Supporting Information

Stereoselective synthesis of a KRAS^{G12C} inhibitor with quinoline-piperazine scaffold

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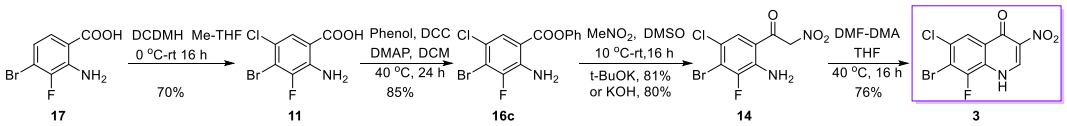
1. General Methods

Unless otherwise indicated, all starting materials purchased from commercial suppliers were used without further purification. All reactions that require heating were conducted with an oil bath as the heat source, unless otherwise noted. Melting points (M. P.) were recorded on a melting point apparatus (INESA WRS-2C). NMR data were obtained for ^{1}H NMR at 400 MHz, ^{19}F NMR at 565 MHz, and for ^{13}C NMR at 151 MHz. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard in $CDCl_3$ or DMSO-d_6 solution. NMR data are reported as follows: chemical shifts, multiplicity (s: singlet, d: doublet, dd: doublet of doublets, t: triplet, q: quartet, p: quintet, m: multiplet, br: broad signal), coupling constant (Hz), and integration. ESI HRMS was recorded on a Agilent 1290–6546 UPLC-QTOF. TLC was performed on glass-backed silica plates. UV detection was monitored at 254 nm. Column chromatography was performed on silica gel (300-400 mesh).

2. Synthesis of the indole intermediate 3



2-Amino-4-bromo-5-chloro-3-fluorobenzoic acid (11)

The solution of **17** (15.4 g, 66 mmol, 1 equiv) in Me-THF (80 mL) was slowly added DCDMH (14.3 g, 72.7 mmol, 1.1 equiv) at 0 °C, stirred at room temperature for 16 hours. Then EA (65 mL) and 20% sodium thiosulfate (65 mL) were added, stirred for 30 minutes. The mixture was extracted with ethyl acetate (60 mL × 2). The combined organic phase was washed with saturated sodium carbonate and the organic solvent was removed in vacuo and purification by silica gel column chromatography (PE: EA = 3: 1 with glacial acetic acid 1%, Rf = 0.3) to give brown solid **11** (12.3 g, 70%).

M. P. 252.3-254.7 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67 (d, J = 2.0 Hz, 1H), 6.90 (s, 2H).

Phenyl 2-amino-4-bromo-5-chloro-3-fluorobenzoate (16c)

To a solution of **11** (12 g, 44.7 mmol, 1 equiv) in DCM (120 mL) was added DCC (13.8 g, 67 mmol 1.5 equiv), DMAP (5.45 g, 44.7 mmol, 1 equiv), phenol (5.04 g, 53.6 mmol, 1.2 equiv). The mixture was reflux at 40 °C for 24 h. Then H_2O (80 mL) was added. The aqueous phase was extracted with ethyl acetate (60 mL × 2). The combined organic phase was removed in vacuo, and purified by silica gel column chromatography (PE: EA = 20:1 with 5% glacial acetic acid, Rf = 0.2) to give **16c** as a white solid (13 g, 85%).

M. P. 128.8-130.9 °C.

^{1}H NMR (400 MHz, Chloroform-d) δ 8.01 (d, J = 2.0 Hz, 1H), 7.45 (t, J = 7.9 Hz, 2H), 7.30 (t, J = 7.5 Hz, 1H), 7.21 – 7.14 (m, 2H), 6.03 – 5.83 (m, 2H).

^{13}C NMR (151 MHz, Chloroform-d) δ 165.0 (d, J = 3.0 Hz), 150.3, 149.0 (d, J = 241.6 Hz), 139.3 (d, J = 16.6 Hz), 129.6, 126.5 (d, J = 4.5 Hz), 126.3, 121.7, 120.6, 117.0 (d, J = 19.6 Hz), 110.5 (d, J = 4.5 Hz).

^{19}F NMR (565 MHz, Chloroform-d) δ -121.31.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{13}H_9BrClFNO_2^+$ 343.9484; Found 343.9485.

1-(2-Amino-4-bromo-5-chloro-3-fluorophenyl)-2-nitroethan-1-one (14)

The solution of t-BuOK (11.6 g, 104 mmol, 3 equiv) in DMSO (120 mL) was added $MeNO_2$ (6.3 g, 104 mmol, 3 equiv) dropwise at 10 °C, stirred for 20 min, and then dropwise added **16c** (12 g, 34.7 mmol, 1 equiv) in DMSO (120 mL), then rised to room temperature and continued stirring for 16 h. Then the mixture was added to cold H_2O (200 mL). HCl (2 N) was used to adjust pH = 4-5. The mixture was extracted with ethyl acetate (200 mL × 2). The combined organic phase was washed with H_2O and brine, concentrated. The organic solvent was removed in vacuo. And purified by silica gel column chromatography (PE: EA=10: 1 with 0.5 % glacial acetic acid, Rf = 0.15). The crude was stirred in hexane, filtrated to get a yellow solid **14** (8.7 g, 81%).

The base was changed to KOH in 1 g scale of **16c**, the yield was 80%.

M. P. 192.9-195.1 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (d, J = 2.0 Hz, 1H), 7.45 (s, 2H), 6.44 (s, 2H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 188.5, 148.9 (d, J = 244.6 Hz), 140.0 (d, J = 16.6 Hz), 126.9 (d, J = 4.5 Hz), 117.9, 116.3 (d, J = 19.6 Hz), 115.0 (d, J = 6 Hz), 83.46.

^{19}F NMR (565 MHz, DMSO-d_6) δ -118.74.

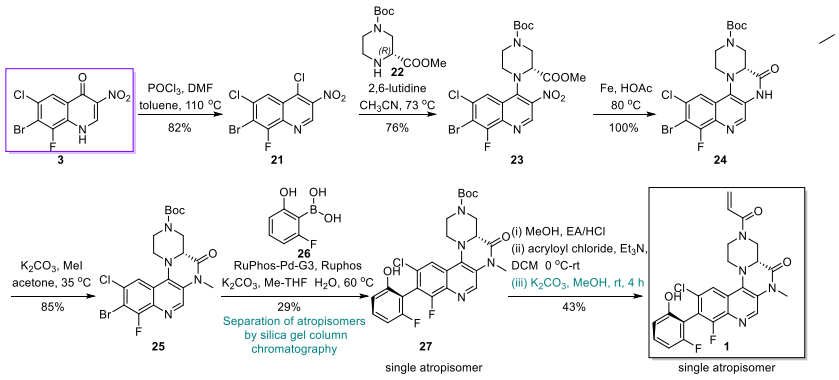
7-Bromo-6-chloro-8-fluoro-3-nitroquinolin-4(1H)-one (3)

To the solution of **14** (8 g, 25.7 mmol, 1 equiv) in dried THF (120 mL) was added DMF-DMA (4.6 g, 38.6 mmol, 1.5 equiv) dropwise at 40 °C and the mixture was stirred at 40 °C for 16 h. Then quenched the reaction using acetic acid (15.4 g, 257 mmol, 10 equiv) at 6 °C. The mixture was stirred at rt for 30 minutes and directly removed the solvent in vacuo. Finally, added ethyl acetate (90 mL) into the crude mixture for 2 hours. After filtration, the solid was washed with EA and PE, dried to get a light yellow solid **3** (6.27 g, 76%).

M. P. 368.2-370.9 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 (s, 1H), 8.14 (d, J = 1.8 Hz, 1H).

3. Adaptation of existing literature methods for the synthesis of 1



7-Bromo-4,6-dichloro-8-fluoro-3-nitroquinoline (21)

To the solution of **3** (6.3 g, 19.6 mmol, 1 equiv) in toluene (90 mL) was added $POCl_3$ (9.2 mL, 98 mmol, 5 equiv). The mixture was heated to 110 °C (pre-heated oil bath). DMF (0.2 mL) was added dropwise at 110 °C. The mixture was stirred at 110 °C for 20 h. After cooling, the mixture

was concentrated in vacuo. DCM (100 mL) and saturated $NaHCO_3$ (100 mL) were added. The aqueous phase was extracted with DCM (200 mL × 2). The combined organic phase was washed with brine, dried over Na_2SO_4, and purified by silica gel column chromatography (PE: DCM = 1: 1, Rf = 0.2) to give **21** as a milky white solid (5.5 g, 82%).
M. P. 156.3-157.9 °C.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.27 (s, 1H), 8.37 (d, *J* = 2.0 Hz, 1H).

1-(Tert-butyl) 3-methyl (R)-4-(7-bromo-6-chloro-8-fluoro-3-nitroquinolin-4-yl) piperazine-1,3 -dicarboxylate (23)
2, 6-Lutidine (1.8 g, 16.4 mmol, 2 equiv) in CH_3CN (4 mL) was added to **21** (2.8 g, 8.2 mmol, 1 equiv) and 1-(tert-butyl) 3-methyl (R)-piperazine-1,3-dicarboxylate **22** (2.2 g, 9 mmol, 1.1 equiv) in CH_3CN (24 mL) under argon. The mixture was heated to 75 °C for 16 h. The mixture was concentrated in vacuo. DCM (20 mL) was added. The mixture was washed with citric acid (10%, 20 mL). The organic phase was concentrated, and purified by silica gel column chromatography (PE: EA = 5: 1, Rf = 0.15) to give **23** as a yellow solid (3.42 g, 76%).
M. P. 138.3-140.6 °C.
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (s, 1H), 8.33 (s, 1H), 4.34 (s, 1H), 4.12 (br s, 1H), 3.84 (br s, 1H), 3.69 (dd, *J* = 13.4, 4.1 Hz, 1H), 3.66 – 3.58 (m, 1H), 3.53 (s, 3H), 3.30 – 3.11 (m, 2H), 1.42 (s, 9H).

Tert-butyl (R)-10-bromo-11-chloro-9-fluoro-5-oxo-1,2,4,4a,5,6-hexahydro-3H-pyrazino [1',2': 4,5]pyrazino[2,3-c]quinoline-3-carboxylate (24)
23 (3 g, 5.5 mmol, 1 equiv) in HOAc (24 mL) was added dropwise to Fe (1.2 g, 22 mmol, 4 equiv) in HOAc (15 mL) at 60 °C. The mixture was heated to 80 °C for 4 h. After cooling, citric acid (10%, 44 mL) was added dropwise. The mixture was stirred at rt for 1 h, and filtrated. The solid was washed with H_2O and PE. The solid was dissolved in THF. The mixture was dried over Na_2SO_4, filtrated from celite. The filtrate was concentrated in vacuo to get a light yellow solid **24** (2.7 g, 100%).
M. P. 253.6-256.3 °C.
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 8.58 (s, 1H), 8.03 (s, 1H), 4.66 (d, *J* = 13.4 Hz, 1H), 3.80 (br s, 2H), 3.28 – 3.02 (m, 3H), 2.68 (br s, 1H), 1.41 (s, 9H).

Tert-butyl (R)-10-bromo-11-chloro-9-fluoro-6-methyl-5-oxo-1,2,4,4a,5,6-hexahydro-3H-pyrazino[1',2':4,5]pyrazino[2,3-c]quinoline-3-carboxylate (25)
MeI (1.3 g, 9 mmol, 2 equiv) was added dropwise to **24** (2.18 g, 4.5 mmol, 1 equiv) and K_2CO_3 (1.2 g, 9 mmol, 2 equiv) in acetone (36 mL) at 35 °C. The mixture was stirred at 35°C for 16 h. EA (40 mL) was added. The mixture was filtrated. The filtrate was concentrated in vacuo, and purified by silica gel column chromatography (PE: EA = 1:1, Rf = 0.3) to give **25** as a yellow solid (1.9 g, 85%).
M. P. 221.4-223.9 °C.
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 (s, 1H), 8.10 (s, 1H), 4.71 (d, *J* = 13.4 Hz, 1H), 3.94 – 3.71 (m, 2H), 3.46 (s, 3H), 3.29 – 3.09 (m, 3H), 2.62 (br s, 1H), 1.42 (s, 9H).

Tert-butyl (R)-11-chloro-10-(2,6-difluorophenyl)-9-fluoro-6-methyl-5-oxo-1,2,4,4a,5,6-hexa

hydro-3H-pyrazino[1',2':4,5]pyrazino[2,3-c]quinoline-3-carboxylate (27)

Me-THF (30 mL) and H_2O (10 mL) were added to **25** (1 g, 2 mmol, 1 equiv), (2-fluoro-6-hydroxyphenyl) boronic acid **26** (620 mg, 4 mmol, 2 equiv), K_2CO_3 (1.7 g, 12 mmol, 3 equiv), RuPhos-Pd-G3 (160 mg, 0.2 mmol, 0.1 equiv), and RuPhos (100 mg, 0.2 mmol, 0.1 equiv) under argon. The mixture was heated to 60 ℃ for 30 h. After cooling, the organic phase was washed with 10% citric acid. 10% Citric acid was added to adjust aqueous phase to pH = 2-3, then extracted with DCM (10 mL × 2). The combined organic phase was concentrated. The residue was stirred in DCM (30 mL) and filtrated. The solid was major the undesired isomer. The filtrate was concentrated and purified by silica gel column chromatography (DCM: Et_3N = 30: 1, Rf = 0.25) three times to give desired atropisomer of **27** as a yellow solid (309 mg, 29%).

M. P. 178.9-181 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.30 (s, 1H), 8.95 (s, 1H), 8.06 (s, 1H), 7.34 (q, *J* = 7.9 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.79 (t, *J* = 8.7 Hz, 1H), 4.69 (d, *J* = 11.1 Hz, 1H), 3.86 (br m, 2H), 3.40 (s, 3H), 3.29 – 3.21 (m, 2H), 2.71 (br s, 1H), 1.43 (s, 9H).

(4aR)-3-acryloyl-11-chloro-9-fluoro-10-(2-fluoro-6-hydroxyphenyl)-6-methyl-2,3,4,4a-tetra hydro-1H-pyrazino[1',2':4,5]pyrazino[2,3-c]quinolin-5(6H)-one (1)

HCl-EA solution (2 mL, 1.3 N) was added to **27** (60 mg, 0.1 mmol, 1 equiv) in MeOH (1 mL). The mixture was stirred at rt for 16 h, and concentrated in vacuo (the water bath not exceed to 30 °C).

DCM (5 mL) and Et_3N (70 mg, 0.7 mmol, 6 equiv) were added to the residue. Acryloyl chloride (32 mg, 0.3 mmol, 3 equiv) in DCM (0.5 mL) was added dropwise at -10 ℃. The mixture was stirred at rt for 1 h. The mixture was concentrated in vacuo (the water bath not exceed to 30 °C).

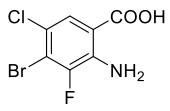
The residue was dissolved in MeOH (3 mL). K_2CO_3 (61 mg, 0.4 mmol, 4 equiv) was added. The mixture was stirred at rt for 4 h. The mixture was concentrated in vacuo (the water bath not exceed to 40 °C). 10% citric acid was added to adjust pH = 5-6. The mixture was extracted with EA (5 mL × 3). The combined organic phase was washed with brine, concentrated, and purified by silica gel column chromatography (PE: EA = 1: 1-100%, PE: EA = 1: 1 Rf = 0.2) to get a yellow solid **1** (single atropisomer, 23 mg, 43%, for three steps).

M. P. 210.5-213.3 ℃.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (d, *J* = 1.8 Hz, 1H), 8.98 (s, 1H), 8.11 (s, 1H), 7.34 (q, *J* = 7.9 Hz, 1H), 7.05 (dd, *J* = 16.9, 10.6 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.79 (t, *J* = 8.7 Hz, 1H), 6.13 (dd, *J* = 16.8, 2.3 Hz, 1H), 5.80 – 5.66 (m, 1H), 4.76 (d, *J* = 13.9 Hz, 1H), 4.42 (d, *J* = 13.1 Hz, 1H), 4.04 – 3.87 (m, 1H), 3.60 (d, *J* = 13.9 Hz, 1H), 3.47 (s, 3H), 3.18 (t, *J* = 12.6 Hz, 1H), 2.63 (t, *J* = 11.9 Hz, 1H).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.62 (s, 1H), 7.90 (s, 1H), 7.29 (dd, *J* = 8.4, 6.7 Hz, 1H), 7.02 (dd, *J* = 16.8, 10.7 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.74 (t, *J* = 8.6 Hz, 1H), 6.36 (dd, *J* = 16.8, 1.8 Hz, 1H), 5.81 (d, *J* = 11.0 Hz, 1H), 4.96 – 4.81 (m, 1H), 4.73 – 4.58 (m, 1H), 3.65 – 3.53 (m, 2H), 3.46 (s, 3H), 3.29 – 3.05 (m, 2H), 2.80 – 2.67 (m, 1H).

5. ^{1}H, ^{13}C ,^{19}F NMR and HRMS Spectra



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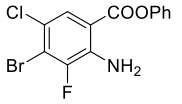
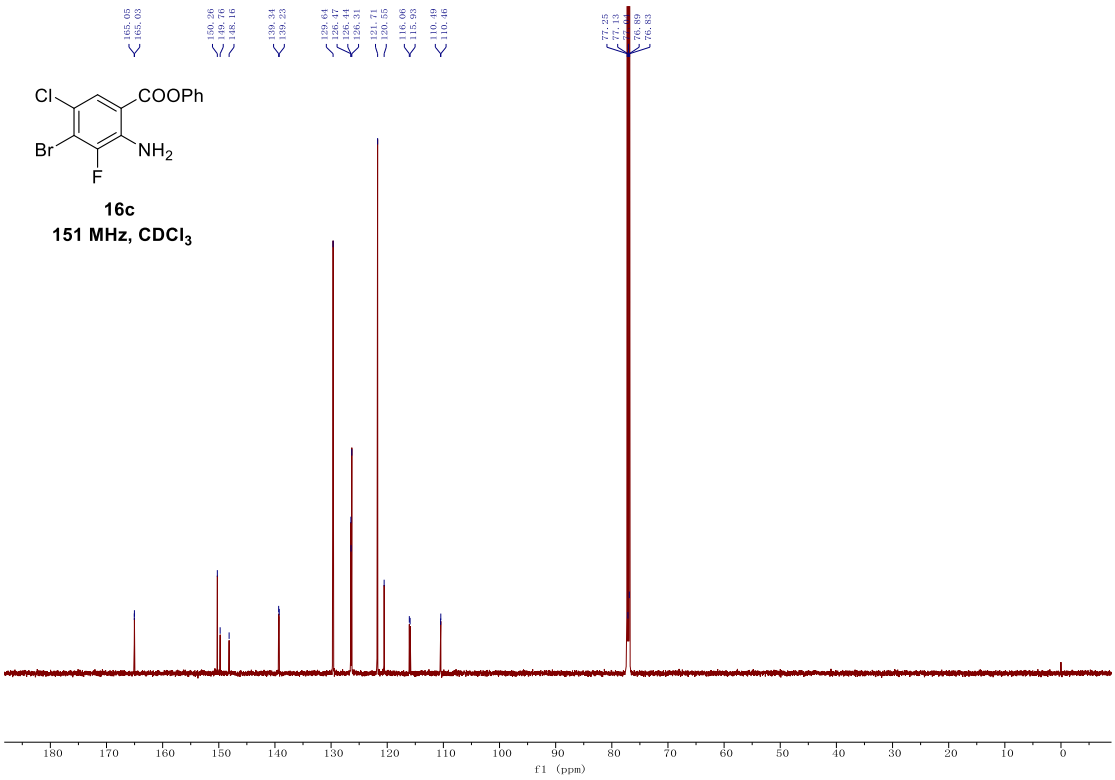
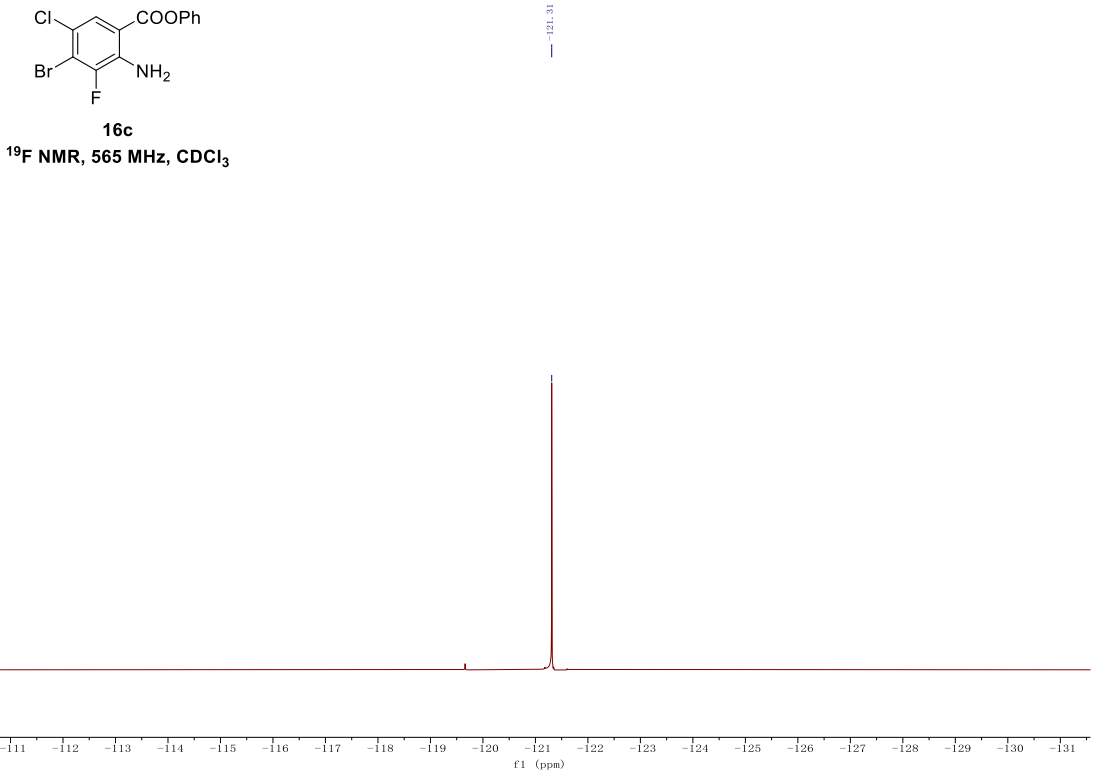


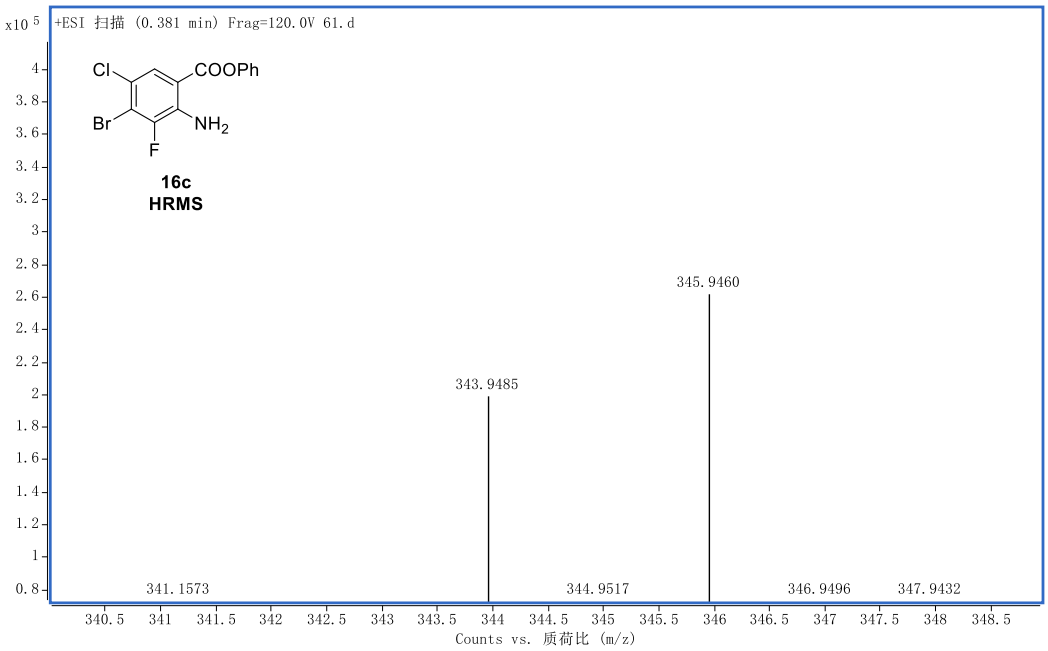
16c
400 MHz, $CDCl_3$



16c
151 MHz, $CDCl_3$



16c
^{19}F NMR, 565 MHz, $CDCl_3$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NH2
F
16c
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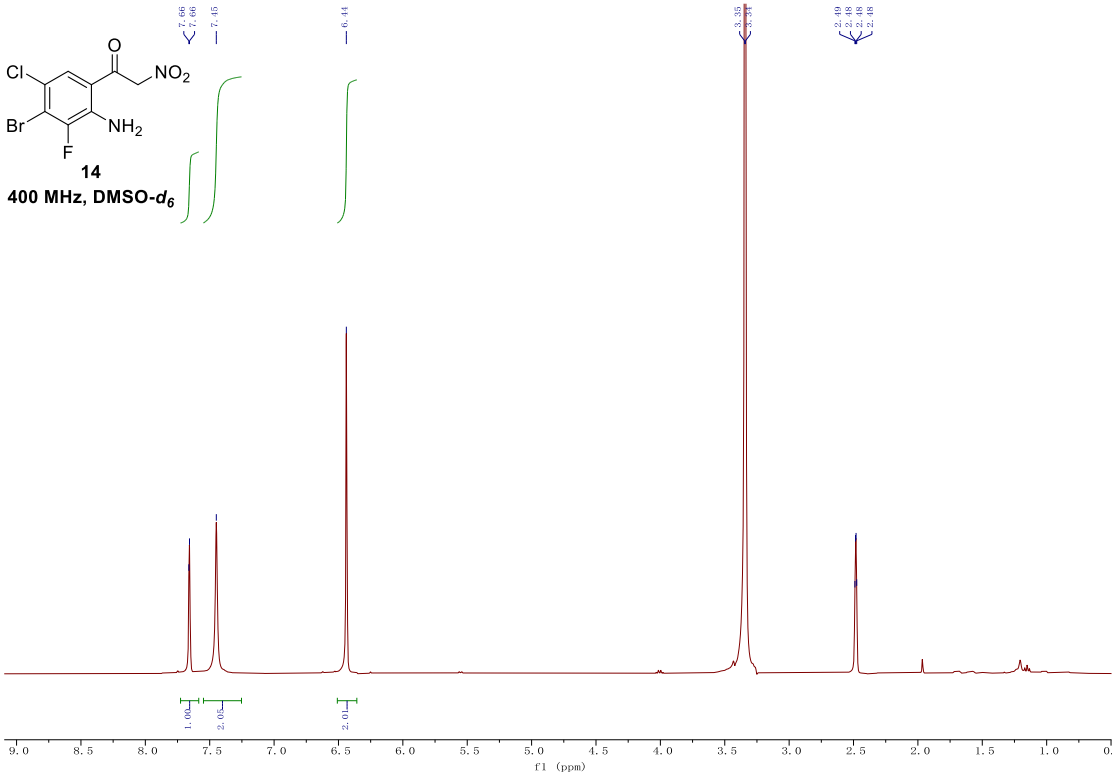
Counts vs. 质荷比 (m/z)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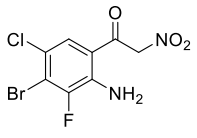
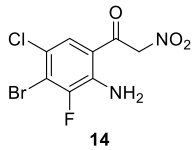
O
NO2
Br
NH2
F
14
400 MHz, DMSO-d6
f1 (ppm)



14

151 MHz, DMSO-*d*$_6$



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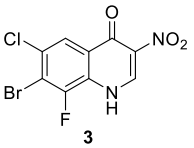

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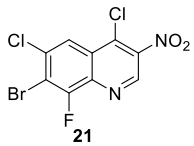

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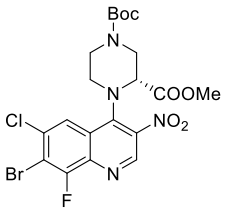
400 MHz, $CDCl_3$



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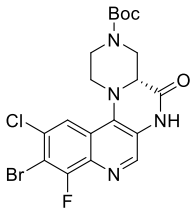
400 MHz, DMSO-d_6



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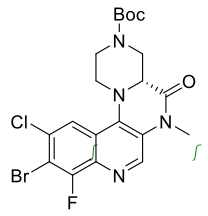

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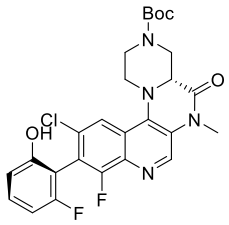
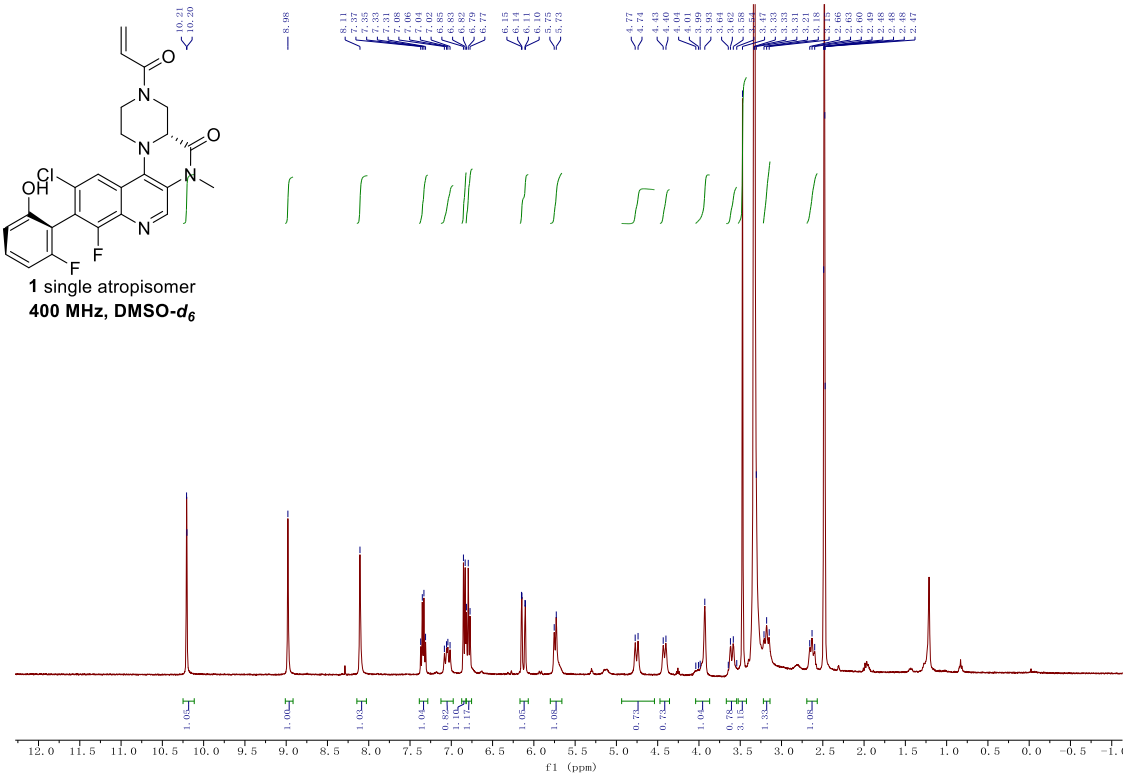
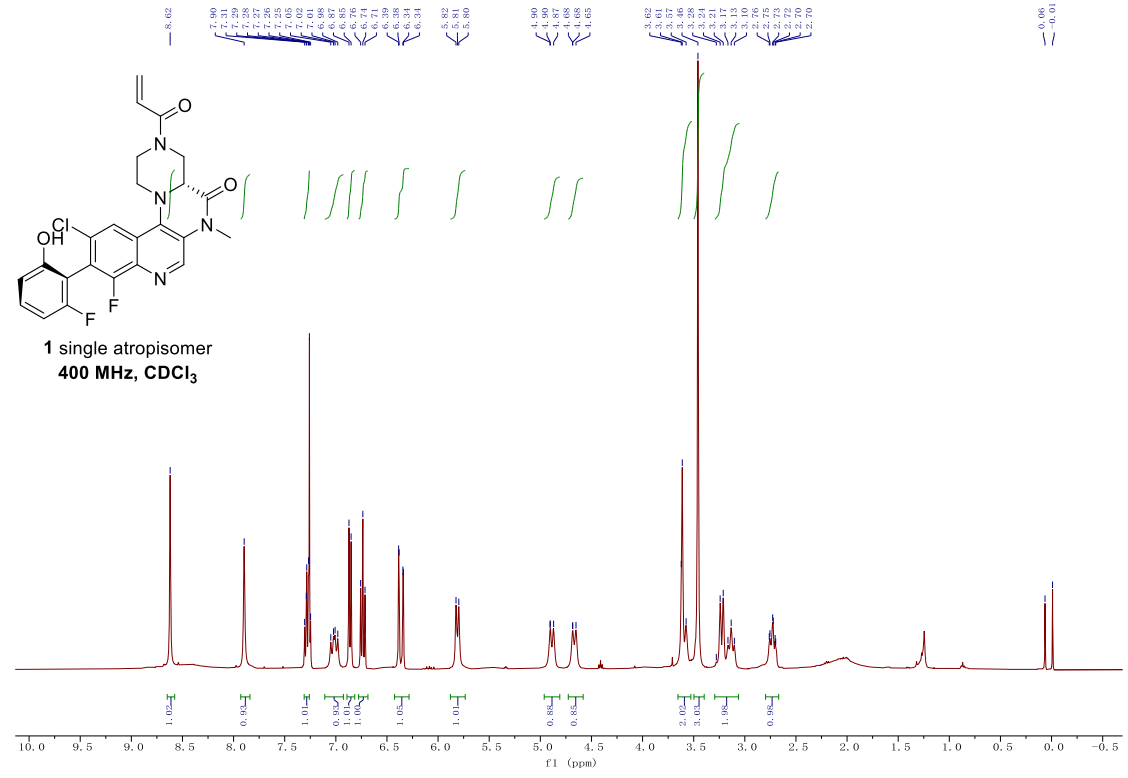


27 single atropisomer

400 MHz, DMSO-d_6


1 single atropisomer
400 MHz, DMSO-d_6
f1 (ppm)


1 single atropisomer
400 MHz, $CDCl_3$
f1 (ppm)