Electronic supplementary materials *Mendeleev Commun.*, 2026, **36**, 326–327

An alternative synthesis of the antidepressant Navacaprant

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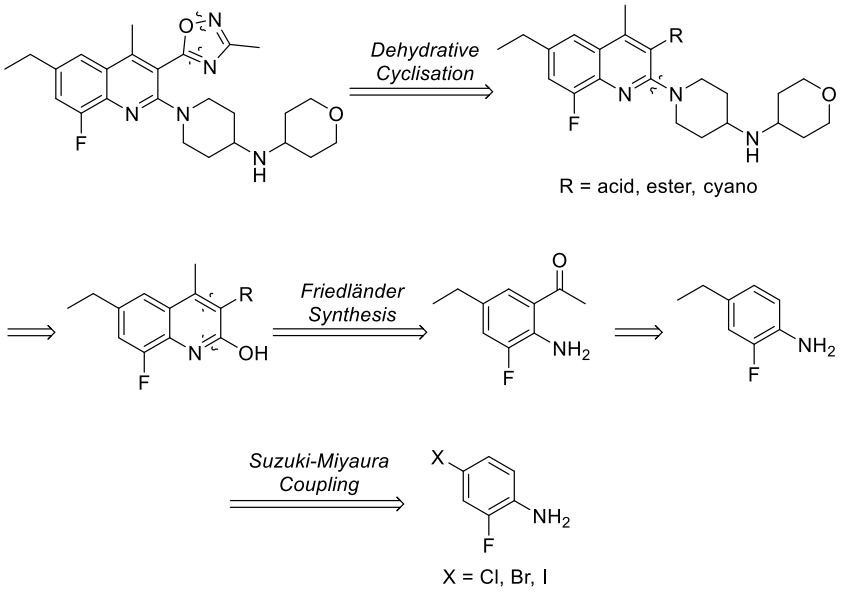
Retrosynthetic analysis

The substitution of 2-(3-methyl-1,2,4-oxadiazol-5-yl)acetic acid with carboxylic acid, ester, or nitrile precursors permits the construction of the oxadiazole ring *via* a dehydrative cyclization of an (*Z*)-*N'*-hydroxyacetimidamide.[S1,S2] The key intermediate, 2-hydroxyquinoline, is synthesized *via* a Friedländer synthesis from 1-(2-amino-5-ethyl-3-fluorophenyl)ethan-1-one and a *β*-diketone intermediate.[S3,S4] The original starting material, 4-ethyl-2-fluoroaniline, can be prepared through the Suzuki–Miyaura coupling between a halogenated aniline and ethylboronic acid.[S5,S6]



Scheme S1 Retrosynthetic analysis

Experimental

General

All commercial starting materials were purchased from Beijing InnoChem Science & Technology Co., Ltd. and Anhui Senrise Technologies Co., Ltd., and were used without further purification. ^{1}H NMR spectra were recorded on Bruker AVANCE III spectrometers (400 or 600 MHz) using tetramethylsilane (TMS) as the internal standard (chemical shifts in δ, ppm; coupling constants in *J*, Hz). ^{13}C NMR spectra were acquired on a Bruker AVANCE III 400 MHz spectrometer (101 MHz for ^{13}C) with TMS as the internal standard (δ, ppm; *J*, Hz). Mass spectrometry analyses were conducted on a Waters 2695-ZQ2000 LC/MS instrument equipped with an electrospray ionization (ESI) source. Chemical purity was determined using an Agilent

1260 Infinity II HPLC system equipped with a ZORBAX Eclipse XDB-C18 column (5 μm, 4.6 × 250 mm; Agilent Technologies). Melting points were determined on an X-5 digital microscope melting point apparatus (Gongyi Yuhua Instrument Co., Ltd, China) and are uncorrected. Column chromatography was performed on silica gel (200-300 mesh; Qingdao Haiyang Chemical Ltd.). Analytical TLC was carried out on plates precoated with silica gel (GF254, 0.25 mm; Qingdao Haiyang Chemical Ltd.), and compounds were visualized using iodine vapor.

Synthesis of *N*-(tetrahydro-2*H*-pyran-4-yl)piperidin-4-amine

A mixture of 1-benzylpiperidin-4-amine (9.92 mL, 0.053 mol), tetrahydro-4*H*-pyran-4-one (7.28 mL, 0.079 mol), and AcOH (4.50 mL, 0.079 mol) in 1,2-DCE/MeOH (16:1, 170 mL) was stirred at room temperature for 3 h. Then, STAB (16.70 g, 0.079 mol) was added, and the mixture was stirred at room temperature for another 17 h. The reaction was quenched with aq. NaOH solution (2 M, 150 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 1-benzyl-*N*-(tetrahydro-2*H*-pyran-4-yl)piperidin-4-amine as a yellow oil in 88% yield (12.66 g, 0.046 mol). LC/MS: (M + 1) *m/z* = 275.46. The crude product (10.60 g, 0.039 mol) was hydrogenated with 10% Pd/C (1.02 g, 0.010 mol) in a mixture of MeOH and CH_2Cl_2 (2:1, 240 mL) at room temperature for 40 hours under 1 atm of H_2. The mixture was filtered and concentrated under reduced pressure to give product as a pale-yellow solid in 96% yield (6.84 g, 0.037 mol), which was used directly in the next step without further purification. LC/MS: (M + 1) *m/z* = 185.40.

Synthesis of 4-ethyl-2-fluoroaniline (**2**)

A mixture of **1** (5.00 g, 0.026 mol), ethylboronic acid (3.89 g, 0.053 mol), $Pd_2(dba)_3$ (1.20 g, 0.0013 mol), S-Phos (2.16 g, 0.0053 mol), and K_2CO_3 (10.92 g, 0.079 mol) in toluene (80 mL) was heated at 90 °C for 14 h. After cooling to room temperature, the mixture was filtered and the filtrate was washed with brine (3 × 30 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography on silica gel (PE (40-60°C)/EtOAc, 0-5% EtOAc) afforded **2** as a pale yellow or colorless oil in 91% yield (3.35 g, 0.024 mol). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.83 (dd, *J* = 12.1, 1.9 Hz, 1H), 6.76 (dd, *J*

= 8.0, 1.9 Hz, 1H), 6.69 (dd, *J* = 9.3, 8.0 Hz, 1H), 3.57 (s, 2H), 2.53 (q, *J* = 7.6 Hz, 2H), 1.18 (td, *J* = 7.6, 1.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 131.84, 123.52 (*J* = 3.03 Hz), 116.97, 114.58 (*J* = 18.18 Hz), 101.80, 84.89, 27.87, 15.63. MS (ESI) m/z calcd for $C_8H_{11}FN^+$ $[M+H]^+$ 140.0870, found 140.0868.

Synthesis of 4-ethyl-2-fluoro-6-iodoaniline (**3**)

A mixture of **2** (2.09 g, 0.015 mol) and NIS (3.72 g, 0.016 mol) in AcOH (25 mL) was cooled to 0 °C and stirred at room temperature for 1.5 h. The mixture was diluted with EtOAc (50 mL), washed sequentially with sat. aq. $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (PE (40-60°C)/EtOAc, 0-1% EtOAc) to give the product as a reddish oil in 69% yield (2.76 g, 0.010 mol). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.23 (s, 1H), 6.80 (dd, *J* = 11.6, 1.8 Hz, 1H), 3.97 (s, 2H), 2.48 (q, *J* = 7.6 Hz, 2H), 1.16 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.92 (*J* = 244.42 Hz), 136.12 (*J* = 6.06 Hz), 133.78, 132.86 (*J* = 3.03 Hz), 114.78 (*J* = 19.19 Hz), 84.14, 27.47, 15.48. MS (ESI) m/z calcd for $C_8H_{10}FIN^+$ $[M+H]^+$ 265.9842, found 265.9832.

Synthesis of 1-(2-amino-5-ethyl-3-fluorophenyl)ethan-1-one (**4**)

A mixture of **3** (5.80 g, 0.022 mol), 2-(vinyloxy)ethan-1-ol (11.80 mL, 0.13 mol), K_2CO_3 (3.63 g, 0.026 mol), DPPP (0.45 g, 0.0011 mol), and $Pd(OAc)_2$ (0.05 g, 0.00022 mol) in H_2O/toluene (8:1, 90 mL) was heated at 90 °C for 22 h. After cooling to room temperature, the mixture was treated slowly with concentrated HCl (10.0 mL) and stirred for 2 h. The solution was neutralized with sat. aq. $NaHCO_3$ and extracted with EtOAc (3 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (PE (40-60°C)/EtOAc, 0-2% EtOAc) afforded the product as a pale-yellow solid in 47% yield (1.85 g, 0.010mol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (s, 1H), 6.99 (dd, *J* = 12.1, 1.9 Hz, 1H), 6.14 (s, 2H), 2.61-2.51 (m, 5H), 1.21 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.38 (*J* = 3.03 Hz), 151.58 (*J* = 241.39 Hz), 137.30 (*J* = 13.13 Hz), 130.47 (*J* = 6.06 Hz), 125.38 (*J* = 3.03 Hz), 119.81 (*J* = 4.04 Hz), 118.46 (*J* = 17.17 Hz), 28.07, 27.91, 15.61. MS (ESI) m/z calcd for $C_{10}H_{13}FNO^+$ $[M+H]^+$ 182.0976, found

182.0974.

Synthesis of ethyl 6-ethyl-8-fluoro-2-hydroxy-4-methylquinoline-3-carboxylate (**5**)

A mixture of **4** (1.85 g, 0.010 mol) and Et_3N (2.14 mL, 0.015 mol) in CH_2Cl_2 (60 mL) was treated with ethyl 3-chloro-3-oxopropanoate (1.95 mL, 0.015 mol) at 0 °C and stirred at room temperature for 5 h. The mixture was washed with brine (3 × 30 mL), and the organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a pale brown oil. The crude oil was dissolved in EtONa/EtOH (40 mL, 20% w/w) and heated at 80 °C for 3 h. After cooling to room temperature, the pH was adjusted to < 4 with 10% aq. HCl. The mixture was diluted with water (200 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 0-1% MeOH) to afford the product as a pale gray solid in 65% yield (1.83 g, 0.0066 mol). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.63 (s, 1H), 7.30 (s, 1H), 7.17 (dd, *J* = 11.1, 1.6 Hz, 1H), 4.46 (q, *J* = 7.2 Hz, 2H), 2.72 (q, *J* = 7.6 Hz, 2H), 2.48 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.05, 158.40, 154.03, 146.70 (*J* = 248.46 Hz), 139.01 (*J* = 6.06 Hz), 127.75, 124.74, 121.19, 119.32 (*J* = 3.03 Hz), 116.20 (*J* = 16.16 Hz), 61.88, 28.63, 16.54, 15.50, 14.19. MS (ESI) m/z calcd for $C_{15}H_{17}FNO_3^+$ $[M+H]^+$ 276.1041, found 276.1040.

Synthesis of ethyl 2-chloro-6-ethyl-8-fluoro-4-methylquinoline-3-carboxylate (**6**)

A mixture of **5** (1.22 g, 0.0044 mol) and $POCl_3$ (7 mL) was heated at 80 °C for 3 h. After concentration under reduced pressure, the residue was quenched with ice/water and stirred at room temperature for 30 min. The resulting precipitate was collected by filtration and purified by column chromatography (PE (40-60°C)/EtOAc, 0-10% EtOAc) to afford the product as a white solid in 88% yield (1.14 g, 0.0038 mol). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.55 (s, 1H), 7.35 (dd, *J* = 10.9, 1.7 Hz, 1H), 4.51 (q, *J* = 7.2 Hz, 2H), 2.84 (q, 2H), 2.66 (s, 3H), 1.45 (t, *J* = 7.2 Hz, 3H), 1.34 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.25, 157.13 (*J* = 260.58 Hz), 148.91, 144.11, 135.74, 132.06, 127.77, 118.60, 117.61, 116.09 (*J* = 18.18 Hz), 62.38, 29.34, 16.45, 15.21, 14.09. MS (ESI) m/z calcd for C15H16ClFNO2$^+$ $[M+H]^+$ 296.0848, found 296.0843. MS (ESI) m/z calcd for $C_{15}H_{16}ClFNNaO_2^+$ $[M+Na]^+$ 318.0668, found 318.0662.

Synthesis of ethyl 6-ethyl-8-fluoro-4-methyl-2-(4-((tetrahydro-2*H*-pyran-4-yl)amino) piperidin-1-yl)quinoline-3-carboxylate (**7**)

A mixture of **6** (0.52 g, 0.0018 mol), *N*-(tetrahydro-2*H*-pyran-4-yl)piperidin-4-amine (0.80 g, 0.0044 mol), and DIPEA (0.61 mL, 0.0035 mol) in EtOH (60 mL) was stirred at 130 °C for 14 h. After cooling to room temperature, the mixture was concentrated under reduced pressure and purified by column chromatography (CH_2Cl_2/MeOH, 0-5% MeOH) to afford the product as a yellow solid in 69% yield (0.54 g, 0.0012 mol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (s, 1H), 7.35-7.28 (m, 1H), 7.19 (dd, *J* = 11.5, 1.7 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.05-3.77 (m, 5H), 3.54-3.30 (m, 3H), 3.00 (ddd, *J* = 13.5, 11.7, 2.4 Hz, 2H), 2.91-2.82 (m, 2H), 2.81-2.72 (m, 2H), 2.56 (s, 3H), 2.00-1.89 (m, 2H), 1.89-1.75 (m, 2H), 1.51-1.35 (m, 2H), 1.41 (t, *J* = 7.2 Hz, 3H), 1.30 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.14, 158.27, 156.33, 155.75, 142.86, 139.92 (*J* = 7.07 Hz), 135.36 (*J* = 11.11 Hz), 125.42 (*J* = 3.03 Hz), 122.58, 117.50 (*J* = 4.04 Hz), 114.96 (*J* = 19.19 Hz), 66.92, 61.67, 51.14, 50.37, 48.60, 34.19, 33.11, 29.69, 29.07, 16.00, 15.47, 14.26. MS (ESI) m/z calcd for $C_{25}H_{35}FN_3O_3^+$ $[M+H]^+$ 444.2657, found 444.2651.

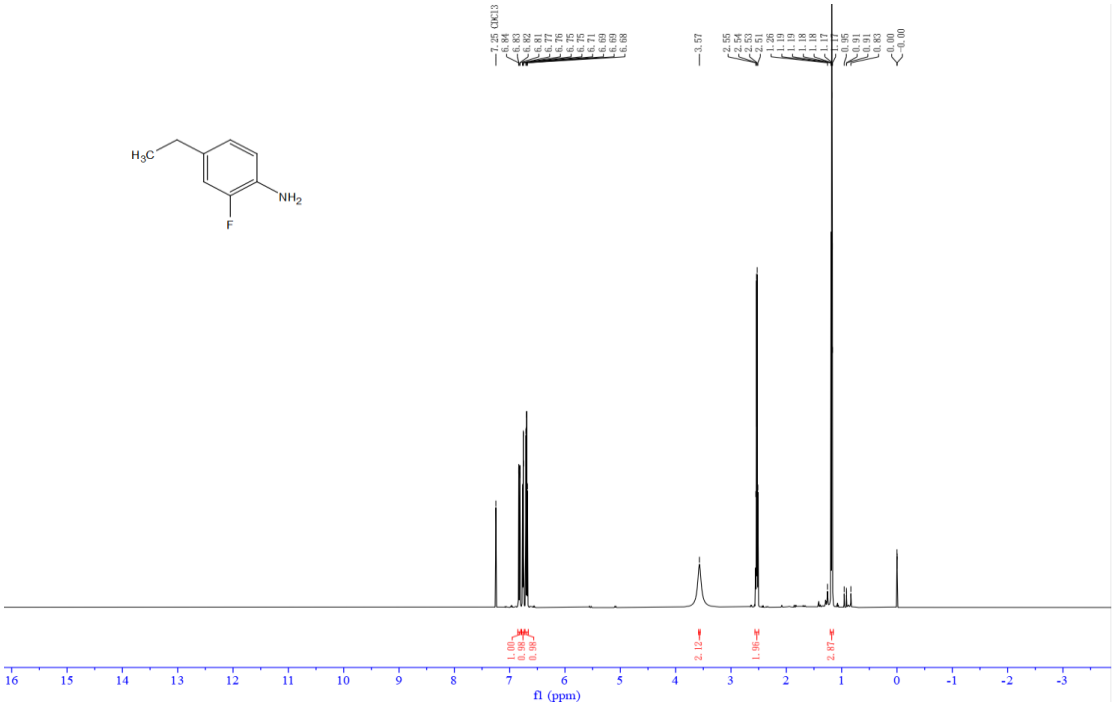
Synthesis of 6-ethyl-8-fluoro-4-methyl-2-(4-((tetrahydro-2*H*-pyran-4-yl)amino)piperidin-1-yl)quinoline-3-carboxylic acid (**8**)

A mixture of **7** (1.28 g, 0.0029 mol) and NaOH (1.15 g, 0.029 mol) in EtOH/H_2O (4:1, 100 mL) was heated at 100 °C for 16 h. After cooling to room temperature, the mixture was concentrated under reduced pressure. MeOH was added, and the pH was adjusted to < 2 with 15% aq. HCl. The resulting precipitate was collected by filtration, and the filter cake was concentrated under reduced pressure to afford intermediate **8** as a white solid in 98% yield (1.17 g, 0.0028 mol), which was used directly in the next step without further purification. ^{1}H NMR (600 MHz, CD_3OD): δ = 7.51 (s, 1H), 7.16 (dd, *J* = 11.6 Hz, 1H), 4.45-4.40 (m, 2H), 4.09-3.95 (m, 2H), 3.51-3.25 (m, 5H), 3.06-2.94 (m, 2H), 2.80-2.71 (m, 2H), 2.63 (s, 3H), 2.14-1.56 (m, 8H), 1.30 (t, *J* = 8.1 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ = 158.01, 155.33 (*J* = 36.36 Hz), 152.36, 139.80, 133.91, 126.07, 124.53, 117.35, 113.41 (*J* = 18.18 Hz), 65.52, 51.83, 50.45, 47.42, 47.21, 47.00, 46.93, 46.63, 29.39, 28.57, 28.40, 15.13, 14.68, 7.93. MS (ESI) m/z calcd for $C_{23}H_{31}FN_3O_3^+$ $[M+H]^+$ 414.2198, found 414.2198.

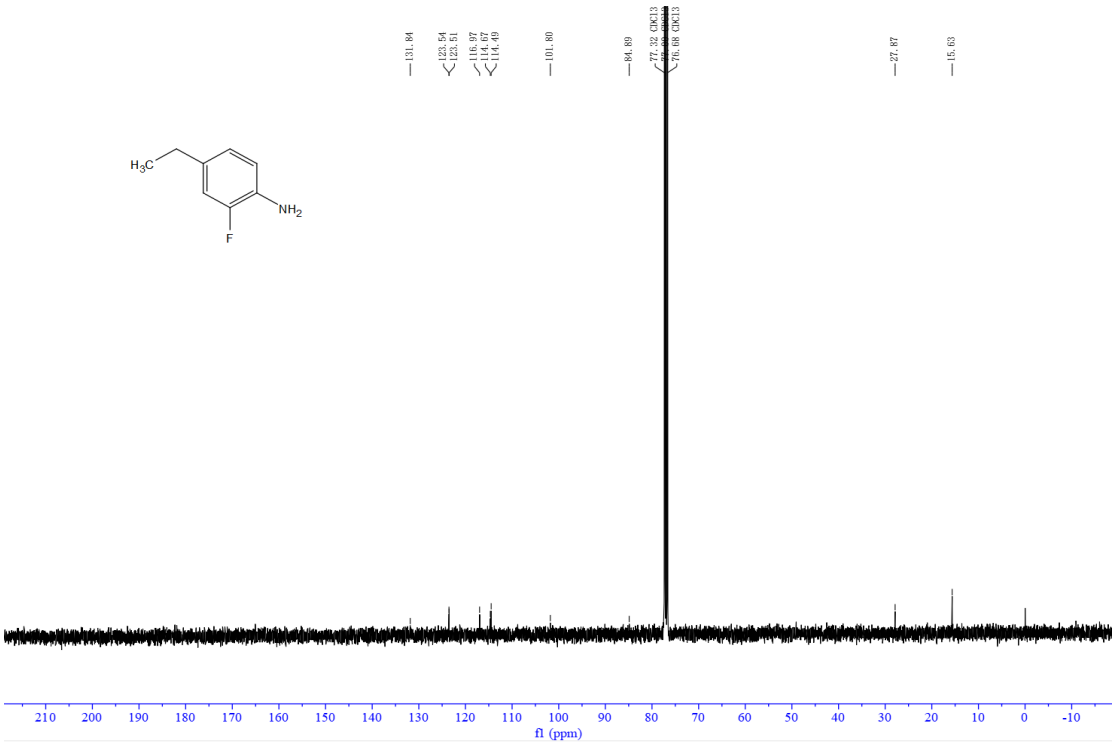
Synthesis of 1-(6-ethyl-8-fluoro-4-methyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)quinolin -2-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)piperidin-4-amine (**9**)

A mixture of carboxylic acid **8** (1.01 g, 0.0024 mol), (*Z*)-*N'*-hydroxyacetimidamide (0.18 g, 0.0024 mol), HOBt (0.33 g, 0.0024 mol), EDCI (0.46 g, 0.0024 mol), and K_2CO_3 (0.46 g, 0.0033 mol) in DMF (50 mL) was heated at 100 °C for 16 h. After cooling to room temperature, the mixture was diluted with water (300 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 0-1% MeOH) to afford the product as a pale-yellow solid in 42% yield (0.46 g, 0.0010mol), m.p. = 190.6-192.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (s, 1H), 7.26 (dd, *J* = 11.4, 1.7 Hz, 1H), 3.97 (d, *J* = 11.5 Hz, 2H), 3.59 (d, *J* = 13.3 Hz, 2H), 3.39 (td, *J* = 11.7, 2.0 Hz, 2H), 2.94-2.72 (m, 4H), 2.55 (s, 3H), 2.50 (s, 3H), 1.86-1.75 (m, 2H), 1.53-1.48 (m, 9H), 1.31 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.26, 167.62, 157.67, 157.02 (*J* = 255.53 Hz), 147.62 (*J* = 3.03 Hz), 140.24 (*J* = 7.07 Hz), 136.26 (*J* = 11.11 Hz), 125.12 (*J* = 2.02 Hz), 117.83 (*J* = 4.04 Hz), 115.95 (*J* = 18.18 Hz), 113.19, 66.89, 50.89, 50.24, 48.49, 34.26, 32.87, 29.06, 16.41, 15.42, 11.82. MS (ESI) m/z calcd for $C_{25}H_{33}FN_5O_2^+$ $[M+H]^+$ 454.2613, found 454.2605. HPLC (MeCN/H_2O, 10-95% MeCN, 1 mL/min, 25 °C): t_R 26.13 min (98.44%).

Graphical presentation of NMR spectra and HRMS of compound 2, 3, 4, 5, 6, 7, 8, 9



The ^{1}H NMR spectrum of compound **2**



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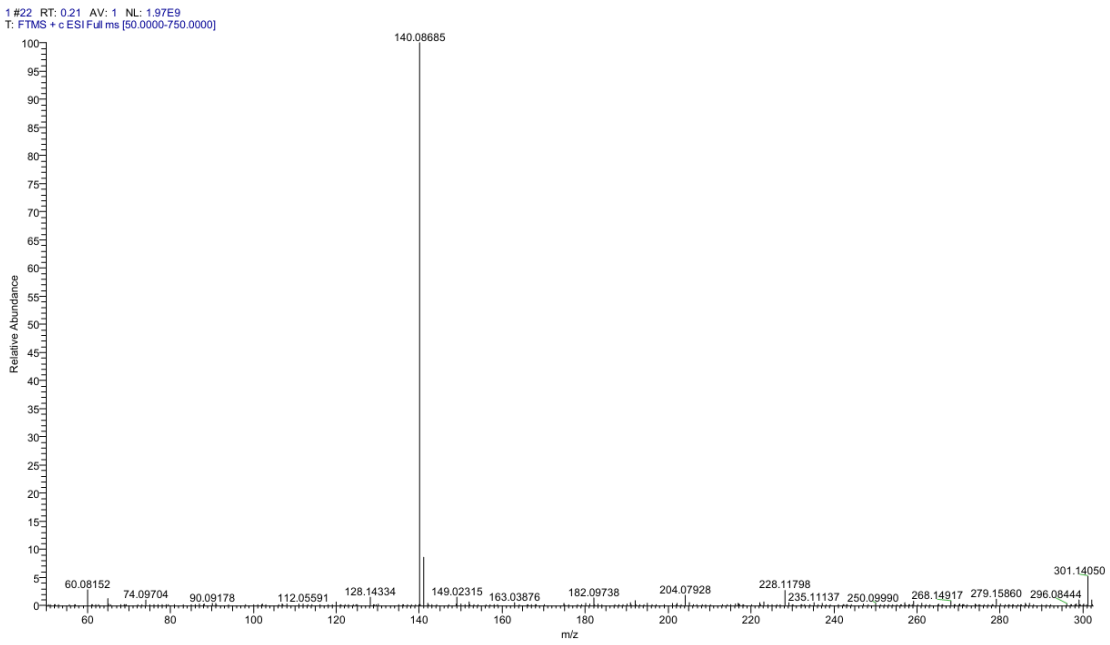

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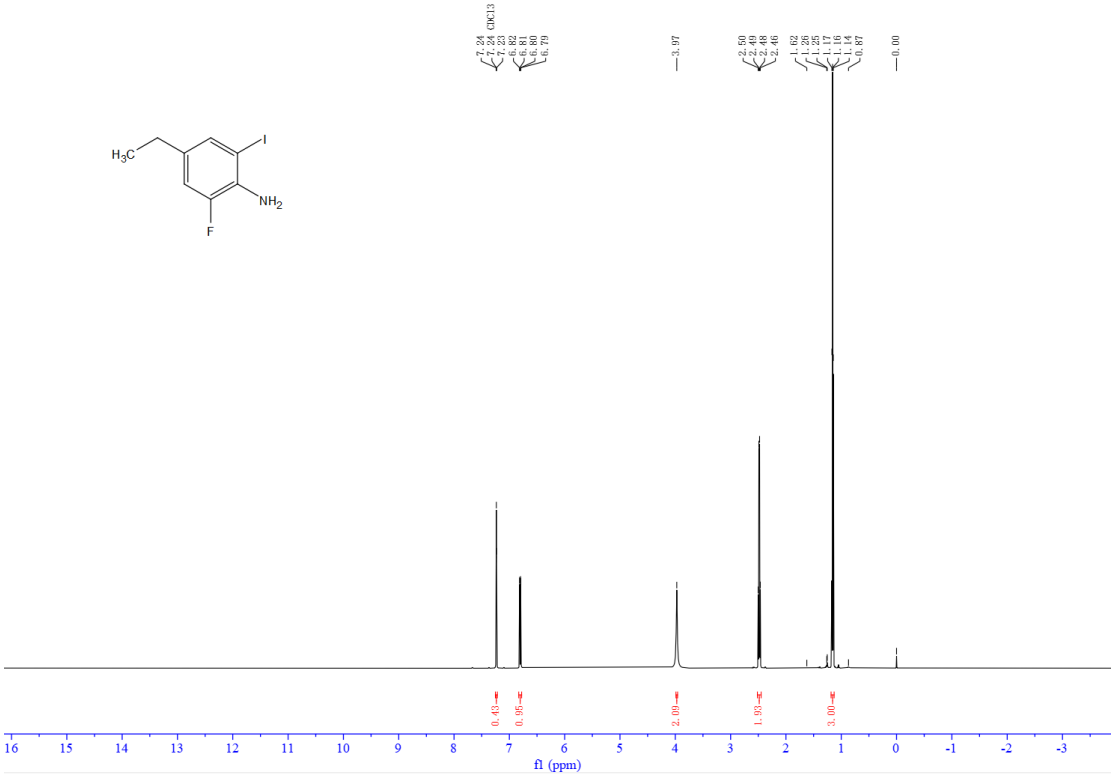

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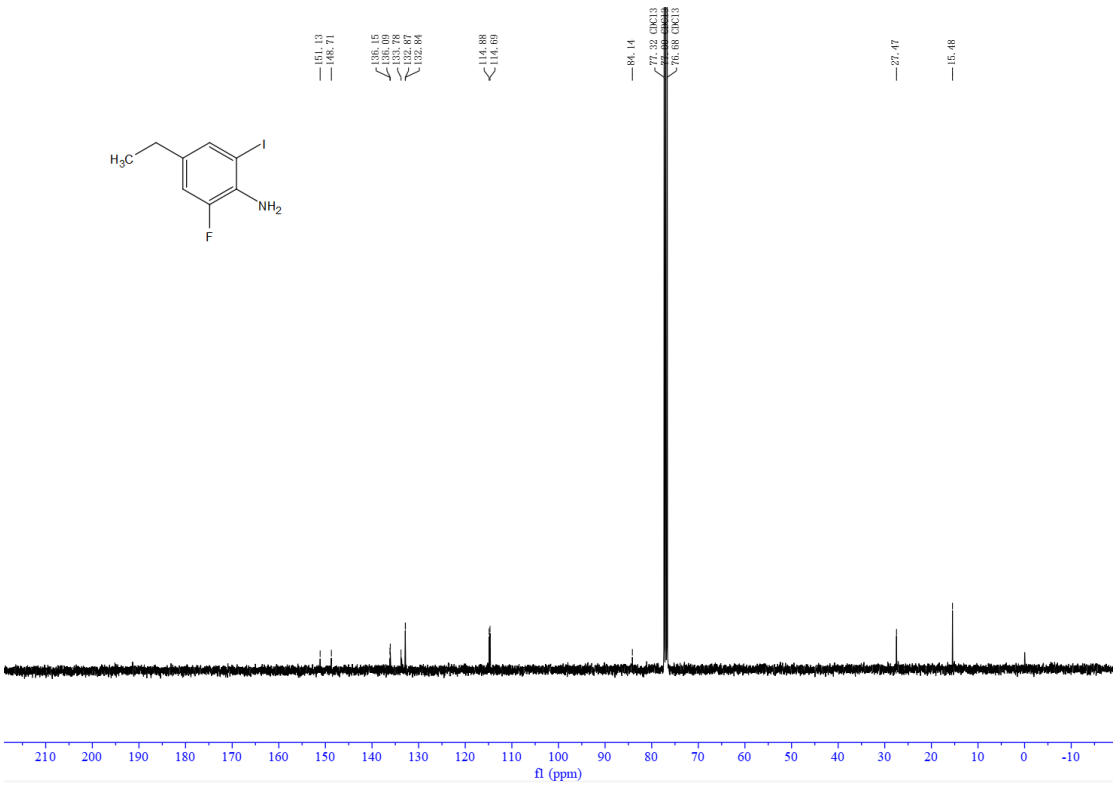

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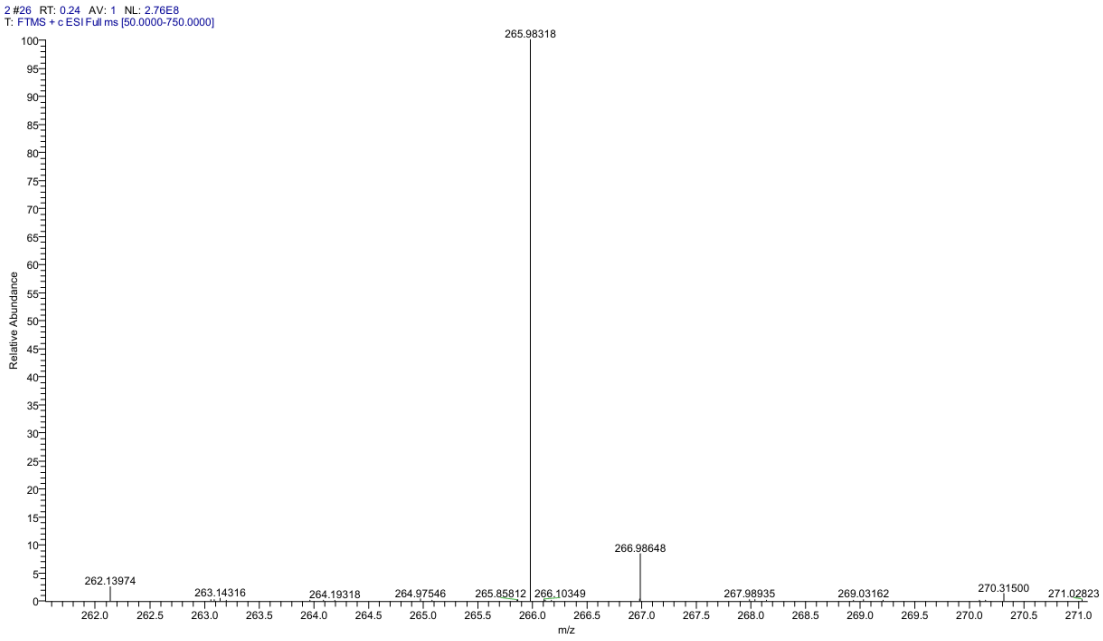

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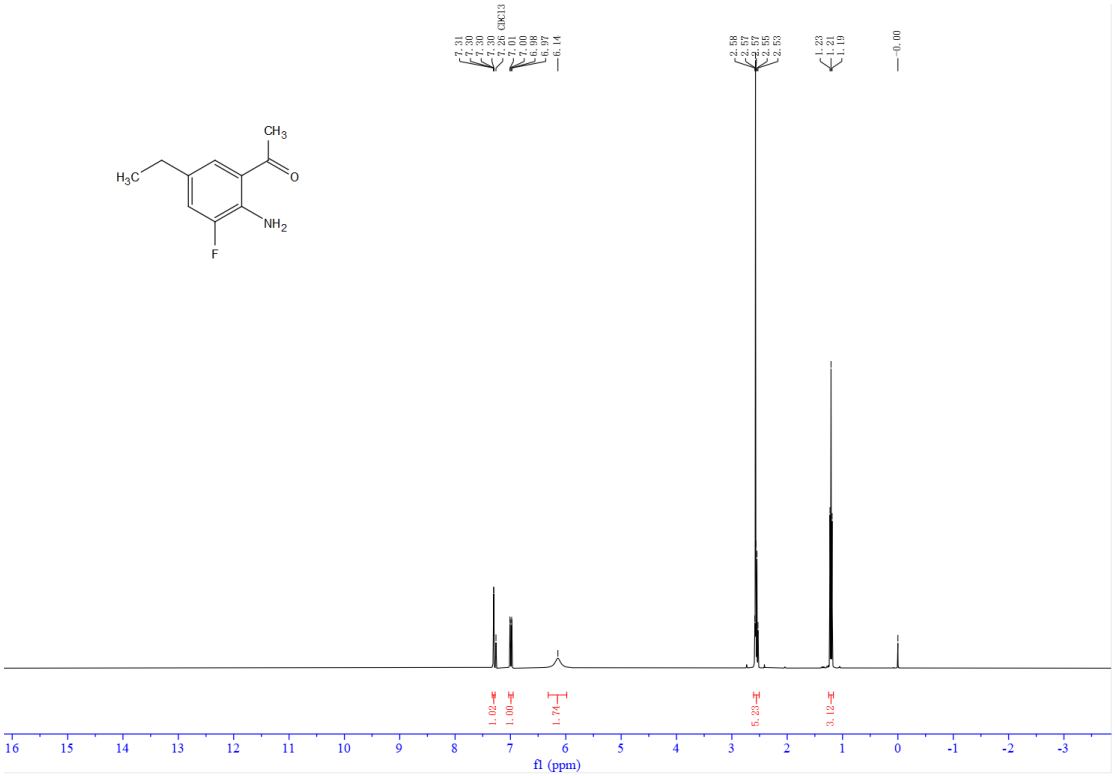

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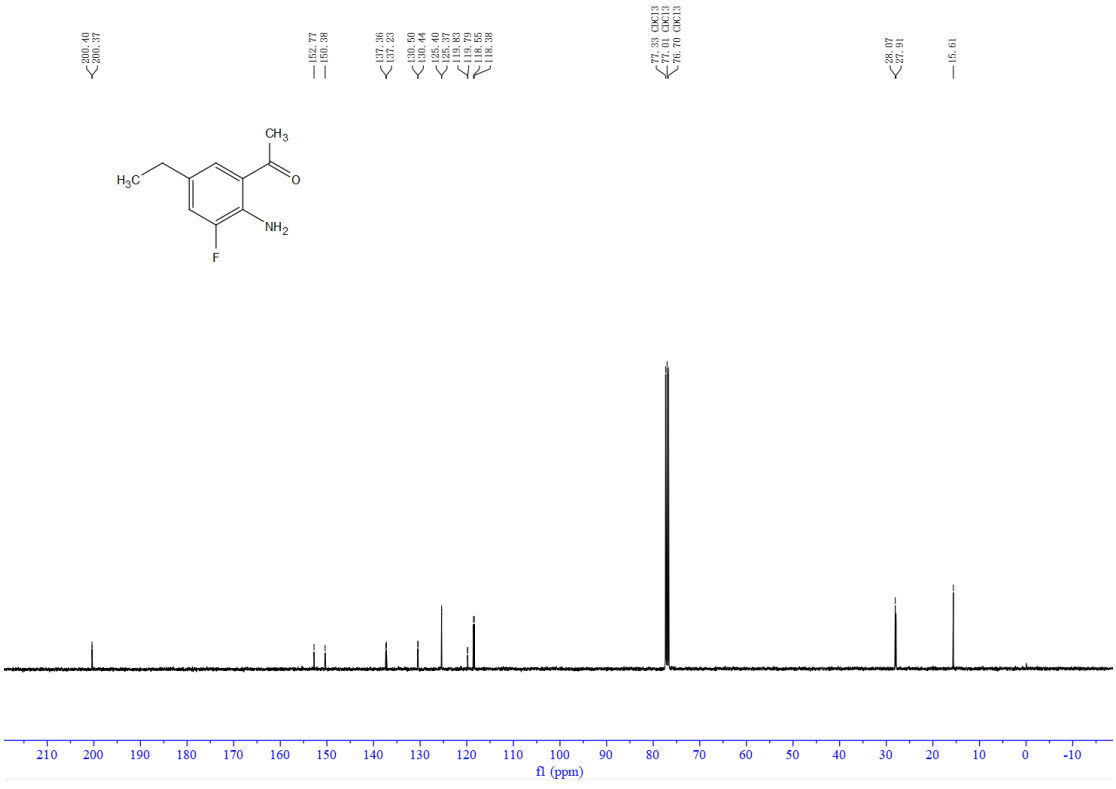
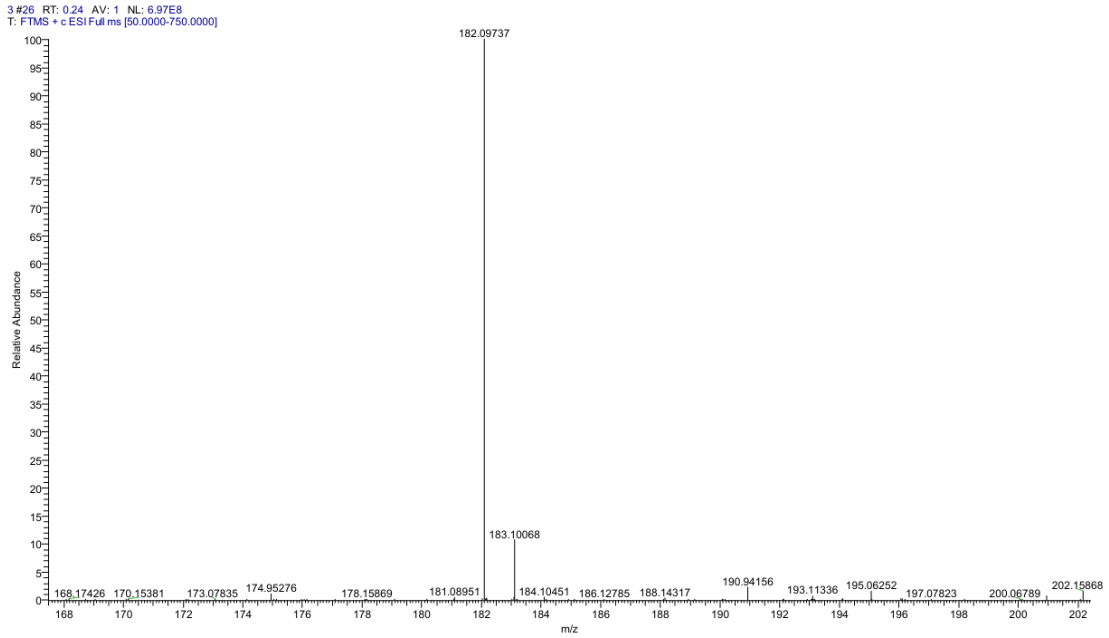


The ^{13}C NMR spectrum of compound **4**



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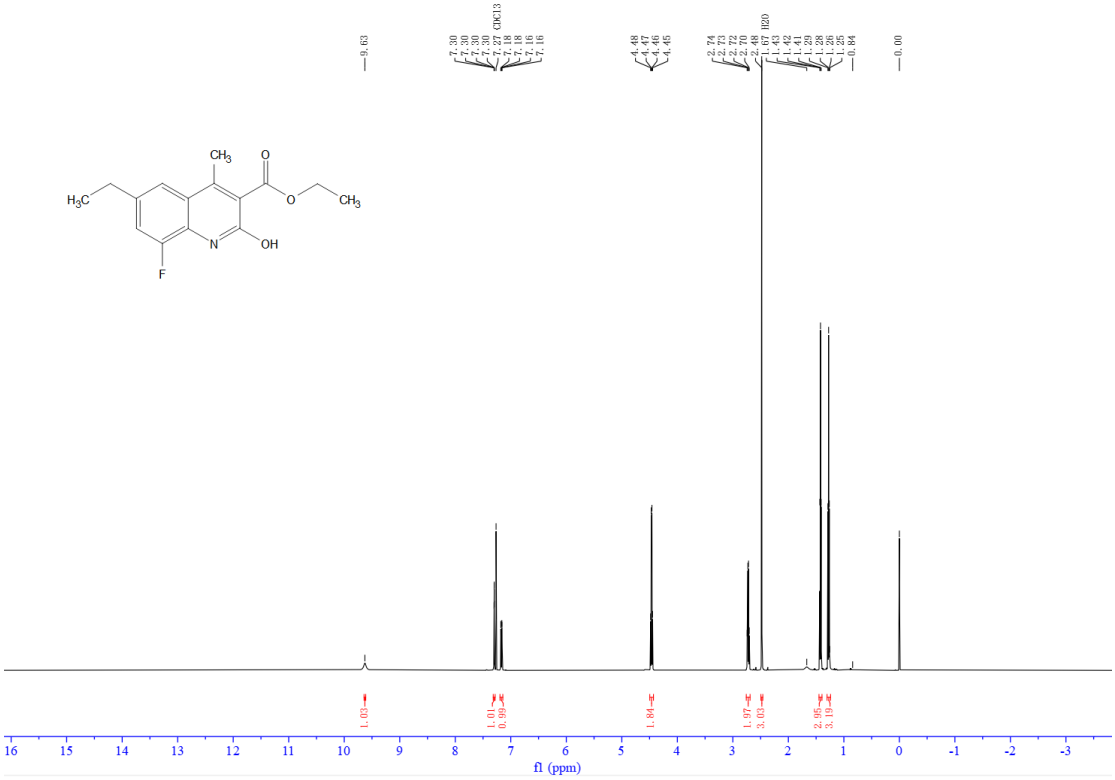

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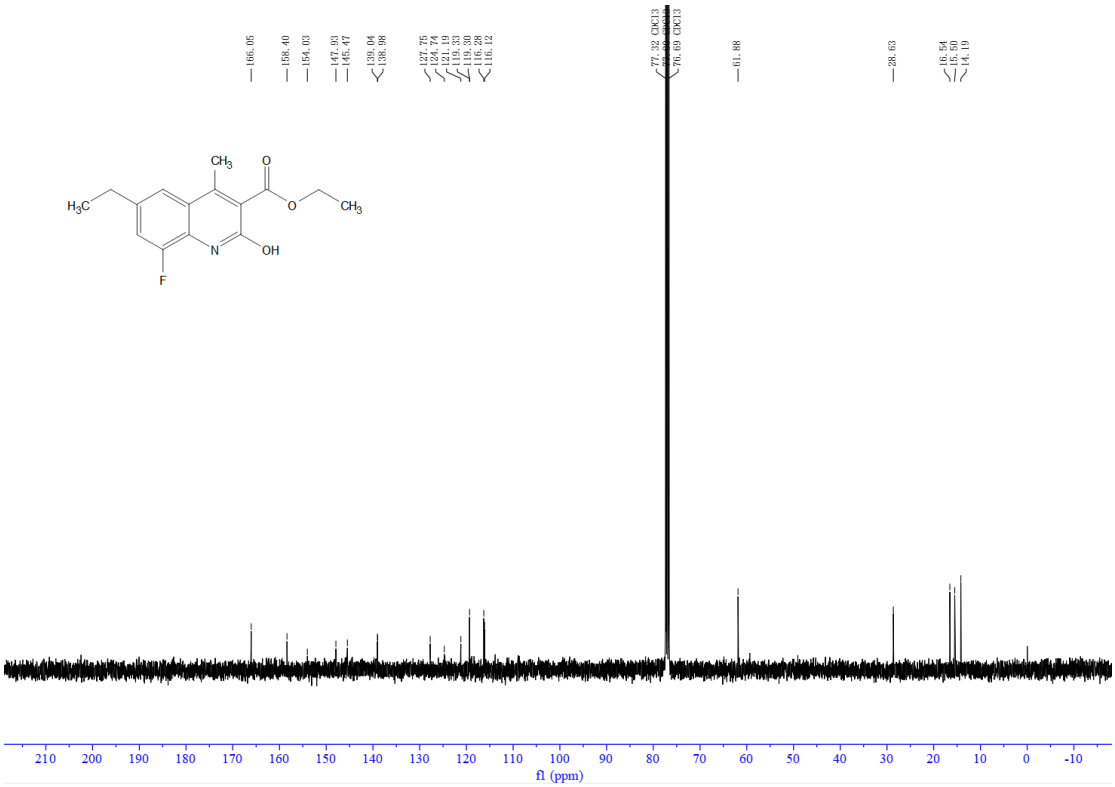
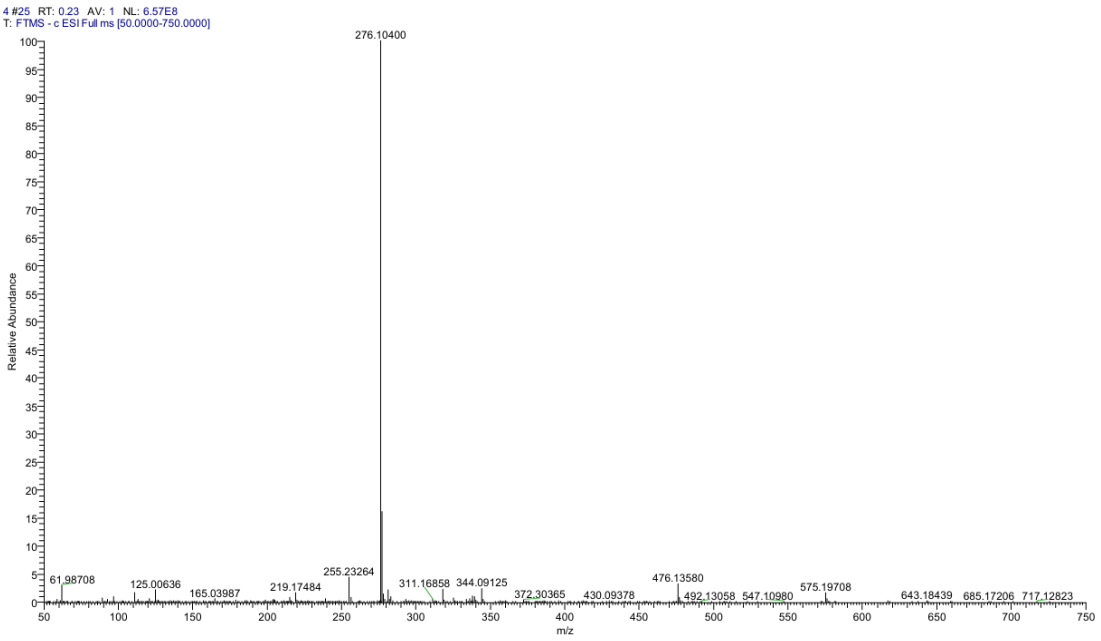


The ^{13}C NMR spectrum of compound **5**



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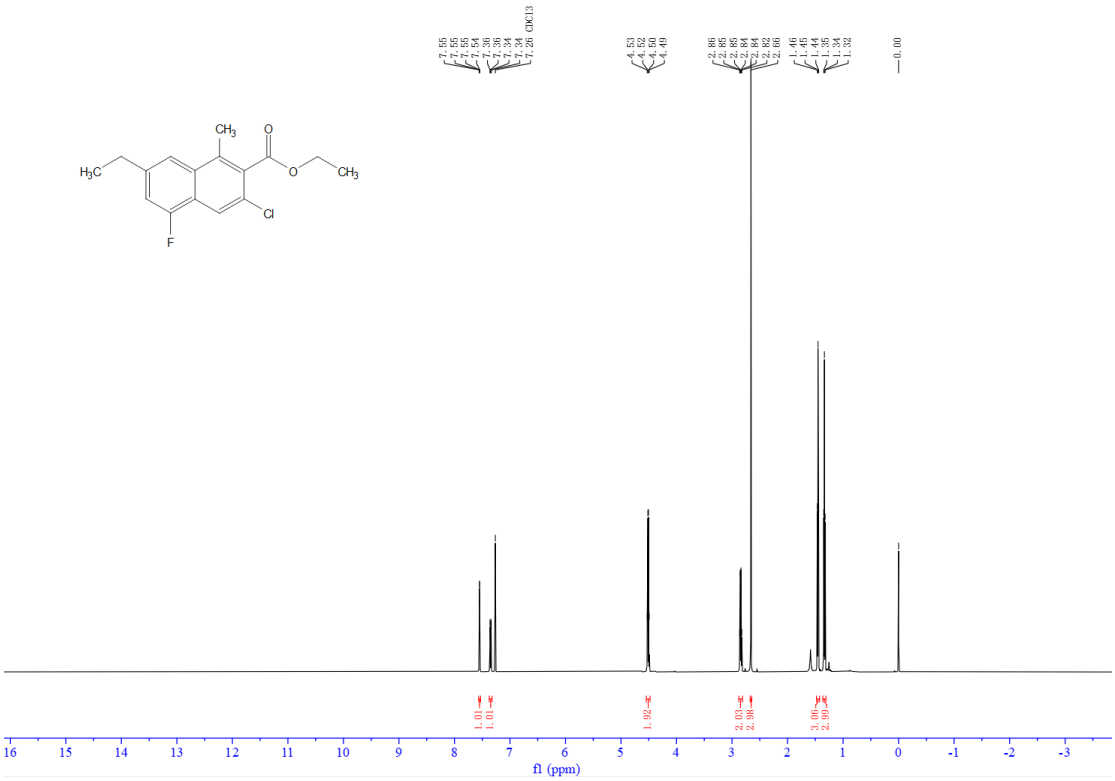

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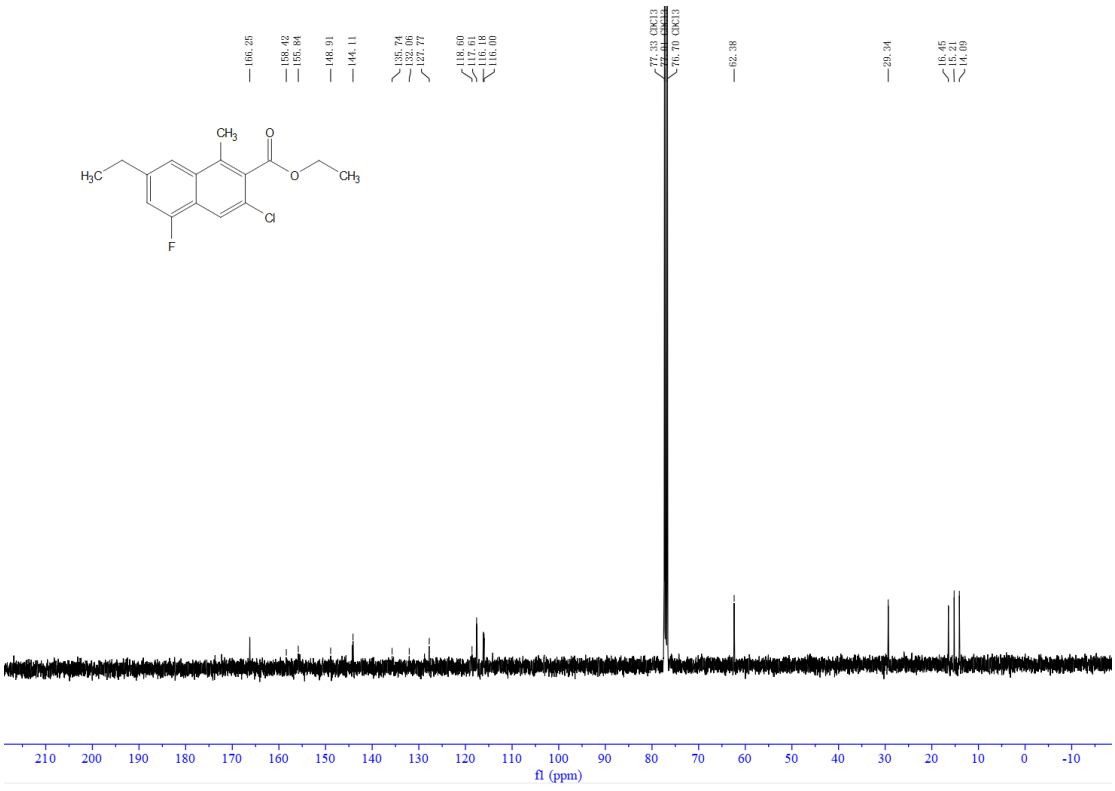
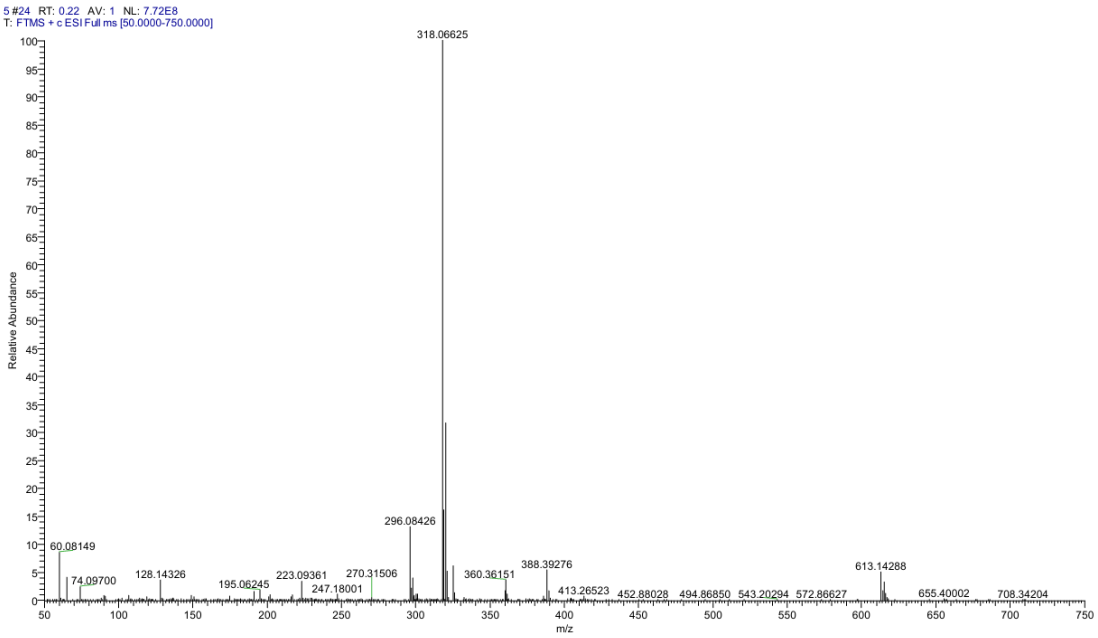
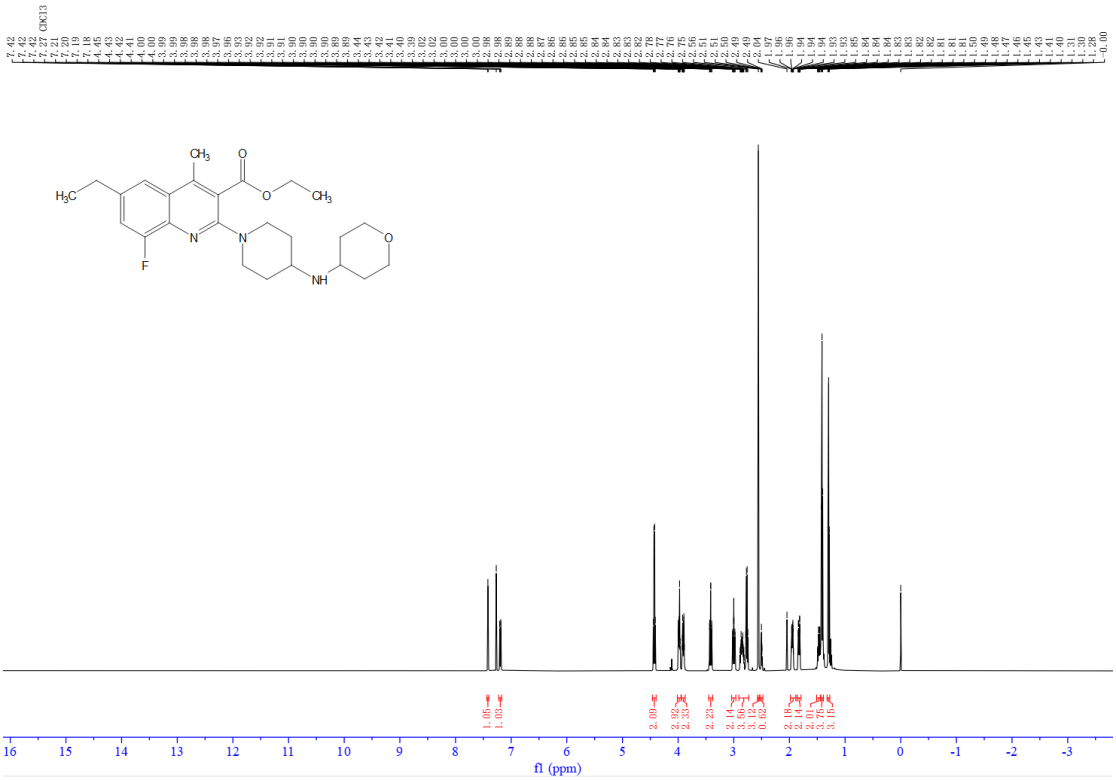


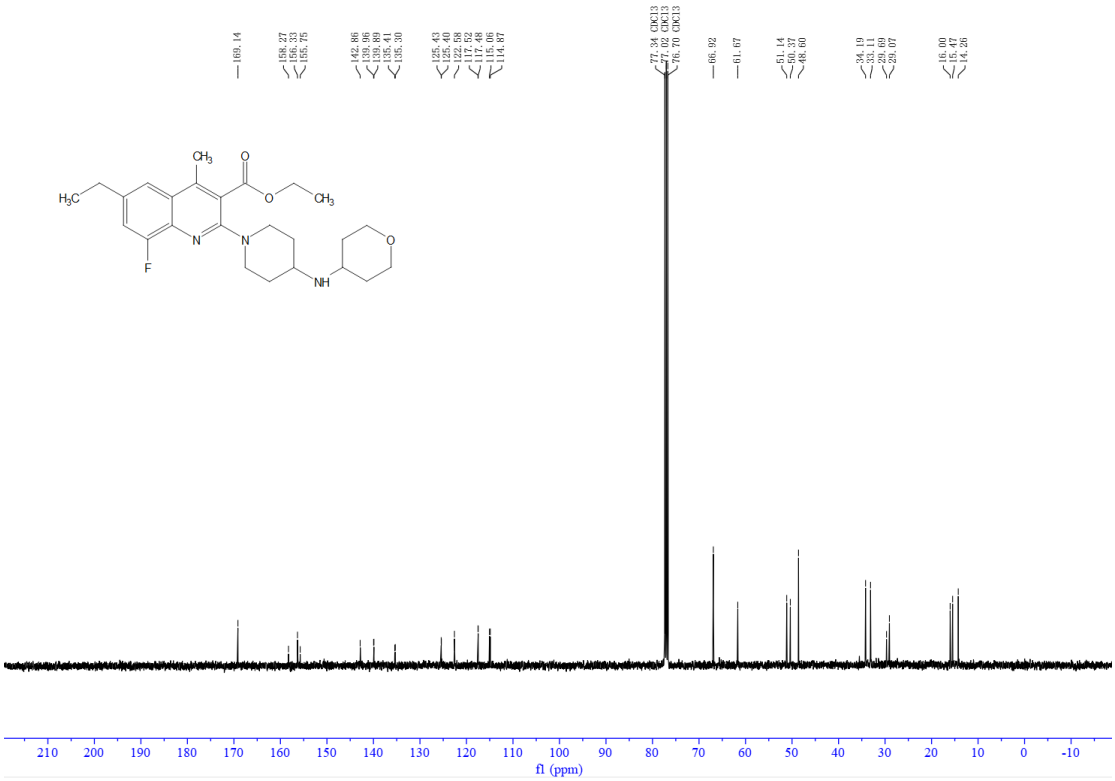
The ^{13}C NMR spectrum of compound **6**



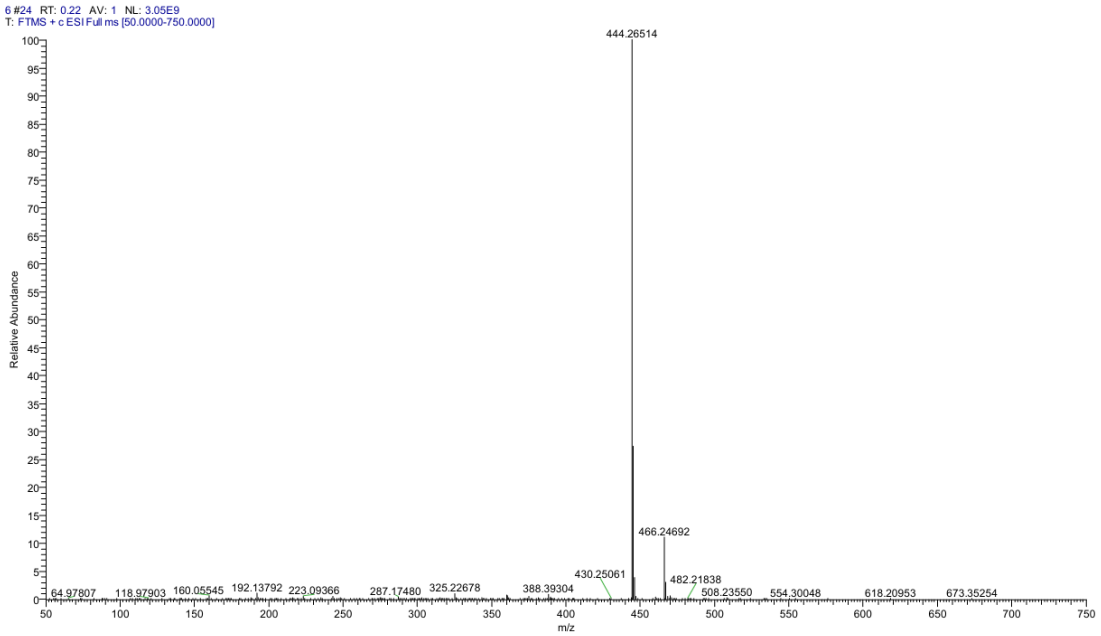
The High-Resolution Mass Spectrometry of compound **6**



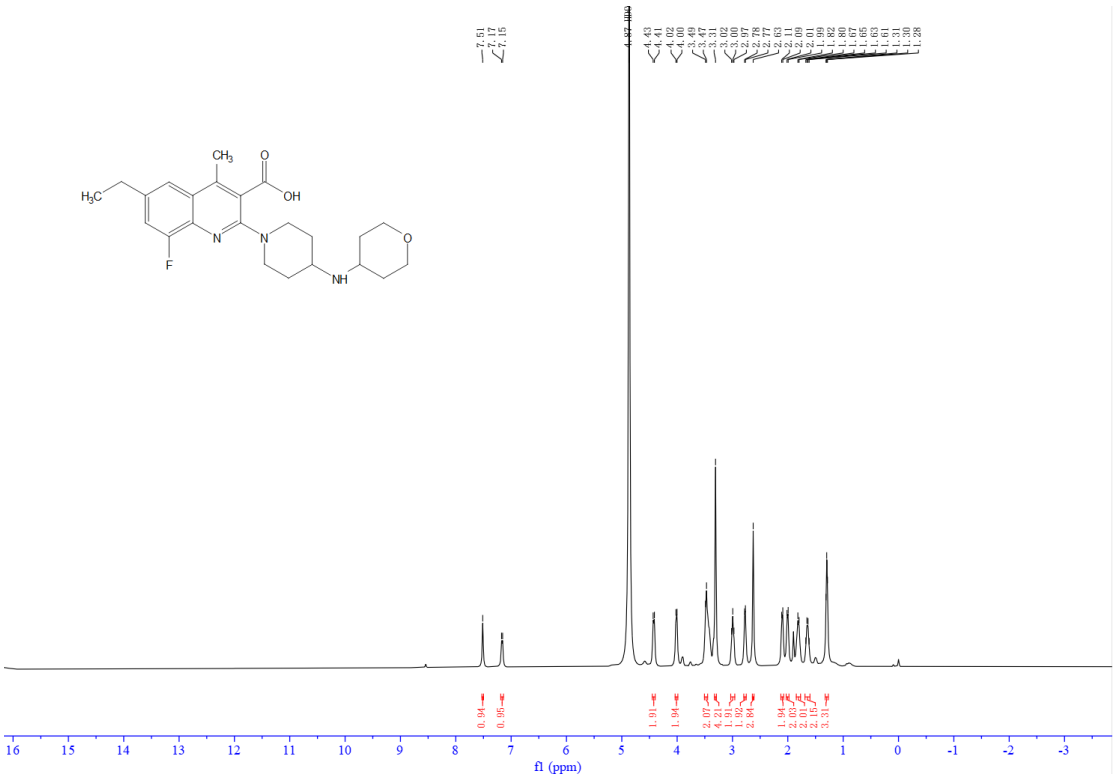
The ^{1}H NMR spectrum of compound **7**



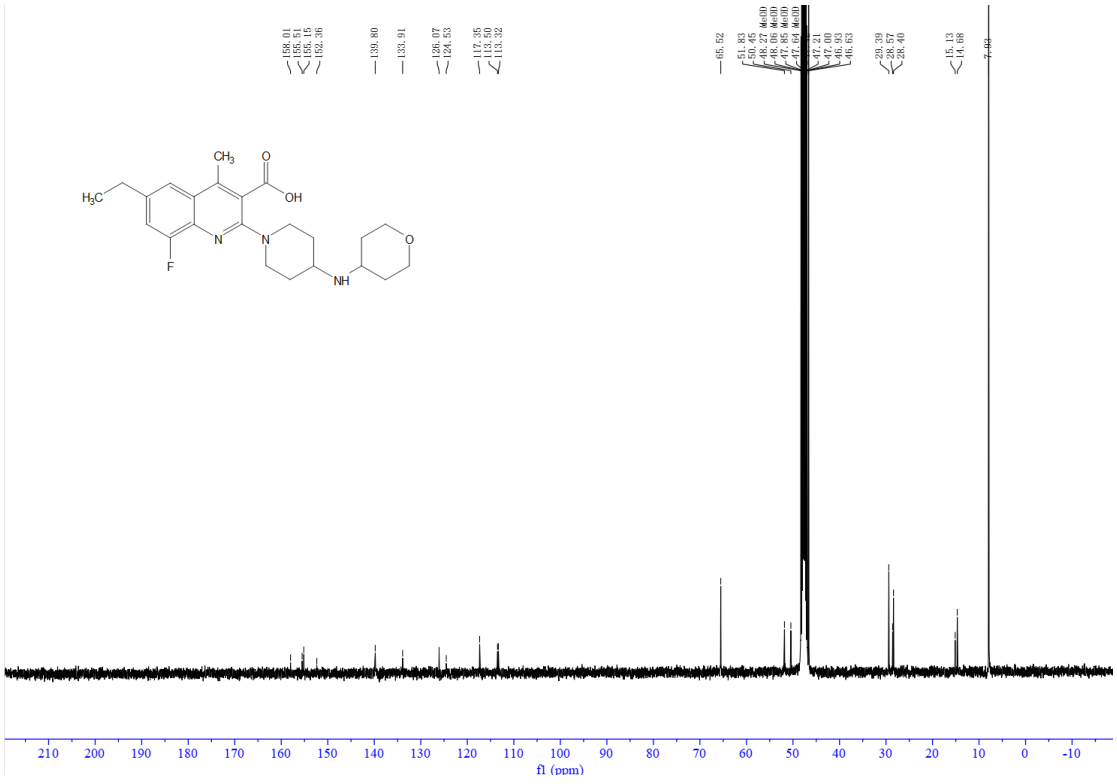
The ^{13}C NMR spectrum of compound **7**



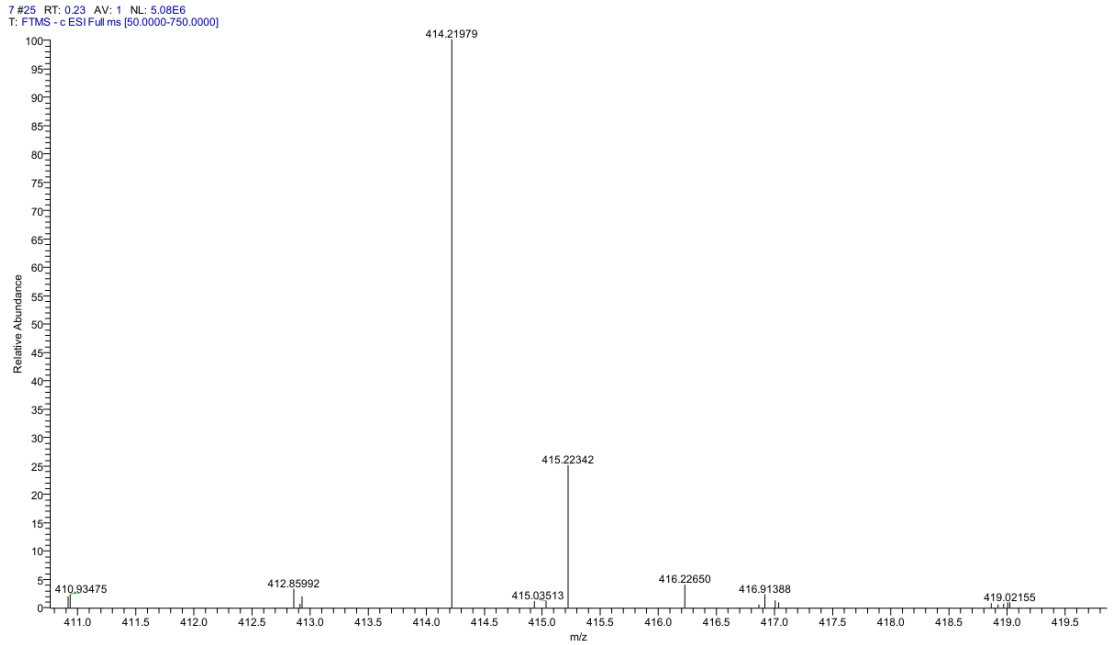
The High-Resolution Mass Spectrometry of compound **7**



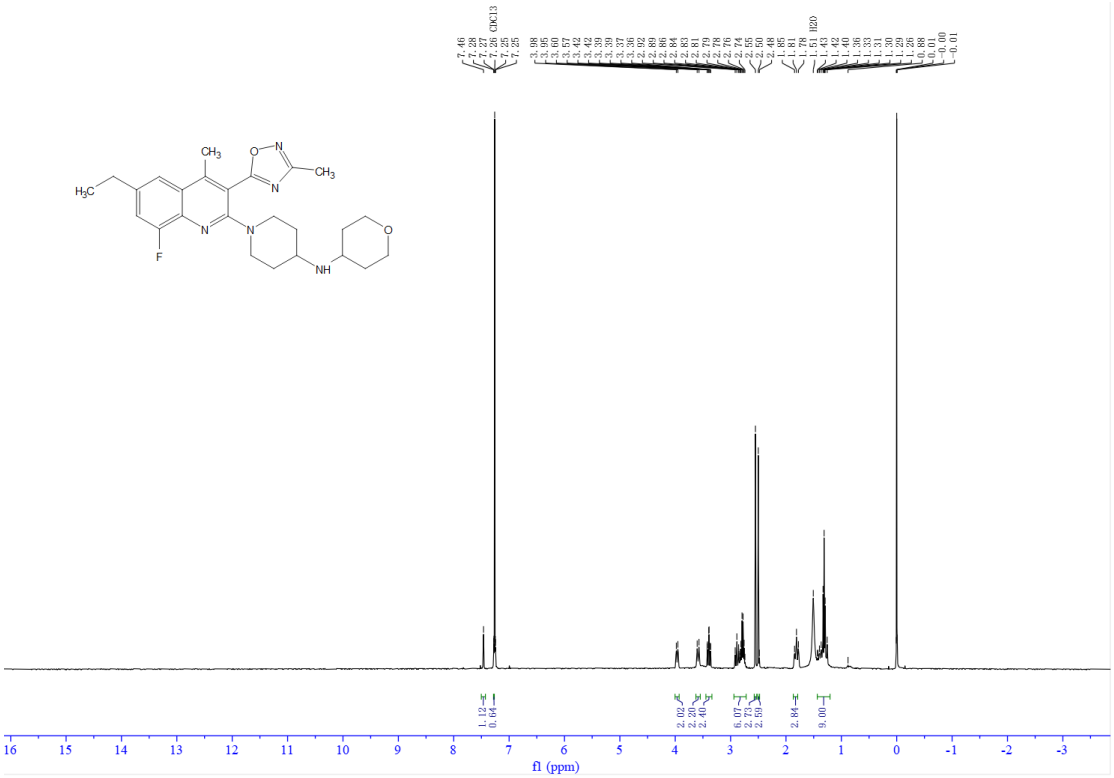
The ^{1}H NMR spectrum of compound **8**



The ^{13}C NMR spectrum of compound **8**

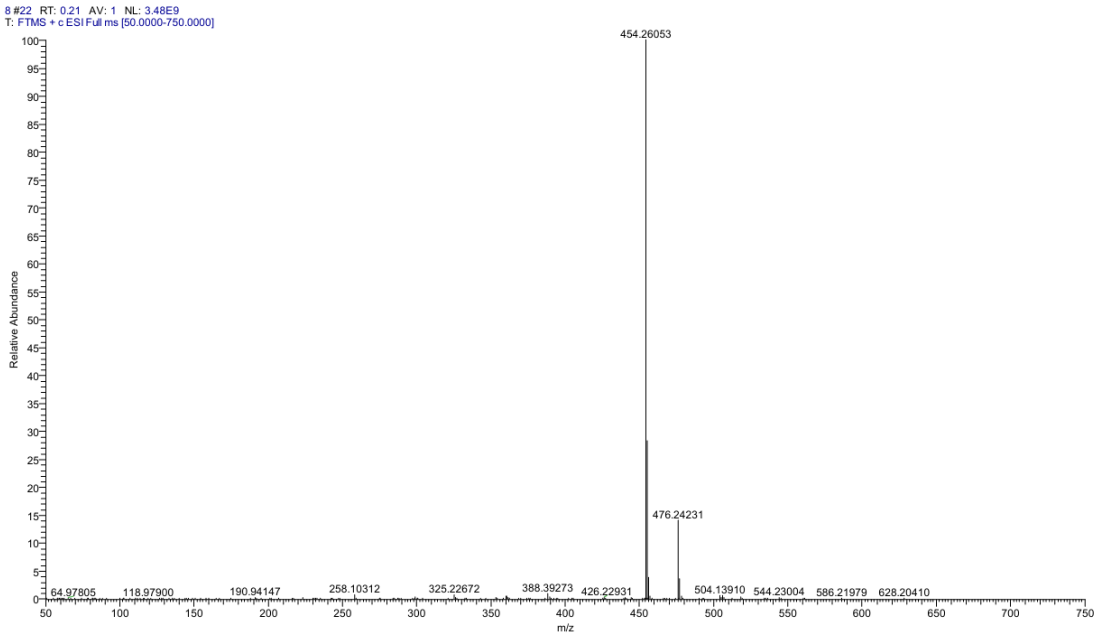


The High-Resolution Mass Spectrometry of compound **8**



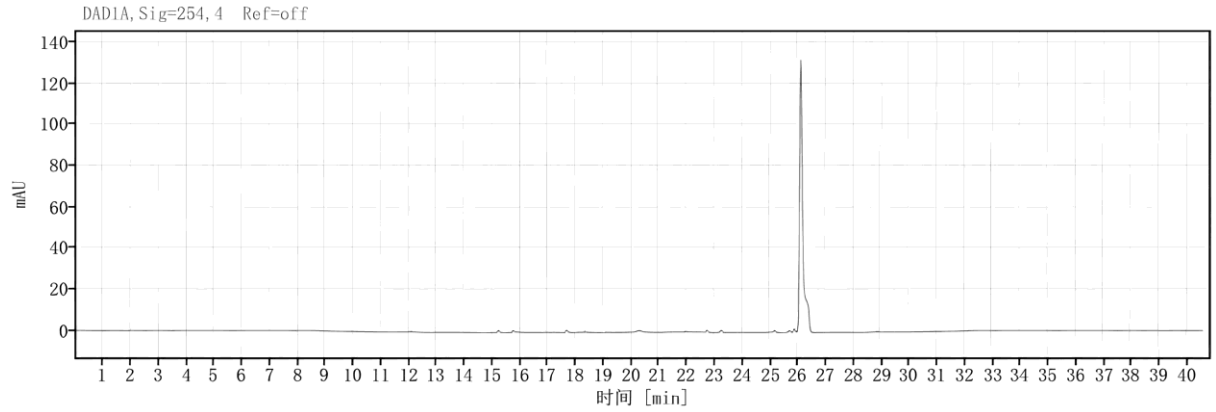
The ^{1}H NMR spectrum of compound **9**

The ^{13}C NMR spectrum of compound **9**



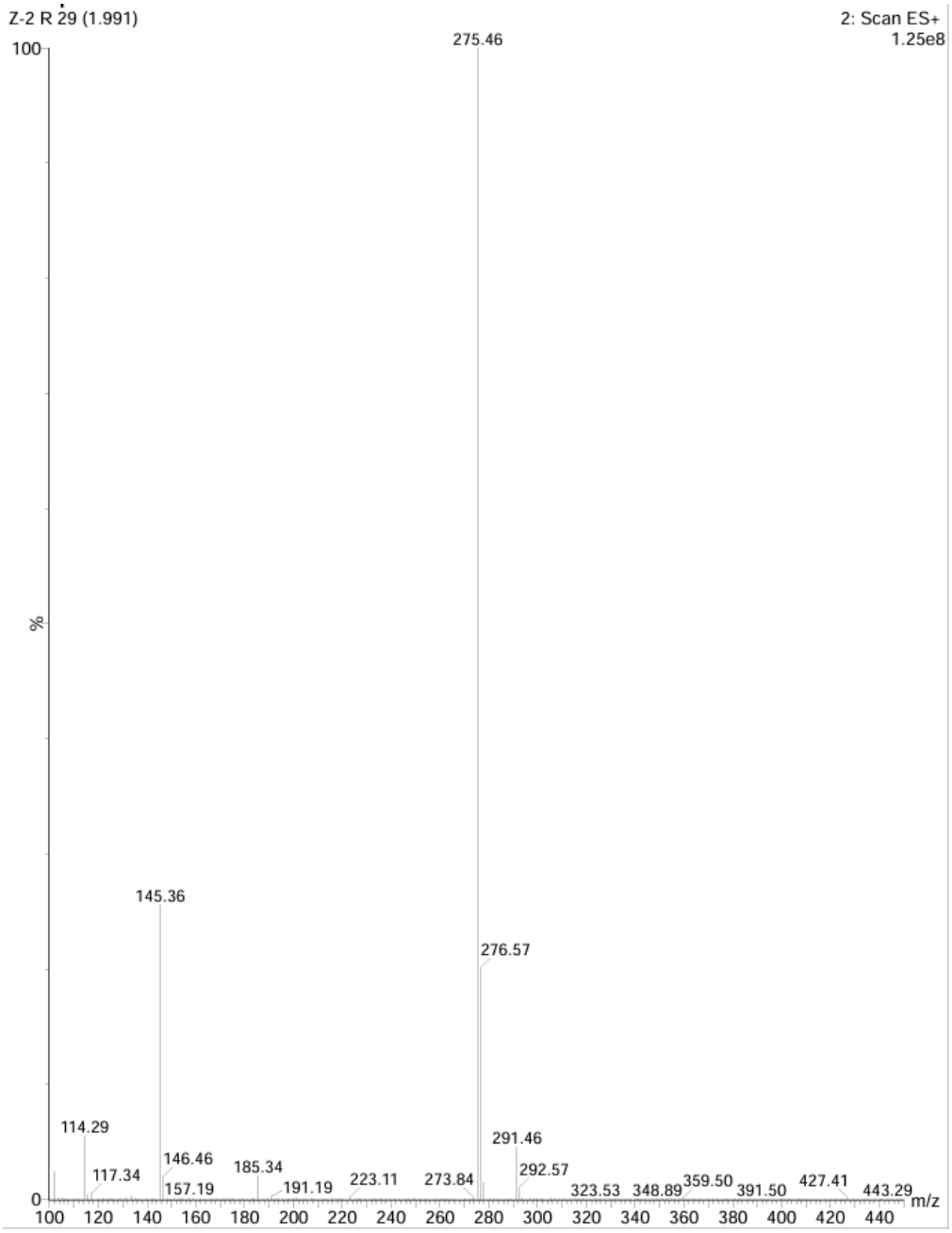
The High-Resolution Mass Spectrometry of compound **9**

Graphical presentation of high performance liquid chromatography of 9

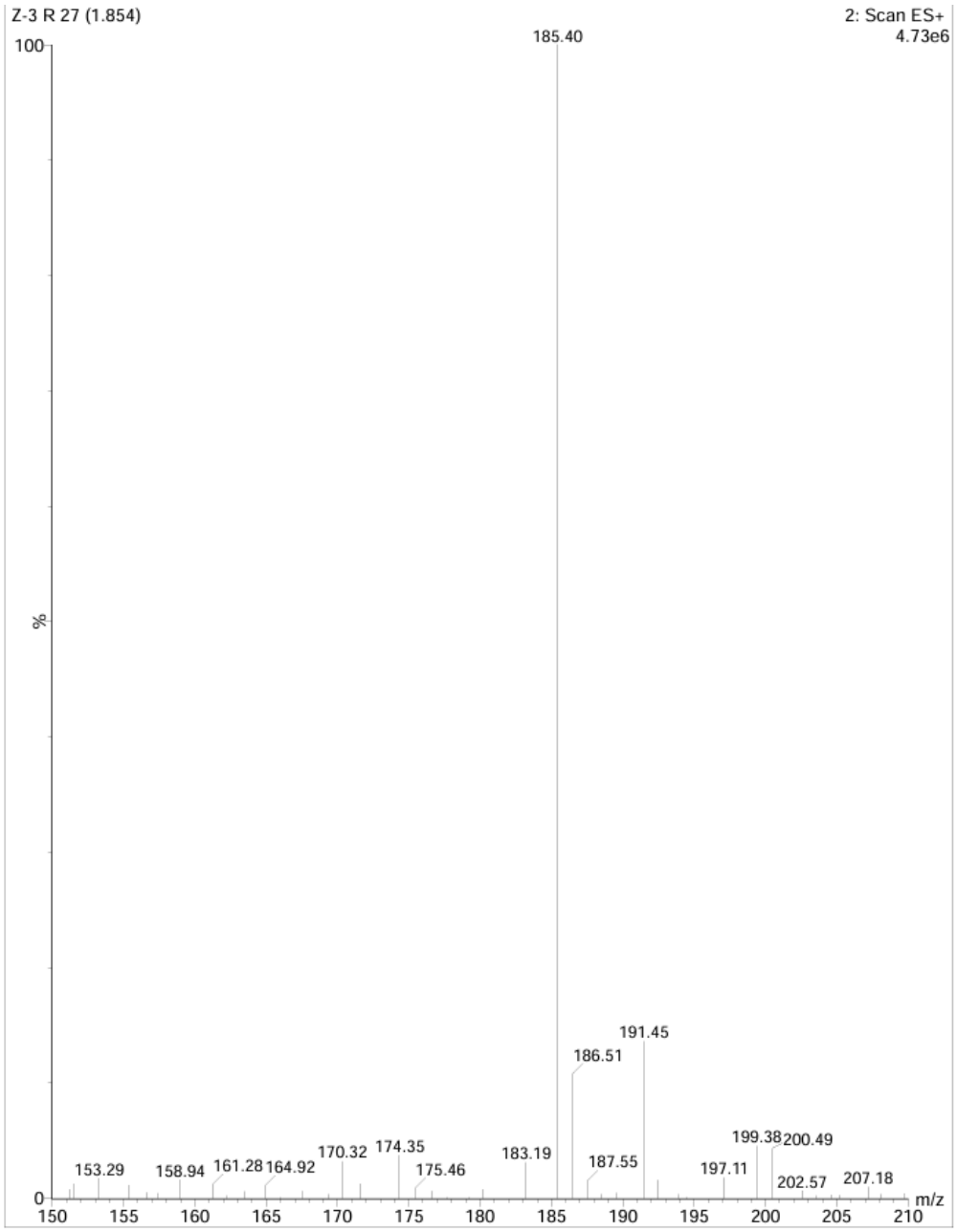


High performance liquid chromatography of **9**

Graphical presentation of mass spectrometry of 1-benzyl-*N*-(tetrahydro-2*H*-pyran-4-yl)piperidin-4-amine and *N*-(tetrahydro-2*H*-pyran-4-yl)piperidin-4-amine



Mass spectrometry of 1-benzyl-*N*-(tetrahydro-2*H*-pyran-4-yl)piperidin-4-amine



Mass spectrometry of *N*-(tetrahydro-2*H*-pyran-4-yl)piperidin-4-amine

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