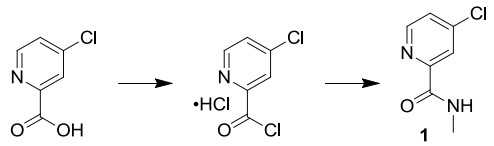
Supplementary Note

Synthetic Procedures

Table of Contents

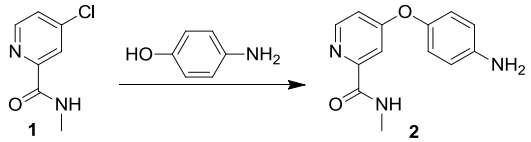
General Chemical Methods. All solvents were purchased from Sigma-Aldrich and were used as received; anhydrous solvents were used for chemical reactions, and HPLC grade solvents were used for aqueous work-ups, recrystallizations and chromatography. Reagents were purchased from various vendors and were used as received. Reactions were run as described in the individual procedures using standard double manifold and syringe techniques. Glassware was dried by baking in an oven at 130 °C for 12h prior to use or was flame-dried. The pH of aqueous solutions was estimated using pH paper. Vacuum filtrations were carried out using a house vacuum line (~100 torr). In the individual procedures, the phrases "concentration under vacuum" and "concentrated to dryness" mean that solvent was removed on a rotary evaporator using a diaphragm pump (with an automatic vacuum regulator) and remaining traces of volatiles were removed on a high-vacuum (<1 torr) oil pump. Unless specified otherwise, the term "flask" refers to the round-bottomed variety. Reactions were monitored by TLC using EMD silica gel 60 F_{254} (250 µm) glass-backed plates (visualized by UV fluorescence quenching and/or stained with basic $KMnO_4$ solution) and by liquid chromatography-tandem mass spectrometry (LC-MS). Analysis by reverse-phase LC-MS was carried out on a Waters Acquity I-Class UPLC system, with a C18 column (2.1 x 30 mm; 1.7 µm particle size), heated at 50 °C, eluted at 0.6 mL/min, and using a 3 min linear gradient method with a mobile phase consisting of water/acetonitrile (0.1% v/v formic acid added to each): 95:5→1:99(0-2.5 min), then 1:99(2.5-3 min). Sample runs were monitored using alternating positive/negative electrospray ionization (50-1000 amu) and UV detection at 254 nm. Dimensions of plugs, pads and columns for filtration or flash chromatography are reported as: ((diameter x length) cm). The 5¾ inch pipets (4 mL) used for filtration and micro scale flash chromatography were purchased from Fisher Scientific (product number 22-378-893). Preparative normal-phase chromatography was carried out with an Interchim PuriFlash 450 purification system with a diode array detector (runs were monitored scanning at 220-400 nm). Pre-packed silica gel cartridges (12, 25 and 40 g; 15 µm particle size) were employed for normal-phase (silica gel) chromatography, eluting at 20-30 mL/min. Preparative reverse-phase chromatography was carried out with an Agilent 1260 Infinity using a C18 column (30 x 100 mm; 5 µm particle size) with a multiwavelength detector, eluting at 40 mL/min with a pressure limit of 200 bar; crude samples were injected with an autosampler, typically in a 90:10 mixture of MeOH/DMSO (1.5 mL/injection). Carbon-decoupled ^{1}H NMR spectra were recorded at 400 MHz on a Bruker spectrometer and are reported in ppm using the residual solvent signal (dimethylsulfoxide-d6 = 2.50 ppm) as an internal standard. Data are reported as: {(shift), [(s=singlet, d=doublet, dd=doublet of doublets, ddd=doublet of a doublet of doublets, t=triplet, dt=doublet of triplets, q=quartet, sept=septet, m=multiplet, br=broad, ap=apparent), (*J*=coupling constant in Hz), (integration)]}. Proton-decoupled ^{13}C NMR spectra were recorded at 100 MHz on a Bruker spectrometer and are reported in ppm using the residual solvent signal (dimethylsulfoxide-d_6 = 39.5 ppm) as an internal standard. Proton-decoupled ^{19}F NMR spectra were recorded at 376 MHz on a Bruker spectrometer and are reported in ppm using added $CFCl_3$ (0.00 ppm) as an internal standard; compounds with only one signal were integrated relative to a known amount of the internal standard.

Synthesis of Sorafenib, Regorafenib and Corresponding Intermediates[1]



4-Chloro-*N*-methylpicolinamide (1).

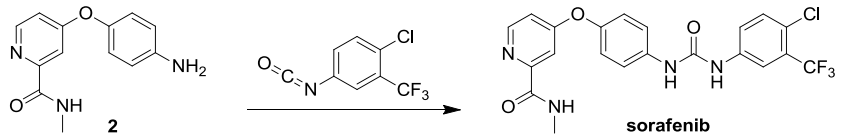
A flame-dried 250 mL flask, cooled under Ar, was charged with 4-chloropicolinic acid (10.0 g, 63.5 mmol), and THF (125 mL). The mixture was cooled to 0 °C and oxalyl chloride (6.70 mL, 79.2 mmol) was added dropwise over 5 min via syringe, followed by DMF (0.1 mL), which was added by syringe in one shot (**CAUTION:** rapid release of gas). After 30 min the reaction mixture was allowed to warm to room temperature and was stirred under a balloon of Ar for 15 h. The resulting brown solution was concentrated on a rotary-evaporator; a drying tube filled with KOH pellets was used to trap residual HCl. The remaining oil was concentrated to dryness from toluene (3 x 10 mL) and then was dried further under high vacuum to provide a solid. The crude 4-chloropicolinoyl chloride hydrochloride salt was placed under Ar and THF (50 mL) was added. The dark solution was cooled to 0 °C and methylamine (160 mL, 2.0 M solution in THF, 320 mmol) was added dropwise over 20 min via syringe. After 5 min the reaction was allowed to warm to room temperature and was stirred for 16 h. The reaction mixture was diluted with water (200 mL) and extracted with EtOAc (3 x 150 mL). The organic extracts were pooled, washed with water (100 mL) and brine (2 x 100 mL), dried (Na_2SO_4) and filtered. Concentration under vacuum gave ~11 g of a red-brown oil, which was purified by silica gel chromatography (40 g cartridge), eluting at 30 mL/min and using a linear gradient of hexanes/EtOAc: 100:0→0:100 over 30 column volumes. The appropriate fractions were pooled and concentrated to dryness. The remaining clear colorless oil (~10 g) was dissolved in a mixture of hexanes/CH_2Cl_2 (4:1; 150 mL) and allowed to stand at –20 °C for 12 h. The resulting precipitate was isolated by vacuum filtration, washed with hexanes (2 x 30 mL) and air-dried to yield 8.90 g (82%) of the title compound as a white solid: **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.85 (br ap d, *J*=3.4 Hz, 1H), 8.62 (dd, *J*=5.3, 0.6 Hz, 1H), 8.01 (dd, *J*=2.2, 0.6 Hz, 1H), 7.75 (dd, *J*=5.3, 2.2 Hz, 1H), 2.82 (d, *J*=4.9 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 163.1, 151.8, 150.0, 144.5, 126.3, 121.8, 26.1; **LC-MS** (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_7H_8ClN_2O$ 171.0; Found 171.1.



4-(4-Aminophenoxy)-*N*-methylpicolinamide (2).

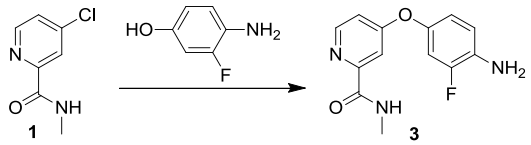
A two-necked 100 mL flask (equipped with an inlet adapter and septum) was flame-dried under vacuum and cooled under Ar. The flask was charged with 4-aminophenol (2.09 g, 19.2 mmol) and DMF (30 mL). To the stirred solution was added potassium *tert*-butoxide (2.14 g, 19.1 mmol) in portions over 1 min. The resulting light-brown mixture was stirred for 2 h, then **1** (2.17 g, 12.7 mmol) was added in one portion, and the reaction was heated at 80 °C for 4 h under a balloon of Ar. The reaction was allowed to cool to room temperature and then was poured into stirred ice-water (100 mL). Stirring was continued for 15 min and then the mixture was extracted with EtOAc (1 x 100 mL and 2 x 50 mL). The organic extracts were pooled, washed with 1 M KOH (3 x 50 mL), water (50 mL) and brine (2 x 50 mL), dried (Na_2SO_4) and filtered. Concentration under vacuum gave 3.23 g of an orange oil, which was purified by silica gel chromatography (40 g cartridge), eluting at 30 mL/min and using a linear gradient of hexanes/EtOAc: 100:0→0:100 over 35 column volumes. Obtained 2.69 g (87%) of the title compound as an off-white solid: **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.73 (br q, *J*=4.6 Hz, 1H), 8.45 (d, *J*=5.6 Hz, 1H), 7.34 (d, *J*=2.5 Hz, 1H), 7.06 (dd, *J*=5.5, 2.6 Hz, 1H), 6.86 (d, *J*=8.8 Hz, 2H), 6.64 (d, *J*=8.8 Hz, 2H), 5.17 (s, 2H), 2.78 (d, *J*=4.9

Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 166.8, 163.9, 152.3, 150.1, 146.9, 142.8, 121.6, 114.9, 113.7, 108.3, 26.0; **LC-MS** (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{14}N_3O_2$ 244.1; Found 244.2.



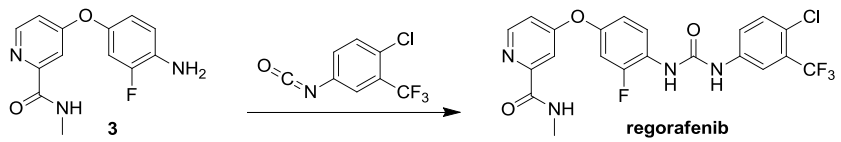
***N*-Methyl-4-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenoxy)picolinamide (sorafenib).**

A solution of 1-chloro-4-isocyanato-2-(trifluoromethyl)benzene (463 mg, 2.09 mmol) and CH_2Cl_2 (5 mL) was added to a solution of **2** (500 mg, 2.06 mmol) and CH_2Cl_2 (5 mL), in a 20 mL vial under Ar. Stirred for 24 h and isolated the product by vacuum filtration; washed with CH_2Cl_2 (x2) and air-dried. Obtained 889 mg (93%) of the title compound as a white powder: **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 9.00 (s, 1H), 8.76 (br q, *J*=4.9 Hz, 1H), 8.50 (d, *J*=5.6 Hz, 1H), 8.12 (d, *J*=2.4 Hz, 1H), 7.69-7.56 (m, 4H), 7.38 (d, *J*=2.4 Hz, 1H), 7.17 (d, *J*=9.0 Hz, 2H), 7.15 (dd, *J*=5.6, 2.7 Hz, 1H), 2.78 (d, *J*=4.9 Hz, 3H); **^{19}F NMR** (376 MHz, DMSO-d_6) δ -61.0 (s, 3F); **LC-MS** (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{17}ClF_3N_4O_3$ 465.1; Found 465.3.



4-(4-Amino-3-fluorophenoxy)-*N*-methylpicolinamide (3).

An oven-dried two-necked 100 mL flask (equipped with an inlet adapter and septum), under Ar, was charged with 4-amino-3-fluorophenol (1.12 g, 8.81 mmol) and DMF (18 mL). To the stirred solution was added potassium *tert*-butoxide (978 mg, 8.72 mmol) in portions over 2 min. The resulting dark-purple mixture was stirred for 3 h, then **1** (1.06 g, 6.21 mmol) was added in one portion, and the reaction was heated at 90 °C for 10 h under a balloon of Ar. The reaction was allowed to cool to room temperature and then was poured into stirred ice-water (50 mL). Stirring was continued for 15 min and then the mixture was extracted with EtOAc (3 x 50 mL). The organic extracts were pooled, washed with 1 M KOH (3 x 50 mL), water (50 mL) and brine (2 x 50 mL), dried (Na_2SO_4) and filtered. Concentration under vacuum gave a brown solid, which was purified by silica gel chromatography (40 g cartridge), eluting at 30 mL/min and using a linear gradient of hexanes/EtOAc: 100:0→0:100 over 38 column volumes. Obtained 882 mg (54%) of the title compound as a light-brown solid: **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.74 (br q, *J*=4.6 Hz, 1H), 8.47 (d, *J*=5.6 Hz, 1H), 7.35 (d, *J*=2.5 Hz, 1H), 7.09 (dd, *J*=5.6, 2.7 Hz, 1H), 7.01 (dd, *J*=11.9, 2.6 Hz, 1H), 6.81-6.89 (m, 1H), 6.76-6.80 (m, 1H), 5.22 (br s, 2H), 2.78 (d, *J*=4.9 Hz, 3H); **^{19}F NMR** (376 MHz, DMSO-d_6) δ -130.7 (s, 1F); **LC-MS** (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{13}FN_3O_2$ 262.1; Found 262.1.

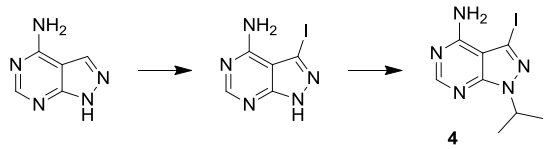


4-(4-(3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido)-3-fluorophenoxy)-*N*-methylpicolinamide (regorafenib).

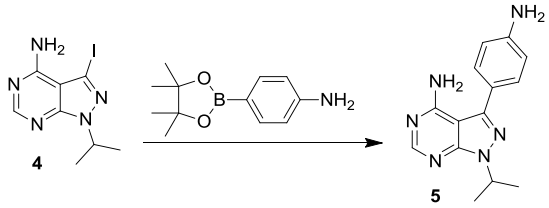
A solution of 1-chloro-4-isocyanato-2-(trifluoromethyl)benzene (384 mg, 1.73 mmol) and CH_2Cl_2 (2.5 mL) was added to a solution of **3** (450 mg, 1.72 mmol) and CH_2Cl_2 (2.5 mL), in an 8 mL vial under Ar. Stirred for 24 h and isolated the product by vacuum filtration; washed with CH_2Cl_2 (x2) and air-dried. Obtained 720 mg (87%) of the title compound as a white powder: **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.52 (s, 1H), 8.78 (br q, *J*=4.8 Hz, 1H), 8.73 (d, *J*=1.0 Hz, 1H), 8.53 (d, *J*=5.6 Hz, 1H), 8.10-8.20 (m, 2H), 7.63 (s, 2H), 7.42 (d, *J*=2.5 Hz, 1H), 7.34 (dd, *J*=11.5, 2.7 Hz, 1H), 7.18 (dd, *J*=5.5, 2.6 Hz, 1H), 7.07 (dd, *J*=8.8, 1.5

Hz, 1H), 2.79 (d, *J*=4.9 Hz, 3H); **^{19}F NMR** (376 MHz, DMSO-d_6) δ -61.1 (s, 3F), -124.0 (s, 1F); **LC-MS** (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{16}ClF_4N_4O_3$ 483.1; Found 483.2.

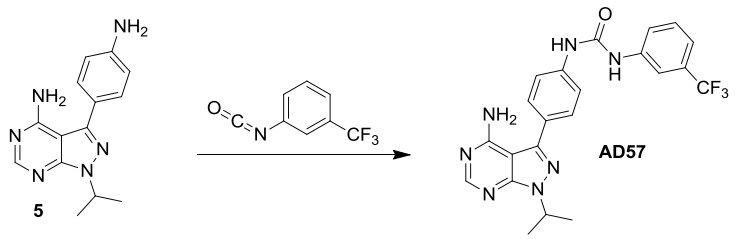
Synthesis of AD-series and Corresponding Intermediates[2]



3-Iodo-1-isopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (4).
A flame-dried 100 mL flask, cooled under Ar, was charged with 1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (5.00 g, 37.0 mmol), *N*-iodosuccinimide (12.5 g, 55.6 mmol) and DMF (40 mL). The mixture was heated at 80 °C, under a balloon of Ar, for 22 h. The reaction mixture was allowed to cool to room temperature, diluted with water (40 mL) and stirred for 20 min. The solid was collected by vacuum filtration, washed with water (3 x 10 mL) and air-dried to provide 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (8.16 g, 31.3 mmol) as an off-white solid. The solid was added to a flame-dried 200 mL flask, under Ar, followed by oven-dried K_2CO_3 (5.19 g, 37.6 mmol) and DMF (60 mL). 2-Bromopropane (3.00 mL, 32.0 mmol) was added by syringe in a steady stream and the mixture was heated at 80 °C under a balloon of Ar for 18 h. The reaction was allowed to cool to room temperature, diluted with water (150 mL) and extracted with EtOAc (3 x 150 mL). The organic extracts were pooled, washed with water (2 x 100 mL) and brine (2 x 100 mL), dried (Na_2SO_4) and filtered. Concentration under vacuum gave an orange solid, which was recrystallized from MeOH (~100 mL). The solid was isolated by vacuum filtration, washed with EtOH (25 mL) and hexanes (2 x 25 mL), and then air-dried. Obtained 6.13 g (65% over two steps) of the title compound as white needles: **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 8.19 (s, 1H), 7.19 (br s, 2H), 4.96 (sept, *J*=6.7 Hz, 1H), 1.42 (d, *J*=6.6 Hz, 6H); **LC-MS** (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_8H_{11}IN_5$ 304.0, found 304.2.

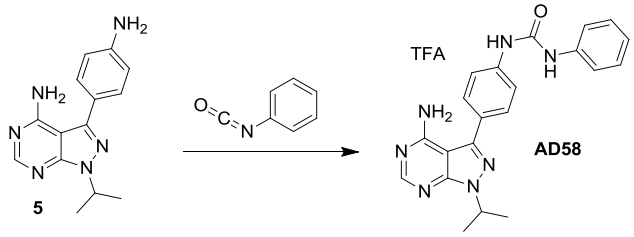


3-(4-Aminophenyl)-1-isopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (5).
A 40 mL vial was charged with **4** (618 mg, 2.04 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (581 mg, 2.65 mmol), Na_2CO_3 (650 mg, 6.13 mmol) and tetrakis(triphenylphosphine)-palladium(0) (118 mg, 0.102 mmol), then 1,4-dioxane (16 mL) and water (4 mL) were added (both solvents were deoxygenated by sparging with Ar for 10 min). The headspace was purged with Ar, the vial was sealed with a screwcap and the reaction mixture was heated at 90 °C for 24 h. After the reaction had cooled to room temperature it was diluted with a mixture (95:5) of CH_2Cl_2/MeOH (15 mL) and water (5 mL), and then vacuum filtered through a pad (3 x 3 cm) of Celite; the pad was washed with CH_2Cl_2 (2 x 10 mL). The combined filtrates were transferred to a separatory funnel, diluted with brine (40 mL) and the layers were separated; the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The organic extracts were pooled, dried (Na_2SO_4), filtered and concentrated to dryness. The remaining semi-solid was purified by silica gel chromatography (25 g cartridge), eluting at 25 mL/min and using a linear gradient of CH_2Cl_2/MeOH: 100:0→90:10 over 30 column volumes. Obtained 520 mg (95%) of the title compound as an off-white solid: **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 8.19 (s, 1H), 7.31 (d, *J*=8.6 Hz, 2H), 6.70 (d, *J*=8.6 Hz, 2H), 5.41 (br s, 2H), 5.01 (sept, *J*=6.7 Hz, 1H), 1.46 (d, *J*=6.6 Hz, 6H), the signal corresponding to the $-NH_2$ group on the pyrimidine ring was not well resolved due to broadening into the baseline, but it appears to span the region 5.75-7.75 ppm; **LC-MS** (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{17}N_6$ 269.2, found 269.4.



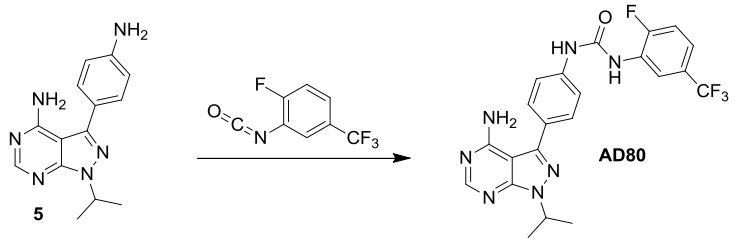
1-(4-(4-Amino-1-isopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-3-(3-(trifluoromethyl)phenyl)urea (AD57).

An 8 mL vial with sepcap, under Ar, was charged with **5** (110 mg, 0.410 mmol) and CH_2Cl_2 (4 mL) under Ar. The mixture was cooled to 0°C and 3-(trifluoromethyl)phenyl isocyanate (60.0 uL, 0.435 mmol) was added dropwise over 1 min. The reaction was allowed to warm to room temperature over night and was stirred for a total of 12 h. The reaction mixture was adsorbed onto silica gel (~1 g) and purified by silica gel chromatography (25 g cartridge), eluting at 20 mL/min and using a linear gradient of CH_2Cl_2/MeOH: 100:0→90:10 over 32 column volumes. Obtained 74.7 mg (40%) of the title compound as a white solid: **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 9.10 (s, 1H), 9.03 (s, 1H), 8.23 (s, 1H), 8.05 (s, 1H), 7.56-7.69 (m, 5H), 7.49-7.56 (m, 1H), 7.33 (d, *J*=7.6 Hz, 1H), 5.06 (sept, *J*=6.8 Hz, 1H), 1.49 (d, *J*=6.6 Hz, 6H); **^{19}F NMR** (376 MHz, DMSO-d_6) δ -60.8 (s, 3F); **LC-MS** (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{21}F_3N_7O$ 456.2; Found 456.7.



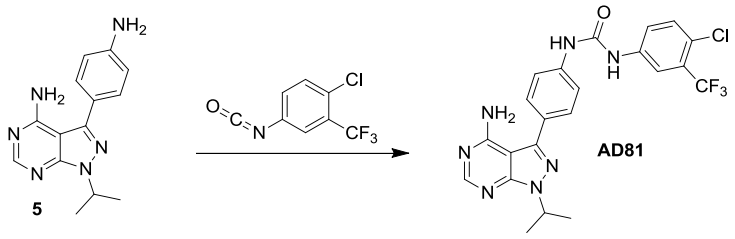
1-(4-(4-Amino-1-isopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-3-phenylurea 2,2,2-trifluoroacetate (AD58).

An 8 mL vial with sepcap, under Ar, was charged with **5** (110 mg, 0.410 mmol) and CH_2Cl_2 (4 mL). The mixture was cooled to 0°C and phenyl isocyanate (45.0 uL, 0.414 mmol) was added dropwise over 2 min. The reaction was allowed to warm to room temperature over night and was stirred for a total of 12 h. The reaction mixture was concentrated to dryness and purified by reverse-phase chromatography, eluting at 40 mL/min and using a linear gradient of H_2O (with 0.1% v/v TFA)/MeCN: 90:10→1:99 over 16 minutes. Obtained 20.0 mg (10%) of the title compound as a white solid: **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 9.07 (s, 1H), 8.87 (s, 1H), 8.38 (s, 1H), 7.63-7.70 (m, 2H), 7.56-7.62 (m, 2H), 7.49 (dd, *J*=8.6, 1.0 Hz, 2H), 7.25-7.34 (m, 2H), 6.95-7.02 (m, 1H), 5.09 (sept, *J*=6.7 Hz, 2H), 1.51 (d, *J*=6.8 Hz, 6H), a minor impurity was observed in the range 7.00-7.25 ppm, X=impurity; **^{13}C NMR** (100 MHz, DMSO-d_6) δ 158.1, 155.4, 153.2, 152.4, 143.1, 140.1, 139.6, 128.8, 126.5, 121.9, 118.4, 118.2, 97.4, 48.0, 21.8; **^{19}F NMR** (376 MHz, DMSO-d_6) δ -73.8 (s, 3F); **LC-MS** (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{22}N_7O$ 388.2; Found 388.3.



1-(4-(4-Amino-1-isopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-3-(2-fluoro-5-(trifluoromethyl)phenyl)urea (AD80).

An 8 mL vial with sepcap, under Ar, was charged with **5** (110 mg, 0.410 mmol) and CH_2Cl_2 (4 mL). The mixture was cooled to 0°C and 2-fluoro-5-(trifluoromethyl)phenyl isocyanate (60.0 uL, 0.415 mmol) was added dropwise over 2 min. The reaction was allowed to warm to room temperature over night and was stirred for a total of 12 h. The reaction mixture was adsorbed onto silica gel (~1 g) and purified by silica gel chromatography (25 g cartridge), eluting at 20 mL/min and using a linear gradient of CH_2Cl_2/MeOH: 100:0→90:10 over 32 column volumes. Obtained 38.8 mg (20%) of the title compound as a white solid: **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 9.39 (s, 1H), 8.96 (d, *J*=2.4 Hz, 1H), 8.65 (dd, *J*=7.3, 2.2 Hz, 1H), 8.23 (s, 1H), 7.63-7.67 (m, 2H), 7.59-7.63 (m, 2H), 7.51 (dd, *J*=10.3, 8.8 Hz, 1H), 7.37-7.44 (m, 1H), 5.06 (sept, *J*=6.7 Hz, 1H), 1.49 (d, *J*=6.6 Hz, 6H); **^{19}F NMR** (376 MHz, DMSO-d_6) δ -60.2 (s, 3F), -123.7 (s, 1F); **LC-MS** (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{20}F_4N_7O$ 474.2; Found 474.3.



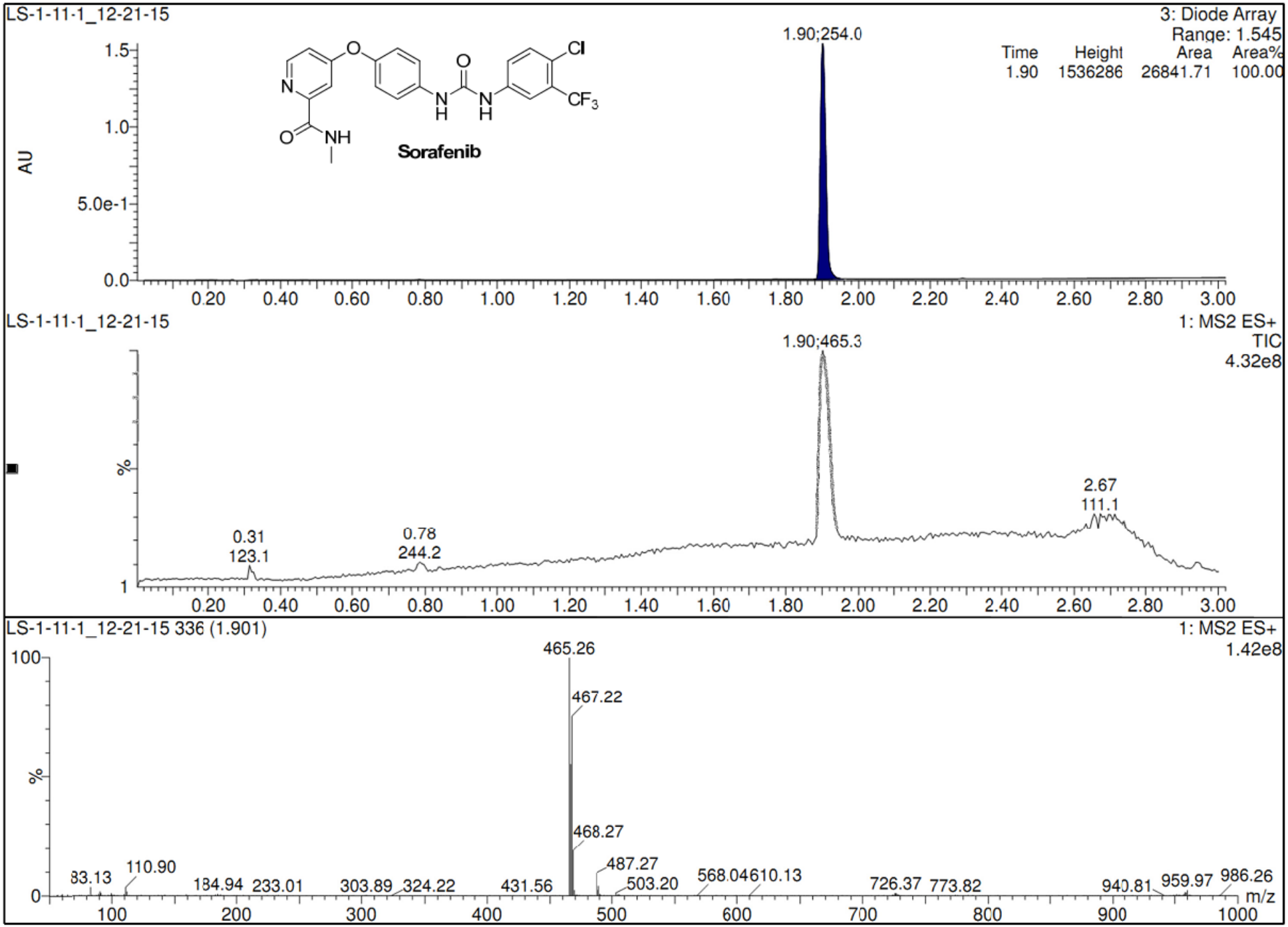
1-(4-(4-Amino-1-isopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (AD81).

An 8 mL vial with sepcap, under Ar, was charged with **5** (110 mg, 0.410 mmol) and CH_2Cl_2 (3 mL). The mixture was cooled to 0°C and a solution of 4-chloro-3-(trifluoromethyl)phenyl isocyanate (91.0 mg, 0.411 mmol) and CH_2Cl_2 (1 mL) was added dropwise over 2 min. The reaction was allowed to warm to room temperature over night and was stirred for a total of 12 h. The reaction mixture was adsorbed onto silica gel (~1 g) and purified by silica gel chromatography (25 g cartridge), eluting at 20 mL/min and using a linear gradient of CH_2Cl_2/MeOH: 100:0→90:10 over 32 column volumes. Obtained 36.2 mg (18%) of the title compound as a white solid: **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 9.23 (s, 1H), 9.09 (s, 1H), 8.23 (s, 1H), 8.14 (d, *J*=2.4 Hz, 1H), 7.56-7.70 (m, 6H), 5.05 (sept, *J*=6.6 Hz, 1H), 1.49 (d, *J*=6.6 Hz, 6H); **^{19}F NMR** (376 MHz, DMSO-d_6) δ -61.0 (s, 3F); **LC-MS** (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{20}ClF_3N_7O$ 490.1; Found 490.4.

References

1. D. Bankston, J. Dumas, R. Natero, B. Riedl, M.-K. Monahan, R. Sibley, A scalable synthesis of BAY 43-9006: a potent Raf kinase inhibitor for the treatment of cancer. *Org. Process Res. Dev.* **6**, 777–781 (2002).
2. Dar, A. C., Das, T. K., Shokat, K. M. & Cagan, R. L. Chemical genetic discovery of targets and anti-targets for cancer polypharmacology. *Nature* **486**, 80-84, doi:10.1038/nature11127 (2012).

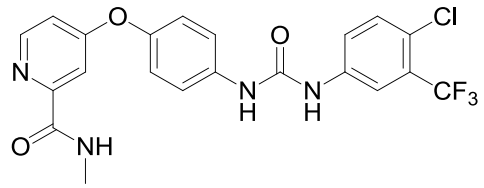
LC-MS and ^{1}H NMR Spectra

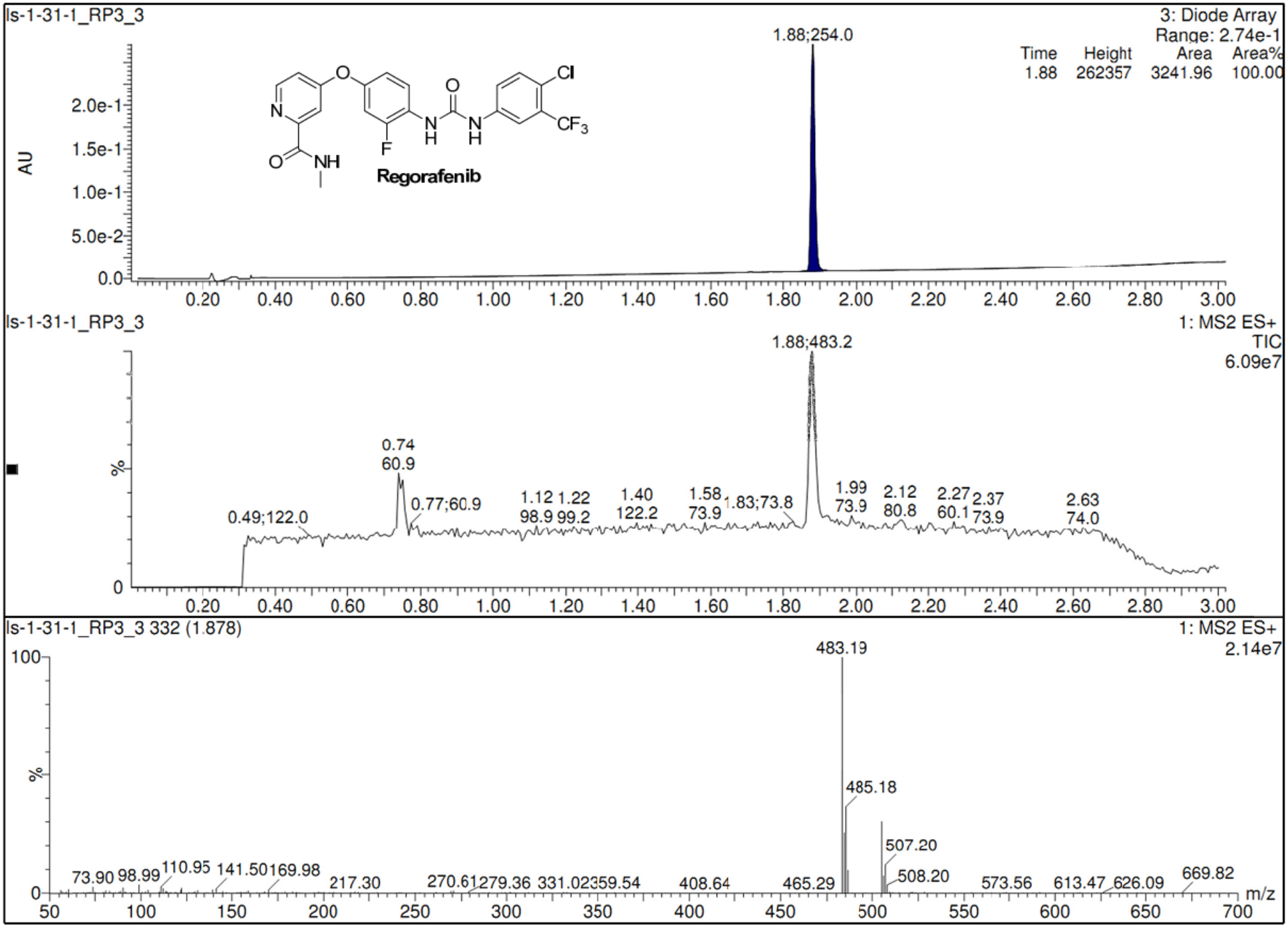

LS-1-11-1_12-21-15
3: Diode Array
Range: 1.545
1.90;254.0
Time Height Area Area%
1.90 1536286 26841.71 100.00
AU
Sorafenib
LS-1-11-1_12-21-15
1: MS2 ES+
TIC
4.32e8
1.90;465.3
0.31
123.1
0.78
244.2
2.67
111.1
%
LS-1-11-1_12-21-15 336 (1.901)
1: MS2 ES+
1.42e8
465.26
467.22
468.27
487.27
503.20
568.04610.13
726.37
773.82
940.81
959.97
986.26
83.13
110.90
184.94
233.01
303.89
324.22
431.56
m/z

Sorafenib

^{1}H NMR 400 MHz

DMSO-d_6

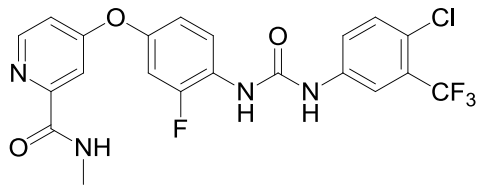


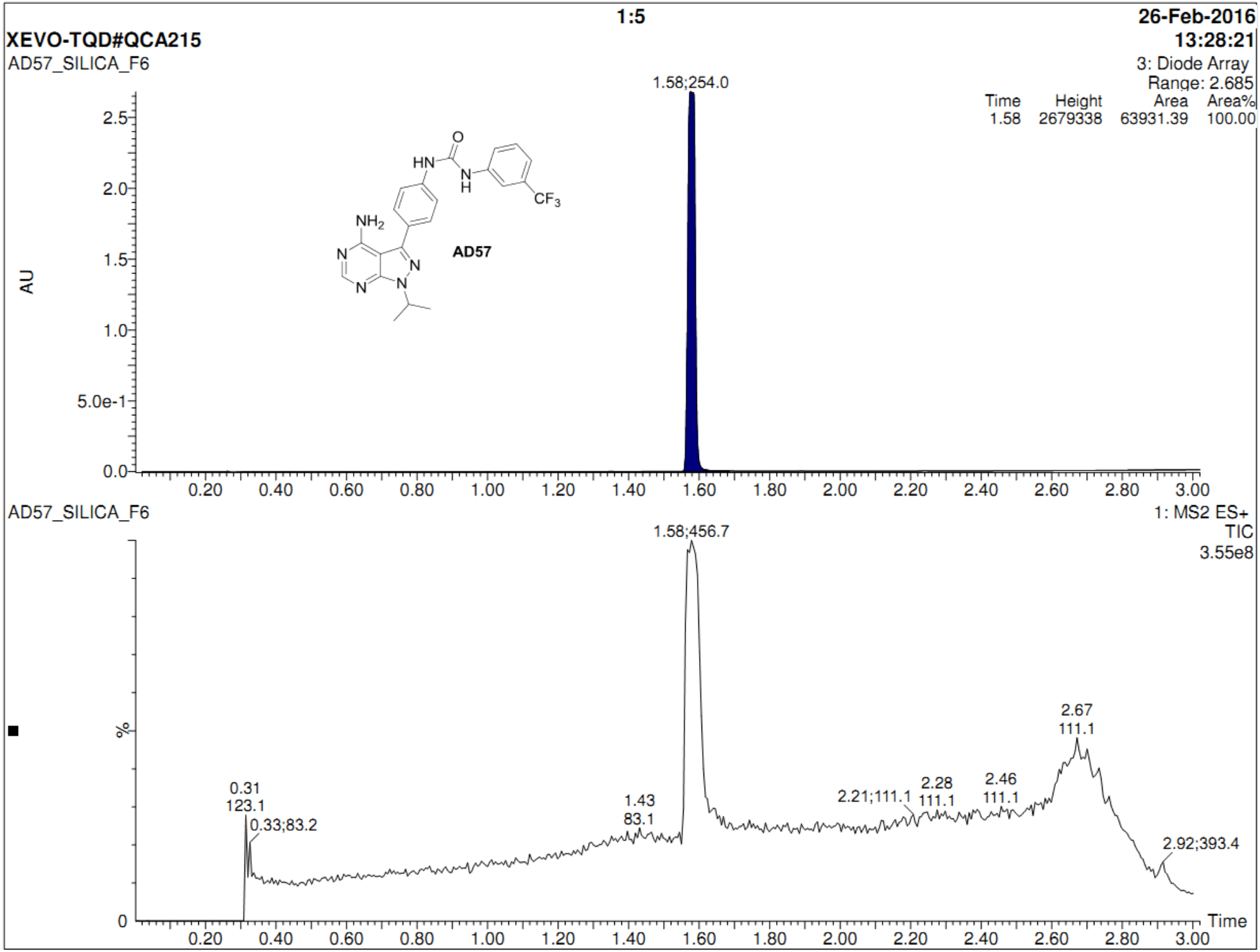

ls-1-31-1_RP3_3
3: Diode Array
Range: 2.74e-1
Time Height Area Area%
1.88 262357 3241.96 100.00
1.88;254.0
AU
Regorafenib
ls-1-31-1_RP3_3
1: MS2 ES+
TIC
6.09e7
1.88;483.2
0.74
60.9
0.77;60.9
0.49;122.0
1.12 1.22
98.9 99.2
1.40
122.2
1.58
73.9
1.83;73.8
1.99
73.9
2.12
80.8
2.27
60.1
2.37
73.9
2.63
74.0
%
ls-1-31-1_RP3_3 332 (1.878)
1: MS2 ES+
2.14e7
483.19
485.18
507.20
508.20
73.90 98.99 110.95 141.50 169.98 217.30 270.61 279.36 331.02 359.54 408.64 465.29 573.56 613.47 626.09 669.82
m/z

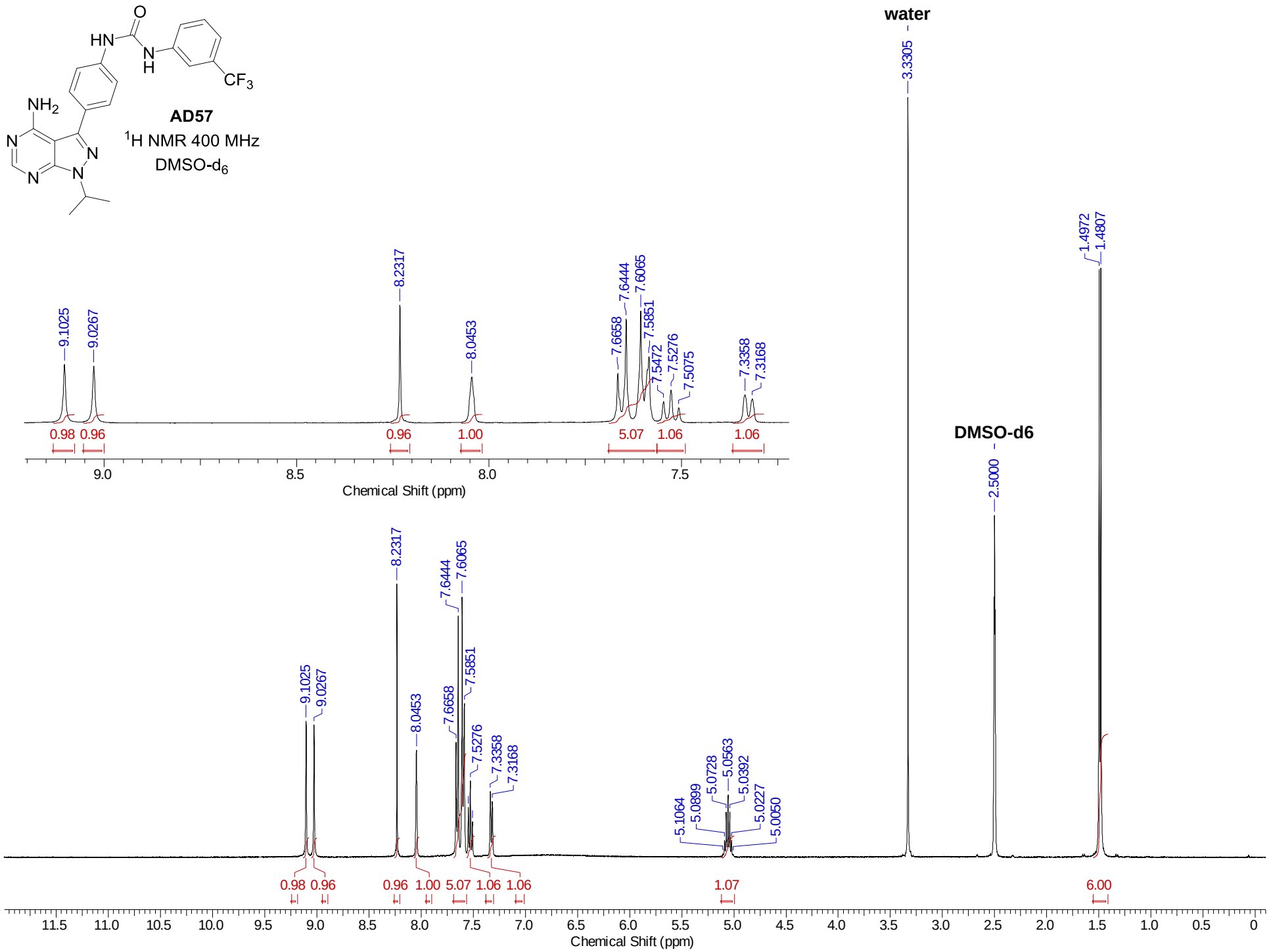
Regorafenib

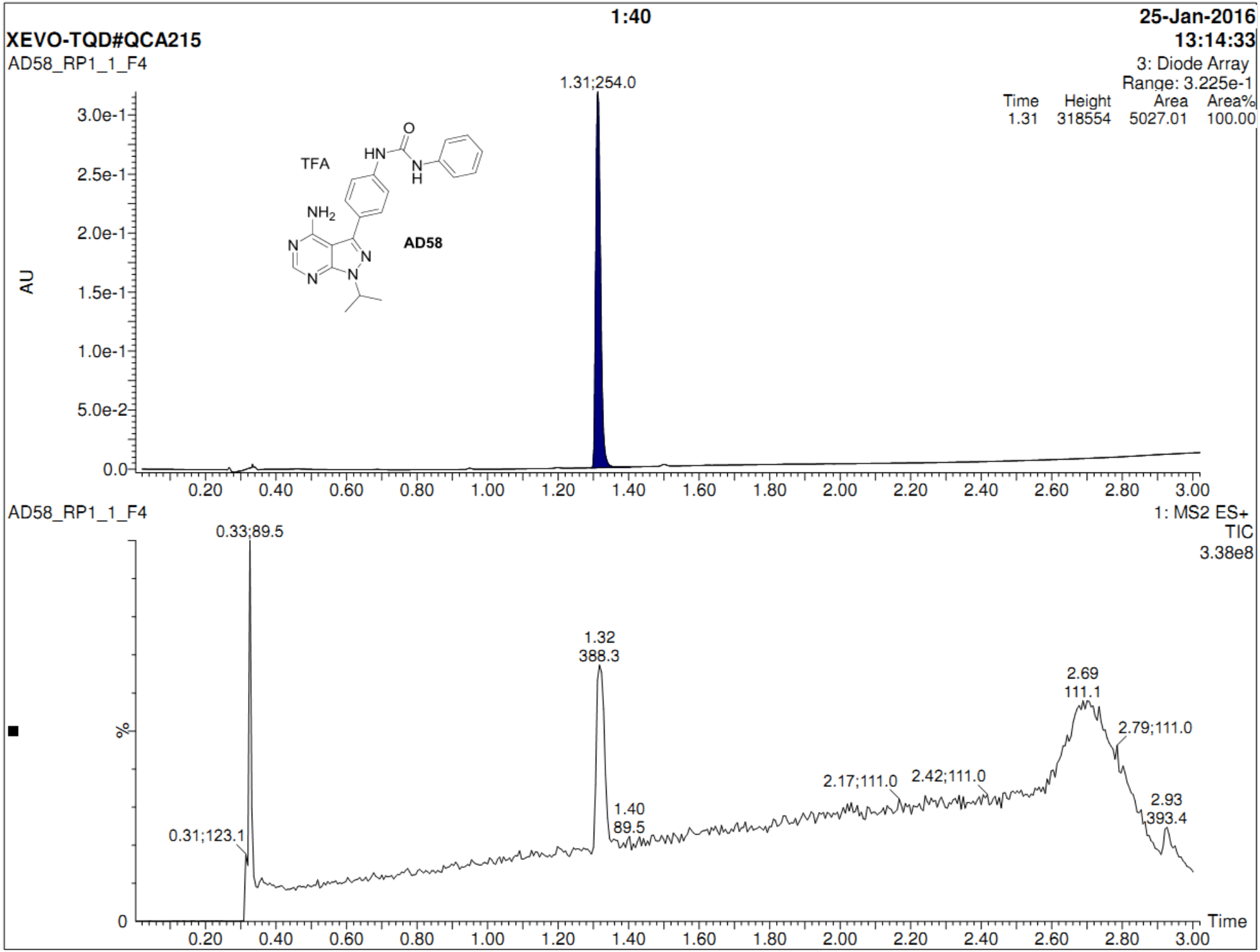
^{1}H NMR 400 MHz

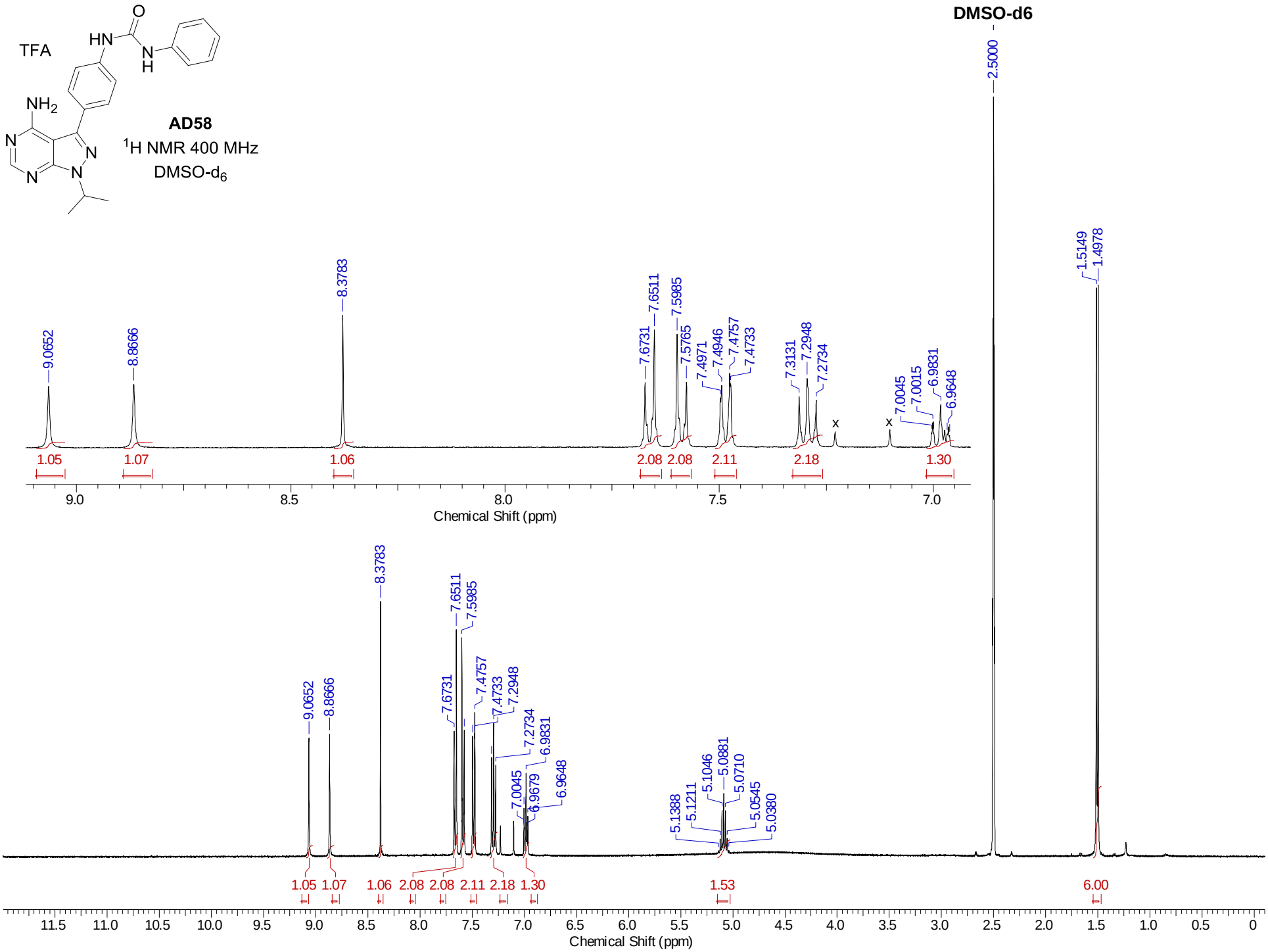
DMSO-d_6

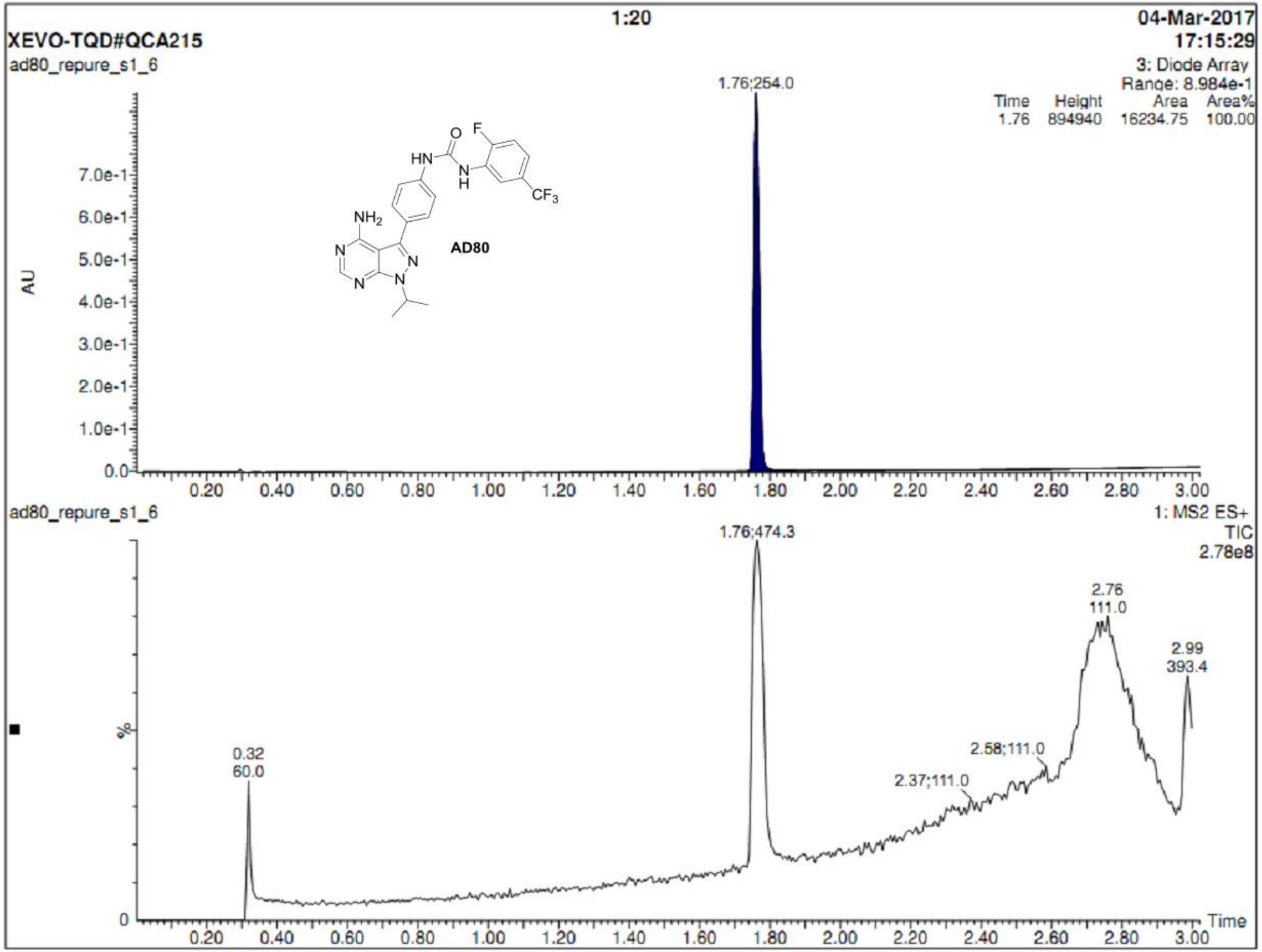


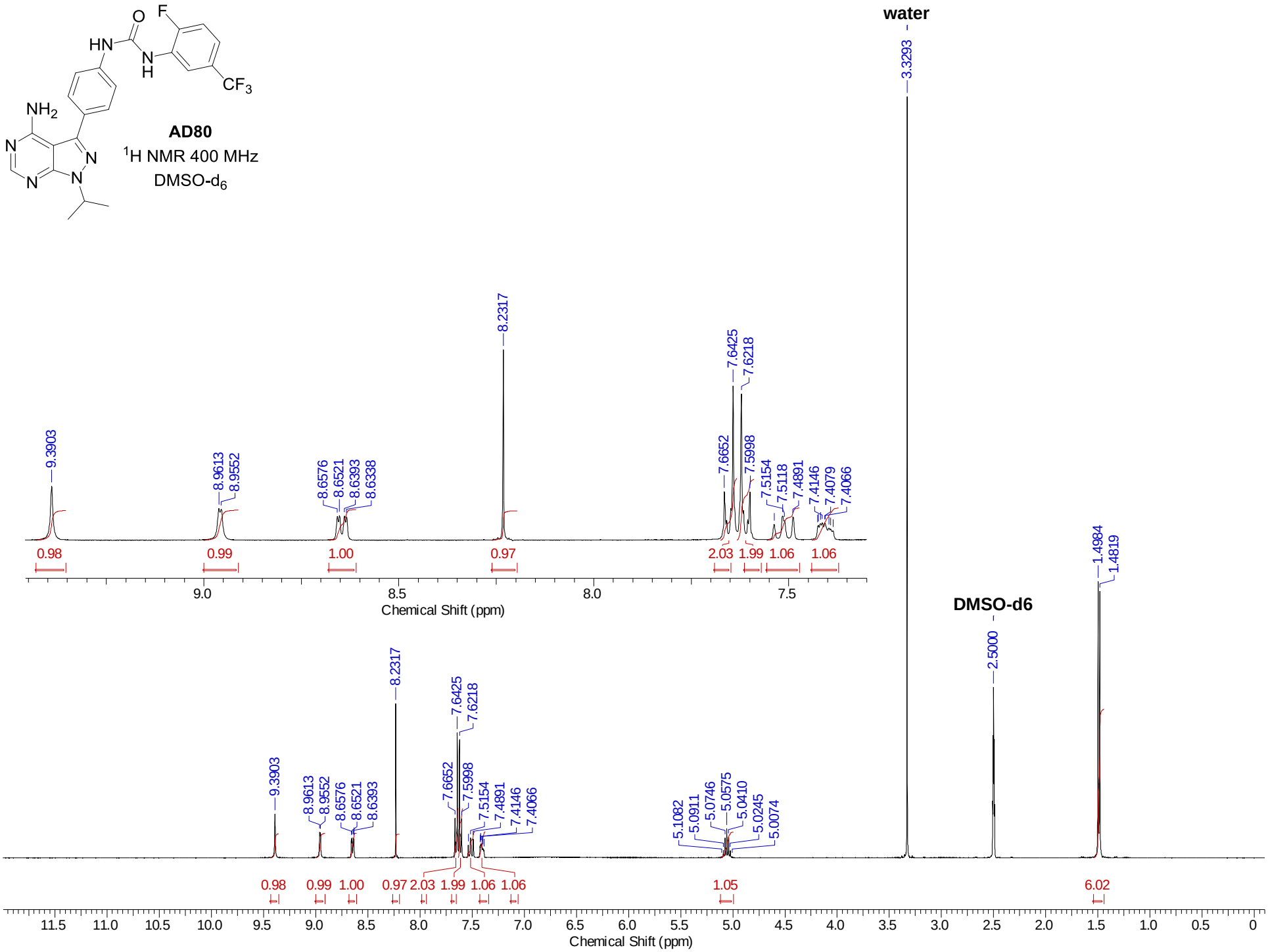

1:5
26-Feb-2016
XEVO-TQD#QCA215
13:28:21
AD57_SILICA_F6
3: Diode Array
Range: 2.685
Time Height Area Area%
1.58 2679338 63931.39 100.00
1.58;254.0
AD57
AU
AD57_SILICA_F6
1: MS2 ES+
TIC
3.55e8
1.58;456.7
0.31
123.1
0.33;83.2
1.43
83.1
2.21;111.1
2.28
111.1
2.46
111.1
2.67
111.1
2.92;393.4
%
Time

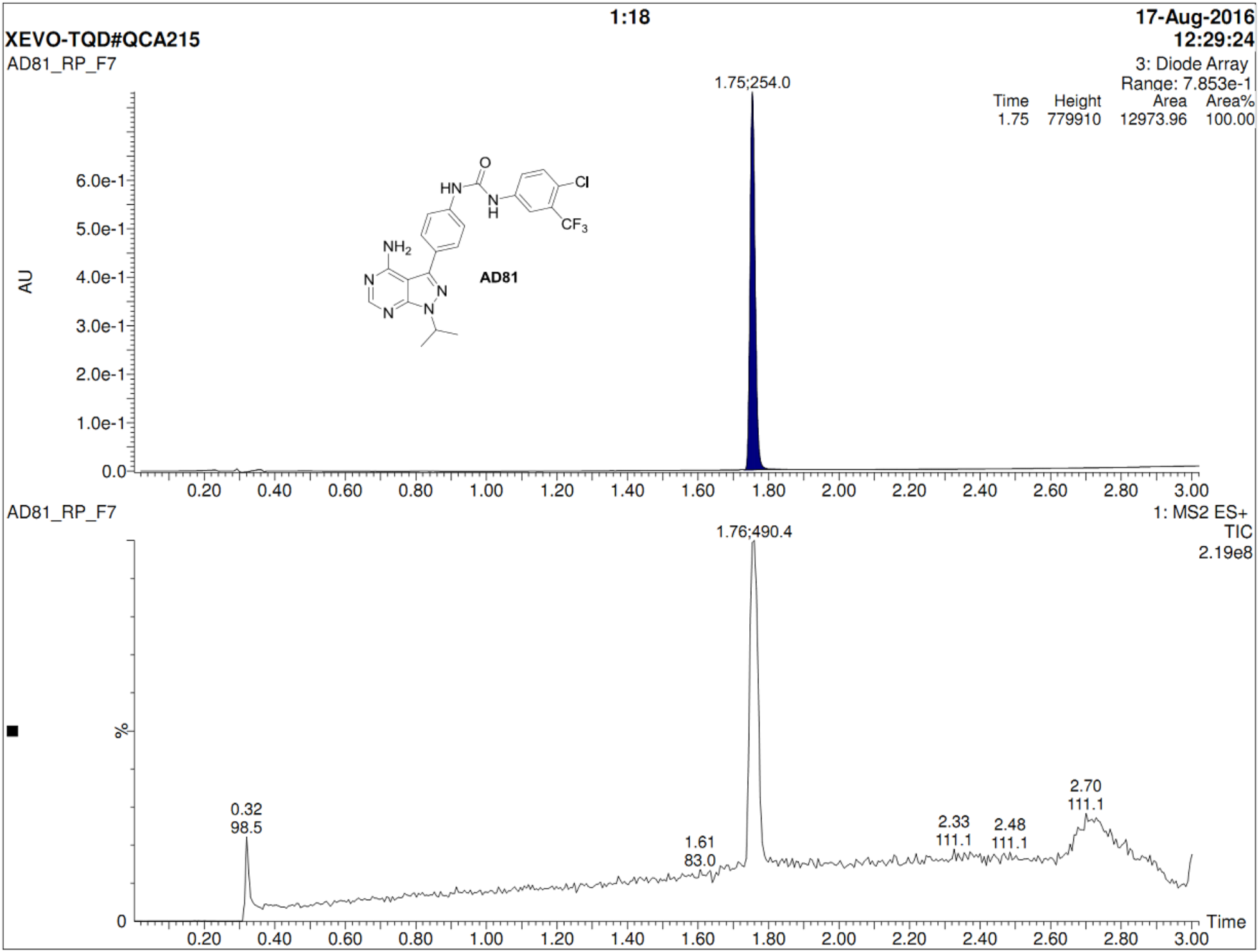

AD57
1H NMR 400 MHz
DMSO-d6
water
DMSO-d6
Chemical Shift (ppm)

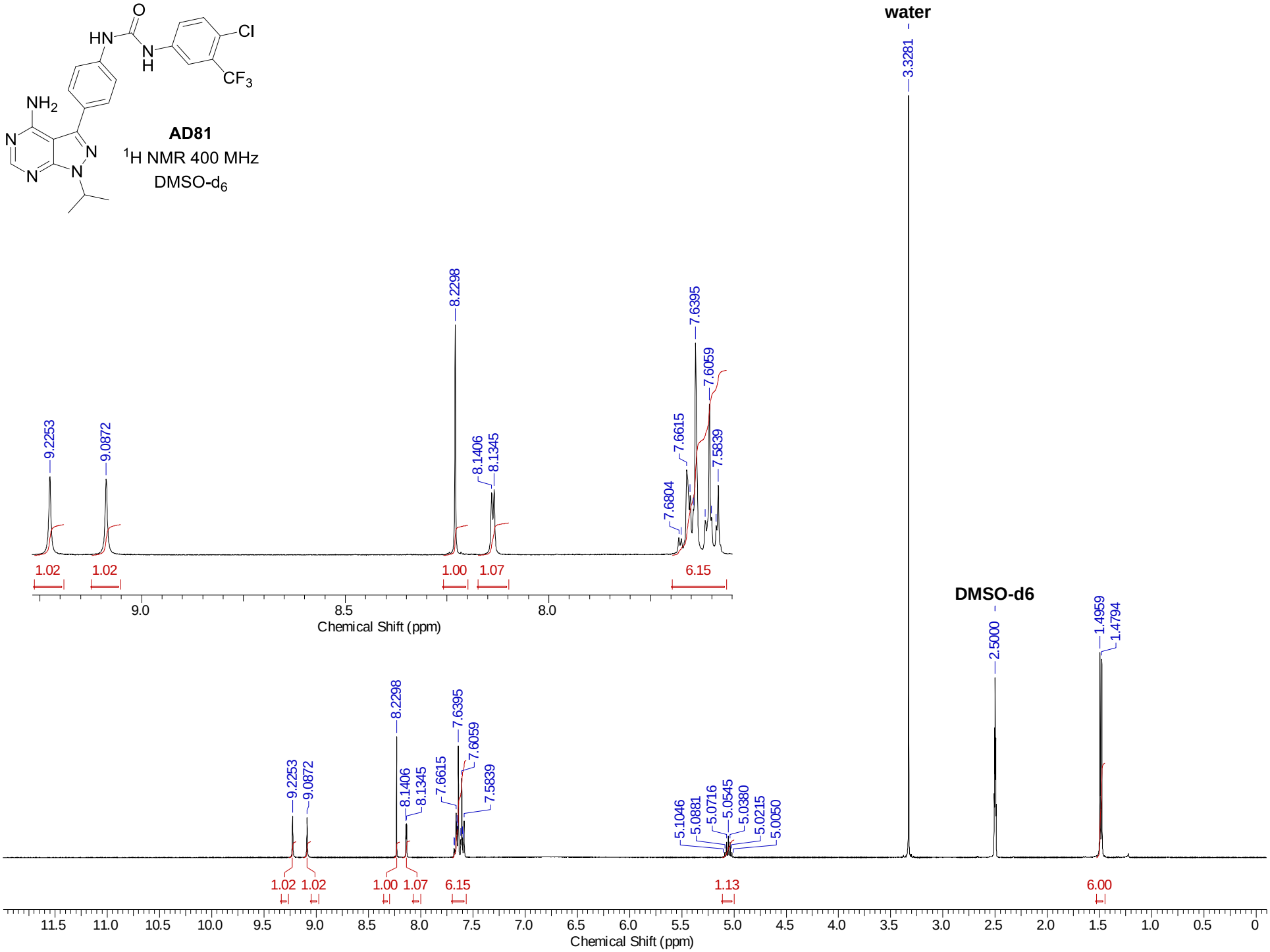

1:40
25-Jan-2016
13:14:33
XEVO-TQD#QCA215
AD58_RP1_1_F4
3: Diode Array
Range: 3.225e-1
Time Height Area Area%
1.31 318554 5027.01 100.00
1.31;254.0
TFA
AD58
AU
3.0e-1
2.5e-1
2.0e-1
1.5e-1
1.0e-1
5.0e-2
0.0
0.20 0.40 0.60 0.80 1.00 1.20 1.40 1.60 1.80 2.00 2.20 2.40 2.60 2.80 3.00
AD58_RP1_1_F4
1: MS2 ES+
TIC
3.38e8
0.33;89.5
1.32
388.3
2.69
111.1
2.79;111.0
2.17;111.0
2.42;111.0
2.93
393.4
1.40
89.5
0.31;123.1
%
0
Time
0.20 0.40 0.60 0.80 1.00 1.20 1.40 1.60 1.80 2.00 2.20 2.40 2.60 2.80 3.00


TFA
HN
O
N
H
NH2
N
N
N
N
AD58
1H NMR 400 MHz
DMSO-d6
DMSO-d6
2.5000
1.5149
1.4978
9.0652
8.8666
8.3783
7.6731
7.6511
7.5985
7.5765
7.4971
7.4946
7.4757
7.4733
7.3131
7.2948
7.2734
7.0045
7.0015
6.9831
6.9679
6.9648
5.1388
5.1211
5.1046
5.0881
5.0710
5.0545
5.0380
1.05
1.07
1.06
2.08
2.08
2.11
2.18
1.30
1.53
6.00
Chemical Shift (ppm)


1:20
04-Mar-2017
17:15:29
XEVO-TQD#QCA215
ad80_repure_s1_6
3: Diode Array
Range: 8.984e-1
Time Height Area Area%
1.76 894940 16234.75 100.00
1.76;254.0
AD80
AU
7.0e-1
6.0e-1
5.0e-1
4.0e-1
3.0e-1
2.0e-1
1.0e-1
0.0
0.20 0.40 0.60 0.80 1.00 1.20 1.40 1.60 1.80 2.00 2.20 2.40 2.60 2.80 3.00
ad80_repure_s1_6
1: MS2 ES+
TIC
2.78e8
1.76;474.3
2.76
111.0
2.99
393.4
2.58;111.0
2.37;111.0
0.32
60.0
%
0
Time
0.20 0.40 0.60 0.80 1.00 1.20 1.40 1.60 1.80 2.00 2.20 2.40 2.60 2.80 3.00


AD80
1H NMR 400 MHz
DMSO-d6
water
DMSO-d6
Chemical Shift (ppm)
Chemical Shift (ppm)


1:18
17-Aug-2016
12:29:24
XEVO-TQD#QCA215
AD81_RP_F7
3: Diode Array
Range: 7.853e-1
Time Height Area Area%
1.75 779910 12973.96 100.00
1.75;254.0
AU
6.0e-1
5.0e-1
4.0e-1
3.0e-1
2.0e-1
1.0e-1
0.0
0.20 0.40 0.60 0.80 1.00 1.20 1.40 1.60 1.80 2.00 2.20 2.40 2.60 2.80 3.00
AD81
AD81_RP_F7
1: MS2 ES+
TIC
2.19e8
1.76;490.4
%
0.32
98.5
1.61
83.0
2.33
111.1
2.48
111.1
2.70
111.1
0
Time
0.20 0.40 0.60 0.80 1.00 1.20 1.40 1.60 1.80 2.00 2.20 2.40 2.60 2.80 3.00


AD81
1H NMR 400 MHz
DMSO-d6
water
3.3281
DMSO-d6
2.5000
1.4959
1.4794
9.2253
9.0872
8.2298
8.1406
8.1345
7.6615
7.6395
7.6059
7.6804
7.5839
5.1046
5.0881
5.0716
5.0545
5.0380
5.0215
5.0050
1.02
1.02
1.00
1.07
6.15
1.13
6.00
Chemical Shift (ppm)