Supporting Information

Development of a potent Nurr1 agonist tool for in vivo applications

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Supplementary Figures & Tables

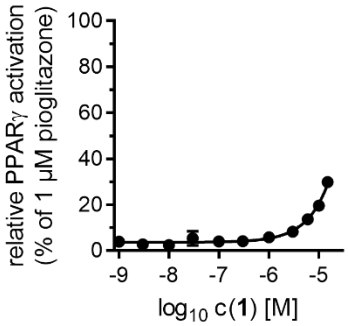


Figure S1. Activity of **1** on PPARγ. Data are the mean±S.E.M., n=3.

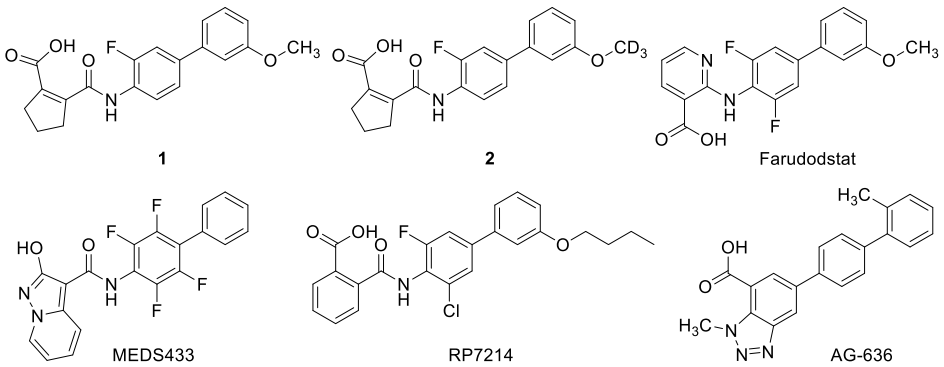


Figure S2. Chemical structures of DHODH inhibitors related to **1**. Their activity on Nurr1 in a hybrid Gal4-Nurr1 and a full-length Nurr1 (NBRE) reporter gene assay is shown in Figure 1g.

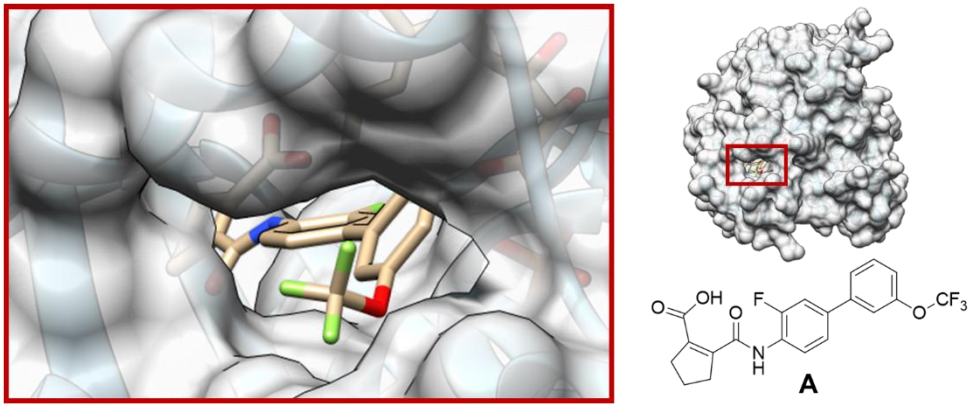


Figure S3. Co-crystal structure of hDHODH in complex with **A** (pdb ID 2bxv[1]). The alkoxy substituent is exposed to solvent.

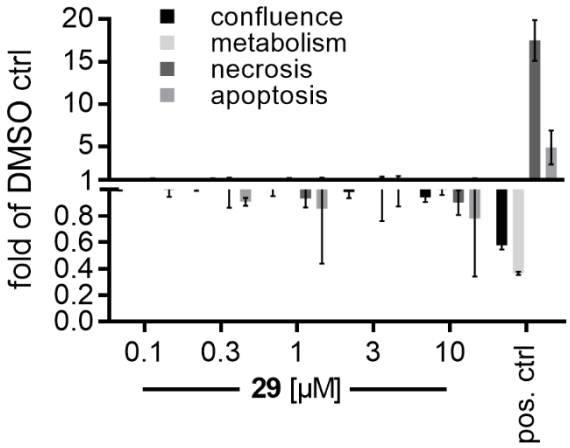


Figure S4. **29** exhibited no toxic effects in a multiplex toxicity assay in COS-7 cells. Data are the mean±S.E.M.; n≥3; bexarotene (necrosis, metabolism) and flavopiridol (confluence, apoptosis) as pos. controls.

Synthetic procedures

General. All chemicals were of reagent grade, purchased from commercial sources (e.g., Sigma-Aldrich, abcr, Enamine and BLDpharm) and used without further purification unless otherwise specified. All reactions were conducted in oven-dried Schlenk glassware under Ar atmosphere and in absolute solvents. Other solvents, especially for work-up procedures, were of reagent grade or purified by distillation (*i*-hexane, EtOAc, EtOH). Reactions were monitored by thin layer chromatography (TLC) on TLC Silica gel 60 F_{254} aluminium sheets by Merck and visualized under ultraviolet light (254 nm) or by in-process LC/MS. Purification of compounds **25**–**32** by column chromatography (CC) was performed on a puriFlash® XS520Plus system (Advion, Ithaca, NY, USA) using high performance spherical silica columns (SIHP, 50 µM) by Interchim and a gradient of *i*-hexane to EtOAc, reversed-phase CC was performed on a puriFlash® 5.250 system (Advion) using C18HP columns (SIHP, 15 µM) by Interchim and a gradient of 0.1% FA in H_2O, 10 to 100% acetonitrile (HPLC gradient grade). All other compounds were purified with a Biotage Isolera One combiflash chromatography system (SEPAFLASH, 40-63Å) with the solvent mixtures specified in the corresponding experiment. Preparative HPLC was performed using a combiflash reversed-phase chromatography (C18) Boston ODS 40 g Flash 35mL-50mL/min at 200 psi with gradient A: 0.1% NH_4HCO_3 in water, 10-100% ACN, or with gradient B: 0.1% TFA in water, 10-100% ACN. Melting points (uncorrected) were determined using glass capillaries on a M3000 melting point meter (Krüss). Mass spectra were obtained on a puriFlash®-CMS system (Advion) using atmospheric pressure chemical ionization (APCI) or on an Ion Trap Esquire 3000+ instrument (Bruker Corporation, Billerica, MA, USA) using electrospray ionization (ESI-LCMS). HRMS were obtained with a Thermo Finnigan LTQ FT instrument for electrospray ionization (ESI). NMR spectra were recorded on Bruker Avance III HD 400 MHz or 500 MHz spectrometers equipped with CryoProbe™ Prodigy broadband probe (Bruker). Chemical shifts are reported in δ values (ppm), coupling constants (*J*) in hertz (Hz). Signals are described as br for broad. Purity of **25**–**28** was analyzed on a system consisting of a Sciex API 3200 QTrap triple quadrupole mass spectrometer, a quarternary Agilent 1100 pump (G1311A) with degasser (G1322A), an Agilent 1100 oven (G1316A), an Agilent 1100 DAD (G1315B) and a Shimadzu SIL 20A HT autosampler under the control of Analyst 1.6 (Sciex). As stationary phase a Zorbax SBAq (3.5 µm, 100 mm x 3 mm, Agilent, protected with a 0.5 µm and a 0.2 µm frit) was used in combination with 5 mM ammonium formate (A) and acetonitrile (B) as mobile phase at a flow rate of 500 µL/min. Compounds were investigated by 10 µL injections of 1 µM and 10 µM sample solutions (100 mM stock solutions in DMSO diluted in mobile phase) under isocratic conditions (A/B 50:50 or 60:40, v/v). MS detection was done under negative ESI conditions recording corresponding $[(M - H)]^-$ ions in the SIM mode and mass transitions based on the loss of 44 Da (CO_2) in the MRM mode. UV detection was done recording spectra in a range from 210 nm – 360 nm. Purity of all other compounds was analyzed on an Agilent Technologies 1200 Series machine under the following conditions: LC-Mass Method 1: column: Sunfire C18, 4.6*50 mm, 3.5 µm; mobile phase: A: water (0.01% TFA), B: ACN (0.01% TFA); gradient: 5% - 95% B in 1.5 min; flow rate: 2.0 mL/min; oven temperature: 50 °C; mass range: 110-1000; detection: UV (214 nm, 254 nm) or LC-Mass Method 2: column: Xbridge C18(2) (4.6*50 mm, 3.5 µm); mobile phase: A: H_2O (10 mmol NH_4HCO_3), B: ACN; elution program: gradient from 10 to 95% of B in 1.5 min at 1.8 mL/min; temperature: 50 ºC; detection: UV (214 nm, 254 nm) and MS (ESI, Pos mode,103 to 800 amu). CD_3I used for deuteration had ≥99% isotopic purity, the deuterated products had ≥98% isotopic purity according to NMR. All compounds for biological testing had a purity >95% based on the 254 nm UV-trace.

General procedures

General procedure for Suzuki Miyaura coupling with XPhos-Pd-G2 (GP1)

The respective phenylboronic acid derivative **25a–28a** (1.2 eq), 2-[(4-Bromo-2-fluorophenyl)carbamoyl]cyclopent-1-ene-1-carboxylic acid (**33f**, 1.0 eq) and Cs_2CO_3 (3.0 eq) were evacuated for 10 minutes. A solvent mixture of toluene (6 mL), EtOH (4 mL), DMF (2 mL) and H_2O (1 mL) was degassed by the freeze-pump-thaw method (3x) and added under Ar. Then XPhos-Pd-G2 (0.1 eq) was added and the reaction was heated at 100°C for 18 h. After cooling to rt, EtOAc (10 mL) and H_2O (10 mL) was added and the mixture was filtered through Celite. All solvents were removed under reduced pressure and the resulting residue was dissolved in aqueous HCl (10%, 10 mL). The aqueous layer was extracted with EtOAc (3 x). The organic layers were combined, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by reversed-phase CC.

General procedure for Suzuki Miyaura coupling with other Pd catalysts (GP2)

The respective boronic acid or its pinacol ester **31a–31c** (1.00–1.30 eq), a carbonate salt (1.50–3.30 eq) and a Pd catalyst (0.01–0.09 eq) were added to a solution of the respective aryl bromide **2b–7b** and **19b–24b** (1.00 eq) in 1,4-dioxane and H_2O. The mixture was stirred at 90 °C under N_2 for 2 h-3 h, cooled to rt, diluted with H_2O and extracted with EtOAc (3 x). The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated and the resulting residue was purified by CC (PE:EtOAc = 10:1–8:1).

Synthesis and analytical characterization of **2-29**

2-{[3-Fluoro-3'-($^2H_3$)methoxy[1,1'-biphenyl]-4-yl]carbamoyl}cyclopent-1-ene-1-carboxylic acid (2). A solution of compound **2a** (9.0 g, 41 mmol) and 1-cyclopentene-1,2-dicarboxylic anhydride (**30a**, 5.6 g, 41 mmol) in MeCN (100 mL) was heated at 40 °C overnight and then allowed to reach rt. The mixture was filtered and the filter cake was washed with MeCN (20 mL x 2). The solid was dried in vacuum to afford compound **2** (12 g, yield: 82%) as a light yellow solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 13.04 (br s, 1H), 10.58 (s, 1H), 8.07 (t, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 12.4 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.27–7.23 (m, 2H), 6.94 (dd, *J* = 8.0, 2.0 Hz, 1H), 2.80 (br s, 2H), 2.69 (br s, 2H), 1.93–1.85 (m, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 166.17, 164.77, 159.79, 153.70 (d, *J* = 245.3 Hz), 147.12, 139.88, 137.18 (d, *J* = 7.1 Hz), 134.80, 130.03, 125.28 (d, *J* = 11.8 Hz), 123.89, 122.49 (d, *J* = 3.0 Hz), 118.76, 113.67, 113.48 (d, *J* = 5.2 Hz), 111.92, 54.36 (m), 36.43, 34.30, 21.13. LCMS (ESI): *m/z* 359.0 ([M+H]$^+$).

2-{[3'-($^2H_3$)Methoxy[1,1'-biphenyl]-4-yl]carbamoyl}cyclopent-1-ene-1-carboxylic acid (3). 1-Cyclopentene-1,2-dicarboxylic anhydride (**30a**, 81 mg, 0.59 mmol) was added to a solution of compound **3a** (0.10 g, 0.49 mmol) in CH_2Cl_2 (5 mL). After stirring for 5 h at rt the mixture was concentrated and the resulting residue was purified by preparative HPLC (gradient B) to afford compound **2** (63 mg, yield: 37%) as a colorless solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.75 (br s, 1H), 10.34 (s, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.40 (t, *J* = 8.4 Hz, 2H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.17 (t, *J* = 2.0 Hz, 1H), 6.90 (dd, *J* = 2.0, 8.0 Hz, 1H), 2.79 (t, *J* = 7.6 Hz, 2H), 2.67 (t, *J* = 7.2 Hz, 2H), 1.93 (q, *J* = 7.6 Hz, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 165.48, 165.24, 159.75, 147.76, 141.20, 138.56, 134.99, 133.48, 129.93, 127.00, 119.72, 118.58, 112.62, 111.77, 54.28 (m), 36.36, 33.60, 21.42. LCMS (ESI): *m/z* 341.2 ([M+H]$^+$).

2-{[3,5-Difluoro-3'-($^2H_3$)methoxy[1,1'-biphenyl]-4-yl]carbamoyl}cyclopent-1-ene-1-carboxylic acid (4). 1-Cyclopentene-1,2-dicarboxylic anhydride (**30a**, 6.95 g, 50.3 mmol) was added to a solution of compound **4a** (10.0 g, 42.0 mmol) in MeCN (20 mL) and then stirred at rt for 16 h. The mixture was filtered, and the filter cake was washed with MeCN. The solid was dried under reduced pressure to afford compound **4** (13.0 g, yield: 82%) as a colorless solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.95 (br s, 1H), 10.13 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.32–7.28 (m, 2H), 6.99 (dd, *J* = 1.8, 8.3 Hz, 1H), 2.81–2.79 (m, 2H), 2.69–2.66 (m, 2H), 1.97–1.89 (m, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 165.79, 164.90, 159.81, 157.83 (dd, *J* = 248.8, 6.3 Hz), 145.25, 140.06 (t, *J* = 9.5 Hz), 138.84, 136.03, 130.12, 118.99, 114.38, 112.99 (t, *J* = 17.5 Hz), 112.13, 110.01 (m), 54.44 (m), 36.19, 34.09, 21.41. LCMS (ESI): *m/z* 377.3 ([M+H]$^+$).

2-({3-Fluoro-5-[3-($^2H_3$)methoxyphenyl]pyridin-2-yl}carbamoyl)cyclopent-1-ene-1-carboxylic acid (5). 1-Cyclopentene-1,2-dicarboxylic anhydride (**30a**, 0.13 g, 0.94 mmol) was added to a solution of compound **5a** (0.20 g, 0.91 mmol) in CH_2Cl_2 (5 mL). After stirring for 4 d at 30 °C the mixture was concentrated and the resulting residue was purified by preparative HPLC (gradient B) to afford compound **5** (0.17 g, yield: 52%) as a colorless solid. ^{1}H-NMR (500 MHz, MeOD) δ 8.50 (br s, 1H), 7.99 (d, *J* = 9.0 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.25–7.21 (m, 2H), 6.99 (dd, *J* = 8.5, 2.0 Hz, 1H), 2.97–2.93 (m, 2H), 2.86–2.83 (m, 2H), 2.03–1.97 (m, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 165.73, 159.88, 150.41 (m), 146.17, 141.55 (d, *J* = 5.0 Hz), 138.61 (m), 136.77, 134.98, 130.24, 122.57 (d, *J* = 18.6 Hz), 119.12, 114.26, 112.32, 36.30, 33.90, 21.51. LCMS (ESI): *m/z* 360.1 ([M+H]$^+$).

2-[(4-(3-($^2H_3$)methoxyphenyl)naphthalen-1-yl)carbamoyl]cyclopent-1-ene-1-carboxylic acid (6). 1-Cyclopentene-1,2-dicarboxylic anhydride (**30a**, 0.20 g, 1.4 mmol) was added to a solution of compound **6a** (0.30 g, 1.2 mmol) in MeCN (5 mL) and stirred for 6 h at rt. The resulting mixture was filtered and the filter cake was washed with MeCN. The solid was dried in vacuum to afford compound **6** (0.20 g, yield: 43%) as a colorless solid. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 13.11 (br s, 1H), 10.49 (s, 1H), 8.23 (d, *J* = 7.5 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.57–7.43 (m, 4H), 7.05–7.00 (m, 3H), 2.92–2.89 (m, 2H), 2.75–2.71 (m, 2H), 2.00–1.93 (m, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 165.98, 165.79, 159.25, 147.73, 141.30, 137.22, 134.22, 132.79, 131.39, 129.64, 129.51, 128.47, 126.38, 125.76, 125.61, 123.53, 122.13, 121.77, 115.42, 112.92, 54.50 (m), 36.59, 34.00, 21.36. LCMS (ESI): *m/z* 391.2 ([M+H]$^+$).

2-({7-[3-($^2H_3$)methoxyphenyl]-2,3-dihydro-1*H*-inden-4-yl}carbamoyl)cyclopent-1-ene-1-carboxylic acid (7). 1-Cyclopentene-1,2-dicarboxylic anhydride (**30a**, 0.10 g, 0.72 mmol) was added to a solution of compound **7a** (0.15 g, 0.62 mmol) in CH_2Cl_2 (5 mL). After stirring for 8 h at rt the mixture was concentrated and the resulting residue was purified by preparative HPLC (gradient B) to afford compound **7** (0.15 g, yield: 64%) as a colorless solid. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 13.11 (br s, 1H), 10.11 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.96 (t, *J* = 1.8 Hz, 1H), 6.90 (dd, *J* = 8.0, 2.0 Hz, 1H), 2.96–2.87 (m, 4H), 2.83–2.80 (m, 2H), 2.72–2.68 (m, 2H), 2.00–1.86 (m, 4H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 166.11, 164.38, 159.21, 147.39, 142.27, 141.93, 136.86, 134.49, 133.91, 133.17, 129.39, 126.74, 121.03, 120.51, 113.74, 112.39, 54.25 (m), 36.56, 34.42, 32.93, 30.68, 24.96, 21.04. LCMS (ESI): *m/z* 381.3 ([M+H]$^+$).

2-({4-[3-($^2H_3$)Methoxyphenyl]bicyclo[2.2.2]octan-1-yl}carbamoyl)cyclopent-1-ene-1-carboxylic acid (8). 1-Cyclopentene-1,2-dicarboxylic anhydride (**30a**, 0.40 g, 2.9 mmol) was added to compound **8a** (0.29 g, 1.2 mmol) in THF. After stirring for 12 h at 60 °C the mixture was concentrated and the resulting residue was purified by preparative HPLC (gradient B) to give compound **8** (0.11 g, yield: 24%) as a colorless solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.83 (br s, 1H), 7.18 (t, *J* = 8.0 Hz, 1H), 6.89 (dd, *J* = 1.2, 8.8 Hz, 1H), 6.83 (t, *J* = 2.2 Hz, 1H), 6.73–6.71 (m, 1H), 2.65–2.57 (m, 4H), 1.97–1.93 (m, 6H), 1.85–1.80 (m, 6H), 1.78–1.67 (m, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 174.26, 166.39 (m), 165.61, 159.05, 150.85, 129.65, 128.95, 117.60, 111.54, 110.60, 50.72, 36.11, 33.89, 32.02, 29.95, 20.72. LCMS (ESI): *m/z* 373.3 ([M+H]$^+$).

2-{[3-Fluoro-3'-($^2H_3$)methoxy[1,1'-biphenyl]-4-yl](methyl)carbamoyl}cyclopent-1-ene-1-carboxylic acid (9). 1-Cyclopentene-1,2-dicarboxylic anhydride (**30a**, 70 mg, 0.51 mmol) was added to a solution of compound **9a** (0.10 g, 0.43 mmol) in CH_2Cl_2 (5 mL). After stirring for 2 h at rt the mixture was concentrated and the resulting residue was purified by preparative HPLC (gradient A) to afford compound **9** (0.02 g, yield: 14%) as a colorless solid. ^{1}H-NMR (400 MHz, CD_3OD, E/Z-isomers in a ratio of approx. 1:1) δ 7.52–7.43 (m, 3H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 2.0 Hz, 1H), 6.95 (dd, *J* = 1.8, 8.2 Hz, 1H), 3.32–3.30 (m, 3H), 2.88 (t, *J* = 7.4 Hz, 0.5 x 1H), 2.76 (t, *J* = 7.4 Hz, 0.5 x 1H), 2.57 (br s, 1.5 x 1H), 2.42 (br s, 1.5x 1H), 2.16–1.71 (m, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 168.05, 165.39, 160.27, 158.08 (d, *J* = 247.6 Hz), 148.23 (m), 142.02 (d, *J* = 7.3 Hz), 139.64, 133.70 (m), 130.59, 130.11, 129.54 (d, *J* = 12.2 Hz), 123.19, 119.47, 114.82 (d, *J* = 21.3 Hz), 114.60, 112.55, 54.87 (m), 36.56, 35.78, 32.94, 22.50. LCMS (ESI): *m/z* 373.1 ([M+H]$^+$).

4-{[3,5-Difluoro-3'-($^2H_3$)methoxy[1,1'-biphenyl]-4-yl]carbamoyl}-2,5-dihydrofuran-3-carboxylic acid (10). Compound **30b** (0.24 g, 1.7 mmol) was added to a solution of compound **4a** (0.20 g, 0.84 mmol) in MeCN (5 mL) and stirred at rt for 6 h, filtered and the filter cake was washed with MeCN. The solid was dried in vacuum to afford compound **10** (80 mg, yield: 25%) as a colorless solid. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 10.89 (br s, 1H), 7.58 (d, *J* = 9.5 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.33–7.28 (m, 2H), 6.99 (dd, *J* = 2.3, 8.3 Hz, 1H), 4.97 (t, *J* = 5.3 Hz, 2H), 4.89 (t, *J* = 5.0 Hz, 2H), 3.43 (br s, 1H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 163.70, 160.63, 159.82, 157.54 (dd, *J* = 248.7, 6.1 Hz), 141.24, 140.26 (t, *J* = 9.4 Hz), 138.76, 132.66, 130.13, 119.01, 114.45, 112.51 (t, *J* = 17.3 Hz), 112.14, 110.13 (m), 77.40, 76.36, 54.43 (m). LCMS (ESI): *m/z* 379.2 ([M+H]$^+$).

4-{[3,5-Difluoro-3'-($^2H_3$)methoxy[1,1'-biphenyl]-4-yl]carbamoyl}-2,5-dihydrothiophene-3-carboxylic acid (11). 4*H*,6*H*-Thieno[3,4-*c*]furan-1,3-dione (**30c**, 0.50 g, 3.2 mmol) was added to a solution of compound **4a** (0.31 g, 1.3 mmol) in MeCN (5 mL). The mixture was stirred at rt for 6 h, filtered and the filter cake was washed with MeCN. The solid was dried in vacuum to afford compound **11** (0.40 g, yield: 78%) as a colorless solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 13.01 (br s, 1H), 10.20 (s, 1H), 7.54 (d, *J* = 9.2 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.32–7.28 (m, 2H), 6.99 (dd, *J* = 2.4, 8.0 Hz, 1H), 4.15–4.11 (m, 2H), 4.03–4.00 (m, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 164.17, 163.74, 159.81, 157.75 (dd, *J* = 249.3, 6.4 Hz), 144.24, 140.12 (t, *J* = 9.5 Hz), 138.83, 133.17, 130.12, 119.00, 114.38, 112.76 (t, *J* = 17.3 Hz), 112.15, 110.06 (m), 54.43 (m), 40.82, 38.65. LCMS (ESI): *m/z* 395.2 ([M+H]$^+$).

2-{[3,5-Difluoro-3'-($^2H_3$)methoxy[1,1'-biphenyl]-4-yl]carbamoyl}-4,4-difluorocyclopent-1-ene-1-carboxylic acid (12). 5,5-Difluoro-5,6-dihydro-1*H*-cyclopenta[*c*]furan-1,3(4*H*)-dione (**30d**, 0.18 g, 1.2 mmol) was added to a solution of compound **4a** (0.20 g, 0.84 mmol) in MeCN (5 mL). The mixture was stirred at rt for 6 h, filtered and the filter cake was washed with MeCN. The solid was dried in vacuum to afford compound **12** (0.12 g, yield: 35%) as a colorless solid. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.39–7.33

(m, 3H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.16 (t, *J* = 2.0 Hz, 1H), 6.98–6.95 (m, 1H), 3.45–3.27 (m, 4H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 164.22, 162.65, 159.81, 157.68 (dd, *J* = 249.1, 6.3 Hz), 140.41, 140.21 (t, *J* = 9.1 Hz), 138.79, 131.24, 130.12, 129.62 (t, *J* = 249.3 Hz), 119.01, 114.42, 112.60 (t, *J* = 17.0 Hz), 112.14, 110.10 (m), 54.42 (m), 45.13 (t, *J* = 28.4 Hz), 43.32 (t, *J* = 28.0 Hz). LCMS (ESI): *m/z* 413.0 ([M+H]$^+$).

***N*-[3,5-Difluoro-3'-($^2H_3$)methoxy[1,1'-biphenyl]-4-yl]cyclopent-1-ene-1,2-dicarboxamide (13)**. NH_4Cl (28 mg, 0.52 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (51 mg, 0.27 mmol) and 4-dimethylaminopyridine (39 mg, 0.32 mmol) were added to a solution of compound **4** (100 mg, 266 µmol) in DMF (5 mL). The mixture was stirred 70 °C for 8 h, cooled to rt, diluted with H_2O and extracted with EtOAc (3 x). The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated and purified by preparative HPLC (gradient B) to afford compound **13** (35 mg, yield: 35%) as a colorless solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.59 (br s, 1H), 7.85 (d, *J* = 5.2 Hz, 2H), 7.56 (d, *J* = 9.2 Hz, 2H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.33–7.28 (m, 2H), 6.99 (dd, *J* = 2.2, 8.2 Hz, 1H), 2.84–2.78 (m, 4H), 1.88–1.80 (m, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 167.88, 162.87, 159.81, 157.54 (dd, *J* = 247.9, 6.4 Hz), 141.17, 140.84, 139.74 (t, *J* = 9.7 Hz), 138.83, 130.11, 118.97, 114.38, 113.40 (t, *J* = 16.3 Hz), 112.07, 110.02 (m), 54.44 (m), 36.37, 36.03, 20.62. LCMS (ESI): *m/z* 376.2 ([M+H]$^+$).

***N*^{1}-[3,5-Difluoro-3'-($^2H_3$)methoxy[1,1'-biphenyl]-4-yl]-*N*^{2}-hydroxycyclopent-1-ene-1,2-dicarboxamide (14)**. Carbonyldiimidazole (0.12 g, 0.75 mmol) was added to a solution of compound **4** (200 mg, 530 µmol) in THF (5 mL). The mixture was stirred at rt for 1 h, then hydroxylamine hydrochloride (73 mg, 1.1 mmol) was added. The resulting mixture was stirred at rt for 8 h, diluted with H_2O and extracted with EtOAc (3 x). The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated and purified by preparative HPLC (gradient B) to afford compound **14** (0.15 g, yield: 74%) as a colorless solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.43 (s, 1H), 11.16 (s, 1H), 9.35 (s, 1H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.33–7.28 (m, 2H), 6.98 (dd, *J* = 1.8, 8.2 Hz, 1H), 2.79–2.75 (m, 4H), 1.90–1.82 (m, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 162.66 (m), 159.81, 157.59 (dd, *J* = 248.1, 6.4 Hz), 141.52, 139.75 (t, *J* = 9.3 Hz), 138.80, 138.42, 130.11, 118.97, 114.39, 113.34 (t, *J* = 17.6 Hz), 112.06, 110.00 (m), 35.69, 35.59, 20.91. LCMS (ESI): *m/z* 492.2 ([M+H]$^+$).

***N*^{1}-[3,5-Difluoro-3'-($^2H_3$)methoxy[1,1'-biphenyl]-4-yl]-*N*^{2}-hydroxy-*N*^{2}-methylcyclopent-1-ene-1,2-dicarboxamide (15)**. Carbonyldiimidazole (250 mg, 1.54 mmol) was added to a solution of compound **4** (0.29 g, 0.77 mmol) in THF (5 mL). The mixture was stirred at rt for 1 h. Then *N*-methylhydroxylamine hydrochloride (128 mg, 1.53 mmol) was added and the mixture was stirred at rt overnight, diluted with H_2O and extracted with EtOAc (3 x). The organic layer was washed with brine, dried over Na_2SO_4, concentrated and purified by preparative HPLC (gradient B) to give compound **15** (0.03 g, yield: 8%) as a colorless solid. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.94 (br s, 1H), 9.41 (s, 1H), 7.56 (d, *J* = 9.0 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.28 (s, 1H), 6.98 (dd, *J* = 2.0, 8.0 Hz, 1H), 3.11 (s, 3H), 2.77–2.66 (m, 4H), 2.01–1.95 (m, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 167.80, 162.75, 159.82, 158.06 (m), 146.04, 140.14 (m), 138.80, 133.68, 130.13, 118.98, 114.38, 113.40 (t, *J* = 16.4 Hz), 112.12, 109.94 (m), 35.77, 35.64, 32.92, 22.19. LCMS (ESI): *m/z* 405.9 ([M+H]$^+$).

***N*^{1}-[3,5-Difluoro-3'-($^2H_3$)methoxy[1,1'-biphenyl]-4-yl]-*N*^{2}-methoxycyclopent-1-ene-1,2-dicarboxamide (16)**. *O*-Methylhydroxylamine (132 mg, 2.80 mmol), dicyclohexylcarbodiimide (246 mg, 1.19 mmol), 4-dimethylaminopyridine (97 mg, 0.79 mmol) and triethylamine (0.30 mL, 2.2 mmol) were added to a solution of compound **4** (300 mg, 0.797 mmol) in CH_2Cl_2 (25 mL). Then mixture was stirred at 60 °C for 8 h in a sealed tube, cooled to rt, concentrated and purified by preparative HPLC (gradient A) to afford compound **16** (45 mg, 14%) as a colorless solid. ^{1}H-NMR (500 MHz, CD_3OD) δ 7.40–7.32 (m, 3H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.16 (s, 1H), 6.97 (dd, *J* = 8.3, 2.3 Hz, 1H), 3.75 (s, 3H), 2.92–2.88 (m, 2H), 2.82–2.78 (m, 2H), 2.06–2.00 (m, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 163.01 (m), 159.82, 157.80 (dd, *J* = 248.0, 6.3 Hz), 140.68, 140.05 (t, *J* = 9.5 Hz), 139.46, 138.80, 130.12, 118.99, 114.40, 113.21 (t, *J* = 17.1 Hz), 112.10, 110.02 (m), 63.09, 54.44 (m), 35.27, 35.05, 21.44. LCMS (ESI): *m/z* 406.2 ([M+H]$^+$).

***N*^{1}-Cyano-*N*^{2}-[3,5-difluoro-3'-($^2H_3$)methoxy[1,1'-biphenyl]-4-yl]cyclopent-1-ene-1,2-dicarboxamide (17)**. Cyanamide (34 mg, 0.81 mmol), 3-oxo-1-[*bis*(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium hexafluorophosphate (0.18 g, 0.48 mmol) and *N,N*-diisopropylethylamine (134 mg, 1.06 mmol) were added to a solution of compound **4** (150 mg, 0.399 mmol) in DMF (5 mL).

Then mixture was stirred at rt for 8 h, diluted with H_2O and extracted with EtOAc (3 x). The organic layer was washed with brine, dried over Na_2SO_4, concentrated and purified by preparative HPLC (gradient B) to give compound **17** (36 mg, yield: 22%) as a colorless solid. ^{1}H-NMR (500 MHz, CD_3OD) δ 7.40–7.34 (m, 3H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 2.0 Hz, 1H), 6.97 (dd, *J* = 2.3, 8.3 Hz, 1H), 2.99 (d, *J* = 7.3 Hz, 2H), 2.85 (d, *J* = 7.5 Hz, 2H), 2.12–2.04 (m, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 162.80, 159.81, 157.90 (dd, *J* = 248.6, 6.3 Hz), 141.35 (m), 140.28 (t, *J* = 9.1 Hz), 138.78, 130.12, 119.00, 114.44, 113.04 (t, *J* = 17.0 Hz), 112.11, 110.01 (m), 35.11, 34.46, 21.86. LCMS (ESI): *m/z* 401.2 ([M+H]$^+$).

***N*^{1}-[3,5-Difluoro-3'-($^2H_3$)methoxy[1,1'-biphenyl]-4-yl]-*N*^{2}-(methylsulfonyl)cyclopent-1-ene-1,2-dicarboxamide (18)**. Methanesulfonamide (101 mg, 1.06 mmol), dicyclohexylcarbodiimide (109 mg, 0.53 mmol), 4-dimethylaminopyridine (97 mg, 0.79 mmol) and triethylamine (0.1 mL) were added to a solution of compound **4** (200 mg, 0.532 mmol) in CH_2Cl_2 (5 mL) . The mixture was stirred at 60 °C for 8 h in a sealed tube, cooled to rt, diluted with H_2O and extracted with EtOAc (3 x). The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated and purified by preparative HPLC (gradient A) to afford compound **18** (28 mg, yield: 12%) as a colorless solid. ^{1}H-NMR (500 MHz, CD_3OD) δ 7.38–7.32 (m, 3H), 7.20 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.17–7.16 (m, 1H), 6.96 (dd, *J* = 2.7, 8.3 Hz, 1H), 3.18 (s, 3H), 2.92–2.86 (m, 4H), 2.01–1.95 (m, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 162.95, 159.80, 157.85 (dd, *J* = 248.3, 6.2 Hz), 139.92 (m), 138.88, 138.26 (m), 130.10, 118.98, 114.39, 113.55 (m), 112.07 (m), 110.01 (m), 54.43 (m), 40.50, 35.11 (m), 21.14 (m). LCMS (ESI): *m/z* 544.3 ([M+H]$^+$).

2-{[3,5-Difluoro-2'-($^2H_3$)methoxy[1,1'-biphenyl]-4-yl]carbamoyl}cyclopent-1-ene-1-carboxylic acid (19). Compound **30a** (0.24 g, 1.7 mmol) was added to a solution of compound **19a** (0.35 g, 1.5 mmol) in MeCN (5 mL). The mixture was stirred at rt for 2 h, filtered and the filter cake was washed with MeCN. The solid was dried in vacuum to afford compound **19** (0.30 g, yield: 54%) as a colorless solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.09 (s, 1H), 7.42–7.39 (m, 2H), 7.28 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.07–7.02 (m, 1H), 2.82–2.78 (m, 2H), 2.70–2.65 (m, 2H), 1.97–1.88 (m, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 165.77, 165.00, 157.12 (dd, *J* = 248.2, 6.4 Hz), 156.03, 145.30, 138.11 (t, *J* = 9.9 Hz), 135.96, 130.26, 129.94, 126.97, 120.84, 112.52 (m), 112.40 (m), 111.89, 54.77 (m), 36.21, 34.08, 21.41. LCMS (ESI): *m/z* 377.3 ([M+H]$^+$).

2-({2,6-Difluoro-4-[2-($^2H_3$)methoxythiazol-4-yl]phenyl}carbamoyl)cyclopent-1-ene-1-carboxylic acid (20). Compound **30a** (68 mg, 0.49 mmol) was added to a solution of compound **20a** (0.10 g, 0.41 mmol) in MeCN (5 mL). The mixture was stirred at rt for 2 h, filtered and the filter cake was washed with MeCN. The solid was dried in vacuum to afford compound **20** (50 mg, yield: 32%) as a colorless solid. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.58–7.53 (m, 2H), 7.34 (s, 1H), 2.96–2.90 (m, 2H), 2.87–2.81 (m, 2H), 2.04–1.96 (m, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 174.17, 165.81, 164.80, 157.78 (dd, *J* = 249.0, 6.3 Hz), 145.37, 145.09, 136.17, 133.98 (t, *J* = 9.9 Hz), 113.16 (t, *J* = 17.1 Hz), 108.89, 108.66 (m), 58.35 (m), 36.14, 34.12, 21.39. LCMS (ESI): *m/z* 384.1 ([M+H]$^+$).

2-({2,6-Difluoro-4-[6-($^2H_3$)methoxypyridin-2-yl]phenyl}carbamoyl)cyclopent-1-ene-1-carboxylic acid (21). Compound **30a** (0.14 g, 1.0 mmol) was added to a solution of compound **21a** (0.20 g, 0.84 mmol) in MeCN (5 mL) . The mixture was stirred at rt for 2 h, concentrated and purified by preparative HPLC (gradient B) to afford compound **21** (70 mg, yield: 22%) as a colorless solid. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 12.98 (br s, 1H), 10.19 (s, 1H), 7.91 (d, *J* = 9.5 Hz, 2H), 7.83 (t, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 1H), 2.82–2.77 (m, 2H), 2.69–2.65 (m, 2H), 1.96–1.89 (m, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 165.81, 164.78, 163.18, 157.77 (dd, *J* = 248.6, 6.0 Hz), 150.67, 145.21, 140.30, 138.28 (t, *J* = 8.9 Hz), 136.08, 114.36 (t, *J* = 17.4 Hz), 113.48, 110.67, 109.57 (m), 52.29 (m), 36.18, 34.09, 21.42. LCMS (ESI): *m/z* 378.2 ([M+H]$^+$).

2-({2,6-Difluoro-4-[2-($^2H_3$)methoxypyridin-4-yl]phenyl}carbamoyl)cyclopent-1-ene-1-carboxylic acid (22). Compound **30a** (0.14 g, 1.0 mmol) was added to a solution of compound **22a** (0.20 g, 0.84 mmol) in MeCN (5 mL). The mixture was stirred at rt for 2 h, filtered and the filter cake was washed with MeCN. The solid was dried in vacuum to afford compound **22** (60 mg, yield: 19%) as a colorless solid. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 12.90 (br s, 1H), 10.21 (s, 1H), 8.25 (d, *J* = 5.5 Hz, 1H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 5.5 Hz, 1H), 7.23 (s, 1H), 2.81–2.77 (m, 2H), 2.69–2.65 (m, 2H), 1.96–1.89 (m, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 165.76, 164.86, 164.55, 157.81 (dd, *J* = 249.4, 6.2 Hz), 147.69, 147.43, 145.36, 136.82 (t, *J* = 9.3 Hz), 135.85, 114.86, 114.59 (t, *J* = 17.3 Hz), 110.42 (m), 107.73, 36.21, 34.00, 21.45. LCMS (ESI): *m/z* 378.1 ([M+H]$^+$).

2-{[4-(Benzo[*d*][1,3]dioxol-4-yl)-2,6-difluorophenyl]carbamoyl}cyclopent-1-ene-1-carboxylic acid (23). Compound **30a** (0.10 g, 0.72 mmol) was added to a solution of compound **23a** (0.15 g, 0.60 mmol) in MeCN (5 mL). The mixture was stirred at rt for 6 h, filtered and the filter cake was washed with MeCN. The solid was dried in vacuum to afford compound **24** (0.18 g, yield: 77%) as a colorless solid. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 12.91 (br s, 1H), 10.18 (s, 1H), 7.57 (d, *J* = 9.0 Hz, 2H), 7.24 (dd, *J* = 1.4, 7.3 Hz, 1H), 6.99–6.95 (m, 2H), 6.13 (s, 2H), 2.80–2.77 (m, 2H), 2.69–2.64 (m, 2H), 1.93 (q, *J* = 7.5 Hz, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 165.84, 164.85, 157.60 (dd, *J* = 248.6, 6.3 Hz), 147.84, 145.04, 144.55, 136.27, 135.04 (t, *J* = 10.0 Hz), 122.32, 120.50, 119.24, 113.15 (t, *J* = 17.4 Hz), 110.68 (m), 108.77, 101.11, 36.17, 34.17, 21.39. LCMS (ESI): *m/z* 388.1 ([M+H]$^+$).

2-{[4-(Benzo[*d*]oxazol-4-yl)-2,6-difluorophenyl]carbamoyl}cyclopent-1-ene-1-carboxylic acid (24). Compound **30a** (0.10 g, 0.72 mmol) was added to a solution of compound **24a** (0.15 g, 0.61 mmol) in MeCN (5 mL). The mixture was stirred at rt for 6 h, filtered and the filter cake was washed with MeCN. The solid was dried in vacuum to afford compound **24** (0.14 g, yield: 60%) as a colorless solid. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.51 (s, 1H), 7.80 (d, *J* = 9.0 Hz, 2H), 7.71–7.68 (m, 2H), 7.53 (t, *J* = 8.0 Hz, 1H), 2.92–2.87 (m, 4H), 1.97–1.91 (m, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 166.64 (m), 164.31, 157.43 (dd, *J* = 247.5, 6.5 Hz), 154.63, 150.04, 137.14, 135.36 (m), 129.08, 125.99, 123.25, 114.47 (m), 111.59 (m), 111.38, 36.00, 35.79 (m), 20.87. LCMS (ESI): *m/z* 385.2 ([M+H]$^+$).

2-[(3-Fluoro-3'-isopropoxy-[1,1'-biphenyl]-4-yl)carbamoyl]cyclopent-1-ene-1-carboxylic acid (25). Preparation according to the GP1, using commercially available 3-isopropoxyphenylboronic acid (**25a**, 32 mg, 0.18 mmol) and compound **33f** (49 mg, 0.15 mmol). Further purification was performed by reversed-phase CC to give compound **25** (45 mg, 78%) as a yellow solid. ^{1}H-NMR (500 MHz, acetone-d_6) δ 10.45 (br s, 1H), 8.25 (t, *J* = 8.3 Hz, 1H), 7.56–7.46 (m, 2H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.26–7.17 (m, 2H), 6.97–6.87 (m, 1H), 4.75 (h, *J* = 6.0 Hz, 1H), 3.09–2.97 (m, 2H), 2.97–2.81 (m, 2H), 1.93 (p, *J* = 7.7 Hz, 2H), 1.33 (d, *J* = 6.0 Hz, 6H). ^{13}C NMR (126 MHz, acetone-d_6) δ 166.43, 164.67, 159.51, 154.95 (d, *J* = 245.6 Hz), 146.36, 141.49 (d, *J* = 2.0 Hz), 140.18, 139.51 (d, *J* = 7.3 Hz), 130.89, 125.97 (d, *J* = 11.5 Hz), 124.69, 123.52 (d, *J* = 3.1 Hz), 119.67, 115.97, 115.02, 114.36 (d, *J* = 20.5 Hz), 70.34, 37.29, 37.10, 22.33, 21.35. MS (+APCI): *m*/*z* 383.6 ([M+H]$^+$).

2-[(3-Fluoro-3'-isobutoxy-[1,1'-biphenyl]-4-yl)carbamoyl]cyclopent-1-ene-1-carboxylic acid (26). Preparation according to the GP1, using commercially available 3-isobutoxyphenylboronic acid (**26a**, 35 mg, 0.18 mmol) and compound **33f** (49 mg, 0.15 mmol). Further purification was performed by reversed-phase CC to give compound **26** (53 mg, 89%) as a yellow solid. ^{1}H-NMR (500 MHz, Acetone) δ 10.49 (br s, 1H), 8.26 (t, *J* = 8.3 Hz, 1H), 7.57–7.46 (m, 2H), 7.43–7.32 (m, 1H), 7.29–7.18 (m, 2H), 7.03–6.85 (m, 1H), 3.86 (d, *J* = 6.5 Hz, 2H), 3.06–2.96 (m, 2H), 2.95–2.83 (m, 2H), 2.13–2.07 (m, 1H), 1.93 (p, *J* = 7.7 Hz, 2H), 1.04 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, acetone-d_6) δ 166.61, 164.65, 160.85, 154.93 (d, *J* = 245.5 Hz), 146.20, 141.46 (d, *J* = 1.9 Hz), 140.31, 139.41 (d, *J* = 7.3 Hz), 130.84, 126.09 (d, *J* = 11.5 Hz), 124.64, 123.53 (d, *J* = 3.2 Hz), 119.73, 114.85, 114.37 (d, *J* = 20.5 Hz), 113.63, 75.01, 37.29, 37.17, 29.11, 21.36, 19.49. MS (+APCI): *m*/*z* 397.6 ([M+H]$^+$).

2-[(3'-Butoxy-3-fluoro-[1,1'-biphenyl]-4-yl)carbamoyl]cyclopent-1-ene-1-carboxylic acid (27). Preparation according to the GP1, using commercially available 3-butoxyphenylboronic acid (**27a**, 31.4 mg, 162 µmol) and compound **33f** (44.3 mg, 135 µmol). Further purification was performed by reversed-phase CC to give compound **27** (53 mg, 99%) as a yellow solid. ^{1}H-NMR (500 MHz, acetone-d_6) δ 10.50 (s, 1H), 8.25 (t, *J* = 8.4 Hz, 1H), 7.58–7.46 (m, 2H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.28–7.17 (m, 2H), 6.98–6.90 (m, 1H), 4.09 (t, *J* = 6.4 Hz, 2H), 3.06 – 2.98 (m, 2H), 2.94–2.83 (m, 2H), 1.93 (p, *J* = 7.7 Hz, 2H), 1.83–1.74 (m, 2H), 1.57–1.46 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, acetone-d_6) δ 166.56, 164.65, 160.77, 154.94 (d, *J* = 245.5 Hz), 146.28, 141.44 (d, *J* = 2.1 Hz), 140.25, 139.44 (d, *J* = 7.2 Hz), 130.84, 126.06 (d, *J* = 11.6 Hz), 124.65, 123.53 (d, *J* = 3.2 Hz), 119.70, 114.80, 114.37 (d, *J* = 20.4 Hz), 113.61, 68.31, 37.29, 37.15, 32.15, 21.35, 19.93, 14.12. MS (+APCI): *m*/*z* 397.6 ([M+H]$^+$).

2-{[3-Fluoro-3'-(2-methoxyethoxy)[1,1'-biphenyl]-4-yl]carbamoyl}cyclopent-1-ene-1-carboxylic acid (28). Preparation according to the GP1, using commercially available 3-(2-methoxyethoxy)phenylboronic acid (**28a**, 31.8 mg, 162 µmol) and compound **33f** (44.3 mg, 135 µmol). Further purification was performed by reversed-phase CC to give compound **28** (32 mg, 59%) as a yellow solid. ^{1}H-NMR (500 MHz, acetone-d_6) δ 10.47 (s, 1H), 8.25 (t, *J* = 8.4 Hz, 1H), 7.58–7.48 (m, 2H), 7.42–7.33 (m, 1H), 7.30–7.20 (m, 2H), 7.00–6.92 (m, 1H), 4.26–4.17 (m, 2H), 3.78–3.68 (m, 2H), 3.38 (s, 3H), 3.07–2.97 (m, 2H), 2.93–2.83 (m, 2H), 1.93 (p, *J* = 7.7 Hz, 2H). ^{13}C NMR (126 MHz, acetone-d_6) δ 166.46, 164.66, 160.54, 154.94 (d, *J* = 245.5 Hz), 146.39, 141.46 (d, *J* = 1.9 Hz), 140.14, 139.40 (d, *J* = 7.3 Hz), 130.88, 126.04 (d, *J* = 11.5 Hz), 124.66, 123.55 (d, *J* = 3.2 Hz), 119.93, 114.85, 114.39 (d, *J* = 20.5 Hz), 113.67, 71.74, 68.22, 58.94, 37.29, 37.10, 21.36. MS (+APCI): *m*/*z* 399.5 ([M+H]$^+$).

2-[(3-Fluoro-3'-prop-2-yn-1-yloxy[1,1'-biphenyl]-4-yl)carbamoyl]cyclopent-1-ene-1-carboxylic acid (29). 2N NaOH (3 mL) was added to a solution of compound **29b** (0.45 g, 1.1 mmol) in MeOH (1 mL) and THF (3 mL) at 0 °C. After stirring for 3 h at rt the pH was adjusted to 5–6. This mixture was concentrated and the resulting residue was purified by reversed-phase CC (0.1% TFA in H_2O, 10 to 100% MeCN) to give compound **29** (0.34 g, yield: 83%) as a yellow solid. Mp 190 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.51–13.55 (br s, 1H), 10.69 (br s, 1H), 8.09 (t, J = 8.4 Hz, 1H), 7.63 (dd, J = 12.4, 1.6 Hz, 1H), 7.53 (dd, J = 8.4, 1.3 Hz, 1H), 7.40 (t, J = 7.9 Hz, 1H), 7.35–7.27 (m, 2H), 7.00 (dd, J = 8.1, 1.9 Hz, 1H), 4.90 (d, J = 2.4 Hz, 2H), 3.61–3.56 (t, J = 2.1 Hz, 1H), 2.81 (t, J = 7.0 Hz, 2H), 2.70 (t, J = 7.2 Hz, 2H), 1.90 (p, J = 7.7 Hz, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 166.7, 165.2, 158.2, 154.2 (d, $^1J_{CF}$ = 245.6 Hz), 147.3, 140.3, 137.4 (d, $^3J_{CF}$ = 7.0 Hz), 135.6, 130.5, 125.9 (d, $^2J_{CF}$ = 11.9 Hz), 124.4, 123.0 (d, $^4J_{CF}$ = 2.8 Hz), 119.9, 114.8, 114.1 (d, $^2J_{CF}$ = 20.5 Hz), 113.3, 79.7, 78.8, 55.9, 36.9, 34.9, 21.6. LCMS (ESI): *m/z* 380.2 ([M+H]$^+$). HRMS (ESI): *m/z* calculated for $C_{22}H_{18}FNO_4$ + H^+: 380.12926, found: 380.12894 ([M+H]$^+$).

Synthesis and analytical characterization of intermediates

5-Fluoro-3'-($^2H_3$)methoxy[1,1'-biphenyl]-4-amine (2a). Preparation according to the GP2, using 1-bromo-3-($^2H_3$)methoxybenzene (**2b**, 16.0 g, 84.2 mmol), Na_2CO_3 (26.8 g, 253 mmol), $Pd(dppf)Cl_2$ (6.1 g, 7.5 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**31b**, 20.0 g, 84.4 mmol) in 1,4-dioxane (100 mL) and H_2O (25 mL) yielded compound **2a** (13.7 g, yield: 74%) as an off-white solid. LCMS (ESI): *m/z* 221.3 ($[M+H]^+$).

3'-($^2H_3$)Methoxy[1,1'-biphenyl]-4-amine (3a). Preparation according to the GP2, using 4-bromoaniline (**3b**, 0.15 g, 0.87 mmol), Cs_2CO_3 (0.86 g, 2.6 mmol), $Pd(PPh_3)_4$ (20 mg, 17 µmol) and [3-($^2H_3$)methoxyphenyl]boronic acid (**31a**, 0.16 g, 1.1 mmol) in 1,4-dioxane (5 mL) and H_2O (0.5 mL) yielded compound **3a** (0.10 g, yield: 57%) as a yellow solid. LCMS (ESI): *m/z* 203.2 ($[M+H]^+$).

3,5-Difluoro-3'-($^2H_3$)methoxy[1,1'-biphenyl]-4-amine (4a). Preparation according to the GP2, using 1-bromo-3-($^2H_3$)methoxybenzene (**4b**, 37.1 g, 195 mmol), Na_2CO_3 (62.3 g, 588 mmol), $Pd(dppf)Cl_2$ (5.0 g, 6.8 mmol) and 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**31c**, 50.0 g, 196 mmol) in 1,4-dioxane (250 mL) and H_2O (25 mL) yielded compound **4a** (35.0 g, yield: 75%) as a yellow solid. LCMS (ESI): *m/z* 238.3 ($[M+H]^+$).

3-Fluoro-5-[3-($^2H_3$)methoxyphenyl]pyridin-2-amine (5a). Preparation according to the GP2, using [3-($^2H_3$)methoxyphenyl]boronic acid (**31a**, 0.39 g, 2.5 mmol), Cs_2CO_3 (2.4 g, 6.3 mmol), $Pd(dppf)Cl_2$ (40 mg, 55 µmol) and 5-bromo-3-fluoropyridin-2-amine (**5b**, 0.40 g, 2.1 mmol) in 1,4-dioxane (5 mL) and H_2O (0.5 mL) yielded compound **5a** (0.42 g, yield: 91%) as a yellow solid. LCMS (ESI): *m/z* 222.0 ($[M+H]^+$).

4-[3-($^2H_3$)Methoxyphenyl]naphthalen-1-amine (6a). Preparation according to the GP2, using [3-($^2H_3$)methoxyphenyl]boronic acid (**31a**, 0.34 g, 2.2 mmol), Na_2CO_3 (0.75 g, 7.1 mmol), $Pd(dppf)Cl_2$ (40 mg, 55 µmol) and 4-bromonaphthalen-1-amine (**6b**, 0.40 g, 1.8 mmol) in 1,4-dioxane (5 mL) and H_2O (0.5 mL) yielded compound **6a** (0.30 g, yield: 66%) as a yellow solid. LCMS (ESI): *m/z* 252.9 ($[M+H]^+$).

7-[3-($^2H_3$)Methoxyphenyl]-2,3-dihydro-1*H*-inden-4-amine (7a). Preparation according to the GP2, using [3-($^2H_3$)methoxyphenyl]boronic acid (**31a**, 0.18 g, 1.2 mmol), Na_2CO_3 (0.30 g, 2.8 mmol), $Pd(dppf)Cl_2$ (20 mg, 27 µmol) and 7-bromo-2,3-dihydro-1*H*-inden-4-amine (**7b**, 0.20 g, 0.94 mmol) in 1,4-dioxane (5 mL) and H_2O (0.5 mL) yielded compound **7a** (0.15 g, yield: 62%) as a yellow solid. LCMS (ESI): *m/z* 243.3 ($[M+H]^+$).

4-[3-($^2H_3$)methoxyphenyl]bicyclo[2.2.2]octan-1-amine hydrochloride (8a). HCl (4 M in MeOH, 2 mL) was added to the mixture of compound **8h** (0.51 g, 1.5 mmol) in MeOH. The mixture was stirred at rt for 3 h and then concentrated to get compound **8a** (0.36 g, yield: 100%) as a colorless solid. LCMS (ESI): *m/z* 235.3 ($[M+H]^+$).

1-(1,3-Dioxoisoindolin-2-yl) 4-methyl bicyclo[2.2.2]octane-1,4-dicarboxylate (8c). *N,N*-Diisopropylcarbodiimide (3.6 g, 29 mmol) was added to a solution 4-(methoxycarbonyl)bicyclo[2.2.2]octane-1-carboxylic acid (**8b**, 5.0 g, 24 mmol), 2-hydroxyisoindoline-1,3-dione (3.8 g, 23 mmol), 4-dimethylaminopyridine (0.86 g, 7.1 mmol) and CH_2Cl_2 (50 mL) at rt under N_2. The mixture was stirred at rt overnight, washed with H_2O (2 x 300 mL), dried (Na_2SO_4), filtered, concentrated and the resulting residue was purified by CC (PE:EtOAc = 1:1) to give compound **8c** (4.6 g, yield: 55%) as a colorless solid. LCMS (ESI): *m/z* 380.2 ($[M+Na]^+$).

Methyl 4-(3-methoxyphenyl)bicyclo[2.2.2]octane-1-carboxylate (8d). LiCl (2.7 g, 64 mmol) and $ZnCl_2$ (20 mL, 1M in THF) at rt were added to a mixture of (3-methoxyphenyl)magnesium bromide (42 mL, 1M in THF). The mixture was stirred at rt for 1 h to give bis(3-Methoxyphenyl)zinc as a solution in THF. A solution of bis(3-Methoxyphenyl)zinc in THF (~20 mmol) was added to a solution of compound **8c** (3.0 g, 8.4 mmol), 6,6'-dimethyl-2,2'-bipyridine (0.93 g, 5.0 mmol), $Ni(acac)_2$ (1.1 g, 4.3 mmol) in MeCN (50 mL) at rt. The mixture was degassed with 3 vacuum-nitrogen cycles, stirred at 80 °C overnight, cooled to rt, concentrated, diluted with H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine (2 x 50 mL), dried (Na_2SO_4), filtered, concentrated and the resulting residue was purified by CC (PE:EtOAc = 2:1) to give compound **8d** (1.9 g, yield: 83%) as a light yellow solid. LCMS (ESI): *m/z* 275.3 ($[M+H]^+$).

Methyl 4-(3-hydroxyphenyl)bicyclo[2.2.2]octane-1-carboxylate (8e). BBr_3 (10 mL, 1M in BBr_3) was added to a mixture of compound **8d** (1.9 g, 6.9 mmol) in CH_2Cl_2 (40 mL). The mixture was stirred at rt for 4 h, diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined the organic layer was washed with brine, dried (Na_2SO_4), filtered, concentrated and the resulting residue was purified by CC (PE:EtOAc = 1:1) to give compound **8e** (1.6 g, yield: 89%) as a colorless solid. LCMS (ESI): *m/z* 260.8 ($[M+H]^+$).

Methyl 4-[3-($^2H_3$)methoxyphenyl]bicyclo[2.2.2]octane-1-carboxylate (8f). CD_3I (1.8 g, 12 mmol) and K_2CO_3 (1.7 g, 12 mmol) were added to compound **8e** (1.6 g, 6.2 mmol) in MeCN (20 mL). The mixture was stirred at 60 °C for 12 h, cooled to rt, diluted with H_2O (80 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, concentrated and the resulting residue was purified by CC (PE:EtOAc = 3:2) to give compound **8f** (1.6 g, yield: 94%) as a colorless solid. LCMS (ESI): *m/z* 278.3 ($[M+H]^+$).

4-[3-($^2H_3$)Methoxyphenyl]bicyclo[2.2.2]octane-1-carboxylic acid (8g). Aqueous LiOH (5 mL, 2M) was added to compound **8f** (1.6 g, 5.8 mmol) in MeOH (20 mL). The mixture was stirred at rt for 12 h, concentrated and adjusted pH to 6 with HCl. Then the mixture was purified by preparative HPLC (gradient A) to afford compound **8g** (1.5 g, yield: 99%) as colorless solid. LCMS (ESI): *m/z* 264.0 ($[M+H]^+$).

***tert*-Butyl {4-[3-($^2H_3$)methoxyphenyl]bicyclo[2.2.2]octan-1-yl}carbamate (8h).** $(Boc)_2O$ (1.3 g, 6.0 mmol), diphenylphosphoryl azide (1.7 g, 6.2 mmol) and NEt_3 (1.2 g, 12 mmol) were added to compound **8g** (1.5 g, 5.7 mmol) in toluene (30 mL). The mixture was stirred at 80 °C for 12 h, cooled to rt, poured into H_2O (80 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, concentrated and the resulting residue was purified by CC (PE:EtOAc = 3:2) to give compound **8h** (0.51 g, yield: 27%) as a colorless solid. LCMS (ESI): *m/z* 335.0 ($[M+H]^+$).

3-Fluoro-3'-($^2H_3$)methoxy-*N*-methyl-[1,1'-biphenyl]-4-amine hydrochloride (9a). HCl (4 M in 1,4-dioxane, 5 mL) was added to a solution of compound **9c** (0.30 g, 0.88 mmol) in 1,4-dioxane (5 mL). The mixture was stirred at rt for 1 h, then concentrated to afford compound **9a** as a colorless solid, which was used for the next step without purification. LCMS (ESI): *m/z* 235.1 ($[M-Cl]^-$).

***tert*-Butyl [3-fluoro-3'-($^2H_3$)methoxy[1,1'-biphenyl]-4-yl]carbamate (9b).** (5 mL) Di-*tert*-butyl pyrocarbonate (834 mg, 3.82 mmol) and *N,N*-diisopropylethylamine (469 mg, 3.63 mmol) were added to a solution of 3-fluoro-3'-($^2H_3$)methoxy[1,1'-biphenyl]-4-amine (**2a**, 400 mg, 1.82 mmol) in DMF. Then the mixture was stirred at rt for 8 h, diluted with H_2O and extracted with EtOAc (3 x). The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated and the resulting residue was purified by preparative HPLC (gradient A) to afford compound **9b** (450 mg, yield: 77%) as a yellow solid. LCMS (ESI): *m/z* 265.0 ($[M-t\text{-Bu}+H]^+$).

***tert*-Butyl [3-fluoro-3'-($^2H_3$)methoxy[1,1'-biphenyl]-4-yl](methyl)carbamate (9c).** At 0°C NaH (250 mg, 60%wt) was added to a solution of compound **9b** (400 mg, 1.25 mmol) in dry THF (5 mL). The mixture was stirred at 0 °C for 1 h, then CH_3I (266 mg, 1.87 mmol) was added and the mixture was allowed to reach rt. After 4 h, the mixture was carefully diluted with H_2O and extracted with EtOAc (3 x). The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated and the resulting residue was purified by preparative HPLC (gradient A) to afford compound **9c** (300 mg, yield: 72%) as a colorless solid. LCMS (ESI): *m/z* 279.1 ($[M-t\text{-Bu}+H]^+$).

3,5-Difluoro-2'-($^2H_3$)methoxy[1,1'-biphenyl]-4-amine (19a). Preparation according to the GP2, using 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**31c**, 0.68 g, 2.7 mmol), Cs_2CO_3 (1.3 g, 4.0 mmol), $Pd(PPh_3)_4$ (50 mg, 43 µmol) and 1-bromo-2-($^2H_3$)methoxybenzene (**19b**, 0.50 g, 2.6 mmol) in 1,4-dioxane (10 mL) and H_2O (1 mL) yielded compound **19a** (0.40 g, yield: 64%) as a colorless solid. LCMS (ESI): *m/z* 239.2 ($[M+H]^+$).

2,6-Difluoro-4-[2-($^2H_3$)methoxythiazol-4-yl]aniline (20a). Preparation according to the GP2, using 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**31c**, 0.26 g, 1.0 mmol), Cs_2CO_3 (0.50 g, 1.5 mmol), $Pd(PPh_3)_4$ (30 mg, 26 µmol) and **20b** (0.20 g, 1.0 mmol) in 1,4-dioxane (5 mL) and H_2O (0.5 mL) yielded compound **20a** (0.20 g, yield: 80%) as a colorless solid. LCMS (ESI): *m/z* 246.1 ($[M+H]^+$).

4-Bromo-2-($^2H_3$)methoxythiazole (20b). NaOH (0.65 g, 16 mmol) and CD_3OD (0.13 g, 3.6 mmol) was added to a solution of 2,4-dibromothiazole (**20c**, 0.30 g, 1.2 mmol) in THF (10 mL). The mixture was stirred at rt for 2 h, concentrated and the resulting residue was purified by CC (PE:EtOAc = 10:1) to give compound **20b** (0.22 g, yield: 91%) as an oil. LCMS (ESI): *m/z* 197.1/199.1 ($[M+H]^+$).

2,6-Difluoro-4-[6-($^2H_3$)methoxypyridin-2-yl]aniline (21a). Preparation according to the GP2, using 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**31c**, 0.30 g, 1.2 mmol), Cs_2CO_3 (0.56 g, 1.7 mmol) and $Pd(PPh_3)_4$ (30 mg, 26 µmol) and compound **21b** (0.20 g, 1.0 mmol) in 1,4-dioxane (5 mL) and H_2O (0.5 mL) yielded compound **21a** (0.24 g, yield: 96%) as a colorless solid. LCMS (ESI): m/z 240.2 ($[M + H]^+$).

2-Bromo-6-($^2H_3$)methoxypyridine (21b). To a solution of 2,6-dibromopyridine (**21c**, 0.30 g, 1.3 mmol) in THF (10 mL) was added NaOH (0.66 g, 17 mmol) and CD_3OD (0.14 g, 3.9 mmol). The mixture was stirred at rt for 2 h, concentrated and the resulting residue was purified by CC (PE:EtOAc = 10:1) to give compound **21b** (0.22 g, yield: 91%) as an oil. LCMS (ESI): *m/z* 191.1/193.1 ($[M+H]^+$).

2,6-Difluoro-4-[2-($^2H_3$)methoxypyridin-4-yl]aniline (22a). Preparation according to the GP2, using 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**31c**, 0.40 g, 1.6 mmol), Cs_2CO_3 (0.77 g, 2.4 mmol) and $Pd(PPh_3)_4$ (30 mg, 26 µmol) and compound **22b** (0.30 g, 1.6 mmol) in 1,4-dioxane (5 mL) and H_2O (0.5 mL) yielded compound **22a** (0.25 g, yield: 67%) as a colorless solid. LCMS (ESI): *m/z* 240.3 ($[M+H]^+$).

4-Bromo-2-($^2H_3$)methoxypyridine (22b). To a solution of 4-bromo-2-fluoropyridine (**22c**, 0.40 g, 2.3 mmol) in dry THF (10 mL) was added NaH (0.15 g, 60%wt, 3.8 mmol) at 0 °C. The mixture was stirred at rt for 20 minutes, then CD_3OD (0.13 g, 3.6 mmol) was added. The mixture was stirred at rt for 2 h, carefully diluted with H_2O and extracted with EtOAc (3 x). The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated and the resulting residue was purified by CC (PE:EtOAc = 10:1) to give compound **22b** (0.30 g, yield: 69%) as an oil. LCMS (ESI): *m/z* 190.9/192.9 ($[M+H]^+$).

4-(Benzo[*d*][1,3]dioxol-4-yl)-2,6-difluoroaniline (23a). Preparation according to the GP2, using 4-bromobenzo[*d*][1,3]dioxole (**23b**, 0.20 g, 1.0 mmol), 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**31c**, 0.31 g, 1.2 mmol), Na_2CO_3 (0.41 g, 3.9 mmol) and $PdCl_2(PPh_3)_2$ (20 mg, 28 µmol) in 1,4-dioxane (5 mL) and H_2O (0.5 mL) yielded compound **23a** (150 mg, yield: 60%) as a yellow solid. LCMS (ESI): *m/z* 250.2 ($[M+H]^+$).

4-(Benzo[*d*]oxazol-4-yl)-2,6-difluoroaniline (24a). By using 4-bromobenzo[*d*]oxazole (**24b**, 0.20 g, 1.0 mmol) under the conditions described for compound **23a**, the intermediate **24a** (0.15 g, yield: 60%) was obtained as a yellow solid. LCMS (ESI): *m/z* 246.9 ($[M+H]^+$).

Prop-2-yn-1-yl 2-[(3-fluoro-3'-prop-2-yn-1-yloxy[1,1'-biphenyl]-4-yl)carbamoyl]cyclopent-1-ene-1-carboxylate (29b). 3-Bromoprop-1-yne (0.35 mg, 2.9 mmol) and K_2CO_3 (0.61 g, 4.4. mmol) were added to a solution of 2-[(3-fluoro-3'-hydroxy-[1,1'-biphenyl]-4-yl)carbamoyl]cyclopent-1-ene-1-carboxylic acid (**29a**, 0.50 g, 1.5 mmol; prepared according to Lit.[2]) in DMF (10 mL). The mixture was heated at 60 °C for 16 h, cooled to rt, diluted with H_2O and extracted with EtOAc (3 x). The combined organic layer was washed with brine, dried with Na_2SO_4 and concentrated. The resulting residue was purified by CC (PE:EtOAc = 2:1) to afford compound **29b** (0.45 g, yield: 74%) as a yellow solid. LCMS (ESI): *m/z* 418.2 ($[M+H]^+$).

***4H*,6*H*-Furo[3,4-c]furan-1,3-dione (30b)**. To a solution of **32c** (400 mg, 2.53 mmol) in toluene (5 mL) was added AcCl (385 mg, 4.90 mmol) and then the mixture was stirred at 110 °C for 4 h, cooled to rt and concentrated to afford compound **30b** (300 mg, yield: 84%) as a yellow solid. LCMS (ESI): *m/z* 140.1 ($[M+H]^+$).

Dimethyl 2,5-dihydrofuran-3,4-dicarboxylate (32b). To a solution of methyl 4-{[(trifluoromethyl)sulfonyl]oxy}-2,5-dihydrofuran-3-carboxylate (**32a**, 2.00 g, 7.24 mmol; commercially available or prepared according to Lit.[3]) in MeOH (15 mL) and DMF (5 mL) was added 1,1′-*bis*(diphenylphosphino)ferrocene (0.42 g, 0.76 mmol) and $Pd_2(dba)_3$ (0.32 g, 0.35 mmol). The mixture was stirred at 50 °C under CO (1 atm) overnight, allowed to reach rt, diluted with H_2O and extracted with EtOAc (3 x). The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated and

the resulting residue was purified by CC (PE:EtOAc = 10:1) to give compound **32b** (1.1 g, yield: 82%) as a yellow oil. LCMS (ESI): *m/z* 187.1 ($[M+H]^+$).

2,5-Dihydrofuran-3,4-dicarboxylic acid (32c). A solution of compound **32b** (1.1 g, 5.1 mmol) in HCl (9 mL) and HOAc (3 mL) was stirred at 100 °C for 2 h and cooled to rt. The organic layer was separated, and concentrated to give compound **32c** (750 mg, yield: 80%) as a yellow solid. LCMS (ESI): *m/z* 159.1 ($[M+H]^+$).

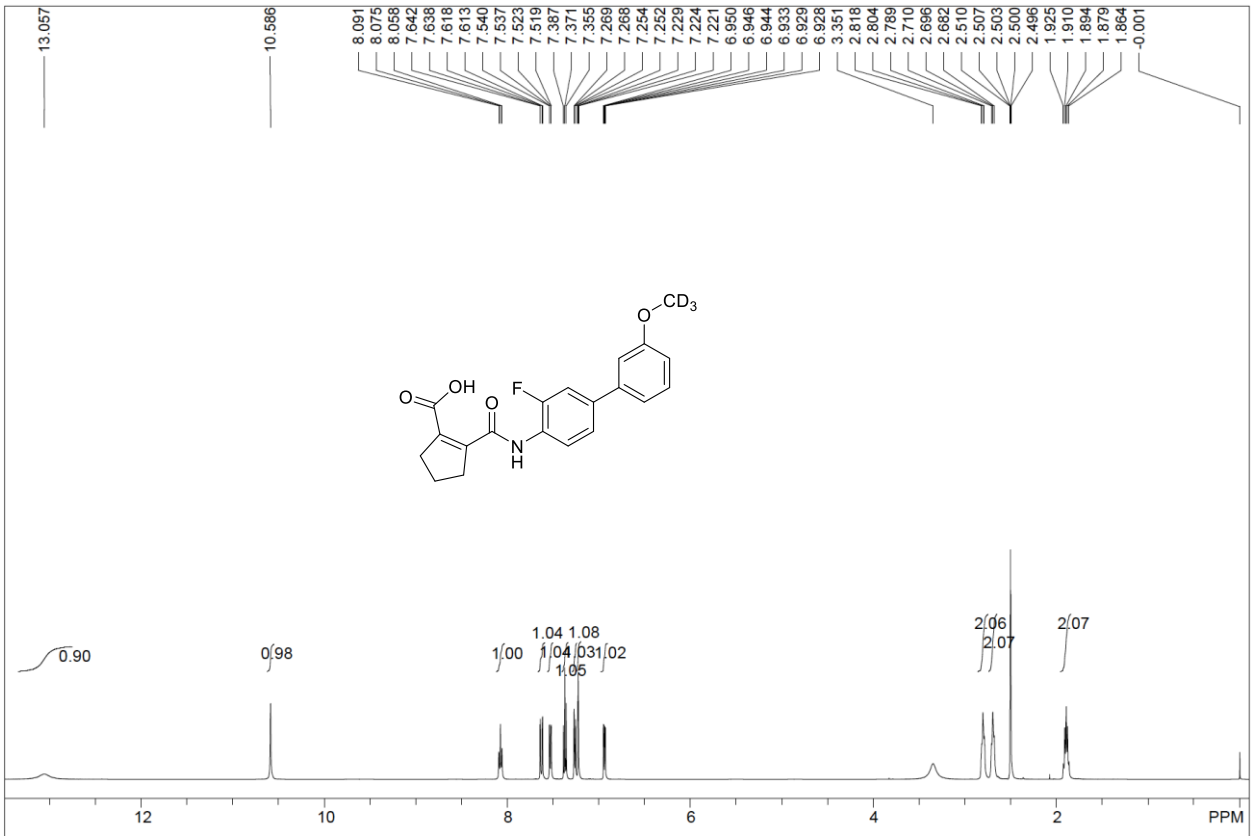
Methyl 2-{[(trifluoromethyl)sulfonyl]oxy}cyclopent-1-enecarboxylate (33b). Methyl cyclopentanone-2-carboxylate (**33a**, 2.1 g, 15 mmol) was dissolved in 50 mL anhydrous Et_2O. Then NaH (60% dispersion in mineral oil, 0.84 g, 21 mmol) was added in portions at 0 °C under an atmosphere of Ar. The solution was stirred at 0 °C for 45 minutes before triflic anhydride (3.0 mL, 18 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 1 hour and carefully quenched with H_2O (50 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL). The organic layers were combined, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by CC to give compound **33b** (2.87 g, 70%) as a clear oil. MS (+APCI): *m/z* 274.7 ($[M+H]^+$).

2-(Methoxycarbonyl)cyclopent-1-ene-1-carboxylic acid (33c). Compound **33b** (2.31 g, 8.43 mmol) was dissolved in 30 mL anhydrous DMF and 4 Å molecular sieves were added under an atmosphere of Ar. Then sodium formate (1.72 g, 25.3 mmol) and LiCl (1.07 g, 25.3 mmol) were added and the resulting mixture was cooled to 0 °C. Acetic anhydride (1.59 mL, 16.9 mmol) and *N,N*-diisopropylamine (2.36 mL, 16.9 mmol) were added dropwise under ice-bath cooling. The mixture was allowed to warm to rt and XPhos-Pd-G2 (664 mg, 843 µmol) was added. Next the reaction was stirred at 50 °C for 18 hours. The resulting mixture was diluted with EtOAc (30 mL) and filtered through Celite. All solvents were removed under reduced pressure and the residue was dissolved in EtOAc (30 mL). The organic phase was extracted with H_2O (3 x 30 mL, pH 7). The combined aqueous layers were acidified with aqueous HCl (10%) and extracted with EtOAc (3 x 50 mL). The latter organic layers were combined, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by reversed-phase CC to give compound **33c** (811 mg, 57%) as a yellow oil. MS (-APCI): *m/z* 168.7 ($[M-H]^-$).

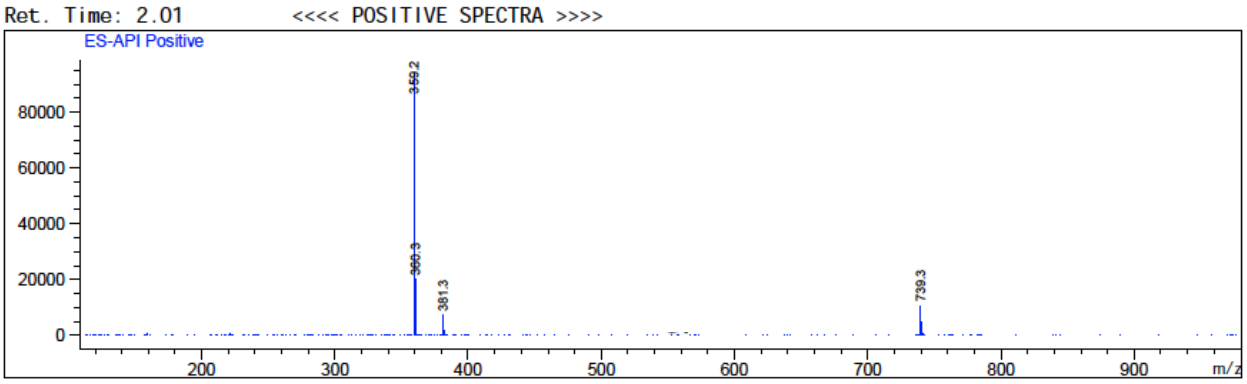
Methyl 2-[(4-bromo-2-fluorophenyl)carbamoyl]cyclopent-1-ene-1-carboxylate (33e). Compound **33c** (1.38 g, 8.13 mmol) was dissolved in 200 mL chloroform and EDC·HCl (2.03 g, 10.6 mmol) was added. The solution was stirred at ambient temperature for two hours, until the complete conversion of **33c** was observed according to TLC. Compound **33d** (1.55 g, 8.13 mmol) and NEt_3 (4.53 mL, 32.5 mmol) were added and the mixture was stirred under reflux for 18 h. After cooling to rt, H_2O (200 mL) was added and the aqueous phase was extracted with EtOAc (3 x 200 mL). The organic layers were combined, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by reversed-phase CC to give compound **33e** (353 mg, 13%) as a white solid. MS (+APCI): *m/z* 341.6 ($[M+H]^+$).

2-[(4-Bromo-2-fluorophenyl)carbamoyl]cyclopent-1-ene-1-carboxylic acid (33f). A solution of LiOH (112 mg, 4.68 mmol) in 30 mL H_2O was added to a solution of compound **33e** (320 mg, 935 µmol) in 30 mL THF. The mixture was stirred at ambient temperature for 20 minutes and then acidified with aqueous HCl (10%, 50 mL). The mixture was extracted with EtOAc (4 x 100 mL). The organic layers were combined, dried over Na_2SO_4, filtered and evaporated to give compound **33f** (292 mg, 95%) as a yellow solid. MS (-APCI): *m/z* 325.6 ($[M-H]^-$).

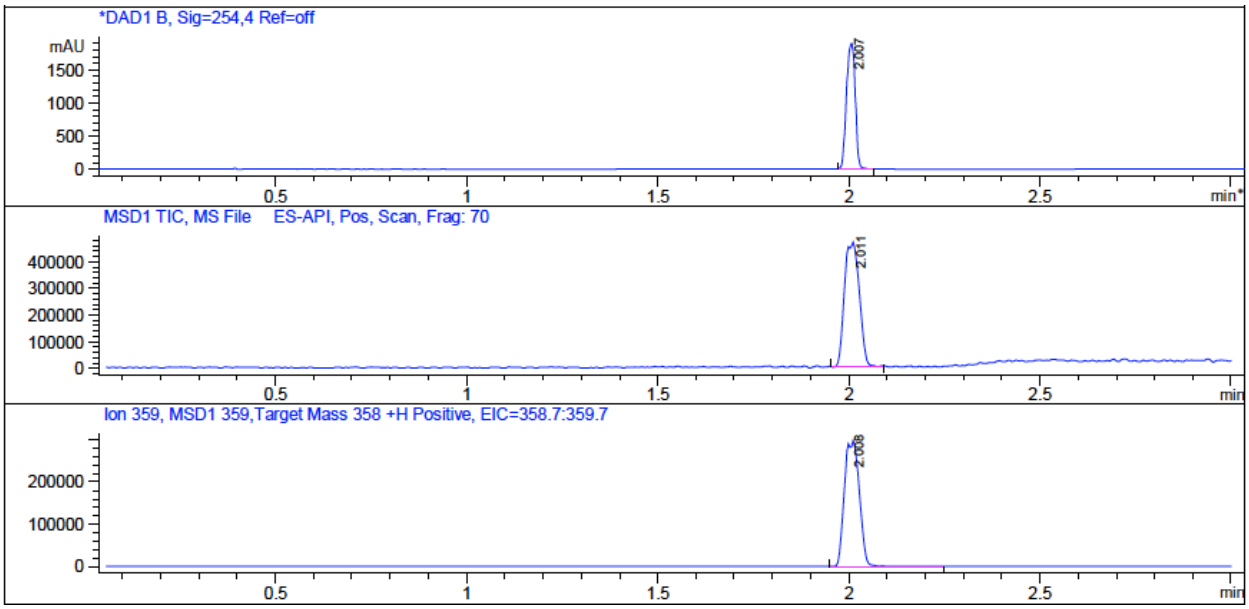
NMR spectra, MS spectra and LCMS data of **2–29**



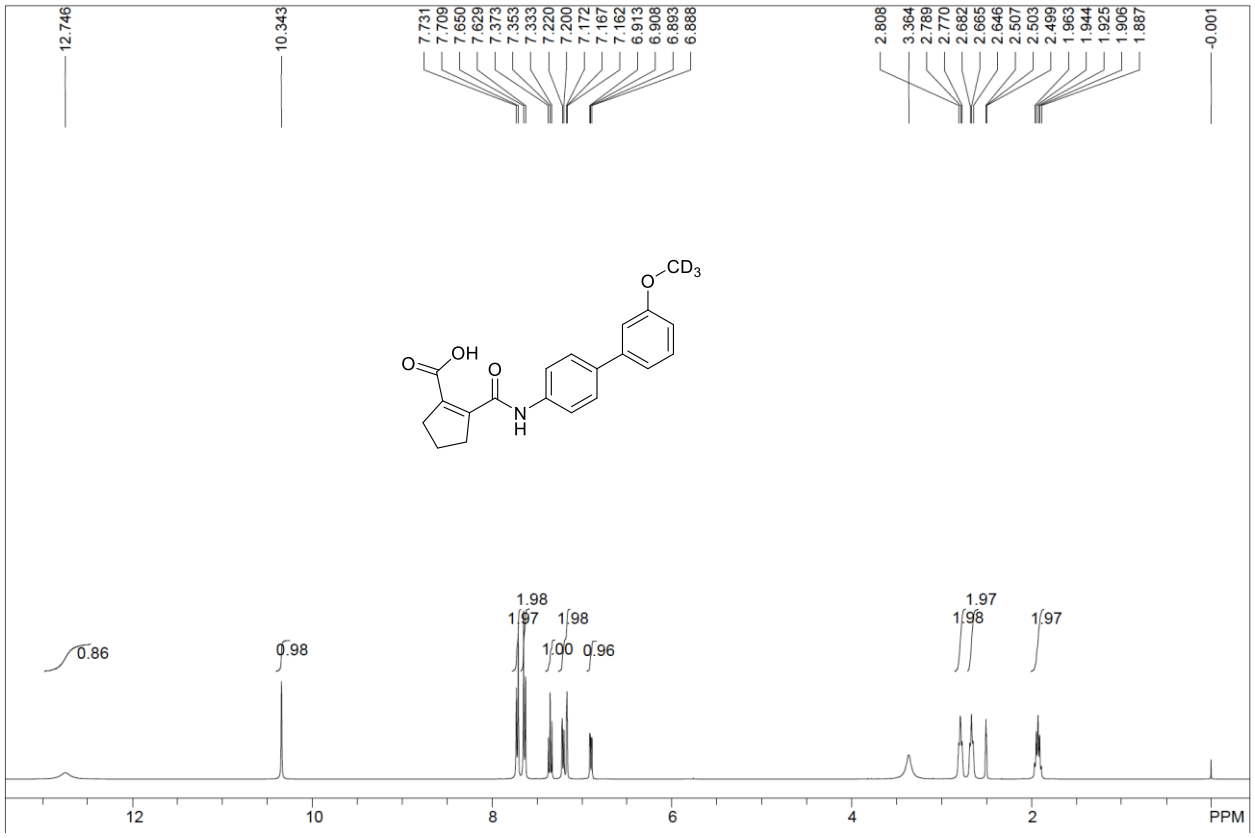
^{1}H-NMR (500 MHz, DMSO-d_6) of compound **2**



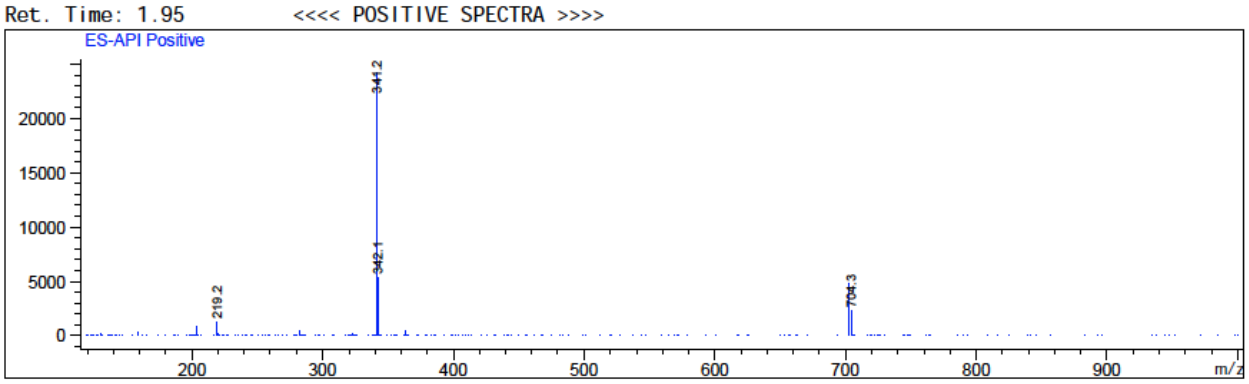
MS of compound **2**



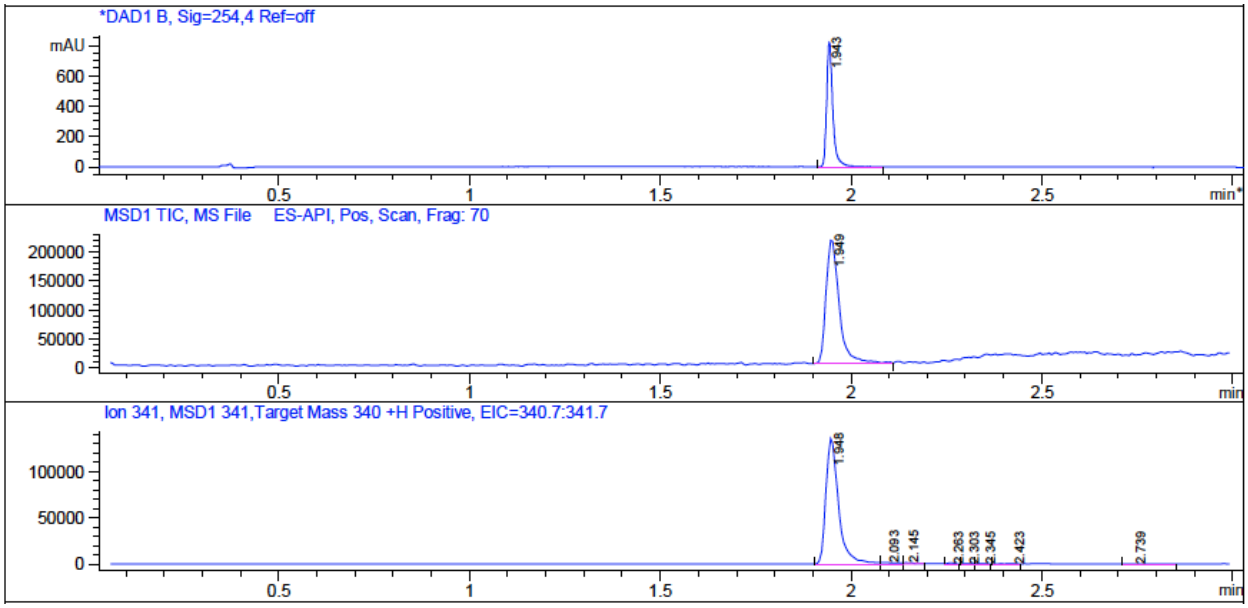
Chromatographic purity analysis of compound **2**



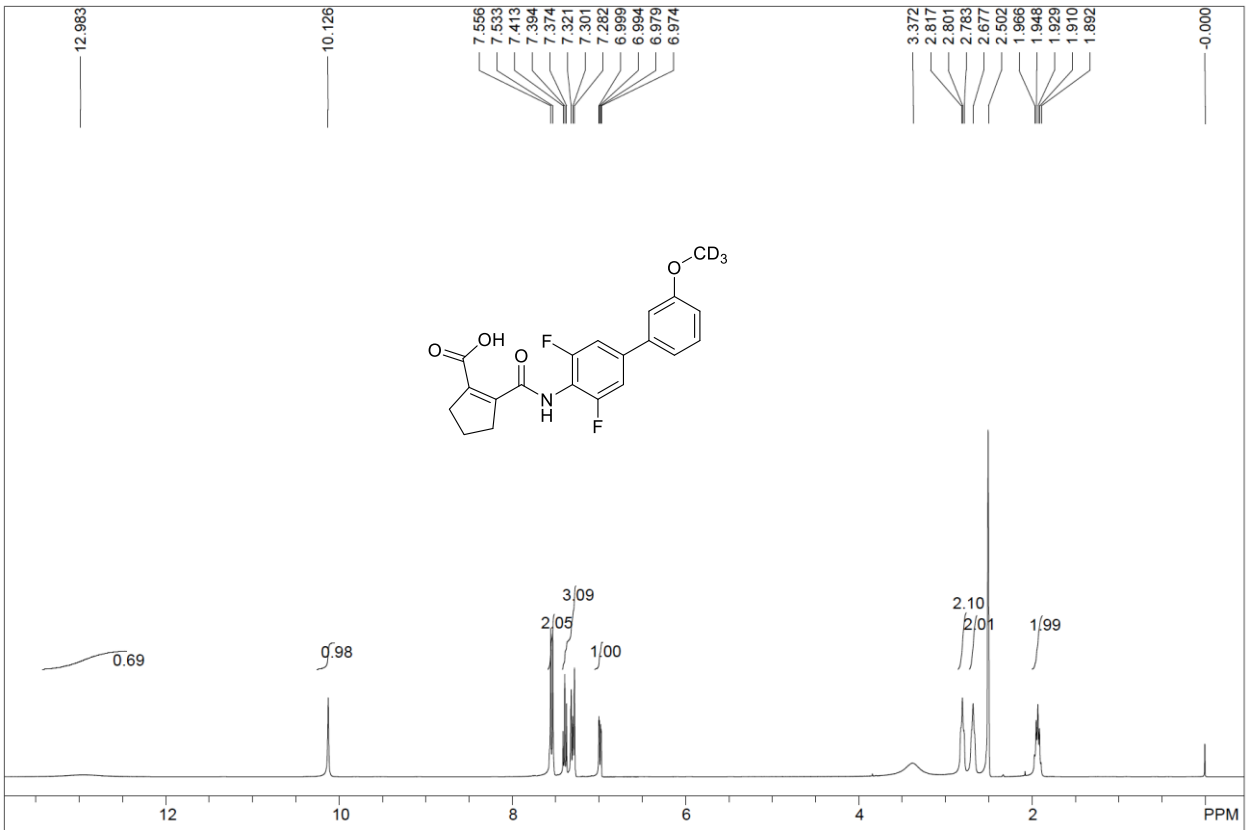
^{1}H-NMR (400 MHz, DMSO-d_6) of compound **3**



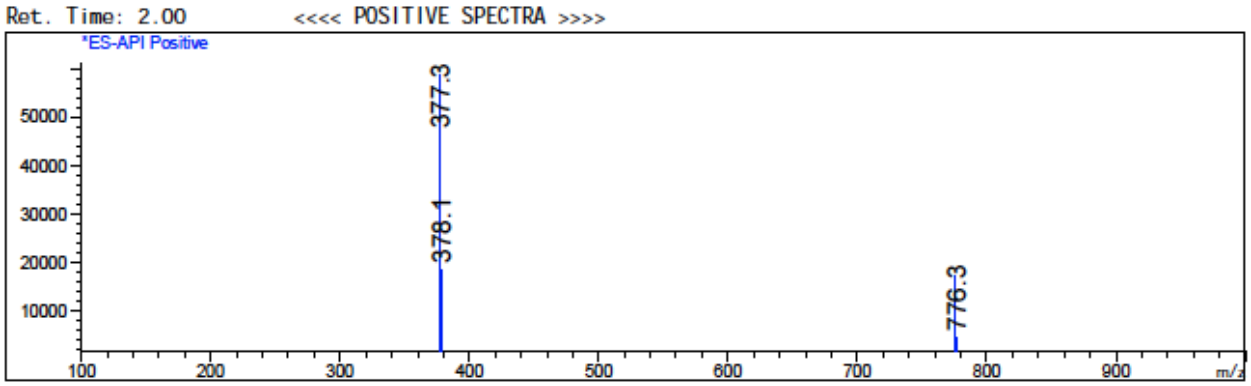
MS of compound **3**



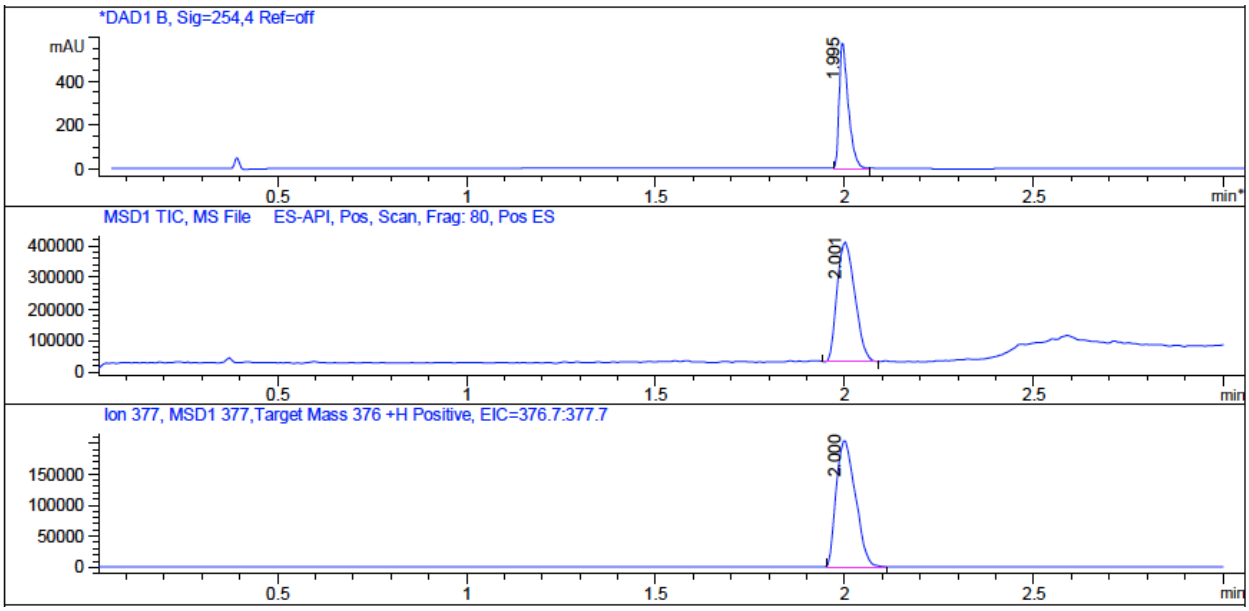
Chromatographic purity analysis of compound **3**



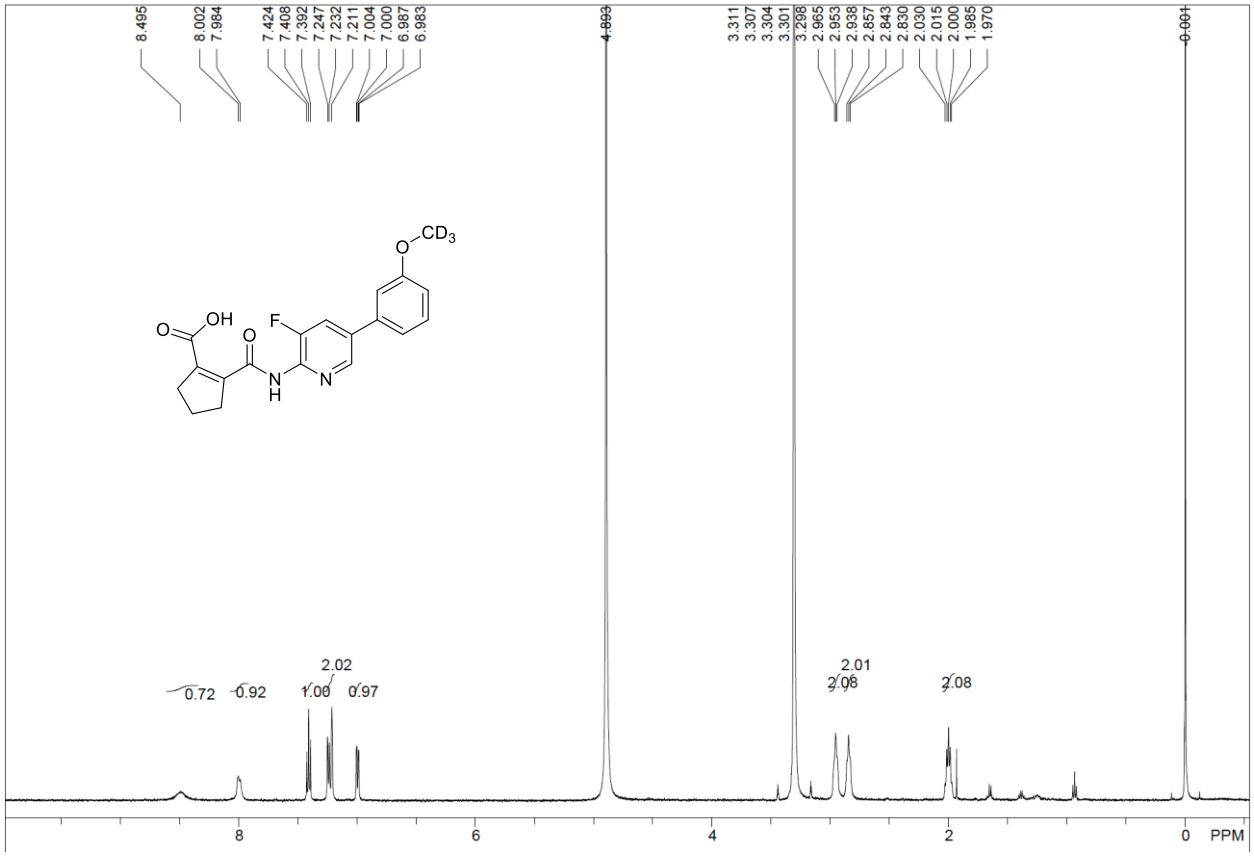
^{1}H-NMR (400 MHz, DMSO-d_6) of compound **4**



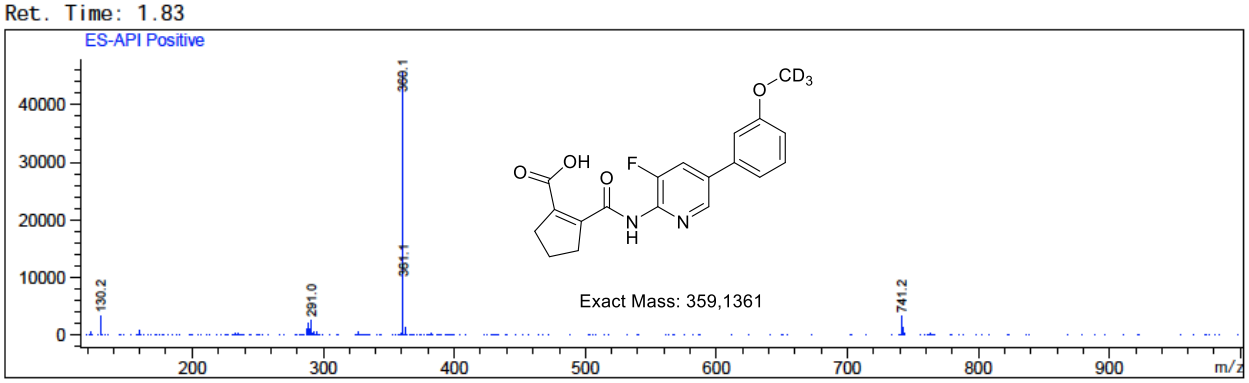
MS of compound **4**



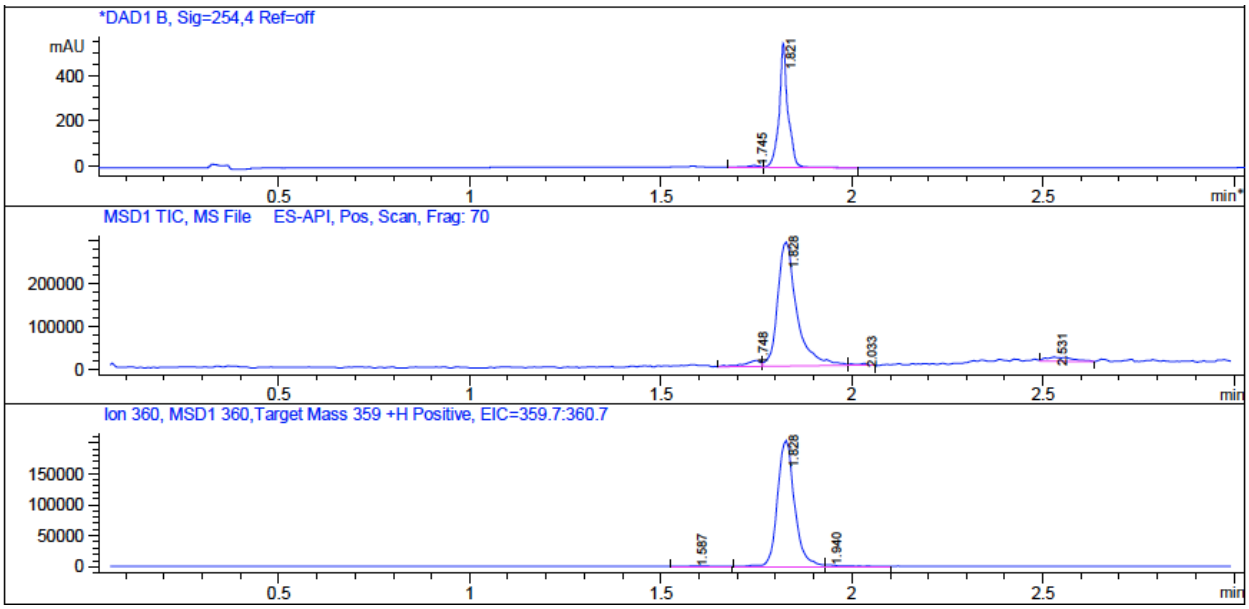
Chromatographic purity analysis of compound **4**



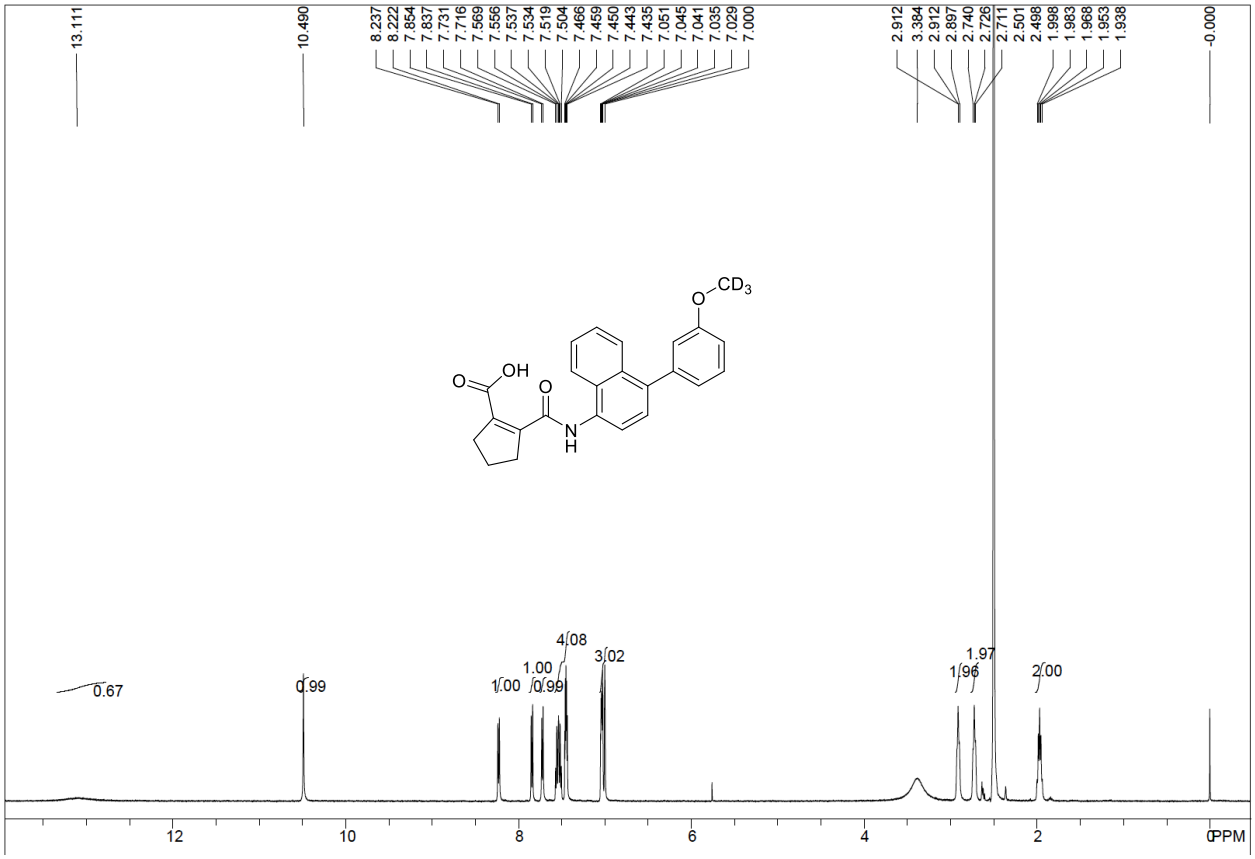
^{1}H-NMR (500 MHz, CD_3OD) of compound **5**



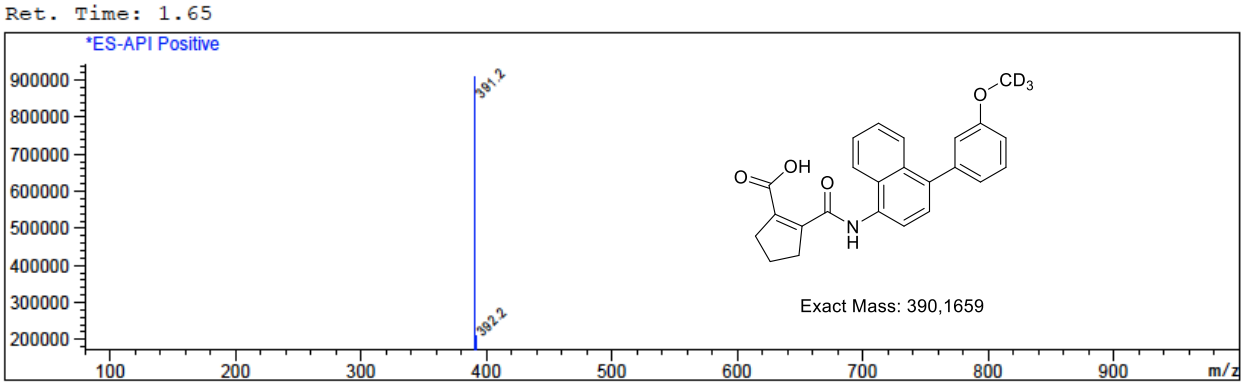
MS of compound **5**



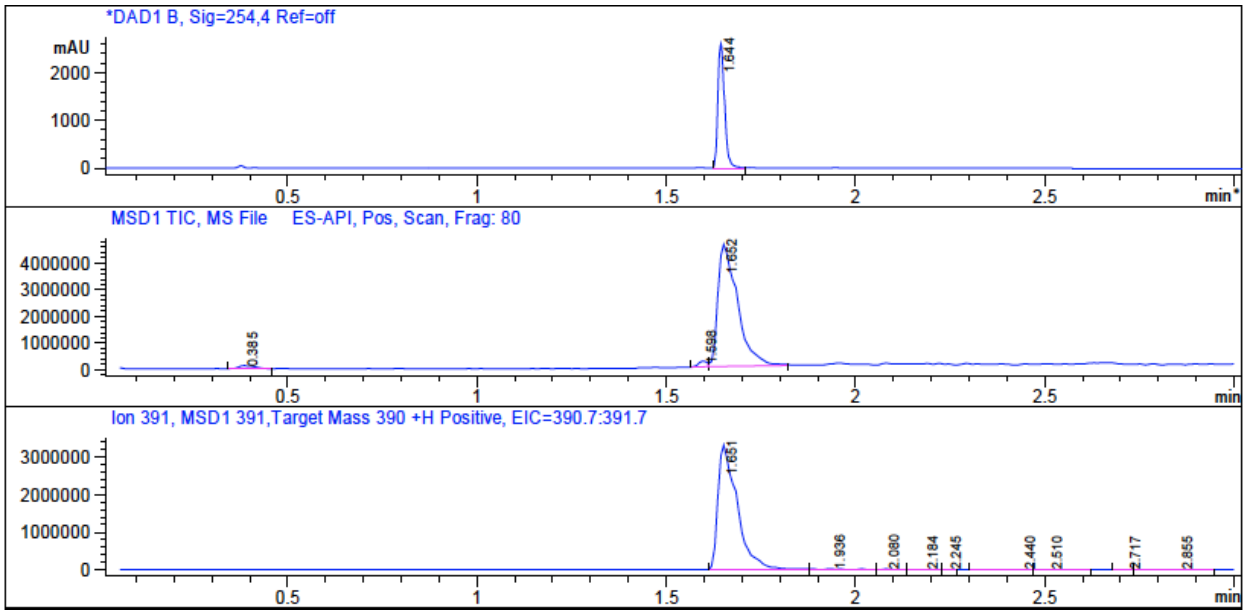
Chromatographic purity analysis of compound **5**



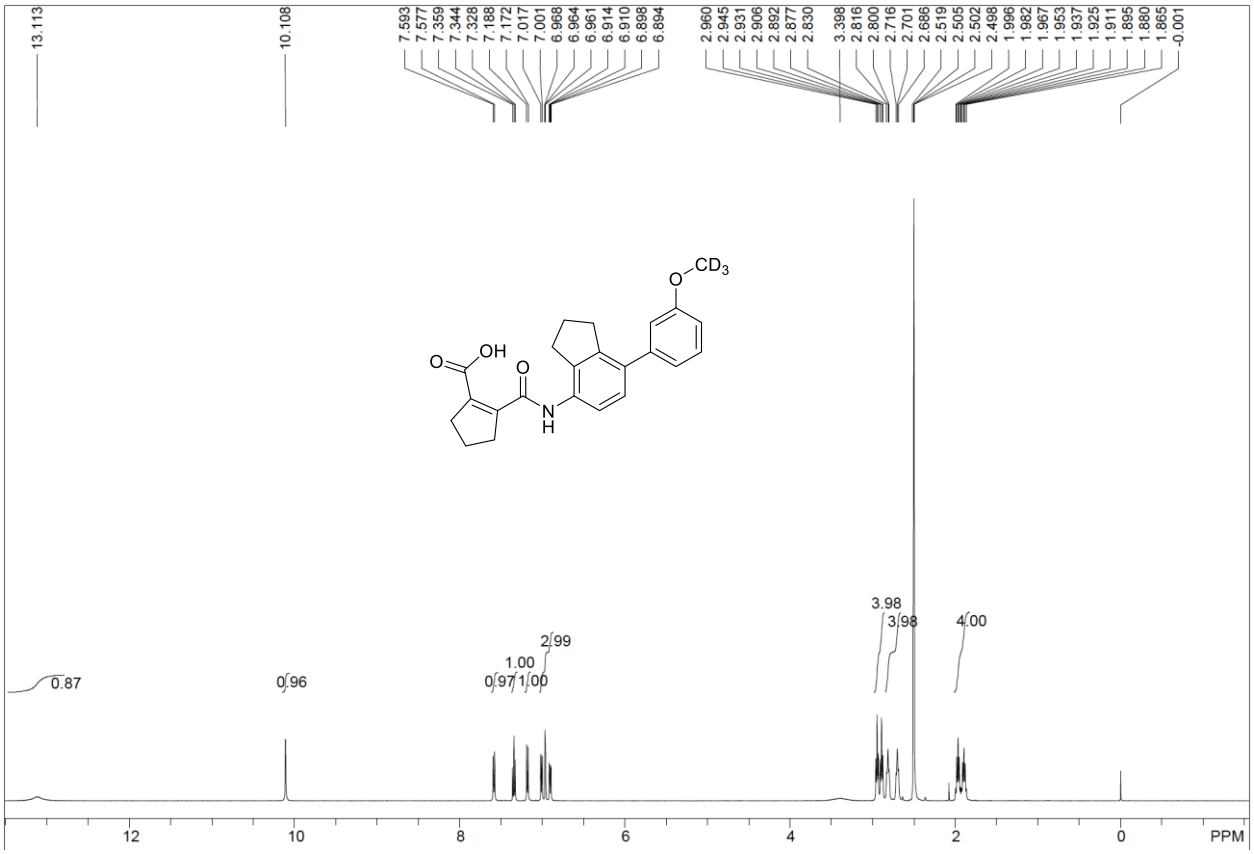
^{1}H-NMR (500 MHz, DMSO-d_6) of compound **6**



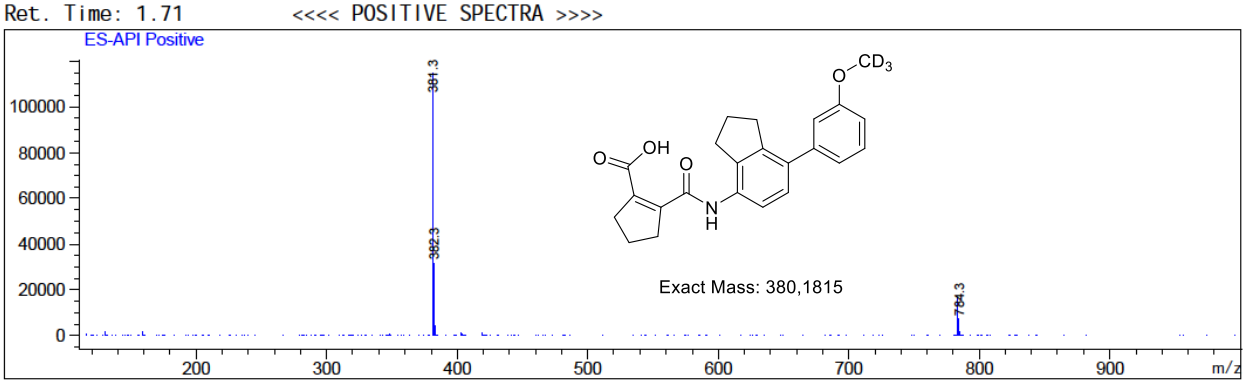
MS of compound **6**



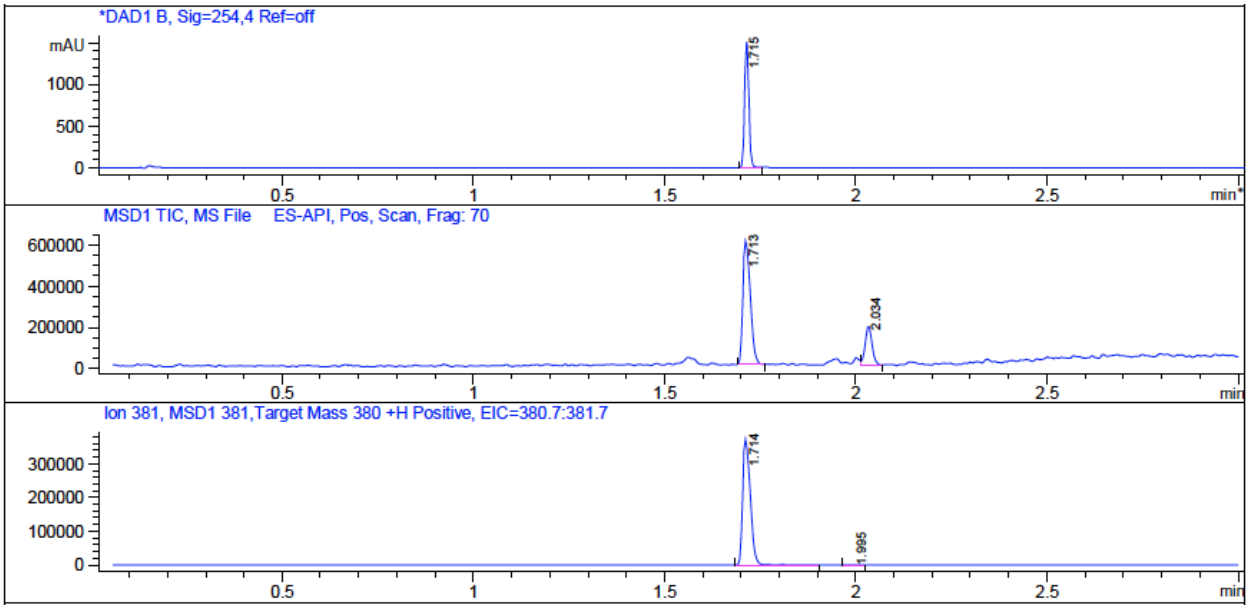
Chromatographic purity analysis of compound **6**



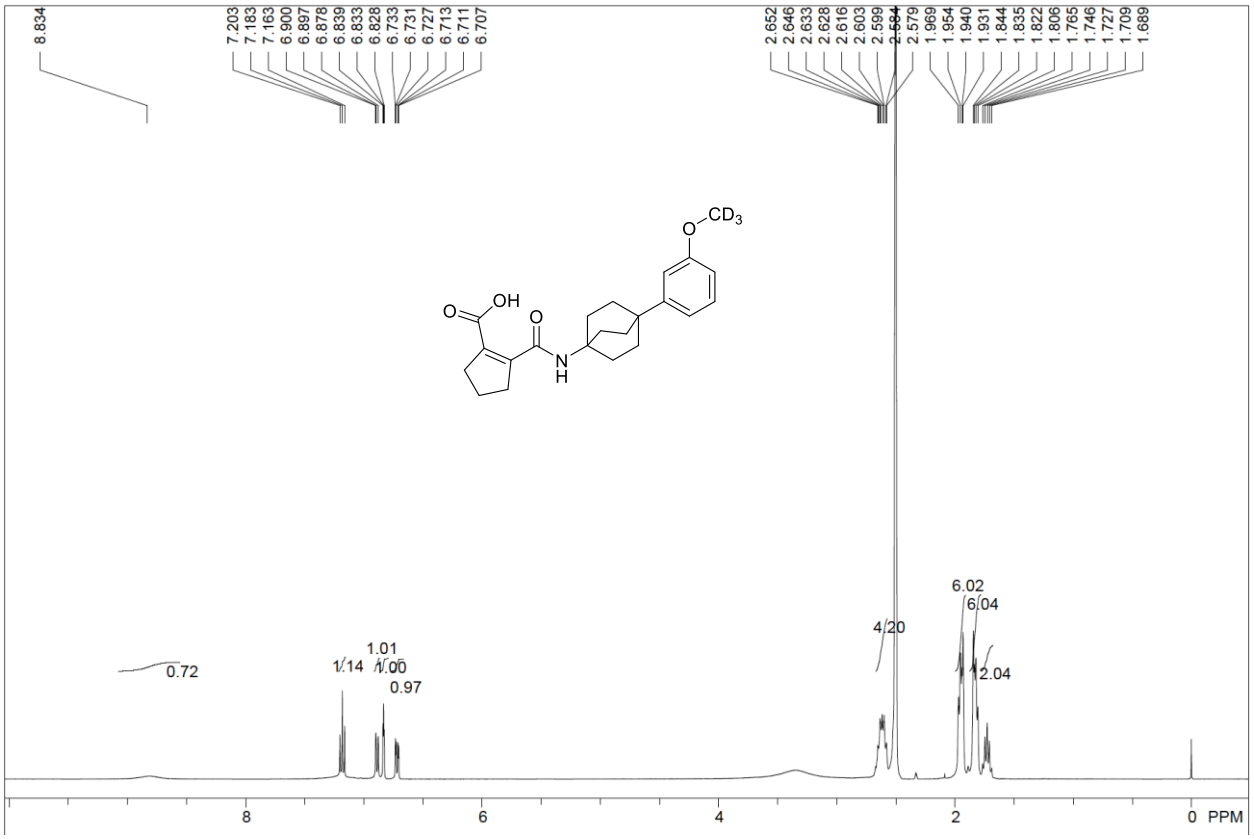
^{1}H-NMR (500 MHz, DMSO-d_6) of compound **7**



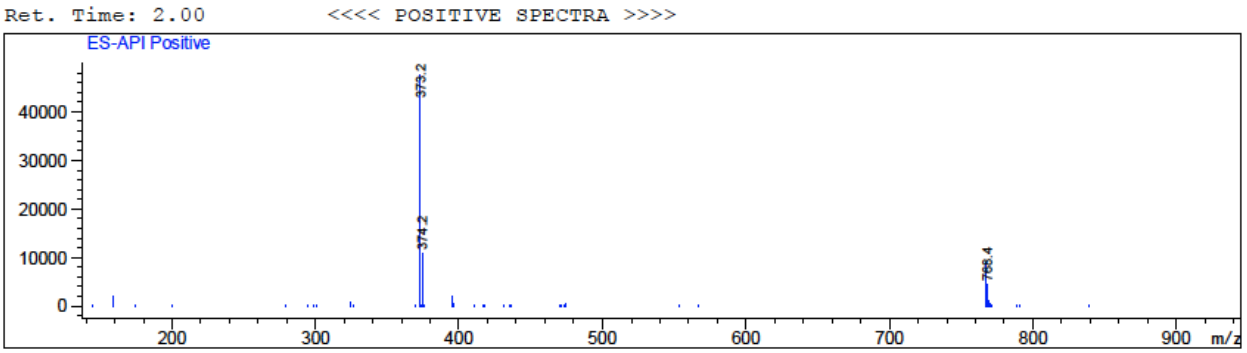
MS of compound **7**



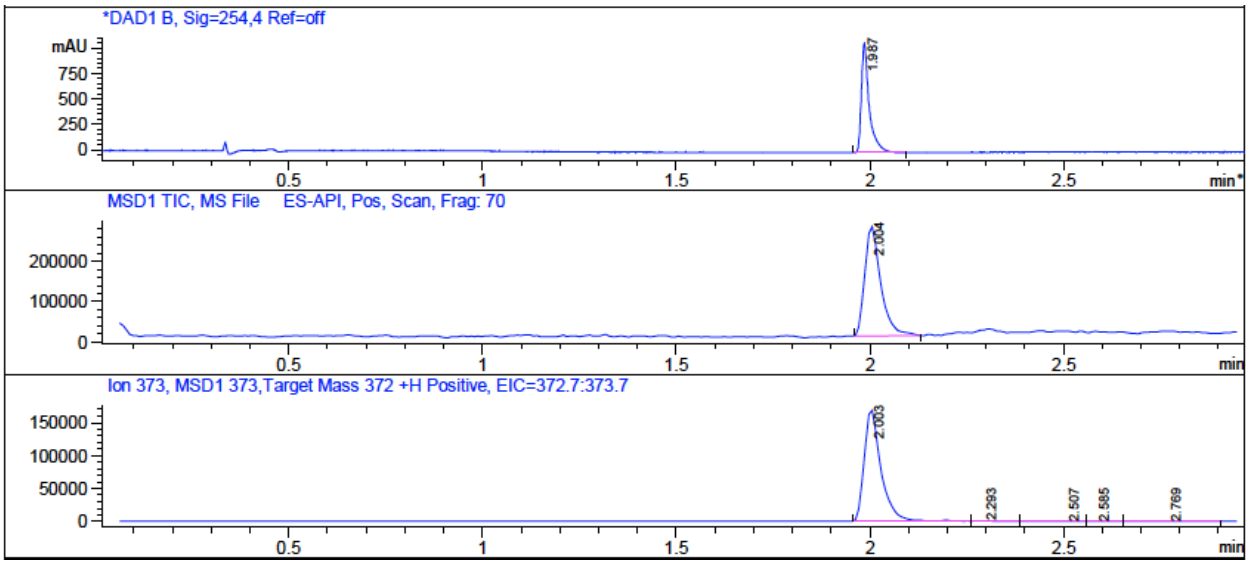
Chromatographic purity analysis of compound **7**



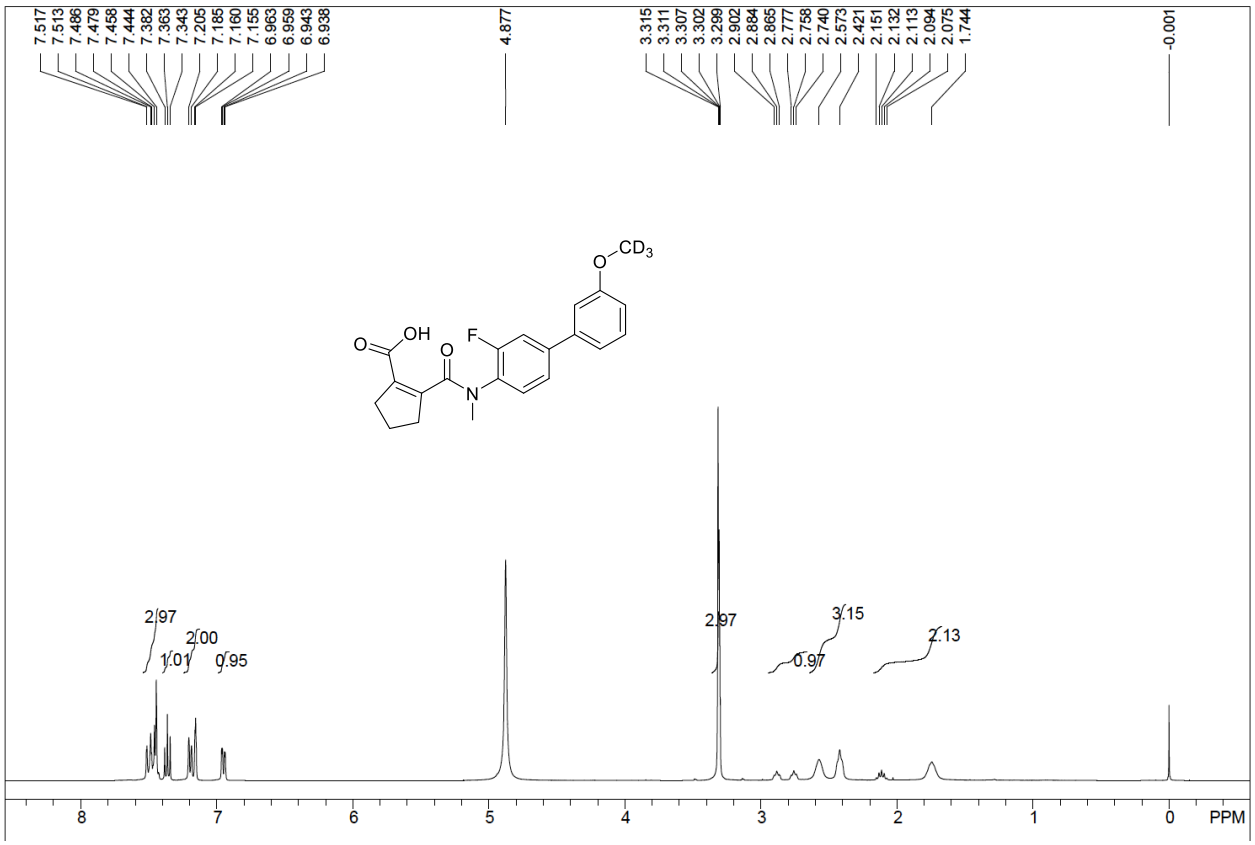
^{1}H-NMR (400 MHz, DMSO-d_6) of compound **8**



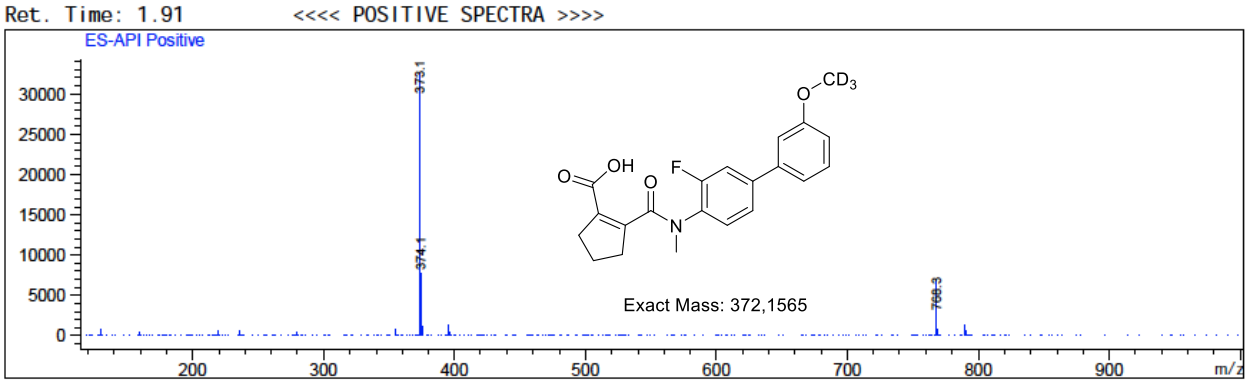
MS of compound **8**



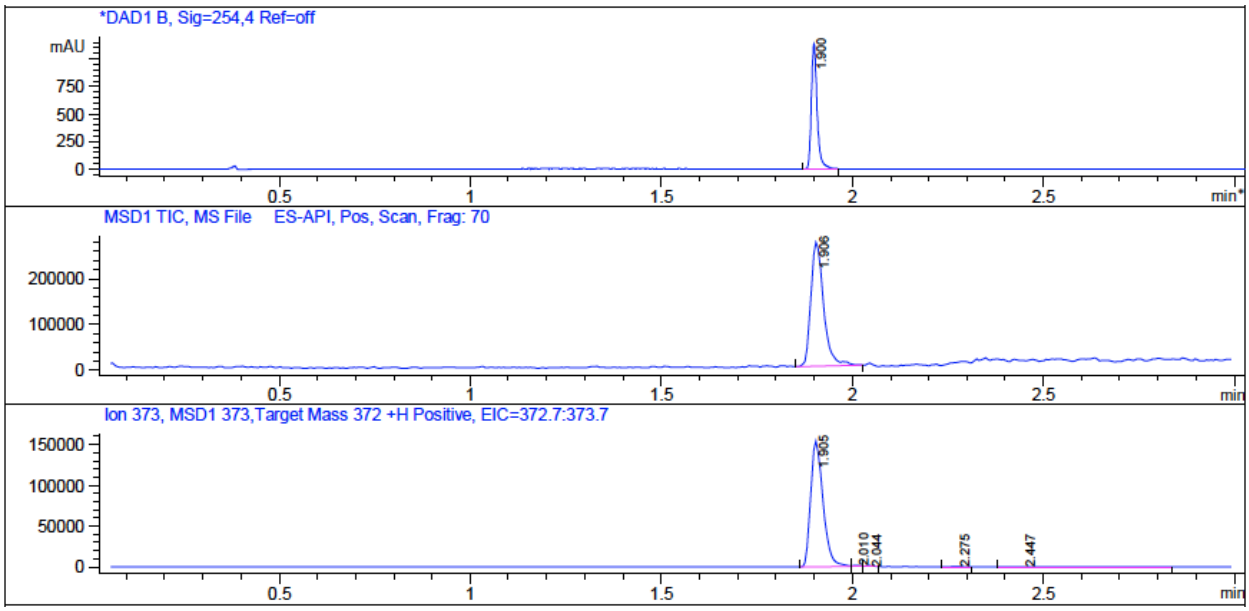
Chromatographic purity analysis of compound **8**



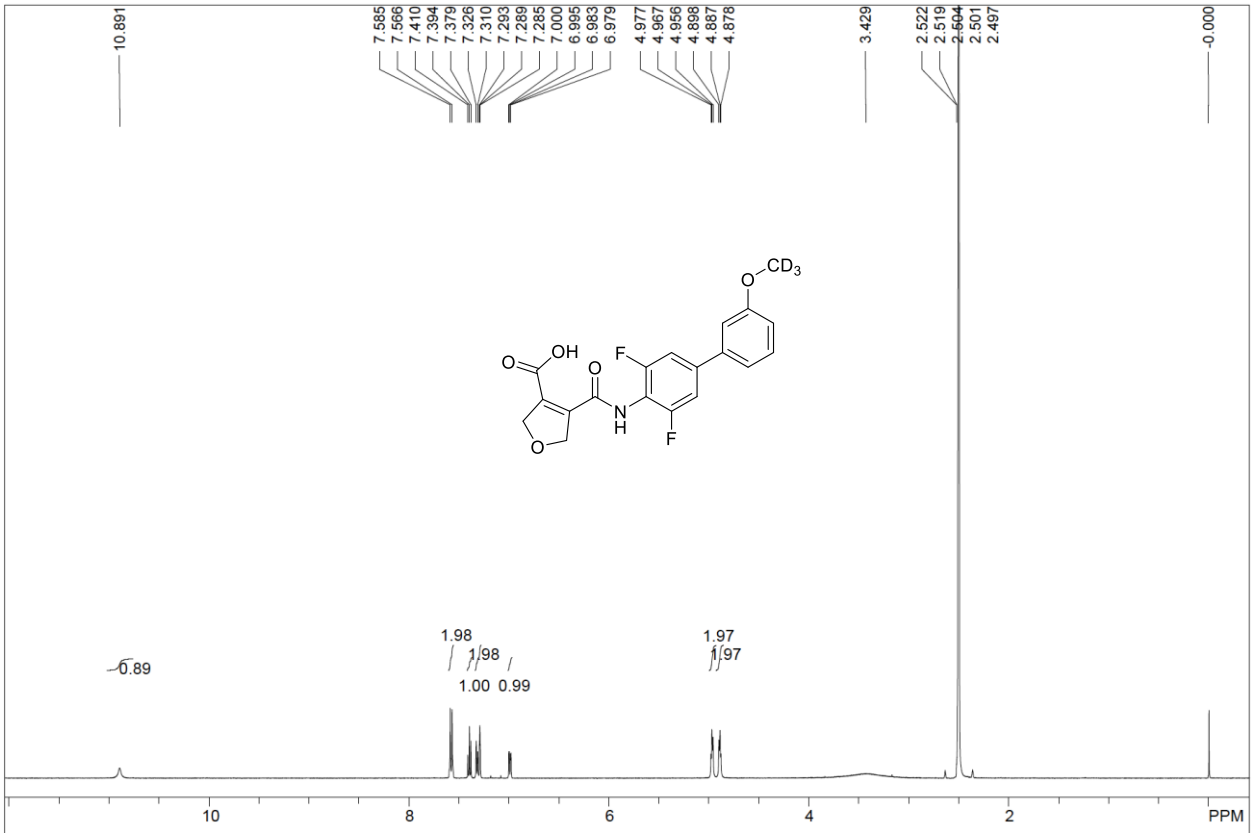
^{1}H-NMR (400 MHz, CD_3OD) of compound **9**



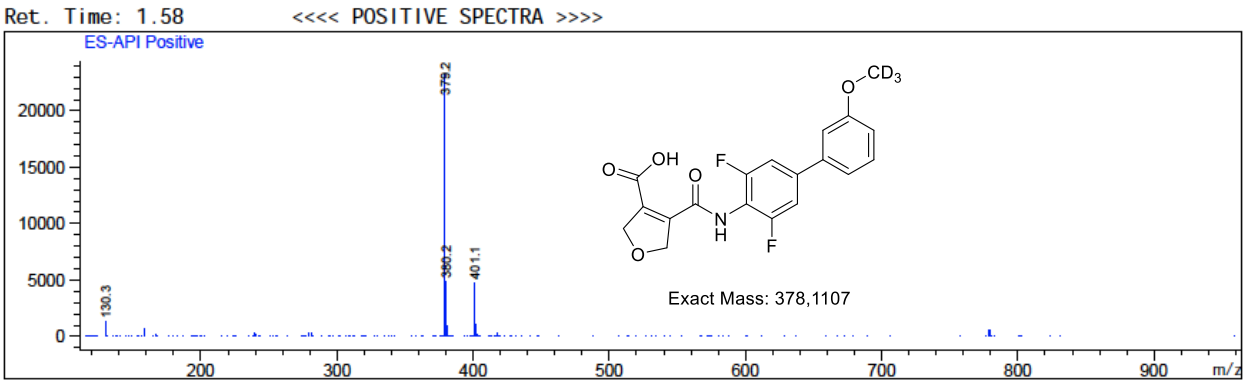
MS of compound **9**



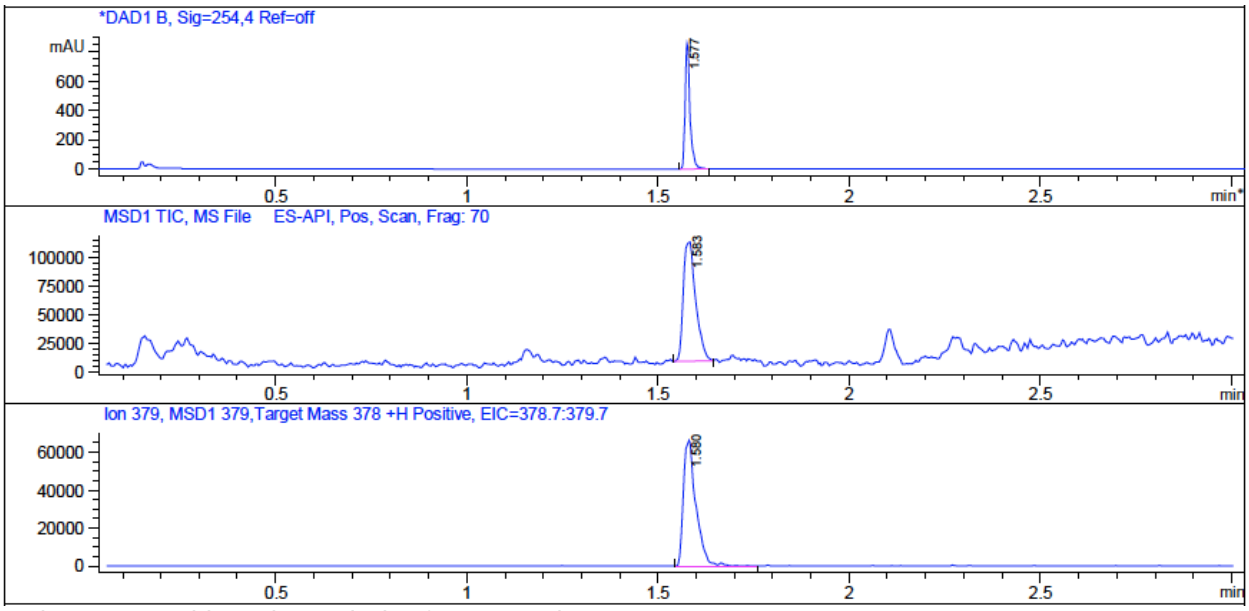
Chromatographic purity analysis of compound **9**



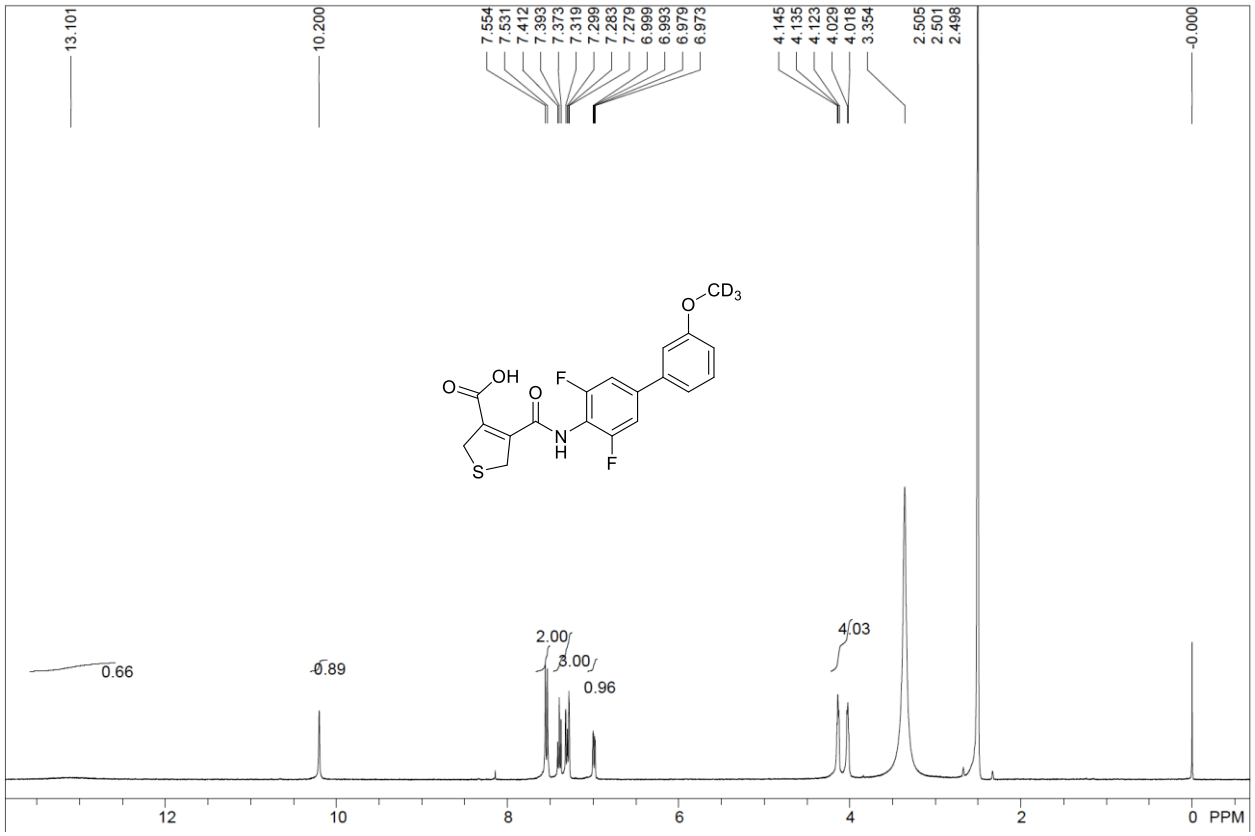
^{1}H-NMR (500 MHz, DMSO-d_6) of compound **10**



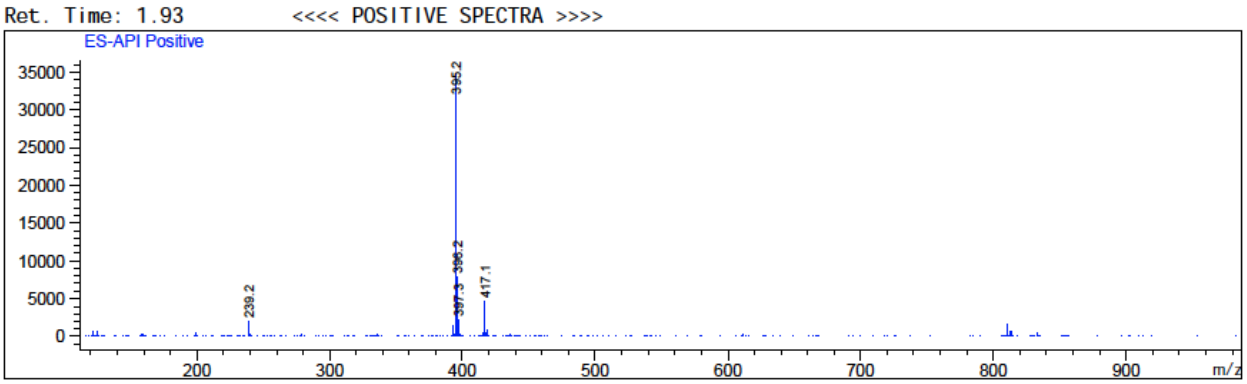
MS of compound **10**



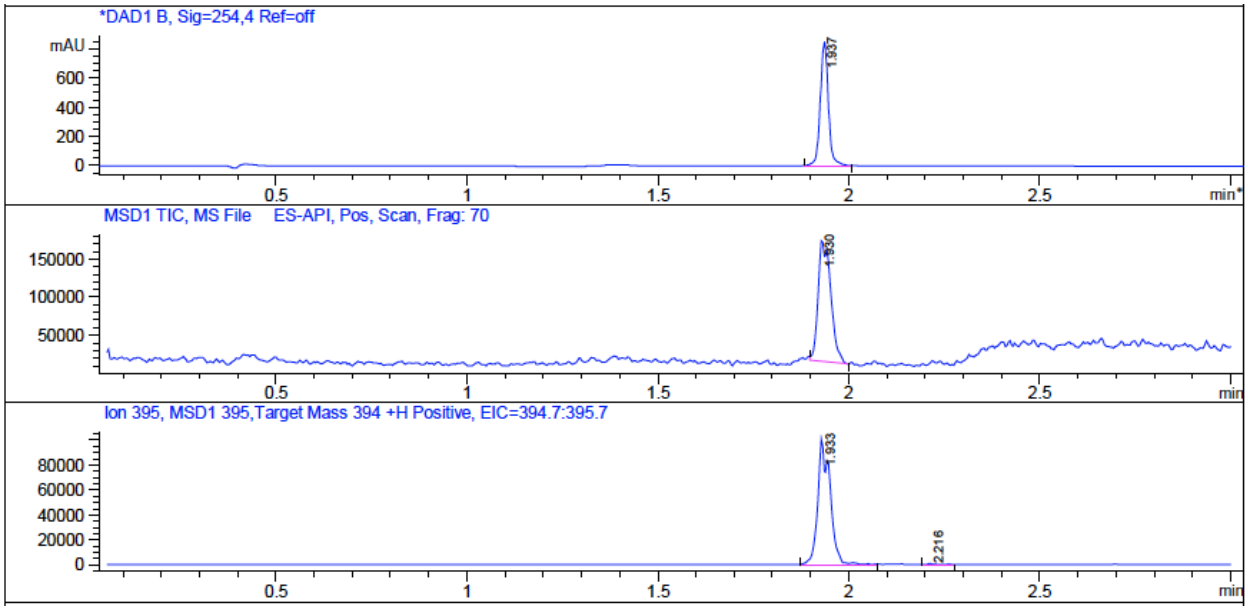
Chromatographic purity analysis of compound **10**



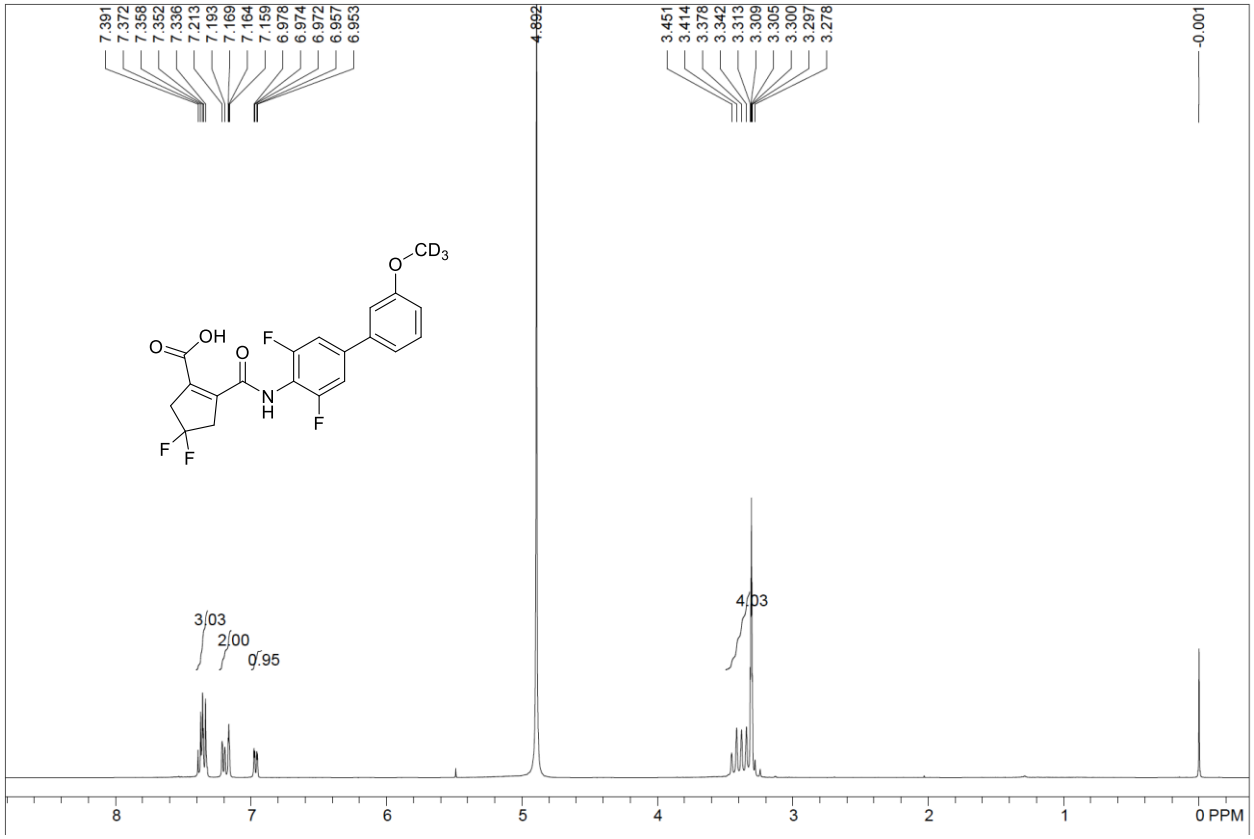
^{1}H-NMR (400 MHz, DMSO-d_6) of compound **11**



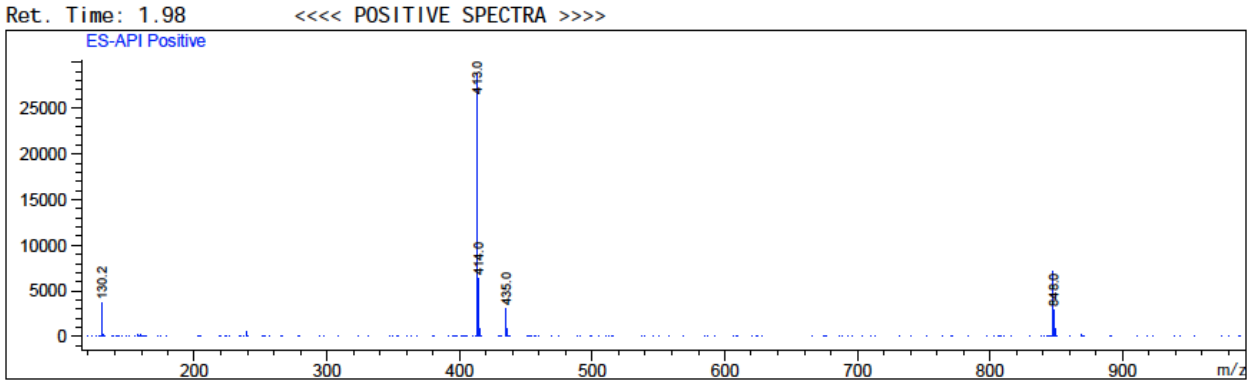
MS of compound **11**



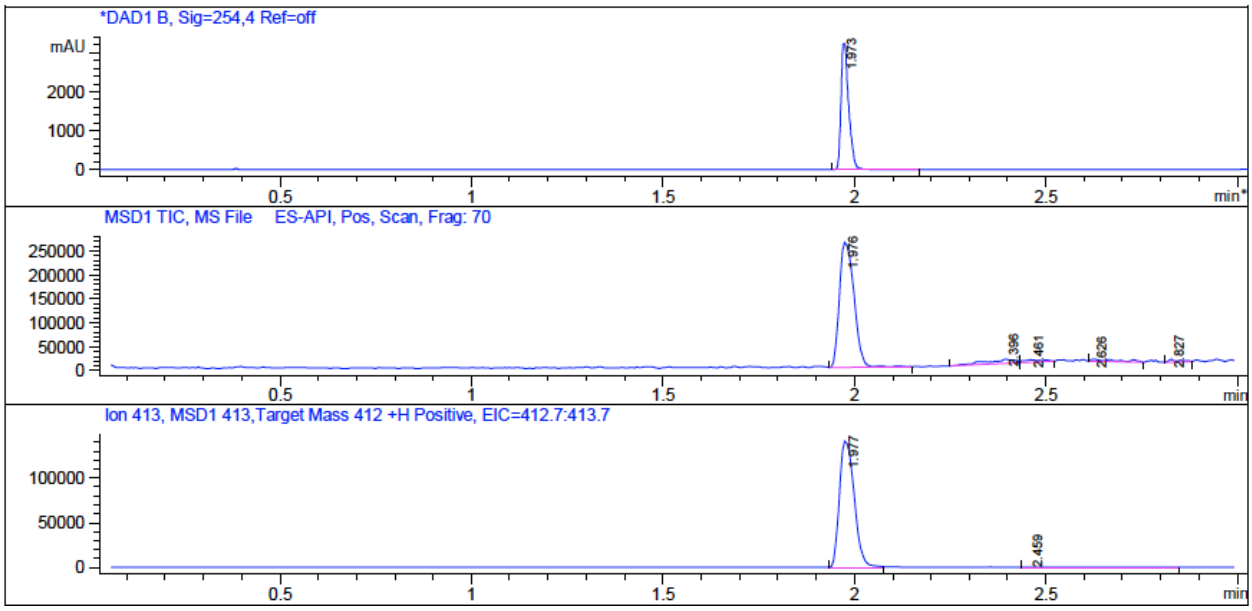
Chromatographic purity analysis of compound **11**



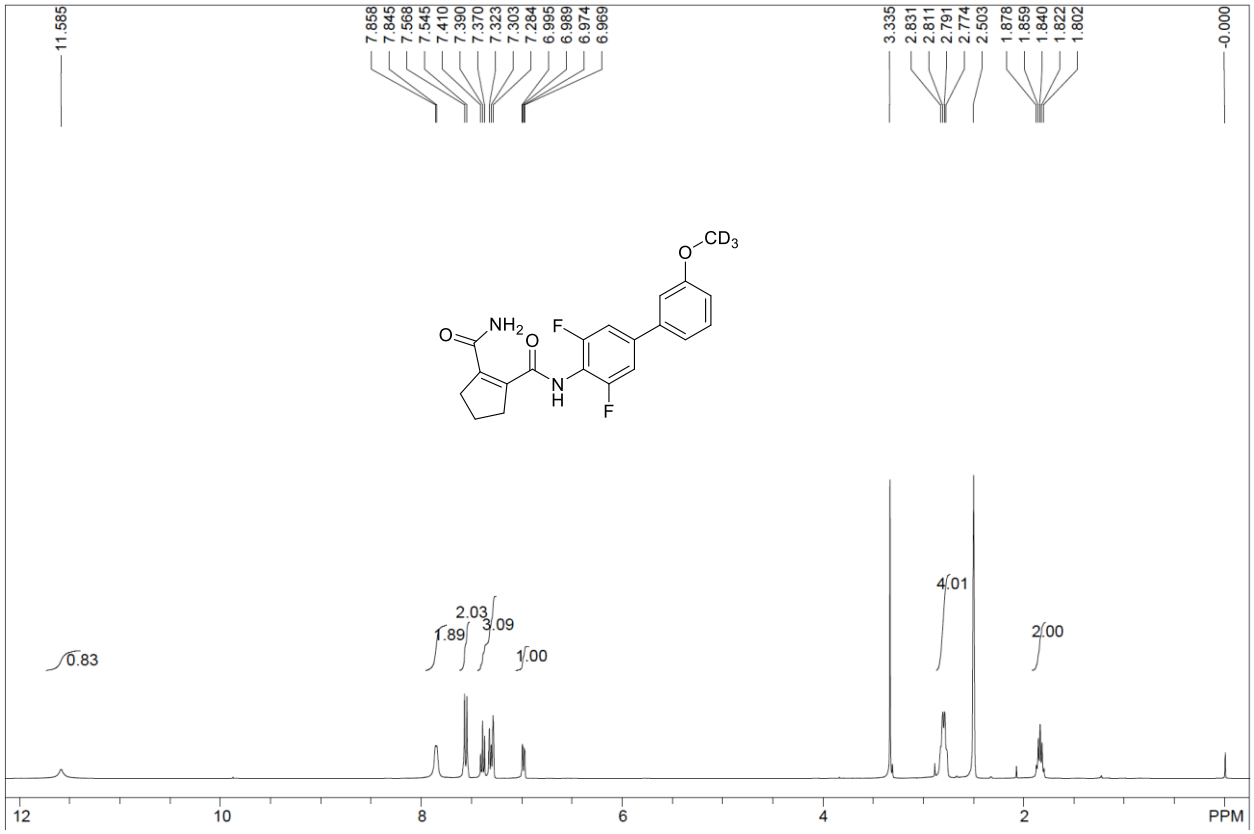
^{1}H-NMR (400 MHz, CD_3OD) of compound **12**



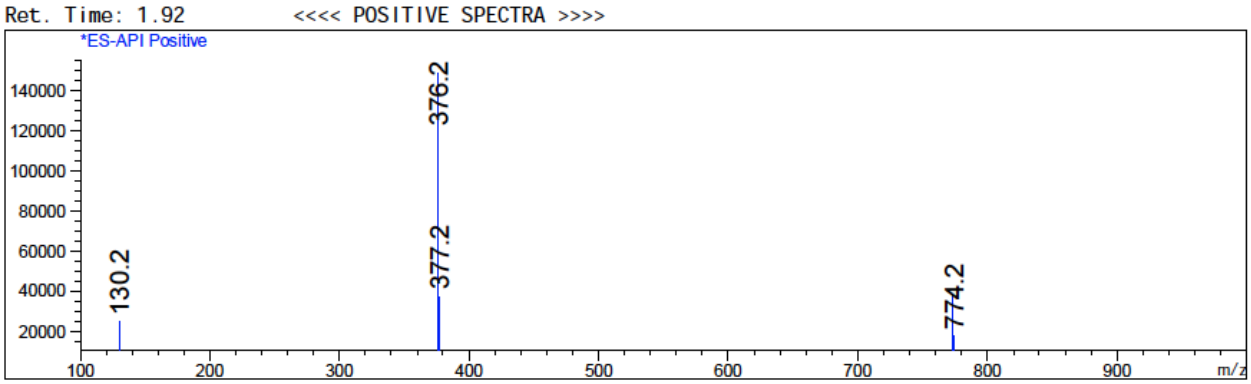
MS of compound **12**



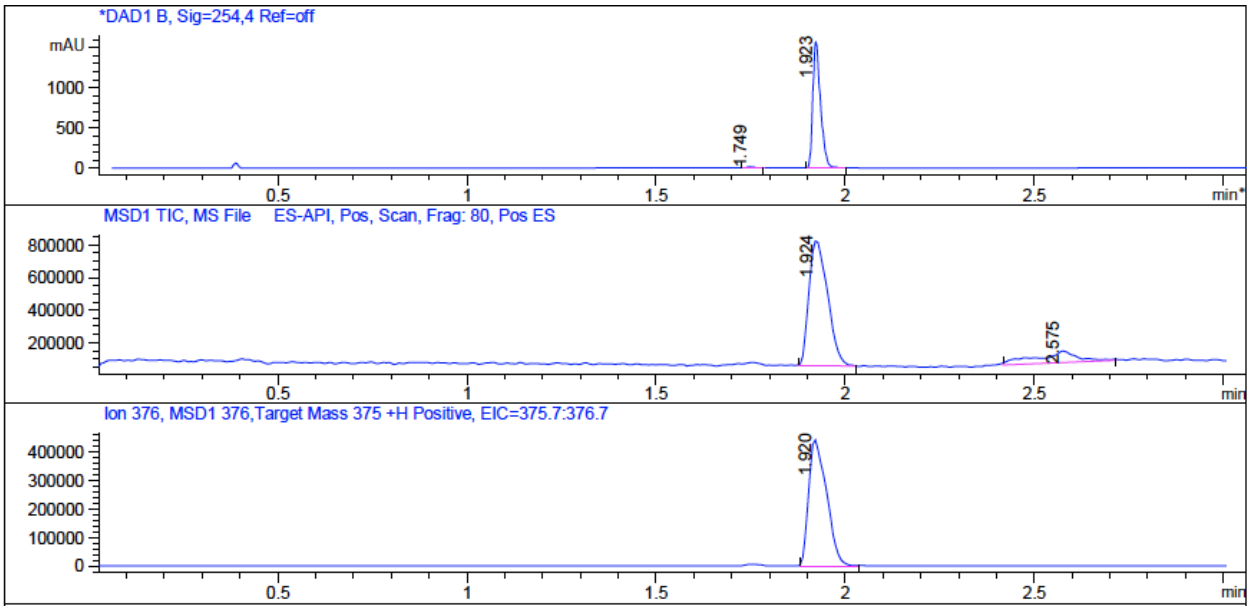
Chromatographic purity analysis of compound **12**



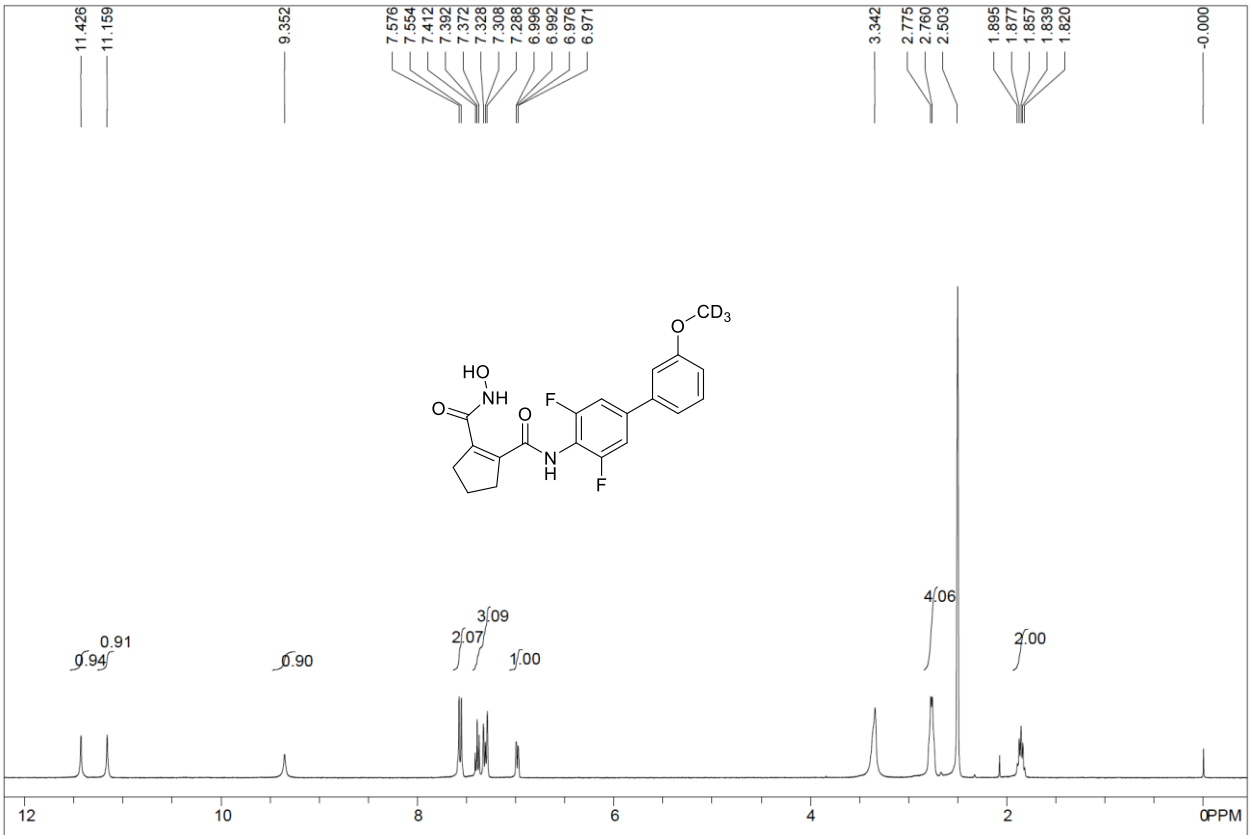
^{1}H-NMR (400 MHz, DMSO-d_6) of compound **13**



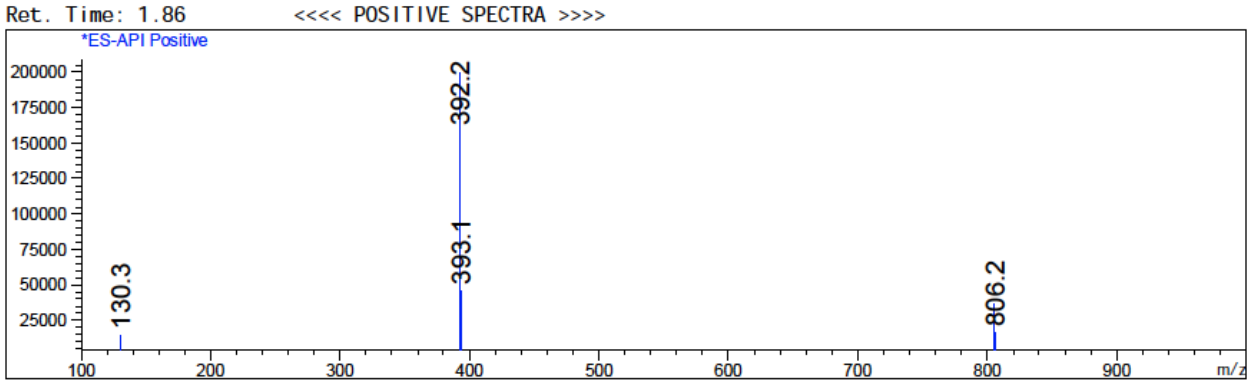
MS of compound **13**



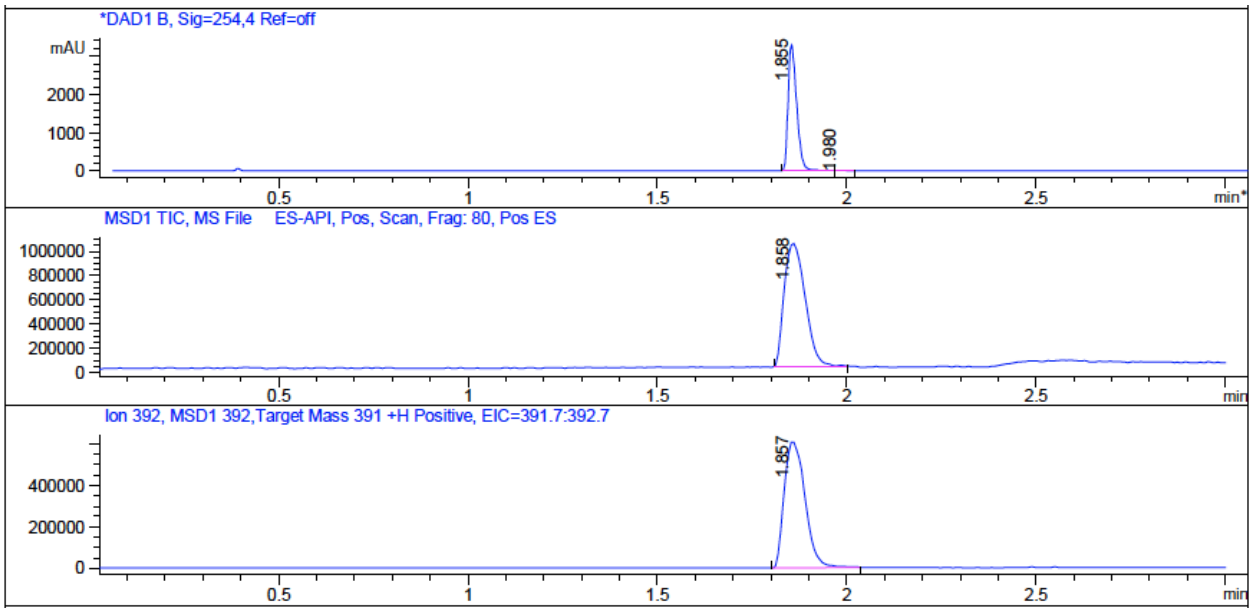
Chromatographic purity analysis of compound **13**



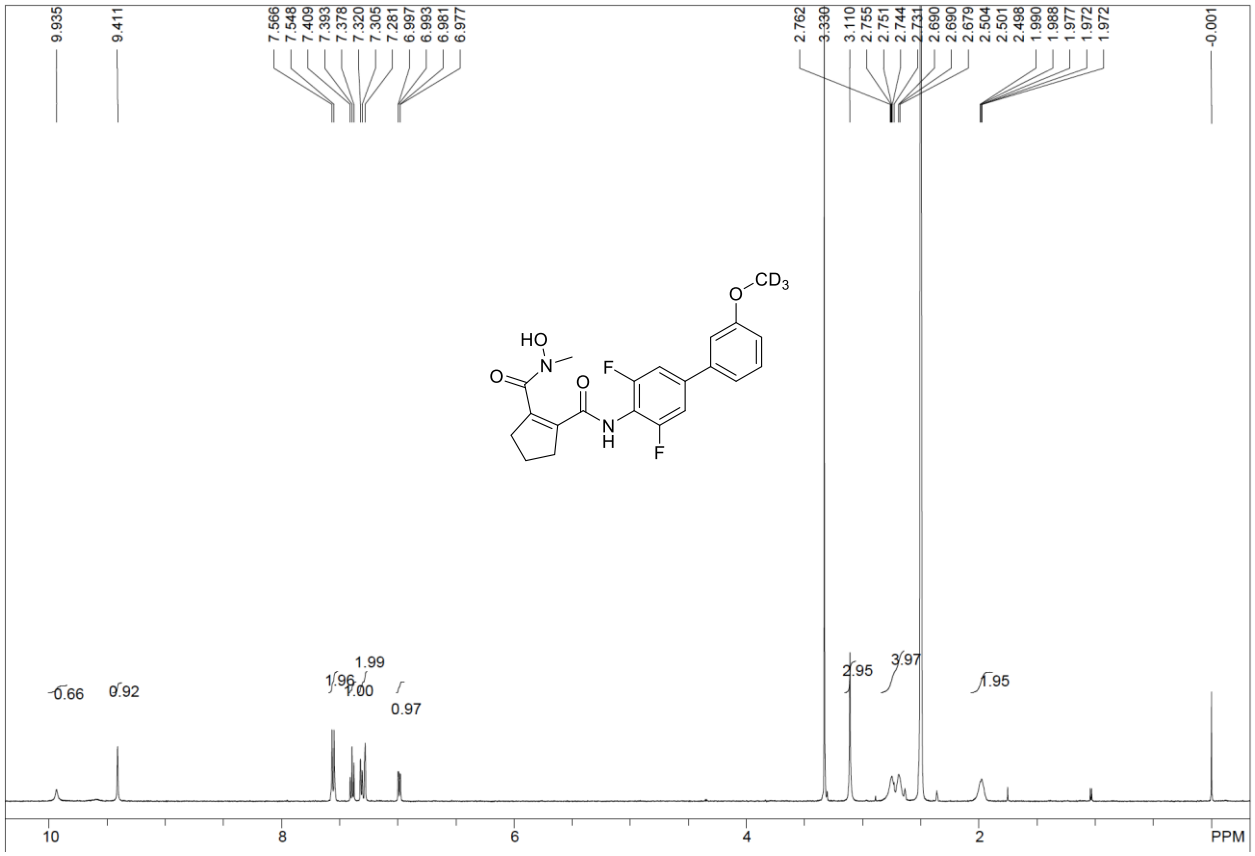
^{1}H-NMR (400 MHz, DMSO-d_6) of compound **14**



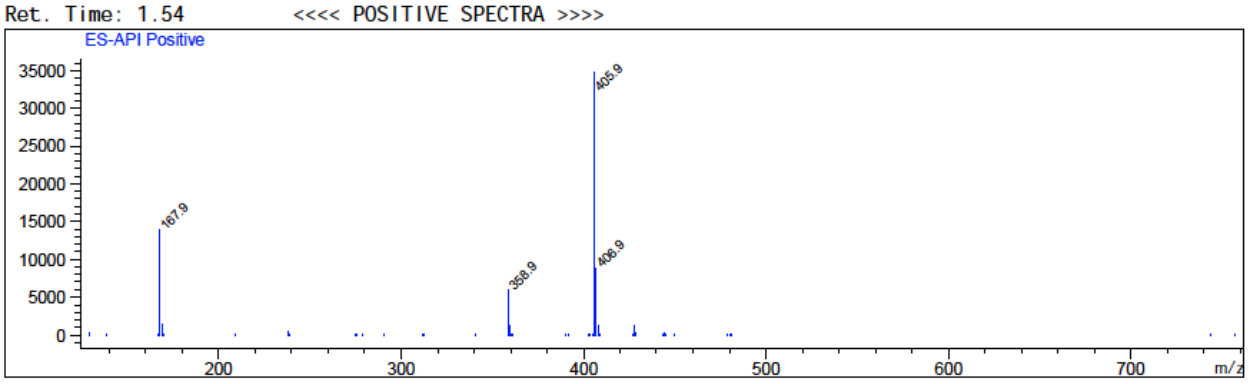
MS of compound **14**



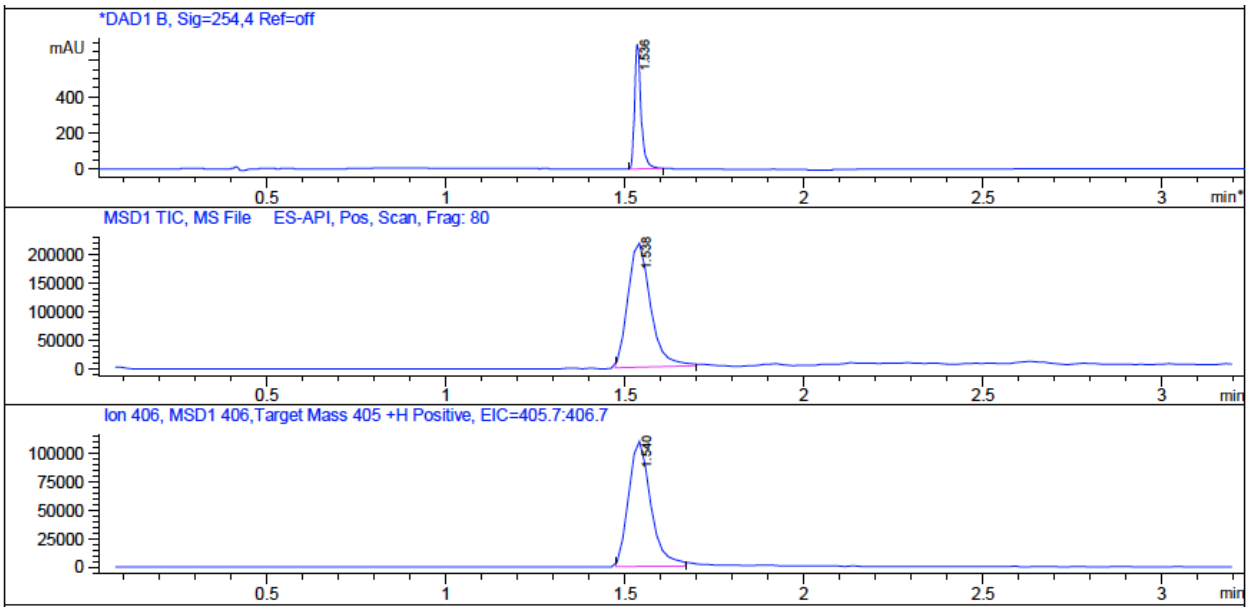
Chromatographic purity analysis of compound **14**



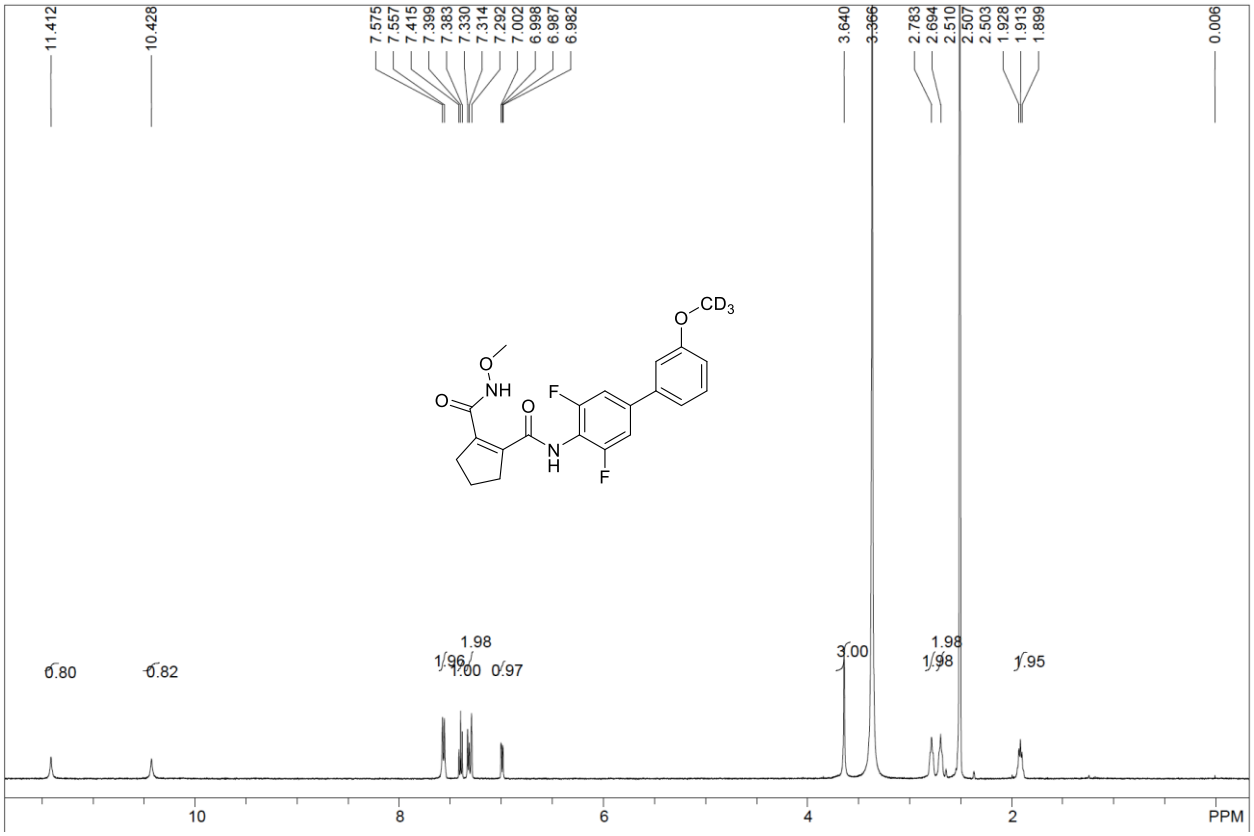
^{1}H-NMR (500 MHz, DMSO-d_6) of compound **15**



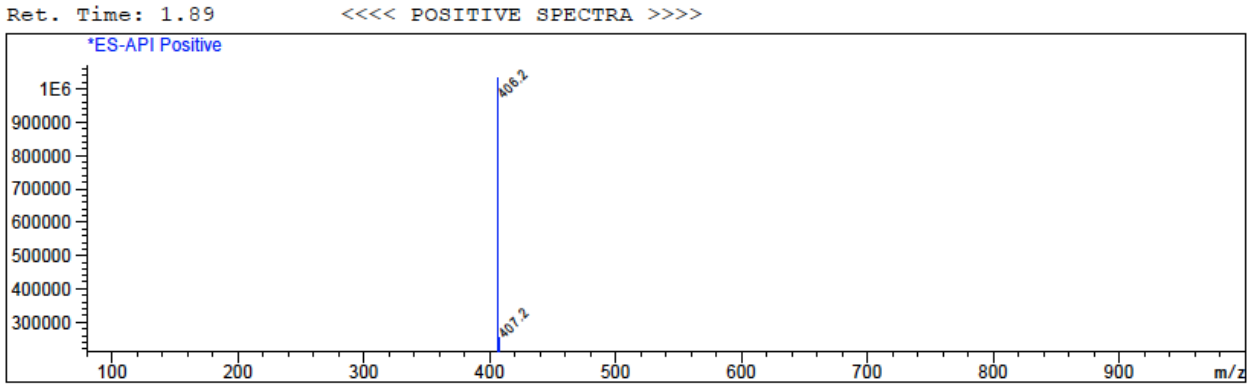
MS of compound **15**



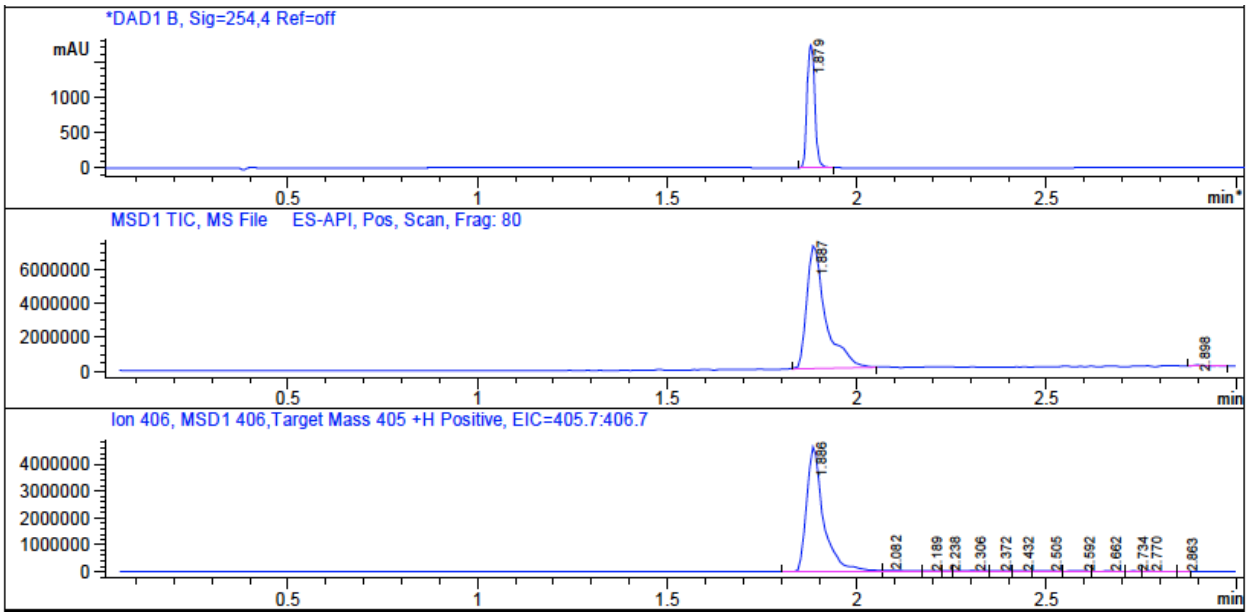
Chromatographic purity analysis of compound **15**



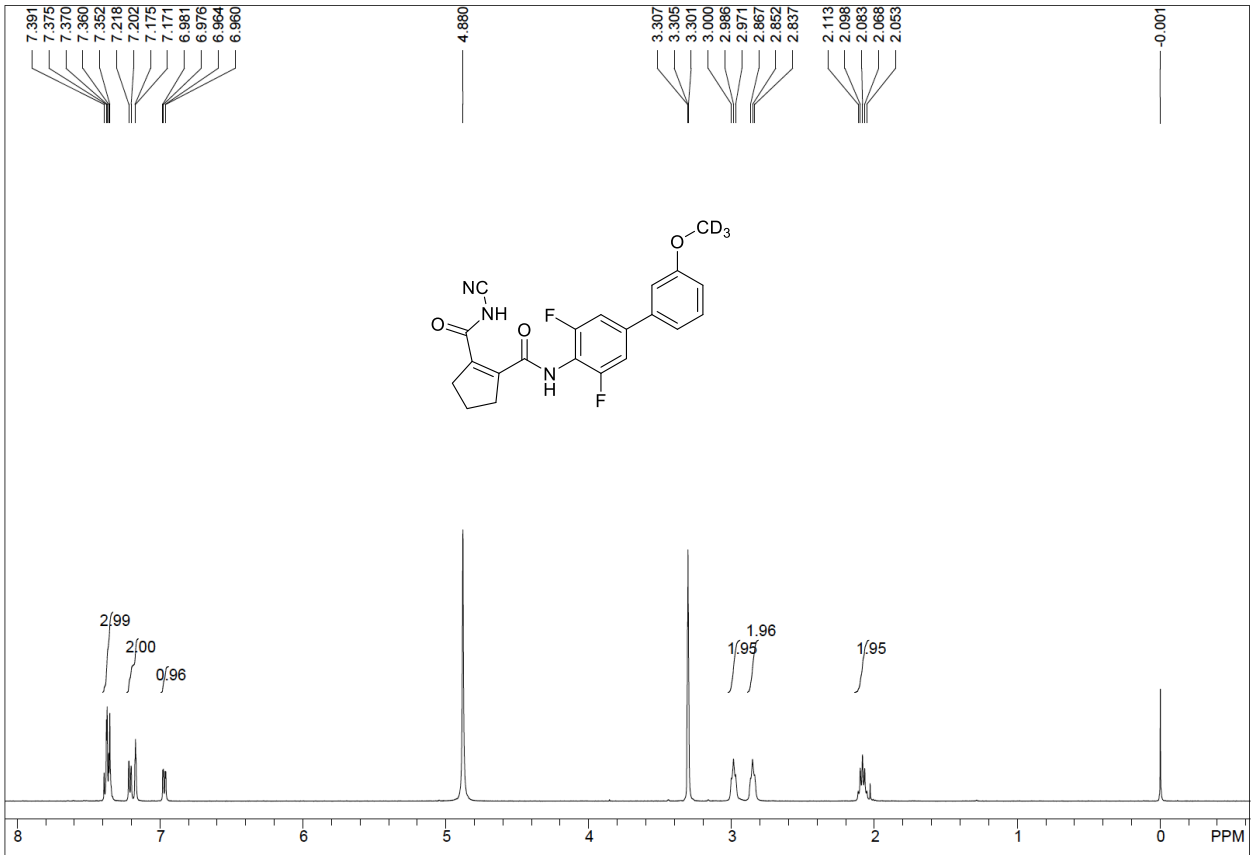
^{1}H-NMR (500 MHz, DMSO-d_6) of compound **16**



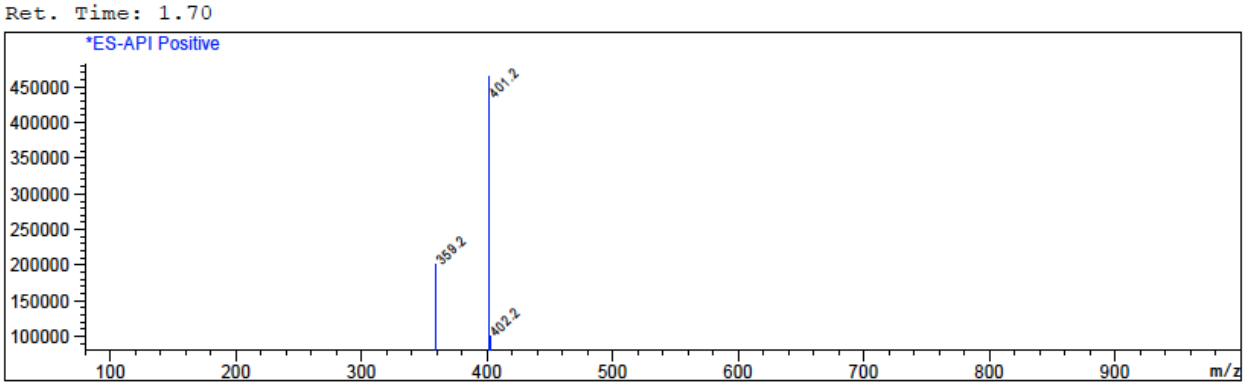
MS of compound **16**



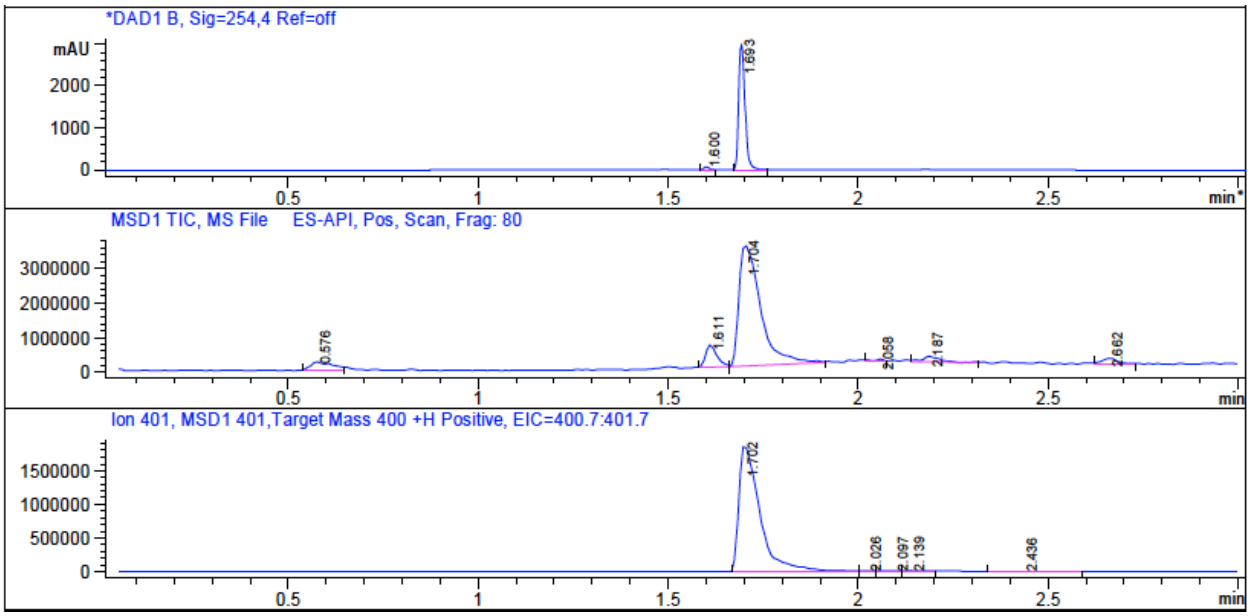
Chromatographic purity analysis of compound **16**



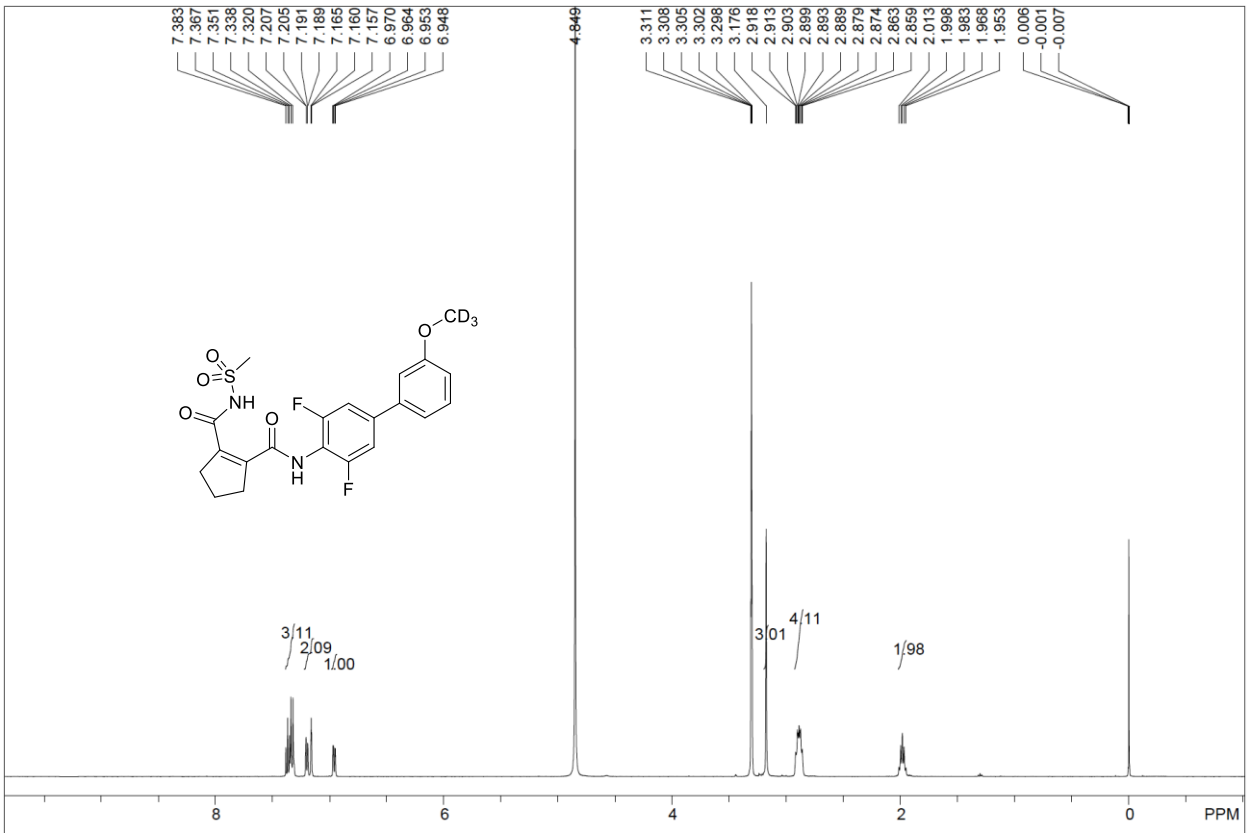
^{1}H-NMR (500 MHz, CD_3OD) of compound **17**



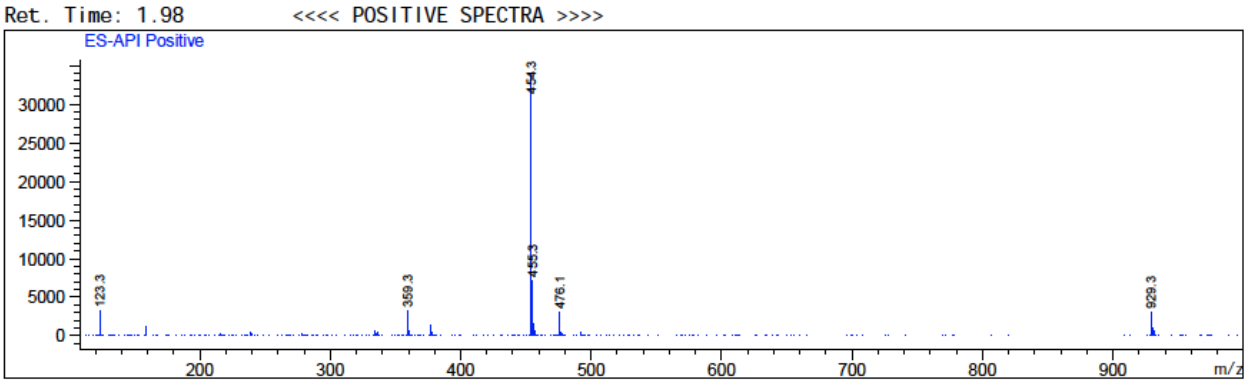
MS of compound **17**



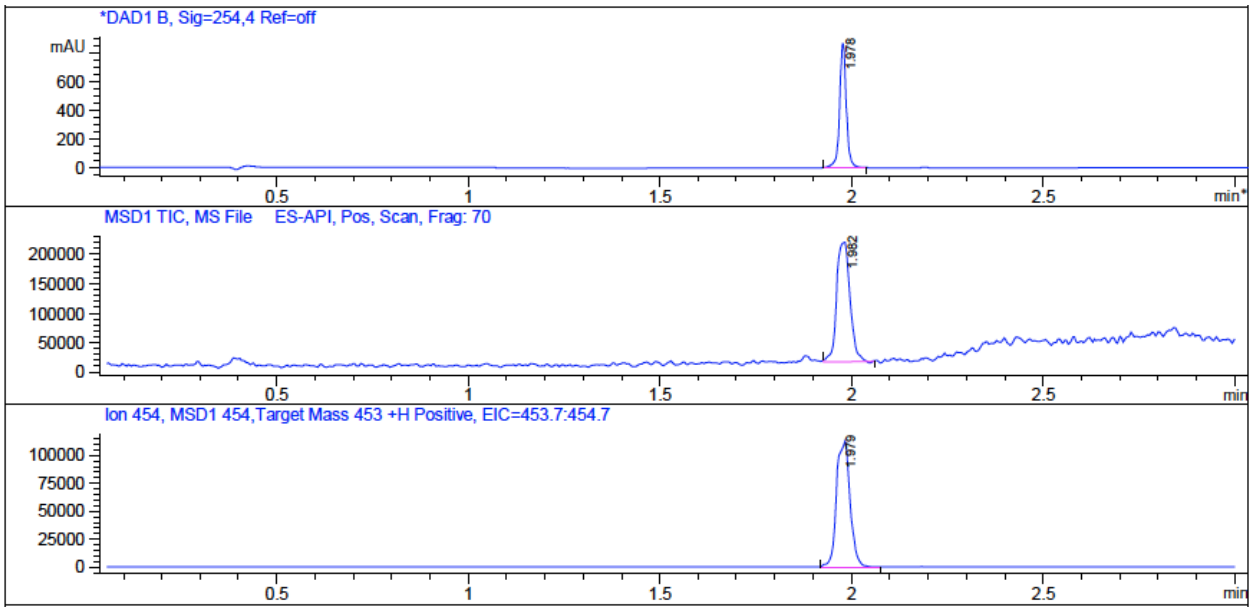
Chromatographic purity analysis of compound **17**



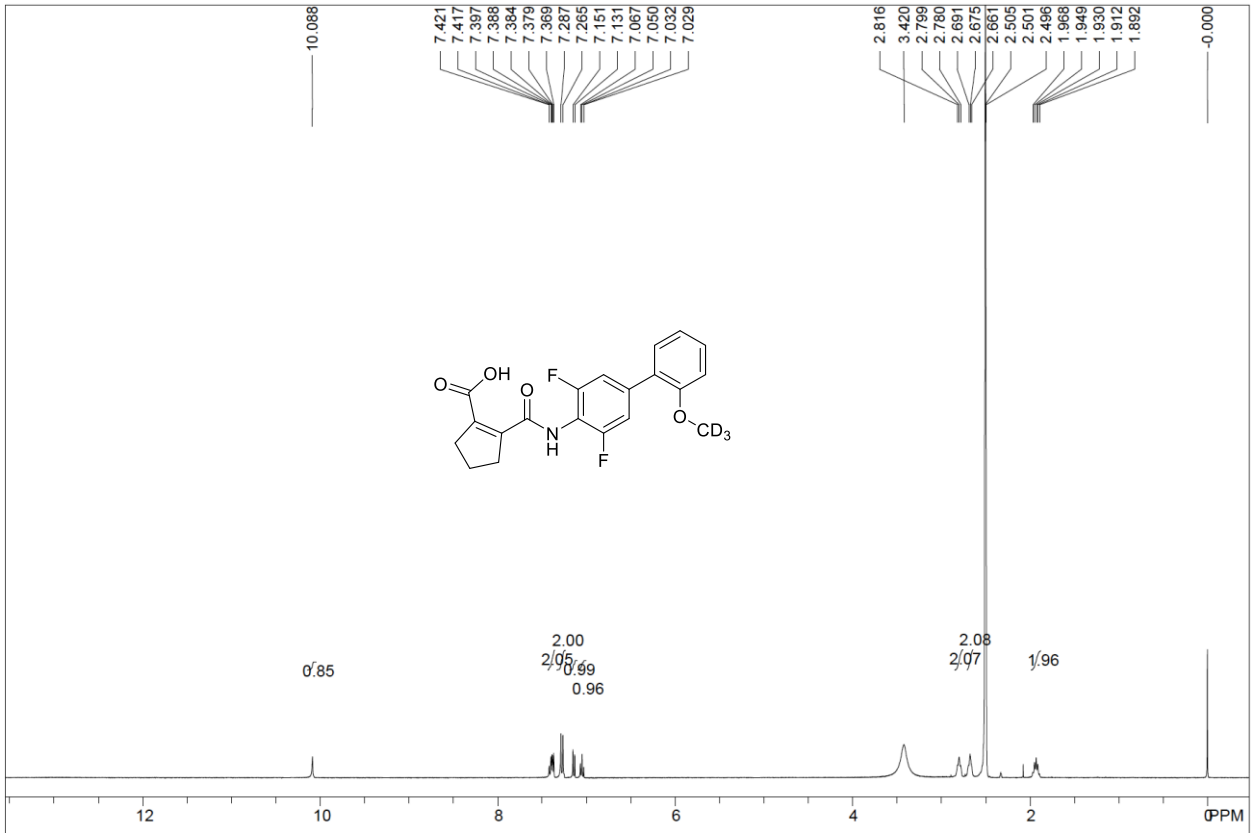
^{1}H-NMR (500 MHz, CD_3OD) of compound **18**



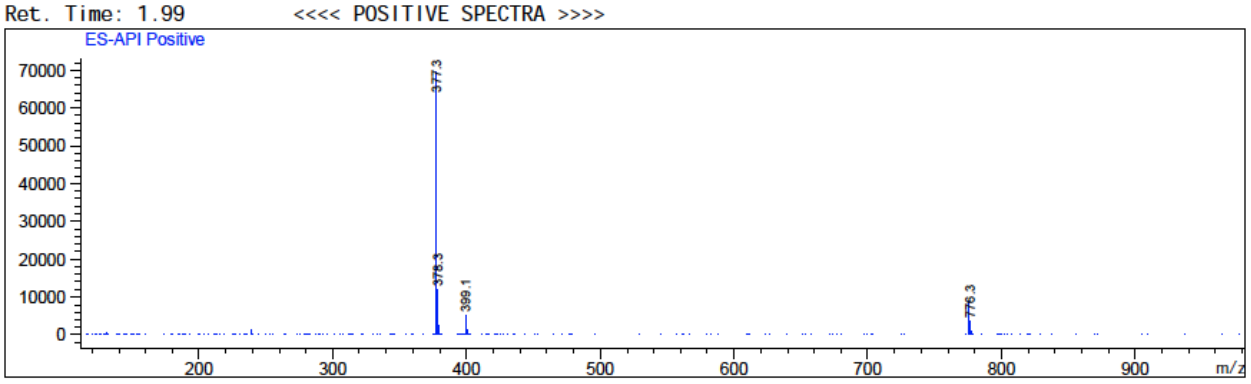
MS of compound **18**



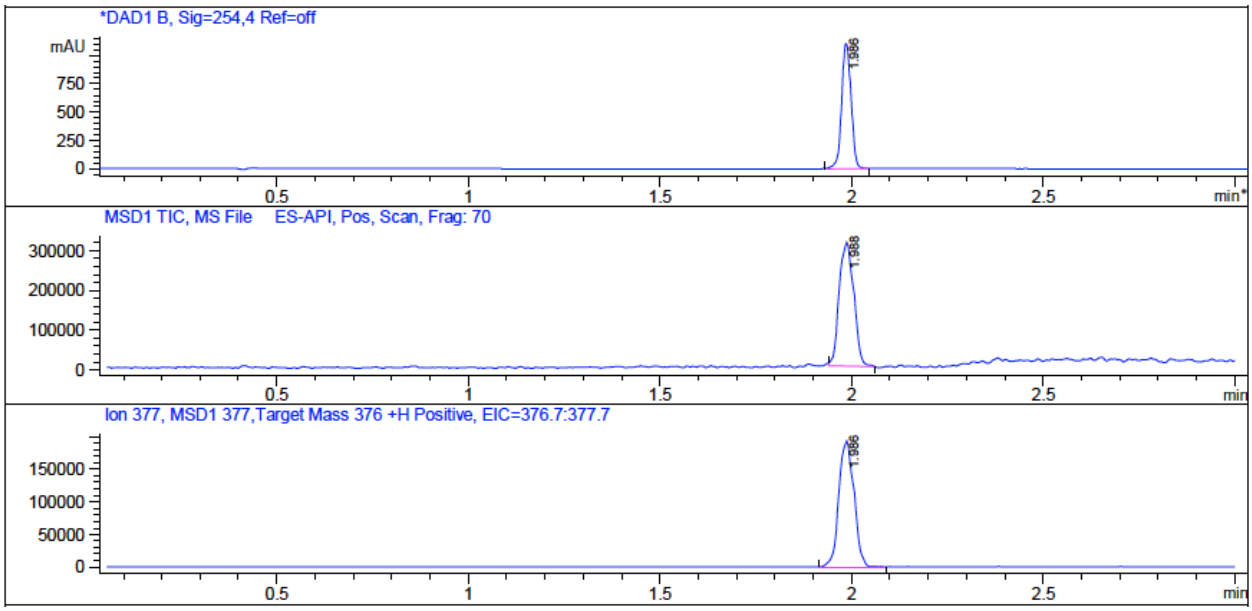
Chromatographic purity analysis of compound **18**



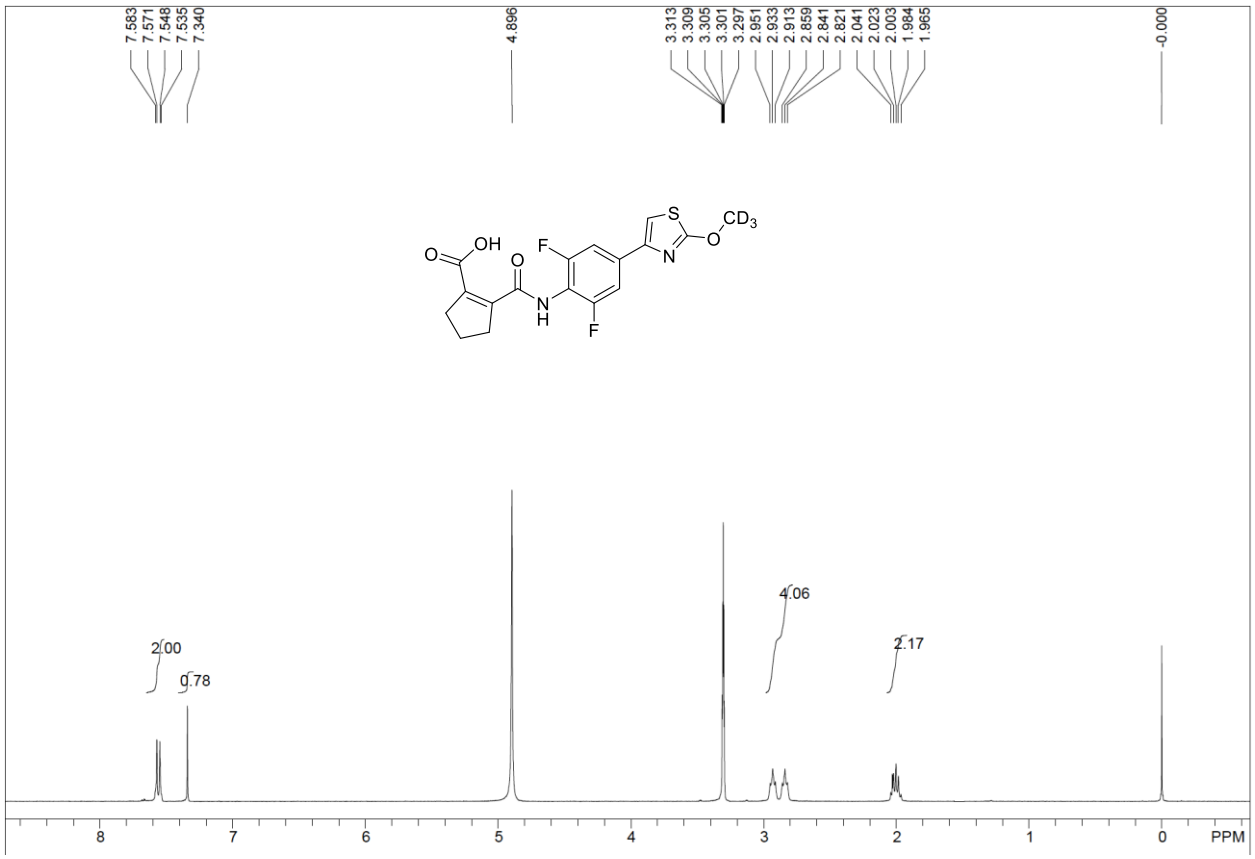
^{1}H-NMR (400 MHz, DMSO-d_6) of compound **19**



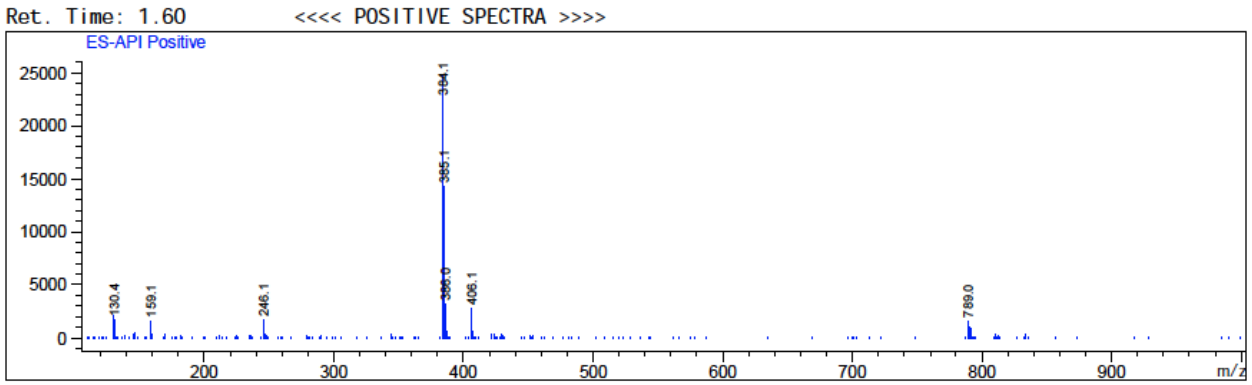
MS of compound **19**



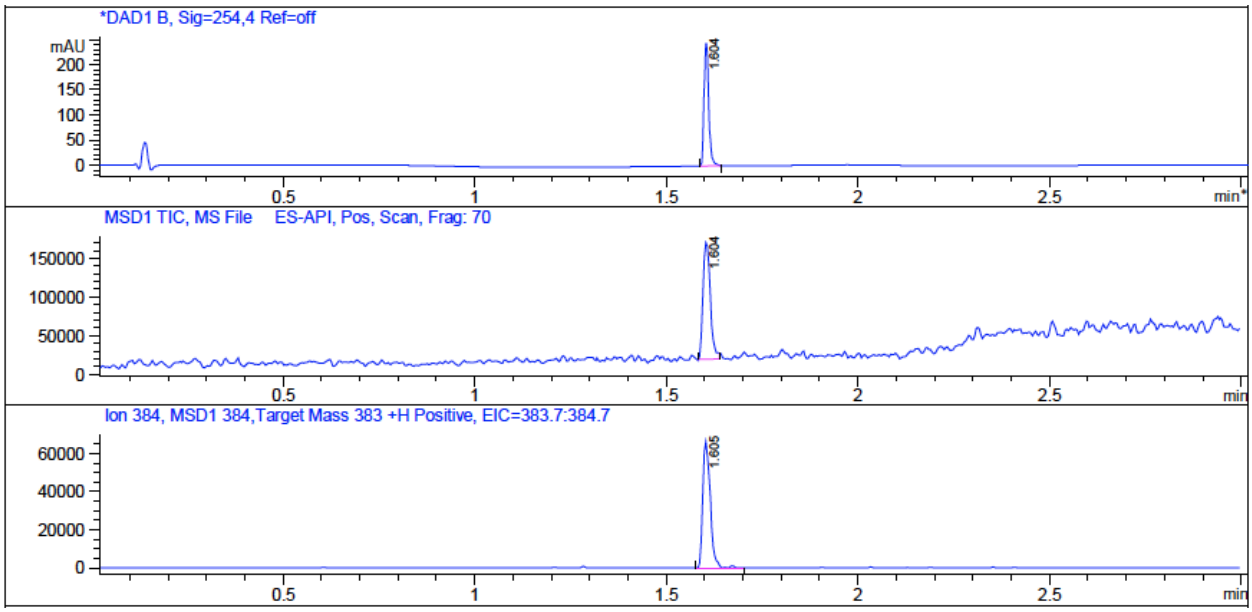
Chromatographic purity analysis of compound **19**



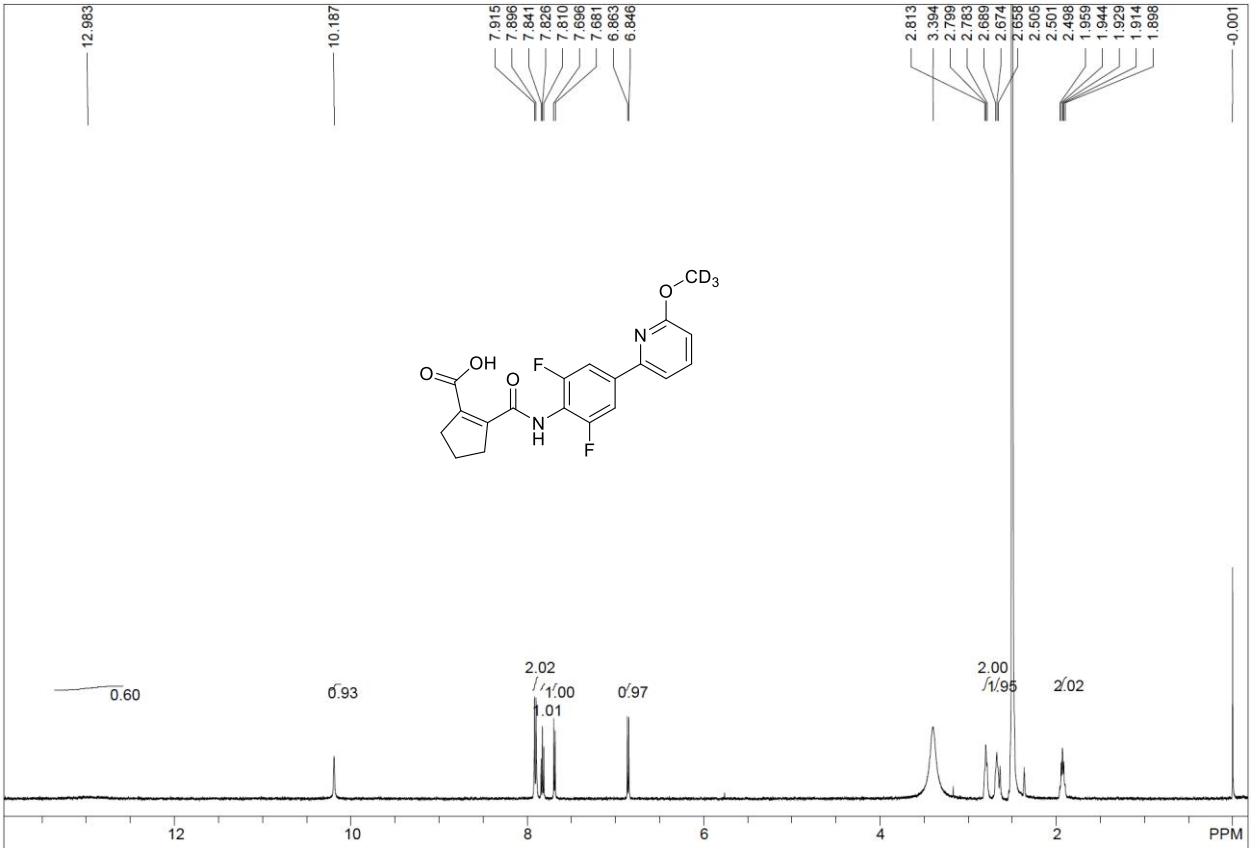
^{1}H-NMR (400 MHz, CD_3OD) of compound **20**



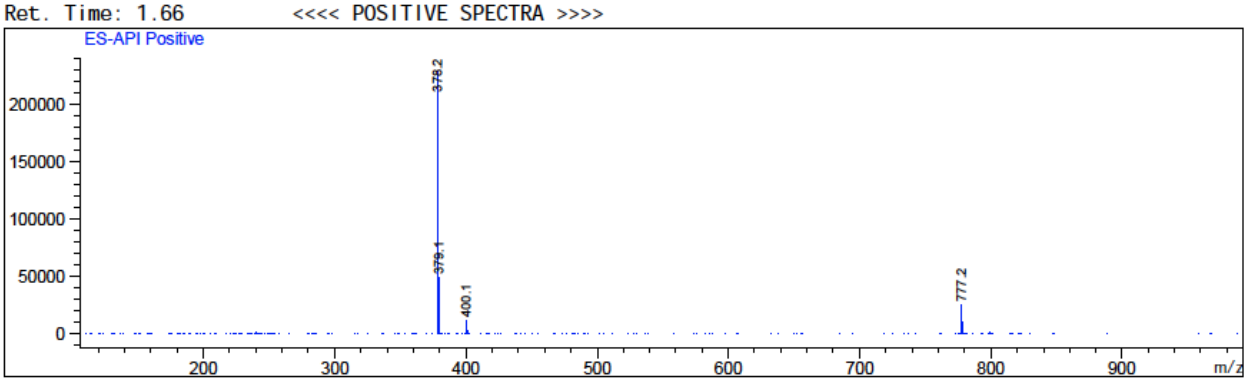
MS of compound **20**



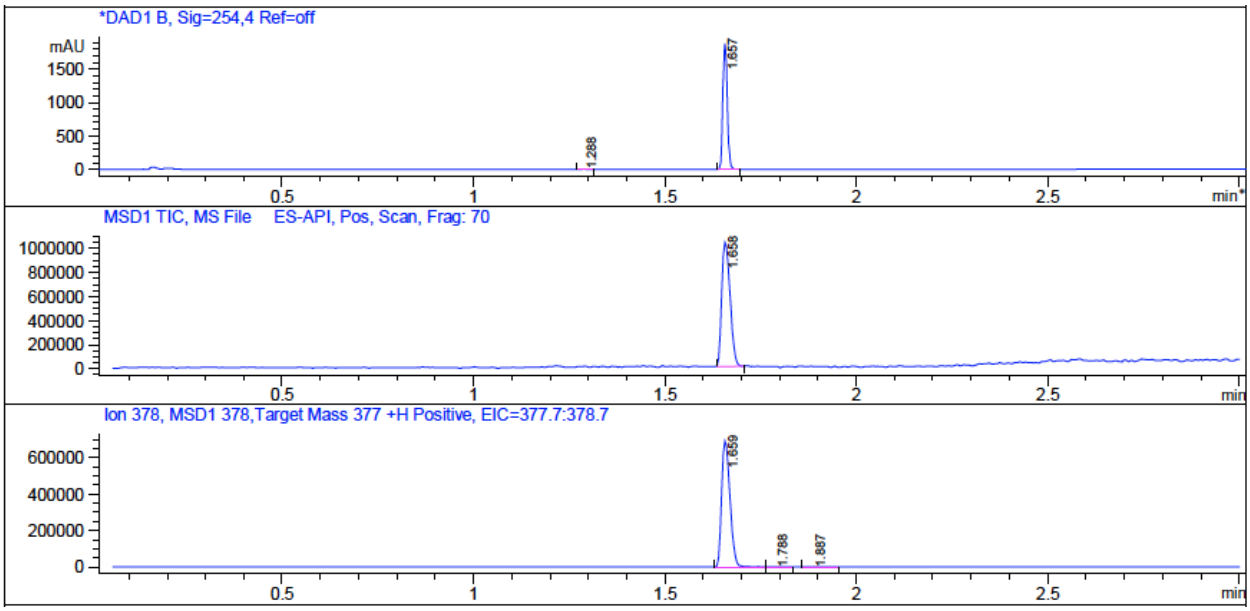
Chromatographic purity analysis of compound **20**



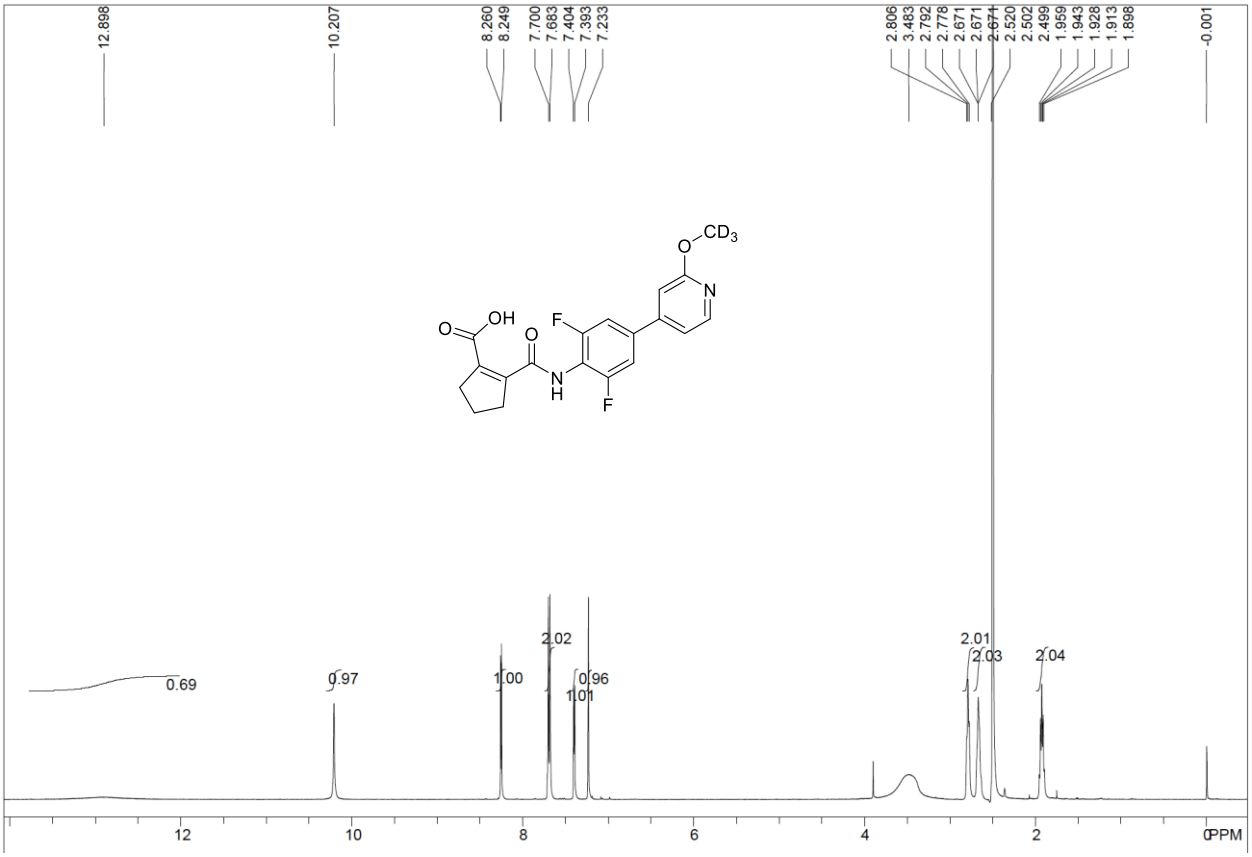
^{1}H-NMR (500 MHz, DMSO-d_6) of compound **21**



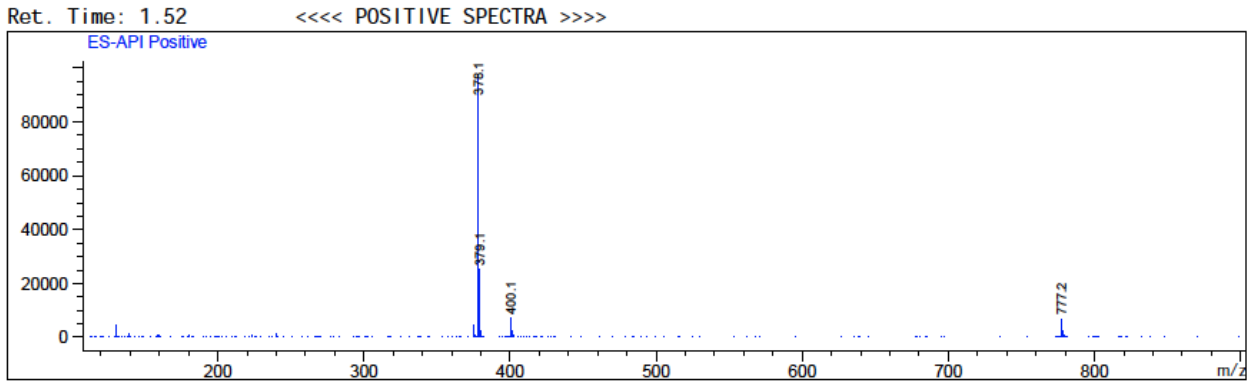
MS of compound **21**



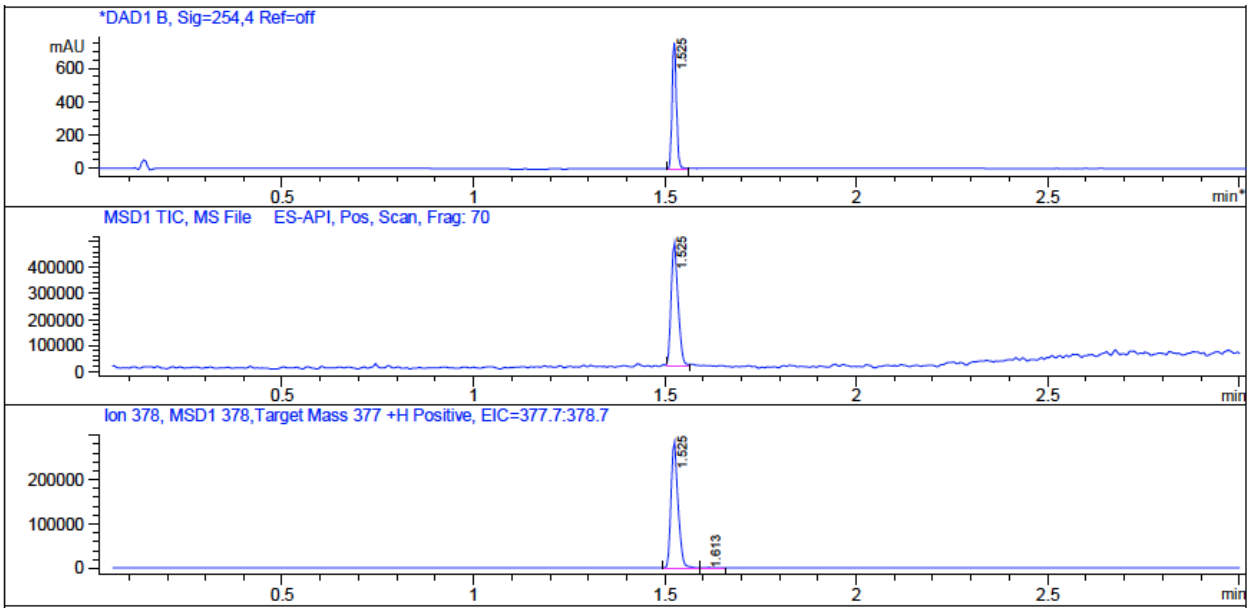
Chromatographic purity analysis of compound **21**



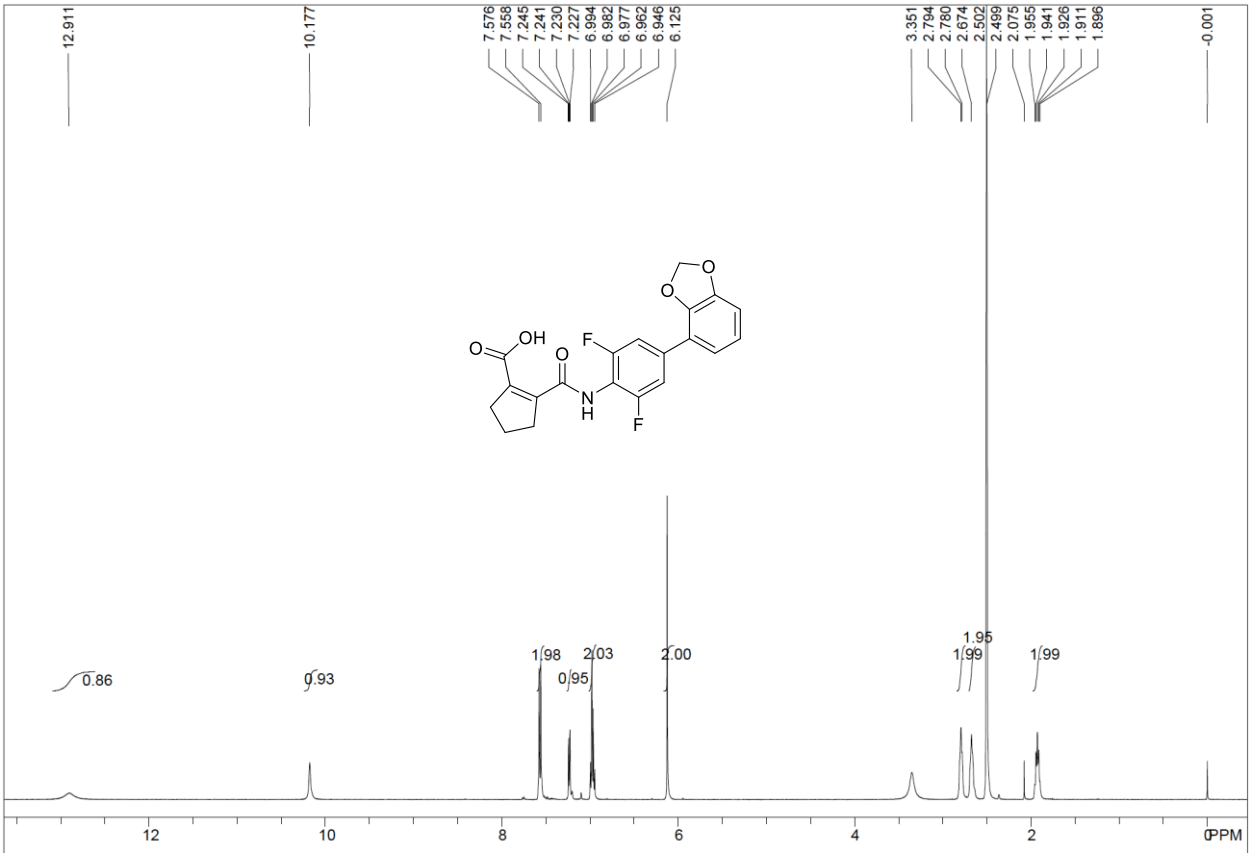
^{1}H-NMR (500 MHz, DMSO-d_6) of compound **22**



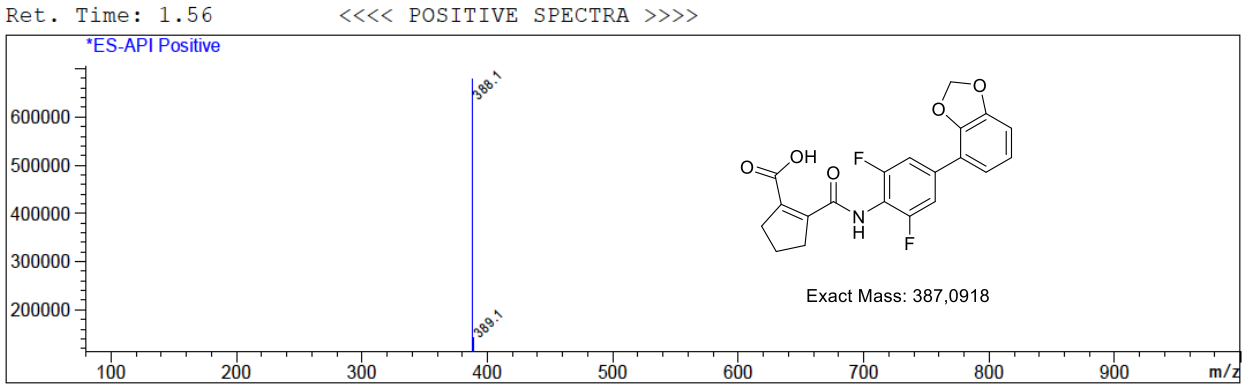
MS of compound **22**



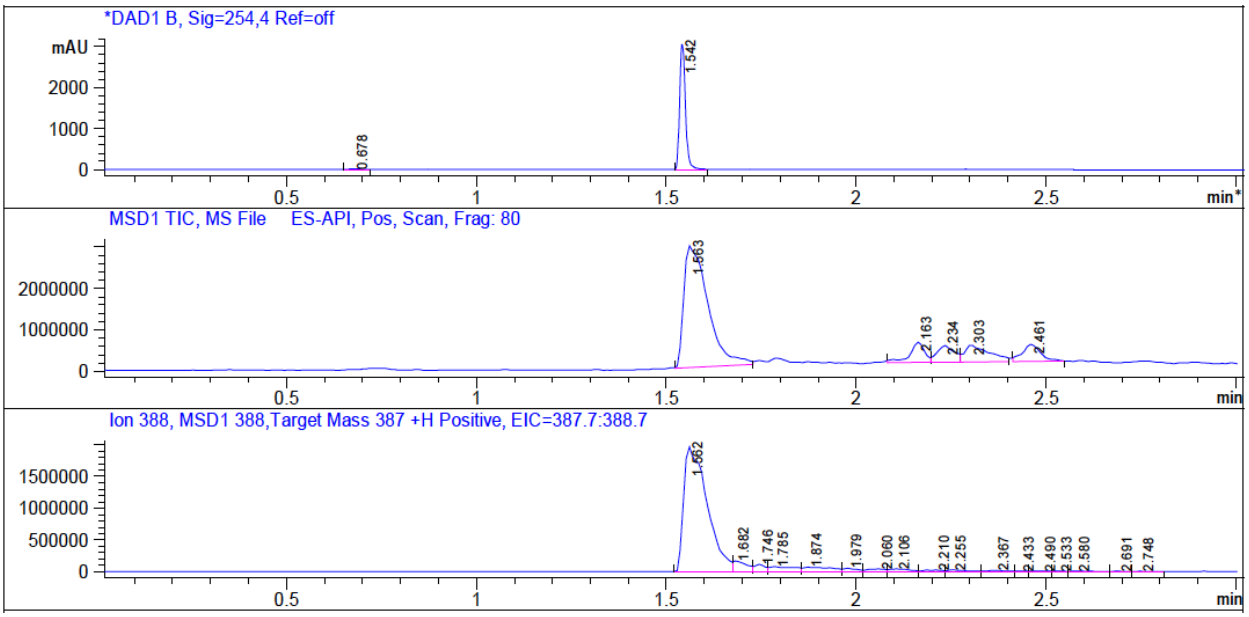
Chromatographic purity analysis of compound **22**



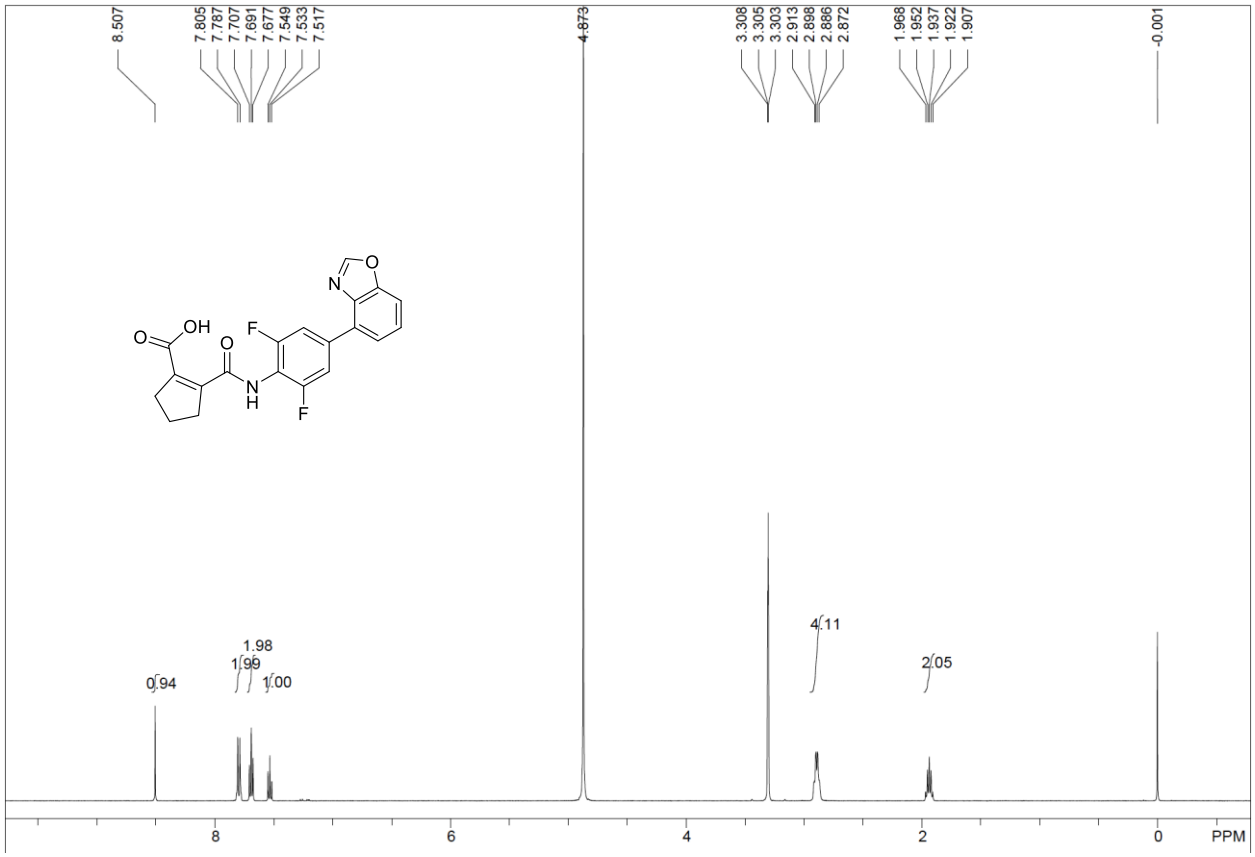
^{1}H-NMR (500 MHz, DMSO-d_6) of compound **23**



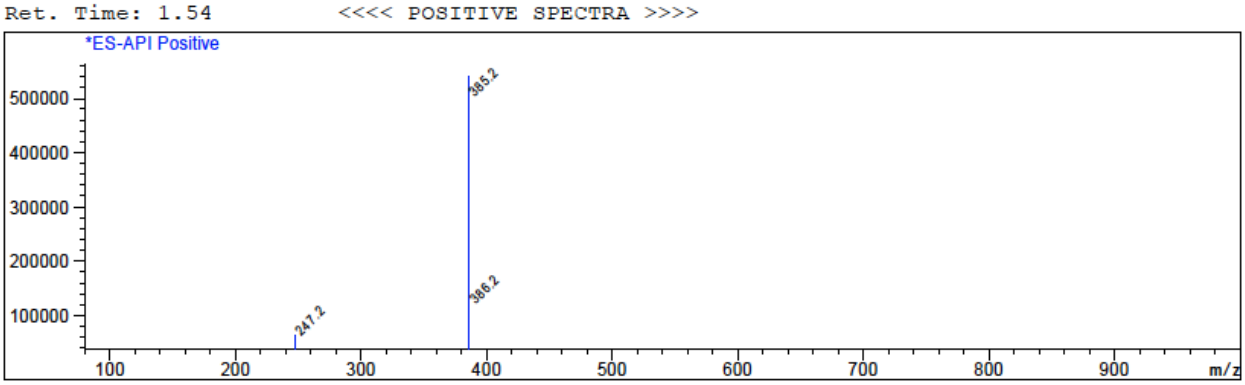
MS of compound **23**



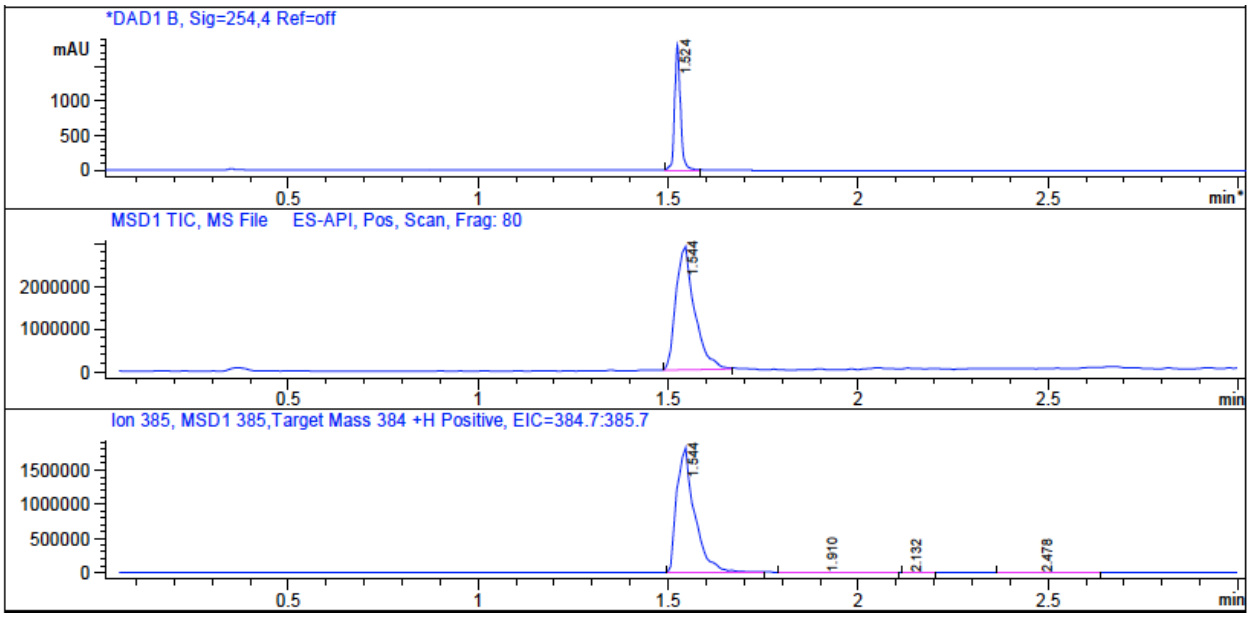
Chromatographic purity analysis of compound **23**



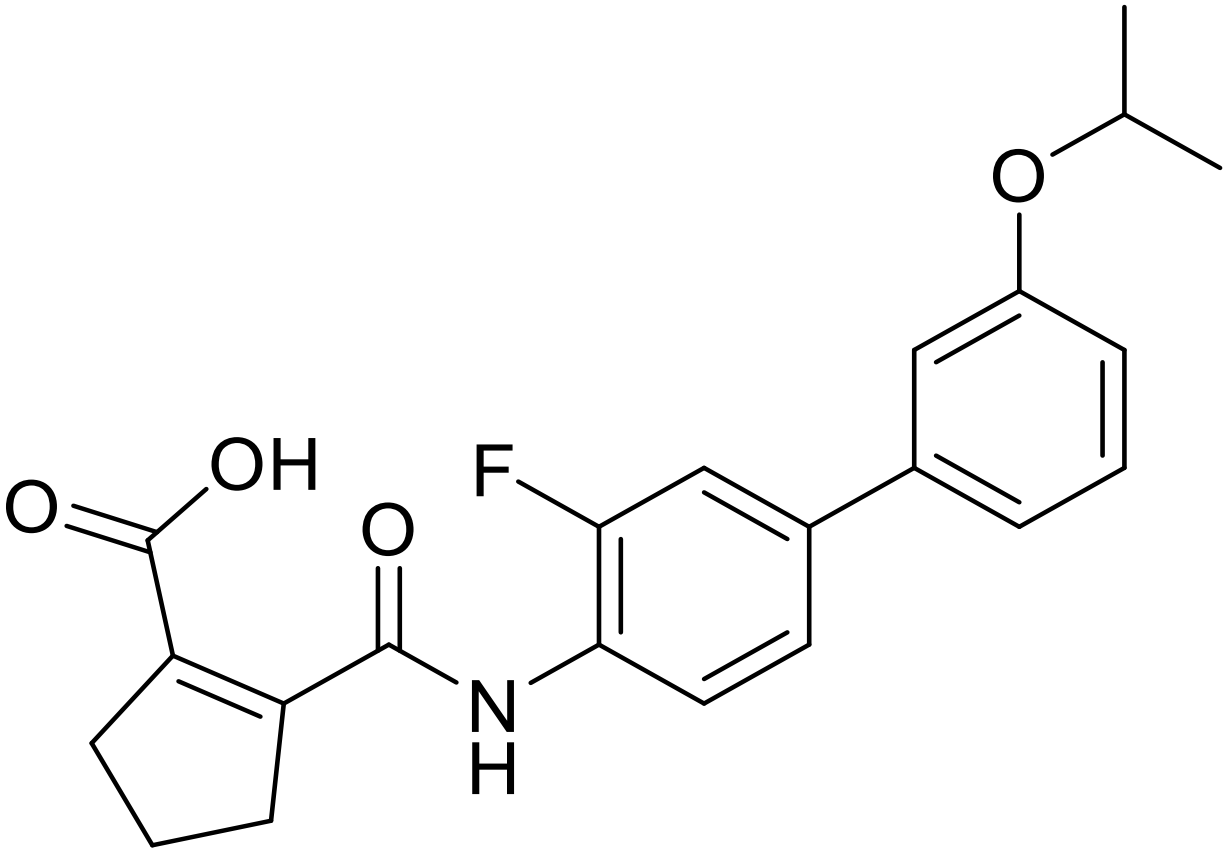
^{1}H-NMR (500 MHz, CD_3OD) of compound **24**



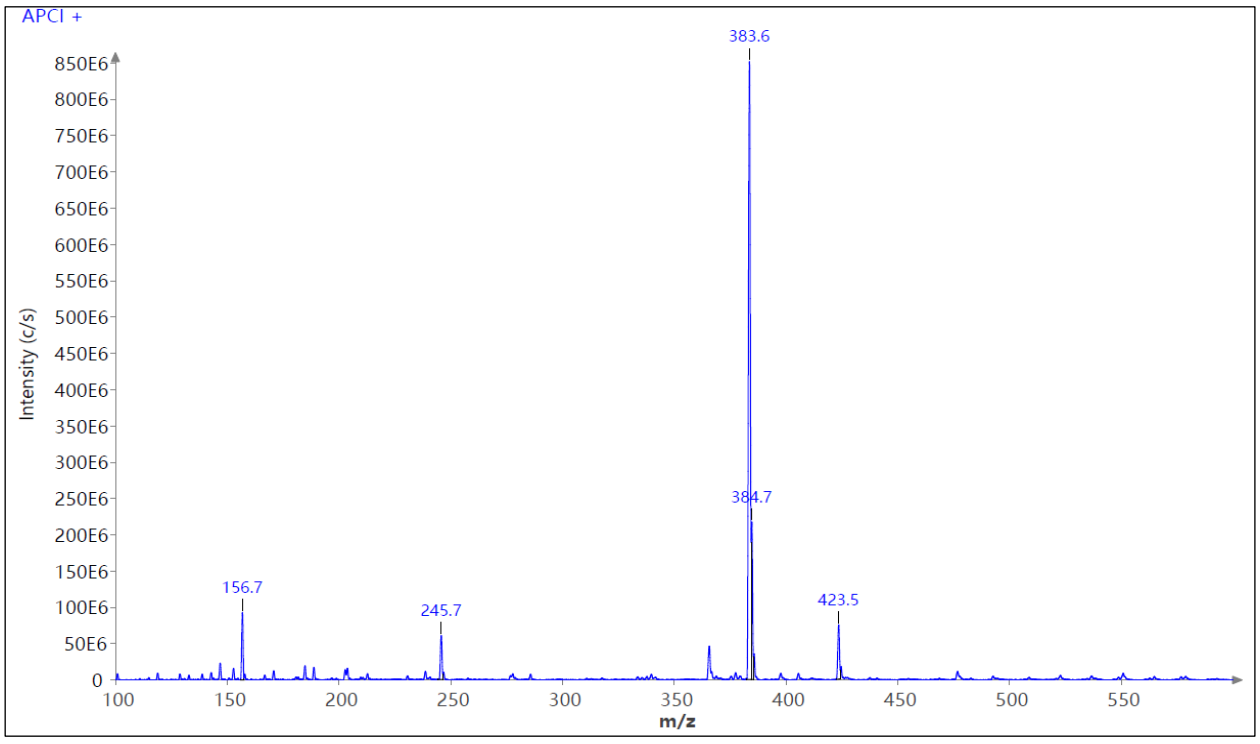
MS of compound **24**



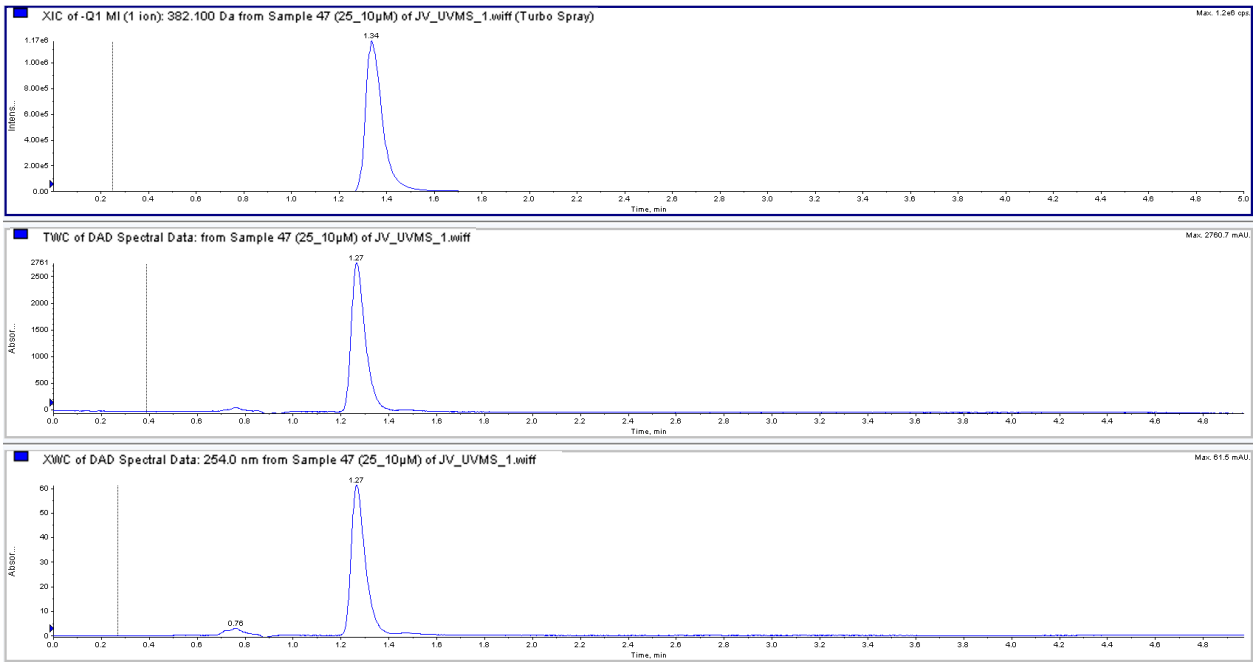
Chromatographic purity analysis of compound **24**



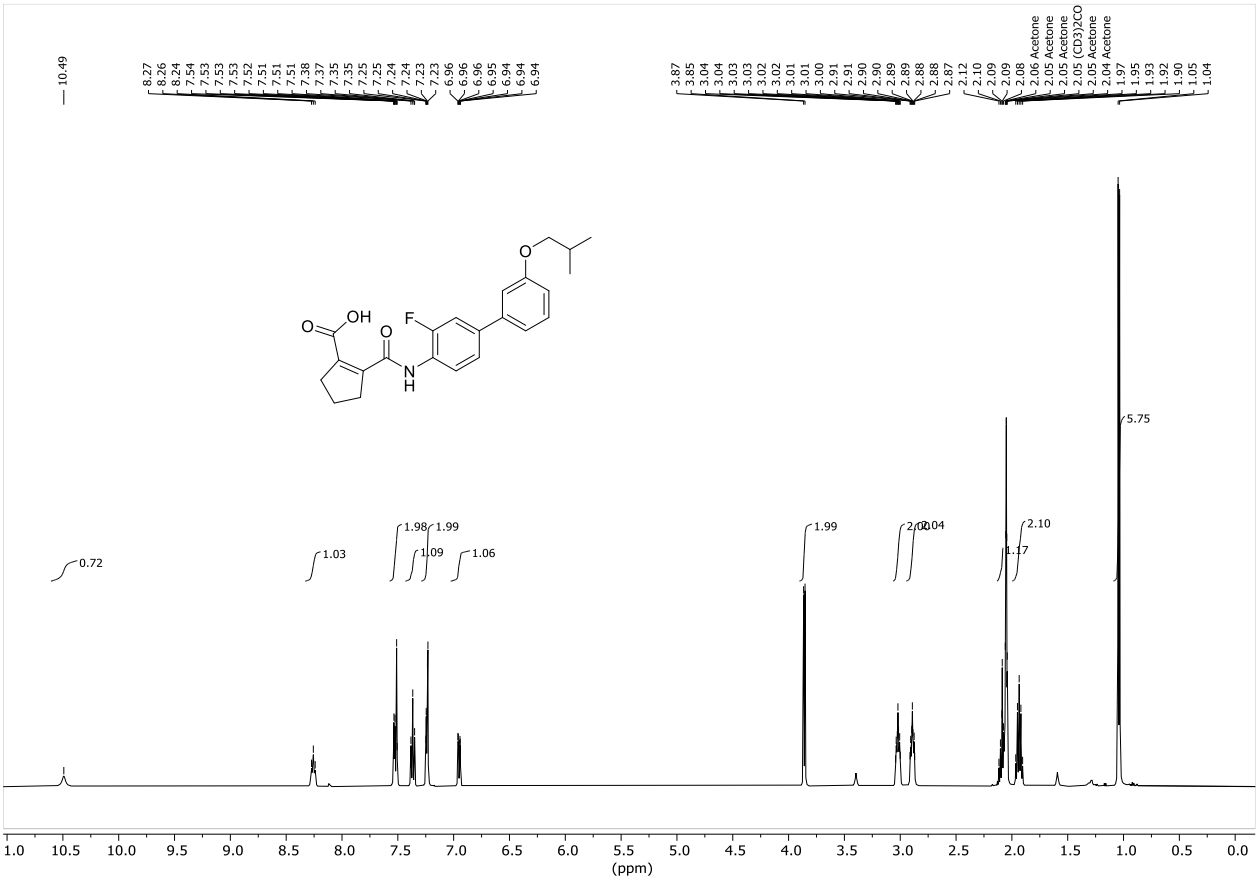
^{1}H-NMR (500 MHz, acetone-d_6) of compound **25**



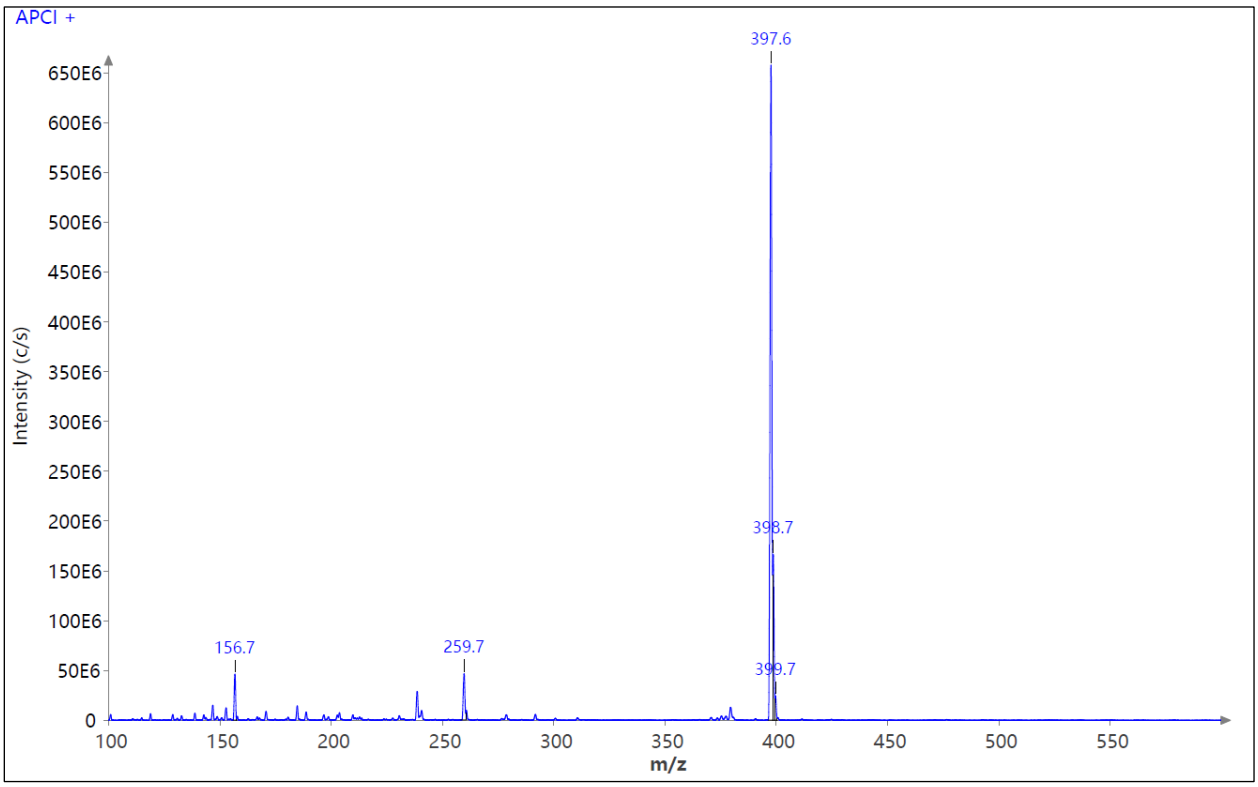
MS of compound **25**



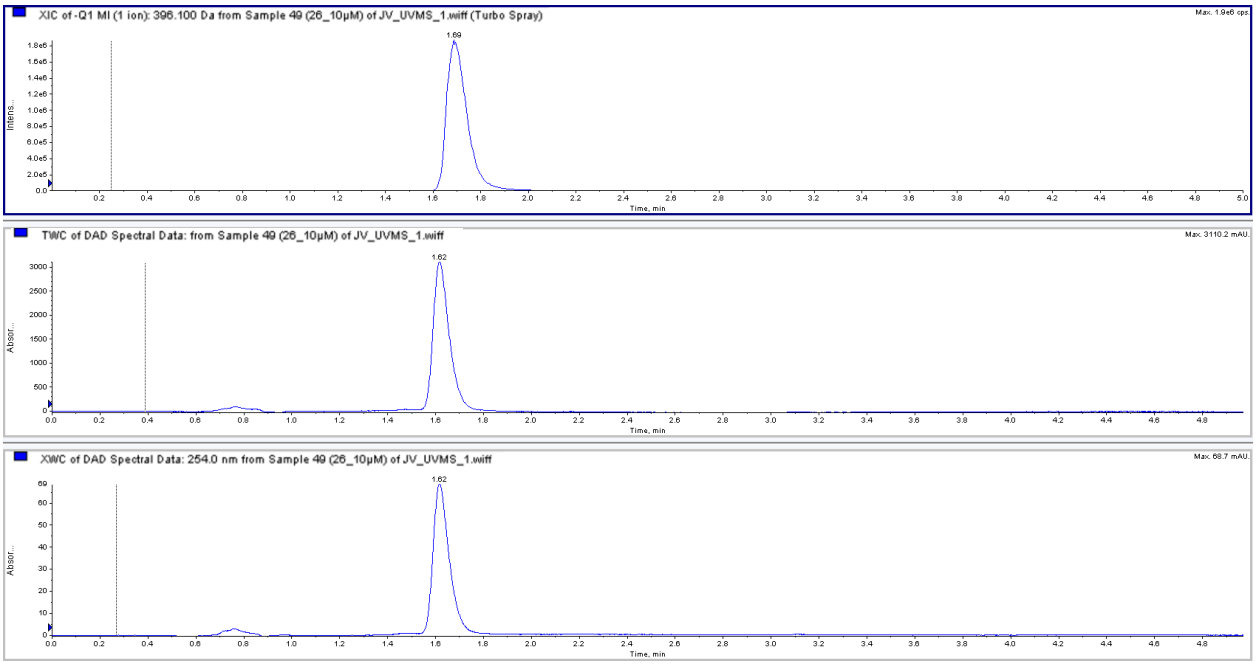
Chromatographic purity analysis of compound **25**



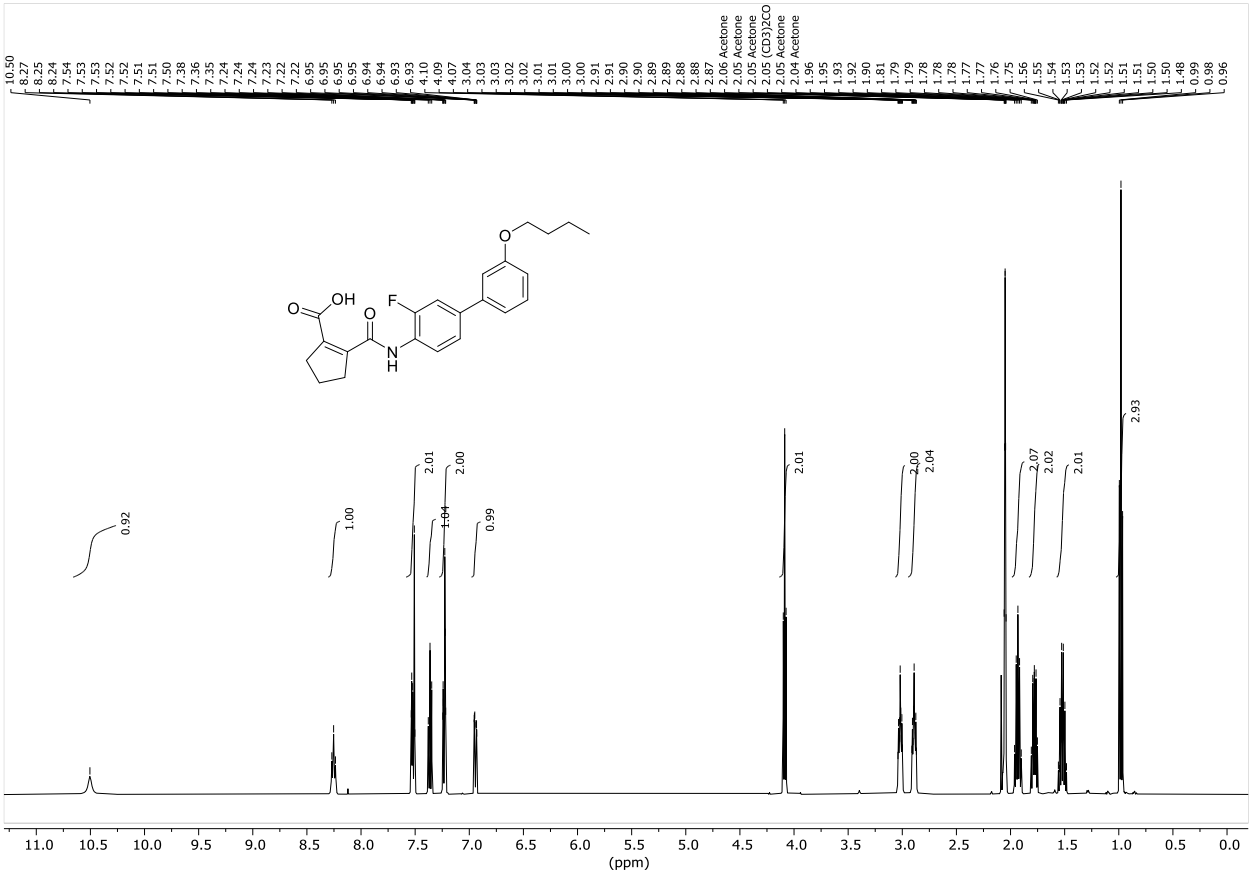
^{1}H-NMR (500 MHz, acetone-d_6) of compound **26**



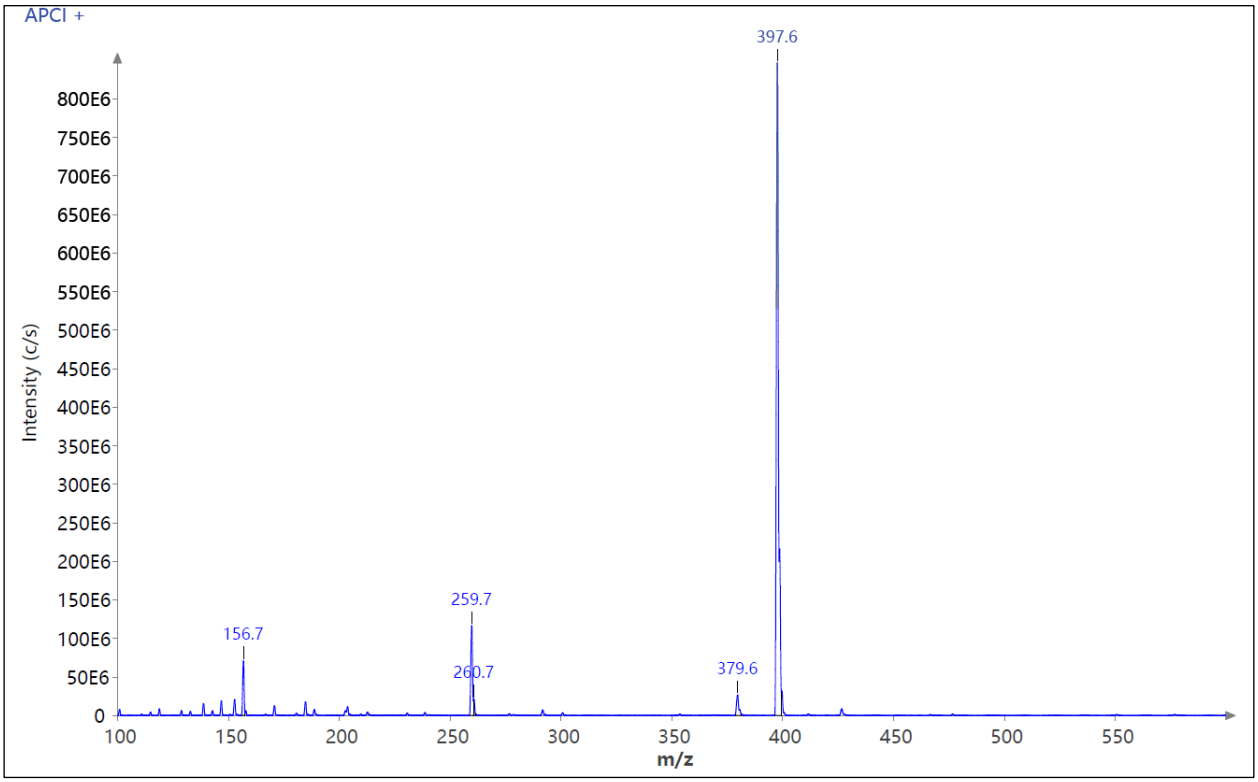
MS of compound **26**



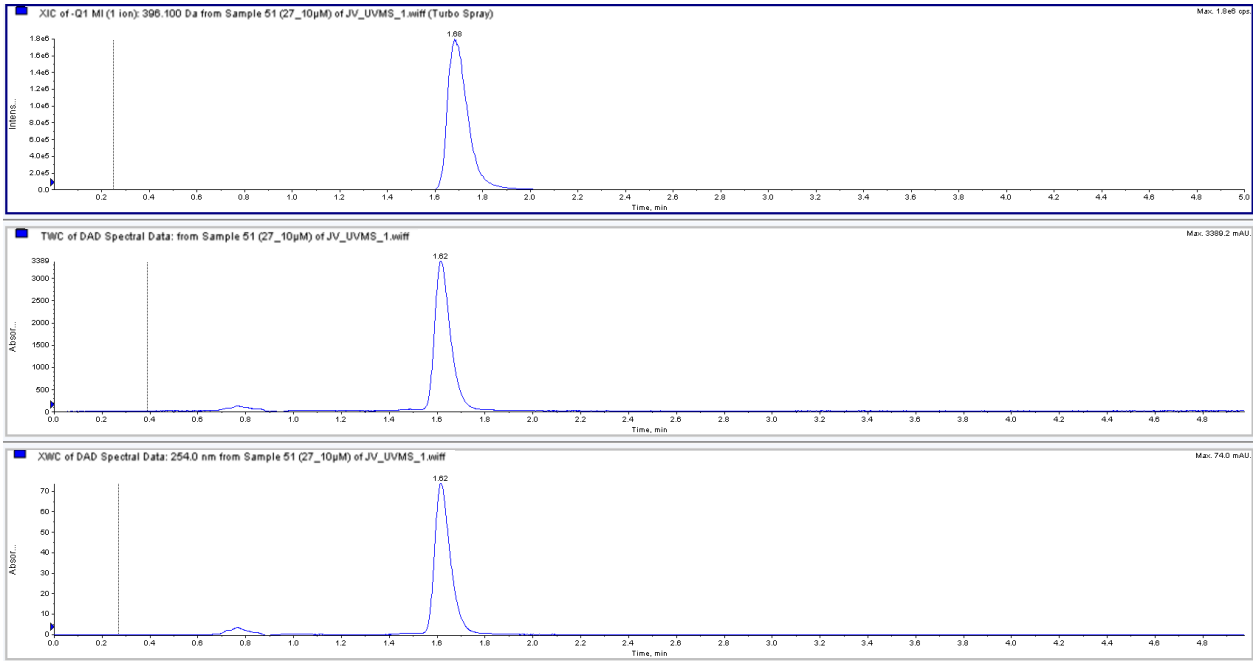
Chromatographic purity analysis of compound **26**



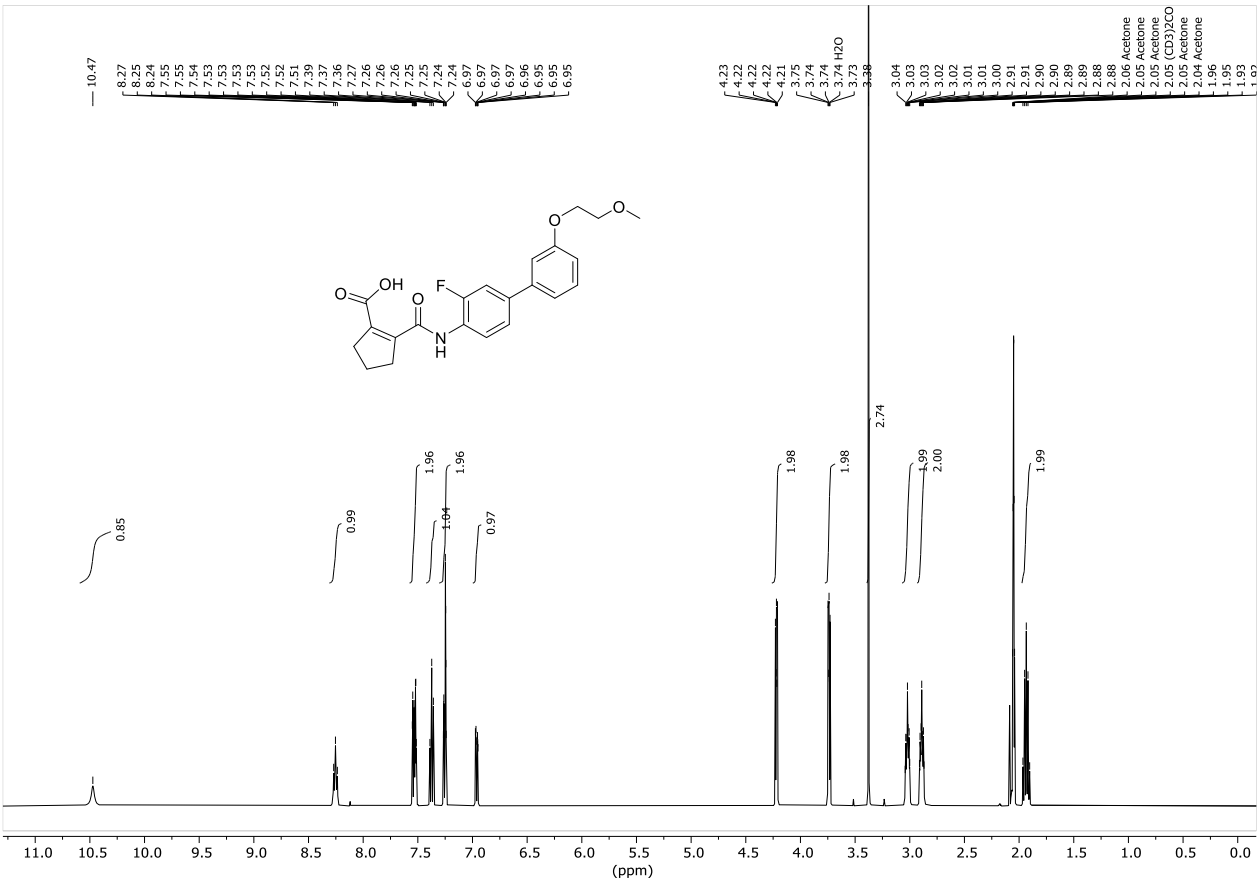
^{1}H-NMR (500 MHz, acetone-d_6) of compound **27**



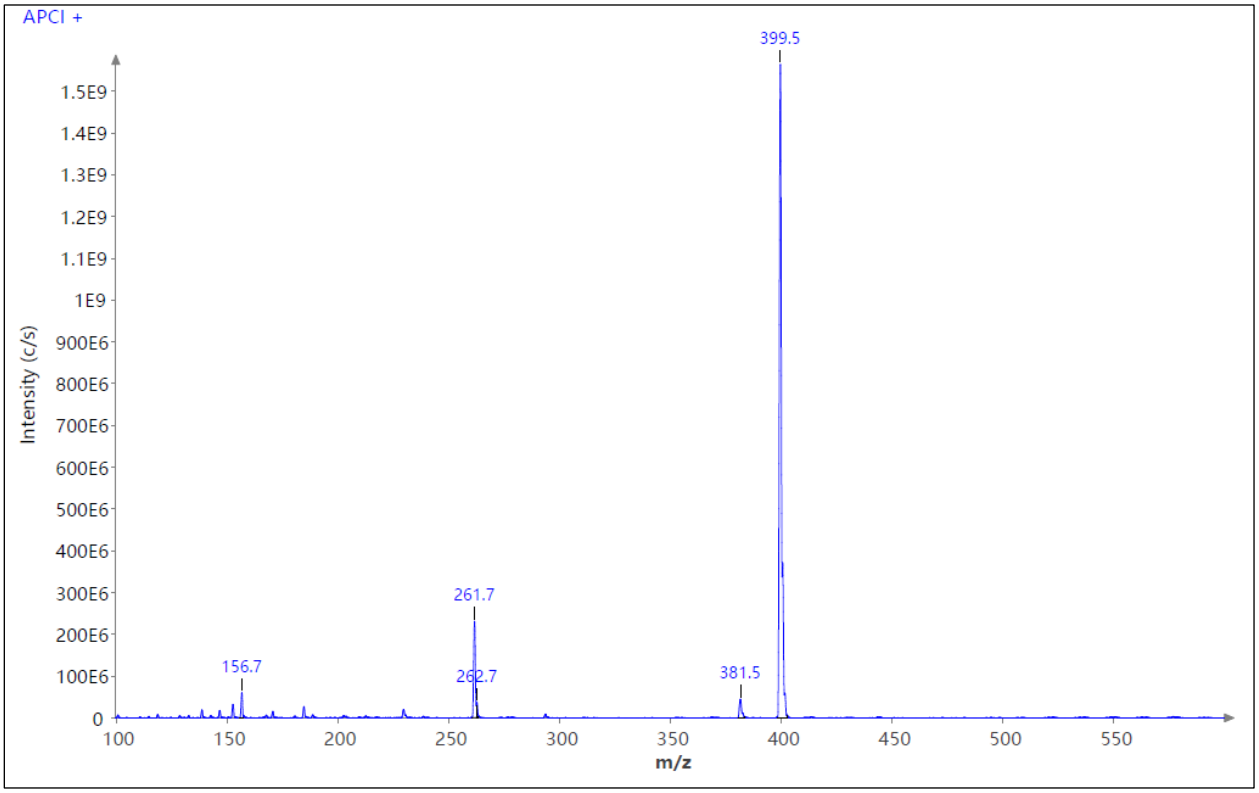
MS of compound **27**



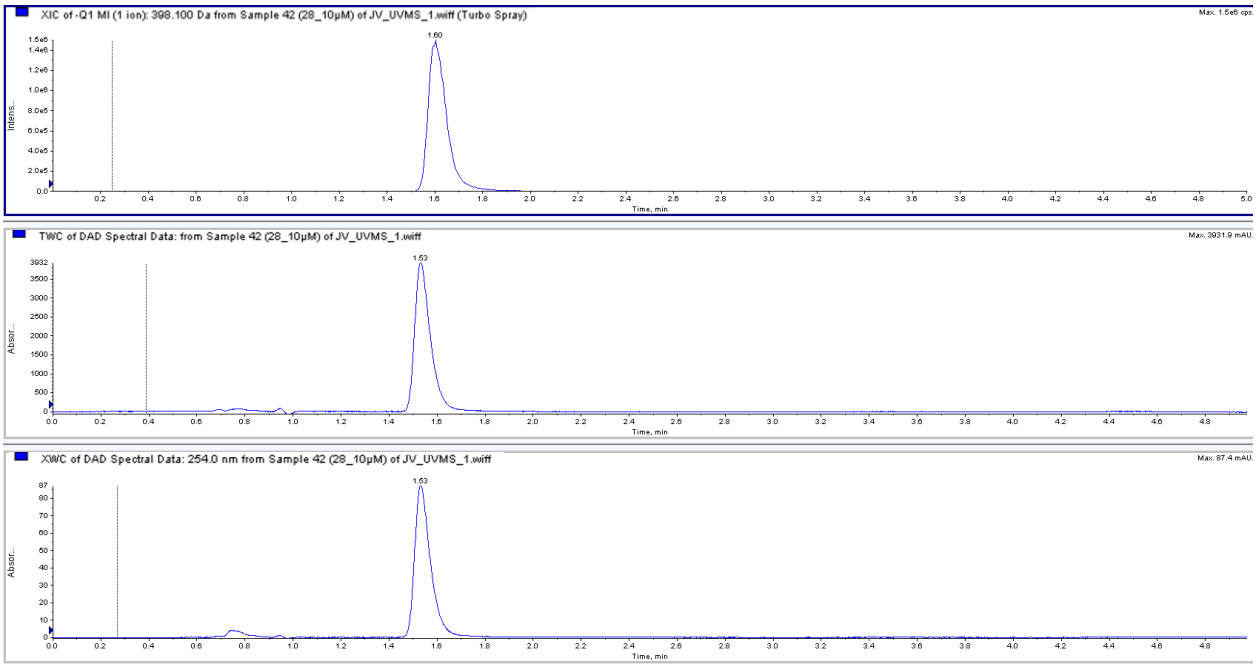
Chromatographic purity analysis of compound **27**



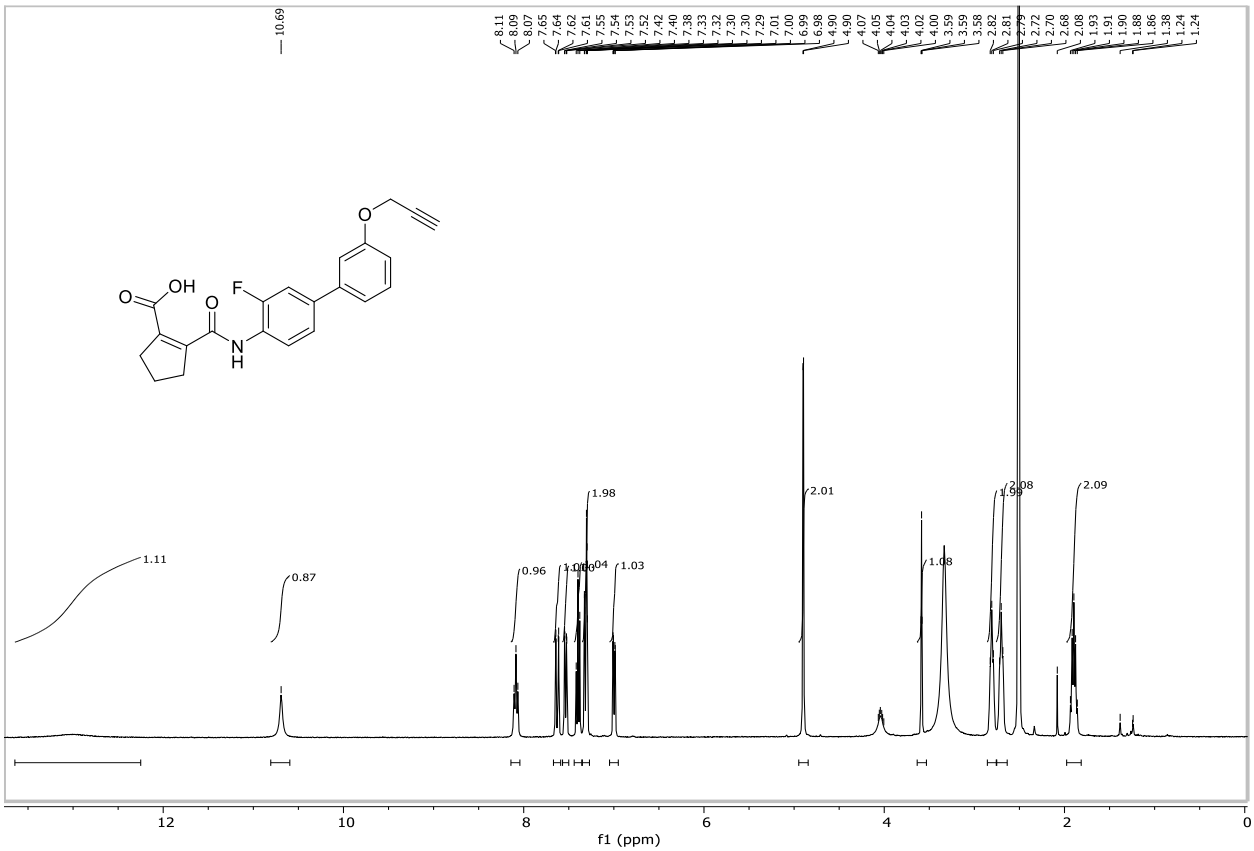
^{1}H-NMR (500 MHz, acetone-d_6) of compound **28**



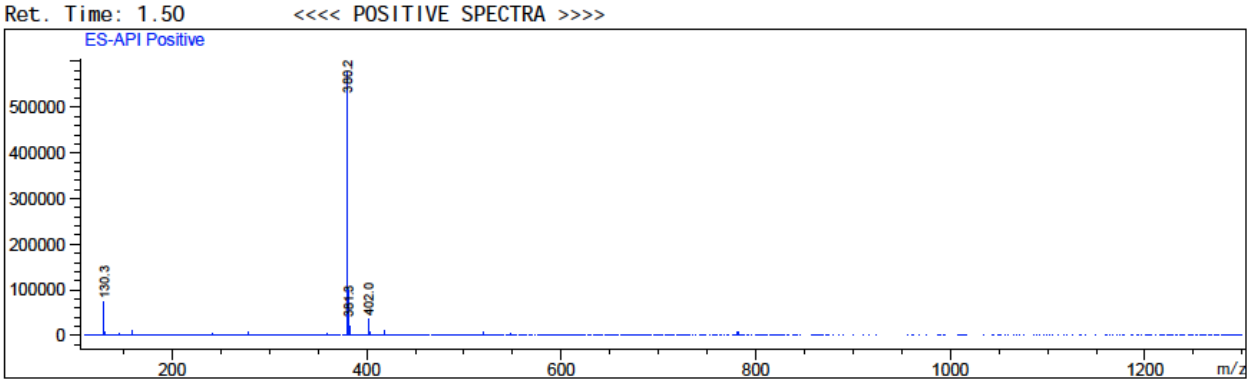
MS of compound **28**



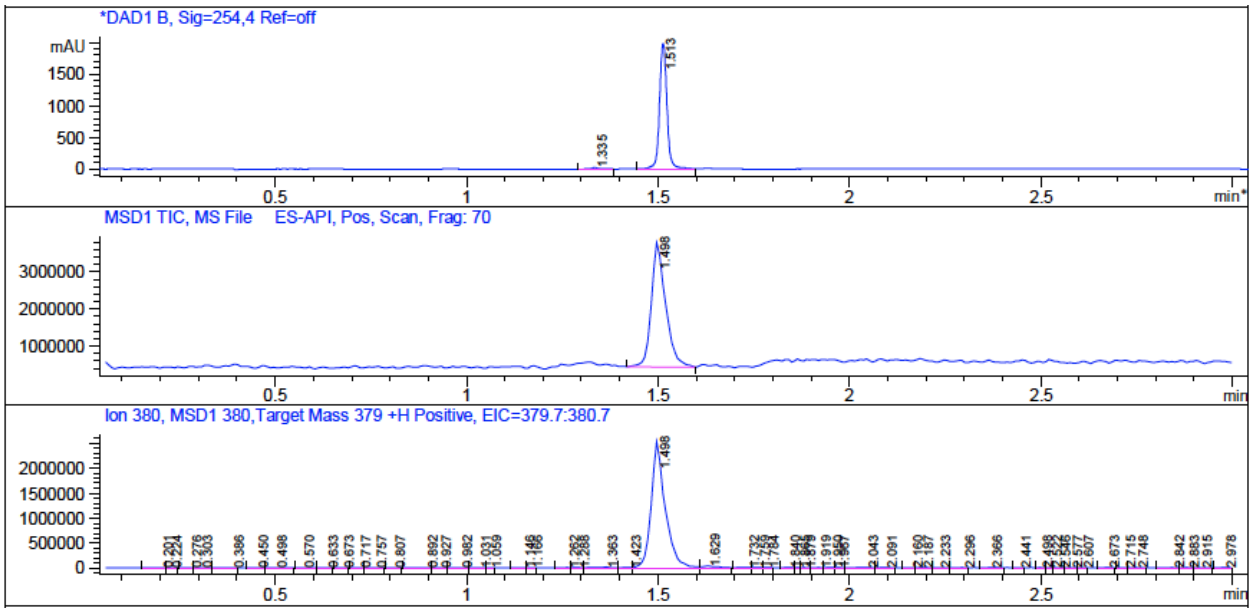
Chromatographic purity analysis of compound **28**



^{1}H-NMR (400 MHz, DMSO-d_6) of compound **29**



MS of compound **29**



Chromatographic purity analysis of compound **29**

Supplementary References

(1) Baumgartner, R.; Walloschek, M.; Kralik, M.; Gotschlich, A.; Tasler, S.; Mies, J.; Leban, J. Dual Binding Mode of a Novel Series of DHODH Inhibitors. *J. Med. Chem.* **2006**, *49* (4), 1239–1247.

(2) Leban, J.; Saeb, W.; Garcia, G.; Baumgartner, R.; Kramer, B. Discovery of a Novel Series of DHODH Inhibitors by a Docking Procedure and QSAR Refinement. *Bioorg. Med. Chem. Lett.* **2004**, *14* (1), 55–58.

(3) Harvey, A. J.; Avery, T. D.; Schaeffer, L.; Joseph, C.; Huff, B. C.; Singh, R.; Morice, C.; Giethlen, B.; Grishin, A. A.; Coles, C. J.; Kolesik, P.; Wagner, S.; Andriambeloson, E.; Huyard, B.; Poiraud, E.; Paul, D.; O'Connor, S. M. Discovery of BNC375, a Potent, Selective, and Orally Available Type i Positive Allosteric Modulator of A7 NAChRs. *ACS Med. Chem. Lett.* **2019**, *10* (5), 754–760.