Experimental Section

All Chemicals and solvents were supplied from Adamas-beta and were used without further purification.^{1}H and^{13}C NMR spectra were recorded on a Bruker AMX-400 instrument. Proton-coupling patterns were described as singlet, doublet, triplet, quartet, multiplet, and broad. Mass spectra were given with an electric ionization (ESI) produced by HP5973N analytical mass spectrometer. HRMS spectra were recorded with AB 5600+ Q TOF instrument. Purities of tested compounds were determined by HPLC analysis and were ≥95%

6-amino-3, 4-dihydronaphthalen-1(2*H*)-one(7)

Step 1: the preparation of 2-Bromo-2-methylpropanamide: A 250-mL, three-necked, round-bottomed flask, fitted with a thermometer, pressure-equalizing dropping funnel and equipped with a mechanical stirrer is charged with 28.0-30.0% aqueous ammonium hydroxide (35.7 mL, approximately 600 mmol) and water (44.3 mL). The dropping funnel is charged with 2-bromo-2-methylpropanoyl bromide (50.0 g, 217.5 mmol), and the mixture is cooled below 5 °C (internal temperature) using a brine/ice bath with stirring. The 2-bromo-2-methylpropanoyl bromide is added drop-wise slowly with stirring so that the internal temperature does not rise above 15 °C with cooling using a brine/ice bath. Stirring is continued for 1 h after the addition is complete, with the temperature of the reaction mixture maintained between 0 and 5 °C. The resulting white precipitate is collected by filtration on a glass filter funnel and washed three times with 40 mL of water to give (33.0 g, 91.4 %) a white crystalline powder.

Step 2 A 500-mL, three-necked, round-bottomed flask, fitted with a reflux condenser, Thermometer, addition funnel and equipped with a large magnetic stirring bar is charged with 3,4-dihydro-6-hydroxy-1(2*H*)-naphthalenone (10.0 g, 61.7 mmol) and *N*,*N*-dimethylacetamide (90 mL). Sodium hydroxide (7.40 g, 185 mmol) is added into the flask by temporarily removing the addition funnel and the resulting mixture is stirred at 20-30 °C for 1 h. 2-Bromo-2-methylpropanamide (30.7 g, 185 mmol) is added to the reaction mixture through the addition funnel, and the resulting mixture is

stirred at 25-35 °C for 5 h. After the reaction period, sodium hydroxide (22.2 g, 555 mmol) is added, and the resulting mixture is stirred for 1 h with heating to 50-60 °C (internal temperature) using an oil bath. After the reaction period, water (90 mL) is added by use of an addition funnel, and the mixture is heated at reflux using an oil bath for 1 h (internal temperature is 85-95 °C). Water (180 mL) is added to the reaction solution using an addition funnel, and the resulting precipitated mixture is allowed to cool slowly to 20-30 °C. The precipitated crystalline powder is collected by filtration on a glass filter funnel and washed three times with 90 mL of water to give (6.28 g, 63.2%) a brown crystalline powder **7**.

6-bromo-3, 4-dihydronaphthalen-1(2*H*)-one (8)

To the solution of **7** (5g, 31mmol) in a mixture of hydrobromic acid (50mL, 47%) and water (50mL) cooled by brine-bath, a solution of sodium nitrite (2.5g, 36mmol) in water (20mL) was added dropwise. The resulting mixture was stirred for 15 min before a solution of cuprous bromide (5.14g, 36mmol) in hydrobromic acid (20mL,47%) was added dropwise. The resulting mixture was then stirred for 15min. The aqueous layers were washed with ethyl acetate (3×15 mL). The organic layers were combined and was dried over Na_2SO_4, filtered, and evaporated. The resulting yellow oil was purified by chromatography (petroleum ether: ethyl acetate 40:1) to yield 6.03g of **8** as a light yellow oil. (85% yield)

General procedure A the preparation of (9a-9l)

To the solution of **8** (5.00g, 22.22mol) in toluene, phenylboronic acid (4.06g, 33.33mmol) and potassium carbonate (6.13g, 44.44mmol), catalytic amount of tetrakis(triphenylphosphine)palladium(0) (50mg, 0.04mmol)was added under argon. The resulting mixture was then heated to reflux overnight. The reaction mixture was then filtered and evaporated under low pressure to give **9a** of (5.93g, 78% yield) after chromatography (petroleum ether: ethyl acetate 30:1).

General procedure B the preparation of (10a-10l)

To the solution of **9a** (1.51g, 6.8mmol) in acetonitrile (20mL), *N*-methyl-*N*-methylenemethanaminium (1.28g, 14mmol) was added, and the mixture was stirred overnight at room temperature. The reaction mixture was evaporated to get a yellow residue. A mixture of water (20mL) and ethyl acetate (15mL) was added to the residue and the resulting solution was then basified with NaOH to pH=10. The aqueous layers were then washed with ethyl acetate (2 × 15 mL). The organic layers were combined and was dried over Na_2SO_4, filtered, and evaporated to obtain 1.67g of a yellow residue. The product was used without further purification in the next procedure. (~88% yield).

General procedure C for the preparation of (6a-6h)

3-Bromoanisole (1.55mL, 12.3mmol) was dissolved in THF (10mL) in an oven dried round bottom flask under argon and the resulting solution was cooled to -78 °C. BuLi (4.92 mL of a 2.5 M solution in hexanes, 12.3mmol) was syringed in and the resulting solution stirred at -78 °C for 1 h. **10a** (687mg, 2.46mmol) was syringed in and the resulting solution stirred at -78 °C for 2h before adding 10 mL satd. aq. NH_4Cl to the cold solution. This mixture was then warmed to room temperature, the layers were separated, and the aqueous phase extracted ethyl acetate (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting yellow oil was purified by chromatography (dichloromethane:methanol 80:1) to yield 781 mg of **6a** as a light yellow oil (75% yield). Aryllithium addition reaction gives a mixture with diastereomers (about 80% for cis-isomer). In our study, the abundance of the cis-isomer could be improved to 95% by thin-layer chromatography.

General procedure D for the preparation of (6i-6t)

(3-bromophenoxy)(tert-butyl)dimethylsilane (1.78mL, 12.3mmol) was dissolved in THF (10mL) in an oven dried round bottom flask under argon and the resulting solution was cooled to -78 °C. BuLi (4.92 mL of a 2.5 M solution in hexanes, 12.3mmol) was syringed in and the resulting solution stirred at -78 °C for 1 h. **10a**

(687mg, 2.46mmol) was syringed in and the resulting solution stirred at -78 ℃ for 2h before adding 10 mL satd. aq. NH_4Cl to the cold solution. This mixture was then warmed to room temperature, the layers were separated, and the aqueous phase extracted ethyl acetate (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulted yellow oil was dissolved in 20ml DMF and 2ml H_2O, and Cs_2CO_3 (400mg, 1.23mmol) was added into the solution. After stirred at rt for 1 h, the resulting mixture was diluted with 20ml ethyl acetate and 10 ml H_2O. The layers were separated, and the aqueous phase extracted ethyl acetate (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting yellow oil was purified by chromatography (dichloromethane:methanol 80:1) to yield 662 mg of **6i** as a light yellow oil.(70% yield) Aryllithium addition reaction gives a mixture with diastereomers (about 80% for cis-isomer). In our study, the abundance of the cis-isomer could be improved to 95% by thin-layer chromatography.

2-((dimethylamino)methyl)-1-(3-methoxyphenyl)-6-phenyl-1,2,3,4-tetrahydronaphthalen-1-ol (6a)

White powder 78 mg 54% **^{1}H NMR (400 MHz ， DMSO-d^6)** ^{1}H NMR (400 MHz, DMSO) δ 7.63 (d, *J* = 7.3 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 3H), 7.39 – 7.28 (m, 2H), 7.23 (d, *J* = 8.2 Hz, 1H), 7.15 (t, *J* = 7.9 Hz, 1H), 6.83 – 6.70 (m, 3H), 6.60 (d, *J* = 7.8 Hz, 1H), 3.68 (s, 3H), 3.00 (d, *J* = 5.2 Hz, 2H), 2.30 – 2.11 (m, 8H), 1.78 – 1.63 (m, 2H), 1.53 – 1.37 (m, 1H).**^{13}C NMR (101 MHz, DMSO)** δ 159.29, 149.83, 143.54, 141.89, 139.10, 137.25, 131.00, 129.35, 127.85, 126.84, 124.71, 120.86, 119.63, 114.57, 113.49, 111.88, 75.50, 59.32, 55.48, 42.77, 42.15, 28.82, 23.98, 23.36. ESI-MS m/z 388.1[M+H]$^+$ HRMS *m/z* calcd for $C_{26}H_{29}NO_2$ [M + H]+,388.2271; found, 388.2275.

2-((dimethylamino)methyl)-1-(3-methoxyphenyl)-6-(2-methoxyl-phenyl)-1,2,3,4-tetrahydronaphthalen-1-ol (6b)

White powder 52 mg 44% **^{1}H NMR (400 MHz ， DMSO-d^6)** δ 9.65 (s, 1H), 7.36 – 7.30 (m, 1H), 7.29 – 7.22 (m, 3H), 7.16 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.12 – 7.06 (m, 2H),

7.00 (t, *J* = 7.4 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 6.85 (dd, *J* = 8.1, 2.3 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 5.97 (s, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.10 – 2.98 (m, 2H), 2.90 (d, *J* = 16.6 Hz, 1H), 2.77 (d, *J* = 8.8 Hz, 1H), 2.70 (d, *J* = 4.2 Hz, 3H), 2.56 – 2.52 (m, 1H), 2.45 (d, *J* = 4.3 Hz, 3H), 2.17 (d, *J* = 11.8 Hz, 1H), 2.03 – 1.91 (m, 1H). **^{13}C NMR (101 MHz, DMSO)** δ 159.35, 156.62, 149.49, 141.00, 137.27, 136.19, 130.76, 129.98, 129.91, 129.40, 129.36, 129.29, 127.41, 121.18, 119.62, 113.50, 112.13, 111.97, 75.26, 65.39, 59.10, 55.89, 55.50, 44.97, 42.45, 41.47, 28.82. ESI-MS m/z 418.2 $[M+H]^+$ HRMS *m*/*z* calcd for $C_{27}H_{31}NO_3$ [M + H]+,418.2377; found, 418.2375.

2-((dimethylamino)methyl)-1-(3-methoxyphenyl)-6-(3-methoxyl-phenyl)-1,2,3,4-tetrahydronaphthalen-1-ol(6c)

White powder 88 mg 47% **^{1}H NMR (400 MHz ， DMSO-d^6)** δ 10.27 (s, 1H), 7.47 (d, *J* = 1.4 Hz, 1H), 7.36 (ddd, *J* = 7.9, 4.7, 3.0 Hz, 2H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 1H), 7.17 – 7.13 (m, 1H), 7.08 (s, 1H), 6.93 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.90 – 6.81 (m, 3H), 5.97 (s, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.12 – 2.92 (m, 3H), 2.85–2.54 (m, 5H), 2.48 – 2.33 (m, 3H), 2.28 (s, 1H), 2.03 – 1.90 (m, 1H). **^{13}C NMR(101 MHz, DMSO-d^6)** δ 160.18, 159.34, 149.54, 141.85, 141.79, 139.04, 137.16, 130.96, 130.41, 129.39, 126.94, 124.84, 119.61, 119.40, 113.47, 113.37, 112.64, 112.00, 75.31, 59.02, 55.59, 55.50, 42.50, 28.73, 23.40. ESI-MS m/z 418.2 $[M+H]^+$ HRMS *m*/*z* calcd for $C_{27}H_{31}NO_3$ [M + H]+,418.2377; found, 418.2380.

2-((dimethylamino)methyl)-1-(3-methoxyphenyl)-6-(4-methoxyl-phenyl)-1,2,3,4-tetrahydronaphthalen-1-ol(6d)

White powder 71 mg 60% **^{1}H NMR (400 MHz ， DMSO-d^6)** δ 9.67 (s, 1H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.40 (s, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 7.25 (t, *J* = 8.0 Hz, 1H), 7.06 (s, 1H), 7.00 (d, *J* = 8.7 Hz, 2H), 6.89 – 6.79 (m, 3H), 5.96 (s, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.11 – 2.90 (m, 3H), 2.84 – 2.75 (m, 1H), 2.70 (d, *J* = 3.6 Hz, 3H), 2.55 – 2.53 (s, 1H), 2.45 (d, *J* = 3.7 Hz, 3H), 2.15 (d, *J* = 11.1 Hz, 1H), 2.02 – 1.88 (m, 1H). **^{13}C NMR (101 MHz, DMSO)** δ 159.34, 149.55, 140.89, 138.82, 137.08, 132.62, 130.96, 129.38, 128.13, 126.23, 124.28, 119.62, 114.79, 113.47, 111.99, 75.29, 59.02,

55.64, 55.49, 44.92, 42.47, 41.51, 28.75, 23.39. ESI-MS m/z 418.2 $[M+H]^+$ HRMS *m/z* calcd for $C_{27}H_{31}NO_3$ [M + H]+,418.2377; found, 418.2379.

2-((dimethylamino)methyl)-1-(3-methoxyphenyl)-6-(4-trifluoromethyl-phenyl)-1, 2,3,4-tetrahydronaphthalen-1-ol(6e)

White powder 73 mg 65% **^{1}H NMR (400 MHz, DMSO)** δ 7.88 (d, *J* = 8.2 Hz, 2H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 1.6 Hz, 1H), 7.44 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 7.01 (s, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.81 (dd, *J* = 8.1, 2.8 Hz, 2H), 3.75 (s, 3H), 3.48 – 3.22 (m, 1H), 3.06 – 2.89 (m, 2H), 2.56 (s, 1H), 2.35 – 1.99 (m, 8H), 1.93 – 1.79 (m, *J* = 16.0 Hz, 1H). **^{13}C NMR (101 MHz, DMSO)** δ 163.93, 155.18, 149.17, 148.29, 142.43, 142.02, 135.87, 133.84, 133.02, 132.80, 131.94, 130.94, 130.51, 129.68, 128.71, 124.37, 118.25, 116.33, 80.71, 64.69, 60.18, 49.99, 48.12, 33.66, 28.00 ESI-MS m/z 456.2 $[M+H]^+$ HRMS *m/z* calcd for $C_{27}H_{28}F_3NO_2$ [M + H]+,456.2145; found, 456.2156.

2-((dimethylamino)methyl)-1-(3-methoxyphenyl)-6-(4-choloro-phenyl)-1,2,3,4-tet rahydronaphthalen-1-ol(6f)

White powder 49 mg 66% **^{1}H NMR (400 MHz, DMSO)** δ 7.67 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 1.6 Hz, 1H), 7.36 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.22 (t, *J* = 7.9 Hz, 1H), 7.01 (s, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.81 (dd, *J* = 8.1, 2.6 Hz, 2H), 3.74 (s, 3H), 3.37 (s, 1H), 3.04 – 2.87 (m, 2H), 2.59 (s, 1H), 2.26 (d, *J* = 32.1 Hz, 7H), 2.07 (d, *J* = 12.2 Hz, 1H), 1.86 (s, 1H). **^{13}C NMR (101 MHz, DMSO)** δ 163.93, 155.16, 153.44, 147.53, 143.96, 142.26, 137.41, 135.77, 134.05, 133.85, 131.54, 129.33, 124.38, 118.24, 117.13, 116.35, 80.65, 60.17, 49.82, 48.06, 41.13, 34.20, 33.64, 28.02. ESI-MS m/z 422.2 $[M+H]^+$ HRMS *m/z* calcd for $C_{26}H_{28}ClNO_2$ [M + H]+,422.1881; found, 422.1882.

2-((dimethylamino)methyl)-1-(3-methoxyphenyl)-6-(3,4-dicholoro-phenyl)-1,2,3,4 -tetrahydronaphthalen-1-ol(6g)

White powder 58 mg 57% **^{1}H NMR (400 MHz, DMSO)** δ 7.92 (d, *J* = 2.0 Hz, 1H), 7.73 – 7.63 (m, 2H), 7.52 (d, *J* = 1.6 Hz, 1H), 7.41 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.21 (t, *J* = 7.9 Hz, 1H), 6.99 (s, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.80 (dd, *J* = 8.2, 2.4 Hz, 2H), 3.74 (s, 3H), 3.37 (s, 2H), 2.96 (d, *J* = 4.6 Hz, 2H), 2.39 – 2.11 (m, 7H), 2.05 (d, *J* = 11.2 Hz, 1H), 1.84 (s, 1H). **^{13}C NMR (101 MHz, DMSO)** δ163.92, 155.36, 148.20, 145.78, 142.42, 140.90, 136.90, 136.18, 135.82, 135.24, 133.83, 133.49, 131.97, 131.75, 129.42, 124.37, 118.25, 116.31, 80.74, 64.71, 60.18, 50.04, 48.11, 34.20, 33.57, 27.98. ESI-MS m/z 456.2 $[M+H]^+$ HRMS *m/z* calcd for $C_{26}H_{27}Cl_2NO_2$ [M + H]+,456.1492; found, 456.1506.

2-((dimethylamino)methyl)-1-(3-methoxyphenyl)-6-(2-methyl-phenyl)-1,2,3,4-tetrahydronaphthalen-1-ol(6h)

White powder 59 mg 53% **^{1}H NMR (400 MHz, DMSO)** δ 10.10 (s, 1H), 7.31 – 7.22 (m, 4H), 7.20 – 7.15 (m, 1H), 7.14 (s, 1H), 7.10 (s, 1H), 7.05 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 6.85 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 5.98 (s, 1H), 3.77 (s, 3H), 3.12 – 2.89 (m, 2H), 2.77 (s, 2H), 2.68 (s, 3H), 2.56 (d, *J* = 10.6 Hz, 1H), 2.43 (s, 3H), 2.24 (d, *J* = 6.5 Hz, 4H), 2.05 – 1.93 (m, 1H). **^{13}C NMR (101 MHz, DMSO)** δ 159.35, 149.47, 141.38, 141.03, 140.33, 136.49, 135.11, 130.81, 130.21, 129.92, 129.43, 129.11, 127.73, 127.08, 126.38, 119.59, 113.51, 112.01, 75.30, 59.09, 55.49, 44.97, 42.37, 41.51, 28.68, 23.33, 20.69. ESI-MS m/z 402.0 $[M+H]^+$ HRMS *m/z* calcd for $C_{27}H_{31}NO_2$ [M + H]+,402.2428; found, 402.2429.

2-((dimethylamino)methyl)-1-(3-hydroxyphenyl)-6-phenyl-1,2,3,4-tetrahydronaphthalen-1-ol(6i)

White powder 30 mg 39% **^{1}H NMR (400 MHz ， DMSO-d^{6})** δ 9.31 (s, 1H), 7.64 (d, *J* = 7.1 Hz, 2H), 7.50 – 7.40 (m, 4H), 7.33 (dd, *J* = 16.2, 7.7 Hz, 2H), 7.07 (t, *J* = 7.9 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.60 (d, *J* = 7.7 Hz, 1H), 6.51 (s, 1H), 6.01 (s, 1H), 3.18 (dd, *J* = 17.8, 9.2 Hz, 1H), 3.04 (s, 2H), 2.09 – 1.98 ((m, 6H), 2.46 – 2.32 (m, 2H), 2.09 – 1.98 (m, 1H), 1.72 – 1.58 (m, 1H). **^{13}C NMR (101 MHz, DMSO)** δ

156.32, 146.65, 143.41, 140.04, 138.32, 136.10, 128.91, 128.44, 127.91, 127.31, 126.56, 126.03, 124.34, 118.53, 115.17, 113.30, 76.20, 44.81, 42.06, 29.83, 29.05, 28.32, 23.14. ESI-MS m/z 374.1 $[M+H]^+$ HRMS *m/z* calcd for $C_{25}H_{27}NO_2$ [M + H]+,374.2115; found, 374.2121.

2-((dimethylamino)methyl)-1-(3-hydroxyphenyl)-6-(2-methoxyl-phenyl)-1,2,3,4-tetrahydronaphthalen-1-ol(6j)

White powder 48 mg 47% **^{1}H NMR (400 MHz ， DMSO-d^6)**δ 9.36 (s, 2H), 7.37 – 7.29 (m, 1H), 7.24 (dd, *J* = 6.8, 2.3 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.16 – 7.07 (m, 2H), 7.01 (t, *J* = 7.4 Hz, 1H), 6.87 (s, 1H), 6.80 (t, *J* = 8.4 Hz, 2H), 6.66 (dd, *J* = 7.9, 2.0 Hz, 1H), 5.91 (s, 1H), 3.74 (s, 3H), 3.11 – 2.76 (m, 4H), 2.72 (s, 3H), 2.14 – 2.04 (m, 4H), 2.14 – 2.04 (m, 1H), 2.02 – 1.88 (m, 1H). **^{13}C NMR (101 MHz, DMSO)** δ 156.78, 156.02, 148.73, 140.58, 136.63, 135.53, 130.17, 129.50, 129.31, 128.70, 126.83, 120.59, 117.28, 113.84, 113.50, 111.51, 74.60, 58.52, 55.29, 44.32, 42.16, 40.91, 28.29, 22.87. ESI-MS m/z 404.3 $[M+H]^+$ HRMS *m/z* calcd for $C_{26}H_{29}NO_3$ [M + H]+,404.2220; found, 404.2221. (+)-**6j** $[\alpha]^{20}_D$= +6.7(c 0.6, MeOH) The optical purity of (+)-**6j** was determined to be 98% by HPLC analyses (CHIRALPAK ID (0.46 cm×15 cm; Hexane/IPA/DEA =50/50/0.1 with flow rate = 1.0 mL/min and a UV detector at 254 nm; retention time = 3.284 min). (-)-**6j** $[\alpha]^{20}_D$= -6.7(c 0.6, MeOH) The optical purity of (-)-**6j** was determined to be 98% by HPLC analyses (CHIRALPAK ID (0.46 cm×15 cm; Hexane/IPA/DEA =50/50/0.1 with flow rate = 1.0 mL/min and a UV detector at 254 nm; retention time = 3.934 min).

2-((dimethylamino)methyl)-1-(3-hydroxyphenyl)-6-(3-methoxyl-phenyl)-1,2,3,4-tetrahydronaphthalen-1-ol (6k)

White powder 79 mg 52% **^{1}H NMR (400 MHz ， DMSO-d^6)** δ 9.73 (s, 1H), 9.38 (s, 1H), 7.46 (s, 1H), 7.40 – 7.32 (m, 2H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.13 (dd, *J* = 13.1, 5.1 Hz, 2H), 6.95 – 6.87 (m, 2H), 6.85 (s, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.66 (dd, *J* = 7.9, 1.9 Hz, 1H), 5.92 (s, 1H), 3.81 (s, 3H), 3.01 (dt, *J* = 13.2, 9.8 Hz, 3H), 2.87 – 2.77 (m, 1H), 2.70 (s, 3H), 2.44 (s, 4H), 2.21 – 2.08 (d, *J* = 10.7 Hz, 1H), 2.02 – 1.87

(m, 1H). **^{13}C NMR (101 MHz, DMSO)** δ 159.58, 156.80, 148.75, 141.35, 141.29, 138.43, 136.50, 130.48, 129.83, 128.63, 126.31, 124.26, 118.81, 117.27, 113.86, 113.54, 112.78, 112.03, 74.63, 58.37, 55.00, 44.27, 42.16, 40.87, 28.19, 22.88. ESI-MS m/z 404.3 $[M+H]^+$ HRMS *m/z* calcd for $C_{26}H_{29}NO_3$ [M + H]+,404.2220; found, 404.2219.

2-((dimethylamino)methyl)-1-(3-hydroxyphenyl)-6-(4-methoxyl-phenyl)-1,2,3,4-tetrahydronaphthalen-1-ol(6l)

White powder 69 mg 62% **^{1}H NMR (400 MHz ， DMSO-d^{6})** δ 9.36 (s, 1H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.39 (s, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.12 (t, *J* = 7.9 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.90 – 6.82 (m, 2H), 6.76 (d, *J* = 7.7 Hz, 1H), 6.65 (dd, *J* = 7.9, 2.0 Hz, 1H), 5.91 (s, 1H), 3.79 (s, 3H), 2.98 (dt, *J* = 21.6, 14.0 Hz, 3H), 2.88 – 2.77 (m, 1H), 2.71 (s, 3H), 2.48 – 2.34 (m, 4H), 2.17 – 2.04 (m, 1H), 2.01 – 1.88 (m, 1H). **^{13}C NMR (101 MHz, DMSO)** δ 158.79, 156.62, 150.08, 141.50, 138.04, 136.75, 132.35, 130.50, 128.37, 127.64, 125.67, 123.73, 117.48, 114.30, 113.95, 113.14, 75.46, 59.51, 55.16, 44.82, 43.22, 28.57, 22.84. ESI-MS m/z 404.3 $[M+H]^+$ HRMS *m/z* calcd for $C_{26}H_{29}NO_3$ [M + H]+,404.2220; found, 404.2223.

2-((dimethylamino)methyl)-1-(3-hydroxyphenyl)-6-(4-trifluoromethyl-phenyl)-1,2,3,4-tetrahydronaphthalen-1-ol(6m)

White powder 78 mg 54% **^{1}H NMR （400 MHz ， DMSO-d^{6}）** δ 9.85 (s, 1H), 9.40 (s, 1H), 7.88 (d, *J* = 8.3 Hz, 2H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 1.6 Hz, 1H), 7.47 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.14 (t, *J* = 7.9 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.86 (s, 1H), 6.77 (d, *J* = 7.7 Hz, 1H), 6.67 (dd, *J* = 7.9, 1.9 Hz, 1H), 5.97 (s, 1H), 3.11 – 2.96 (m, 3H), 2.83 (d, *J* = 12.3 Hz, 1H), 2.70 (s, 3H), 2.44 (s, 4H), 2.24 – 2.14 (m, 1H), 2.03 – 1.89 (m, 1H). **^{13}C NMR (101 MHz, DMSO)** δ 156.95, 148.73, 143.85, 142.40, 137.02, 136.96, 130.87, 128.81, 127.91, 127.37, 126.79, 125.75, 124.56, 123.04, 117.39, 113.96, 113.73, 74.75, 58.46, 44.40, 42.20, 41.01, 28.28, 22.92. ESI-MS m/z 442.2 $[M+H]^+$ HRMS *m/z* calcd for $C_{26}H_{26}F_3NO_2$ [M + H]+,442.1988; found, 442.1989.

2-((dimethylamino)methyl)-1-(3-hydroxyphenyl)-6-(4-choloro-phenyl)-1,2,3,4-tetrahydronaphthalen-1-ol(6n)

White powder 28 mg 43% **^{1}H NMR （400 MHz ， DMSO-d^{6}）** δ 10.05 (s, 1H), 9.40 (s, 1H), 7.68 (d, *J* = 8.6 Hz, 2H), 7.55 – 7.45 (m, 3H), 7.39 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.13 (t, *J* = 7.9 Hz, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 6.86 (s, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.67 (dd, *J* = 7.7, 2.1 Hz, 1H), 5.92 (s, 1H), 2.99 (ddd, *J* = 17.3, 16.8, 8.2 Hz, 3H), 2.89 – 2.78 (m, 1H), 2.69 (s, 3H), 2.43 (s, 4H), 2.27 – 2.15 (m, 1H), 2.03 – 1.88 (m, 1H). **^{13}C NMR (101 MHz, DMSO)** δ 156.94, 148.80, 141.73, 138.65, 137.26, 136.81, 132.26, 130.77, 128.86, 128.78, 128.35, 126.31, 124.18, 117.39, 113.97, 113.69, 74.74, 58.46, 44.38, 42.24, 40.99, 28.29, 22.96. ESI-MS m/z 408.2 $[M+H]^+$ HRMS *m*/*z* calcd for $C_{25}H_{26}ClNO_2$ [M + H]+,408.1725; found, 408.1723.

2-((dimethylamino)methyl)-1-(3-hydroxyphenyl)-6-(3,4-dicholoro-phenyl)-1,2,3,4-tetrahydronaphthalen-1-ol(6o)

White powder 67 mg 80% **^{1}H NMR (400 MHz ， DMSO-d^{6})**δ 9.97 (s, 1H), 9.40 (s, 1H), 7.93 (d, *J* = 2.0 Hz, 1H), 7.74 – 7.64 (m, 2H), 7.55 (d, *J* = 1.6 Hz, 1H), 7.49 – 7.41 (m, 1H), 7.13 (t, *J* = 7.9 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 6.85 (s, 1H), 6.76 (d, *J* = 7.7 Hz, 1H), 6.67 (dd, *J* = 7.9, 2.1 Hz, 1H), 5.96 (s, 1H), 3.12 – 2.92 (m, 3H), 2.82 (dd, *J* = 21.6, 10.1 Hz, 1H), 2.70 (s, 3H), 2.44 (s, 4H), 2.19 (s, 1H), 2.02 – 1.87 (m, 1H). **^{13}C NMR (101 MHz, DMSO)** δ 156.82, 148.60, 142.17, 140.31, 136.82, 135.76, 131.58, 130.87, 130.70, 129.98, 128.67, 128.15, 126.66, 126.41, 124.15, 117.25, 113.83, 113.60, 74.60, 58.31, 44.27, 42.07, 40.87, 28.10, 22.79. ESI-MS m/z 442.2 $[M+H]^+$ HRMS *m*/*z* calcd for $C_{25}H_{25}Cl_2NO_2$ [M + H]+,442.1335; found, 442.1331.

2-((dimethylamino)methyl)-1-(3-hydroxyphenyl)-6-(2-methyl-phenyl)-1,2,3,4-tetrahydronaphthalen-1-ol(6p)

White powder 71 mg 83% **^{1}H NMR （400 MHz ， DMSO-d^{6}）** δ 9.30 (s, 1H), 7.31 – 7.20 (m, 3H), 7.20 – 7.14 (m, 1H), 7.14 – 7.07 (m, 2H), 7.04 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 2H), 6.75 (d, *J* = 7.7 Hz, 1H), 6.63 (dd, *J* = 8.0, 1.9 Hz, 1H), 3.37 (d, *J* = 8.7 Hz, 1H), 2.99 – 2.88 (m, 2H), 2.63 (d, *J* = 10.7 Hz, 1H), 2.24 (s, 10H),

2.07 (d, *J* = 11.8 Hz, 1H), 1.97 – 1.82 (m, 1H). **^{13}C NMR (101 MHz, DMSO)** δ 162.78, 157.16, 150.22, 141.93, 140.02, 136.60, 135.11, 130.79, 130.23, 129.93, 129.00, 127.65, 126.97, 117.92, 114.40, 113.69, 75.78, 44.93, 43.57, 36.25, 31.24, 29.03, 23.29, 20.72. ESI-MS m/z 388.0 $[M+H]^+$ HRMS *m/z* calcd for $C_{26}H_{29}NO_2$ [M + H]+,388.2271; found, 388.2272.

2-((dimethylamino)methyl)-6-(2-fluorophenyl)-1-(3-hydroxyphenyl)-1,2,3,4-tetra hydronaphthalen-1-ol(6q)

White powder 66 mg 81% **^{1}H NMR （400 MHz ，DMSO-d^6）** δ 9.32 (s, 1H), 7.58 – 7.47 (m, 1H), 7.46 – 7.21 (m, 5H), 7.09 (dt, *J* = 12.7, 7.8 Hz, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.84 (s, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 6.63 (dd, *J* = 13.7, 5.9 Hz, 1H), 3.33 (d, *J* = 10.4 Hz, 1H), 2.96 (ddd, *J* = 20.7, 12.2, 4.1 Hz, 2H), 2.66 (s, 1H), 2.35 (d, *J* = 55.1 Hz, 7H), 2.10 (d, *J* = 10.4 Hz, 1H), 2.03 – 1.76 (m, 1H). **^{13}C NMR (101 MHz, DMSO)** δ 160.82, 158.38, 157.20, 150.03, 142.88, 137.00, 133.89, 131.15, 130.70, 129.85, 128.98, 128.44, 126.75, 125.35, 117.91, 116.65, 115.59, 114.40, 113.81, 75.71, 59.72, 49.06, 43.42, 28.95, 23.28. ESI-MS m/z 392.1 $[M+H]^+$ HRMS *m/z* calcd for $C_{25}H_{26}FNO_2$ [M + H]+, 392.2020; found, 392.2017.

6-(2-chlorophenyl)-2-((dimethylamino)methyl)-1-(3-hydroxyphenyl)-1,2,3,4-tetra hydronaphthalen-1-ol(6r)

White powder 75 mg 83% **^{1}H NMR （400 MHz ，DMSO-d^6）** δ 9.30 (s, 1H), 7.55 (ddd, *J* = 7.7, 3.6, 1.8 Hz, 1H), 7.46 – 7.34 (m, 3H), 7.15 (dddd, *J* = 20.1, 18.8, 16.0, 8.2 Hz, 3H), 6.94 – 6.70 (m, 2H), 6.66 – 6.55 (m, 2H), 3.35 (s, 1H), 3.07 – 2.82 (m, 2H), 2.55 (s, 1H), 2.41 – 2.12 (m, 6H), 2.06 (d, *J* = 12.0 Hz, 1H), 1.96 – 1.72 (m, 2H).**^{13}C NMR (101 MHz, DMSO)** δ 157.14, 150.21, 144.08, 142.95, 140.03, 137.41, 136.70, 131.97, 130.34, 129.51, 128.91, 127.96, 127.16, 117.90, 115.57, 114.36, 113.68, 75.81, 59.93, 49.06, 43.72, 42.55, 29.13, 23.25. ESI-MS m/z 408.2 $[M+H]^+$ HRMS *m/z* calcd for $C_{25}H_{26}ClNO_2$ [M + H]+,408.1725; found, 408.1718.

2-((dimethylamino)methyl)-1-(3-hydroxyphenyl)-6-(2-(trifluoromethyl)phenyl)-1,

2,3,4-tetrahydronaphthalen-1-ol(6s)

White powder 61 mg 78% **^{1}H NMR （400 MHz ， DMSO-d^{6}）** δ 9.33 (s, 1H), 7.83 (dd, *J* = 7.7, 3.2 Hz, 1H), 7.71 (dd, *J* = 11.7, 7.2 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.39 (dd, *J* = 12.1, 7.6 Hz, 1H), 7.06 (ddd, *J* = 27.7, 12.1, 8.0 Hz, 3H), 6.93 – 6.50 (m, 4H), 3.39 (dd, *J* = 55.5, 34.6 Hz, 1H), 3.06 – 2.77 (m, 2H), 2.61 (s, 1H), 2.46 – 2.12 (m, 7H), 2.07 (d, *J* = 10.9 Hz, 1H), 1.98 – 1.75 (m, 1H). **^{13}C NMR (101 MHz, DMSO)** δ 157.19, 150.12, 144.00, 142.80, 141.07, 138.10, 136.27, 132.70, 129.96, 128.93, 128.77, 128.37, 127.83, 126.64, 126.55, 119.00, 117.89, 115.54, 114.38, 113.74, 75.82, 59.84, 43.45, 42.46, 28.90, 23.24. ESI-MS m/z 442.2 $[M+H]^+$ HRMS *m/z* calcd for $C_{26}H_{26}F_3NO_2$ [M + H]+,442.1988; found, 442.1984.

2-((dimethylamino)methyl)-1-(3-hydroxyphenyl)-6-(2-(trifluoromethoxy)phenyl)-1,2,3,4-tetrahydronaphthalen-1-ol(6t)

White powder 77 mg 82% **^{1}H NMR (400 MHz, DMSO)** δ 9.39 (s, 1H), 7.63 – 7.40 (m, 4H), 7.26 (s, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.11 (t, *J* = 7.9 Hz, 1H), 6.96 – 6.81 (m, 2H), 6.73 (d, *J* = 7.7 Hz, 1H), 6.65 (dd, *J* = 7.9, 1.8 Hz, 1H), 2.98 (ddd, *J* = 29.8, 27.1, 16.6 Hz, 3H), 2.76 (d, *J* = 22.4 Hz, 1H), 2.37 (s, 7H), 2.15 (d, *J* = 11.1 Hz, 1H), 2.04 – 1.81 (m, 1H).**^{13}C NMR (101 MHz, DMSO)** δ 157.29, 149.65, 145.80, 142.62, 136.81, 134.97, 134.57, 132.13, 130.53, 129.77, 129.06, 128.32, 126.87, 121.64, 119.22, 117.86, 114.39, 113.94, 75.52, 59.49, 44.11, 43.08, 28.86, 23.30. ESI-MS m/z 458.2 $[M+H]^+$ HRMS *m/z* calcd for $C_{26}H_{26}F_3NO_3$ [M + H]+,458.1938; found, 458.1944.

Radio ligand binding assay

Chinese hamster ovary (CHO) cells stably transfected with the human κ-opioid receptor, δ-opioid receptor, and the μ-opioid receptor were obtained from SRI International (Palo Alto, CA, USA) and George Uh1 (NIDA Intramural Program, Bethesda, MD, USA), respectively. The cells were grown in 100 mM dishes in Dulbecco's modified Eagle's media(DMEM) supplemented with 10% fetal bovine serum (FBS) and penicillin–streptomycin (10000 U/mL) at 37℃ under 5% CO_2 atmosphere. The affinity and selectivity of the compounds for the multiple opioid

receptors were determined by incubating the membranes with radiolabeled ligands and 12 different concentrations of the compounds at 25℃ in a final volume of 1 mL of 50 mM Tris-HCl, pH 7.5. Incubation times of 60 min were used for the μ-selective peptide [^{3}H]DAMGO, the κ-selective ligand[^{3}H]U69593 and the δ-selective antagonist[^{3}H]DPDPE.

[^{35}S]GTP-γ-S functional assay

In a final volume of 0.5 mL, various concentrations of each tested compound were incubated with 7.5 mg (μ) of CHO cell membranes that stably expressed the human μ opioid receptor. The assay buffer consisted of 50 mM Tris-HCl, pH 7.4, 3 mM $MgCl_2$, 0.2 mM EGTA, 3 mM GDP, and 100 mM NaCl. The final concentration of [^{35}S]GTP-γ-S was 0.08 nM. Nonspecific binding was measured by inclusion of 10 mM GTP-γ-S. Binding was initiated by the addition of the membranes. After an incubation of 60 min at 30℃, reactions were terminated by rapid filtration and radioactivity was determined by liquid scintillation counting.

Molecular modeling

The 3D structure of tramadol, M1, morphine, and codeine were built with program SYBYL6.9 and optimized at the DFT/B3LYP/6-31G**level. The 3D structures of the compounds were also superimposed using the software packages in SYBYL6.9. The crystal structure of DOR (PDB: 4EJ4) was added hydrogen and removed waters by DS3.5 for docking study.

Molecular docking was carried out using GOLD 5.0.1[1].The binding site was defined to include all residues within a 15.0 Å radius of the conserved D3.32 Cγ carbon atom. A hydrogen-bond constraint was set between the protonated nitrogen atom (N1) of ligand and D3.32 side chain. Ten conformations were produced for each ligand, and Gold-Score was used as scoring function. Other parameters were set as standard default. High-scoring complexes were inspected visually to select the most reasonable solution.

Reference

(1) Jones, G.; Willett, P.; Glen, R. C.; Leach, A. R.; Taylor, R. Development and validation of a genetic algorithm for flexible docking. *J. Mol. Biol.* **1997**, *267*, 727-748.