Comprehensive synthesis of 20 fentanyl derivatives for their rapid differentiation by GC-MS analysis

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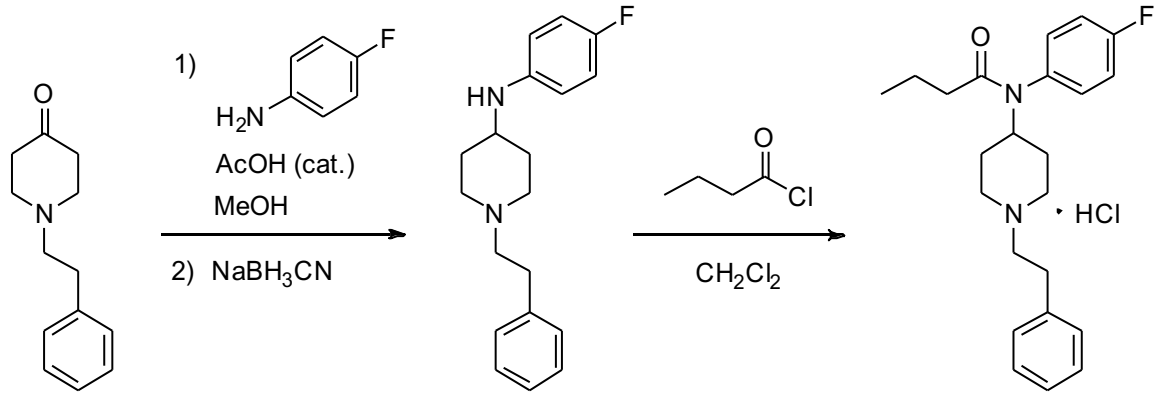
General

All chemicals were purchased from Sigma-Aldrich Co. LLC, Kanto Chemicals Co. Inc., Tokyo Chemical Industry Co. Ltd., FUJIFILM Wako Pure Chemical Industries Ltd., and were used without further purification. Reactions were followed by thin-layer chromatography (TLC) (60 F254, Merck), and spots were visualized by UV irradiation with a handheld UV lamp (254 nm)(UVP) and iodine vapor or ninhydrin reagent. Silica gel for column chromatography was packed columns for medium pressure column chromatography (Inject column / Hi-Flash column)(Si or NH)(Yamazen). ^{1}H and ^{13}C NMR spectra were measured on an ECZ 600R spectrometer (JEOL) using deuterated solvents. Chemical shift values (ppm) are expressed in δ (ppm) with tetramethylsilane (TMS, 0.00 for ^{1}H NMR in $CDCl_3$) or residual solvent peak (^{1}H NMR : 2.50 for DMSO-d_6 and 3.31 for MeOH-d_4 ; ^{13}C NMR : 77.16 for $CDCl_3$, 39.52 for DMSO-d_6 and 49.00 for MeOH-d_4) as internal standards. High-resolution mass spectrometry (HRMS) was measured by electrospray ionization using Shimadzu IT-TOF MS (Shimadzu). HPLC-PDA (ACQUITY UPLC I-Class, Waters, Milford, MA, USA) were used for purity check. The analyses were performed using an ACQUITY HSS T3 column (2.1 mm i.d. x 100 mm, 1.8 μm, Waters) with Van Guard Pre-Column HSS T3 (2.1 mm i.d. x 5 mm, 1.8 μm, Waters). The column temperature was maintained at 40 °C, and the following isocratic system was used with a mobile phase A (1% formic acid), mobile phase B (1% formic acid/acetonitrile) delivered at 0.3 mL/min and the analysis time was 30 minutes. The composition ratio of isocratic mobile phase A for each compound measurement is as follows; *p*-fluorobutylfentanyl (**4**), cyclopropylfentanyl (**7**), *o*-fluorofentanyl (**12**), sufentanil (**15**), 3-methyfentanyl (**16**) and 3-methylthiofentanyl (**17**):A 75%, valerylfentanyl (**5**) and cyclopentylfentanyl (**8**): A 72%, crotonylfentanyl (**6**): A 77%, methoxyacetylfentanyl (**9**), furanylfentanyl (**10**), *p*-fluorofentanyl (**11**), thiofentanyl(**13**), alfentanil (**3**), β-hydroxy-3-methylfentanyl (**18**), α-methylfentanyl (**19**), α-methylthiofentanyl (**20**) and α-methylacetylfentanyl (**21**): A 80%, furanylethylfentanyl (**14**): A 82%, remifentanil (**2**) A 85%. The injection volume was 2 μL of 1 mg/mL methanol solution and the wavelength of the PDA detector was set from 210 to 450 nm.

Synthesis of fentanyl derivatives

A. Non-propionyl series

***p*-Fluorobutylfentanyl (4)**



p-Fluoro-ANPP (**S1**) **4**

To a solution of 1-phenethyl-4-piperidone (2.03 g, 10.0 mmol) in MeOH (50 mL) was added 4-fluoroaniline (1.0 mL, 10.3 mmol), followed by AcOH (57 μL) at room temperature. The reaction mixture was stirred at 50 °C for 17 h. After cooling to 0 °C, the reaction mixture was slowly added $NaBH_3CN$ (0.97 g, 15.5 mmol) in some portions. After completion of the addition, the reaction mixture was allowed to warm up to room temperature. After being stirred for 8 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, and then concentrated under reduced pressure to remove a majority of MeOH. The residue was added 2M aqueous NaOH to basify (pH > 8), and extracted with CH_2Cl_2 (50 mL x 3), and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (*n*-Hexane/EtOAc = 1 : 3) to afford *p*-Fluoro-ANPP (**S1**) as a white solid (1.36 g, 46%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.43 – 1.50 (m, 2H), 2.03 – 2.06 (m, 2H), 2.17 (t, J = 9.6 Hz, 2H), 2.58 – 2.61 (m, 2H), 2.78 – 2.81 (m, 2H), 2,95 (d, J = 9.6Hz, 2H), 3.22 – 3.26 (m, 1H), 3.36 (brs, 1H), 6.53 – 6.55 (m, 2H), 6.87 (t, J = 8.1 Hz, 2H), 7.17 – 7.21 (m, 3H), 7.26 – 7.29 (m, 2H).

LR-MS (ESI) : *m*/*z* 299.17.

To a mixture of *p*-Fluoro-ANPP (625 mg, 2.09 mmol) in CH_2Cl_2 (20 mL) was added

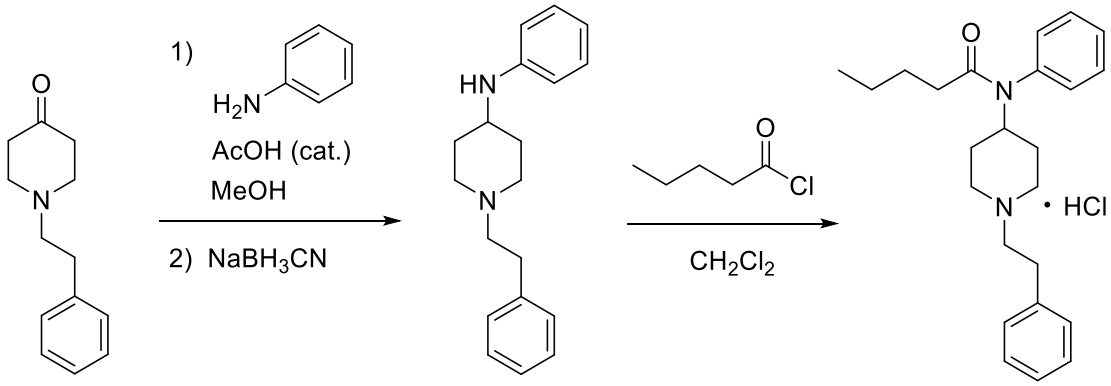
dropwise butyryl chloride (1.5 mL, 14.1 mmol) at 0 °C. After being stirred at room temperature for 7.5 h, the reaction mixture was concentrated under reduced pressure to dryness. The residue was suspended in Et_2O, and the resulting precipitate was collected by filtration, washed with Et_2O, dried under vacuum to afford compound **4** as a white solid (817 mg, 95%; *p*-fluorobutylfentanyl hydrochloride).

^{1}H NMR (600 MHz, $CDCl_3$) δ 0.81 (t, J = 6.6 Hz, 3H), 1.53 – 1.61 (m, 2H), 1.91 (t, J = 8.4 Hz, 2H), 1.96 – 1.99 (m, 2H), 2.16 – 2.23 (m, 2H), 2.81 (q, J = 10.2 Hz, 2H), 3.08 – 3.13 (m, 2H), 3.20 – 3.23 (m, 2H), 3.60 (d, J = 11.4 Hz, 2H), 4.75 – 4.80 (m, 1H), 7.07 – 7.09 (m, 2H), 7.15 (t, J = 7.8 Hz, 2H), 7.22 (d, J = 7.8 Hz, 2H), 7.24 – 7.26 (m, 1H), 7.31 (t, J = 7.8 Hz, 2H) .

^{13}C NMR (151 MHz, MeOH-d_4) δ 14.0, 19.7, 29.0 (2C), 31.4, 37.9, 51.2, 53.3 (2C), 59.0, 117.7 (d, J = 23.1 Hz, 2C), 128.4, 129.7 (2C), 130.0 (2C), 133.5 (d, J = 8.7 Hz, 2C), 135.5, 137.4, 164.1 (d, J = 248.5 Hz), 175.3.

HRMS (ESI) : m/z calcd. for $C_{23}H_{30}FN_2O$ $[M+H]^+$ 369.2331, found 369.2379.

Valerylfentanyl (5)



ANPP (**22**) **5**

To a solution of 1-phenethyl-4-piperidone (1.04 g, 5.12 mmol) in MeOH (50 mL) was added aniline (0.94 mL, 10.3 mmol), followed by AcOH (70 μL) at room temperature. The reaction mixture was stirred at 50 °C for 6 h. After cooling to 0 °C, the reaction mixture was slowly added $NaBH_3CN$ (0.53 g, 8.50 mmol) in some portions. After completion of the addition, the reaction mixture was allowed to warm up to room temperature. After being stirred for 22 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, and then concentrated under reduced pressure to remove a

majority of MeOH. The residue was added 2M aqueous NaOH to basify (pH > 8), and extracted with CH_2Cl_2 (25 mL x 3), and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (*n*-Hexane/EtOAc = 1 : 1) to afford compound **22** as a light yellow solid (0.63 g, 42%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.48 – 1.53 (m, 2H), 2.09 (d, *J* = 12.0 Hz, 2H), 2.21 (t, *J* = 10.2 Hz, 2H), 2.60 – 2.63 (m, 2H), 2.81 – 2.83 (m, 2H), 2.97 (d, *J* = 10.2 Hz, 2H), 3.32 (brs, 1H), 3.52 (brs, 1H), 6.60 (d, *J* = 8.4 Hz, 2H), 6.67 – 6.70 (m, 1H), 7.15 – 7.22 (m, 5H), 7.28 – 7.30 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 32.7, 34.0, 50.0, 52.6, 60.8, 113.3, 117.3, 126.2, 128.5, 128.8, 129.4, 140.5, 147.2.

HRMS (ESI) : *m*/*z* calcd. for $C_{19}H_{25}N_2$ $[M+H]^+$ 281.2012, found 281.2077.

To a mixture of compound **22** (367 mg, 1.31 mmol) in CH_2Cl_2 (5 mL) was added dropwise valeryl chloride (401 mg, 3.34 mmol) at room temperature. After being stirred at 60 °C for 16 h, the reaction mixture was concentrated under reduced pressure to dryness. The residue was suspended in Et_2O, and the resulting precipitate was collected by filtration, washed with Et_2O, dried under vacuum to afford compound **5** as a white solid (516 mg, 98%; valerylfentanyl hydrochloride).

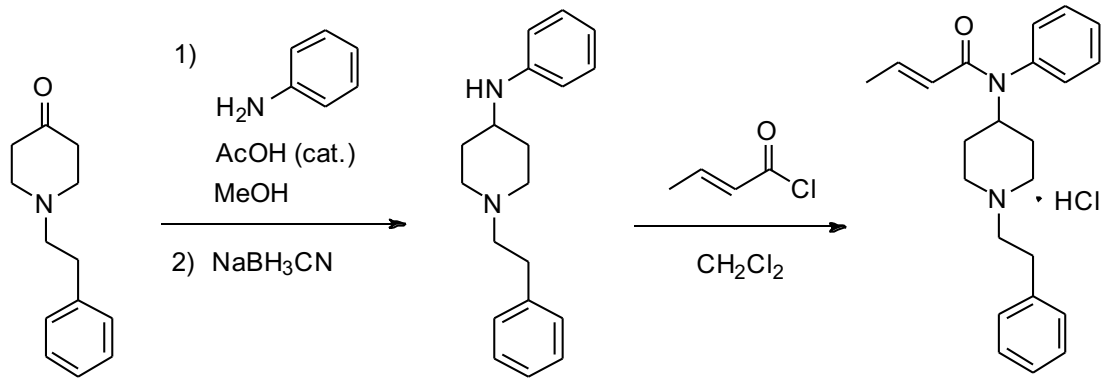
^{1}H NMR (600 MHz, MeOH-d_4) δ 0.79 (t, *J* = 7.8 Hz, 3H), 1.18 (sext, *J* = 7.8 Hz, 2H), 1.50 (quin, *J* = 7.8 Hz, 2H), 1.69 (brs, 2H), 1.98 (t, *J* = 7.8 Hz, 2H), 2.14 (d, *J* = 12.0 Hz, 2H), 3.00 (brs, 2H), 3.18 (dd, *J* = 12.0, 12.0 Hz, 2H), 3.26 – 3.28 (m, 2H), 3.65 (d. *J* = 12 Hz, 2H), 4.79 – 4.83 (m, 1H), 7.23 – 7.27 (m, 5H), 7.30 – 7.33 (m, 2H), 7.47 – 7.54 (m, 3H).

^{13}C NMR (151 MHz, MeOH-d_4) δ 14.0, 23.3, 28.6, 29.1 (2C), 31.4, 35.6, 51.2, 53.4 (2C), 59.0, 128.3, 129.8 (2C), 130.0 (2C), 130.3, 131.0 (2C), 131.5 (2C).

HRMS (ESI): *m*/*z* calcd. for $C_{24}H_{33}N_2O$ $[M+H]^+$ 365.2587, found 365.2584.

Compound **6-10** were synthesized in a procedure similar to that described for the preparation of compound **5**.

Crotonylfentanyl (6)



ANPP (**22**) **6**

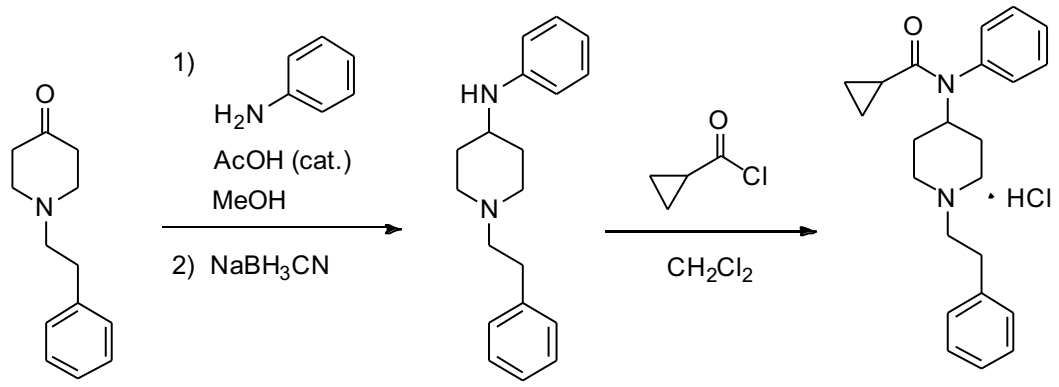
To a mixture of compound **22** (280 mg, 1.0 mmol) in CH_2Cl_2 (3 mL) was added dropwise crotonyl chloride (90%, 213 μL, 2.0 mmol) at room temperature. After being stirred at 50 °C for 3 h, the reaction mixture was concentrated under reduced pressure to dryness. The residue was suspended in Et_2O, and the resulting precipitate was collected by filtration, washed with Et_2O, dried under vacuum to afford compound **6** as a white solid (367 mg, 95%; crotonylfentanyl hydrochloride).

^{1}H NMR (600 MHz, DMSO-d_6) δ 1.62 (d, J = 7.2 Hz, 3H), 1.66 (ddd, J = 16.8, 13.8, 3.6 Hz, 2H), 1.95 (d, J = 12.0 Hz, 2H), 2.96 – 2.99 (m, 2H), 3.11 (dd, J = 12.0, 12.0 Hz, 2H), 3.13 – 3.19 (m, 2H), 3.52 (d, J = 12.0 Hz, 2H), 4.72 – 4.76 (m, 1H), 5.39 (d, J = 14.7 Hz, 1H), 6.72 (dq, J = 14.7, 7.2 Hz, 1H), 7.18 – 7.24 (m, 5H), 7.29 – 7.33 (m, 2H), 7.46 – 7.52 (m, 3H), 10.31 (brs, 1H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 17.7, 27.2 (2C), 29.4, 49.3, 50.9 (2C), 56.4, 123.0, 126.8, 128.7 (5C), 129.5 (2C), 130.5 (2C), 137.1, 137.7, 141.1, 164.3.

HRMS (ESI): m/z calcd. for $C_{23}H_{29}N_2O$ $[M+H]^+$ 349.2274, found 349.2271.

Cyclopropylfentanyl (**7**)



ANPP (**22**) **7**

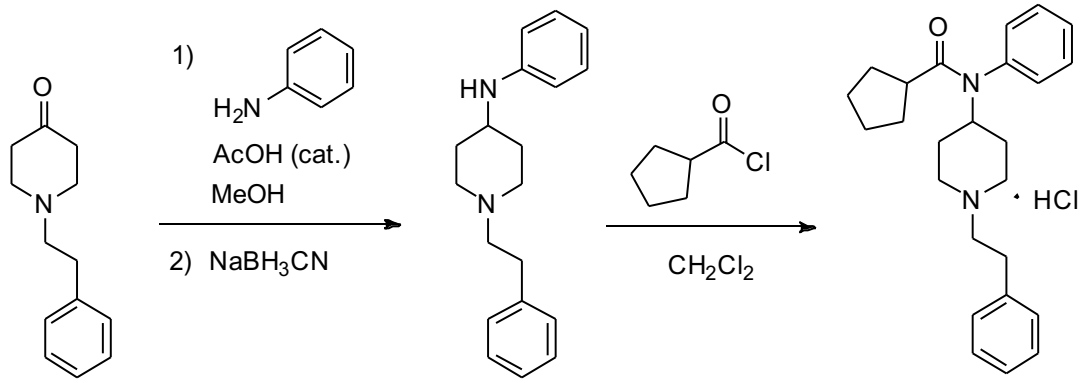
To a mixture of compound **22** (420 mg, 1.50 mmol) in CH_2Cl_2 (10 mL) was added dropwise cyclopropanecarbonyl chloride (273 μL, 3.0 mmol) at 0 °C. After being stirred at room temperature for 3 h, the reaction mixture was concentrated under reduced pressure to dryness. The residue was suspended in Et_2O, and the resulting precipitate was collected by filtration, washed with Et_2O, dried under vacuum to afford compound **7** as a white solid (566 mg, 98%; cyclopropylfentanyl hydrochloride).

^{1}H NMR (600 MHz, MeOH-d_4) δ 0.62 – 0.65 (m, 2H), 0.86 – 0.92 (m, 2H), 1.13 – 1.17 (m, 1H), 1.69 – 1.76 (m, 2H), 2.15 (dt, J = 13.8 Hz, 2H), 2.96 – 2.99 (m, 2H), 3.18 (t, J = 6.0 Hz, 2H), 3.26 – 3.28 (m, 2H), 3.65 (d, J = 12.3 Hz, 2H), 4.75 – 4.80 (m, 1H), 7.24 – 7.26 (m, 3H), 7.30 – 7.35 (m, 4H), 7.49 (t, J = 7.2 Hz, 1H), 7.54 (t, J = 7.2 Hz, 2H).

^{13}C NMR (151 MHz, MeOH-d_4) δ 9.2 (2C), 14.2, 29.1 (2C), 31.4, 51.5, 53.4 (2C), 58.9, 128.4, 129.7 (2C), 130.0 (2C), 130.2, 131.0 (2C), 131.7 (2C), 137.4, 139.5, 175.8.

HRMS (ESI) : m/z calcd. for $C_{23}H_{29}N_2O$ $[M+H]^+$ 349.2274, found 349.2323.

Cyclopentylfentanyl (8)



ANPP (**22**) **8**

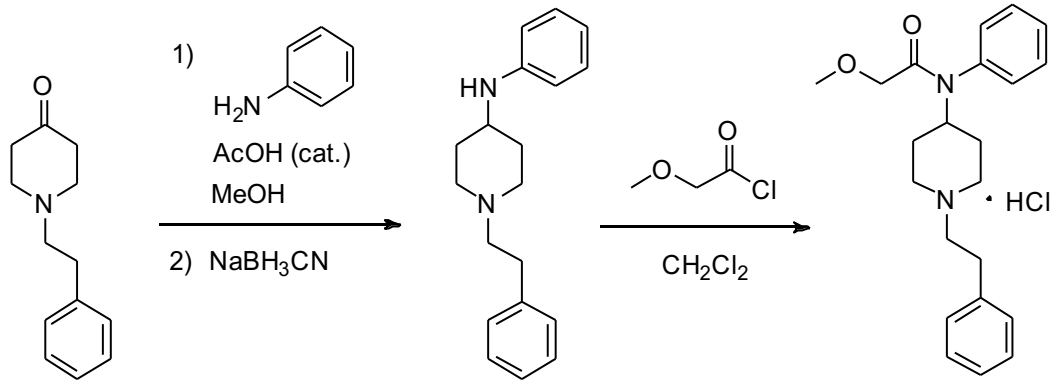
To a mixture of compound **22** (220 mg, 0.78 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise a solution of cyclopentanecarbonyl chloride (189 μL, 1.57 mmol) in CH_2Cl_2 (1.4 mL) at room temperature. After being stirred at room temperature for 3 h, the reaction mixture was concentrated under reduced pressure to dryness. The residue was suspended in Et_2O, and the resulting precipitate was collected by filtration, washed with Et_2O, dried under vacuum to afford compound **8** as a white solid (295 mg, 92%; cyclopentylfentanyl).

^{1}H NMR (600 MHz, DMSO-d_6) δ 1.27 – 1.33 (m, 2H), 1.42 – 1.48 (m, 2H), 1.52 – 1.65 (m, 6H), 1.92 (d, J = 13.8 Hz, 2H), 2.24 (quint, J = 8.4 Hz, 1H), 2.95 – 2.98 (m, 2H), 3.09 (dd, J = 12.0, 12.0 Hz, 2H), 3.15 – 3.18 (m, 2H), 3.52 (d, J = 12.0 Hz, 2H), 4.70 (dddd, J = 12.0, 12.0, 3.6, 3.6 Hz, 1H), 7.22 – 7.24 (m, 5H), 7.31 (t, J = 6.6 Hz, 2H), 7.45 (t, J = 7.8 Hz, 1H), 7.50 (t, J = 6.6 Hz, 2H), 10.17 (brs, 1H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 25.7 (2C), 27.3 (2C), 29.4, 30.5 (2C), 42.0, 49.1, 51.0 (2C), 56.4, 126.8 (2C), 128.5, 128.6 (3C), 129.4 (2C), 130.5 (2C), 137.0, 138.0, 175.0.

HRMS (ESI): m/z calcd. for $C_{25}H_{33}N_2O$ $[M+H]^+$ 377.2587, found 337.2582.

Methoxyacetylfentanyl (9)



ANPP (**22**) **9**

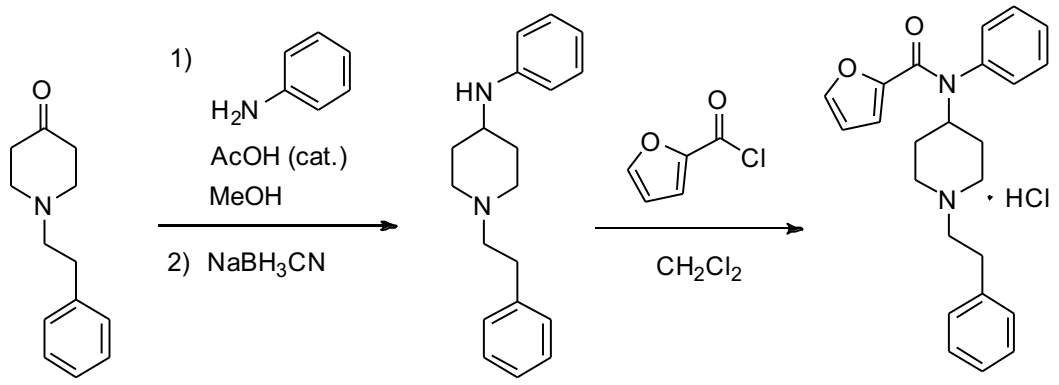
To a mixture of compound **22** (387 mg, 1.38 mmol) in CH_2Cl_2 (10 mL) was added dropwise methoxyacetyl chloride (1.5 mL, 16.4 mmol) at room temperature. After being stirred at 50 °C for 2 h, the reaction mixture was concentrated under reduced pressure to dryness. The residue was suspended in Et_2O, and the resulting precipitate was collected by filtration, washed with Et_2O, dried under vacuum to afford compound **9** as a white solid (512 mg, 100%; methoxyacetylfentanyl hydrochloride).

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.01 (d, J = 13.8 Hz, 2H), 2.20 (qd, J = 13.2, 3.6 Hz, 2H), 2.84 (q, J = 12.0 Hz, 2H), 3.08 – 3.14 (m, 2H), 3.18 – 3.23 (m, 2H), 3.31 (s, 3H), 3.60 (d, J = 10.8 Hz, 2H), 3.64 (s, 2H), 4.80 (tt, J = 12.6, 3.6 Hz, 1H), 7.10 – 7.15 (m, 2H), 7.21 (d, J = 7.8 Hz, 2H), 7.23 – 7.25 (m, 1H), 7.30 (t, J = 7.8 Hz, 2H), 7.45 – 7.51 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 27.4 (2C), 30.2, 50.1, 52.3 (2C), 58.6, 59.2, 70.9, 127.4, 128.7 (2C), 129.0 (2C), 129.6 (2C), 129.8, 130.2 (2C), 135.7, 135.9, 169.3.

HRMS (ESI): m/z calcd. for $C_{22}H_{29}N_2O_2$ $[M+H]^+$ 353.2224, found 353.2228.

Furanylfentanyl (10)



ANPP (**22**) **10**

To a mixture of compound **22** (140 mg, 0.5 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise 2-furoyl chloride (98 μL, 1.0 mmol) at room temperature. After being stirred at 50 °C for 2 h, the reaction mixture was concentrated under reduced pressure to dryness. The residue was suspended in Et_2O, and the resulting precipitate was collected by filtration, washed with Et_2O, dried under vacuum to afford compound **10** as a white solid (194 mg, 94%; furanylfentanyl hydrochloride).

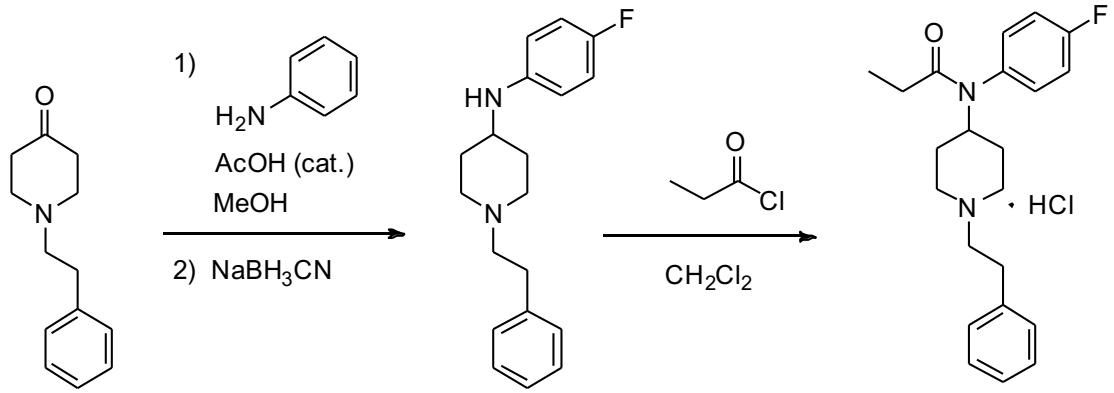
^{1}H NMR (600 MHz, DMSO-d_6) δ 1.78 (dd, J = 12.0, 12.0 Hz, 2H), 2.04 (d, J = 12.0 Hz, 2H), 3.00 – 3.03 (m, 2H), 3.14 – 3.21 (m, 4H), 3.56 (d, J = 12.0 Hz, 2H), 4.83 (dddd, J = 12.0, 12.0, 3.0, 3.0 Hz, 1H), 5.41 (brs, 1H), 6.32 (dd, J = 3.3, 1.8 Hz, 1H), 7.23 – 7.24 (m, 3H), 7.30 – 7.33 (m, 4H), 7.49 – 7.51 (m, 3H), 7.66 (s, 1H), 10.68 (brs, 1H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 27.0 (2C), 29.4, 50.3 (2C), 50.8, 56.4, 111.3, 115.8, 126.8, 128.7 (4C), 129.1, 129.4 (2C), 130.7 (2C), 137.2, 137.8, 145.2, 146.5, 158.0.

HRMS (ESI): m/z calcd. for $C_{24}H_{27}N_2O_2$ $[M+H]^+$ 375.2067, found 375.2063.

B. Replaced-aryl series

***p*-Fluorofentanyl (11)**



p-Fluoro-ANPP (**S1**) **11**

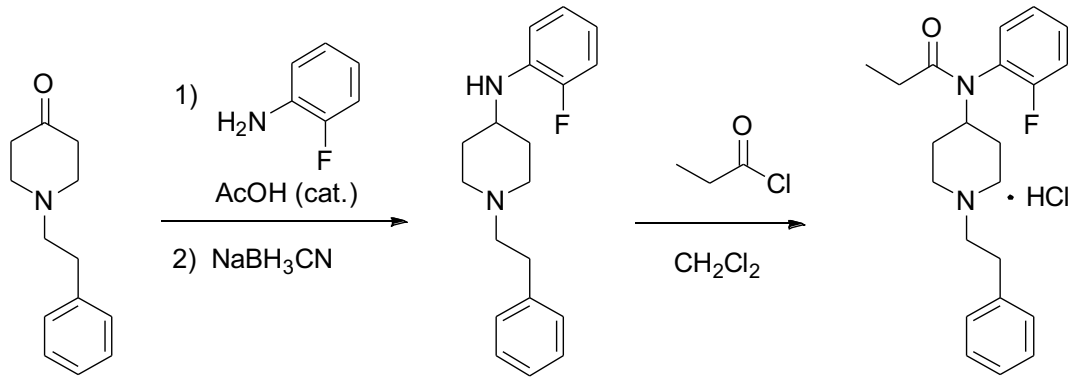
To a mixture of compound **S1** (1.30 g, 4.36 mmol) and Et_3N (1.0 mL, 7.08 mmol) in CH_2Cl_2 (20 mL) was added dropwise propionyl chloride (0.4 mL, 4.60 mmol) at 0 °C. After being stirred at room temperature for 7.5 h, the reaction mixture was poured into sat. $NaHCO_3$ aq., extracted with CH_2Cl_2 (30 mL x 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (*n*-Hexane/EtOAc = 1 : 2) to afford compound **11** as a white solid (1.14 g, 74%; *p*-fluorofentanyl).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.02 (t, *J* = 7.5 Hz, 3H), 1.93 – 1.99 (m, 4H), 2.16 – 2.22 (m, 2H), 2.80 – 2.86 (m, 2H), 3.13 (d, *J* = 5.4 Hz, 2H), 3.20 – 3.23 (m, 2H), 3.60 (d, *J* = 12.0 Hz, 2H), 4.78 (dd, *J* = 12.6 Hz, 1H), 7.07 – 7.10 (m, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 7.8 Hz, 2H), 7.24 – 7.27 (m, 2H), 7.29 – 7.32 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 9.4, 27.5 (2C), 28.4, 30.2, 50.0, 52.4 (2C), 58.5, 117.0 (d, *J* = 23.1 Hz, 2C), 127.3, 128.6 (2C), 129.0 (2C), 131.4 (d, *J* = 8.7 Hz, 2C), 133.5, 135.9, 162.6 (d, *J* = 250.0 Hz), 174.2.

HRMS (ESI) : *m*/*z* calcd. for $C_{22}H_{28}FN_2O$ $[M+H]^+$ 355.2107, found 355.1974.

***o*-Fluorofentanyl (12)**



o-Fluoro-ANPP (**S2**)

12

To a solution of 1-phenethyl-4-piperidone (1.07 g, 5.26 mmol) in MeOH (15 mL) was added 2-fluoroaniline (1.0 mL, 10.3 mmol), followed by AcOH (70 μL) at room temperature. The reaction mixture was stirred at 50 °C for 6 h. After cooling to 0 °C, the reaction mixture was slowly added $NaBH_3CN$ (0.48 g, 7.67 mmol) in some portions. After completion of the addition, the reaction mixture was allowed to warm up to room temperature. After being stirred for 22 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, and then concentrated under reduced pressure to remove a majority of MeOH. The residue was added 2M aqueous NaOH to basify (pH > 8), and extracted with CH_2Cl_2 (25 mL x 3), and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (*n*-Hexane/EtOAc = 1 : 1) to afford *o*-Fluoro-ANPP (**S2**) as a light yellow solid (0.67 g, 43%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.53 – 1.59 (m, 2H), 2.08 – 2.11 (m, 2H), 2.23 (t, J = 9.0 Hz, 2H), 2.61 – 2.63 (m, 2H), 2.81 – 2.84 (m, 2H), 2.95 – 2.98 (m, 2H), 3.32 – 3.34 (m, 1H), 3.78 (brs, 1H), 6.58 – 6.62 (m, 1H), 6.71 (t, J = 9.0 Hz, 1H), 6.95 – 6.98 (m, 2H), 7.19 – 7.22 (m, 3H), 7.29 (t, J = 7.2 Hz, 2H).

HRMS (ESI) : *m*/*z* calcd. for $C_{19}H_{24}FN_2$ $[M+H]^+$ 299.1918, found 299.1986.

To a mixture of compound **S2** (664 mg, 2.22 mmol) in CH_2Cl_2 (20 mL) was added dropwise propionyl chloride (1.5 mL, 17.1 mmol) at 0 °C. After being stirred at room temperature for 7.5 h, the reaction mixture was concentrated under reduced pressure to dryness. The residue was suspended in Et_2O, and the resulting precipitate was collected by filtration, washed with Et_2O, dried under vacuum to afford compound **12** as a white

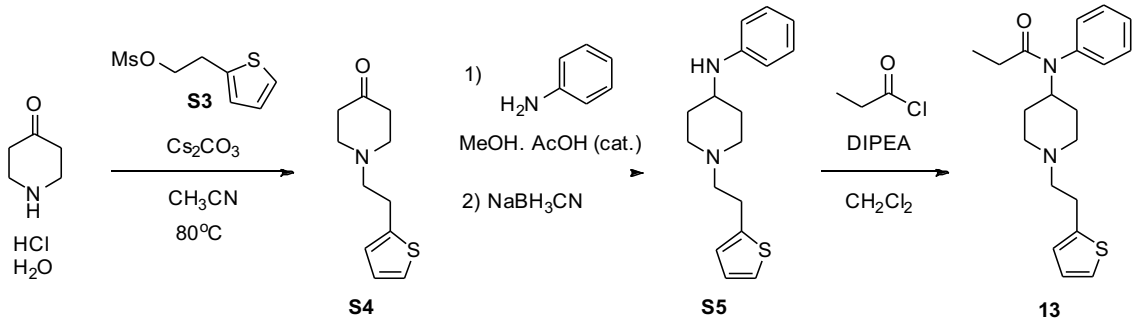
solid (817 mg, 95%; *o*-fluorofentanyl hydrochloride).

^{1}H NMR (600 MHz, MeOH-d_4) δ 0.99 (t, J = 7.2 Hz, 3H), 1.65 – 1.81 (m, 2H), 1.93 – 2.04 (m, 2H), 2.12 – 2.19 (m, 2H), 2.98 – 3.02 (m, 2H), 3.16 – 3.21 (m, 2H), 3.27 – 3.29 (m, 2H), 3.66 (d, J = 12.0 Hz, 2H), 4.80 – 4.84 (m, 1H), 7.21 – 7.25 (m, 3H), 7.28 – 7.36 (m, 5H), 7.50 – 7.56 (m, 1H).

^{13}C NMR (151 MHz, MeOH-d_4) δ 9.6, 28.2, 28.8, 29.1, 31.4, 51.8, 53.3 (2C), 59.0, 118.1 (d, J = 21.0 Hz, 2C), 126.7 (d, J = 4.0 Hz), 128.3, 129.8 (2C), 130.0 (2C), 132.7 (d, J = 8.0 Hz), 133.6, 137.4, 160.5 (d, J = 247.1 Hz), 176.1.

HRMS (ESI) : m/z calcd. for $C_{22}H_{28}FN_2O$ $[M+H]^+$ 355.2175, found 355.2212.

Thiofentanyl (**13**)



To a mixture of 2-thiopheneethanol (5.13 g, 40.0 mol) and Et_3N (6.7 mL, 48.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise a solution of methanesulfonyl chloride (3.7 mL, 48.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After being stirred at room temperature for 12 h, the reaction mixture was diluted with EtOAc (100 mL), washed with 1M HCl, sat. $NaHCO_3$ aq., brine. The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (*n*-Hexane/EtOAc = 4 : 1 to 1 : 2) to afford compound **S3** as a dark brown oil (4.35 g, 52%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.93 (s, 3H), 4.42 (td, J = 6.6, 0.6 Hz, 2H), 4.42 (t, J = 6.6 Hz, 2H), 6.91 (dd, J = 3.6, 1.2 Hz, 1H), 6.96 (dd, J = 4.8, 3.6 Hz, 1H), 7.20 (dd, J = 4.8, 1.2 Hz, 1H).

To a suspension of 4-piperidone hydrochloride monohydrate (2.22 g, 14.5 mmol) in CH_3CN (80 mL) was added Cs_2CO_3 (11.3 g, 34.7 mmol), followed by compound **S3** (3.63

g, 17.3 mmol). After being stirred at 80 °C for 16 h, the reaction mixture was concentrated under reduced pressure. The residue was poured into water, extracted with CH_2Cl_2 (100 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (*n*-Hexane/EtOAc = 4 : 1 to 1 : 2) to afford compound **S4** as a yellow oil (2.03 g, 67%).
^{1}H NMR (600 MHz, $CDCl_3$) δ 2.44 – 2.50 (m, 4H), 2.77 – 2.84 (m, 4H), 3.07 (dd, *J* = 6.6 Hz, 2H), 3.77 (dd, *J* = 6.0 Hz, 2H), 6.85 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.94 (dd, *J* = 5.4, 3.6 Hz, 1H), 7.15 (dd, *J* = 5.4, 1.2 Hz, 1H).

To a solution of compound **S4** (1.05 g, 5.0 mmol) in MeOH (12 mL) was added aniline (458 μL, 5.0 mmol), followed by AcOH (29 μL) at room temperature. The reaction mixture was stirred at 50 °C for 3 h. After cooling to 0 °C, the reaction mixture was slowly added $NaBH_3CN$ (0.47 g, 7.5 mmol) in some portions. After completion of the addition, the reaction mixture was allowed to warm up to room temperature. After being stirred for 16 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, and then concentrated under reduced pressure to remove a majority of MeOH. The residue was added 2M aqueous NaOH to basify (pH > 8), and extracted with CH_2Cl_2 (20 mL x 2), and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (*n*-Hexane/EtOAc = 4 : 1 to 1 : 4) to afford compound **S5** as a light yellow solid (0.54 g, 38%).
^{1}H NMR (600 MHz, $CDCl_3$) δ 1.50 – 1.55 (m, 2H), 2.09 (d, *J* = 12.0 Hz, 2H), 2.24 (t, *J* = 7.2 Hz, 2H), 2.67 – 2.71 (m, 2H), 2.95 (d, *J* = 12.0 Hz, 2H), 3.04 (t, *J* = 7.2 Hz, 2H), 3.31 – 3.34 (m, 1H), 3.53 (brs, 1H), 6.60 (dd, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 7.2 Hz, 1H), 6.83 (d, *J* = 3.3 Hz, 1H), 6.93 (dd, *J* = 4.8, 3.3 Hz, 1H), 7.13 (dd, *J* = 4.8 Hz, 1H), 7.17 (dd, *J* = 8.4, 7.2 Hz, 2H).
LRMS (ESI): *m*/*z* $[M+H]^+$ 287.4.

To a mixture of compound **S5** (0.45 g, 1.57 mmol) and DIPEA (0.41 mL, 2.36 mmol) in CH_2Cl_2 (10 mL) was added dropwise propionyl chloride (206 μL, 2.36 mmol) at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was diluted with CH_2Cl_2, washed with water, brine. The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure. The residue was purified by flash NH silica gel

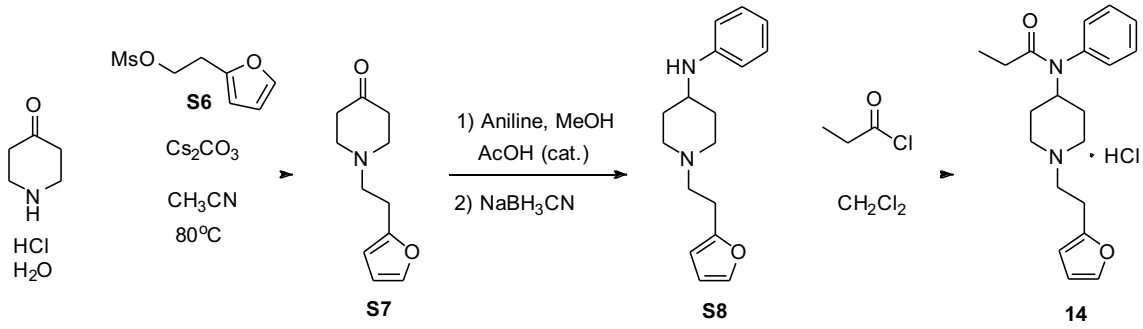
column chromatography (*n*-Hexane/EtOAc = 19 : 1 to 6 : 1) to afford compound **13** as a pale yellow solid (340 mg, 63%; thiofentanyl).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.02 (t, *J* = 7.8 Hz, 3H), 1.43 (d, *J* = 10.8 Hz, 2H), 1.80 (d, *J* = 12.0 Hz, 2H), 1.93 (q, *J* = 7.8 Hz, 2H), 2.19 (dd, *J* = 12.0 Hz, 2H), 2.61 (dd, *J* = 7.8 Hz, 2H), 2.94 – 2.99 (m, 4H), 4.66 – 4.70 (m, 1H), 6.77 (d, *J* = 3.3 Hz, 1H), 6.89 (dd, *J* = 4.8, 3.3 Hz, 1H), 7.08 – 7.10 (m, 3H), 7.35 – 7.41 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 9.6, 27.8, 28.5 (2C), 30.5, 52.1, 53.0 (2C), 60.0, 123.4, 124.5, 126.6, 128.2, 129.3 (2C), 130.4 (2C), 138.8, 142.5, 173.5.

HRMS (ESI) : *m*/*z* calcd. for $C_{20}H_{27}N_2OS$ $[M+H]^+$ 343.1839, found 343.1822.

Furanylethylfentanyl (14)



To a mixture of 2-(furan-2-yl)ethan-1-ol (0.90 g, 8.0 mmol) and Et_3N (1.57 mL, 11.2 mmol) in CH_2Cl_2 (8 mL) was added dropwise at 0 °C. After being stirred at that temperature for 30 min, the reaction mixture was diluted with EtOAc, washed with 1M HCl, sat. $NaHCO_3$ aq., brine. The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (*n*-Hexane/EtOAc = 9 : 1 to 3 : 2) to afford compound **S6** as a brown oil (1.42 g, 93%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.92 (s, 3H), 3.10 (t, *J* = 6.6 Hz, 2H), 4.46 (t, *J* = 6.6 Hz, 2H), 6.17 (s, 1H), 6.32 (s, 1H), 7.35 (s, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 28.5, 37.5, 67.7, 107.5, 110.6, 142.0, 150.3.

To a suspension of 4-piperidone hydrochloride monohydrate (0.87 g, 5.65 mmol) in CH_3CN (11 mL) was added Cs_2CO_3 (4.42 g, 13.6 mmol), followed by compound **S6** (1.29 g, 13.6 mmol). After being stirred at 80 °C for 14 h, the reaction mixture was concentrated

under reduced pressure. The residue was poured into water, extracted with CH_2Cl_2 (40 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure. The residue was purified by flash NH silica gel column chromatography (*n*-Hexane/EtOAc = 4 : 1 to 0 : 1) to afford compound **S7** as a yellow oil (760 mg, 70%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.47 (t, *J* = 6.0 Hz, 4H), 2.79 – 2.81 (m, 6H), 2.88 (t, *J* = 7.5 Hz, 2H), 6.05 – 6.06 (m, 1H), 6.29 – 6.30 (m, 1H), 7.32 (s, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 26.6, 41.4 (2C), 53.0 (2C), 55.8, 105.7, 110.4, 141.2, 154.0, 209.2.

To a solution of compound **S7** (750 mg, 3.88 mmol) in MeOH (10 mL) was added aniline (0.53 mL, 5.82 mmol), followed by AcOH (56 μL) at room temperature. The reaction mixture was stirred at 50 °C for 5 h. After cooling to 0 °C, the reaction mixture was slowly added $NaBH_3CN$ (487 mg, 7.76 mmol) in some portions. After completion of the addition, the reaction mixture was allowed to warm up to room temperature. After being stirred for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, and then concentrated under reduced pressure to remove a majority of MeOH. The residue was added 2M aqueous NaOH to basify (pH > 8), and extracted with CH_2Cl_2 (50 mL x 3), and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (*n*-Hexane/EtOAc = 1 : 3) to afford compound **S8** as a white solid (510 mg, 49%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.49 (qd, *J* = 10.8, 3.6 Hz, 2H), 2.07 (d, *J* = 10.8 Hz, 2H), 2.20 (t, *J* = 11.1 Hz, 2H), 2.69 (t, *J* = 7.8 Hz, 2H), 2.85 (t, *J* = 7.8 Hz, 2H), 2.92 (d, *J* = 11.4 Hz, 2H), 3.31 (br, 1H), 3.51 (br, 1H), 6.03 (d, *J* = 3.0 Hz, 1H), 6.29 (s, 1H), 6.60 (d, *J* = 8.4 Hz, 2H), 6.68 (t, *J* = 7.8 Hz, 1H), 7.17 (t, *J* = 7.2 Hz, 2H), 7.31 (s, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 26.3 (2C), 32.6, 50.0, 52.4 (2C), 57.0, 105.4, 110.3, 113.3 (2C), 117.3, 129.4 (2C), 141.1, 147.2, 154.4.

HRMS (ESI) : *m*/*z* calcd. for $C_{17}H_{23}N_2O$ $[M+H]^+$ 271.1805, found 271.1829.

To a mixture of compound **S8** (500 mg, 1.89 mmol) in CH_2Cl_2 (10 mL) was added dropwise propionyl chloride (1.3 mL, 15.1 mmol) at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was concentrated under reduced pressure to dryness. The residue was suspended in Et_2O, and the resulting precipitate was collected

by filtration, washed with Et_2O, dried under vacuum to afford compound **14** as a white solid (600 mg, 87%; furanylethylfentanyl hydrochloride).

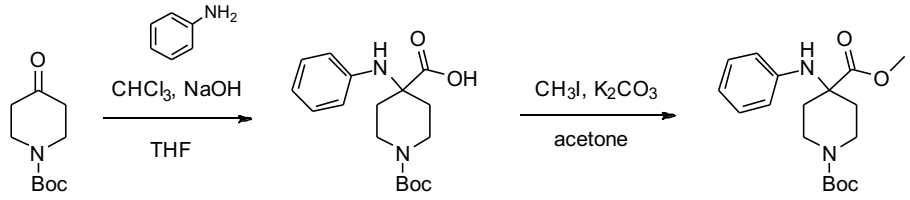
^{1}H NMR (600 MHz, $CDCl_3$) δ 1.00 (t, *J* = 7.8 Hz, 3H), 1.91 – 2.03 (m, 4H), 2.15 (br, 2H), 2.78 (br, 2H), 3.02 (br, 2H), 3.30 (t, *J* = 7.2 Hz, 2H), 3.52 (d, *J* = 11.4 Hz, 2H), 4.77 (t, *J* = 6.6 Hz, 1H), 6.15 (s, 1H), 6.29 (s, 1H), 7.08 (d, *J* = 7.8 Hz, 2H), 7.31 (s, 1H), 7.39 – 7.50 (m, 3H).

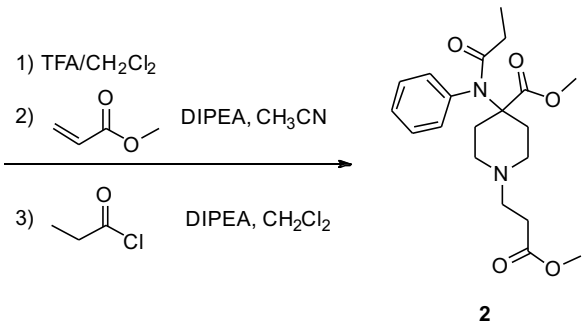
^{13}C NMR (151 MHz, $CDCl_3$) δ 9.4, 23.2, 27.6 (2C), 28.4, 49.9, 52.5 (2C), 55.4, 107.6, 110.7, 129.2, 129.7 (2C), 130.0 (2C), 137.6, 142.1, 149.4, 174.2.

HRMS (ESI) : *m*/*z* calcd. for $C_{20}H_{27}N_2O_2$ $[M+H]^+$ 327.2067, found 327.2066.

C. Quaternary carbon series

Remifentanil (**2**)





To a solution of aniline (0.93 g, 10. 0 mmol) and 1-(*tert*-butoxycarbonyl)-4-piperidone (5.98 g, 30.0 mmol) in THF (400 mL) was added powdered NaOH (2.0 g, 50.0 mmol). To this mixture was added $CHCl_3$ (2.4 mL, 30.0 mmol) at 0 °C. After being stirred at room temperature for 16 h, the reaction mixture was concentrated under reduced pressure to remove a majority of THF. The residue was added water (100 mL), washed with Et_2O (30 mL x 3), and the aqueous layer was added AcOH to adjust the pH 5-6, extracted with EtOAc (150 mL x 2). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure to give compound **S9** as a light

yellow foam solid (4.16 g), which was used in next step without further purification.

To a mixture of compound **S9** (3.71 g, 8.91 mmol) and K_2CO_3 (1.85 g, 13.4 mmol) in acetone (89 mL) was added dropwise CH_3I (0.83 mL, 13.4 mmol) at 0 °C. After being stirred at room temperature for 12 h, the reaction mixture was diluted with EtOAc (200 mL), washed with sat. $NaHCO_3$ aq., brine. The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (*n*-Hexane/EtOAc = 9 : 1 to 2 : 1) to afford compound **S10** as a white solid (2.22 g, 75%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.97 – 1.99 (m, 2H), 2.11 – 2.15 (m, 2H), 3.33 (ddd, *J* = 13.2, 9.6, 2.4 Hz, 2H), 3.68 (s, 3H), 3.70 – 3.72 (m, 2H), 3.86 (s., 1H), 6.59 (d, *J* = 7.8 Hz, 2H), 6.79 (t, *J* = 7.8 Hz, 1H), 7.16 (dd, *J* = 7.8 Hz, 2H).

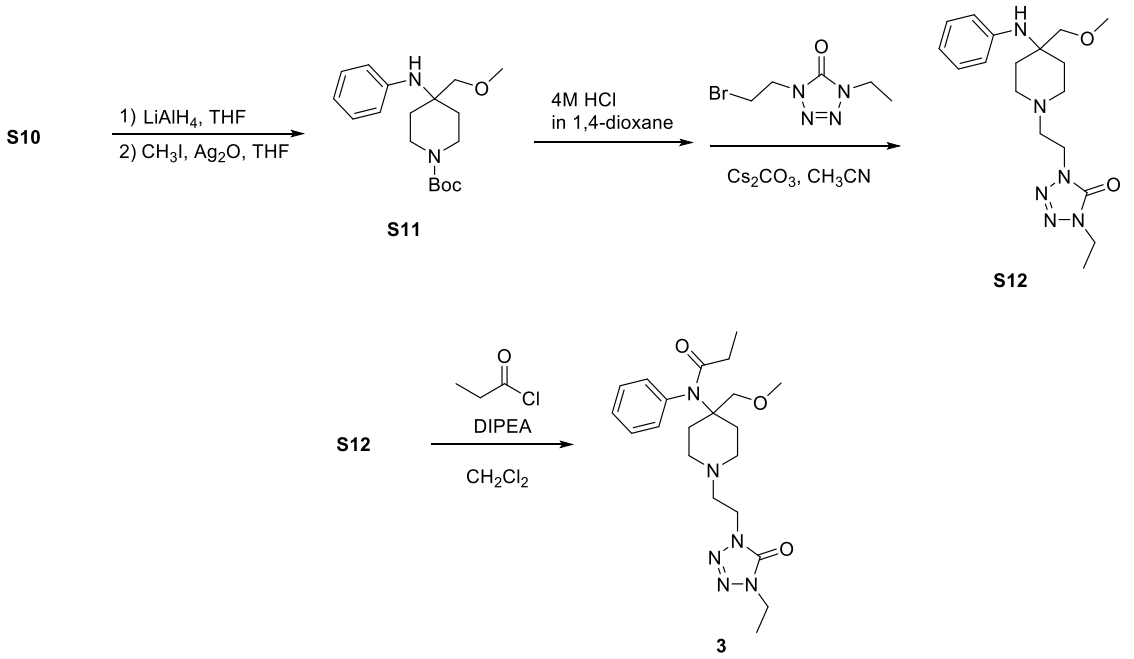
To a solution of compound **S10** (1.47 g, 4.40 mmol) in CH_2Cl_2 (4 mL) was added trifluoroacetic acid (8 mL), and the reaction mixture was stirred at room temperature. After 3 h, the reaction mixture was concentrated under vacuum to remove the volatiles. The obtained crude product was suspended in CH_3CN (20 mL), and added to DIPEA (2.3 mL, 13.2 mmol), followed by methyl acrylate (0.59 mL, 6.6 mmol). After being stirred at 50 °C for 8 h, the reaction mixture was concentrated under reduced pressure to give a light brown oil. To a mixture of the obtained crude product in CH_2Cl_2 (20 mL) and DIPEA (1.05 mL, 6.0 mmol) was added propionyl chloride (0.53 mL, 3.0 mmol) at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was added sat. $NaHCO_3$ aq., extracted with CH_2Cl_2 (40 mL x 2). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure. The residue was purified by flash NH silica gel column chromatography (*n*-Hexane/EtOAc = 9 : 1 to 1 : 1) to afford compound **2** as a pale yellow oil (390 mg, 52%; remifentanil).

^{1}H NMR (600 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.5 Hz, 3H), 1.62 – 1.67 (m, 2H), 1.87 (q, *J* = 7.8 Hz, 2H), 2.27 (d, *J* = 13.2 Hz, 2H), 2.41 – 2.45 (m, 4H), 2.61 (d, *J* = 12.0 Hz, 2H), 2.65 (t, *J* = 7.5 Hz, 2H), 3.64 (s, 3H), 3.79 (s, 3H), 7.29 – 7.32 (m, 2H), 7.40 – 7.44 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 9.1, 29.0 (2C), 32.0, 33.4, 49.6 (2C), 51.5, 52.0, 53.2, 62.7, 128.6, 129.3 (2C), 130.6 (2C), 139.3, 172.8, 173.9, 174.0.

HRMS (ESI) : *m*/*z* calcd. for $C_{20}H_{29}N_2O_5$ $[M+H]^+$ 377.2071, found 377.2053.

Alfentanil (3)



To a solution of compound **S10** (3.05 g, 9.12 mmol) in THF (91 mL) was slowly added $LiAlH_4$ (1.04 g, 27.4 mmol) at 0 °C under stirring. After being stirred at room temperature for 16 h, the reaction mixture was quenched by the addition of 2M NaOH at 0 °C. The resulting mixture was added EtOAc, and the supernatant was separated from the precipitate by decantation. The collected supernatant was washed with water, brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure to give a brown oil (2.45 g), which was used in next step without further purification.

To a solution of the above product (2.45 g) in THF (20 mL) was added Ag_2O (9.27 g, 40.0 mmol), followed by CH_3I (4.98 mL, 80.0 mmol), and the reaction mixture was stirred at room temperature for 48 h. The reaction mixture was filtered through a pad of celite to remove the precipitate. The filtrated was concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (*n*-Hexane/EtOAc = 9 : 1 to 1 : 1) to afford compound **S11** as a light brown oil (1.05 g, 41%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.60 – 1.65 (m, 2H), 1.85 – 1.88 (m, 2H), 3.28 (s, 2H), 3.30 (s, 3H), 3.34 – 3.39 (m, 2H), 3.69 (br, 2H), 6.82 (d, J = 7.2 Hz, 2H), 6.87 (t, J = 7.2 Hz, 1H), 7.18 (dd, J = 7.2, 7.2 Hz, 2H).

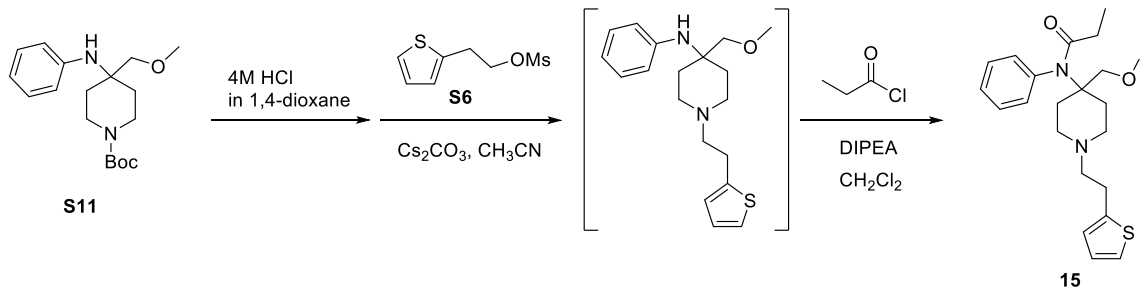
Compound **S11** (320 mg, 1.0 mmol) was treated with a mixture of 4M HCl in 1,4-dioxane (4mL) and MeOH (1 mL) at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure to remove the volatiles. The residue was suspended in CH_3CN (10 mL), added to Cs_2CO_3 (0.78 g, 2.4 mmol), followed by 1-(2-bromoethyl)-4-ethyl-1,4-dihydro-5*H*-tetrazol-5-one (149 μL, 1.2 mmol). After being stirred at 60 °C for 12 h, the reaction mixture was concentrated under reduced pressure to dryness. The residue was poured into water (5 mL), extracted with CH_2Cl_2 (20 mL x 2). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure to give a light brown oil. To a mixture of the resulting crude product and DIPEA (261 μL, 1.5 mmol) in CH_2Cl_2 (5 mL) was added dropwise propionyl chloride (130 μL, 1.5 mmol) at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was added sat. $NaHCO_3$, extracted with CH_2Cl_2 (20 mL x 2). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure. The residue was purified by flash NH silica gel column chromatography (*n*-Hexane/EtOAc = 9 : 1 to 2 : 1) to afford compound **3** as a pale yellow oil (325 mg, 78%; alfentanil).

^{1}H NMR (600 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.5 Hz, 3H), 1.42 (t, *J* = 7.8 Hz, 3H), 1.62 – 1.67 (m, 2H), 1.81 (dd, *J* = 14.4, 7.2 Hz, 2H), 2.18 – 2.26 (m, 4H), 2.61 – 2.63 (m, 2H), 2.72 (t, *J* = 6.9 Hz, 2H), 3.42 (s, 3H), 3.96 – 4.04 (m, 4H), 4.06 (s, 2H), 7.26 – 7.28 (m, 2H), 7.30 – 7.35 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 9.5, 13.9, 30.7, 33.0 (2C), 40.1, 42.4, 50.1 (2C), 55.7, 59.2, 61.4, 70.5, 127.8, 128.6 (2C), 131.3 (2C), 141.2, 150.6, 174.6.

HRMS (ESI) : *m*/*z* calcd. for $C_{21}H_{33}N_6O_3$ $[M+H]^+$ 417.2609, found 417.2587.

Sufentanil (**15**)



Compound **S11** (320 mg, 1.0 mmol) was treated with a mixture of 4M HCl in 1,4-dioxane

(4 mL) and MeOH (1 mL) at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure to remove the volatiles. The residue was suspended in CH_3CN (10 mL), added to Cs_2CO_3 (0.78 g, 2.4 mmol), followed by compound **S6** (251 mg, 1.2 mmol). After being stirred at 60 °C for 12 h, the reaction mixture was concentrated under reduced pressure to dryness. The residue was poured into water (5 mL), extracted with CH_2Cl_2 (20 mL x 2). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure to give a light brown oil. To a mixture of the resulting crude product and DIPEA (261 μL, 2.0 mmol) was added dropwise propionyl chloride (131 μL, 2.0 mmol) at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was added sat. $NaHCO_3$, extracted with CH_2Cl_2 (20 mL x 2). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure. The residue was purified by flash NH silica gel column chromatography (*n*-Hexane/EtOAc = 19 : 1 to 9 : 1) to afford compound **15** as a pale yellow oil (280 mg, 55%; sufentanil).

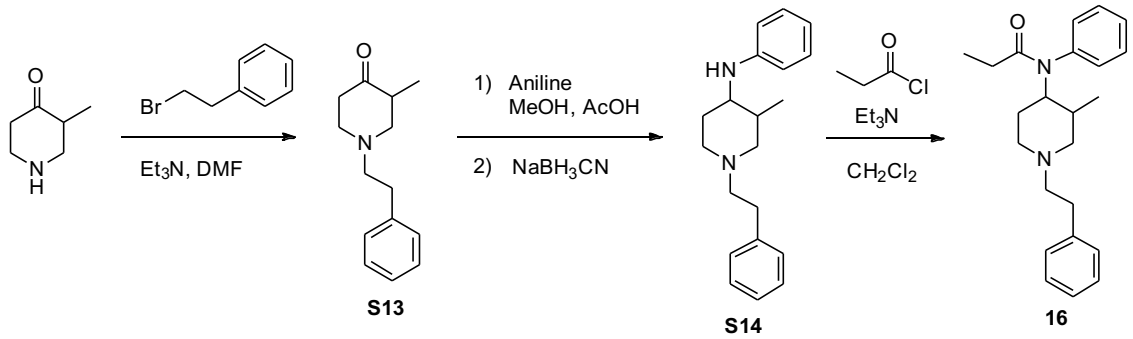
^{1}H NMR (600 MHz, $CDCl_3$) δ 0.94 (t, *J* = 7.2 Hz, 3H), 1.70 – 1.73 (m, 2H), 1.83 (q, *J* = 7.2 Hz, 2H), 2.19 – 2.27 (m, 4H), 2.60 (dd, *J* = 8.4, 7.8 Hz, 2H), 2.67 (d, *J* = 11.4, Hz, 2H), 2.96 (dd, *J* = 8.4, 7.8 Hz, 2H), 3.43 (s, 3H), 4.07 (s, 2H), 6.77 (d, *J* = 3.6 Hz, 1H), 6.89 (dd, *J* = 3.9, 3.6 Hz, 1H), 7.10 (d, *J* = 3.9 Hz, 1H), 7.29 – 7.36 (m, 5H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 9.5, 27.8, 30.6, 33.1 (2C), 50.1 (2C), 59.1, 60.0, 61.5, 70.4, 123.4, 124.5, 126.5, 127.7, 128.5 (2C), 131.3 (2C), 141.2, 142.7, 174.5.

HRMS (ESI) : *m*/*z* calcd. for $C_{22}H_{31}N_2O_2S$ $[M+H]^+$ 387.2101, found 387.2148.

D. 3-Methyl series

3-Methylfentanyl (16)



To a mixture of 3-methyl-4-piperidone (1.13 g, 10.0 mmol) and Et_3N (1.67 mL, 12.0

mmol) in DMF (15 mL) was added (2-bromoethyl)benzene (1.62 mL, 12.0 mmol). After being stirred at 90 °C for 24 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (*n*-Hexane/EtOAc = 5 : 1 to 2 : 1) to afford compound **S13** as a yellow oil (0.47 g, 20%).
^{1}H NMR (600 MHz, $CDCl_3$) δ 1.03 (t, *J* = 7.2 Hz, 3H), 2.16 (t, *J* = 11.4 Hz, 1H), 2.37 (dt, *J* = 14.4, 2.4 Hz, 1H), 2.46 (td, *J* = 11.4, 2.4 Hz, 1H), 2.60 – 2.68 (m, 2H), 2.70 – 2.73 (m, 2H), 2.83 – 2.86 (m, 2H), 3.18 – 3.22 (m, 2H), 7.20 – 7.26 (m, 3H), 7.30 (t, *J* = 7.2 Hz, 2H).

To a solution of compound **S13** (407 mg, 1.38 mmol) in MeOH (10 mL) was added aniline (0.2 mL, 2.19 mmol), followed by AcOH (40 μL) at room temperature. The reaction mixture was stirred at 50 °C for 5 h. After cooling to 0 °C, the reaction mixture was slowly added $NaBH_3CN$ (181 mg, 2.9 mmol) in some portions. After completion of the addition, the reaction mixture was allowed to warm up to room temperature. After being stirred for 18 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, and then concentrated under reduced pressure to remove a majority of MeOH. The residue was added 2M aqueous NaOH to basify (pH > 8), and extracted with CH_2Cl_2 (20 mL x 2), and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (*n*-Hexane/EtOAc = 2 : 1) to afford compound **S14** as a light yellow oil (356 mg, 88%).
^{1}H NMR (600 MHz, $CDCl_3$) δ 0.98 – 1.03 (m, 4H), 2.16 (t, *J* = 11.4 Hz, 2H), 2.37 (dt, *J* = 14.4, 2.4 Hz, 1H), 2.46 (td, *J* = 11.4, 2.4 Hz, 1H), 2.55 – 2.68 (m, 2H), 2.70 – 2.73 (m, 2H), 2.83 – 2.86 (m, 2H), 3.17 – 3.22 (m, 2H), 6.58 – 6.68 (m, 1H), 7.14 – 7.17 (m, 1H), 7.20 – 7.23 (m, 5H), 7.27 – 7.31 (m, 3H).

To a mixture of compound **S14** (356 mg, 1.20 mmol) and Et_3N (180 μL, 1.29 mmol) in CH_2Cl_2 (5 mL) was added dropwise propionyl chloride (150 μL, 1.72 mmol) at 0 °C. After being stirred at room temperature for 13 h, the reaction mixture was added sat. $NaHCO_3$, extracted with CH_2Cl_2 (20 mL x 2). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (*n*-Hexane/EtOAc = 4 : 1 to 2 : 1) to afford compound **16** as a pale yellow oil (162 mg, 45%; 3-methylfentanyl,

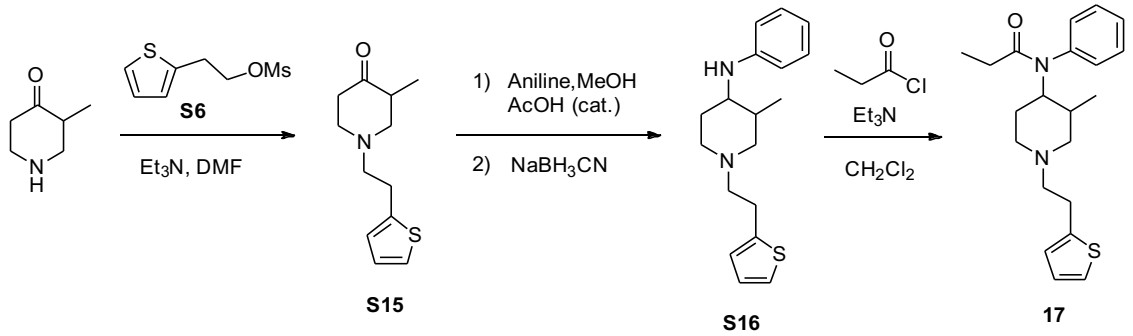
racemic mixture).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.01 (t, 7.8 Hz, 3H), 1.10 (d, *J* = 7.2 Hz, 3H), 1.94 (q, *J* = 7.8 Hz, 2H), 2.28 (dd, *J* = 12.0, 3.0 Hz, 1H), 2.39 – 2.45 (m, 1H), 2.47 – 2.54 (m, 2H), 2.64 – 2.82 (m, 7H), 4.41 (dt, *J* = 13.2, 4.2 Hz, 1H), 7.13 – 7.18 (m, 5H), 7.24 (d, *J* = 6.6 Hz, 1H), 7.33 – 7.43 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 9.5, 13.6, 28.4, 28.9, 29.9, 55.1, 57.6, 59.6, 61.7, 72.2 127.9, 128.4 (2C), 128.6 (2C), 128.6 (2C), 129.3, 129.6 (2C), 130.9, 138.5, 174.4.

HRMS (ESI) : *m*/*z* calcd. for $C_{23}H_{31}N_2O$ $[M+H]^+$ 351.2431, found 351.2387.

3-Methylthiofentanyl (17)



To a mixture of 3-methyl-4-piperidone (0.78 g, 6.91 mmol) and Et_3N (1.3 mL, 9.3 mmol) in DMF (15 mL) was added compound **S6** (1.40 g, 6.80 mmol). After being stirred at 90 °C for 15 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (*n*-Hexane/EtOAc = 4 : 1 to 1 : 1) to afford compound **S15** as a light yellow oil (1.61 g, quant.).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.03 (d, *J* = 6.6 Hz, 3H), 2.19 (t, *J* = 12.0 Hz, 1H), 2.37 (dt, *J* = 12.0, 3.0 Hz, 1H), 2.49 (td, *J* = 12.0, 3.0 Hz, 1H), 2.61 – 2.71 (m, 2H), 2.76 (t, *J* = 9.0 Hz, 2H), 3.06 (t, *J* = 6.6 Hz, 2H), 3.15 – 3.20 (m, 2H), 6.85 (d, *J* = 6.0 Hz, 1H), 6.94 (t, *J* = 6.0 Hz, 1H), 7.15 (d, *J* = 6.0 Hz, 1H).

To a solution of compound **S15** (1.61 g, 7.22 mmol) in MeOH (10 mL) was added aniline (0.85 mL, 9.33 mmol), followed by AcOH (40 μL) at room temperature. The reaction mixture was stirred at 50 °C for 9 h. After cooling to 0 °C, the reaction mixture was slowly added $NaBH_3CN$ (740 mg, 11.8 mmol) in some portions. After completion of the addition,

the reaction mixture was allowed to warm up to room temperature. After being stirred for 14 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, and then concentrated under reduced pressure to remove a majority of MeOH. The residue was added 2M aqueous NaOH to basify (pH > 8), and extracted with CH_2Cl_2 (30 mL x 2), and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by flash NH silica gel column chromatography (*n*-Hexane/EtOAc = 10 : 1 to 5 : 1) to afford compound **S16** as a light yellow oil (801 mg, 38%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 0.99 (d, *J* = 6.6 Hz, 3H), 1.36 – 1.42 (m, 1H), 1.63 – 1.69 (m, 1H), 1.87 (t, *J* = 10.2 Hz, 1H), 2.46 (td, *J* = 11.4, 2.4 Hz, 1H), 2.09 – 2.16 (m, 2H), 2.62 – 2.67 (m, 2H), 2.91 (td, *J* = 10.2, 3.0 Hz, 1H), 2.97 – 3.05 (m, 4H), 6.58 (d, *J* = 7.2 Hz, 2H), 6.66 (t, *J* = 7.2 Hz, 1H), 6.82 – 6.85 (m, 1H), 6.90-6.96 (m, 1H), 7.13 – 7.18 (m, 3H).

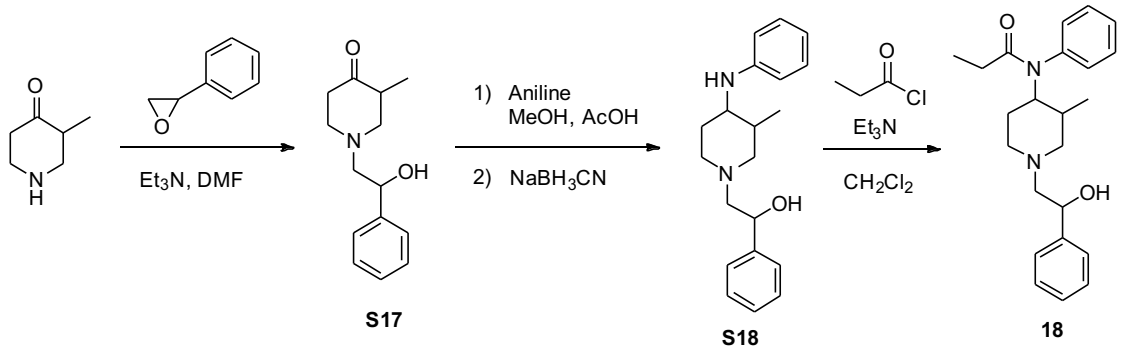
To a mixture of compound **S16** (800 mg, 2.53 mmol) and Et_3N (0.5 mL, 3.58 mmol) in CH_2Cl_2 (5 mL) was added dropwise propionyl chloride (0.3 mL, 3.45 mmol) at 0 °C. After being stirred at room temperature for 13 h, the reaction mixture was added sat. $NaHCO_3$, extracted with CH_2Cl_2 (30 mL x 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure. The residue was purified by flash NH silica gel column chromatography (*n*-Hexane/EtOAc = 10 : 1) to afford compound **17** as a pale brown oil (162 mg, 17%; 3-methylthiofentanyl, racemic mixture).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.02 (t, *J* = 7.8 Hz, 3H), 1.13 (d, *J* = 6.6 Hz, 3H), 1.28 (d, *J* = 9.6 Hz, 1H), 1.44 (qd, *J* = 12.6, 3.6 Hz, 1H), 1.60 – 1.80 (m, 1H), 1.90 – 1.98 (m, 2H), 2.01 – 2.07 (m, 1H), 2.32 (d, *J* = 9.0 Hz, 1H), 2.47 – 2.57 (m, 2H), 2.73 – 2.79 (m, 2H), 2.87 – 2.98 (m, 2H), 4.42 (dt, *J* = 13.2, 4.2 Hz, 1H), 6.79 (d, *J* = 3.0 Hz, 1H), 6.90 (dd, *J* = 5.4, 3.6 Hz, 1H), 7.10 (d, *J* = 5.4 Hz, 1H), 7.29 – 7.43 (m, 5H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 9.6, 14.0, 26.3, 27.8, 29.0, 31.4, 54.0, 57.6, 59.5, 59.6, 123.4, 124.4, 126.3 (2C), 127.9 (2C), 128.2, 129.7, 140.6, 143.2, 174.4.

HRMS (ESI) : *m*/*z* calcd. for $C_{21}H_{29}N_2OS$ $[M+H]^+$ 357.1995, found 357.1956.

β-Hydroxy-3-methylfentanyl (18)



To a suspension of 3-methyl-4-piperidone (1.13 g, 10.0 mmol) in DMF (15 mL) was added Et_3N (1.67 mL, 12.6 mmol), followed by styrene oxide (1.62 mL, 12.0 mmol). After being stirred at 90 °C for 24 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (*n*-Hexane/EtOAc = 5 : 1 to 2 : 1) to afford compound **S17** as a light yellow oil (0.47 g, 20%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 0.98 (q, *J* = 6.0 Hz, 3H), 2.32 – 2.69 (m, 7H), 3.00 – 3.04 (m, 1H), 3.28 – 3.32 (m, 1H), 3.78 (brs, 1H), 4.69 – 4.74 (m, 1H), 7.23 (t, *J* = 6.6 Hz, 1H), 7.28 – 7.33 (m, 4H).

To a solution of compound **S17** (407 mg, 1.38 mmol) in MeOH (10 mL) was added aniline (0.2 mL, 2.19 mmol), followed by AcOH (40 μL) at room temperature. The reaction mixture was stirred at 50 °C for 5 h. After cooling to 0 °C, the reaction mixture was slowly added $NaBH_3CN$ (181 mg, 2.9 mmol) in some portions. After completion of the addition, the reaction mixture was allowed to warm up to room temperature. After being stirred for 16 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, and then concentrated under reduced pressure to remove a majority of MeOH. The residue was added 2M aqueous NaOH to basify (pH > 8), and extracted with CH_2Cl_2 (20 mL x 2), and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (*n*-Hexane/EtOAc = 2 : 1) to afford compound **S18** as a light yellow oil (356 mg, 88%).

To a mixture of compound **S18** (356 mg, 1.20 mmol) and Et_3N (180 μL, 1.32 mmol) in CH_2Cl_2 (5 mL) was added dropwise propionyl chloride (150 μL, 1.72 mmol) at 0 °C.

After being stirred at room temperature for 13 h, the reaction mixture was added sat. $NaHCO_3$, extracted with CH_2Cl_2 (20 mL x 2). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure. The residue was purified by flash NH silica gel column chromatography (*n*-Hexane/EtOAc = 4 : 1 to 2 : 1) to afford a pale brown oil (670 mg). The obtained material (670 mg) was dissolved in MeOH (5 mL), and added K_2CO_3 (459 mg, 3.27 mmol). After being stirred at room temperature for 24 h, the reaction mixture was added water, and extracted with CH_2Cl_2 (20 mL x 2). The combined organic extracts were dried over Na_2SO_4, filtered, concentrated under reduce pressure. The residue was treated with 4M HCl in 1,4-dioxane (10 mL), and concentrated under reduced pressure to afford compound **18** (338 mg, 70%; β-hydroxy-3-methylfentanyl) as a hydrochloride salt of diastereomeric mixture.

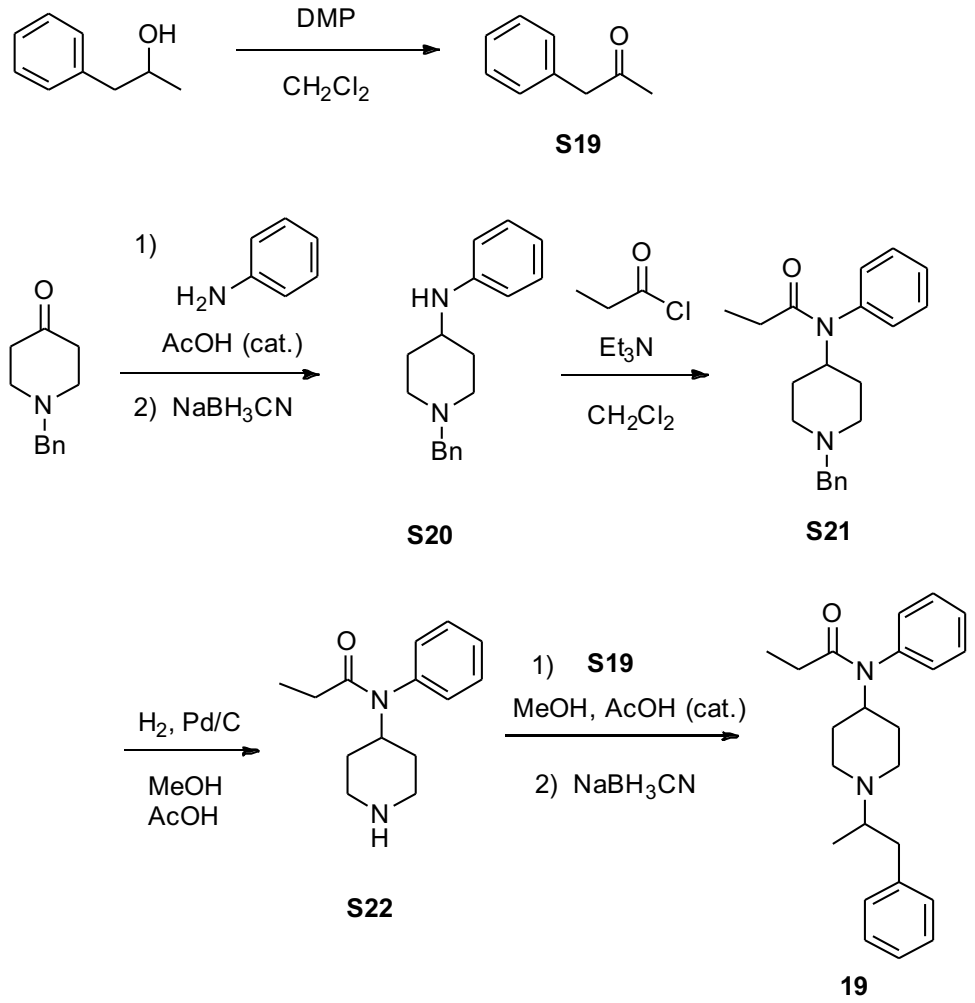
^{1}H NMR (600 MHz, $CDCl_3$) δ 0.85 – 1.36 (m, 8H), 1.70 – 1.88 (m, 3H), 2.97 – 3.10 (m, 3H), 3.51 – 3.67 (m, 4H), 4.46 – 4.55 (m, 1H), 5.19 – 5.36 (m, 1H), 6.86 – 7.04 (m, 1H), 7.17 – 7.23 (m, 4H), 7.27 – 7.42 (m, 5H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 9.1, 16.5, 27.8, 32.4, 37.6, 51.6, 52.7, 56.3, 63.5, 72.8, 112.9, 113.2, 116.9, 126.5 (2C), 127.8, 128.3 (2C), 129.2 (2C), 139.6, 147.8, 173.6.

HRMS (ESI) : *m*/*z* calcd. for $C_{23}H_{31}N_2O_2$ $[M+H]^+$ 367.2386, found 367.2360.

E. 3-Methyl series

α-Methylfentanyl (19)



To a solution of 1-phenyl-2-propanol (0.68 g, 5.0 mmol) in CH_2Cl_2 (20 mL) was added Dess-Martin reagent (3.18 g, 7.5 mmol) at 0 °C. After being stirred at room temperature for 1 h, the reaction mixture was filtered to remove the precipitate. The filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (*n*-Hexane/EtOAc = 19 : 1 to 3 : 1) to afford compound **S19** as a colorless oil (0.63 g, 94%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.50 (s, 3H), 3.69 (s, 2H), 7.20 – 7.21 (m, 2H), 7.26 – 7.29 (m, 1H), 7.32 – 7.35 (m, 2H).

To a suspension of 1-benzyl-4-piperidone (7.57 g, 40.0 mmol) in MeOH (50 mL) was added aniline (3.72 g, 40.0 mmol), followed by AcOH (228 μL, 4.0 mmol), and the reaction mixture was stirred at 50 °C for 3 h. After cooling to 0 °C, the reaction mixture

was slowly added $NaBH_3CN$ (3.78 g, 60.0 mmol) in some portion. After being stirred at room temperature for 12 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, and then concentrated under reduced pressure to remove a majority of MeOH. The residue was added 2M aqueous NaOH to basify (pH > 8), and extracted with CH_2Cl_2 (60 mL x 3), and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (*n*-Hexane/EtOAc = 19 : 1 to 2 : 1) to afford compound **S20** as a white solid (5.9 g, 71%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.45 – 1.52 (m, 2H), 2.04 (d, *J* = 7.5 Hz, 2H), 2.16 (dd, *J* = 11.1 Hz, 2H), 2.85 (d, *J* = 5.4 Hz, 2H), 3.30 (brs, 1H), 3.50 (br, 1H), 3.53 (s, 2H), 6.58 (dd, *J* = 8.4, 1.2 Hz, 2H), 6.67 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.15 (dd, *J* = 8.4, 7.2 Hz, 2H), 7.25 – 7.27 (m, 1H), 7.31 – 7.33 (m, 4H).

LRMS (ESI): *m*/*z* $[M+H]^+$ 267.5.

To a mixture of compound **S20** (5.0 g, 18.8 mmol) and Et_3N (3.19 mL, 22.9 mmol) in CH_2Cl_2 (50 mL) was added dropwise propionyl chloride (2.5 mL, 28.2 mmol) at 0 °C. After being stirred at room temperature for 3 h, the reaction mixture was added sat. $NaHCO_3$, extracted with CH_2Cl_2 (80 mL x 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (*n*-Hexane/EtOAc = 9 : 1 to 2 : 1) to afford compound **S21** as a pale brown oil (2.11 g, 35%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.00 (t, *J* = 7.5 Hz, 3H), 1.38 (ddd, *J* = 12.0, 12.0, 3.6 Hz, 2H), 1.75 (d, *J* = 13.5 Hz, 2H), 1.91 (q, *J* = 7.5 Hz, 2H), 2.10 (ddd , *J* = 13.5, 12.0, 1.2 Hz, 2H), 2.87 (d, *J* = 12.0 Hz, 2H), 3.43 (s, 2H), 4.65 (ddd, *J* = 12.0, 12.0, 3.6 Hz, 1H), 7.06 (d, *J* = 6.6 Hz, 2H), 7.20 – 7.23 (m, 3H), 7.25 – 7.27 (m, 2H), 7.35 – 7.40 (m, 3H).

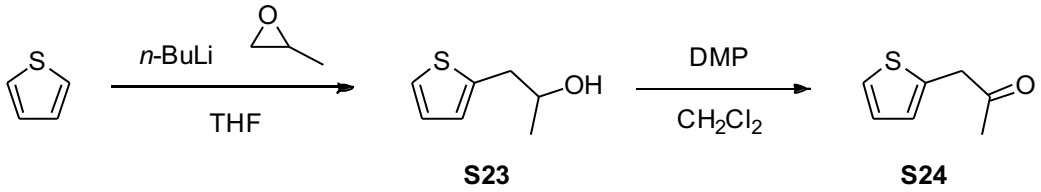
LRMS (ESI): *m*/*z* $[M+H]^+$ 323.5.

To a solution of compound **S21** (4.7 g, 14.6 mmol) in a mixture of MeOH/AcOH (40 mL/4 mL) was added 10% Pd/C (932 mg). After being stirred at room temperature under H_2 gas atmosphere for 48 h. the reaction mixture was filtered through a pad of celite to remove a catalyst. The filtrate was concentrated under reduced pressure, and the residue was basified (pH > 9) with 2M NaOH aq., extracted with CH_2Cl_2 (100 mL x 2). The combined organic extracts were dried over Na_2SO_4 filtered, concentrated under reduced

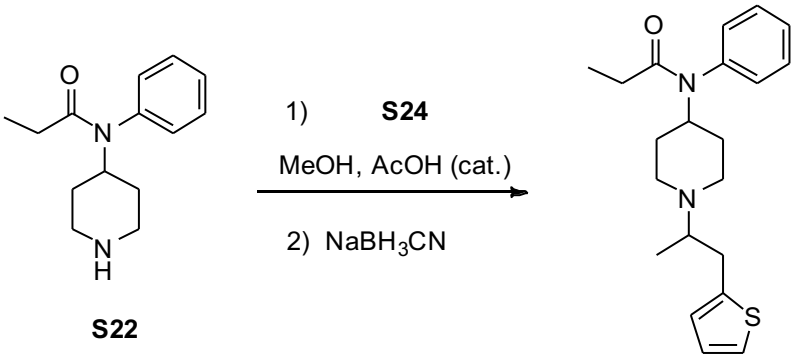
pressure to give compound **S22** (3.2 g) as a light yellow solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 1.01 (t, *J* = 7.8 Hz, 3H), 1.25 (dddd, *J* = 12.6, 12.0, 2.1, 2.1 Hz, 2H), 1.77 – 1.79 (m, 2H), 1.92 (q, *J* = 7.8 Hz, 2H), 2.73 (ddd, *J* = 12.0, 12.0, 2.4 Hz, 2H), 3.04 – 3.06 (m, 2H), 4.75 (dddd, *J* = 12.0, 12.0, 4.2, 4.2 Hz, 1H), 7.07 – 7.09 (m, 2H), 7.35 – 7.41 (m, 3H).

To a solution of compound **S22** (464 mg, 2.0 mmol) in MeOH (5 mL) was added compound **S19** (268 mg, 2.0 mmol), followed by AcOH (11 μL, 0.2 mmol). After being stirred at room temperature for 18 h, the reaction mixture was slowly added $NaBH_3CN$ (251 mg, 4.0 mmol) at 0 °C. After being stirred at room temperature for 12 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, and then concentrated under reduced pressure to remove a majority of MeOH. The residue was added 2M aqueous NaOH to basify (pH > 8), and extracted with CH_2Cl_2 (30 mL x 2), and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by flash NH silica gel column chromatography (*n*-Hexane/EtOAc = 9 : 1 to 6 : 1) to afford compound **19** as a colorless viscous oil (260 mg, 37%; α-methylfentanyl, racemic mixture). The obtained product was treated with 4M HCl in 1,4-dioxane, and evaporated under vacuum to provide hydrochloride form of **19**.
^{1}H NMR (600 MHz, $CDCl_3$) δ 1.02 (t, *J* = 7.2 Hz, 3H), 1.24 (d, *J* = 6.6 Hz, 3H), 1.97 (q, *J* = 7.2 Hz, 2H), 2.02 (d, *J* = 11.4 Hz, 2H), 2.26 (ddd, *J* = 12.6, 12.6, 3.0 Hz, 1H), 2.34 (ddd, *J* = 12.6, 12.6, 3.6 Hz, 1H), 2.54 (dd, *J* = 12.0, 11.4 Hz, 1H), 2.99 (ddd, *J* = 12.6, 12.0, 2.4 Hz, 2H), 3.48 – 3.42 (m, 3H), 3.64 (dd, *J* = 12.0, 2.1 Hz, 1H), 4.77 (dddd, *J* = 12.6, 12.0, 3.6, 3.0 Hz, 1H), 7.12 (t, *J* = 6.6 Hz, 2H), 7.22 – 7.26 (m, 3H), 7.30 (t, *J* = 7.2 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.2 Hz, 2H), 12.27 (brs, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 9.6, 12.7, 27.6, 27.7, 28.5, 37.7, 47.1, 49.5, 50.5, 63.5, 127.4, 129.0 (2C), 129.2, 129.4 (2C), 129.8 (2C), 130.0 (2C), 136.1, 137.8, 174.3.
HRMS (ESI) : *m*/*z* calcd. for $C_{23}H_{31}N_2O$ $[M+H]^+$ 351.2436, found 351.2433.

α-Methylthiofentanyl (20)



S23 **S24**



S22 **20**

To a solution of thiophene (4.21 g, 50.0 mmol) in anhydrous THF (22 mL) was added dropwise *n*-BuLi (1.6M in *n*-hexane, 28 mL, 45.0 mmol) over 10 min at 0 °C. After being stirred at room temperature for 1 h, the reaction mixture was quenched with sat. NH_4Cl aq., concentrated under reduced pressure to remove a majority of THF. The residue was extracted with EtOAc, dried over Na_2SO_4, filtered, concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (*n*-Hexane/EtOAc = 9 : 1 to 2 : 1) to afford compound **S23** as a pale brown oil (3.09 g, 43%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.26 (d, *J* = 6.0 Hz, 3H), 1.75 (s, 1H), 2.90 (d, *J* = 14.4 Hz, 1H), 3.01 (d, *J* = 14.4 Hz, 1H), 4.02 (dd, *J* = 12.6, 6.0 Hz, 1H), 6.87 (d, *J* = 1.6 Hz, 1H), 6.96 – 6.97 (m, 1H), 7.07 (dd, *J* = 5.4, 1.6 Hz, 1H).

To a solution of compound **S23** (0.71 g, 5.0 mmol) in CH_2Cl_2 (20 mL) was added Dess-Martin reagent (3.18 g, 7.5 mmol) at 0 °C. After being stirred at room temperature for 1 h, the reaction mixture was filtered to remove the precipitate. The filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (*n*-Hexane/EtOAc = 19 : 1 to 3 : 2) to afford compound **S24** as a pale brown oil (0.64 g, 91%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.21 (s, 3H), 3.90 (s, 2H), 6.89 – 6.90 (m, 1H), 6.98 – 6.99

(m, 1H), 7.23 – 7.26 (m, 1H).

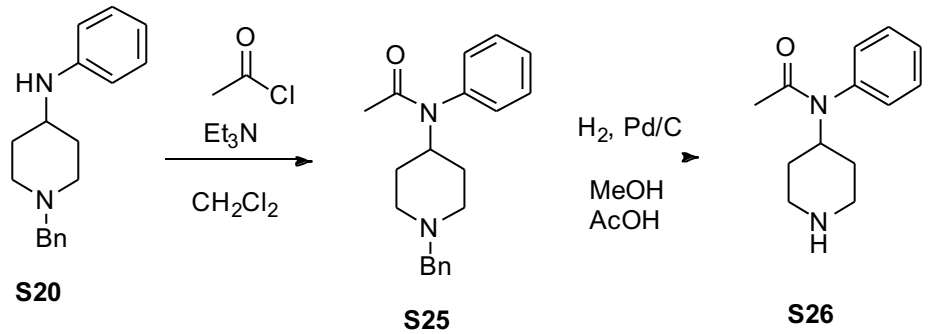
To a solution of compound **S22** (613 mg, 2.64 mmol) in MeOH (6.6 mL) was added compound **S24** (370 mg, 2.64 mmol), followed by AcOH (15 μL, 0.26 mmol). After being stirred at room temperature for 18 h, the reaction mixture was slowly added $NaBH_3CN$ (332 mg, 5.28 mmol) at 0 °C. After being stirred at room temperature for 12 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, and then concentrated under reduced pressure to remove a majority of MeOH. The residue was added 2M aqueous NaOH to basify (pH > 8), and extracted with CH_2Cl_2 (30 mL x 2), and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by flash NH silica gel column chromatography (*n*-Hexane/EtOAc = 9 : 1 to 6 : 1) to afford compound **20** as a pale brown oil (198 mg, 21%; α-methylthiofentanyl, rotamer mixtures). The obtained product was treated with 4M HCl in 1,4-dioxane, and evaporated under vacuum to provide hydrochloride form of **20**.

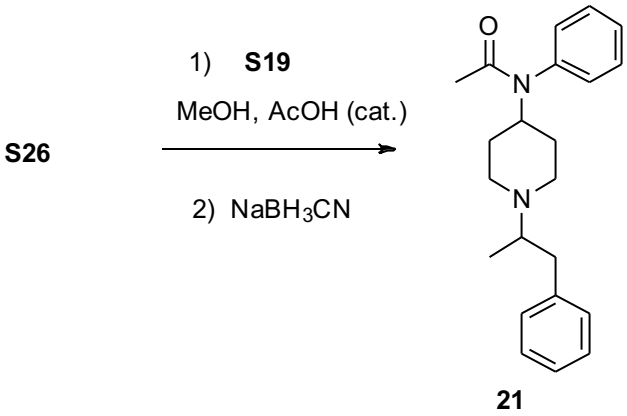
^{1}H NMR (600 MHz, $CDCl_3$) δ 1.02 (t, *J* = 7.2 Hz, 3H), 1.34 (d, *J* = 7.2 Hz, 3H), 1.97 (q, *J* = 7.2 Hz, 2H), 1.99 – 2.04 (m, 2H), 2.31 (dddd, *J* = 12.9, 12.9, 3.6, 3.6 Hz, 2H), 2.91 – 3.01 (m, 3H), 3.43 – 3.47 (m, 3H), 3.77 (dd, *J* = 12.9, 2.4 Hz, 1H), 4.76 (dddd, *J* = 12.9, 12.9, 3.6, 3.6 Hz, 1H), 6.91 (d, *J* = 2.4 Hz, 1H), 6.94 (dd, *J* = 4.8, 2.4 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 2H), 7.19 (d, *J* = 4.8 Hz, 1H), 7.40 – 7.43 (m, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 12.41 (brs, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 9.6, 13.5, 27.5, 27.6, 28.5, 31.7, 47.7, 49.4, 50.4, 63.3, 125.1, 127.2, 127.5, 129.3, 129.8 (2C), 130.1 (2C), 137.6, 137.8, 174.3.

HRMS (ESI) : *m*/*z* calcd. for $C_{21}H_{29}N_2OS$ $[M+H]^+$ 357.2001, found 357.1991.

α-Methylacetylfentanyl (21)





To a mixture of compound **S20** (2.76 g, 10.4 mmol) and Et_3N (5.29 mL, 31.1 mmol) in CH_2Cl_2 (42 mL) was added dropwise acetyl chloride (1.11 mL, 15.5 mmol) at 0 °C. After being stirred at room temperature for 3 h, the reaction mixture was added sat. $NaHCO_3$, extracted with CH_2Cl_2 (80 mL x 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (*n*-Hexane/EtOAc = 9 : 1 to 1 : 1) to afford compound **S25** as a brown oil (1.66 g, 52%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.39 – 1.43 (m, 2H), 1.73 (s, 3H), 1.74 – 1.80 (m, 2H), 2.11 (t, *J* = 11.4 Hz, 2H), 2.87 (d, *J* = 11.4 Hz, 2H), 3.44 (s, 2H), 4.62 – 4.67 (m, 1H), 7.07 (d, *J* = 7.2 Hz, 2H), 7.20 – 7.27 (m, 5H), 7.36 – 7.40 (m, 3H).

LRMS (ESI): *m*/*z* $[M+H]^+$ 309.4.

To a solution of compound **S25** (1.66 g, 5.38 mmol) in a mixture of MeOH/AcOH (9 mL/1 mL) was added 10% Pd/C (328 mg). After being stirred at room temperature under H_2 gas atmosphere for 36 h. the reaction mixture was filtered through a pad of celite to

remove a catalyst. The filtrate was concentrated under reduced pressure, and the residue was basified (pH > 9) with 2M NaOH aq., extracted with CH_2Cl_2 (30 mL x 2). The combined organic extracts were dried over Na_2SO_4 filtered, concentrated under reduced pressure to give compound **S26** (1.05 g) as a pale yellow powder.

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.26 (ddd, *J* = 12.6, 12.0, 4.2 Hz, 2H), 1.75 (s, 3H), 1.78 – 1.80 (m, 2H), 2.73 (ddd, *J* = 12.6, 12.0, 3.0 Hz, 2H), 3.05 (d, *J* = 9.6 Hz, 2H), 4.73 (dddd, *J* = 12.0, 12.0, 3.6, 3.6 Hz, 1H), 7.08 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.36 – 7.42 (m, 3H).

LRMS(ESI): *m*/*z* $[M+H]^+$ 219.3.

To a solution of compound **S26** (436 mg, 2.0 mmol) in MeOH (4 mL) was added compound **S19** (268 mg, 2.0 mmol), followed by AcOH (11 μL, 0.2 mmol). After being stirred at room temperature for 18 h, the reaction mixture was slowly added $NaBH_3CN$ (376 mg, 6.0 mmol) at 0 °C. After being stirred at room temperature for 12 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, and then concentrated under reduced pressure to remove a majority of MeOH. The residue was added 2M aqueous NaOH to basify (pH > 8), and extracted with CH_2Cl_2 (30 mL x 2), and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by flash NH silica gel column chromatography (*n*-Hexane/EtOAc = 9 : 1 to 6 : 1) to afford compound **21** as a pale yellow oil (243 mg, 36%; α-methylacetylfentanyl, racemic mixture). The obtained product was treated with 4M HCl in 1,4-dioxane, and evaporated under vacuum to provide hydrochloride form of **21**.

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.24 (d, *J* = 7.2 Hz, 3H), 1.79 (s, 3H), 2.02 – 2.04 (m, 2H), 2.28 (dddd, *J* = 12.6, 12.0, 3.6, 3.6 Hz, 1H), 2.36 (dddd, *J* = 12.6, 12.0, 3.0, 3.0 Hz, 1H), 2.53 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.99 (ddd, *J* = 12.0, 12.0, 2.4 Hz, 2H), 3.43 – 3.47 (m, 3H), 3.64 (dd, *J* = 12.0, 2.4 Hz, 1H), 4.76 (dddd, *J* = 12.6, 12.6, 4.2, 3.0 Hz, 1H), 7.13 (br, 2H), 7.22 – 7.26 (m, 3H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.2 Hz, 1H), 7.47 (dd, *J* = 7.2, 7.2 Hz, 2H), 12.30 (brs, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 12.7, 23.5, 27.5, 27.7, 37.8, 47.0, 49.6, 50.5, 63.5, 127.5, 129.0 (2C), 129.4, 129.4 (2C), 129.7 (2C), 130.1 (2C), 136.0, 138.2, 171.1.

HRMS (ESI) : *m*/*z* calcd. for $C_{22}H_{29}N_2O$ $[M+H]^+$ 337.2280, found 337.2270.