

Supporting information

The Development of HEC-866 and Its Analogues for the Treatment of Idiopathic Pulmonary Fibrosis

Runfeng Lin^{1†}, Zheng Zhang^{1†}, Shengtian Cao¹, Wen Yang¹, Yinglin Zuo¹, Xinye Yang¹, Jiancun Zhang¹, Juan Xu¹, Jing Li¹, Xiaojun Wang^{1*}

¹HEC Pharma Co. Ltd, Dongguan 523871, P. R. China

[†]These two authors contributed equally to this work

Corresponding author: Xiaojun Wang, Email: WangXiaojun@hec.cn

Table of Contents

1. General information and materials

(1) Chemistry part.....	3
(2) Biology part.....	3
<1> General information and materials.....	3
<2> Cell culture.....	4
<3> Cell viability and cytotoxicity assays.....	4
<4> Western blot analysis.....	5
<5> QPCR.....	5
<6> Male Spraguee-Dawley rats.....	5
<7> Hydroxyproline assay.....	6
<8> Rat PK.....	6
<9> Stability in liver microsomes.....	6
<10> Cytochrome P450 (CYP) Inhibition.....	7
<11> Automatic electrophysiological Qpatch detection for hERG.....	7
<12> Mini-Ames assay.....	7
2. Experimental procedure and compounds characterization.....	8

3. ^1H NMR, ^{13}C NMR and ^{19}F NMR Spectrums.....73

General information and materials

Chemistry part:

Reagents and solvents purchased from commercial sources were used without further purification. Where indicated, solvents were dried over anhydrous activated alumina. Reactions were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring unless otherwise noted. TLC analysis was performed on glass backed silica gel plates and visualized by UV light. ^1H NMR spectra were recorded at 400 (Bruker AVIIIHD 400) and chemical shifts (δ) are reported in ppm relative to the internal reference (CDCl_3 , 7.26 ppm). Tabulated ^1H NMR data are reported as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, with coupling constants in Hz. ^{13}C NMR spectra were recorded at 100 MHz (Bruker AVIII 400) and chemical shifts (δ) are reported in ppm relative to the internal reference (CDCl_3 , 77.16 ppm). Tabulated ^{13}C NMR data are reported as singlets unless noted as follows: d = doublet, q = quartet. HRMS spectra were recorded with an LCT Premier using electrospray ionization and quadrupole time of flight mass analyzer (Waters Micromass). All biologically tested compounds were determined to be >95% pure by ^1H and ^{13}C NMR analysis.

Biology part:

General information and materials

Chemicals and reagent: HEC -866 (**16**) (purity, $\geq 99\%$) and Pirfenidone (purity, $\geq 99\%$) were supplied by HEC Pharm Co. Ltd (Dongguan, China). Human

recombinant transforming growth factor ($\text{TGF-}\beta 1$) (H8541-5ug, Sigma) was reconstituted in 4 mM HCl (containing 0.1% recombinant human serum albumin) to make a 50 ng/ μl stock solution of active growth factor. Fluorescent quantitation PCR assay (DRR420) was brought from TAKARA. Assay kits for TM BCA Protein (Prod#23227) and TM Fast Western Blot (Prod#35050) were all provided by Thermo Scientific.

All animal studies were approved by the ethical committee of animal experiment in HEC Pharma. Co. Ltd., Dongguan, Guangzhou, China.

The accreditation number for operating experimental animals is SYXK2019-0135 and was given by the Department of Science & Technology, Guangdong, China.

Cell culture

The human lung fibroblast cells HFL1 (Cat# CCL-153, ATCC, Manassas, VA) using F-12k containing 10% FBS were incubated at 37 ° C in a 5% CO₂-humidified atmosphere. The cells were stimulated for 24h or 48 h with culture medium alone (control) or with pirfenidone and HEC-866 (**16**) with or without 10 ng/ml of $\text{TGF-}\beta 1$.

Cell viability and cytotoxicity assays (Table1)

Cell viability of cultured cells was quantified using the Cell Counting Kit (CKK)-8 (Cat# 35004, Biolite) and SpectraMax M5 Microplate Reader (Molecular Devices). The logarithmic growth phase cells were collected and resuspend with complete medium, then cell concentration was adjusted to $5 \times 10^4/\text{mL}$, and the cells were seeded into 96-well plates with 100 μl cell suspension added to each well. Cells were incubated overnight at 37 ° C in an incubator with 100% relative humidity and 5% CO₂. After the cells were synchronized, the serum-free medium was removed and the diluted compound was added into the cells with 100 $\mu\text{L}/\text{well}$. The compounds were all double diluted, with 3 duplication and a total of 7 concentration points. 24 hours after dosing, 10 μl (1/10 of the volume of the culture medium) CCK-8 solution was added to each

well, and incubated in the incubator for about 2 hours. The absorbance (A) value of each well was detected at 450 nm on a microplate reader. Set 3 parallel wells for each concentration. According to the measured A values of 3 parallel wells, first calculate the average A value (Aave) and then calculate the cell proliferation inhibition rate of each compound. The cell proliferation inhibition rate (IR) = (1-treatment group (Aave) value / Control group (Aave value) × 100%, and finally the IC50 value of each compound was calculated using GraphPad.

Western blot analysis (Figure 3A)

Experiment was carried out on total protein extracts from HFL1 cells. HFL1 cells were homogenized by gentle rocking in lysis buffer followed by centrifugation to clear the lysate. Equal amounts of protein lysates were separated by SDS-PAGE, transferred to PVDF membrane, and subjected to immunoblot analysis for α -SMA which antibody was bought from Merck-millipore (2699605). Proteins were visualized using the ECL detection system (Pierce) with the appropriate secondary antibodies: 800cw Goat anti-mouse antibody, LI-COR(C70712-11).

QPCR (Figure 3B)

Total RNA was extracted from the HFL1 cells seeded in 6-wells after stimulated for 24h and 2 μ g RNA was used for reverse transcription. Real-time PCR was performed with a Bio-rad CFX96 real-time PCR detection system (Hercules, CA, USA). COL1 α 1-F: 5'-CCTTGTGTAAGTGTGTG-3', COL1 α 1-R: 5'-CCATCACATAGATGTAGCA-3'. COL3-F: 5'-GTCTGATATTTAGACATGATGAG-3', COL3-R: 5'-GGAACATCCTCCTTCAAC-3'. The reaction conditions were set at 95 °C for 30 s, followed by 30 cycles at 94 °C for 5 s, 55 °C for 30 s, and 72 °C for 60 s. The mRNA level was determined with SYBR Green RT-PCR kit and results were analyzed and expressed as the relative mRNA expression of CT (Threshold Cycle) value and we used the $2^{-\text{exCt}}$ method to calculate the fold change. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as an internal control.

Male Spraguee-Dawley rats

Male Spraguee-Dawley rats weighing 220g -250 g were obtained from Hunan SJA Laboratory Animal Co.,Ltd. Rats were housed in the Animal House Facility of HEC Pharmaceutical Co., Ltd. under international standards for temperature, humidity and light control system with 4-6 animals in each cage. All rats were acclimatized for 1 week prior to experimental procedures. Pulmonary fibrosis was induced by a single intratracheal instillation of 5mg/kg BLM into the lung. Control rats received an equal volume of normal saline only (without BLM, 0.1 ml/100 g body weight). The BLM-treated rats were randomly divided into four groups. Three BLM-treated groups were orally administered daily with 100mg/kg of PFD and 2,6mg/kg of HEC-866 (**16**) from day 1 to 14 after modeling.

Hydroxyproline assay (Figure 4)

Total liver collagen was quantified by hydroxyproline assay (NJJC, P. R. China) according to the manufacturer's instructions. Firstly, 80-100 mg tissue was accurately weighed, cut it into pieces, and the added 1 ml of 6 mol/L HCl into a grinding tube with a cap. Then hydrolysis was performed at 95°C, or in a boiling water bath for 5 hours, or in an oven at 100°C for 5 hours. Secondly, adjusting pH of hydrolysate to 6.0~6.8. Thirdly, three kind of reagents were added at 65°C water bath for 15 minutes. After cooling, supernatant was centrifuged at 3500 r/min for 10 minutes, then measured the absorbance of each tube at 550nm, light diameter 1 cm.

Rat PK (Table 2, 3, 4, 5)

HEC-866 (16) was intravenously or orally administered at different dose levels. Rats, dog and monkey were restricted from food overnight prior to dosing (approx. 12 h) and fed 2 h post-dose. Water was provided ad libitum. Approximately 150 μ L of whole blood were collected from the orbital plexus using glass capillary and collected into a

tube which contained potassium EDTA. The plasma samples were stored at -70°C prior to analysis. An aliquot of 10 μ L of the supernatant was injected into the LC-MS/MS system for analysis.

Table 5

Stability in liver microsomes

The liver microsomes from various species were incubated with HEC-866 (**16**) at 37°C in the presence of the co-factor, NADPH for 0, 5, 15, 30, 60 min. The reaction was terminated by the addition of ice-cold acetonitrile. HEC-866 (**16**) concentrations were determined by an LC-MS/MS analytical method. At the end of incubations with hepatic microsomes from human, monkey, dog, rat and mouse liver tissue.

Cytochrome P450 (CYP) Inhibition (Table 6)

The microsomes (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4) were incubated with specific probe substrates and **16** at various concentrations (0.0~10 μ M). Subsequently, the enzyme activities of CYP isoforms were monitored by LC-MS/MS methods.

Automatic electrophysiological Qpatch detection for hERG (Table 7)

Automatic QPatch system (Sohion) is used for whole cell current recording. The cells used in this study were CHO cell lines transfected with HERG cDNA and stable expression of HERG channels. To achieve the IC₅₀ of compound that was tested in Six standard concentrations (30, 10, 3, 1, 0.3, and 0.1 μ m). Then to record the cell current, cells were first clamped at -80 mV and then depolarized to +20 mV to activate the HERG potassium channel, then clamped to -50 mV 5 seconds later to eliminate the inactivation and generate the tail current. The peak tail current is used as a value for the HERG current.

Mini-Ames assay (Table 7)

The objective of this study is to evaluate the mutagenic potential of HEC-866 (**16**) to induce reverse gene mutations at the histidine locus in five strains of *Salmonella typhimurium* (TA98, TA100) using the bacterial reverse mutation assay. Based on a preliminary dose range finding study, test article HEC585 was dissolved in dimethylsulfoxide (DMSO), and the highest dose in the study was 1000.0 μ g/plate (precipitation dose), the other doses tested were 7.8, 15.6, 31.3, 62.5, 125.0, 250.0, 500.0 and 1000 μ g/plate. All concentrations of the test article, as well as the concurrent vehicle (DMSO) and positive control articles, were evaluated with three plates per treatment using the standard plate incorporation method. The number of revertant colonies on each plate was counted after incubation at 37 ± 1 °C for approximately 48~72 hours. Toxicity of sixty-four SD rats were used in the experiment. In the experiment, 0 (solvent), 50 (low dose), 150 (medium dose) and 500 (high dose) mg/kg groups were administered orally at 10 mL/kg, once a day, for 28 days. No animal death and obvious abnormalities were observed during the experiments. Compared with the solvent control group, the body weight of animals in 150 and 500 mg/kg groups was reduced (the maximum loss was not more than 20.7%), and recovered to the normal level from the 22nd day. Monocytes and red cell distribution width were significantly increased in female 150 mg/kg and 500 mg/kg groups. Cholesterol increased in female 50, 150 and 500 mg/kg dose groups; The levels of ALB, ALT and A/G increased in the 50, 150 and 500 mg/kg groups. No obvious abnormality was observed in other indicators. The results of histological examination showed that there was mild submucosal gastritis in all experimental groups, which had nothing to do with the test products, and there was no worrying toxicological variation.

Experimental procedure (chemistry) and compounds characterization

Example 1 (the preparation of **3a**):

To a degassed solution of Triethyl phosphite (300 g, 1.59 mol, 1.00 eq.) was added 1-(bromomethyl)-3-fluorobenzene (303 g, 1.83 mmol, 1.15 eq.). The reaction was stirred

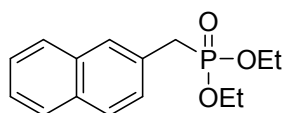
under N₂ and heated to 87 °C overnight. After cooled to r.t., the crude product **3a** was taken to the next step without further purification (colorless oil).

[ES-MS] (ESI⁺): m/z calcd for C₁₁H₁₆FO₃P [M + H]⁺ 247.1; found, 247.1.

¹H NMR (400 MHz, DMSO) δ 7.36 (dd, *J* = 14.5, 7.6 Hz, 1H), 7.17 – 7.03 (m, 3H), 3.97 (dq, *J* = 14.3, 7.1 Hz, 4H), 3.28 (d, *J* = 21.7 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 6H).

¹⁹F NMR (376 MHz, CDCl₃) δ -113.22 (d, *J* = 1.9 Hz).

The preparations of **3b-h** were the same as **3a**

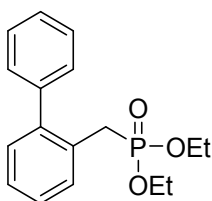


3b

2-(bromomethyl) naphthalene was converted to **3b** as colorless oil.

[ES-MS] (ESI⁺): m/z calcd for C₁₅H₁₉O₃P [M + H]⁺, 279.1; found, 279.1.

¹H NMR (400 MHz, CDCl₃) δ 7.72 (dd, *J* = 12.1, 7.0 Hz, 4H), 7.42 – 7.34 (m, 3H), 4.01 – 3.90 (m, 4H), 3.25 (d, *J* = 21.7 Hz, 2H), 1.17 (t, *J* = 7.1 Hz, 6H).

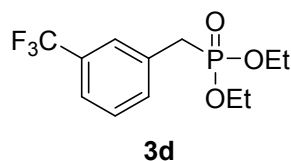


3c

2-(bromomethyl)-1,1'-biphenyl was converted to **3c** as colorless oil.

[ES-MS] (ESI⁺): m/z calcd for C₁₇H₂₁O₃P [M + H]⁺, 305.1; found, 305.1

¹H NMR (400 MHz, DMSO) δ 7.52 (d, *J* = 7.3 Hz, 1H), 7.49 – 7.28 (m, 7H), 7.23 (d, *J* = 7.2 Hz, 1H), 3.95 – 3.82 (m, 4H), 3.17 (d, *J* = 22.0 Hz, 2H), 1.13 (t, *J* = 7.1 Hz, 6H).

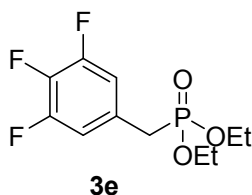


1-(bromomethyl)-3-(trifluoromethyl) benzene was converted to **3d** as colorless oil.

[ES-MS] (ESI⁺): m/z calcd for C₁₂H₁₆F₃O₃P [M + H]⁺, 297.1; found, 297.1

¹H NMR (400 MHz, DMSO) δ 7.67 (s, 1H), 7.63 – 7.48 (m, 3H), 4.04 – 3.92 (m, 4H), 3.42 (s, 2H), 1.16 (t, *J* = 7.1 Hz, 6H).

¹⁹F NMR (376 MHz, CDCl₃) δ -62.73 (s).

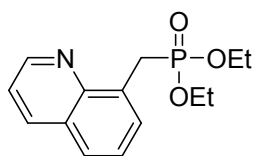


5-(bromomethyl)-1, 2, 3-trifluorobenzene was converted to **3e** as colorless oil.

[ES-MS] (ESI⁺): m/z calcd for C₁₁H₁₄F₃O₃P [M + H]⁺, 283.1; found, 283.1

¹H NMR (400 MHz, DMSO) δ 7.28 – 7.15 (m, 2H), 3.99 (dq, *J* = 14.2, 7.1 Hz, 4H), 3.33 (d, *J* = 1.6 Hz, 2H), 1.19 (t, *J* = 7.1 Hz, 6H).

¹⁹F NMR (376 MHz, CDCl₃) δ -134.51 (s), -134.57 (s), -162.96 (dt, *J* = 20.6, 10.2 Hz).

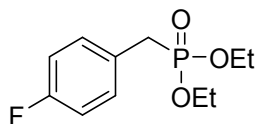


3f

8-(bromomethyl) quinolone was converted to **3f** as colorless oil.

[ES-MS] (ESI⁺): m/z calcd for C₁₄H₁₈NO₃P [M + H]⁺, 280.1; found, 280.1

¹H NMR (400 MHz, CDCl₃) δ 8.94 (dd, *J* = 4.0, 1.5 Hz, 1H), 8.15 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.85 (dd, *J* = 6.4, 3.3 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.41 (dd, *J* = 8.2, 4.2 Hz, 1H), 4.08 – 3.99 (m, 6H), 1.15 (t, *J* = 7.1 Hz, 6H).



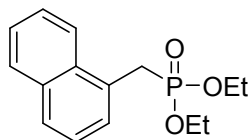
3g

1-(bromomethyl)-4-fluorobenzene was converted to **3g** as colorless oil.

[ES-MS] (ESI⁺): m/z calcd for C₁₁H₁₆FO₃P [M + H]⁺, 247.1; found, 247.1

¹H NMR (400 MHz, DMSO) δ 7.23 (s, 2H), 7.01 (s, 2H), 3.90 (d, *J* = 6.4 Hz, 4H), 3.22 – 2.99 (m, 2H), 1.10 (d, *J* = 4.4 Hz, 6H).

¹⁹F NMR (376 MHz, CDCl₃) δ -115.97 (d, *J* = 5.7 Hz).



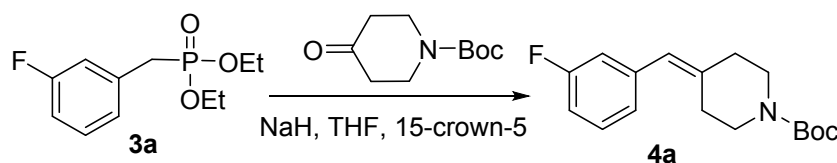
3h

1-(bromomethyl) naphthalene was converted to **3h** as colorless oil.

[ES-MS] (ESI⁺): m/z calcd for C₁₅H₁₉O₃P [M + H]⁺, 279.1; found, 279.1

^1H NMR (400 MHz, DMSO) δ 8.17 (d, J = 8.1 Hz, 1H), 7.95 – 7.89 (m, 1H), 7.83 (d, J = 7.1 Hz, 1H), 7.59 – 7.44 (m, 4H), 3.97 – 3.85 (m, 4H), 3.72 (d, J = 22.0 Hz, 2H), 1.10 (t, J = 7.1 Hz, 6H).

Example 2 (the preparation of **4a**):



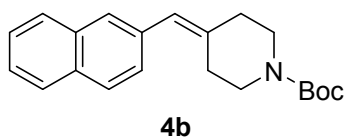
To an ice-cooled stirred solution of 60%NaH (136 g, 5.69 mol, 4.20 eq.) in anhydrous THF (500 mL) was added a solution of **3a** (350 g, 1.42 mol, 1.05 eq.) and 15-crown-5 (5.0 mL) in anhydrous THF(1500 mL) by drop wise, added completed, remove cooling bath and stirred at r.t. for another 30 min. The reaction mixture was cooling at ice bath again, a solution of N-Boc-4-oxopiperidine (269 g, 1.35 mol, 1.00 eq.) in anhydrous THF (1000 mL) was added to the mixture by drop wise, added completed, remove cooling bath and stirred at r.t. overnight. Then the mixture was diluted with 500 mL water at r.t. and extracted with 500 mL ethyl acetate twice. Then it was washed with 500 mL brine, dried over anhydrous Na_2SO_4 . The solution was filtrated and the solvent was removed under reduce pressure. The crude product was purified by chromatography on silica gel (PE: EA = 15: 1) to get **4a** as colorless oil (234.83 g). yield: 59.7%.

[ES-MS] (ESI⁺): m/z calcd for $\text{C}_{17}\text{H}_{22}\text{FNO}_2$ [$\text{M} + \text{H} - t\text{-Bu}$]⁺, 236.1; found,236.1

^1H NMR (400 MHz, CDCl_3) δ 7.33 – 7.22 (m, 1H), 6.96 (d, J = 7.6 Hz, 1H), 6.91 (dd, J = 13.9, 5.5 Hz, 2H), 6.33 (s, 1H), 3.59 – 3.47 (m, 2H), 3.47 – 3.37 (m, 2H), 2.46 (t, J = 5.5 Hz, 2H), 2.34 (t, J = 5.4 Hz, 2H), 1.49 (s, 9H).

^{19}F NMR (376 MHz, CDCl_3) δ -113.66 (s).

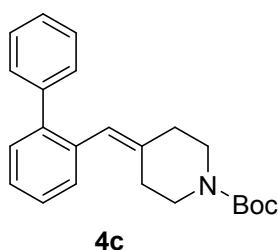
The preparations of **4b-h** were the same as **4a**



4b as 2.21 g white solid, yield: 68.3%.

[ES-MS] (ESI⁺): m/z calcd for C₂₁H₂₅NO₂ [M + H - ^tBu]⁺, 268.1; found, 268.1

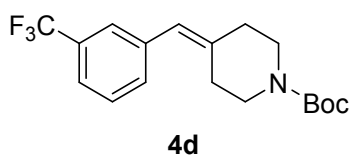
¹H NMR (400 MHz, CDCl₃) δ 7.83 (t, *J* = 7.8 Hz, 3H), 7.67 (s, 1H), 7.48 (pd, *J* = 6.9, 3.4 Hz, 2H), 7.37 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.54 (s, 1H), 3.62 – 3.55 (m, 2H), 3.50 – 3.42 (m, 2H), 2.58 (t, *J* = 5.4 Hz, 2H), 2.46 – 2.38 (m, 2H), 1.53 (s, 9H).



4c as 1.97 g white solid, yield: 56.2%.

[ES-MS] (ESI⁺): m/z calcd for C₂₃H₂₇NO₂ [M + H - ^tBu]⁺, 294.1; found, 294.2

¹H NMR (400 MHz, DMSO) δ 7.44 – 7.29 (m, 8H), 7.23 (dd, *J* = 5.5, 2.2 Hz, 1H), 6.15 (s, 1H), 3.33 – 3.26 (m, 2H), 3.09 (t, *J* = 5.5 Hz, 2H), 2.12 (t, *J* = 5.4 Hz, 4H), 1.39 (s, 9H).

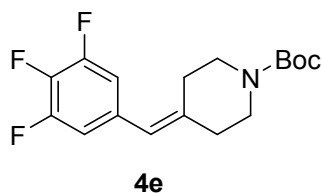


4d as 5.50 g yellow oil, yield: 92.0%

[ES-MS] (ESI⁺): m/z calcd for C₁₈H₂₂F₃NO₂ [M + 1 - ^tBu]⁺, 286.1; found, 286.1

¹H NMR (400 MHz, CDCl₃) δ 7.40 (t, *J* = 9.7 Hz, 3H), 7.32 (d, *J* = 7.3 Hz, 1H), 6.33 (s, 1H), 3.57 – 3.45 (m, 2H), 3.45 – 3.34 (m, 2H), 2.52 – 2.34 (m, 2H), 2.34 – 2.25 (m, 2H), 1.45 (s, 9H).

¹⁹F NMR (376 MHz, CDCl₃) δ -62.69 (s).

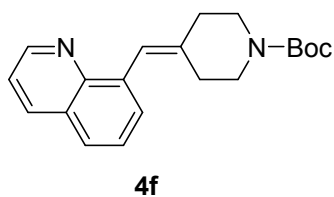


4e as 2.04 g white oil, yield: 62.3%.

[ES-MS] (ESI⁺): m/z calcd for C₁₇H₂₀F₃NO₂ [M + H - ^tBu]⁺, 272.1; found, 272.1

¹H NMR (400 MHz, DMSO) δ 7.16 (dd, *J* = 9.1, 7.0 Hz, 2H), 6.31 (s, 1H), 3.47 – 3.38 (m, 2H), 3.36 (d, *J* = 5.6 Hz, 2H), 2.38 (t, *J* = 5.5 Hz, 2H), 2.28 (t, *J* = 5.5 Hz, 2H), 1.41 (s, 9H).

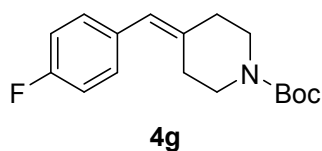
¹⁹F NMR (376 MHz, CDCl₃) δ -134.91 (d, *J* = 20.6 Hz), -135.10 (d, *J* = 20.4 Hz), -163.28 (t, *J* = 20.5 Hz), -163.84 (s).



4f as 2.0 g yellow oil, yield: 85.84%.

[ES-MS] (ESI⁺): m/z calcd for C₂₀H₂₄N₂O₂ [M + H]⁺, 325.2; found, 325.2

¹H NMR (400 MHz, CDCl₃) δ 8.98 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.74 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.60 – 7.47 (m, 2H), 7.42 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.17 (s, 1H), 3.68 – 3.58 (m, 2H), 3.52 – 3.43 (m, 2H), 2.60 – 2.53 (m, 2H), 2.52 – 2.43 (m, 2H), 1.50 (s, 9H).

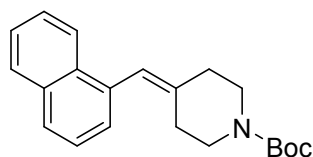


4g as 1.50 g yellow oil, yield: 51.6%.

[ES-MS] (ESI⁺): m/z calcd for C₁₇H₂₂FNO₂ [M + H - ^tBu]⁺, 236.1; found, 236.1

^1H NMR (400 MHz, CDCl_3) δ 7.16 (dd, $J = 8.3, 5.6$ Hz, 2H), 7.02 (t, $J = 8.7$ Hz, 2H), 6.33 (s, 1H), 3.55 – 3.49 (m, 2H), 3.45 – 3.38 (m, 2H), 2.43 (t, $J = 5.5$ Hz, 2H), 2.34 (t, $J = 5.4$ Hz, 2H), 1.50 (s, 9H).

^{19}F NMR (376 MHz, CDCl_3) δ -116.03 (s).



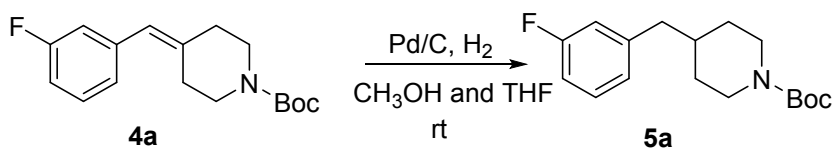
4h

4h as 560 mg white oil, yield: 34.6%.

[ES-MS] (ESI^+): m/z calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_2$ [$\text{M} + \text{H} - \text{tBu}$] $^+$, 268.1; found, 268.1

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.99 (dt, $J = 6.3, 3.1$ Hz, 1H), 7.96 – 7.91 (m, 1H), 7.84 (d, $J = 8.2$ Hz, 1H), 7.57 – 7.46 (m, 3H), 7.31 (dt, $J = 7.1, 1.1$ Hz, 1H), 6.81 (s, 1H), 3.51 (t, $J = 5.8$ Hz, 2H), 3.30 (d, $J = 6.4$ Hz, 2H), 2.46 – 2.40 (m, 2H), 2.20 (t, $J = 5.8$ Hz, 2H), 1.42 (s, 9H).

Example 3 (the preparation of **5a**)



To a degassed solution of methanol (250 mL) and THF (250 mL) was added **4a** (240 g, 823 mmol, 1.0 eq.) followed by 10% Pd-C (24 g, 10%). stirred under a H_2 balloon at r.t. overnight. The Pd/C was filtrated and the solvent was remove under reduce pressure. The crude product was taken to the next step without further purification.

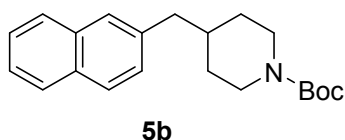
5a as 231.51 g colorless oil, yield: 95.8%.

[ES-MS] (ESI^+): m/z calcd for $\text{C}_{17}\text{H}_{24}\text{FNO}_2$ [$\text{M} + \text{H} - \text{tBu}$] $^+$, 238.1; found, 238.1

^1H NMR (400 MHz, Chloroform- d) δ 7.24 (td, $J = 7.9, 6.1$ Hz, 1H), 6.95 – 6.81 (m, 3H), 4.09 (s, 2H), 2.65 (t, $J = 13.1$ Hz, 2H), 2.54 (d, $J = 7.1$ Hz, 2H), 1.74 – 1.56 (m, 3H), 1.47 (s, 9H), 1.15 (qd, $J = 12.5, 4.3$ Hz, 2H).

^{19}F NMR (376 MHz, CDCl_3) δ -113.88 (s).

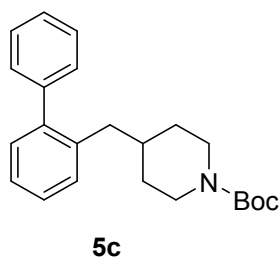
The preparation of **5b-h** were the same as **5a**.



5b as 2.02 g colorless oil, yield: 90.8%.

[ES-MS] (ESI^+): m/z calcd for $\text{C}_{21}\text{H}_{27}\text{NO}_2$ [$\text{M} + \text{H} - \text{tBu}$] $^+$, 270.1; found, 270.2

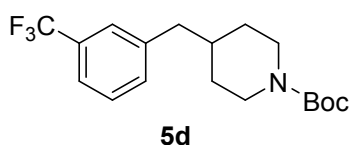
^1H NMR (400 MHz, DMSO) δ 7.88 – 7.77 (m, 3H), 7.64 (s, 1H), 7.45 (pd, $J = 6.8$, 1.2 Hz, 2H), 7.33 (dd, $J = 8.4$, 1.2 Hz, 1H), 3.91 (d, $J = 9.8$ Hz, 2H), 2.64 (d, $J = 7.1$ Hz, 4H), 1.72 (tdd, $J = 9.7$, 6.7, 3.0 Hz, 1H), 1.53 (d, $J = 12.2$ Hz, 2H), 1.38 (s, 9H), 1.10 – 0.97 (m, 2H).



5c as 1.91 g colorless oil, yield: 96.6%.

[ES-MS] (ESI^+): m/z calcd for $\text{C}_{23}\text{H}_{29}\text{NO}_2$ [$\text{M} + \text{H} - \text{tBu}$] $^+$, 296.2; found, 296.2

^1H NMR (400 MHz, DMSO) δ 7.43 (t, $J = 7.3$ Hz, 2H), 7.39 – 7.31 (m, 1H), 7.26 (ddt, $J = 8.8$, 5.5, 4.4 Hz, 5H), 7.15 (d, $J = 7.3$ Hz, 1H), 3.77 (d, $J = 12.0$ Hz, 2H), 2.51 (d, $J = 7.1$ Hz, 4H), 1.52 – 1.41 (m, 1H), 1.40 – 1.29 (m, 11H), 0.86 – 0.71 (m, 2H).

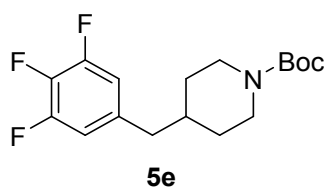


5d as 5.41 g colorless oil, yield: 97.8%.

[ES-MS] (ESI⁺): m/z calcd for C₁₈H₂₄F₃NO₂ [M + H - ^tBu]⁺, 288.1; found, 288.1

¹H NMR (400 MHz, CDCl₃) δ 7.48 (d, *J* = 7.8 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.33 (d, *J* = 7.4 Hz, 1H), 4.21 – 3.96 (m, 2H), 2.65 (dd, *J* = 23.8, 9.7 Hz, 4H), 1.76 – 1.68 (m, 1H), 1.62 (d, *J* = 12.5 Hz, 2H), 1.47 (s, 9H), 1.18 (qd, *J* = 12.5, 4.1 Hz, 2H).

¹⁹F NMR (376 MHz, CDCl₃) δ -62.55 (s).

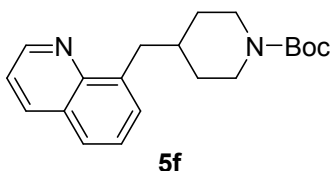


5e as 2.02 g colorless oil, yield: 98.4%.

[ES-MS] (ESI⁺): m/z calcd for C₁₇H₂₂F₃NO₂ [M + H - ^tBu]⁺, 274.1; found, 274.1

¹H NMR (400 MHz, CDCl₃) δ 6.80 – 6.70 (m, 2H), 4.11 (s, 2H), 2.65 (t, *J* = 12.3 Hz, 2H), 2.49 (d, *J* = 6.9 Hz, 2H), 1.64 (dd, *J* = 7.4, 3.8 Hz, 1H), 1.59 (d, *J* = 13.9 Hz, 2H), 1.46 (s, 9H), 1.13 (tt, *J* = 12.6, 6.1 Hz, 2H).

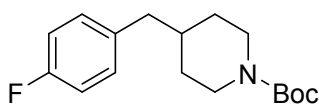
¹⁹F NMR (376 MHz, CDCl₃) δ -135.16 (d, *J* = 20.5 Hz), -164.33 (t, *J* = 20.5 Hz).



5f as 2.0 g yellow oil, yield: 85.84%.

[ES-MS] (ESI⁺): m/z calcd for C₂₀H₂₆N₂O₂ [M + H]⁺, 327.2; found, 327.2

¹H NMR (400 MHz, DMSO) δ 8.92 (d, *J* = 2.3 Hz, 1H), 8.31 (d, *J* = 7.9 Hz, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 6.1 Hz, 1H), 7.50 (dd, *J* = 7.8, 4.1 Hz, 2H), 3.88 (d, *J* = 9.6 Hz, 2H), 3.11 (d, *J* = 6.9 Hz, 2H), 2.56 (s, 2H), 1.92 (s, 1H), 1.50 (d, *J* = 12.4 Hz, 2H), 1.37 (s, 9H), 1.10 (dd, *J* = 21.0, 11.6 Hz, 2H).



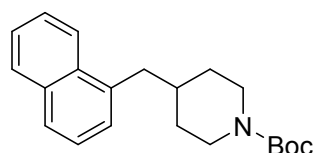
5g

5g as 1.37 g light yellow oil, yield: 90.7%.

[ES-MS] (ESI⁺): m/z calcd for C₁₇H₂₄FNO₂ [M + H - ^tBu]⁺, 238.1; found, 238.1

¹H NMR (400 MHz, CDCl₃) δ 7.10 (dd, *J* = 8.5, 5.6 Hz, 2H), 6.98 (t, *J* = 8.7 Hz, 2H), 4.14 (dd, *J* = 18.1, 10.9 Hz, 2H), 2.65 (t, *J* = 12.4 Hz, 2H), 2.52 (d, *J* = 6.8 Hz, 2H), 1.69 – 1.57 (m, 3H), 1.47 (s, 9H), 1.14 (tt, *J* = 12.8, 6.2 Hz, 2H).

¹⁹F NMR (376 MHz, CDCl₃) δ -117.55 (s).



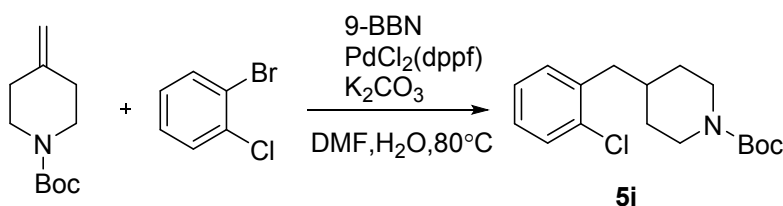
5h

5h as 572 mg colorless oil, yield: 80.0%.

[ES-MS] (ESI⁺): m/z calcd for C₂₁H₂₇NO₂ [M + H - ^tBu]⁺, 270.1; found, 270.2

¹H NMR (400 MHz, DMSO) δ 8.07 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.59 – 7.46 (m, 2H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 6.7 Hz, 1H), 3.91 (d, *J* = 9.1 Hz, 2H), 2.95 (d, *J* = 7.0 Hz, 2H), 2.64 (dd, *J* = 37.3, 14.8 Hz, 2H), 1.77 (ddd, *J* = 11.0, 7.3, 3.7 Hz, 1H), 1.55 (d, *J* = 12.0 Hz, 2H), 1.39 (s, 9H), 1.16 – 1.07 (m, 2H).

Example 4 (the preparation of **5i**):

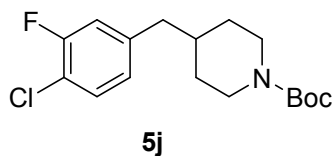


To a degassed sample of tert-butyl 4-methylenepiperidine-1-carboxylate (3g, 15.21 mmol, 1.00 eq.) was added 9-BBN (30 mL of a 0.5 M solution in THF, 15 mmol, 1.00 eq.). The resulting solution was refluxed for 3 h. After cooling to room temperature, the solution was added to a mixture of 1-bromo-2-chlorobenzene (2.77 g, 14.45 mmol, 0.95 eq.), Pd(dppf)Cl₂ (330mg, 0.45mmol, 3% eq.), DMF (30 mL), water (5 mL), and K₂CO₃ (2.5 g, 18.25 mmol, 1.20 eq.). The resulting mixture was heated at 60 °C overnight. After the mixture was cooled to room temperature and poured into water, the pH was adjusted to 11 with 10% aqueous NaOH and the mixture was extracted with ethyl acetate. The combined organic extracts were dried with brine and Na₂SO₄, filtrated, solvent was remove at reduce pressure, the crude product was purified by chromatography on silica gel (PE: EtOAc = 4:1) to provide **5i** as 4.00 g white solid, yield:84.9%.

[ES-MS] (ESI⁺): m/z calcd for C₁₇H₂₄ClNO₂ [M + H - ^tBu]⁺, 254.1; found, 254.1

¹H NMR (400 MHz, CDCl₃) δ 7.35 – 7.30 (m, 1H), 7.20 – 7.09 (m, 3H), 4.21 – 3.92 (m, 2H), 2.63 (dd, *J* = 16.6, 9.6 Hz, 4H), 1.76 (ttd, *J* = 11.0, 7.3, 3.7 Hz, 1H), 1.59 (d, *J* = 12.5 Hz, 2H), 1.45 (s, 9H), 1.27 – 1.12 (m, 2H).

The preparations of **5j-l** were the same as **5i**.

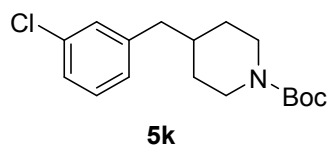


5j as 1.35 g colorless oil, yield: 41.1%.

[ES-MS] (ESI⁺): m/z calcd for C₁₇H₂₃ClFNO₂ [M + H - ^tBu]⁺, 272.1; found, 272.1

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.46 (t, *J* = 8.1 Hz, 1H), 7.24 (dd, *J* = 10.6, 2.0 Hz, 1H), 7.04 (dd, *J* = 8.3, 1.9 Hz, 1H), 3.91 (d, *J* = 13.1 Hz, 2H), 2.63 (s, 2H), 2.11 (t, *J* = 5.9 Hz, 2H), 1.67 (ddh, *J* = 11.1, 7.3, 3.7 Hz, 1H), 1.48 (dd, *J* = 7.9, 4.7 Hz, 2H), 1.38 (s, 9H), 1.01 (qd, *J* = 12.4, 4.2 Hz, 2H).

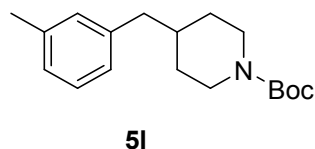
¹⁹F NMR (376 MHz, CDCl₃) δ -116.09 (s).



5k as 3.73g coreless oil, yield: 59.4%.

[ES-MS] (ESI⁺): m/z calcd for C₁₇H₂₄ClNO₂ [M + H - ^tBu]⁺, 254.1; found, 254.1

¹H NMR (400 MHz, DMSO) δ 7.35 – 7.27 (m, 1H), 7.24 (dd, *J* = 6.7, 1.0 Hz, 2H), 7.14 (d, *J* = 7.4 Hz, 1H), 3.91 (d, *J* = 11.8 Hz, 2H), 2.63 (s, 2H), 2.51 (d, *J* = 2.9 Hz, 2H), 1.73 – 1.62 (m, 1H), 1.51 (d, *J* = 13.7 Hz, 2H), 1.38 (s, 9H), 1.01 (qd, *J* = 12.5, 4.2 Hz, 2H).

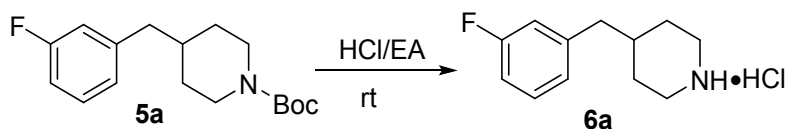


5l as 572 mg colorless oil, yield: 101.5%.

[ES-MS] (ESI⁺): m/z calcd for C₁₈H₂₇NO₂ [M + H - ^tBu]⁺, 234.1; found, 234.2

^1H NMR (400 MHz, Chloroform-*d*) δ 7.17 (t, $J = 7.5$ Hz, 1H), 7.01 (d, $J = 7.5$ Hz, 1H), 6.97 – 6.91 (m, 2H), 4.08 (s, 2H), 2.64 (t, $J = 12.8$ Hz, 2H), 2.50 (d, $J = 6.8$ Hz, 2H), 2.34 (s, 3H), 1.72 – 1.58 (m, 3H), 1.47 (s, 9H), 1.14 (qd, $J = 12.4, 4.3$ Hz, 2H).

Example 5 (the preparation of **6a**)



A solution of 20.00 g **5a** in L 3.2 N HCl/EA was stirred at rt overnight. The solvent was then removed at reduce pressure. The residue was washed with ethyl acetate and dried in vaccum to offer **6a** as 7.40 g white solid, yield 47.0%.

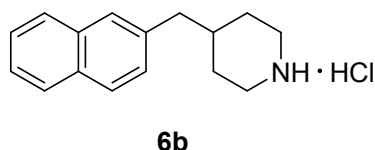
[ES-MS] (ESI⁺): m/z calcd for $\text{C}_{12}\text{H}_{16}\text{FN}$ $[\text{M} + \text{H}]^+$, 194.1; found, 194.1

^1H NMR (400 MHz, Methanol-*d*₄) δ 7.35 – 7.28 (m, 1H), 7.04 (d, $J = 7.6$ Hz, 1H), 6.96 (td, $J = 10.3, 4.9$ Hz, 2H), 3.39 (d, $J = 12.7$ Hz, 2H), 2.96 (td, $J = 12.9, 2.9$ Hz, 2H), 2.65 (d, $J = 7.1$ Hz, 2H), 1.96 (ddt, $J = 14.8, 7.4, 3.6$ Hz, 1H), 1.87 (d, $J = 14.5$ Hz, 2H), 1.55 – 1.41 (m, 2H).

NH proton was not observed in the spectrum.

^{19}F NMR (376 MHz, MeOD) δ -115.75 (s).

The preparations of **6b-I** were the same as **6a**.

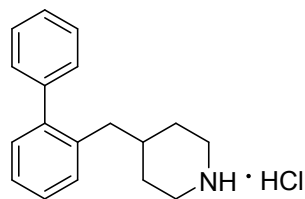


6b as 1.39 g white soil, yield: 85.5%.

[ES-MS] (ESI⁺): m/z calcd for $\text{C}_{16}\text{H}_{19}\text{N}$ $[\text{M} + \text{H}]^+$, 226.2; found, 226.2

^1H NMR (400 MHz, DMSO) δ 7.91 – 7.80 (m, 3H), 7.68 (s, 1H), 7.47 (dq, $J = 12.8, 6.5$ Hz, 2H), 7.40 – 7.33 (m, 1H), 3.20 (dt, $J = 12.9, 3.5$ Hz, 2H), 2.82 – 2.68 (m, 4H), 1.97 – 1.84 (m, 1H), 1.75 – 1.69 (m, 2H), 1.50 – 1.37 (m, 2H).

NH proton was not observed in the spectrum.



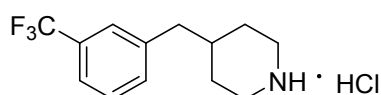
6c

6c as 1.55 g white soil, yield: 112.5%.

[ES-MS] (ESI⁺): m/z calcd for C₁₈H₂₁N [M + H]⁺, 252.2; found, 252.2

¹H NMR (400 MHz, DMSO) δ 7.45 (t, *J* = 7.2 Hz, 2H), 7.37 (dd, *J* = 11.7, 4.3 Hz, 1H), 7.35 – 7.25 (m, 5H), 7.17 (d, *J* = 7.7 Hz, 1H), 3.09 (d, *J* = 12.5 Hz, 2H), 2.65 (d, *J* = 10.4 Hz, 2H), 2.55 – 2.52 (m, 2H), 1.69 – 1.56 (m, 1H), 1.51 (d, *J* = 13.1 Hz, 2H), 1.18 – 1.05 (m, 2H).

NH proton was not observed in the spectrum.



6d

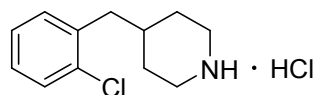
6d as 1.76 g white solid, yield: 91.2%.

[ES-MS] (ESI⁺): m/z calcd for C₁₃H₁₆F₃N [M + H]⁺, 244.1; found, 244.1

¹H NMR (400 MHz, DMSO) δ 7.61 – 7.46 (m, 4H), 3.20 (d, *J* = 12.4 Hz, 2H), 2.77 (dd, *J* = 22.4, 11.3 Hz, 2H), 2.64 (d, *J* = 7.1 Hz, 2H), 1.84 (ddd, *J* = 11.0, 7.4, 3.6 Hz, 1H), 1.67 (d, *J* = 13.1 Hz, 2H), 1.49 – 1.33 (m, 2H).

NH proton was not observed in the spectrum.

¹⁹F NMR (376 MHz, MeOD) δ -64.03 (s).



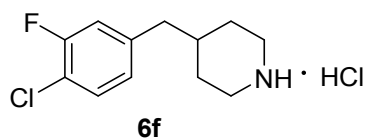
6e

6e as 2.0 g white solid, yield: 62.9%.

[ES-MS] (ESI⁺): m/z calcd for C₁₂H₁₆ClN [M + H]⁺, 210.1; found, 210.1

^1H NMR (400 MHz, DMSO) δ 7.42 (dd, $J = 7.5, 1.7$ Hz, 1H), 7.29 (dtd, $J = 17.3, 7.4, 2.2$ Hz, 3H), 3.21 (dt, $J = 12.8, 3.3$ Hz, 2H), 2.78 (td, $J = 12.8, 3.1$ Hz, 2H), 2.66 (d, $J = 7.1$ Hz, 2H), 1.86 (dq, $J = 11.2, 7.4, 3.6$ Hz, 1H), 1.68 (dd, $J = 14.1, 3.4$ Hz, 2H), 1.45 (qd, $J = 12.5, 4.0$ Hz, 2H).

NH proton was not observed in the spectrum.



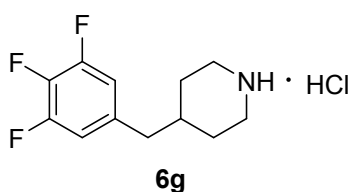
6f as 1.01 g white solid, yield: 92.8%.

[ES-MS] (ESI^+): m/z calcd for $\text{C}_{12}\text{H}_{15}\text{ClFN}$ $[\text{M} + \text{H}]^+$, 228.1; found, 228.1

^1H NMR (400 MHz, Methanol- d_4) δ 7.41 (t, $J = 8.0$ Hz, 1H), 7.14 (dd, $J = 10.3, 2.0$ Hz, 1H), 7.07 – 7.01 (m, 1H), 3.43 – 3.35 (m, 2H), 2.96 (td, $J = 13.0, 3.0$ Hz, 2H), 2.65 (d, $J = 7.0$ Hz, 2H), 1.95 (dp, $J = 10.8, 3.5$ Hz, 1H), 1.91 – 1.84 (m, 2H), 1.44 (tdd, $J = 14.4, 11.3, 4.1$ Hz, 2H).

NH proton was not observed in the spectrum.

^{19}F NMR (376 MHz, MeOD) δ -118.19 (s).



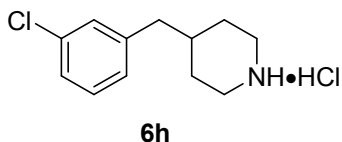
6g as 1.63 g white solid, yield: 99%.

[ES-MS] (ESI^+): m/z calcd for $\text{C}_{12}\text{H}_{14}\text{F}_3\text{N}$ $[\text{M} + \text{H}]^+$, 230.1; found, 230.1

^1H NMR (400 MHz, DMSO) δ 7.21 (dd, $J = 8.9, 6.9$ Hz, 2H), 3.20 (d, $J = 12.6$ Hz, 2H), 2.82 – 2.70 (m, 2H), 2.54 (d, $J = 7.2$ Hz, 2H), 1.81 (ddt, $J = 11.1, 7.2, 3.6$ Hz, 1H), 1.66 (d, $J = 13.1$ Hz, 2H), 1.43 – 1.30 (m, 2H).

NH proton was not observed in the spectrum.

^{19}F NMR (376 MHz, MeOD) δ -137.81 (d, $J = 19.9$ Hz), -167.53 (t, $J = 19.8$ Hz).

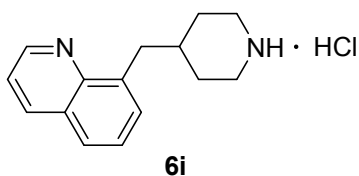


6h as 2.0 g white solid, yield: 84%.

[ES-MS] (ESI⁺): m/z calcd for C₁₂H₁₆ClN [M + H]⁺, 210.1; found, 210.1

¹H NMR (400 MHz, DMSO) δ 7.32 (t, *J* = 7.6 Hz, 1H), 7.26 (d, *J* = 9.0 Hz, 2H), 7.16 (d, *J* = 7.4 Hz, 1H), 3.19 (d, *J* = 12.6 Hz, 2H), 2.81 – 2.69 (m, 2H), 2.54 (d, *J* = 7.1 Hz, 2H), 1.80 (ddd, *J* = 11.1, 7.5, 3.6 Hz, 1H), 1.66 (d, *J* = 12.8 Hz, 2H), 1.46 – 1.32 (m, 2H).

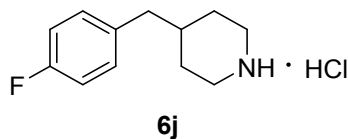
NH proton was not observed in the spectrum.



6i as 2.3 g light yellow solid, yield: 113.67%.

[ES-MS] (ESI⁺): m/z calcd for C₁₅H₁₈N₂ [M + H]⁺, 227.1; found, 227.2

¹H NMR (400 MHz, DMSO) δ 8.55 – 8.43 (m, 2H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.38 (dd, *J* = 8.3, 5.5 Hz, 1H), 7.31 (d, *J* = 7.1 Hz, 1H), 7.17 (t, *J* = 7.7 Hz, 1H), 2.61 (d, *J* = 12.8 Hz, 2H), 2.56 (d, *J* = 7.5 Hz, 2H), 2.16 (t, *J* = 12.1 Hz, 2H), 1.35 (dtd, *J* = 11.3, 7.6, 3.8 Hz, 1H), 1.14 (d, *J* = 13.8 Hz, 2H), 0.95 – 0.80 (m, 2H). NH proton was not observed in the spectrum.

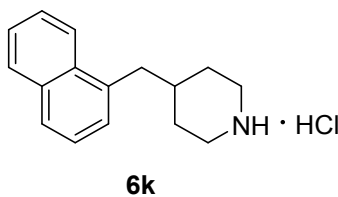


6j as 1.07 g white solid, yield: 99%.

[ES-MS] (ESI⁺): m/z calcd for C₁₂H₁₆FN [M + H]⁺, 194.1; found, 194.1

¹H NMR (400 MHz, DMSO) δ 7.22 (dd, *J* = 8.4, 5.8 Hz, 2H), 7.11 (t, *J* = 8.9 Hz, 2H), 3.21 (d, *J* = 12.6 Hz, 2H), 2.78 (d, *J* = 10.8 Hz, 2H), 2.50 (d, *J* = 1.6 Hz, 2H), 1.77 (ddd, *J* = 11.0, 7.4, 3.6 Hz, 1H), 1.68 (d, *J* = 13.5 Hz, 2H), 1.33 (td, *J* = 14.5, 3.8 Hz, 2H). NH proton was not observed in the spectrum.

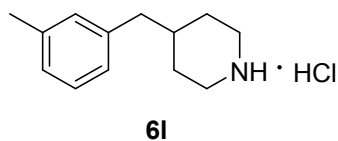
¹⁹F NMR (376 MHz, MeOD) δ -119.27 (s).



6k as 373 mg white oil, yield: 81.1%.

[ES-MS] (ESI⁺): m/z calcd for C₁₆H₁₉N [M + H]⁺, 226.2; found, 226.2

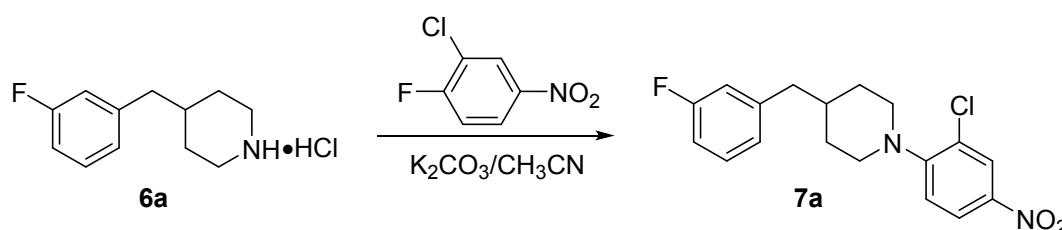
¹H NMR (400 MHz, DMSO) δ 8.09 (d, *J* = 8.2 Hz, 1H), 7.93 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.60 – 7.50 (m, 2H), 7.44 (dd, *J* = 8.2, 6.9 Hz, 1H), 7.35 (dd, *J* = 7.1, 1.3 Hz, 1H), 3.20 (d, *J* = 12.7 Hz, 2H), 3.00 (d, *J* = 7.0 Hz, 2H), 2.82 – 2.68 (m, 2H), 1.92 (ddt, *J* = 14.6, 10.9, 5.5 Hz, 1H), 1.74 (d, *J* = 13.8 Hz, 2H), 1.56 – 1.42 (m, 2H). NH proton was not observed in the spectrum.



[ES-MS] (ESI⁺): m/z calcd for C₁₃H₁₉N [M + H]⁺, 190.2; found, 190.2

^1H NMR (400 MHz, DMSO) δ 7.17 (t, J = 7.5 Hz, 1H), 7.02 – 6.93 (m, 3H), 3.19 (dt, J = 12.7, 3.3 Hz, 2H), 2.76 (td, J = 12.8, 3.0 Hz, 2H), 2.47 (d, J = 7.0 Hz, 2H), 2.27 (s, 3H), 1.77 (ddp, J = 11.2, 7.4, 3.6 Hz, 1H), 1.67 (dd, J = 13.9, 3.3 Hz, 2H), 1.37 (qd, J = 13.3, 4.0 Hz, 2H). NH proton was not observed in the spectrum.

Example 6 (the preparation of **7a**)



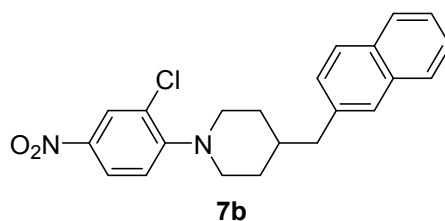
A solution of 74g **6a** in 500mL CH_3CN was stirred at r.t. for 10min. Then 133g K_2CO_3 and 56g 2-chloro-1-fluoro-4-nitrobenzene were added to the solution and it was stirred at 80°C under N_2 overnight. The reaction mixture was then filtered and the solvent was removed under reduced pressure. The crude product (yellow oil) was taken to the next step without further purification.

[ES-MS] (ESI^+): m/z calcd for $\text{C}_{18}\text{H}_{18}\text{ClFN}_2\text{O}_2$ [$\text{M} + \text{H}$] $^+$, 349.1; found, 349.1

^1H NMR (400 MHz, DMSO) δ 8.15 (d, J = 2.6 Hz, 1H), 8.09 (dd, J = 9.0, 2.6 Hz, 1H), 7.32 (dd, J = 14.4, 7.4 Hz, 1H), 7.20 (d, J = 9.0 Hz, 1H), 7.01 (dd, J = 16.1, 8.0 Hz, 3H), 3.49 (d, J = 12.1 Hz, 2H), 2.72 (t, J = 11.5 Hz, 2H), 2.58 (d, J = 7.0 Hz, 2H), 1.78 – 1.70 (m, 1H), 1.67 (d, J = 12.7 Hz, 2H), 1.42 – 1.29 (m, 2H).

^{19}F NMR (376 MHz, CDCl_3) δ -113.74 (s).

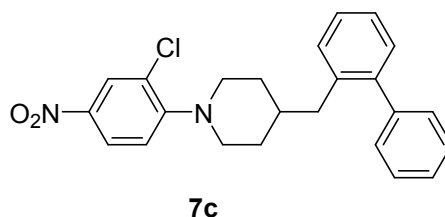
The preparations of **7b-7l** were the same as **7a**.



The crude product was purified by chromatography on silica gel (PE : EA = 20 : 1) to get **7b** as 1.05 g yellow oil, yield: 32.9%.

[ES-MS] (ESI⁺): *m/z* calcd for C₂₂H₂₁ClN₂O₂ [M + H]⁺, 381.1; found, 381.1

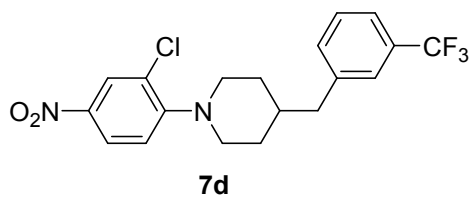
¹H NMR (400 MHz, DMSO) δ 8.18 (d, *J* = 2.7 Hz, 1H), 8.11 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.86 (t, *J* = 8.4 Hz, 3H), 7.70 (s, 1H), 7.52 – 7.42 (m, 2H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.22 (d, *J* = 9.1 Hz, 1H), 3.49 (dd, *J* = 14.0, 8.5 Hz, 2H), 2.79 – 2.67 (m, 4H), 1.83 (ddd, *J* = 11.1, 7.4, 3.8 Hz, 1H), 1.72 (d, *J* = 12.6 Hz, 2H), 1.48 – 1.35 (m, 2H).



The crude product was purified by chromatography on silica gel (PE : EA = 10 : 1) to get **7c** as 1.45 g yellow solid, yield: 57.8%.

[ES-MS] (ESI⁺): *m/z* calcd for C₂₄H₂₃ClN₂O₂ [M + H]⁺, 407.1; found, 407.2

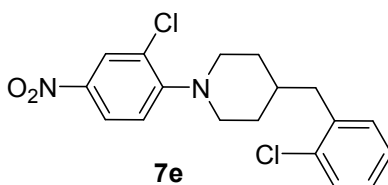
¹H NMR (400 MHz, CDCl₃) δ 8.22 (d, *J* = 2.6 Hz, 1H), 8.06 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.48 – 7.27 (m, 9H), 6.96 (d, *J* = 9.0 Hz, 1H), 3.47 (d, *J* = 12.1 Hz, 2H), 2.71 – 2.57 (m, 4H), 1.62 (d, *J* = 10.6 Hz, 2H), 1.54 (ddd, *J* = 14.4, 7.1, 3.5 Hz, 1H), 1.32 (dd, *J* = 11.6, 2.7 Hz, 2H).



The crude product was used in the next step without further purification.(yellow solid)
 [ES-MS] (ESI⁺): m/z calcd for C₁₉H₁₈ClF₃N₂O₂ [M + H]⁺, 399.1; found, 399.1

¹H NMR (400 MHz, DMSO) δ 8.19 (d, *J* = 2.7 Hz, 1H), 8.12 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 4H), 7.23 (d, *J* = 9.1 Hz, 1H), 3.51 (d, *J* = 12.1 Hz, 2H), 2.80 – 2.66 (m, 4H), 1.77 (ddd, *J* = 11.1, 7.4, 4.0 Hz, 1H), 1.68 (d, *J* = 12.9 Hz, 2H), 1.38 (d, *J* = 5.1 Hz, 2H).

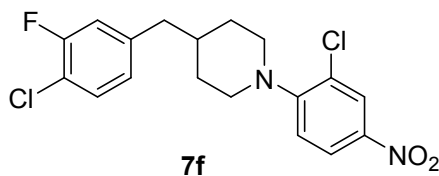
¹⁹F NMR (376 MHz, CDCl₃) δ -62.52 (s).



The crude product was purified by flash chromatography on silica gel(PE: EA = 8:1) to provide **7e** as 0.5 g yellow oil, yield: 33.7%.

[ES-MS] (ESI⁺): m/z calcd for C₁₈H₁₈Cl₂N₂O₂ [M + H]⁺, 365.1; found, 365.1

¹H NMR (400 MHz, CDCl₃) δ 8.25 (d, *J* = 2.6 Hz, 1H), 8.08 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.39 (d, *J* = 7.1 Hz, 1H), 7.19 (ddd, *J* = 9.2, 7.4, 4.1 Hz, 3H), 7.02 (d, *J* = 9.0 Hz, 1H), 3.60 (d, *J* = 12.2 Hz, 2H), 2.81 – 2.69 (m, 4H), 1.89 (tdd, *J* = 15.4, 7.7, 4.0 Hz, 1H), 1.81 (d, *J* = 13.2 Hz, 2H), 1.65 – 1.60 (m, 1H), 1.55 (dd, *J* = 12.4, 3.5 Hz, 1H).

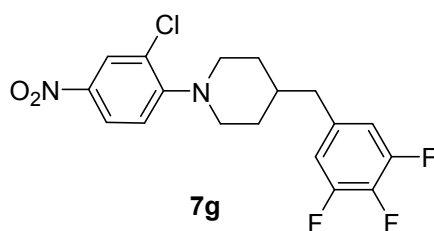


The crude product was purified by column chromatography (PE:EA=20:1) to provide **7f** as 1.0 g yellow oil, yield: 76.6%..

[ES-MS] (ESI⁺): m/z calcd for C₁₈H₁₇Cl₂FN₂O₂ [M + H]⁺, 383.1; found, 383.1

^1H NMR (400 MHz, CDCl_3) δ 8.24 (d, $J = 2.7$ Hz, 1H), 8.08 (dd, $J = 9.0, 2.7$ Hz, 1H), 7.31 (dd, $J = 15.6, 7.8$ Hz, 1H), 7.04 – 6.96 (m, 2H), 6.92 (dd, $J = 8.3, 2.0$ Hz, 1H), 3.59 (dp, $J = 11.7, 2.0$ Hz, 2H), 2.74 (td, $J = 12.0, 2.2$ Hz, 2H), 2.61 (d, $J = 6.8$ Hz, 2H), 1.93 – 1.86 (m, 1H), 1.78 (dt, $J = 12.8, 2.6$ Hz, 2H), 1.51 (ddd, $J = 12.7, 4.1, 2.2$ Hz, 2H).

^{19}F NMR (376 MHz, CDCl_3) δ -115.95 (s).

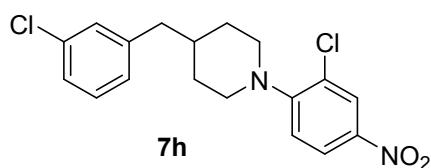


The solvent was removed under vacuum to get **7g** as 1.63 g white solid, yield: 100%.
The crude product was used in the next step without further purification.

[ES-MS] (ESI^+): m/z calcd for $\text{C}_{18}\text{H}_{16}\text{ClF}_3\text{N}_2\text{O}_2$ $[\text{M} + \text{H}]^+$, 385.1; found, 385.1

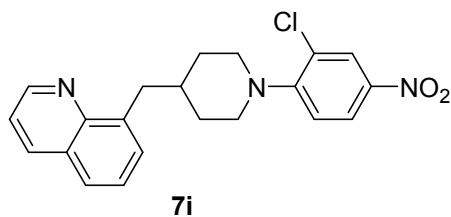
^1H NMR (400 MHz, DMSO) δ 8.19 (d, $J = 2.7$ Hz, 1H), 8.12 (dd, $J = 9.0, 2.7$ Hz, 1H), 7.26 – 7.16 (m, 3H), 3.51 (d, $J = 12.2$ Hz, 2H), 2.74 (t, $J = 11.3$ Hz, 2H), 2.58 (d, $J = 7.1$ Hz, 2H), 1.75 (ddd, $J = 14.7, 7.4, 3.7$ Hz, 1H), 1.67 (d, $J = 13.1$ Hz, 2H), 1.36 (qd, $J = 12.5, 3.5$ Hz, 2H).

^{19}F NMR (376 MHz, CDCl_3) δ -134.99 (d, $J = 20.5$ Hz), -164.12 (t, $J = 20.5$ Hz).



The crude product was purified by flash chromatography on silica gel (PE: EA = 8:1) to provide 2.2 g yellow oil, yield: 74%.

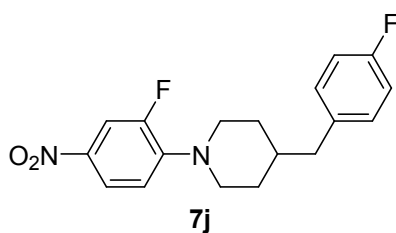
^1H NMR (400 MHz, DMSO) δ 8.15 (d, $J = 2.7$ Hz, 1H), 8.09 (dd, $J = 9.0, 2.7$ Hz, 1H), 7.31 (t, $J = 7.7$ Hz, 1H), 7.27 – 7.22 (m, 2H), 7.20 (d, $J = 9.0$ Hz, 1H), 7.16 (d, $J = 7.5$ Hz, 1H), 3.48 (d, $J = 12.1$ Hz, 2H), 2.71 (t, $J = 11.4$ Hz, 2H), 2.57 (d, $J = 6.9$ Hz, 2H), 1.78 – 1.69 (m, 1H), 1.66 (d, $J = 13.4$ Hz, 2H), 1.34 (tt, $J = 12.5, 6.4$ Hz, 2H).



The crude product **7i** was collected as 2.95 g brown oil, yield: 87.8%, It was used in the next step without further purification

[ES-MS] (ESI⁺): m/z calcd for C₂₁H₂₀ClN₃O₂ [M + H]⁺, 382.1; found, 382.1

¹H NMR (400 MHz, DMSO) δ 8.95 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.33 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.16 (d, *J* = 2.6 Hz, 1H), 8.08 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.83 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.60 (d, *J* = 6.1 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.17 (d, *J* = 9.1 Hz, 1H), 3.47 (d, *J* = 12.1 Hz, 2H), 3.20 (d, *J* = 7.1 Hz, 2H), 2.68 (t, *J* = 11.3 Hz, 2H), 2.02 – 1.95 (m, 1H), 1.66 (d, *J* = 11.4 Hz, 2H), 1.52 – 1.38 (m, 2H).

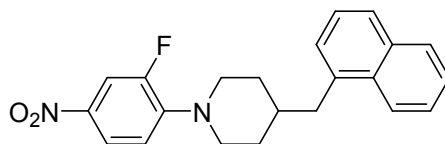


The crude product **7j** was collected as 1.54 g yellow soil, yield: 99.5%.

[ES-MS] (ESI⁺): m/z calcd for C₁₈H₁₈F₂N₂O₂ [M + H]⁺, 333.1; found, 333.1

¹H NMR (400 MHz, DMSO) δ 7.91 (dd, *J* = 9.0, 2.3 Hz, 1H), 7.86 (dd, *J* = 13.7, 2.5 Hz, 1H), 7.17 (dd, *J* = 8.3, 5.8 Hz, 2H), 7.05 (td, *J* = 9.1, 2.5 Hz, 3H), 3.61 (d, *J* = 12.5 Hz, 2H), 2.79 (t, *J* = 11.8 Hz, 2H), 2.49 (d, *J* = 7.0 Hz, 2H), 1.77 – 1.65 (m, 1H), 1.62 (d, *J* = 13.0 Hz, 2H), 1.33 – 1.19 (m, 2H).

¹⁹F NMR (376 MHz, CDCl₃) δ -117.31 (s), -118.88 (s).



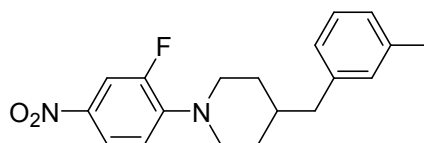
7k

The crude product **7k** was collected as 2.86 g yellow oil, yield: 85.5%.

[ES-MS] (ESI⁺): *m/z* calcd for C₂₂H₂₁FN₂O₂ [M + H]⁺, 365.2; found, 365.2

¹H NMR (400 MHz, DMSO) δ 8.11 (d, *J* = 8.2 Hz, 1H), 7.95 (ddd, *J* = 16.2, 7.9, 5.4 Hz, 3H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.59 – 7.48 (m, 2H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 6.8 Hz, 1H), 7.09 (t, *J* = 9.2 Hz, 1H), 3.65 (d, *J* = 12.7 Hz, 2H), 3.01 (d, *J* = 7.1 Hz, 2H), 2.80 (t, *J* = 11.7 Hz, 2H), 1.88 (ddd, *J* = 11.0, 7.3, 3.8 Hz, 1H), 1.70 (d, *J* = 12.5 Hz, 2H), 1.43 (qd, *J* = 12.8, 3.5 Hz, 2H).

¹⁹F NMR (376 MHz, CDCl₃) δ -118.87 (s).



7l

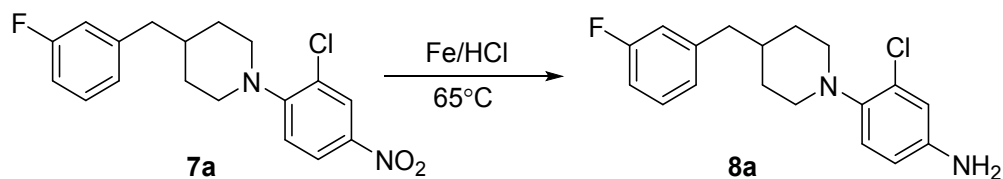
The crude product **7l** was collected as 645 mg yellow oil, yield: 124.2%.

[ES-MS] (ESI⁺): *m/z* calcd for C₁₉H₂₁FN₂O₂ [M + H]⁺, 329.2; found, 329.2

¹H NMR (400 MHz, CDCl₃) δ 7.97 (dd, *J* = 9.0, 1.9 Hz, 1H), 7.89 (dd, *J* = 13.3, 2.6 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 12.0 Hz, 2H), 6.90 (t, *J* = 8.9 Hz, 1H), 3.73 (d, *J* = 12.5 Hz, 2H), 2.86 (t, *J* = 11.9 Hz, 2H), 2.60 (d, *J* = 6.7 Hz, 2H), 2.38 (s, 3H), 1.86 – 1.73 (m, 3H), 1.54 – 1.41 (m, 2H).

¹⁹F NMR (376 MHz, CDCl₃) δ -118.87 (s).

Example 7 (the preparation of **8a**)



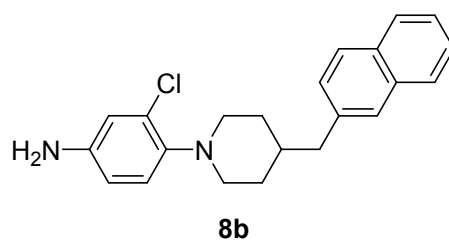
Iron (80.16g, 1.44 mol) in water (200mL) was stirred at 65°C before HCl solution (6mL) was added. After 15min, a solution of **7a** (83.5g, 239.20mmol) in methanol (500mL) and THF (1.0 L) was added to the mixture and it was heated to 65°C overnight. After the reaction was completed, the solution was filtrated and the solvent was remove under reduce pressure. The crude product was taken to the next step without further purification.(gray solid)

[ES-MS] (ESI⁺): m/z calcd for C₁₈H₂₀ClFN₂ [M + H]⁺, 319.1; found, 319.1

¹H NMR (400 MHz, DMSO) δ 7.31 (td, *J* = 7.7, 6.1 Hz, 1H), 7.06 – 6.96 (m, 3H), 6.84 (d, *J* = 8.6 Hz, 1H), 6.63 (d, *J* = 2.6 Hz, 1H), 6.47 (dd, *J* = 8.5, 2.6 Hz, 1H), 4.98 (s, 2H), 3.01 (dt, *J* = 12.0, 3.3 Hz, 2H), 2.57 (d, *J* = 6.5 Hz, 2H), 2.45 (td, *J* = 11.7, 2.1 Hz, 2H), 1.59 (d, *J* = 10.4 Hz, 3H), 1.33 (qd, *J* = 12.3, 3.2 Hz, 2H).

¹⁹F NMR (376 MHz, CDCl₃) δ -114.04 (s).

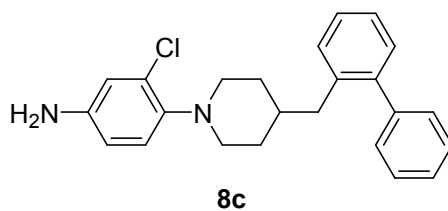
The preparations of **8b-I** were the same as **8a**.



8b (909 mg) was collected as light yellow oil. Yield: 94.0%.

[ES-MS] (ESI⁺): m/z calcd for C₂₂H₂₃ClN₂ [M + H]⁺, 351.2; found, 351.2

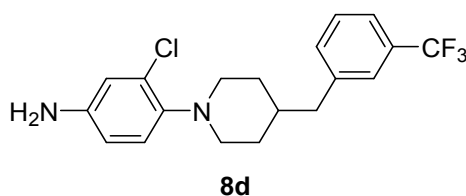
¹H NMR (400 MHz, DMSO) δ 7.85 (dd, *J* = 13.1, 5.7 Hz, 3H), 7.69 (s, 1H), 7.52 – 7.42 (m, 2H), 7.39 (d, *J* = 8.4 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 1H), 6.62 (d, *J* = 2.4 Hz, 1H), 6.46 (dd, *J* = 8.5, 2.4 Hz, 1H), 4.98 (s, 2H), 3.02 (d, *J* = 11.2 Hz, 2H), 2.73 (d, *J* = 6.6 Hz, 2H), 2.46 (t, *J* = 11.7 Hz, 2H), 1.75 – 1.59 (m, 3H), 1.38 (q, *J* = 11.1 Hz, 2H).



8c (1.25 g) was collected as light yellow oil. Yield: 93.1%.

[ES-MS] (ESI⁺): m/z calcd for C₂₄H₂₅ClN₂ [M + H]⁺, 377.2; found, 377.2

¹H NMR (400 MHz, DMSO) δ 7.45 (t, *J* = 7.3 Hz, 2H), 7.37 (t, *J* = 7.3 Hz, 1H), 7.34 – 7.22 (m, 5H), 7.16 (d, *J* = 7.2 Hz, 1H), 6.77 (d, *J* = 8.6 Hz, 1H), 6.59 (d, *J* = 2.5 Hz, 1H), 6.43 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.97 (s, 2H), 2.88 (d, *J* = 11.3 Hz, 2H), 2.58 (d, *J* = 6.6 Hz, 2H), 2.30 (t, *J* = 10.9 Hz, 2H), 1.47 – 1.31 (m, 3H), 1.15 – 1.03 (m, 2H).

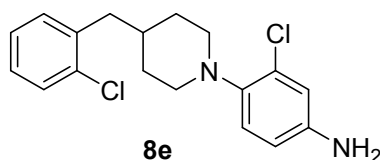


The crude product was purified by chromatography on silica gel (PE: EA = 4:1) to provide **8d** (4.0 g) as a light yellow solid. Yield: 94.6%.

[ES-MS] (ESI⁺): m/z calcd for C₁₉H₂₀ClF₃N₂ [M + H]⁺, 369.1; found, 369.1

¹H NMR (400 MHz, DMSO) δ 7.59 – 7.49 (m, 4H), 6.84 (d, *J* = 8.6 Hz, 1H), 6.62 (d, *J* = 2.5 Hz, 1H), 6.46 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.98 (s, 2H), 3.01 (d, *J* = 11.3 Hz, 2H), 2.66 (d, *J* = 6.6 Hz, 2H), 2.45 (t, *J* = 11.0 Hz, 2H), 1.59 (d, *J* = 10.0 Hz, 3H), 1.35 (q, *J* = 12.0 Hz, 2H).

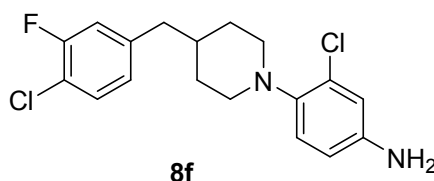
¹⁹F NMR (376 MHz, CDCl₃) δ -62.47 (s).



The crude product was purified by chromatography on silica gel (PE: EA = 4:1) to provide **8e** as 373 mg light yellow oil, Yield: 60.0%

[ES-MS] (ESI⁺): m/z calcd for C₁₈H₂₀Cl₂N₂ [M + H]⁺, 335.1; found, 335.1

^1H NMR (400 MHz, CDCl_3) δ 7.40 – 7.35 (m, 1H), 7.24 – 7.14 (m, 3H), 6.88 (d, J = 8.5 Hz, 1H), 6.76 (d, J = 2.6 Hz, 1H), 6.55 (dd, J = 8.5, 2.7 Hz, 1H), 3.52 (s, 2H), 3.23 (d, J = 11.7 Hz, 2H), 2.76 (d, J = 6.8 Hz, 2H), 2.58 – 2.48 (m, 2H), 1.83 – 1.69 (m, 3H), 1.58 (qd, J = 12.1, 3.5 Hz, 2H).

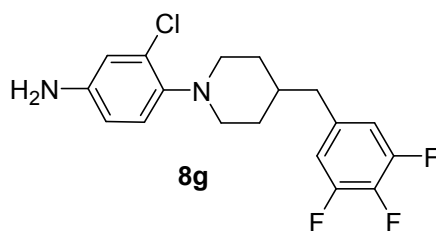


The crude product was purified by chromatography on silica gel (PE: EA = 20:1-4:1) to provide **8f** (820.0 mg) as a yellow solid. Yield: 89.0%

[ES-MS] (ESI^+): m/z calcd for $\text{C}_{18}\text{H}_{19}\text{Cl}_2\text{FN}_2$ [$\text{M} + \text{H}$] $^+$, 353.1; found, 353.1

^1H NMR (400 MHz, CDCl_3) δ 7.30 (dd, J = 12.5, 4.6 Hz, 1H), 6.98 (dd, J = 10.1, 1.8 Hz, 1H), 6.91 (dd, J = 8.1, 1.3 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 6.76 (d, J = 2.7 Hz, 1H), 6.56 (dd, J = 8.5, 2.7 Hz, 1H), 3.53 (s, 2H), 3.23 (d, J = 11.8 Hz, 2H), 2.59 (d, J = 6.9 Hz, 2H), 2.53 (dd, J = 16.6, 6.7 Hz, 2H), 1.90 (ddd, J = 9.0, 7.6, 4.8 Hz, 1H), 1.70 (d, J = 12.7 Hz, 2H), 1.54 – 1.46 (m, 2H).

^{19}F NMR (376 MHz, CDCl_3) δ -116.16 (d, J = 79.9 Hz).



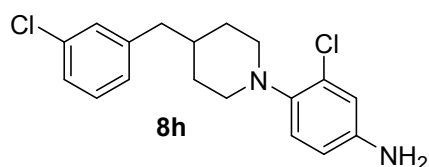
8g (2.03 g) was collected as yellow oil. Yield: 99.2%.

[ES-MS] (ESI^+): m/z calcd for $\text{C}_{18}\text{H}_{18}\text{ClF}_3\text{N}_2$ [$\text{M} + \text{H}$] $^+$, 355.1; found, 355.1

^1H NMR (400 MHz, DMSO) δ 7.16 (dd, J = 8.7, 7.0 Hz, 2H), 6.83 (d, J = 8.6 Hz, 1H), 6.62 (d, J = 2.4 Hz, 1H), 6.47 (dd, J = 8.5, 2.5 Hz, 1H), 4.98 (s, 2H), 3.01 (d, J =

11.2 Hz, 2H), 2.54 (d, J = 6.6 Hz, 2H), 2.44 (t, J = 11.0 Hz, 2H), 1.57 (d, J = 9.5 Hz, 3H), 1.32 (q, J = 11.9 Hz, 2H).

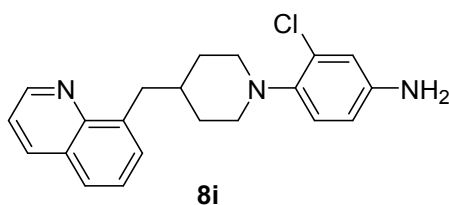
^{19}F NMR (376 MHz, CDCl_3) δ -135.38 (d, J = 20.5 Hz), -164.64 (t, J = 20.5 Hz).



The crude product was purified by chromatography on silica gel (PE: EA = 4:1) to provide **8h** (1.9 g) as yellow oil. Yield: 94.0%.

[ES-MS] (ESI^+): m/z calcd for $\text{C}_{18}\text{H}_{20}\text{Cl}_2\text{N}_2$ $[\text{M} + \text{H}]^+$, 335.1; found, 335.1

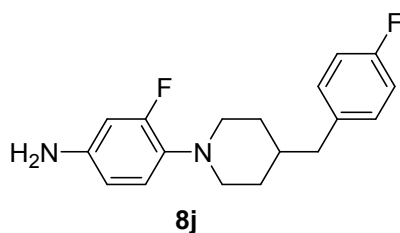
^1H NMR (400 MHz, DMSO) δ 7.31 (t, J = 7.7 Hz, 1H), 7.28 – 7.22 (m, 2H), 7.16 (d, J = 7.4 Hz, 1H), 6.84 (d, J = 8.6 Hz, 1H), 6.63 (d, J = 2.5 Hz, 1H), 6.47 (dd, J = 8.5, 2.5 Hz, 1H), 4.98 (s, 2H), 3.01 (d, J = 11.3 Hz, 2H), 2.56 (d, J = 6.4 Hz, 2H), 2.44 (t, J = 11.0 Hz, 2H), 1.59 (d, J = 10.2 Hz, 3H), 1.39 – 1.27 (m, 2H).



The crude product was purified by chromatography (PE: EA = 4:1) to provide **8i** (0.6 g) as a white solid. Yield: 21.9%.

[ES-MS] (ESI^+): m/z calcd for $\text{C}_{21}\text{H}_{22}\text{ClN}_3$ $[\text{M} + \text{H}]^+$, 352.2; found, 352.1

^1H NMR (400 MHz, DMSO) δ 8.95 (dd, J = 4.1, 1.7 Hz, 1H), 8.34 (dd, J = 8.3, 1.6 Hz, 1H), 7.83 (dd, J = 8.0, 1.0 Hz, 1H), 7.60 (d, J = 6.1 Hz, 1H), 7.56 – 7.47 (m, 2H), 6.81 (d, J = 8.6 Hz, 1H), 6.62 (d, J = 2.5 Hz, 1H), 6.45 (dd, J = 8.5, 2.5 Hz, 1H), 4.96 (d, J = 8.3 Hz, 2H), 3.19 (d, J = 7.1 Hz, 2H), 2.99 (d, J = 11.4 Hz, 2H), 2.40 (t, J = 10.7 Hz, 2H), 1.86 (ddd, J = 11.1, 7.3, 3.9 Hz, 1H), 1.59 (d, J = 11.0 Hz, 2H), 1.43 (qd, J = 12.3, 3.3 Hz, 2H).

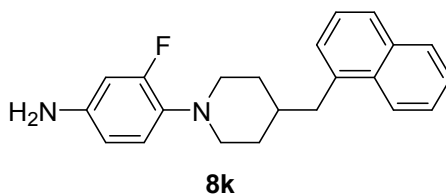


The crude product was purified by chromatography on silica gel (PE: EA = 5: 1) to get **8j** (945.0 mg) as white oil. Yield: 67.5%.

[ES-MS] (ESI⁺): m/z calcd for C₁₈H₂₀F₂N₂ [M + H]⁺, 303.2; found, 303.2

¹H NMR (400 MHz, DMSO) δ 7.21 (dd, *J* = 8.4, 5.8 Hz, 2H), 7.09 (t, *J* = 8.8 Hz, 2H), 6.78 – 6.68 (m, 1H), 6.30 (ddd, *J* = 11.4, 10.8, 2.3 Hz, 2H), 4.93 (s, 2H), 3.05 (d, *J* = 11.4 Hz, 2H), 2.53 (d, *J* = 6.7 Hz, 2H), 2.46 (t, *J* = 11.1 Hz, 2H), 1.58 (d, *J* = 12.6 Hz, 2H), 1.55 – 1.47 (m, 1H), 1.36 – 1.25 (m, 2H).

¹⁹F NMR (376 MHz, CDCl₃) δ -117.77 (s), -122.51 (s).

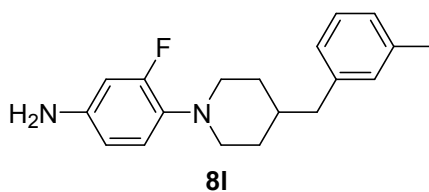


The crude product was purified by chromatography on silica gel (PE: EA = 5: 1) to get **8k** (309.0 mg) as white oil. Yield: 52.2%.

[ES-MS] (ESI⁺): m/z calcd for C₂₂H₂₃FN₂ [M + H]⁺, 335.2; found, 335.2

¹H NMR (400 MHz, DMSO) δ 8.11 (d, *J* = 8.3 Hz, 1H), 7.92 (d, *J* = 7.4 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.60 – 7.48 (m, 2H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 6.5 Hz, 1H), 6.75 – 6.66 (m, 1H), 6.32 (dd, *J* = 14.4, 2.3 Hz, 1H), 6.27 (dd, *J* = 8.5, 2.2 Hz, 1H), 4.91 (d, *J* = 8.4 Hz, 2H), 3.04 (t, *J* = 11.2 Hz, 4H), 2.42 (t, *J* = 11.0 Hz, 2H), 1.79 – 1.59 (m, 3H), 1.53 – 1.38 (m, 2H).

¹⁹F NMR (376 MHz, CDCl₃) δ -122.49 (s).



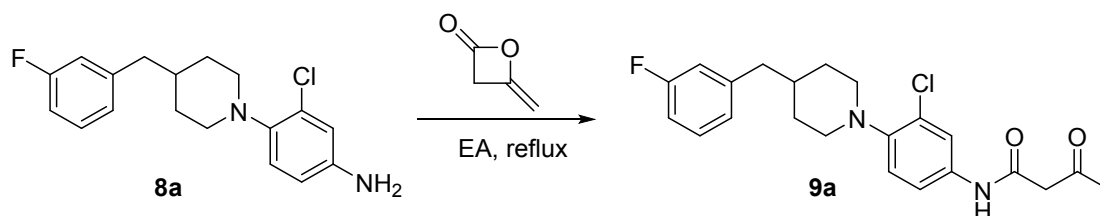
The crude product was purified by chromatography on silica gel (PE: EA = 8: 1) to get 309 mg white oil. Yield: 52.2%.

[ES-MS] (ESI⁺): m/z calcd for C₁₉H₂₃FN₂ [M + H]⁺, 299.2; found, 299.2

¹H NMR (400 MHz, CDCl₃) δ 7.07 (dd, *J* = 14.2, 10.2 Hz, 2H), 6.87 (dd, *J* = 18.5, 9.7 Hz, 1H), 6.47 – 6.39 (m, 2H), 3.55 (s, 2H), 3.32 (d, *J* = 11.5 Hz, 2H), 2.69 – 2.55 (m, 4H), 2.42 (s, 3H), 1.79 (d, *J* = 12.2 Hz, 2H), 1.68 (dtd, *J* = 14.0, 7.1, 3.6 Hz, 1H), 1.59 – 1.49 (m, 2H).

¹⁹F NMR (376 MHz, CDCl₃) δ -122.47 (s).

Example 8 (the preparation of **9a**)



A solution of **8a** (2.0g, 6.27mmol) in EA (30mL) was added **9a** (1.58g,

18.82mmol) and the reaction mixture was stirred at 90°C under N₂ overnight.

Then the solvent was removed at reduced pressure. The crude product was purified by chromatography (PE: EA = 8:1-2:1) to provide **9a** as 1.94 g light yellow solid, Yield: 76.8%.

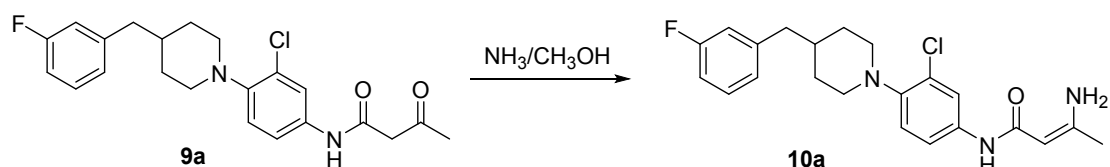
[ES-MS] (ESI⁺): m/z calcd for C₂₂H₂₄ClFN₂O₂ [M + H]⁺, 403.2; found, 403.2

¹H NMR (400 MHz, DMSO) δ 10.11 (s, 1H), 7.76 (d, *J* = 2.3 Hz, 1H), 7.42 – 7.27 (m, 2H), 7.03 (dq, *J* = 17.6, 8.9 Hz, 4H), 3.52 (s, 2H), 3.17 (d, *J* = 11.1 Hz, 2H), 2.58 (d, *J*

= 6.5 Hz, 2H), 2.50 (d, J = 10.7 Hz, 2H), 2.20 (s, 3H), 1.63 (d, J = 11.6 Hz, 3H), 1.45 – 1.28 (m, 2H).

^{19}F NMR (376 MHz, CDCl_3) δ -113.99 (s).

Example 9 (the preparation of **10a**)

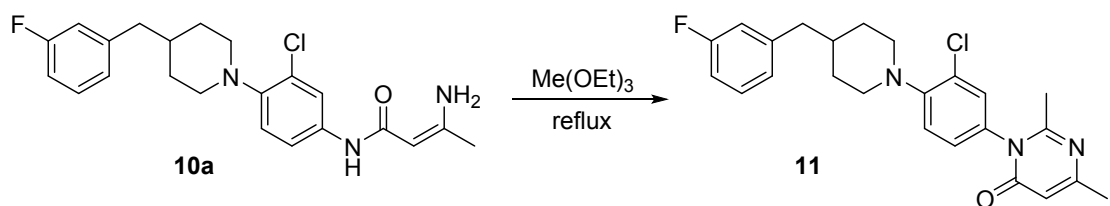


A solution of **9a** (1.0g, 2.48mmol) in methanol (10mL) was added ammonium hydrate (10mL). The reaction mixture was stirred at r.t. under N_2 overnight. Then the solvent was removed under reduced pressure and the crude product **10a** was taken to the next step without further purification. (brown solid)

^1H NMR (400 MHz, DMSO) δ 9.14 (s, 1H), 7.78 (t, J = 6.6 Hz, 1H), 7.38 – 7.29 (m, 2H), 7.03 (dd, J = 18.5, 8.9 Hz, 4H), 4.45 (s, 1H), 3.18 – 3.09 (m, 2H), 2.59 (d, J = 6.5 Hz, 2H), 2.52 (d, J = 10.8 Hz, 2H), 1.84 – 1.77 (m, 3H), 1.63 (d, J = 10.1 Hz, 3H), 1.42 – 1.30 (m, 2H).

^{19}F NMR (376 MHz, CDCl_3) δ -114.04 (s).

Example 10 (the preparation of **11**)



A solution of **10a** (1.0g, 2.5mmol) in $\text{Me}_3\text{C}(\text{OEt})_3$ was stirred at 150°C under N_2 for 18hrs. Then the solvent was removed under reduced pressure. The crude product was purified by chromatography (PE: EA = 4:1-1:1) to provide **11** (Yield: 53.1%) (off-white solid)

Melting Point: 182.8°C

[ES-MS] (ESI^+): m/z calcd for $\text{C}_{24}\text{H}_{25}\text{ClFN}_3\text{O}$ [$\text{M} + \text{H}$] $^+$, 426.2; found, 426.2

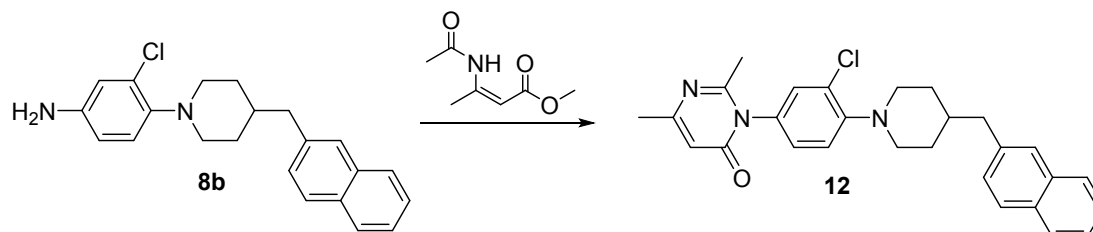
^1H NMR (600 MHz, CDCl_3) δ 7.30 – 7.25 (m, 1H), 7.21 (d, $J = 2.5$ Hz, 1H), 7.13 (d, $J = 8.6$ Hz, 1H), 7.04 (dd, $J = 8.5, 2.5$ Hz, 1H), 6.97 (dt, $J = 7.5, 1.3$ Hz, 1H), 6.92 (td, $J = 10.2, 2.1$ Hz, 2H), 6.29 (s, 1H), 3.50 (ddd, $J = 11.6, 5.0, 2.8$ Hz, 1H), 3.44 – 3.38 (m, 1H), 2.75 – 2.57 (m, 4H), 2.31 (s, 3H), 2.20 (s, 3H), 1.77 (dtd, $J = 14.7, 5.3, 4.7, 2.3$ Hz, 2H), 1.71 (ddp, $J = 11.2, 7.3, 3.7$ Hz, 1H), 1.58 – 1.48 (m, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 164.08, 163.11, 162.51, 161.64, 158.64, 150.96, 143.07 (d, $J = 7.1$ Hz), 131.51, 129.56, 126.60, 124.80, 121.26, 115.83 (d, $J = 20.6$ Hz), 112.79 (d, $J = 20.9$ Hz), 110.81, 51.95, 51.72, 42.90, 37.61, 32.33, 23.96, 23.75.

^{19}F NMR (376 MHz, CDCl_3) δ -113.90 (s).

HPLC: purity = 99.01%.

Example 11 (the preparation of **12**)



A solution of **8b** (909 mg, 2.59 mmol, 1.0 eqv) in toluene (20 mL) was stirred at r.t. under N_2 . Then 2M Me_3Al in toluene (5.2 mL, 10.40 mmol, 4.0 eqv) was added drop wise to the aforementioned solution. After the addition was completed, the reaction mixture was stirred at r.t. for another 30 min before a solution of (Z)-methyl 3-acetamidobut-2-enoate (489 mg, 3.11 mmol, 1.2 eqv) in toluene (2 mL) was added to the reaction mixture carefully. Finally, the reaction mixture was stirred at r.t. for 72 hrs.

The reaction was quenched by saturated NH_4Cl solution (50 mL). The mixture was filtered and the organic layer as separated. Then the aqueous layer was extracted with DCM (50 mL) and the organic layer was combined, washed with 100mL brine, dried over anhydrous Na_2SO_4 and filtered. The solvent was remove under reduce pressure.

The crude product was purified by flash chromatography on silica gel (PE: EA = 1:1) to provide **12** (613.0 mg) as light yellow solid. Yield: 51.7%.

Melting Point: 140.4°C

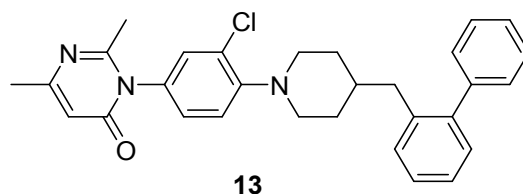
[ES-MS] (ESI⁺): m/z calcd for C₂₈H₂₈ClN₃O [M + H]⁺, 458.2; found, 458.2

¹H NMR (400 MHz, CDCl₃) δ 7.80 (t, *J* = 9.4 Hz, 3H), 7.62 (s, 1H), 7.50 – 7.39 (m, 2H), 7.34 (d, *J* = 6.9 Hz, 1H), 7.19 (d, *J* = 2.4 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 1H), 7.01 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.27 (s, 1H), 3.44 (dd, *J* = 37.8, 12.0 Hz, 2H), 2.79 (d, *J* = 4.4 Hz, 2H), 2.64 (dt, *J* = 36.3, 10.8 Hz, 2H), 2.28 (s, 3H), 2.17 (s, 3H), 1.80 (d, *J* = 9.5 Hz, 3H), 1.36 – 1.26 (m, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 163.17, 162.58, 158.70, 151.07, 138.07, 133.58, 132.10, 131.45, 129.64, 129.56, 127.85, 127.66, 127.47, 127.35, 126.60, 125.99, 125.24, 121.29, 110.86, 52.05, 51.83, 43.39, 37.82, 32.50, 24.02, 23.81.

HPLC: purity = 95.04%.

The preparations of **13-22** were the same as **12**.



The crude product was purified by flash chromatography on silica gel (PE: EA = 1:1) to provide **13** (463.0 mg) as light yellow solid. Yield: 28.8%.

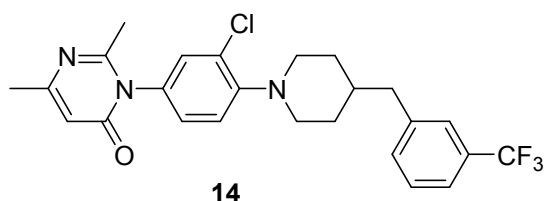
Melting Point: 107.7°C

[ES-MS] (ESI⁺): m/z calcd for C₃₀H₃₀ClN₃O [M + H]⁺, 484.2; found, 484.2

¹H NMR (400 MHz, CDCl₃) δ 7.41 (t, *J* = 7.2 Hz, 2H), 7.36 (d, *J* = 7.2 Hz, 1H), 7.33 – 7.27 (m, 5H), 7.22 (d, *J* = 7.9 Hz, 1H), 7.16 (d, *J* = 2.3 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 6.99 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.26 (s, 1H), 3.31 (dd, *J* = 41.3, 12.0 Hz, 2H), 2.64 (d, *J* = 6.9 Hz, 2H), 2.50 (dt, *J* = 21.3, 9.6 Hz, 2H), 2.28 (s, 3H), 2.15 (s, 3H), 1.49 (dd, *J* = 7.1, 3.6 Hz, 1H), 1.37 – 1.28 (m, 4H).

^{13}C NMR (101 MHz, CDCl_3) δ 163.12, 162.48, 158.66, 150.94, 142.40, 142.04, 137.91, 131.41, 130.16, 130.00, 129.51, 129.33, 128.08, 127.19, 126.82, 126.59, 125.86, 121.22, 110.76, 51.95, 51.72, 39.75, 37.17, 32.29, 23.93, 23.75.

HPLC: purity = 92.25%.



The crude product was purified by flash chromatography on silica gel (PE: EA = 1:1) to provide **14** (1.0 g) as light yellow oil. Yield: 55.2%.

Melting Point: 118.1°C

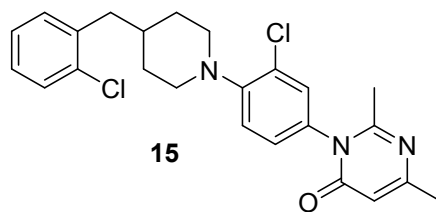
[ES-MS] (ESI^+): m/z calcd for $\text{C}_{25}\text{H}_{25}\text{ClF}_3\text{N}_3\text{O}$ $[\text{M} + \text{H}]^+$, 476.2; found, 476.2

^1H NMR (400 MHz, CDCl_3) δ 7.49 – 7.40 (m, 3H), 7.37 (t, $J = 7.3$ Hz, 1H), 7.20 (d, $J = 2.3$ Hz, 1H), 7.11 (d, $J = 8.5$ Hz, 1H), 7.02 (dd, $J = 8.5, 2.3$ Hz, 1H), 6.27 (s, 1H), 3.43 (dd, $J = 31.3, 11.3$ Hz, 2H), 2.74 – 2.54 (m, 4H), 2.28 (s, 3H), 2.17 (s, 3H), 1.81 – 1.65 (m, 3H), 1.59 – 1.45 (m, 2H).

^{13}C NMR (151 MHz, CDCl_3) δ 163.14, 162.53, 158.67, 150.90, 141.38, 132.56, 131.52, 129.54, 128.69, 125.64 (d, $J = 3.6$ Hz), 125.63, 122.85, 121.18, 110.78, 51.88, 51.67, 42.94, 37.64, 32.28, 32.25, 23.95, 23.72.

^{19}F NMR (376 MHz, CDCl_3) δ -62.50 (s).

HPLC: purity = 97.20%.



The crude product was purified by flash chromatography on silica gel (PE: EA = 1:1) to provide **15** (400.0 mg) as a white solid. Yield: 37.7%.

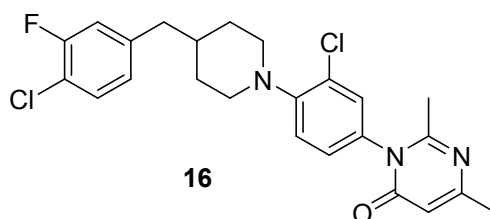
Melting Point: 167.0°C

[ES-MS] (ESI⁺): m/z calcd for C₂₄H₂₅Cl₂N₃O [M + H]⁺, 442.1; found, 442.1

¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.34 (m, 1H), 7.22 – 7.18 (m, 3H), 7.18 – 7.13 (m, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 7.02 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.28 (s, 1H), 3.43 (dd, *J* = 36.0, 11.2 Hz, 2H), 2.75 (t, *J* = 7.7 Hz, 2H), 2.64 (dtd, *J* = 41.4, 11.6, 2.2 Hz, 2H), 2.29 (d, *J* = 0.4 Hz, 3H), 2.18 (s, 3H), 1.87 – 1.71 (m, 3H), 1.60 – 1.50 (m, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 163.11, 162.53, 158.67, 151.02, 138.12, 134.20, 131.47, 129.64, 129.57, 129.54, 127.48, 126.59, 126.50, 110.83, 51.99, 51.76, 40.54, 36.08, 32.38, 32.34, 24.01, 23.79.

HPLC: purity = 97.60%.



The crude product was purified by flash chromatography on silica gel (PE: EA =4:1-1:1) to provide **16** (669.0 mg) as a yellow solid. Yield: 69.4%.

Melting Point: 168.9°C

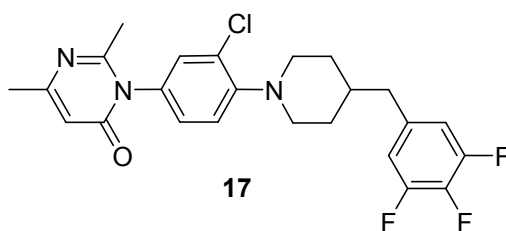
[ES-MS] (ESI⁺): m/z calcd for C₂₄H₂₄Cl₂FN₃O [M + H]⁺, 460.1; found, 460.1

¹H NMR (400 MHz, CDCl₃) δ 7.31 (dd, *J* = 15.3, 7.4 Hz, 1H), 7.22 (d, *J* = 2.4 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 1H), 7.04 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.99 (dd, *J* = 10.0, 1.8 Hz, 1H), 6.92 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.29 (s, 1H), 3.45 (dd, *J* = 33.5, 11.5 Hz, 2H), 2.75 – 2.55 (m, 4H), 2.31 (s, 3H), 2.20 (s, 3H), 1.76 (d, *J* = 13.2 Hz, 2H), 1.68 (dtd, *J* = 10.9, 7.1, 3.6 Hz, 1H), 1.58 – 1.45 (m, 2H).

^{13}C NMR (151 MHz, CDCl_3) δ 163.08, 162.43, 158.65, 158.61, 157.01, 150.82, 141.54, 141.50, 131.57, 130.20, 129.53, 126.64, 125.61 (d, $J = 3.3$ Hz), 121.28, 118.15 (d, $J = 17.6$ Hz), 117.08 (d, $J = 20.3$ Hz), 110.76, 51.83, 51.64, 42.42, 37.52, 32.22, 23.98, 23.77.

^{19}F NMR (376 MHz, CDCl_3) δ -116.10 (s).

HPLC: purity = 99.91%.



The crude product was purified by flash chromatography on silica gel (PE: EA = 1:1) to provide **17** (1.36 g) as a white solid. Yield: 51.5%.

Melting Point: 163.7°C

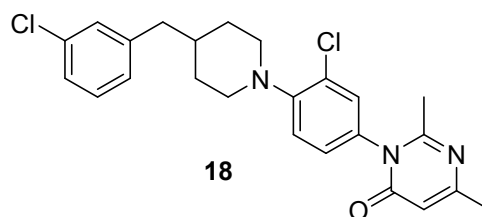
[ES-MS] (ESI^+): m/z calcd for $\text{C}_{24}\text{H}_{23}\text{ClF}_3\text{N}_3\text{O}$ [$\text{M} + \text{H}$] $^+$, 462.1; found, 462.2

^1H NMR (400 MHz, CDCl_3) δ 7.20 (d, $J = 2.4$ Hz, 1H), 7.12 (d, $J = 8.5$ Hz, 1H), 7.03 (dd, $J = 8.5, 2.4$ Hz, 1H), 6.82 – 6.75 (m, 2H), 6.28 (s, 1H), 3.44 (dd, $J = 33.5, 12.0$ Hz, 2H), 2.74 – 2.52 (m, 4H), 2.29 (s, 3H), 2.18 (s, 3H), 1.74 (d, $J = 13.5$ Hz, 2H), 1.70 – 1.65 (m, 1H), 1.53 – 1.44 (m, 2H).

^{13}C NMR (151 MHz, CDCl_3) δ 163.16, 162.52, 158.62, 151.78 (dd, $J = 9.7, 3.9$ Hz), 150.81, 150.13 (dd, $J = 9.8, 3.9$ Hz), 138.94 (t, $J = 15.3$ Hz), 137.29 (t, $J = 15.4$ Hz), 136.73 (dd, $J = 11.6, 7.0$ Hz), 131.61, 129.63, 129.56, 126.62, 121.28, 112.87, 112.85, 112.77, 112.74, 110.79, 51.81, 51.60, 42.47, 37.47, 32.16, 23.95, 23.73.

^{19}F NMR (376 MHz, CDCl_3) δ -135.18 (d, $J = 20.5$ Hz), -164.38 (t, $J = 20.5$ Hz).

HPLC: purity = 97.15%.



The crude product was purified by flash chromatography on silica gel (PE: EA = 1:1) to provide **18** (1.3g) as a white solid. Yield: 52%.

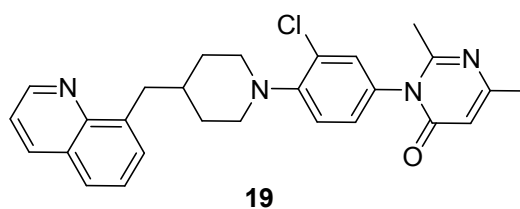
Melting Point: 149.2°C

[ES-MS] (ESI⁺): m/z calcd for C₂₄H₂₅Cl₂N₃O [M + H]⁺, 442.1; found, 442.1

¹H NMR (400 MHz, CDCl₃) δ 7.27 – 7.20 (m, 2H), 7.20 – 7.16 (m, 2H), 7.11 (d, *J* = 8.5 Hz, 1H), 7.06 (d, *J* = 7.2 Hz, 1H), 7.02 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.28 (s, 1H), 3.44 (dd, *J* = 36.2, 11.4 Hz, 2H), 2.74 – 2.63 (m, 1H), 2.63 – 2.53 (m, 3H), 2.29 (s, 3H), 2.18 (s, 3H), 1.75 (d, *J* = 12.5 Hz, 2H), 1.71 – 1.68 (m, 1H), 1.51 (qd, *J* = 11.7, 3.7 Hz, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 163.13, 162.54, 158.66, 150.95, 142.56, 134.04, 131.50, 129.63, 129.55, 129.52, 129.13, 127.37, 126.60, 126.14, 121.28, 110.83, 51.94, 51.72, 42.84, 37.64, 32.31, 24.00, 23.78.

HPLC: purity = 99.18%.



The crude product was purified by flash chromatography on silica gel (PE: EA = 1:1) to provide **19** (0.1 g) as a white solid. Yield: 12.7%.

Melting Point: 98.6°C

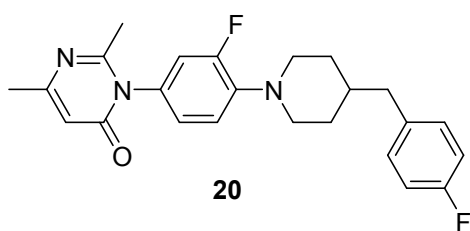
[ES-MS] (ESI⁺): m/z calcd for C₂₇H₂₇ClN₄O [M + H]⁺, 459.2; found, 459.2

¹H NMR (400 MHz, CDCl₃) δ 8.96 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.16 (d, *J* = 7.0 Hz, 1H), 7.71 (d, *J* = 7.0 Hz, 1H), 7.56 (d, *J* = 5.9 Hz, 1H), 7.52 – 7.45 (m, 1H), 7.41 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 7.00 (dd, *J* = 8.5,

2.4 Hz, 1H), 6.27 (s, 1H), 3.51 – 3.33 (m, 2H), 3.32 – 3.22 (m, 2H), 2.62 (ddd, $J = 47.7$, 11.7, 9.3 Hz, 2H), 2.28 (s, 3H), 2.17 (s, 3H), 1.85 – 1.71 (m, 2H), 1.44 – 1.24 (m, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 163.12, 162.60, 158.74, 151.21, 149.35, 147.12, 139.24, 136.36, 131.26, 130.03, 129.62, 129.49, 128.53, 126.50, 126.25, 126.08, 121.25, 120.85, 110.84, 52.09, 51.83, 38.64, 36.59, 32.74, 32.62, 23.99, 23.76.

HPLC: purity=93.26%.



The crude product was purified by flash chromatography on silica gel (PE: EA = 1:1) to provide **20** (362.0 mg) as light yellow oil. Yield: 28.3%.

Melting Point: 146.4°C

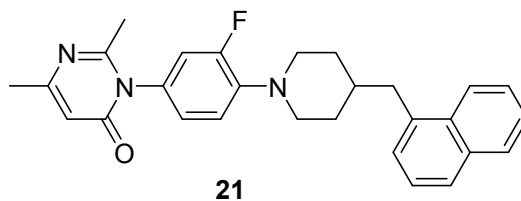
[ES-MS] (ESI^+): m/z calcd for $\text{C}_{24}\text{H}_{25}\text{F}_2\text{N}_3\text{O}$ $[\text{M} + \text{H}]^+$, 410.2; found, 410.2

^1H NMR (400 MHz, DMSO) δ 7.23 (dt, $J = 8.0$, 4.5 Hz, 3H), 7.14 – 7.02 (m, 4H), 6.22 (s, 1H), 3.41 (t, $J = 12.8$ Hz, 2H), 2.65 (dd, $J = 19.5$, 10.5 Hz, 2H), 2.55 (t, $J = 11.0$ Hz, 2H), 2.19 (s, 3H), 2.07 (s, 3H), 1.66 (d, $J = 11.0$ Hz, 3H), 1.36 (d, $J = 11.7$ Hz, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 162.98, 162.50, 162.45, 160.08, 158.75, 156.63, 154.15, 141.63 (d, $J = 8.2$ Hz), 135.91 (d, $J = 3.1$ Hz), 130.39 (d, $J = 7.7$ Hz), 130.12 (d, $J = 9.6$ Hz), 123.57 (d, $J = 3.2$ Hz), 119.70 (d, $J = 4.0$ Hz), 115.66 (d, $J = 23.2$ Hz), 114.93 (d, $J = 21.0$ Hz), 110.70, 51.06 (d, $J = 4.0$ Hz), 50.72 (d, $J = 2.8$ Hz), 42.21, 37.72, 32.11 (d, $J = 4.6$ Hz), 23.78, 23.68.

^{19}F NMR (376 MHz, CDCl_3) δ -117.57 (s), -118.93 (s).

HPLC: purity = 97.19%.



The crude product was purified by flash chromatography on silica gel (PE: EA = 1:1) to provide **21** (110.0 mg) as white oil. Yield: 27.0%.

Melting Point: 89.0°C

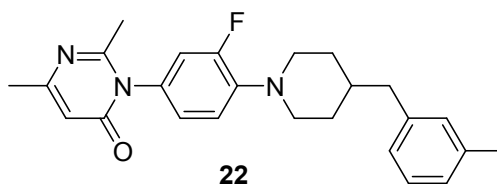
[ES-MS] (ESI⁺): m/z calcd for C₂₈H₂₈FN₃O [M + H]⁺, 442.2; found, 442.2

¹H NMR (600 MHz, CDCl₃) δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.58 – 7.54 (m, 1H), 7.52 (t, *J* = 7.0 Hz, 1H), 7.48 – 7.40 (m, 1H), 7.34 (d, *J* = 6.8 Hz, 1H), 7.08 – 6.98 (m, 1H), 6.93 – 6.85 (m, 2H), 6.30 (s, 1H), 3.52 (dd, *J* = 52.7, 12.2 Hz, 2H), 3.14 – 3.03 (m, 2H), 2.74 – 2.59 (m, 2H), 2.31 (s, 3H), 2.20 (s, 3H), 1.96 – 1.87 (m, 1H), 1.82 (d, *J* = 13.0 Hz, 2H), 1.63 (td, *J* = 12.2, 3.5 Hz, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 163.08, 162.63, 158.83, 156.35, 154.69, 141.80 (d, *J* = 8.2 Hz), 136.42, 134.03, 132.14, 130.10 (d, *J* = 9.6 Hz), 128.87, 127.28, 126.85, 125.79, 125.42 (d, *J* = 19.3 Hz), 124.00, 123.54 (d, *J* = 3.2 Hz), 119.78 (d, *J* = 4.0 Hz), 115.68 (d, *J* = 23.2 Hz), 110.88, 51.21, 50.82, 40.24, 36.92, 32.78, 32.70, 23.92, 23.80.

¹⁹F NMR (376 MHz, CDCl₃) δ -118.96 (s).

HPLC: purity = 96.14%.



The crude product was purified by flash chromatography on silica gel (PE: EA = 1:1) to provide **22** (207.0 mg) as blue oil. Yield: 70.9%.

Melting Point: 105.5°C

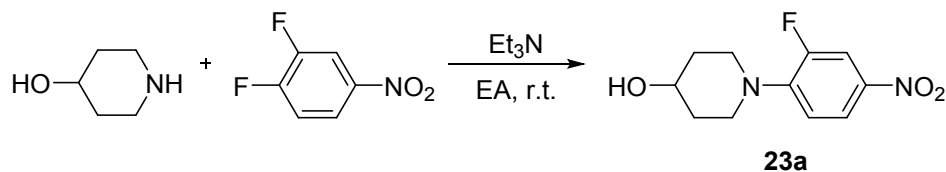
[ES-MS] (ESI⁺): m/z calcd for C₂₅H₂₈FN₃O [M + H]⁺, 406.2; found, 406.2

^1H NMR (400 MHz, CDCl_3) δ 7.19 (t, $J = 7.5$ Hz, 1H), 7.06 – 6.94 (m, 4H), 6.87 (d, $J = 10.2$ Hz, 2H), 6.28 (s, 1H), 3.50 (dd, $J = 36.6, 11.2$ Hz, 2H), 2.75 – 2.60 (m, 2H), 2.57 (d, $J = 7.0$ Hz, 2H), 2.35 (s, 3H), 2.29 (s, 3H), 2.18 (s, 3H), 1.76 (s, 2H), 1.72 – 1.61 (m, 1H), 1.53 – 1.45 (m, 2H). ^{13}C NMR (151 MHz, CDCl_3) δ 163.06, 162.61, 158.84, 156.27, 154.60, 141.82 (d, $J = 8.2$ Hz), 140.31, 137.76, 129.95, 128.14, 126.69, 126.19, 123.55 (d, $J = 3.1$ Hz), 119.76 (d, $J = 4.0$ Hz), 115.75, 115.60, 110.84, 51.24 (d, $J = 4.1$ Hz), 50.83 (d, $J = 2.6$ Hz), 43.12, 37.76, 32.33 (d, $J = 7.1$ Hz), 23.90, 23.78, 21.46.

^{19}F NMR (376 MHz, CDCl_3) δ -118.94 (s).

HPLC: purity = 98.45%.

Example 12 (the preparation of **23a**)



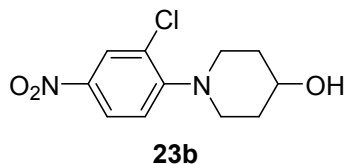
To a degassed solution of EtOAc (50 mL) was added piperidin-4-ol (3.64 g, 36.0 mmol, 1.20 eqv), Et_3N (9.11 g, 90.0 mmol, 3.00 eqv) and followed by 1,2-difluoro-4-nitrobenzene (4.77 g, 30.0 mmol, 1.00 eqv). The reaction mixture was stirred under N_2 at r.t. overnight. Then the reaction was filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (PE: EA = 4:1) to provide **23a** as a yellow solid.

[ES-MS] (ESI^+): m/z calcd for $\text{C}_{11}\text{H}_{13}\text{FN}_2\text{O}_3$ [$\text{M} + \text{H}$] $^+$, 241.1; found, 241.1

^1H NMR (400 MHz, DMSO) δ 8.04 – 7.88 (m, 2H), 7.15 (t, $J = 9.2$ Hz, 1H), 4.78 (d, $J = 4.1$ Hz, 1H), 3.71 (tq, $J = 8.0, 3.8$ Hz, 1H), 3.61 – 3.49 (m, 2H), 3.14 – 3.00 (m, 2H), 1.91 – 1.79 (m, 2H), 1.59 – 1.44 (m, 2H).

^{19}F NMR (376 MHz, CDCl_3) δ -118.72 (s).

The preparation of **23b** was the same as **23a**.



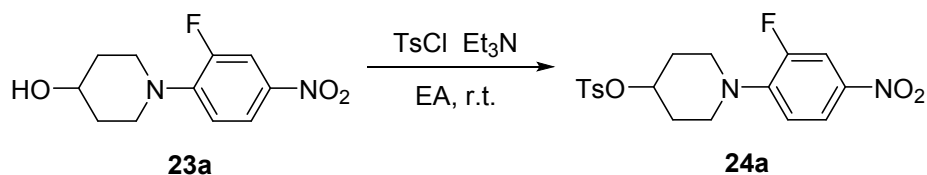
23b (143.6 g) was collected as a yellow solid. Yield: 94.4%.

The product was taken to the next step without further purification.

[ES-MS] (ESI⁺): m/z calcd for C₁₁H₁₃ClN₂O₃ [M + H]⁺, 257.1; found, 257.1

¹H NMR (400 MHz, CDCl₃) δ 8.25 (d, *J* = 2.6 Hz, 1H), 8.09 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.06 (d, *J* = 9.0 Hz, 1H), 3.97 (s, 1H), 3.54 – 3.42 (m, 2H), 3.01 (ddd, *J* = 12.1, 9.0, 3.0 Hz, 2H), 2.13 – 2.03 (m, 2H), 1.86 – 1.75 (m, 2H), 1.73 (s, 1H).

Example 13 (the preparation of **24a**)



To a degassed solution of EtOAc (20 mL) was added 4-methylbenzene-1-sulfonyl chloride (3.81 g, 20.0 mmol, 1.20 eqv), Et₃N (1.68g, 16.6 mmol, 1.00 eqv) and followed by **23a** (4.0 g, 16.6 mmol, 1.00 eqv). The reaction mixture was stirred under N₂ at r.t. overnight. The solvent was then removed under reduce pressure. The crude product was purified by flash chromatography on silica gel (PE: EA = 8:1) to provide **24a** as a yellow solid

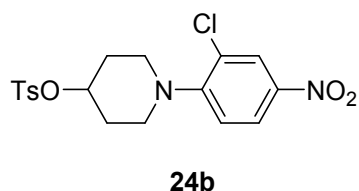
[ES-MS] (ESI⁺): m/z calcd for C₁₈H₁₉FN₂O₅S [M + H]⁺, 395.1; found, 395.1

¹H NMR (400 MHz, DMSO) δ 8.03 – 7.94 (m, 2H), 7.84 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.16 (t, *J* = 9.2 Hz, 1H), 4.77 (tt, *J* = 7.6, 3.7 Hz, 1H), 3.46 – 3.38

(m, 2H), 3.20 (ddd, $J = 12.8, 8.0, 3.9$ Hz, 2H), 2.43 (s, 3H), 1.95 – 1.86 (m, 2H), 1.79 – 1.67 (m, 2H).

^{19}F NMR (376 MHz, CDCl_3) δ -118.70 (s).

The preparation of **24b** was the same as 24a.

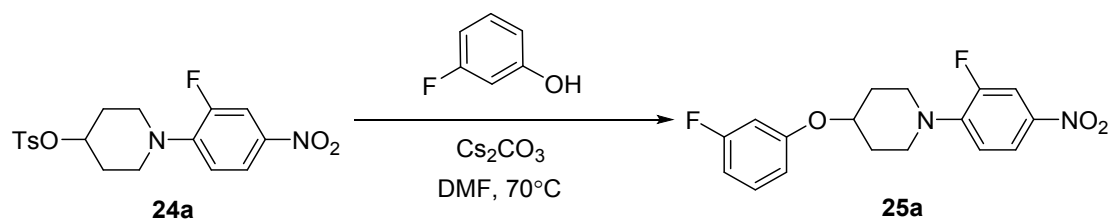


24b (135.2 g) was collected as a yellow solid. Yield: 58.8%. The product was taken to the next step without further purification.

[ES-MS] (ESI^+): m/z calcd for $\text{C}_{18}\text{H}_{19}\text{ClN}_2\text{O}_5\text{S}$ [$\text{M} + \text{H}$] $^+$, 411.1; found, 411.1

^1H NMR (400 MHz, CDCl_3) δ 8.20 (d, $J = 2.6$ Hz, 1H), 8.06 (dd, $J = 8.9, 2.6$ Hz, 1H), 7.82 (d, $J = 8.3$ Hz, 2H), 7.37 (d, $J = 8.1$ Hz, 2H), 7.03 (d, $J = 9.0$ Hz, 1H), 4.81 – 4.72 (m, 1H), 3.32 (ddd, $J = 11.6, 7.9, 3.4$ Hz, 2H), 3.14 – 3.03 (m, 2H), 2.46 (s, 3H), 2.08 – 1.89 (m, 4H).

Example 14 (the preparation of **25a**)



To a degassed solution of DMF (20 mL) was added 3-fluorophenol (0.85g, 7.58 mmol, 1.20 eqv), Cs_2CO_3 (4.13g, 21.4 mmol, 2.80 eqv) and followed by 24a (2.5 g, 6.34mmol, 1.00 eqv). The reaction mixture was stirred under N_2 at 70°C overnight. After the reaction was completed, it was cooled to r.t. and 100 mL CH_2Cl_2 was poured into the mixture. The mixture was washed with 100 mL $\times$ 2 H_2O , 100 mL $\times$ 2 brine, and dried over anhydrous Na_2SO_4 . The solution was filtered and the solvent was removed

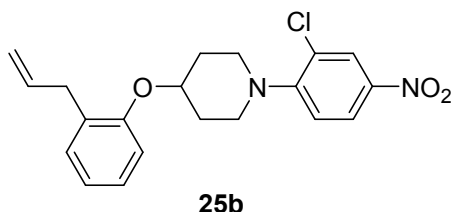
under reduce pressure. The crude product was purified by column chromatography (PE: EA = 4:1) to provide **25a**

[ES-MS] (ESI⁺): m/z calcd for C₁₇H₁₆F₂N₂O₃ [M + H]⁺, 335.1; found, 335.1

¹H NMR (400 MHz, DMSO) δ 8.05 – 7.95 (m, 2H), 7.31 (dd, *J* = 15.5, 8.2 Hz, 1H), 7.20 (t, *J* = 9.1 Hz, 1H), 6.93 – 6.82 (m, 2H), 6.76 (td, *J* = 8.4, 2.0 Hz, 1H), 4.73 – 4.64 (m, 1H), 3.57 (dd, *J* = 10.4, 4.4 Hz, 2H), 3.30 – 3.20 (m, 2H), 2.14 – 2.03 (m, 2H), 1.82 – 1.70 (m, 2H).

¹⁹F NMR (376 MHz, CDCl₃) δ -111.39 (s), -118.71 (s).

The preparation of **25b** was the same as **25a**.

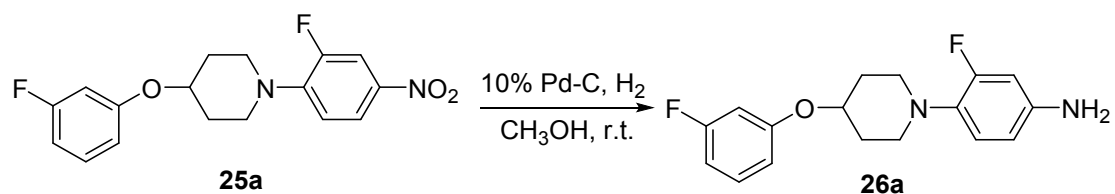


The crude product was purified by chromatography on silica gel (PE : EA = 8 : 1) to get **25b** (0.5 g) as yellow solid. Yield: 34.5%.

[ES-MS] (ESI⁺): m/z calcd for C₂₀H₂₁ClN₂O₃ [M + H]⁺, 373.1; found, 373.1

¹H NMR (400 MHz, DMSO) δ 8.22 (d, *J* = 2.7 Hz, 1H), 8.14 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.31 (d, *J* = 9.0 Hz, 1H), 7.21 – 7.11 (m, 2H), 7.07 – 7.01 (m, 1H), 6.87 (t, *J* = 7.1 Hz, 1H), 6.03 – 5.87 (m, 1H), 5.09 – 4.97 (m, 2H), 4.71 – 4.63 (m, 1H), 3.36 (dd, *J* = 9.7, 5.5 Hz, 4H), 3.22 – 3.10 (m, 2H), 2.15 – 2.02 (m, 2H), 1.86 (dd, *J* = 9.8, 6.6 Hz, 2H).

Example 15 (the preparation of **26a**)



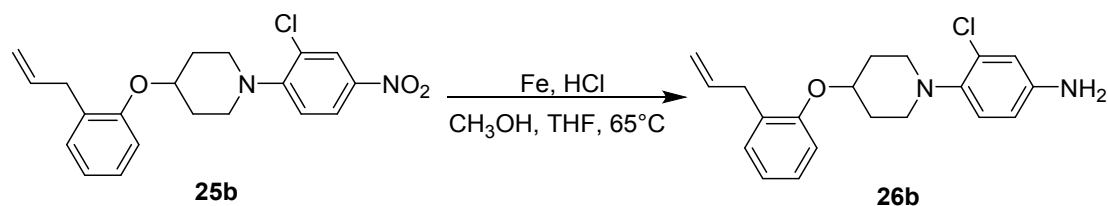
To a degassed solution of methanol (20mL) was added **25a** (0.6 g, 1.79 mmol, 1 eqv) and followed by 10% Pd-C (0.06 g, 10%). The mixture was stirred under a H₂ balloon at r.t. overnight. Then the mixture was filtered and the solvent was remove under reduce pressure. The crude product was purified by column chromatography (PE: EtOAc=4:1) to provide **26a**. Yield: 92%.(grey solid)

[ES-MS] (ESI⁺): m/z calcd for C₁₇H₁₈F₂N₂O [M + H]⁺, 305.1; found, 305.2

¹H NMR (400 MHz, DMSO) δ 7.29 (dd, *J* = 15.5, 8.1 Hz, 1H), 6.89 – 6.68 (m, 4H), 6.36 (ddd, *J* = 11.4, 10.8, 2.3 Hz, 2H), 4.98 (s, 2H), 4.54 – 4.44 (m, 1H), 3.14 – 2.99 (m, 2H), 2.77 (dd, *J* = 14.5, 5.8 Hz, 2H), 2.03 (d, *J* = 11.4 Hz, 2H), 1.82 – 1.69 (m, 2H).

¹⁹F NMR (376 MHz, CDCl₃) δ -111.71 (s), -122.47 (s).

Example 16 (the preparation of **26b**)

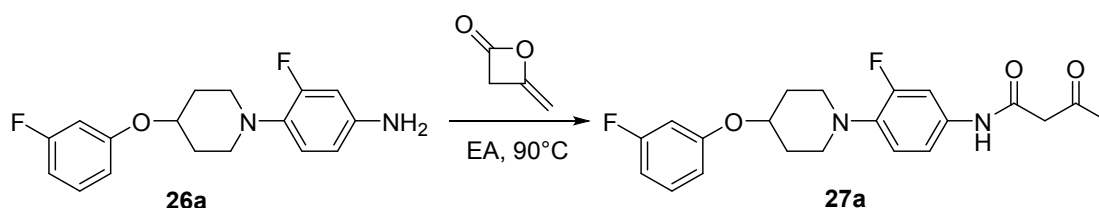


Iron (1.20 g, 21.5 mmol, 10 eqv) was added to the concentrated HCl (0.5 mL) in water (10 mL). The mixture was heated to 65°C for 15 min and then the solution of **25b** (0.8 g, 2.15 mmol, 1 eqv) in methanol (10 mL) and THF (10 mL) was added. The mixture was heated to 65°C for 1h. After cooled down to r.t., the reaction pH was adjusted to 10 by adding Et₃N. The solution was filtered and the solvent was remove under reduce pressure. The resulting residue was dissolved in DCM (100 mL) and washed with water (100 mL*2) and brine (100 mL). The organic layer was dried over anhydrous Na₂SO₄ and filtered. The solvent was removed under reduce pressure. The crude product was purified by chromatography on silica gel (PE: EtOAc = 4:1) to provide **26b** (370.0 mg) as light yellow oil. Yield: 50.3%.

[ES-MS] (ESI⁺): m/z calcd for C₂₀H₂₃ClN₂O [M + H]⁺, 343.2; found, 343.2

^1H NMR (400 MHz, DMSO) δ 7.20 – 7.10 (m, 2H), 7.01 (d, J = 8.1 Hz, 1H), 6.93 – 6.83 (m, 2H), 6.65 (d, J = 2.5 Hz, 1H), 6.50 (dd, J = 8.5, 2.5 Hz, 1H), 5.97 (ddt, J = 16.7, 10.0, 6.7 Hz, 1H), 5.04 (dt, J = 9.9, 3.6 Hz, 4H), 4.59 – 4.47 (m, 1H), 3.36 (d, J = 7.3 Hz, 2H), 3.06 – 2.96 (m, 2H), 2.82 – 2.71 (m, 2H), 2.08 – 2.00 (m, 2H), 1.80 (dt, J = 16.7, 6.1 Hz, 2H).

Example 17 (the preparation of **27a**)



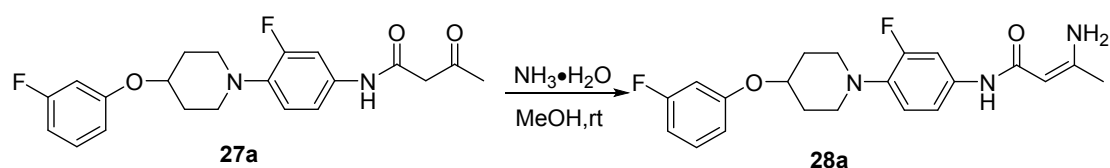
To a degassed solution of EtOAc (20mL) was added 4-methyleneoxetan-2-one (414 mg, 4.92 mmol, 2.14 eqv) and followed by 26a (700 mg, 2.3 mmol, 1.0 eqv). The mixture was stirred under N_2 at 80°C overnight. The solvent was removed under reduce pressure and the crude product was purified by column chromatography (PE: EA=1:1) to provide **27a**. Yield: 73.1%. (brown oil)

[ES-MS] (ESI^+): m/z calcd for $\text{C}_{21}\text{H}_{22}\text{F}_2\text{N}_2\text{O}_3$ [$\text{M} + \text{H}$] $^+$, 389.2; found, 389.2

^1H NMR (400 MHz, DMSO) δ 10.11 (s, 1H), 7.53 (dd, J = 14.8, 2.2 Hz, 1H), 7.31 (dd, J = 15.5, 8.2 Hz, 1H), 7.18 (dd, J = 8.7, 1.6 Hz, 1H), 7.03 (t, J = 9.3 Hz, 1H), 6.88 (dt, J = 11.4, 2.2 Hz, 1H), 6.84 (dd, J = 8.3, 1.7 Hz, 1H), 6.75 (td, J = 8.4, 1.9 Hz, 1H), 4.63 – 4.52 (m, 1H), 3.53 (s, 2H), 3.26 – 3.15 (m, 2H), 2.90 (t, J = 9.0 Hz, 2H), 2.20 (s, 3H), 2.12 – 2.01 (m, 2H), 1.84 – 1.71 (m, 2H).

^{19}F NMR (376 MHz, CDCl_3) δ -111.65 (s), -120.62 (s).

Example 18 (the preparation of **28a**)

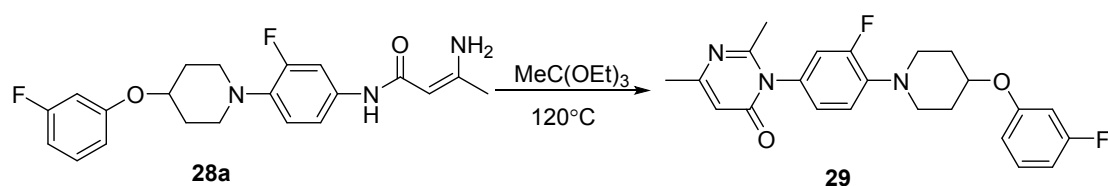


A solution of **27a** (700 mg, 1.8 mmol, 1.0 eqv) in methanol (10 mL) and NH₃·H₂O (10 mL) was stirred under N₂ at r.t. overnight. The solvent was removed under reduce pressure and the crude product was taken to the next step without further purification. (brown oil)

¹H NMR (400 MHz, DMSO) δ 9.16 (s, 1H), 7.57 (dd, J = 15.3, 2.2 Hz, 1H), 7.31 (dd, J = 15.5, 8.1 Hz, 1H), 7.12 (dd, J = 8.7, 1.7 Hz, 1H), 7.00 – 6.91 (m, 1H), 6.86 (ddd, J = 13.7, 7.1, 1.9 Hz, 2H), 6.75 (td, J = 8.4, 1.8 Hz, 1H), 4.62 – 4.50 (m, 1H), 4.46 (s, 1H), 3.24 – 3.12 (m, 2H), 2.94 – 2.81 (m, 2H), 2.06 (d, J = 11.8 Hz, 2H), 1.80 (s, 3H), 1.79 – 1.72 (m, 2H).

¹⁹F NMR (376 MHz, CDCl₃) δ -111.70 (s), -121.32 (s).

Example 19 (the preparation of **29**)



A solution of **28a** (500 mg, 1.28 mmol, 1.0 eqv) in CH₃(OEt)₃ (10 mL) was stirred under N₂ at 120°C overnight. The solvent was removed under reduce pressure and the crude product was purified by column chromatography (PE: EA=1:1) to provide **29**. Yield: 66.0%. (light yellow solid)

Melting Point: 147.2°C

[ES-MS] (ESI⁺): m/z calcd for C₂₃H₂₃F₂N₃O₂ [M + H]⁺, 412.2; found, 412.2

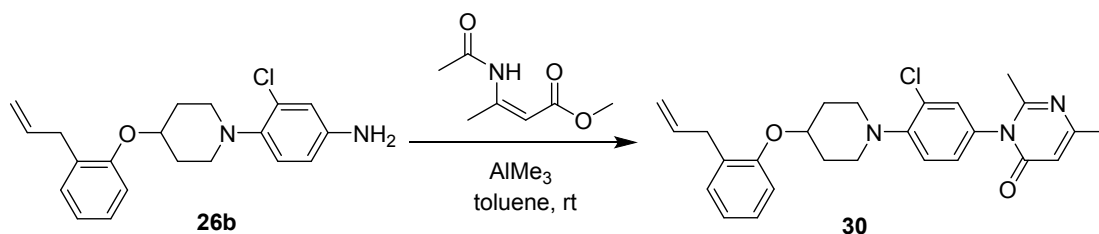
¹H NMR (400 MHz, DMSO) δ 7.37 – 7.25 (m, 2H), 7.21 (t, J = 9.0 Hz, 1H), 7.12 (dd, J = 8.5, 1.7 Hz, 1H), 6.90 (dd, J = 11.4, 2.2 Hz, 1H), 6.88 – 6.83 (m, 1H), 6.76 (td, J = 8.4, 1.8 Hz, 1H), 6.33 (s, 1H), 4.70 – 4.59 (m, 1H), 3.35 (d, J = 13.6 Hz, 2H), 3.05 (dd, J = 21.7, 9.5 Hz, 2H), 2.26 (s, 3H), 2.16 (s, 3H), 2.11 (d, J = 10.5 Hz, 2H), 1.80 (d, J = 8.7 Hz, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 164.89, 163.07, 162.48 (d, $J = 3.5$ Hz), 158.69 (t, $J = 5.3$ Hz), 156.67, 154.19, 141.21 (d, $J = 8.3$ Hz), 130.49 (d, $J = 9.6$ Hz), 130.30 (d, $J = 10.1$ Hz), 123.67 (d, $J = 3.3$ Hz), 119.82 (d, $J = 3.8$ Hz), 115.81 (d, $J = 23.1$ Hz), 111.73 (d, $J = 2.7$ Hz), 110.75, 107.69 (d, $J = 21.3$ Hz), 103.62 (d, $J = 24.4$ Hz), 72.10, 47.49 (d, $J = 3.8$ Hz), 47.35 (d, $J = 3.2$ Hz), 30.70, 23.82, 23.71.

^{19}F NMR (376 MHz, CDCl_3) δ -111.56 (s), -118.88 (s).

HPLC: purity = 98.20%

Example 20 (the preparation of **30**)



A solution of **26b** (370 mg, 1.08 mmol, 1.0 eqv) in toluene (5 mL) was stirred at r.t. under N_2 . Then 2M Me_3Al in toluene (2.2mL, 4.4 mmol, 4.0 eqv) was added dropwise. After the Addition was completed, the mixture was stirred at r.t. for another 30 min. Then a solution of (Z)-methyl 3-acetamidobut-2-enoate (203 mg, 1.29 mmol, 1.2 eqv) in toluene (5 mL) was added to the aforementioned mixture carefully. The mixture was stirred at r.t. for 48 hrs.

The reaction was quenched by saturated NH_4Cl (5 mL) and it was filtered. The organic layer was separated and the aqueous layer was extracted with 50 mL $\times$ 2 DCM. The organic layers were combined, washed with 100 mL of brine and dried over anhydrous Na_2SO_4 . It was then filtered and the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel (PE: EA = 1:1) to provide **30** (150.0 mg) as light yellow oil. Yield: 31%.

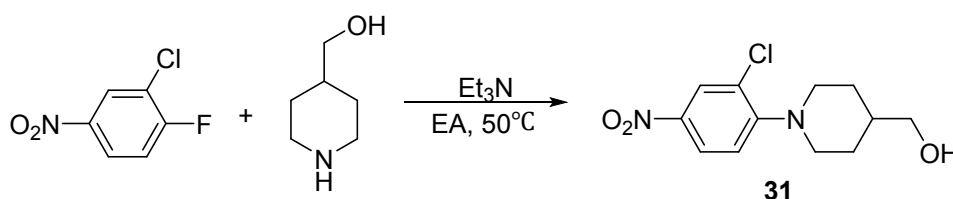
Melting Point: 54.0°C

[ES-MS] (ESI^+): m/z calcd for $\text{C}_{26}\text{H}_{28}\text{ClN}_3\text{O}_2$ [$\text{M} + \text{H}$] $^+$, 450.2; found, 450.2

^1H NMR (400 MHz, CDCl_3) δ 7.22 (d, $J = 2.4$ Hz, 1H), 7.18 (dd, $J = 7.7, 5.5$ Hz, 3H), 7.06 (dd, $J = 8.5, 2.4$ Hz, 1H), 6.91 (t, $J = 7.2$ Hz, 2H), 6.29 (s, 1H), 6.01 (ddt, $J = 16.7, 10.0, 6.6$ Hz, 1H), 5.13 – 5.00 (m, 2H), 4.62 – 4.50 (m, 1H), 3.44 (d, $J = 6.6$ Hz, 2H), 3.40 – 3.23 (m, 2H), 3.16 – 2.96 (m, 2H), 2.30 (s, 3H), 2.19 (s, 3H), 2.14 (dt, $J = 17.1, 8.5$ Hz, 2H), 2.06 (ddd, $J = 13.4, 6.6, 3.3$ Hz, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 163.16, 162.52, 158.58, 154.88, 150.73, 137.12, 131.78, 130.26, 129.73, 129.68, 129.65, 127.23, 126.69, 121.31, 120.67, 115.45, 112.79, 110.85, 71.27, 48.35, 48.28, 34.63, 31.05, 24.00, 23.78.

Example 21 (the preparation of **31**)

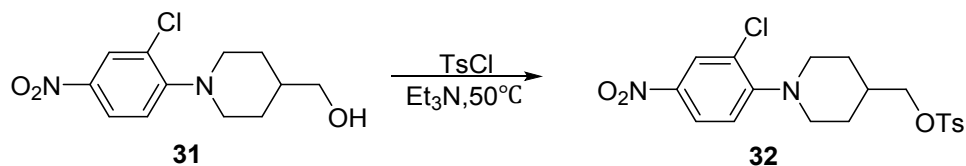


To a solution of 2-chloro-1-fluoro-4-nitrobenzene (3.51 g, 20 mmol, 1.0 eqv) and piperidin-4-ylmethanol (2.53 g, 22 mmol, 1.1 eqv) in EtOAc (30 mL) was added Et_3N (7.29 g, 72 mmol, 3.6 eqv). Then the mixture was stirred at 50°C for 1 hr before it was cooled down to r.t. and stirred for 39 hrs. The solvent was removed by reduced pressure and the crude product was purified by chromatography on silica gel (PE: EA = 10:1-8:1) to get **31** (4.78 g) as a yellow solid. Yield: 88.3%.

[ES-MS] (ESI^+): m/z calcd for $\text{C}_{12}\text{H}_{15}\text{ClN}_2\text{O}_3$ [$\text{M} + \text{H}$] $^+$, 271.1; found, 271.1

^1H NMR (400 MHz, CDCl_3) δ 8.24 (d, $J = 2.6$ Hz, 1H), 8.08 (dd, $J = 9.0, 2.6$ Hz, 1H), 7.05 (d, $J = 9.0$ Hz, 1H), 3.62 (dd, $J = 14.4, 9.1$ Hz, 4H), 2.81 (td, $J = 12.0, 1.9$ Hz, 2H), 1.95 – 1.85 (m, 2H), 1.80 – 1.68 (m, 1H), 1.60 (t, $J = 5.0$ Hz, 1H), 1.51 (qd, $J = 12.3, 3.8$ Hz, 2H).

Example 22 (the preparation of **32**)

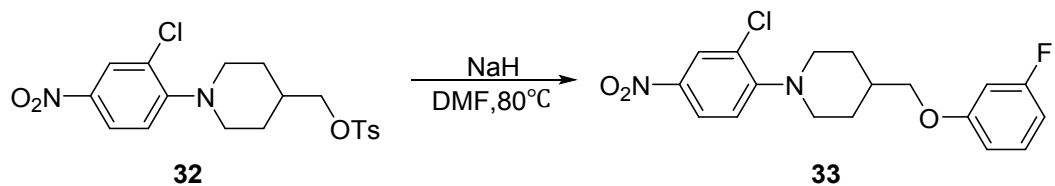


To a solution of **31** (4.78 g, 17.7 mmol, 1.0 eqv) in Et₃N (20 mL) was added 4-methylbenzene-1-sulfonyl chloride (4.04 g, 21.2 mmol, 1.2 eqv). Then the mixture was stirred at 50°C overnight before it was cooled down to r.t.. Water (100 mL) was added to the mixture and it was then extracted by EtOAc (40 mL×3). The organic layer was washed by brine (50 mL), dried over anhydrous Na₂SO₄ and filtered. The solvent was removed by reduced pressure and the crude product was purified by chromatography on silica gel (PE: EA = 10 : 1-4:1) to get **32** (6.75 g) as a yellow solid. Yield: 90.0%.

[ES-MS] (ESI⁺): m/z calcd for C₁₉H₂₁ClN₂O₅S [M + H]⁺, 425.1; found, 425.1

¹H NMR (400 MHz, CDCl₃) δ 8.24 (d, *J* = 2.6 Hz, 1H), 8.08 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 1H), 3.95 (d, *J* = 6.5 Hz, 2H), 3.58 (d, *J* = 12.1 Hz, 2H), 2.76 (dd, *J* = 12.0, 10.4 Hz, 2H), 2.48 (s, 3H), 2.00 – 1.88 (m, 1H), 1.85 (d, *J* = 13.2 Hz, 2H), 1.47 (qd, *J* = 12.4, 3.8 Hz, 2H).

Example 23 (the preparation of **33**)



A solution of 60% NaH (1.91 g, 47.66 mmol, 3.0 eqv) in DMF (50 mL) was stirred at 0°C under N₂. 3-fluorophenol (2.14 g, 19.06 mmol, 1.2 eqv) was added to the mixture carefully. The mixture was stirred for 30 min before **32** (6.75 g, 15.89 mmol, 1.0 eqv) in DMF (10 mL) was added. Then the mixture was stirred at 80°C under N₂ overnight. The mixture was cooled down to r.t. and quenched by H₂O. DCM (100 mL) was added to the mixture and it was washed by H₂O (100 mL×3). The organic layer was dried over

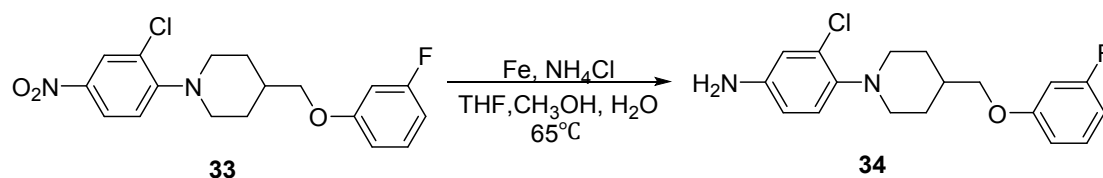
Na₂SO₄, filtered and the solvent was removed by reduced pressure. The crude product was purified by chromatography on silica gel (PE: EA = 10:1-5:1) to provide **33** (2.09 g) as a yellow solid. Yield: 36.0%

[ES-MS] (ESI⁺): m/z calcd for C₁₈H₁₈ClFN₂O₃ [M + H]⁺, 365.1; found, 365.1

¹H NMR (400 MHz, CDCl₃) δ 8.27 (d, *J* = 2.6 Hz, 1H), 8.11 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.27 – 7.21 (m, 1H), 7.07 (d, *J* = 9.0 Hz, 1H), 6.75 – 6.61 (m, 3H), 3.89 (d, *J* = 6.1 Hz, 2H), 3.67 (d, *J* = 12.1 Hz, 2H), 2.90 – 2.80 (m, 2H), 2.01 (d, *J* = 12.5 Hz, 3H), 1.71 – 1.62 (m, 2H).

¹⁹F NMR (376 MHz, CDCl₃) δ -111.63 (s).

Example 24 (the preparation of **34**)



To a solution of **33** (6.01 g, 16.5 mmol, 1.0 eqv) in THF (60 mL), CH₃OH (60 mL) and H₂O (30 mL) was added Fe (4.59 g, 82.2 mmol, 5.0 eqv) and NH₄Cl (1.76 g, 32.9 mmol, 2.0 eqv). Then the mixture was stirred at 60°C overnight. To the mixture was added Et₃N until pH = 10-12 and then filtered through a celite pad. The solvent was removed by reduced pressure. The crude product was dissolved in EtOAc (100 mL) and washed by water (40 mL×3). The organic layer was wash by brine (50 mL), dried over anhydrous Na₂SO₄ and filtered. The solvent was removed by reduced pressure. The crude product was purified by chromatography on silica gel (PE: EA = 6:1-4:1) to provide **34** (3.14 g) as a yellow solid. Yield: 57.0%.

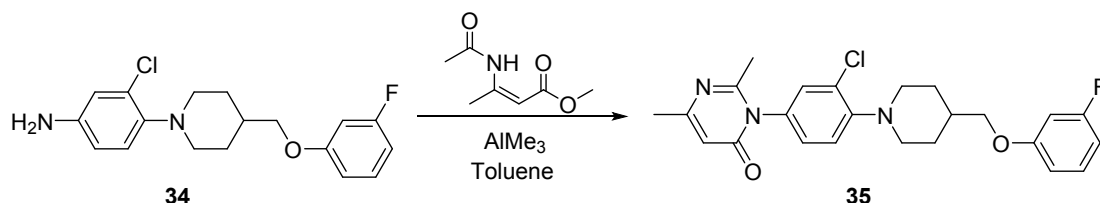
[ES-MS] (ESI⁺): m/z calcd for C₁₈H₂₀ClFN₂O [M + H]⁺, 335.1; found, 335.1

¹H NMR (400 MHz, CDCl₃) δ 7.30 – 7.20 (m, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 6.77 (d, *J* = 2.6 Hz, 1H), 6.75 – 6.62 (m, 3H), 6.58 (dd, *J* = 8.5, 2.7 Hz, 1H), 3.87 (d, *J* = 6.0

Hz, 2H), 3.55 (s, 2H), 3.29 (t, $J = 12.1$ Hz, 2H), 2.64 (t, $J = 10.9$ Hz, 2H), 2.01 – 1.85 (m, 3H), 1.71 – 1.60 (m, 2H).

^{19}F NMR (376 MHz, CDCl_3) δ -111.80 (s).

Example 25 (the preparation of **35**)



A solution of **34** (1.00 g, 3.0 mmol, 1.0 eqv) in toluene (20 mL) was stirred at r.t. under N_2 . Then 2M Me_3Al in toluene (5.3 mL, 10.6 mmol, 3.5 eqv) was added dropwise. After the addition was completed, the mixture was stirred at r.t. for another 30 min before a solution of (Z)-methyl 3-acetamidobut-2-enoate (707 mg, 4.5 mmol, 1.5 eqv) in toluene (5 mL) was added. The reaction mixture was stirred at r.t. for 43 hrs. It was quenched by saturated NH_4Cl solution (50 mL) and the mixture was filtered. The aqueous phase was extracted with EtOAc (30 mL $\times$ 3) and the organic layer was washed with brine (50 mL $\times$ 2), dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (PE: EA =4:1-1:1) to provide **35** (989.0 mg) as a white solid. Yield: 74.6%.

Melting Point: 156.9°C

[ES-MS] (ESI^+): m/z calcd for $\text{C}_{24}\text{H}_{25}\text{ClFN}_3\text{O}_2$ $[\text{M} + \text{H}]^+$, 442.2; found, 442.2

^1H NMR (400 MHz, CDCl_3) δ 7.29 – 7.20 (m, 2H), 7.16 (d, $J = 8.5$ Hz, 1H), 7.05 (dd, $J = 8.5, 2.4$ Hz, 1H), 6.74 – 6.56 (m, 3H), 6.28 (s, 1H), 3.87 (d, $J = 7.8$ Hz, 2H), 3.51 (dd, $J = 34.8, 11.5$ Hz, 2H), 2.75 (dt, $J = 23.8, 12.7$ Hz, 2H), 2.29 (s, 3H), 2.19 (s, 3H), 2.06 – 1.90 (m, 3H), 1.64 (td, $J = 12.4, 3.7$ Hz, 2H).

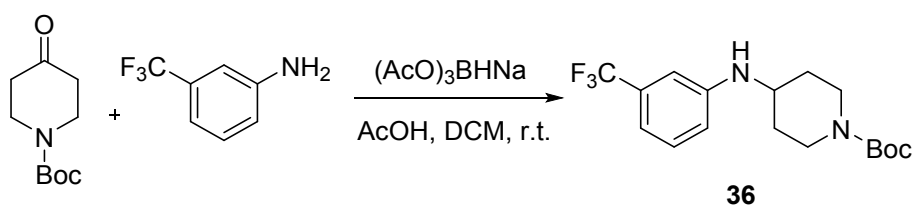
^{13}C NMR (151 MHz, CDCl_3) δ 164.45, 162.98 (d, $J = 47.3$ Hz), 162.51, 160.46 (d, $J = 10.8$ Hz), 158.62, 150.87, 131.66, 130.20 (d, $J = 10.0$ Hz), 129.67, 129.60, 126.66,

121.34, 110.82, 110.32 (d, $J = 2.6$ Hz), 107.42 (d, $J = 21.2$ Hz), 102.17 (d, $J = 24.7$ Hz), 72.72, 51.59, 51.37, 35.68, 29.32, 29.21, 24.00, 23.79.

^{19}F NMR (376 MHz, CDCl_3) δ -111.71 (s).

HPLC: purity = 99.24%

Example 26 (the preparation of **36**)



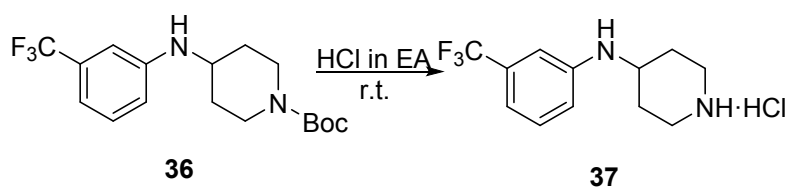
Sodium triacetoxyborohydride (6.38 g, 30.11 mmol, 1.5 equiv) was added portionwise to a solution of 4-Boc-piperidone (4.0 g, 20.08 mmol, 1 equiv), 3-(trifluoromethyl)aniline (3.88 g, 24.09 mmol, 1.2 equiv) and acetic acid (7.23 g, 120.45 mmol, 6 eq.) in dichloroethane (30 mL) at 0 °C. The reaction mixture was allowed to warm up to r.t. over 2 h and then slowly poured into a cold 3M NaOH (100mL) solution. The reaction mixture was then separated and the organic layer was dried over Na_2SO_4 , filtered and concentrated to give a tan solid. The crude product was purified by chromatography on silica gel (PE: EtOAc = 5:1) to get **36** (5.8g) as a white solid. Yield: 98.1%.

[ES-MS] (ESI⁺): m/z calcd for C₁₇H₂₃F₃N₂O₂ [M + H - ^tBu]⁺, 289.1; found, 289.1

¹H NMR (400 MHz, CDCl₃) δ 7.30 – 7.23 (m, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.80 (s, 1H), 6.75 (d, *J* = 8.1 Hz, 1H), 4.16 – 4.00 (m, 2H), 3.78 (d, *J* = 7.8 Hz, 1H), 3.46 (dt, *J* = 17.9, 7.1 Hz, 1H), 2.96 (t, *J* = 11.9 Hz, 2H), 2.04 (dd, *J* = 8.8, 3.8 Hz, 2H), 1.49 (s, 9H), 1.34 (dd, *J* = 16.9, 7.4 Hz, 2H).

¹⁹F NMR (376 MHz, CDCl₃) δ -62.88 (s).

Example 27 (the preparation of **37**)



To a degassed solution of EtOAc (10 mL) was added **36** (6.8 g, 19.75 mmol, 1.00 eqv) and followed by 4M HCl in EtOAc (27mL, 118.5 mmol, 6 eqv). The mixture was stirred under N₂ at r.t. overnight. The solvent was removed under reduced pressure and **37** (5.5 g) was collected as a white solid. Yield: 95%

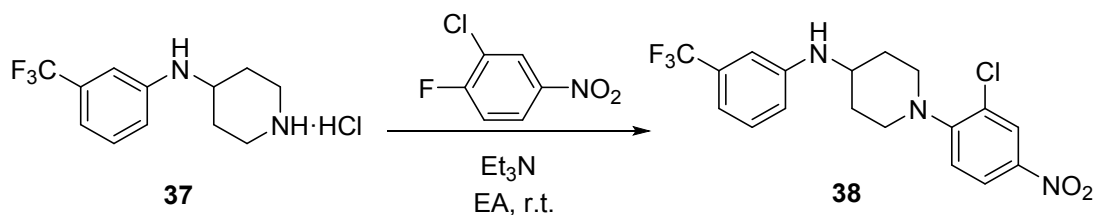
The crude product was taken to the next step without further purification(white solid)

[ES-MS] (ESI⁺): m/z calcd for C₁₂H₁₅F₃N₂ [M + H]⁺, 245.1; found, 245.1

¹H NMR (400 MHz, DMSO) δ 9.14 (d, *J* = 29.0 Hz, 2H), 7.31 (t, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 9.6 Hz, 2H), 6.87 (d, *J* = 7.5 Hz, 1H), 3.68 – 3.57 (m, 1H), 3.28 (d, *J* = 12.7 Hz, 2H), 2.98 (dd, *J* = 21.4, 11.4 Hz, 2H), 2.03 (d, *J* = 11.1 Hz, 2H), 1.66 (td, *J* = 13.6, 3.5 Hz, 2H).

¹⁹F NMR (376 MHz, MeOD) δ -64.33 (s).

Example 28 (the preparation of **38**)



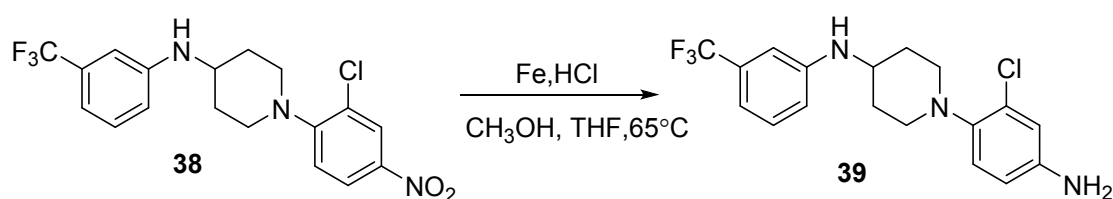
To a degassed solution of EtOAc (30 mL) was added **37** (5.5 g, 19.59 mmol, 1 eqv.) and Et₃N (9.91 g, 97.96 mmol, 3 eq.). Then 2-chloro-1-fluoro-4-nitrobenzene (3.10 g, 17.63 mmol, 0.9 eqv) was added to the mixture and it was stirred under N₂ at r.t. for 24 hrs. The mixture was filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (PE: EtOAc = 8:1) to provide **38** (2.2 g) as yellow oil. Yield: 28.0%.

[ES-MS] (ESI⁺): m/z calcd for C₁₈H₁₇ClF₃N₃O₂ [M + H]⁺, 400.1; found, 400.1

¹H NMR (400 MHz, CDCl₃) δ 8.27 (d, *J* = 2.6 Hz, 1H), 8.12 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.29 (dd, *J* = 9.4, 6.4 Hz, 1H), 7.09 (d, *J* = 9.0 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.84 (s, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 3.86 (s, 1H), 3.59 (t, *J* = 14.5 Hz, 3H), 3.06 – 2.95 (m, 2H), 2.25 (d, *J* = 11.7 Hz, 2H), 1.80 – 1.67 (m, 2H).

¹⁹F NMR (376 MHz, CDCl₃) δ -62.85 (s).

Example 29 (the preparation of **39**)



Concentrated HCl (1.0 mL) was added to iron (3.07 g, 55 mmol, 10 eqv) in water (20 mL). The mixture was heated to 65°C for 15 min. Then the water was decanted and a solution of **38** (2.2 g, 5.5 mmol, 1 eqv) in methanol (10 mL) and THF (10 mL) was added. The mixture was heated to 65°C for 30min. After cooled down to r.t., the reaction pH was adjusted to 10 by adding Et₃N. The mixture was filtered and the solvent was removed under reduced pressure. The resulting residue was dissolved into DCM (100 mL) and washed with water (100 mL*2), brine (100 mL) and dried over anhydrous

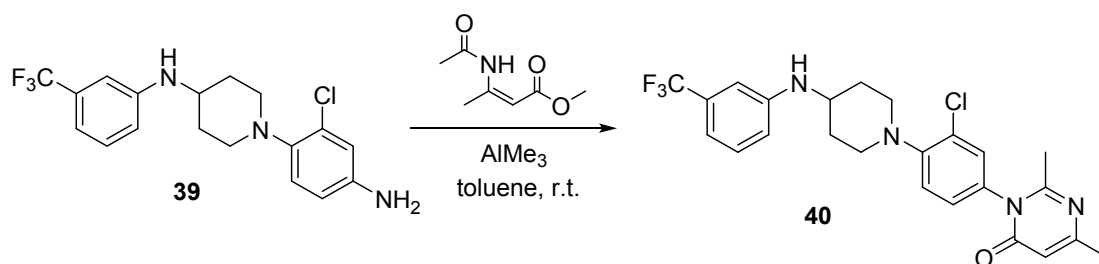
Na₂SO₄. The solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel (PE: EtOAc = 4:1) to provide **39** (1.0 g) as red brown oil. Yield: 50%.

[ES-MS] (ESI⁺): m/z calcd for C₁₈H₁₉ClF₃N₃ [M + H]⁺, 370.1; found, 370.1

¹H NMR (400 MHz, CDCl₃) δ 7.30 (t, *J* = 7.8 Hz, 1H), 6.97 (t, *J* = 8.6 Hz, 2H), 6.88 (s, 1H), 6.79 (t, *J* = 5.7 Hz, 2H), 6.59 (dd, *J* = 8.5, 2.6 Hz, 1H), 3.89 (s, 1H), 3.60 (s, 2H), 3.47 (s, 1H), 3.27 (d, *J* = 12.0 Hz, 2H), 2.79 (dd, *J* = 16.5, 6.0 Hz, 2H), 2.15 (t, *J* = 13.1 Hz, 2H), 1.69 (td, *J* = 13.7, 3.5 Hz, 2H).

¹⁹F NMR (376 MHz, CDCl₃) δ -62.84 (s).

Example 30 (the preparation of **40**)



A solution of **39** (0.95 g, 2.57 mmol, 1.0 eq.) in toluene (5 mL) was stirred at r.t. under N₂. Then 2M Me₃Al in toluene (5.2 mL, 10.4 mmol, 4.0 eq.) was added dropwise. After the addition was completed, the reaction was stirred at r.t. for another 30 min before a solution of (Z)-methyl 3-acetamidobut-2-enoate (485 mg, 3.08 mmol, 1.2 eq.) in toluene (5 mL) was added carefully. Then the reaction mixture was stirred at r.t. for 96 hrs. The reaction was quenched by saturated NH₄Cl (10 mL) and it was filtered. The organic layer was separated and the aqueous layer was extracted with DCM (50 mL×2). The organic layers were combined and washed with brine (100mL), dried over anhydrous Na₂SO₄ and filtered. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (PE: EtOAc = 1:1) to provide **40** (800mg) as light yellow oil. Yield: 65%.

Melting Point: 201.3°C

[ES-MS] (ESI⁺): m/z calcd for C₂₄H₂₄ClF₃N₄O [M + H]⁺, 477.2; found, 477.2

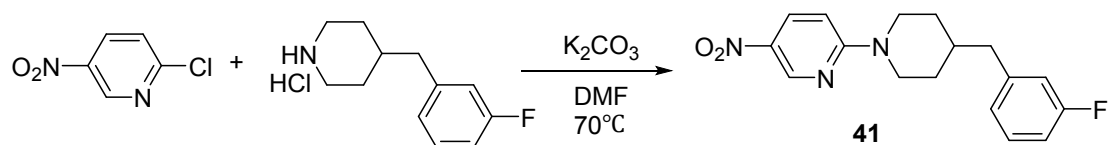
^1H NMR (400 MHz, CDCl_3) δ 7.28 – 7.20 (m, 2H), 7.15 (d, J = 8.5 Hz, 1H), 7.06 (dd, J = 8.5, 2.3 Hz, 1H), 6.91 (d, J = 7.6 Hz, 1H), 6.82 (s, 1H), 6.75 (d, J = 8.1 Hz, 1H), 6.29 (s, 1H), 3.45 (ddd, J = 28.3, 12.9, 9.3 Hz, 3H), 2.86 (dt, J = 20.8, 10.9 Hz, 2H), 2.29 (s, 3H), 2.23 – 2.10 (m, 5H), 1.67 (td, J = 13.6, 3.5 Hz, 2H).

^{13}C NMR (151 MHz, CDCl_3) δ 163.31, 162.56, 158.61, 150.49, 147.29, 131.86, 131.57 (d, J = 31.6 Hz), 129.71 (d, J = 4.4 Hz), 129.65, 126.75, 125.30, 123.49, 121.36, 116.12, 113.49, 113.45 (q, J = 3.5 Hz), 110.79, 109.22 (dd, J = 7.6, 3.7 Hz), 50.38, 50.28, 49.48, 32.48, 32.41, 23.96, 23.75.

^{19}F NMR (376 MHz, CDCl_3) δ -62.86 (s).

HPLC: purity = 98.12%.

Example 31 (the preparation of **41**)



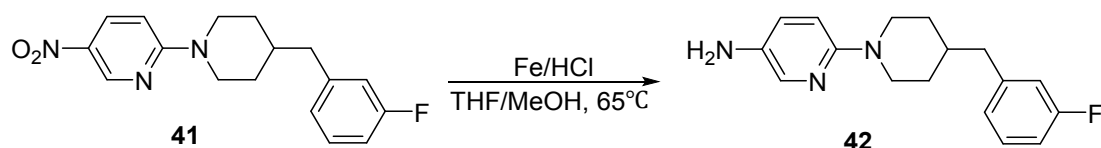
To a solution of 2-chloro-5-nitropyridine (1.59 g, 10.0 mmol, 1.00 eq.) and 4-(3-fluorobenzyl)piperidine hydrochloride (2.76 g, 12.0 mmol, 1.20 eq.) in DMF (20 mL) was added K_2CO_3 (6.91 g, 50.0 mmol, 5.00 eqv). Then the mixture was stirred at 70°C for 4 hrs. It was cooled down to r.t. and H_2O (180 mL) was added to the mixture. The solution was then extracted by EtOAc (30 mL $\times$ 6) and the organic layer was washed by water (50 mL $\times$ 3), brine (50 mL $\times$ 2), dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel (PE: EtOAc = 8:1-4:1) to provide **41** (3.13 g) as a yellow solid. Yield: 99.3%.

[ES-MS] (ESI^+): m/z calcd for $\text{C}_{17}\text{H}_{18}\text{FN}_3\text{O}_2$ [$\text{M} + \text{H}$] $^+$, 316.1; found, 316.1

¹H NMR (400 MHz, DMSO) δ 8.94 (d, J = 2.8 Hz, 1H), 8.17 (dd, J = 9.6, 2.8 Hz, 1H), 7.33 (dd, J = 14.3, 7.9 Hz, 1H), 7.07 – 6.98 (m, 3H), 6.92 (d, J = 9.7 Hz, 1H), 4.52 (d, J = 10.9 Hz, 2H), 2.99 (t, J = 11.8 Hz, 2H), 2.56 (d, J = 7.2 Hz, 2H), 1.91 (ddd, J = 14.7, 7.5, 3.7 Hz, 1H), 1.67 (d, J = 12.6 Hz, 2H), 1.26 – 1.05 (m, 2H).

¹⁹F NMR (376 MHz, CDCl₃) δ -113.62 (s).

Example 32 (the preparation of **42**)



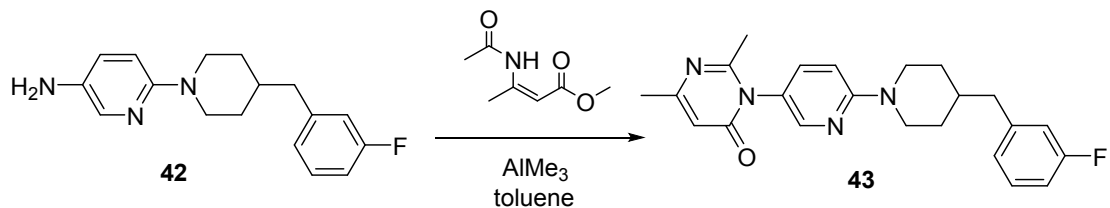
Concentrated HCl (0.5 mL) was added to iron (5.54 g, 99.3 mmol, 10 eq.) in water (20 mL). The mixture was heated to 65°C for 15 min and the water was decanted. Then a solution of **41** (3.13 g, 9.93 mmol, 1 eq.) in THF (30 mL) and H₂O (30 mL) were added. The mixture was acidified to pH 2~3 with con. HCl. Then the mixture was stirred at 65°C for 2hrs. After it was cooled down to r.t., the reaction pH was adjusted to 10 by adding Et₃N. The solution was filtered and the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel (PE: EtOAc = 8:1-1:1) to provide **42** (2.13 g) as red oil. Yield: 75.2%.

[ES-MS] (ESI⁺): m/z calcd for C₁₇H₂₀FN₃ [M + H]⁺, 286.2; found, 286.2

¹H NMR (400 MHz, DMSO) δ 7.58 (d, J = 2.5 Hz, 1H), 7.32 (dd, J = 14.3, 7.6 Hz, 1H), 7.07 – 6.96 (m, 3H), 6.89 (dd, J = 8.8, 2.9 Hz, 1H), 6.60 (d, J = 8.8 Hz, 1H), 4.55 (s, 2H), 3.94 (d, J = 12.7 Hz, 2H), 2.54 (d, J = 7.1 Hz, 2H), 2.51 (d, J = 1.8 Hz, 2H), 1.67 (ddd, J = 11.1, 7.4, 3.7 Hz, 1H), 1.58 (d, J = 12.9 Hz, 2H), 1.19 (dd, J = 12.0, 3.2 Hz, 2H).

¹⁹F NMR (376 MHz, CDCl₃) δ -114.00 (s).

Example 33 (the preparation of **43**)



A solution of **42** (1.0 g, 3.50 mmol, 1.0 eq.) in toluene (20 mL) was stirred at r.t. under N₂. Then 2M Me₃Al in toluene (7 mL, 14 mmol, 4.0 eq.) was added dropwise. After the addition was completed, the reaction was stirred at r.t. for another 30 min before a solution of (Z)-methyl 3-acetamidobut-2-enoate (826 mg, 5.26 mmol, 1.5 eq.) in toluene (5 mL) was added to the reaction mixture carefully. The reaction mixture was stirred at r.t. for 67 hrs and was quenched by saturated NH₄Cl solution (50 mL). The mixture was filtered and the organic layer was separated. The aqueous phase was extracted with EtOAc (20 mL×3) and the organic layers were combined and washed with brine (20 mL×2), dried over anhydrous Na₂SO₄ and filtered. The solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel (PE: EtOAc =2:1-1:2) to provide **43** (0.32 g) as a brown solid. Yield: 23.3%.

Melting Point: 141.7°C

[ES-MS] (ESI⁺): m/z calcd for C₂₃H₂₅FN₄O [M + H]⁺, 393.2; found, 393.2

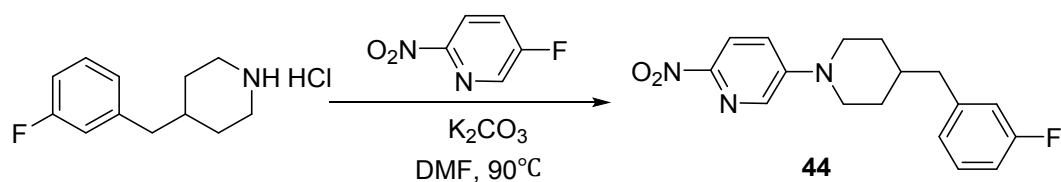
¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, *J* = 2.6 Hz, 1H), 7.27 (dd, *J* = 7.9, 3.2 Hz, 2H), 6.99 – 6.84 (m, 3H), 6.74 (d, *J* = 9.1 Hz, 1H), 6.30 (s, 1H), 4.45 – 4.30 (m, 2H), 2.86 (q, *J* = 13.7 Hz, 2H), 2.59 (d, *J* = 7.0 Hz, 2H), 2.31 (s, 3H), 2.23 (s, 3H), 1.90 – 1.80 (m, 1H), 1.75 (t, *J* = 15.8 Hz, 3H), 1.31 (dd, *J* = 12.0, 3.6 Hz, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 163.64, 162.94 (d, *J* = 21.0 Hz), 162.02, 159.32, 158.87, 146.25, 142.78 (d, *J* = 7.1 Hz), 136.37, 129.66 (d, *J* = 8.3 Hz), 124.79 (d, *J* = 2.6 Hz), 122.78, 115.82 (d, *J* = 20.6 Hz), 112.85 (d, *J* = 21.0 Hz), 110.70, 107.08, 45.44, 45.26, 42.79, 38.06, 31.60, 31.57, 24.10, 23.75.

¹⁹F NMR (376 MHz, CDCl₃) δ -113.82 (s).

HPLC: purity = 97.59%.

Example 34 (the preparation of **44**)



To a solution of 5-fluoro-2-nitropyridine (1.55 g, 10.92 mmol, 1.00 eq.) and 4-(3-fluorobenzyl)piperidine hydrochloride (2.76 g, 12.01 mmol, 1.10 eq.) in DMF (40 mL) was added K_2CO_3 (4.54 g, 32.85 mmol, 3.00 eq.). Then the mixture was stirred at 90°C overnight. The mixture was cooled down to r.t. and diluted with DCM (100.0 ml). The organic layer was then washed by H_2O (100 mL $\times$ 2), brine (100 mL $\times$ 2) and dried over anhydrous Na_2SO_4 . The solution was filtered and the solvent was removed under reduced pressure. **44** (2.17 g) was collected as yellow oil. Yield: 63.0%.

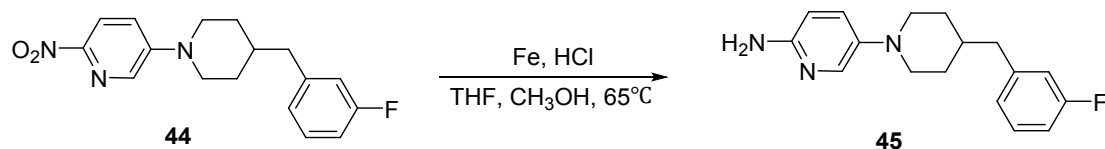
[ES-MS] (ESI^+): m/z calcd for $\text{C}_{17}\text{H}_{18}\text{FN}_3\text{O}_2$ $[\text{M} + \text{H}]^+$, 316.1; found, 316.2

^1H NMR (400 MHz, DMSO) δ 8.23 (d, $J = 3.0$ Hz, 1H), 8.12 (d, $J = 9.3$ Hz, 1H), 7.44 (dd, $J = 9.3, 3.0$ Hz, 1H), 7.33 (dd, $J = 14.3, 7.9$ Hz, 1H), 7.03 (t, $J = 8.8$ Hz, 3H), 4.08 (d, $J = 13.4$ Hz, 2H), 2.97 (t, $J = 11.8$ Hz, 2H), 2.57 (d, $J = 7.2$ Hz, 2H), 1.87 (ddd, $J = 11.2, 7.4, 3.9$ Hz, 1H), 1.66 (d, $J = 12.7$ Hz, 2H), 1.29 – 1.17 (m, 2H).

^{19}F NMR (376 MHz, CDCl_3) δ -113.54 (s).

The crude product was taken to the next step without further purification.

Example 35 (the preparation of **45**)



Concentrated HCl (1.0 mL) was added to iron (3.84 g, 68.81 mmol, 10 eq.) in water (40 mL) and the mixture was heated to 65°C for 15 min. The water was then decanted and a solution of **44** (2.17 g, 6.88 mmol, 1 eq.) in methanol (50 mL) and THF (50 mL) was added. The mixture was acidified to pH 2~3 with con. HCl. Then the mixture was

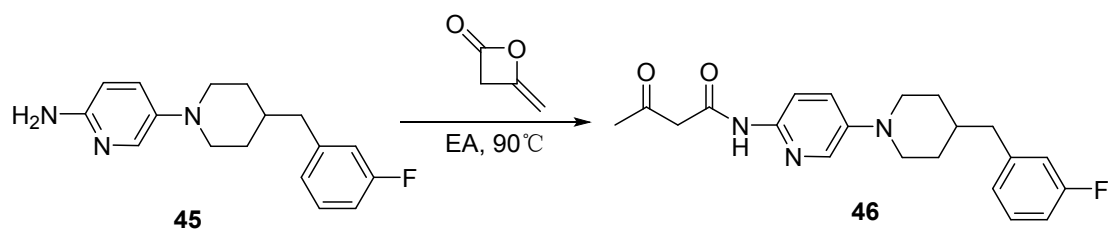
stirred at 65°C overnight. After cooled down to r.t., the reaction pH was adjusted to 10 by adding Et₃N. The mixture was filtered and the solvent was removed under reduced pressure. The resulting residue was dissolved in DCM (100 mL) and washed with water (100 mL×2) and brine (100 mL×2). The solution was dried over anhydrous Na₂SO₄, filtered and the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel (PE: EtOAc =1:1) to provide **45** (1.13 g) as a light yellow solid. Yield: 57.6%.

[ES-MS] (ESI⁺): m/z calcd for C₁₇H₂₀FN₃ [M + H]⁺, 286.2; found, 286.2

¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, *J* = 2.6 Hz, 1H), 7.30 – 7.24 (m, 1H), 7.18 (dd, *J* = 8.8, 2.9 Hz, 1H), 6.91 (ddd, *J* = 8.7, 7.6, 4.4 Hz, 3H), 6.48 (d, *J* = 8.5 Hz, 1H), 4.19 (s, 2H), 3.40 (d, *J* = 12.0 Hz, 2H), 2.58 (dd, *J* = 18.2, 4.8 Hz, 4H), 1.76 (d, *J* = 13.1 Hz, 2H), 1.64 (dtd, *J* = 14.6, 7.4, 3.7 Hz, 1H), 1.44 (qd, *J* = 12.3, 3.8 Hz, 2H).

¹⁹F NMR (376 MHz, CDCl₃) δ -113.94 (s).

Example 36 (the preparation of **46**)



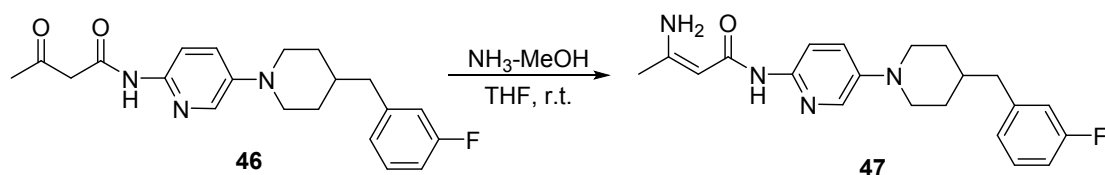
A solution of **45** (1.13 g, 3.96mmol, 1.00 eq.) in EtOAc (45mL) was stirred at r.t. and 4-methyleneoxetan-2-one (666 mg, 7.92 mmol, 2.00 eq.) was added. Then the reaction mixture was stirred and heated to 90°C under N₂ overnight. After the reaction was cooled down to r.t., the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel (PE: EtOAc =1:1) to provide **46** (1.07 g) as a light yellow solid. Yield: 73.1%.

[ES-MS] (ESI⁺): m/z calcd for C₂₁H₂₄FN₃O₂ [M + H]⁺, 370.2; found, 370.2

^1H NMR (400 MHz, DMSO) δ 10.24 (d, J = 44.1 Hz, 1H), 7.96 (d, J = 2.6 Hz, 1H), 7.88 (d, J = 9.0 Hz, 1H), 7.40 – 7.28 (m, 2H), 7.01 (dd, J = 13.8, 8.0 Hz, 3H), 3.62 (d, J = 12.3 Hz, 2H), 3.57 (s, 2H), 2.58 (dd, J = 20.1, 8.7 Hz, 4H), 2.17 (s, 3H), 1.73 – 1.57 (m, 3H), 1.32 – 1.24 (m, 2H).

^{19}F NMR (376 MHz, CDCl_3) δ -113.84 (s).

Example 37 (the preparation of **47**)



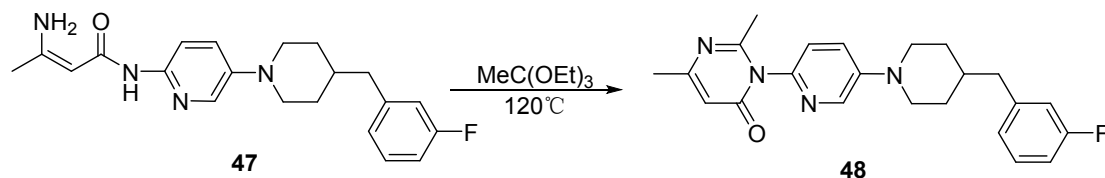
A solution of **46** (1.07 g, 2.90 mmol, 1.00 eq.) in methanol (2.0 mL) and $\text{NH}_3\text{-MeOH}$ (7 mol/L in methanol, 5.0 mL, 35 mmol, 12.0 eq.) was stirred at r.t. overnight. Then the solvent was removed under reduced pressure to provide **47** (1.07 g) as a light yellow solid. Yield: 98.3%. The crude product was taken to the next step without further purification.

[ES-MS] (ESI^+): m/z calcd for $\text{C}_{21}\text{H}_{25}\text{FN}_4\text{O}$ $[\text{M} + \text{H}]^+$, 369.2; found, 369.2

^1H NMR (400 MHz, DMSO) δ 9.35 (s, 1H), 7.96 (d, J = 9.1 Hz, 1H), 7.88 (d, J = 2.8 Hz, 1H), 7.36 – 7.26 (m, 2H), 7.07 – 6.98 (m, 3H), 4.65 (s, 1H), 3.56 (d, J = 12.5 Hz, 2H), 2.56 (t, J = 10.0 Hz, 4H), 1.78 (s, 3H), 1.65 (t, J = 11.2 Hz, 3H), 1.35 – 1.26 (m, 2H).

^{19}F NMR (376 MHz, CDCl_3) δ -113.89 (s).

Example 38 (the preparation of **48**)



A solution of **47** (1.07 g, 2.90 mmol, 1.00 eq.) in MeC(OEt)₃ (35 mL, 188.80 mmol, 35.00 eq.) was stirred and heated to 120°C under N₂ overnight. After the mixture was cooled down to r.t., the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel (PE: EtOAc =1:1) to provide **48** (755.0 mg) as a light yellow solid. Yield: 66.2%.

Melting Point: 150.0°C

[ES-MS] (ESI⁺): m/z calcd for C₂₃H₂₅FN₄O [M + H]⁺, 393.2; found, 393.2

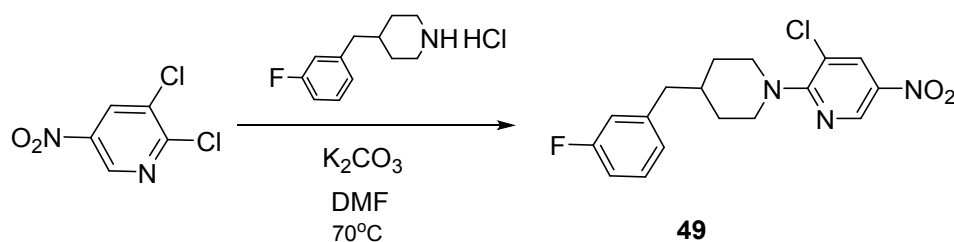
¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, *J* = 2.6 Hz, 1H), 7.31 – 7.18 (m, 2H), 7.10 (d, *J* = 8.7 Hz, 1H), 6.96 – 6.82 (m, 3H), 6.24 (s, 1H), 3.74 (d, *J* = 12.4 Hz, 2H), 2.77 (t, *J* = 11.7 Hz, 2H), 2.57 (d, *J* = 6.6 Hz, 2H), 2.25 (s, 3H), 2.14 (s, 3H), 1.73 (dd, *J* = 22.6, 7.9 Hz, 3H), 1.44 – 1.30 (m, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 164.02, 162.93 (d, *J* = 48.1 Hz), 161.58, 158.75, 147.27, 142.60 (d, *J* = 7.1 Hz), 140.37, 137.18, 129.69 (d, *J* = 8.3 Hz), 124.75 (d, *J* = 2.7 Hz), 124.00, 122.64, 115.77 (d, *J* = 20.6 Hz), 112.87 (d, *J* = 21.0 Hz), 110.82, 48.32, 42.59, 37.34, 31.39, 23.74, 23.18.

¹⁹F NMR (376 MHz, CDCl₃) δ -113.72 (s).

HPLC: purity = 95.88%.

Example 39 (the preparation of **49**)



To a degassed solution of DMF (30mL) was added

4-(3-fluorobenzyl)piperidine hydrochloride (4.29g, 18.65mmol, 1.20eq.) and KHCO₃ (4.5367g, 32.82mmol, 3.20eq.) followed by 2,3-dichloro-5-nitropyridine (3.00g, 15.55mmol, 1.00eq.). The mixture was stirred under N₂ at r.t. overnight. After the reaction was completed, it was cooled down to r.t. and

DCM (100 ml) was poured into the mixture. The mixture was washed with H₂O (100 mL×2), brine (100 mL×2), dried over anhydrous Na₂SO₄ and filtered.

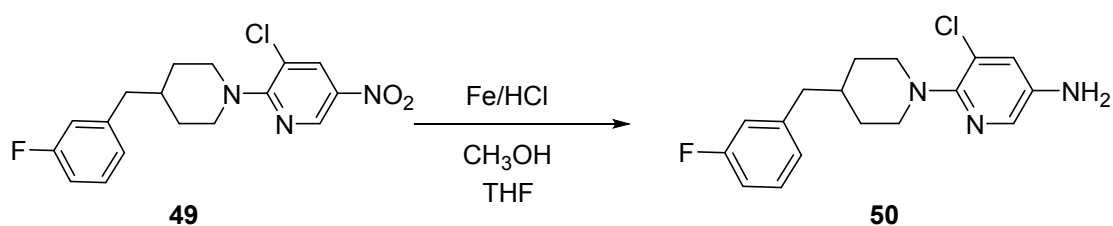
The solvent was removed under reduced pressure. The crude product **49** was taken to the next step without further purification.(yellow solid)

[ES-MS] (ESI⁺): m/z calcd for C₁₇H₁₇ClFN₃O₂ [M + H]⁺, 350.1; found, 350.1

¹H NMR (400 MHz, DMSO) δ 8.92 (d, *J* = 2.4 Hz, 1H), 8.38 (d, *J* = 2.4 Hz, 1H), 7.32 (dd, *J* = 14.2, 7.5 Hz, 1H), 7.06 – 6.95 (m, 3H), 4.24 (d, *J* = 13.1 Hz, 2H), 2.97 (t, *J* = 11.9 Hz, 2H), 2.55 (t, *J* = 10.3 Hz, 2H), 1.85 (ddd, *J* = 11.1, 7.4, 3.8 Hz, 1H), 1.68 (d, *J* = 11.7 Hz, 2H), 1.29 (qd, *J* = 12.8, 3.5 Hz, 2H).

¹⁹F NMR (376 MHz, CDCl₃) δ -113.70 (s).

Example 40 (the preparation of **50**)



To a solution of 8ml HCl in 50ml H₂O was added iron (10.25g, 183.54mmol, 10eq.) carefully. Then the mixture was stirred at 65°C under N₂ for 15 min. The water was decanted and the solution of **49** (6.42g, 18.35mmol, 1eq.) in THF (70 ml) and MeOH (70 ml) was added to the mixture. Then the con. HCl was added to bring the pH to 2~3. The mixture was stirred at 65°C overnight. The reaction mixture was cooled down to r.t. Then Et₃N was added to bring the pH to 10. The mixture was filtered and the solvent was removed under reduced pressure. The crude product was purified by chromatography (PE: EA= 6:10-4:1) to provide **50** (4.55g) as brown oil. Yield: 77.5%.

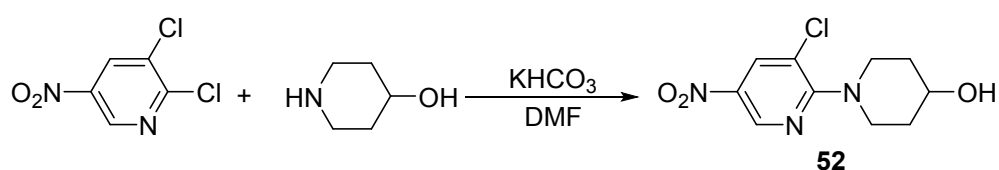
[ES-MS] (ESI⁺): m/z calcd for C₁₇H₁₉ClFN₃ [M + H]⁺, 320.1; found, 320.1

^{13}C NMR (101 MHz, CDCl_3) δ 164.03, 162.81 (d, $J = 98.6$ Hz), 161.59, 158.74, 158.44, 144.08, 142.95 (d, $J = 7.1$ Hz), 137.87, 129.61 (d, $J = 8.3$ Hz), 126.77, 124.77 (d, $J = 2.6$ Hz), 121.91, 115.81 (d, $J = 20.6$ Hz), 112.76 (d, $J = 21.0$ Hz), 110.65, 49.27, 42.88, 37.81, 32.01, 24.04, 23.74.

^{19}F NMR (376 MHz, CDCl_3) δ -113.88 (s).

HPLC: purity=97.50%.

Example 42 (the preparation of **52**)



To a solution of 2,3-dichloro-5-nitropyridine (1.93 g, 10.0 mmol, 1.00 eq.) and piperidin-4-ol (1.11 g, 11.0 mmol, 1.10 eq.) in DMF (20 mL) was added K_2CO_3 (2.00 g, 20.0 mmol, 2.00 eq.). Then the mixture was stirred at r.t. for 1 h. To the mixture was added H_2O (50 mL) and the precipitate was filtered and washed by water. The precipitate was dissolved in DCM and dried over anhydrous Na_2SO_4 . After filtration, the solvent was removed under reduced pressure to provide **52** (2.78 g) as a yellow solid.

[ES-MS] (ESI^+): m/z calcd for $\text{C}_{10}\text{H}_{12}\text{ClN}_3\text{O}_3$ [$\text{M} + \text{H}$] $^+$, 258.1; found, 258.1

^1H NMR (400 MHz, DMSO) δ 8.96 (d, $J = 2.4$ Hz, 1H), 8.49 – 8.36 (m, 1H), 4.80 (d, $J = 4.1$ Hz, 1H), 4.01 – 3.93 (m, 2H), 3.78 (dt, $J = 12.3, 4.1$ Hz, 1H), 3.41 – 3.33 (m, 2H), 1.87 (dd, $J = 8.1, 4.1$ Hz, 2H), 1.57 – 1.45 (m, 2H).

Example 43 (the preparation of **53**)

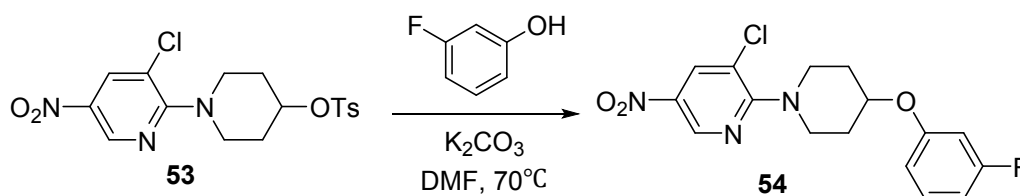


To a solution of **52** (2.78 g, 10.8 mmol, 1.00 eq.) in Et₃N (50 mL) was added 4-methylbenzene-1-sulfonyl chloride (9.88 g, 52 mmol, 4.8 eq.) and DMAP (264 mg, 2.20 mmol, 0.20 eq.). Then the mixture was stirred at 50°C overnight. The reaction mixture was cooled down to r.t. and was filtered. The solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel (PE : EtOAc = 10:1-1:1) to provide **53** (4.06 g) as a yellow solid. Yield: 91.3%.

[ES-MS] (ESI⁺): m/z calcd for C₁₇H₁₈ClN₃O₅S [M + H]⁺, 412.1; found, 412.1

¹H NMR (400 MHz, DMSO) δ 8.96 (d, *J* = 2.4 Hz, 1H), 8.46 (d, *J* = 2.4 Hz, 1H), 7.84 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 4.84 (tt, *J* = 7.8, 3.9 Hz, 1H), 3.85 – 3.74 (m, 2H), 3.49 (dd, *J* = 9.3, 4.1 Hz, 2H), 2.43 (s, 3H), 1.96 – 1.85 (m, 2H), 1.78 – 1.67 (m, 2H).

Example 44 (the preparation of **54**)



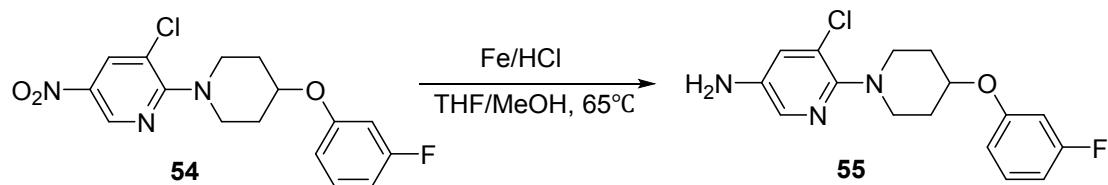
To a solution of **53** (4.06 g, 9.86 mmol, 1.00 eq.) and 3-fluorophenol (1.33 g, 11.83 mmol, 1.20 eq.) in DMF (60 mL) was added K₂CO₃ (2.73 g, 19.72 mmol, 2.00 eq.). Then the mixture was stirred at 80°C for 48 hrs. It was then filtered and the solvent was removed by reduced pressure. The crude product was purified by chromatography on silica gel (PE : EtOAc = 50:1) to provide **54** (1.28 g) as yellow oil. Yield: 36.9%.

[ES-MS] (ESI⁺): m/z calcd for C₁₆H₁₅ClFN₃O₃ [M + H]⁺, 352.1; found, 352.1

¹H NMR (400 MHz, DMSO) δ 8.93 (d, *J* = 2.4 Hz, 1H), 8.39 (d, *J* = 2.4 Hz, 1H), 7.29 (dd, *J* = 15.5, 8.2 Hz, 1H), 6.91 – 6.80 (m, 2H), 6.73 (td, *J* = 8.4, 1.8 Hz, 1H), 4.71 (dt, *J* = 11.2, 3.7 Hz, 1H), 3.94 (ddd, *J* = 9.7, 5.9, 3.3 Hz, 2H), 3.59 – 3.48 (m, 2H), 2.14 – 2.03 (m, 2H), 1.80 – 1.69 (m, 2H).

^{19}F NMR (376 MHz, CDCl_3) δ -111.38 (s).

Example 45 (the preparation of **55**)



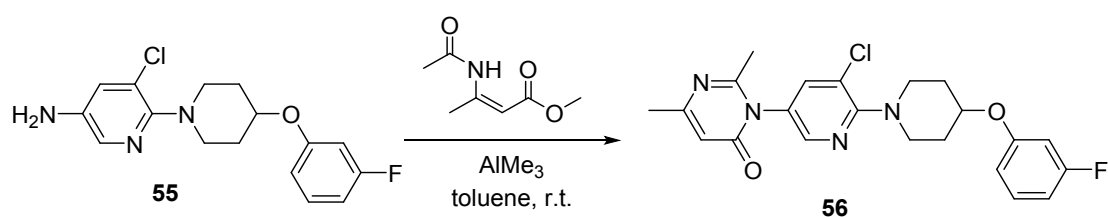
Concentrated HCl (0.5 mL) was added to iron (2.03 g, 36.3 mmol, 10 eq.) in water (20 mL). The mixture was heated to 65°C for 15 min and the water was decanted. Then a solution of **54** (1.28 g, 3.63 mmol, 1 eq.) in THF (20 mL) and CH_3OH (20 mL) was added. The pH of mixture was acidified to 2~3 with *con.* HCl. Then the mixture was stirred at 65°C for 3 hrs. After cooled down to r.t., the reaction pH was adjusted to 10 by adding Et_3N . The mixture was filtered and the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel (PE: EtOAc = 8:1-1:1) to provide **55** (776.0 mg) as brown oil. Yield: 66.4%.

[ES-MS] (ESI^+): m/z calcd for $\text{C}_{16}\text{H}_{17}\text{ClFN}_3\text{O}$ $[\text{M} + \text{H}]^+$, 322.1; found, 322.1

^1H NMR (400 MHz, DMSO) δ 7.65 (d, $J = 2.5$ Hz, 1H), 7.29 (dd, $J = 15.6, 8.1$ Hz, 1H), 7.07 (d, $J = 2.5$ Hz, 1H), 6.91 – 6.77 (m, 2H), 6.73 (td, $J = 8.5, 1.9$ Hz, 1H), 5.15 (s, 2H), 4.63 – 4.46 (m, 1H), 3.30 – 3.21 (m, 2H), 2.97 – 2.86 (m, 2H), 2.03 (d, $J = 11.5$ Hz, 2H), 1.80 – 1.68 (m, 2H).

^{19}F NMR (376 MHz, CDCl_3) δ -111.76 (d, $J = 12.1$ Hz).

Example 46 (the preparation of **56**)



A solution of **55** (776 mg, 2.41 mmol, 1.0 eq.) in toluene (20 mL) was stirred at r.t. under N₂. Then 2M Me₃Al in toluene (5.0 mL, 10 mmol, 4.0 eq.) was added dropwise. After the addition was completed, the mixture was stirred at r.t. for another 30 min before a solution of (Z)-methyl 3-acetamidobut-2-enoate (569 mg, 3.62 mmol, 1.5 eq.) in toluene (5 mL) was added carefully. The reaction mixture was stirred at r.t. for 42 hrs and it was quenched by saturated NH₄Cl solution (50 mL). The mixture was filtered and the organic layer was separated. The aqueous layer was extracted with EtOAc (20 mL×3). The organic layers were combined and washed with brine (20 mL×2), dried over anhydrous Na₂SO₄ and filtered. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (PE: EtOAc = 1:1-1:3) to provide **56** (340.0 mg) as yellow oil. Yield: 33%.

Melting Point: 157.7°C

[ES-MS] (ESI⁺): m/z calcd for C₂₂H₂₂ClFN₄O₂ [M + H]⁺, 429.1; found, 429.2

¹H NMR (400 MHz, CDCl₃) δ 8.00 (d, *J* = 2.0 Hz, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.21 (dd, *J* = 15.4, 8.1 Hz, 1H), 6.71 (d, *J* = 8.7 Hz, 1H), 6.64 (t, *J* = 7.9 Hz, 2H), 6.27 (s, 1H), 4.56 – 4.46 (m, 1H), 3.79 – 3.65 (m, 2H), 3.36 (d, *J* = 8.6 Hz, 2H), 2.28 (s, 3H), 2.21 (s, 3H), 2.17 – 2.07 (m, 2H), 1.97 (d, *J* = 3.3 Hz, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 164.48, 163.13 (d, *J* = 82.1 Hz), 162.36, 158.69 (d, *J* = 10.7 Hz), 158.50, 158.39, 144.16, 137.99, 130.29 (d, *J* = 10.1 Hz), 127.15, 122.06, 111.75, 110.71, 107.70 (d, *J* = 21.3 Hz), 103.64 (d, *J* = 24.3 Hz), 72.51, 45.97, 45.86, 30.58, 30.54, 24.11, 23.80.

¹⁹F NMR (376 MHz, CDCl₃) δ -111.60 (s).

HPLC: purity = 94.95%.

