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Synthesis of 6,14-epoxymorphinan derivatives and their pharmacologies

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ABSTRACT

A novel 6,14-epoxymorphinan benzamide derivative (NS22) that was previously reported showed opioid κ receptor agonistic activity and analgesic activity. The unsatisfactory κ selectivity of NS22 led us to synthesize its derivatives to improve the opioid κ receptor selectivity and the agonist activity. In the course of SAR of the various derivatives, 17-benzyl-6,14-epoxymorphinan derivatives (KNT-33, 53, 55, 80, 90, 133) were found to show high selectivities and affinities for the opioid κ receptor. In addition, KNT-33, 53, 55 showed dose-dependent analgesic effects in acetic acid writhing tests. Therefore, 17-benzyl substituents may play an important role for developing κ selectivity.

1. Introduction

Three types of opioid receptors (μ, δ, κ) are now well established not only by pharmacological studies but also by molecular biological characterizations.[1–4] Narcotic addiction is believed to be derived from the μ receptor type, and therefore the δ and κ types are promising drug targets for analgesics without addiction. A putative ε receptor, which has not been cloned yet, has also been proposed as another opioid receptor type and much pharmacological data supporting its existence have been reported.[5] To obtain ideal analgesia without addiction and other side effects derived from the μ receptor, we have synthesized various kinds of naltrexone (Fig. 1) derivatives and have reported selective ligands for the κ,[6–9] δ,[10–13] and ε[14] receptors. Quite recently, one of our designed κ selective agonist, TRK-820,[6,7] was launched in Japan as an antipruritic agent for kidney dialysis patients.[15]

Although many arylacetamide derivatives such as U50,488H and U69,593 (Fig. 1)[1,16–19] were synthesized and developed as κ agonists all over the world, all of these derivatives had serious aversive side effects like psychotomimetic reactions[20–22] and were thus excluded from clinical trials.

On the other hand, TRK-820 showed neither aversive nor addictive effects. We were interested in the difference of the pharmacological effects between TRK-820 and the arylacetamide derivatives, and carried out the conformational analysis of them and detailed SAR investigation of TRK-820 derivatives to develop the working hypothesis that when TRK-820 binds to the κ receptor, the C-ring would adopt a boat conformation.[8,23,24]

According to the above hypothesis, the 14-hydroxy group may interact with the 6-amide side chain in TRK-820 and this orientation of the amide side chain would assist the adaptation of the ligand to the κ receptor (Fig. 2). On the basis of the hypothesis, we previously synthesized NS22 and have reported its pharmacology.[24] Although NS22 showed affinity for all three opioid receptors, its antinociceptive effect was derived from only the κ opioid receptor (in the present paper, we have changed the name of NS22 to KNT-1). However, as the κ selectivity of NS22 was not high in the binding assay, we decided to synthesize additional 6,14-epoxymorphinan derivatives in an effort to improve the κ selectivity.

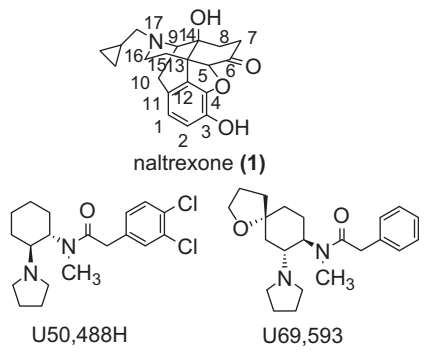

Figure 1. The structures of naltrexone and representative arylacetamide κ agonists.

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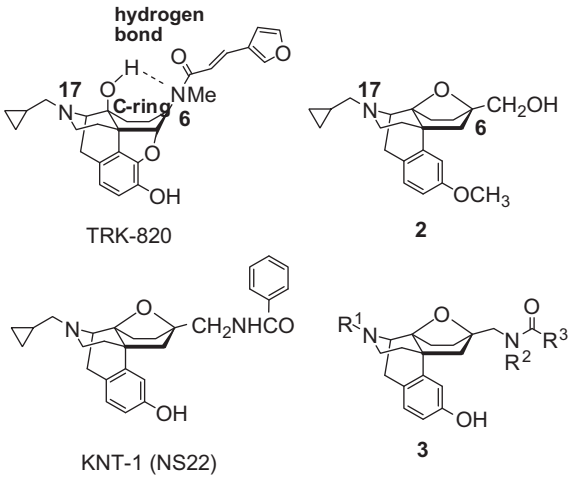


Figure 2. The structures of TRK-820, KNT-1 and compounds 2, 3.

Here, we report the synthesis of 6,14-epoxymorphinan derivatives **3** and their pharmacologies.

2. Results

2.1. Chemistry

Synthesis of 17-cyclopropylmethyl analogs with various 6-amide side chains (Scheme 1) commenced with azide **4** prepared from compound **2**[25] by our previously reported method.[24] The reduction of azide **4** with Pd–C under H_2 afforded amine **5**. The resulting amine **5** was amidated with various acyl halides followed by *O*-demethylation of the obtained amides **6** with 1-C_3H_7SK in DMF.[26] The *N*-methylamide derivatives (KNT-2 and 17) were synthesized by the amidation of compound **5** followed by *N*-methylation of amide **6** and subsequent *O*-demethylation. KNT-32 was synthesized by *O*-demethylation of compound **5** followed by amidation (esterification) and subsequent hydrolysis of the ester moiety.

To examine the influences of the 17-substituents on κ selectivities, we converted the 17-cyclopropylmethyl substituent to methyl (KNT-18, Scheme 2), isobutyl (KNT-27, 45, 46, and 47, Scheme 3), benzyl (KNT-33, 53, 55, 80, 90, 132, and 133, Scheme 4), phenethyl (KNT-34, Scheme 5), and cyclobutlmethl (KNT-67, Scheme 5) analogs.

The azide **9**, which was derived from compound **4** using chloroformate,[27] was converted to compound **10** by reductive amination with HCHO and $NaBH_4$ (Scheme 2). The resulting compound **10** was reduced by catalytic hydrogenation (Pd-C) under hydrogen, followed by amidation with benzoic anhydride and subsequent *O*-demethylation to give KNT-18.

Hydrogenation of compound **4** in the presence of PtO_2 catalyst gave 17-isobutyl derivative **12** (Scheme 3).[28,29] Compound **12** was converted to KNT-27, 45, 46, and 47 by the same method shown in Scheme 1.

To obtain 17-benzyl derivatives, compound **14**, which was derived from compound **5** for *N*-protection of the primary amine, was transformed into secondary amine **16** by a previously reported method (Scheme 4).[30] The resulting amine **16** was benzylated by benzyl bromide, followed by the deprotection of the carbamate **17** to give compound **18**. The compound **18** was converted to KNT-33, 53, 55, 80, 90, 132, and 133 by the same method as that shown in Scheme 1.

The amides **23a** and **b** with the respective 17-phenethyl and 17-cyclobutylmethyl substituents were prepared by alkylation of amine **22**, which was obtained from 17-cyclopropylmethyl derivative **6j** via carbamate **21** (Scheme 5). *O*-Demethylation of the amides **23** gave the corresponding analogs KNT-34 and 67.

2.2. Pharmacological activity

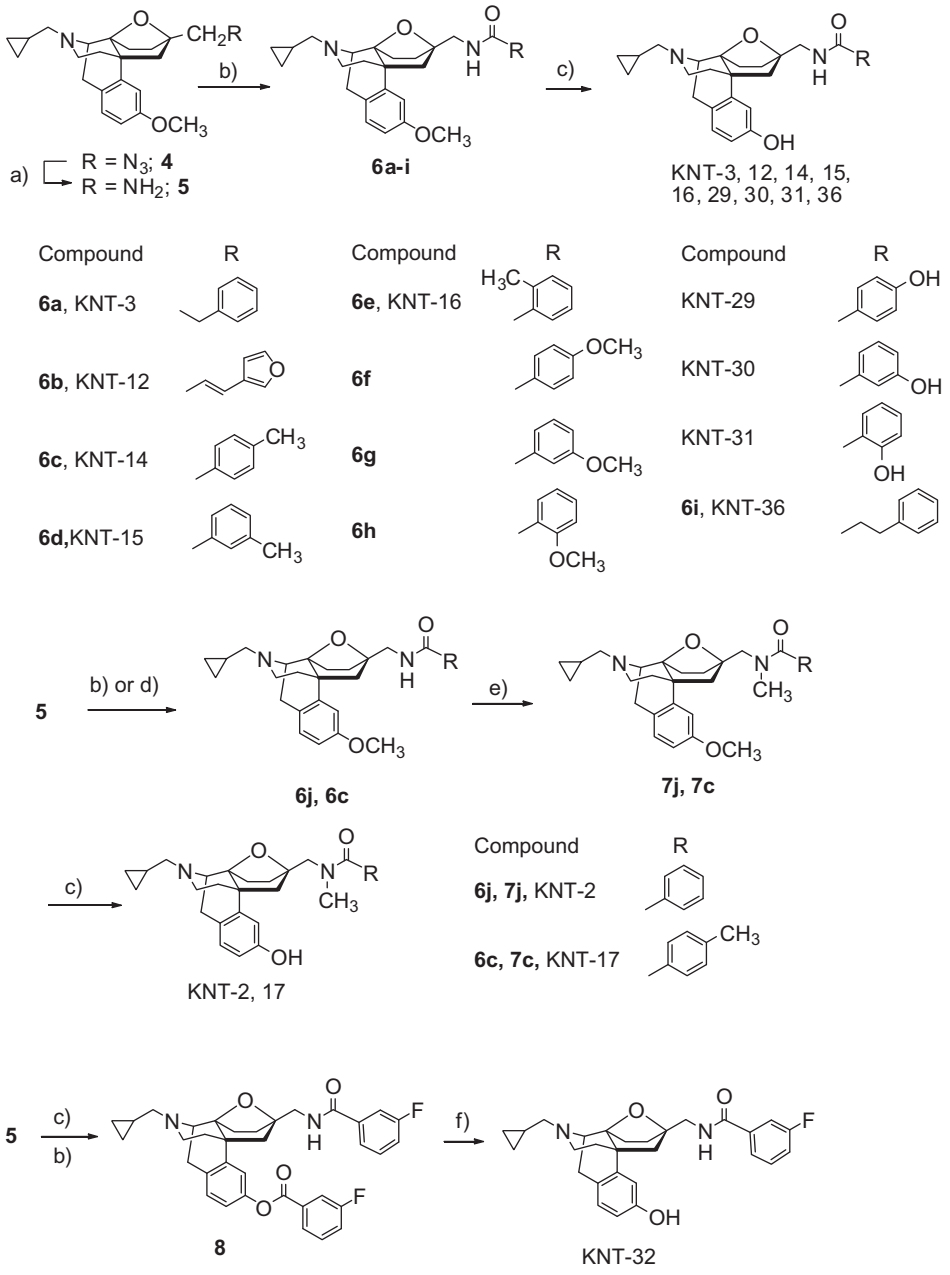
To evaluate the binding affinities of KNT-compounds for opioid receptors, we demonstrated the competitive displacement of bound [^{3}H]DAMGO (the μ opioid receptor ligand), [^{3}H]NTI (the δ opioid receptor ligand), or [^{3}H]U69,593 (the κ opioid receptor ligand), using homogenates of guinea-pig brain (μ and δ: forebrain, κ: cerebellum). The binding affinities of KNT-compounds are shown in Table 1 along with those of the representative κ opioid ligands TRK-820 and nor-BNI.[31–34] All KNT-compounds showed sufficient affinities for the κ opioid receptor. As a general trend, the 17-isobutyl derivatives (KNT-27, 45, 46, 47) tended to be more selective for the κ receptor than the 17-cyclopropylmethyl derivatives (KNT-1, 2, 3, 12, 14, 15, 16, 17, 29, 30, 31, 32, 36), the 17-methyl derivative (KNT-18), the 17-phenethyl derivative (KNT-34), and the 17-cyclobutylmethyl derivative (KNT-67). However, among the 17-isobutyl derivatives, KNT-45, 46, and 47 showed less selectivity for the κ receptor than did KNT-27. Among KNT-compounds, 17-benzyl derivatives (KNT-33, 53, 55, 80, 90, 133) showed the highest selectivities for the κ receptor.

In the 17-cyclopropylmethyl derivatives, the amide side chains had little influence on the κ selectivity, but influenced the affinities for the κ receptor. In the 17-benzyl derivatives, the substituent on the benzamide side chain also influenced the κ selectivity. Among the hydroxyl benzamide derivatives (KNT-55, 90, 53), the *para*-hydroxy derivative (KNT-53) showed the best selectivity for the κ receptor (*para* > *meta* > *ortho*). A similar tendency was observed in the monofluoro-benzamide derivatives (KNT-80, 132, 133).

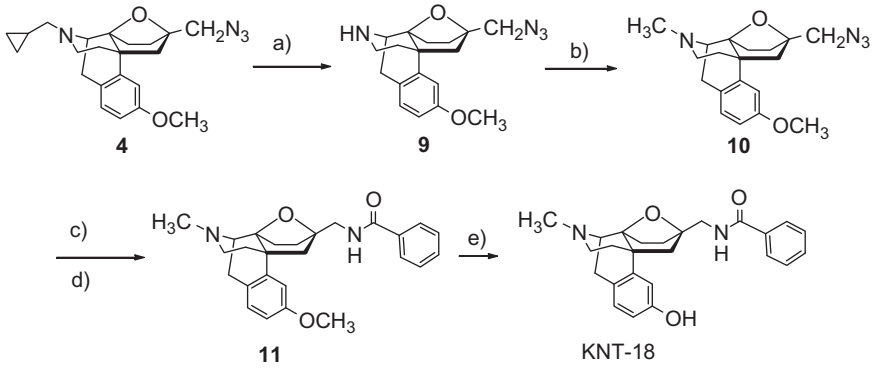
We next evaluated the antinociceptive effects of selected compounds (KNT-1, 33, 53, and 55) by acetic acid writhing tests (AAW). All compounds administered subcutaneously showed dose-dependent analgesic effects. Their ED_{50} values are shown in Table 2. KNT-33 produced the most potent antinociceptive effects among the 17-benzyl derivatives (KNT-33, 53, and 55). However, its potency was less than the corresponding 17-cyclopropylmethyl derivative (KNT-1).

3. Discussion

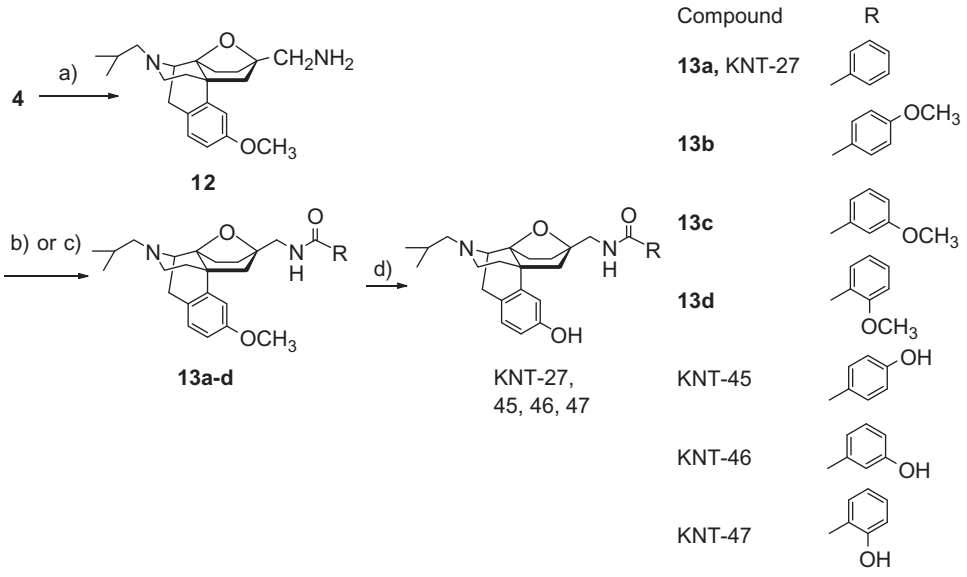
We synthesized a series of 6,14-epoxymorphinan derivatives and evaluated their pharmacologies. Although significant differences in κ selectivity were not obtained in the 17-cyclopropylmethyl derivatives [(Table 1), KNT-1, 2, 3, 12, 14, 15, 16, 17, 29, 30, 31, 32, 36], the presence of an amide side chain influenced the affinities for the κ receptor. For example, KNT-30, 31, 32, and 36 exhibited higher affinities for the κ receptor than KNT-1, and they also showed a degree of selectivity for the κ receptor which was similar to that of KNT-1. Based on these results, we focused on the conversion of the substituents at other positions to improve the κ selectivity. Generally speaking, in morphinan derivatives, the 17-nitrogen substituent plays an important role in distinguishing agonist from antagonist in μ ligands. For example, morphine with a 17-methyl substituent is an agonist, and naltrexone with 17-cyclopropylmethyl group is an antagonist. On the other hand, the 17-substituent had some influence on the κ selectivity. TRK-820 with a 17-cyclopropylmethyl substituent showed the best κ selectivity and was the most potent κ agonist among the TRK-820 derivatives modified with different 17-substituents (cyclopropylmethyl, methyl, hydrogen, phenethyl).[7] As the role of the 17-nitrogen substituent has not yet been clarified in 6,14-epoxymorphinan derivatives, we expected that the 17-substituent



Scheme 1. Reagents and conditions: (a) Pd–C, CSA, H_2, CH_3OH, rt; (b) RCOCl, $(C_2H_5)_3N$, THF, 0 °C, 43–90% (two steps or three steps); (c) 1-C_3H_7SH, $(CH_3)_3COK$, DMF, 150 °C, 57–91%; (d) $(PhCO)_2O$, Py, rt, 60% (two steps from **4**); (e) CH_3I, NaH, THF, 0 °C, 77% (**7j**), 60% (**7c**); (f) 4 M NaOH, CH_3OH, THF, rt, 78%.



Scheme 2. Reagents and conditions: (a) 1-chloroethylchloroformate, 1,1,2,2-tetrachloroethane, 100 °C, then CH_3OH, reflux, 60%; (b) 37% HCHO, CH_3COONa, 2 M AcOH, rt, after 3 h, $NaBH_4$, 0 °C, 66%; (c) Pd–C, CSA, H_2, MeOH, rt; (d) $(PhCO)_2O$, Py, rt; (e) 1-C_3H_7SH, $(CH_3)_3COK$, DMF, 150 °C, 57% (three steps from **10**).



Scheme 3. Reagents and conditions: (a) PtO_2, CSA, MeOH, H_2, rt; (b) $(PhCO)_2O$, Py, rt, 37% (two steps from **4**); (c) corresponding acyl halides, $(C_2H_5)_3N$, THF, 0 °C; 53% (**13b**: two steps); (d) 1-C_3H_7SH, $(CH_3)_3COK$, DMF, 150 °C, 63% (KNT-27), 49% (KNT-45), 35% (KNT-46: three steps), 46% (KNT-47: three steps).

in the 6,14-epoxymorphinan derivatives may influence selectivities for the different receptor types. Among derivatives with various 17-substituents, the 17-benzyl compounds showed the higher κ selectivity [(Table 1), KNT-33, 53, 55, 90]. In the 17-benzyl derivatives, the substituent on the benzamide side chain also influenced the κ selectivity. Among the hydroxyl benzamide derivatives (KNT-55, 90, 53), the *para*-hydroxyl derivative (KNT-53) showed the best selectivity for the κ receptor (*para* > *meta* > *ortho*). A similar tendency was obtained in the monofluoro-benzamide derivatives (KNT-80, 132, 133). These results suggest that the hydroxyl or the fluoro group in the *para* position may participate in the optimum pharmacophore binding to the κ receptor.

Table 2 shows the results of acetic acid writhing (AAW) tests of KNT-1, 33, 53, 55, and TRK-820 in adult male mice. Based on the ED_{50} values, KNT-33 showed antinociceptive effects that were 3.2- and 3.8-fold more potent than those of the phenolic-amide derivatives KNT-53 and KNT-55, respectively. These weak activities of KNT-53, 55 may result from the presence of the phenolic hydroxyl groups on the 6-amide substituents which might be easily metabolized (e.g., *O*-glucuronidation). In considering the design of future analogs that are more potent, we should consider the use of substituents that are resistant to metabolism. Another reason for the difference in antinociceptive effect may be the higher polarity of the derivatives which would decrease permeability across the in blood-brain barrier. Therefore, compounds with more lipophilic substituents may display more potent antinociceptive activity.

In this research, we found that 17-benzyl derivatives showed higher selectivity for the κ receptor. The introduction of the benzyl group to the 17-position would be applicable to the other morphinan to improve the κ receptor selectivity. For example, 17-benzyl derivatives of KNT-63,[8] which is one of the our previously designed κ agonists with an oxabicyclo[2.2.2]octane skeleton may improve the selectivity for the κ receptor. We are currently synthesizing some morphinan derivatives with 17-benzyl substituent to obtain more selective ligands for the κ receptor.

4. Conclusion

We synthesized various 17-substituted 6,14-epoxymorphinan derivatives. We found that 17-benzyl-6,14-epoxymorphinan derivatives (KNT-33, 53, 55, 80, 90, and 133) showed higher κ selectivities. All the tested 17-benzyl derivatives (KNT-33, 53, and 55) exhibited analgesic effects in AAW tests. Our data indicate that the conversion of the 17-substituent to a benzyl group may give more selective κ agonists.

5. Experimental

5.1. Chemistry

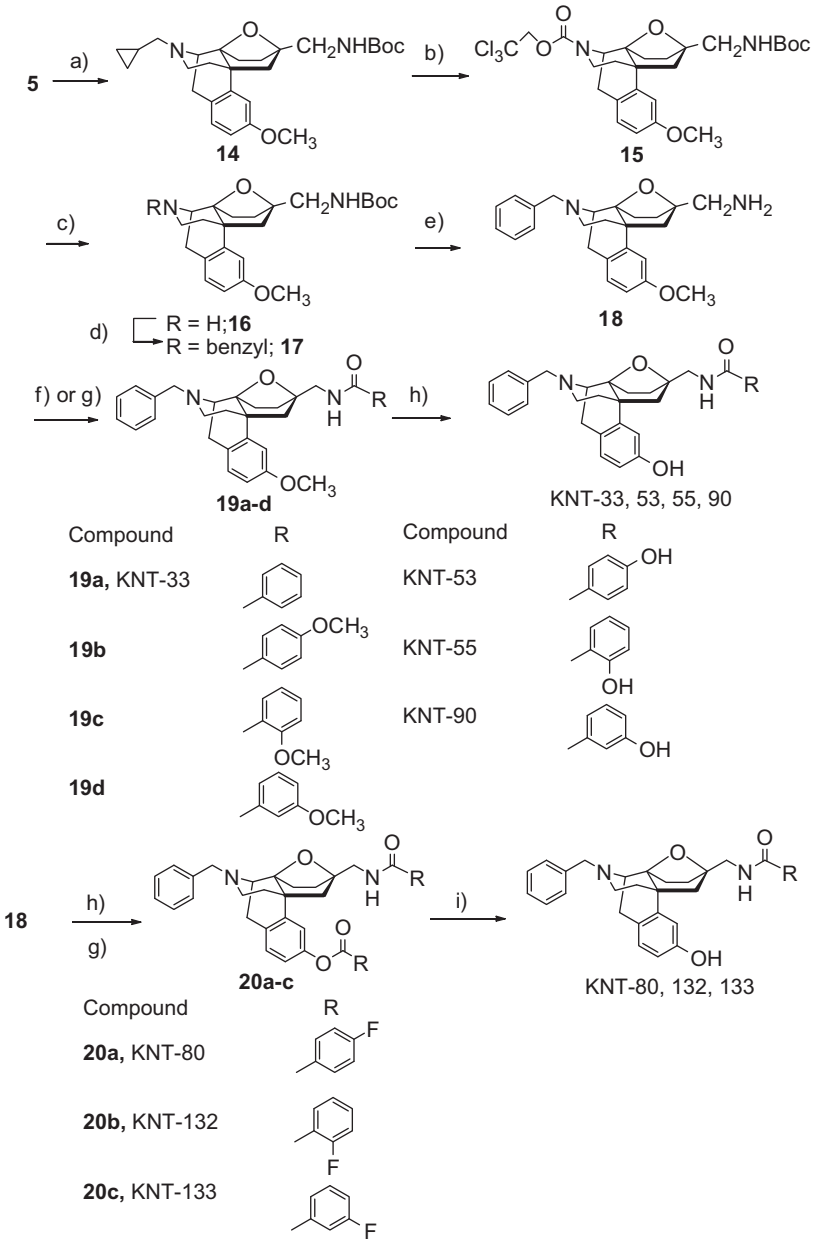
Melting points were determined on a Yazawa BY-1 melting point apparatus and were uncorrected. Infrared (IR) spectra were recorded on a JASCO FT/IR-460Plus. Nuclear magnetic resonance (NMR) spectra were recorded on a Valian Mercury-300 or Varian UNITY-400 for ^1H NMR. Chemical shifts were reported as δ values (ppm) related to tetramethylsilane (TMS). Mass spectra (MS) were obtained on a JMS-AX505HA or JMS-700M station instruments by applying a fast atom bombardment (FAB) ionization method. Elemental analyses were determined with a Yanako MT-5 for carbon, hydrogen, and nitrogen. The progress of the reaction was determined on Merck Silica Gel Art. 5715. Column chromatographies were carried out using Kanto Silica Gel 60 N (40–100 μm).

5.1.1. (17-Cyclopropylmethyl-6β,14β-epoxy-3-methoxymorphinan-6α-yl)methanamine (5)

To a stirred solution of **4** (630 mg, 1.66 mmol) and 10-camphorsulfonic acid (962 mg, 4.14 mmol) in MeOH (10 mL) was added 10%Pd-C (300 mg) and stirred at rt under a H_2 atmosphere. After 12 h with stirring, the reaction mixture was filtrated and evaporated in vacuo. The resulting mixture was basified (pH 9) with 1 M NaOH aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine twice, dried over Na_2SO_4. Evaporation of the solvent gave an oil residue **5** (541 mg) which was used for next reaction without purification.

5.1.2. 2-Phenyl-*N*-[(17-cyclopropylmethyl-6β,14β-epoxy-3-methoxymorphinan-6α-yl)methyl]acetamide (6a)

To a stirred solution of **5** (185 mg) in THF (5 mL) and triethylamine (0.43 mL, 3.13 mmol) was added phenylacetyl chloride (0.21 ml, 1.57 mmol) at 0 °C under an Ar atmosphere. After 1.5 h with stirring, water was added to the reaction mixture and the

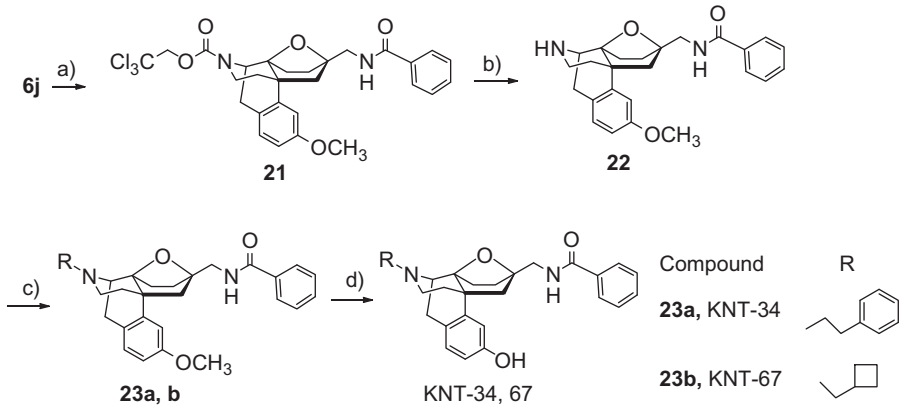


Scheme 4. Reagents and conditions: (a) Boc_2O, py, rt, 61% (two steps from **4**); (b) Cl_3CCH_2OCOCl, proton sponge, CH_2Cl_2, rt, 96%; (c) Zn, CH_3COOH, rt; (d) $C_6H_5CH_2Br$, K_2CO_3, DMF, rt, 85% (two steps); (e) 2 M HCl, CH_3OH, 60 °C; (f) $(PhCO)_2O$, Py, rt; (g) RCOCl, $(C_2H_5)_3N$, THF, 0 °C, 36–92% (two steps or three steps); (h) 1-C_3H_7SH, $(CH_3)_3COK$, DMF, 150 °C, 50% (KNT-33), 95% (KNT-53), 83% (KNT-55), 74% (KNT-90); (i) 4 M NaOH, CH_3OH, THF, rt, 98% (KNT-80), 95% (KNT-132), 94% (KNT-133).

mixture was evaporated in vacuo. To the resulting mixture was added 1 M NaOH aqueous solution and extracted with ethyl acetate three times. The combined organic extracts were washed with brine twice, dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica gel (25 g; $CHCl_3$/MeOH = 50:1–20:1) to give **6a** (116 mg, 43%, two steps from **4**) as a white amorphous solid. IR (film): 1659 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.04–0.18 (2H, m), 0.43–0.60 (2H, m), 0.86–1.00 (1H, m), 1.10 (1H, dt, J = 12.5, 2.0 Hz), 1.32–1.40 (1H, m), 1.43–1.58 (2H, m), 1.60–1.81 (3H, m), 1.91 (1H, dt, J = 4.5, 13.0 Hz), 2.02 (1H, dt, J = 2.0, 13.0 Hz), 2.32–2.49 (2H, m), 2.50–2.65 (2H, m), 3.08 (1H, d, J = 18.0 Hz), 3.50–3.65 (4H, m), 3.76 (3H, s), 3.79 (1H, dd, J = 6.5, 14.0 Hz), 6.06 (1H, t, J = 6.5 Hz), 6.52 (1H, d, J = 2.5 Hz), 6.68 (1H, dd, J = 2.5, 8.0 Hz), 6.97 (1H, d, J = 8.0 Hz), 7.20–7.38 (5H, m). MS (FAB) m/z = 473 $[M+H]^+$. HRMS (FAB) Calcd for $C_{30}H_{37}N_2O_3$ $[M+H]^+$: 473.2804. Found: 473.2814.

5.1.3. 2-Phenyl-*N*-[(17-cyclopropylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]acetamide (KNT-3)

To a stirred solution of **6a** (118 mg, 0.26 mmol) in DMF (6 mL) were added *t*-BuOK (196 mg, 1.75 mmol) and 1-propanethiol (0.23 ml, 2.54 mmol) and stirred at 150 °C for 8 h. The reaction mixture was evaporated in vacuo. The resulting mixture was basified (pH 9) with 1 M HCl aqueous solution and $NaHCO_3$, and extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine twice, dried over Na_2SO_4. The residue was chromatographed on silica gel (11 g; $CHCl_3$/MeOH = 20:1–15:1) to give KNT-3 (94 mg, 82%) as a white solid. IR (film): 1653 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.04–0.18 (2H, m), 0.43–0.60 (2H, m), 0.83–0.97 (1H, m), 1.10 (1H, dt, J = 12.5, 2.0 Hz), 1.22–1.31 (1H, m), 1.41–1.78 (5H, m), 1.90 (1H, dt, J = 4.5, 13.0 Hz), 2.06 (1H, dt, J = 2.0, 13.0 Hz), 2.38 (1H, dd, J = 6.5, 13.0 Hz), 2.40–2.49 (1H, m), 2.50–2.62 (2H, m), 3.06



Scheme 5. Reagents and conditions: (a) Cl_3CCH_2OCOCl, proton sponge, CH_2Cl_2, rt, 98%; (b) Zn, CH_3COOH, rt; (c) corresponding alkyl halides, K_2CO_3, DMF, rt, 50% (**23a**: two steps), 56% (**23b**: two steps); (d) 1-C_3H_7SH, $(CH_3)_3COK$, DMF, 150 °C, 67% (KNT-34), 87% (KNT-67).

(1H, d, *J* = 18.0 Hz), 3.50–3.65 (4H, m), 3.76 (1H, dd, *J* = 6.5, 14.0 Hz), 6.21 (1H, t, *J* = 6.5 Hz), 6.53 (1H, d, *J* = 2.5 Hz), 6.63 (1H, dd, *J* = 2.5, 8.0 Hz), 6.92 (1H, d, *J* = 8.0 Hz), 7.20–7.38 (5H, m), one proton (OH) was not observed. MS (FAB) *m*/*z* = 459 $[M+H]^+$. HRMS (FAB) Calcd for $C_{29}H_{35}N_2O_3$ $[M+H]^+$: 459.2648. Found: 459.2649.

5.1.4. 2-Phenyl-*N*-[(17-cyclopropylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]acetamide hydrochloride (KNT-3·HCl)

To a solution of KNT-3 (58 mg, 0.13 mmol) in MeOH (3 mL) was added HCl–MeOH (3 mL) dropwise. After evaporation, to the residue was added Et_2O to give a white solid. The solid was filtrated and dried under reduced pressure at 80 °C to give KNT-3·HCl salt (44 mg, 82%) as a white solid: mp 172–174 °C (dec). Anal. Calcd for $C_{29}H_{34}N_2O_3{\cdot}HCl{\cdot}0.7H_2O$: C, 68.61; H, 7.23; N, 5.52. Found: C, 68.52; H, 7.31; N, 5.37.

5.1.5. (2*E*)-*N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-methoxymorphinan-6α-yl)methyl]-(3-furyl)acrylamide (6b)

Compound **6b** was prepared from compound **5** according to the procedure used to prepare compound **6a** by use of 3-(3-furyl)acryloyl chloride, which was synthesized from 3-(3-furyl)acrylic acid, instead of phenylacetyl chloride. Yield, 46% (two steps from **4**). IR (film): 1668, 1623 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.05–0.20 (2H, m), 0.44–0.62 (2H, m), 0.88–1.02 (1H, m), 1.26 (1H, dt, *J* = 12.5, 2.0 Hz), 1.41–1.49 (1H, m), 1.52–1.92 (5H, m), 2.07 (1H, dt, *J* = 2.0, 13.0 Hz), 2.22 (1H, dd, *J* = 4.5, 13.0 Hz), 2.28–2.42 (2H, m), 2.50–2.70 (2H, m), 3.10 (1H, d, *J* = 18.0 Hz), 3.64–3.77 (2H, m), 3.76 (3H, s), 3.96 (1H, dd, *J* = 6.5, 15.0 Hz), 6.21 (1H, d, *J* = 15.0 Hz), 6.44 (1H, t, *J* = 6.5 Hz), 6.56 (1H, d, *J* = 2.5 Hz), 6.56–6.60 (1H, m), 6.68 (1H, dd, *J* = 2.5, 8.0 Hz), 6.99 (1H, d, *J* = 8.0 Hz), 7.38–7.42 (1H, m), 7.55 (1H, dd, *J* = 0.5, 15.0 Hz), 7.60 (1H, m). MS (FAB) *m*/*z* = 475 $[M+H]^+$. HRMS (FAB) Calcd for $C_{29}H_{35}N_2O_4$ $[M+H]^+$: 475.2597. Found: 475.2570.

5.1.6. (2*E*)-*N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-(3-furyl)acrylamide (KNT-12)

KNT-12 was prepared from compound **6b** according to the procedure used to prepare KNT-3. Yield, 57%. IR (film): 1666, 1619 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.04–0.18 (2H, m), 0.43–0.60 (2H, m), 0.93 (1H, m), 1.20–1.40 (2H, m), 1.50–1.65 (2H, m), 1.70–1.84 (3H, m), 2.04–2.28 (2H, m), 2.36 (1H, dd, *J* = 7.0, 12.5 Hz), 2.50–2.70 (3H, m), 3.10 (1H, d, *J* = 18.0 Hz), 3.69 (1H, dd, *J* = 6.5, 15.0 Hz), 3.70 (1H, d, *J* = 5.5 Hz), 3.91 (1H, dd, *J* = 6.5, 15.0 Hz), 6.21 (1H, d, *J* = 15.0 Hz), 6.52 (1H, t, *J* = 6.5 Hz), 6.56 (1H, d, *J* = 1.5 Hz), 6.61 (1H, d, *J* = 2.5 Hz), 6.67 (1H, dd, *J* = 2.5, 8.0 Hz), 6.94 (1H, d, *J* = 8.0 Hz), 7.40 (1H, t, *J* = 1.5 Hz), 7.54 (1H, dd, *J* = 0.5, 15.0 Hz), 7.60 (1H, dd, *J* = 0.5, 1.5 Hz), one proton (OH) was not observed. MS (FAB) *m*/*z* = 461 $[M+H]^+$. HRMS (FAB) Calcd for $C_{28}H_{33}N_2O_4$ $[M+H]^+$: 461.2440. Found: 461.2441.

5.1.7. (2*E*)-*N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-(3-furyl)acrylamide hydrochloride (KNT-12·HCl)

KNT-12·HCl was prepared from KNT-12 according to the procedure used to prepare KNT-3·HCl. Yield, 66%. Mp 198–201 °C (dec). Anal. Calcd for $C_{28}H_{32}N_2O_4{\cdot}0.9HCl{\cdot}0.8H_2O$: C, 66.23; H, 6.85; N, 5.52. Found: C, 66.30; H, 7.11; N, 5.39.

5.1.8. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-methoxymorphinan-6α-yl)methyl]-4-methylbenzamide (6c)

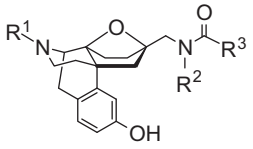
Compound **6c** was prepared from compound **5** according to the procedure used to prepare compound **6a** by use of 4-toluoyl chloride instead of phenylacetyl chloride. Yield, 52% (two steps from **4**). IR (film): 1645 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.04–0.22 (2H, m), 0.44–0.63 (2H, m), 0.91–1.04 (1H, m), 1.26 (1H, dt, *J* = 12.5, 2.0 Hz), 1.41–1.50 (1H, m), 1.52–1.96 (5H, m), 2.00–2.32 (3H, m), 2.40 (3H, s), 2.50–2.72 (3H, m), 3.13 (1H, d, *J* = 18.0 Hz), 3.71 (1H, d, *J* = 5.5 Hz), 3.77 (3H, s), 3.82–4.04 (2H, m), 6.57 (1H, d, *J* = 2.5 Hz), 6.70 (1H, dd, *J* = 2.5, 8.0 Hz), 6.77–6.84 (1H, m), 7.00 (1H, d, *J* = 8.0 Hz), 7.25 (2H, dd, *J* = 2.5, 8.0 Hz), 7.76 (2H, dd, *J* = 2.5, 8.0 Hz). MS (FAB) *m*/*z* = 473 $[M+H]^+$. HRMS (FAB) Calcd for $C_{30}H_{37}N_2O_3$ $[M+H]^+$: 473.2804. Found: 473.2789.

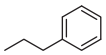
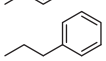
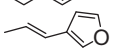
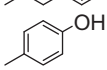
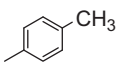
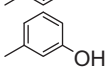
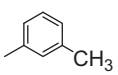
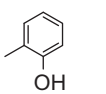
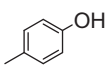
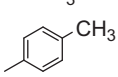
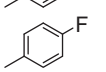
5.1.9. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-4-methylbenzamide (KNT-14)

KNT-14 was prepared from compound **6c** according to the procedure used to prepare KNT-3. Yield, 60%. IR (film): 1642 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.04–0.24 (2H, m), 0.44–0.62 (2H, m), 0.96–1.04 (1H, m), 1.27 (1H, dt, *J* = 12.5, 2.0 Hz), 1.31–1.41 (1H, m), 1.51–1.90 (5H, m), 2.00–2.34 (3H, m), 2.40 (3H, s), 2.52–2.75 (3H, m), 3.12 (1H, d, *J* = 18.0 Hz), 3.74 (1H, d, *J* = 5.5 Hz), 3.85–4.02 (2H, m), 6.62 (1H, d, *J* = 2.5 Hz), 6.67 (1H, dd, *J* = 2.5, 8.0 Hz), 6.83–6.92 (1H, m), 6.94 (1H, d, *J* = 8.0 Hz), 7.27 (2H, dd, *J* = 2.5, 8.0 Hz), 7.77 (2H, dd, *J* = 2.5, 8.0 Hz), one proton (OH) was not observed. MS (FAB) *m*/*z* = 459 $[M+H]^+$. HRMS (FAB) Calcd for $C_{29}H_{35}N_2O_3$ $[M+H]^+$: 459.2648. Found: 459.2635.

Table 1
Binding affinities of TRK-820, nor-BNI, and KNT-compounds for the μ, δ, κ opioid receptors

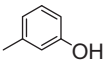
Compound	κ [^{3}H]U-69593	μ [^{3}H]DAMGO	δ [^{3}H]NTI	Selectivity (K_i)		
	K_i (nM)	K_i (nM)	K_i (nM)	μ/κ	δ/κ	δ/μ
TRK-820	0.225	0.582	96.5	2.6	456	166
nor-BNI	0.861	28.20	29.3	33	34	1
KNT-1 (NS22)	0.135	0.134	0.658	1	4.9	4.9
KNT-2	0.326	0.188	0.835	0.6	2.6	4.4
KNT-3	0.124	0.132	0.259	1.1	2.1	2
KNT-12	0.147	0.0828	0.769	0.6	5.2	9.3
KNT-14	0.132	0.129	0.709	1	5.4	5.5
KNT-15	0.126	0.156	0.692	1.2	5.5	4.4
KNT-16	0.12	0.109	0.751	0.9	6.3	6.9
KNT-17	0.71	0.27	5.07	0.4	7.1	18.8
KNT-18	0.228	0.0522	0.731	0.2	3.2	14
KNT-27	0.108	0.29	12.5	2.7	115.7	43.1
KNT-29	0.384	0.12	1.98	0.3	5.2	16.5
KNT-30	0.0754	0.121	0.688	1.6	9.1	5.7
KNT-31	0.088	0.147	0.573	1.7	6.5	3.9
KNT-32	0.0812	0.11	0.867	1.4	10.7	7.9
KNT-33	1.05	4.38	353	4.2	336.2	80.6
KNT-34	1.12	0.243	0.904	0.2	0.8	3.7
KNT-36	0.0833	0.182	0.337	2.2	4	1.9
KNT-45	2.31	0.946	47.7	0.4	20.6	50.4
KNT-46	0.116	0.389	9.87	3.4	85.1	25.4
KNT-47	0.141	0.466	4.19	3.3	29.7	9
KNT-53	0.543	27.2	263	50.1	484.3	9.7
KNT-55	1.82	17.4	240	9.6	131.9	13.8
KNT-67	0.133	0.138	2.65	1	19.9	19.2
KNT-80	1.13	6.16	NC[a]	5.5	–	–
KNT-90	0.699	18.3	160	26.2	228.9	8.7
KNT-132	8.56	6.79	286	0.8	33.4	42.1
KNT-133	0.438	1.35	137	3.1	312.8	101.5



Compound	R^1	R^2	R^3	Compound	R^1	R^2	R^3
KNT-1 (NS22)		H		KNT-33		H	
KNT-2		CH_3		KNT-34		H	
KNT-3		H		KNT-36		H	
KNT-12		H		KNT-45		H	
KNT-14		H		KNT-46		H	
KNT-15		H		KNT-47		H	
KNT-16		H		KNT-53		H	
KNT-17		CH_3		KNT-55		H	
KNT-18	CH_3	H		KNT-67		H	
KNT-27		H		KNT-80		H	
KNT-29		H		KNT-90		H	

(*continued on next page*)

Table 1 (*continued*)

Compound	R^1	R^2	R^3	Compound	R^1	R^2	R^3
KNT-30		H		KNT-132		H	
KNT-31		H		KNT-133		H	
KNT-32		H					

[a] Not calculated [the IC_{50} value was more than 1000 nM].

Table 2
Antinociceptive effects induced by sc administration of TRK-820, KNT-1, 33, 53, and 55 in acetic acid writhing tests[a]

Compound	AAW ED_{50}
TRK-820	3.3 μg/kg[b]
KNT-1	0.12 mg/kg
KNT-33	3.26 mg/kg
KNT-53	10.54 mg/kg
KNT-55	12.48 mg/kg

[a] Antinociceptive effects were evaluated using the acetic acid writhing test in adult mice, as describe in Section 5.
[b] Ref. 7.

5.1.10. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-4-methylbenzamide hydrochloride (KNT-14·HCl)

KNT-14·HCl was prepared from KNT-14 according to the procedure used to prepare KNT-3·HCl. Yield, 59%. Mp 184–187 °C (dec). Anal. Calcd for $C_{29}H_{34}N_2O_3 \cdot HCl \cdot H_2O$: C, 67.89; H, 7.27; N, 5.46. Found: C, 67.60; H, 7.26; N, 5.44.

5.1.11. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-methoxymorphinan-6α-yl)methyl]-3-methylbenzamide (6d)

Compound **6d** was prepared from compound **5** according to the procedure used to prepare compound **6a** by use of 3-toluoyl chloride instead of phenylacetyl chloride. Yield, 65% (two steps from **4**). IR (film): 1650 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.03–0.22 (2H, m), 0.44–0.64 (2H, m), 0.91–1.05 (1H, m), 1.26 (1H, dt, J = 12.5, 2.0 Hz), 1.27–1.33 (1H, m), 1.44–1.82 (5H, m), 1.86–2.26 (3H, m), 2.40 (3H, s), 2.50–2.71 (3H, m), 3.12 (1H, d, J = 18.0 Hz), 3.68–3.75 (1H, m), 3.77 (3H, s), 3.86–4.02 (2H, m), 6.58 (1H, d, J = 2.5 Hz), 6.71 (1H, dd, J = 2.5, 8.0 Hz), 6.76–6.84 (1H, m), 7.02 (1H, d, J = 8.0 Hz), 7.28–7.38 (2H, m), 7.56–7.75 (2H, m). MS (FAB) m/z = 473 $[M+H]^+$. HRMS (FAB) Calcd for $C_{30}H_{37}N_2O_3$ $[M+H]^+$: 473.2804. Found: 473.2804.

5.1.12. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-3-methylbenzamide (KNT-15)

KNT-15 was prepared from compound **6d** according to the procedure used to prepare KNT-3. Yield, 75%. IR (film): 1644 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.05–0.23 (2H, m), 0.44–0.62 (2H, m), 0.90–1.03 (1H, m), 1.26 (1H, dt, J = 12.5, 2.0 Hz), 1.29–1.39 (1H, m), 1.51–1.88 (5H, m), 2.00–2.34 (3H, m), 2.40 (3H, s), 2.52–2.74 (3H, m), 3.12 (1H, d, J = 18.0 Hz), 3.74 (1H, d, J = 5.5 Hz), 3.85–4.02 (2H, m), 6.62 (1H, d, J = 2.5 Hz), 6.67 (1H, dd, J = 2.5, 8.0 Hz), 6.85–6.93 (1H, m), 6.92 (1H, d, J = 8.0 Hz), 7.28–7.36 (2H, m), 7.58–7.74 (2H, m), one proton (OH) was not observed. MS (FAB) m/z = 459 $[M+H]^+$. HRMS (FAB) Calcd for $C_{29}H_{35}N_2O_3$ $[M+H]^+$: 459.2648. Found: 459.2640.

5.1.13. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-3-methylbenzamide hydrochloride (KNT-15·HCl)

KNT-15·HCl was prepared from KNT-15 according to the procedure used to prepare KNT-3·HCl. Yield, 62%. Mp 176–180 °C (dec). Anal. Calcd for $C_{29}H_{34}N_2O_3 \cdot HCl \cdot 0.8H_2O$: C, 68.37; H, 7.27; N, 5.50. Found: C, 68.31; H, 7.15; N, 5.35.

5.1.14. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-methoxymorphinan-6α-yl)methyl]-2-methylbenzamide (6e)

Compound **6e** was prepared from compound **5** according to the procedure used to prepare compound **6a** by use of 2-toluoyl chloride instead of phenylacetyl chloride. Yield, 62% (two steps from **4**). IR (film): 1651 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.03–0.20 (2H, m), 0.40–0.62 (2H, m), 0.85–0.99 (1H, m), 1.20–1.40 (2H, m), 1.46–1.98 (5H, m), 2.00–2.40 (3H, m), 2.48 (3H, s), 2.51–2.70 (3H, m), 3.12 (1H, d, J = 18.0 Hz), 3.70 (1H, d, J = 5.5 Hz), 3.80 (3H, s), 3.85–4.02 (2H, m), 6.42–6.49 (1H, m), 6.60 (1H, d, J = 2.5 Hz), 6.70 (1H, dd, J = 2.5, 8.0 Hz), 7.02 (1H, d, J = 8.0 Hz), 7.17–7.48 (4H, m). MS (FAB) m/z = 473 $[M+H]^+$. HRMS (FAB) Calcd for $C_{30}H_{37}N_2O_3$ $[M+H]^+$: 473.2804. Found: 473.2804.

5.1.15. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-2-methylbenzamide (KNT-16)

KNT-16 was prepared from compound **6e** according to the procedure used to prepare KNT-3. Yield, 60%. IR (film): 1645 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.02–0.22 (2H, m), 0.40–0.62 (2H, m), 0.84–0.98 (1H, m), 1.28 (1H, dt, J = 12.5, 2.0 Hz), 1.35–1.45 (1H, m), 1.51–1.94 (5H, m), 2.00–2.40 (3H, m), 2.48 (3H, s), 2.51–2.73 (3H, m), 3.10 (1H, d, J = 18.0 Hz), 3.70 (1H, d, J = 5.5 Hz), 3.85–4.00 (2H, m), 6.42–6.54 (1H, m), 6.60 (1H, d, J = 2.5 Hz), 6.63 (1H, dd, J = 2.5, 8.0 Hz), 6.93 (1H, d, J = 8.0 Hz), 7.17–7.48 (4H, m), one proton (OH) was not observed. MS (FAB) m/z = 459 $[M+H]^+$. HRMS (FAB) Calcd for $C_{29}H_{35}N_2O_3$ $[M+H]^+$: 459.2648. Found: 459.2662.

5.1.16. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-2-methylbenzamide hydrochloride (KNT-16·HCl)

KNT-16·HCl was prepared from KNT-16 according to the procedure used to prepare KNT-3·HCl. Yield, 69%. Mp 181–185 °C (dec). Anal. Calcd for $C_{29}H_{34}N_2O_3 \cdot HCl \cdot 0.8H_2O$: C, 68.37; H, 7.24; N, 5.50. Found: C, 68.48; H, 7.27; N, 5.43.

5.1.17. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-methoxymorphinan-6α-yl)methyl]-4-methoxybenzamide (6f)

Compound **6f** was prepared from compound **5** according to the procedure used to prepare compound **6a** by use of 4-methoxybenzoyl chloride instead of phenylacetyl chloride. Yield, 60% (two steps from **4**). IR (film): 1643 cm^{-1}: ^1H NMR (300 MHz, $CDCl_3$) δ: 0.04–0.20 (2H, m), 0.43–0.63 (2H, m), 0.98 (1H, m), 1.26 (1H, dt, J = 12.5, 2.0 Hz), 1.46 (1H, m), 1.53–1.95 (5H, m), 2.07 (1H, dt, J = 2.0, 12.5 Hz), 2.24 (1H, dt, J = 4.5, 13.0 Hz), 2.37 (1H, dd, J = 7.0, 13.0 Hz), 2.52–2.70 (3H, m), 3.13 (1H, d, J = 18.0 Hz), 3.72 (1H, m), 3.77 (3H, s), 3.84 (3H, s), 3.88 (1H, dd, J = 6.5, 14.0 Hz), 3.99 (1H, dd, J = 6.5, 14.0 Hz), 6.57 (1H, d, J = 2.5 Hz), 6.69 (1H, dd, J = 2.5, 8.0 Hz), 6.80 (1H, t, J = 6.5 Hz), 6.94 (2H, dd, J = 2.5, 8.0 Hz), 7.00 (1H, d, J = 8.0 Hz), 7.84 (2H, dd, J = 2.5, 8.0 Hz). MS (FAB) m/z = 489 $[M+H]^+$. HRMS (FAB) Calcd for $C_{30}H_{37}N_2O_4$ $[M+H]^+$: 489.2753. Found: 489.2765.

5.1.18. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-4-hydroxybenzamide (KNT-29)

KNT-29 was prepared from Compound **6f** according to the procedure used to prepare KNT-3. Yield, 91%. IR (KBr): 1641 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ: 0.14–0.28 (2H, m), 0.48–0.68 (2H, m), 0.87–0.99 (1H, m), 1.16–1.23 (1H, m), 1.47–1.67 (3H, m), 1.72–1.92 (3H, m), 2.12–2.28 (2H, m), 2.45 (1H, dd, J = 7.0, 12.5 Hz), 2.54–2.62 (1H, m), 2.61 (1H, dd, J = 6.0, 12.5 Hz), 2.65 (1H, dd, J = 5.5, 18.0 Hz), 3.14 (1H, d, J = 18.0 Hz), 3.66 (1H, d, J = 14.5 Hz), 3.71 (1H, d, J = 5.5 Hz), 4.00 (1H, d, J = 14.5 Hz), 6.48 (1H, d, J = 2.5 Hz), 6.57 (1H, dd, J = 2.5, 8.0 Hz), 6.84 (2H, dd, J = 2.5, 8.0 Hz), 6.94 (1H, d, J = 8.0 Hz), 7.80 (2H, dd, J = 2.5, 8.0 Hz). MS (FAB) m/z = 461 $[M+H]^+$. HRMS (FAB) Calcd for $C_{28}H_{33}N_2O_4$ $[M+H]^+$: 461.2440. Found: 461.2456.

5.1.19. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-4-hydroxybenzamide hydrochloride (KNT-29·HCl)

KNT-29·HCl was prepared from KNT-29 according to the procedure used to prepare KNT-3·HCl. Yield, 69%. Mp 215–220 °C (dec). Anal. Calcd for $C_{28}H_{32}N_2O_4$·HCl·H_2O: C, 65.30; H, 6.85; N, 5.44. Found: C, 65.07; H, 6.87; N, 5.35.

5.1.20. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-methoxymorphinan-6α-yl)methyl]-3-methoxybenzamide (6g)

Compound **6g** was prepared from compound **5** according to the procedure used to prepare compound **6a** by use of 3-methoxybenzoyl chloride instead of phenylacetyl chloride. Yield, 90% (two steps from **4**). IR (film): 1652 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.06–0.24 (2H, m), 0.46–0.67 (2H, m), 0.91–1.05 (1H, m), 1.26 (1H, dt, J = 12.5, 2.0 Hz), 1.43–1.53 (1H, m), 1.56–1.97 (5H, m), 2.04–2.14 (1H, m), 2.18–2.33 (1H, m), 2.33–2.43 (1H, m), 2.50–2.72 (3H, m), 3.13 (1H, d, J = 18.0 Hz), 3.76 (1H, m), 3.77 (3H, s), 3.87 (3H, s), 3.87–4.07 (2H, m), 6.58 (1H, d, J = 2.5 Hz), 6.71 (1H, dd, J = 2.5, 8.0 Hz), 6.98–7.08 (2H, m), 7.30–7.52 (3H, m), one proton (NH) was not observed. MS (FAB) m/z = 489 $[M+H]^+$. HRMS (FAB) Calcd for $C_{30}H_{37}N_2O_4$ $[M+H]^+$: 489.2753. Found: 489.2754.

5.1.21. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-3-hydroxybenzamide (KNT-30)

KNT-30 was prepared from compound **6g** according to the procedure used to prepare KNT-3. Yield, 73%. IR (KBr): 1640 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ: 0.13–0.30 (2H, m), 0.48–0.66 (2H, m), 0.87–0.99 (1H, m), 1.17–1.27 (1H, m), 1.47–1.69 (3H, m), 1.72–1.94 (3H, m), 2.11–2.30 (2H, m), 2.44 (1H, dd, J = 7.0, 12.5 Hz), 2.52–2.59 (1H, m), 2.59 (1H, dd, J = 6.0, 12.5 Hz), 2.65 (1H, dd, J = 5.5, 18.0 Hz), 3.14 (1H, d, J = 18.0 Hz), 3.67 (1H, d, J = 14.5 Hz), 3.70 (1H, d, J = 5.5 Hz), 4.00 (1H, d, J = 14.5 Hz), 6.48 (1H, d, J = 2.5 Hz), 6.58 (1H, dd, J = 2.5, 8.0 Hz), 6.94–6.99 (1H, d, J = 8.0 Hz), 6.97 (1H, m), 7.24–7.38 (3H, m). MS (FAB) m/z = 461 $[M+H]^+$. HRMS (FAB) Calcd for $C_{28}H_{33}N_2O_4$ $[M+H]^+$: 461.2440. Found: 461.2447.

5.1.22. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-3-hydroxybenzamide hydrochloride (KNT-30·HCl)

KNT-30·HCl was prepared from KNT-30 according to the procedure used to prepare KNT-3·HCl. Yield, 70%. Mp 202–208 °C (dec). Anal. Calcd for $C_{28}H_{32}N_2O_4$·HCl·H_2O: C, 65.30; H, 6.85; N, 5.44. Found: C, 65.41; H, 6.82; N, 5.30.

5.1.23. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-methoxymorphinan-6α-yl)methyl]-2-methoxybenzamide (6h)

Compound **6h** was prepared from compound **5** according to the procedure used to prepare compound **6a** by use of 2-methoxybenzoyl chloride instead of phenylacetyl chloride. Yield, 88% (two steps from **4**). IR (film): 1652 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.06–0.22 (2H, m), 0.46–0.58 (2H, m), 0.90–1.01 (1H, m), 1.24 (1H, dt, J = 12.5, 2.0 Hz), 1.46–1.54 (1H, m), 1.57–1.95 (5H, m), 2.04–2.14 (1H, m), 2.19–2.34 (1H, m), 2.40–2.74 (4H, m), 3.14 (1H, d, J = 18.0 Hz), 3.64 (1H, d, J = 5.5 Hz), 3.78 (3H, s), 3.82 (1H, dd, J = 6.5, 14.0 Hz), 4.02 (3H, s), 4.08 (1H, dd, J = 6.5, 14.0 Hz), 6.57 (1H, d, J = 2.5 Hz), 6.69 (1H, dd, J = 2.5, 8.0 Hz), 6.98 (1H, d, J = 8.0 Hz), 7.01 (1H, dd, J = 2.0, 8.0 Hz), 7.08 (1H, dt, J = 2.0, 8.0 Hz), 7.45 (1H, dt, J = 2.0, 8.0 Hz), 8.22 (1H, dd, J = 2.0, 8.0 Hz), 8.40 (1H, t, J = 6.5 Hz). MS (FAB) m/z = 489 $[M+H]^+$. HRMS (FAB) Calcd for $C_{30}H_{37}N_2O_4$ $[M+H]^+$: 489.2753. Found: 489.2753.

5.1.24. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-2-hydroxybenzamide (KNT-31)

KNT-31 was prepared from compound **6h** according to the procedure used to prepare KNT-3. Yield, 84%. IR (KBr): 1642 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ: 0.16–0.30 (2H, m), 0.48–0.70 (2H, m), 0.89–1.01 (1H, m), 1.18–1.26 (1H, m), 1.49–1.72 (3H, m), 1.72–1.94 (3H, m), 2.18–2.34 (2H, m), 2.57 (1H, dd, J = 7.0, 12.5 Hz), 2.57–2.66 (1H, m), 2.64 (1H, dd, J = 6.0, 12.5 Hz), 2.74 (1H, dd, J = 5.5, 18.0 Hz), 3.15 (1H, d, J = 18.0 Hz), 3.76 (1H, d, J = 14.5 Hz), 3.77 (1H, d, J = 5.5 Hz), 3.99 (1H, d, J = 14.5 Hz), 6.50 (1H, d, J = 2.5 Hz), 6.59 (1H, dd, J = 2.5, 8.0 Hz), 6.85 (1H, dd, J = 2.0, 8.0 Hz), 6.88 (1H, dt, J = 2.0, 8.0 Hz), 6.95 (1H, d, J = 8.0 Hz), 7.36 (1H, dt, J = 2.0, 8.0 Hz), 7.89 (1H, dd, J = 2.0, 8.0 Hz). MS (FAB) m/z = 461 $[M+H]^+$. HRMS (FAB) Calcd for $C_{28}H_{33}N_2O_4$ $[M+H]^+$: 461.2440. Found: 461.2436.

5.1.25. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-2-hydroxybenzamide hydrochloride (KNT-31·HCl)

KNT-31·HCl was prepared from KNT-31 according to the procedure used to prepare KNT-3·HCl. Yield, 66%. Mp 198–202 °C (dec). Anal. Calcd for $C_{28}H_{32}N_2O_4$·HCl·1.25H_2O: C, 64.73; H, 6.89; N, 5.39. Found: C, 64.63; H, 6.74; N, 5.31.

5.1.26. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-methoxymorphinan-6α-yl)methyl]-3-phenylpropionamide (6i)

Compound **6i** was prepared from compound **5** according to the procedure used to prepare compound **6a** by use of hydrocinnamoyl chloride instead of phenylacetyl chloride. Yield, 46% (two steps from **4**). IR (film): 1660 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.06–0.21 (2H, m), 0.46–0.63 (2H, m), 0.91–1.02 (1H, m), 1.16 (1H, dt, J = 12.5, 2.0 Hz), 1.33–1.42 (1H, m), 1.42–1.62 (2H, m), 1.63–1.82 (3H, m), 2.08 (1H, dt, J = 2.0, 12.5 Hz), 2.20 (1H, dt, J = 4.5, 12.5 Hz), 2.40 (1H, dd, J = 7.0, 12.5 Hz), 2.52–2.72 (5H, m), 2.90–3.07 (2H, m), 3.12 (1H, d, J = 18.0 Hz), 3.49 (1H, dd, J = 6.0, 14.0 Hz), 3.72 (1H, d, J = 5.5 Hz), 3.79 (3H, s), 3.86 (1H, dd, J = 6.0, 14.0 Hz), 6.40 (1H, t, J = 6.0 Hz), 6.54 (1H, d, J = 2.5 Hz), 6.70 (1H,

dd, J = 2.5, 8.0 Hz), 6.99 (1H, d, J = 8.0 Hz), 7.12–7.31 (5H, m). MS (FAB) m/z = 487 $[M+H]^+$. HRMS (FAB) Calcd for $C_{31}H_{39}N_2O_3$ $[M+H]^+$: 487.2961. Found: 487.2948.

5.1.27. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-3-phenylpropionamide (KNT-36)

KNT-36 was prepared from compound **6i** according to the procedure used to prepare KNT-3. Yield, 62%. IR (film): 1658 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.04–0.20 (2H, m), 0.43–0.60 (2H, m), 0.85–0.99 (1H, m), 1.18 (1H, dt, J = 12.5, 2.0 Hz), 1.18–1.34 (2H, m), 1.38–1.78 (5H, m), 1.98–2.18 (2H, m), 2.36 (1H, dd, J = 7.0, 12.5 Hz), 2.52–2.62 (4H, m), 2.90–3.06 (2H, m), 3.08 (1H, d, J = 18.0 Hz), 3.57 (1H, dd, J = 6.0, 14.0 Hz), 3.66 (1H, d, J = 5.5 Hz), 3.76 (1H, dd, J = 6.0, 14.0 Hz), 6.28 (1H, t, J = 6.0 Hz), 6.59 (1H, d, J = 2.5 Hz), 6.66 (1H, dd, J = 2.5, 8.0 Hz), 6.93 (1H, d, J = 8.0 Hz), 7.14–7.31 (5H, m), one proton (OH) was not observed. MS (FAB) m/z = 473 $[M+H]^+$. HRMS (FAB) Calcd for $C_{30}H_{37}N_2O_3$ $[M+H]^+$: 473.2804. Found: 473.2811.

5.1.28. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-3-phenylpropionamide hydrochloride (KNT-36·HCl)

KNT-36·HCl was prepared from KNT-36 according to the procedure used to prepare KNT-3·HCl. Yield, 55%. Mp 160–164 °C (dec). Anal. Calcd for $C_{30}H_{36}N_2O_3$·HCl·1.33H_2O: C, 67.59; H, 7.50; N, 5.25. Found: C, 67.43; H, 7.28; N, 5.17.

5.1.29. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-methoxymorphinan-6α-yl)methyl]-*N*-methylbenzamide (6j)

To a stirred solution of **5** (250 mg) in pyridine (2 mL) was added benzoic anhydride (208 mg, 0.92 mmol) at rt under an Ar atmosphere. After 3 h with stirring, the reaction mixture was evaporated in vacuo. The resulting mixture was basified (pH 9) with a saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine twice, dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica gel (50 g; $CHCl_3$/MeOH = 50:1–25:1) to give **6j** (221 mg, 63%, two steps from **4**) as a white amorphous solid. IR (film): 1651 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.04–0.20 (2H, m), 0.40–0.62 (2H, m), 0.91–1.04 (1H, m), 1.27 (1H, dt, J = 13.0, 2.0 Hz), 1.42–1.51 (1H, m), 1.53–2.16 (6H, m), 2.25 (1H, dt, J = 4.5, 13.0 Hz), 2.37 (1H, dd, J = 7.0, 12.5 Hz), 2.54–2.68 (3H, m), 3.14 (1H, d, J = 18.0 Hz), 3.72 (1H, d, J = 5.5 Hz), 3.77 (3H, s), 3.88–4.02 (2H, m), 6.58 (1H, d, J = 2.5 Hz), 6.69 (1H, dd, J = 2.5, 8.0 Hz), 6.84 (1H, dt, J = 2.0, 6.0 Hz), 7.00 (1H, d, J = 8.0 Hz), 7.39–7.56 (3H, m), 7.80–7.89 (2H, m). MS (FAB) m/z = 459 $[M+H]^+$. HRMS (FAB) Calcd for $C_{29}H_{35}N_2O_3$ $[M+H]^+$: 459.2648. Found: 459.2639.

5.1.30. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-methoxymorphinan-6α-yl)methyl]-*N*-methylbenzamide (7j)

To a stirred solution of **6j** (81 mg, 0.18 mmol) in THF (2.0 mL) were added sodium hydride (60% dispersion in meneral oil, 80 mg, 18.3 mmol) and iodomethane (0.1 ml, 1.6 mmol) at 0 °C under an Ar atmosphere. After 0.5 h, to the reaction mixture was added water and the mixture was evaporated in vacuo. The resulting mixture was extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine twice, dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica gel (11 g; $CHCl_3$/MeOH = 50:1–20:1) to give **7j** (64 mg, 77%) as a white amorphous solid. IR (film): 1620 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.04–0.19 (2H, m), 0.40–0.60 (2H, m), 0.84–0.98 (1H, m), 1.25 (1H, dt, J = 12.5, 2.0 Hz), 1.46–1.82 (5H, m), 1.86–2.03 (2H, m), 2.06–2.30 (2H, m), 2.32–2.78 (3H, m), 3.20 (3H, s), 3.26 (1H, d, J = 18.0 Hz), 3.61–3.71 (1H, m), 3.78 (3H, s), 3.90 (1H, d, J = 14.5 Hz), 4.21 (1H, d, J = 14.5 Hz), 6.60 (1H, d, J = 2.5 Hz), 6.70 (1H, dd, J = 2.5, 8.5 Hz), 7.01 (1H, d, J = 8.5 Hz), 7.34–7.50 (5H, m). MS (FAB) m/z = 473 $[M+H]^+$. HRMS (FAB) Calcd for $C_{30}H_{37}N_2O_3$ $[M+H]^+$: 473.2804. Found: 473.2803.

5.1.31. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-*N*-methylbenzamide (KNT-2)

KNT-2 was prepared from compound **7j** according to the procedure used to prepare KNT-3. Yield, 84%. IR (film): 1621 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.04–0.19 (2H, m), 0.40–0.60 (2H, m), 0.83–0.98 (1H, m), 1.25 (1H, dt, J = 12.5, 2.0 Hz), 1.36–1.77 (4H, m), 1.83 (1H, dt, J = 4.5, 13.0 Hz), 1.90 (1H, dt, J = 13.0, 2.0 Hz), 2.10–2.28 (2H, m), 2.38–2.49 (1H, m), 2.52–2.74 (3H, m), 3.05–3.17 (1H, m), 3.16 (3H, s), 3.62–3.79 (1H, m), 3.97 (1H, d, J = 14.5 Hz), 4.10 (1H, d, J = 14.5 Hz), 6.59 (1H, d, J = 2.0 Hz), 6.63 (1H, dd, J = 2.0, 8.0 Hz), 6.92 (1H, d, J = 8.0 Hz), 7.34–7.48 (5H, m), one proton (OH) was not observed. MS (FAB) m/z = 459 $[M+H]^+$. HRMS (FAB) Calcd for $C_{29}H_{35}N_2O_3$ $[M+H]^+$: 459.2648. Found: 459.2633.

5.1.32. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-*N*-methylbenzamide hydrochloride (KNT-2·HCl)

KNT-2·HCl was prepared from KNT-2 according to the procedure used to prepare KNT-3·HCl. Yield, 59%. Mp 177–183 °C (dec). Anal. Calcd for $C_{29}H_{34}N_2O_3$·HCl·1.2H_2O: C, 67.51; H, 7.51; N, 5.36. Found: C, 67.36; H, 7.31; N, 5.28.

5.1.33. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-methoxymorphinan-6α-yl)methyl]-*N*,4-dimethylbenzamide (7c)

Compound **7c** was prepared from compound **6c** according to the procedure used to prepare compound **7j**. Yield 60%. IR (film): 1632 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.04–0.18 (2H, m), 0.42–0.58 (2H, m), 0.84–0.97 (1H, m), 1.16–1.32 (2H, m), 1.48–1.80 (4H, m), 1.84–2.00 (2H, m), 2.08–2.28 (2H, m), 2.38 (3H, s), 2.52–2.76 (3H, m), 3.14 (1H, d, J = 18.0 Hz), 3.20 (3H, s), 3.65 (1H, d, J = 5.5 Hz), 3.78 (3H, s), 3.86 (1H, d, J = 14.5 Hz), 4.20 (1H, d, J = 14.5 Hz), 6.59 (1H, d, J = 2.5 Hz), 6.69 (1H, dd, J = 2.5, 8.5 Hz), 7.00 (1H, d, J = 8.5 Hz), 7.21 (2H, dd, J = 2.5, 8.0 Hz), 7.34 (2H, dd, J = 2.5, 8.0 Hz). MS (FAB) m/z = 487 $[M+H]^+$. HRMS (FAB) Calcd for $C_{31}H_{39}N_2O_3$ $[M+H]^+$: 487.2961. Found: 487.2968.

5.1.34. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-*N*,4-dimethylbenzamide (KNT-17)

KNT-17 was prepared from compound **7c** according to the procedure used to prepare KNT-3. Yield, 95%. IR (film): 1613 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.05–0.22 (2H, m), 0.42–0.61 (2H, m), 0.86–1.01 (1H, m), 1.13–1.32 (2H, m), 1.37–1.77 (5H, m), 1.77–1.96 (2H, m), 2.13–2.26 (1H, m), 2.38 (3H, s), 2.52–2.79 (3H, m), 3.18 (3H, s), 3.20 (1H, d, J = 18.0 Hz), 3.73 (1H, d, J = 5.5 Hz), 3.98 (1H, d, J = 14.5 Hz), 4.08 (1H, d, J = 14.5 Hz), 6.58 (1H, d, J = 2.5 Hz), 6.64 (1H, dd, J = 2.5, 8.5 Hz), 6.92 (1H, d, J = 8.5 Hz), 7.22 (2H, dd, J = 2.5, 8.0 Hz), 7.34 (2H, dd, J = 2.5, 8.0 Hz), one proton (OH) was not observed. MS (FAB) m/z = 473 $[M+H]^+$. HRMS (FAB) Calcd for $C_{30}H_{37}N_2O_3$ $[M+H]^+$: 473.2804. Found: 473.2823.

5.1.35. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-*N*,4-dimethylbenzamide hydrochloride (KNT-17·HCl)

KNT-17·HCl was prepared from KNT-17 according to the procedure used to prepare KNT-3·HCl. Yield, 77%. Mp 170–174 °C (dec). Anal. Calcd for $C_{30}H_{36}N_2O_3$·HCl·1.1H_2O: C, 68.13; H, 7.47; N, 5.30. Found: C, 68.01; H, 7.35; N, 5.18.

5.1.36. *N*-{[17-Cyclopropylmethyl-6β,14β-epoxy-3-(3-fluorobenzoyloxy)morphinan-6α-yl]methyl}-3-fluorobenzamide (8)

Compound **8** was prepared from compound **5** according to the demethylation procedure used to prepare KNT-3 and the

subsequent acylation procedure used to prepare compound **6a** by use of 3-fluorobenzoyl chloride instead of phenylacetyl chloride. Yield, 49% (three steps from **4**). IR (film): 1739, 1659 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.04–0.36 (2H, m), 0.41–0.70 (2H, m), 0.84–0.98 (1H, m), 1.06–1.40 (2H, m), 1.42–1.92 (5H, m), 2.10–2.70 (4H, m), 2.84–3.04 (2H, m), 3.30 (1H, d, J = 18.0 Hz), 3.73 (1H, dd, J = 6.5, 14.5 Hz), 4.02 (1H, d, J = 5.5 Hz), 4.10 (1H, dd, J = 6.5, 14.5 Hz), 6.94 (1H, d, J = 2.5 Hz), 7.05 (1H, dd, J = 2.5, 8.0 Hz), 7.08–7.17 (1H, m), 7.20 (1H, d, J = 8.0 Hz), 7.30–7.40 (2H, m), 7.45–7.54 (1H, m), 7.64–7.76 (2H, m), 7.80–7.90 (1H, m), 7.94–8.01 (1H, m), one proton (NH) was not observed. MS (FAB) m/z = 585 $[M+H]^+$. HRMS (FAB) Calcd for $C_{35}H_{35}F_2N_2O_4$ $[M+H]^+$: 585.2565. Found: 585.2565.

5.1.37. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-3-fluorobenzamide (KNT-32)

To a stirred solution of **8** (100 mg, 0.17 mmol) in THF (2 mL) and MeOH (2 mL) was added 4 M NaOH (1 mL) at rt under an Ar atmosphere. After 10 h with stirring, the reaction mixture was basified (pH 9) with 2 M HCl and extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine twice, dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica gel (20 g; $CHCl_3$/MeOH = 50:1–33:1) to give KNT-32 (62 mg, 78%) as a white amorphous solid. IR (film): 1649 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.04–0.18 (2H, m), 0.41–0.60 (2H, m), 0.83–0.98 (1H, m), 1.26 (1H, dt, J = 13.0, 2.0 Hz), 1.32–1.41 (1H, m), 1.52–1.84 (5H, m), 2.10 (1H, dt, J = 2.0, 12.5 Hz), 2.21 (1H, dt, J = 4.5, 12.5 Hz), 2.36 (1H, dd, J = 7.0, 12.5 Hz), 2.50–2.67 (3H, m), 3.10 (1H, d, J = 18.0 Hz), 3.71 (1H, d, J = 5.5 Hz), 3.81 (1H, dd, J = 6.5, 14.5 Hz), 3.96 (1H, dd, J = 6.5, 14.5 Hz), 6.58 (1H, d, J = 2.5 Hz), 6.66 (1H, dd, J = 2.5, 8.0 Hz), 6.92 (1H, d, J = 8.0 Hz), 6.95 (1H, t, J = 6.0 Hz), 7.15–7.24 (1H, m), 7.35–7.44 (1H, m), 7.55–7.66 (2H, m), one proton (OH) was not observed. MS (FAB) m/z = 463 $[M+H]^+$. HRMS (FAB) Calcd for $C_{28}H_{32}FN_2O_3$ $[M+H]^+$: 463.2397. Found: 463.2388.

5.1.38. *N*-[(17-Cyclopropylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-3-fluorobenzamide hydrochloride (KNT-32·HCl)

KNT-32·HCl was prepared from KNT-32 according to the procedure used to prepare KNT-3·HCl. Yield, 50%. Mp 182–187 °C (dec). Anal. Calcd for $C_{28}H_{31}FN_2O_3{\cdot}2HCl{\cdot}0.67H_2O$: C, 61.43; H, 6.32; N, 5.12. Found: C, 61.57; H, 6.24; N, 4.88.

5.1.39. 6α-Azidemethyl-6β,14β-epoxy-3-methoxymorphinan (9)

To a stirred solution of **4** (2.68 g, 7.05 mmol) in 1,1,2,2-tetrachloroethane (25 mL) was added 1-chloroethyl chloroformate (3.8 ml, 35.2 mmol) under an Ar atmosphere and stirred at 100 °C for 2.5 h. The reaction mixture was evaporated in vacuo and then the residue was dissolved in MeOH and refluxed for 2 h. The resulting mixture was added to a saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine twice and dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica gel (50 g; $CHCl_3$/MeOH = 33:1–20:1) to give **9** (1.38 g, 60%) as orange oil. IR (film): 2101 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.23 (1H, dt, J = 12.5, 2.0 Hz), 1.40–1.76 (4H, m), 1.85 (1H, d, J = 12.0 Hz), 1.90 (1H, dd, J = 2.0, 12.0 Hz), 2.04 (1H, dt, J = 4.5, 12.5 Hz), 2.51–2.58 (1H, m), 2.66 (1H, ddd, J = 2.0, 4.5, 12.5 Hz), 3.01 (1H, d, J = 18.0 Hz), 3.15 (1H, dd, J = 5.5, 18.0 Hz), 3.48 (1H, d, J = 5.5 Hz), 3.57 (1H, d, J = 13.0 Hz), 3.72 (1H, d, J = 13.0 Hz), 3.78 (3H, s), 6.56 (1H, d, J = 2.5 Hz), 6.72 (1H, dd, J = 2.5, 8.5 Hz), 7.06 (1H, d, J = 8.5 Hz), one proton (NH) was not observed. MS (FAB) m/z = 327 $[M+H]^+$. HRMS (FAB) Calcd for $C_{18}H_{23}N_4O_2$ $[M+H]^+$: 327.1821. Found: 327.1831.

5.1.40. 6α-Azidemethyl-6β,14β-epoxy-3-methoxy-17-methylmorphinan (10)

To a stirred solution of **9** (1.3 g, 3.98 mmol) in 2 M AcOH (150 mL) were added anhydrous sodium acetate (1.6 g, 19.9 mmol) and 37% formaldehyde solution (1.60 mL) at rt under an Ar atmosphere. After 3 h with stirring, to the stirred solution was added $NaBH_4$ (1.5 g 39.8 mmol) at 0 °C under an Ar atmosphere. After 5 min, the reaction mixture was filtered and evaporated in vacuo. The residue was basified (pH 9) with NH_4OH and was extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine twice, dried over Na_2SO_4, and evaporated. The residue was crystallized from C_2H_5OH solution to give a white solid (0.90 g, 66%). Mp 120–121 °C. IR (KBr): 2091 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.28 (1H, dt, J = 12.5, 2.0 Hz), 1.40–1.78 (4H, m), 1.84–1.94 (2H, m), 2.15 (1H, dt, J = 2.0, 12.5 Hz), 2.26 (1H, dt, J = 4.0, 12.5 Hz), 2.38–2.44 (1H, m), 2.44 (3H, s), 2.64 (1H, dd, J = 5.5, 18.0 Hz), 3.20 (1H, d, J = 18.0 Hz), 3.30 (1H, d, J = 5.5 Hz), 3.70 (1H, d, J = 13.0 Hz), 3.71 (1H, d, J = 13.0 Hz), 3.78 (3H, s), 6.57 (1H, d, J = 2.5 Hz), 6.70 (1H, dd, J = 2.5, 8.5 Hz), 7.04 (1H, d, J = 8.5 Hz). MS (FAB) m/z = 341 $[M+H]^+$. HRMS (FAB) Calcd for $C_{19}H_{25}N_4O_2$ $[M+H]^+$: 341.1978. Found: 341.1992.

5.1.41. *N*-[(6β,14β-Epoxy-3-methoxy-17-methylmorphinan-6α-yl)methyl]benzamide (11)

Compound **10** was converted to the amine according to the procedure used to prepare compound **5**. The obtained amine was used for next reaction without purification. Compound **11**was prepared from the amine according to the procedure used to prepare compound **6j**. The crude compound was chromatographed on silica gel, but not purified completely. The resulting compound **11** was used for the next reaction without further purification.

5.1.42. *N*-[(6β,14β-Epoxy-3-hydroxy-17-methylmorphinan-6α-yl)methyl]benzamide (KNT-18)

KNT-18 was prepared from compound **11** according to the procedure used to prepare KNT-3. Yield 57% (three steps from **10**). IR (film): 1644 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.29 (1H, dt, J = 12.5, 2.0 Hz), 1.33–1.42 (1H, m), 1.50–1.92 (6H, m), 2.12–2.32 (2H, m), 2.50 (3H, s), 2.66 (1H, dd, J = 5.5, 18.0 Hz), 3.22 (1H, d, J = 18.0 Hz), 3.34 (1H, d, J = 5.5 Hz), 3.92 (1H, dd, J = 6.5, 14.5 Hz), 3.96 (1H, dd, J = 6.5, 14.5 Hz), 6.60 (1H, d, J = 2.0 Hz), 6.68 (1H, dd, J = 2.0, 8.0 Hz), 6.94 (1H, t, J = 6.5 Hz), 6.96 (1H, d, J = 8.0 Hz), 7.40–7.56 (3H, m), 7.80–7.92 (2H, m), one proton (OH) was not observed. MS (FAB) m/z = 405 $[M+H]^+$. HRMS (FAB) Calcd for $C_{25}H_{29}N_2O_3$ $[M+H]^+$: 405.2178. Found: 405.2166.

5.1.43. *N*-[(6β,14β-Epoxy-3-hydroxy-17-methylmorphinan-6α-yl)methyl]benzamide hydrochloride (KNT-18·HCl)

KNT-18·HCl was prepared from KNT-18 according to the procedure used to prepare KNT-3·HCl. Yield, 68%. Mp 181–185 °C (dec). Anal. Calcd for $C_{25}H_{28}N_2O_3{\cdot}HCl{\cdot}0.9H_2O$: C, 65.71; H, 6.85; N, 6.11. Found: C, 65.77; H, 6.84; N, 5.99.

5.1.44. (6β,14β-Epoxy-17-isobutyl-3-methoxymorphinan-6α-yl)methanamine (12)

To a stirred solution of **4** (1.09 g, 2.87 mmol) and 10-camphorsulfonic acid (4.0 g, 17.2 mmol) in CH_3OH (15 mL) was added PtO_2 (546 mg, 2.4 mmol) and stirred at rt under a H_2 atmosphere. After 96 h with stirring, the reaction mixture was filtrated and evaporated in vacuo. The residue was basified (pH 9) with 1 M NaOH aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine twice and dried over Na_2SO_4. After evaporation of the solvent, the obtained residue **12** (937 mg) was used for the next reaction without further purification.

5.1.45. *N*-[(6β,14β-Epoxy-17-isobutyl-3-methoxymorphinan-6α-yl)methyl]benzamide (13a)

Compound **13a** was prepared from compound **12** according to the procedures used to prepare compound **6j**. Yield, 37% (two steps from **4**). IR (film): 1652 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.96 (6H, d, J = 6.0 Hz), 1.17–1.27 (1H, m), 1.42–1.95 (7H, m), 1.99–2.08 (1H, m), 2.11–2.25 (2H, m), 2.29–2.48 (2H, m), 2.59–2.72 (1H, m), 3.14 (1H, d, J = 18.0 Hz), 3.34 (1H, d, J = 5.5 Hz), 3.76 (3H, s), 3.85 (1H, dd, J = 6.0, 14.5 Hz), 4.04 (1H, dd, J = 6.0, 14.5 Hz), 6.56 (1H, d, J = 2.5 Hz), 6.70 (1H, dd, J = 2.5, 8.0 Hz), 6.84 (1H, t, J = 6.0 Hz), 7.01 (1H, d, J = 8.0 Hz), 7.38–7.56 (3H, m), 7.81–7.92 (2H, m). MS (FAB) m/z = 461 $[M+H]^+$. HRMS (FAB) Calcd for $C_{29}H_{37}N_2O_3$ $[M+H]^+$: 461.2804. Found: 461.2799.

5.1.46. *N*-[(6β,14β-Epoxy-3-hydroxy-17-isobutylmorphinan-6α-yl)methyl]benzamide (KNT-27)

KNT-27 was prepared from compound **13a** according to the procedure used to prepare KNT-3. Yield, 63%. IR (film): 1644 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.93 (6H, d, J = 6.0 Hz), 1.18–1.28 (1H, m), 1.31–1.42 (1H, m), 1.48–1.90 (8H, m), 2.11–2.20 (1H, m), 2.24–2.50 (2H, m), 2.55–2.68 (1H, m), 3.13 (1H, d, J = 18.0 Hz), 3.32 (1H, d, J = 5.5 Hz), 3.87 (1H, dd, J = 6.0, 14.5 Hz), 3.99 (1H, dd, J = 6.0, 14.5 Hz), 6.59 (1H, d, J = 2.5 Hz), 6.66 (1H, dd, J = 2.5, 8.0 Hz), 6.94 (1H, t, J = 6.0 Hz), 6.95 (1H, d, J = 8.0 Hz), 7.40–7.56 (3H, m), 7.81–7.92 (2H, m), one proton (OH) was not observed. MS (FAB) m/z = 447 $[M+H]^+$. HRMS (FAB) Calcd for $C_{28}H_{35}N_2O_3$ $[M+H]^+$: 447.2648. Found: 447.2663.

5.1.47. *N*-[(6β,14β-Epoxy-3-hydroxy-17-isobutylmorphinan-6α-yl)methyl]benzamide hydrochloride (KNT-27·HCl)

KNT-27·HCl was prepared from KNT-27 according to the procedure used to prepare KNT-3·HCl. Yield, 74%. Mp 184–188 °C (dec). Anal. Calcd for $C_{28}H_{34}N_2O_3$·HCl·1.33H_2O: C, 66.32; H, 7.49; N, 5.52. Found: C, 66.52; H, 7.21; N, 5.28.

5.1.48. *N*-[(6β,14β-Epoxy-17-isobutyl-3-methoxymorphinan-6α-yl)methyl]-4-methoxybenzamide (13b)

Compound **13b** was prepared from compound **12** according to the procedures used to prepare compound **6f**. Yield, 53% (two steps from **4**). IR (film): 1651 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.96 (6H, d, J = 5.5 Hz), 1.20 (1H, dt, J = 12.5, 2.0 Hz), 1.42–1.67 (3H, m), 1.70–1.92 (6H, m), 2.14 (1H, dt, J = 4.5, 12.5 Hz), 2.32 (1H, dd, J = 7.0, 12.5 Hz), 2.40 (1H, dd, J = 6.5, 12.5 Hz), 2.64 (1H, dd, J = 5.5, 18.0 Hz), 3.14 (1H, d, J = 18.0 Hz), 3.31 (1H, d, J = 5.5 Hz), 3.76 (3H, s), 3.76–3.84 (1H, m), 3.85 (3H, s), 4.03 (1H, dd, J = 6.5, 14.5 Hz), 6.56 (1H, d, J = 2.5 Hz), 6.69 (1H, dd, J = 2.5, 8.0 Hz), 6.72–6.80 (1H, m), 6.94 (2H, dd, J = 2.5, 8.0 Hz), 7.02 (1H, d, J = 8.0 Hz), 7.82 (2H, dd, J = 2.5, 8.0 Hz). MS (FAB) m/z = 491 $[M+H]^+$. HRMS (FAB) Calcd for $C_{30}H_{39}N_2O_4$ $[M+H]^+$: 491.2910. Found: 491.2914.

5.1.49. *N*-[(6β,14β-Epoxy-3-hydroxy-17-isobutylmorphinan-6α-yl)methyl]-4-hydroxybenzamide (KNT-45)

KNT-45 was prepared from compound **13b** according to the procedure used to prepare compound KNT-3. Yield, 49%. IR (KBr): 1637 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ: 0.96 (3H, d, J = 5.0 Hz), 0.98 (3H, d, J = 5.0 Hz), 1.18 (1H, dt, J = 12.5, 2.0 Hz), 1.47–1.65 (3H, m), 1.70–1.92 (4H, m), 2.12–2.24 (2H, m), 2.27 (1H, dd, J = 7.0, 12.5 Hz), 2.39 (1H, dt, J = 4.5, 12.5 Hz), 2.45 (1H, dd, J = 6.5, 12.5 Hz), 2.63 (1H, dd, J = 5.5, 18.0 Hz), 3.14 (1H, d, J = 18.0 Hz), 3.36 (1H, d, J = 5.5 Hz), 3.62 (1H, d, J = 14.5 Hz), 4.03 (1H, d, J = 14.5 Hz), 6.48 (1H, d, J = 2.5 Hz), 6.57 (1H, dd, J = 2.5, 8.0 Hz), 6.82–6.89 (2H, m), 6.93 (1H, d, J = 8.0 Hz), 7.75–7.82 (2H, m). MS (FAB) m/z = 463 $[M+H]^+$. HRMS (FAB) Calcd for $C_{28}H_{35}N_2O_4$ $[M+H]^+$: 463.2597. Found: 463.2591.

5.1.50. *N*-[(6β,14β-Epoxy-3-hydroxy-17-isobutylmorphinan-6α-yl)methyl]-4-hydroxybenzamide hydrochloride (KNT-45·HCl)

KNT-45·HCl was prepared from KNT-45 according to the procedure used to prepare KNT-3·HCl. Yield, 59%. Mp 203–208 °C (dec). Anal. Calcd for $C_{28}H_{34}N_2O_4$·HCl·1.33H_2O: C, 64.29; H, 7.26; N, 5.36. Found: C, 64.33; H, 7.03; N, 5.28.

5.1.51. *N*-[(6β,14β-Epoxy-17-isobutyl-3-methoxymorphinan-6α-yl)methyl]-3-methoxybenzamide (13c)

Compound **13c** was prepared from compound **12** according to the procedures used to prepare compound **6g**. The crude compound was chromatographed on silica gel, but not purified completely. The resulting compound **13c** was used for the next reaction without further purification.

5.1.52. *N*-[(6β,14β-Epoxy-3-hydroxy-17-isobutylmorphinan-6α-yl)methyl]-3-hydroxybenzamide (KNT-46)

KNT-46 was prepared from compound **13c** according to the procedure used to prepare KNT-3. Yield, 35% (three steps from **4**). IR (KBr): 1640 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ: 0.95 (3H, d, J = 5.0 Hz), 0.97 (3H, d, J = 5.0 Hz), 1.17 (1H, dt, J = 12.5, 2.0 Hz), 1.45–1.66 (3H, m), 1.68–1.90 (4H, m), 2.10–2.32 (3H, m), 2.37 (1H, dt, J = 4.5, 12.5 Hz), 2.43 (1H, dd, J = 6.5, 12.5 Hz), 2.61 (1H, dd, J = 5.5, 18.0 Hz), 3.13 (1H, d, J = 18.0 Hz), 3.34 (1H, d, J = 5.5 Hz), 3.62 (1H, d, J = 14.5 Hz), 4.03 (1H, d, J = 14.5 Hz), 6.48 (1H, d, J = 2.5 Hz), 6.58 (1H, dd, J = 2.5, 8.0 Hz), 6.93 (1H, d, J = 8.0 Hz), 6.93–6.99 (1H, m), 7.24–7.37 (3H, m). MS (FAB) m/z = 463 $[M+H]^+$. HRMS (FAB) Calcd for $C_{28}H_{35}N_2O_4$ $[M+H]^+$: 463.2597. Found: 463.2597.

5.1.53. *N*-[(6β,14β-Epoxy-3-hydroxy-17-isobutylmorphinan-6α-yl)methyl]-3-hydroxybenzamide hydrochloride (KNT-46·HCl)

KNT-46·HCl was prepared from KNT-46 according to the procedure used to prepare KNT-3·HCl. Yield, 78%. Mp 182–186 °C (dec). Anal. Calcd for $C_{28}H_{34}N_2O_4$·HCl·0.8H_2O: C, 65.50; H, 7.18; N, 5.46. Found: C, 65.50; H, 7.15; N, 5.43.

5.1.54. *N*-[(6β,14β-Epoxy-17-isobutyl-3-methoxymorphinan-6α-yl)methyl]-2-methoxybenzamide (13d)

Compound **13d** was prepared from compound **12** according to the procedures used to prepare compound **6h**. The crude compound was chromatographed on silica gel, but not purified completely. The resulting compound **13d** was used for the next reaction without further purification.

5.1.55. *N*-[(6β,14β-Epoxy-3-hydroxy-17-isobutylmorphinan-6α-yl)methyl]-2-hydroxybenzamide (KNT-47)

KNT-47 was prepared from compound **13d** according to the procedures used to prepare KNT-3. Yield, 46% (three steps from **4**). IR (KBr): 1639 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ: 0.97 (3H, d, J = 5.0 Hz), 0.99 (3H, d, J = 5.0 Hz), 1.19 (1H, dt, J = 12.5, 2.0 Hz), 1.49–1.70 (3H, m), 1.71–1.94 (4H, m), 2.18–2.32 (2H, m), 2.38–2.53 (2H, m), 2.57 (1H, dd, J = 6.5, 12.5 Hz), 2.75 (1H, dd, J = 5.5, 18.0 Hz), 3.16 (1H, d, J = 18.0 Hz), 3.48 (1H, d, J = 5.5 Hz), 3.73 (1H, d, J = 14.5 Hz), 4.03 (1H, d, J = 14.5 Hz), 6.50 (1H, d, J = 2.5 Hz), 6.60 (1H, dd, J = 2.5, 8.0 Hz), 6.86–6.95 (2H, m), 6.96 (1H, d, J = 8.0 Hz), 7.38 (1H, ddd, J = 1.5, 2.0, 8.0 Hz), 7.87 (1H, dd, J = 2.0, 8.0 Hz). MS (FAB) m/z = 463 $[M+H]^+$. HRMS (FAB) Calcd for $C_{28}H_{35}N_2O_4$ $[M+H]^+$: 463.2597. Found: 463.2586.

5.1.56. *N*-[(6β,14β-Epoxy-3-hydroxy-17-isobutylmorphinan-6α-yl)methyl]-2-hydroxybenzamide hydrochloride (KNT-47·HCl)

KNT-47·HCl was prepared from KNT-47 according to the procedure used to prepare KNT-3·HCl. Yield, 49%. Mp 180–185 °C (dec). Anal. Calcd for $C_{28}H_{34}N_2O_4$·HCl·0.67H_2O: C, 65.81; H, 7.17; N, 5.48. Found: C, 65.79; H, 7.18; N, 5.37.

5.1.57. *t*-Butyl *N*-[(17-cyclopropylmethyl-6β,14β-epoxy-3-methoxymorphinan-6α-yl)methyl]carbamate (14)

To a stirred solution of **5** (1.32 g) in pyridine (8 mL) was added di-*tert*-butyl dicarbonate (2.6 mL, 11.2 mmol) at rt under an Ar atmosphere. After 3 h with stirring, to the reaction mixture was added water and the mixture was evaporated in vacuo. The residue was basified (pH 9) with a saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine twice, dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica gel (50 g; $CHCl_3$/MeOH = 50:1) to give **14** (1.13 g, 61%, two steps from **4**) as a white amorphous solid. IR (film): 1712 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.03–0.20 (2H, m), 0.40–0.60 (2H, m), 0.87–1.01 (1H, m), 1.26 (1H, dt, J = 13.0, 2.0 Hz), 1.34–1.42 (1H, m), 1.45 (9H, s), 1.50–1.92 (5H, m), 2.06 (1H, dt, J = 2.0, 12.5 Hz), 2.23 (1H, dt, J = 4.5, 12.5 Hz), 2.31 (1H, dd, J = 7.0, 12.5 Hz), 2.48–2.68 (3H, m), 3.11 (1H, d, J = 18.0 Hz), 3.54 (1H, dd, J = 6.5, 13.5 Hz), 3.59 (1H, dd, J = 6.5, 13.5 Hz), 3.68 (1H, d, J = 5.5 Hz), 3.77 (3H, s), 5.12 (1H, t, J = 6.5 Hz), 6.57 (1H, d, J = 2.5 Hz), 6.68 (1H, dd, J = 2.5, 8.0 Hz), 7.00 (1H, d, J = 8.0 Hz). MS (FAB) m/z = 455 $[M+H]^+$. HRMS (FAB) Calcd for $C_{27}H_{39}N_2O_4$ $[M+H]^+$: 455.2910. Found: 455.2901.

5.1.58. *t*-Butyl *N*-[(6β,14β-epoxy-3-methoxy-17-(2,2,2-trichloroethoxycarbonyl)morphinan-6α-yl)methyl]carbamate (15)

To a stirred solution of **14** (1.0 g) in CH_2CH_2 (30 mL) were added proton sponge (1.04 g, 4.84 mmol) and 2,2,2-trichloroethyl chloroformate (2.6 ml, 11.2 mmol) at rt under an Ar atmosphere. After 2 h with stirring, to the reaction mixture was added 1 M HCl and extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine twice, dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica gel (30 g; $CHCl_3$) to give **15** (1.22 g, 96%) as a white amorphous solid. IR (film): 1784, 1713 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.20–1.40 (2H, m), 1.48 (9H, s), 1.54–1.92 (4H, m), 2.12 (1H, dt, J = 4.5, 13.0 Hz), 2.66–3.02 (2H, m), 2.93 (1H, d, J = 18.0 Hz), 3.22 (1H, dd, J = 5.5, 18.0 Hz), 3.54 (1H, dd, J = 5.5, 13.5 Hz), 3.54–3.66 (1H, m), 3.80 (3H, s), 3.87–3.96 (1H, m), 4.50–5.13 (4H, m), 6.60 (1H, d, J = 2.5 Hz), 6.71–6.78 (1H, m), 7.00–7.08 (1H, m). MS (FAB) m/z = 597 $[M+Na]^+$. HRMS (FAB) Calcd for $C_{26}H_{33}Cl_3N_2O_6Na$ $[M+Na]^+$: 597.1302. Found: 597.1331.

5.1.59. *t*-Butyl *N*-[(6β,14β-epoxy-3-methoxymorphinan-6α-yl)-methyl]carbamate (16)

To a stirred solution of **15** (1.22 g) in CH_3COOH (8 mL) was added Zinc dust (555 mg, 8.48 mmol) at rt under an Ar atmosphere. After 6 h with stirring, the reaction mixture was filtrated and evaporated in vacuo. The resulting residue was basified (pH 9) with NH_4OH and extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine twice and dried over Na_2SO_4. After evaporation of the solvent, the obtained residual **16** (921 mg) was used for the next reaction without purification.

5.1.60. *t*-Buthyl *N*-[(17-benzyl-6β,14β-epoxy-3-methoxymorphinan-6α-yl)methyl]carbamate (17)

To a stirred solution of **16** (920 mg) in DMF (10 mL) were added K_2CO_3 (1.59 g, 11.5 mmol) and benzyl bromide (0.81 ml, 6.9 mmol) at rt under an Ar atmosphere. After 40 min with stirring, to the reaction mixture was added water and the mixture was evaporated in vacuo. The resulting residue was extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine twice and dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica gel (30 g; $CHCl_3$) to give **17** (884 mg, 85%, two steps from **15**) as a white amorphous solid. IR (film): 1712 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.23 (1H, dt, J = 13.0, 2.0 Hz), 1.33–1.43 (1H, m), 1.47 (9H, s), 1.48–1.91 (5H, m), 2.14–2.32 (2H, m), 2.48 (1H, ddd, J = 2.0, 4.5, 12.0 Hz), 2.64 (1H, dd, J = 5.5, 18.0 Hz), 3.26 (1H, d, J = 18.0 Hz), 3.35 (1H, d, J = 5.5 Hz), 3.54 (1H, dd, J = 6.5, 13.5 Hz), 3.64 (1H, dd, J = 6.5, 13.5 Hz), 3.76 (1H, d, J = 5.5 Hz), 3.78 (3H, s), 3.85 (1H, d, J = 13.5 Hz), 5.15 (1H, t, J = 6.5 Hz), 6.58 (1H, d, J = 2.5 Hz), 6.71 (1H, dd, J = 2.5, 8.0 Hz), 7.05 (1H, d, J = 8.0 Hz), 7.22–7.45 (5H, m). MS (FAB) m/z = 491 $[M+H]^+$. HRMS (FAB) Calcd for $C_{30}H_{39}N_2O_4$ $[M+H]^+$: 491.2910. Found: 491.2917.

5.1.61. (17-Benzyl-6β,14β-epoxy-3-methoxymorphinan-6α-yl)-methanamine (18)

To a stirred solution of **17** (890 mg) in CH_3OH (8 mL) was added 1 M HCl (4 ml) at 60 °C under an Ar atmosphere. After 8 h with stirring, the reaction mixture was basified (pH 9) with a saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine twice and dried over Na_2SO_4. After evaporation of the solvent, the obtained residual oil **18** (701 mg) was used for the next reaction without purification.

5.1.62. *N*-[(17-Benzyl-6β,14β-epoxy-3-methoxymorphinan-6α-yl)methyl]benzamide (19a)

Compound **19a** was prepared from compound **18** according to the procedures used to prepare compound **6j**. Yield, 81% (two steps from **17**). IR (film): 1656 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.24 (1H, dt, J = 12.5, 2.0 Hz), 1.41–1.96 (6H, m), 2.13–2.28 (2H, m), 2.37–2.52 (1H, m), 2.65 (1H, dd, J = 5.5, 18.0 Hz), 3.24 (1H, d, J = 18.0 Hz), 3.36 (1H, d, J = 5.5 Hz), 3.74–3.82 (2H, m), 3.76 (3H, s), 3.90 (1H, dd, J = 6.5, 14.0 Hz), 4.02 (1H, dd, J = 6.5, 14.0 Hz), 6.58 (1H, d, J = 2.5 Hz), 6.72 (1H, dd, J = 2.5, 8.0 Hz), 6.80 (1H, t, J = 6.5 Hz), 7.04 (1H, d, J = 8.0 Hz), 7.22–7.56 (8H, m), 7.80–7.90 (2H, m). MS (FAB) m/z = 495 $[M+H]^+$. HRMS (FAB) Calcd for $C_{32}H_{35}N_2O_3$ $[M+H]^+$: 495.2648. Found: 495.2659.

5.1.63. *N*-[(17-Benzyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]benzamide (KNT-33)

KNT-33 was prepared from compound **19a** according to the procedure used to prepare KNT-3. Yield, 50%. IR (film): 1644 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.18 (1H, dt, J = 12.5, 2.0 Hz), 1.26–1.82 (6H, m), 2.04–2.25 (2H, m), 2.34–2.46 (1H, m), 2.55 (1H, dd, J = 5.5, 18.0 Hz), 3.16 (1H, d, J = 18.0 Hz), 3.28 (1H, d, J = 5.5 Hz), 3.62–3.74 (2H, m), 3.82 (1H, dd, J = 6.5, 14.0 Hz), 3.92 (1H, dd, J = 6.5, 14.0 Hz), 6.53 (1H, d, J = 2.5 Hz), 6.60 (1H, dd, J = 2.5, 8.0 Hz), 6.82 (1H, t, J = 6.5 Hz), 6.92 (1H, d, J = 8.0 Hz), 7.17–7.49 (8H, m), 7.72–7.85 (2H, m), one proton (OH) was not observed. MS (FAB) m/z = 481 $[M+H]^+$. HRMS (FAB) Calcd for $C_{31}H_{33}N_2O_3$ $[M+H]^+$: 481.2491. Found: 481.2474.

5.1.64. *N*-[(17-Benzyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]benzamide hydrochloride (KNT-33·HCl)

KNT-33·HCl was prepared from KNT-33 according to the procedure used to prepare KNT-3·HCl. Yield, 58%. Mp 186–192 °C (dec). Anal. Calcd for $C_{31}H_{32}N_2O_3$·HCl·1.4H_2O: C, 68.66; H, 6.65; N, 5.17. Found: C, 68.51; H, 6.55; N, 5.19.

5.1.65. *N*-[(17-Benzyl-6β,14β-epoxy-3-methoxymorphinan-6α-yl)methyl]-4-methoxybenzamide (19b)

Compound **19b** was prepared from compound **18** according to the procedures used to prepare compound **6f**. Yield, 72% (two steps from **17**). IR (film): 1655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.24 (1H, dt, J = 12.5, 2.0 Hz), 1.42–1.96 (6H, m), 2.13–2.28 (2H, m), 2.39–2.49 (1H, m), 2.65 (1H, dd, J = 5.5, 18.0 Hz), 3.24 (1H, d, J = 18.0 Hz), 3.38 (1H, d, J = 5.5 Hz), 3.74–3.89 (3H, m), 3.76 (3H, s), 3.85 (3H, s), 3.98–4.09 (1H, m), 6.57 (1H, d, J = 2.5 Hz), 6.72 (1H, dd, J = 2.5, 8.0 Hz), 6.82 (1H, t, J = 6.5 Hz), 7.02–7.10 (2H, m), 7.22–7.48 (8H, m). MS (FAB) m/z = 525 $[M+H]^+$. HRMS (FAB) Calcd for $C_{33}H_{37}N_2O_4$ $[M+H]^+$: 525.2753. Found: 525.2736.

5.1.66. *N*-[(17-benzyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-4-hydroxybenzamide (KNT-53)

KNT-53 was prepared from compound **19b** according to the procedure used to prepare KNT-3. Yield, 95%. IR (KBr): 1640 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ: 1.15–1.24 (1H, m), 1.36–1.60 (3H, m), 1.66–1.76 (1H, m), 1.78–1.91 (2H, m), 2.22 (1H, dt, J = 4.5, 12.5 Hz), 2.30 (1H, dt, J = 2.0, 12.5 Hz), 2.46–2.53 (1H, m), 2.57 (1H, dd, J = 5.5, 18.0 Hz), 3.24 (1H, d, J = 5.5 Hz), 3.28 (1H, d, J = 18.0 Hz), 3.64 (1H, d, J = 14.0 Hz), 3.74 (1H, d, J = 13.5 Hz), 3.78 (1H, d, J = 13.5 Hz), 4.03 (1H, d, J = 14.0 Hz), 6.50 (1H, d, J = 2.5 Hz), 6.59 (1H, dd, J = 2.5, 8.0 Hz), 6.94–7.02 (2H, m), 7.21–7.38 (6H, m), 7.38–7.46 (2H, m). MS (FAB) m/z = 497 $[M+H]^+$. HRMS (FAB) Calcd for $C_{31}H_{33}N_2O_4$ $[M+H]^+$: 497.2440. Found: 497.2456.

5.1.67. *N*-[(17-Benzyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-4-hydroxybenzamide hydrochloride (KNT-53·HCl)

KNT-53·HCl was prepared from KNT-53 according to the procedure used to prepare KNT-3·HCl. Yield, 68%. Mp 177–181 °C (dec). Anal. Calcd for $C_{31}H_{32}N_2O_4$·HCl·0.8H_2O: C, 68.01; H, 6.37; N, 5.12. Found: C, 67.87; H, 6.38; N, 5.03.

5.1.68. *N*-[(17-Benzyl-6β,14β-epoxy-3-methoxymorphinan-6α-yl)methyl]-2-methoxybenzamide (19c)

Compound **19c** was prepared from compound **18** according to the procedures used to prepare compound **6h**. Yield, 80% (two steps from **17**). IR (film): 1654 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.17 (1H, dt, J = 12.5, 2.0 Hz), 1.47–1.98 (6H, m), 2.14–2.27 (1H, m), 2.32–2.44 (2H, m), 2.69 (1H, dd, J = 5.5, 18.0 Hz), 3.26 (1H, d, J = 18.0 Hz), 3.45 (1H, d, J = 5.5 Hz), 3.63–3.83 (3H, m), 3.77 (3H, s), 3.84 (3H, s), 4.24 (1H, dd, J = 6.5, 14.0 Hz), 6.56 (1H, d, J = 2.5 Hz), 6.72 (1H, dd, J = 2.5, 8.0 Hz), 6.94 (1H, d, J = 8.0 Hz), 7.20–7.48 (9H, m), 8.49–8.58 (1H, m). MS (FAB) m/z = 525 $[M+H]^+$. HRMS (FAB) Calcd for $C_{33}H_{37}N_2O_4$ $[M+H]^+$: 525.2753. Found: 525.2748.

5.1.69. *N*-[(17-Benzyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-2-hydroxybenzamide (KNT-55)

KNT-55 was prepared from compound **19c** according to the procedure used to prepare KNT-3. Yield, 83%. IR (KBr): 1639 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ: 1.15–1.21 (1H, m), 1.40–1.66 (3H, m), 1.67–1.74 (1H, m), 1.83–1.90 (2H, m), 2.26 (1H, dt, J = 4.5, 12.5 Hz), 2.33 (1H, dt, J = 2.0, 12.5 Hz), 2.45–2.51 (1H, m), 2.62 (1H, dd, J = 5.5, 18.0 Hz), 3.26 (1H, d, J = 18.0 Hz), 3.28 (1H, d, J = 5.5 Hz), 3.73 (1H, d, J = 14.0 Hz), 3.78 (1H, d, J = 13.5 Hz), 3.83 (1H, d, J = 13.5 Hz), 4.03 (1H, d, J = 14.0 Hz), 6.50 (1H, d, J = 2.5 Hz), 6.59 (1H, dd, J = 2.5, 8.0 Hz), 6.88–6.95 (2H, m), 6.98 (1H, d, J = 8.0 Hz), 7.21–7.46 (5H, m), 7.86–7.92 (2H, m). MS (FAB) m/z = 497 $[M+H]^+$. HRMS (FAB) Calcd for $C_{31}H_{33}N_2O_4$ $[M+H]^+$: 497.2440. Found: 497.2444.

5.1.70. *N*-[(17-Benzyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-2-hydroxybenzamide hydrochloride (KNT-55·HCl)

KNT-55·HCl was prepared from KNT-55 according to the procedure used to prepare KNT-3·HCl. Yield, 74%. Mp 182–187 °C (dec). Anal. Calcd for $C_{31}H_{32}N_2O_4$·HCl·0.67H_2O: C, 68.31; H, 6.35; N, 5.14. Found: C, 68.38; H, 6.41; N, 5.18.

5.1.71. *N*-[(17-Benzyl-6β,14β-epoxy-3-methoxymorphinan-6α-yl)methyl]-3-methoxybenzamide (19d)

Compound **19d** was prepared from compound **18** according to the procedures used to prepare compound **6g**. Yield, 92% (two steps from **17**). IR (film): 1651 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.24 (1H, dt, J = 12.5, 2.0 Hz), 1.41–1.80 (4H, m), 1.84–1.96 (2H, m), 2.18–2.24 (1H, m), 2.33–2.39 (1H, m), 2.42–2.49 (1H, m), 2.65 (1H, dd, J = 5.5, 18.0 Hz), 3.26 (1H, d, J = 18.0 Hz), 3.40 (1H, d, J = 5.5 Hz), 3.74–3.89 (3H, m), 3.78 (3H, s), 3.84 (3H, s), 4.04 (1H, dd, J = 6.5, 14.0 Hz), 6.58 (1H, d, J = 2.5 Hz), 6.72 (1H, dd, J = 2.5, 8.0 Hz), 6.86 (1H, t, J = 6.5 Hz), 7.00–7.08 (2H, m), 7.05 (1H, d, J = 8.0 Hz), 7.25–7.46 (7H, m). MS (FAB) m/z = 525 $[M+H]^+$. HRMS (FAB) Calcd for $C_{33}H_{37}N_2O_4$ $[M+H]^+$: 525.2753. Found: 525.2769.

5.1.72. *N*-[(17-Benzyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-3-hydroxybenzamide (KNT-90)

KNT-90 was prepared from compound **19d** according to the procedure used to prepare KNT-3. Yield, 74%. IR (KBr): 1640 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ: 1.16–1.23 (1H, m), 1.38–1.63 (3H, m), 1.66–1.76 (1H, m), 1.82–1.89 (2H, m), 2.22 (1H, dt, J = 4.5, 12.5 Hz), 2.30 (1H, dt, J = 2.0, 12.5 Hz), 2.44–2.51 (1H, m), 2.56 (1H, dd, J = 5.5, 18.0 Hz), 3.24 (1H, d, J = 5.5 Hz), 3.22–3.32 (1H, m), 3.63 (1H, d, J = 13.5 Hz), 3.73 (1H, d, J = 14.0 Hz), 3.78 (1H, d, J = 13.5 Hz), 4.03 (1H, d, J = 14.0 Hz), 6.49 (1H, d, J = 2.5 Hz), 6.59 (1H, dd, J = 2.5, 8.0 Hz), 6.93–6.99 (1H, m), 6.98 (1H, d, J = 8.0 Hz), 7.20–7.38 (6H, m), 7.38–7.44 (2H, m). MS (FAB) m/z = 497 $[M+H]^+$. HRMS (FAB) Calcd for $C_{31}H_{33}N_2O_4$ $[M+H]^+$: 497.2440. Found: 497.2451.

5.1.73. *N*-[(17-Benzyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-3-hydroxybenzamide hydrochloride (KNT-90·HCl)

KNT-90·HCl was prepared from KNT-90 according to the procedure used to prepare KNT-3·HCl. Yield, 70%. Mp 190–195 °C (dec). Anal. Calcd for $C_{31}H_{32}N_2O_4$·HCl·H_2O: C, 67.56; H, 6.40; N, 5.08. Found: C, 67.43; H, 6.48; N, 5.18.

5.1.74. *N*-[(17-Benzyl-6β,14β-epoxy-3-(4-fluorobenzoyloxy)morphinan-6α-yl)methyl]-4-fluorobenzamide (20a)

Compound **20a** was prepared from compound **18** according to the procedure used to prepare compound **8** by use of 4-fluorobenzoyl chloride instead of 3-fluorobenzoyl chloride. Yield, 47% (three steps from **17**). IR (film): 1738, 1658 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.22–1.30 (1H, m), 1.42–1.96 (6H, m), 2.13–2.30 (2H, m), 2.44–2.54 (1H, m), 2.72 (1H, dd, J = 5.5, 18.0 Hz), 3.33 (1H, d, J = 18.0 Hz), 3.40 (1H, d, J = 5.5 Hz), 3.72–3.83 (2H, m), 3.91 (1H, dd, J = 6.5, 15.0 Hz), 3.96 (1H, dd, J = 6.5, 15.0 Hz), 6.77 (1H, t, J = 6.5 Hz), 6.90 (1H, d, J = 2.5 Hz), 7.02 (1H, dd, J = 2.5, 8.0 Hz), 7.08–7.46 (10H, m), 7.82–7.92 (2H, m), 8.16–8.24 (2H, m). MS (FAB) m/z = 621 $[M+H]^+$. HRMS (FAB) Calcd for $C_{38}H_{35}N_2O_4F_2$ $[M+H]^+$: 621.2565. Found: 621.2557.

5.1.75. *N*-[(17-Benzyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-4-fluorobenzamide (KNT-80)

KNT-80 was prepared from compound **20a** according to the procedure used to prepare KNT-32. Yield, 98%. IR (KBr): 1647 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ: 1.20–1.27 (1H, m), 1.43–1.94 (6H, m), 2.18–2.40 (2H, m), 2.48–2.55 (1H, m), 2.61 (1H, dd, J = 5.5, 18.0 Hz), 3.26 (1H, d, J = 18.0 Hz), 3.34 (1H, d, J = 5.5 Hz), 3.68–3.82 (3H, m), 4.02 (1H, dd, J = 6.5, 15.0 Hz), 6.52 (1H, d, J = 2.5 Hz), 6.63 (1H, dd, J = 2.5, 8.0 Hz), 7.02 (1H, d, J = 8.0 Hz), 7.22–7.40 (5H, m), 7.42–7.48 (2H, m), 7.95–8.04 (2H, m). MS (FAB) m/z = 499 $[M+H]^+$. HRMS (FAB) Calcd for $C_{31}H_{32}$ F N_2O_3 $[M+H]^+$: 499.2397. Found: 499.2382.

5.1.76. *N*-[(17-Benzyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-4-fluorobenzamide hydrochloride (KNT-80·HCl)

KNT-80·HCl was prepared from KNT-80 according to the procedure used to prepare KNT-3·HCl. Yield, 68%. Mp 183–187 °C (dec). Anal. Calcd for $C_{31}H_{31}FN_2O_3$·HCl·1.67H_2O: C, 65.89; H, 6.30; N, 4.96. Found: C, 65.94; H, 6.30; N, 4.84.

5.1.77. *N*-[(17-Benzyl-6β,14β-epoxy-3-(2-fluorobenzoyloxy) morphinan-6α-yl)methyl]-2-fluorobenzamide (20b)

Compound **20b** was prepared from compound **18** according to the procedure used to prepare compound **8** by use of 2-fluorobenzoyl chloride instead of 3-fluorobenzoyl chloride. Yield, 40% (three steps from **17**). IR (film): 1746, 1664 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.19–1.26 (1H, m), 1.46–1.94 (6H, m), 2.22–2.32 (2H, m), 2.45–2.51 (1H, m), 2.78 (1H, dd, J = 5.5, 18.0 Hz), 3.30 (1H, d, J = 18.0 Hz), 3.42 (1H, d, J = 5.5 Hz), 3.80–3.92 (3H, m), 4.08 (1H, ddd, J = 1.5, 6.5, 15.0 Hz), 6.92 (1H, d, J = 2.5 Hz), 7.04 (1H, dd, J = 2.5, 8.0 Hz), 7.10–7.53 (12H, m), 7.56–7.64 (1H, m), 8.04–8.16 (2H, m). MS (FAB) m/z = 621 $[M+H]^+$. HRMS (FAB) Calcd for $C_{38}H_{35}F_2N_2O_4$ $[M+H]^+$: 621.2565. Found: 621.2563.

5.1.78. *N*-[(17-Benzyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-2-fluorobenzamide (KNT-132)

KNT-132 was prepared from compound **20b** according to the procedure used to prepare KNT-32. Yield, 95%. IR (KBr): 1649 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.14–1.22 (1H, m), 1.36–1.90 (6H, m), 2.16–2.30 (2H, m), 2.38–2.48 (1H, m), 2.66 (1H, dd, J = 5.5, 18.0 Hz), 3.21 (1H, d, J = 18.0 Hz), 3.35 (1H, d, J = 5.5 Hz), 3.74–3.84 (2H, m), 3.88 (1H, dd, J = 6.5, 15.0 Hz), 4.06 (1H, dd, J = 6.5, 15.0 Hz), 6.57 (1H, d, J = 2.5 Hz), 6.65 (1H, dd, J = 2.5, 8.0 Hz), 6.98 (1H, d, J = 8.0 Hz), 7.12–7.18 (1H, m), 7.20–7.52 (7H, m), 8.07–8.13 (1H, m), two protons (OH) were not observed. MS (FAB) m/z = 499 $[M+H]^+$. HRMS (FAB) Calcd for $C_{31}H_{32}FN_2O_3$ $[M+H]^+$: 499.2397. Found: 499.2395.

5.1.79. *N*-[(17-Benzyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-2-fluorobenzamide hydrochloride (KNT-132·HCl)

KNT-132·HCl was prepared from KNT-132 according to the procedure used to prepare KNT-3·HCl. Yield, 67%. Mp 186–189 °C (dec). Anal. Calcd for $C_{31}H_{31}FN_2O_3\cdot HCl\cdot 0.8H_2O$: C, 67.76; H, 6.16; N, 5.10. Found: C, 67.93; H, 6.42; N, 5.16.

5.1.80. *N*-[(17-Benzyl-6β,14β-epoxy-3-(3-fluorobenzoyloxy)morphinan-6α-yl)methyl]-3-fluorobenzamide (20c)

Compound **20c** was prepared from compound **18** according to the procedure used to prepare compound **8**. Yield, 36% (three steps from **17**). IR (film): 1739, 1667 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.23–1.32 (1H, m), 1.44–1.97 (6H, m), 2.15–2.34 (2H, m), 2.42–2.53 (1H, m), 2.73 (1H, dd, J = 5.5, 18.0 Hz), 3.34 (1H, d, J = 18.0 Hz), 3.42 (1H, d, J = 5.5 Hz), 3.76–3.83 (2H, m), 3.88 (1H, dd, J = 6.5, 15.0 Hz), 4.01 (1H, dd, J = 6.5, 15.0 Hz), 6.88–6.94 (1H, m), 6.92 (1H, d, J = 2.5 Hz), 7.04 (1H, dd, J = 2.5, 8.0 Hz), 7.16–7.64 (12H, m), 7.83–7.89 (1H, m), 7.96–8.00 (1H, m). MS (FAB) m/z = 621 $[M+H]^+$. HRMS (FAB) Calcd for $C_{38}H_{35}F_2N_2O_4$ $[M+H]^+$: 621.2565. Found: 621.2563.

5.1.81. *N*-[(17-Benzyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-3-fluorobenzamide (KNT-133)

KNT-133 was prepared from compound **20c** according to the procedure used to prepare KNT-32. Yield, 94%. IR (KBr): 1649 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.18–1.28 (1H, m), 1.31–1.83 (6H, m), 2.08–2.28 (2H, m), 2.43–2.50 (1H, m), 2.61 (1H, dd, J = 5.5, 18.0 Hz), 3.26 (1H, d, J = 18.0 Hz), 3.35 (1H, d, J = 5.5 Hz), 3.68–3.80 (3H, m), 4.04 (1H, dd, J = 6.5, 15.0 Hz), 6.56 (1H, d, J = 2.5 Hz), 6.68 (1H, dd, J = 2.5, 8.0 Hz), 6.98 (1H, d, J = 8.0 Hz), 7.10–7.45 (8H, m), 7.57–7.68 (2H, m), one proton (OH) was not observed. MS (FAB) m/z = 499 $[M+H]^+$. HRMS (FAB) Calcd for $C_{31}H_{32}FN_2O_3$ $[M+H]^+$: 499.2397. Found: 499.2396.

5.1.82. *N*-[(17-Benzyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]-3-fluorobenzamide hydrochloride (KNT-133·HCl)

KNT-133·HCl was prepared from KNT-133 according to the procedure used to prepare KNT-3·HCl. Yield, 88%. Mp 200–201 °C (dec). Anal. Calcd for $C_{31}H_{31}FN_2O_3\cdot HCl\cdot H_2O$: C, 67.32; H, 6.20; N, 5.07. Found: C, 67.58; H, 6.33; N, 5.07.

5.1.83. *N*-[(6β,14β-Epoxy-3-methoxy-17-(2,2,2-trichloroethoxycarbonyl)morphinan-6α-yl)methyl] benzamide (21)

Compound **21** was prepared from compound **6j** according to the procedure used to prepare compound **15**. Yield, 98%. IR (film): 1712, 1652 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.22–1.33 (1H, m), 1.44–1.58 (1H, m), 1.60–1.98 (5H, m), 2.03–2.15 (1H, m), 2.67–2.86 (1H, m), 2.94 (1H, d, J = 18.0 Hz), 3.22 (1H, dd, J = 5.5, 18.0 Hz), 3.72–3.96 (2H, m), 3.78 (3H, s), 3.98–4.12 (1H, m), 4.58–5.08 (3H, m), 6.60 (1H, d, J = 2.5 Hz), 6.64 (1H, t, J = 6.5 Hz), 6.74 (1H, dd, J = 2.5, 8.5 Hz), 7.01–7.06 (1H, m), 7.42–7.58 (3H, m), 7.78–7.86 (2H, m). MS (FAB) m/z = 579 $[M+H]^+$. HRMS (FAB) Calcd for $C_{28}H_{30}Cl_3N_2O_5$ $[M+H]^+$: 579.1220. Found: 579.1215.

5.1.84. *N*-[(6β,14β-Epoxy-3-methoxymorphinan-6α-yl)methyl]-benzamide (22)

Compound **22** was prepared from compound **21** according to the procedure used to prepare compound **16**, and used for the next reaction without further purification.

5.1.85. *N*-[(6β,14β-Epoxy-3-methoxy-17-phenethylmorphinan-6α-yl)methyl]benzamide (23a)

Compound **23a** was prepared from compound **22** according to the procedure used to prepare compound **17** by use of phenethyl bromide instead of benzyl bromide. Yield, 50% (two steps from **21**). IR (film): 1658 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.26–1.34 (1H, m), 1.42–1.98 (6H, m), 2.08–2.32 (2H, m), 2.54–2.65 (1H, m), 2.64 (1H, dd, J = 5.5, 18.0 Hz), 2.72–2.96 (4H, m), 3.22 (1H, d, J = 18.0 Hz), 3.51 (1H, d, J = 5.5 Hz), 3.78 (3H, s), 3.87–4.05 (2H, m), 6.59 (1H, d, J = 2.5 Hz), 6.70 (1H, dd, J = 2.5, 8.0 Hz), 6.80 (1H, t, J = 6.5 Hz), 7.02 (1H, d, J = 8.0 Hz), 7.16–7.34 (5H, m), 7.41–7.56 (3H, m), 7.80–7.90 (2H, m). MS (FAB) m/z = 509 $[M+H]^+$. HRMS (FAB) Calcd for $C_{33}H_{37}N_2O_3$ $[M+H]^+$: 509.2804. Found: 509.2788.

5.1.86. *N*-[(6β,14β-Epoxy-3-hydroxy-17-phenethylmorphinan-6α-yl)methyl]benzamide (KNT-34)

KNT-34 was prepared from compound **23a** according to the procedure used to prepare KNT-3. Yield, 67%. IR (film): 1644 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.20–1.42 (2H, m), 1.50–1.90 (5H, m), 2.12–2.32 (2H, m), 2.54–2.63 (1H, m), 2.64 (1H, dd, J = 5.5, 18.0 Hz), 2.70–2.94 (4H, m), 3.20 (1H, d, J = 18.0 Hz), 3.52 (1H, d, J = 5.5 Hz), 3.92 (1H, dd, J = 6.5, 14.0 Hz), 3.96 (1H, dd, J = 6.5, 14.0 Hz), 6.64 (1H, d, J = 2.5 Hz), 6.70 (1H, dd, J = 2.5, 8.0 Hz), 6.96 (1H, d, J = 8.0 Hz), 6.98 (1H, t, J = 6.5 Hz), 7.14–7.32 (5H, m), 7.39–7.56 (3H, m), 7.82–7.91 (2H, m), one proton (OH) was not observed. MS (FAB) m/z = 495 $[M+H]^+$. HRMS (FAB) Calcd for $C_{32}H_{35}N_2O_3$ $[M+H]^+$: 495.2648. Found: 495.2653.

5.1.87. *N*-[(6β,14β-Epoxy-3-hydroxy-17-phenethylmorphinan-6α-yl)methyl]benzamide hydrochloride (KNT-34·HCl)

KNT-34·HCl was prepared from KNT-34 according to the procedure used to prepare KNT-3·HCl. Yield, 69%. Mp 183–187 °C (dec). Anal. Calcd for $C_{32}H_{34}N_2O_3\cdot HCl\cdot H_2O$: C, 69.99; H, 6.79; N, 5.10. Found: C, 70.09; H, 6.74; N, 5.13.

5.1.88. *N*-[(17-Cyclobutylmethyl-6β,14β-epoxy-3-methoxymorphinan-6α-yl)methyl]benzamide (23b)

Compound **23b** was prepared from compound **22** according to the procedure used to prepare compound **17** by use of

cyclobutylmethyl bromide instead of benzyl bromide. Yield, 56% (two steps from **21**). IR (film): 1653 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.24 (1H, dt, J = 12.5, 2.0 Hz), 1.41–1.96 (10H, m), 1.96–2.20 (4H, m), 2.23 (1H, dd, J = 4.5, 12.5 Hz), 2.40–2.48 (1H, m), 2.56–2.70 (3H, m), 3.22 (1H, d, J = 18.0 Hz), 3.35 (1H, d, J = 5.5 Hz), 3.76 (3H, s), 3.85 (1H, dd, J = 6.5, 14.0 Hz), 4.02 (1H, dd, J = 6.5, 14.0 Hz), 6.56 (1H, d, J = 2.5 Hz), 6.70 (1H, dd, J = 2.5, 8.0 Hz), 6.95 (1H, t, J = 6.5 Hz), 7.02 (1H, d, J = 8.0 Hz), 7.40–7.54 (3H, m), 7.80–7.90 (2H, m). MS (FAB) m/z = 473 $[M+H]^+$. HRMS (FAB) Calcd for $C_{30}H_{37}N_2O_3$ $[M+H]^+$: 473.2804. Found: 473.2787.

5.1.89. *N*-[(17-Cyclobutylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]benzamide (KNT-67)

KNT-67 was prepared from compound **23b** according to the procedure used to prepare KNT-3. Yield, 87%. IR (film): 1645 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.16–1.36 (2H, m), 1.44–1.92 (9H, m), 1.94–2.24 (4H, m), 2.34–2.42 (1H, m), 2.54 (1H, dd, J = 5.5, 18.0 Hz), 2.54–2.64 (3H, m), 3.18 (1H, d, J = 18.0 Hz), 3.31 (1H, d, J = 5.5 Hz), 3.83 (1H, dd, J = 6.5, 14.0 Hz), 3.93 (1H, dd, J = 6.5, 14.0 Hz), 6.60 (1H, d, J = 2.5 Hz), 6.68 (1H, dd, J = 2.5, 8.0 Hz), 6.94 (1H, d, J = 8.0 Hz), 6.95 (1H, t, J = 6.5 Hz), 7.37–7.54 (3H, m), 7.80–7.88 (2H, m), one proton (OH) was not observed. MS (FAB) m/z = 459 $[M+H]^+$. HRMS (FAB) Calcd for $C_{29}H_{35}N_2O_3$ $[M+H]^+$: 459.2648. Found: 459.2651.

5.1.90. *N*-[(17-Cyclobuthylmethyl-6β,14β-epoxy-3-hydroxymorphinan-6α-yl)methyl]benzamide hydrochloride (KNT-67·HCl)

KNT-67·HCl was prepared from KNT-67 according to the procedure used to prepare KNT-3·HCl. Yield, 67%. Mp 188–193 °C (dec). Anal. Calcd for $C_{29}H_{34}N_2O_3 \cdot 1.5HCl \cdot 0.6H_2O$: C, 66.49; H, 7.11; N, 5.33. Found: C, 66.76; H, 6.98; N, 5.07.

5.2. Opioid receptor binding assay

For membrane preparation, the brain was quickly removed from guinea pigs and dissected forebrain and cerebellum and immediately frozen in liquid nitrogen. These tissues were homogenized in ice-cold 50 mM Tris−HCl buffer (pH 7.4). The homogenate was centrifuged at 12,000*g* at 4 °C for 20 min, and the pellet was resuspended in ice-cold Tris buffer. Binding affinities for the μ and δ receptors were determined by displacing [^{3}H]DAMGO and [^{3}H]NTI from guinea pig forebrain membrane binding sites, and binding affinity for the κ receptor was measured by displacement of [^{3}H]U-69,593 from guinea pig cerebellum membrane binding sites.

The homogenized membrane fractions (0.2−0.6 mg of protein/assay) were incubated at 25 °C for 2 h in 50 mM Tris−HCl buffer with various concentrations of tested compounds and 0.5 nM [^{3}H]DAMGO, [^{3}H]NTI or 0.1 nM [^{3}H]U-69,593. Specific bindings were defined as the difference in bindings observed in the absence and presence of 1 mM nontritiated ligand in each experiment (μ: DAMGO, δ: NTI, κ: U-69,593). Incubations were terminated by collecting membranes on GF/B filters (Whatman). The filters were transferred to scintillation vials. Then, 5 mL of Creasol II (Nacalai Tesque) was added to the vials. The radioactivity in the samples was determined in a liquid scintillation counter (Packard, liquid scintillation analyzer TRI-CARB 1900). Calculated IC_{50} values were converted into K_i values (equilibrium inhibition constants) according to the Cheng and Prusoff equation[35] $K_i = IC_{50}/(1 + L/K_d)$, where L is the concentration of the tritiated ligands. The equilibrium dissociation constants K_d were determined by displacement of the tritiated ligands by the particular nontritiated ones and were compared to the K_d values resulting from the saturation binding experiments. All reactions were carried out in duplicate.

5.3. Acetic acid writhing method

Male mice were used in this test. After ip-administration of 0.1 mL of 0.6% aqueous AcOH per 10 g of body weight, the number of writhing reactions occurring in 10 min starting from 10 min after the ip-administration was evaluated as the indicator. The test compound was subcutaneously administerd into the rostral back of the animals 15 min before the administration of acetic acid.

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References and notes

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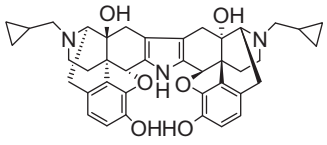
31. The structure of nor-BNI.



nor-BNI

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