Supporting Information

Proteochemometric Modeling Identifies Chemically Diverse Norepinephrine Transporter Inhibitors

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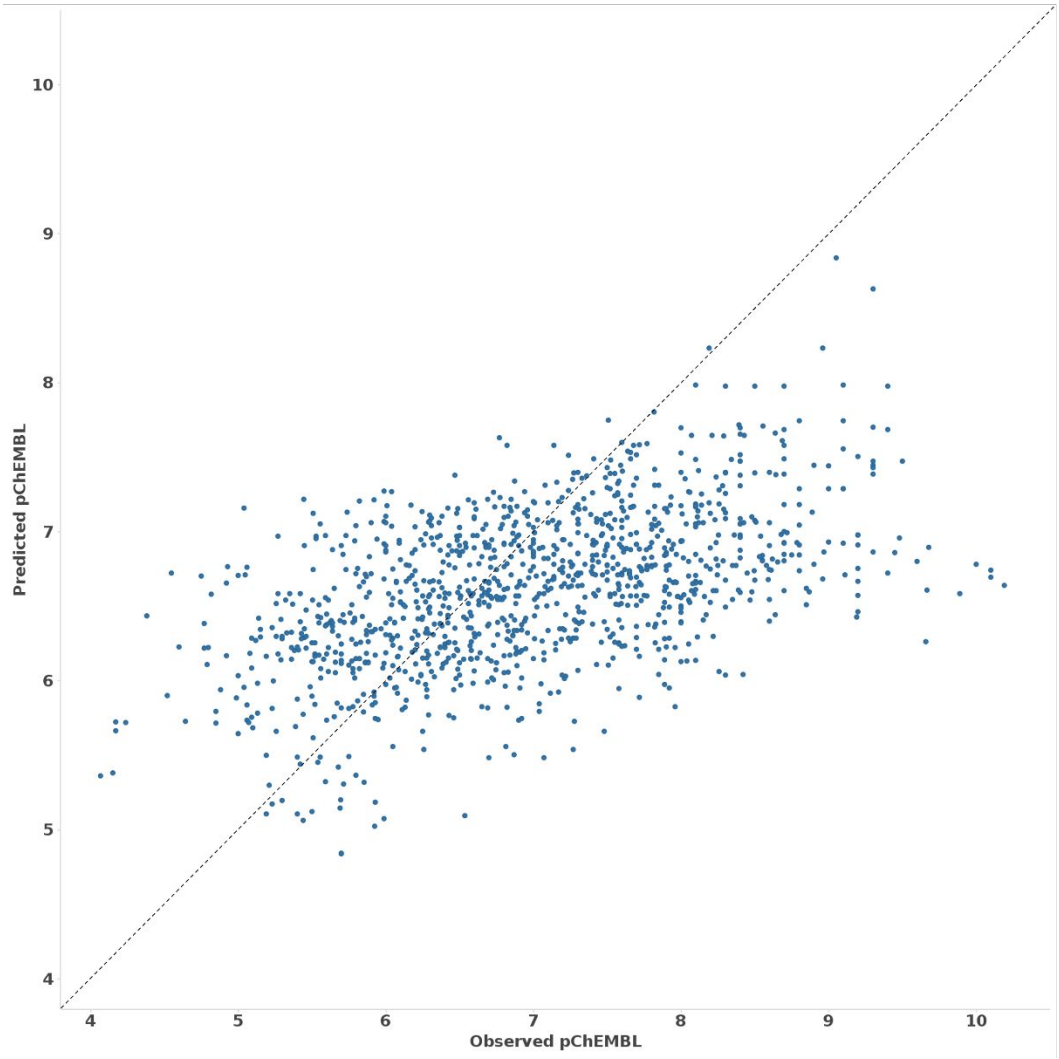


Figure S1. Predicted pChEMBL values of temporal split correlated to the observed values. Temporal split prediction where all known interactions of ChEMBL of 2010 and before were used as training set (15.106 data points) and those of 2011 and later (5.083 data points) were used as the test set. R^2 was 0.24 and RMSE was 1.02.

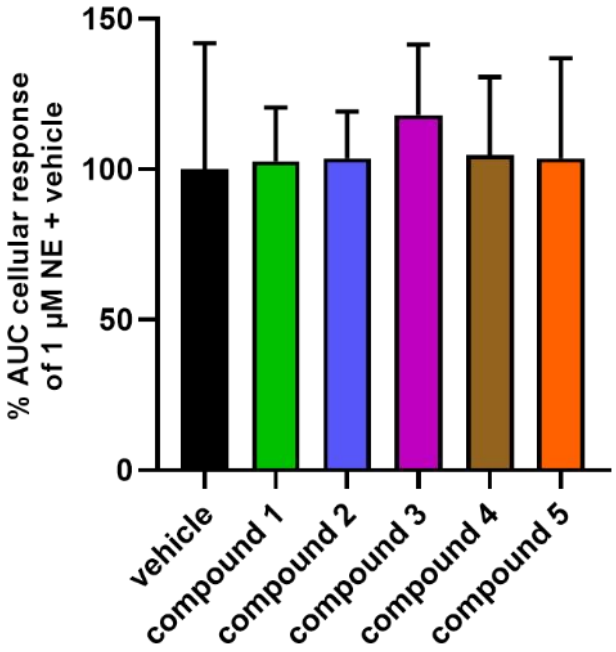


Figure S2. Counter screen of the five hit compounds in a label-free impedance-based TRACT assay. JumpIn-NET were not induced with doxycycline and as such did not express NET. Cells were pretreated for 1 h with either vehicle or 10 µM of the hit compound. Subsequently, cells were stimulated with 1 µM norepinephrine (NE) and Cell Index (CI) was measured for 30 min. Cellular responses are expressed as the net area under the curve (AUC) of the first 30 minutes after stimulation with NE. Data were normalized to the response of NE only (vehicle, 100%). Data are shown as the mean +/- SD of two separate experiments each performed in duplicate.

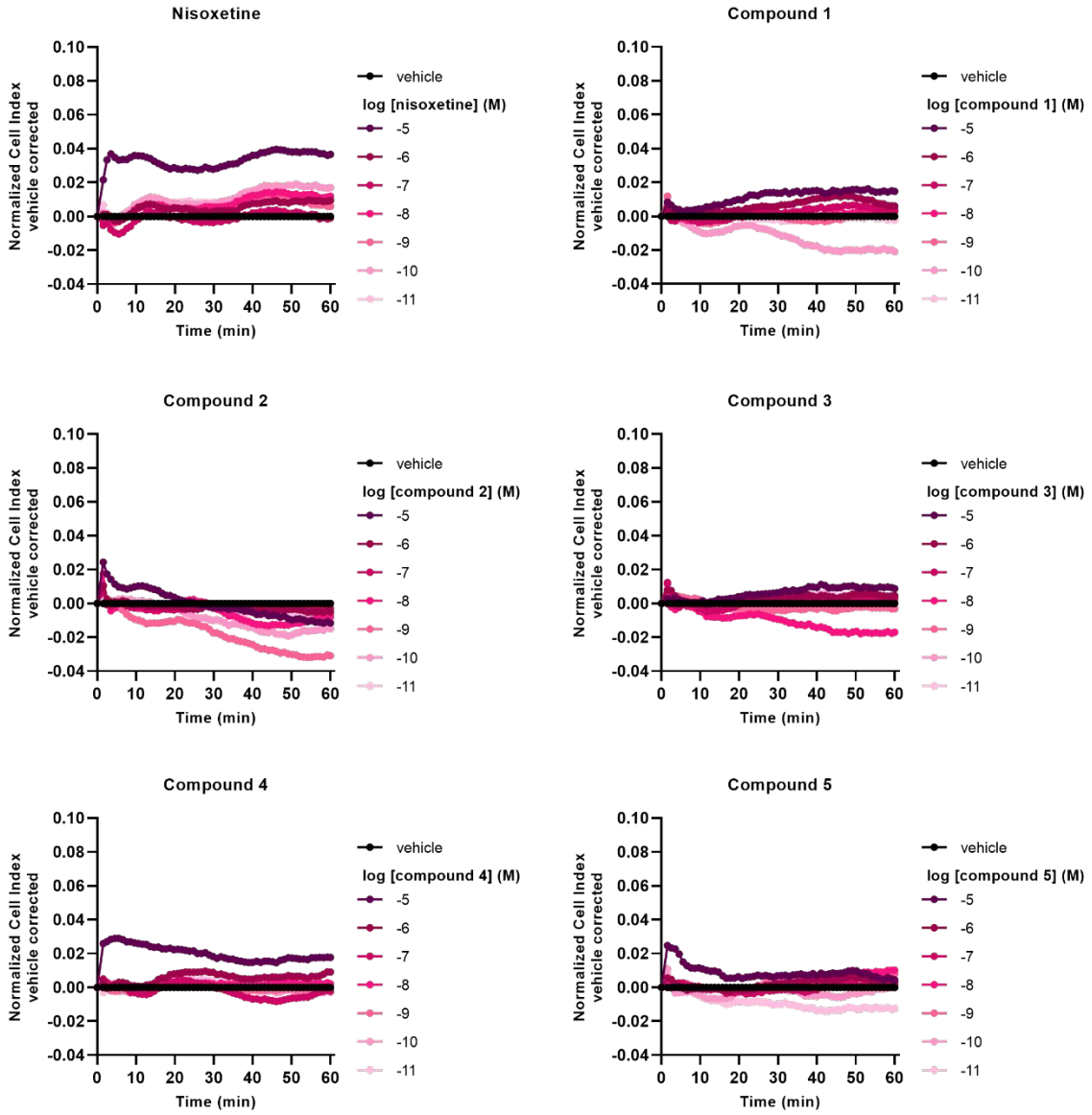


Figure S3. Representative xCELLigence traces of JumpIn-NET cells during inhibitor pretreatment in a label-free impedance-based TRACT assay. Cells were pretreated for 1 h with either vehicle or increasing concentrations of nisoxetine or hit compound. Cell Index was normalized to the time point prior to inhibitor addition (t = 0 min). Data are shown as the mean of a representative experiment.

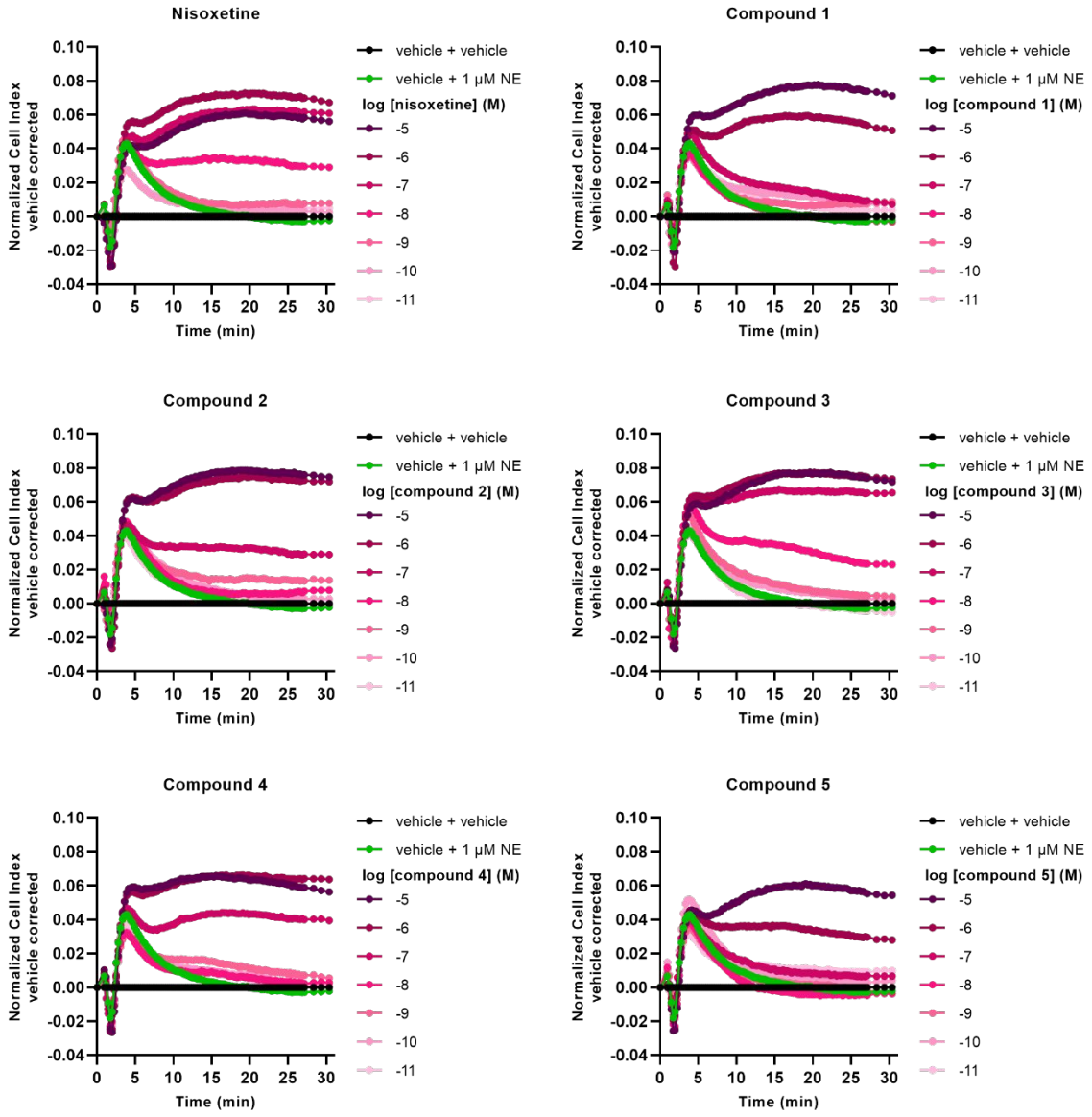


Figure S4. Representative xCELLigence traces of JumpIn-NET cells during norepinephrine (NE) stimulation in a label-free impedance-based TRACT assay. Cells were pretreated for 1 h with either vehicle or increasing concentrations of nisoxetine or hit compound, and subsequently stimulated with vehicle or 1 µM NE. Cell Index was normalized to the time point prior to NE addition (t = 0 min). Data are shown as the mean of a representative experiment.

Table S1. Molecular and Protein descriptors used throughout the model building process.

Molecular Descriptors		Protein Descriptors	
ALogP	SCFC 6	Amino Acid Composition	ACC c scales
Molecular Weight	FPFC 6	Dipeptide Composition	ACC DPPS
Number of Hydrogen Donors	EPFC 6	Auto Correlation Descriptors	ACC E scales
Number of Hydrogen Acceptors	LPFC 6	Composition Transition Distribution	ACC G scales
Number of Rotatable Bonds	SPFC 6	Quasi Sequence Order Descriptors	ACC HESH
Number of Bridge Bonds	FEFC 6	Pseudo Amino Acid Composition	ACC HSEHPCSV
Number of Atoms	EEFC 6	Amphiphilic Pseudo Amino Acid Composition	ACC Norinder
Number of Rings	LEFC 6	Total Amino Acid Properties	ACC Kidera
Number of Aromatic Rings	SEFC 6	Aligned Z scales Sandberg	ACC P scales
Number of Fragments	FHFC 6	Aligned FASGAI	ACC QCP
N Plus O Count	EHFC 6	Aligned BLOSUM	ACC Sneath
Molecular Solubility	LHFC 6	ACC Z scales Hellberg	ACC SVEEVA
Molecular Surface Area	SHFC 6	ACC Z scales Jonsson	ACC SVHEHS
Molecular Polar Surface Area	FCFP 6	ACC Z scales Sandberg	ACC SVRG
Molecular Polar Solvent-Accessible Surface Area (SASA)	ECFP 6	ACC Z scales binary	ACC SVWG
Estate Keys	LCFP 6	ACC T scales	ACC V scales
Estate Counts	SCFP 6	ACC ST scales	ACC VSGETAWAY
MDLPublicKeys	FPFP 6	ACC VHSE	ACC VSTPV
MDL2DKeys960	EPFP 6	ACC ISA ECI	ACC VSW
MDL2DKeys166	LPFP 6	ACC GRID t-score	ACC VTSA
PHFP 2-4	SPFP 6	ACC VSTV	ACC SVGER
PHRFP 2-4	FEFP 6	ACC MSWHIM	ACC PSM
PHPFP 2-4	EEFP 6	ACC_FASGAI	ACC SSIA AM1
PHFC 2-4	LEFP 6	ACC_BLOSUM	ACC SSIA PM3
PHPFC 2-4	SEFP 6	ACC_VARIMAX	ACC SSIA HF
PHRFC 2-4	FHFP 6	ACC Protein fingerprint numerical	ACC SSIA DFT
FCFC 6	EHFP 6	ACC Protein fingerprint hash	
ECFC 6	LHFP 6		
LCFC 6	SHFP 6		

Table S2. Optimal settings obtained from stepwise feature selection and grid parameter optimization. *Displayed are the optimal settings for random forest, gradient boosting, partial least squares, and the final model which contained an ensemble of random Forest and gradient boosting, with a partial least squares stack on top of it.*

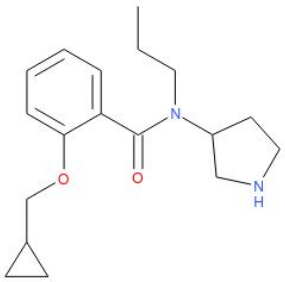
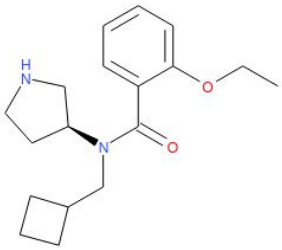
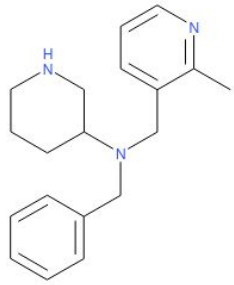
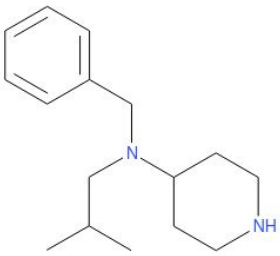
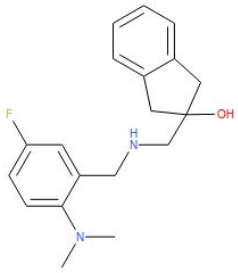
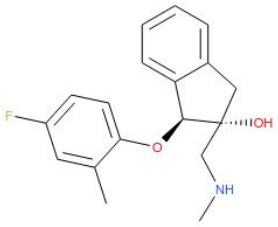
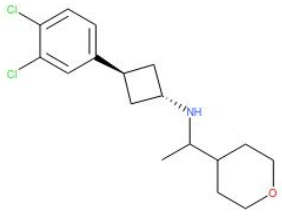
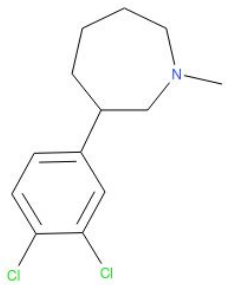
Optimal Model	Optimal Features	Optimal Parameters	
Random Forest	Num_H_Donors Num_RotatableBonds Num_Atoms Molecular_Solubility Molecular_SurfaceArea PHPFC2 PHRFC2 SCFC6 G9TotalAminoAcidProperties ACC_ISA_ECI ACC_ProtFP_hash	Number of Trees	1000
		Number of Descriptors	Sqrt(D)*
		Minimum Node Size	1
		Maximum Depth	None
Gradient Boosting	MDLPublicKeys MDL2DKeys960 G4CompositionTransitionDistribution Aligned_FASGAI ACC_VARIMAX ACC_ProtFP_numerical ACC_DPPS ACC_HESH ACC_SVHEHS ACC_VSTPV	Maximum number of Trees	1000
		Learning Rate	0.1
		Gamma	0.3
		Maximum Depth	7
		Data Fraction	1.0
		Descriptor Fraction	0.5
Partial Least Squares	MDL2DKeys960 LEFC6 SCFP6 FPFP6 FEFP6 G1AminoAcidComposition ACC_FASGAI ACC_Norinder ACC_SVRG ACC_SVGER	Number of Variables	200
1st stack Random Forest & Gradient Boost **2nd Stack Partial Least Squares**	AlogP Num_H_Acceptors Num_BridgeBonds Molecular_Solubility Estate_Counts PHPFC2 G1AminoAcidComposition G9TotalAminoAcidProperties ACC_ISA_ECI Gradient Boost Preditions Random Forest Predictions Random Forest Predictions StdDev	Number of Variables	100

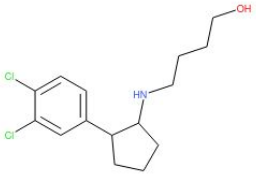
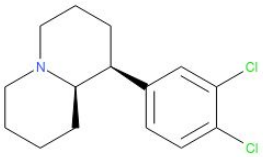
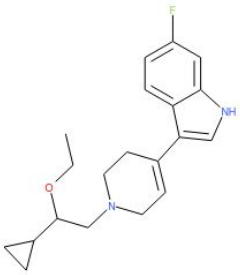
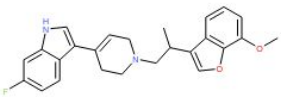
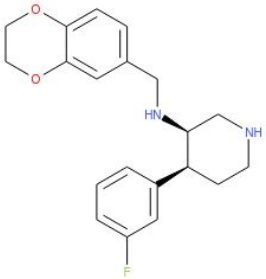
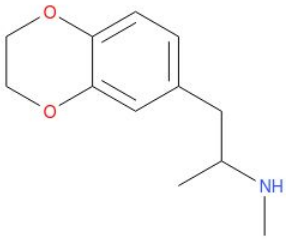
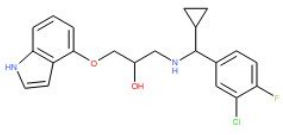
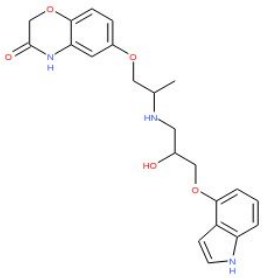
Table S3. Cluster centers that were chosen for experimental follow-up (46 centers). *Of these, 32 were able to be synthesized, as shown in the right-most column.*

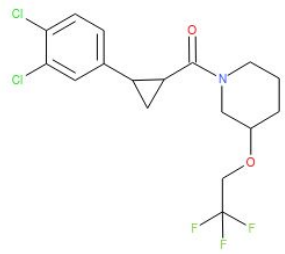
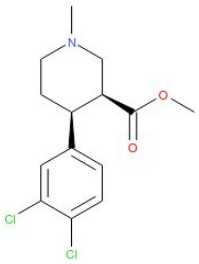
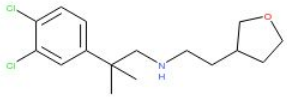
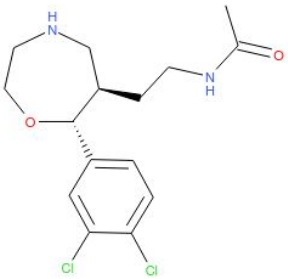
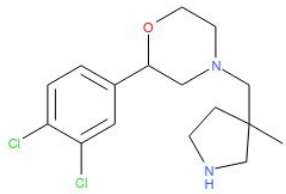
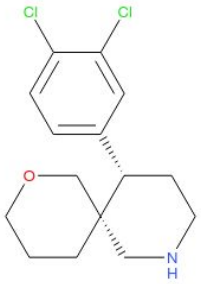
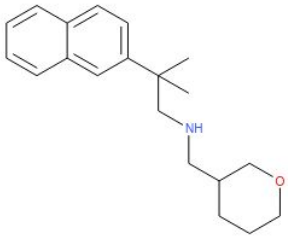
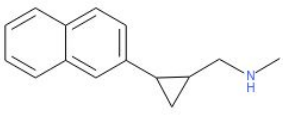
Enamine ID Number	SMILES	Synthesized
Z2393213853	CCCN(C(=O)C1=CC=CC=C1OCC1CC1)C1CCNC1	Yes
Z2444727652	CC1=NC=CC=C1CN(CC1=CC=CC=C1)C1CCCNC1	No
Z2769565776	CN(C)C1=CC=C(F)C=C1CNCC1(O)CC2=CC=CC=C2C1	Yes
Z1986623199	CC(N[C@H]1C[C@H](C2=CC=C(Cl)C(Cl)=C2)C1)C1CCOCC1	Yes
Z1904820040	OCCCCNC1CCCC1C1=CC=C(Cl)C(Cl)=C1	Yes
PV-001918160326	CCOC(CN1CC=C(C2=C[NH]C3=CC(F)=CC=C23)CC1)C1CC1	Yes
Z2569757498	FC1=CC=CC([C@@H]2CCNC[C@@H]2NCC2=CC=C3OCCOC3=C2)=C1	Yes
PV-001919825446	OC(CNC(C1=CC=C(F)C(Cl)=C1)C1CC1)COC1=CC=CC2=C1C=C[NH]2	No
Z1083362508	O=C(C1CC1C1=CC=C(Cl)C(Cl)=C1)N1CCCC(OCC(F)(F)F)C1	Yes
Z1783772638	CC(C)(CNCCC1CCOC1)C1=CC=C(Cl)C(Cl)=C1	Yes
Z2444828348	CC1(CN2CCOC(C3=CC=C(Cl)C(Cl)=C3)C2)CCNC1	Yes
Z2698567135	CC(C)(CNCC1CCCOC1)C1=CC=C2C=CC=CC2=C1	Yes
Z1663514926	CC(C)C(NCCC1CCOC1)C1=CC=C(Cl)C(Cl)=C1	Yes
PV-000916662553	C#CCCNCC1CCCN1C(=O)C1=CC=CC2=C1OCC2(C)C	No
PV-001921689112	CCN1CCC(N[C@@H]2CCO[C@H]2C2=CC=C(Cl)C(F)=C2)C1=O	Yes
Z2447436630	ClC1=CC=CC(C2=NC(CN(C3CC3)C3CCNC3)=CO2)=C1	Yes
Z2843312692	CN1C=C(C2CC3CCC(C2)N3CC(O)C2=CC=C(Cl)C(F)=C2)C=N1	Yes
PV-001918950467	FC1=CC=CC(CCN2CCN(C3=C(Cl)C=CC=C3Cl)CC2)=C1	Yes
PV-001919382948	CC1(C2=CC=CC(Cl)=C2)CCN(CC(O)COC2=CC=CC3=C2C=C[NH]3)CC1	No
PV-001919716605	CCC1=CC=C(N2CCN(CC(O)COC3=CC=CC4=C3C=C[NH]4)CC2)C=C1Cl	No
Z2444770829	FC(F)(F)C1=CC(CN(C2CC2)C2CCNC2)=CC=C1Cl	No
Z2445178480	ClC1=CC=C(CCC2=NC(C3CCNCC3)=NO2)C=C1Cl	No
Z2617873335	ClC1=CC=CC(OCC2=NOC(C[C@H]3CCNC3)=N2)=C1Cl	Yes
Z2846041003	CC(C1=CC=C(Cl)C(Cl)=C1)N1C=C(C2CCCNC2)N=N1	Yes
Z2488796202	CCC1(C(=O)N2CC=C(C3=C[NH]C4=CC(F)=CC=C34)CC2)CCCN1	Yes
Z2354724931	COC1=CC=C(CNC2CNCCC2(F)F)C=C1OCC1=CC=CC=C1	No
PV-000923491934	CCCNCC1(C)CCN(C(=O)C2=C[NH]C3=CC=C(F)C=C23)C1	No
PV-001917796783	CCN(CC1(C2=CC=C(Cl)C(Cl)=C2)CCC1)C1CC1	No
Z1421251686	OC(COC1=CC=CC2=C1C=C[NH]2)CN1CCC(C2=CC=C(F)C(F)=C2)CC1	No
Z2436746713	O=C(CCC1CCNC1)N1CCOC(C2=CC=C(Cl)C(Cl)=C2)C1	Yes
PV-001930327687	ClC1=CC=C(C2CCCC2NC[C@@H]2CCCO2)C=C1Cl	No
PV-001923897672	CCC1CC(NCC(C)(C)C2=CC=C(Cl)C(Cl)=C2)CCO1	Yes
Z1505378916	C1=CC=C(C2CN(CCN3C=CN=C3)CC3=CC=CC=C32)C=C1	No
Z2201777668	OCC(NC1CCN(CC2=CC=CC=C2Cl)CC1)C1=CC=C(Br)C(F)=C1	Yes
PV-001918897538	CC1CC(CN(CCO)CC2=CC=C(Cl)C(Cl)=C2)C1	Yes
PV-001917367008	ClC1=CC=C(C2CN(CC[C@@H]3C[C@H]3C3CC3)CCO2)C=C1Cl	Yes
Z2361435743	CC(C)(CNC(=O)NCC1CNCCO1)C1=CC=C(Cl)C(Cl)=C1	Yes
Z1485114833	OC(COC1=CC=CC=C1F)CN1CC=C(C2=C[NH]C3=CC(F)=CC=C23)CC1	Yes
Z3045122589	OC(CNCC1CSC2=CC=CC=C2O1)C1=CC=C(F)C(F)=C1	Yes
PV-001926691632	CC1=CC(Cl)=CC=C1OC1=CC=C(F)C=C1CNC[C@H]1C[C@H](O)C1	Yes

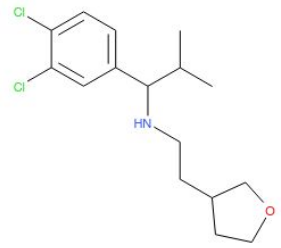
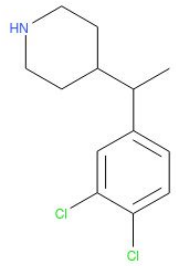
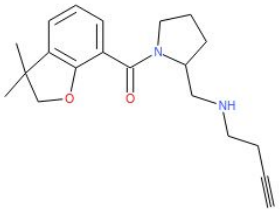
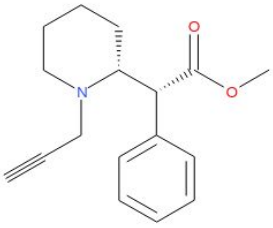
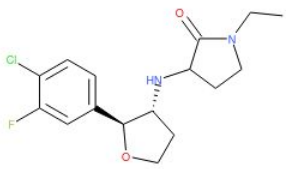
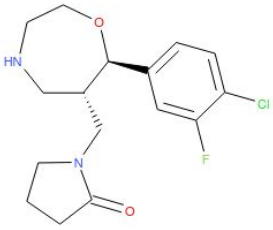
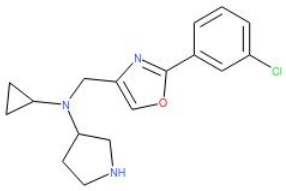
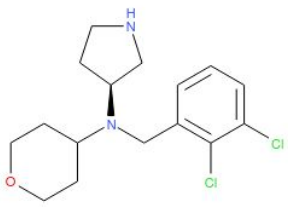
PV-001919611983	CC(C)NC(=O)OCC1CCCCN1C[C@H](O)C1=CC=C(Cl)C(Cl)=C1	Yes
Z2722622816	OC(CNC1CCN(C2=CC=C(Cl)C=C2F)C1)C1=CC=CC(F)=C1	Yes
Z2444696415	CCCN(CC1=CC=C(F)C=C1C(F)(F)F)C1CCNCC1	No
Z3100431738	O=C(C1=CN=C(C2CCNCC2)O1)N(CC1=CC=C(Cl)C(Cl)=C1)C1CC1	Yes
PV-001925822957	CC1=CC(Cl)=CC=C1OC1=CC=C(F)C=C1CNCC(C)CN(C)C	Yes
Z2488563933	CCCN(C(=O)C1=CC=C2[NH]C=CC2=C1)C1CCNC1	Yes

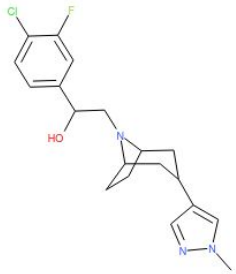
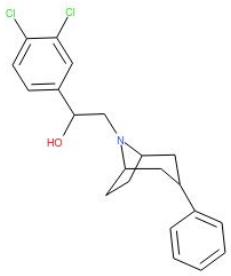
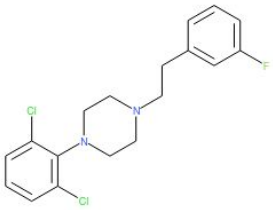
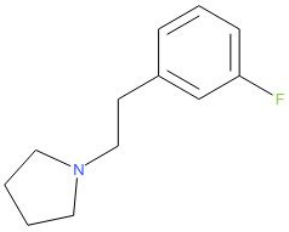
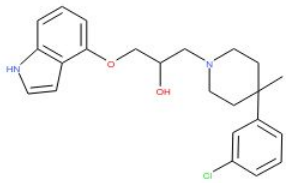
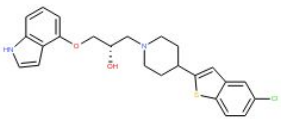
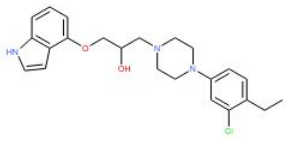
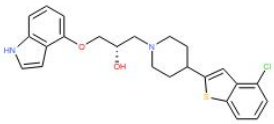
Table S4: Selected cluster compounds and their nearest structurally similar compound in the training set. *Based on Tanimoto Similarity (ECFP_6). The Enamine 'Q-Code' refers to the codes found in Table S6.*

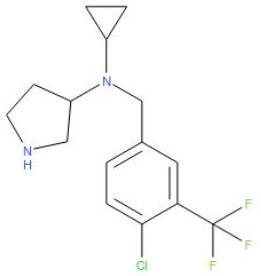
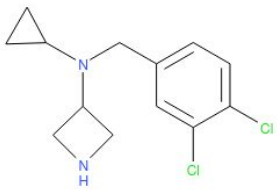
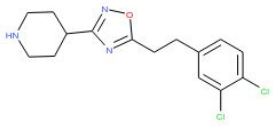
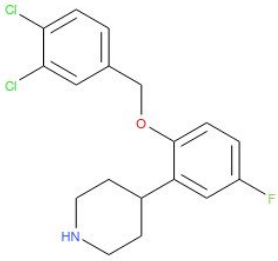
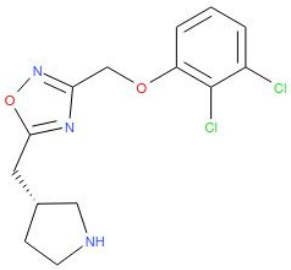
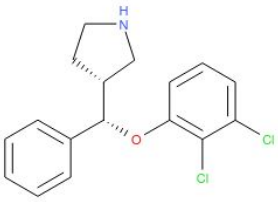
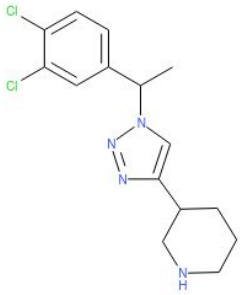
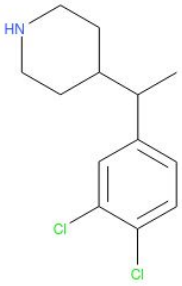
Cluster Molecule		Nearest Training Molecule	
	**Cluster SMILES** CCCN(C(=O)C1=CC=CC=C1OCC1CC1)C1CCNC1 **Enamine ID** Z2393213853 **Enamine Q-Code** Q754936$1		**Training SMILES** CCOc1ccccc1C(=O)N(CC2CCC2)[C@H]3CCNC3 **ChEMBL ID** CHEMBL551471 **Tanimoto Similarity** 0.557
	**Cluster SMILES** CC1=NC=CC=C1CN(CC1=CC=CC=C1)C1CCCNC1 **Enamine ID** Z2444727652 **Enamine Q-Code** n/a		**Training SMILES** CC(C)CN(Cc1ccccc1)C2CCNCC2 **ChEMBL ID** CHEMBL207837 **Tanimoto Similarity** 0.333
	**Cluster SMILES** CN(C)C1=CC=C(F)C=C1CNCC1(O)CC2=CC=CC=C2C1 **Enamine ID** Z2769565776 **Enamine Q-Code** Q754914$1		**Training SMILES** CNC[C@]1(O)Cc2ccccc2[C@@H]1Oc3ccc(F)cc3C **ChEMBL ID** CHEMBL506137 **Tanimoto Similarity** 0.245
	**Cluster SMILES** CC(N[C@H]1C[C@H](C2=CC=C(Cl)C(Cl)=C2)C1)C1CCOCC1 **Enamine ID** Z1986623199 **Enamine Q-Code** Q754932$4		**Training SMILES** CN1CCCCC(C1)c2ccc(Cl)c(Cl)c2 **ChEMBL ID** CHEMBL2326691 **Tanimoto Similarity** 0.311

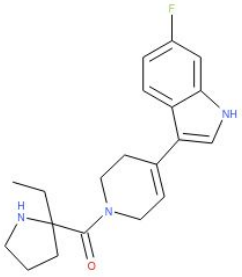
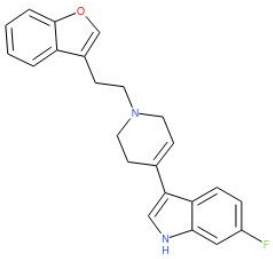
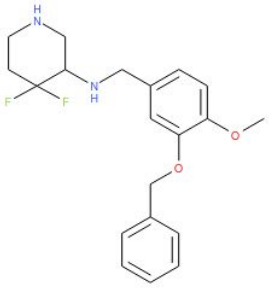
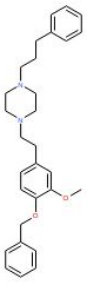
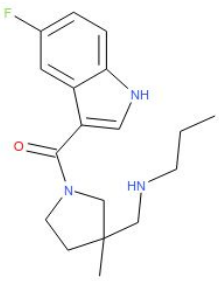
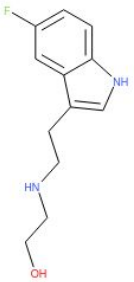
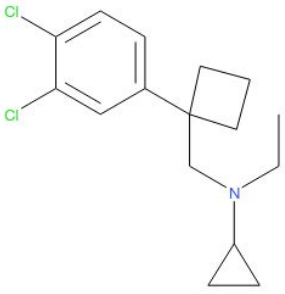
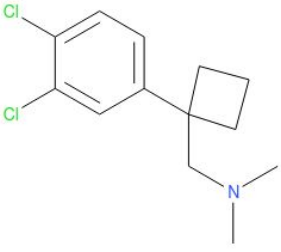
	**Cluster SMILES** OCCCCNC1CCCC1C1=CC=C(Cl)C(Cl)=C1 **Enamine ID** Z1904820040 **Enamine Q-Code** Q754913$15		**Training SMILES** Clc1ccc(cc1Cl)[C@@H]2CCCN3CCCC[C@H]23 **ChEMBL ID** CHEMBL559186 **Tanimoto Similarity** 0.320
	**Cluster SMILES** CCOC(CN1CC=C(C2=C[NH]C3=CC(F)=CC=C23)CC1)C1CC1 **Enamine ID** PV-001918160326 **Enamine Q-Code** Q754917$41		**Training SMILES** COc1cccc2c(coc12)C(C)CN3CCC(=CC3)c4c[nH]c5cc(F)ccc4 5 **ChEMBL ID** CHEMBL597479 **Tanimoto Similarity** 0.500
	**Cluster SMILES** FC1=CC=CC([C@@H]2CCNC[C@@H]2NCC2=CC=C3OCCOC3=C2)=C1 **Enamine ID** Z2569757498 **Enamine Q-Code** Q754942$4		**Training SMILES** CNC(C)Cc1ccc2OCCOc2c1 **ChEMBL ID** CHEMBL3603954 **Tanimoto Similarity** 0.287
	**Cluster SMILES** OC(CNC(C1=CC=C(F)C(Cl)=C1)C1CC1)COC1=CC=CC2=C1C=C[NH]2 **Enamine ID** PV-001919825446 **Enamine Q-Code** n/a		**Training SMILES** CC(COc1ccc2OCC(=O)Nc2c1)NCC(O)COc3cccc4[nH]ccc34 **ChEMBL ID** CHEMBL183921 **Tanimoto Similarity** 0.397

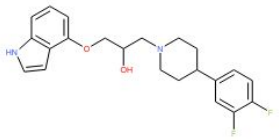
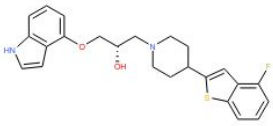
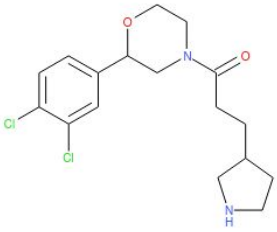
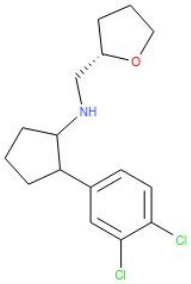
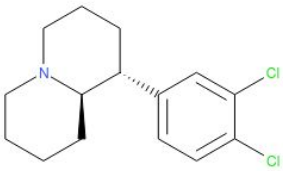
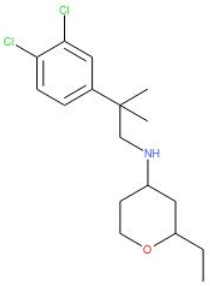
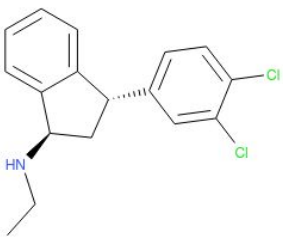
	**Cluster SMILES** O=C(C1CC1C1=CC=C(Cl)C(Cl)=C1)N1CCCC(OCC(F)(F)F)C1 **Enamine ID** Z1083362508 **Enamine Q-Code** Q754940$2		**Training SMILES** COC(=O)[C@@H]1CN(C)CC[C@@H]1c2ccc(Cl)c(Cl)c2 **ChEMBL ID** CHEMBL397490 **Tanimoto Similarity** 0.333
	**Cluster SMILES** CC(C)(CNCCC1CCOC1)C1=CC=C(Cl)C(Cl)=C1 **Enamine ID** Z1783772638 **Enamine Q-Code** Q754928$34		**Training SMILES** CC(=O)NCC[C@@H]1CNCCO[C@H]1c2ccc(Cl)c(Cl)c2 **ChEMBL ID** CHEMBL3593401 **Tanimoto Similarity** 0.206
	**Cluster SMILES** CC1(CN2CCOC(C3=CC=C(Cl)C(Cl)=C3)C2)CCNC1 **Enamine ID** Z2444828348 **Enamine Q-Code** Q754918$1		**Training SMILES** Clc1ccc(cc1Cl)[C@@H]2CCNC[C@@]23CCCOC3 **ChEMBL ID** CHEMBL1173607 **Tanimoto Similarity** 0.286
	**Cluster SMILES** CC(C)(CNCC1CCCOC1)C1=CC=C2C=CC=CC2=C1 **Enamine ID** Z2698567135 **Enamine Q-Code** Q905064$2		**Training SMILES** CNCC1CC1c2ccc3ccccc3c2 **ChEMBL ID** CHEMBL249331 **Tanimoto Similarity** 0.253

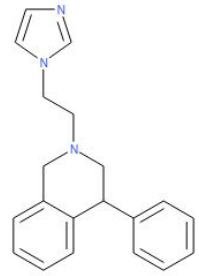
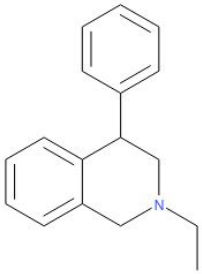
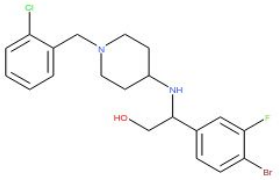
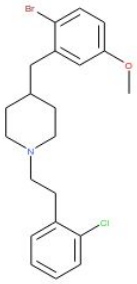
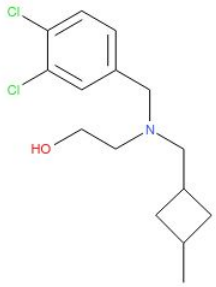
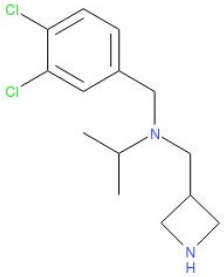
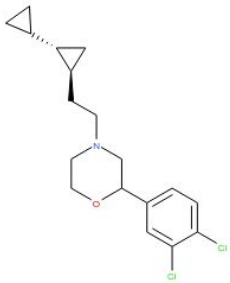
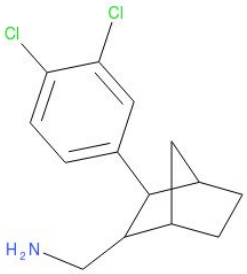
	**Cluster SMILES** CC(C)C(NCCC1CCO C1)C1=CC=C(Cl)C(Cl)=C1 **Enamine ID** Z1663514926 **Enamine Q-Code** Q754931$3		**Training SMILES** CC(C1CCNCC1)c2cc c(Cl)c(Cl)c2 **ChEMBL ID** CHEMBL2407334 **Tanimoto Similarity** 0.288
	**Cluster SMILES** C#CCCNCC1CCCN1 C(=O)C1=CC=CC2=C 1OCC2(C)C **Enamine ID** PV-000916662553 **Enamine Q-Code** n/a		**Training SMILES** COC(=O)[C@@H] ([C@H]1CCCCN1CC# C)c2ccccc2 **ChEMBL ID** CHEMBL1254282 **Tanimoto Similarity** 0.168
	**Cluster SMILES** CCN1CCC(N[C@@H]2CCO[C@H]2C2=C C=C(Cl)C(F)=C2)C1= O **Enamine ID** PV-001921689112 **Enamine Q-Code** Q754922$1		**Training SMILES** Fc1cc(ccc1Cl)[C@@ H]2OCCNC[C@H]2 CN3CCCC3=O **ChEMBL ID** CHEMBL3818953 **Tanimoto Similarity** 0.347
	**Cluster SMILES** ClC1=CC=CC(C2=NC (CN(C3CC3)C3CCNC 3)=CO2)=C1 **Enamine ID** Z2447436630 **Enamine Q-Code** Q754948$1		**Training SMILES** Clc1cccc(CN(C2CCO CC2) [C@H]3CCNC3)c1Cl **ChEMBL ID** CHEMBL245880 **Tanimoto Similarity** 0.333

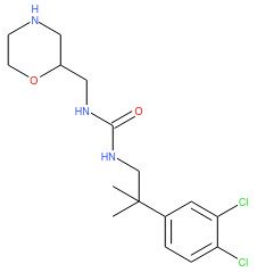
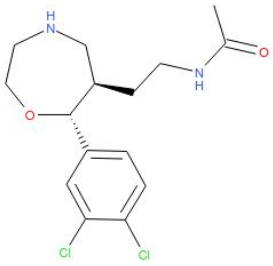
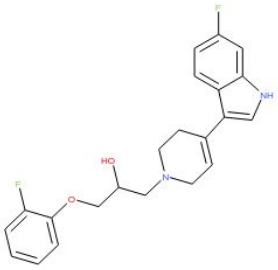
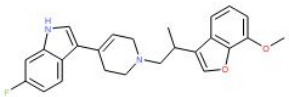
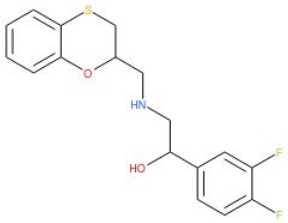
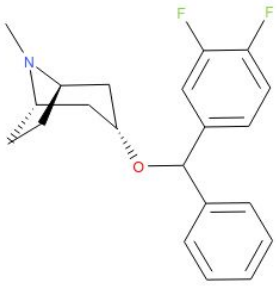
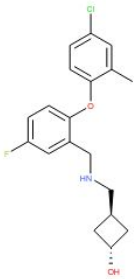
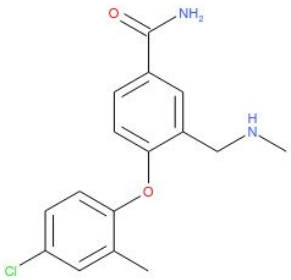
	**Cluster SMILES** CN1C=C(C2CC3CCC(C2)N3CC(O)C2=CC=C(Cl)C(F)=C2)C=N1 **Enamine ID** Z2843312692 **Enamine Q-Code** Q754923$6		**Training SMILES** OC(CN1C2CCC1CC(C2)c3ccccc3)c4ccc(Cl)c(Cl)c4 **ChEMBL ID** CHEMBL127013 **Tanimoto Similarity** 0.476
	**Cluster SMILES** FC1=CC=CC(CCN2CCN(C3=C(Cl)C=CC=C3Cl)CC2)=C1 **Enamine ID** PV-001918950467 **Enamine Q-Code** Q754934$8		**Training SMILES** Fc1cccc(CCN2CCCC2)c1 **ChEMBL ID** CHEMBL2030636 **Tanimoto Similarity** 0.561
	**Cluster SMILES** CC1(C2=CC=CC(Cl)=C2)CCN(CC(O)COC2=CC=CC3=C2C=C[NH]3)CC1 **Enamine ID** PV-001919382948 **Enamine Q-Code** n/a		**Training SMILES** O[C@H](COc1cccc2[nH]ccc12)CN3CCC(CC3)c4cc5cc(Cl)ccc5s4 **ChEMBL ID** CHEMBL56303 **Tanimoto Similarity** 0.505
	**Cluster SMILES** CCC1=CC=C(N2CCN(CC(O)COC3=CC=CC4=C3C=C[NH]4)CC2)C=C1Cl **Enamine ID** PV-001919716605 **Enamine Q-Code** n/a		**Training SMILES** O[C@H](COc1cccc2[nH]ccc12)CN3CCC(CC3)c4cc5c(Cl)cccc5s4 **ChEMBL ID** CHEMBL57296 **Tanimoto Similarity** 0.495

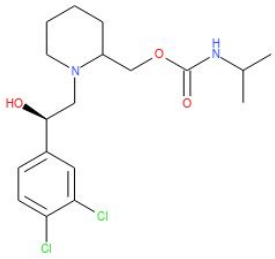
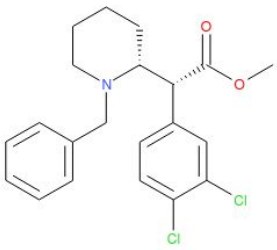
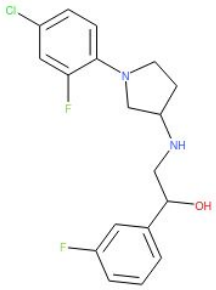
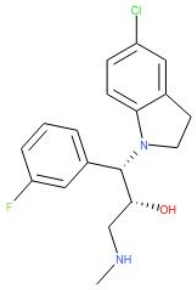
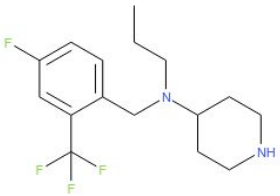
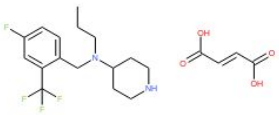
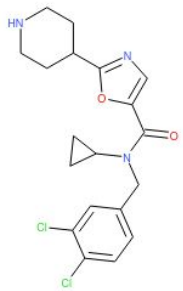
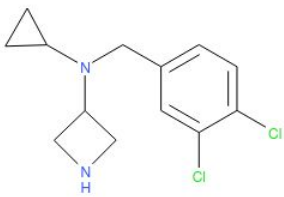
	**Cluster SMILES** FC(F)(F)C1=CC(CN(C2CC2)C2CCNC2)=CC=C1Cl **Enamine ID** Z2444770829 **Enamine Q-Code** n/a		**Training SMILES** Clc1ccc(CN(C2CC2)C3CNC3)cc1Cl **ChEMBL ID** CHEMBL3331484 **Tanimoto Similarity** 0.469
	**Cluster SMILES** ClC1=CC=C(CCC2=NC(C3CCNCC3)=NO2)C=C1Cl **Enamine ID** Z2445178480 **Enamine Q-Code** n/a		**Training SMILES** Fc1ccc(OCc2ccc(Cl)c(Cl)c2)c(c1)C3CCNCC3 **ChEMBL ID** CHEMBL573971 **Tanimoto Similarity** 0.318
	**Cluster SMILES** ClC1=CC=CC(OCC2=NOC(C[C@H]3CCNC3)=N2)=C1Cl **Enamine ID** Z2617873335 **Enamine Q-Code** Q805275$4		**Training SMILES** Clc1cccc(O[C@@H]([C@@H]2CCNC2)c3ccccc3)c1Cl **ChEMBL ID** CHEMBL2337603 **Tanimoto Similarity** 0.293
	**Cluster SMILES** CC(C1=CC=C(Cl)C(Cl)=C1)N1C=C(C2CCCNC2)N=N1 **Enamine ID** Z2846041003 **Enamine Q-Code** Q754915$3		**Training SMILES** CC(C1CCNCC1)c2ccc(Cl)c(Cl)c2 **ChEMBL ID** CHEMBL2407334 **Tanimoto Similarity** 0.312

	**Cluster SMILES** CCC1(C(=O)N2CC=C(C3=C[NH]C4=CC(F)=CC=C34)CC2)CCCN1 **Enamine ID** Z2488796202 **Enamine Q-Code** Q754937$42		**Training SMILES** Fc1ccc2c(c[nH]c2c1)C3=CCN(CCc4coc5ccccc45)CC3 **ChEMBL ID** CHEMBL599985 **Tanimoto Similarity** 0.387
	**Cluster SMILES** CCCN(C(=O)C1=CC=CC=C1OCC1CC1)C1CCNC1 **Enamine ID** Z2354724931 **Enamine Q-Code** n/a		**Training SMILES** COc1cc(CCN2CCN(CCCc3ccccc3)CC2)ccc1OCc4ccccc4 **ChEMBL ID** CHEMBL551471 **Tanimoto Similarity** 0.557
	**Cluster SMILES** CCCNCC1(C)CCN(C(=O)C2=C[NH]C3=CC=C(F)C=C23)C1 **Enamine ID** PV-000923491934 **Enamine Q-Code** n/a		**Training SMILES** OCCNCCc1c[nH]c2ccc(F)cc12 **ChEMBL ID** CHEMBL2347166 **Tanimoto Similarity** 0.266
	**Cluster SMILES** CCN(CC1(C2=CC=C(Cl)C(Cl)=C2)CCC1)C1CC1 **Enamine ID** PV-001917796783 **Enamine Q-Code** n/a		**Training SMILES** CN(C)CC1(CCC1)c2ccc(Cl)c(Cl)c2 **ChEMBL ID** CHEMBL1683883 **Tanimoto Similarity** 0.596

	**Cluster SMILES** OC(COC1=CC=CC2=C1C=C[NH]2)CN1CCC(C2=CC=C(F)C(F)=C2)CC1 **Enamine ID** Z1421251686 **Enamine Q-Code** n/a		**Training SMILES** O[C@H](COc1cccc2[nH]ccc12)CN3CCC(CC3)c4cc5c(F)cccc5s4 **ChEMBL ID** CHEMBL301677 **Tanimoto Similarity** 0.616
	**Cluster SMILES** O=C(CCC1CCNC1)N1CCOC(C2=CC=C(Cl)C(Cl)=C2)C1 **Enamine ID** Z2436746713 **Enamine Q-Code** Q754947$2		**Training SMILES** NC(=O)[C@@H]1CNCCO[C@H]1c2ccc(Cl)c(Cl)c2 **ChEMBL ID** CHEMBL3593397 **Tanimoto Similarity** 0.308
	**Cluster SMILES** ClC1=CC=C(C2CCCC2NC[C@@H]2CCCO2)C=C1Cl **Enamine ID** PV-001930327687 **Enamine Q-Code** n/a		**Training SMILES** Clc1ccc(cc1Cl)[C@H]2CCCN3CCCC[C@H]23 **ChEMBL ID** CHEMBL556365 **Tanimoto Similarity** 0.308
	**Cluster SMILES** CCC1CC(NCC(C)(C)C2=CC=C(Cl)C(Cl)=C2)CCO1 **Enamine ID** PV-001923897672 **Enamine Q-Code** Q754950$3		**Training SMILES** CCN[C@@H]1C[C@@H](c2ccc(Cl)c(Cl)c2)c3ccccc13 **ChEMBL ID** CHEMBL147983 **Tanimoto Similarity** 0.216

	**Cluster SMILES** C1=CC=C(C2CN(CCN3C=CN=C3)CC3=CC=CC=C32)C=C1 **Enamine ID** Z1505378916 **Enamine Q-Code** n/a		**Training SMILES** CCN1CC(c2ccccc2)c3ccccc3C1 **ChEMBL ID** CHEMBL286455 **Tanimoto Similarity** 0.529
	**Cluster SMILES** OCC(NC1CCN(CC2=CC=CC=C2Cl)CC1)C1=CC=C(Br)C(F)=C1 **Enamine ID** Z2201777668 **Enamine Q-Code** Q754941$1		**Training SMILES** COc1ccc(Br)c(CC2CCN(CCc3ccccc3Cl)CC2)c1 **ChEMBL ID** CHEMBL3913057 **Tanimoto Similarity** 0.267
	**Cluster SMILES** CC1CC(CN(CCO)CC2=CC=C(Cl)C(Cl)=C2)C1 **Enamine ID** PV-001918897538 **Enamine Q-Code** Q754938$4		**Training SMILES** CC(C)N(CC1CNC1)Cc2ccc(Cl)c(Cl)c2 **ChEMBL ID** CHEMBL3331503 **Tanimoto Similarity** 0.557
	**Cluster SMILES** ClC1=CC=C(C2CN(CC[C@@H]3C[C@H]3C3CC3)CCO2)C=C1Cl **Enamine ID** PV-001917367008 **Enamine Q-Code** Q754916$4		**Training SMILES** NCC1C2CCC(C2)C1c3ccc(Cl)c(Cl)c3 **ChEMBL ID** CHEMBL172523 **Tanimoto Similarity** 0.262

	**Cluster SMILES** CC(C)(CNC(=O)NCC1CNCCO1)C1=CC=C(Cl)C(Cl)=C1 **Enamine ID** Z2361435743 **Enamine Q-Code** Q754949$3		**Training SMILES** CC(=O)NCC[C@@H]1CNCCO[C@H]1c2ccc(Cl)c(Cl)c2 **ChEMBL ID** CHEMBL3593401 **Tanimoto Similarity** 0.326
	**Cluster SMILES** OC(COC1=CC=CC=C1F)CN1CC=C(C2=C[NH]C3=CC(F)=CC=C23)CC1 **Enamine ID** Z1485114833 **Enamine Q-Code** Q754935$2		**Training SMILES** COc1cccc2c(coc12)C(C)CN3CCC(=CC3)c4c[nH]c5cc(F)ccc4 5 **ChEMBL ID** CHEMBL597479 **Tanimoto Similarity** 0.491
	**Cluster SMILES** OC(CNCC1CSC2=CC=CC=C2O1)C1=CC=C(F)C(F)=C1 **Enamine ID** Z3045122589 **Enamine Q-Code** Q754924$1		**Training SMILES** CN1[C@@H]2CC[C@H]1C[C@H](C2)OC(c3ccccc3)c4ccc(F)c(F)c4 **ChEMBL ID** CHEMBL3084908 **Tanimoto Similarity** 0.196
	**Cluster SMILES** CC1=CC(Cl)=CC=C1OC1=CC=C(F)C=C1CNC[C@H]1C[C@H](O)C1 **Enamine ID** PV-001926691632 **Enamine Q-Code** Q753945$26		**Training SMILES** CNCc1cc(ccc1Oc2ccc(Cl)cc2C)C(=O)N **ChEMBL ID** CHEMBL401819 **Tanimoto Similarity** 0.388

	**Cluster SMILES** CC(C)NC(=O)OCC1CCCCN1C[C@H](O)C1=CC=C(Cl)C(Cl)=C1 **Enamine ID** PV-001919611983 **Enamine Q-Code** Q754930$6		**Training SMILES** COC(=O)[C@@H]([C@H]1CCCCN1Cc2ccccc2)c3ccc(Cl)c(Cl)c3 **ChEMBL ID** CHEMBL1254674 **Tanimoto Similarity** 0.314
	**Cluster SMILES** OC(CNC1CCN(C2=CC=C(Cl)C=C2F)C1)C1=CC=CC(F)=C1 **Enamine ID** Z2722622816 **Enamine Q-Code** Q754933$1		**Training SMILES** CNC[C@@H](O)[C@@H](N1CCc2cc(Cl)ccc12)c3cccc(F)c3 **ChEMBL ID** CHEMBL598168 **Tanimoto Similarity** 0.327
	**Cluster SMILES** CCCN(CC1=CC=C(F)C=C1C(F)(F)F)C1CCNCC1 **Enamine ID** Z2444696415 **Enamine Q-Code** n/a		**Training SMILES** CCCN(Cc1ccc(F)cc1C(F)(F)F)C2CCNCC2.OC(=O)\C=C\C(=O) O **ChEMBL ID** CHEMBL207854 **Tanimoto Similarity** 0.833
	**Cluster SMILES** O=C(C1=CN=C(C2CCNCC2)O1)N(CC1=CC=C(Cl)C(Cl)=C1)C1CC1 **Enamine ID** Z3100431738 **Enamine Q-Code** Q754929$5		**Training SMILES** Clc1ccc(CN(C2CC2)C3CNC3)cc1Cl **ChEMBL ID** CHEMBL3331484 **Tanimoto Similarity** 0.341

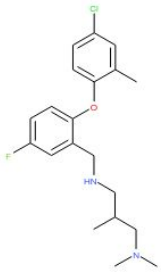
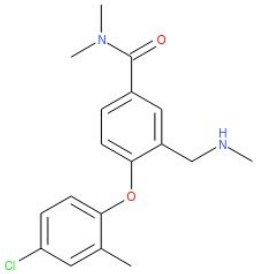
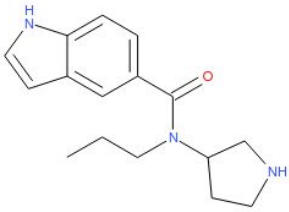
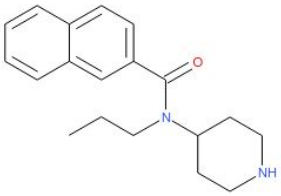
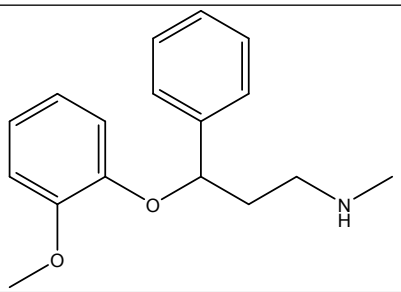
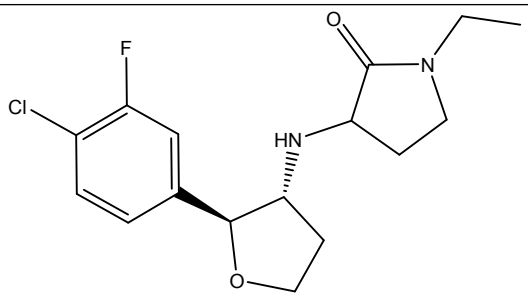
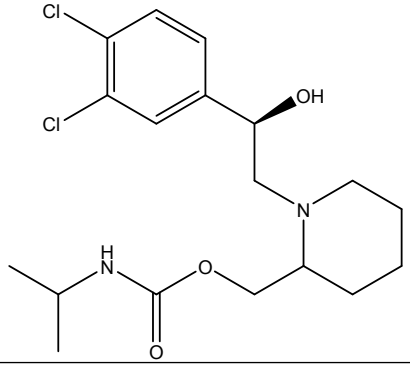
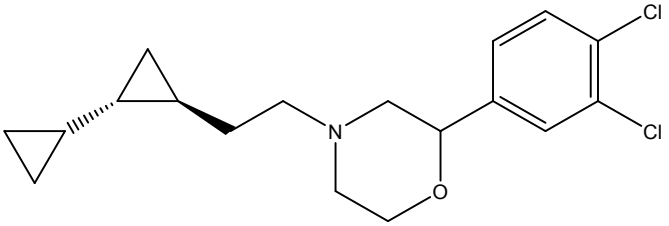
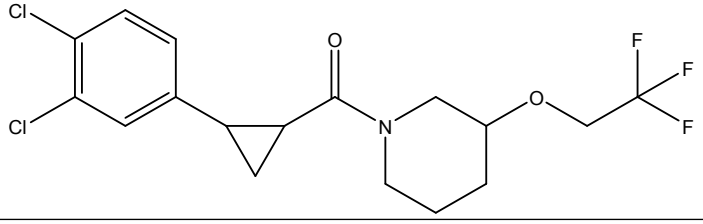
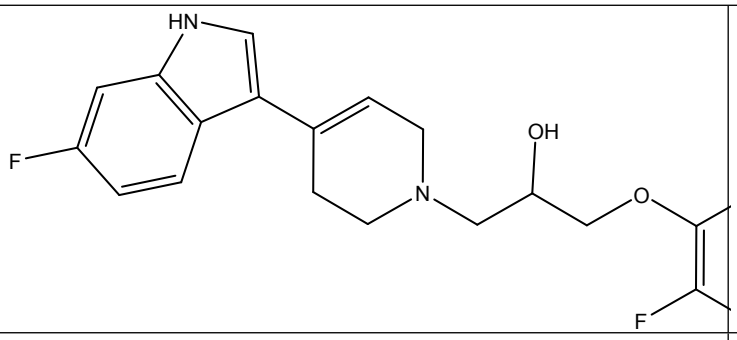
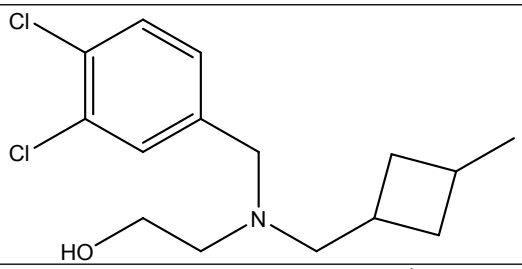
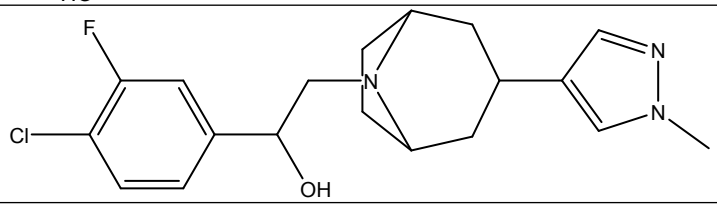
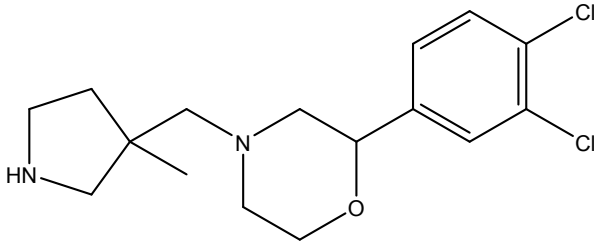
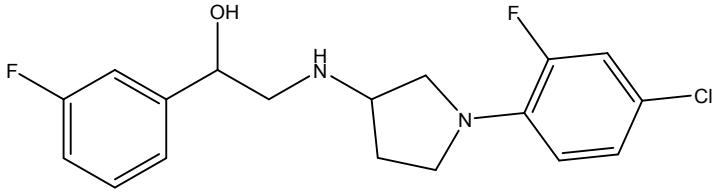
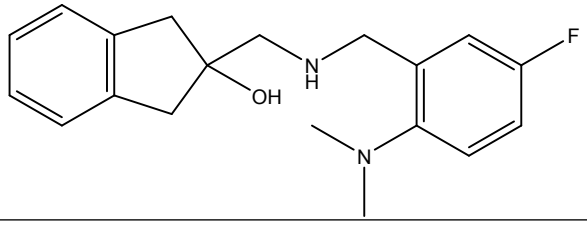
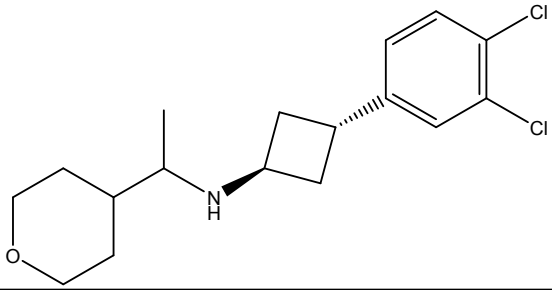
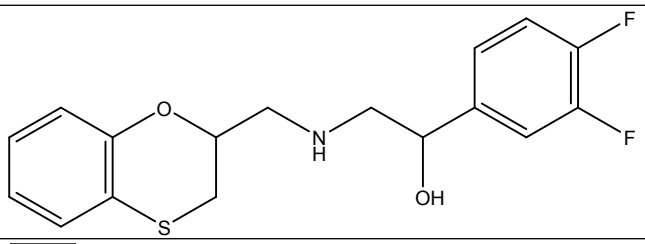
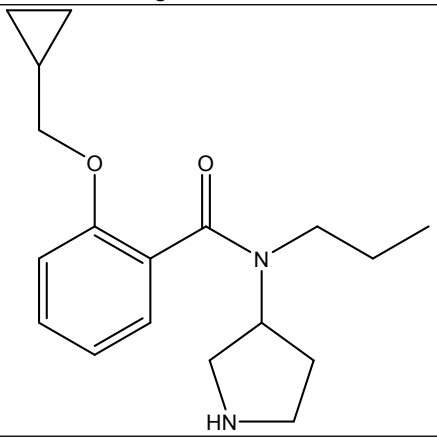
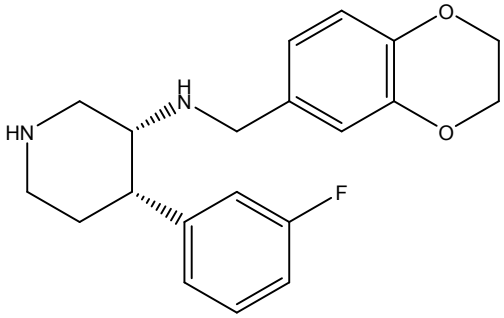
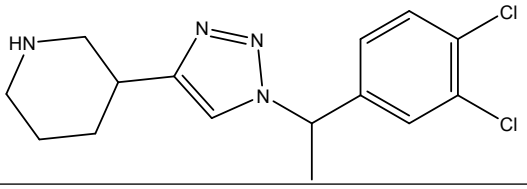
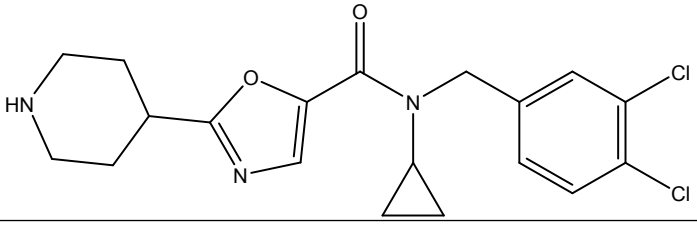
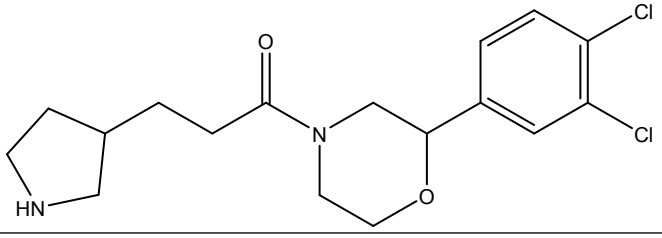
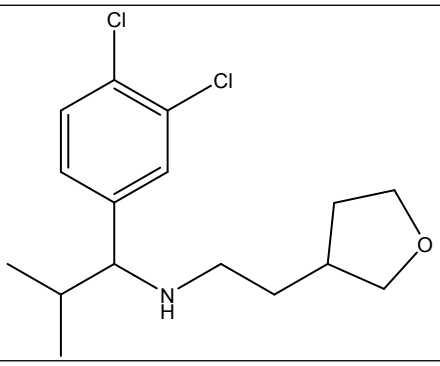
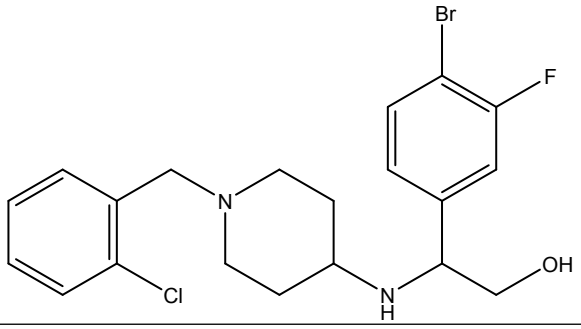
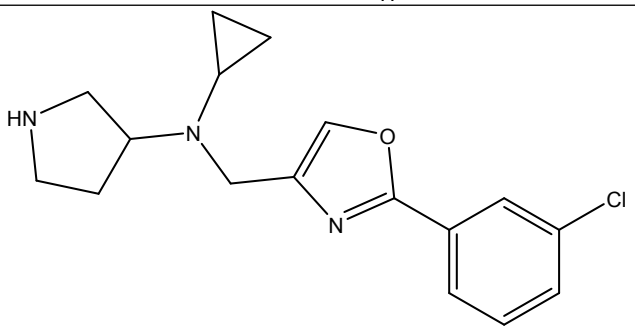
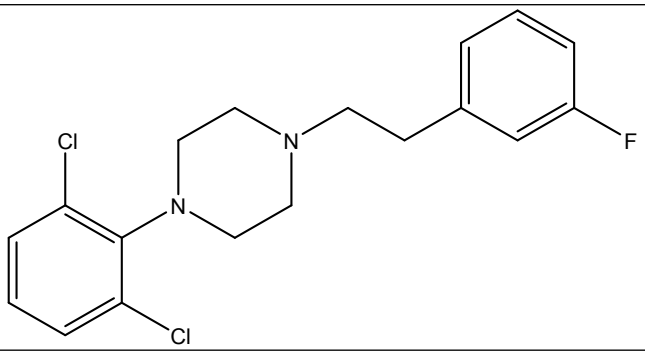
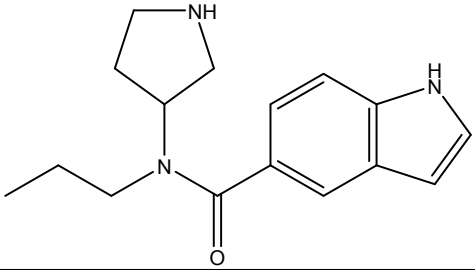
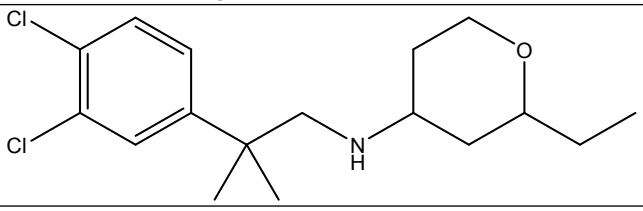
	**Cluster SMILES** CC1=CC(Cl)=CC=C1OC1=CC=C(F)C=C1CNCC(C)CN(C)C **Enamine ID** PV-001925822957 **Enamine Q-Code** Q754951$48		**Training SMILES** CNCc1cc(ccc1Oc2ccc(Cl)cc2C)C(=O)N(C)C **ChEMBL ID** CHEMBL272493 **Tanimoto Similarity** 0.407
	**Cluster SMILES** CCCN(C(=O)C1=CC=C2[NH]C=CC2=C1)C1CCNC1 **Enamine ID** Z2488563933 **Enamine Q-Code** Q754912$22		**Training SMILES** CCCN(C1CCNCC1)C(=O)c2ccc3ccccc3c2 **ChEMBL ID** CHEMBL565638 **Tanimoto Similarity** 0.434

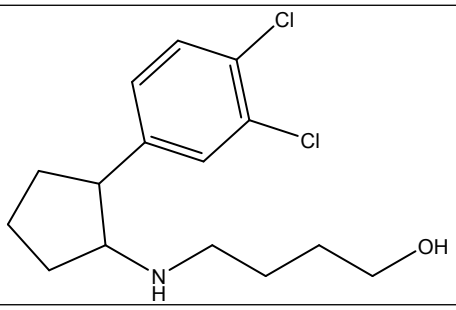
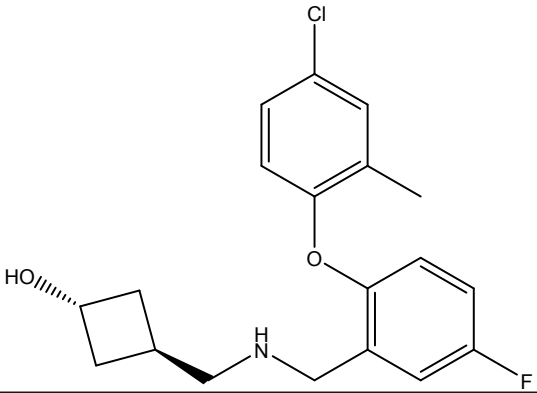
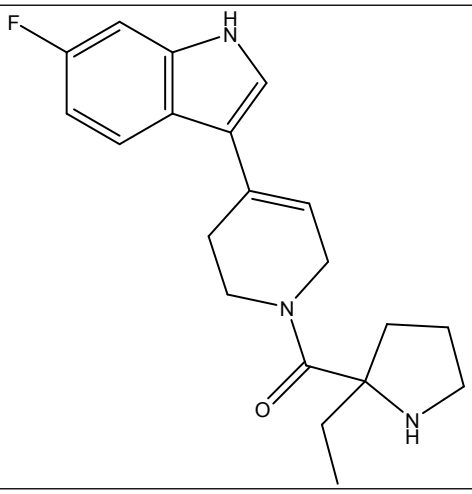
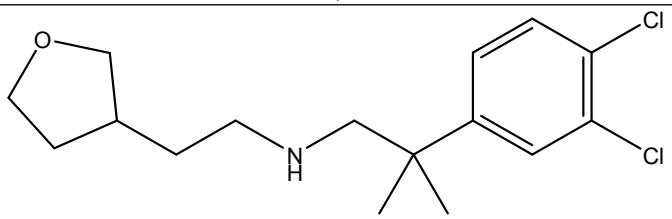
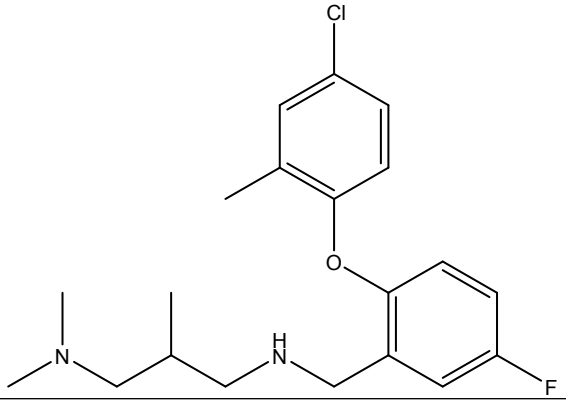
Table S5. Single Point screen compounds and their inhibitory activity at 10 µM. *Nisoxertine was set as the baseline 100% (pIC_{50} of 8.0). These values correspond to Figure 8 in the main Manuscript. Data are reported as the mean (in %) ± SEM of three individual experiments each performed in duplicate. Structures shown here might slightly deviate in orientation compared to the main manuscript.*

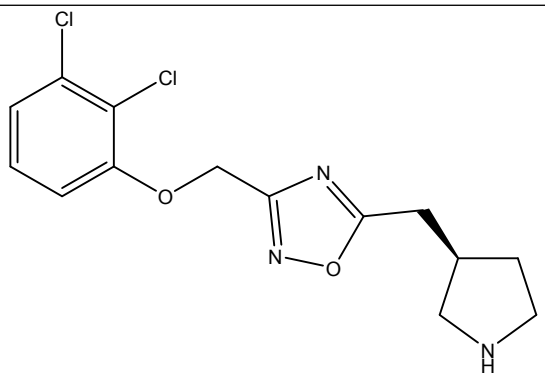
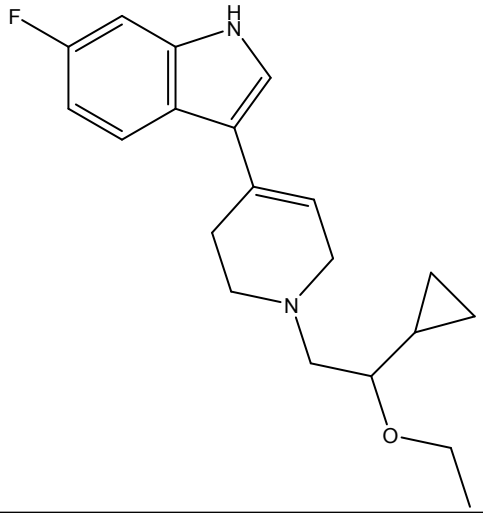
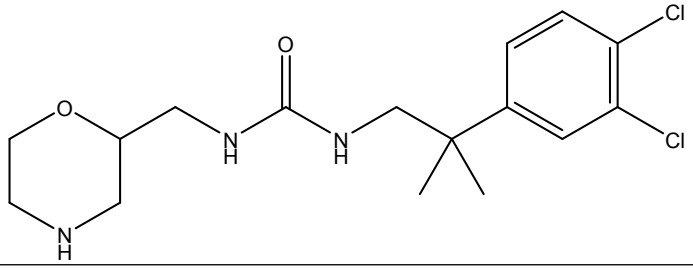
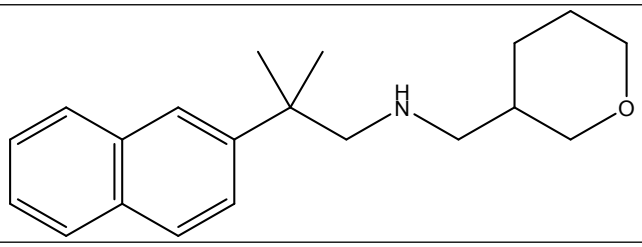
Enamine ID	ID	Structure (based on SMILES)	Mean (%)	± SEM
Nisoxetine			100	12
PV-001921689112	01		8	9
PV-001919611983	02		14	11
PV-001917367008	03		7	9
Z1083362508	04		19	15

Z1485114833	05		21	4
PV-001918897538	06		32	3
Z2843312692	07		53	7
Z2444828348	08		58	4
Z2722622816	09		10	7
Z2769565776	10		-4	3
Z1986623199	11		15	5

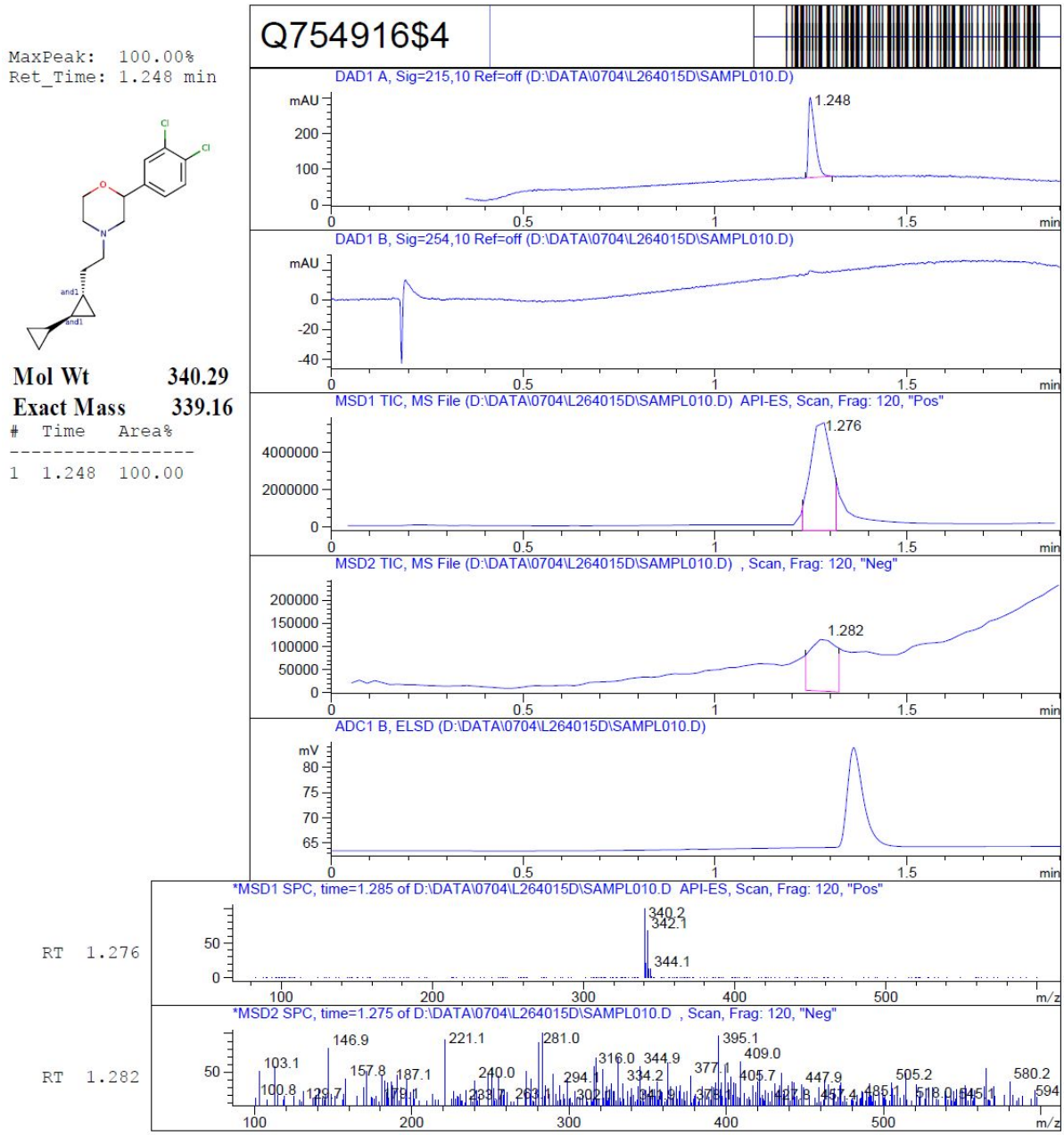
Z3045122589	12		10	10
Z2393213853	13		117	10
Z2569757498	14		48	9
Z2846041003	15		56	8
Z3100431738	16		108	12
Z2436746713	17		35	9

Z1663514926	18		62	7
Z2201777668	19		25	13
Z2447436630	20		23	7
PV-001918950467	21		21	7
Z2488563933	22		117	5
PV-001923897672	23		38	2

Z1904820040	24		100	11
PV-001926691632	25		19	6
Z2488796202	26		11	10
Z1783772638	27		52	8
PV-001925822957	28		32	12

Z2617873335	29		5	6
PV-001918160326	30		-10	7
Z2361435743	31		75	5
Z2698567135	32		90	11

S6. **Analytical spectra for the 32 synthesized compounds selected for experimental follow-up.** Data provided by Enamine.



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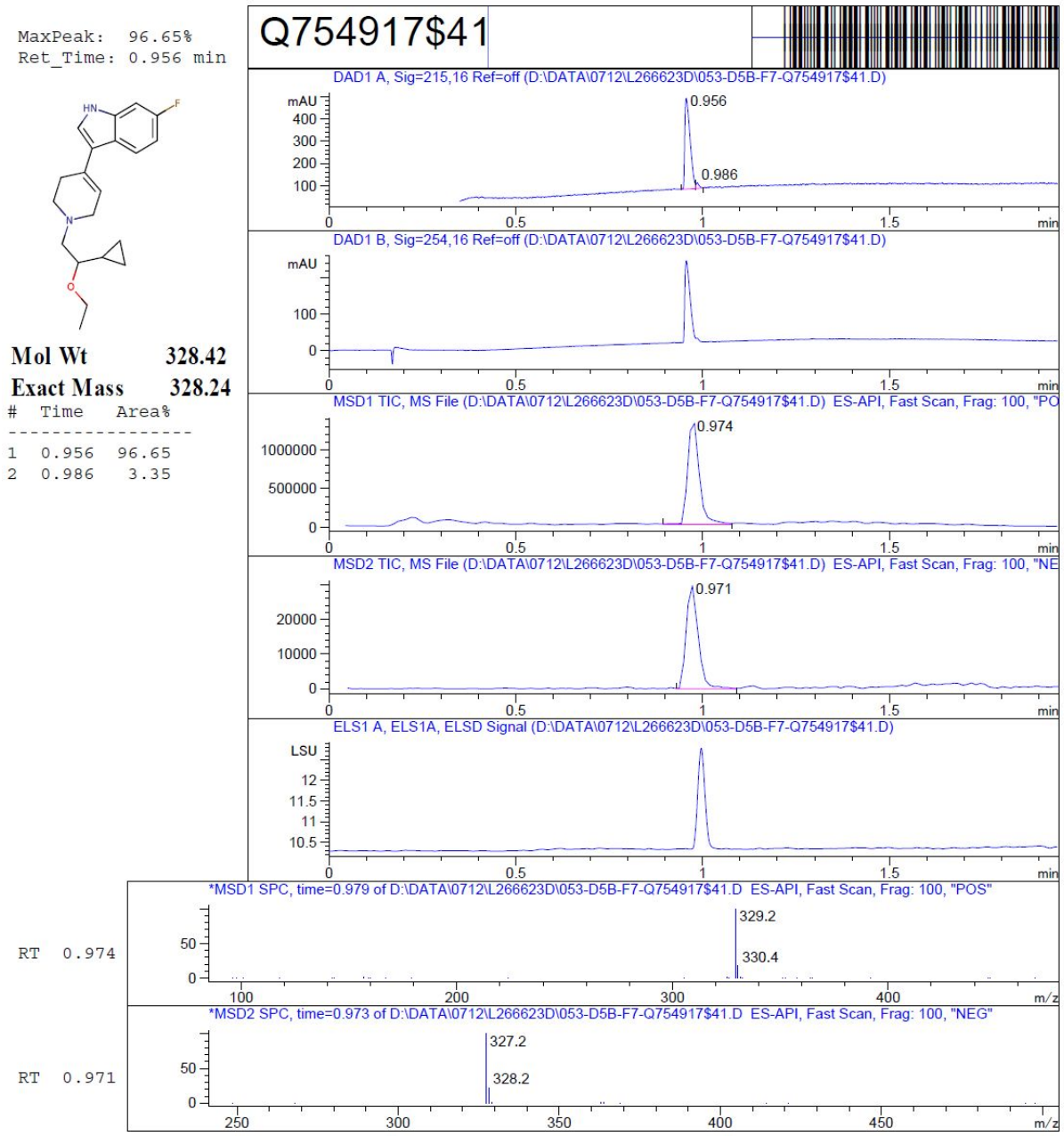

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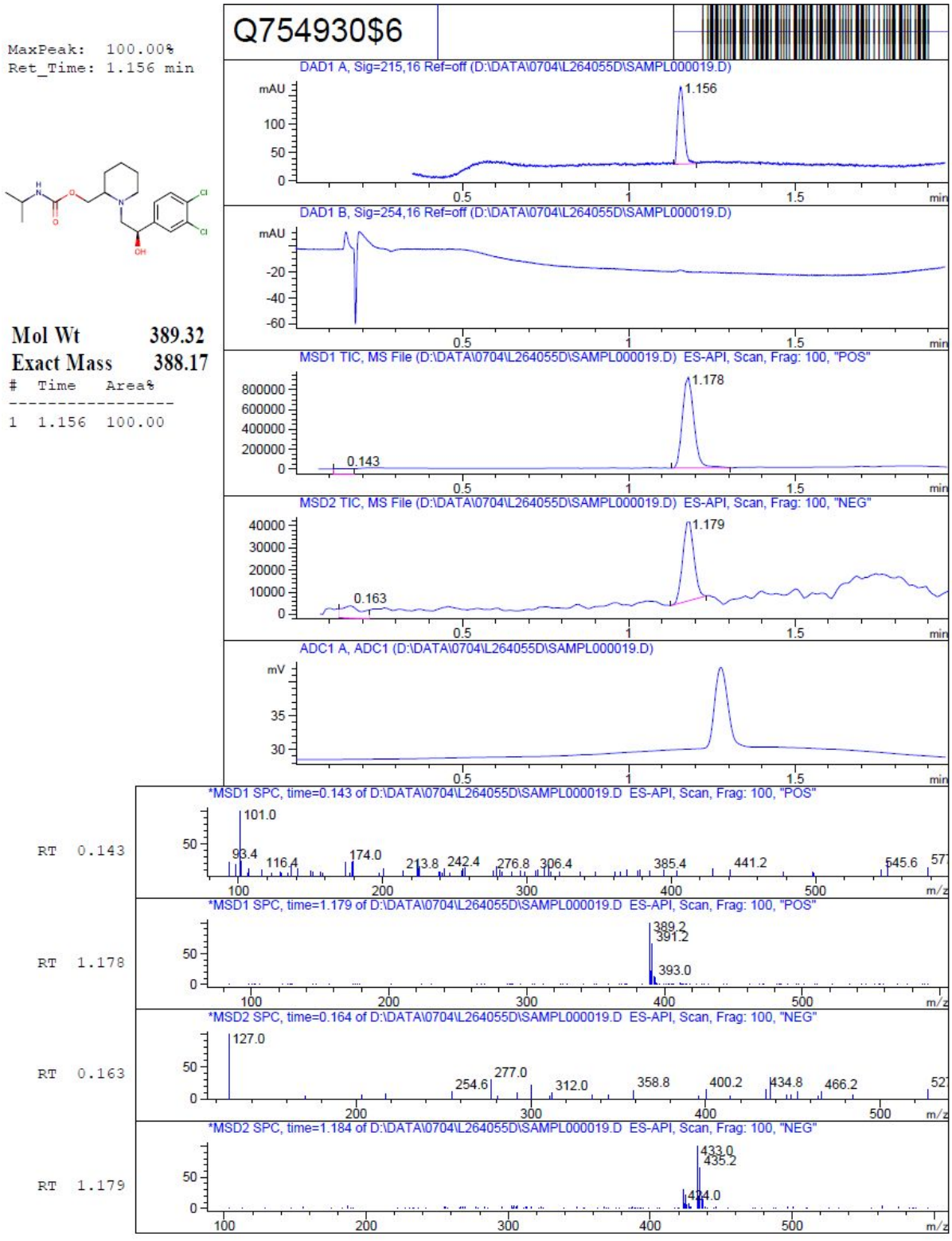

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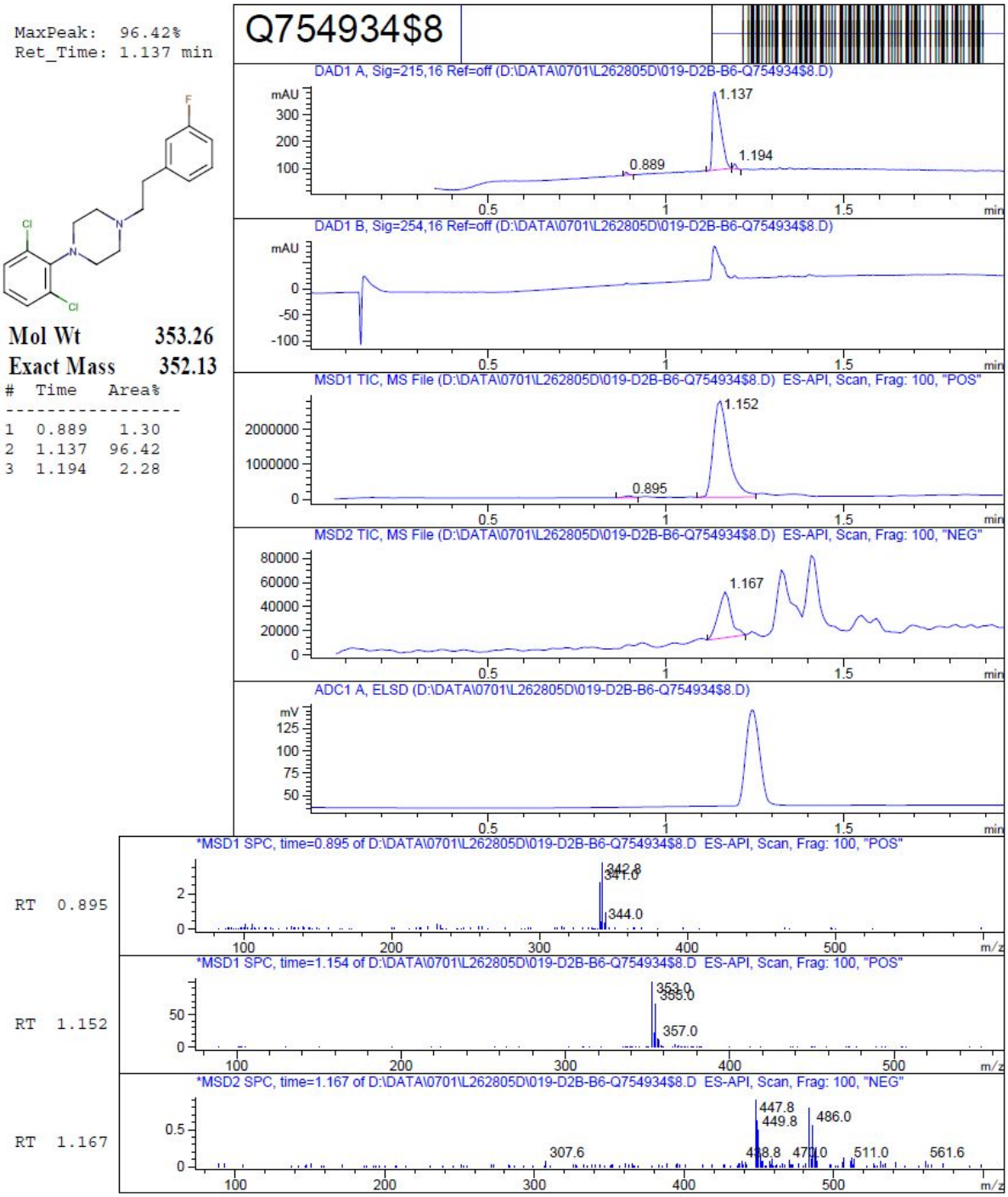

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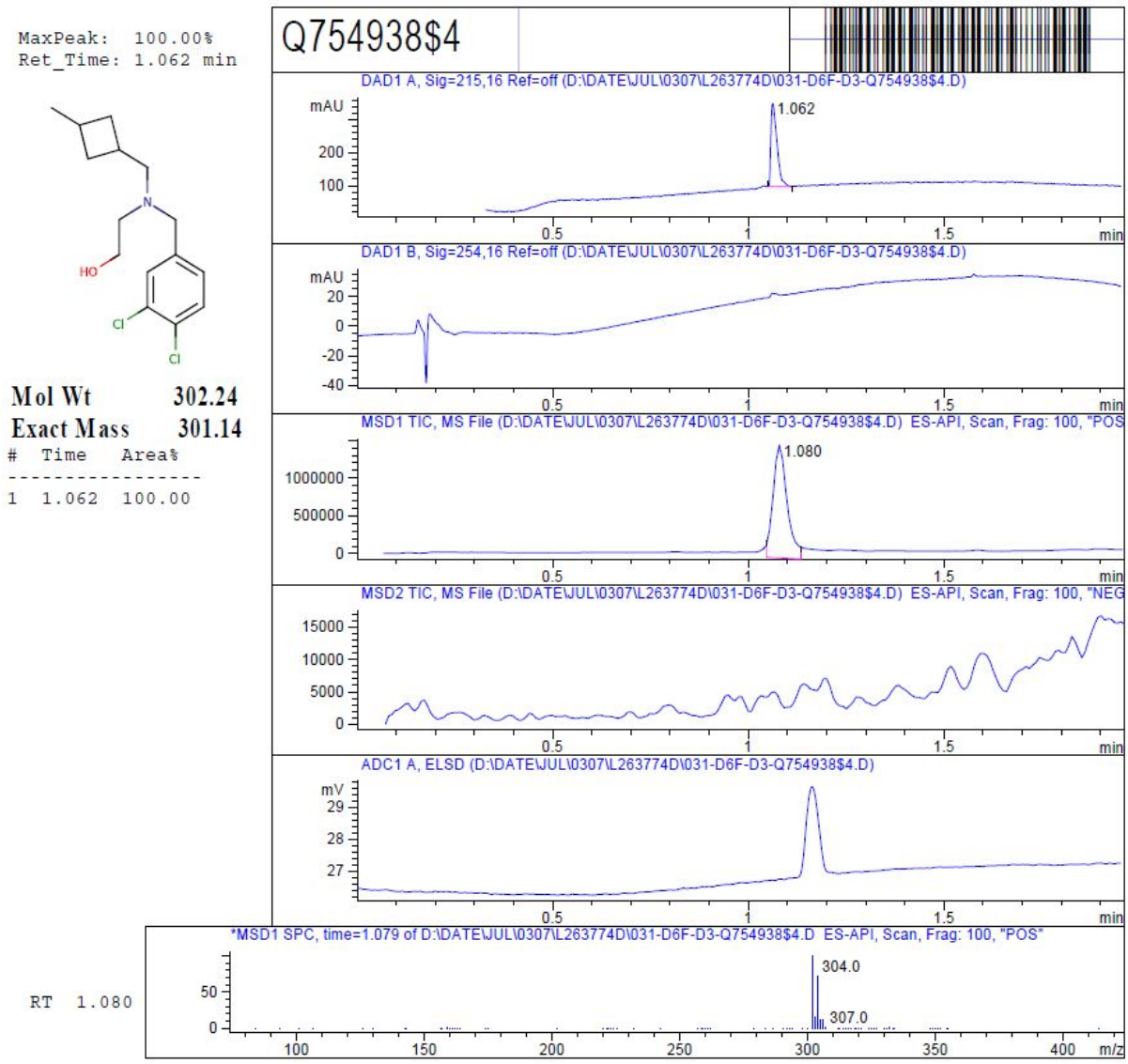

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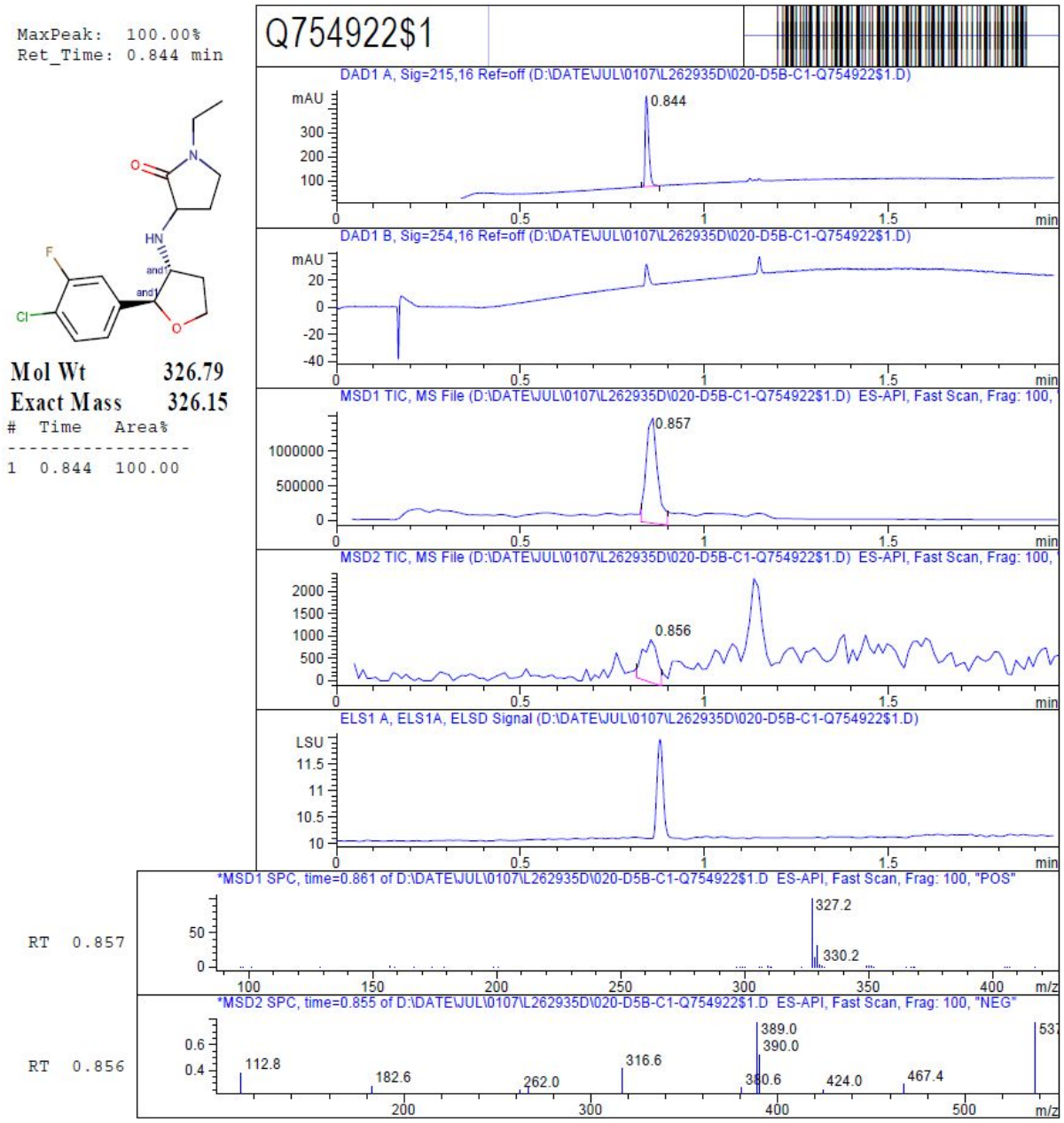

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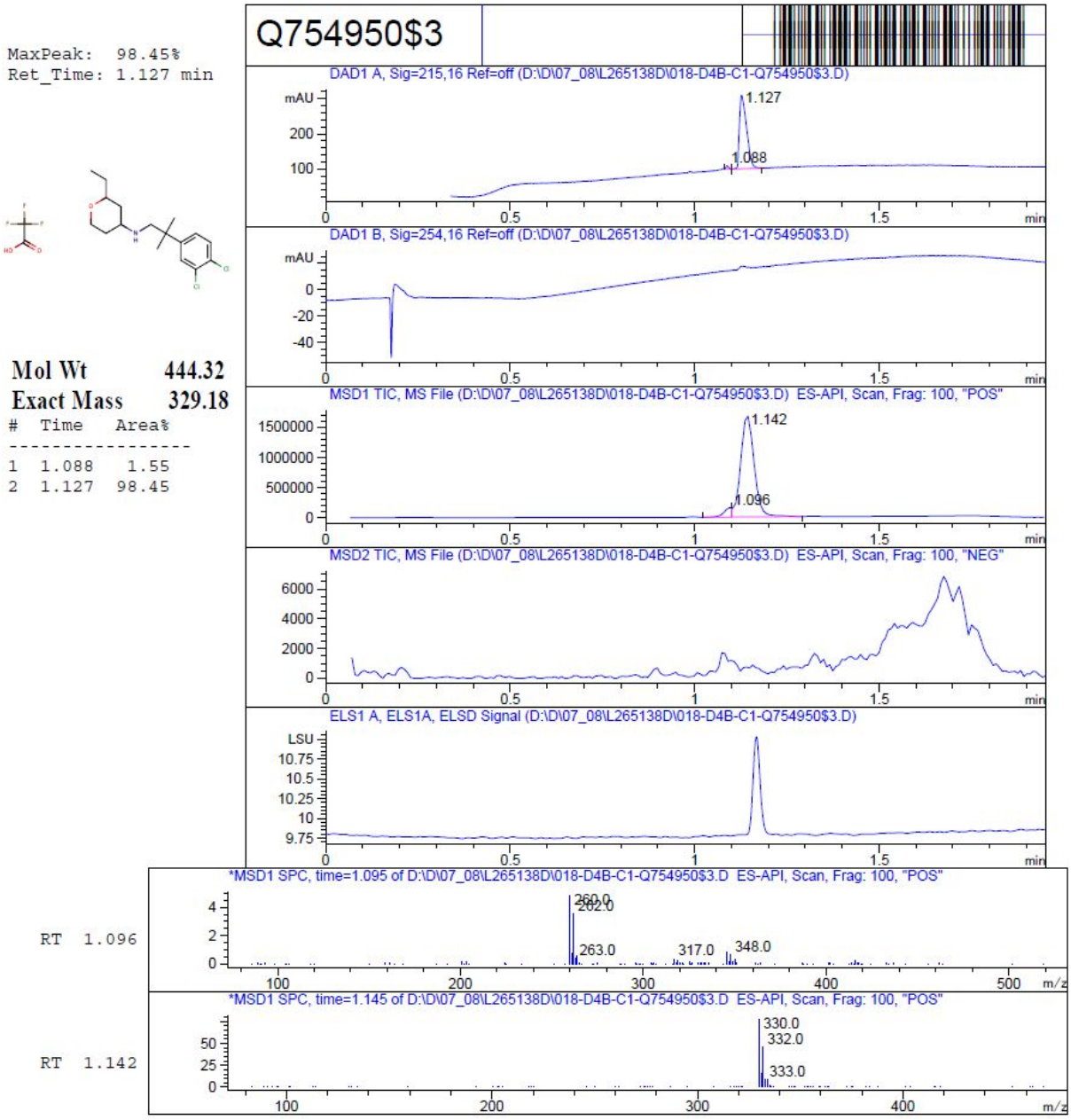

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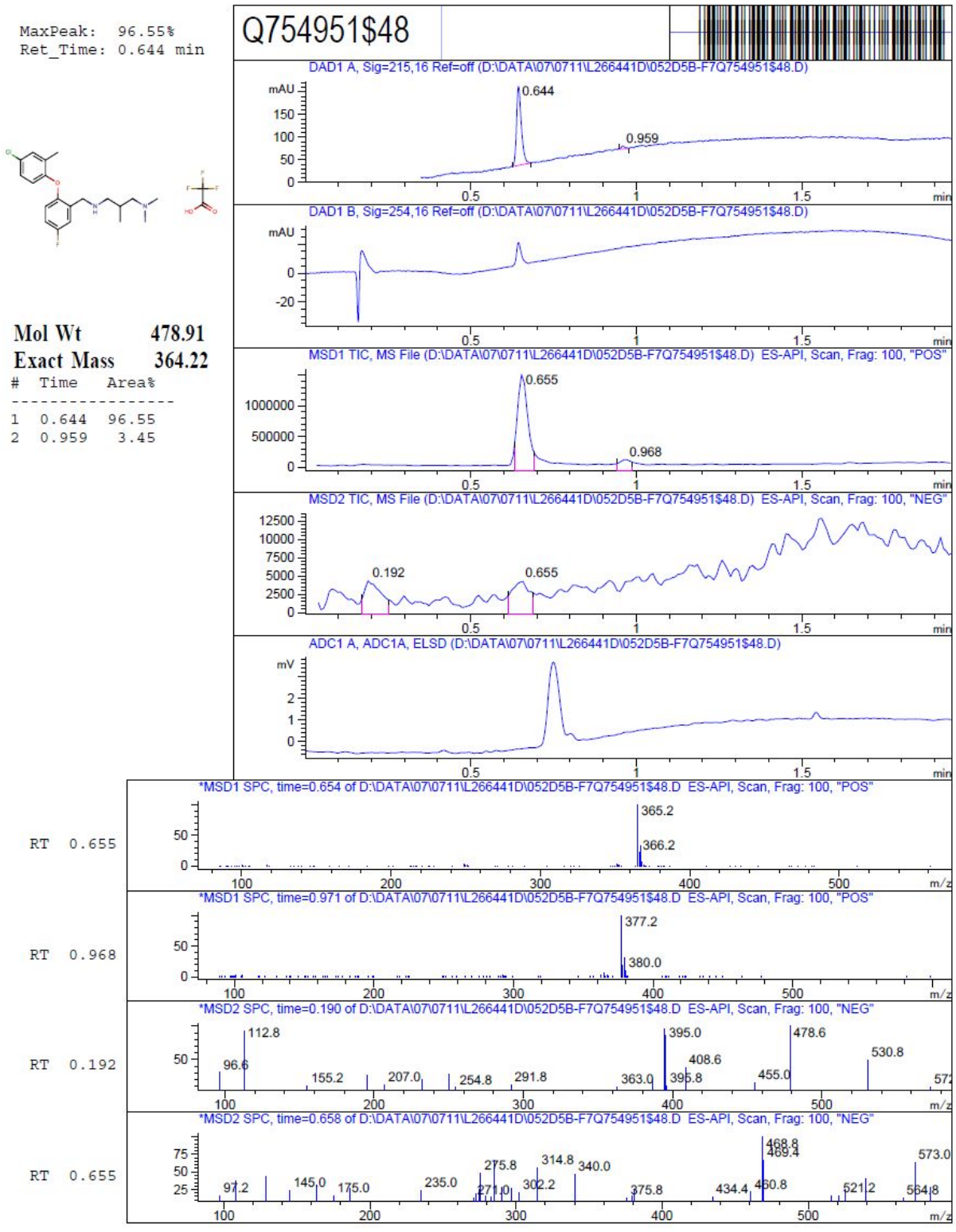

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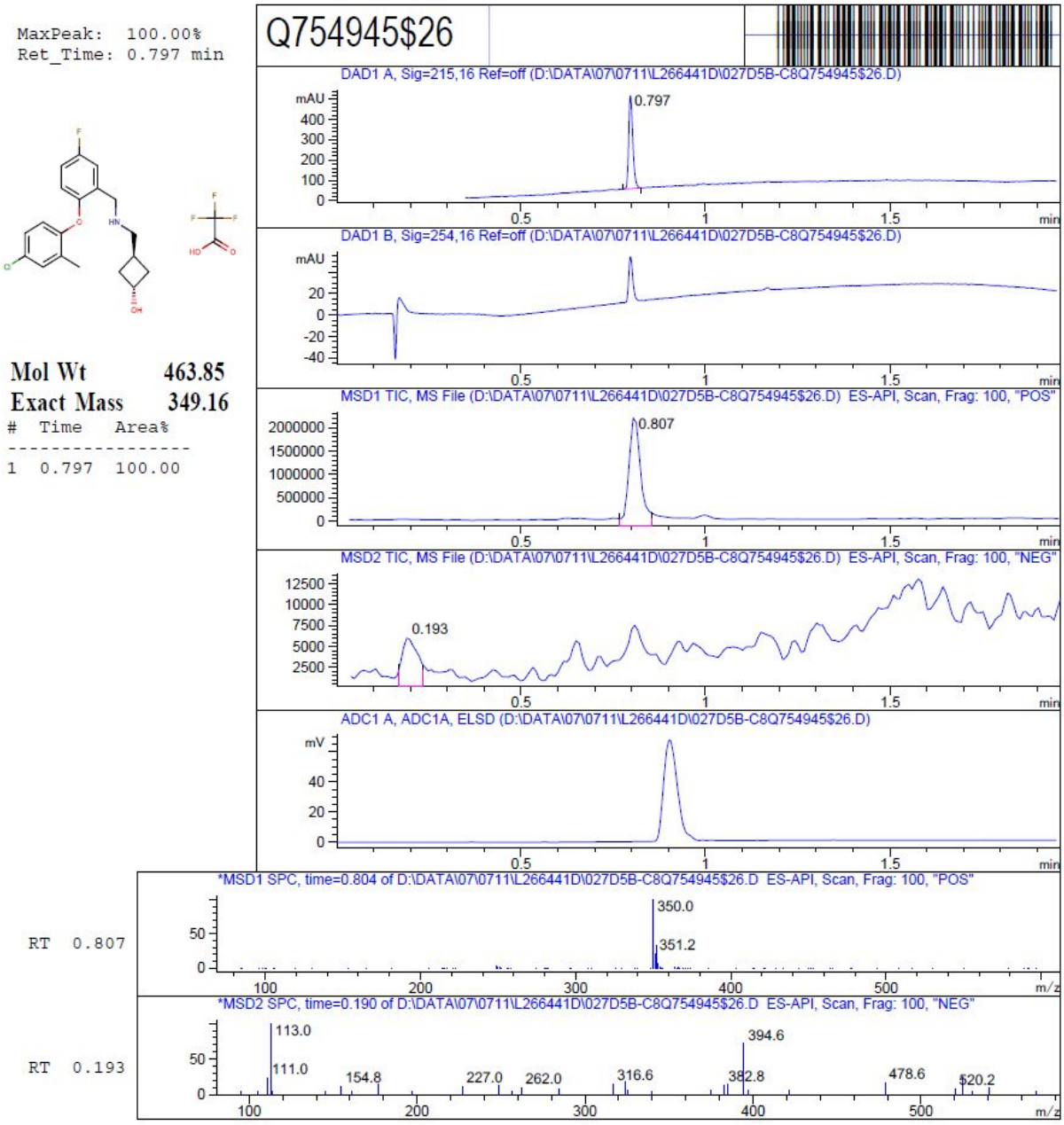

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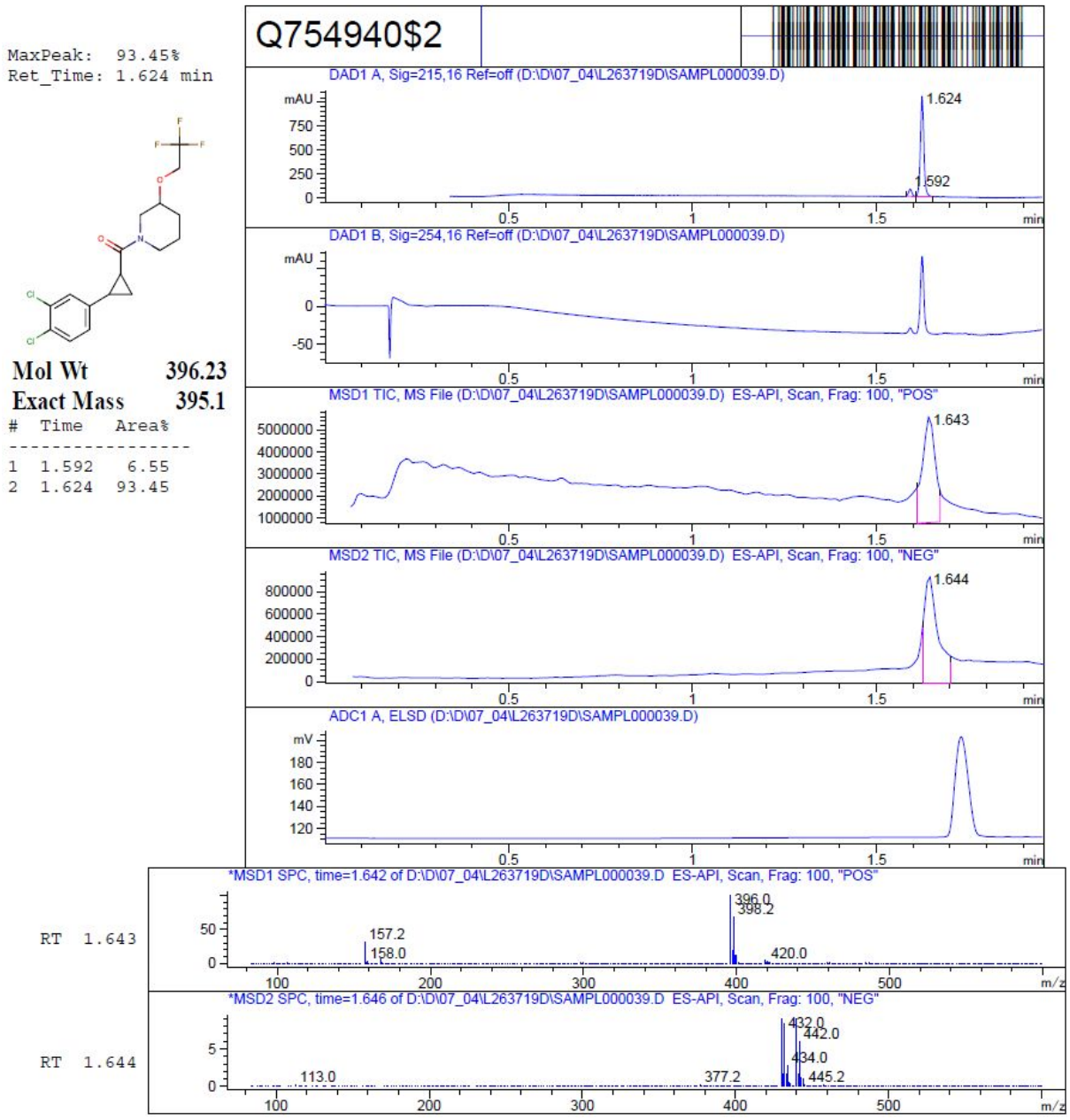

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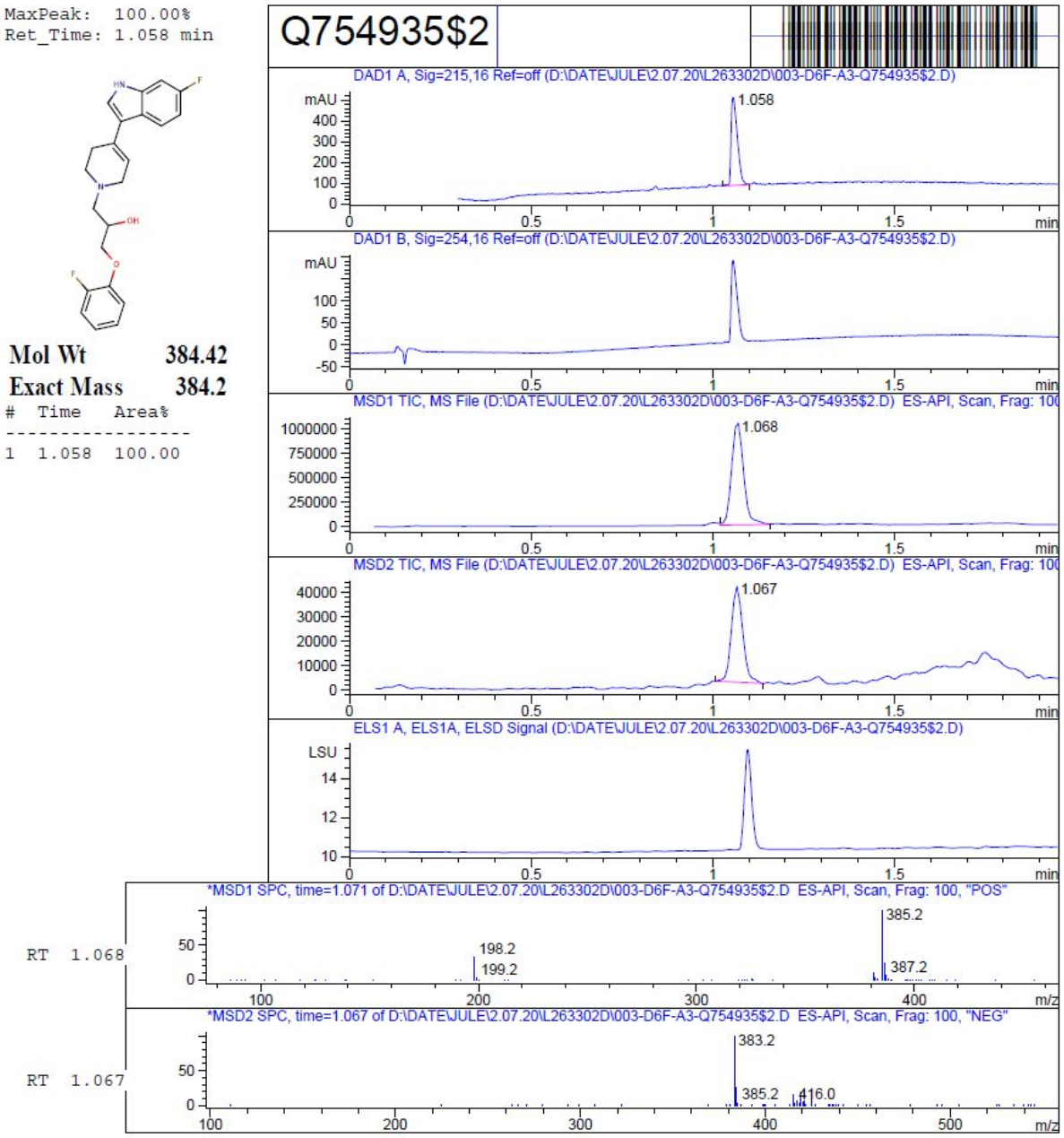

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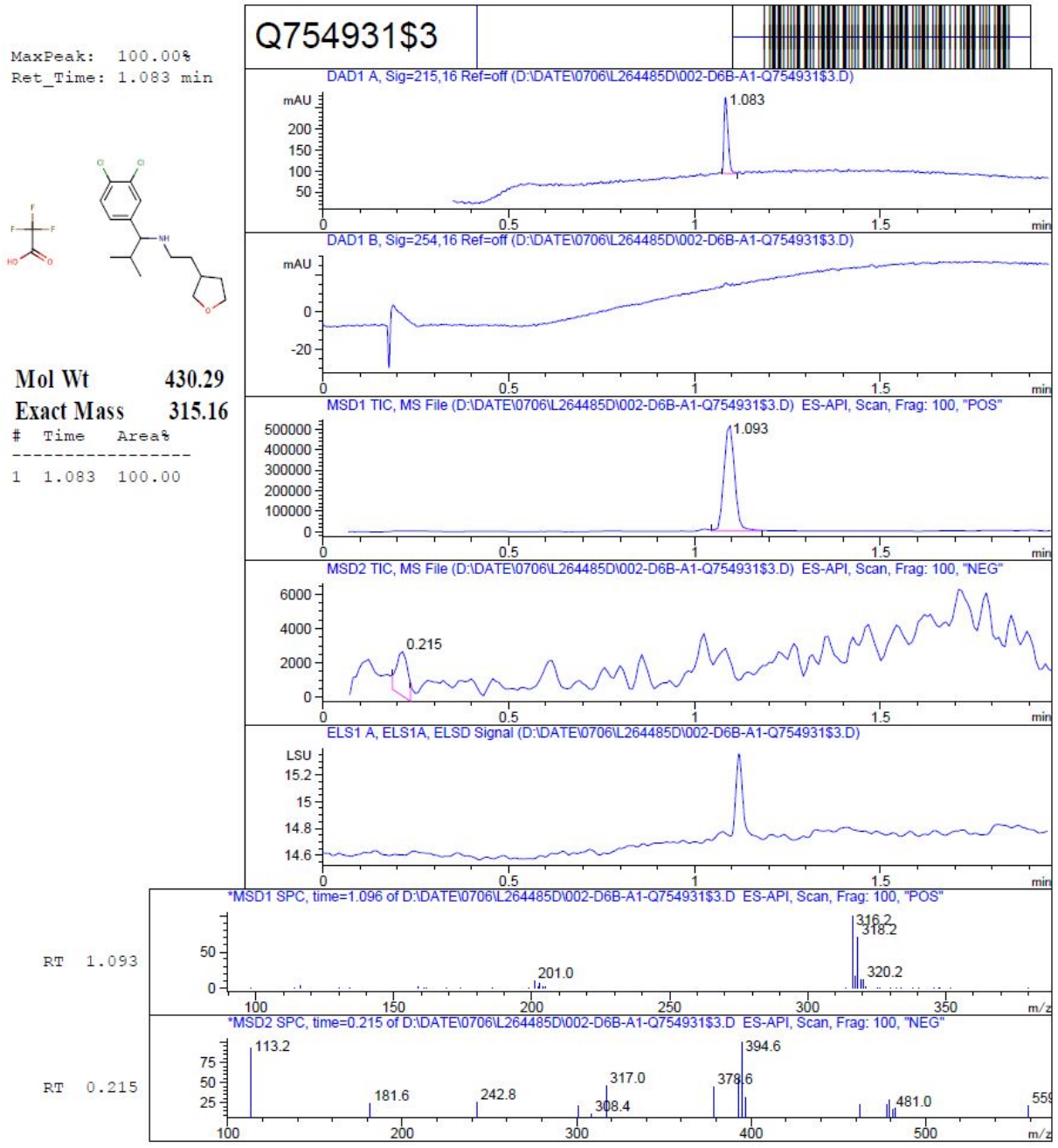

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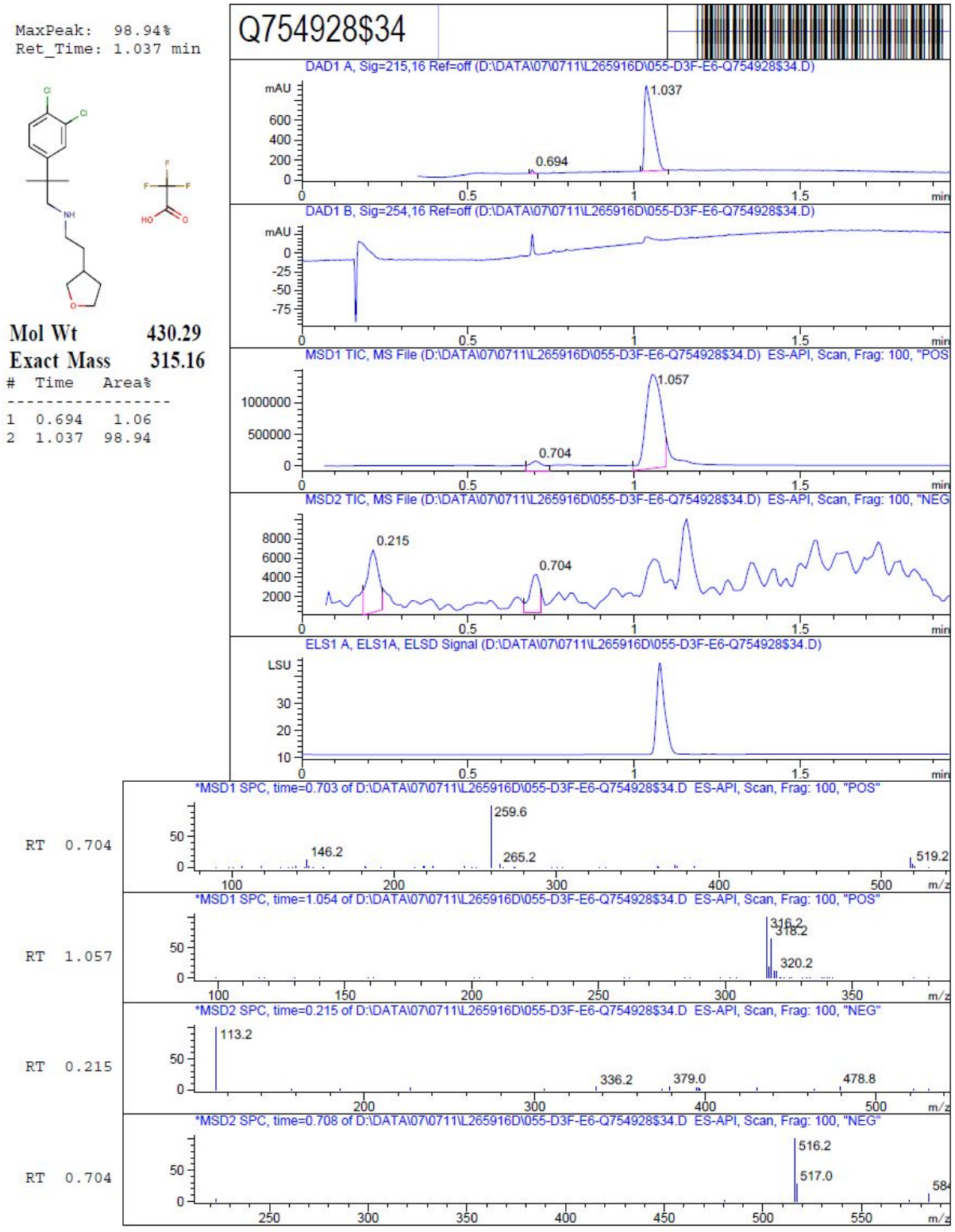

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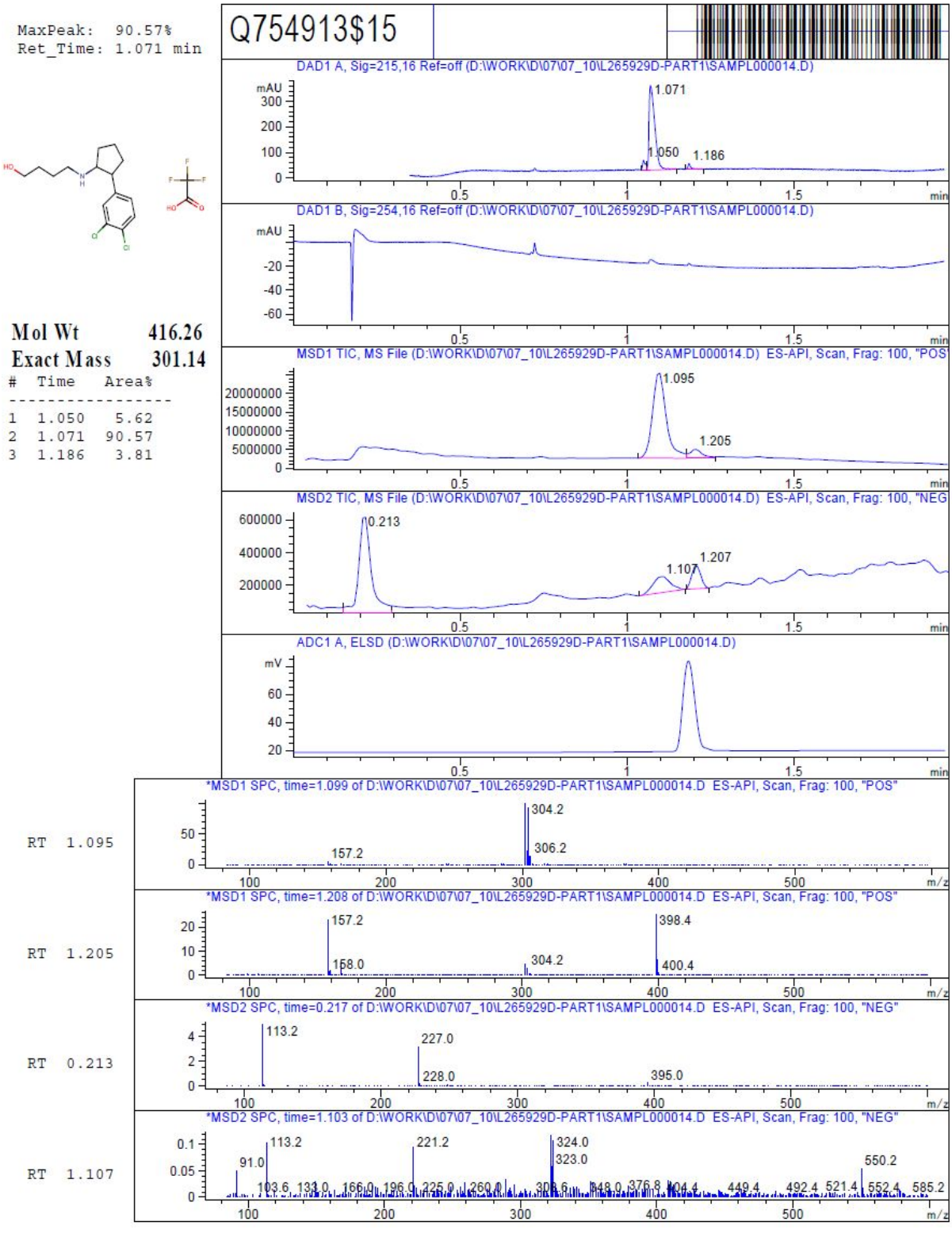

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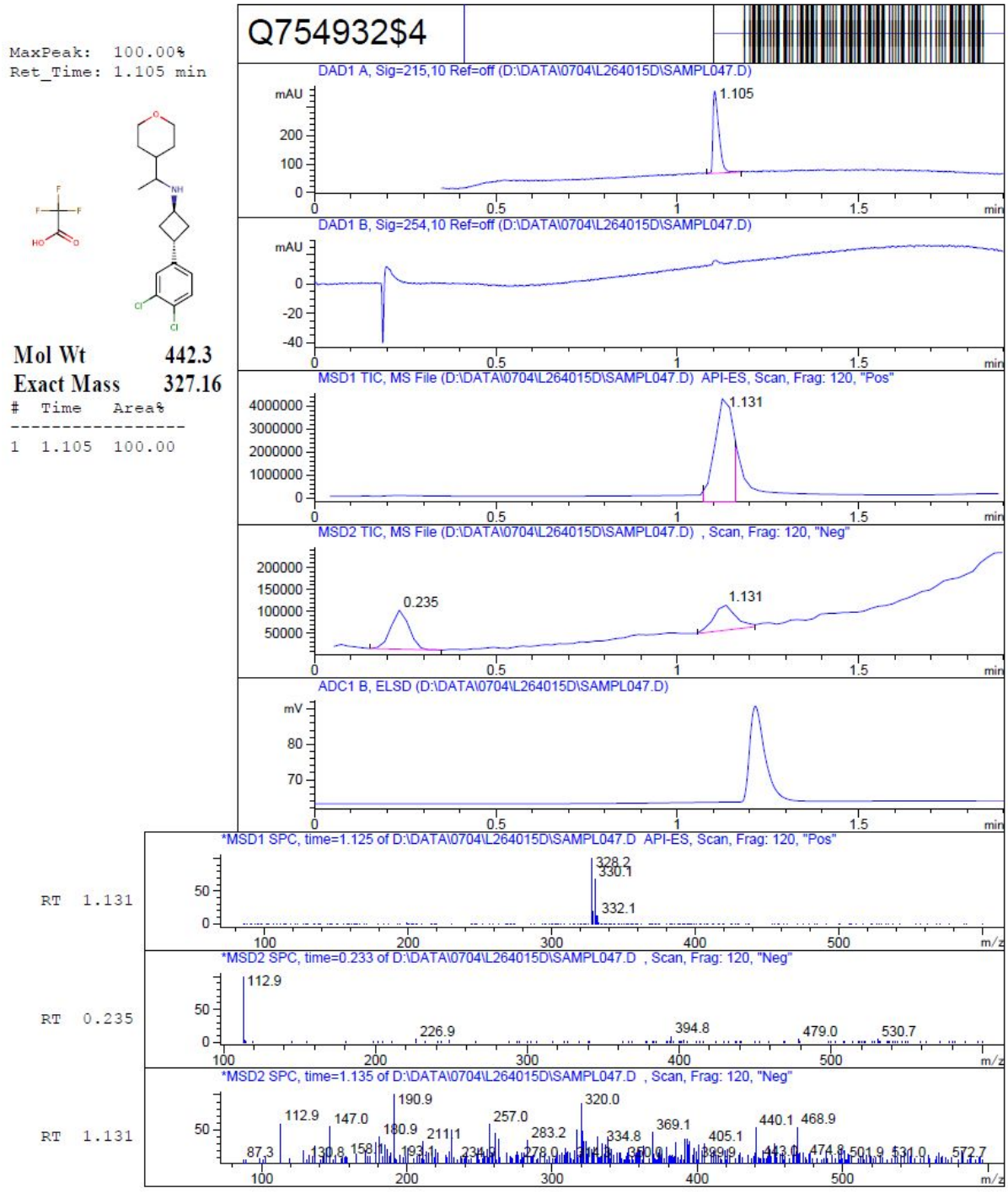

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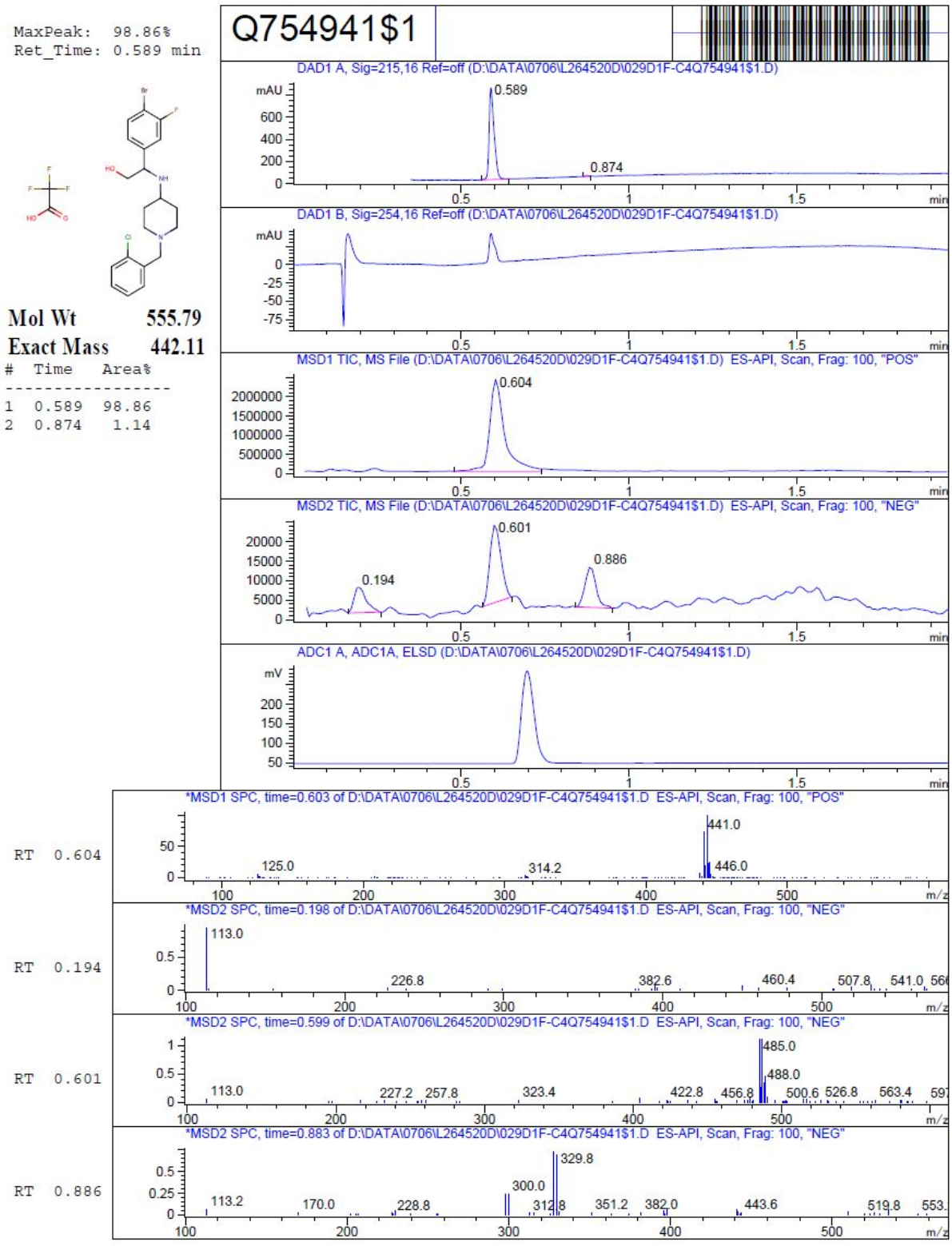

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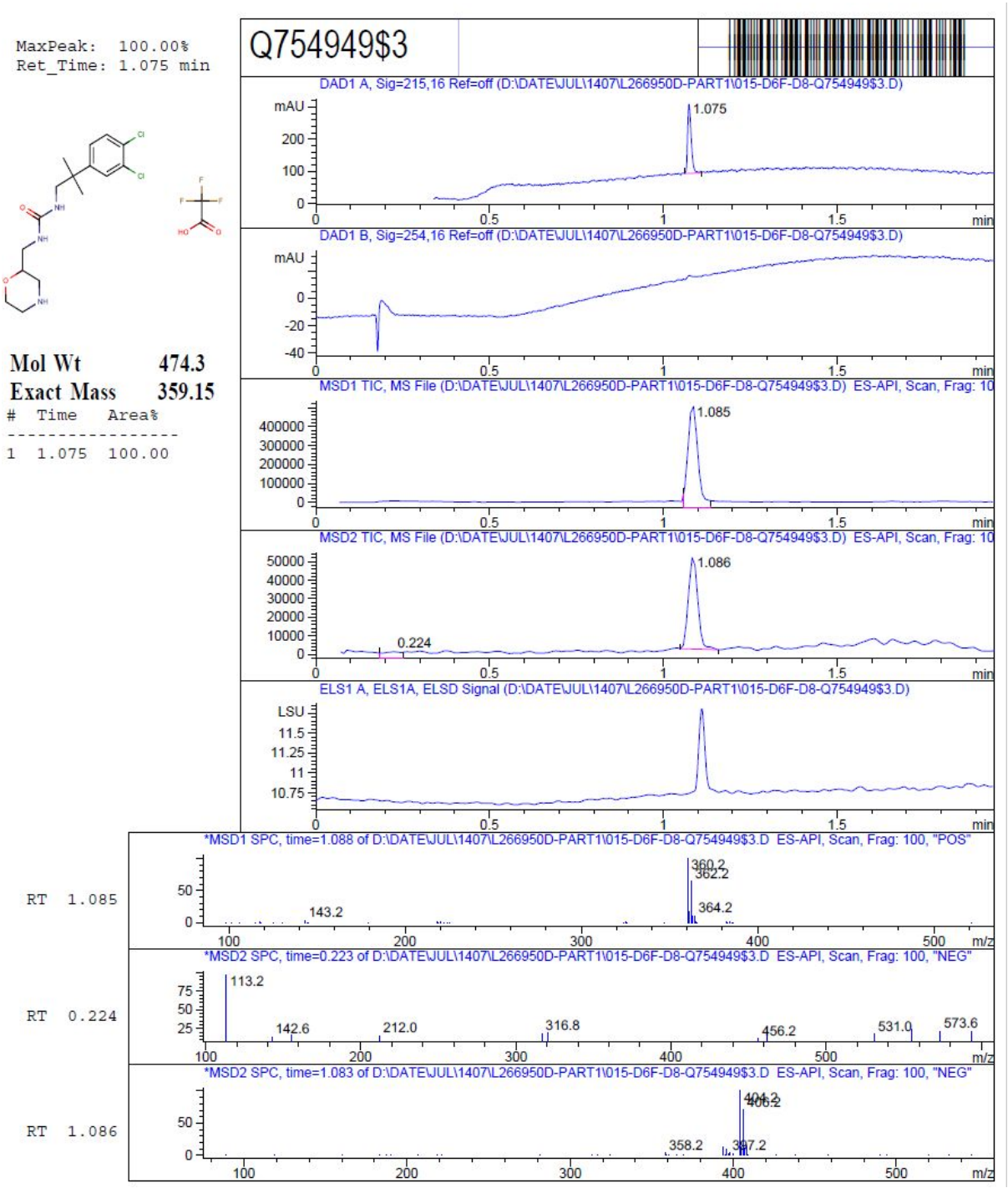

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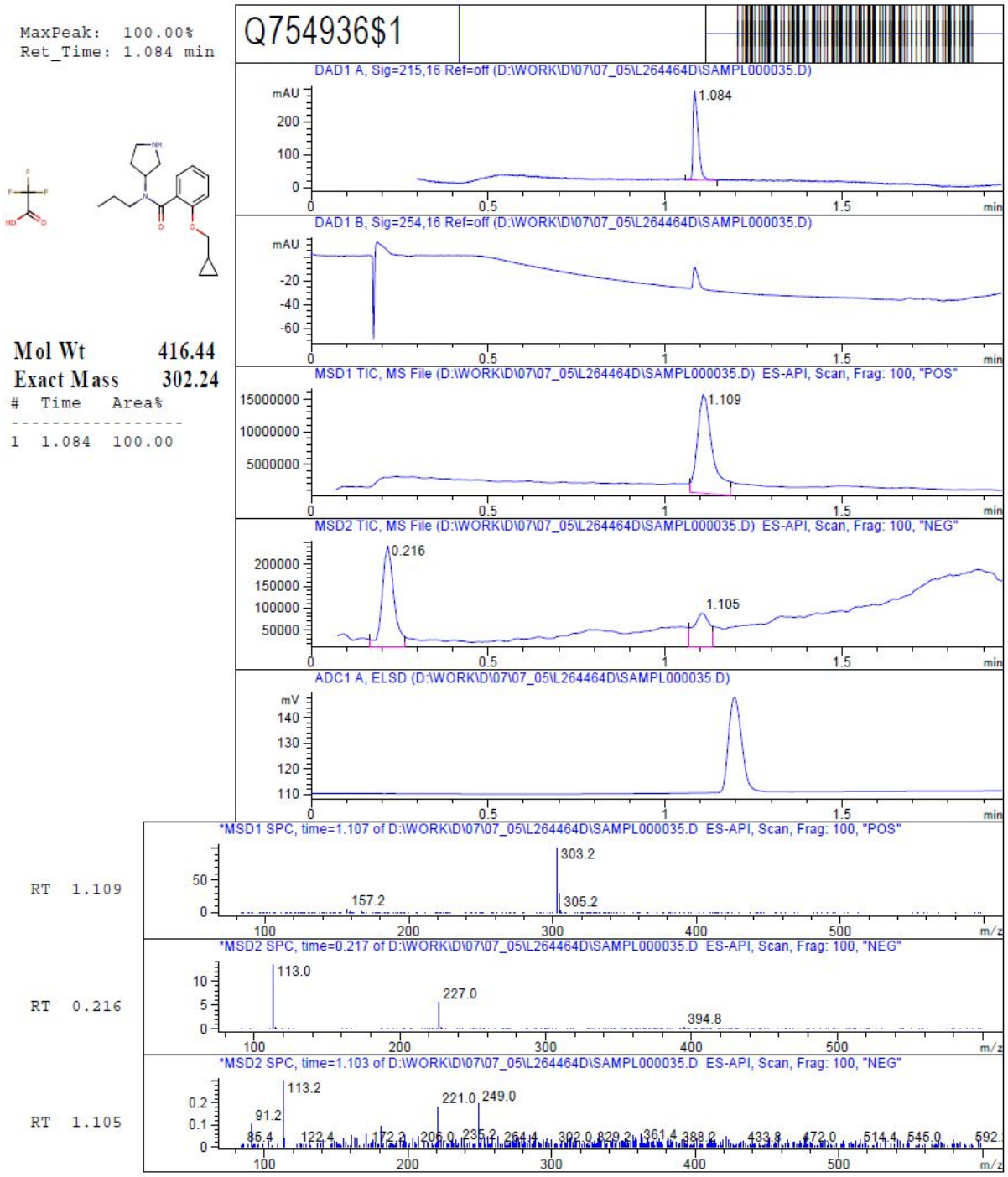

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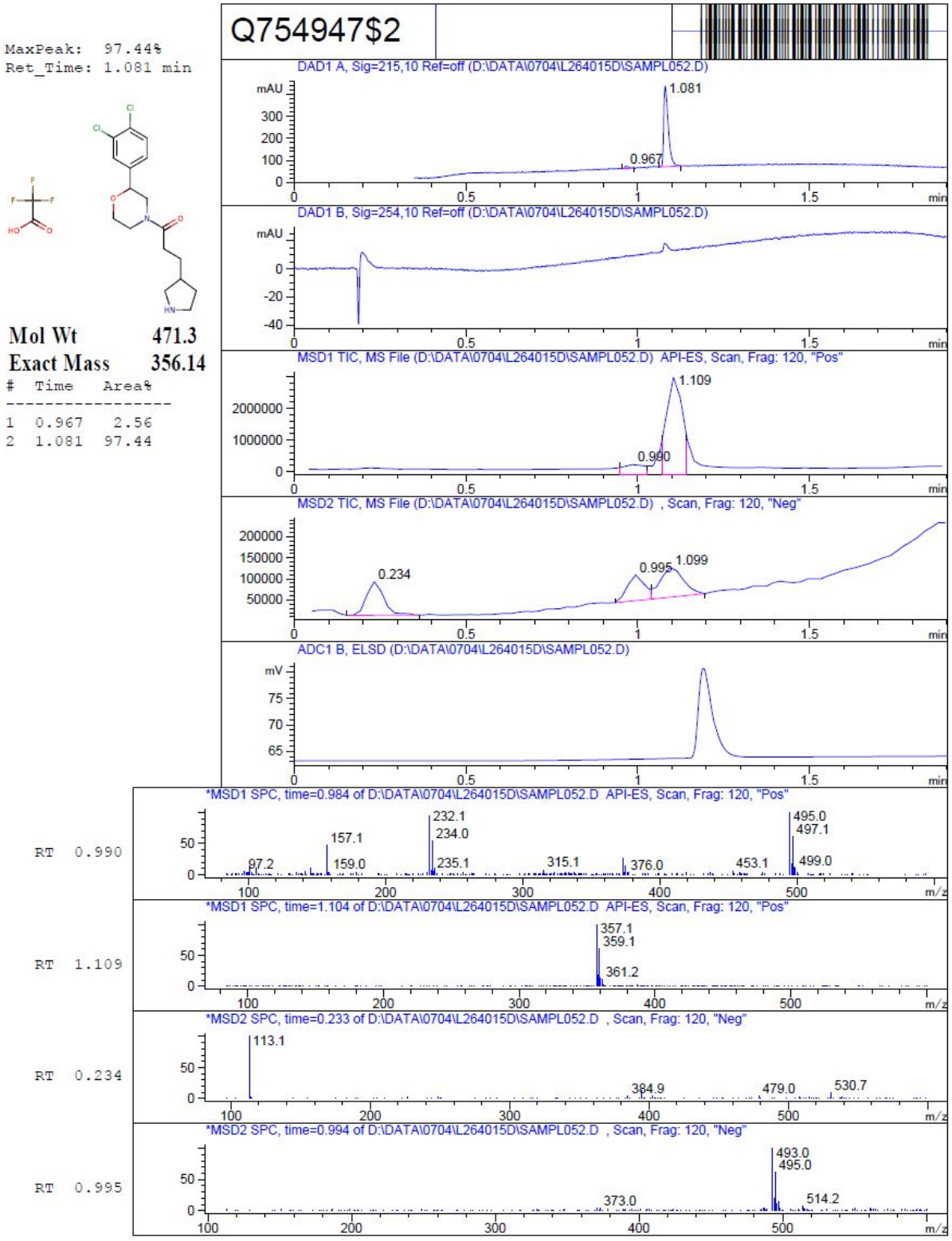

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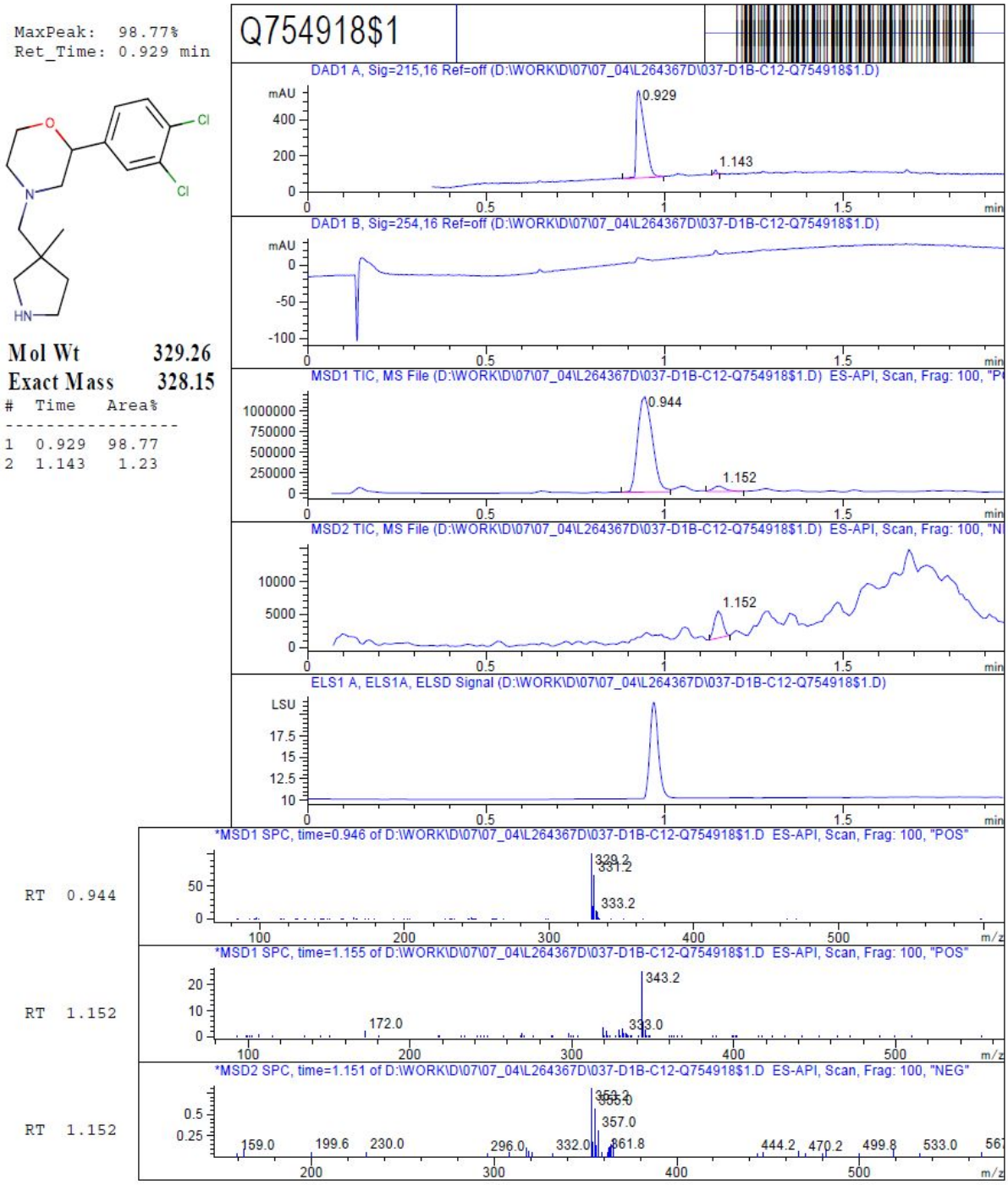

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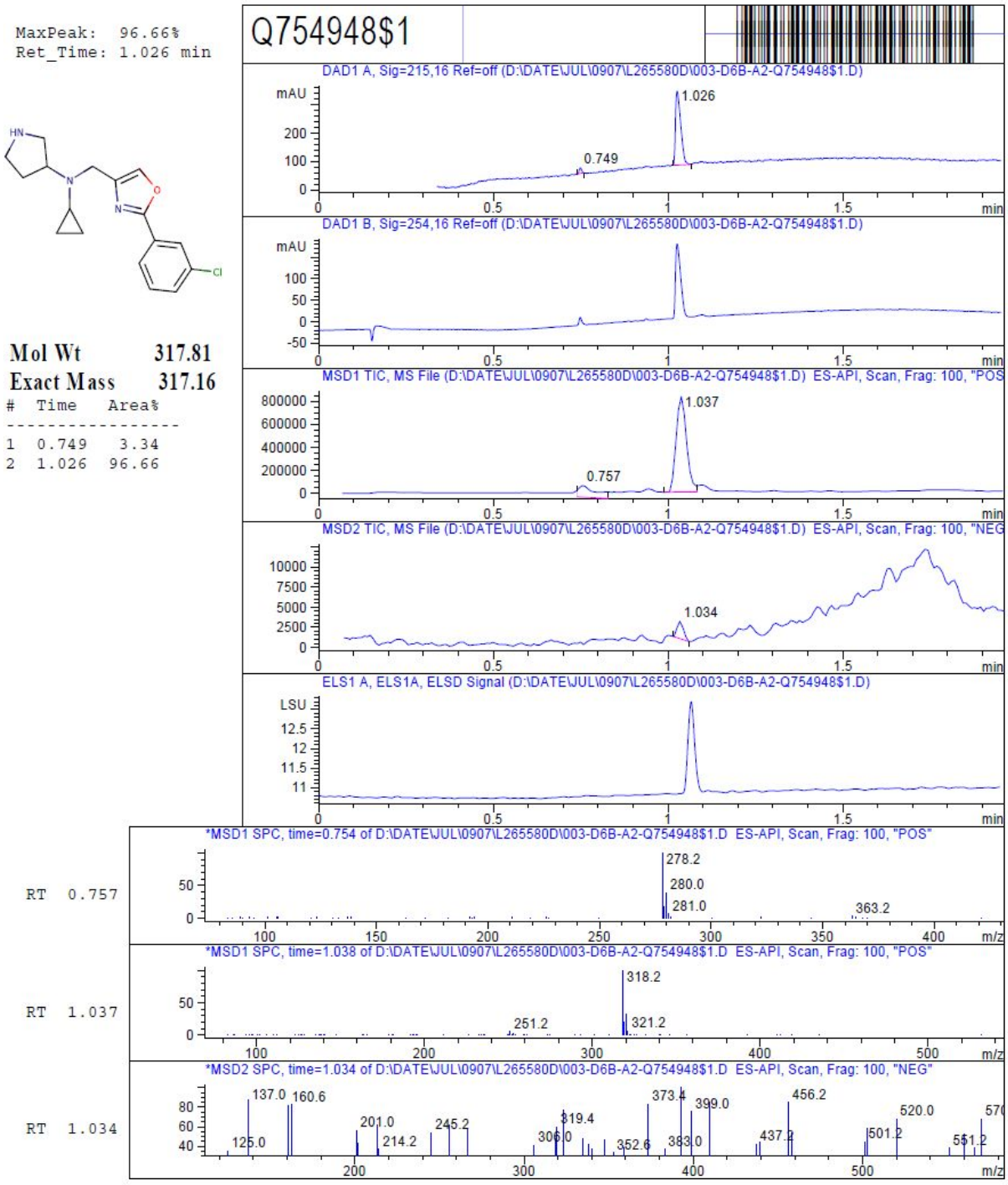

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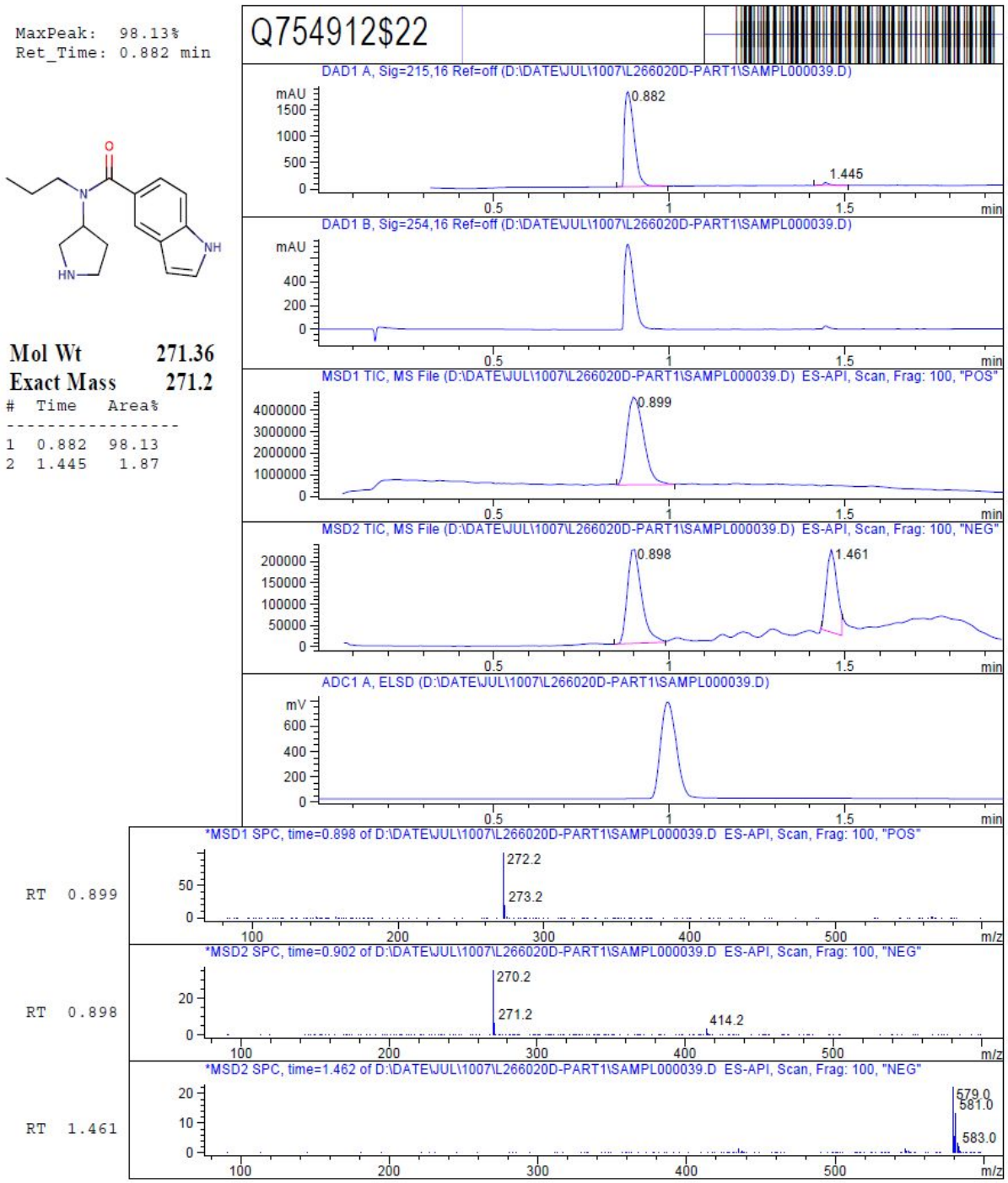

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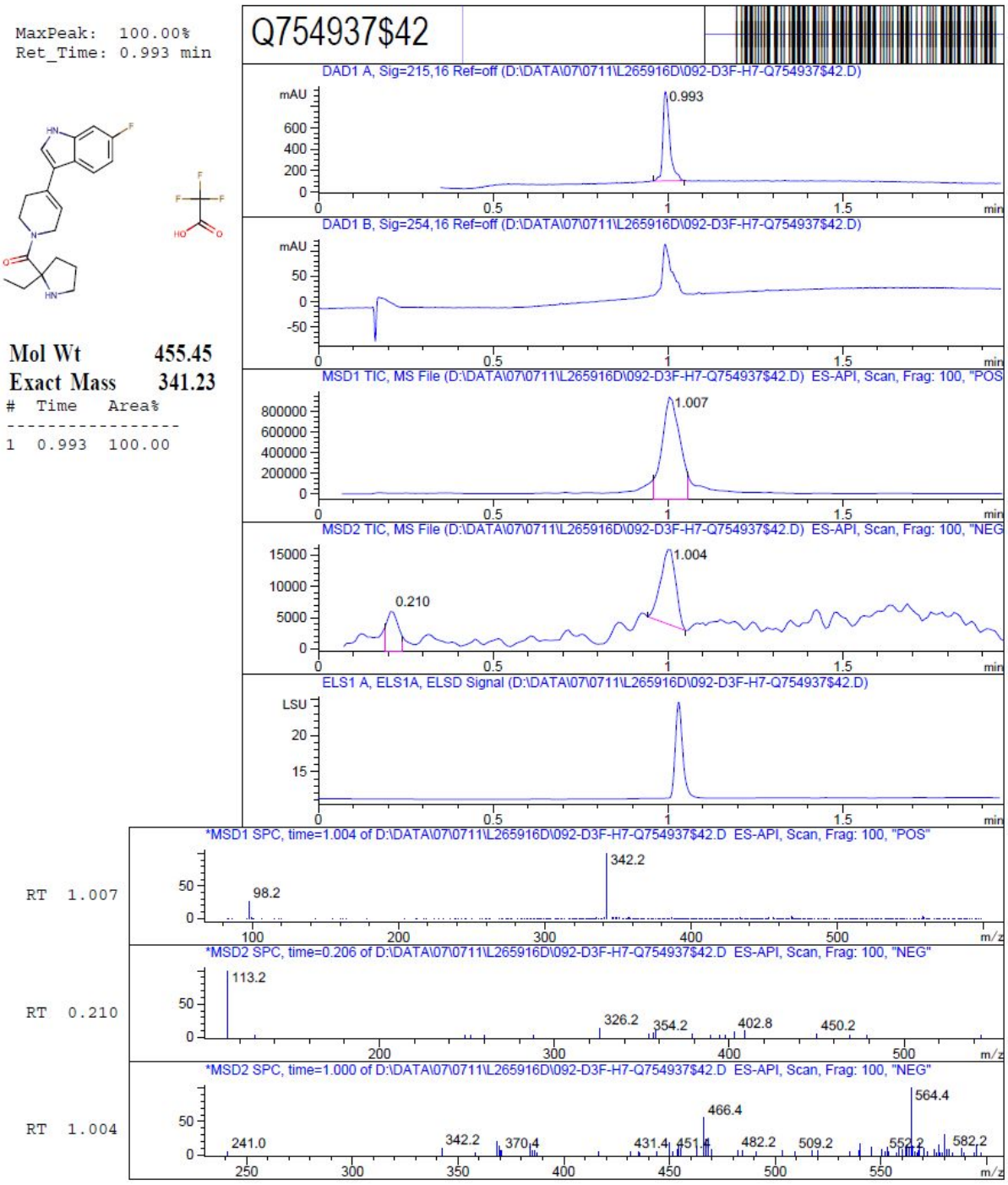

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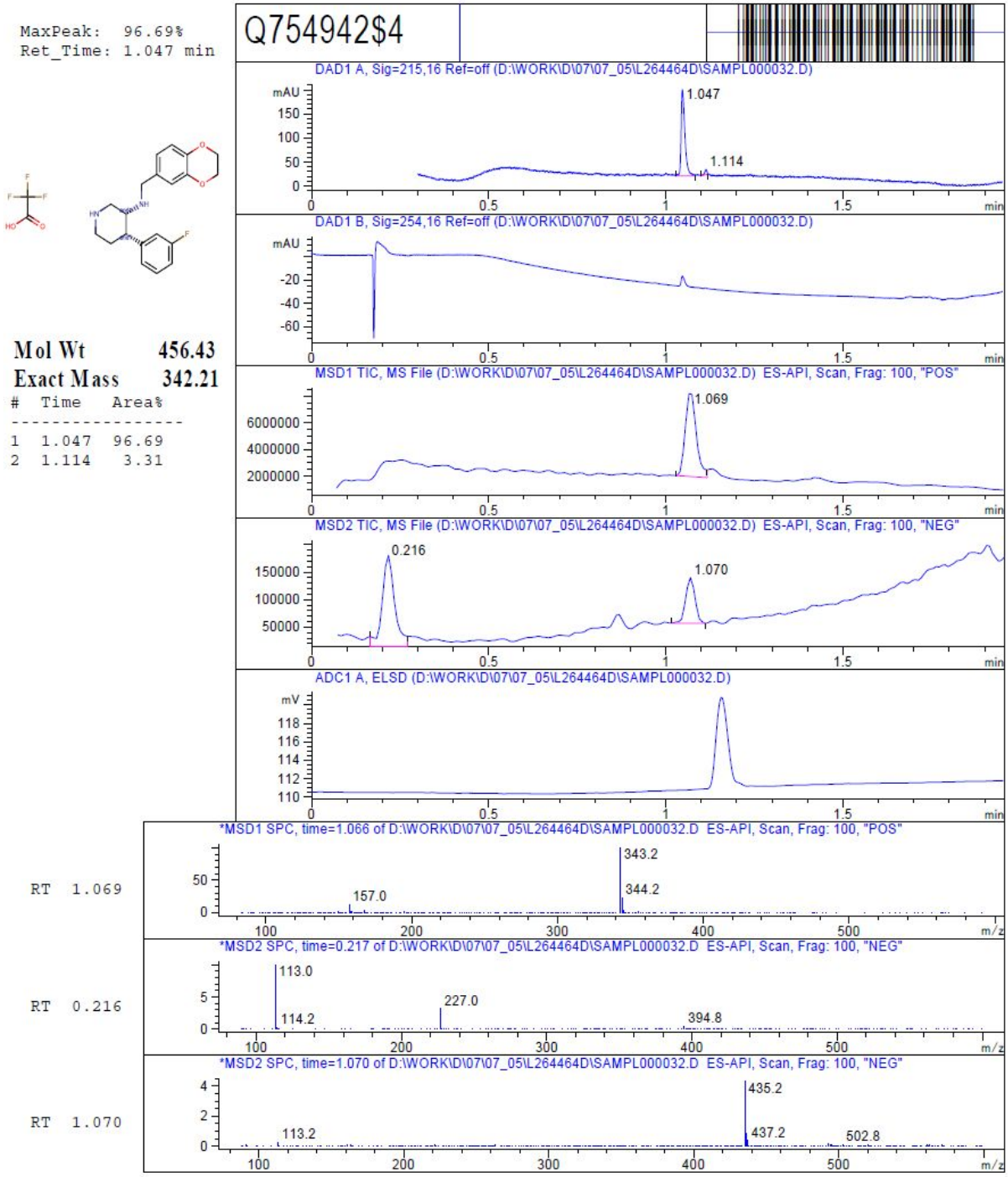

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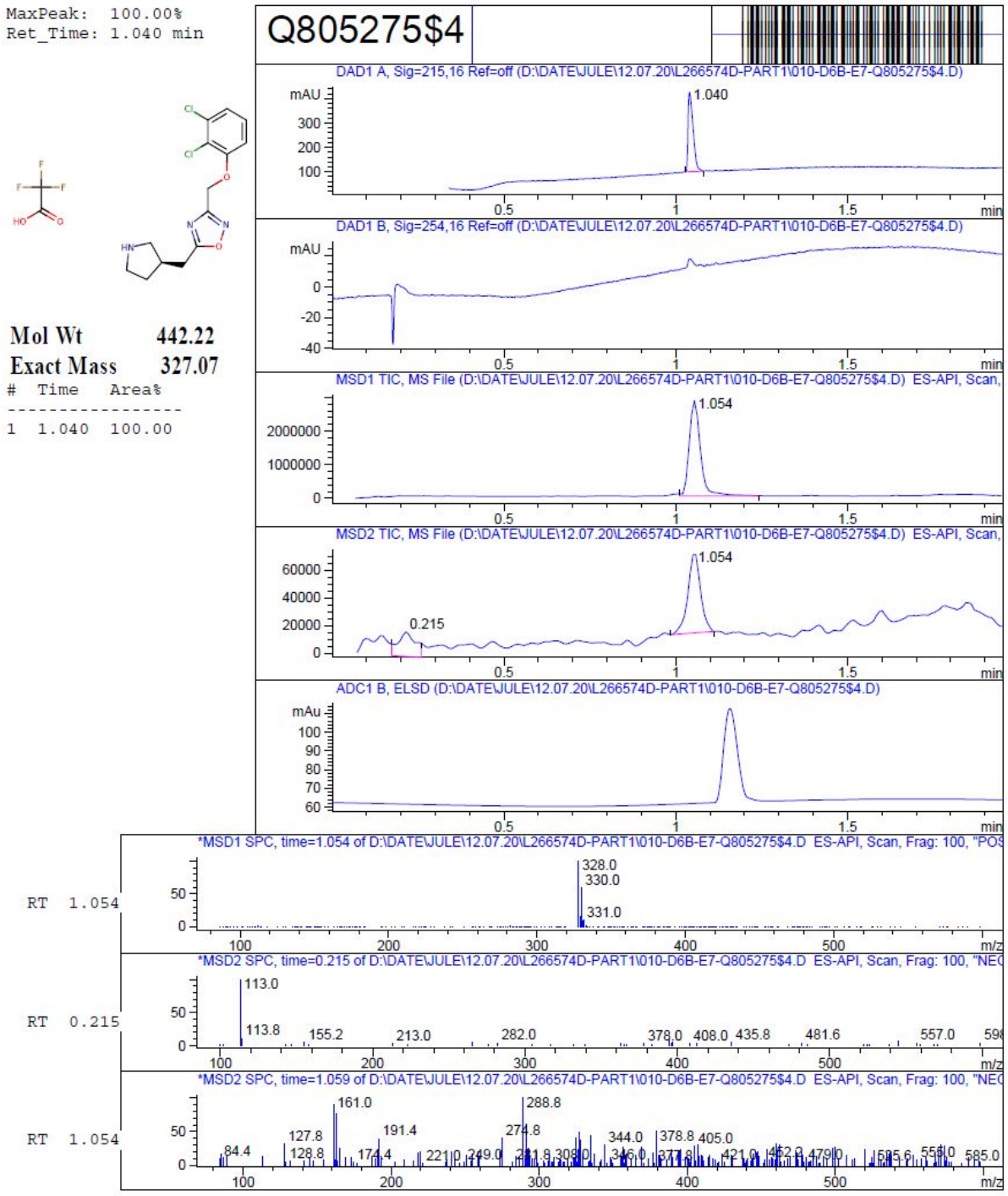

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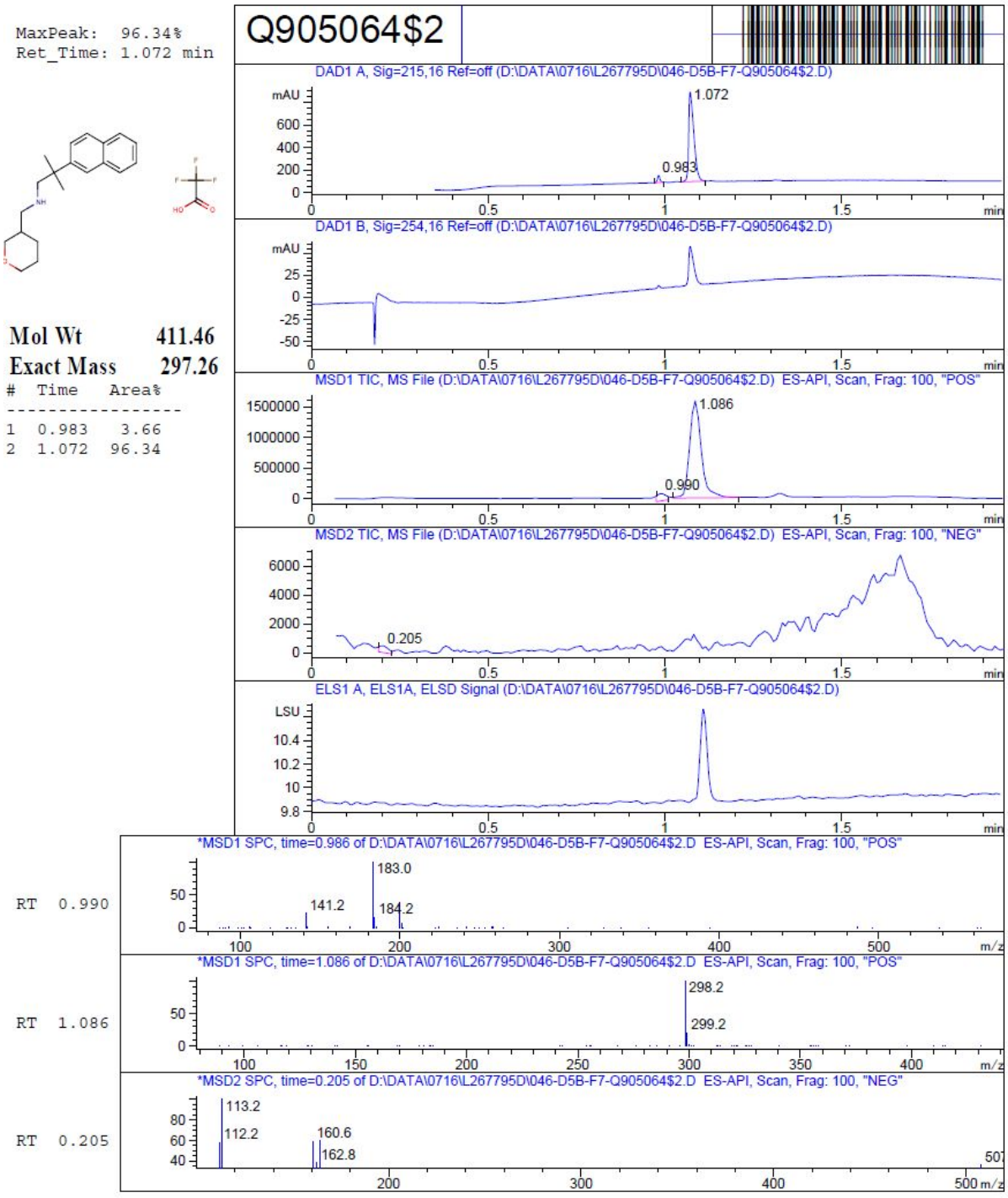

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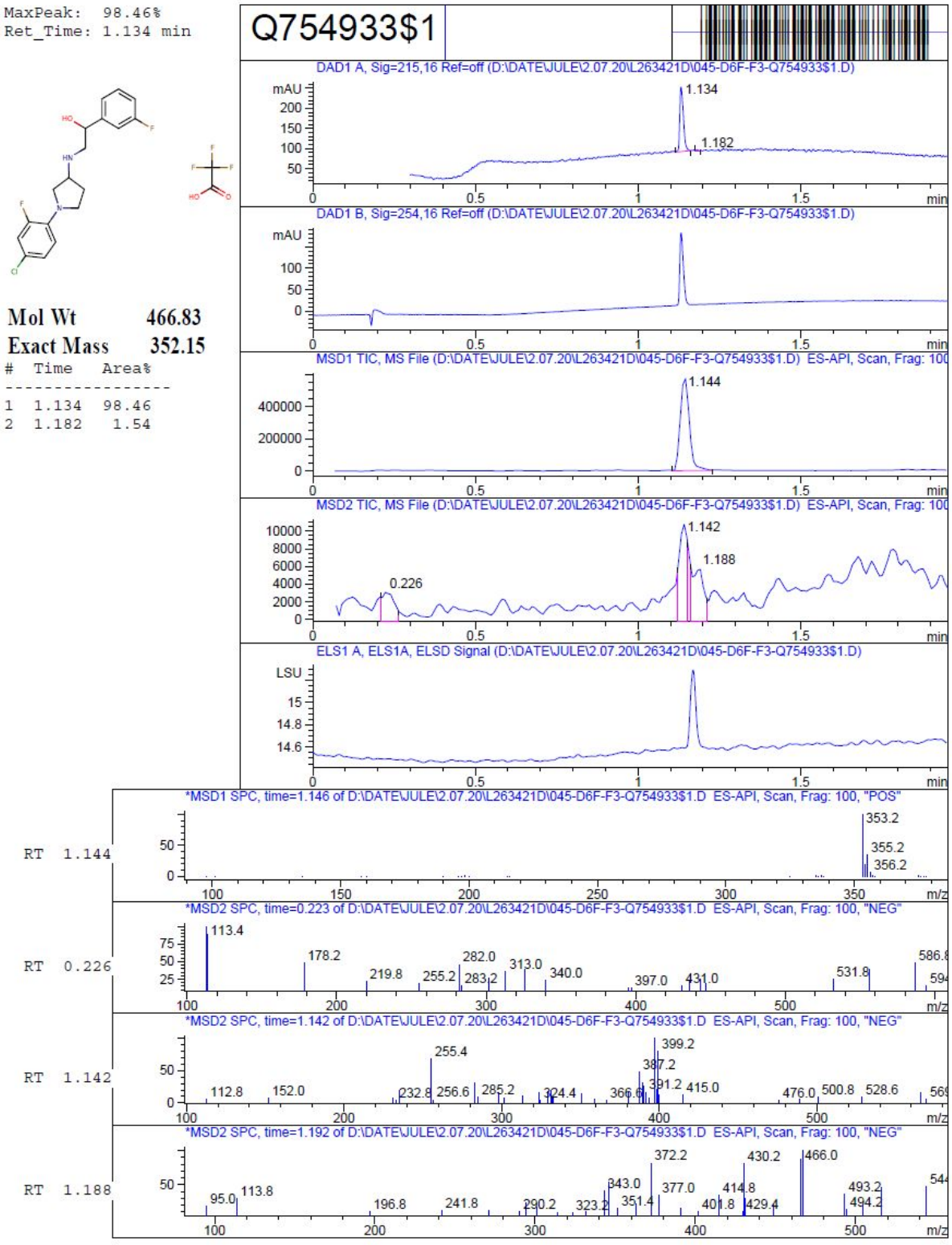

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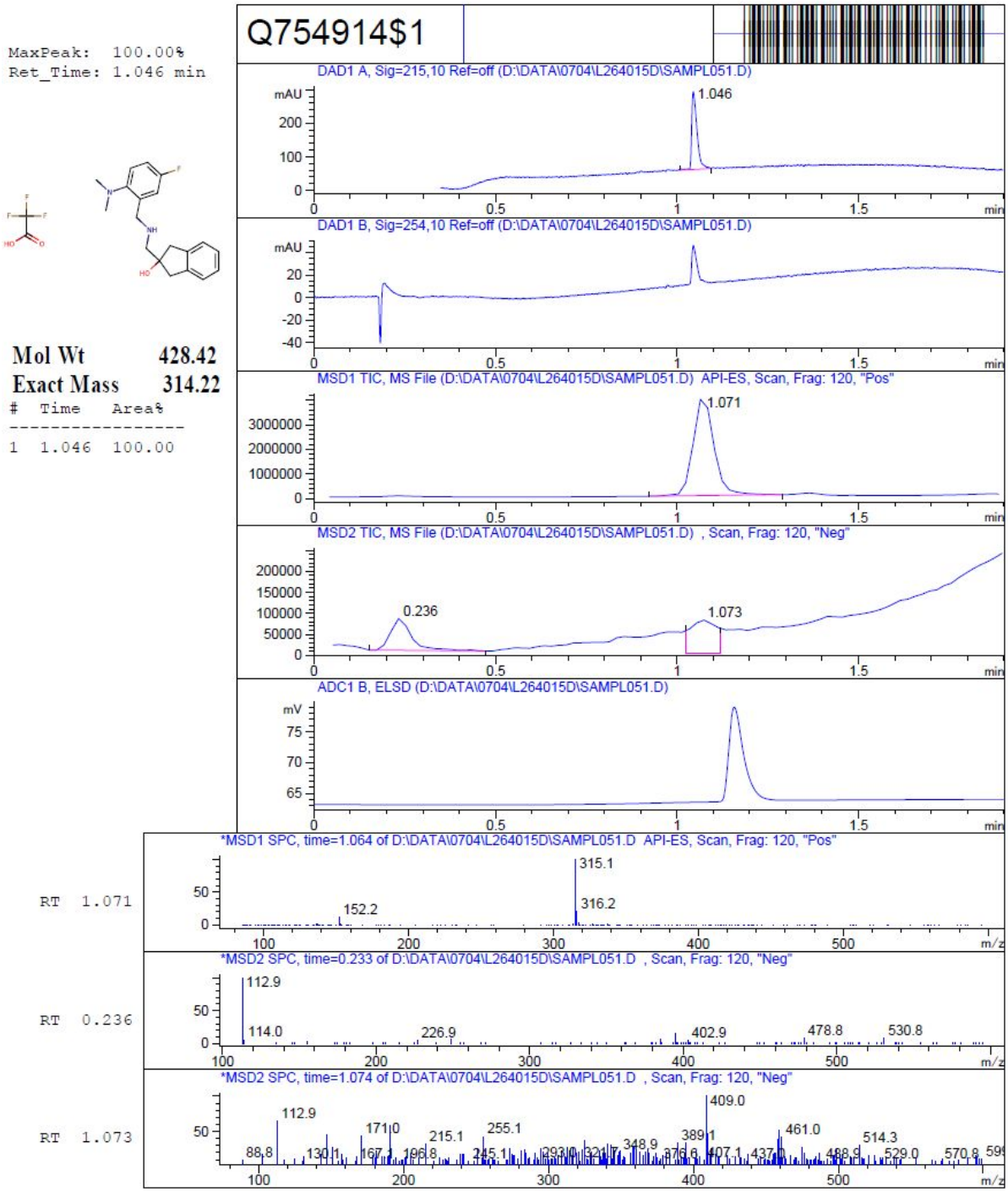

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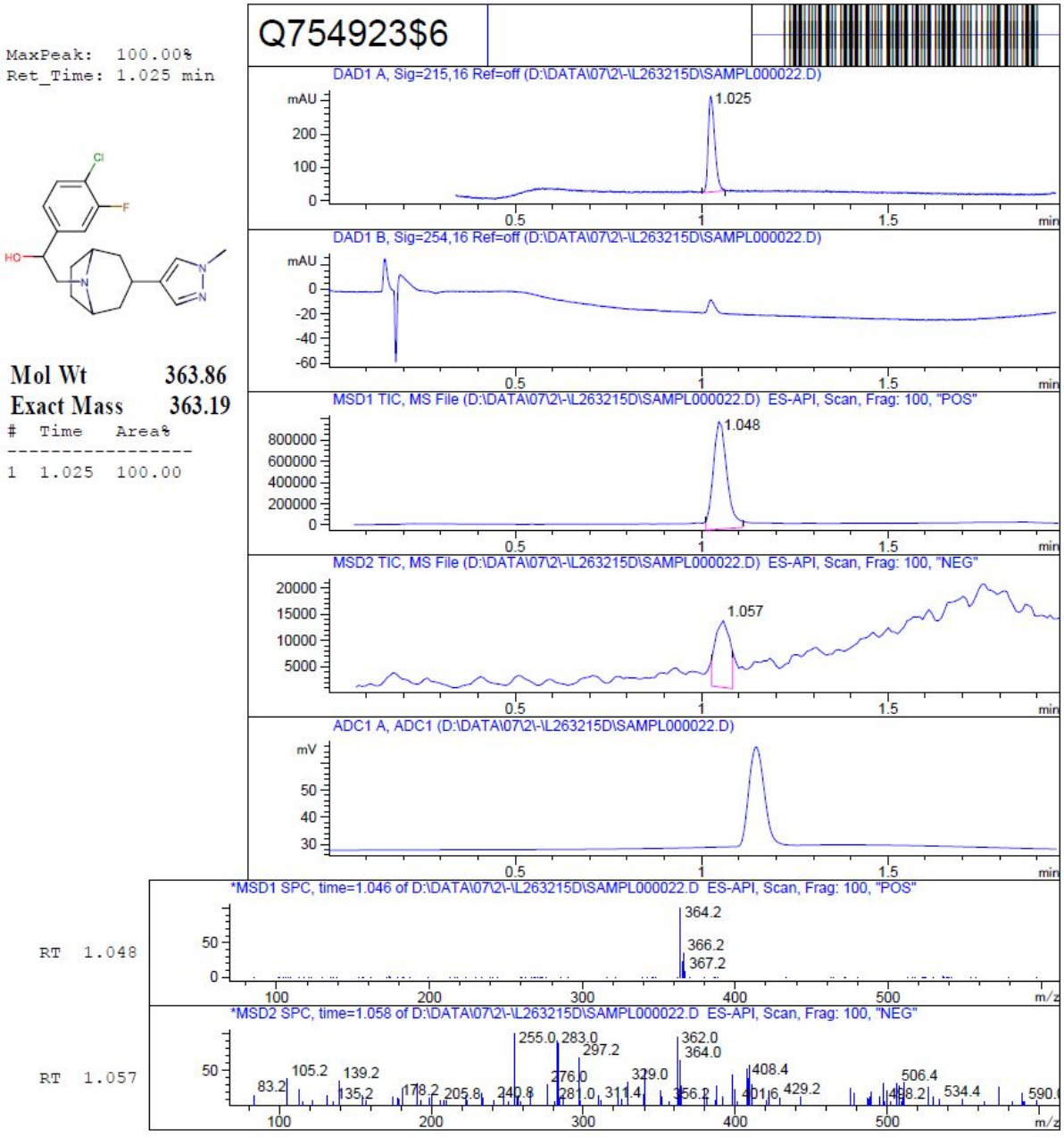

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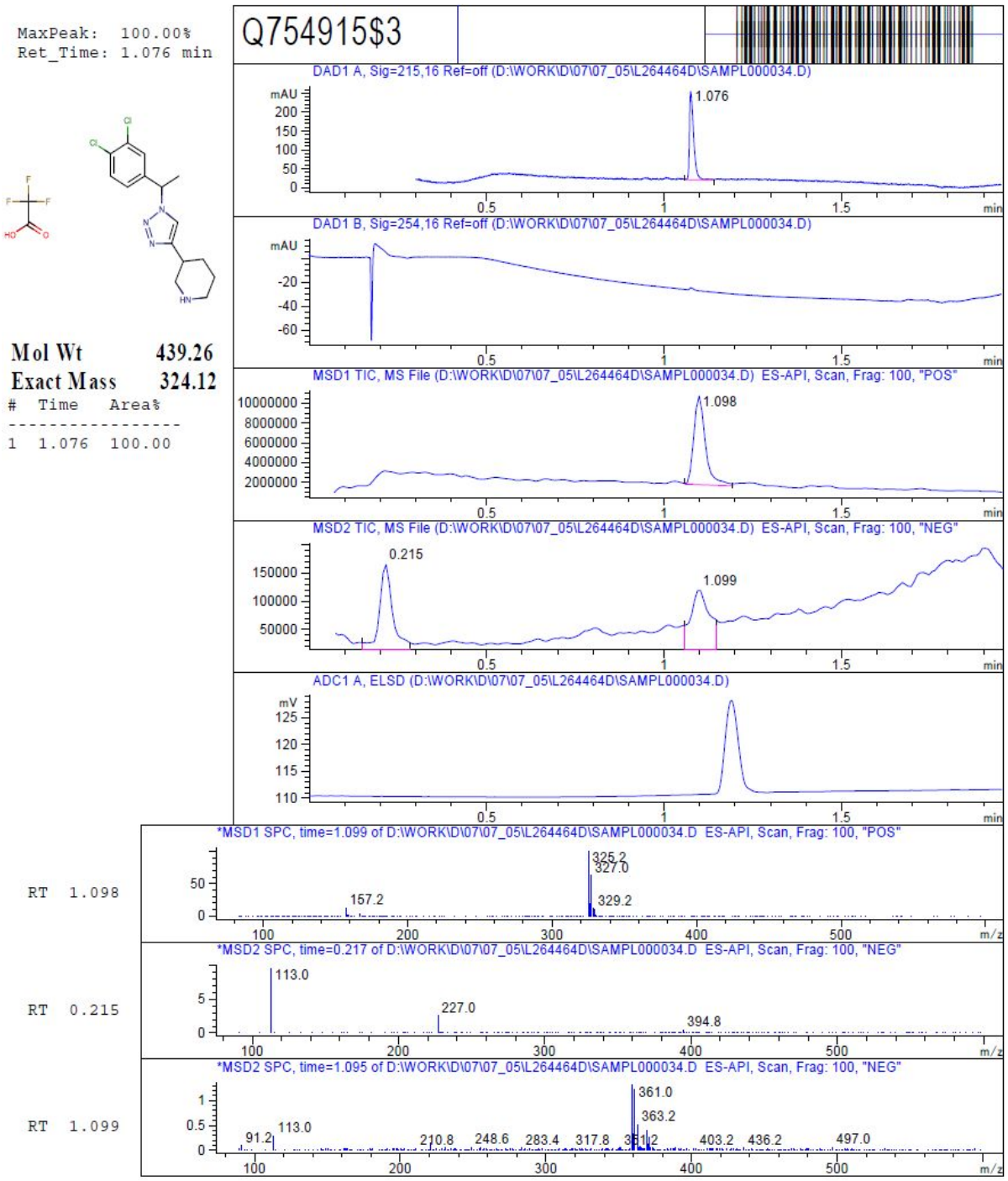

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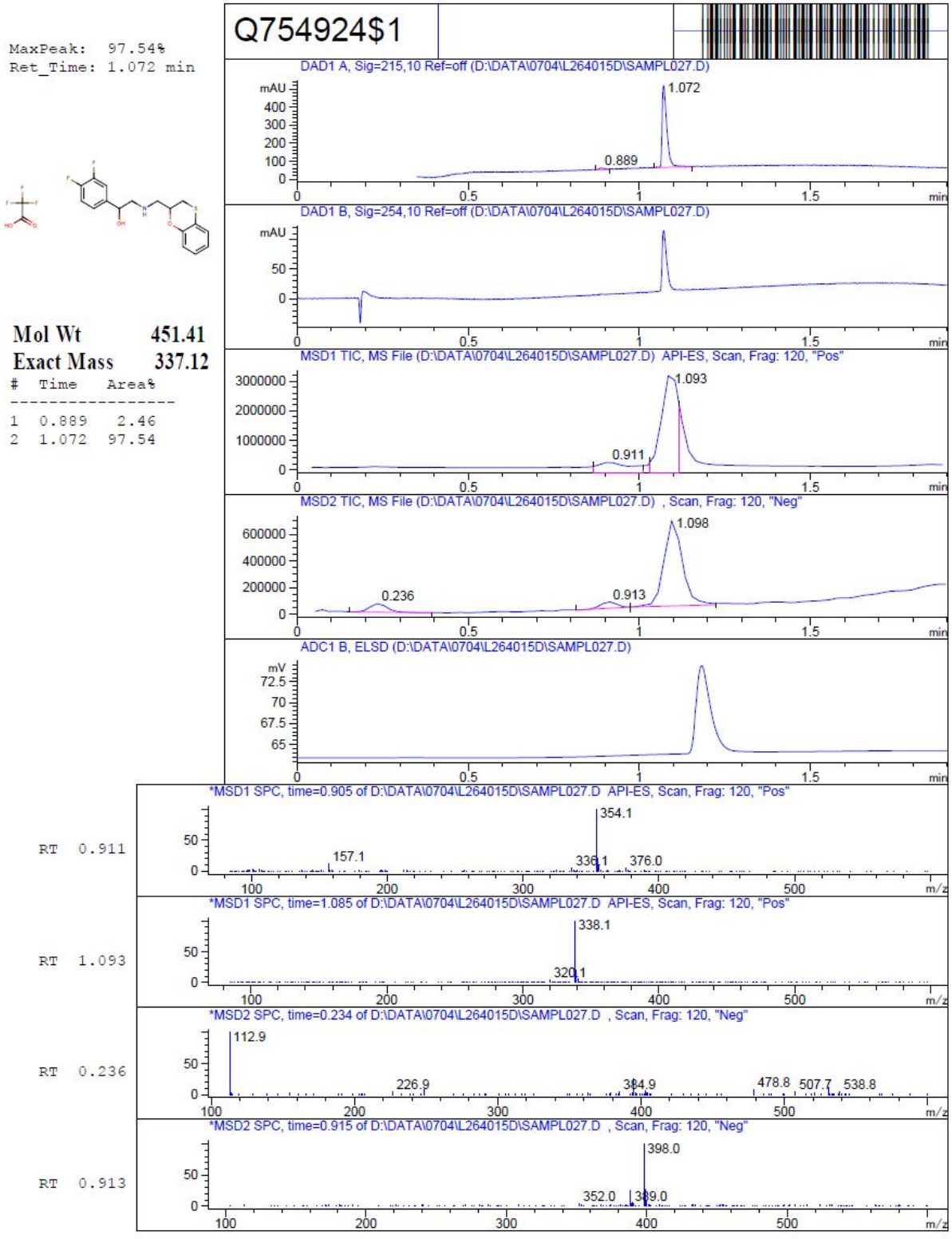

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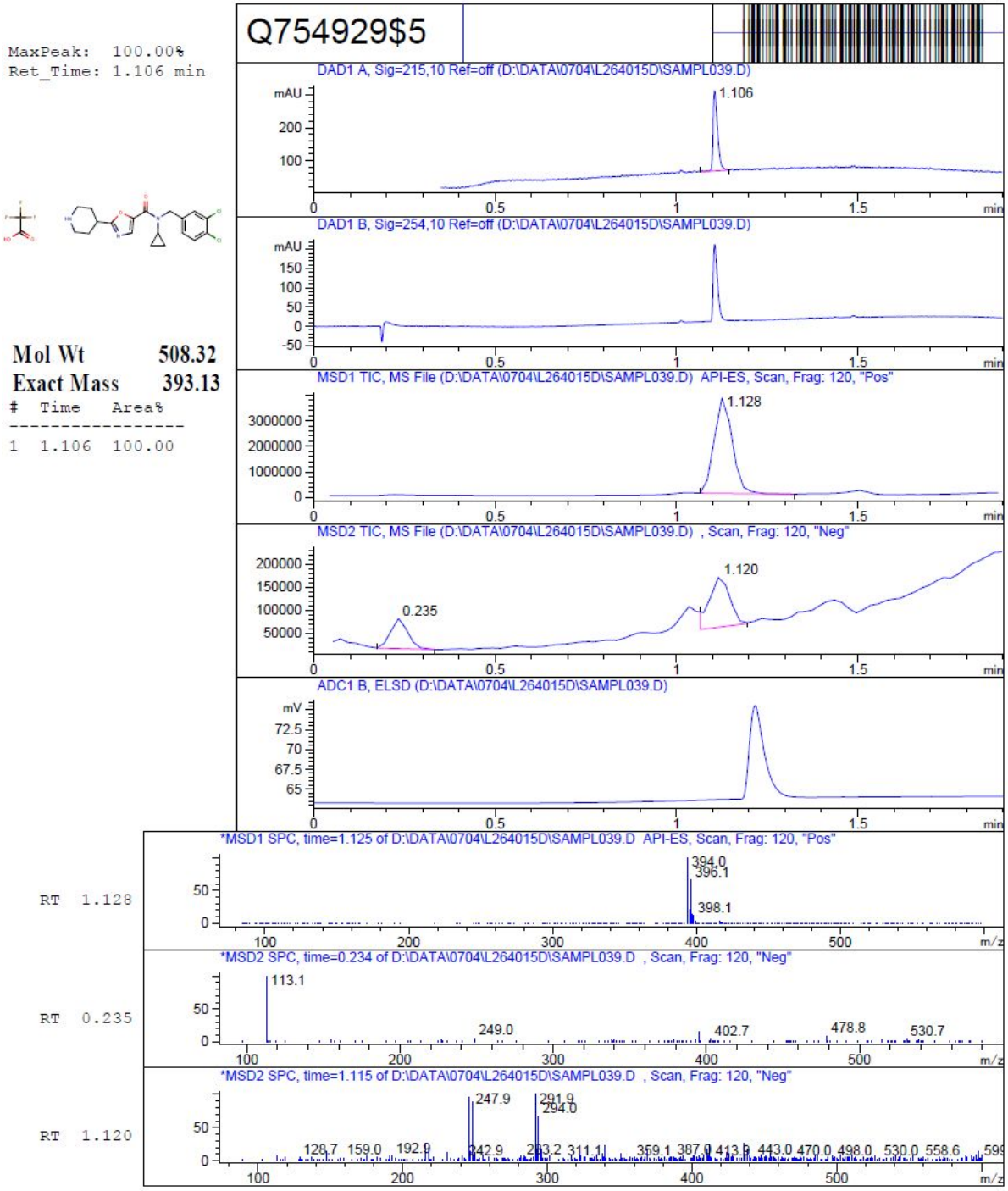

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