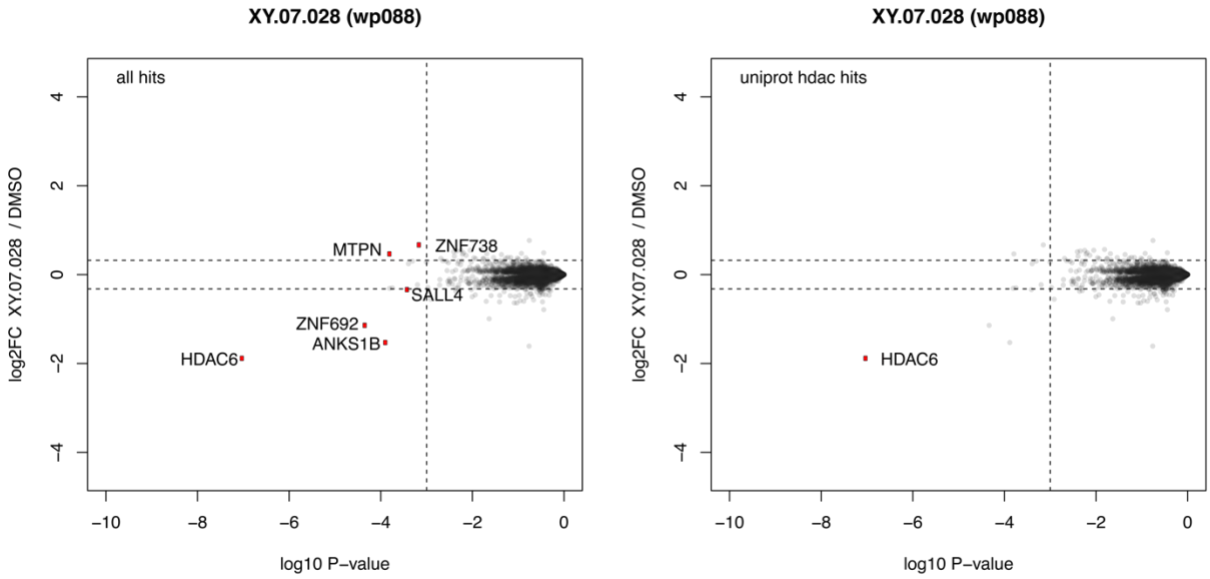
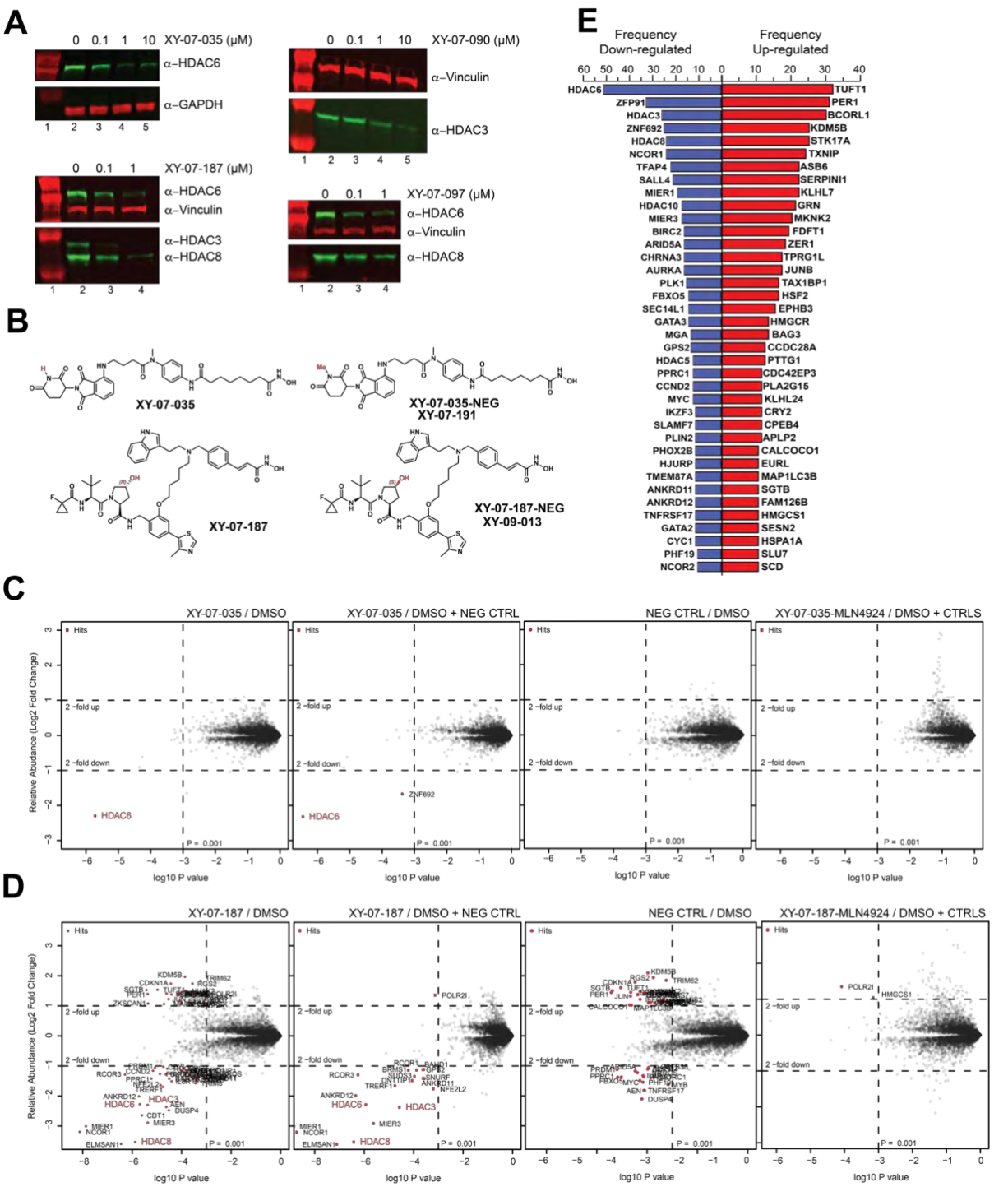
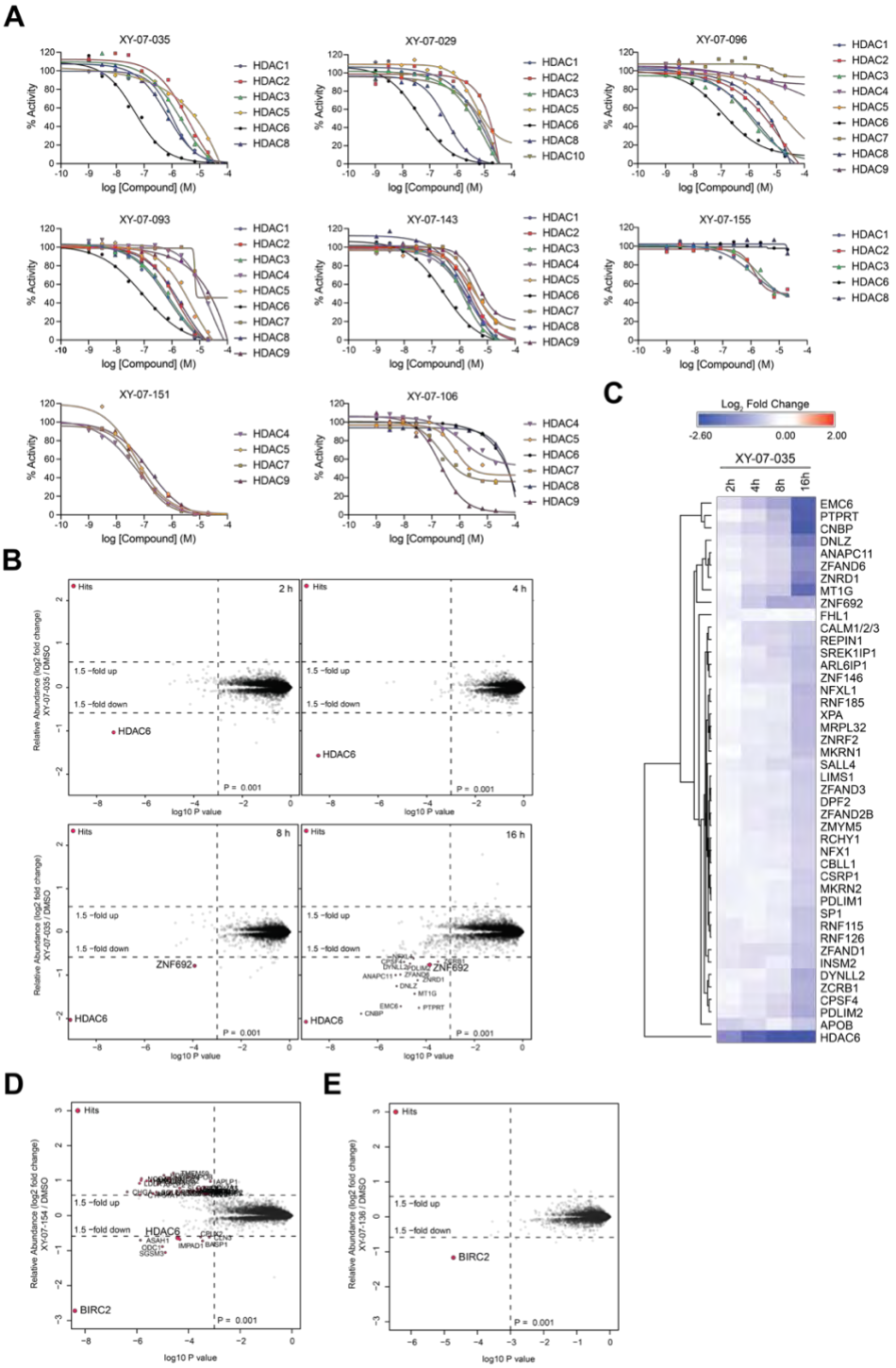


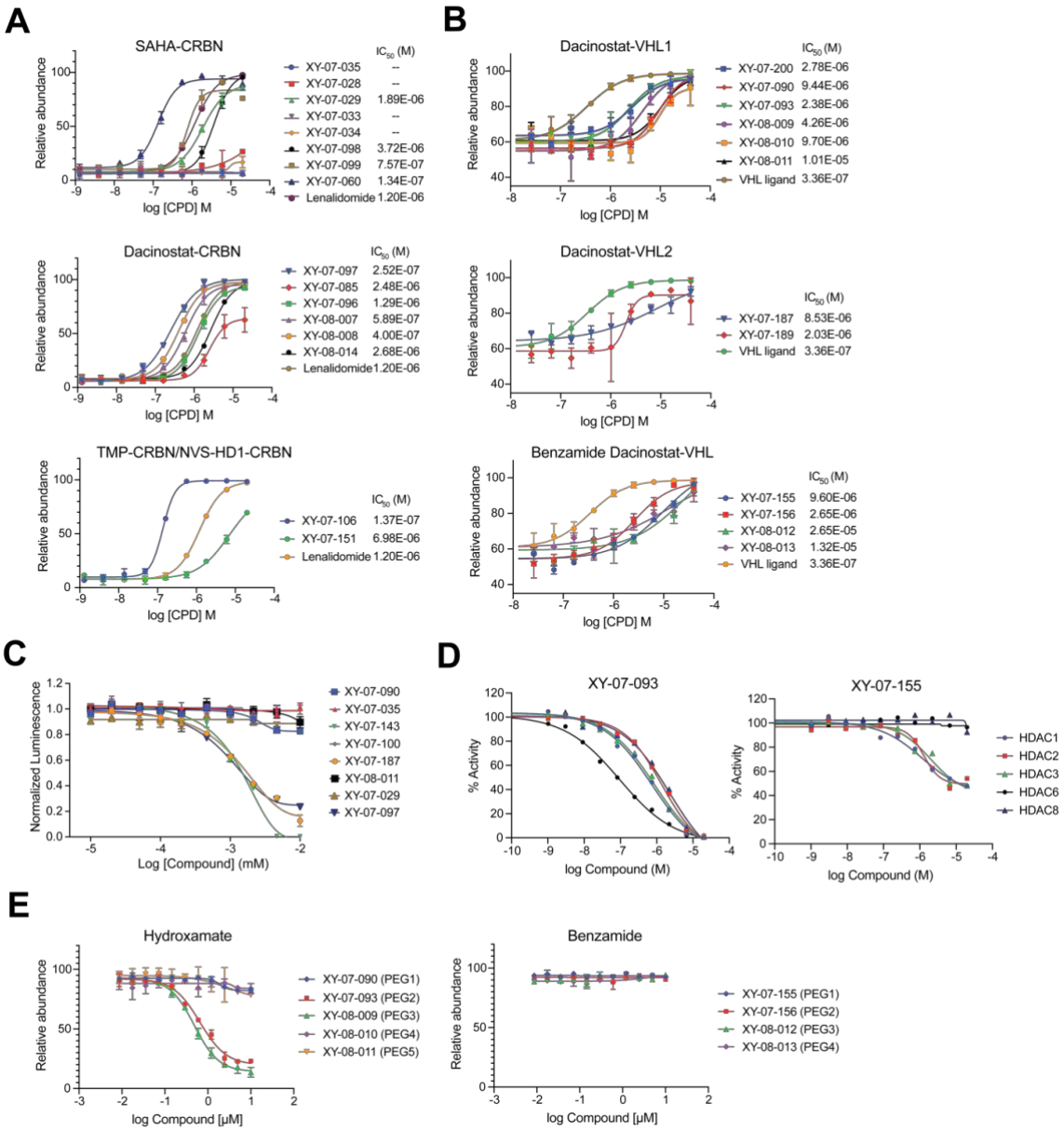
Supplementary Figure S1 | Proteomics scatterplots profiling 52 HDAC-targeted degraders over 101 independent treatments included in this study. Scatterplots depicting the fold change in relative protein abundance in response to indicated treatment determined using global quantitative proteomics. Log_2FC is displayed on the y-axis and $log_{10}P$-value on the x-axis. Example plots for a single treatment (XY-07-028) are displayed here. Scatterplots for all 101 independent treatments can be found in a separate PDF data file “Data S2”. Left. All proteins determined to be hits are colored red and labelled. Right. All HDAC’s determined to be hits are colored red and labelled. Significant changes were assessed by moderated t-test as implemented in the limma package (Ritchie et al., 2015). A hit is defined as a protein that has a FC > 1.25 and P-value < 0.001 in response to treatment compared to DMSO control. Data are from *n = 1-3* biologically independent samples. Related to Figure 1-4, Table S1-2 and Data S2.



Supplementary Figure S2 | (**A**) Immunoblots quantifying HDAC expression level after dose response treatment with indicated degraders. (**B**) Chemical structures for XY-07-035 and XY-07-187 and their respective negative control compounds. (**C**) Scatterplots depicting the log_2FC in relative protein abundance in response to treatment with indicated compounds. (**D**) As in **C**, with indicated compounds. CTRLS in the far right plot refers to MLN4924 and NEG CTRL treatments. (**E**) Bar plot displaying the number of times that proteins are determined to be up- and down-regulated hits. Only the top moving proteins are displayed, data is contained within the corresponding data Table S3. Related to Figure 1-2 and Table S1-3.



Supplementary Figure S3 | (**A**) Percentage of *in vitro* HDAC enzymatic activity remaining in response to increasing concentrations of indicated degraders. Data is from *n = 1* ten-point titrations. (**B**) Scatterplots displaying the log_2FC in relative abundance for downregulated proteins in response to a time course treatment with XY-07-035 at 2, 4, 8, and 16 h. (**C**) Heatmap depicting the same time course data for XY-07-035 from **B**. (**D**) Scatterplots depicting the log_2FC in relative protein abundance in response to treatment with XY-07-154. (**E**) As in **D**, for compound XY-07-136. Proteomics data is from *n = 1-2* biologically independent treatment samples. Related to Figure 2-4 and Table S1-3.



Supplementary Figure S4 | (**A**) Cellular CRBN engagement assay depicting relative protein abundance of BRD4^{BD2}-GFP in response to increasing concentration of indicated degraders which act to outcompete the binding of dBET6 (CRBN-based BRD4^{BD2} degrader). Data is the mean of *n = 2* biologically independent treatment samples ± SD. (**B**) Cellular VHL engagement assay depicting increasing level of BRD4^{BD2}-GFP in response to increasing concentration of indicated degraders which act to outcompete the binding of AT1 (VHL-based BRD4^{BD2} degrader). Data is the mean of *n = 2* biologically independent treatment samples ± SD. (**C**) Cell viability assays in response to treatment with the indicated degraders. Viability data is the mean of *n = 3* biological replicates. (**D**) Percentage of *in vitro* HDAC enzymatic activity remaining in response to increasing concentrations of degraders XY-07-093 and XY-07-155. Data is from *n = 1* ten-point titrations. (**E**) Relative protein abundance of HDAC8-GFP fusion plotted in response to increasing concentrations of indicated dacinostat-VHL degraders with different linker lengths. Data is the mean of *n = 2* biological replicates ± SD. Related to Figure 3-4 and Table S3.

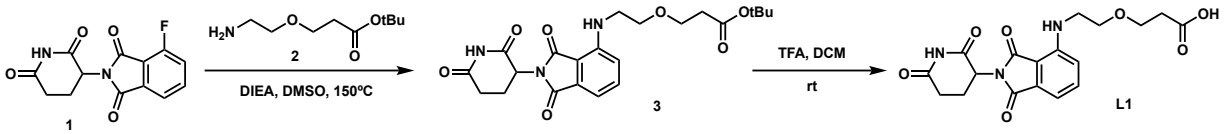
Data S1 | Compound synthesis and characterization. Related to Figure 1.

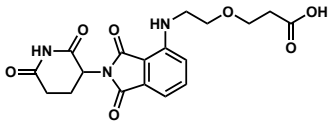
General

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. All reactions were monitored using a Waters Acquity UPLC/MS system using Acquity UPLC® BEH C18 column (2.1 x 50 mm, 1.7 µm particle size). UPLC method A: solvent gradient = 80% A at 0 min, 5% A at 1.8 min; method B: solvent gradient = 100% A at 0 min, 5% A at 1.8 min; solvent A = 0.1% formic acid in H_2O; solvent B = 0.1% formic acid in acetonitrile; flow rate: 0.6 mL/min; or an Agilent LC/MS system (Agilent 1200LC/G6130A MS) using SunFire™ C18 column (4.6 x 50 mm, 3.5 µm particle size). LC method: solvent gradient = 95% A to 5% A; solvent A = 0.01% TFA in Water; solvent B = 0.01% TFA in ACN; flow rate: 2.0 mL/min, column temperature 50°C. Purification of reaction products was carried out by flash chromatography using CombiFlash®Rf with Teledyne Isco RediSep® normal-phase silica flash columns; or Waters HPLC system using SunFireTM C18 column (19 x 100 mm, 5 µm particle size): solvent gradient 0% to 100% acetonitrile or MeOH in H_2O (0.035% TFA as additive); flow rate: 20 mL/min, or SunFireTM C18 column (30 x 250 mm, 5 µm particle size): solvent gradient 0% to 100% acetonitrile or MeOH in H_2O (0.035% TFA as additive); flow rate: 40 mL/min. ^{1}H NMR and ^{13}C NMR spectra were obtained using Bruker Avance III spectrometers (400 MHz or 500 MHz for ^{1}H, and 125 MHz for ^{13}C). Chemical shifts are reported relative to deuterated methanol (δ = 3.31) or dimethyl sulfoxide (δ = 2.50) for ^{1}H NMR. Spectra are given in ppm (δ) and as br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and coupling constants *J* are reported in Hertz.

Synthesis of Preformed Linkers

Ligand based on thalidomide

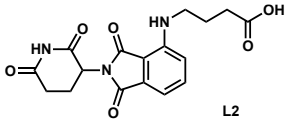




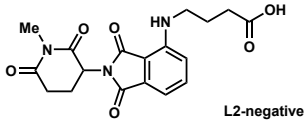
3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)propanoic acid, L1:

Compound **1** (405 mg, 1.47 mmol, 1.0 eq.) and DIEA (510 µL, 2.0 eq.) were dissolved in DMSO (7 mL) in a sealed tube, to the mixture was added *tert*-butyl 3-(2-aminoethoxy)propanoate (250 mg, 0.9 eq.) in one batch, and the reaction was sealed and immediately heated to 150 °C. After 30 min, the reaction mixture was cooled to room temperature, and H_2O was added and the mixture was extracted with ethyl acetate. The organic layers were combined and washed with H_2O, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified using ISCO (dichloromethane/methanol, 0%-10%) to yield protected compound **3** as a yellow oil (506 mg, 86% yield). **UPLC-MS** RT: 1.32 min (Method A), Mass m/z: 389.87 $[M\text{-}tBu+H]^+$.

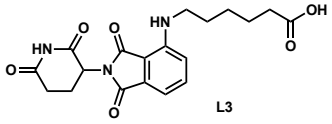
Compound **3** (44 mg, 0.10 mmol, 1.0 eq.) was dissolved in dichloromethane (3 mL) and treated with TFA (0.5 mL). The reaction was monitored by UPLC and when the starting material was consumed, the mixture was concentrated *in vacuo.* The residue was purified with HPLC (H_2O/MeOH, 0%-100%) to yield compound **L1** as a yellow oil (30 mg, quant. yield). **UPLC-MS** RT: 0.82 min (Method A), Mass m/z: 389.87 $[M+H]^+$.



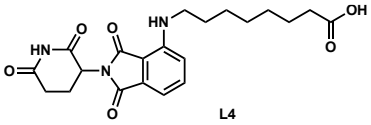
4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butanoic acid, L2 was synthesized from compounds **1** and *tert*-butyl 4-aminobutanoate using similar procedures and was obtained as a yellow oil. **UPLC-MS** RT: 0.85 min (Method A), Mass m/z: 360.27 $[M+H]^+$.



4-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butanoic acid, L2-negative was synthesized from 4-fluoro-2-(1-methyl-2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione and *tert*-butyl 4-aminobutanoate using similar procedures and was obtained as a yellow oil.

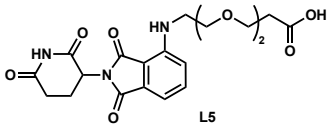


6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexanoic acid, L3 was synthesized directly from compounds **1** and 6-aminohexanoic acid using similar procedures and was obtained as a yellow oil. **UPLC-MS** RT: 1.00 min (Method A), Mass m/z: 387.97 $[M+H]^+$.



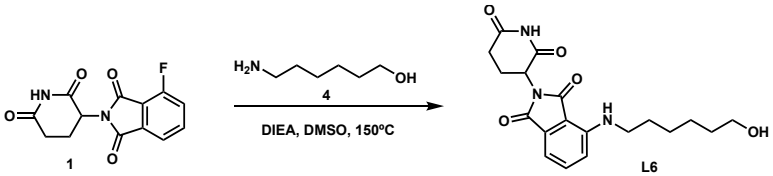
L4

8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octanoic acid, L4 was synthesized directly from compounds **1** and 8-aminooctanoic acid using similar procedures and was obtained as a yellow oil. **UPLC-MS** RT: 1.15 min (Method A), Mass m/z: 415.97 $[M+H]^+$.



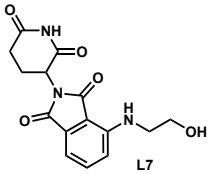
L5

3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy) propanoic acid, L5 was synthesized from compound **1** and *tert*-butyl 3-(2-aminoethoxy)-4-methoxybutanoate using similar procedures and was obtained as a yellow oil. **UPLC-MS** RT: 1.32 min (Method A), Mass m/z: 433.87 $[M+H]^+$.



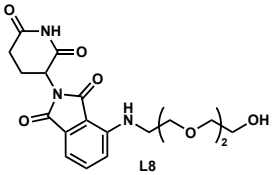
1 L6

2-(2,6-dioxopiperidin-3-yl)-4-((6-hydroxyhexyl)amino)isoindoline-1,3-dione, L6: Compound **1** (400 mg, 1.45 mmol, 1.0 eq.) and DIEA (378 µL, 1.5 eq.) were dissolved in DMSO (6 mL) in a sealed tube, to the mixture was added 6-aminohexan-1-ol (204 mg, 1.2 eq.) in one batch, and the reaction was sealed and immediately heated to 150 °C. After 1 hour, the reaction mixture was cooled to room temperature, and H_2O was added and the mixture was extracted with ethyl acetate. The organic layers were combined and washed with H_2O, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield **L6** as a yellow oil (409 mg, 76% yield). **UPLC-MS** RT: 1.04 min (Method A), Mass m/z: 374.17 $[M+H]^+$.



L7

2-(2,6-dioxopiperidin-3-yl)-4-((2-hydroxyethyl)amino)isoindoline-1,3-dione, L7 was synthesized from compound **1** and 2-aminoethan-1-ol using similar procedures and was obtained as a yellow oil. **UPLC-MS** RT: 0.75 min (Method A), Mass m/z: 318.17 $[M+H]^+$.

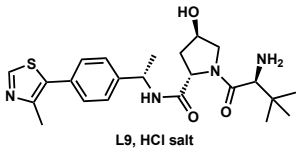


L8

2-(2,6-dioxopiperidin-3-yl)-4-((2-(2-(2-hydroxyethoxy)ethoxy)ethyl)amino) isoindoline-1,3-dione, L8 was synthesized from compound **1** and 2-(2-(2-

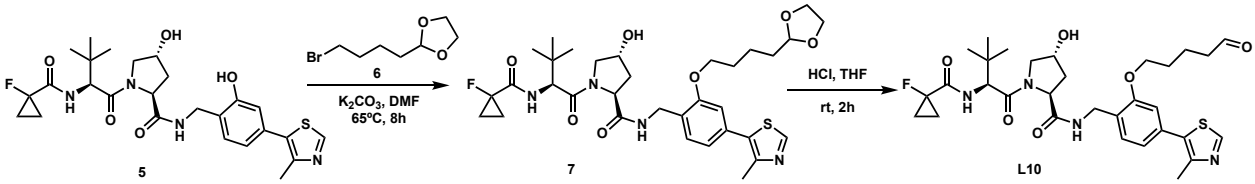
aminoethoxy)ethoxy)ethan-1-ol using similar procedures and was obtained as a yellow oil. **UPLC-MS** RT: 0.82 min (Method A), Mass m/z: 406.27 $[M+H]^+$.

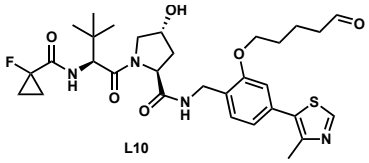
Ligand based on VHL ligand



L9, HCl salt

(2*S*,4*R*)-1-((*S*)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide, L9 was purchased from MedChem Express as an HCl salt.

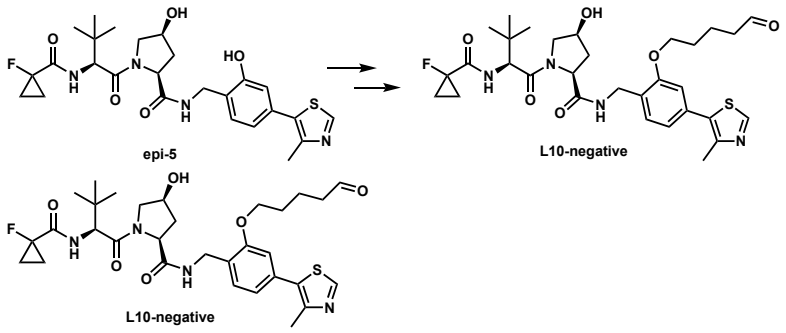




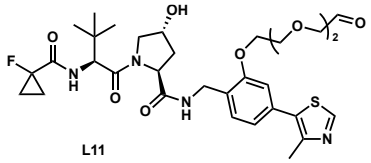
(2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)-2-((5-oxopentyl)oxy)benzyl)pyrrolidine-2-carboxamide, L10

To a solution of compound **5** (Zoppi et al., 2019) (150 mg, 0.28 mmol, 1.0 eq.) and 2-(4-bromobutyl)-1,3-dioxolane (**6**) (71 mg, 1.2 eq.) in DMF (1.5 mL) was added K_2CO_3 (58 mg, 1.5 eq.). The reaction mixture was heated to 65 °C and stirred for 4h. The reaction was monitored by UPLC-MS. Once the starting materials were consumed, the reaction was filtered and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* The residue was purified using ISCO (dichloromethane/methanol, 0%-10%) to yield compound **7** (187 mg, quant. yield). **UPLC-MS** RT: 1.28 min (Method A), Mass m/z: 661.50 $[M+H]^+$.

Compound **7** (30 mg, 0.045 mmol, 1.0 eq.) was treated with a 1:1 mixture of 2N aqueous HCl in THF (0.75 mL) at room temperature. The reaction was stirred for 2 h, and monitored by UPLC-MS. Once the limiting starting material was consumed, the reaction was quenched with aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to yield **L10** and the residue was used in the next step without further purification. **UPLC-MS** RT: 1.15 min (Method A), Mass m/z: 617.29 $[M+H]^+$.

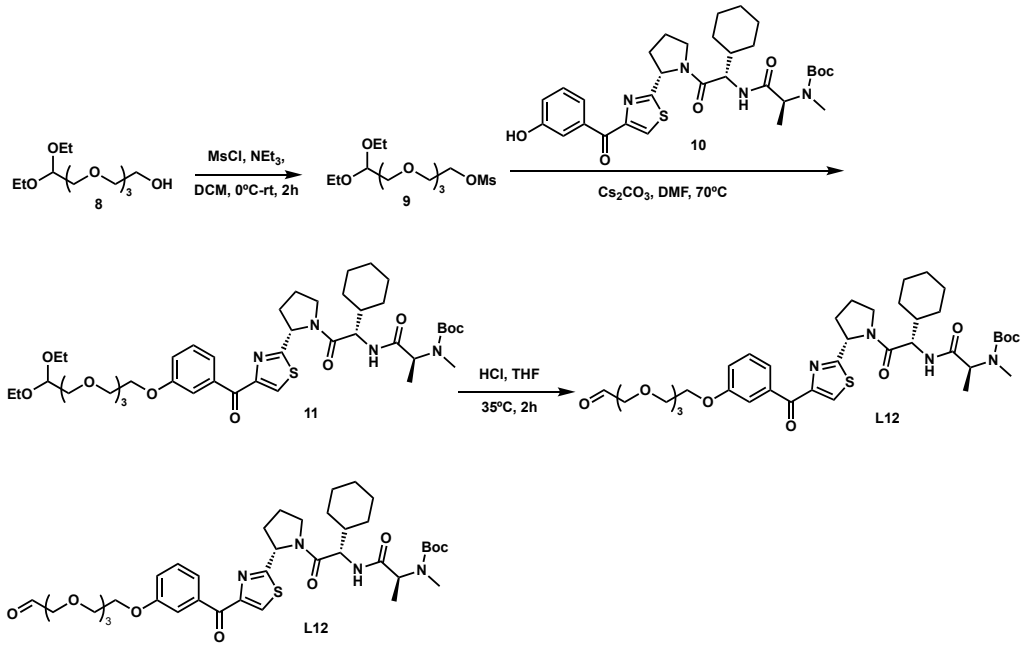


(2*S*,4*S*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)-2-((5-oxopentyl)oxy)benzyl)pyrrolidine-2-carboxamide, L10-negative was synthesized from **epi-5** (Zoppi et al., 2019) using similar procedures. **UPLC-MS** RT: 0.95 min (Method A), Mass m/z: 662.90 $[M+H]^+$.



(2*S*,4*R*)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)-2-(2-(2-(2-oxoethoxy)ethoxy)ethoxy)benzyl) pyrrolidine-2-carboxamide, L11 was synthesized from 2-(2-(2,2-diethoxyethoxy)ethoxy)ethyl methanesulfonate using similar procedures. **UPLC-MS** RT: 0.95 min (Method A), Mass m/z: 662.90 $[M+H]^+$.

Ligand based on IAP ligand LCL-161

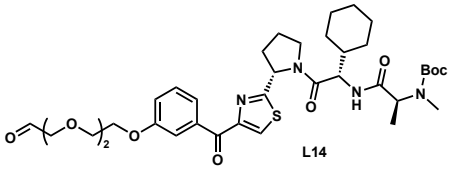


***tert*-butyl ((*S*)-1-(((*S*)-1-cyclohexyl-2-oxo-2-((*S*)-2-(4-(3-(2-(2-(2-(2-oxoethoxy)ethoxy)ethoxy) ethoxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)ethyl)amino)-1-oxopropan-2-yl)(methyl) carbamate, L12**

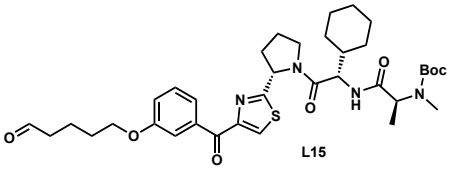
To a solution of acetal **8** (133 mg, 0.5 mmol, 1.0 eq.) in dichloromethane (3 mL) were added MsCl (94 μL, 2.4 eq.) and NEt_3 (209 μL, 3 eq.) at 0ºC. The reaction was stirred for 30 min and monitored by UPLC-MS. Once the limiting starting material was consumed, the reaction was quenched with H_2O and extracted with dichloromethane. The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to yield compound **9** and the residue was used in the next step without further purification. **UPLC-MS** RT: 0.96 min (Method A), Mass m/z: 367.27 $[M+Na]^+$.

A mixture of compound **10** (Shibata et al., 2018) (200 mg, 0.33 mmol, 1.0 eq.) and **9** (1.5 eq, crude from last step) in DMF (3 mL) was treated with Cs_2CO_3 (82 mg, 2 eq.). The reaction mixture was heated at 70ºC for 12h and monitored by UPLC-MS. Once the limiting starting material was consumed, the reaction was filtered and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*. The residue was purified using ISCO (dichloromethane/methanol, 0%-10%) to yield compound **11**. **UPLC-MS** RT: 1.76 min (Method A), Mass m/z: 869.52 $[M+Na]^+$.

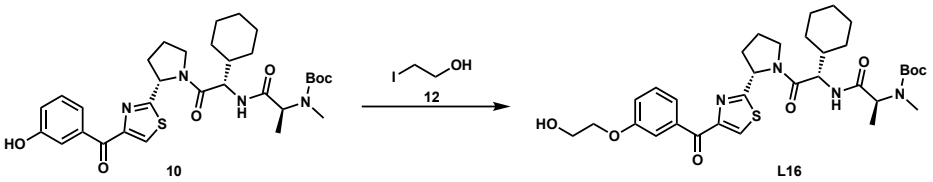
A solution of **11** (40 mg, 0.047 mmol, 1.0 eq.) in THF (0.5 mL) was treated with 2N aqueous HCl (250 μL, 10 eq.). The reaction was stirred at 35ºC for 2 h and monitored by UPLC-MS. Once the limiting starting material was consumed, the reaction was quenched with aqueous $NaHCO_3$ and extracted with iPrOH/$CHCl_3$. The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to yield **L12** and the residue was used in the next step without further purification. **UPLC-MS** RT: 1.46 min (Method A), Mass m/z: 795.41 $[M+Na]^+$.



***tert*-butyl ((*S*)-1-(((*S*)-1-cyclohexyl-2-oxo-2-((*S*)-2-(4-(3-(2-(2-(2-oxoethoxy)ethoxy)ethoxy) benzoyl)thiazol-2-yl)pyrrolidin-1-yl)ethyl)amino)-1-oxopropan-2-yl)(methyl)carbamate, L14** was synthesized from 2-(2-(2,2-diethoxyethoxy)ethoxy)ethan-1-ol using similar procedures. **UPLC-MS** RT: 1.41 min (Method A), Mass m/z: 728.71 $[M+H]^+$.

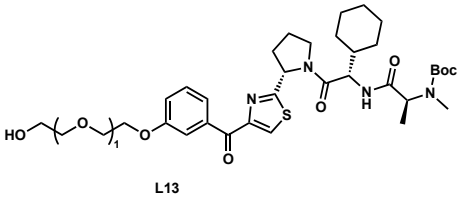


***tert*-butyl ((*S*)-1-(((*S*)-1-cyclohexyl-2-oxo-2-((*S*)-2-(4-(3-((5-oxopentyl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)ethyl)amino)-1-oxopropan-2-yl)(methyl)carbamate, L15** was synthesized from 2-(4-bromobutyl)-1,3-dioxolane using similar procedures. **UPLC-MS** RT: 1.69 min (Method A), Mass m/z: 683.60 $[M+H]^+$.



***tert*-butyl ((*S*)-1-(((*S*)-1-cyclohexyl-2-((*S*)-2-(4-(3-(2-hydroxyethoxy)benzoyl)thiazol-2-yl) pyrrolidin-1-yl)-2-oxoethyl)amino)-1-oxopropan-2-yl)(methyl)carbamate, L16**

A mixture of compound **10** (Shibata et al., 2018) (50 mg, 0.083 mmol, 1.0 eq.) and 2-iodoethan-1-ol (**12**) (15.4 μL, 2.4 eq.) in DMF (1 mL) was treated with K_2CO_3 (17 mg, 1.5 eq.). The reaction mixture was heated at 70ºC for 2 days and monitored by UPLC-MS. Once the limiting starting material was consumed, the reaction was filtered and extracted with ethyl acetate. The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*. The residue was purified using a short silica column (dichloromethane/MeOH) to yield compound **L16**. **UPLC-MS** RT: 1.44 min (Method A), Mass m/z: 643.00 $[M+H]^+$.

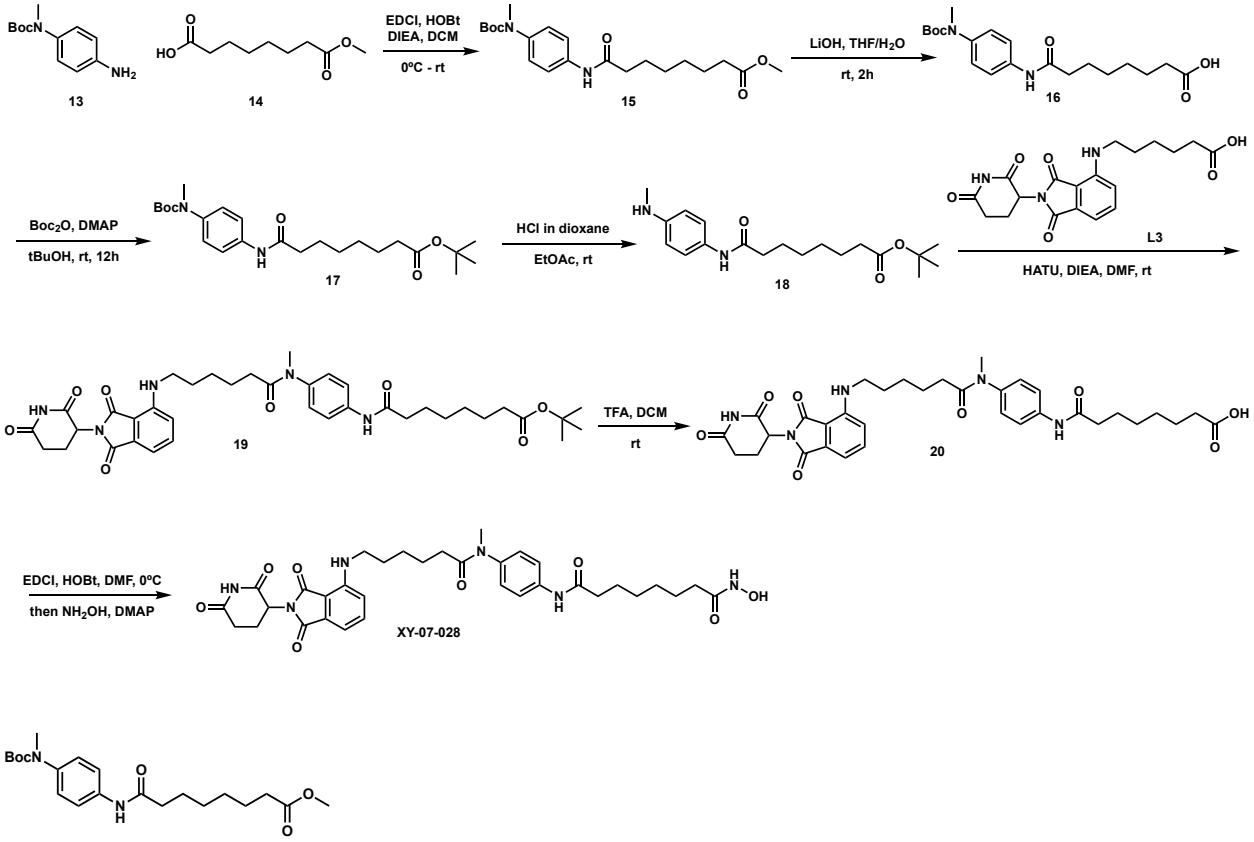


L13

***tert*-butyl ((*S*)-1-(((*S*)-1-cyclohexyl-2-((*S*)-2-(4-(3-(2-(2-hydroxyethoxy)ethoxy)benzoyl) thiazol-2-yl)pyrrolidin-1-yl)-2-oxoethyl)amino)-1-oxopropan-2-yl)(methyl)carbamate, L13** was synthesized from compound **10** and 2-(2-bromoethoxy)ethan-1-ol using similar procedures. **UPLC-MS** RT: 1.44 min (Method A), Mass m/z: 687.00 $[M+H]^+$.

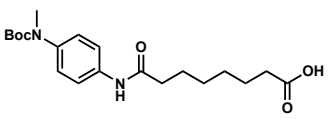
Synthesis to assemble heterobifunctional degraders

General procedure for degraders based on SAHA and thalidomide – I



methyl 8-((4-((*tert*-butoxycarbonyl)(methyl)amino)phenyl)amino)-8-oxooctanoate, 15

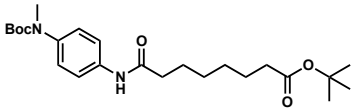
To a mixture of *tert*-butyl (4-aminophenyl)(methyl)carbamate (**13**) (1 g, 4.5 mmol, 1.0 eq.) and 8-methoxy-8-oxooctanoic acid (**14**) (847 mg, 1.0 eq.) in dichloromethane (18 mL) were added EDCI (951 mg, 1.1 eq.), HOBt (669 mg, 1.1 eq.) and DIEA (1.17 mL, 1.5 eq.) at 0 °C. The mixture was warmed to room temperature, stirred for an additional 2 h. The reaction was monitored by UPLC-MS. Once the reaction was complete, the mixture was quenched with H_2O and extracted with dichloromethane. The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified using ISCO (hexanes/ethyl acetate, 20%-80%) to yield compound **15** (1.49 g, 84% yield). **UPLC-MS** RT: 1.45 min (Method A), Mass m/z: 393.37 $[M+H]^+$.



8-((4-((*tert*-butoxycarbonyl)(methyl)amino)phenyl)amino)-8-oxooctanoic acid, 16

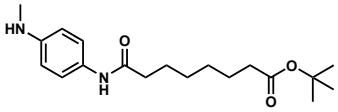
Compound **15** (1.34 g, 3.4 mmol, 1.0 eq.) was dissolved in a mixture of THF and H_2O (1:1, 30 mL). The mixture was treated with LiOH (287 mg, 2.0 eq.) and stirred at room temperature for 4

h. Once the reaction was complete, the mixture was acidified with 2N aqueous HCl. The precipitate was filtered, washed with cold H_2O and dried with a stream of nitrogen. The residue was used without further purification (1.07 g, 83% yield). **UPLC-MS** RT: 1.23 min (Method A), Mass m/z: 322.87 $[M\text{-}tBu+H]^+$.



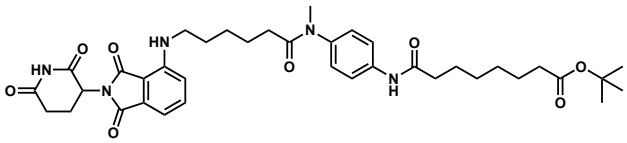
***tert*-butyl 8-((4-((*tert*-butoxycarbonyl)(methyl)amino)phenyl)amino)-8-oxooctanoate, 17**

A solution of **16** (500 mg, 1.32 mmol, 1.0 eq.) in *tert*-butanol (7 mL) was treated with Boc_2O (577 mg, 2.0 eq.) and catalytic amount of DMAP (24 mg, 0.15 eq.). The mixture was stirred at room temperature for 12 h. The reaction was monitored by UPLC-MS, and once the reaction was complete, the mixture was concentrated *in vacuo* and passed through a silica plug. The eluent was collected, concentrated *in vacuo* and the residue was used without further purification. **UPLC-MS** RT: 1.71 min (Method A), Mass m/z: 378.97 $[M\text{-}tBu+H]^+$.



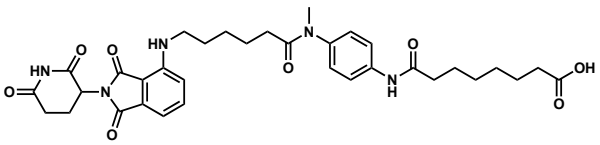
***tert*-butyl 8-((4-(methylamino)phenyl)amino)-8-oxooctanoate, 18**

To a solution of **17** (1.0 eq., crude from last step) in ethyl acetate (13 mL) was added 4N HCl in dioxane (1.63 mL, 5.0 eq.), and the mixture was stirred at room temperature for 20 h. Additional HCl (0.82 mL, 2.5 eq.) was added, and the mixture was stirred for an additional 2 h. Once the reaction was complete, solvent was removed *in vacuo* to yield the title compound **18** (150 mg, 34% yield over 2 steps). **UPLC-MS** RT: 1.11 min (Method A), Mass m/z: 334.97 $[M+H]^+$.



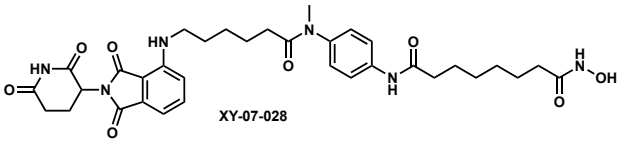
***tert*-butyl 8-((4-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-*N*-methylhexanamido)phenyl)amino)-8-oxooctanoate, 19**

To a solution of **18** (30 mg, 0.054 mmol, 1.0 eq.) in DMF (1 mL) was added 6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexanoic acid (**L3**) (35 mg, 1.0 eq.). The mixture was treated with HATU (41 mg, 1.2 eq.) and DIEA (31 μL, 2 eq.), and the reaction mixture was stirred at room temperature for 1 h. The reaction was monitored by UPLC-MS, and once the reaction was complete, the mixture was quenched with H_2O and extract three times with ethyl acetate. The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified using ISCO (dichloromethane/methanol, 0%-10%) to yield the title compound **19**. **UPLC-MS** RT: 1.54 min (Method A), Mass m/z: 647.90 $[M\text{-}tBu+H]^+$.



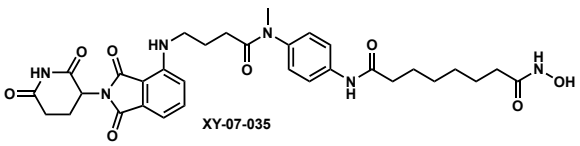
8-((4-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-*N*-methylhexanamido) phenyl)amino)-8-oxooctanoic acid, 20

Compound **19** was treated with a mixture of TFA/dichloromethane (1:5 mixture). The mixture was stirred at room temperature for 2 h. The reaction was monitored by UPLC-MS, and once the reaction was complete, solvent was removed *in vacuo*, and the residue was used in the next step without further purification. **UPLC-MS** RT: 1.13 min (Method A), Mass m/z: 647.90 $[M+H]^+$.



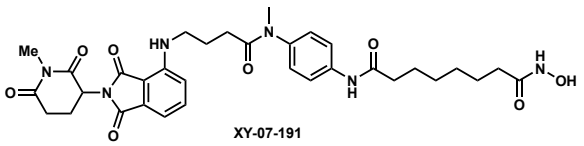
N^1-(4-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-*N*-methylhexanamido) phenyl)-N^8-hydroxyoctanediamide (XY-07-028)

To a solution of **20** (17 mg, 0.03 mmol, 1.0 eq.) in DMF (0.5 mL) were added EDCI (5.6 mg, 1.1 eq.) and HOBt (3.9 mg, 1.1 eq.) at 0 °C. The mixture was stirred at 0 °C for 1 h, then freshly made NH_2OH in methanol (2.0 eq) (Remiszewski et al., 2003) was added, followed by DMAP (cat. 1 crystal). The reaction was gradually warmed to room temperature and stirred for 1 h. Once the reaction was complete, solvent was removed, and the residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **XY-07-028** as a yellow powder (3.2 mg, 19% yield). **UPLC-MS** RT: 1.00 min (Method A), Mass m/z: 662.90 $[M+H]^+$. Purity is >95%.



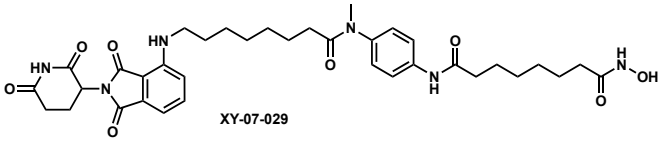
N^1-(4-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-*N*-methylbutanamido) phenyl)-N^8-hydroxyoctanediamide (XY-07-035)

XY-07-035 was synthesized from compound **18** and **L2** using similar procedures and was obtained as a yellow powder. **UPLC-MS** RT: 0.76 min (Method A), Mass m/z: 635.32 $[M+H]^+$. Purity is >95%. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.08 (s, 1H), 10.33 (s, 1H), 9.96 (s, 1H), 8.65 (s, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.6 Hz, 1H), 7.00 (d, *J* = 7.0 Hz, 1H), 6.58 – 6.51 (m, 1H), 5.04 (dd, *J* = 12.8, 5.4 Hz, 1H), 3.20 (d, *J* = 7.1 Hz, 2H), 3.11 (s, 3H), 2.88 (ddd, *J* = 16.9, 14.0, 5.4 Hz, 1H), 2.63 – 2.46 (m, 2H), 2.29 (t, *J* = 7.4 Hz, 2H), 2.08 (t, *J* = 6.8 Hz, 2H), 2.02 (dtd, *J* = 12.7, 5.2, 2.2 Hz, 1H), 1.94 (t, *J* = 7.4 Hz, 2H), 1.77 – 1.67 (m, 2H), 1.57 (p, *J* = 7.1 Hz, 2H), 1.49 (p, *J* = 7.4 Hz, 2H), 1.35 – 1.21 (m, 4H). **^{13}C NMR** (126 MHz, DMSO) δ 172.83, 171.37, 171.35, 170.14, 169.12, 168.79, 167.32, 146.30, 138.53, 138.44, 136.19, 132.21, 127.62 (2C), 119.83 (2C), 117.24, 110.39, 109.05, 48.53, 41.38, 36.86, 36.37, 32.25, 30.99, 30.61, 28.41, 28.41, 25.04, 25.00, 24.40, 22.16.



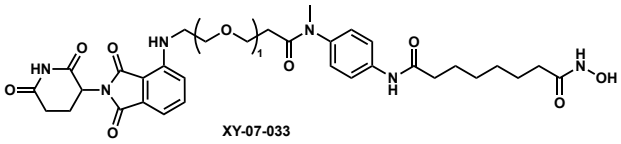
***N*1-hydroxy-*N*8-(4-(*N*-methyl-4-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butanamido)phenyl)octanediamide (XY-07-191)**

XY-07-191 was synthesized from compound **18** and **L2-negative** using similar procedures and was obtained as a yellow powder. **UPLC-MS** RT: 0.96 min (Method A), Mass m/z: 649.36 $[M+H]^+$. Purity is >95%. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 10.33 (s, 1H), 9.96 (s, 1H), 8.65 (s, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 8.6 Hz, 1H), 7.01 (d, *J* = 7.0 Hz, 1H), 6.55 (s, 1H), 5.11 (dd, *J* = 13.0, 5.5 Hz, 1H), 3.20 (dd, *J* = 13.1, 6.0 Hz, 2H), 3.11 (s, 3H), 3.01 (s, 3H), 2.94 (ddd, *J* = 17.1, 13.9, 5.4 Hz, 1H), 2.76 (ddd, *J* = 17.2, 4.5, 2.6 Hz, 1H), 2.58 – 2.47 (m, 1H), 2.29 (t, *J* = 7.4 Hz, 2H), 2.11 – 2.00 (m, 3H), 1.94 (t, *J* = 7.4 Hz, 2H), 1.77 – 1.68 (m, 2H), 1.57 (p, *J* = 7.4 Hz, 2H), 1.49 (p, *J* = 7.4 Hz, 2H), 1.34 – 1.20 (m, 4H).



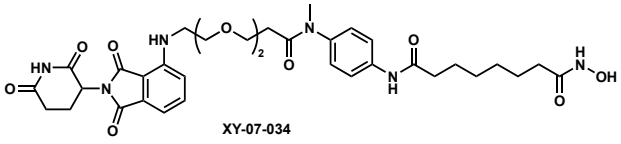
***N*^{1}-(4-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-*N*-methyloctanamido)phenyl)-*N*^{8}-hydroxyoctanediamide (XY-07-029)**

XY-07-029 was synthesized from compound **18** and **L4** using similar procedures and was obtained as a yellow powder. **UPLC-MS** RT: 1.12 min (Method A), Mass m/z: 690.80 $[M+H]^+$. Purity is >95%.



***N*^{1}-(4-(3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)-*N*-methylpropanamido)phenyl)-*N*^{8}-hydroxyoctanediamide (XY-07-033)**

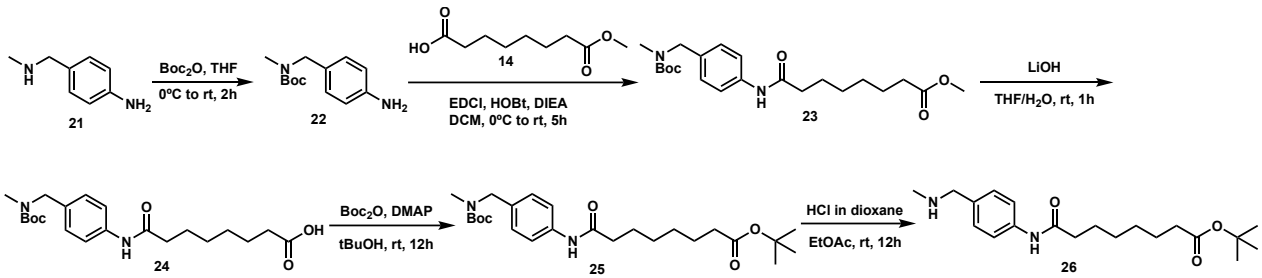
XY-07-033 was synthesized from compound **18** and **L1** using similar procedures and was obtained as a yellow powder. **UPLC-MS** RT: 0.91 min (Method A), Mass m/z: 664.80 $[M+H]^+$. Purity is >95%. **^{1}H NMR** (500 MHz, Methanol-d_4) δ 9.82 (s, 1H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.54 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 2H), 7.09 – 7.03 (m, 2H), 5.09 (dd, *J* = 12.4, 5.4 Hz, 1H), 3.70 (t, *J* = 5.9 Hz, 2H), 3.61 (t, *J* = 5.1 Hz, 2H), 3.46 (t, *J* = 5.3 Hz, 2H), 3.22 (s, 3H), 2.88 (ddd, *J* = 18.6, 13.7, 5.3 Hz, 1H), 2.79 – 2.68 (m, 2H), 2.41 – 2.33 (m, 4H), 2.16 – 2.06 (m, 3H), 1.74 – 1.59 (m, 4H), 1.46 – 1.34 (m, 4H).

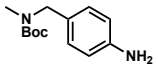


***N*^{1}-(4-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)-*N*-methylpropanamido)phenyl)-*N*^{8}-hydroxyoctanediamide (XY-07-034)**

XY-07-034 was synthesized from compound **18** and **L5** using similar procedures and was obtained as a yellow powder. **UPLC-MS** RT: 0.91 min (Method A), Mass m/z: 708.80 $[M+H]^+$. Purity is >95%.

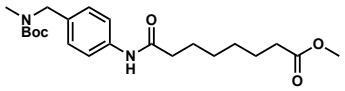
Synthesis of SAHA intermediate





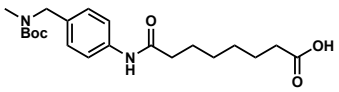
tert-butyl (4-aminobenzyl)(methyl)carbamate, 22

To a solution of 4-((methylamino)methyl)aniline (**21**) (1 g, 7.35 mmol, 1.0 eq.) in THF (37 mL) was added Boc_2O (1.9 g, 1.2 eq.) at 0 °C. The mixture was warmed to room temperature and stirred for 2 h. When the starting material was consumed, solvent was removed *in vacuo*, and the residue was purified using ISCO (hexanes/ethyl acetate, 0%-45%) to yield the title compound **22** (1.68 g, 97% yield). **UPLC-MS** RT: 0.83 min (Method A), Mass m/z: 105.92 [M-CH_3NBoc].



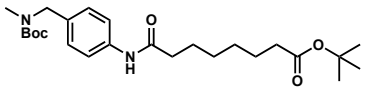
methyl 8-((4-(((_tert_-butoxycarbonyl)(methyl)amino)methyl)phenyl)amino)-8-oxooctanoate, 23

To a mixture of **22** (1.43 g, 6.06 mmol, 1.0 eq.) and 8-methoxy-8-oxooctanoic acid (**14**) (1.14 g, 1.0 eq.) in dichloromethane (30 mL) were added EDCI (1.28 g, 1.1 eq.), HOBt (900 mg, 1.1 eq.) and DIEA (1.58 mL, 1.5 eq.) at 0 °C. The mixture was warmed to room temperature and stirred for 5 h. When the starting material was consumed, the mixture was quenched with H_2O and extracted three times with dichloromethane. The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified using ISCO (dichloromethane/ethyl acetate, 0%-40%) to yield the title compound **23** (2.28 g, 93% yield). **UPLC-MS** RT: 1.49 min (Method A), Mass m/z: 407.37 $[M+H]^+$.



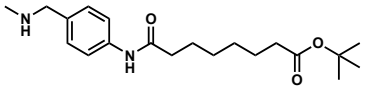
8-((4-(((_tert_-butoxycarbonyl)(methyl)amino)methyl)phenyl)amino)-8-oxooctanoic acid, 24

Compound **23** (1.14 g, 2.81 mmol, 1.0 eq.) was dissolved in a mixture of THF and H_2O (1:1 mixture, 15 mL) and the reaction mixture was treated with LiOH (236 mg, 2.0 eq.) and stirred at room temperature for 1 h. When the starting material was consumed, the mixture was acidified with 2N aqueous HCl and extract three times with ethyl acetate. The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was used in the next step without further purification. **UPLC-MS** RT: 1.28 min (Method A), Mass m/z: 393.17 $[M+H]^+$.



tert-butyl 8-((4-(((_tert_-butoxycarbonyl)(methyl)amino)methyl)phenyl)amino)-8-oxooctanoate, 25

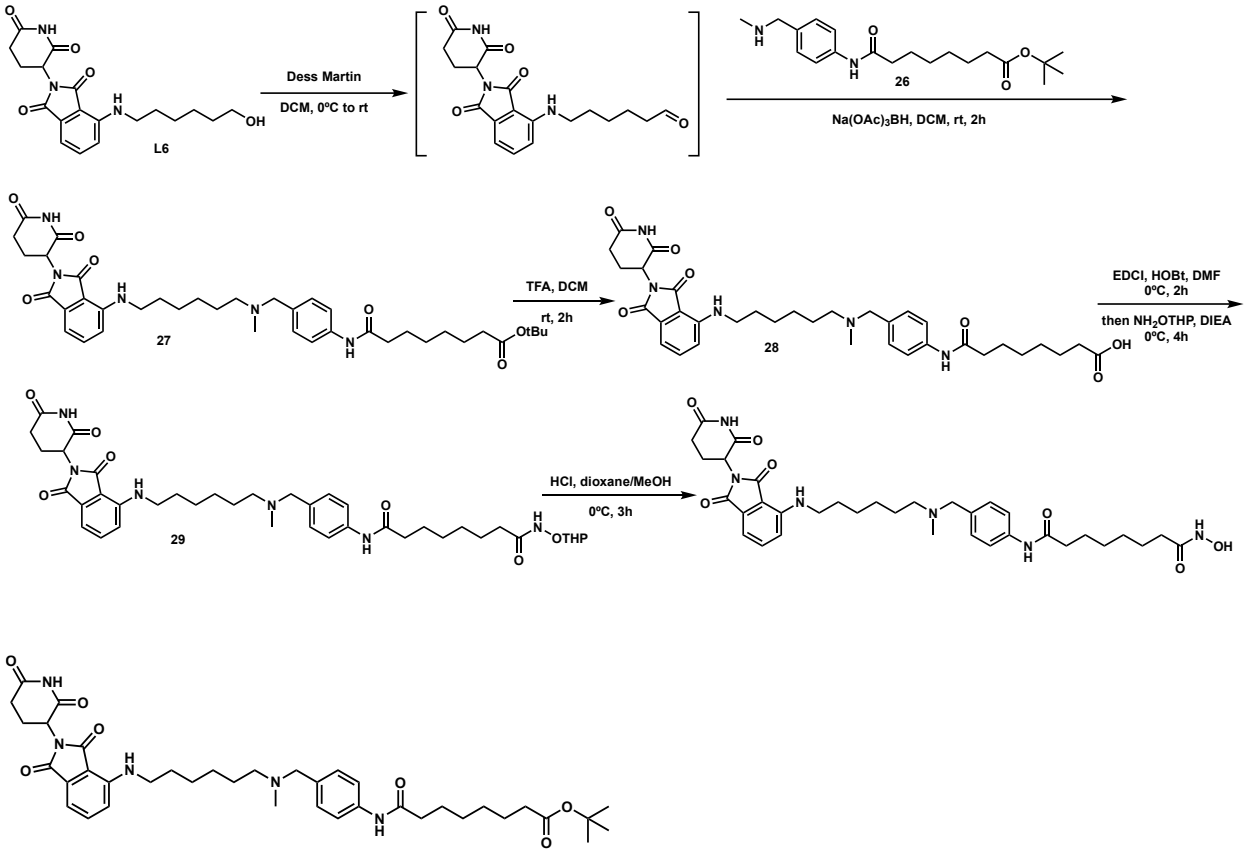
To a solution of **24** (1.10 g, 2.81 mmol, 1.0 eq. crude from last step) in *tert*-butanol (14 mL) were added Boc_2O (918 mg, 1.5 eq.) and DMAP (69 mg, 0.2 eq.). The mixture was stirred at room temperature for 24 h. When the starting material was consumed, solvent was removed *in vacuo*, and the residue was purified using ISCO (dichloromethane/ethyl acetate, 0%-30%) to yield the title compound **25** (670 mg, 53% yield). **UPLC-MS** RT: 1.75 min (Method A), Mass m/z: 349.17 $[M-Boc+H]^+$.



tert-butyl 8-((4-((methylamino)methyl)phenyl)amino)-8-oxooctanoate, 26

A solution of **25** (670 mg, 1.49 mmol, 1.0 eq.) in ethyl acetate (7.5 mL) was treated with 4N HCl in dioxane (3 mL, 8.0 eq.), and the reaction mixture was stirred at room temperature for 12 h. When the starting material was consumed, the mixture was basified with 2N aqueous NaOH and extract three times with ethyl acetate. The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified using ISCO (dichloromethane/methanol, 0%-10%) to yield the title compound **26** (350 mg, 67% yield). **UPLC-MS** RT: 0.93 min (Method A), Mass m/z: 349.17 $[M+H]^+$.

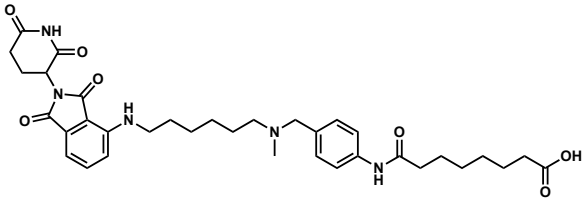
General procedure for degraders based on SAHA and thalidomide – II



***tert*-butyl 8-((4-(((6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexyl)(methyl)amino)methyl)phenyl)amino)-8-oxooctanoate, 27**

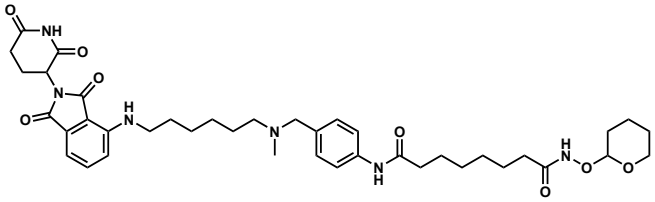
A solution of 2-(2,6-dioxopiperidin-3-yl)-4-((6-hydroxyhexyl)amino)isoindoline-1,3-dione (**L6**) (40 mg, 0.11 mmol, 1.0 eq.) in dichloromethane (1 mL) was treated with Dess-Martin periodinane (48 mg, 1.05 eq.) at 0 °C. The reaction mixture was warmed gradually to room temperature and stirred for 2 h. When the starting material was consumed, the reaction mixture was quenched with aqueous $NaHCO_3$, extract three times with ethyl acetate. The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was passed through a short column and the eluent was collected and concentrated *in vacuo*. The residue was used in the next step without further purification. **UPLC-MS** RT: 1.14 min (Method A), Mass m/z: 354.17 $[M\text{-}H_2O+H]^+$.

The crude residue from last step (30 mg, 1.0 eq.) was dissolved in dichloromethane (2 mL), and **26** (28.2 mg, 1.0 eq.) was added at room temperature, followed by $NaBH(OAc)_3$ (25.8 mg, 1.5 eq.). The reaction mixture was stirred at room temperature for 2 h. When the limiting starting material was consumed, the reaction was quench with aqueous $NaHCO_3$, extract three times with dichloromethane. The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified using ISCO (dichloromethane/methanol, 0%-10%) to yield the title compound **27** (40 mg, 53% yield). **UPLC-MS** RT: 1.29 min (Method A), Mass m/z: 704.60 $[M+H]^+$.



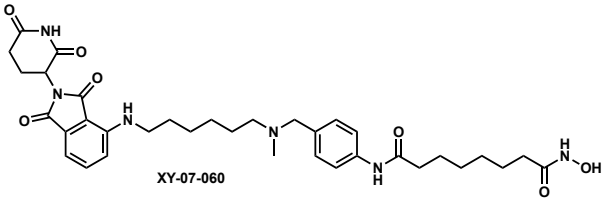
8-((4-(((6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexyl)(methyl)amino)methyl)phenyl)amino)-8-oxooctanoic acid, 28

Compound **27** (40 mg, 0.057 mmol, 1.0 eq.) was treated with a mixture of TFA/dichloromethane (1:5) at room temperature. The reaction was stirred for 2 h. When the starting material was consumed, solvent was removed *in vacuo*, and the residue was used in the next step without further purification. **UPLC-MS** RT: 0.95 min (Method A), Mass m/z: 647.90 $[M+H]^+$.



***N*^{1}-(4-(((6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexyl)(methyl)amino)methyl)phenyl)-*N*^{8}-((tetrahydro-2*H*-pyran-2-yl)oxy)octanediamide, 29**

To a solution of **28** (18 mg, 0.028 mmol, 1.0 eq.) in DMF (0.5 mL) were added EDCI (6.4 mg, 1.2 eq.) and HOBt (4.5 mg, 1.2 eq.) at 0 °C. The mixture was stirred at 0 °C for 2 h, then NH_2OTHP (4.9 mg, 1.5 eq.) and DIEA (9.7 μL, 2 eq.) were added at 0 °C. The reaction mixture was gradually warmed to room temperature and stirred for another 4 h. When the starting material was consumed, solvent was removed *in vacuo*, and the residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **29**. **UPLC-MS** RT: 1.00 min (Method A), Mass m/z: 747.01 $[M+H]^+$.

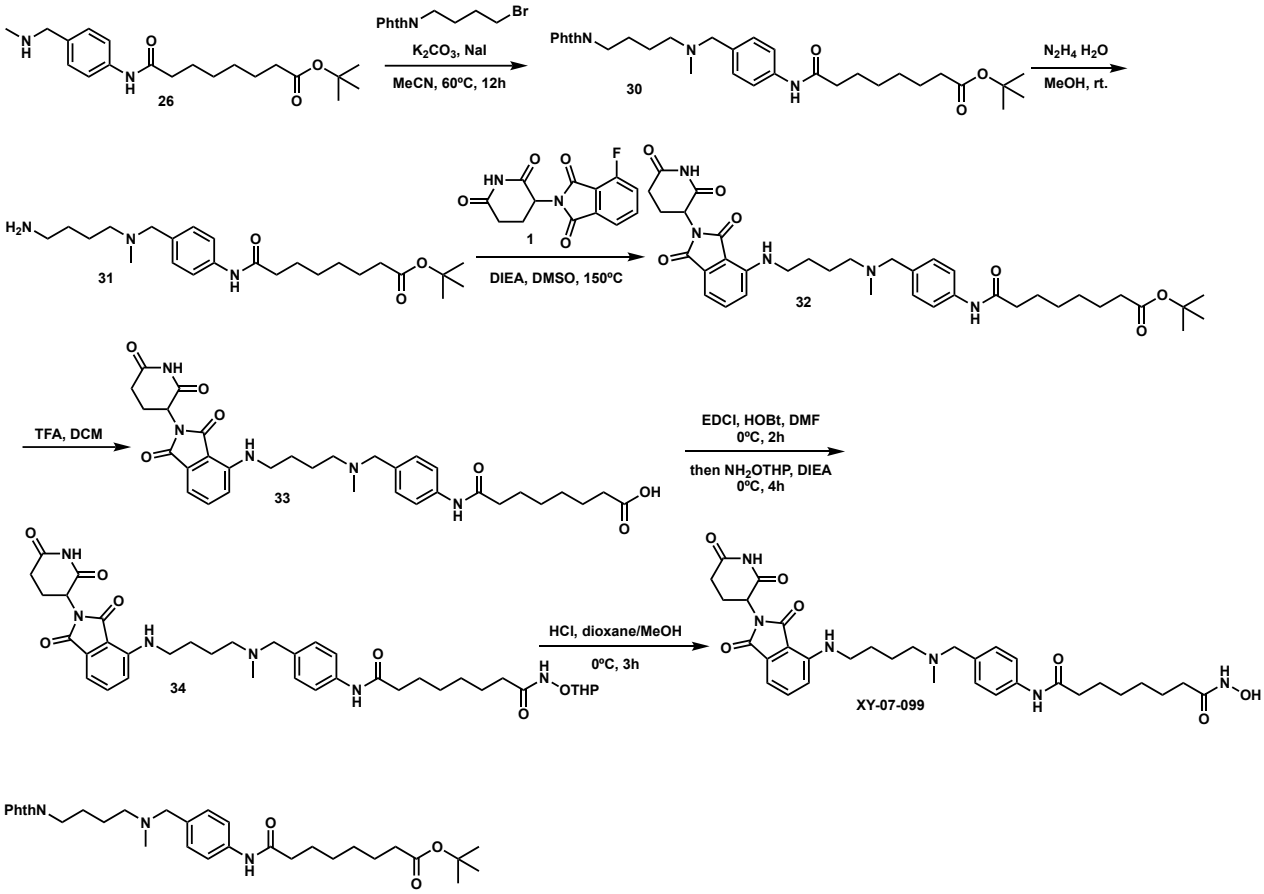


***N*^{1}-(4-(((6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexyl)(methyl)amino)methyl)phenyl)-*N*^{8}-hydroxyoctanediamide (XY-07-060)**

A solution of **29** (1.0 eq. from last step) in solvent mixture of dioxane and methanol (1:1, 1 mL) was treated with 4N HCl in dioxane (70 μL, 10 eq.) at 0 °C. The reaction was warmed to room temperature and stirred for 3 h. When the starting material was consumed, solvent was removed *in vacuo*, and the residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title

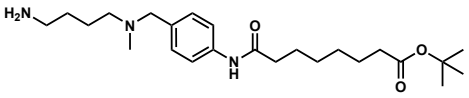
compound **XY-07-060** as a yellow powder (3.4 mg, 18% yield over 2 steps). **UPLC-MS** RT: 0.83 min (Method A), Mass m/z: 662.90 $[M+H]^+$.

General procedure for degraders based on SAHA and thalidomide – III



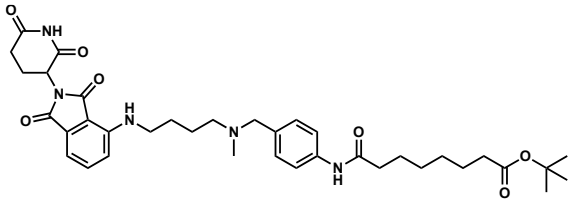
***tert*-butyl 8-((4-(((4-(1,3-dioxoisoindolin-2-yl)butyl)(methyl)amino)methyl)phenyl)amino)-8-oxooctanoate, 30**

To a solution of **26** (92 mg, 0.26 moml, 1.0 eq.) and 2-(4-bromobutyl)isoindoline-1,3-dione (112 mg, 1.5 eq.) in acetonitrile (2.6 mL) were added K_2CO_3 (73 m, 2 eq.) and NaI (4 mg, 0.1 eq.) in one portion. The reaction mixture was heated to 65 °C and stirred for 12 h. When the limiting starting material was consumed, the mixture was filtered through a pad of Celite®, concentrate *in vacuo*, and the residue was purified using ISCO (dichloromethane/ethyl acetate, 0%-75%) to yield the title compound **30** (112 mg, 77% yield). **UPLC-MS** RT: 1.24 min (Method A), Mass m/z: 549.89 $[M+H]^+$.



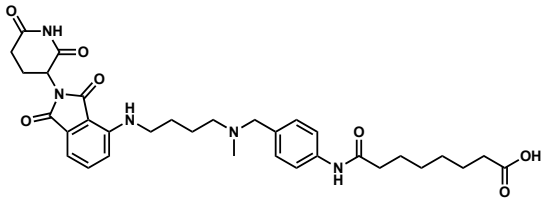
***tert*-butyl 8-((4-(((4-aminobutyl)(methyl)amino)methyl)phenyl)amino)-8-oxooctanoate, 31**

A solution of **30** (112 mg, 0.20 mmol, 1.0 eq.) in methanol (2 mL) was treated with N_2H_4•H_2O (50 μL, 5.0 eq.). The reaction mixture was stirred at room temperature for 12 h. When the starting material was consumed, the mixture was acidified with 2N aqueous HCl to pH 1, washed twice with diethyl ether. The aqueous layer was then basified with 2N aqueous NaOH to pH >10, and back extracted three times with ethyl acetate. The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified using ISCO (dichloromethane/methanol/NH_3, 0%-15%) to yield the title compound **31** (85 mg, quant. yield). **UPLC-MS** RT: 0.73 min (Method A), Mass m/z: 420.17 $[M+H]^+$.



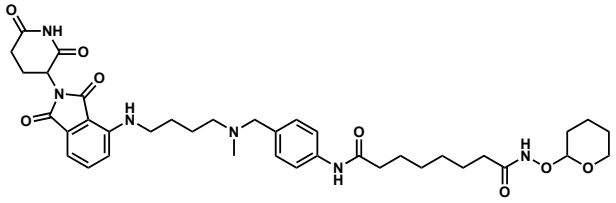
***tert*-butyl 8-((4-(((4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)(methyl)amino)methyl)phenyl)amino)-8-oxooctanoate, 32**

To a solution of **31** (85 mg, 0.20 mmol, 1.0 eq.) and 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (**1**) (67 mg, 1.2 eq.) in DMSO (2 mL) was added DIEA (106 μL, 3.0 eq.). The reaction was sealed and heated to 150 °C and stirred for 1 h. When the limiting starting material was consumed, the reaction was cooled to room temperature, DIEA was removed *in vacuo* and the residue was purified first using HPLC (H_2O/acetonitrile, 0%-100%), and then with ISCO (dichloromethane/methanol, 0%-10%) to yield the title compound **32**. **UPLC-MS** RT: 1.23 min (Method A), Mass m/z: 676.00 $[M+H]^+$.



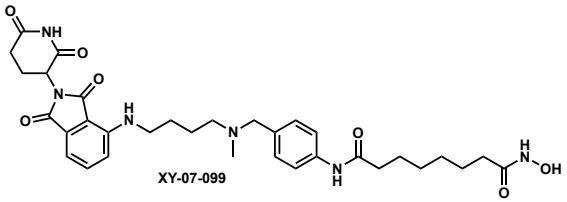
8-((4-(((4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)(methyl)amino)methyl)phenyl)amino)-8-oxooctanoic acid, 33

Compound **32** (80 mg, 1.0 eq. from last step) was treated with a mixture of TFA/dichloromethane (1:5), and the reaction was stirred at room temperature for 6 h. When the starting material was consumed, solvent was removed *in vacuo*, and the residue was used in the next step without further purification (30 mg, 24% yield over 2 steps). **UPLC-MS** RT: 0.88 min (Method A), Mass m/z: 619.99 $[M+H]^+$.



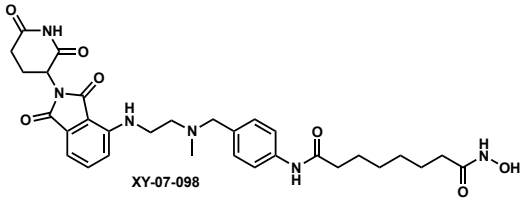
N^1-(4-(((4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)(methyl)amino) methyl)phenyl)-N^8-((tetrahydro-2*H*-pyran-2-yl)oxy)octanediamide, 34

To a solution of **33** (30 mg, 0.048 mmol, 1.0 eq.) in DMF (0.5 mL) were added EDCI (10.2 mg, 1.2 eq.), HOBt (7.2 mg, 1.2 eq.) at 0 °C, and the mixture was stirred at 0 °C for 2 h, then NH_2OTHP (7.8 mg, 1.5 eq.) and DIEA (15 μL, 2.0 eq.) were added at 0 °C. The reaction mixture was stirred at 0 °C and gradually warmed to room temperature and stirred for another 4 h. Solvent was then removed *in vacuo*, and the residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **34**. **UPLC-MS** RT: 0.86 min (Method A), Mass m/z: 718.90 $[M+H]^+$.



N^1-(4-(((4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)(methyl)amino) methyl)phenyl)-N^8-hydroxyoctanediamide (XY-07-099)

A solution of **34** (1.0 eq. from last step) in solvent mixture of dioxane and methanol (1:1, 1 mL) was treated with 4N HCl in dioxane (121 μL, 10 eq.) at 0 °C. The reaction was warmed to room temperature and stirred for 3 h. When the starting material was consumed, solvent was removed *in vacuo*, and the residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **XY-07-099** as a yellow powder (14.9 mg, 49% yield over 2 steps). **UPLC-MS** RT: 0.70 min (Method A), Mass m/z: 635.00 $[M+H]^+$. Purity is > 95% by UPLC. **^{1}H NMR** (500 MHz, DMSO-d_6, as a TFA salt) δ 11.09 (s, 1H), 10.32 (s, 1H), 10.03 (s, 1H), 9.40 (s, 1H, tertiary R_3NH^+), 8.64 (s, 1H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.60 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 8.6 Hz, 1H), 7.05 (d, *J* = 7.0 Hz, 1H), 6.63 (t, *J* = 6.1 Hz, 1H), 5.05 (dd, *J* = 12.8, 5.5 Hz, 1H), 4.30 (dd, *J* = 13.0, 4.1 Hz, 1H), 4.14 (dd, *J* = 13.1, 6.0 Hz, 1H), 3.37 – 3.31 (m, 2H), 3.18 – 3.09 (m, 1H), 3.00 (tt, *J* = 11.3, 5.6 Hz, 1H), 2.89 (ddd, *J* = 17.0, 13.8, 5.4 Hz, 1H), 2.64 (d, *J* = 4.8 Hz, 3H), 2.62 – 2.55 (m, 1H), 2.54 – 2.52 (m, 1H), 2.30 (t, *J* = 7.4 Hz, 2H), 2.06 – 1.99 (m, 1H), 1.93 (t, *J* = 7.4 Hz, 2H), 1.83 – 1.67 (m, 2H), 1.64 – 1.52 (m, 4H), 1.48 (p, *J* = 7.2 Hz, 2H), 1.34 – 1.20 (m, 4H).

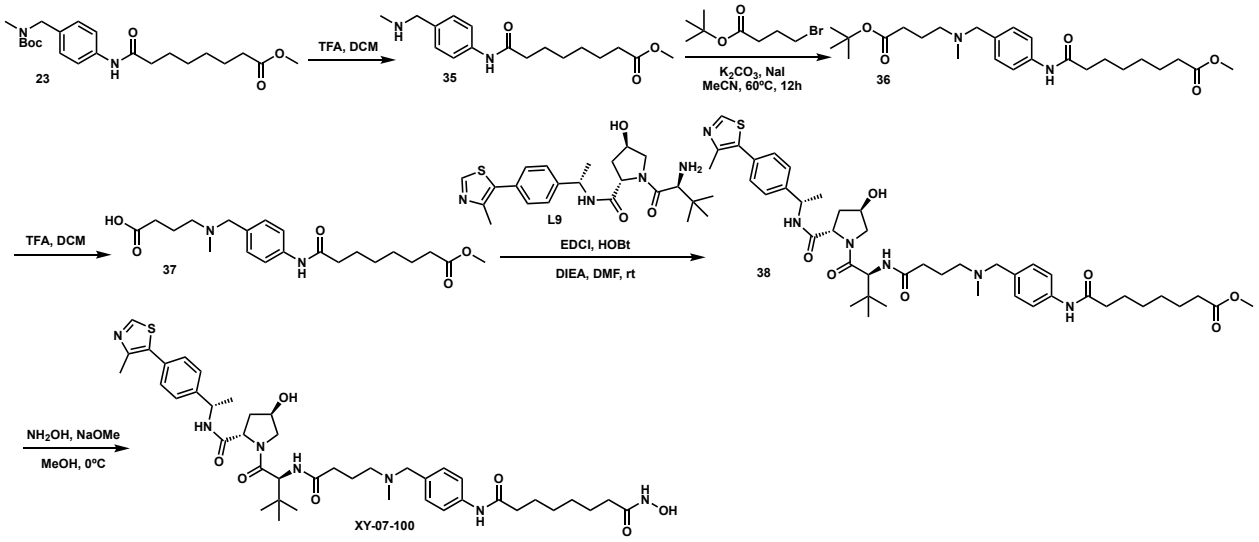


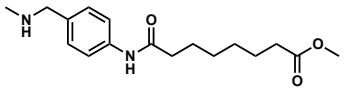
N^1-(4-(((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)(methyl)amino) methyl)phenyl)-N^8-hydroxyoctanediamide (XY-07-098)

XY-07-098 was synthesized from **26** and 2-(2-bromoethyl)isoindoline-1,3-dione using similar procedures, as a yellow powder. **UPLC-MS** RT: 0.58 min (Method A), Mass m/z: 606.99 $[M+H]^+$. Purity is > 95% by UPLC. **^{1}H NMR** (500 MHz, DMSO-d_6, as a TFA salt) δ 11.11 (d, *J* = 4.4 Hz, 1H), 10.32 (s, 1H), 9.96 (d, *J* = 21.8 Hz, 1H), 9.52 (d, *J* = 22.7 Hz, 1H, tertiary R_3NH^+), 8.65 (s,

1H), 7.66 – 7.55 (m, 3H), 7.38 (dd, *J* = 11.1, 8.3 Hz, 2H), 7.14 – 7.04 (m, 2H), 6.86 (q, *J* = 7.2 Hz, 1H), 5.07 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.40 – 4.30 (m, 1H), 4.29 – 4.20 (m, 1H), 3.81 – 3.63 (m, 2H), 3.36 – 3.28 (m, 1H), 3.23 – 3.11 (m, 1H), 2.90 (ddd, *J* = 17.1, 13.8, 5.4 Hz, 1H), 2.78 (dd, *J* = 10.1, 4.6 Hz, 3H), 2.65 – 2.56 (m, 1H), 2.56 – 2.51 (m, 1H), 2.29 (t, *J* = 7.6 Hz, 2H), 2.12 – 2.01 (m, 1H), 1.94 (t, *J* = 7.4 Hz, 2H), 1.57 (p, *J* = 7.3 Hz, 2H), 1.49 (p, *J* = 7.2 Hz, 2H), 1.33 – 1.19 (m, 4H). **^{13}C NMR** (126 MHz, DMSO) δ 172.84, 171.51, 170.22, 169.09, 168.59, 167.21, 145.16, 140.44, 136.25, 132.29, 131.77, 131.76, 123.83, 118.93, 118.81, 117.15, 111.22, 110.22, 58.56, 52.84, 48.61, 39.52, 36.97, 36.36, 32.24, 30.99, 28.41, 28.40, 25.03, 24.91, 22.15.

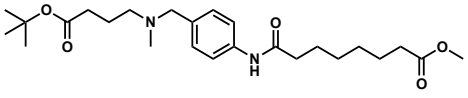
General procedure for degraders based on SAHA and VHL ligand





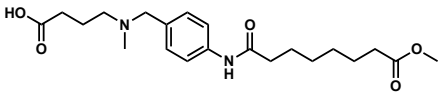
methyl 8-((4-((methylamino)methyl)phenyl)amino)-8-oxooctanoate, 35

Compound **23** (500 mg, 1.23 mmol, 1.0 eq.) was treated with a mixture of TFA/dichloromethane (1:5), and the reaction was stirred at room temperature for 3 h. When the starting material was consumed, solvent was removed *in vacuo*, and the residue was treated with 4N HCl in dioxane and concentrated *in vacuo* to exchange out the TFA counterion and to form the HCl salt. The residue was used in the next step without further purification (434 mg, quant. yield). **UPLC-MS** RT: 0.73 min (Method A), Mass m/z: 306.87 $[M+H]^+$.



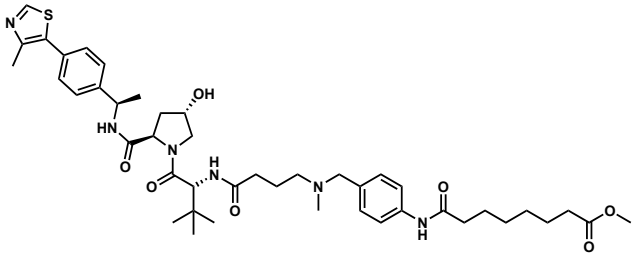
methyl 8-((4-(((4-(*tert*-butoxy)-4-oxobutyl)(methyl)amino)methyl)phenyl)amino)-8-oxooctanoate, 36

To a solution of **35** (87 mg, 0.28 mmol, 1.0 eq.) and *tert*-butyl 4-bromobutanoate (82 mg, 1.5 eq.) in acetonitrile (2.5 mL) were added K_2CO_3 (85 mg, 2.5 eq.) and NaI (3.7 mg, 0.1 eq.) in one portion. The reaction mixture was heated to 60 °C and stirred for 12 h. When the limiting starting material was consumed, the mixture was filtered through a pad of Celite®, concentrate *in vacuo*, and the residue was purified using ISCO (dichloromethane/methanol, 0%-10%) to yield the title compound **36** (95 mg, 85% yield). **UPLC-MS** RT: 1.03 min (Method A), Mass m/z: 448.98 $[M+H]^+$.



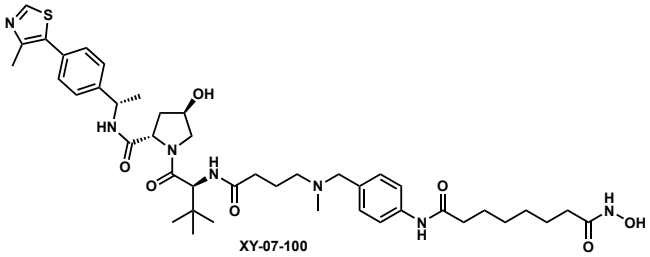
4-((4-(8-methoxy-8-oxooctanamido)benzyl)(methyl)amino)butanoic acid, 37

Compound **36** (95 mg, 0.21 mmol, 1.0 eq.) was treated with a mixture of TFA/dichloromethane (1:5), and the reaction was stirred at room temperature for 6 h. When the starting material was consumed, solvent was removed *in vacuo*, and the residue was used in the next step without further purification (90 mg). **UPLC-MS** RT: 0.75 min (Method A), Mass m/z: 393.07 $[M+H]^+$.



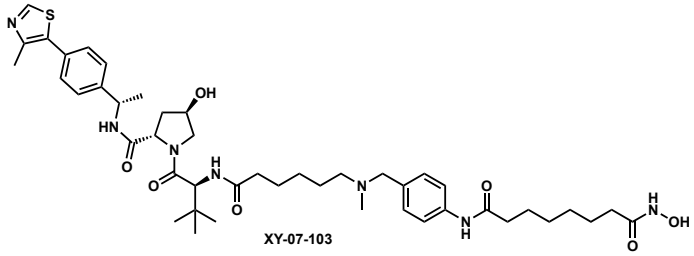
methyl 8-((4-(((4-(((*R*)-1-((2*R*,4*S*)-4-hydroxy-2-(((*R*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl) carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-4-oxobutyl)(methyl)amino) methyl)phenyl)amino)-8-oxooctanoate, 38

To a solution of **37** (30 mg, 0.076 mmol, 1.0 eq.) and (2*R*,4*S*)-1-((*R*)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*R*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (**L9**) (37 mg, 1.0 eq.) in DMF (0.8 mL), were added EDCI (17.7 mg, 1.2 eq.), HOBt (12.4 mg, 1.2 eq.) and DIEA (40 μL, 3eq.). The reaction mixture was stirred at room temperature for 12 h. When the limiting starting material was consumed, solvent was removed *in vacuo*, and the residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **38** (42 mg, 67% yield). **UPLC-MS** RT: 1.10 min (Method A), Mass m/z: 818.81 $[M+H]^+$.

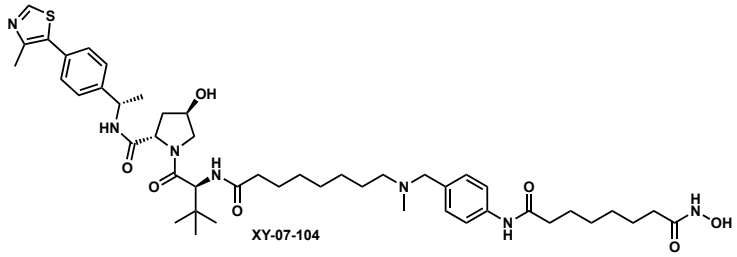


N^1-hydroxy-N^8-(4-(((4-(((*R*)-1-((2*R*,4*S*)-4-hydroxy-2-(((*R*)-1-(4-(4-methylthiazol-5-yl)phenyl) ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-4-oxobutyl)(methyl) amino)methyl)phenyl)octanediamide (XY-07-100)

A solution of **38** (42 mg, 0.051 mmol, 1.0 eq.) in methanol (1 mL) was treated with 50 wt% aqueous NH_2OH (32 μL, 10 eq.), followed by 25 wt% NaOMe in methanol (59 μL, 5 eq.) at 0 °C. The reaction mixture was gradually warmed to room temperature and stirred for 7 h. When the starting material was consumed, solvent was removed *in vacuo*, and the residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **XY-07-100** as a white powder (5.2 mg, 12.4% yield). **UPLC-MS** RT: 0.89 min (Method A), Mass m/z: 819.91 $[M+H]^+$. **^{1}H NMR** (500 MHz, DMSO-d_6, as a TFA salt) δ 10.32 (s, 1H), 10.04 (s, 1H), 9.58 (s, 1H, tertiary R_3NH^+), 8.99 (s, 1H), 8.73 (s, 1H), 8.36 (dd, *J* = 7.9, 2.2 Hz, 1H), 8.02 (dd, *J* = 9.3, 7.1 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 5.09 (s, 1H), 4.92 (p, *J* = 7.0 Hz, 1H), 4.51 (d, *J* = 7.4 Hz, 1H), 4.42 (t, *J* = 8.1 Hz, 1H), 4.34 – 4.26 (m, 2H), 4.21 – 4.13 (m, 1H), 3.65 – 3.53 (m, 2H), 3.15 – 3.00 (m, 1H), 3.00 – 2.88 (m, 1H), 2.66 (dd, *J* = 6.7, 4.9 Hz, 3H), 2.45 (s, 3H), 2.39 – 2.21 (m, 4H), 2.02 (dd, *J* = 13.3, 8.1 Hz, 1H), 1.93 (t, *J* = 7.4 Hz, 2H), 1.92 – 1.84 (m, 2H), 1.84 – 1.77 (m, 1H), 1.57 (p, *J* = 7.0 Hz, 2H), 1.48 (p, *J* = 7.2 Hz, 2H), 1.37 (d, *J* = 7.0 Hz, 3H), 1.33 – 1.21 (m, 4H), 0.93 (s, 9H). **^{13}C NMR** (126 MHz, DMSO) δ 171.57, 170.98, 170.55, 169.30, 169.08, 151.51, 147.76, 144.58, 140.46, 131.76, 131.72, 131.10, 129.72, 128.83 (2C), 126.40 (2C), 124.02, 118.99 (2C), 68.78, 58.58, 58.14, 56.59, 56.30, 54.28, 47.69, 38.68, 37.80, 36.39, 35.28, 32.23, 31.70, 28.39 (2C), 26.43 (3C), 25.02, 24.97, 22.37, 19.80, 15.98.



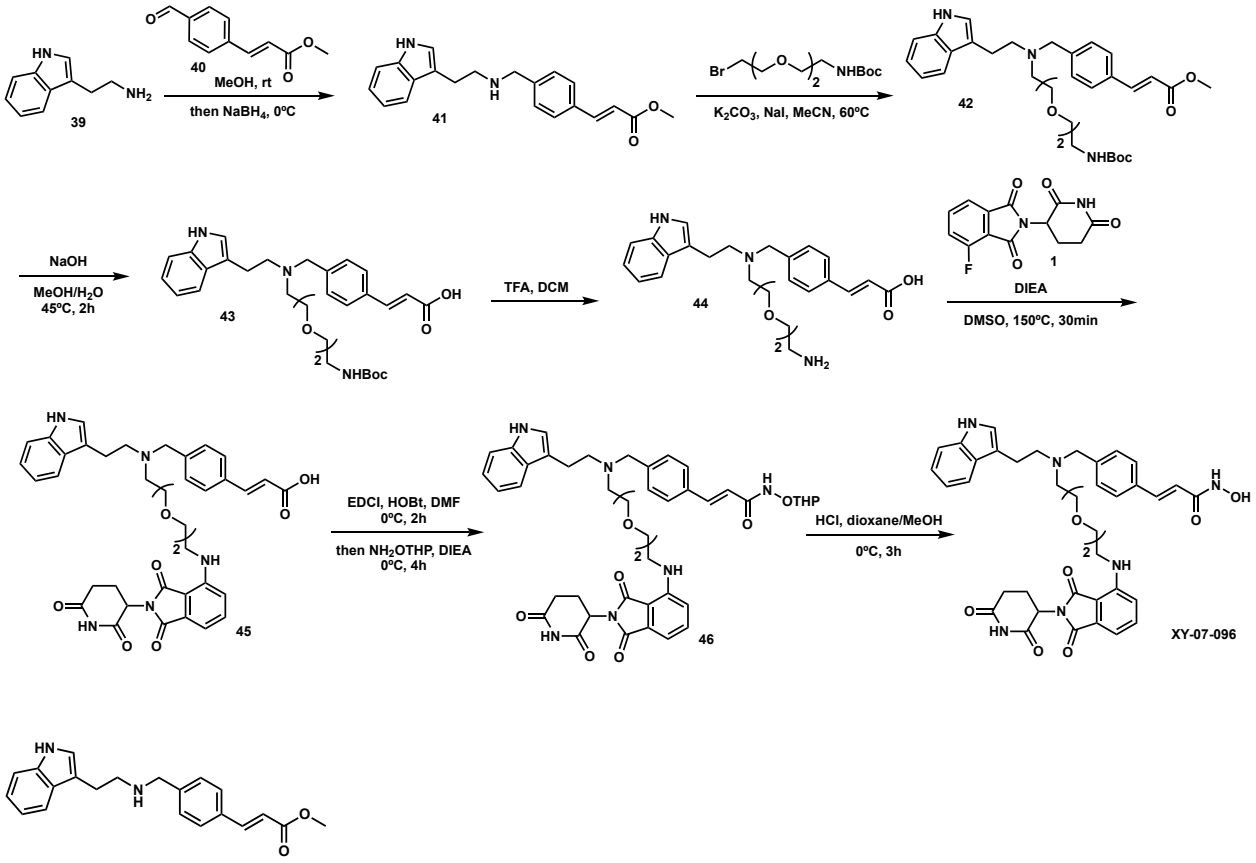
N^1-hydroxy-N^8-(4-(((6-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-(((*S*)-1-(4-(4-methylthiazol-5-yl) phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-6-oxohexyl)(methyl)amino)methyl)phenyl)octanediamide (XY-07-103) was synthesized from **23** and *tert*-butyl 6-bromohexanoate using similar procedures, and was obtained as a white powder. **UPLC-MS** RT: 0.88 min (Method A), Mass m/z: 847.92 $[M+H]^+$.



N^1-hydroxy-N^8-(4-(((6-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-(((*S*)-1-(4-(4-methylthiazol-5-yl) phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-6-

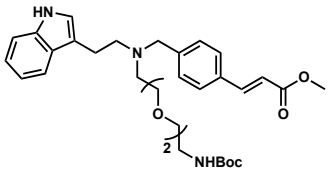
oxohexyl)(methyl)amino)methyl)phenyl)octanediamide (XY-07-104) was synthesized from **23** and *tert*-butyl 8-bromooctanoate using similar procedures, and was obtained as a white powder. **UPLC-MS** RT: 0.96 min (Method A), Mass m/z: 875.72 $[M+H]^+$. Purity is > 95% by UPLC.

General procedure for degraders based on dacinostat and thalidomide



methyl (*E*)-3-(4-(((2-(1*H*-indol-3-yl)ethyl)amino)methyl)phenyl)acrylate, 41

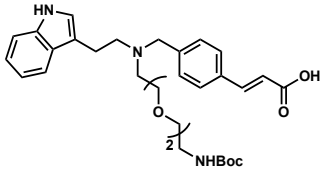
To a solution of tryptamine (**39**) (1.26g, 7.88 mmol, 1.0 eq.) in methanol was added methyl (*E*)-3-(4-formylphenyl)acrylate (**40**) (1.5 g, 1.0 eq.) at 0 °C, and the reaction mixture was warmed to room temperature and stirred for 2 h. The mixture was cooled to 0 °C again, and $NaBH_4$ (600 mg, 2.0 eq.) was added in several batches. The mixture was gradually warmed to room temperature and stirred for an additional 12 h. When the limiting starting material was consumed, the reaction was quench with aqueous $NaHCO_3$ and extract three times with ethyl acetate. The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified using ISCO (dichloromethane/methanol, 0%-10%) to yield the title compound **41**. **UPLC-MS** RT: 0.80 min (Method A), Mass m/z: 334.97 $[M+H]^+$.



methyl (*E*)-3-(4-(2-(2-(1*H*-indol-3-yl)ethyl)-14,14-dimethyl-12-oxo-5,8,13-trioxa-2,11-diazapentadecyl)phenyl)acrylate, 42

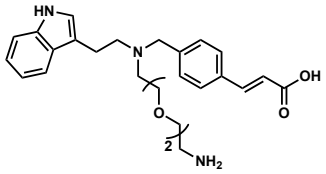
To a solution of **41** (150 mg, 0.45 mmol, 1.0 eq.) and *tert*-butyl (2-(2-(2-bromoethoxy)ethoxy)ethyl)carbamate (168 mg, 1.2 eq.) in acetonitrile (4.5 mL) were added K_2CO_3

(124 mg, 2.0 eq.) and NaI (6.7 mg, 0.1 eq.) in one portion. The reaction mixture was heated to 60 °C and stirred for 18 h. When the starting material was consumed, the mixture was filtered through a pad of Celite®, concentrate *in vacuo*, and the residue was purified using ISCO (dichloromethane/methanol, 0%-10%) to yield the title compound **42** (237mg, 93% yield). **UPLC-MS** RT: 1.22 min (Method A), Mass m/z: 565.89 $[M+H]^+$.



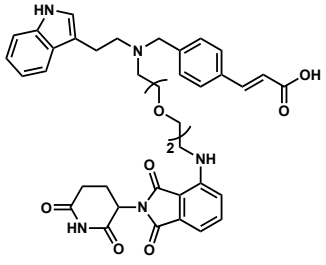
(*E*)-3-(4-(2-(2-(1*H*-indol-3-yl)ethyl)-14,14-dimethyl-12-oxo-5,8,13-trioxa-2,11-diazapentadecyl)phenyl)acrylic acid, 43

A solution of **42** (237 mg, 0.42 mmol, 1.0 eq.) in a solvent mixture of methanol/H_2O (1:1, 4 mL) was treated with 2N aqueous NaOH (629 μL, 3 eq.). The reaction was heated to 45 °C and stirred for 1 h. When the starting material was consumed, the reaction was neutralized with 2N aqueous HCl and extract three times with ethyl acetate. The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified using ISCO (dichloromethane/methanol, 0%-10%) to yield the title compound **43** (187 mg, 81% yield). **UPLC-MS** RT: 0.85 min (Method A), Mass m/z: 552.32 $[M+H]^+$.



(*E*)-3-(4-(((2-(1*H*-indol-3-yl)ethyl)(2-(2-(2-aminoethoxy)ethoxy)ethyl)amino)methyl)phenyl) acrylic acid, 44

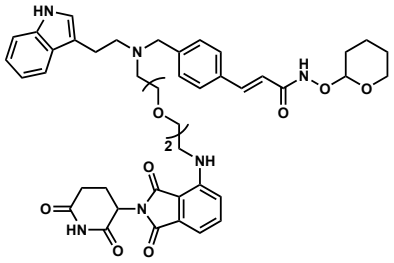
Compound **43** (82 mg, 0.15 mmol, 1.0 eq.) was treated with a mixture of TFA/dichloromethane (1:5), and the reaction was stirred at room temperature for 4 h. When the starting material was consumed, solvent was removed *in vacuo*, and the residue was used in the next step without further purification. **UPLC-MS** RT: 0.59 min (Method A), Mass m/z: 451.88 $[M+H]^+$.



(*E*)-3-(4-(((2-(1*H*-indol-3-yl)ethyl)(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)amino)methyl)phenyl)acrylic acid, 45

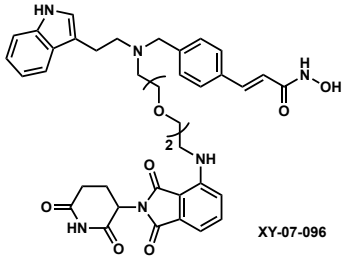
To a solution of **44** (1.0 eq. crude from last step) in DMSO (1.5 mL) were added 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (**1**) (49 mg, 1.2 eq.) and DIEA (78 μL, 3.0 eq.). The reaction mixture was heated to 150 °C and stirred for 90 min. When the starting material was

consumed, the reaction was cooled to room temperature, DIEA was removed *in vacuo* and the residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **45** (35 mg, 33% yield over 2 steps). **UPLC-MS** RT: 0.96 min (Method A), Mass m/z: 707.80 $[M+H]^+$.



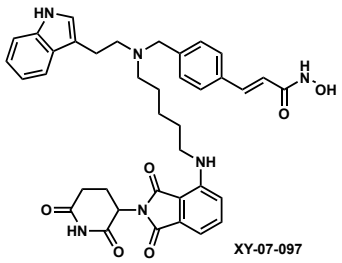
(*E*)-3-(4-(((2-(1*H*-indol-3-yl)ethyl)(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)amino)methyl)phenyl)-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy) acrylamide, 46

To a solution of **45** (35 mg, 0.050 mmol, 1.0 eq.) in DMF (1 mL) were added EDCI (10.6 mg, 1.1 eq.), HOBt (7.4 mg, 1.1 eq.) at 0 °C, and the mixture was stirred at 0 °C for 2 h, then NH_2OTHP (7.6 mg, 1.3 eq.) and DIEA (19 μL, 2 eq.) were added at 0 °C. The reaction mixture was stirred at 0 °C and gradually warmed up to room temperature and stirred for another 5 h. When the starting material was consumed, solvent was removed *in vacuo*, and the residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **46** (23 mg, 58% yield). **UPLC-MS** RT: 1.11 min (Method A), Mass m/z: 806.71 $[M+H]^+$.

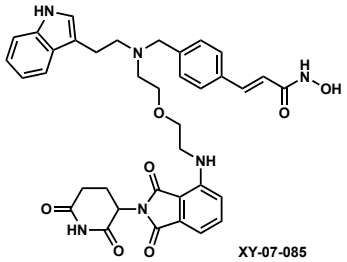


(*E*)-3-(4-(((2-(1*H*-indol-3-yl)ethyl)(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)amino)methyl)phenyl)-*N*-hydroxyacrylamide (XY-07-096)

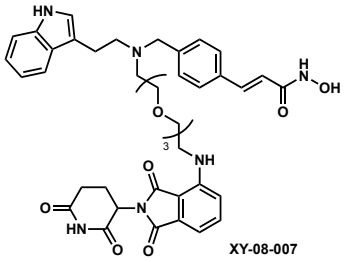
Compound **46** (23 mg, 0.029 mmol, 1.0 eq.) was treated with a mixture of TFA/dichloromethane (1:5), and the reaction was stirred at room temperature for 8 h. When the starting material was consumed, solvent was removed *in vacuo*, and the residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **XY-07-096** as a yellow powder (7 mg, 34% yield). **UPLC-MS** RT: 0.93 min (Method A), Mass m/z: 722.90 $[M+H]^+$. Purity is > 95% by UPLC.



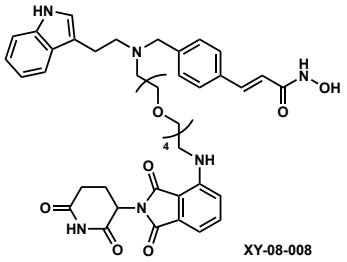
(*E*)-3-(4-(((2-(1*H*-indol-3-yl)ethyl)(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl) amino)pentyl)amino)methyl)phenyl)-*N*-hydroxyacrylamide (XY-07-097) was synthesized from **41** and 2-(5-bromopentyl)isoindoline-1,3-dione using similar procedures, and was obtained as a yellow powder. **UPLC-MS** RT: 1.02 min (Method A), Mass m/z: 676.80 $[M+H]^+$. Purity is > 95% by UPLC. **^{1}H NMR** (500 MHz, DMSO-d_6, as a TFA salt) δ 11.09 (s, 1H), 10.97 (s, 1H), 10.82 (s, 1H), 9.64 (s, 1H, tertiary R_3NH^+), 9.10 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.63 – 7.56 (m, 3H), 7.49 (d, *J* = 15.8 Hz, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.22 (d, *J* = 2.4 Hz, 1H), 7.10 (d, *J* = 8.7 Hz, 1H), 7.10 – 7.06 (m, 1H), 7.04 (d, *J* = 6.9 Hz, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.56 (d, *J* = 6.0 Hz, 1H), 6.53 (dd, *J* = 7723.5, 15.9 Hz, 1H), 5.05 (dd, *J* = 12.8, 5.5 Hz, 1H), 4.48 (d, *J* = 5.2 Hz, 2H), 3.30 (p, *J* = 7.9, 7.3 Hz, 4H), 3.22 – 3.04 (m, 4H), 2.88 (ddd, *J* = 17.0, 13.8, 5.4 Hz, 1H), 2.65 – 2.45 (m, 2H), 2.06 – 1.97 (m, 1H), 1.87 – 1.70 (m, 2H), 1.61 (p, *J* = 7.3 Hz, 2H), 1.37 (p, *J* = 7.5 Hz, 2H). **^{13}C NMR** (126 MHz, DMSO) δ 172.83, 170.12, 168.97, 167.29, 162.43, 146.38, 137.41, 136.32, 136.23, 136.05, 132.23, 131.66 (2C), 131.11, 127.94 (2C), 126.57, 123.45, 121.29, 120.45, 118.52, 118.04, 117.19, 111.63, 110.50, 109.09, 108.76, 55.62, 51.91, 51.90, 48.56, 41.53, 30.98, 28.17, 23.41, 22.64, 22.17, 19.44.



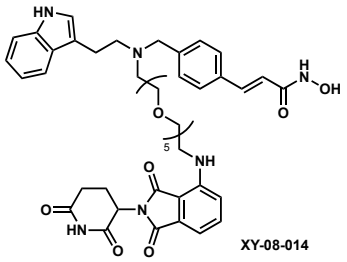
(*E*)-3-(4-(((2-(1*H*-indol-3-yl)ethyl)(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethyl)amino)methyl)phenyl)-*N*-hydroxyacrylamide (XY-07-085) was synthesized from **41** and *tert*-butyl (2-(2-bromoethoxy)ethyl)carbamate using similar procedures, and was obtained as a yellow powder. **UPLC-MS** RT: 0.93 min (Method A), Mass m/z: 678.90 $[M+H]^+$. Purity is > 95% by UPLC. **^{1}H NMR** (500 MHz, Methanol-d_4) δ 10.44 (s, 1H), 7.62 – 7.55 (m, 3H), 7.53 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 2H), 7.34 (dd, *J* = 8.2, 2.8 Hz, 2H), 7.11 (s, 1H), 7.08 (t, *J* = 3.9 Hz, 1H), 7.06 – 7.02 (m, 2H), 6.91 (t, *J* = 7.5 Hz, 1H), 6.54 (d, *J* = 15.8 Hz, 1H), 4.94 – 4.89 (m, 1H), 3.92 (s, 2H), 3.75 (s, 2H), 3.60 (s, 2H), 3.54 (s, 4H), 3.37 (s, 2H), 3.30 – 3.17 (m, 2H), 2.74 (ddd, *J* = 17.5, 13.8, 5.3 Hz, 1H), 2.66 – 2.58 (m, 1H), 2.52 – 2.37 (m, 1H), 1.85 – 1.76 (m, 1H).



(*E*)-3-(4-(2-(2-(1*H*-indol-3-yl)ethyl)-13-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl) amino)-5,8,11-trioxa-2-azatridecyl)phenyl)-*N*-hydroxyacrylamide (XY-08-007) was synthesized from **41** and *tert*-butyl (2-(2-(2-(2-bromoethoxy)ethoxy)ethoxy)ethyl)carbamate using similar procedures, and was obtained as a yellow powder. **UPLC-MS** RT: 0.96 min (Method A), Mass m/z: 766.91 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm) 11.10 (s, 1H), 10.73 (s, 1H), 7.60 – 7.46 (m, 3H), 7.45 – 7.26 (m, 5H), 7.13 – 6.99 (m, 4H), 6.89 (t, *J* = 7.4 Hz, 1H), 6.65 – 6.37 (m, 2H), 5.05 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.70 (d, *J* = 10.0 Hz, 2H), 3.58 (t, *J* = 5.4 Hz, 2H), 3.55 – 3.40 (m, 12H), 2.93 – 2.78 (m, 3H), 2.78 – 2.61 (m, 5H), 2.61 – 2.53 (m, 1H), 1.99 (dd, *J* = 6.7, 3.9 Hz, 1H).



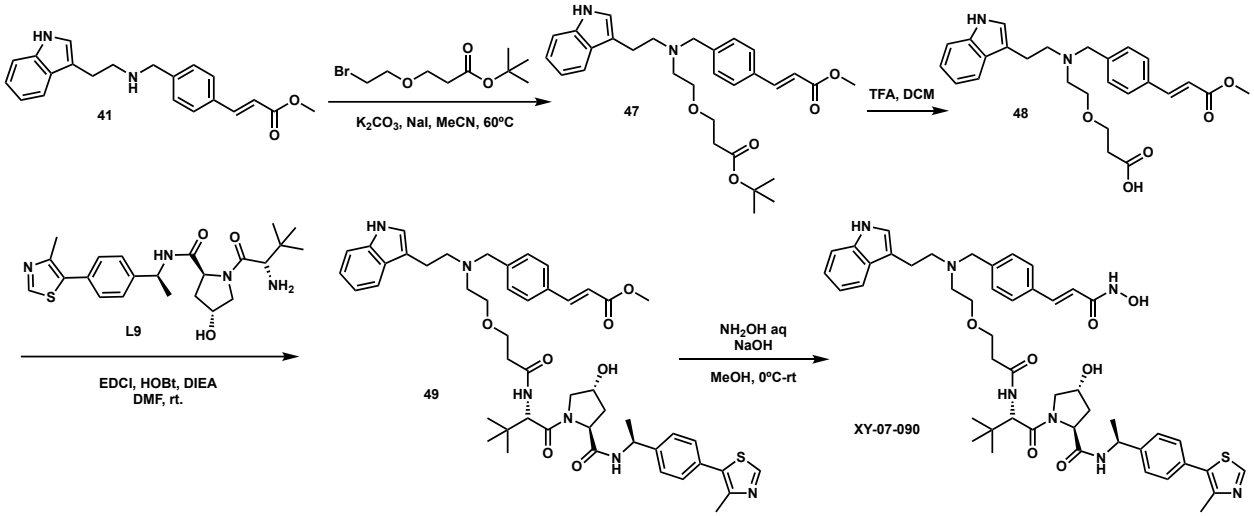
(*E*)-3-(4-(2-(2-(1*H*-indol-3-yl)ethyl)-13-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl) amino)-5,8,11-trioxa-2-azatridecyl)phenyl)-*N*-hydroxyacrylamide (XY-08-008) was synthesized from **41** and *tert*-butyl (14-bromo-3,6,9,12-tetraoxatetradecyl)carbamate using similar procedures, and was obtained as a yellow powder. **UPLC-MS** RT: 0.98 min (Method A), Mass m/z: 810.81 $[M+H]^+$. Purity is > 95% by UPLC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm) 10.73 (s, 2H), 8.50 (s, 1H), 7.75 – 7.43 (m, 3H), 7.32 (dd, *J* = 21.6, 8.8 Hz, 4H), 7.06 (dt, *J* = 15.2, 8.4 Hz, 4H), 6.89 (t, *J* = 7.6 Hz, 1H), 6.59 (s, 1H), 6.44 (d, *J* = 15.8 Hz, 1H), 5.05 (dd, *J* = 13.0, 5.2 Hz, 1H), 3.71 (s, 2H), 3.58 (d, *J* = 5.1 Hz, 2H), 3.55 – 3.42 (m, 14H), 2.97 – 2.62 (m, 6H), 2.02 (t, *J* = 17.3 Hz, 2H), 1.52 – 1.12 (m, 4H).

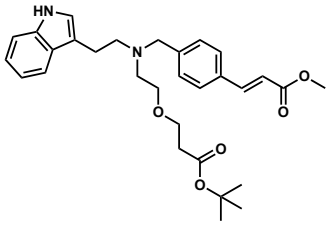


(*E*)-3-(4-(2-(2-(1*H*-indol-3-yl)ethyl)-19-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl) amino)-5,8,11,14,17-pentaoxa-2-azanonadecyl)phenyl)-*N*-hydroxyacrylamide (XY-08-014) was synthesized from **41** and *tert*-butyl (17-bromo-3,6,9,12,15-pentaoxaheptadecyl)carbamate using similar procedures, and was obtained as a yellow powder. **UPLC-MS** RT: 1.02 min (Method

A), Mass m/z: 854.82 $[M+H]^+$. Purity is > 95% by UPLC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm) 11.39 (s, 1H), 11.11 (s, 1H), 10.97 (s, 1H), 8.95 (s, 1H), 7.66 (d, *J* = 7.8 Hz, 2H), 7.62 – 7.46 (m, 5H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.07 (ddd, *J* = 22.1, 17.1, 8.0 Hz, 4H), 6.54 (dd, *J* = 42.8, 10.6 Hz, 2H), 5.05 (dd, *J* = 12.7, 5.3 Hz, 1H), 4.24 (s, 2H), 3.96 (s, 2H), 3.66 – 3.49 (m, 21H), 3.21 (s, 3H), 3.12 – 3.04 (m, 2H), 2.89 (dd, *J* = 22.9, 8.3 Hz, 1H), 2.60 (dd, *J* = 37.8, 19.8 Hz, 2H), 2.08 – 1.96 (m, 1H).

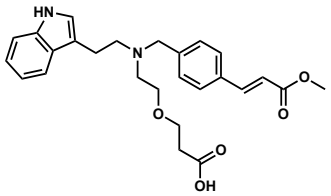
General procedure for degraders based on dacinostat and VHL ligand – I





methyl (*E*)-3-(4-(((2-(1*H*-indol-3-yl)ethyl)(2-(3-(*tert*-butoxy)-3-oxopropoxy)ethyl)amino) methyl)phenyl)acrylate, 47

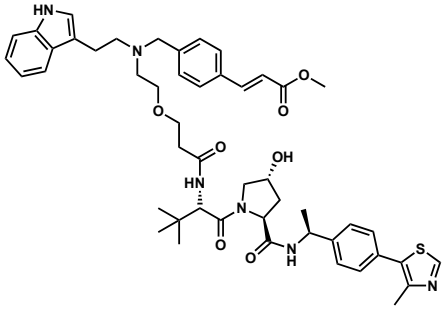
To a solution of compound **41** (75 mg, 0.22 mmol, 1.0 eq.) and *tert*-butyl 3-(2-bromoethoxy)propanoate (87 mg, 1.3 eq.) in acetonitrile (1.2 mL) were added K_2CO_3 (62 mg, 2 eq.) and NaI (3.4 mg, 0.1 eq.) in one portion. The reaction mixture was heated up to 60 °C and stirred for 16 h. When the limiting starting material was consumed, the mixture was filtered through a pad of Celite®, concentrate *in vacuo*, and the residue was purified using ISCO (dichloromethane/methanol, 0%-10%) to yield the title compound **47**. **UPLC-MS** RT: 1.21 min (Method A), Mass m/z: 506.98 $[M+H]^+$.



(*E*)-3-(2-((2-(1*H*-indol-3-yl)ethyl)(4-(3-methoxy-3-oxoprop-1-en-1-yl)benzyl)amino)ethoxy) propanoic acid, 48

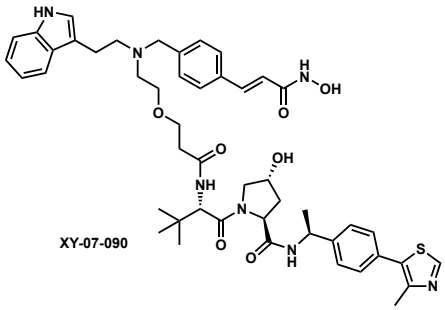
Compound **47** (1.0 eq. from last step) was treated with a mixture of TFA/dichloromethane (1:5), and the reaction was stirred at room temperature for 9 h. When the starting material was consumed,

solvent was removed *in vacuo*, and the residue was used in the next step without further purification. **UPLC-MS** RT: 0.94 min (Method A), Mass m/z: 450.98 $[M+H]^+$.



methyl (*E*)-3-(4-(((2-(1*H*-indol-3-yl)ethyl)(2-(3-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-(((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl) amino)-3-oxopropoxy)ethyl)amino)methyl)phenyl)acrylate, 49

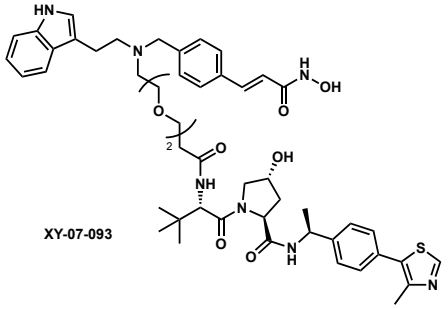
To a solution of **48** (1.0 eq. crude from last step) and (2*R*,4*S*)-1-((*R*)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*R*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (**L9**) (108 mg, 1.0 eq.) in DMF (3 mL), were added EDCI (51.6 mg, 1.2 eq.), HOBt (36.4 mg, 1.2 eq.) and DIEA (120 μL, 3 eq.). The reaction mixture was stirred at room temperature for 7 h. When the limiting starting material was consumed, solvent was removed *in vacuo*, and the residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **49** (59 mg, 30% yield over 3 steps). **UPLC-MS** RT: 1.32 min (Method A), Mass m/z: 876.72 $[M+H]^+$.



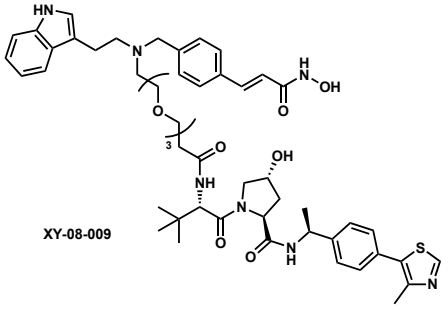
(2*S*,4*R*)-1-((*S*)-2-(3-(2-((2-(1*H*-indol-3-yl)ethyl)(4-((*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl) benzyl)amino)ethoxy)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (XY-07-090)

A solution of **49** (32 mg, 0.037 mmol, 1.0 eq.) in methanol (1 mL) was treated with 50 wt% aq. NH_2OH (22 μL, 10 eq.), followed by 25 wt% NaOMe in methanol (42 μL, 5 eq.) at 0 °C. The reaction mixture was gradually warmed to room temperature and stirred for 2 h. When the starting material was consumed, solvent was removed *in vacuo*, and the residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **XY-07-090** as a white powder (9.9 mg, 31% yield). **UPLC-MS** RT: 0.98 min (Method A), Mass m/z: 877.62 $[M+H]^+$. Purity is > 95% by UPLC. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 10.96 (s, 1H), 10.82 (s, 1H), 9.66 (d, J = 26.1 Hz, 1H), 9.08 (br s, 1H, tertiary R_3NH^+), 8.98 (s, 1H), 8.35 (t, J = 7.7 Hz, 1H), 8.02 (dd, J = 26.3, 9.2 Hz, 1H), 7.72 – 7.54 (m, 4H), 7.50 (d, J = 15.9 Hz, 1H), 7.45 – 7.39 (m, 3H), 7.39 – 7.33 (m, 3H), 7.22

(d, *J* = 2.4 Hz, 1H), 7.08 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.53 (d, *J* = 15.8 Hz, 1H), 5.12 (br s, 1H), 4.90 (td, *J* = 7.3, 2.9 Hz, 1H), 4.51 (dd, *J* = 16.1, 8.4 Hz, 3H), 4.41 (q, *J* = 8.1 Hz, 1H), 4.28 (s, 1H), 3.88 – 3.24 (m, 10H), 3.25 – 3.04 (m, 2H), 2.68 – 2.57 (m, 1H), 2.49 – 2.40 (m, 4H), 2.01 (dt, *J* = 14.0, 7.7 Hz, 1H), 1.78 (dt, *J* = 12.3, 6.5 Hz, 1H), 1.35 (dd, *J* = 7.0, 4.7 Hz, 3H), 0.90 (d, *J* = 6.4 Hz, 9H).**^{13}C NMR** (126 MHz, DMSO) δ 170.51, 170.01, 169.42, 169.33, 151.50, 147.75, 144.58, 136.23 (2C), 136.04, 131.87 (2C), 131.14, 131.09, 129.71, 128.82 (2C), 127.86 (2C), 126.58, 126.37 (2C), 123.41, 121.26, 120.39, 118.50, 118.03, 111.61, 108.71, 68.76, 66.86, 64.02, 58.58, 56.58, 56.36, 56.29, 52.60, 51.11, 47.69, 37.78, 35.26, 34.93, 26.38 (3C), 22.35, 19.48, 15.97.

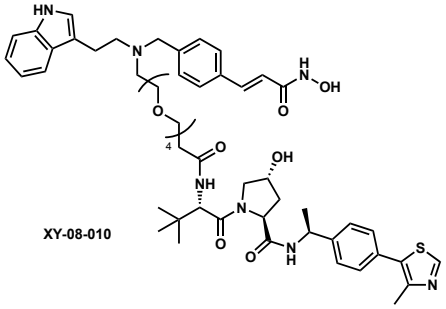


(2*S*,4*R*)-1-((*S*)-14-(*tert*-butyl)-3-(4-((*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl)benzyl)-1-(1*H*-indol-3-yl)-12-oxo-6,9-dioxa-3,13-diazapentadecan-15-oyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (XY-07-093) was synthesized from compound **41** and *tert*-butyl 3-(2-(2-bromoethoxy) ethoxy)propanoate using similar procedures, and was obtained as a white powder. **UPLC-MS** RT: 0.81 min (Method A), Mass m/z: 922.59 $[M+H]^+$. Purity is > 95% by UPLC. ^{1}H NMR (500 MHz, DMSO-d_6, as a TFA salt) δ 10.96 (s, 1H), 10.82 (s, 1H), 9.69 (s, 1H, tertiary R_3NH^+), 9.15 (s, 1H), 8.98 (s, 1H), 8.36 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 9.3 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 7.8 Hz, 2H), 7.49 (d, *J* = 15.8 Hz, 1H), 7.45 – 7.40 (m, 3H), 7.39 – 7.33 (m, 3H), 7.21 (s, 1H), 7.08 (t, *J* = 7.0 Hz, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.53 (d, *J* = 15.9 Hz, 1H), 5.12 (s, 1H), 4.90 (p, *J* = 7.2 Hz, 1H), 4.59 – 4.45 (m, 3H), 4.41 (t, *J* = 8.1 Hz, 1H), 4.28 (s, 1H), 3.90 – 3.75 (m, 2H), 3.72 – 3.41 (m, 8H), 3.43 – 3.27 (m, 4H), 3.25 – 3.07 (m, 2H), 2.55 – 2.47 (m, 1H), 2.45 (s, 3H), 2.33 (dt, *J* = 14.8, 6.1 Hz, 1H), 2.07 – 1.97 (m, 1H), 1.79 (ddd, *J* = 12.9, 8.7, 4.6 Hz, 1H), 1.36 (d, *J* = 7.0 Hz, 3H), 0.91 (s, 9H).

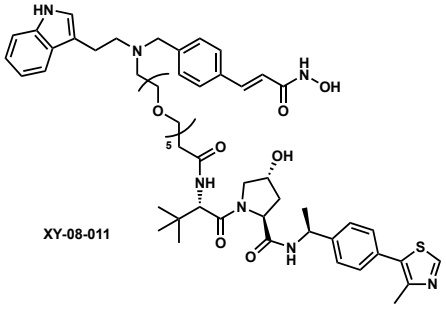


(2*S*,4*R*)-1-((*S*)-17-(*tert*-butyl)-3-(4-((*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl)benzyl)-1-(1*H*-indol-3-yl)-15-oxo-6,9,12-trioxa-3,16-diazaoctadecan-18-oyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (XY-08-009) was synthesized from compound **41** and *tert*-butyl 3-(2-(2-(2-bromoethoxy)ethoxy)ethoxy)propanoate using similar

procedures, and was obtained as a white powder. **UPLC-MS** RT: 1.03 min (Method A), Mass m/z: 965.93 $[M+H]^+$. Purity is > 95% by UPLC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm) 13.11 – 12.53 (m, 2H), 10.75 (s, 3H), 9.02 (d, *J* = 24.1 Hz, 2H), 8.40 (d, *J* = 7.9 Hz, 1H), 8.14 (s, 1H), 7.88 (d, *J* = 8.9 Hz, 1H), 7.80 – 7.23 (m, 6H), 7.04 (dd, *J* = 55.3, 28.0 Hz, 4H), 6.46 (s, 1H), 5.12 (d, *J* = 3.2 Hz, 1H), 4.92 (d, *J* = 6.9 Hz, 1H), 4.61 – 4.17 (m, 3H), 3.73 (s, 1H), 3.41 (d, *J* = 50.8 Hz, 14H), 2.83 (s, 1H), 2.59 (d, *J* = 64.7 Hz, 6H), 2.45 (s, 3H), 2.31 (d, *J* = 17.1 Hz, 1H), 2.3 (s, 1H), 2.01 (s, 1H), 1.78 (s, 1H), 1.37 (d, *J* = 6.9 Hz, 3H), 0.92 (s, 9H).



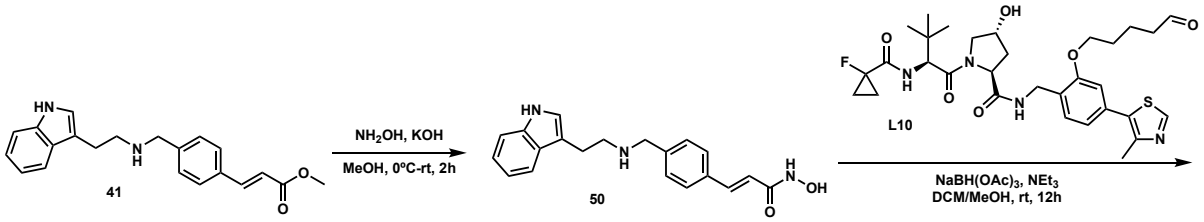
(2*S*,4*R*)-1-((*S*)-20-(*tert*-butyl)-3-(4-((*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl)benzyl)-1-(1*H*-indol-3-yl)-18-oxo-6,9,12,15-tetraoxa-3,19-diazahenicosan-21-oyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (XY-08-010) was synthesized from compound **41** and *tert*-butyl 1-bromo-3,6,9,12-tetraoxapentadecan-15-oate using similar procedures, and was obtained as a white powder. **UPLC-MS** RT: 0.99 min (Method A), Mass m/z: 1009.42 $[M+H]^+$. Purity is > 95% by UPLC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm) 11.39 (s, 1H), 10.98 (s, 1H), 8.99 (s, 3H), 8.40 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 9.4 Hz, 1H), 7.67 (d, *J* = 7.4 Hz, 2H), 7.53 (t, *J* = 12.0 Hz, 4H), 7.41 (dd, *J* = 23.9, 8.4 Hz, 5H), 7.30 – 7.20 (m, 1H), 7.11 (dd, *J* = 13.8, 6.6 Hz, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 6.49 (d, *J* = 15.8 Hz, 1H), 4.97 – 4.84 (m, 1H), 4.58 – 4.39 (m, 2H), 4.26 (d, *J* = 14.3 Hz, 4H), 3.98 (s, 2H), 3.52 (s, 18H), 3.20 (s, 2H), 3.12 – 3.01 (m, 2H), 2.55 (dd, *J* = 13.8, 6.2 Hz, 1H), 2.46 (s, 3H), 2.36 (dd, *J* = 13.2, 7.0 Hz, 1H), 2.08 – 1.94 (m, 1H), 1.79 (ddd, *J* = 12.9, 8.7, 4.6 Hz, 1H), 1.42 (dd, *J* = 37.8, 6.9 Hz, 3H), 0.94 (s, 9H).

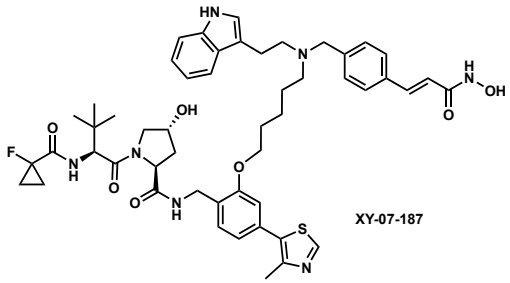


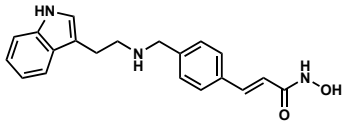
(2*S*,4*R*)-1-((*S*)-23-(*tert*-butyl)-3-(4-((*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl)benzyl)-1-(1*H*-indol-3-yl)-21-oxo-6,9,12,15,18-pentaoxa-3,22-diazatetracosan-24-oyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (XY-08-011) was synthesized from compound **41** and *tert*-butyl 1-bromo-3,6,9,12,15-pentaoxaoctadecan-18-oate using similar procedures, and was obtained as a white powder. **UPLC-MS** RT: 1.02 min (Method A), Mass m/z: 1053.51 $[M+H]^+$. Purity is > 95% by UPLC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm) 11.45 (s, 1H), 11.04 (s, 1H), 9.05 (s, 3H), 8.46 (d, *J* = 7.8 Hz, 1H), 7.94 (d, *J* = 9.2 Hz, 1H), 7.83 – 7.53 (m, 6H), 7.45 (dt, *J* = 20.1, 9.9 Hz, 5H), 7.34 – 7.23 (m, 1H), 7.17 (dd, *J* = 14.7, 7.5 Hz, 1H), 7.06 (dd, *J* = 16.0, 9.0 Hz, 1H), 6.58 (t, *J* = 17.1 Hz, 1H), 4.96 (dd, *J* = 14.3, 7.0 Hz, 1H), 4.64

– 4.47 (m, 2H), 4.32 (d, *J* = 14.8 Hz, 3H), 4.04 (s, 2H), 3.61 (ddd, *J* = 28.8, 16.5, 9.8 Hz, 22H), 3.27 (s, 2H), 3.18 – 3.08 (m, 2H), 2.61 (dd, *J* = 13.5, 6.0 Hz, 1H), 2.52 (s, 3H), 2.45 – 2.36 (m, 1H), 2.12 – 2.04 (m, 1H), 1.85 (ddd, *J* = 12.8, 8.5, 4.6 Hz, 1H), 1.48 (dd, *J* = 37.2, 7.0 Hz, 3H), 1.00 (s, 9H).

General procedure for degraders based on dacinostat and VHL ligand – II

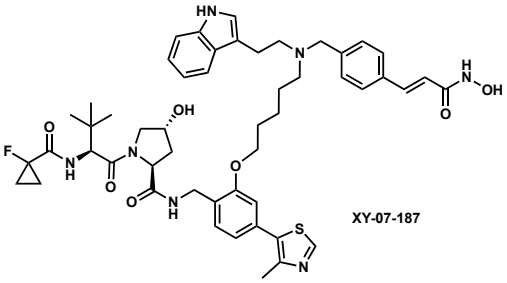






(*E*)-3-(4-(((2-(1*H*-Indol-3-yl)ethyl)amino)methyl)phenyl)-*N*-hydroxyacrylamide, 50

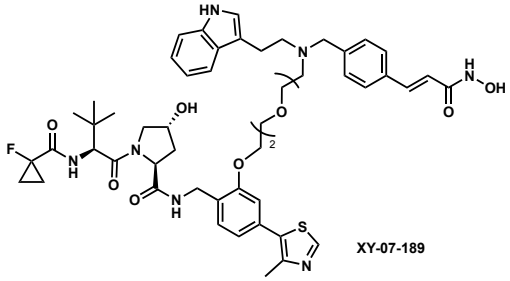
To a solution of compound **41** (250 mg, 0.75 mmol, 1.0 eq.) in MeOH (4 mL) was added freshly made NH_2OH in MeOH (2M solution, 3.75 mL, 10 eq.), followed by KOH in MeOH (1.9 M solution, 1.2 mL, 3.0 eq.) at 0 °C. The mixture was gradually warmed up to room temperature, and monitored by UPLC-MS. Once the starting material was consumed, the reaction was quenched with H_2O, and the pH was adjusted to 8. The mixture was extracted three times with iPrOH/$CHCl_3$. The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*. The residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **50**. UPLC-MS RT: 0.69 min (Method A), Mass m/z: 336.27 $[M+H]^+$.



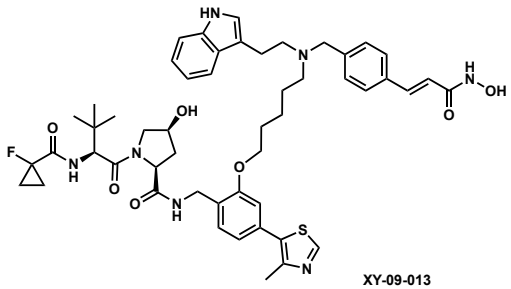
(2*S*,4*R*)-*N*-(2-((5-((2-(1*H*-indol-3-yl)ethyl)(4-((*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl)benzyl)amino)pentyl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-

fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide (XY-07-187)

Compound **L10** (1.0 eq, crude from deprotection step of 30 mg corresponding acetal) and compound **50** (15 mg, 0.045 mmol, 1.0 eq.) were dissolved in a solvent mixture of dichloromethane/MeOH (2 mL/10 drops), and the mixture was treated with NEt_3 (48 μL, 4 eq.) and $NaBH(OAc)_3$ (40 mg, 2 eq.) at room temperature. The reaction was stirred for 12 h, and monitored by UPLC-MS. Once the limiting starting material was consumed, the reaction was quench with aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*. The residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **XY-07-187** as a white powder (27 mg, 32% yield over 2 steps). **UPLC-MS** RT: 1.45 min (Method A), Mass m/z: 936.62 $[M+H]^+$. Purity is > 95% by UPLC. **^{1}H NMR** (500 MHz, Methanol-d_4) δ 8.86 (s, 1H), 7.61 – 7.54 (m, 3H), 7.53 – 7.46 (m, 3H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.09 (s, 1H), 7.06 (t, *J* = 7.7 Hz, 1H), 7.01 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.96 (d, *J* = 1.6 Hz, 1H), 6.94 (t, *J* = 7.7 Hz, 1H), 6.51 (d, *J* = 15.8 Hz, 1H), 4.73 (s, 1H), 4.63 (t, *J* = 8.3 Hz, 1H), 4.50 – 4.36 (m, 3H), 4.21 (br s, 2H), 4.03 (h, *J* = 3.5 Hz, 2H), 3.83 (d, *J* = 11.0 Hz, 1H), 3.75 (dd, *J* = 11.0, 3.8 Hz, 1H), 3.26 – 3.18 (m, 2H), 3.14 (d, *J* = 7.6 Hz, 2H), 3.04 (br s, 2H), 2.47 (s, 3H), 2.25 – 2.16 (m, 1H), 2.07 (ddd, *J* = 13.3, 9.1, 4.4 Hz, 1H), 1.88 – 1.72 (m, 4H), 1.59 – 1.48 (m, 2H), 1.42 – 1.21 (m, 4H), 1.01 (s, 9H). **^{13}C NMR** (126 MHz, MeOD) δ 174.27, 171.78, 171.47 (d, $J_{C,F}$ = 20 Hz), 166.00, 157.86, 152.83, 149.08, 140.66, 138.22, 136.96, 133.60, 132.80, 132.07 (2C), 129.49, 129.30 (2C), 128.22, 127.91, 123.93, 122.63, 122.51, 119.90, 119.55, 119.00, 113.04, 112.51, 79.15 (d, $J_{C,F}$ = 232 Hz), 71.03, 68.90, 60.82, 58.69, 58.58, 58.16, 54.56, 54.46, 39.31, 38.91, 37.29, 29.78, 26.88 (3C), 25.62, 24.65, 22.30, 15.92, 14.02 (d, $J_{C,F}$ = 16 Hz), 13.94 (d, $J_{C,F}$ = 16 Hz).



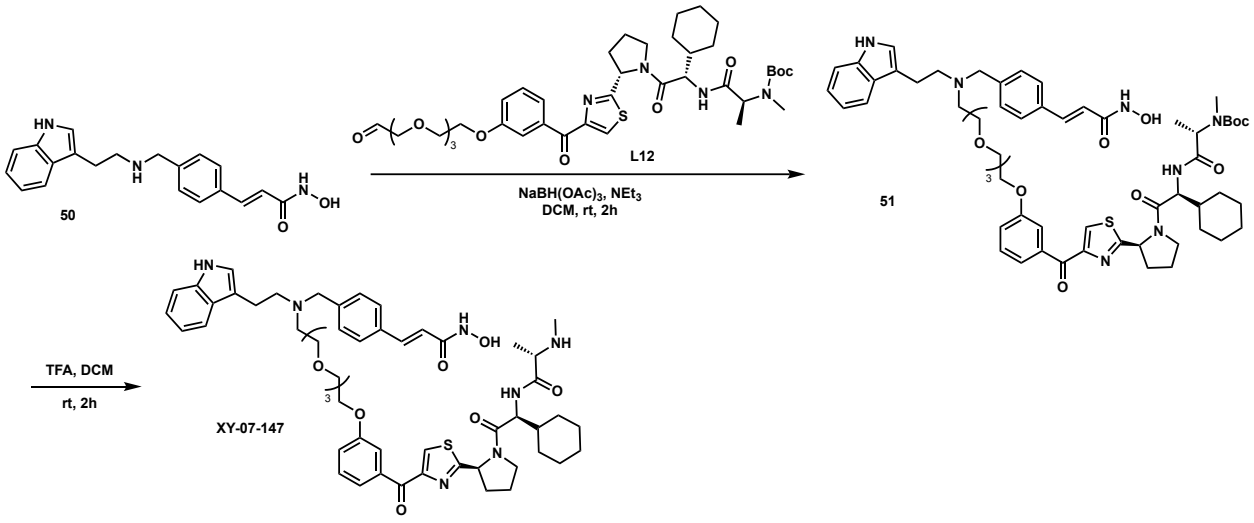
(2*S*,4*R*)-*N*-(2-(2-(2-(2-((2-(1*H*-indol-3-yl)ethyl)(4-((*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl) benzyl)amino)ethoxy)ethoxy)ethoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide (XY-07-189) was synthesized from compound **41** and **L11** using similar procedures, and was obtained as a white powder. **UPLC-MS** RT: 1.25 min (Method A), Mass m/z: 981.83 $[M+H]^+$. Purity is > 95% by UPLC.

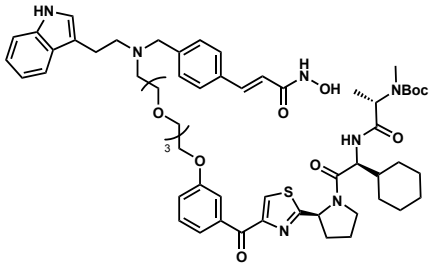


XY-09-013

(2*S*,4*S*)-*N*-(2-((5-((2-(1*H*-indol-3-yl)ethyl)(4-((*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl)benzyl)amino)pentyl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide (XY-09-013) was synthesized from compound **41** and **L10-negative** using similar procedures, and was obtained as a white powder. **UPLC-MS** RT: 1.07 min (Method A), Mass m/z: 935.73 $[M+H]^+$. Purity is > 95% by UPLC. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 10.73 (s, 2H), 9.02 (s, 1H), 8.97 (s, 1H), 8.57 (t, *J* = 6.0 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.44 (d, *J* = 15.9 Hz, 1H), 7.42 – 7.35 (m, 3H), 7.35 – 7.27 (m, 3H), 7.08 (s, 1H), 7.04 – 6.97 (m, 2H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.87 (t, *J* = 7.4 Hz, 1H), 6.44 (d, *J* = 15.8 Hz, 1H), 5.45 (d, *J* = 7.3 Hz, 1H), 4.54 (d, *J* = 8.9 Hz, 1H), 4.45 (dd, *J* = 8.6, 6.1 Hz, 1H), 4.34 (dd, *J* = 16.5, 6.3 Hz, 1H), 4.27 – 4.16 (m, 2H), 4.02 (t, *J* = 6.3 Hz, 2H), 3.85 (dd, *J* = 10.2, 5.6 Hz, 1H), 3.67 (br s, 2H), 3.46 (dd, *J* = 10.1, 5.3 Hz, 1H), 2.84 (br s, 2H), 2.69 (br s, 2H), 2.57 (br s, 2H), 2.45 (s, 3H), 2.35 (ddd, *J* = 12.7, 8.8, 5.8 Hz, 1H), 1.81 – 1.68 (m, 3H), 1.57 (br s, 2H), 1.47 (q, *J* = 7.6 Hz, 2H), 1.41 – 1.29 (m, 2H), 1.27 – 1.15 (m, 2H), 0.96 (s, 9H). **^{13}C NMR** (126 MHz, DMSO) δ 172.39, 169.15, 168.37 (d, $J_{C,F}$ = 21 Hz), 162.84, 155.90, 151.43, 147.85, 138.21, 136.18, 133.37, 131.32, 130.97, 129.08 (2C), 127.67, 127.34 (2C), 127.14, 126.67, 122.46, 120.77, 120.65, 118.47, 118.14, 118.05, 111.65, 111.30, 78.02 (d, $J_{C,F}$ = 233 Hz), 69.05, 67.71, 58.71, 57.60, 56.72, 55.69, 54.11, 53.26, 37.43, 36.82, 35.44, 28.58, 26.45, 26.15 (3C), 23.39, 22.40, 15.97, 12.91 (d, $J_{C,F}$ = 23 Hz), 12.83 (d, $J_{C,F}$ = 22 Hz).

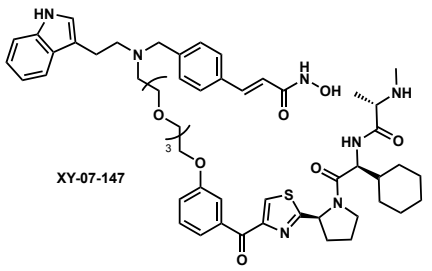
General procedure for degraders based on dacinostat and IAP ligand





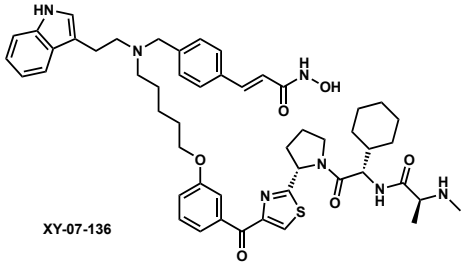
***tert*-Butyl ((*S*)-1-(((*S*)-1-cyclohexyl-2-((*S*)-2-(4-(3-((3-(4-((*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl)benzyl)-1-(1*H*-indol-3-yl)-6,9,12-trioxa-3-azatetradecan-14-yl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-2-oxoethyl)amino)-1-oxopropan-2-yl)(methyl)carbamate, 51**

Compounds **50** (16 mg, 0.048 mmol, 1.0 eq.), and **L12** (1.0 eq, crude from deprotection step of 40 mg corresponding acetal) were dissolved in a solvent mixture of dichloromethane and MeOH (0.5 mL/10 drops). To the mixture were added NEt_3 (13 μL, 2.0 eq.) and $NaBH(OAc)_3$ (12 mg, 1.2 eq.) at room temperature. The reaction was stirred for 2 h and monitored by UPLC-MS. Once the limiting starting material was consumed, the reaction was quenched with aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*. The residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **51**. **UPLC-MS** RT: 1.54 min (Method A), Mass m/z: 1092.65 $[M+H]^+$.

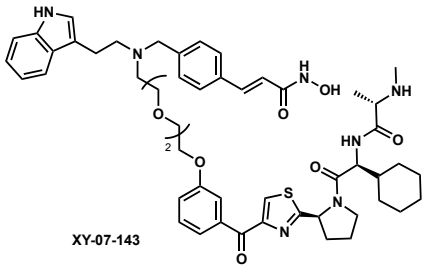


(*E*)-3-(4-(2-(2-(1*H*-Indol-3-yl)ethyl)-13-(3-(2-((*S*)-1-((*S*)-2-cyclohexyl-2-((*S*)-2-(methylamino) propanamido)acetyl)pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)-5,8,11-trioxa-2-azatridecyl)phenyl)-*N*-hydroxyacrylamide (XY-07-147)

Compound **51** (1.0 eq. from last step) was treated with a mixture of TFA/dichloromethane. The reaction was stirred for 2h, and monitored by UPLC-MS. Once the starting material was consumed, the reaction was concentrated *in vacuo*. The residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **XY-07-147** as a white powder (9.3 mg, 20% yield over 3 steps). **UPLC-MS** RT: 1.23 min (Method A), Mass m/z: 992.63 $[M+H]^+$. Purity is > 95% by UPLC. **^{1}H NMR** (500 MHz, Methanol-d_4) δ 8.23 (s, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.57 – 7.51 (m, 4H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.39 – 7.32 (m, 3H), 7.17 (s, 1H), 7.13 – 7.06 (m, 2H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.49 (d, *J* = 15.8 Hz, 1H), 5.45 (dd, *J* = 8.0, 3.3 Hz, 1H), 4.57 (d, *J* = 7.1 Hz, 1H), 4.55 – 4.35 (m, 2H), 4.06 – 4.00 (m, 2H), 4.00 – 3.81 (m, 5H), 3.77 – 3.70 (m, 2H), 3.67 – 3.59 (m, 8H), 3.55 – 3.40 (m, 4H), 3.29 – 3.14 (m, 2H), 2.67 (s, 3H), 2.41 – 2.05 (m, 4H), 1.84 – 1.66 (m, 3H), 1.61 (d, *J* = 9.7 Hz, 2H), 1.49 (d, *J* = 7.0 Hz, 3H), 1.25 – 1.01 (m, 6H). **^{13}C NMR** (126 MHz, MeOD) δ 188.21, 174.31, 172.52, 170.24, 165.75, 160.19, 154.54, 140.29, 139.78, 138.29, 137.95, 132.71 (2C), 131.90, 130.54, 130.37, 129.54 (2C), 127.84, 124.66, 124.37, 122.93, 120.77, 120.29, 120.22, 118.93, 116.51, 112.68, 109.36, 71.69, 71.53, 71.40, 71.38, 70.72, 68.81, 65.34, 60.30, 58.27, 58.22, 57.57, 54.51, 53.63, 48.98, 41.14, 33.12, 31.82, 30.81, 29.61, 27.09, 27.00, 26.89, 25.55, 21.23, 16.30.

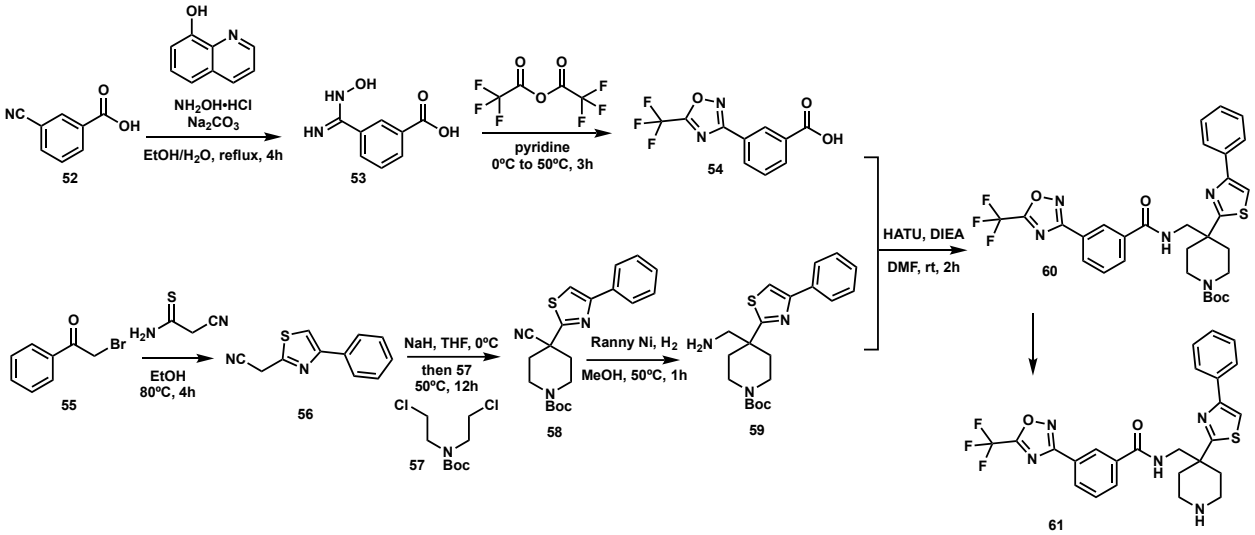


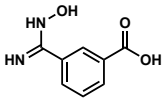
(*E*)-3-(4-(((2-(1*H*-Indol-3-yl)ethyl)(5-(3-(2-((*S*)-1-((*S*)-2-cyclohexyl-2-((*S*)-2-(methylamino) propanamido)acetyl)pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)pentyl)amino)methyl) phenyl)-*N*-hydroxyacrylamide (XY-07-136) was synthesized from compound **50** and **L15** using similar procedures, and was obtained as a white powder. **UPLC-MS** RT: 1.21 min (Method A), Mass m/z: 901.83 $[M+H]^+$. Purity is > 95% by UPLC. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.88, 11.39 (s, 1H), 10.98 (s, 1H), 9.81 (s, 1H, tertiary NH^+), 8.85 (d, *J* = 34.2 Hz, 2H), 8.71 (dd, *J* = 8.2, 2.9 Hz, 1H), 7.80 (d, *J* = 7.9 Hz, 2H), 7.73 – 7.55 (m, 4H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.36 – 7.24 (m, 1H), 7.22 (s, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.01 – 6.85 (m, 3H), 6.62 (d, *J* = 16.0 Hz, 1H), 5.57 – 5.17 (m, 1H), 4.59 – 4.37 (m, 3H), 3.97 (s, 2H), 3.90 – 3.68 (m, 3H), 3.52 – 3.25 (m, 2H), 3.24 – 3.07 (m, 4H), 2.57 – 2.34 (m, 3H), 2.26 – 1.92 (m, 4H), 1.89 – 1.53 (m, 9H), 1.53 – 1.38 (m, 2H), 1.33 (d, *J* = 7.0 Hz, 3H), 1.25 – 0.94 (m, 6H).



(*E*)-3-(4-(((2-(1*H*-Indol-3-yl)ethyl)(2-(2-(2-(3-(2-((*S*)-1-((*S*)-2-cyclohexyl-2-((*S*)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)ethoxy)ethoxy)ethyl)amino)methyl)phenyl)-*N*-hydroxyacrylamide (XY-07-143) was synthesized from compound **50** and **L14** using similar procedures, and was obtained as a white powder. **UPLC-MS** RT: 1.32 min (Method A), Mass m/z: 948.53 $[M+H]^+$. Purity is > 95% by UPLC.

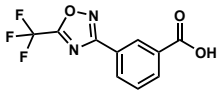
Synthesis of TMP intermediate





3-(*N*-hydroxycarbamimidoyl)benzoic acid, 53

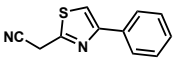
8-hydroxyquinoline (11.8 mg, 0.3 mol%) was added to a solution of 3-cyanobenzoic acid **52** (4 g, 27.2 mmol, 1.0 eq.) in ethanol (204 mL). To the reaction mixture was added hydroxylamine hydrochloride (4.04 g, 2.1 eq.) solution in water (30 mL), followed by the solution of sodium carbonate (4.67 g, 1.6 eq.) in water (31 mL). The mixture was heated to reflux for 4 hours. After removal of ethanol under reduced pressure, the residue was diluted with water (100 mL), and the aqueous solution was acidified to pH~3 with 2N HCl solution. The resulting white precipitate was filtered, washed with water and dried under vacuum to afford the target compound **53** as a white solid (6 g, crude, 100% yield). **^{1}H-NMR** (DMSO-d_6, 400 MHz): δ (ppm) 9.75 (s, 1H), 8.27 (s, 1H), 7.91 (dd, *J* = 15.2, 8.1 Hz, 2H), 7.50 (t, *J* = 7.8 Hz, 1H), 5.92 (s, 2H). One active hydrogen was not shown.



3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzoic acid, 54

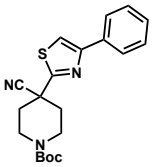
A solution of compound **53** (3 g, 16.7 mmol, 1.0 eq.) in anhydrous pyridine (45 mL) was cooled down to 0 °C and then trifluoroacetic anhydride (10.52 g, 3.0 eq.) was added dropwise. The reaction mixture was warmed slowly to room temperature and further heated at 50 °C for 3 hours. The reaction mixture was poured into ice water, adjusted to pH~4 with 1.5 N HCl solution, and extracted with ethyl acetate (60 mL X 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum, the residue was purified by flash column chromatography on silica gel (ethyl acetate in petroleum ether (24%v/v), with 1% v/v of trifluoroacetic acid) to furnish the target compound **54** as a white solid (2 g, 46.5%

yield). **LC-MS**: Mass m/z: 259 $[M+H]^+$. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 8.79 (s, 1H), 8.31 (d, *J* = 7.7 Hz, 1H), 8.24 (d, *J* = 7.8 Hz, 1H), 7.61 (t, *J* = 7.9 Hz, 1H). One active hydrogen was not shown.



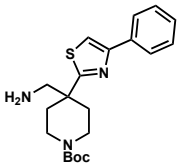
2-(4-phenylthiazol-2-yl)acetonitrile, 56

A mixture of 2-bromoacetophenone **55** (6 g, 30.3 mmol, 1.0 eq.) and 2-cyanothioacetamide (3.03 g, 1.0 eq.) in ethanol (75 mL) was heated at 80 °C for 4 hours. The reaction mixture was cooled down to room temperature and poured into an aqueous ammonia solution (final pH >7). The mixture was then extracted with ethyl acetate (30 mL X 3). The combined organic layers were washed with brine (30 mLX2), dried over anhydrous Na_2SO_4 and concentrated under vacuum, the residue was purified by flash column chromatography on silica gel (ethyl acetate in petroleum ether, 20%v/v) to afford the target compound **56** as a solid (4.5 g, 74.2% yield). **LC-MS**: Mass m/z: 201 $[M+H]^+$. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.88 (dd, *J* = 5.3, 3.3 Hz, 2H), 7.48 (d, *J* = 4.2 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.37 (dtd, *J* = 7.3, 4.8, 2.3 Hz, 1H), 4.18 (d, *J* = 4.9 Hz, 2H).



***tert*-butyl 4-cyano-4-(4-phenylthiazol-2-yl)piperidine-1-carboxylate, 58**

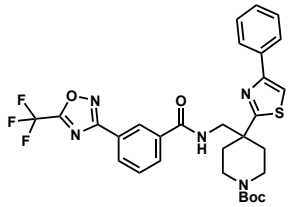
A solution of compound **56** (3.4 g, 17 mmol, 1.0 eq.) in anhydrous THF (102 mL) was cooled down to 0 °C. NaH (2.04 g, 60% dispersion in oil, 3.0 eq.) was added portionwise over 10 minutes. The resulting mixture was allowed to warm up to room temperature and stirred at room temperature for 30 minutes. *N*-Boc-*N*,*N*-bis(2-chloroethyl)amine **57** (12.3 g, 3.0 eq.) was added dropwise. The reaction mixture was further stirred at 50 °C overnight. The resulted mixture was quenched with saturated NH_4Cl solution (50 mL), and extracted with ethyl acetate (50 mL X 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum, the residue was purified by flash column chromatography on silica gel (ethyl acetate in petroleum ether, 18% v/v) to furnish the target compound **58** as a solid (2.0 g, 31.8% yield). **LC-MS**: Mass m/z: 314 $[M-tBu+H]^+$. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 – 7.83 (m, 2H), 7.50 (s, 1H), 7.47 – 7.40 (m, 2H), 7.39 – 7.30 (m, 1H), 4.23 (s, 2H), 3.27 (s, 2H), 2.37 (d, *J* = 13.1 Hz, 2H), 2.29 – 2.18 (m, 2H), 1.49 (s, 9H).



***tert*-butyl 4-(aminomethyl)-4-(4-phenylthiazol-2-yl)piperidine-1-carboxylate, 59**

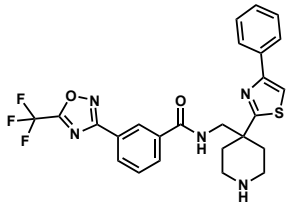
A solution of compound **58** (0.8 g, 2.2 mmol, 1.0 eq.), Raney Ni (slurry in water, 0.8 g) and ammonia (4 mL) in methanol (80 mL) was stirred at 50 °C under hydrogen (1 atm) for one hour. The resulting mixture was filtered through a pad of diatomite®, the cake was washed with a mixed

solution of methanol (5 mL) and dichloromethane (50 mL), the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (methanol in dichloromethane, 16%v/v) to afford the target compound **59** as an oil (0.7 g, 85.6% yield). **LC-MS**: Mass m/z: 374 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.06 (s, 1H), 7.96 (d, *J* = 7.9 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 1H), 3.72 (d, *J* = 13.4 Hz, 2H), 3.03 (s, 2H), 2.77 (s, 2H), 2.11 (d, *J* = 13.9 Hz, 2H), 1.86 – 1.70 (m, 2H), 1.39 (s, 9H). Two active hydrogens were not shown.



***tert*-butyl 4-(4-phenylthiazol-2-yl)-4-((3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamido) methyl)piperidine-1-carboxylate, 60**

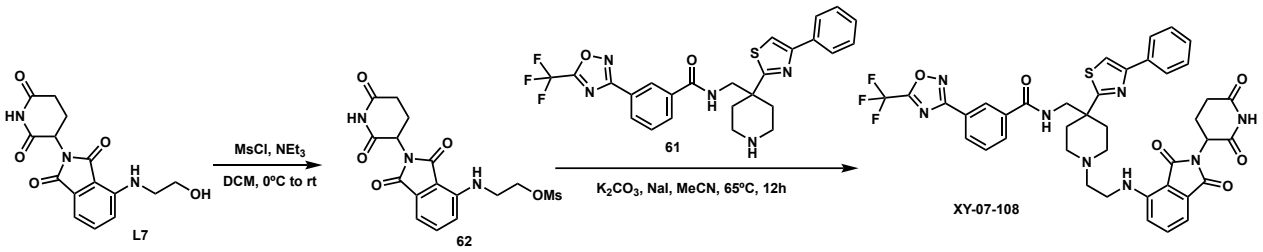
To a solution of compound **59** (0.4 g, 1.07 mmol, 1.0 eq.) and compound **54** (0.304 g, 1.1 eq.) in anhydrous DMF (7 mL) at 0 °C were added HATU (0.448 g, 1.1 eq.) and DIPEA (0.277 g, 2.0 eq.). The reaction mixture was stirred at room temperature for 2 hours under nitrogen atmosphere. The mixture was quenched with water (30 mL) and extracted with ethyl acetate (30 mL X 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum, the residue was purified by flash column chromatography on silica gel (ethyl acetate in petroleum ether, 35% v/v) to afford the target compound **60** as a white solid (0.38 g, 57.8 % yield). **LC-MS**: Mass m/z: 614 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.81 (t, J = 6.2 Hz, 1H), 8.45 (s, 1H), 8.21 (t, *J* = 10.4 Hz, 1H), 8.12 – 8.02 (m, 2H), 7.94 (d, *J* = 7.5 Hz, 2H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 3.85 (d, *J* = 13.3 Hz, 2H), 3.58 (d, *J* = 6.1 Hz, 2H), 2.96 (s, 2H), 2.28 (d, *J* = 13.7 Hz, 2H), 1.88 (t, *J* = 10.4 Hz, 2H), 1.39 (s, 9H).

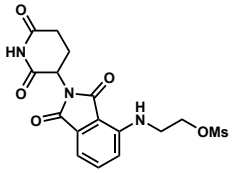


***N*-((4-(4-phenylthiazol-2-yl)piperidin-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide, 61**

Compound **60** (21 mg, 0.034 mmol, 1.0 eq.) was dissolved in dichloromethane (3 mL) and treated with TFA (0.5 mL). The reaction was monitored by UPLC and when the starting material was consumed, the mixture was concentrated *in vacuo* and used in the next step without further purification. **UPLC-MS** RT: 1.22 min (Method A), Mass m/z: 514.28 $[M+H]^+$.

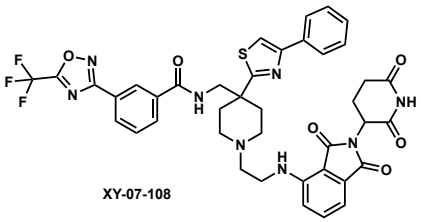
General procedure for degraders based on TMP scaffold and thalidomide – I





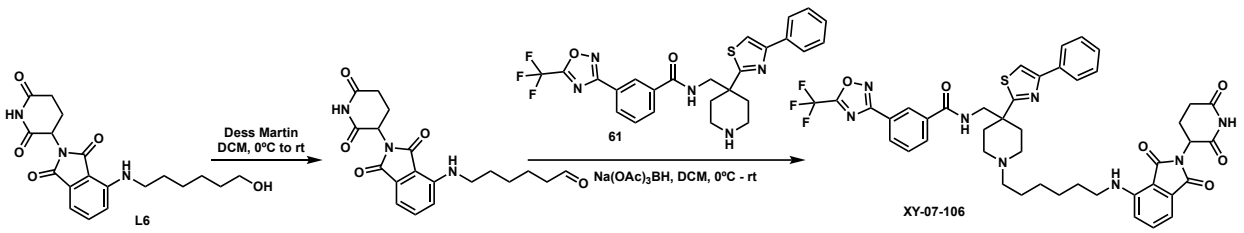
2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl methanesulfonate, 62

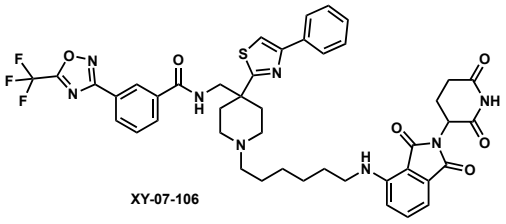
To a solution of compound **L7** (20 mg, 0.063 mmol, 1.0 eq.) in dichloromethane (1 mL) were added MsCl (7.3 μL, 1.5 eq.) and NEt_3 (1.8 μL, 1.8 eq.) at 0ºC. The reaction was warmed up to room temperature and stirred for 2 h and monitored by UPLC-MS. Once the starting material was consumed, the reaction was quenched with H_2O and extracted three times with dichloromethane, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to yield the title compound **62**. The residue was used in the next step without further purification. **UPLC-MS** RT: 0.85 min (Method A), Mass m/z: 395.87 $[M+H]^+$.



***N*-((1-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)-4-(4-phenylthiazol-2-yl)piperidin-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl) benzamide (XY-07-108)**

To a solution of compound **61** (24 mg, 0.046 mmol, 1.0 eq. crude from deprotection step) and compound **62** (25 mg, 1.0 eq. crude from last step) in acetonitrile (1 mL) were added K_2CO_3 (17 mg, 2.5 eq.) and NaI (0.73 mg, 0.1 eq.) in one portion. The reaction mixture was heated to 65 °C and stirred for 12 h. When the starting material was consumed, the mixture was filtered through a pad of Celite®, concentrate *in vacuo*, and the residue was purified using ISCO (dichloromethane/methanol, 0%-10%) to yield the title compound **XY-07-108** as a yellow powder (13.5 mg, 35% yield over three steps). **UPLC-MS** RT: 1.51 min (Method A), Mass m/z: 812.71 $[M+H]^+$. Purity is > 95% by UPLC.



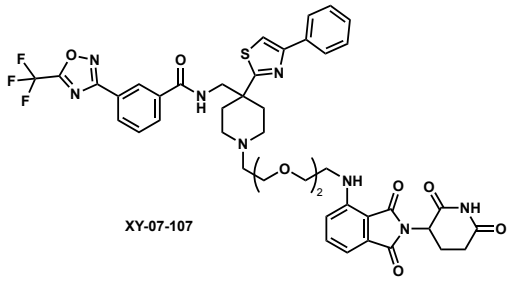


_N_-((1-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexyl)-4-(4-phenylthiazol-2-yl)piperidin-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl) benzamide (XY-07-106)

A solution of 2-(2,6-dioxopiperidin-3-yl)-4-((6-hydroxyhexyl)amino)isoindoline-1,3-dione (**L6**) (25 mg, 0.067 mmol, 1.0 eq.) in dichloromethane (1 mL) was treated with Dess-Martin periodinane (30 mg, 1.05 eq.) at 0 °C. The reaction mixture was warmed gradually to room temperature and stirred for 3 h. When the starting material was consumed, the reaction mixture was quenched with aqueous $NaHCO_3$, extract three times with ethyl acetate. The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was used in the next step without further purification. **UPLC-MS** RT: 1.14 min (Method A), Mass m/z: 354.17 $[M-H_2O+H]^+$.

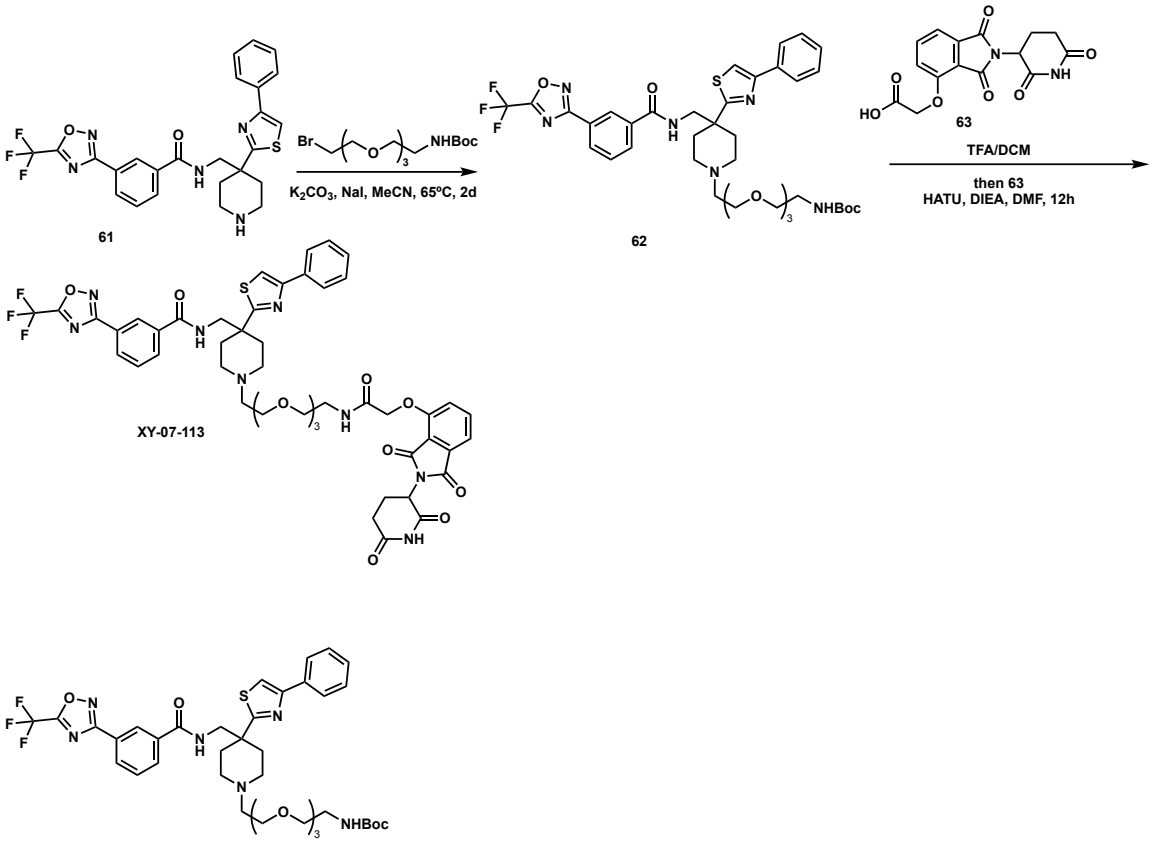
The crude residue from last step (25 mg, 0.067 mmol, 1.0 eq.) was dissolved in dichloromethane (1 mL), and **61** (34 mg, 1.0 eq., crude from deprotection step) was added at room temperature, followed by $NaBH(OAc)_3$ (21 mg, 1.5 eq.). The reaction mixture was stirred at room temperature for 18 h. When the limiting starting material was consumed, the reaction was quench with aqueous $NaHCO_3$, extract three times with dichloromethane. The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified using ISCO (dichloromethane/methanol, 0%-10%), followed by HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **XY-07-106** as a yellow powder (5.9 mg, 10% yield over 3 steps). **UPLC-MS** RT: 1.59 min (Method A), Mass m/z: 869.42 $[M+H]^+$. Purity is > 95% by UPLC. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.08 (s, 1H), 8.72 (t, *J* = 6.4 Hz, 1H), 8.43 (t, *J* = 1.8 Hz, 1H), 8.18 (dt, *J* = 7.8, 1.5 Hz, 1H), 8.07 – 8.02 (m, 2H), 7.92 (d, *J* = 7.0 Hz, 2H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.56 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.07 (d, *J* = 8.6 Hz, 1H), 7.00 (d, *J* = 7.0 Hz, 1H), 6.51 (t, *J* = 6.0 Hz, 1H), 5.04 (dd, *J* = 12.8, 5.5 Hz, 1H), 3.53 (d, *J* = 6.3 Hz, 2H), 3.26 (q, *J* = 6.8 Hz, 2H), 2.87 (ddd, *J* = 16.8, 13.7, 5.4 Hz, 1H), 2.75 (br s, 2H), 2.61 – 2.45 (m, 2H), 2.31 (s, 1H), 2.28 (s, 1H), 2.19 (br s, 2H), 2.12 – 1.89 (m, 5H), 1.55 (p, *J* = 7.1 Hz, 2H), 1.45 – 1.35 (m, 2H), 1.35 – 1.22 (m, 4H).**^{13}C NMR** (126 MHz, DMSO) δ 172.81, 170.09, 168.94, 168.10, 167.30, 165.64, 165.32, 164.97, 153.71, 146.43, 136.27, 135.77, 134.38, 132.19, 131.25, 129.84, 129.62 (2C), 128.61 (2C), 127.75, 126.31, 125.97 (2C),

124.55, 117.18, 114.24, 110.36, 108.99, 57.90, 49.71 (3C), 48.53, 44.76, 41.79, 33.65, 33.65, 30.97, 28.61, 26.66, 26.23, 26.18, 22.16.



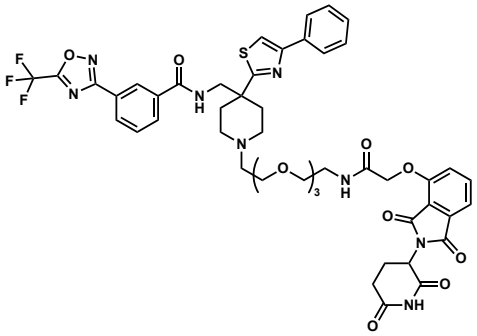
***N*-((1-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy) ethyl)-4-(4-phenylthiazol-2-yl)piperidin-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide (XY-07-107)** was synthesized from compound **61** and **L8** using similar procedures, and was obtained as a yellow powder. **UPLC-MS** RT: 1.44 min (Method A), Mass m/z: 900.72 $[M+H]^+$. Purity is > 95% by UPLC. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.09 (s, 1H), 8.79 (s, 1H), 8.44 (s, 1H), 8.18 (d, *J* = 7.7 Hz, 1H), 8.11 – 8.02 (m, 2H), 7.92 (d, *J* = 7.7 Hz, 2H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 1H), 7.02 (d, *J* = 7.0 Hz, 1H), 6.57 (t, *J* = 5.9 Hz, 1H), 5.04 (dd, *J* = 12.7, 5.4 Hz, 1H), 3.64 – 3.48 (m, 12H), 3.44 (q, *J* = 5.6 Hz, 2H), 2.86 (ddd, *J* = 16.7, 13.7, 5.4 Hz, 1H), 2.66 – 2.43 (m, 2H), 2.35 (s, 2H), 2.22 – 1.94 (m, 3H). Four protons (on piperidine) were not observed.

General procedure for degraders based on TMP scaffold and thalidomide – II



tert-butyl (2-(2-(2-(2-(4-(4-phenylthiazol-2-yl)-4-((3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamido)methyl)piperidin-1-yl)ethoxy)ethoxy)ethoxy)ethyl) carbamate, 62

To a solution of compound **61** (25 mg, 0.049 mmol, 1.0 eq. crude from deprotection step) and *tert*-butyl (2-(2-(2-(2-bromoethoxy)ethoxy)ethoxy)ethyl)carbamate (33 mg, 1.9 eq.) in acetonitrile (0.5 mL) were added K_2CO_3 (17 mg, 2.5 eq.) and NaI (0.73 mg, 0.1 eq.) in one portion. The reaction mixture was heated to 65 °C and stirred for 2 days. When the limiting starting material was consumed, the mixture was filtered through a pad of Celite®, concentrate *in vacuo*, and the residue was purified using ISCO (dichloromethane/methanol, 0%-10%) to yield the title compound **62**. **UPLC-MS** RT: 1.30 min (Method A), Mass m/z: 788.81 $[M+H]^+$.

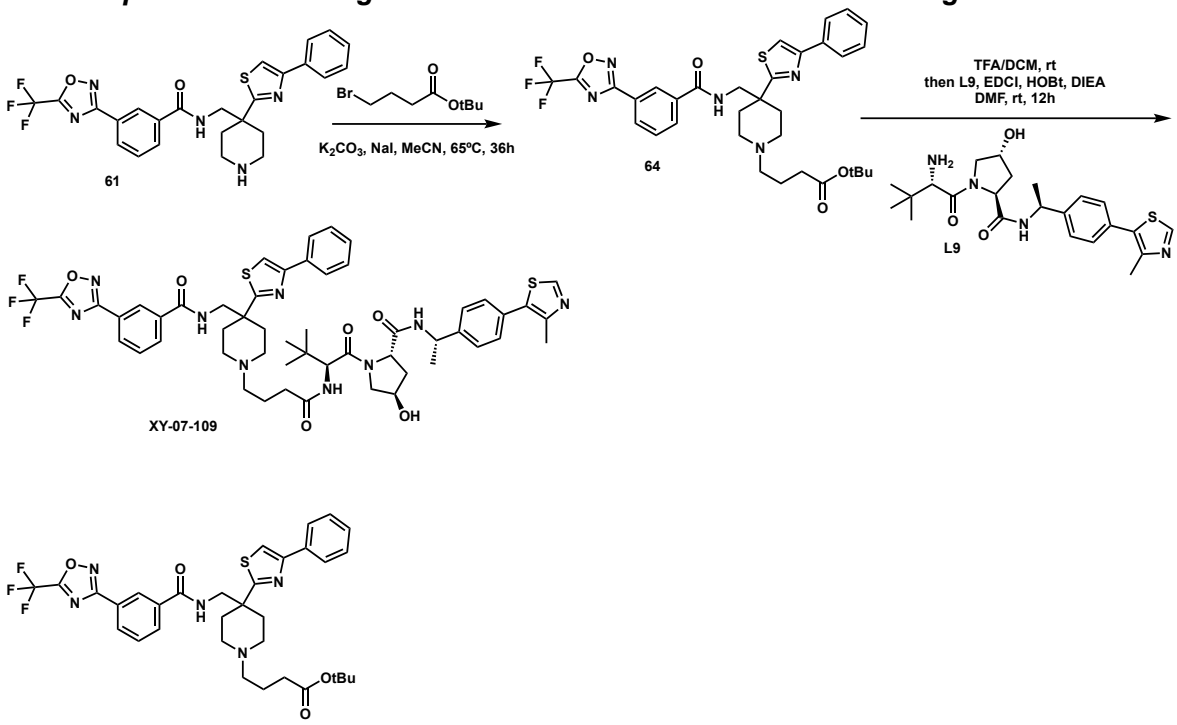


***N*-((1-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)-2-oxo-5,8,11-trioxa-3-azatridecan-13-yl)-4-(4-phenylthiazol-2-yl)piperidin-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide (XY-07-113)**

Compound **62** (38 mg, 0.049 mmol, 1.0 eq.) was treated with a mixture of TFA/dichloromethane (1:5) at room temperature. The reaction was stirred for 2 h and monitored by UPLC-MS. When the starting material was consumed, solvent was removed *in vacuo*, and the residue was used in the next step without further purification. **UPLC-MS** RT: 1.16 min (Method A), Mass m/z: 688.80 $[M+H]^+$.

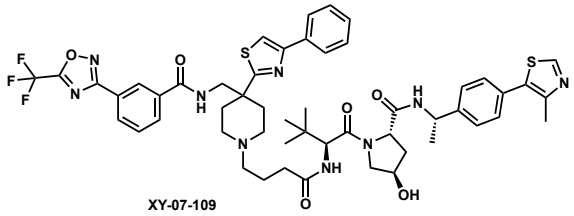
The crude residue from last step (1.0 eq.) and 2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetic acid **63** (6.5 mg, 0.6 eq.) were dissolved in DMF (1 mL). The mixture was treated with HATU (14.6 mg, 1.2 eq.) and DIEA (14 μL, 2.5 eq.), and the reaction mixture was stirred at room temperature for 12 h. The reaction was monitored by UPLC-MS, once the reaction was complete, the mixture was quenched with H_2O, extract three times with ethyl acetate. The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **XY-07-113** as a white powder (3.3 mg, 6.8% yield over 3 steps). **UPLC-MS** RT: 1.33 min (Method A), Mass m/z: 1002.73 $[M+H]^+$. Purity is > 95% by UPLC.

General procedure for degraders based on TMP scaffold and VHL ligand



***tert*-butyl 4-(4-(4-phenylthiazol-2-yl)-4-((3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl) benzamido)methyl)piperidin-1-yl)butanoate, 64**

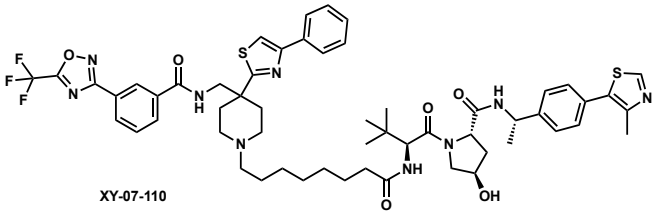
To a solution of compound **61** (25 mg, 0.049 mmol, 1.0 eq. crude from deprotection step) and *tert*-butyl 4-bromobutanoate (16 mg, 1.5 eq.) in acetonitrile (1 mL) were added K_2CO_3 (17 mg, 2.5 eq.) and NaI (0.73 mg, 0.1 eq.) in one portion. The reaction mixture was heated to 65 °C and stirred for 36 h. When the starting material was consumed, the mixture was filtered through a pad of Celite®, concentrate *in vacuo*, and the residue was purified using ISCO (dichloromethane/methanol, 0%-10%) to yield the title compound **64** (30 mg, 94% yield over 2 steps). **UPLC-MS** RT: 1.37 min (Method A), Mass m/z: 655.80 $[M+H]^+$.



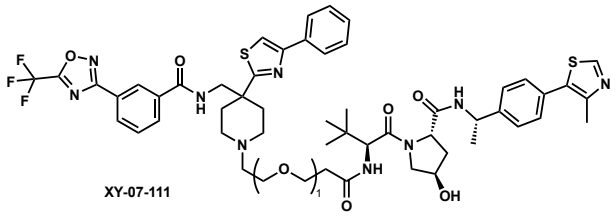
(2*S*,4*R*)-1-((*S*)-3,3-dimethyl-2-(4-(4-(4-phenylthiazol-2-yl)-4-((3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamido)methyl)piperidin-1-yl)butanamido)butanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (XY-07-109)

Compound **64** (30 mg, 0.046 mmol, 1.0 eq.) was treated with a mixture of TFA/dichloromethane (1:5) at room temperature. The reaction was stirred for 3 h. When the starting material was consumed, solvent was removed *in vacuo*, and the residue was used without further purification. **UPLC-MS** RT: 1.34 min (Method A), Mass m/z: 599.79 $[M+H]^+$.

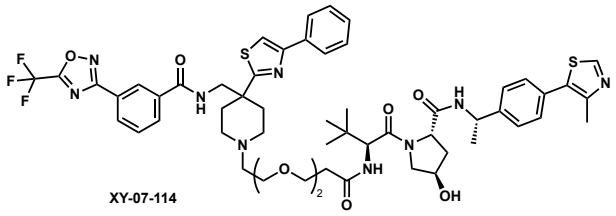
The crude residue from last step (1.0 eq.) and **L9** (2.0 mg, 0.041 mmol, 0.9 eq.) were dissolved in DMF (0.5 mL). The mixture was treated with EDCI (9.7 mg, 1.1 eq.), HOBt (6.8 mg, 0.051 mmol, 1.1 eq.) and DIEA (28 μL, 2.0 eq.), and the reaction mixture was stirred at room temperature for 12 h. The reaction was monitored by UPLC-MS, once the reaction was complete, the mixture was quenched with H_2O, extract three times with ethyl acetate. The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **XY-07-109** as a white powder (13.5 mg, 32 % yield over 2 steps). **UPLC-MS** RT: 1.60 min (Method A), Mass m/z: 1025.64 $[M+H]^+$. Purity is > 95% by UPLC. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.77 (br s, 1H), 8.44 (s, 1H), 8.36 (d, *J* = 7.8 Hz, 1H), 8.19 (dd, *J* = 7.7, 1.6 Hz, 1H), 8.11 – 8.02 (m, 2H), 7.93 (d, *J* = 6.8 Hz, 2H), 7.82 (br s, 1H), 7.69 (t, *J* = 7.9 Hz, 1H), 7.45 – 7.34 (m, 6H), 7.30 (t, *J* = 7.3 Hz, 1H), 5.09 (d, *J* = 3.5 Hz, 1H), 4.91 (p, *J* = 7.1 Hz, 1H), 4.49 (d, *J* = 9.3 Hz, 1H), 4.41 (t, *J* = 8.0 Hz, 1H), 4.27 (s, 1H), 3.66 – 3.47 (m, 4H), 3.01 – 2.57 (m, 2H), 2.45 (s, 3H), 2.42 – 1.92 (m, 11H), 1.78 (ddd, *J* = 12.9, 8.5, 4.7 Hz, 1H), 1.74 – 1.57 (m, 2H), 1.37 (d, *J* = 7.0 Hz, 3H), 0.92 (s, 9H). **^{13}C NMR** (126 MHz, DMSO) δ 171.81, 170.60, 169.51, 168.09, 165.73, 165.33, 164.99, 153.77, 151.49, 147.76, 144.64, 135.67, 134.33, 131.29, 131.11, 129.91, 129.70, 129.65, 129.50, 128.82 (2C), 128.63 (2C), 127.82, 126.38 (2C), 126.32, 126.00 (2C), 124.59, 114.67, 68.76, 58.55, 57.98, 56.46, 56.25, 49.46, 47.70, 44.76, 37.73, 35.21, 26.44 (3C), 22.41, 15.98. Four CH_2 carbons of the piperidine ring, and three CH_2 carbons of the propyl linker are not observed in ^{13}C NMR.



(2*S*,4*R*)-1-((*S*)-3,3-dimethyl-2-(8-(4-(4-phenylthiazol-2-yl)-4-((3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamido)methyl)piperidin-1-yl)octanamido)butanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (XY-07-110) was synthesized from compound **61** and *tert*-butyl 8-bromooctanoate using similar procedures, and was obtained as a white powder. **UPLC-MS** RT: 1.52 min (Method A), Mass m/z: 1081.75 $[M+H]^+$. Purity is > 95% by UPLC. **^{1}H NMR** (500 MHz, Methanol-d_4) δ 8.87 (s, 1H), 8.48 (t, *J* = 1.6 Hz, 1H), 8.25 (dt, *J* = 7.8, 1.5 Hz, 1H), 8.00 – 7.97 (m, 1H), 7.94 – 7.88 (m, 2H), 7.86 (s, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.46 – 7.38 (m, 4H), 7.38 – 7.31 (m, 2H), 7.31 – 7.24 (m, 1H), 5.00 (q, *J* = 7.0 Hz, 1H), 4.64 – 4.52 (m, 2H), 4.42 (s, 1H), 3.86 (d, *J* = 11.1 Hz, 1H), 3.78 – 3.70 (m, 3H), 2.84 (s, 4H), 2.66 (s, 2H), 2.47 (s, 3H), 2.31 – 2.17 (m, 3H), 1.95 (ddd, *J* = 13.4, 9.1, 4.5 Hz, 1H), 1.69 – 1.53 (m, 4H), 1.50 (d, *J* = 7.0 Hz, 3H), 1.41 – 1.25 (m, 6H), 1.02 (s, 9H). Four protons (on piperidine) were not observed.

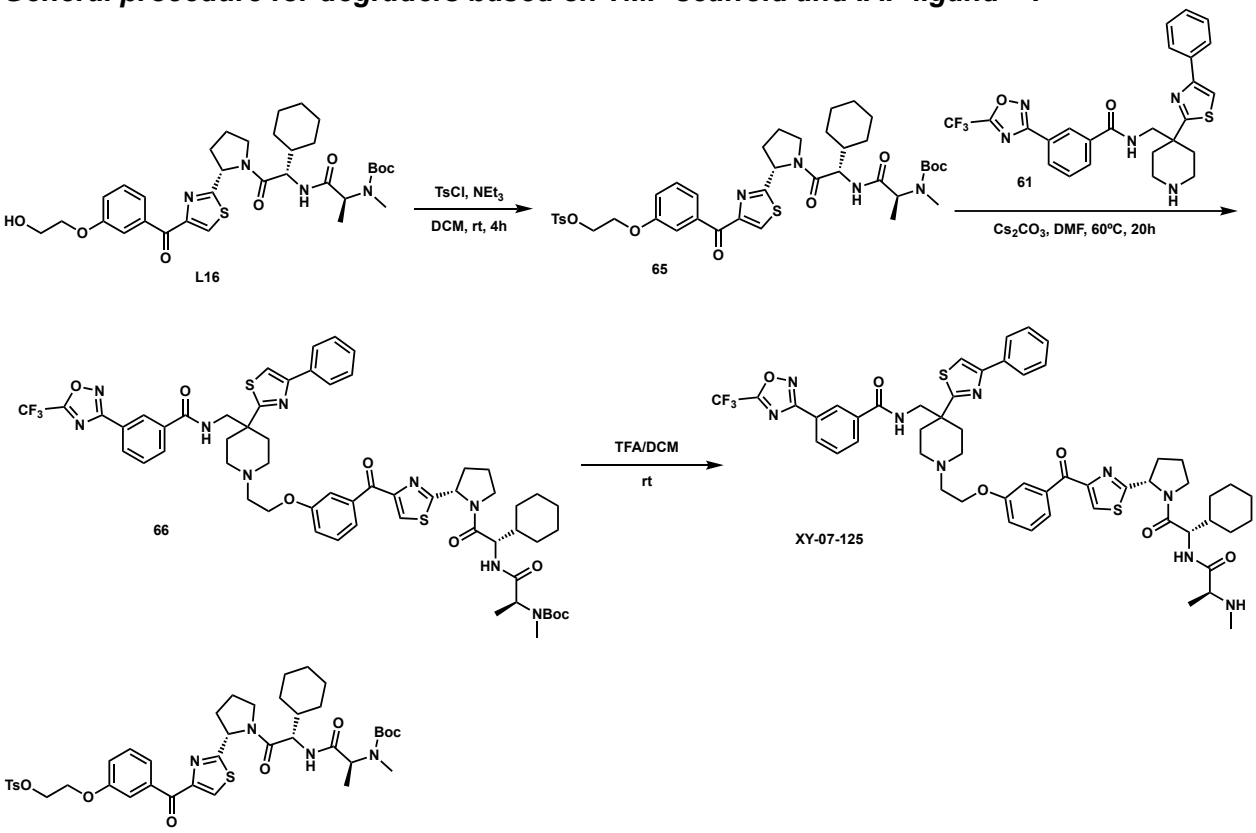


(2*S*,4*R*)-1-((*S*)-3,3-dimethyl-2-(3-(2-(4-(4-phenylthiazol-2-yl)-4-((3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamido)methyl)piperidin-1-yl)ethoxy)propanamido)butanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (XY-07-111) was synthesized from compound **61** and *tert*-butyl 3-(2-bromoethoxy)propanoate using similar procedures, and was obtained as a white powder. **UPLC-MS** RT: 1.56 min (Method A), Mass m/z: 1055.74 $[M+H]^+$. Purity is > 95% by UPLC.



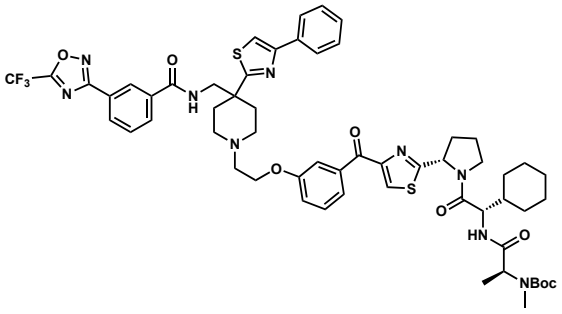
(2*S*,4*R*)-1-((*S*)-3,3-dimethyl-2-(3-(2-(2-(4-(4-phenylthiazol-2-yl)-4-((3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamido)methyl)piperidin-1-yl)ethoxy)ethoxy)propanamido)butanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (XY-07-114) was synthesized from compound **61** and *tert*-butyl 3-(2-(2-bromoethoxy)ethoxy)propanoate using similar procedures, and was obtained as a white powder. **UPLC-MS** RT: 1.37 min (Method A), Mass m/z: 1099.65 $[M+H]^+$. Purity is > 95% by UPLC.

General procedure for degraders based on TMP scaffold and IAP ligand – I



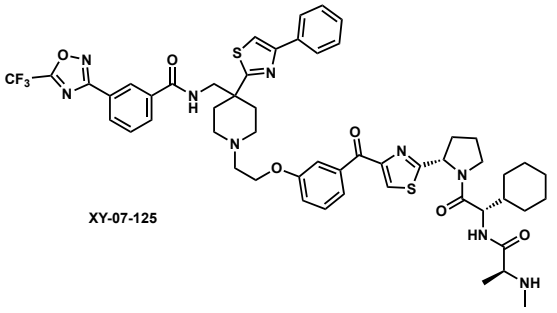
2-(3-(2-((*S*)-1-((*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)(methyl)amino)propanamido)-2-cyclohexylacetyl)pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)ethyl-4-methylbenzenesulfonate, 65

To a solution of compound **L16** (54 mg, 1.0 eq.) in dichloromethane (1 mL) were added TsCl (32 μL, 2.0 eq.) and NEt_3 (35 μL, 3.0 eq.) at 0ºC. The reaction was warmed up to room temperature and stirred for 4 h and monitored by UPLC-MS. Once the starting material was consumed, the reaction was quenched with H_2O and extracted three times with dichloromethane, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified using ISCO (dichloromethane/methanol, 0%-10%) to yield the title compound **65**. **UPLC-MS** RT: 1.77 min (Method A), Mass m/z: 796.81 $[M+H]^+$.



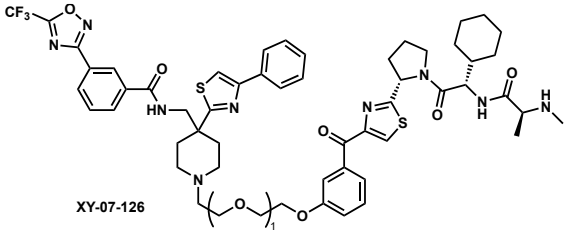
***tert*-butyl ((*S*)-1-(((*S*)-1-cyclohexyl-2-oxo-2-((*S*)-2-(4-(3-(2-(4-(4-phenylthiazol-2-yl)-4-((3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamido)methyl)piperidin-1-yl)ethoxy)benzoyl) thiazol-2-yl)pyrrolidin-1-yl)ethyl)amino)-1-oxopropan-2-yl)(methyl)carbamate, 66**

To a solution of compound **61** (77 mg, 0.15 mmol, 1.5 eq.) and compound **65** (1.0 eq., from last step) in DMF (1 mL) was added Cs_2CO_3 (41 mg, 1.5 eq.) in one portion. The reaction mixture was heated to 60 °C and stirred for 20 h. When the starting material was consumed, the mixture was filtered through a pad of Celite®, concentrate *in vacuo*, and the residue was purified using ISCO (dichloromethane/methanol, 0%-10%) to yield the title compound **66** (56 mg, 49% yield over 3 steps). **UPLC-MS** RT: 1.37 min (Method A), Mass m/z: 1137.56 $[M+H]^+$.



***N*-((1-(2-(3-(2-((*S*)-1-((*S*)-2-cyclohexyl-2-((*S*)-2-(methylamino)propanamido)acetyl) pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)ethyl)-4-(4-phenylthiazol-2-yl)piperidin-4-yl) methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide (XY-07-125)**

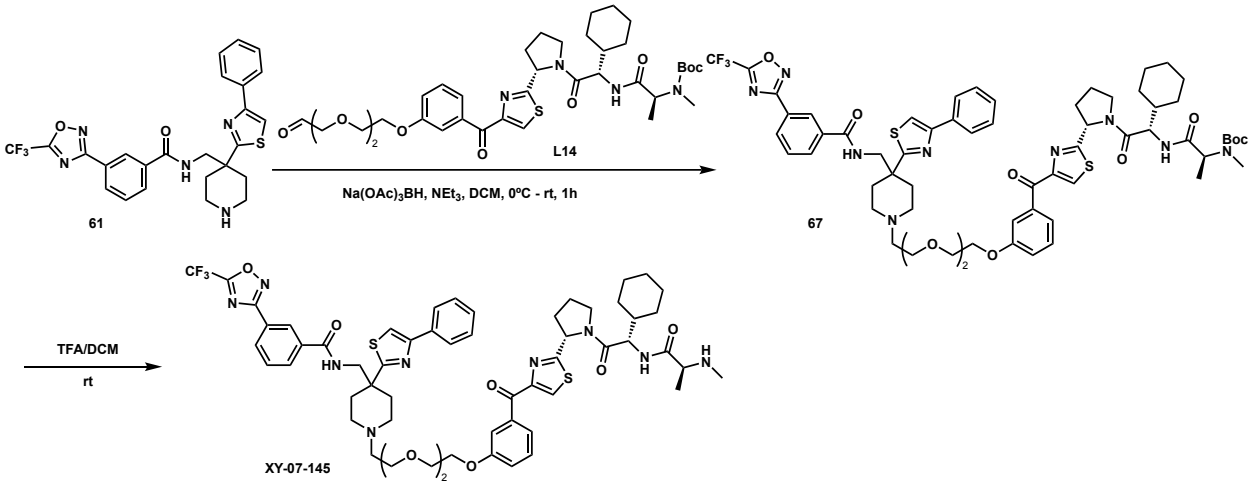
Compound **66** (28 mg, 0.025 mmol, 1.0 eq.) was treated with a mixture of TFA/dichloromethane (1:5) at room temperature. The reaction was monitored by UPLC-MS. When the starting material was consumed, solvent was removed *in vacuo*, and the residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **XY-07-125** as a white powder (9.2 mg, 36 % yield). **UPLC-MS** RT: 1.62 min (Method A), Mass m/z: 1037.74 $[M+H]^+$. Purity is > 95% by UPLC. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 9.97 – 9.73 (m, 1H, tertiary NH^+), 8.97 (t, *J* = 6.6 Hz, 1H), 8.97 – 8.76 (m, 1H), 8.72 (d, *J* = 8.1 Hz, 1H), 8.53 – 8.46 (m, 2H), 8.22 (d, *J* = 7.7 Hz, 1H), 8.18 (s, 1H), 8.13 – 8.07 (m, 1H), 7.95 (d, *J* = 7.2 Hz, 2H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.72 (t, *J* = 7.8 Hz, 1H), 7.60 (s, 1H), 7.47 (t, *J* = 7.9 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.26 (dd, *J* = 8.1, 2.6 Hz, 1H), 5.38 (dd, *J* = 7.7, 3.4 Hz, 1H), 4.48 (t, *J* = 7.6 Hz, 1H), 4.38 (s, 2H), 3.88 (q, *J* = 6.4 Hz, 1H), 3.84 – 3.73 (m, 2H), 3.72 – 3.62 (m, 2H), 3.57 – 3.48 (m, 4H), 3.12 – 2.98 (m, 2H), 2.56 (d, *J* = 14.3 Hz, 2H), 2.53 – 2.48 (m, 3H), 2.38 – 2.26 (m, 2H), 2.25 – 2.14 (m, 2H), 2.11 – 1.96 (m, 2H), 1.78 – 1.50 (m, 5H), 1.33 (d, *J* = 6.9 Hz, 3H), 1.20 – 0.94 (m, 6H).

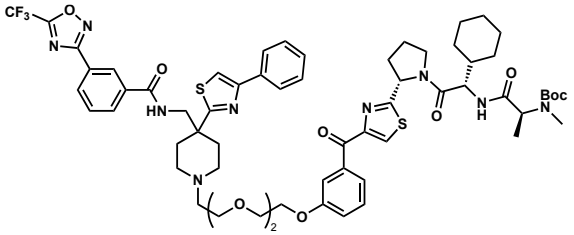


***N*-((1-(2-(2-(3-(2-((*S*)-1-((*S*)-2-cyclohexyl-2-((*S*)-2-(methylamino)propanamido)acetyl) pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)ethoxy)ethyl)-4-(4-phenylthiazol-2-yl) piperidin-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide (XY-07-126)** was synthesized from compound **61** and **L13** using similar procedures, and was obtained as a white powder. **UPLC-MS** RT: 1.20 min (Method A), Mass m/z: 1082.11 $[M+H]^+$. Purity is > 95%

by UPLC. **^{1}H NMR** (500 MHz, Methanol-d_4) δ 8.47 (s, 1H), 8.24 (d, *J* = 7.6 Hz, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.89 (d, *J* = 7.4 Hz, 2H), 7.86 (s, 1H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.66 – 7.58 (m, 2H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.26 (t, *J* = 7.3 Hz, 1H), 7.21 (dd, *J* = 8.1, 2.6 Hz, 1H), 5.69 – 5.38 (m, 1H), 4.57 (d, *J* = 7.1 Hz, 1H), 4.36 – 4.14 (m, 2H), 3.98 (q, *J* = 8.7, 8.0 Hz, 2H), 3.94 – 3.83 (m, 6H), 3.75 – 3.65 (m, 4H), 3.36 – 3.29 (m, 2H), 3.12 (t, *J* = 13.0 Hz, 2H), 2.76 (d, *J* = 14.9 Hz, 2H), 2.69 – 2.64 (m, 3H), 2.42 – 2.06 (m, 6H), 1.85 – 1.56 (m, 5H), 1.49 (d, *J* = 7.0 Hz, 2H), 1.34 – 1.02 (m, 6H). **^{13}C NMR** (126 MHz, MeOD) δ 188.20, 174.31, 172.52, 172.24, 170.22, 169.97, 169.52, 162.55 (d, *J* = 31.5 Hz), 160.15, 156.80, 154.58, 139.90, 136.76, 135.62, 132.16, 131.58, 130.70, 130.64, 130.39, 129.68, 129.68, 129.17, 127.74, 127.39, 127.39, 126.78, 124.68, 120.88, 116.35, 115.55, 70.86, 68.65, 65.75, 60.29, 58.21, 57.56, 57.34, 51.70, 51.11, 51.11, 49.34, 45.38, 41.15, 33.09, 32.50, 31.82, 30.82, 29.62, 27.10, 27.00, 26.90, 25.56, 25.56, 16.31. One carbon (CF_3) was not observed.

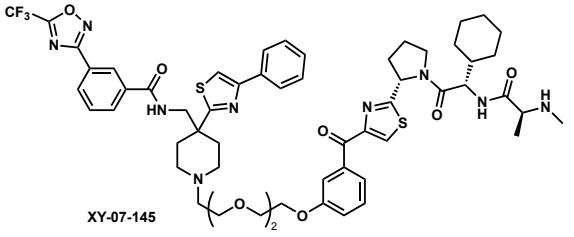
General procedure for degraders based on TMP scaffold and IAP ligand – II





***tert*-butyl ((*S*)-1-(((*S*)-1-cyclohexyl-2-oxo-2-((*S*)-2-(4-(3-(2-(2-(2-(4-(4-phenylthiazol-2-yl)-4-((3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamido)methyl)piperidin-1-yl)ethoxy) ethoxy)ethoxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)ethyl)amino)-1-oxopropan-2-yl)(methyl) carbamate, 67**

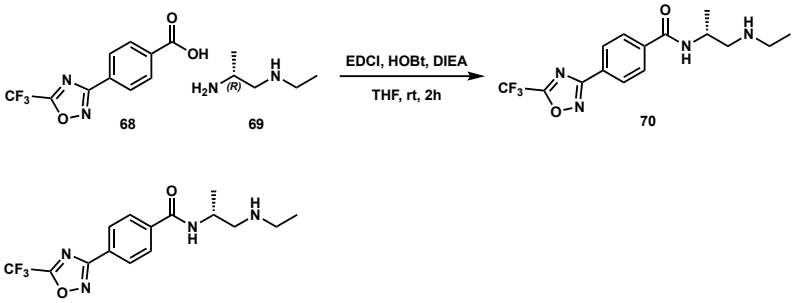
Compound **61** (23 mg, 0.033 mmol, 1.0 eq., crude from the deprotection step) was dissolved in dichloromethane (1 mL), and **L14** (12 mg, 0.7 eq., crude from deprotection step of 25 mg corresponding acetal) and NEt_3 (4.6 μL, 2.0 eq.) were added at room temperature, followed by $NaBH(OAc)_3$ (8.4 mg, 1.2 eq.). The reaction mixture was stirred at room temperature for 1 h and monitored by UPLC-MS. When the starting material was consumed, the reaction was quench with aqueous $NaHCO_3$ and extract three times with dichloromethane. The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified using ISCO (dichloromethane/methanol, 0%-10%), followed by HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **67**. **UPLC-MS** RT: 2.16 min (Method A), Mass m/z: 1227.50 $[M+H]^+$.



***N*-((1-(2-(2-(2-(3-(2-((*S*)-1-((*S*)-2-cyclohexyl-2-((*S*)-2-(methylamino)propanamido)acetyl) pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)ethoxy)ethoxy)ethyl)-4-(4-phenylthiazol-2-yl)piperidin-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide (XY-07-145)**

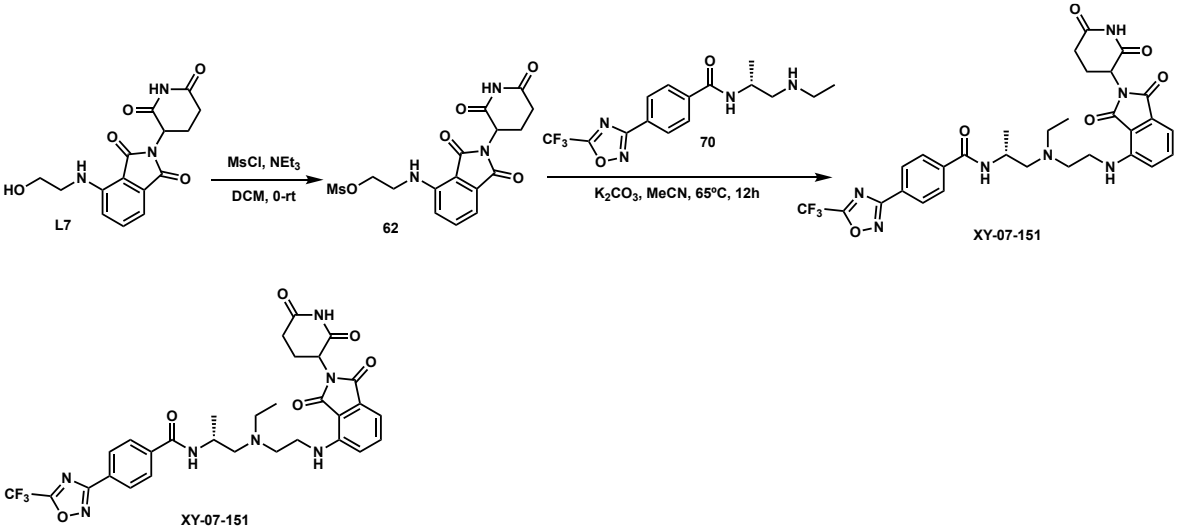
Compound **67** (1.0 eq. from last step) was treated with a mixture of TFA/dichloromethane (1:5) at room temperature for 2h. The reaction was monitored by UPLC-MS. When the starting material was consumed, solvent was removed *in vacuo*, and the residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **XY-07-145** as a white powder (10.1 mg, 29 % yield over 3 steps). **UPLC-MS** RT: 1.49 min (Method A), Mass m/z: 1125.56 $[M+H]^+$. Purity is > 95% by UPLC. **^{1}H NMR** (500 MHz, Methanol-d_4) δ 8.53 (d, *J* = 7.7 Hz, 1H), 8.46 (d, *J* = 1.8 Hz, 1H), 8.28 (s, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 7.0 Hz, 2H), 7.86 (s, 1H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.65 (s, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.30 – 7.20 (m, 2H), 5.71 – 5.36 (m, 1H), 4.62 – 4.17 (m, 1H), 4.23 – 4.17 (m, 2H), 4.04 – 3.47 (m, 15H), 3.35 (s, 3H), 3.26 (t, *J* = 5.0 Hz, 2H), 3.08 (t, *J* = 13.1 Hz, 2H), 2.75 (d, *J* = 14.9 Hz, 2H), 2.48 – 2.05 (m, 6H), 1.83 – 1.56 (m, 5H), 1.48 (d, *J* = 6.9 Hz, 3H), 1.37 – 0.99 (m, 6H).

General procedure for degraders based on NVS-HD1 scaffold and thalidomide – I



(*R*)-*N*-(1-(ethylamino)propan-2-yl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide, 70

A mixture of 4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzoic acid (**68**) (632 mg, 2.45 mmol, 1.0 eq.) and (*R*)-N^1-ethylpropane-1,2-diamine (**69**) (250 mg, 1.0 eq.) in THF (9.8 mL) was treated with EDCI (706 mg, 1.5 eq.), HOBt (430 mg, 1.3 eq.) and DIEA (1.278 mL, 3.0 eq.) at room temperature. The reaction mixture was stirred for 2h and monitored by UPLC-MS. When the limiting starting material was consumed, the reaction was quench with aqueous $NaHCO_3$, extract three times with ethyl acetate. The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified using ISCO (dichloromethane/methanol, 0%-10%) to yield the title compound **70** as a white powder (440 mg, 52.5% yield). **UPLC-MS** RT: 0.99 min (Method A), Mass m/z: 343.07 $[M+H]^+$.



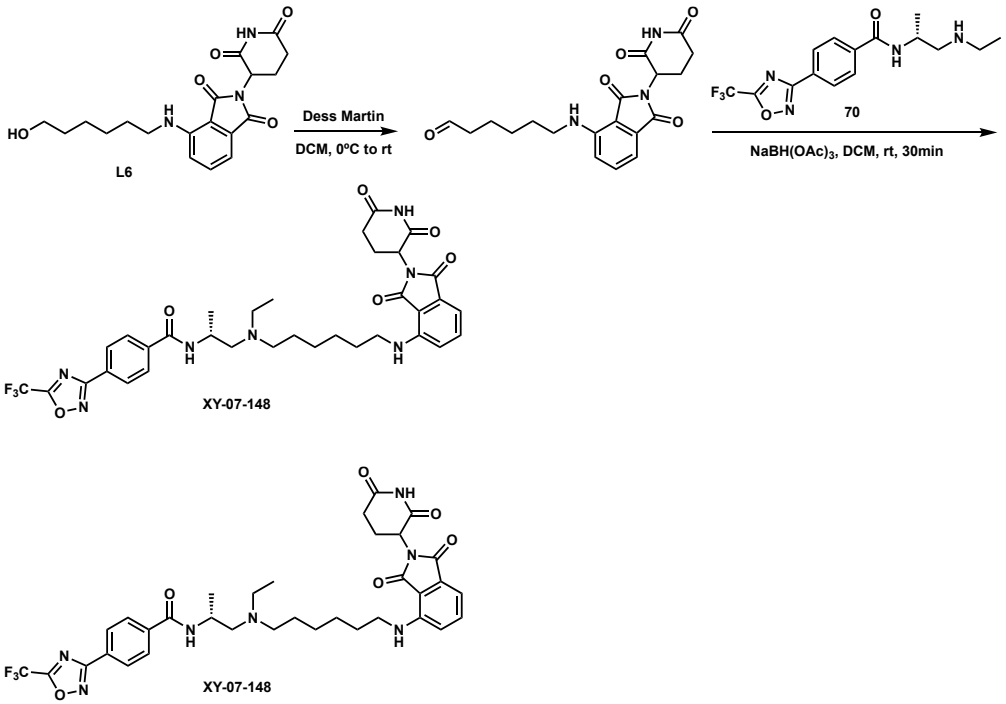
***N*-((2*R*)-1-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)(ethyl) amino)propan-2-yl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide (XY-07-151)**

To a solution of compound **L7** (25 mg, 0.079 mmol, 1.0 eq.) in dichloromethane (1 mL) were added MsCl (36.8 μL, 6.0 eq.) and NEt_3 (79 μL, 7.2 eq.) at 0ºC. The reaction was warmed up to room temperature and stirred for 3 h and monitored by UPLC-MS. Once the starting material was consumed, the reaction was quenched with H_2O and extracted three times with dichloromethane, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to yield compound **62**. The residue was used in the next step without further purification. **UPLC-MS** RT: 0.85 min (Method A), Mass m/z: 395.87 $[M+H]^+$.

To a solution of compound **70** (24 mg, 0.070 mmol, 0.9 eq.) and compound **62** (1.0 eq. crude from last step) in acetonitrile (1 mL) was added K_2CO_3 (22 mg, 2.0 eq.) in one portion. The reaction

mixture was heated to 65 °C and stirred for 12 h. When the starting material was consumed, the mixture was filtered through a pad of Celite®, concentrate *in vacuo*, and the residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **XY-07-151** as a yellow powder (2.7 mg, 5.3% yield over two steps). **UPLC-MS** RT: 1.13 min (Method A), Mass m/z: 641.90 $[M+H]^+$. Purity is > 95% by UPLC.

General procedure for degraders based on NVS-HD1 scaffold and thalidomide – II

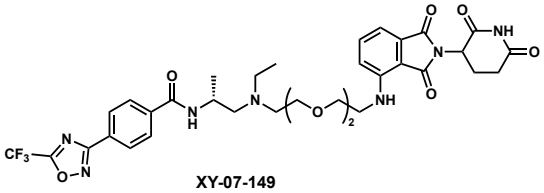


***N*-((2*R*)-1-((6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexyl)(ethyl) amino)propan-2-yl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide (XY-07-148)**

A solution of 2-(2,6-dioxopiperidin-3-yl)-4-((6-hydroxyhexyl)amino)isoindoline-1,3-dione (**L6**) (25 mg, 0.067 mmol, 1.0 eq.) in dichloromethane (1 mL) was treated with Dess-Martin periodinane (30 mg, 1.05 eq.) at 0 °C. The reaction mixture was warmed gradually to room temperature and stirred for 4 h. When the starting material was consumed, the reaction mixture was quenched with aqueous $NaHCO_3$, extract three times with ethyl acetate. The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was used in the next step without further purification. **UPLC-MS** RT: 1.09 min (Method A), Mass m/z: 354.17 $[M-H_2O+H]^+$.

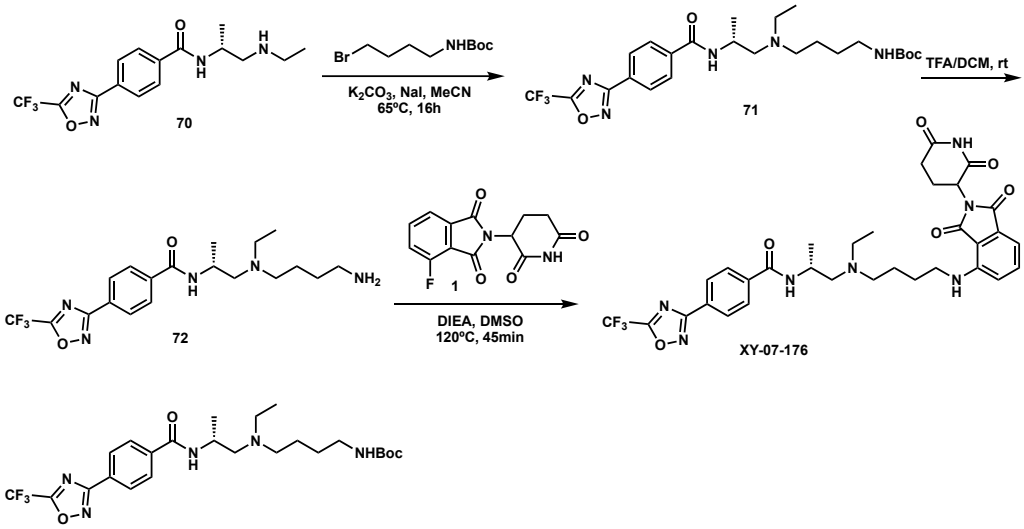
The crude residue from last step (1.0 eq.) was dissolved in dichloromethane (1 mL), and compound **70** (23 mg, 1.0 eq.) was added at room temperature, followed by $NaBH(OAc)_3$ (21 mg, 1.5 eq.). The reaction mixture was stirred at room temperature for 30 min and monitored by UPLC-MS. When the starting material was consumed, the reaction was quench with aqueous $NaHCO_3$ and extract three times with ethyl acetate. The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **XY-07-148** as a yellow

powder (3.1 mg, 7% over two steps). **UPLC-MS** RT: 1.31 min (Method A), Mass m/z: 698.50 $[M+H]^+$. Purity is > 95% by UPLC.



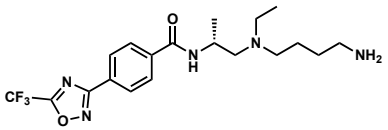
XY-07-149

***N*-((2*R*)-1-((2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy) ethoxy)ethyl)(ethyl)amino)propan-2-yl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl) benzamide (XY-07-149)** was synthesized from compound **70** and linker **L8** using similar procedures, and was obtained as a yellow powder. **UPLC-MS** RT: 1.29 min (Method A), Mass m/z: 730.41 $[M+H]^+$. Purity is > 95% by UPLC.



***tert*-butyl (*R*)-(4-(ethyl(2-(4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamido)propyl) amino)butyl)carbamate, 71**

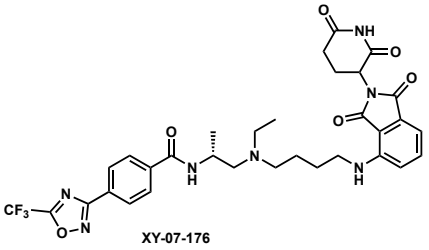
To a solution of **70** (50 mg, 0.5 mmol, 1.0 eq.) and *tert*-butyl (4-bromobutyl)carbamate (75 mg, 2.0 eq.) in acetonitrile (1 mL) were added K_2CO_3 (60 mg, 2.0 eq.) and NaI (2 mg, 0.1 eq.) in one portion. The reaction mixture was heated to 65 °C and stirred for 16 h. When the starting material was consumed, the mixture was filtered through a pad of Celite® and concentrate *in vacuo*. The residue was purified using ISCO (dichloromethane/methanol, 0%-10%) to yield the title compound **71** (75 mg, quant. yield). **UPLC-MS** RT: 1.19 min (Method A), Mass m/z: 513.78 $[M+H]^+$.



(*R*)-*N*-(1-((4-aminobutyl)(ethyl)amino)propan-2-yl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide, 72

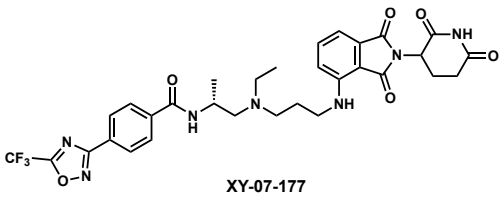
Compound **71** (75 mg, 0.15 mmol, 1.0 eq.) was treated with a mixture of TFA/dichloromethane (1:5), and the reaction was stirred at room temperature for 2 h. When the starting material was

consumed, solvent was removed *in vacuo*, and the residue was used in the next step without further purification. **UPLC-MS** RT: 0.90 min (Method A), Mass m/z: 414.07 $[M+H]^+$.



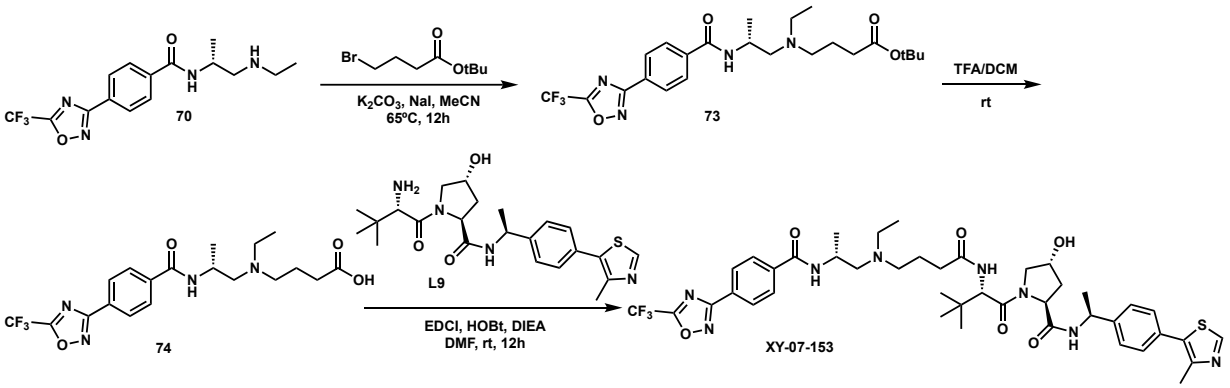
***N*-((2*R*)-1-((4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)(ethyl) amino)propan-2-yl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide (XY-07-176)**

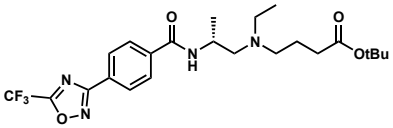
Compound **72** (37.5 mg crude from the deprotection step, 1.0 eq.) and DIEA (32 µL, 2.5 eq.) were dissolved in DMSO (1 mL) in a sealed tube. To the mixture was added compound **1** (30 mg, 1.5 eq.) in one batch, and the reaction was sealed and immediately heated to 120 °C. After 45 min, the reaction mixture was cooled to room temperature, and residual DIEA was removed *in vacuo*. The residual DMSO solution was directly purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **XY-07-176** as a yellow powder (8.7 mg, 14 % yield over 2 steps). **UPLC-MS** RT: 1.19 min (Method A), Mass m/z: 669.80 $[M+H]^+$. Purity is > 95% by UPLC. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.08 (s, 1H), 9.14 (br s, 1H, tertiary NH^+), 8.79 (dd, *J* = 8.5, 3.5 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 2H), 8.11 (d, *J* = 8.5 Hz, 1H), 7.58 (ddd, *J* = 9.0, 7.0, 2.4 Hz, 1H), 7.11 (dd, *J* = 8.6, 6.9 Hz, 1H), 7.03 (dd, *J* = 7.1, 1.9 Hz, 1H), 6.66 – 6.55 (m, 1H), 5.04 (ddd, *J* = 12.8, 5.5, 2.7 Hz, 1H), 4.57 – 4.44 (m, 1H), 3.42 – 3.10 (m, 8H), 2.88 (dddd, *J* = 16.6, 14.1, 5.5, 2.0 Hz, 1H), 2.62 – 2.50 (m, 2H), 2.07 – 1.97 (m, 1H), 1.82 – 1.67 (m, 2H), 1.66 – 1.57 (m, 2H), 1.28 – 1.20 (m, 6H). **^{13}C NMR** (126 MHz, DMSO) δ 172.79, 170.08, 168.89, 167.89, 167.25, 165.40, 165.20 (d, *J* = 33.0 Hz), 146.24, 137.39, 136.28, 132.22, 128.63 (2C), 127.35 (2C), 127.08 (d, *J* = 236.4 Hz), 126.97, 117.23, 110.55, 109.20, 55.41, 52.35, 48.54, 48.42, 41.17, 41.10, 30.96, 25.76, 22.15, 20.53, 18.98, 8.34.



***N*-((2*R*)-1-((3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)(ethyl) amino)propan-2-yl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide (XY-07-177)** was synthesized from compound **70** and *tert*-butyl (3-bromopropyl)carbamate using similar procedures, and was obtained as a yellow powder. **UPLC-MS** RT: 1.19 min (Method A), Mass m/z: 656.50 $[M+H]^+$. Purity is > 95% by UPLC.

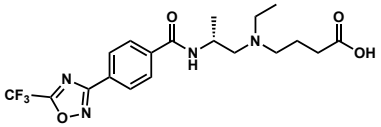
General procedure for degraders based on NVS-HD1 scaffold and VHL ligand





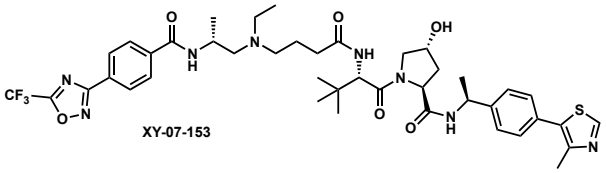
***tert*-butyl (*R*)-4-(ethyl(2-(4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamido)propyl) amino)butanoate, 73**

To a solution of **70** (40 mg, 0.12 mmol, 1.0 eq.) and *tert*-butyl 4-bromobutanoate (21 μL, 1.2 eq.) in acetonitrile (1 mL) were added K_2CO_3 (32 mg, 2.0 eq.) and NaI (1.8 mg, 0.1 eq.) in one portion. The reaction mixture was heated to 65 °C and stirred for 12 h. When the starting material was consumed, the mixture was filtered through a pad of Celite® and concentrate *in vacuo*. The residue was purified using ISCO (dichloromethane/methanol, 0%-10%) to yield the title compound **73**. **UPLC-MS** RT: 1.28 min (Method A), Mass m/z: 484.98 $[M+H]^+$.



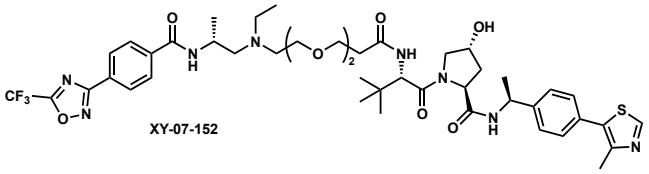
(*R*)-4-(ethyl(2-(4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamido)propyl)amino) butanoic acid, 74

Compound **73** (1.0 eq. from last step) was treated with a mixture of TFA/dichloromethane (1:5), and the reaction was stirred at room temperature for 4 h. When the starting material was consumed, solvent was removed *in vacuo* and the residue was used in the next step without further purification. **UPLC-MS** RT: 1.03 min (Method A), Mass m/z: 428.97 $[M+H]^+$.



(2*S*,4*R*)-1-((*S*)-2-(4-(ethyl((*R*)-2-(4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamido) propyl)amino)butanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (XY-07-153)

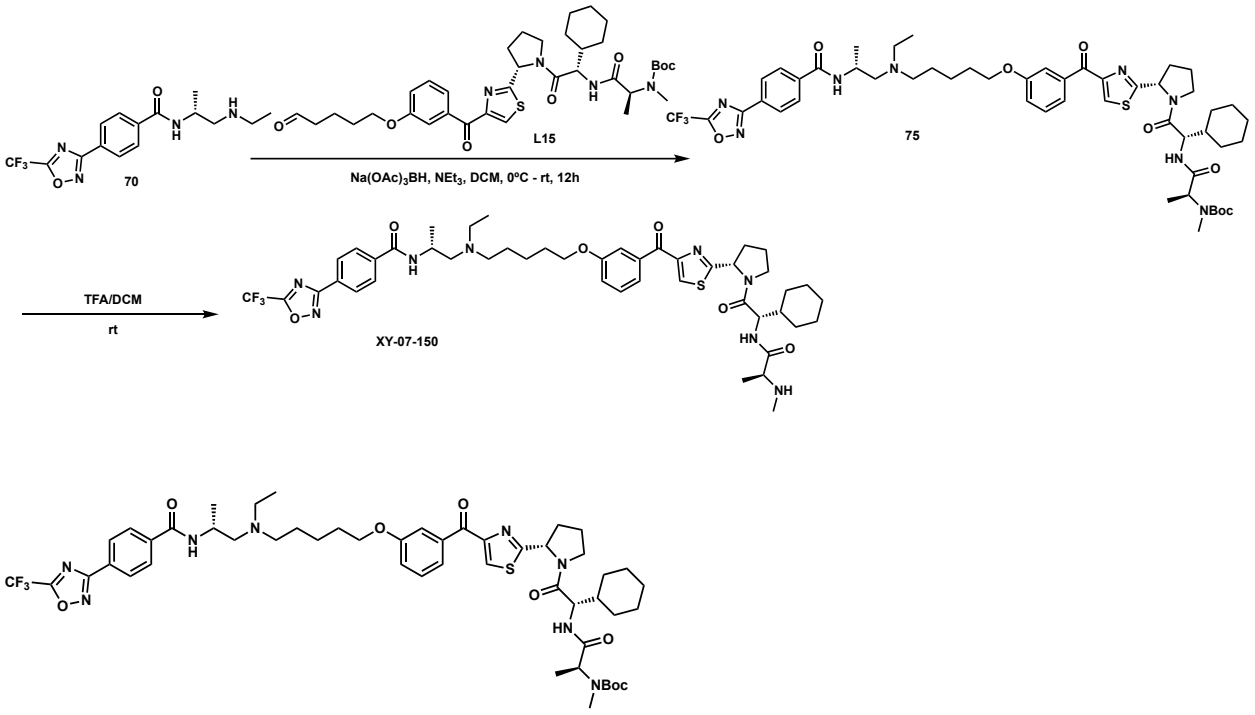
The crude residue from last step (1.0 eq.) and **L9** (28 mg, 0.5 eq.) was dissolved in DMF (1 mL). The mixture was treated with EDCI (13.5 mg, 0.6 eq.), HOBt (9.5 mg, 0.6 eq.) and DIEA (20 μL, 1.0 eq.), and the reaction mixture was stirred at room temperature for 12 h. The reaction was monitored by UPLC-MS, once the reaction was complete, the mixture was quenched with H_2O, extract three times with ethyl acetate. The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **XY-07-153** as a white powder (1.4 mg, 1.4 % yield over 3 steps). **UPLC-MS** RT: 1.33 min (Method A), Mass m/z: 854.82 $[M+H]^+$.



XY-07-152

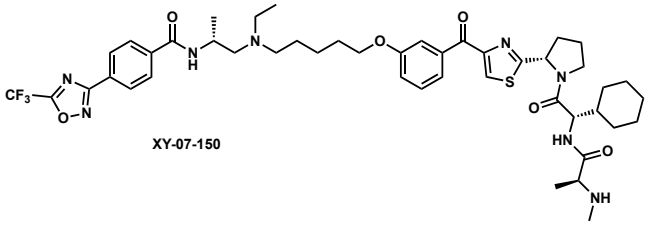
(2*S*,4*R*)-1-((3*R*,16*S*)-16-(*tert*-butyl)-5-ethyl-3-methyl-1,14-dioxo-1-(4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)phenyl)-8,11-dioxa-2,5,15-triazaheptadecan-17-oyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (XY-07-152) was synthesized from compound **70** and *tert*-butyl 3-(2-(2-bromoethoxy)ethoxy)propanoate using similar procedures, and was obtained as a white powder. **UPLC-MS** RT: 1.29 min (Method A), Mass m/z: 928.82 $[M+H]^+$. Purity is > 95% by UPLC. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.73 (dd, *J* = 21.3, 8.4 Hz, 1H), 8.36 (d, *J* = 7.8 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 2H), 8.10 (dd, *J* = 8.4, 2.0 Hz, 2H), 7.87 (dd, *J* = 9.4, 5.7 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 4.91 (p, *J* = 7.1 Hz, 1H), 4.59 – 4.46 (m, 2H), 4.42 (t, *J* = 8.1 Hz, 1H), 4.28 (s, 1H), 3.78 (q, *J* = 6.4, 5.1 Hz, 2H), 3.66 – 3.47 (m, 9H), 3.44 – 3.22 (m, 6H), 2.57 – 2.51 (m, 1H), 2.45 (d, *J* = 2.9 Hz, 5H), 2.40 – 2.31 (m, 1H), 2.06 – 1.97 (m, 1H), 1.79 (ddd, *J* = 13.0, 8.6, 4.6 Hz, 1H), 1.37 (d, *J* = 7.0 Hz, 3H), 1.29 – 1.19 (m, 6H), 0.93 (s, 9H). **^{13}C NMR** (126 MHz, DMSO) δ 170.56, 169.82, 169.40, 167.91, 165.50, 157.96 (d, *J* = 33.6 Hz), 151.50, 147.75, 144.61, 137.43, 131.10, 129.71, 128.83 (2C), 128.65 (2C), 127.09 (d, *J* = 234.3 Hz), 127.40 (2C), 127.06, 126.38 (2C), 126.15, 69.66, 69.22, 68.75, 66.90, 64.11, 58.56, 56.57, 56.32 (2C), 52.25, 49.50, 47.69, 41.21, 37.77, 35.61, 35.38, 26.39 (3C), 22.38, 18.83, 15.97, 8.68.

General procedure for degraders based on NVS-HD1 scaffold and IAP ligand



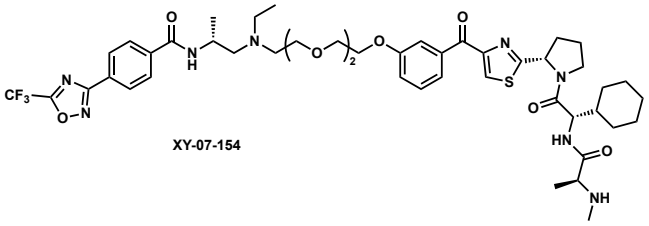
***tert*-butyl ((*S*)-1-(((*S*)-1-cyclohexyl-2-((*S*)-2-(4-(3-((5-(ethyl((*R*)-2-(4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamido)propyl)amino)pentyl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-2-oxoethyl)amino)-1-oxopropan-2-yl)(methyl)carbamate, 75**

Compound **70** (13.2 mg, 0.039 mmol, 0.8 eq.) was dissolved in dichloromethane (0.5 mL), and linker **L15** (33 mg, 1.0 eq., crude from deprotection step of 35 mg corresponding acetal) was added at 0 °C, followed by NEt_3 (13 μL, 2.0 eq.) and $NaBH(OAc)_3$ (10 mg, 1.0 eq.). The reaction mixture was stirred at room temperature for 1 h. When the starting material was consumed, the reaction was quench with aqueous $NaHCO_3$, extract three times with ethyl acetate. The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified using ISCO (dichloromethane/methanol, 0%-10) to yield the title compound **75**. **UPLC-MS** RT: 1.83 min (Method A), Mass m/z: 1009.63 $[M+H]^+$.



***N*-((*R*)-1-((5-(3-(2-((*S*)-1-((*S*)-2-cyclohexyl-2-((*S*)-2-(methylamino)propanamido)acetyl) pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)pentyl)(ethyl)amino)propan-2-yl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide (XY-07-150)**

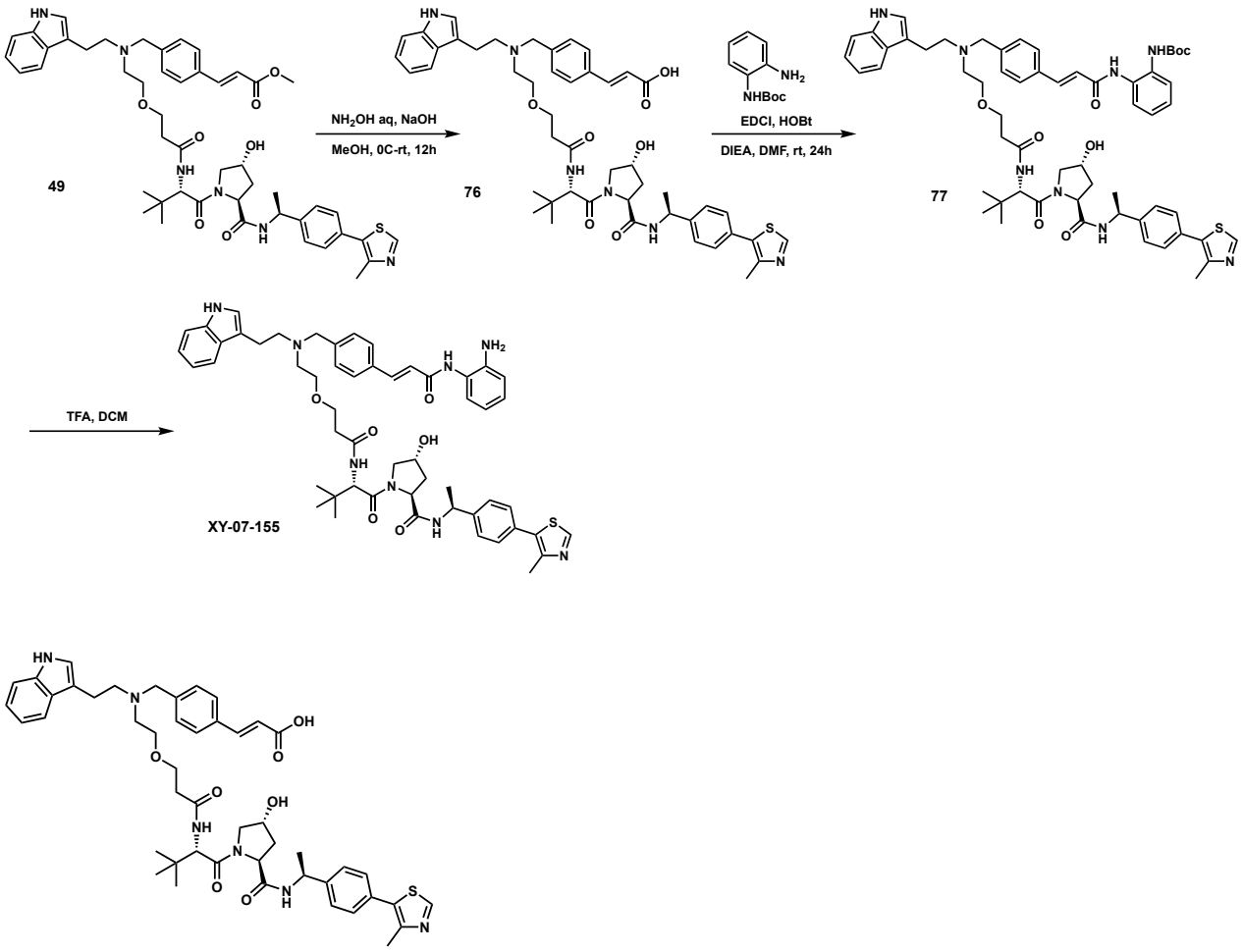
The residue from last step (1.0 eq.) was treated with a mixture of TFA/dichloromethane (1:5) at room temperature for 90 min. The reaction was monitored by UPLC-MS. When the starting material was consumed, solvent was removed *in vacuo*, and the residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **XY-07-150** as a white powder (12.6 mg, 36 % yield over 3 steps). **UPLC-MS** RT: 1.61 min (Method A), Mass m/z: 908.82 $[M+H]^+$. Purity is > 95% by UPLC. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 9.02 (br s, 1H, tertiary NH^+), 8.94 – 8.78 (m, 1H), 8.76 (t, *J* = 7.6 Hz, 1H), 8.72 (d, *J* = 8.1 Hz, 1H), 8.48 (d, *J* = 3.4 Hz, 1H), 8.19 (dd, *J* = 8.4, 2.0 Hz, 2H), 8.10 (dd, *J* = 8.5, 2.5 Hz, 2H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.56 (dt, *J* = 13.8, 2.2 Hz, 1H), 7.45 (td, *J* = 8.0, 4.6 Hz, 1H), 7.26 – 7.18 (m, 1H), 5.44 – 5.32 (m, 1H), 4.60 – 4.40 (m, 2H), 4.04 (dt, *J* = 12.9, 6.3 Hz, 2H), 3.91 – 3.75 (m, 3H), 3.38 – 3.05 (m, 6H), 2.54 – 2.44 (m, 3H), 2.30 – 2.12 (m, 2H), 2.04 (d, *J* = 7.6 Hz, 2H), 1.87 – 1.39 (m, 11H), 1.33 (d, *J* = 6.9 Hz, 3H), 1.30 – 1.18 (m, 6H), 1.18 – 0.93 (m, 6H).



XY-07-154

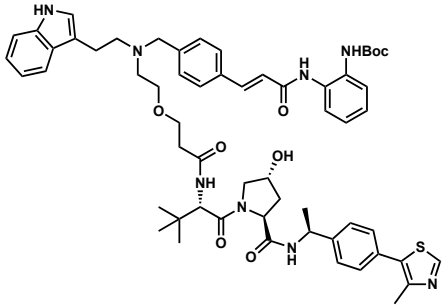
***N*-((2*R*)-1-((2-((1-(3-(2-((*S*)-1-((*S*)-2-cyclohexyl-2-((*S*)-2-(methylamino)propanamido)acetyl) pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)-3-methoxypropan-2-yl)oxy)ethyl)(ethyl) amino)propan-2-yl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide (XY-07-154)** was synthesized from compound **70** and linker **L14** using similar procedures, and was obtained as a white powder. **UPLC-MS** RT: 1.25 min (Method A), Mass m/z: 954.63 $[M+H]^+$. Purity is > 95% by UPLC. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 9.09 (s, 1H, tertiary NH^+), 8.90 (s, 1H), 8.82 (s, 1H), 8.72 (d, *J* = 8.1 Hz, 1H), 8.48 (s, 1H), 8.19 (d, *J* = 8.5 Hz, 2H), 8.09 (dd, *J* = 8.5, 2.9 Hz, 2H), 7.69 (s, 1H), 7.57 (d, *J* = 9.4 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.24 (ddd, *J* = 8.0, 4.9, 2.6 Hz, 1H), 5.39 (dd, *J* = 7.9, 3.3 Hz, 1H), 4.60 – 4.52 (m, 1H), 4.48 (t, *J* = 7.6 Hz, 1H), 4.21 – 4.10 (m, 2H), 3.96 – 3.17 (m, 17H), 2.55 – 2.47 (m, 3H), 2.30 – 2.13 (m, 2H), 2.13 – 1.98 (m, 2H), 1.78 – 1.50 (m, 5H), 1.33 (d, *J* = 6.9 Hz, 3H), 1.27 – 1.19 (m, 6H), 1.19 – 0.96 (m, 6H). **^{13}C NMR** (126 MHz, DMSO) δ 185.88, 172.76, 170.00, 168.68, 167.90, 165.59, 158.23, 152.54, 138.24, 137.43, 129.99, 129.53, 129.00, 128.63 (2C), 127.36 (2C), 122.83, 119.57, 114.92, 69.69 (2C), 69.66, 68.86 (2C), 67.38, 64.10, 58.26, 56.52, 55.84, 55.38, 49.44, 47.22, 41.19, 31.47, 30.76, 29.03, 27.84, 25.63, 25.47, 25.34, 24.16, 18.74, 15.72, 8.66. Two carbons were not observed.

General Procedure for benzamide degraders based on dacinostat and VHL ligand



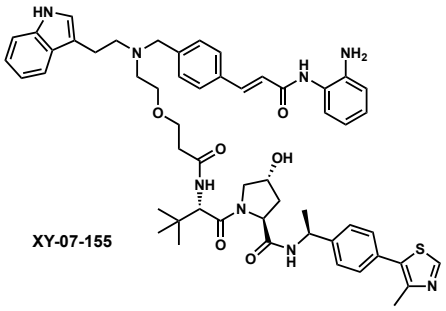
(*E*)-3-(4-(((2-(1*H*-indol-3-yl)ethyl)(2-(3-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-(((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl) amino)-3-oxopropoxy)ethyl)amino)methyl)phenyl)acrylic acid, 76

Compound **76** was obtained as a side product from the reaction of compound **49** to **XY-07-090** (10 mg, 32% yield). **UPLC-MS** RT: 1.04 min (Method A), Mass m/z: 862.72 $[M+H]^+$.



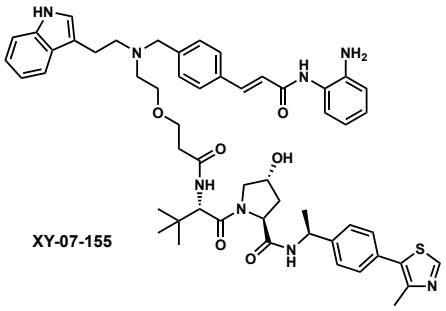
***tert*-butyl (2-((*E*)-3-(4-(((2-(1*H*-indol-3-yl)ethyl)(2-(3-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-(((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropoxy)ethyl)amino)methyl)phenyl)acrylamido)phenyl)carbamate, 77**

To a solution of compound **76** (10 mg, 0.012 mmol, 1.0 eq.) and *tert*-butyl (2-aminophenyl)carbamate (3.7 mg, 1.5 eq.) in DMF (0.5 mL) were added EDCI (2.7 mg, 1.2 eq.), HOBt (1.9 mg, 1.2 eq.) and DIEA (4 μL, 2 eq.). The reaction mixture was stirred at room temperature for 24 h and monitored by UPLC-MS. Once the limiting starting material was consumed, the reaction was quenched with H_2O and extracted with ethyl acetate. The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified using ISCO (dichloromethane/methanol, 0%-10) to yield the title compound **77**. **UPLC-MS** RT: 1.43 min (Method A), Mass m/z: 1052.64 $[M+H]^+$.

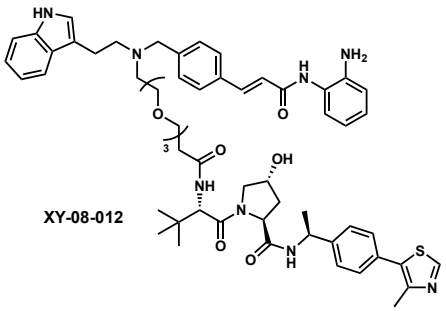


(2*S*,4*R*)-1-((*S*)-2-(3-(2-((2-(1*H*-indol-3-yl)ethyl)(4-((*E*)-3-((2-aminophenyl)amino)-3-oxoprop-1-en-1-yl)benzyl)amino)ethoxy)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide, compound XY-07-155

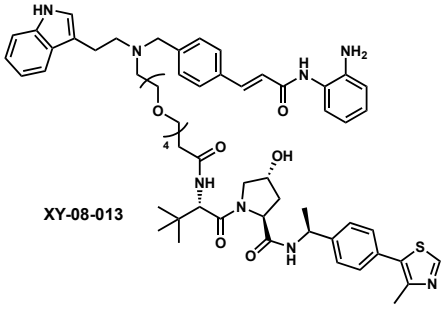
Compound **77** (1.0 eq. from last step) was treated with a mixture of TFA/dichloromethane (1:5). The reaction was stirred for 3h, and monitored by UPLC-MS. Once the starting material was consumed, the reaction was concentrated *in vacuo*. The residue was purified using HPLC (H_2O/acetonitrile, 0%-100%) to yield the title compound **XY-07-155** as a white powder (1.3 mg, 12% yield over 2 steps). **UPLC-MS** RT: 1.17 min (Method A), Mass m/z: 952.73 $[M+H]^+$. Purity is > 95% by UPLC.



(2*S*,4*R*)-1-((*S*)-3-(4-((*E*)-3-((2-aminophenyl)amino)-3-oxoprop-1-en-1-yl)benzyl)-14-(*tert*-butyl)-1-(1*H*-indol-3-yl)-12-oxo-6,9-dioxa-3,13-diazapentadecan-15-oyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (XY-07-156) was synthesized using similar procedures, and was obtained as a white powder. **UPLC-MS** RT: 1.20 min (Method A), Mass m/z: 996.83 $[M+H]^+$. Purity is > 95% by UPLC.

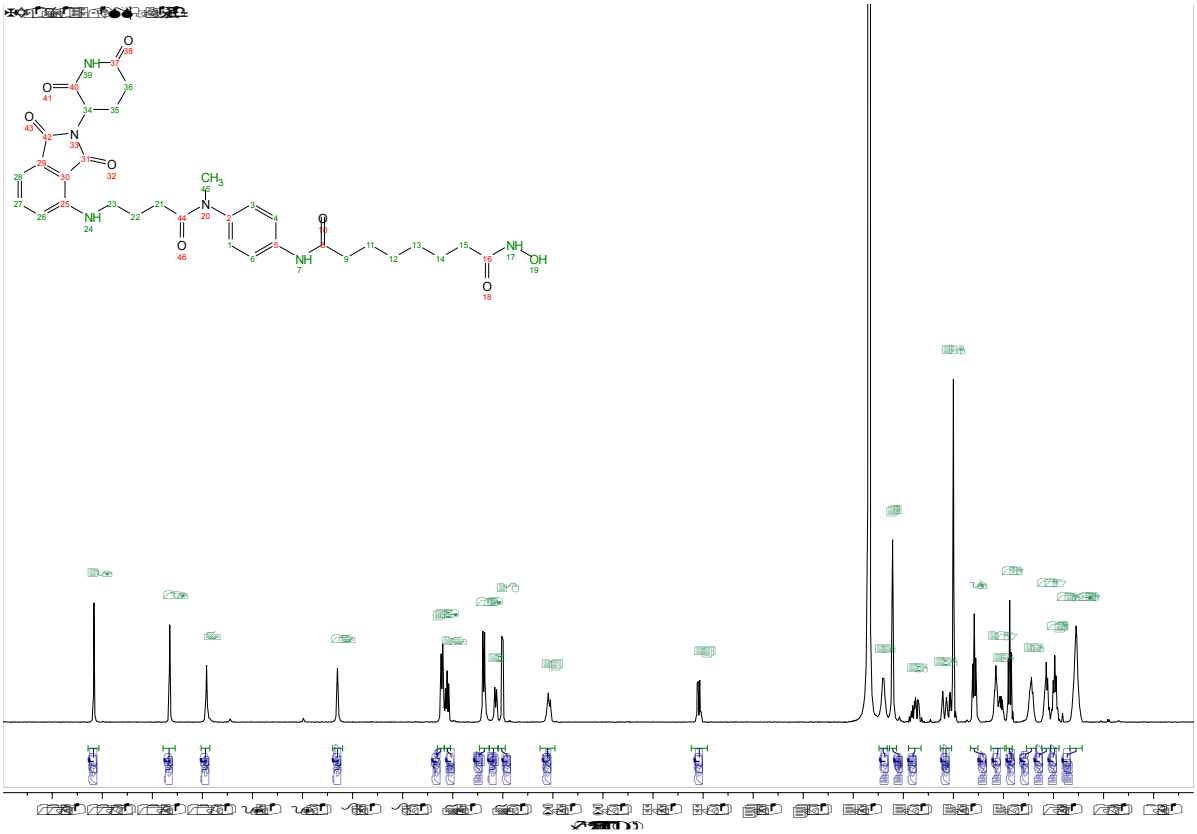


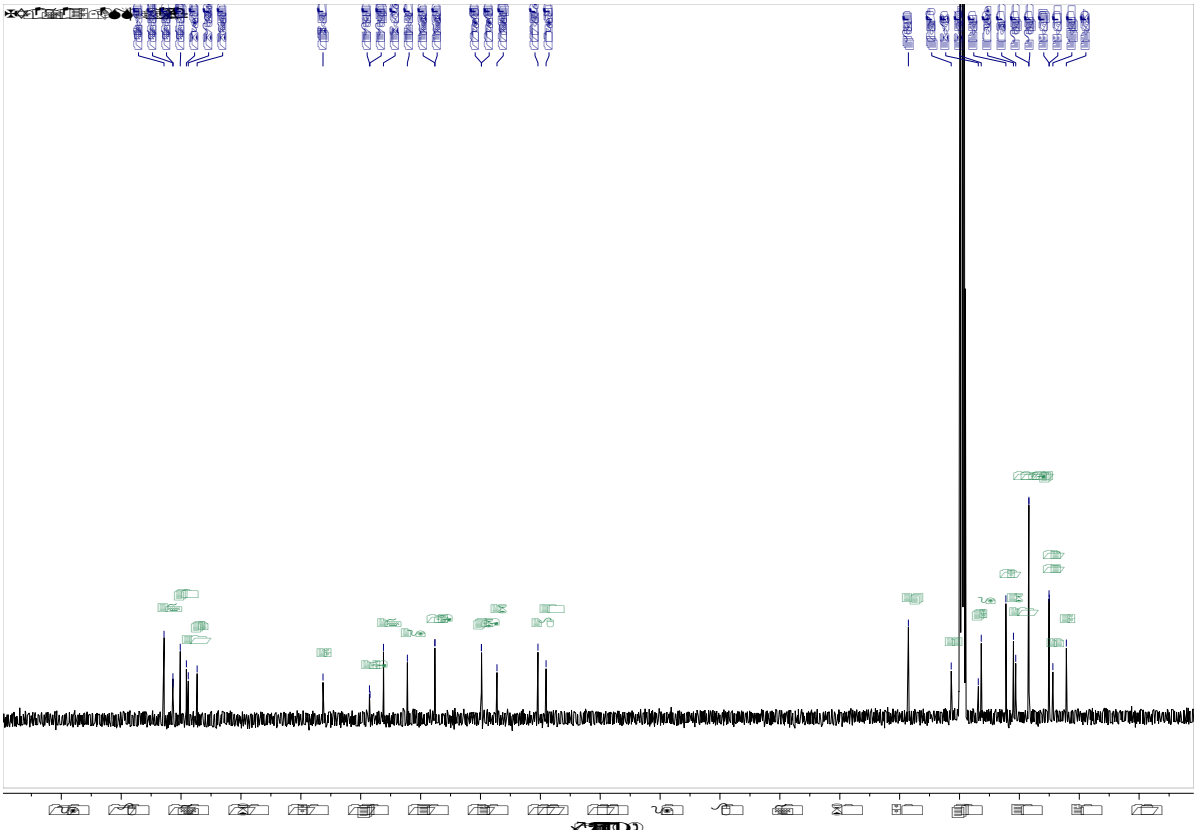
(2*S*,4*R*)-1-((*S*)-3-(4-((*E*)-3-((2-aminophenyl)amino)-3-oxoprop-1-en-1-yl)benzyl)-17-(*tert*-butyl)-1-(1*H*-indol-3-yl)-15-oxo-6,9,12-trioxa-3,16-diazaoctadecan-18-oyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (XY-08-012) was synthesized using similar procedures, and was obtained as a white powder. **LCMS** Mass m/z: 521.9 $[M/2+H]^+$. Purity is > 95% by UPLC. **^{1}HNMR** (400 MHz, CD_3OD) δ (ppm) 8.80 (s, 2H), 7.64 (dd, *J* = 28.2, 11.8 Hz, 4H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.40 – 7.05 (m, 11H), 7.05 – 6.99 (m, 1H), 6.88 (t, *J* = 13.3 Hz, 2H), 4.48 (dd, *J* = 18.2, 10.4 Hz, 3H), 4.27 (d, *J* = 32.9 Hz, 1H), 3.85 – 3.69 (m, 3H), 3.68 – 3.60 (m, 2H), 3.56 – 3.42 (m, 11H), 2.52 – 2.23 (m, 6H), 2.15 – 2.05 (m, 1H), 1.84 (s, 1H), 1.41 (dd, *J* = 31.3, 7.0 Hz, 3H), 1.21 (d, *J* = 18.1 Hz, 2H), 0.87 (dd, *J* = 35.7, 14.7 Hz, 12H).

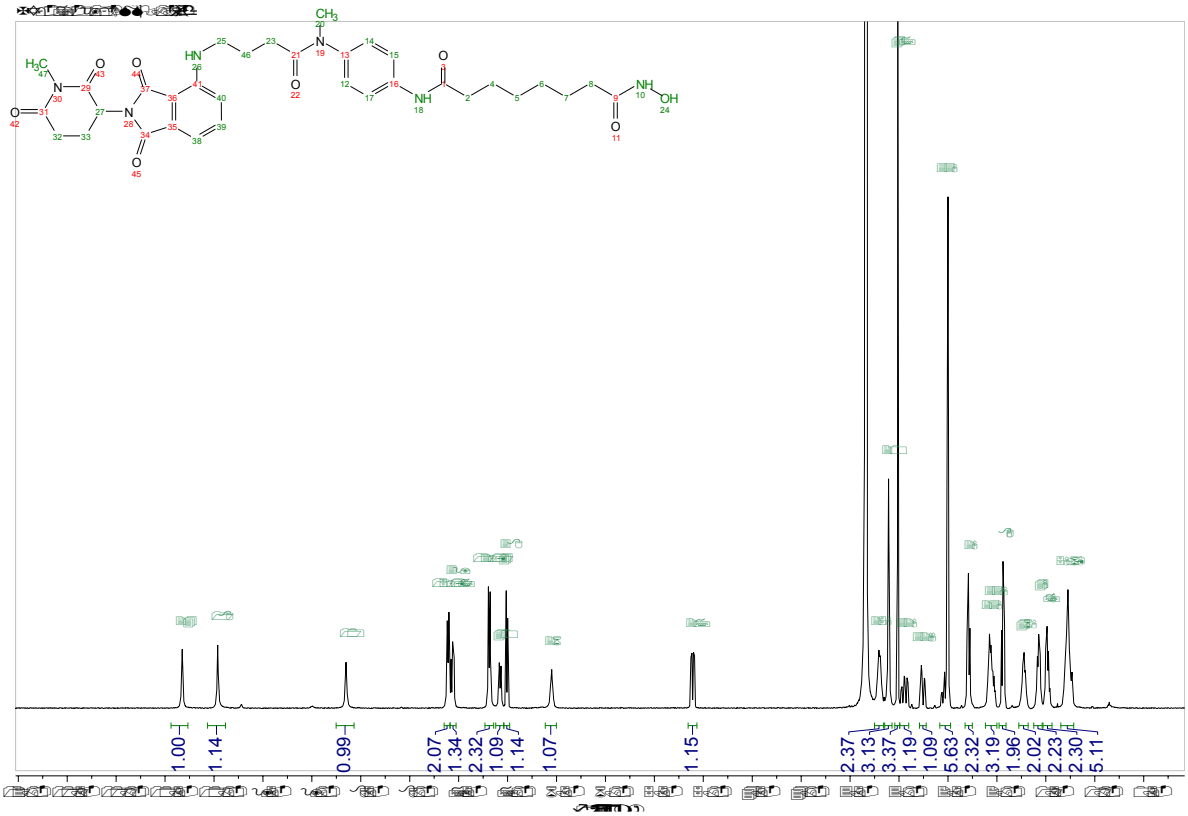


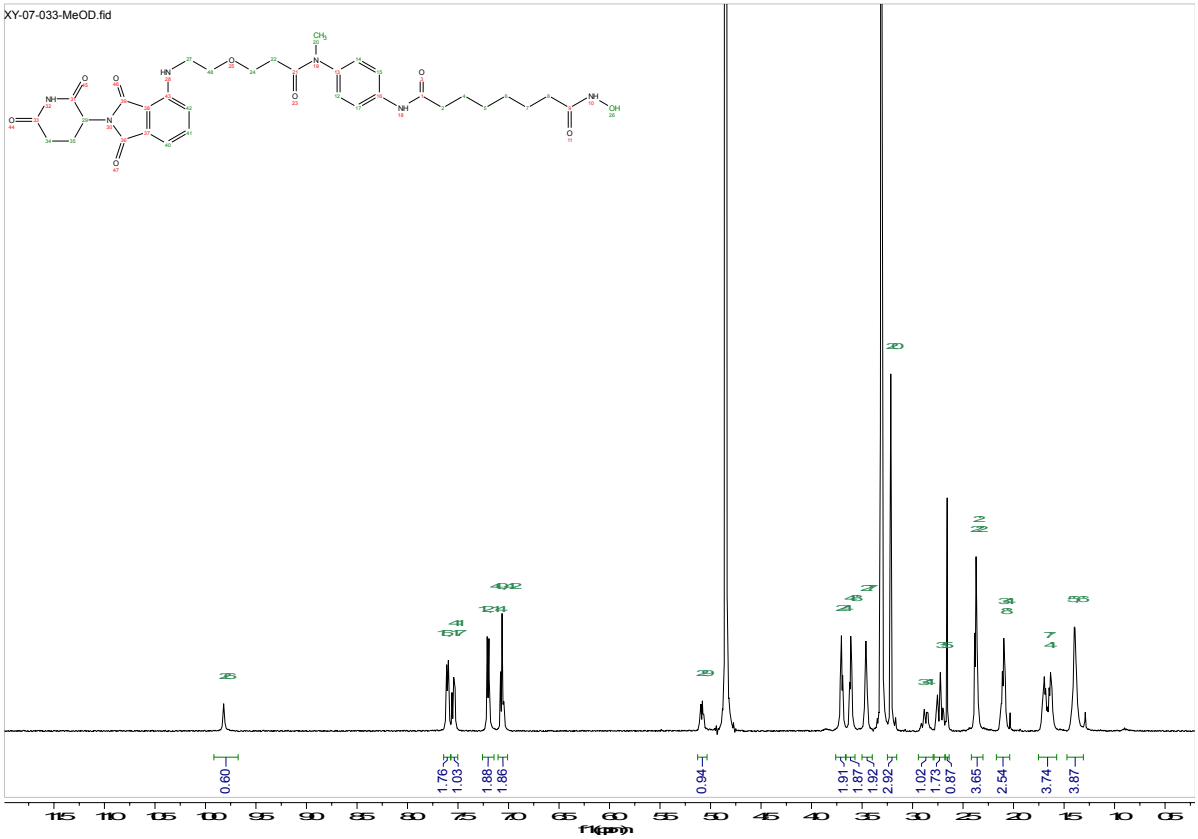
(2*S*,4*R*)-1-((*S*)-3-(4-((*E*)-3-((2-aminophenyl)amino)-3-oxoprop-1-en-1-yl)benzyl)-20-(*tert*-butyl)-1-(1*H*-indol-3-yl)-18-oxo-6,9,12,15-tetraoxa-3,19-diazahenicosan-21-oyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (XY-08-013) was synthesized using similar procedures, and was obtained as a white powder. **LCMS** Mass m/z: 543.4 $[M/2+H]^+$. Purity is > 95% by UPLC. **^{1}HNMR** (400 MHz, CD_3OD) δ (ppm) 9.76 (s, 2H), 7.73 (d, *J* = 15.6 Hz, 1H), 7.61 (s, 2H), 7.36 (ddd, *J* = 34.4, 24.7, 14.9 Hz, 13H), 7.13 (s, 1H), 7.02 (s, 1H), 6.90 (d, *J* = 14.6 Hz, 2H), 5.25 (s, 1H), 4.90 (d, *J* = 5.7 Hz, 3H), 4.58 – 4.42 (m, 4H), 4.31 (s, 1H), 3.83 – 3.72 (m, 3H), 3.58 – 3.43 (m, 12H), 2.49 (s, 3H), 2.36 (d, *J* = 30.3 Hz, 2H), 2.10 (d, *J* = 10.7 Hz, 1H), 1.87 (d, *J* = 42.1 Hz, 2H), 1.56 – 1.45 (m, 2H), 1.39 (d, *J* = 6.5 Hz, 3H), 1.23 (s, 3H), 0.92 (s, 9H), 0.80 (s, 2H).

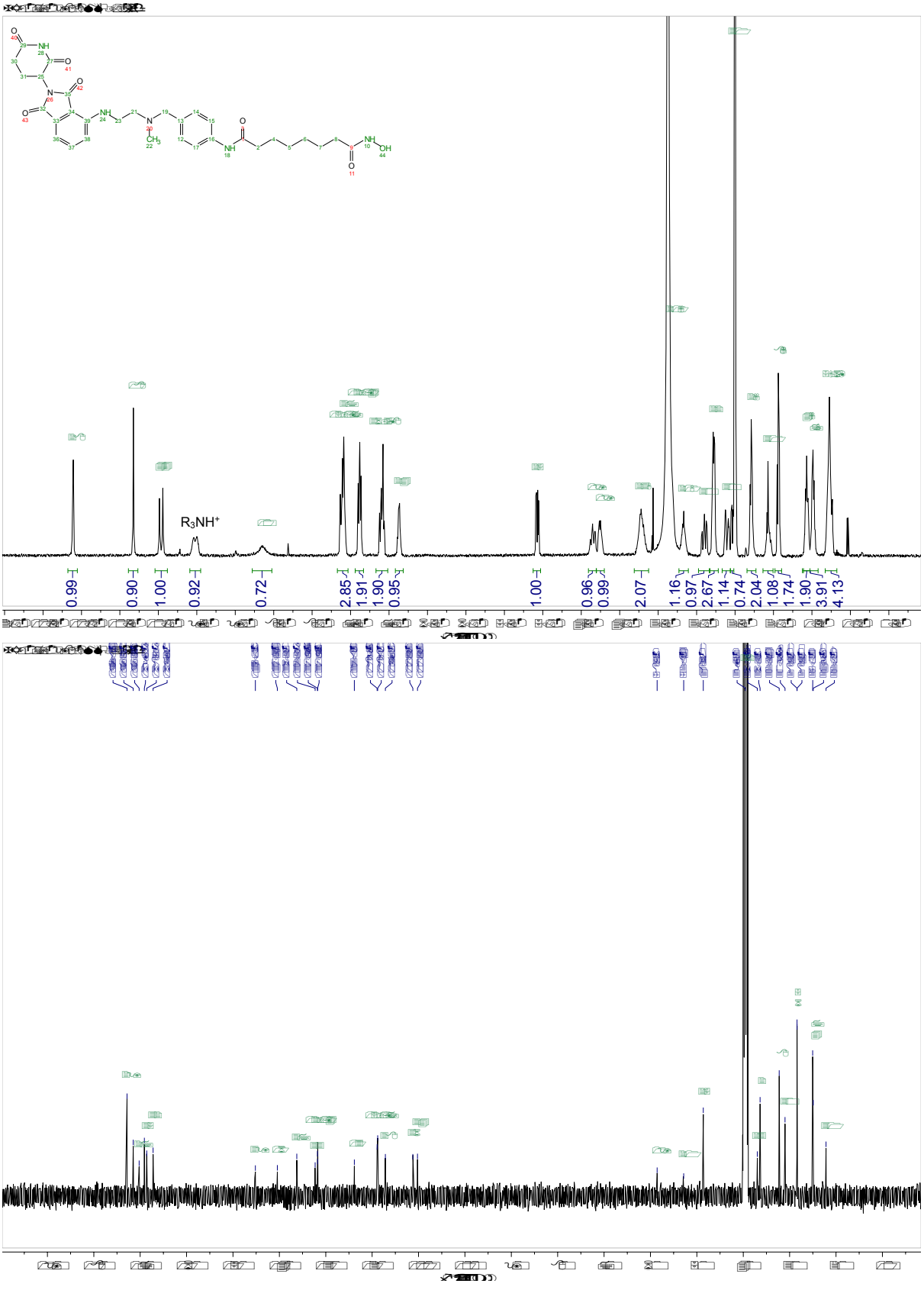
Selected NMR spectra








XY-07-033-MeOD.fid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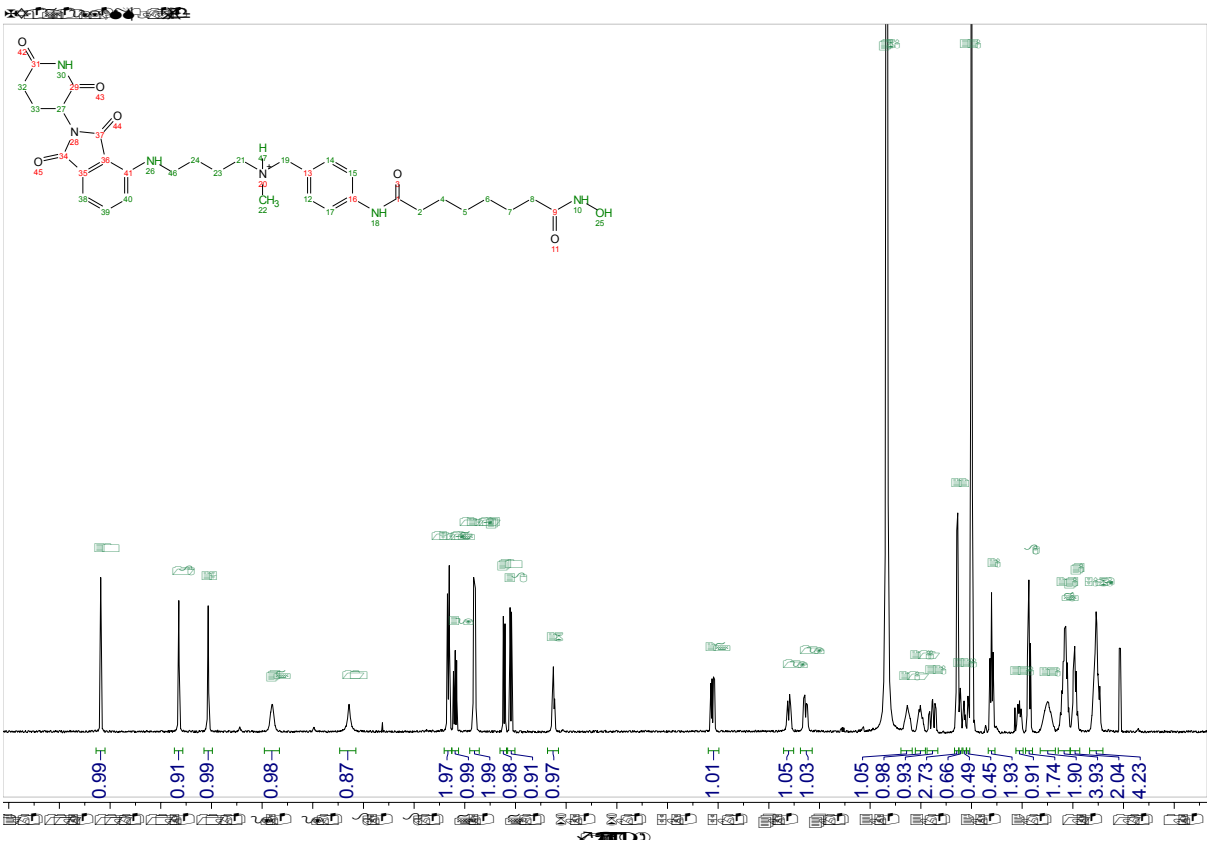
1.08
1.74
1.90
3.91
4.13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0.98
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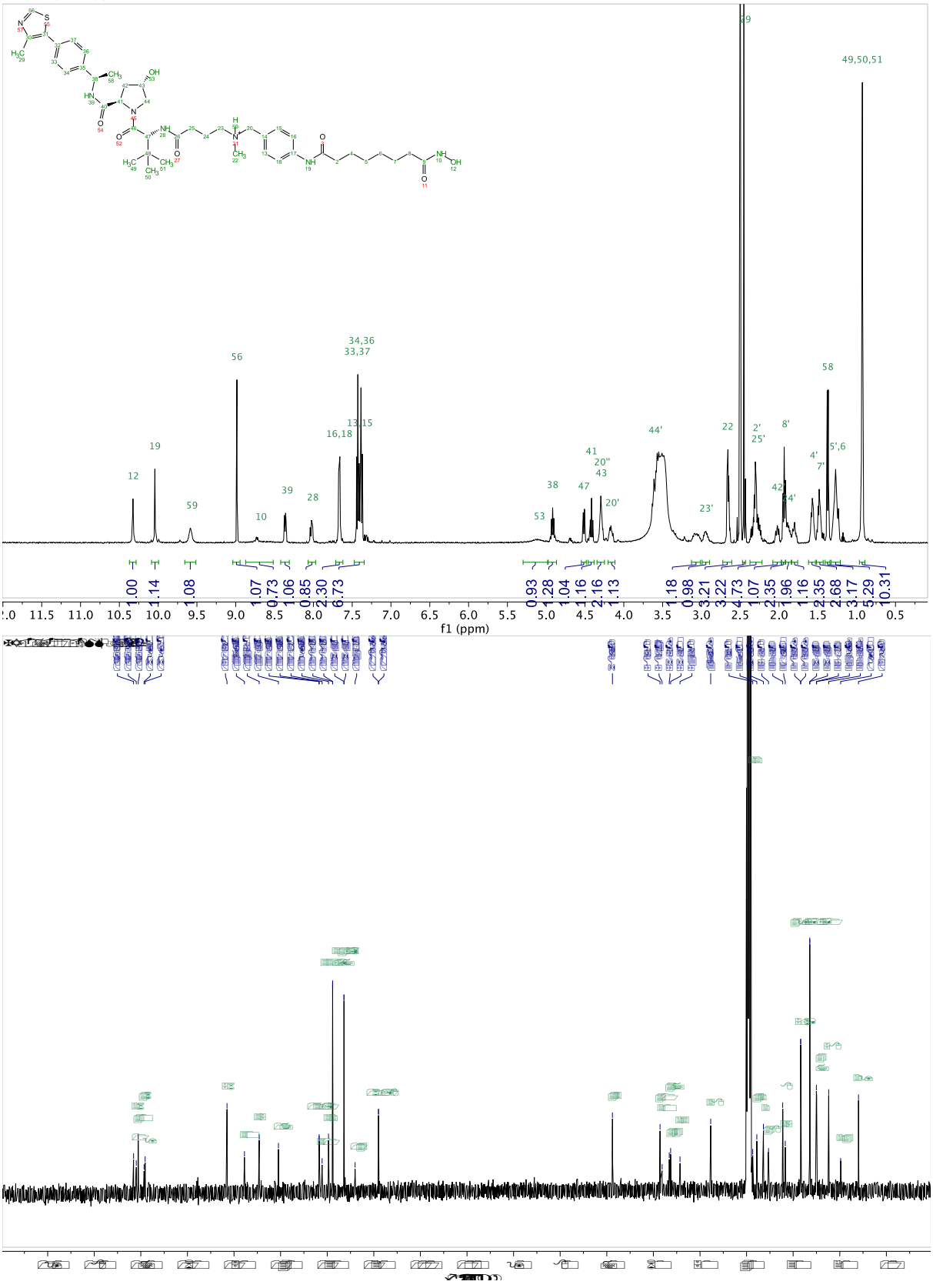
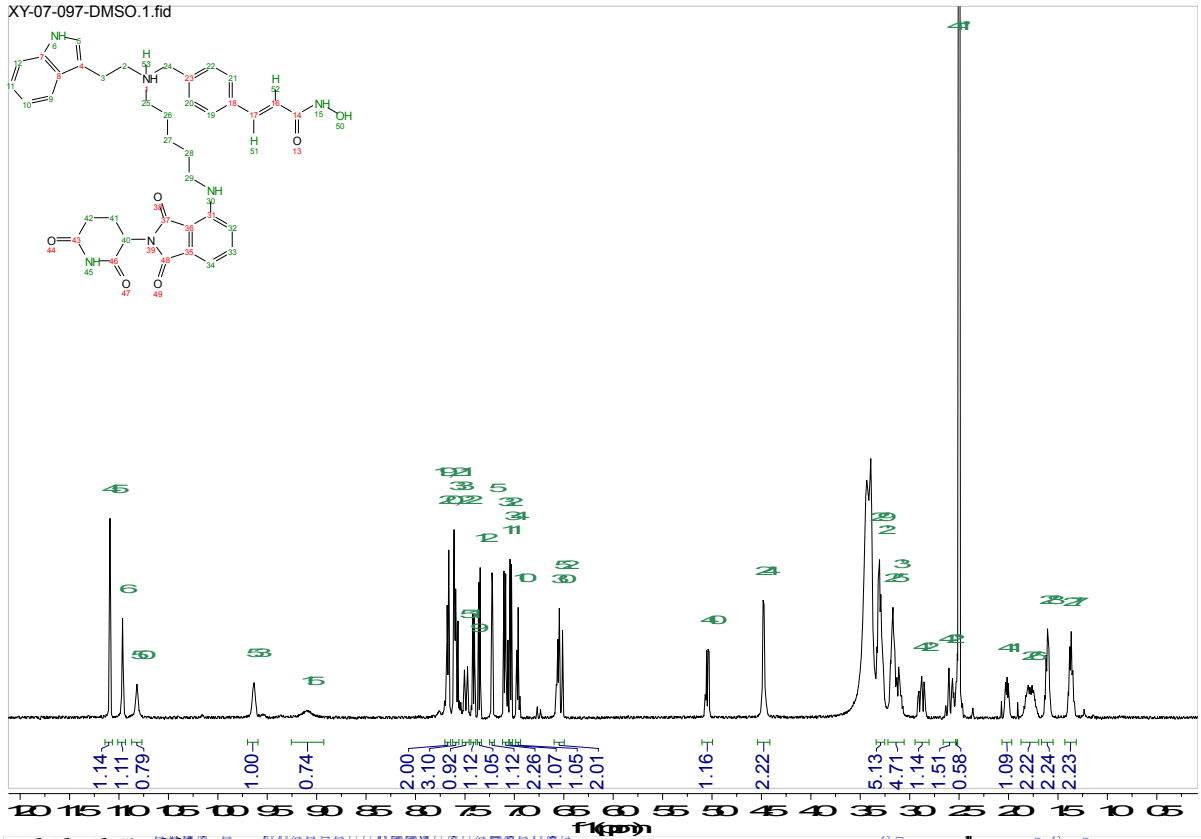
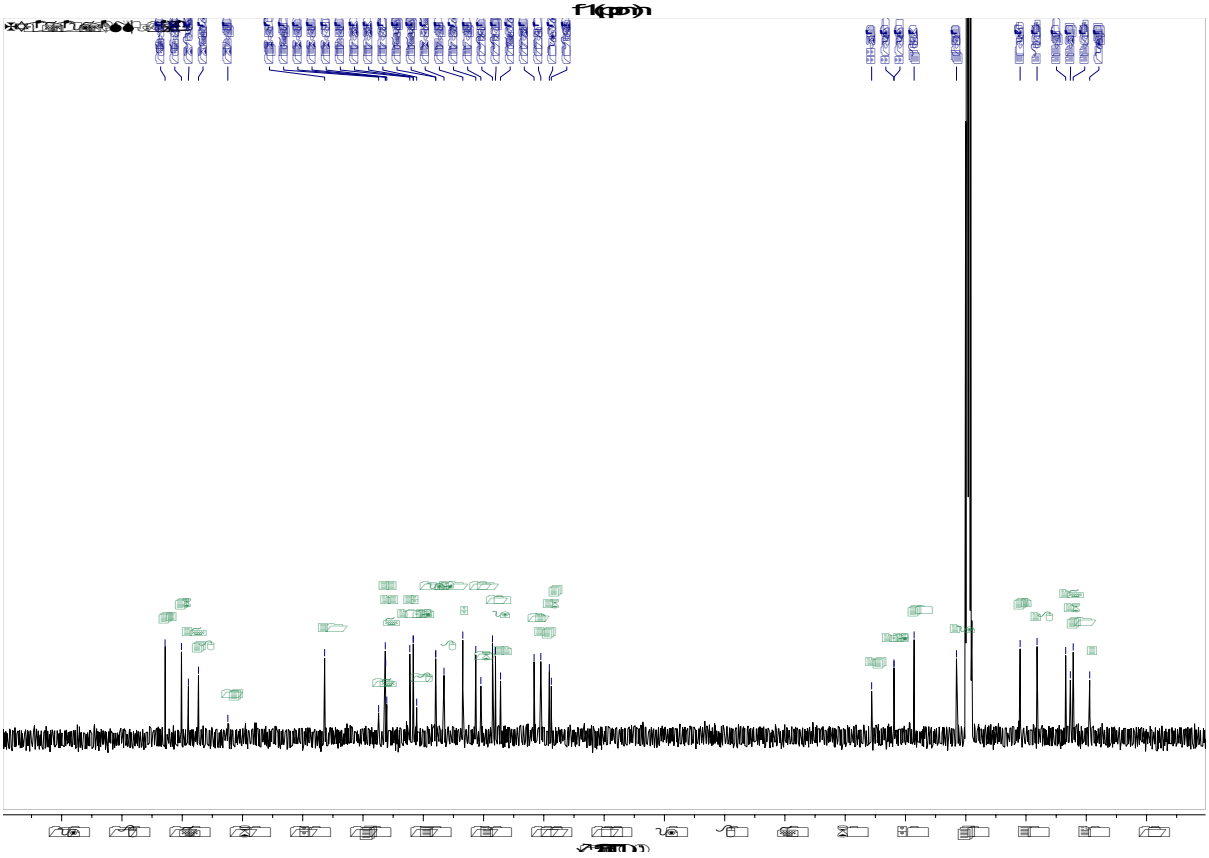
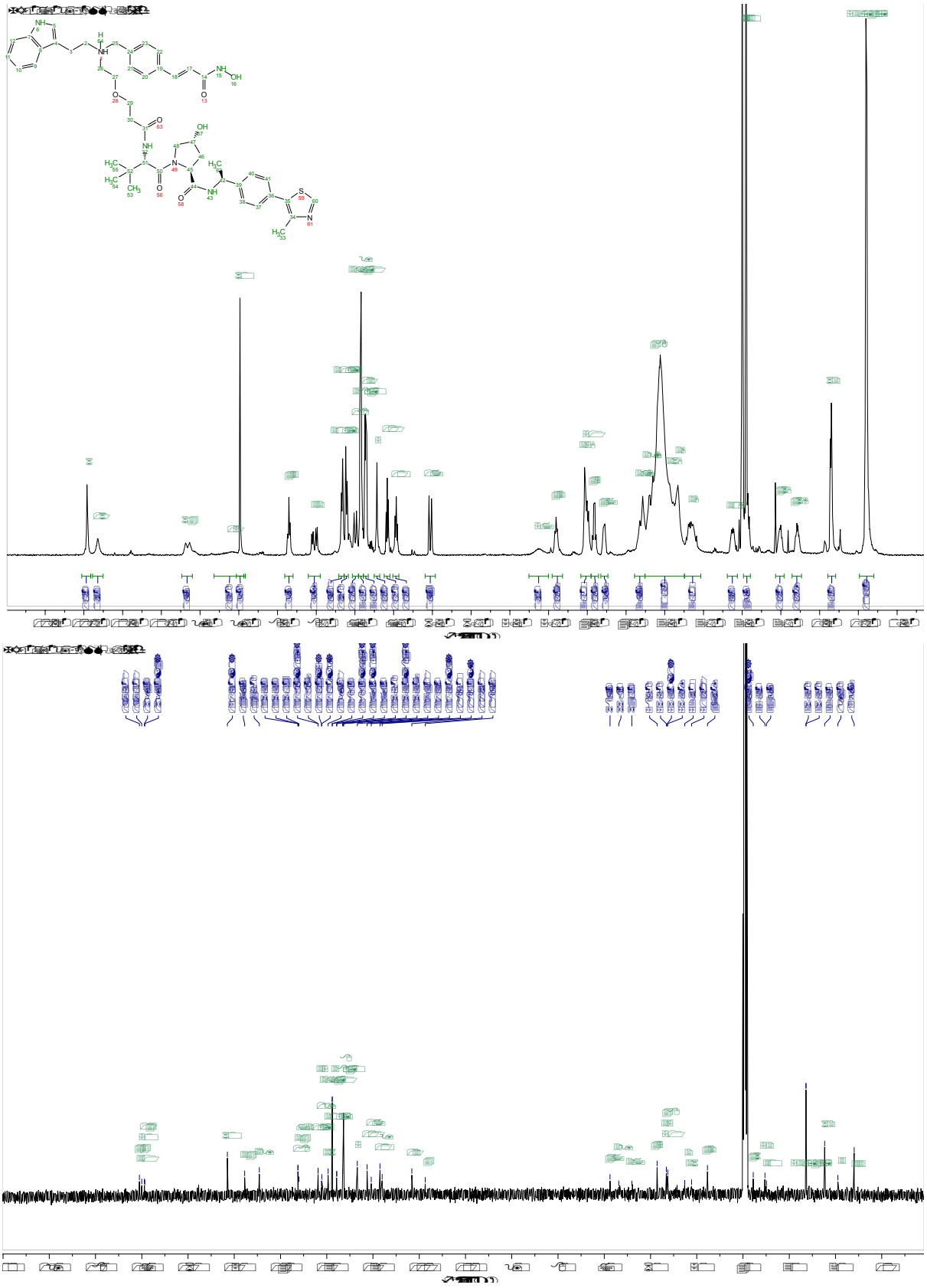
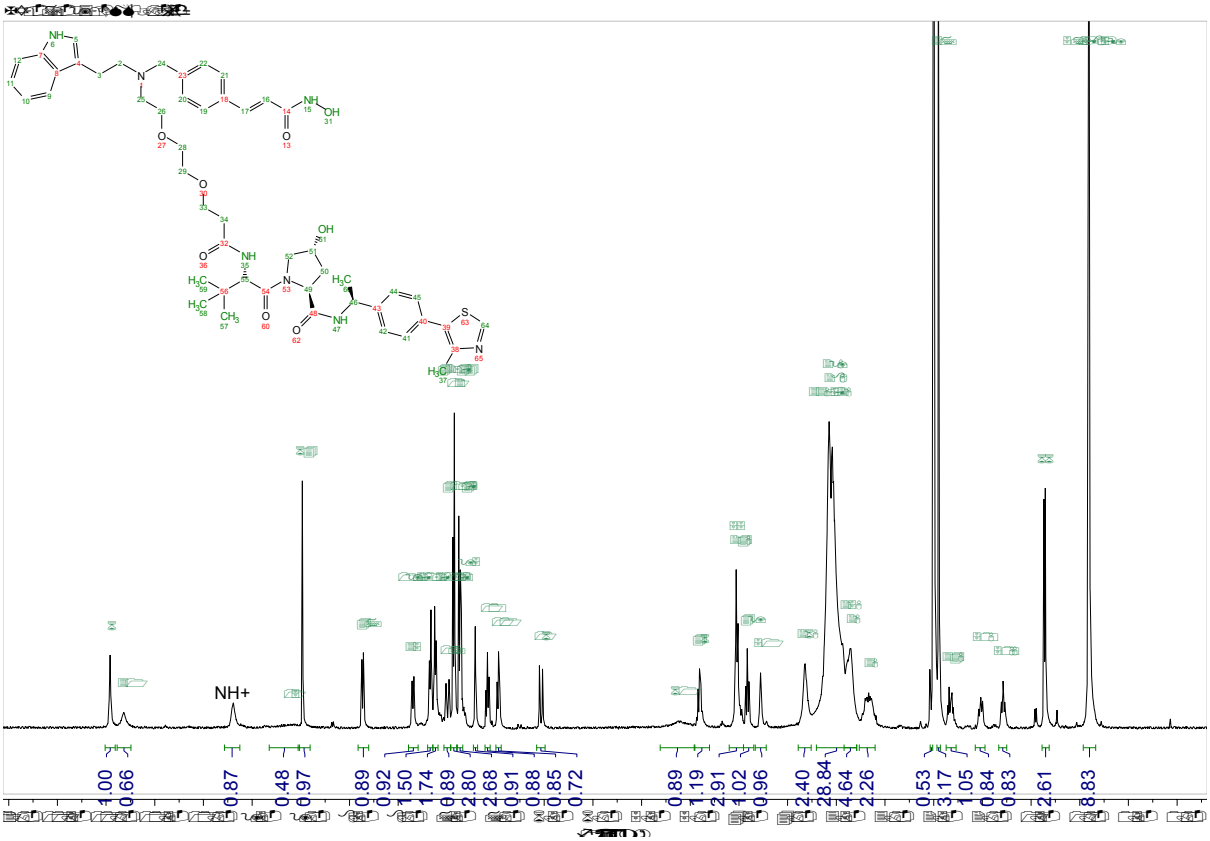


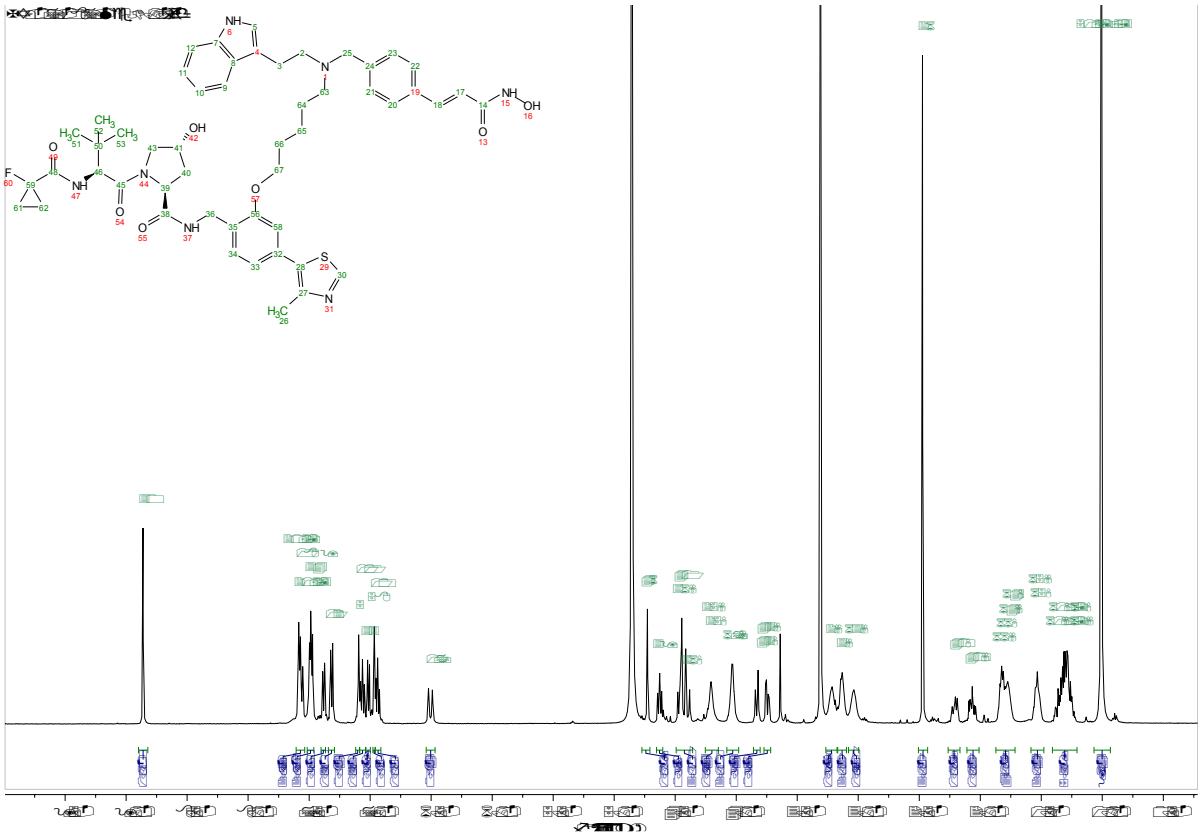
XY-07-097-DMSO.1.fid

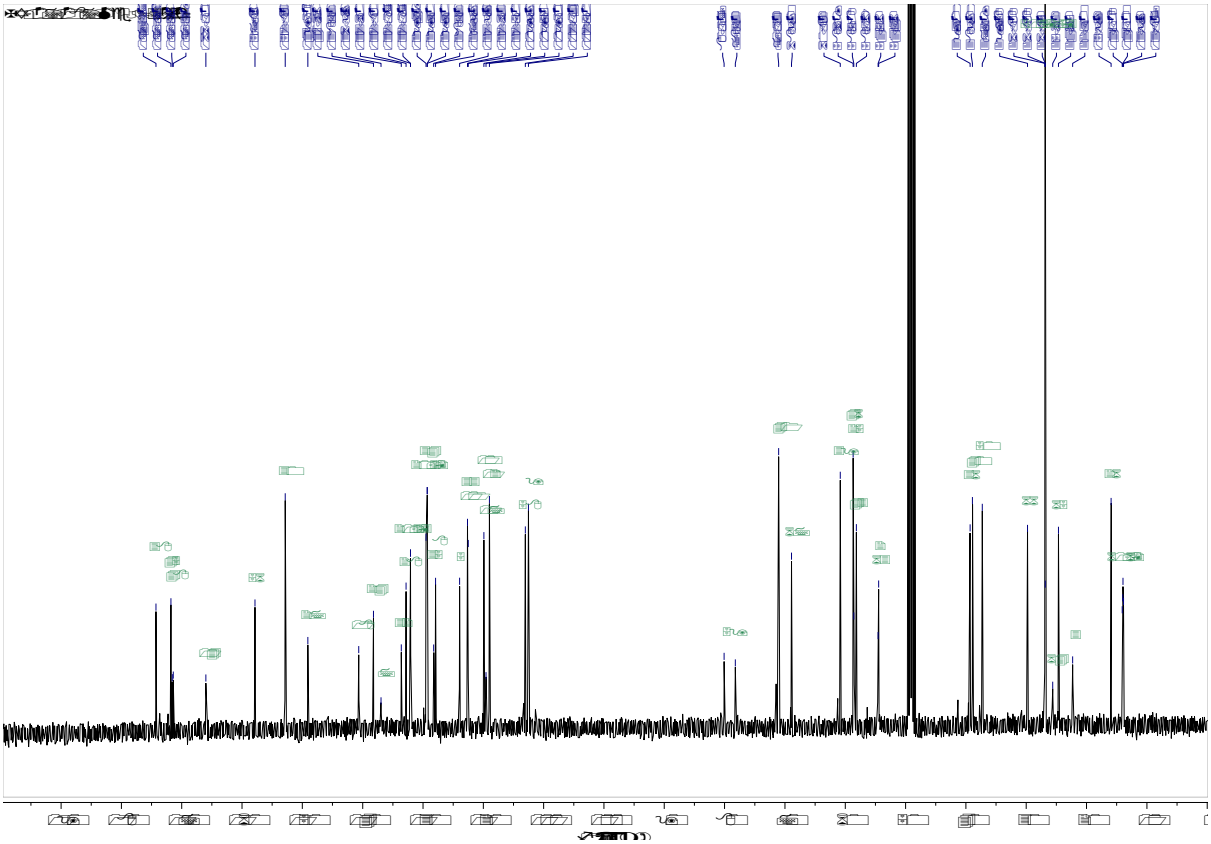


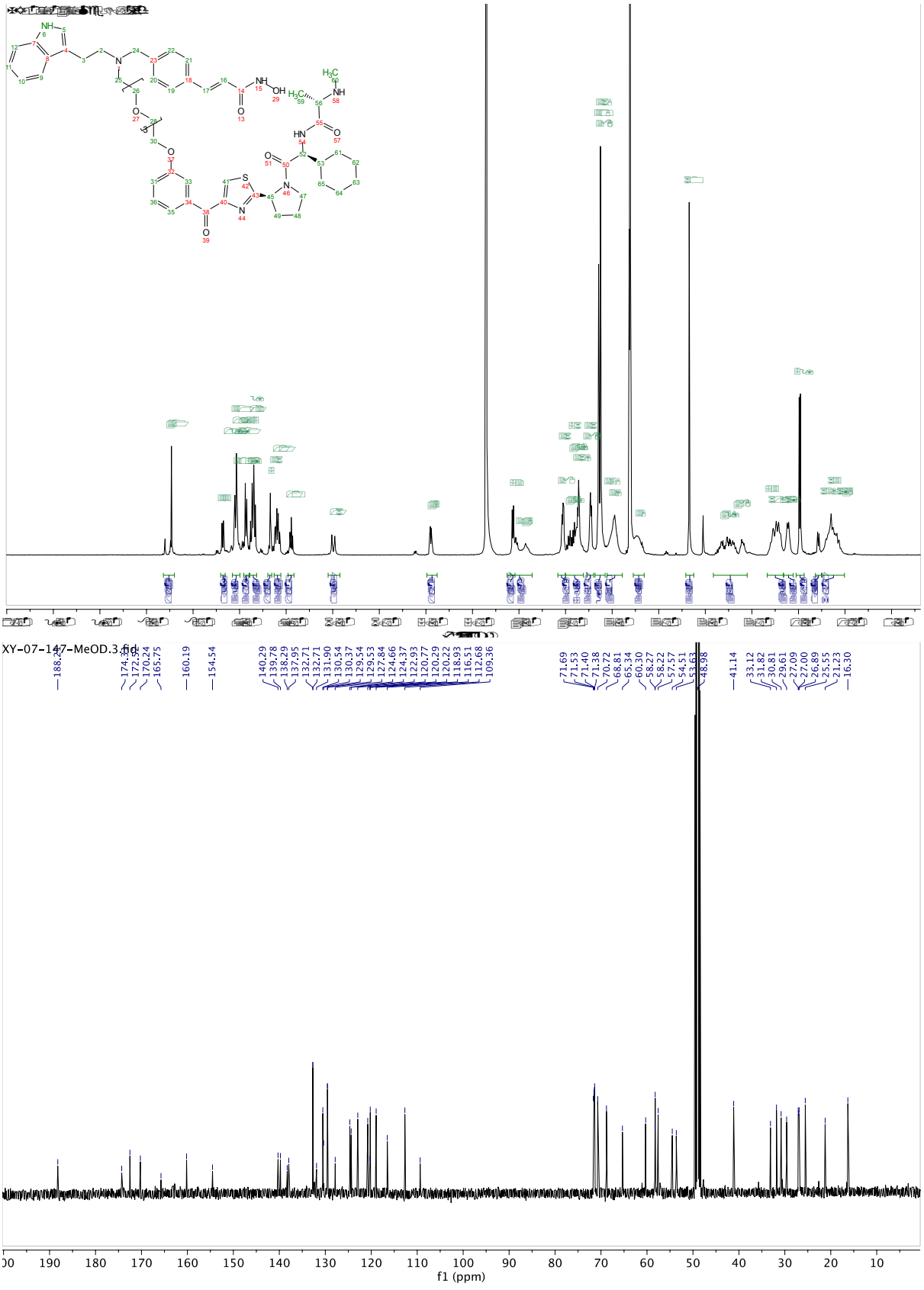


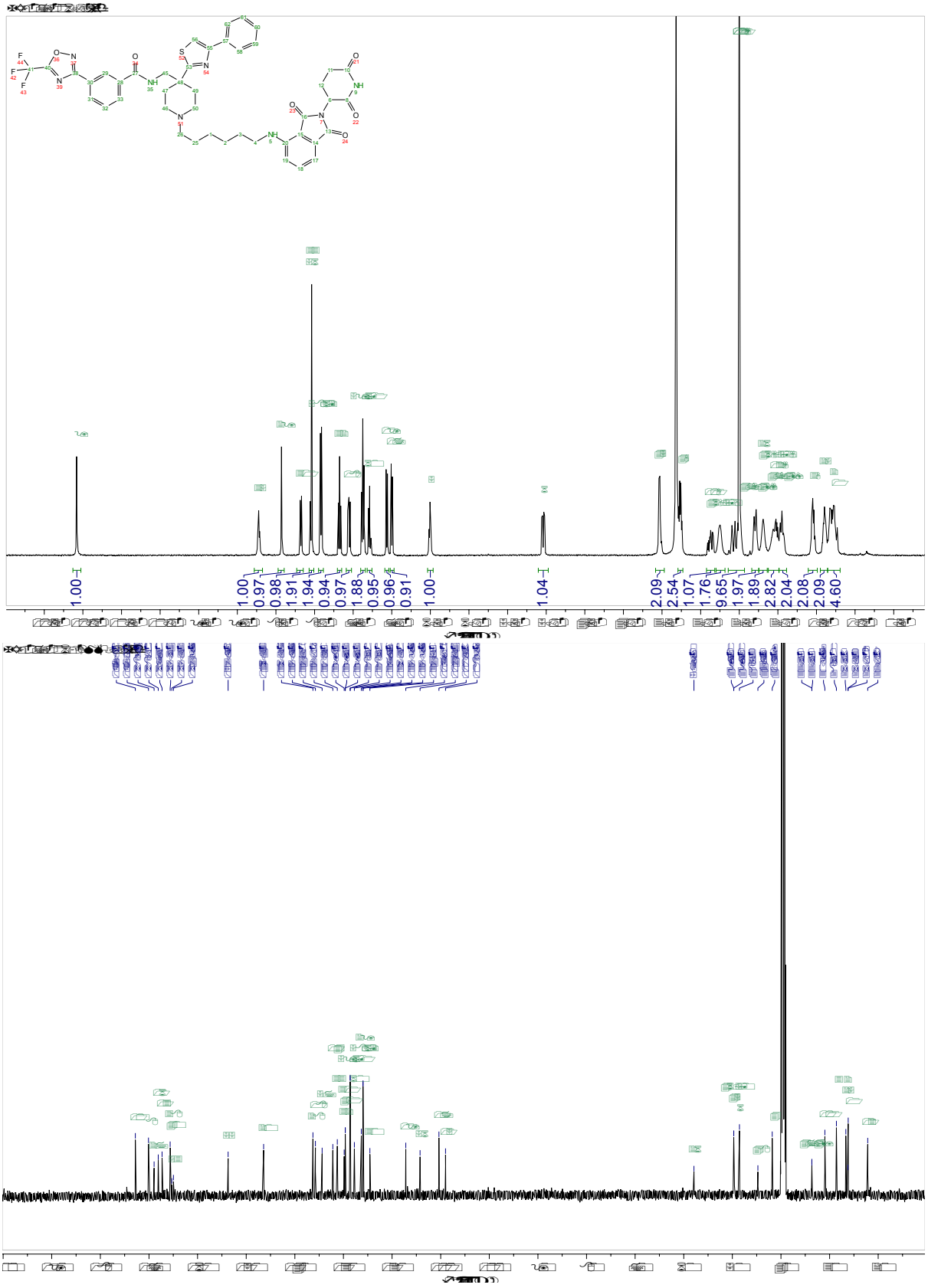


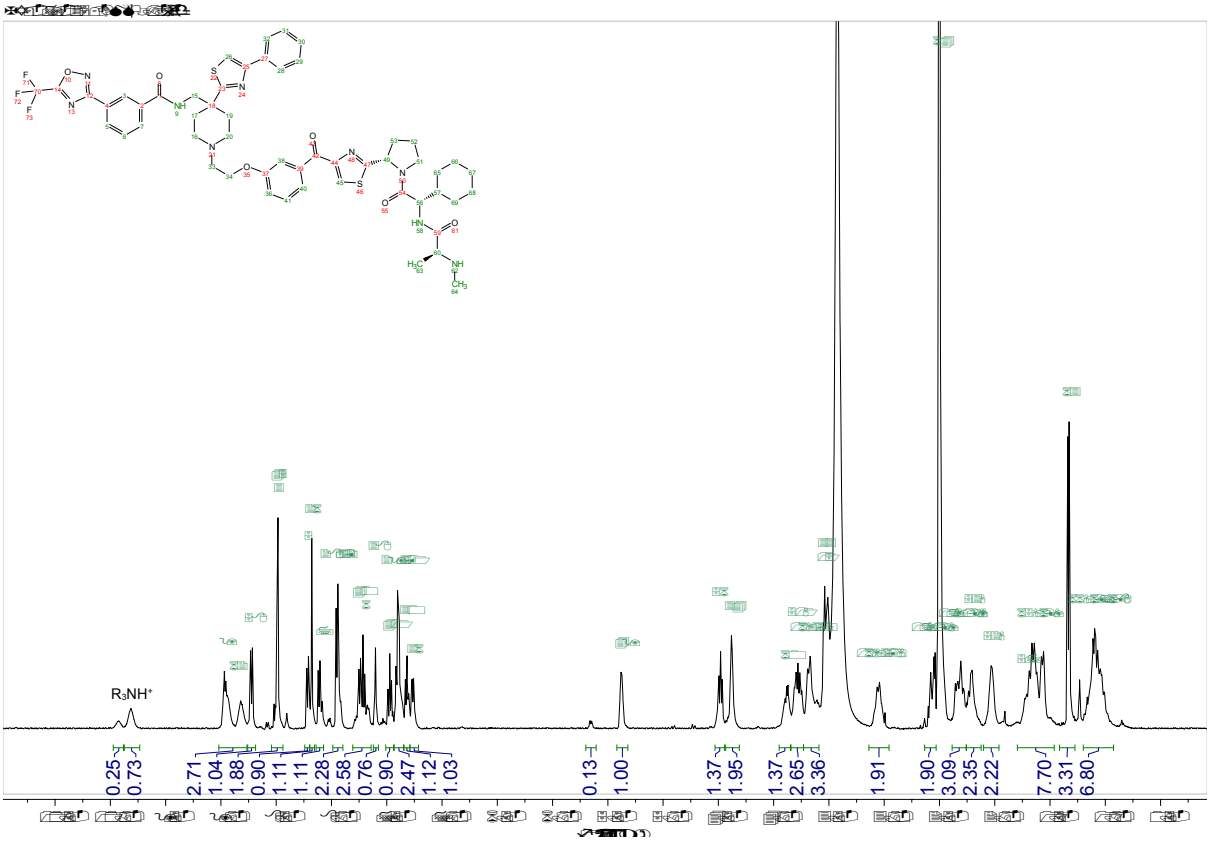

NH+
1.00
0.66
0.87
0.48
0.97
0.89
0.92
1.50
1.74
0.89
2.80
2.68
0.91
0.88
0.85
0.72
0.89
1.19
2.91
1.02
0.96
2.40
28.84
7.64
2.26
0.53
3.17
1.05
0.84
0.83
2.61
8.83

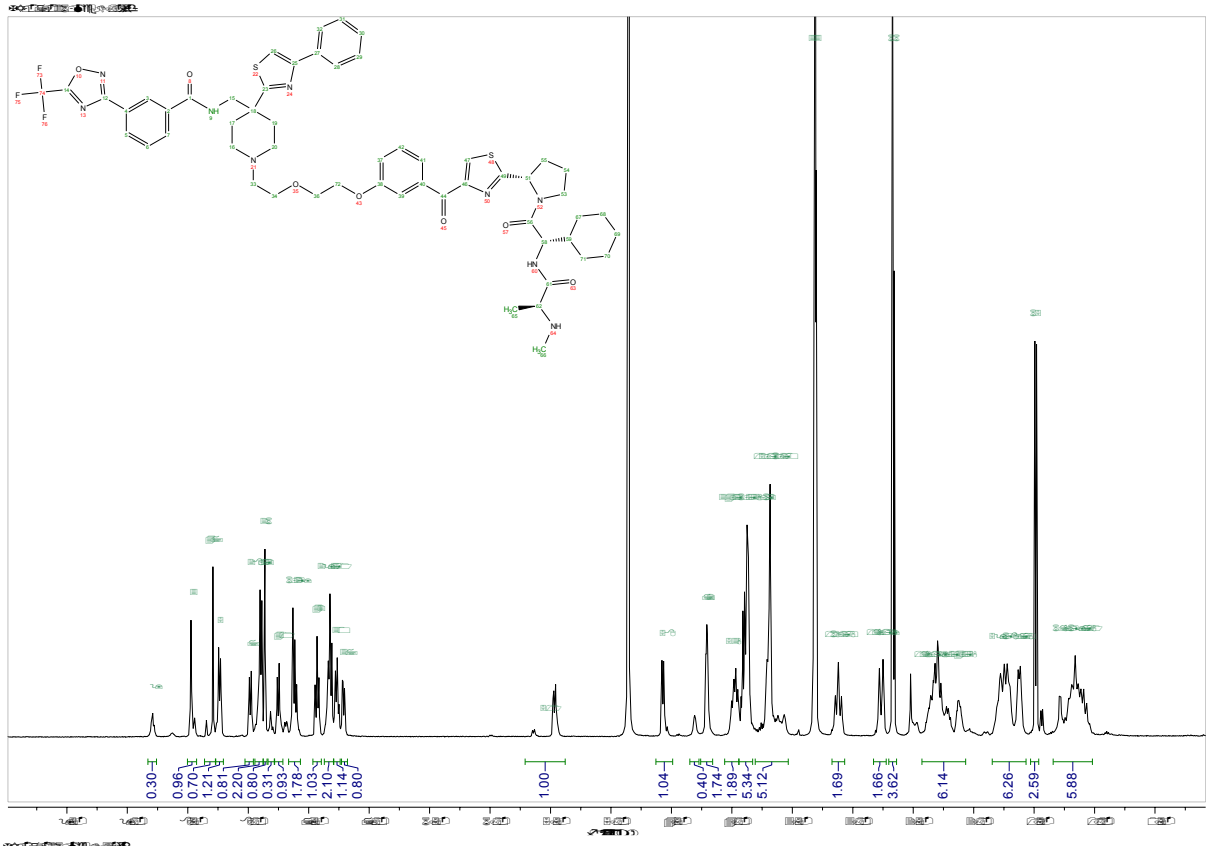


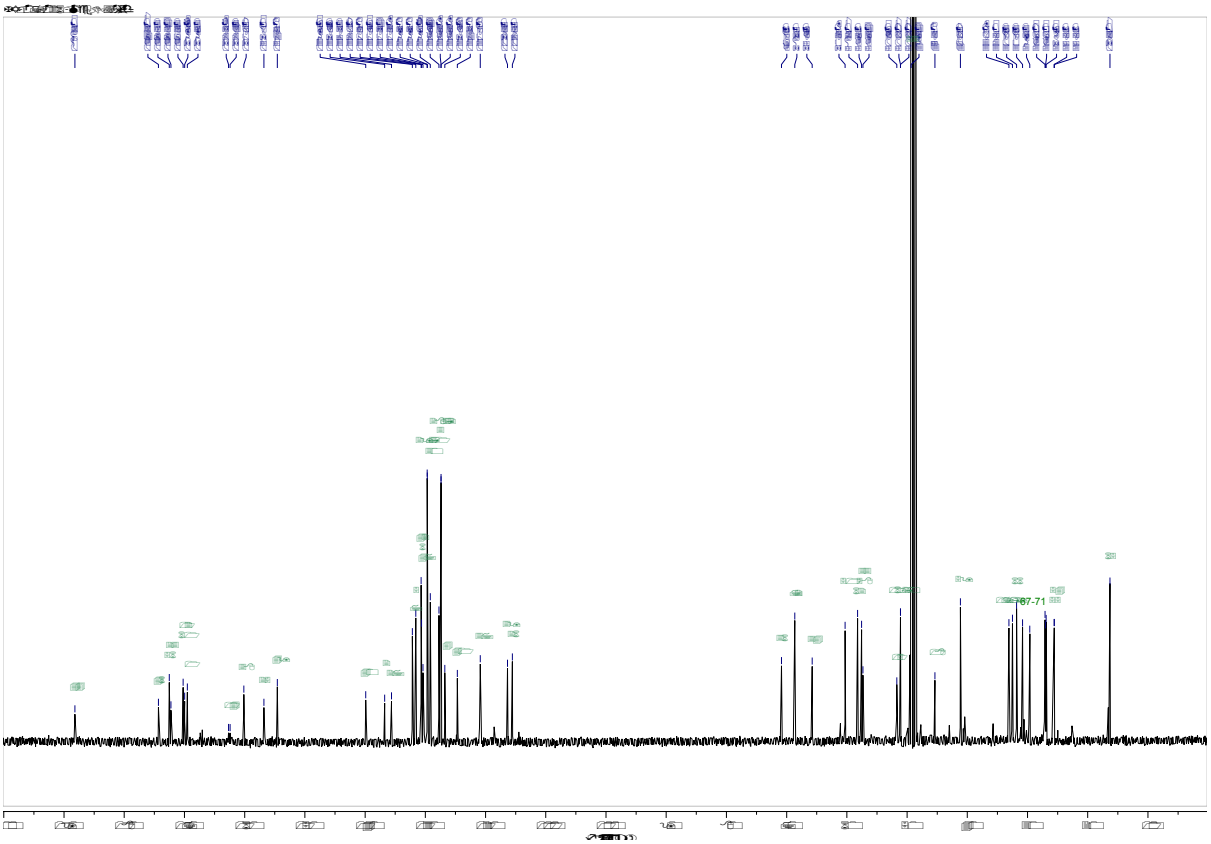


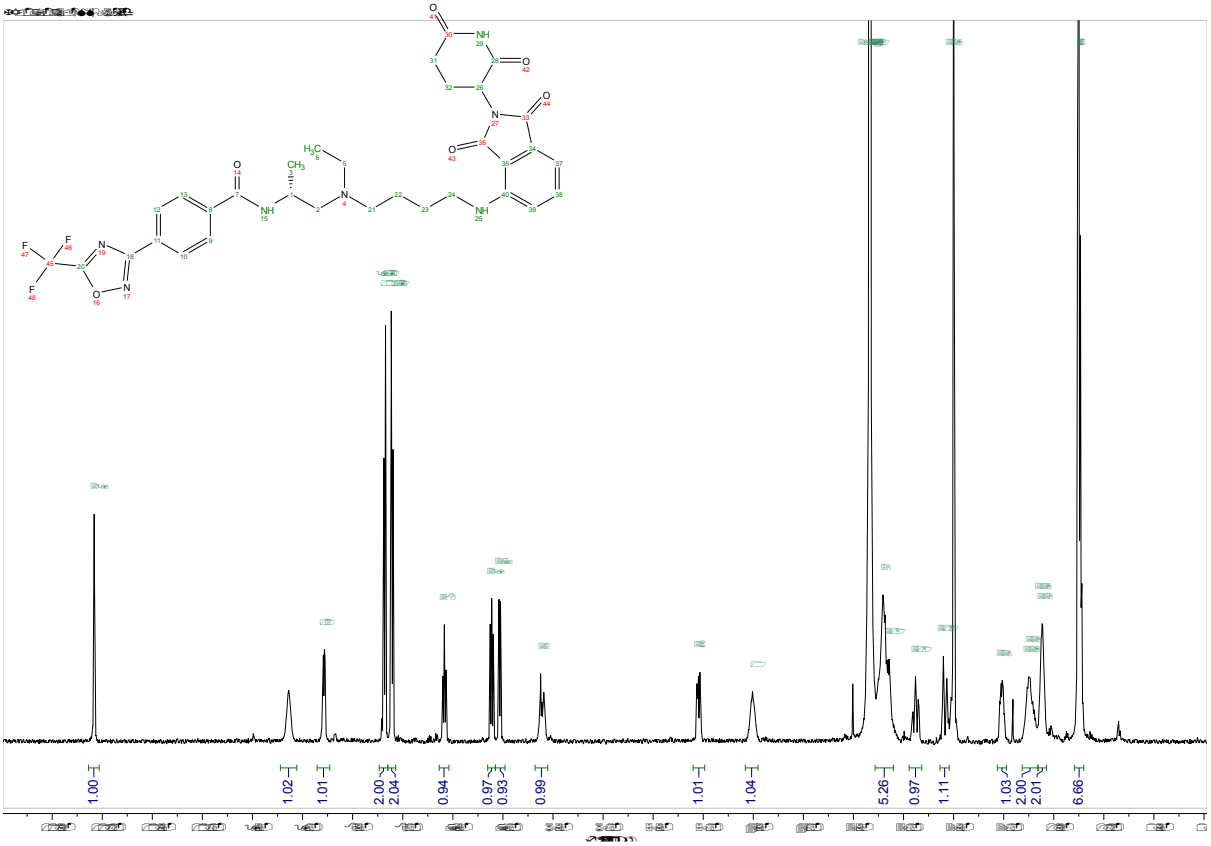

XY-07-147-MeOD.3.fid
188.42
174.56
172.52
170.24
165.75
160.19
154.54
140.29
139.78
138.29
137.95
132.71
132.71
131.90
130.54
130.37
129.54
129.53
127.84
124.66
124.37
122.93
120.77
120.29
120.22
118.93
116.51
112.68
109.36
71.69
71.53
71.40
71.38
70.72
68.81
65.34
60.30
58.27
58.22
57.57
54.51
53.63
48.98
41.14
33.12
31.82
30.81
29.61
27.09
27.00
26.89
25.55
21.23
16.30
f1 (ppm)

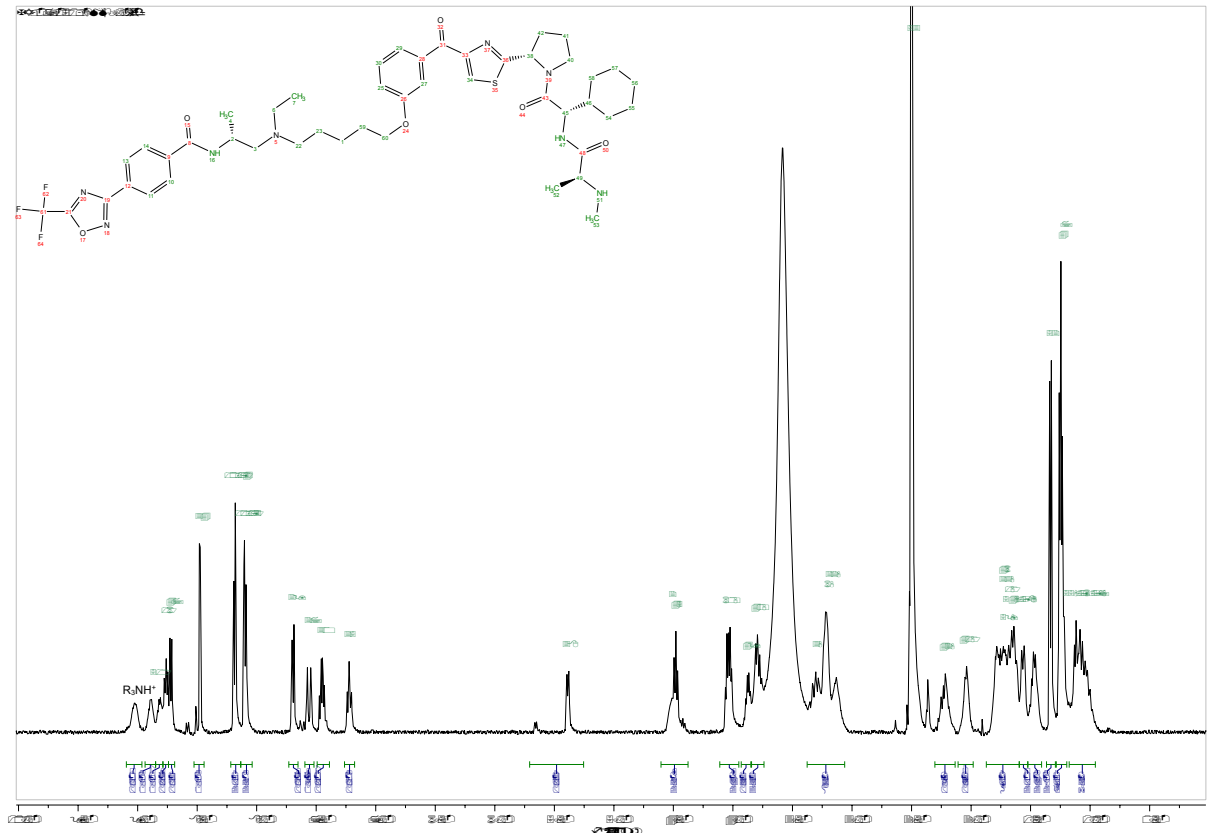


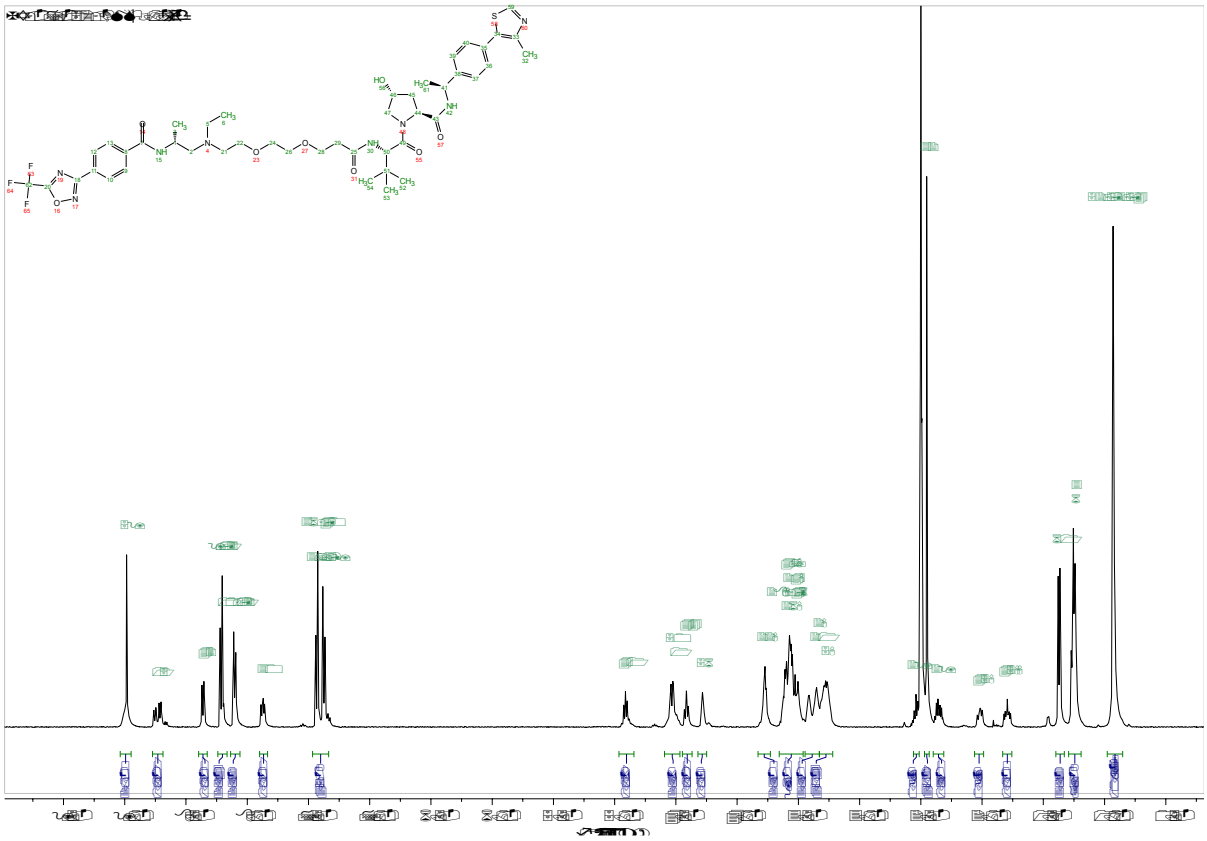

R3NH+
0.25
0.73
2.71
1.04
1.88
0.90
1.11
1.11
2.28
2.58
0.76
0.90
2.47
1.12
1.03
0.13
1.00
1.37
1.95
1.37
2.65
3.36
1.91
1.90
3.09
2.35
2.22
7.70
3.31
6.80

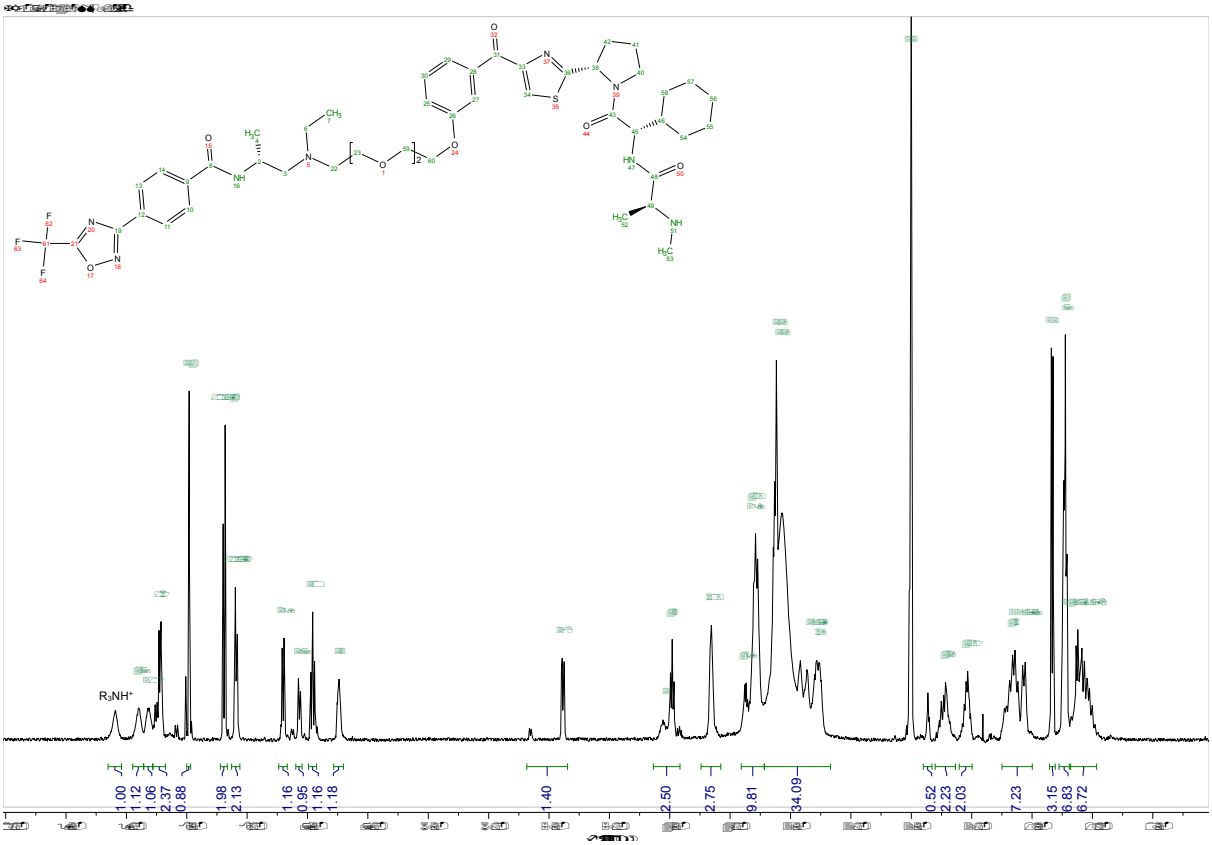

0.30
0.96
0.70
1.21
0.81
2.20
0.80
0.31
0.93
1.78
1.03
2.10
1.14
0.80
1.00
1.04
0.40
1.74
1.89
5.34
5.12
1.69
1.66
3.62
6.14
6.26
2.59
5.88


67-71


1.00
1.02
1.01
2.00
2.04
0.94
0.97
0.93
0.99
1.01
1.04
5.26
0.97
1.11
1.03
2.00
2.01
6.66

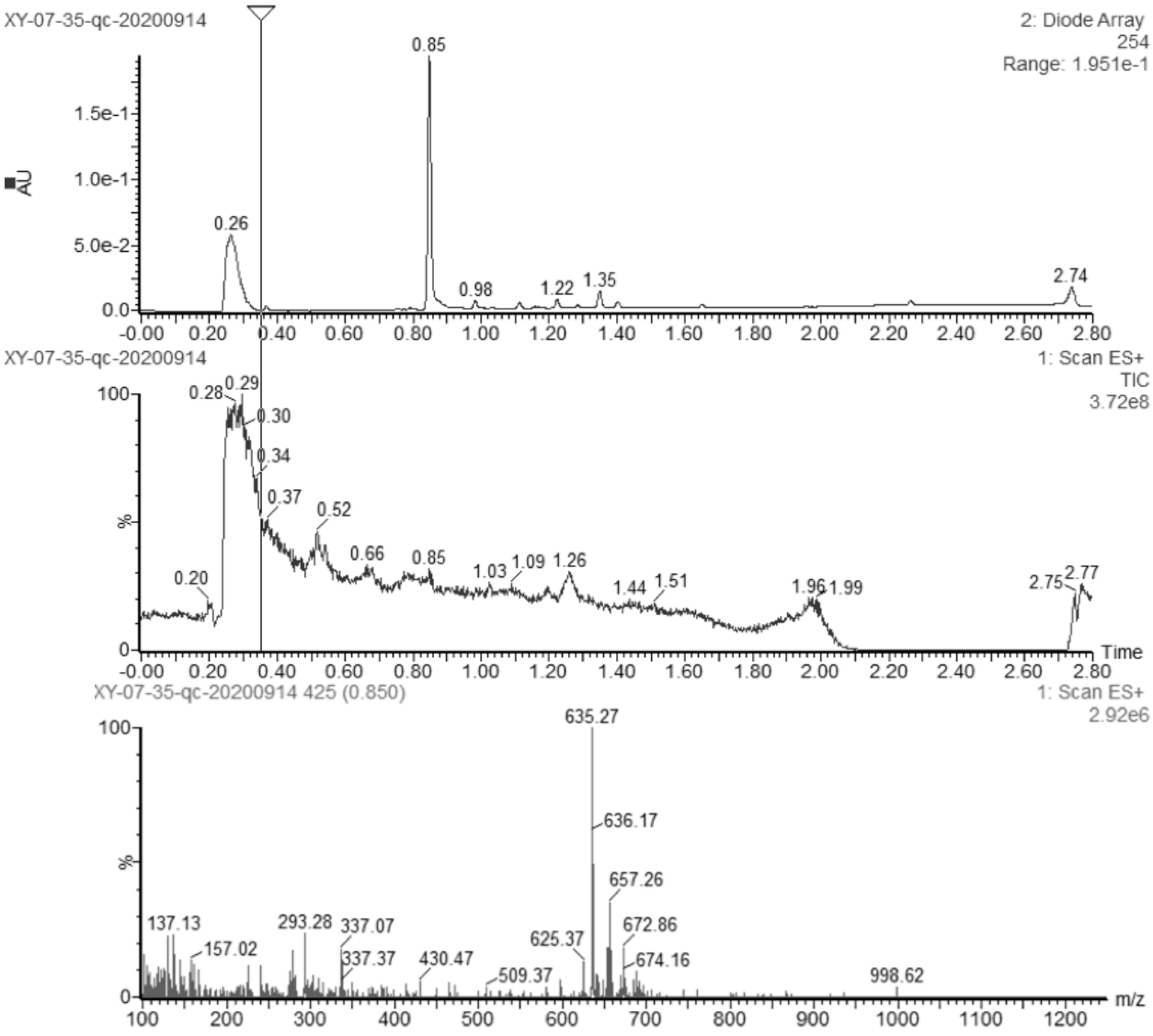

R2NH+



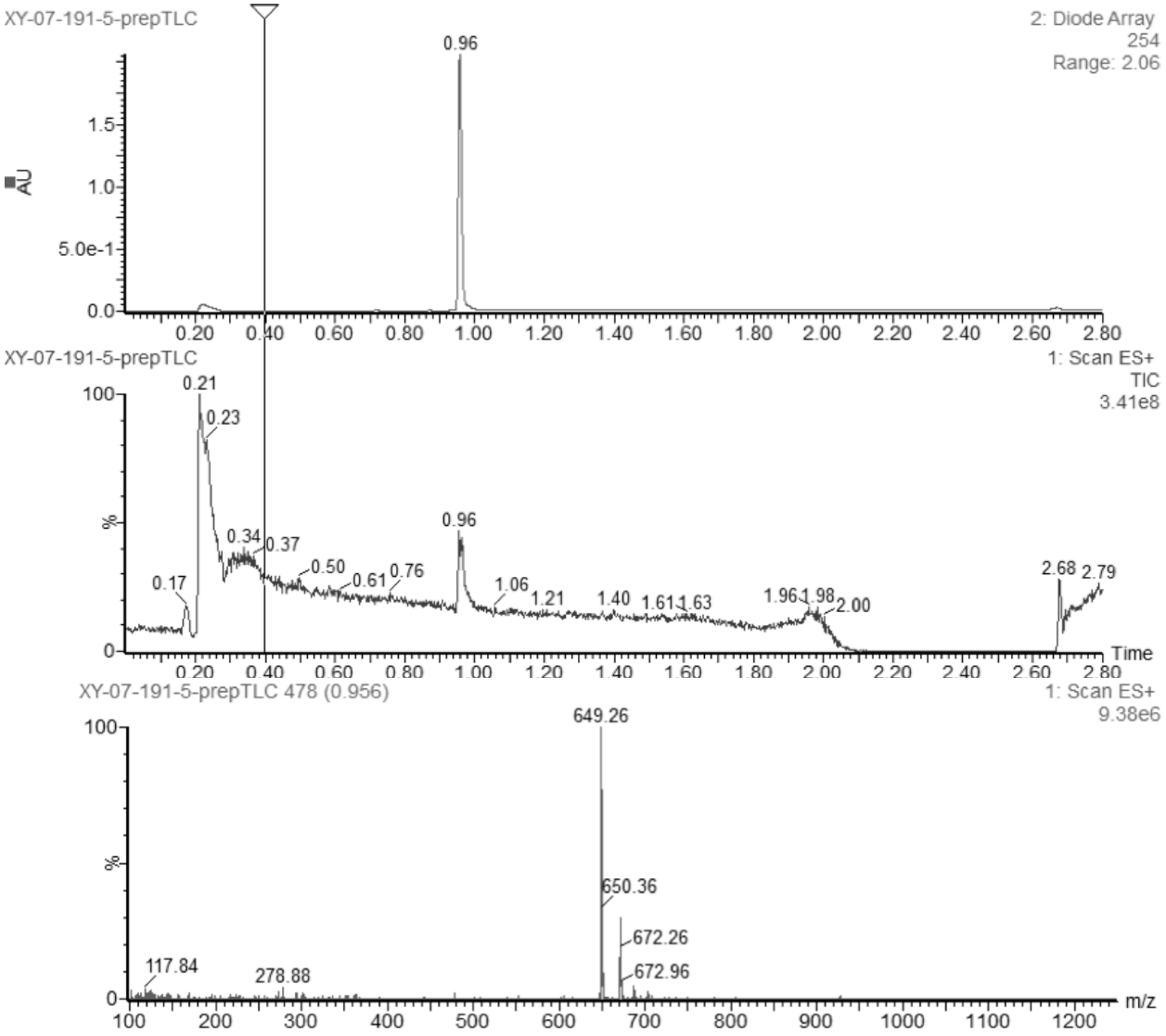

R3NH+
1.00
1.12
1.06
2.37
0.88
1.98
2.13
1.16
0.95
1.16
1.18
1.40
2.50
2.75
9.81
34.09
0.52
2.23
2.03
7.23
3.15
6.83
6.72

UPLC-MS spectra for final compounds

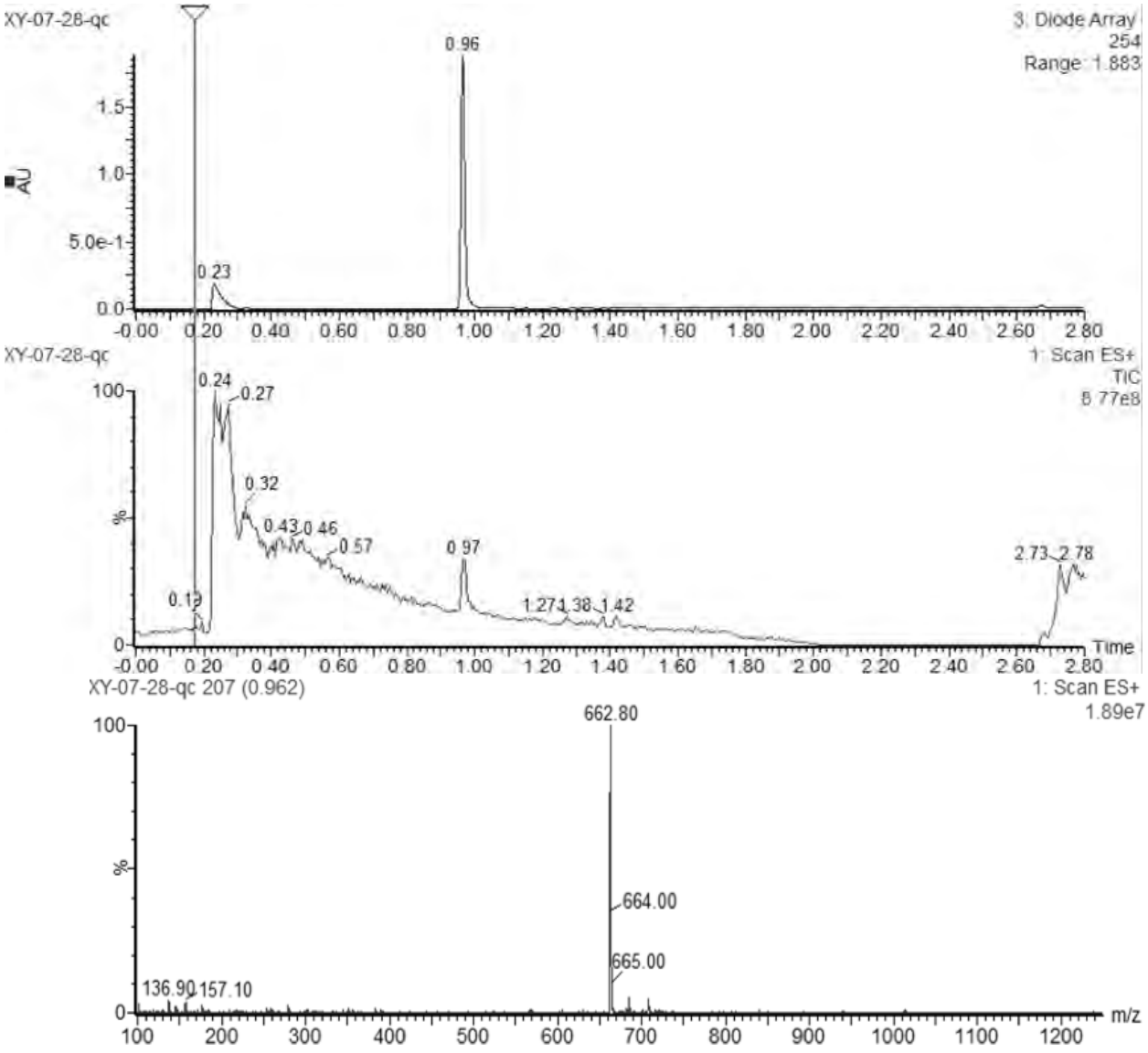
XY-07-035



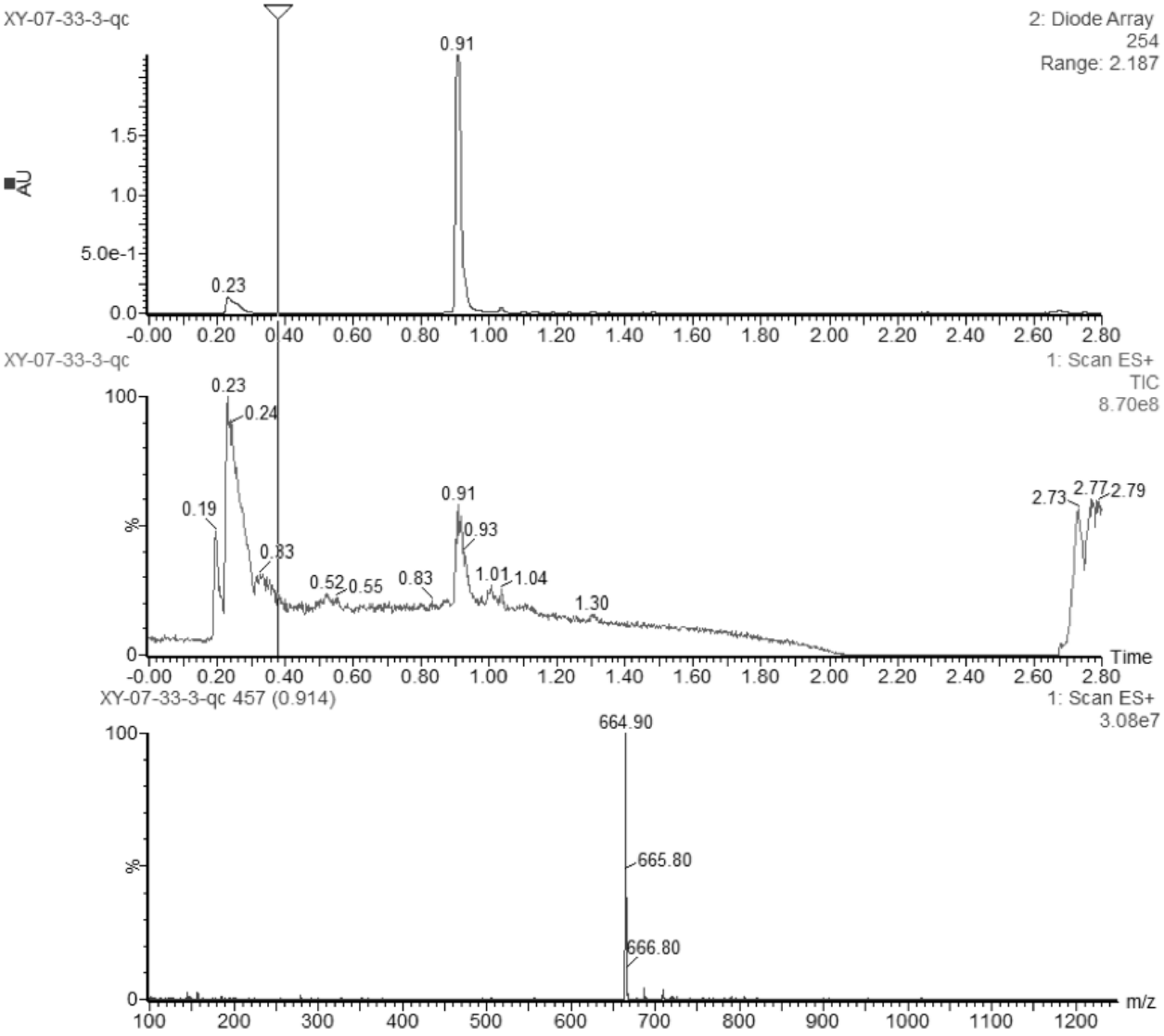
XY-07-191


XY-07-191-5-prepTLC
2: Diode Array
254
Range: 2.06
0.96
AU
XY-07-191-5-prepTLC
1: Scan ES+
TIC
3.41e8
0.21
0.23
0.34
0.37
0.50
0.61
0.76
0.96
1.06
1.21
1.40
1.61
1.63
1.96
1.98
2.00
2.68
2.79
0.17
%
Time
XY-07-191-5-prepTLC 478 (0.956)
1: Scan ES+
9.38e6
649.26
650.36
672.26
672.96
117.84
278.88
m/z

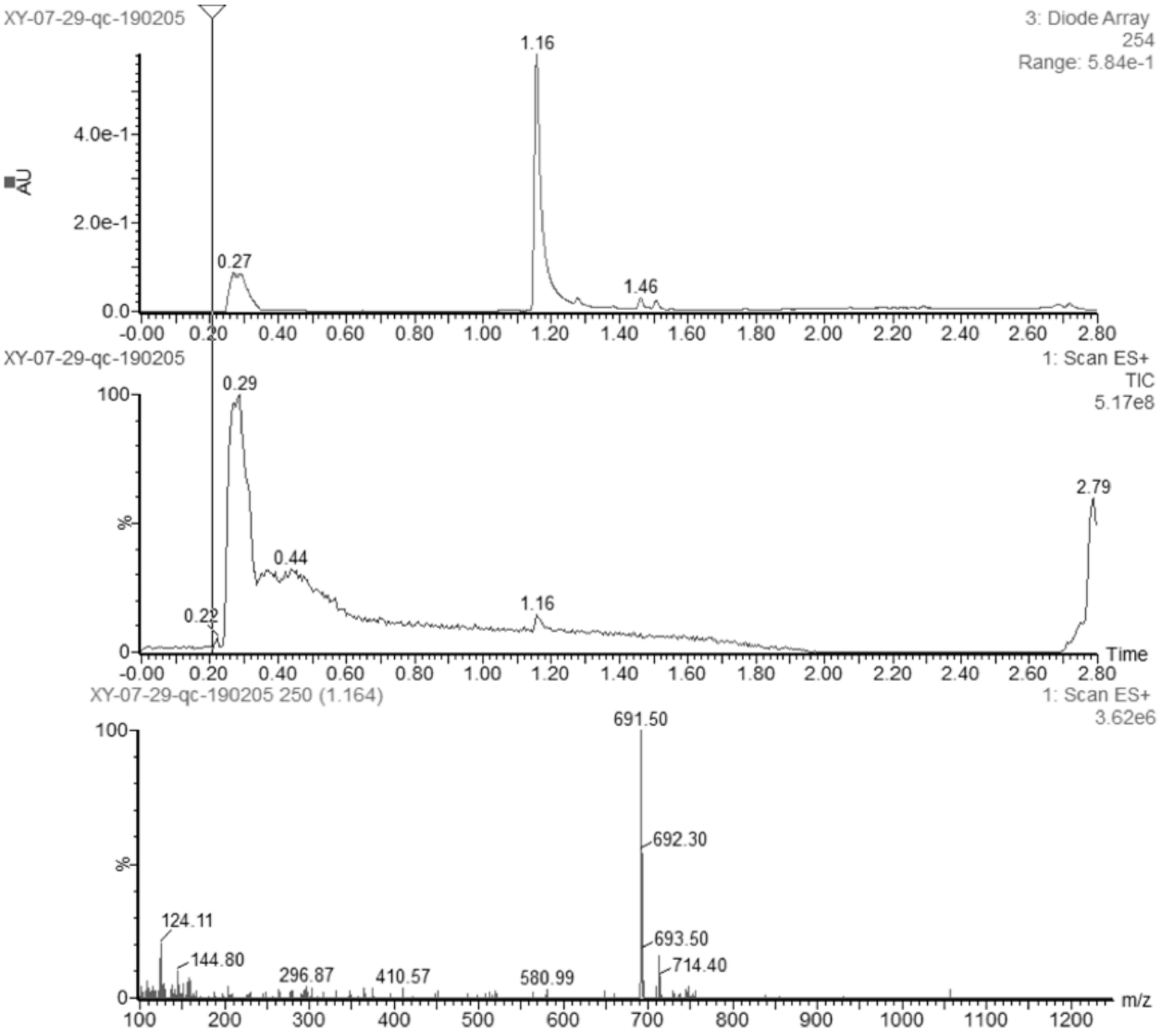
XY-07-028


XY-07-28-qc
3: Diode Array
254
Range: 1.883
AU
0.96
0.23
XY-07-28-qc
1: Scan ES+
TIC
5.77e8
%
0.24
0.27
0.32
0.43
0.46
0.57
0.97
0.13
1.27
1.38
1.42
2.73
2.78
Time
XY-07-28-qc 207 (0.962)
1: Scan ES+
1.89e7
662.80
664.00
665.00
136.90
157.10
m/z

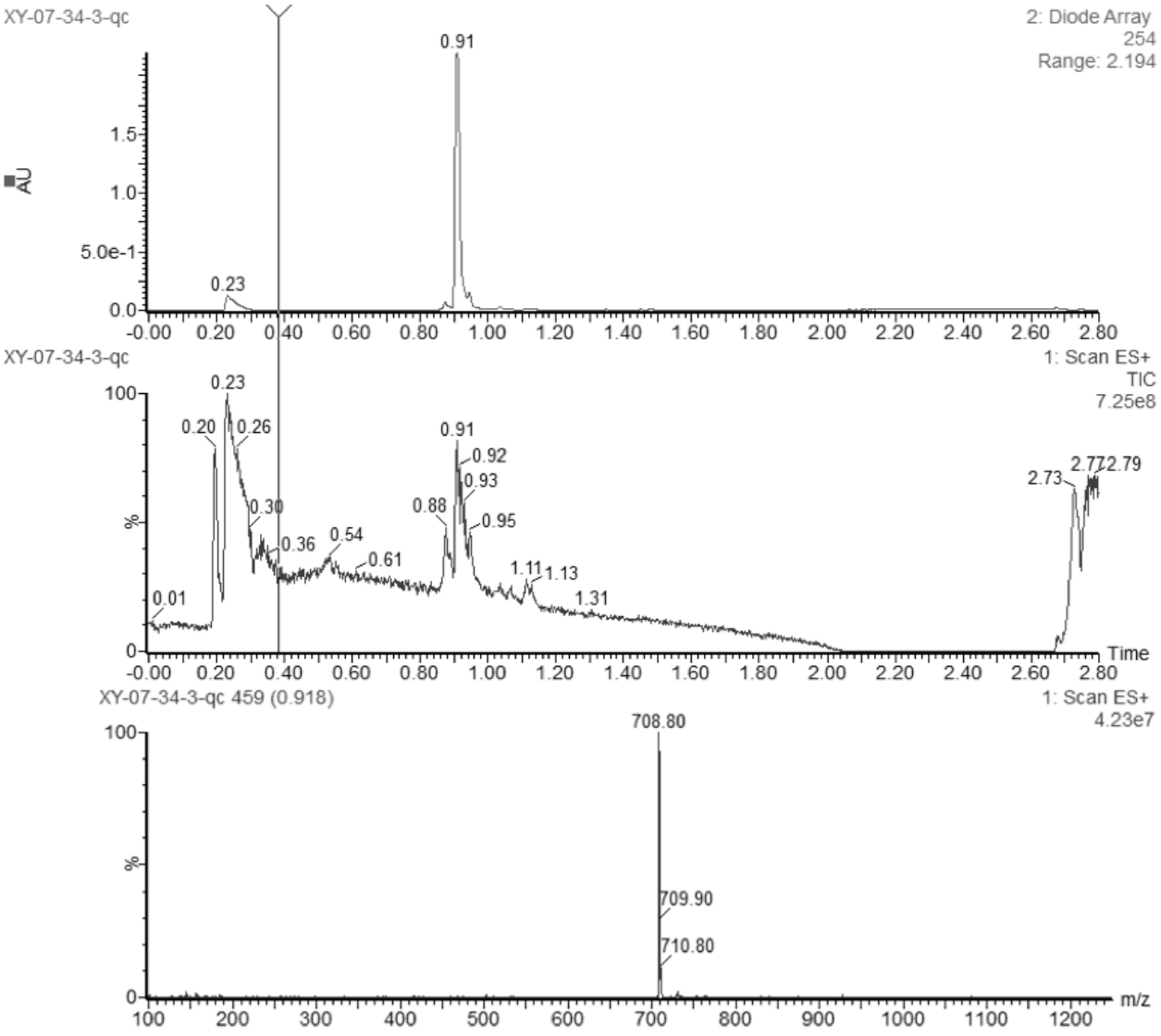
XY-07-033


XY-07-33-3-qc
2: Diode Array
254
Range: 2.187
AU
0.91
0.23
XY-07-33-3-qc
1: Scan ES+
TIC
8.70e8
%
0.23
0.24
0.19
0.91
0.93
0.83
0.52
0.55
0.83
1.01
1.04
1.30
2.73
2.77
2.79
Time
XY-07-33-3-qc 457 (0.914)
1: Scan ES+
3.08e7
664.90
665.80
666.80
m/z

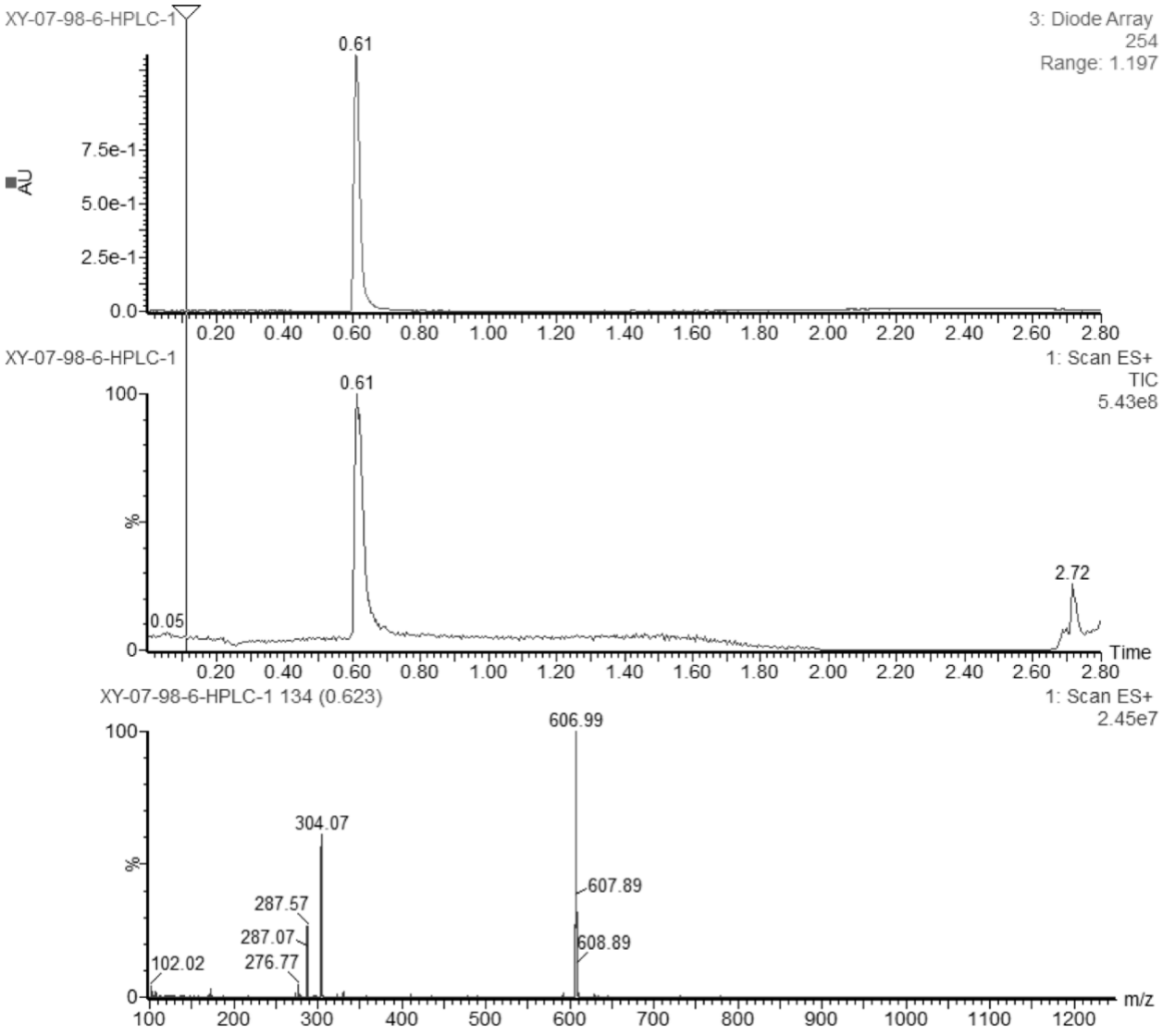
XY-07-029


XY-07-29-qc-190205
3: Diode Array
254
Range: 5.84e-1
1.16
4.0e-1
2.0e-1
AU
0.27
1.46
0.0
-0.00 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
XY-07-29-qc-190205
1: Scan ES+
TIC
5.17e8
0.29
100
%
2.79
0.44
1.16
0.22
0
Time
-0.00 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
XY-07-29-qc-190205 250 (1.164)
1: Scan ES+
3.62e6
691.50
100
692.30
%
124.11
693.50
144.80
714.40
296.87
410.57
580.99
0
m/z
100 200 300 400 500 600 700 800 900 1000 1100 1200

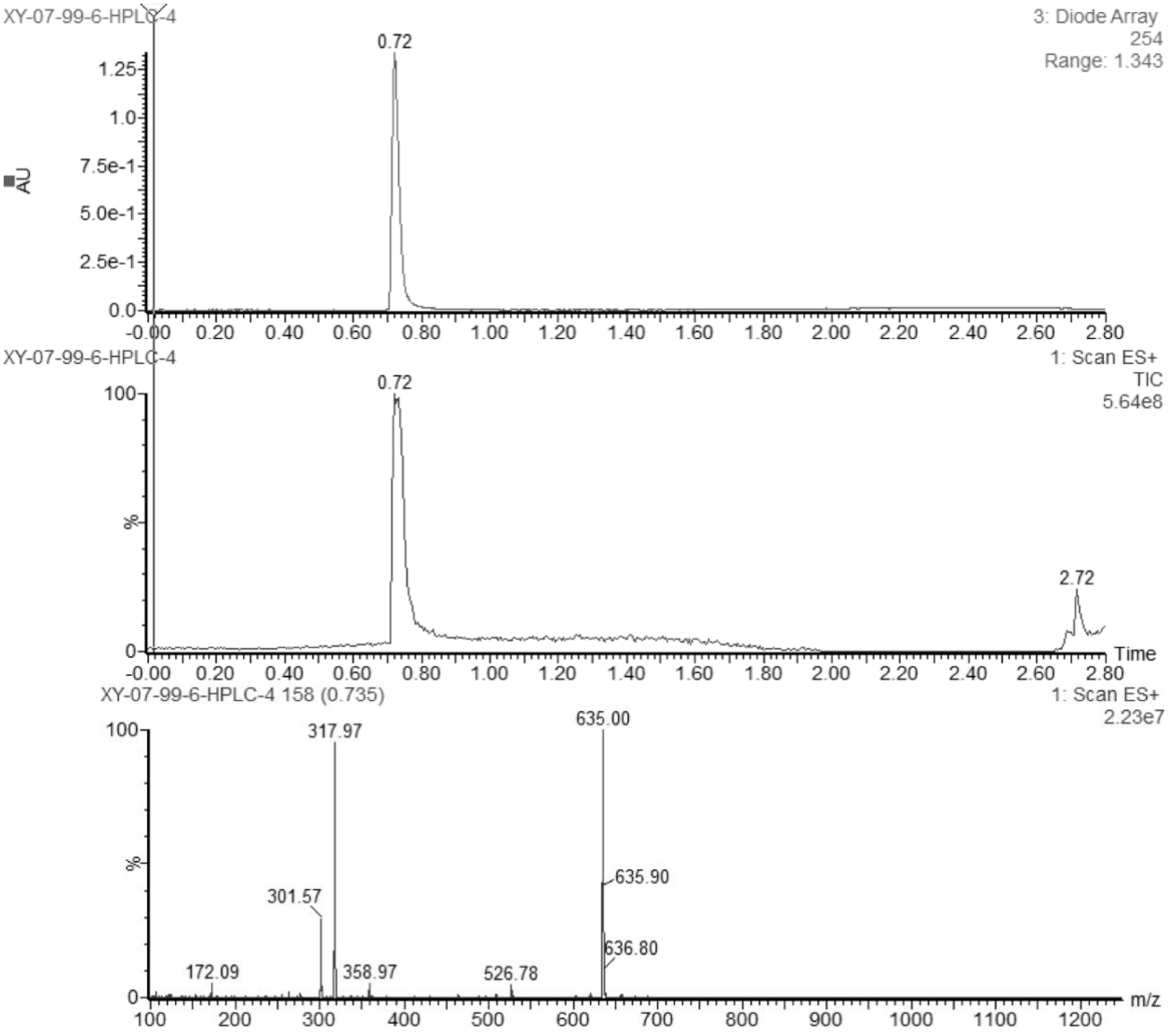
XY-07-034


XY-07-34-3-qc
2: Diode Array
254
Range: 2.194
AU
0.91
0.23
XY-07-34-3-qc
1: Scan ES+
TIC
7.25e8
%
0.23
0.20
0.26
0.30
0.36
0.54
0.61
0.91
0.92
0.93
0.88
0.95
1.11
1.13
1.31
0.01
2.73
2.77
2.79
Time
XY-07-34-3-qc 459 (0.918)
1: Scan ES+
4.23e7
708.80
709.90
710.80
m/z

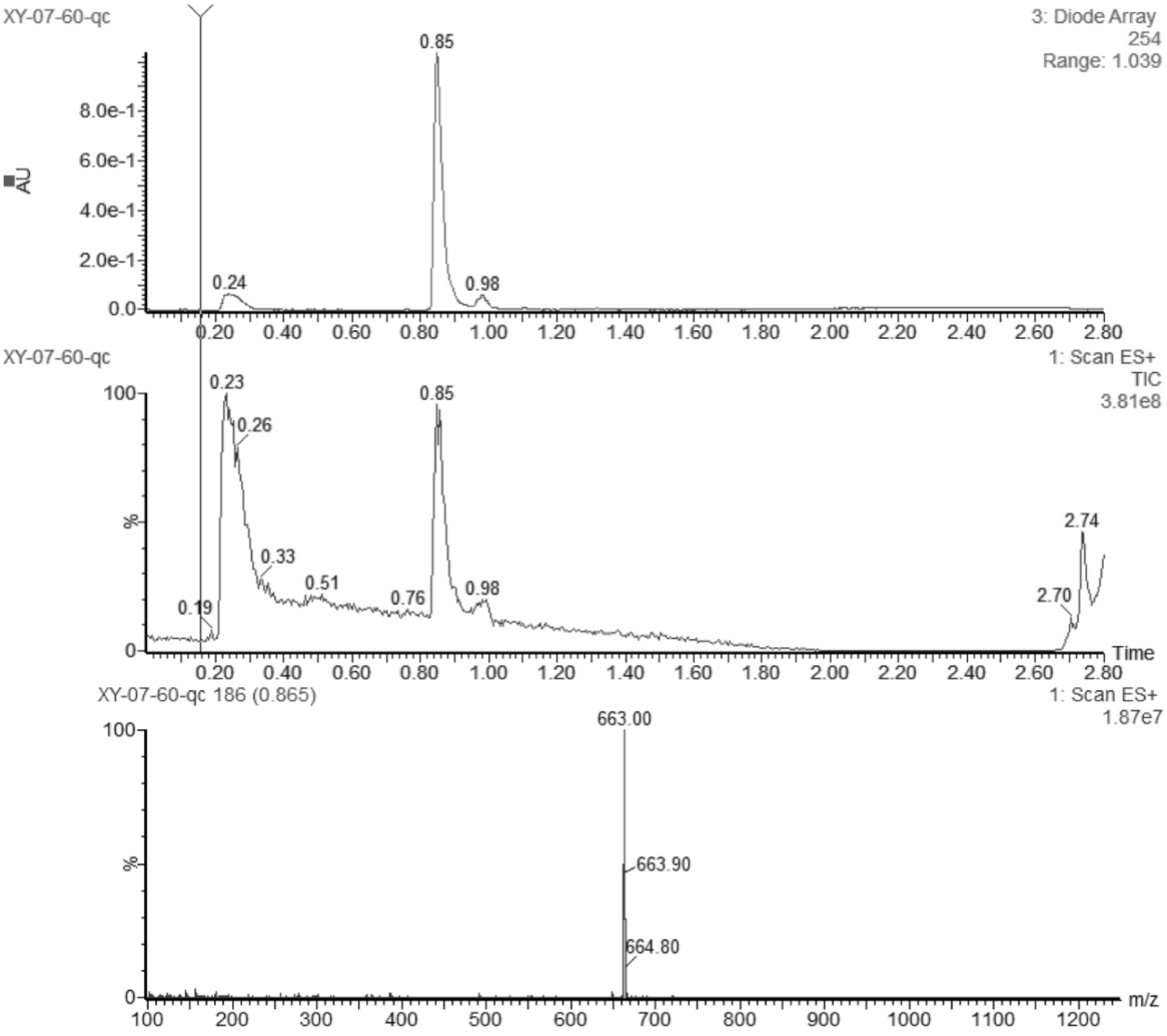
XY-07-098


XY-07-98-6-HPLC-1
3: Diode Array
254
Range: 1.197
0.61
AU
7.5e-1
5.0e-1
2.5e-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
XY-07-98-6-HPLC-1
1: Scan ES+
TIC
5.43e8
0.61
100
%
2.72
0.05
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
XY-07-98-6-HPLC-1 134 (0.623)
1: Scan ES+
2.45e7
606.99
100
304.07
%
607.89
287.57
287.07
608.89
276.77
102.02
0
m/z
100 200 300 400 500 600 700 800 900 1000 1100 1200

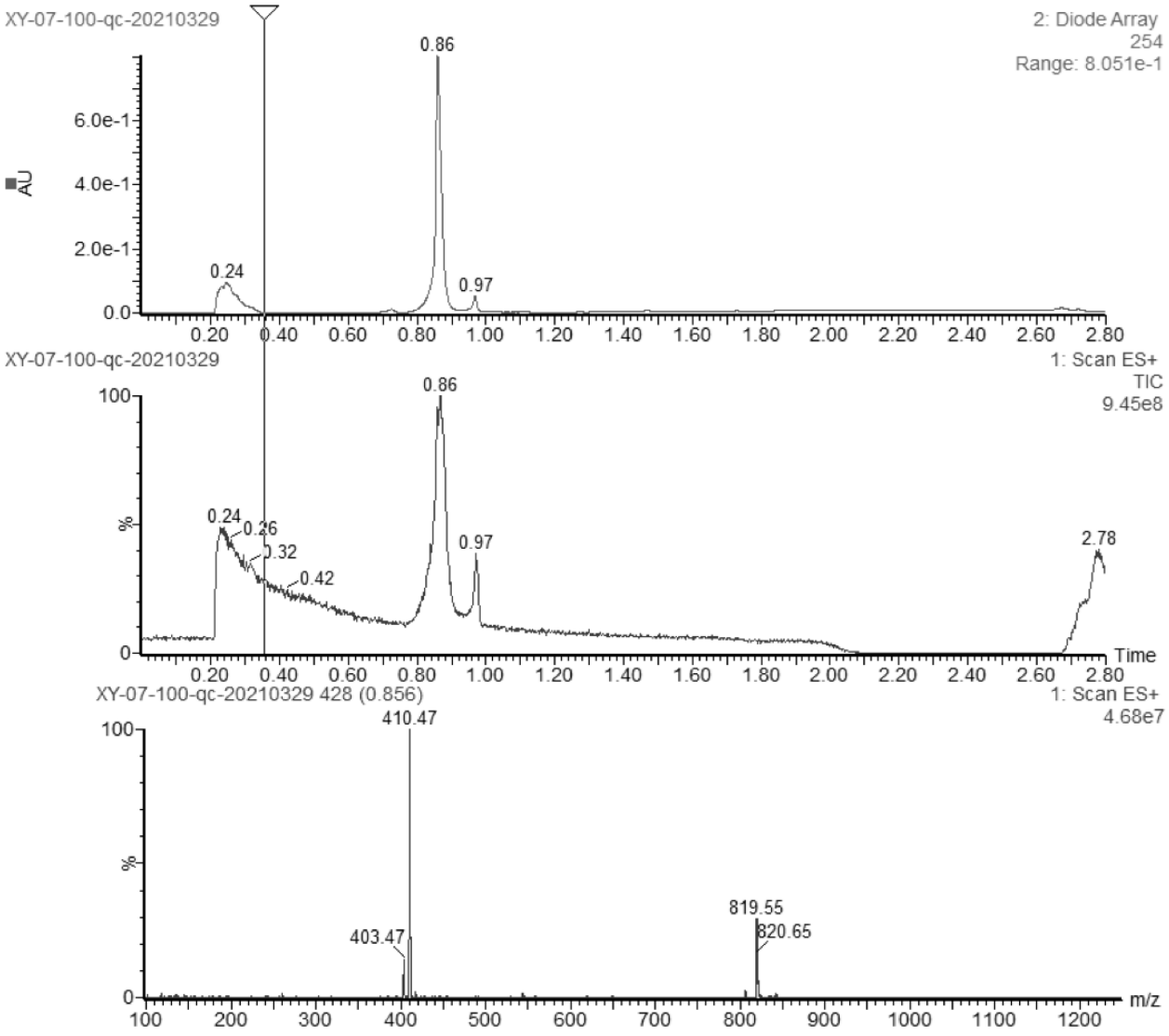
XY-07-099


XY-07-99-6-HPLC-4
3: Diode Array
254
Range: 1.343
0.72
AU
1.25
1.0
7.5e-1
5.0e-1
2.5e-1
0.0
-0.00 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
XY-07-99-6-HPLC-4
1: Scan ES+
TIC
5.64e8
0.72
100
%
2.72
0
Time
-0.00 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
XY-07-99-6-HPLC-4 158 (0.735)
1: Scan ES+
2.23e7
100
317.97
635.00
%
635.90
301.57
636.80
172.09
358.97
526.78
0
m/z
100 200 300 400 500 600 700 800 900 1000 1100 1200

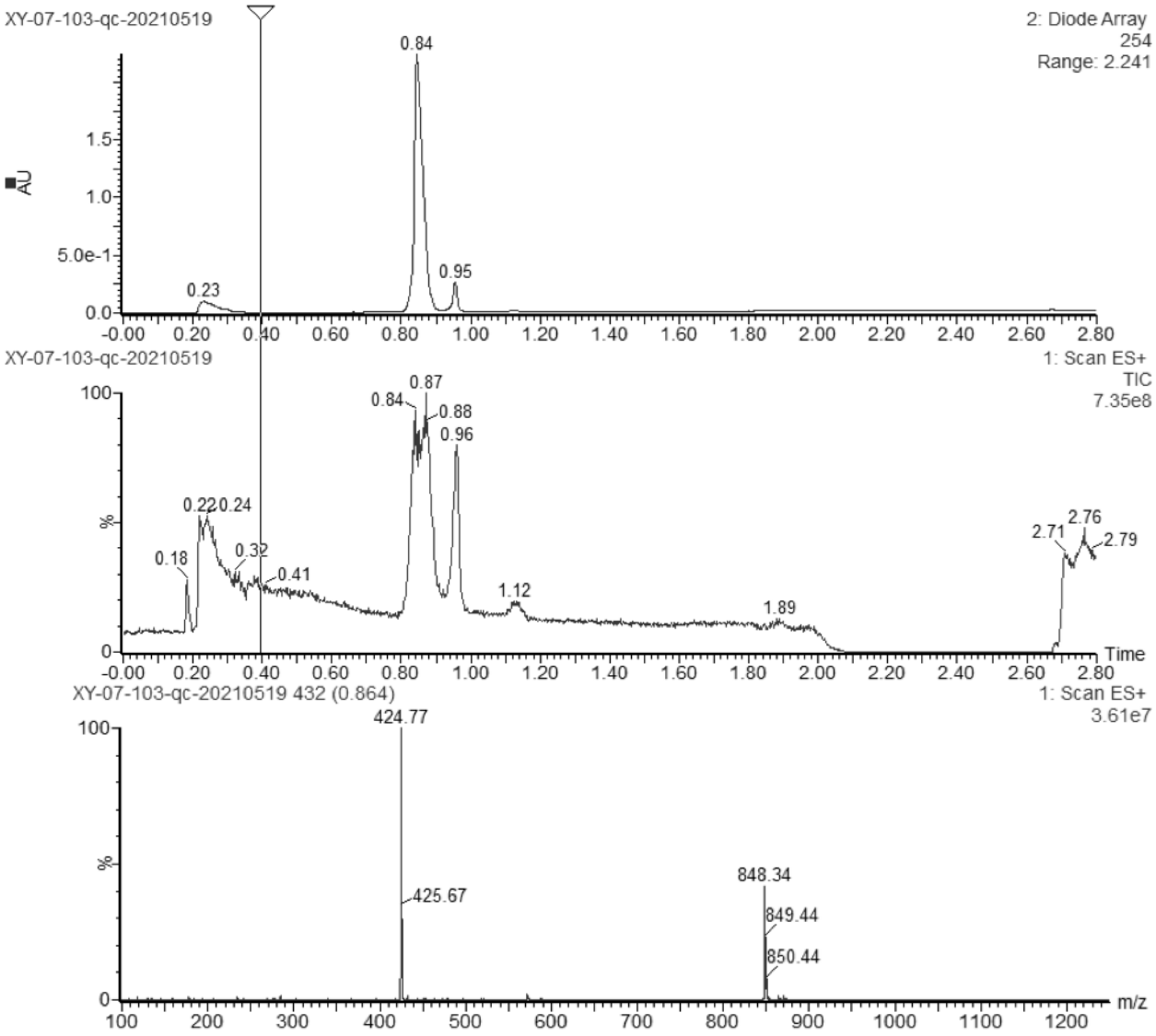
XY-07-060


XY-07-60-qc
3: Diode Array
254
Range: 1.039
AU
0.85
0.24
0.98
XY-07-60-qc
1: Scan ES+
TIC
3.81e8
%
0.23
0.26
0.85
0.33
0.51
0.19
0.76
0.98
2.74
2.70
Time
XY-07-60-qc 186 (0.865)
1: Scan ES+
1.87e7
663.00
663.90
664.80
m/z

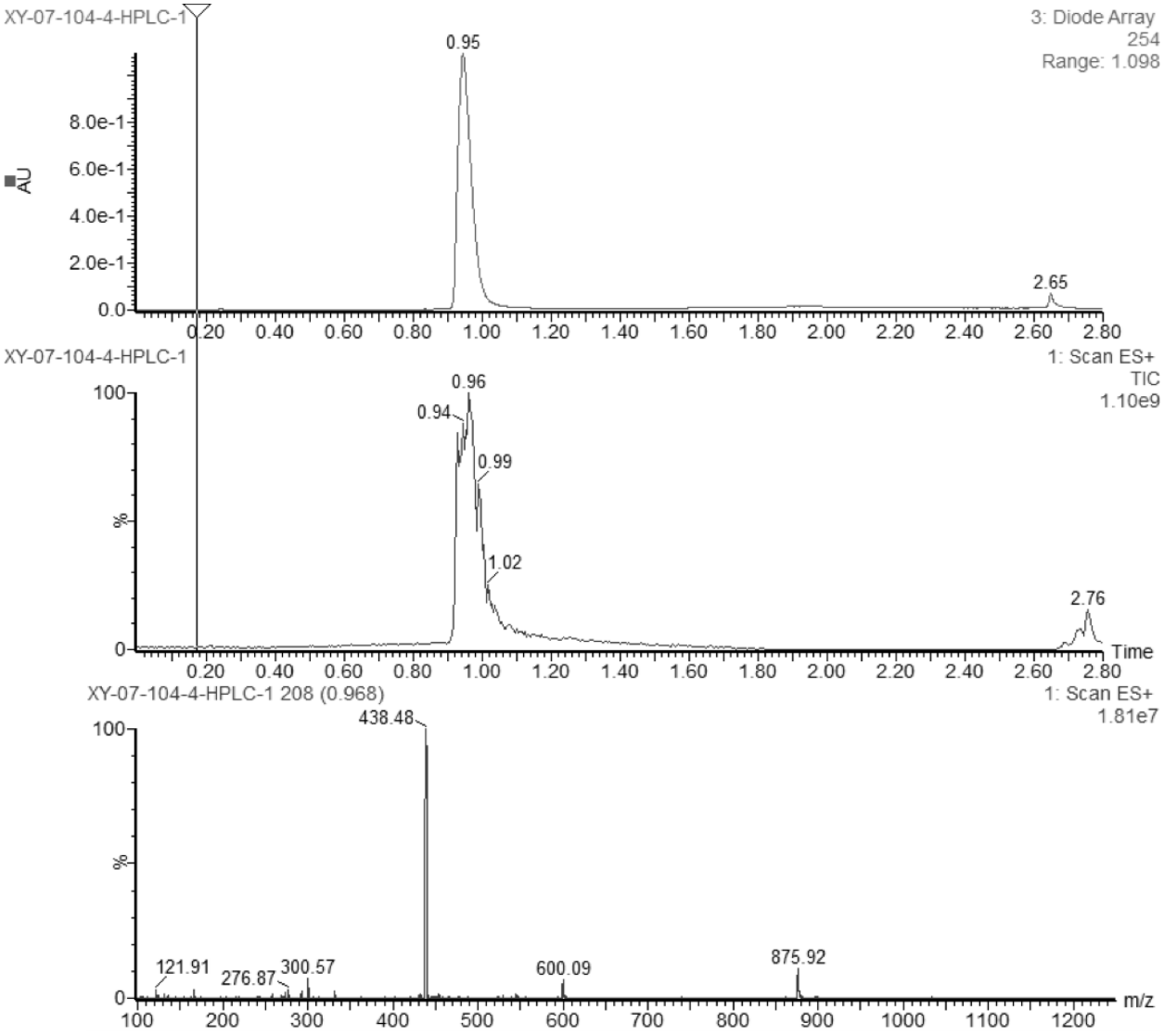
XY-07-100


XY-07-100-qc-20210329
2: Diode Array
254
Range: 8.051e-1
AU
0.86
0.24
0.97
XY-07-100-qc-20210329
1: Scan ES+
TIC
9.45e8
%
0.86
0.24
0.26
0.32
0.42
0.97
2.78
Time
XY-07-100-qc-20210329 428 (0.856)
1: Scan ES+
4.68e7
410.47
403.47
819.55
820.65
m/z

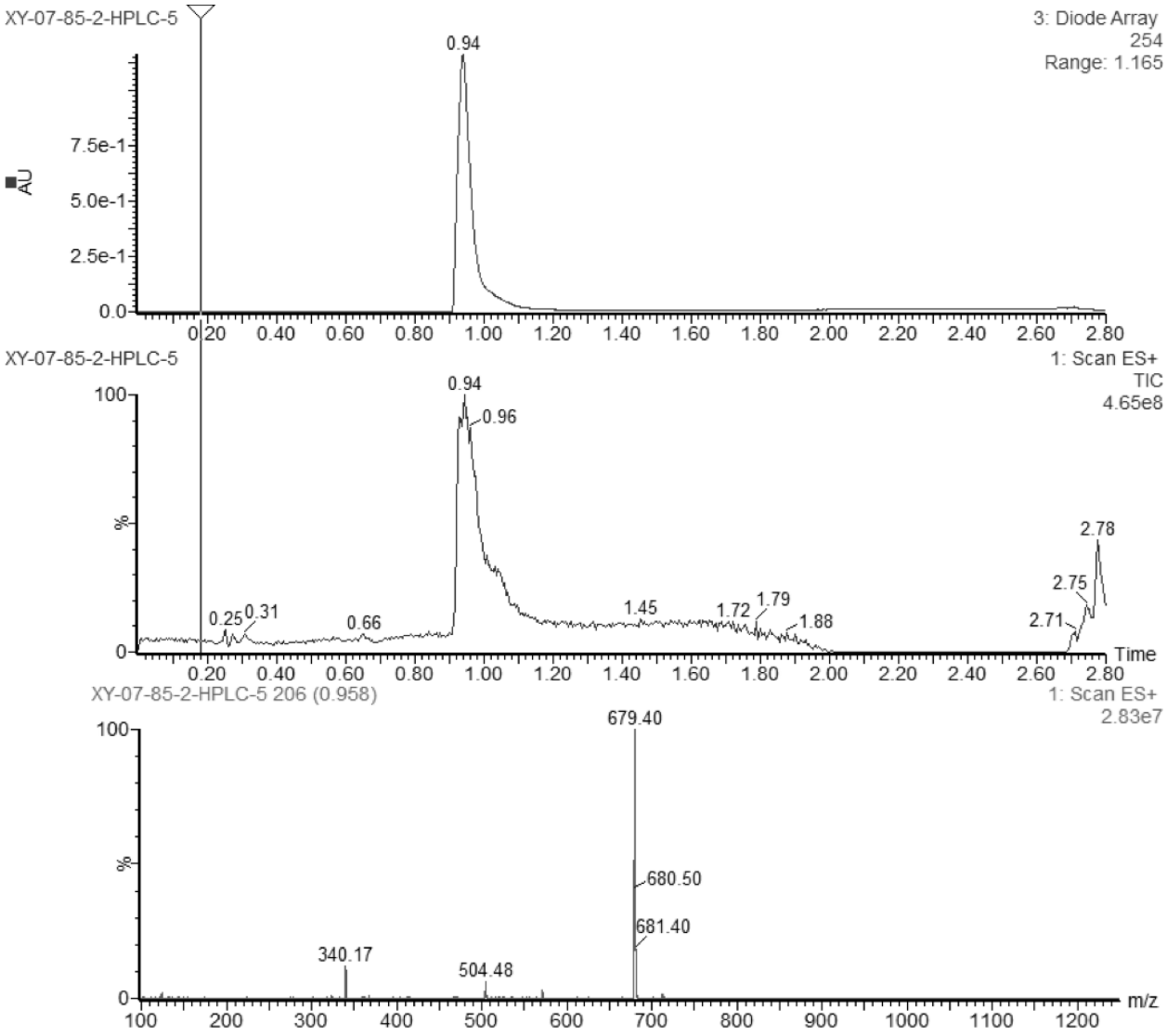
XY-07-103


XY-07-103-qc-20210519
2: Diode Array
254
Range: 2.241
AU
0.84
0.95
0.23
XY-07-103-qc-20210519
1: Scan ES+
TIC
7.35e8
%
0.87
0.84
0.88
0.96
0.22
0.24
0.18
0.32
0.41
1.12
1.89
2.71
2.76
2.79
Time
XY-07-103-qc-20210519 432 (0.864)
1: Scan ES+
3.61e7
%
424.77
425.67
848.34
849.44
850.44
m/z

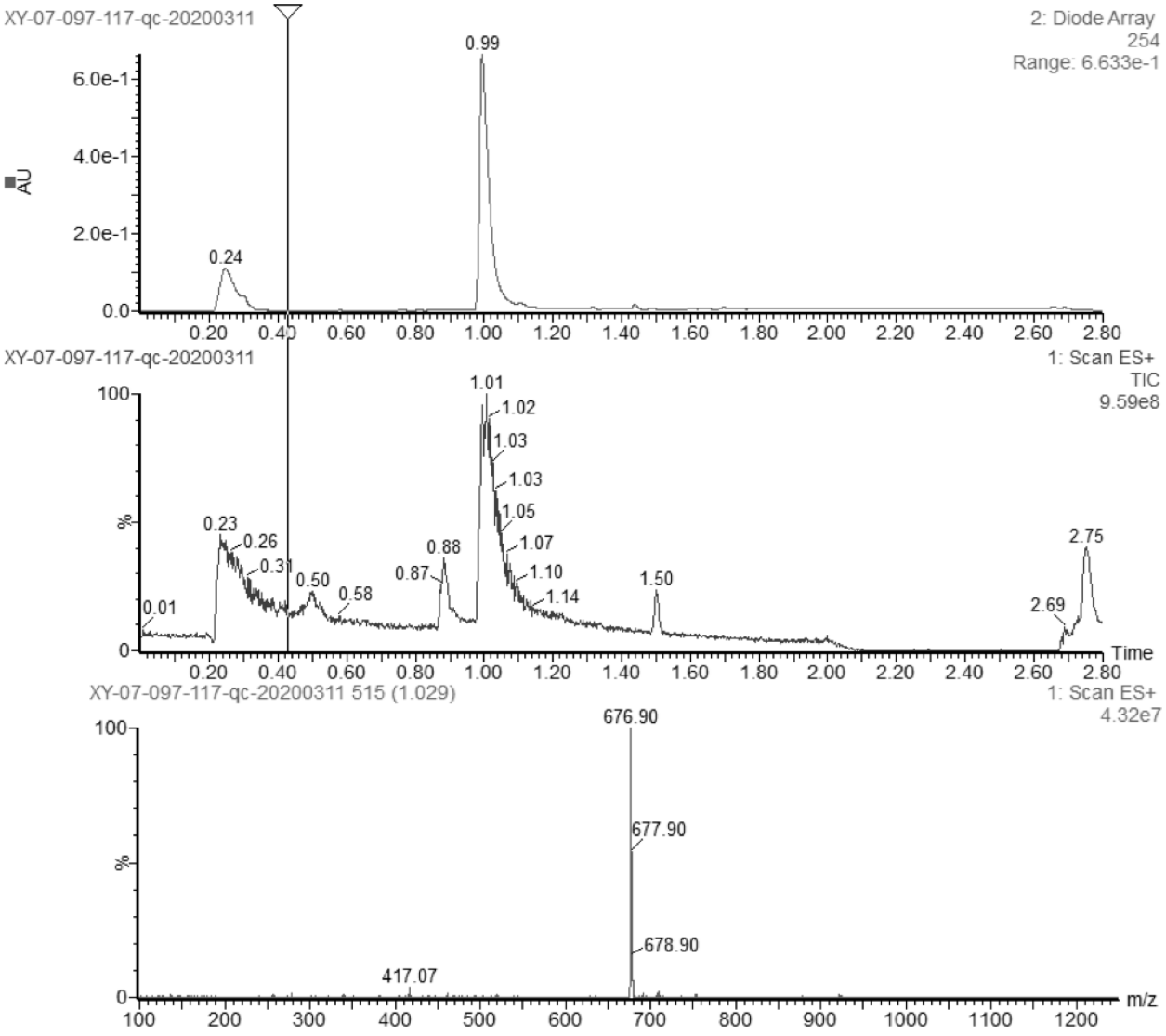
XY-07-104


XY-07-104-4-HPLC-1
3: Diode Array
254
Range: 1.098
0.95
2.65
AU
8.0e-1
6.0e-1
4.0e-1
2.0e-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
XY-07-104-4-HPLC-1
1: Scan ES+
TIC
1.10e9
0.96
0.94
0.99
1.02
2.76
100
%
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
XY-07-104-4-HPLC-1 208 (0.968)
1: Scan ES+
1.81e7
438.48
100
%
121.91
276.87
300.57
600.09
875.92
0
m/z
100 200 300 400 500 600 700 800 900 1000 1100 1200

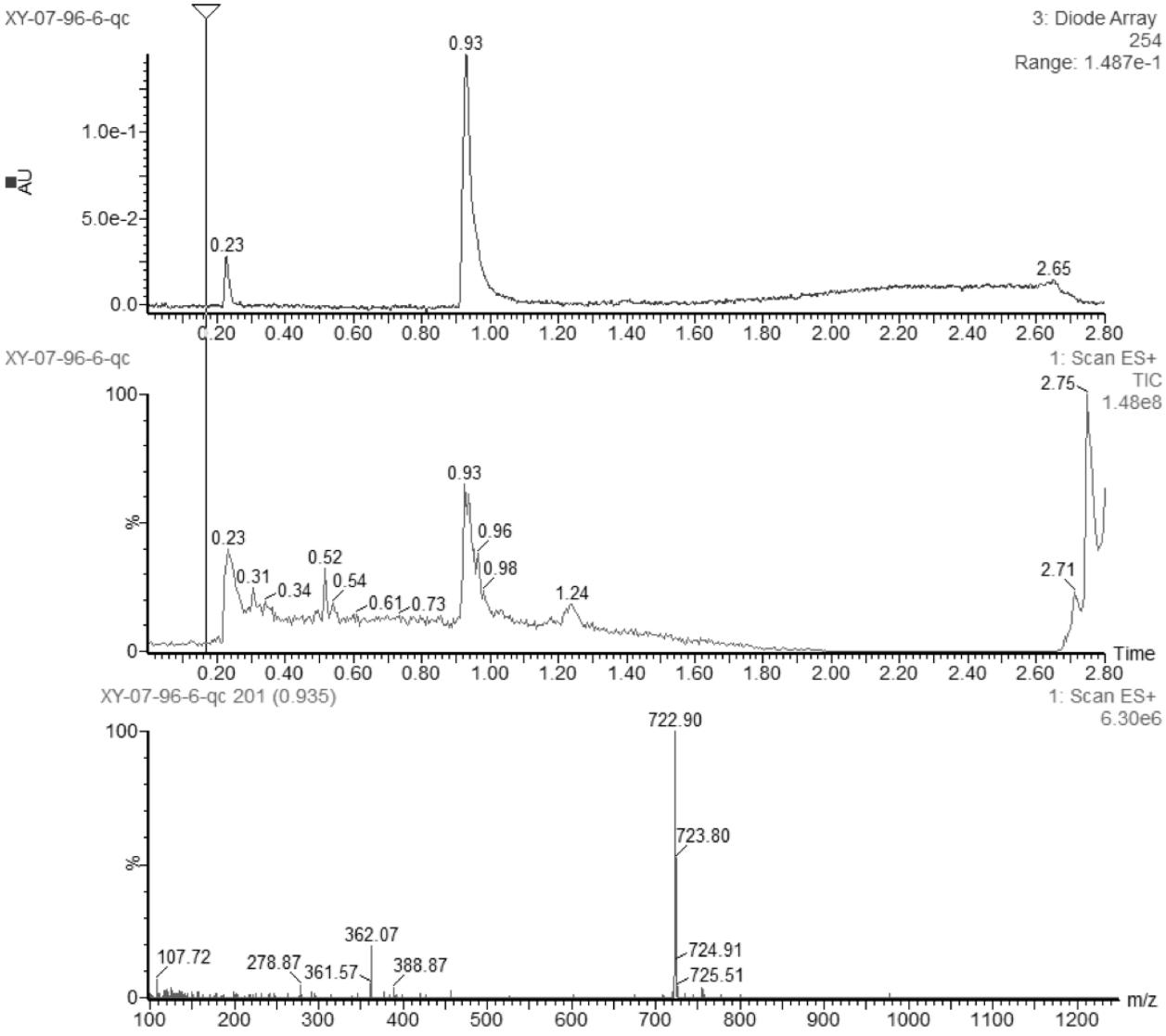
XY-07-085


XY-07-85-2-HPLC-5
3: Diode Array
254
Range: 1.165
0.94
AU
7.5e-1
5.0e-1
2.5e-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
XY-07-85-2-HPLC-5
1: Scan ES+
TIC
4.65e8
100
%
0
0.94
0.96
0.25
0.31
0.66
1.45
1.72
1.79
1.88
2.71
2.75
2.78
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
XY-07-85-2-HPLC-5 206 (0.958)
1: Scan ES+
2.83e7
100
%
0
679.40
680.50
681.40
340.17
504.48
m/z
100 200 300 400 500 600 700 800 900 1000 1100 1200

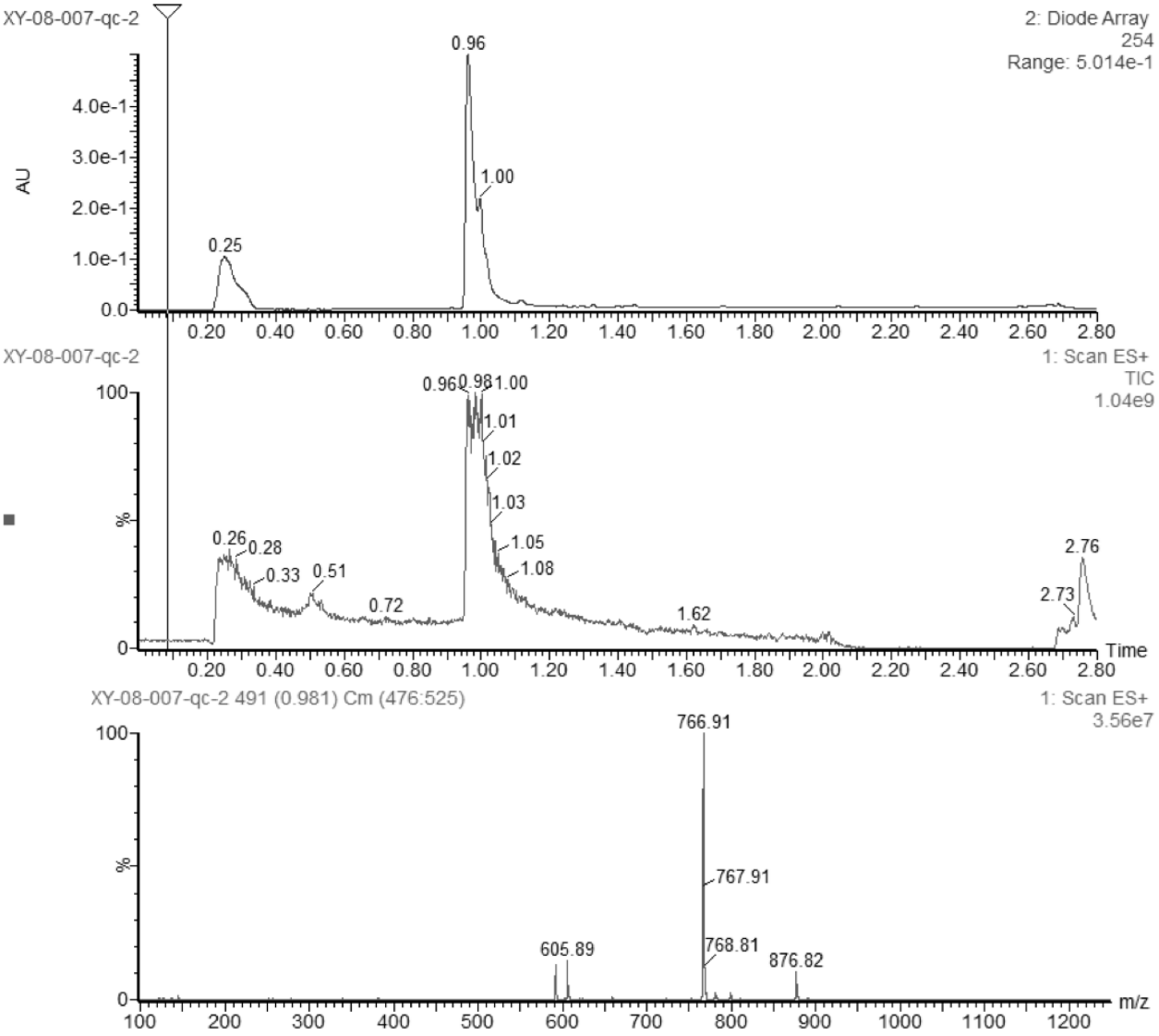
XY-07-097


XY-07-097-117-qc-20200311
2: Diode Array
254
Range: 6.633e-1
AU
0.99
0.24
XY-07-097-117-qc-20200311
1: Scan ES+
TIC
9.59e8
%
1.01
1.02
1.03
1.03
1.05
1.07
1.10
1.14
0.23
0.26
0.31
0.50
0.58
0.88
0.87
1.50
2.75
2.69
0.01
Time
XY-07-097-117-qc-20200311 515 (1.029)
1: Scan ES+
4.32e7
676.90
677.90
678.90
417.07
m/z

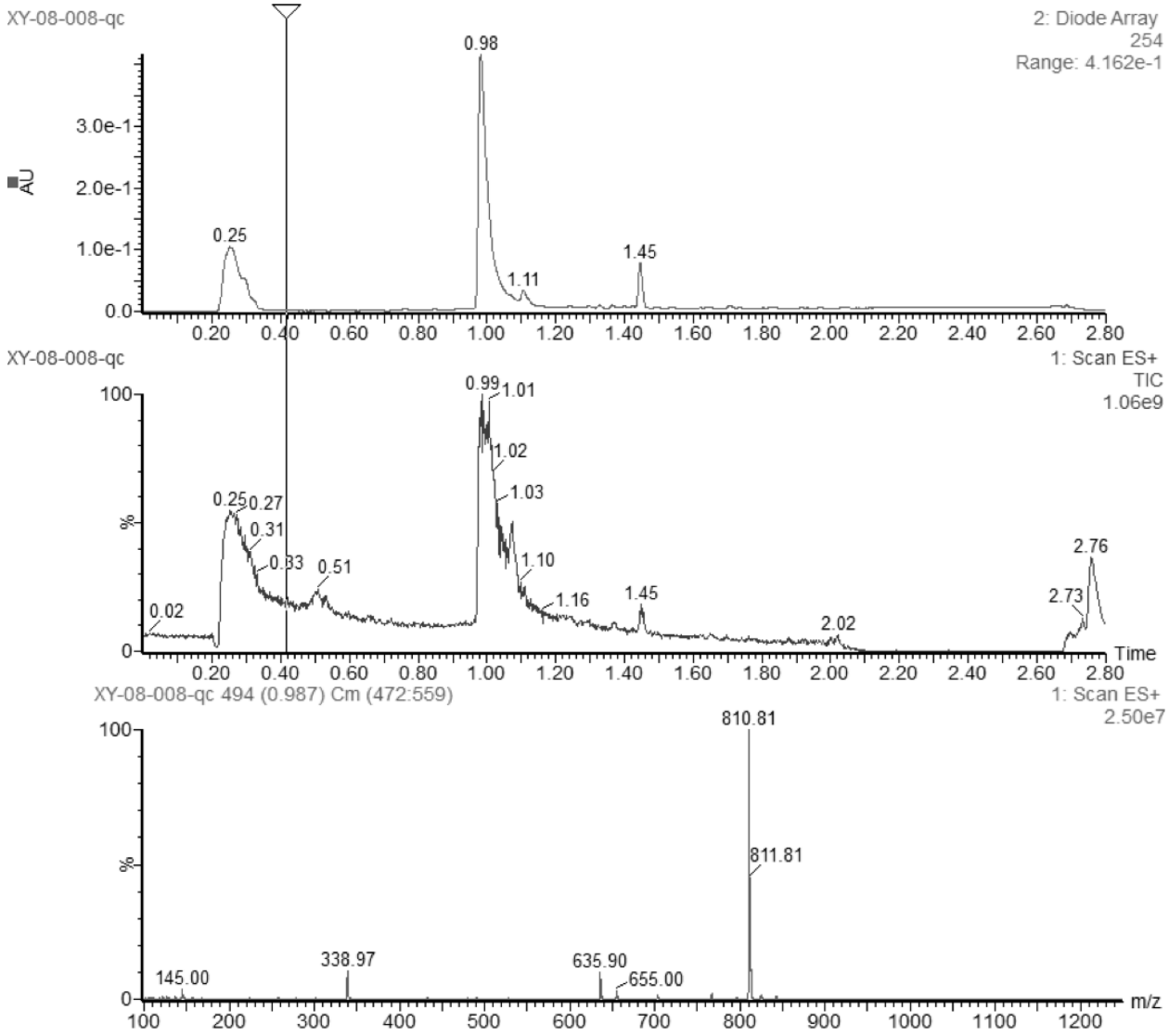
XY-07-096


XY-07-96-6-qc
3: Diode Array
254
Range: 1.487e-1
AU
1.0e-1
5.0e-2
0.0
0.23
0.93
2.65
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
XY-07-96-6-qc
1: Scan ES+
TIC
1.48e8
100
%
0
2.75
0.93
0.23
0.96
0.52
0.31
0.98
0.54
0.34
0.61
0.73
1.24
2.71
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
XY-07-96-6-qc 201 (0.935)
1: Scan ES+
6.30e6
100
%
0
722.90
723.80
362.07
107.72
278.87
361.57
388.87
724.91
725.51
m/z
100 200 300 400 500 600 700 800 900 1000 1100 1200

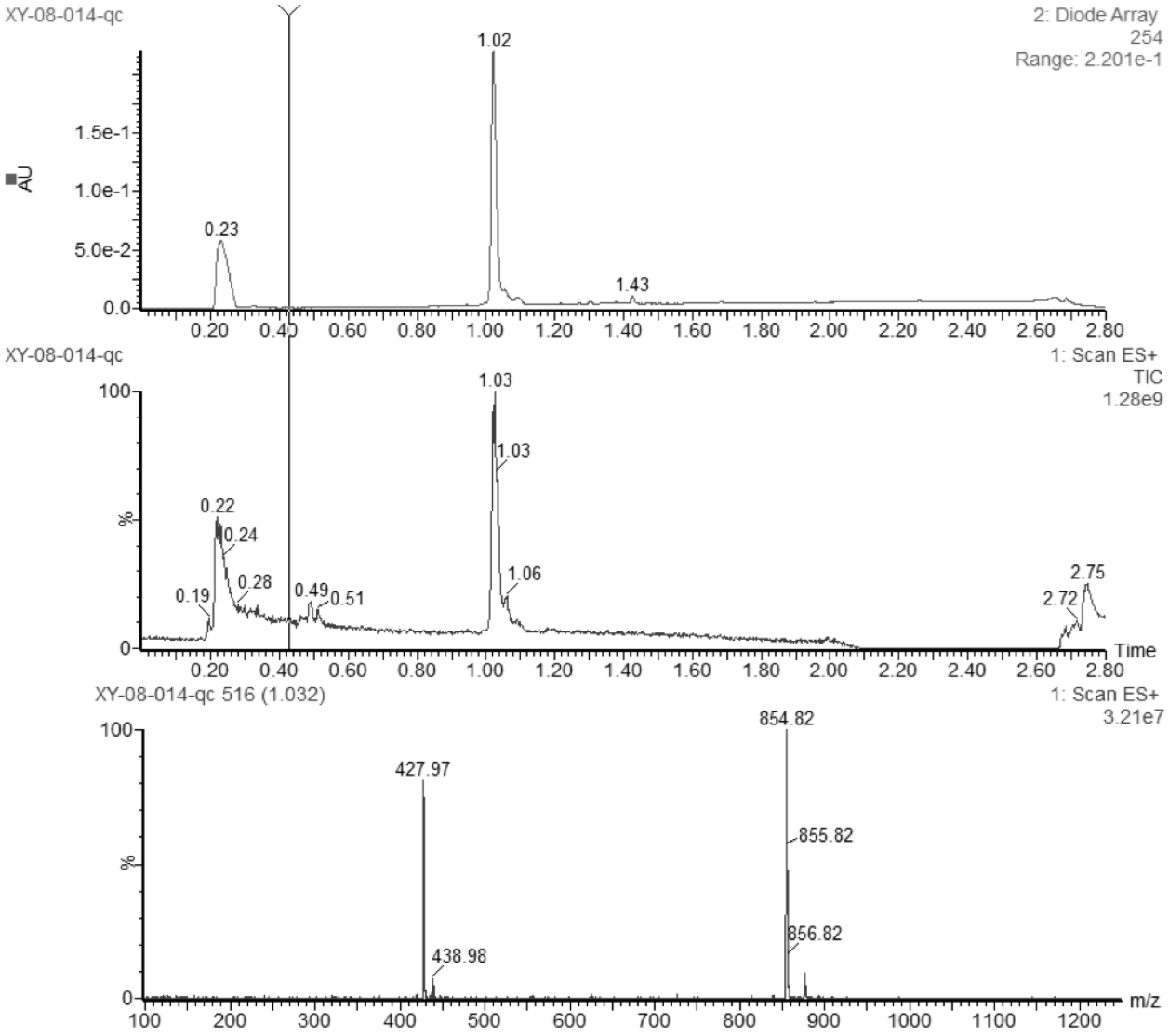
XY-08-007


XY-08-007-qc-2
2: Diode Array
254
Range: 5.014e-1
AU
0.96
1.00
0.25
XY-08-007-qc-2
1: Scan ES+
TIC
1.04e9
%
0.96
0.98
1.00
1.01
1.02
1.03
1.05
1.08
0.26
0.28
0.33
0.51
0.72
1.62
2.73
2.76
Time
XY-08-007-qc-2 491 (0.981) Cm (476:525)
1: Scan ES+
3.56e7
766.91
767.91
768.81
605.89
876.82
m/z

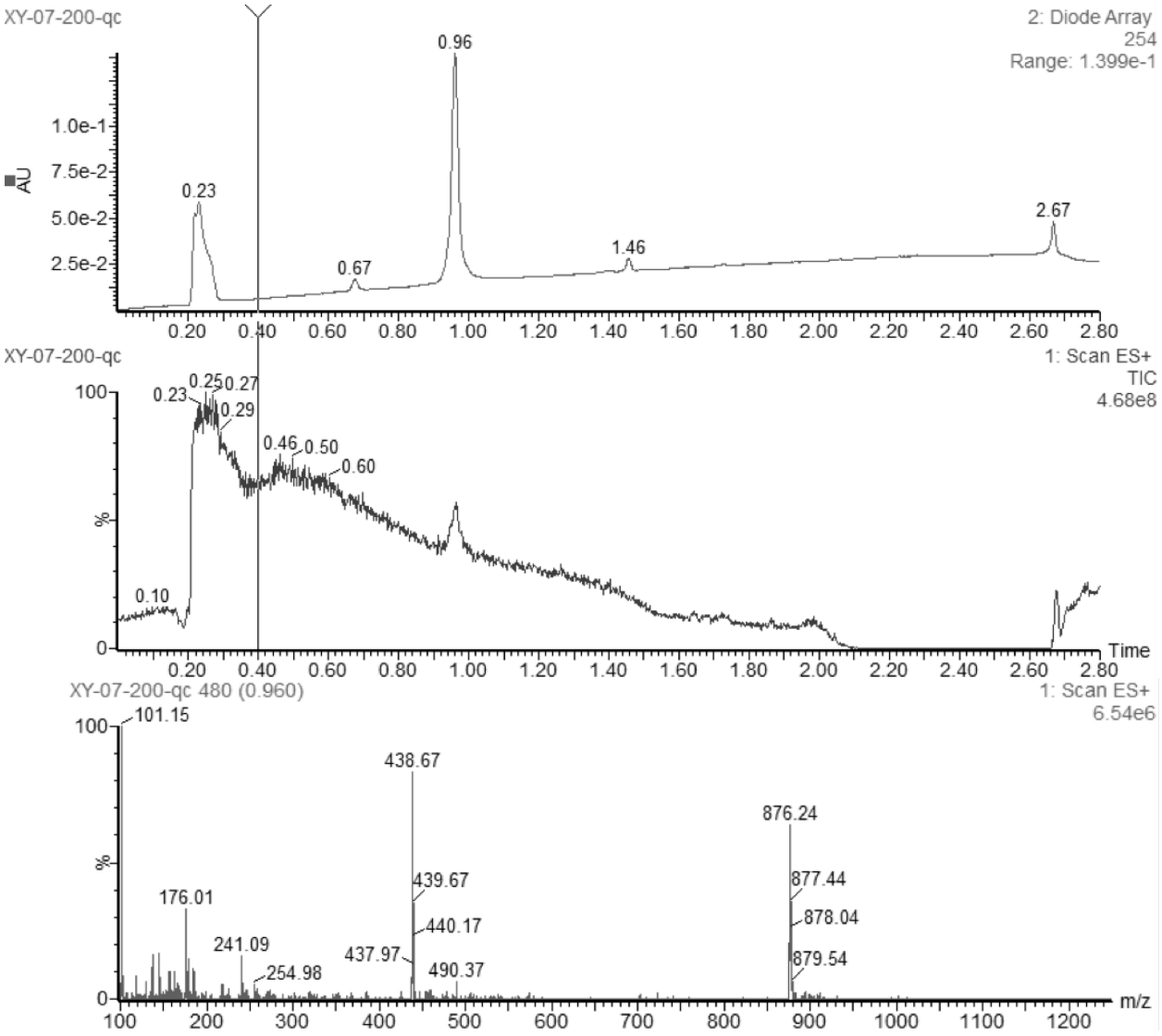
XY-08-008


XY-08-008-qc
2: Diode Array
254
Range: 4.162e-1
AU
0.98
0.25
1.45
1.11
XY-08-008-qc
1: Scan ES+
TIC
1.06e9
%
0.99
1.01
1.02
1.03
0.25
0.27
0.31
0.33
0.51
1.10
1.16
1.45
2.76
2.73
0.02
2.02
Time
XY-08-008-qc 494 (0.987) Cm (472:559)
1: Scan ES+
2.50e7
810.81
811.81
338.97
635.90
655.00
145.00
m/z

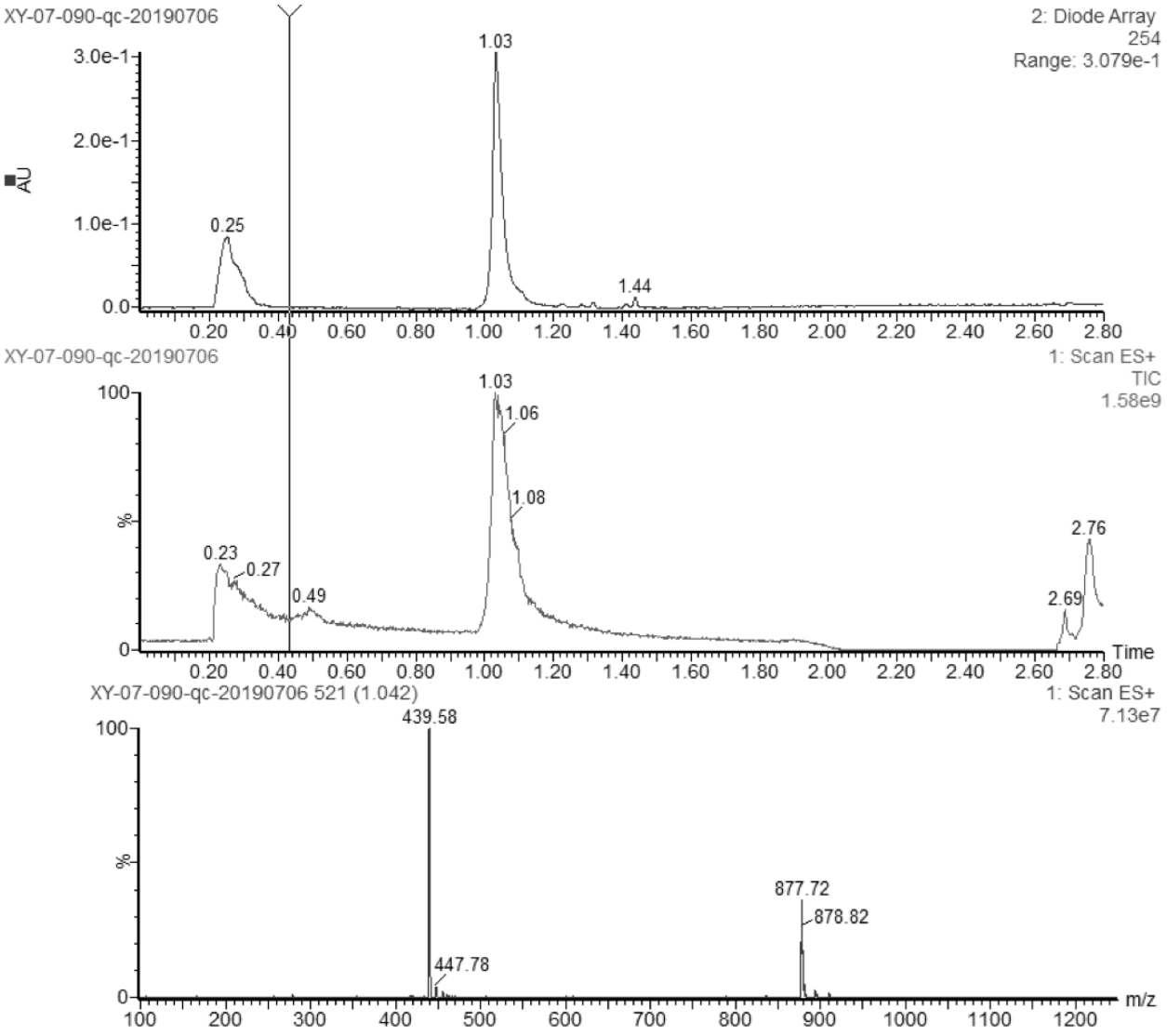
XY-08-014


XY-08-014-qc
2: Diode Array
254
Range: 2.201e-1
AU
1.02
0.23
1.43
XY-08-014-qc
1: Scan ES+
TIC
1.28e9
%
1.03
0.22
0.24
0.19
0.28
0.49
0.51
1.06
2.75
2.72
Time
XY-08-014-qc 516 (1.032)
1: Scan ES+
3.21e7
854.82
427.97
855.82
856.82
438.98
m/z

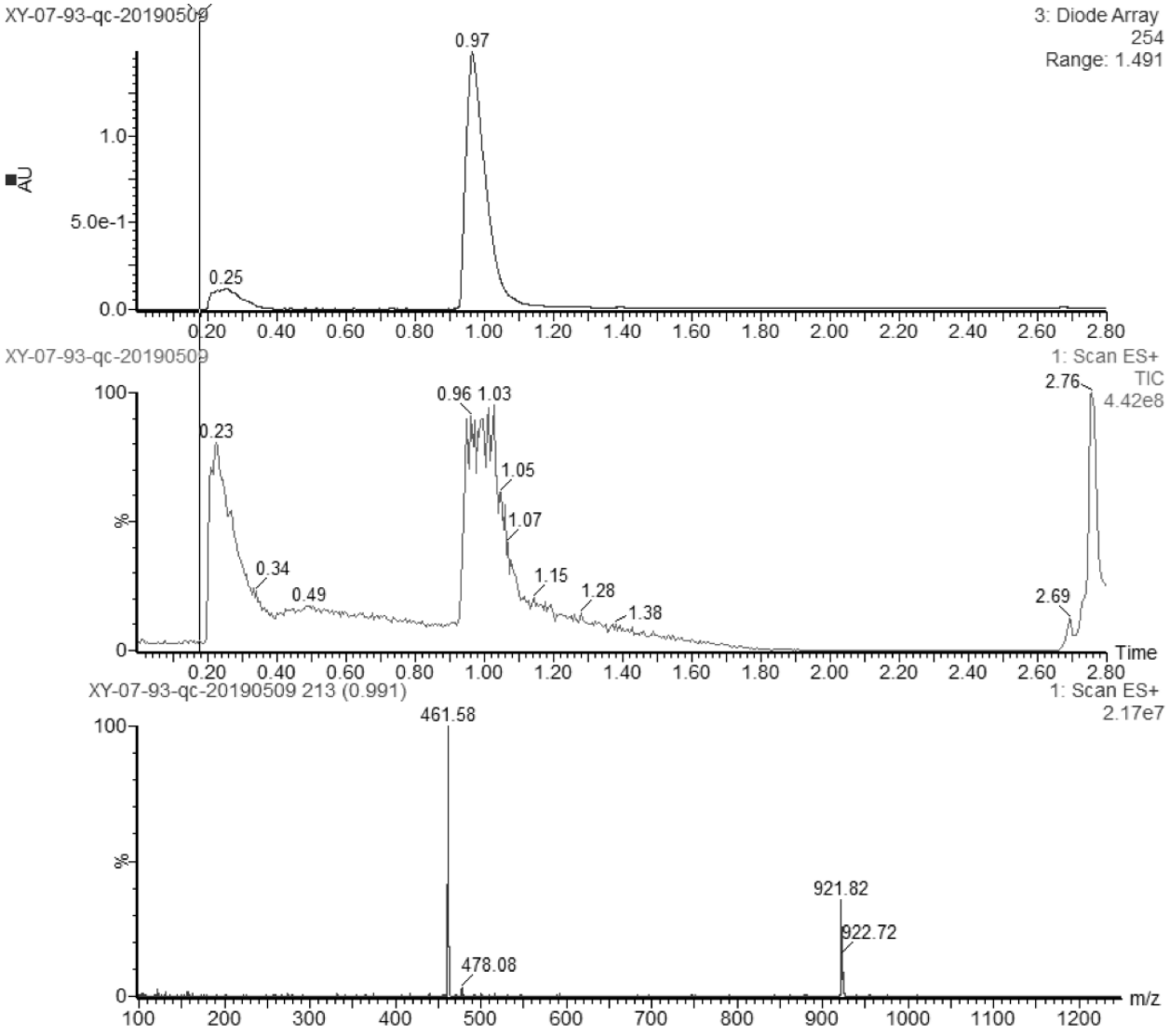
XY-07-200


XY-07-200-qc
2: Diode Array
254
Range: 1.399e-1
AU
0.96
0.23
0.67
1.46
2.67
XY-07-200-qc
1: Scan ES+
TIC
4.68e8
%
0.23
0.25
0.27
0.29
0.46
0.50
0.60
0.10
Time
XY-07-200-qc 480 (0.960)
1: Scan ES+
6.54e6
101.15
438.67
876.24
439.67
877.44
176.01
440.17
878.04
241.09
437.97
879.54
254.98
490.37
m/z

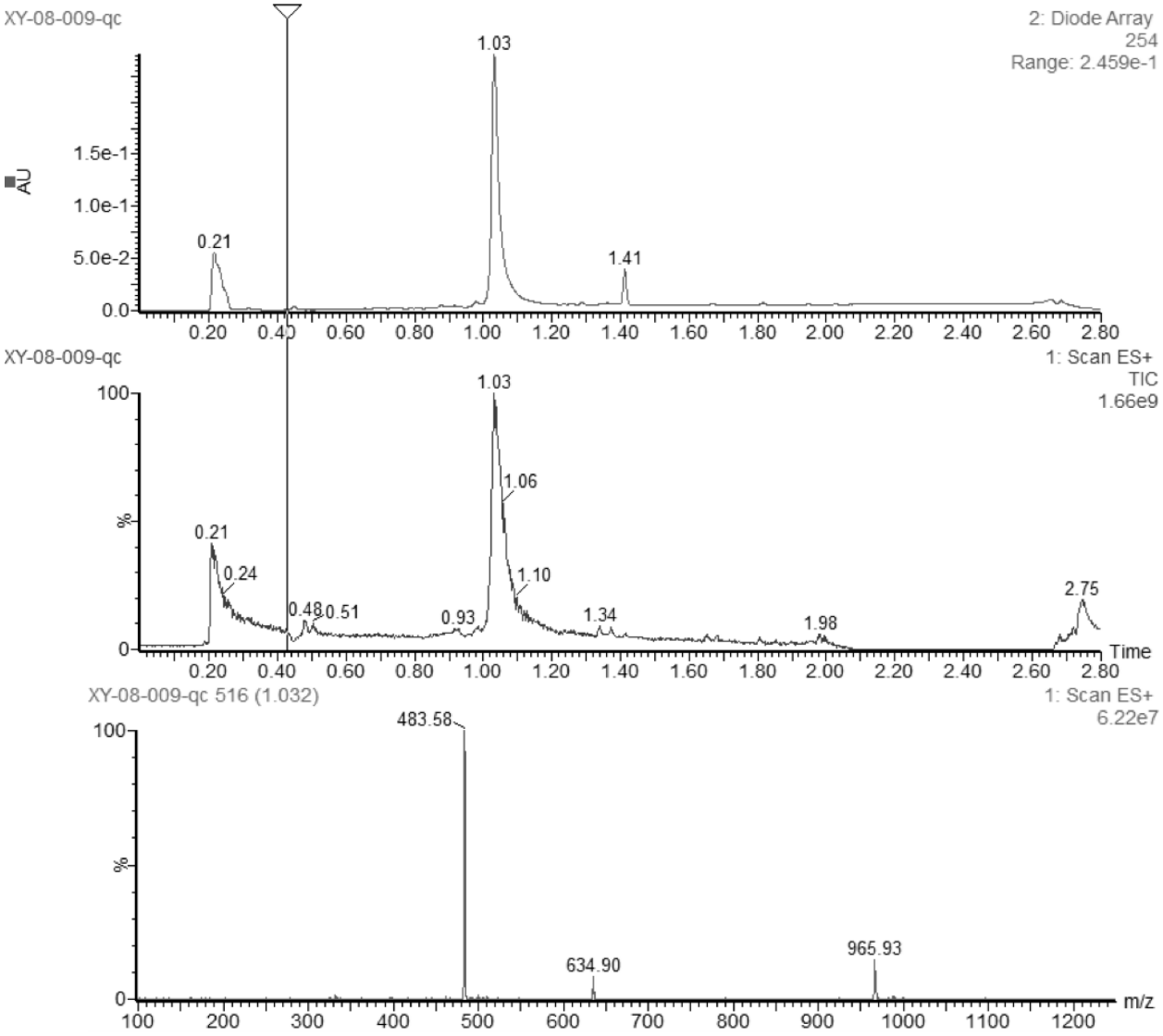
XY-07-090


XY-07-090-qc-20190706
2: Diode Array
254
Range: 3.079e-1
AU
1.03
0.25
1.44
XY-07-090-qc-20190706
1: Scan ES+
TIC
1.58e9
%
1.03
1.06
1.08
0.23
0.27
0.49
2.76
2.69
Time
XY-07-090-qc-20190706 521 (1.042)
1: Scan ES+
7.13e7
439.58
877.72
878.82
447.78
m/z

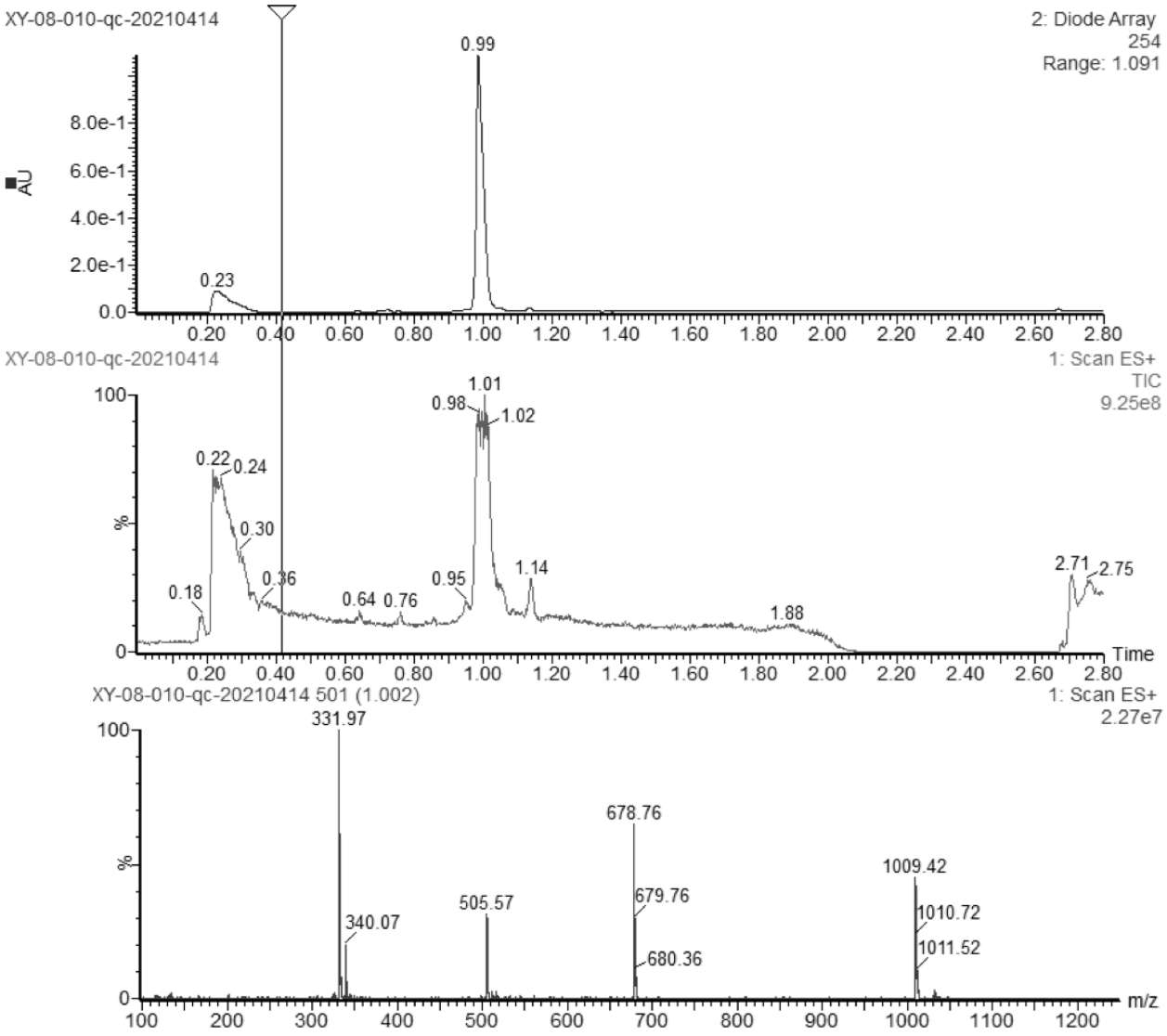
XY-07-093


XY-07-93-qc-20190509
3: Diode Array
254
Range: 1.491
0.97
0.25
AU
1.0
5.0e-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
XY-07-93-qc-20190509
1: Scan ES+
TIC
4.42e8
2.76
0.96 1.03
0.23
1.05
1.07
0.34
0.49
1.15
1.28
1.38
2.69
%
100
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
XY-07-93-qc-20190509 213 (0.991)
1: Scan ES+
2.17e7
461.58
921.82
922.72
478.08
%
100
0
m/z
100 200 300 400 500 600 700 800 900 1000 1100 1200

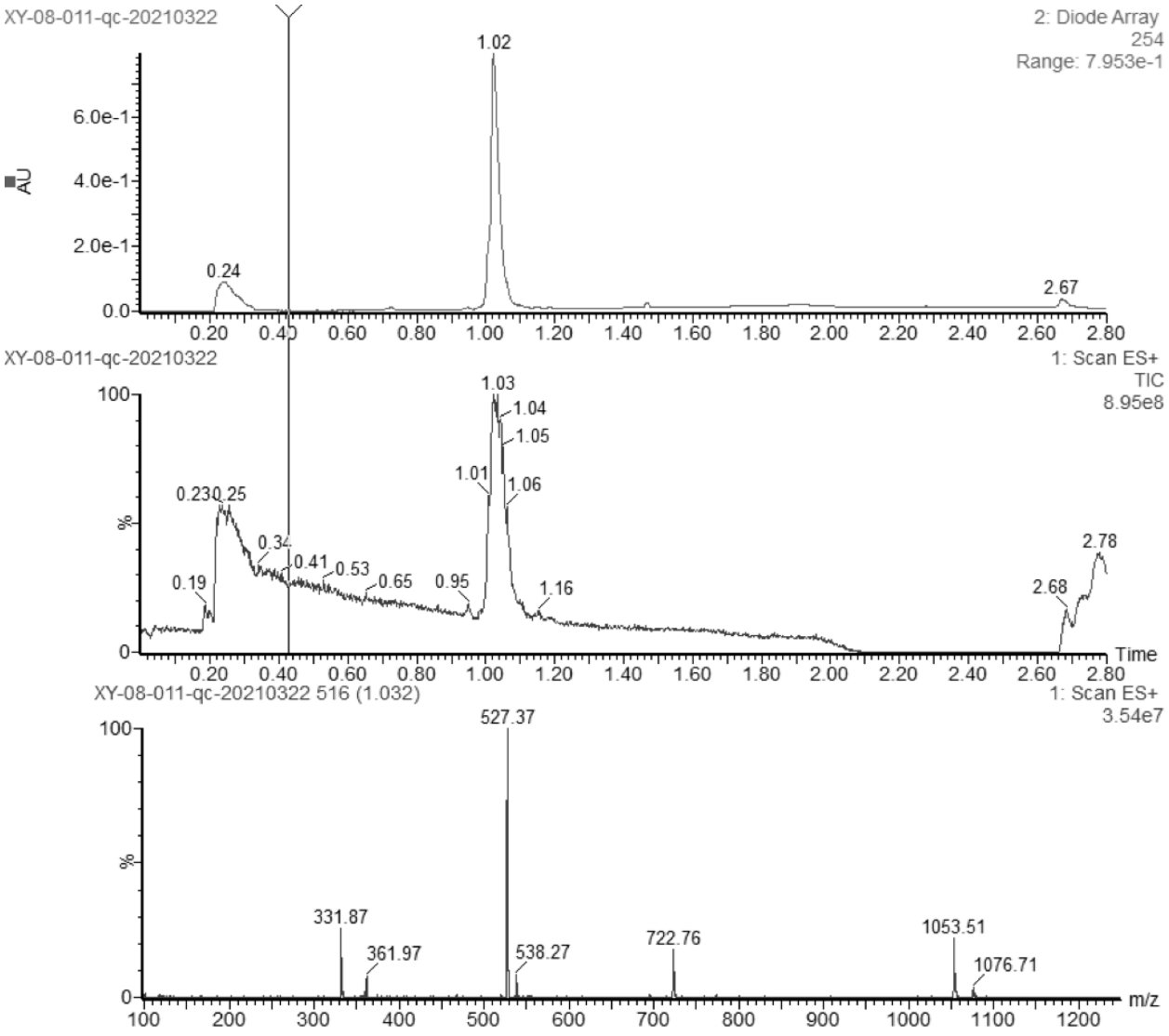
XY-08-009


XY-08-009-qc
2: Diode Array
254
Range: 2.459e-1
AU
1.03
0.21
1.41
XY-08-009-qc
1: Scan ES+
TIC
1.66e9
%
1.03
1.06
0.21
0.24
0.48
0.51
0.93
1.10
1.34
1.98
2.75
Time
XY-08-009-qc 516 (1.032)
1: Scan ES+
6.22e7
483.58
634.90
965.93
m/z

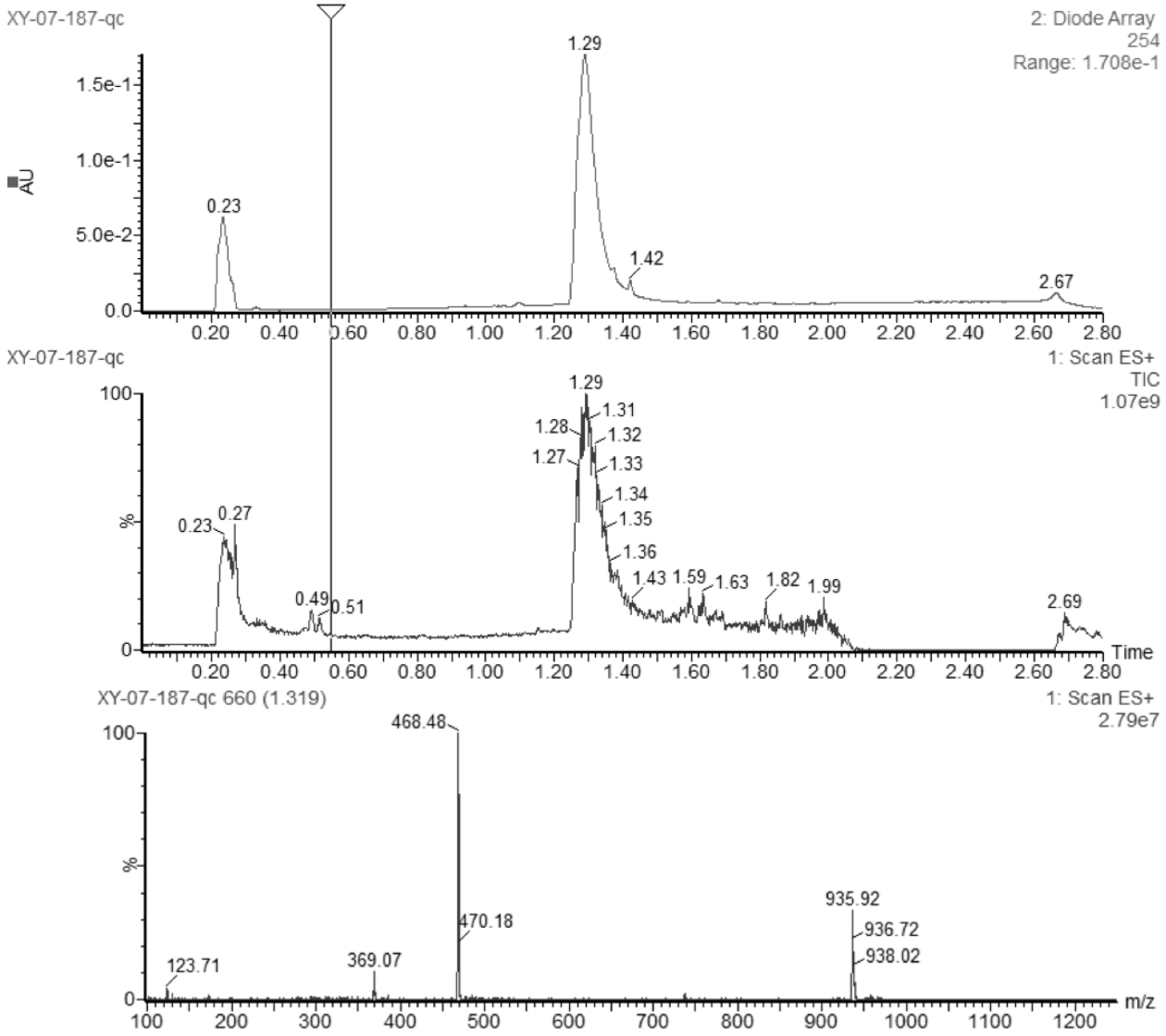
XY-08-010


XY-08-010-qc-20210414
2: Diode Array
254
Range: 1.091
AU
0.99
0.23
XY-08-010-qc-20210414
1: Scan ES+
TIC
9.25e8
%
1.01
0.98
1.02
0.22
0.24
0.30
0.18
0.36
0.64
0.76
0.95
1.14
1.88
2.71
2.75
Time
XY-08-010-qc-20210414 501 (1.002)
1: Scan ES+
2.27e7
331.97
678.76
1009.42
679.76
505.57
340.07
1010.72
680.36
1011.52
m/z

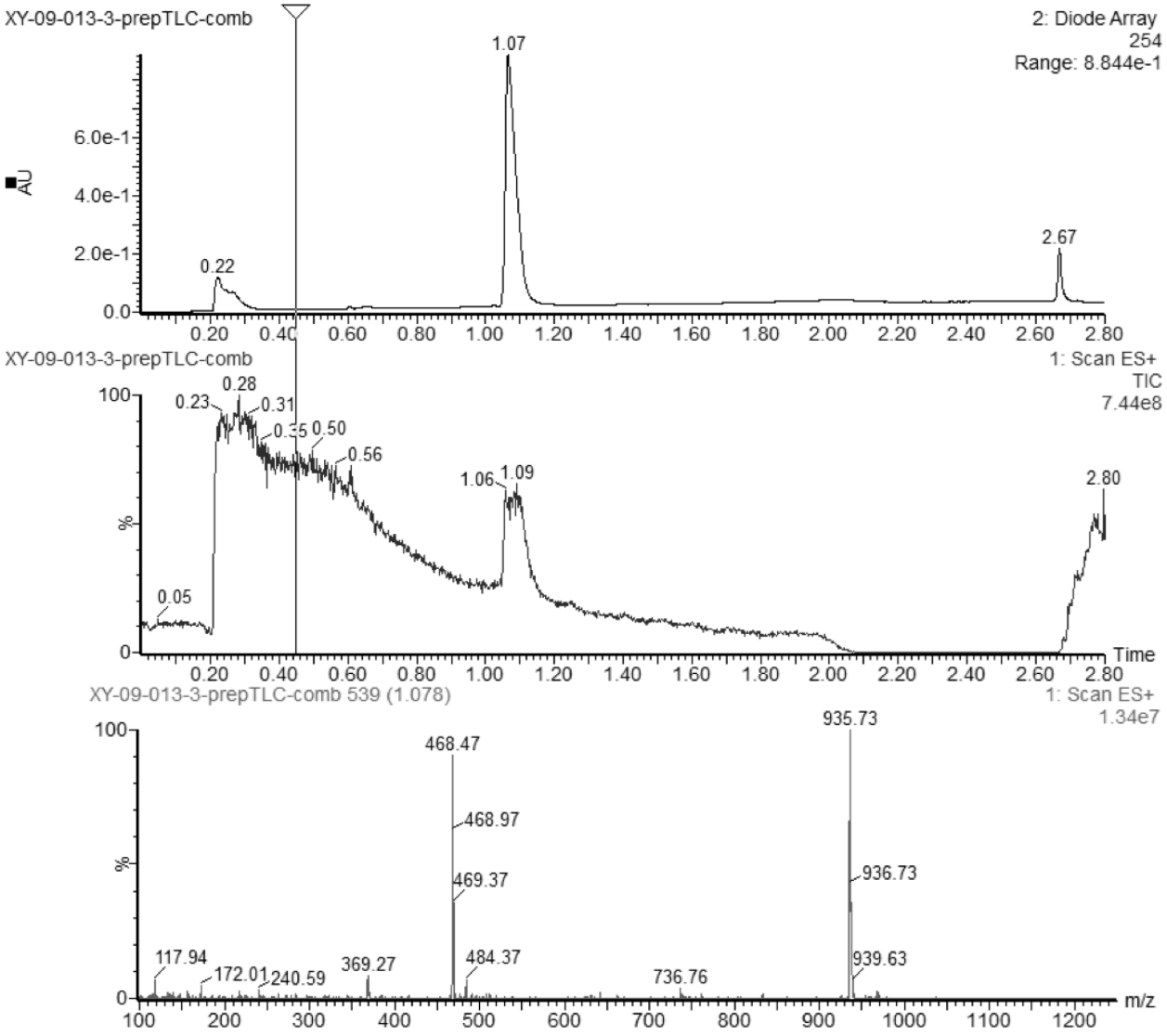
XY-08-011


XY-08-011-qc-20210322
2: Diode Array
254
Range: 7.953e-1
AU
1.02
0.24
2.67
XY-08-011-qc-20210322
1: Scan ES+
TIC
8.95e8
%
1.03
1.04
1.05
1.01
1.06
0.23
0.25
0.34
0.41
0.53
0.65
0.95
1.16
0.19
2.78
2.68
Time
XY-08-011-qc-20210322 516 (1.032)
1: Scan ES+
3.54e7
527.37
331.87
361.97
538.27
722.76
1053.51
1076.71
m/z

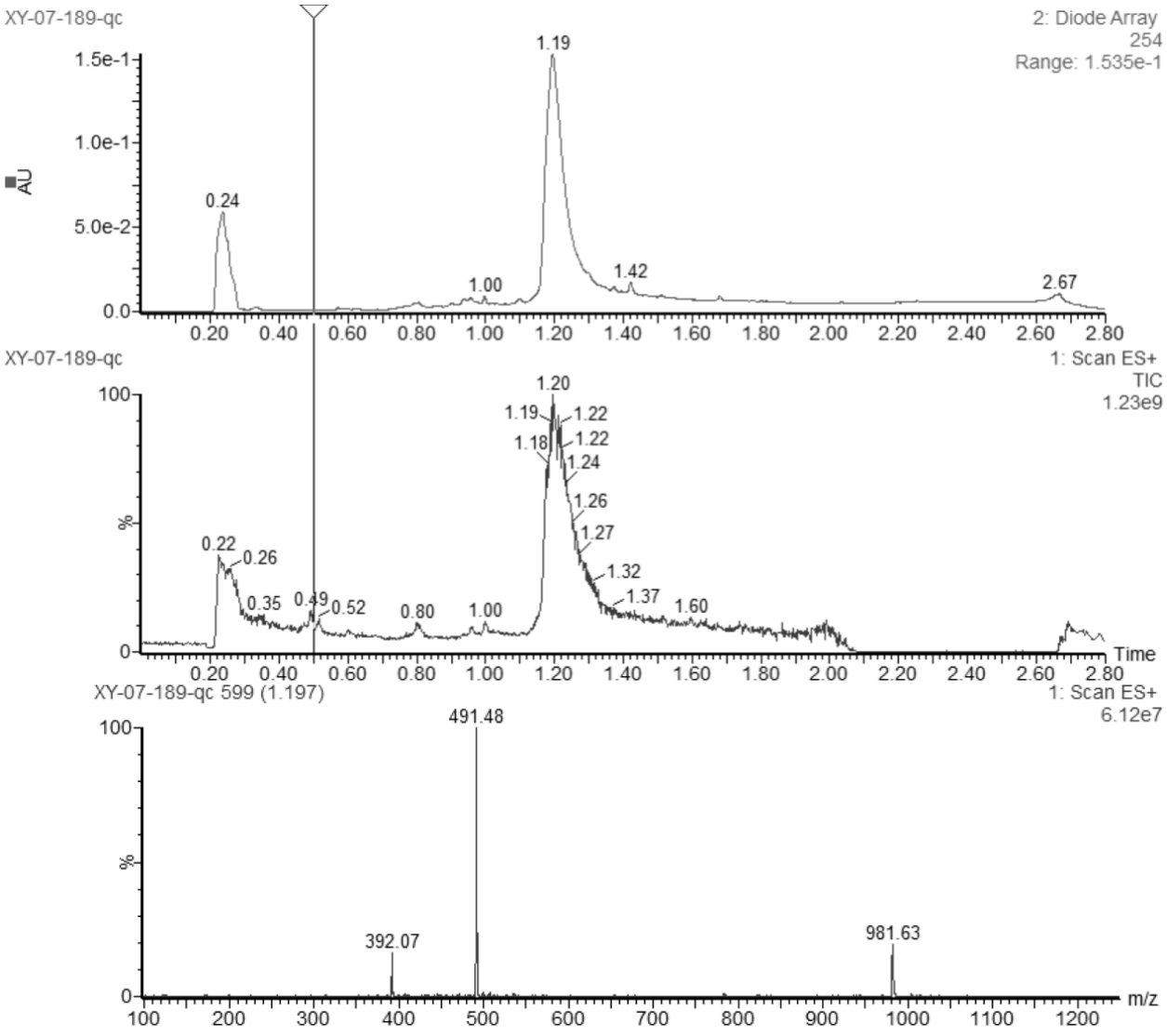
XY-07-187


XY-07-187-qc
2: Diode Array
254
Range: 1.708e-1
AU
1.29
0.23
1.42
2.67
XY-07-187-qc
1: Scan ES+
TIC
1.07e9
%
1.29
1.31
1.28
1.32
1.27
1.33
1.34
1.35
1.36
0.23
0.27
1.43
1.59
1.63
1.82
1.99
0.49
0.51
2.69
Time
XY-07-187-qc 660 (1.319)
1: Scan ES+
2.79e7
468.48
935.92
470.18
936.72
938.02
123.71
369.07
m/z

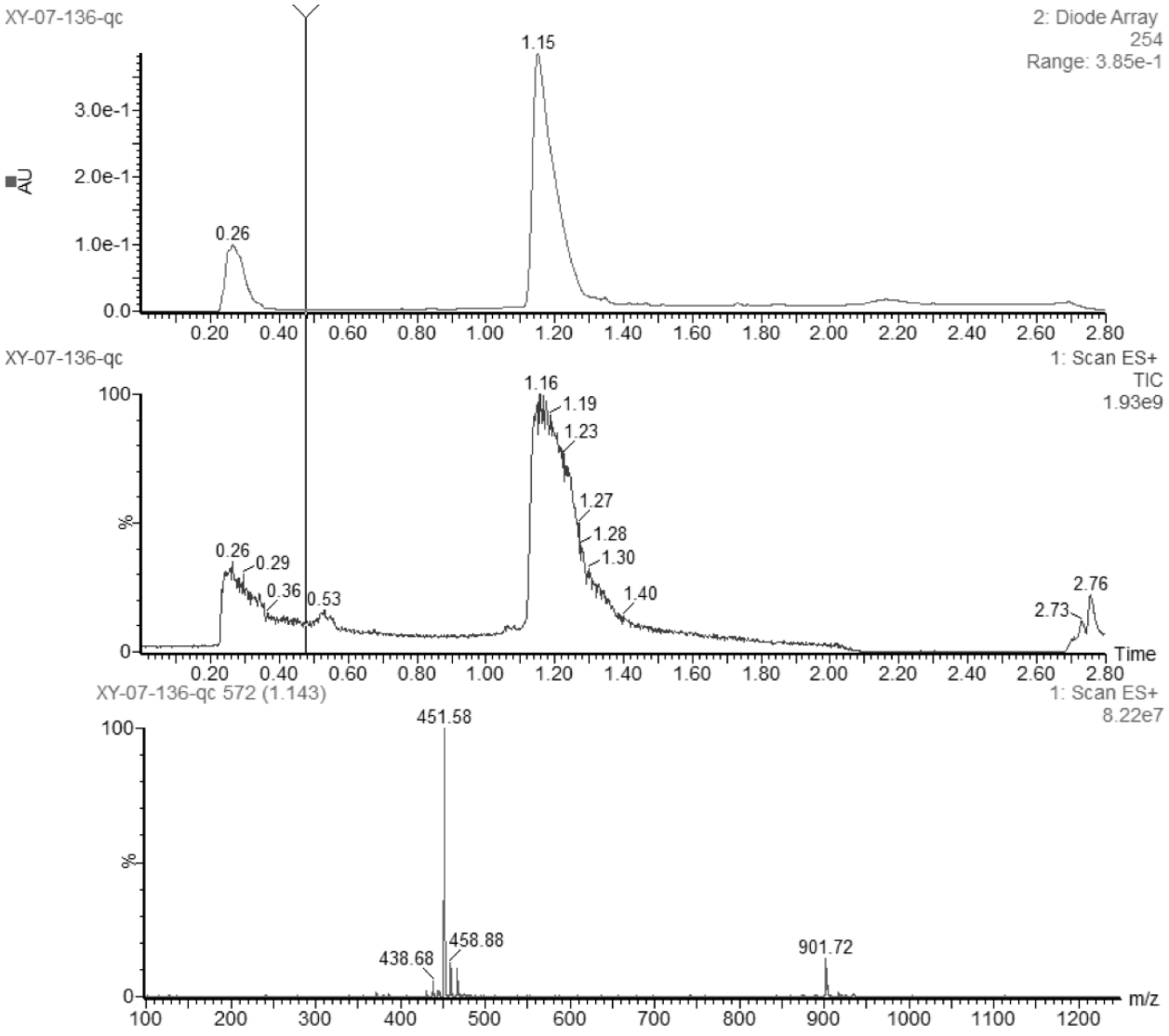
XY-09-013


XY-09-013-3-prepTLC-comb
2: Diode Array
254
Range: 8.844e-1
AU
1.07
0.22
2.67
XY-09-013-3-prepTLC-comb
1: Scan ES+
TIC
7.44e8
%
0.23
0.28
0.31
0.35
0.50
0.56
1.06
1.09
2.80
0.05
Time
XY-09-013-3-prepTLC-comb 539 (1.078)
1: Scan ES+
1.34e7
468.47
468.97
469.37
935.73
936.73
939.63
117.94
172.01
240.59
369.27
484.37
736.76
m/z

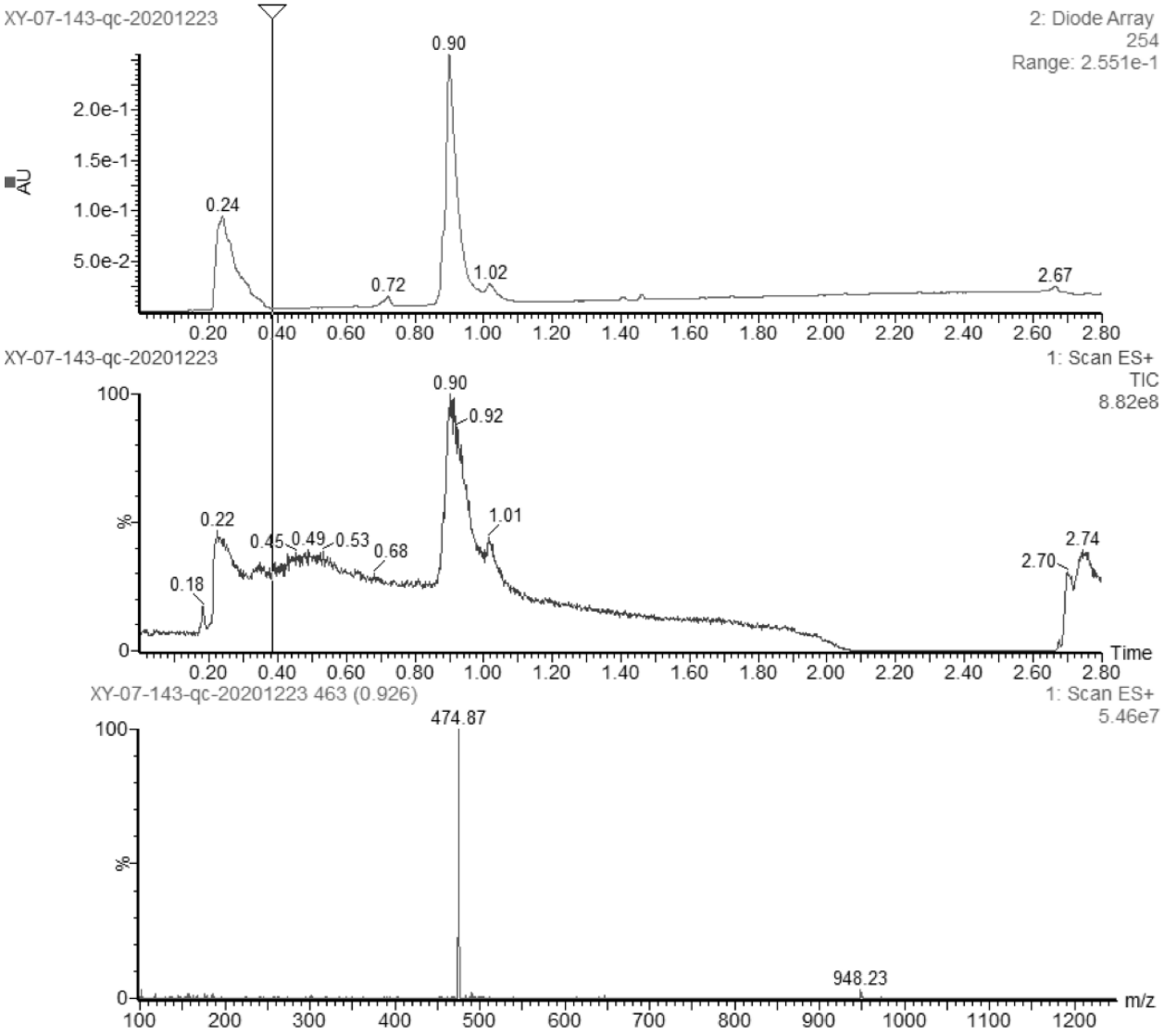
XY-07-189


XY-07-189-qc
2: Diode Array
254
Range: 1.535e-1
AU
1.5e-1
1.0e-1
5.0e-2
0.0
0.24
1.00
1.19
1.42
2.67
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
XY-07-189-qc
1: Scan ES+
TIC
1.23e9
100
%
0
1.20
1.19
1.22
1.18
1.22
1.24
1.26
1.27
1.32
1.37
1.60
0.22
0.26
0.35
0.49
0.52
0.80
1.00
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
XY-07-189-qc 599 (1.197)
1: Scan ES+
6.12e7
100
%
0
491.48
392.07
981.63
m/z
100 200 300 400 500 600 700 800 900 1000 1100 1200

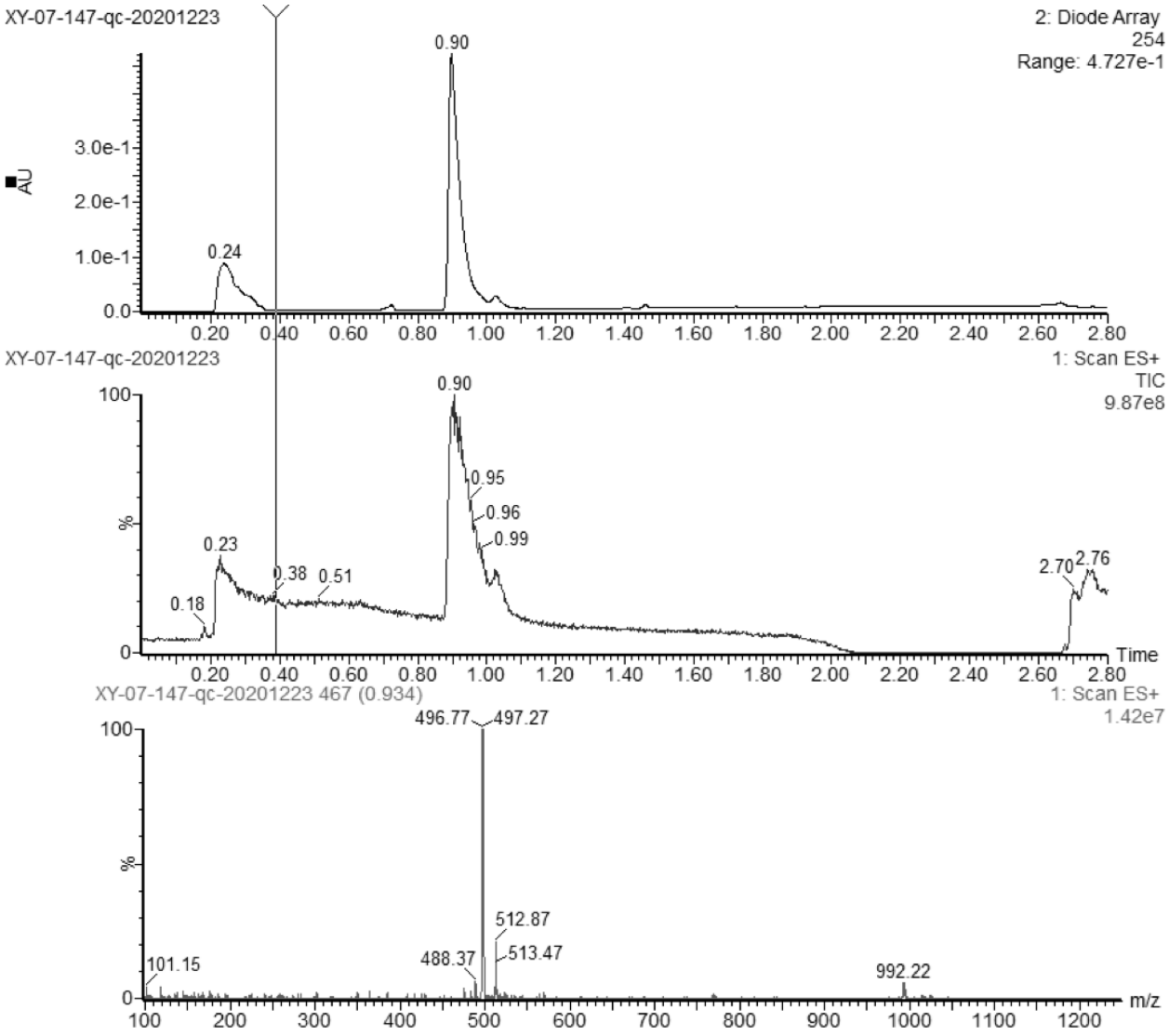
XY-07-136


XY-07-136-qc
2: Diode Array
254
Range: 3.85e-1
AU
1.15
0.26
XY-07-136-qc
1: Scan ES+
TIC
1.93e9
%
1.16
1.19
1.23
1.27
1.28
1.30
1.40
0.26
0.29
0.36
0.53
2.76
2.73
Time
XY-07-136-qc 572 (1.143)
1: Scan ES+
8.22e7
451.58
458.88
438.68
901.72
m/z

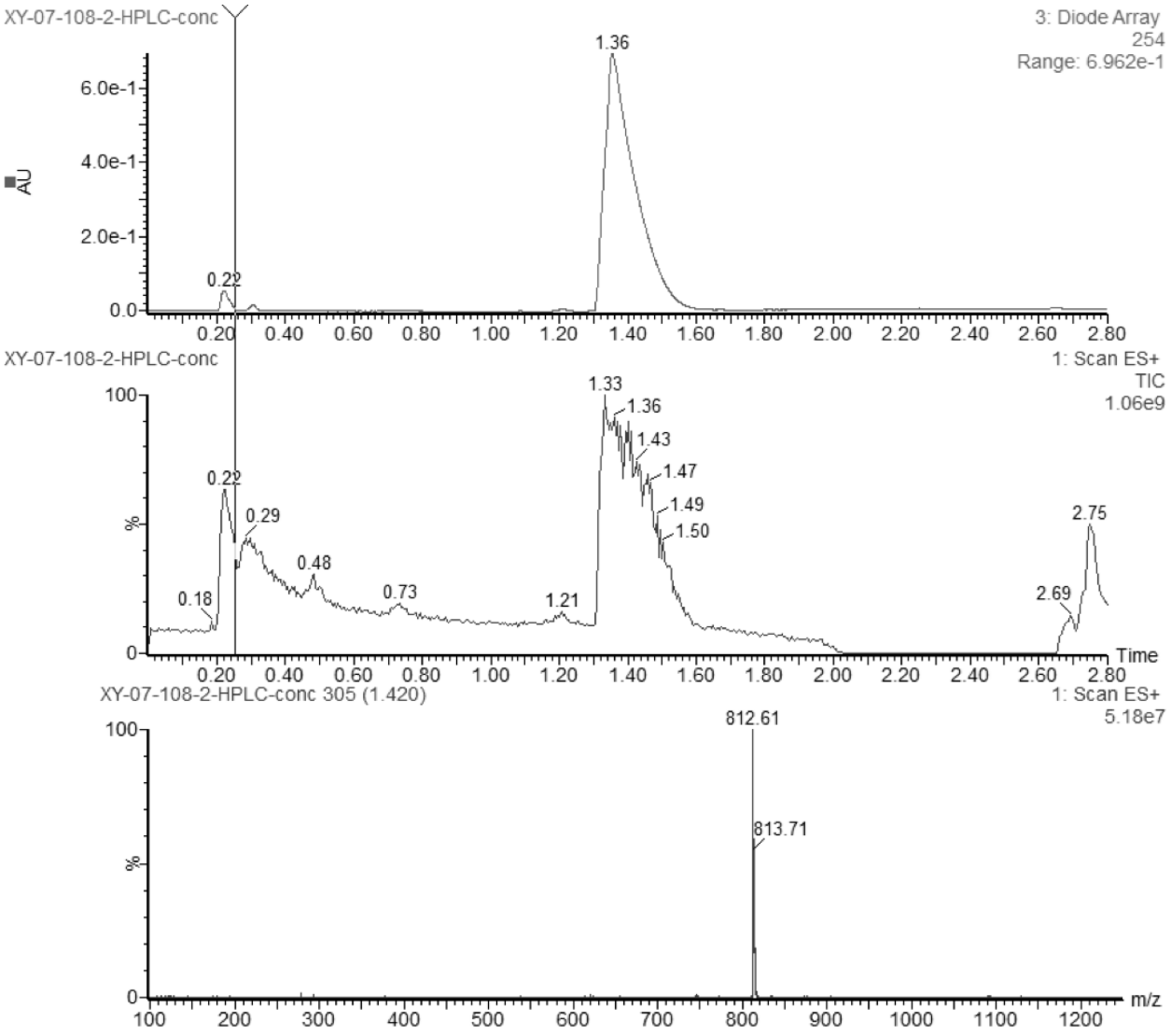
XY-07-143


XY-07-143-qc-20201223
2: Diode Array
254
Range: 2.551e-1
AU
0.90
0.24
0.72
1.02
2.67
XY-07-143-qc-20201223
1: Scan ES+
TIC
8.82e8
%
0.90
0.92
0.22
0.45
0.49
0.53
0.68
1.01
0.18
2.74
2.70
Time
XY-07-143-qc-20201223 463 (0.926)
1: Scan ES+
5.46e7
474.87
948.23
m/z

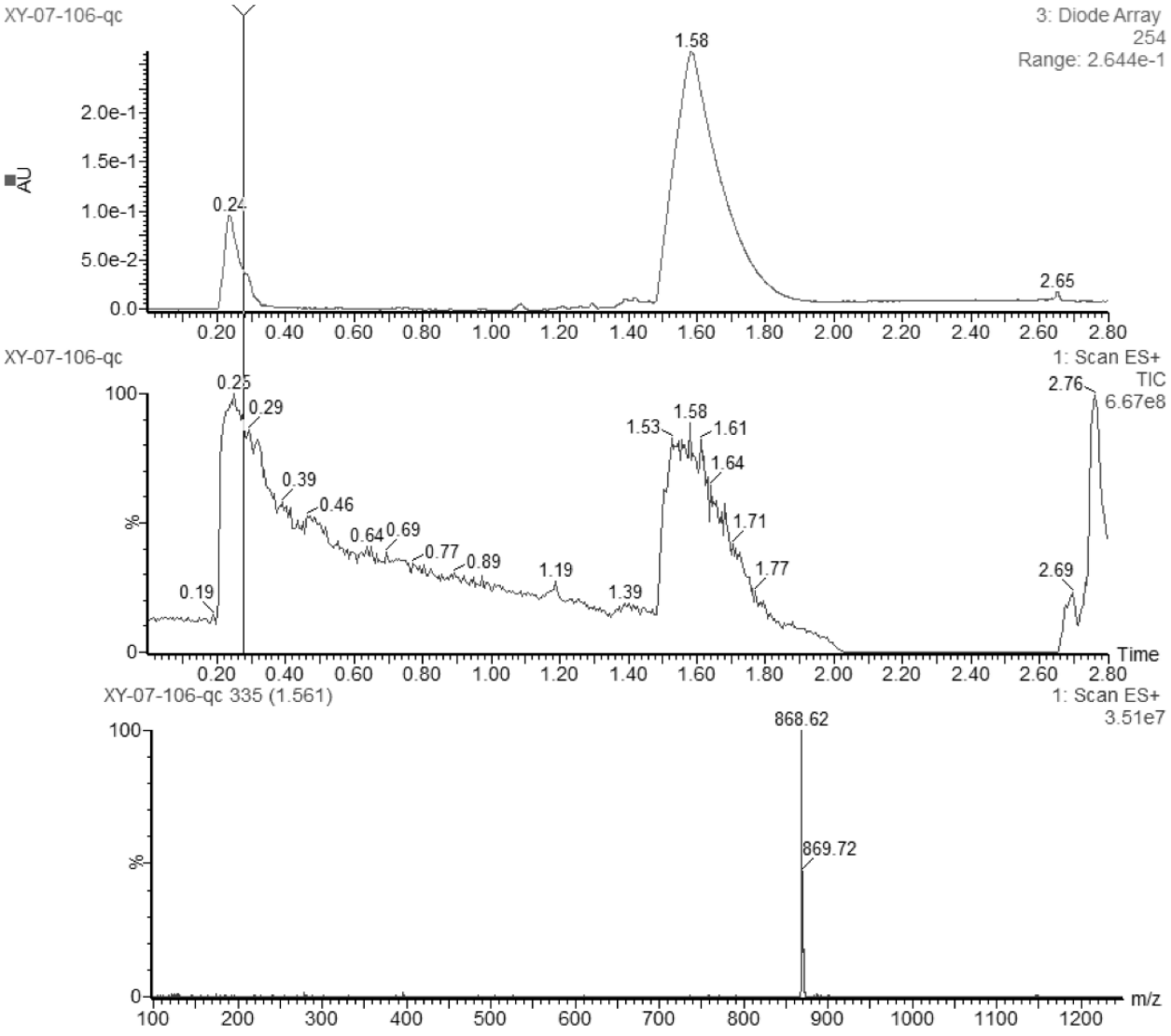
XY-07-147


XY-07-147-qc-20201223
2: Diode Array
254
Range: 4.727e-1
AU
0.90
0.24
XY-07-147-qc-20201223
1: Scan ES+
TIC
9.87e8
%
0.90
0.95
0.96
0.99
0.23
0.38
0.51
0.18
2.70
2.76
Time
XY-07-147-qc-20201223 467 (0.934)
1: Scan ES+
1.42e7
496.77
497.27
512.87
513.47
488.37
101.15
992.22
m/z

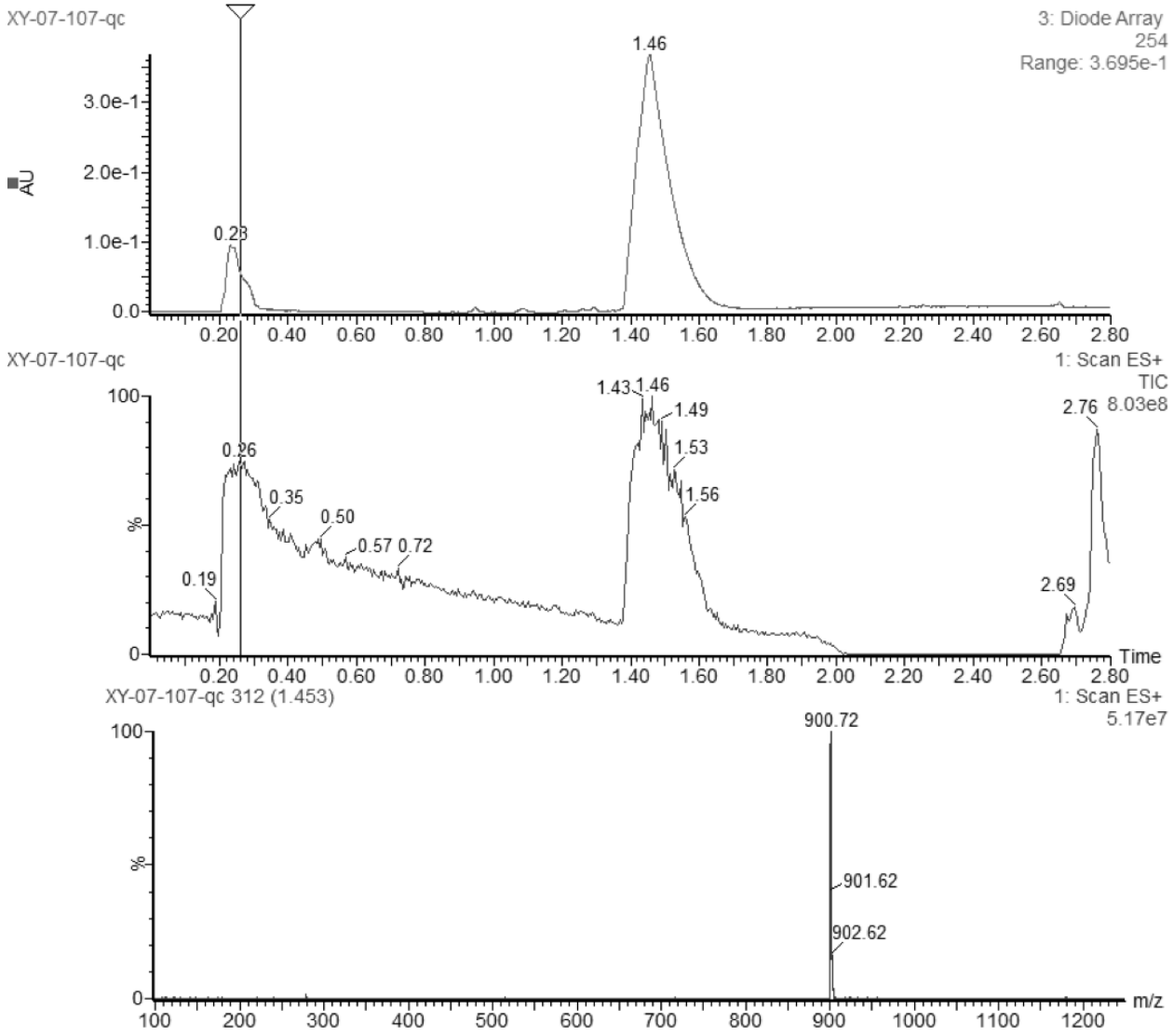
XY-07-108


XY-07-108-2-HPLC-conc
3: Diode Array
254
Range: 6.962e-1
AU
1.36
0.22
XY-07-108-2-HPLC-conc
1: Scan ES+
TIC
1.06e9
%
1.33
1.36
1.43
1.47
1.49
1.50
0.22
0.29
0.48
0.18
0.73
1.21
2.75
2.69
Time
XY-07-108-2-HPLC-conc 305 (1.420)
1: Scan ES+
5.18e7
812.61
813.71
m/z

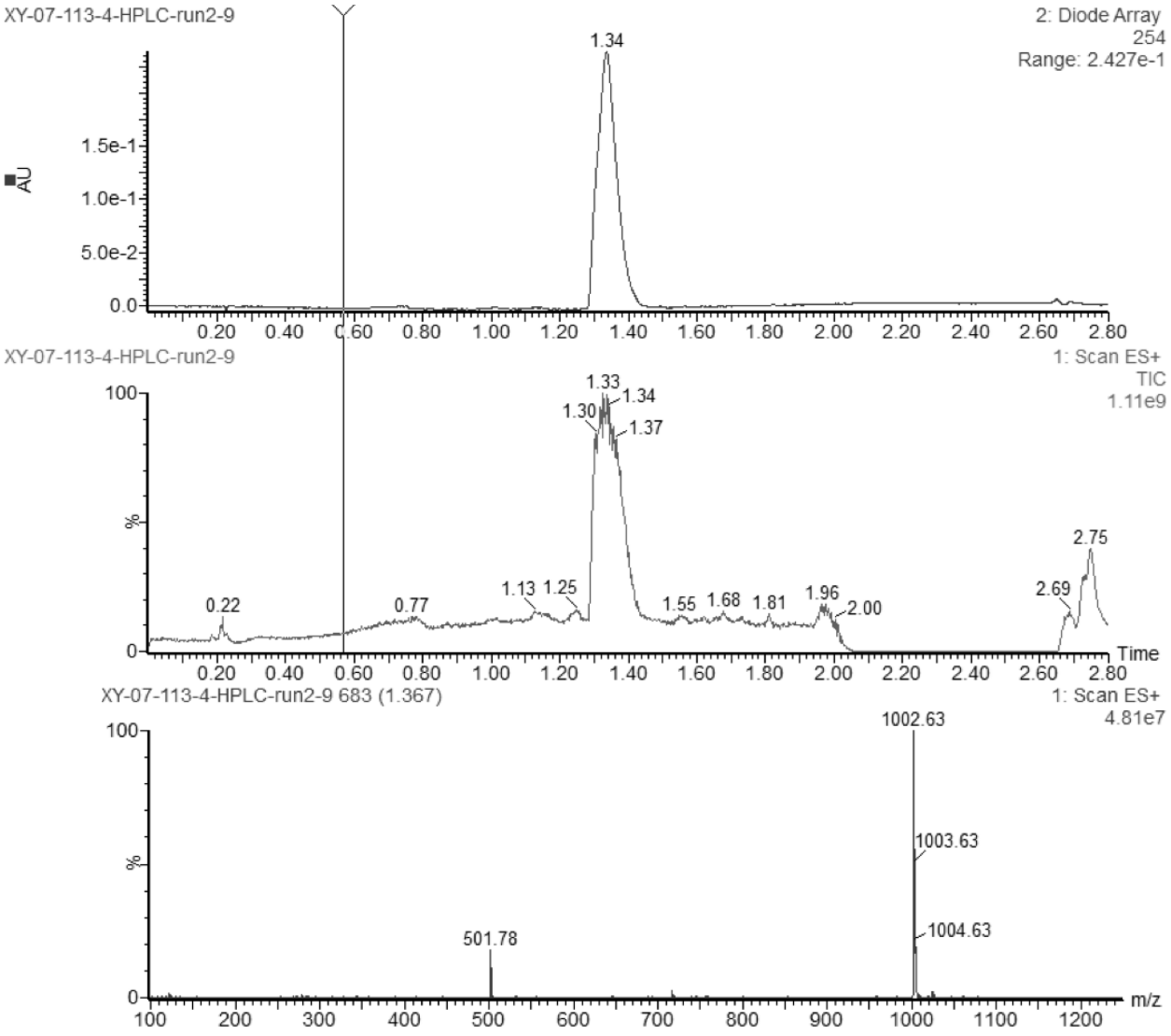
XY-07-106


XY-07-106-qc
3: Diode Array
254
Range: 2.644e-1
AU
1.58
0.24
2.65
XY-07-106-qc
1: Scan ES+
TIC
6.67e8
%
0.25
0.29
0.39
0.46
0.64
0.69
0.77
0.89
1.19
1.39
1.53
1.58
1.61
1.64
1.71
1.77
2.69
2.76
0.19
Time
XY-07-106-qc 335 (1.561)
1: Scan ES+
3.51e7
868.62
869.72
m/z

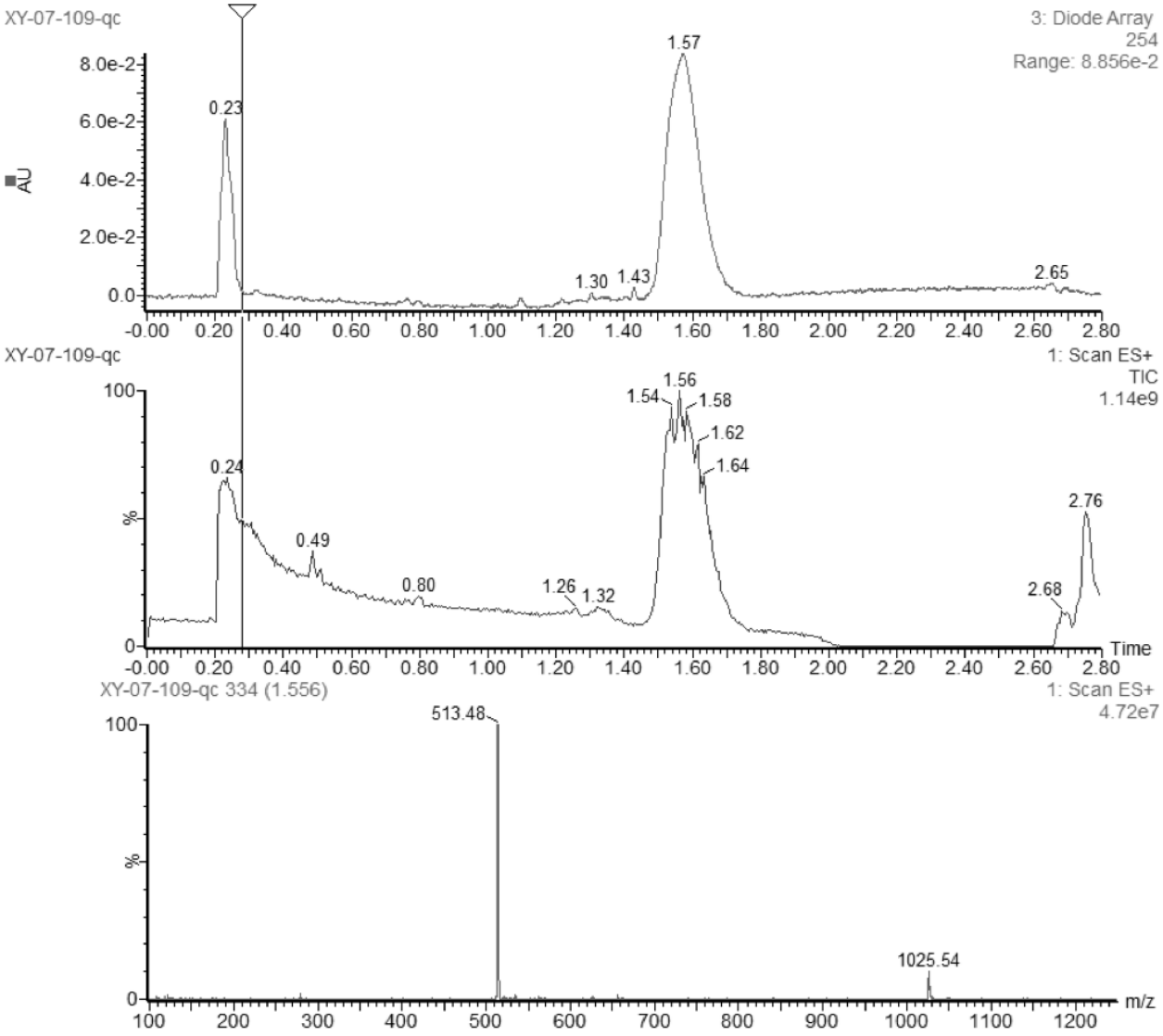
XY-07-107


XY-07-107-qc
3: Diode Array
254
Range: 3.695e-1
AU
1.46
0.23
XY-07-107-qc
1: Scan ES+
TIC
8.03e8
%
1.43
1.46
1.49
1.53
1.56
2.76
0.26
0.35
0.50
0.57
0.72
0.19
2.69
Time
XY-07-107-qc 312 (1.453)
1: Scan ES+
5.17e7
900.72
901.62
902.62
m/z

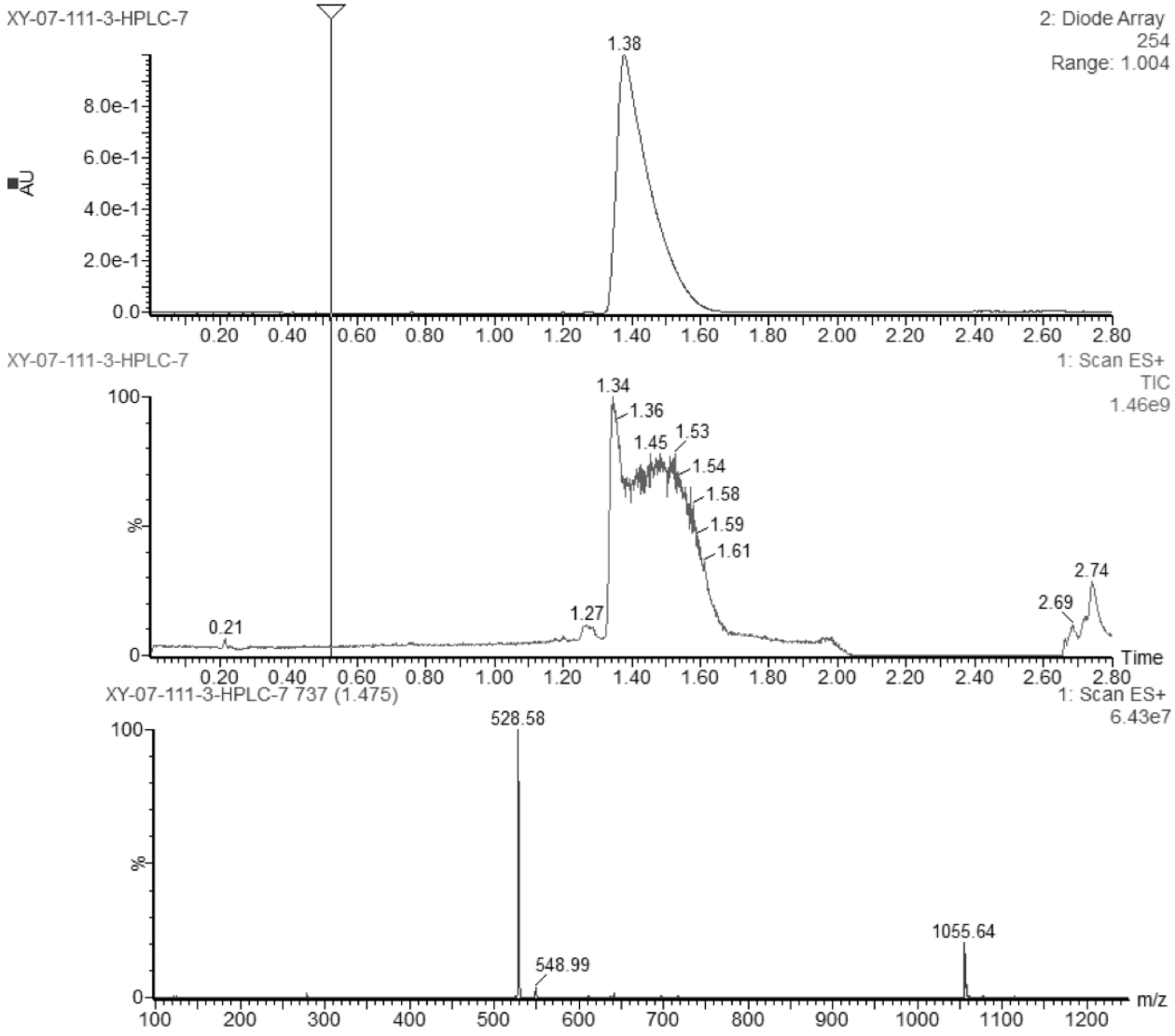
XY-07-113


XY-07-113-4-HPLC-run2-9
2: Diode Array
254
Range: 2.427e-1
1.34
AU
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
XY-07-113-4-HPLC-run2-9
1: Scan ES+
TIC
1.11e9
1.33
1.34
1.30
1.37
%
100
0
0.22
0.77
1.13
1.25
1.55
1.68
1.81
1.96
2.00
2.69
2.75
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
XY-07-113-4-HPLC-run2-9 683 (1.367)
1: Scan ES+
4.81e7
1002.63
1003.63
1004.63
501.78
%
100
0
m/z
100 200 300 400 500 600 700 800 900 1000 1100 1200

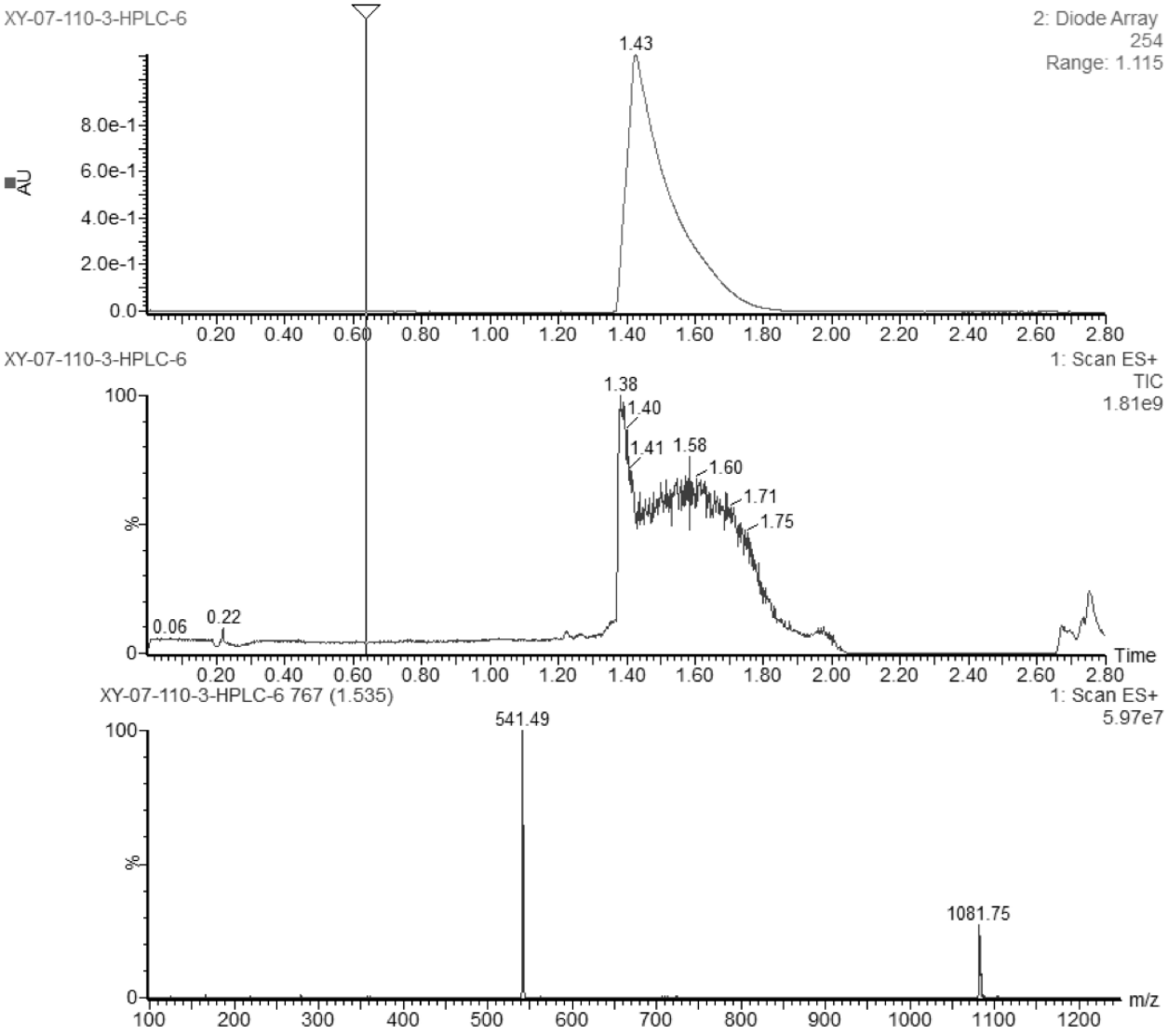
XY-07-109


XY-07-109-qc
3: Diode Array
254
Range: 8.856e-2
AU
0.23
1.30
1.43
1.57
2.65
XY-07-109-qc
1: Scan ES+
TIC
1.14e9
%
0.24
0.49
0.80
1.26
1.32
1.54
1.56
1.58
1.62
1.64
2.68
2.76
Time
XY-07-109-qc 334 (1.556)
1: Scan ES+
4.72e7
513.48
1025.54
m/z

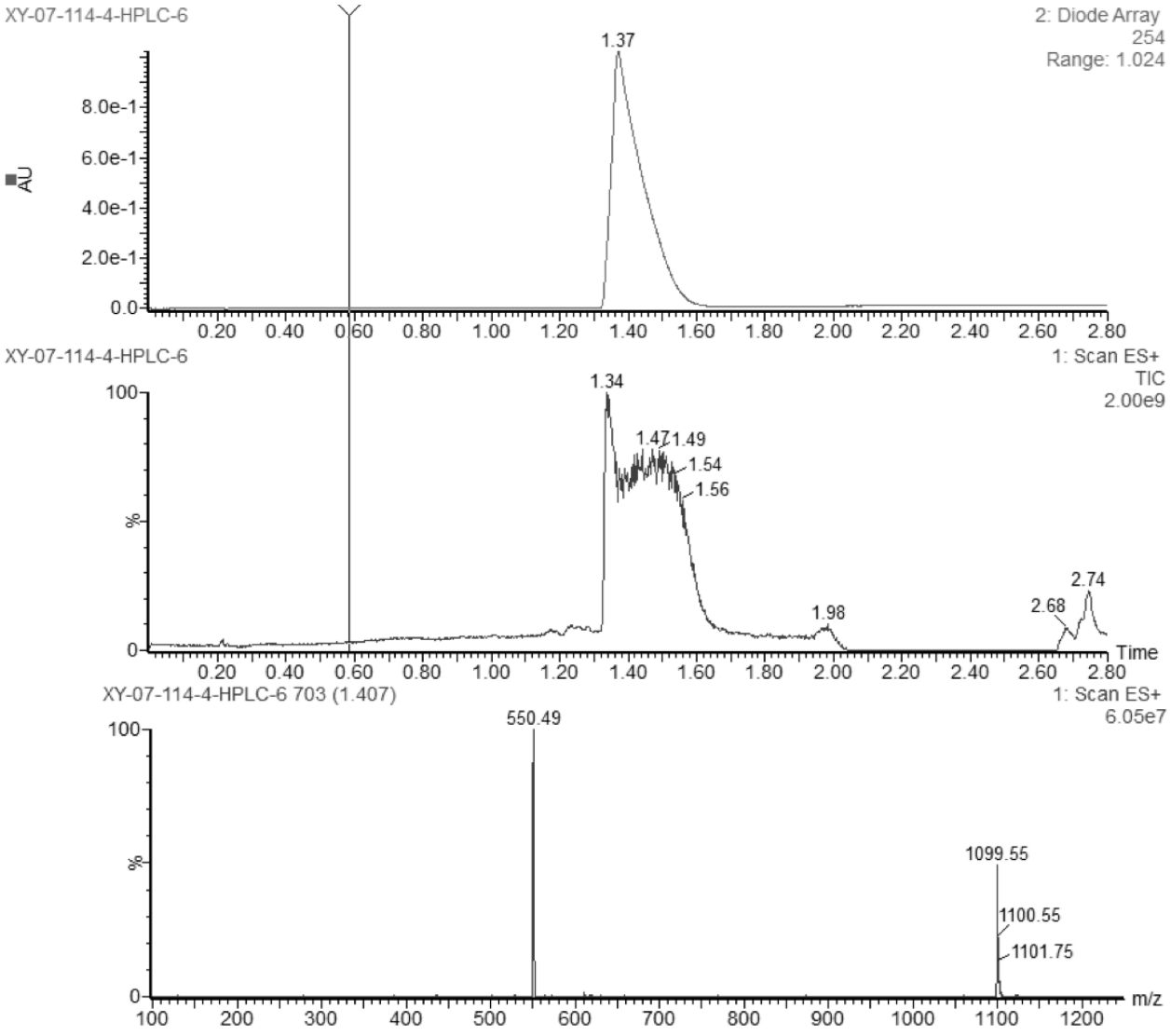
XY-07-111


XY-07-111-3-HPLC-7
2: Diode Array
254
Range: 1.004
1.38
AU
8.0e-1
6.0e-1
4.0e-1
2.0e-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
XY-07-111-3-HPLC-7
1: Scan ES+
TIC
1.46e9
1.34
1.36
1.45
1.53
1.54
1.58
1.59
1.61
2.74
2.69
1.27
0.21
%
100
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
XY-07-111-3-HPLC-7 737 (1.475)
1: Scan ES+
6.43e7
528.58
1055.64
548.99
%
100
0
m/z
100 200 300 400 500 600 700 800 900 1000 1100 1200

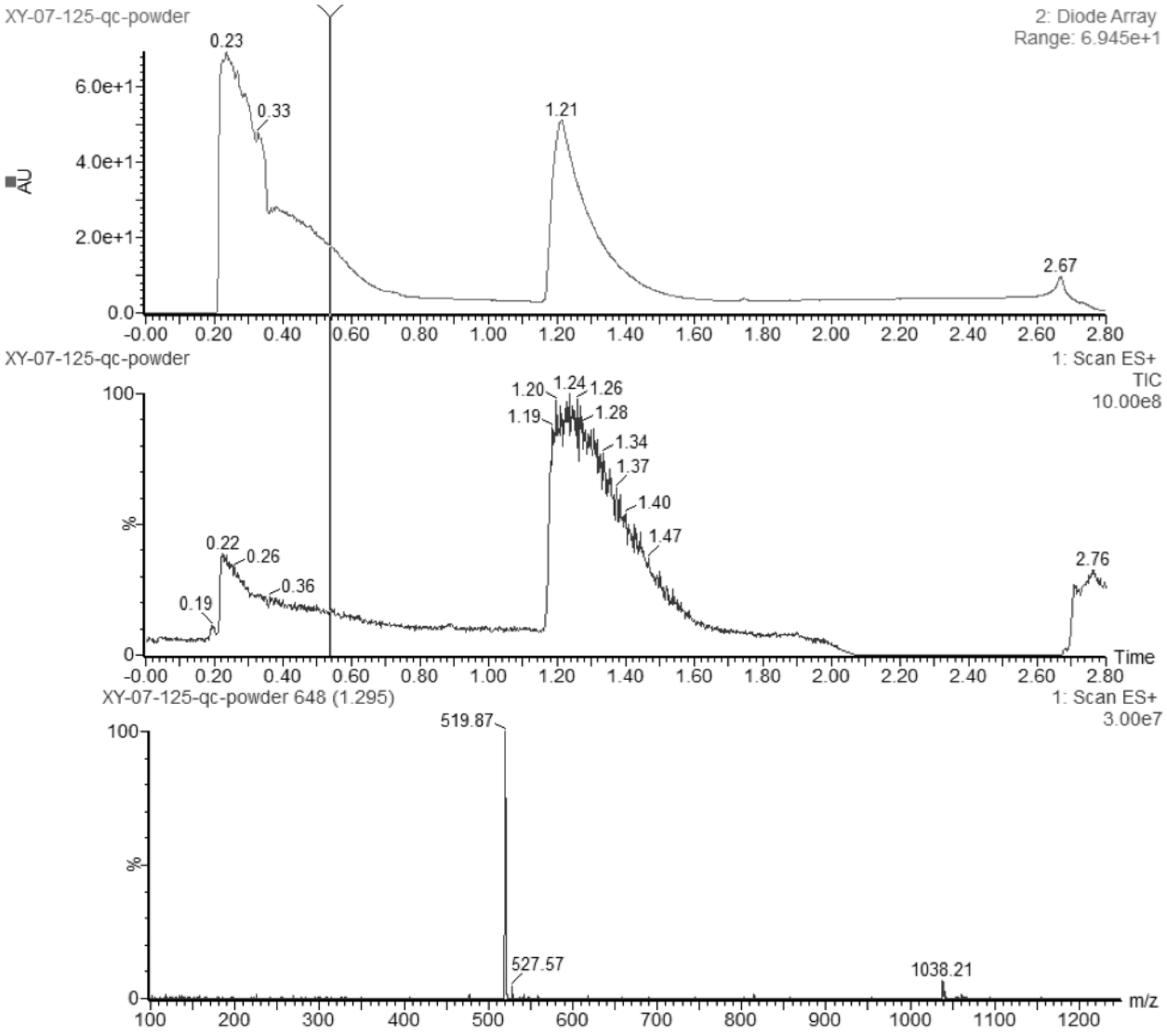
XY-07-110


XY-07-110-3-HPLC-6
2: Diode Array
254
Range: 1.115
1.43
AU
8.0e-1
6.0e-1
4.0e-1
2.0e-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
XY-07-110-3-HPLC-6
1: Scan ES+
TIC
1.81e9
1.38
1.40
1.41
1.58
1.60
1.71
1.75
0.06
0.22
%
100
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
XY-07-110-3-HPLC-6 767 (1.535)
1: Scan ES+
5.97e7
541.49
1081.75
%
100
0
m/z
100 200 300 400 500 600 700 800 900 1000 1100 1200

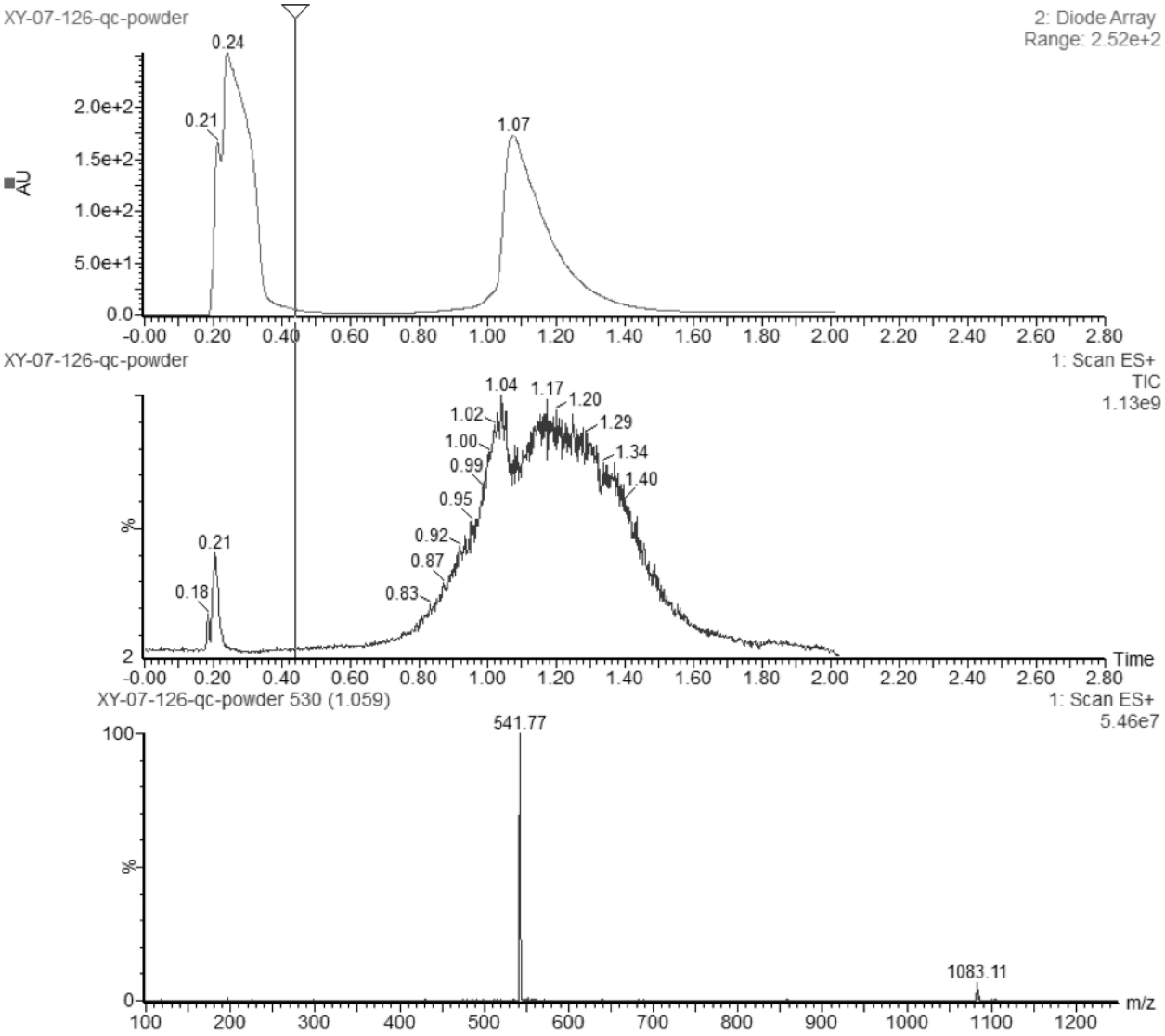
XY-07-114


XY-07-114-4-HPLC-6
2: Diode Array
254
Range: 1.024
1.37
AU
8.0e-1
6.0e-1
4.0e-1
2.0e-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
XY-07-114-4-HPLC-6
1: Scan ES+
TIC
2.00e9
1.34
1.47
1.49
1.54
1.56
1.98
2.68
2.74
%
100
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
XY-07-114-4-HPLC-6 703 (1.407)
1: Scan ES+
6.05e7
550.49
1099.55
1100.55
1101.75
%
100
0
m/z
100 200 300 400 500 600 700 800 900 1000 1100 1200

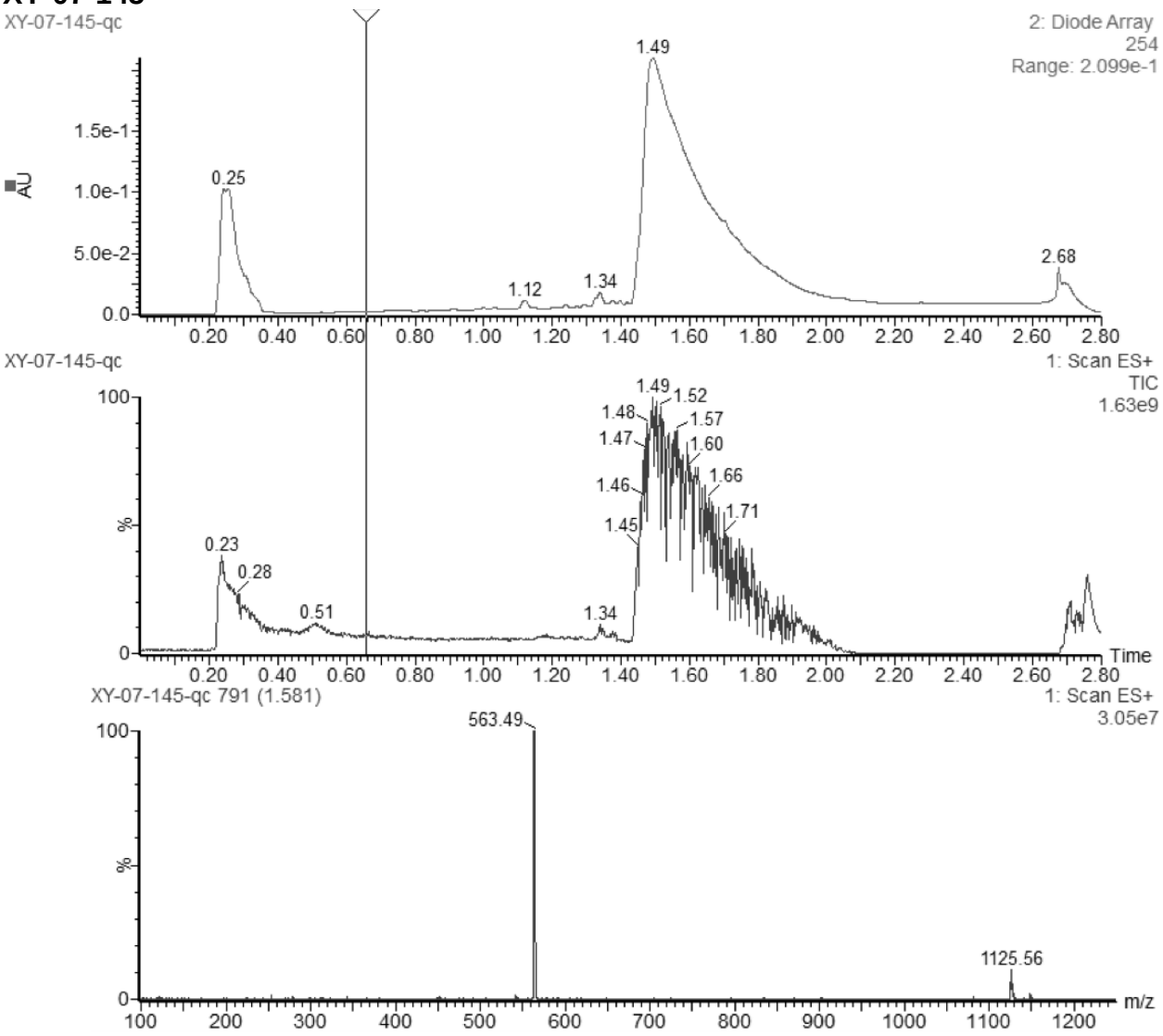
XY-07-125


XY-07-125-qc-powder
2: Diode Array
Range: 6.945e+1
AU
0.23
0.33
1.21
2.67
XY-07-125-qc-powder
1: Scan ES+
TIC
10.00e8
%
0.19
0.22
0.26
0.36
1.19
1.20
1.24
1.26
1.28
1.34
1.37
1.40
1.47
2.76
Time
XY-07-125-qc-powder 648 (1.295)
1: Scan ES+
3.00e7
519.87
527.57
1038.21
m/z

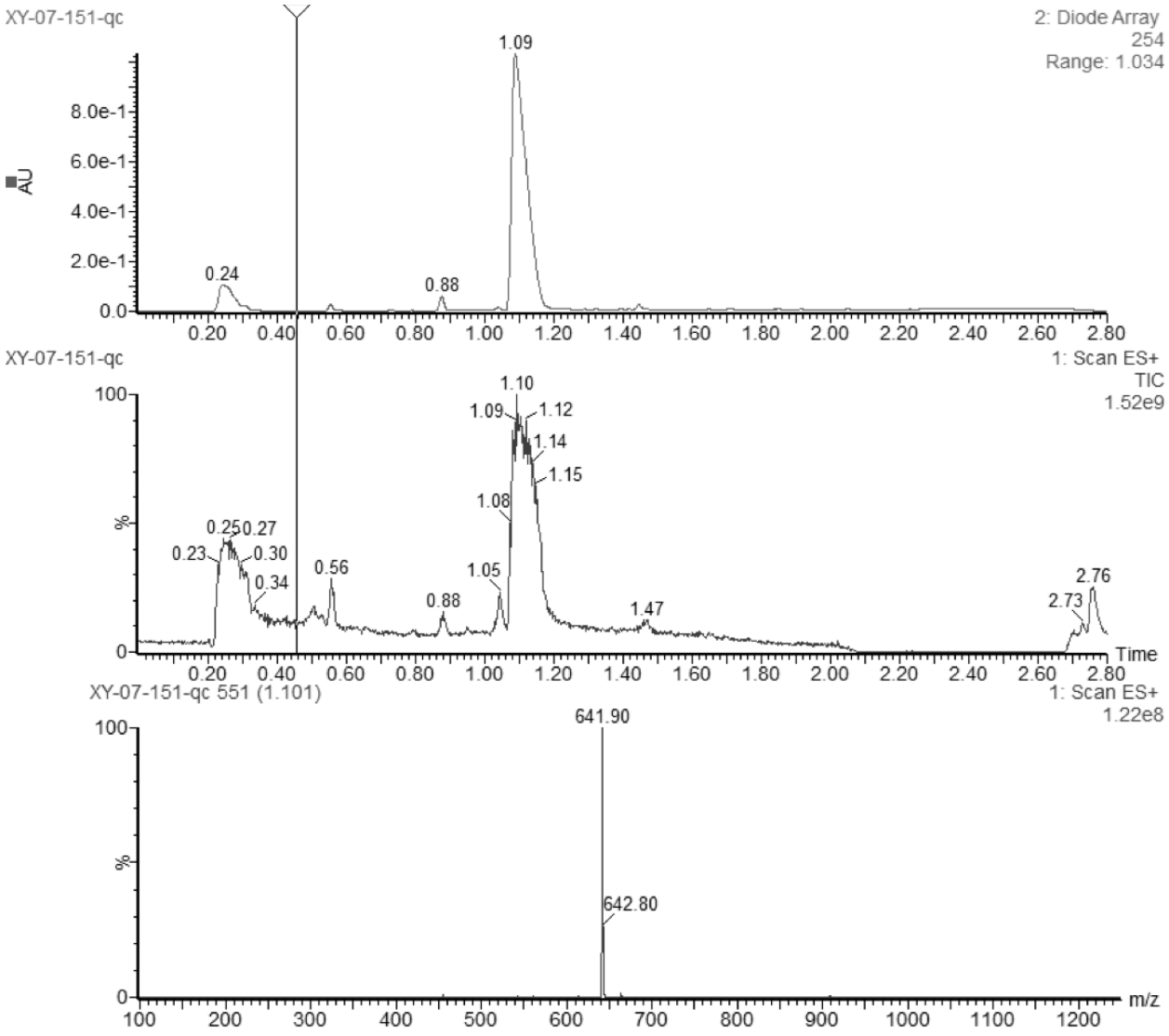
XY-07-126


XY-07-126-qc-powder
2: Diode Array
Range: 2.52e+2
AU
0.24
0.21
1.07
XY-07-126-qc-powder
1: Scan ES+
TIC
1.13e9
%
1.04
1.17
1.20
1.02
1.29
1.00
1.34
0.99
1.40
0.95
0.92
0.21
0.87
0.18
0.83
Time
XY-07-126-qc-powder 530 (1.059)
1: Scan ES+
5.46e7
541.77
1083.11
m/z

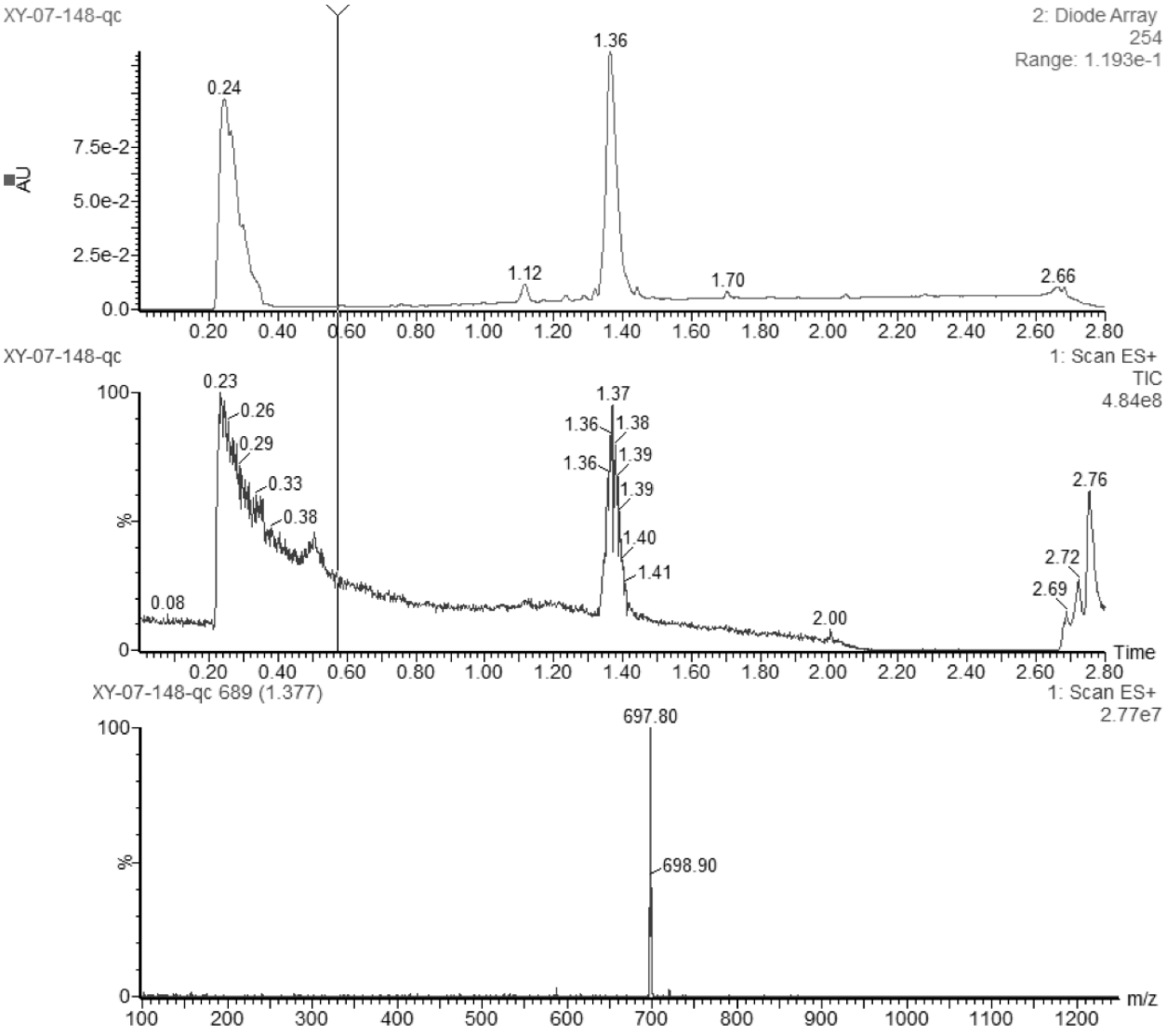
XY-07-145


XY-07-145-qc
2: Diode Array
254
Range: 2.099e-1
AU
1.49
0.25
1.12
1.34
2.68
XY-07-145-qc
1: Scan ES+
TIC
1.63e9
%
1.49
1.52
1.48
1.57
1.47
1.60
1.66
1.46
1.71
1.45
0.23
0.28
0.51
1.34
Time
XY-07-145-qc 791 (1.581)
1: Scan ES+
3.05e7
563.49
1125.56
m/z

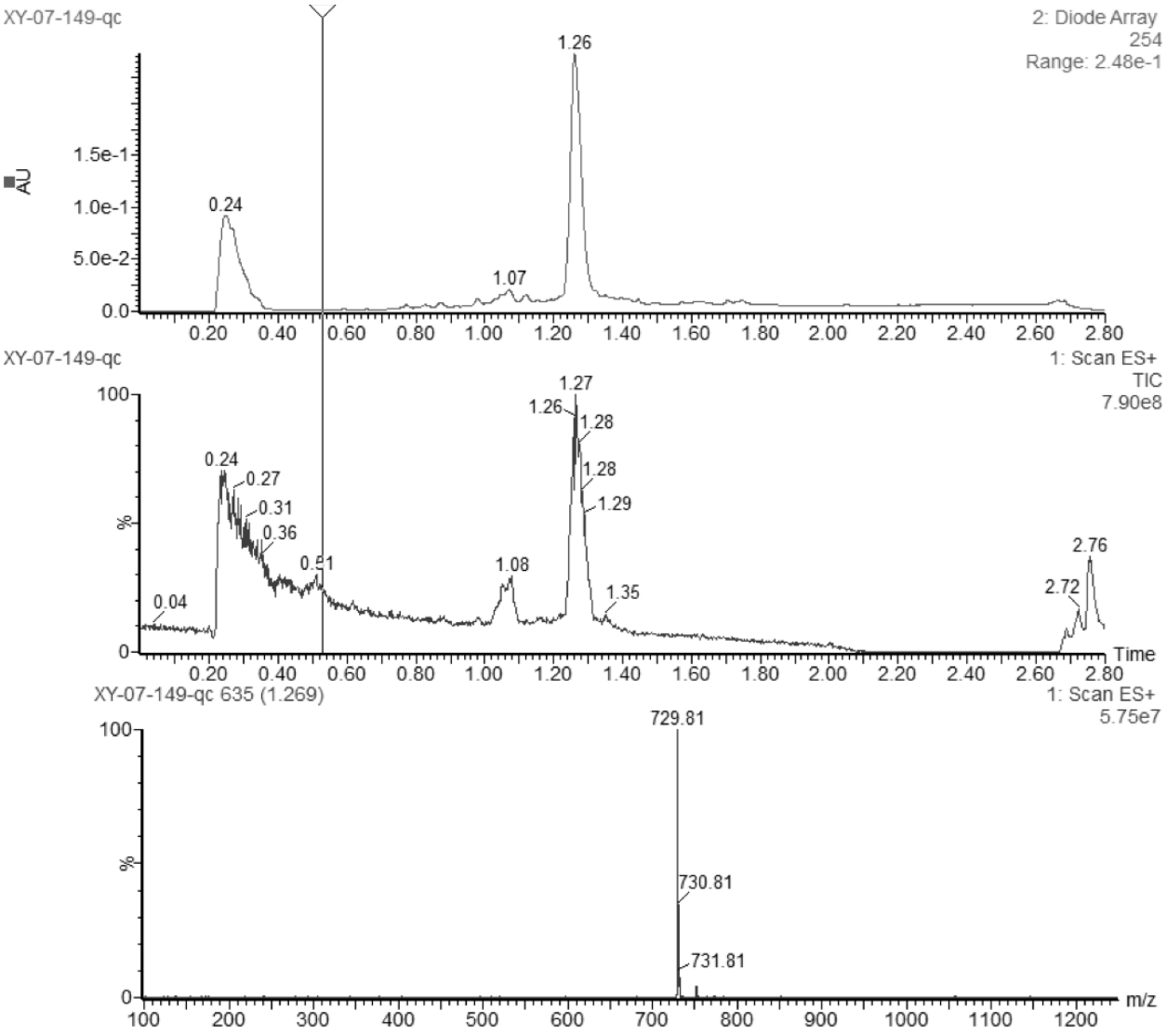
XY-07-151


XY-07-151-qc
2: Diode Array
254
Range: 1.034
AU
1.09
0.24
0.88
XY-07-151-qc
1: Scan ES+
TIC
1.52e9
%
1.10
1.09
1.12
1.14
1.15
1.08
0.25
0.27
0.23
0.30
0.34
0.56
1.05
0.88
1.47
2.76
2.73
Time
XY-07-151-qc 551 (1.101)
1: Scan ES+
1.22e8
641.90
642.80
m/z

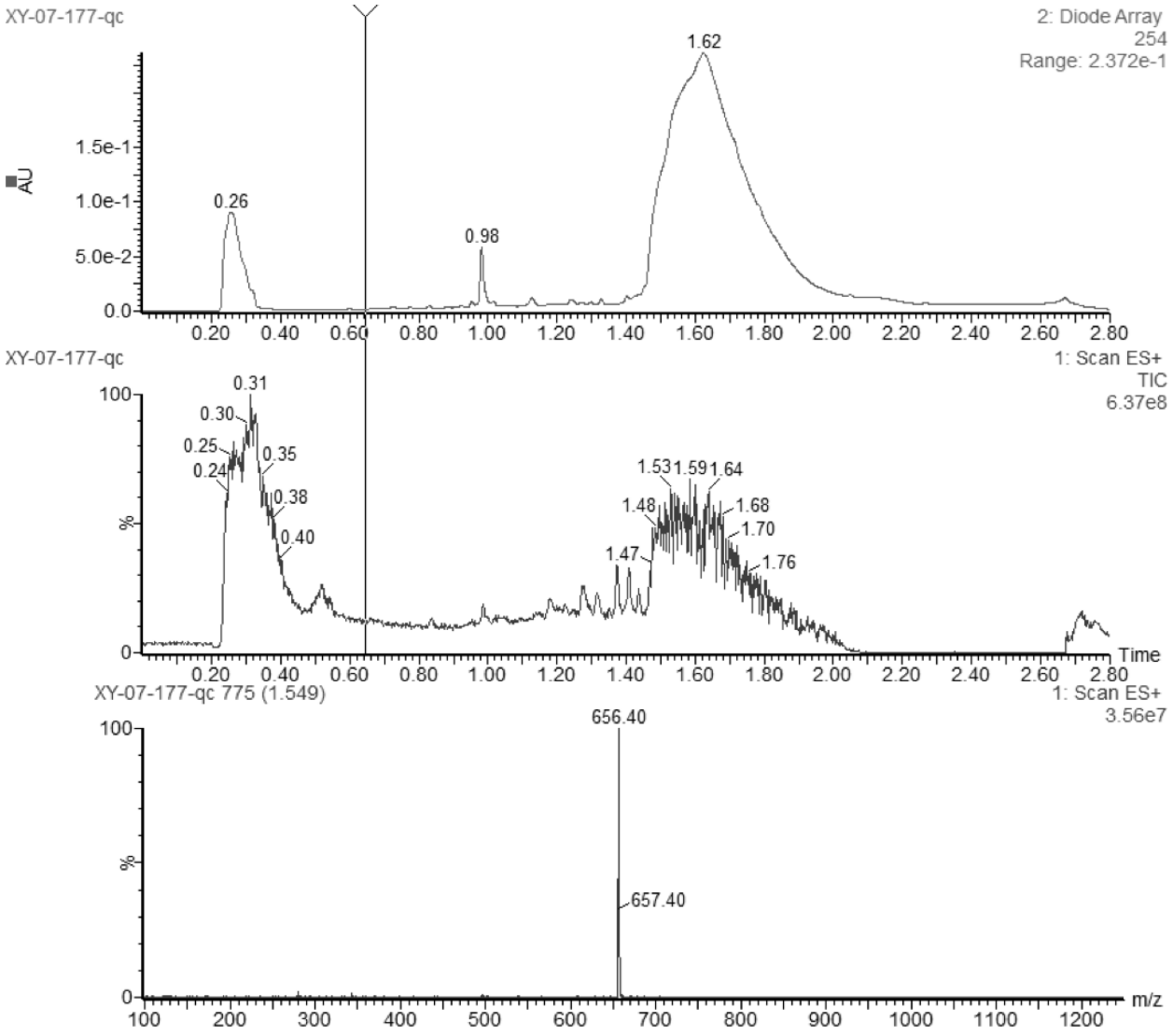
XY-07-148


XY-07-148-qc
2: Diode Array
254
Range: 1.193e-1
AU
0.24
1.36
1.12
1.70
2.66
XY-07-148-qc
1: Scan ES+
TIC
4.84e8
%
0.23
0.26
0.29
0.33
0.38
0.08
1.37
1.36
1.38
1.39
1.40
1.41
2.00
2.76
2.72
2.69
Time
XY-07-148-qc 689 (1.377)
1: Scan ES+
2.77e7
697.80
698.90
m/z

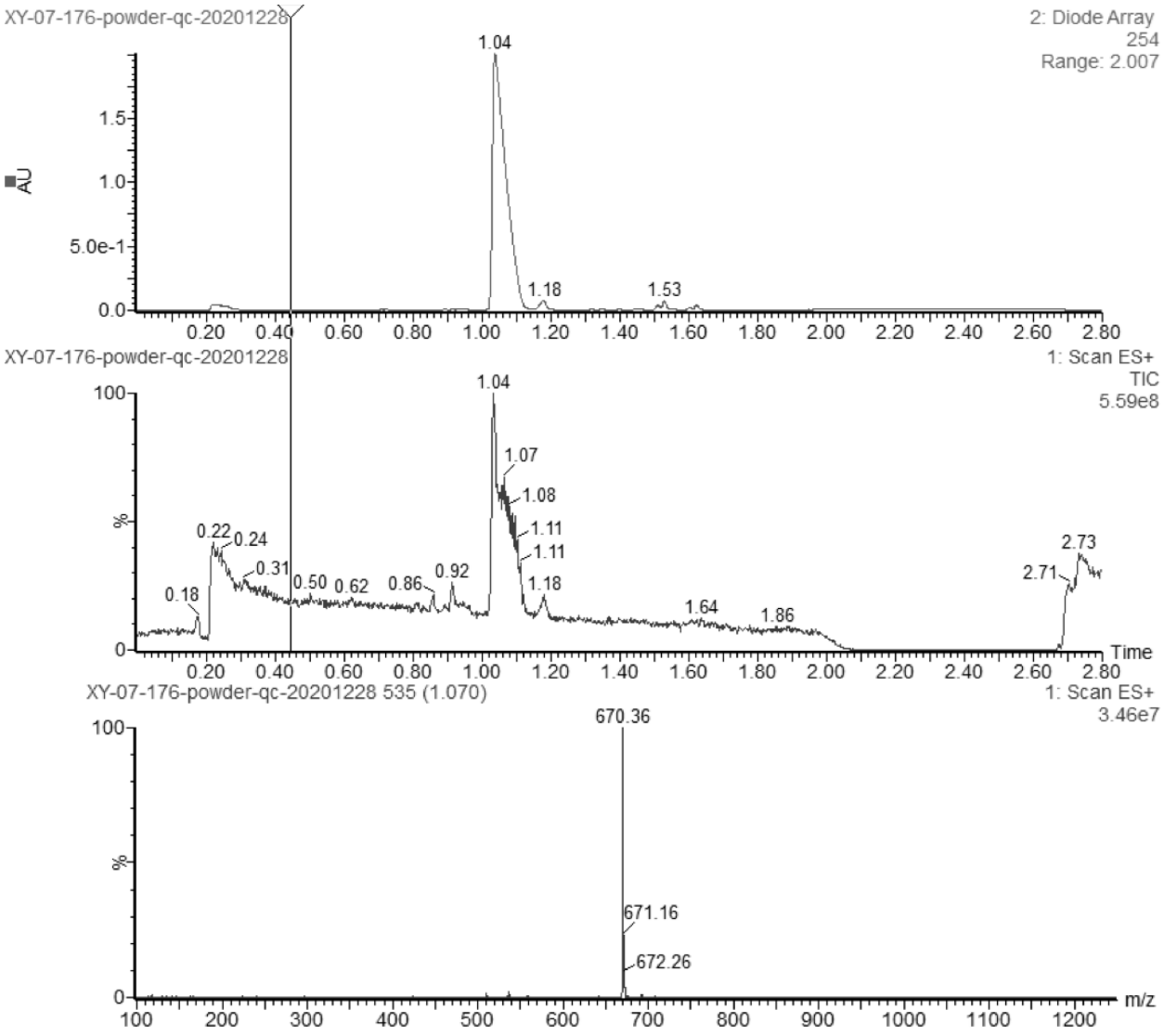
XY-07-149


XY-07-149-qc
2: Diode Array
254
Range: 2.48e-1
AU
1.26
0.24
1.07
XY-07-149-qc
1: Scan ES+
TIC
7.90e8
%
1.27
1.26
1.28
1.28
1.29
0.24
0.27
0.31
0.36
0.51
1.08
1.35
2.76
2.72
0.04
Time
XY-07-149-qc 635 (1.269)
1: Scan ES+
5.75e7
729.81
730.81
731.81
m/z

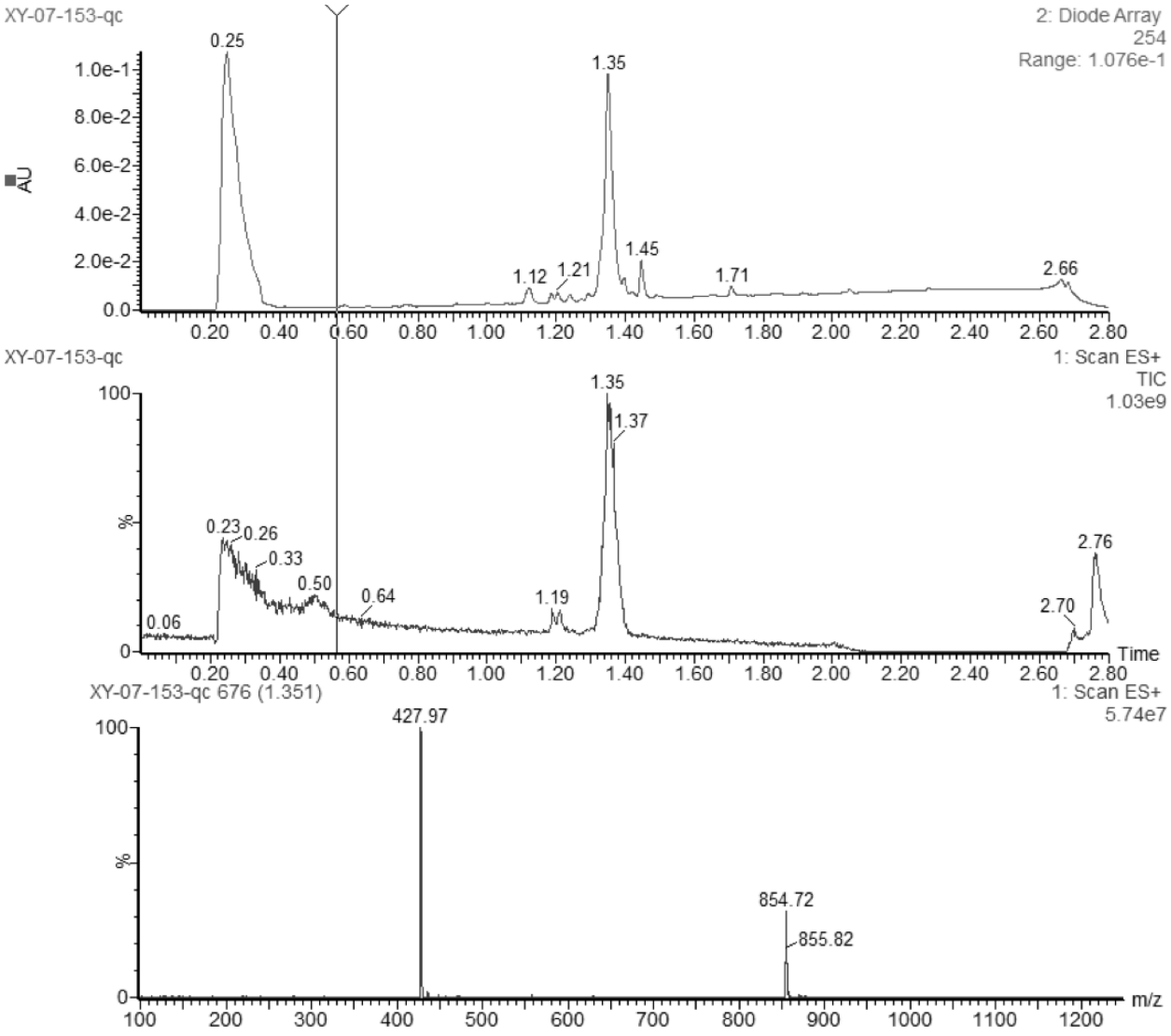
XY-07-177


XY-07-177-qc
2: Diode Array
254
Range: 2.372e-1
AU
1.62
0.26
0.98
XY-07-177-qc
1: Scan ES+
TIC
6.37e8
%
0.31
0.30
0.25
0.24
0.35
0.38
0.40
1.53
1.59
1.64
1.48
1.68
1.70
1.47
1.76
Time
XY-07-177-qc 775 (1.549)
1: Scan ES+
3.56e7
656.40
657.40
m/z

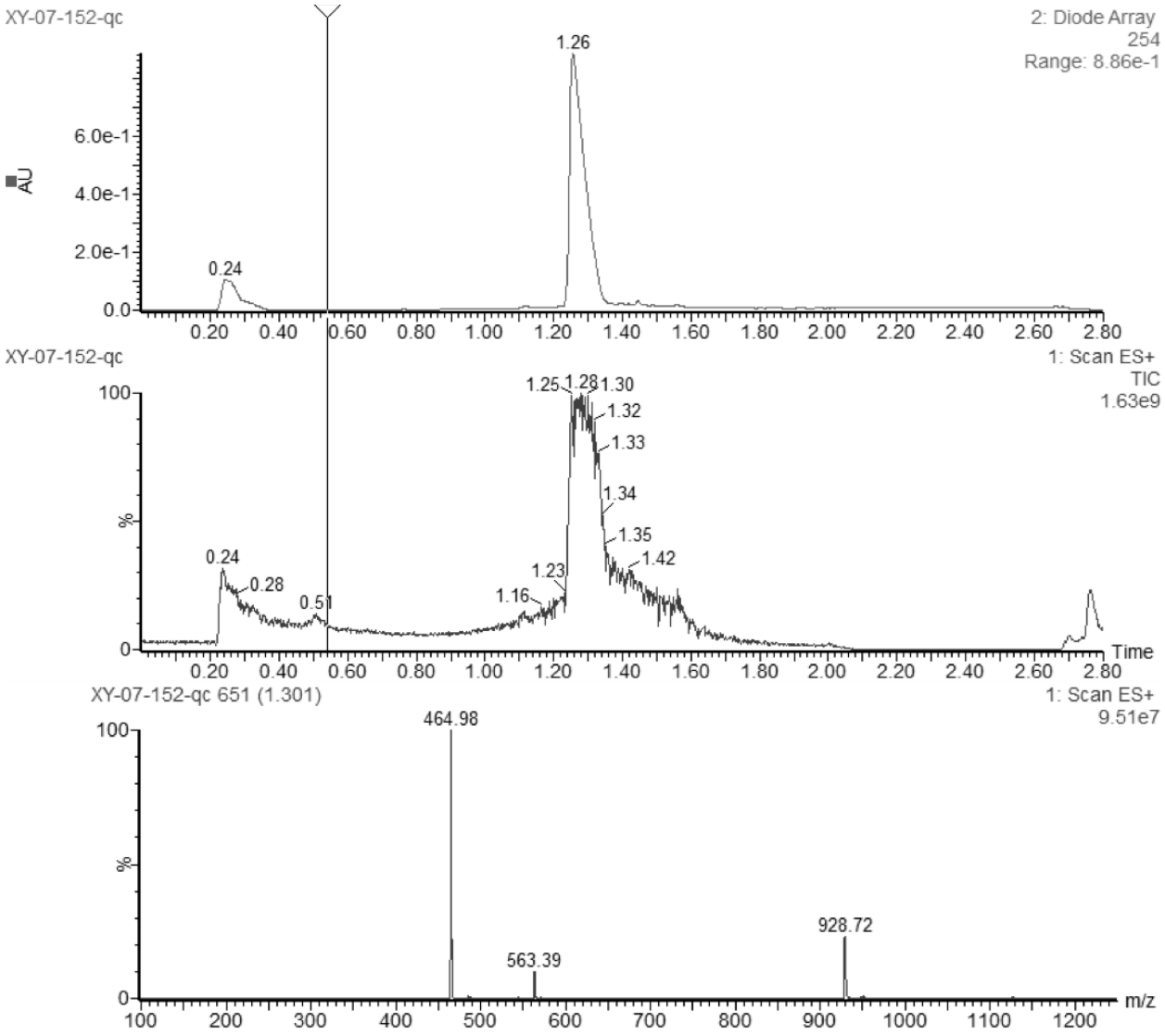
XY-07-176


XY-07-176-powder-qc-20201228
2: Diode Array
254
Range: 2.007
AU
1.04
1.18
1.53
XY-07-176-powder-qc-20201228
1: Scan ES+
TIC
5.59e8
%
1.04
1.07
1.08
1.11
1.11
1.18
0.18
0.22
0.24
0.31
0.50
0.62
0.86
0.92
1.64
1.86
2.71
2.73
Time
XY-07-176-powder-qc-20201228 535 (1.070)
1: Scan ES+
3.46e7
%
670.36
671.16
672.26
m/z

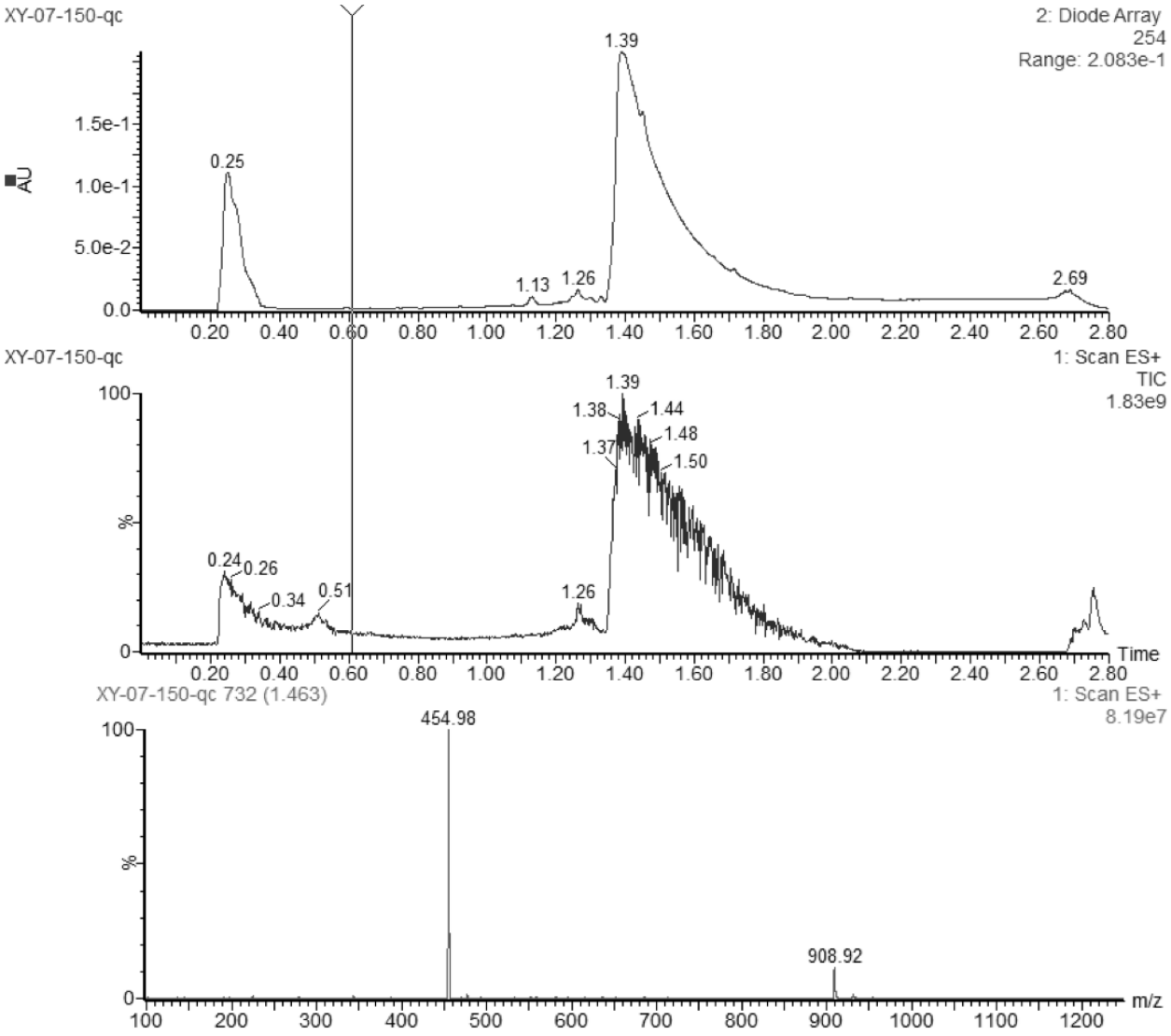
XY-07-153


XY-07-153-qc
2: Diode Array
254
Range: 1.076e-1
AU
0.25
1.35
1.12
1.21
1.45
1.71
2.66
XY-07-153-qc
1: Scan ES+
TIC
1.03e9
%
1.35
1.37
0.23
0.26
0.33
0.50
0.64
1.19
0.06
2.70
2.76
Time
XY-07-153-qc 676 (1.351)
1: Scan ES+
5.74e7
427.97
854.72
855.82
m/z

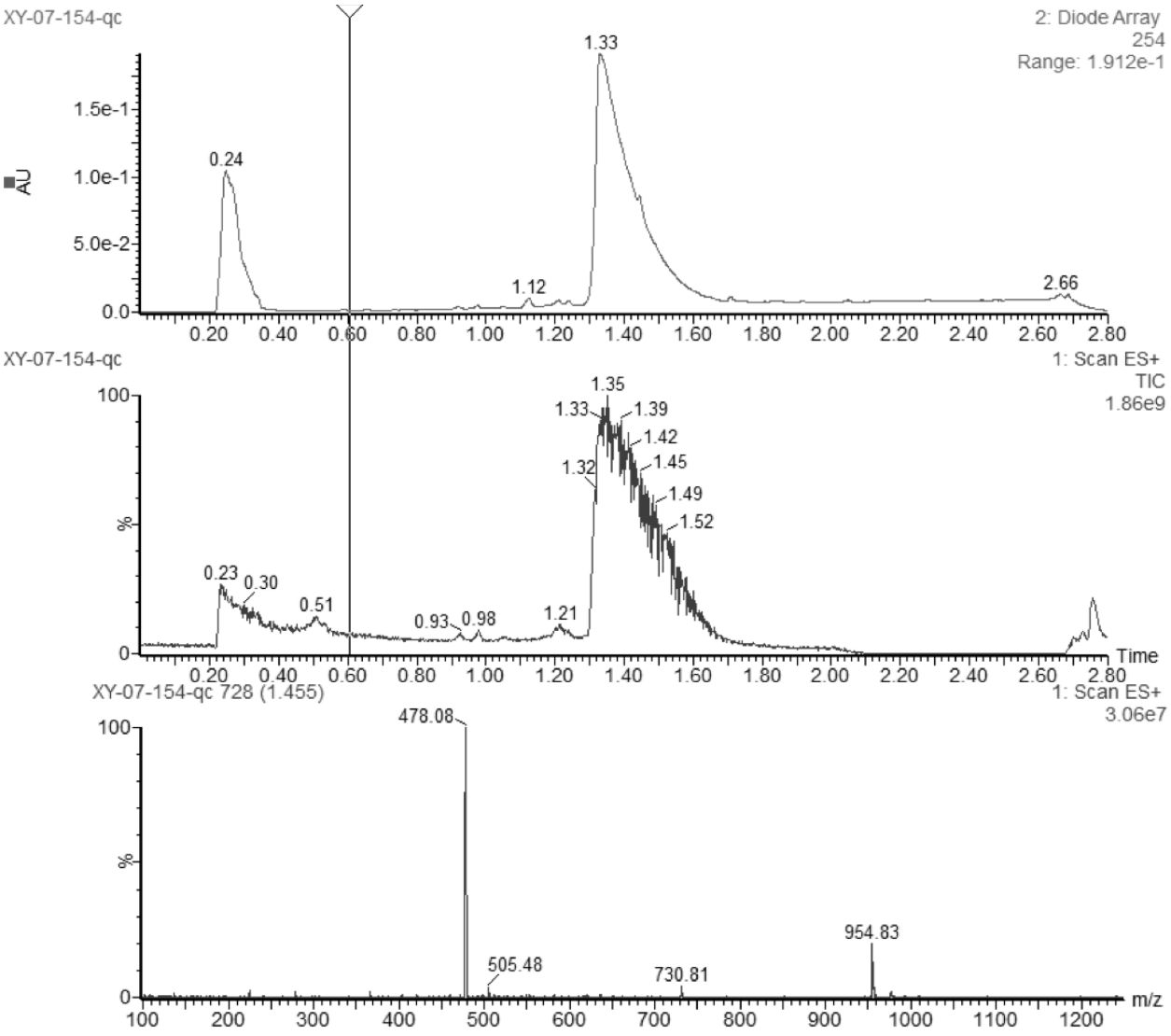
XY-07-152


XY-07-152-qc
2: Diode Array
254
Range: 8.86e-1
AU
1.26
0.24
XY-07-152-qc
1: Scan ES+
TIC
1.63e9
%
1.25
1.28
1.30
1.32
1.33
1.34
1.35
1.42
1.23
1.16
0.24
0.28
0.51
Time
XY-07-152-qc 651 (1.301)
1: Scan ES+
9.51e7
464.98
928.72
563.39
m/z

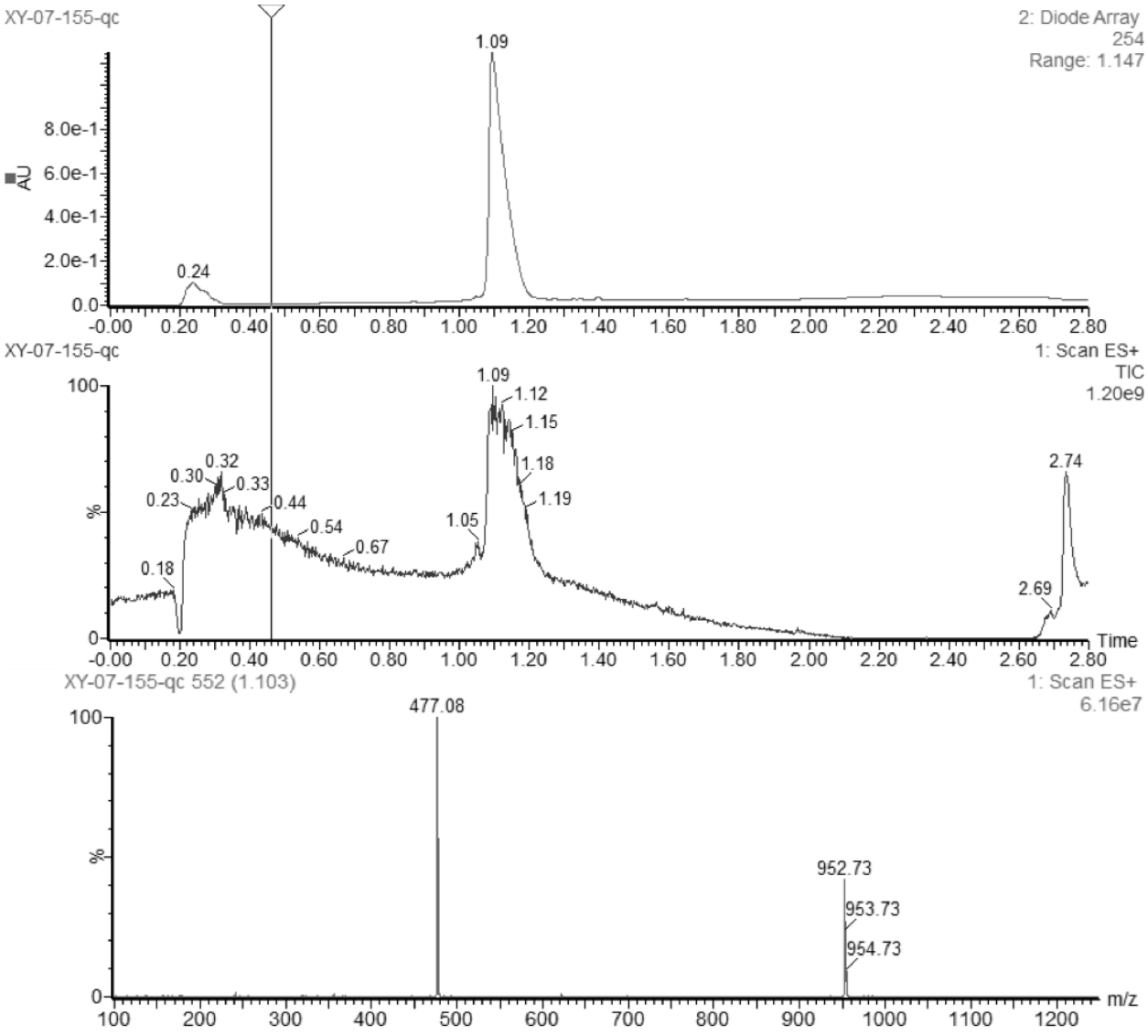
XY-07-150


XY-07-150-qc
2: Diode Array
254
Range: 2.083e-1
AU
1.5e-1
1.0e-1
5.0e-2
0.0
0.25
1.13
1.26
1.39
2.69
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
XY-07-150-qc
1: Scan ES+
TIC
1.83e9
100
%
0
0.24
0.26
0.34
0.51
1.26
1.37
1.38
1.39
1.44
1.48
1.50
Time
XY-07-150-qc 732 (1.463)
1: Scan ES+
8.19e7
454.98
908.92
m/z
100 200 300 400 500 600 700 800 900 1000 1100 1200

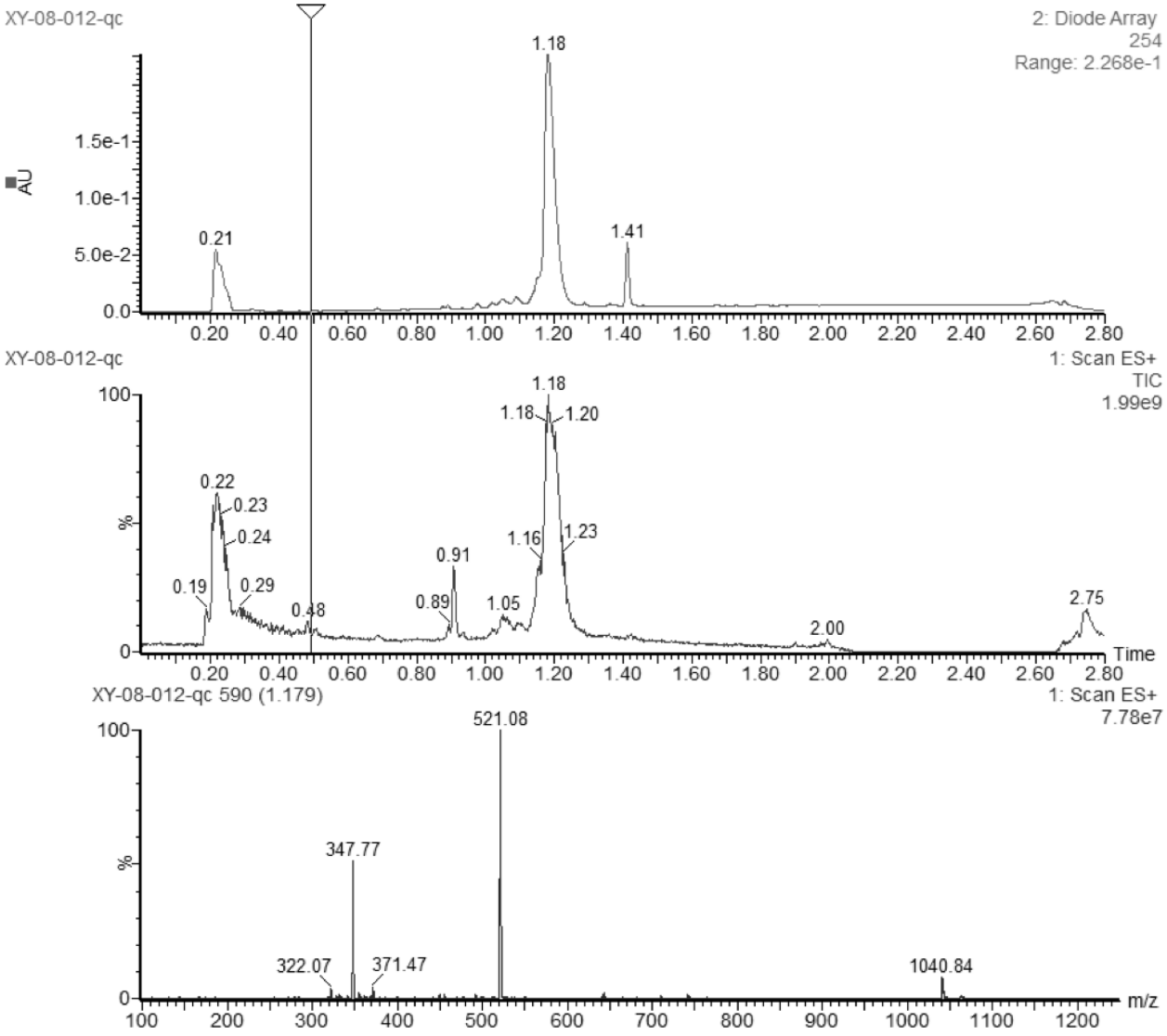
XY-07-154


XY-07-154-qc
2: Diode Array
254
Range: 1.912e-1
AU
1.5e-1
1.0e-1
5.0e-2
0.0
0.24
1.12
1.33
2.66
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
XY-07-154-qc
1: Scan ES+
TIC
1.86e9
%
100
0
0.23
0.30
0.51
0.93
0.98
1.21
1.32
1.33
1.35
1.39
1.42
1.45
1.49
1.52
Time
XY-07-154-qc 728 (1.455)
1: Scan ES+
3.06e7
478.08
505.48
730.81
954.83
m/z
100 200 300 400 500 600 700 800 900 1000 1100 1200

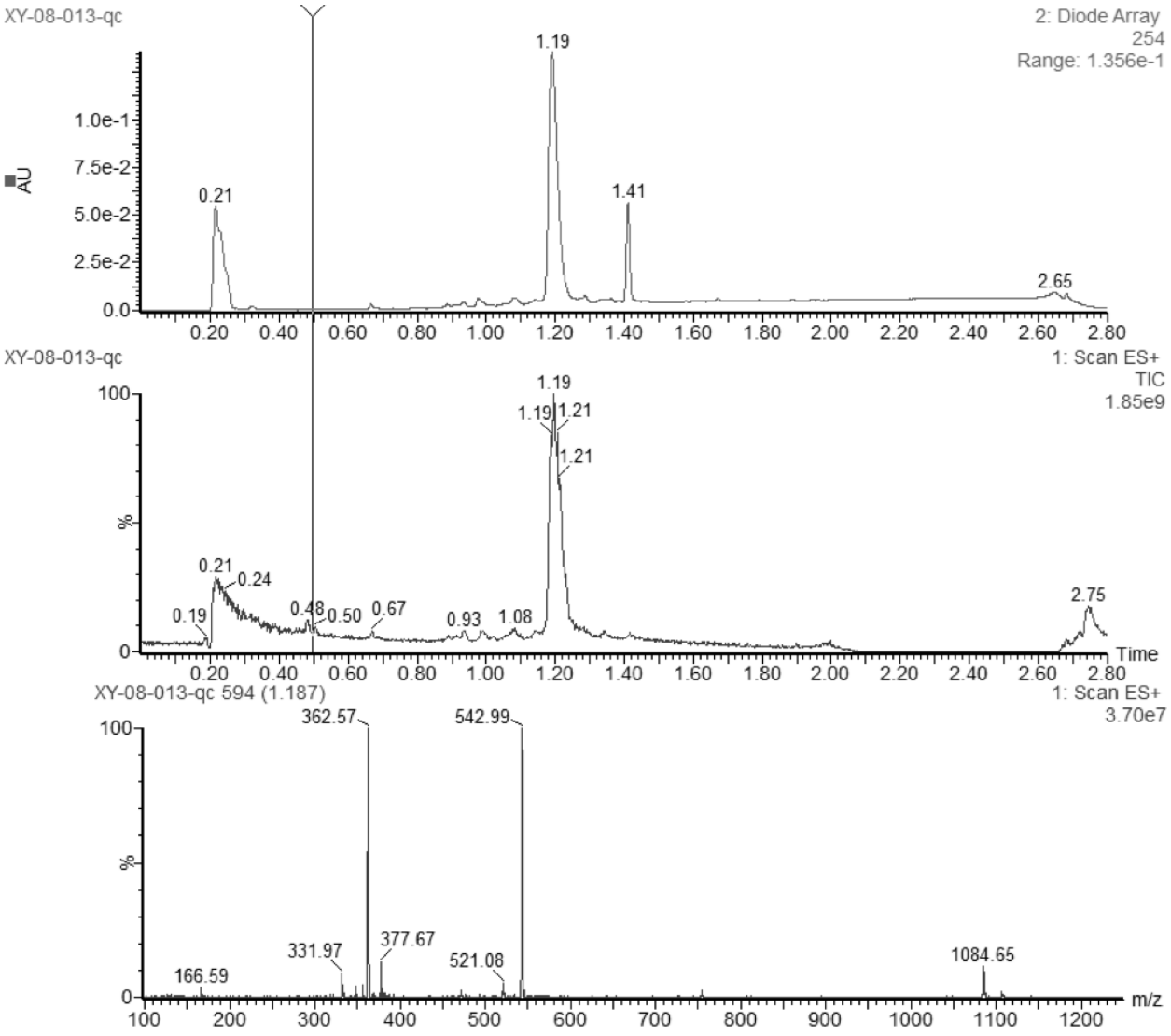
XY-07-155


XY-07-155-qc
2: Diode Array
254
Range: 1.147
AU
1.09
0.24
XY-07-155-qc
1: Scan ES+
TIC
1.20e9
%
1.09
1.12
1.15
1.18
1.19
0.32
0.30
0.33
0.23
0.44
0.54
0.67
1.05
0.18
2.74
2.69
Time
XY-07-155-qc 552 (1.103)
1: Scan ES+
6.16e7
477.08
952.73
953.73
954.73
m/z

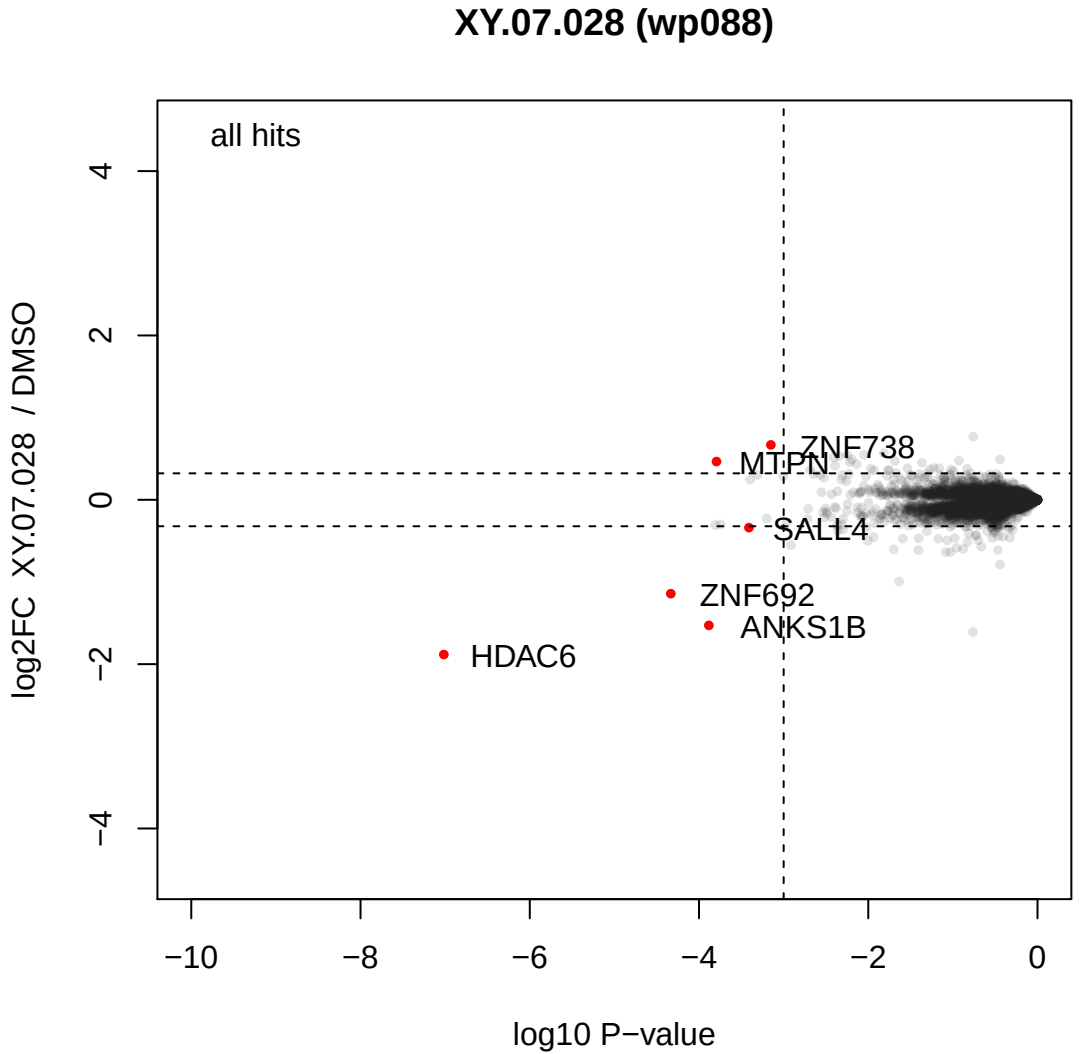
XY-08-012

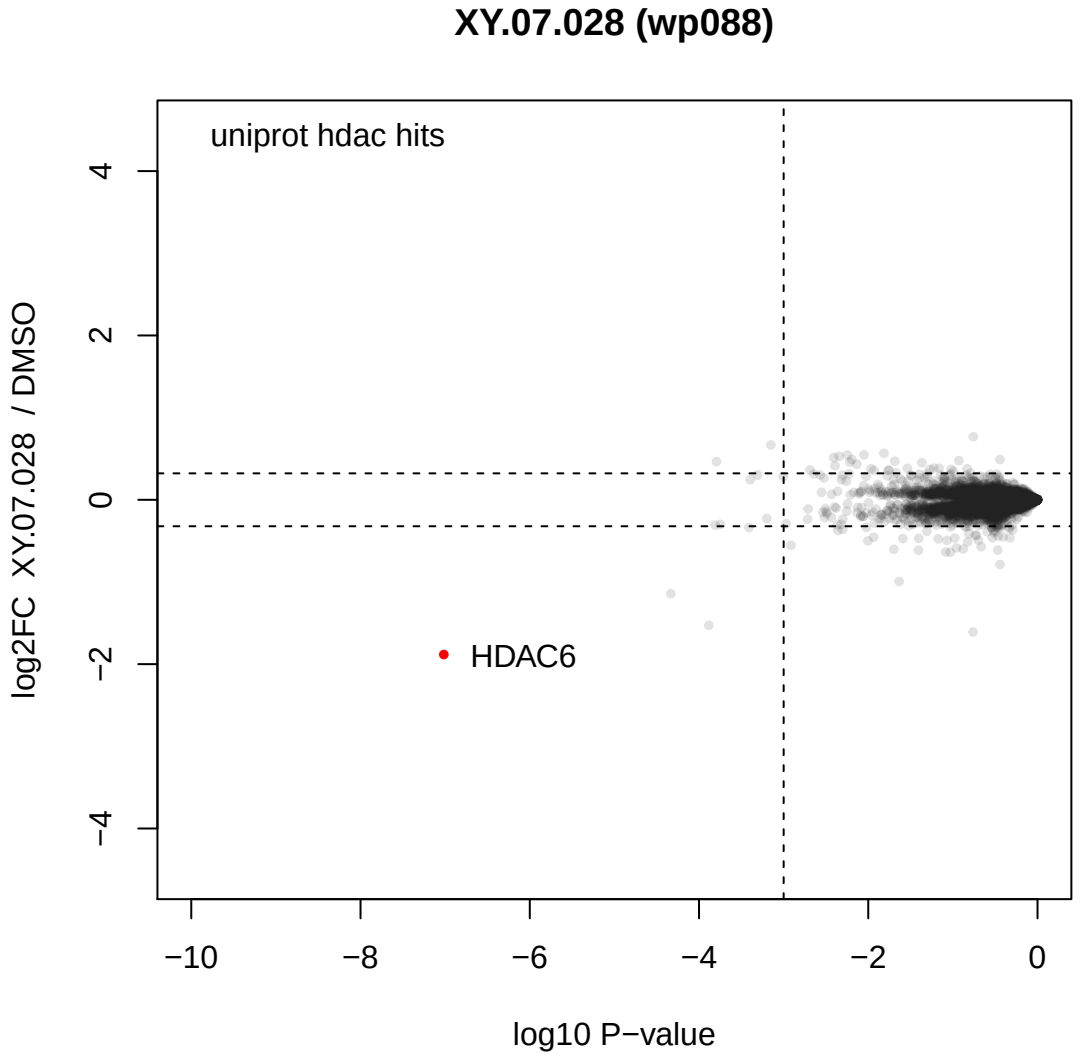

XY-08-012-qc
2: Diode Array
254
Range: 2.268e-1
AU
1.5e-1
1.0e-1
5.0e-2
0.0
1.18
0.21
1.41
0.20 0.40 0.60 0.80 1.00 1.20 1.40 1.60 1.80 2.00 2.20 2.40 2.60 2.80
XY-08-012-qc
1: Scan ES+
TIC
1.99e9
%
100
0
1.18
1.18
1.20
0.22
0.23
0.24
0.19
0.29
0.48
0.91
0.89
1.05
1.16
1.23
2.00
2.75
Time
0.20 0.40 0.60 0.80 1.00 1.20 1.40 1.60 1.80 2.00 2.20 2.40 2.60 2.80
XY-08-012-qc 590 (1.179)
1: Scan ES+
7.78e7
100
%
0
521.08
347.77
322.07
371.47
1040.84
m/z
100 200 300 400 500 600 700 800 900 1000 1100 1200

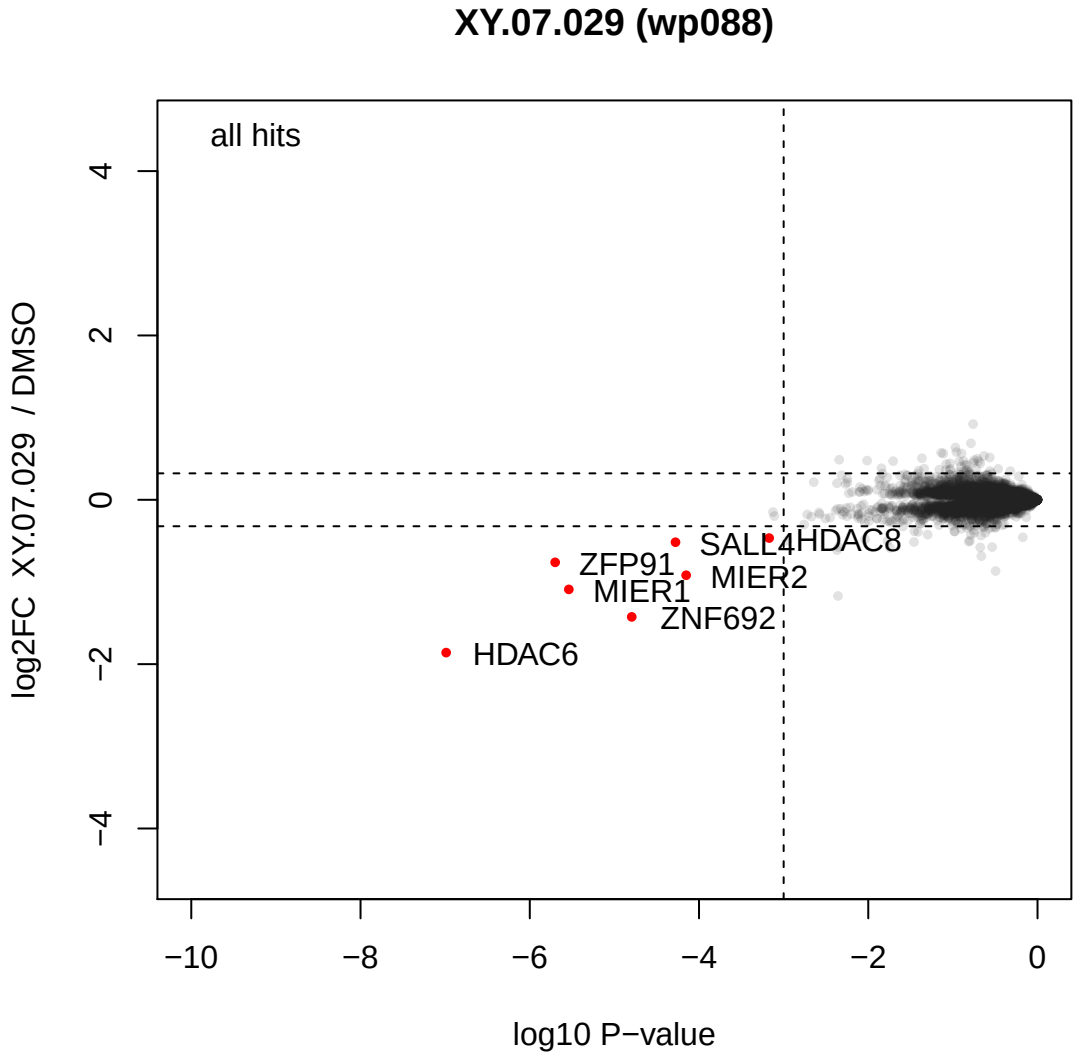
XY-08-013

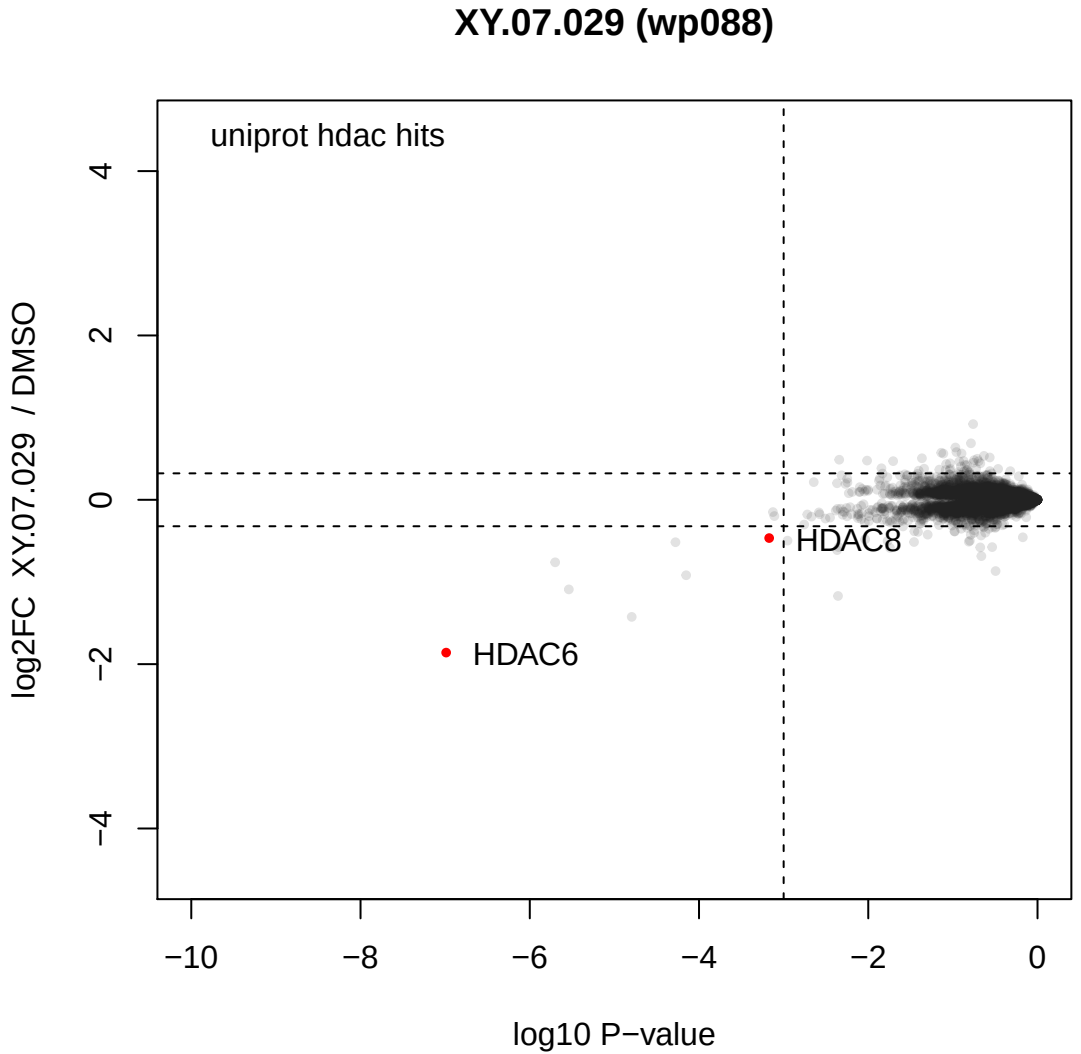

XY-08-013-qc
2: Diode Array
254
Range: 1.356e-1
AU
1.0e-1
7.5e-2
5.0e-2
2.5e-2
0.0
0.21
1.19
1.41
2.65
0.20 0.40 0.60 0.80 1.00 1.20 1.40 1.60 1.80 2.00 2.20 2.40 2.60 2.80
XY-08-013-qc
1: Scan ES+
TIC
1.85e9
%
100
0
1.19
1.19 1.21
1.21
0.21
0.24
0.19
0.48
0.50
0.67
0.93
1.08
2.75
Time
0.20 0.40 0.60 0.80 1.00 1.20 1.40 1.60 1.80 2.00 2.20 2.40 2.60 2.80
XY-08-013-qc 594 (1.187)
1: Scan ES+
3.70e7
%
100
0
362.57
542.99
331.97
377.67
521.08
166.59
1084.65
m/z
100 200 300 400 500 600 700 800 900 1000 1100 1200

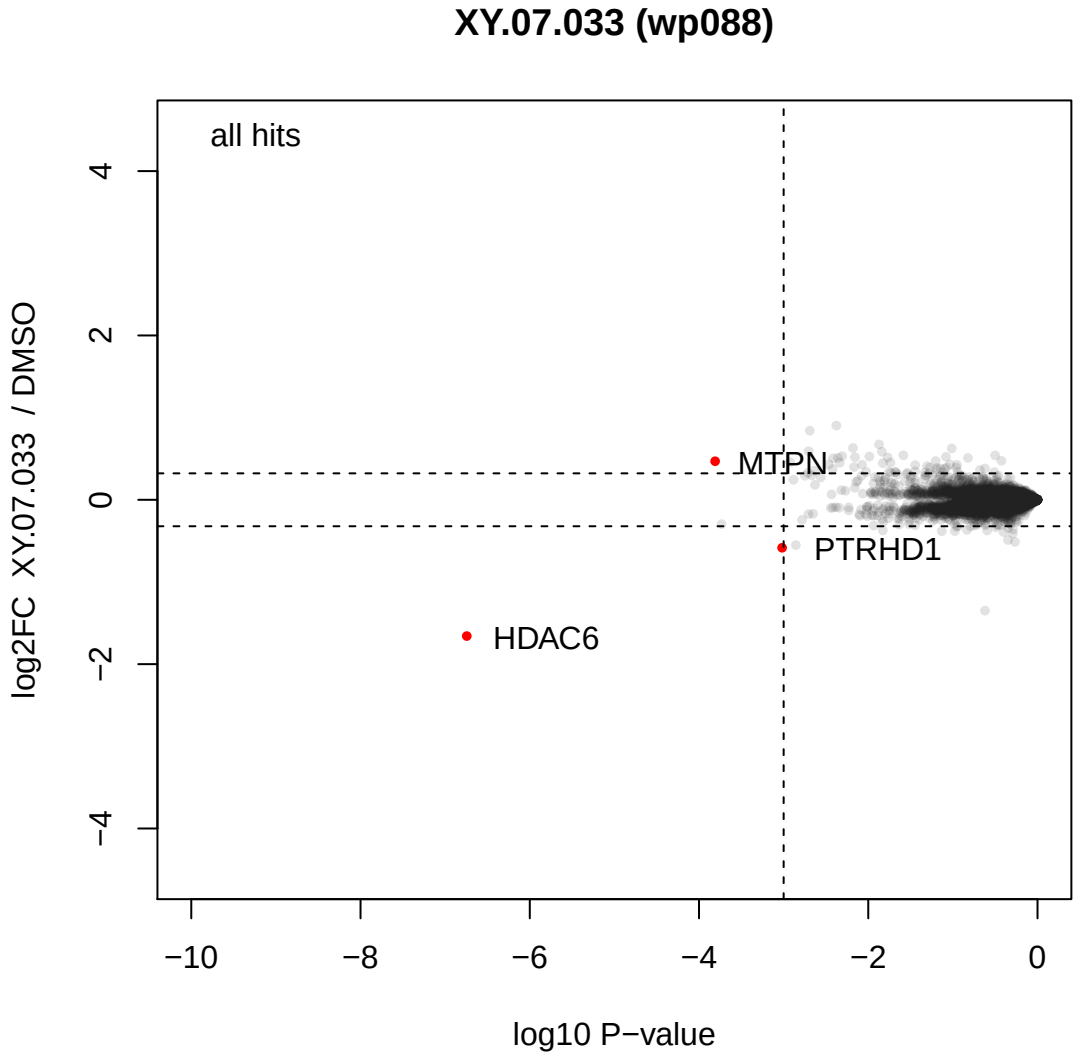
Data S2 | Proteomics scatterplots profiling 52 HDAC-targeted degraders over 101 independent treatments included in this study. Related to Figure 1 and Supplemental Figure S1.

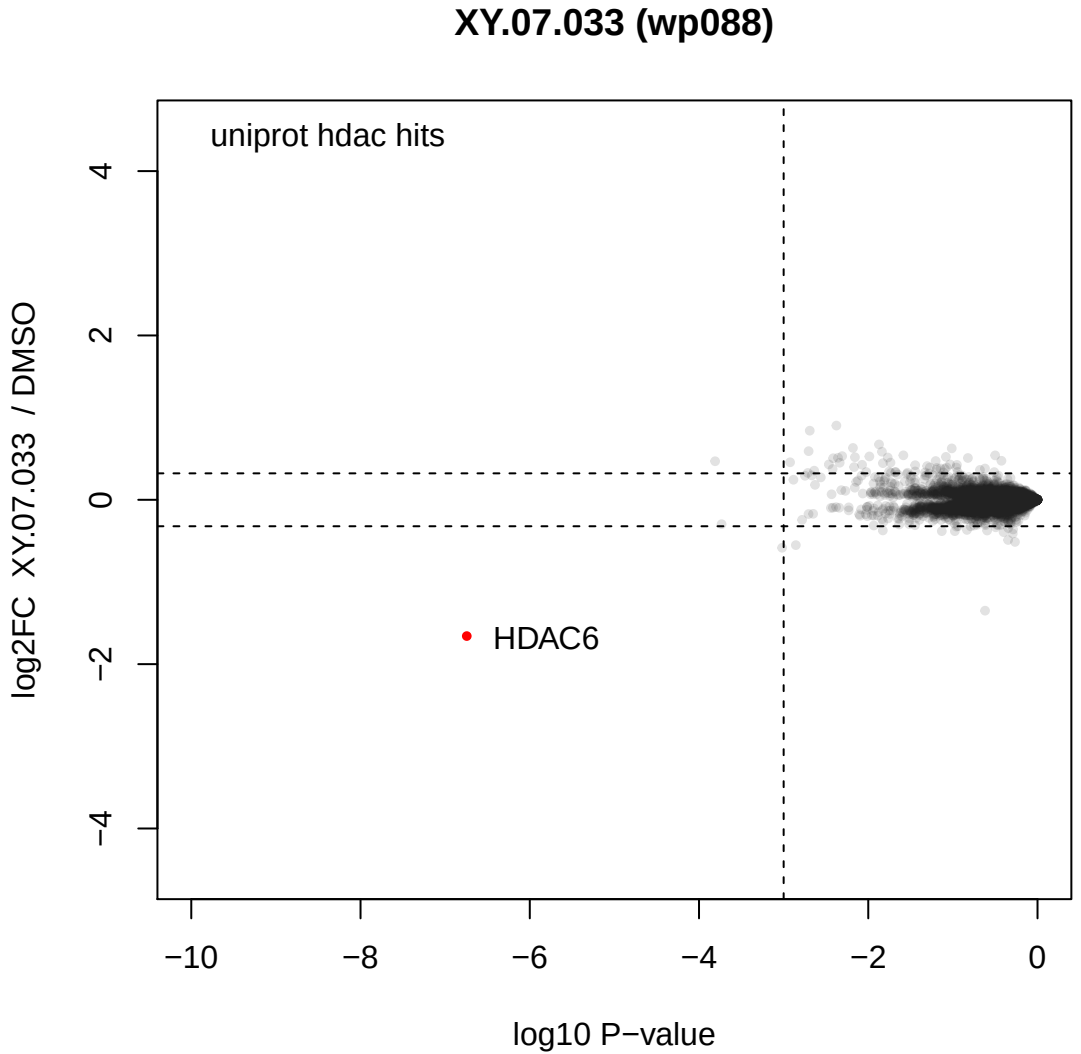

XY.07.028 (wp088)
all hits
ZNF738
MTPN
SALL4
ZNF692
ANKS1B
HDAC6
log2FC XY.07.028 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

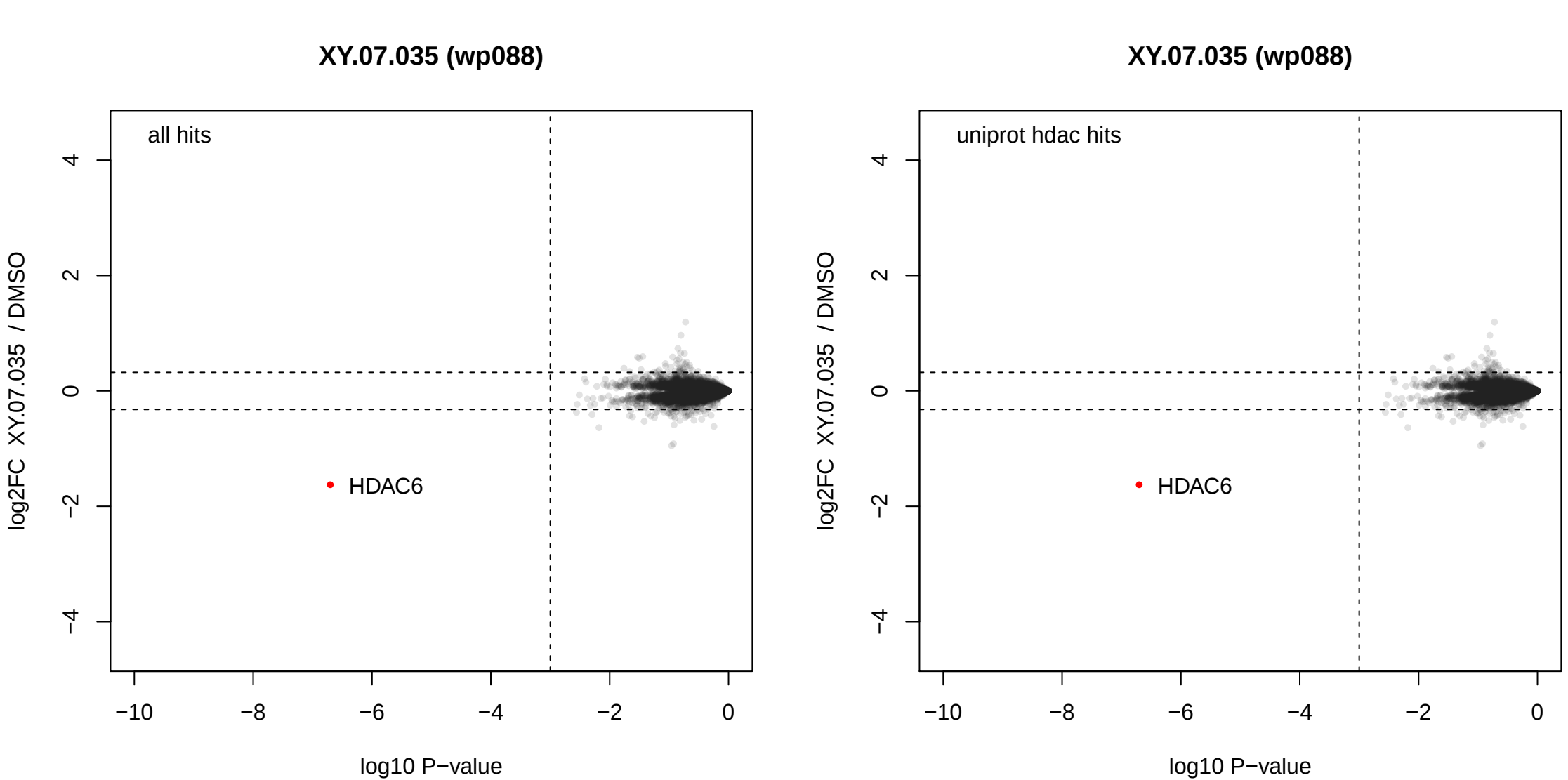

XY.07.028 (wp088)
uniprot hdac hits
HDAC6
log2FC XY.07.028 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

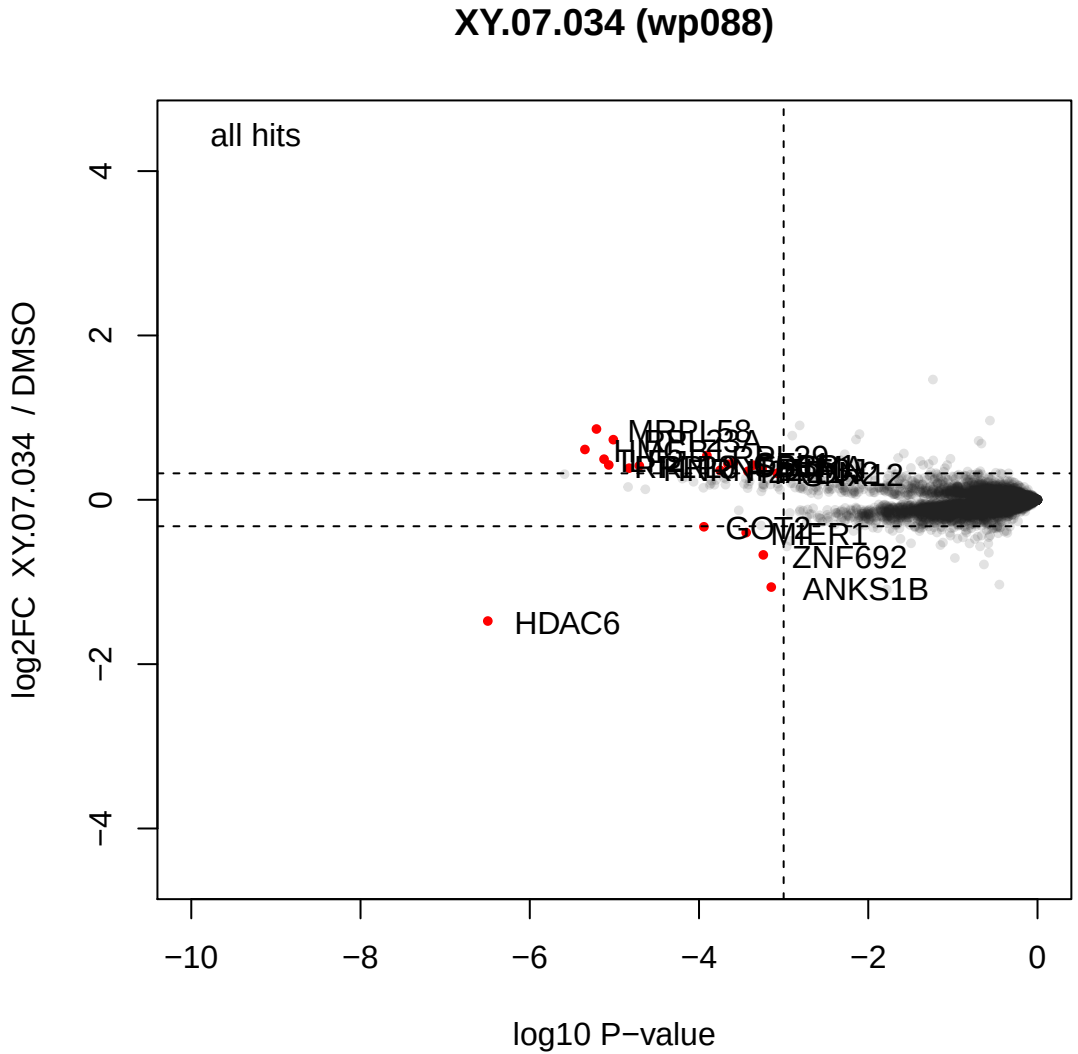

XY.07.029 (wp088)
all hits
log2FC XY.07.029 / DMSO
log10 P−value
HDAC8
SALL4
ZFP91
MIER2
MIER1
ZNF692
HDAC6

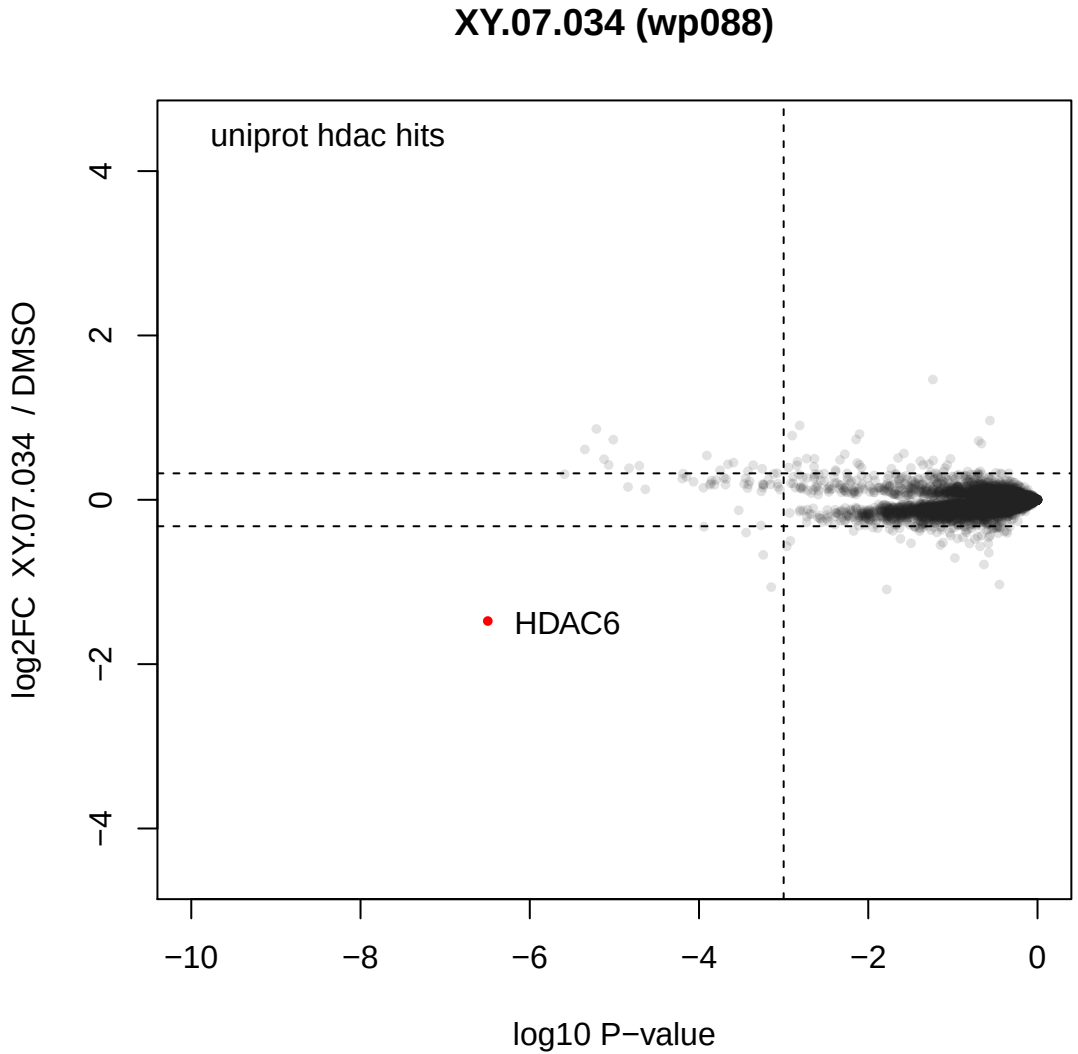

XY.07.029 (wp088)
uniprot hdac hits
log2FC XY.07.029 / DMSO
log10 P−value
HDAC8
HDAC6

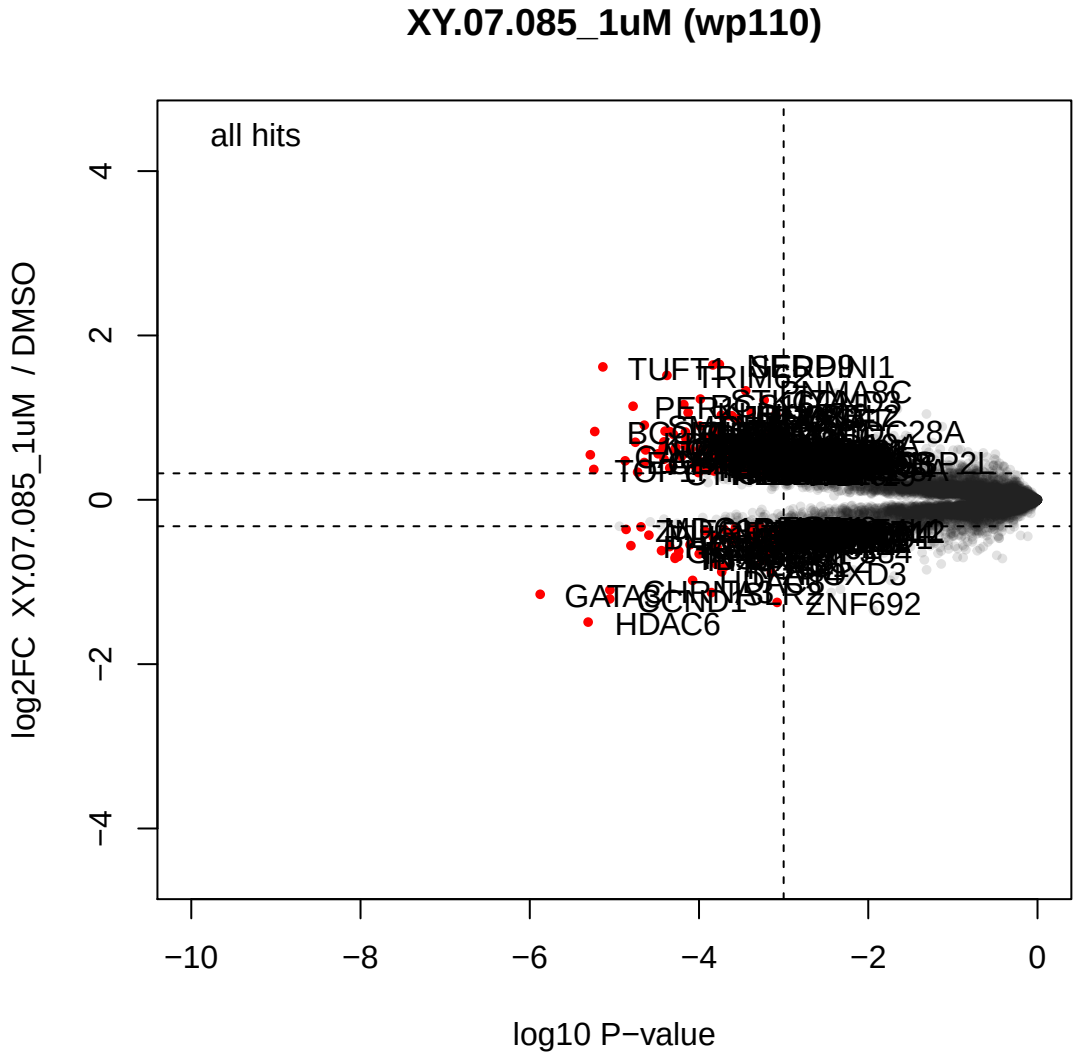

XY.07.033 (wp088)
all hits
MTPN
PTRHD1
HDAC6
log2FC XY.07.033 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

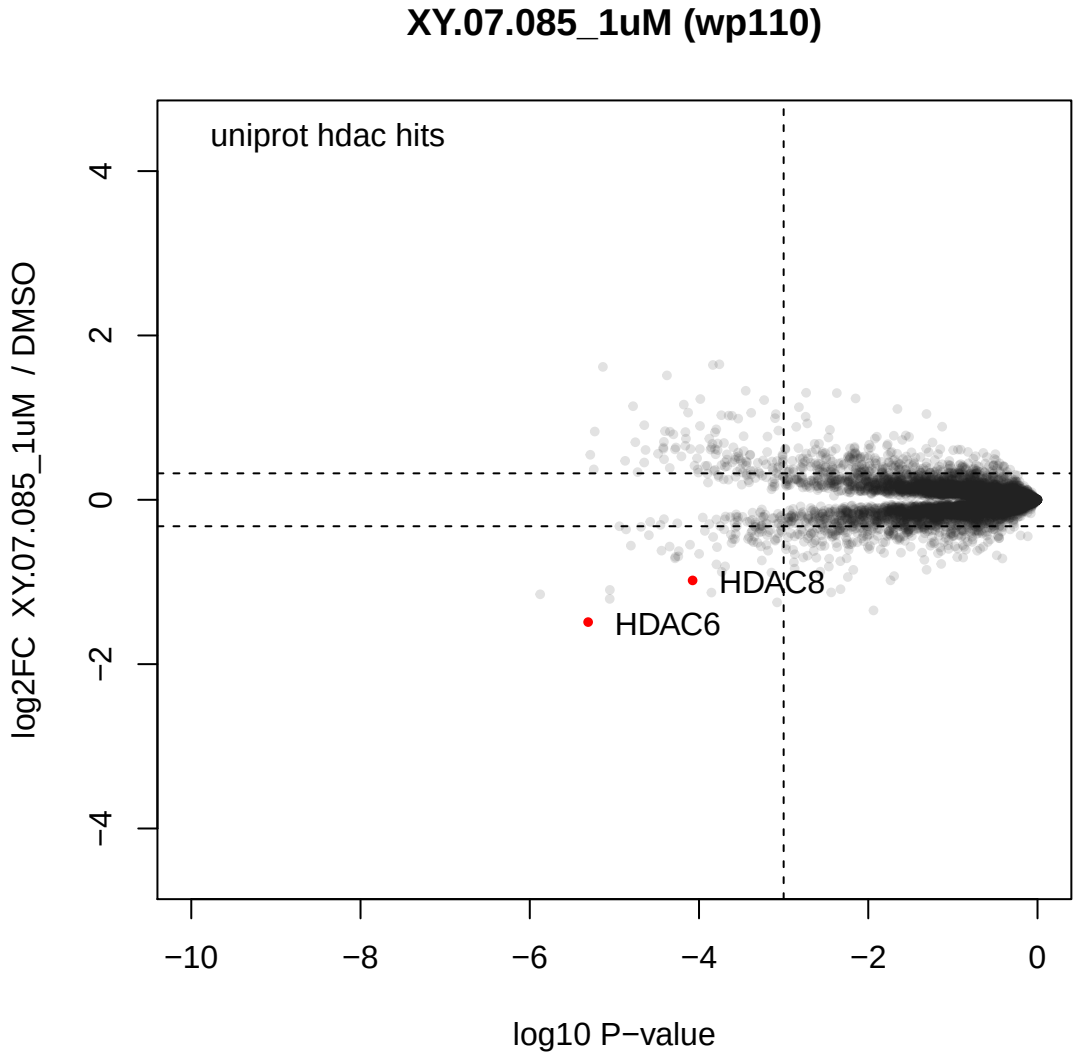

XY.07.033 (wp088)
uniprot hdac hits
HDAC6
log2FC XY.07.033 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

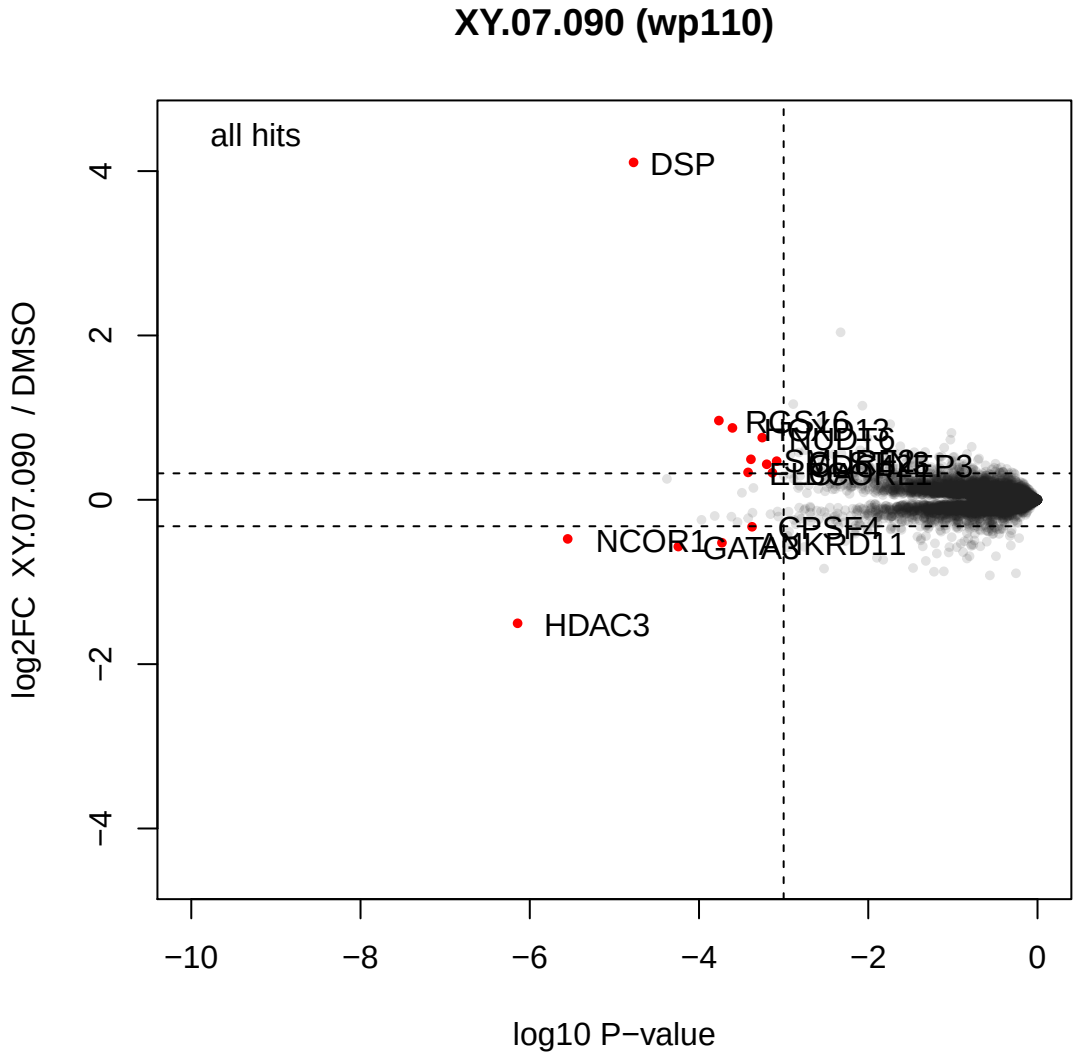

XY.07.035 (wp088)
all hits
HDAC6
log2FC XY.07.035 / DMSO
log10 P−value
XY.07.035 (wp088)
uniprot hdac hits
HDAC6
log2FC XY.07.035 / DMSO
log10 P−value

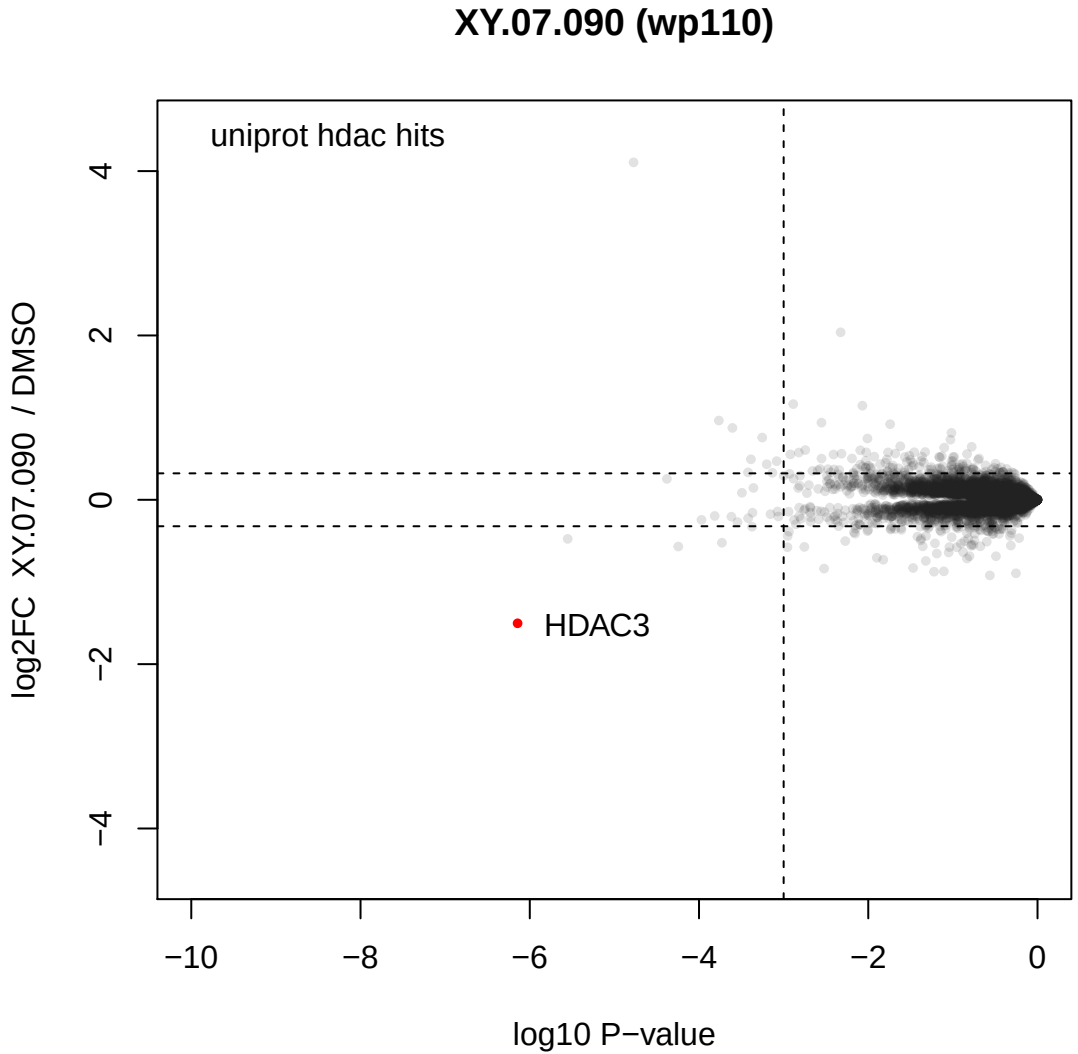

XY.07.034 (wp088)
all hits
log2FC XY.07.034 / DMSO
log10 P−value
HDAC6
ZNF692
ANKS1B

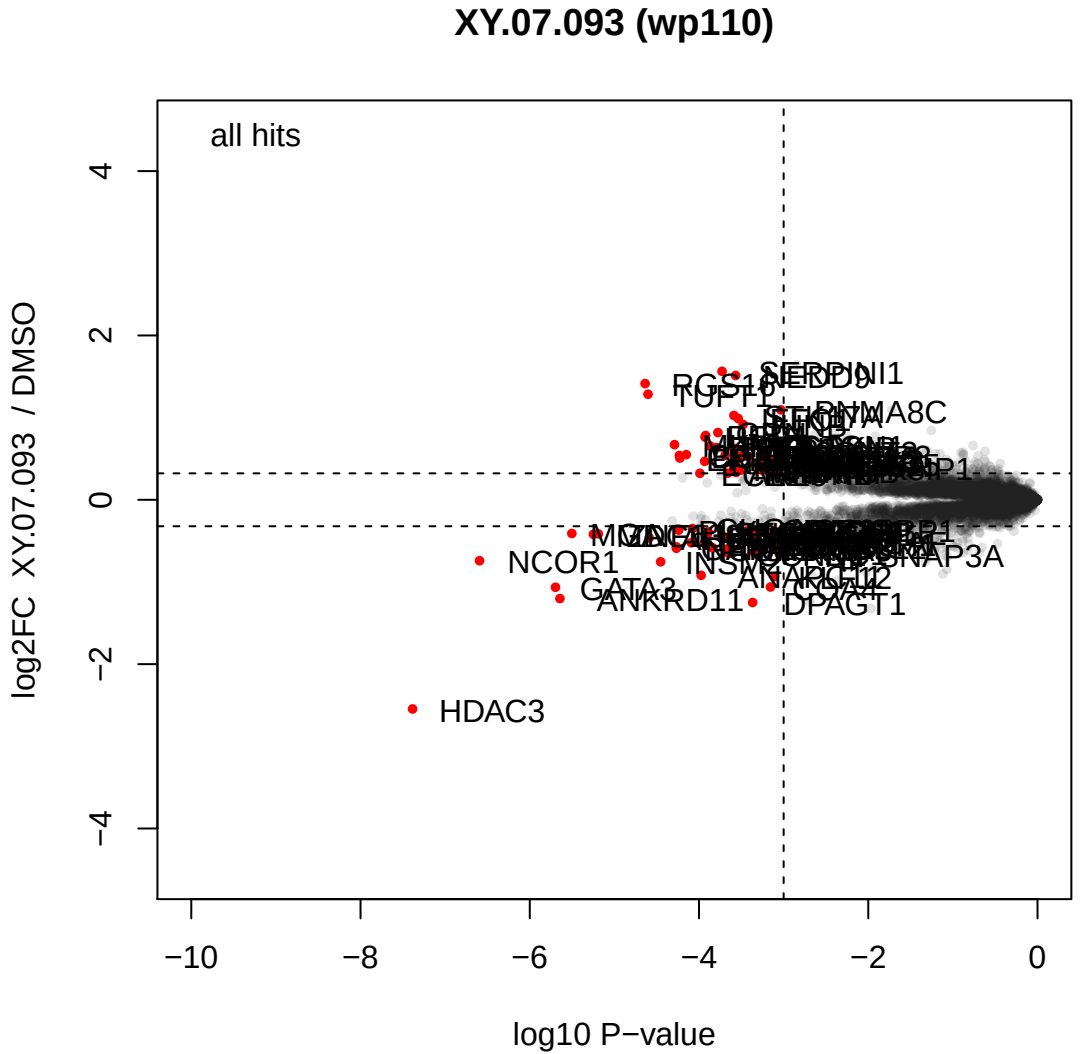

XY.07.034 (wp088)
uniprot hdac hits
log2FC XY.07.034 / DMSO
log10 P−value
HDAC6

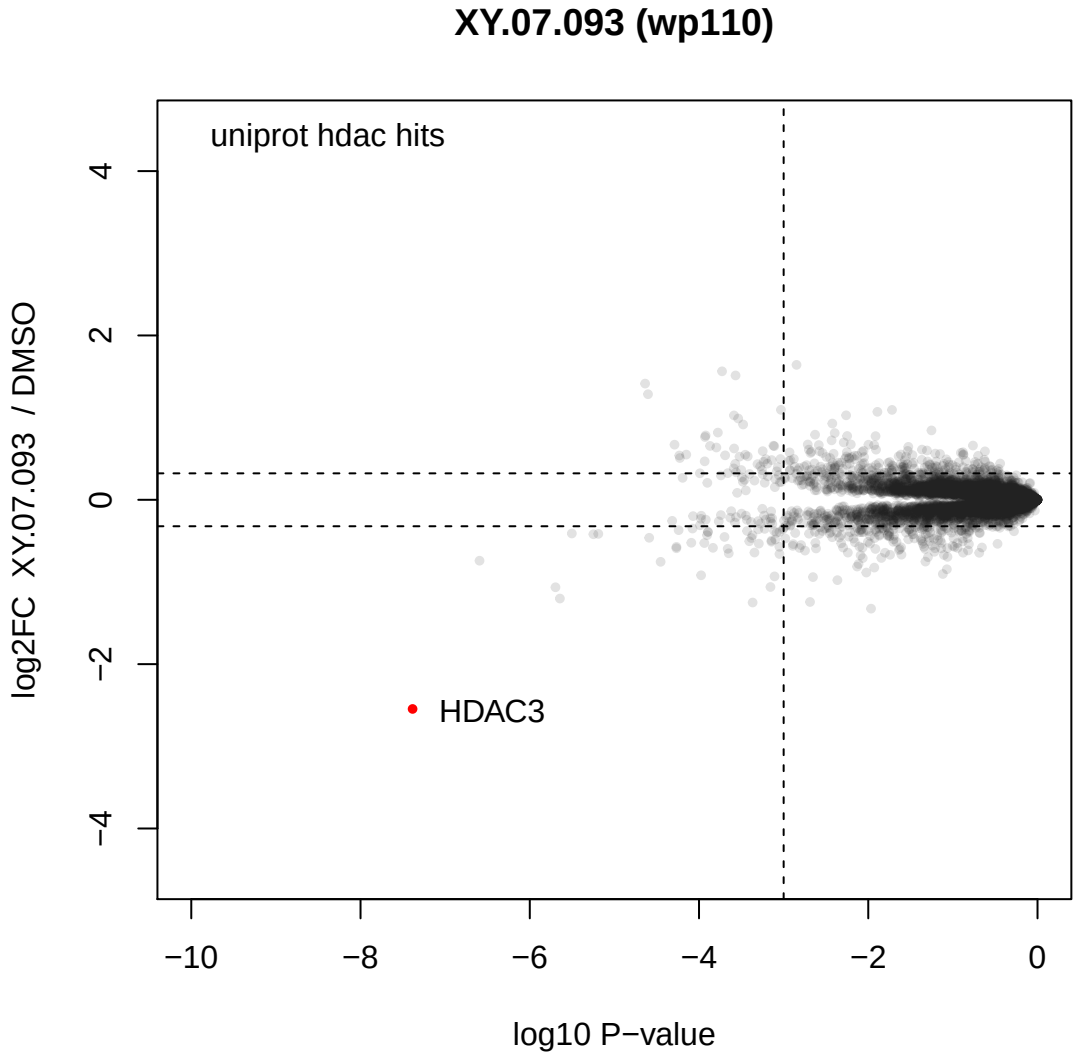

XY.07.085_1uM (wp110)
all hits
log2FC XY.07.085_1uM / DMSO
log10 P−value
TUFT1
HDAC6
ZNF692
GCND1
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

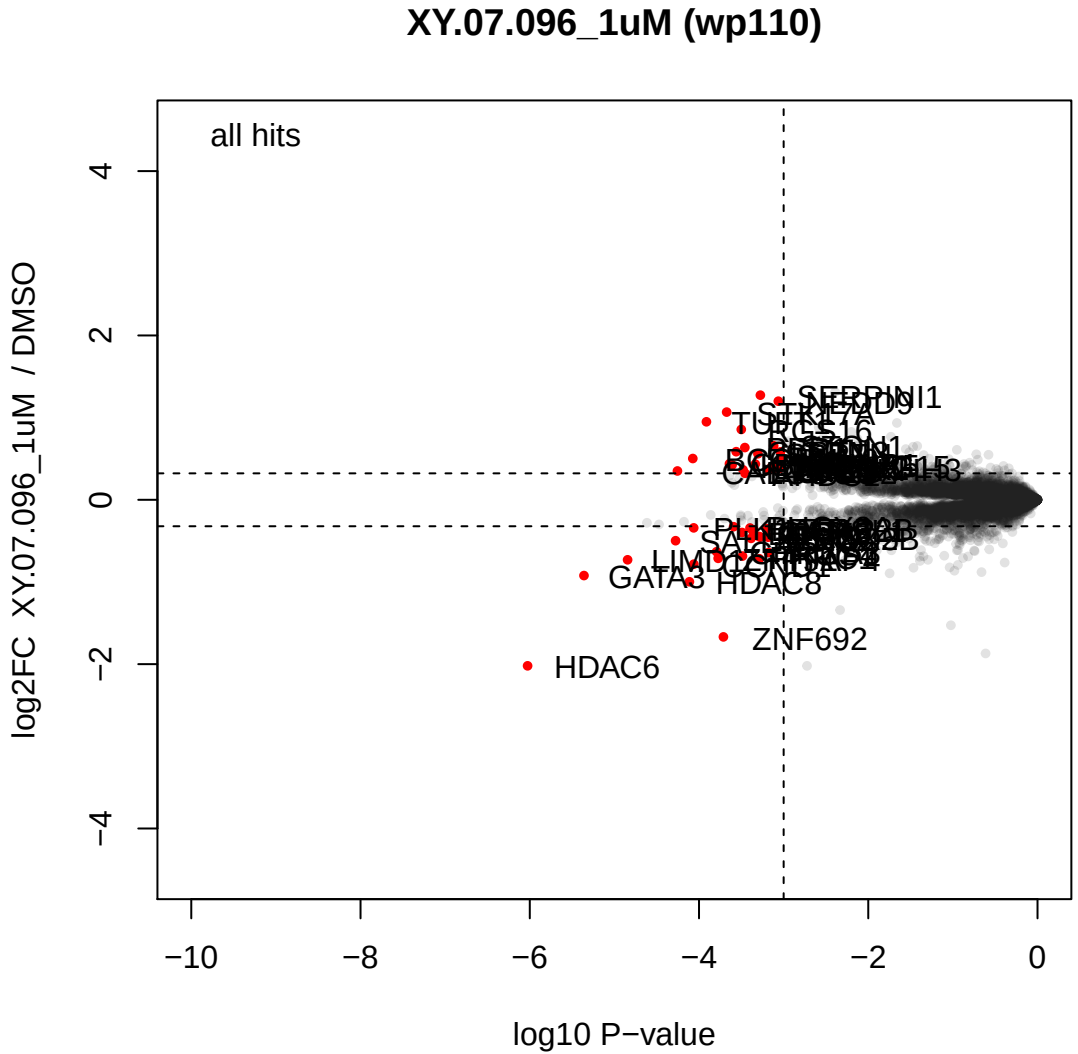

XY.07.085_1uM (wp110)
uniprot hdac hits
log2FC XY.07.085_1uM / DMSO
log10 P−value
HDAC8
HDAC6
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

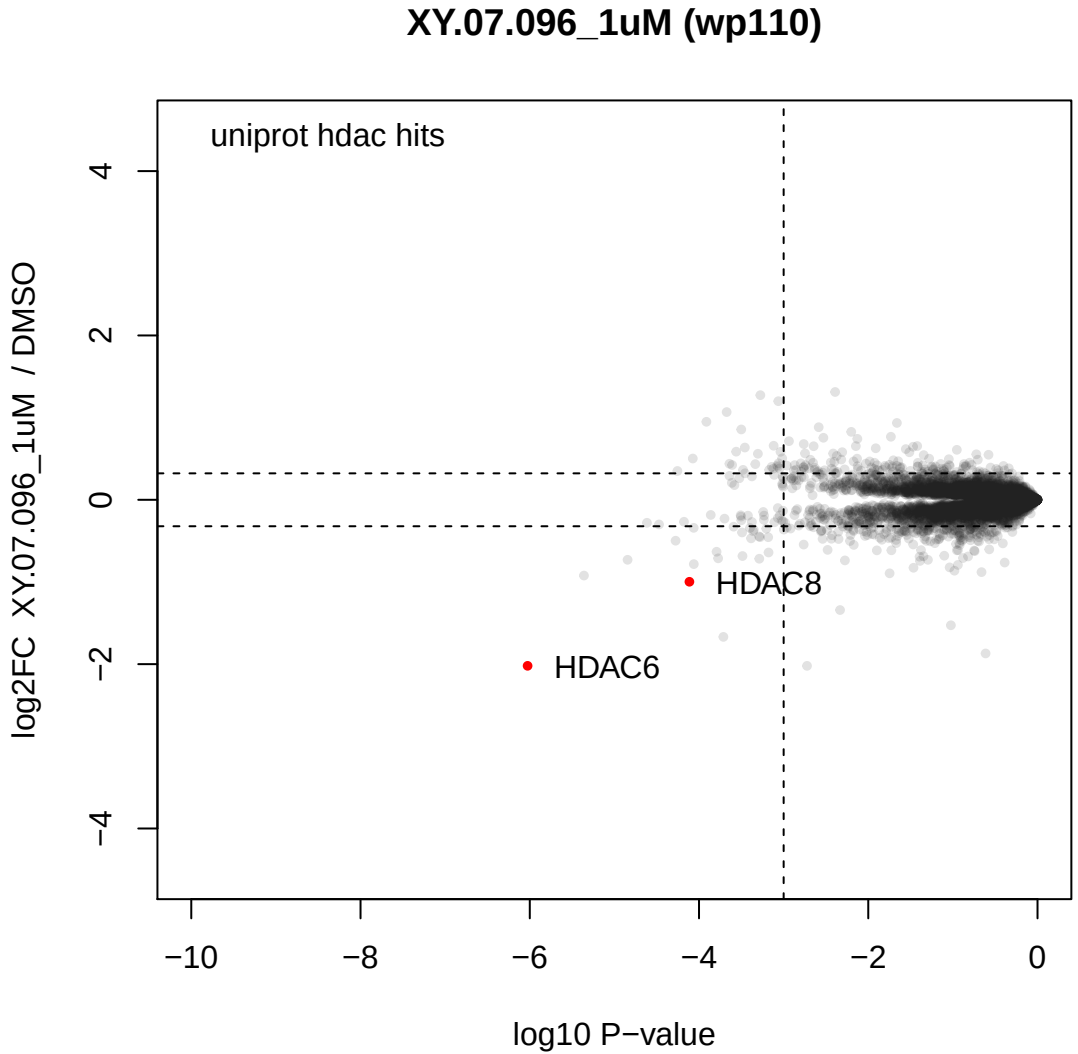

XY.07.090 (wp110)
all hits
DSP
RGS16
NCOR1
GATAD1
CPSF4
IKRD11
HDAC3
log2FC XY.07.090 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

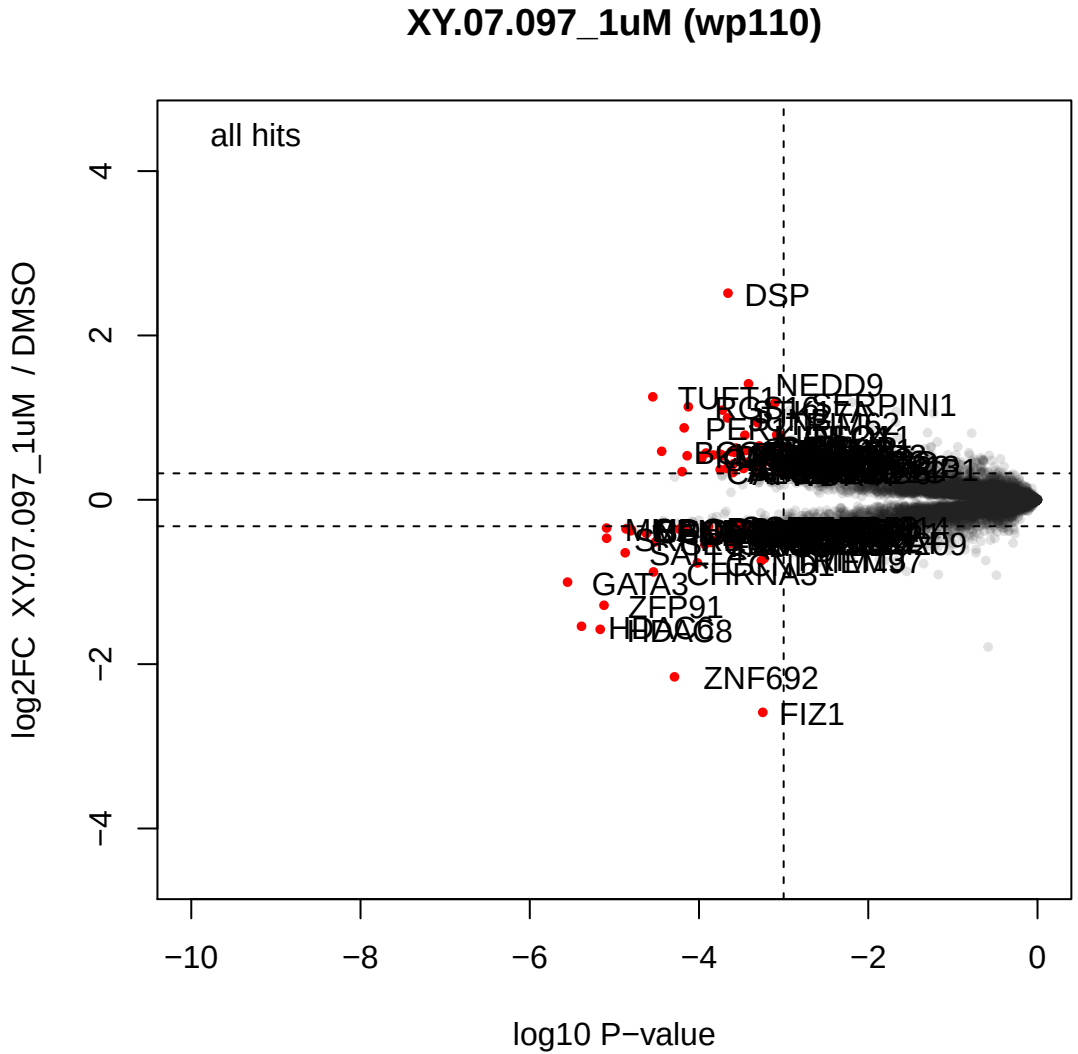

XY.07.090 (wp110)
uniprot hdac hits
HDAC3
log2FC XY.07.090 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

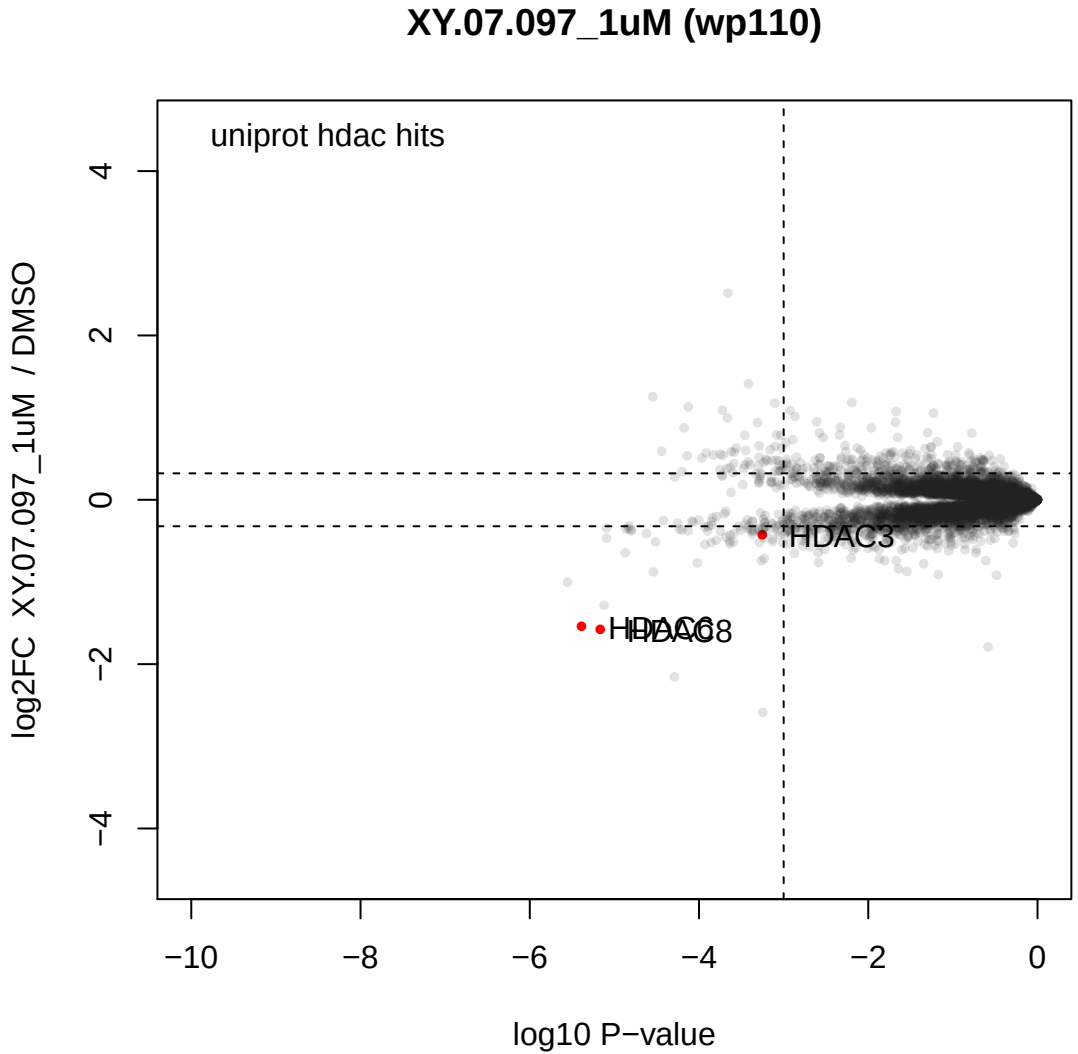

XY.07.093 (wp110)
all hits
log2FC XY.07.093 / DMSO
log10 P−value
HDAC3
NCOR1
GATA2
ANKRD11
DPAGT1
SNAP3A
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

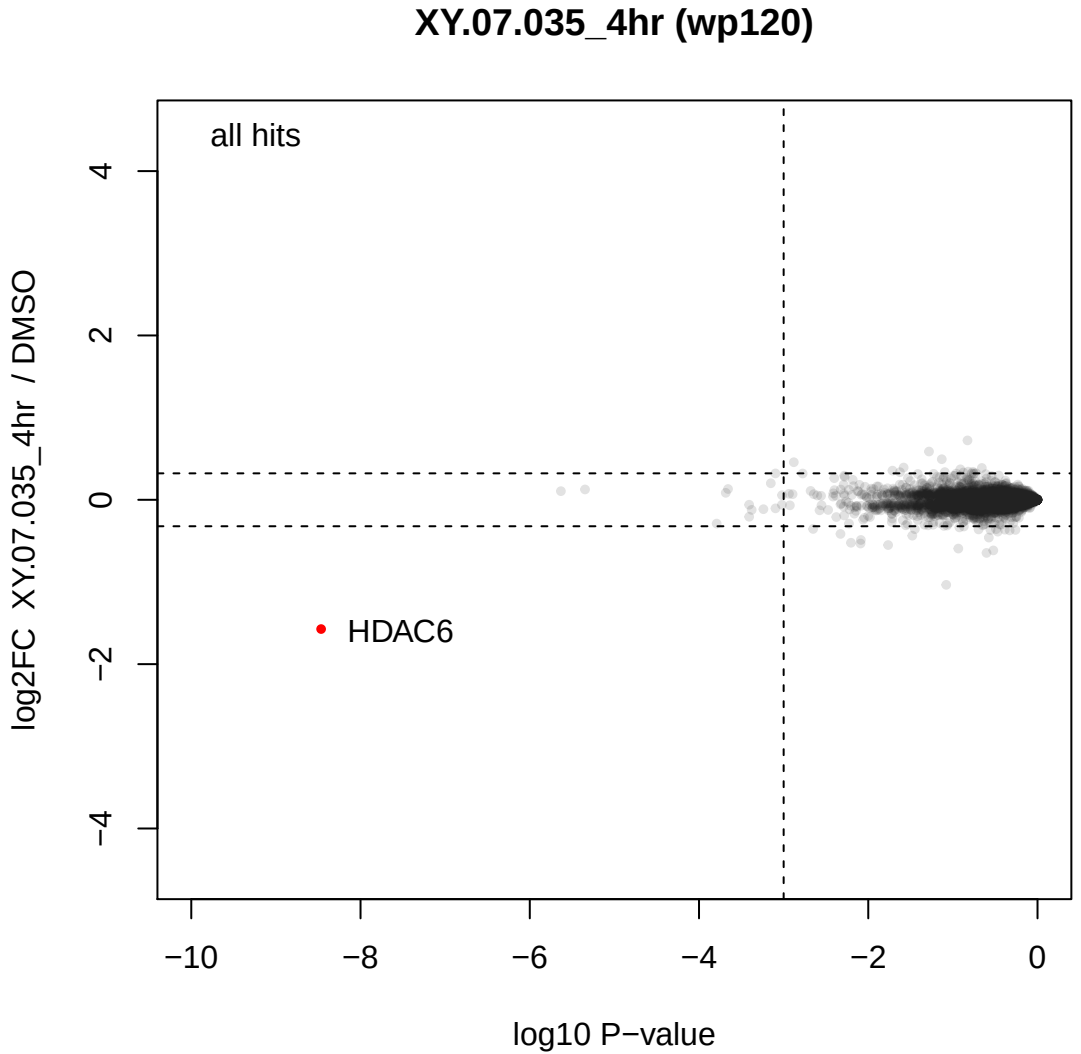

XY.07.093 (wp110)
uniprot hdac hits
log2FC XY.07.093 / DMSO
log10 P−value
HDAC3
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

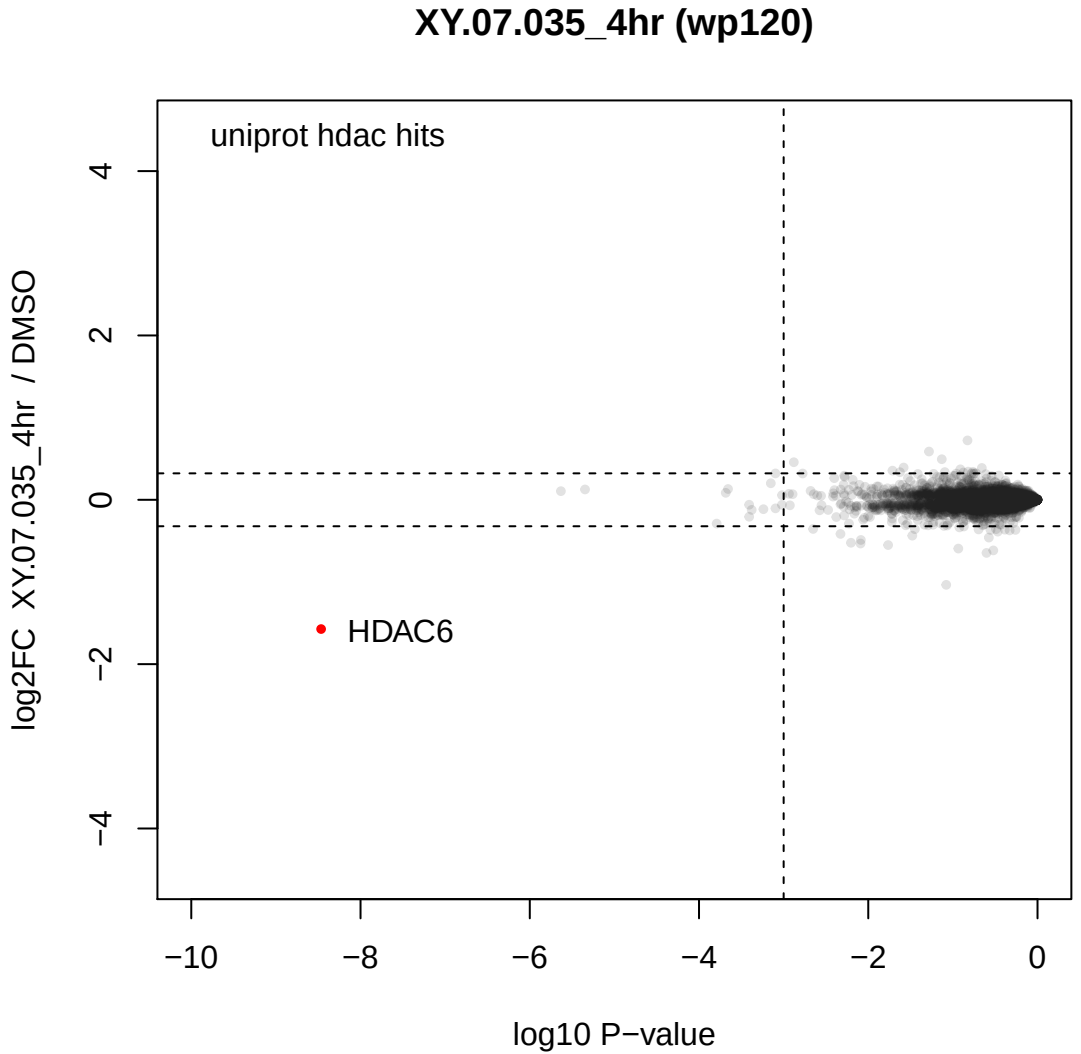

XY.07.096_1uM (wp110)
all hits
log2FC XY.07.096_1uM / DMSO
log10 P−value
HDAC6
GATA3
HDAC8
ZNF692
SERPINI1

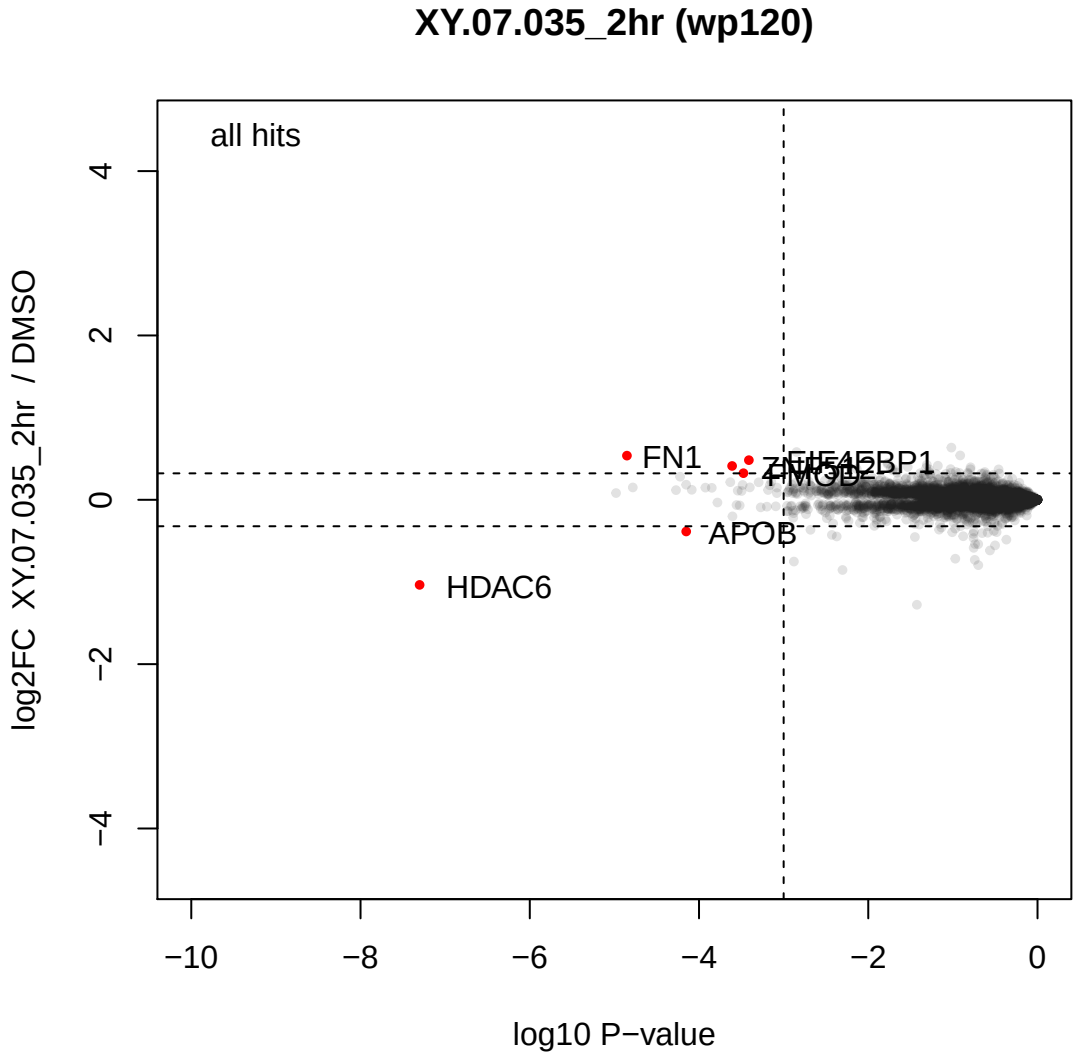

XY.07.096_1uM (wp110)
uniprot hdac hits
log2FC XY.07.096_1uM / DMSO
log10 P−value
HDAC8
HDAC6

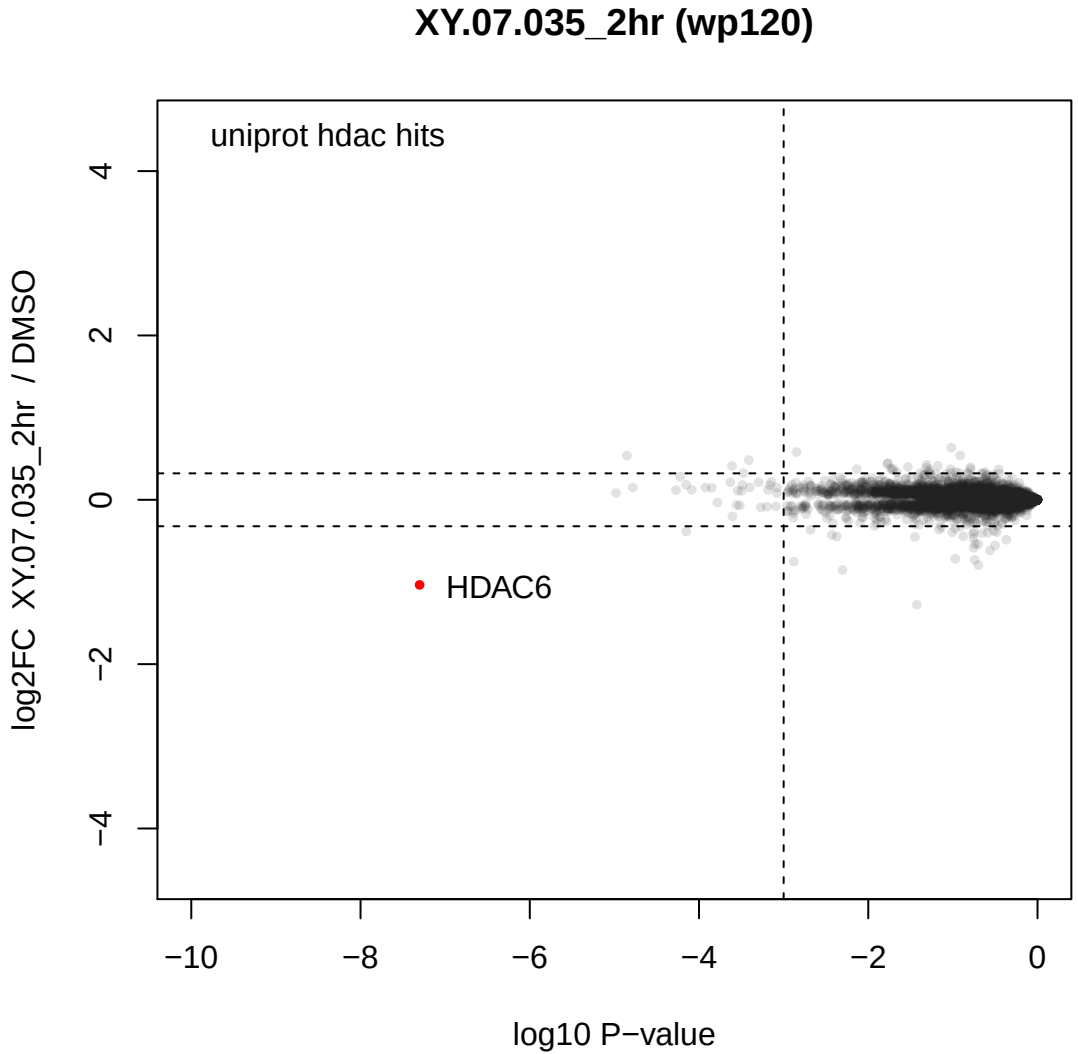

XY.07.097_1uM (wp110)
all hits
DSP
NEDD9
SERPINI1
GATA3
ZFP91
HDAC8
ZNF692
FIZ1
log2FC XY.07.097_1uM / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

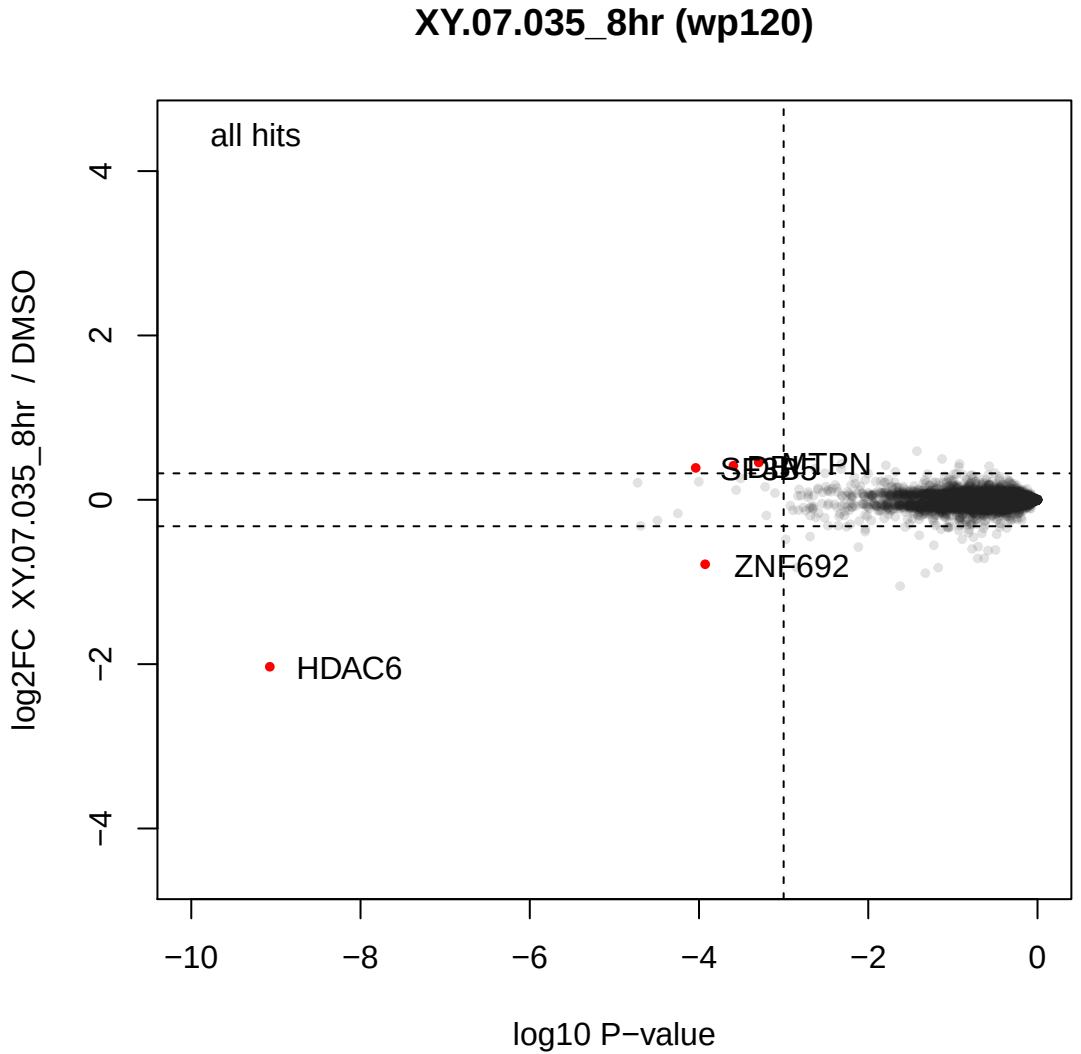

XY.07.097_1uM (wp110)
uniprot hdac hits
HDAC3
HDAC8
log2FC XY.07.097_1uM / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

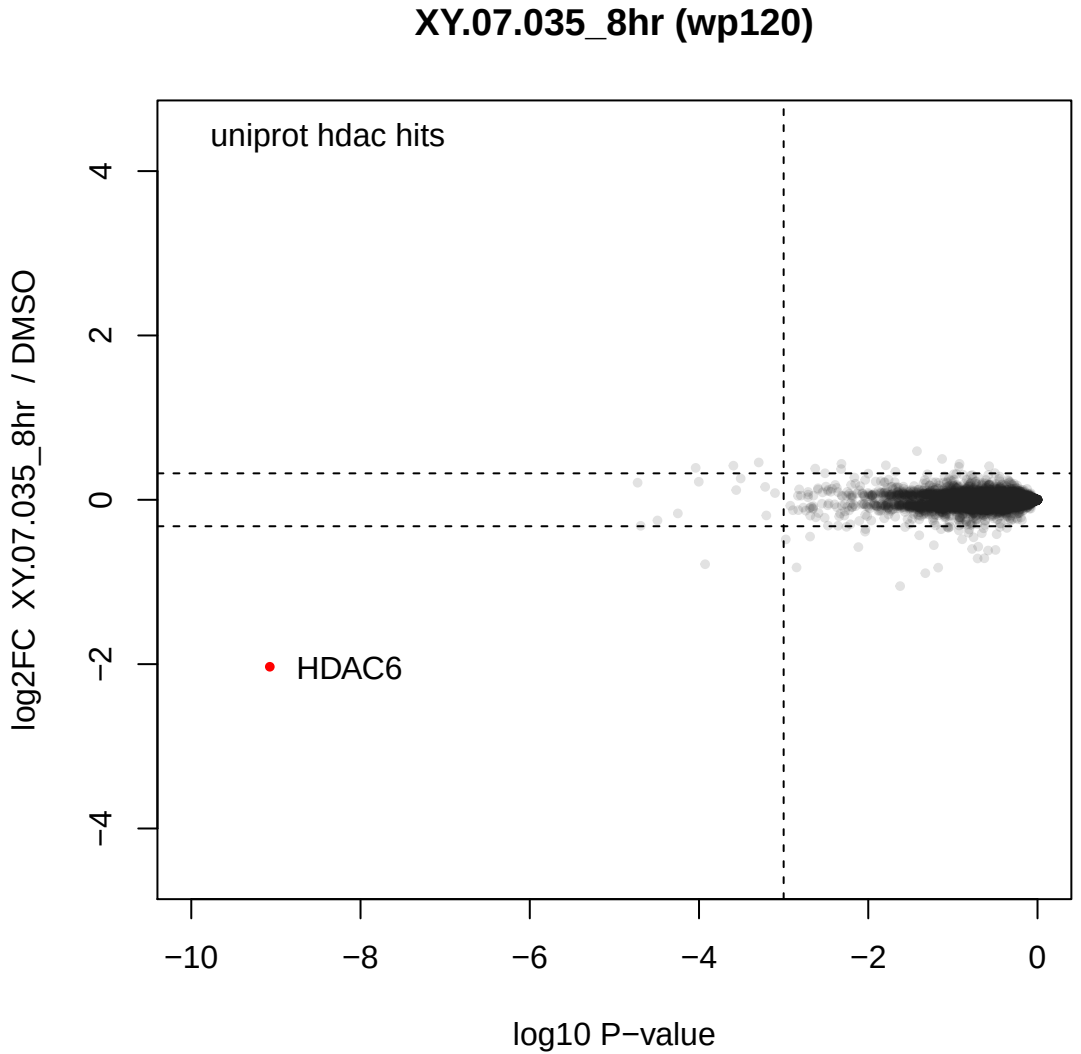

XY.07.035_4hr (wp120)
all hits
HDAC6
log2FC XY.07.035_4hr / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

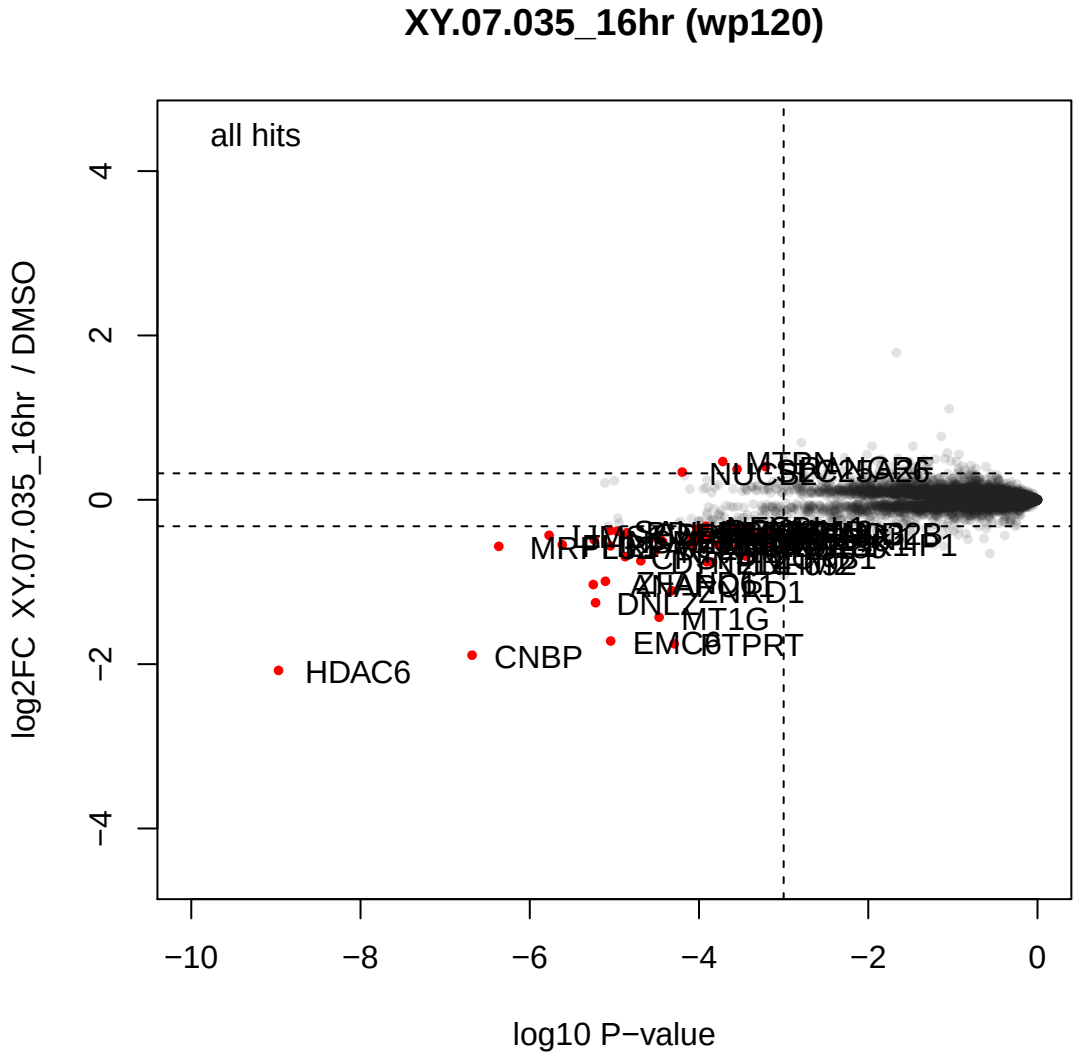

XY.07.035_4hr (wp120)
uniprot hdac hits
HDAC6
log2FC XY.07.035_4hr / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

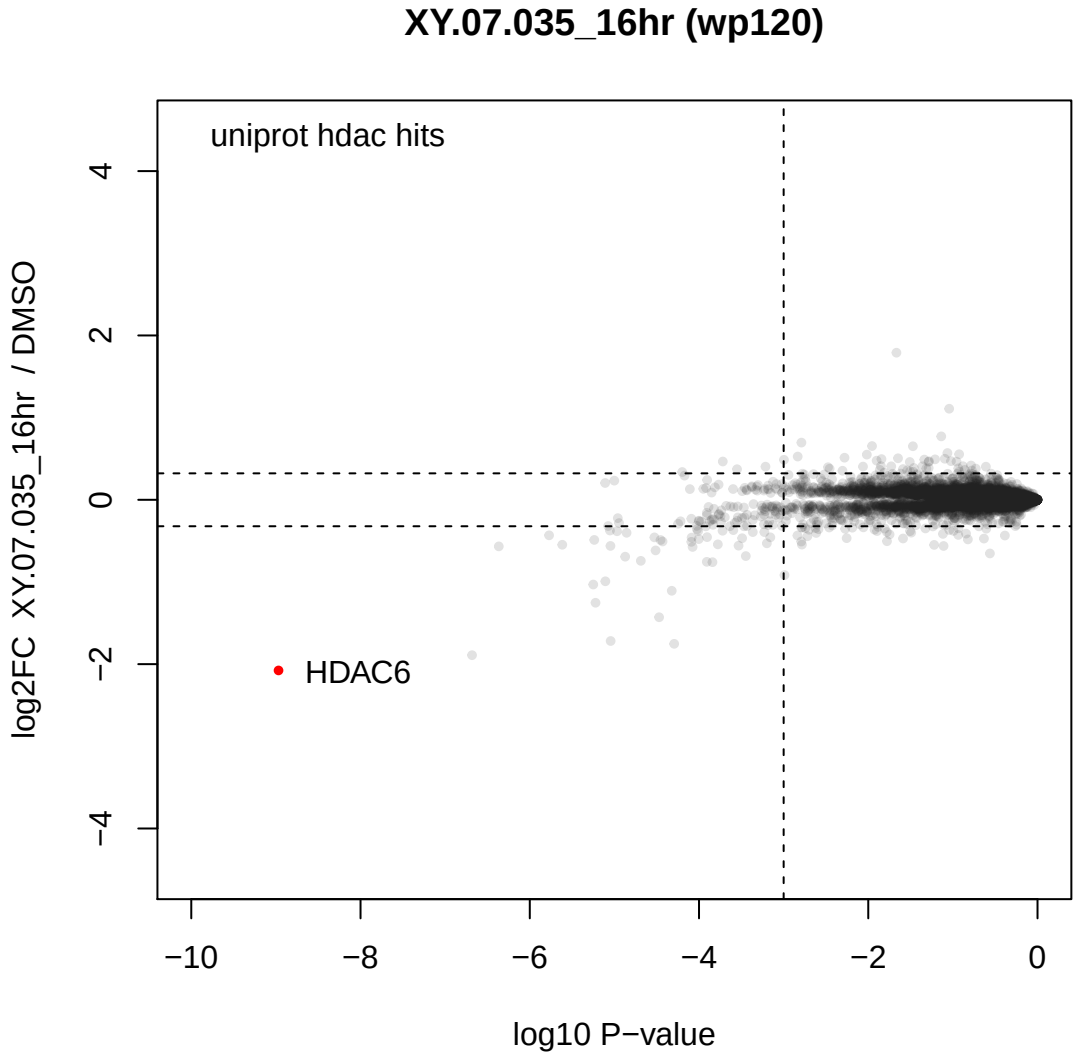

XY.07.035_2hr (wp120)
all hits
FN1
EIF4EBP1
APOB
HDAC6
log2FC XY.07.035_2hr / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

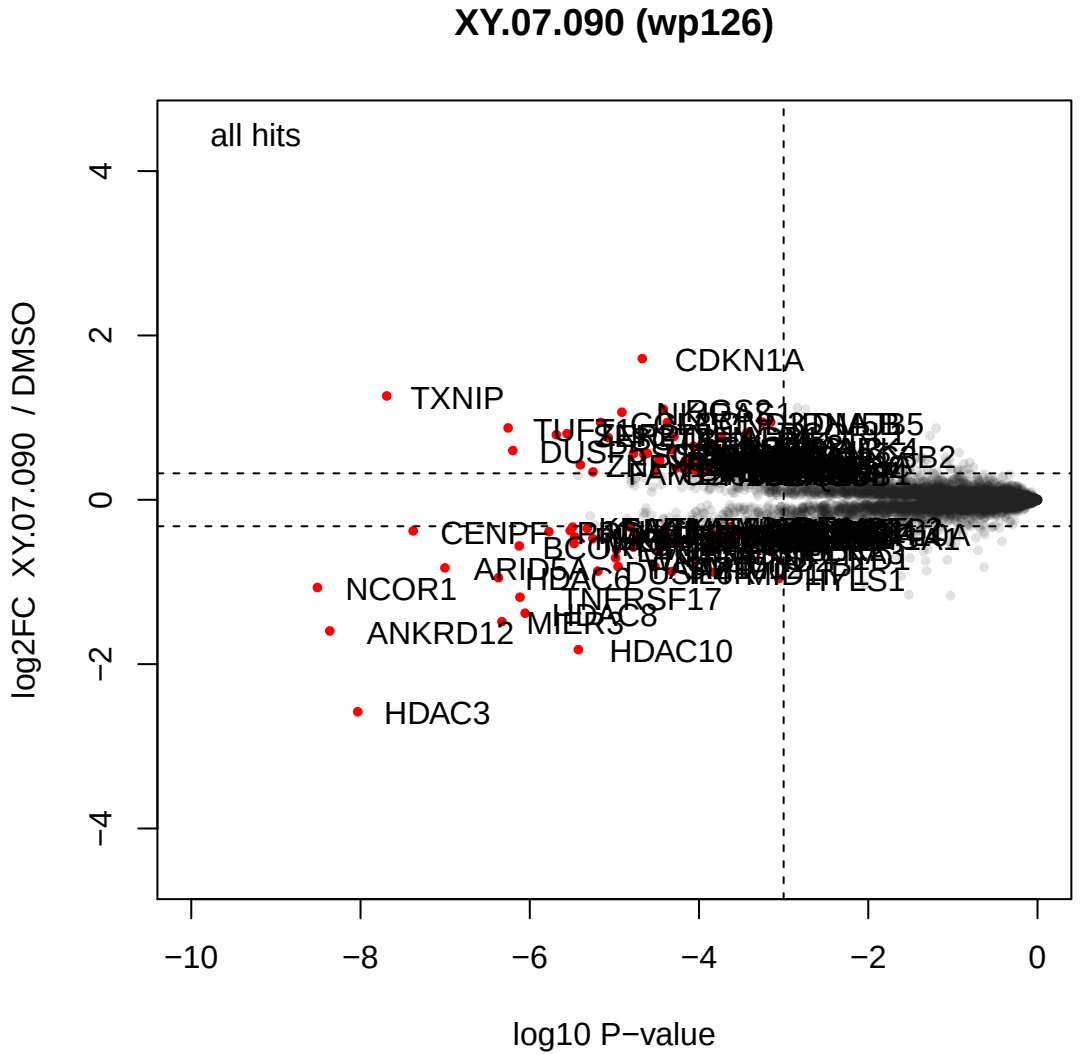

XY.07.035_2hr (wp120)
uniprot hdac hits
HDAC6
log2FC XY.07.035_2hr / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

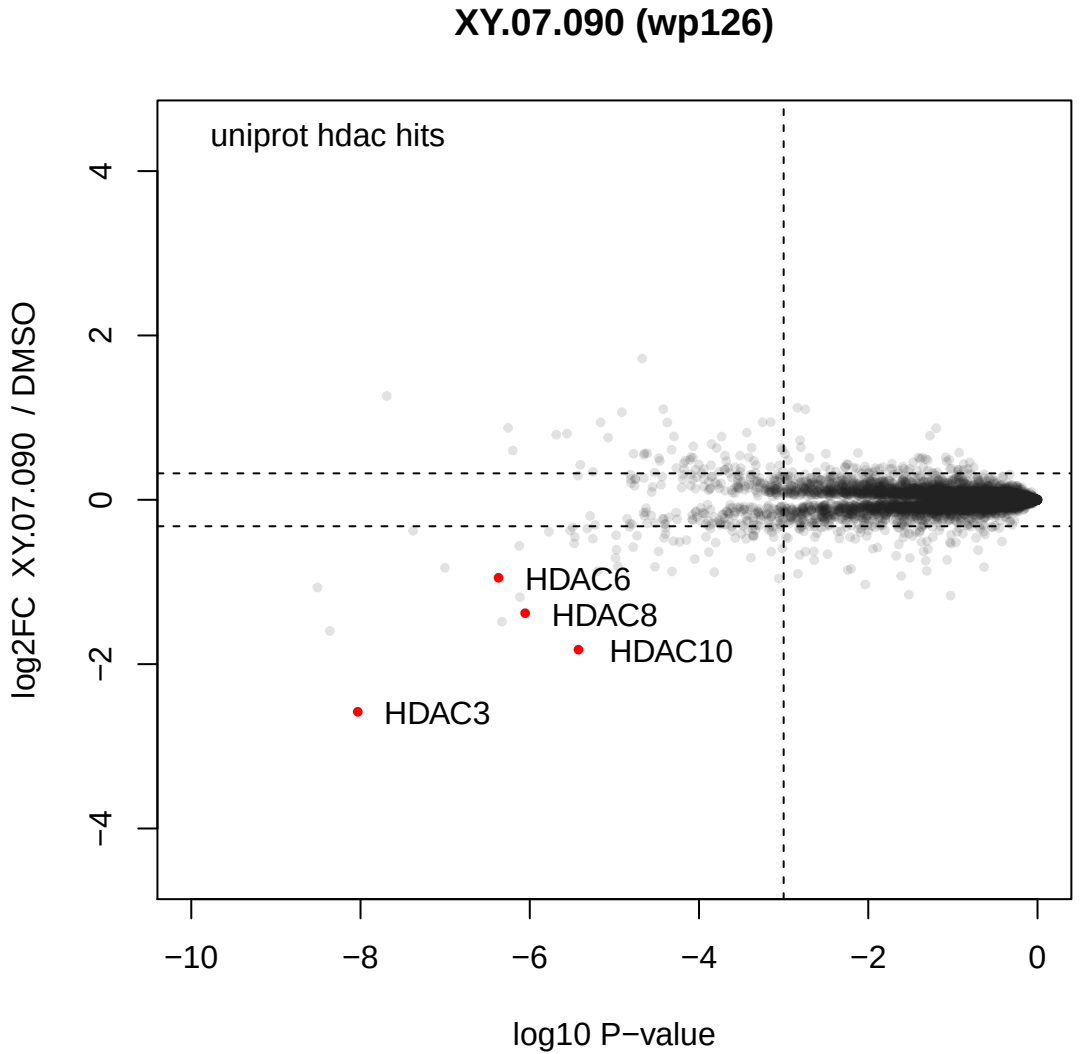

XY.07.035_8hr (wp120)
all hits
log2FC XY.07.035_8hr / DMSO
log10 P−value
HDAC6
ZNF692
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

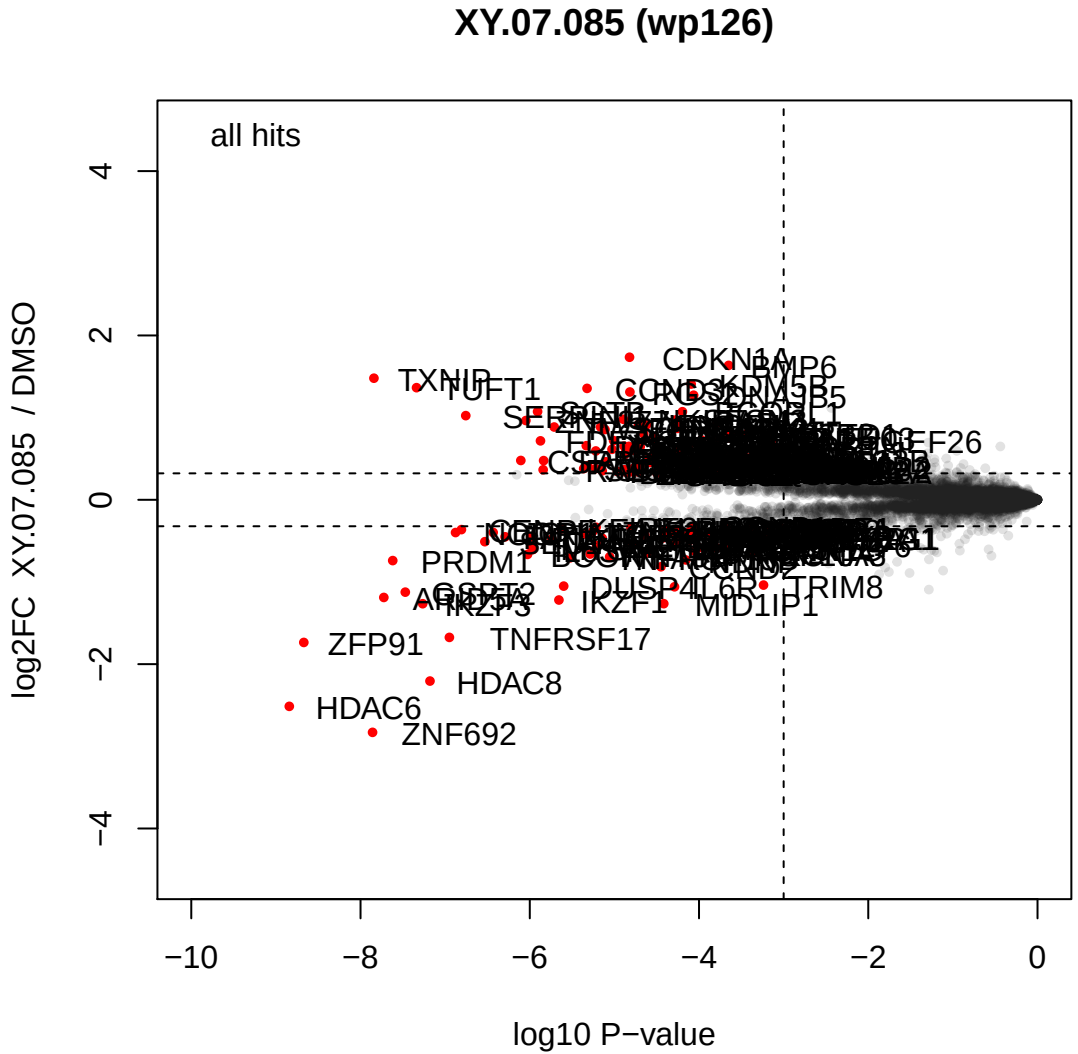

XY.07.035_8hr (wp120)
uniprot hdac hits
log2FC XY.07.035_8hr / DMSO
log10 P−value
HDAC6
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

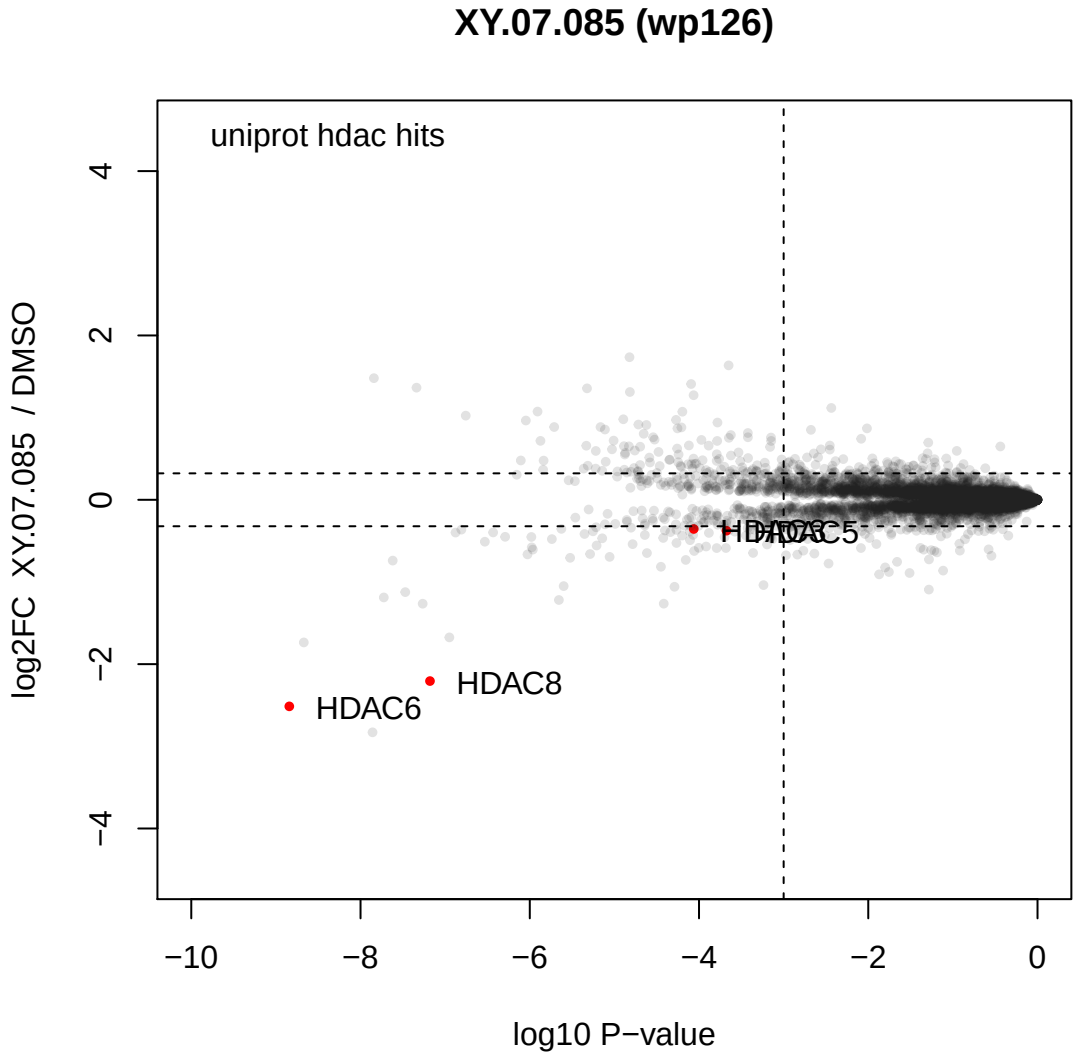

XY.07.035_16hr (wp120)
all hits
log2FC XY.07.035_16hr / DMSO
log10 P−value
HDAC6
CNBP
MT1G
DNL2
EMC6
GTPRT
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

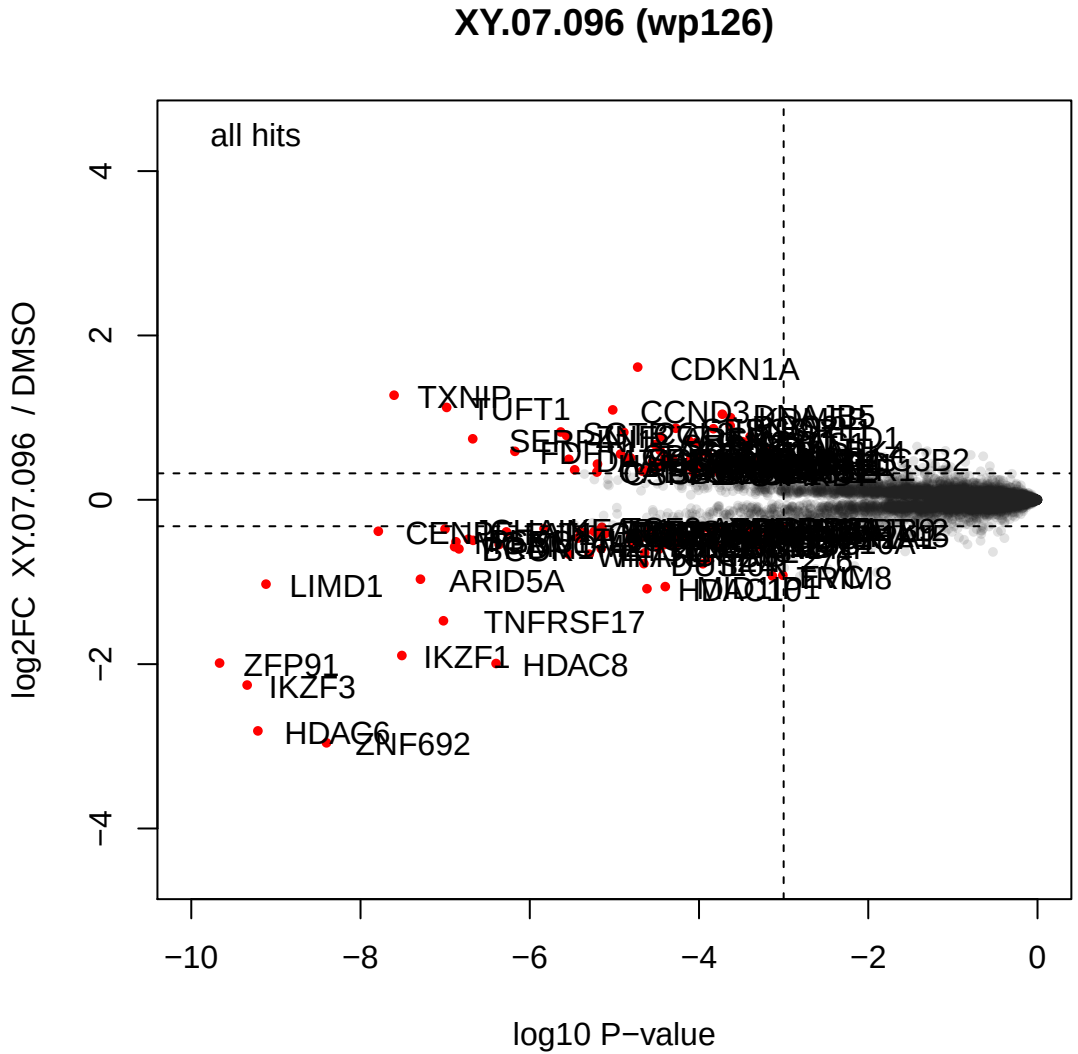

XY.07.035_16hr (wp120)
uniprot hdac hits
log2FC XY.07.035_16hr / DMSO
log10 P−value
HDAC6
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

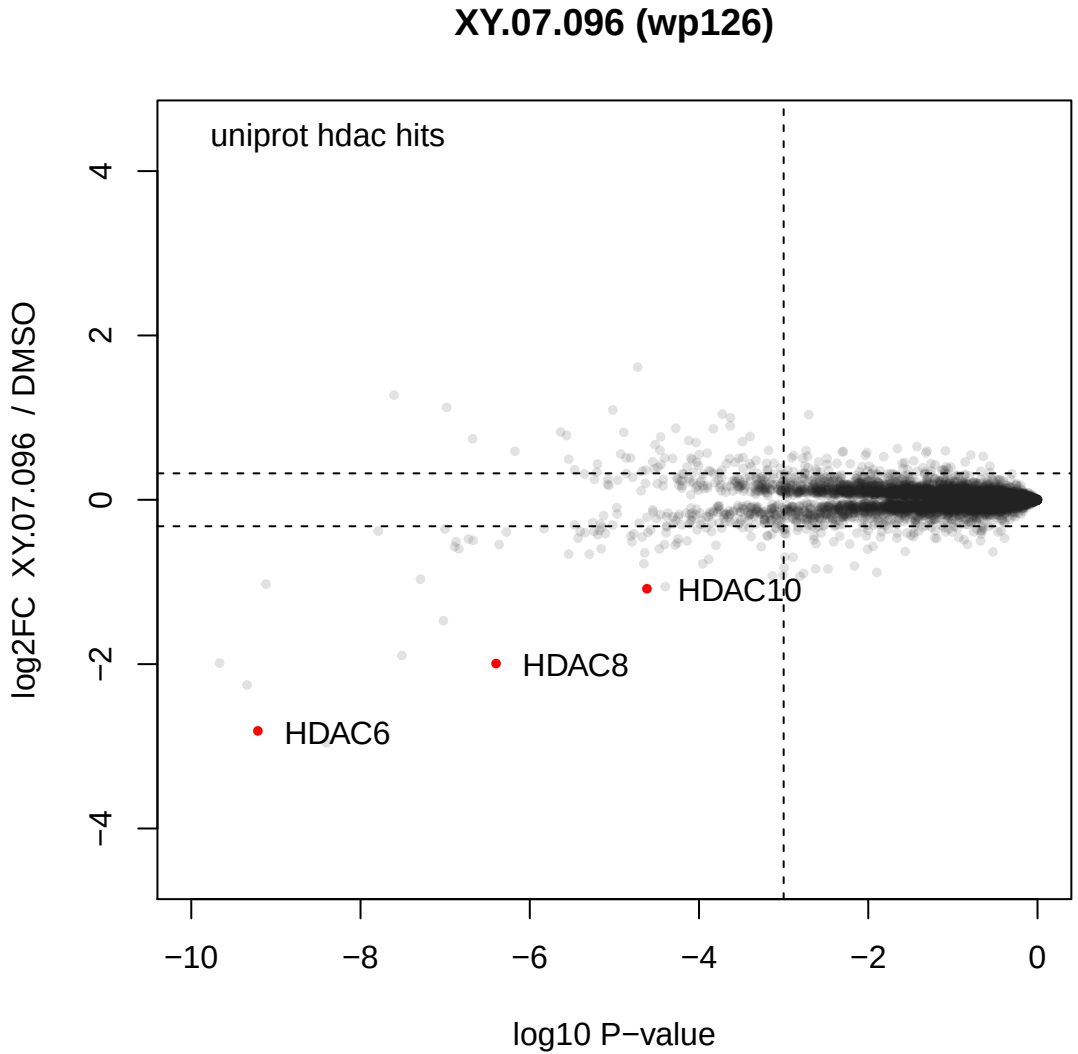

XY.07.090 (wp126)
all hits
log2FC XY.07.090 / DMSO
log10 P−value
CDKN1A
TXNIP
CENPF
NCOR1
ANKRD12
HDAC3
HDAC10
HDAC8
TNFRSF17
ARID5A
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

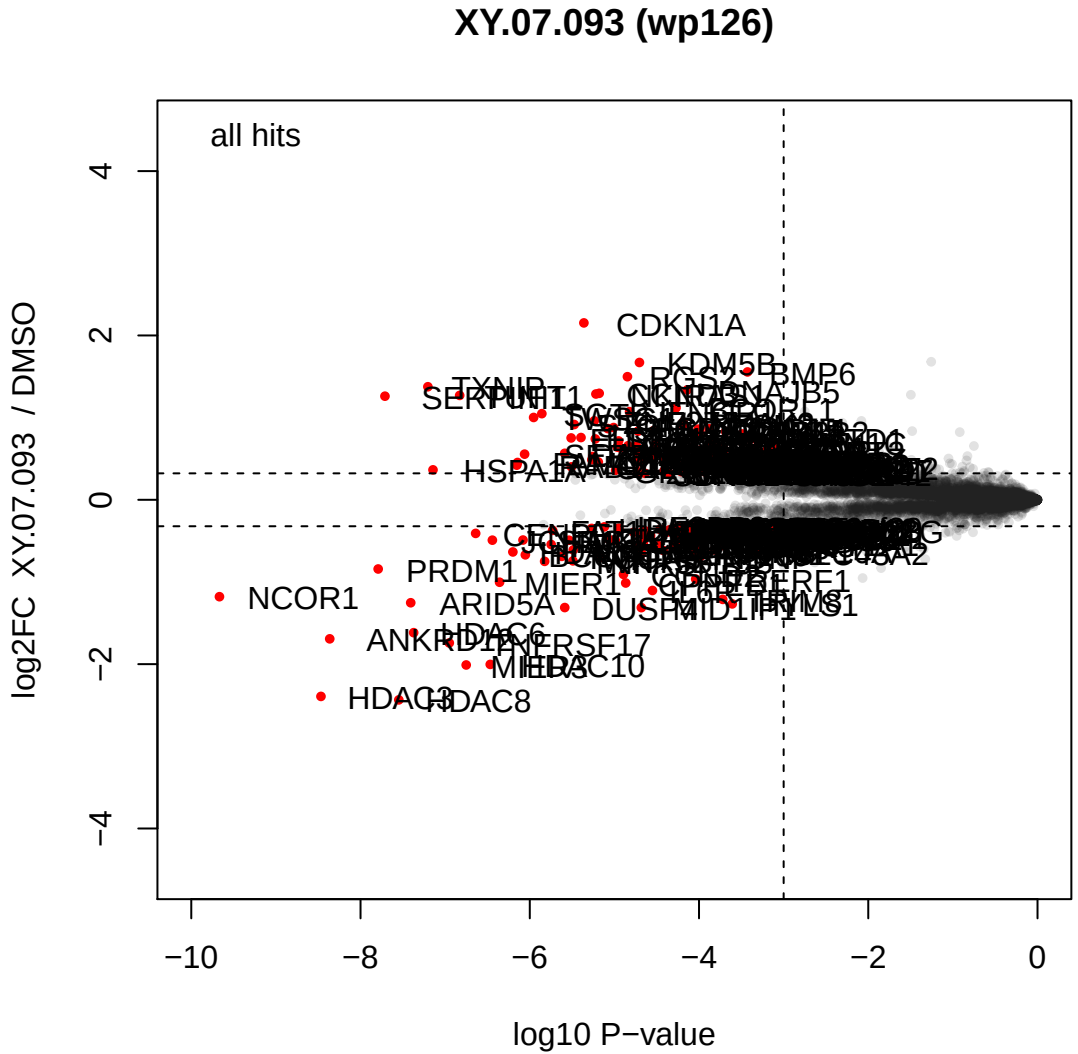

XY.07.090 (wp126)
uniprot hdac hits
log2FC XY.07.090 / DMSO
log10 P−value
HDAC6
HDAC8
HDAC10
HDAC3
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

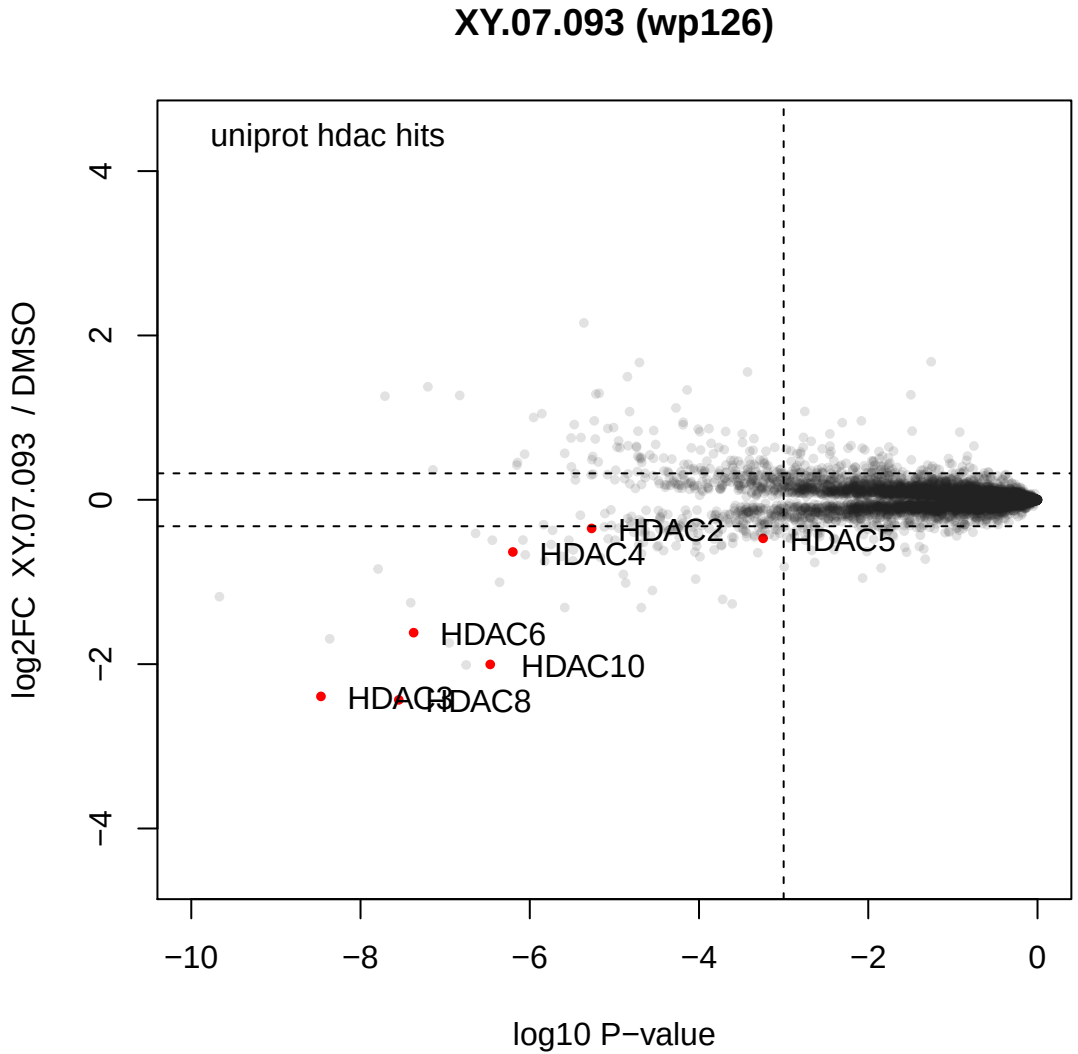

XY.07.085 (wp126)
all hits
log2FC XY.07.085 / DMSO
log10 P−value
TXNIP
TUFT1
CDKN1A
BMP6
PRDM1
IKZF1
MID1IP1
TRIM8
ZFP91
TNFRSF17
HDAC8
HDAC6
ZNF692

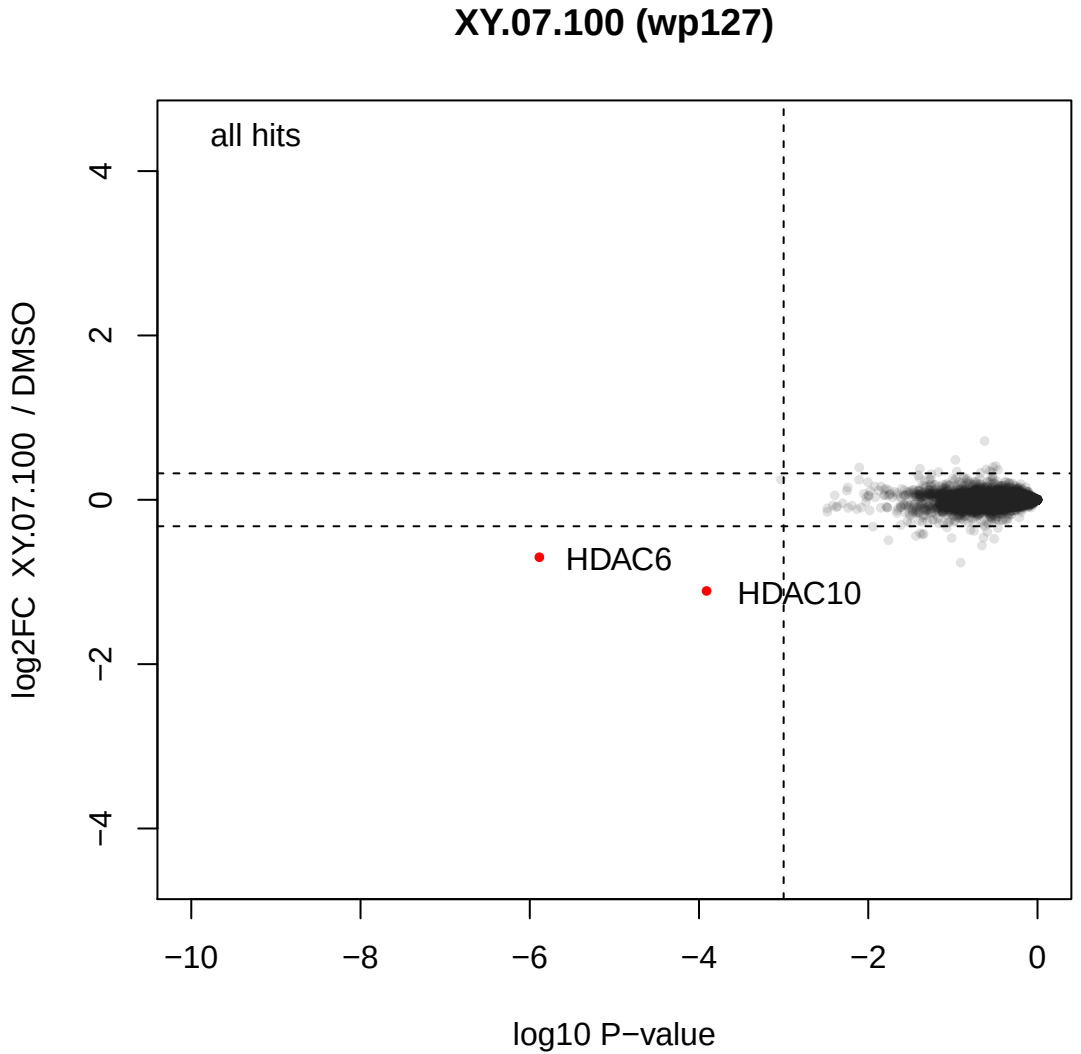

XY.07.085 (wp126)
uniprot hdac hits
log2FC XY.07.085 / DMSO
log10 P−value
HDAC8
HDAC6

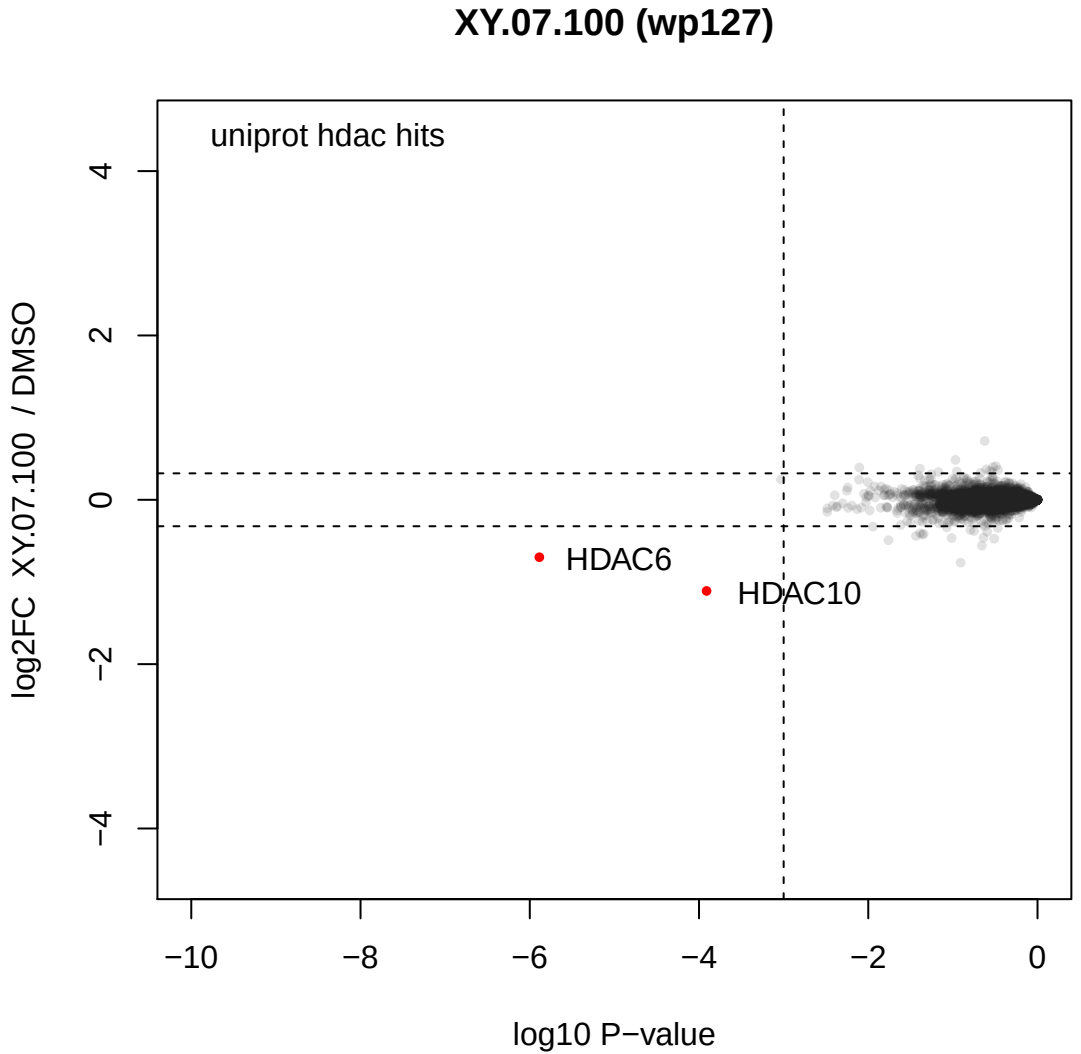

XY.07.096 (wp126)
all hits
log2FC XY.07.096 / DMSO
log10 P−value
CDKN1A
TXNIP
TUFT1
CCND3
LIMD1
ARID5A
TNFRSF17
ZFP91
IKZF3
IKZF1
HDAC8
HDAC6
ZNF692
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

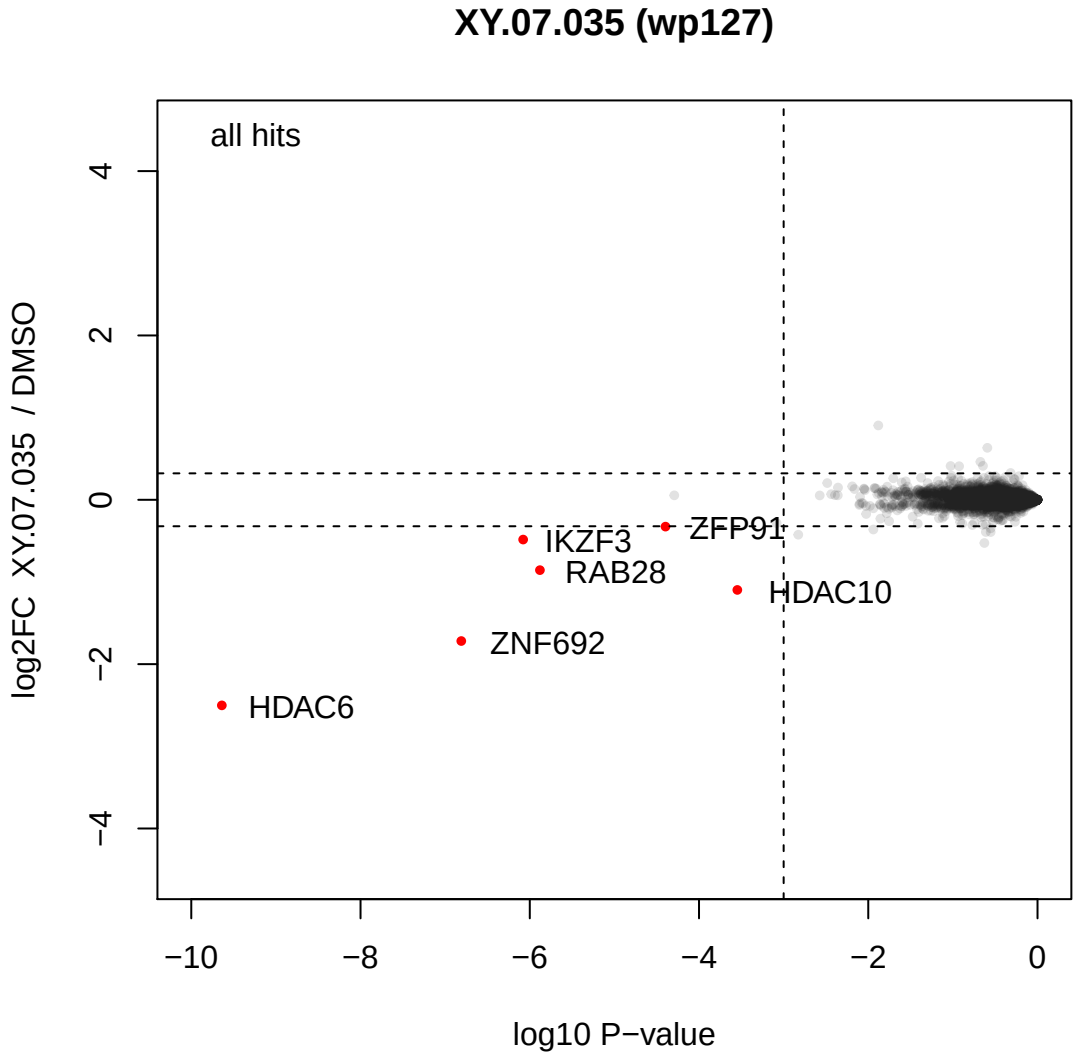

XY.07.096 (wp126)
uniprot hdac hits
log2FC XY.07.096 / DMSO
log10 P−value
HDAC10
HDAC8
HDAC6
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

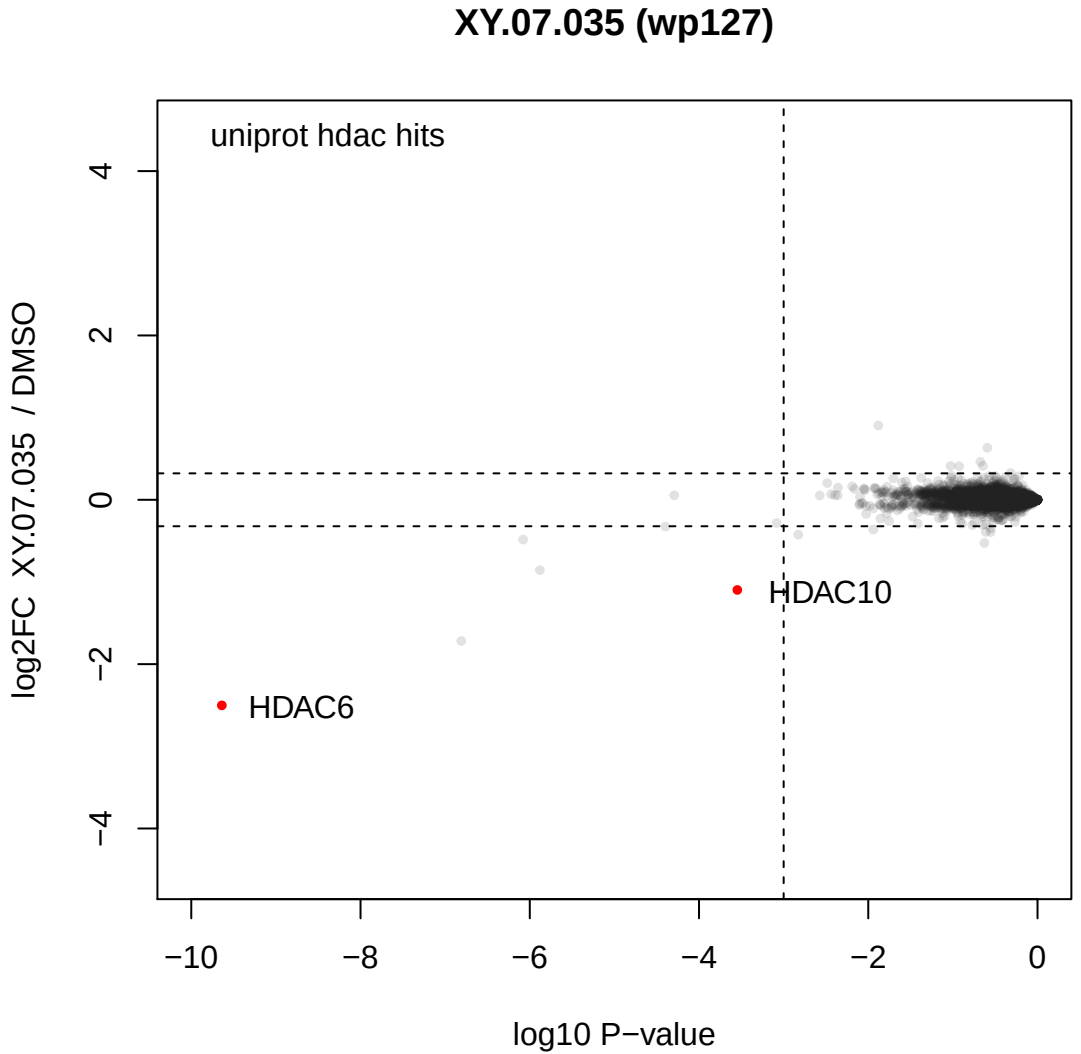

XY.07.093 (wp126)
all hits
log2FC XY.07.093 / DMSO
log10 P−value
CDKN1A
KDM5B
BMP6
TXNIP
SERPINE1
HSPA1A
PRDM1
NCOR1
MIER1
ARID5A
DUSP1
HDAC6
ANKRD1
TNFRSF17
HDAC10
HDAC3
HDAC8

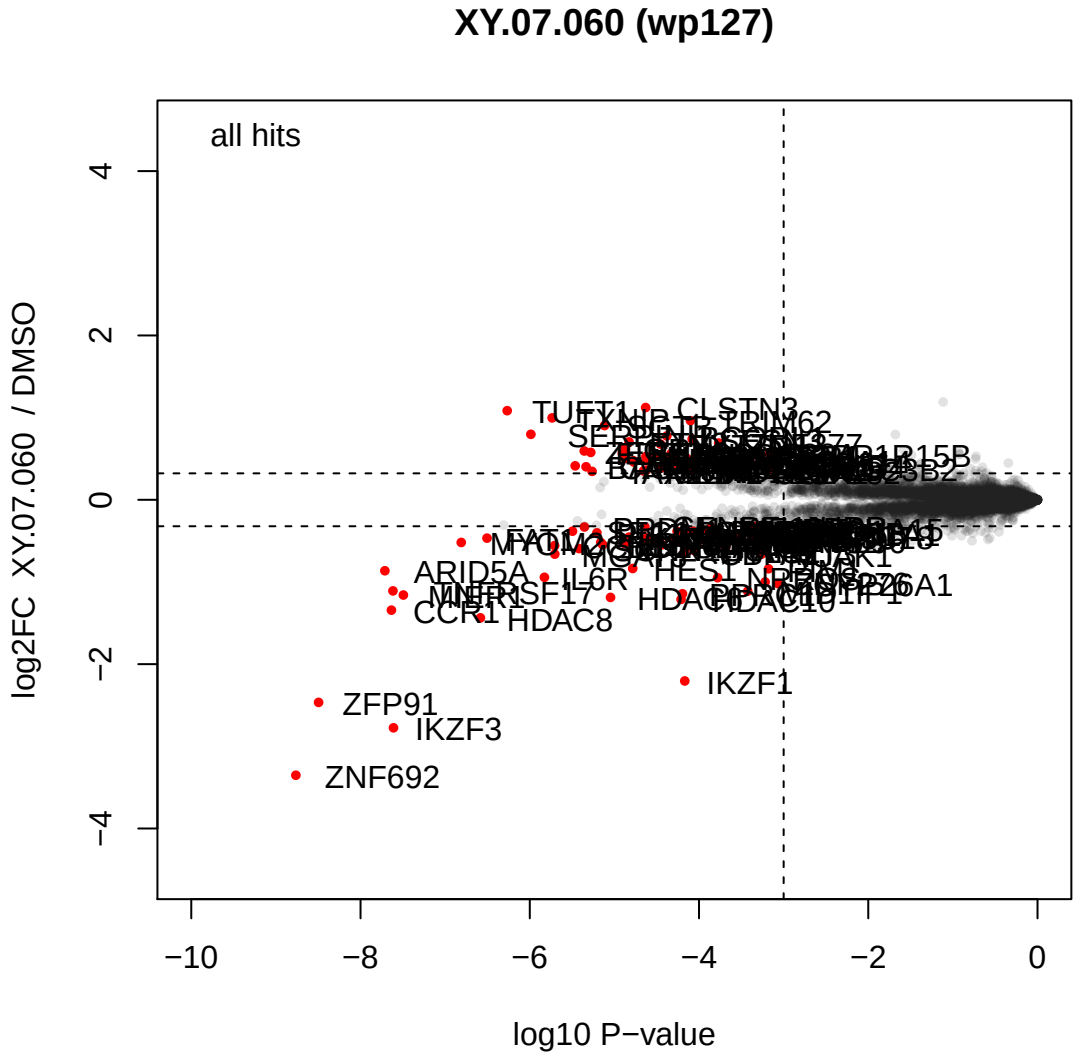

XY.07.093 (wp126)
uniprot hdac hits
log2FC XY.07.093 / DMSO
log10 P−value
HDAC2
HDAC5
HDAC4
HDAC6
HDAC10
HDAC3
HDAC8

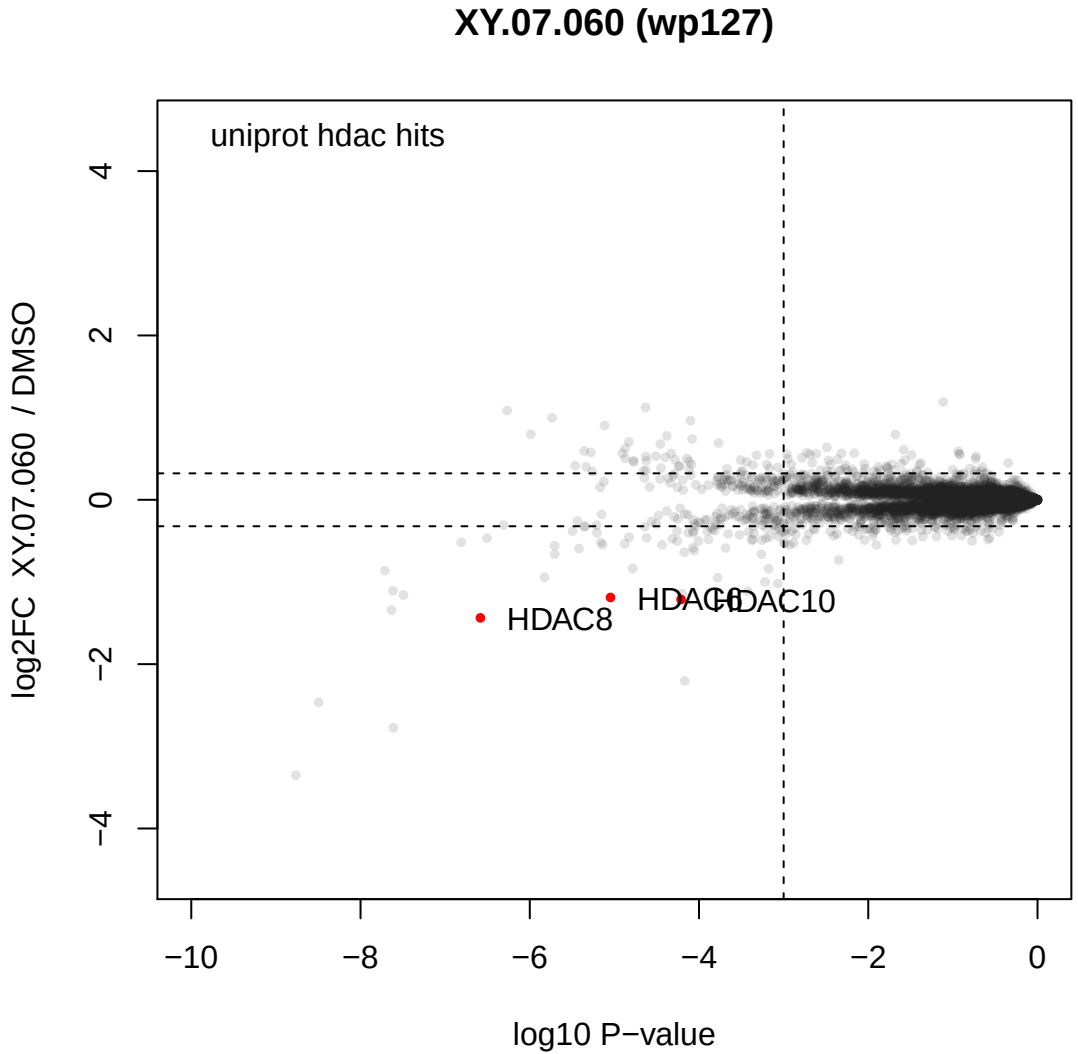

XY.07.100 (wp127)
all hits
HDAC6
HDAC10
log2FC XY.07.100 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

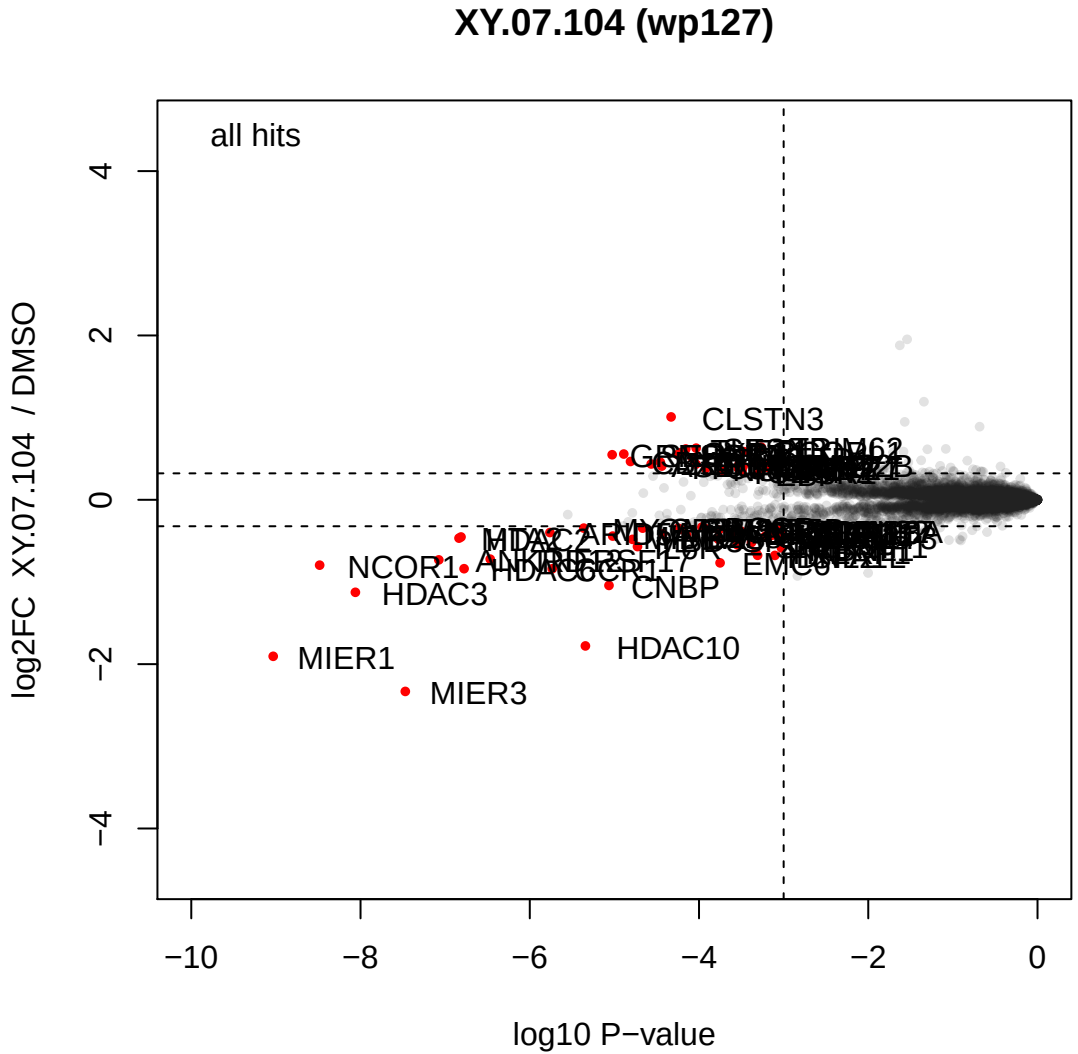

XY.07.100 (wp127)
uniprot hdac hits
HDAC6
HDAC10
log2FC XY.07.100 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

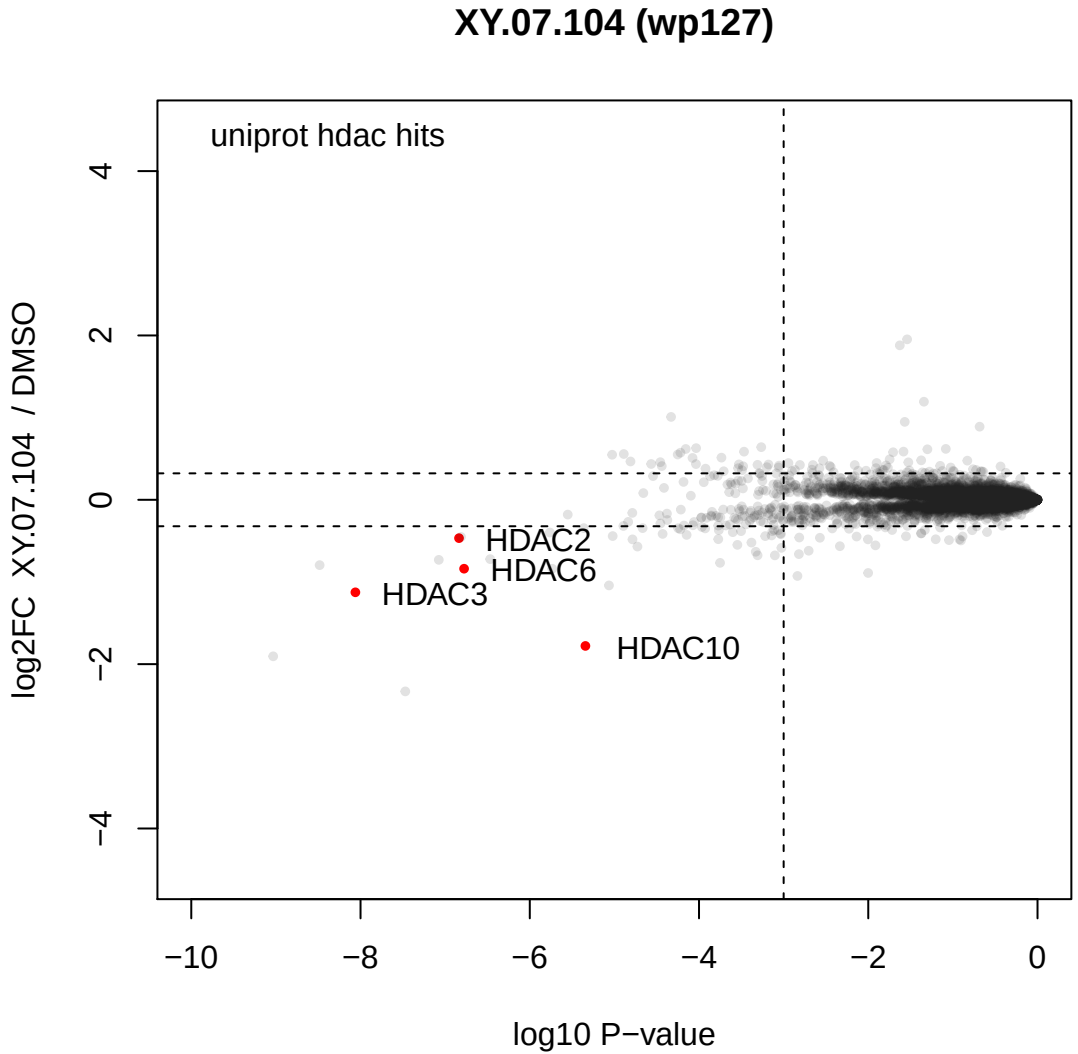

XY.07.035 (wp127)
all hits
log2FC XY.07.035 / DMSO
log10 P−value
IKZF3
ZFP91
RAB28
HDAC10
ZNF692
HDAC6
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

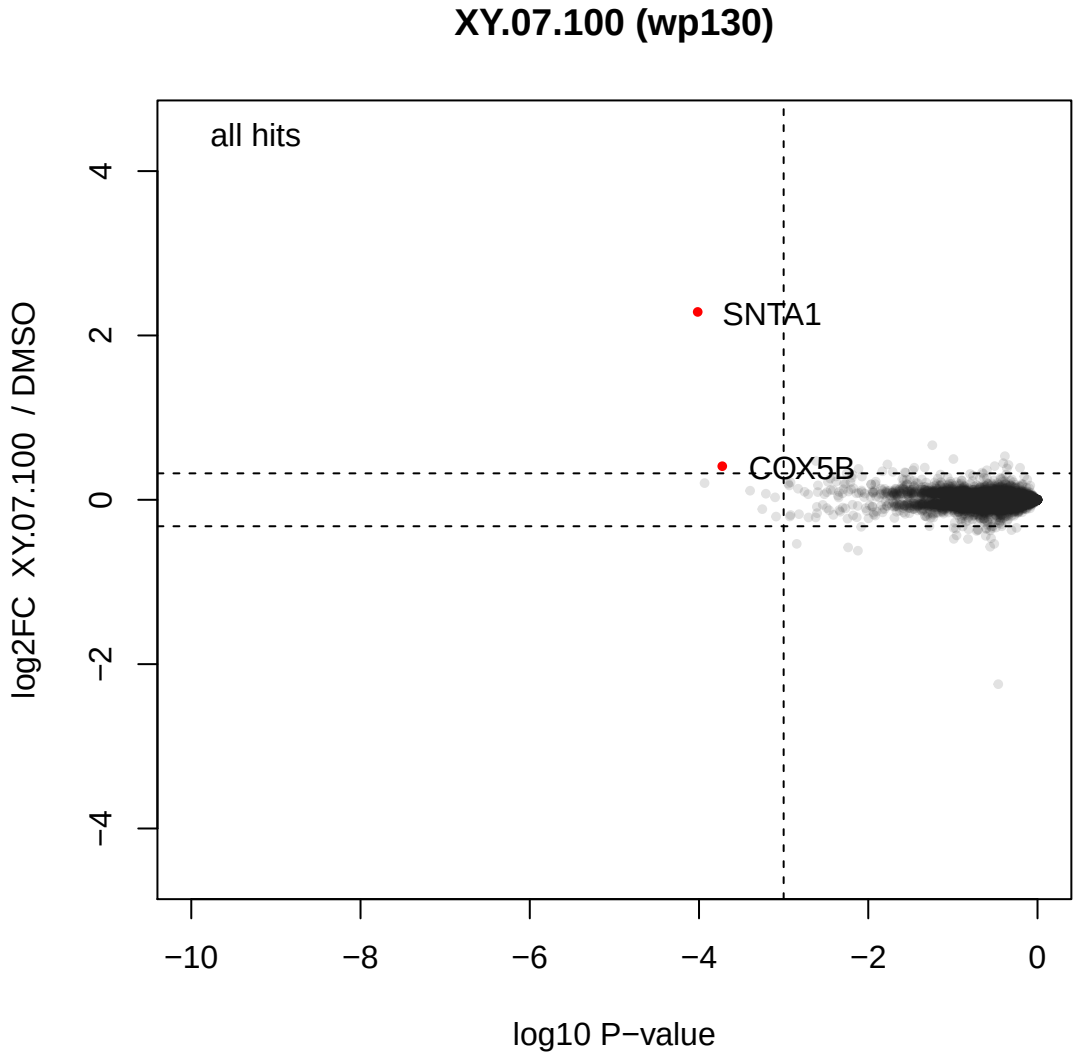

XY.07.035 (wp127)
uniprot hdac hits
log2FC XY.07.035 / DMSO
log10 P−value
HDAC10
HDAC6
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

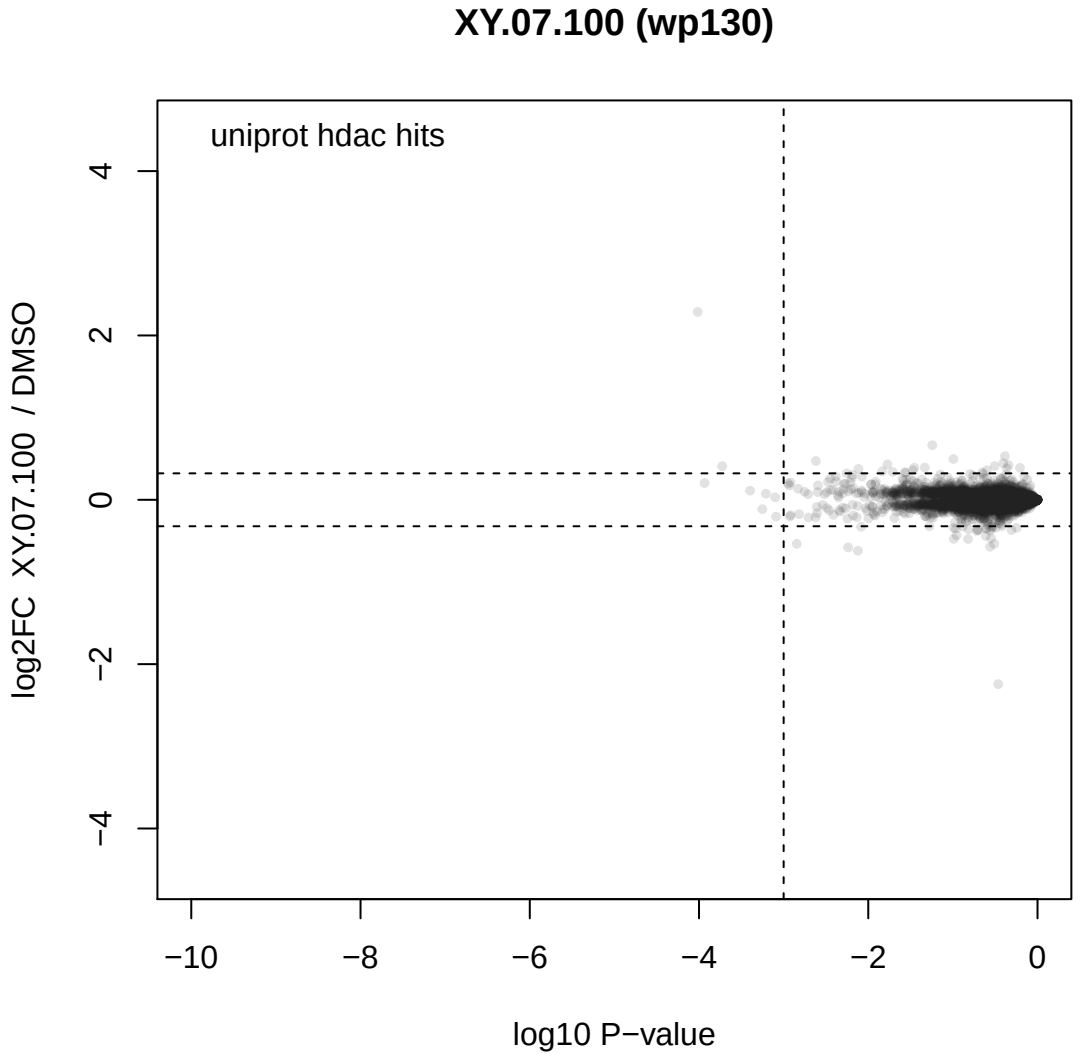

XY.07.060 (wp127)
all hits
log2FC XY.07.060 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0
ZFP91
IKZF3
ZNF692
IKZF1
HDAC8
HDAC10
ARID5A
IL6R
CCR1

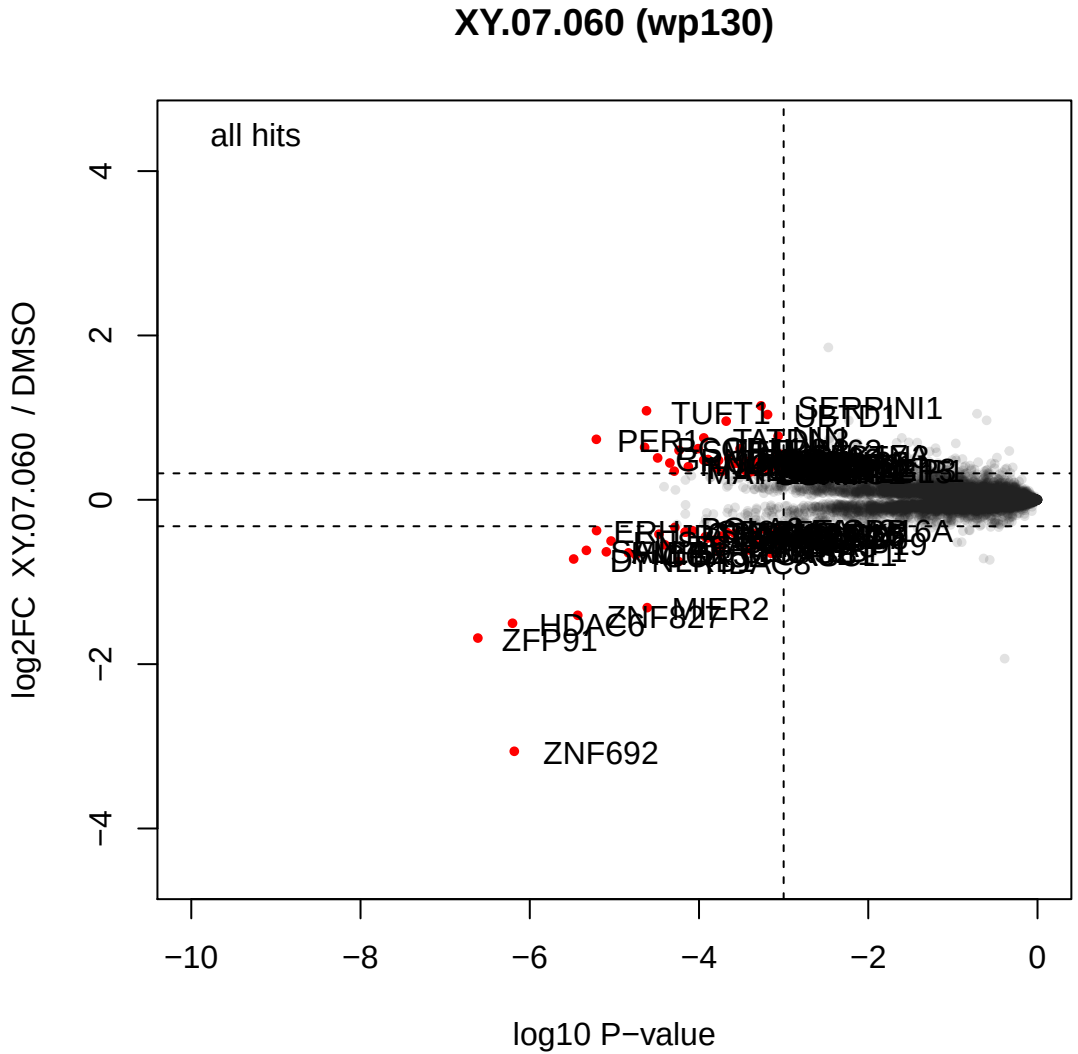

XY.07.060 (wp127)
uniprot hdac hits
log2FC XY.07.060 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0
HDAC8
HDAC6
HDAC10

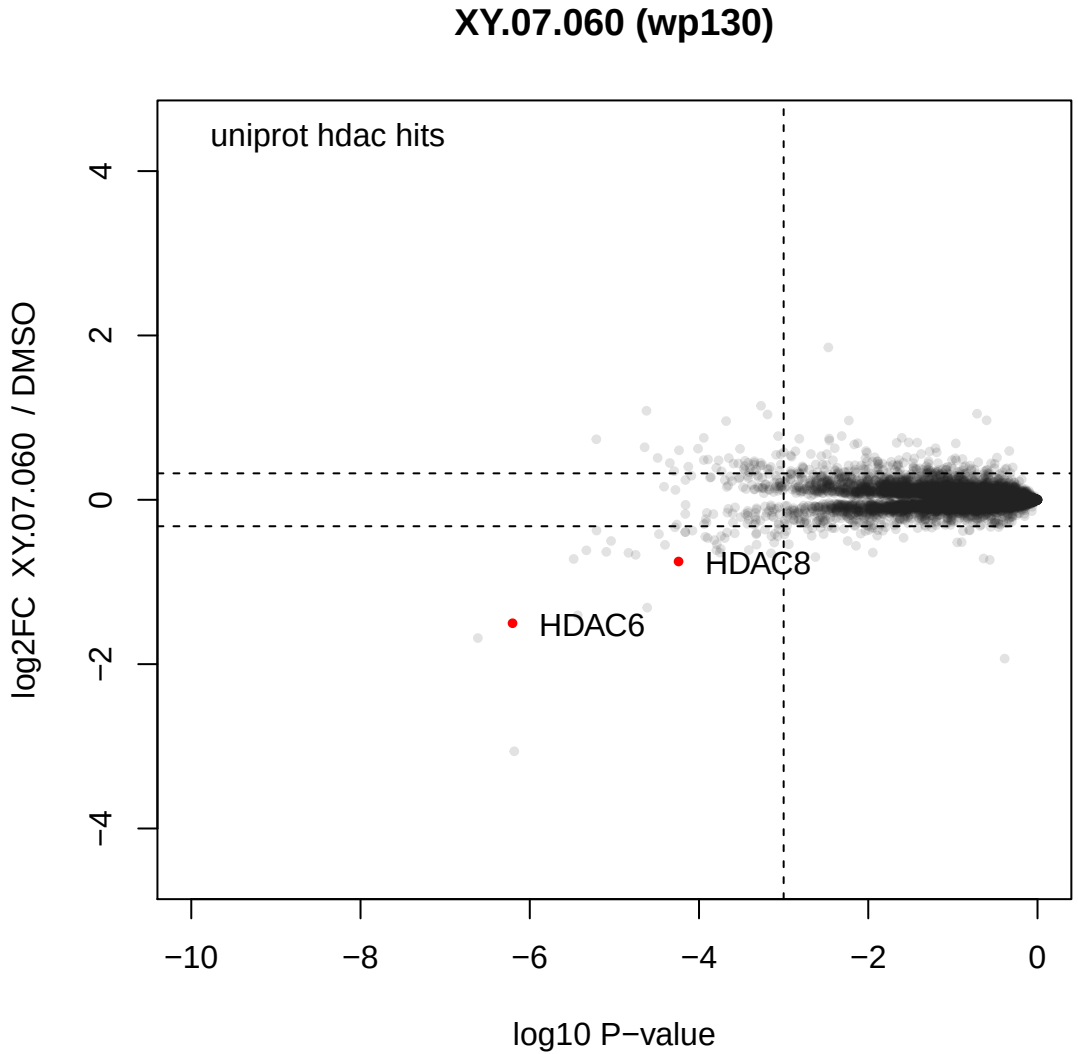

XY.07.104 (wp127)
all hits
log2FC XY.07.104 / DMSO
log10 P−value
CLSTN3
NCOR1
HDAC3
CNBP
HDAC10
MIER1
MIER3
EMC6
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

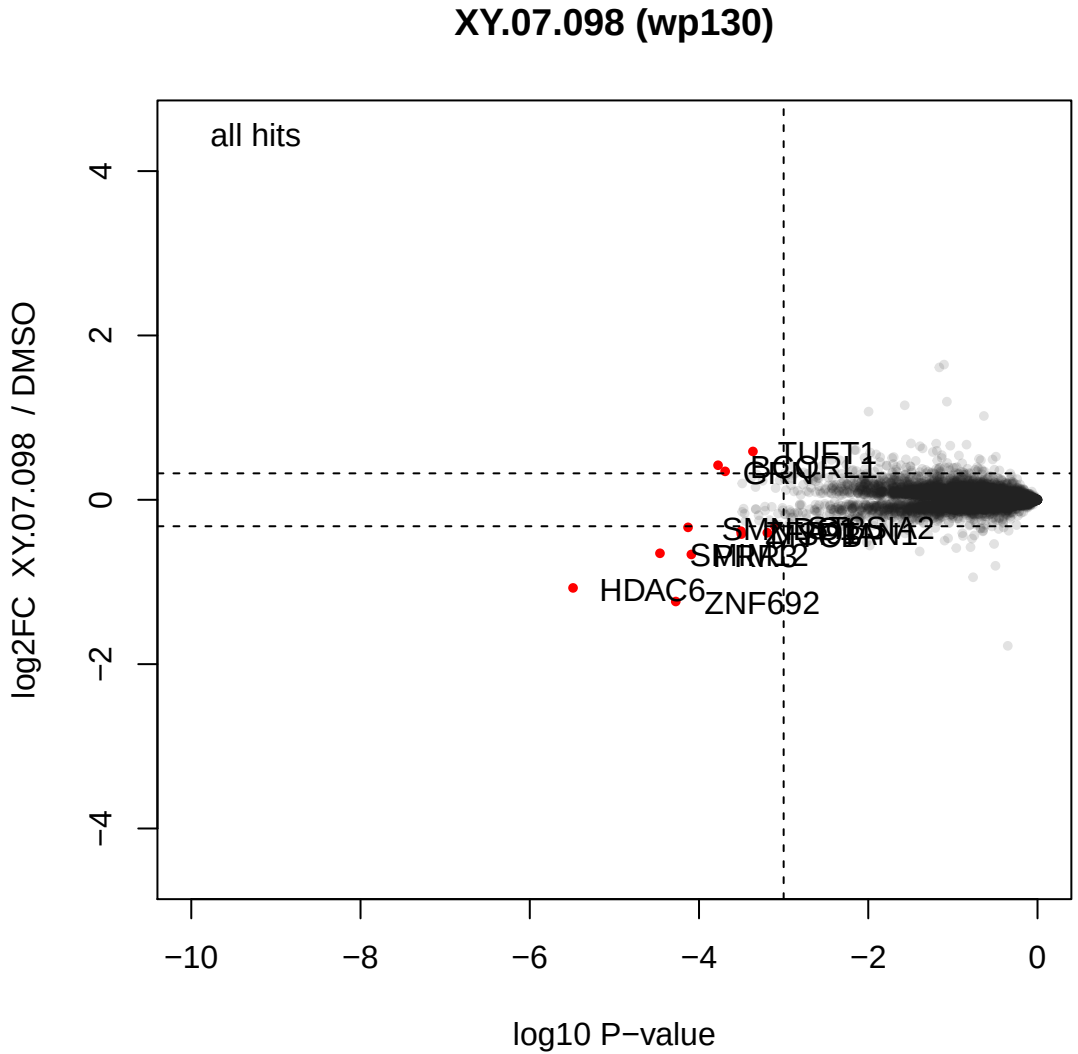

XY.07.104 (wp127)
uniprot hdac hits
log2FC XY.07.104 / DMSO
log10 P−value
HDAC2
HDAC6
HDAC3
HDAC10
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

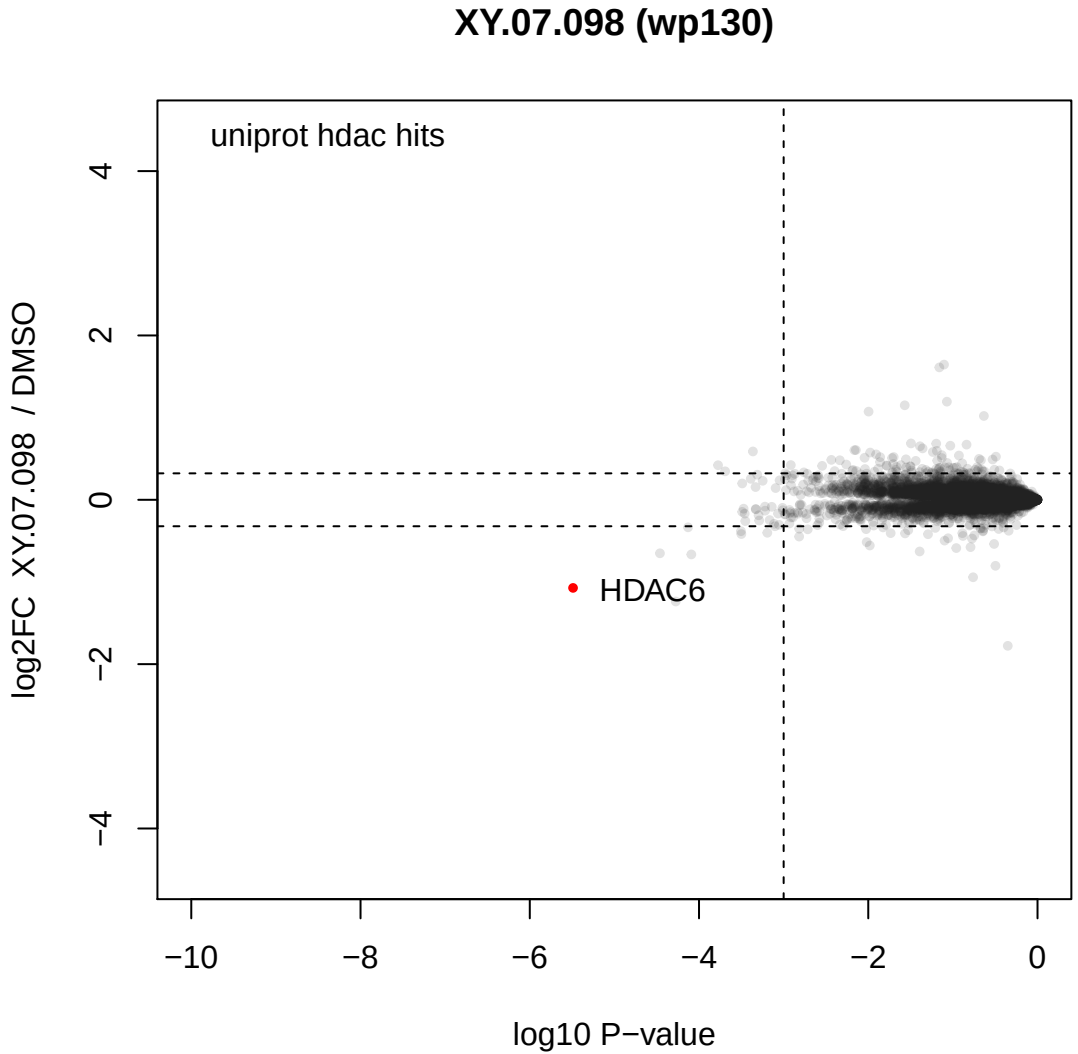

XY.07.100 (wp130)
all hits
SNTA1
COX5B
log2FC XY.07.100 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

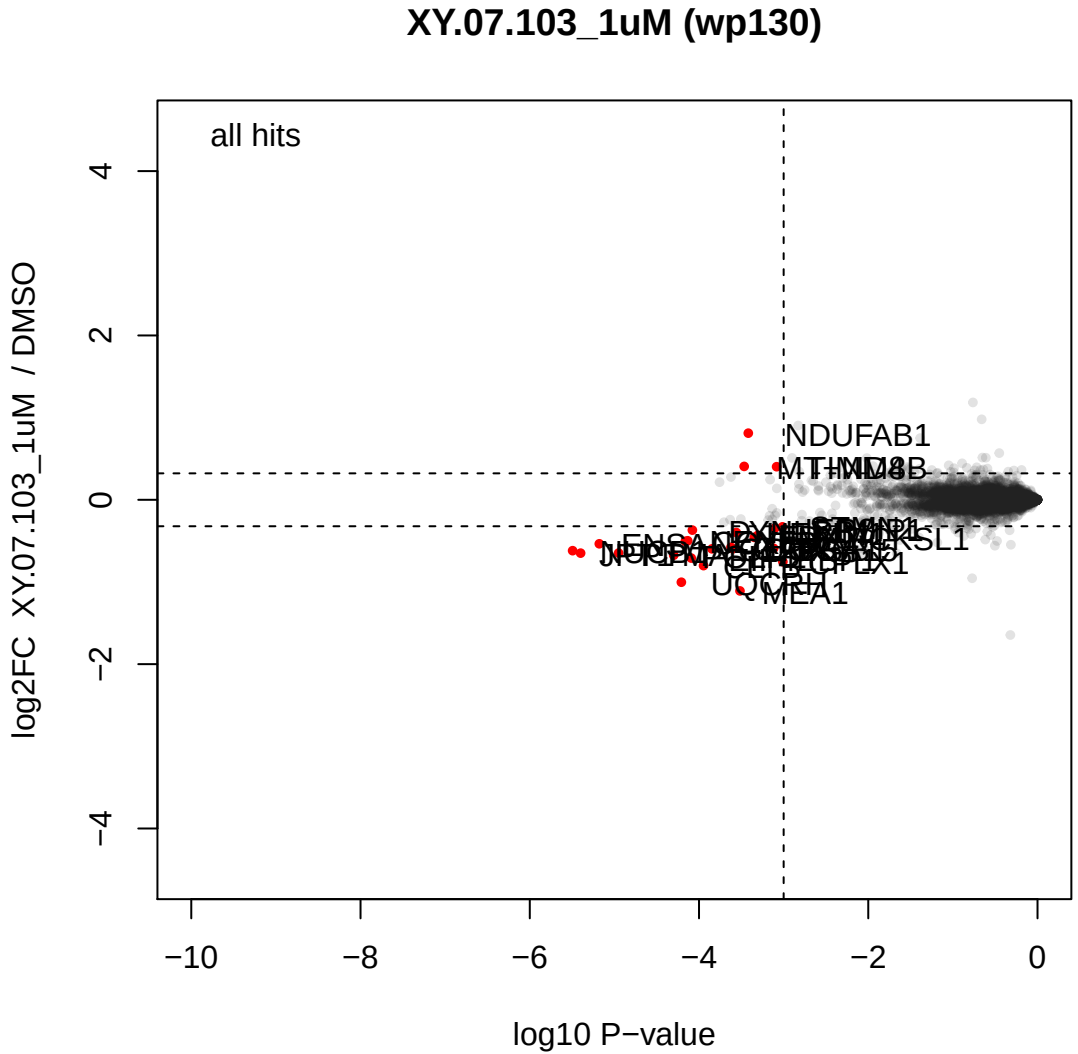

XY.07.100 (wp130)
uniprot hdac hits
log2FC XY.07.100 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

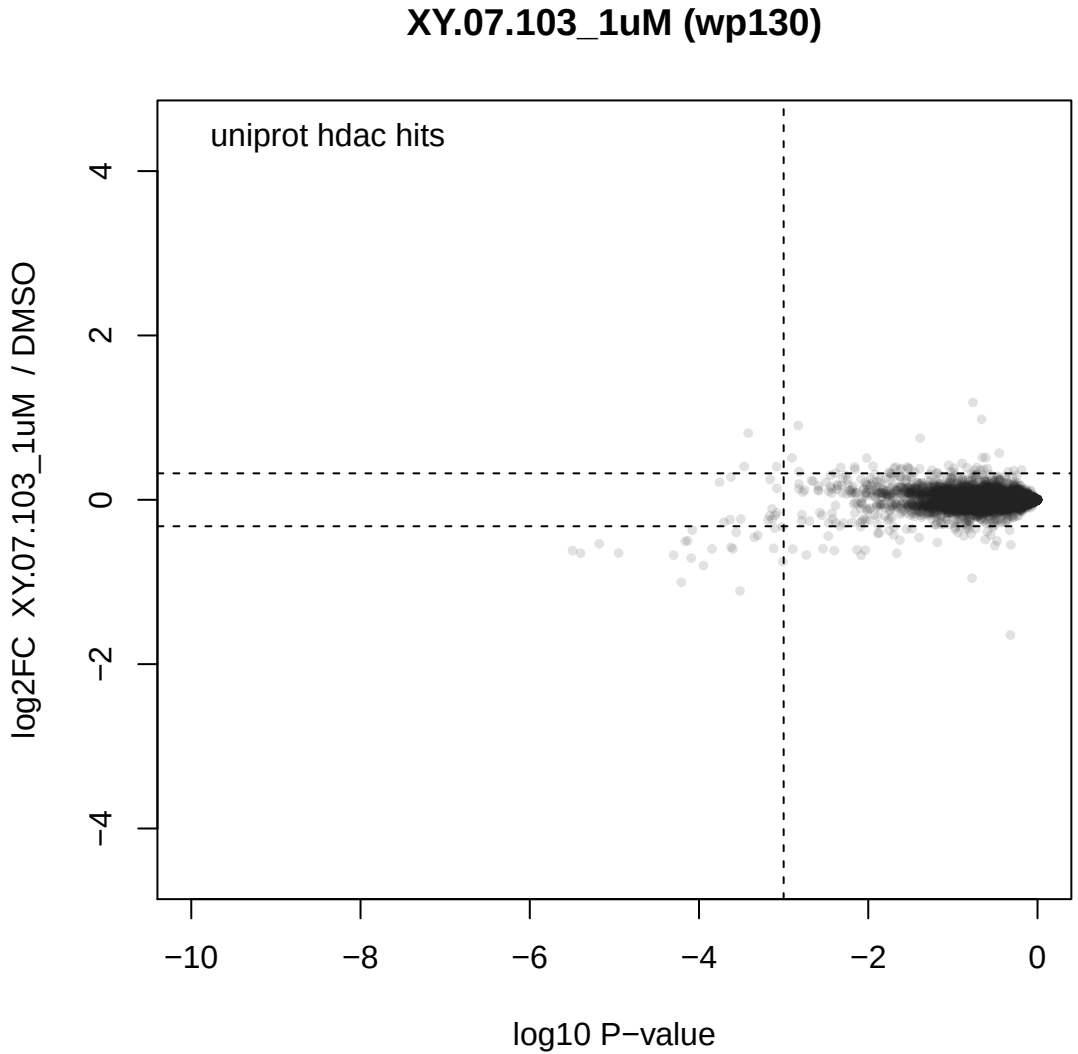

XY.07.060 (wp130)
all hits
log2FC XY.07.060 / DMSO
log10 P−value
TUFT1
SERPINI1
UBTD1
HDAC6
ZFP91
ZNF827
MIER2
ZNF692
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

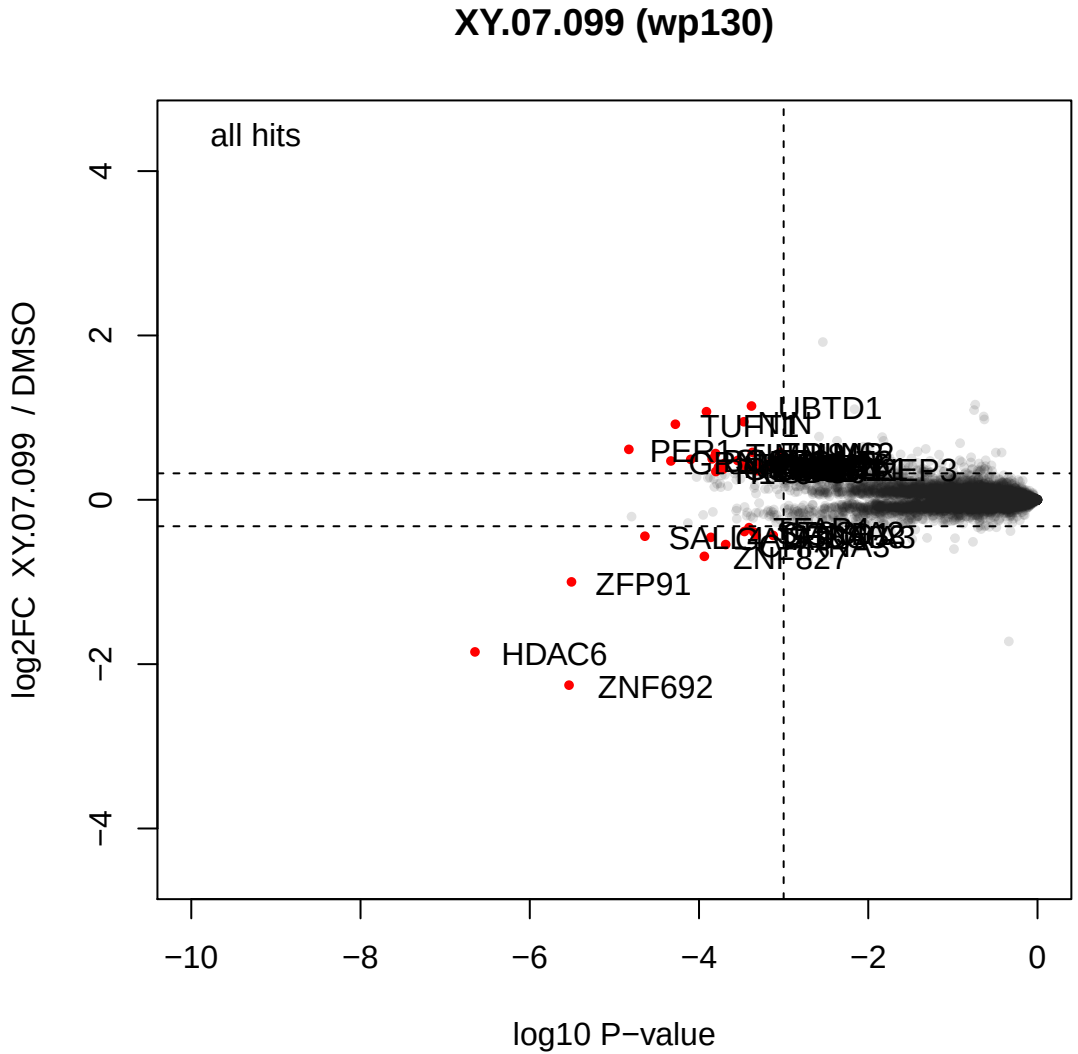

XY.07.060 (wp130)
uniprot hdac hits
log2FC XY.07.060 / DMSO
log10 P−value
HDAC8
HDAC6
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

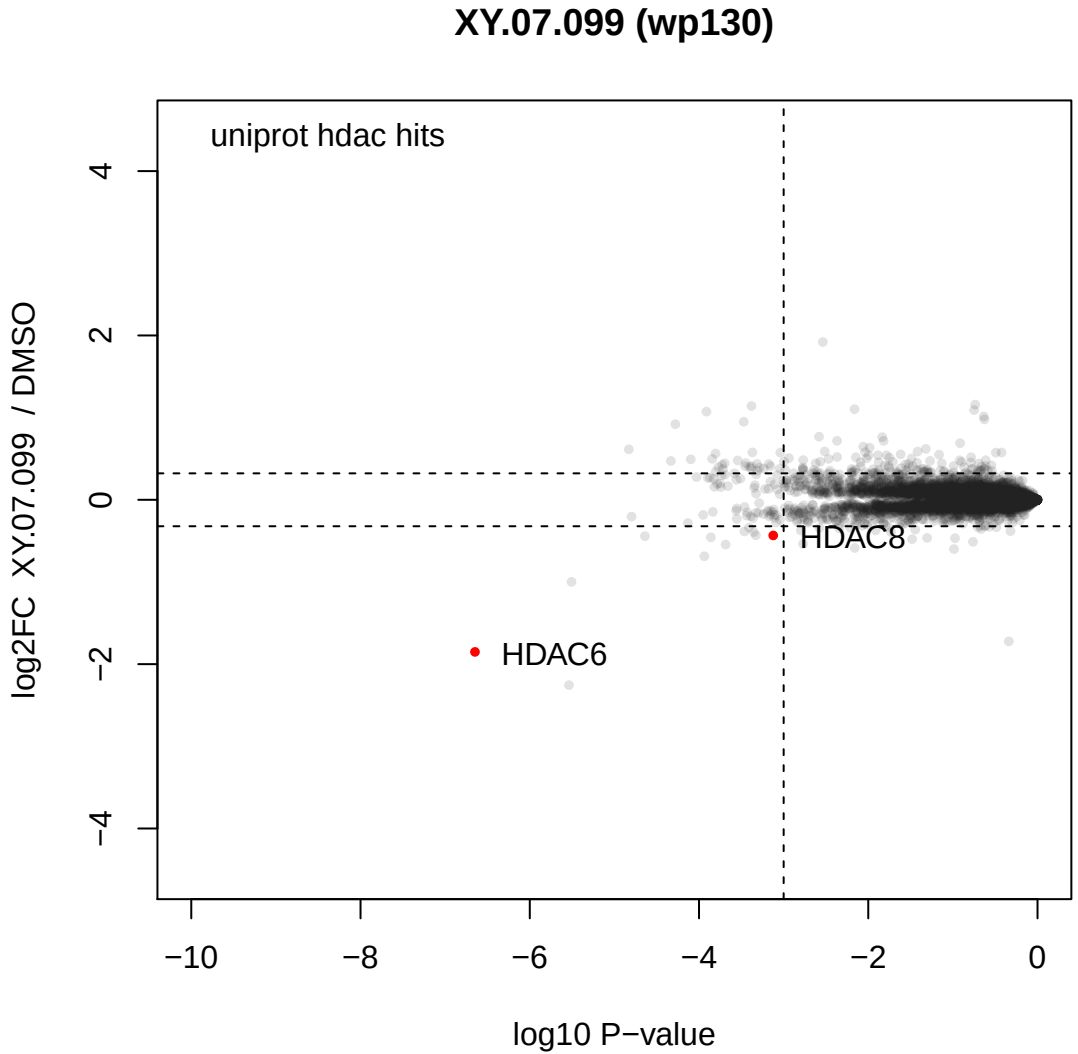

XY.07.098 (wp130)
all hits
log2FC XY.07.098 / DMSO
log10 P−value
HDAC6
ZNF692

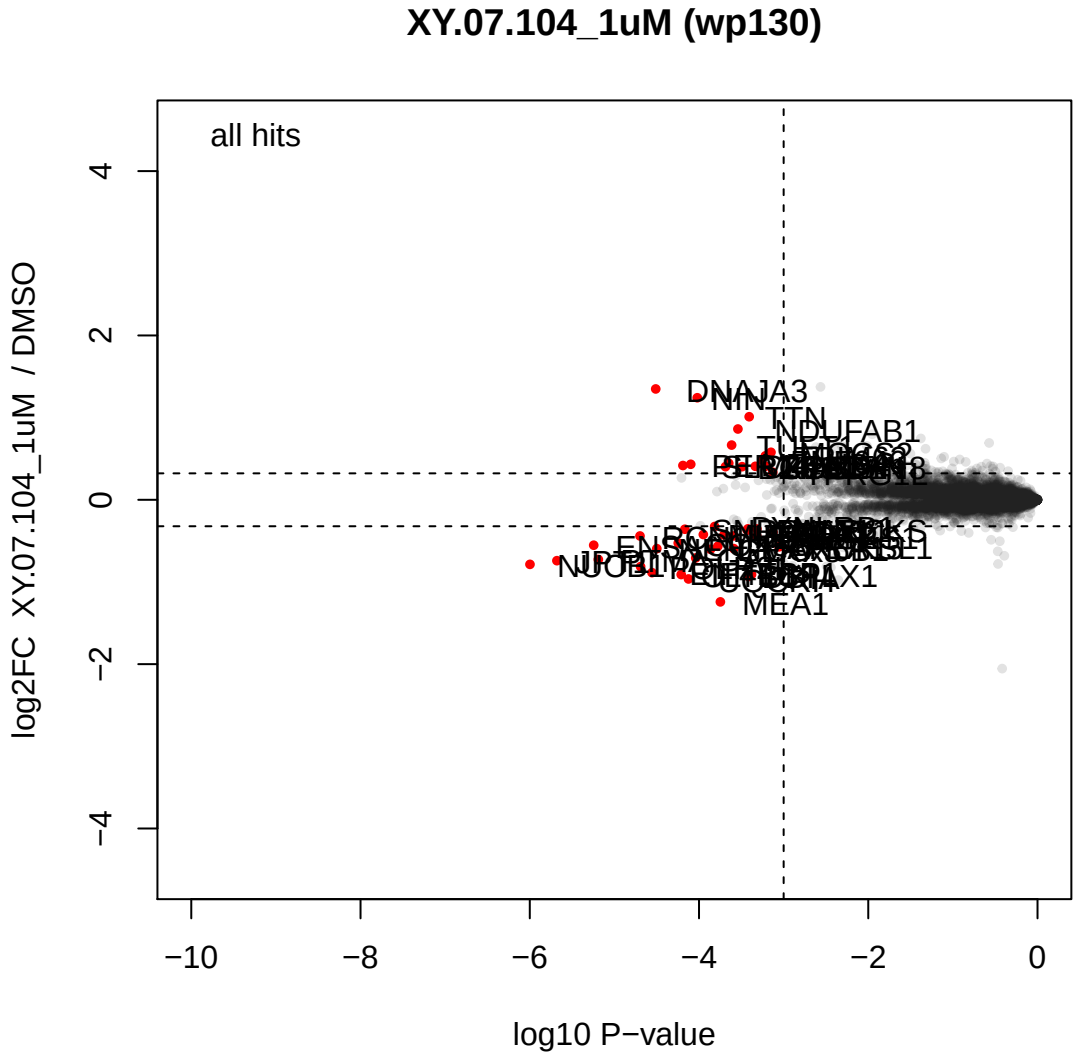

XY.07.098 (wp130)
uniprot hdac hits
log2FC XY.07.098 / DMSO
log10 P−value
HDAC6

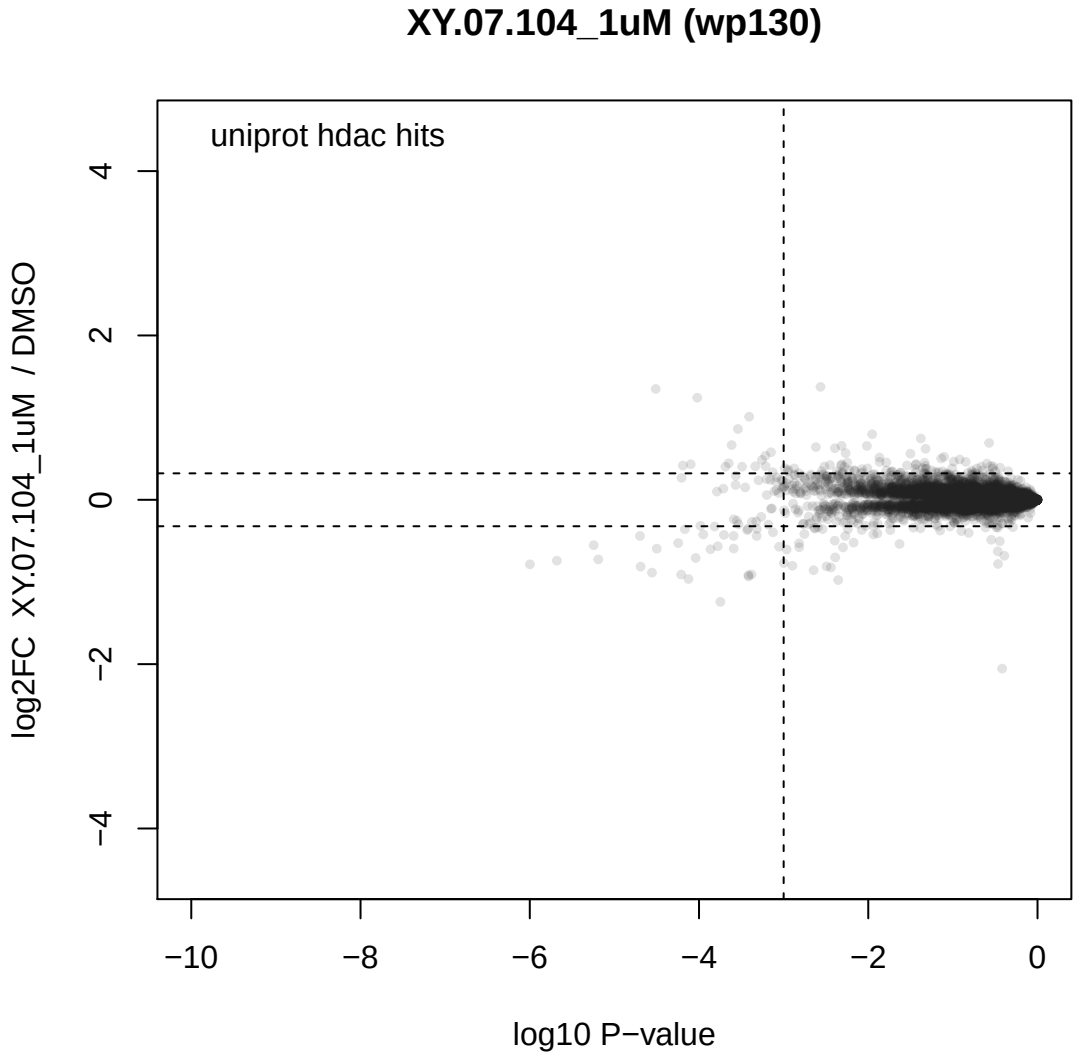

XY.07.103_1uM (wp130)
all hits
NDUFAB1
log2FC XY.07.103_1uM / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

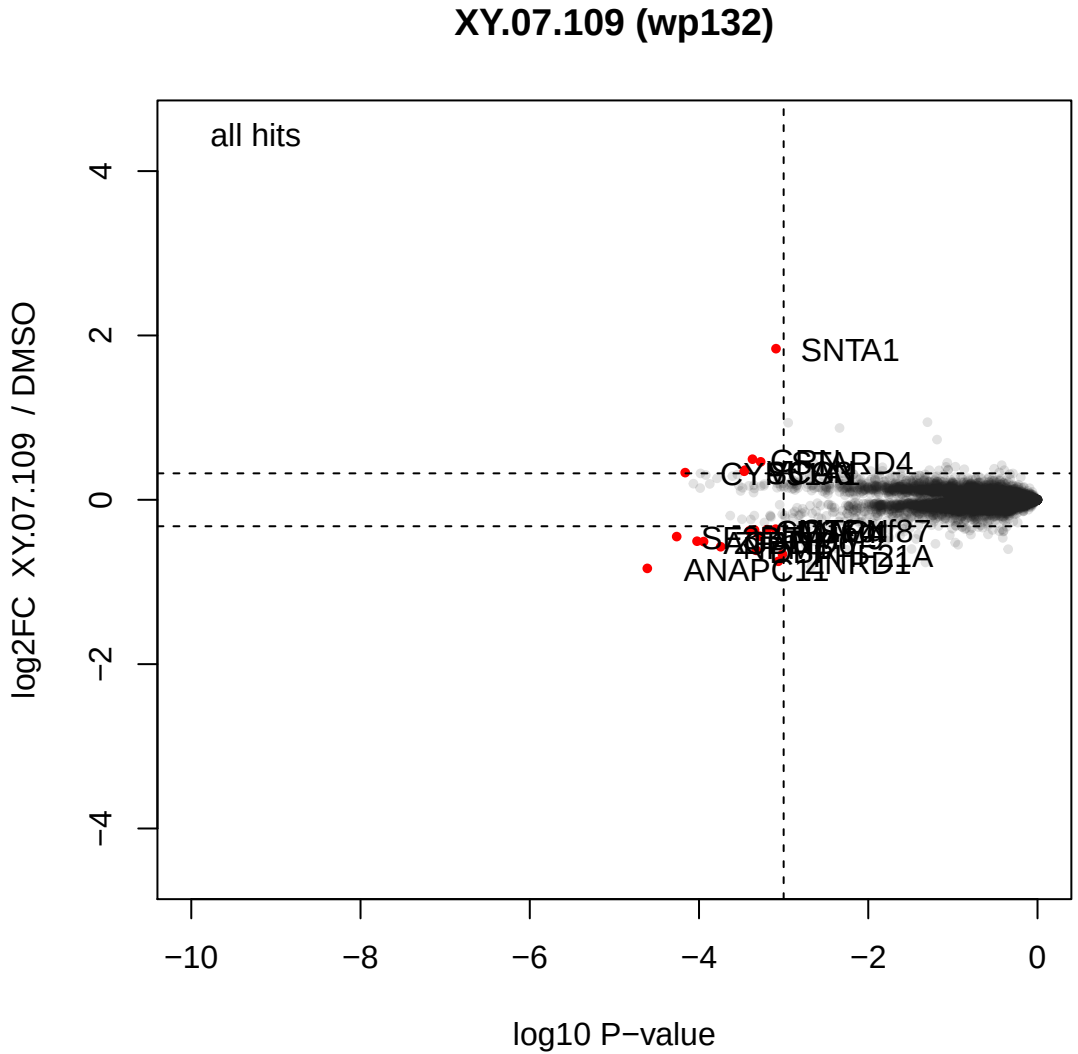

XY.07.103_1uM (wp130)
uniprot hdac hits
log2FC XY.07.103_1uM / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

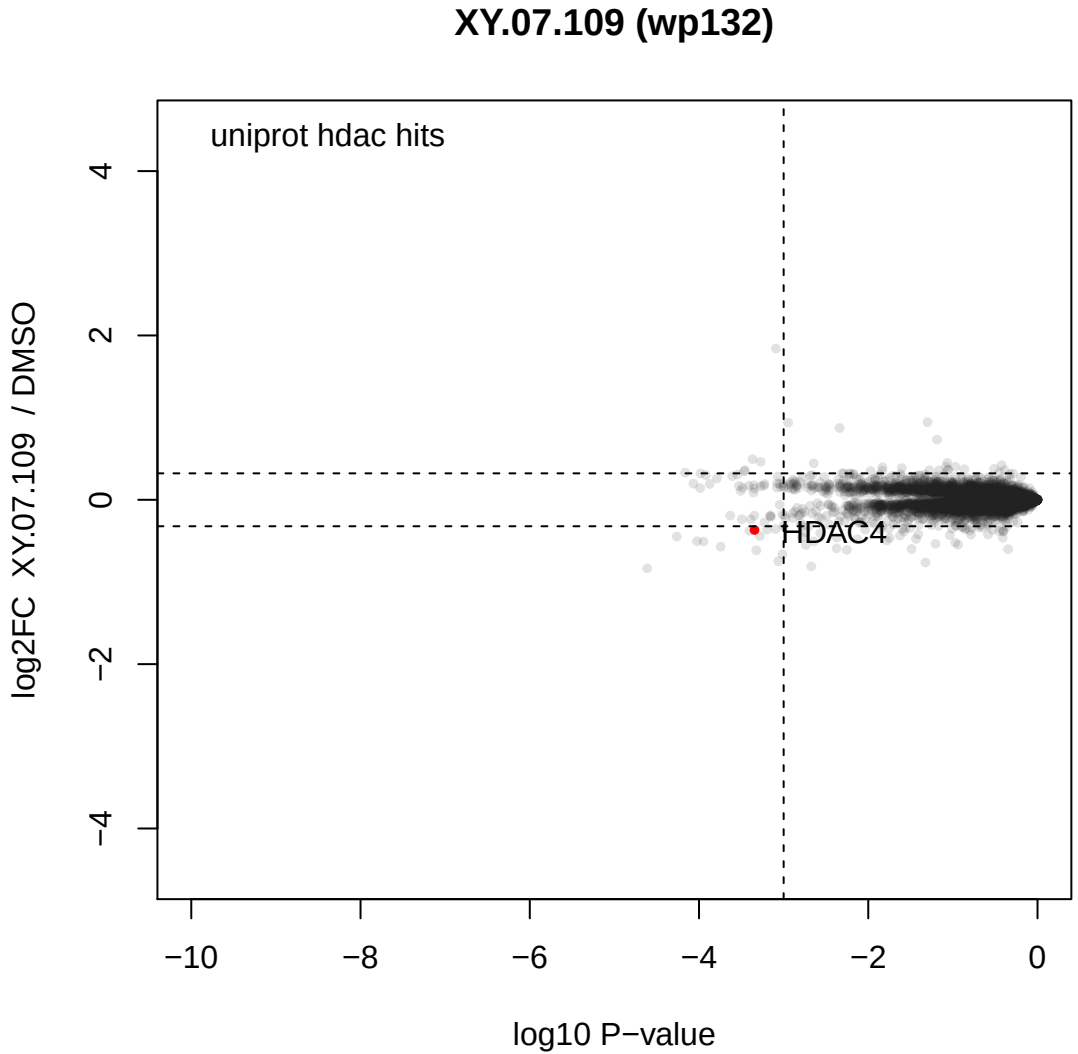

XY.07.099 (wp130)
all hits
log2FC XY.07.099 / DMSO
log10 P−value
UBTD1
ZFP91
HDAC6
ZNF692
ZNF827

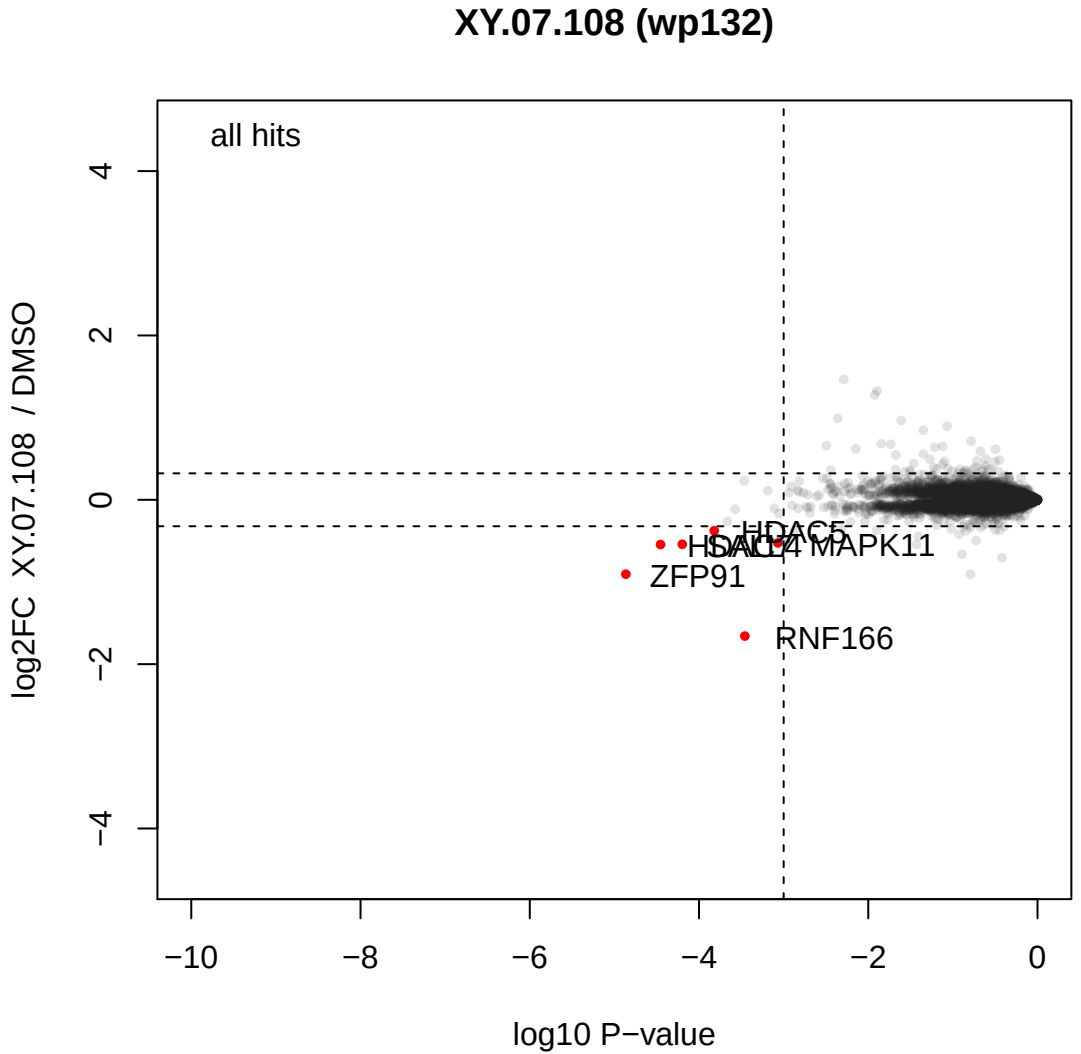

XY.07.099 (wp130)
uniprot hdac hits
log2FC XY.07.099 / DMSO
log10 P−value
HDAC8
HDAC6

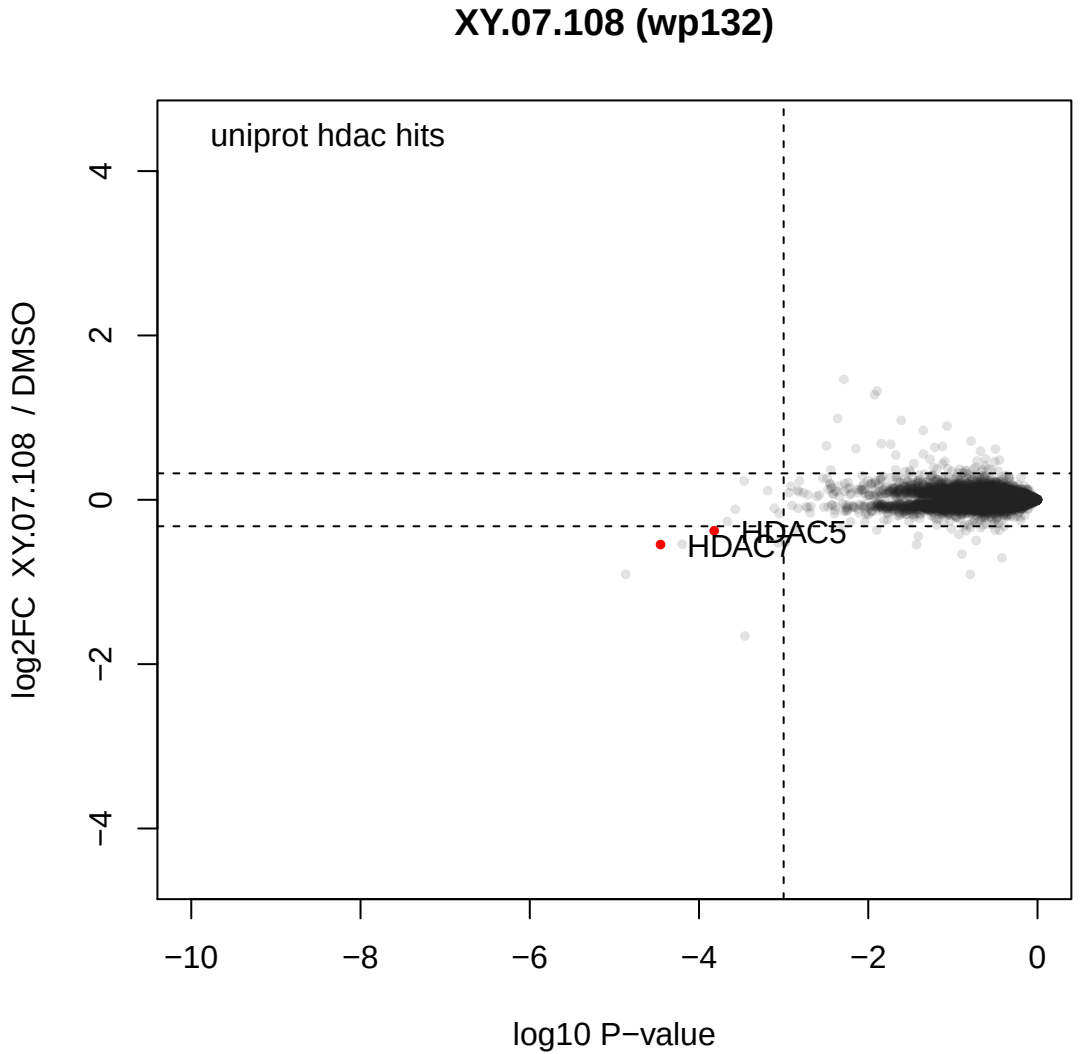

XY.07.104_1uM (wp130)
all hits
log2FC XY.07.104_1uM / DMSO
log10 P−value
DNAJA3
ITN
NDUFAB1
MEA1
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

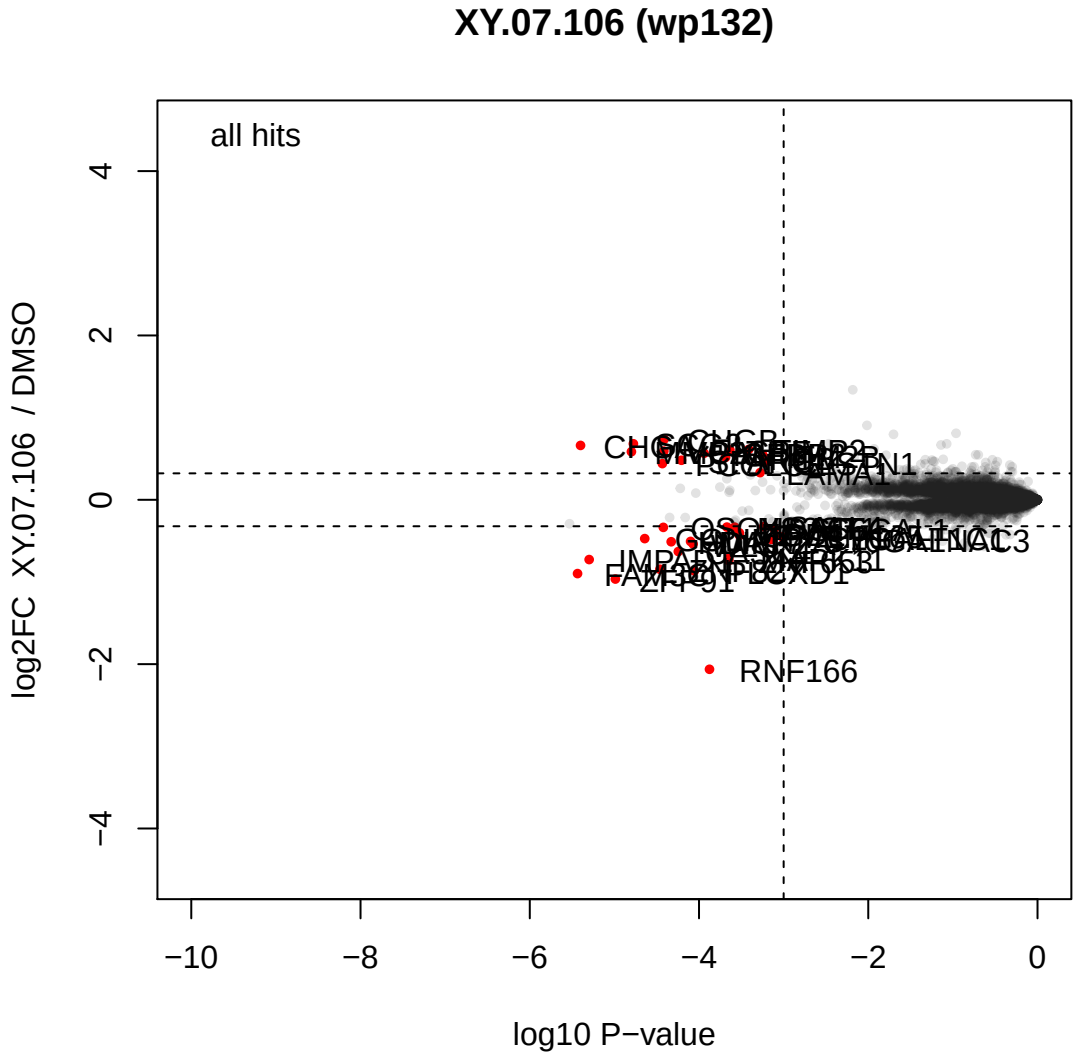

XY.07.104_1uM (wp130)
uniprot hdac hits
log2FC XY.07.104_1uM / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

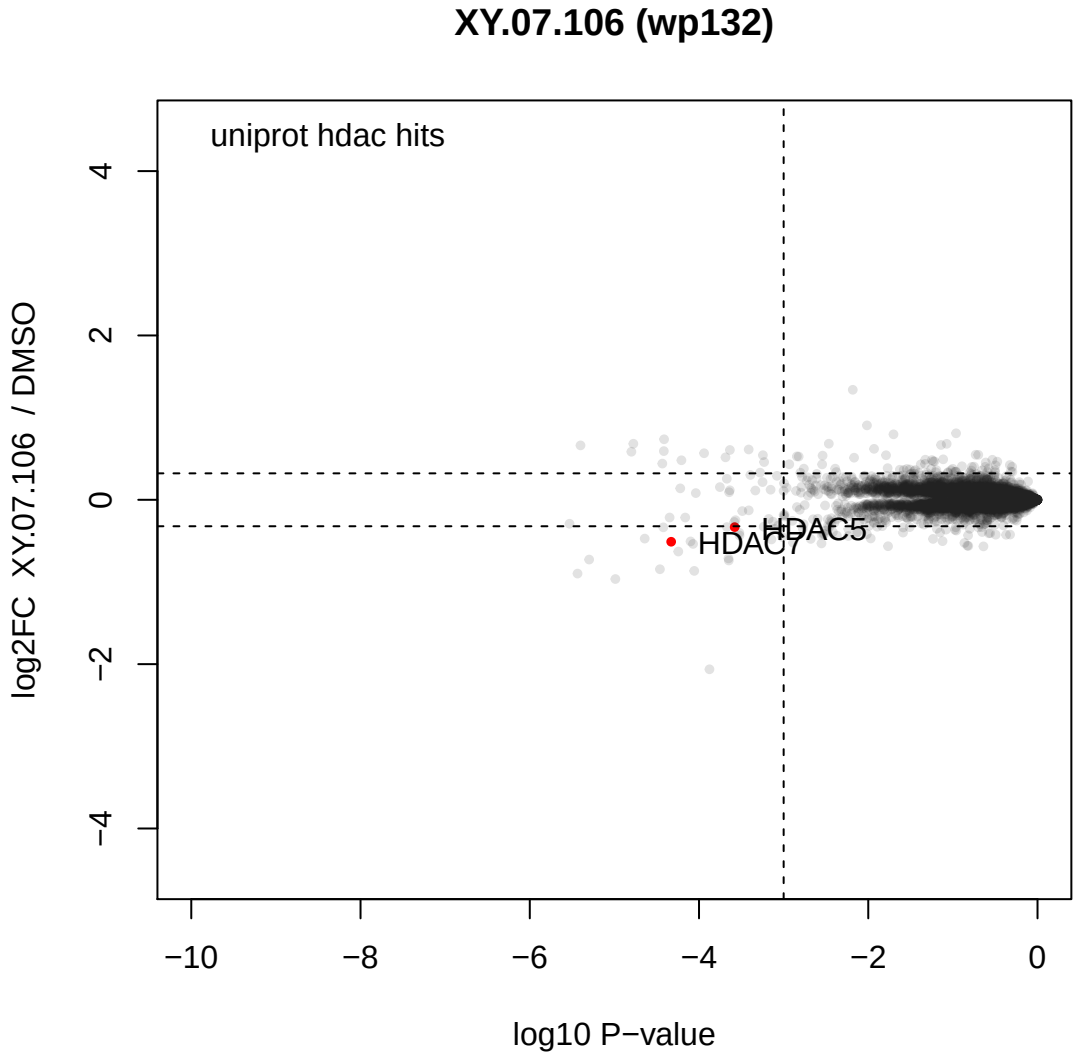

XY.07.109 (wp132)
all hits
SNTA1
ANAPC11
log2FC XY.07.109 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

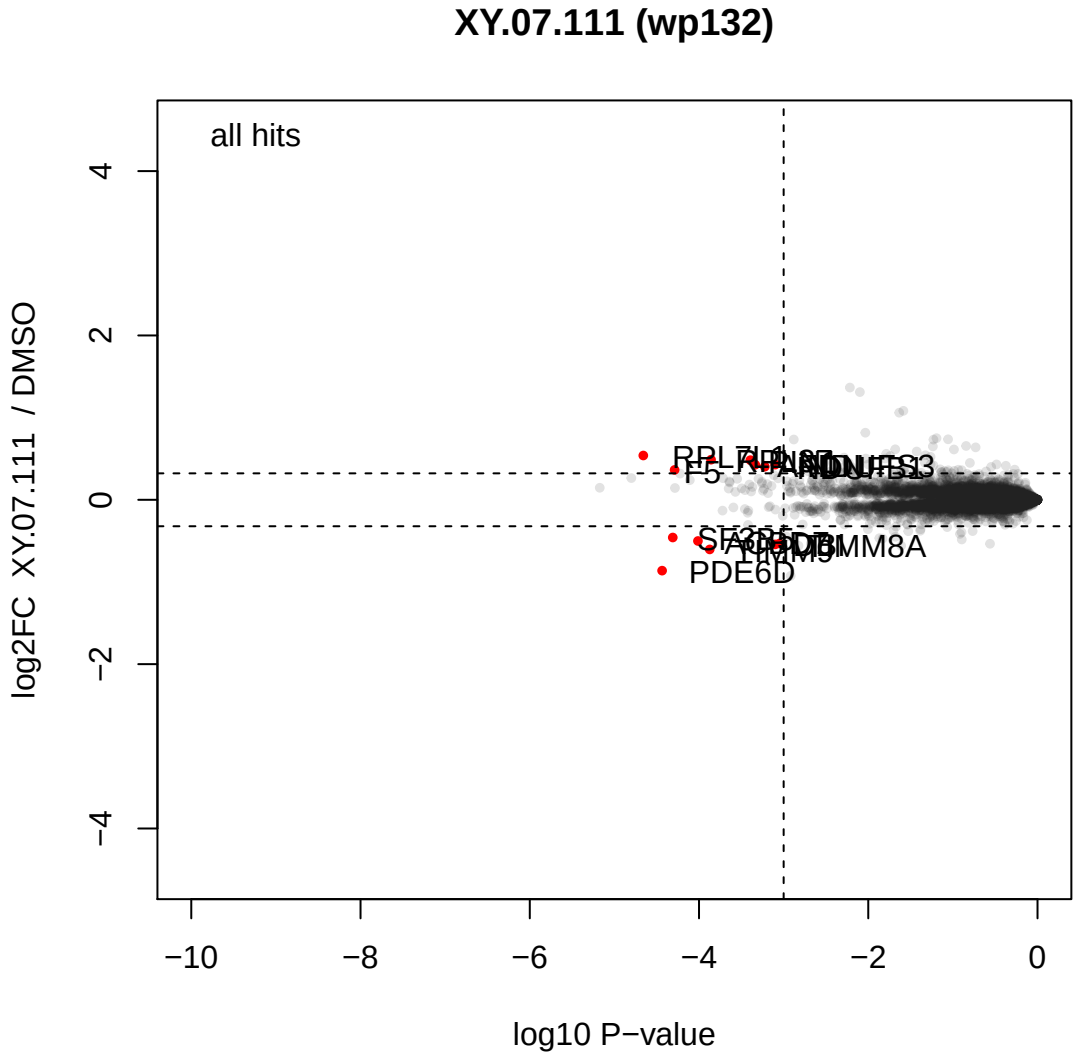

XY.07.109 (wp132)
uniprot hdac hits
HDAC4
log2FC XY.07.109 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

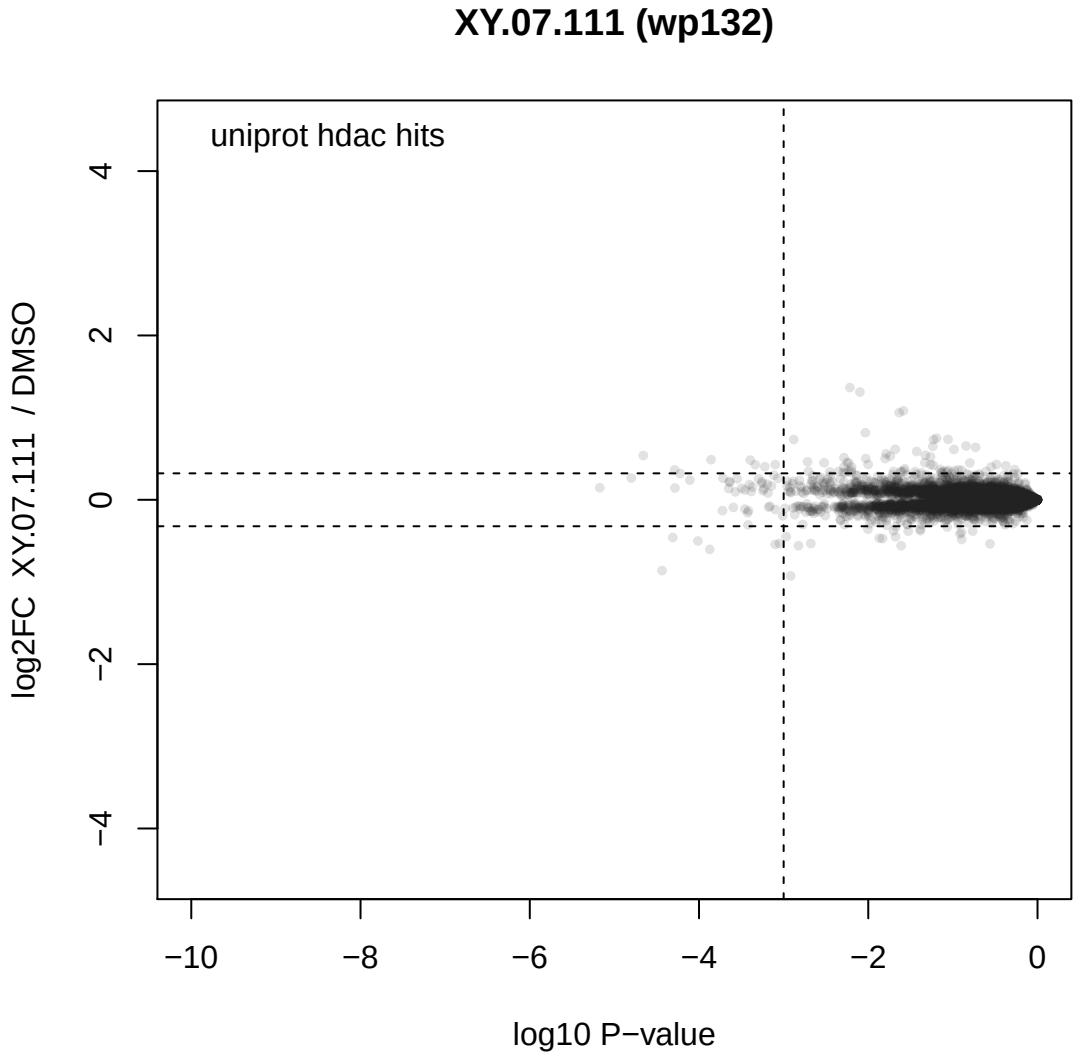

XY.07.108 (wp132)
all hits
log2FC XY.07.108 / DMSO
log10 P−value
HDAC5
HDAC7
MAPK11
ZFP91
RNF166
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

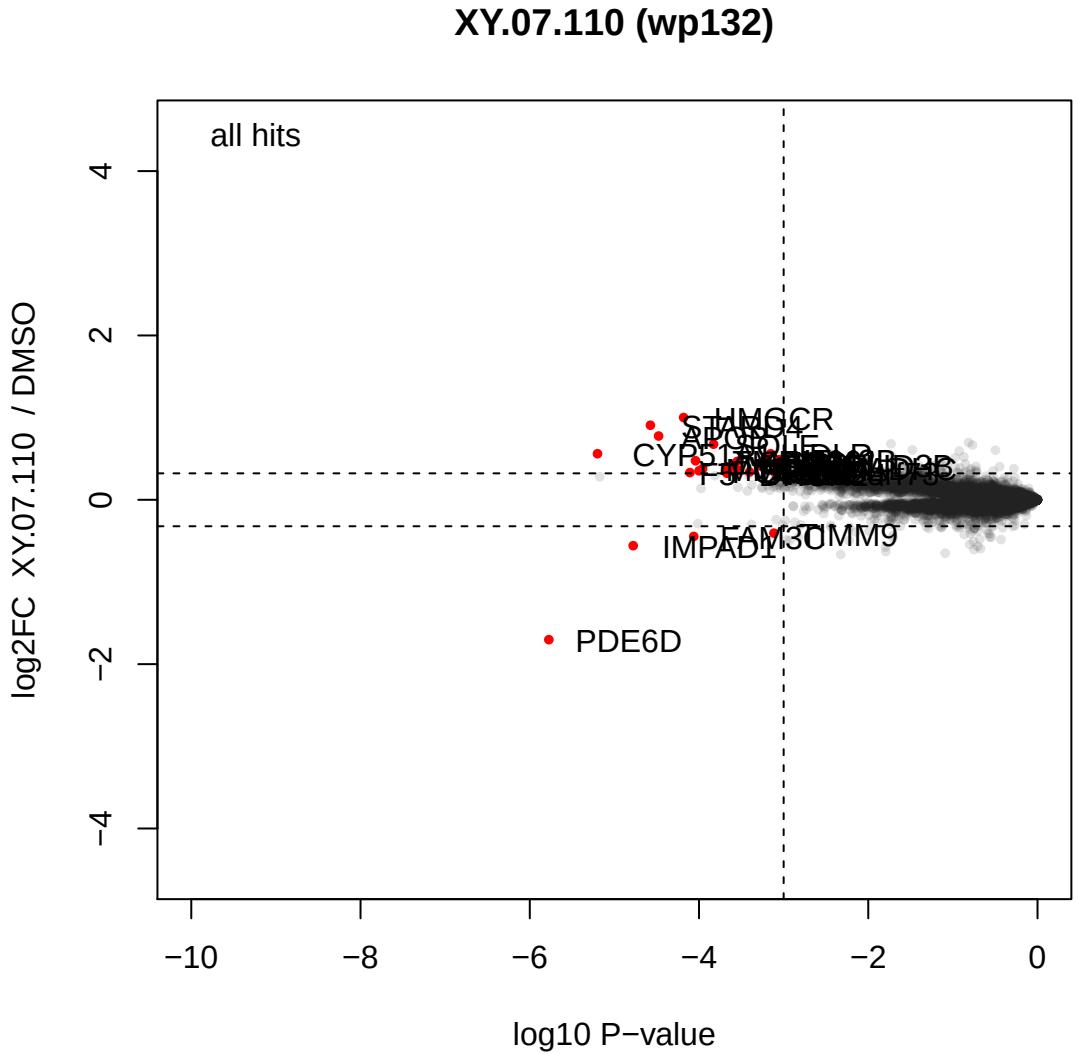

XY.07.108 (wp132)
uniprot hdac hits
log2FC XY.07.108 / DMSO
log10 P−value
HDAC5
HDAC7
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

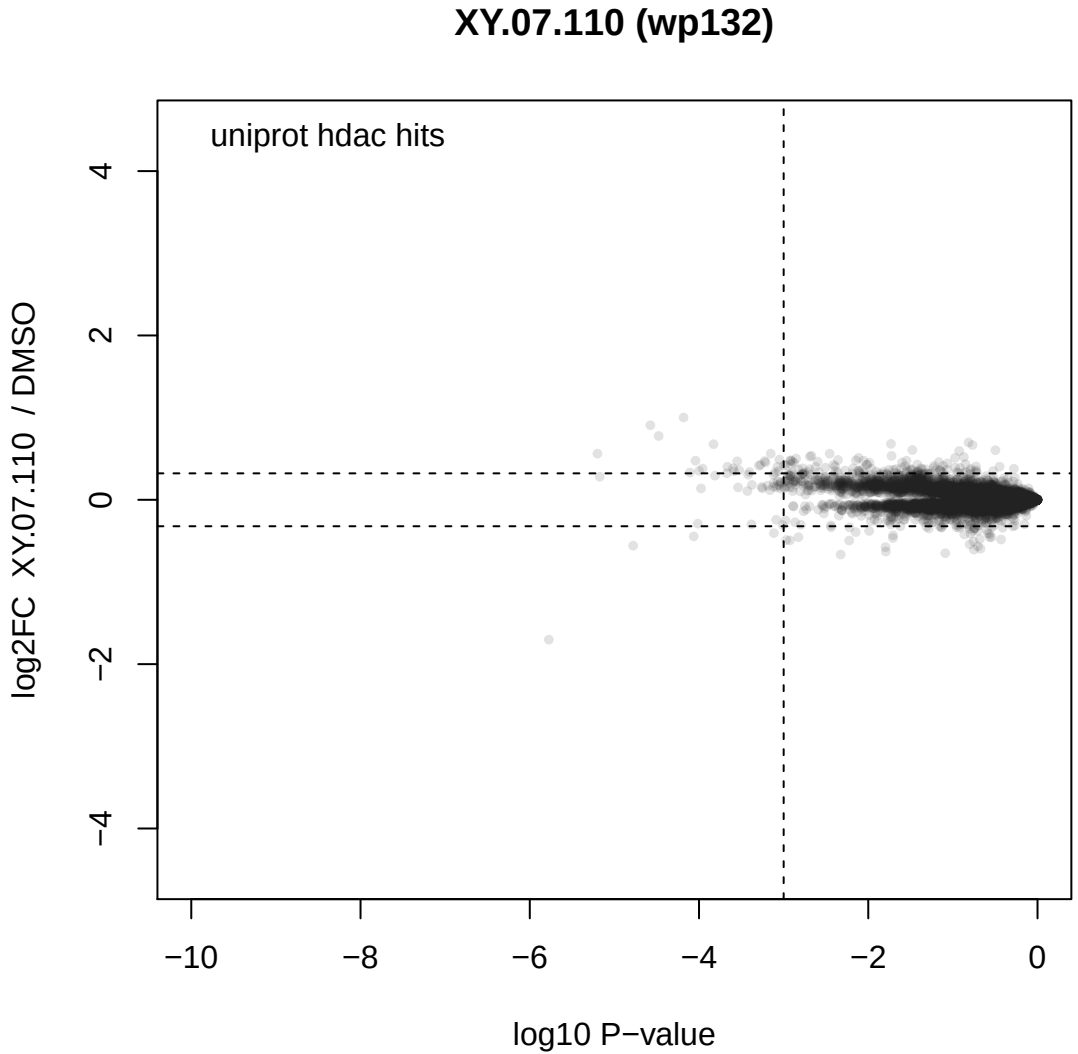

XY.07.106 (wp132)
all hits
log2FC XY.07.106 / DMSO
log10 P−value
RNF166

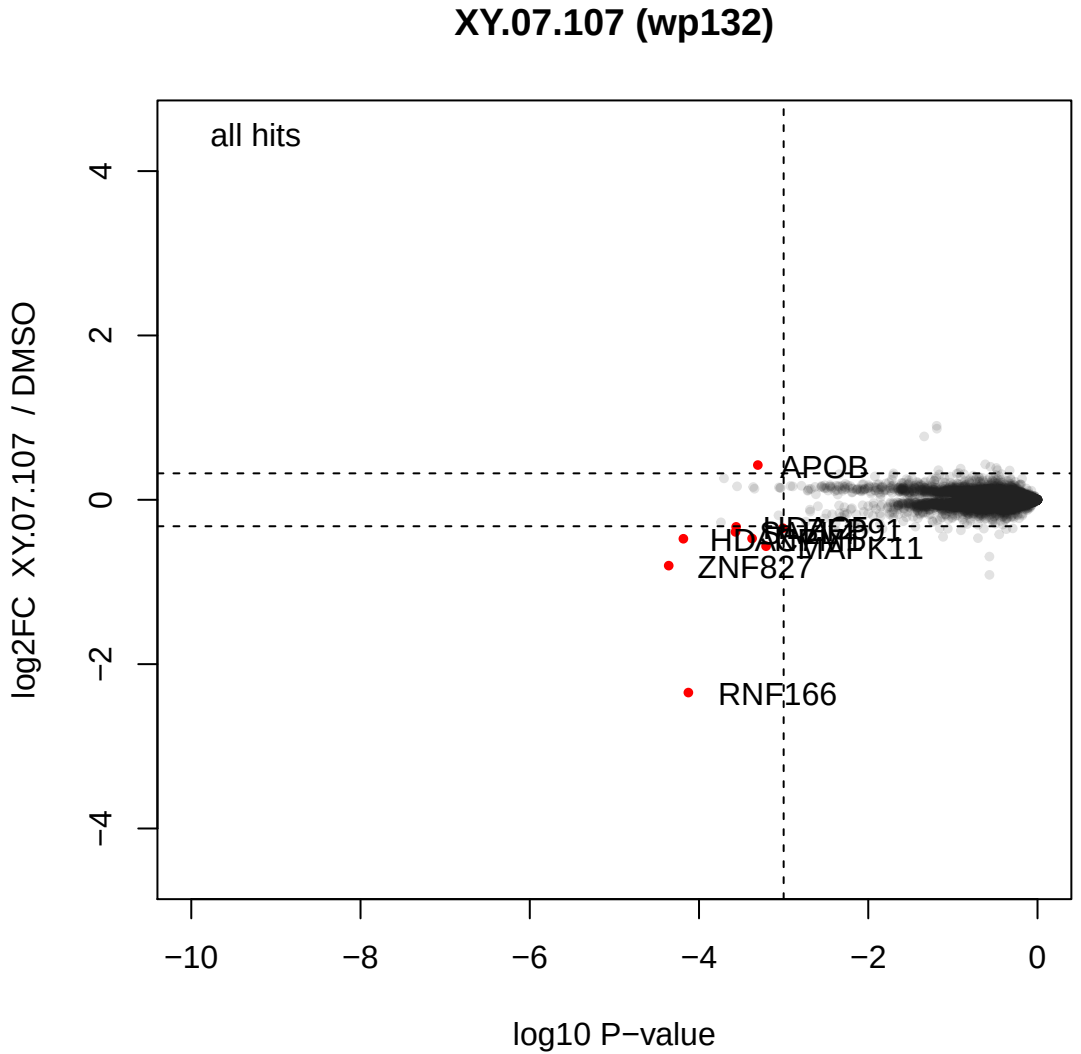

XY.07.106 (wp132)
uniprot hdac hits
log2FC XY.07.106 / DMSO
log10 P−value
HDAC7
HDAC5

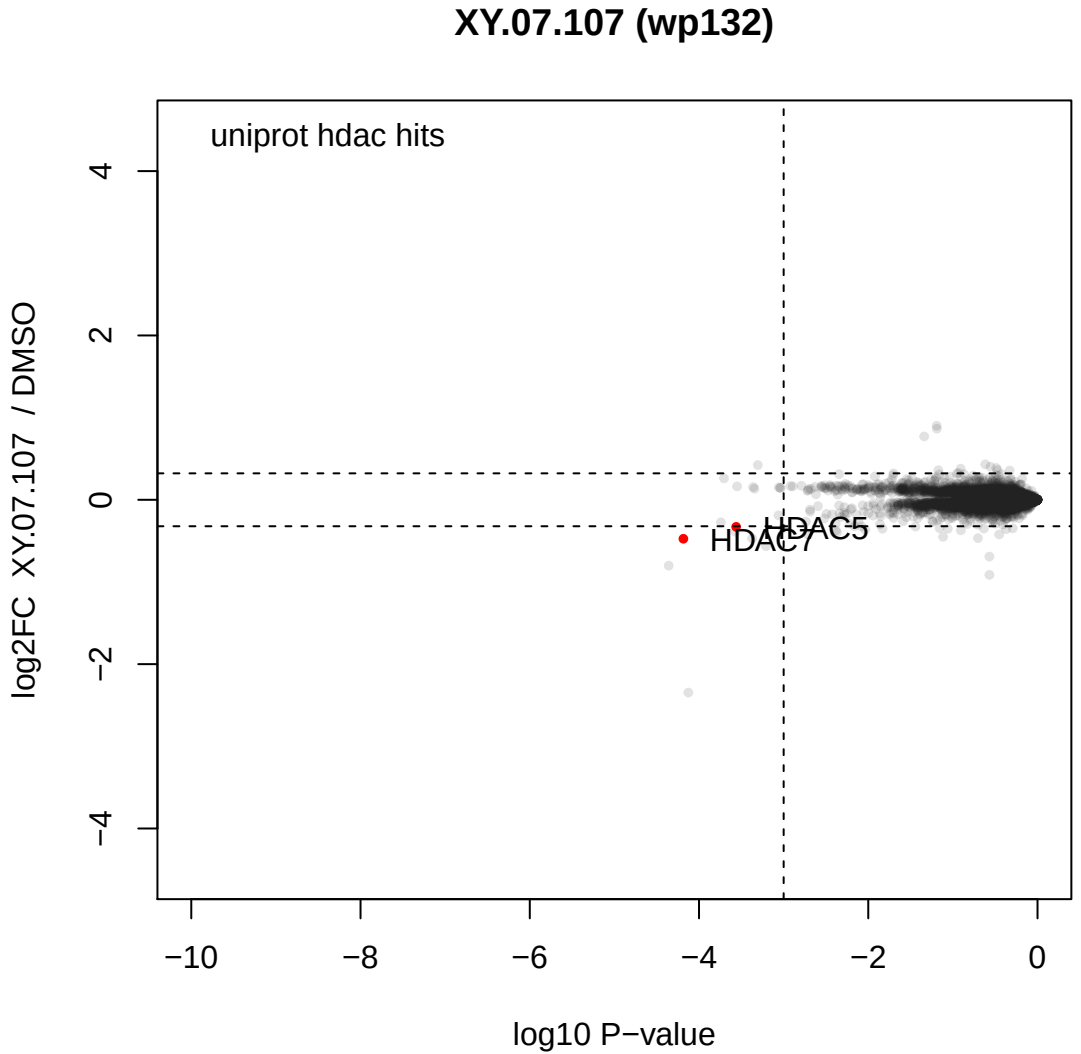

XY.07.111 (wp132)
all hits
log2FC XY.07.111 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0
F5
PDE6D

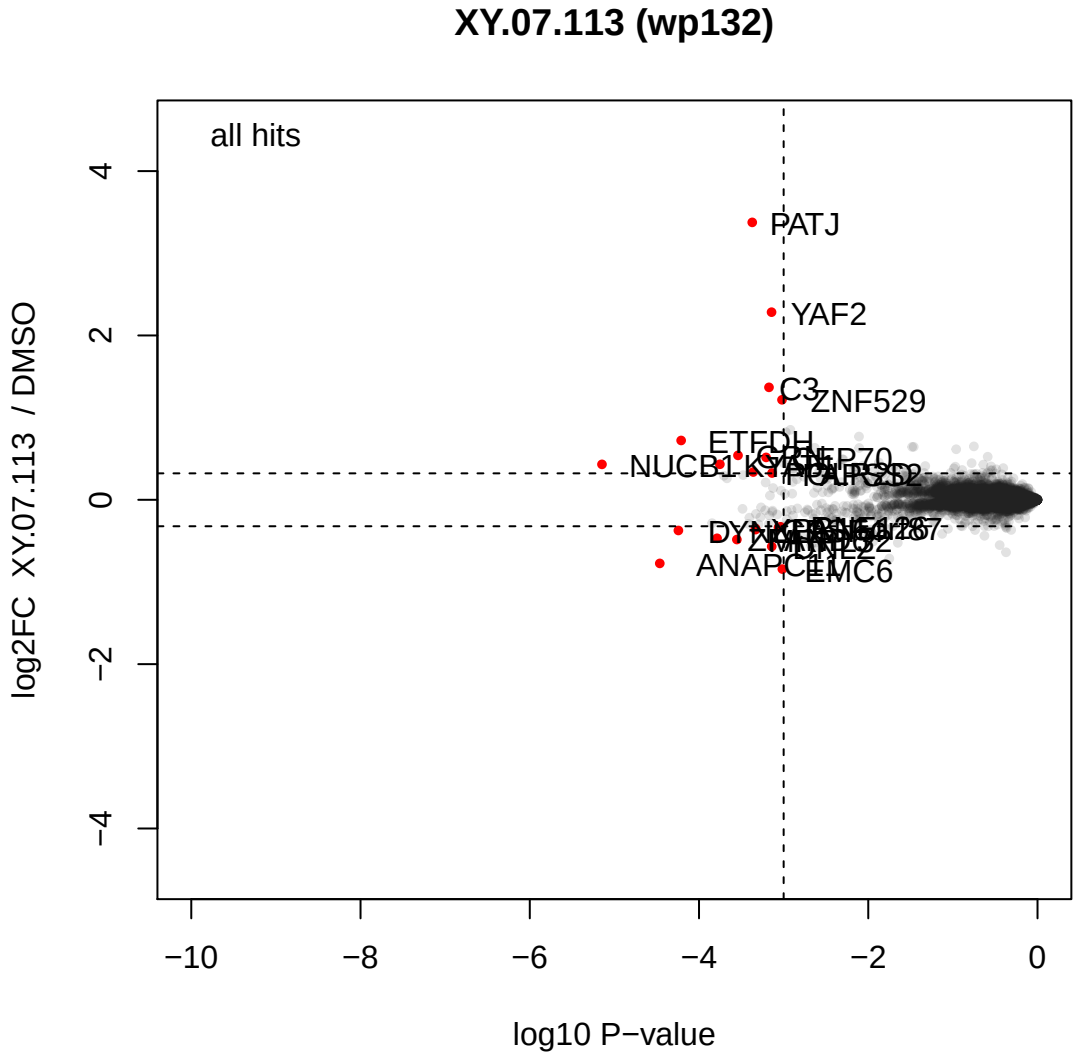

XY.07.111 (wp132)
uniprot hdac hits
log2FC XY.07.111 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

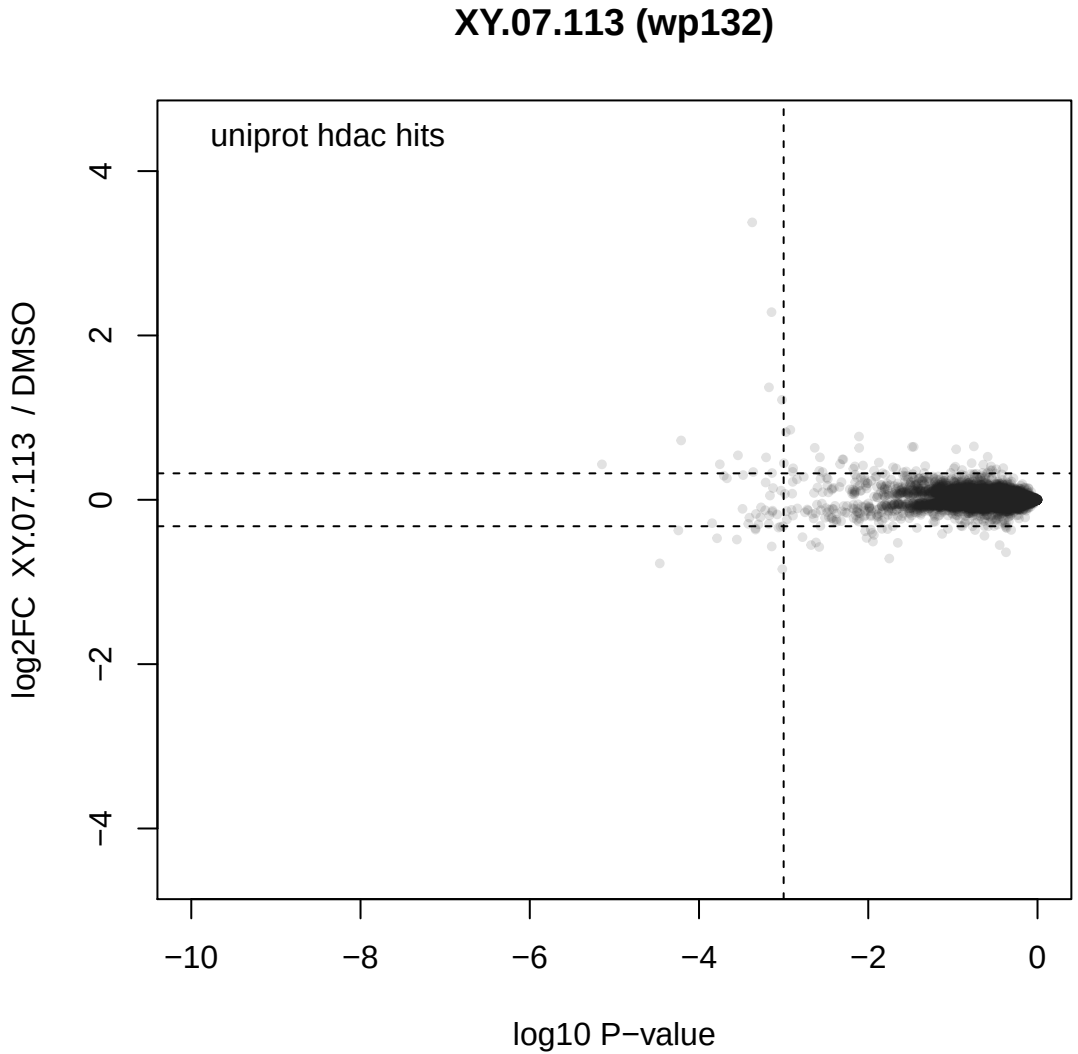

XY.07.110 (wp132)
all hits
log2FC XY.07.110 / DMSO
log10 P−value
HMGCR
IMPAD1
PDE6D
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

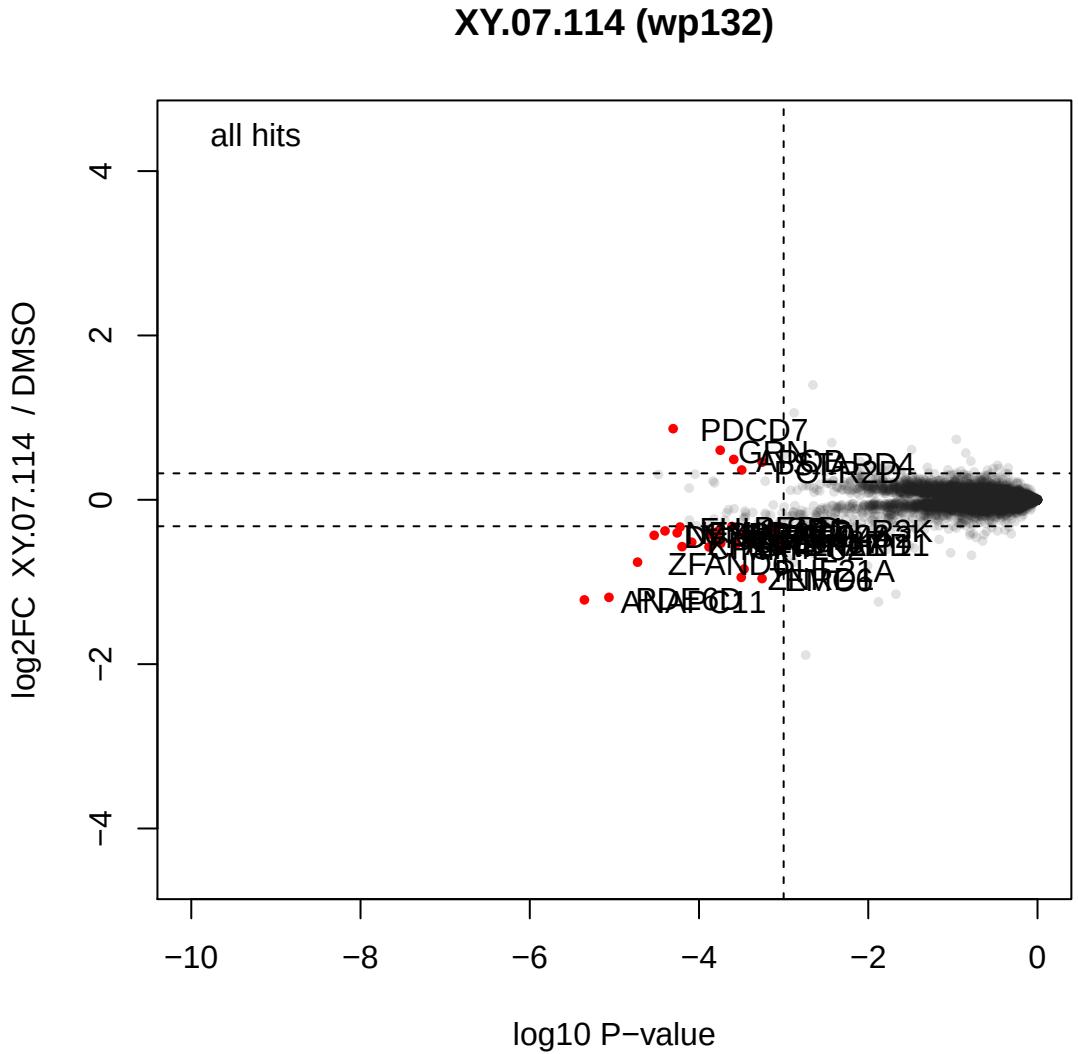

XY.07.110 (wp132)
uniprot hdac hits
log2FC XY.07.110 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

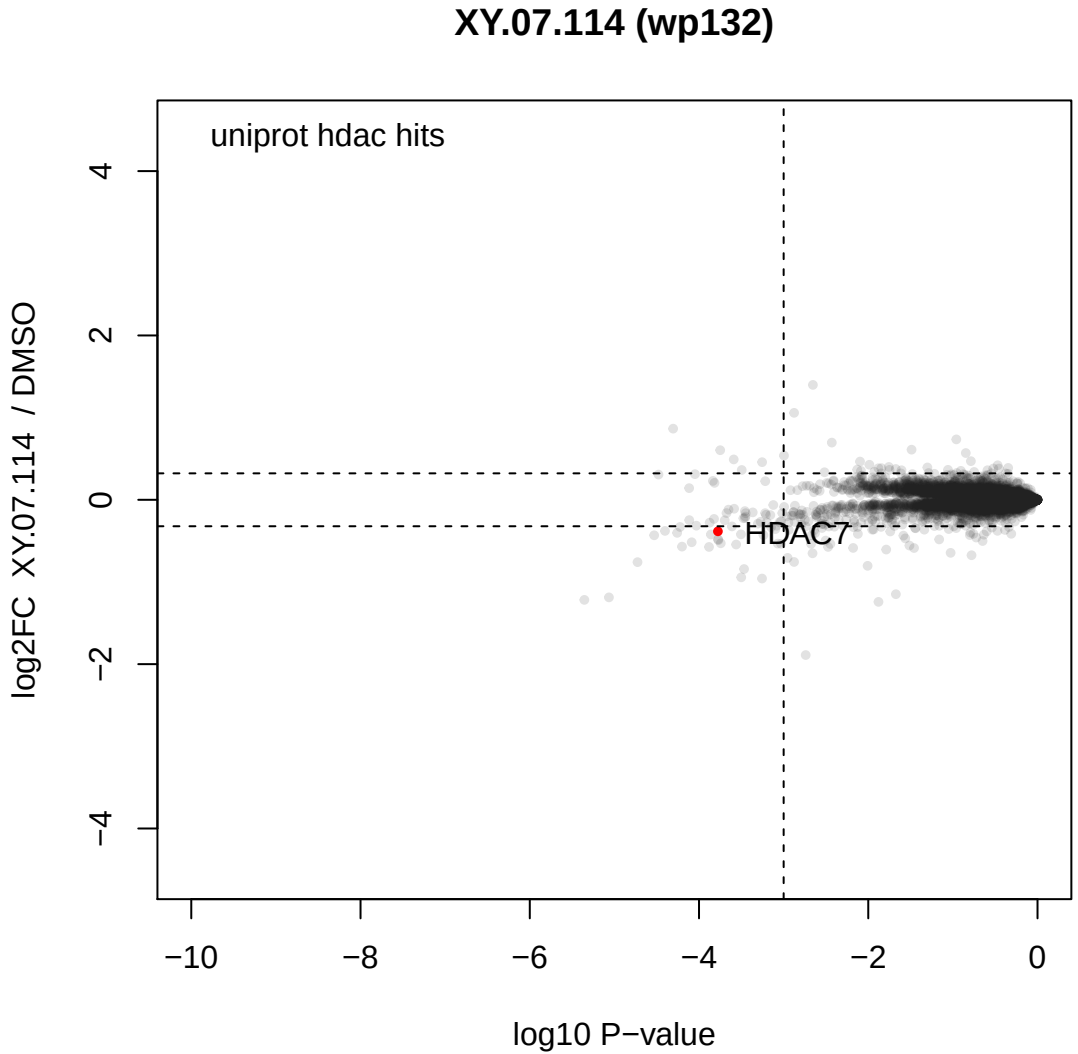

XY.07.107 (wp132)
all hits
log2FC XY.07.107 / DMSO
log10 P−value
APOB
ZNF827
RNF166
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

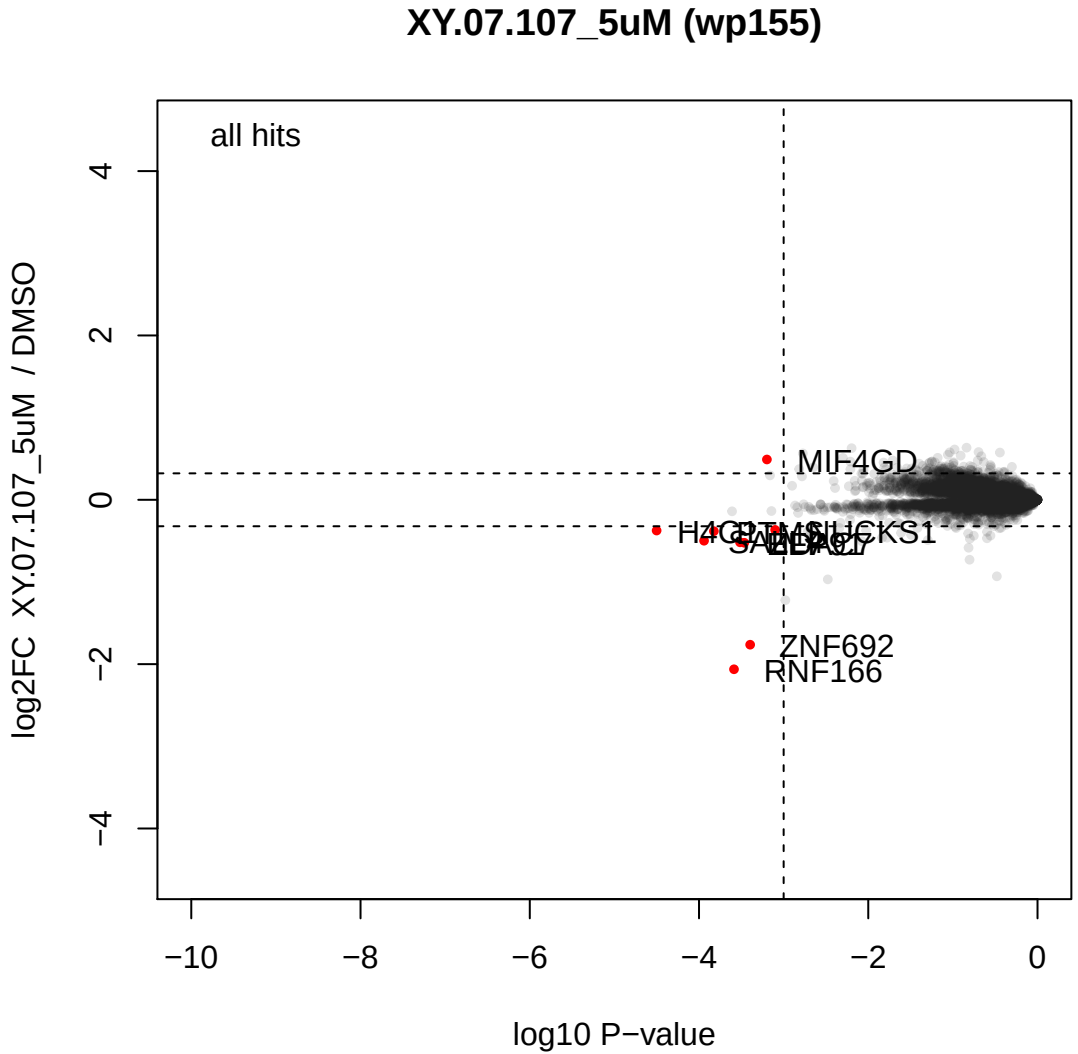

XY.07.107 (wp132)
uniprot hdac hits
log2FC XY.07.107 / DMSO
log10 P−value
HDAC5
HDAC7
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

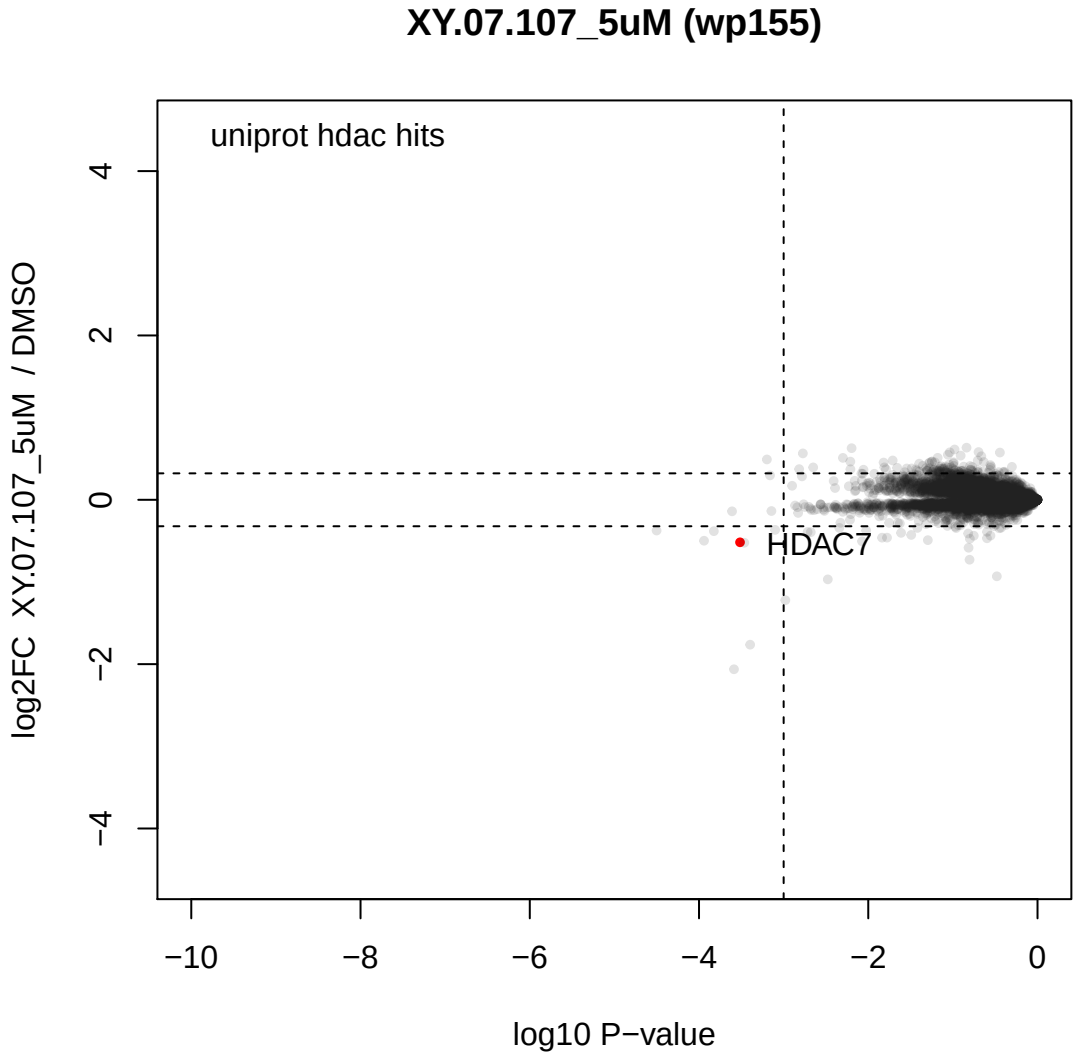

XY.07.113 (wp132)
all hits
PATJ
YAF2
C3
ZNF529
ETFDH
NUCB1
EMC6
log2FC XY.07.113 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

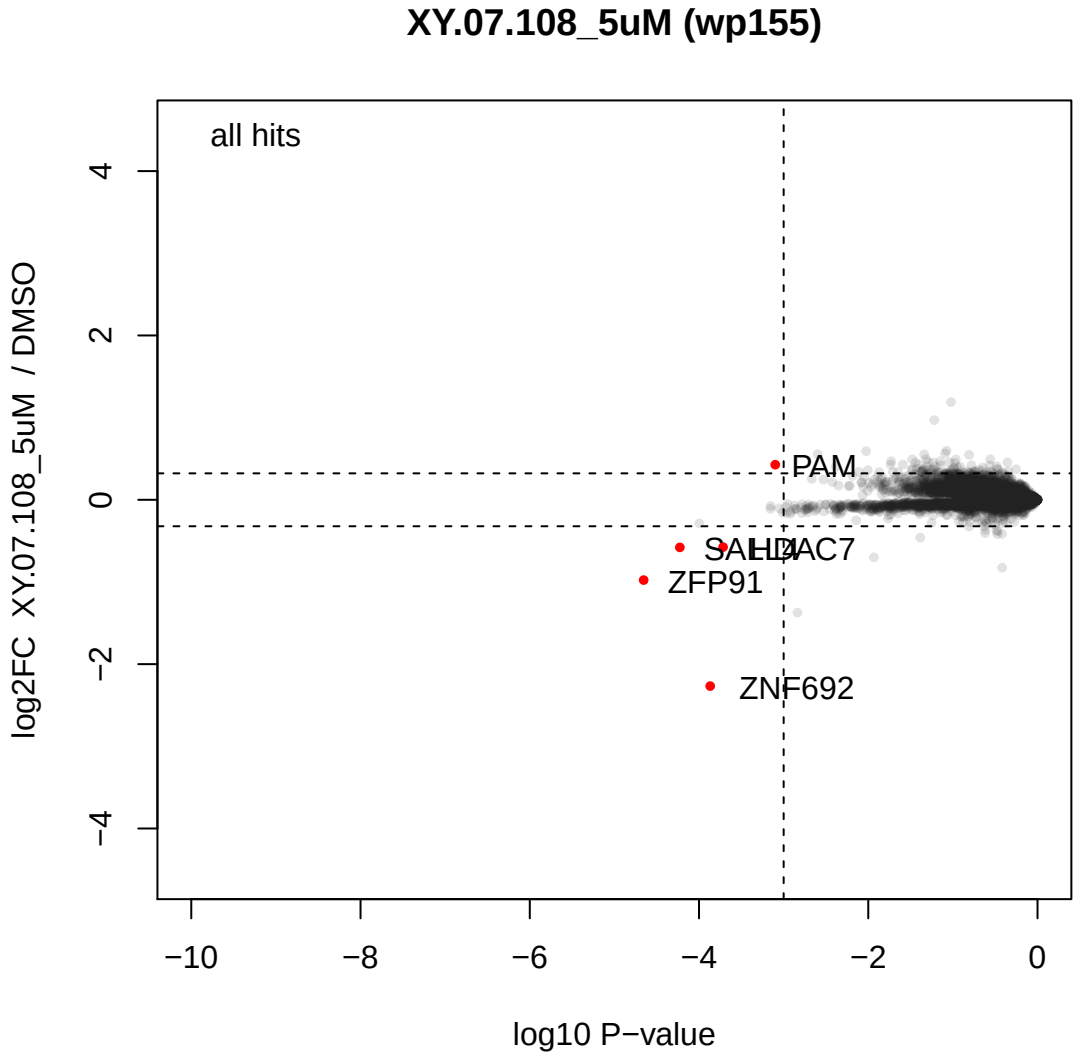

XY.07.113 (wp132)
uniprot hdac hits
log2FC XY.07.113 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

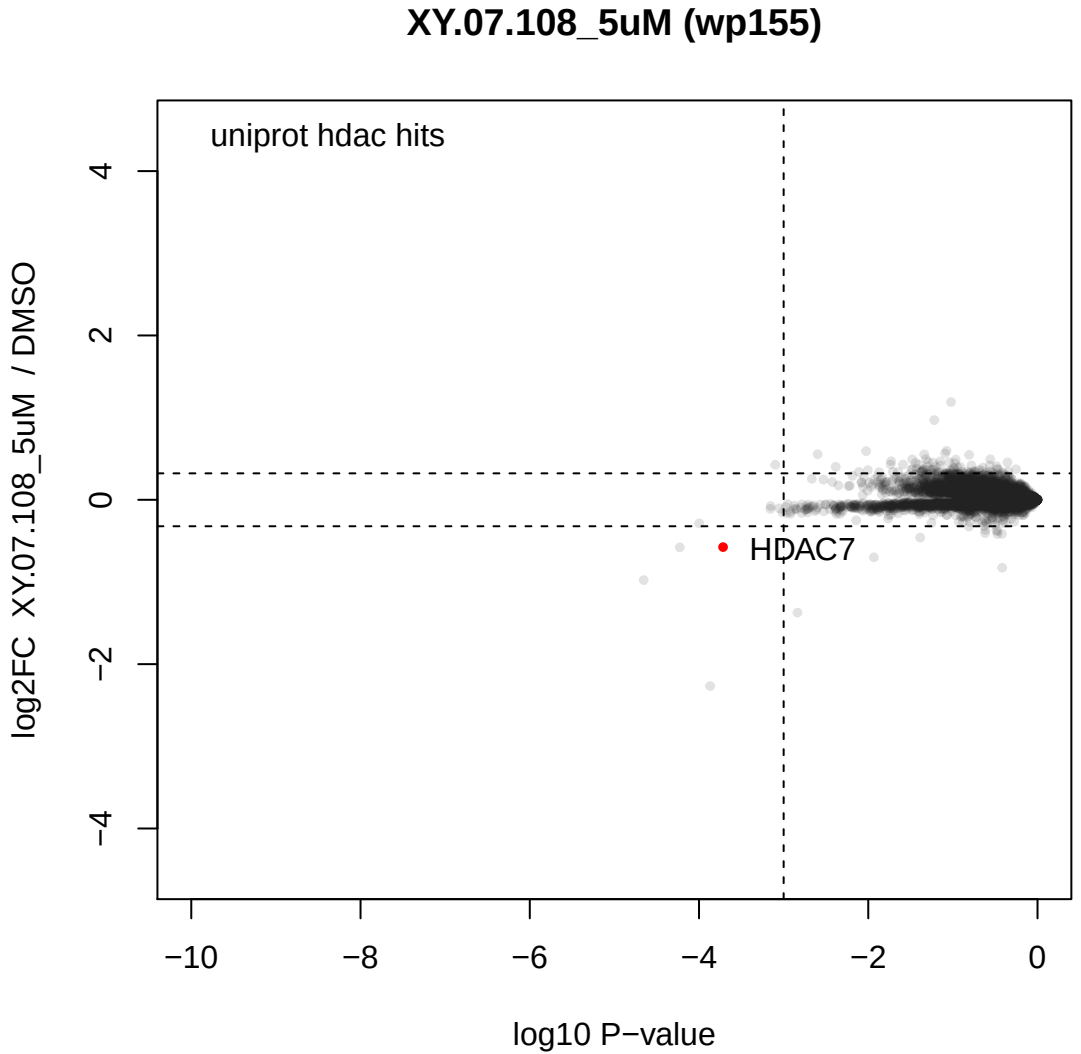

XY.07.114 (wp132)
all hits
log2FC XY.07.114 / DMSO
log10 P−value
PDCD7
HDAC7

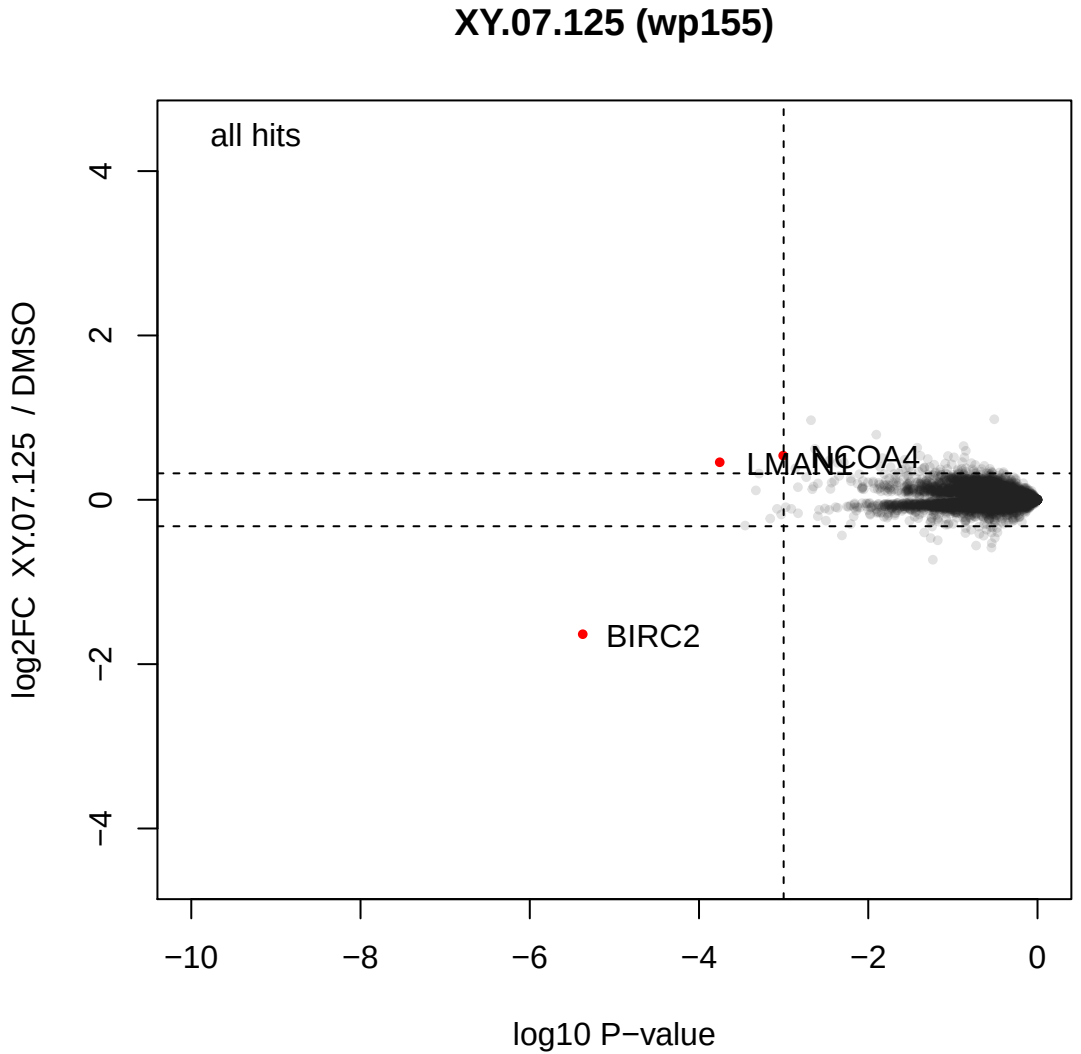

XY.07.114 (wp132)
uniprot hdac hits
log2FC XY.07.114 / DMSO
log10 P−value
HDAC7

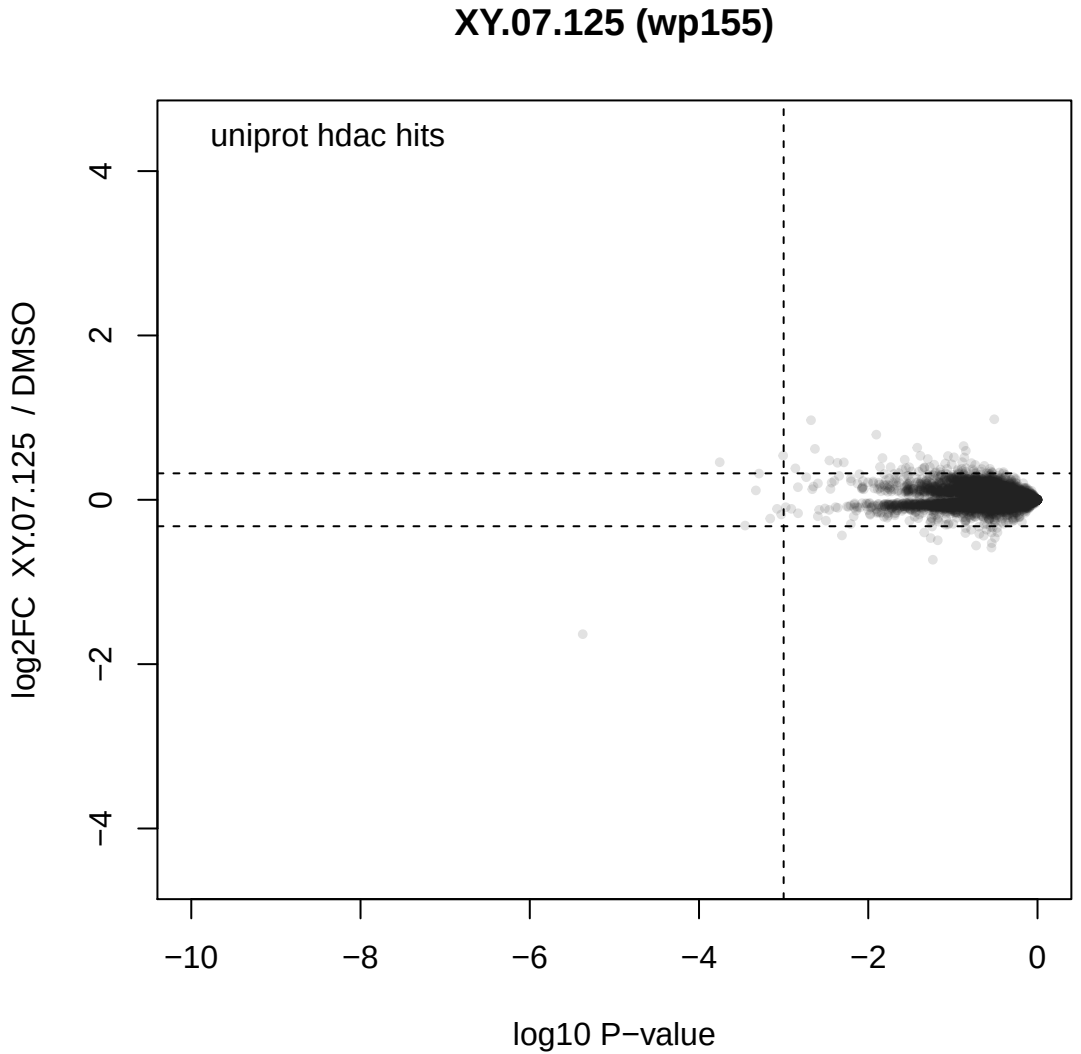

XY.07.107_5uM (wp155)
all hits
log2FC XY.07.107_5uM / DMSO
log10 P−value
MIF4GD
SKP1
ZNF692
RNF166
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

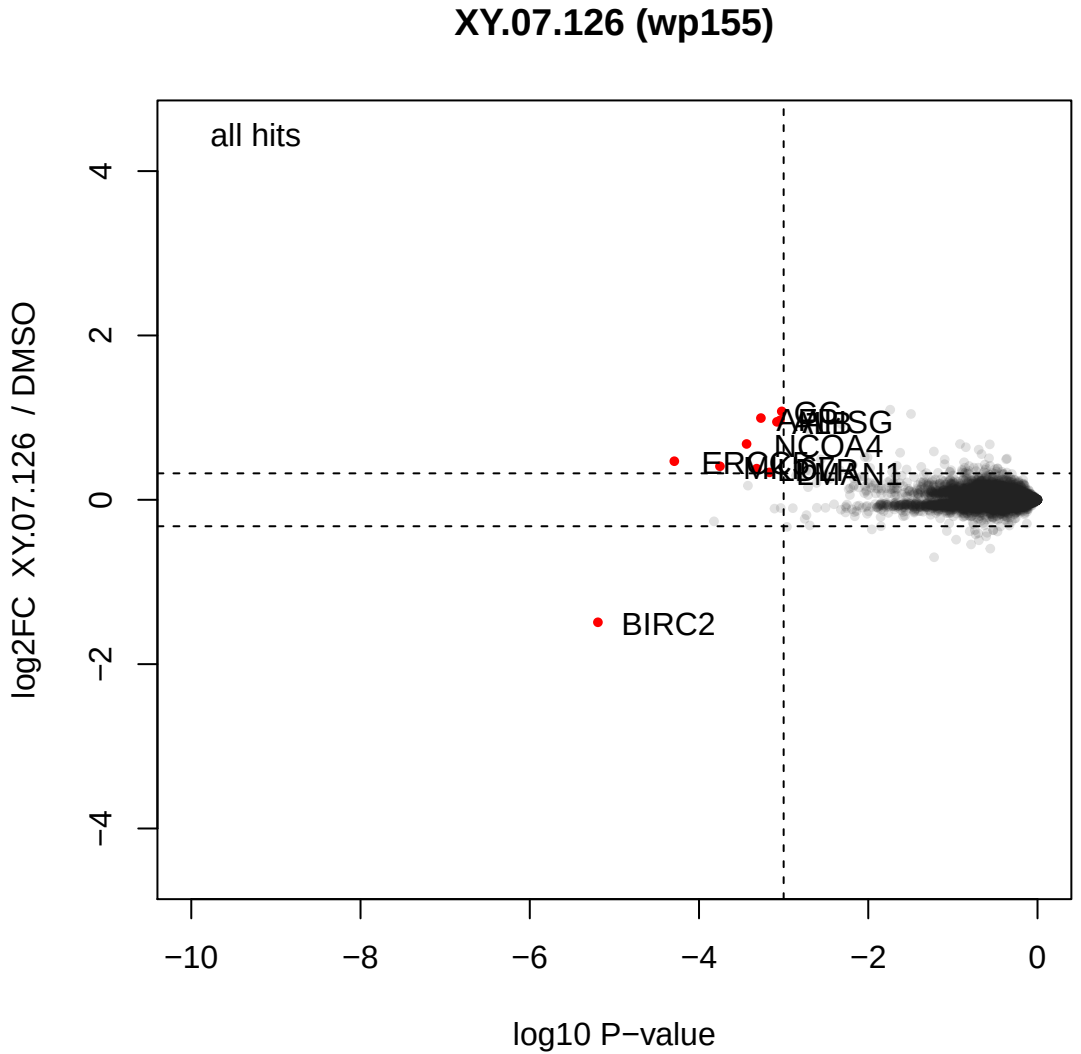

XY.07.107_5uM (wp155)
uniprot hdac hits
log2FC XY.07.107_5uM / DMSO
log10 P−value
HDAC7
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

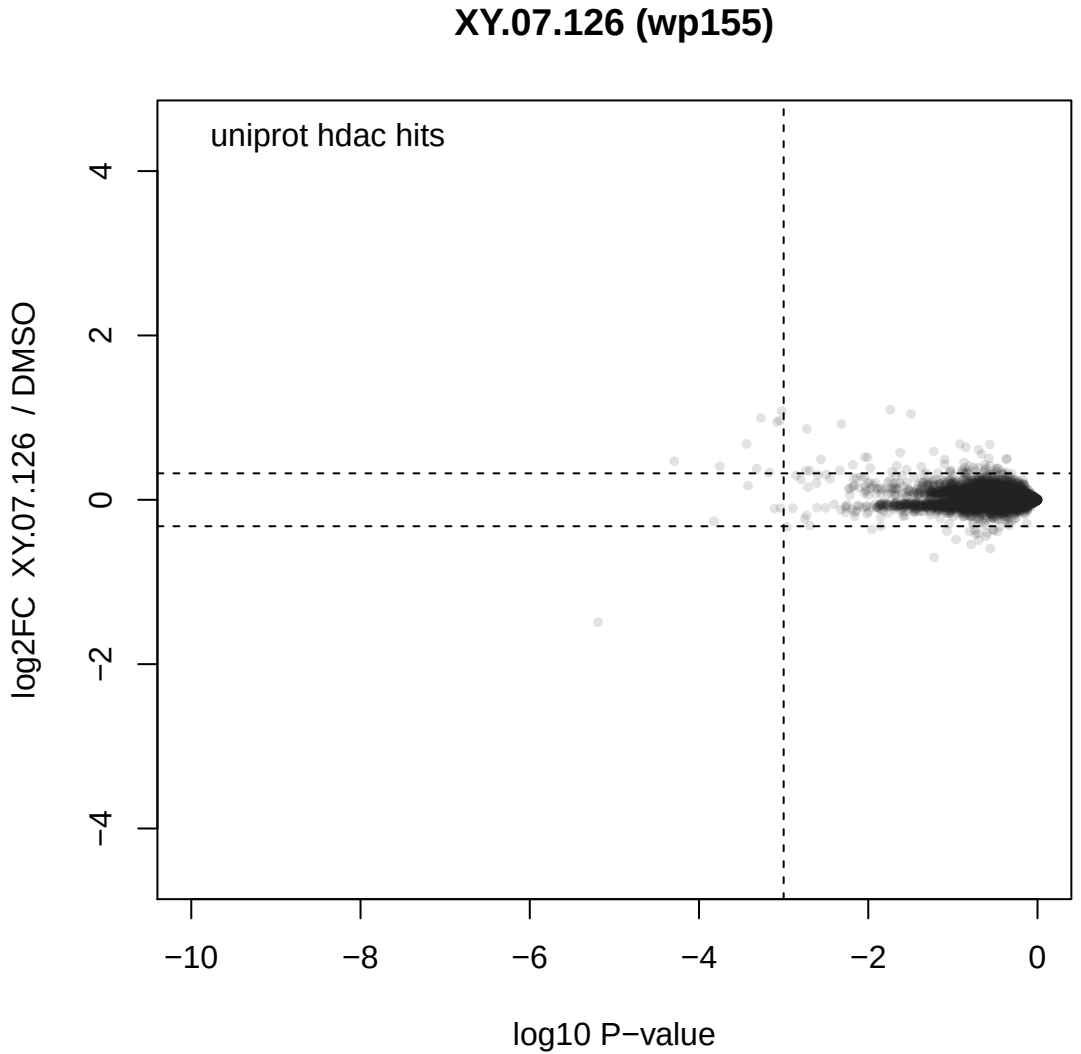

XY.07.108_5uM (wp155)
all hits
PAM
SALL4
HDAC7
ZFP91
ZNF692
log2FC XY.07.108_5uM / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

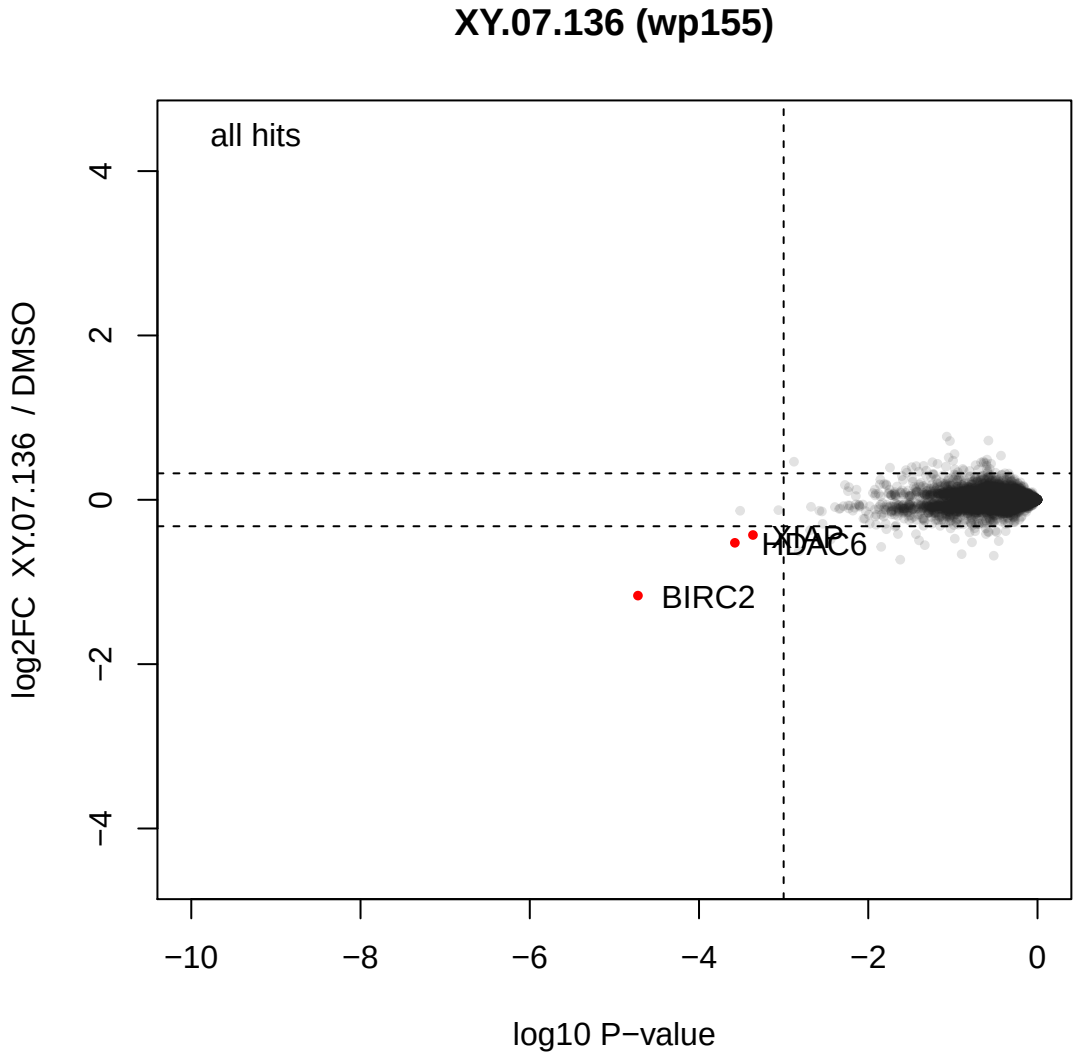

XY.07.108_5uM (wp155)
uniprot hdac hits
HDAC7
log2FC XY.07.108_5uM / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

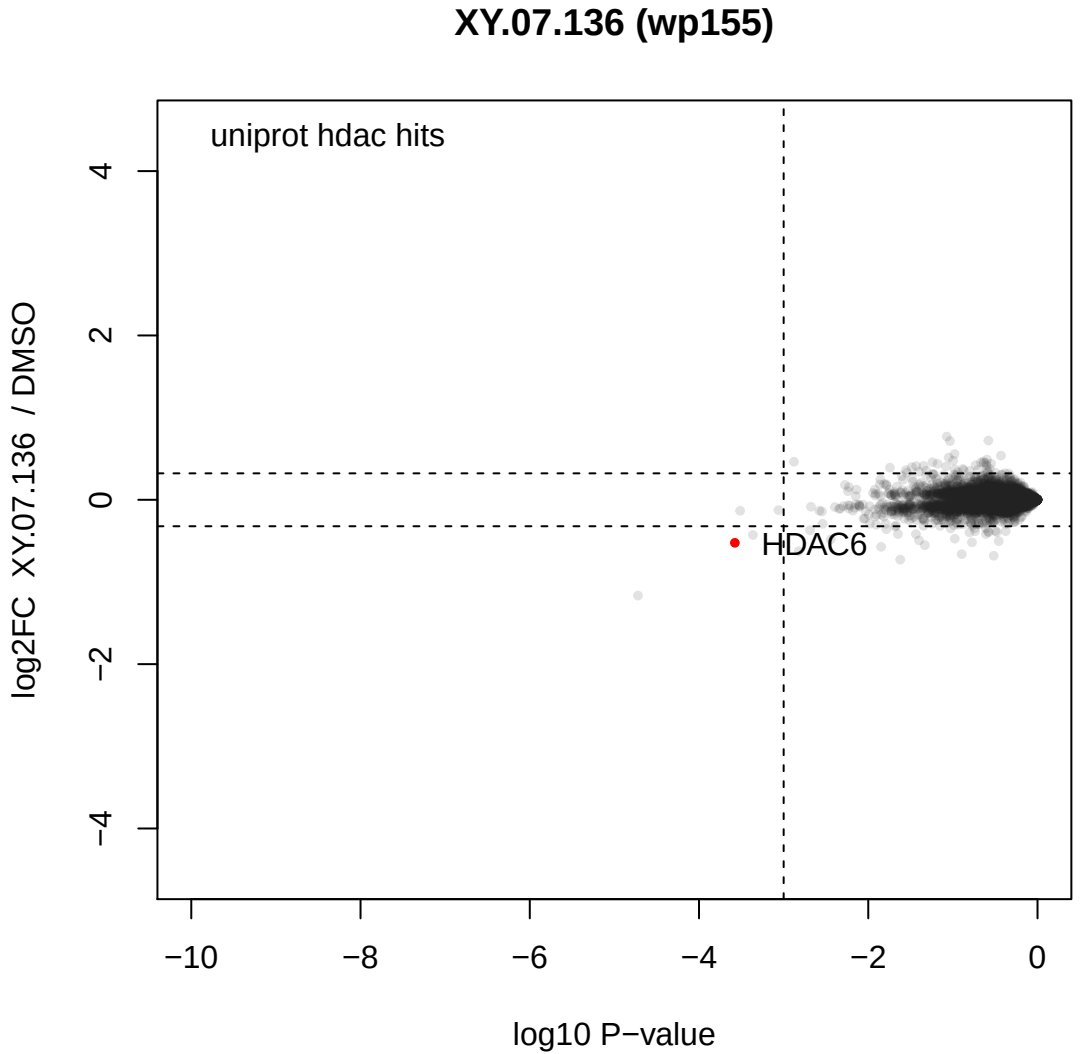

XY.07.125 (wp155)
all hits
LMAN1
NCOA4
BIRC2
log2FC XY.07.125 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

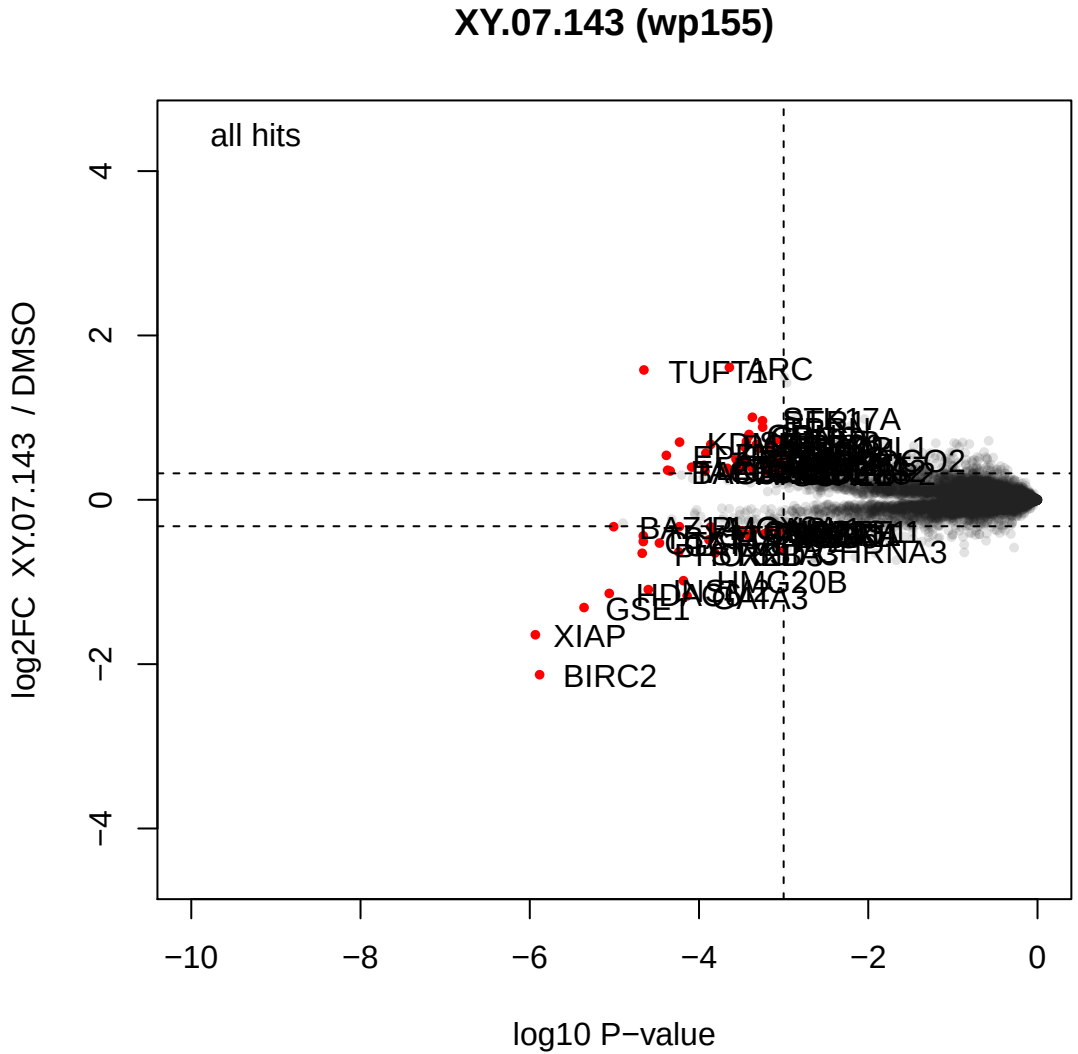

XY.07.125 (wp155)
uniprot hdac hits
log2FC XY.07.125 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

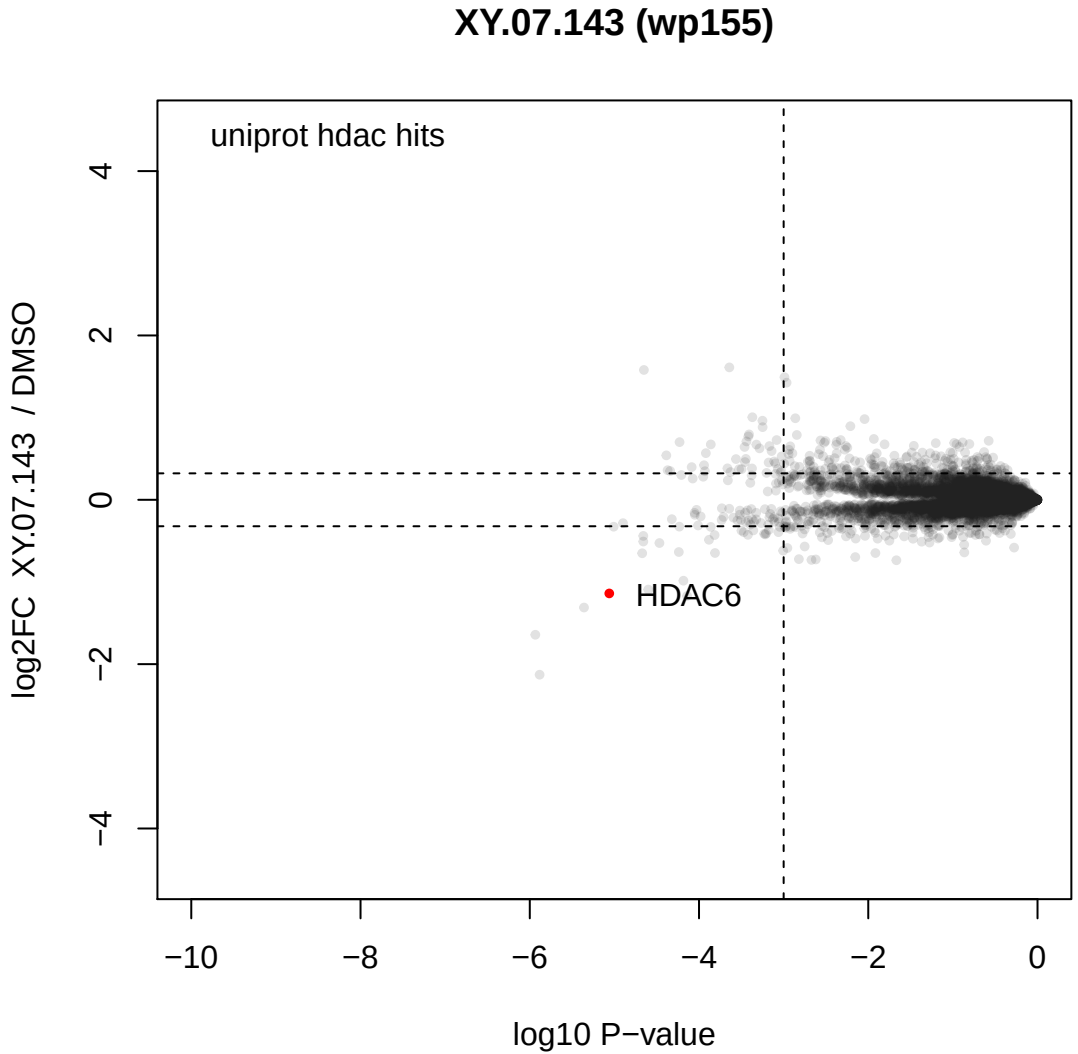

XY.07.126 (wp155)
all hits
log2FC XY.07.126 / DMSO
log10 P−value
BIRC2
NCOA4

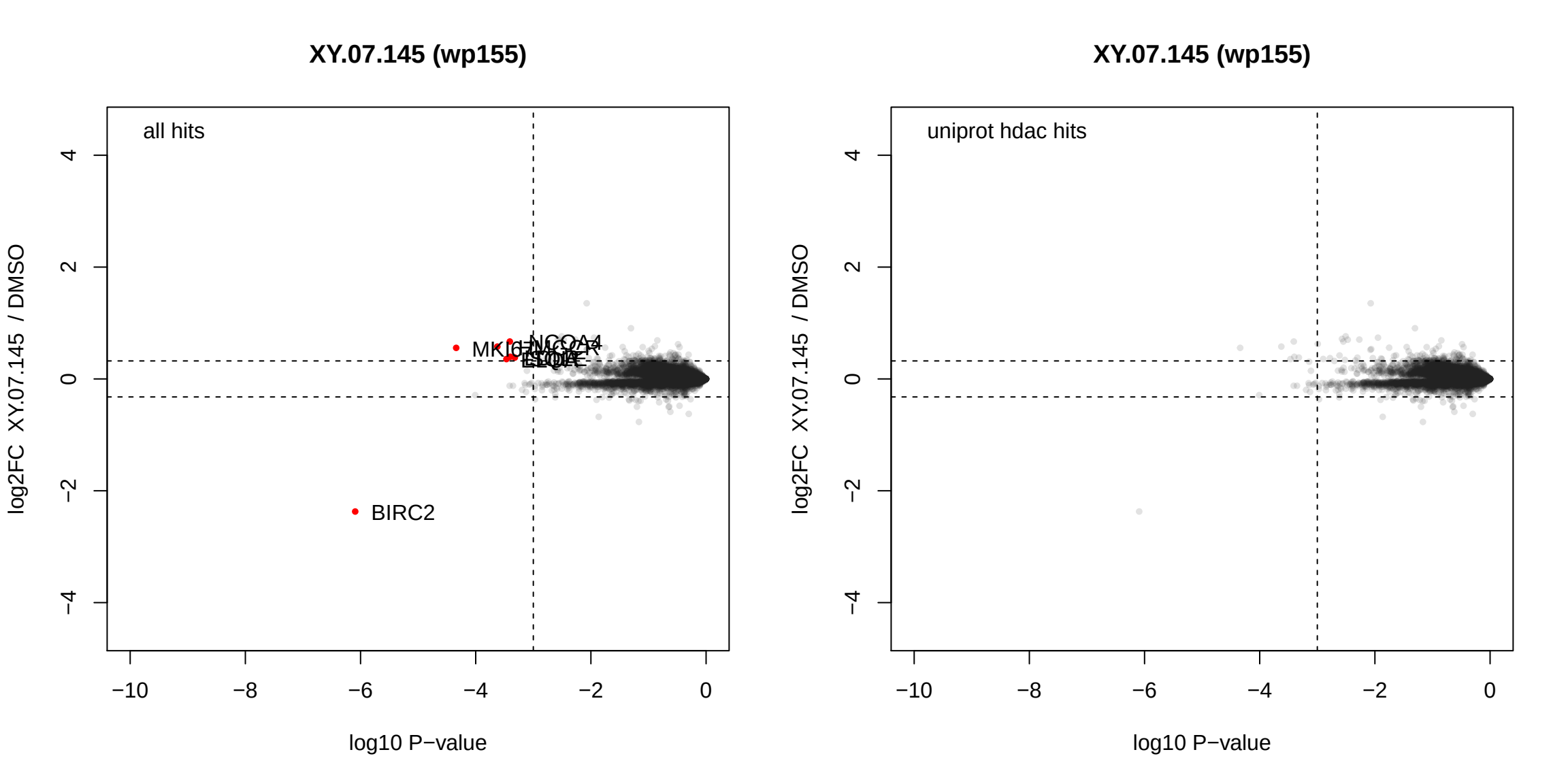

XY.07.126 (wp155)
uniprot hdac hits
log2FC XY.07.126 / DMSO
log10 P−value

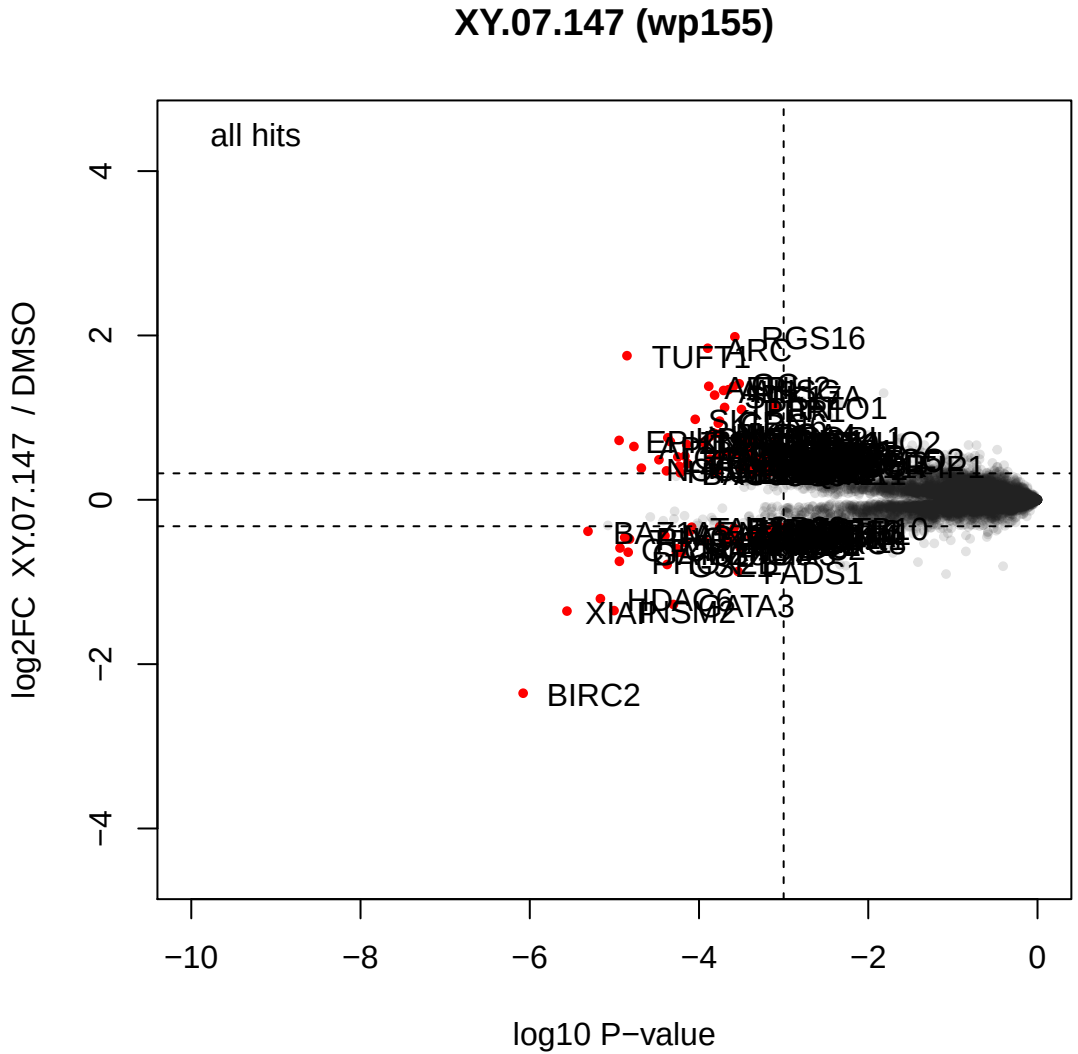

XY.07.136 (wp155)
all hits
log2FC XY.07.136 / DMSO
4
2
0
−2
−4
−10
−8
−6
−4
−2
0
log10 P−value
XIAP
HDAC6
BIRC2

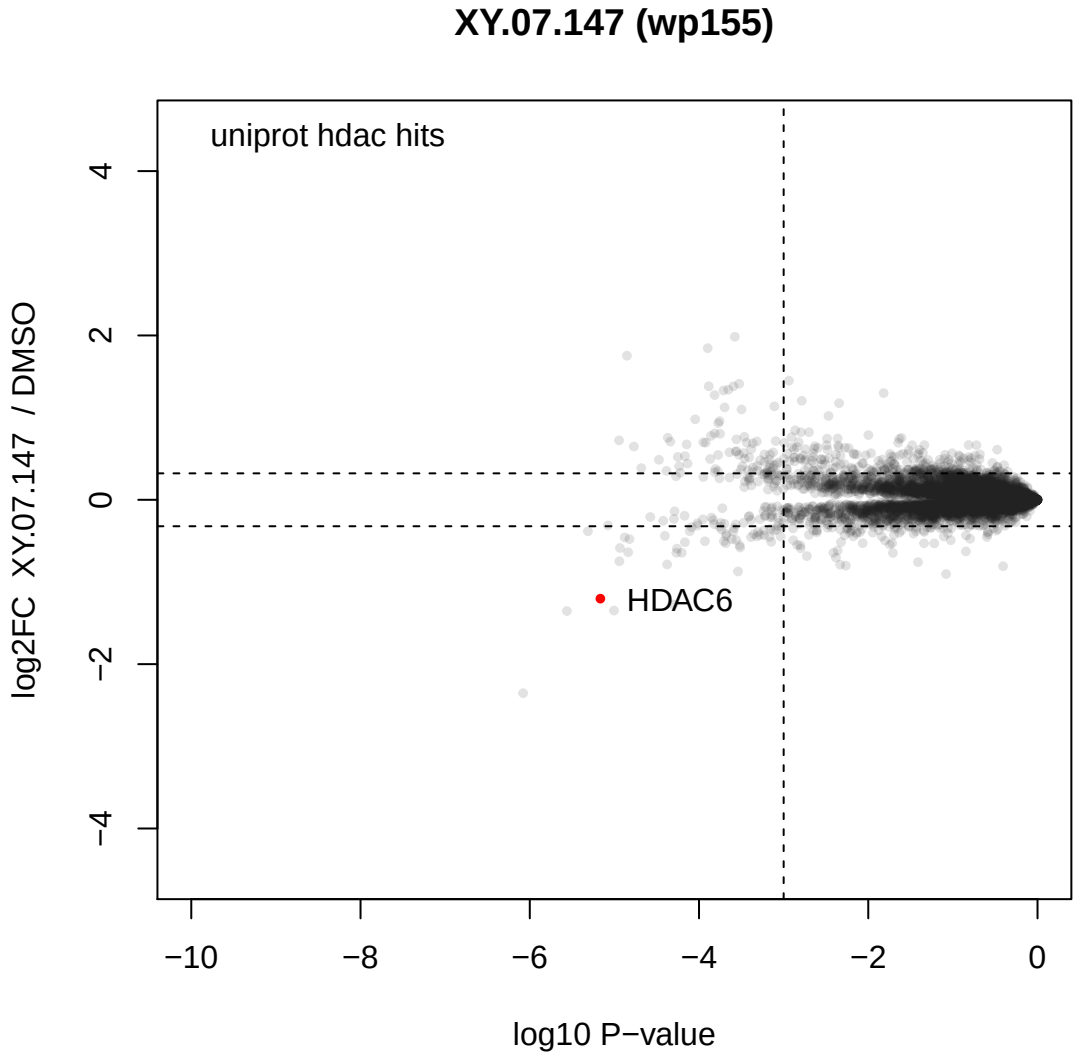

XY.07.136 (wp155)
uniprot hdac hits
log2FC XY.07.136 / DMSO
4
2
0
−2
−4
−10
−8
−6
−4
−2
0
log10 P−value
HDAC6

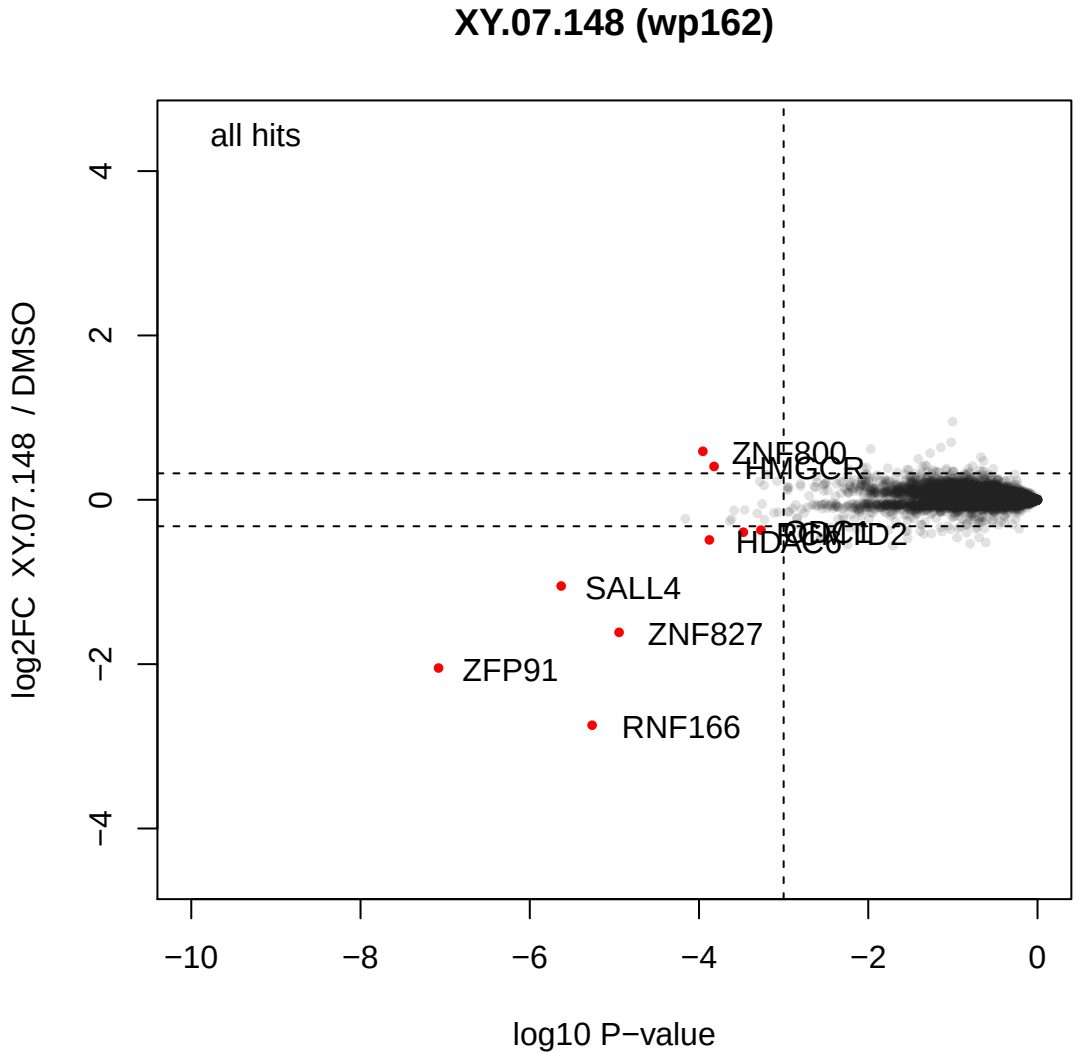

XY.07.143 (wp155)
all hits
log2FC XY.07.143 / DMSO
log10 P−value
TUFT1
ARC
XIAP
BIRC2
GSE1
HMG20B
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

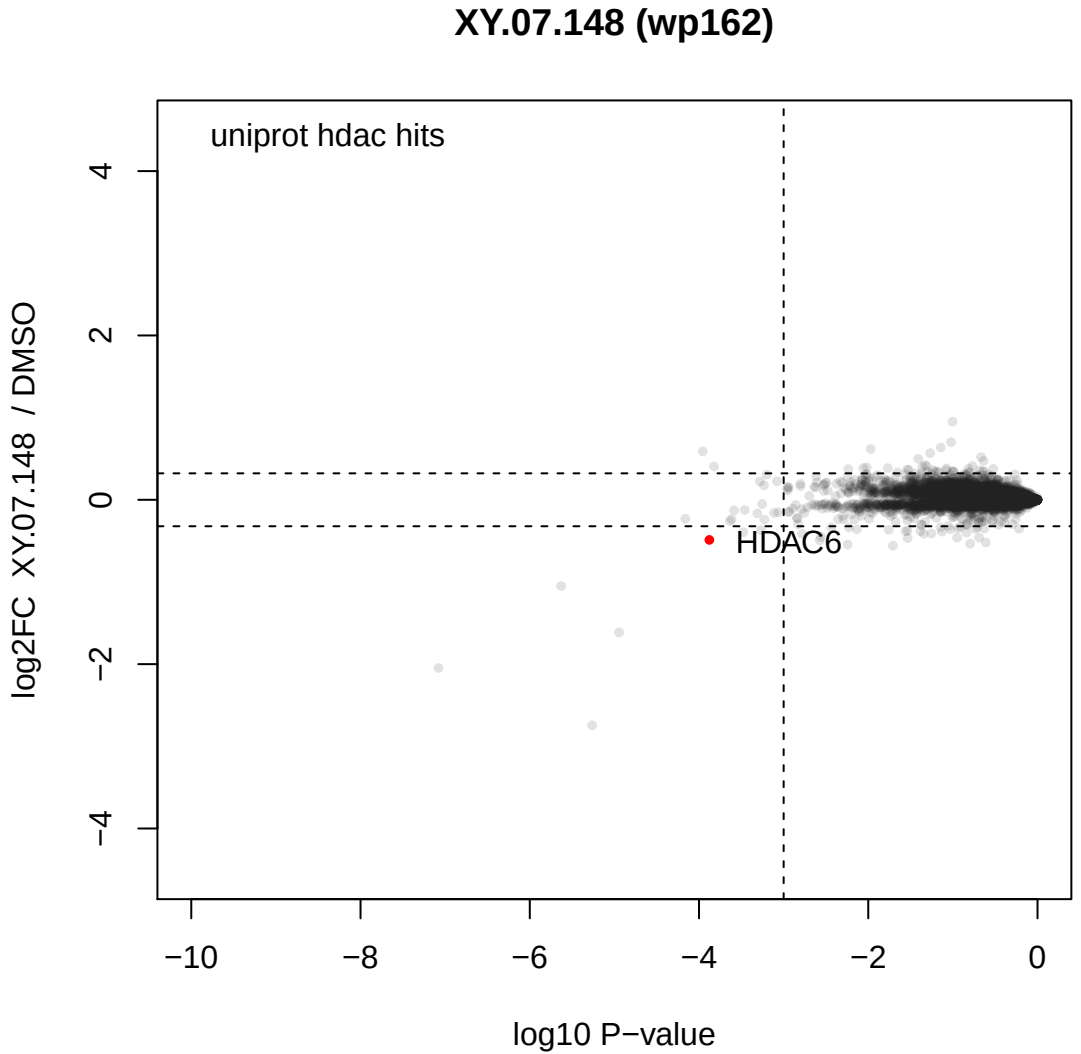

XY.07.143 (wp155)
uniprot hdac hits
log2FC XY.07.143 / DMSO
log10 P−value
HDAC6
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

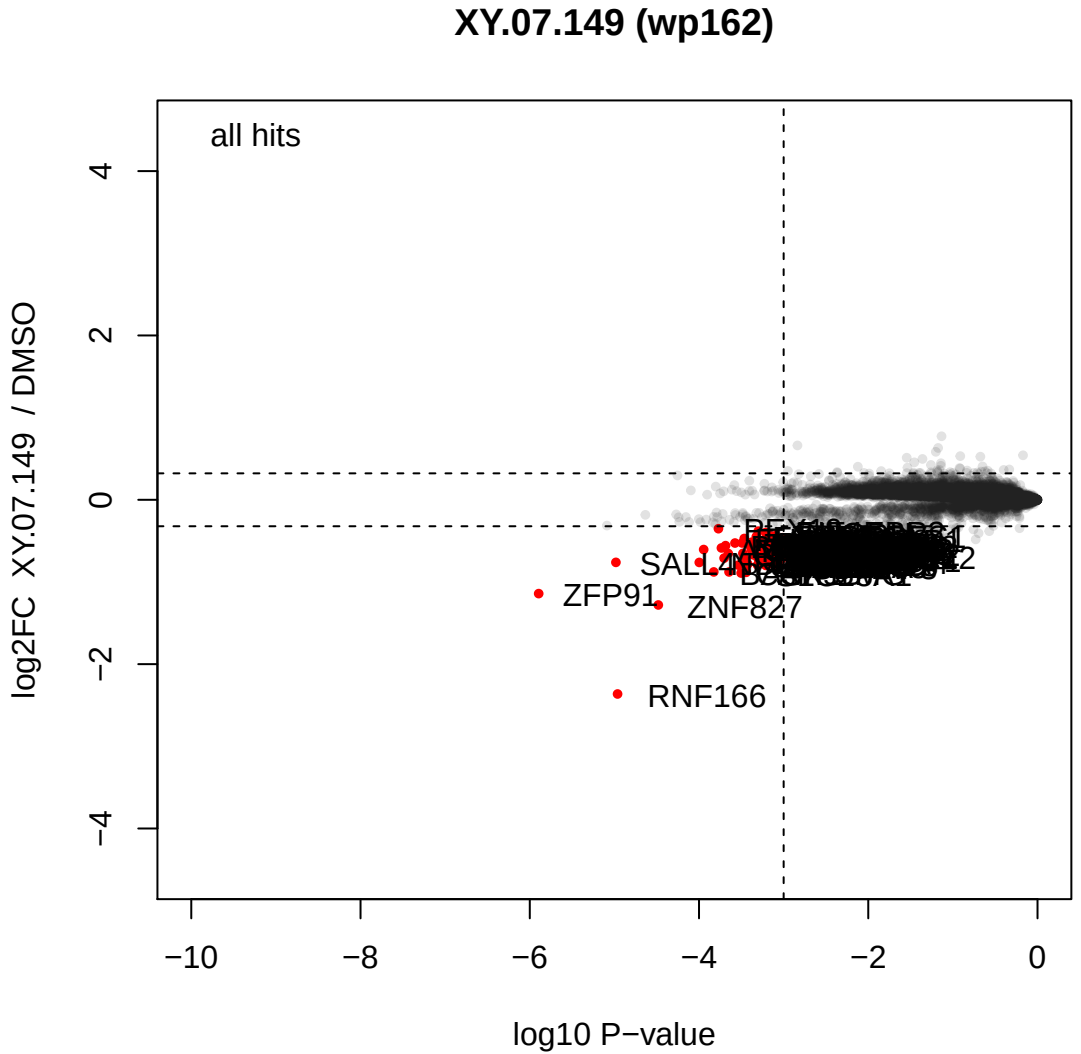

XY.07.145 (wp155)
all hits
log2FC XY.07.145 / DMSO
log10 P−value
BIRC2
XY.07.145 (wp155)
uniprot hdac hits
log2FC XY.07.145 / DMSO
log10 P−value

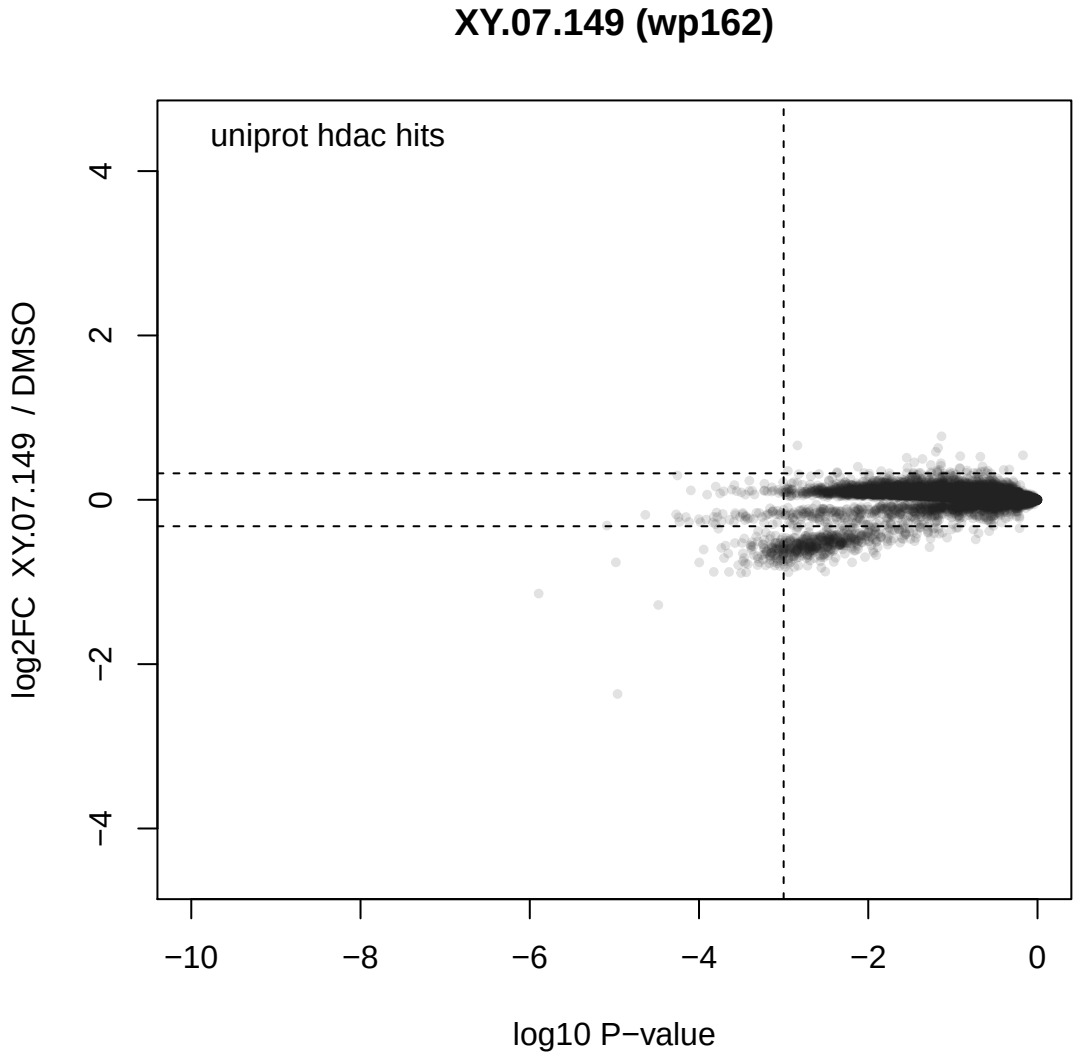

XY.07.147 (wp155)
all hits
log2FC XY.07.147 / DMSO
log10 P−value
RGS16
TUFT1
ARC
HDAC6
BIRC2
FADS1
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

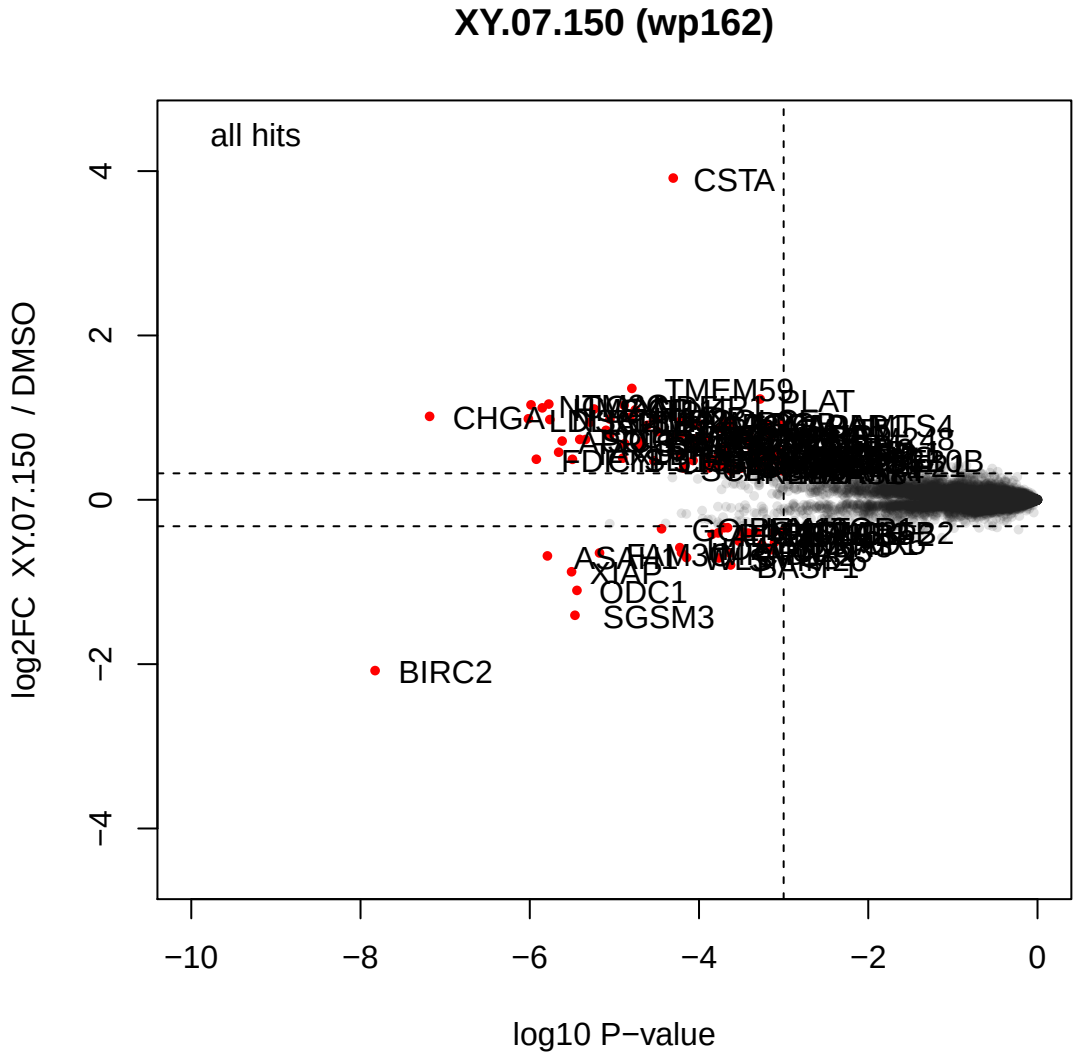

XY.07.147 (wp155)
uniprot hdac hits
log2FC XY.07.147 / DMSO
log10 P−value
HDAC6
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

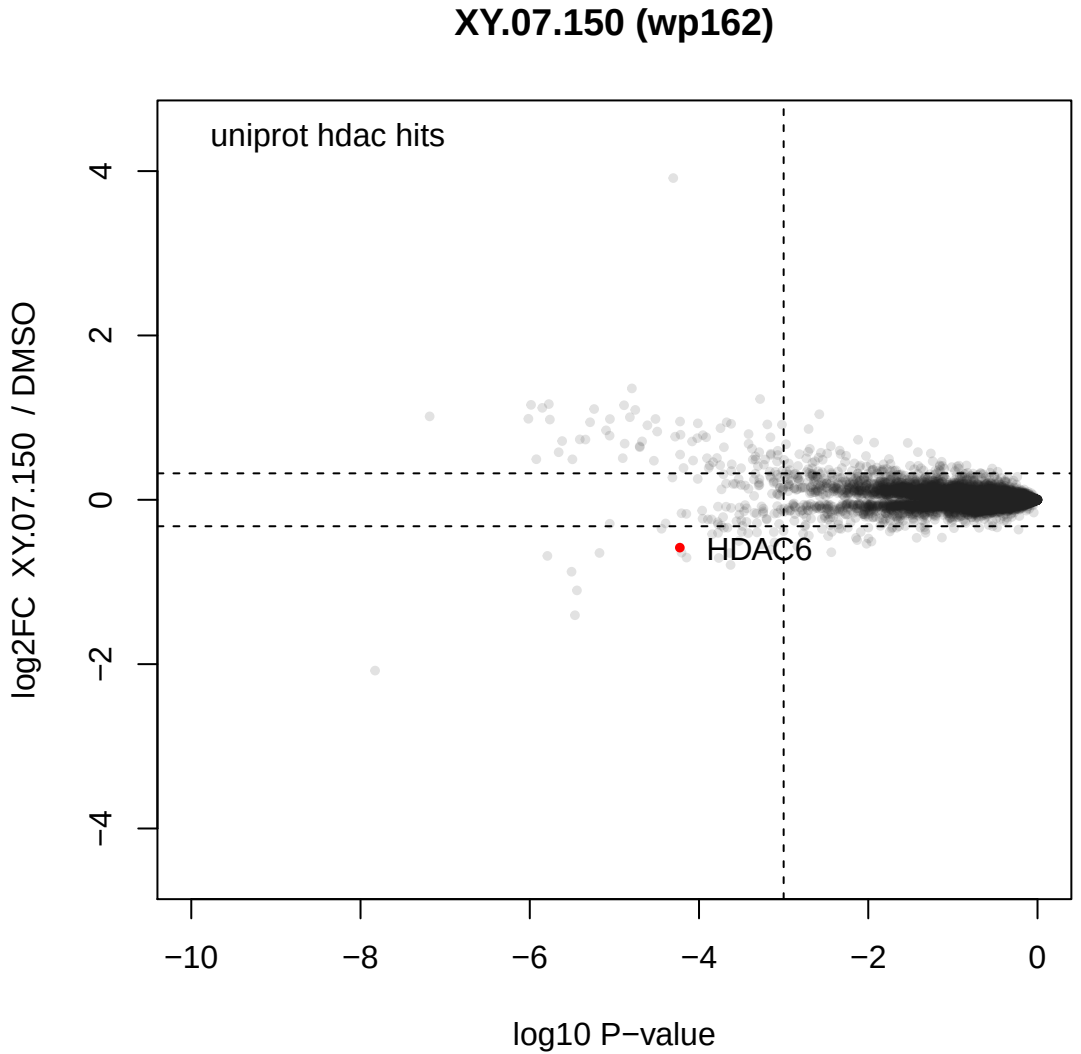

XY.07.148 (wp162)
all hits
log2FC XY.07.148 / DMSO
log10 P−value
ZNF800
HMGCR
HDAC6
SALL4
ZNF827
ZFP91
RNF166
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

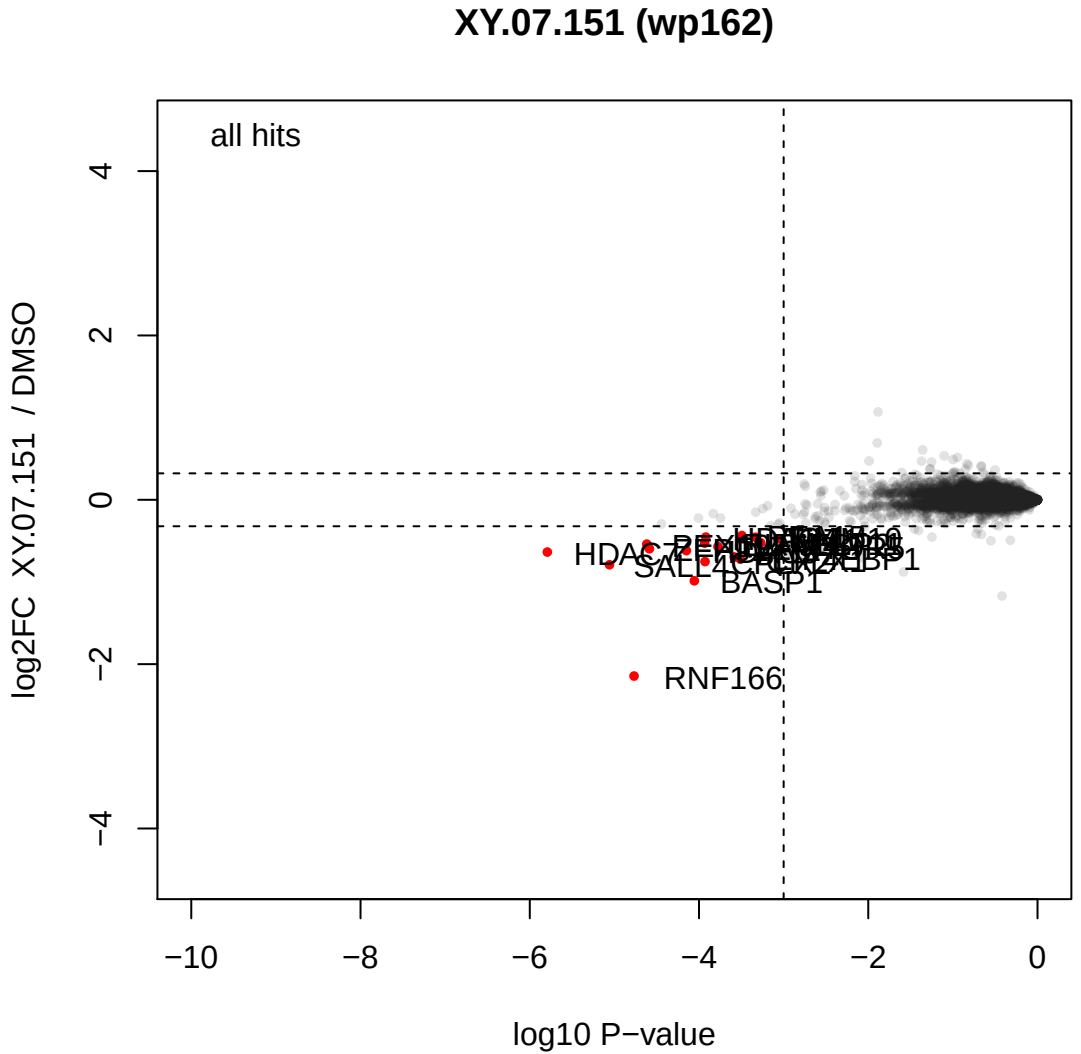

XY.07.148 (wp162)
uniprot hdac hits
log2FC XY.07.148 / DMSO
log10 P−value
HDAC6
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

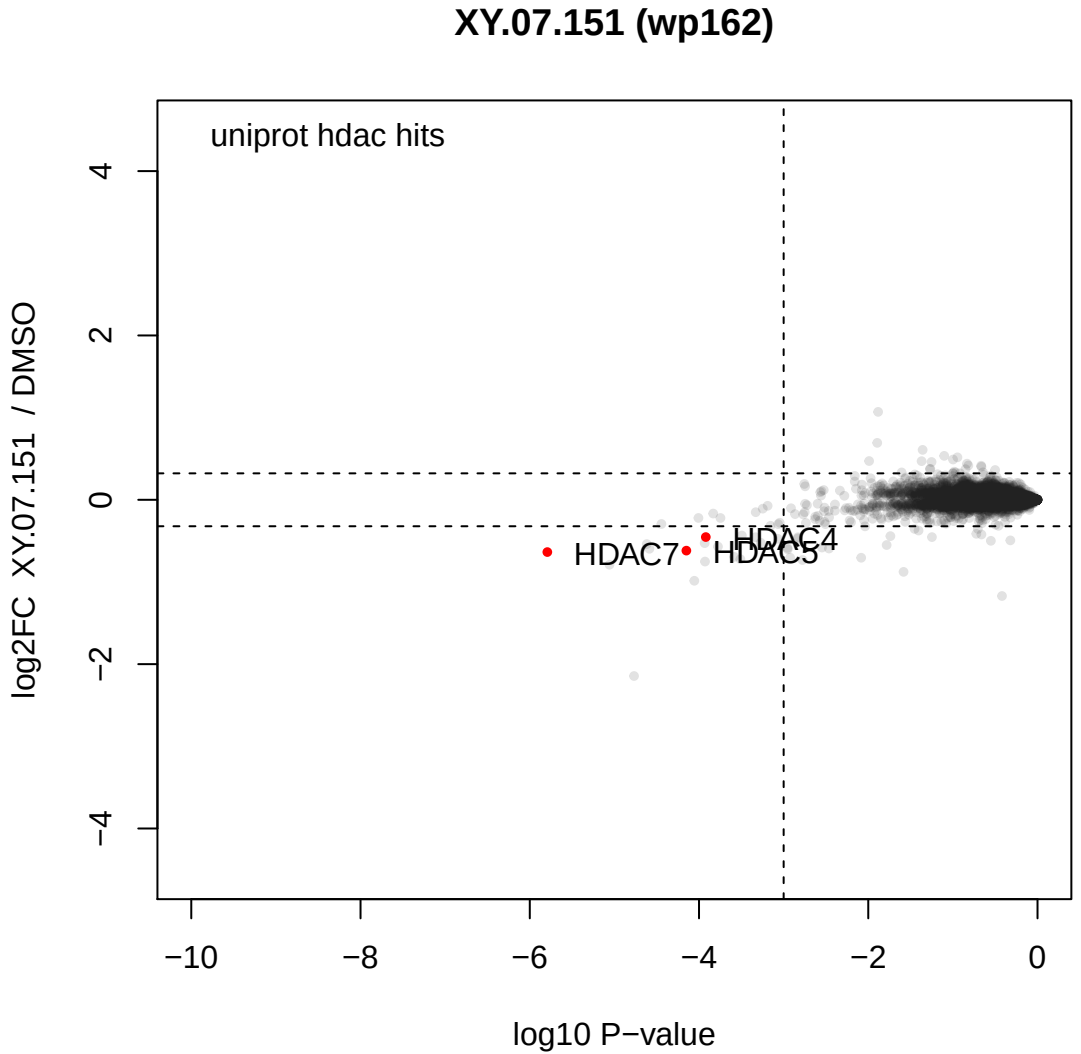

XY.07.149 (wp162)
all hits
log2FC XY.07.149 / DMSO
log10 P−value
ZFP91
ZNF827
RNF166
SALL4
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

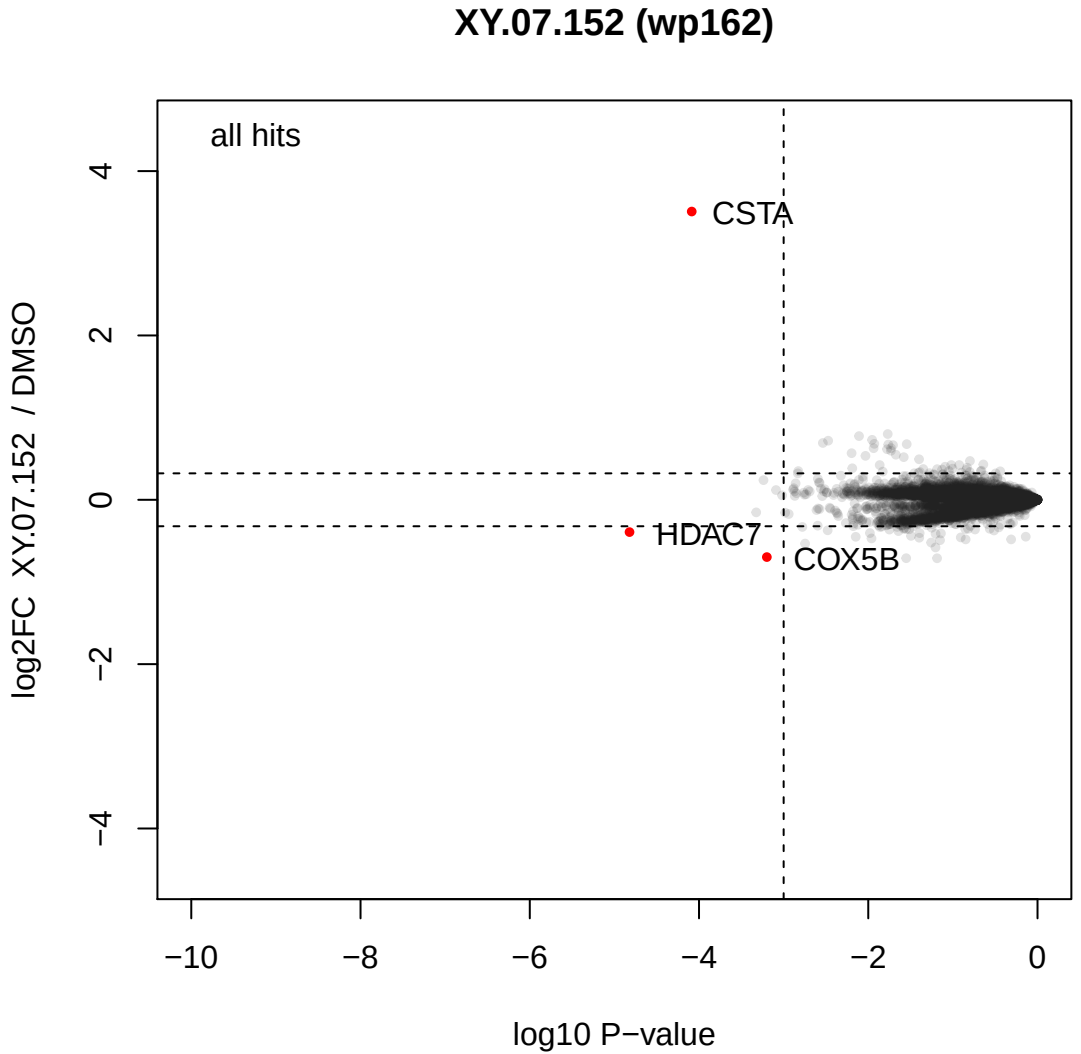

XY.07.149 (wp162)
uniprot hdac hits
log2FC XY.07.149 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

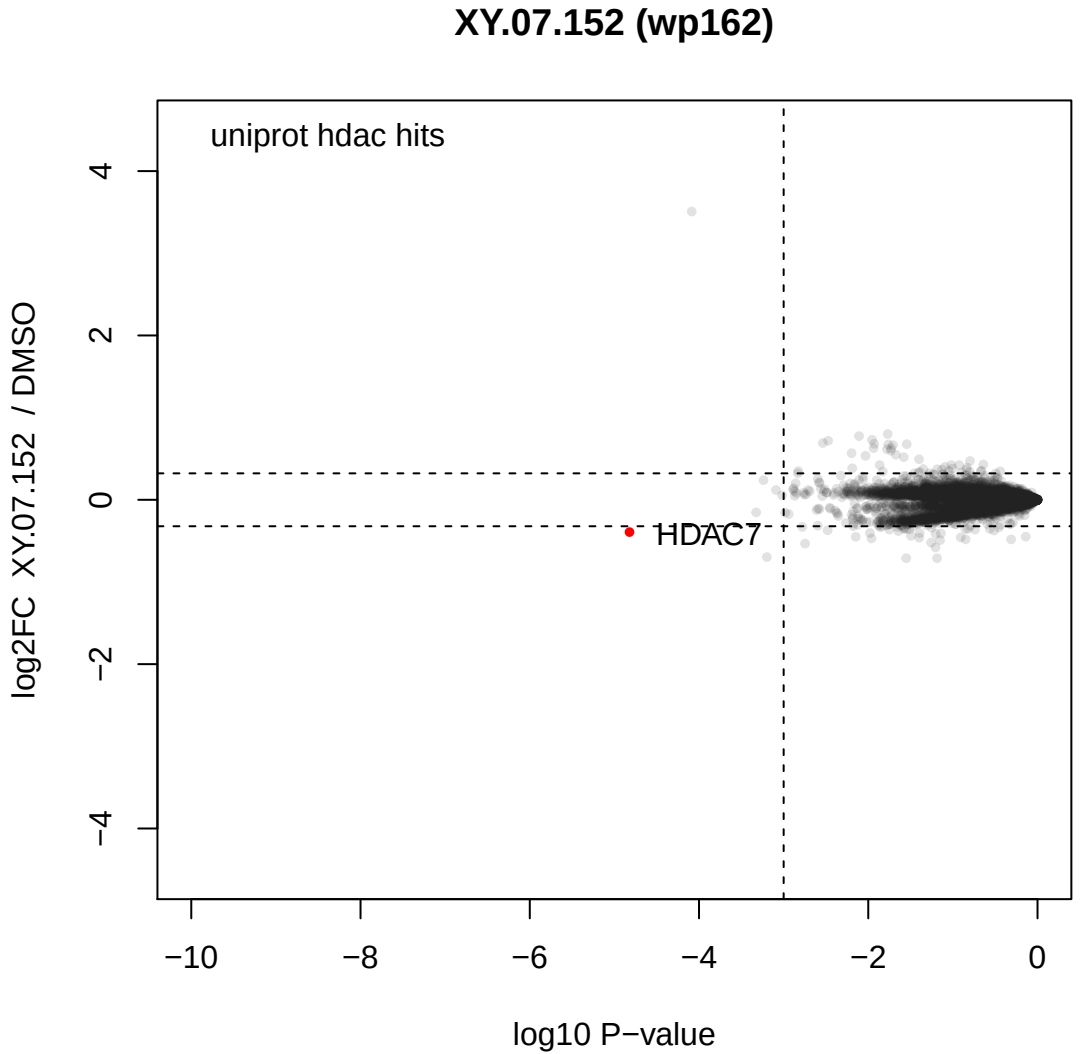

XY.07.150 (wp162)
all hits
CSTA
TMEM59
CHGA
BIRC2
ASAH1
XIAP
ODC1
SGSM3
log2FC XY.07.150 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

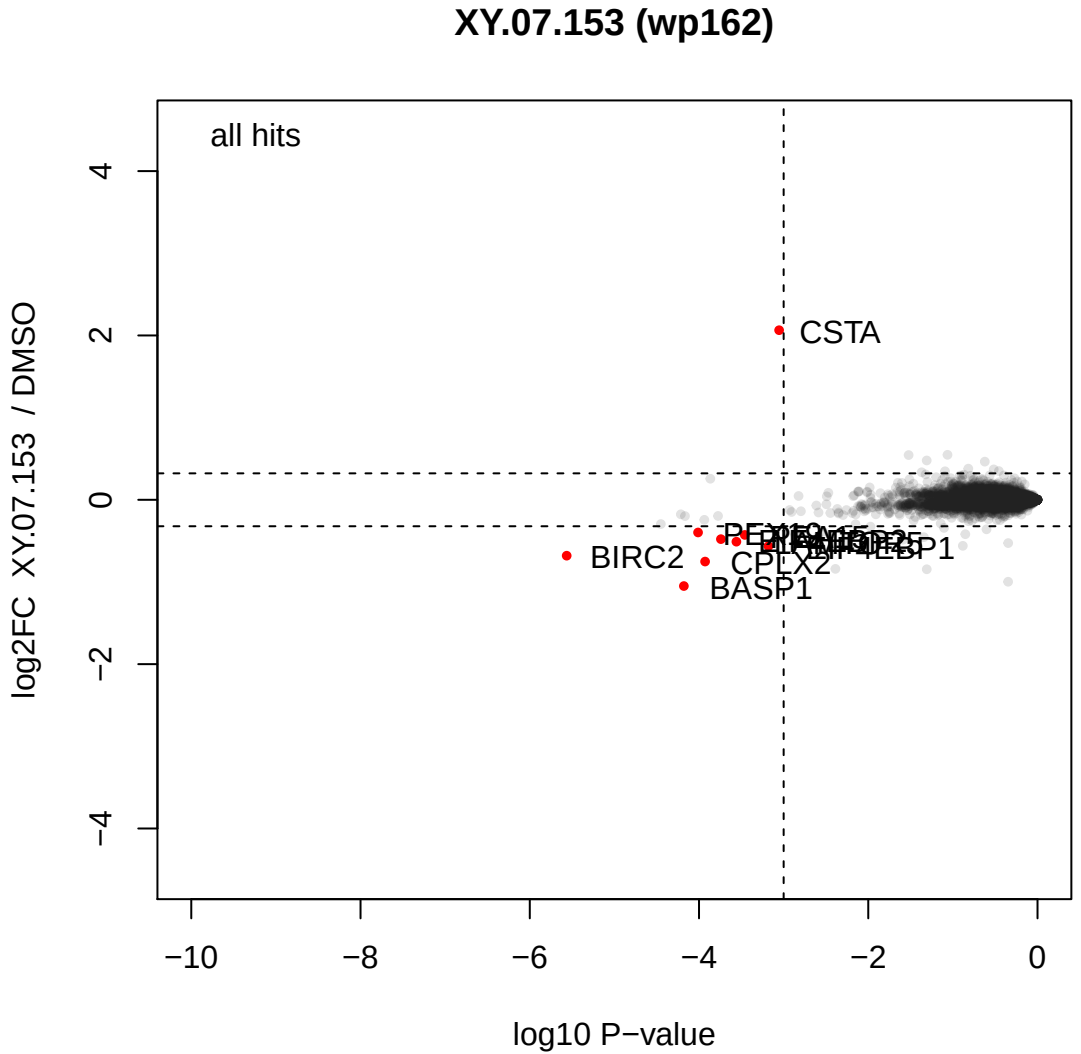

XY.07.150 (wp162)
uniprot hdac hits
HDAC6
log2FC XY.07.150 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

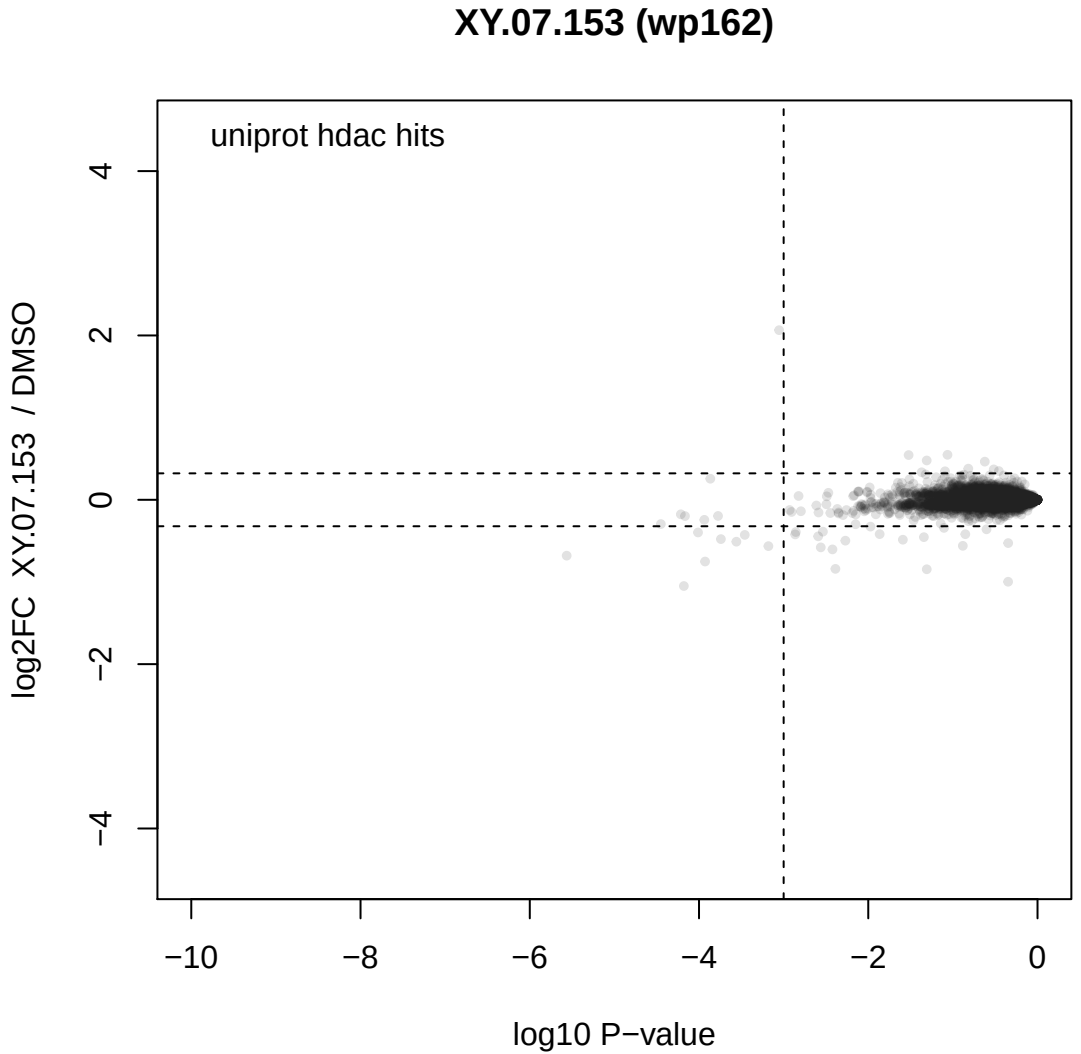

XY.07.151 (wp162)
all hits
log2FC XY.07.151 / DMSO
log10 P−value
HDAC7
BASP1
RNF166
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

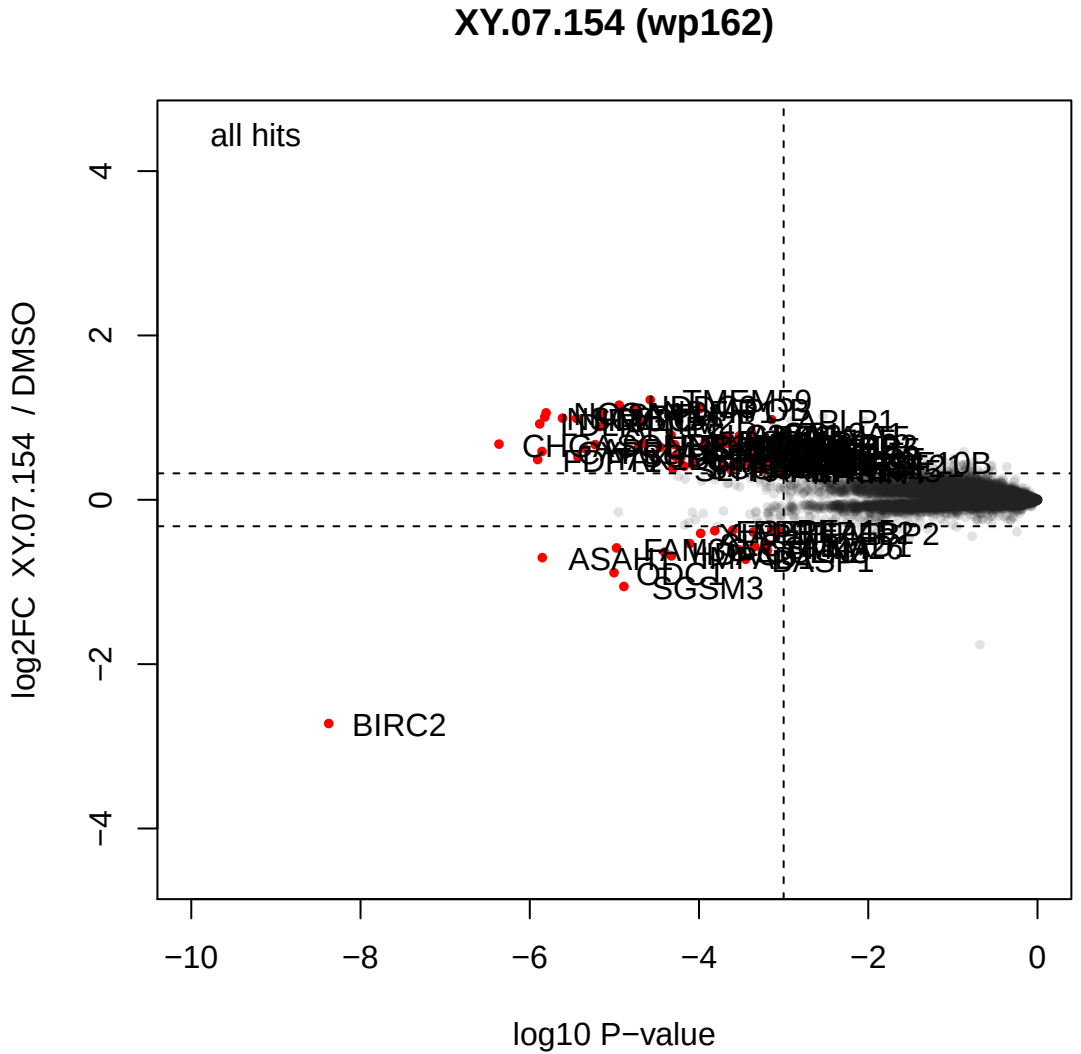

XY.07.151 (wp162)
uniprot hdac hits
log2FC XY.07.151 / DMSO
log10 P−value
HDAC7
HDAC5
HDAC4
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

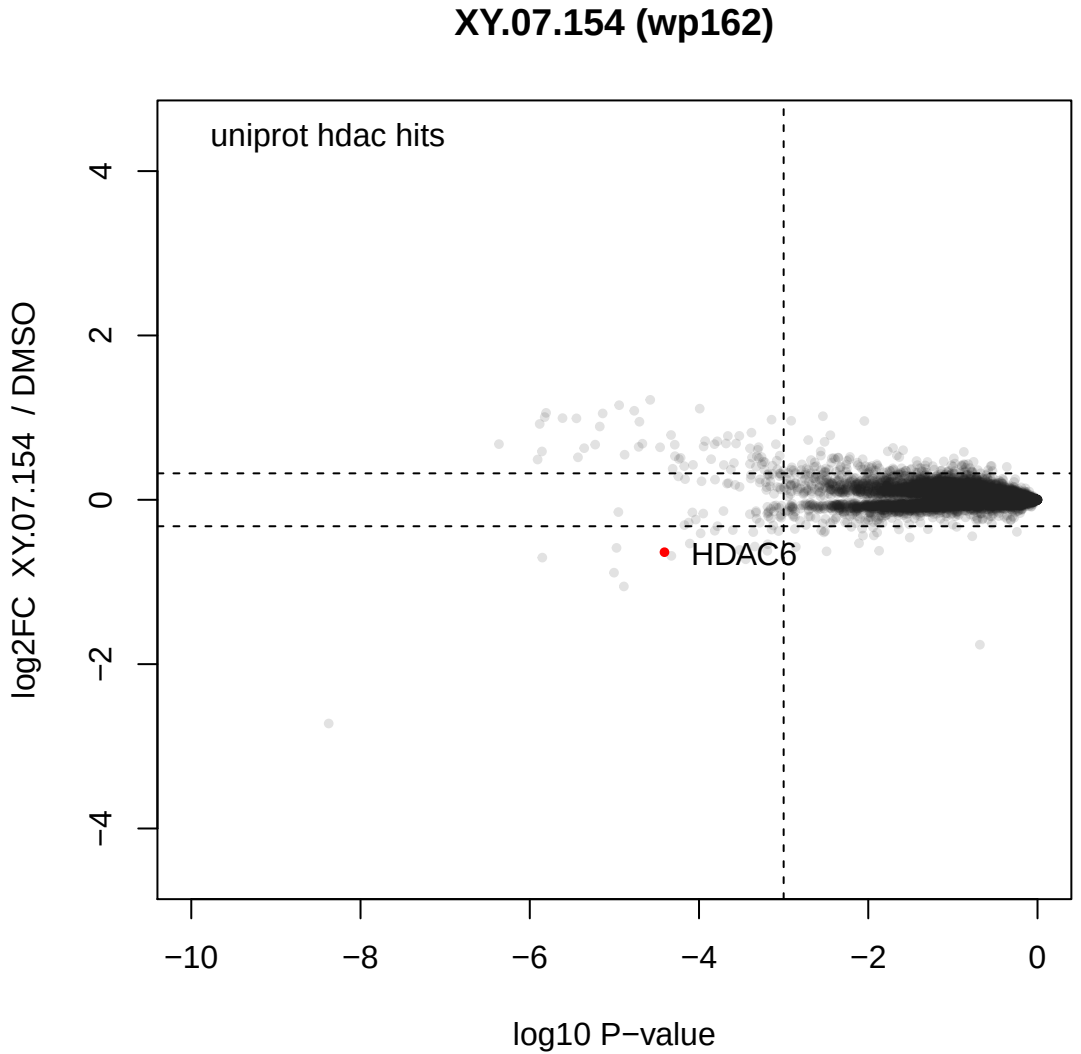

XY.07.152 (wp162)
all hits
CSTA
HDAC7
COX5B
log2FC XY.07.152 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

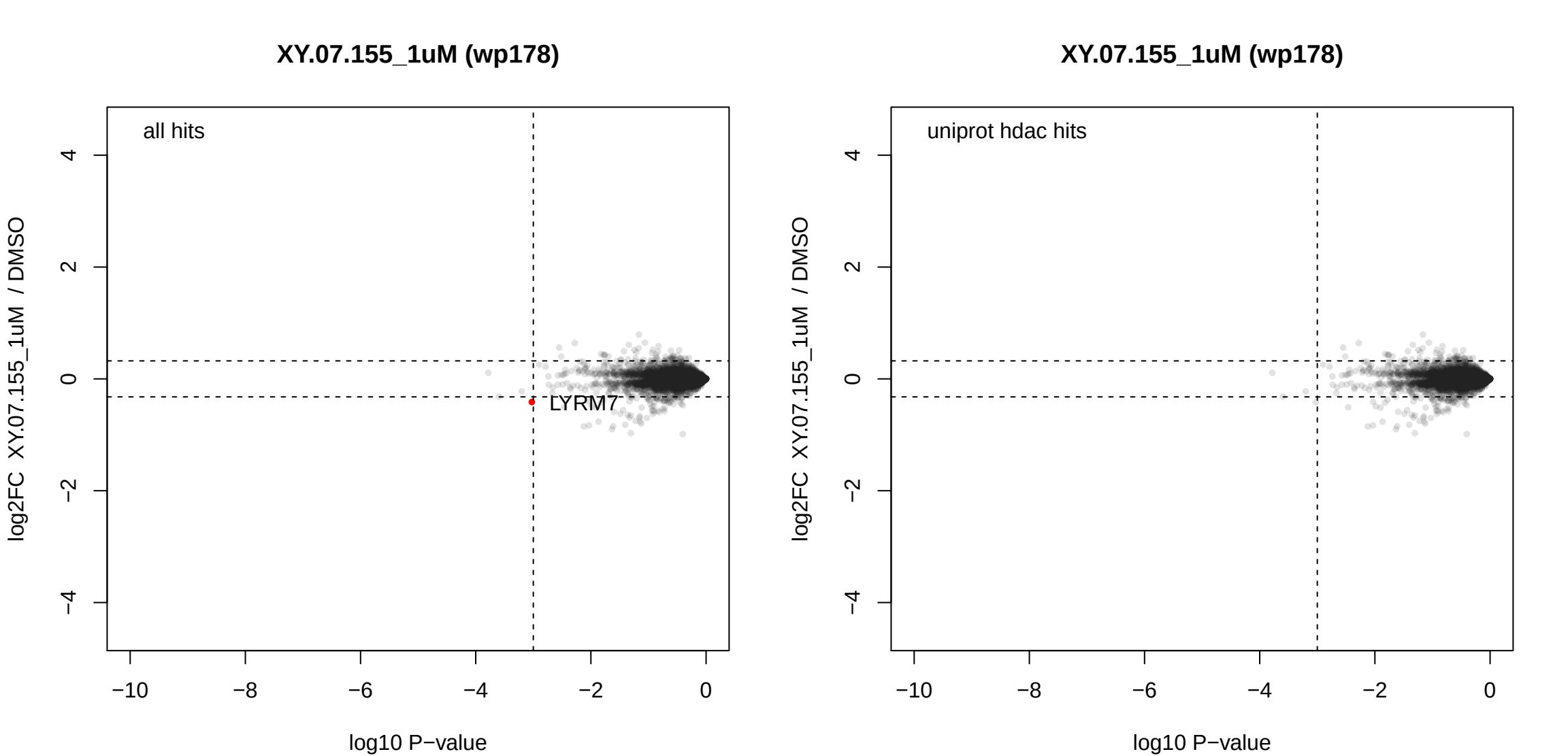

XY.07.152 (wp162)
uniprot hdac hits
HDAC7
log2FC XY.07.152 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

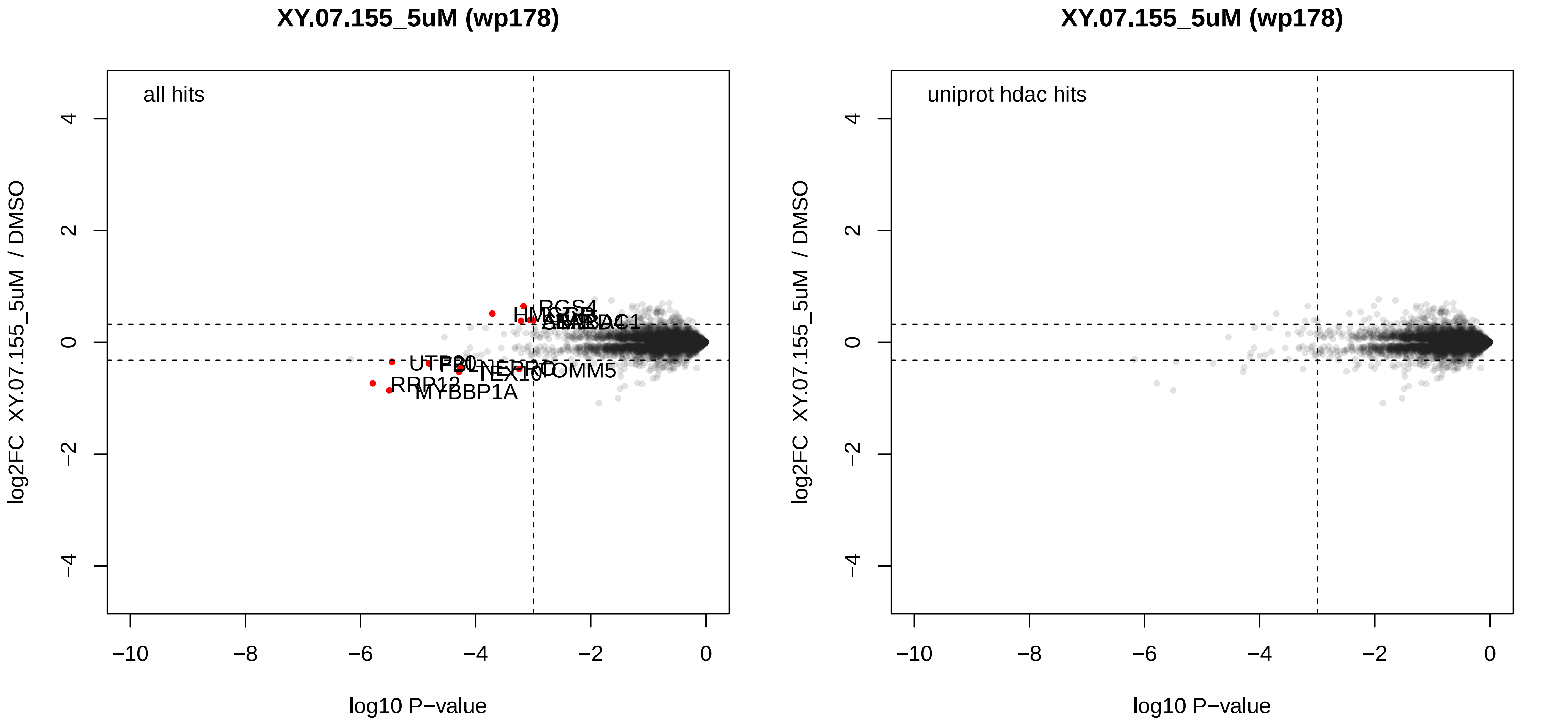

XY.07.153 (wp162)
all hits
CSTA
BIRC2
CPLX2
BASP1
log2FC XY.07.153 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0


XY.07.153 (wp162)
uniprot hdac hits
log2FC XY.07.153 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

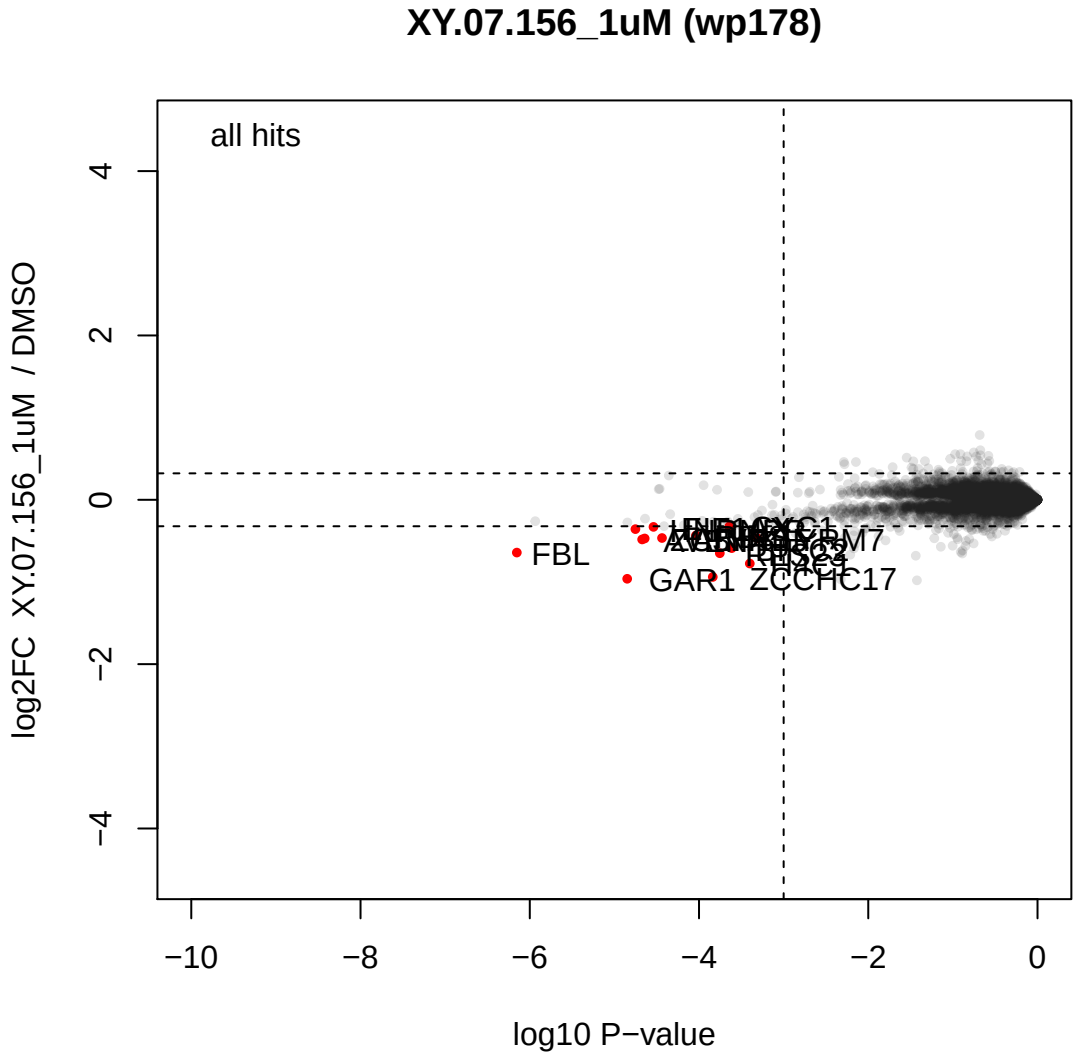

XY.07.154 (wp162)
all hits
log2FC XY.07.154 / DMSO
log10 P−value
BIRC2
ASAH1
SGSM3
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

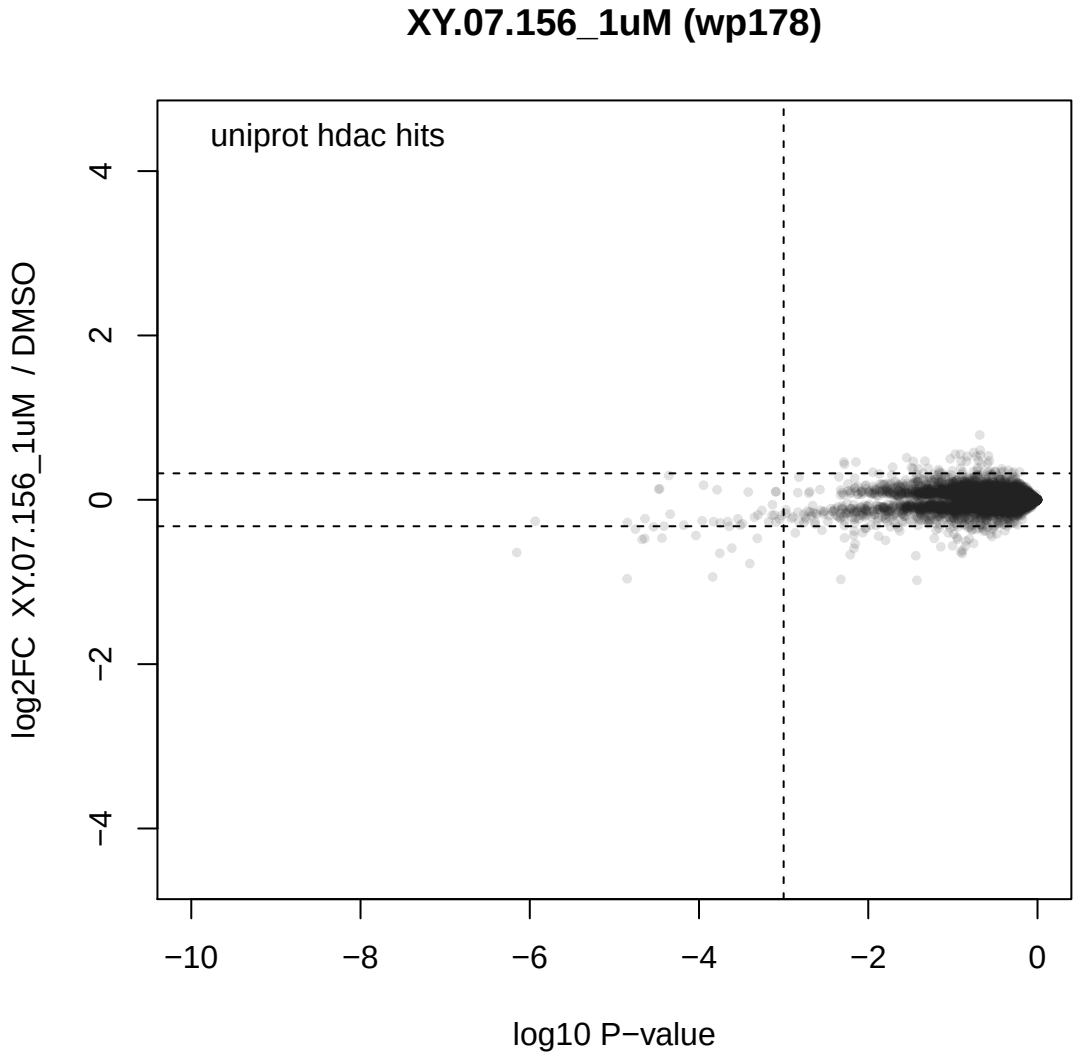

XY.07.154 (wp162)
uniprot hdac hits
log2FC XY.07.154 / DMSO
log10 P−value
HDAC6
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

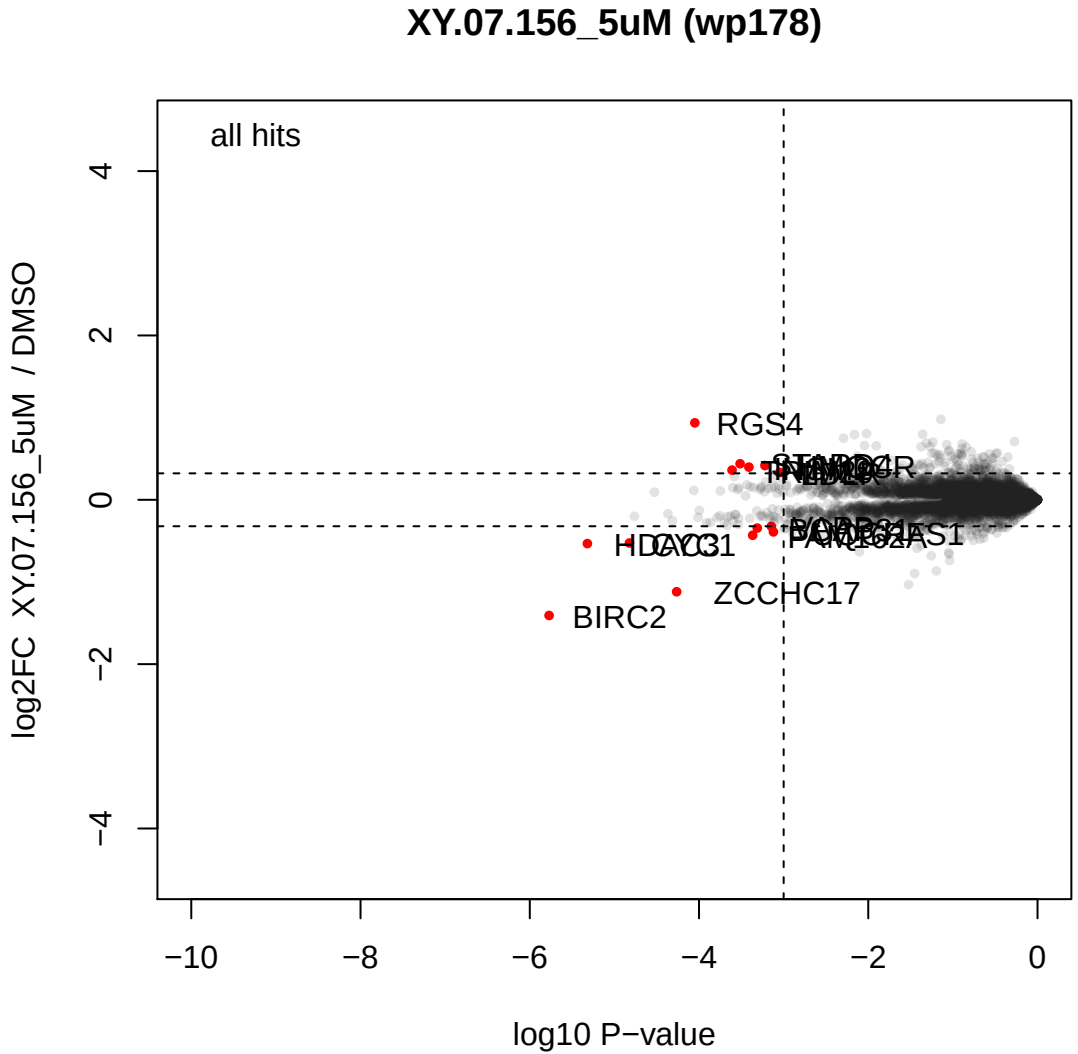

XY.07.155_1uM (wp178)
all hits
LYRM7
log2FC XY.07.155_1uM / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0
XY.07.155_1uM (wp178)
uniprot hdac hits
log2FC XY.07.155_1uM / DMSO
log10 P−value

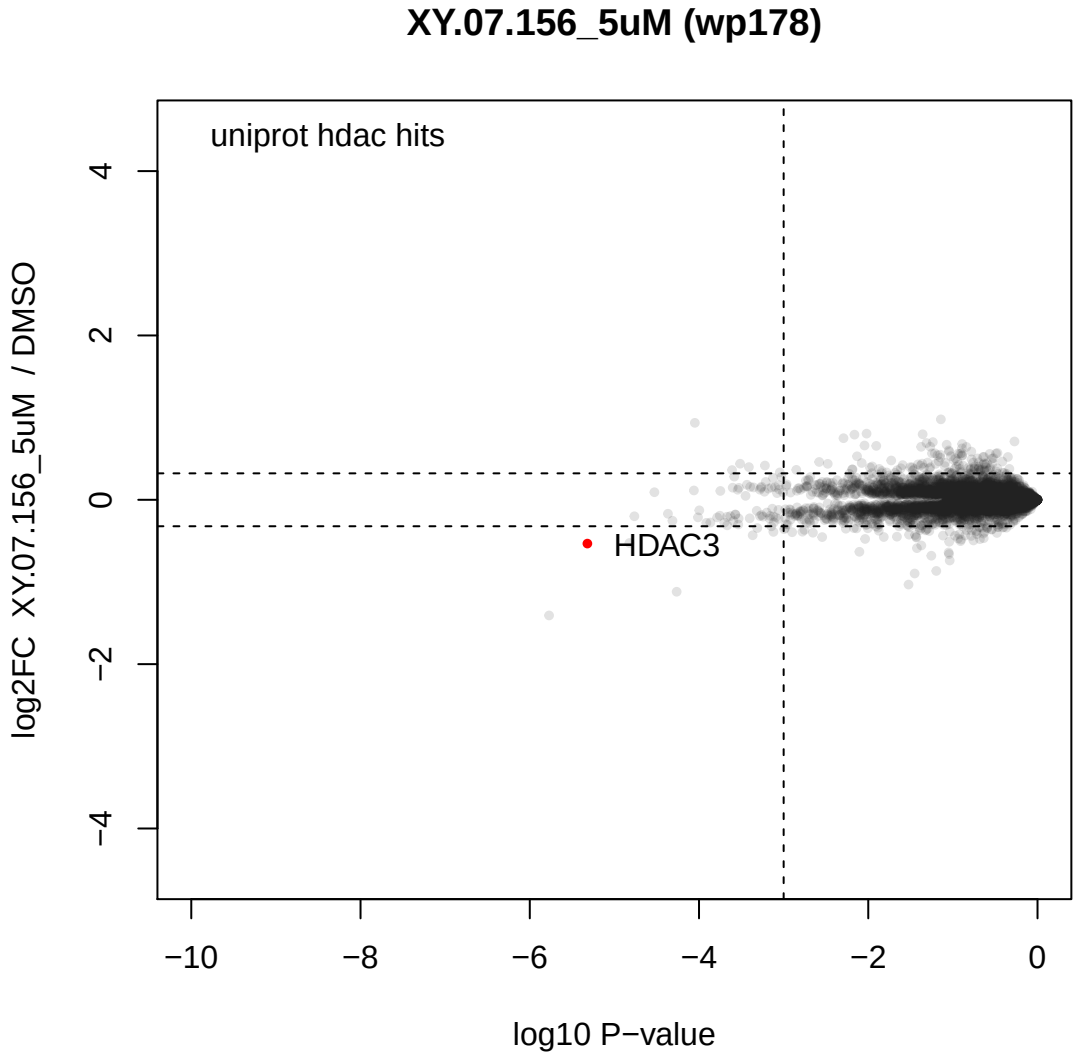


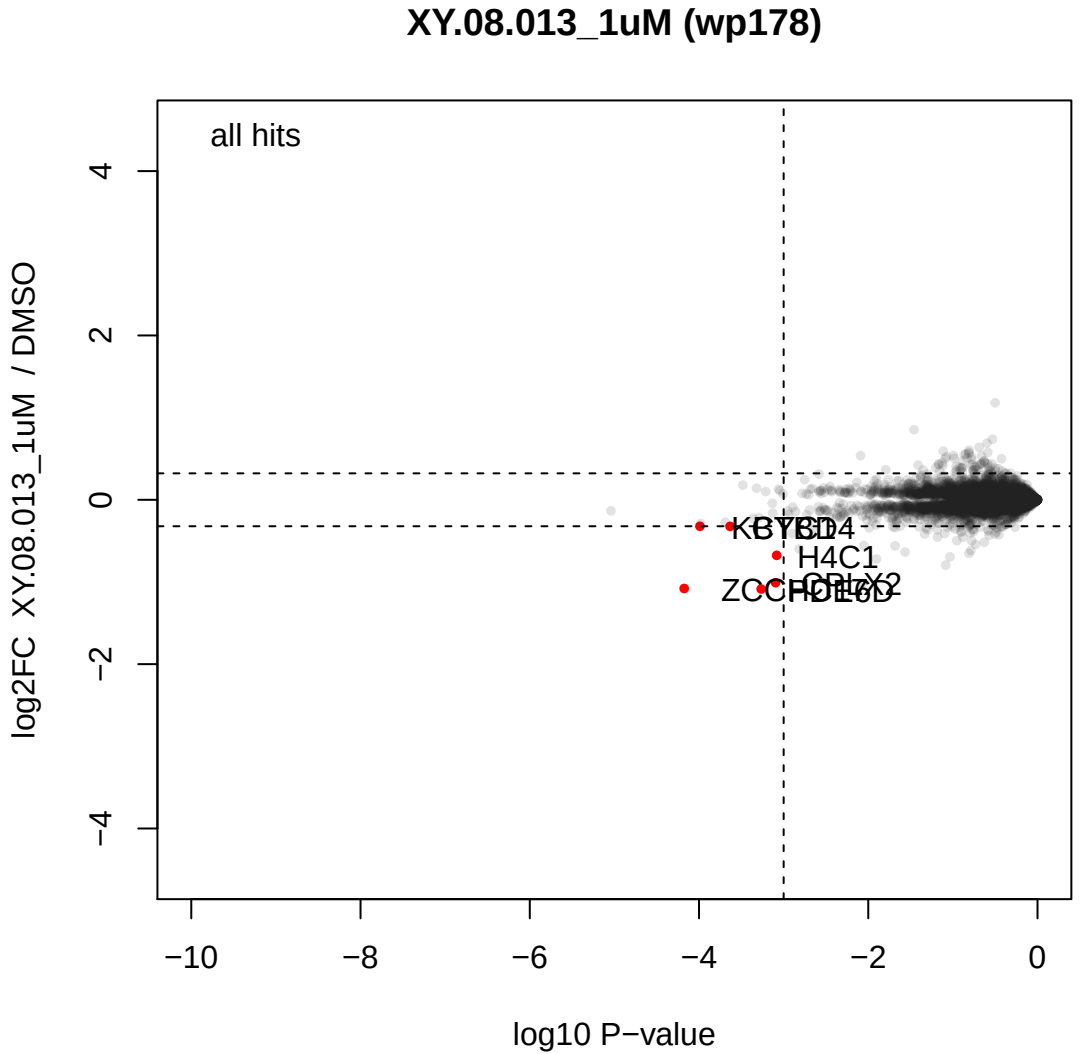
XY.07.155_5uM (wp178)
all hits
log2FC XY.07.155_5uM / DMSO
log10 P−value
−10
−8
−6
−4
−2
0
4
2
0
−2
−4
TOMM5
TEX10
RRP12
MYBBP1A
XY.07.155_5uM (wp178)
uniprot hdac hits
log2FC XY.07.155_5uM / DMSO
log10 P−value

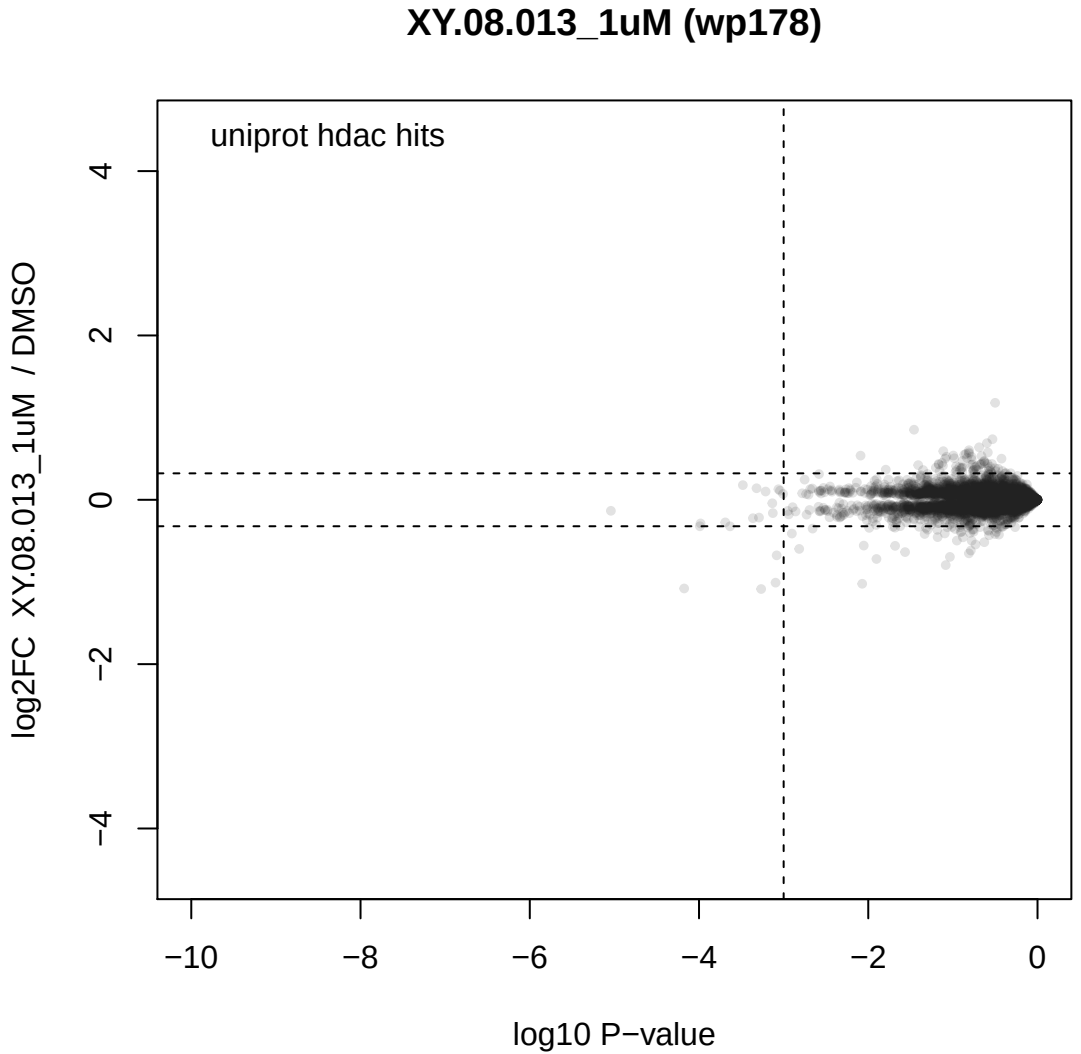

XY.07.156_1uM (wp178)
all hits
log2FC XY.07.156_1uM / DMSO
log10 P−value
FBL
GAR1
ZCCHC17
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

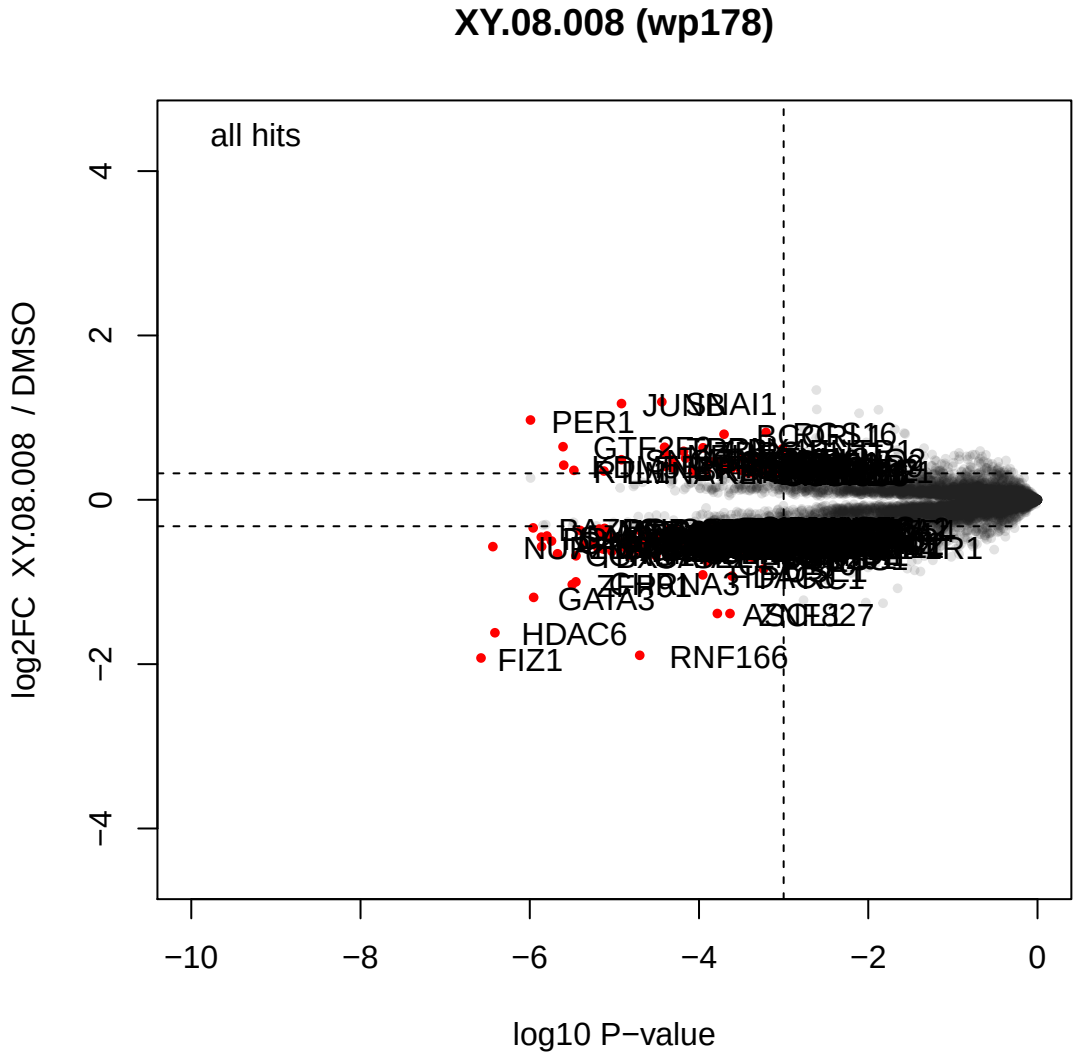

XY.07.156_1uM (wp178)
uniprot hdac hits
log2FC XY.07.156_1uM / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

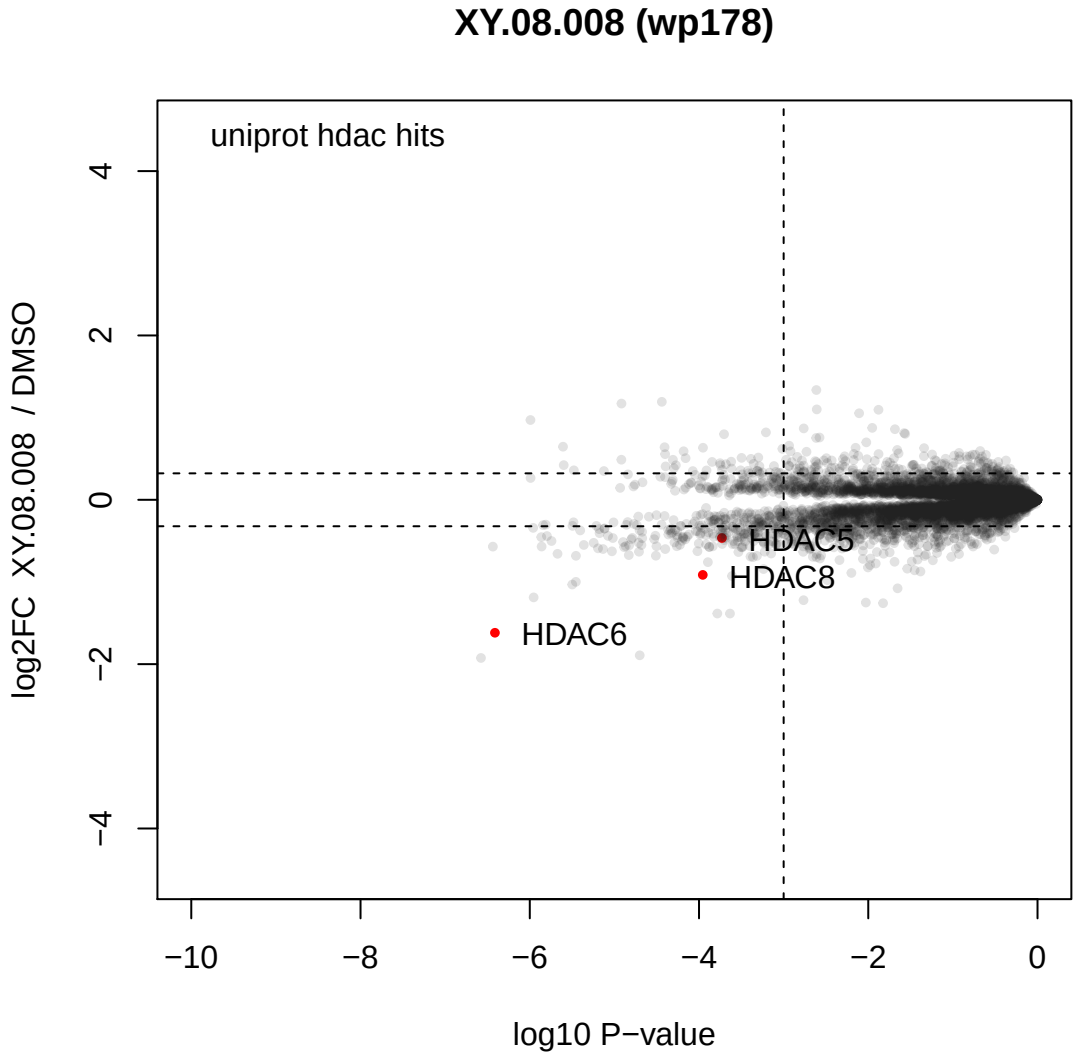

XY.07.156_5uM (wp178)
all hits
log2FC XY.07.156_5uM / DMSO
log10 P−value
RGS4
HDAC3
ZCCHC17
BIRC2
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

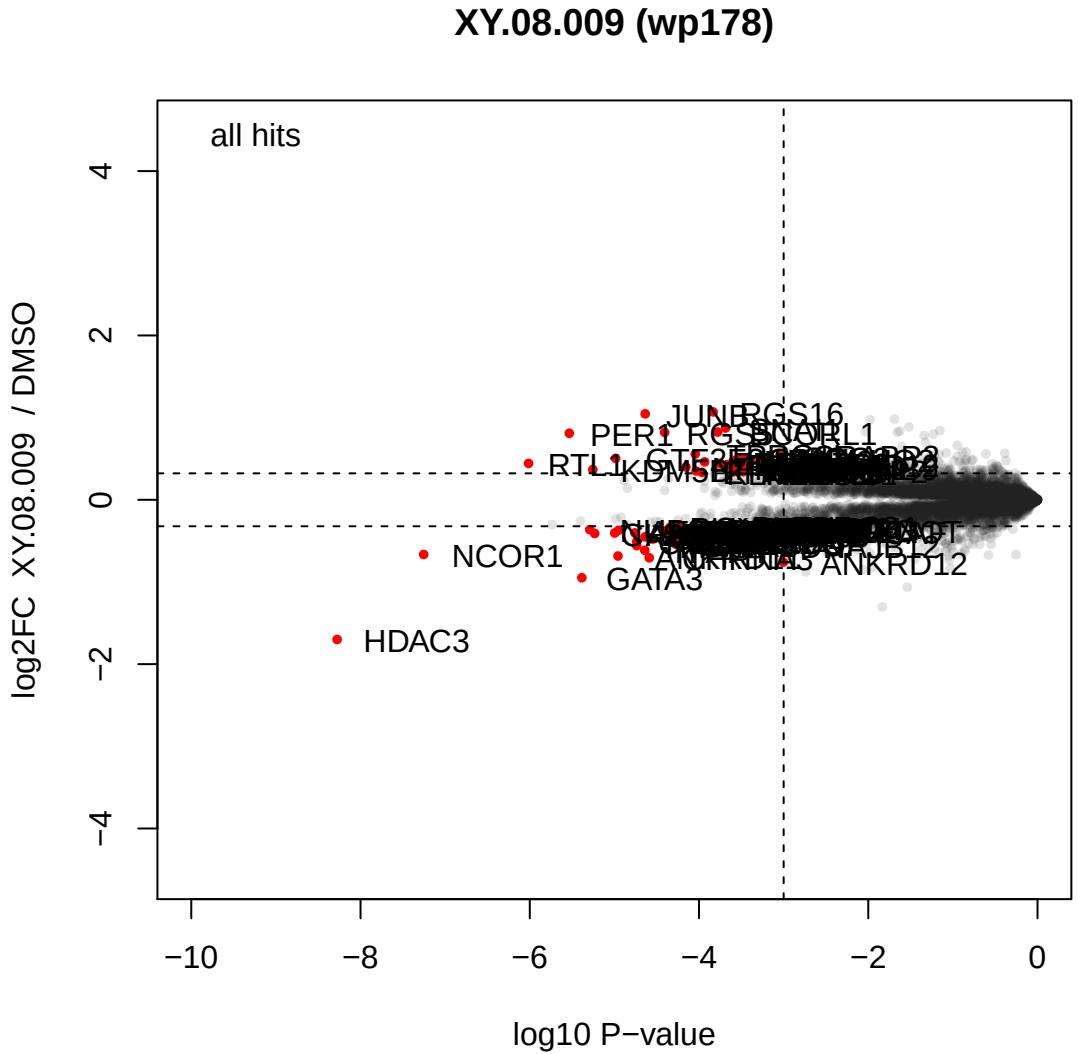

XY.07.156_5uM (wp178)
uniprot hdac hits
log2FC XY.07.156_5uM / DMSO
log10 P−value
HDAC3
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

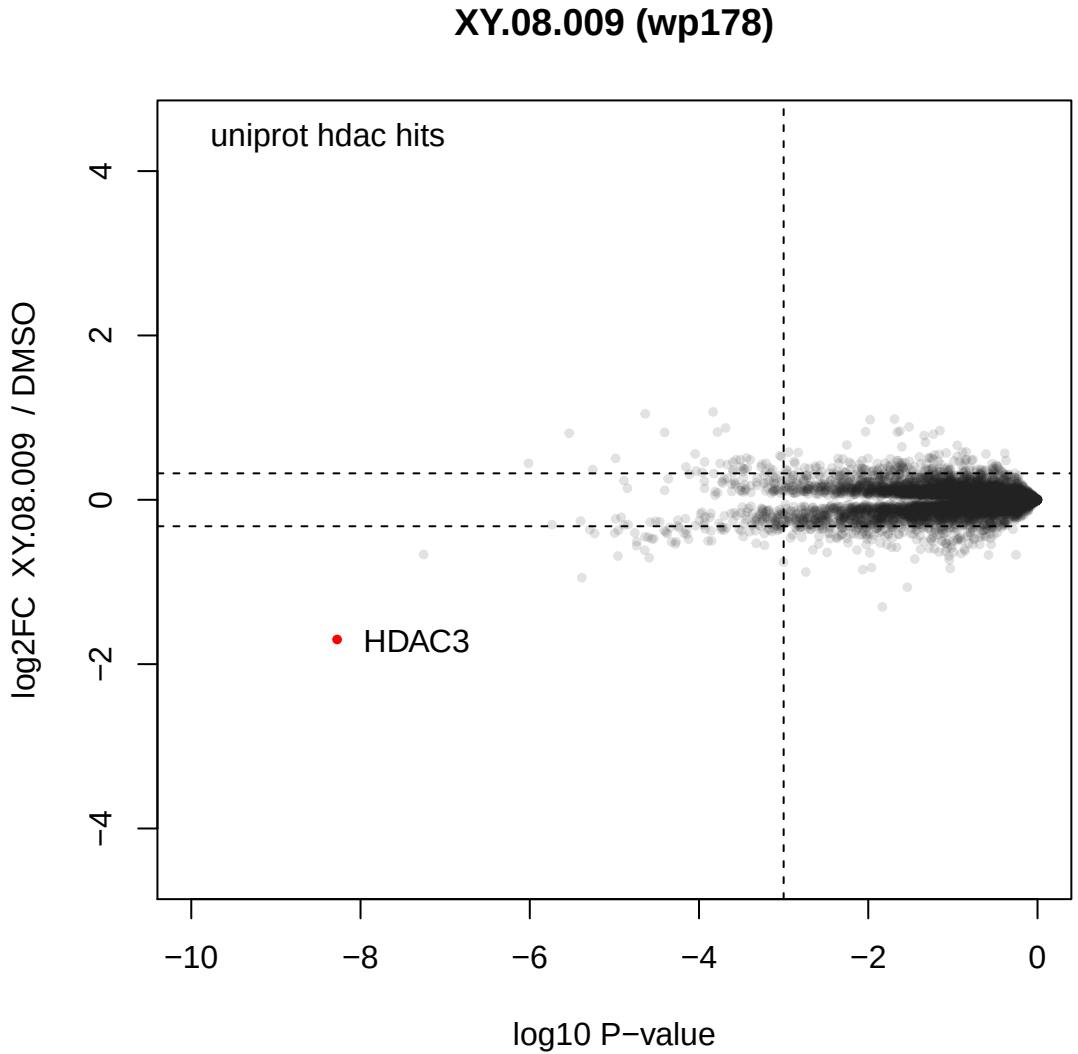

XY.08.013_1uM (wp178)
all hits
log2FC XY.08.013_1uM / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0
H4C1

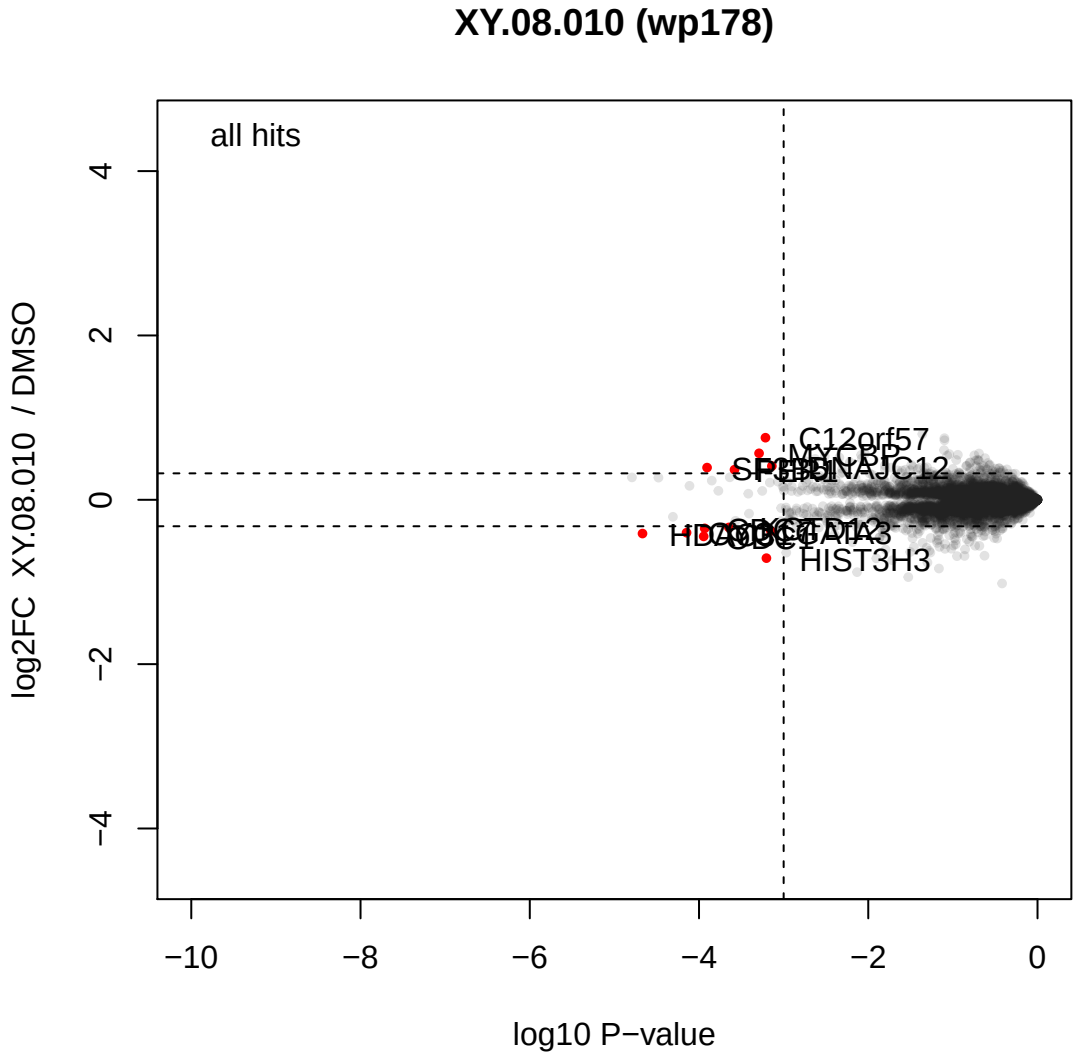

XY.08.013_1uM (wp178)
uniprot hdac hits
log2FC XY.08.013_1uM / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

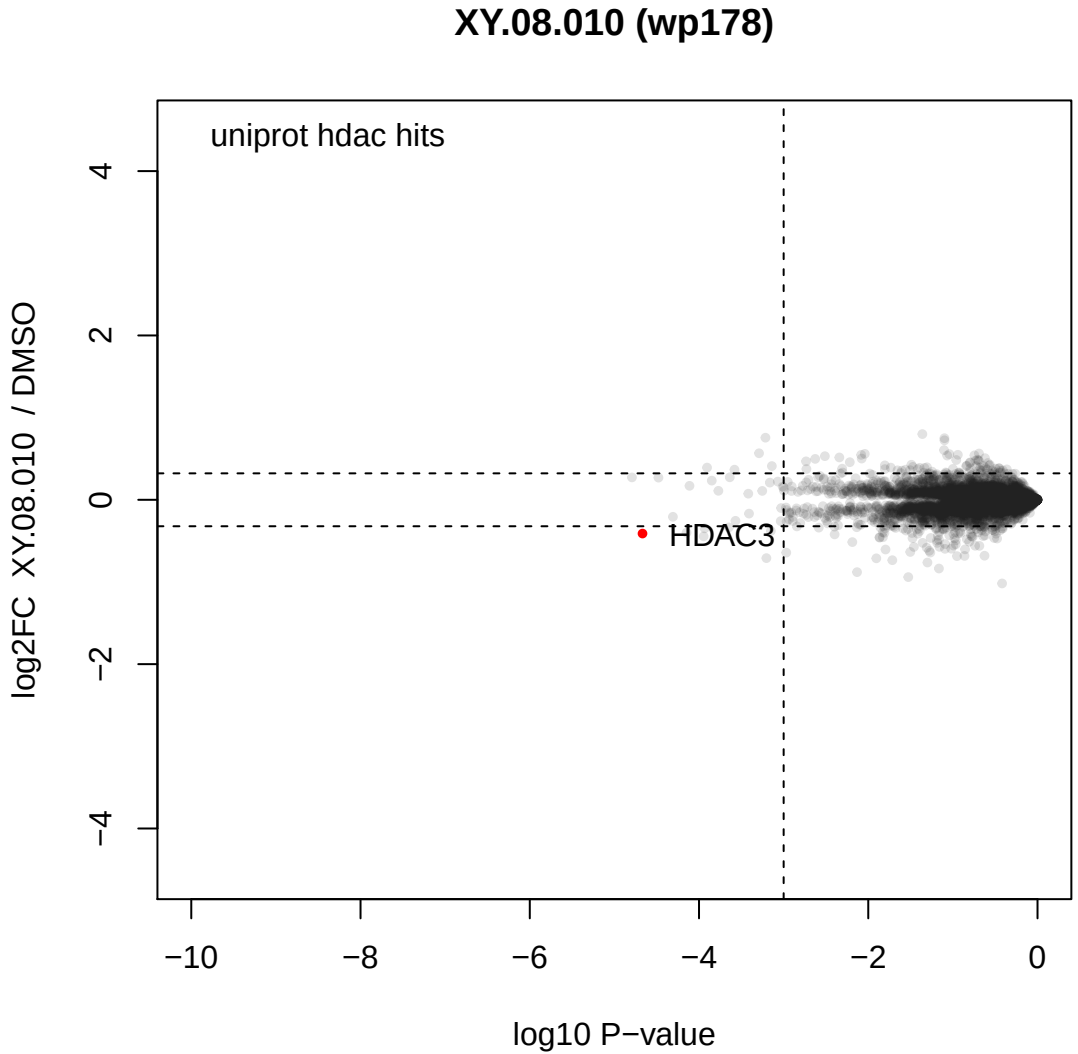

XY.08.008 (wp178)
all hits
log2FC XY.08.008 / DMSO
log10 P−value
PER1
JUNB
SNAI1
GATA3
HDAC6
FIZ1
RNF166
ZNF827

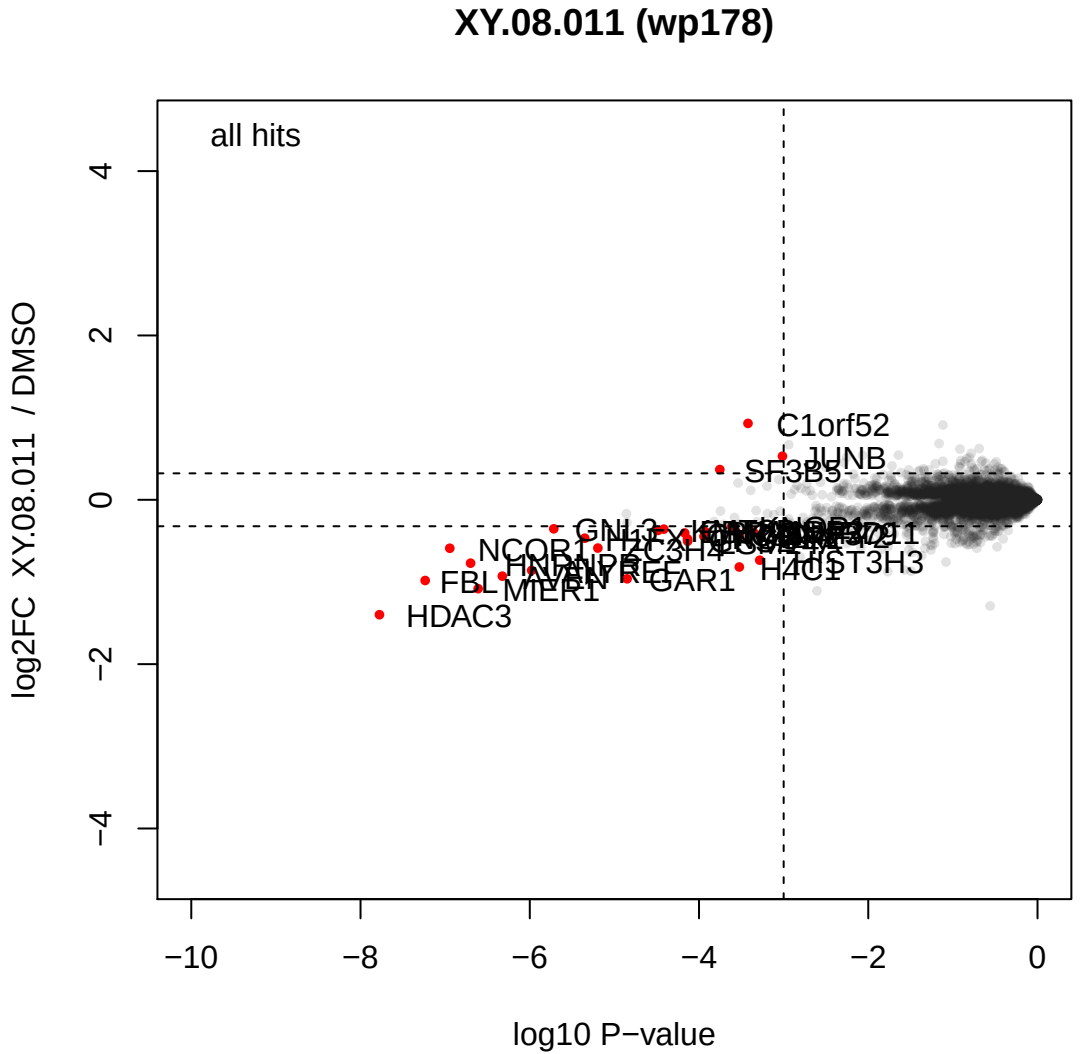

XY.08.008 (wp178)
uniprot hdac hits
log2FC XY.08.008 / DMSO
log10 P−value
HDAC5
HDAC8
HDAC6

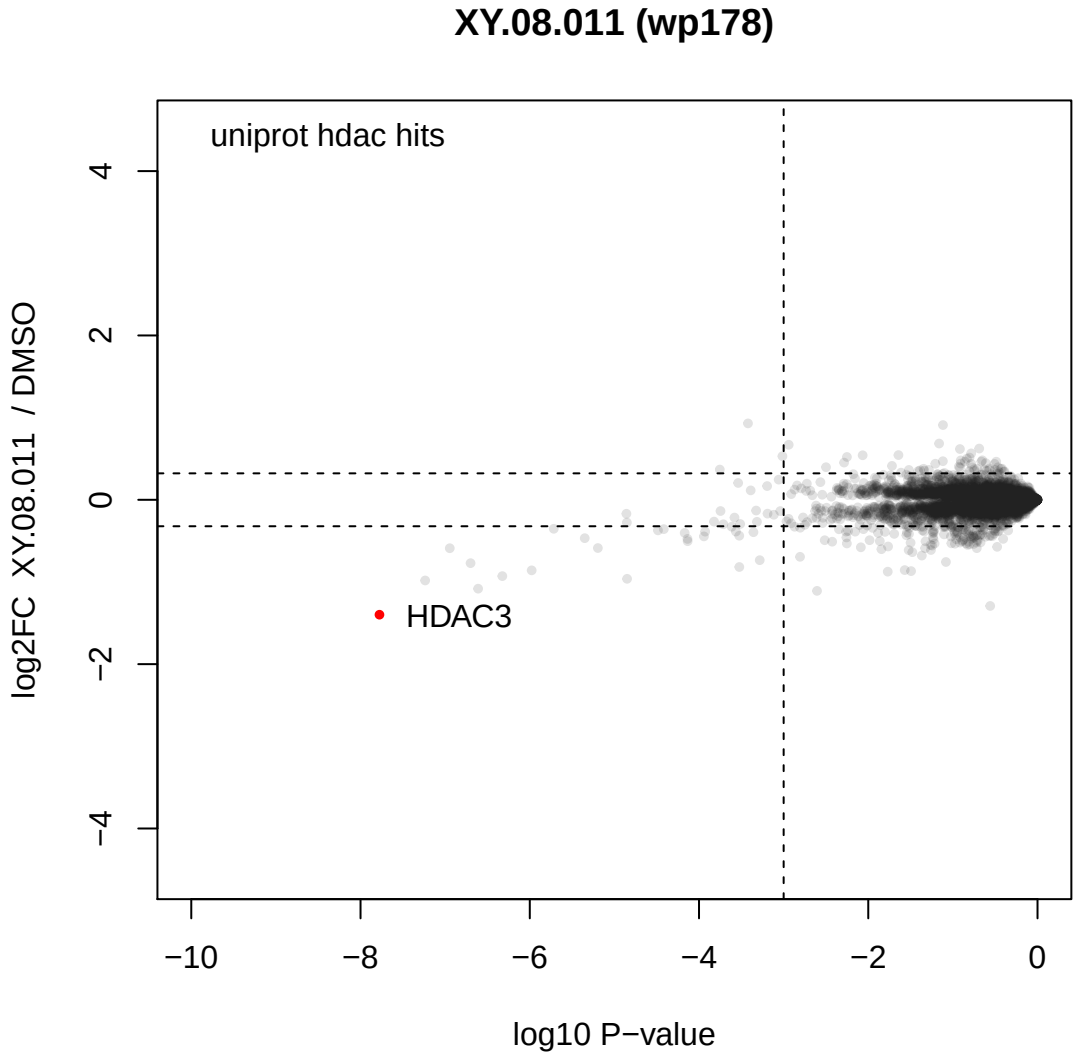

XY.08.009 (wp178)
all hits
log2FC XY.08.009 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0
JUNB
RGS16
PER1
RGS2
RTL1
NCOR1
GATA3
ANKRD12
HDAC3

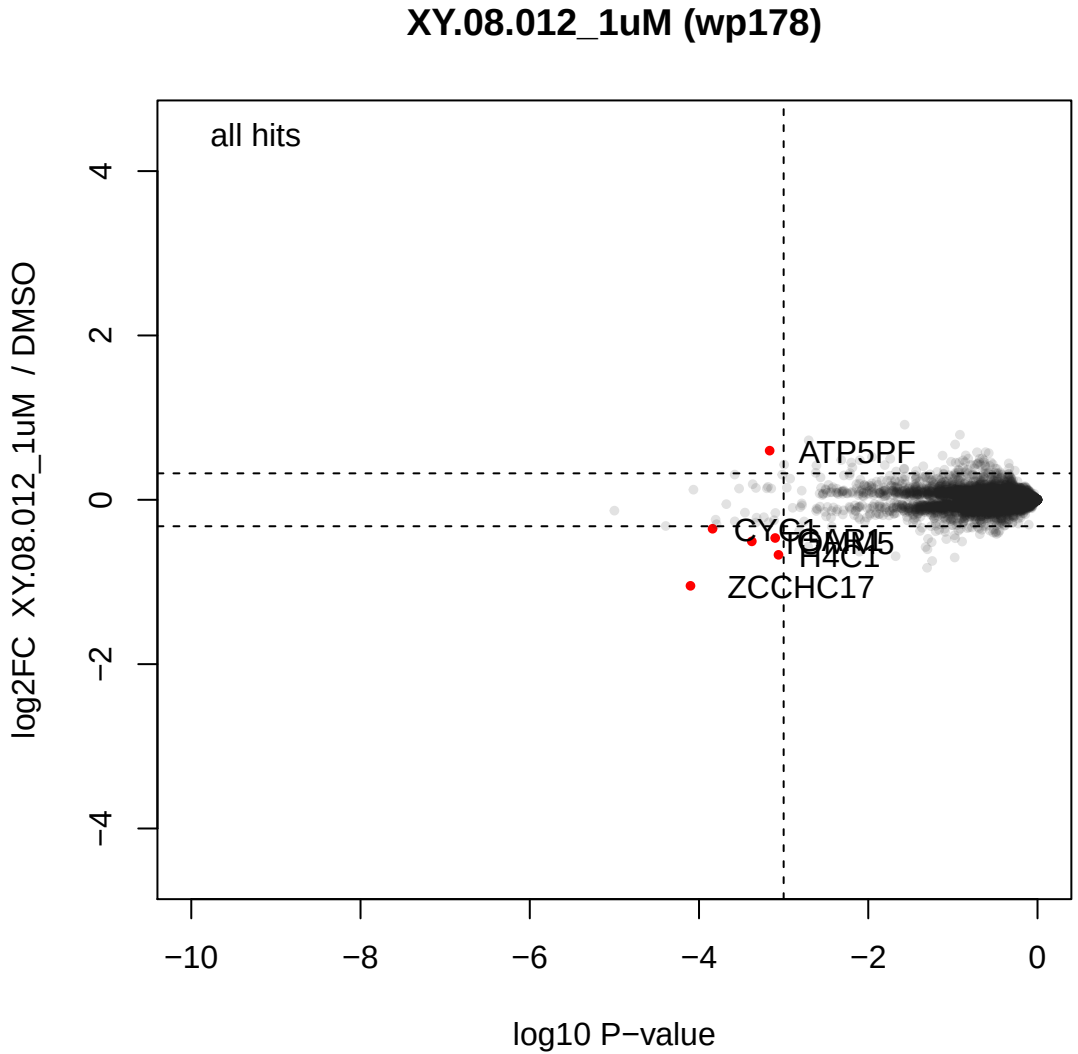

XY.08.009 (wp178)
uniprot hdac hits
log2FC XY.08.009 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0
HDAC3

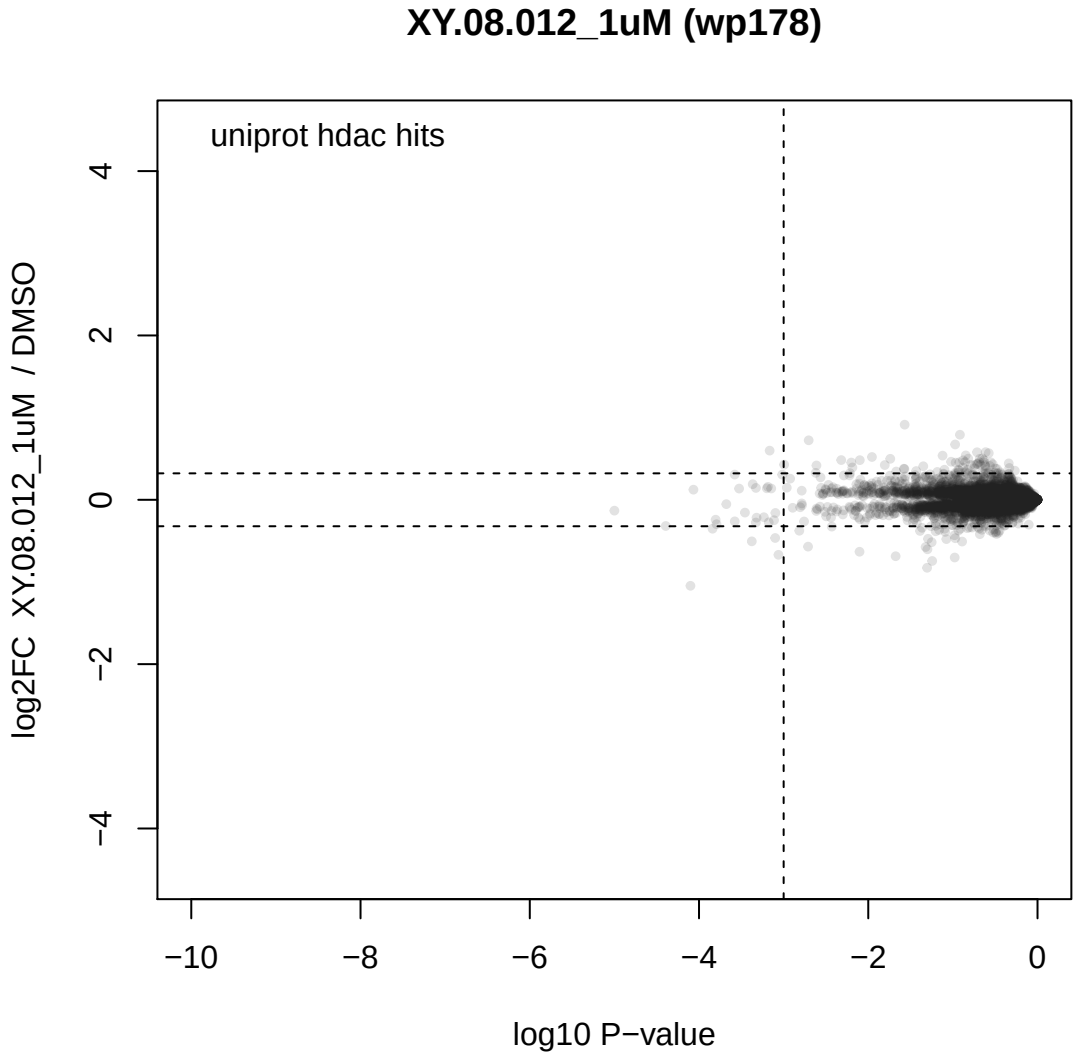

XY.08.010 (wp178)
all hits
log2FC XY.08.010 / DMSO
log10 P−value
C12orf57
MYCBP
DNAJC12
HIST3H3

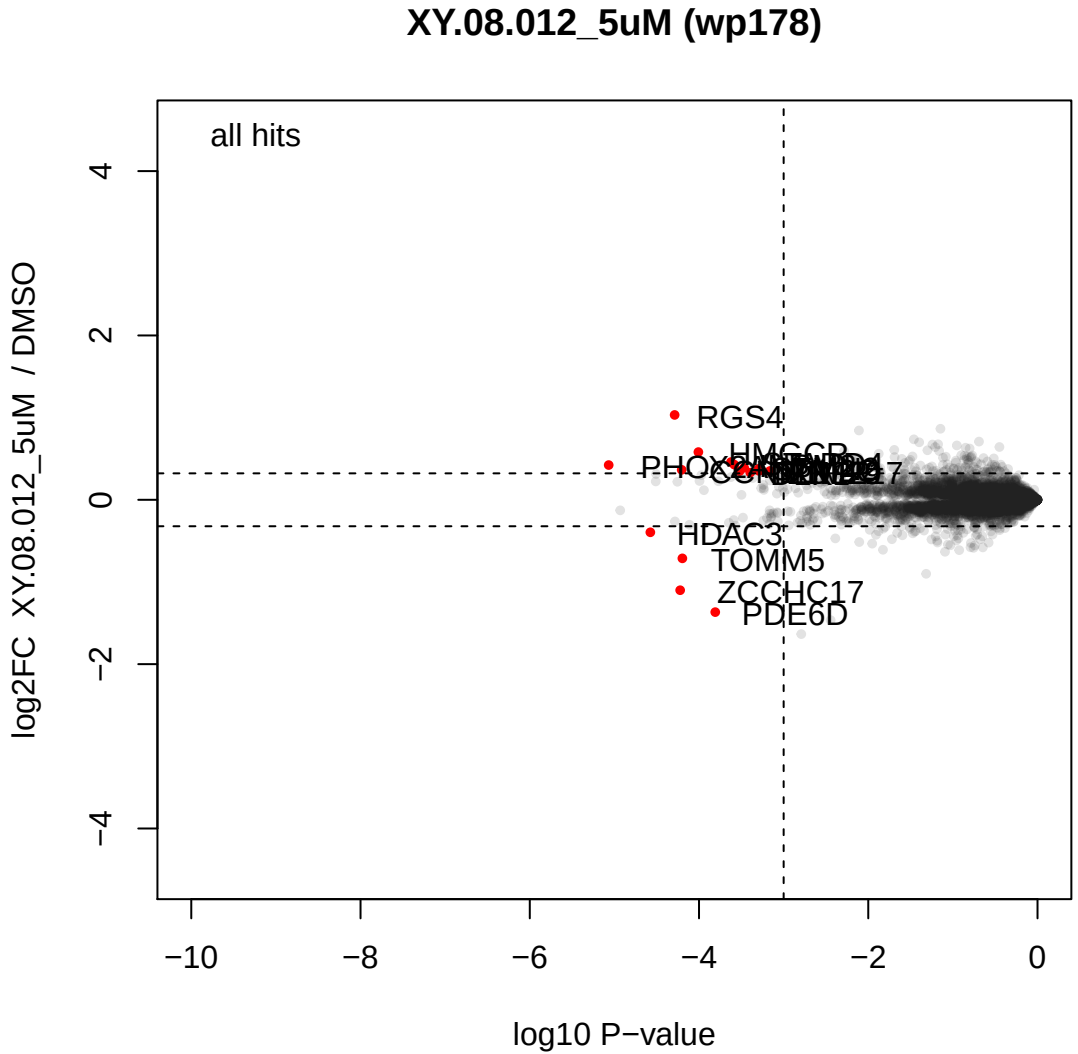

XY.08.010 (wp178)
uniprot hdac hits
log2FC XY.08.010 / DMSO
log10 P−value
HDAC3

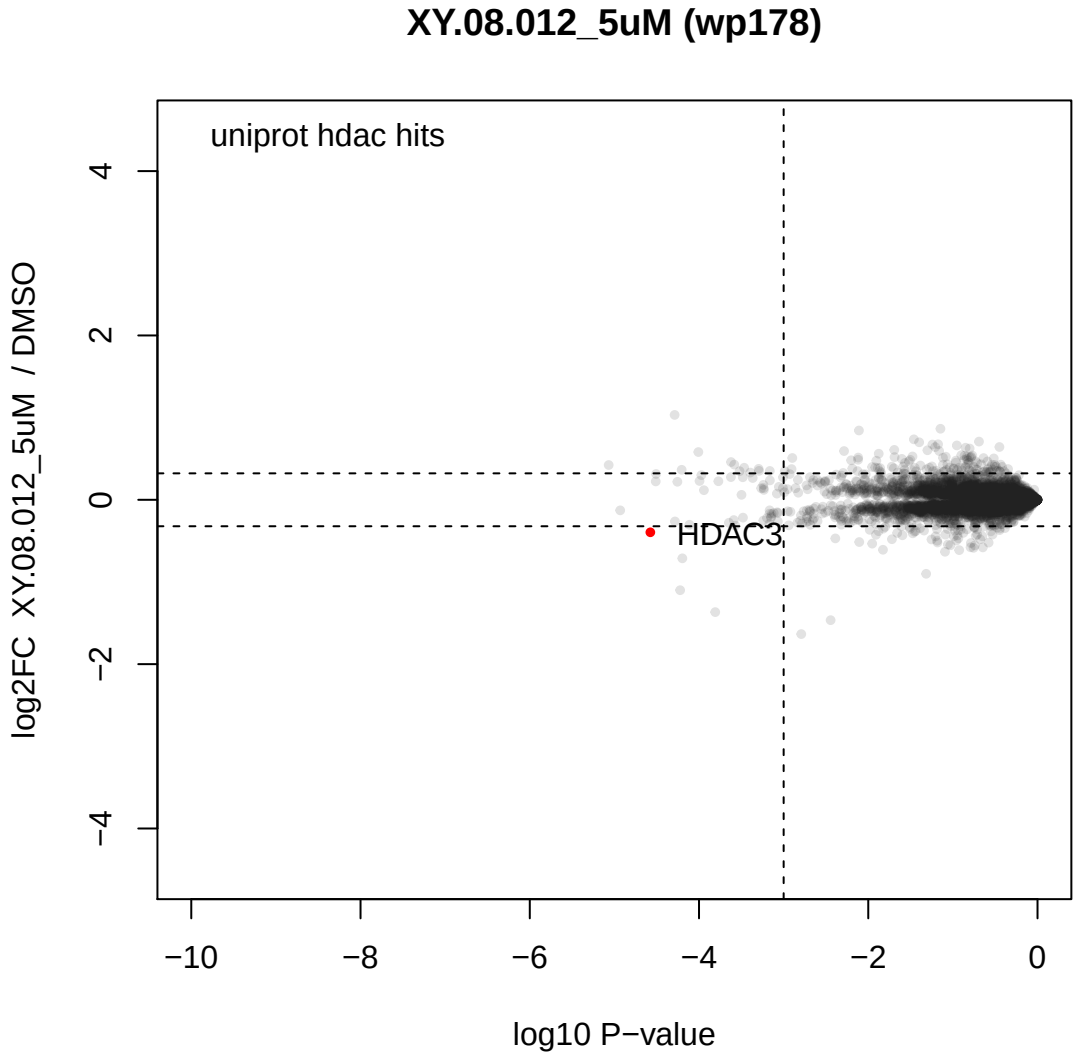

XY.08.011 (wp178)
all hits
log2FC XY.08.011 / DMSO
log10 P−value
C1orf52
JUNB
SF3B5
NCOR1
FBL
MIER1
GAR1
H4C1
HDAC3
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

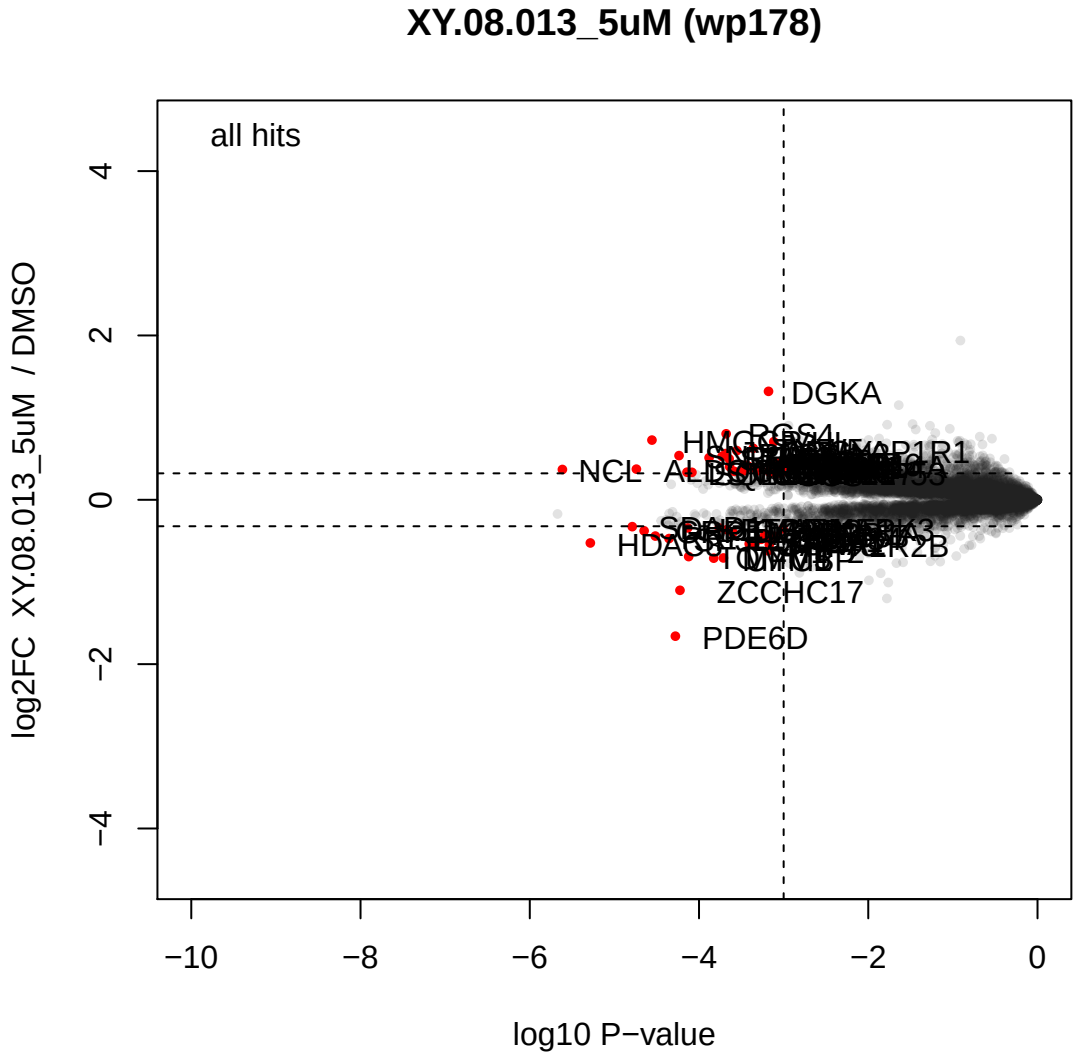

XY.08.011 (wp178)
uniprot hdac hits
log2FC XY.08.011 / DMSO
log10 P−value
HDAC3
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

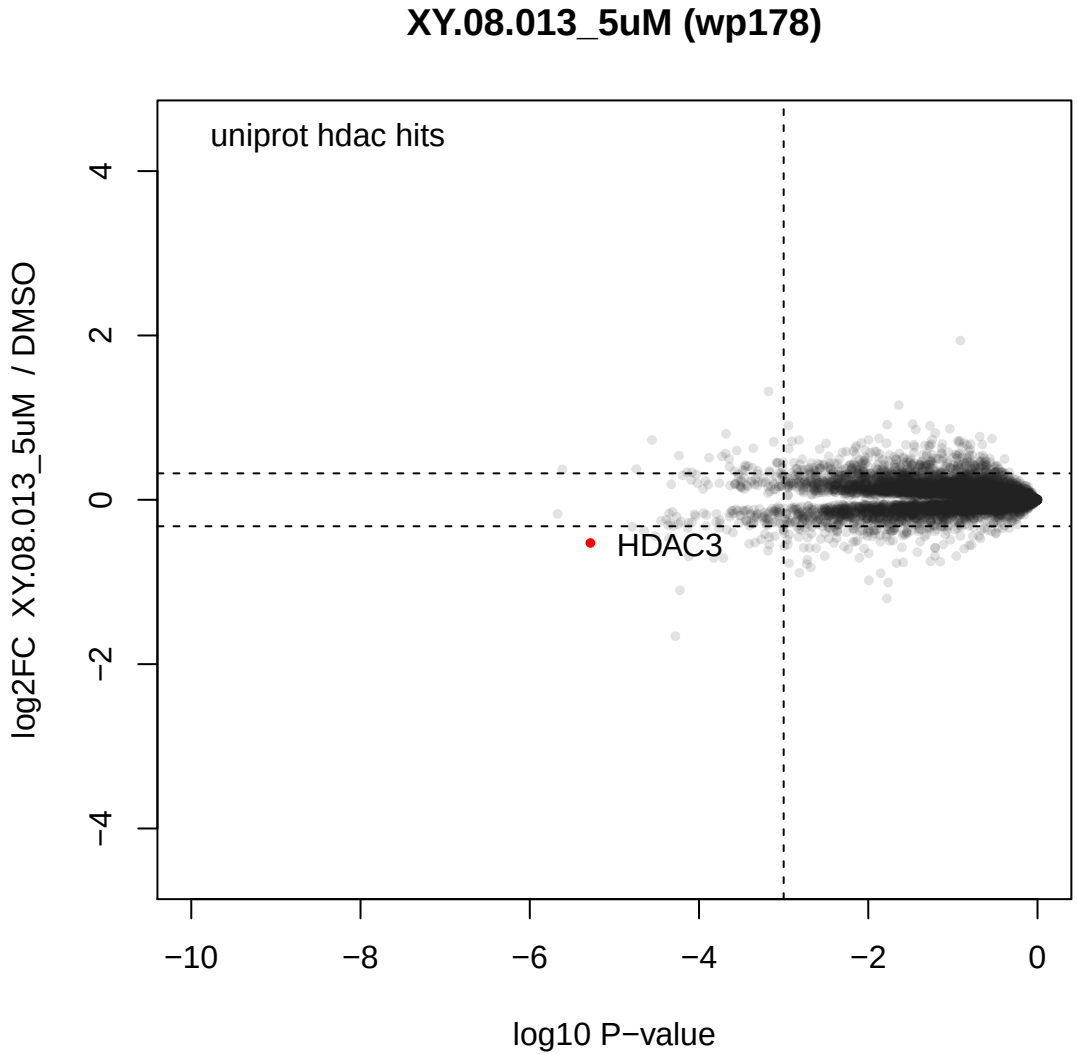

XY.08.012_1uM (wp178)
all hits
log2FC XY.08.012_1uM / DMSO
log10 P−value
ATP5PF
CYC1
TOMM5
H4C1
ZCCHC17
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

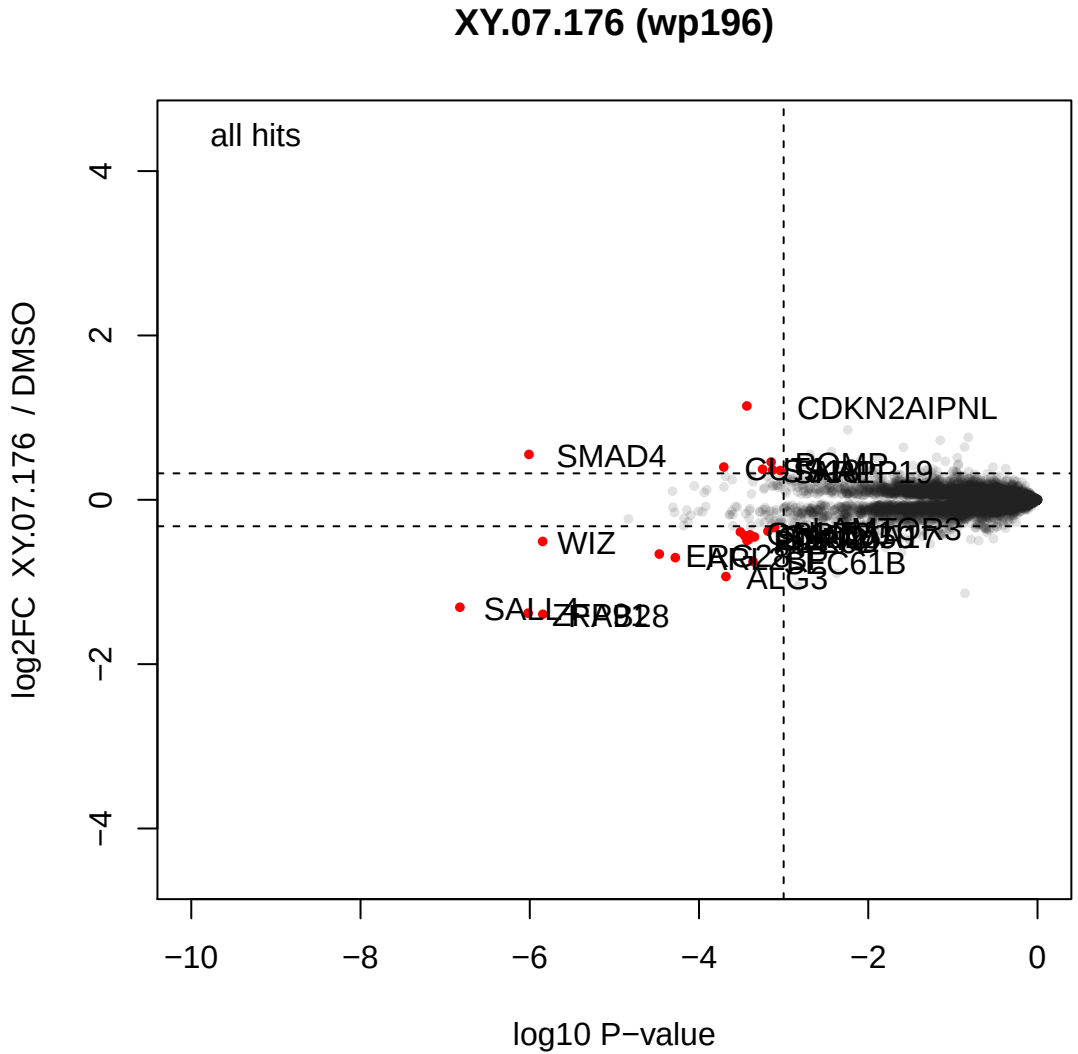

XY.08.012_1uM (wp178)
uniprot hdac hits
log2FC XY.08.012_1uM / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

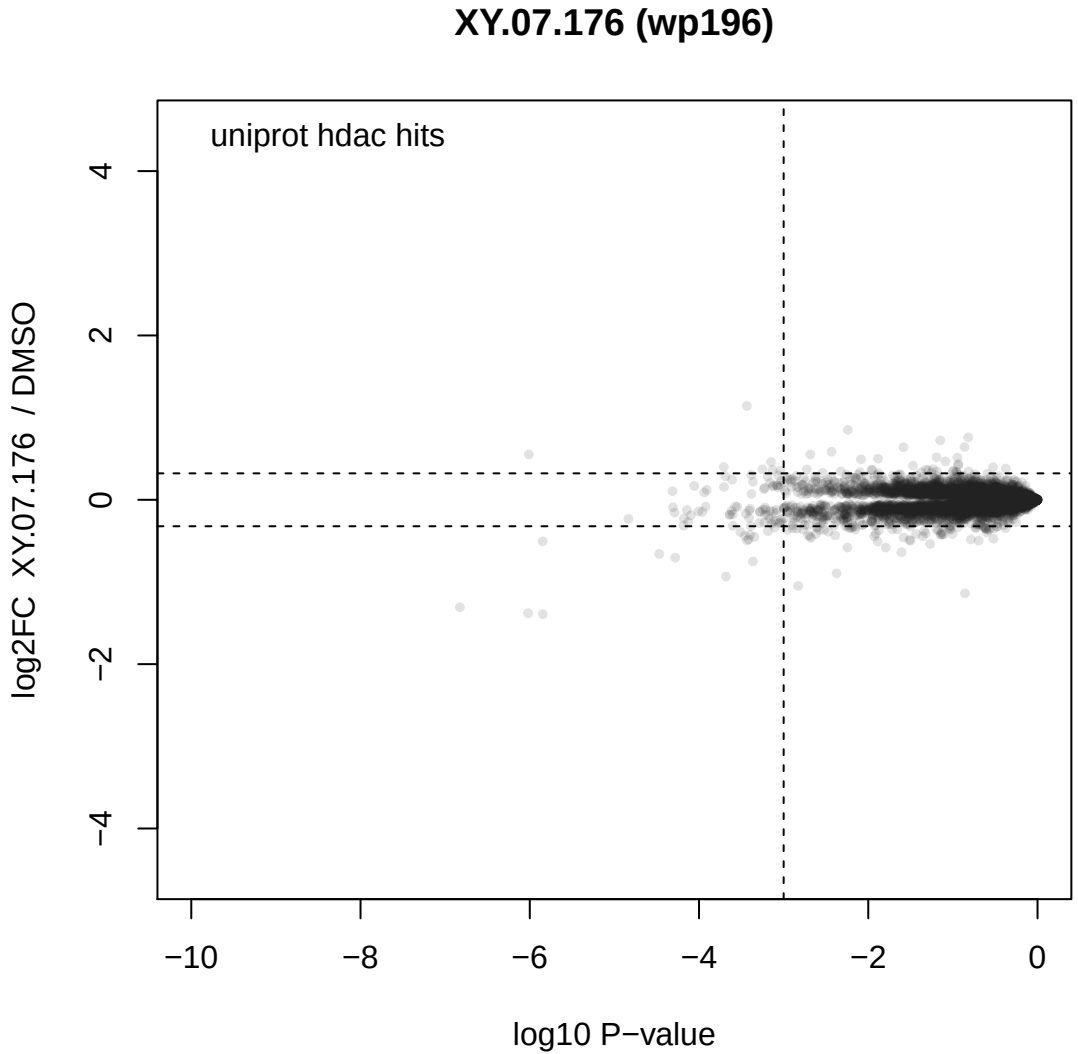

XY.08.012_5uM (wp178)
all hits
RGS4
HDAC3
TOMM5
ZCCHC17
PDE6D
log2FC XY.08.012_5uM / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

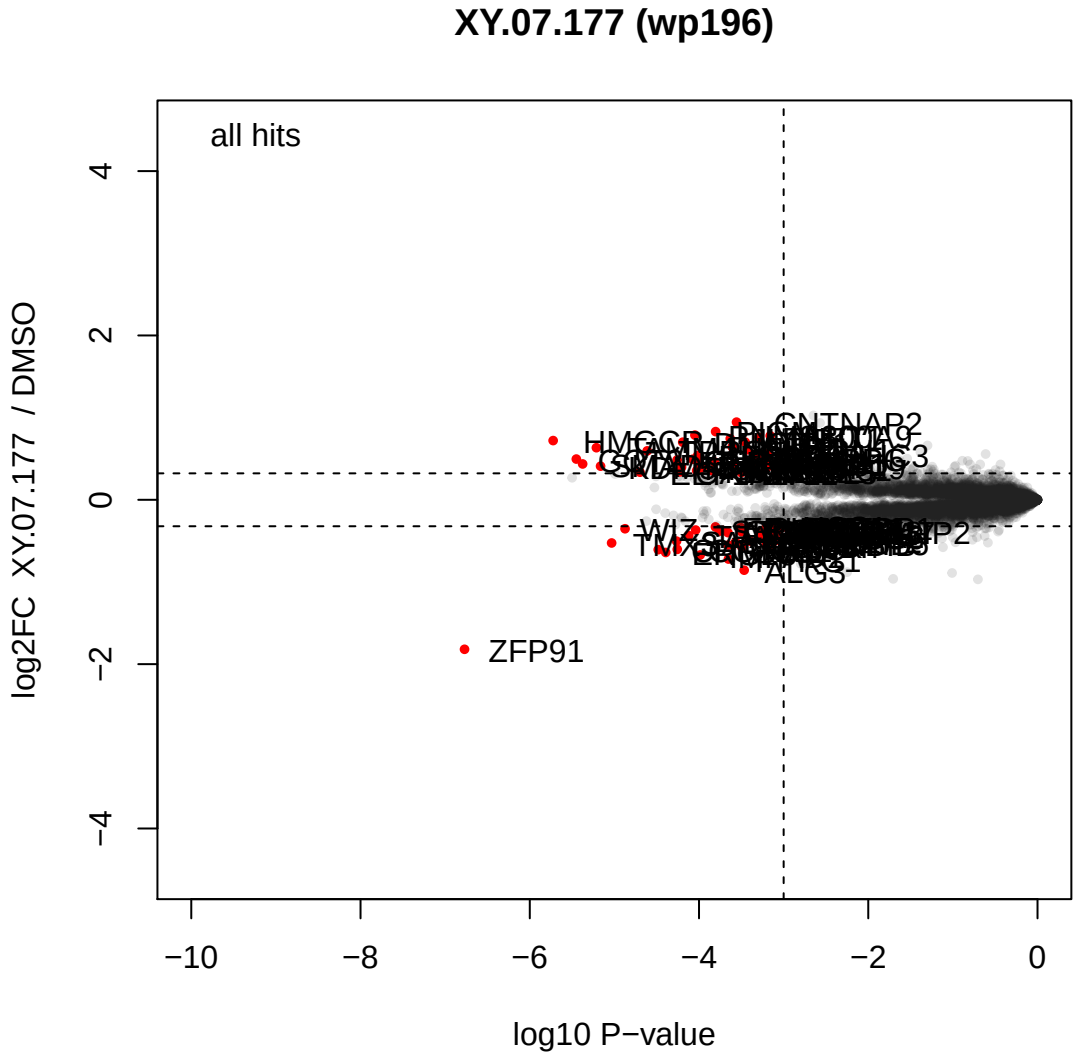

XY.08.012_5uM (wp178)
uniprot hdac hits
HDAC3
log2FC XY.08.012_5uM / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

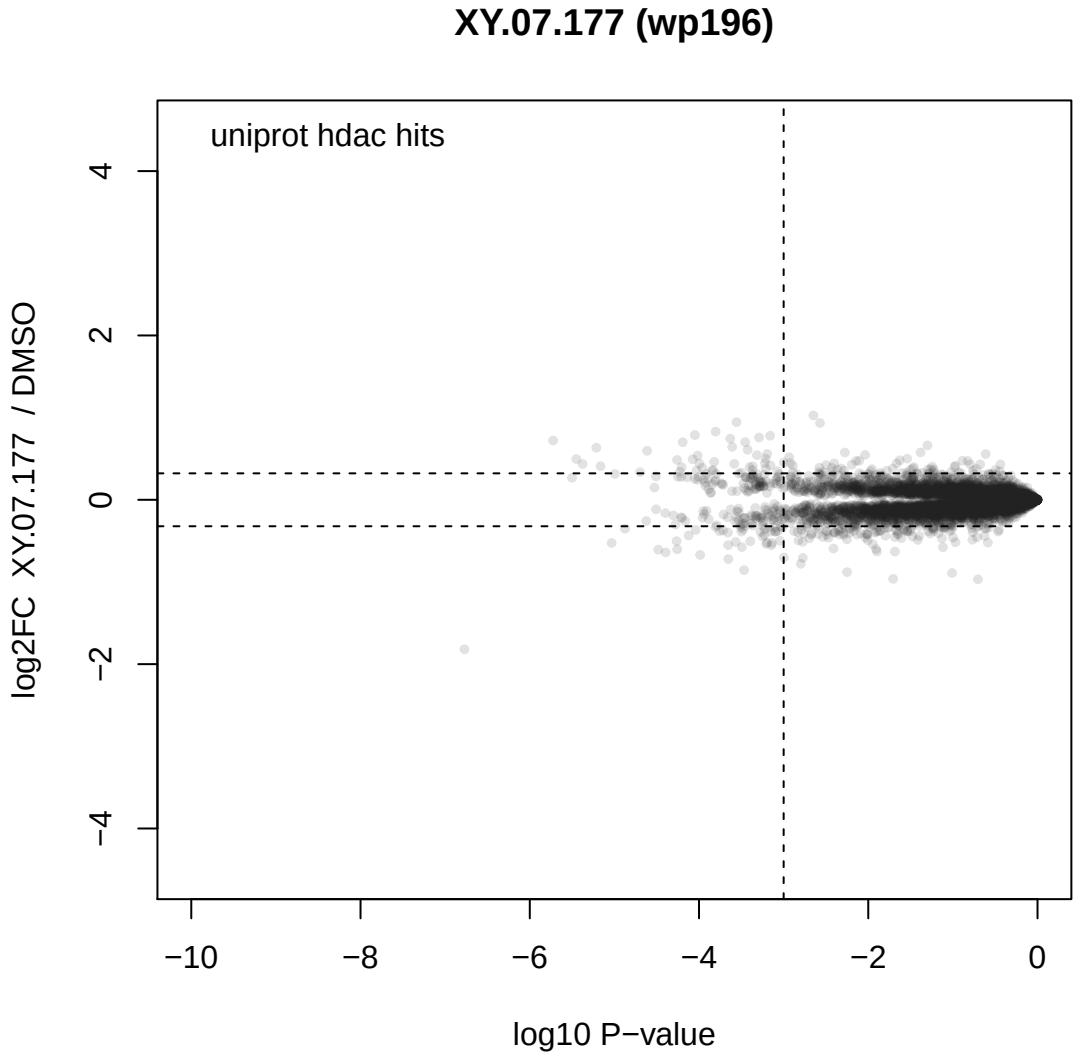

XY.08.013_5uM (wp178)
all hits
log2FC XY.08.013_5uM / DMSO
log10 P−value
DGKA
NCL
HDAC3
ZCCHC17
PDE6D

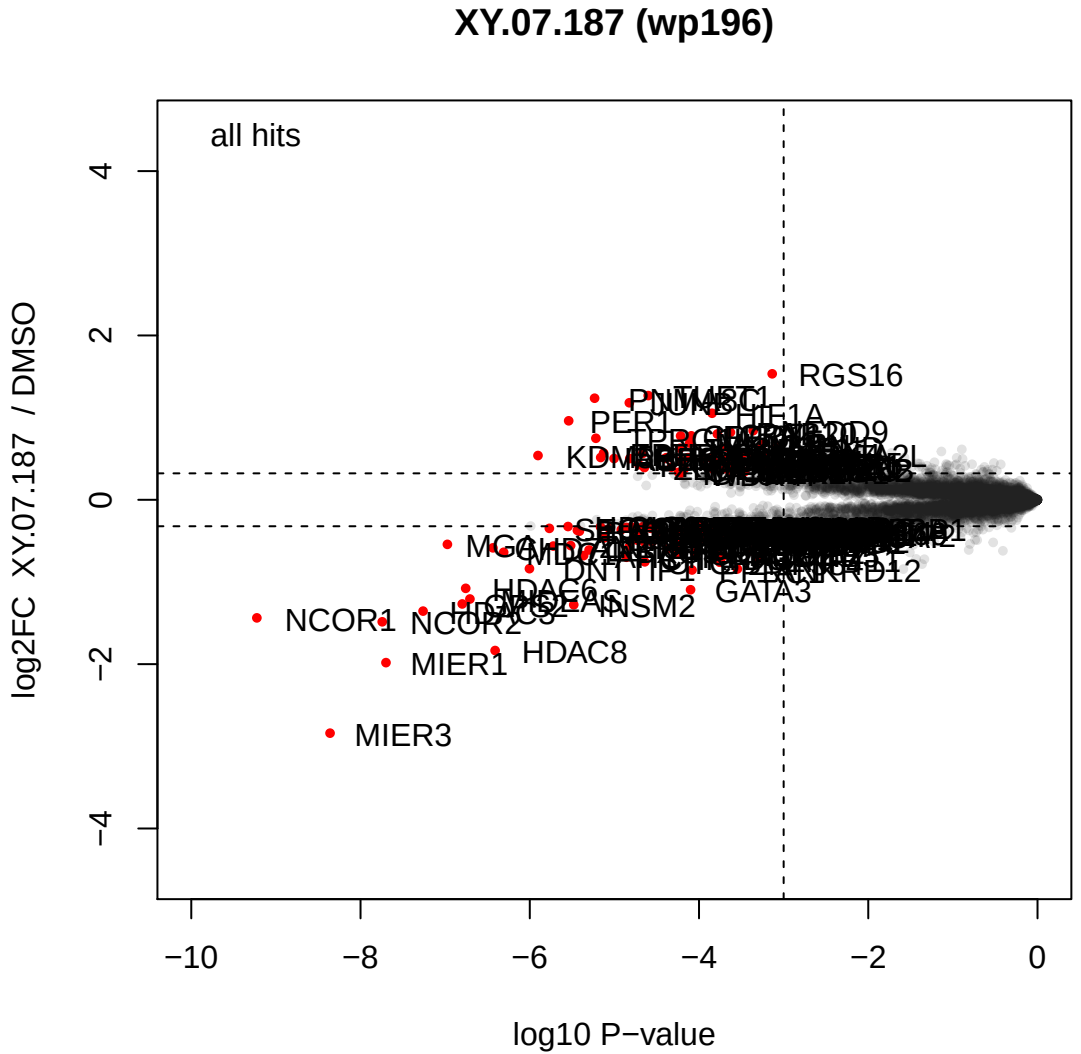

XY.08.013_5uM (wp178)
uniprot hdac hits
log2FC XY.08.013_5uM / DMSO
log10 P−value
HDAC3

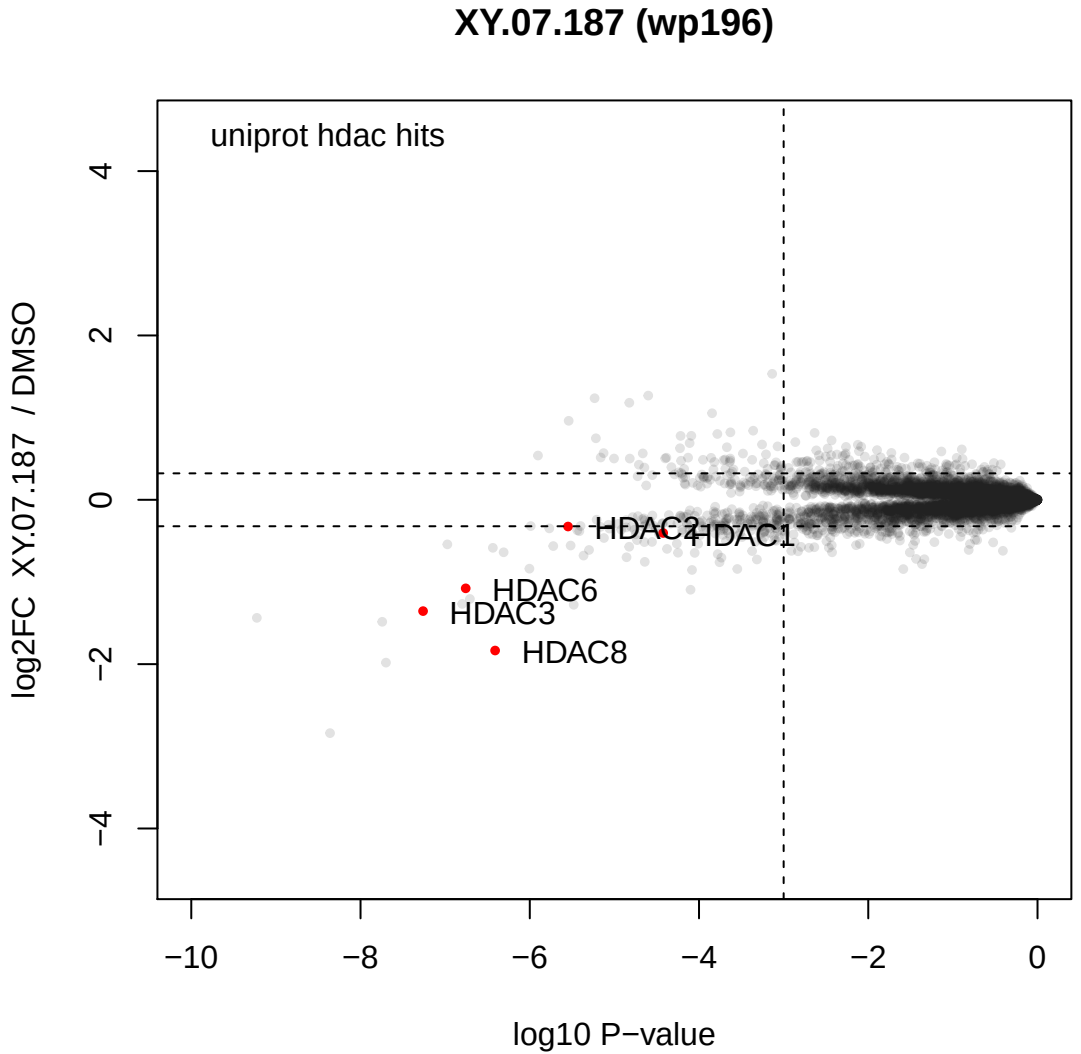

XY.07.176 (wp196)
all hits
log2FC XY.07.176 / DMSO
log10 P−value
CDKN2AIPNL
SMAD4
WIZ
ALG3
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

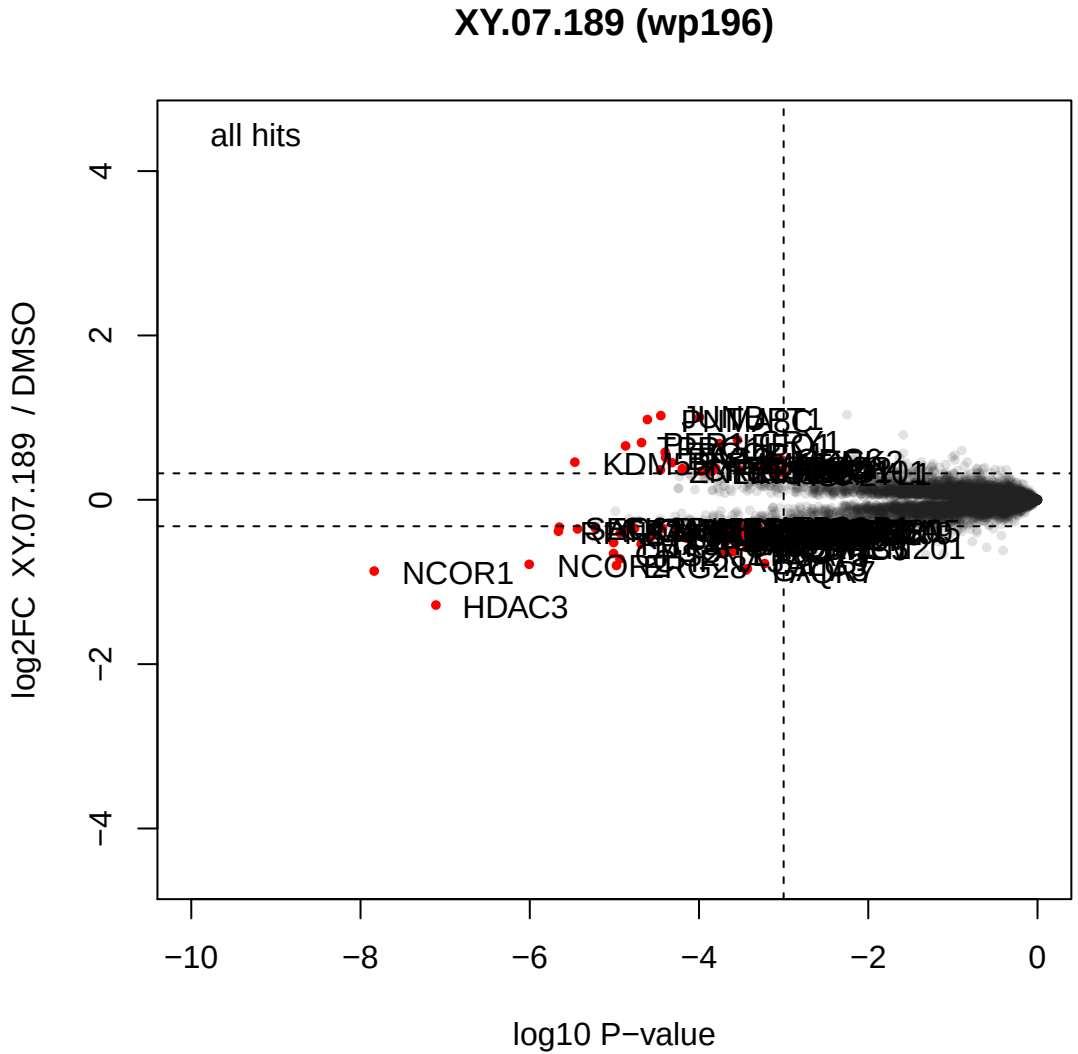

XY.07.176 (wp196)
uniprot hdac hits
log2FC XY.07.176 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

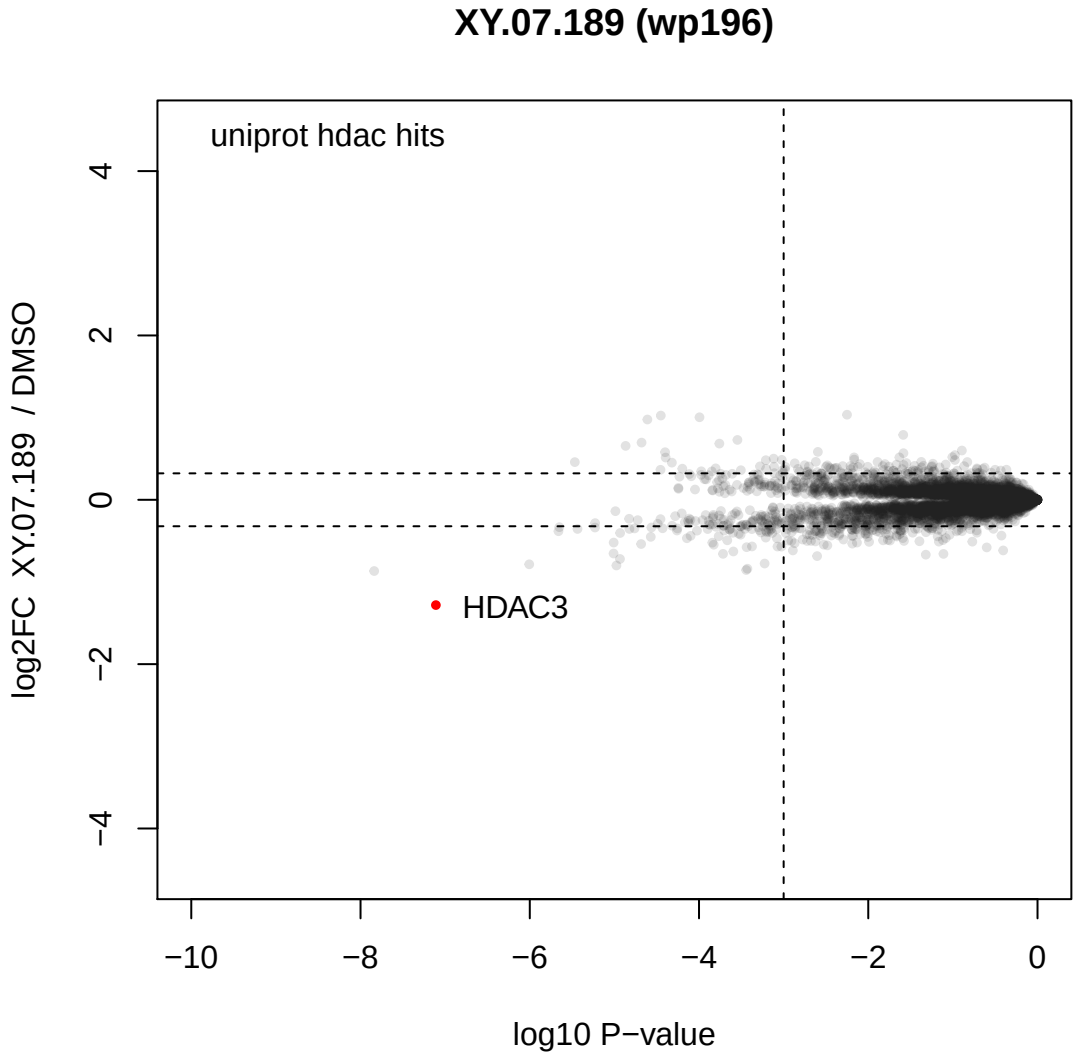

XY.07.177 (wp196)
all hits
log2FC XY.07.177 / DMSO
log10 P−value
ZFP91
ALG3

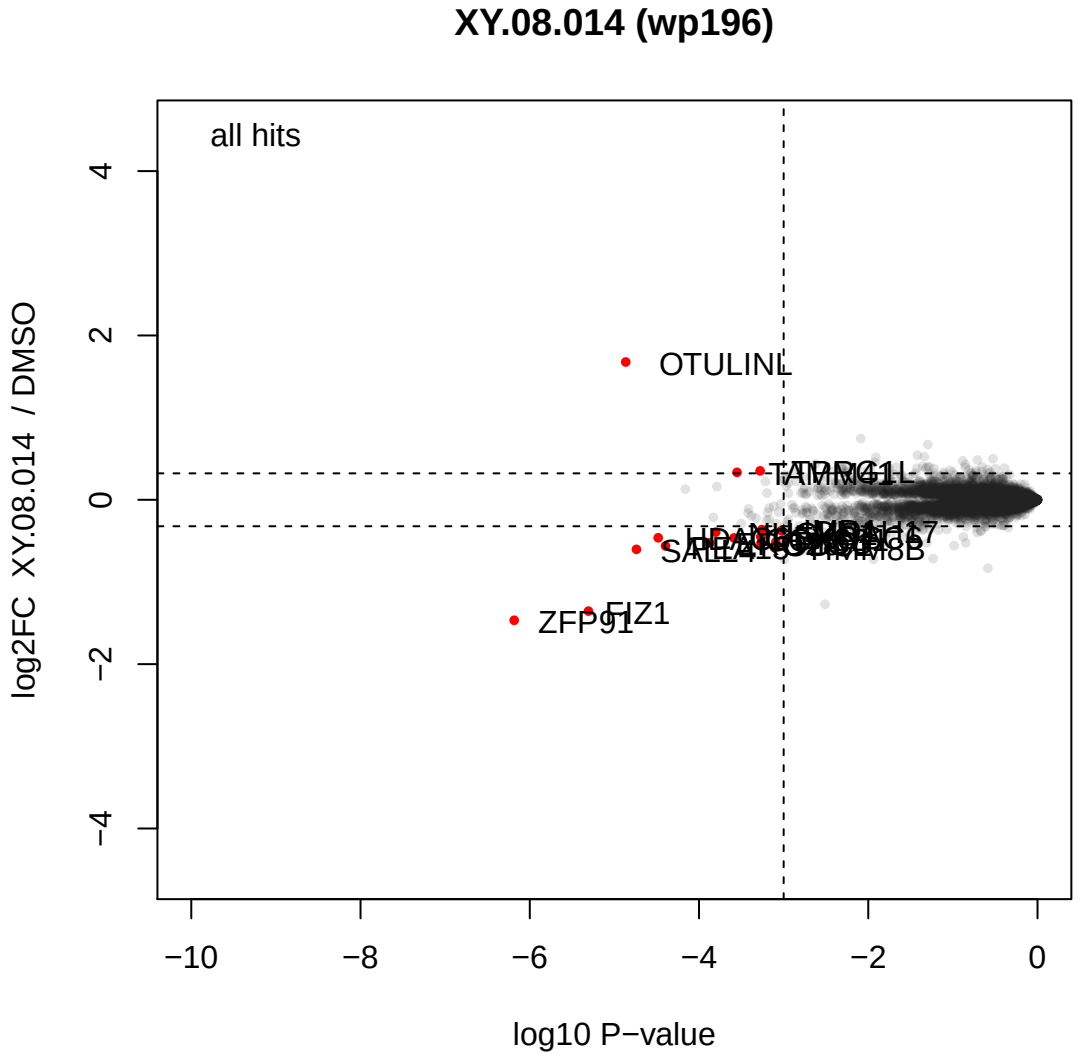

XY.07.177 (wp196)
uniprot hdac hits
log2FC XY.07.177 / DMSO
log10 P−value

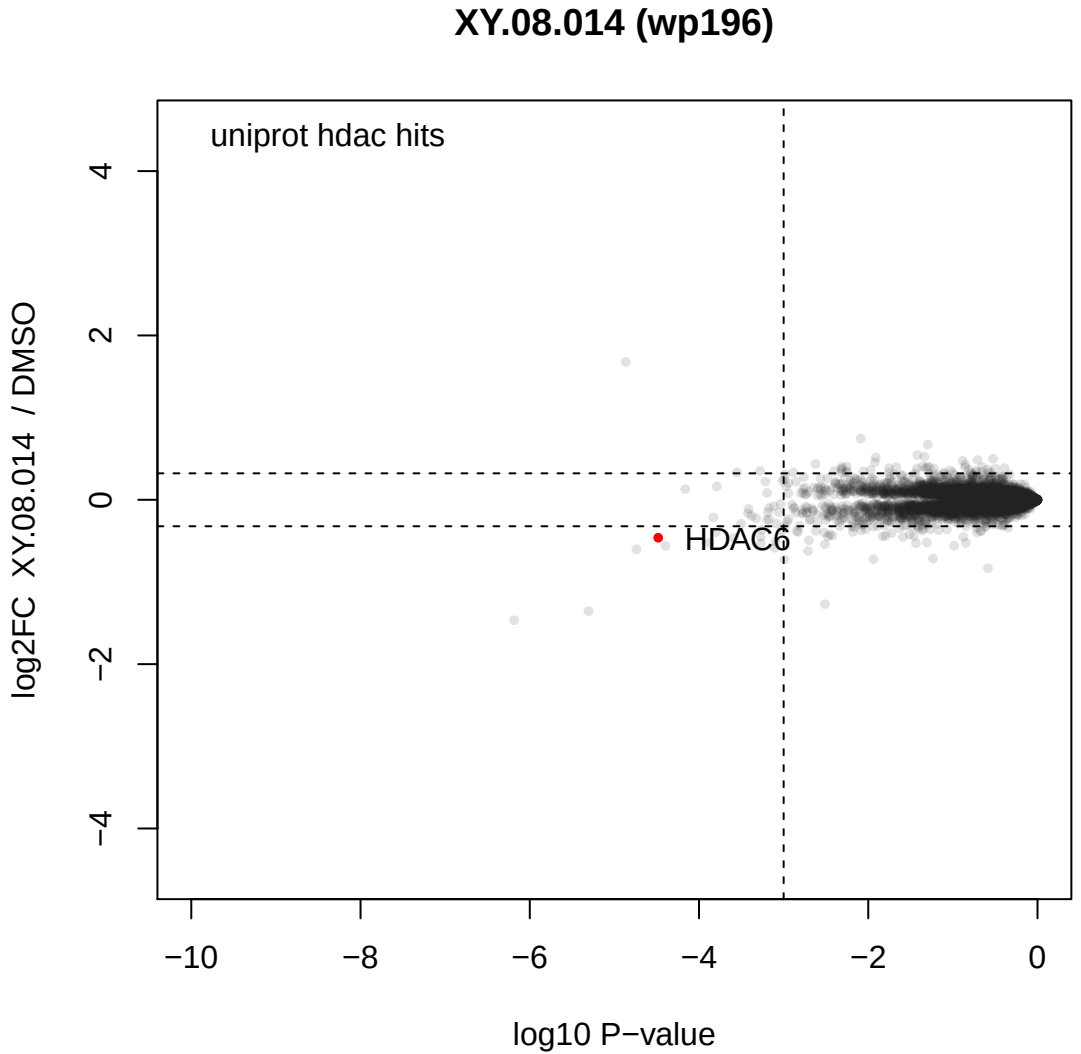

XY.07.187 (wp196)
all hits
log2FC XY.07.187 / DMSO
log10 P−value
RGS16
PER1
KDM
MCC
NCOR1
NCOR2
MIER1
MIER3
HDAC8
HDAC6
INSM2
GATA3
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

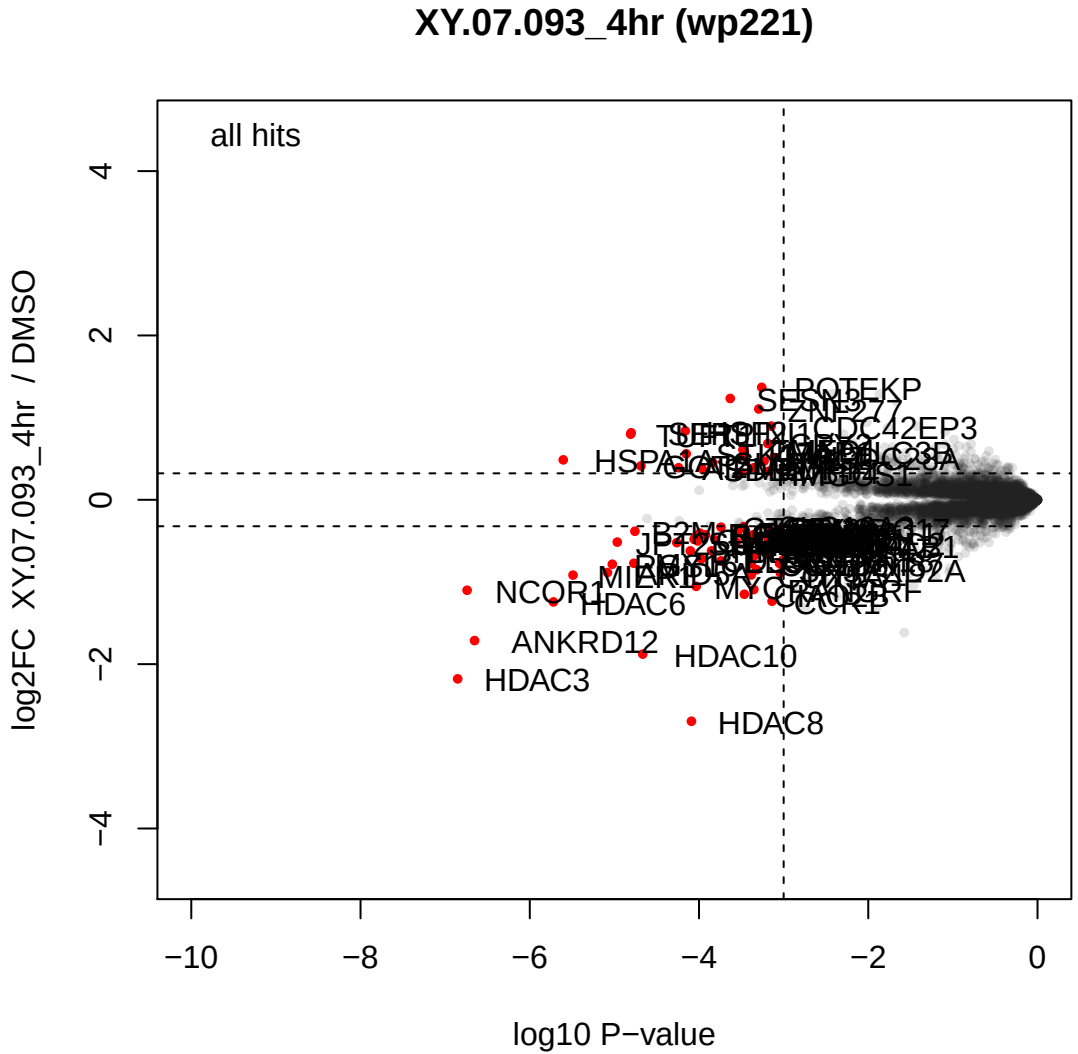

XY.07.187 (wp196)
uniprot hdac hits
log2FC XY.07.187 / DMSO
log10 P−value
HDAC2
HDAC1
HDAC6
HDAC3
HDAC8
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

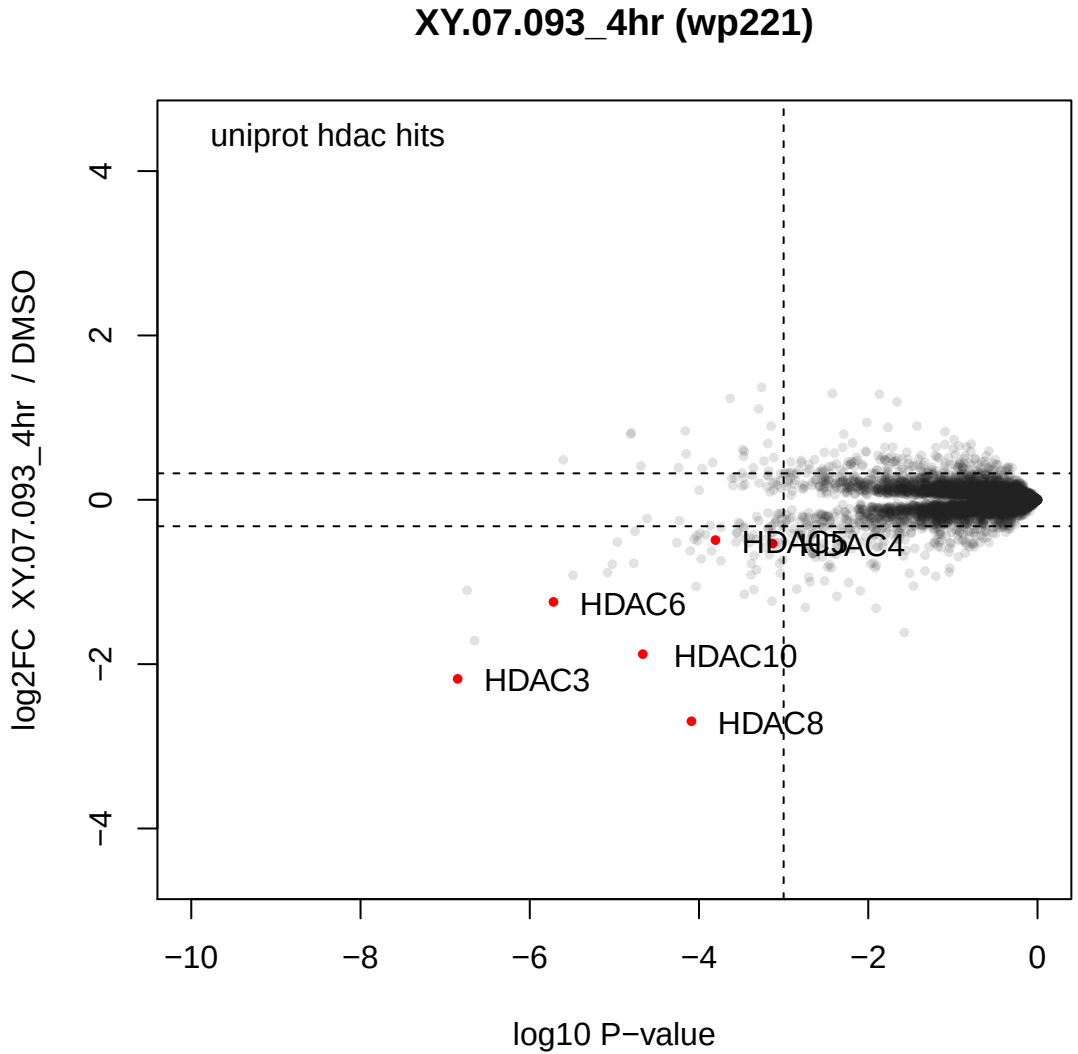

XY.07.189 (wp196)
all hits
log2FC XY.07.189 / DMSO
log10 P−value
NCOR1
HDAC3
KDM
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

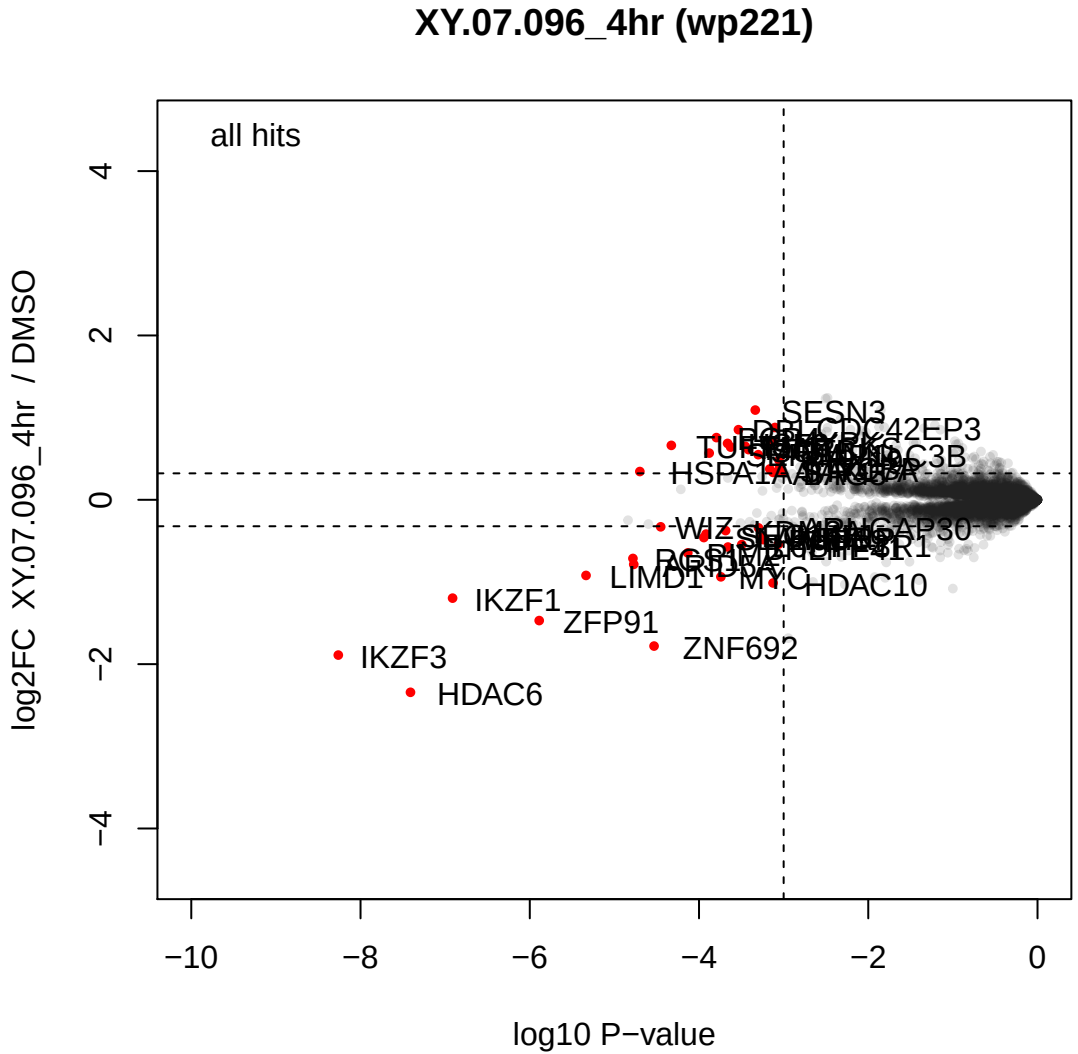

XY.07.189 (wp196)
uniprot hdac hits
log2FC XY.07.189 / DMSO
log10 P−value
HDAC3
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

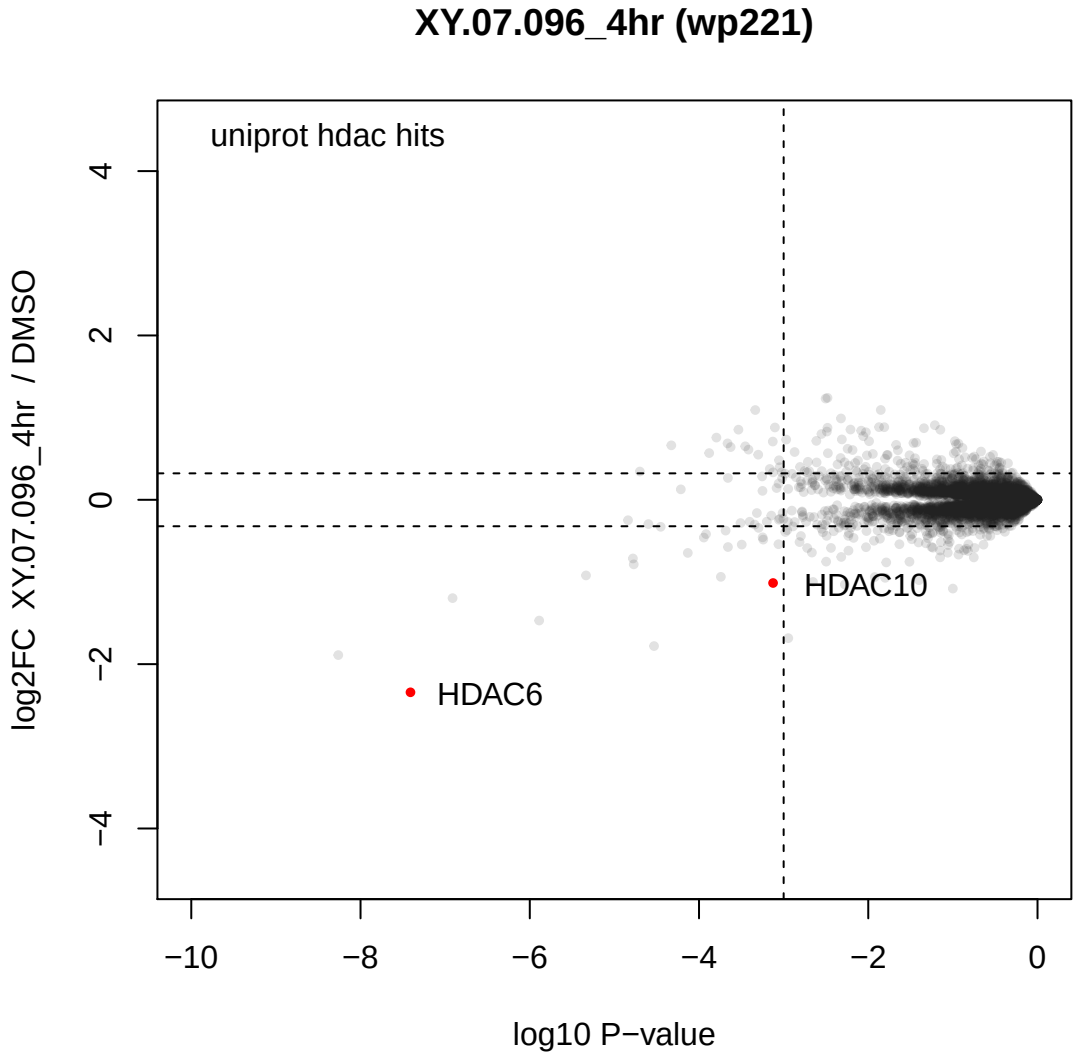

XY.08.014 (wp196)
all hits
OTULINL
ZFP91
FIZ1
log2FC XY.08.014 / DMSO
log10 P−value

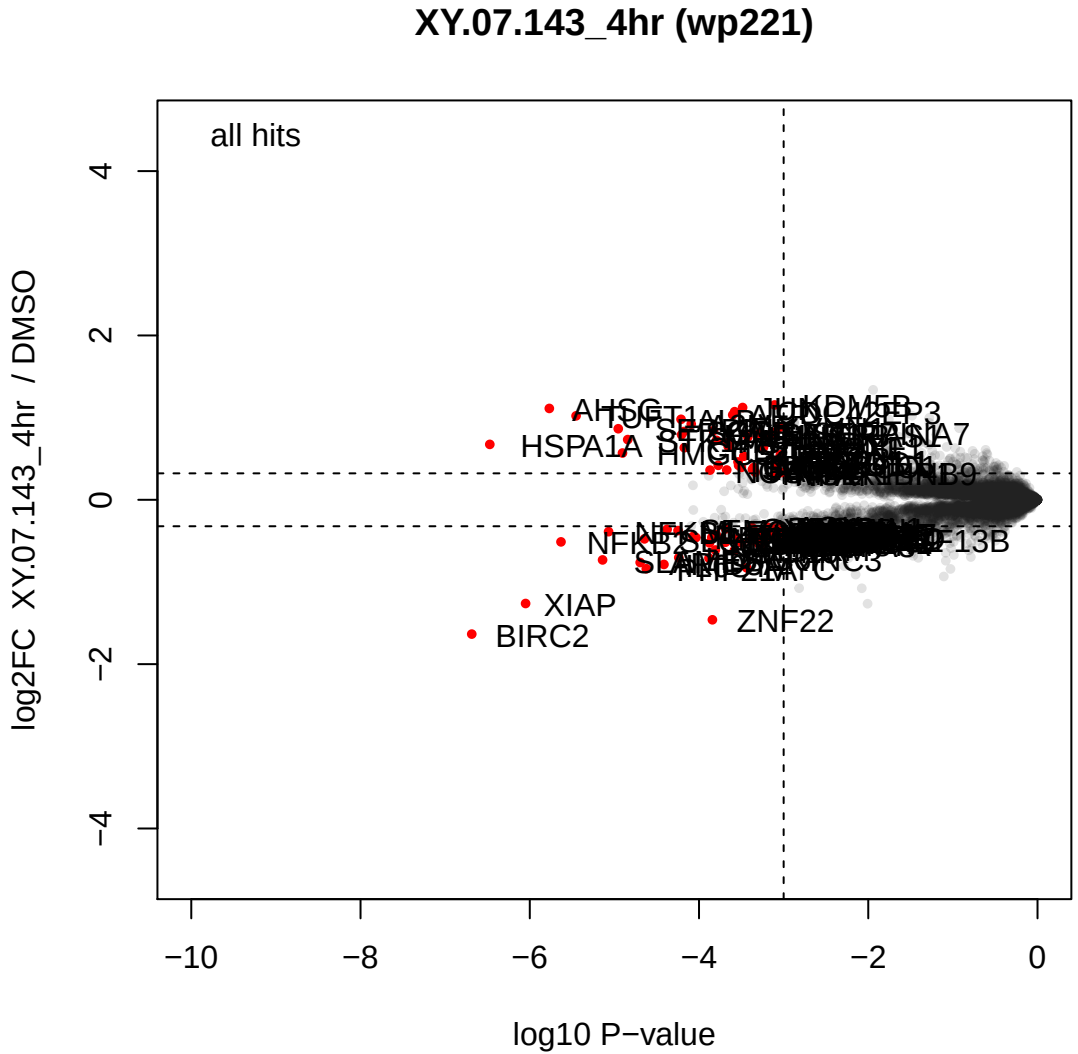

XY.08.014 (wp196)
uniprot hdac hits
HDAC6
log2FC XY.08.014 / DMSO
log10 P−value

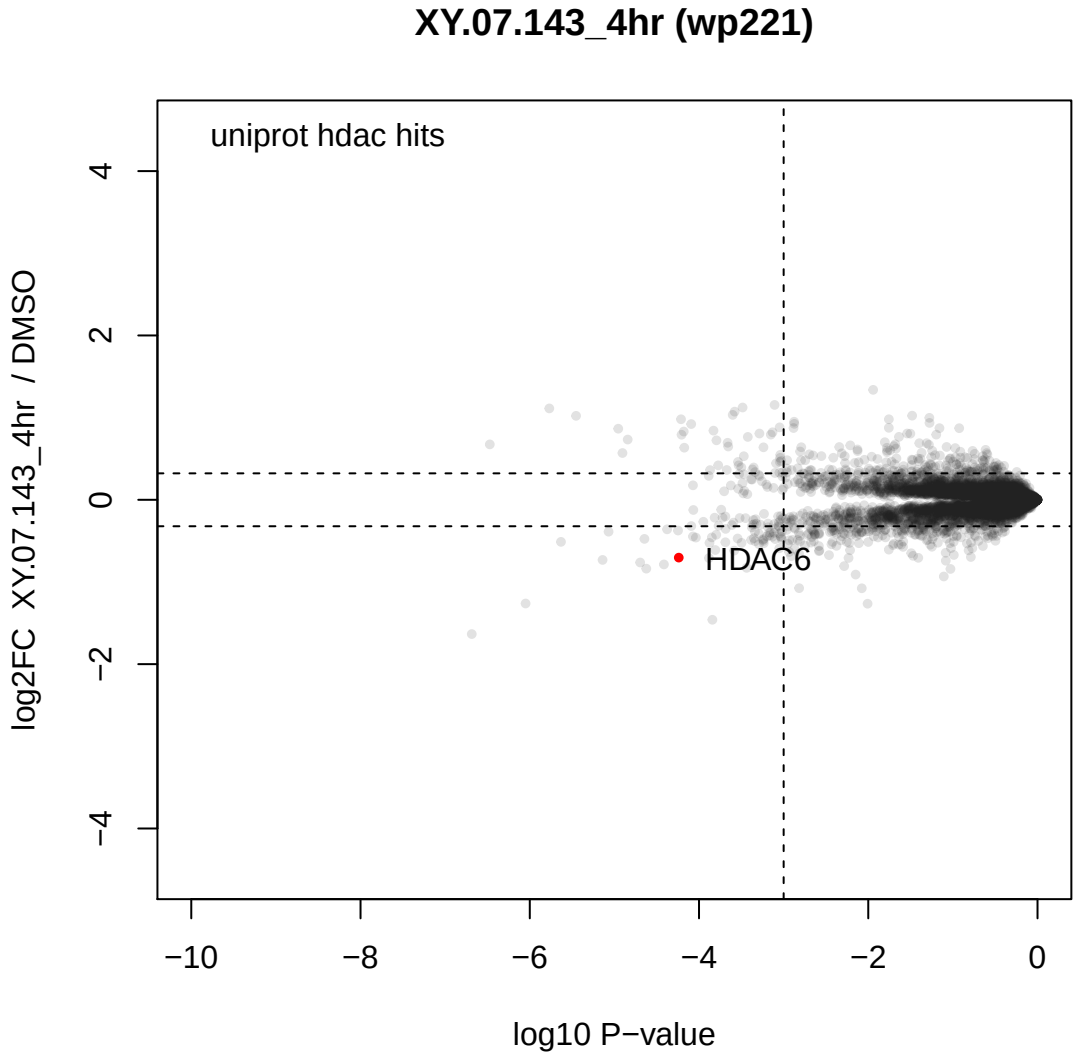

XY.07.093_4hr (wp221)
all hits
log2FC XY.07.093_4hr / DMSO
log10 P−value
HDAC6
HDAC10
HDAC3
HDAC8
ANKRD12
NCOR1

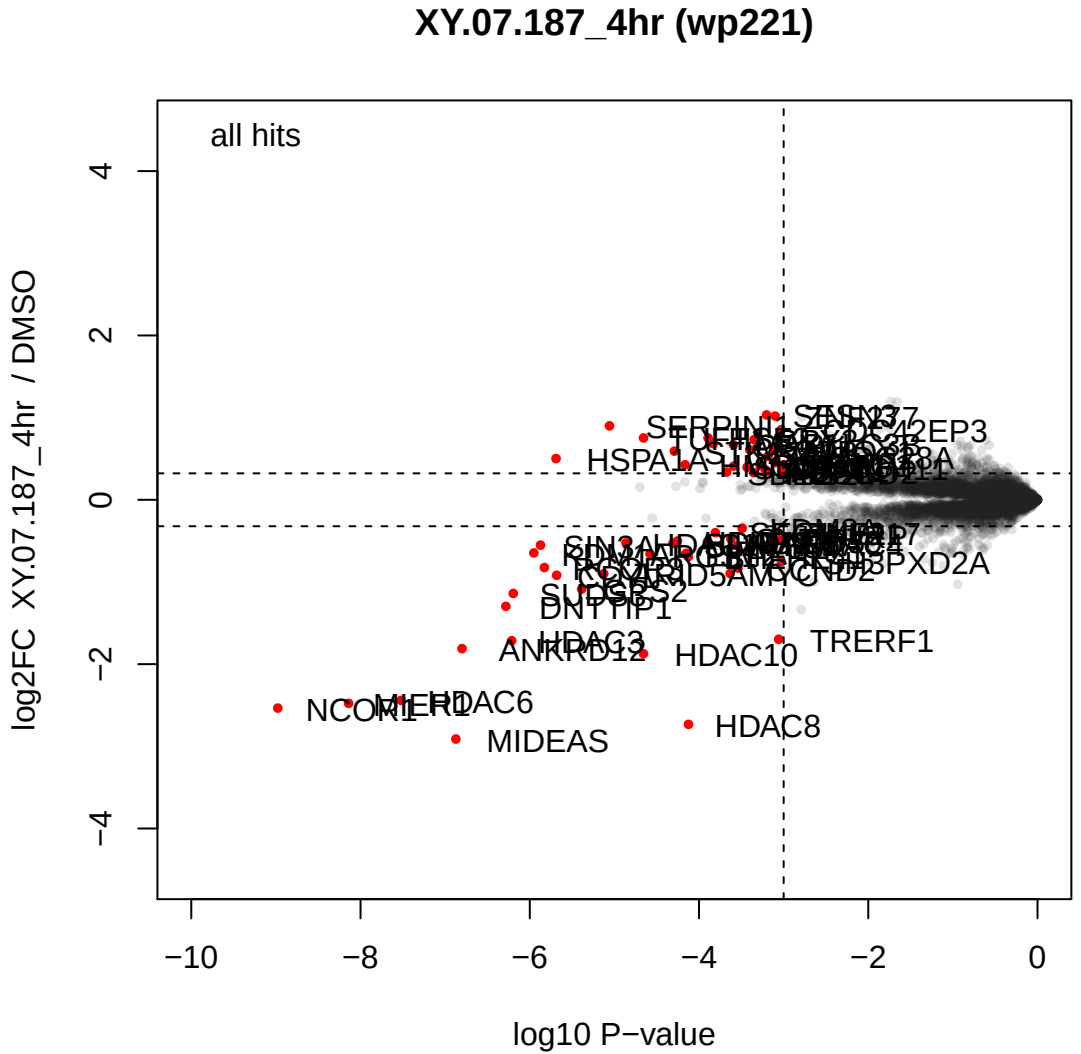

XY.07.093_4hr (wp221)
uniprot hdac hits
log2FC XY.07.093_4hr / DMSO
log10 P−value
HDAC5
HDAC4
HDAC6
HDAC10
HDAC3
HDAC8

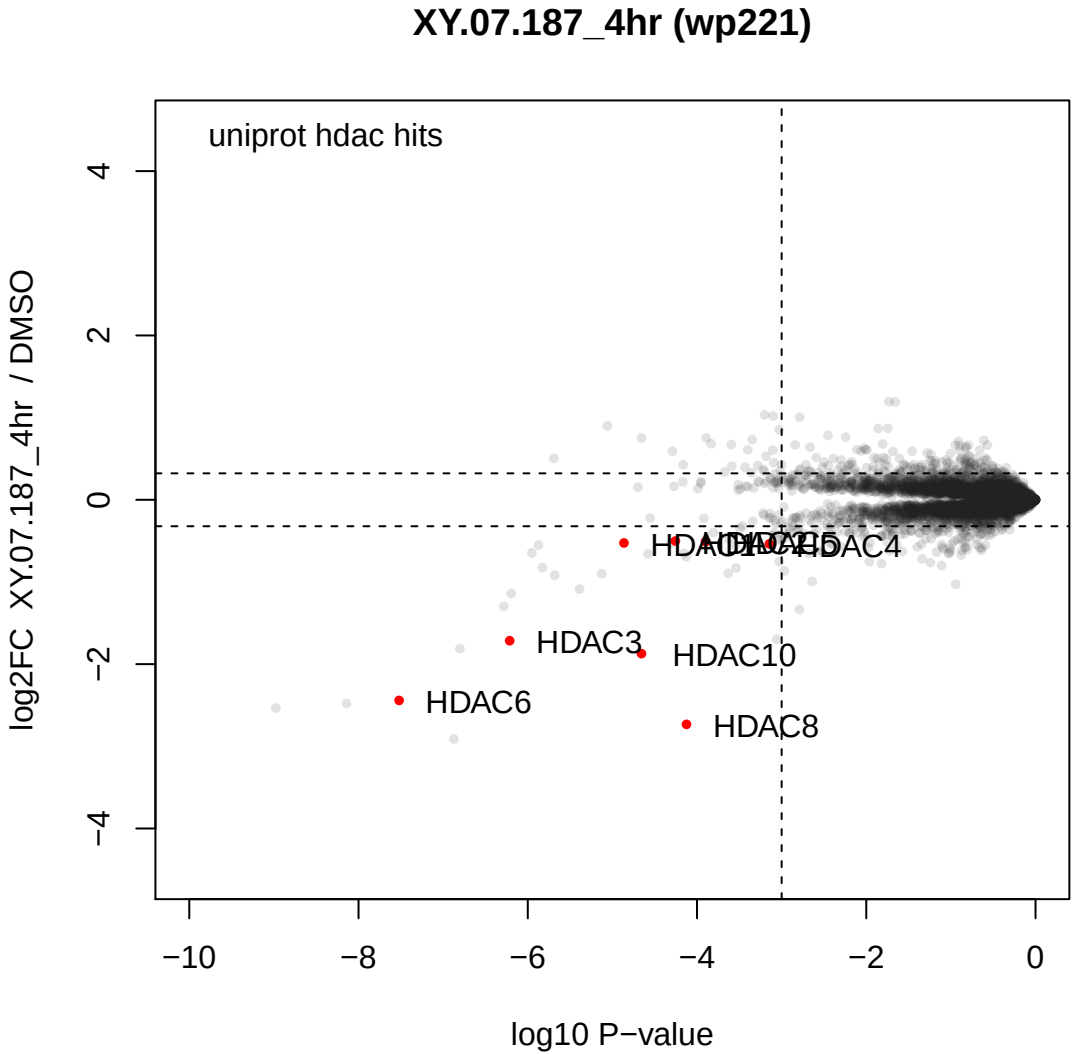

XY.07.096_4hr (wp221)
all hits
log2FC XY.07.096_4hr / DMSO
log10 P−value
SESN3
CDC42EP3
HSPA1A
WIZ
LIMD1
MYC
HDAC10
IKZF1
ZFP91
ZNF692
IKZF3
HDAC6

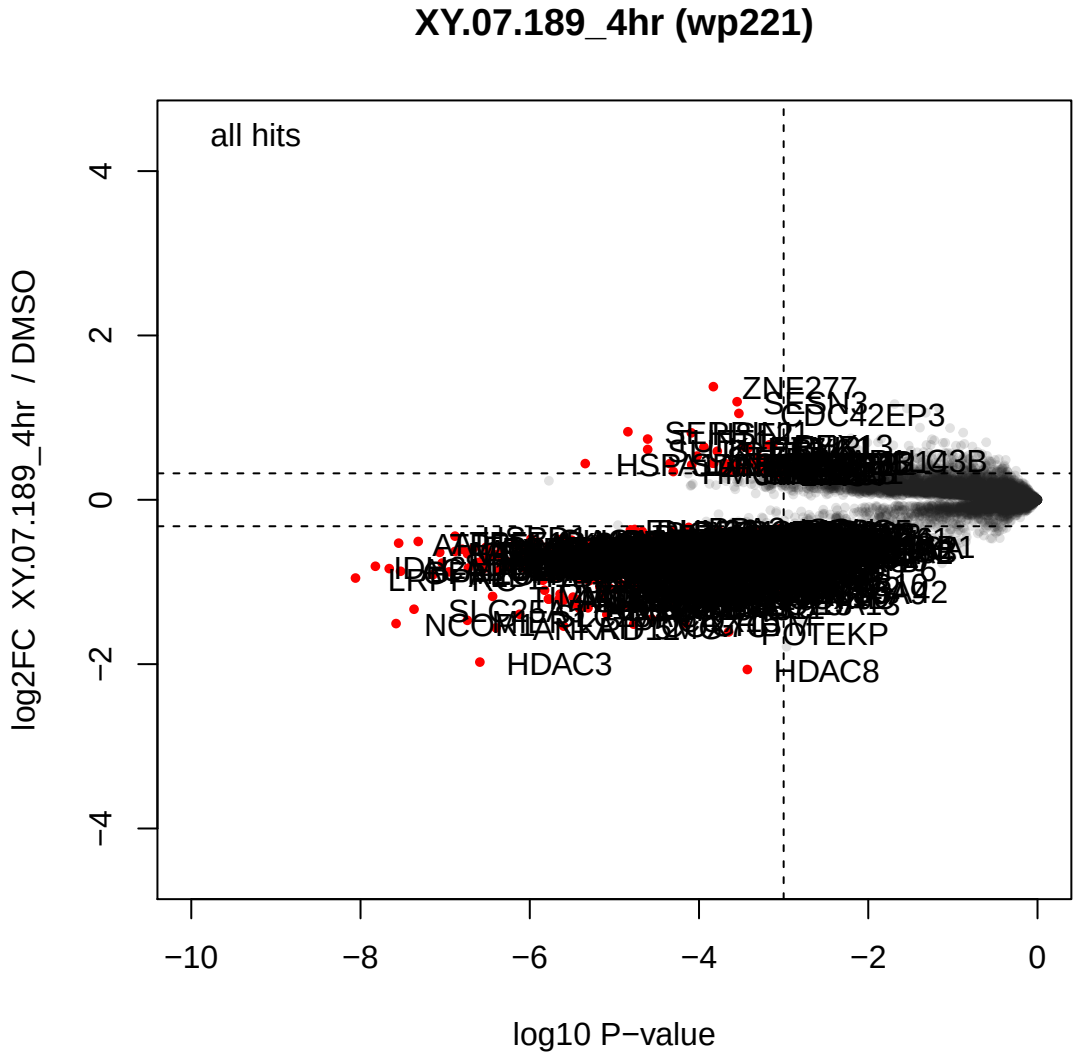

XY.07.096_4hr (wp221)
uniprot hdac hits
log2FC XY.07.096_4hr / DMSO
log10 P−value
HDAC10
HDAC6

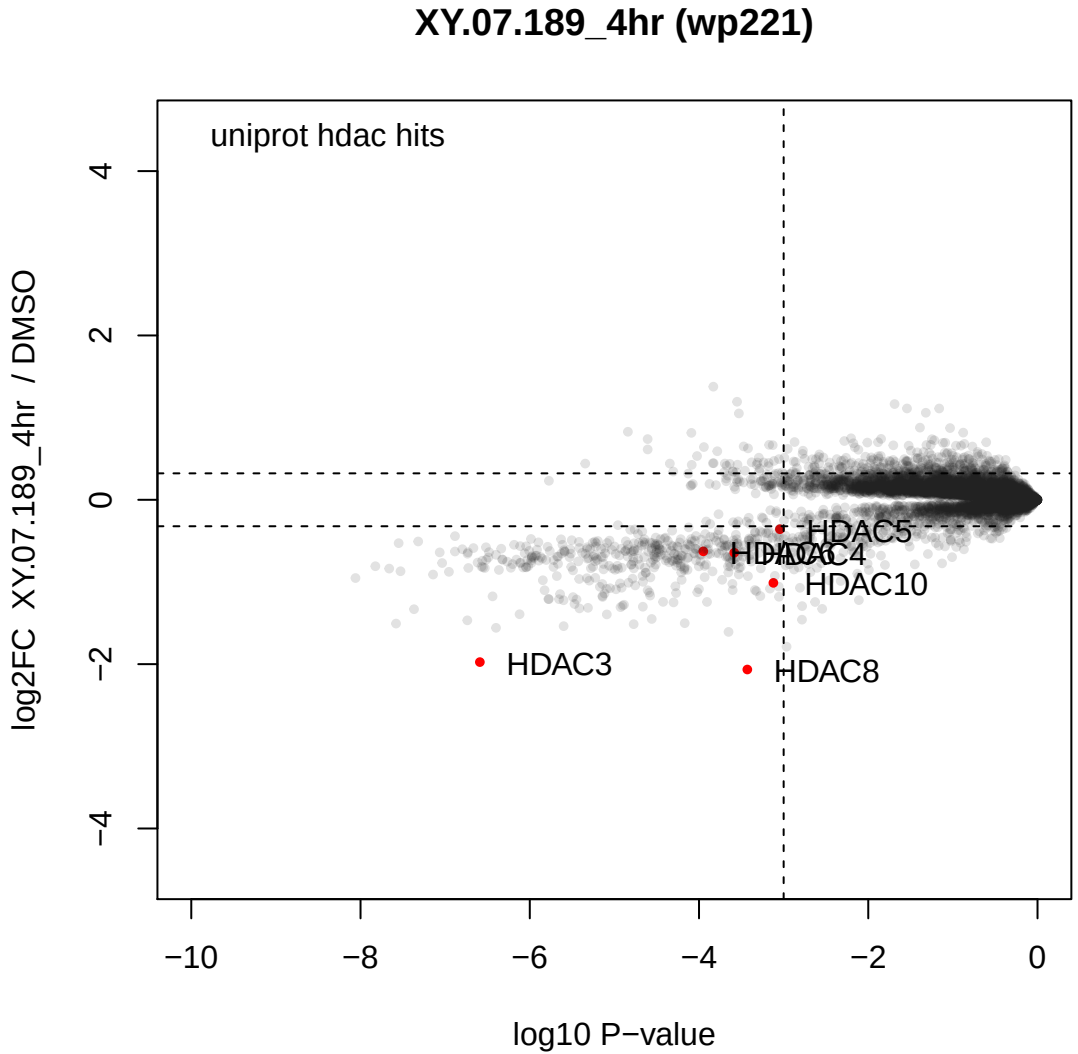

XY.07.143_4hr (wp221)
all hits
log2FC XY.07.143_4hr / DMSO
log10 P−value
AHSG
HSPA1A
NFKB2
XIAP
BIRC2
ZNF22
F13B
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

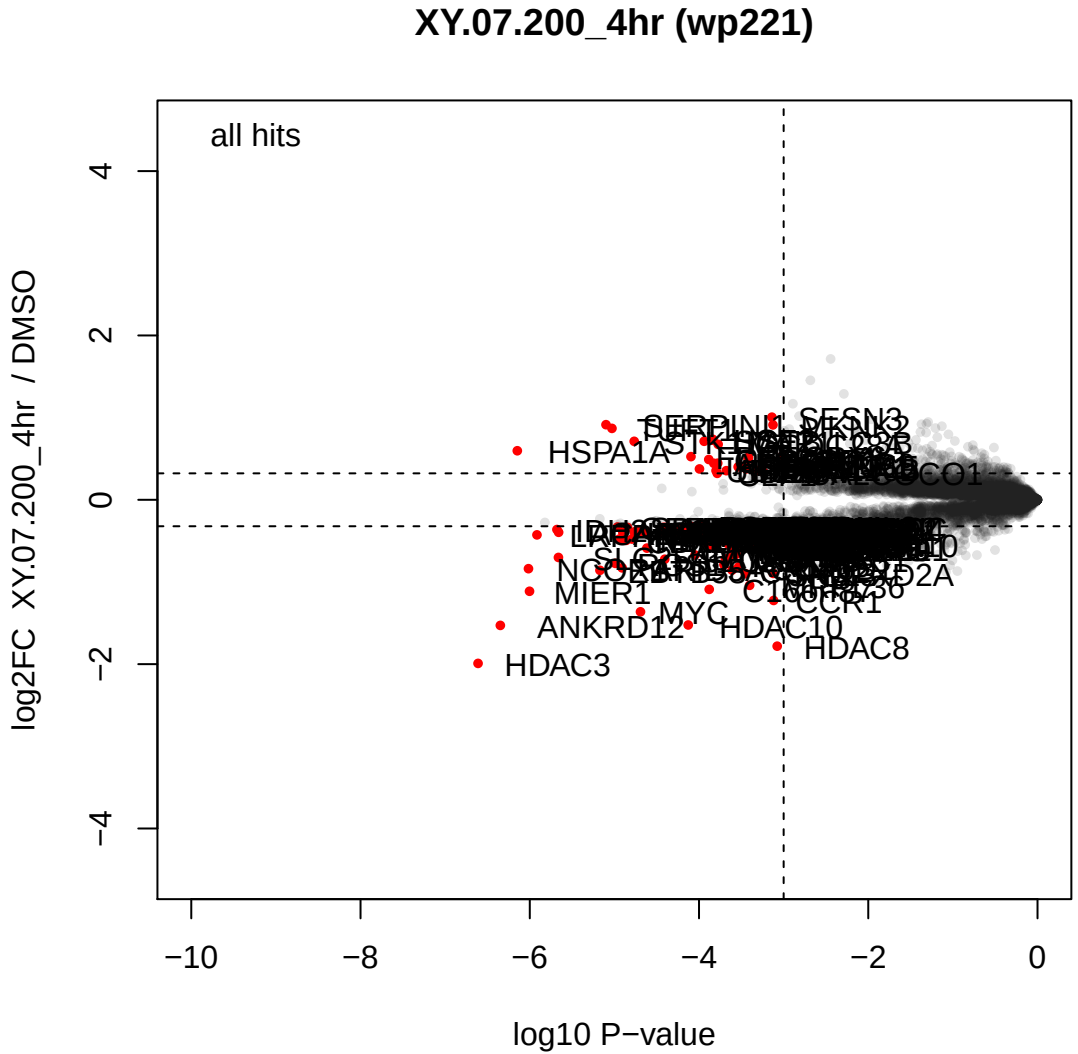

XY.07.143_4hr (wp221)
uniprot hdac hits
log2FC XY.07.143_4hr / DMSO
log10 P−value
HDAC6
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

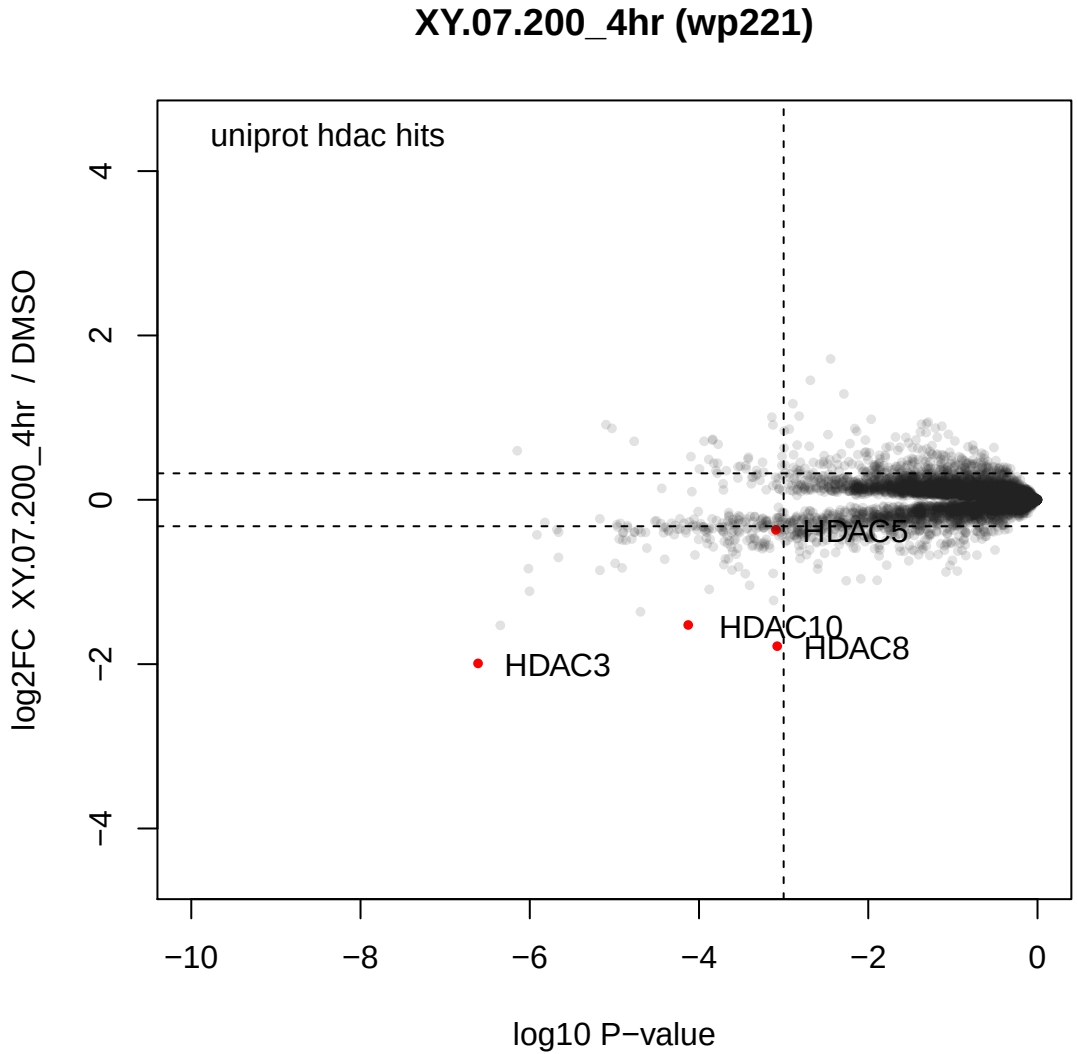

XY.07.187_4hr (wp221)
all hits
log2FC XY.07.187_4hr / DMSO
log10 P−value
HSPA1A
DNTTIP1
HDAC3
ANKRD12
HDAC10
TRERF1
NCOR1
MIER1
HDAC6
MIDEAS
HDAC8
PXD2A

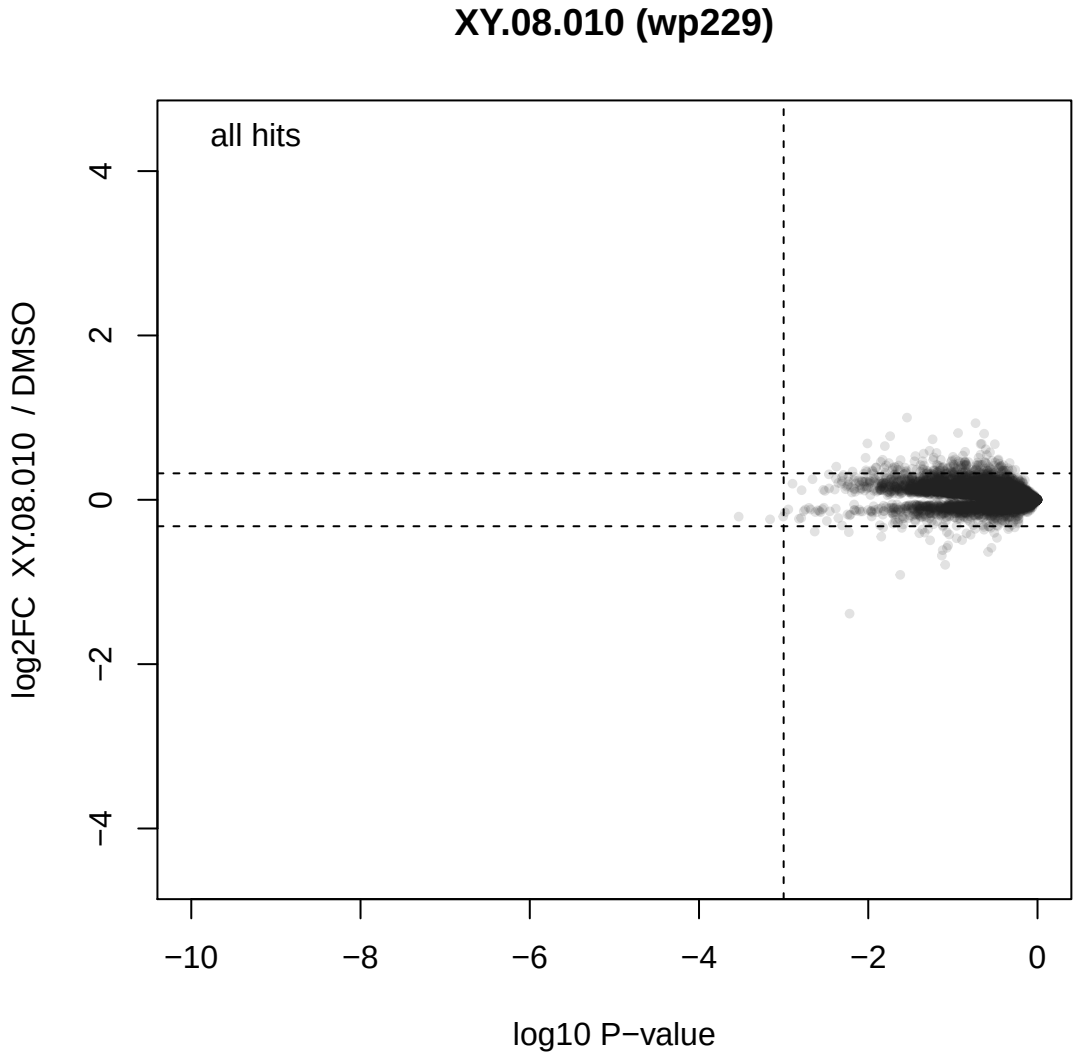

XY.07.187_4hr (wp221)
uniprot hdac hits
log2FC XY.07.187_4hr / DMSO
log10 P−value
HDAC4
HDAC3
HDAC10
HDAC6
HDAC8

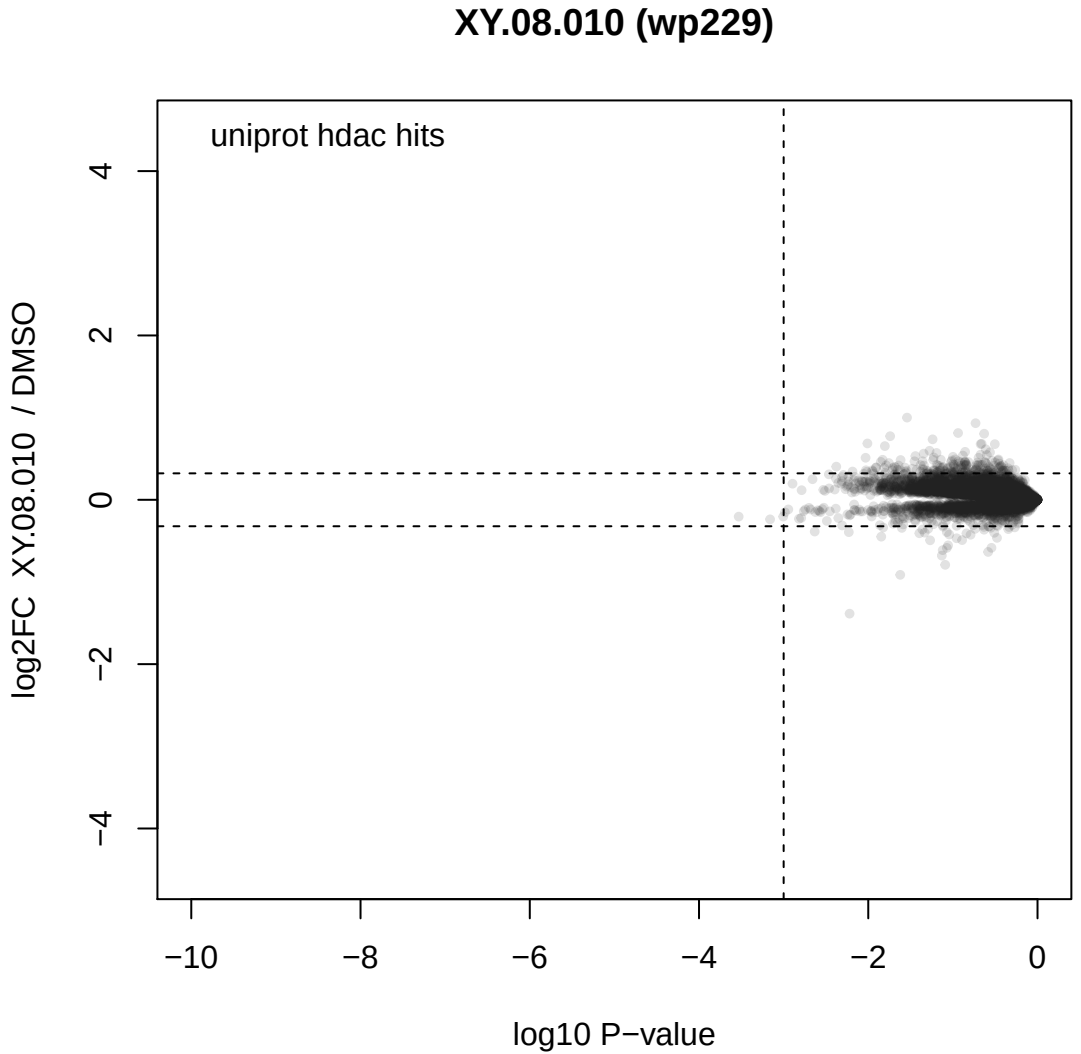

XY.07.189_4hr (wp221)
all hits
log2FC XY.07.189_4hr / DMSO
log10 P−value
ZNF277
SESN3
SEDC42EP3
HSP
HDAC3
HDAC8
PCTEKP

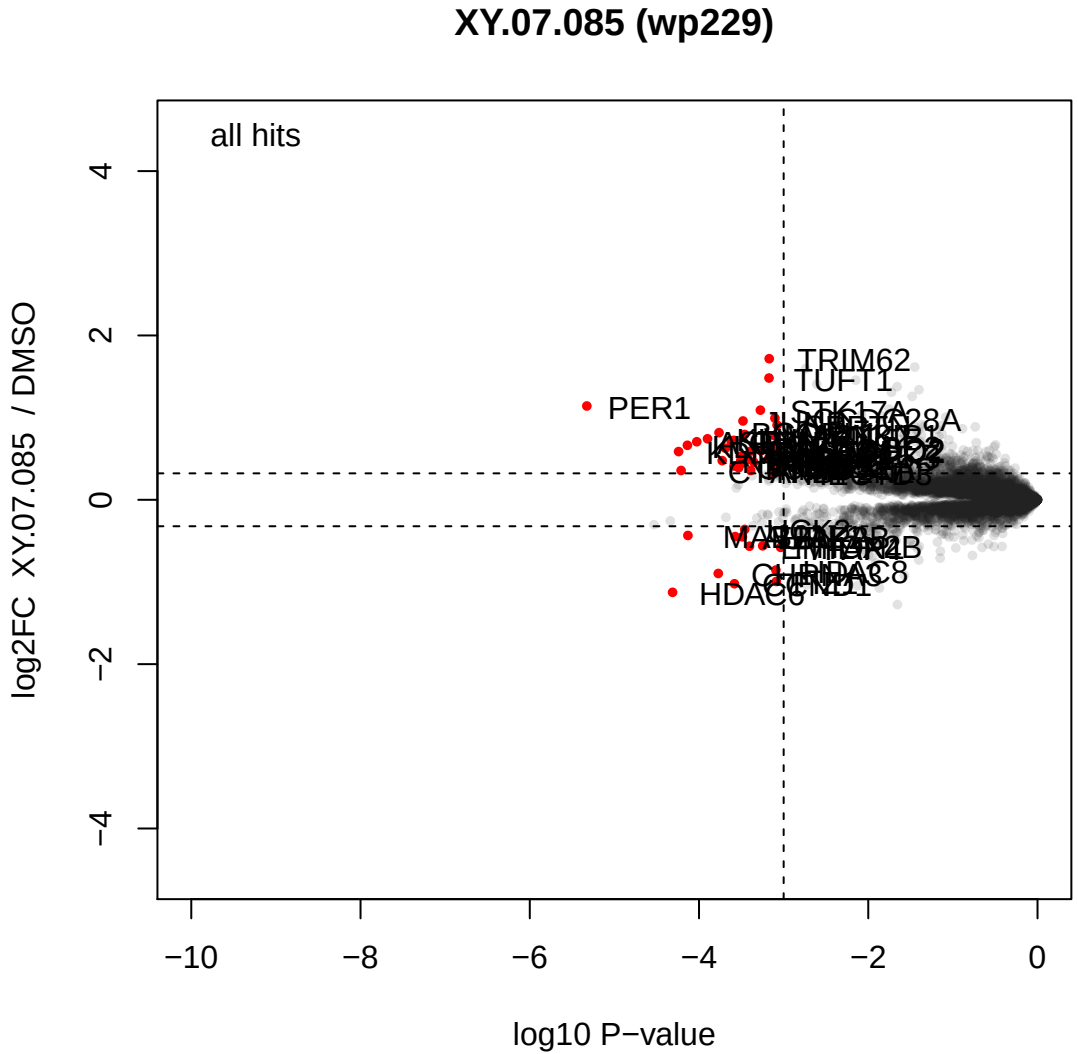

XY.07.189_4hr (wp221)
uniprot hdac hits
log2FC XY.07.189_4hr / DMSO
log10 P−value
HDAC5
HDAC4
HDAC10
HDAC3
HDAC8

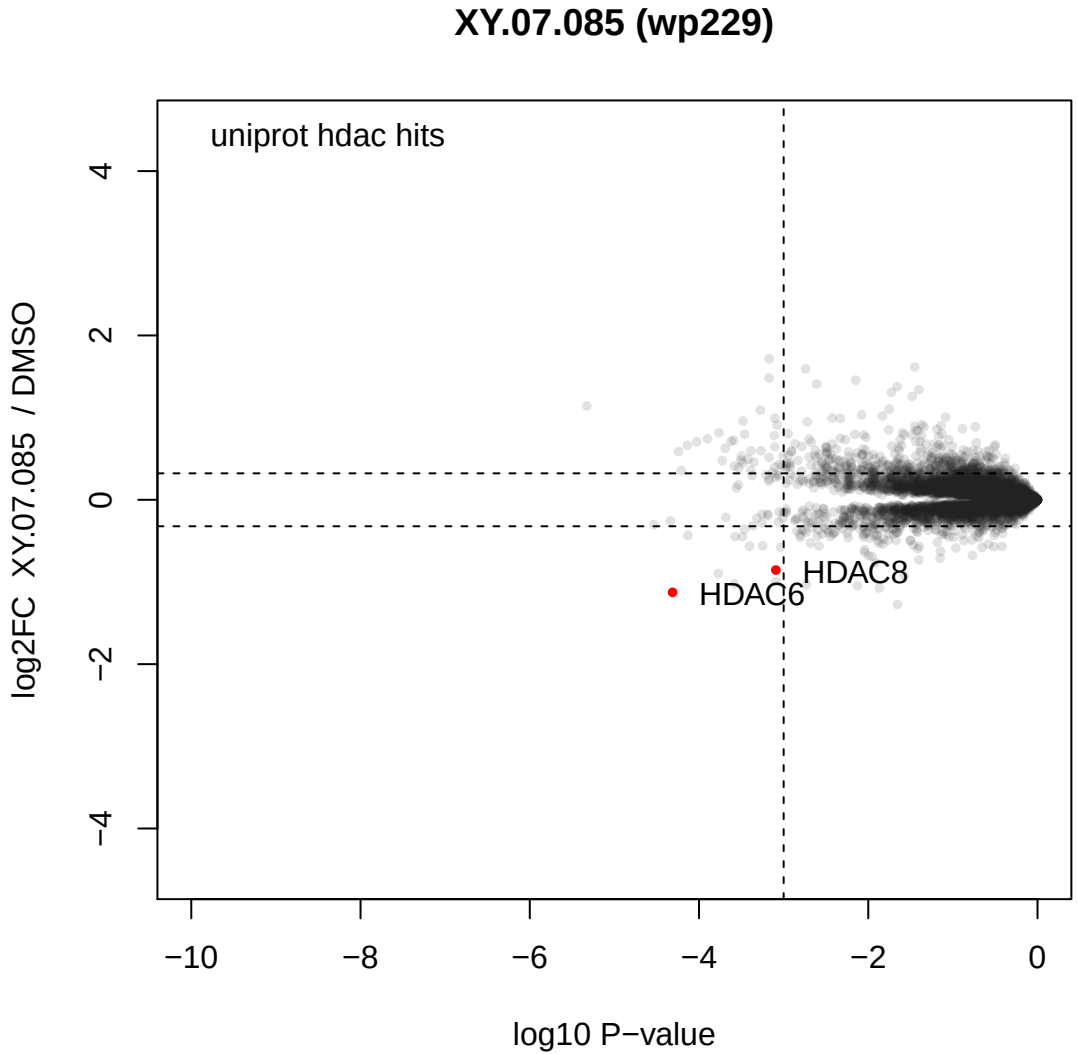

XY.07.200_4hr (wp221)
all hits
log2FC XY.07.200_4hr / DMSO
log10 P−value
HSPA1A
MIER1
MYC
ANKRD12
HDAC10
HDAC8
HDAC3
CCR1
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

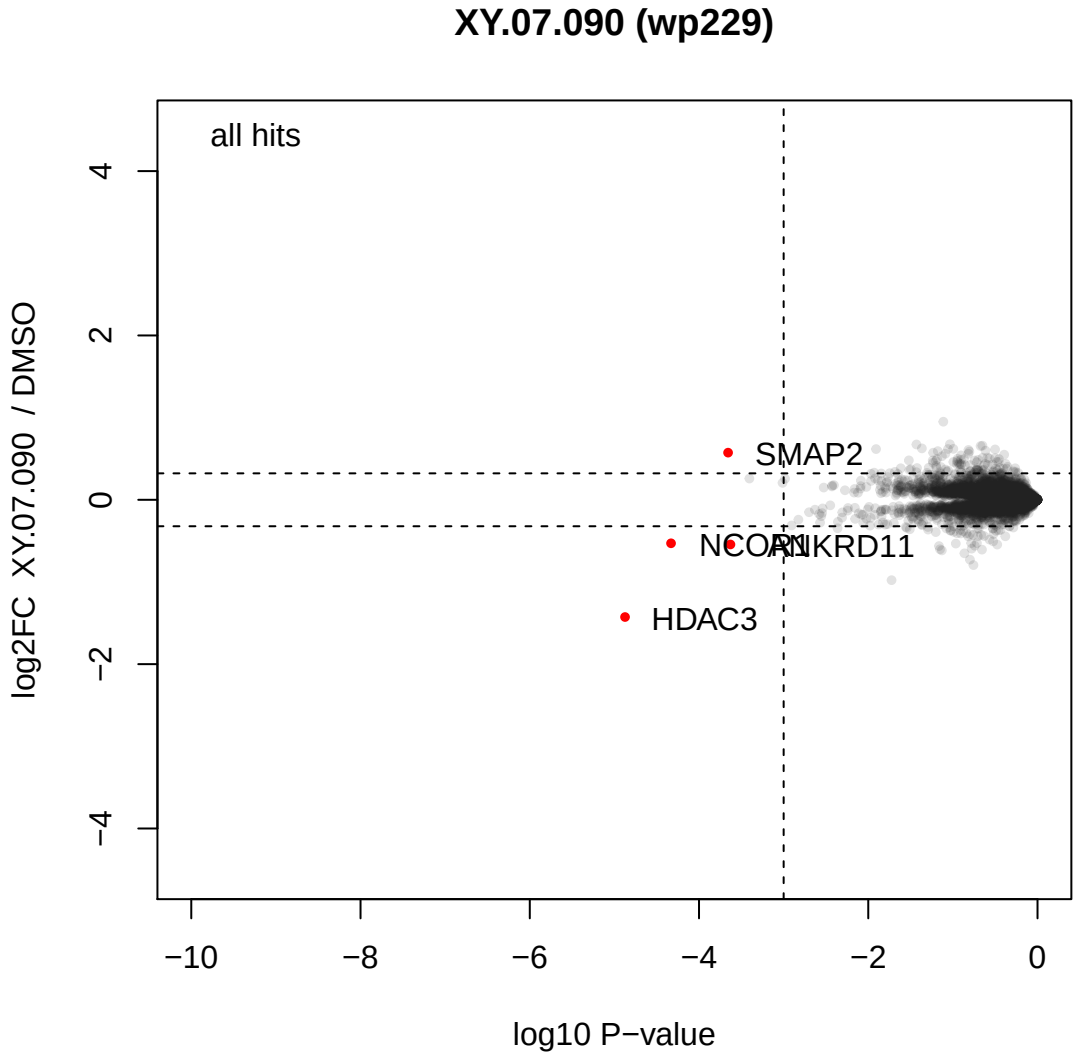

XY.07.200_4hr (wp221)
uniprot hdac hits
log2FC XY.07.200_4hr / DMSO
log10 P−value
HDAC5
HDAC10
HDAC8
HDAC3
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

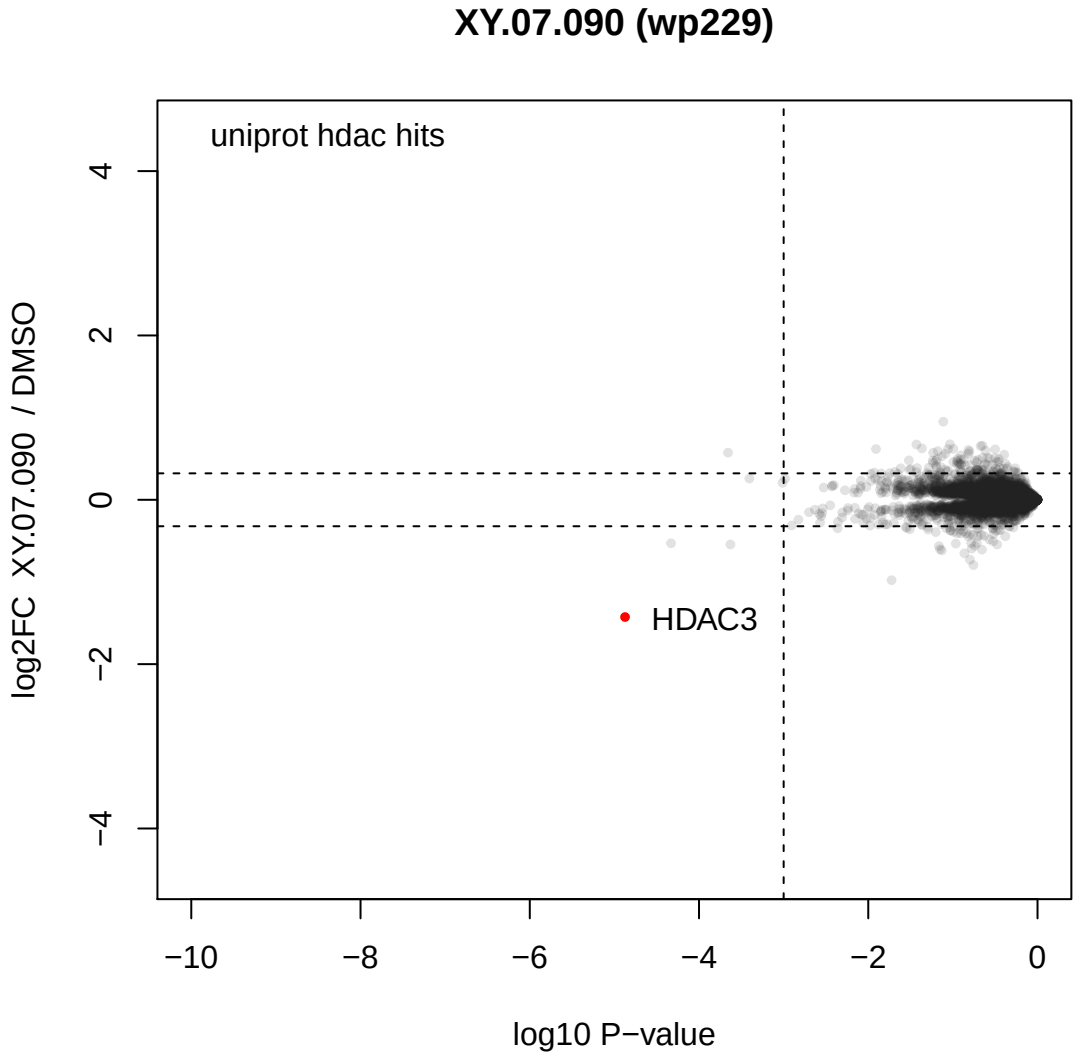

XY.08.010 (wp229)
all hits
log2FC XY.08.010 / DMSO
4
2
0
−2
−4
−10
−8
−6
−4
−2
0
log10 P−value

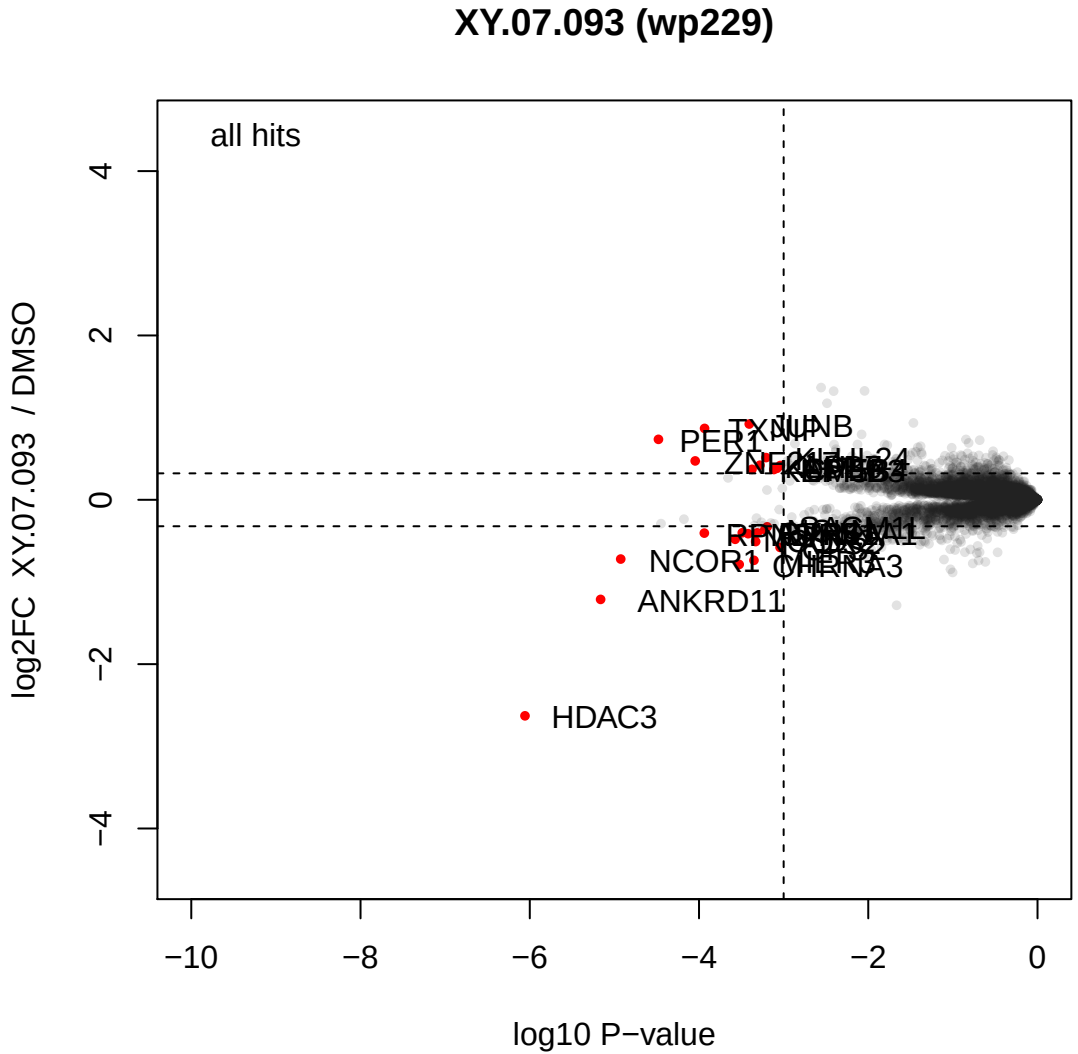

XY.08.010 (wp229)
uniprot hdac hits
log2FC XY.08.010 / DMSO
4
2
0
−2
−4
−10
−8
−6
−4
−2
0
log10 P−value

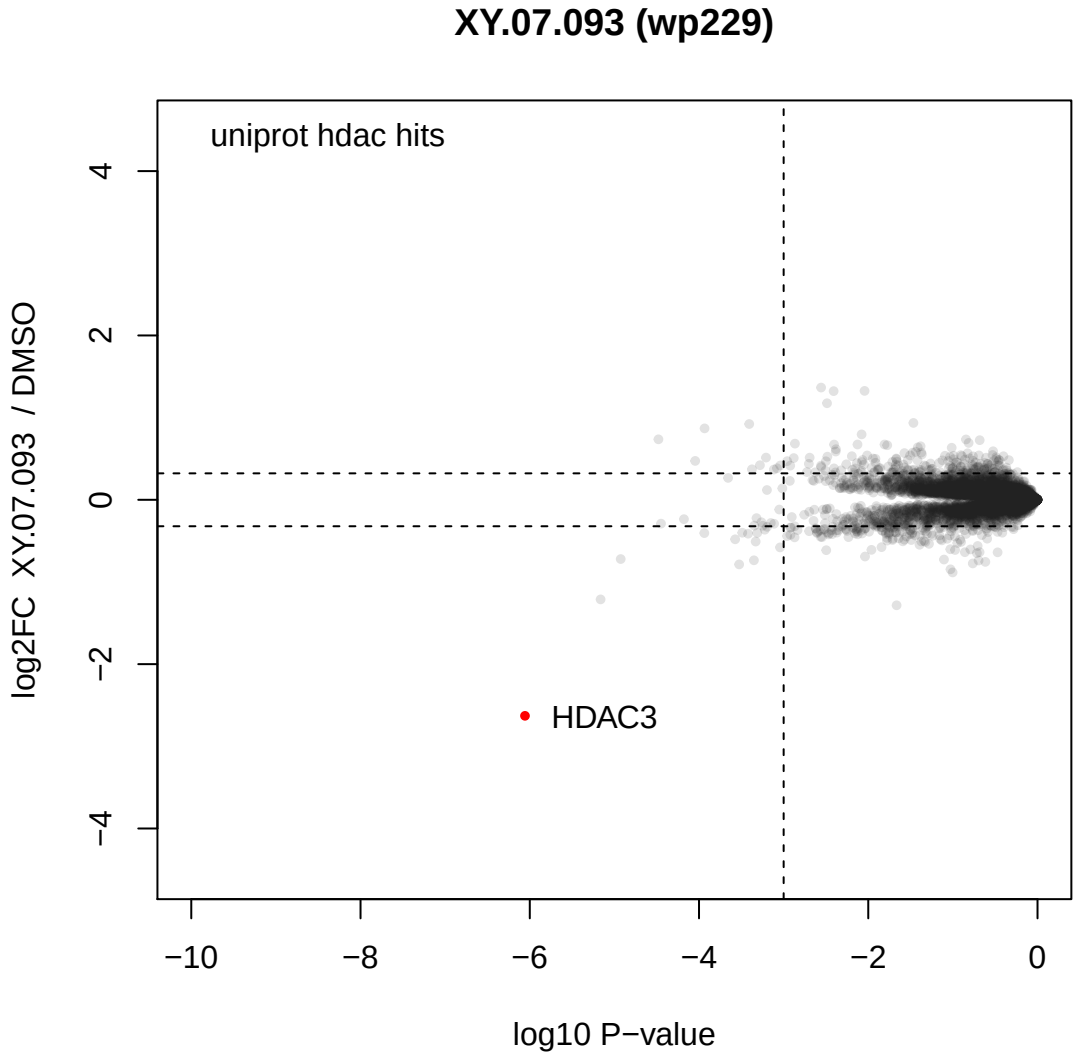

XY.07.085 (wp229)
all hits
log2FC XY.07.085 / DMSO
log10 P−value
PER1
TRIM62
TUFT1
HDAC6
HDAC8

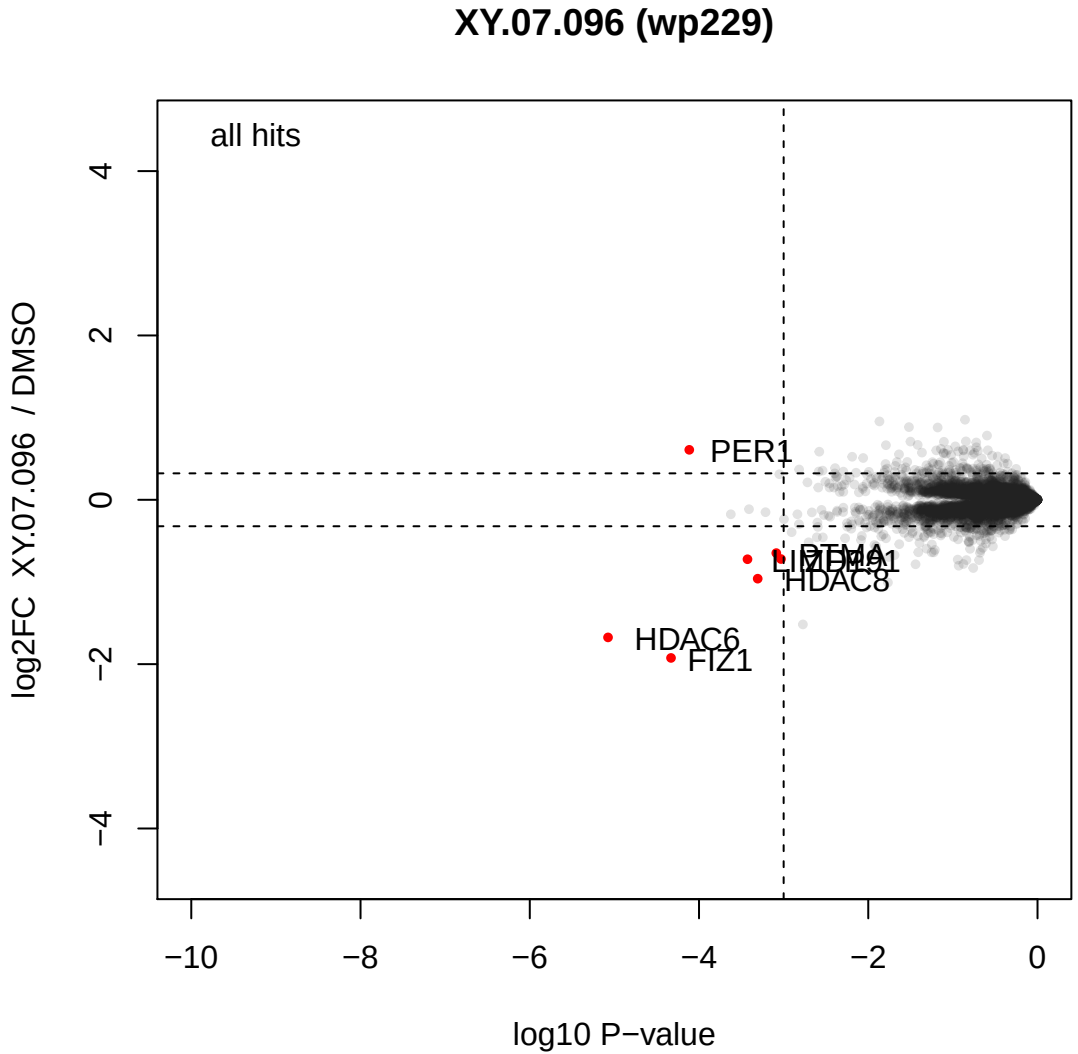

XY.07.085 (wp229)
uniprot hdac hits
log2FC XY.07.085 / DMSO
log10 P−value
HDAC6
HDAC8

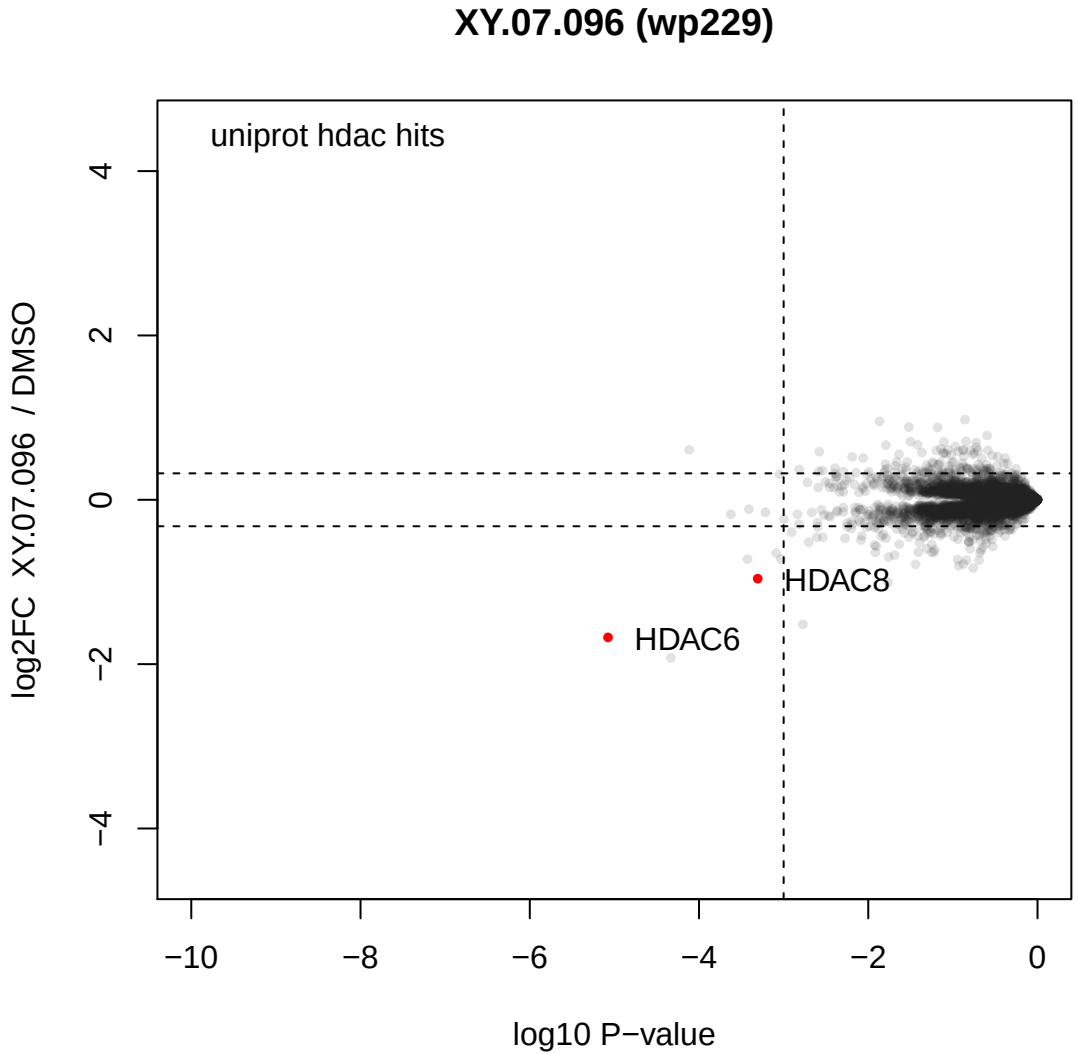

XY.07.090 (wp229)
all hits
SMAP2
NCOR1
NKRD11
HDAC3
log2FC XY.07.090 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

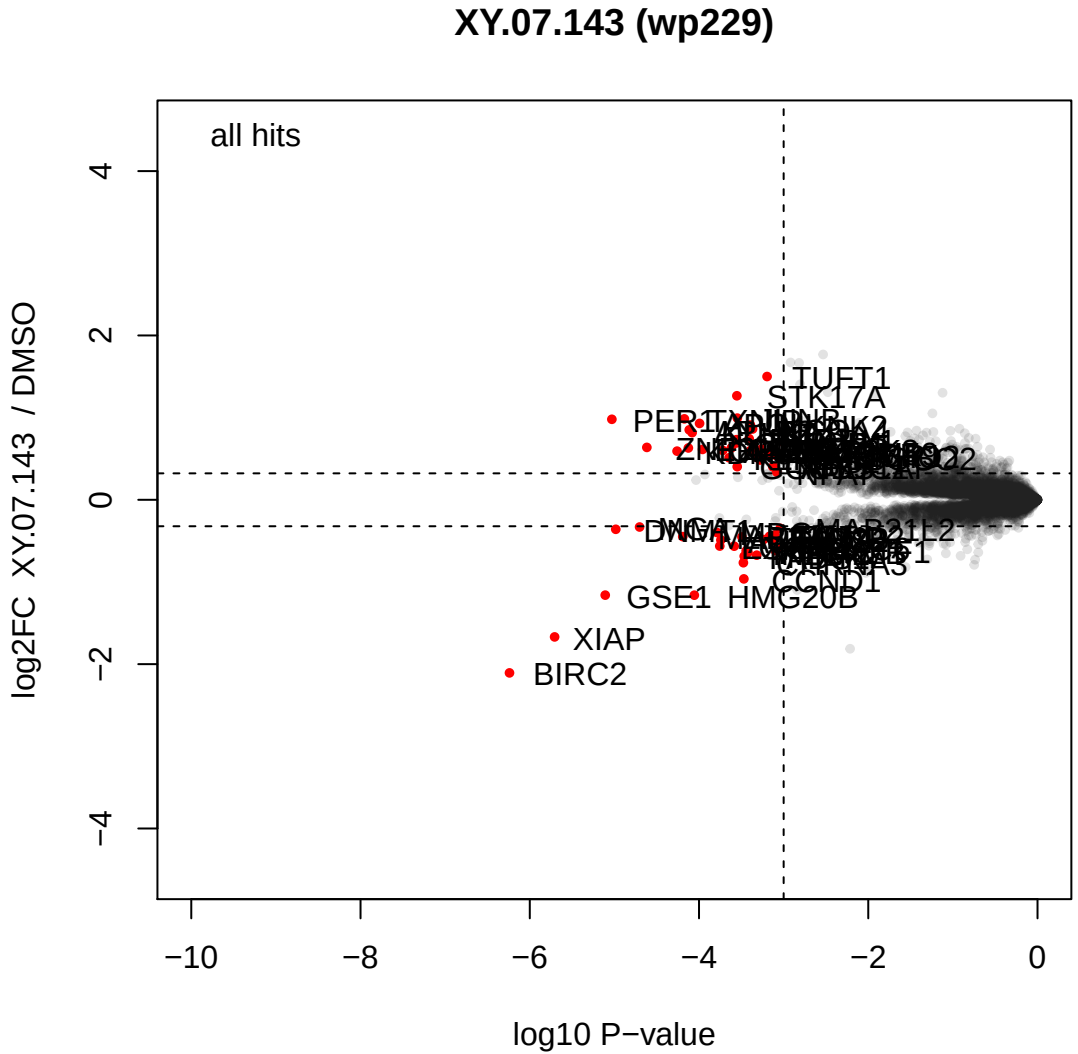

XY.07.090 (wp229)
uniprot hdac hits
HDAC3
log2FC XY.07.090 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

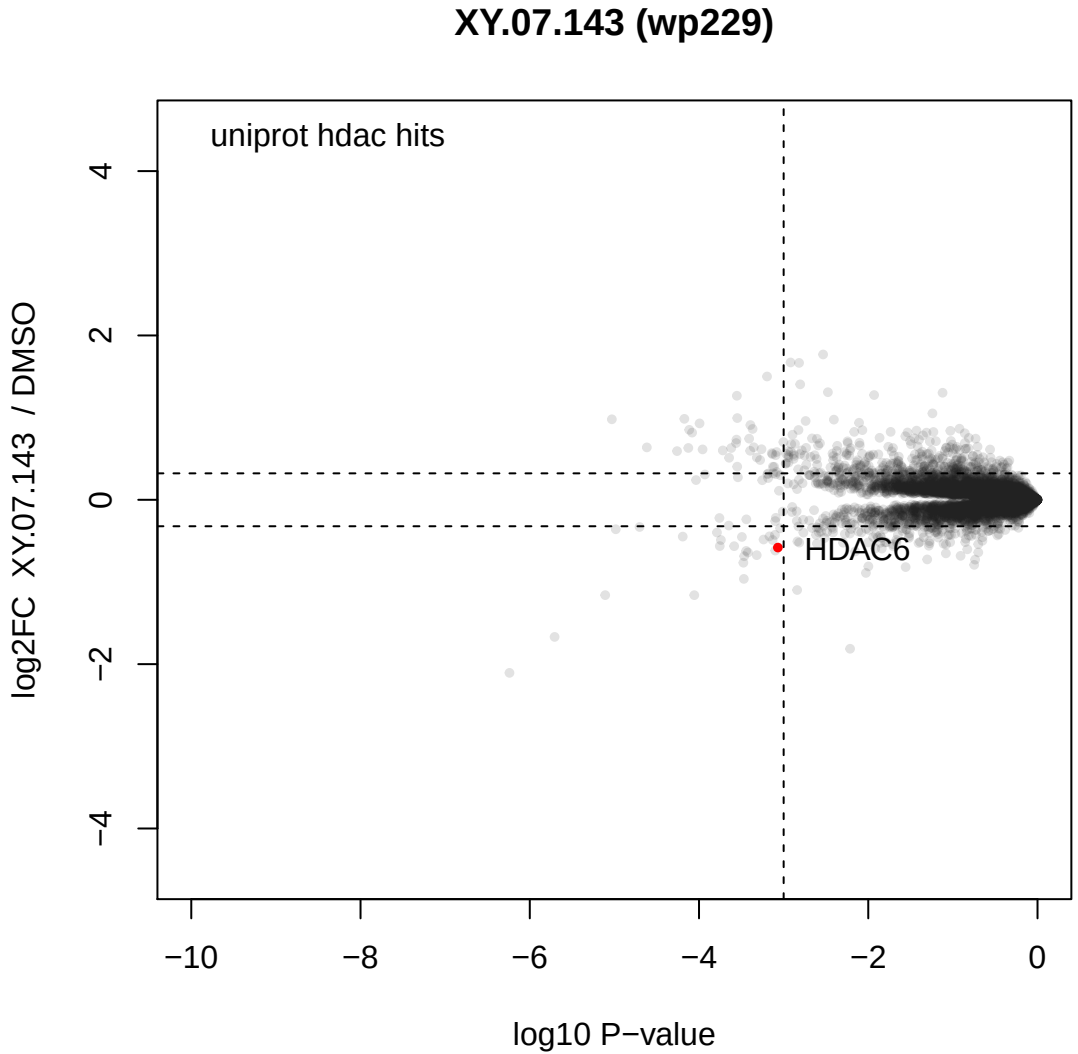

XY.07.093 (wp229)
all hits
log2FC XY.07.093 / DMSO
log10 P−value
HDAC3
NCOR1
ANKRD11
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

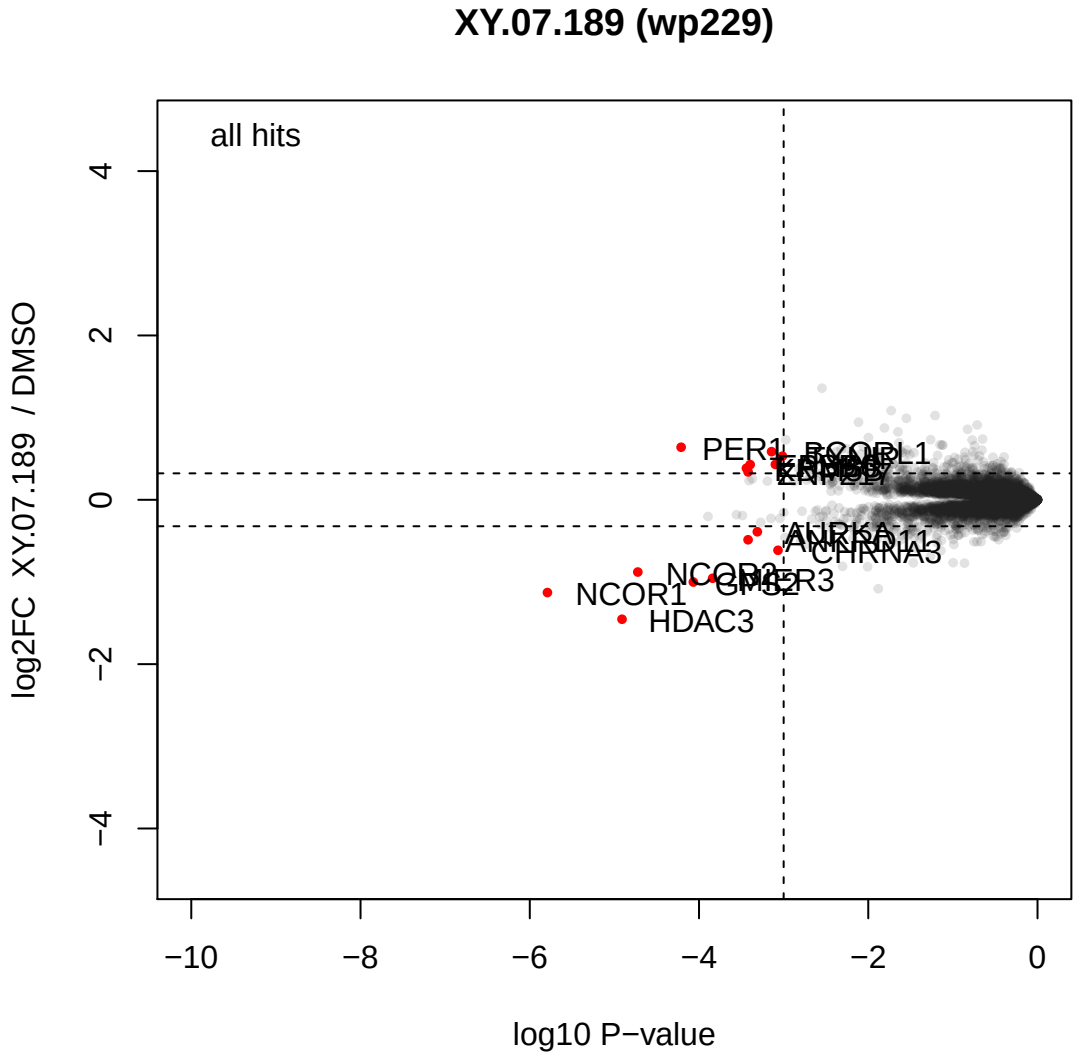

XY.07.093 (wp229)
uniprot hdac hits
log2FC XY.07.093 / DMSO
log10 P−value
HDAC3
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

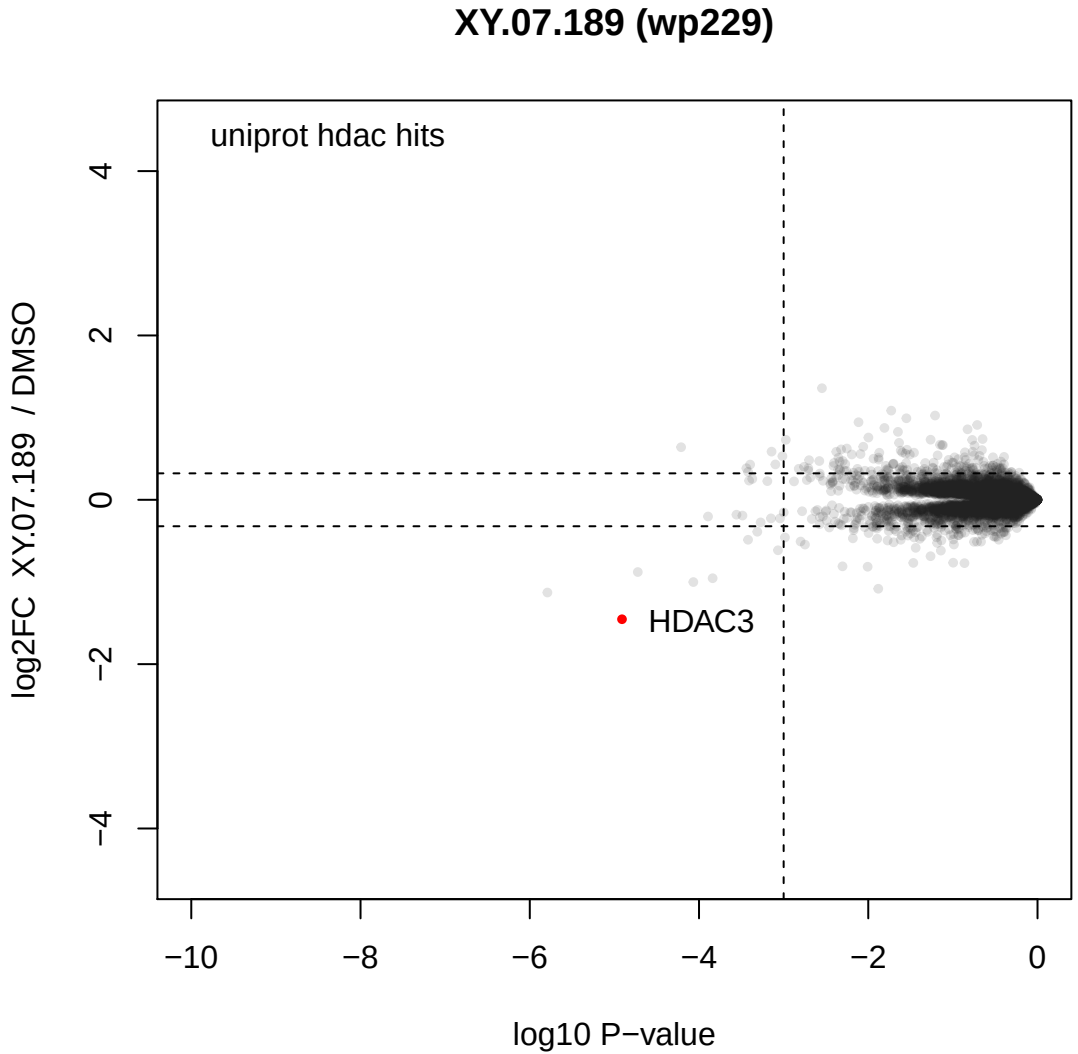

XY.07.096 (wp229)
all hits
PER1
LIMD1
HDAC8
HDAC6
FIZ1
log2FC XY.07.096 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

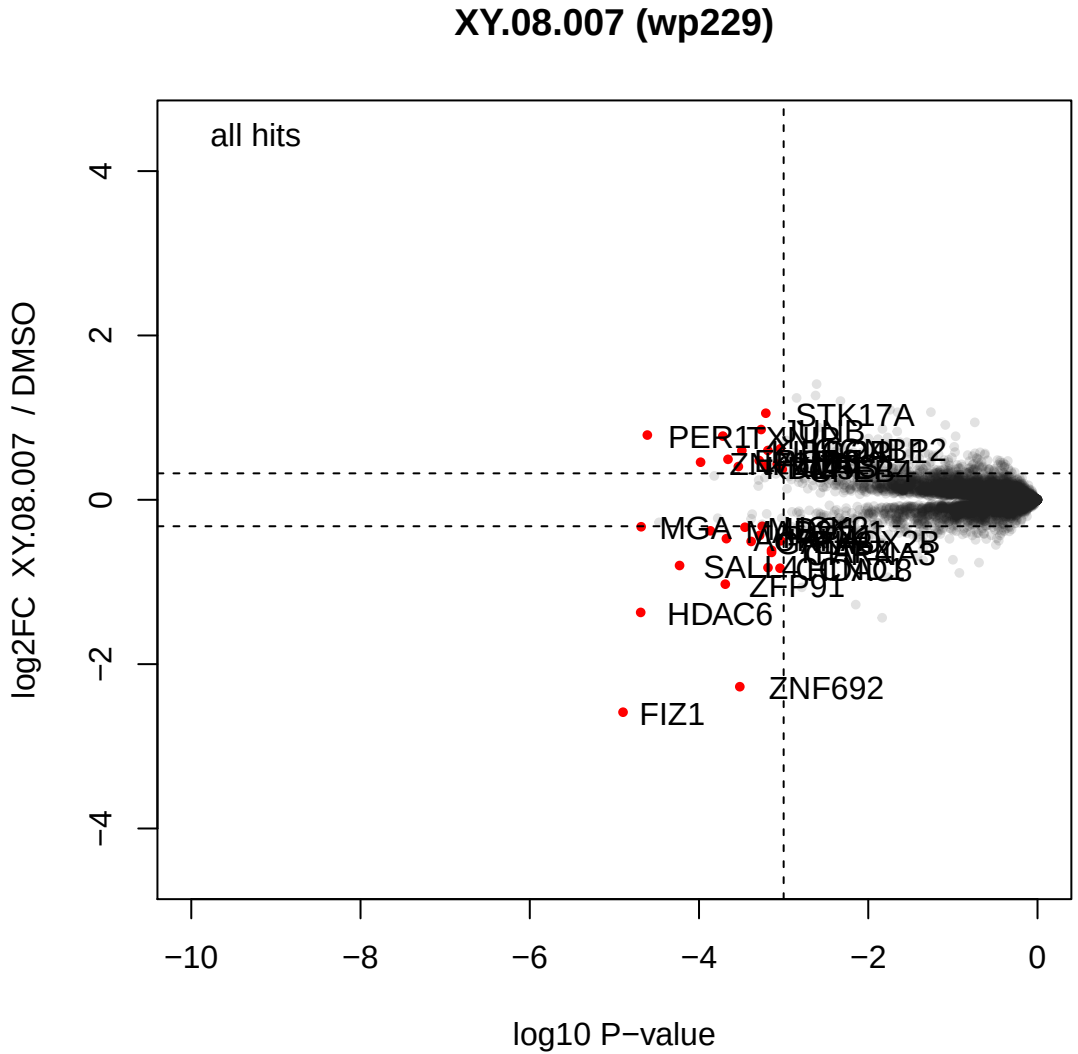

XY.07.096 (wp229)
uniprot hdac hits
HDAC8
HDAC6
log2FC XY.07.096 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

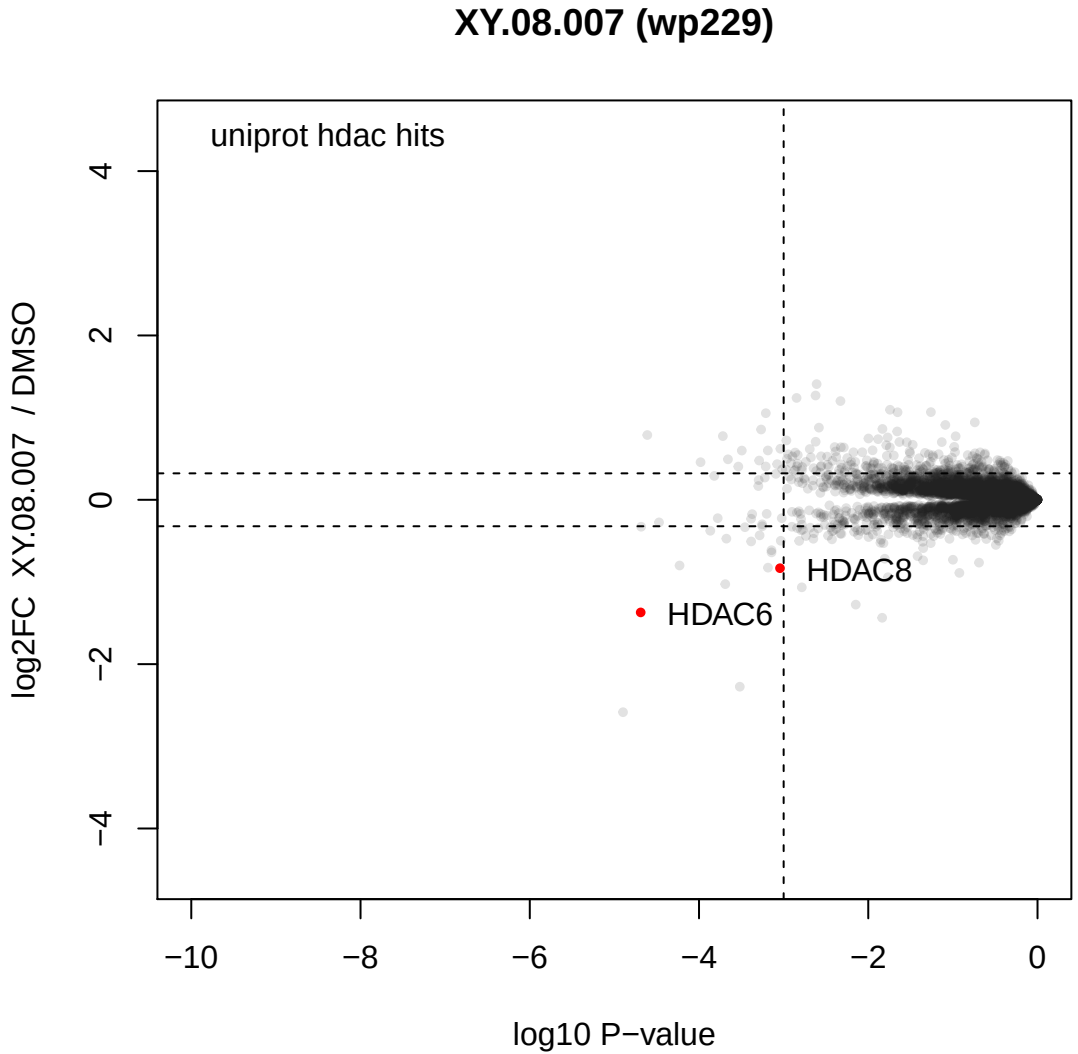

XY.07.143 (wp229)
all hits
log2FC XY.07.143 / DMSO
log10 P−value
TUFT1
STK17A
GSE1
HMG20B
XIAP
BIRC2
CCND1

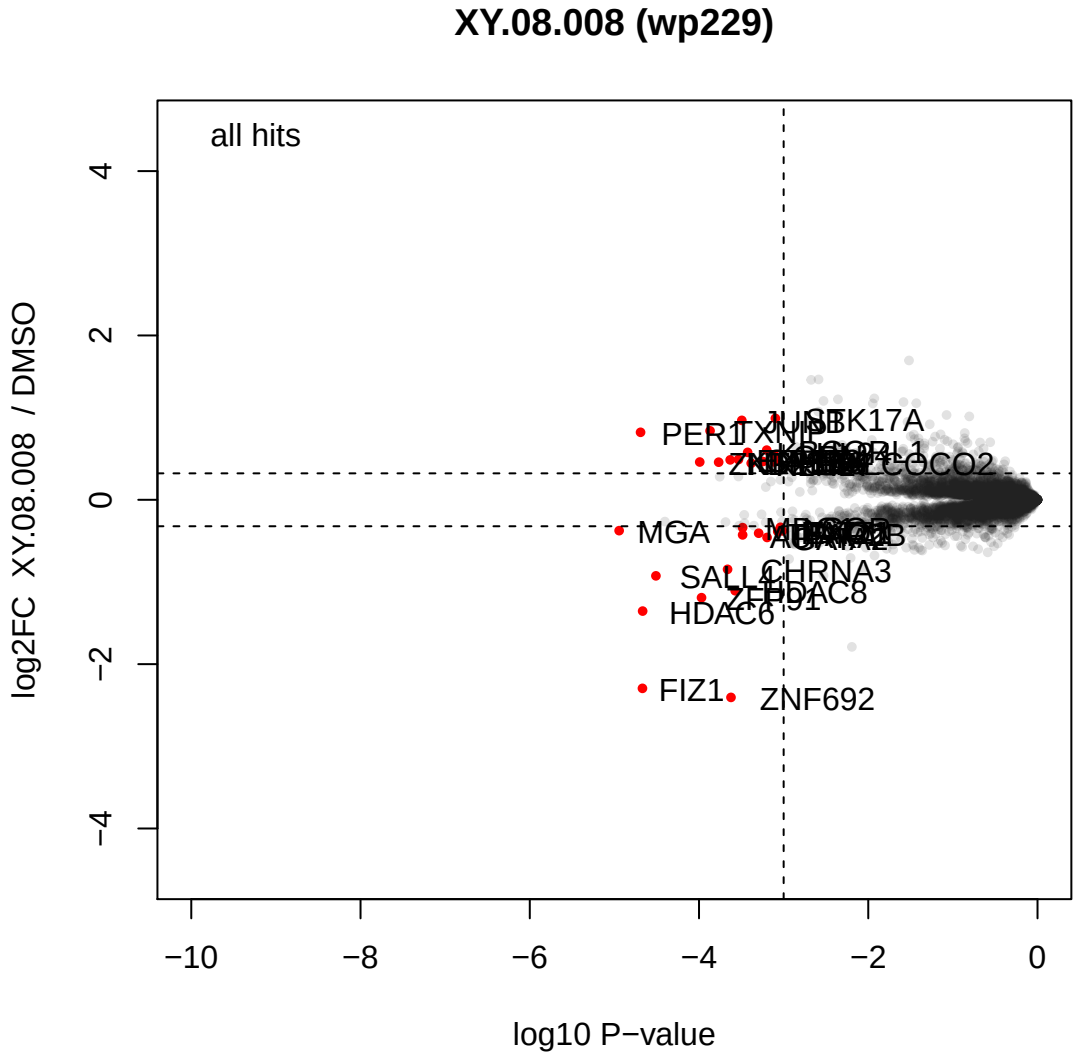

XY.07.143 (wp229)
uniprot hdac hits
log2FC XY.07.143 / DMSO
log10 P−value
HDAC6

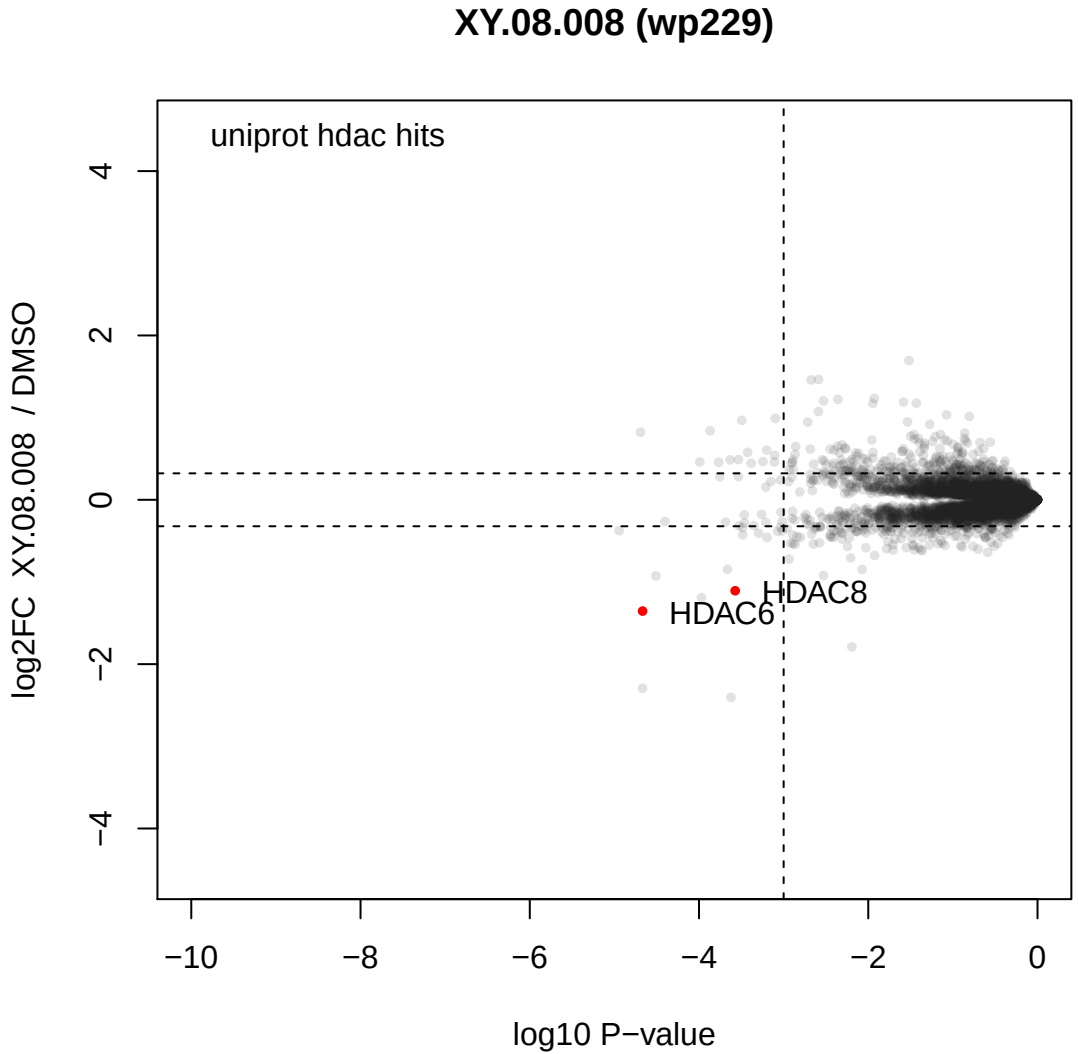

XY.07.189 (wp229)
all hits
log2FC XY.07.189 / DMSO
log10 P−value
PER1
NCOR1
HDAC3
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

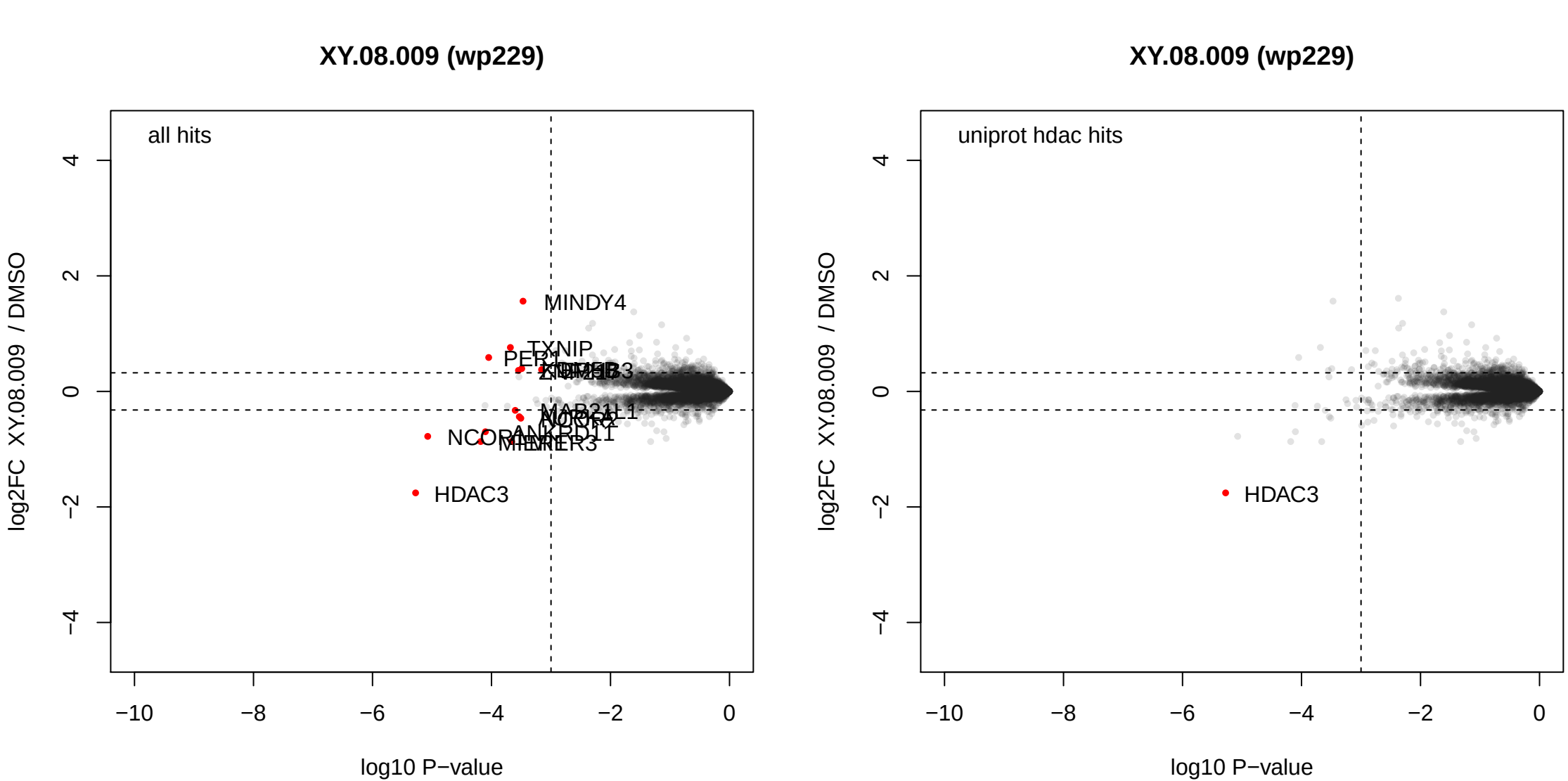

XY.07.189 (wp229)
uniprot hdac hits
log2FC XY.07.189 / DMSO
log10 P−value
HDAC3
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

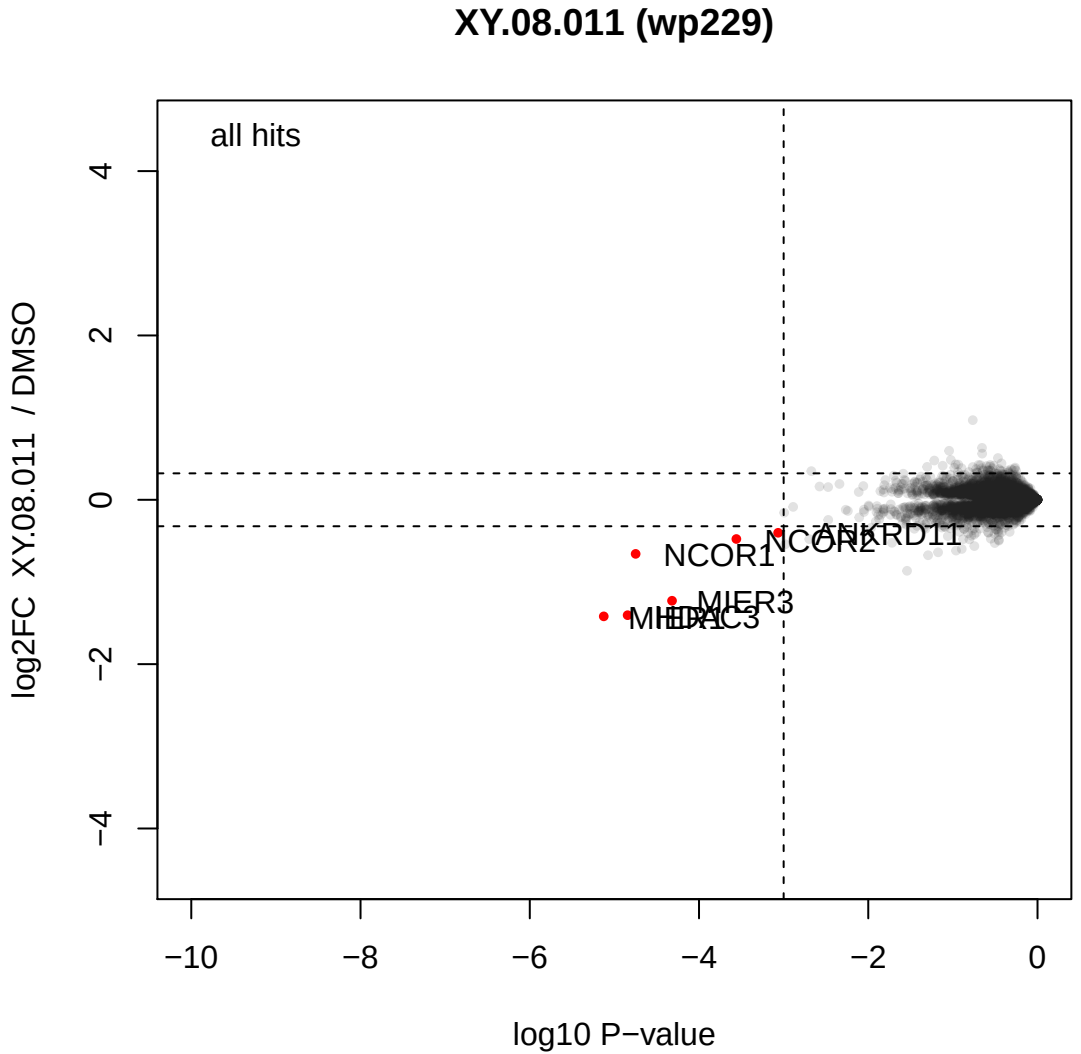

XY.08.007 (wp229)
all hits
log2FC XY.08.007 / DMSO
log10 P−value
STK17A
HDAC6
ZNF692
FIZ1
ZFP91

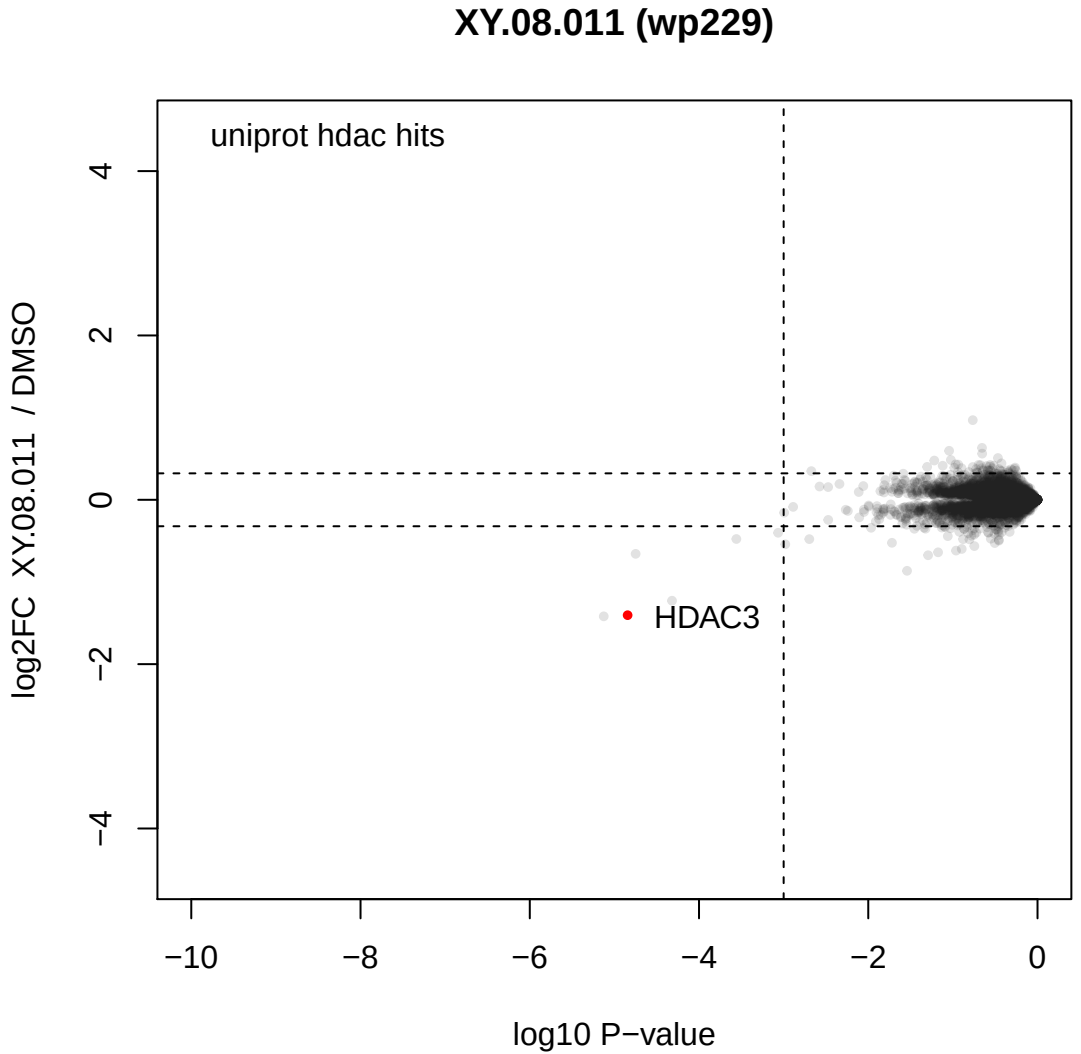

XY.08.007 (wp229)
uniprot hdac hits
log2FC XY.08.007 / DMSO
log10 P−value
HDAC8
HDAC6

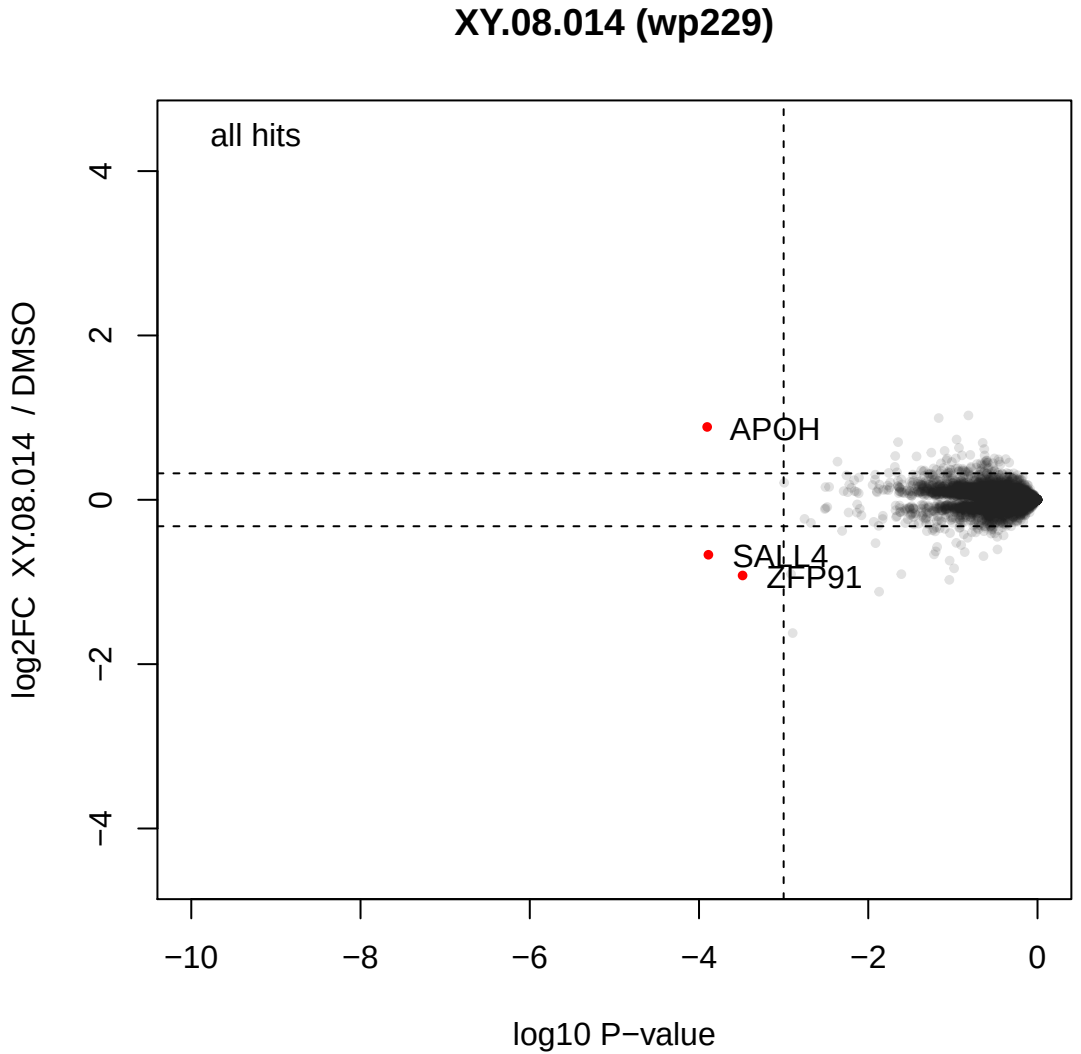

XY.08.008 (wp229)
all hits
log2FC XY.08.008 / DMSO
log10 P−value
PER1
MGA
SALL4
HDAC6
FIZ1
ZNF692
CHRNA3
HDAC8
ZFP91

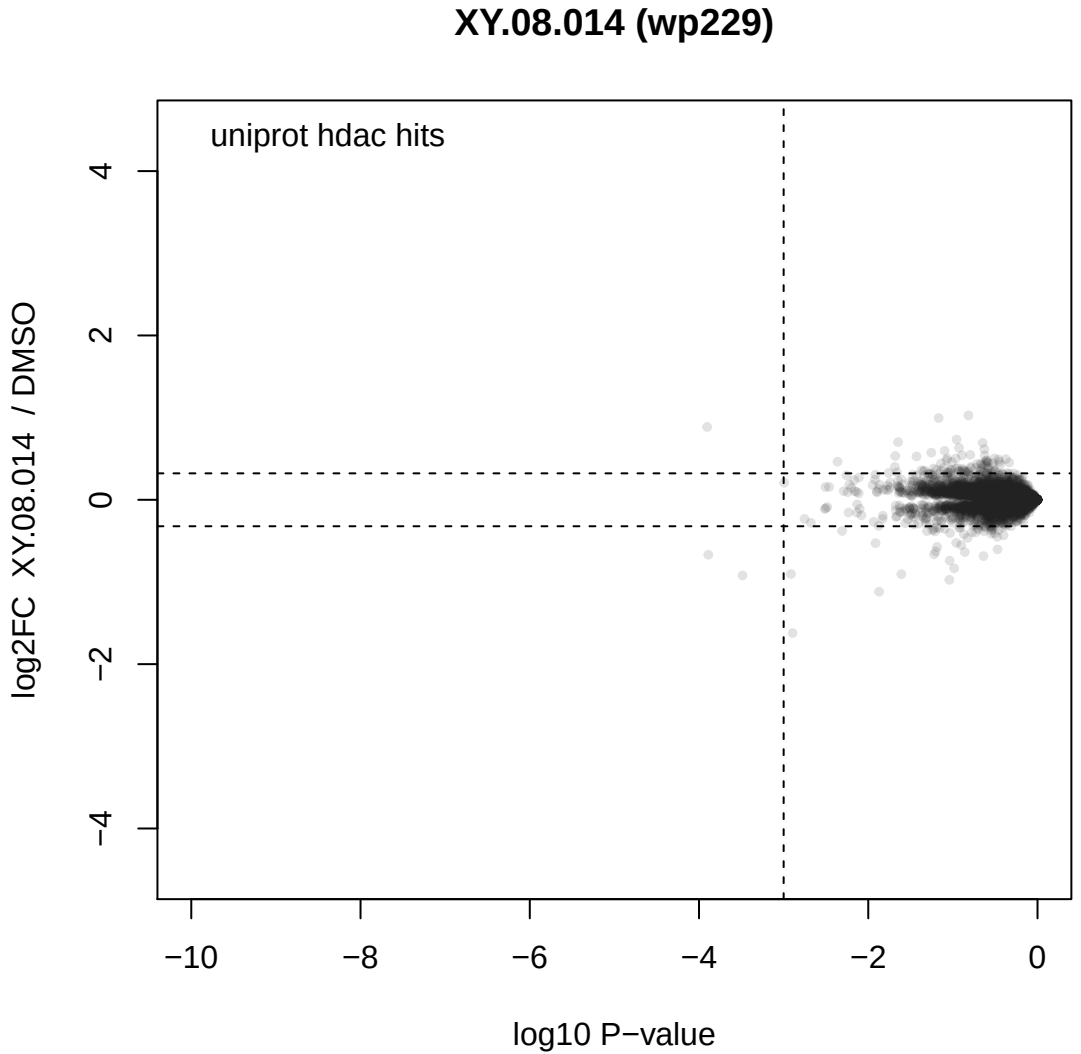

XY.08.008 (wp229)
uniprot hdac hits
log2FC XY.08.008 / DMSO
log10 P−value
HDAC6
HDAC8

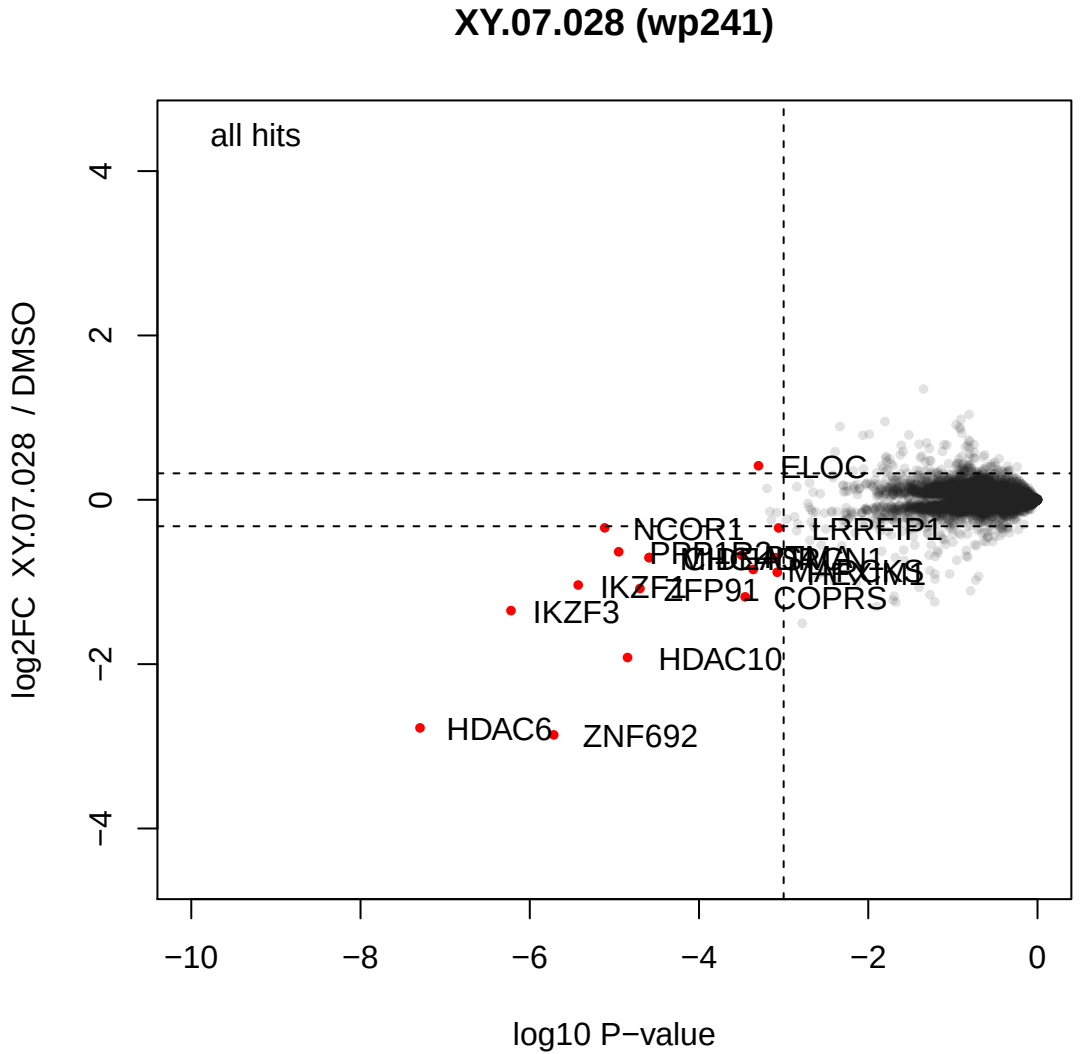

XY.08.009 (wp229)
all hits
MINDY4
TXNIP
PER1
MAB21L1
NCOR2
HDAC3
log2FC XY.08.009 / DMSO
log10 P−value
XY.08.009 (wp229)
uniprot hdac hits
HDAC3
log2FC XY.08.009 / DMSO
log10 P−value

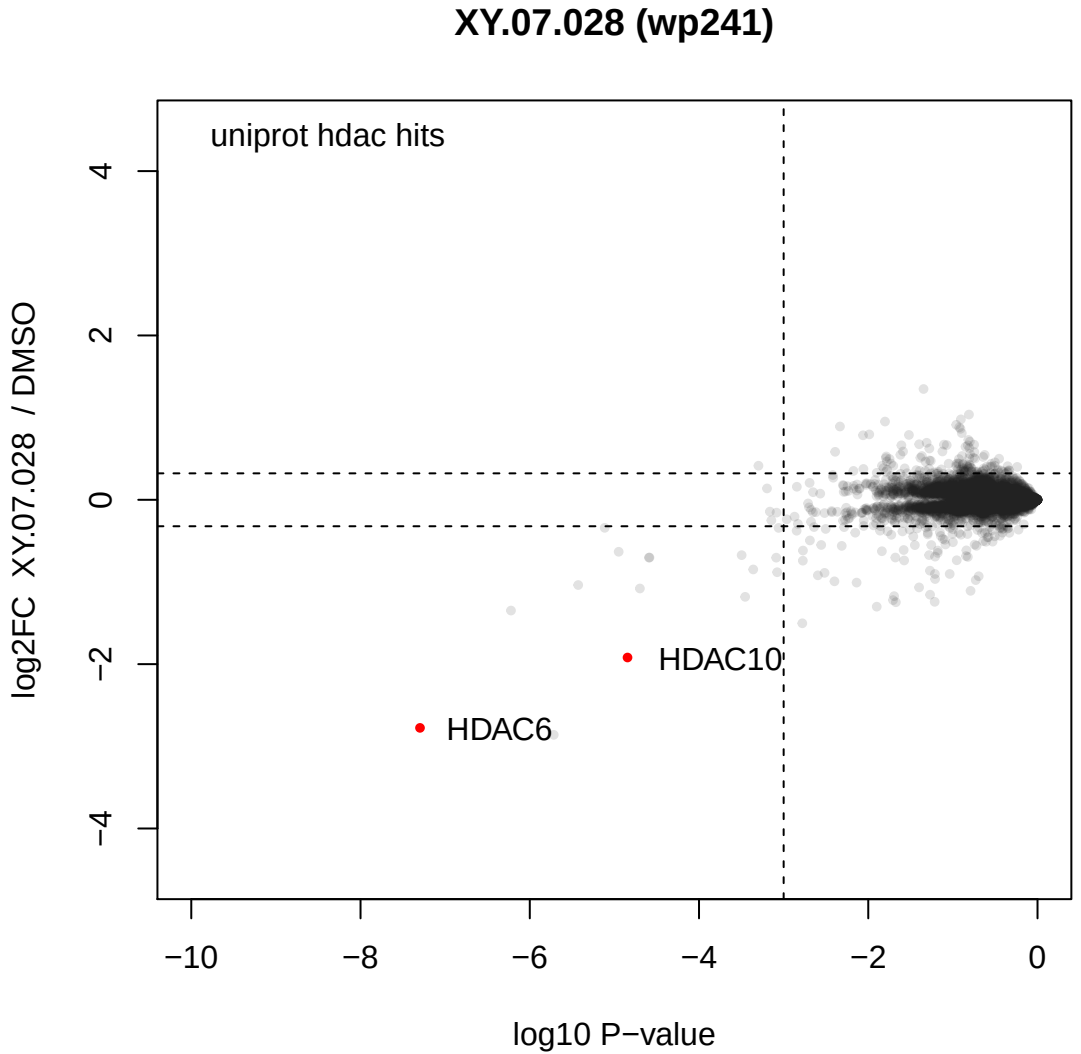

XY.08.011 (wp229)
all hits
log2FC XY.08.011 / DMSO
log10 P−value
NCOR1
NCOR2
ANKRD11
MIER3
HDAC3
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

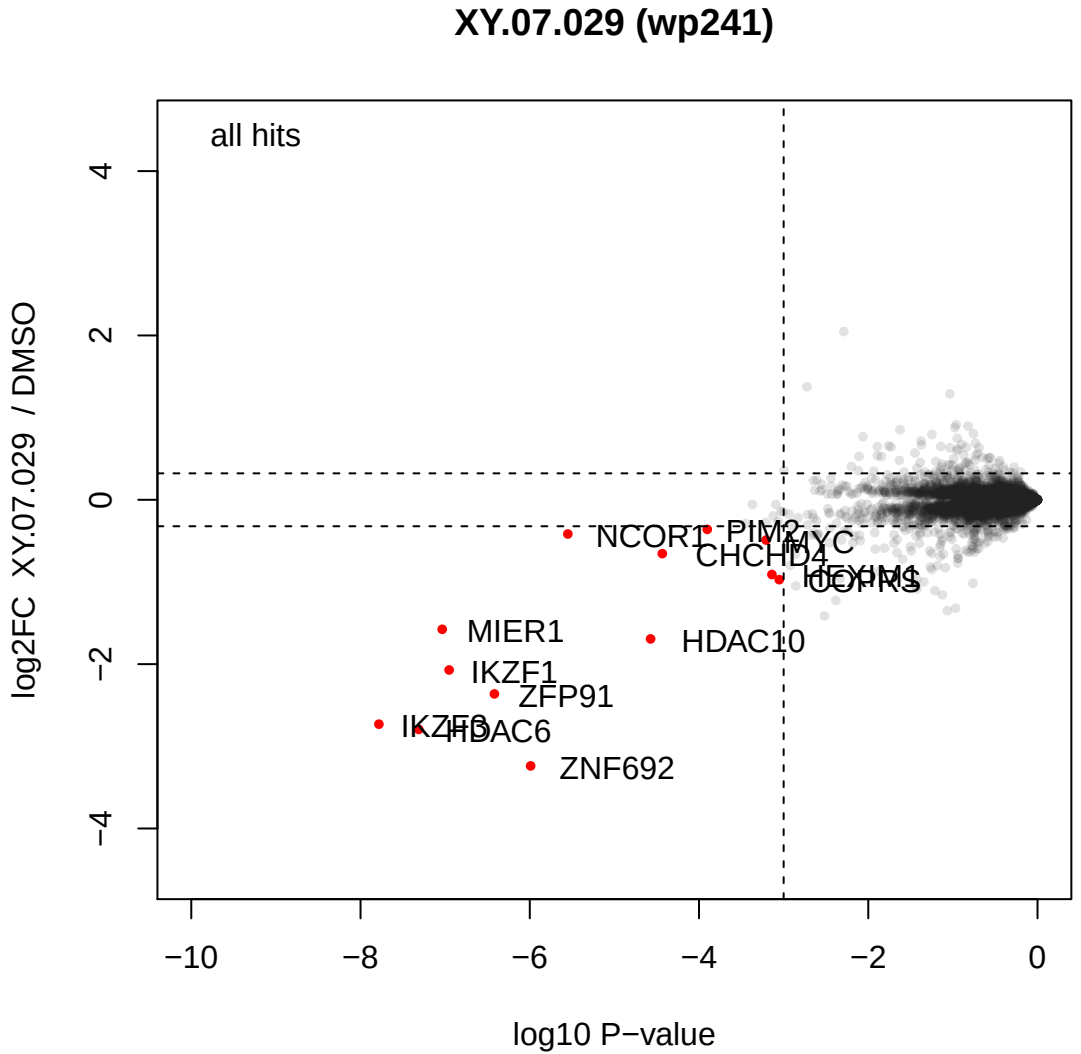

XY.08.011 (wp229)
uniprot hdac hits
log2FC XY.08.011 / DMSO
log10 P−value
HDAC3
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

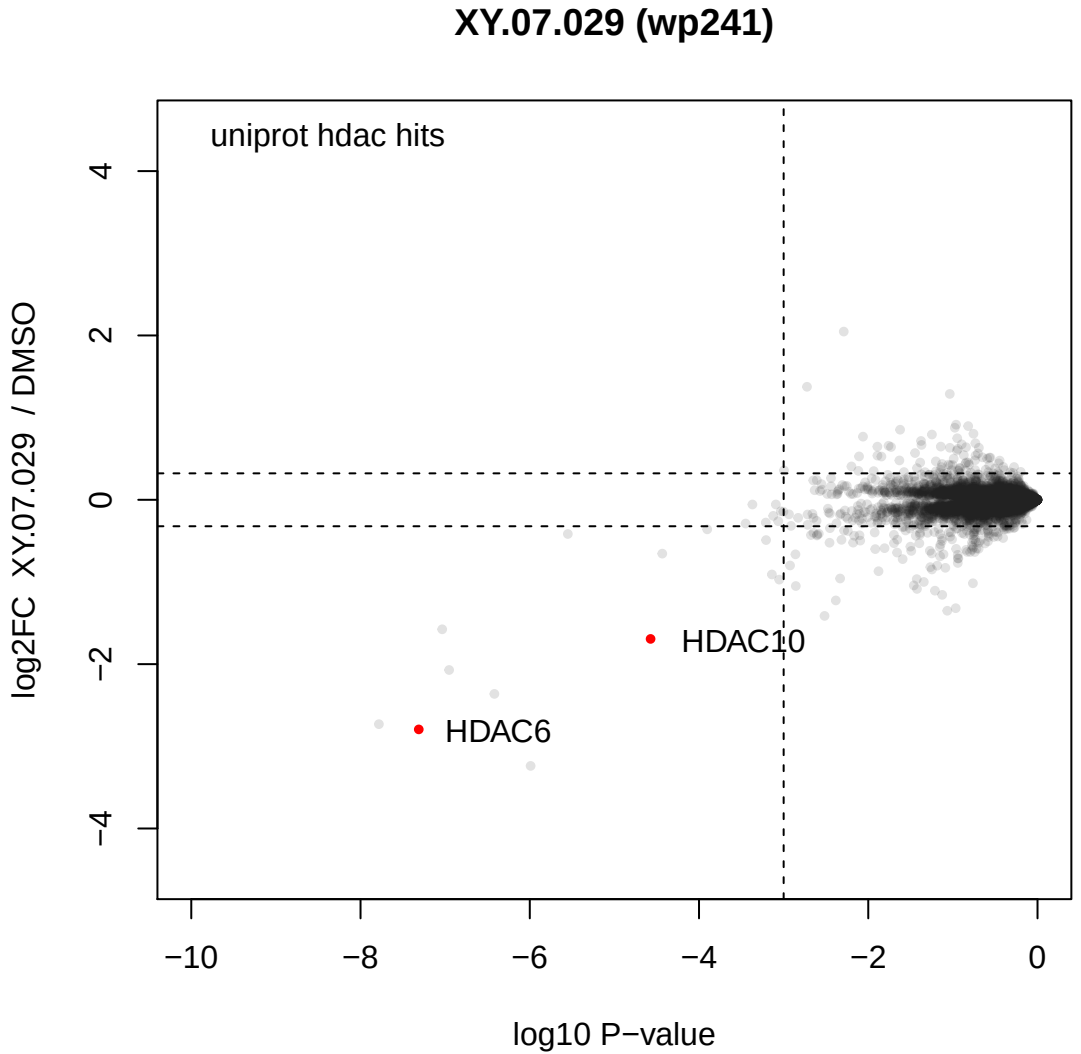

XY.08.014 (wp229)
all hits
APOH
SALL4
ZFP91
log2FC XY.08.014 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

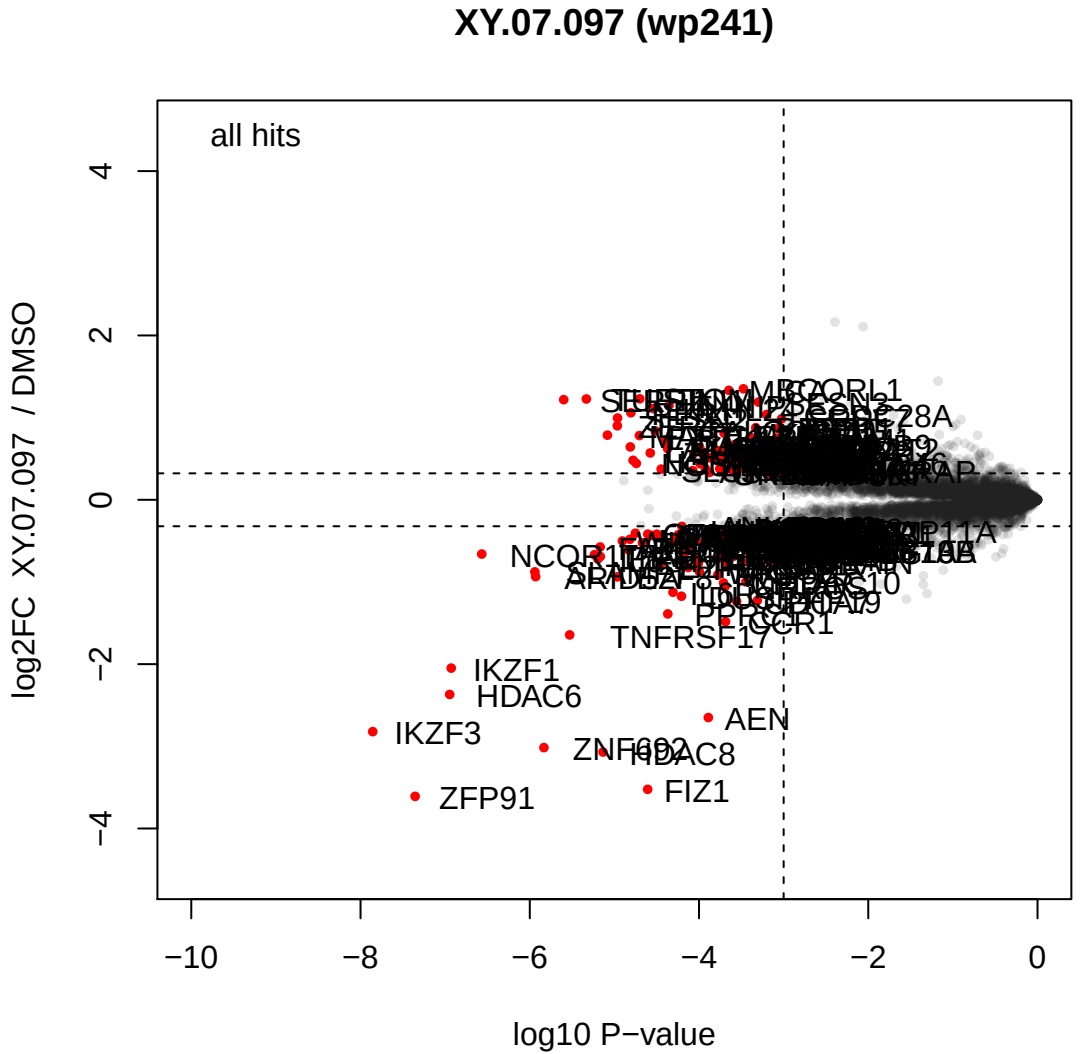

XY.08.014 (wp229)
uniprot hdac hits
log2FC XY.08.014 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

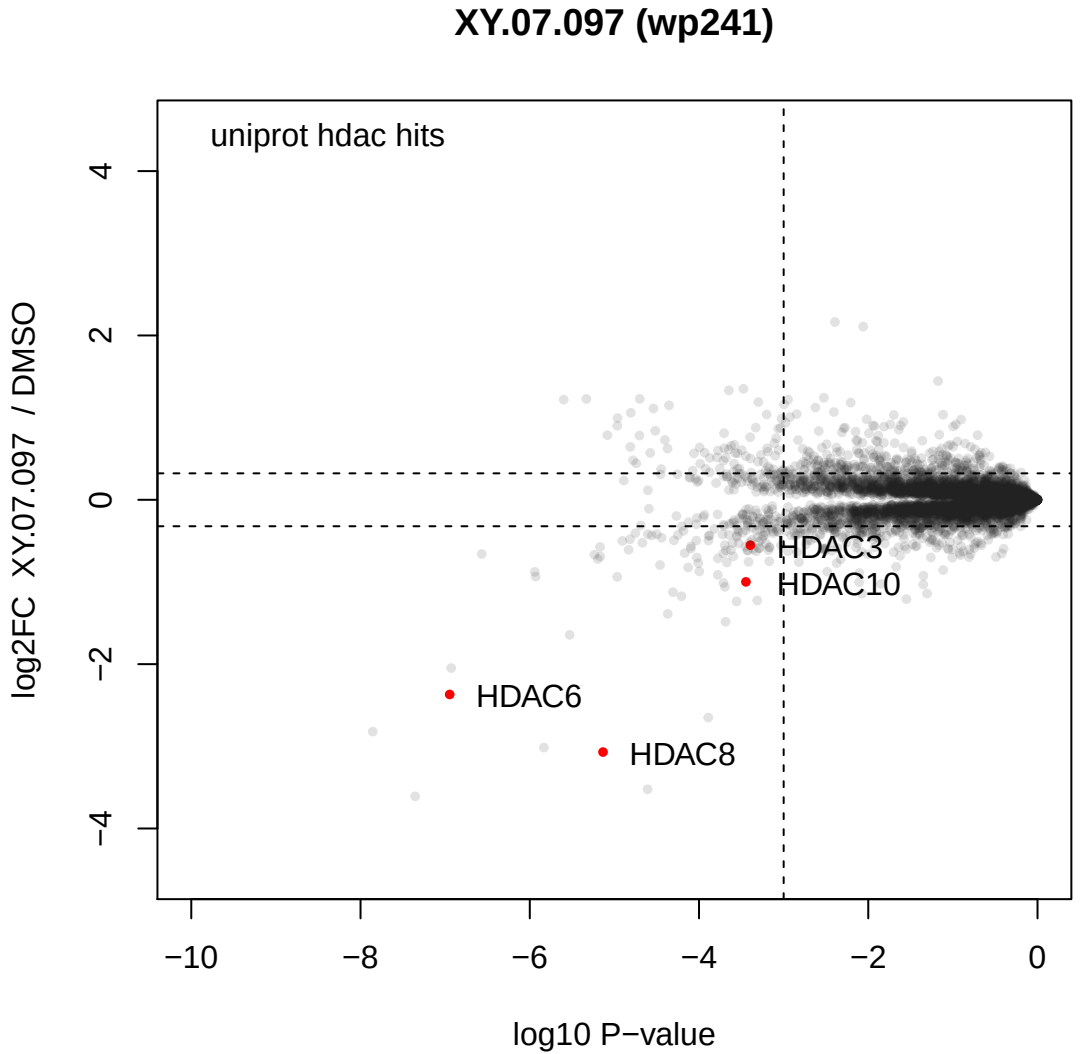

XY.07.028 (wp241)
all hits
log2FC XY.07.028 / DMSO
log10 P−value
ELOC
NCOR1
LRRFIP1
IKZF1
ZFP91
COPRS
IKZF3
HDAC10
HDAC6
ZNF692

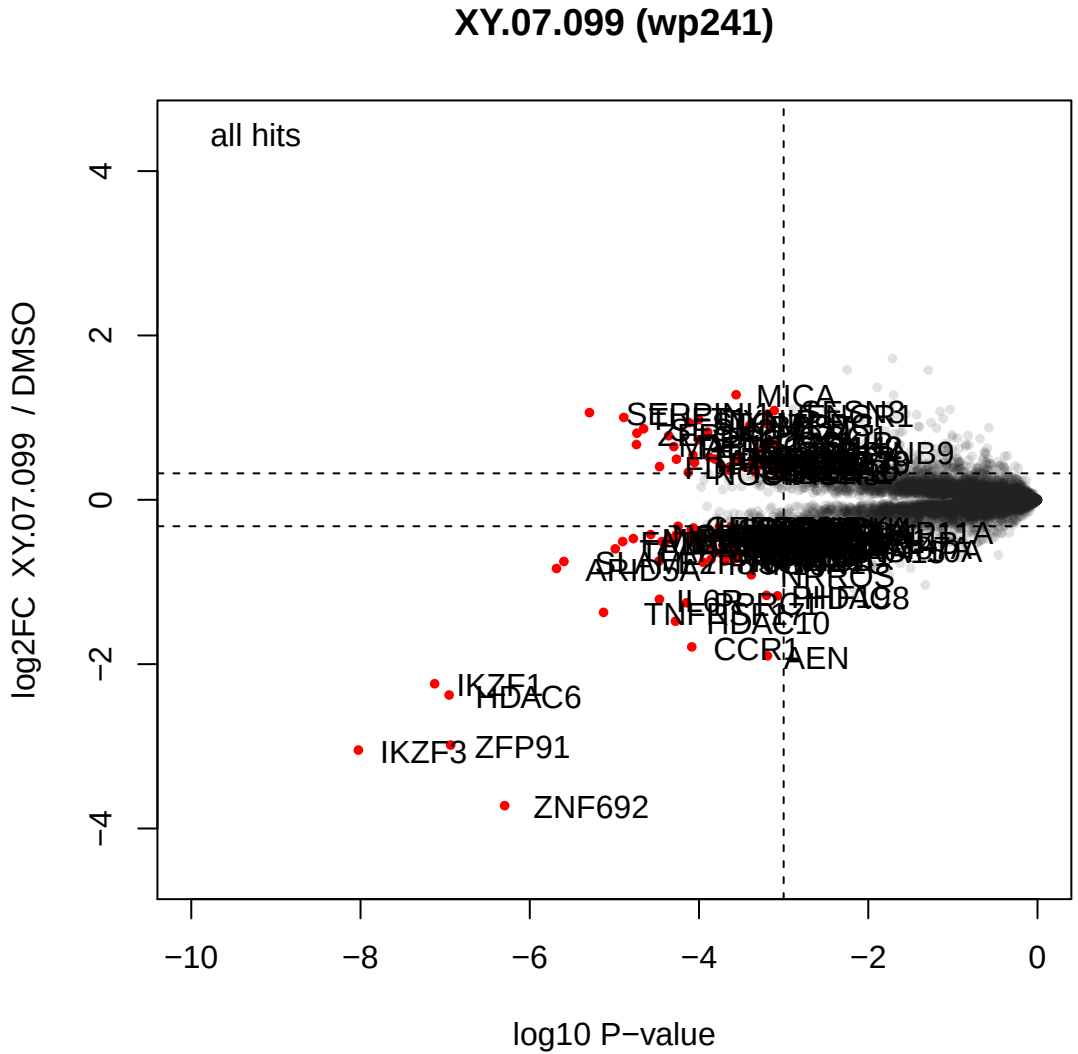

XY.07.028 (wp241)
uniprot hdac hits
log2FC XY.07.028 / DMSO
log10 P−value
HDAC10
HDAC6

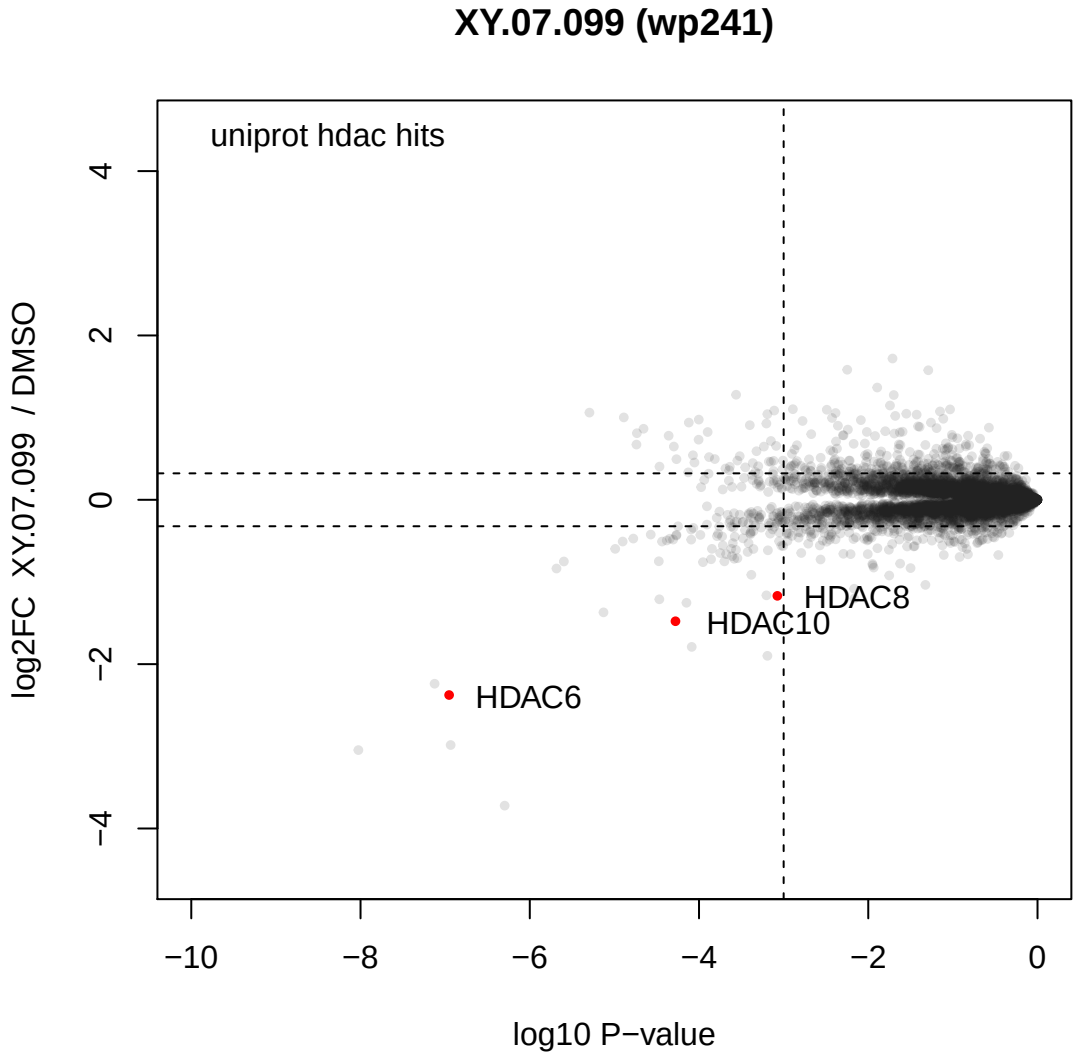

XY.07.029 (wp241)
all hits
log2FC XY.07.029 / DMSO
log10 P−value
NCOR1
PIM2
MYC
CHCHD4
HDAC10
MIER1
IKZF1
ZFP91
HDAC6
ZNF692

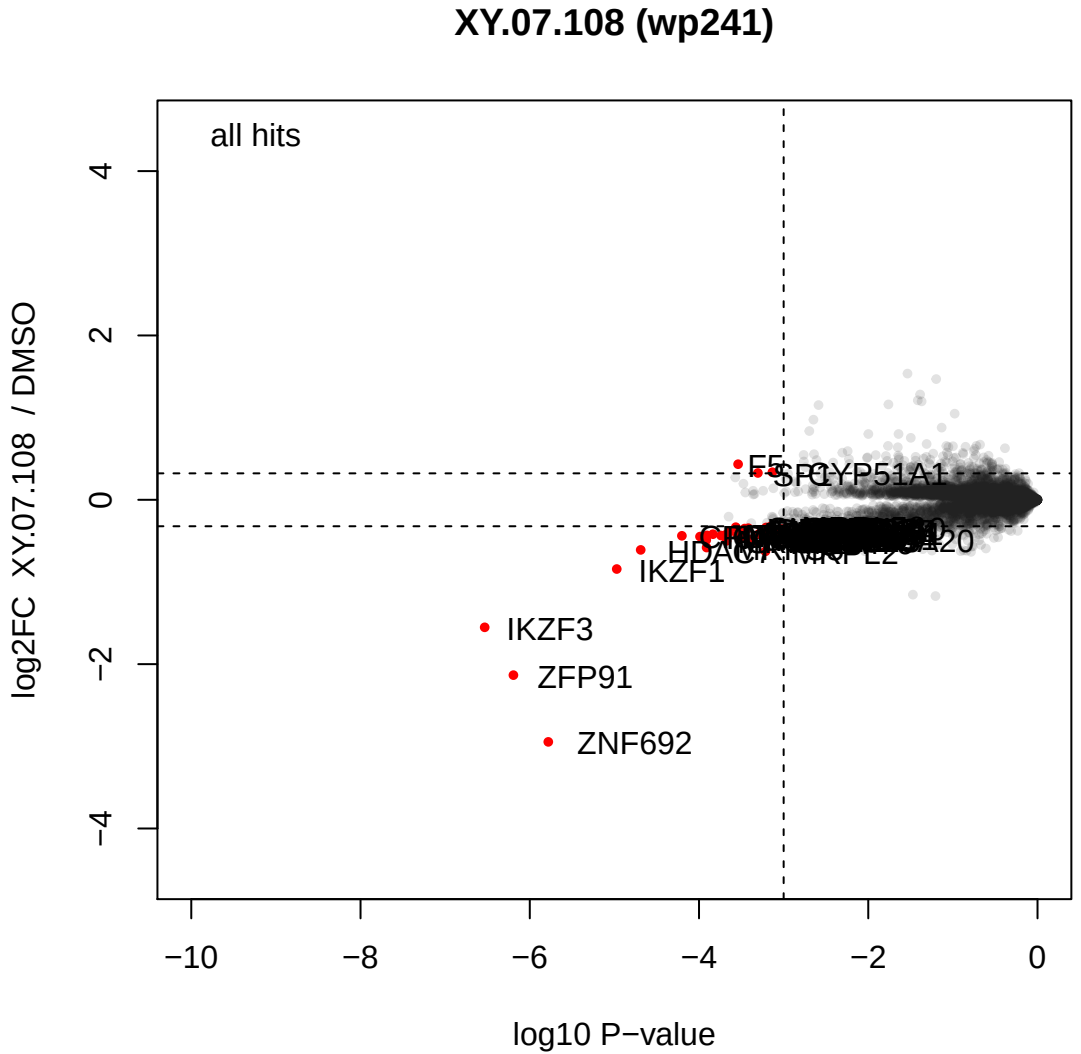

XY.07.029 (wp241)
uniprot hdac hits
log2FC XY.07.029 / DMSO
log10 P−value
HDAC10
HDAC6

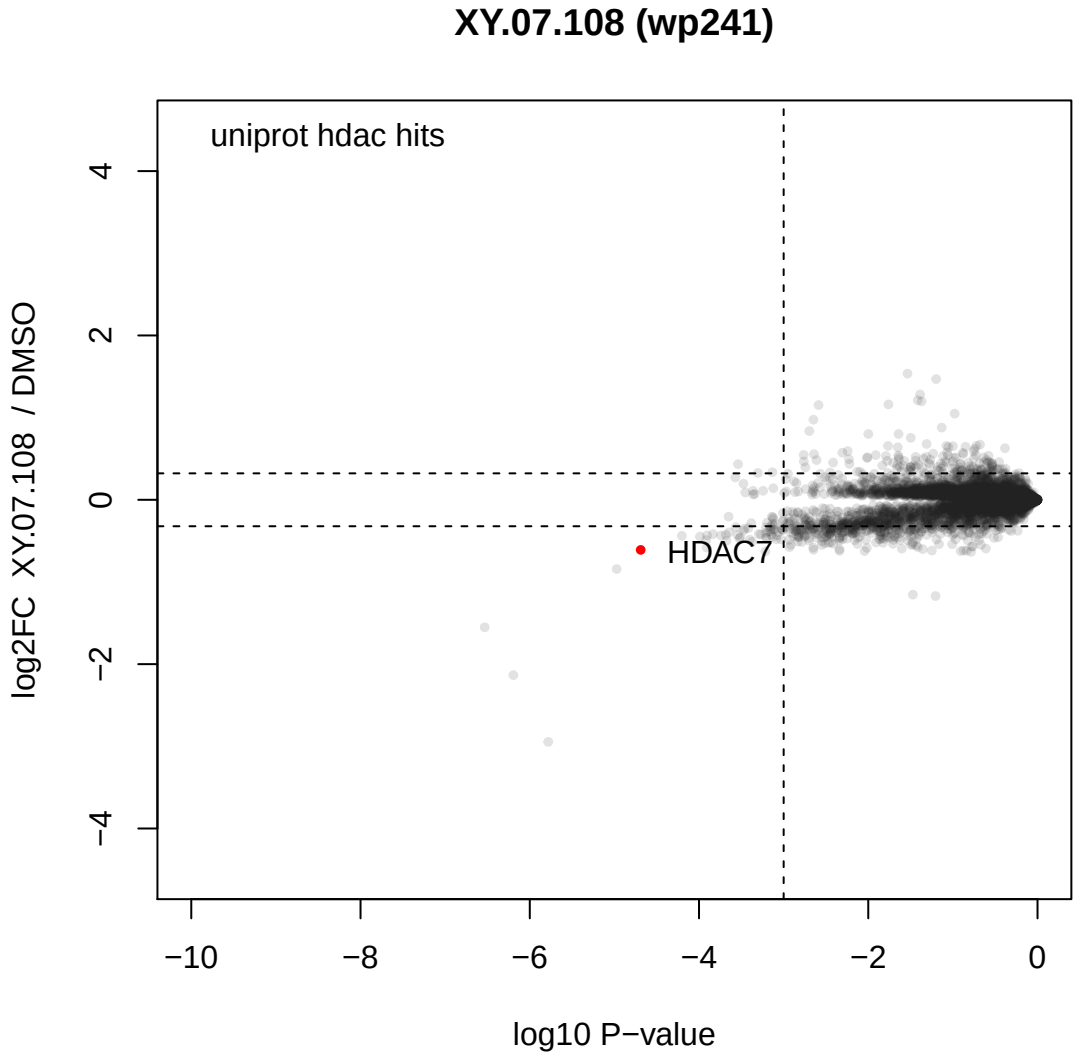

XY.07.097 (wp241)
all hits
log2FC XY.07.097 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0
NCOR1
TNFRSF17
IKZF1
HDAC6
IKZF3
ZNF692
HDAC8
AEN
ZFP91
FIZ1

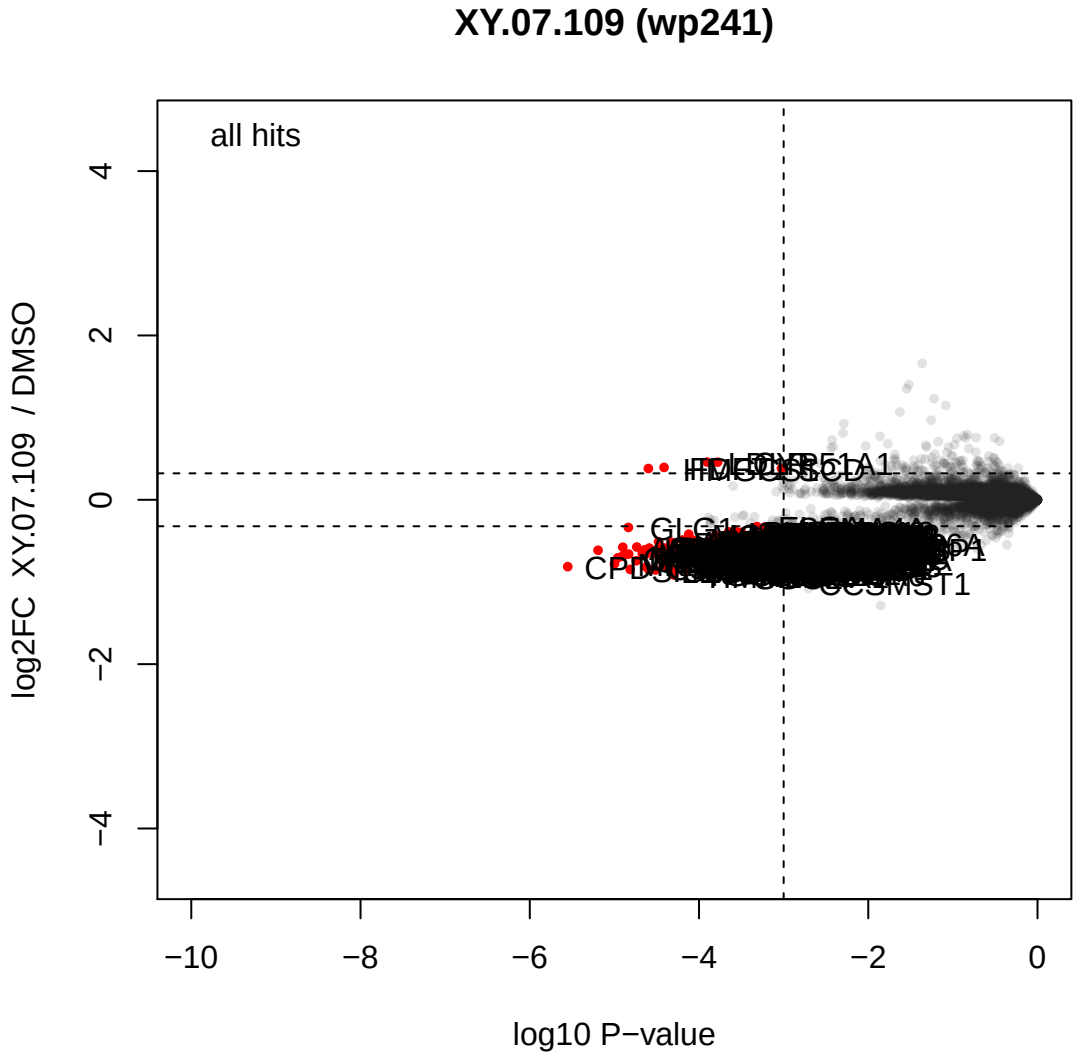

XY.07.097 (wp241)
uniprot hdac hits
log2FC XY.07.097 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0
HDAC3
HDAC10
HDAC6
HDAC8

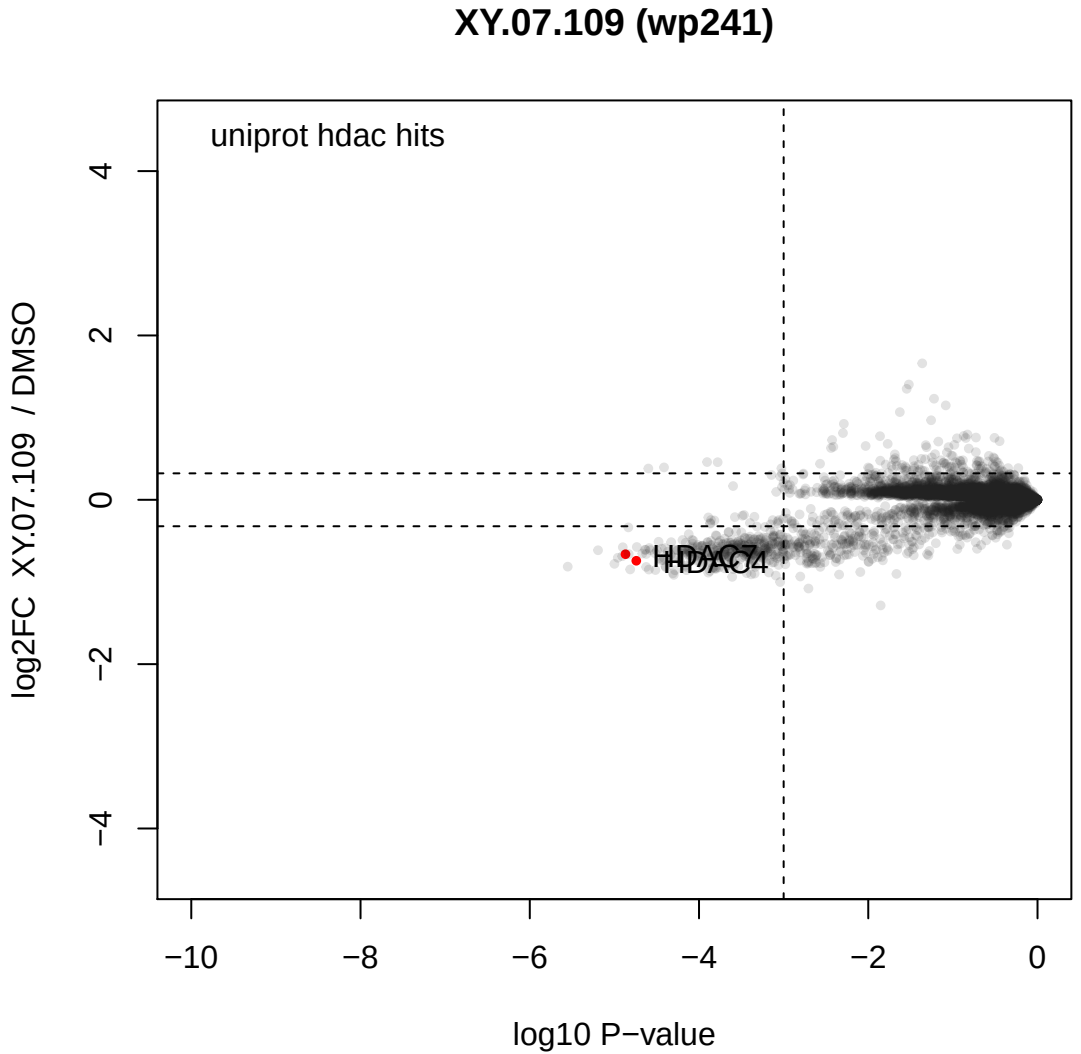

XY.07.099 (wp241)
all hits
log2FC XY.07.099 / DMSO
log10 P−value
MICA
IKZF1
HDAC6
IKZF3
ZFP91
ZNF692
HDAC10
CCR1
AEN
NRROS
HDAC8
ARID5A
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

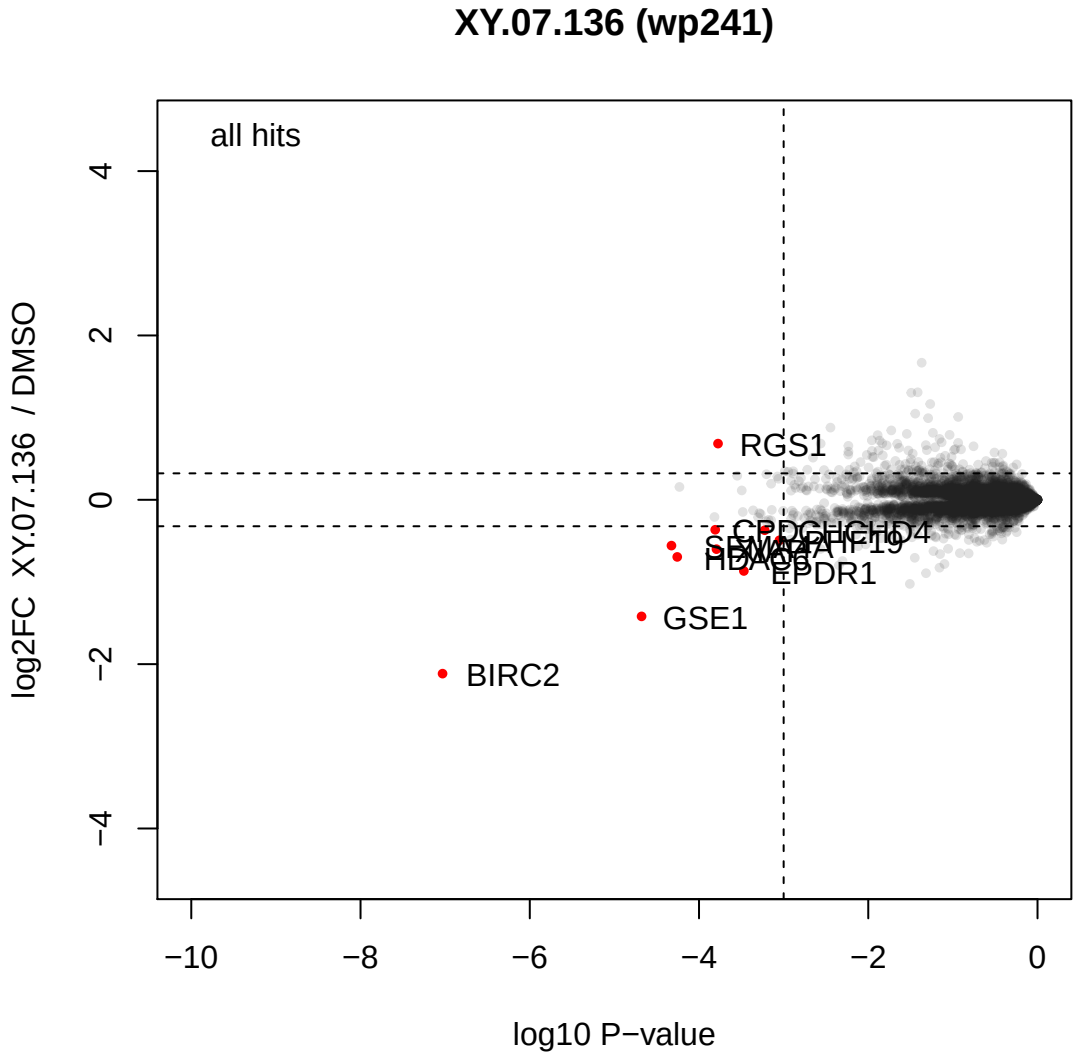

XY.07.099 (wp241)
uniprot hdac hits
log2FC XY.07.099 / DMSO
log10 P−value
HDAC8
HDAC10
HDAC6
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

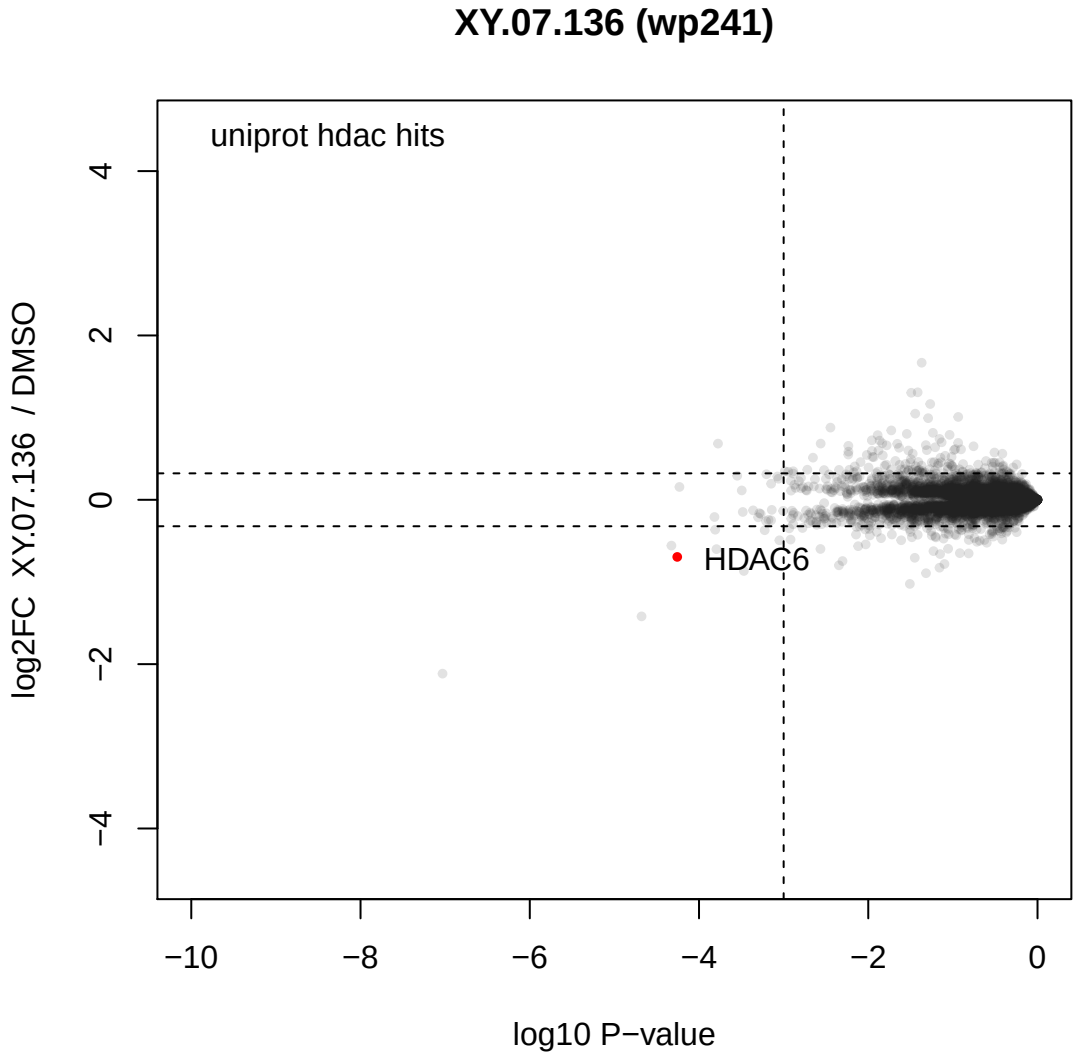

XY.07.108 (wp241)
all hits
log2FC XY.07.108 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0
F5
SP1
YP51A1
IKZF1
IKZF3
ZFP91
ZNF692

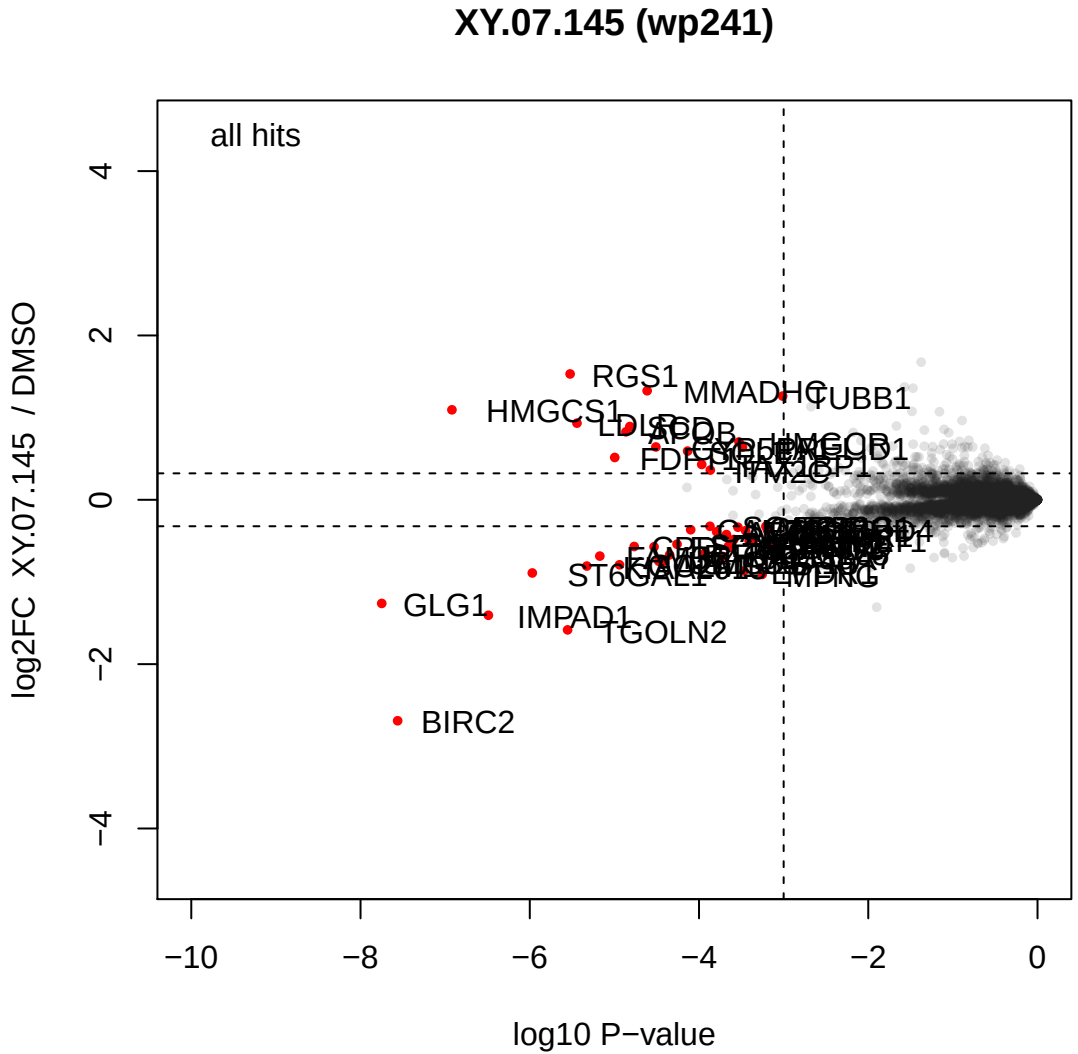

XY.07.108 (wp241)
uniprot hdac hits
log2FC XY.07.108 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0
HDAC7

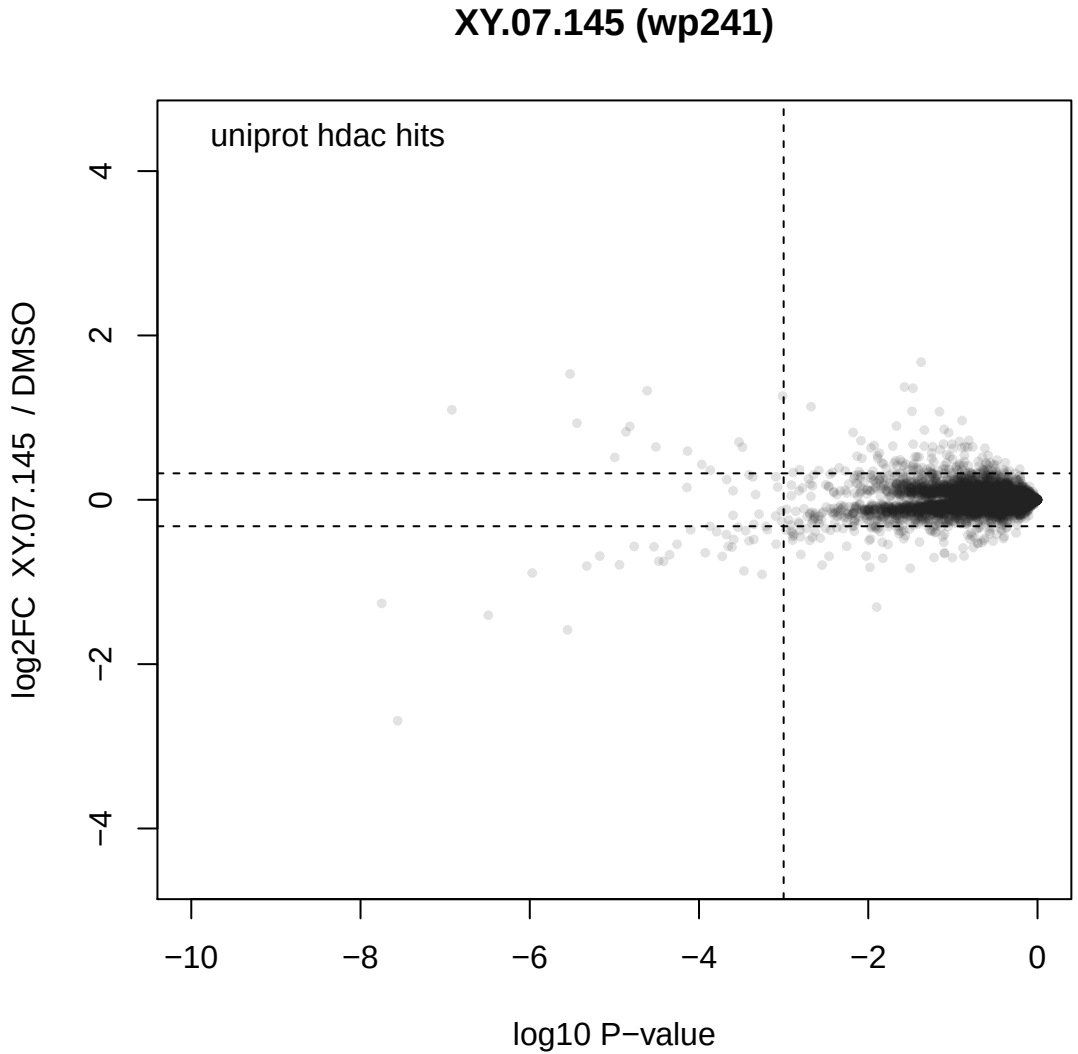

XY.07.109 (wp241)
all hits
log2FC XY.07.109 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

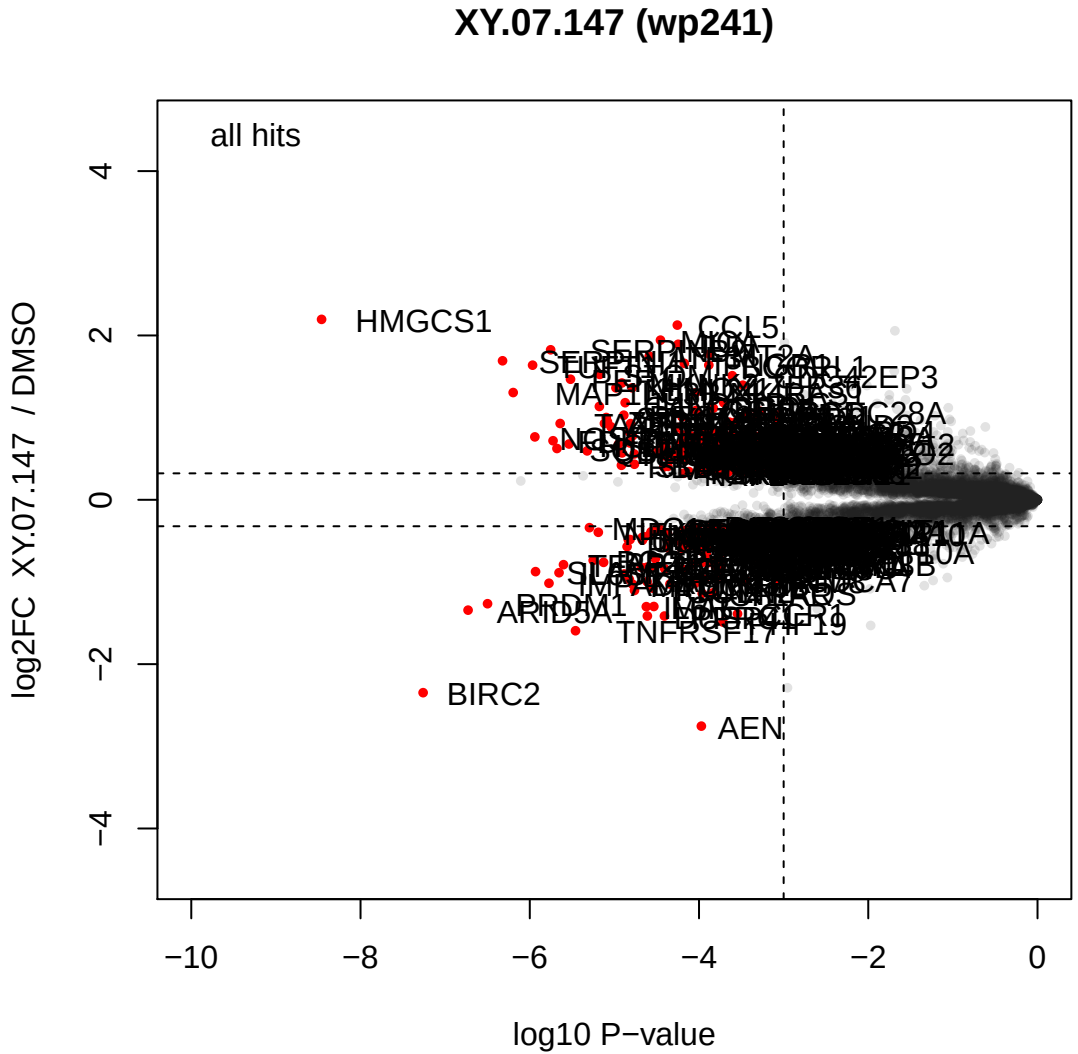

XY.07.109 (wp241)
uniprot hdac hits
log2FC XY.07.109 / DMSO
log10 P−value
HDAC4
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

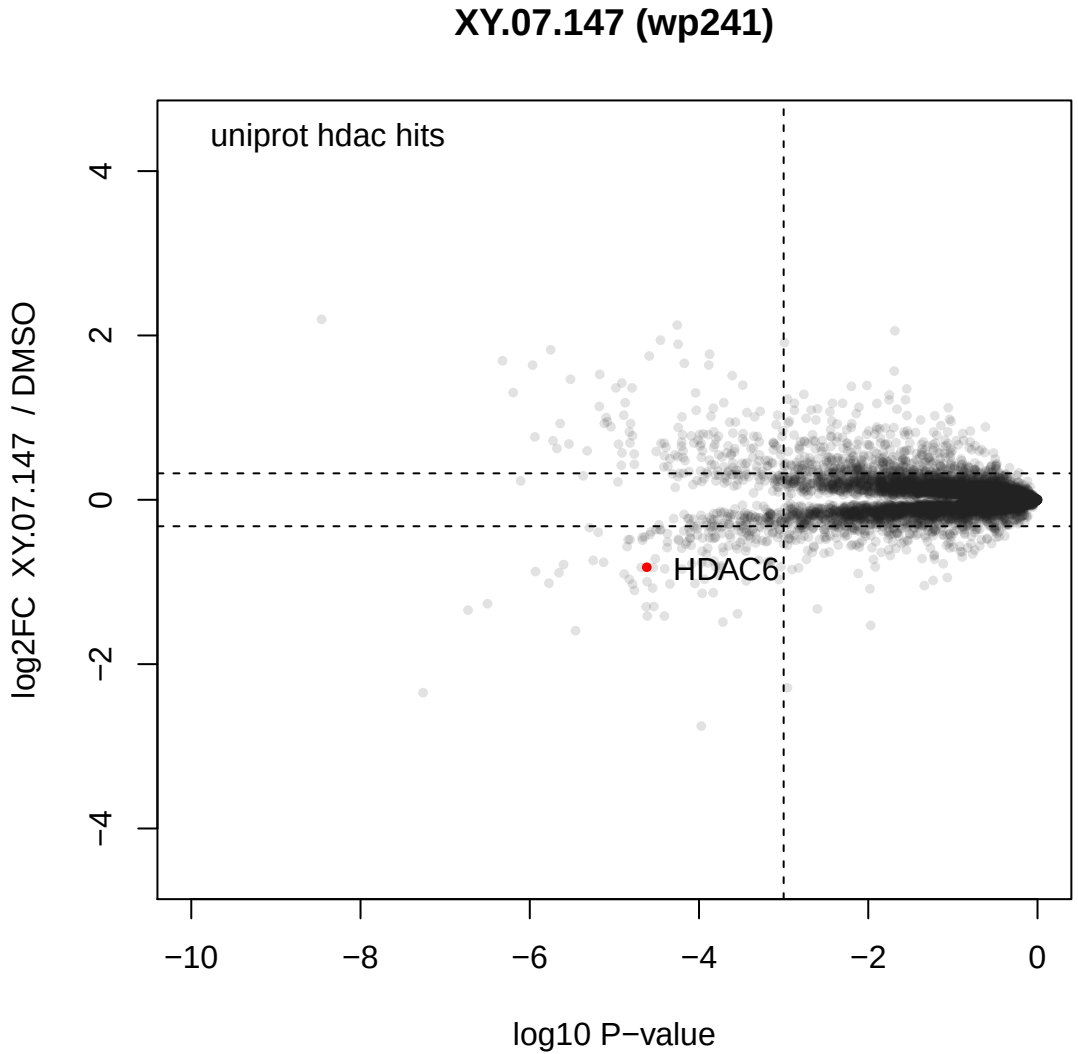

XY.07.136 (wp241)
all hits
RGS1
GSE1
BIRC2
EPDR1
log2FC XY.07.136 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

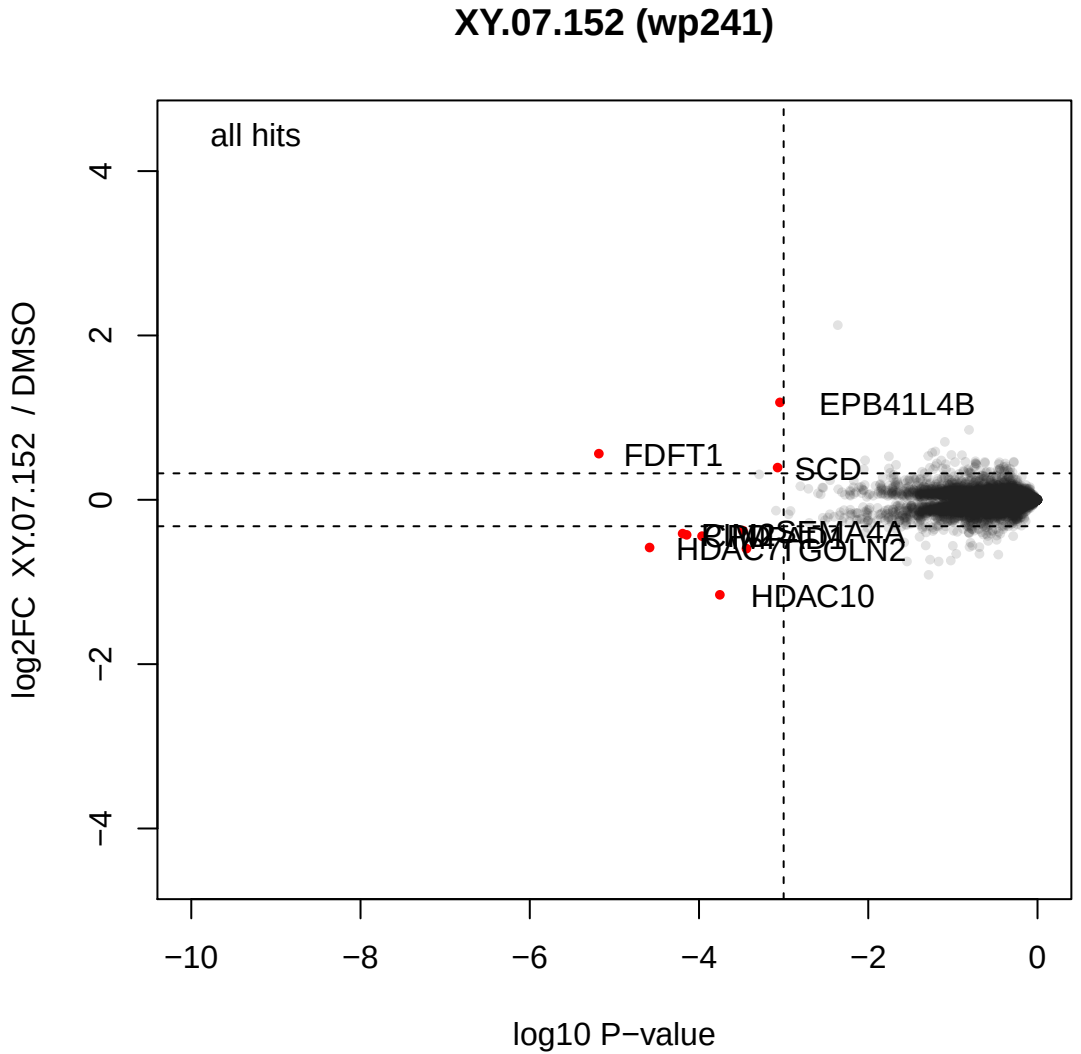

XY.07.136 (wp241)
uniprot hdac hits
HDAC6
log2FC XY.07.136 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

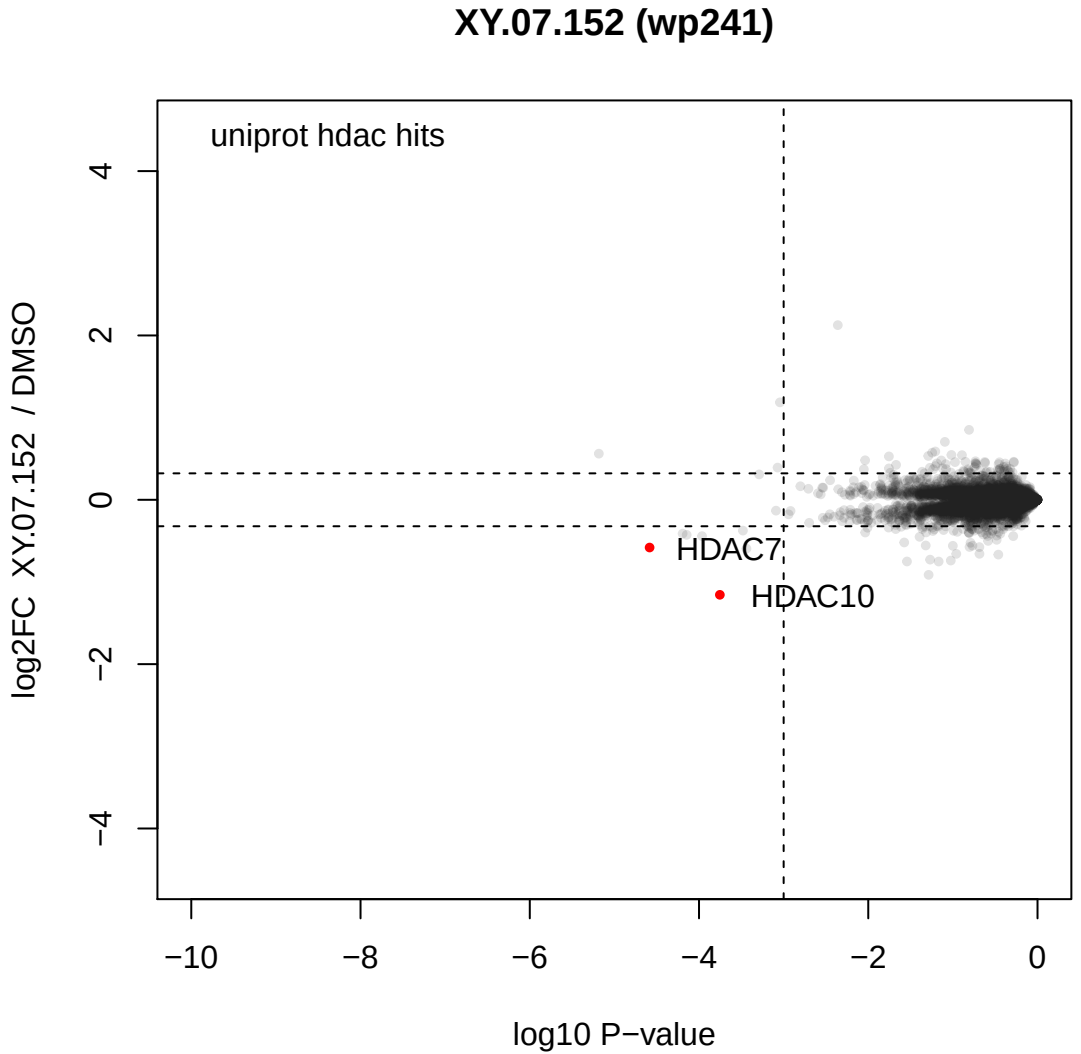

XY.07.145 (wp241)
all hits
RGS1
HMGCS1
MMADHC
TUBB1
FDFT1
GLG1
IMPAD1
TGOLN2
ST6GAL1
BIRC2
log2FC XY.07.145 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

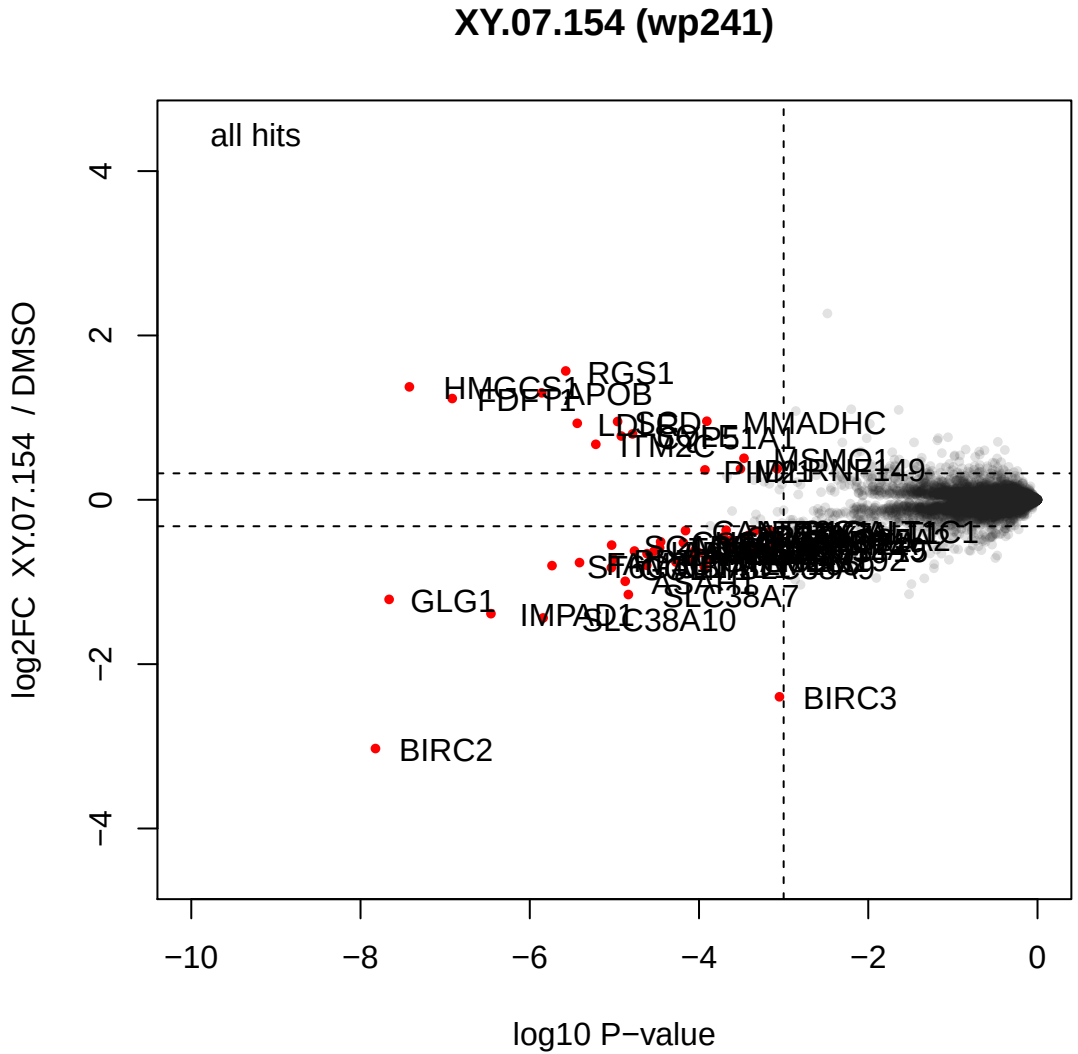

XY.07.145 (wp241)
uniprot hdac hits
log2FC XY.07.145 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

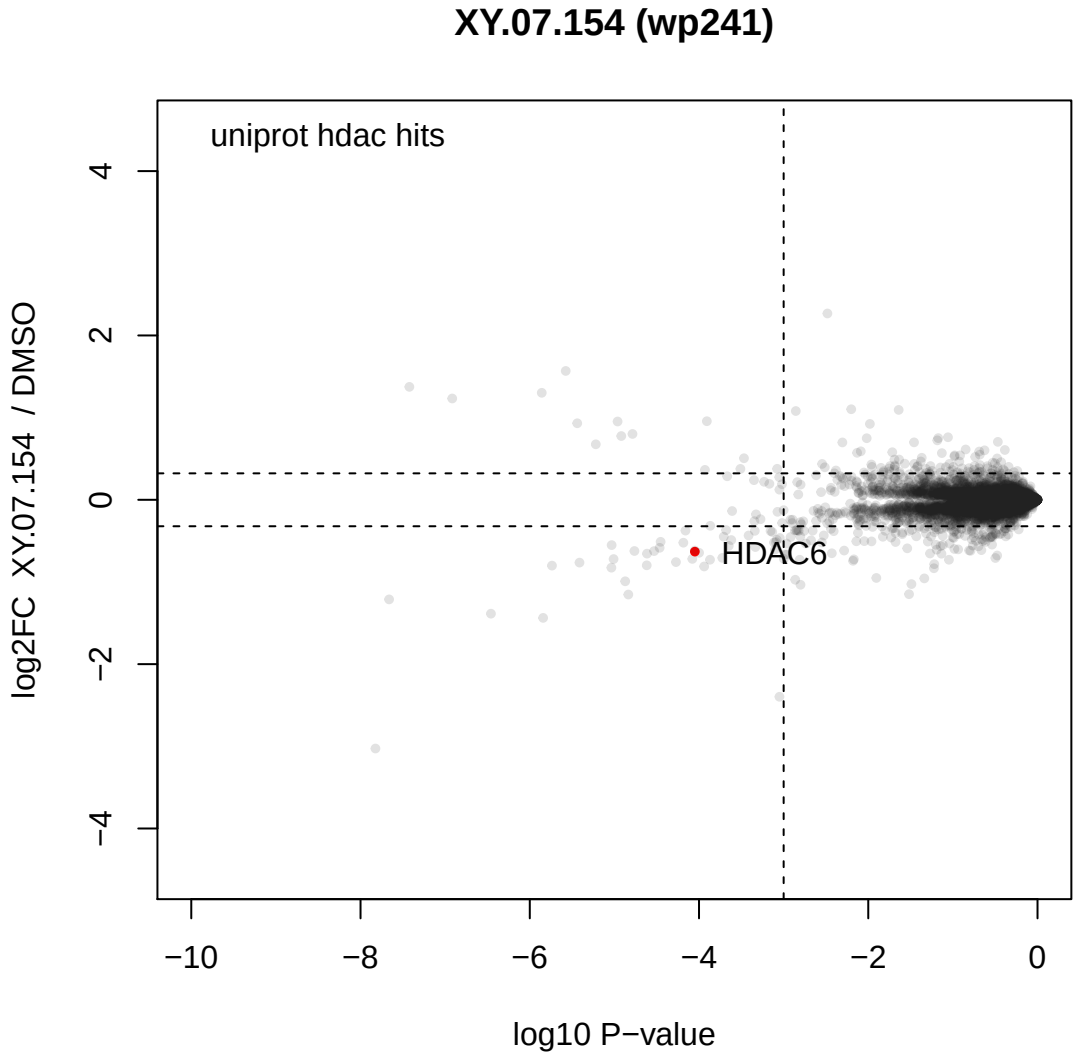

XY.07.147 (wp241)
all hits
HMGCS1
CCL5
BIRC2
AEN
log2FC XY.07.147 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

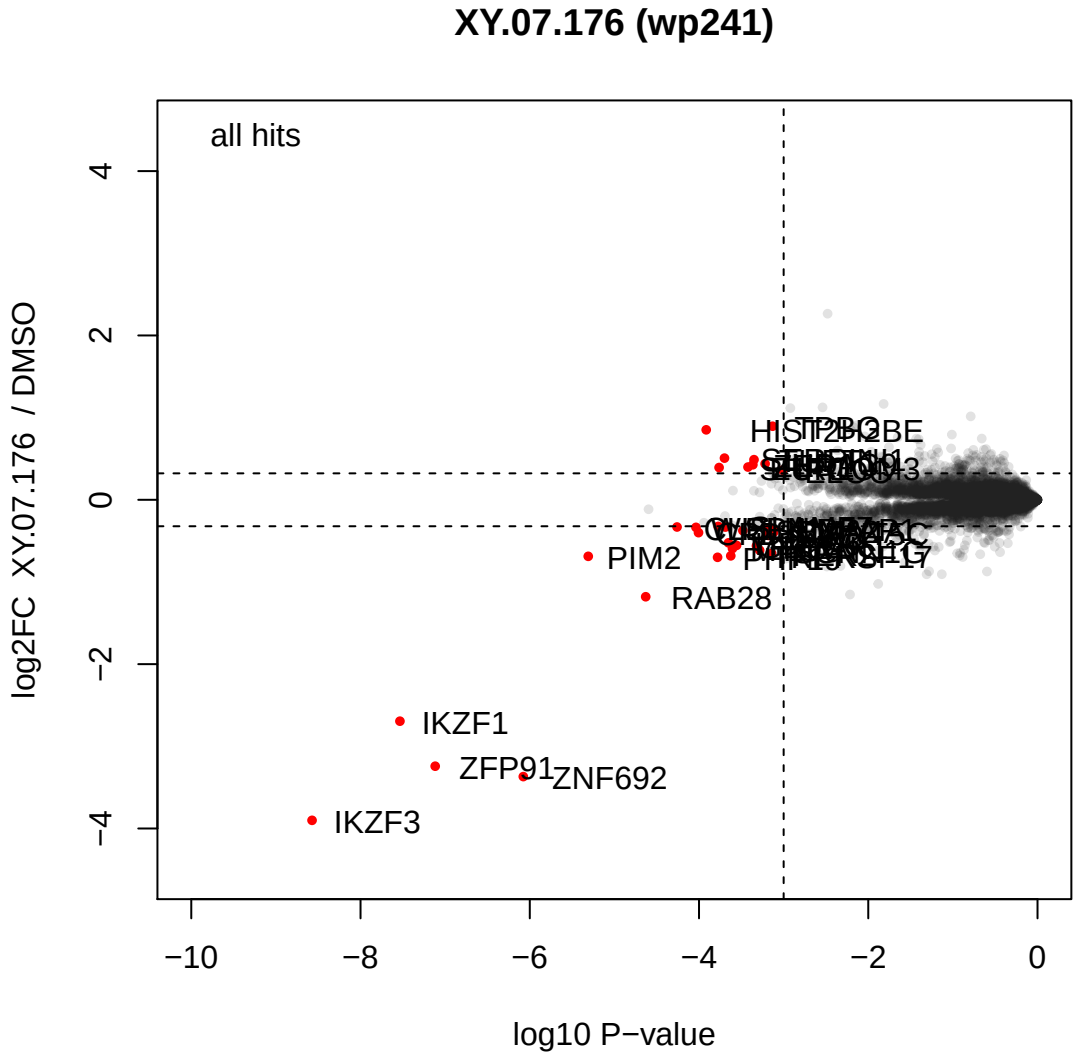

XY.07.147 (wp241)
uniprot hdac hits
HDAC6
log2FC XY.07.147 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

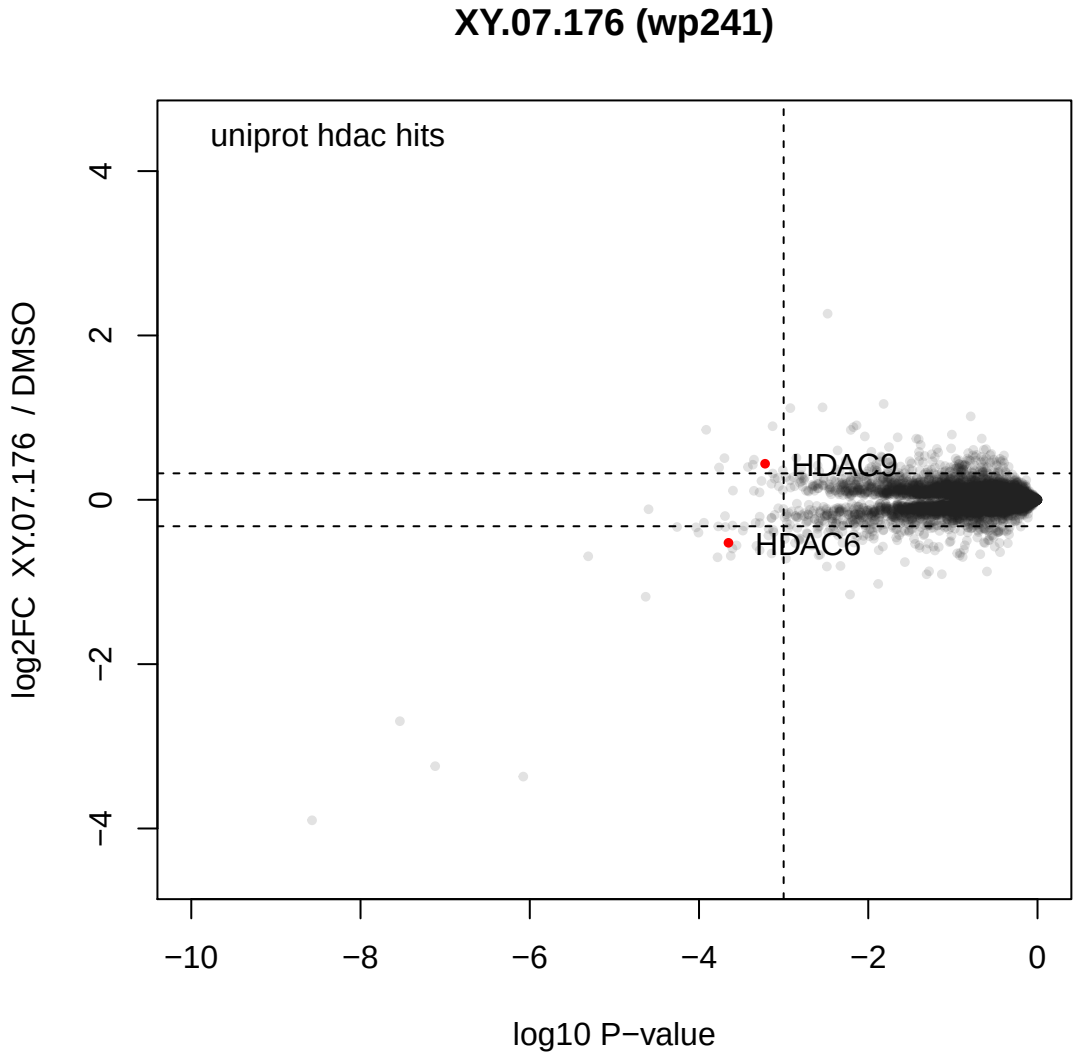

XY.07.152 (wp241)
all hits
log2FC XY.07.152 / DMSO
log10 P−value
EPB41L4B
FDFT1
SCD
HDAC7
TGOLN2
HDAC10
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

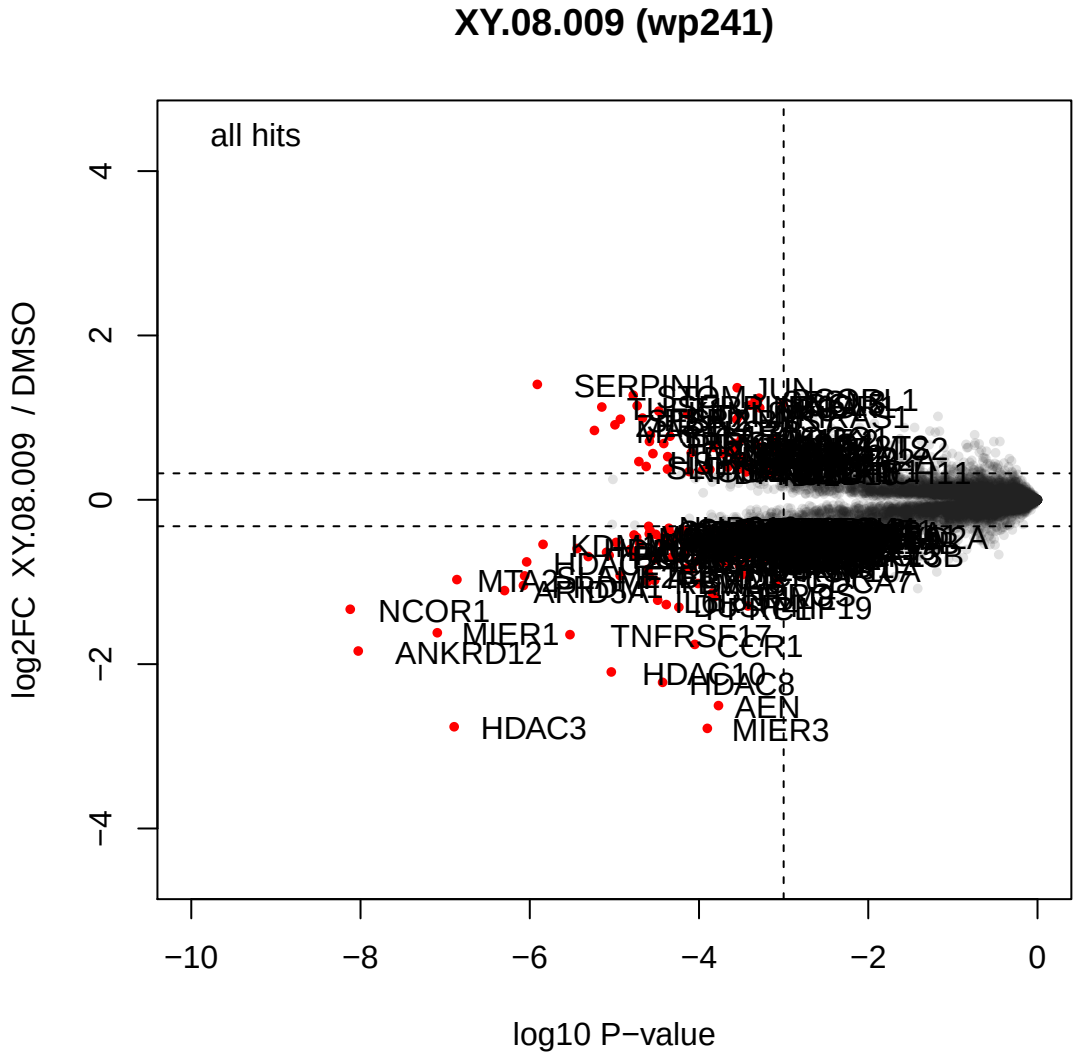

XY.07.152 (wp241)
uniprot hdac hits
log2FC XY.07.152 / DMSO
log10 P−value
HDAC7
HDAC10
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

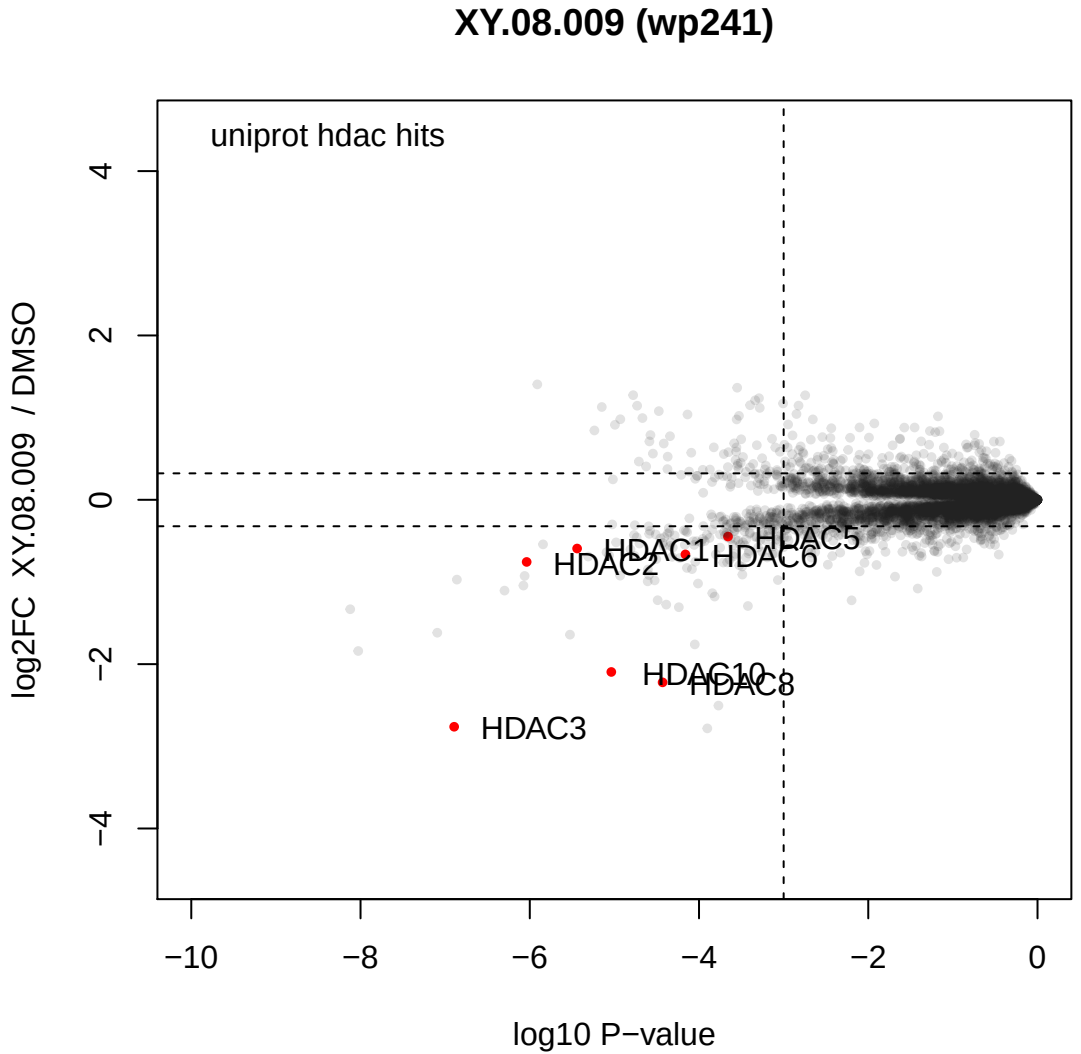

XY.07.154 (wp241)
all hits
log2FC XY.07.154 / DMSO
log10 P−value
RGS1
HMGCS1
FDFT1
APOB
MMADHC
TM2C
MSMO1
PIN1
RNF149
GLG1
IMPAD1
SLC38A10
SLC38A7
BIRC3
BIRC2

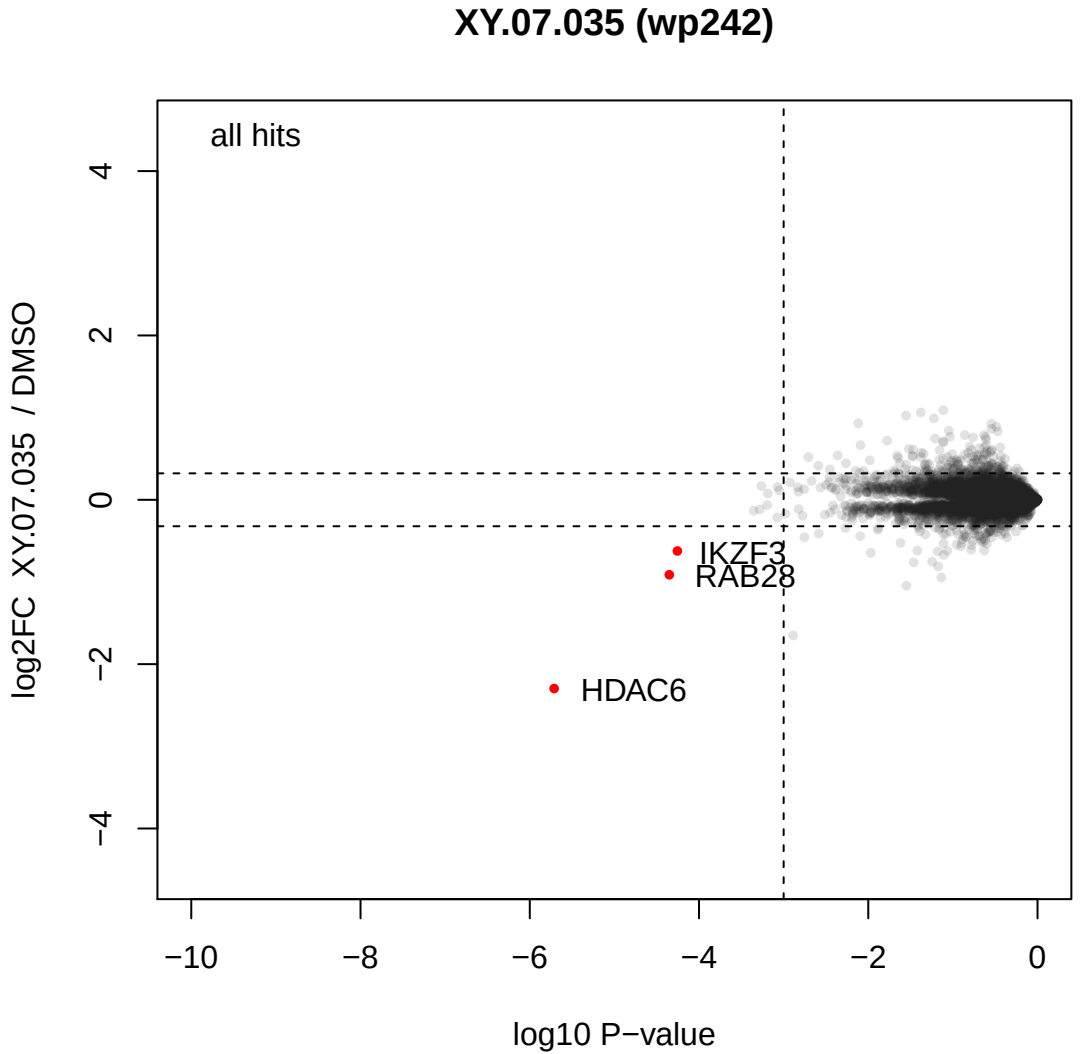

XY.07.154 (wp241)
uniprot hdac hits
log2FC XY.07.154 / DMSO
log10 P−value
HDAC6

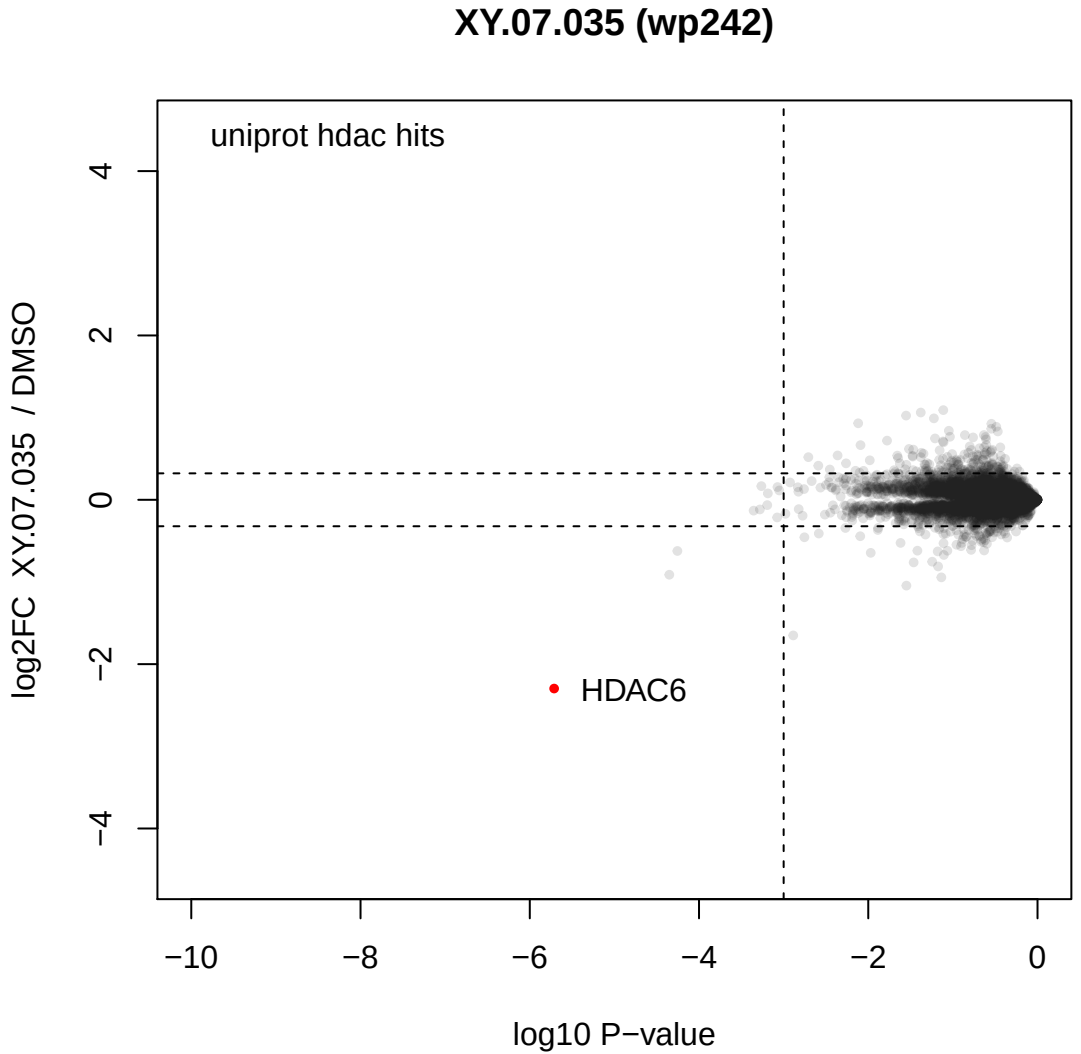

XY.07.176 (wp241)
all hits
log2FC XY.07.176 / DMSO
log10 P−value
PIM2
RAB28
IKZF1
ZFP91
ZNF692
IKZF3
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

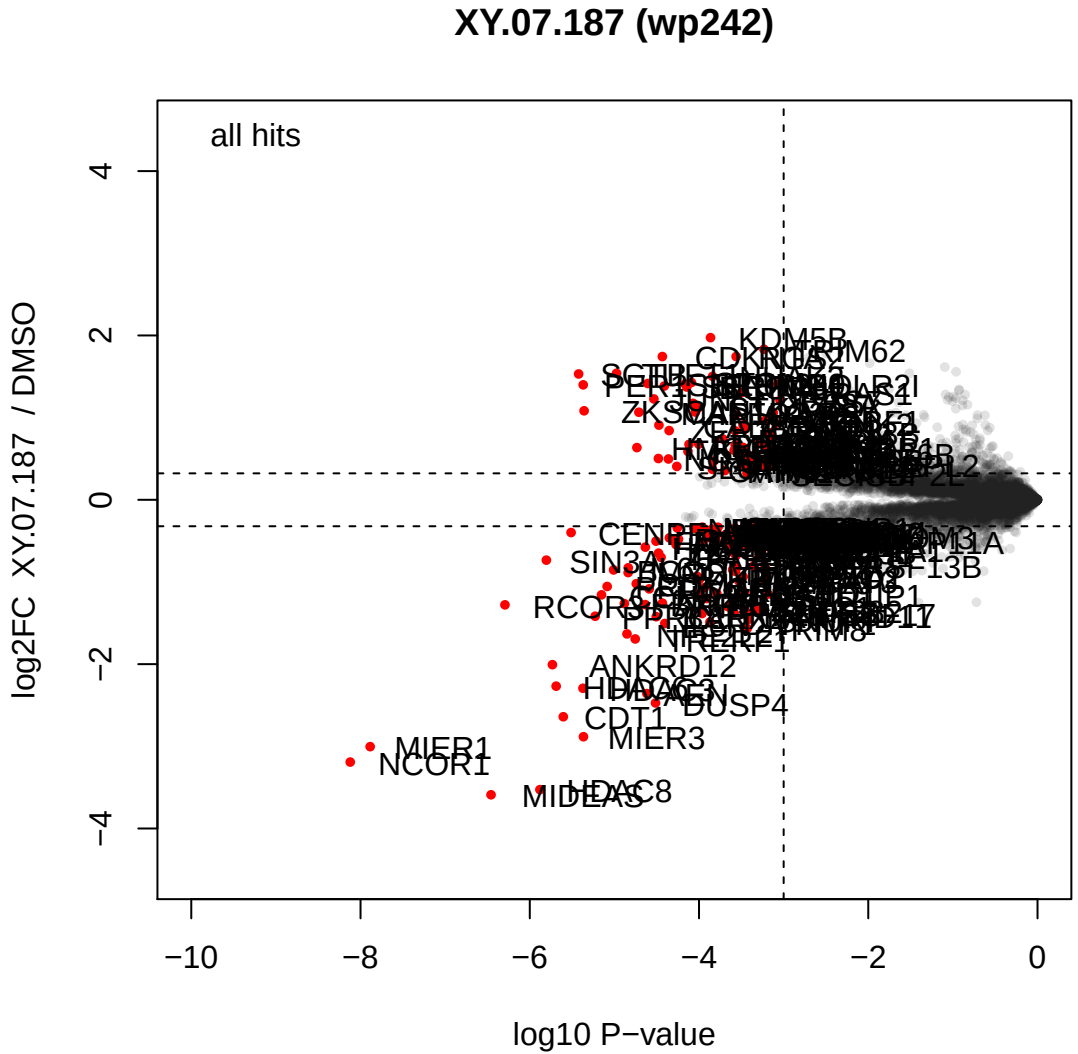

XY.07.176 (wp241)
uniprot hdac hits
log2FC XY.07.176 / DMSO
log10 P−value
HDAC9
HDAC6
4
2
0
−2
−4
−10
−8
−6
−4
−2
0

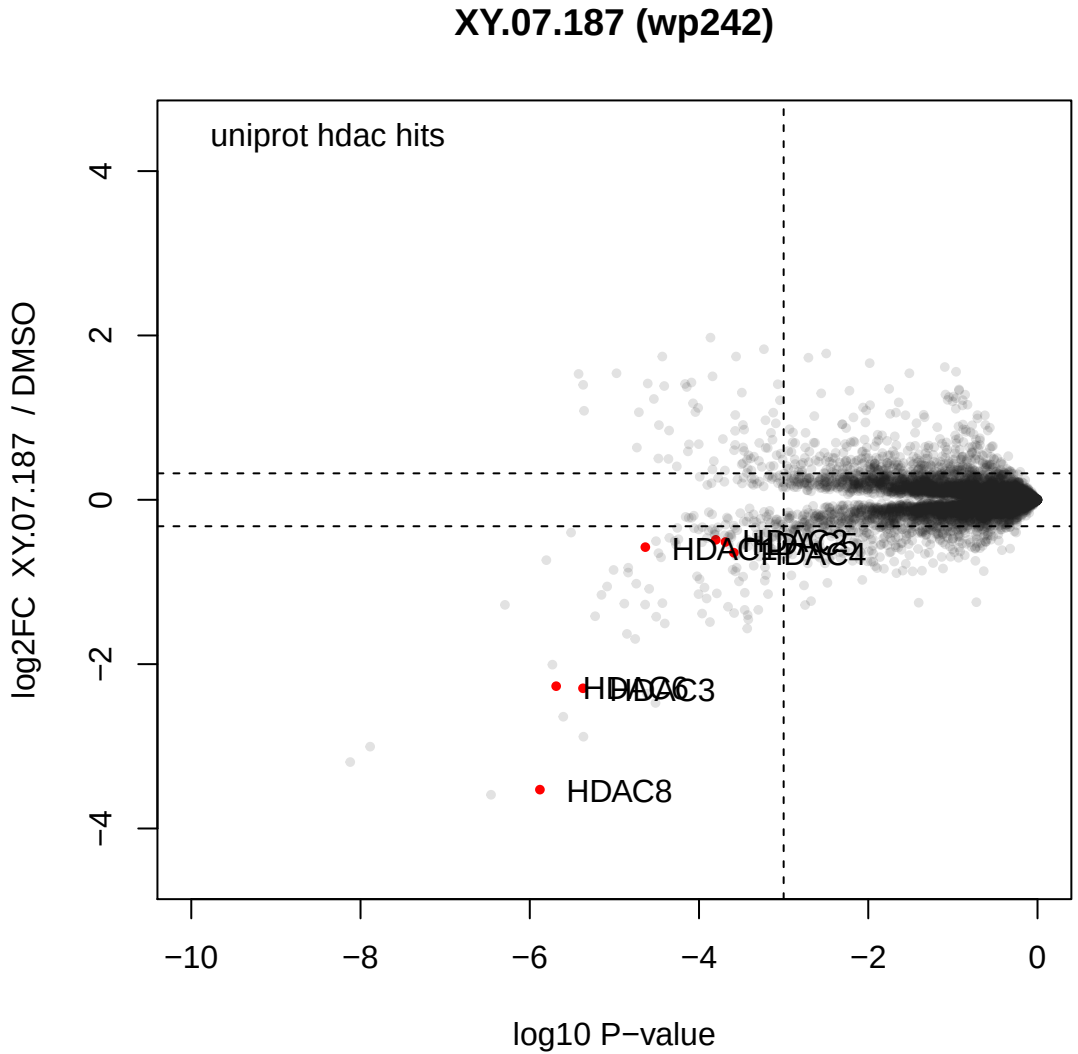

XY.08.009 (wp241)
all hits
log2FC XY.08.009 / DMSO
log10 P−value
SERPINI1
JUN
NCOR1
MIER1
ANKRD12
TNFRSF17
CCR1
HDAC10
HDAC8
AEN
HDAC3
MIER3
4
2
0
−2
−4
−10
−8
−6
−4
−2
0


XY.08.009 (wp241)
uniprot hdac hits
log2FC XY.08.009 / DMSO
log10 P−value
HDAC1
HDAC2
HDAC5
HDAC6
HDAC10
HDAC8
HDAC3
4
2
0
−2
−4
−10
−8
−6
−4
−2
0


XY.07.035 (wp242)
all hits
IKZF3
RAB28
HDAC6
log2FC XY.07.035 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0


XY.07.035 (wp242)
uniprot hdac hits
HDAC6
log2FC XY.07.035 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0


XY.07.187 (wp242)
all hits
log2FC XY.07.187 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0
KDM5B
CDK19
ZKSCAN1
CENPB
SIN3A
RCOR3
ANKRD12
HDAC3
BUSP4
CDT1
MIER3
MIER1
NCOR1
MIDEAS
HDAC8


XY.07.187 (wp242)
uniprot hdac hits
log2FC XY.07.187 / DMSO
log10 P−value
4
2
0
−2
−4
−10
−8
−6
−4
−2
0
HDAC2
HDAC4
HDAC3
HDAC8