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Design, synthesis, and structure–activity relationship of novel opioid κ-agonists

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ABSTRACT

By focusing on 4,5-epoxymorphinan, a traditional opioid skeleton but a new structure in the opioid κ-agonist research field, and by rationally applying the 'message-address concept' and 'accessory site hypothesis,' we discovered a new chemical class opioid κ-agonist, TRK-820 (**1**). Its development as an antipruritus is now in the final stage. Here, the full scope of its design, synthesis, and structure–activity relationship are described.

1. Introduction

For the past three decades, considerable efforts have focused on the search for an opioid κ-selective agonist without the undesirable morphine-like side effects (e.g., respiratory depression, constipation, physical dependence, etc.). In 1982, U-50488H was discovered to be a highly selective κ-agonist.[1] Subsequently, several research groups modified its structure and succeeded in preparing more selective and potent κ-agonists (Fig. 1).[2,3] All these compounds had potent antinociceptive effects in animal models and also lacked the morphine-like side effects. However, the compounds were not developed for clinical use since they, too, had side effects, such as dysphoria and psychotomimetic effects.[4] These analogous compounds share a structure similar to the [N-C-C-N(sp^2)] pharmacophore sequence[5] (shaded structures, Fig. 1) of U-50488H. They lack the tyrosine structure which is essential for opioid activity from the viewpoint of endogenous opioid chemistry (Fig. 2). We questioned whether these compounds were authentic κ-opioid agonists. Therefore, we designed a new type of non-peptide κ-agonist with a novel chemical structure which incorporated tyrosine moiety in order to distinguish the side effects of these prototype κ-agonists. Here, we report the design of a κ-selective full agonist with the 4,5-epoxymorphinan structure (Chart 1).[6,7]

1.1. Design rationale

Portoghese et al. applied the 'message-address concept' for synthesizing selective δ- and κ-antagonists (Fig. 3: NTI (**3**) and nor-BNI (**4**)).[8,9] The 4,5-epoxymorphinan skeleton, found in NTI and nor-BNI, was defined as the message subsite, and is necessary for producing the opioid effects. The other structural site was defined as the address site and is involved in the selectivity of the receptor type. The receptor type selectivity of these opioid antagonists can be regulated by alteration of the structural size of the address site (Fig. 3). The message-address concept was applied to design a selective opioid antagonist, and thus, to design a selective opioid agonist with opposing effects, it was necessary to modify this concept.

In general, when an agonist binds a receptor, the receptor can alter its shape to accommodate the structure of the ligand ('induced fit'). This conformational change of the receptor protein would lead to the next signal transduction so that the agonist exhibits its effects. As opposed to an agonist, an antagonist contains a structural element that interferes with the structural change of the receptor. Thus, even if the antagonist binds the receptor, it does not show an effect. The structural site that mediates the interference of 'induced fit' is called an 'accessory site,' and is usually a highly hydrophobic and sterically hindered site.[10] The structural difference between an antagonist and an agonist lies mainly in whether the compound has an accessory site or not.

To design a new κ-opioid agonist based on the κ-selective antagonist nor-BNI, we proposed to remove the accessory site of

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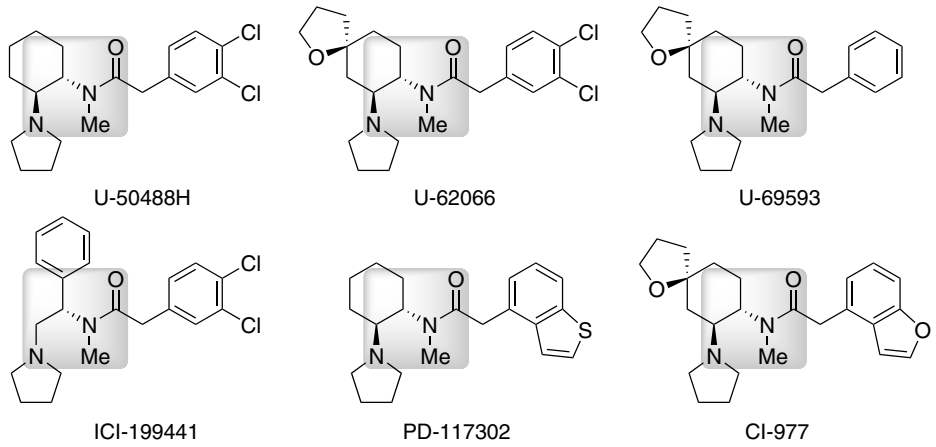


Figure 1. Structure of U-50488H and its derivatives.

Endomorphin-1 (μ) **Tyr**-Pro-Trp-Phe-NH_2
Endomorphin-2 (μ) **Tyr**-Pro-Phe-Phe-NH_2

[Met^5]enkephalin (δ) **Tyr**-Gly-Gly-Phe-Met
[Leu^5]enkephalin (δ) **Tyr**-Gly-Gly-Phe-Leu

Dynorphin A (κ) **Tyr**-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln

Endogenous Opioids

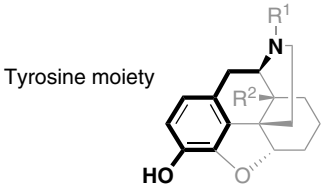


Figure 2. Sequence of typical opioid peptides.

nor-BNI, while still maintaining the address structure. The message site of nor-BNI, a 4,5-epoxymorphinan skeleton with a cyclopropylmethyl substituent, could be indispensable for opioid activity because it corresponds to the tyrosine residue found in endogenous opioid peptides. Therefore, we speculated that the accessory site of nor-BNI might be located within the address subsite of this antagonist. A key aspect of our design of a κ-selective agonist was to explore which part of the address subsite of nor-BNI corresponded to the accessory site.

The meso form analog of nor-BNI (**5**) has κ-selectivity and antagonist activity similar to those of nor-BNI (Fig. 4).[11] Furthermore, compound **6**, which lacks the phenol ring in the address site of nor-BNI, maintained κ-receptor antagonist selectivity comparable to nor-BNI.[12] Thus, neither the phenol ring nor the hydroxyl group of the ring junction in the address site of nor-BNI were required for the κ-selectivity and antagonist activity. Upon comparing the κ-antagonist, compound **6**, with naltrexone and NTI, we proposed that the structural distance of the address site from the message site was an essential factor of the address subsite for receptor selectivity (Fig. 3). Bearing this in mind, to design a κ-selective agonist, the accessory site of compound **6** must be removed while still maintaining the length of the address site for

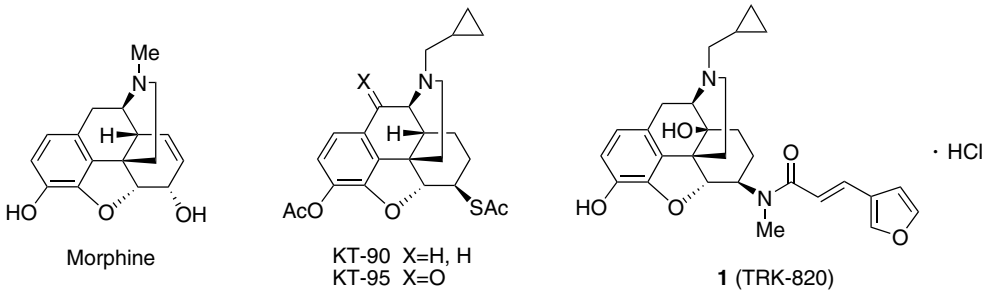


Chart 1. Structures of morphine, KT-90, KT-95, and compound **1** (TRK-820).

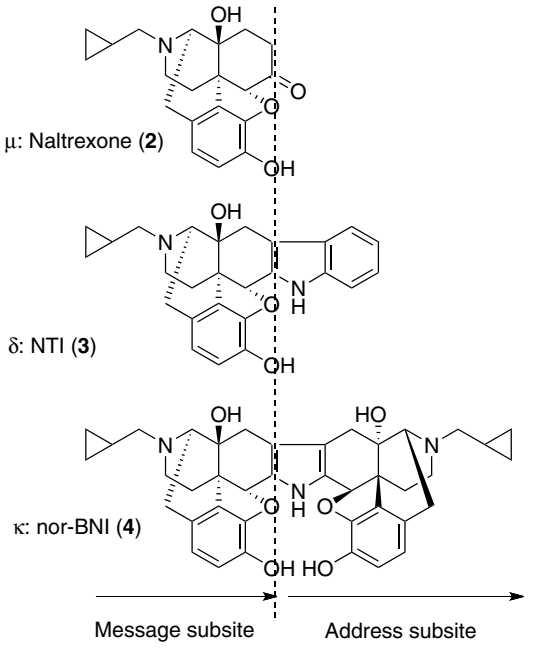


Figure 3. Message-address concept in opioid antagonist field.

the κ-receptor interaction. Therefore, we made the address subsite less-hindered and synthesized compound (**A**) to couple C6 and X (hetero atom) with a single bond (Fig. 4). This single bond is expected to give structural flexibility to the ligand, so that the structural changes that the receptor undergoes in induced fit will occur easily to express agonist activity.

Based on these ideas for design, a number of compounds were synthesized to attain the proper structural size and length on the side chain (address subsite) for a κ-agonist. We found that the side-chain structure of the 6-position had a major influence to receptor selectivity and opioid activity (the SARs are stated below). As a result, we identified compound **1**, (2*E*)-*N*-[(5*R*,6*R*)-17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide hydrochloride (TRK-820), which was synthesized from 6β-*N*-methylnaltorexamine[13] (β-**7b**) and 3-(3-furyl)acryloyl chloride, as a potent and selective κ-agonist.

2. Results and discussion

2.1. Chemistry

For the basic design, we used naltrexone (**2**) as a starting material because its 6-oxo moiety can be readily modified with various side chains. We synthesized many derivatives to identify the most suitable spacer X, side chain, and stereochemistry. The effects of substitutions at the 17-nitrogen were also examined and various *N*-alkyl compounds were synthesized starting from noroxycodone (**24**).[14]

Scheme 1 shows the synthetic routes for the screening targets. Thioester **14** and thioether **13c** were derived from hydroxy intermediates **12**[15] via S_N2-type reactions under the appropriate reaction conditions.[16] Etherification and amidation transformations were conducted under typical reaction conditions starting from the corresponding hydroxy[15] and amino[13,17] intermediates (**10** and **7**) to give various side-chain derivatives, **11**, **1**, and **8a**–**r**. Reduction of amidomorphinan **8a** with boran-dimethylsulfide afforded amino compound **9a**.

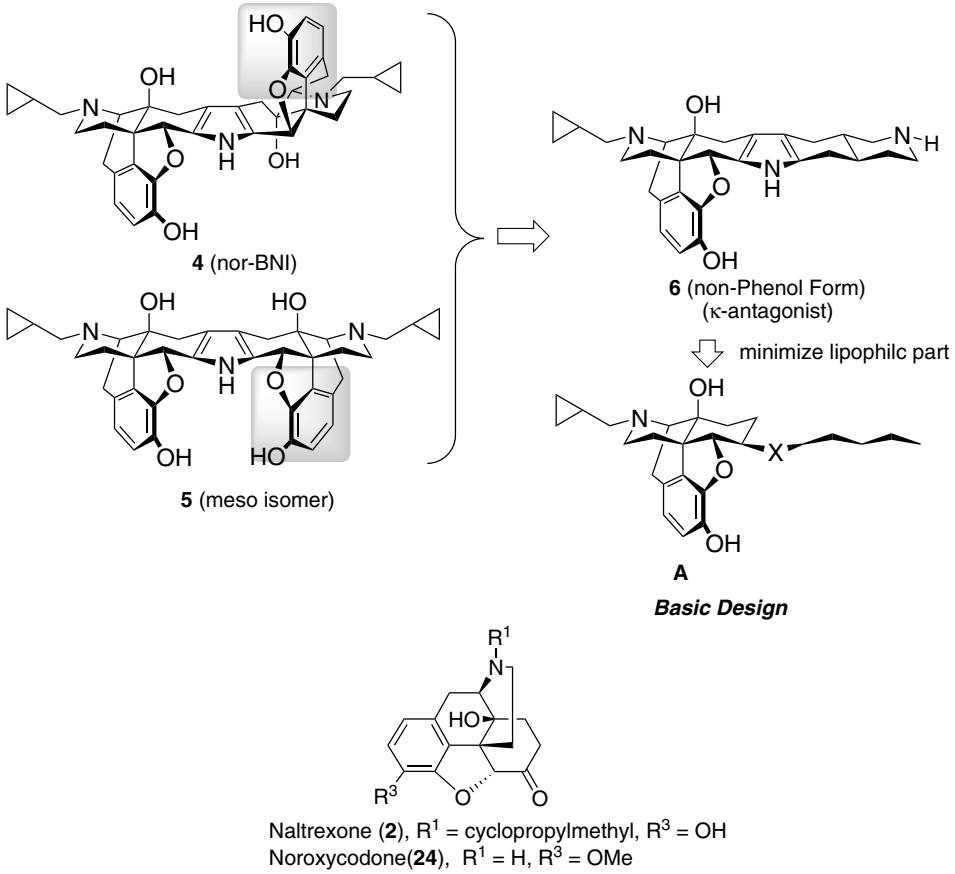
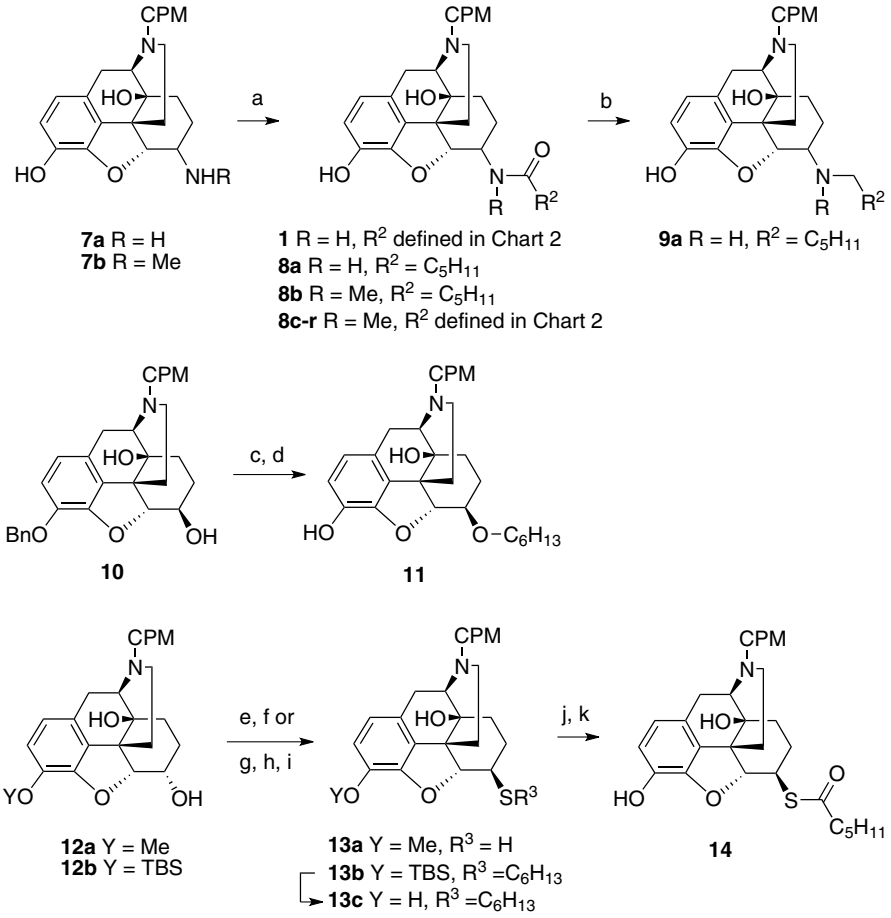


Figure 4. Basic design of a new chemical class opioid κ-agonist.



Scheme 1. Synthesis of screening targets. Reagents and conditions: (a) R^2COCl, Na_2CO_3, THF/H_2O or R^2COOH, condensing agent; (b) $BH_3{\cdot}SMe_2$, THF; (c) $C_6H_{13}Br$, NaH, DMF; (d) H_2, Pd/C, PhCOOH, MeOH; (e) Ph_3P, *i*PrOCON = NCOO*i*Pr, AcSH, THF; (f) NaOHaq, MeOH; (g) MsCl, TEA, CH_2Cl_2; (h) $C_6H_{13}SH$, LDA, THF; (i) TBAF, THF/H_2O; (j) $C_5H_{11}COCl$, Na_2CO_3, THF/H_2O; (k) BBr_3, CH_2Cl_2.

A derivative of **1** was synthesized starting from the appropriately substituted 6-oxo morphinans obtained from **2** or **24** (Fig. 4).[14]

2.2. Pharmacology and discussion

We screened several compounds for the most appropriate spacer X for opioid κ-agonist activity (Table 1). We fixed the side chain at six carbons in length, which is similar to the size of the address part of nor-BNI. Opioid receptor selectivity and agonistic activity were evaluated using electrically stimulated mouse vas deferens (MVD) or guinea pig ileum (GPI) preparations.[18] The agonist potencies were expressed as IC_{50} values, and the receptor selectivity of each test agonist was evaluated by the Ke value. After detecting an opioid agonist activity of the test compounds in vitro, the acetic acid writhing (AAW) test[19] using mice was conducted to estimate in vivo potency. We also confirmed that an analgesic effect of the test compounds could be effectively antagonized by pretreatment with the opioid κ-antagonist nor-BNI.

In the MVD assay, almost all the compounds showed similar agonistic activity. KT-90 and KT-95,[20–22] which have thioester structures, were reported to show opioid κ-agonist activity, but **14** showed almost no agonistic activity in vitro or in vivo. This result emphasizes the importance of the chemical structure of the 'address' part of the agonist analog. Amide compounds, particularly the *N*-methyl amido compound **8b,** showed the most potent agonistic activity in the AAW test and demonstrated the greatest κ-selectivity in the MVD assay.

We examined the effects of the introduction of an unsaturated bond and a lipophilic moiety at the side chain in the *N*-methyl amide derivatives (**8c–8f**, Chart 2) on agonist activity and selectivity (Table 2). We also attempted to optimize the length of the side chain. We found an attractive lead compound **8f**, a 6β-cinnamamido derivative which showed highly selective opioid κ-agonist activity in the MVD assay and pronounced in vivo agonist potency in the AAW test, even by po-administration. Furthermore, the duration of the agonist effect in in vivo tests was adequate. However, **8f** showed a weak but significant aversive effect in the rat conditioned place preference (CPP) test (data not shown).[23]

We then performed a lead optimization study by focusing on the stereochemistry, length, and aromatic ring structure of the side chain. Many derivatives of **8f** were synthesized (Chart 2) by condensing α- and β-*N*-methylnaltrexamine with various carboxylic acids and were evaluated (Table 3). Compounds α- and β-**8g** were categorized by simple combination of the morphinan structure with U-50488H, since they have a common side chain (3,4-dichlorophenylacetamido). However, their analgesic activities, especially when administered orally, were neither potent nor long lasting. Studies on simple derivatives of the U-50488H chemical structure failed to identify any new drug candidates. Nonetheless, in the course of the lead optimization process, we identified a few trends in structure–activity relationships. (1) Compounds having the 6β-amido structure showed lower sc/po potency ratio and long po-duration in the AAW test. (2) The aromatic ring structure in the C6-side chain is one of the most important components to optimize the pharmacological profile, particularly with respect to

Table 1
SAR on the variation of the spacer X

Compound	X-R^2	MVD[a]				AAW, ED_{50}[b] (mg/kg)		
		IC_{50} (nM)	Ke[c] (nM)			sc	po	po/sc
			μ[d]	δ[e]	κ[f]			
11	O–C_6H_{13}	16 (6.7–26)	4.5	1.5	0.12	1.78 (1.12–2.84)	ND[g]	ND[g]
13c	S–C_6H_{13}	Partial agonist (1 μM: 38% inhibition)				15.8 (7.57–32.8)	ND[g]	ND[g]
14	SC(=O)–C_5H_{11}	Not effective				Not effective		
8a	NHC(=O)–C_5H_{11}	25 (3.1–46)	4.4	2.3	0.26	10 mg/kg: 25% inhibition		
9a	NH–C_6H_{11}	2.0 (1.3–2.7)	14	NC[h]	0.3	0.29 (0.23–0.36)	ND[g]	ND[g]
8b	NMeC(=O)–C_5H_{11}	15 (11–19)	UD[i]	89.6[j]	0.046[k]	0.77 (0.06–0.10)	0.63 (0.42–0.95)	8.2

[a] $n = 4$–9 (95% confidence limits).
[b] $n = 10$ (95% confidence limits).
[c] Ke values were calculated from the following equation: Ke = [antagonist]/(IC_{50} ratio − 1); [antagonist]: concentration of the antagonist; IC_{50} ratio: IC_{50} without the antagonist per IC_{50} with the antagonist. Each preparation was incubated with a selective antagonist for 20 min before the addition of a test compound.
[d] Naloxone (30 nM) was used as a μ-selective antagonist.
[e] NTI (10 nM) was used as a δ-selective antagonist.
[f] nor-BNI (10 nM) was used as a κ-selective antagonist.
[g] Not determined.
[h] Not calculated (the IC_{50} ratio was too small to calculate the Ke value).
[i] Undetectable (IC_{50} was not changed up to 100 nM naloxone).
[j] NTI (100 nM) was used.
[k] nor-BNI (20 nM) was used.

attenuation of psychotomimetic effects. Finally, we identified compound **1** as the optimum structure, which was characterized by a furanylacrylamide side chain.

Evaluation of the pharmacological profile of **1** revealed that the agonist potency was 6000- and 1800-fold stronger than that of morphine in the MVD and GPI preparations, respectively (Table 4). In comparison to U-50488H, TRK-820, **1** was 140 times and 30 times more potent on GPI and MVD, respectively. According to the μ/κ ratios of the observed Ke values in the GPI assay, compound **1** was 75 times more effective with κ receptors than with the μ receptors while U-50488H showed a 390-fold preference for the κ receptors. Furthermore, U-50488H was the superior κ-selective compound as compared to **1** as long as the κ_1-selective antagonist, nor-BNI,[24,25] is used. However, this result suggests that **1** may have an affinity to a κ-receptor subtype other than that targeted by U-50488H. Compound **1** was also evaluated for its antinociceptive effects in the AAW and tail flick (TF) methods in mice, and showed high activity in both tests (Table 4). The ED_{50} values of **1**, indicated that this compound was 85–175 times more potent as an analgesic than morphine and 80–350 times more potent than U-50488H. This analgesic effect was antagonized only by the κ-receptor antagonist, nor-BNI, but not by NTI or by low-dose naloxone.[7] Furthermore, **1** was characterized by its low psychotomimetic effect. Morphine showed a significant preferential effect and the test animals appeared to show aversion on U-50488H administration.[26,27] In this study, we thus concluded that **1** was neutral and was expected to show less psychotomimetic side effects.[28,29]

After the identification of **1** as the optimum candidate, we tried to clarify which part of its structure was responsible for its excellent pharmacological profile. The AAW test (sc) in mice was selected to evaluate structure–activity and structure–absorption, –distribution, –metabolism, and –excretion relationships as a whole. Table 5 summarizes the results of a SAR study on the AAW test (sc) of compound **1** derivatives **15**–**23**. Although, the main factors determining the activity in the AAW test remain to be clarified, our data imply the importance of each feature of the chemical structure of **1**. The tyrosine components (17-nitrogen and the 3-hydroxy group) are indispensable for the in vivo activity of **1** and the 17-cyclopropylmethyl, 14-hydroxy, and *N*-methyl substituents also contribute to its agonist activity.

Compound **1** was originally investigated for use as an analgesic to be delivered by iv and im injections for the control of moderate to severe surgical pain. It was concluded that the drug was effective but its safety margin was not as sufficient as was expected from results of animals to conduct further clinical development on this type of pain. Additional nonclinical pharmacological studies demonstrated that Compound **1** at very low doses inhibited itching induced by morphine and Substance P injection.[30–33] Pruritus is a common affliction found in patients maintained on regular hemodialysis, and full development of Compound **1** for uremic pruritus was initiated after confirming its efficacy in the Phase IIa clinical study. Presently, **1** is under application for approval as an antipruritus in Japan.

3. Conclusion

We obtained a morphinan derivative, which is a new chemical class of opioid κ-agonist without the [N-C-C-N(sp^2)] pharmacophore sequence of the U-50488H derivative. We verified that the 'message-address concept' and the 'accessory site hypothesis' were applicable in the development of this opioid κ-agonist. TRK-820 (**1**) showed a significant opioid κ-agonist activity and induced neither aversion nor preference in the CPP test. Presently, **1** is under appli-

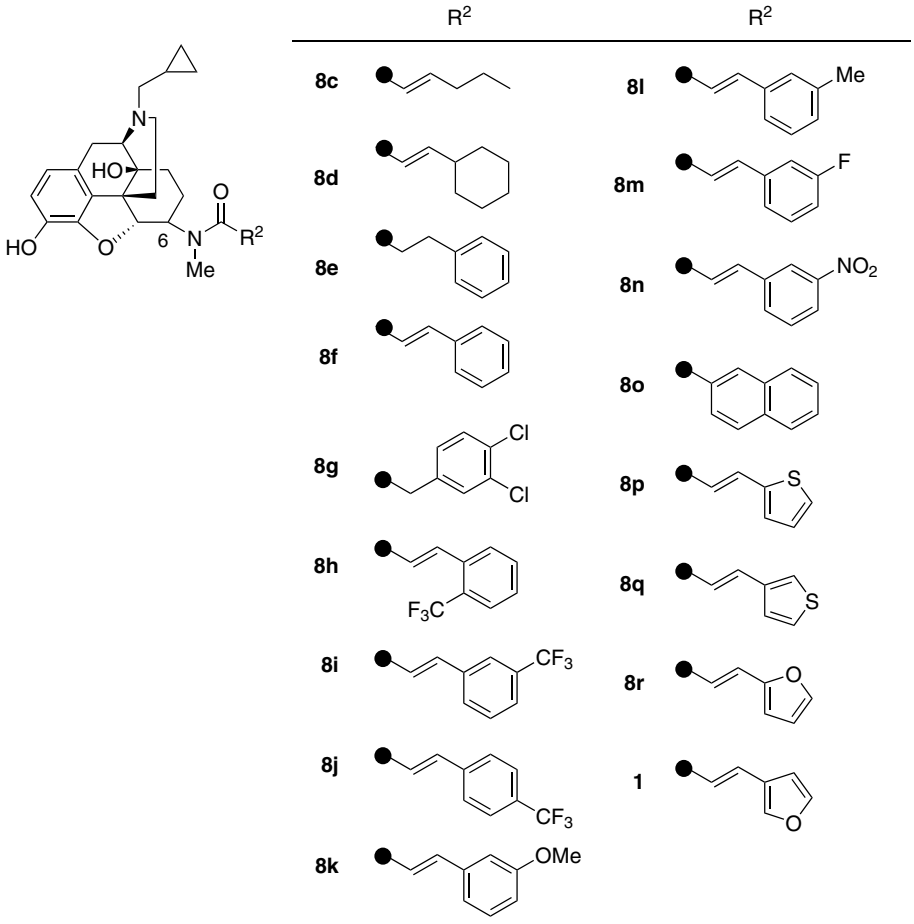


Chart 2. Structure of morphinan-6-amido derivatives.

Table 2
SAR on the variation of the side-chain R^2

Compound	MVD[a]				AAW, ED_{50}[b] (mg/kg)			
	IC_{50}(nM)	Ke[c] (nM)			sc	po	po/sc	Duration[g]
		μ[d]	δ[e]	κ[f]				
8b	15(11–19)	UD[h]	89.6[i]	0.046[j]	0.77(0.06–0.10)	0.63(0.42–0.95)	8.2	ND[k]
8c	0.647(0.492–0.851)	1797	UD[h]	0.072	0.024(0.018–0.031)	0.21 (0.16–0.29)	8.8	S
8d	0.457(0.322–0.647)	5713	143	1.08	0.004(0.003–0.007)	0.071(0.0–4–0.11)	17.0	L
8e	0.019(0.0015–0.23)	UD[h]	188	0.008	0.040(0.025–0.063)	0.29 (0.24–0.35)	7.3	S
8f	0.166(0.124–0.222)	922	263	0.861	0.002(0.001–0.003)	0.011(0.008–0.051)	5.5	L

[a] $n = 4–9$ (95% confidence limits).
[b] $n = 10$ (95% confidence limits).
[c] Ke values were calculated as described in Table 1.
[d] Naloxone (30 nM) was used as a μ-selective antagonist.
[e] NTI (10 nM) was used as a δ-selective antagonist.
[f] nor-BNI (10 nM) was used as a κ-selective antagonist.
[g] Dose that can inhibit 90% AAW behavior at 30 min after test compound administration (sc). AAW test was performed at each point of 60, 120, 180, and 240 min post-administration. S (short): effect decreased within 120 min; L (long): effect continued until 180 min or more.
[h] Undetectable.
[i] NTI (100 nM) was used.
[j] nor-BNI (20 nM) was used.
[k] Not determined.

cation for approval as an antipruritus in Japan. At present, throughout the world, no other κ agonist remains in clinical trial or in the approval stage except TRK-820. We also obtained SAR information which pointed out the importance of the 17-cyclopropylmethyl and 14-hydroxy moieties, and the *N*-methylamido side-chain structure of **1** for its opioid κ-agonist activity.

4. Experimental

4.1. Materials

Synthetic reagents were purchased from Aldrich (Milwaukee, WI, USA), Kanto Kagaku Co. (Tokyo, Japan), TCI (Tokyo, Japan), or

Table 3
SAR on the Variation of the Side-Chain Configuration and R^2

Compound	6-α or 6-β	MVD [a]				AAW, ED_{50} [b] (mg/kg)			Duration[g]
		IC_{50} (nM)	Ke[c] (nM)			sc	po	po/sc	
			μ[d]	δ[e]	κ[f]				
8f	β	0.166 (0.124–0.222)	922	263	0.861	0.002 (0.001–0.003)	0.011 (0.008–0.051)	5.5	L
	α	0.12 (0.09–0.17)	16.5	0.43	4.90	0.0058 (0.0044–0.0075)	0.23 (0.16–0.33)	39.3	L
8g	β	17.0 (12.9–22.4)	17000	1113	1.37	0.46 (0.37–0.56)	17.99 (13.69–23.63)	39.1	ND[h]
	α	0.40 (0.29–0.54)	53.0	17.1	0.55	0.017 (0.013–0.022)	0.83 (0.57–1.20)	48.0	S
8h	β	ND[h]	—	—	—	0.18 (0.14–0.23)	ND[h]	—	ND[h]
8i	β	0.47 (0.26–0.84)	UD[i]	291	3.20	0.0046 (0.0034–0.0062)	0.034 (0.027–0.044)	7.4	ND[h]
8j	β	0.07 (0.03–0.18)	524	78.0	0.20	0.023 (0.014–0.037)	0.026 (0.018–0.038)	1.1	L
8k	β	0.75 (0.44–1.27)	60.9	96.4	1.60	0.0011 (0.0008–0.0014)	0.0048 (0.0036–0.0070)	4.4	L
81	β	0.32 (0.14–0.72)	1778	64.5	1.95	0.0049 (0.0031–0.0077)	0.064 (0.034–0.120)	9.7	L
8m	β	1.60 (0.81–3.18)	UD[i]	276	2.37	0.0019 (0.0012–0.0031)	0.0070 (0.0012–0.010)	3.7	L
8n	β	0.23 (0.17–0.30)	185	89.0	1.40	0.017 (0.010–0.028)	0.220 (0.150–0.300)	12.9	ND[h]
8o	β	ND[h]	ND[h]	ND[h]	ND[h]	3.6	ND[h]	—	ND[h]
8p	β	0.10 (0.07–0.13)	UD[i]	89.6	0.28	0.0027 (0.0024–0.0031)	0.026 (0.021–0.032)	9.6	L
8q	β	0.10 (0.07–0.15)	UD[i]	UD[i]	1.71	0.0042 (0.0011–0.0029)	0.040 (0.008–0.015)	9.5	L
8r	β	0.55 (0.40–0.74)	UD[i]	UD[i]	0.20	0.0016 (0.0011–0.0024)	0.015 (0.012–0.019)	9.4	L
1	α	0.049 (0.038–0.062)	31.9	245	0.91	0.0081 (0.0054–0.012)	0.13 (0.10–0.18)	16.0	ND[h]
	β	0.42 (0.28–0.64)	14,000	41.6	0.16	0.0033 (0.0025–0.0043)	0.032 (0.025–0.041)	9.7	L

[a] n = 4–9 (95% confidence limits).
[b] n = 10 (95% confidence limits).
[c] Ke values were calculated as described in Table 1.
[d] Naloxone (30 nM) was used as a μ-selective antagonist.
[e] NTI (10 nM) was used as a δ-selective antagonist.
[f] nor-BNI (10 nM) was used as a κ-selective antagonist.
[g] Dose that can inhibit 90% AAW behavior at 30 min after test compound administration (sc). AAW test was performed at each point of 60, 120, 180, and 240 min post-administration. S (short): effect decreased within 120 min; L (long): effect continued until 180 min or more.
[h] Not determined.
[i] Undetectable.

Sigma Chemical Co. (St. Louis, MO, USA). All reagents and solvents used were of analytical grade from a standard commercial source or were purified by standard methods before use.

4.2. General

Melting points were determined on a Yanaco MP-500D melting point apparatus and were uncorrected values. NMR data were taken on VALIAN GEMINI-300 (300 MHz) or JEOL GX-400 (400 MHz) spectrometers and reported in δ (ppm) downfield from tetramethylsilane. IR spectra were determined on a JASCO FT/IR-5000 spectrophotometer. MS were obtained on a JEOL JES-D-300, JEOL JMS-D-303 or VG ZAB-HF instrument by applying an EI method or a FAB ionization method. Elemental analyses were performed using a Heraeus CHN-ORAPID for carbon, hydrogen, and nitrogen; KYOTO ELECTRONICS AT-118 for chlorine; and YOKOGAWA IC-7000 for fluorine, bromine, and sulfur. Elemental analyses results were within 0.4% of the theoretical values. The progress of the reactions and purity of the final products were determined on Merck Silica Gel Art.5715. Column chromatography was carried out using Merck Silica Gel (70–230 mesh).

4.3. Amidation

4.3.1. General method A

Naltrexamine derivative **7** and Et_3N (3 equiv) were dissolved in $CHCl_3$ (ca. 0.1 M). To this solution, various acid chlorides (2 equiv) were added dropwise at 0 °C. After completion of dropwise addition, the reaction solution was stirred for 1 h at rt, followed by the addition of saturated aqueous $NaHCO_3$ for separation. The aqueous layer was then extracted twice with $CHCl_3$. After drying over anhydrous Na_2SO_4, the combined organic layers were concentrated. The residue was dissolved in MeOH and $CHCl_3$ (ca. 0.2 M). To this solution, K_2CO_3 (5 equiv) was added at rt, and then stirred for 30 min at the same temperature. Water and $CHCl_3$ were added to the reaction mixture for separation, and the aqueous layer was extracted twice with $CHCl_3$. After drying over anhydrous Na_2SO_4, the combined organic layers were concentrated. The resulting residue was purified by silica gel column chromatography or recrystallization.

4.3.2. General method B

Compound **7** was dissolved in a solution of water and THF (1:1, ca. 0.2 M). To the solution, Na_2CO_3 (2 equiv) was added, and the atmosphere of the reaction system was replaced with Ar. Then, acid chloride (1.1 equiv) was dissolved in THF (ca. 1 M) and added dropwise. After stirring for 30 min, MeOH (1/5 volume of the reaction mixture) and 3 N aqueous NaOH (4 equiv) were added and stirred for 1 h. AcOEt and saturated aqueous $NaHCO_3$ were added to the reaction mixture for separation, and the aqueous layer was re-extracted with AcOEt. After washing with brine, the resulting organic layer was dried over Na_2SO_4 and concentrated. The resulting residue was purified by silica gel column chromatography or recrystallization.

4.4. Spectral data of amido compounds 1, 8a–8r, 15–18, 21–22

4.4.1. (2*E*)-*N*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide (1) hydrochloride

Yield 85%. Mp 207–217 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 0.41 (1H, m), 0.54 (1H, m), 0.60 (1H, m), 0.68 (1H, m), 1.09 (1H, m), 1.20–1.50 (3H, m), 1.74 (1H, d, J = 13.7 Hz), 2.15 (1H, m), 2.45 (1H, m), 2.57 (1H, m), 2.90 (1H, m), 2.93 (1.8H, s), 3.07 (2H, m), 3.17 (1.2H, s), 3.32 (2H, m), 3.58 (0.6H, m), 3.88 (1H, m), 4.20 (0.4H, m), 4.88 (0.6H, d, J = 8.1 Hz), 4.94 (0.4H, d, J = 8.5 Hz), 6.35 (0.6H, d, J = 15.5 Hz), 6.50 (0.4H, s), 6.61 (0.6H, s), 6.62 (0.6H, s), 6.64 (0.4H, d, J = 8.1 Hz), 6.71 (0.6H, d, J = 8.1 Hz), 6.72 (0.4H, d,

Table 4
Detail comparison of compound **1** with morphine and U-50488H

Compound	GPI				MVD					AAW (sc) ED_{50}[a] (mg/kg)	TF (sc) ED_{50}[a] (mg/kg)
	IC_{50}[a] (nM)	Ke[b] (nM)		μ/κ	IC_{50}[a] (nM)	Ke[b] (nM)					
		κ	μ			κ	μ	δ	μ/κ	δ/κ	
1	0.0081(0.0057–0.011)	0.070[c]	5.5[f]	78.6	0.080 (0.067–0.095)	0.049[c]	48[f]	NC[i]	980	–	0.0033 (0.0025–0.0043)	0.062 (0.032–0.119)
Morphine	49.3 (37.6–64.6)	20.5[d]	5.06[g]	0.25	145.1 (111.2–189.3)	53.5[d]	3.29[g]	7.35[h]	0.06	0.14	0.58 (0.48–0.71)	5.26 (3.79–7.32)
U-50488H	1.12 (0.70–1.81)	0.031[c]	12.1[f]	390	2.35 (1.91–2.90)	0.031[e]	31.5[f]	41.2[h]	1016	1329	1.16 (0.90–1.51)	5.18 (2.35–11.43)

[a] $n = 5$–7 (95% confidence limits).
[b] Ke values were calculated as described in Table 1.
[c] nor-BNI (10 nM) was used as a κ-selective antagonist.
[d] nor-BNI (100 nM) was used as a κ-selective antagonist.
[e] nor-BNI (1 nM) was used as a κ-selective antagonist.
[f] Naloxone (100 nM) was used as a μ-selective antagonist.
[g] Naloxone (20 nM) was used as a μ-selective antagonist.
[h] NTI (100 nM) was used as a δ-selective antagonist.
[i] Not calculated.

J = 8.1 Hz), 6.86 (0.6H, d, J = 8.1 Hz), 6.90 (0.4H, d, J = 15.1 Hz), 7.00 (0.4H, s), 7.22 (0.6H, d, J = 15.5 Hz), 7.37 (0.4H, d, J = 15.1 Hz), 7.66 (0.6H, s), 7.72 (0.4H, s), 7.92 (0.6H, s), 8.03 (0.4H, s), 8.89 (1H, br s), 9.29 (0.4H, s), 9.70 (0.6H, s). IR (KBr, cm^{-1}): 3382, 1647, 1506, 1155, 1124. MS (FAB) m/z $(M+H)^+$ = 477. Anal. Calcd for $C_{28}H_{32}N_2O_5 \cdot HCl \cdot 0.43H_2O$: C, 64.58; H, 6.55; N, 5.38; Cl, 6.81. Found: C, 64.64; H, 6.76; N, 5.55; Cl, 6.85.

4.4.2. (2*E*)-*N*-[(5*R*,6*S*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide (α-1) tartrate

Yield 39%. Mp 243–254 °C (dec). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.10–0.30 (2H, m), 0.44–0.63 (2H, m), 0.83–0.1.30 (2H, m), 1.30–1.42 (1H, m), 1.42–1.60 (2H, m), 1.69–1.83 (1H, m), 2.12–2.41 (2H, m), 2.41–2.65 (2H, m), 2.65–2.82 (2H, m), 2.82–2.98 (1H, m), 3.05 (3H, s), 3.05–3.16 (1H, m), 3.16–3.39 (1H, m), 2.80–3.80 (1H, br s), 4.07 (1H, s), 4.55 (0.2H, m), 4.63 (0.8H, d, J = 2.9 Hz), 4.68 (0.2H, br s), 4.96 (0.8H, dt, J = 13.6, 4.0 Hz), 6.52 (1H, d, J = 8.3 Hz), 6.63 (1H, d, J = 7.8 Hz), 6.72–6.87 (0.4H, m), 6.96 (0.8H, d, J = 15.1 Hz), 7.01 (0.8H, s), 7.43 (1H, d, J = 15.1 Hz), 7.72 (0.8H, s), 7.70–7.78 (1H, m), 8.80–9.60 (1H, br s). IR (KBr, cm^{-1}): 3360, 1651, 1510, 1160, 1120. MS (FAB) m/z $(M+H)^+$ = 477. Anal. Calcd for $C_{28}H_{32}N_2O_5 \cdot 0.5(C_4H_6O_6) \cdot 0.8H_2O$: C, 63.66; H, 6.52; N, 4.95. Found: C, 63.42; H, 6.50; N, 4.87.

4.4.3. *N*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-hexanamide (8a) hydrochloride

Yield 37%. Mp > 210 °C (dec). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.40 (1H, m), 0.51 (1H, m), 0.58 (1H, m), 0.66 (1H, m), 0.86 (3H, t, J = 6.8 Hz), 1.09 (1H, m), 1.20–1.40 (6H, m), 1.40–1.55 (4H, m), 1.65–1.75 (2H, m), 2.06 (2H, t, J = 7.1 Hz), 2.35–2.50 (2H, m), 2.85 (1H, m), 2.95–3.10 (2H, m), 3.25–3.45 (2H, m), 3.86 (1H, d, J = 5.1 Hz), 4.55 (1H, d, J = 7.8 Hz), 6.24 (1H, s), 6.63 (1H, d, J = 8.2 Hz), 6.72 (1H, d, J = 8.2 Hz), 8.09 (1H, d, J = 7.8 Hz), 8.87 (1H, br s), 9.37 (1H, s). IR (KBr, cm^{-1}): 3245, 1652, 1504, 1128. MS (FAB) m/z $(M+H)^+$ = 441. Anal. Calcd for $C_{26}H_{36}N_2O_4 \cdot HCl \cdot 0.7H_2O$: C, 63.78; H, 7.90; N, 5.72; Cl, 7.24. Found: C, 63.74; H, 7.95; N, 5.72; Cl, 7.28.

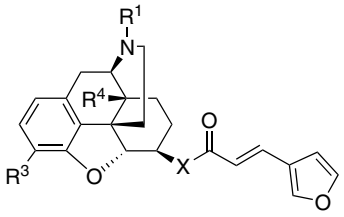
4.4.4. *N*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-*N*-methylhexanamide (8b) tartrate

Yield 43%. Mp 150–158 °C (dec). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.23 (2H, m), 0.48–0.59 (2H, m), 0.79 (2.1H, br t, J = 6.8 Hz), 0.88 (0.9H, br t, J = 6.8 Hz), 0.92 (1H, m), 1.11–1.22 (3H, m), 1.23–1.51 (6H, m), 1.58 (1H, m), 1.98–2.33 (5H, m), 2.52 (1H, m), 2.67–2.82 (3H, m), 2.77 (2.1H, s), 2.93 (0.9H, s). 3.11 (1H, br d, J = 19.1 Hz), 3.33 (1H, m), 3.48 (1H, m), 3.50 (5H, br s), 4.08 (2H, s), 4.60 (0.7H, d, J = 8.3 Hz), 4.72 (0.3H, d, J = 8.3 Hz), 6.56 (0.3H, d, J = 7.8 Hz), 6.60 (0.7H, d, J = 7.8 Hz), 6.62 (0.3H, d, J = 7.8 Hz), 6.67 (0.7H, d, J = 7.8 Hz), 9.26 (1H, br s). IR (KBr, cm^{-1}): 3314, 1719, 1618, 1460, 1120. MS (FAB) m/z $(M+H)^+$ = 455. Anal. Calcd for $C_{27}H_{38}N_2O_4 \cdot C_4H_6O_6 \cdot H_2O$: C, 59.79; H, 7.45; N, 4.50. Found: C, 59.59; H, 7.46; N, 4.67.

4.4.5. (2*E*)-*N*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-*N*-methylhex-2-enamide (8c) tartrate

Yield 52%. Mp > 145 °C (dec). ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 0.25 (2H, m), 0.48–0.59 (2H, m), 0.79 (2.1H, t, J = 7.3 Hz), 0.90 (0.9H, t, J = 7.3 Hz), 0.92 (1H, m), 1.20–1.48 (5H, m), 1.58 (1H, m), 1.91–2.20 (4H, m), 2.29 (1H, m), 2.53 (1H, m), 2.67–2.85 (3H, m), 2.81 (2.1H, s), 3.01 (0.9H, s), 3.11 (1H, br d, J = 18.6 Hz), 3.31 (1H, m), 3.45 (4.2H, br s), 3.57 (1H, m), 4.06 (1.6H, s), 4.62 (0.7H, d, J = 7.8 Hz), 4.74 (0.3H, d, J = 7.8 Hz), 6.05 (0.7H, d, J = 15.1 Hz), 6.35–6.44 (1H, m), 6.64–6.71 (2.3H, m), 9.26 (1H, br s). IR (KBr, cm^{-1}): 3396, 1736, 1655, 1460, 1123. MS (FAB) m/z

Table 5
SAR on the compound **1** derivatives



Compound	R^1	R^3	R^4	X	MVD[a]				AAW ED_{50}[b] (mg/kg, sc)
					IC_{50}(nM)	Ke[c] (nM)			
						μ[d]	δ[e]	κ[f]	
1	CPM	OH	OH	NMe	0.42 (0.28–0.64)	14,000	41.6	0.16	0.0033 (0.0025–0.0043)
15	Me	OH	OH	NMe	55 (36–84)	8.1	33	6.3	1.03 (0.74–1.43)
16	H	OH	OH	NMe	ND[h]	—	—	—	7.07 (3.02–16.6)
17	Phenethyl	OH	OH	NMe	ND[h]	—	—	—	1.03 (0.54–1.93)
18	CPM	H	OH	NMe	27.2 (25.0–29.4)	12.0	8.40	0.07	0.013 (0.0087–0.018)
19	CPM	NH_2	OH	NMe	ND[h]	—	—	—	0.20 (0.13–0.30)
20	CPM	NHAc	OH	NMe	ND[h]	—	—	—	>10
21	CPM	OH	H	NMe	0.035 (0.029–0.041)	8.04	1.31	0.07	0.02 (0.015–0.026)
22	CPM	OH	OH	NH	0.869 (0.055–1.15)	UD[g]	8100.00	0.44	0.95 (0.69–1.30)
23	CPM	OH	OH	S	ND[h]	—	—	—	>10

[a] $n = 10$ (95% confidence limits).
[b] $n = 4$–9 (95% confidence limits).
[c] Ke values were calculated as described in Table 1.
[d] Naloxone (30 nM) was used as a μ-selective antagonist.
[e] NTI (10 nM) was used as a δ-selective antagonist.
[f] nor-BNI (10 nM) was used as a κ-selective antagonist.
[g] Undetectable.
[h] Not determined.

$(M+H)^+ = 453$. Anal. Calcd for $C_{27}H_{36}N_2O_4 \cdot 0.8(C_4H_6O_6) \cdot 1.1H_2O$: C, 61.22; H, 7.32; N, 4.73. Found: C, 61.13; H, 7.23; N, 4.82.

4.4.6. (2*E*)-*N*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-3-cyclohexyl-*N*-methylprop-2-enamide (8d) tartrate

Yield 77%. Mp 154 °C (dec). ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 0.16–0.32 (2H, m), 0.42–0.62 (2H, m), 0.82–1.02 (2H, m), 1.02–1.42 (7H, m), 1.42–1.80 (6H, m), 1.88–2.33 (4H, m), 2.42–2.58 (1H, m), 2.58–2.87 (3H, m), 2.81 (2.1H, s), 3.01 (0.9H, s), 3.09 (1H, br d, $J = 18.3$ Hz), 3.28 (1H, br s), 3.60 (0.7H, m), 4.05 (1H, s), 4.11 (0.3H, m), 4.61 (0.7H, d, $J = 7.9$ Hz), 4.73 (0.3H, d, $J = 8.5$ Hz), 5.93 (0.7H, d, $J = 15.3$ Hz), 6.33 (0.7H, d, $J = 15.3$ Hz), 6.34 (0.3H, d, $J = 15.3$ Hz), 6.52–6.62 (1.6H, m), 6.66 (0.7H, d, $J = 8.5$ Hz), 8.60–9.60 (1H, br s). IR (KBr, cm^{-1}): 3322, 1651, 1601, 1450, 1410, 1129. MS (FAB) m/z $(M+H)^+ = 493$. Anal. Calcd for $C_{30}H_{40}N_2O_4 \cdot 0.7(C_4H_6O_6) \cdot 0.8H_2O$: C, 64.36; H, 7.54; N, 4.58. Found: C, 64.37; H, 7.67; N, 4.58.

4.4.7. *N*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-3-phenyl-*N*-methylprop-2-anamide (8e) hydrochloride

Yield 84%. Mp 207 °C (dec). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.31–0.47 (1H, m), 0.47–0.55 (1H, m), 0.55–0.63 (1H, m), 0.63–0.75 (1H, m), 0.99–1.13 (1H, m), 1.13–1.50 (3H, m), 1.60–1.78 (1H, m), 1.98–2.16 (1H, m), 2.28–2.52 (3H, m), 2.52–2.95 (2H, m), 2.83 (2.4H, s), 2.96 (0.6H, s), 2.95–3.16 (2H, m), 3.22–3.35 (2H, m), 3.36–3.53 (1H, m), 3.83 (1H, m), 4.79 (0.8H, d, $J = 7.8$ Hz), 4.85 (0.2H, d, $J = 8.3$ Hz), 6.38 (0.2H, m), 6.46 (0.8H, m), 6.60–6.80 (2H, m), 7.02–7.32 (5H, m), 8.82 (1H, br s), 9.29 (0.2H, s), 9.56 (0.8H, s). IR (KBr, cm^{-1}): 3416, 1622, 1502, 1125. MS (FAB) m/z $(M+H)^+ = 489$. Anal. Calcd for $C_{30}H_{36}N_2O_4Cl_2 \cdot HCl \cdot 0.2H_2O$: C, 67.92; H, 7.11; N, 5.28; Cl, 6.68. Found: C, 67.96; H, 7.06; N, 5.27; Cl, 6.85.

4.4.8. (2*E*)-*N*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-3-phenyl-*N*-methylprop-2-enamide (8f) hydrochloride

Yield 46%. Mp 225 °C (dec). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.42 (1H, m), 0.50 (1H, m), 0.59 (1H, m), 0.68 (1H, m), 1.07 (1H, m), 1.20–1.50 (3.5H, m), 1.72 (1H, m), 2.13 (1H, m), 2.40–2.60 (2.5H, m), 2.87 (1H, m), 2.92 (2H, s), 3.06 (2H, m), 3.19 (1H, s), 3.32 (2H, m), 3.60–4.30 (2H, m), 4.85 (0.5H, m), 4.92 (0.5H, m), 6.30 (1H, m), 6.68 (2H, m), 6.88 (0.5H, d, $J = 8.3$ Hz), 7.30–7.50 (5H, m), 7.71 (0.5H, d, $J = 6.4$ Hz), 8.79 (1H, m), 9.29 (0.5H, s), 9.70 (0.5H, s). IR (KBr, cm^{-1}): 3380, 1642, 1499, 1127. MS (FAB) m/z $(M+H)^+ = 487$. Anal. Calcd for $C_{30}H_{34}N_2O_4 \cdot HCl \cdot 0.3H_2O$: C, 68.18; H, 6.79; N, 5.30; Cl, 6.71. Found: C, 68.06; H, 7.11; N, 5.46; Cl, 6.37.

4.4.9. (2*E*)-*N*-[(5*R*,6*S*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-3-phenyl-*N*-methylprop-2-enamide (α-8f) tartrate

Yield 74%. Mp 254–257 °C (dec). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.21 (1H, m), 0.52 (1H, m), 0.91 (1H, m), 1.20 (1.5H, m), 1.48 (3H, m), 1.78 (1H, m), 2.26 (2.5H, m), 2.58 (1H, m), 2.73 (2H, m), 2.91 (0.5H, s), 3.06 (1H, m), 3.09 (2.5H, s), 3.20–3.90 (4H, br), 4.03 (1H, s), 4.50–5.10 (2H, m), 6.52 (1H, d, $J = 7.9$ Hz), 6.62 (1H, d, $J = 7.9$ Hz), 7.09 (0.2H, d, $J = 15.9$ Hz), 7.23 (0.8H, d, $J = 15.9$ Hz), 7.40–7.60 (4H, m), 7.60–7.80 (2H, m), 8.80–9.20 (1H, br). IR (KBr, cm^{-1}): 3400, 1644, 1593, 1118. MS (FAB) m/z $(M+H)^+ = 487$. Anal. Calcd for $C_{30}H_{34}N_2O_4 \cdot 0.5(C_4H_6O_6) \cdot 0.8H_2O$: C, 66.72; H, 6.75; N, 4.86. Found: C, 66.56; H, 6.74; N, 5.08.

4.4.10. *N*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-3-(3,4-dichlorophenyl)-*N*-methylacetamide (8g) hydrochloride

Yield 51%. Mp 194–196 °C (dec). ^{1}H NMR ($CDCl_3$+D_2O, 400 MHz, free base) δ: 0.09–0.17 (2H, m), 0.49–0.57 (2H, m), 0.78–0.89 (2H,

m), 1.05 (0.7H, dt, J = 13.2, 3.4 Hz), 1.42–1.51 (0.3H, m), 1.49 (2H, br d, J = 13.2 Hz), 1.97–2.29 (3H, m), 2.36 (2H, d, J = 6.4 Hz), 2.56–2.69 (2H, m), 2.92 (2.1H, s), 2.99 (0.9H, s), 3.00–3.08 (2H, m), 3.48 (0.7H, d, J = 15.6 Hz), 3.49–3.56 (1H, m), 3.66 (0.7H, d, J = 15.6 Hz), 3.70 (0.6H, s), 4.55 (0.3H, d, J = 8.3 Hz), 4.58 (0.7H, d, J = 8.3 Hz), 6.57 (0.3H, d, J = 8.3 Hz), 6.73 (0.3H, d, J = 8.3 Hz), 6.78–6.82 (1.4H, m), 6.83 (0.7H, d, J = 8.3 Hz), 7.11 (0.3H, dd, J = 8.3, 2.5 Hz), 7.23 (0.7H, d, J = 8.3 Hz), 7.36 (0.3H, d, J = 2.0 Hz), 7.39 (0.3H, d, J = 8.3 Hz), 7.63 (0.7H, d, J = 2.0 Hz). IR (KBr, cm^{-1}): 3420, 1620, 1127. MS (FAB) m/z $(M+H)^+$ = 543. Anal. Calcd for $C_{29}H_{32}N_2O_4Cl_2 \cdot HCl \cdot 0.7H_2O$: C, 58.78; H, 5.85; N, 4.73; Cl, 17.95. Found: C, 58.72; H, 5.86; N, 4.71; Cl, 18.03.

4.4.11. *N*-[(5*R*,6*S*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-3-(3,4-dichlorophenyl)-*N*-methylacetamide (α-8g) hydrochloride

Yield 58%. Mp 252–254 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.43 (2H, m), 0.65 (2H, m), 1.05 (1H, m), 1.16 (1.5H, m), 1.37 (1H, m), 1.58 (2H, m), 1.92 (1H, m), 2.43 (1H, m), 2.68 (1H, m), 2.81 (0.5H, s), 2.96 (2.5H, s), 3.05 (2.5H, m), 3.30 (2H, m), 3.85 (3H, m), 4.48 (0.2H, m), 4.62 (0.8H, d, J = 3.9 Hz), 4.75 (0.2H, m), 4.96 (0.8H, m), 6.21 (0.8H, m), 6.46 (0.2H, m), 6.58 (1H, d, J = 8.3 Hz), 6.72 (1H, d, J = 8.3 Hz), 7.25 (1H, m), 7.55 (2H, m), 8.80 (1H, br s), 9.32 (1H, br s). IR (KBr, cm^{-1}): 3370, 1620, 1510, 1120. MS (FAB) m/z $(M+H)^+$ = 543. Anal. Calcd for $C_{29}H_{32}N_2O_4Cl_2 \cdot HCl \cdot 0.5\ H_2O$: C, 59.14; H, 5.82; N, 4.75; Cl, 18.06. Found: C, 59.34; H, 5.78; N, 4.78; Cl, 17.78.

4.4.12. (2*E*)-*N*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-3-(2-trifluoromethylphenyl)-*N*-methylprop-2-enamide (8h) hydrochloride

Yield 93%. Mp 196–199 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.41 (1H, m), 0.53 (1H, m), 0.59 (1H, m), 0.67 (1H, m), 1.09 (1H, m), 1.30–1.50 (3H, m), 1.73 (1H, d, J = 13.2 Hz), 2.20 (1H, m), 2.40–2.60 (2H, m), 2.88 (1H, m), 2.97 (2H, s), 3.00–3.10 (2H, m), 3.23 (1H, s), 3.30–3.40 (2H, m), 3.68 (0.7H, m), 3.87 (1H, br s), 4.18 (0.3H, m), 4.88 (0.7H, d, J = 7.8 Hz), 4.97 (0.3H, d, J = 8.3 Hz), 6.60–6.90 (2.7H, m), 7.28 (0.3H, d, J = 15.1 Hz), 7.50–7.70 (1.7H, m), 7.70–7.90 (3H, m), 8.14 (0.3H, d, J = 7.8 Hz). IR (KBr, cm^{-1}): 3400, 1649, 1605, 1460, 1125. MS (FAB) m/z $(M+H)^+$ = 555. Anal. Calcd for $C_{31}H_{33}N_2O_4F_3 \cdot 1.1HCl \cdot 0.4H_2O$: C, 61.86; H, 5.84; N, 4.65; Cl, 6.48; F, 9.47. Found: C, 61.88; H, 5.94; N, 4.67; Cl, 6.44; F, 9.47.

4.4.13. (2*E*)-*N*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-3-(3-trifluoromethylphenyl)-*N*-methylprop-2-enamide (8i) tartrate

Yield 84%. Mp 156–159 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.21 (2H, m), 0.52 (2H, m), 0.91 (1H, m), 1.20–1.50 (3H, m), 1.57 (1H, d, J = 13.2 Hz), 2.12 (2H, m), 2.29 (1H, m), 2.49 (1H, m), 2.60–2.80 (3H, m), 2.90 (2H, s), 3.08 (1H, d, J = 18.6 Hz), 3.17 (1H, s), 3.26 (1H, m), 3.67 (0.7H, m), 4.02 (1H, s), 4.21 (0.3H, m), 4.68 (0.7H, d, J = 7.8 Hz), 4.79 (0.3H, d, J = 8.3 Hz), 6.60–6.80 (2.6H, m), 7.37 (1H, dd, J = 7.3, 16.1 Hz), 7.50–7.80 (3.8H, m), 8.02 (0.3H, d, J = 7.8 Hz), 8.14 (0.3H, s). IR (KBr, cm^{-1}): 3350, 1649, 1601, 1168, 1127. MS (FAB) m/z $(M+H)^+$ = 555. Anal. Calcd for $C_{31}H_{33}N_2O_4F_3 \cdot 0.5(C_4H_6O_6) \cdot 0.3\ H_2O$: C, 62.41; H, 5.81; N, 4.41; F, 8.98. Found: C, 62.32; H, 5.99; N, 4.48; F, 8.88.

4.4.14. (2*E*)-*N*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-3-(4-trifluoromethylphenyl)-*N*-methylprop-2-enamide (8j) tartrate

Yield 84%. Mp 167–170 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.21 (2H, m), 0.52 (2H, m), 0.91 (1H, m), 1.20–1.40 (3H, m), 1.58 (1H, m), 2.10–2.20 (2H, m), 2.30 (1H, m), 2.49 (1H, m), 2.60–2.80 (3H, m), 2.90 (2H, s), 3.16 (1H, s), 3.18 (1H, d, J = 18.6 Hz), 3.24 (1H, m), 3.65 (0.7H, m), 4.03 (1H, s), 4.20 (0.3H, m), 4.68 (0.7H, d, J = 8.3 Hz), 4.79 (0.3H, d, J = 7.8 Hz), 6.50–6.70 (1.3H, m), 6.80–6.90 (1.4H, m), 7.34 (1H, d, J = 15.6 Hz), 7.51 (0.3H, d, J = 15.6 Hz), 7.70–7.80 (3.7H, m), 7.94 (0.3H, d, J = 8.3 Hz). IR (KBr, cm^{-1}): 3400, 1649, 1601, 1168, 1114. MS (FAB) m/z $(M+H)^+$ = 555. Anal. Calcd for $C_{31}H_{33}N_2O_4F_3 \cdot 0.5(C_4H_6O_6) \cdot 0.3\ H_2O$: C, 62.41; H, 5.81; N, 4.41; F, 8.98. Found: C, 62.36; H, 5.80; N, 4.41; F, 8.98.

4.4.15. (2*E*)-*N*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-3-(3-methoxyphenyl)-*N*-methylprop-2-enamide (8k) tartrate

Yield 88%. Mp 160 °C (dec). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.15–0.35 (2H, m), 0.45–0.65 (2H, m), 0.85–1.05 (1H, m), 1.20–1.50 (3H, m), 1.52–1.70 (1H, m), 2.00–2.25 (2H, m), 2.25–2.42 (1H, m), 2.63–2.77 (3H, m), 2.90 (1.8H, s), 2.90–4.20 (3H, br s), 3.05–3.22 (1H, m), 3.15 (1.2H, s), 3.22–3.42 (1H, m), 3.50–3.74 (1.6H, m), 3.77 (1.8H, s), 3.80 (1.2H, s), 4.00 (1H, s), 4.20 (0.4H, br s), 4.71 (0.6H, d, J = 7.8 Hz), 4.80 (0.4H, d, J = 8.3 Hz), 6.55–6.71 (2.6H, m), 6.92 (0.6H, dd, J = 8.3, 2.5 Hz), 6.95–7.03 (1H, m), 7.10 (0.6H, d, J = 7.3 Hz), 7.17 (0.4H, d, J = 15.1 Hz), 7.23–7.35 (2.4H, m), 7.42 (0.4H, d, J = 15.6 Hz), 9.07 (0.4H, br s), 9.37 (0.6H, br s). IR (KBr, cm^{-1}): 3390, 1642, 1599, 1460, 1127. MS (FAB) m/z $(M+H)^+$ = 517. Anal. Calcd for $C_{31}H_{36}N_2O_5 \cdot 0.5(C_4H_6O_6) \cdot 0.7\ H_2O$: C, 65.59; H, 6.74; N, 4.64. Found: C, 65.46; H, 6.78; N, 4.70.

4.4.16. (2*E*)-*N*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-3-(3-methylphenyl)-*N*-methylprop-2-enamide (8l) hydrochloride

Yield 87%. Mp 245 °C (dec). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.42 (1H, m), 0.50 (1H, m), 0.59 (1H, m), 0.69 (1H, m), 1.07 (1H, m), 1.20–1.50 (3H, m), 1.72 (1H, d, J = 13.7 Hz), 2.12 (1H, m), 2.34 (3H, s), 2.40–2.60 (2H, m), 2.88 (1H, m), 2.92 (2H, s), 3.00–3.10 (2H, m), 3.18 (1H, s), 3.30–3.40 (2H, m), 3.66 (0.7H, m), 3.83 (1H, m), 4.20 (0.3H, m), 4.83 (0.7H, d, J = 7.8 Hz), 4.90 (0.3H, d, J = 8.3 Hz), 6.60–6.80 (2H, m), 6.85 (0.7H, d, J = 8.3 Hz), 7.10–7.30 (4.4H, m), 7.41 (0.3H, d, J = 15.1 Hz), 7.48 (0.3H, d, J = 7.3 Hz), 7.54 (0.3H, br s). IR (KBr, cm^{-1}): 3390, 1647, 1605, 1323, 1127. MS (FAB) m/z $(M+H)^+$ = 501. Anal. Calcd for $C_{31}H_{36}N_2O_4 \cdot HCl \cdot 0.8H_2O$: C, 67.51; H, 7.06; N, 5.08; Cl, 6.43. Found: C, 67.35; H, 7.05; N, 5.17; Cl 6.53.

4.4.17. (2*E*)-*N*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-3-(3-fluorophenyl)-*N*-methylprop-2-enamide (8m) tartrate

Yield 81%. Mp 145–153 °C ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.20–0.32 (2H, m), 0.46–0.62 (2H, m), 0.88–1.00 (1H, m), 1.20–1.50 (3H, m), 1.55–1.65 (1H, m), 2.00–2.40 (3H, m), 2.42–2.60 (2H, m), 2.70–2.88 (3H, m), 2.90 (2.1H, s), 3.05–4.00 (7H, m), 3.15 (0.9H, s), 4.11 (2H, s), 4.71 (0.7H, d, J = 8.1 Hz), 4.81 (0.3H, d, J = 8.1 Hz), 6.58–6.68 (3H, m), 7.14–7.68 (5H, m), 9.15 (0.3H, br s), 9.45 (0.7H, br s). IR (KBr, cm^{-1}): 3320, 1731, 1647, 1127. MS (FAB) m/z $(M+H)^+$ = 505. Anal. Calcd for $C_{30}H_{33}N_2O_4\ F \cdot C_4H_6O_6 \cdot H_2O$: C, 60.71; H, 6.14; N, 4.16; F, 2.82. Found: C, 60.63; H, 6.22; N, 4.07; F, 2.81.

4.4.18. (2*E*)-*N*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-3-(3-nitrophenyl)-*N*-methylprop-2-enamide (8n) hydrochloride

Yield 47%. Mp 161–164 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.18–0.30 (2H, m), 0.46–0.60 (2H, m), 0.85–0.97 (1H, m), 1.22–1.50 (3H, m), 1.53–1.62 (1H, m), 2.03–2.21 (2H, m), 2.23–2.35 (1H, m), 2.50–2.90 (4H, m), 2.91 (2.1H, s), 3.18 (0.9H, s), 3.10–4.20 (3H, m), 4.05 (1H, s), 4.67 (0.7H, d, J = 8.3 Hz), 4.81 (0.3H, d, J = 8.3 Hz), 6.58 (0.3H, d, J = 7.8 Hz), 6.84 (0.7H, d, J = 15.6 Hz), 7.42 (0.3H, d, J = 15.9 Hz), 7.45 (0.7H, d, J = 15.6 Hz), 7.57 (0.3H, d, J = 15.6 Hz), 7.66 (0.7H, dd, J = 8.3, 7.8 Hz), 7.71 (0.3H, dd,

J = 8.3, 7.8 Hz), 7.93 (0.7H, d, *J* = 7.8 Hz), 8.15–8.27 (2H, m), 8.60 (0.3H, s), 9.12 (0.3H, br s), 9.28 (0.7H, br s). IR (KBr, cm^{-1}): 3380, 1649, 1601, 1531, 1127. MS (FAB) *m*/*z* $(M+H)^+$ = 532. Anal. Calcd for $C_{30}H_{33}N_3O_6{\cdot}0.5(C_4H_6O_6){\cdot}2.2H_2O$: C, 59.47; H, 6.30; N, 6.50. Found: C, 59.42; H, 5.96; N, 6.25.

4.4.19. *N*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-*N*-methyl-1-naphthamide (8o) hydrochloride

Yield 95%. Mp 220 °C (dec). ^1H NMR (DMSO-d_6, 400 MHz) δ: 0.34 (1H, m), 0.47 (1H, m), 0.54 (1H, m), 0.62 (1H, m), 0.87 (1H, m), 0.99 (1H, m), 1.28 (1H, m), 1.40–1.60 (2H, m), 2.17 (1H, m), 2.34 (1H, m), 2.52 (1H, m), 2.70–2.90 (2H, m), 3.01 (1H, m), 3.10 (2H, s), 3.20–3.40 (3.7H, m), 3.70 (0.7H, m), 3.87 (0.3H, m), 4.15 (0.3H, m), 5.00 (0.7H, d, *J* = 7.8 Hz), 5.06 (0.3H, m), 6.37 (0.3H, m), 6.39 (0.7H, d, *J* = 7.8 Hz), 6.58 (0.7H, d, *J* = 8.3 Hz), 6.71 (0.3H, m), 7.60–8.00 (7H, m). IR (KBr, cm^{-1}): 3400, 1620, 1319, 1176, 1120. MS (FAB) *m*/*z* $(M+H)^+$ = 511. Anal. Calcd for $C_{32}H_{34}N_2O_4{\cdot}HCl{\cdot}0.4H_2O$: C, 69.34; H, 6.51; N, 5.05; Cl, 6.40. Found: C, 69.13; H, 6.86; N, 4.96; Cl, 6.73.

4.4.20. (2*E*)-*N*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-3-(thiophen-2-yl)-*N*-methylprop-2-enamide (8p) tartrate

Yield 84%. Mp 178–171 °C. ^1H NMR (DMSO-d_6, 400 MHz) δ: 0.22 (2H, m), 0.53 (2H, m), 0.91 (1H, m), 1.20–1.40 (3H, m), 1.58 (1H, d, *J* = 10.4 Hz), 2.14 (2H, m), 2.27 (1H, m), 2.50 (1H, m), 2.60–2.80 (3H, m), 2.88 (1.8H, s), 3.08 (1H, d, *J* = 17.1 Hz), 3.11 (1.2H, s), 3.24 (1H, m), 3.59 (0.6H, m), 4.02 (1H, s), 4.20 (0.4H, m), 4.66 (0.6H, d, *J* = 8.6 Hz), 4.76 (0.4H, d, *J* = 8.6 Hz), 6.42 (0.6H, d, *J* = 7.9 Hz), 6.48 (0.4H, d, *J* = 12.2 Hz), 6.57 (1H, d, *J* = 7.9 Hz), 6.75 (0.6H, d, *J* = 7.9 Hz), 6.85 (0.4H, d, *J* = 15.3 Hz), 7.07 (0.6H, t, *J* = 3.7 Hz), 7.12 (0.4H, t, *J* = 4.9 Hz), 7.32 (0.6H, d, *J* = 3.1 Hz), 7.45–7.48 (1H, m), 7.58–7.67 (1.4H, m). IR (KBr, cm^{-1}): 3350, 1636, 1590, 1460, 1035. MS (FAB) *m*/*z* $(M+H)^+$ = 493. Anal. Calcd for $C_{28}H_{32}N_2O_4S{\cdot}0.5(C_4H_6O_6){\cdot}0.5\ H_2O$: C, 62.48; H, 6.29; N, 4.86; S, 5.56. Found: C, 62.32; H, 6.36; N, 4.92; S, 5.57.

4.4.21. (2*E*)-*N*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-3-(thiophen-3-yl)-*N*-methylprop-2-enamide (8q) methansulfonate

Yield 88%. Mp 235 °C. ^1H NMR (DMSO-d_6, 400 MHz) δ: 0.42 (1H, m), 0.51 (1H, m), 0.60 (1H, m), 0.68 (1H, m), 1.08 (1H, m), 1.20–1.50 (3H, m), 1.72 (1H, d, *J* = 12.2 Hz), 2.12 (1H, m), 2.34 (3H, s), 2.40–2.50 (2H, m), 2.86 (1H, m), 2.91 (2H, s), 3.00–3.10 (2H, m), 3.15 (1H, s), 3.30–3.50 (2H, m), 3.61 (0.7H, m), 3.82 (1H, br s), 4.19 (0.3H, m), 4.81 (0.7H, d, *J* = 7.8 Hz), 4.89 (0.3H, d, *J* = 8.3 Hz), 6.46 (0.7H, d, *J* = 15.6 Hz), 6.60–6.70 (1.3H, m), 6.85 (0.7H, d, *J* = 7.8 Hz), 7.00 (0.3H, d, *J* = 15.1 Hz), 7.26 (0.7H, d, *J* = 4.9 Hz), 7.31 (0.7H, d, *J* = 15.6 Hz), 7.46 (0.3H, d, *J* = 15.1 Hz), 7.50–7.70 (2H, m), 7.87 (0.3H, s). IR (KBr, cm^{-1}): 3410, 1642, 1595, 1323, 1127. MS (FAB) *m*/*z* $(M+H)^+$ = 493. Anal. Calcd for $C_{28}H_{32}N_2O_4S{\cdot}CH_3SO_3\,H{\cdot}0.2\ H_2O$: C, 58.80; H, 6.19; N, 4.73; S, 10.83. Found: C, 58.60; H, 6.42; N, 4.72; S, 10.82.

4.4.22. (2*E*)-*N*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-3-(furan-2-yl)-*N*-methylprop-2-enamide (8r) hydrochloride

Yield 80%. Mp 200 °C (dec). ^1H NMR (DMSO-d_6, 400 MHz) δ: 0.42 (1H, m), 0.53 (1H, m), 0.61 (1H, m), 0.69 (1H, m), 1.08 (1H, m), 1.28 (0.5H, m), 1.30–1.50 (2.5H, m), 1.74 (1H, m), 2.15 (1H, m), 2.40–2.60 (2.5H, m), 2.80–2.90 (1.5H, m), 2.93 (1.5H, s), 3.00–3.10 (2H, m), 3.16 (1.5H, s), 3.30–3.40 (2H, m), 3.61 (0.5H, m), 3.85 (1H, br s), 4.20 (0.5H, m), 4.85 (0.5H, d, *J* = 7.3 Hz), 4.91 (0.5H, d, *J* = 7.8 Hz), 6.40–6.70 (3.5H, m), 6.80–6.90 (1.5H, m), 7.14 (0.5H, d, *J* = 15.1 Hz), 7.28 (0.5H, d, *J* = 15.6 Hz), 7.68 (0.5H, s), 7.80 (0.5H, s). IR (KBr, cm^{-1}): 3390, 1647, 1597, 1127. MS (FAB) *m*/*z* $(M+H)^+$ = 477. Anal. Calcd for $C_{28}H_{32}N_2O_5{\cdot}HCl{\cdot}0.6\ H_2O$: C, 64.20; H, 6.58; N, 5.35; Cl, 6.77. Found: C, 64.21; H, 6.84; N, 5.38; Cl, 6.69.

4.4.23. (2*E*)-*N*-[(5*R*,6*R*)-4,5-Epoxy-3,14-dihydroxy-17-methylmorphinan-6-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide (15) hydrochloride

Mp > 250 °C (dec). ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.20–1.45 (3H, m), 1.66 (1H, d, *J* = 14.2 Hz), 2.12 (1H, m), 2.80–2.85 (3H, m), 2.90–3.15 (4.6H, m), 3.30–3.35 (2H, m), 3.35 (1.2H, s), 3.57 (1.8H, br s), 4.20 (0.4H, br s), 4.86 (0.6H, d, *J* = 8.0 Hz), 4.91 (0.4H, d, *J* = 8.3 Hz), 6.34 (0.6H, d, *J* = 15.6 Hz), 6.40 (0.4H, s), 6.51 (0.6H, s), 6.60–6.75 (2H, m), 6.84 (0.6H, d, *J* = 8.1 Hz), 6.90 (0.4H, d, *J* = 15.1 Hz), 7.00 (0.4H, s), 7.21 (0.6H, d, *J* = 15.6 Hz), 7.36 (0.4H, d, *J* = 15.1 Hz), 7.66 (0.6H, s), 7.73 (0.4H, s), 7.92 (0.6H, s), 8.04 (0.4H, s), 9.19 (1H, br s), 9.31 (0.4H, s), 9.72 (0.6H, s). IR (KBr, cm^{-1}): 3376, 1647, 1503, 1157, 1122. MS (FAB) *m*/*z* $(M+H)^+$ = 437. Anal. Calcd for $C_{25}H_{28}N_2O_5{\cdot}HCl{\cdot}0.6H_2O{\cdot}0.14AcOEt$: C, 61.88; H, 6.36; N, 5.65; Cl, 7.15. Found: C, 61.97; H, 6.48; N, 5.43; Cl, 7.22.

4.4.24. (2*E*)-*N*-[(5*R*,6*R*)-4,5-Epoxy-3,14-dihydroxymorphinan-6-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide (16) tartrate

Yield 78%. Mp > 160 °C (dec). ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.36 (2H, m), 1.62 (1H, m), 2.07 (1H, m), 2.44 (2H, m), 2.89 (2H, s), 2.98 (1H, m), 3.11 (2H, m), 3.53 (1.5H, m), 3.90 (6H, br s), 3.85 (2H, s), 4.18 (0.5H, m), 4.71 (0.5H, d, *J* = 7.8 Hz), 4.80 (0.5H, d, *J* = 8.3 Hz), 6.36 (0.5H, d, *J* = 15.6 Hz), 6.62 (1H, br s), 6.65 (0.5H, d, *J* = 7.8 Hz), 6.69 (0.5H, d, *J* = 7.8 Hz), 6.81 (0.5H, d, *J* = 7.8 Hz), 6.89 (0.5H, d, *J* = 15.6 Hz), 6.99 (0.5H, br s), 7.21 (0.5H, d, *J* = 15.6 Hz), 7.36 (0.5H, d, *J* = 15.6 Hz), 7.66 (0.5H, br s), 7.72 (0.5H, br s), 7.91 (0.5H, s), 8.03 (0.5H, s), 9.67 (1H, br s). IR (KBr, cm^{-1}): 3858, 1651, 1595, 1410, 1135. MS (FAB) *m*/*z* $(M+H)^+$ = 423. Anal. Calcd for $C_{24}H_{26}N_2O_5{\cdot}C_4H_6O_6$: C, 58.74; H, 5.63; N, 4.89. Found: C, 58.66; H, 5.76; N, 4.93.

4.4.25. (2*E*)-*N*-[(5*R*,6*R*)-4,5-Epoxy-3,14-dihydroxy-17-phenethylmorphinan-6-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide (17) hydrochloride

Mp 225 °C (dec). ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.28 (0.4H, m), 1.30–1.50 (2.6H, m), 1.75 (1H, d, *J* = 13.4 Hz), 2.16 (1H, m), 2.50–2.60 (2H, m), 2.85–2.95 (3H, m), 3.00–3.25 (6H, m), 3.35–3.50 (1.6H, m), 3.80 (1H, m), 4.21 (0.4H, m), 4.88 (0.6H, d, *J* = 8.1 Hz), 4.93 (0.4H, d, *J* = 8.3 Hz), 6.36 (0.6H, d, *J* = 15.6 Hz), 6.46 (0.4H, br s), 6.57 (0.6H, br s), 6.60–6.75 (2H, m), 6.86 (0.6H, d, *J* = 8.1 Hz), 6.91 (0.4H, d, *J* = 15.1 Hz), 7.01 (0.4H, s), 7.23 (0.6H, d, *J* = 15.4 Hz), 7.25–7.50 (5.4H, m), 7.67 (0.6H, s), 7.73 (0.4H, s), 7.92 (0.6H, s), 8.03 (0.4H, s), 9.18 (1H, br s), 9.31 (0.4H, s), 9.70 (0.6H, s). IR (KBr, cm^{-1}): 3377, 1647, 1503, 1158, 1126. MS (FAB) *m*/*z* $(M+H)^+$ = 527. Anal. Calcd for $C_{32}H_{34}N_2O_5{\cdot}HCl{\cdot}0.4H_2O{\cdot}0.1AcOEt$: C, 67.20; H, 6.37; N, 4.84; Cl, 6.12. Found: C, 67.10; H, 6.41; N, 4.83; Cl, 6.01.

4.4.26. (2*E*)-*N*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-14-hydroxymorphinan-6-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide (18) hydrochloride

Yield 44%. Mp 190–195 °C (dec). ^1H NMR (DMSO-d_6, 400 MHz) δ: 0.44 (1H, m), 0.53 (1H, m), 0.60 (1H, m), 0.69 (1H, m), 1.09 (1H, m), 1.25 (0.5H, m), 1.35–1.45 (2H, m), 1.51 (0.5H, m), 1.75 (1H, m), 2.14 (1H, m), 2.35–2.60 (2H, m), 2.88 (1H, m), 2.93 (1.5H, s), 3.05 (1H, m), 3.16 (1.5H, s), 3.18 (1H, m), 3.43 (0.5H, d, *J* = 7.3 Hz), 3.48 (0.5H, d, *J* = 8.3 Hz), 3.63 (0.5H, m), 3.92 (1H, m), 4.24 (0.5H, m), 4.84 (0.5H, d, *J* = 8.3 Hz), 4.91 (0.5H, d, *J* = 8.3 Hz), 6.35 (0.5H, d, *J* = 15.6 Hz), 6.50 (0.5H, s), 6.66 (0.5H, d, *J* = 7.8 Hz),

6.70 (0.5H, d, J = 7.8 Hz), 6.84 (0.5H, d, J = 7.8 Hz), 6.85–7.00 (1.5H, m), 7.18 (0.5H, t, J = 7.8 Hz), 7.21 (0.5H, t, J = 7.8 Hz), 7.30 (0.5H, d, J = 15.1 Hz), 7.36 (0.5H, d, J = 15.1 Hz), 7.70 (0.5H, s), 7.72 (0.5H, s), 7.96 (0.5H, s), 8.03 (0.5H, s). IR (KBr, cm^{-1}): 3300, 1650, 1504, 1122, 1023. MS (FAB) m/z $(M+H)^+$ = 461. Anal. Calcd for $C_{28}H_{32}N_2O_4 \cdot HCl \cdot 0.3H_2O$: C, 66.93; H, 6.74; N, 5.57; Cl, 7.06. Found: C, 66.86; H, 6.81; N, 5.66; Cl, 6.96.

4.4.27. (2*E*)-*N*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3-hydroxymorphinan-6-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide (21) hydrochloride

Mp 225–230 °C (dec). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.38 (1H, m), 0.51 (1H, m), 0.63 (2H, m), 0.97 (1H, m), 1.21 (1H, m), 1.40–1.72 (3.8H, m), 2.29 (1H, m), 2.40–2.52 (1.2H, m), 2.57 (0.2H, m), 2.70 (0.8H, m), 2.80–2.96 (1.2H, m), 2.89 (2.4H, s), 3.00–3.18 (1.6H, m), 3.14 (0.6H, s), 3.18–3.35 (2.2H, m), 3.48 (0.8H, m), 3.95–4.10 (1.2H, m), 4.65–4.95 (1H, m), 6.27–8.32 (7H, m). IR (KBr, cm^{-1}): 3370, 1651, 1593, 1156. MS (FAB) m/z $(M+H)^+$ = 461. Anal. Calcd for $C_{28}H_{32}N_2O_4 \cdot 1.7HCl \cdot 0.5H_2O$: C, 63.27; H, 6.58; N, 5.27; Cl, 11.34. Found: C, 63.24; H, 6.60; N, 5.09; Cl, 11.55.

4.4.28. (2*E*)-*N*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-3-(furan-3-yl)prop-2-enamide (22) hydrochloride

Mp 240 °C (dec). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.41 (1H, m), 0.52 (1H, m), 0.59 (1H, m), 0.67 (1H, m), 1.07 (1H, m), 1.32–1.49 (2H, m), 1.57 (1H, m), 1.68–1.83 (2H, m), 2.37–2.47 (2H, m), 2.86 (1H, m), 2.98–3.12 (2H, m), 3.27–3.39 (2H, m), 3.52 (1H, m), 3.86 (1H, br d, J = 4.9 Hz), 4.60 (1H, d, J = 7.8 Hz), 6.23 (1H, br s), 6.33 (1H, d, J = 15.6 Hz), 6.65 (1H, d, J = 7.8 Hz), 6.72 (1H, d, J = 7.8 Hz), 6.73 (1H, br s), 7.32 (1H, d, J = 15.6 Hz), 7.74 (1H, br s), 8.01 (1H, s), 8.40 (1H, d, J = 7.8 Hz), 8.86 (1H, m), 9.36 (1H, s). IR (KBr, cm^{-1}): 3376, 1663, 1508, 1460, 1156, 1127. MS (FAB) m/z $(M+H)^+$ = 463. Anal. Calcd for $C_{27}H_{30}N_2O_5 \cdot HCl \cdot 0.2H_2O$: C, 64.52; H, 6.30; N, 5.57; Cl, 7.05. Found: C, 64.50; H, 6.39; N, 5.53; Cl, 7.00.

4.5. Synthesis of *N*-hexyl-[(5*R*,6*R*)-17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan]-6-amine (9a) hydrochloride

Amidomorphinan **8a** (290 mg, 0.66 mmol) dissolved in dried THF (3 mL) was added to the THF solution of $BH_3 \cdot Me_2S$ (2.0 M, 1.0 mL, 2.0 mmol). The resulting mixture was heated for refluxing and stirred for 1 h. $BH_3 \cdot Me_2S$ (2.0 M, 0.25 mL, 0.5 mmol) was added and refluxing was continued for an additional 2 h. To the reaction mixture, 6 N HCl (1.2 mL), water (2.0 mL), and MeOH (3.0 mL) were added and stirred for 1 h under a reflux condition. The reaction mixture was cooled to rt and was separated with AcOEt and saturated aqueous ammonia. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give a crude product. The resulting crude product was purified by silica gel column chromatography (AcOEt $\sim$ AcOEt/NH_4OH = 100:1 $\sim$ AcOEt/MeOH/NH_4OH = 100:3:1). The purified material was dissolved in AcOEt, and then HCl/MeOH was added. The precipitated hydrochloric acid salt was collected by filtration to give the captioned compound as white powder (283.4 mg, 86%). Mp 225 °C (dec). ^{1}H NMR ($CDCl_3$, 400 MHz, free base) δ: 0.12 (2H, m), 0.52 (2H, m), 0.83 (1H, m), 0.91 (3H, t, J = 7.1 Hz), 1.28–1.45 (6H, m), 1.56–1.69 (4H, m), 1.94 (1H, m), 2.13 (1H, ddd, J = 12.2, 12.2, 3.4 Hz), 2.21 (1H, ddd, J = 12.2, 12.2, 4.4 Hz), 2.36 (2H, d, J = 7.8 Hz), 2.52–2.73 (5H, m), 2.99 (1H, d, J = 18.5 Hz), 3.04 (1H, d, J = 5.4 Hz), 4.19 (1H, d, J = 7.3 Hz), 5.12 (3H, br s), 6.53 (1H, d, J = 8.1 Hz), 6.63 (1H, d, J = 8.1 Hz). IR (neat, cm^{-1}, free base): 3386, 1638, 1607, 1504, 1149, 1116. MS (FAB) m/z $(M+H)^+$ = 412. Anal. Calcd for $C_{26}H_{38}N_2O_3 \cdot 2HCl \cdot 0.4H_2O$: C, 61.63; H, 8.12; N, 5.53; Cl, 13.99. Found: C, 61.69; H, 8.15; N, 5.83; Cl, 13.70.

4.6. Synthesis of (5*R*,6*R*)-17-(cyclopropylmethyl)-4,5-epoxy-6-hexyloxy-3,14-dihydroxymorphinan (11) hydrochloride

NaH (60% mineral oil, 115.4 mg, 2.89 mmol) was washed with dried pentane. After the solid was suspended with DMF (10 mL), 3-*O*-benzyl-6β-naltrexol (**10**, 308 mg, 0.69 mmol) was added. To the reaction mixture, *n*-hexyl bromide (0.12 mL, 0.94 mmol) was added, and the resulting mixture was stirred for 24 h at 70 °C. After removing the solvent, saturated aqueous NH_4Cl, saturated ammonia, and AcOEt were added for separation. The organic layer was washed with water and brine, and then dried over Na_2SO_4. The crude material obtained by concentration was purified by silica gel column chromatography (*c*-hexane:AcOEt = 2/1) to give a benzyl ether compound as an oil (254.2 mg, 71%).

The benzyl ether moiety of the compound (254.2 mg, 0.49 mmol) was deprotected by 10% Pd/C (250 mg) catalyzed hydrogenolysis with $PhCO_2H$ (84.0 mg, 0.69 mmol) in MeOH (10 mL). After removing the catalyst, saturated aqueous $NaHCO_3$ and AcOEt were added for separation. The organic layer was washed with brine and then concentrated to give a crude product. The crude material was purified by silica gel column chromatography (*c*-hexane/AcOEt/NH_4OH = 275:25:2 $\sim$ 200:100:2) and dissolved in AcOEt, and then HCl/MeOH was added to the resulting mixture. The precipitated hydrochloric acid salt was collected by filtration to give the captioned compound as white powder (184.3 mg, 81%). Mp 240–245 °C (dec). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.40 (1H, m), 0.51 (1H, m), 0.59 (1H, m), 0.67 (1H, m), 0.87 (3H, t, J = 6.8 Hz), 1.07 (1H, m), 1.20–1.35 (7H, m), 1.39 (1H, d, J = 8.8 Hz), 1.40–1.50 (2H, m), 1.65–1.75 (3H, m), 2.35–2.45 (2H, m), 2.85 (1H, m), 2.95–3.05 (3H, m), 3.25–3.35 (2H, m), 3.47 (2H, dd, J = 6.3, 2.2 Hz), 3.87 (1H, d, J = 5.4 Hz), 4.44 (1H, d, J = 6.4 Hz), 6.30 (1H, s), 6.60 (1H, d, J = 8.3 Hz), 6.72 (1H, d, J = 8.3 Hz), 8.84 (1H, br s), 9.41 (1H, s). IR (KBr, cm^{-1}): 3233, 1636, 1505, 1116, 1035. MS (FAB) m/z $(M+H)^+$ = 428. Anal. Calcd for $C_{26}H_{37}NO_4 \cdot HCl \cdot 0.15H_2O$: C, 66.91; H, 8.27; N, 3.00; Cl, 7.60. Found: C, 66.84; H, 8.25; N, 3.05; Cl, 7.53.

4.7. Synthesis of (5*R*,6*R*)-17-(cyclopropylmethyl)-4,5-epoxy-6-hexylthio-3,14-dihydroxymorphinan (13c) hydrochloride

3-*O*-*t*-butyldimethylsilyl-6α-naltrexol (**12b**, 0.50 g, 1.09 mmol) was dissolved in CH_2Cl_2 (10 mL). To the solution, Et_3N (0.43 mL, 3.06 mmol) and MsCl (0.12 mL, 1.53 mmol) were added, and the solution was stirred for 3 h at 0 °C. To the solution, saturated aqueous NH_4Cl and AcOEt were added for separation. The organic layer was washed with water and brine, and was dried over Na_2SO_4. The crude 6α-mesylate compound was obtained by concentration.

To the THF solution of *n*-hexanethiol (0.83 mL, 5.94 mmol), LDA (1.5 M in THF, 4.0 mL, 6.0 mmol) was added at 0 °C. After 20 min of stirring, the above crude 6α-mesylate compound dissolved in THF (3 mL) was added dropwise to the reaction mixture. Stirring was continued for 6 h at 0 °C. To the reaction mixture, brine and AcOEt were added for separation. The organic layer was washed with water and brine, dried over Na_2SO_4, and then concentrated to give a crude product. The obtained crude product was purified by silica gel column chromatography (hexane/EtOAc = 4:1) to give silyl ether compound **13b**.

Deprotection of **13b** was conducted in THF (18 mL) using TBAF (1.0 M in THF, 0.84 mL, 8.4 mmol) catalyzed by two drops of water at rt. To the reaction mixture, brine and AcOEt were added for separation. The organic layer was washed with water and brine, dried over Na_2SO_4, and then concentrated to give a crude product. The obtained crude product was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to give a free base of the captioned product (**13c**, 0.36 g, 65%). The purified material (0.15 g, 3.38 mmol) was dissolved in AcOEt, and then HCl/MeOH was

added. The precipitated hydrochloric acid salt was collected by filtration to give the captioned compound as white powder (0.12 g, 75%). Mp > 235 °C (dec). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.40 (1H, m), 0.50 (1H, m), 0.59 (1H, m), 0.67 (1H, m), 0.85 (1H, t, J = 7.1 Hz), 1.07 (1H, m), 1.20–1.40 (8H, m), 1.45–1.55 (2H, m), 1.60–1.75 (2H, m), 1.85 (1H, m), 2.36 (1H, m), 2.42 (1H, d, J = 8.1 Hz), 2,60 (1H, dt, J = 12.7, 7.1 Hz), 2.69 (1H, dt, J = 12.7, 7.1 Hz), 2.85 (1H, m), 2.95–3.05 (2H, m), 3.25–3.35 (3H, m), 3.84 (1H, d, J = 4.9 Hz), 4.53 (1H, d, J = 8.1 Hz), 6.33 (1H, s), 6.62 (1H, d, J = 8.1 Hz), 6.74 (1H, d, J = 8.1 Hz), 8.87 (1H, br s), 9.40 (1H, s). IR (KBr, cm^{-1}): 3247, 1641, 1503, 1118, 1030. MS (FAB) m/z (M+H)$^+$ = 444. Anal. Calcd for $C_{26}H_{37}NO_3S{\cdot}HCl{\cdot}0.15H_2O$: C, 64.68; H, 8.00; N, 2.90; Cl, 7.34; S, 6.64. Found: C, 64.29; H, 7.92; N, 2.83; Cl, 7.52; S, 6.39.

4.8. Synthesis of thioester compounds

4.8.1. *S*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3, 14-dihydroxymorphinan-6-yl]hexanthioate (14) tartrate

To the THF (20 mL) solution of PPh_3 (1.65 g, 6.3 mmol), DIPAD (1.2 mL, 5.7 mmol) was added at 0 °C, and the resulting reaction mixture was stirred for 10 min at the same temperature. To the reaction mixture, ethanethioic *S*-acid (0.44 mL, 5.7 mmol) and then the THF (10 mL) solution of 3-*O*-methyl-6α-naltrexol (**12a**, 1.02 g, 2.85 mmol) were added. The reaction mixture was allowed to warm to rt and was stirred for 24 h. After concentration, 1 N HCl and AcOEt were added to the residue for separation. The organic layer was washed with 1H HCl. The combined aqueous layer was made basic using saturated aqueous $NaHCO_3$, and the product was extracted with AcOEt. The organic layer was dried over Na_2SO_4, and concentrated to give a crude product. The crude material was purified by silica gel column chromatography (*c*-hexane/AcOEt/MeOH = 350:50:5) to give a thioacetyl compound.

The thioacetyl compound (910 mg, 2.19 mmol) was hydrolyzed with 0.05 N NaOH (6 mL) in MeOH (30 mL) at rt. To the reaction mixture, aqueous saturated $NaHCO_3$ and $CHCl_3$ were added for separation. The organic layer was dried over Na_2SO_4 and concentrated. Then, the obtained crude product was purified by silica gel column chromatography ($CHCl_3$/NH_4OH = 100:1) to give thiol compound **13a** (718 mg, 88%).

Compound **13a** (629.5 mg, 1.69 mmol) and Na_2SO_4 (268 mg, 2.52 mmol) were dissolved in a mixture of THF (10 ml) and water (10 mL). To the reaction mixture, hexanoyl chloride (318 mg, 2.37 mmol) was added. Acylation was completed by stirring at rt for 2 h. Aqueous saturated $NaHCO_3$ and AcOEt were added for separation. The organic layer was dried over Na_2SO_4 and then concentrated. Silica gel column chromatography ($CHCl_3 \sim CHCl_3$/MeOH = 200:4 ~ 200:5) was performed to produce a thioester compound.

The deprotection of 3-methylether moiety was conducted with BBr_3 (1.0 M CH_2Cl_2, 14 mL, 14 mmol) in $CHCl_3$ (20 mL) at 0 °C. The reaction mixture was poured onto ice water, and then saturated ammonia, aqueous saturated $NaHCO_3$, and $CHCl_3$ were added for separation. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated. The crude product was purified by silica gel column chromatography ($CHCl_3 \sim CHCl_3$/MeOH = 40:1) to give a free base of the captioned compound (**14**, 403 mg, 55%). The purified material (0.15 g, 3.38 mmol) was dissolved in MeOH, and then tartaric acid was added. The precipitated tartaric acid salt was collected by filtration to give the captioned compound as white powder. Mp 175–176 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.15–0.20 (2H, m), 0.45–0.55 (2H, m), 0.86 (3H, t, J = 6.8 Hz), 0.90 (1H, m), 1.20–1.40 (6H, m), 1.50–1.60 (4H, m), 1.94 (1H, dt, J = 13.4, 10.7 Hz), 2.11 (1H, m), 2.23 (1H, m), 2.47 (1H, m), 2.57 (2H, t, J = 7.31), 2.60–2.75 (3H, m), 3.05–3.15 (2H, m), 3.25 (1H, br s), 4.03 (1H, s), 4.46 (1H, d, J = 8.8 Hz), 6.58 (1H, d, J = 8.3 Hz), 6.64 (1H, d, J = 8.3 Hz). IR (KBr, cm^{-1}): 3375, 1684, 1604, 1504, 1119. MS (FAB) m/z (M+H)$^+$ = 458. Anal. Calcd for $C_{26}H_{35}NO_4S{\cdot}0.5(C_4H_6O_6){\cdot}0.15H_2O$: C, 63.63; H, 7.050; N, 2.56; S, 5.86. Found: C, 63.58; H, 7.16; N, 2.53; S, 5.71.

4.8.2. *S*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-3-(furan-3-yl)prop-2-enthioate (23) tartrate

Yield 63%. Mp 225 °C (dec). ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 0.15–0.24 (2H, m), 0.45–0.57 (2H, m), 0.84–0.93 (1H, m), 1.23–1.43 (2H, m), 1.52–1.67 (2H, m), 1.92–2.29 (3H, m), 2.40–2.52 (1H, m), 2.53–2.78 (3H, m), 3.08 (1H, d, J = 19.1 Hz), 3.19–3.30 (1H, m), 4.01 (1H, s), 4.52 (1H, d, J = 8.8 Hz), 6.60 (1H, d, J = 7.8 Hz), 6.64 (1H, d, J = 7.8 Hz), 6.74 (1H, d, J = 15.6 Hz), 7.01 (1H, d, J = 1.5 Hz), 7.50 (1H, d, J = 15.6 Hz), 7.76 (1H, br s), 8.18 (1H, s), 9.18 (1H, br s). IR (KBr, cm^{-1}): 3402, 1665, 1315, 1040. MS (FAB) m/z (M+H)$^+$ = 480. Anal. Calcd for $C_{27}H_{29}NO_5S{\cdot}0.5(C_4H_6O_6){\cdot}0.3H_2O$: C, 62.19; H, 5.87; N, 2.50; S, 5.73. Found: C, 62.21; H, 5.86; N, 2.57; S, 5.65.

4.9. Synthesis of 3-amino and 3-amido compound

4.9.1. (2*E*)-*N*-[(5*R*,6*R*)-3-Amino-17-(cyclopropylmethyl)-4,5-epoxy-14-hydroxymorphinan-6-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide (19) tartrate

To the CH_2Cl_2 (10 mL) solution of **1** (506 mg, 1.1 mmol), pyridine (0.9 mL, 11.1 mmol) and Tf_2O (0.35 mL, 2.1 mmol) were added at 0 °C. After stirring for 30 min at the same temperature, the reaction mixture was poured onto saturated aqueous Na_2CO_3, and then Et_2O was added for separation. The organic layer was washed with brine, and then dried over Na_2SO_4. The crude material obtained by concentration was purified by silica gel column chromatography to give 3-triflate.

3-Triflate (160 mg, 0.26 mmol) was dissolved in toluene (7 mL). To the solution, dppf (37 mg, 0.07 mmol), $CsCO_3$ (253 mg, 0.78 mmol), $Pd(dba)_2$ (47 mg, 0.05 mmol), and benzophenoneimine (0.15 mL, 0.89 mmol) were added. The reaction mixture was heated for refluxing, and then stirred for 6 h. After cooling to rt, the reaction mixture was poured onto saturated aqueous Na_2CO_3, and then AcOEt was added for separation. The organic layer was washed with brine, and then dried over Na_2SO_4. The crude material obtained by concentration was purified by silica gel column chromatography to give a 3-diphenylmethyleneamino compound.

The yielded 3-diphenylmethyleneamino compound (122 mg, 0.19 mmol) was dissolved in THF (5 mL), and then 1 N HCl (1.9 mL) was added. After stirring for 3 h at rt, the reaction mixture was poured onto saturated aqueous Na_2CO_3, and then AcOEt was added for separation. The organic layer was washed with brine, and then dried over Na_2SO_4. The crude material, obtained by concentration, was purified by silica gel column chromatography to give a free base of the captioned compound (51%). The free base was dissolved in MeOH and then L-(+)-tartaric acid was added to give captioned salt. Mp > 120 °C (dec). ^{1}H NMR ($CDCl_3$, 300 MHz, free base) δ: 0.06–0.20 (2H, m), 0.46–0.60 (2H, m), 0.77–0.94 (1H, m), 1.41–1.73 (3.5H, m), 2.08–2.37 (3.25H, m), 2.37 (2H, d, J = 6.6 Hz), 2.55–2.70 (2.25H, m), 2.96–3.17 (2H, m), 3.03 (3H, s), 3.40 (2H, br s), 3.72–3.84 (0.75H, m), 4.47–4.64 (0.5H, m), 4.57 (0.75H, d, J = 8.0 Hz), 6.40 (0.75H, d, J = 15.4 Hz), 6.51–6.67 (3.25H, m), 7.39 (0.75H, s), 7.42 (0.25H, s), 7.52 (0.75H, d, J = 15.4 Hz), 7.54 (0.25H, d, J = 15.4 Hz), 7.61 (1H, s). IR (KBr, cm^{-1}, free base): 3345, 1652, 1157, 1112. MS (EI, free base) m/z (M)$^+$ = 475. Anal. Calcd for $C_{28}H_{33}N_3O_4{\cdot}1.8(C_4H_6O_6){\cdot}0.2H_2O$: C, 56.48; H, 6.11; N, 5.56. Found: C, 56.42; H, 5.95; N, 5.61.

4.9.2. (2*E*)-*N*-[(5*R*,6*R*)-3-Acetamido-17-(cyclopropylmethyl)-4,5-epoxy-14-hydroxymorphinan-6-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide (20) tartrate

To the CH_2Cl_2 (5 mL) solution of compound **19** (66 mg, 0.14 mmol), pyridine (0.023 mL, 0.28 mmol) and Ac_2O (0.015 mL, 0.16 mmol) were added at 0 °C. After stirring for 3 h at the same temperature, the reaction mixture was poured onto saturated aqueous Na_2CO_3, and then AcOEt was added for separation. The organic layer was washed with brine, and then dried over Na_2SO_4. The crude material, obtained by concentration, was purified by silica gel column chromatography to give a free base of the captioned compound (58%). The free base was dissolved in MeOH and then L-(+)-tartaric acid was added to give captioned salt. Mp > 135 °C (dec). ^{1}H NMR ($CDCl_3$, 300 MHz, free base) δ: 0.08–0.21 (2H, m), 0.49–0.60 (2H, m), 0.77–0.93 (1H, m), 1.37–1.79 (4H, m), 1.70 (2.1H, s), 2.04–2.35 (3H, m), 2.15 (0.9H, s), 2.39 (2H, d, J = 6.6 Hz), 2.58–2.73 (2H, m), 3.00–3.17 (2H, m), 3.06 (2.1H, s), 3.14 (0.9H, s), 3.74–3.84 (0.7H, m), 4.45–4.58 (0.3H, m), 4.59 (0.3H, d, J = 8.0 Hz), 4.62 (0.7H, d, J = 8.0 Hz), 5.11 (1H, br s), 6.22–6.31 (1.4H, m), 6.59–6.80 (1.6H, m), 6.98 (0.7H, br s), 7.40–7.47 (1H, m), 7.51–7.76 (2.3H, m), 7.64 (0.3H, br s), 8.17 (0.7H, d, J = 8.2 Hz). IR (KBr, cm^{-1}, free base): 3410, 1683, 1652, 1604, 1425, 1412. MS (EI, free base) m/z $(M)^+$ = 517. Anal. Calcd for $C_{30}H_{35}N_3O_5 \cdot C_4H_6O_6 \cdot 2.6H_2O$: C, 57.43; H, 6.26; N, 5.66. Found: C, 57.17; H, 6.52; N, 5.88.

4.10. Opioid receptor selectivity assay

Each vas deferens isolated from male ddy strain mice was hung in a Magnus tube, which was maintained at 37 °C, filled with a Krebes Henseleit solution (118 mM NaCl, 4.7 mM KCl, 2.5 mM $CaCl_2$, 1.1 mM KH_2PO_4, 25 mM $NaHCO_3$, 11 mM glucose), and aerated with 5% CO_2 and 95% O_2. Electric stimulation was applied through upper and lower ring-shaped platinum electrodes (0.1 Hz, 5.0 mS) using the NIHON KOHDEN SEN-7203 electric stimulation system and NIHON KOHDEN SEG-3104 amplifier. Tissue contraction was recorded on a polygraph using an isometric transducer (NIHON KOHDEN WT-687G).

Each test compound was added in a cumulative manner to determine the IC_{50} values (concentration for 50% inhibition of contraction induced by electric stimulation). Next, a solution of antagonists selective for each type of opioid receptor was initially added to the system, and 20 min later, a test compound was added in a cumulative manner. According to the above procedure, the ratio of the IC_{50} values of the test compound in the presence of the selective antagonists to that in the absence of the selective antagonists was determined.

4.11. Acetic acid writhing method

Male mice (5 weeks old) 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 administered sc into the rostral back of the animals or po 15 min before the administration of acetic acid.

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