# Supporting Information

## A Scalable and Eco-friendly Total Synthesis of Poly (ADP-Ribose) Polymerase Inhibitor Olaparib

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Table of Contents

**1. General Information.** Unless otherwise noted, all commercial reagents were used without further purification. All the reactions were performed in round bottom flask, stirred with a magnetic bar under nitrogen atmosphere and monitored by Thin-layer chromatography (0.2 mm silica gel-coated GF 254 plates) and visualized under UV or by staining with dragendorff solution. Flash column chromatography was carried out on Silica Gel 60-120 and 100-200 mesh basified by triethylamine. Nuclear magnetic resonance (NMR) spectra were recorded using Bruker Avance 400 Spectrometer.$^{1}$H and $^{13}$C chemical shifts are reported in ppm downfield of tetramethylsilane and referenced to residual solvent peak [$CHCl_3$; $\delta_H$ = 7.26 and $\delta_C$ = 77.0; DMSO-$d_6$; $\delta_H$ = 2.54 and $\delta_C$= 39.5].Multiplicities were given as: s (singlet); brs (broad singlet), d (doublet); t (triplet); q (quartet); dd (doublets of doublet); m (multiplets).High resolution mass spectra were taken with a 3000-mass spectrometer, using Waters Agilent 6520-Q-TofMS/MS system and JEOL-Accu TOF JMST100LC. Melting points are uncorrected and were determined in capillary tubes on SMP 10 melting point apparatus.

## 2. Synthetic details and experimental section.

**Cyclopropyl (piperazin-1-yl) methanone (15):** Acetic acid (10 ml) was treated with piperazine (2.5g, 29.02 mmol) portion wise over 15 minutes with stirring under nitrogen. The reaction mixture was warmed to 40 °C and maintained at this temperature until a complete solution was obtained. Cyclopropane carbonyl chloride (2.89 ml, 31.92 mmol) was added over 15 minutes. The reaction mixture was stirred at room temperature for 8h. The reaction mixture was filtered and the filtrate distilled under reduced pressure until acetic acid was fully evaporated. Ethyl acetate was charged to the reaction mixture and filtrate distilled under reduced pressure. A further charge of ethyl acetate was added and reduced pressure distillation continued until white precipitation of (**15**).White solid (3.9g), Melting point-149 $^{o}$C, yield-88%, **$^{1}$H NMR** (400MHz, DMSO-$d_6$) δ 9.73 (1H,brs), 3.93-3.41 (5H, m), 3.09-3.06 (3H, s), 2.03-1.95 (1H, m), 0.80-0.74 (4H, m); **$^{13}$C{$^{1}$H} NMR** (100 MHz, DMSO-$d_6$) δ 171.9, 42.9, 42.2, 10.7, 7.6; **HRMS(ESI):** Calculated for $C_8H_{15}N_2O$ $(M+H)^+$-155.1179, found 155.1183.

**(4-(5-bromo-2-fluorobenzoyl)piperazin-1-yl)(cyclopropyl)methanone (14):** To a stirred mixture of 2-fluoro-5-bromo benzoic acid (5.54 g, 25.29 mmol) in anhydrous DMF (25 ml) was added DIPEA (13.22 ml, 75.87 mmol), HBTU (9.59 g, 25.29 mmol), followed by cyclopropyl (piperazin-1-yl) methanone (3.9 g, 25.29 mmol) at 0 °C under nitrogen atmosphere. After the addition, the mixture was allowed to stir at room temperature for 15h. After distilling DMF, the mixture was diluted with dichloromethane, washed with saturated citric acid, followed by saturated sodium bicarbonate, brine, dried over anhydrous sodium sulfate, and concentrated. White solid of (4-(5-bromo-2-fluorobenzoyl)piperazin-1-yl)(cyclopropyl)methanone was obtained by recrystallization using EtOAc. White solid (6.74 g), Melting point- 93 $^{o}$C, yield-75%, **$^{1}$H NMR** (400MHz, $CDCl_3$) δ 7.48-7.44 (2H, m), 6.97-6.93 (1H, m), 3.71-3.27 (8H, m), 1.68 (1H, brs), 0.96-0.93 (2H, m), 0.74 (2H, brs); **$^{13}$C{$^{1}$H} NMR** (100 MHz, $CDCl_3$) δ 172.3, 163.9, 157.1 (d, *J* = 248.3 Hz), 134.5 (d, *J* = 8.0 Hz), 132.1 (d, *J* =

3.5 Hz), 125.5 (d, *J* = 21.7 Hz), 117.7 (d, *J* = 23.1 Hz), 117.4 (d, *J* = 3.1 Hz), 47.2, 42.3, 11.0, 7.7; **HRMS(ESI):** Calculated for $C_{15}H_{17}BrFN_2O_2$ $(M+H)^+$- 355.0452, found 355.0462.

**2-(2-(3-(4-(cyclopropanecarbonyl) piperazine-1-carbonyl)-4-fluorophenyl) acetyl) benzoic acid (12):** In a 50 ml schlenk tube, 2-acetylbenzoic acid (9.34 g, 56.92 mmol), (4-(5-bromo-2-fluorobenzoyl)piperazin-1-yl)(cyclopropyl)methanone (6.74 g, 18.97 mmol) and sodium *tert* butoxide (9.12 g, 94.85 mmol) were taken and then 20 ml of DMF was added to it under argon atmosphere. After that, mixture was heated to 120 $^oC$ for 36-40h. After completion of the reaction was monitored by TLC or LCMS, the mixture was extracted with chilled ethyl acetate and the extract dried with $Na_2SO_4$. Crude NMR was taken and used subsequently without further purification for next step. The product (**12**) was obtained as Colourless oil (7.07 g), yield- 85%, **$^1$H NMR** (400MHz, $CDCl_3$) δ 7.98 (1H, s), 7.84-7.83 (1H, m), 7.67-7.52 (2H, m), 7.41- 7.39 (1H, m), 7.33 (1H, s), 6.82-6.80 (1H, m), 3.78-3.74 (4H, m), 3.58 (2H,s), 3.30 (2H, brs), 2.96 (2H, s), 1.88-1.75 (1H, m), 0.99 (2H, s), 0,79 (2H, brs); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) δ 174.1, 172.5, 168.4, 162.8, 156.5 (d, *J* = 243.4 Hz), 148.8, 133.1 (d, *J* = 3.3 Hz), 131.6 (d, *J* = 7.8 Hz), 130.2, 129.6 (d, *J* = 18.5 Hz), 129.3, 128.8, 127.2, 125.2, 122.1, 118.6 (d, *J* = 20.4 Hz), 113.4, 46.5, 45.2, 42.2, 41.8, 36.6, 11.0, 7.7; **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ −117.03; **HRMS(ESI):** Calculated for $C_{24}H_{24}FN_2O_5$ $(M+H)^+$- 439.1664, found 439.1662.

**4-(3-(4-(cyclopropanecarbonyl) piperazine-1-carbonyl)-4-fluorobenzyl) phthalazin-1(2H)-one (1):** Add hydrazine hydrate (0.7 ml, 20.96 mmol) to a solution of 2-(2-(3-(4-(cyclopropanecarbonyl) piperazine-1-carbonyl)-4-fluorophenyl) acetyl) benzoic acid (7.07 g, 16.12 mmol) in EtOH (15 ml). Reflux the reaction mixture for 15h. Cool the mixture and distilled off the ethanol using rotavapour. The collected ethanol was reused. Then the reaction mixture was purified without any solvent extraction. The final product (**1**) was purified by flash chromatography. HPLC purity: 99.9 %.White solid (6.30 g), Melting point- 208 $^oC$, yield-90%, **IR** ν ($cm^{-1}$): 3912.64, 3885.22, 3781.66, 3696.08, 3657.28, 3404.03, 3011.49, 2922.83, 1633.92, 1468.48, 1438.75, 1357.09, 1287.40, 1229.20, 1159.16, 1064.56, 1014.22, 841.68, 774.12, 646.79, 559.42, 485.55; **$^1$H NMR** (400MHz, DMSO-$d_6$) δ 12.59 (1H, s), 8.28-8.26 (1H, m), 7.98-7.82 (3H, m), 7.46-7.37 (2H, m), 7.27-7.22 (1H, m), 4.34 (2H, s), 3.75-3.60 ( 6H, m), 3.23-3.17 (2H, m), 1.99 (1H,s), 0.75-0.72 (4H, m); **$^{13}$C{$^1$H} NMR** (100 MHz, DMSO-$d_6$) δ 171.8, 164.5, 159.9, 156.8 (d, *J* = 244.2 Hz), 145.3, 135.3 (d, *J* = 2.5 Hz), 133.9, 132.2 (d, *J* = 7.7 Hz), 132.0, 129.5, 129.4 (d, *J* = 3.5 Hz), 128.4, 126.5, 125.9, 124.0 (d, *J* = 18.2 Hz), 116.4 (d, *J* = 21.6 Hz), 46.7, 45.4, 42.2, 41.6, 36.9, 10.8, 7.6; **$^{19}$F NMR** (376 MHz, DMSO-$d_6$) δ −118.05; **HRMS (ESI):** Calculated for $C_{24}H_{24}FN_4O_3$ $(M+H)^+$- 435.1827, found 435.1833.

**(5-bromo-2-fluorophenyl)(4-methoxypiperidin-1-yl)methanone (21):** To a stirred mixture of 2-fluoro-5-bromo benzoic acid (200 mg, 0.91 mmol) in anhydrous DMF (5 ml) was added DIPEA (320 mg, 2.74 mmol), HBTU (346 mg, 0.91 mmol), followed by 4-methoxypiperidine (105 mg, 0.91 mmol) at 0 °C under nitrogen atmosphere. After the addition, the mixture was allowed to stir at room

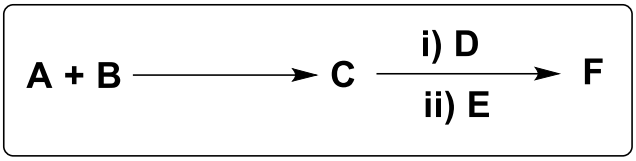
temperature for 15h. After distilling DMF, the mixture was diluted with dichloromethane (50 ml), washed with saturated citric acid (100 ml×2), followed by saturated sodium bicarbonate (100 ml×2), brine (50 ml), dried over anhydrous sodium sulfate, and concentrated. White solid (5-bromo-2-fluorophenyl)(4-methoxypiperidin-1-yl)methanone was obtained by recrystallization using EtOAc. White solid, Melting point- 89 ºC, yield-78%, **$^{1}$H NMR** (400MHz, $CDCl_3$) δ 7.50-7.47 (2H, m), 7.01-6.97 (1H, m), 3.96 (1H,brs), 3.61 (1H, brs), 3.51-3.46 (2H, m), 3.36 (3H, s), 3.16 (1H, brs), 1.96-1.80 (2H, m), 1.75-1.61 (2H, m); **$^{13}$C{$^{1}$H} NMR** (100 MHz, $CDCl_3$) δ 163.4, 157.1 (d, *J* = 249.0 Hz), 133.9 (d, *J* = 7.9 Hz), 131.7 (d, *J* = 3.6 Hz), 126.4 (d, *J* = 19.8 Hz), 117.6 (d, *J* = 23.1 Hz), 117.2 (d, *J* = 3.5 Hz), 74.9, 55.8, 44.1, 38.9, 31.0, 29.9; **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ −117.46; **HRMS(ESI):** Calculated for $C_{13}H_{16}BrFNO_2(M+H)^+$- 316.0343, found 316.0349.

**4-(4-fluoro-3-(4-methoxypiperidine-1-carbonyl)benzyl)phthalazin-1(2H)-one (19):** In a 30 ml glass vial, 2-acetylbenzoic acid (792mg, 4.8 mmol), (5-bromo-2-fluorophenyl)(4-methoxypiperidin-1-yl)methanone (500 mg, 1.58 mmol) and sodium *tert* butoxide (760 mg, 7.9 mmol) were taken and then 5ml of DMF was added to it under argon atmosphere. After that, the reaction mixture was heated to 120 ºC for 36-40h. After completion of the reaction, DMF distilled off. Then the mixture was extracted with ethyl acetate and the extract dried with $Na_2SO_4$. The crude oily product (500mg) was used in next step without further purification. The crude oily product (500mg) was dissolved in EtOH and then adds hydrazine hydrate (480 µl, 1.54 mmol) to it. Reflux the reaction mixture for 15h. Cool the mixture and distilled off the ethanol using rotavapour. Then the mixture was extracted with ethyl acetate and the extract dried with $Na_2SO_4$. The final product (**19**) was purified by flash chromatography. HPLC purity: 99.9 %. White solid, Melting point-80 ºC, yield-68%, **IR** ν ($cm^{-1}$): 3913.12, 3885.50, 3781.85, 3432.25, 2931.78, 2121.60, 1633.49, 1451.27, 1407.43, 1353.38, 1268.99, 1228.48, 1182.74, 1154.96, 1092.96, 1024.47, 938.29, 846.02, 754.33, 685.04, 647.23, 560.24, 485.67; **$^{1}$H NMR** (400MHz, DMSO-$d_6$) δ 12.60 (1H, s), 8.28-8.25 (1H, m), 7.97-7.95 (1H, m), 7.89-7.79 (2H, m), 7.43-7.34 (2H, m), 7.23-7.18 (1H, m), 4.33 (2H, s), 3.91 ( 1H, brs), 3.42-3.38 (3H, m), 3.23 (3H,s), 3.05-2.99 (1H, m), 1.88-1.84 (1H, m), 1.72-1.69 (1H, m), 1.47-1.39 (1H, m), 1.32-1.29 (1H, m); **$^{13}$C{$^{1}$H} NMR** (100 MHz, DMSO-$d_6$) δ 163.7, 159.4, 156.4 (d, *J* = 244.1 Hz), 144.9, 134.8 (d, *J* = 3.2 Hz), 133.5, 131.5, 131.4 (d, *J* = 7.9 Hz), 129.1, 128.6 (d, *J* = 3.5 Hz), 127.9, 126.1, 125.5, 124.2 (d, *J* = 18.7 Hz), 115.8 (d, *J* = 21.6 Hz), 74.8, 55.0, 43.9, 38.5, 36.5, 30.7, 30.1; **$^{19}$F NMR** (376 MHz, DMSO-$d_6$) δ −120.16; **HRMS (ESI):** Calculated for $C_{22}H_{23}FN_3O_3$ $(M+H)^+$- 396.1718, found 396.1711.

## 3. Calculations of Green Chemistry Metrics.

The green chemistry metrics of our method and literature reported method were calculated on the basis of Green Chemistry equations.[1]

**Steps involved in this process (linear reactions) are:**

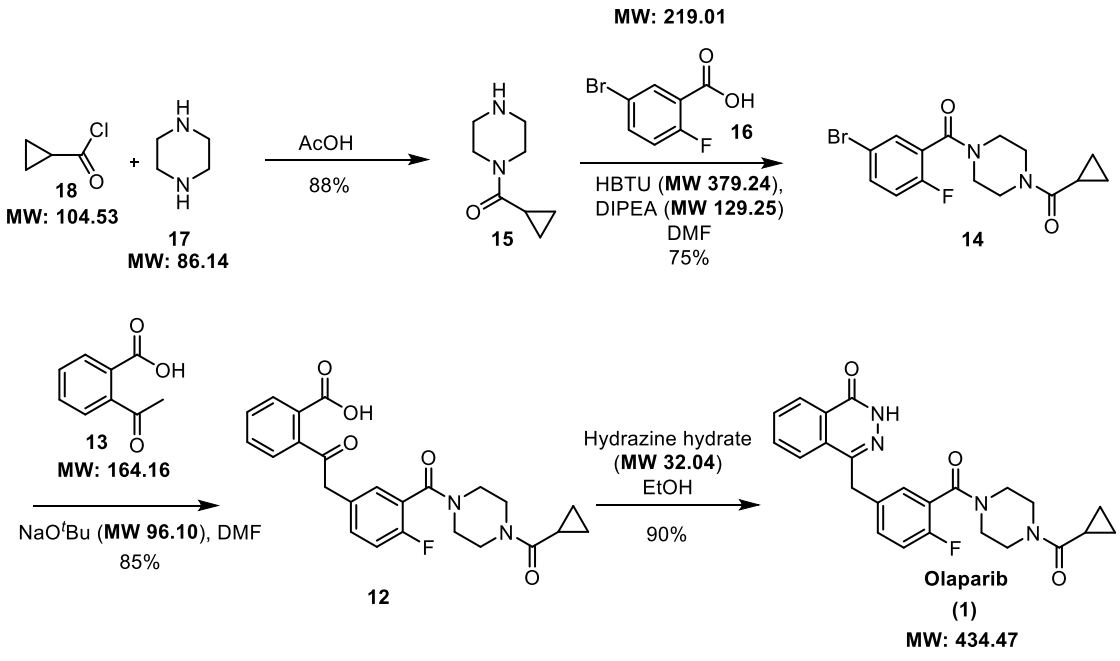



The reactants and reagents efficiently participate in product formation excluding intermediates. The Green Chemistry Metrics are calculated based on general formula[1] as below:

1. No. of steps = No. of steps involved in the process
2. Atom economy = [(M.W. of product F)/ (M.W. of A+ M.W. of B+ M.W. of D+ M.W. of E)]x100
3. Overall yield = (Yield of formation of C x Yield of formation of F)/100
4. Atom efficiency = % yield x Atom economy
5. Process Mass Intensity = (Total mass used in the process / Mass of the product)
6. Mass productivity = (1/ Mass intensity) x100
7. E-factor = (Mass intensity – 1)
8. Effective Mass Yield = (1/ E-factor) x100
9. Reaction Mass Efficiency = [(Mass of product F) / (Mass of A + Mass of B + Mass of D + Mass of E)] x 100.

**A)** Calculation of **Green Chemistry Metrics** for our method

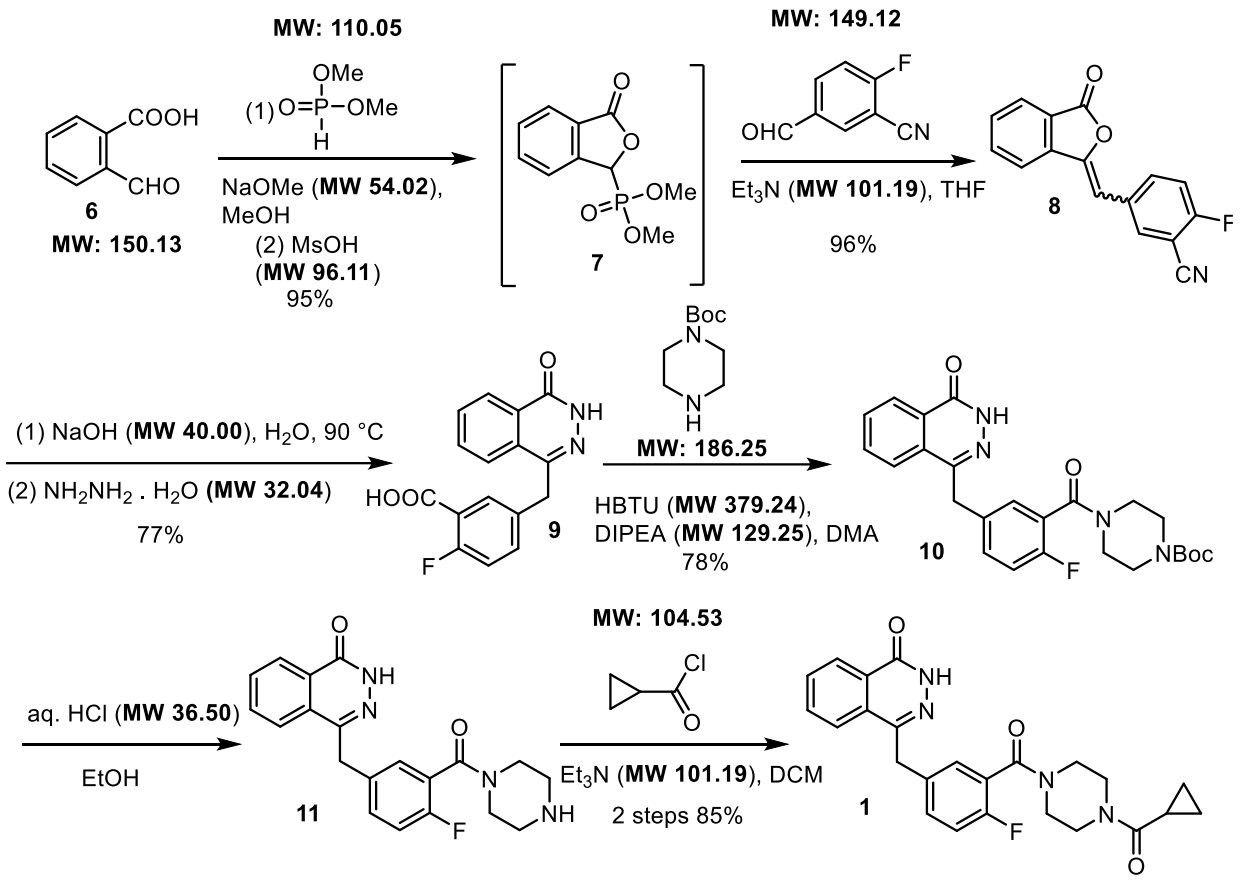
**Steps involved in this process are:**



1. No. of steps = 4.
2. Atom economy = [(434.47) / (104.53+86.14+219.01+379.24+129.25+164.16+96.10+32.04)]x100 = [434.47/1210.47]x100 = 35.89% ≈ 35.9%.
3. Overall yield = 51.0%.
4. Atom efficiency = [(51.0/100)x35.9] = 18.3%.
5. Process Mass Intensity (PMI) = [(3.32+2.50+10.50+5.54+9.59+9.81+23.60+9.34+9.12+18.90+0.70+11.80)/6.30] = [114.72/6.30] = 18.21 g/g ≈ 18.2 g/g.
6. Mass productivity = [(1/18.2)x100] = [0.0549x100] = 5.5%.
7. E-factor = 18.2-1 = 17.2 g/g.
8. Effective Mass Yield = [(1/17.2)x100] = [0.0581x100] = 5.8%.
9. Reaction Mass Efficiency (RME) = [{6.30/(3.32+2.50+5.54+9.59+9.81+9.34+9.12+0.70)}x100] = [{6.30/49.92}x100] = 12.62% ≈ 12.6%.

**B)** Calculation of **Green Chemistry Metrics** for Literature reported method[2] **(WO 2004/080976 A1** & **WO 2008/047082 A2)**

***Consideration:*** All calculations are done based on two literature reported patents (WO 2004/080976 A1 & WO 2008/047082 A2). In our work, 6.30 g Olaparib was synthesized. The two above-mentioned patents disclosed all reactions procedures, such as equivalent of reactants, mmol, yield etc. But the scaling of all steps is different. So, for mass calculation purpose and comparison with our method, we assume the scale of Olaparib synthesis in 6.30 g by using reported patents data (such as equivalent of reactants, mmol, yield etc).




1. No. of steps = 6.
2. Atom economy = [(434.47) / (150.13+110.05+54.02+96.11+149.12+101.19+40.00+32.04+186.25+379.24+129.25+36.50+104.53+101.19)]x100 = [434.47/1669.62]x100 = 26.02% ≈ 26.0%.
3. Overall yield = 46.0%.
4. Atom efficiency = [(46.0/100)x26.0] = 11.96% ≈ 12.0%.
5. Process Mass Intensity (PMI) = [(4.82+7.11+13.96+6.83+36.21+4.57+3.10+64.16+3.54+1.42+15.91+5.07+11.19+6.46+26.49+12.91+5.14+1.68+1.63+94.40)/6.30] = [326.60/6.30] = 51.84 g/g ≈ 51.8 g/g.
6. Mass productivity = [(1/51.8)x100] = [0.0193x100] = 1.9%.
7. E-factor = 51.8-1 = 50.8 g/g
8. Effective Mass Yield = [(1/50.8)x100] = [0.0197x100] = 1.97% ≈ 2.0%.
9. Reaction Mass Efficiency (RME) = [{6.30/(4.82+7.11+13.96+6.83+4.57+3.10+3.54+1.42+5.07+11.19+6.46+12.91+1.68+1.63)} x100] = [{6.30/84.29}x100] = 7.47% ≈ 7.5%.

**4. Table S1:** Table of comparing the shifts ($^1$H NMR spectrum) of final compound Olaparib (**1**) with the literature reported[3] values.

| **$^1$H NMR** (400MHz, DMSO-$d_6$) **Compound 1** **(**δ ppm) | **$^1$H NMR** (400MHz, DMSO-$d_6$) **Literature reported compound**[3] **(**δ ppm) |
|---|---|
| 12.59 (1H, s) | 12.53 (1H, s) |
| 8.28-8.26 (1H, m) | 8.25 (1H, dd) |
| 7.98-7.82 (3H, m) | 7.92 (1H, d), 7.83 (1H, dt), 7.77 (1H, dt) |
| 7.46-7.37 (2H, m) | 7.41 (1H, m), 7.34 (1H, dd) |
| 7.27-7.22 (1H, m) | 7.17 (1H, t) |
| 4.34 (2H, s) | 4.31 (2H, s) |
| 3.75-3.60 (6H, m) | 3.56 (6H, m) |
| 3.23-3.17 (2H, m) | 3.20 (2H, brs) |
| 1.99 (1H, s) | 1.88 (1H, brs) |
| 0.75-0.72 (4H, m) | 0.70 (4H, m) |

**5. A) Table S2:** Table of comparing the shifts ($^1$H NMR spectrum) of final compound AZD2461(**19**) with the literature reported[4] values.

| **$^1$H NMR** (400MHz, DMSO-$d_6$) **Compound 19** **(**δ ppm) | **$^1$H NMR** (500MHz, $CDCl_3$) **Literature reported compound**[4] **(**δ ppm) |
|---|---|
| 12.60 (1H, s) | 12.12 (1H, s) |
| 8.28-8.25 (1H, m) | 8.41-8.39 (1H, m) |
| 7.97-7.95 (1H, m), 7.89-7.79 (2H, m) | 7.66-7.65 (3H, m) |
| 7.43-7.34 (2H, m) | 7.28-7.24 (1H, m), 7.23-7.21 (1H, m) |
| 7.23-7.18 (1H, m) | 6.94-6.90 (1H, m) |
| 4.33 (2H, s) | 4.22 (2H, s) |
| 3.91 (1H, brs) | 3.91 (1H, brs) |
| 3.42-3.38 (3H, m) | 3.50-3.39 (1H, m), 3.31-3.27 (2H, m) |

| | |
|---|---|
| 3.23 (3H, s) | 3.12 (3H, s) |
| 3.05-2.99 (1H, m) | 3.05-2.81 (1H, m) |
| 1.88-1.84 (1H, m) | 1.86-1.82 (1H, m) |
| 1.72-1.69 (1H, m) | 1.69 (1H, brs) |
| 1.47-1.39 (1H, m) | 1.64-1.62 (1H, brs) |
| 1.32-1.29 (1H, m) | 1.60-1.59 (1H, m) |

**B) Table S3:** Table of comparing the shifts $^{13}C\{^{1}H\}$ NMR spectrum of final compound AZD2461(**19**) with the literature reported[4] values.

| **$^{13}$C NMR** (100MHz, DMSO-$d_6$) **Compound 19** (δ ppm) | **$^{13}$C NMR** (125MHz, $CDCl_3$) **Literature reported compound**[4] (δ ppm) |
|---|---|
| 163.73 | 164.75 |
| 159.44 | 161.10 |
| 157.61 & 155.18 | 157.96 & 155.99 |
| 144.96 | 145.55 |
| 134.83 & 134.80 | 134.20 & 134.18 |
| 133.48 | 133.46 |
| 131.55 | 131.34 |
| 131.44 & 131.36 | 131.04 & 130.97 |
| 129.10 | 129.48 |
| 128.61 & 128.57 | 128.81 & 128.78 |
| 127.93 | 128.16 |
| 126.10 | 126.93 |
| 125.46 | 125.02 |
| 124.29 & 124.10 | 124.51& 124.36 |
| 115.96 & 115.75 | 116.03 & 115.86 |
| 74.76 | 74.97 |
| 55.04 | 55.86 |
| 43.90 | 44.08 |
| 38.52 | 38.81 |
| 36.48 | 37.86 |
| 30.72 | 30.91 |
| 30.10 | 29.94 |

## 6. References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# 7. Spectra of compounds

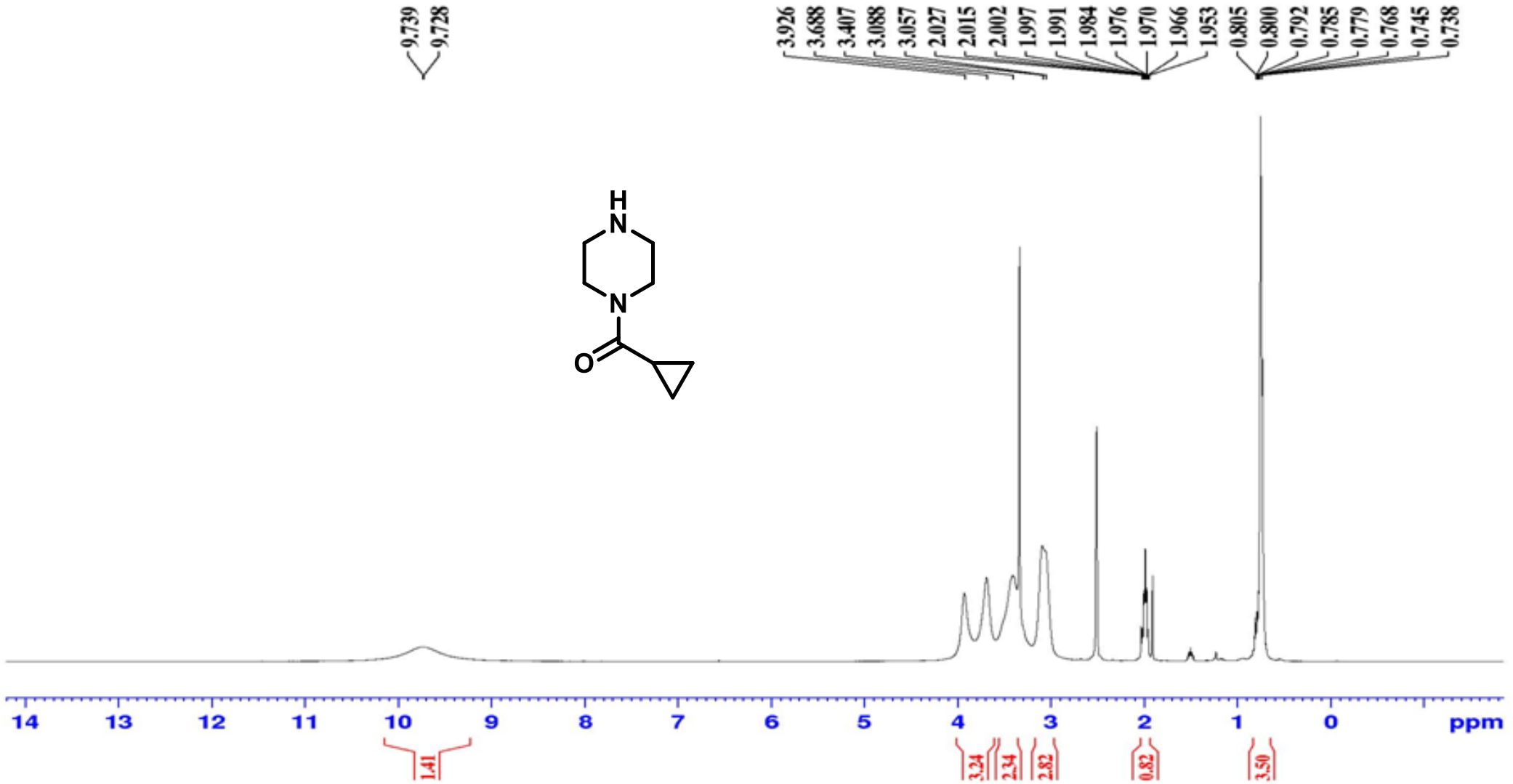


**Figure S1. $^{1}$H NMR of Cyclopropyl (piperazin-1-yl) methanone (15)**

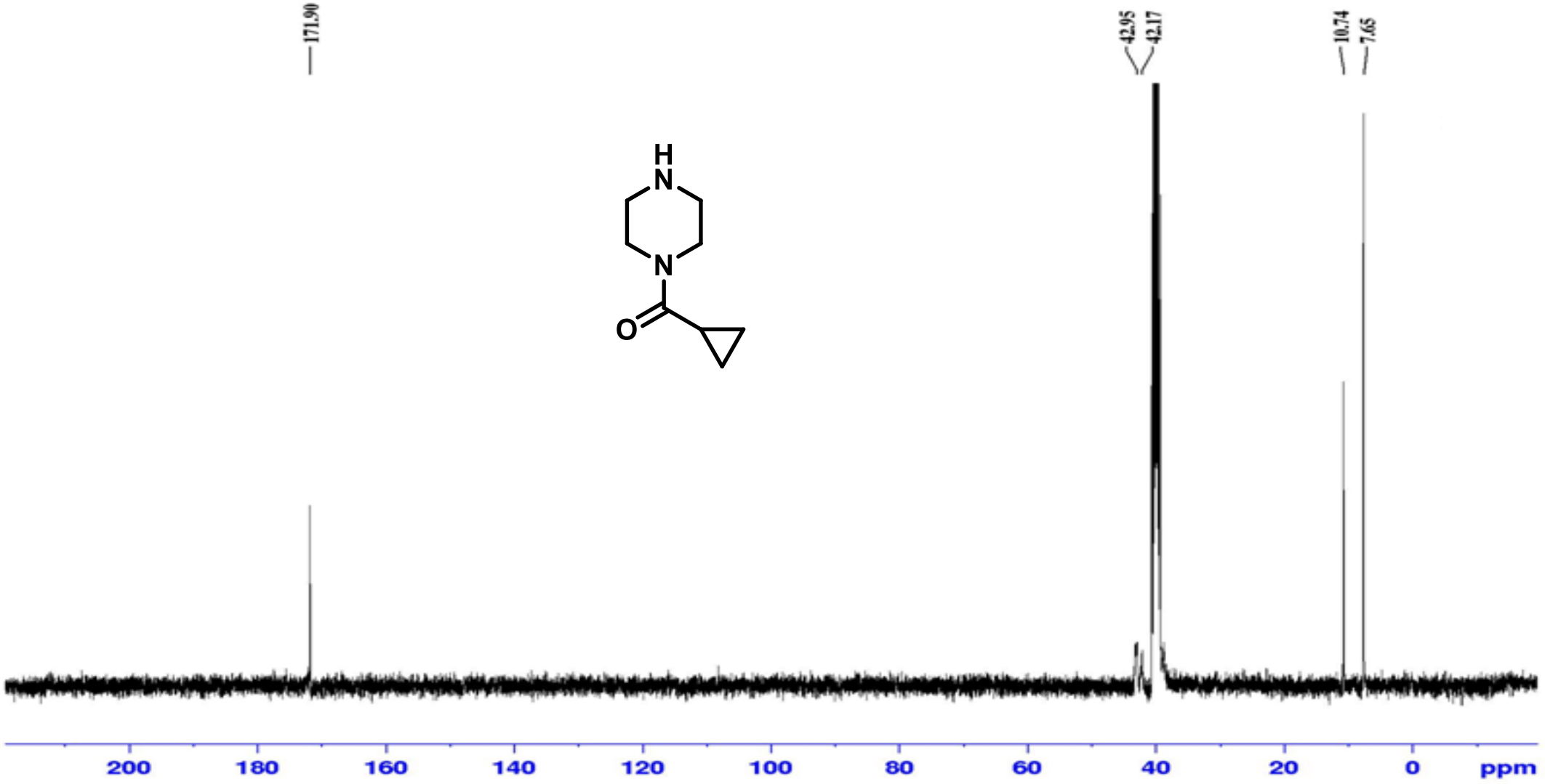


**Figure S2. $^{13}C\{^{1}H\}$ NMR spectra of Cyclopropyl (piperazin-1-yl) methanone (15)**

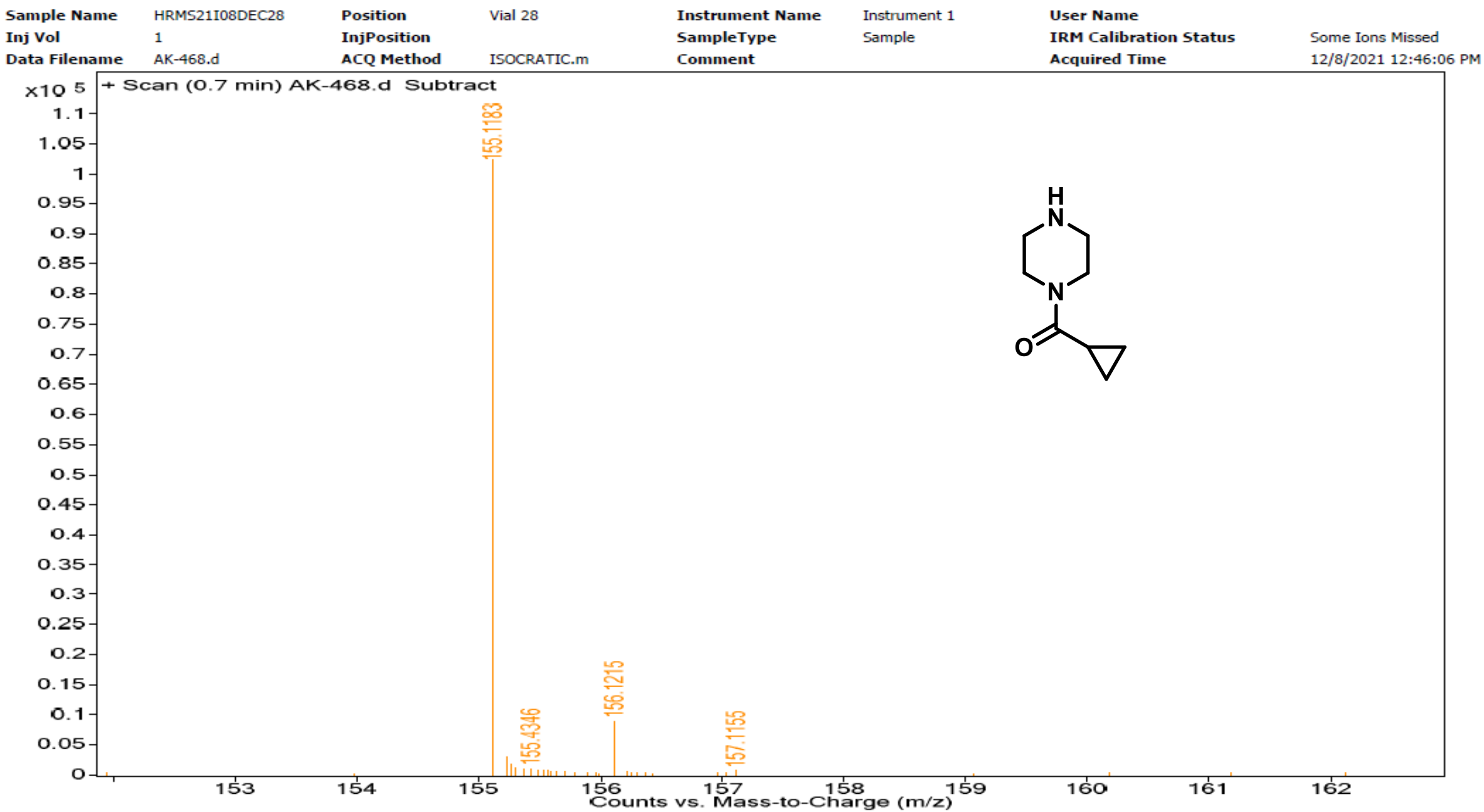


**Figure S3. HRMS spectra of Cyclopropyl (piperazin-1-yl) methanone (15)**

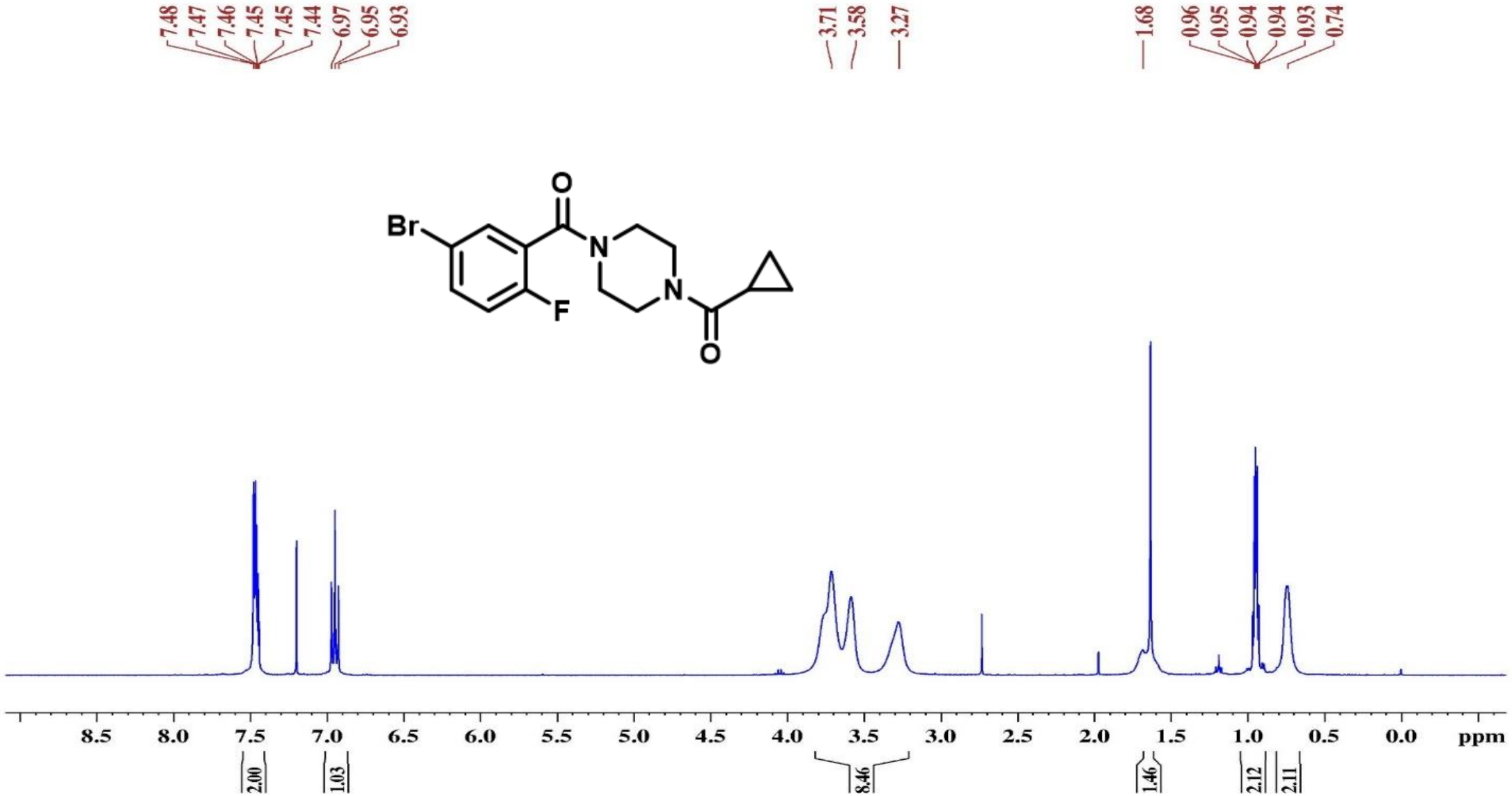


**Figure S4. $^{1}$H NMR spectra of (4-(5-bromo-2-fluorobenzoyl)piperazin-1-yl)(cyclopropyl)methanone (14)**

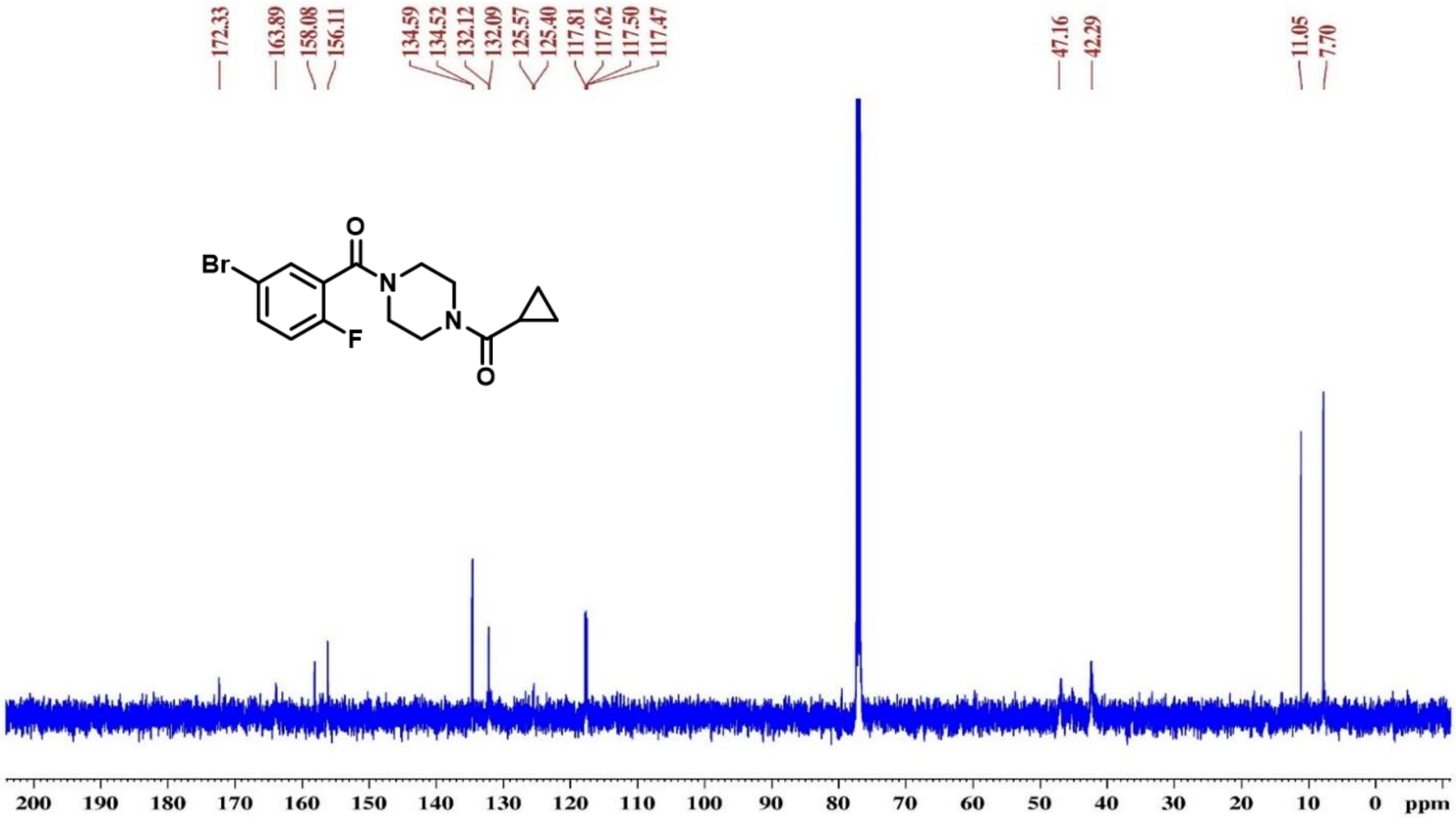


**Figure S5.** $^{13}C\{^{1}H\}$ **NMR spectra of (4-(5-bromo-2-fluorobenzoyl)piperazin-1-yl)(cyclopropyl)methanone (14)**

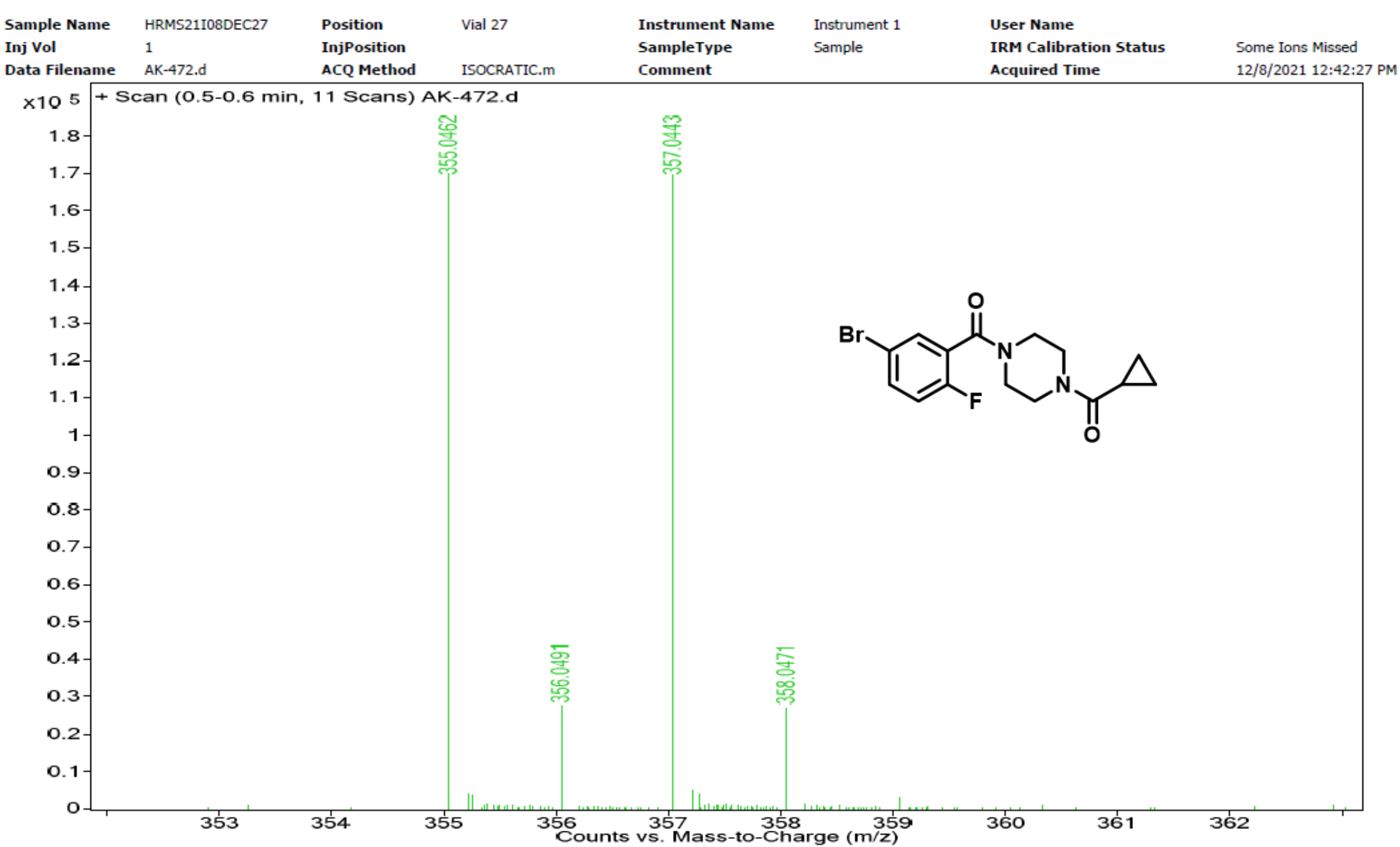


**Figure S6. HRMS spectra of (4-(5-bromo-2-fluorobenzoyl)piperazin-1-yl)(cyclopropyl)methanone (14)**

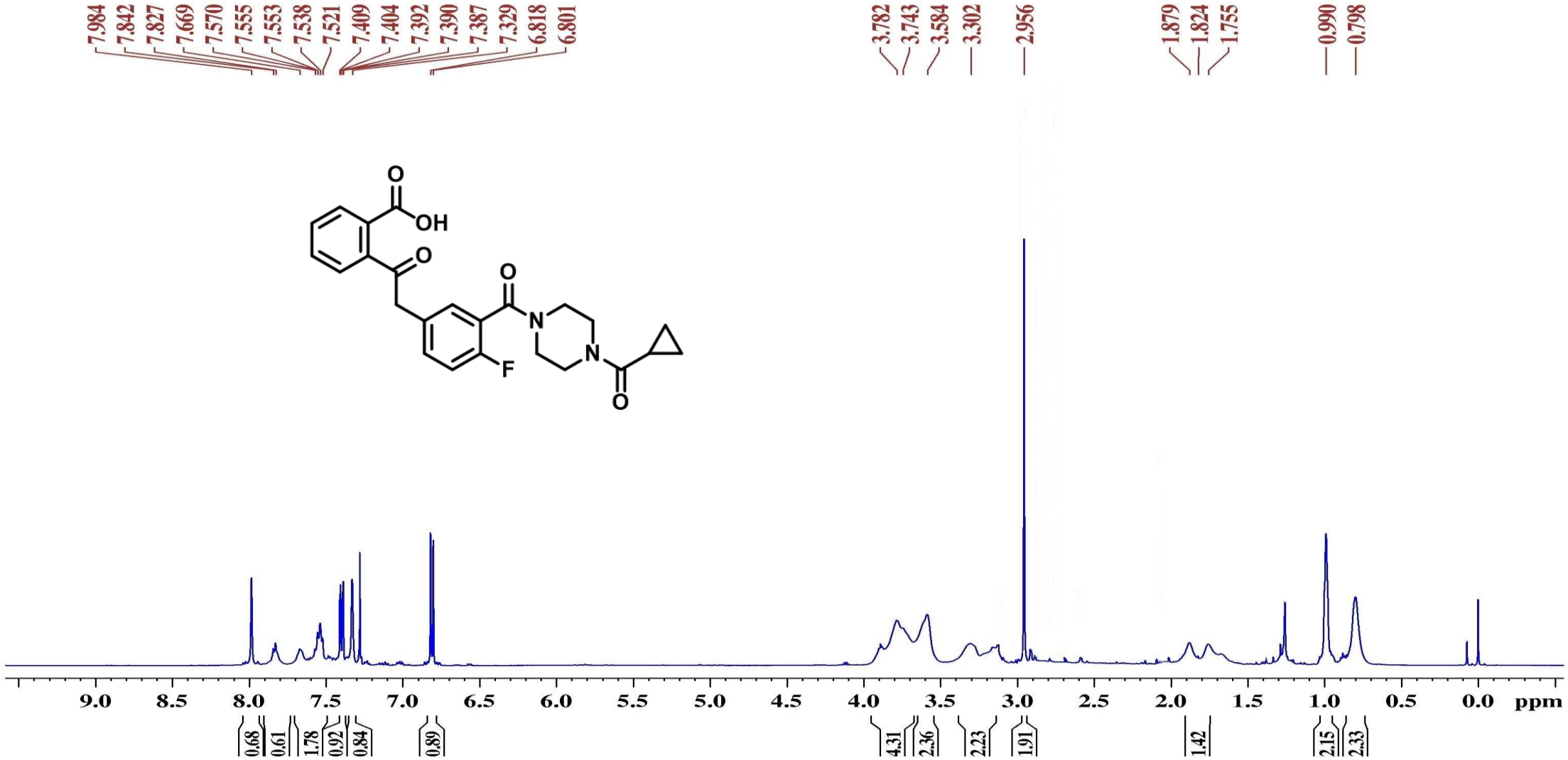


**Figure S7. $^{1}$H NMR spectra of 2-(2-(3-(4-(cyclopropanecarbonyl) piperazine-1-carbonyl)-4-fluorophenyl) acetyl) benzoic acid (12)**

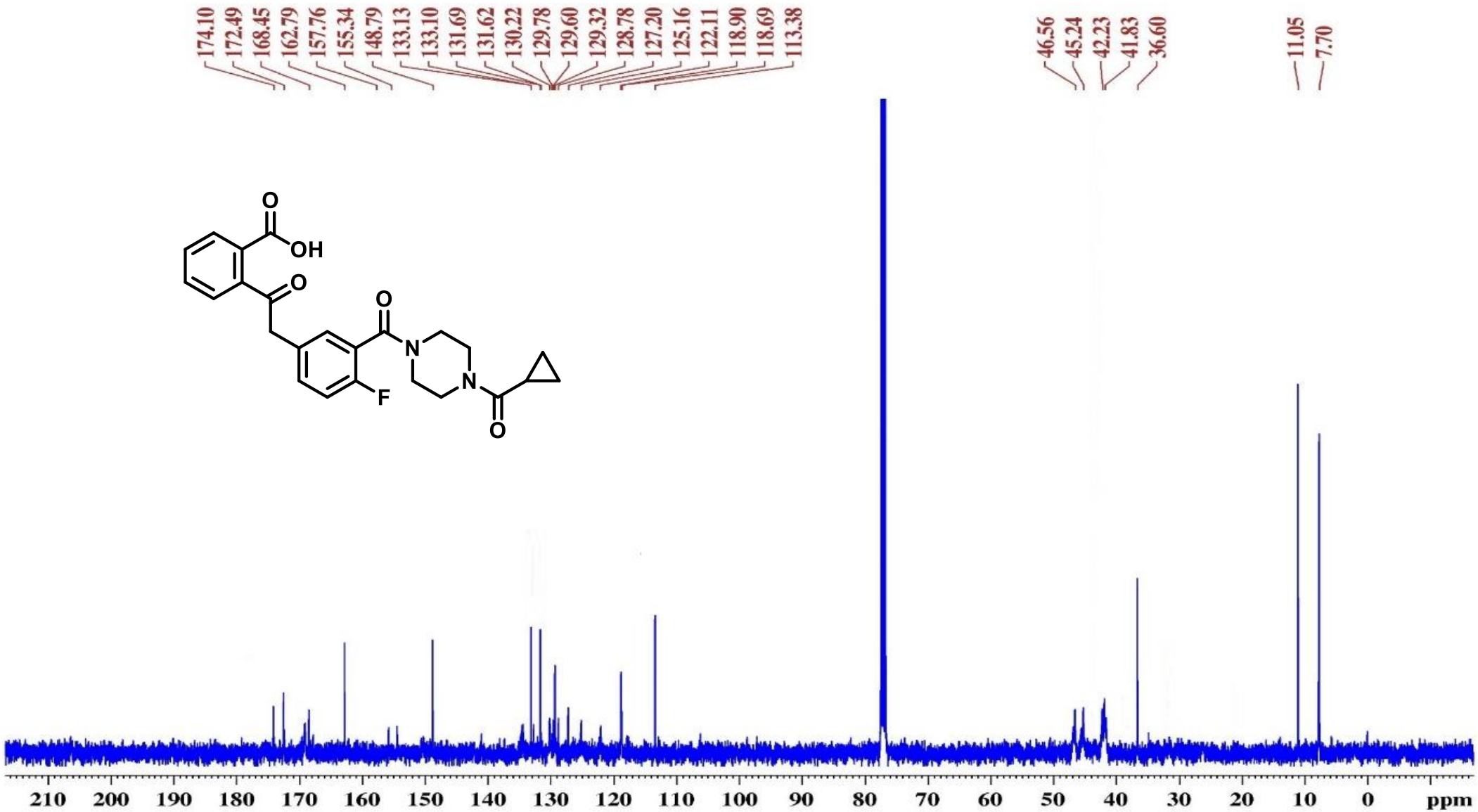


**Figure S8. $^{13}C\{^{1}H\}$ NMR spectra of 2-(2-(3-(4-(cyclopropanecarbonyl) piperazine-1-carbonyl)-4-fluorophenyl) acetyl) benzoic acid (12)**

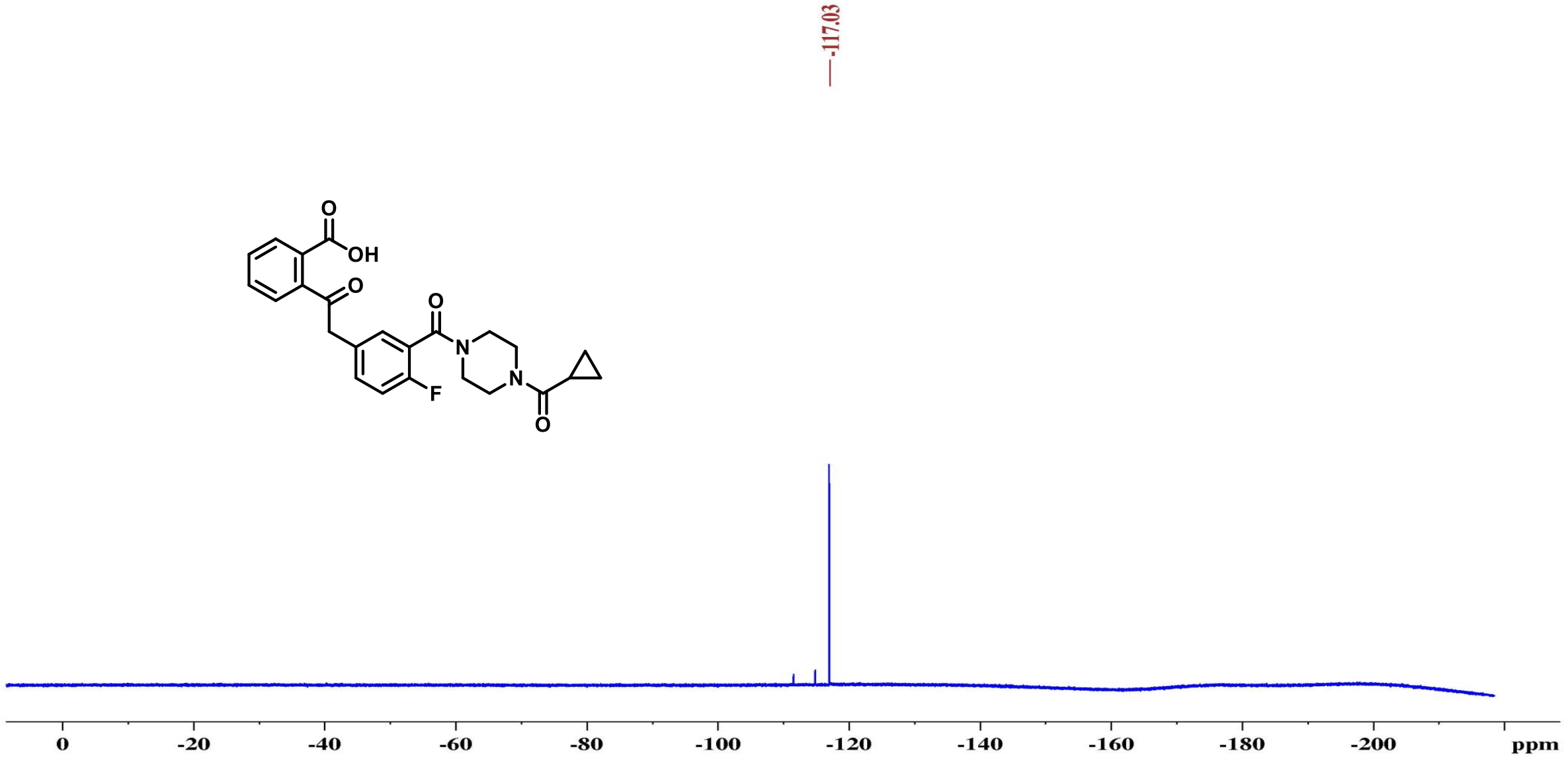


**Figure S9. $^{19}$F NMR spectra of 2-(2-(3-(4-(cyclopropanecarbonyl) piperazine-1-carbonyl)-4-fluorophenyl) acetyl) benzoic acid (12)**

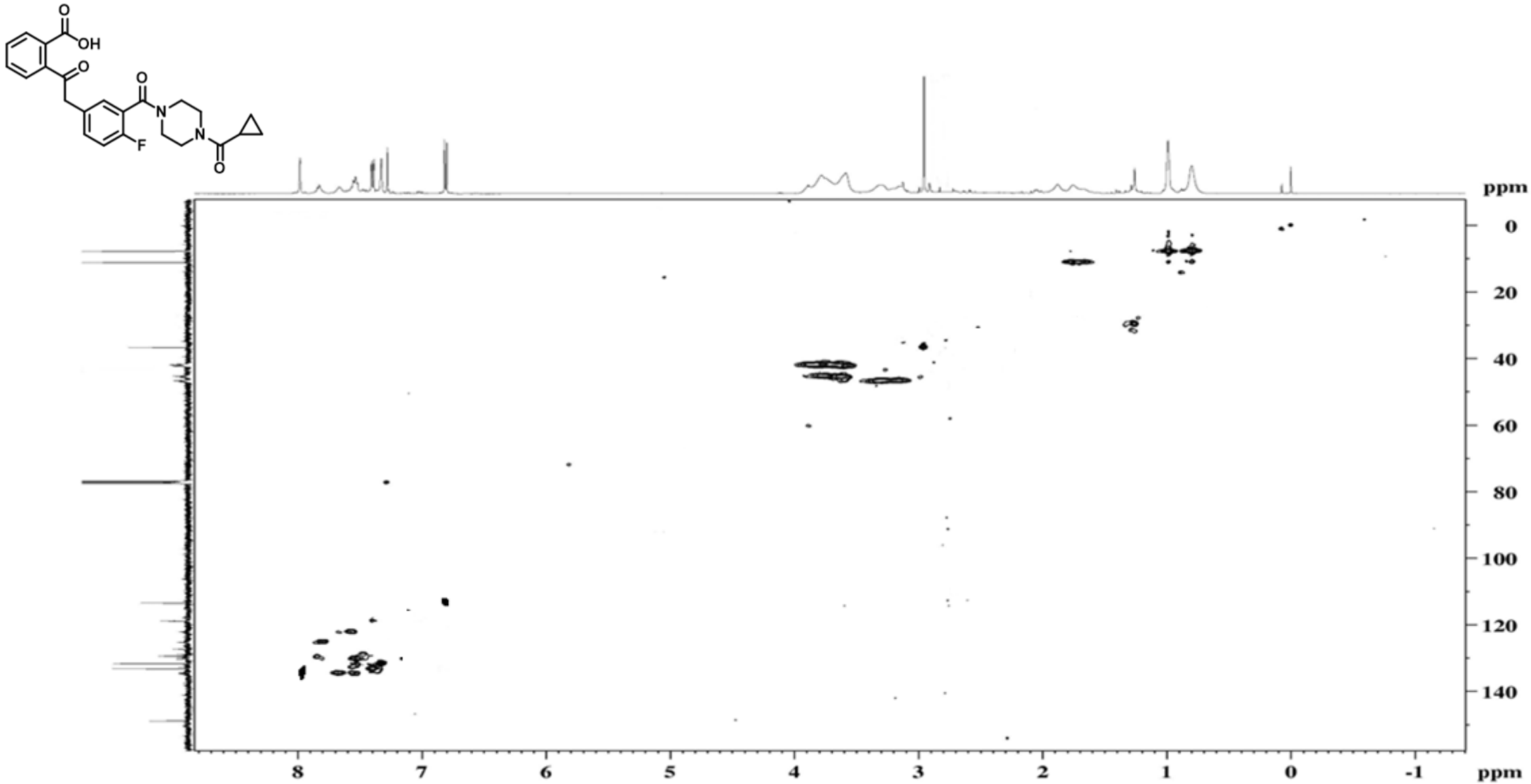


**Figure S10. HSQC spectra of 2-(2-(3-(4-(cyclopropanecarbonyl) piperazine-1-carbonyl)-4-fluorophenyl) acetyl) benzoic acid (12)**

Sample: 267
File:ESMS23I06SEP56
Vial:1:E,8
Date:06-Sep-2023
ID:ESMS23I06SEP56
Time:14:40:16

Printed: Wed Sep 06 15:36:34 2023

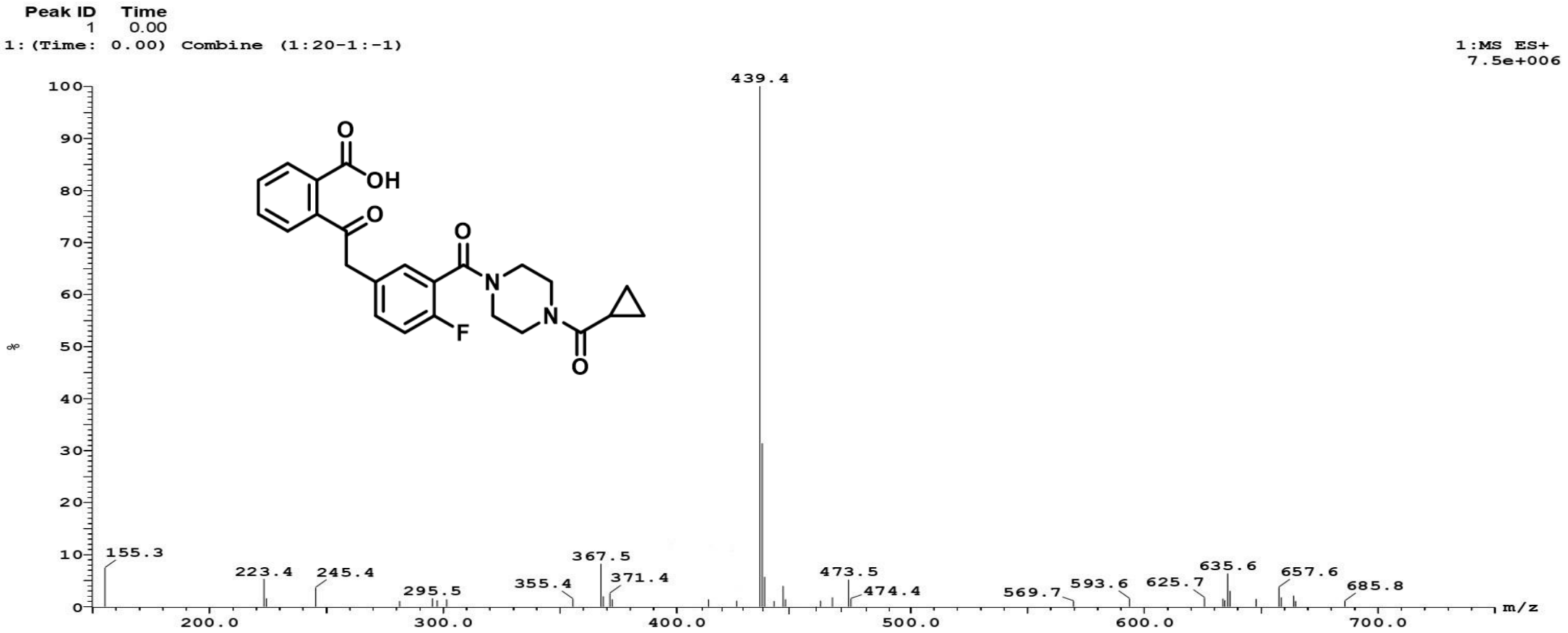


**Figure S11. ESMS spectra of 2-(2-(3-(4-(cyclopropanecarbonyl) piperazine-1-carbonyl)-4-fluorophenyl) acetyl) benzoic acid (12)**

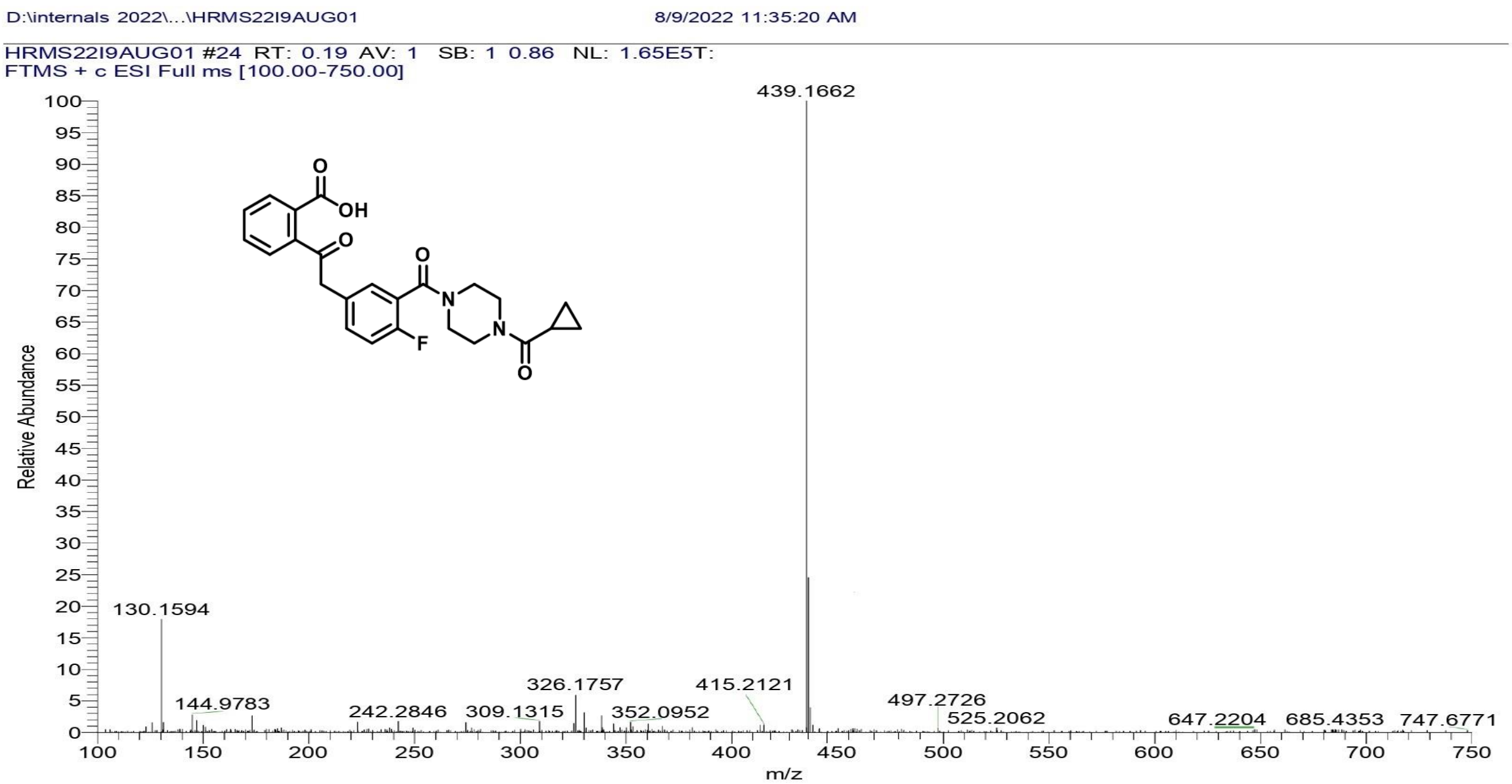


**Figure S12. HRMS spectra of 2-(2-(3-(4-(cyclopropanecarbonyl) piperazine-1-carbonyl)-4-fluorophenyl) acetyl) benzoic acid (12)**

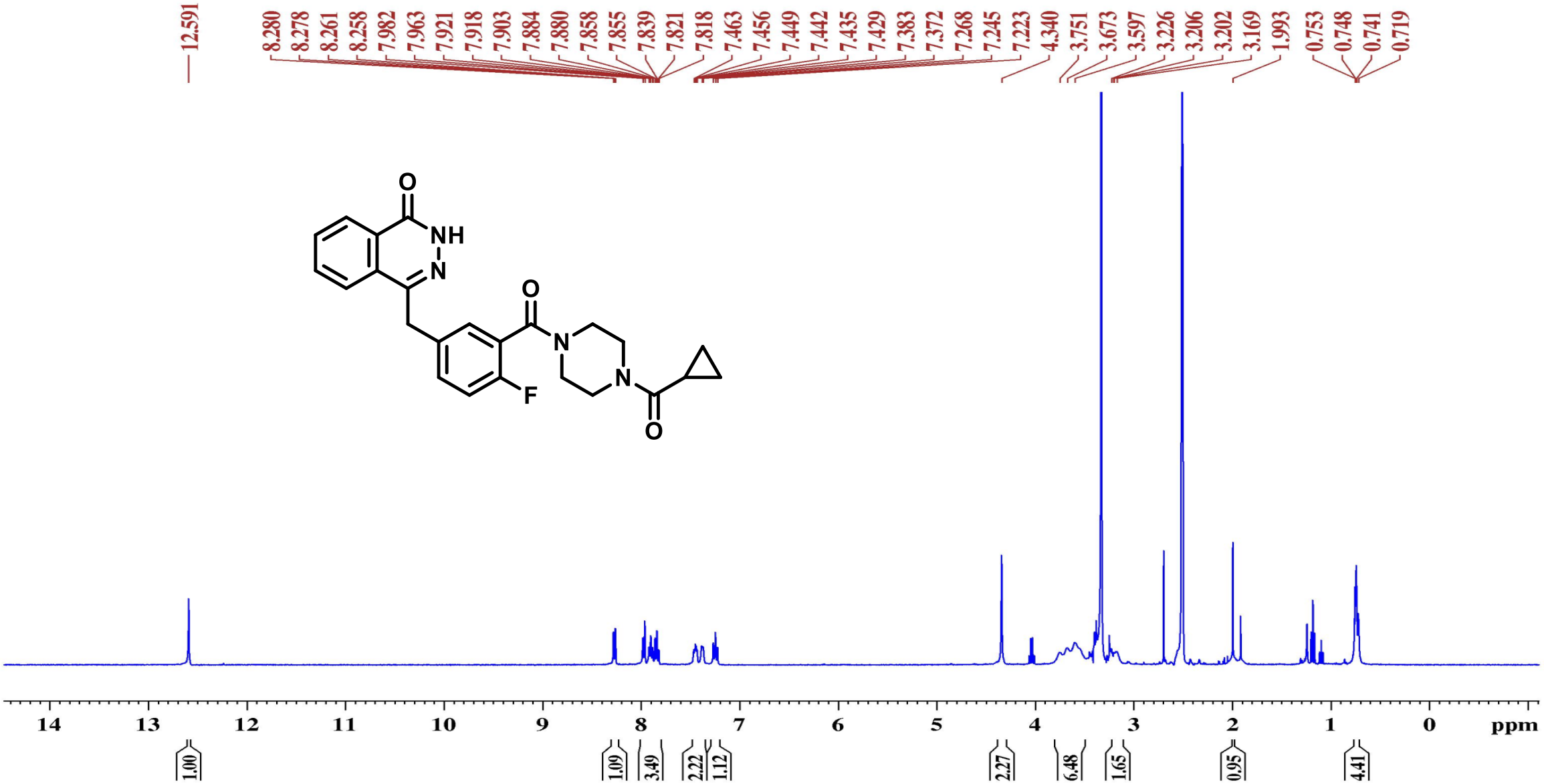


**Figure S13. $^{1}$H NMR spectra of 4-(3-(4-(cyclopropanecarbonyl) piperazine-1-carbonyl)-4-fluorobenzyl) phthalazin-1(2H)-one (1)**

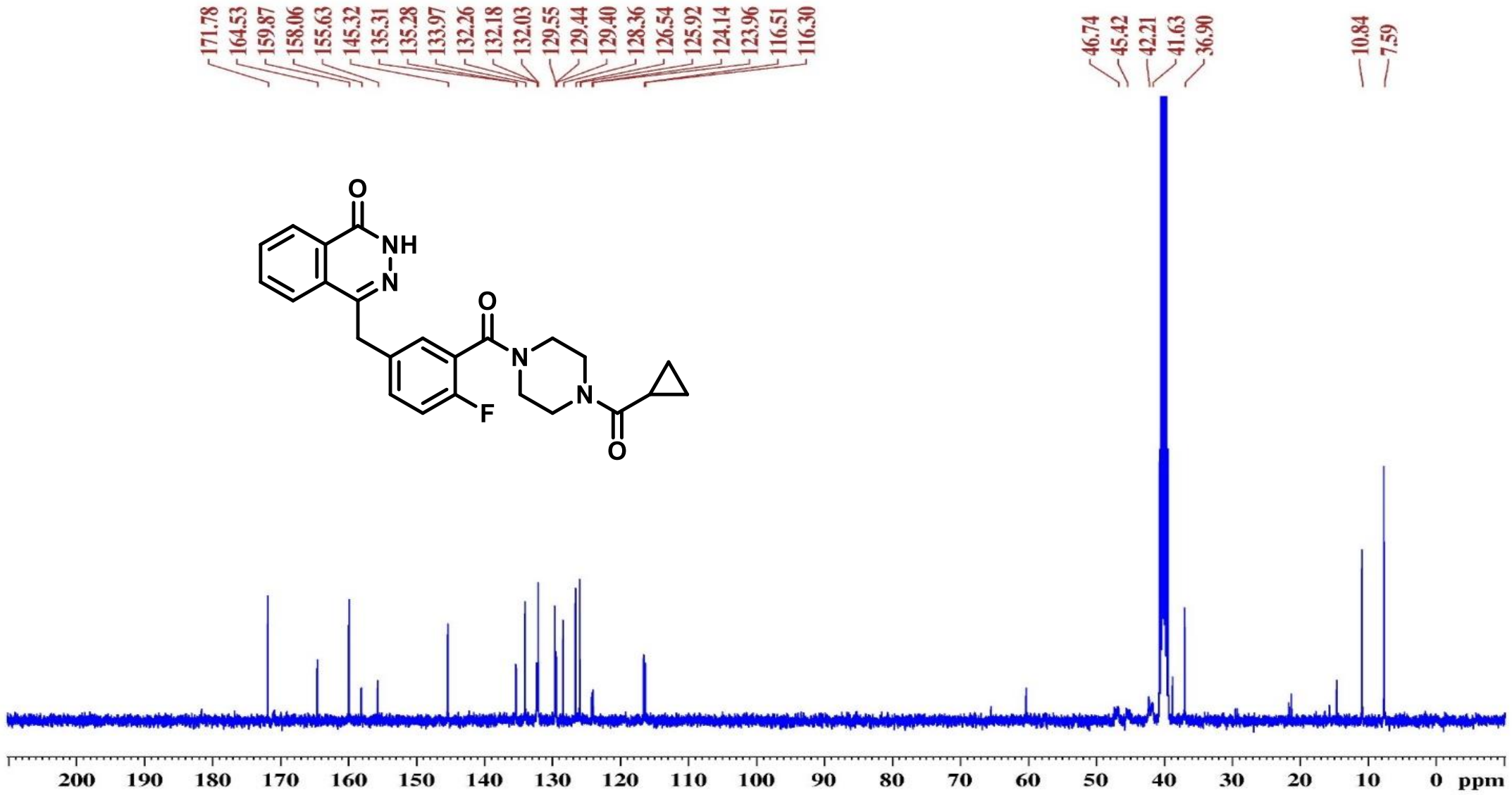


**Figure S14. $^{13}C\{^{1}H\}$ NMR spectra of 4-(3-(4-(cyclopropanecarbonyl) piperazine-1-carbonyl)-4-fluorobenzyl) phthalazin-1(2H)-one (1)**

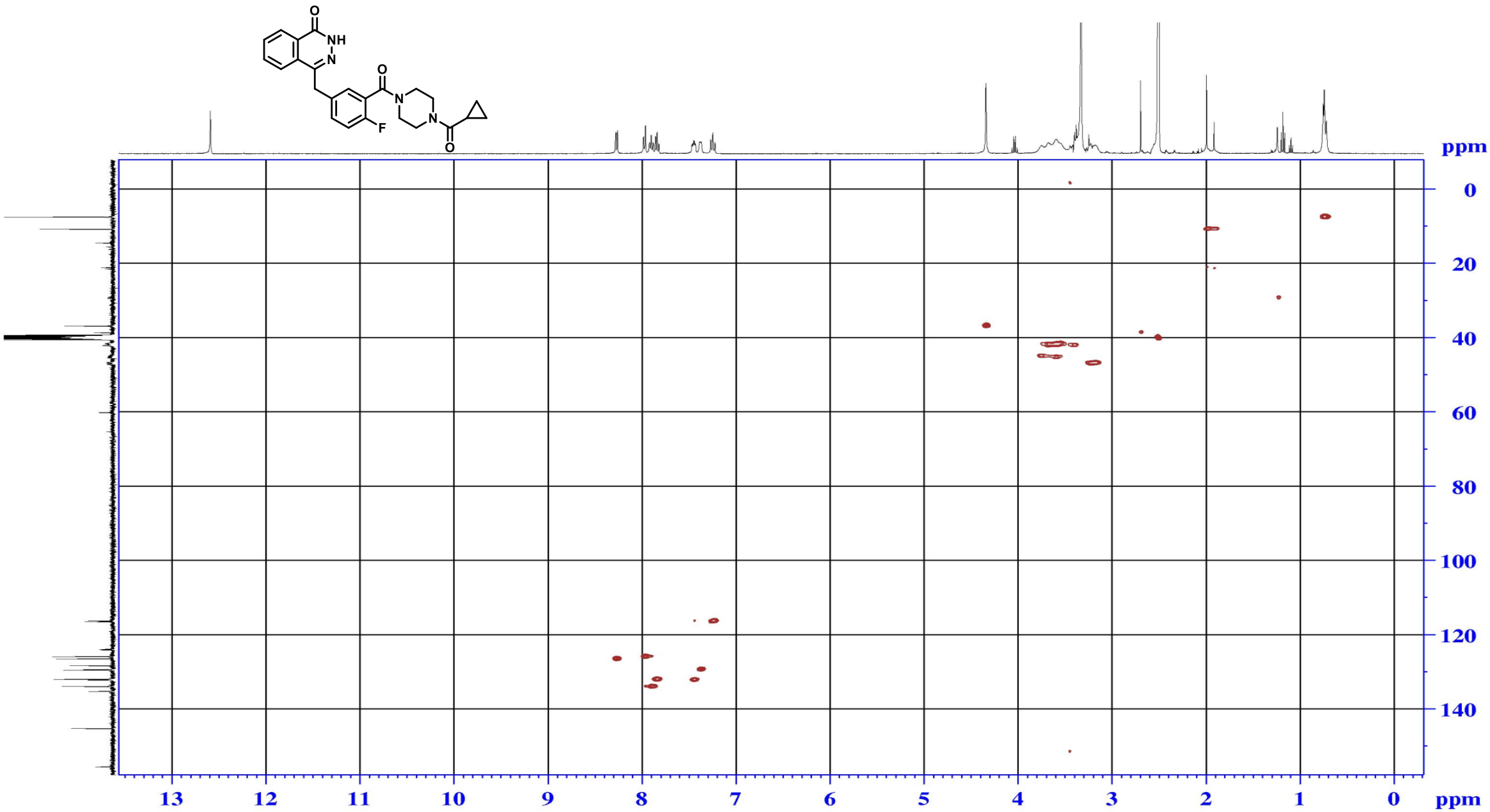


**Figure S15. HSQC spectra of 4-(3-(4-(cyclopropanecarbonyl) piperazine-1-carbonyl)-4-fluorobenzyl) phthalazin-1(2H)-one (1)**

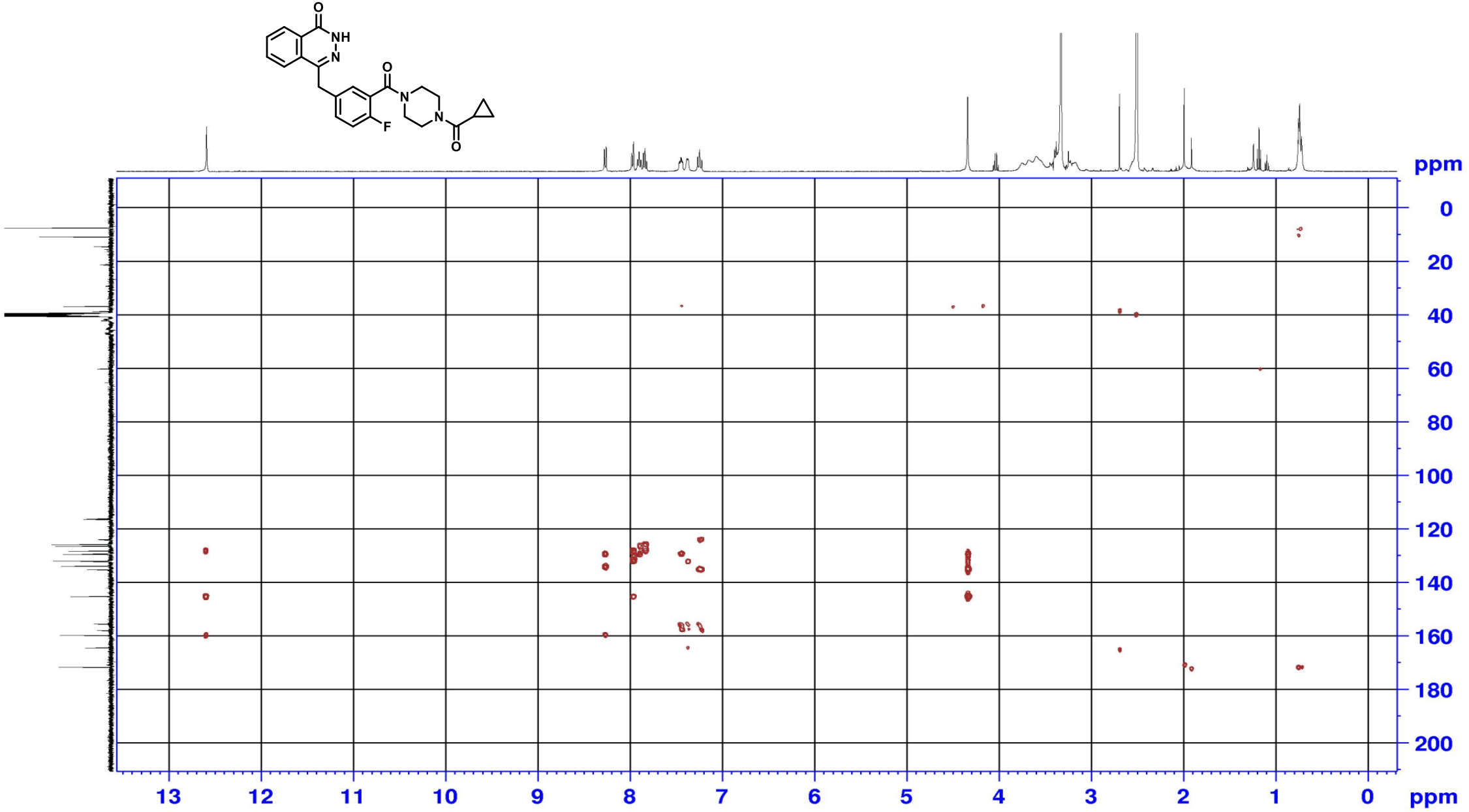


**Figure S16. HMBC spectra of 4-(3-(4-(cyclopropanecarbonyl) piperazine-1-carbonyl)-4-fluorobenzyl) phthalazin-1(2H)-one (1)**

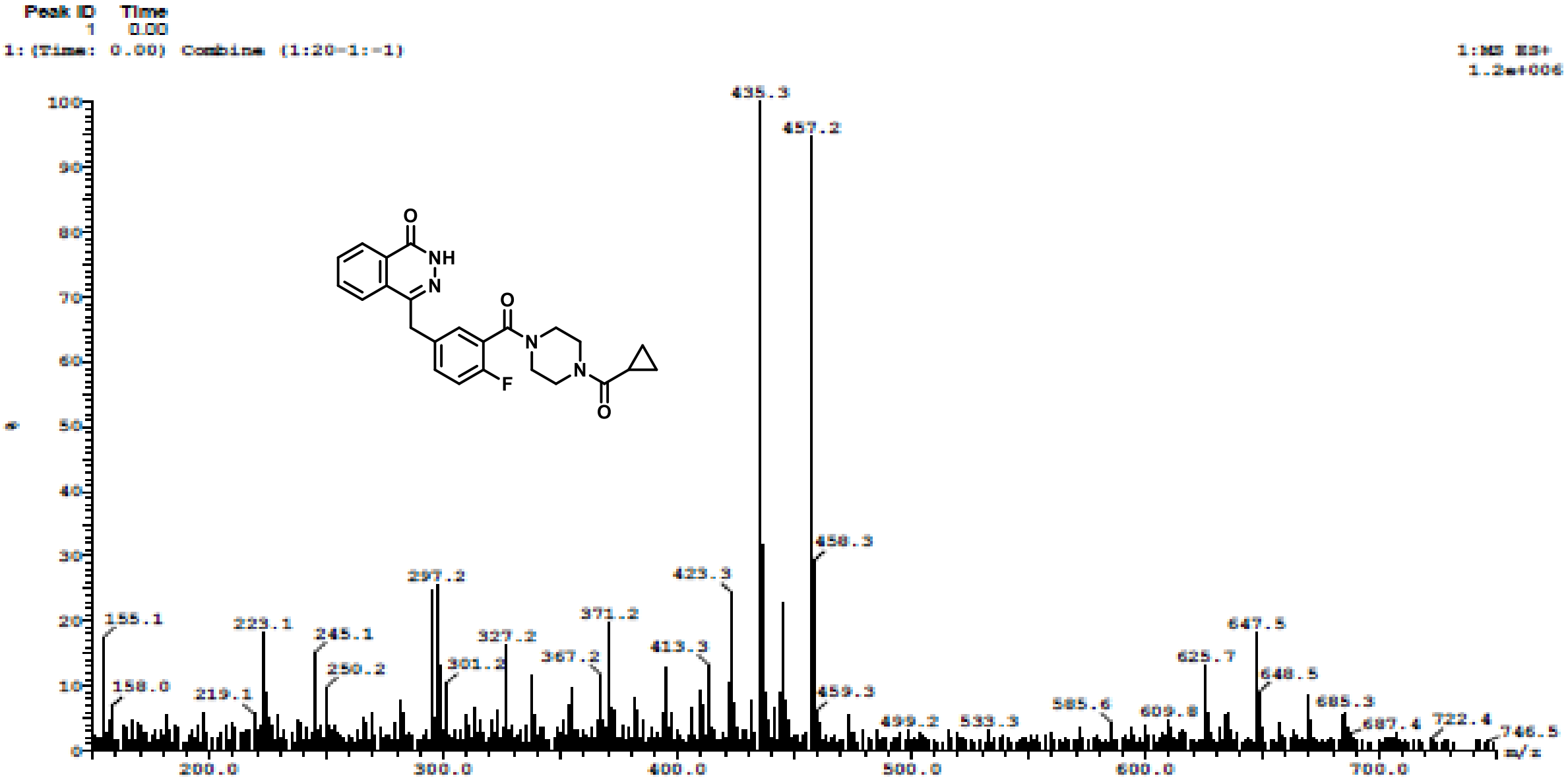


**Figure S17. ESMS spectra of 4-(3-(4-(cyclopropanecarbonyl) piperazine-1-carbonyl)-4-fluorobenzyl) phthalazin-1(2H)-one (1)**

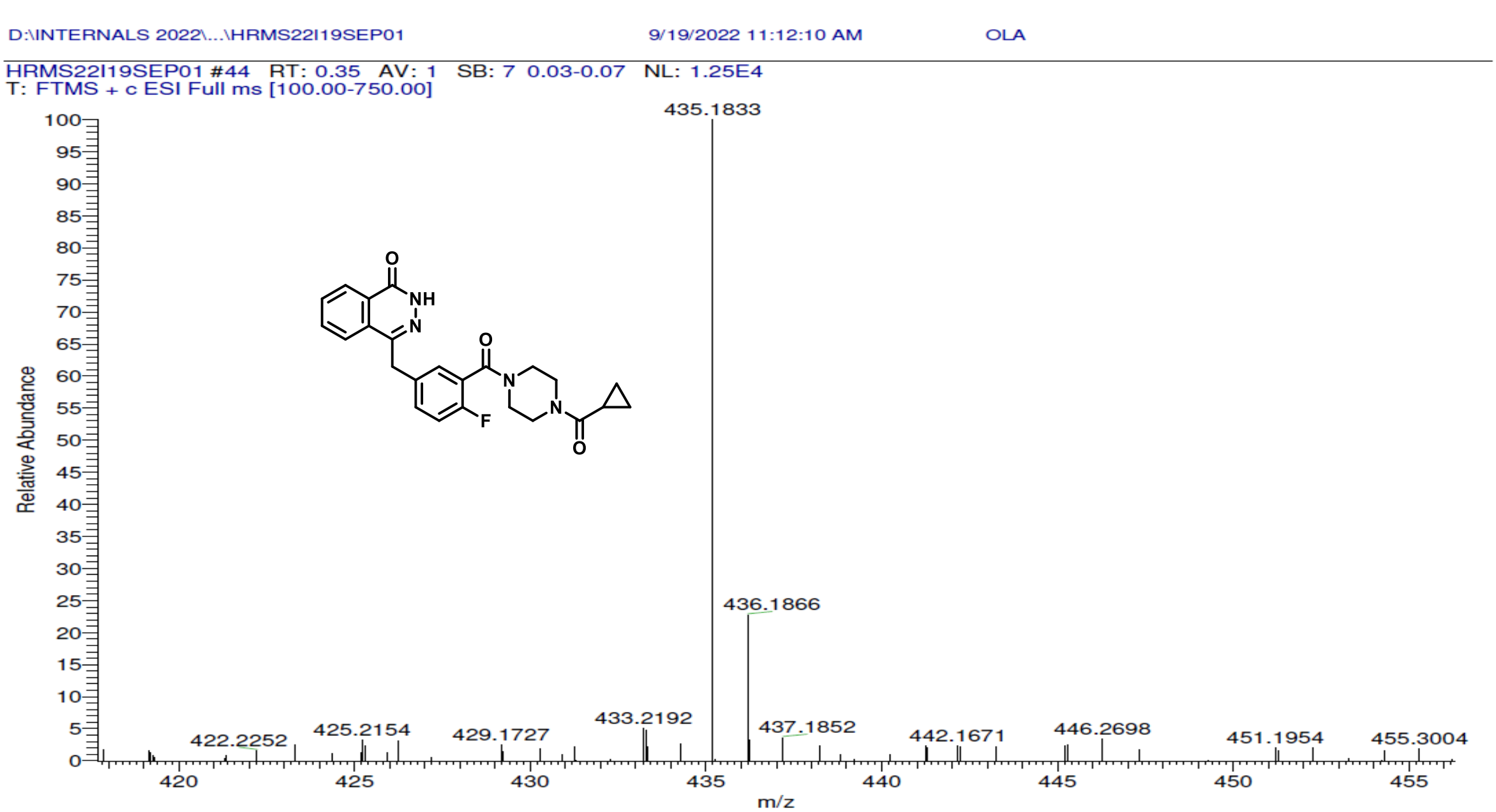


**Figure S18. HRMS spectra of 4-(3-(4-(cyclopropanecarbonyl) piperazine-1-carbonyl)-4-fluorobenzyl) phthalazin-1(2H)-one (1)**

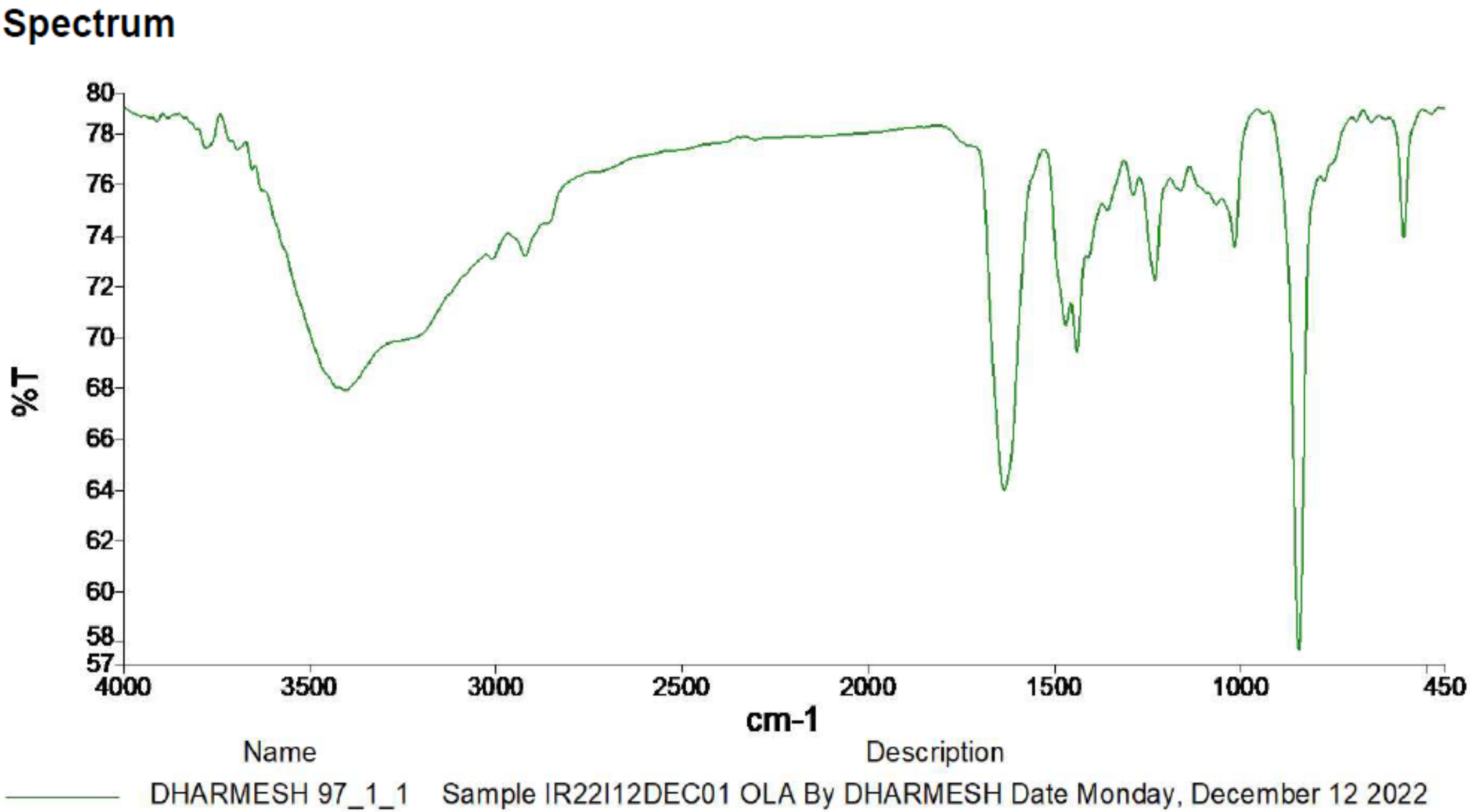




**Figure S19. IR spectra of 4-(3-(4-(cyclopropanecarbonyl) piperazine-1-carbonyl)-4-fluorobenzyl) phthalazin-1(2H)-one (1)**

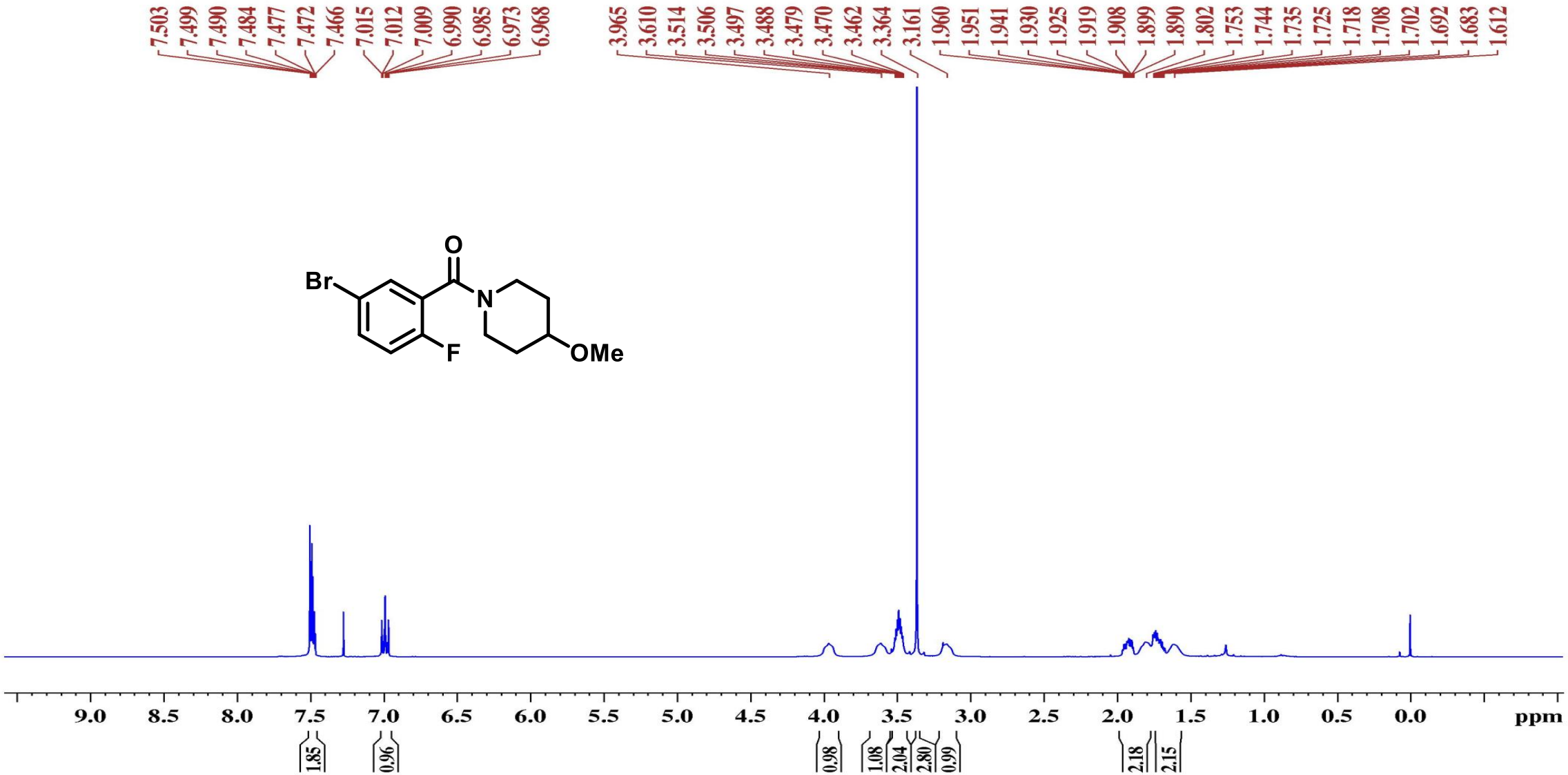


**Figure S20. $^{1}$H NMR spectra of (5-bromo-2-fluorophenyl)(4-methoxypiperidin-1-yl)methanone (21)**

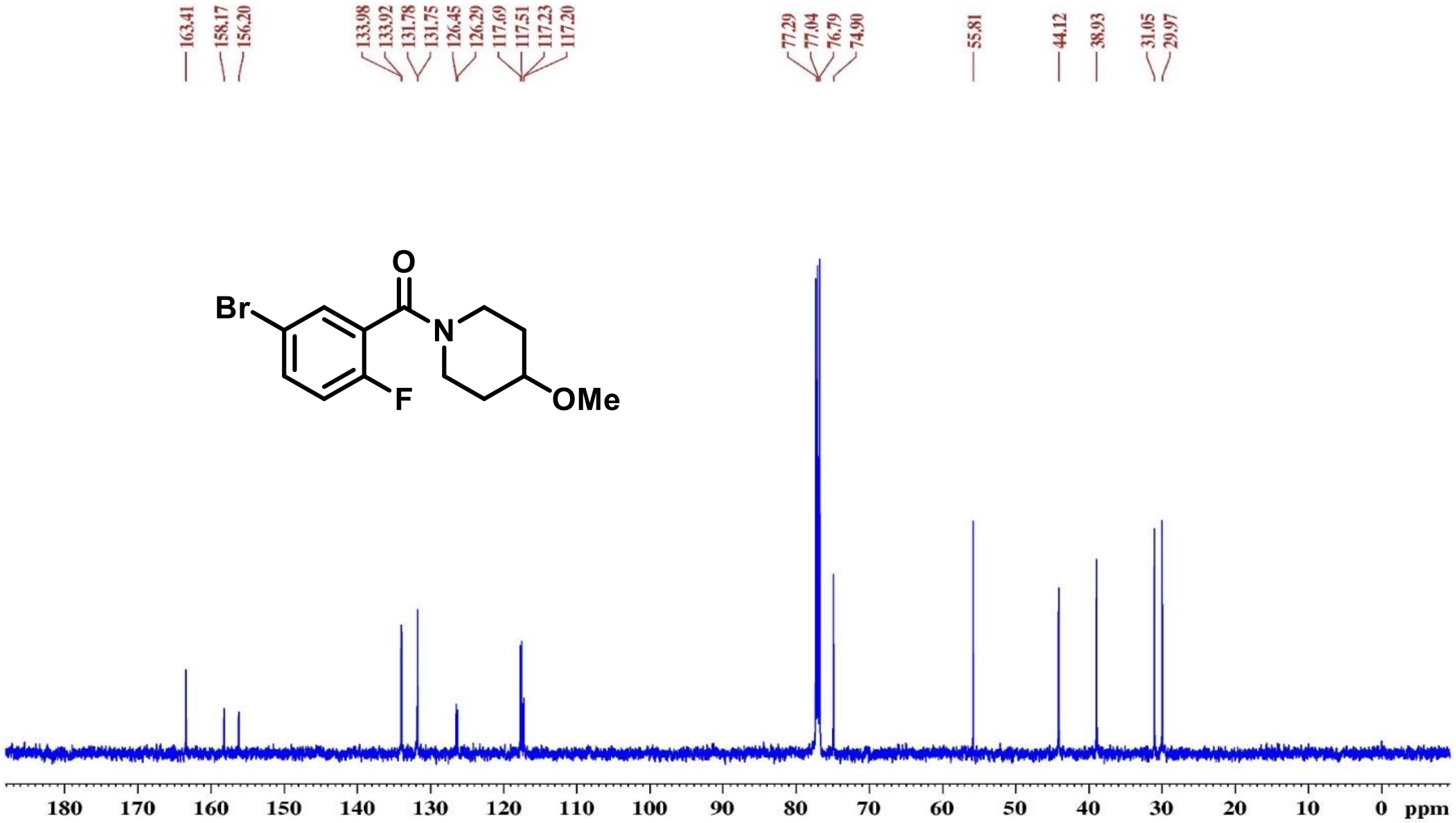


**Figure S21.** $^{13}C\{^{1}H\}$ **NMR spectra of (5-bromo-2-fluorophenyl)(4-methoxypiperidin-1-yl)methanone (21)**

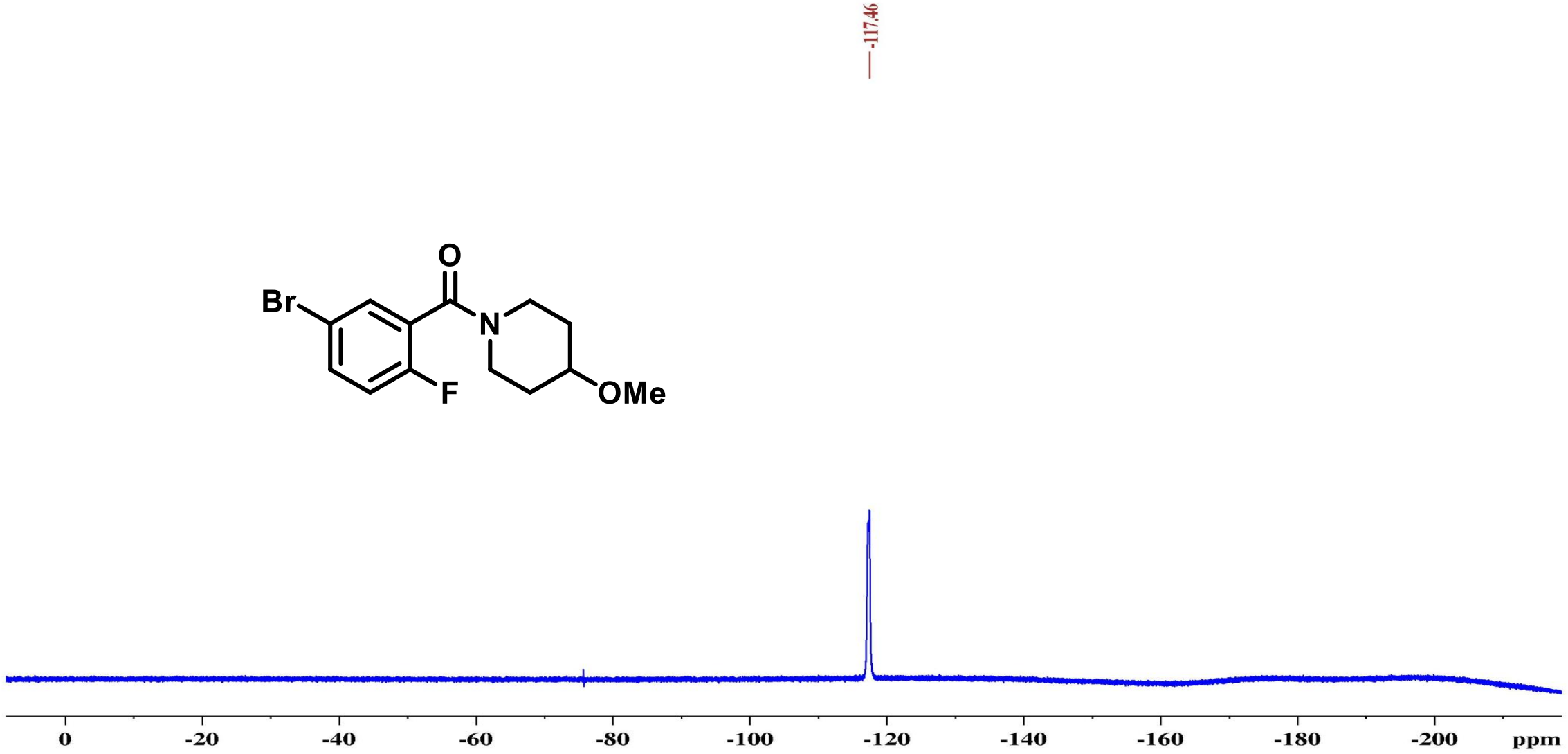


**Figure S22. $^{19}$F NMR spectra of (5-bromo-2-fluorophenyl)(4-methoxypiperidin-1-yl)methanone (21)**

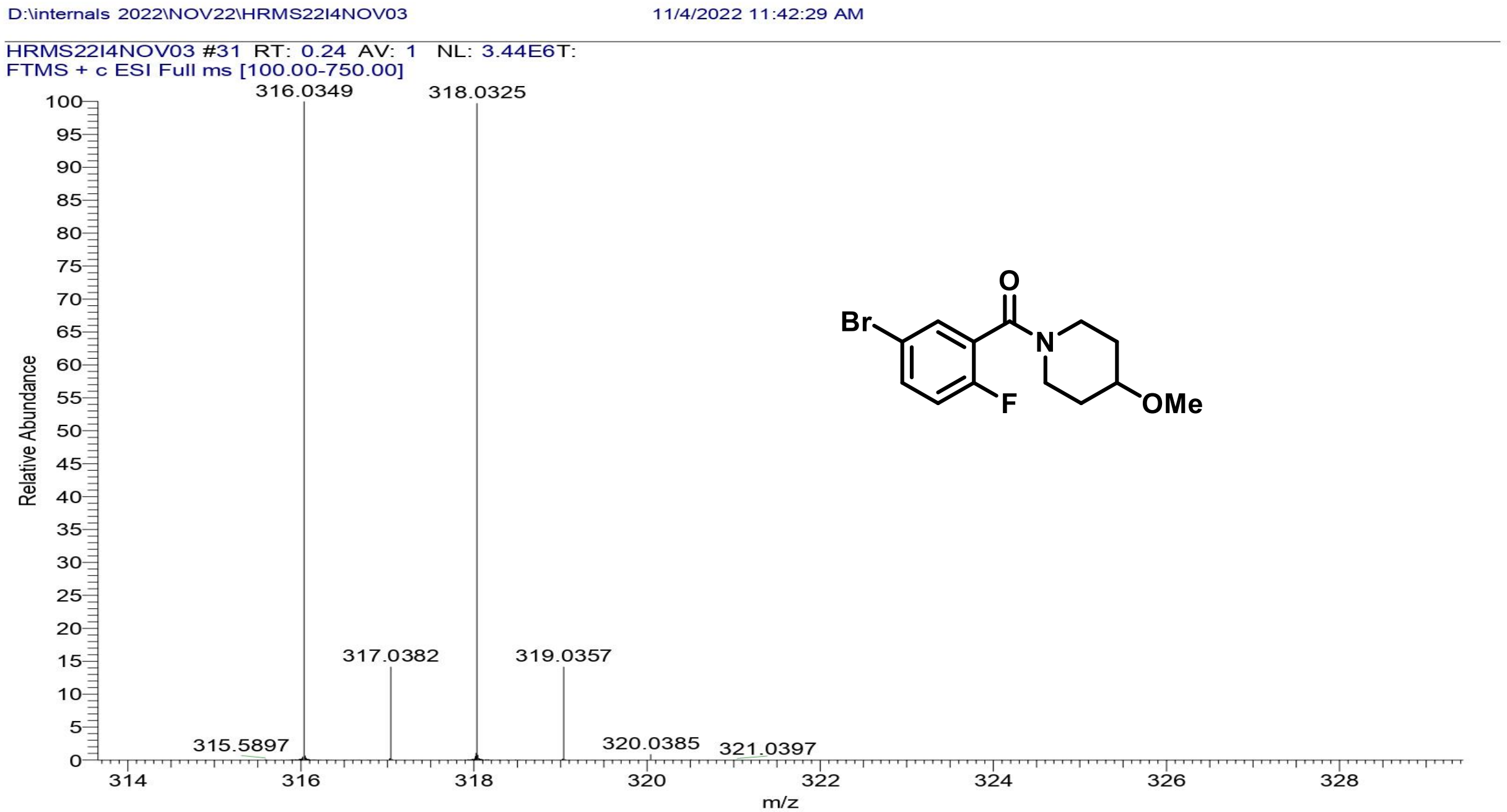


**Figure S23. HRMS spectra of (5-bromo-2-fluorophenyl)(4-methoxypiperidin-1-yl)methanone (21)**

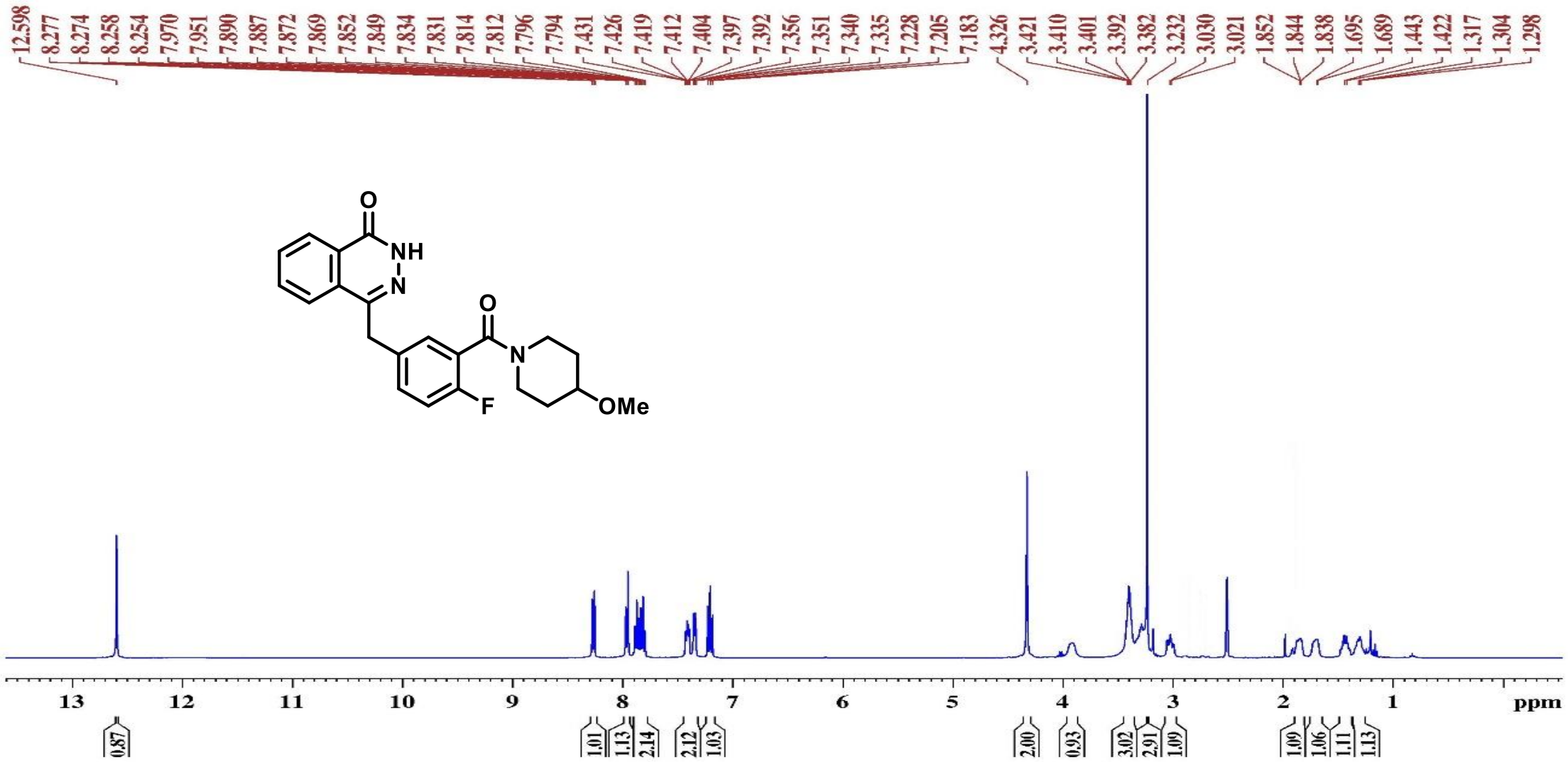


**Figure S24. $^{1}$H NMR spectra of 4-(4-fluoro-3-(4-methoxypiperidine-1-carbonyl) benzyl) phthalazin-1(2H)-one (19)**

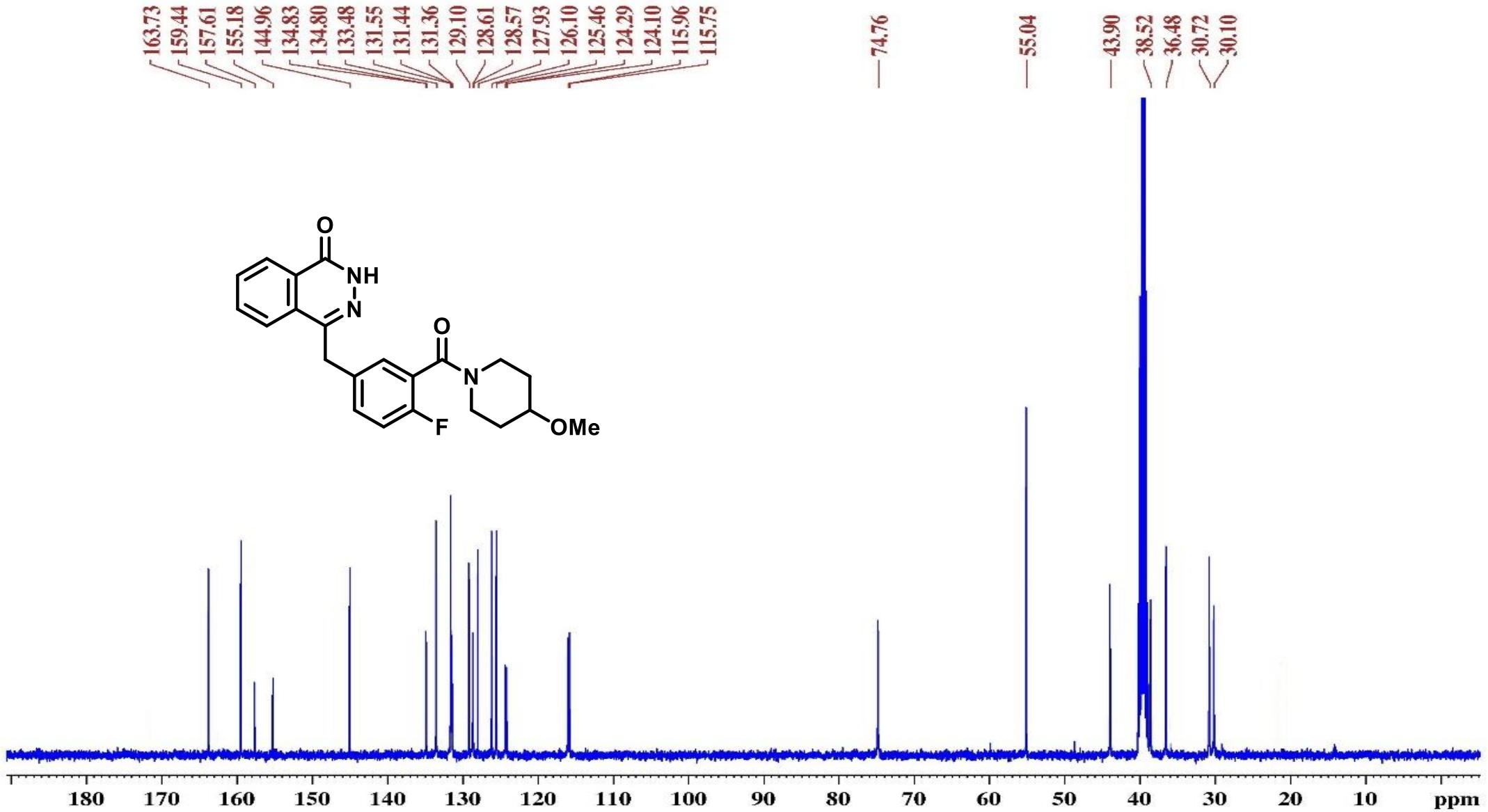


**Figure S25. $^{13}C\{^{1}H\}$ NMR spectra of 4-(4-fluoro-3-(4-methoxypiperidine-1-carbonyl) benzyl) phthalazin-1(2H)-one (19)**

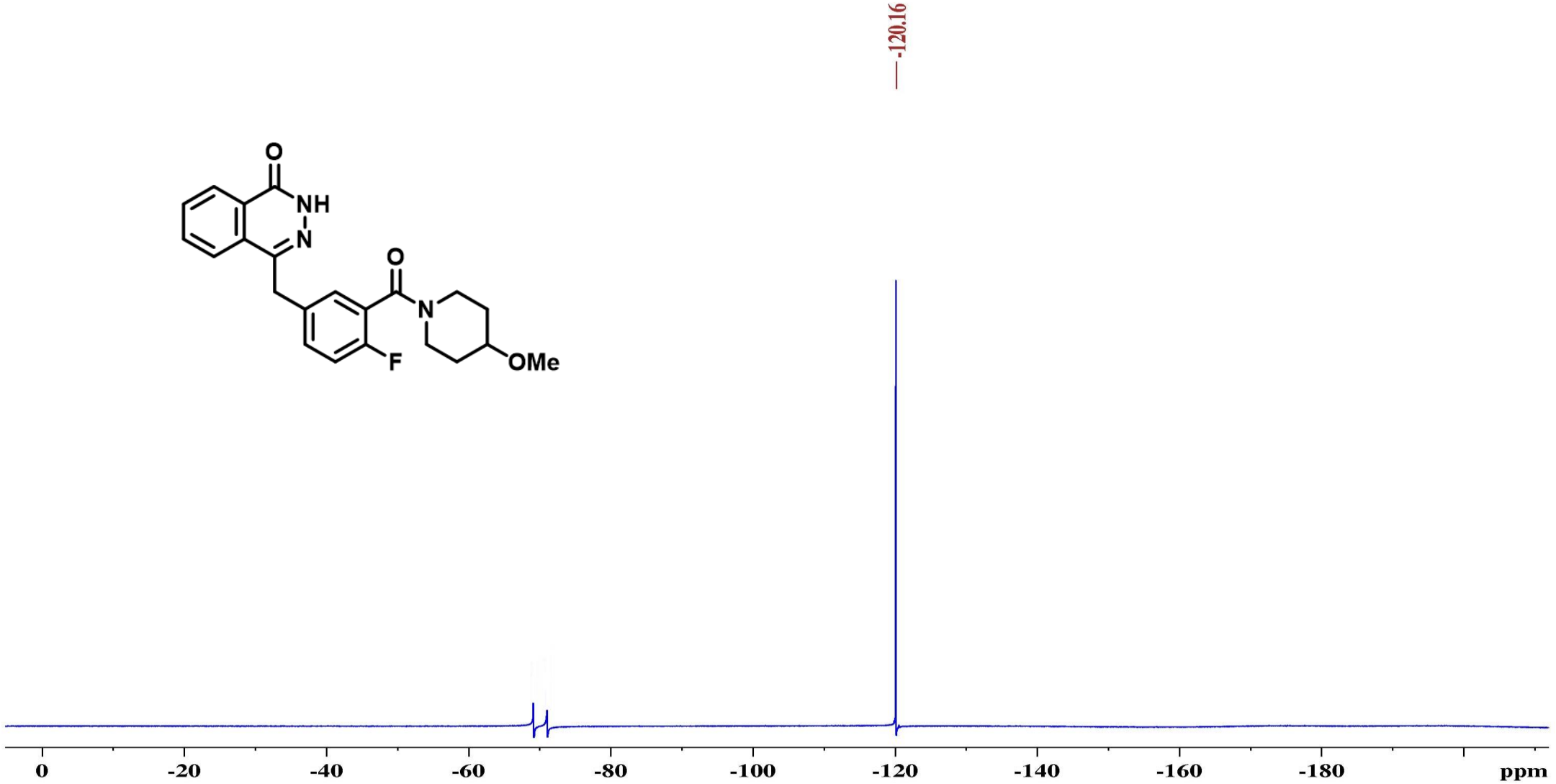


**Figure S26. $^{19}$F NMR spectra of 4-(4-fluoro-3-(4-methoxypiperidine-1-carbonyl) benzyl) phthalazin-1(2H)-one (19)**

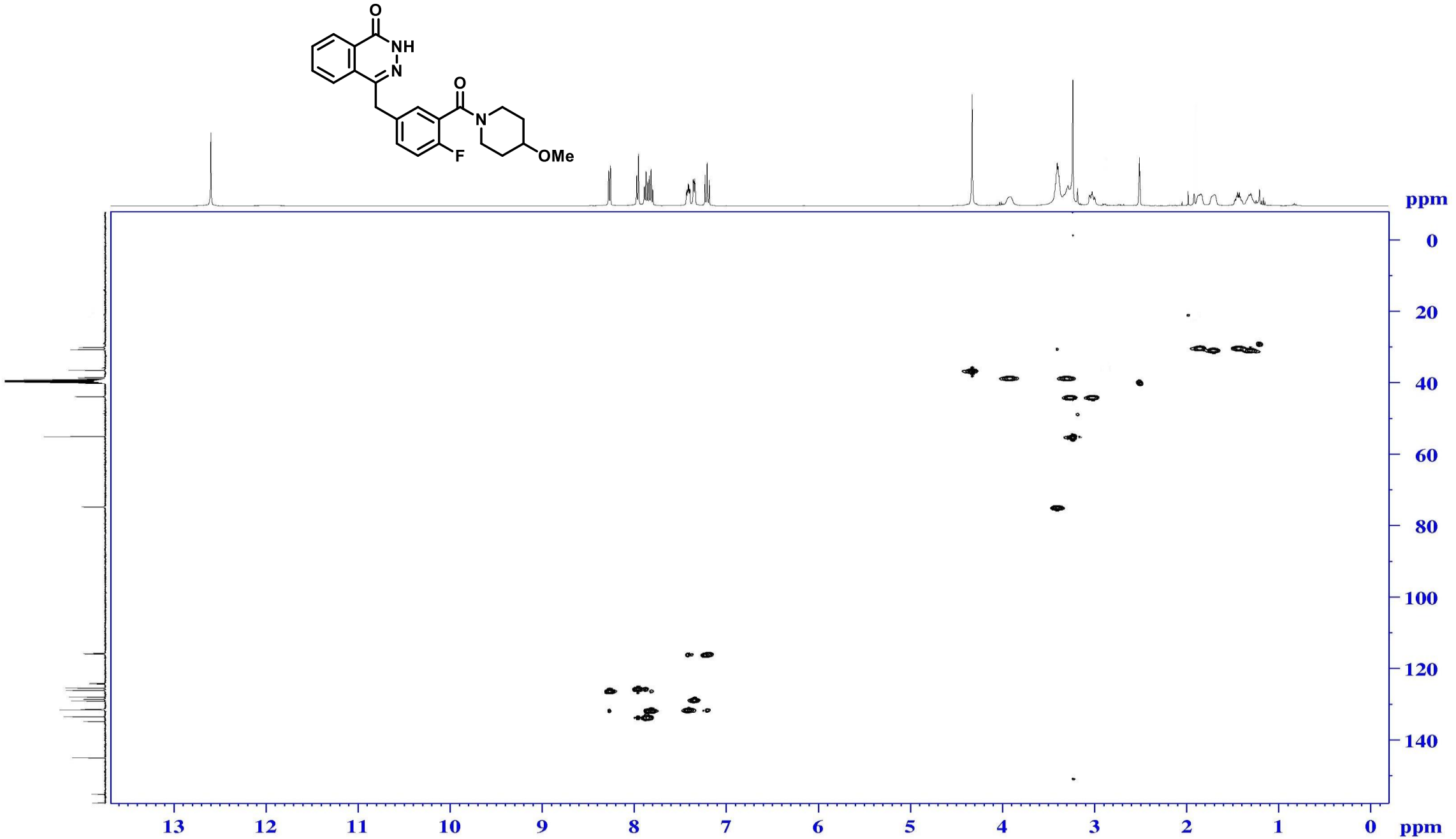


**Figure S27. HSQC spectra of 4-(4-fluoro-3-(4-methoxypiperidine-1-carbonyl) benzyl) phthalazin-1(2H)-one (19)**

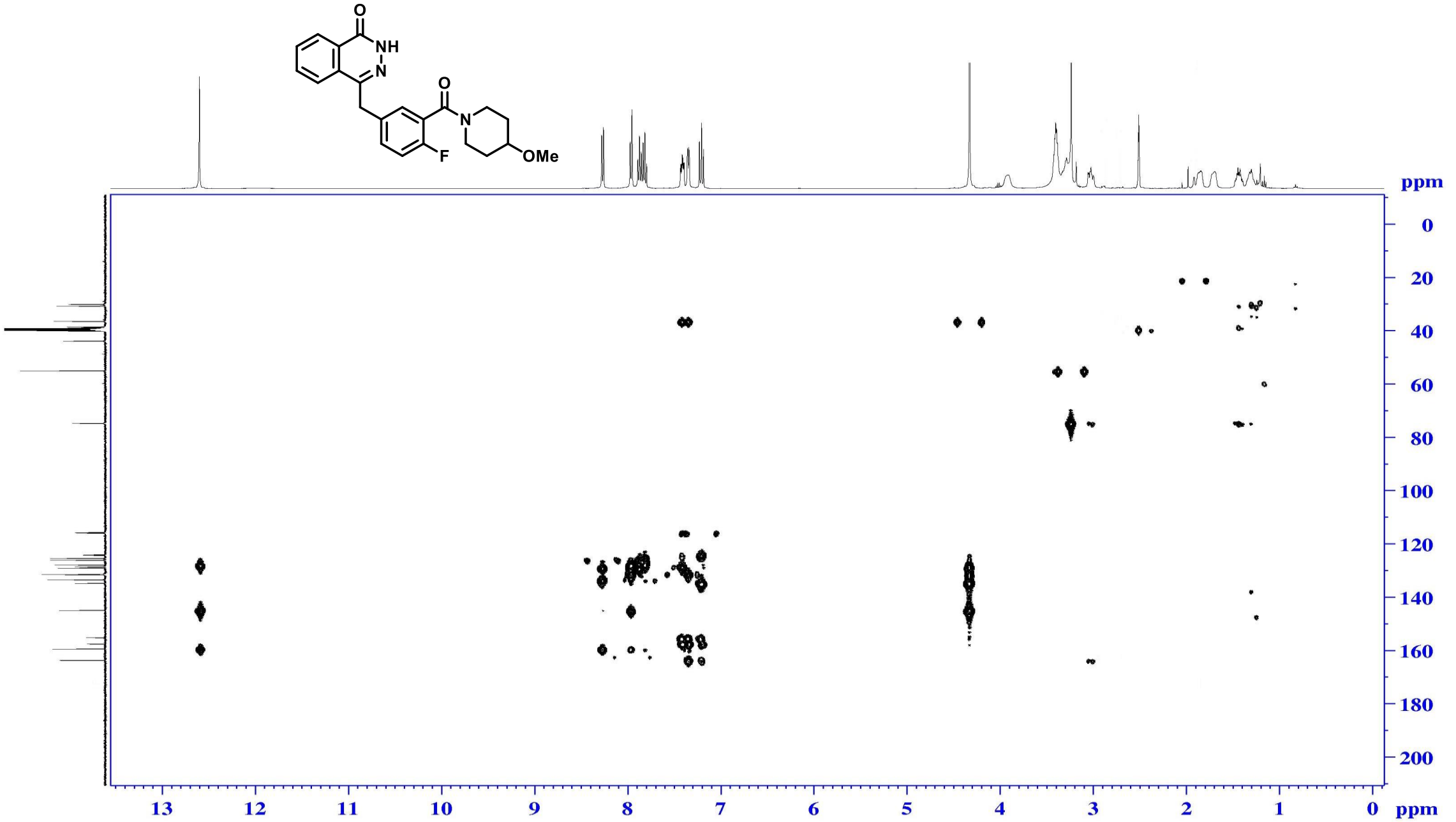


**Figure S28. HMBC spectra of 4-(4-fluoro-3-(4-methoxypiperidine-1-carbonyl) benzyl) phthalazin-1(2H)-one (19)**

Sample: 864
File:ESMS22I27OCT19
Description:INDR-201

Vial:1:B,7
Date:27-Oct-2022

ID:ESMS22I27OCT19
Time:11:44:49

Printed: Thu Oct 27 13:42:27 2022

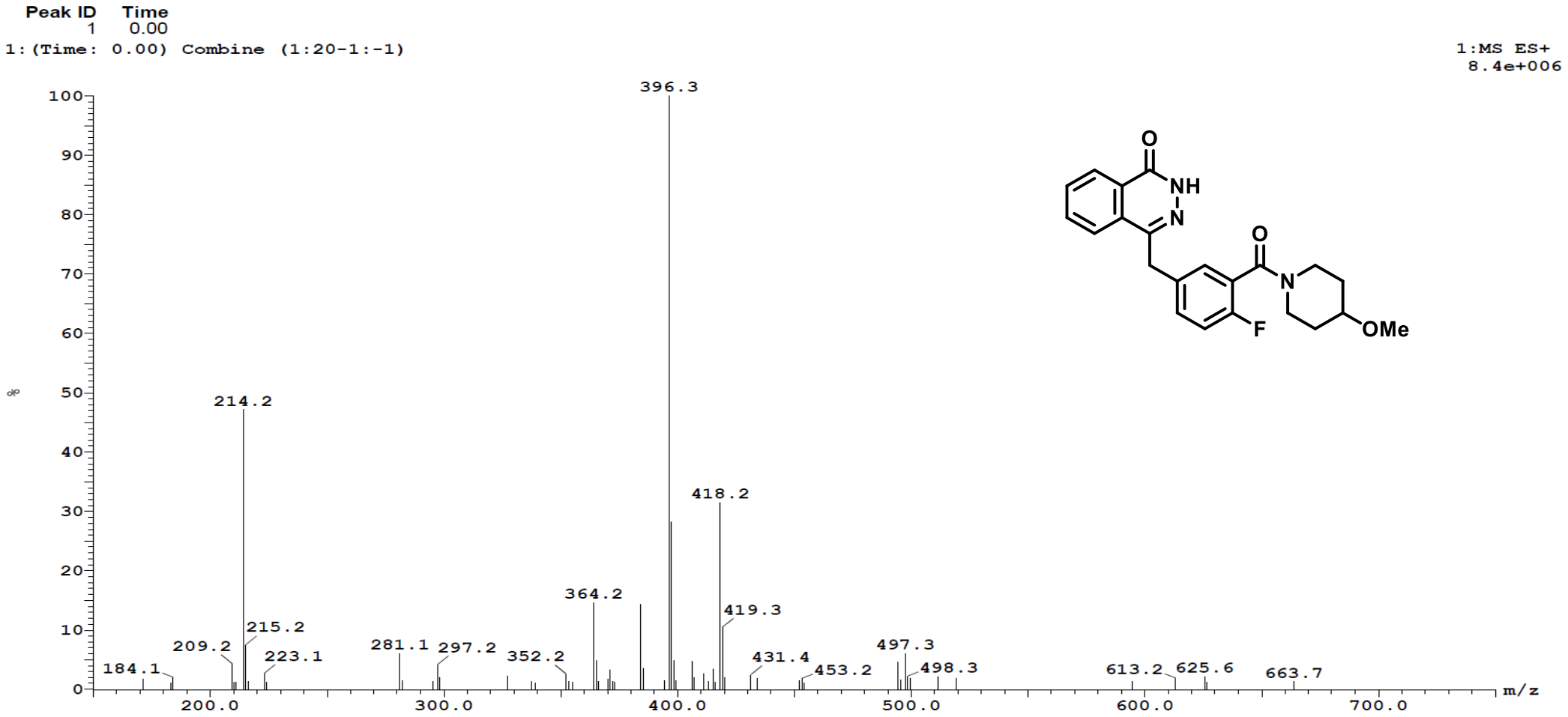


**Figure S29. ESMS spectra of 4-(4-fluoro-3-(4-methoxypiperidine-1-carbonyl) benzyl) phthalazin-1(2H)-one (19)**

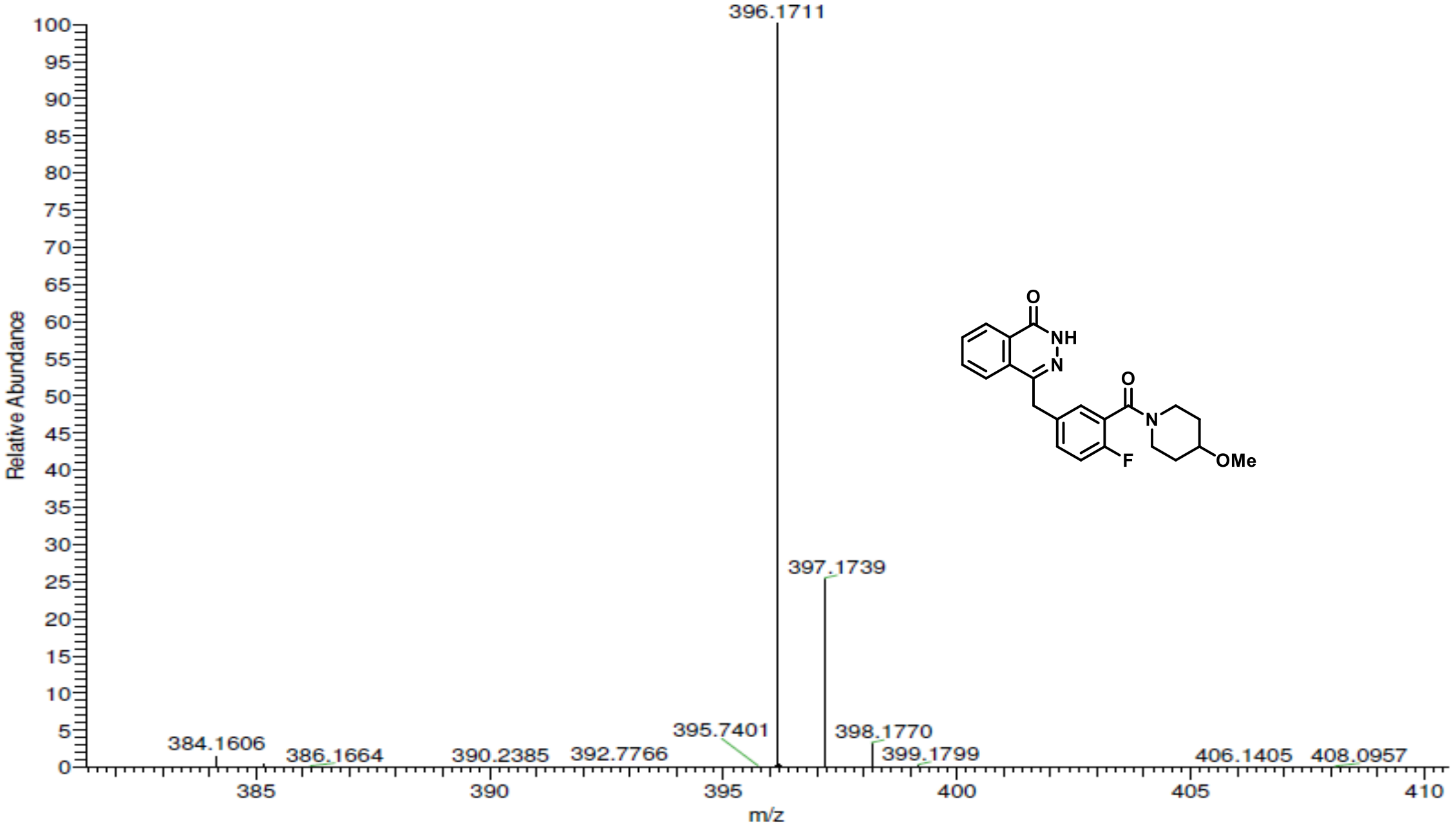


**Figure S30. HRMS spectra of 4-(4-fluoro-3-(4-methoxypiperidine-1-carbonyl) benzyl) phthalazin-1(2H)-one (19)**

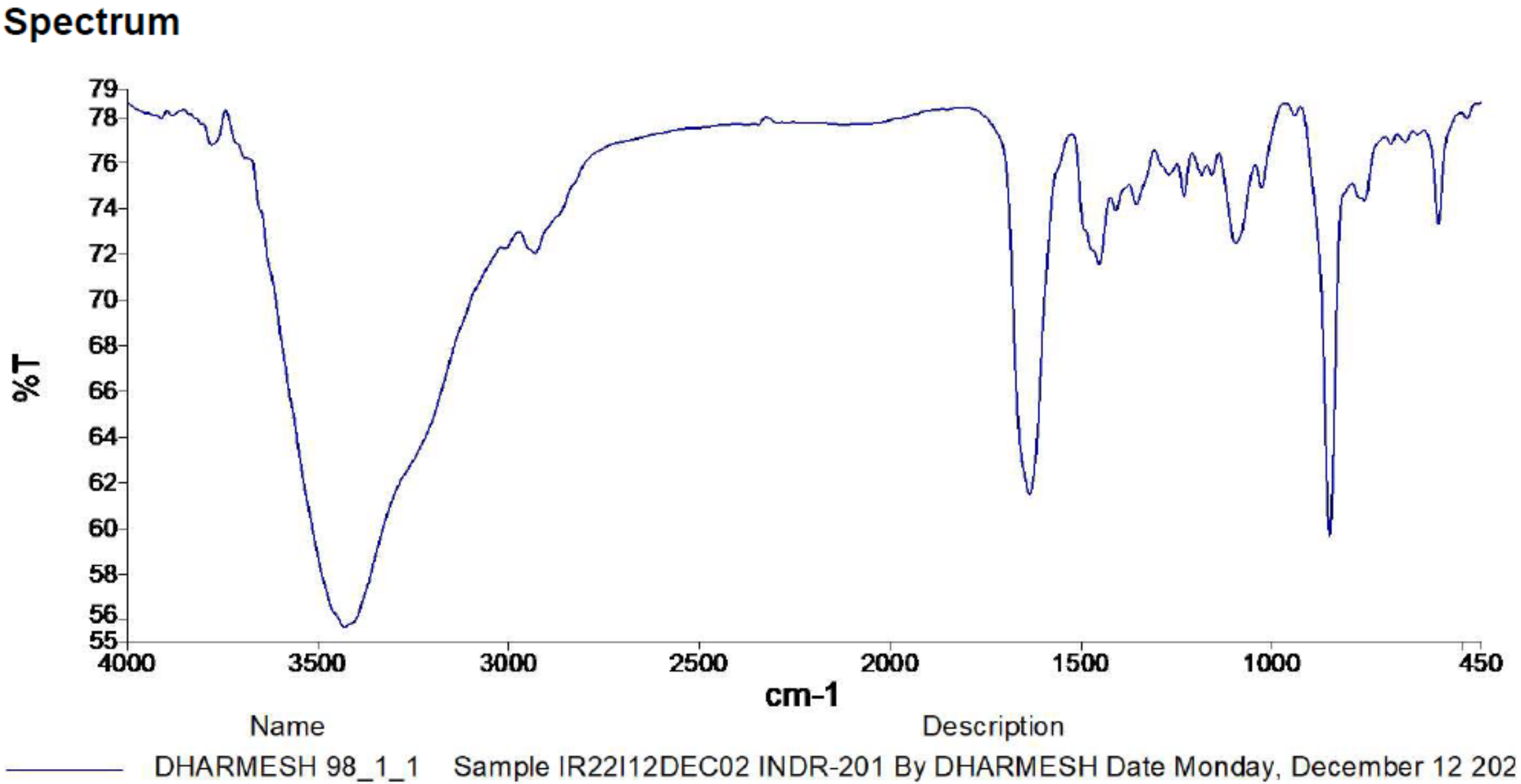


**Figure S31. IR spectra of 4-(4-fluoro-3-(4-methoxypiperidine-1-carbonyl) benzyl) phthalazin-1(2H)-one (19)**

## 8. Analytical information of compounds.

```
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Acq. Operator   : CBRS-REPOSITORY          Seq. Line :  1
Acq. Instrument : Instrument 1             Location : Vial 93
Injection Date  : 3/2/2022 12:17:39 PM         Inj :  1
                                       Inj Volume : 5.000 µl
Acq. Method     : C:\CHEM32\1\DATA\BHAWANA-02-03-2022-2 2022-03-02 12-15-46\ACN-WATER--GRAD.M
Last changed    : 2/28/2022 4:11:07 PM by CBRS-REPOSITORY
Analysis Method : C:\CHEM32\1\METHODS\ACN-WATER--GRAD.M
Last changed    : 2/28/2022 4:11:07 PM by CBRS-REPOSITORY
Method Info     : OSDD
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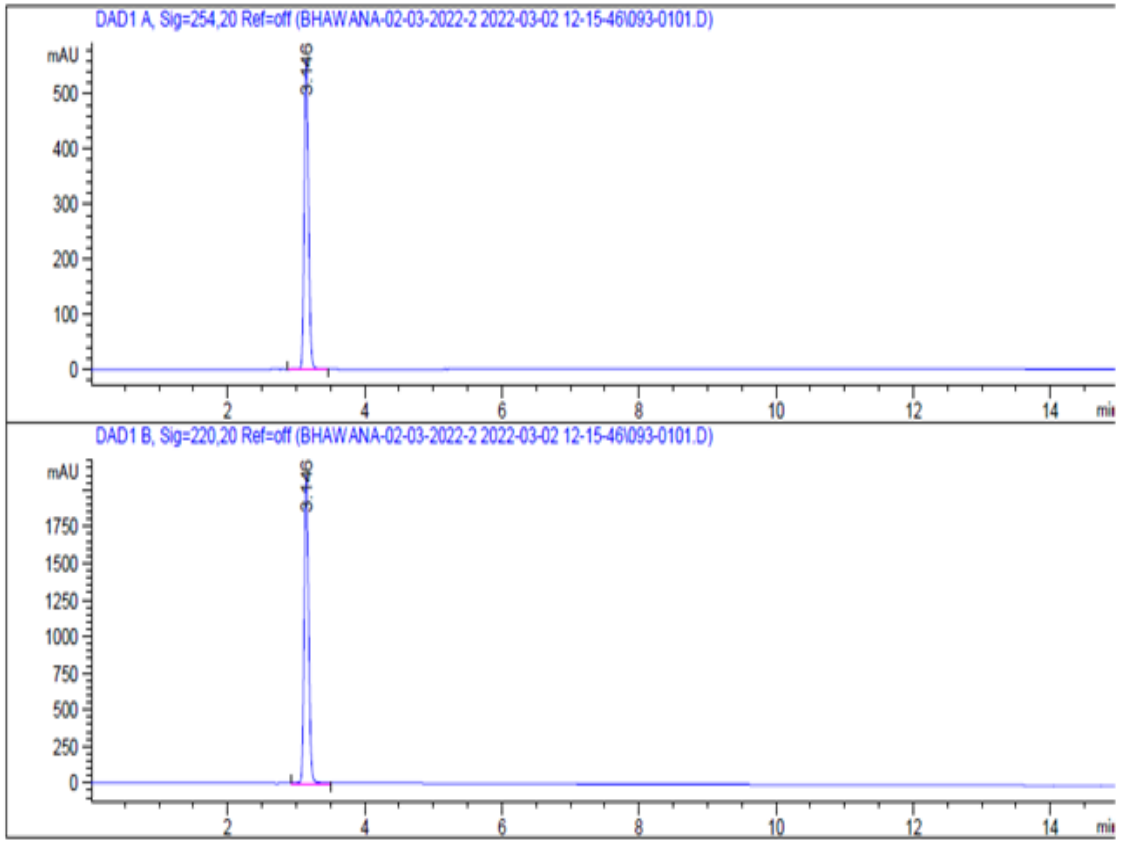


Signal 1: DAD1 A, Sig=254,20 Ref=off

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|---|---|---|---|---|---|---|
| 1 | 3.146 | VV | 0.0672 | 2377.38477 | 564.30432 | 100.0000 |
| Totals : | | | | 2377.38477 | 564.30432 | |

Signal 2: DAD1 B, Sig=220,20 Ref=off

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|---|---|---|---|---|---|---|
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| Totals : | | | | 9319.29199 | 2104.14697 | |

**System: Waters e2695-2998 Series Mobile phase: Mobile phase A: $H_2O$, Mobile phase B: MeCN**

**Detector: UV at 254 nm**

**Column: Thermo C-18 4.6 ×250 mm, 5µ**

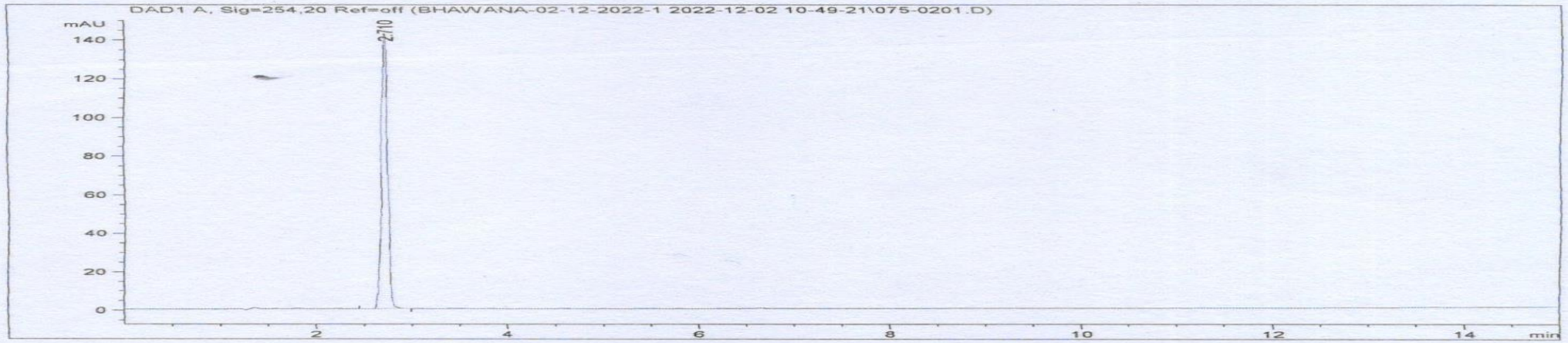
**Column Temperature: 25°C**



**Figure S32. HPLC spectra of 4-(3-(4-(cyclopropanecarbonyl) piperazine-1-carbonyl)-4-fluorobenzyl) phthalazin-1(2H)-one (1)**

Data File C:\CHEM32\1\DATA\BHAWANA-02-12-2022-1 2022-12-02 10-49-21\075-0201.D
Sample Name: INDR-201

| | | | |
|---|---|---|---|
| Acq. Operator | : CBRS-REPOSITORY | Seq. Line | : 2 |
| Acq. Instrument | : Instrument 1 | Location | : Vial 75 |
| Injection Date | : 12/2/2022 11:13:11 AM | Inj | : 1 |
| | | Inj Volume | : 5.000 µl |
| Acq. Method | : C:\CHEM32\1\DATA\BHAWANA-02-12-2022-1 2022-12-02 10-49-21\ACN-WATER-40-60-150MMGRAD.M | | |
| Last changed | : 11/28/2022 1:24:40 PM by CBRS-REPOSITORY | | |
| Analysis Method | : C:\CHEM32\1\METHODS\ACN-WATER-40-60-150MMGRAD.M | | |
| Last changed | : 12/2/2022 1:05:49 PM by CBRS-REPOSITORY | | |
| Method Info | : OSDD | | |




Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,20 Ref=off

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 2.710 | BB | 0.0742 | 664.58521 | 142.96146 | 100.0000 |
| Totals : | | | | 664.58521 | 142.96146 | |

Instrument 1 12/2/2022 3:24:45 PM CBRS-REPOSITORY Page 1 of 1

**Figure S33. HPLC spectra of 4-(4-fluoro-3-(4-methoxypiperidine-1-carbonyl) benzyl) phthalazin-1(2H)-one (19)**

## 9. Biological evaluation of Olaparib (1)

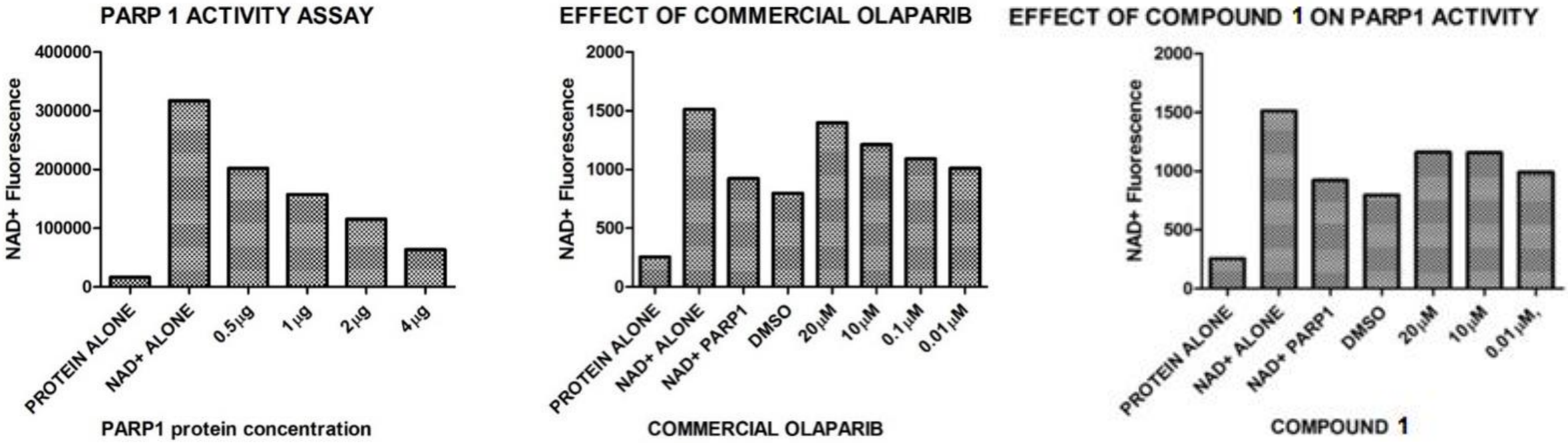



**Figure S34. (A) PARP1 activity was measured at different concentrations and concentration dependent activity was observed. (B) The fluorescence intensity of NAD+ (substrate of PARP1) was measured in each reaction in the presence and absence of inhibitors. In Fig B, lane 4, NAD+ intensity was lower than lane 3 as it was used up by PARP1 for its activity. In lanes 5-7, the concentration of NAD+ was higher in the presence of Olaparib, indication inhibition of PARP1 activity. (C) Our synthesized compound 1 showed more or less similar activity with commercially sourced olaparib.**