SUPPLEMENTAL INFORMATION

Selectively Targeting Prostate Cancer with Antiandrogen Equipped Histone Deacetylase Inhibitors

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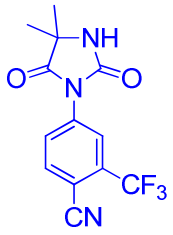
Compound Synthesis

General

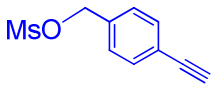
α-Bromoalkanoic acids and 7-bromoheptane nitrile were purchased from Sigma–Aldrich. Enzalutamide was purchased from Selleckchem (Houston, TX). Bicalutamide and testosterone were a kind gift from Dr. Shafiq Khan (Clark Atlanta University, Atlanta, GA). All other chemicals (including SAHA) were purchased from Sigma Aldrich. Anhydrous solvents and other reagents were purchased and used without further purification. Analtech silica gel plates (60 F_{254}) were used for analytical TLC, and Analtech preparative TLC plates (UV 254, 2000 μm) were used for purification. UV light was used to examine the spots. 200-400 Mesh silica gel was used in column chromatography. NMR spectra were recorded on a Varian-Gemini 400 magnetic resonance spectrometer. ^{1}H NMR spectra are recorded in parts per million (ppm) relative to the peak of $CDCl_3$, (7.24 ppm), CD_3OD (3.31 ppm), or DMSO-d_6 (2.49 ppm). ^{13}C spectra were recorded relative to the central peak of the $CDCl_3$ triplet (77.0 ppm), CD_3OD (49.0 ppm), or the DMSO-d_6 septet (39.7 ppm), and were recorded with complete hetero-decoupling. Multiplicities are described using the abbreviation s, singlet; d, doublet, t, triplet; q, quartet; m, multiplet; and app, apparent. All biologically evaluated compounds were established to be > 95% pure using HPLC. These HPLC analyses were done on a Beckman Coulter instrument with a Phenomenex RP C-18 column (250 mm X 4.6 mm), using 0.1% TFA in water (solvent A) and 0.1% TFA in acetonitrile (solvent B), starting with 5% B for 4 minutes, then a gradient increase of 5% to 100% of B over 25 minutes. The flow rate was 1.0 mL/min and detection was at 254 nm and 280 nM. High-resolution mass spectra were recorded at the Georgia Institute of Technology mass spectrometry facility in Atlanta. Common abbreviations include: TBTU (O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate), EDC (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide), DMF (*N,N′*-dimethylformamide), DCM (dichloromethane), TLC (thin layer chromatography), THF (tetrahydrofuran), DIPEA (*N,N′*-diisopropylethylamine), DMSO (dimethyl sulfoxide).



1

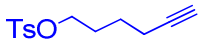
Procedure for synthesis of cyano-nilutamide (1) (as we reported previously – Dreaden, E. C. *et al. Bioconjugate Chem.* **2012**, 23, 1507-1512).

4-Fluoro-2-(trifluoromethyl)benzonitrile (4.02 g, 21.3 mmol) was added to a mixture of hydantoin (13.6 g, 106.3 mmol) and potassium carbonate (4.40 g, 31.9 mmol) in DMF (60 mL) and stirred at 45°C under argon for 48 h. Reaction mixture was diluted in ethyl acetate and washed three times with water. The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (eluent 30:1 DCM/Methanol) gave **1** as a white solid (4.62 g, 74%). ^{1}H NMR (400 MHz, $(CD_3)_2$-CO) δ 1.54 (6H, s), 7.80 (1H, s), 8.13 (1H, dd, J = 1.8 Hz, J = 8.4 Hz), 8.20 (1H, d, J = 8.4 Hz), 8.26 (1H, d, J = 1.8 Hz).



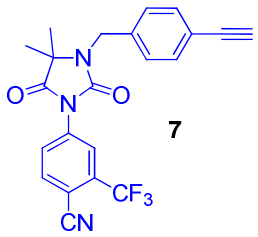
5

Procedure for conversion of 4-Ethynylbenzyl alcohol into 4-Ethynylbenzyl mesylate (5)
4-Ethynylbenzyl alcohol (2.02 g, 15.3 mmol) was dissolved in DCM (20 mL) at -10°C. Trimethylamine (4.2 mL, 30.5 mmol) and mesyl chloride (1.4 mL, 18.3 mmol) were added and the mixture was stirred at -10 °C for 40 min at. The reaction was quenched with saturated $NaHCO_3$ (100 mL), extracted with DCM (2 x 75 mL). The combined organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to give crude **5** (2.8 g, 87%) which was used directly without purification.



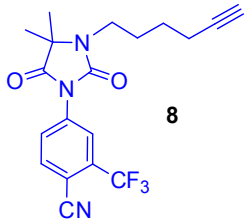
6

Procedure for conversion of 5-Hexynyl alcohol into 5-Hexynyl tosylate (6)
5-Hexynyl alcohol (3.00 g, 30.6 mmol), triethylamine (6.4 mL, 45.8 mmol) and tosyl chloride (8.7 g, 45.8 mmol) were dissolved in DCM (100 mL), followed by addition of catalytic amount of 4-dimethylaminopyridine. The reaction was stirred for 48 h at ambient temperature, then solution was washed with H_2O (200 mL), saturated aqueous NH_4Cl (150 mL), and brine (150 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (eluent 12:1 hexanes/EtOAc) gave **6** as a clear liquid (7.0 g, 90%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 – 1.60 (2H, m), 1.61 – 1.81 (2H, m), 1.89 (1H, s), 2.10 (2H, t, J = 5.5 Hz), 2.39 (3H, s), 4.00 (2H, t, J = 6.1 Hz), 7.30 (2H, d, J = 7.8 Hz), 7.73 (2H, d, J = 7.9 Hz).



7

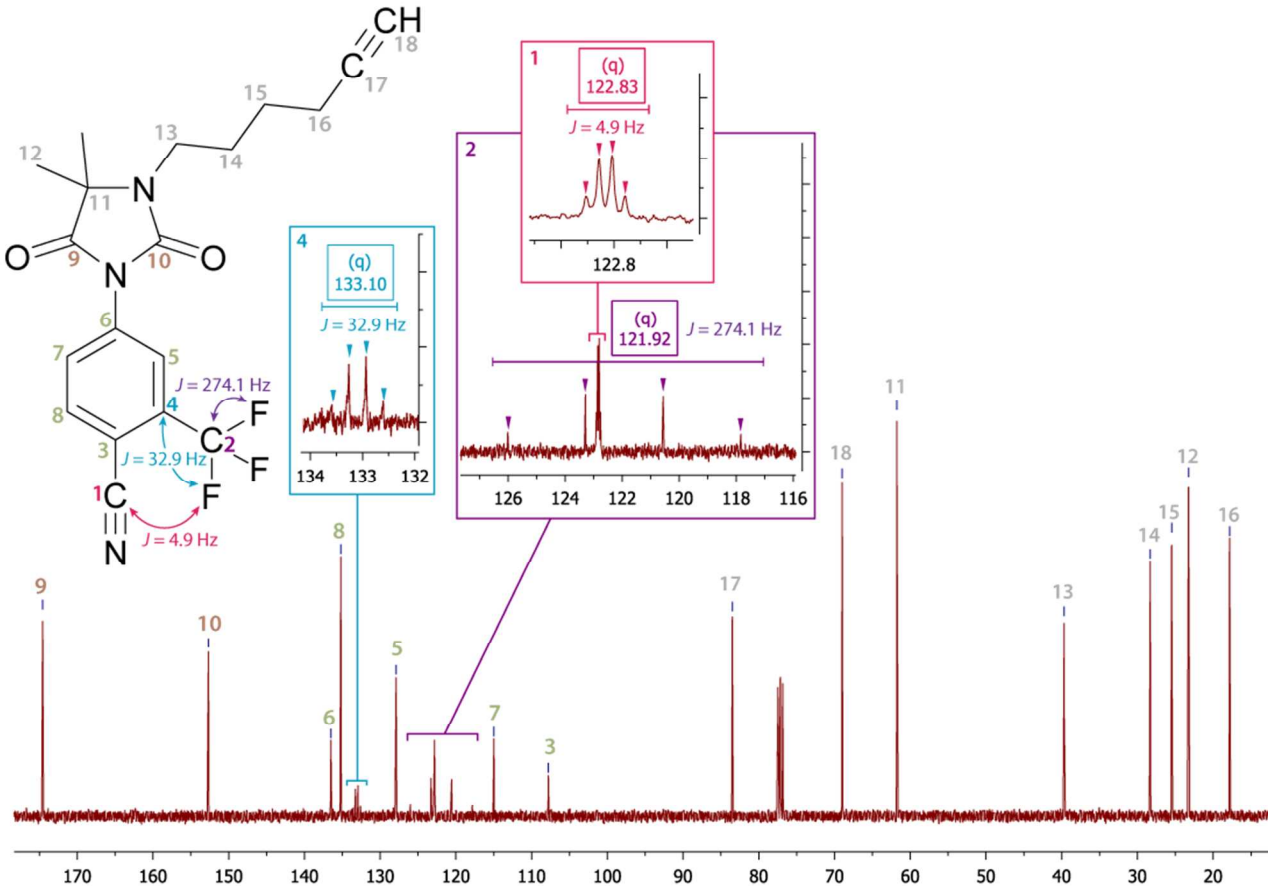
Representative procedure for synthesis of cyano-nilutamide-alkynes. 4-[3-[(4-ethynylphenyl)methyl]-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl]-2-(trifluoromethyl)-benzonitrile (7)
Compound **1** (2.44 g, 8.2 mmol) was dissolved in DMF (28 mL) under argon, followed by addition of NaH (60% in mineral oil, 558 mg, 13.9 mmol) and stirring for 2 h at ambient temperature. Then **5** (3.27 g, 15.5 mmol) was added and the reaction was stirred for 5 h at 53°C. To the reaction was added EtOAc (150 mL) and the mixture was successively washed with brine (5 x 125 mL) and H_2O (3 x 125 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. Trituration with MeOH/H_2O (7:1) gave **4** as a white solid (quantitative yield). ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (6H, s), 3.09 (1H, s), 4.57 (2H, s), 7.30 (2H, d, J = 8.4 Hz), 7.41 (2H, d, J = 8.3 Hz), 7.86 (1H, d, J = 8.4 Hz), 8.00 (1H, dd, J = 1.9, 8.4 Hz), 8.14 (1H, d, J = 7.3 Hz).

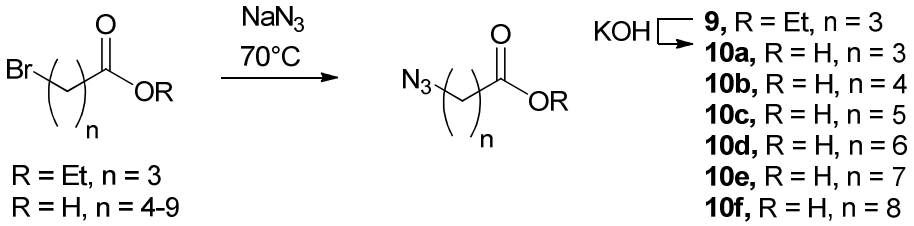


8

4-[3-(4-ethynylbutyl)-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl]-2-(trifluoromethyl)benzonitrile (8)

Reaction of **1** (1.00 g, 3.4 mmol) with NaH and then **6** (1.70 g, 6.7 mmol) as described for the synthesis of **7**, followed by column chromatography (eluent 3:1 hexanes/EtOAc) gave **8** as a white solid (1.154 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (5H, s), 1.52 – 1.63 (2H, m), 1.67 – 1.85 (2H, m), 1.88 – 2.02 (1H, m), 2.05 – 2.33 (2H, m), 3.18 – 3.46 (2H, m), 7.87 (1H, d, J = 8.4 Hz), 7.97 (1H, dd, J = 1.8, 8.4 Hz), 8.11 (1H, d, J = 1.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.56, 152.67, 136.51, 135.19, 133.10 (q, J = 32.9 Hz), 127.90, 122.83 (q, J = 4.9 Hz), 121.92 (q, J = 274.1 Hz), 114.98, 107.79, 83.50, 68.99, 61.78, 39.68, 28.31, 25.49, 23.26, 17.84. Carbon peak identification highlighting ^{13}C-^{19}F heterocoupling is shown below:





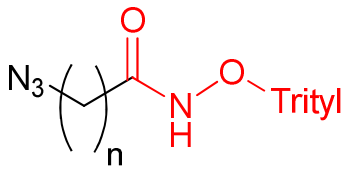
Representative procedure for synthesis of ω-azidoalkanoic acids.

4-Azidobutanoic acid (10a)

Ethyl 4-bromobutanoate (17.11 g, 87.7 mmol) and NaN_3 (28.50 g, 438.5 mmol) were dissolved in DMF (70 mL) and the mixture was stirred at 77°C for 30 h. EtOAc/hexanes (4:1, 250 mL) was added, and the mixture was washed with saturated $NaHCO_3$ (2 x 250 mL), and H_2O (200 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to give ethyl 4-azidobutanoate **9** (13.26 g, 96%). Ethyl 4-azidobutanoate **9** (6.18 g, 39.3 mmol) was saponified using excess KOH in 12:10 methanol/H_2O at 0 °C for 5 min and then ambient temperature for 11 h. Methanol was evaporated and residue was taken up into DCM and H_2O, and was washed with DCM (2 x 150 mL). Aqueous layer was acidified to pH = 1 with 2N HCl, extracted with EtOAc (5 x 150 mL), EtOAc layers combined, dried over sodium sulfate and evaporated to yield 4-azidobutanoic acid **10a** (4.69 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71 – 1.98 (2H, m), 2.45 (2H, t, J = 7.2 Hz), 3.35 (2H, t, J = 6.7 Hz), 11.21 (1H, s).

ω-Azidoalkanoic acid (10b-f)

Reaction of ω-bromoalkanoic acid and NaN_3, as described for the synthesis of **9**, gave ω-azidoalkanoic acids **10b-f** which were used without further purification.



11a, n = 3
11b, n = 4
11c, n = 5
11d, n = 6
11e, n = 7
11f, n = 8

Procedure for conversion of 4-azidobutanoic acid to 4-azido-*O*-tritylbutylhydroxamate (11a)

4-Azidobutanoic acid **10a** (1.01 g, 7.8 mmol), TBTU (4.2 g, 13.1 mmol) and diisopropylethylamine (1.7 g, 13.1 mmol) were added to DCM (100 mL) at ambient temperature. To the mixture was added *O*-tritylhydroxylamine (1.80 g, 6.5 mmol) and the reaction was stirred for 10 h. Solvent was removed *in vacuo*, and column chromatography (eluent 4:1 hexanes/ EtOAc) gave **11a** as a clear semi-solid (2.53 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 – 1.61 (2H, m), 1.60 – 1.80 (2H, m), 2.86 – 3.18 (2H, m), 7.21 – 7.61 (15H, m), 7.78 (1H, s).

Representative procedure for conversion of ω-azidoalkanoic acids to *O*-trityl hydroxamates. 5-Azido-*O*-tritylpentahydroxamate (11b)

5-Azidopentanoic acid **10b** (1.10 g, 7.7 mmol) was dissolved in anhydrous THF. N-methylmorpholine (0.84 mL, 7.7 mmol) was added to the solution. The reaction mixture was then cooled down to -15 °C and stirred for 5 min. Isobutyl-chloroformate (1.00, 7.7 mmol) was added and the mixture was stirred for 10 min at -15 °C. *O*-tritylhydroxylamine (2.11 g, 7.7 mmol) was added followed by additional two equivalents of N-methylmorpholine. Stirring continued for 15 min at -15 ^{o}C and 2 h at room temperature. Afterwards the mixture was poured into 2M HCl and extracted with EtOAc (3 x 200 mL). Drying over sodium sulfate, and concentrating *in vacuo* yielded 2.78 g (90%) of **11b** as a white solid with no further purification required. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.17-1.25 (4H, m), 1.79 (2H, t, J = 5.8 Hz), 3.15 (2H, t, J = 6.1 Hz), 7.27-7.31 (15H, m), 10.22 (1H, s).

7-Azido-*O*-tritylheptahydroxamate (11d)

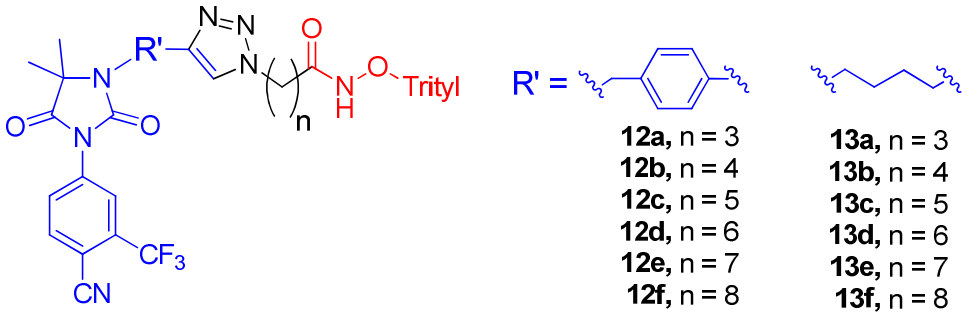
Reaction of 7-azidoheptanoic acid **10d** (0.43 g, 2.5 mmol) and *O*-tritylhydroxylamine (0.70 g, 2.5 mmol) as described for the synthesis of **11b**, followed by flash chromatography (eluent 2:1 hexanes/EtOAc) gave 0.84 g (77%) of **11d** as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.94-1.01 (2H, m), 1.06-1.19 (4H, m), 1.71-1.78 (4H, m), 3.59 (1H, s), 4.34 (2H, t, J = 8), 7.25-7.36 (16H, m), 7.44-7.47 (1H, m), 8.07 (1H, s), 8.17-8.20 (1H, m), 8.51-8.52 (1H, m), 8.68 (1H, s), 9.03-9.04 (1H, m), 10.16 (1H, s).

8-Azido-*O*-trityloctahydroxamate (11e)

Reaction of 8-azidooctanoic acid **10e** (1.71 g, 9.2 mmol) and *O*-tritylhydroxylamine (2.55 g, 9.3 mmol) as described for the synthesis of **11b**, followed by flash chromatography (eluent 2:1 hexanes/EtOAc) gave 2.59 g (88%) of **11e** as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88–1.39 (8H, m), 1.39–1.54 (4H, m), 3.12 (2H, t, J = 6.9 Hz), 7.10–7.49 (15H, m), 7.67 (1H, s).

9-Azido-*O*-tritylnonahydroxamate (11f)

Reaction of 9-azidononanoic acid **11f** (0.84 g, 4.2 mmol) and *O*-tritylhydroxylamine (1.2 g, 4.6 mmol) overnight as described for the synthesis of **11a**, followed by flash chromatography (eluent 5:1 hexanes/EtOAc) gave 1.3 g (68%) of **11f** as a sticky white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (10H, m), 1.57 (4H, m), 3.24 (2H, t, J = 6.8 Hz), 7.34 (15H, m), 7.74 (1H, s).



Representative procedure for Cu(I)-catalyzed cycloaddition reaction. *O*-Trityl-cyanonilutamide-benzyl-triazolylbutylhydroxamate (12a)

Compound **7** (0.15 g, 0.4 mmol), 4-azido-*O*-tritylbutylhydroxamate **11a** (0.17 g, 0.4 mmol) and DIPEA (0.09 g, 0.7 mmol) were dissolved anhydrous DMSO (2.55 mL) under argon. Copper(I) iodide (0.03 g, 0.2 mmol) was added and the reaction mixture was stirred under argon at ambient temperature overnight. The reaction was diluted with DCM (30 mL) and washed with 1:4 NH_4OH/saturated NH_4Cl (3 x 30 mL) and saturated NH_4Cl (30 mL), and organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (eluent 80:4:1 DCM/Acetone/Methanol) gave **12a** as a white solid (0.22 g, 76%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.39 (6H, s), 1.69 – 1.90 (4H, m), 4.00 – 4.17 (2H, m), 4.63 (2H, s), 7.22 – 7.43 (15H, m), 7.50 (2H, d, J = 8.1 Hz), 7.78 (2H, d, J = 8.1 Hz), 8.09 (1H, d, J = 8.4 Hz), 8.24 (1H, s), 8.32 (1H, d, J = 8.4 Hz), 8.37 (1H, s), 10.30 (1H, s).

***O*-Trityl-cyanonilutamide-benzyl-triazolylpentahydroxamate (12b)**

Reaction of **7** and **11b** as described for **12a** gave the product **12b** (178 mg) in 58% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (2H, s), 1.41 (6H, s), 1.49 – 1.75 (4H, m), 4.13 – 4.26 (2H, m), 4.63 (2H, s), 7.15 – 7.49 (15H, m), 7.41 (2H, d, J = 8.0 Hz), 7.74 (1H, s), 7.79 (2H, d, J = 7.9 Hz), 7.89 (1H, d, J = 8.4 Hz), 8.03 (1H, dd, J = 1.7, 8.5 Hz), 8.19 (1H, d, J = 1.4 Hz).

***O*-Trityl-cyanonilutamide-benzyl-triazolylhexahydroxamate (12c)**

Reaction of **7** and **11c** as described for **12a** gave the product **12c** (315 mg) in 98% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 – 1.15 (2H, m), 1.18 – 1.33 (2H, m), 1.40 (6H, s), 1.50 – 1.63 (2H, m), 1.66 – 1.81 (3H, m), 4.18 – 4.33 (2H, m), 4.63 (2H, s), 7.34 (15H, dd, J = 9.1, 55.1 Hz), 7.41 (2H, d, J = 7.2 Hz), 7.76 (1H, s), 7.80 (2H, d, J = 8.1 Hz), 7.83 (1H, s), 7.88 (1H, d, J = 8.4 Hz), 8.02 (1H, dd, J = 1.7, 8.4 Hz), 8.18 (1H, d, J = 1.6 Hz).

***O*-Trityl-cyanonilutamide-benzyl-triazolylheptahydroxamate (12d)**

Reaction of **7** and **11d** as described for **12a** gave the product **12d** (262 mg) in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 – 1.32 (6H, m), 1.42 (6H, s), 1.75 – 1.95 (4H, m), 4.32 (2H, s), 4.64 (2H, s), 7.35 (15H, dd, J = 14.2, 54.1 Hz), 7.42 (2H, d, J = 8.1 Hz), 7.74 (1H, s), 7.81 (2H, d, J = 8.1 Hz), 7.90 (1H, d, J = 8.5 Hz), 8.04 (1H, dd, J = 1.8, 8.4 Hz), 8.19 (1H, s).

***O*-Trityl-cyanonilutamide-benzyl-triazolyloctahydroxamate (12e)**

Reaction of **7** and **11e** as described for **12a** gave the product **12e** (276 mg) in 92% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.03 (2H, m), 1.23 (6H, m), 1.42 (6H, s), 1.56 (2H, m), 1.87 (2H, m), 4.35 (2H, t, J = 7.1), 4.65 (2H, s), 7.32 (15H, m), 7.42 (2H, d, J = 8.2), 7.61 (1H, s), 7.76 (1H, s), 7.82 (2H, d, J = 8.2), 7.91 (1H, d, J = 8.4), 8.04 (1H, dd, J = 1.8, 8.4), 8.19 (1H, d, J = 1.7).

***O*-Trityl-cyanonilutamide-benzyl-triazolylnonahydroxamate (12f)**
Reaction of **7** and **11f** as described for **12a** gave the product **12f** (184 mg) in 87% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 – 1.34 (11H, m), 1.42 (6H, s), 1.47 – 1.65 (2H, m), 1.74 – 1.95 (3H, m), 4.35 (2H, t, J = 7.1 Hz), 4.64 (2H, s), 7.35 (15H, dd, J = 12.0, 40.9 Hz), 7.42 (2H, d, J = 8.4 Hz), 7.77 (1H, s), 7.82 (2H, d, J = 8.3 Hz), 7.90 (1H, d, J = 8.5 Hz), 8.04 (1H, dd, J = 2.0, 8.4 Hz), 8.19 (1H, d, J = 2.0 Hz).

***O*-Trityl-cyanonilutamide-butyl-triazolylbutylhydroxamate (13a)**
Reaction of **8** and **11a** as described for **12a** gave the product **13a** (241 mg) in 87% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.43 (6H, s), 1.58 – 1.73 (6H, m), 1.73 – 1.85 (2H, m), 2.62 (2H, t, J = 6.9 Hz), 3.99 (2H, t, J = 6.8 Hz), 7.10 – 7.40 (15H, m), 7.66 (1H, s), 8.01 (1H, dd, J = 2.0, 8.4 Hz), 8.17 (1H, d, J = 1.8 Hz), 8.28 (1H, d, J = 8.4 Hz), 10.29 (1H, s).

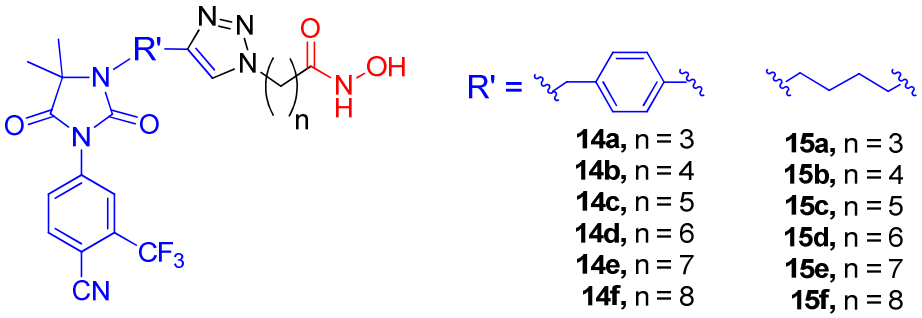
***O*-Trityl-cyanonilutamide-butyl-triazolylpentahydroxamate (13b)**
Reaction of **8** and **11b** as described for **12a** gave the product **13b** (374 mg) in 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 – 1.29 (2H, m), 1.50 (6H, s), 1.52 – 1.67 (4H, m), 1.69 – 1.80 (4H, m), 2.75 (2H, t, J = 6.8 Hz), 3.37 (2H, t, J = 7.2 Hz), 4.13 (2H, t, J = 6.7 Hz), 7.24 (1H, s), 7.25 – 7.50 (15H, m), 7.78 (1H, s), 7.88 (1H, d, J = 8.4 Hz), 7.98 (1H, dd, J = 1.9, 8.5 Hz), 8.14 (1H, d, J = 1.7 Hz).

***O*-Trityl-cyanonilutamide-butyl-triazolylhexahydroxamate (13c)**
Reaction of **8** and **11c** as described for **12a** gave the product **13c** (248 mg) in 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 – 1.16 (2H, m), 1.18 – 1.33 (2H, m), 1.50 (6H, s), 1.63 – 1.95 (8H, m), 2.72 – 2.79 (2H, m), 3.32 – 3.41 (2H, m), 4.20 (2H, t, J = 7.1 Hz), 7.14 – 7.53 (15H, m), 7.77 (1H, s), 7.87 (1H, d, J = 8.5 Hz), 7.98 (1H, dd, J = 1.7, 8.5 Hz), 8.14 (1H, d, J = 1.7 Hz).

***O*-Trityl-cyanonilutamide-butyl-triazolylheptahydroxamate (13d)**
Reaction of **8** and **11d** as described for **12a** gave the product **13d** (265 mg) in 82% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.87 – 0.97 (2H, m), 0.97 – 1.07 (2H, m), 1.08 – 1.18 (2H, m), 1.42 (6H, s), 1.55 – 1.69 (6H, m), 1.73 (2H, t, J = 7.2 Hz), 2.57 – 2.68 (2H, m), 3.27 – 3.36 (2H, m), 4.20 (2H, t, J = 7.1 Hz), 7.18 – 7.39 (15H, m), 7.81 (1H, s), 8.01 (1H, dd, J = 2.0, 8.4 Hz), 8.17 (1H, d, J = 1.7 Hz), 8.28 (1H, d, J = 8.4 Hz), 10.15 (1H, s).

***O*-Trityl-cyanonilutamide-butyl-triazolyloctahydroxamate (13e)**
Reaction of **8** and **11e** as described for **12a** gave the product **13e** (299 mg) in 92% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.08 (8H, m), 1.49 (6H, s), 1.54 (2H, m), 1.77 (6H, m), 2.75 (2H, s), 3.37 (2H, s), 4.25 (2H, t, J = 7.17, 7.17), 7.31 (15H, s), 7.61 (1H, s), 7.76 (1H, s), 7.87 (1H, d, J = 8.4), 7.97 (1H, dd, J = 1.8, 8.4), 8.13 (1H, d, J = 1.5).

***O*-Trityl-cyanonilutamide-butyl-triazolylnonahydroxamate (13f)**
Reaction of **8** and **11f** as described for **12a** gave the product **13f** (197 mg) in 97% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 – 1.42 (12H, m), 1.49 (6H, s), 1.67 – 1.87 (6H, m), 2.75 (2H, s), 3.36 (2H, s), 4.26 (2H, t, J = 7.1 Hz), 7.30 (15H, s), 7.76 (1H, s), 7.86 (1H, d, J = 8.4 Hz), 7.98 (1H, dd, J = 1.7, 8.4 Hz), 8.13 (1H, d, J = 1.2 Hz).



Representative procedure for deprotection of *O*-trityl-hydroxamates. 4-(4-(4-((3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-2,4-dioxoimidazolidin-1-yl)methyl)phenyl)-1*H*-1,2,3-triazol-1-yl)-*N*-hydroxybutanamide (14a)

Compound **12a** (0.2 g, 0.2 mmol) was dissolved in DCM (9.1 mL) and triisopropylsilane (0.2 mL) at ambient temperature. Trifluoroacetic acid (0.18 mL) was added, and then triisopropylsilane (0.8 mL) was added dropwise until solution turned from yellow to clear over 1 min., and reaction was stirred for 5 min. Solvent was removed *in vacuo*, and residue was triturated with petroleum ether (10 mL). Preperative TLC (eluent 37:1 acetonitile/water) provided 0.10 g (71%) of **14a** as a light yellow semisolid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.38 (6H, s), 1.85 – 2.19 (4H, m), 4.27 – 4.49 (2H, m), 4.62 (2H, s), 7.50 (2H, d, J = 7.2 Hz), 7.80 (2H, d, J = 6.8 Hz), 8.08 (1H, d, J = 7.1 Hz), 8.23 (1H, s), 8.30 (1H, d, J = 7.0 Hz), 8.57 (1H, s), 10.52 (1H, s); ^{13}C NMR (100 MHz, acetone) δ 175.64, 170.00, 154.32, 147.49, 138.57, 138.30, 136.49, 132.78 (q, J = 32.4 Hz), 131.51, 129.95, 129.26, 126.31, 124.25 (q, J = 5.0 Hz), 123.40 (q, J = 270.7 Hz), 121.61, 115.87, 108.15, 63.02, 50.02, 43.54, 26.86, 23.48. HRMS (MALDI) calculated for [$C_{26}H_{24}F_3N_7O_4$+H] 556.1915, found 556.1907.

5-(4-(4-((3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-2,4-dioxoimidazolidin-1-yl)methyl)phenyl)-1*H*-1,2,3-triazol-1-yl)-*N*-hydroxypentanamide (14b)

Reaction of **12b** with trifluoroacetic acid as described for **14a** gave the product **14b** (78 mg) in 63% yield. ^{1}H NMR (400 MHz, DMSO) δ 1.39 (s, 6H), 1.48 (dd, J = 15.2, 7.6 Hz, 2H), 1.86 – 1.73 (m, 2H), 1.98 (t, J = 7.4 Hz, 2H), 4.38 (t, J = 7.1 Hz, 2H), 4.63 (s, 2H), 7.51 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 8.3 Hz, 2H), 8.09 (d, J = 8.3 Hz, 1H), 8.24 (d, J = 1.7 Hz, 1H), 8.33 (d, J = 8.5 Hz, 1H), 8.55 (s, 1H), 10.35 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.66, 170.77, 153.48, 147.06, 137.15, 136.60, 135.44, 133.48 (q, J = 33.0 Hz), 130.10, 128.61, 128.21, 126.18, 123.15 (q, J = 5.0 Hz), 122.10 (q, J = 274.2 Hz), 120.60, 115.14, 108.28, 62.39, 50.07, 43.50, 31.03, 29.39, 23.68, 22.26. HRMS (MALDI) calculated for [$C_{27}H_{26}F_3N_7O_4$+H]$^+$ 570.2071, found 570.2100.

6-(4-(4-((3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-2,4-dioxoimidazolidin-1-yl)methyl)phenyl)-1*H*-1,2,3-triazol-1-yl)-*N*-hydroxyhexanamide (14c)

Reaction of **12c** with trifluoroacetic acid as described for **14a** gave the product **14c** (44 mg) in 48% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 2H), 1.39 – 1.32 (m, 2H), 1.44 (s, 6H), 1.61 (s, 4H), 1.75 – 1.64 (m, 4H), 1.99 – 1.89 (m, 2H), 2.15 (s, 2H), 4.39 (t, J = 4.3 Hz, 2H), 4.65 (s, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 5.4 Hz, 2H), 7.82 (s, 1H), 7.93 (d, J = 8.3 Hz, 1H), 8.04 (d, J = 8.5 Hz, 1H), 8.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.65, 170.11, 153.12, 146.03, 137.44, 136.90, 136.05, 131.05 (q, J = 32.2 Hz), 128.95, 128.23, 127.51, 125.11, 124.42 – 124.04 (m), 122.29 (q, J = 273.6 Hz), 121.19, 115.25, 106.76, 62.00, 49.33, 42.32, 31.73, 29.31, 25.19, 24.12, 22.71. HRMS (MALDI) calculated for [$C_{28}H_{28}F_3N_7O_4$+H]$^+$ 584.2188, found 584.2217.

7-(4-(4-((3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-2,4-dioxoimidazolidin-1-yl)methyl)phenyl)-1*H*-1,2,3-triazol-1-yl)-*N*-hydroxyheptanamide (14d)
Reaction of **12d** with trifluoroacetic acid as described for **14a** gave the product **14d** (95 mg) in 67% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23 (d, *J* = 12.6 Hz, 4H), 1.39 (s, 6H), 1.44 (s, 2H), 1.83 (s, 2H), 1.91 (t, *J* = 7.3 Hz, 2H), 4.36 (t, *J* = 7.0 Hz, 2H), 4.63 (s, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.79 (d, *J* = 8.2 Hz, 2H), 8.08 (dd, *J* = 8.5, 1.8 Hz, 1H), 8.24 (d, *J* = 1.8 Hz, 1H), 8.33 (d, *J* = 8.4 Hz, 1H), 8.56 (s, 1H), 8.65 (s, 1H), 10.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.65, 171.21, 153.39, 147.08, 136.94, 136.53, 135.41, 133.43 (q, *J* = 33.2 Hz), 130.29, 128.57, 128.20, 126.12, 123.12 (q, *J* = 4.5 Hz), 122.03 (q, *J* = 274.4 Hz), 120.29, 115.12, 108.16, 62.34, 50.25, 43.45, 31.02, 29.92, 28.00, 25.76, 25.07, 23.65. HRMS (MALDI) calculated for $[C_{29}H_{30}F_3N_7O_4+H]^+$ 598.2345, found 598.2395.

8-(4-(4-((3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-2,4-dioxoimidazolidin-1-yl)methyl)phenyl)-1*H*-1,2,3-triazol-1-yl)-*N*-hydroxyoctanamide (14e)
Reaction of **12e** with trifluoroacetic acid as described for **14a** gave the product **14e** (46 mg) in 35% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 6H), 1.41 (s, 6H), 1.53 (dd, *J* = 8.3, 5.2 Hz, 2H), 1.85 (s, 2H), 2.15 – 2.01 (m, 2H), 4.33 (s, 2H), 4.62 (s, 2H), 7.40 (d, *J* = 7.9 Hz, 2H), 7.78 (d, *J* = 7.8 Hz, 2H), 7.82 (s, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 8.16 (d, *J* = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.57, 171.46, 153.32, 147.05, 136.82, 136.48, 135.30, 133.45 (q, *J* = 33.2 Hz), 130.33, 128.52, 128.07, 126.09, 123.04 (q, *J* = 4.8 Hz), 121.96 (q, *J* = 274.2 Hz), 119.98, 115.01, 108.17, 62.25, 50.25, 43.43, 30.89, 29.94, 28.46, 28.05, 25.82, 24.96, 23.60. HRMS (MALDI) calculated for $[C_{30}H_{32}F_3N_7O_4+H]^+$ 612.2501, found 612.2524.

9-(4-(4-((3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-2,4-dioxoimidazolidin-1-yl)methyl)phenyl)-1*H*-1,2,3-triazol-1-yl)-*N*-hydroxynonanamide (14f)
Reaction of **12f** with trifluoroacetic acid as described for **14a** gave the product **14f** (123 mg) in 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 0.63 – 1.32 (10H, m), 1.39 (6H, s), 1.45 – 1.68 (2H, m), 1.72 – 2.00 (2H, m), 4.34 (2H, bs), 4.60 (2H, s), 7.39 (2H, bs), 7.68 – 7.84 (2H, m), 7.90 (1H, d, *J* = 6.4 Hz), 7.99 (1H, d, *J* = 6.7 Hz), 8.13 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.46, 168.77, 153.04, 146.49, 136.78, 136.16, 134.98, 132.35 (q, *J* = 33.3 Hz), 129.41, 128.15, 127.87, 125.32, 122.85 – 122.56 (m), 121.59 (q, *J* = 273.5 Hz), 120.36, 114.44, 107.20, 61.87, 49.79, 42.47, 33.14, 30.11, 29.45, 28.25, 28.03, 25.59, 24.09, 22.29. HRMS (MALDI) calculated for $[C_{31}H_{34}F_3N_7O_4+H]$ 626.2697, found 626.2673.

4-(4-(4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-2,4-dioxoimidazolidin-1-yl)butyl)-1*H*-1,2,3-triazol-1-yl)-*N*-hydroxybutanamide (15a)

Reaction of **13a** with trifluoroacetic acid as described for **14a** gave the product **15a** (109 mg) in quantitative yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 – 1.52 (6H, m), 1.65 (4H, s), 1.97 (4H, s), 2.65 (2H, s), 3.34 (2H, s), 4.29 (2H, d, J = 6.1 Hz), 7.86 (1H, s), 8.03 (1H, d, J = 8.2 Hz), 8.18 (1H, s), 8.30 (1H, d, J = 8.3 Hz), 10.47 (1H, s); ^{13}C NMR (100 MHz, acetone-d_6) δ 175.72, 169.71, 153.73, 147.91, 138.32, 136.50, 132.78 (q, J = 32.6 Hz), 129.84, 124.14 (q, J = 5.1 Hz), 123.40 (q, J = 273.0 Hz), 122.23, 115.89, 108.04, 62.69, 49.69, 40.49, 29.56, 27.48, 26.97, 25.71, 23.28. HRMS (MALDI) calculated for [$C_{23}H_{26}F_3N_7O_4$+H] 522.2077, found 522.2064.

5-(4-(4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-2,4-dioxoimidazolidin-1-yl)butyl)-1*H*-1,2,3-triazol-1-yl)-*N*-hydroxypentanamide (15b)

Reaction of **13b** with trifluoroacetic acid as described for **14a** gave the product **15b** (23 mg) in 28% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 2H), 1.51 (s, 7H), 1.65 – 1.53 (m, 3H), 1.75 (s, 4H), 1.87 (s, 2H), 2.16 (s, 1H), 2.74 (s, 2H), 3.37 (s, 2H), 4.29 (s, 2H), 7.37 (s, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 7.4 Hz, 1H), 8.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.76, 170.44, 153.10, 147.97, 136.60, 135.46, 133.52 (q, J = 33.1 Hz), 128.24, 123.19 (q, J = 4.7 Hz), 122.12 (q, J = 274.2 Hz), 121.47, 115.17, 108.26, 62.13, 49.91, 40.16, 29.81, 29.41, 28.97, 26.74, 25.06, 23.53, 22.29. HRMS (MALDI) calculated for [$C_{24}H_{28}F_3N_7O_4$+H]$^+$ 536.2228, found 536.2230.

6-(4-(4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-2,4-dioxoimidazolidin-1-yl)butyl)-1*H*-1,2,3-triazol-1-yl)-*N*-hydroxyhexanamide (15c)

Reaction of **13c** with trifluoroacetic acid as described for **14a** gave the product **15c** (39 mg) in 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 2H), 1.51 (s, 6H), 1.60 (dt, J = 12.0, 5.9 Hz, 2H), 1.74 (s, 4H), 1.89 – 1.79 (m, 2H), 2.16 – 1.99 (m, 2H), 2.75 (q, J = 5.5 Hz, 2H), 3.40 – 3.32 (m, 2H), 4.28 (t, J = 6.4 Hz, 2H), 7.35 (s, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.5 Hz, 1H), 8.10 (d, J = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.70, 170.94, 152.97, 147.37, 136.53, 135.39, 133.34 (q, J = 33.4 Hz), 128.19, 123.09 (q, J = 4.6 Hz), 122.04 (q, J = 273.3 Hz), 121.31, 115.12, 108.02, 62.05, 49.93, 40.06, 32.46, 29.75, 28.89, 26.73, 25.66, 24.96, 24.58, 23.41. HRMS (MALDI) calculated for [$C_{25}H_{30}F_3N_7O_4$+H]$^+$ 550.2345, found 550.2383.

7-(4-(4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-2,4-dioxoimidazolidin-1-yl)butyl)-1*H*-1,2,3-triazol-1-yl)-*N*-hydroxyheptanamide (15d)

Reaction of **13d** with trifluoroacetic acid as described for **14a** gave the product **15d** (58 mg) in 38% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 4H), 1.49 (s, 6H), 1.55 (d, J = 4.9 Hz, 2H), 1.74 (s, 4H), 1.82 (s, 2H), 2.15 – 1.99 (m, 4H), 2.73 (s, 2H), 3.36 (s, 2H), 4.26 (s, 2H), 7.34 (s, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 7.7 Hz, 1H), 8.10 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.74, 171.25, 152.97, 147.57, 136.60, 135.38, 133.44 (q, J = 33.2 Hz), 128.14, 123.10 (q, J = 4.9 Hz), 122.07 (q, J = 274.2 Hz), 121.19, 115.13, 108.10, 62.05, 50.03, 40.11, 32.51, 30.98, 29.90, 28.93, 27.97, 26.79, 25.76, 25.02, 23.47. HRMS (MALDI) calculated for [$C_{26}H_{32}F_3N_7O_4$+H]$^+$ 564.2541, found 564.2596.

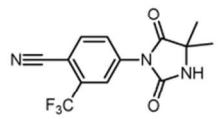
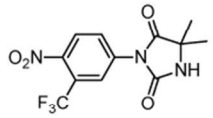
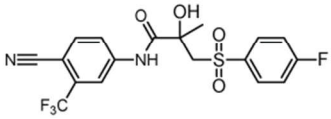
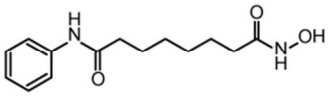
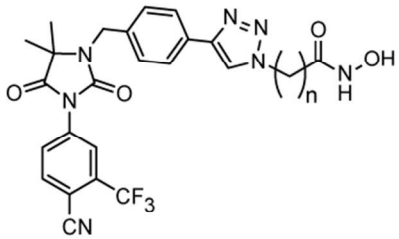
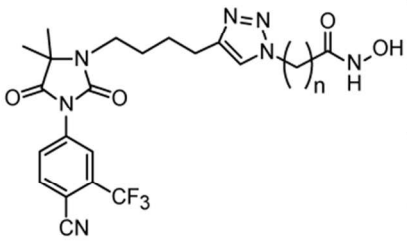
8-(4-(4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-2,4-dioxoimidazolidin-1-yl)butyl)-1*H*-1,2,3-triazol-1-yl)-*N*-hydroxyoctanamide (15e)

Reaction of **13e** with trifluoroacetic acid as described for **14a** gave the product **15e** (74 mg) in 49% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 6H), 1.51 (d, J = 19.1 Hz, 8H), 1.74 (s, 4H),

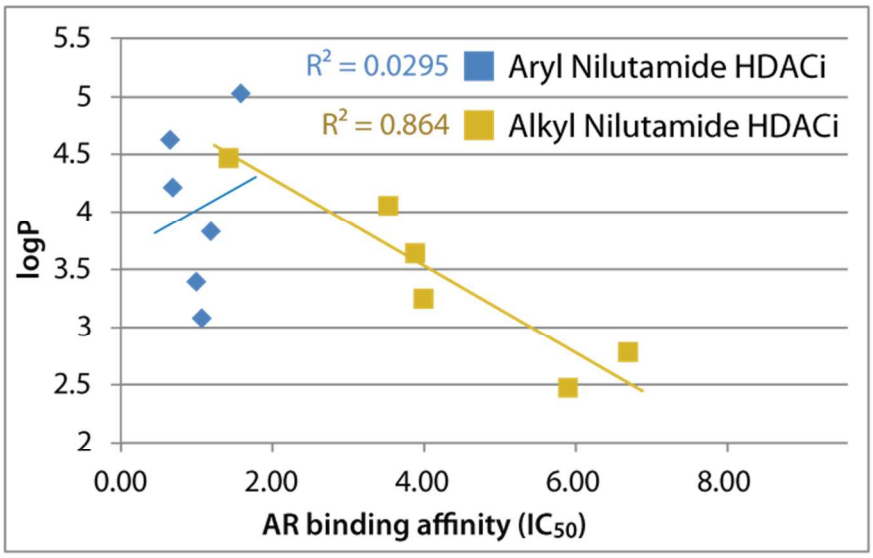
1.87 – 1.77 (m, 2H), 2.14 – 2.00 (m, 2H), 2.74 (s, 2H), 3.36 (s, 2H), 4.27 (t, J = 6.6 Hz, 2H), 7.33 (s, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 8.3 Hz, 1H), 8.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.76, 171.32, 152.95, 147.41, 136.61, 135.36, 133.45 (q, J = 33.0 Hz), 128.12, 123.09 (q, J = 4.9 Hz), 122.06 (q, J = 274.2 Hz), 121.08, 115.13, 108.11, 62.04, 50.11, 40.10, 32.66, 30.98, 29.99, 28.93, 28.55, 28.12, 26.80, 25.90, 25.01, 23.47. HRMS (MALDI) calculated for $[C_{27}H_{34}F_3N_7O_4+H]^+$ 578.2658, found 578.2678.

9-(4-(4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-2,4-dioxoimidazolidin-1-yl)butyl)-1*H*-1,2,3-triazol-1-yl)-*N*-hydroxynonanamide (15f)

Reaction of **13f** with trifluoroacetic acid as described for **14a** gave the product **15f** (102 mg) in 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 – 1.40 (10H, m), 1.48 (6H, s), 1.52 – 1.62 (2H, m), 1.64 – 1.95 (6H, m), 2.05 – 2.20 (2H, m), 3.34 (2H, bs), 4.29 (2H, bs), 7.89 (1H, s), 7.95 (1H, s), 8.09 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.73, 171.39, 152.88, 147.32, 136.55, 135.34, 133.41 (q, J = 30.7 Hz), 128.10, 123.05 (q, J = 4.5 Hz), 122.02 (q, J = 274.3 Hz), 121.05, 115.11, 108.01, 62.01, 50.19, 40.06, 32.84, 30.04, 28.89, 28.71, 28.58, 28.35, 26.78, 26.06, 25.28, 24.96, 23.43. HRMS (MALDI) calculated for $[C_{28}H_{36}F_3N_7O_4]^+$ 591.2781, found 591.2826.

		logP	logD	MlogP	MW	Hydrogen Bond Donors	TPSA (Å^2)
cyano-nilutamide **1**		2.353	2.351	2.247	297.24	1	73.2
nilutamide **2**		2.327	2.325	2.637	317.23	1	95.23
bicalutamide **3**		2.608	2.587	1.928	430.38	2	107.26
SAHA **4**		1.644	1.643	2.057	264.33	3	78.43
Aryl Nilutamide HDACi 	**14a**, n = 3	3.080	3.076	3.332	555.52	2	144.45
	14b, n = 4	3.394	3.390	3.528	569.55	2	144.45
	14c, n = 5	3.829	3.826	3.723	583.57	2	144.45
	14d, n = 6	4.213	4.209	3.914	597.60	2	144.45
	14e, n = 7	4.623	4.619	4.103	611.63	2	144.45
	14f, n = 8	5.030	5.027	4.290	625.66	2	144.45
Alkyl Nilutamide HDACi 	**15a**, n = 3	2.473	2.470	2.673	521.50	2	144.45
	15b, n = 4	2.780	2.777	2.879	535.53	2	144.45
	15c, n = 5	3.249	3.246	3.081	549.56	2	144.45
	15d, n = 6	3.638	3.635	3.281	563.58	2	144.45
	15e, n = 7	4.055	4.052	3.478	577.61	2	144.45
	15f, n = 8	4.465	4.462	3.672	591.64	2	144.45

Supplemental Table 1: Chemical properties and predicted ADMET properties of antiandrogens, SAHA and dual-targeting AR-HDACi compounds. Predicted values: logP = octanol/water partition coefficient, logD = logP at pH 7.4, MlogP = Moriguchi estimation of logP, TPSA = Topological polar surface area in square angstroms. All parameters were calculated using MedChem Designer software (version 2.0.0.34) from Simulations Plus, Inc.



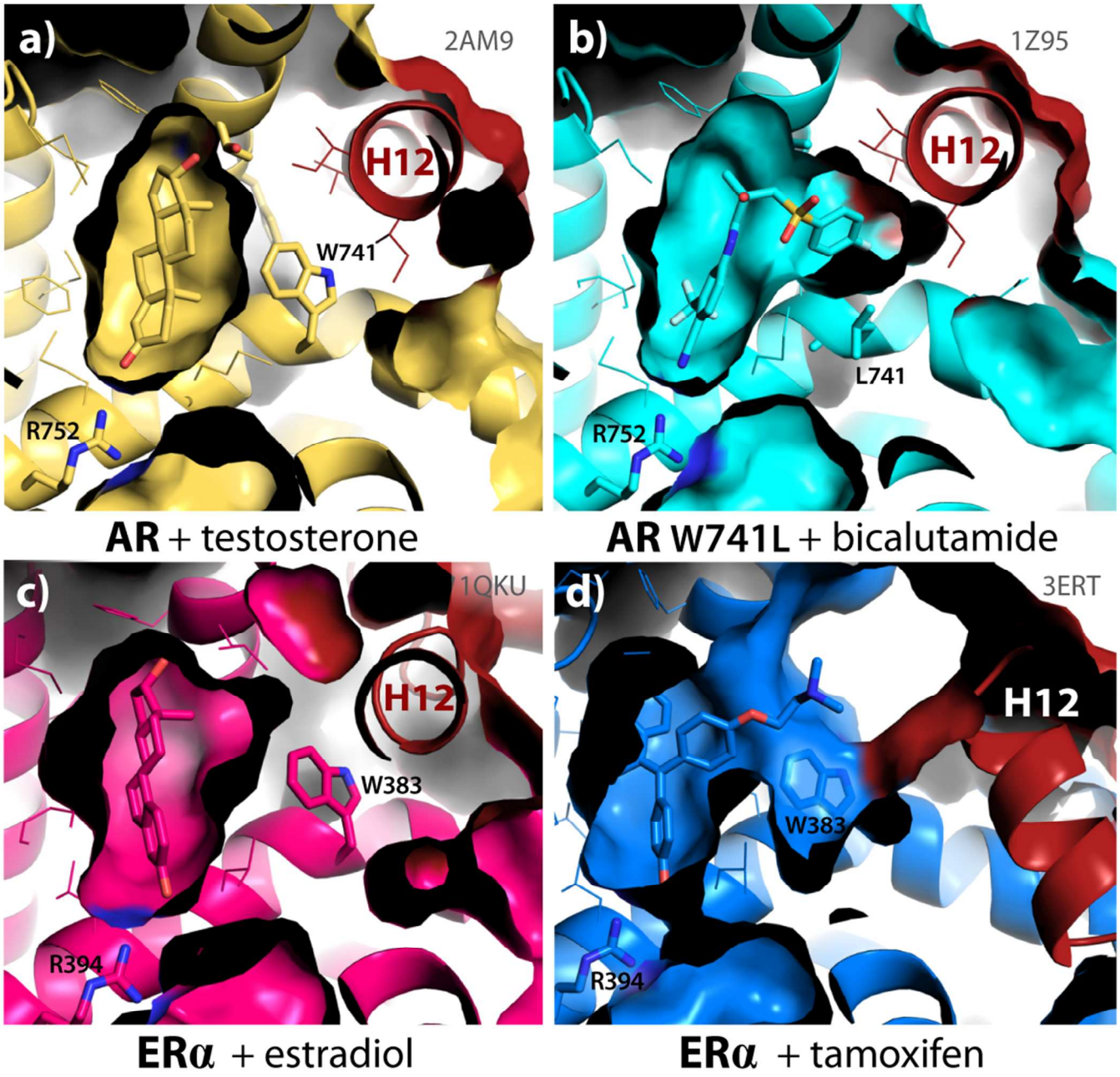
Supplemental Figure 1: logP versus AR binding affinity trends for AR-HDACi conjugates.

Supplemental Table 2. Anti-proliferative activity of selected compounds against expanded cell lines.

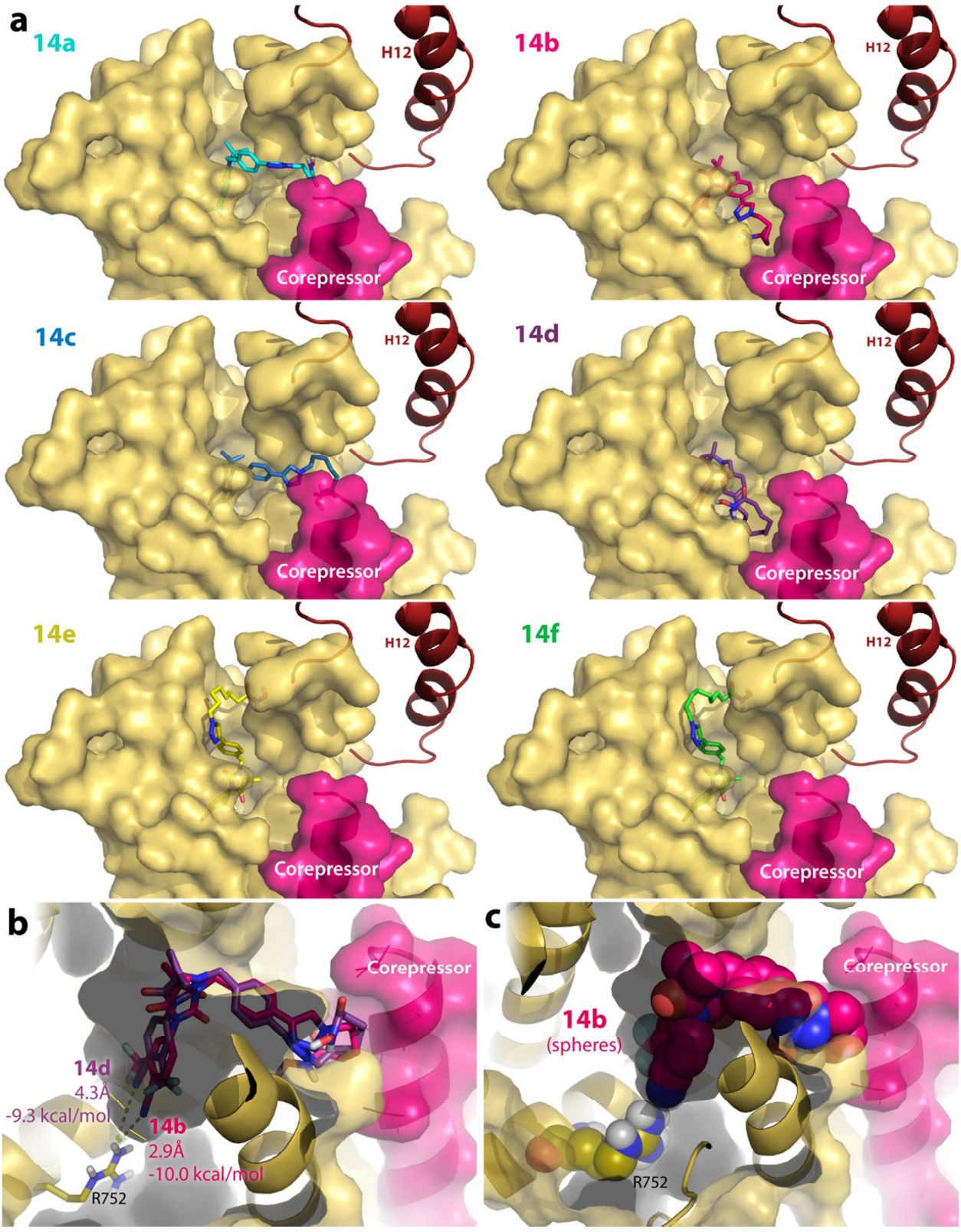
Antiproliferative Activity (IC_{50})[a]

	VERO (healthy kidney cells)	RWPE-1 (Benign AR+ Prostate Hyperplasia cells)	PC3 (AR- PCa cells)	MCF7 (Breast Cancer cells)	MDA-MB-231 (AR-, ER-, PR- breast cancer cells)
14d	11.0	0.48	3.31	4.24	1.45
15d	>20	12.1	15.7	14.6	>20
SAHA	1.45	3.64	2.58	4.22	2.14

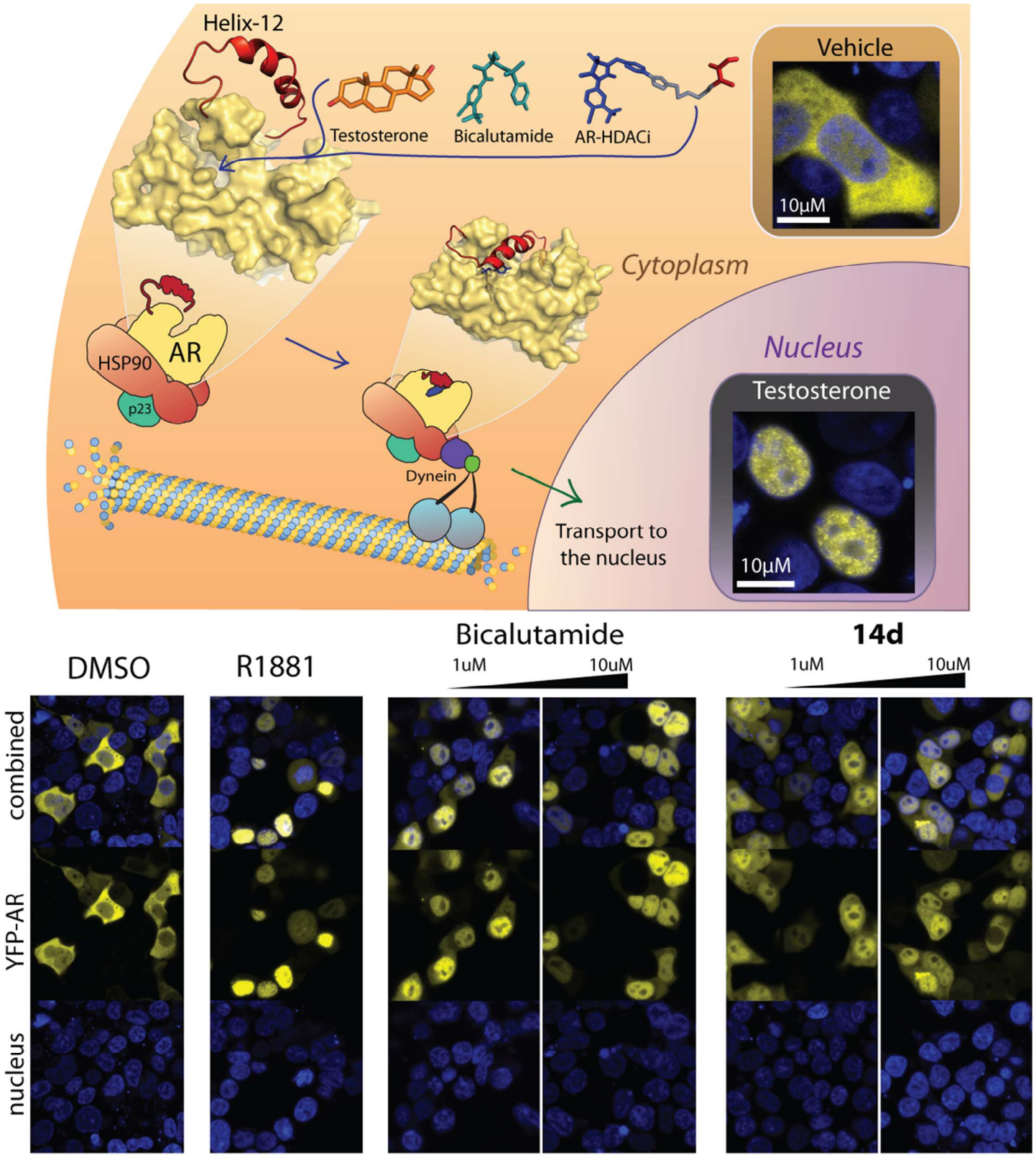
[a]IC_{50} values are an average of at least two independent experiments (in duplicate or triplicate).



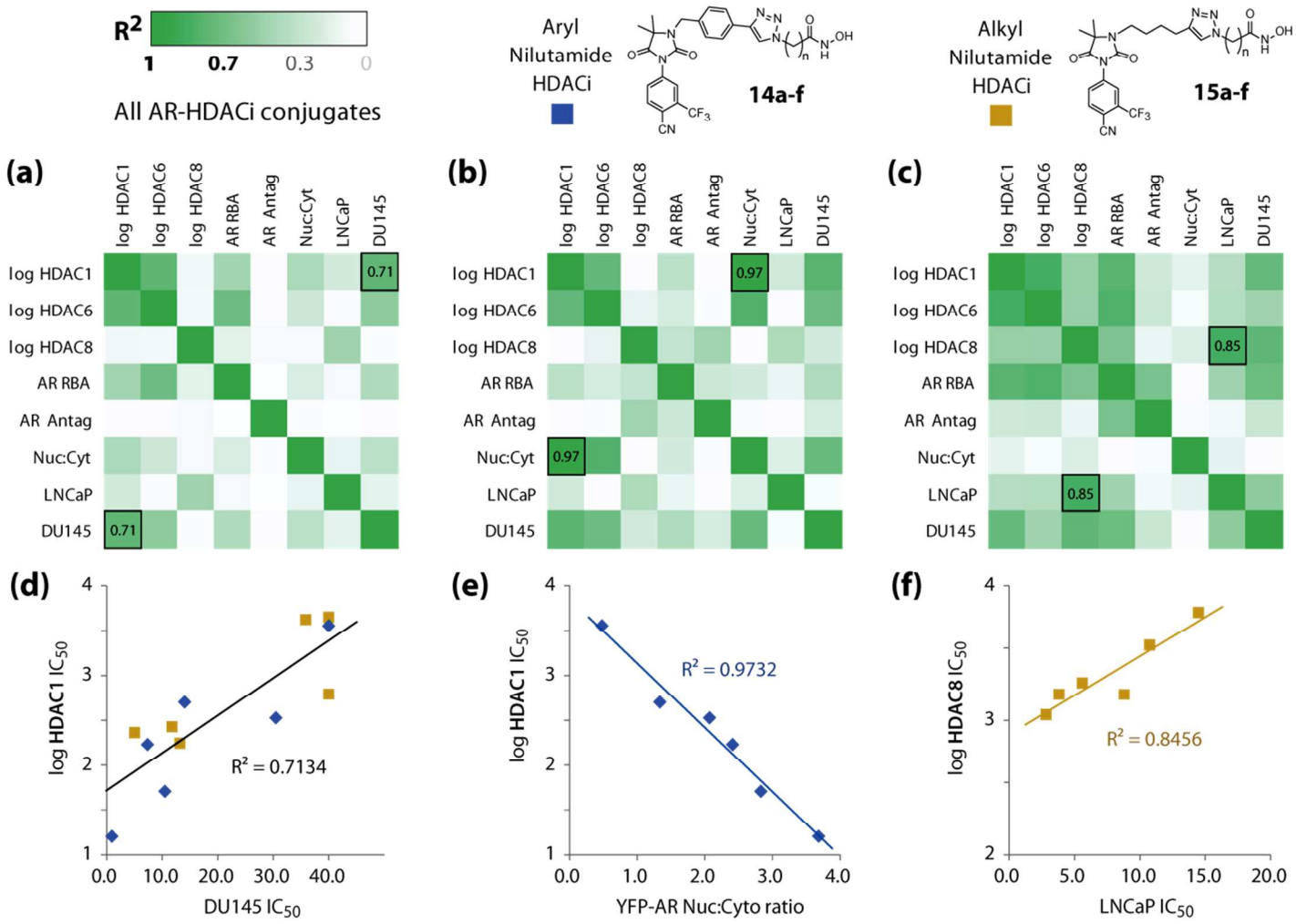
Supplemental Figure 2. AR and ER bound to agonists and antagonist. (a) Testosterone bound to AR wild type (PDB:2AM9) and (b) bicalutamide bound to AR mutant W741L (PDB:1Z95). (c) Agonist estradiol (PDB:1QKU) and (d) antagonist tamoxifen bound to ERα (PDB:3ERT). Helix 12 (H12) is shown in red.



Supplemental Figure 3. (a) **14a-f** docked into apo-AR-CoRNR homology model. (b) **14b** and **14d** superimposed, showing bond distance between their cyano nitrogen and the *N*-hydrogen of arginine 752 (R752) and the resulting binding affinity in kcal/mol. (c) **14b** as spheres to show space filling.

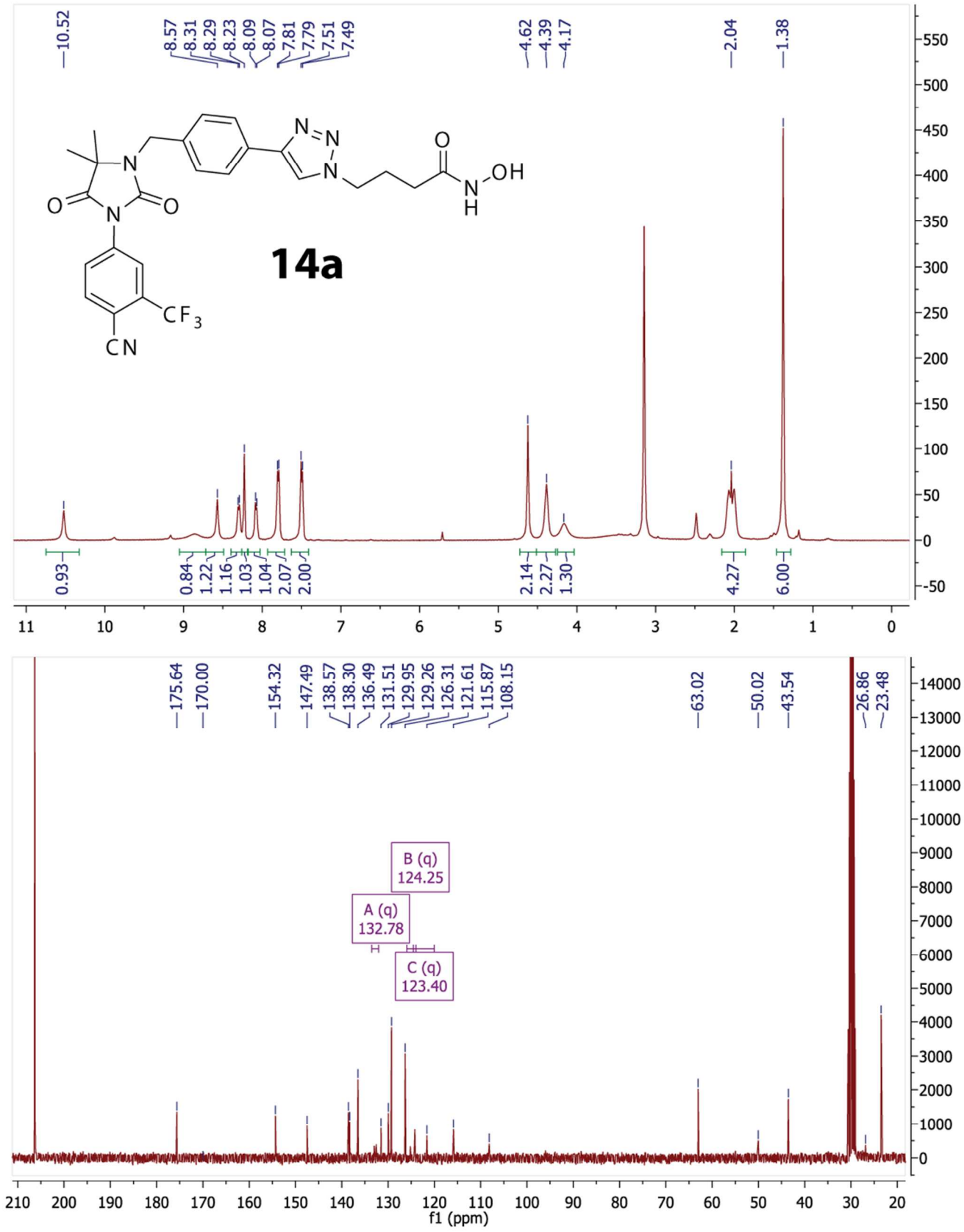


Supplemental Figure 4. YFP-AR localization in response to vehicle (DMSO), agonist R1881 (1 μM), bicalutamide and **14d**. Both bicalutamide and **14d** induce the same extent of nuclear localization at 1 μM and 10 μM.

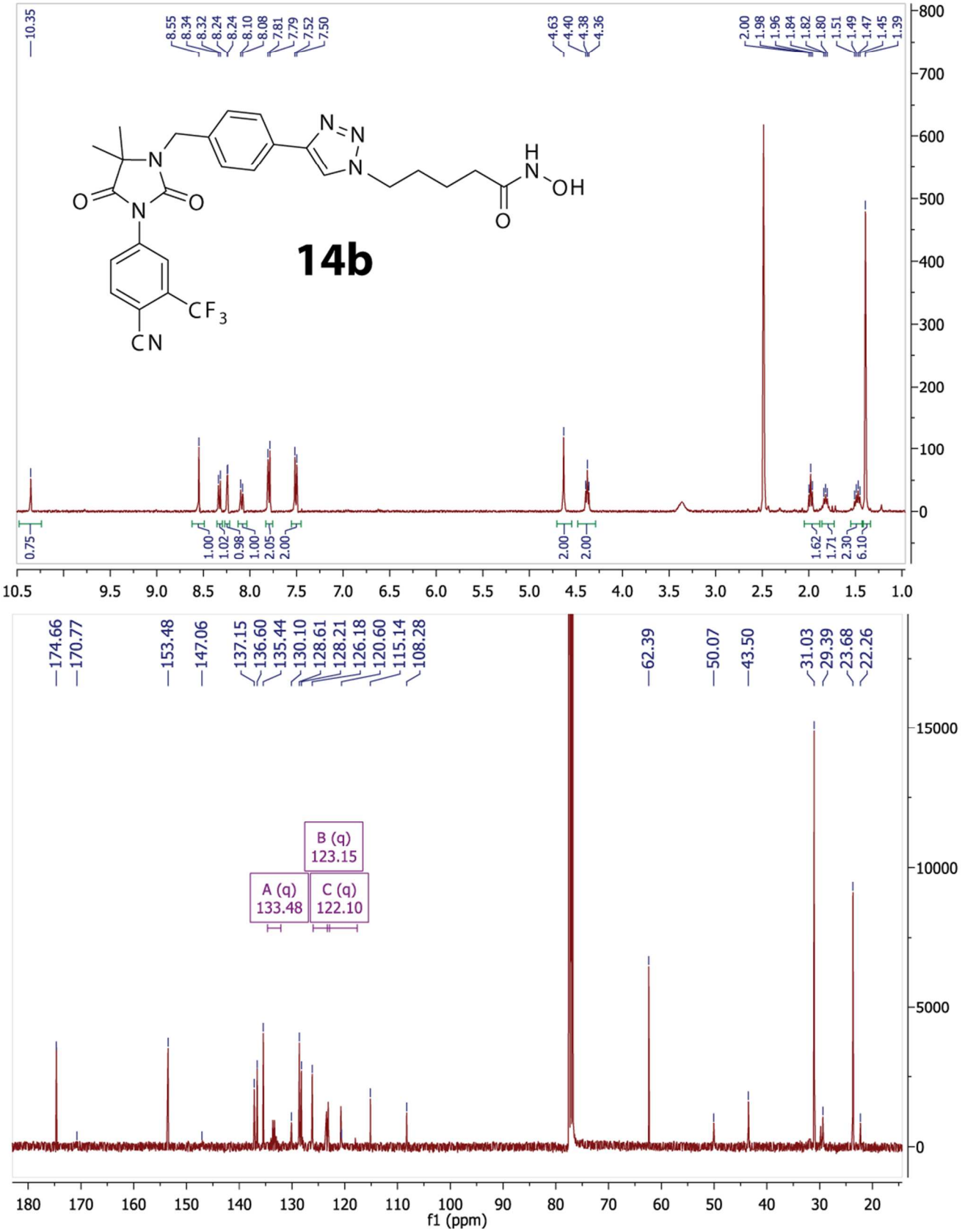


Supplemental Figure 5. Correlation heat maps from the square of the Pearson product-moment correlation coefficient (R^2) for all AR-HDACi conjugates (a), for **14a-f** (b), and for **15a-f** (c). The strongest trend across all conjugates was the correlation between HDAC1 inhibition activity and the antiproliferative activity in DU145 cells (d). Within the series of Aryl Nilutamide HDACi **14a-f**, the strongest correlation is seen between nuclear transport of YFP-AR and HDAC1 activity (e). Finally, within the series of Alkyl Nilutamide HDACi **15a-f**, stronger HDAC8 inhibition trends closely with more potent antiproliferative activity against LNCaP (f). Log HDAC, log of the HDAC inhibition IC_{50} for the given isoform; AR RBA, androgen receptor relative binding affinity IC_{50}; AR Antag, relative fluorescent units from AR antagonist activity assays; Nuc:Cyt, the ratio of YFP-AR in the nucleus versus the cytoplasm as measured under confocal microscopy; LNCaP and DU145, the dose at which cell growth was reduced by 50%. All data used here is reported in the main manuscript.

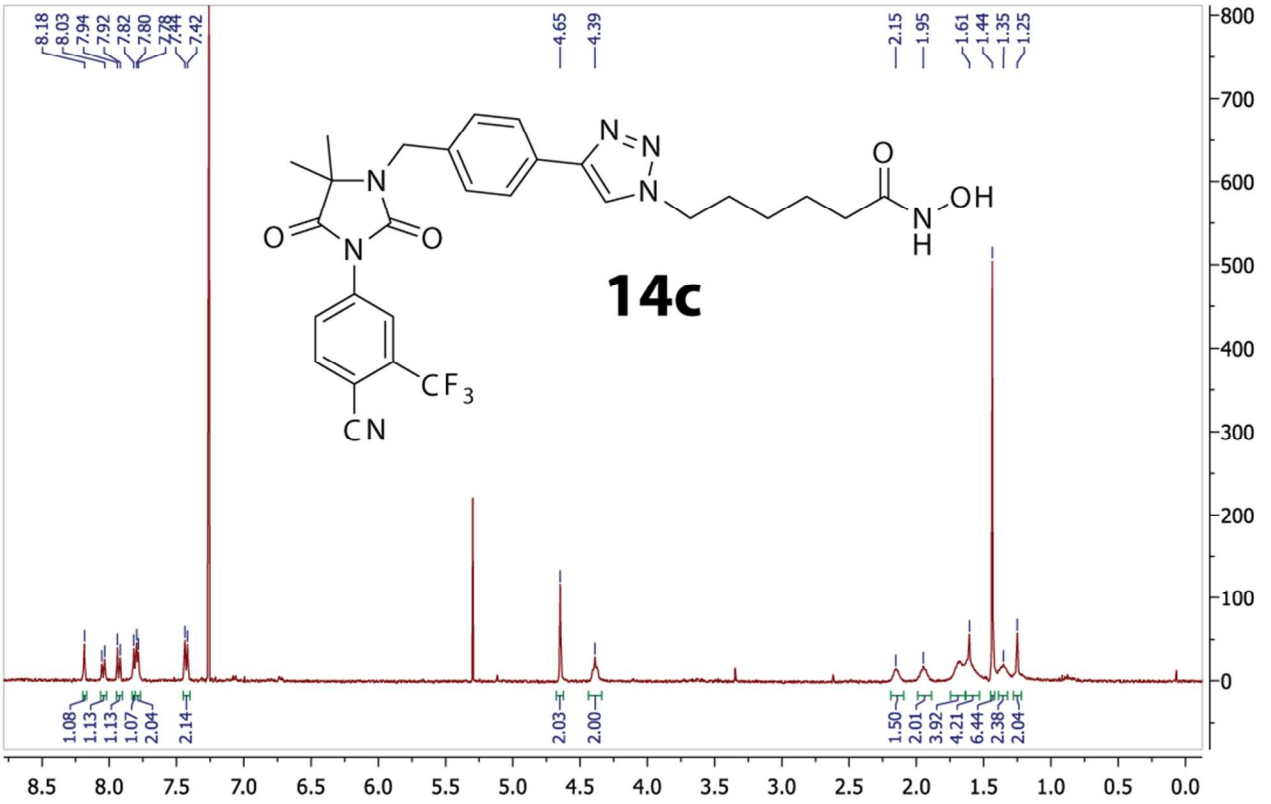
^{1}H and ^{13}C NMR of AR-HDACi **14a**

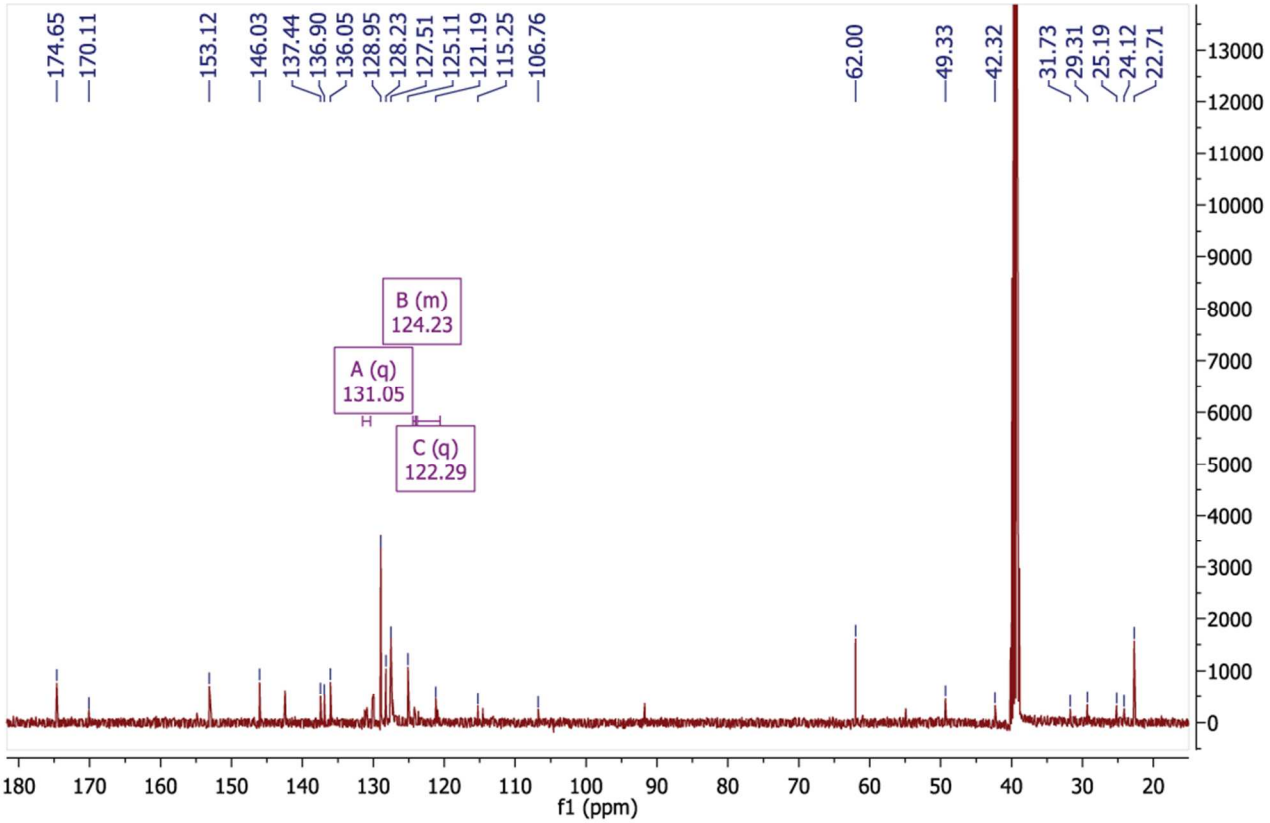


^{1}H and ^{13}C NMR of AR-HDACi **14b**

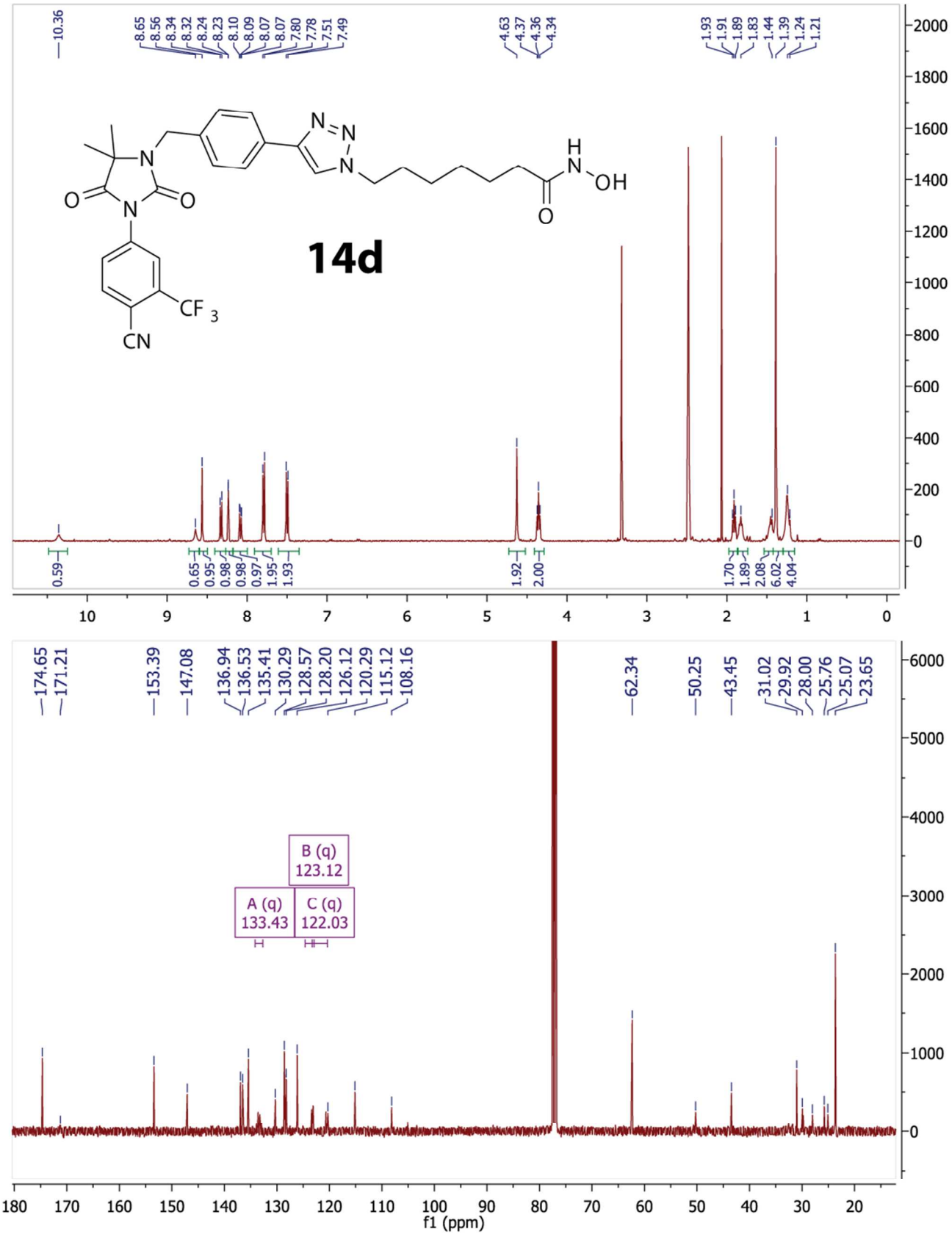


^{1}H and ^{13}C NMR of AR-HDACi **14c**

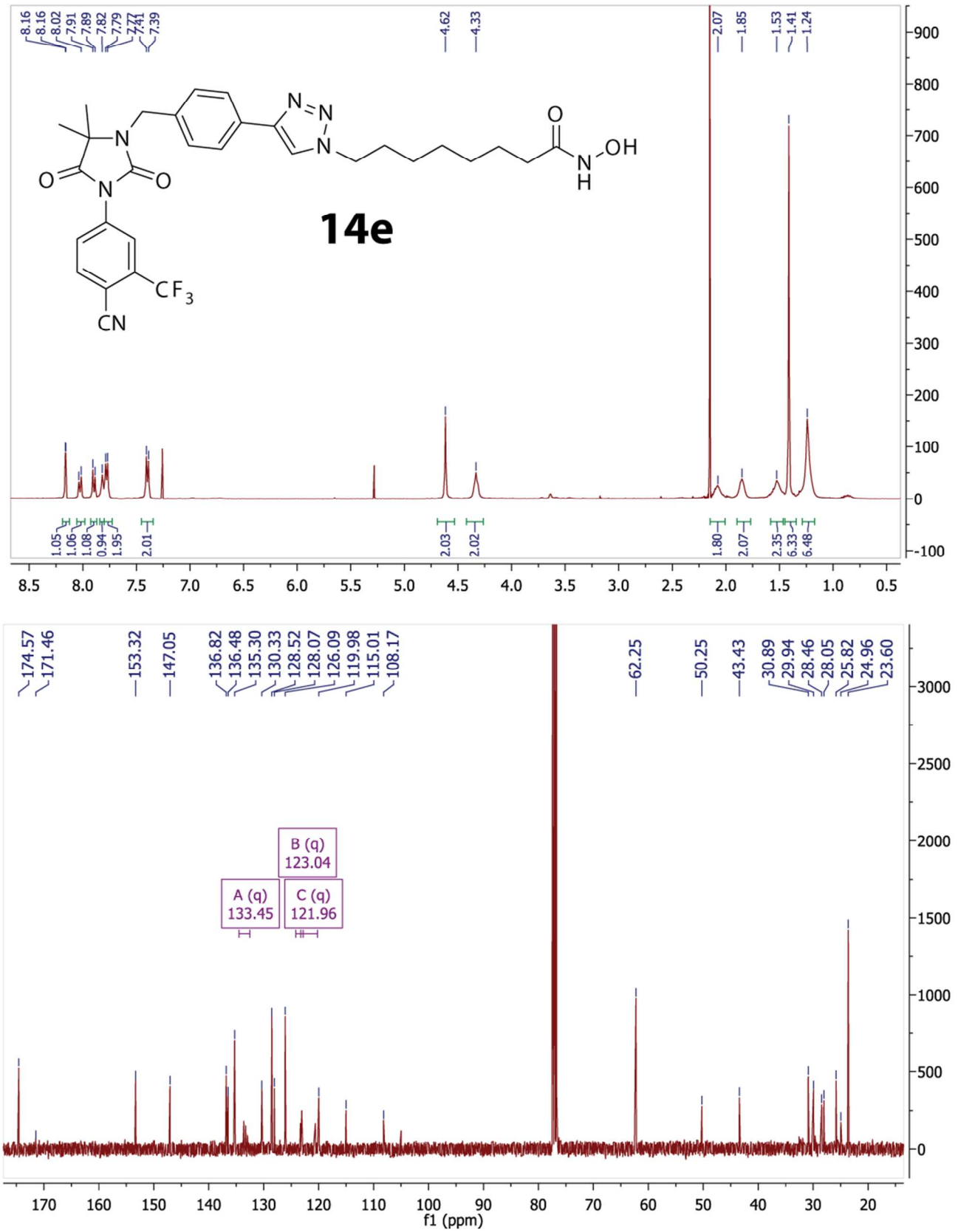




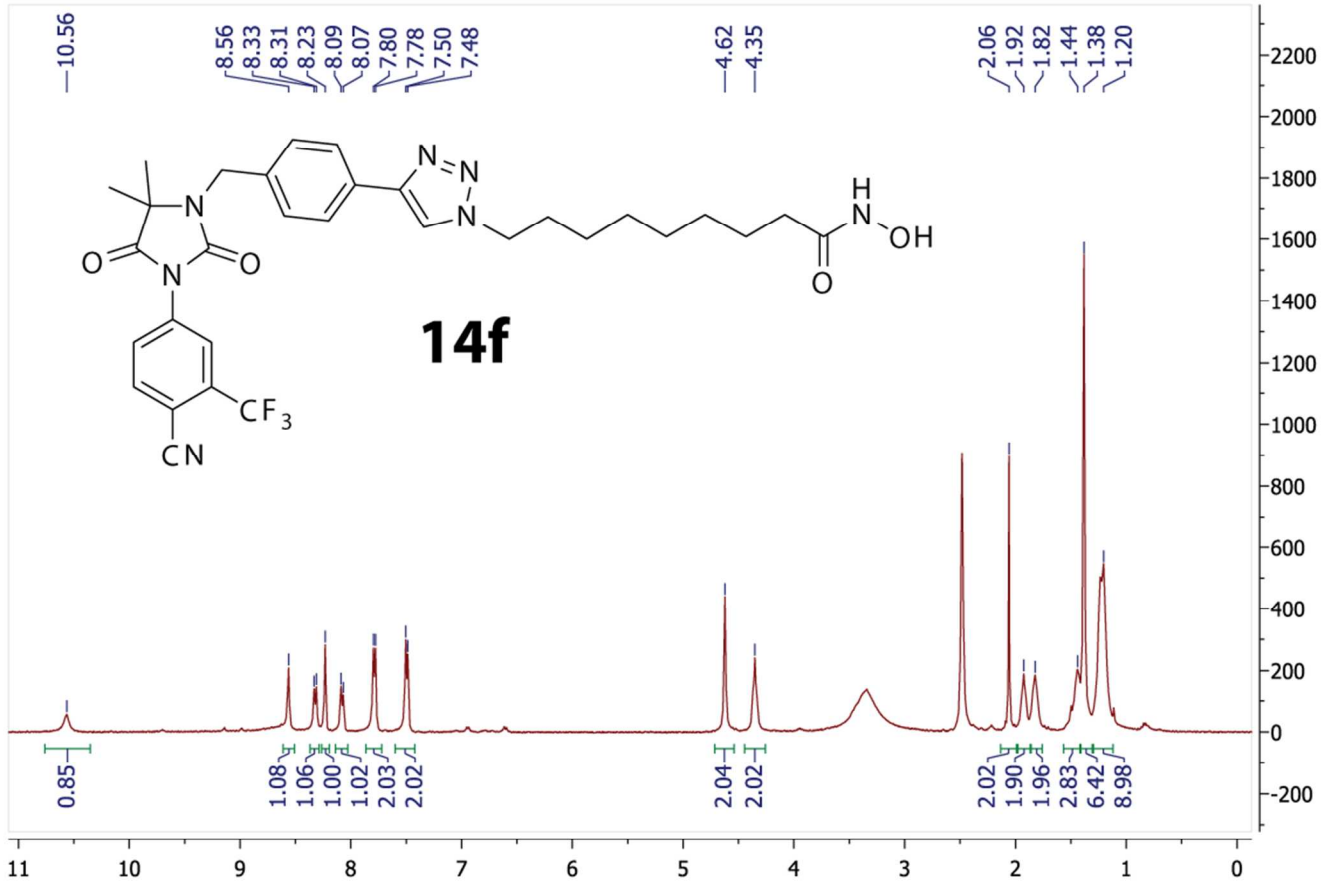
^{1}H and ^{13}C NMR of AR-HDACi **14d**

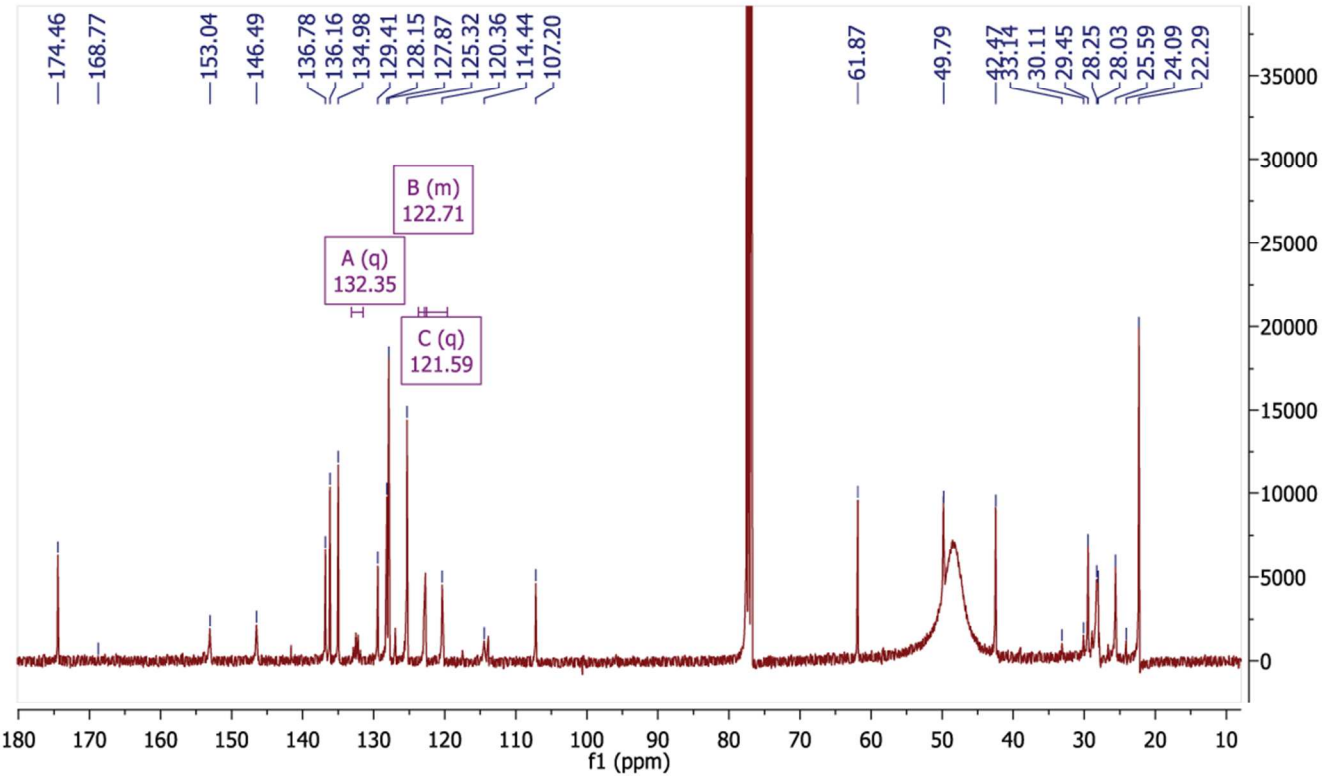


^{1}H and ^{13}C NMR of AR-HDACi **14e**

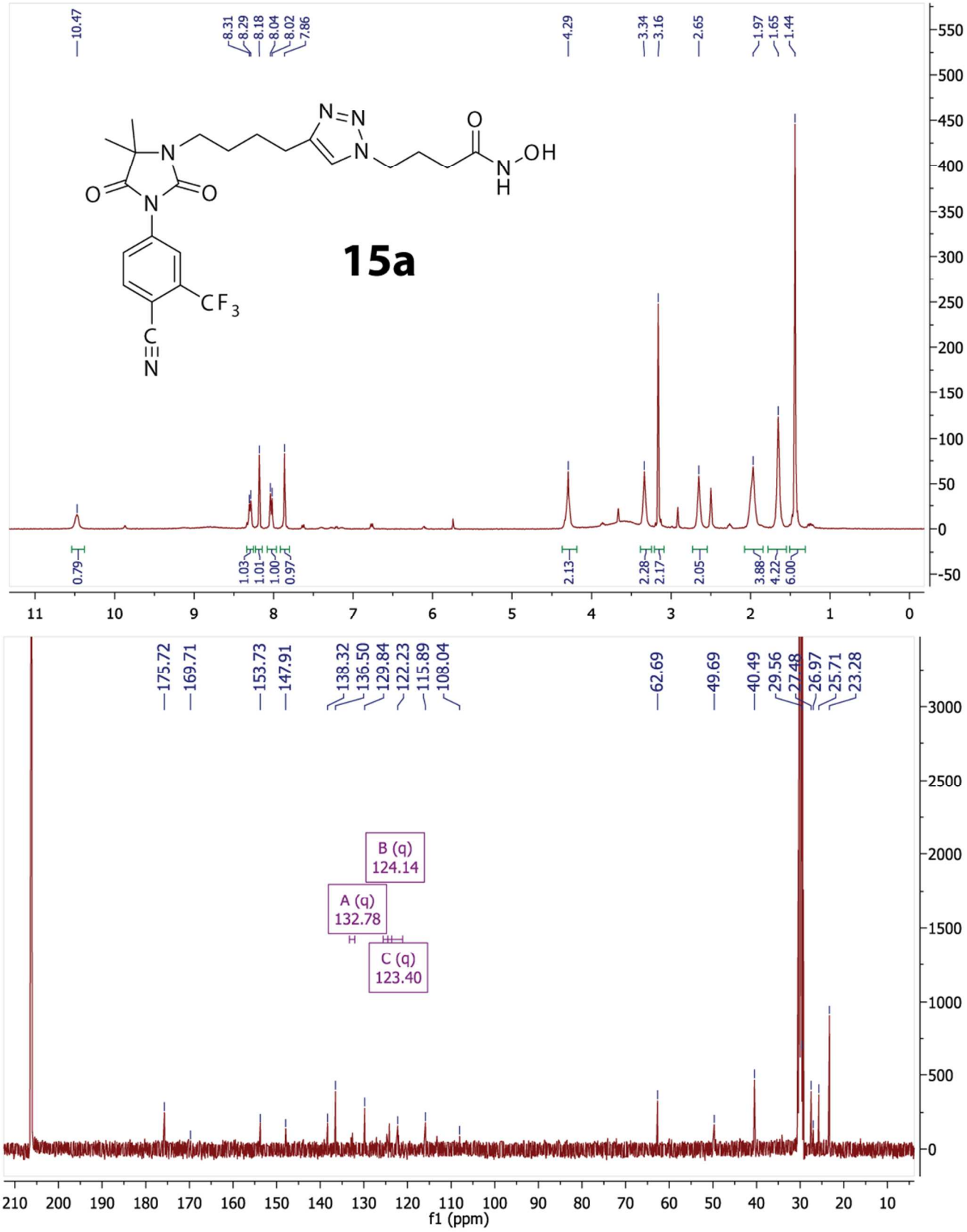


^{1}H and ^{13}C NMR of AR-HDACi **14f**

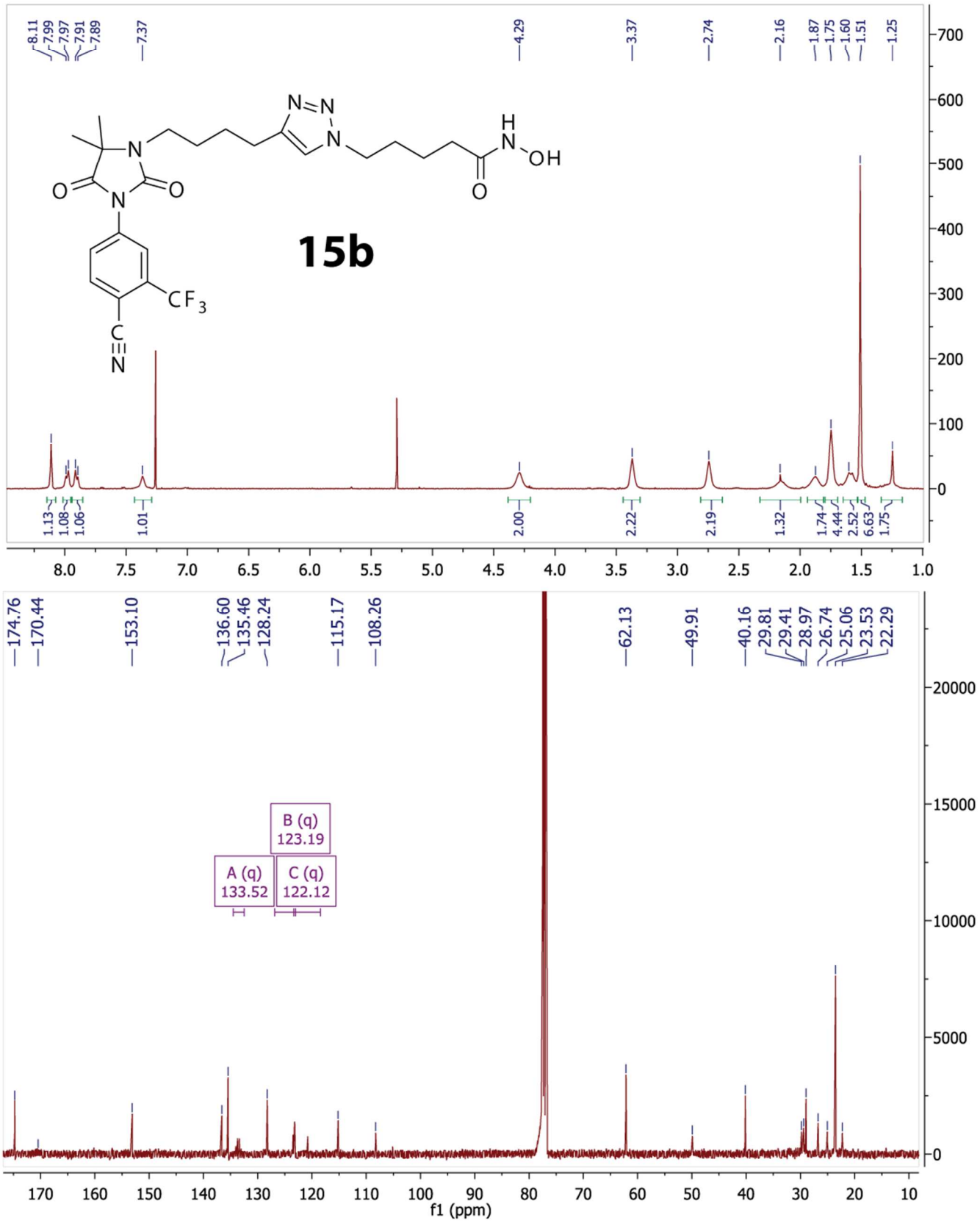




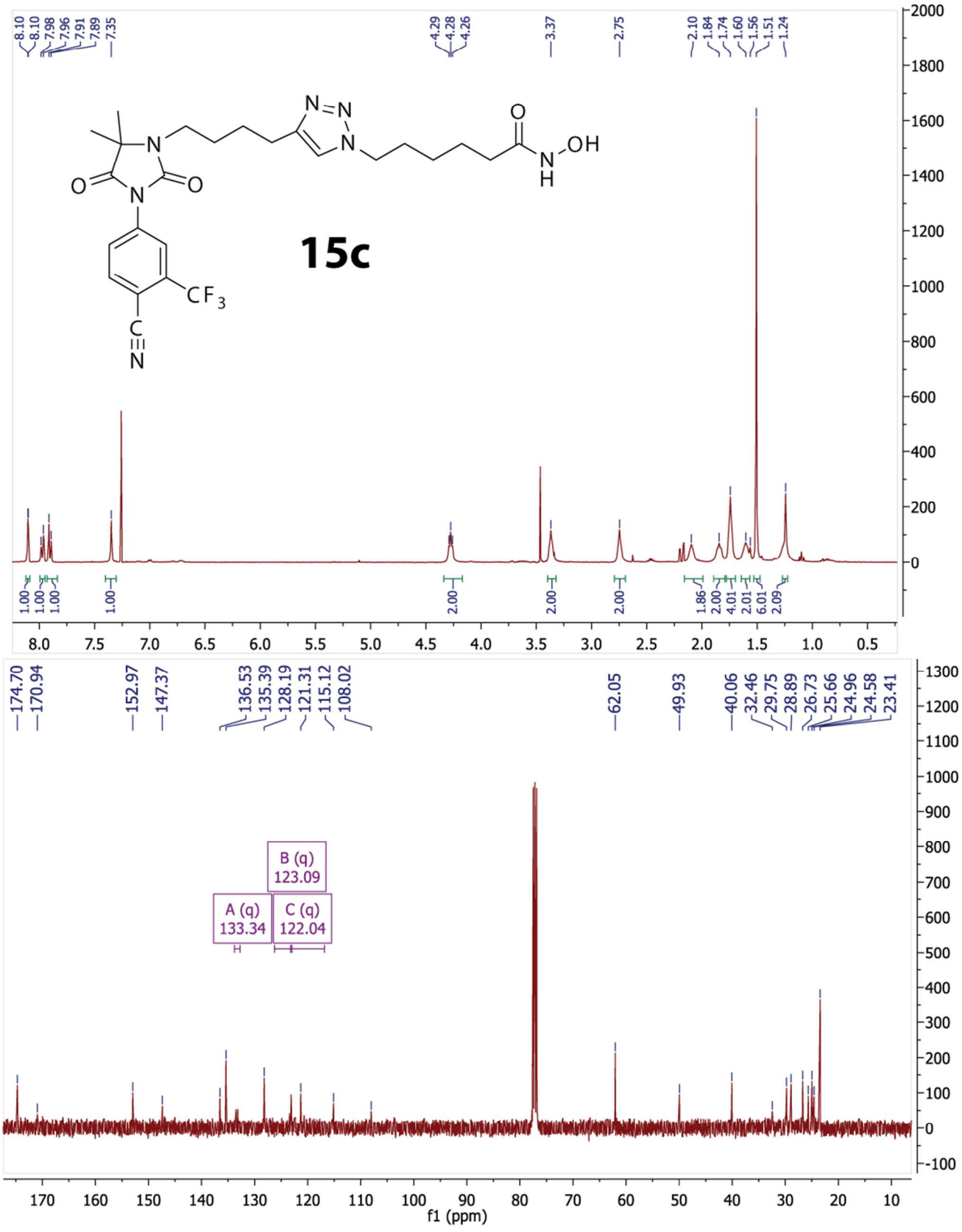
^{1}H and ^{13}C NMR of AR-HDACi **15a**



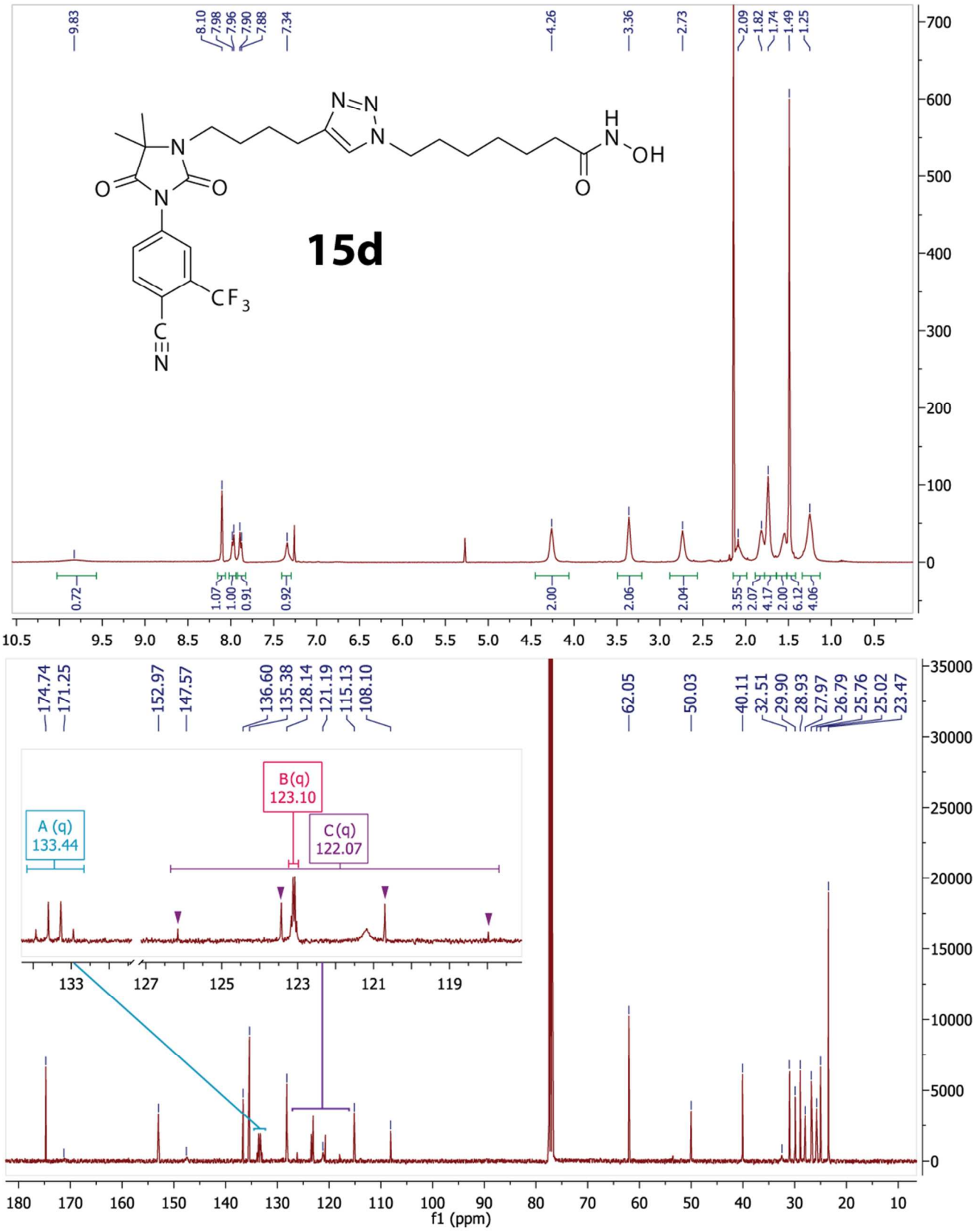
^{1}H and ^{13}C NMR of AR-HDACi **15b**



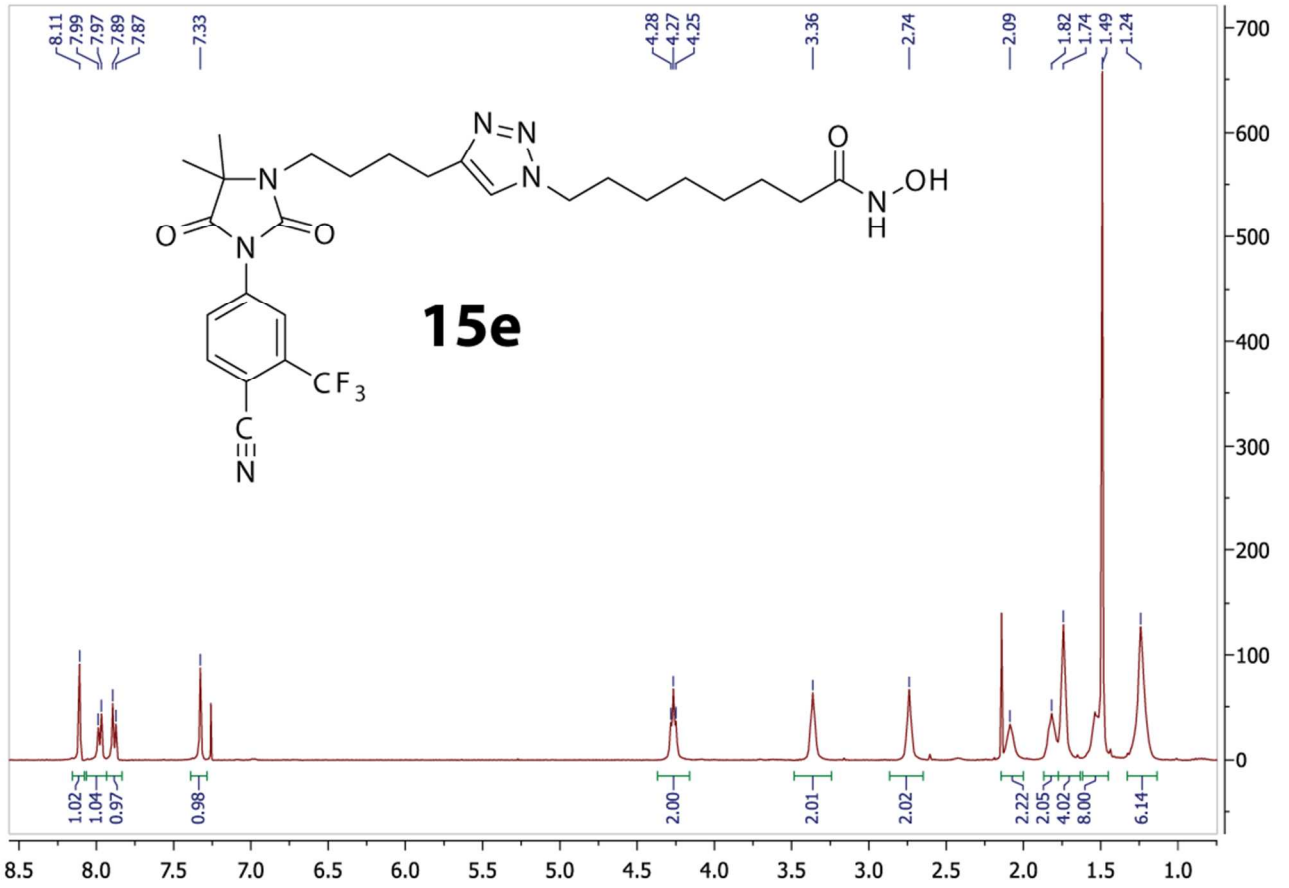
^{1}H and ^{13}C NMR of AR-HDACi **15c**

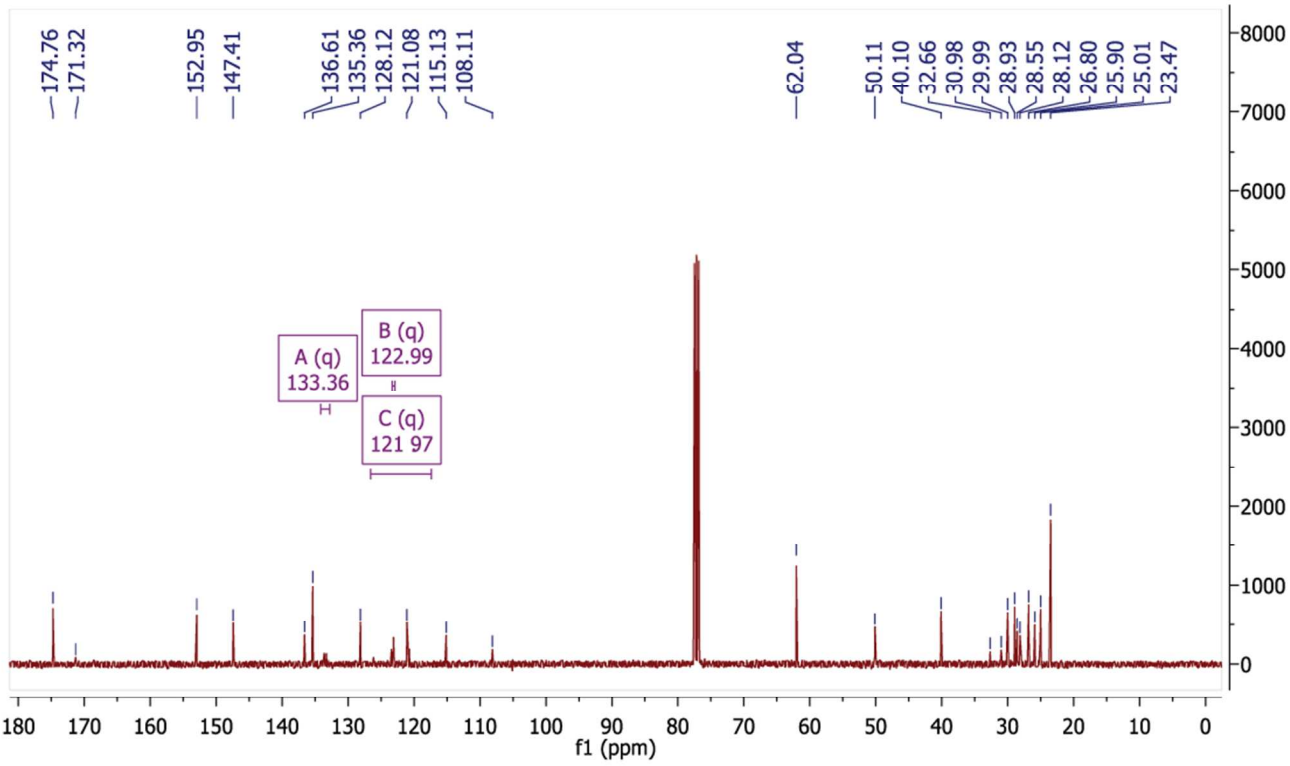


^{1}H and ^{13}C NMR of AR-HDACi **15d**



^{1}H and ^{13}C NMR of AR-HDACi **15e**





^{1}H and ^{13}C NMR of AR-HDACi **15f**