κ-selective. The decrease of affinity was less than that observed in 10-ketomorphinans. The affinity of the 3-amino analogues **39**−**41** was decreased 16−37-fold at μ and 5−47-fold at κ receptor compared to their corresponding 3-OH congeners. Replacement of the 3-OH by a tetrazole moiety (compounds **42** and **43**) gave a 2−3-orders of magnitude decrease in the affinity at μ and κ receptors. Extension of the amino group by one methylene unit further decreased the affinity at both κ and μ receptors (compounds **44** and **45**) compared to the corresponding 3-amino substituted analogues **39** and **41**. However, high affinity was observed in the 3-carboxamido morphinans **46**−**48**. Compared to their parents (**2a**−**c**), similar or slightly lower affinity was observed at κ receptor (1−5-fold). The three analogues were comparable to their corresponding 3-OH congeners. The different H-bonding and electrostatic properties of the 3-carboxamido substitution pattern from the 3-OH prototypes may provide novel pharmacological properties. These findings, combined with recently reported observations in the benzomorphan series,[31] suggested that recognition sites at both κ and μ opioid receptors in the carboxamido analogues differed from that in the phenol prototypes.

Conclusion

This study demonstrated that introduction of a 10-keto group into the morphinan template provided a series of compounds with mixed μ and κ receptor pharmacological profile. The binding affinity at all three opioid receptors generally was somewhat lower than the corresponding morphinans without the keto group.[23,24] In most cases, high affinity at μ and κ receptors and lower affinity at δ receptor were observed, which produced higher selectivity for μ and κ versus δ receptors. The affinity at μ and κ receptors could be ultimately adjusted by introduction of different N-substituents without impact of the receptor selectivity profile. It was apparent that there was a large hydrophobic recognition pocket around the nitrogen which could tolerate a variety of hydrophobic groups with variant structural features and sizes. *N*-(*S*)-tetrahydrofurfuryl analogue **11** displayed high affinity at all three receptors, with improved binding properities over **1**. The *N*-cyclobutylmethyl analogue **13** gave both high affinity and selectivity at κ receptor, and *N*-2-phenylethyl analogue **18** exhibited good affinity and selectivity at μ receptor. Further elaboration of the 3-substituent indicated that one H-bond donor contributed to the good affinity at μ and κ receptors.

Similar modification was applied to the morphinans (**2a**−**c**) without the 10-keto group, whose N-substituents have been previously well-documented.[23,24] The 3-amino bioisosteric analogues (**40** and **41**) displayed reasonably good affinity at μ and κ receptors, although it was much lower than the 3-OH congeners. Differing from the ketomorphan analogues, the 3-carboxamido replacement (compounds **46**−**48**) in the morphinan subseries gave substantially identical affinity compared to the corresponding 3-OH congeners. This suggested that different recognition sites and binding modes existed at both κ and μ opioid receptors in the carboxamido substitution pattern. Combined with recent observations in the benzomorphan series,[31] the high affinity of the carboxamide analogues along with their greater lipophilicity and metabolic stability, make them promising candidates for further pharmacological investigation.

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 Brucker AC300 spectrometer using tetramethylsilane as an internal reference. Elemental 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 with TLC. 3-Methoxy-*N*-methylmorphinan **3**, 3-methoxy-10-keto-*N*-methylmorphinan **4**, 3-hydroxy-10-keto-normorphinan **5** (MCL-164), and 3-methoxy-10-keto-normorphinan **7** (MCL-165) were prepared as before.[23]

3-Hydroxy-10-keto-*N*-methylmorphinan 6 (MCL-172). The crude ether **4** (10 mmol) was dissolved in CH_2Cl_2 (50 mL) and cooled to 0 °C, and a solution of boron tribromide (1M in CH_2Cl_2, 50 mL) was added slowly. The resulting brown solution was stirred at room temperature overnight. MeOH (200 mL) was introduced cautiously to quench the reaction. After completion of gas evolution, the mixture was heated to reflux (77−80 °C) for 2 h. The solvent was evaporated under reduced pressure, and the residue was taken up in $CHCl_3$ (100 mL) and basified with NH_4OH. The layers were separated, and the aqueous phase was extracted with $CHCl_3$ (3 × 50 mL). Organic phases were combined, washed with water and brine, and then dried over Na_2SO_4. After removal of the solvent, a pale yellow solid was obtained (75.3%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.00 (d, *J* = 6.9 Hz, 1H), 6.76 (m, 2H), 5.30 (s, 1H), 3.05 (s, 1H), 2.67 (d, *J* = 9.9 Hz, 1H), 2.38 (s, 3H), 2.36 (m, 1H), 2.11 (t, *J* = 11.1 Hz, 1H), 1.91 (m, 1H), 1.30 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 194.0, 163.3, 148.4, 129.0, 127.7, 114.4, 112.7, 68.4, 47.7, 46.9, 43.0, 40.7, 37.9, 36.3, 25.9, 21.8. Anal. ($C_{17}H_{21}NO_2$) C, H, N.

General Procedure for Preparation of 3-Hydroxy/3-Alkoxy-10-keto-*N*-alkylmorphinans 8,9,12,13. A mixture of **5** (300 mg, 1.16 mmol), propargyl bromide or cyclobutylmethyl bromide (1.2 equiv.), and $NaHCO_3$ (117 mg, 1.4 mmol) in dry DMF (15 mL) was heated under nitrogen at 75 °C for 24 h. Solvent was removed under reduced pressure. The remaining material was taken up with $CHCl_3$ (50 mL), washed with water (2 × 25 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (hexane/EtOAc: 4/1) to yield the products **8** and **12** or **9** and **13**.

3-*O*-Propargyl-10-keto-*N*-propargylmorphinan 8 (MCL-155). Pale-yellow solid (30%). Mp: 120−122 °C; MS: *m/e* 333 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.06 (dd, *J* = 3.0, 8.4 Hz, 1H), 6.92 (m, 2H), 4.77 (m, 2H), 3.41 (m, 1H), 3.16 (m, 2H), 2.92 (dd, *J* = 2.4, 11.1 Hz, 1 H), 2.58 (dd, *J* = 2.4, 4.8 Hz, 1H), 2.39 (d, *J* = 13.5 Hz, 1H), 2.24 (m, 1H), 2.10 (m, 3H), 1.47 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 194.3, 162.7, 147.8, 129.3, 128.4, 112.5, 80.5, 77.8, 72.9, 72.4, 66.6, 55.7, 47.1, 45.3, 44.5, 41.0, 38.5, 36.4, 26.0, 25.8, 21.8. Anal. ($C_{22}H_{23}NO_2 \cdot 0.2H_2O$) C, H, N.

3-Hydroxy-10-keto-*N*-propargylmorphinan 12 (MCL-156). Pale-yellow solid (43%). Mp: 221−223 °C (dec). MS: *m/e* 295 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.98 (dd, *J* = 1.8, 8.4 Hz, 1H), 6.79 (m, 2H), 3.42 (dt, *J* = 2.4, 16.5 Hz, 1H), 3.24 (m, 2H), 3.15 (m, 1H), 2.93 (m, 1H), 2.35 (d, *J* = 13.8 Hz, 1 H), 2.24 (m, 1H), 2.10 (m, 3H), 1.93 (m, 2H), 1.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 194.5, 162.2, 148.5, 128.9, 128.4, 114.3, 112.6, 79.7, 72.9, 72.7, 66.7, 47.0, 45.3, 44.5, 40.9, 38.4, 36.3, 26.0, 25.9. Anal. ($C_{19}H_{21}NO_2 \cdot 0.5HCl$) C, H, N.

3-*O*-Cyclobutylmethyl-10-keto-*N*-cyclobutylmethylmorphinan 9 (MCL-157). Pale-yellow oil (18%). MS: *m/e* 393 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.01 (d, *J* = 8.7 Hz, 1H), 6.83 (dd, *J* = 2.1, 8.7 Hz, 1H), 6.77 (d, *J* = 2.1 Hz, 1H), 3.98 (d, *J* = 6.6 Hz, 2H), 2.99 (d, *J* = 2.7 Hz, 1H), 2.78 (m, 1H), 2.62 (m, 3H), 2.30 (m, 2H), 2.16 (m, 2H), 1.78 (m, 21H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 195.1, 164.5, 147.9, 128.7, 128.3, 112.0, 111.9, 72.0, 67.3, 61.6, 47.2, 45.8, 41.3, 38.6, 36.4, 34.5, 34.1, 27.6, 26.9, 26.1, 26.0, 24.8, 24.7, 22.0, 18.7, 18.5. Anal. ($C_{26}H_{35}NO_2 \cdot 1.0H_2O$) C, H, N.

3-Hydroxy-10-keto-*N*-cyclobutylmethylmorphinan 13 (MCL-158). Pale-yellow solid (47%). Mp: 194−195 °C (dec); MS: *m/e* 325 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.98 (d, *J* = 8.1 Hz, 1H), 6.77 (m, 2H), 3.99 (m, 1H), 3.05 (m, 1H), 2.59 (m, 3H), 2.30 (m, 2H), 2.05 (m, 4H), 1.62 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 194.7, 162.4, 148.6, 128.8, 128.4, 114.2, 112.5, 67.3, 61.7, 46.9, 45.9, 41.0, 38.5, 36.4, 33.9, 27.9, 27.0, 26.0, 24.8, 21.9, 18.7. Anal. ($C_{21}H_{27}NO_2 \cdot 0.5H_2O$) C, H, N.

General Procedure for Preparation of 3-Hydroxy-10-keto-*N*-alkylmorphinans 14−19. To a solution of **5** (300 mg, 1.16 mmol) in 10 mL of anhydrous EtOH was added a solution of Et_3N (1.2 equiv.), followed by alkyl bromide (1.2 equiv.). The resulting mixture was heated under nitrogen at 75 °C for 48 h. Solvent was removed under reduced pressure and the remaining material was taken up in $CHCl_3$ (50 mL), washed with brine (2 × 25 mL), dried (Na_2SO_4), and concentrated. The residue was further purified by flash chromatography (hexane/EtOAc: 4/1) to yield the corresponding 3-hydroxy-10-keto *N*-alkylmorphinan (50−62% yield).

3-Hydroxy-10-keto-*N*-(3,3-dimethylallyl)morphinan 14 (MCL-159). Pale-yellow solid (50%). Mp: 214−215 °C; MS: *m/e* 325 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.00 (d, *J* = 8.4 Hz, 1H), 6.75 (m, 2H), 5.23 (brs, 1H), 3.13 (m, 2H), 2.92 (m, 1H), 2.73 (m, 1H), 2.31 (d, *J* = 12 Hz, 1 H), 2.02 (m, 3H), 1.69

(s, 3H), 1.60 (s, 3H), 1.33 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 195.0, 162.1, 148.6, 135.8, 128.8, 120.8, 114.2, 112.5, 67.1, 53.1, 47.2, 45.4, 41.1, 38.6, 36.4, 26.0, 25.9, 21.9, 18.1, 7.4. Anal. ($C_{21}H_{27}NO_2 \cdot {}^1/_3H_2O$) C, H, N.

3-Hydroxy-10-keto-*N*-(3-fluoropropyl)morphinan 15 (MCL-160). Pale-yellow solid (54.0%). Mp: 207−208 °C; MS: *m/e* 317 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.99 (d, J = 8.4 Hz, 1H), 6.77 (m, 2H), 4.26 (m, 2H), 3.11 (s, 1H), 2.70 (m, 3H), 2.89 (m, 3H), 2.00 (m, 4H), 1.51 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 194.8, 161.9, 148.4, 128.6, 128.4, 113.9, 112.3, 82.1 (d, J = 163.0 Hz), 65.9, 50.6, 46.8, 45.9, 40.9, 38.3, 36.1, 27.9, 27.7, 25.8, 21.6. Anal. ($C_{19}H_{24}FNO_2 \cdot 0.1H_2O$) C, H, N.

3-Hydroxy-10-keto-*N*-(2-fluoroethyl)morphinan 16 (MCL-162). Pale-yellow viscous solid (28.6%). MS: *m/e* 303 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.95 (d, J = 8.4 Hz, 1H), 6.81 (m, 2H), 4.60 (m, 2H), 3.12 (m, 1H), 2.89 (m, 3H), 2.13 (m, 4H), 1.49 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 195.0, 163.2, 148.7, 128.8, 127.7, 114.4, 112.7, 81.3 (d, J = 167.02 Hz), 66.8, 55.2, 54.9, 46.8, 46.3, 40.8, 38.2, 36.2, 26.0, 21.8. Anal. ($C_{18}H_{22}FNO_2 \cdot 0.1H_2O$) C, H, N.

3-Hydroxy-10-keto-*N*-(2-methoxyethyl)morphinan 17 (MCL-161). White solid (56.5%). Mp: 196−197 °C; MS: *m/e* 315 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.97 (d, J = 8.4 Hz, 1H), 6.79 (m, 2H), 3.58 (m, 2H), 3.34 (s, 3H), 3.12 (s, 1H), 2.81 (m, 2H), 2.54 (m, 1H), 2.08 (m, 4H), 1.36 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 195.2, 163.1, 148.6, 128.7, 127.8, 114.4, 112.6, 69.4, 66.4, 58.7, 54.4, 46.6, 46.3, 40.8, 38.3, 36.3, 26.0, 21.9. Anal. ($C_{19}H_{25}NO_3 \cdot 0.5H_2O$) C, H, N.

3-Hydroxy-10-keto-*N*-(2-phenylethyl)morphinan 18 (MCL-163). Pale-yellow solid (50.6%). Mp: 183−184 °C; MS: *m/e* 361 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.92 (d, J = 8.4 Hz, 1H), 7.23 (m, 5H), 6.76 (m, 2H), 3.17 (s, 1H), 3.00 (d, J = 14.7 Hz, 1H), 2.52 (m, 5H), 2.02 (m, 3H), 1.35 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 195.0, 163.4, 148.3, 139.9, 128.5, 128.4, 128.3, 128.1, 127.8, 125.7, 113.8, 113.6, 112.3, 66.0, 57.1, 48.6, 46.8, 46.2, 40.8, 38.3, 36.2, 33.5, 25.9, 21.7. Anal. ($C_{24}H_{27}NO_2$) C, H, N.

3-Hydroxy-10-keto-*N*-(2-naphthylmethyl)morphinan 19 (MCL-166). Pale-yellow solid (64.2%). Mp: 224−225 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.05 (m, 1H), 7.76 (m, 4H), 7.50 (d, J = 7.5 Hz, 1H), 7.41 (m, 2H), 6.83 (d, J = 7.5 Hz, 1H), 6.71 (s, 1H), 4.00 (d, J = 13.5 Hz, 1H), 3.49 (d, J = 13.5 Hz, 1H), 3.16 (s, 1H), 2.61 (d, J = 10.8 Hz, 1H), 2.21 (d, J = 12.6 Hz, 1H), 2.07 (m, 2H), 1.78 (m, 1H), 1.30 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 195.5, 162.5, 148.8, 135.8, 133.2, 132.7, 128.9, 128.3, 127.9, 127.8, 127.7, 127.5, 127.4, 125.8, 125.5, 114.3, 112.6, 66.8, 59.6, 47.1, 45.4, 41.0, 38.5, 36.3, 26.0, 25.9, 21.9. Anal. ($C_{27}H_{27}NO_2 \cdot 0.25H_2O$) C, H, N.

3-Carboxyl-10-keto-*N*-cyclobutylmethyl morphinan 22 (MCL-171). The nitrile **21** (171 mg, 0.51 mmol) in MeOH (5 mL) was added 25% potassium hydroxide (3 mL) and 2 drops 30% hydrogen peroxide solution. The mixture was refluxed for 5 h. After cooling to room temperature, the reaction mixture was extracted with EtOAc (3 × 20 mL). The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatograph (EtOAc) yielding the product **22** as pale yellow foam (50 mg, 28%). MS (EI): 354 ($M^+ + 1$);^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.10 (m, 3H), 3.4 (brs, 1H), 3.05 (d, J = 6.3 Hz, 1H), 2.79 (m, 3H), 2.57 (m, 3H), 2.35 (d, J = 12.6 Hz, 1H), 2.12 (m, 6H), 1.58 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 194.7, 169.9, 166.4, 145.1, 138.7, 137.0, 128.0, 126.2, 66.2, 61.1, 46.1, 45.6, 39.7, 38.1, 35.9, 32.6, 27.9, 27.1, 26.0, 25.7, 21.7, 18.6. Anal. ($C_{22}H_{27}NO_3$) C, H, N.

3-(Benzhydrylideneamino)-10-keto-*N*-cyclobutylmethylmorphinan 23. The triflate **20** (500 mg, 1.09 mmol) in THF (20 mL) were added palladium(II) acetate (5 mg, 0.022 mmol), *rac*-2,2′-bis (diphenylphosphino)-1,1′-binaphthyl (20 mg, 0.032 mmol), benzophenone imine (237 mg, 1.31 mmol), cesium carbonate (497 mg, 1.5 mmol), and 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (20 mg) under nitrogen. The mixture was heated to 65−70 °C with stirring overnight. The solvent was removed. The residue was diluted with CH_2Cl_2, washed with brine, dried, and concentrated. The crude product was purified by column chromatograph (hexane: EtOAc = 10:1) to yield imine **23** as pale-yellow foam (200 mg, 37.3%), the triflate **20** (200 mg) was recovered at the same time. The crude **23** was used for next step without further purification.

3-Amino-10-keto-*N*-cyclobutylmethylmorphinan 24 (MCL-167). To a solution of the crude imine **23** (200 mg, 0.43 mmol) in MeOH (8 mL) at room temperature were added NaOAc (85 mg, 1.03 mmol) and hydroxylamine hydrochloride (54 mg, 0.774 mmol). The mixture was stirred at room temperature for 2 days. The solution was partitioned between 0.1 M NaOH and CH_2Cl_2. The organic layer was separated and dried over anhydrous Na_2SO_4 and then concentrated in vacuo. The crude product was purified by column chromatograph (hexane:EtOAc = 3:1) producing the amine **24** as a white solid (120 mg, 90.4%). M.p.: 214−215°C; MS (EI): 324 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.88 (d, J = 8.4 Hz, 1H), 6.54 (d, J = 8.4 Hz, 1H), 6.48 (s, 1H), 4.14 (s, 2H), 2.96 (s, 1H), 2.63 (m, 4H), 2.89 (m, 3H), 1.99 (m, 3H), 1.76 (m, 4H), 1.41 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 194.4, 152.3, 148.0, 128.4, 126.7, 112.7, 110.4, 67.4, 61.6, 47.3, 45.9, 41.4, 38.4, 36.5, 34.2, 27.7, 26.9, 26.2, 26.1, 22.0, 18.7. Anal. ($C_{21}H_{28}N_2O$) C, H, N.

3-Benzylamino-10-keto-*N*-cyclobutylmethylmorphinan 25 (MCL-170). Prepared according to the similar procedure used for the preparation of imine **23** using benzylamine as the amination reagent. The crude product was purified by column chromatograph (hexane:EtOAc = 4:1) giving the amine **25** (26.0%) as a foam. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.90 (d, J = 8.7 Hz, 1H), 7.34 (m, 5H), 6.53 (d, J = 8.7 Hz, 1H), 6.40 (s, 1H), 4.60 (s, 1H), 4.39 (s, 2H), 2.95 (s, 1H), 2.62 (m, 4H), 2.25 (m, 3H), 2.02 (m, 3H), 1.72 (m, 6H), 1.35 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 194.2, 153.1, 147.8, 138.2, 128.7, 128.3, 127.6, 127.5, 125.9, 110.7, 108.4, 67.4, 61.6, 47.7, 47.4, 45.9, 41.5, 38.5, 36.6, 34.2, 27.7, 26.9, 26.1, 21.9, 18.7. Anal. ($C_{28}H_{34}N_3O \cdot 0.2H_2O$), C, H, N.

3-Carboxamido-10-keto-*N*-cyclobutylmethylmorphinan 26 (MCL-173) and 3-Tetrazolo- 10-keto-*N*-cyclobutylmethylmorphinan 27 (MCL-174). A mixture of **21** (115 mg, 0.34 mmol), tributylstannyl chloride (370 uL, 1.37 mmol), and sodium azide (90 mg, 1.37 mmol) in DMF (5 mL) was heated under nitrogen at 120 °C for 24 h. Saturated Na_2CO_3 was added, and the mixture was extracted with EtOAc (3 × 60 mL). The extracts were combined, washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc: 1/1) to give the amide **26** as pale yellow oil (13 mg, 10.6%), and further chromatography with EtOAc/MeOH (20/1) gave the tetrazole **27** as a yellow solid (61 mg, 46.9%).

26 (MCL-173): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.09 (d, J = 8.4 Hz, 1H), 7.87 (s, 1H), 7.65 (d, J = 8.4 Hz, 1H), 6.15 (s, 1H), 5.82 (s, 1H), 3.06 (s, 1H), 2.16 (m, 3H), 2.27 (dd, J = 6.9, 6.9 Hz, 1H), 0.92−2.12 (m, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 196.4, 168.6, 146.2, 138.4, 137.6, 126.3, 126.0, 124.4, 67.1, 61.4, 46.8, 45.5, 41.0, 38.6, 36.1, 33.9, 27.5, 26.8, 26.2, 25.8, 21.9, 18.7. Anal. ($C_{22}H_{28}N_2O_2$) C, H, N.

27 (MCL-174): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.20 (m, 1H), 8.09 (m, 2H), 3.28 (m, 2H), 2.70 (m, 3H), 2.48 (m, 1H), 1.14−2.17 (m, 17H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 195.7, 162.0, 147.2, 137.5, 135.9, 127.5, 125.9, 68.1, 62.5, 49.8, 47.5, 41.2, 39.4, 37.0, 34.3, 28.4, 27.8, 27.1, 27.0, 23.0, 19.4. Anal. ($C_{23}H_{27}N_5O.0.7HCl$) H, N; C: calcd, 64.40; found, 64.85.

3-Trifluoromethyl(sulfonyl)oxy-*N*-methylmorphinan 28 was prepared according to the literature procedure[27a] in 78% yield. ^{1}H NMR (300 MHz) δ 7.15 (d, J = 8.1 Hz, 1H), 7.08 (s, 1H), 6.99 (dd, J = 2.1, 8.4 Hz, 1H), 3.01 (d, J = 18.6 Hz, 1H), 2.81 (d, J = 3.0 Hz, 1H), 2.61 (dd, J = 5.4, 18.3 Hz, 1H), 2.37−1.17 (complex, 16H).

3-Cyano-*N*-methylmorphinan 29 (MCL-137) was prepared according to Kubota's procedure[27b] in 72.5% yield. Mp 98−100 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.50 (s, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.17 (d, J = 7.8 Hz, 1H), 3.03 (d, J = 19.2 Hz, 1H), 2.80 (s, 1H), 2.65 (dd, J = 4.5, 18.6 Hz, 1H), 2.43−1.31 (complex, 16H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.0,

142.4, 129.8, 128.9, 128.8, 119.7, 110.2, 57.6, 46.9, 45.1, 42.9, 42.0, 37.4, 36.4, 26.8, 26.5, 24.8, 22.1. Anal. ($C_{18}H_{22}N_2 \cdot 1.5H_2O$) C, H; N: calcd, 9.55; found, 9.03.

3-Cyano-normorphinan 30 was prepared from nitrile **29** according to the same procedure for the preparation of compound **7** in 77.7% yield. MS (EI): 252 (M^+), 253 ($M^+ + 1$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.57 (s, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.26 (d, J = 9.9 Hz, 1H), 3.33−0.88 (complex, 16H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 142.8, 141.5, 130.1, 129.5, 129.1, 119.5, 110.9, 50.8, 44.1, 41.2, 38.3, 37.9, 36.3, 32.8, 26.3, 26.5, 21.9.

3-Cyano-*N*-cyclobutylmethylmorphinan 32 (MCL-150) was prepared according to the same procedure used for the preparation of **12** in 78% yield. MS (EI): 320 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35 (s, 1H), 7.37 (d, J = 8.1, 1H), 7.20 (d, J = 7.8 Hz, 1H), 3.07−1.23 (complex, 25H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.3, 142.6, 129.8, 128.8, 128.7, 119.7, 110.1, 61.6, 55.7, 45.5, 44.9, 42.0, 38.0, 36.4, 34.9, 27.8, 26.9, 26.6, 25.6, 22.2, 19.0. Anal. ($C_{22}H_{28}N_2 \cdot 0.1H_2O$) C, H, N.

3-Trifluoromethyl(sulfonyl)oxy-*N*-cyclopropylmethylmorphinan 34. Triflate **28** was demethylated according to the procedure used for the preparation of **5** giving the intermediate **33**. Alkylation of **33** was carried out using the same procedure for the preparation of **12** in 72% yield.[27a]

3-Trifluoromethyl(sulfonyl)oxy-*N*-cyclobutylmethylmorphinan 35 was prepared from triflate **28** according to the same procedure used for the preparation of **34**.

Amine **39**−**41** were prepared according to the same procedure used for the preparation of **24**.

3-(Benzhydrylideneamino)-*N*-methylmorphinan 36. Pale-yellow oil (63.3%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.74 (m, 2H), 7.41 (m, 3H), 7.22 (m, 3H), 7.09 (m, 2H), 6.93 (d, J = 8.1 Hz, 1H), 6.66 (dd, J = 2.1, 7.8 Hz, 1H), 6.46 (d, J = 2.1 Hz, 1H), 2.91 (d, J = 18.3 Hz, 1H), 2.76−0.97 (complex, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 149.7, 140.6, 140.0, 136.8, 132.9, 130.8, 129.7, 129.4, 128.5, 128.4, 128.0, 119.3, 118.0, 58.1, 47.3, 45.5, 42.9, 42.2, 37.1, 36.6, 27.0, 26.7, 23.8, 22.4.

3-Amino-*N*-methylmorphinan 39 (MCL-181). Pale-yellow oil (57%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.89 (d, J = 8.1 Hz, 1H), 6.61 (d, J = 2.4 Hz, 1H), 6.50 (dd, J = 2.4, 8.4 Hz, 1H), 3.51 (s, 2H), 2.93 (d, J = 18 Hz, 1H), 2.79−1.17 (complex, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.6, 141.5, 128.6, 128.2, 113.4, 112.1, 58.2, 47.5, 45.8, 43.0, 42.3, 37.2, 36.8, 27.0, 26.8, 23.5, 22.5. Anal. ($C_{17}H_{24}N_2 \cdot 0.4H_2O$) C, H, N.

3-Amino-*N*-cyclopropylmethylmorphinan 40 (MCL-149). Pale-yellow oil (70%). MS(EI): 296 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.86 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 2.4 Hz, 1H), 6.48 (dd, J = 2.7, 8.4 Hz, 1H), 3.50 (s, 2H), 3.06−0.47 (complex, 23H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.8, 137.9, 124.7, 124.5, 109.5, 108.3, 56.4, 52.3, 42.2, 41.8, 38.4, 34.1, 33.1, 23.3, 23.1, 20.3, 18.7, 5.9. Anal. ($C_{20}H_{28}N_2 \cdot 0.1H_2O$) C, H, N.

3-Amino-*N*-cyclobutylmethylmorphinan 41 (MCL-182). Pale yellow oil (78%),^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.88 (d, J = 7.8 Hz, 1H), 6.59 (d, J = 2.4 Hz, 1H), 6.48 (dd, J = 2.4, 8.1 Hz, 1H), 3.50 (s, 2H), 2.89 (d, J = 18 Hz, 1H), 2.78−1.09 (complex, 24H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.6, 141.6, 128.6, 128.3, 113.3, 112.1, 61.7, 56.2, 46.2, 45.4, 42.1, 37.7, 36.8, 35.2, 28.1, 27.1, 26.8, 24.2, 22.5, 19.0. Anal. ($C_{21}H_{30}N_2$) C, H, N.

3-(1′*H*-Tetrazol-5′-yl)-*N*-methylmorphinan 42 (MCL-151) was prepared using the same procedure for the preparation of **27**. White solid (68%), Mp: 295−297 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.88 (s, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.12 (d, J = 7.8 Hz, 1H), 3.05−0.68 (complex, 19H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.7, 138.2, 134.8, 129.3, 128.7, 124.9, 123.8, 60.2, 43.4, 41.3, 40.1, 37.1, 36.2, 29.2, 27.9, 26.9, 25.6, 22.9, 20.0, 14.0, 9.2. Anal. ($C_{18}H_{23}N_5 \cdot 2H_2O$) C, H, N.

3-(1′*H*-Tetrazol-5′-yl)-*N*-cyclobutylmethylmorphinan 43 (MCL-152) was prepared according to the procedure for the preparation **42**. White solid (63.7%), Mp: 200−202 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.93 (s, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.17 (d, J = 8.1 Hz, 1H), 3.21−1.05 (complex, 25H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.6, 139.3, 135.7, 130.5, 129.8, 126.1, 125.0, 59.9, 53.6, 37.5, 36.3, 32.4, 28.0, 27.0, 22.9, 19.4. Anal. ($C_{22}H_{29}N_5 \cdot 1.25H_2O$) C, H, N.

3-Aminomethyl-*N*-methylmorphinan 44 (MCL-154). A solution of nitrile **29** (0.22 mmol) in THF was added $LiAlH_4$ (76 mg, 2 mmol) at room temperature. The mixture was stirred for 20 h, and then excess $LiAlH_4$ was decomposed with 10 mL of EtOAc. Saturated ammonium tartrate was added, and the mixture was stirred for additional 1 h. The solution was filtered, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried and concentrated to yield crude product which was purified by column chromatography on silica gel ($CHCl_3$:MeOH = 1:1) giving the amine **44** (12 mg, 14%) as pale yellow oil. MS (EI): 270 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.10 (s, 1H), 6.89 (s, 2H), 3.76 (s, 2H), 3.03−1.07 (complex, 21H). Anal. ($C_{18}H_{26}N_2$) C, H, N.

3-Aminomethyl-*N*-cyclobutylmethylmorphinan 45 (MCL-175) was prepared using the same procedure for preparation of compound **44**. Pale yellow oil (27%), MS (EI): 324 (M^+); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.06 (s, 1H), 6.81 (s, 2H), 3.66 (s, 2H), 3.03−1.07 (complex, 27H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.9, 135.4, 133.1, 128.89, 127.0, 126.2, 58.5, 57.3, 46.1, 45.8, 42.9, 41.4, 38.6, 36.4, 35.1, 31.5, 27.1, 27.0, 25.9, 22.8, 18.3. Anal. ($C_{22}H_{32}N_2$) calcd. C, H, N.

General Procedure for the Preparation of Amide 46−**48.** The nitriles **29**, **31**, **32** (1.09 mmol) in MeOH (10 mL) were added 25% potassium hydroxide (5 mL) and 2 drops of 30% hydrogen peroxide solution. The mixture was refluxed for 3 h. After cooling to room temperature, the reaction mixture was extracted with EtOAc. The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatograph (hexane:EtOAc:Et_3N = 100:100:1) affording the corresponding amides.

3-Carboxamido-*N*-methylmorphinan 46 (MCL-138). Pale yellow solid (68%), Mp 245−247 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.77 (d, J = 1.8 Hz, 1H), 7.50 (dd, J = 2.1, 7.8 Hz, 1H), 7.18 (d, J = 7.8 Hz, 1H), 6.02 (brs, 1H), 5.98 (brs, 1H), 3.08 (d, J = 19.2 Hz, 1H), 2.86−1.23 (complex, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.6, 142.5, 141.2, 131.4, 127.9, 125.0, 123.9, 57.6, 46.9, 45.1, 42.7, 41.8, 37.2, 36.3, 26.7, 26.4, 24.4, 22.1. Anal. ($C_{18}H_{24}N_2O \cdot 0.6H_2O$) C, H; N: calcd, 9.44; found, 9.03.

3-Carboxamido-*N*-cyclopropylmethylmorphinan 47 (MCL-180). Pale yellow foam (57%), ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.79 (d, J = 1.8 Hz, 1H), 7.51 (dd, J = 2.1, 7.8 Hz, 1H), 7.17 (d, J = 7.8 Hz, 1H), 6.05 (brs, 1H), 5.93 (brs, 1H), 3.24−0.14 (complex, 23H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.8, 141.2, 137.8, 131.8, 128.2, 125.3, 124.3, 59.8, 55.8, 45.7, 44.5, 41.3, 37.9, 36.3, 26.9, 26.6, 25.3, 22.3, 9.0, 4.3, 4.1. Anal. ($C_{21}H_{28}N_2O \cdot 2/3H_2O$) C, H, N.

3-Carboxamido-*N*-cyclobutylmethylmorphinan 48 (MCL-148). Colorless foam (66%), ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.76 (s, 1H), 7.50 (d, J = 8.1 Hz, 1H), 7.17 (d, J = 7.8 Hz, 1H), 6.08 (brs, 1H), 5.95 (brs, 1H), 3.07−1.01 (complex, 25H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.0, 143.1, 141.7, 131.4, 128.1, 125.2, 124.1, 61.7, 55.9, 45.7, 45.2, 42.0, 38.0, 36.5, 35.1, 28.0, 27.0, 26.7, 25.4, 22.4, 19.0. MS (EI): 338 (M^+). Anal. ($C_{22}H_{30}N_2O \cdot 0.2H_2O$) calcd. C, H, N.

Acknowledgment. This work was supported, in part, by NIDA Grants K05-DA 00360, U-19-DA 11007, K05-DA00101, and R01-DA14251. Levorphanol tartrate was generously donated by Mallinckrodt Inc.. We gratefully acknowledge the calculation of the interatomic distances and conformational analysis of compound **10** by Dr. Suobao Rong.

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JM0304156