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Synthesis of quinolinomorphinan derivatives as highly selective δ opioid receptor ligands

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ABSTRACT

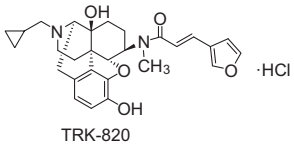
We have reported previously the novel δ opioid agonist KNT-127 which showed high affinity and selectivity for the δ receptor. Moreover, the analgesic effect of subcutaneously administered KNT-127 was more potent than that of a prototypical δ agonist (−)-TAN-67 in the acetic acid writhing test. This study of the structure–activity relationship of KNT-127 derivatives focused on the introduction of substituents onto the 5′-, 6′-, 7′- or 8′-position of the quinoline ring and revealed that many derivatives with 5′- or 8′-substituents showed high affinities and selectivities for the δ receptor. Especially, SYK-153 with an 8′-OH group showed the highest affinity and the most balanced and highest selectivity for the δ receptor among the synthesized compounds.

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 effort has been expended on obtaining an opioid κ selective agonist to eliminate undesirable morphine-like side effects such as addiction. We recently reported a novel κ agonist, TRK-820 (nalfurafine hydrochloride)[2–5] which is the first opioid drug without addiction and aversion (Fig. 1). TRK-820 was launched in Japan as an antipruritic drug for kidney dialysis patients in 2009.

Our next target for development was a highly selective and potent δ agonist. Although nonpeptide δ opioid agonists BW373U86,[6] SNC80,[7,8] OMI,[9,10] ADL5747[11] and AZD2327[12] have already been described (Fig. 2), the detailed pharmacological character of the δ opioid receptor has not yet been clarified due to unavailability of a sufficiently active, especially systemically active, δ agonist without side effects. So we have designed and synthesized a sufficiently active δ selective agonist that displays especially good systemic activity.

In a previous report, we synthesized the highly selective δ agonist (−)-TAN-67[13,14] which was designed from the δ selective antagonist naltrindole (NTI)[15,16] by removing postulated accessory sites[17] and converting the indole structure to a quinoline. TAN-67



TRK-820

Figure 1. The structure of TRK-820.

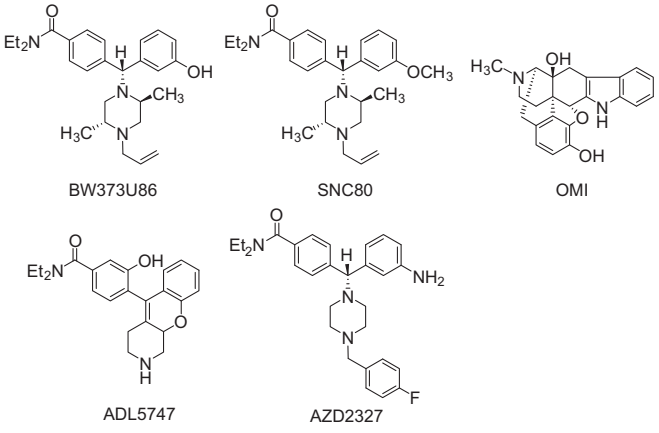


Figure 2. The structures of BW373U86, SNC80, OMI, ADL5747, and AZD2327.

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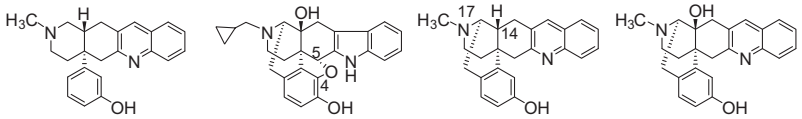


Figure 3. The structures of TAN-67, NTI, SN-28, and KNT-127.

showed high agonist activity for the δ receptor and analgesic activity (ED_{50} = 31.4 mg/kg) (Fig. 3).[13,14] Recently, we have reported a novel δ agonist, SN-28 (Fig. 3), which showed about 15- and 334-times more potent agonist activities than (−)-TAN-67 and SNC80, respectively, and almost equivalent selectivity to (−)-TAN-67 in an in vitro assay.[18] However, SN-28 at subcutaneously (s.c.) administered dosages over 30 mg/kg showed no analgesic effect in the acetic acid writhing test. In an effort to understand why SN-28 was not effective by the s.c. route in the test, we considered that SN-28 does not penetrate through the blood–brain barrier (BBB). To confirm this hypothesis, we examined the analgesic effect of SN-28 administered by intrathecal (i.t.) injection in the acetic acid writhing test. As we expected, SN-28 showed a strong analgesic effect (ED_{50} = 0.095 nM) in this test, which supported the idea that the compound does not cross the BBB. On the basis of the above hypothesis, we designed KNT-127 which is effective in systemic administration (Fig. 3).[19]

KNT-127 showed higher selectivity for the δ receptor than did SN-28, and showed almost the same potent agonistic activity (ED_{50} = 0.149 nM) as did SN-28 (ED_{50} = 0.095 nM) by i.t. injection in the acetic acid writhing test.[19] Moreover, a strong dose-dependent analgesia of KNT-127 was observed by s.c. injection in this test in mice (ED_{50} = 1.2 mg/kg). The discovery of KNT-127 led us to investigate the structure–activity relationship (SAR) for KNT-127 derivatives to obtain more selective and more potent agonists for the δ receptor.

The 17-nitrogen and the 3-phenolic hydroxyl groups of the morphinan derivatives have been generally considered as the key functionalities that mediate associations between the drug molecule and the opioid receptor site. To bind to the δ receptor, the quinoline groups of (−)-TAN-67, SN-28, and KNT-127 are considered to be essential parts required for δ receptor agonist activities. Therefore, we especially kept the quinoline ring of KNT-127, and synthesized compounds with various functional groups (Cl, F, OH, OCH_3, CH_3, CF_3, NO_2, $N(CH_3)_2$) on the quinoline ring to examine the relationship between the quinoline substituent and the opioid receptor binding property (Fig. 4). Herein, we report the syntheses of KNT-127 derivatives and their binding affinities and selectivities for the opioid receptors.

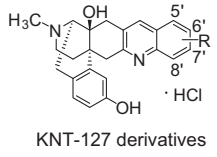


Figure 4. The structures of KNT-127 derivatives.

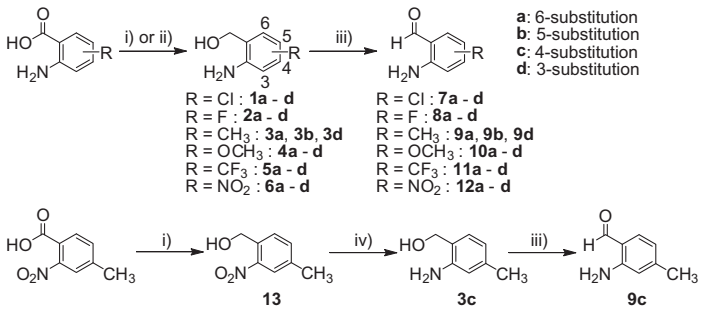
2. Results

2.1. Chemistry

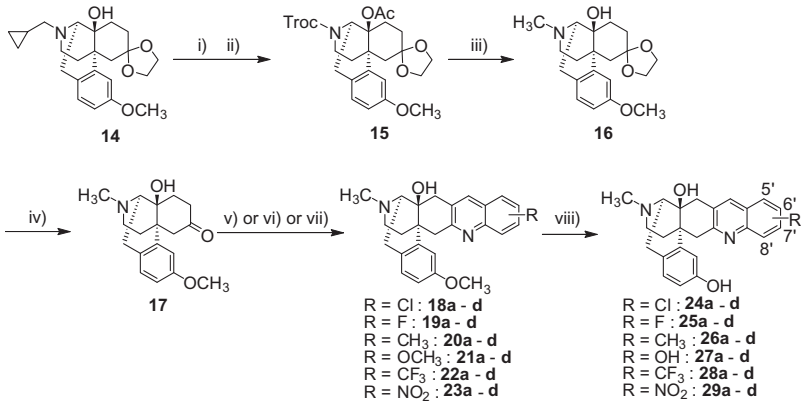
We synthesized KNT-127 derivatives with various substituents on the quinoline ring. The quinoline rings of KNT-127 derivatives were formed by using 2-aminobenzaldehyde derivatives **7**–**12**. 2-Aminobenzaldehyde derivatives **7**–**12**, with the exception of compounds **7b**, **9b**, **9c**, and **9d**, were synthesized from the corresponding anthranilic acids by the reduction with BH_3–THF or $LiAlH_4$, followed by oxidation with MnO_2 in CH_2Cl_2 (Scheme 1). 2-Aminobenzaldehyde derivatives **7b**, **9b**, and **9d** were synthesized from the commercially available 2-aminobenzyl alcohols **1b**, **3b**, and **3d** by the oxidation with MnO_2 in CH_2Cl_2 (Scheme 1). 2-Aminobenzaldehyde derivative **9c** was synthesized from 2-aminobenzyl alcohol **3c** by the oxidation with MnO_2 in CH_2Cl_2. Compound **3c** was prepared from 4-methyl-2-nitrobenzoic acid by the reduction with BH_3–THF followed by the hydrogenation with 10% Pd–C under a H_2 atmosphere (Scheme 1).

The morphinan **14** was synthesized from naltrexone by the reported method.[20–23] As shown in Scheme 2, the 17-cyclopropylmethyl group of compound **14** was converted to a 17-methyl group in **17** in four steps by a previously reported method (acetylation, carbamoylation–dealkylation, reduction, and hydrolysis).[19,24,25] Compound **17** was converted to the objective compounds **24–29** by the formation of quinoline rings with 2-aminobenzaldehyde derivatives **7–12** in the presence of the acid followed by *O*-demethylation with BBr_3 in CH_2Cl_2 (Scheme 2).[26]

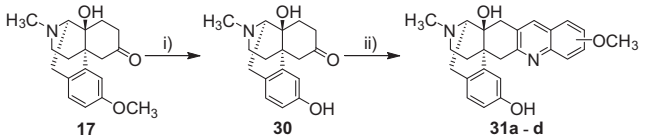
To obtain the compounds with the methoxy group on the quinoline ring, compound **17** was firstly demethylated with BBr_3 in CH_2Cl_2, followed by the formation of a quinoline ring with 2-aminobenzaldehyde derivatives **10** to afford the objective



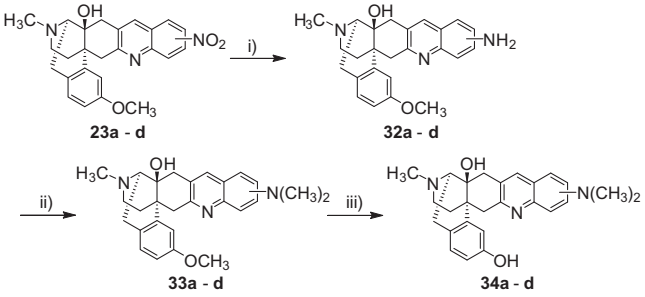
Scheme 1. Reagents and conditions: (i) BH_3–THF, THF, 0 to 30 °C, 49%-quant.; (ii) $LiAlH_4$, THF, 0 °C to rt, 77%; (iii) MnO_2, CH_2Cl_2, rt, 57%-quant.; (iv) 10% Pd–C, H_2, MeOH, rt, 74%.



Scheme 2. Reagents and conditions: (i) Ac_2O, reflux; (ii) Troc-Cl, K_2CO_3, $Cl_2CHCHCl_2$, reflux, 95% (2 steps from compound **14**); (iii) $LiAlH_4$, THF, 0 °C to rt, 76%; (iv) 2 M HCl, 80 °C, 91%; (v) 2-aminobenzaldehyde derivatives (**7b–d**, **8a–c**, **9a–c**, **10a–d**, **11a–d**, or **12b–c**), CH_3SO_3H, EtOH, reflux, 49%-quant.; (vi) 2-aminobenzaldehyde derivatives (**7a** or **8d**), CH_3SO_3H, CH_3COOH, reflux, 75–85%; (vii) 2-aminobenzaldehyde derivatives (**9d**, **12a**, or **12d**), TFA, reflux, 61%-quant.; (viii) BBr_3, CH_2Cl_2, 0 °C to rt, 46%-quant.



Scheme 3. Reagents and conditions: (i) BBr_3, CH_2Cl_2, 0 °C to rt, 59%; (ii) **10a–d**, CH_3SO_3H, EtOH, reflux, 54–96%.



Scheme 4. Reagents and conditions: (i) Fe, 2 M HCl, EtOH, 80 °C, 36–85%; (ii) 37% HCHO, $NaBH_3CN$, CH_3COOH, CH_3CN, rt, 67%-quant.; (iii) BBr_3, CH_2Cl_2, 0 °C to rt, 72–95%.

compounds **31** with the methoxy group on the quinoline ring (Scheme 3).

Compounds **23** with the nitro group on the quinoline ring were converted to compounds **32** with an amino group on the quinoline ring by the reduction of the nitro group with Fe and 2 M HCl in ethanol (Scheme 4).[27] The resulting compounds **32** were dimethylated with 37% HCHO solution, $NaBH_3CN$ and acetic acid in acetonitrile,[28] followed by demethylation of the methoxy group by the same method as shown in Scheme 2 to afford the objective compounds **34** with the dimethylamino group on the quinoline ring.

To evaluate the binding profiles of the thus synthesized compounds for the opioid receptors, the resulting compounds **24**–**29**, **31**, and **34** were converted into the respective hydrochlorides (SYK-compounds).

2.2. Binding of the synthesized compounds to the opioid receptors

We evaluated the binding affinities and selectivities of the synthesized compounds toward opioid μ, δ, and κ receptors (Table 1). For the purpose of comparison, the results of the standard δ antagonist NTI and δ agonist KNT-127 were also determined.

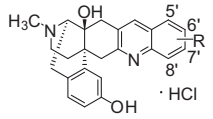
Almost all synthesized quinolinomorphinan derivatives showed high affinities and selectivities for the δ receptor. Especially, compounds with 5′-F, 8′-F, 5′-CH_3, 8′-OH or 5′-OCH_3 substituents on the quinoline ring (SYK-19, SYK-21, SYK-65, SYK-153 and SYK-336) showed higher affinities for the δ receptor than KNT-127. Compounds with 5′-Cl, 8′-Cl, 5′-CH_3, 8′-CH_3, 8′-OH, 5′-CF_3 or 8′-CF_3 substituents on the quinoline ring (SYK-27, SYK-16, SYK-65, SYK-68, SYK-153, SYK-338, and SYK-73) showed higher selectivities for the δ receptor over the μ receptor (μ/δ selectivity) than KNT-127, and compounds with 7′-F, 8′-F and 8′-OCH_3 substituents on the quinoline ring (SYK-13, SYK-21, and SYK-38) showed higher selectivities for the δ receptor over the κ receptor (κ/δ selectivity) than KNT-127. Among the synthesized compounds, SYK-153, modified with the 8′-OH substituent on the quinoline ring, showed the highest δ affinity and the most balanced and highest selectivity for the δ receptor.

3. Discussion

In an investigation of the SAR of a series of KNT-127 derivatives with various substituents on the quinoline ring, we evaluated the analogs' affinity and selectivity for the δ opioid receptor and compared the results with KNT-127. In Table 1, with regard to the influence of the position of substitution on the quinoline ring on the receptor binding properties, the compounds with 5′- or 8′-substituents showed higher affinities and more balanced selectivities for the δ receptor than the corresponding derivatives with 6′- or 7′-substituents. To the best of our knowledge, this is the first report in which the quinolinomorphinan derivatives with 5′- or 8′-substituents showed higher affinities and selectivities for the δ receptor than the corresponding derivatives bearing 6′- or 7′-substituents on the quinoline ring.

With respect to the structural properties of the substituents in the new δ agonists, steric factors such as molar refractivity (MR)[29,30] may influence the binding to the δ receptor more than electronic factors such as the electron-donating or withdrawing properties. For example, although the δ affinities of 8′-substituted compounds with an electron-donating group were significantly different from each other, they exhibited a general trend that was dependent on their size [OH (MR = 0.29), K_i = 0.092 nM; CH_3 (MR = 0.57), K_i = 0.267 nM; OCH_3 (MR = 0.79), K_i = 0.498 nM; $N(CH_3)_2$ (MR = 1.56), K_i = 0.631 nM]. We also observed similar tendencies among the compounds with the other substituents. Among the derivatives with 8′-substituents, SYK-21 (with 8′-F) showed

Table 1
The binding affinities and selectivities of SYK-compounds for opioid μ, δ, and κ receptors[a].



KNT-127 and SYK-compounds

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Compounds	R	Affinity (K_i, nM)			Selectivity	
		μ	δ	κ	μ/δ	κ/δ
NTI		15.0	0.17	9.04	88.2	53.2
KNT-127	H	21.3	0.16	153.0	133.5	960.5
SYK-27	5′-Cl	58.39	0.353	47.86	165.5	135.6
SYK-15	6′-Cl	24.93	0.583	132.01	42.7	226.5
SYK-28	7′-Cl	29.29	0.403	393.8	72.8	978.4
SYK-16	8′-Cl	34.78	0.235	126.8	147.1	538.9
SYK-19	5′-F	6.76	0.143	59.73	47.2	417.1
SYK-20	6′-F	8.27	0.730	195.5	11.3	267.9
SYK-13	7′-F	10.09	0.255	411.9	39.5	1614
SYK-21	8′-F	12.09	0.146	153.7	86.9	1052
SYK-65	5′-CH_3	31.15	0.148	71.85	210.8	486.1
SYK-66	6′-CH_3	32.44	0.340	48.66	95.55	143.3
SYK-67	7′-CH_3	34.60	0.362	187.0	95.71	517.3
SYK-68	8′-CH_3	71.51	0.267	169.9	268.1	637.0
SYK-337	5′-OH	17.18	2.725	15.45	6.30	5.67
SYK-151	6′-OH	12.00	2.447	22.70	4.90	9.28
SYK-152	7′-OH	20.32	0.280	21.98	72.6	78.5
SYK-153	8′-OH	45.05	0.092	67.24	489.7	730.9
SYK-336	5′-OCH_3	20.12	0.151	80.43	133.5	533.7
SYK-37	6′-OCH_3	29.39	0.874	77.84	33.6	89.1
SYK-154	7′-OCH_3	21.89	0.808	77.08	27.1	95.5
SYK-38	8′-OCH_3	39.84	0.498	1753	90.8	3522
SYK-338	5′-CF_3	61.01	0.244	97.29	250.0	398.7
SYK-339	6′-CF_3	52.27	0.923	97.43	56.6	105.6
SYK-72	7′-CF_3	152.6	1.291	>1000	118.2	-
SYK-73	8′-CF_3	130.7	0.493	338.4	265.1	686.4
SYK-350	5′-NO_2	12.19	0.344	36.89	35.4	107.2
SYK-70	6′-NO_2	24.48	2.655	65.83	9.22	24.7
SYK-71	7′-NO_2	20.32	1.001	280.0	20.3	279.7
SYK-349	8′-NO_2	27.71	0.218	166.3	127.1	762.8
SYK-362	5′-$N(CH_3)_2$	32.76	0.621	275.5	52.7	443.6
SYK-80	6′-$N(CH_3)_2$	33.44	0.963	348.8	34.7	362.2
SYK-81	7′-$N(CH_3)_2$	67.44	1.65	392.9	40.9	238.1
SYK-363	8′-$N(CH_3)_2$	22.25	0.631	343.3	35.3	544.1

[a] Evaluated by ability of each compound to displace [^{3}H]DAMGO (μ), [^{3}H]DPDPE (δ), or [^{3}H]U-69,593 (κ) binding to membranes of mouse whole brain without cerebellum (μ and δ) or the guinea pig cerebellum (κ). The data represent means of three samples.

high δ affinity (K_i = 0.146 nM) and SYK-153 (with 8′-OH) showed the highest δ affinity (K_i = 0.092 nM). While they (with smaller value of MR) also showed higher affinities for the δ receptor than KNT-127, the other derivatives with 8′-substituents (with larger values of MR) showed lower affinities for the δ receptor than KNT-127. These results suggest that moderately sized 8′-substituents (MR: F = 0.09, OH = 0.29) which are also hydrogen bond donors, would have especially favorable influence on the δ affinity.

Among the 7′-substituted derivatives, the compounds (SYK-13 or SYK-152) with 7′-F or 7′-OH substituent showed relatively higher affinities for the δ receptor. The affinity of SYK-152 was higher than that of the 5′-OH substituted variant (SYK-337). To account for these observations, we propose that the mesomeric electron-donating property of a 7′-F or 7′-OH substituent could increase the electron density of the nitrogen atom on the quinoline ring, thereby enhancing the association between the compounds with these substituents and the δ receptor. Although the compounds (SYK-154 or SYK-81) with a 7′-OCH_3 or 7′-$N(CH_3)_2$ substituent would be expected to show high δ affinity, they did not. The larger size of these substituents compared to those of F and OH substituents may decrease the δ affinities. The protonation of the 7′-$N(CH_3)_2$ substituent may decrease the binding affinity for the δ receptor. Contrary to our expectation, SYK-337 showed low affinity for the δ receptor in spite of possessing a small electron-donating OH substituent at the 5′-position. The existence of 5′-OH group might lead to unfavorable electronic interactions with the δ receptor. Among the 5′-substituted derivatives except those with 5′-OH substituent or 5′-$N(CH_3)$ substituent (the larger size: MR = 1.56), the compounds (SYK-19 or SYK-336) with 5′-F (MR: F = 0.09) or 5′-OCH_3 (MR: OCH_3 = 0.79) substituent showed higher affinities for the δ receptor than KNT-127. It may result from the mesomeric electron-donating property of a 5′-F or 5′-OCH_3 substituent as is the case with the compounds with 7′-F or 7′-OH substituent. SYK-65 with 5′-CH_3 substituent (MR: CH_3 = 0.57) also showed higher affinity for the δ receptor than KNT-127. These results suggest that moderately sized 5′-substituents, would have favorable

influence on the δ affinity and that the size of the 5′-substituent would have a larger influence on the affinity for the δ receptor than did that of the 7′-substituent.

In this study, almost all synthesized KNT-127 derivatives showed high affinities and selectivities for the δ receptor. The novel compounds with the quinoline skeleton as in KNT-127 were expected to provide a useful tool to clarify the real pharmacological effects via the δ receptor.

4. Conclusion

KNT-127 derivatives with 5′-F, 8′-F, 8′-OH, 5′-OCH_3 or 5′-CH_3 substituents showed higher δ affinities than KNT-127. KNT-127 derivatives with 5′-Cl, 8′-Cl, 8′-OH, 5′-CH_3, 8′-CH_3, 5′-CF_3 or 8′-CF_3 substituents showed higher μ/δ selectivity than KNT-127, and those with 7′-F, 8′-F or 8′-OCH_3 substituents showed higher κ/δ selectivity than KNT-127. These results showed that the 5′- and 8′-positions on the quinoline ring would be the most appropriate sites for modification to enhance the affinity and selectivity of the novel compounds for the δ receptor. Moreover, SYK-153, which has an 8′-OH substituent on the quinoline ring, showed the highest δ affinity and the most balanced and highest selectivity for the δ receptor among the synthesized compounds.

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 Agilent Technologies Mercury-300 or Agilent Technologies NMR System-400 for ^{1}H NMR and ^{13}C NMR. Chemical shifts were reported as δ values (ppm) related to tetramethylsilane (TMS). Mass spectra (MS) were obtained on a JMS-AX505HA, JMS-700 MStation, or JMS-100LP instrument by applying an electron ionization (EI), 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 (TLC). Column chromatographies were carried out using Kanto Silica Gel 60 N (40–100 μm).

5.1.1. 6,6-Ethylenedioxy-3-methoxy-17-(2,2,2-trichloroethoxycarbonyl)morphinan-14β-yl acetate (15)

The solution of **14** (8.8 g, 22.8 mmol) in acetic anhydride (20 mL) was refluxed under an Ar atmosphere. After 1.5 h with stirring, the reaction mixture was evaporated in vacuo and the residual solvent was azeotropically removed with toluene. To the solution of the resulting compound (10.6 g, 24.9 mmol) in 1,1,2,2-tetrachloroethane (50 mL) were added potassium carbonate (7.6 g, 55.1 mmol) and 2,2,2-trichloroethyl chloroformate (6.8 mL, 49.7 mmol), and refluxed under an Ar atmosphere. After 17 h with stirring, to the reaction mixture was added 1 M HCl 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 (110 g, $CHCl_3$/MeOH = 100/0–10/1) to give **15** (12.9 g, 95%; 2 steps from compound **14**) as a brown amorphous solid.

IR (KBr): 2957, 1742, 1712, 1432, 1248, 1137 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.09–1.19 (1H, m), 1.58–1.86 (3H, m), 2.03–2.12 (4H, m), 2.22 (1H, dt, J = 5.4, 12.9 Hz), 2.36 (1H, d, J = 14.4 Hz), 2.53–2.84 (2H, m), 2.89 (1H, d, J = 17.7 Hz), 3.25 (1H, dd, J = 5.4, 18.1 Hz), 3.77–3.98 (5H, m), 3.79 (3H, s), 4.60–4.72 (1H, m), 4.82–4.89 (1H, m), 5.46–5.49 (1H, m), 6.75 (1H, d, J = 8.6 Hz), 6.85 (1H, d, J = 2.5 Hz), 7.00 (1H, dd, J = 2.5, 8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.92, 21.94, 24.95, 24.97, 30.7, 32.5, 33.0, 34.9, 35.4, 37.4, 37.6, 37.7, 42.3, 42.6, 49.8, 49.9, 55.3, 63.9, 64.3, 74.8, 75.0, 80.2, 80.5, 95.6, 95.8, 107.78, 107.80, 112.0, 112.7, 125.4, 125.6, 128.5, 128.6, 139.7, 139.8, 153.9, 154.2, 157.68, 157.73, 169.4, 169.6. HRMS (FAB) Calcd for $C_{24}H_{28}Cl_3NO_7$Na $[M+Na]^+$: 570.0829. Found: 570.0829.

5.1.2. 6,6-Ethylenedioxy-3-methoxy-17-methylmorphinan-14β-ol (16)

To a stirred suspension of $LiAlH_4$ (3.5 g, 92.1 mmol) in THF (60 mL) was added a solution of compound **15** (5.0 g, 9.21 mmol) in THF (40 mL) at 0 °C under an Ar atmosphere and stirred at rt. After 2 h with stirring, AcOEt and saturated Na_2SO_4 aqueous solution were added to the solution. The obtained solid was removed by filtration and the filterate was concentrated in vacuo. To the residue was added water, and extracted with AcOEt. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was chromatographed on silica gel (90 g, $CHCl_3$/MeOH/25% ammonia aqueous solution = 100/0/0–100/9/1) and crystallized from AcOEt to give **16** (2.2 g, 76%) as a white prism crystal.

Mp 175–176 °C. IR (KBr): 3418, 2933, 1613, 1499, 1276, 1122, 1076, 1047, 988 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.03–1.11 (1H, m), 1.49–1.58 (2H, m), 1.70–1.78 (1H, m), 1.97–2.08 (2H, m), 2.12–2.30 (4H, m), 2.35 (3H, s), 2.68 (1H, d, J = 6.0 Hz), 2.77 (1H, dd, J = 6.0, 18.0 Hz), 3.08 (1H, d, J = 18.2 Hz), 3.75–3.80 (1H, m), 3.78 (3H, s), 3.83–3.89 (2H, m), 3.92–3.98 (1H, m), 6.70 (1H, dd, J = 2.6, 8.5 Hz), 6.74 (1H, d, J = 2.6 Hz), 6.99 (1H, d, J = 8.5 Hz), a proton (OH) was not observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.9, 29.9, 30.8, 37.4, 37.7, 41.7, 42.6, 45.6, 55.3, 62.7, 63.8, 64.3, 68.8, 109.1, 111.4, 112.5, 127.1, 127.9, 141.9, 157.2. HRMS (FAB) Calcd for $C_{20}H_{28}NO_4$ $[M+H]^+$: 346.2018. Found: 346.2013.

5.1.3. 14β-Hydroxy-3-methoxy-17-methylmorphinan-6-one (17)

The solution of **16** (1.8 g, 5.40 mmol) in 2 M HCl (8 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 AcOEt three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was crystallized from $CHCl_3$ to give **17** (1.4 g, 91%) as a white prism crystal.

Mp 194–195 °C. IR (KBr): 3430, 2927, 1718, 1506, 1238, 1036 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.13–1.21 (1H, m), 1.75–1.89 (2H, m), 2.08–2.18 (3H, m), 2.33–2.37 (1H, m), 2.40 (3H, s), 2.70–2.84 (4H, m), 3.04 (1H, d, J = 14.1 Hz), 3.15 (1H, d, J = 18.4 Hz), 3.76 (3H, s), 6.69 (1H, dd, J = 2.7, 8.4 Hz), 6.79 (1H, d, J = 2.7 Hz), 7.00 (1H, d, J = 8.4 Hz), a proton (OH) was not observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.7, 31.8, 36.8, 37.5, 42.7, 44.98, 45.01, 46.4, 55.3, 62.1, 69.1, 111.0, 112.6, 127.0, 128.5, 140.4, 158.3, 210.1. HRMS (ESI) Calcd for $C_{18}H_{24}NO_3$ $[M+H]^+$: 302.1756. Found: 302.1750.

5.1.4. 2-Amino-6-chlorobenzyl alcohol (1a)

To a solution of 6-chloroanthranilic acid (1.5 g, 8.74 mmol) in THF (5 mL) was added dropwise 1.08 M borane–tetrahydrofuran complex in THF (24.3 mL, 26.2 mmol) at 0 °C under an Ar atmosphere for 10 min. After 1.5 h with stirring at 30 °C, the solution was cooled at 0 °C, added aqueous THF (THF/H_2O = 1:1, 60 mL) and potassium carbonate, and extracted with diethyl ether three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was crystallized from AcOEt to give **1a** (1.2 g, 88%) as a white needle crystal.

Mp 76–78 °C. IR (KBr): 3388, 3107, 1451, 1004, 780 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.29 (2H, br s), 4.86 (2H, s), 6.57 (1H, dd, J = 0.9, 8.1 Hz), 6.77 (1H, dd, J = 0.9, 7.8 Hz), 7.00 (1H, t, J = 8.1 Hz), a proton (OH) was not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 59.4, 114.6, 119.1, 122.0, 129.6, 134.1, 147.9. HRMS (EI) Calcd for C_7H_8ClNO $[M]^+$: 157.0294. Found: 157.0293.

5.1.5. 2-Amino-6-chlorobenzaldehyde (7a)

To a solution of **1a** (1.2 g, 7.61 mmol) in CH_2Cl_2 (20 mL) was added MnO_2 (2.6 g, 30.1 mmol) and stirred at rt under an Ar atmosphere. After 23 h with stirring, the reaction mixture was filtrated and evaporated. The residue was crystallized from AcOEt to give **7a** (1.0 g, 85%) as a yellow needle crystal.

Mp 96–97 °C. IR (KBr): 3422, 3315, 1650, 1624, 1542, 1398, 1234, 919, 772 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ: 6.60 (1H, dd, J = 0.8, 7.6 Hz), 6.68 (1H, td, J = 0.8, 8.4 Hz), 7.18 (1H, dd, J = 7.6, 8.4 Hz), 10.41 (1H, d, J = 0.8 Hz). ^{13}C NMR (100 MHz, CD_3OD) δ: 114.6, 117.0, 117.5, 136.7, 140.2, 154.6, 193.3. HRMS (EI) Calcd for C_7H_6ClNO $[M]^+$: 155.0138. Found: 155.0141.

5.1.6. 5′-Chloro-6,7-didehydro-3-methoxy-17-methylquinolino[2′,3′:6,7]morphinan-14β-ol (18a)

To a stirred solution of **17** (100 mg, 0.33 mmol) in acetic acid (10 mL) were added methanesulfonic acid (43 μL, 0.66 mmol) and **7a** (312 mg, 2.01 mmol), and refluxed under an Ar atmosphere. After 24 h with stirring, the reaction mixture was evaporated in vacuo. The residue 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/25% ammonia aqueous solution = 200/10/1) to give **18a** (110 mg, 79%) as a white amorphous solid.

IR (KBr): 3425, 2917, 1498, 1274, 1046, 814 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.39–1.47 (1H, m), 2.20–2.29 (2H, m), 2.41–2.49 (1H, m), 2.44 (3H, s), 2.91–3.02 (3H, m), 3.13 (1H, d, J = 17.6 Hz), 3.27 (1H, d, J = 18.0 Hz), 3.58 (1H, d, J = 17.2 Hz), 3.63 (3H, s), 3.71 (1H, d, J = 17.6 Hz), 6.61 (1H, dd, J = 2.8, 8.4 Hz), 6.88 (1H, d, J = 2.8 Hz), 7.01 (1H, d, J = 8.8 Hz), 7.45 (1H, dd, J = 2.0, 7.6 Hz), 7.49 (1H, t, J = 7.6 Hz), 7.90 (1H, dd, J = 2.0, 7.2 Hz), 8.07 (1H, s), a proton (OH) was not observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.0, 36.3, 36.7, 39.3, 40.6, 43.0, 45.5, 55.1, 61.7, 69.4, 110.9, 112.1, 125.36, 125.42, 127.6 (2C), 128.0, 128.5, 129.3, 130.3, 132.0, 141.0, 147.2, 158.2, 158.3. HRMS (FAB) Calcd for $C_{25}H_{26}ClN_2O_2$ $[M+H]^+$: 421.1683. Found: 421.1680.

5.1.7. 5′-Chloro-6,7-didehydro-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol (24a)

To a stirred solution of **18a** (100 mg, 0.26 mmol) in CH_2Cl_2 (2 mL) was added 1 M BBr_3 in CH_2Cl_2 (1.6 mL, 1.6 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 6% ammonia aqueous solution, and extracted with $CHCl_3$/EtOH = 3/1 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/25% ammonia aqueous solution = 200/10/1) to give **24a** (76 mg, 71%) as a yellow amorphous solid.

IR (KBr): 3280, 2915, 1499, 1280, 1047, 808 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 1.23–1.27 (1H, m), 2.04–2.24 (2H, m), 2.37 (3H, s), 2.37–2.42 (1H, m), 2.96–2.83 (3H, m), 3.06 (1H, d, J = 17.4 Hz), 3.17 (1H, d, J = 18.3 Hz), 3.34 (1H, d, J = 17.4 Hz), 3.54 (1H, d, J = 17.4 Hz), 4.75 (1H, s), 6.45 (1H, dd, J = 2.4, 8.1 Hz), 6.67 (1H, d, J = 2.4 Hz), 6.93 (1H, d, J = 8.1 Hz), 7.63 (1H, dd, J = 2.4, 6.0 Hz), 7.64 (1H, t, J = 6.0 Hz), 7.91 (1H, dd, J = 3.0, 6.0 Hz), 8.06 (1H, s), 9.01 (1H, s). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 23.6, 36.0, 36.1, 42.6, 45.2, 52.6, 60.9, 68.9, 79.2, 111.4, 113.5, 124.5, 125.7, 126.3, 127.6, 128.5, 128.6, 129.2, 130.4, 130.9, 140.6, 146.4, 155.4, 158.7. HRMS (FAB) Calcd for $C_{24}H_{24}ClN_2O_2$ $[M+H]^+$: 407.1526. Found: 407.1520.

5.1.8. 5′-Chloro-6,7-didehydro-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol hydrochloride (SYK-27)

To a solution of **24a** in $CHCl_3$ was added HCl–MeOH dropwise. After evaporation, to the residue was added AcOEt to give a white solid. Filtration followed by drying the solid gave SYK-27 (45 mg, 98%) as a white amorphous solid.

Mp 245–247 °C (dec). Anal. Calcd for $C_{24}H_{23}ClN_2O_2 \cdot 2.0HCl \cdot 2.2H_2O$: C, 55.49; H, 5.70; N, 5.39. Found: C, 55.37; H, 5.45; N, 5.57.

5.1.9. 2-Amino-5-chlorobenzaldehyde (7b)

Compound **7b** was prepared from 2-amino-5-chrolobenzyl alcohol (**1b**) according to the procedure used to prepare compound **7a**. Yield, 83%; a yellow needle crystal.

Mp 70–72 °C. IR (KBr): 3439, 3341, 2738, 1684, 1550, 1475, 1181, 1156, 822, 729 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ: 6.73 (1H, d, J = 8.7 Hz), 7.23 (1H, dd, J = 2.4, 9.0 Hz), 7.47 (1H, d, J = 2.7 Hz), 9.74 (1H, s). ^{13}C NMR (75 MHz, CD_3OD) δ: 118.8, 120.1, 120.6, 135.1, 136.1, 150.9, 194.4. HRMS (EI) Calcd for C_7H_6ClNO $[M]^+$: 155.0138. Found: 155.0138.

5.1.10. 6′-Chloro-6,7-didehydro-3-methoxy-17-methylquinolino[2′,3′:6,7]morphinan-14β-ol (18b)

To a stirred solution of **17** (100 mg, 0.33 mmol) in ethanol (7 mL) were added methanesulfonic acid (100 μL, 1.54 mmol) and **7b** (377 mg, 2.44 mmol), and refluxed under an Ar atmosphere. After 25.5 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 ($CHCl_3$/MeOH/25% ammonia aqueous solution = 100/0/0–100/10/1) to give **18b** (123 mg, 88%) as a white amorphous solid.

IR (film): 3399, 2934, 1484, 1272, 1240, 1042, 754 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.39–1.48 (1H, m), 2.29–2.38 (2H, m), 2.51–2.66 (1H, m), 2.55 (3H, s), 2.98–3.05 (3H, m), 3.25 (1H, d, J = 19.2 Hz), 3.27 (1H, br s), 3.56 (1H, d, J = 17.6 Hz), 3.63 (3H, s), 3.68 (1H, d, J = 17.6 Hz), 6.63 (1H, dd, J = 2.8, 8.4 Hz), 6.89 (1H, d, J = 2.4 Hz), 7.01 (1H, d, J = 8.4 Hz), 7.50 (1H, dd, J = 2.4, 9.2 Hz), 7.57 (1H, s), 7.58 (1H, d, J = 2.0 Hz), 7.90 (1H, d, J = 8.8 Hz), a proton (OH) was not observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.4, 36.1, 39.2, 40.2, 42.8, 45.9, 55.1 (2C), 61.9, 69.4, 111.0, 112.3, 125.4, 127.9, 128.6, 128.9, 129.3, 129.9, 131.0, 134.4, 140.6, 144.9, 157.4, 158.4, 158.7. HRMS (ESI) Calcd for $C_{25}H_{26}ClN_2O_2$ $[M+H]^+$: 421.1683. Found: 421.1679.

5.1.11. 6′-Chloro-6,7-didehydro-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol (24b)

Compound **24b** was prepared from compound **18b** according to the procedure used to prepare **24a**. Yield, 49%; a white amorphous solid.

IR (film): 3397, 2924, 1484, 1051, 806 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ: 1.33–1.42 (1H, m), 2.23–2.32 (2H, m), 2.45 (3H, s), 2.45–2.51 (1H, m), 2.89–2.97 (2H, m), 3.01 (1H, d, J = 6.4 Hz), 3.13 (1H, d, J = 18.0 Hz), 3.29 (1H, d, J = 17.6 Hz), 3.45 (1H, d, J = 17.2 Hz), 3.62 (1H, d, J = 17.6 Hz), 6.51 (1H, dd, J = 2.4, 8.4 Hz), 6.73 (1H, d, J = 2.8 Hz), 6.97 (1H, d, J = 8.4 Hz), 7.57 (1H, dd, J = 2.4, 9.2 Hz), 7.72 (1H, d, J = 2.4 Hz), 7.75 (1H, s), 7.87 (1H, d, J = 9.2 Hz). ^{13}C NMR (100 MHz, CD_3OD) δ: 25.0, 37.2, 37.6, 39.7, 41.5, 43.2, 46.7, 63.0, 70.9, 112.8, 115.1, 127.0, 128.0, 129.4, 129.8, 129.9, 130.8, 131.4, 132.5, 136.5, 141.8, 145.4, 157.1, 159.5. HRMS (ESI) Calcd for $C_{24}H_{24}ClN_2O_2$ $[M+H]^+$: 407.1526. Found: 407.1524.

5.1.12. 6′-Chloro-6,7-didehydro-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol hydrochloride (SYK-15)

SYK-15 was prepared from compound **24b** according to the procedure used to prepare SYK-27.

Yield, quant.; a pale yellow amorphous solid. Mp: 239–243 °C (dec). Anal. Calcd for $C_{24}H_{23}ClN_2O_2 \cdot 2.0HCl \cdot 0.5H_2O$: C, 58.97; H, 5.36; N, 5.73. Found: C, 58.95; H, 5.55; N, 5.74.

5.1.13. 2-Amino-4-chlorobenzyl alcohol (1c)

Compound **1c** was prepared from 4-chroloanthranilic acid according to the procedure used to prepare compound **1a**. Yield, 88%; a yellow needle crystal.

Mp 142–144 °C. IR (KBr): 3384, 3153, 1604, 1496, 998 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.52 (2H, s), 6.60 (1H, dd, J = 2.1, 8.1 Hz), 6.73 (1H, d, J = 1.8 Hz), 7.03 (1H, d, J = 8.1 Hz), three protons (NH_2, OH) were not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 62.9, 116.1, 118.0, 125.2, 130.8, 135.0, 149.1. HRMS (FAB) Calcd for C_7H_9ClNO $[M+H]^+$: 158.0373. Found: 158.0370.

5.1.14. 2-Amino-4-chlorobenzaldehyde (7c)

Compound **7c** was prepared from compound **1c** according to the procedure used to prepare compound **7a**. Yield, 84%; a yellow needle crystal.

Mp 74–76 °C. IR (KBr): 3425, 3300, 1658, 1539, 1195, 929 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ: 6.63 (1H, dd, J = 2.0, 8.4 Hz), 6.76 (1H, d, J = 2.0 Hz), 7.47 (1H, d, J = 8.4 Hz), 9.77 (1H, s), two protons (NH_2) were not observed. ^{13}C NMR (100 MHz, CD_3OD) δ: 116.1, 116.8, 118.3, 138.4, 142.5, 153.1, 194.6. HRMS (EI) Calcd for C_7H_6ClNO $[M]^+$: 155.0138. Found: 155.0138.

5.1.15. 7′-Chloro-6,7-didehydro-3-methoxy-17-methylquinolino[2′,3′:6,7]morphinan-14β-ol (18c)

Compound **18c** was prepared from compound **17** and compound **7c** according to the procedure used to prepare compound **18b**. Yield, 89%; a yellow amorphous solid.

IR (KBr): 3413, 2908, 1618, 1486, 1275, 1046 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.38–1.47 (1H, m), 2.22–2.31 (2H, m), 2.43–2.51 (1H, m), 2.46 (3H, s), 2.92–3.08 (4H, m), 3.26 (1H, d, J = 18.8 Hz), 3.56 (1H, d, J = 17.6 Hz), 3.63 (3H, s), 3.68 (1H, d, J = 17.6 Hz), 6.62 (1H, dd, J = 2.8, 8.4 Hz), 6.88 (1H, d, J = 2.8 Hz), 7.01 (1H, d, J = 8.4 Hz), 7.33 (1H, dd, J = 2.0, 8.8 Hz), 7.53 (1H, d, J = 8.8 Hz), 7.62 (1H, s), 7.97 (1H, d, J = 2.0 Hz), a proton (OH) was not observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.1, 36.0, 36.5, 39.4, 40.5, 42.9, 45.6, 55.1, 61.7, 69.4, 110.8, 112.3, 125.6, 126.5, 127.3, 127.4, 128.0, 128.3, 128.5, 134.0, 135.0, 140.9, 146.9, 158.3, 158.4. HRMS (ESI) Calcd for $C_{25}H_{26}ClN_2O_2$ $[M+H]^+$: 421.1683. Found: 421.1663.

5.1.16. 7′-Chloro-6,7-didehydro-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol (24c)

Compound **24c** was prepared from compound **18c** according to the procedure used to prepare compound **24a**. Yield, 74%; a yellow amorphous solid.

IR (KBr): 3349, 2928, 1620, 1485, 1280, 1046 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ: 1.21–1.24 (1H, m), 2.06–2.20 (2H, m), 2.36 (3H, s), 2.36–2.42 (1H, m), 2.78–2.97 (4H, m), 3.15 (1H, d, J = 18.4 Hz), 3.29 (1H, d, J = 17.2 Hz), 3.49 (1H, d, J = 17.2 Hz), 4.76 (1H, br s), 6.43 (1H, dd, J = 2.4, 8.4 Hz), 6.65 (1H, d, J = 2.4 Hz), 6.91 (1H, d, J = 8.0 Hz), 7.46 (1H, dd, J = 2.4, 8.8 Hz), 7.78 (1H, d, J = 8.8 Hz), 7.87 (1H, s), 7.91 (1H, d, J = 2.0 Hz), 9.00 (1H, s). ^{13}C NMR (100 MHz, C_5D_5N) δ: 24.5, 36.9, 37.0, 40.4, 41.0, 43.0, 46.0, 62.2, 69.9, 113.2, 114.9, 126.3, 126.4, 126.9, 127.9, 129.2, 129.4, 130.0, 133.8, 135.2, 142.0, 147.4, 157.6, 159.9. HRMS (ESI) Calcd for $C_{24}H_{24}ClN_2O_2$ $[M+H]^+$: 407.1526. Found: 407.1516.

5.1.17. 7′-Chloro-6,7-didehydro-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol hydrochloride (SYK-28)

SYK-28 was prepared from compound **24c** according to the procedure used to prepare SYK-27.

Yield, 72%; a white amorphous solid. Mp 241–250 °C (dec). Anal. Calcd for $C_{24}H_{23}ClN_2O_2 \cdot 1.0HCl \cdot 1.0H_2O$: C, 62.48; H, 5.68; N, 6.07. Found: C, 62.66; H, 5.76; N, 5.97.

5.1.18. 2-Amino-3-chlorobenzyl alcohol (1d)

Compound **1d** was prepared from 3-chloroanthranilic acid according to the procedure used to prepare compound **1a**. Yield, 75%; a white needle crystal.

Mp 69–70 °C. IR (KBr): 3367, 1619, 1459, 999, 772, 733 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.58 (3H, br s), 4.68 (2H, s), 6.66 (1H, t, J = 7.5 Hz), 6.97 (1H, dd, J = 1.5, 7.5 Hz), 7.23 (1H, dd, J = 1.5, 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 64.3, 118.3, 120.3, 126.1, 127.5, 129.3, 142.1. HRMS (FAB) Calcd for C_7H_9ClNO $[M+H]^+$: 158.0373. Found: 158.0377.

5.1.19. 2-Amino-3-chlorobenzaldehyde (7d)

Compound **7d** was prepared from compound **1d** according to the procedure used to prepare compound **7a**. Yield, 74%; a brown needle crystal.

Mp 48–49 °C. IR (KBr): 3480, 3358, 2860, 2774, 1678, 1612, 1579, 1195, 1146, 1071, 887, 766, 727, 677 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.72 (1H, t, J = 7.5 Hz), 7.43 (1H, dd, J = 1.5, 7.5 Hz), 7.45 (1H, dd, J = 1.5, 7.5 Hz), 9.87 (1H, s), two protons (NH_2) were not observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 116.2, 119.5, 119.7, 134.4, 134.6, 145.9, 193.3. HRMS (EI) Calcd for C_7H_6ClNO $[M]^+$: 155.0138. Found: 155.0136.

5.1.20. 8′-Chloro-6,7-didehydro-3-methoxy-17-methylquinolino[2′,3′:6,7]morphinan-14β-ol (18d)

Compound **18d** was prepared from compound **17** and compound **7d** according to the procedure used to prepare compound **18b**. Yield, 76%; a white amorphous solid.

IR (film): 3417, 2915, 1501, 1274, 1242, 1042, 731 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.37–1.48 (1H, m), 2.18–2.29 (2H, m), 2.39–2.45 (1H, m), 2.43 (3H, s), 2.87–3.11 (4H, m), 3.26 (1H, d, J = 17.6 Hz), 3.63 (1H, d, J = 17.4 Hz), 3.64 (3H, s), 3.84 (1H, d, J = 17.5 Hz), 6.61 (1H, dd, J = 2.7, 8.4 Hz), 6.94 (1H, d, J = 2.7 Hz), 7.00 (1H, d, J = 8.4 Hz), 7.26 (1H, t, J = 8.0 Hz), 7.49 (1H, dd, J = 1.3, 8.2 Hz), 7.62 (1H, s), 7.66 (1H, dd, J = 1.3, 7.5 Hz), a proton (OH) was not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9, 36.0, 36.6, 39.7, 40.7, 43.0, 45.5, 55.1, 61.6, 69.3, 111.0, 112.2, 125.1, 125.9, 127.5, 128.36, 128.39, 128.5, 129.1, 132.4, 135.4, 141.1, 142.8, 158.2, 158.5. HRMS (ESI) Calcd for $C_{25}H_{26}ClN_2O_2$ $[M+H]^+$: 421.1683. Found: 421.1697.

5.1.21. 8′-Chloro-6,7-didehydro-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol (24d)

Compound **24d** was prepared from compound **18d** according to the procedure used to prepare compound **24a**. Yield, 71%; a white amorphous solid.

IR (KBr): 3347, 2916, 1447, 1281, 1241, 910, 731 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.19–1.30 (1H, m), 2.12 (1H, dt, J = 5.1, 12.5 Hz), 2.23 (1H, dt, J = 2.9, 12.5 Hz), 2.38–2.46 (1H, m), 2.42 (3H, s), 2.83–2.98 (3H, m), 3.07 (1H, d, J = 18.1 Hz), 3.24 (1H, d, J = 18.3 Hz), 3.60 (1H, d, J = 17.4 Hz), 3.80 (1H, d, J = 17.4 Hz), 6.56 (1H, dd, J = 2.4, 8.2 Hz), 6.92 (1H, d, J = 8.2 Hz), 6.98 (1H, d, J = 2.4 Hz), 7.16 (1H, t, J = 7.7 Hz), 7.33 (1H, dd, J = 1.2, 7.5 Hz), 7.44 (1H, dd, J = 1.2, 8.1 Hz), 7.62 (1H, s), two protons (OH) were not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9, 35.9, 36.2, 38.9,

40.4, 43.0, 45.5, 61.6, 69.3, 113.1, 114.4, 125.1, 125.9, 126.7, 128.45, 128.57, 128.58, 129.4, 131.7, 136.2, 140.7, 142.3, 155.2, 158.9. HRMS (ESI) Calcd for $C_{24}H_{24}ClN_2O_2$ $[M+H]^+$: 407.1526. Found: 407.1536.

5.1.22. 8′-Chloro-6,7-didehydro-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol hydrochloride (SYK-16)

SYK-16 was prepared from compound **24d** according to the procedure used to prepare SYK-27.

Yield, 55%; a yellow amorphous solid. Mp 244–248 °C (dec). Anal. Calcd for $C_{24}H_{23}ClN_2O_2{\cdot}2.0HCl{\cdot}2.5H_2O$: C, 54.92; H, 5.89; N, 5.44. Found: C, 54.92; H, 5.76; N, 5.32.

5.1.23. 2-Amino-6-fluorobenzyl alcohol (2a)

To a stirred suspension of $LiAlH_4$ (740 mg, 19.5 mmol) in THF (20 mL) was added a solution of 6-fluoroanthranilic acid (1.01 g, 6.51 mmol) in THF (10 mL) at 0 °C under an Ar atmosphere and stirred at rt. After 4 h with stirring, AcOEt and saturated Na_2SO_4 aqueous solution were added to the solution. The resulting solid was removed by filtration and the obtained filtrate was basified (pH 9) with saturated $NaHCO_3$ aqueous solution, and extracted with AcOEt three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The crude compound was chromatographed on silica gel, but not purified completely. The resulting compound **2a** was used for the next reaction without further purification.

5.1.24. 2-Amino-6-fluorobenzaldehyde (8a)

Compound **8a** was prepared from compound **2a** according to the procedure used to prepare compound **7a**. Yield, 59% (2 steps from 6-fluoroanthranilic acid); a yellow amorphous solid.

IR (KBr): 3426, 3316, 1653, 1598, 1550, 1468, 1258, 1044 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.31 (1H, ddd, J = 0.9, 8.1, 11.1 Hz), 6.39 (2H, br s), 6.40 (1H, dd, J = 0.7, 8.5 Hz), 7.23 (1H, dt, J = 6.3, 8.3 Hz), 10.3 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 101.8 (d, J = 21.3 Hz), 108.1 (d, J = 10.1 Hz), 111.9 (d, J = 3.4 Hz), 136.5 (d, J = 12.3 Hz), 151.4 (d, J = 4.3 Hz), 166.4 (d, J = 256.0 Hz), 189.2 (d, J = 11.8 Hz). HRMS (EI) Calcd for C_7H_6FNO $[M]^+$: 139.0433. Found: 139.0432.

5.1.25. 6,7-Didehydro-5′-fluoro-3-methoxy-17-methylquinolino[2′,3′:6,7]morphinan-14β-ol (19a)

Compound **19a** was prepared from compound **17** and **8a** according to the procedure used to prepare compound **18b**. Yield, 72%; a pale yellow amorphous solid.

IR (KBr): 3439, 2918, 1608, 1498, 1274, 1046 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.39–1.45 (1H, m), 2.20–2.30 (2H, m), 2.42–2.48 (1H, m), 2.43 (3H, s), 2.87–3.00 (3H, m), 3.10 (1H, d, J = 17.5 Hz), 3.26 (1H, d, J = 17.5 Hz), 3.58 (1H, d, J = 17.5 Hz), 3.63 (3H, s), 3.70 (1H, d, J = 17.5 Hz), 4.74 (1H, s), 6.62 (1H, dd, J = 2.5, 8.0 Hz), 6.89 (1H, d, J = 2.5 Hz), 7.01 (1H, d, J = 8.0 Hz), 7.04 (1H, ddd, J = 1.0, 8.5, 10.0 Hz), 7.49 (1H, dt, J = 6.0, 8.5 Hz), 7.77 (1H, dd, J = 1.0, 8.5 Hz), 7.93 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9, 35.9, 36.7, 39.5, 40.6, 43.0, 45.5, 55.1, 61.6, 69.4, 108.9 (d, J = 19.3 Hz), 110.9, 112.2, 118.0 (d, J = 16.3 Hz), 124.2 (d, J = 4.0 Hz), 127.6, 127.7 (d, J = 9.0 Hz), 128.3 (d, J = 4.3 Hz), 128.49, 128.51 (d, J = 2.8 Hz), 141.0, 147.5 (d, J = 3.2 Hz), 157.4 (d, J = 253.8 Hz), 158.2, 158.4. HRMS (FAB) Calcd for $C_{25}H_{26}FN_2O_2$ $[M+H]^+$: 405.1978. Found: 405.1974.

5.1.26. 6,7-Didehydro-5′-fluoro-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol (25a)

Compound **25a** was prepared from compound **19a** according to the procedure used to prepare compound **24a**. Yield, 72%; a white amorphous solid.

IR (KBr): 3354, 2916, 1607, 1499, 1282, 1241, 1048 cm^{-1}. ^1H NMR (300 MHz, THF-d_8) δ: 1.44–1.53 (1H, m), 2.32–2.48 (2H, m), 2.58 (3H, s), 2.65–2.74 (1H, m), 3.01–3.13 (3H, m), 3.27 (1H, d, J = 17.5 Hz), 3.41 (1H, d, J = 17.5 Hz), 3.65 (1H, d, J = 17.5 Hz), 3.74 (1H, d, J = 17.5 Hz), 4.76 (1H, s), 6.59 (1H, dd, J = 2.5, 8.0 Hz), 6.88 (1H, d, J = 2.5 Hz), 7.05 (1H, d, J = 8.0 Hz), 7.23 (1H, ddd, J = 1.0, 8.5, 10.0 Hz), 7.64 (1H, dt, J = 6.0, 8.5 Hz), 7.86 (1H, dd, J = 1.0, 8.5 Hz), 8.04–8.11 (2H, m). ^{13}C NMR (75 MHz, THF-d_8) δ: 25.1, 37.8, 38.1, 41.0, 41.8, 43.7, 47.0, 63.4, 70.5, 109.8 (d, J = 19.3 Hz), 113.0, 115.1, 119.3 (d, J = 15.9 Hz), 125.9 (d, J = 4.0 Hz), 127.6, 128.46, 128.52 (d, J = 11.6 Hz), 129.7, 131.0 (d, J = 2.6 Hz), 142.3, 149.1 (d, J = 3.2 Hz), 157.7, 158.9 (d, J = 252.6 Hz), 160.3. HRMS (FAB) Calcd for $C_{24}H_{24}FN_2O_2$ $[M+H]^+$: 391.1822. Found: 391.1819.

5.1.27. 6,7-Didehydro-5′-fluoro-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol hydrochloride (SYK-19)

SYK-19 was prepared from compound **25a** according to the procedure used to prepare SYK-27.

Yield, 87%; a pale yellow amorphous solid. Mp 227–247 °C (dec). Anal. Calcd for $C_{24}H_{23}FN_2O_2{\cdot}2.0HCl{\cdot}0.5H_2O$: C, 61.02; H, 5.55; N, 5.93. Found: C, 60.99; H, 5.76; N, 5.87.

5.1.28. 2-Amino-5-fluorobenzyl alcohol (2b)

Compound **2b** was prepared from 5-fluoroanthranilic acid according to the procedure used to prepare compound **2a**. The crude compound was chromatographed on silica gel, but not purified completely. The resulting compound **2b** was used for the next reaction without further purification.

5.1.29. 2-Amino-5-fluorobenzaldehyde (8b)

Compound **8b** was prepared from compound **2b** according to the procedure used to prepare compound **7a**. Yield, 30% (2 steps from 5-fluoroanthranilic acid); a yellow amorphous solid.

IR (KBr): 3441, 1672, 1561, 1488, 1231, 1136 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.00 (2H, br s), 6.62 (1H, dd, J = 4.0, 8.5 Hz), 7.08 (1H, ddd, J = 2.5, 8.5, 9.0 Hz), 7.17 (1H, dd, J = 2.5, 8.5 Hz), 9.80 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 117.4 (d, J = 6.7 Hz), 118.1 (d, J = 5.4 Hz), 119.4 (d, J = 21.4 Hz), 123.4 (d, J = 23.7 Hz), 146.4, 154.0 (d, J = 235.4 Hz), 192.8 (d, J = 2.6 Hz). HRMS (EI) Calcd for C_7H_6FNO $[M]^+$: 139.0433. Found: 139.0437.

5.1.30. 6,7-Didehydro-6′-fluoro-3-methoxy-17-methylquinolino[2′,3′:6,7]morphinan-14β-ol (19b)

Compound **19b** was prepared from compound **17** and **8b** according to the procedure used to prepare compound **18b**. Yield, 91%; a white amorphous solid.

IR (KBr): 3438, 2916, 1609, 1498, 1268, 1236, 1044 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.39–1.44 (1H, m), 2.20–2.30 (2H, m), 2.43 (3H, s), 2.44–2.48 (1H, m), 2.86–2.99 (3H, m), 3.06 (1H, d, J = 17.5 Hz), 3.26 (1H, d, J = 17.5 Hz), 3.55 (1H, d, J = 17.5 Hz), 3.63 (3H, s), 3.68 (1H, d, J = 17.5 Hz), 4.72 (1H, s), 6.62 (1H, dd, J = 2.5, 8.0 Hz), 6.90 (1H, d, J = 2.5 Hz), 7.01 (1H, d, J = 8.0 Hz), 7.21 (1H, dt, J = 2.5, 9.0 Hz), 7.34 (1H, ddd, J = 2.5, 8.5, 9.0 Hz), 7.59 (1H, m), 7.95 (1H, dd, J = 5.5, 8.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9, 36.0, 36.7, 39.3, 40.6, 43.0, 45.5, 55.1, 61.7, 69.4, 109.6 (d, J = 21.2 Hz), 110.9, 112.1, 118.5 (d, J = 25.8 Hz), 127.6, 127.7 (d, J = 10.0 Hz), 128.5, 129.0, 130.7 (d, J = 9.2 Hz), 134.5 (d, J = 5.2 Hz), 141.1, 143.7, 156.6 (d, J = 2.9 Hz), 158.2, 159.8 (d, J = 243.5 Hz). HRMS (FAB) Calcd for $C_{25}H_{26}FN_2O_2$ $[M+H]^+$: 405.1978. Found: 405.1974.

5.1.31. 6,7-Didehydro-6′-fluoro-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol (25b)

Compound **25b** was prepared from compound **19b** according to the procedure used to prepare compound **24a**. Yield, 75%; a white amorphous solid.

IR (KBr): 3398, 2915, 1611, 1498, 1279, 1239, 1114, 1053 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.36–1.44 (1H, m), 2.16 (1H, dd, J = 5.5, 12.5 Hz), 2.28–2.37 (1H, m), 2.42–2.49 (1H, m), 2.44 (3H, s), 2.87–3.00 (3H, m), 3.08 (1H, d, J = 17.5 Hz), 3.30 (1H, d, J = 17.5 Hz), 3.61 (1H, d, J = 17.5 Hz), 3.66 (1H, d, J = 17.5 Hz), 4.80 (1H, br s), 6.65 (1H, dd, J = 2.5, 8.0 Hz), 6.81 (1H, ddd, J = 2.5, 8.5, 9.0 Hz), 7.01 (1H, d, J = 8.0 Hz), 7.03 (1H, d, J = 2.5 Hz), 7.05–7.20 (2H, m), 7.59 (1H, m), one proton (OH) was not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.0, 35.9, 36.1, 38.6, 40.4, 43.0, 45.5, 61.6, 69.4, 109.4 (d, J = 21.6 Hz), 113.1, 115.1, 118.6 (d, J = 25.9 Hz), 126.9, 128.2, 129.0 (d, J = 3.7 Hz), 129.5 (d, J = 8.6 Hz), 129.4, 135.3 (d, J = 5.5 Hz), 140.5, 142.3, 155.4, 156.9 (d, J = 3.0 Hz), 159.7 (d, J = 248.0 Hz). HRMS (FAB) Calcd for $C_{24}H_{24}FN_2O_2$ $[M+H]^+$: 391.1822. Found: 391.1810.

5.1.32. 6,7-Didehydro-6′-fluoro-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol hydrochloride (SYK-20)

SYK-20 was prepared from compound **25b** according to the procedure used to prepare SYK-27.

Yield, 84%; a pale yellow amorphous solid. Mp 237–253 °C (dec). Anal. Calcd for $C_{24}H_{23}FN_2O_2{\cdot}2.0HCl{\cdot}0.5H_2O$: C, 61.02; H, 5.55; N, 5.93. Found: C, 61.07; H, 5.72; N, 5.99.

5.1.33. 2-Amino-4-fluorobenzyl alcohol (2c)

Compound **2c** was prepared from 4-fluoroanthranilic acid according to the procedure used to prepare compound **2a**. Yield, 77%; a white needle crystal.

Mp 100–101 °C. IR (KBr): 3389, 1616, 1600, 1510, 1161, 995, 849 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.30 (2H, br s), 4.62 (2H, s), 6.35–6.42 (2H, m), 6.94–7.02 (1H, m), a proton (OH) was not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 63.8, 102.6 (d, J = 24.8 Hz), 104.3 (d, J = 21.6 Hz), 120.5 (d, J = 2.6 Hz), 130.5 (d, J = 10.3 Hz), 147.9 (d, J = 11.0 Hz), 163.7 (d, J = 244.6 Hz). HRMS (EI) Calcd for C_7H_8FNO $[M]^+$: 141.0590. Found: 141.0592.

5.1.34. 2-Amino-4-fluorobenzaldehyde (8c)

Compound **8c** was prepared from compound **2c** according to the procedure used to prepare compound **7a**. Yield, 87%; a yellow amorphous solid.

IR (KBr): 3480, 3358, 2860, 2774, 1678, 1612, 1579, 1195, 1146, 1071, 887, 766, 727, 677 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.29 (2H, br s), 6.31 (1H, dd, J = 2.5, 10.0 Hz), 6.45 (1H, dt, J = 2.5, 8.5 Hz), 7.45 (1H, dd, J = 6.5, 8.5 Hz), 9.80 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 101.7 (d, J = 24.9 Hz), 104.8 (d, J = 23.6 Hz), 116.1 (d, J = 1.2 Hz), 138.6 (d, J = 12.5 Hz), 152.1 (d, J = 13.2 Hz), 167.3 (d, J = 254.3 Hz), 192.6. HRMS (EI) Calcd for C_7H_6FNO $[M]^+$: 139.0433. Found: 139.0452.

5.1.35. 6,7-Didehydro-7′-fluoro-3-methoxy-17-methylquinolino[2′,3′:6,7]morphinan-14β-ol (19c)

Compound **19c** was prepared from compound **17** and **8c** according to the procedure used to prepare compound **18b**. Yield, 90%; a pale yellow amorphous solid.

IR (KBr): 3415, 2928, 1629, 1499, 1273, 1240, 1046 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.39–1.45 (1H, m), 2.20–2.26 (2H, m), 2.43 (3H, s), 2.44–2.48 (1H, m), 2.86–2.99 (3H, m), 3.06 (1H, d, J = 17.5 Hz), 3.26 (1H, d, J = 17.5 Hz), 3.56 (1H, d, J = 17.5 Hz), 3.64 (3H, s), 3.68 (1H, d, J = 17.5 Hz), 4.74 (1H, s), 6.62 (1H, dd, J = 2.5, 8.0 Hz), 6.89 (1H, d, J = 2.5 Hz), 7.01 (1H, d, J = 8.0 Hz), 7.18 (1H, dt, J = 2.5, 9.0 Hz), 7.58 (1H, dd, J = 6.5, 9.0 Hz), 7.57–7.65 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9, 35.9, 36.7, 39.5, 40.6, 43.0, 45.5, 55.1, 61.6, 69.4, 110.8, 111.8 (d, J = 20.2 Hz), 112.2, 115.9 (d, J = 25.6 Hz), 124.3, 127.4 (d, J = 2.8 Hz), 127.5, 128.4, 128.7 (d, J = 10.1 Hz), 135.1, 141.1, 147.3 (d, J = 12.4 Hz), 158.2, 158.5, 162.4 (d, J = 248.0 Hz). HRMS (FAB) Calcd for $C_{25}H_{26}FN_2O_2$ $[M+H]^+$: 405.1978. Found 405.1972.

5.1.36. 6,7-Didehydro-7′-fluoro-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol (25c)

Compound **25c** was prepared from compound **19c** according to the procedure used to prepare compound **24a**. Yield, 96%; a white amorphous solid.

IR (KBr): 3276, 1628, 1500, 1282, 1239 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 1.17–1.26 (1H, m), 2.00–2.21 (2H, m), 2.34 (3H, s), 2.34–2.41 (1H, m), 2.74–2.91 (3H, m), 2.94 (1H, d, J = 17.5 Hz), 3.12 (1H, d, J = 17.5 Hz), 3.28 (1H, d, J = 17.5 Hz), 3.48 (1H, d, J = 17.5 Hz), 4.68 (1H, s), 6.42 (1H, dd, J = 2.5, 8.0 Hz), 6.65 (1H, d, J = 2.5 Hz), 6.90 (1H, d, J = 8.0 Hz), 7.36 (1H, dt, J = 2.5, 9.0 Hz), 7.59 (1H, dd, J = 2.5, 10.0 Hz), 7.82 (1H, dd, J = 6.5, 9.0 Hz), 7.85–7.89 (1H, m), 8.30 (1H, s). ^{13}C NMR (75 MHz, C_5D_5N) δ: 24.5, 36.8, 37.1, 40.4, 41.0, 43.1, 46.0, 62.2, 69.9, 112.3 (d, J = 19.7 Hz), 113.1, 114.9, 115.9 (d, J = 25.4 Hz), 125.0, 126.9, 129.0 (d, J = 2.6 Hz), 129.4, 129.8 (d, J = 10.1 Hz), 135.7, 142.0, 147.8 (d, J = 12.4 Hz), 157.6, 159.8, 162.8 (d, J = 246.3 Hz). HRMS (FAB) Calcd for $C_{24}H_{24}FN_2O_2$ $[M+H]^+$: 391.1822. Found: 391.1815.

5.1.37. 6,7-Didehydro-7′-fluoro-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol hydrochloride (SYK-13)

SYK-13 was prepared from compound **25c** according to the procedure used to prepare SYK-27.

Yield, 87%; a pale yellow amorphous solid. Mp 220–241 °C (dec). Anal. Calcd for $C_{24}H_{23}FN_2O_2{\cdot}2.0HCl{\cdot}1.0H_2O$: C, 59.88; H, 5.65; N, 5.82. Found: C, 59.83; H, 5.95; N, 5.95.

5.1.38. 2-Amino-3-fluorobenzyl alcohol (2d)

Compound **2d** was prepared from 3-fluoroanthranilic acid according to the procedure used to prepare compound **2a**. The crude compound was chromatographed on silica gel, but not purified completely. The resulting compound **2d** was used for the next reaction without further purification.

5.1.39. 2-Amino-3-fluorobenzaldehyde (8d)

Compound **8d** was prepared from compound **2d** according to the procedure used to prepare compound **7a**. Yield, 70% (2 steps from 3-fluoroanthranilic acid); a yellow amorphous solid.

IR (KBr): 3435, 1672, 1561, 1482, 1221 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.15 (2H, br s), 6.68 (1H, dt, J = 4.5, 8.0 Hz), 7.15 (1H, ddd, J = 1.5, 7.9, 11.3 Hz), 7.30 (1H, td, J = 1.1, 8.0 Hz), 9.90 (1H, d, J = 1.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 115.2 (d, J = 6.8 Hz), 119.4 (d, J = 18.4 Hz), 120.5 (d, J = 4.3 Hz), 130.4 (d, J = 3.2 Hz), 138.8 (d, J = 13.7 Hz), 150.8 (d, J = 241.3 Hz), 193.5 (d, J = 2.9 Hz). HRMS (EI) Calcd for C_7H_6FNO $[M]^+$: 139.0433. Found: 139.0432.

5.1.40. 6,7-Didehydro-8′-fluoro-3-methoxy-17-methylquinolino[2′,3′:6,7]morphinan-14β-ol (19d)

Compound **19d** was prepared from compound **17** and **8d** according to the procedure used to prepare compound **18a**. Yield, 81%; a white amorphous solid.

IR (KBr): 3443, 2902, 1609, 1497, 1275, 1044 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.39–1.45 (1H, m), 2.20–2.26 (2H, m), 2.43 (3H, s), 2.43–2.47 (1H, m), 2.86–2.99 (3H, m), 3.08 (1H, d, J = 17.5 Hz), 3.26 (1H, d, J = 17.5 Hz), 3.59 (1H, d, J = 17.5 Hz), 3.64 (3H, s), 3.82 (1H, d, J = 17.5 Hz), 4.75 (1H, s), 6.62 (1H, dd, J = 2.5, 8.0 Hz), 6.92 (1H, d, J = 2.5 Hz), 7.00 (1H, d, J = 8.0 Hz), 7.20–7.39 (3H, m), 7.65 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9, 36.1, 36.7, 39.6, 40.6, 43.0, 45.5, 55.2, 61.6, 69.3, 110.8, 112.32 (d, J = 19.0 Hz), 112.33, 122.4 (d, J = 4.5 Hz), 125.0 (d, J = 8.1 Hz), 127.5, 128.4, 129.0 (d, J = 2.8 Hz), 129.3, 134.9 (d, J = 3.2 Hz), 136.8 (d, J = 11.6 Hz), 141.1, 157.5 (d, J = 255.3 Hz), 157.9 (d, J = 1.5 Hz), 158.2. HRMS (FAB) Calcd for $C_{25}H_{26}FN_2O_2$ $[M+H]^+$: 405.1978. Found: 405.1977.

5.1.41. 6,7-Didehydro-8′-fluoro-17-methylquinolino[2′,3′:6,7] morphinan-3,14β-diol (25d)

Compound **25d** was prepared from compound **19d** according to the procedure used to prepare compound **24a**. Yield, 77%; a white amorphous solid.

IR (KBr): 3415, 2930, 1609, 1493, 1280, 1243, 1111, 1048 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.29–1.38 (1H, m), 2.15 (1H, dt, J = 4.5, 12.5 Hz), 2.25 (1H, dt, J = 2.5, 12.5 Hz), 2.38–2.45 (1H, m), 2.42 (3H, s), 2.83–2.98 (3H, m), 3.06 (1H, d, J = 17.5 Hz), 3.25 (1H, d, J = 17.5 Hz), 3.57 (1H, d, J = 17.5 Hz), 3.74 (1H, d, J = 17.5 Hz), 6.59 (1H, dd, J = 2.5, 8.0 Hz), 6.90–6.99 (3H, m), 7.14 (1H, dt, J = 4.5, 8.0 Hz), 7.28 (1H, d, J = 8.0 Hz), 7.60 (1H, s), two protons (OH) were not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9, 36.0, 36.2, 39.0, 40.5, 43.0, 45.5, 61.7, 69.4, 112.3 (d, J = 18.8 Hz), 113.0, 114.3, 122.3 (d, J = 4.5 Hz), 125.0 (d, J = 8.2 Hz), 126.8, 128.6, 128.9 (d, J = 2.7 Hz), 129.6, 135.4 (d, J = 3.0 Hz), 136.0 (d, J = 12.0 Hz), 140.7, 155.2, 156.9 (d, J = 255.5 Hz), 158.2. HRMS (FAB) Calcd for $C_{24}H_{24}FN_2O_2$ $[M+H]^+$: 391.1822. Found: 391.1832.

5.1.42. 6,7-Didehydro-8′-fluoro-17-methylquinolino[2′,3′:6,7] morphinan-3,14β-diol hydrochloride (SYK-21)

SYK-21 was prepared from compound **25d** according to the procedure used to prepare SYK-27.

Yield, 97%; a pale yellow amorphous solid. Mp 244–252 °C (dec). Anal. Calcd for $C_{24}H_{23}FN_2O_2{\cdot}2.0HCl{\cdot}0.5H_2O$: C, 61.02; H, 5.55; N, 5.93. Found: C, 61.26; H, 5.75; N, 5.93.

5.1.43. 2-Amino-6-methylbenzyl alcohol (3a)

Compound **3a** was prepared from 6-methylanthranilic acid according to the procedure used to prepare compound **1a**. Yield, 83%; a white needle crystal.

Mp 82–84 °C. IR (KBr): 3391, 3161, 1590, 1469, 998, 783, 743 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.31 (3H, s), 4.67 (2H, s), 6.55 (1H, d, J = 8.1 Hz), 6.60 (1H, d, J = 7.5 Hz), 7.00 (1H, t, J = 7.8 Hz), three protons (NH_2, OH) were not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.4, 58.7, 114.3, 120.7, 123.3, 128.7, 136.7, 146.3. HRMS (EI) Calcd for $C_8H_{11}NO$ $[M]^+$: 137.0841. Found: 137.0844.

5.1.44. 2-Amino-6-methylbenzaldehyde (9a)

Compound **9a** was prepared from compound **3a** according to the procedure used to prepare compound **7a**. Yield, 77%; a yellow amorphous solid.

IR (KBr): 3423, 3316, 1639, 1610, 1556, 1460, 1205, 1169, 782 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.56 (3H, s), 6.39 (2H, br s), 6.44 (1H, dd, J = 0.9, 7.5 Hz), 6.49 (1H, dd, J = 0.6, 8.4 Hz), 7.16 (1H, dd, J = 7.5, 8.4 Hz), 10.36 (1H, s). ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ: 19.1, 115.8, 116.8, 118.6, 135.9, 143.3, 152.7, 192.9. HRMS (EI) Calcd for C_8H_9NO $[M]^+$: 135.0684. Found: 135.0685.

5.1.45. 6,7-Didehydro-3-methoxy-5′,17-dimethylquinolino [2′,3′:6,7]morphinan-14β-ol (20a)

Compound **20a** was prepared from compound **17** and **9a** according to the procedure used to prepare compound **18b**. Yield, 51%; a white amorphous solid.

IR (KBr): 3429, 2929, 1497, 1274, 1046 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.37–1.48 (1H, m), 2.19–2.30 (2H, m), 2.39–2.46 (1H, m), 2.44 (3H, s), 2.54 (3H, s), 2.89–3.00 (3H, m), 3.12 (1H, d, J = 17.4 Hz), 3.26 (1H, d, J = 18.0 Hz), 3.57 (1H, d, J = 17.4 Hz), 3.62 (3H, s), 3.71 (1H, d, J = 17.4 Hz), 6.08 (1H, dd, J = 2.7, 8.7 Hz), 6.92 (1H, d, J = 2.4 Hz), 7.00 (1H, d, J = 8.4 Hz), 7.20 (1H, d, J = 6.9 Hz), 7.46 (1H, dd, J = 6.9, 8.4 Hz), 7.82 (1H, s), 7.83 (1H, d, J = 8.4 Hz), a proton (OH) was not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.5, 24.0, 36.3, 36.7, 39.4, 40.6, 43.0, 45.6, 55.1, 61.7, 69.5, 110.8, 112.2, 125.8, 126.6 (2C), 127.48, 127.51, 128.0, 128.4, 131.8, 133.5, 141.2, 146.8, 156.6, 158.2. HRMS (ESI) Calcd for $C_{26}H_{29}N_2O_2$ $[M+H]^+$: 401.2229. Found: 401.2215.

5.1.46. 6,7-Didehydro-5′,17-dimethylquinolino[2′,3′:6,7] morphinan-3,14β-diol (26a)

Compound **26a** was prepared from compound **20a** according to the procedure used to prepare compound **24a**. Yield, 72%; a white amorphous solid.

IR (KBr): 3411, 2928, 1498, 1281, 1049 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.36–1.40 (1H, m), 2.19 (1H, dt, J = 4.5, 12.3 Hz), 2.30 (1H, dt, J = 2.7, 12.3 Hz), 2.43–2.78 (1H, m), 2.44 (3H, s), 2.50 (3H, s), 2.88–2.98 (3H, m), 3.12 (1H, d, J = 18.0 Hz), 3.28 (1H, d, J = 18.0 Hz), 3.58 (1H, d, J = 17.4 Hz), 3.67 (1H, d, J = 17.1 Hz), 6.61 (1H, dd, J = 2.7, 8.4 Hz), 6.94 (1H, d, J = 2.4 Hz), 6.98 (1H, d, J = 8.4 Hz), 7.08 (1H, d, J = 6.9 Hz), 7.19 (1H, dd, J = 6.9, 8.4 Hz), 7.40 (1H, d, J = 8.1 Hz), 7.81 (1H, s), two protons (OH) were not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.5, 24.0, 36.2, 36.4, 38.9, 40.5, 43.1, 45.5, 61.7, 69.5, 112.9, 114.5, 125.6, 125.9, 126.5, 127.1, 127.7, 128.1, 128.8, 132.4, 133.4, 141.0, 146.0, 155.0, 156.7. HRMS (ESI) Calcd for $C_{25}H_{27}N_2O_2$ $[M+H]^+$: 387.2073. Found: 387.2059.

5.1.47. 6,7-Didehydro-5′,17-dimethylquinolino[2′,3′:6,7] morphinan-3,14β-diol hydrochloride (SYK-65)

SYK-65 was prepared from compound **26a** according to the procedures used to prepare SYK-27.

Yield, 99%; a light brown amorphous solid. Mp: 244–246 °C (dec). Anal. Calcd for $C_{25}H_{26}N_2O_2{\cdot}2.0HCl{\cdot}1.8H_2O$: C, 61.05; H, 6.48; N, 5.70. Found: C, 61.11; H, 6.69; N, 5.68.

5.1.48. 2-Amino-5-methylbenzaldehyde (9b)

Compound **9b** was prepared from 2-amino-5-methylbenzyl alcohol (**3b**) according to the procedure used to prepare compound **7a**. Yield, 60%; a yellow needle crystal.

Mp 50–51 °C. IR (KBr): 3467, 3344, 1661, 1581, 1554, 1487, 1229, 1153, 829 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ: 2.23 (3H, s), 6.66 (1H, d, J = 8.8 Hz), 7.13 (1H, ddd, J = 0.4, 2.1, 8.4 Hz), 7.27 (1H, d, J = 2.0 Hz), 9.75 (1H, d, J = 0.4 Hz). ^{13}C NMR (75 MHz, CD_3OD) δ: 20.1, 117.2, 119.6, 125.9, 136.1, 137.7, 150.3, 195.6. HRMS (EI) Calcd for C_8H_9NO $[M]^+$: 135.0684. Found: 135.0687.

5.1.49. 6,7-didehydro-3-methoxy-6′,17-dimethylquinolino [2′,3′:6,7]morphinan-14β-ol (20b)

Compound **20b** was prepared from compound **17** and **9b** according to the procedure used to prepare compound **18b**. Yield, 85%; a yellow amorphous solid.

IR (KBr): 3430, 2916, 1608, 1498, 1444, 1273, 1238, 1045, 822 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.37–1.45 (1H, m), 2.19–2.28 (2H, m), 2.39–2.49 (1H, m), 2.43 (3H, s), 2.45 (3H, s), 2.88–2.98 (3H, m), 3.06 (1H, d, J = 17.6 Hz), 3.25 (1H, d, J = 18.0 Hz), 3.55 (1H, d, J = 17.2 Hz), 3.62 (3H, s), 3.68 (1H, d, J = 17.2 Hz), 6.60 (1H, dd, J = 2.8, 8.4 Hz), 6.91 (1H, d, J = 2.8 Hz), 6.99 (1H, d, J = 8.4 Hz), 7.35 (1H, d, J = 1.6 Hz), 7.40 (1H, dd, J = 1.6, 8.4 Hz), 7.55 (1H, s), 7.86 (1H, d, J = 8.8 Hz), a proton (OH) was not observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.4, 24.0, 36.1, 36.7, 39.3, 40.6, 43.0, 45.6, 55.1, 61.7, 69.4, 110.8, 112.2, 125.6, 127.3, 127.5, 127.9 (2C), 128.4, 130.7, 134.6, 135.0, 141.2, 145.2, 156.2, 158.2. HRMS (FAB) Calcd for $C_{26}H_{29}N_2O_2$ $[M+H]^+$: 401.2229. Found: 401.2230.

5.1.50. 6,7-Didehydro-6′,17-dimethylquinolino[2′,3′:6,7] morphinan-3,14β-diol (26b)

Compound **26b** was prepared from compound **20b** according to the procedure used to prepare compound **24a**. Yield, quant.; a yellow amorphous solid.

IR (KBr): 3386, 2916, 1609, 1498, 1446, 1281, 1239, 1052, 753 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.35–1.39 (1H, m), 2.14 (1H, dt, J = 5.4, 12.6 Hz), 2.31 (1H, dt, J = 3.0, 12.0 Hz), 2.35 (3H, s), 2.39–2.44 (1H, m), 2.44 (3H, s), 2.87–2.98 (3H, m), 3.08 (1H, d,

J = 17.7 Hz), 3.28 (1H, d, J = 17.7 Hz), 3.58 (1H, d, J = 17.1 Hz), 3.68 (1H, d, J = 17.1 Hz), 6.64 (1H, dd, J = 2.4, 8.1 Hz), 6.93 (1H, dd, J = 1.8, 8.7 Hz), 6.98 (1H, d, J = 8.1 Hz), 7.05 (1H, d, J = 2.1 Hz), 7.14 (1H, d, J = 8.7 Hz), 7.21 (1H, d, J = 1.8 Hz), 7.53 (1H, s), two protons (OH) were not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.4, 24.0, 35.9, 36.1, 38.5, 40.4, 43.0, 45.5, 61.7, 69.5, 113.2, 115.0, 125.2, 126.3, 126.5, 127.2, 128.1, 128.7, 130.7, 134.9, 135.3, 140.6, 143.9, 155.6, 156.2. HRMS (FAB) Calcd for $C_{25}H_{27}N_2O_2$ $[M+H]^+$: 387.2073. Found: 387.2073.

5.1.51. 6,7-Didehydro-6′,17-dimethylquinolino[2′,3′:6,7] morphinan-3,14β-diol hydrochloride (SYK-66)

SYK-66 was prepared from compound **26b** according to the procedure used to prepare SYK-27.

Yield, 79%; a white amorphous solid. Mp 245–253 °C (dec). Anal. Calcd for $C_{25}H_{26}N_2O_2{\cdot}2.0HCl{\cdot}1.3H_2O$: C, 62.19; H, 6.39; N, 5.80. Found: C, 62.09; H, 6.33; N, 5.85.

5.1.52. 4-Methyl-2-nitrobenzyl alcohol (13)

Compound **13** was prepared from 4-methyl-2-nitrobenzoic acid according to the procedure used to prepare compound **1a**. Yield, 84%; a yellow needle crystal.

Mp: 86–87 °C. IR (KBr): 3231, 1526, 1343, 1021, 813 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.43 (3H, s), 2.76 (1H, t, J = 6.3 Hz), 4.88 (2H, d, J = 6.3 Hz), 7.45 (1H, d, J = 8.1 Hz), 7.56 (1H, d, J = 7.8 Hz), 7.88 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.8, 62.3, 125.2, 130.0, 133.8, 134.8, 139.0, 147.5. HRMS (FAB) Calcd for $C_8H_9NO_3Na$ $[M+Na]^+$: 190.0480. Found: 190.0488.

5.1.53. 2-Amino-4-methylbenzyl alcohol (3c)

To a stirred solution of compound **13** (1.4 g, 8.40 mmol) in CH_3OH (12 mL) was added 10% Pd–C (426 mg, 0.011 mmol) and stirred at rt under a H_2 atmosphere. After 24 h with stirring, the reaction mixture was filtrated and evaporated in vacuo. The residue was crystallized from CH_3OH to give **3c** (853 mg, 74%) as a white needle crystal.

Mp 138–139 °C. IR (KBr): 3383, 3201, 1002, 816 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD) δ: 2.22 (3H, s), 4.54 (2H, s), 6.51 (1H, d, J = 7.5 Hz), 6.59 (1H, s), 6.96 (1H, d, J = 7.5 Hz). ^{13}C NMR (75 MHz, CD_3OD) δ: 21.3, 63.4, 118.0, 120.0, 124.3, 129.9, 139.6, 147.1. HRMS (EI) Calcd for $C_8H_{11}NO$ $[M]^+$: 137.0841. Found: 137.0844.

5.1.54. 2-Amino-4-methylbenzaldehyde (9c)

Compound **9c** was prepared from compound **3c** according to the procedure used to prepare compound **7a**. Yield, 76%; a white needle crystal.

IR (KBr): 3489, 3365, 1663, 1625, 1577, 1542, 1201, 799 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.29 (3H, s), 6.06 (2H, br s), 6.45 (1H, d, J = 0.6 Hz), 6.56 (1H, ddd, J = 0.6, 1.6, 8.1 Hz), 7.36 (1H, dd, J = 1.8, 8.1 Hz), 9.80 (1H, dd, J = 0.6, 1.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.9, 116.0, 117.0, 117.9, 135.6, 146.4, 150.0, 193.3. HRMS (EI) Calcd for C_8H_9NO $[M]^+$: 135.0684. Found: 135.0683.

5.1.55. 6,7-Didehydro-3-methoxy-7′,17-dimethylquinolino [2′,3′:6,7]morphinan-14β-ol (20c)

Compound **20c** was prepared from compound **17** and **9c** according to the procedure used to prepare compound **18b**. Yield, 79%; a brown amorphous solid.

IR (KBr): 3423, 2911, 1499, 1275, 1045 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.36–1.46 (1H, m), 2.17–2.29 (2H, m), 2.38–2.46 (1H, m), 2.42 (3H, s), 2.50 (3H, s), 2.86–2.97 (3H, m), 3.06 (1H, d, J = 17.4 Hz), 3.25 (1H, d, J = 16.8 Hz), 3.55 (1H, d, J = 17.1 Hz), 3.62 (3H, s), 3.68 (1H, d, J = 17.4 Hz), 6.60 (1H, dd, J = 2.4, 8.4 Hz), 6.91 (1H, d, J = 2.7 Hz), 6.99 (1H, d, J = 8.4 Hz), 7.21 (1H, dd, J = 1.5, 8.1 Hz), 7.48 (1H, d, J = 8.1 Hz), 7.59 (1H, s), 7.75 (1H, d, J = 1.5 Hz), a proton (OH) was not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.8, 23.9, 36.0, 36.7, 39.5, 40.6, 43.0, 45.5, 55.1, 61.7, 69.4, 110.8, 112.2, 125.3, 126.4, 127.0, 127.3, 127.56, 127.60, 128.3, 134.9, 138.4, 141.2, 146.8, 157.0, 158.2. HRMS (ESI) Calcd for $C_{26}H_{29}N_2O_2$ $[M+H]^+$: 401.2229. Found: 401.2214.

5.1.56. 6,7-Didehydro-7′,17-dimethylquinolino[2′,3′:6,7] morphinan-3,14β-diol (26c)

Compound **26c** was prepared from compound **20c** according to the procedure used to prepare compound **24a**. Yield, quant.; a brown amorphous solid.

IR (KBr): 3400, 2916, 1500, 1447, 1283, 1239, 1052 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.35–1.39 (1H, m), 2.05 (3H, s), 2.14 (1H, dt, J = 6.3, 12.3 Hz), 2.34 (1H, dt, J = 2.7, 12.0 Hz), 2.41–2.45 (1H, m), 2.44 (3H, s), 2.89 (1H, d, J = 6.0 Hz), 2.94–2.99 (2H, m), 3.07 (1H, d, J = 17.7 Hz), 3.29 (1H, d, J = 17.4 Hz), 3.60 (1H, d, J = 17.1 Hz), 3.70 (1H, d, J = 16.8 Hz), 6.67 (1H, dd, J = 2.1, 8.1 Hz), 6.85 (1H, s), 6.96 (1H, d, J = 8.1 Hz), 7.00 (1H, d, J = 8.4 Hz), 7.13 (1H, d, J = 2.1 Hz), 7.30 (1H, d, J = 8.4 Hz), 7.54 (1H, s), two protons (OH) were not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.6, 24.0, 35.8, 36.1, 38.5, 40.4, 43.0, 45.5, 61.7, 69.5, 113.4, 115.3, 125.1, 125.5, 126.0, 126.5, 127.2, 127.6, 128.8, 135.6, 138.4, 140.5, 145.4, 155.8, 157.0. HRMS (ESI) Calcd for $C_{25}H_{27}N_2O_2$ $[M+H]^+$: 387.2073. Found: 387.2082.

5.1.57. 6,7-Didehydro-7′,17-dimethylquinolino[2′,3′:6,7] morphinan-3,14β-diol hydrochloride (SYK-67)

SYK-67 was prepared from compound **26c** according to the procedure used to prepare SYK-27.

Yield, 90%; a light brown amorphous solid. Mp 243–248 °C (dec). Anal. Calcd for $C_{25}H_{26}N_2O_2{\cdot}2.0HCl{\cdot}2.2H_2O$: C, 60.17; H, 6.54; N, 5.61. Found: C, 60.18; H, 6.58; N, 5.66.

5.1.58. 2-Amino-3-methylbenzaldehyde (9d)

Compound **9d** was prepared from 2-amino-3-methylbenzyl alcohol (**3d**) according to the procedure used to prepare compound **7a**. Yield, 87%; a yellow oil.

IR (neat): 3478, 3347, 1660, 1614, 1566, 1468, 1222 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.17 (3H, s), 6.21 (2H, br s), 6.71 (1H, t, J = 7.5 Hz), 7.24 (1H, dd, J = 1.2, 7.2 Hz), 7.38 (1H, dd, J = 1.2, 7.5 Hz), 9.88 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.5, 115.9, 118.2, 122.5, 133.7, 135.7, 148.3, 194.1. HRMS (EI) Calcd for C_8H_9NO $[M]^+$: 135.0684. Found: 135.0686.

5.1.59. 6,7-Didehydro-3-methoxy-8′,17-dimethylquinolino [2′,3′:6,7]morphinan-14β-ol (20d)

To a stirred solution of **17** (80 mg, 0.27 mmol) in trifluoroacetic acid (10 mL) were added **8d** (408 mg, 3.02 mmol) and refluxed under an Ar atmosphere. After 34 h with stirring, the reaction mixture was evaporated in vacuo, and the residue 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/25% ammonia aqueous solution = 200/10/1) to give **20d** (65 mg, 61%) as a white amorphous solid.

IR (film): 3416, 2917, 1612, 1502, 1273, 1239, 1042 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.35–1.46 (1H, m), 2.18–2.29 (2H, m), 2.37–2.44 (1H, m), 2.41 (3H, s), 2.79 (3H, s), 2.86–2.97 (3H, m), 3.05 (1H, d, J = 17.1 Hz), 3.24 (1H, d, J = 17.4 Hz), 3.58 (1H, d, J = 17.4 Hz), 3.62 (3H, s), 3.73 (1H, d, J = 17.4 Hz), 6.59 (1H, dd, J = 2.4, 8.4 Hz), 6.92 (1H, d, J = 2.4 Hz), 6.98 (1H, d, J = 8.4 Hz), 7.24 (1H, t, J = 7.5 Hz), 7.40 (1H, d, J = 7.2 Hz), 7.42 (1H, d, J = 7.8 Hz), 7.58 (1H, s), a proton (OH) was not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.1, 23.9, 36.0, 36.7, 39.8, 40.7, 43.0, 45.5, 55.0, 61.7, 69.4, 111.1, 111.9, 124.8, 124.9, 127.1, 127.5,

127.6, 128.2, 128.3, 135.1, 136.2, 141.3, 145.8, 156.1, 158.1. HRMS (ESI) Calcd for $C_{26}H_{29}N_2O_2$ $[M+H]^+$: 401.2229. Found: 401.2227.

5.1.60. 6,7-Didehydro-8′,17-dimethylquinolino[2′,3′:6,7]morphinan-3,14β-diol (26d)

Compound **26d** was prepared from compound **20d** according to the procedure used to prepare compound **24a**. Yield, 87%; a white amorphous solid.

IR (KBr): 3398, 2917, 1610, 1445, 1238, 1052, 762 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.27–1.36 (1H, m), 1.60 (3H, s), 2.18 (1H, dt, J = 6.0, 12.6 Hz), 2.35 (1H, dt, J = 3.3, 12.3 Hz), 2.42–2.47 (1H, m), 2.44 (3H, s), 2.87–3.01 (3H, m), 3.09 (1H, d, J = 18.0 Hz), 3.29 (1H, d, J = 18.3 Hz), 3.73 (1H, d, J = 16.8 Hz), 3.81 (1H, d, J = 16.8 Hz), 6.60 (1H, dd, J = 2.4, 8.4 Hz), 6.87 (1H, d, J = 6.9 Hz), 6.98 (1H, d, J = 8.1 Hz), 7.15 (1H, t, J = 7.5 Hz), 7.23 (1H, d, J = 2.4 Hz), 7.40 (1H, d, J = 8.1 Hz), 7.67 (1H, s), two protons (OH) were not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.3, 24.0, 35.8, 36.3, 38.6, 40.6, 43.0, 45.5, 61.7, 69.4, 112.9, 114.8, 124.7, 125.2, 126.6, 127.3, 128.0, 128.8, 129.2, 135.3, 136.6, 140.5, 144.9, 155.7, 157.0. HRMS (ESI) Calcd for $C_{25}H_{27}N_2O_2$ $[M+H]^+$: 387.2073. Found: 387.2062.

5.1.61. 6,7-Didehydro-8′,17-dimethylquinolino[2′,3′:6,7]morphinan-3,14β-diol hydrochloride (SYK-68)

SYK-68 was prepared from compound **26d** according to the procedure used to prepare SYK-27.

Yield, 91%; a light brown amorphous solid. Mp 238–240 °C (dec). Anal. Calcd for $C_{25}H_{26}N_2O_2{\cdot}2.0HCl{\cdot}1.2H_2O$: C, 62.42; H, 6.37; N, 5.82. Found: C, 62.57; H, 6.54; N, 5.78.

5.1.62. 2-Amino-6-methoxybenzyl alcohol (4a)

Compound **4a** was prepared from 6-methoxyanthranilic acid according to the procedure used to prepare compound **1a**. Yield, 90%; a yellow oil.

IR (neat): 3366, 1601, 1474 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.76 (3H, s), 4.70 (2H, s), 6.34 (1H, d, J = 8.1 Hz), 6.39 (1H, d, J = 8.1 Hz), 7.00 (1H, t, J = 8.1 Hz), three protons (NH_2, OH) were not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.4, 56.0, 101.9, 110.7, 114.7, 130.2, 149.1, 159.5. HRMS (EI) Calcd for $C_8H_{11}NO_2$ $[M]^+$: 153.0790. Found: 153.0793.

5.1.63. 2-Amino-6-methoxybenzaldehyde (10a)

Compound **10a** was prepared from compound **4a** according to the procedure used to prepare compound **7a**. Yield, 67%; a yellow oil.

IR (neat): 3457, 3332, 1640, 1590, 1469, 1276 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ: 3.82 (3H, s), 6.10 (1H, d, J = 8.1 Hz), 6.27 (1H, d, J = 8.4 Hz), 7.19 (1H, t, J = 8.4 Hz), 10.30 (1H, s). ^{13}C NMR (75 MHz, CD_3OD) δ: 56.0, 97.5, 109.4, 109.9, 138.0, 154.1, 164.9, 192.5. HRMS (EI) Calcd for $C_8H_9NO_2$ $[M]^+$: 151.0633. Found: 151.0631.

5.1.64. 6,7-Didehydro-3,5′-dimethoxy-17-methylquinolino[2′,3′:6,7]morphinan-14β-ol (21a)

Compound **21a** was prepared from compound **17** and **10a** according to the procedure used to prepare compound **18b**. Yield, 77%; a white amorphous solid.

IR (KBr): 3427, 2910, 1569, 1258, 1046, 810 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.34–1.46 (1H, m), 2.17–2.28 (2H, m), 2.38–2.44 (1H, m), 2.41 (3H, s), 2.87–2.97 (3H, m), 3.08 (1H, d, J = 17.4 Hz), 3.24 (1H, d, J = 17.4 Hz), 3.56 (1H, d, J = 17.1 Hz), 3.61 (3H, s), 3.67 (1H, d, J = 17.1 Hz), 3.90 (3H, s), 6.58 (1H, dd, J = 2.7, 8.4 Hz), 6.69 (1H, d, J = 7.5 Hz), 6.88 (1H, d, J = 2.7 Hz), 6.98 (1H, d, J = 8.4 Hz), 7.46 (1H, t, J = 7.8 Hz), 7.57 (1H, d, J = 8.4 Hz), 8.07 (1H, s), a proton (OH) was not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9, 36.1, 36.6, 39.4, 40.6, 43.0, 45.5, 55.1, 55.6, 61.7, 69.4, 103.1, 110.8, 112.2, 119.7, 120.6, 127.2, 127.6, 128.1, 128.3, 130.0, 141.1, 147.4, 154.6, 157.4, 158.1. HRMS (ESI) Calcd for $C_{26}H_{29}N_2O_3$ $[M+H]^+$: 417.2178. Found: 417.2174.

5.1.65. 6,7-Didehydro-17-methylquinolino[2′,3′:6,7]morphinan-3,5′,14β-triol (27a)

To a stirred solution of **21a** (75 mg, 0.18 mmol) in CH_2Cl_2 (10 mL) was added 1 M BBr_3 in CH_2Cl_2 (1.6 mL, 1.6 mmol) at 0 °C and refluxed under an Ar atmosphere. After 20 h with stirring, the reaction mixture was basified (pH 9) with 6% ammonia aqueous solution, and extracted with $CHCl_3$/EtOH = 3/1 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/25% ammonia aqueous solution = 200/10/1) to give a compound **27a** (47 mg, 68%) as a yellow amorphous solid.

IR (KBr): 3369, 1573, 1449, 1375, 1281, 812, 754 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ: 1.28–1.40 (1H, m), 2.21–2.32 (2H, m), 2.44 (3H, s), 2.44–2.54 (1H, m), 2.89–3.02 (3H, m), 3.13 (1H, d, J = 17.4 Hz), 3.26 (1H, d, J = 17.4 Hz), 3.42 (1H, d, J = 17.4 Hz), 3.61 (1H, d, J = 17.4 Hz), 6.52 (1H, dd, J = 2.4, 8.4 Hz), 6.74 (1H, d, J = 2.4 Hz), 6.76 (1H, dd, J = 1.5, 6.6 Hz), 6.96 (1H, d, J = 8.4 Hz), 7.39 (1H, t, J = 6.6 Hz), 7.41 (1H, dd, J = 1.5, 6.6 Hz), 8.17 (1H, s). ^{13}C NMR (75 MHz, CD_3OD) δ: 25.0, 37.3, 37.6, 39.5, 41.4, 43.2, 46.7, 63.2, 71.0, 108.8, 112.8, 115.1, 118.4, 120.8, 127.9, 128.3, 129.9, 130.5, 132.5, 141.9, 148.2, 154.6, 157.0, 158.5. HRMS (ESI) Calcd for $C_{24}H_{25}N_2O_3$ $[M+H]^+$:389.1865. Found: 389.1862.

5.1.66. 6,7-Didehydro-17-methylquinolino[2′,3′:6,7]morphinan-3,5′,14β-triol hydrochloride (SYK-337)

SYK-337 was prepared from compound **27a** according to the procedure used to prepare SYK-27.

Yield, 70%; a brown amorphous solid. Mp 265–268 °C (dec). Anal. Calcd for $C_{24}H_{24}N_2O_3{\cdot}2.0HCl{\cdot}1.8H_2O$: C, 58.37; H, 6.04; N, 5.67. Found: C, 58.58; H, 5.86; N, 5.69.

5.1.67. 17-Methyl-3,14β-hydroxymorphinan-6-one (30)

Compound **30** was prepared from compound **17** according to the procedure used to prepare compound **24a**. Yield, 59%; a white prism crystal.

Mp 234 °C. IR (KBr): 3197, 1686, 1583, 1502, 1237, 950 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.15–1.20 (1H, m), 1.77–1.82 (1H, m), 1.88 (1H, dt, J = 5.2, 13.2 Hz), 2.10–2.20 (3H, m), 2.33–2.42 (1H, m), 2.39 (3H, s), 2.68–2.87 (4H, m), 3.04 (1H, d, J = 14.0 Hz), 3.13 (1H, d, J = 18.4 Hz), 6.65 (1H, dd, J = 2.4, 8.4 Hz), 6.87 (1H, d, J = 2.4 Hz), 6.94 (1H, d, J = 8.4 Hz), two protons (OH) were not observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.7, 31.6, 36.7, 37.5, 42.7, 44.9 (2C), 46.3, 62.1, 69.2, 112.5, 114.2, 126.3, 128.7, 140.1, 155.0, 212.1. HRMS (FAB) Calcd for $C_{17}H_{22}NO_3$ $[M+H]^+$: 288.1600. Found 288.1595.

5.1.68. 6,7-Didehydro-5′-methoxy-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol (31a)

Compound **31a** was prepared from compound **30** and **10a** according to the procedure used to prepare compound **18b**. Yield, 59%; a yellow amorphous solid.

IR (KBr): 3348, 2932, 1470, 1262, 809 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.35–1.46 (1H, m), 2.16–2.28 (2H, m), 2.37–2.44 (1H, m), 2.42 (3H, s), 2.87–2.98 (3H, m), 3.09 (1H, d, J = 17.7 Hz), 3.25 (1H, d, J = 17.4 Hz), 3.59 (1H, d, J = 17.7 Hz), 3.86 (1H, d, J = 17.4 Hz), 4.06 (3H, s), 6.60 (1H, dd, J = 2.7, 8.4 Hz), 6.91 (1H, dd, J = 1.2, 7.8 Hz), 6.97 (1H, d, J = 2.4 Hz), 6.99 (1H, d, J = 8.4 Hz), 7.16 (1H, dd, J = 1.2, 8.1 Hz), 7.28 (1H, t, J = 8.1 Hz), 7.61 (1H, s), two protons (OH) were not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.0, 36.0, 36.2, 38.6, 40.4, 43.0, 45.5, 55.5, 61.7, 69.5, 103.2, 113.0, 114.8, 119.2, 119.6, 126.7, 127.3, 128.2, 128.7, 130.8, 140.6, 146.2,

154.2, 155.5, 157.4. HRMS (ESI) Calcd for $C_{25}H_{27}N_2O_3$ $[M+H]^+$: 403.2022. Found: 403.2027.

5.1.69. 6,7-Didehydro-5′-methoxy-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol hydrochloride (SYK-336)

SYK-336 was prepared from compound **31a** according to the procedure used to prepare SYK-27.

Yield, 99%; a yellow amorphous solid. Mp 246–250 °C (dec). Anal. Calcd for $C_{25}H_{26}N_2O_3{\cdot}2.0HCl{\cdot}0.5H_2O$: C, 61.99; H, 6.03; N, 5.78. Found: C, 62.03; H, 6.13; N, 5.89.

5.1.70. 2-Amino-5-methoxybenzyl alcohol (4b)

Compound **4b** was prepared from 5-methoxyanthranilic acid according to the procedure used to prepare compound **1a**. Yield, 78%; a brown amorphous solid.

IR (KBr): 3383, 1508, 1256, 1049, 1017, 868 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.71 (3H, s), 4.54 (2H, s), 6.61 (1H, d, J = 8.4 Hz), 6.64 (1H, d, J = 2.8 Hz), 6.69 (1H, dd, J = 2.8, 8.4 Hz), three protons (NH_2, OH) were not observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.8, 63.9, 114.4, 114.9, 117.4, 126.7, 139.1, 152.5. HRMS (EI) Calcd for $C_8H_{11}NO_2$ $[M]^+$: 153.0790. Found: 153.0789.

5.1.71. 2-Amino-5-methoxybenzaldehyde (10b)

Compound **10b** was prepared from compound **4b** according to the procedure used to prepare compound **7a**. Yield, 57%; a yellow oil.

IR (neat): 3460, 3350, 1661, 1556, 1488, 1239, 1160, 1036 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.79 (3H, s), 5.84 (2H, br s), 6.62 (1H, d, J = 8.8 Hz), 6.96 (1H, d, J = 3.2 Hz), 7.00 (1H, dd, J = 3.2, 8.8 Hz), 9.84 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.9, 116.7, 117.7, 118.4, 124.6, 144.8, 150.7, 193.5. HRMS (EI) Calcd for $C_8H_9NO_2$ $[M]^+$: 151.0633. Found: 151.0625.

5.1.72. 6,7-Didehydro-3,6′-dimethoxy-17-methylquinolino[2′,3′:6,7]morphinan-14β-ol (21b)

Compound **21b** was prepared from compound **17** and **10b** according to the procedure used to prepare compound **18b**. Yield, 67%; a white amorphous solid.

IR (KBr): 3428, 2916, 1606, 1496, 1225, 1043, 828 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.35–1.46 (1H, m), 2.18–2.29 (2H, m), 2.39–2.46 (1H, m), 2.42 (3H, s), 2.85–2.98 (3H, m), 3.05 (1H, d, J = 17.4 Hz), 3.25 (1H, d, J = 17.1 Hz), 3.53 (1H, d, J = 17.4 Hz), 3.62 (3H, s), 3.66 (1H, d, J = 17.4 Hz), 3.85 (3H, s), 6.60 (1H, dd, J = 2.7, 8.4 Hz), 6.84 (1H, d, J = 2.7 Hz), 6.91 (1H, d, J = 2.7 Hz), 7.00 (1H, d, J = 8.4 Hz), 7.22 (1H, dd, J = 2.7, 9.3 Hz), 7.50 (1H, s), 7.86 (1H, d, J = 9.3 Hz), a proton (OH) was not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.0, 36.1, 36.7, 39.2, 40.6, 43.0, 45.5, 55.1, 55.4, 61.7, 69.4, 104.3, 110.9, 112.1, 121.0, 127.5, 128.1, 128.2, 128.4, 129.7, 134.1, 141.3, 142.7, 154.5, 156.9, 158.2. HRMS (ESI) Calcd for $C_{26}H_{29}N_2O_3$ $[M+H]^+$: 417.2178. Found: 417.2177.

5.1.73. 6,7-Didehydro-17-methylquinolino[2′,3′:6,7]morphinan-3,6′,14β-triol (27b)

Compound **27b** was prepared from compound **21b** according to the procedure used to prepare compound **27a**. Yield, 77%; a white amorphous solid.

IR (KBr): 3368, 1609, 1499, 1238 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ: 1.22–1.32 (1H, m), 2.12–2.25 (2H, m), 2.33–2.45 (1H, m), 2.38 (3H, s), 2.76–2.95 (3H, m), 3.02 (1H, d, J = 18.0 Hz), 3.22 (1H, d, J = 18.0 Hz), 3.36 (1H, d, J = 17.4 Hz), 3.55 (1H, d, J = 17.4 Hz), 6.52 (1H, dd, J = 2.4, 8.4 Hz), 6.75 (1H, d, J = 2.4 Hz), 6.87 (1H, d, J = 2.7 Hz), 6.94 (1H, d, J = 8.4 Hz), 7.17 (1H, dd, J = 2.7, 9.3 Hz), 7.47 (1H, s), 7.73 (1H, d, J = 9.3 Hz). ^{13}C NMR (75 MHz, CD_3OD) δ: 25.0, 37.1, 37.6, 39.2, 41.4, 43.2, 46.6, 63.1, 70.9, 108.8, 112.8, 115.1, 122.6, 127.9, 129.1, 129.88, 129.91, 130.1, 135.8, 142.0, 142.3, 155.1, 156.5, 157.0. HRMS (ESI) Calcd for $C_{24}H_{25}N_2O_3$ $[M+H]^+$: 389.1865. Found: 389.1854.

5.1.74. 6,7-Didehydro-17-methylquinolino[2′,3′:6,7]morphinan-3,6′,14β-triol hydrochloride (SYK-151)

SYK-151 was prepared from compound **27b** according to the procedure used to prepare SYK-27.

Yield, 91%; a browned yellow amorphous solid. Mp 249–250 °C (dec). Anal. Calcd for $C_{24}H_{24}N_2O_3{\cdot}2.0HCl{\cdot}1.0H_2O$: C, 60.13; H, 5.89; N, 5.84. Found: C, 59.91; H, 6.03; N, 5.92.

5.1.75. 6,7-Didehydro-6′-methoxy-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol (31b)

Compound **31b** was prepared from compound **30** and **10b** according to the procedure used to prepare compound **18b**. Yield, 96%; a white amorphous solid.

IR (KBr): 3389, 2914, 1608, 1498, 1224, 1051, 911, 754 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.30–1.37 (1H, m), 2.10 (1H, dt, J = 5.6, 12.8 Hz), 2.30 (1H, dt, J = 3.2, 12.4 Hz), 2.37–2.45 (1H, m), 2.41 (3H, s), 2.85–2.98 (3H, m), 3.04 (1H, d, J = 17.6 Hz), 3.26 (1H, d, J = 17.6 Hz), 3.54 (1H, d, J = 16.8 Hz), 3.64 (1H, d, J = 16.8 Hz), 3.77 (3H, s), 6.58 (1H, dd, J = 2.8, 9.2 Hz), 6.64 (1H, d, J = 3.2 Hz), 6.66 (1H, dd, J = 2.4, 8.0 Hz), 6.93 (1H, d, J = 9.2 Hz), 6.97 (1H, d, J = 8.4 Hz), 7.06 (1H, d, J = 2.4 Hz), 7.41 (1H, s), two protons (OH) were not observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.0, 35.9, 36.0, 38.2, 40.4, 43.0, 45.5, 55.1, 61.8, 69.5, 103.8, 113.4, 115.1, 121.3, 126.5, 127.6, 128.0, 128.5, 128.8, 134.9, 140.6, 141.2, 154.5, 155.8, 156.8. HRMS (ESI) Calcd for $C_{25}H_{27}N_2O_3$ $[M+H]^+$: 403.2022; Found 403.2023.

5.1.76. 6,7-Didehydro-6′-methoxy-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol hydrochloride (SYK-37)

SYK-37 was prepared from compound **31b** according to the procedure used to prepare SYK-27.

Yield, 43%; a white amorphous solid. Mp: 241–242 °C (dec). Anal. Calcd for $C_{25}H_{26}N_2O_3{\cdot}2.0HCl{\cdot}0.8H_2O$: C, 61.30; H, 6.09; N, 5.72. Found: C, 61.27; H, 6.38; N, 5.77.

5.1.77. 2-Amino-4-methoxybenzyl alcohol (4c)

Compound **4c** was prepared from 4-methoxyanthranilic acid according to the procedure used to prepare compound **1a**. Yield, 66%; a white needle crystal.

Mp: 75–76 °C. IR (KBr): 3394, 3210, 1621, 1515, 1166, 995, 856 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.74 (3H, s), 4.55 (2H, s), 6.22 (1H, d, J = 2.4 Hz), 6.25 (1H, dd, J = 2.4, 7.8 Hz), 6.93 (1H, d, J = 7.8 Hz), three protons (NH_2, OH) were not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.1, 63.6, 101.7, 103.1, 117.9, 130.3, 147.2, 160.7. HRMS (EI) Calcd for $C_8H_{11}NO_2$ $[M]^+$: 153.0790. Found: 153.0793.

5.1.78. 2-Amino-4-methoxybenzaldehyde (10c)

Compound **10c** was prepared from compound **4c** according to the procedure used to prepare compound **7a**. Yield, 75%; a yellow amorphous solid.

IR (KBr): 3425, 3317, 1651, 1621, 1209 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.80 (3H, s), 6.06 (1H, d, J = 2.4 Hz), 6.24 (2H, br s), 6.31 (1H, dd, J = 2.4, 8.7 Hz), 7.36 (1H, d, J = 8.4 Hz), 9.70 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.3, 98.4, 105.1, 113.8, 137.7, 152.2, 165.2, 192.0. HRMS (EI) Calcd for $C_8H_9NO_2$ $[M]^+$: 151.0633. Found: 151.0627.

5.1.79. 6,7-Didehydro-3,7′-dimethoxy-17-methylquinolino[2′,3′:6,7]morphinan-14β-ol (21c)

Compound **21c** was prepared from compound **17** and **10c** according to the procedure used to prepare compound **18b**. Yield, 49%; a yellow amorphous solid.

IR (KBr): 3423, 1623, 1500, 1243, 1042 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.34–1.45 (1H, m), 2.17–2.28 (2H, m), 2.38–2.44 (1H, m), 2.41 (3H, s), 2.83–2.98 (3H, m), 3.03 (1H, d,

J = 17.4 Hz), 3.24 (1H, d, *J* = 17.4 Hz), 3.53 (1H, d, *J* = 17.1 Hz), 3.62 (3H, s), 3.66 (1H, d, *J* = 17.1 Hz), 3.90 (3H, s), 6.60 (1H, dd, *J* = 2.7, 8.4 Hz), 6.91 (1H, d, *J* = 2.7 Hz), 6.99 (1H, d, *J* = 8.4 Hz), 7.02 (1H, dd, *J* = 2.4, 9.0 Hz), 7.31 (1H, d, *J* = 2.4 Hz), 7.45 (1H, d, *J* = 9.0 Hz), 7.53 (1H, s), a proton (OH) was not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.0, 35.8, 36.7, 39.4, 40.5, 42.9, 45.5, 55.1, 55.3, 61.7, 69.4, 106.2, 110.9, 112.0, 118.6, 122.5, 125.5, 127.5, 127.7, 128.3, 135.0, 141.2, 148.0, 157.1, 158.2, 159.9. HRMS (ESI) Calcd for $C_{26}H_{29}N_2O_3$ $[M+H]^+$: 417.2178. Found: 417.2177.

5.1.80. 6,7-Didehydro-17-methylquinolino[2′,3′:6,7]morphinan-3,7′,14β-triol (27c)

Compound **27c** was prepared from compound **21c** according to the procedure used to prepare compound **27a**. Yield, 71%; a white amorphous solid.

IR (KBr): 3423, 1619, 1476, 1244, 1047 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD) δ: 1.26–1.37 (1H, m), 2.18–2.29 (2H, m), 2.38–2.51 (1H, m), 2.42 (3H, s), 2.80 (1H, d, *J* = 17.7 Hz), 2.87–2.99 (2H, m), 3.05 (1H, d, *J* = 17.7 Hz), 3.26 (1H, d, *J* = 18.0 Hz), 3.38 (1H, d, *J* = 17.4 Hz), 3.56 (1H, d, *J* = 17.4 Hz), 6.52 (1H, dd, *J* = 2.4, 8.4 Hz), 6.74 (1H, d, *J* = 2.7 Hz), 6.80 (1H, d, *J* = 8.4 Hz), 7.00 (1H, dd, *J* = 2.4, 8.7 Hz), 7.18 (1H, d, *J* = 2.4 Hz), 7.50 (1H, d, *J* = 9.0 Hz), 7.61 (1H, s). ^{13}C NMR (75 MHz, CD_3OD) δ: 25.1, 36.9, 37.6, 39.4, 41.4, 43.2, 46.7, 63.1, 71.0, 108.9, 112.8, 115.0, 119.9, 123.4, 126.5, 128.0, 129.5, 129.8, 137.4, 142.0, 148.7, 157.0, 158.3, 160.2. HRMS (ESI) Calcd for $C_{24}H_{25}N_2O_3$ $[M+H]^+$: 389.1865. Found: 389.1866.

5.1.81. 6,7-Didehydro-17-methylquinolino[2′,3′:6,7]morphinan-3,7′,14β-triol hydrochloride (SYK-152)

SYK-152 was prepared from compound **27c** according to the procedure used to prepare SYK-27.

Yield, 70%; a browned yellow amorphous solid. Mp 249–250 °C (dec). Anal. Calcd for $C_{24}H_{24}N_2O_3{\cdot}2.0HCl{\cdot}2.0H_2O$: C, 57.95; H, 6.08; N, 5.63. Found: C, 58.12; H, 6.21; N, 5.68.

5.1.82. 6,7-Didehydro-7′-methoxy-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol (31c)

Compound **31c** was prepared from compound **30** and **10c** according to the procedure used to prepare compound **18b**. Yield, 54%; a yellow amorphous solid.

IR (KBr): 3424, 1627, 1500, 1459 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.45–1.49 (1H, m), 2.19 (1H, dt, *J* = 5.8, 12.6 Hz), 2.36 (1H, dt, *J* = 3.2, 11.8 Hz), 2.41–2.50 (1H, m), 2.44 (3H, s), 2.91–3.02 (4H, m), 3.07 (3H, s), 3.31 (1H, d, *J* = 18.4 Hz), 3.63 (1H, d, *J* = 17.0 Hz), 3.70 (1H, d, *J* = 17.0 Hz), 5.96 (1H, d, *J* = 2.4 Hz), 6.62 (1H, dd, *J* = 2.5, 9.0 Hz), 6.73 (1H, dd, *J* = 2.4, 8.2 Hz), 6.99 (1H, d, *J* = 8.3 Hz), 7.13 (1H, d, *J* = 9.0 Hz), 7.15 (1H, d, *J* = 2.5 Hz), 7.42 (1H, s), two protons (OH) were not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.0, 35.7, 35.9, 38.4, 40.4, 43.1, 45.5, 54.5, 61.7, 69.5, 103.8, 115.1, 116.4, 118.8, 122.2, 125.4, 127.1, 127.3, 128.7, 135.5, 140.6, 146.3, 155.6, 157.0, 159.3. HRMS (ESI) Calcd for $C_{25}H_{27}N_2O_3$ $[M+H]^+$: 403.2022. Found: 403.2026.

5.1.83. 6,7-Didehydro-7′-methoxy-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol hydrochloride (SYK-154)

SYK-154 was prepared from compound **31c** according to the procedure used to prepare SYK-27.

Yield, 84%; a yellow amorphous solid. Mp 249–250 °C (dec). Anal. Calcd for $C_{25}H_{26}N_2O_3{\cdot}2.0HCl{\cdot}2.0H_2O$: C, 57.95; H, 6.08; N, 5.63. Found: C, 58.12; H, 6.21; N, 5.68.

5.1.84. 2-Amino-3-methoxybenzyl alcohol (4d)

Compound **4d** was prepared from 3-methoxyanthranilic acid according to the procedure used to prepare compound **1a**. Yield, quant.; a brown oil.

IR (neat): 3367, 1618, 1484, 1240, 1003, 735 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.86 (3H, s), 4.66 (2H, s), 6.68 (1H, t, *J* = 7.6 Hz), 6.72 (1H, dd, *J* = 1.6, 7.6 Hz), 6.79 (1H, dd, *J* = 1.6, 7.6 Hz), three protons (NH_2, OH) were not observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.6, 63.7, 110.2, 117.3, 121.1, 125.1, 135.5, 147.4. HRMS (EI) Calcd for $C_8H_{11}NO_2$ $[M]^+$: 153.0790. Found: 153.0791.

5.1.85. 2-Amino-3-methoxybenzaldehyde (10d)

Compound **10d** was prepared from compound **4d** according to the procedure used to prepare compound **7a**. Yield, 74%; a yellow oil.

IR (neat): 3484, 3357, 1664, 1550, 1478, 1268, 1222, 718 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.86 (3H, s), 6.66 (1H, t, *J* = 8.0 Hz), 6.86 (1H, dd, *J* = 0.8, 8.0 Hz), 7.10 (1H, dd, *J* = 1.2, 8.0 Hz), 9.87 (1H, s), two protons (NH_2) were not observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.6, 113.5, 114.9, 118.6, 126.4, 140.8, 146.5, 193.8. HRMS (EI) Calcd for $C_8H_9NO_2$ $[M]^+$: 151.0633. Found: 151.0641.

5.1.86. 6,7-Didehydro-3,8′-dimethoxy-17-methylquinolino[2′,3′:6,7]morphinan-14β-ol (21d)

Compound **21d** was prepared from compound **17** and **10d** according to the procedure used to prepare compound **18b**. Yield, 63%; a yellow amorphous solid.

IR (KBr): 3410, 2933, 1494, 1264, 1042, 752 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.35–1.46 (1H, m), 2.17–2.28 (2H, m), 2.39–2.44 (1H, m), 2.42 (3H, s), 2.87–2.98 (3H, m), 3.08 (1H, d, *J* = 17.1 Hz), 3.25 (1H, d, *J* = 17.1 Hz), 3.59 (1H, d, *J* = 17.7 Hz), 3.63 (3H, s), 3.86 (1H, d, *J* = 17.7 Hz), 4.06 (3H, s), 6.60 (1H, dd, *J* = 2.6, 8.4 Hz), 6.91 (1H, dd, *J* = 1.1, 7.7 Hz), 6.96 (1H, d, *J* = 2.6 Hz), 6.99 (1H, d, *J* = 8.4 Hz), 7.16 (1H, dd, *J* = 1.2, 8.3 Hz), 7.28 (1H, t, *J* = 8.0 Hz), 7.61 (1H, s), a proton (OH) was not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.0, 36.0, 36.8, 39.6, 40.6, 42.9, 45.5, 55.2, 55.9, 61.7, 69.3, 106.6, 111.3, 111.9, 118.8, 125.3, 127.5, 128.28, 128.34, 128.5, 135.1, 138.6, 141.4, 154.8, 156.2, 158.2. HRMS (ESI) Calcd for $C_{26}H_{28}N_2NaO_3$ $[M+Na]^+$: 439.1998. Found: 439.1993.

5.1.87. 6,7-Didehydro-17-methylquinolino[2′,3′:6,7]morphinan-3,8′,14β-triol (27d)

Compound **27d** was prepared from compound **21d** according to the procedure used to prepare compound **27a**. Yield, 57%; a yellow oil.

IR (neat): 3367, 2919, 1496, 1239, 753 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD) δ: 1.28–1.38 (1H, m), 2.18–2.30 (2H, m), 2.40–2.48 (1H, m), 2.41 (3H, s), 2.83–2.98 (3H, m), 3.09 (1H, d, *J* = 17.7 Hz), 3.25 (1H, d, *J* = 17.7 Hz), 3.42 (1H, d, *J* = 17.4 Hz), 3.70 (1H, d, *J* = 17.4 Hz), 6.51 (1H, dd, *J* = 2.4, 8.3 Hz), 6.79 (1H, d, *J* = 2.4 Hz), 6.94 (1H, dd, *J* = 1.1, 7.6 Hz), 6.95 (1H, d, *J* = 8.3 Hz), 7.10 (1H, dd, *J* = 1.1, 8.3 Hz), 7.22 (1H, t, *J* = 7.9 Hz), 7.64 (1H, s). ^{13}C NMR (75 MHz, CD_3OD) δ: 25.0, 37.2, 37.7, 39.8, 41.5, 43.2, 46.7, 63.1, 71.1, 110.9, 113.0, 115.0, 118.4, 127.3, 128.0, 129.5, 129.8, 130.3, 136.5, 138.2, 142.2, 153.3, 156.88, 156.90. HRMS (ESI) Calcd for $C_{24}H_{25}N_2O_3$ $[M+H]^+$: 389.1865. Found: 389.1880.

5.1.88. 6,7-Didehydro-17-methylquinolino[2′,3′:6,7]morphinan-3,8′,14β-triol hydrochloride (SYK-153)

SYK-153 was prepared from compound **27d** according to the procedure used to prepare SYK-27.

Yield, 85%; a browned yellow amorphous solid. Mp 237–239 °C (dec). Anal. Calcd for $C_{24}H_{24}N_2O_3{\cdot}2.0HCl{\cdot}1.2H_2O$: C, 59.68; H, 5.93; N, 5.80. Found: C, 59.44; H, 5.92; N, 5.77.

5.1.89. 6,7-Didehydro-8′-methoxy-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol (31d)

Compound **31d** was prepared from compound **30** and **10d** according to the procedure used to prepare compound **18b**. Yield, 60%; a white amorphous solid.

IR (KBr): 3408, 2932, 1609, 1473, 1265, 1111, 1051, 753 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.30–1.38 (1H, m), 2.13 (1H, dt, J = 5.6, 12.8 Hz), 2.28 (1H, dt, J = 2.8, 12.0 Hz), 2.36–2.44 (1H, m), 2.41 (3H, s), 2.88 (1H, dd, J = 6.8, 18.4 Hz), 2.94 (1H, d, J = 17.6 Hz), 2.94–3.01 (1H, m), 2.98 (3H, s), 3.04 (1H, d, J = 17.6 Hz), 3.24 (1H, d, J = 18.8 Hz), 3.59 (1H, d, J = 16.8 Hz), 3.78 (1H, d, J = 16.8 Hz), 6.32 (1H, d, J = 7.2 Hz), 6.61 (1H, dd, J = 2.0, 8.0 Hz), 6.91 (1H, d, J = 8.0 Hz), 6.99–7.12 (3H, m), 7.56 (1H, s), two protons (OH) were not observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.9, 35.9, 36.0, 38.5, 40.5, 43.0, 45.6, 54.5, 61.8, 69.5, 106.2, 114.2, 115.0, 118.0, 125.6, 126.3, 128.0, 128.2, 128.9, 135.4, 137.5, 140.5, 153.9, 156.0, 156.5. HRMS (ESI) Calcd for $C_{25}H_{27}N_2O_3$ $[M+H]^+$: 403.2022. Found: 403.2015.

5.1.90. 6,7-Didehydro-8′-methoxy-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol hydrochloride (SYK-38)

SYK-38 was prepared from compound **31d** according to the procedure used to prepare SYK-27.

Yield, 51%; a pale yellow amorphous solid. Mp 237–240 °C (dec). Anal. Calcd for $C_{25}H_{26}N_2O_3 \cdot 2.0HCl \cdot 0.8H_2O$: C, 61.30; H, 6.09; N, 5.72. Found: C, 61.32; H, 6.33; N, 5.76.

5.1.91. 2-Amino-6-(trifluoromethyl)benzyl alcohol (5a)

Compound **5a** was prepared from 6-(trifluoromethyl)anthranilic acid according to the procedure used to prepare compound **1a**. Yield, 49%; a white amorphous solid.

IR (KBr): 3377, 1610, 1473, 1321, 1099, 825, 745 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.71 (2H, s), 6.82 (1H, d, J = 7.8 Hz), 6.98 (1H, d, J = 7.8 Hz), 7.17 (1H, t, J = 7.8 Hz), three protons (NH_2, OH) were not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 58.4, 115.3 (q, J = 6.1 Hz), 120.9, 123.3, 126.1 (q, J = 271.3 Hz), 129.5, 129.9 (q, J = 29.2 Hz), 150.5. HRMS (EI) Calcd for $C_8H_8F_3NO$ $[M]^+$: 191.0558. Found: 191.0553.

5.1.92. 2-Amino-6-(trifluoromethyl)benzaldehyde (11a)

Compound **11a** was prepared from compound **5a** according to the procedure used to prepare compound **7a**. Yield, 88%; a yellow amorphous solid.

IR (KBr): 3457, 3343, 1656, 1621, 1553, 1462, 1303, 1227, 1116, 801 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ: 6.96 (1H, dd, J = 0.6, 7.5 Hz), 7.02 (1H, dd, J = 0.6, 8.7 Hz), 7.36 (1H, t, J = 8.1 Hz), 10.21 (1H, s). ^{13}C NMR (75 MHz, CD_3OD) δ: 113.3, 114.6 (q, J = 6.6 Hz), 122.9, 125.7 (q, J = 271.9 Hz), 133.2 (q, J = 30.6 Hz), 135.0, 154.4, 192.0. HRMS (EI) Calcd for $C_8H_6F_3NO$ $[M]^+$: 189.0401. Found: 189.0394.

5.1.93. 6,7-Didehydro-3-methoxy-17-methyl-5′-trifluoromethylquinolino[2′,3′:6,7]morphinan-14β-ol (22a)

Compound **22a** was prepared from compound **17** and **11a** according to the procedure used to prepare compound **18b**. Yield, 65%; a yellow amorphous solid.

IR (KBr): 3443, 2911, 1497, 1301, 1157, 1121, 1048 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.38–1.49 (1H, m), 2.21–2.32 (2H, m), 2.44–2.49 (1H, m), 2.45 (3H, s), 2.91–3.02 (3H, m), 3.13 (1H, d, J = 17.7 Hz), 3.27 (1H, d, J = 18.0 Hz), 3.58 (1H, d, J = 17.7 Hz), 3.64 (3H, s), 3.73 (1H, d, J = 17.4 Hz), 6.63 (1H, dd, J = 2.5, 8.4 Hz), 6.91 (1H, d, J = 2.5 Hz), 7.03 (1H, d, J = 8.4 Hz), 7.60 (1H, t, J = 7.8 Hz), 7.76 (1H, d, J = 7.2 Hz), 7.99 (1H, s), 8.16 (1H, d, J = 7.8 Hz), a proton (OH) was not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.0, 36.4, 36.7, 39.3, 40.5, 42.9, 45.5, 55.1, 61.6, 69.3, 111.0, 112.0, 123.3, 124.0 (q, J = 5.8 Hz), 124.4 (q, J = 272.1 Hz), 125.3 (q, J = 30.3 Hz), 126.6, 127.4, 128.6, 129.7, 131.68, 131.71, 133.1, 140.9, 146.7, 158.2. HRMS (ESI) Calcd for $C_{26}H_{26}F_3N_2O_2$ $[M+H]^+$: 455.1946. Found: 455.1942.

5.1.94. 6,7-Didehydro-17-methyl-5′-trifluoromethylquinolino[2′,3′:6,7]morphinan-3,14β-diol (28a)

Compound **28a** was prepared from compound **22a** according to the procedure used to prepare compound **24a** Yield, 46%; a yellow amorphous solid.

IR (KBr): 3357, 2914, 1497, 1156, 1108 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.39–1.43 (1H, m), 2.15 (1H, dt, J = 5.4, 12.6 Hz), 2.34 (1H, dt, J = 2.7, 11.7 Hz), 2.42–2.49 (1H, m), 2.45 (3H, s), 2.90–3.04 (3H, m), 3.14 (1H, d, J = 17.7 Hz), 3.30 (1H, d, J = 18.3 Hz), 3.61 (1H, d, J = 17.1 Hz), 3.72 (1H, d, J = 17.1 Hz), 6.68 (1H, dd, J = 2.1, 8.4 Hz), 6.95 (1H, t, J = 8.1 Hz), 7.02 (1H, d, J = 8.4 Hz), 7.09 (1H, d, J = 2.1 Hz), 7.19 (1H, d, J = 8.4 Hz), 7.45 (1H, d, J = 7.2 Hz), 7.94 (1H, s), two protons (OH) were not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.0, 36.0, 36.3, 38.6, 40.4, 43.0, 45.4, 61.6, 69.4, 113.1, 115.3, 123.0, 123.95 (q, J = 5.5 Hz), 123.96 (q, J = 271.9 Hz), 124.9 (q, J = 30.4 Hz), 126.7, 126.8, 129.2, 130.2, 131.0, 132.4, 140.3, 145.2, 155.4, 158.5. HRMS (ESI) Calcd for $C_{25}H_{24}F_3N_2O_2$ $[M+H]^+$: 441.1790. Found: 441.1782.

5.1.95. 6,7-Didehydro-17-methyl-5′-trifluoromethylquinolino[2′,3′:6,7]morphinan-3,14β-diol hydrochloride (SYK-338)

SYK-338 was prepared from compound **28a** according to the procedure used to prepare SYK-27.

Yield, quant.; a white amorphous solid. Mp 234–238 °C (dec). Anal. Calcd for $C_{25}H_{23}F_3N_2O_2 \cdot 1.3HCl \cdot 0.9H_2O$: C, 59.57; H, 5.22; N, 5.56. Found: C, 59.68; H, 5.50; N, 5.53.

5.1.96. 2-Amino-5-(trifluoromethyl)benzyl alcohol (5b)

Compound **5b** was prepared from 5-(trifluoromethyl)anthranilic acid according to the procedure used to prepare compound **1a**. Yield, 87%; a white amorphous solid.

IR (KBr): 3376, 1621, 1335, 1119, 1009, 843 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.06 (1H, br s), 4.49 (2H, br s), 4.64 (2H, s), 6.68 (1H, d, J = 8.4 Hz), 7.29 (1H, d, J = 1.8 Hz), 7.36 (1H, dd, J = 1.8, 8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 63.9, 115.2, 119.5 (q, J = 32.4 Hz), 123.9, 124.7 (q, J = 268.9 Hz), 126.2 (q, J = 4.05 Hz), 126.5 (q, J = 3.75 Hz), 149.0. HRMS (EI) Calcd for $C_8H_8F_3NO$ $[M]^+$: 191.0558. Found: 191.0559.

5.1.97. 2-Amino-5-(trifluoromethyl)benzaldehyde (11b)

Compound **11b** was prepared from compound **5b** according to the procedure used to prepare compound **7a**. Yield, 78%; a brown amorphous solid.

IR (KBr): 3435, 3323, 1665, 1634, 1567, 1315, 1194, 1156, 1112, 1076, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.50 (2H, br s), 6.70 (1H, d, J = 8.7 Hz), 6.48 (1H, dd, J = 2.1, 8.7 Hz), 7.74 (1H, d, J = 1.2 Hz), 9.87 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 116.3, 117.4, 118.4 (q, J = 33.5 Hz), 124.1 (q, J = 268.7 Hz), 131.4 (q, J = 3.2 Hz), 133.1 (q, J = 4.0 Hz), 151.9, 193.2. HRMS (EI) Calcd for $C_8H_6F_3NO$ $[M]^+$: 189.0401. Found: 189.0409.

5.1.98. 6,7-Didehydro-3-methoxy-17-methyl-6′-trifluoromethylquinolino[2′,3′:6,7]morphinan-14β-ol (22b)

Compound **22b** was prepared from compound **17** and **11b** according to the procedure used to prepare compound **18b**. Yield, quant.; a yellow amorphous solid.

IR (KBr): 3419, 2935, 1270, 1120 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.37–1.48 (1H, m), 2.17–2.29 (2H, m), 2.40–2.46 (1H, m), 2.43 (3H, s), 2.90 (1H, d, J = 9.0 Hz), 2.94–3.00 (2H, m), 3.08 (1H, d, J = 17.7 Hz), 3.26 (1H, d, J = 17.7 Hz), 3.59 (1H, d, J = 18.3 Hz), 3.62 (3H, s), 3.72 (1H, d, J = 17.7 Hz), 6.61 (1H, dd, J = 2.1, 8.1 Hz), 6.88 (1H, d, J = 2.4 Hz), 7.01 (1H, d, J = 8.4 Hz), 7.67 (1H, s), 7.72 (1H, d, J = 8.7 Hz), 7.87 (1H, s), 8.05 (1H, d, J = 9.0 Hz), a proton (OH) was not observed. ^{13}C NMR (75 MHz,

$CDCl_3$) δ: 23.9, 36.0, 36.6, 39.6, 40.5, 42.9, 45.5, 55.1, 61.6, 69.3, 110.9, 112.1, 124.0, 124.1 (q, J = 270.4 Hz), 124.7 (q, J = 4.4 Hz), 126.1, 127.2 (q, J = 35.2 Hz), 127.4, 128.5, 129.4, 129.6, 135.8, 140.9, 147.4, 158.2, 159.9. HRMS (ESI) Calcd for $C_{26}H_{26}F_3N_2O_2$ $[M+H]^+$: 455.1946. Found: 455.1929.

5.1.99. 6,7-Didehydro-17-methyl-6′-trifluoromethylquinolino[2′,3′:6,7]morphinan-3,14β-diol (28b)

Compound **28b** was prepared from compound **22b** according to the procedure used to prepare compound **24a**. Yield, 84%; a yellow amorphous solid.

IR (KBr): 3389, 2918, 1461, 1274, 1122 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.26–1.34 (1H, m), 2.09 (1H, dt, J = 5.1, 12.6 Hz), 2.27 (1H, dt, J = 2.4, 12.0 Hz), 2.39–2.50 (1H, m), 2.43 (3H, s), 2.89 (1H, d, J = 6.3 Hz), 2.96–2.99 (2H, m), 3.08 (1H, d, J = 17.7 Hz), 3.27 (1H, d, J = 17.7 Hz), 3.49 (1H, d, J = 17.4 Hz), 3.69 (1H, d, J = 17.7 Hz), 6.68 (1H, dd, J = 2.1, 8.3 Hz), 7.01 (2H, d, J = 8.3 Hz), 7.04 (1H, d, J = 2.1 Hz), 7.28 (1H, d, J = 8.3 Hz), 7.58 (1H, s), 7.63 (1H, s), two protons (OH) were not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9, 35.8, 36.1, 38.8, 40.3, 42.9, 45.4, 61.5, 69.3, 113.1, 115.2, 123.78 (q, J = 270.5 Hz), 123.79 (q, J = 3.1 Hz), 124.5 (q, J = 4.3 Hz), 125.7, 126.8, 127.0 (q, J = 32.3 Hz), 127.7, 129.0, 129.9, 136.6, 140.4, 145.9, 155.4, 160.0. HRMS (ESI) Calcd for $C_{25}H_{24}F_3N_2O_2$ $[M+H]^+$: 441.1790. Found: 441.1775.

5.1.100. 6,7-Didehydro-17-methyl-6′-trifluoromethylquinolino[2′,3′:6,7]morphinan-3,14β-diol hydrochloride (SYK-339)

SYK-339 was prepared from compound **28b** according to the procedure used to prepare SYK-27.

Yield, 83%; a white amorphous solid. Mp 235–237 °C (dec). Anal. Calcd for $C_{25}H_{23}F_3N_2O_2{\cdot}1.5HCl{\cdot}1.2H_2O$: C, 58.11; H, 5.25; N, 5.42. Found: C, 58.04; H, 5.38; N, 5.45.

5.1.101. 2-Amino-4-(trifluoromethyl)benzyl alcohol (5c)

To a stirred solution of 4-(trifluoromethyl)anthranilic acid (1 g, 4.87 mmol) in THF (10 mL) was added a solution of 1.06 M boran - THF complex in THF (14 mL, 14.6 mmol) at 0 °C under an Ar atmosphere and stirred at rt. After 1.5 h with stirring, 4 M NaOH aqueous solution was added to the solution and stirred for 30 min, and extracted with AcOEt three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The crude compound was recrystalized from AcOEt solution to give **5c** (0.9 g, 99%) as a white needle crystal.

Mp: 69–70 °C. IR (KBr): 3406, 3320, 1641, 1443, 1336, 1128, 984, 827 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.73 (1H, br s), 4.37 (2H, br s), 4.69 (2H, s), 6.91 (1H, d, J = 0.8 Hz), 6.94 (1H, dd, J = 0.8, 7.6 Hz), 7.15 (1H, d, J = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 63.9, 112.2 (q, J = 3.8 Hz), 114.5 (q, J = 3.7 Hz), 124.1 (q, J = 272.6 Hz), 127.6, 129.3, 131.5 (q, J = 32.3 Hz), 146.3. HRMS (FAB) Calcd for $C_8H_8F_3NO$ $[M]^+$: 191.0558. Found: 191.0560.

5.1.102. 2-Amino-4-(trifluoromethyl)benzaldehyde (11c)

Compound **11c** was prepared from compound **5c** according to the procedure used to prepare compound **7a**. Yield, 88%; a white needle crystal.

Mp 41–42 °C. IR (KBr): 3454, 3345, 1670, 1559, 1501, 1351, 1329, 1269, 1173, 1131, 937, 807, 789 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.30 (2H, br s), 6.91 (1H, d, J = 0.8 Hz), 6.95 (1H, dd, J = 0.8, 8.0 Hz), 7.51 (1H, d, J = 8.0 Hz), 9.94 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 112.5 (q, J = 3.8 Hz), 113.1 (q, J = 3.8 Hz), 120.2, 123.4 (q, J = 273.5 Hz), 136.2 (q, J = 32.1 Hz), 136.4, 149.5, 193.6. HRMS (EI) Calcd for $C_8H_6F_3NO$ $[M]^+$: 189.0401. Found: 189.0392.

5.1.103. 6,7-Didehydro-3-methoxy-17-methyl-7′-trifluoromethylquinolino[2′,3′:6,7]morphinan-14β-ol (22c)

Compound **22c** was prepared from compound **17** and **11c** according to the procedure used to prepare compound **18b**. Yield, quant.; a colorless oil.

IR (neat): 3411, 2936, 1611, 1502, 1441, 1325, 1161, 1121, 754 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.36–1.48 (1H, m), 2.18–2.29 (2H, m), 2.40–2.48 (1H, m), 2.43 (3H, s), 2.90–3.00 (3H, m), 3.10 (1H, d, J = 17.6 Hz), 3.27 (1H, d, J = 18.0 Hz), 3.59 (1H, d, J = 17.6 Hz), 3.63 (3H, s), 3.72 (1H, d, J = 17.6 Hz), 6.61 (1H, dd, J = 2.4, 8.4 Hz), 6.88 (1H, d, J = 2.8 Hz), 7.01 (1H, d, J = 8.4 Hz), 7.54 (1H, dd, J = 2.0, 8.0 Hz), 7.68 (1H, s), 7.70 (1H, d, J = 8.0 Hz), 8.29 (1H, d, J = 2.0 Hz), a proton (OH) was not observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.9, 36.2, 36.6, 39.5, 40.6, 43.0, 45.5, 55.1, 61.6, 69.3, 110.9, 112.2, 121.0 (q, J = 3.1 Hz), 124.1 (q, J = 272.7 Hz), 126.2 (q, J = 4.6 Hz), 127.4, 127.9, 128.5, 128.7, 130.1 (q, J = 32.1 Hz), 130.4, 134.9, 140.9, 145.4, 158.3, 159.1. HRMS (ESI) Calcd for $C_{26}H_{26}F_3N_2O_2$ $[M+H]^+$: 455.1946. Found: 455.1925.

5.1.104. 6,7-Didehydro-17-methyl-7′-trifluoromethylquinolino[2′,3′:6,7]morphinan-3,14β-diol (28c)

Compound **28c** was prepared from compound **22c** according to the procedure used to prepare compound **24a**. Yield, 83%; a white needle crystal.

Mp 286–287 °C. IR (KBr): 3267, 2936, 1610, 1446, 1326, 1163, 1121, 1060, 910, 754 cm^{-1}. ^1H NMR (400 MHz, THF-d_8) δ: 1.27–1.40 (1H, m), 2.17–2.32 (2H, m), 2.38–2.47 (1H, m), 2.42 (3H, s), 2.79–2.98 (3H, m), 3.10 (1H, d, J = 17.6 Hz), 3.25 (1H, d, J = 18.0 Hz), 3.51 (1H, d, J = 17.6 Hz), 3.62 (1H, d, J = 17.6 Hz), 6.43 (1H, dd, J = 2.8, 8.4 Hz), 6.72 (1H, d, J = 2.8 Hz), 6.89 (1H, d, J = 8.4 Hz), 7.57 (1H, dd, J = 1.6, 8.4 Hz), 7.77 (1H, s), 7.82 (1H, d, J = 8.4 Hz), 8.20 (1H, d, J = 1.6 Hz), two protons (OH) was not observed. ^{13}C NMR (100 MHz, THF-d_8) δ: 25.1, 37.7, 38.0, 40.9, 41.8, 43.7, 47.0, 63.3, 70.4, 113.0, 115.1, 121.8 (q, J = 3.0 Hz), 126.5 (q, J = 272.9 Hz), 127.4 (q, J = 4.5 Hz), 127.5, 129.8 (2C), 130.5, 130.7 (q, J = 32.1 Hz), 133.0, 135.8, 142.2, 146.8, 157.6, 161.2. HRMS (ESI) Calcd for $C_{25}H_{24}F_3N_2O_2$ $[M+H]^+$: 441.1790. Found: 441.1781.

5.1.105. 6,7-Didehydro-17-methyl-7′-trifluoromethylquinolino[2′,3′:6,7]morphinan-3,14β-diol hydrochloride (SYK-72)

SYK-72 was prepared from compound **28c** according to the procedure used to prepare SYK-27.

Yield, 73%; a white amorphous solid. Mp 233–234 °C (dec). Anal. Calcd for $C_{25}H_{23}F_3N_2O_2{\cdot}1.0HCl{\cdot}0.8H_2O$: C, 61.11; H, 5.25; N, 5.70. Found: C, 61.11; H, 5.36; N, 5.83.

5.1.106. 2-Amino-3-(trifluoromethyl)benzyl alcohol (5d)

Compound **5d** was prepared from 3-(trifluoromethyl)anthranilic acid according to the procedure used to prepare compound **5c**. Yield, 93%; a white needle crystal.

Mp 58–59 °C. IR (KBr): 3752, 3348, 1639, 1465, 1336, 1287, 1095, 1023, 792, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.67 (1H, br s), 4.71 (2H, s), 4.82 (2H, br s), 6.72 (1H, t, J = 7.8 Hz), 7.21 (1H, d, J = 7.2 Hz), 7.42 (1H, d, J = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 64.4, 114.3 (q, J = 29.6 Hz), 116.6, 125.2 (q, J = 277.6 Hz), 125.8, 126.7 (q, J = 5.2 Hz), 132.7, 144.5. HRMS (FAB) Calcd for $C_8H_8F_3NO$ $[M]^+$: 191.0558. Found: 191.0564.

5.1.107. 2-Amino-3-(trifluoromethyl)benzaldehyde (11d)

Compound **11d** was prepared from compound **5d** according to the procedure used to prepare compound **7a**. Yield, 82%; a white needle crystal.

Mp 46–47 °C. IR (KBr): 3454, 3340, 1675, 1627, 1575, 1457, 1199, 1170, 1102, 898, 749, 668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.80 (1H, t, J = 8.0 Hz), 7.61 (1H, d, J = 8.0 Hz), 7.66 (1H, d,

J = 8.0 Hz), 9.90 (1H, s), two protons (NH_2) were not observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 114.4 (q, J = 31.8 Hz), 115.1, 119.8, 124.4 (q, J = 272.5 Hz), 132.8 (q, J = 5.1 Hz), 140.1, 147.4, 193.6. HRMS (FAB) Calcd for $C_8H_7F_3NO$ $[M+H]^+$: 190.0480. Found: 190.0477.

5.1.108. 6,7-Didehydro-3-methoxy-17-methyl-8′-trifluoromethylquinolino[2′,3′:6,7]morphinan-14β-ol (22d)

Compound **22d** was prepared from compound **17** and **11d** according to the procedure used to prepare compound **18b**. Yield, 62%; a colorless oil.

IR (neat): 3412, 2914, 1609, 1501, 1306, 1139, 1042, 758 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.37–1.49 (1H, m), 2.18–2.31 (2H, m), 2.38–2.51 (1H, m), 2.43 (3H, s), 2.88–2.98 (3H, m), 3.05 (1H, d, J = 18.0 Hz), 3.26 (1H, d, J = 18.0 Hz), 3.61 (3H, s), 3.63 (1H, d, J = 17.2 Hz), 3.78 (1H, d, J = 17.2 Hz), 6.60 (1H, dd, J = 2.7, 8.4 Hz), 6.90 (1H, d, J = 2.6 Hz), 6.99 (1H, d, J = 8.4 Hz), 7.40 (1H, t, J = 7.6 Hz), 7.62 (1H, s), 7.73 (1H, d, J = 7.6 Hz), 7.89 (1H, d, J = 7.6 Hz), a proton (OH) was not observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.9, 36.0, 36.4, 39.9, 40.8, 43.0, 45.5, 54.9, 61.7, 69.4, 110.0, 113.1, 123.8, 124.3 (q, J = 273.5 Hz), 126.6 (q, J = 5.6 Hz), 126.8 (q, J = 29.2 Hz), 127.5, 127.6, 128.4, 129.1, 131.2, 134.8, 140.9, 143.0, 158.2, 158.6. HRMS (ESI) Calcd for $C_{26}H_{26}F_3N_2O_2$ $[M+H]^+$: 455.1946. Found: 455.1935.

5.1.109. 6,7-Didehydro-17-methyl-8′-trifluoromethylquinolino[2′,3′:6,7]morphinan-3,14β-diol (28d)

Compound **28d** was prepared from compound **22d** according to the procedure used to prepare compound **24a**. Yield, 72%; a white prism crystal.

Mp 189–190 °C. IR (film): 3280, 2935, 1609, 1579, 1489, 1283, 1141, 1052, 911, 768 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ: 1.28–1.38 (1H, m), 2.16–2.30 (2H, m), 2.37–2.49 (1H, m), 2.42 (3H, s), 2.79–2.98 (3H, m), 3.07 (1H, d, J = 18.0 Hz), 3.28 (1H, d, J = 18.4 Hz), 3.42 (1H, d, J = 17.6 Hz), 3.71 (1H, d, J = 17.6 Hz), 6.54 (1H, dd, J = 2.4, 8.4 Hz), 6.82 (1H, d, J = 2.4 Hz), 6.99 (1H, d, J = 8.4 Hz), 7.35 (1H, t, J = 8.0 Hz), 7.47 (1H, s), 7.70 (1H, d, J = 8.0 Hz), 7.84 (1H, d, J = 6.8 Hz). ^{13}C NMR (100 MHz, CD_3OD) δ: 25.1, 37.3, 37.7, 40.5, 41.4, 43.2, 46.7, 63.0, 71.0, 113.0, 115.0, 125.1, 125.8 (q, J = 271.8 Hz), 127.5 (q, J = 30.9 Hz), 127.8 (q, J = 6.0 Hz), 128.0, 129.0, 129.9, 130.7, 132.9, 136.4, 142.3, 144.0, 157.0, 160.0. HRMS (ESI) Calcd for $C_{25}H_{24}F_3N_2O_2$ $[M+H]^+$: 441.1790. Found 441.1801.

5.1.110. 6,7-Didehydro-17-methyl-8′-trifluoromethylquinolino[2′,3′:6,7]morphinan-3,14β-diol hydrochloride (SYK-73)

SYK-73 was prepared from compound **28d** according to the procedure used to prepare SYK-27.

Yield, 84%; a white amorphous solid. Mp 236–237 °C (dec). Anal. Calcd for $C_{25}H_{23}F_3N_2O_2{\cdot}1.0HCl{\cdot}0.6H_2O$: C, 61.56; H, 5.21; N, 5.74. Found: C, 61.40; H, 5.35; N, 5.74.

5.1.111. 2-Amino-6-nitrobenzyl alcohol (6a)

Compound **6a** was prepared from 2-amino-6-nitrobenzoic acid according to the procedure used to prepare compound **1a**. Yield, 83%; a white needle crystal.

Mp 82–84 °C. IR (film): 3303, 1523 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ: 4.65 (2H, s), 6.97 (1H, dd, J = 0.6, 8.4 Hz), 7.00 (1H, dd, J = 0.9, 8.1 Hz), 7.17 (1H, t, J = 8.1 Hz). ^{13}C NMR (75 MHz, CD_3OD) δ: 57.4, 113.0, 118.4, 120.5, 129.8, 150.5, 152.6. HRMS (EI) Calcd for $C_7H_8N_2O_3$ $[M]^+$: 168.0535. Found: 168.0532.

5.1.112. 2-Amino-6-nitrobenzaldehyde (12a)

Compound **12a** was prepared from compound **6a** according to the procedure used to prepare compound **7a**. Yield, 88%; a brown amorphous solid.

IR (KBr): 3467, 3354, 1666, 1626, 1596, 1517, 1349, 1170 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ: 7.02 (1H, d, J = 8.7 Hz), 7.04 (1H, d, J = 7.8 Hz), 7.36 (1H, t, J = 8.1 Hz), 9.96 (1H, s). ^{13}C NMR (75 MHz, CD_3OD) δ: 109.7, 112.1, 122.7, 135.0, 153.4, 155.5, 190.8. HRMS (EI) Calcd for $C_7H_6N_2O_3$ $[M]^+$: 166.0378. Found: 166.0381.

5.1.113. 6,7-Didehydro-3-methoxy-17-methyl-5′-nitroquinolino[2′,3′:6,7]morphinan-14β-ol (23a)

Compound **23a** was prepared from compound **17** and **12a** according to the procedure used to prepare compound **20d**. Yield, quant.; a brown amorphous solid.

IR (KBr): 3430, 2912, 1525, 1274, 1045, 827 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.38–1.49 (1H, m), 2.20–2.30 (2H, m), 2.40–2.48 (1H, m), 2.44 (3H, s), 2.90–3.05 (3H, m), 3.15 (1H, d, J = 17.7 Hz), 3.27 (1H, d, J = 18.0 Hz), 3.58 (1H, d, J = 17.7 Hz), 3.63 (3H, s), 3.70 (1H, d, J = 17.7 Hz), 6.62 (1H, dd, J = 2.4, 8.4 Hz), 6.86 (1H, d, J = 2.4 Hz), 7.02 (1H, d, J = 8.7 Hz), 7.62 (1H, t, J = 8.4 Hz), 8.19 (1H, d, J = 7.5 Hz), 8.26 (1H, d, J = 8.4 Hz), 8.51 (1H, s), a proton (OH) was not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9, 36.56, 36.58, 39.2, 40.5, 42.9, 45.5, 55.1, 61.5, 69.3, 111.0, 112.0, 120.1, 123.6, 126.2, 127.5, 128.6, 130.9, 132.0, 135.5, 140.7, 144.7, 146.7, 158.2, 159.2. HRMS (ESI) Calcd for $C_{25}H_{26}N_3O_4$ $[M+H]^+$: 432.1923. Found: 432.1922.

5.1.114. 6,7-Didehydro-17-methyl-5′-nitroquinolino[2′,3′:6,7]morphinan-3,14β-diol (29a)

Compound **29a** was prepared from compound **23a** according to the procedure used to prepare compound **24a**. Yield, quant.; a yellow amorphous solid.

IR (KBr): 3358, 1523, 1407, 1323, 1281 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.35–1.50 (1H, m), 2.21 (1H, dt, J = 2.1, 12.3 Hz), 2.32 (1H, dt, J = 3.0, 12.3 Hz), 2.45–2.51 (1H, m), 2.46 (3H, s), 2.90–3.06 (3H, m), 3.17 (1H, d, J = 18.3 Hz), 3.31 (1H, d, J = 18.3 Hz), 3.63 (1H, d, J = 17.7 Hz), 3.69 (1H, d, J = 17.7 Hz), 6.63 (1H, dd, J = 2.4, 8.4 Hz), 6.92 (1H, d, J = 2.4 Hz), 7.03 (1H, d, J = 8.1 Hz), 7.30 (1H, t, J = 8.1 Hz), 7.66 (1H, dd, J = 0.9, 8.4 Hz), 8.05 (1H, dd, J = 0.9, 7.8 Hz), 8.49 (1H, s), two protons (OH) was not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.0, 36.2, 36.5, 39.0, 40.4, 43.0, 45.4, 61.5, 69.3, 112.7, 114.9, 120.0, 123.5, 126.3, 127.4, 129.2, 131.4, 132.3, 134.2, 140.5, 144.6, 145.8, 154.7, 159.4. HRMS (ESI) Calcd for $C_{24}H_{24}N_3O_4$ $[M+H]^+$: 418.1767. Found: 418.1784.

5.1.115. 6,7-Didehydro-17-methyl-5′-nitroquinolino[2′,3′:6,7]morphinan-3,14β-diol hydrochloride (SYK-350)

SYK-350 was prepared from compound **29a** according to the procedure used to prepare SYK-27.

Yield, 87%; a light brown amorphous solid. Mp 242–246 °C (dec). Anal. Calcd for $C_{24}H_{23}N_3O_4{\cdot}1.5HCl{\cdot}0.8H_2O$: C, 59.24; H, 5.41; N, 8.64. Found: C, 59.35; H, 5.52; N, 8.48.

5.1.116. 5′-Amino-6,7-didehydro-3-methoxy-17-methylquinolino[2′,3′:6,7]morphinan-14β-ol (32a)

To a stirred solution of **23a** (216 mg, 0.50 mmol) in ethanol (6 mL) were added 2 M HCl (6 mL) and iron powder (419 mg, 7.50 mmol), and stirred at 80 °C under an Ar atmosphere. After 1.5 h with stirring, the reaction mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution. The solid was removed by filtration and the filtrate was 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/25% ammonia aqueous solution = 120/10/1) to give **32a** (81 mg, 40%) as a yellow amorphous solid.

IR (KBr): 3371, 2918, 1614, 1568, 1498, 1272, 1042, 811 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.36–1.47 (1H, m), 2.17–2.29 (2H, m), 2.39–2.46 (1H, m), 2.43 (3H, s), 2.88–2.99 (3H, m), 3.08 (1H,

d, J = 17.4 Hz), 3.25 (1H, d, J = 17.4 Hz), 3.54 (1H, d, J = 17.1 Hz), 3.62 (3H, s), 3.68 (1H, d, J = 17.1 Hz), 3.96 (1H, br s), 6.61 (1H, dd, J = 2.7, 7.8 Hz), 6.62 (1H, d, J = 7.5 Hz), 6.90 (1H, d, J = 2.4 Hz), 6.99 (1H, d, J = 8.4 Hz), 7.34 (1H, t, J = 7.8 Hz), 7.44 (1H, d, J = 8.4 Hz), 7.63 (1H, s), two protons (NH_2) were not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.0, 36.2, 36.7, 39.3, 40.6, 43.0, 45.5, 55.1, 61.7, 69.5, 109.0, 110.8, 112.3, 117.9, 119.2, 126.5, 127.5, 128.4, 128.81, 128.85, 141.2, 141.4, 147.4, 156.9, 158.2. HRMS (ESI) Calcd for $C_{25}H_{28}N_3O_2$ $[M+H]^+$: 402.2182. Found: 402.2177.

5.1.117. 6,7-Didehydro-5′-(*N*,*N*-dimethylamino)-3-methoxy-17-methylquinolino[2′,3′:6,7]morphinan-14β-ol (33a)

To a stirred solution of **32a** (81 mg, 0.20 mmol) in acetonitrile (4 mL) were added 37% formaldehyde solution (163 μL, 2.02 mmol), sodium cyanoborohydride (38.1 mg, 0.61 mmol) and acetic acid (13.2 μL), and stirred at rt under an Ar atmosphere. After 2 h with stirring, the reaction mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution, and extracted with AcOEt three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was chromatographed by silica gel ($CHCl_3$/MeOH/25% ammonia aqueous solution = 200/10/1) to give **33a** (82 mg, 94%) as a yellow oil.

IR (neat): 3408, 2936, 1500, 1274, 1241, 1043, 730 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.36–1.47 (1H, m), 2.18–2.29 (2H, m), 2.39–2.45 (1H, m), 2.43 (3H, s), 2.79 (6H, s), 2.87–2.99 (3H, m), 3.09 (1H, d, J = 18.0 Hz), 3.25 (1H, d, J = 18.0 Hz), 3.55 (1H, d, J = 17.1 Hz), 3.62 (3H, s), 3.68 (1H, d, J = 17.1 Hz), 6.59 (1H, dd, J = 2.7, 8.1 Hz), 6.90 (1H, d, J = 2.7 Hz), 6.95 (1H, d, J = 8.6 Hz), 6.98 (1H, d, J = 8.1 Hz), 7.47 (1H, t, J = 8.5 Hz), 7.65 (1H, d, J = 8.5 Hz), 8.04 (1H, s), a proton (OH) was not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.0, 36.2, 36.6, 39.2, 40.6, 43.0, 45.2 (2C), 45.5, 55.1, 61.7, 69.5, 110.8, 112.2, 113.2, 122.9, 123.0, 127.0, 127.5, 128.2, 128.3, 131.9, 141.1, 147.7, 150.2, 156.6, 158.2. HRMS (ESI) Calcd for $C_{27}H_{32}N_3O_2$ $[M+H]^+$: 430.2495. Found: 430.2513.

5.1.118. 6,7-Didehydro-5′-(*N*,*N*-dimethylamino)-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol (34a)

Compound **34a** was prepared from compound **33a** according to the procedure used to prepare compound **24a**. Yield, 72%; a yellow oil.

IR (neat): 2936, 1573, 1452, 1281, 910, 731 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26–1.43 (1H, m), 2.11 (1H, dt, J = 5.6, 12.5 Hz), 2.27 (1H, dt, J = 2.8, 12.1 Hz), 2.37–2.47 (1H, m), 2.41 (3H, s), 2.76 (6H, s), 2.86–3.01 (3H, m), 3.11 (1H, d, J = 18.0 Hz), 3.24 (1H, d, J = 18.0 Hz), 3.54 (1H, d, J = 17.1 Hz), 3.69 (1H, d, J = 17.1 Hz), 6.62 (1H, dd, J = 2.4, 8.2 Hz), 6.79 (1H, dd, J = 1.3, 7.1 Hz), 6.93 (1H, d, J = 8.3 Hz), 7.04 (1H, d, J = 2.3 Hz), 7.07 (1H, t, J = 7.2 Hz), 7.12 (1H, dd, J = 1.3, 7.4 Hz), 8.06 (1H, s), two protons (OH) was not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9, 36.1, 36.2, 38.4, 40.4, 43.0, 45.2 (2C), 45.5, 61.7, 69.5, 112.8, 113.3, 114.6, 121.7, 122.9, 126.3, 127.2, 128.3, 128.7, 132.6, 140.6, 146.7, 149.9, 155.7, 156.7. HRMS (ESI) Calcd for $C_{26}H_{30}N_3O_2$ $[M+H]^+$: 416.2338. Found: 416.2341.

5.1.119. 6,7-Didehydro-5′-(*N*,*N*-dimethylamino)-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol hydrochloride (SYK-362)

SYK-362 was prepared from compound **34a** according to the procedure used to prepare SYK-27.

Yield, 78%; a red amorphous solid. Mp 222–224 °C (dec). Anal. Calcd for $C_{26}H_{29}N_3O_2{\cdot}2.0HCl{\cdot}1.5H_2O$: C, 60.58; H, 6.65; N, 8.15. Found: C, 60.59; H, 6.45; N, 8.24.

5.1.120. 2-Amino-5-nitrobenzyl alcohol (6b)

Compound **6b** was prepared from 5-nitroanthranilic acid according to the procedure used to prepare compound **5c**. Yield, 98%; a brown needle crystal.

Mp: 200–201 °C. IR (KBr): 3379, 3194, 1650, 1589, 1494, 1327, 1018 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD) δ: 4.57 (2H, s), 6.69 (1H, d, J = 9.2 Hz), 7.96 (1H, dd, J = 2.4, 9.2 Hz), 8.07 (1H, d, J = 2.4 Hz). ^{13}C NMR (100 MHz, CD_3OD) δ: 62.4, 114.6, 125.0, 125.6, 126.2, 138.4, 154.6. HRMS (EI) Calcd for $C_7H_8N_2O_3$ $[M]^+$: 168.0535. Found: 168.0534.

5.1.121. 2-Amino-5-nitrobenzaldehyde (12b)

Compound **12b** was prepared from compound **6b** according to the procedure used to prepare compound **7a**. Yield, 83%; a brown needle crystal.

Mp 200–201 °C. IR (KBr): 3416, 3315, 1664, 1634, 1327, 1103 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD) δ: 6.83 (1H, d, J = 9.6 Hz), 8.13 (1H, dd, J = 2.4, 9.6 Hz), 8.55 (1H, d, J = 2.4 Hz), 9.90 (1H, s). ^{13}C NMR (CD_3OD, 100 MHz) δ: 117.2, 117.8, 130.7, 134.1, 137.9, 156.5, 194.5. HRMS (EI) Calcd for $C_7H_6N_2O_3$ $[M]^+$: 166.0378. Found: 166.0385.

5.1.122. 6,7-Didehydro-3-methoxy-17-methyl-6′-nitroquinolino[2′,3′:6,7]morphinan-14β-ol (23b)

Compound **23b** was prepared from compound **17** and **12b** according to the procedure used to prepare compound **18b**. Yield, 95%; a yellow amorphous solid.

IR (film): 3410, 2935, 1612, 1527, 1344, 1272, 1240, 1042, 755 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.37–1.48 (1H, m), 2.18–2.29 (2H, m), 2.41–2.48 (1H, m), 2.43 (3H, s), 2.88–3.03 (2H, m), 2.95 (1H, d, J = 17.6 Hz), 3.09 (1H, d, J = 17.6 Hz), 3.28 (1H, d, J = 18.4 Hz), 3.58 (1H, d, J = 17.6 Hz), 3.62 (3H, s), 3.73 (1H, d, J = 17.6 Hz), 6.61 (1H, dd, J = 2.4, 8.4 Hz), 6.87 (1H, d, J = 2.4 Hz), 7.02 (1H, d, J = 8.4 Hz), 7.71 (1H, s), 8.01 (1H, d, J = 9.2 Hz), 8.25 (1H, dd, J = 2.0, 9.2 Hz), 8.49 (1H, d, J = 2.0 Hz), a proton (OH) was not observed. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 23.9, 36.0, 36.6, 39.7, 40.5, 42.9, 45.4, 55.1, 61.5, 69.2, 111.0, 112.0, 121.8, 123.6, 125.8, 127.4, 128.6, 129.9, 130.5, 136.6, 140.7, 144.6, 148.4, 158.2, 161.8. HRMS (ESI) Calcd for $C_{25}H_{26}N_3O_4$ $[M+H]^+$: 432.1923. Found: 432.1907.

5.1.123. 6,7-Didehydro-17-methyl-6′-nitroquinolino[2′,3′:6,7]morphinan-3,14β-diol (29b)

Compound **29b** was prepared from compound **23b** according to the procedure used to prepare compound **24a**. Yield, 92%; a yellow oil.

IR (neat): 3365, 2918, 1612, 1528, 1345, 1239, 1051, 755 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27–1.35 (1H, m), 2.11 (1H, dt, J = 5.3, 12.8 Hz), 2.25 (1H, dt, J = 2.8, 12.0 Hz), 2.36–2.48 (1H, m), 2.43 (3H, s), 2.90–3.00 (2H, m), 2.96 (1H, d, J = 18.0 Hz), 3.10 (1H, d, J = 18.0 Hz), 3.27 (1H, d, J = 18.0 Hz), 3.52 (1H, d, J = 17.6 Hz), 3.65 (1H, d, J = 17.6 Hz), 6.63 (1H, dd, J = 2.4, 8.4 Hz), 6.93 (1H, d, J = 2.4 Hz), 7.01 (1H, d, J = 8.4 Hz), 7.34 (1H, d, J = 9.6 Hz), 7.61 (1H, dd, J = 2.0, 9.6 Hz), 7.67 (1H, s), 8.29 (1H, d, J = 2.0 Hz), two protons (OH) were not observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.9, 35.8, 36.1, 39.1, 40.4, 42.9, 45.3, 61.4, 69.2, 112.6, 115.0, 121.7, 123.3, 125.6, 127.0, 128.3, 129.2, 131.0, 137.2, 140.3, 144.4, 147.0, 155.2, 162.0. HRMS (ESI) Calcd for $C_{24}H_{24}N_3O_4$ $[M+H]^+$: 418.1767. Found: 418.1748.

5.1.124. 6,7-Didehydro-17-methyl-6′-nitroquinolino[2′,3′:6,7]morphinan-3,14β-diol hydrochloride (SYK-70)

SYK-70 was prepared from compound **29b** according to the procedure used to prepare SYK-27.

Yield, 95%; a light brown amorphous solid. Mp 236–239 °C (dec). Anal. Calcd for $C_{24}H_{23}N_3O_4 \cdot 1.0HCl \cdot 1.3H_2O$: C, 60.39; H, 5.62; N, 8.80. Found: C, 60.54; H, 5.56; N, 8.60.

5.1.125. 6′-Amino-6,7-didehydro-3-methoxy-17-methylquinolino[2′,3′:6,7]morphinan-14β-ol (32b)

Compound **32b** was prepared from compound **23b** according to the procedure used to prepare compound **32a**. Yield, 62%; a yellow amorphous solid.

IR (KBr): 3376, 2916, 1631, 1501, 1274, 1243, 1041 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.34–1.44 (1H, m), 2.16–2.28 (2H, m), 2.38–2.44 (1H, m), 2.42 (3H, s), 2.82–2.96 (3H, m), 3.02 (1H, d, J = 17.4 Hz), 3.24 (1H, d, J = 17.4 Hz), 3.49 (1H, d, J = 17.4 Hz), 3.62 (3H, s), 3.63 (1H, d, J = 17.4 Hz), 6.60 (1H, dd, J = 2.4, 8.4 Hz), 6.67 (1H, d, J = 2.4 Hz), 6.91 (1H, d, J = 2.4 Hz), 6.99 (1H, d, J = 8.4 Hz), 7.00 (1H, dd, J = 2.4, 9.0 Hz), 7.37 (1H, s), 7.77 (1H, d, J = 9.0 Hz), three protons (NH_2, OH) were not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.0, 36.0, 36.7, 39.0, 40.6, 43.0, 45.6, 55.1, 61.7, 69.4, 106.8, 110.9, 112.1, 120.7, 127.5, 128.1, 128.3, 128.6, 129.2, 133.2, 141.3, 141.7, 143.6, 153.2, 158.2. HRMS (ESI) Calcd for $C_{25}H_{28}N_3O_2$ $[M+H]^+$: 402.2182. Found: 402.2172.

5.1.126. 6,7-Didehydro-6′-(*N*,*N*-dimethylamino)-3-methoxy-17-methylquinolino[2′,3′:6,7]morphinan-14β-ol (33b)

Compound **33b** was prepared from compound **32b** according to the procedure used to prepare compound **33a**. Yield, 67%; a green amorphous solid.

IR (KBr): 3425, 1623, 1501, 1375, 1042 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.35–1.46 (1H, m), 2.17–2.29 (2H, m), 2.39–2.46 (1H, m), 2.43 (3H, s), 2.84–3.09 (4H, m), 3.00 (6H, s), 3.25 (1H, d, J = 16.8 Hz), 3.51 (1H, d, J = 17.4 Hz), 3.63 (3H, s), 3.65 (1H, d, J = 17.4 Hz), 6.60 (1H, dd, J = 2.4, 8.4 Hz), 6.62 (1H, d, J = 2.7 Hz), 6.91 (1H, d, J = 2.1 Hz), 6.99 (1H, d, J = 8.4 Hz), 7.26 (1H, dd, J = 2.7, 8.7 Hz), 7.47 (1H, s), 7.85 (1H, d, J = 9.3 Hz), a proton (OH) was not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.0, 36.0, 36.6, 38.9, 40.6, 40.8 (2C), 42.9, 45.6, 55.1, 61.7, 69.4, 104.6, 110.8, 112.2, 118.8, 127.5, 128.0, 128.3, 128.57, 128.60, 133.5, 140.7, 141.3, 148.0, 152.7, 158.2. HRMS (ESI) Calcd for $C_{27}H_{32}N_3O_2$ $[M+H]^+$: 430.2495. Found: 430.2480.

5.1.127. 6,7-Didehydro-6′-(*N*,*N*-dimethylamino)-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol (34b)

Compound **34b** was prepared from compound **33b** according to the procedure used to prepare compound **24a**. Yield, 95%; a yellow amorphous solid.

IR (KBr): 3398, 2915, 1622, 1507, 1375 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.26–1.37 (1H, m), 2.10 (1H, dt, J = 5.7, 12.6 Hz), 2.29 (1H, dt, J = 3.0, 12.0 Hz), 2.38–2.45 (1H, m), 2.42 (3H, s), 2.84–2.96 (3H, m), 2.89 (6H, s), 3.05 (1H, d, J = 18.0 Hz), 3.25 (1H, d, J = 17.1 Hz), 3.51 (1H, d, J = 16.8 Hz), 3.64 (1H, d, J = 16.8 Hz), 6.45 (1H, d, J = 2.7 Hz), 6.64 (1H, dd, J = 2.4, 8.4 Hz), 6.75 (1H, dd, J = 2.7, 9.3 Hz), 6.95 (1H, d, J = 8.4 Hz), 7.07 (1H, d, J = 2.4 Hz), 7.17 (1H, d, J = 9.3 Hz), 7.40 (1H, s), two protons (OH) were not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.0, 35.9, 36.1, 38.1, 40.4, 40.6 (2C), 43.0, 45.6, 61.8, 69.5, 104.1, 113.1, 114.7, 118.7, 126.3, 127.2, 128.1, 128.5, 128.6, 134.2, 139.6, 140.8, 147.7, 152.6, 155.8. HRMS (ESI) Calcd for $C_{26}H_{30}N_3O_2$ $[M+H]^+$: 416.2338. Found: 416.2338.

5.1.128. 6,7-Didehydro-6′-(*N*,*N*-dimethylamino)-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol hydrochloride (SYK-80)

SYK-80 was prepared from compound **34b** according to the procedure used to prepare SYK-27.

Yield, 87%; an orange amorphous solid. Mp 247–249 °C (dec). Anal. Calcd for $C_{26}H_{29}N_3O_2 \cdot 2.0HCl \cdot 1.7H_2O$: C, 60.16; H, 6.68; N, 8.10. Found: C, 60.26; H, 6.64; N, 8.19.

5.1.129. 2-Amino-4-nitrobenzyl alcohol (6c)

Compound **6c** was prepared from 4-nitroanthranilic acid according to the procedure used to prepare compound **5c**. Yield, 91%; a brown needle crystal.

Mp 122–123 °C. IR (KBr): 3387, 1642, 1509, 1350, 1039, 741 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ: 4.61 (2H, s), 7.31 (1H, d, J = 8.0 Hz), 7.46 (1H, dd, J = 2.4, 8.0 Hz), 7.54 (1H, d, J = 2.4 Hz). ^{13}C NMR (CD_3OD, 100 MHz) δ: 62.5, 110.1, 112.4, 129.4, 133.1, 148.6, 149.7. HRMS (EI) Calcd for $C_7H_8N_2O_3$ $[M]^+$: 168.0535. Found: 168.0533.

5.1.130. 2-Amino-4-nitrobenzaldehyde (12c)

Compound **12c** was prepared from compound **6c** according to the procedure used to prepare compound **7a**. Yield, quant.; a brown needle crystal.

Mp 128–129 °C. IR (KBr): 3469, 3351, 1675, 1577, 1520, 1350, 1196, 829 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ: 7.40 (1H, dd, J = 2.2, 8.6 Hz), 7.60 (1H, d, J = 2.2 Hz), 7.76 (1H, d, J = 8.5 Hz), 9.97 (1H, s). ^{13}C NMR (CD_3OD, 100 MHz) δ: 109.8, 111.8, 122.2, 138.3 152.4, 153.2, 195.0. HRMS (EI) Calcd for $C_7H_6N_2O_3$ $[M]^+$: 166.0378. Found: 166.0385.

5.1.131. 6,7-Didehydro-3-methoxy-17-methyl-7′-nitroquinolino[2′,3′:6,7]morphinan-14β-ol (23c)

Compound **23c** was prepared from compound **17** and **12c** according to the procedure used to prepare compound **18b**. Yield, 64%; a yellow amorphous solid.

IR (KBr): 3396, 2911, 1607, 1526, 1501, 1348, 1237, 1041 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.39–1.48 (1H, m), 2.18–2.30 (2H, m), 2.40–2.52 (1H, m), 2.43 (3H, s), 2.88–3.02 (2H, m), 2.96 (1H, d, J = 18.4 Hz), 3.10 (1H, d, J = 17.6 Hz), 3.27 (1H, d, J = 18.4 Hz), 3.59 (1H, d, J = 18.0 Hz), 3.62 (3H, s), 3.73 (1H, d, J = 18.0 Hz), 6.61 (1H, dd, J = 2.4, 8.4 Hz), 6.97 (1H, d, J = 2.4 Hz), 7.02 (1H, d, J = 8.4 Hz), 7.67 (1H, d, J = 9.2 Hz), 7.68 (1H, d, J = 2.0 Hz), 8.12 (1H, dd, J = 2.0, 9.2 Hz), 8.87 (1H, d, J = 2.0 Hz), a proton (OH) was not observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.9, 36.3, 36.6, 39.5, 40.5, 42.9, 45.4, 55.1, 61.5, 69.2, 110.9, 112.2, 118.9, 124.8, 127.4, 128.2, 128.6, 130.4, 132.0, 134.7, 140.7, 145.2, 147.3, 158.2, 160.4. HRMS (ESI) Calcd for $C_{25}H_{26}N_3O_4$ $[M+H]^+$: 432.1923. Found: 432.1904.

5.1.132. 6,7-Didehydro-17-methyl-7′-nitroquinolino[2′,3′:6,7]morphinan-3,14β-diol (29c)

Compound **29c** was prepared from compound **23c** according to the procedure used to prepare compound **24a**. Yield, 83%; a yellow oil.

IR (neat): 3365, 2919, 1607, 1530, 1348, 1238, 1051, 756 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.48–1.58 (1H, m), 2.22 (1H, dt, J = 5.6, 12.8 Hz), 2.42 (1H, dt, J = 3.2, 12.0 Hz), 2.47 (3H, s), 2.47–2.54 (1H, m), 2.92–3.06 (3H, m), 3.13 (1H, d, J = 18.0 Hz), 3.37 (1H, d, J = 18.4 Hz), 3.68 (1H, d, J = 17.2 Hz), 3.76 (1H, d, J = 17.2 Hz), 6.76 (1H, dd, J = 2.4, 8.4 Hz), 7.14 (1H, d, J = 8.4 Hz), 7.16 (1H, d, J = 2.4 Hz), 7.23 (1H, s), 7.25 (1H, d, J = 8.8 Hz), 7.44 (1H, s), 7.67 (1H, d, J = 8.8 Hz), two protons (OH) were not observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.9, 35.9, 36.1, 39.0, 40.5, 43.1, 45.4, 61.5, 69.3, 114.7, 116.8, 118.8, 122.3, 127.8, 127.9, 129.6, 129.8, 132.9, 135.2, 139.8, 143.1, 146.6, 154.9, 161.0. HRMS (ESI) Calcd for $C_{24}H_{24}N_3O_4$ $[M+H]^+$: 418.1767. Found: 418.1774.

5.1.133. 6,7-Didehydro-17-methyl-7′-nitroquinolino[2′,3′:6,7]morphinan-3,14β-diol hydrochloride (SYK-71)

SYK-71 was prepared from compound **29c** according to the procedure used to prepare SYK-27.

Yield, 98%; a yellow amorphous solid. Mp 247–249 °C (dec). Anal. Calcd for $C_{24}H_{23}N_3O_4 \cdot 1.0HCl \cdot 1.2H_2O$: C, 60.62; H, 5.60; N, 8.84. Found: C, 60.69; H, 5.61; N, 8.85.

5.1.134. 7′-Amino-6,7-didehydro-3-methoxy-17-methylquinolino[2′,3′:6,7]morphinan-14β-ol (32c)

Compound **32c** was prepared from compound **23c** according to the procedure used to prepare compound **32a**. Yield, 85%; a yellow amorphous solid.

IR (KBr): 3382, 1625, 1503, 1275, 1040 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.34–1.44 (1H, m), 2.15–2.27 (2H, m), 2.37–2.45 (1H, m), 2.41 (3H, s), 2.79–2.95 (3H, m), 3.01 (1H, d, J = 17.4 Hz), 3.23 (1H, d, J = 17.4 Hz), 3.50 (1H, d, J = 17.1 Hz), 3.63 (3H, s), 3.64 (1H, d, J = 17.1 Hz), 3.95 (1H, br s), 6.60 (1H, dd, J = 2.7, 8.4 Hz), 6.81 (1H, dd, J = 2.1, 8.7 Hz), 6.90 (1H, d, J = 2.7 Hz), 6.99 (1H, d, J = 8.4 Hz), 7.11 (1H, d, J = 2.1 Hz), 7.37 (1H, d, J = 8.7 Hz), 7.47 (1H, s), two protons (NH_2) were not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.0, 35.8, 36.7, 39.4, 40.6, 43.0, 45.5, 55.1, 61.7, 69.4, 108.5, 110.8, 112.2, 117.7, 121.5, 124.3, 127.6, 127.9, 128.3, 135.2, 141.3, 146.7, 148.0, 157.1, 158.2. HRMS (ESI) Calcd for $C_{25}H_{28}N_3O_2$ $[M+H]^+$: 402.2182. Found: 402.2174.

5.1.135. 6,7-Didehydro-7′-(*N*,*N*-dimethylamino)-3-methoxy-17-methylquinolino[2′,3′:6,7]morphinan-14β-ol (33c)

Compound **33c** was prepared from compound **32c** according to the procedure used to prepare compound **33a**. Yield, quant.; a yellow oil.

IR (neat): 3410, 2912, 1622, 1504, 1373, 1273 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.34–1.45 (1H, m), 2.16–2.27 (2H, m), 2.37–2.44 (1H, m), 2.41 (3H, s), 2.80–3.08 (4H, m), 3.05 (6H, s), 3.24 (1H, d, J = 17.4 Hz), 3.51 (1H, d, J = 17.1 Hz), 3.63 (3H, s), 3.65 (1H, d, J = 17.1 Hz), 6.60 (1H, dd, J = 2.4, 8.4 Hz), 6.92 (1H, d, J = 2.4 Hz), 6.99 (1H, d, J = 8.4 Hz), 7.03 (1H, dd, J = 2.7, 9.0 Hz), 7.09 (1H, d, J = 2.7 Hz), 7.43 (1H, d, J = 9.0 Hz), 7.48 (1H, s), a proton (OH) was not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.0, 35.7, 36.7, 39.2, 40.5, 40.6 (2C), 43.0, 45.5, 55.1, 61.7, 69.4, 106.0, 110.7, 112.2, 115.6, 120.2, 123.6, 127.3, 127.5, 128.3, 135.1, 141.3, 147.9, 150.7, 156.7, 158.2. HRMS (ESI) Calcd for $C_{27}H_{32}N_3O_2$ $[M+H]^+$: 430.2495. Found: 430.2474.

5.1.136. 6,7-Didehydro-7′-(*N*,*N*-dimethylamino)-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol (34c)

Compound **34c** was prepared from compound **33c** according to the procedure used to prepare compound **24a**. Yield, 82%; a yellow amorphous solid.

IR (KBr): 3398, 2912, 1624, 1509, 1375 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.44–1.50 (1H, m), 2.17 (1H, dt, J = 5.7, 12.6 Hz), 2.35 (1H, dt, J = 3.0, 12.3 Hz), 2.43 (3H, s), 2.43–2.50 (1H, m), 2.50 (6H, s), 2.82–2.99 (4H, m), 3.30 (1H, d, J = 18.0 Hz), 3.57 (1H, d, J = 16.8 Hz), 3.68 (1H, d, J = 16.8 Hz), 5.79 (1H, d, J = 2.1 Hz), 6.60 (1H, dd, J = 2.4, 9.0 Hz), 6.71 (1H, dd, J = 2.4, 8.4 Hz), 6.97 (1H, d, J = 8.4 Hz), 7.02 (1H, d, J = 9.3 Hz), 7.18 (1H, d, J = 2.4 Hz), 7.27 (1H, s), two protons (OH) were not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.0, 35.6, 35.9, 38.2, 39.8 (2C), 40.4, 43.1, 45.5, 61.8, 69.6, 103.7, 115.2 (2C), 116.2, 119.9, 123.1, 126.7 (2C), 128.5, 135.5, 140.6, 146.3, 149.8, 155.8, 156.5. HRMS (ESI) Calcd for $C_{26}H_{30}N_3O_2$ $[M+H]^+$: 416.2338. Found: 416.2336.

5.1.137. 6,7-Didehydro-7′-(*N*,*N*-dimethylamino)-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol hydrochloride (SYK-81)

SYK-81 was prepared from compound **34c** according to the procedure used to prepare SYK-27.

Yield, 80%; an orange amorphous solid. Mp 249–254 °C (dec). Anal. Calcd for $C_{26}H_{29}N_3O_2{\cdot}2.0HCl{\cdot}1.6H_2O$: C, 60.37; H, 6.66; N, 8.12. Found: C, 60.24; H, 6.79; N, 7.88.

5.1.138. 2-Amino-3-nitrobenzyl alcohol (6d)

Compound **6d** was prepared from 3-nitroanthranilic acid according to the procedure used to prepare compound **1a**. Yield, 85%; an orange needle crystal.

Mp 104–105 °C. IR (KBr): 3487, 3345, 1639, 1514, 1427, 1245, 1013, 744 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ: 4.65 (2H, s), 6.64 (1H, dd, J = 7.2, 8.7 Hz), 7.41 (1H, dd, J = 0.9, 7.2 Hz), 8.03 (1H, dd, J = 1.5, 8.7 Hz). ^{13}C NMR (75 MHz, CD_3OD) δ: 63.2, 116.3, 126.4, 130.1, 133.4, 135.6, 145.8. HRMS (EI) Calcd for $C_7H_8N_2O_3$ $[M]^+$: 168.0535. Found: 168.0541.

5.1.139. 2-Amino-3-nitrobenzaldehyde (12d)

Compound **12d** was prepared from compound **6d** according to the procedure used to prepare compound **7a**. Yield, 78%; a yellow needle crystal.

Mp 127–129 °C. IR (KBr): 3448, 3315, 1678, 1619, 1559, 1516, 1259, 910, 743 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.81 (1H, dd, J = 7.5, 8.4 Hz), 7.82 (1H, dd, J = 1.8, 7.5 Hz), 8.43 (1H, dd, J = 1.8, 8.4 Hz), 9.92 (1H, s), two protons (NH_2) were not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 114.6, 122.1, 132.7, 133.0, 144.3, 146.3, 192.9. HRMS (EI) Calcd for $C_7H_6N_2O_3$ $[M]^+$: 166.0378. Found: 166.0373.

5.1.140. 6,7-Didehydro-3-methoxy-17-methyl-8′-nitroquinolino[2′,3′:6,7]morphinan-14β-diol (23d)

Compound **23d** was prepared from compound **17** and **12d** according to the procedure used to prepare compound **20d**. Yield, 72%; a yellow oil.

IR (neat): 3410, 2917, 1529, 1501, 1274, 1242, 1042, 731 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.37–1.47 (1H, m), 2.17–2.29 (2H, m), 2.41–2.49 (1H, m), 2.44 (3H, s), 2.87–3.01 (3H, m), 3.06 (1H, d, J = 17.7 Hz), 3.26 (1H, d, J = 17.7 Hz), 3.58 (1H, d, J = 17.7 Hz), 3.65 (3H, s), 3.73 (1H, d, J = 17.7 Hz), 6.61 (1H, dd, J = 2.7, 8.4 Hz), 6.87 (1H, d, J = 2.7 Hz), 7.00 (1H, d, J = 8.4 Hz), 7.37 (1H, t, J = 7.8 Hz), 7.63 (1H, s), 7.72 (1H, dd, J = 1.2, 8.1 Hz), 7.82 (1H, dd, J = 1.2, 7.5 Hz), a proton (OH) was not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9, 36.1, 36.4, 39.7, 40.7, 43.0, 45.4, 55.1, 61.6, 69.3, 110.4, 112.8, 122.3, 123.8, 127.4, 128.1, 128.5, 130.3, 130.7, 134.6, 137.7, 140.8, 147.7, 158.2, 160.5. HRMS (ESI) Calcd for $C_{25}H_{26}N_3O_4$ $[M+H]^+$: 432.1923. Found: 432.1925.

5.1.141. 6,7-Didehydro-17-methyl-8′-nitroquinolino[2′,3′:6,7]morphinan-3,14β-diol (29d)

Compound **29d** was prepared from compound **23d** according to the procedure used to prepare compound **24a**. Yield, 58%; a yellow amorphous solid.

IR (KBr): 3399, 1526, 760 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ: 1.28–1.39 (1H, m), 2.18–2.29 (2H, m), 2.40–2.49 (1H, m), 2.45 (3H, s), 2.80–3.09 (4H, m), 3.29 (1H, d, J = 18.0 Hz), 3.40 (1H, d, J = 18.0 Hz), 3.67 (1H, d, J = 17.7 Hz), 6.60 (1H, dd, J = 2.4, 8.1 Hz), 6.79 (1H, d, J = 2.4 Hz), 7.00 (1H, d, J = 8.4 Hz), 7.36 (1H, t, J = 7.8 Hz), 7.46 (1H, s), 7.68 (1H, dd, J = 1.2, 8.4 Hz), 7.81 (1H, dd, J = 1.2, 7.5 Hz). ^{13}C NMR (75 MHz, CD_3OD) δ: 25.1, 37.3, 37.5, 40.2, 41.4, 43.2, 46.7, 63.1, 70.7, 112.9, 115.2, 123.8, 125.4, 127.8, 129.3, 130.1, 131.8, 132.1, 136.5, 138.3, 142.0, 148.7, 157.1, 161.7. HRMS (ESI) Calcd for $C_{24}H_{24}N_3O_4$ $[M+H]^+$: 418.1767. Found: 418.1756.

5.1.142. 6,7-Didehydro-17-methyl-8′-nitroquinolino[2′,3′:6,7]morphinan-3,14β-diol hydrochloride (SYK-349)

SYK-349 was prepared from compound **29d** according to the procedure used to prepare SYK-27.

Yield, 98%; a brown amorphous solid. Mp 255–262 °C (dec). Anal. Calcd for $C_{24}H_{23}N_3O_4{\cdot}1.5HCl{\cdot}0.5H_2O$: C, 59.91; H, 5.34; N, 8.73. Found: C, 60.10; H, 5.42; N, 8.46.

5.1.143. 8′-Amino-6,7-didehydro-3-methoxy-17-methylquinolino[2′,3′:6,7]morphinan-14β-ol (32d)

Compound **32d** was prepared from compound **23d** according to the procedure used to prepare compound **32a**. Yield, 36%; a yellow amorphous solid.

IR (KBr): 3437, 2930, 1592, 1497, 1273, 1044 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.35–1.46 (1H, m), 2.19–2.31 (2H, m), 2.41–2.48 (1H, m), 2.44 (3H, s), 2.88–3.08 (4H, m), 3.25 (1H, d, J = 18.3 Hz), 3.54 (1H, d, J = 17.4 Hz), 3.64 (3H, s), 3.67 (1H, d, J = 17.4 Hz), 4.63 (1H, br s), 6.60 (1H, dd, J = 2.7, 8.4 Hz), 6.80 (1H, dd, J = 1.2, 7.5 Hz), 6.90 (1H, d, J = 2.4 Hz), 6.94 (1H, dd, J = 1.2, 8.1 Hz), 7.00 (1H, d, J = 8.4 Hz), 7.16 (1H, t, J = 7.8 Hz), 7.55 (1H, s), two protons (NH_2) were not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.0, 36.0, 36.6, 39.3, 40.5, 42.9, 45.6, 55.0, 61.8, 69.5, 109.0, 111.4, 111.5, 115.3, 126.0, 127.5, 127.6, 128.1, 128.3, 135.0, 136.9, 141.3, 143.1, 154.3, 158.1. HRMS (ESI) Calcd for $C_{25}H_{28}N_3O_2$ $[M+H]^+$: 402.2182. Found: 402.2180.

5.1.144. 6,7-Didehydro-8′-(*N*,*N*-dimethylamino)-3-methoxy-17-methylquinolino[2′,3′:6,7]morphinan-14β-ol (33d)

Compound **33d** was prepared from compound **32d** according to the procedure used to prepare compound **33a**. Yield, 94%; a yellow oil.

IR (neat): 3409, 2936, 1499, 1273, 1043, 752 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.35–1.46 (1H, m), 2.19–2.31 (2H, m), 2.40–2.48 (1H, m), 2.44 (3H, s), 2.87–3.02 (4H, m), 3.09 (6H, s), 3.25 (1H, d, J = 18.0 Hz), 3.59 (1H, d, J = 17.1 Hz), 3.61 (3H, s), 3.77 (1H, d, J = 17.1 Hz), 6.60 (1H, dd, J = 2.7, 8.4 Hz), 6.94 (1H, d, J = 2.7 Hz), 6.97 (1H, dd, J = 1.2, 7.4 Hz), 6.99 (1H, d, J = 8.4 Hz), 7.17 (1H, dd, J = 1.3, 8.1 Hz), 7.26 (1H, t, J = 7.8 Hz), 7.59 (1H, s), a proton (OH) was not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.0, 35.9, 36.6, 39.7, 40.7, 42.9, 44.5 (2C), 45.6, 54.9, 61.7, 69.5, 111.0, 112.1, 114.3, 119.9, 125.4, 127.46, 127.51, 128.3, 128.5, 135.4, 140.8, 141.3, 149.6 154.6, 158.1. HRMS (ESI) Calcd for $C_{27}H_{32}N_3O_2$ $[M+H]^+$: 430.2495. Found: 430.2504.

5.1.145. 6,7-Didehydro-8′-(*N*,*N*-dimethylamino)-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol (34d)

Compound **34d** was prepared from compound **33d** according to the procedure used to prepare compound **24a**. Yield, 87%; a yellow oil.

IR (neat): 3348, 2937, 1446, 1280, 1051, 754 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.16–1.26 (1H, m), 2.07–2.21 (2H, m), 2.36–2.42 (1H, m), 2.41 (3H, s), 2.82–3.06 (4H, m), 2.99 (6H, s), 3.18 (1H, d, J = 18.0 Hz), 3.50 (1H, d, J = 17.4 Hz), 3.67 (1H, d, J = 17.4 Hz), 6.45 (1H, dd, J = 2.4, 8.4 Hz), 6.69 (1H, d, J = 2.4 Hz), 6.85 (1H, d, J = 8.4 Hz), 6.97 (1H, dd, J = 1.2, 7.5 Hz), 7.13 (1H, dd, J = 1.2, 7.8 Hz), 7.22 (1H, t, J = 7.8 Hz), 7.55 (s, 1H), two protons (OH) were not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9, 35.8, 36.3, 39.2, 40.4, 43.0, 44.6 (2C), 45.6, 61.7, 69.4, 112.6, 113.6, 114.7, 120.3, 125.3, 126.8, 127.7, 128.3, 128.5, 135.7, 140.6, 141.2, 149.6, 154.7, 155.0. HRMS (ESI) Calcd for $C_{26}H_{30}N_3O_2$ $[M+H]^+$: 416.2338. Found: 416.2318.

5.1.146. 6,7-Didehydro-8′-(*N*,*N*-dimethylamino)-17-methylquinolino[2′,3′:6,7]morphinan-3,14β-diol hydrochloride (SYK-363)

SYK-363 was prepared from compound **34d** according to the procedure used to prepare SYK-27.

Yield, quant.; a pale yellow amorphous solid. Mp: 234–236 °C (dec). Anal. Calcd for $C_{26}H_{29}N_3O_2{\cdot}2.0HCl{\cdot}1.7H_2O$: C, 60.16; H, 6.68; N, 8.10. Found: C, 60.21; H, 6.74; N, 8.14.

5.2. Pharmacology

5.2.1. Opioid receptor binding assay

Mouse whole brain without cerebellum and guinea pig cerebellum membranes were prepared as described previously.[31] The μ, δ or κ opioid receptor binding assays were performed with [^{3}H]DAMGO, [^{3}H]DPDPE ([D-Pen^{2,5}]-Enkephalin) or [^{3}H]U69,593. Nonspecific binding was measured in the presence of 1 μM unlabeled DAMGO, DPDPE or U-69,593. K_i value was calculated according to the Cheng–Prusoff equation.[32]

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