Bioorganic & Medicinal Chemistry 20 (2012) 949–961

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis of quinolinomorphinan-4-ol derivatives as δ opioid receptor agonists

Yoshihiro Ida [a], Toru Nemoto [a], Shigeto Hirayama [a], Hideaki Fujii [a], Yumiko Osa [a], Masayuki Imai [b], Takashi Nakamura [b], Toshiyuki Kanemasa [b], Akira Kato [b], Hiroshi Nagase [a,*]

[a] School of Pharmacy, Kitasato University, 5-9-1, Shirokane, Minato-ku, Tokyo 108-8641, Japan
[b] Pain & Frontier, Discovery Research Laboratories, Shionogi & Co., Ltd, 1405, Gotanda, Koka-cho, Koka, Shiga 520-3423, Japan

ARTICLE INFO

Article history:
Received 15 November 2011
Revised 22 November 2011
Accepted 22 November 2011
Available online 1 December 2011

Keywords:
Opioid
Naltrexone
Analgesics
δ Receptor

ABSTRACT

The previously reported morphinan derivative SN-28 showed high selectivity and agonist activity for the δ opioid receptor. In the course of examining the structure–activity relationship of SN-28 derivatives, the derivatives with the 4-hydroxy group (SN-24, 26, 27) showed higher selectivities for the δ receptor over the μ receptor than the corresponding SN-28 derivatives with the 3-hydroxy group (SN-11, 23, 28). Derivatives with the 4-hydroxy group showed potent agonist activities for the δ receptor in the [^{35}S]GTPγS binding assay. Although the 17-cyclopropylmethyl derivative (SN-11) with a 3-hydroxy group showed the lowest selectivity for the δ receptor among the morphinan derivatives, the agonist activity toward the δ receptor was the most potent for candidates with the 3-hydroxy group.

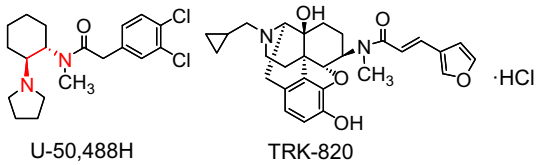
1. Introduction

Three types of opioid receptors (μ, δ, κ) are now well established not only by pharmacological studies, but also through molecular biological studies.[1] For the past three decades, considerable efforts have been expended to obtain an opioid κ-selective agonist without undesirable morphine-like side effects like addiction. In 1982, U-50,488H was discovered to be a highly selective κ-agonist by researchers at Upjohn (now merged with Pfizer).[2–4] Since then, numerous research groups modified the structure of U-50,488H and succeeded in preparing more selective and potent κ-agonists. However, all these compounds have structures similar to that of U-50,488H, with the [N–C–C–N (sp^2)] pharmacophore sequence (Fig. 1), and showed severe aversion like psychotomimetic effects.[5–7] We recently reported a novel κ-agonist, TRK-820 (nalfurafine hydrochloride) which has a structure quite different from U-50,488H (Fig. 1).[8–10]

TRK-820 showed neither addiction nor aversion and was launched in Japan as an antipruritic agent for kidney dialysis patients in 2009.[10,11] This is the first opioid drug that does not cause addiction. Now that we have obtained a selective κ-agonist without morphine-like side effects and aversion, our next target was a highly selective and potent δ-agonist. Nonpeptide δ-opioid agonists BW373U86,[12] SNC80,[13,14] and OMI[15,16] were described (Fig. 2). We also reported the highly selective δ-agonist, (−)-TAN-67,[17,18] which was designed from the δ-selective antagonist, naltrindole (NTI)[16,19] by removing postulated accessory sites,[20] that is, the 4,5-epoxy ring and the 10-methylene bridge and converting the indole structure to a quinoline (Fig. 3).

In an earlier effort to synthesize novel δ opioid receptor agonists, we reviewed the accessory sites of the 4,5-epoxymorphinan skeleton.[21] This study led us to conclude that only the 4,5-epoxy ring would be an accessory site. We subsequently reported a novel δ-agonist, SN-28 (Fig. 4), which showed about 15 times and 334 times more potent agonist activities than (−)-TAN-67 and SNC80, respectively, and had almost equivalent selectivity to (−)-TAN-67 in in vitro assays.[21] The discovery of SN-28 led us to investigate the structure–activity relationships for SN-28 derivatives to obtain more selective agonists for the δ receptor. Usually, the 3-hydroxy group and the 17-nitrogen of the morphinan derivatives have been considered as the key functionalities that play important roles for associations between the drug molecule and the receptor site.[22,23]

The influences of the transposition of the 3-hydroxy group to the 4-position have already been examined in NTI derivatives,



U-50,488H TRK-820

Figure 1. The structures of U-50,488H and TRK-820.

Abbreviations: CPM, cyclopropylmethyl; CBM, cyclobutylmethyl; *c*-Pen, cyclopentyl.

* Corresponding author. Tel.: +81 3 5791 6372; fax: +81 3 3442 5707.
E-mail address: nagaseh@pharm.kitasato-u.ac.jp (H. Nagase).

0968-0896/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2011.11.047

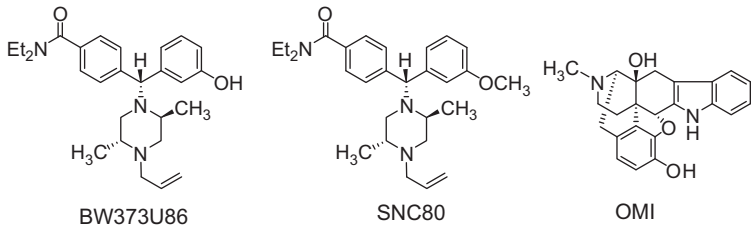


Figure 2. The structures of BW373U86, SNC80, and OMI.

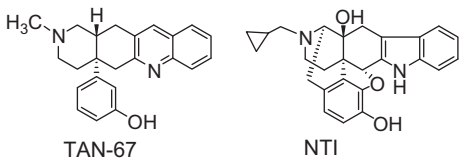


Figure 3. The structures of TAN-67 and NTI.

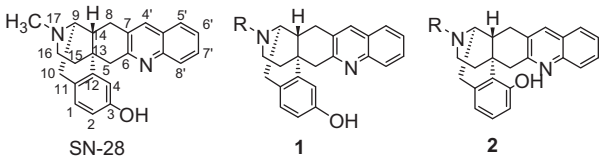
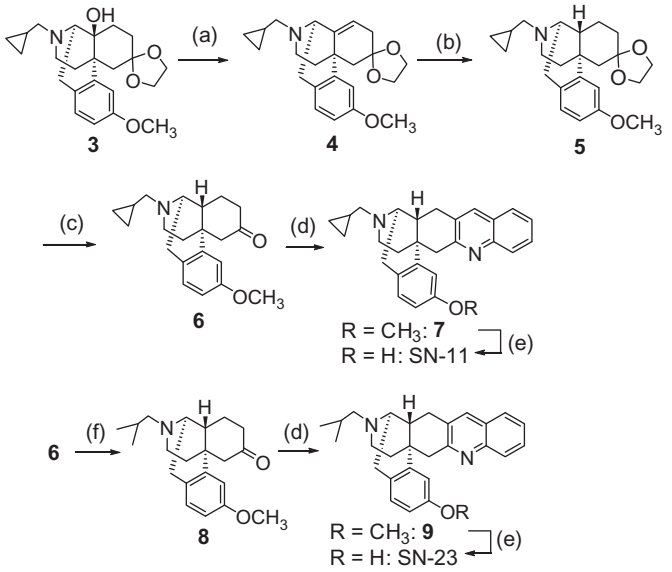


Figure 4. The structures of SN-28 and compounds **1** and **2**.



Scheme 1. Reagents and conditions: (a) $SOCl_2$, pyridine, 0 °C to rt, 71%; (b) PtO_2, H_2, CH_3OH, rt; (c) 2 M HCl, 50 °C, 63% (2 steps from compound **4**); (d) 2-aminobenzaldehyde, CH_3SO_3H, C_2H_5OH, reflux, 96% (**7**), 98% (**9**); (e) BBr_3, CH_2Cl_2, 0 °C to rt, 97% (SN-11), 84% (SN-23); (f) 48% HBr, CH_3OH, PtO_2, H_2, rt, 32%.

which influenced the affinity and the selectivity for the δ receptor.[24] NTI derivatives with the 4-hydroxy group or 3-methoxy group showed lower binding affinity and selectivity for the δ receptor than NTI itself, NTI derivatives with the 3-hydroxy group, or the 4-methoxy group. The conversion of 17-substituents was also examined in NTI and TAN-67 derivatives.[15,17,25] In NTI derivatives, the 17-cyclopropylmethyl (CPM) derivative showed the highest binding affinity and high selectivity for the δ receptor. On the other hand, although the 17-methyl derivative showed the highest selectivity for the δ receptor in TAN-67 derivatives, the 17-CPM derivative showed highest affinity for the δ receptor.

However, as the roles of the 3-hydroxy group and the 17-substituents have not yet been examined in SN-28 derivatives, we especially focused on the influence of the 17-substituents and the position of the hydroxy group in the phenol ring on the selectivities and agonistic activities for the δ receptor. So, we synthesized 3-hydroxy derivatives **1** and 4-hydroxy variants **2** with various 17-substituents (Fig. 4). Herein, we report the synthesis of SN-28 derivatives and their pharmacologies.

2. Results

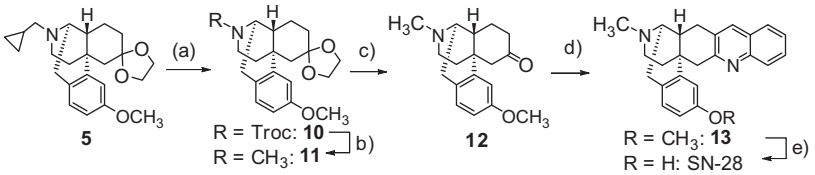
2.1. Chemistry

Three compounds (SN-11, SN-23, and SN-28) with different 17-substituents (CPM, isobutyl, methyl groups) were synthesized (Schemes 1 and 2). The 14-OH-morphinan **3** was synthesized from naltrexone by the reported method,[26–28] and 14-H-morphinan **6** was synthesized from **3** in three steps (Scheme 1).[29] The 17-isobutyl derivative **8** was obtained by the reductive cleavage of the 17-cyclopropyl moiety in compound **6**.[30,31] Compounds **7** and **9** were synthesized from the respective morphinan derivatives **6** and **8** with 2-aminobenzaldehyde in the presence of a catalytic amount of CH_3SO_3H in C_2H_5OH.[17] The methoxy groups in the resulting compounds **7** and **9** were demethylated with BBr_3 in CH_2Cl_2 to afford SN-11 and SN-23, respectively (Scheme 1).[32]

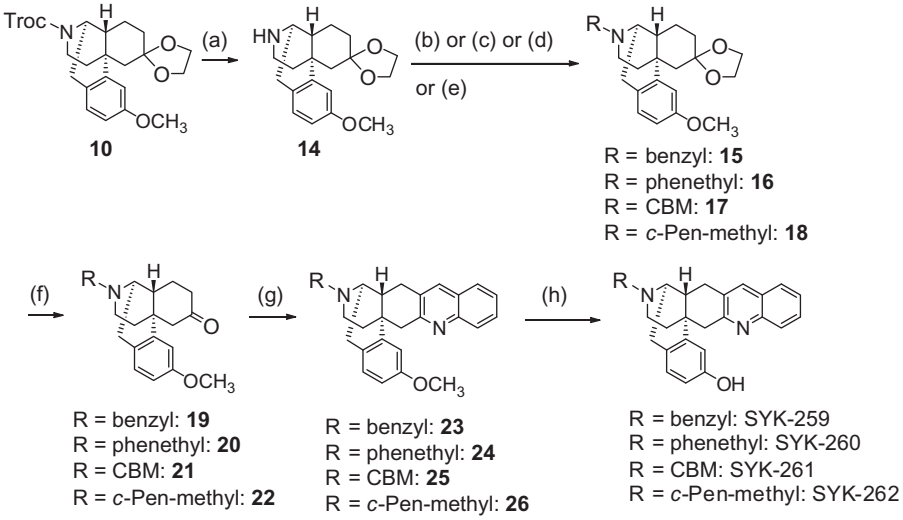
The 17-CPM group of compound **5** was converted to a 17-methyl group by a previously reported method.[33,34] The resulting 17-methyl derivative **11** was converted to SN-28 as shown in Scheme 2.[17,32]

To examine the influence of 17-substituents on the selectivities for the δ receptor, we converted the 17-CPM substituent to benzyl (SYK-259), phenethyl (SYK-260), cyclobutylmethyl (CBM) (SYK-261), and cyclopentylmethyl (*c*-Pen-methyl) (SYK-262) substituents. These derivatives were synthesized from compound **10** by the reported method (Scheme 3).[35]

To obtain the morphinan derivatives with a 4-hydroxy group (SN-24, 26, 27), compound **28** without a 3-hydroxy group, which was derived from naltrexone,[36] was transformed into the 14-H compound **31** according to a previously reported method (Scheme 4).[29] The resulting compound **31** was hydrolyzed to compound **32**. 17-Isobutyl derivative **33** was obtained by the reductive cleavage of the 17-cyclopropyl moiety in compound **31**.[30,31] 17-Methyl derivative **36** was obtained by the same method as shown in Scheme 2 (Scheme 4). The resulting compounds **32**, **33**, and **36** were converted to SN-27, 24, and 26, respectively, by the reductive cleavage of the 4,5-epoxy ring with zinc in acetic acid[28,37] followed by the formation of a quinoline ring with 2-aminobenzaldehyde in the presence of a catalytic amount of CH_3SO_3H in C_2H_5OH (Scheme 4).



Scheme 2. Reagents and conditions: (a) Troc-Cl, K_2CO_3, $(CHCl_2)_2$, reflux, 53%; (b) $LiAlH_4$, THF, 0 °C to rt, 65%; (c) 2 M HCl, 80 °C, 79%; (d) 2-aminobenzaldehyde, CH_3SO_3H, C_2H_5OH, reflux, 95%; (e) BBr_3, CH_2Cl_2, 0 °C to rt, 78%.



Scheme 3. Reagents and conditions: (a) 12 M KOH, DMSO, reflux, quant.; (b) BnBr, K_2CO_3, DMF, rt, 88%; (c) $PhCH_2CHO$, $NaBH(OAc)_3$, CH_2Cl_2, rt, 91%; (d) CBM-Br, K_2CO_3, DMF, 60 °C, 65%; (e) cyclopentanecarbaldehyde, AcOH, $NaBH(OAc)_3$, CH_2Cl_2, rt, 90%; (f) 2 M HCl, 80 °C, 82% (**19**), quant. (**20**), quant. (**21**), quant. (**22**); (g) 2-aminobenzaldehyde, CH_3SO_3H, C_2H_5OH, reflux, 86% (**23**), 90% (**26**); (h) BBr_3, CH_2Cl_2, 0 °C to rt, 88% (SYK-259), 76% (SYK-260: two steps), 38% (SYK-261: two steps), 93% (SYK-262).

To compare the pharmacological profiles of the compounds with and without a 4,5-epoxy ring, the 4,5-epoxymorphinan derivative (SN-25) was also synthesized from compound **40**[29] by the same method as that shown in Scheme 1 (Scheme 5).

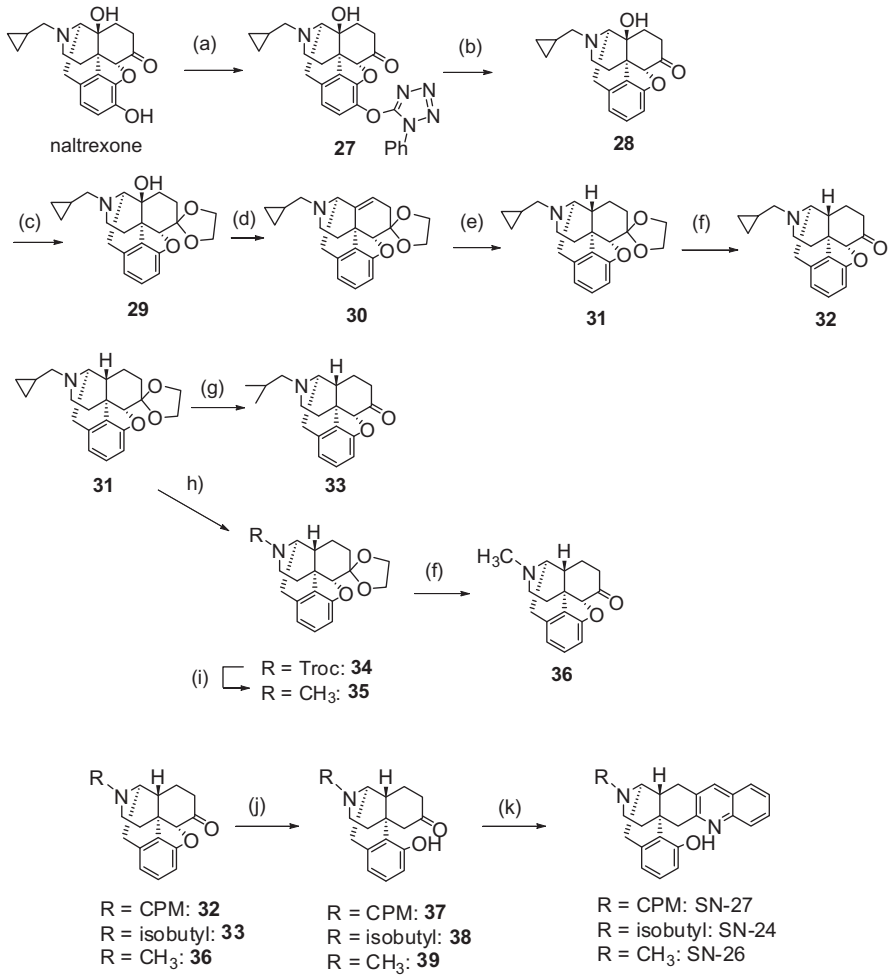
2.2. Pharmacology

Table 1 shows the binding affinities and selectivities of the synthesized compounds toward opioid μ, δ, and κ receptors. For purposes of comparison, the results of δ antagonist NTI and δ agonist (−)-TAN-67 are also described. The standard δ antagonist, NTI ($\mu/\delta = 81.5$, $\kappa/\delta = 48.3$) and agonist, (−)-TAN-67 ($\mu/\delta = 197.3$, $\kappa/\delta = 508.7$) also showed high selectivity for the δ receptor in this binding assay. The 4-OH-morphinan derivatives, SN-24, 26, and 27, showed higher selectivities for the δ receptor than the corresponding 3-OH-morphinan derivatives (SN-23, 28, and 11). SN-24 showed high μ/δ selectivity and κ/δ selectivity, SN-26 showed high κ/δ selectivity, and SN-27 showed high μ/δ selectivity. In the 3-OH-morphinan derivatives with different 17-substituents, SYK-259-262 showed lower selectivities for the δ receptor than SN-28, whose selectivity for the δ receptor was comparable with that of NTI. In the 17-CPM derivatives, including SN-25 with the 4,5-epoxy ring, SN-27 showed the best selectivity for the δ receptor [SN-27 (with a 4-hydroxy group) > SN-25 (with a 4,5-epoxy ring) > SN-11 (with a 3-hydroxy group)]. On the other hand, the 3-OH-morphinan derivatives, SN-11, 23, and 28, showed high affinities for the δ receptor. Although SN-24, 26, and 27 with the 4-hydroxy group showed sufficient affinities for the δ receptor, their affinities were lower than those of the 3-OH-morphinan derivatives SN-11, 23, and 28. In compounds with the different 17-substituents, SYK-259 (with 17-benzyl) and 260 (with 17-phenethyl) showed lower affinities for the δ receptor than SN-11 (with 17-CPM), and SYK-261 (with 17-CBM), 262 (with 17-*c*-Pen-methyl) which showed almost equivalent affinities for the δ receptor as SN-11.

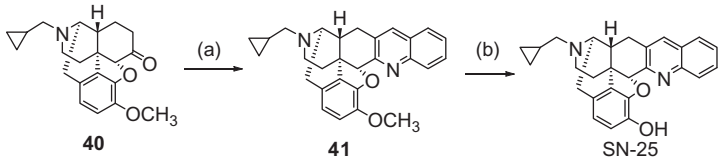
With regard to the functional assay, the 3-OH-morphinan derivatives (SN-11, 23, and 28) showed very high agonist activities for the δ receptor (Table 2) with EC_{50} values = 0.018, 0.06, and 0.047 nM, respectively. They displayed over 10 times greater potency than (−)-TAN-67 ($EC_{50} = 0.70$ nM) and SNC80 ($EC_{50} = 15.7$ nM), compounds which are widely used as nonpeptide δ agonists. The 4-OH-morphinan derivatives (SN-24, 26, and 27) also showed potent δ agonist activities ($EC_{50} = 2.34$, 1.77, and 0.19 nM, respectively). Although these three activities were lower than those of the corresponding 3-OH-morphinan derivatives, only SN-27 (with the 17-CPM functionality) showed more potent activity than (−)-TAN-67. All these tested compounds showed sufficient full agonistic activities compared to endogeneous opioid peptide methionine–enkephalin (Met–enk).

3. Discussion

We synthesized a series of SN-28 derivatives and compared them with SN-28 for δ-selectivity and agonist activity to clarify the SAR of 17-substituents and the position of the hydroxy group in the phenol ring. The 4-OH-morphinan derivatives (SN-24, 26, and 27) showed higher μ/δ selectivities than the corresponding 3-OH-morphinan derivatives (SN-11, 23, and 28). Previously reported SN-11 bearing a 17-CPM group[21] showed the most potent agonist activity among these compounds, but the selectivity was low. This tendency of SN-11 was also observed in the series of TAN-67 derivatives.[17] Although the potent agonistic activity of



Scheme 4. Reagents and conditions: (a) 5-chloro-1-phenyl-1*H*-tetrazole, K_2CO_3, DMF, rt, quant.; (b) 10% Pd/C, AcOH, H_2, 70 °C, 90%; (c) $(CH_2OH)_2$, *p*-toluenesulfonic acid monohydrate, toluene, reflux, 89%; (d) $SOCl_2$, pyridine, 0 °C to rt, 73%; (e) PtO_2, CH_3OH, H_2, rt, quant.; (f) 2 M HCl, 80 °C, 85% (**32**), 81% (**36**); (g) 48% HBr, CH_3OH, PtO_2, H_2, rt, 44%; (h) Troc-Cl, K_2CO_3, $(CHCl_2)_2$, reflux, 80%; (i) $LiAlH_4$, THF, 0 °C to rt, quant.; (j) Zn, AcOH, reflux, quant. (**37**), 81% (**38**), 94% (**39**); (k) 2-aminobenzaldehyde, CH_3SO_3H, C_2H_5OH, reflux, 86% (SN-27), 78% (SN-24), 78% (SN-26) .



Scheme 5. Reagents and conditions: (a) 2-aminobenzaldehyde, CH_3SO_3H, C_2H_5OH, reflux, 77%; (b) BBr_3, CH_2Cl_2, 0 °C to rt, 40%.

CPM derivatives may result from the electron-donating property of the CPM group,[39] the CPM derivative with a 4-hydroxy group (SN-27) showed very high selectivity for the δ receptor. With regard to the role of 17-nitrogen substituent, the order of μ/δ selectivity in 4-OH-morphinan derivatives (SN-24, 26, and 27) is ranked as follows: SN-27 (CPM) > SN-24 (isobutyl) > SN-26 (methyl). On the other hand, in the corresponding 3-OH-morphinan derivatives (SN-11, 23, and 28), the order of μ/δ selectivity is ranked as follows: SN-23 (isobutyl) > SN-28 (methyl) > SN-11 (CPM). These results suggest that the influence of 17-substituents on the selectivities for the δ receptor is quite different between the 4-OH- and 3-OH-morphinan derivatives. Considering the κ/δ selectivity ratio, in the derivatives with some 17-substituents [(Table 1); SN-11, 23, 28, and SYK-259-262], the 17-methyl compound (SN-28) showed the most balanced and highest selectivity for the δ receptor, as well as the 17-methyl compound in KNT-127 (a potent δ opioid receptor agonist) derivatives.[35]

The binding affinities of 4-OH-morphinan derivatives (SN-24, 26, and 27) were lower than those of the corresponding 3-OH-morphinan derivatives (SN-11, 23, and 28). Likewise, the δ-agonist activities of 4-OH morphinan derivatives were less potent than 3-OH morphinan derivatives. However, SN-27 (with a 4-OH substituent) showed not only 2.8 times higher μ/δ selectivity but also 3.7 times more potent activity than (−)-TAN-67. As shown in Table 2 and 3-OH morphinan derivatives (SN-11, 23, and 28) showed very high agonist activities for the δ receptor. To the best of our knowledge, SN-11 was one of the most potent δ-agonists. These results suggest that the 4-hydroxy group may be related to the selectivity

Table 1
The binding affinities and selectivities of SN-11, 23–28, SYK-259–262 for opioid μ, δ and κ receptors[a]

Compounds	17-Substituents	The position of hydroxy group	Affinity (K_i, nM)			Selectivity	
			μ	δ	κ	μ/δ	κ/δ
NTI			23.6	0.29	14.0	81.5	48.3
(−)-TAN-67			284.1	1.44	732.5	197.3	508.7
SN-11	CPM	3-OH	0.77	0.19	0.36	4.1	1.9
SN-23	Isobutyl	3-OH	23.6	0.19	4.41	124.3	23.2
SN-24	Isobutyl	4-OH	322.8	1.22	516.2	264.6	423.1
SN-25[c]	CPM	3-OH	13.0	0.43	14.8	30.2	34.4
SN-26	Methyl	4-OH	51.8	1.00	263.4	51.8	263.4
SN-27	CPM	4-OH	147.8	0.27	17.5	547.6	64.8
SN-28	Methyl	3-OH	11.5	0.14	10.2	82.4	72.9
SN-28 [b]	Methyl	3-OH	23.2	0.29	14.3	81.3	50.2
SYK-259[b]	Benzyl	3-OH	76.9	12.4	50.0	6.2	4.0
SYK-260[b]	Phenethyl	3-OH	12.5	4.68	17.9	2.7	3.8
SYK-261[b]	CBM	3-OH	6.31	0.12	1.07	54.6	9.26
SYK-262[b]	*c*-Pen-methyl	3-OH	20.1	0.35	3.54	57.7	10.2

[a] Ref. 21 Evaluated by ability of each compound to displace [^{3}H]DAMGO (μ), [^{3}H]DADLE (δ), and [^{3}H]U-69,593 (κ) binding to membranes of rat cerebrum (μ and δ) or the guinea pig cerebrum (κ).
[b] Evaluated by ability of each compound to displace [^{3}H]DAMGO (μ), [^{3}H]DPDPE (δ), and [^{3}H]U-69,593 (κ) binding to membranes of mouse whole brain without cerebellum (μ and δ) or the guinea pig cerebellum (κ).
[c] 4,5-Epoxymorphinan derivative.

Table 2
δ Agonist activities of SN-11, 23, 24, and 26–28[a]

Compounds	EC_{50} (nM)	Compounds	17-substituents	The position of hydroxy group	EC_{50} (nM)
(−)-TAN-67	0.7	SN-11	CPM	3-OH	0.018
SNC80	15.7[b]	SN-23	Isobutyl	3-OH	0.06
[Met^5]-enkephalin	1.03	SN-24	Isobutyl	4-OH	2.34
		SN-26	Methyl	4-OH	1.77
		SN-27	CPM	4-OH	0.19
		SN-28	Methyl	3-OH	0.047

[a] Membranes were incubated with [^{35}S] GTPγS and GDP with the compound. The δ human recombinant cell membrane (HEK-293) was used in this assay. (−)-TAN-67 and [Met^5]-enkephalin were used as the standard δ agonists.
[b] Ref. 38

for the δ receptor while the 3-hydroxy group may be related to the potent agonist activity for the δ receptor. This is the first report that the 4-OH derivatives with the quinolinomorphinan skeleton showed higher selectivities for the δ receptor than the 3-OH derivatives.

4. Conclusion

SN-28 derivatives with the 4-hydroxy group (SN-24, 26, 27) showed higher selectivities for the δ receptor over the μ receptor than the corresponding morphinan derivatives with the 3-hydroxy group (SN-11, 23, 28). This is the first report that the 4-OH derivatives with the quinolinomorphinan skeleton showed higher selectivities for the δ receptor than the 3-OH derivatives. Moreover the 4-OH-morphinan derivatives showed high agonist activities for the δ receptor. Among them, the 17-CPM derivative (SN-27) showed the highest selectivity for the δ receptor; on the other hand, although the 17-CPM derivative (SN-11) with a 3-hydroxy group showed the lowest selectivity for the δ receptor in the morphinan derivatives, its agonist activity for the δ receptor was the most potent.

5. Experimental

5.1. Chemistry

Melting points were determined on a Yanako MP-500P 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 Varian Mercury-300 or Varian NMR System-400 for ^{1}H NMR. Chemical shifts were reported as δ values (ppm) related to tetramethylsilane (TMS). Mass spectra (MS) were obtained on a JMS-AX505HA or JMS-700 MStation and JMS-100LP instrument by applying a fast atom bombardment (FAB) ionization method or an electrospray ionization (ESI) method. Elemental analyses were determined with a Yanako MT-5 and JM10 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-8,14-dehydro-3-methoxy-morphinan-6-spiro-2′-(1′,3′-dioxolane) (4)

To a stirred solution of **3** (7 g, 18.2 mmol) in pyridine (70 mL) was added $SOCl_2$ (10.3 mL, 141 mmol) and stirred at 0 °C under an Ar atmosphere. After 10 min, the reaction mixture was stirred at rt for 19 h. The reaction mixture was evaporated in vacuo. The resulting mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution, and extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was chromatographed on silica gel (200 g, $CHCl_3$/MeOH = 25/1) to give **4** (4.7 g, 71%) as a brown amorphous solid. IR (film): 2910, 1609, 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.05–0.16 (2H, m), 0.44–0.55 (2H, m), 0.83–0.95 (1H, m), 1.30 (1H, d, *J* = 12.0 Hz), 2.10 (1H, dd, *J* = 1.6, 14.0 Hz), 2.11 (1H, d, *J* = 14.0 Hz), 2.20–2.47 (6H, m), 2.50 (1H, dd, *J* = 6.4, 12.4 Hz), 2.77 (1H, dd, *J* = 2.0, 15.6 Hz), 2.87 (1H, dd, *J* = 6.0, 17.6 Hz), 3.65 (1H, d, *J* = 6.0 Hz), 3.76 (3H, s), 3.87–3.93 (2H, m), 3.94–4.08 (2H, m), 5.57 (1H, t, *J* = 3.8 Hz), 6.68 (1H, dd, *J* = 2.8, 8.0 Hz), 6.70 (1H, d, *J* = 2.8 Hz), 6.97 (1H, d, *J* = 8.0 Hz). MS (ESI) *m*/*z* = 368 $[M+H]^+$. HRMS (ESI) Calcd for $C_{23}H_{30}NO_3$ $[M+H]^+$: 368.2226; Found 368.2212.

5.1.2. 17-Cyclopropylmethyl-3-methoxymorphinan-6-spiro-2′-(1′,3′-dioxolane) (5)

To a stirred solution of **4** (4.3 g, 11.7 mmol) in MeOH (90 mL) was added PtO_2 (800 mg, 3.5 mmol) and stirred at rt under a H_2 atmosphere. After 20 h with stirring, the reaction mixture was filterated and evaporated in vacuo. The residue was used for the next reaction without purification.

5.1.3. 17-Cyclopropylmethyl-3-methoxymorphinan-6-one (6)

The solution of **5** (30 mg, 0.08 mmol) in 2 M HCl (1.5 mL) was stirred at 80 °C under an Ar atmosphere. After 1 h with stirring, the reaction mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution, and extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by preparative TLC ($CHCl_3$/MeOH = 10/1) to give **6** (63% from compound **4** in 2 steps) as a colorless oil. IR (neat): 2920, 1712, 1502 cm^{-1}; ^1H NMR ($CDCl_3$, 400 Hz) δ: 0.06–0.15 (2H, m), 0.47–0.53 (2H, m), 0.80–0.92 (1H, m), 1.45 (1H, d, J = 12.4 Hz), 1.55 (1H, dq, J = 4.8, 13.2 Hz), 1.76–1.87 (1H, m), 1.92 (1H, dt, J = 2.8, 12.4 Hz), 2.02 (1H, dt, J = 2.8, 12.4 Hz), 2.22 (1H, td, J = 2.4, 14.4 Hz), 2.26–2.40 (3H, m), 2.39 (1H, d, J = 14.4 Hz), 2.48 (1H, dd, J = 6.0, 12.6 Hz), 2.56 (1H, dd, J = 6.0, 18.4 Hz), 2.69 (1H, m), 2.91 (1H, d, J = 18.4 Hz), 3.09 (1H, dd, J = 2.0, 14.4 Hz), 3.29 (1H, dd, J = 3.2, 6.0 Hz), 3.73 (3H, s), 6.65 (1H, dd, J = 2.8, 8.4 Hz), 6.77 (1H, d, J = 2.8 Hz), 6.95 (1H, d, J = 8.4 Hz). MS (ESI) m/z = 326 $[M+H]^+$. HRMS (ESI) Calcd for $C_{21}H_{28}NO_2$ $[M+H]^+$: 326.2120; Found 326.2120.

5.1.4. 17-Cyclopropylmethyl-6,7-didehydro-3-methoxy-quinolino[2′,3′:6,7]morphinan (7)

To a stirred solution of **6** (40 mg, 0.12 mmol) in ethanol (2 mL) were added methanesulfonic acid (30 μL, 0.43 mmol) and 2-aminobenzaldehyde (60 mg, 0.49 mmol) and refluxed under an Ar atmosphere. After 20 h with stirring, the reaction mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution, and extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by preparative TLC ($CHCl_3$/MeOH = 10/1) to give **7** (42.8 mg, 96%) as a colorless oil. IR (neat): 2914, 1609, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.13–0.22 (2H, m), 0.51–0.62 (2H, m), 0.89–1.02 (1H, m), 1.69 (1H, d, J = 12.4 Hz), 2.06 (1H, dt, J = 4.4, 12.4 Hz), 2.19 (1H, dt, J = 2.8, 12.4 Hz), 2.43–2.59 (3H, m), 2.67–2.86 (3H, m), 2.96 (1H, dd, J = 6.0, 17.2 Hz), 3.03 (1H, d, J = 18.8 Hz), 3.12 (1H, d, J = 17.6 Hz), 3.48 (1H, dd, J = 3.2, 6.0 Hz), 3.62 (3H, s), 3.96 (1H, d, J = 17.6), 6.59 (1H, dd, J = 2.8, 8.4 Hz), 6.91 (1H, d, J = 2.8 Hz), 6.97 (1H, d, J = 8.4 Hz), 7.36 (1H, dt, J = 0.8, 8.0 Hz), 7.54–7.62 (3H, m), 7.95 (1H, d, J = 9.2 Hz). MS (ESI) m/z = 411 $[M+H]^+$. HRMS (ESI) Calcd for $C_{28}H_{31}N_2O$ $[M+H]^+$: 411.2436. Found 411.2457.

5.1.5. 17-Cyclopropylmethyl-6,7-didehydro-quinolino[2′,3′:6,7]-morphinan-3-ol hydrochloride (SN-11)

To a stirred solution of **7** (45 mg, 0.11 mmol) in CH_2Cl_2 (4.5 mL) was added 1 M BBr_3 in CH_2Cl_2 (660 μL, 0.66 mmol) at 0 °C under an Ar atmosphere and stirred at rt. After 1 h with stirring, the reaction mixture was basified (pH 9) with 25% ammonia aqueous solution, and extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by preparative TLC ($CHCl_3$/MeOH = 10/1) to give a free base of SN-11 (42 mg, 97%) as a white amorphous solid. To a solution of the free base of SN-11 (42 mg, 0.089 mmol) in $CHCl_3$ was added dropwise HCl–MeOH. After evaporation, to the residue was added AcOEt to give a white solid. Filtration followed by drying the solid gave SN-11 (32 mg, 64%) as a white solid.

(Free base of SN-11)

IR (film): 2919, 1608, 1497 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.03–0.12 (2H, m), 0.40–0.48 (2H, m), 0.82–0.94 (1H, m), 1.46 (1H, d, J = 12.4 Hz), 1.85 (1H, dt, J = 4.4, 12.8 Hz), 2.18 (1H, dt, J = 2.8, 12.4 Hz), 2.43 (2H, dt, J = 2.8, 12.8 Hz), 2.51 (1H, dd, J = 5.6, 12.8 Hz), 2.66–2.77 (2H, m), 2.81 (1H, dd, J = 6.0, 17.6 Hz), 2.86–2.96 (2H, m), 3.01 (1H, d, J = 18.4 Hz), 3.50 (1H, dd, J = 3.2, 6.0 Hz), 3.84 (1H, d, J = 17.6 Hz), 6.59 (1H, dd, J = 2.4, 8.0 Hz), 6.91 (1H, d, J = 2.4 Hz), 6.91 (1H, d, J = 8.0 Hz), 7.18–7.27 (2H, m), 7.36–7.42 (1H, m), 7.48 (1H, m), 7.61 (1H, dd, J = 2.0, 7.2 Hz), a proton (OH) was not observed. MS (ESI) m/z = 397 $[M+H]^+$. HRMS (ESI) Calcd for $C_{27}H_{29}N_2O$ $[M+H]^+$: 397.2280. Found 397.2262.

(SN-11)

Mp 224–226 °C (dec); Anal. Calcd for $C_{27}H_{28}N_2O{\cdot}2HCl{\cdot}1.5H_2O$: C, 65.32; H, 6.70; N, 5.64. Found: C, 65.10; H, 6.80; N, 5.69.

5.1.6. 17-Isobutyl-3-methoxymorphinan-6-one (8)

To a stirred solution of **6** (100 mg, 0.27 mmol) in MeOH (2 mL) were added 48% HBr (2.4 mL) and PtO_2 (320 mg, 0.11 mmol), and stirred at rt under a H_2 atmosphere. After 21 h with stirring, the reaction mixture was filterated and evaporated in vacuo. The resulting mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution, and extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by preparative TLC ($CHCl_3$/MeOH = 10/1) to give **8** (29 mg, 32%) as a colorless oil. IR (neat): 2951, 1713, 1502 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.92 (3H, d, J = 6.8 Hz), 0.93 (3H, d, J = 6.8 Hz), 1.43 (1H, td, J = 2.4, 12.0 Hz), 1.56 (1H, dq, J = 4.8, 13.2 Hz), 1.68–1.86 (2H, m), 1.91 (1H, dt, J = 3.2, 12.0 Hz), 2.08 (1H, dt, J = 2.8, 12.0 Hz), 2.20–2.34 (4H, m), 2.38 (1H, m), 2.40 (1H, d, J = 14.4 Hz), 2.44–2.51 (1H, m), 2.59 (1H, dd, J = 6.4, 18.4 Hz), 2.96 (1H, d, J = 18.8 Hz), 3.00 (1H, s), 3.12 (1H, dd, J = 2.4, 14.4 Hz), 3.76 (3H, s), 6.68 (1H, dd, J = 2.8, 8.4 Hz), 6.79 (1H, d, J = 2.8 Hz), 6.98 (1H, d, J = 8.4 Hz). MS (ESI) m/z = 328 $[M+H]^+$. HRMS (ESI) Calcd for $C_{21}H_{30}NO_2$ $[M+H]^+$: 328.2277. Found 328.2284.

5.1.7. 6,7-Didehydro-17-isobutyl-3-methoxy-quinolino-[2′,3′:6,7]morphinan (9)

Compound **9** was prepared from compound **8** according to the procedure used to prepare compound **7**. Yield, 98%; a colorless oil. IR (neat): 2916, 1608, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.94 (3H, d, J = 6.4 Hz), 0.96 (3H, d, J = 6.4 Hz), 1.65 (1H, m), 1.73–1.85 (1H, m), 2.00 (1H, dt, J = 2.4, 12.0 Hz), 2.22 (1H, dt, J = 2.4, 12.0 Hz), 2.33 (2H, d, J = 7.2 Hz), 2.43–2.52 (1H, m), 2.53 (1H, dt, J = 3.2, 12.0 Hz), 2.72 (1H, dd, J = 12.8, 16.8 Hz), 2.81 (1H, dd, J = 6.0, 18.4 Hz), 2.93 (1H, dd, J = 6.0, 17.2 Hz), 3.06 (1H, d, J = 17.2 Hz), 3.11 (1H, d, J = 17.2 Hz), 3.12–3.17 (1H, m), 3.63 (3H, s), 3.96 (1H, d, J = 17.6 Hz), 6.59 (1H, dd, J = 2.4, 8.4 Hz), 6.91 (1H, d, J = 17.2 Hz), 6.99 (1H, d, J = 8.4 Hz), 7.37 (1H, dt, J = 1.2, 7.2 Hz), 7.54–7.63 (3H, m), 7.96 (1H, dd, J = 0.8, 8.4 Hz). MS (ESI) m/z = 413 $[M+H]^+$. HRMS (ESI) Calcd for $C_{28}H_{33}N_2O$ $[M+H]^+$: 413.2580. Found 413.2574.

5.1.8. 6,7-Didehydro-17-isobutyl-quinolino[2′,3′:6,7]-morphinan-3-ol hydrochloride (SN-23)

A free base of SN-23 was prepared from compound **9** according to the procedure used to prepare the free base of SN-11. Yield, 84%; a white solid.

(Free base of SN-23)

IR (film): 2918, 1609, 1497 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.94 (3H, d, J = 6.4 Hz), 0.95 (3H, d, J = 6.4 Hz), 1.50 (1H, m), 1,71–1.91 (2H, m), 2.24 (1H, dt, J = 2.4, 12.4 Hz), 2.33 (2H, d, J = 7.2 Hz), 2.40–2.48 (1H, m), 2.53 (1H, dt, J = 2.4, 12.4 Hz), 2.70 (1H, dd, J = 12.4, 17.2 Hz), 2.79 (1H, dd, J = 6.0, 18.4 Hz), 2.96 (1H, dd, J = 6.8, 17.6 Hz), 2.96 (1H, d, J = 17.6 Hz), 3.05 (1H, d, J = 18.4 Hz), 3.13 (1H, s), 3.88 (1H, d, J = 17.6 Hz), 6.61 (1H, dd,

J = 2.4, 8.4 Hz), 6.94 (1H, d, *J* = 8.4 Hz), 6.97 (1H, d, *J* = 2.4 Hz), 7.20–7.28 (2H, m), 7.45–7.55 (2H, m), 7.60 (1H, s), a proton (OH) was not observed. MS (ESI) *m/z* = 399 $[M+H]^+$. HRMS (ESI) Calcd for $C_{27}H_{31}N_2O$ $[M+H]^+$: 399.2436. Found 399.2419.

(SN-23)

SN-23 was prepared from the free base of SN-23 according to the procedure used to prepare SN-11. Yield, 77%. A white solid. Mp 216–218 °C (dec); Anal. Calcd for $C_{27}H_{30}N_2O{\cdot}2HCl{\cdot}1.5H_2O$: C, 65.06; H, 7.08; N, 5.62. Found: C, 65.00; H, 7.34; N, 5.62.

5.1.9. 3-Methoxy-17-(2,2,2-trichloroethoxycarbonyl)-morphinan-6-spiro-2′-(1′,3′-dioxolane) (10)

To a stirred solution of **5** (2.1 g, 5.7 mmol) in tetrachloroethane (10 mL) were added K_2CO_3 (1.8 g, 12.5 mmol) and Troc-Cl (1.6 mL, 11.4 mmol) and refluxed under an Ar atmosphere. After 4 h with stirring, the reaction mixture was added 1 M HCl and extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was chromatographed on silica gel (150 g, Hexane/AcOEt = 5/1) to give **10** (1.47 g, 53%) as a yellow oil. IR (neat): 2947, 1712, 1426 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.38–1.80 (8H, m), 2.54–2.78 (3H, m), 3.10–3.19 (1H, m), 3.74–3.81 (1H, m), 3.79 (3H, s), 3.81–3.90 (3H, m), 3.91–3.98 (1H, m), 4.49 (1H, s), 4.70 (1H, d, *J* = 12.0 Hz), 4.77 (0.5H, d, *J* = 12.0 Hz), 4.86 (0.5H, d, *J* = 12.0 Hz), 6.73 (1H, dd, *J* = 2.4, 8.4 Hz), 6.85 (1H, d, *J* = 2.8 Hz), 6.99 (0.5H, d, *J* = 8.4 Hz), 7.00 (0.5H, d, *J* = 8.4 Hz). MS (ESI) *m/z* = 512 $[M+Na]^+$. HRMS (ESI) Calcd for $C_{22}H_{26}Cl_3NNaO_5$ $[M+Na]^+$: 512.0774. Found 512.0773.

5.1.10. 3-Methoxy-17-methylmorphinan-6-spiro-2′-(1′,3′-dioxolane) (11)

To a stirred suspension of $LiAlH_4$ (40 mg, 1.00 mmol) in THF (1 mL) was added a solution of **10** (119 mg, 0.24 mmol) in THF (2 mL) at 0 °C under an Ar atmosphere and stirred at rt. After 1 h with stirring, AcOEt and saturated Na_2SO_4 aqueous solution were added to the solution, filterated, and evaporated in vacuo. The residue was purified by preparative TLC ($CHCl_3$/MeOH = 10/1) to give **11** (52.1 mg, 65%) as a colorless oil. IR (neat): 2931, 1612, 1497 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.38 (1H, td, *J* = 2.4, 12.4 Hz), 1.43–1.54 (2H, m), 1.57 (1H, d, *J* = 14.0 Hz), 1.60–1.74 (3H, m), 1.86 (1H, td, *J* = 3.6, 12.0 Hz), 2.02 (1H, dt, *J* = 3.2, 12.4 Hz), 2.39–2.47 (1H, m), 2.41 (3H, s), 2.59 (1H, dd, *J* = 2.4, 14.0 Hz), 2.65 (1H, dd, *J* = 5.6, 18.4 Hz), 2.91–3.00 (2H, m), 3.71–3.80 (1H, m), 3.76 (3H, s), 3.80–3.87 (2H, m), 3.89–3.96 (1H, m), 6.68 (1H, dd, *J* = 2.8, 8.4 Hz), 6.81 (1H, d, *J* = 2.8 Hz), 6.98 (1H, d, *J* = 8.4 Hz). MS (ESI) *m/z* = 330 $[M+H]^+$. HRMS (ESI) Calcd for $C_{20}H_{28}NO_3$ $[M+H]^+$: 330.2068. Found 330.2054.

5.1.11. 3-Methoxy-17-methylmorphinan-6-one (12)

Compound **12** was prepared from compound **11** according to the procedure used to prepare compound **6**. Yield, 79%; a white solid. IR (KBr): 2923, 1701, 1503 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.47 (1H, d, *J* = 12.0 Hz), 1.58 (1H, dq, *J* = 4.8, 13.2 Hz), 1.79–1.88 (1H, m), 1.90 (1H, dt, *J* = 4.8, 12.4 Hz), 2.09 (2H, dt, *J* = 3.2, 12.0 Hz), 2.20–2.30 (2H, m), 2.33–2.48 (2H, m), 2.43 (3H, s), 2.57 (1H, dd, *J* = 6.0, 18.4 Hz), 2.98–3.07 (2H, m), 3.11 (1H, dd, *J* = 2.4, 14.0 Hz), 3.75 (3H, s), 6.68 (1H, dd, *J* = 2.4, 8.4 Hz), 6.79 (1H, d, *J* = 2.4 Hz), 7.00 (1H, d, *J* = 8.4 Hz). MS (ESI) *m/z* = 286 $[M+H]^+$. HRMS (ESI) Calcd for $C_{18}H_{24}NO_2$ $[M+H]^+$: 286.1807. Found 286.1809.

5.1.12. 6,7-Didehydro-3-methoxy-17-methyl-quinolino-[2′,3′:6,7]morphinan (13)

Compound **13** was prepared from compound **12** according to the procedure used to prepare compound **7**. Yield, 95%; a yellow oil. IR (neat): 2908, 1608, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.69 (1H, d, *J* = 12.0 Hz), 2.02 (1H, dt, *J* = 5.2, 12.6 Hz), 2.25 (1H, dt, *J* = 5.2, 12.8 Hz), 2.44–2.60 (2H, m), 2.49 (3H, s), 2.73 (1H, dd, *J* = 12.4, 17.0 Hz), 2.81 (1H, dd, *J* = 6.4, 18.6 Hz), 2.95 (1H, dd, *J* = 6.4, 17.4 Hz), 3.08 (1H, d, *J* = 17.4 Hz), 3.12 (1H, d, *J* = 18.8 Hz), 3.13–3.20 (1H, m), 3.62 (3H, s), 3.97 (1H, d, *J* = 17.4 Hz), 6.60 (1H, dd, *J* = 2.8, 8.4 Hz), 6.91 (1H, d, *J* = 2.8 Hz), 7.00 (1H, d, *J* = 8.4 Hz), 7.37 (1H, dt, *J* = 1.2, 8.0 Hz), 7.53–7.64 (3H, m), 7.97 (1H, d, *J* = 8.0 Hz). MS (ESI) *m/z* = 371 $[M+H]^+$. HRMS (ESI) Calcd for $C_{25}H_{27}N_2O$ $[M+H]^+$: 371.2123. Found 371.2107.

5.1.13. 6,7-Didehydro-17-methyl-quinolino[2′,3′:6,7]-morphinan-3-ol hydrochloride (SN-28)

A free base of SN-28 was prepared from compound **13** according to the procedure used to prepare the free base of SN-11. Yield, 78%; a yellow solid. SN-28 was prepared from the free base of SN-28 according to the procedure used to prepare SN-11. Yield, 80%; a white solid.

(Free base of SN-28)

IR (film): 2910, 1607, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.52 (1H, d, *J* = 12.4 Hz), 1.85 (1H, dt, *J* = 4.8, 12.6 Hz), 2.25 (1H, dt, *J* = 2.8, 12.4 Hz), 2.38–2.54 (2H, m), 2.43 (3H, s), 2.64–2.95 (4H, m), 3.09 (1H, d, *J* = 18.4 Hz), 3.18 (1H, dd, *J* = 2.8, 6.0 Hz), 3.85 (1H, d, *J* = 17.6 Hz), 6.60 (1H, dd, *J* = 2.8, 8.2 Hz), 6.92 (1H, d, *J* = 2.8 Hz), 6.93 (1H, d, *J* = 8.2 Hz), 7.17–7.25 (2H, m), 7.34–7.44 (1H, m), 7.48 (1H, s), 7.56–7.63 (1H, m), a proton (OH) was not observed. MS (ESI) *m/z* = 357 $[M+H]^+$. HRMS (ESI) Calcd for $C_{24}H_{25}N_2O$ $[M+H]^+$: 357.1967. Found 357.1957.

(SN-28)

Mp 239–242 °C (dec); Anal. Calcd for $C_{24}H_{24}N_2O{\cdot}1.5HCl{\cdot}1.7H_2O$: C, 65.25; H, 6.59; N, 6.34. Found: C, 65.09; H, 6.61; N, 6.34.

5.1.14. 3-Methoxymorphinan-6-spiro-2′-(1′,3′-dioxolane) (14)

To a stirred solution of **10** (1.3 g, 2,65 mmol) in DMSO (8 mL) was added 12 M KOH (8 mL) and stirred at 120 °C under an Ar atmosphere. After 3 h with stirring, to the reaction mixture was added saturated NH_4Cl aqueous solution and then basified (pH 9) with saturated $NaHCO_3$ aqueous solution, and extracted with $CHCl_3$/2-propanol = 2:1 three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was chromatographed on silica gel (20 g, ammonia saturated $CHCl_3$/MeOH = 10/1) to give **14** (0.9 g, quant.) as a yellow oil. IR (neat): 2940, 1612, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.33–1.45 (2H, m), 1.46–1.63 (2H, m), 1.58 (1H, d, *J* = 14.0 Hz), 1.67 (1H, dt, *J* = 4.0, 12.8 Hz), 1.70–1.80 (2H, m), 2.30 (1H, s), 2.50 (1H, dt, *J* = 3.2, 12.8 Hz), 2.56 (1H, dd, *J* = 2.4, 14.4 Hz), 2.64 (1H, ddd, *J* = 1.6, 4.8, 16.4 Hz), 2.72 (1H, d, *J* = 17.6 Hz), 3.14 (1H, dd, *J* = 6.0, 17.6 Hz), 3.14–3.19 (1H, m), 3.74–3.80 (1H, m), 3.77 (3H, s), 3.81–3.88 (2H, m), 3.91–3.97 (1H, m), 6.70 (1H, dd, *J* = 2.4, 8.4 Hz), 6.82 (1H, d, *J* = 2.4 Hz), 7.00 (1H, d, *J* = 8.4 Hz). MS (ESI) *m/z* = 316 $[M+H]^+$. HRMS (ESI) Calcd for $C_{19}H_{26}NO_3$ $[M+H]^+$: 316.1913. Found 316.1922.

5.1.15. 17-Benzyl-3-methoxymorphinan-6-spiro-2′-(1′,3′-dioxolane) (15)

To a stirred solution of **14** (100 mg, 0.32 mmol) in DMF (1 mL) were added K_2CO_3 (220 mg, 1.59 mmol) and BnBr (120 μL, 0.95 mmol), and stirred at rt under an Ar atmosphere. After 4 h with stirring, the reaction mixture was evaporated in vacuo. The resulting mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was chromatographed on silica gel (20 g, Hexane/AcOEt = 1/1) to give **15** (113 mg, 88%) as a yellow oil. IR (neat): 2918, 1611, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.37 (1H, td, *J* = 2.8, 12.0 Hz), 1.44–1.53 (2H, m), 1.61 (1H, d, *J* = 14.0 Hz), 1.65–1.79 (3H, m), 1.83–1.94 (1H, m), 2.06 (1H, dt, *J* = 3.2, 12.0 Hz), 2.44 (1H, ddd, *J* = 1.6, 4.8, 12.0 Hz),

2.62 (1H, dd, J = 2.4, 14.0 Hz), 2.67 (1H, dd, J = 5.2, 18.4 Hz), 2.94–3.00 (1H, m), 3.05 (1H, d, J = 17.6 Hz), 3.63 (1H, d, J = 13.2 Hz), 3.75 (1H, d, J = 13.2 Hz), 3.75–3.82 (1H, m), 3.80 (3H, s), 3.83–3.91 (2H, m), 3.92–4.01 (1H, m), 6.73 (1H, dd, J = 2.4, 8.4 Hz), 6.86 (1H, d, J = 2.4 Hz), 7.05 (1H, d, J = 8.4 Hz), 7.22–7.73 (2H, m), 7.29–7.39 (3H, m). MS (ESI) m/z = 406 $[M+H]^+$. HRMS (ESI) Calcd for $C_{26}H_{32}NO_3$ $[M+H]^+$: 406.2382. Found 406.2364.

5.1.16. 3-Methoxy-17-phenethylmorphinan-6-spiro-2′-(1′,3′-dioxolane) (16)

To a stirred solution of **14** (100 mg, 0.32 mmol) in CH_2Cl_2 (5 mL) were added 50% solution of phenylacetaldehyde (240 μL, 0.95 mmol) in 2-propanol solution and $NaBH(OAc)_3$ (270 mg, 1.27 mmol), and stirred at rt under an Ar atmosphere. After 6 h with stirring, the reaction mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was chromatographed on silica gel (20 g, Hexane/AcOEt = 1/1-$CHCl_3$/MeOH = 10/1) to give **16** (122 mg, 91%) as a white amorphous solid. IR (film): 2921, 1611, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.41 (1H, m), 1.45–1.56 (2H, m), 1.59 (1H, d, J = 14.0 Hz), 1.66 (1H, dt, J = 4.8, 12.6 Hz), 1.69–1.79 (2H, m), 1.85 (1H, td, J = 3.2, 11.6 Hz), 2.02 (1H, dt, J = 2.8, 12.0 Hz), 2.54–2.84 (7H, m), 2.94 (1H, d, J = 18.0 Hz), 3.06 (1H, dd, J = 2.8, 5.6 Hz), 3.72–3.81 (1H, m), 3.77(3H, s), 3.82–3.89 (2H, m), 3.90–3.99 (1H, m), 6.68 (1H, dd, J = 2.4, 8.4 Hz), 6.83 (1H, d, J = 2.4 Hz), 6.97 (1H, d, J = 8.4 Hz), 7.16–7.23 (2H, m), 7.25–7.31 (3H, m). MS (ESI) m/z = 420 $[M+H]^+$. HRMS (ESI) Calcd for $C_{27}H_{34}NO_3$ $[M+H]^+$: 420.2539. Found 420.2526.

5.1.17. 17-Cyclobutylmethyl-3-methoxymorphinan-6-spiro-2′-(1′,3′-dioxolane) (17)

To a stirred solution of **14** (100 mg, 0.32 mmol) in DMF (1 mL) were added K_2CO_3 (310 mg, 2.22 mmol) and (bromomethyl)cyclobutane (150 μL, 1.27 mmol), and stirred at 60 °C under an Ar atmosphere. After 24 h with stirring, the reaction mixture was evaporated in vacuo. The resulting mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by preparative TLC ($CHCl_3$/MeOH = 10/1) to give **17** (79 mg, 65%) as a colorless oil. IR (neat): 2936, 1611, 1497 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.30–1.38 (1H, m), 1.40–1.53 (2H, m), 1.57 (1H, d, J = 14.4 Hz), 1.60–1.92 (8H, m), 1.93–2.12 (3H, m), 2.40–2.62 (5H, m), 2.63 (1H, dd, J = 6.4, 18.0 Hz), 2.92–2.98 (1H, m), 2.94 (1H, d, J = 18.0 Hz), 3.72–3.79 (1H, m), 3.76 (3H, s), 3.80–3.86 (2H, m), 3.89–3.96 (1H, m), 6.68 (1H, dd, J = 2.8, 8.4 Hz), 6.81 (1H, d, J = 2.8 Hz), 6.98 (1H, d, J = 8.4 Hz). MS (ESI) m/z = 384 $[M+H]^+$. HRMS (ESI) Calcd for $C_{24}H_{34}NO_3$ $[M+H]^+$: 384.2539. Found 384.2548.

5.1.18. 17-Cyclopentylmethyl-3-methoxymorphinan-6-spiro-2′-(1′,3′-dioxolane) (18)

To a stirred solution of **14** (150 mg, 0.48 mmol) in CH_2Cl_2 (20 mL) were added cyclopentanecarbaldehyde (200 μL, 1.90 mmol), acetic acid (220 μL, 3.80 mmol), and $NaBH(OAc)_3$ (1 g, 4.76 mmol), and stirred at rt under an Ar atmosphere. After 1 h with stirring, the reaction mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was chromatographed on silica gel (15 g, ammonia saturated $CHCl_3$) to give **18** (169 mg, 90%) as a colorless oil. IR (neat): 2944, 1612, 1497 cm $^{-1}$; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.14–1.28 (2H, m), 1.31–1.38 (1H, m), 1.43–1.64 (7H, m), 1.64–1.79 (5H, m), 1.79–1.86 (1H, m), 1.96 (1H, dt, J = 4.0, 12.0 Hz), 1.98–2.09 (1H, m), 2.31–2.50 (3H, m), 2.60 (1H, dd, Jv2.4, 14.0 Hz), 2.62 (1H, dd, J = 5.2, 12.8 Hz), 2.92 (1H, d, J = 17.6 Hz), 2.92–2.98 (1H, m), 3.74–3.80 (1H, m), 3.77 (3H, s), 3.80–3.89 (2H, m), 3.90–3.98 (1H, m), 6.68 (1H, dd, J = 2.8, 8.4 Hz), 6.82 (1H, d, J = 2.8 Hz), 6.98 (1H, d, J = 8.4 Hz). MS (ESI) m/z = 398 $[M+H]^+$. HRMS (ESI) Calcd for $C_{25}H_{36}NO_3$ $[M+H]^+$: 398.2695. Found 398.2686.

5.1.19. 17-Benzyl-3-methoxymorphinan-6-one (19)

Compound **19** was prepared from compound **15** according to the procedure used to prepare compound **6**. Yield, 82%; a white amorphous solid. IR (film): 2909, 1712, 1610, 1502 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.45 (1H, d, J = 12.4 Hz), 1.56 (1H, dq, J = 4.8, 13.2 Hz), 1.73–1.83 (1H, m), 1.91 (1H, dt, J = 4.8, 12.4 Hz), 2.16 (1H, dt, J = 3.2, 12.4 Hz), 2.20–2.28 (1H, m), 2.29–2.54 (4H, m), 2.62 (1H, dd, J = 6.4, 18.0 Hz), 3.04–3.17 (3H, m), 3.68 (1H, d, J = 13.6 Hz), 3.77 (1H, d, J = 13.6 Hz), 3.77 (3H, s), 6.72 (1H, dd, J = 2.4, 8.6 Hz), 6.82 (1H, d, J = 2.4 Hz), 7.05 (1H, d, J = 8.4 Hz), 7.23–7.29 (2H, m), 7.31–7.42 (3H, m). MS (ESI) m/z = 362 $[M+H]^+$. HRMS (ESI) Calcd for $C_{24}H_{28}NO_2$ $[M+H]^+$: 362.2120. Found 362.2129.

5.1.20. 3-Methoxy-17-phenethylmorphinan-6-one (20)

Compound **20** was prepared from compound **16** according to the procedure used to prepare compound **6**. Yield, quant; a colorless oil. IR (neat): 2928, 1712, 1609, 1501 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.49 (1H, d, J = 12.8 Hz), 1.58 (1H, dq, J = 4.8, 13.2 Hz), 1.78–1.88 (1H, m), 1.94 (1H, dt, J = 4.8, 12.8 Hz), 2.14 (1H, dt, J = 3.2, 12.4 Hz), 2.20–2.46 (4H, m), 2.62 (1H, dd, J = 6.0, 18.4 Hz), 2.62–2.70 (1H, m), 2.71–2.88 (4H, m), 3.00 (1H, d, J = 18.4 Hz), 3.13 (1H, dd, J = 2.0, 14.0 Hz), 3.17 (1H, dd, J = 2.8, 5.6 Hz), 3.76 (3H, s), 6.69 (1H, dd, J = 2.8, 8.4 Hz), 6.82 (1H, d, J = 2.8 Hz), 7.00 (1H, d, J = 8.4 Hz), 7.18–7.26 (3H, m), 7.27–7.33 (2H, m). MS (ESI) m/z = 376 $[M+H]^+$. HRMS (ESI) Calcd for $C_{25}H_{30}NO_2$ $[M+H]^+$: 376.2250. Found 376.2261.

5.1.21. 17-Cyclobutylmethyl-3-methoxymorphinan-6-one (21)

Compound **21** was prepared from compound **17** according to the procedure used to prepare compound **6**. Yield, quant.; a colorless oil. IR (neat): 2928, 1713, 1610, 1502 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.41 (1H, d, J = 12.4 Hz), 1.54 (1H, dq, J = 5.2, 13.4 Hz), 1.61–1.75 (2H, m), 1.75–1.95 (4H, m), 1.98–2.12 (3H, m), 2.22–2.23 (2H, m), 2.23–2.62 (7H, m), 2.98 (1H, d, J = 18.4 Hz), 3.00 (1H, d, J = 8.4 Hz), 3.08 (1H, dd, J = 2.0, 14.4 Hz), 3.74 (3H, s), 6.66 (1H, dd, J = 2.4, 8.4 Hz), 6.77 (1H, d, J = 2.4 Hz), 6.97 (1H, d, J = 8.4 Hz). MS (ESI) m/z = 340 $[M+H]^+$. HRMS (ESI) Calcd for $C_{22}H_{30}NO_2$ $[M+H]^+$: 340.2277. Found 340.2271.

5.1.22. 17-Cyclopentylmethyl-3-methoxymorphinan-6-one (22)

Compound **22** was prepared from compound **18** according to the procedure used to prepare compound **6**. Yield, quant.; a colorless oil. IR (neat): 2945, 1713, 1610, 1502 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.15–1.28 (2H, m), 1.41 (1H, d, J = 12.4 Hz), 1.46–1.64 (5H, m), 1.68–1.84 (3H, m), 1.86 (1H, dt, J = 4.8, 12.4 Hz), 1.98–2.10 (2H, m), 2.17–2.28 (2H, m), 2.30–2.52 (5H, m), 2.55 (1H, dd, J = 6.4, 18.4 Hz), 2.96 (1H, d, J = 18.4 Hz), 3.04 (1H, dd, J = 3.2, 5.6 Hz), 3.08 (1H, dd, J = 1.6, 14.2 Hz), 3.73 (3H, s), 6.65 (1H, dd, J = 2.4, 8.4 Hz), 6.78 (1H, d, J = 2.4 Hz), 6.96 (1H, d, J = 8.4 Hz). MS (ESI) m/z = 354 $[M+H]^+$. HRMS (ESI) Calcd for $C_{23}H_{32}NO_2$ $[M+H]^+$: 354.2433. Found 354.2447.

5.1.23. 17-Benzyl-6,7-didehydro-3-methoxy-quinolino-[2′,3′:6,7]morphinan (23)

Compound **23** was prepared from compound **19** according to the procedure used to prepare compound **7**. Yield, 86%; a white amorphous solid. IR (film): 2908, 1608 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.64–1.70 (1H, m), 2.00 (1H, dt, J = 4.5, 12.0 Hz),

2.29 (1H, dt, J = 3.0, 12.0 Hz), 2.45–2.60 (2H, m), 2.70 (1H, dd, J = 12.0, 17.0 Hz), 2.77–2.91 (2H, m), 3.13 (1H, d, J = 18.0 Hz), 3.16–3.23 (2H, m), 3.64 (3H, s), 3.72 (1H, d, J = 13.5 Hz), 3.81 (1H, d, J = 13.5 Hz), 3.98 (1H, d, J = 17.5 Hz), 6.63 (1H, dd, J = 2.5, 8.0 Hz), 6.94 (1H, d, J = 2.5 Hz), 7.04 (1H, d, J = 8.0 Hz), 7.27–7.31 (1H, m), 7.33–7.45 (5H, m), 7.54–7.60 (3H, m), 7.96–8.00 (1H, m). MS (ESI) m/z = 447 $[M+H]^+$. HRMS (FAB) Calcd for $C_{31}H_{31}N_2O$ $[M+H]^+$: 447.2436. Found 447.2417.

5.1.24. 6,7-Didehydro-3-methoxy-17-phenethyl-quinolino[2′,3′:6,7]morphinan (24)

Compound **24** was prepared from compound **20** according to the procedure used to prepare compound **7**. The crude compound was chromatographed on silica gel, but could not be purified completely. The resulting compound **24** was used for the next reaction without further purification.

5.1.25. 17-Cyclobutylmethyl-6,7-didehydro-3-methoxy-quinolino[2′,3′:6,7]morphinan (25)

Compound **25** was prepared from compound **21** according to the procedure used to prepare compound **7**. The crude compound was chromatographed on silica gel, but could not be purified completely. The resulting compound **25** was used for the next reaction without further purification.

5.1.26. 17-Cyclopentylmethyl-6,7-didehydro-3-methoxy-quinolino[2′,3′:6,7]morphinan (26)

Compound **26** was prepared from compound **22** according to the procedure used to prepare compound **7**. Yield, 90%; a white amorphous solid. IR (film): 2947, 1609, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.19–1.34 (2H, m), 1.48–1.69 (5H, m), 1.72–1.84 (2H, m), 1.97 (1H, dt, J = 4.8, 12.6 Hz), 2.04–2.14 (1H, m), 2.20 (1H, dt, J = 3.2, 12.4 Hz), 2.48–2.53 (3H, m), 2.58 (1H, dd, J = 3.2, 12.0 Hz), 2.72 (1H, dd, J = 12.4, 16.8 Hz), 2.78 (1H, dd, J = 6.4, 18.4 Hz), 2.90 (1H, dd, J = 6.4, 17.2 Hz), 3.07 (1H, d, J = 18.4 Hz), 3.09 (1H, d, J = 17.6 Hz), 3.19 (1H, dd, J = 2.4, 6.0 Hz), 3.62 (3H, s), 3.95 (1H, d, J = 17.6 Hz), 6.58 (1H, dd, J = 2.8, 8.4 Hz), 6.91 (1H, d, J = 2.8 Hz), 6.98 (1H, d, J = 8.4 Hz), 7.36 (1H, dt, J = 1.2, 8.0 Hz), 7.53–7.58 (3H, m), 7.96 (1H, d, J = 9.2 Hz). MS (ESI) m/z = 439 $[M+H]^+$. HRMS (ESI) Calcd for $C_{30}H_{35}N_2O$ $[M+H]^+$: 439.2749. Found 439.2731.

5.1.27. 17-Benzyl-6,7-didehydro-quinolino[2′,3′:6,7]morphinan-3-ol hydrochloride (SYK-259)

A free base of SYK-259 was prepared from compound **23** according to the procedure used to prepare the free base of SN-11. Yield, 88%; a white solid. SYK-259 was prepared from the free base of SYK-259 according to the procedure used to prepare SN-11. Yield, 88%; a yellow solid.

(Free base of SYK-259)

IR (KBr): 2907, 1608 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.42–1.50 (1H, m), 1.76–1.88 (1H, m), 2.28–2.37 (1H, m), 2.44–2.60 (2H, m), 2.67 (1H, dd, J = 12.0, 17.0 Hz), 2.76–2.90 (2H, m), 2.96 (1H, d, J = 18.0 Hz), 3.15–3.22 (2H, m), 3.76 (1H, d, J = 13.5 Hz), 3.79 (1H, d, J = 13.5 Hz), 3.88 (1H, d, J = 17.5 Hz), 6.65 (1H, dd, J = 2.5, 8.0 Hz), 6.96 (1H, d, J = 2.5 Hz), 6.98 (1H, d, J = 8.0 Hz), 7.17–7.24 (2H, m), 7.27–7.38 (3H, m), 7.42–7.47 (3H, m), 7.51–7.57 (2H, m), a proton (OH) was not observed. MS (ESI) m/z = 433 $[M+H]^+$. HRMS (FAB) Calcd for $C_{30}H_{29}N_2O$ $[M+H]^+$: 433.2280. Found 433.2324.

(SYK-259)

Mp 233–237 °C (dec). Anal. Calcd for $C_{30}H_{28}N_2O{\cdot}2HCl{\cdot}0.4H_2O$: C, 70.28; H, 6.06; N, 5.46. Found: C, 70.33; H, 6.23; N, 5.39.

5.1.28. 6,7-Didehydro-17-phenethyl-quinolino[2′,3′:6,7]morphinan-3-ol hydrochloride (SYK-260)

A free base of SYK-260 was prepared from compound **24** according to the procedure used to prepare the free base of SN-11. Yield, 76% (2 steps from **20**); a white solid. SYK-260 was prepared from the free base of SYK-260 according to the procedure used to prepare SN-11. Yield, 95%; a yellow solid.

(Free base of SYK-260)

IR (KBr): 3423, 2909, 1607 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.53–1.60 (1H, m), 1.83–1.94 (1H, m), 2.26–2.35 (1H, m), 2.44–2.53 (1H, m), 2.67–2.86 (6H, m), 2.87–3.02 (3H, m), 3.09 (1H, d, J = 18.0 Hz), 3.30–3.35 (1H, m), 3.92 (1H, d, J = 17.5 Hz), 6.64 (1H, dd, J = 2.5, 8.0 Hz), 6.96 (1H, d, J = 8.0 Hz), 6.97 (1H, d, J = 2.5 Hz), 7.14–7.31 (7H, m), 7.41–7.46 (1H, m), 7.51–7.54 (1H, m), 7.56–7.60 (1H, m), a proton (OH) was not observed. MS (ESI) m/z = 447 $[M+H]^+$. HRMS (FAB) Calcd for $C_{31}H_{31}N_2O$ $[M+H]^+$: 447.2436. Found 447.2414.

(SYK-260)

Mp 229–232 °C (dec). Anal. Calcd for $C_{31}H_{30}N_2O{\cdot}2HCl{\cdot}0.4H_2O$: C, 70.69; H, 6.28; N, 5.32. Found: C, 70.77; H, 6.58; N, 5.32.

5.1.29. 17-Cyclobutylmethyl-6,7-didehydro-quinolino[2′,3′:6,7]morphinan-3-ol hydrochloride (SYK-261)

A free base of SYK-261 was prepared from compound **25** according to the procedure used to prepare the free base of SN-11. Yield, 38% (2 steps from **21**); a white crystal. SYK-261 was prepared from the free base of SYK-261 according to the procedure used to prepare SN-11. Yield, 98%; a yellow solid.

(Free base of SYK-261)

Mp 225–229 °C. IR (KBr): 2923, 1492 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.56–1.97 (7H, m), 2.03–2.16 (2H, m), 2.16–2.26 (1H, dt, J = 2.5, 12.0 Hz), 2.40–2.47 (1H, m), 2.50–2.73 (4H, m), 2.73–2.79 (1H, m), 2.96 (1H, dd, J = 6.5, 17.0 Hz), 3.06 (1H, d, J = 17.0 Hz), 3.09 (1H, d, J = 17.0 Hz), 3.11–3.17 (1H, m), 3.90 (1H, d, J = 17.0 Hz), 6.57 (1H, dd, J = 2.5, 8.0 Hz), 6.89 (1H, d, J = 2.5 Hz), 6.95 (1H, d, J = 8.0 Hz), 7.28–7.33 (1H, m), 7.35–7.40 (1H, m), 7.52–7.57 (1H, m), 7.62–7.69 (2H, m), a proton (OH) was not observed. MS (ESI) m/z = 411 $[M+H]^+$. HRMS (FAB) Calcd for $C_{28}H_{31}N_2O$ $[M+H]^+$: 411.2436. Found 411.2451.

(SYK-261)

Mp 231–235 °C (dec). Anal. Calcd for $C_{28}H_{30}N_2O{\cdot}2HCl{\cdot}0.8H_2O$: C, 67.55; H, 6.80; N, 5.63. Found: C, 67.62; H, 6.89; N, 5.69.

5.1.30. 17-Cyclopentylmethyl-6,7-didehydro-quinolino[2′,3′:6,7]morphinan-3-ol hydrochloride (SYK-262)

A free base of SYK-262 was prepared from compound **26** according to the procedure used to prepare the free base of SN-11. Yield, 93%; a white amorphous solid. SYK-262 was prepared from the free base of SYK-262 according to the procedure used to prepare SN-11. Yield, 92%; a white solid.

(Free base of SYK-262)

IR (film): 2947, 1608, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.10–1.29 (2H, m), 1.34–1.42 (1H, m), 1.44–1.64 (4H, m), 1.66–1.82 (3H, m), 1.96–2.10 (1H, m), 2.18 (1H, dt, J = 3.2, 12.0 Hz), 2.32–2.59 (4H, m), 2.62–2.96 (4H, m), 3.05 (1H, d, J = 18.8 Hz), 3.15–3.25 (1H, m), 3.83 (1H, d, J = 17.2 Hz), 6.61 (1H, dd, J = 2.0, 8.4 Hz), 6.92 (1H, d, J = 8.4 Hz), 6.93 (1H, d, J = 2.0 Hz), 7.16–7.25 (2H, m), 7.36–7.43 (1H, m), 7.46 (1H, s), 7.56–7.64 (1H, m), a proton (OH) was not observed. MS (ESI) m/z = 425 $[M+H]^+$. HRMS (ESI) Calcd for $C_{29}H_{33}N_2O$ $[M+H]^+$: 425.2593. Found 425.2584.

(SYK-262)

Mp 226–228 °C (dec); Anal. Calcd for $C_{29}H_{32}N_2O{\cdot}2HCl{\cdot}H_2O$: C, 67.57; H, 7.04; N, 5.43. Found: C, 67.72; H, 7.13; N, 5.43.

5.1.31. 17-Cyclopropylmethyl-4,5α-epoxy-14β-hydroxy-3-(1-phenyl-1*H*-tetrazol-5-yloxy)morphinan-6-one (27)

To a stirred solution of naltrexone hydrochloride (5 g, 13.2 mmol) in DMF (50 mL) were added K_2CO_3 (4.5 g, 33.1 mmol) and 5-chloro-1-phenyl-1*H*-tetrazol (2.6 g, 14.6 mmol), and stirred at rt under an Ar atmosphere. After 42 h with stirring, the reaction

mixture was evaporated in vacuo. To the resulting mixture was added water and extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was chromatographed on silica gel (200 g, $CHCl_3$/MeOH = 20/1) to give **27** (6.8 g, quant) as a yellow oil. IR (neat): 3529, 2938, 1725, 1540, 1240, 1058 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.09–0.24 (2H, m), 0.49–0.66 (2H, m), 0.80–0.95 (1H, m), 1.63 (1H, dt, J = 3.5, 14.5 Hz), 1.65 (1H, dd, J = 2.5, 10.5 Hz), 1.92 (1H, ddd, J = 2.5, 3.0, 14.5 Hz), 2.16 (1H, dt, J = 4.0, 12.0 Hz), 2.31 (1H, dt, J = 3.0, 14.5 Hz), 2.38–2.51 (3H, m), 2.64 (1H, dd, J = 6.0, 18.5 Hz), 2.74 (1H, dd, J = 4.5, 12.0 Hz), 3.04 (1H, dt, J = 5.0, 13.5 Hz), 3.12 (1H, d, J = 18.5 Hz), 3.23 (1H, d, J = 6.0 Hz), 4.72 (1H, s), 6.75 (1H, d, J = 8.5 Hz), 7.16 (1H, d, J = 8.5 Hz), 7.50 (1H, dt, J = 1.5, 7.5 Hz), 7.59 (2H, ddd, J = 2.5, 7.5, 8.0 Hz), 7.89 (2H, ddd, J = 1.5, 2.5, 8.0 Hz), a proton (OH) was not observed. MS (ESI) m/z = 486 $[M+H]^+$. HRMS (ESI) Calcd for $C_{27}H_{28}N_5O_4$ $[M+H]^+$: 486.2141. Found 486.2148.

5.1.32. 17-Cyclopropylmethyl-4,5α-epoxy-14β-hydroxymorphinan-6-one (28)

To a stirred solution of **27** (4.8 g, 9.9 mmol) in AcOH (50 mL) was added 10% Pd/C(1.8 g, 16.80 mmol) and stirred at 70 °C under a H_2 atmosphere. After 19 h with stirring, the reaction mixture was filtrated and evaporated in vacuo. The resulting mixture was basified (pH 9) with 4 M NaOH aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was chromatographed on silica gel (150 g, ammonia saturated $CHCl_3$) to give **28** (2.88 g, 90%) as a brown amorphous solid. IR (film): 2928, 1726, 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.03–0.12 (2H, m), 0.42–0.53 (2H, m), 0.74–0.86 (1H, m), 1.38–1.45 (1H, m), 1.46–1.58 (1H, m), 1.80 (1H, td, J = 2.4, 13.6 Hz), 1.98–2.08 (1H, m), 2.15–2.24 (1H, m), 2.28–2.40 (3H, m), 2.57–2.66 (1H, m), 2.62 (1H, dd, J = 4.8, 12.0 Hz), 2.96 (1H, dt, J = 3.2, 14.4 Hz), 3.03 (1H, d, J = 18.8 Hz), 3.13 (1H, d, J = 5.6 Hz), 4.55 (1H, d, J = 2.0 Hz), 5.02 (1H, br s), 6.61 (1H, dd, J = 1.6, 8.0 Hz), 6.65 (1H, dd, J = 1.6, 8.0 Hz), 6.97 (1H, dt, J = 2.4, 8.0 Hz). MS (ESI) m/z = 326 $[M+H]^+$. HRMS (ESI) Calcd for $C_{20}H_{24}NO_3$ $[M+H]^+$: 326.1756. F. Found 326.1766.

5.1.33. 17-Cyclopropylmethyl-4,5α-epoxy-14β-hydroxymorphinan-6-spiro-2′-(1′,3′-dioxolane) (29)

To a stirred solution of **28** (2.8 g, 8.60 mmol) in toluene (40 mL) were added *p*-toluenesufonic acid monohydrate (2.5 g, 12.9 mmol) and ethylene glycol (3 mL, 51.62 mmol), and refluxed under an Ar atmosphere. After 13 h with stirring, the reaction mixture was evaporated in vacuo. The resulting mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was chromatographed on silica gel (100 g, $CHCl_3$/MeOH/25% NH_3 aqueous solution = 500/9/1) to give **29** (2.8 g, 89%) as a brown amorphous solid. IR (film): 3412, 2953, 1634, 1457 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.09–0.18 (2H, m), 0.49–0.57 (2H, m), 0.78–0.92 (1H, m), 1.37–1.44 (1H, m), 1.49–1.63(3H, m), 2.11 (1H, dt J = 4.0 12.0 Hz), 2.19–2.33 (2H, m), 2.38 (2H, d, J = 6.4 Hz), 2.58–2.69 (2H, m), 3.06 (1H, d, J = 18.8 Hz), 3.09–3.12 (1H, m), 3.72–3.79 (1H, m), 3.83–3.97 (2H, m), 4.12–4.20 (1H, m), 4.53 (1H, s), 6.60 (1H, dd, J = 2.4, 8.0 Hz), 6.67 (1H, dd, J = 2.4, 8.0 Hz), 7.06 (1H, t, J = 8.0 Hz), a proton (OH) was not observed. MS (ESI) m/z = 392 $[M+Na]^+$. HRMS (ESI) Calcd for $C_{22}H_{27}NNaO_4$ $[M+Na]^+$: 392.1838. Found 392.1847.

5.1.34. 17-Cyclopropylmethyl-8,14-didehydro-4,5α-epoxymorphinan-6-spiro-2′-(1′,3′-dioxolane) (30)

Compound **30** was prepared from compound **29** according to the procedure used to prepare compound **4**. Yield, 73%; a brown oil. IR (neat): 2997, 1628, 1602, 1456 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.08–0.17 (2H, m), 0.49–0.55 (2H, m), 0.85–0.94 (1H, m), 1.70–1.78 (1H, m), 2.00 (1H, dt, J = 4.8, 12.4 Hz), 2.03–2.13 (1H, m), 2.43 (2H, d, J = 6.4 Hz), 2.40–2.49 (1H, m), 2.60 (1H, dt, J = 3.6, 12.8 Hz), 2.72 (1H, dd, J = 6.4, 18.4 Hz), 2.78–2.85 (1H, m), 3.17 (1H, d, J = 18.4 Hz), 3.67–3.74 (2H, m), 3.82–3.91 (2H, m), 4.14–4.21 (1H, m), 4.58 (1H, s), 5.48 (1H, dd, J = 1.6, 6.8 Hz), 6.56 (1H, dd, J = 2.4, 7.6 Hz), 6.63 (1H, dd, J = 2.4, 7.6 Hz), 6.98 (1H, t, J = 7.6 Hz). MS (ESI) m/z = 352 $[M+H]^+$. HRMS (ESI) Calcd for $C_{22}H_{26}NO_3$ $[M+H]^+$: 352.1913. Found 352.1906.

5.1.35. 17-Cyclopropylmethyl-4,5α-epoxymorphinan-6-spiro-2′-(1′,3′-dioxolane) (31)

Compound **31** was prepared from compound **30** according to the procedure used to prepare compound **5**. Yield, quant.; a white amorphous solid. IR (film): 2951, 1632, 1609, 1457 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.12–0.20 (2H, m), 0.50–0.58 (2H, m), 0.83–0.97 (1H, m), 1.08–1.21 (1H, m), 1.49–1.70 (4H, m), 1.95 (1H, dt, J = 3.6, 11.6 Hz), 2.16 (1H, dt, J = 3.2, 12.0 Hz), 2.24–2.48 (3H, m), 2.52 (1H, dd, J = 6.0, 12.4 Hz), 2.76–2.85 (1H, m), 2.93 (1H, d, J = 18.8 Hz), 3.45 (1H, s), 3.73–3.81 (1H, m), 3.85–3.93 (2H, m), 4.10–4.18 (1H, m), 4.43 (1H, s), 6.61 (1H, dd, J = 2.4, 7.6 Hz), 6.66 (1H, dd, J = 2.4, 7.6 Hz), 7.05 (1H, t, J = 7.6 Hz). MS (ESI) m/z = 354 $[M+H]^+$. HRMS (ESI) Calcd for $C_{22}H_{28}NO_3$ $[M+H]^+$: 354.2069. Found 354.2079.

5.1.36. 17-Cyclopropylmethyl-4,5α-epoxymorphinan-6-one (32)

Compound **32** was prepared from compound **31** according to the procedure used to prepare compound **6**. Yield, 85%; a white crystal. Mp 187.7–188.4 °C; IR (KBr): 2923, 1721, 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.03–0.12 (2H, m), 0.42–0.50 (2H, m), 0.75–0.87 (1H, m), 1.09–1.25 (1H, m), 1.64–1.71 (1H, m), 1.75–1.83 (1H, m), 1.97–2.09 (2H, m), 2.25–2.36 (4H, m), 2.43 (1H, dd, J = 6.4, 12.6 Hz), 2.56 (1H, ddd, J = 2.8, 4.0, 12.8 Hz), 2.68–2.79 (1H, m), 2.89 (1H, d, J = 19.2 Hz), 3.41 (1H, dd, J = 2.4, 5.4 Hz), 4.56 (1H, s), 6.60 (1H, dd, J = 2.4, 7.6 Hz), 6.68 (1H, dd, J = 2.4, 7.6 Hz), 6.97 (1H, t, J = 7.6 Hz). MS (ESI) m/z = 310 $[M+H]^+$. HRMS (ESI) Calcd for $C_{20}H_{24}NO_2$ $[M+H]^+$: 310.1807. Found 310.1814.

5.1.37. 4,5α-Epoxy-17-isobutylmorphinan-6-one (33)

Compound **33** was prepared from compound **31** according to the procedure used to prepare compound **8**. Yield, 44%; a colorless oil. IR (neat): 2941, 1723, 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.90 (3H, d, J = 6.4 Hz), 0.92 (3H, d, J = 6.4 Hz), 1.22 (1H, dq, J = 4.8, 12.8 Hz), 1.66–1.86 (3H, m), 2.03 (1H, dt, J = 4.8, 12.0 Hz), 2.15 (1H, dt, J = 3.2, 12.0 Hz), 2.20–2.30 (2H, m), 2.31–2.43 (3H, m), 2.51–2.64 (2H, m), 2.97 (1H, d, J = 18.8 Hz), 3.16 (1H, dd, J = 2.8, 5.2 Hz), 4.59 (1H, s), 6.67 (1H, dd, J = 0.8, 7.6 Hz), 6.64 (1H, dd, J = 0.8, 7.6 Hz), 7.04 (1H, t, J = 7.6 Hz). MS (ESI) m/z = 312 $[M+H]^+$. HRMS (ESI) Calcd for $C_{20}H_{26}NO_2$ $[M+H]^+$: 312.1964. Found 312.1957.

5.1.38. 4,5α-Epoxy-17-(2,2,2-trichloroethoxycarbonyl)-morphinan-6-spiro-2′-(1′,3′-dioxolane) (34)

Compound **34** was prepared from compound **31** according to the procedure used to prepare compound **10**. Yield, 80%; a white amorphous solid. IR (film): 2950, 1711, 1455, 1422 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.12 (0.5H, dt, J = 3.2, 12.4 Hz), 1.16 (0.5H, dt, J = 3.2, 12.4 Hz), 1.46–1.70 (3H, m), 1.71–1.86 (2H, m), 2.07–2.16 (1H, m), 2.71–2.97 (2H, m), 2.97 (1H, dd, J = 5.6, 18.4 Hz), 3.72–3.82 (1H, m), 3.84–3.93 (2H, m), 3.97–4.07 (1H, m), 4.10–4.19 (1H, m), 4.43 (1H, s), 4.68 (1H, dd, J = 4.8, 8.0 Hz), 4.73 (1H, d, J = 12.0 Hz), 4.79 (0.5H, d, J = 12.0 Hz), 4.87 (0.5H, d, J = 12.0 Hz), 6.65 (1H, dd, J = 3.2, 7.6 Hz), 6.70 (1H, dd, J = 3.2, 7.6 Hz), 7.10 (1H, t, J = 7.6 Hz). MS (ESI) m/z = 496 $[M+Na]^+$. HRMS (ESI) Calcd for $C_{21}H_{22}Cl_3NNaO_5$ $[M+Na]^+$: 496.0461. Found 496.0462.

5.1.39. 4,5α-Epoxy-17-methylmorphinan-6-spiro-2′-(1′,3′-dioxolane) (35)

Compound **35** was prepared from compound **34** according to the procedure used to prepare compound **11**. Yield, quant.; a yellow oil. IR (neat): 2928, 1631, 1607, 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.17 (1H, dq, J = 3.6, 12.8 Hz), 1.48–1.56 (2H, m), 1.59–1.69 (2H, m), 1.89 (1H, dt, J = 4.8, 12.4 Hz), 2.21 (1H, dt, J = 4.0, 12.4 Hz), 2.23–2.30 (1H, m), 2.37–2.46 (1H, m), 2.42 (3H, s), 2.53 (1H, ddd, J = 1.2, 4.8, 12.4 Hz), 3.03 (1H, d, J = 18.8 Hz), 3.13 (1H, dd, J = 2.4, 5.2 Hz), 3.73–3.80 (1H, m), 3.85–3.91 (2H, m), 4.10–4.18 (1H, m), 4.42 (1H, s), 6.61 (1H, dd, J = 0.4, 7.6 Hz), 6.68 (1H, dd, J = 0.4, 7.6 Hz), 7.05 (1H, t, J = 7.6 Hz). MS (ESI) m/z = 314 $[M+H]^+$. HRMS (ESI) Calcd for $C_{19}H_{24}NO_3$ $[M+H]^+$: 314.1756. Found 314.1762.

5.1.40. 4,5α-Epoxy-17-methylmorphinan-6-one (36)

Compound **36** was prepared from compound **35** according to the procedure used to prepare compound **6**. Yield, 81%; a white crystal. Mp 199.3–200.4 °C; IR (KBr): 2919, 1717, 1457 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.10–1.23 (1H, m), 1.64–1.82 (2H, m), 2.00 (1H, dt, J = 4.4, 12.0 Hz), 2.11 (1H, dt, J = 3.2, 12.0 Hz), 2.24–2.35 (3H, m), 2.36 (3H, s), 2.44–2.57 (2H, m), 3.00 (1H, d, J = 18.8 Hz), 3.13 (1H, dd, J = 2.8, 5.2 Hz), 4.56 (1H, s), 6.63 (1H, dd, J = 0.4, 7.6 Hz), 6.68 (1H, dd, J = 0.4, 7.6 Hz), 6.98 (1H, t, J = 7.6 Hz). MS (ESI) m/z = 270 $[M+H]^+$. HRMS (ESI) Calcd for $C_{17}H_{20}NO_2$ $[M+H]^+$: 270.1490. Found 270.1504.

5.1.41. 17-Cyclopropylmetyl-4-hydroxymorphinan-6-one (37)

To a stirred solution of **32** (70 mg, 0.23 mmol) in acetic acid (1 mL) was added zinc (75 mg, 1.13 mmol) and was refluxed under an Ar atmosphere. After 4 h with stirring, the reaction mixture was filtrated and evaporated in vacuo. The resulting mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by preparative TLC (ammonia saturated $CHCl_3$/MeOH = 20/1) to give **37** (89 mg, quant) as a colorless oil. IR (neat): 3278, 2923, 1698, 1580, 1460 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.07–0.16 (2H, m), 0.49–0.57 (2H, m), 0.84–0.96 (1H, m), 1.76 (1H, dq, J = 4.8, 13.2 Hz), 1.84–2.01 (3H, m), 2.05 (1H, dt, J = 3.2, 12.2 Hz), 2.24–2.40 (4H, m), 2.49 (1H, dd, J = 7.2, 13.6 Hz), 2.55 (1H, dd, J = 6.0, 13.0 Hz), 2.73 (1H, dd, J = 6.0, 18.8 Hz), 2.82 (1H, d, J = 12.4 Hz), 2.92 (1H, d, J = 18.8), 3.31 (1H, dd, J = 3.2, 5.6 Hz), 4.46 (1H, dd, J = 2.0, 13.4 Hz), 6.58 (1H, dd, J = 2.4, 7.2 Hz), 6.67 (1H, dd, J = 2.4, 7.2 Hz), 6.91 (1H, t, J = 7.6 Hz). MS (ESI) m/z = 312 $[M+H]^+$. HRMS (ESI) Calcd for $C_{20}H_{26}NO_2$ $[M+H]^+$: 312.1964. Found 312.1953.

5.1.42. 4-Hydroxy-17-isobutylmorphinan-6-one (38)

Compound **38** was prepared from compound **33** according to the procedure used to prepare compound **37**. Yield, 81%; a pink amorphous solid. IR (film): 3289, 2950, 1697, 1582, 1461 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.91 (3H, d, J = 6.4 Hz), 0.93 (3H, d, J = 6.4 Hz), 1.68–1.85 (3H, m), 1.85–1.96 (2H, m), 2.08 (1H, dt, J = 2.8, 12.0 Hz), 2.20–2.35 (5H, m), 2.44 (1H, dd, J = 6.8, 13.6 Hz), 2.47–2.56 (1H, m), 2.71 (1H, dd, J = 6.0, 18.8 Hz), 2.95 (1H, d, J = 18.8 Hz), 2.95–3.03 (1H, m), 4.44 (1H, dd, J = 2.4, 13.2 Hz), 6.60 (1H, dd, J = 0.8, 7.6 Hz), 6.73 (1H, dd, J = 0.8, 7.6 Hz), 6.91 (1H, t, J = 7.6 Hz), a proton (OH) was not observed. MS (ESI) m/z = 314 $[M+H]^+$. HRMS (ESI) Calcd for $C_{20}H_{28}NO_2$ $[M+H]^+$: 314.2120. Found 314.2135.

5.1.43. 4-Hydroxy-17-methylmorphinan-6-one (39)

Compound **39** was prepared from compound **36** according to the procedure used to prepare compound **37**. Yield, 94%; a brown amorphous solid IR (film): 3270, 2937, 1703, 1580, 1459 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.74 (1H, dq, J = 4.8, 13.2 Hz), 1.84–2.02 (3H, m), 2.15 (1H, dt, J = 3.6, 12.0 Hz), 2.25 (1H, td, J = 2.4, 14.0 Hz), 2.32–2.46 (2H, m), 2.44 (3H, s), 2.48–2.59 (2H, m), 2.76 (1H, dd, J = 6.0, 18.8 Hz), 3.02 (1H, d, J = 18.8 Hz), 3.09 (1H, dd, J = 3.2, 5.4 Hz), 4.46 (1H, dd, J = 2.0, 13.2 Hz), 6.59 (1H, dd, J = 0.4, 7.6 Hz), 6.60 (1H, dd, J = 0.4, 7.6 Hz), 6.92 (1H, t, J = 7.6 Hz), a proton (OH) was not observed. MS (ESI) m/z = 272 $[M+H]^+$. HRMS (ESI) Calcd for $C_{17}H_{22}NO_2$ $[M+H]^+$: 272.1651. Found 272.1658.

5.1.44. 17-Cyclopropylmethyl-6,7-didehydro-quinolino-[2′,3′:6,7]morphinan-4-ol (SN-27)

A free base of SN-27 was prepared from compound **37** according to the procedure used to prepare compound **7**. Yield, 86%; a colorless oil. SN-27 was prepared from the free base of SN-27 according to the procedure used to prepare SN-11. Yield, 74%; a white solid.

(Free base of SN-27)

IR (neat): 2920, 1579, 1459 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.31–0.20 (2H, m), 0.50–0.57 (2H, m), 0.90–1.01 (1H, m), 2.01 (1H, dt, J = 4.4, 12.8 Hz), 2.20 (1H, d, J = 12.8 Hz), 2.28 (1H, dt, J = 2.4, 12.8 Hz), 2.45–2.60 (3H, m), 2.82–2.95 (3H, m), 2.99 (1H, dd, J = 6.0, 19.2 Hz), 3.07–3.16 (2H, m), 3.49–3.56 (1H, m), 5.34 (1H, d, J = 16.0 Hz), 6.48 (1H, d, J = 7.6 Hz), 6.62 (1H, d, J = 7.2 Hz), 6.68–6.77 (2H, m), 6.80 (1H, t, J = 8.0 Hz), 7.04 (1H, dt, J = 0.8, 6.4 Hz), 7.41 (1H, d, J = 7.6 Hz), 7.60 (1H, s), a proton (OH) was not observed. MS (ESI) m/z = 397 $[M+H]^+$. HRMS (ESI) Calcd for $C_{27}H_{29}N_2O$ $[M+H]^+$: 397.2280. Found 397.2293.

(SN-27)

Mp 229–231 °C (dec); Anal. Calcd for $C_{27}H_{28}N_2O{\cdot}2HCl{\cdot}1.3H_2O$: C, 65.80; H, 6.67; N, 5.68. Found: C, 65.91; H, 6.63; N, 5.69.

5.1.45. 6,7-Didehydro-17-isobutyl-quinolino[2′,3′:6,7]-morphinan-4-ol hydrochloride (SN-24)

A free base of SN-24 was prepared from compound **38** according to the procedure used to prepare compound **7**. Yield, 78%; a colorless oil. SN-24 was prepared from the free base of SN-24 according to the procedure used to prepare SN-11. Yield, 47%; a yellow solid.

(Free base of SN-24)

IR (neat): 2919, 1579, 1458 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.97 (3H, d, J = 6.4 Hz), 0.99 (3H, d, J = 6.4 Hz), 1.78–1.90 (1H, m), 1.98 (1H, dt, J = 2.8, 12.4 Hz), 2.15 (1H, d, J = 12.8 Hz), 2.22–2.43 (3H, m), 2.53 (1H, br s), 2.60–2.70 (1H, m), 2.86 (1H, dd, J = 11.6, 18.0 Hz), 2.93 (1H, d, J = 16.4 Hz), 3.00 (1H, dd, J = 6.0, 18.4 Hz), 3.05–3.23 (3H, m), 5.30 (1H, d, J = 16.0 Hz), 6.47 (1H, dd, J = 7.2 Hz), 6.60 (1H, d, J = 8.4 Hz), 6.62–6.76 (2H, m), 6.80 (1H, t, J = 8.0 Hz), 7.01 (1H, dt, J = 1.2, 8.0 Hz), 7.40 (1H, d, J = 8.0 Hz), 7.61 (1H, s), a proton (OH) was not observed. MS (ESI) m/z = 399 $[M+H]^+$. HRMS (ESI) Calcd for $C_{27}H_{31}N_2O$ $[M+H]^+$: 399.2436. Found 399.2425.

(SN-24)

Mp 223–225 °C (dec); Anal. Calcd for $C_{27}H_{30}N_2O{\cdot}2HCl{\cdot}2H_2O$: C, 63.90; H, 7.15; N, 5.52. Found: C, 63.89; H, 7.20; N, 5.60.

5.1.46. 6,7-Didehydro-17-methyl-quinolino[2′,3′:6,7]-morphinan-4-ol hydrochloride (SN-26)

A free base of SN-26 was prepared from compound **39** according to the procedure used to prepare compound **7**. Yield, 78%; a colorless oil. SN-26 was prepared from the free base of SN-26 according to the procedure used to prepare SN-11. Yield, 65%; a white solid.

(Free base of SN-26)

IR (neat): 2910, 1579, 1459 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.97 (1H, dt, J = 4.4, 12.8 Hz), 2.16–2.24 (1H, m), 2.32 (1H, dt, J = 2.8, 12.0 Hz), 2.45 (3H, s), 2.50 (1H, ddd, J = 2.8, 7.2, 11.6 Hz), 2.60 (1H, dd, J = 2.8, 11.6 Hz), 2.84–2.94 (1H, m), 2.91 (1H, d, J = 16.0 Hz), 2.98 (1H, dd, J = 6.8, 19.2 Hz), 3.08 (1H, dd, J = 6.8, 17.2 Hz), 3.12–3.22 (2H, m), 5.37 (1H, d, J = 16.0 Hz), 6.46 (1H, d, J = 7.6 Hz), 6.64 (1H, d, J = 7.6 Hz), 6.69–6.80 (2H, m), 6.81 (1H, t,

J = 7.6 Hz), 7.03 (1H, dt, J = 1.2, 7.6 Hz), 7.40 (1H, d, J = 8.0 Hz), 7.59 (1H, s), a proton (OH) was not observed. MS (ESI) m/z = 357 $[M+H]^+$. HRMS (ESI) Calcd for $C_{24}H_{25}N_2O$ $[M+H]^+$: 357.1967. Found 357.1962.

(SN-26)

Mp 241–242 °C (dec); Anal. Calcd for $C_{24}H_{24}N_2O{\cdot}2HCl{\cdot}2.5H_2O$: C, 60.76; H, 6.59; N, 5.90. Found: C, 61.00; H, 6.80; N, 5.95.

5.1.47. 17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-3-methoxy-quinolino[2′,3′:6,7]morphinan (41)

Compound **41** was prepared from compound **40** according to the procedure used to prepare compound **7**. The crude compound was chromatographed on silica gel, but could not be purified completely. The resulting compound **41** was used for the next reaction without further purification.

5.1.48. 17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-quinolino[2′,3′:6,7]morphinan-3-ol hydrochloride (SN-25)

A free base of SN-25 was prepared from compound **41** according to the procedure used to prepare the free base of SN-11. Yield, 30% (2 steps from **40**); a white solid. SN-25 was prepared from free base of SN-25 according to the procedure used to prepare SN-11. Yield, 62%; a yellow solid.

(Free base of SN-25)

IR (KBr): 3652 cm^{-1}; ^1H NMR (CD_3COCD_3, 400 MHz) δ: 0.08–0.17 (2H, m), 0.41–0.51 (2H, m), 0.81–0.92 (1H, m), 1.83–1.89 (1H, m), 2.04–2.08 (1H, m), 2.13 (1H, dt, J = 4.5, 12.0 Hz), 2.29–2.41 (2H, m), 2.48 (1H, dd, J = 6.5, 18.0 Hz), 2.50 (1H, dd, J = 6.5, 12.0 Hz), 2.58–2.64 (1H, m), 2.73–2.84 (2H, m), 3.01 (1H, d, J = 18.0 Hz), 3.25–3.31 (1H, m), 3.62 (1H, dd, J = 2.5, 6.5 Hz), 5.55 (1H, s), 6.56 (1H, d, J = 8.0 Hz), 6.60 (1H, d, J = 8.0 Hz), 7.53 (1H, ddd, J = 1.0, 7.0, 7.5 Hz), 7.69 (1H, ddd, J = 1.0, 7.0, 7.5 Hz), 7.78–7.82 (1H, m), 7.90–7.93 (1H, m), 8.01–8.05 (1H, m). MS (ESI) m/z = 411 $[M+H]^+$. HRMS (FAB) Calcd for $C_{27}H_{27}N_2O_2$ $[M+H]^+$: 411.2073. Found 411.2070.

(SN-25)

Mp 235–240 °C (dec). Anal. Calcd for $C_{27}H_{26}N_2O_2{\cdot}2HCl{\cdot}1.2H_2O$: C, 64.21; H, 6.07; N, 5.55. Found: C, 64.25; H, 6.33; N, 5.36.

5.2. Pharmacology

5.2.1. [^{35}S]GTPγS binding assay

δ Human recombinant cell (HEK-293) membrane, which was purchased from PerkinElmer, was incubated in 0.5 mL of assay buffer (50 mM Tris, 1 mM EDTA, 12.5 mM $MgCl_2$, 100 mM NaCl, 0.5% BSA) with various concentrations of the tested compound, 3 mM GDP and 0.1 nM [^{35}S]GTPγS (PerkinElmer). Nonspecific binding was measured in the presence of 10 mM unlabeled GTPγS. [Met^5]-enkephalin was used as the standard δ agonist.

5.2.2. Opioid receptor binding assay of NTI, TAN-67 and SN-11, 23–28

Rat cerebrum and guinea pig cerebellum membranes were prepared as described previously.[40] The μ, δ or κ opioid receptor binding assays were performed with [^{3}H]DAMGO ([D-Ala2, *N*-Me-Phe4, Gly^5-ol]-Enkephalin), [^{3}H]DADLE ([D-Ala2, D-Leu5]-Enkephalin) or [^{3}H]U69,593 (*N*-methyl-2-phenyl-*N*-[(5*R*,7*S*,8*S*)-7-(pyrrolidin-1-yl)-1-oxaspiro[4.5]dec-8-yl]acetamide). Nonspecific binding was measured in the presence of 20 mM unlabeled levallorphan for μ, δ opioid receptor binding assay and 1 mM unlabeled U-69,593 for κ opioid receptor binding assay. K_i value was calculated according to the Cheng–Prusoff equation.[41]

5.2.3. Opioid receptor binding assay of SN-28, and SYK-259–262

Mouse whole brain without cerebellum and guinea pig cerebellum membranes were prepared as described previously.[42] The μ, δ or κ opioid receptor binding assays were performed with [^{3}H]DAMGO, [^{3}H]DPDPE ([D-Pen2,5]-Enkephalin) or [^{3}H]U69,593. Nonspecific binding was measured in the presence of 1 mM unlabeled DAMGO, DPDPE or U-69,593. K_i value was calculated according to the Cheng–Prusoff equation .[41]

Acknowledgments

This work was supported by JSPS KAKENHI (23790139) [Grant-in-Aid for Young Scientists (B)]. We also acknowledge the Institute of Instrumental Analysis of Kitasato University, School of Pharmacy for its facilities.

References and notes

1. Dhawan, B. N.; Cesselin, F.; Reisine, T.; Bradley, P. B.; Portoghese, P. S.; Hamon, M. *Pharmacol. Rev.* **1996**, *48*, 567.
2. Piercey, M. F.; Lahti, R. A.; Schroeder, L. A.; Einspahr, F. J.; Barsuhn, C. *Life Sci.* **1982**, *31*, 1197.
3. Lahti, R. A.; Von Voigtlander, P. F.; Barsuhn, C. *Life Sci.* **1982**, *31*, 2257.
4. Von Voigtlander, P. F.; Lahti, R. A.; Ludens, J. H. J. *Pharmacol. Exp. Ther.* **1983**, *224*, 7.
5. Mucha, R. F.; Herz, A. *Psychopharmacology* **1985**, *86*, 274.
6. Millan, M. J. *Trends Pharmacol. Sci.* **1990**, *11*, 70.
7. Mori, T.; Nomura, M.; Yoshizawa, K.; Nagase, H.; Narata, M.; Suzuki, T. *Life Sci.* **2004**, *75*, 2433.
8. Nagase, H.; Hayakawa, J.; Kawamura, K.; Kawai, K.; Takezawa, Y.; Matsuura, H.; Tajima, C.; Endo, T. *Chem. Pharm. Bull.* **1998**, *46*, 366.
9. Kawai, K.; Hayakawa, J.; Miyamoto, T.; Imamura, Y.; Yamane, S.; Wakita, H.; Fujii, H.; Kawamura, K.; Matsuura, H.; Izumimoto, N.; Kobayashi, R.; Endo, T.; Nagase, H. *Bioorg. Med. Chem.* **2008**, *16*, 9188.
10. Nagase, H.; Fujii, H. *Top. Curr. Chem.* **2011**, *299*, 29.
11. Nakao, K.; Mochizuki, H. *Drugs Today* **2009**, *45*, 323.
12. Chang, K. J.; Rigdon, G. C.; Howard, J. L.; Mcnutt, R. W. *J. Pharmacol. Exp. Ther.* **1993**, *267*, 852.
13. Calderon, S.; Rothman, R. B.; Porreca, F.; Flippen-Anderson, R. W.; Mcnutt, R. W.; Xu, H.; Smith, L. E.; Bilsky, E. J.; Davis, P.; Rice, K. C. *J. Med. Chem.* **1994**, *37*, 2125.
14. Bilsky, E. J.; Calderon, S. N.; Wang, T.; Bernstein, R. N.; Davis, P.; Hruby, V. J.; Mcnutt, R. W.; Rothman, R. B.; Rice, K. C.; Porreca, F. *J. Pharmacol. Exp. Ther.* **1995**, *273*, 359.
15. Portoghese, P. S.; Sultana, M.; Takemori, A. E. J. *J. Med. Chem.* **1990**, *33*, 1714.
16. Takemori, A. E.; Sultana, M.; Nagase, H.; Portoghese, P. S. *Life Sci.* **1992**, *50*, 1491.
17. Nagase, H.; Kawai, K.; Wakita, H.; Mizusuna, A.; Matsuura, H.; Tajima, C.; Takezawa, Y.; Endoh, T. *Chem. Pharm. Bull.* **1998**, *46*, 1695.
18. Nagase, H.; Yajima, Y.; Fujii, H.; Kawamuwa, K.; Narita, M.; Kamei, J.; Suzuki, T. *Life. Sci.* **2001**, *68*, 2227.
19. Portoghese, P. S.; Sultana, M.; Nagase, H.; Takemori, A. E. *J. Med. Chem.* **1988**, *31*, 281.
20. Nogrady, T. *In Medicinal Chemistry, A Biochemical Approach*; Oxford University Press: New York, 1985. pp. 68–69.
21. Nagase, H.; Osa, Y.; Nemoto, T.; Fujii, H.; Imai, M.; Nakamura, T.; Kanemasa, T.; Kato, A.; Gouda, H.; Hirono, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2792.
22. Casy, A. F.; Beckett, A. H. *J. Pharm. Pharmacol.* **1954**, *6*, 986.
23. Beckett, A. H. *J. Pharm. Pharmacol.* **1956**, *8*, 848.
24. Smith, T. A.; Thatcher, L. N.; Coop, A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5175.
25. Portoghese, P. S.; Larson, D. L.; Sultana, M.; Takemori, A. E. *J. Med. Chem.* **1992**, *35*, 4325.
26. Sawa, Y. K.; Tada, H. *Tetrahedron* **1968**, *24*, 6185.
27. Nemoto, T.; Fujii, H.; Nagase, H. *Tetrahedron Lett.* **2007**, *48*, 7413.
28. Nemoto, T.; Fujii, H.; Narita, M.; Miyoshi, K.; Nakamura, A.; Suzuki, T.; Nagase, H. *Bioorg. Med. Chem.* **2008**, *16*, 4304.
29. Osa, Y.; Ida, Y.; Yano, Y.; Furuhata, K.; Nagase, H. *Heterocycles* **2006**, *69*, 271.
30. Fujii, H.; Osa, Y.; Ishihara, M.; Hanamura, S.; Nemoto, T.; Nakajima, M.; Hasebe, K.; Mochizuki, H.; Nagase, H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4978.
31. Fujii, H.; Okada, K.; Ishihara, M.; Hanamura, S.; Osa, Y.; Nemoto, T.; Nagase, H. *Tetrahedron* **2009**, *65*, 10623.
32. Fujii, H.; Narita, M.; Mizoguchi, H.; Murachi, M.; Tanaka, T.; Kawai, K.; Tseng, L. F.; Nagase, H. *Bioorg. Med. Chem.* **2004**, *12*, 4133.
33. Olofson, R. A.; Martz, J. T.; Senet, J.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081.
34. Nemoto, T.; Fujii, H.; Narita, M.; Miyoshi, K.; Nakamura, A.; Suzuki, T.; Nagase, H. *Bioorg. Med. Chem. Lett.* **2008**, *16*, 4304.
35. Nagase, H.; Nemoto, T.; Matsubara, A.; Saito, M.; Yamamoto, N.; Osa, Y.; Hirayama, S.; Nakajima, M.; Nakao, K.; Mochizuki, H.; Fujii, H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6302.
36. Beyerman, H. C.; Buurman, E.; Lie, T. S.; Maat, L. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 43.
37. Coop, A.; Rothman, R. B.; Dersch, C.; Partilla, J.; Porreca, F.; Davis, P.; Jacobson, E.; Rice, K. C. *J. Med. Chem.* **1999**, *42*, 1673.

38. Quock, R. M.; Burkey, T. H.; Varga, E.; Hosohata, Y.; Hosahata, K.; Cowell, S. M.; Slate, C. A.; Ehlert, F. J.; Roeske, W. R.; Yamamura, H. I. *Pharmacol. Rev.* **1999**, *51*, 503.
39. We described that the electron-donating property of the CPM group in the recent reports.[(a), (b)] (a) Nagase, H.; Yamamoto, N.; Nemoto, T.; Yoza, K.; Kamiya, K.; Hirono, S.; Momen, S.; Izumimoto, N.; Hasebe, K.; Mochizuki, H.; Fujii, H. J. *Org. Chem.* **2008**, *73*, 8093; (b) Fujii, H.; Imaide, S.; Watanabe, A.; Nemoto, T.; Nagase, H. *Tetrahedron Lett.* **2008**, *49*, 6293.
40. Choi-Sledeski, Y.; McGarry, D. G.; Green, D. M.; Mason, H. J.; Becker, M. R.; Davis, R. S.; Ewing, W. R.; Dankulich, W. P.; Manetta, V. E.; Morris, R. L.; Spada, A. P.; Cheney, K. D.; Brown, K. D.; Colussi, D. J.; Chu, V.; Heran, C. L.; Morgan, S. R.; Bentley, R. G.; Leadley, R. J.; Maignan, S.; Guilloteau, J.-P.; Dunwiddie, C. T.; Pauls, H. W. *J. Med. Chem.* **1999**, *42*, 3572.
41. Yung-Chi, C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099.
42. Narita, M.; Nakamura, A.; Ozaki, M.; Miyoshi, K.; Suzuki, M.; Suzuki, T. *Neuropsychopharmacology* **2008**, *33*, 1097.