Supplementary Information II (SI-II)

Combining predictive and analytical methods to elucidate pharmaceutical biotransformation in activated sludge

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Table of Contents

S1. Data Table for tested APIs

Supplementary Table S1: List of APIs tested in the sludge biotransformation experiment

Name	Code	SMILES	CAS number
Acalabrutinib	Aca	CC#CC(=O)N1CCCC1C2=NC(=C3N2C=CN=C3N)C4=CC=C(C=C4)C(=O)NC5=CC=CC=N5	1420477-60-6
Aliskiren fumarate	Ali	CC(C)C(CC1=CC(=C(C=C1)OC)OCCCOC)CC(C(CC(C(C)C)C(=O)NCC(C)(C)C(=O)N)O)N	173334-58-2
Amlodipine besylate	Aml	CCOC(=O)C1=C(NC(=C(C1C2=CC=CC=C2Cl)C(=O)OC)C)COCCN	111470-99-6
Atazanavir sulfate	Ata	CC(C)(C)C(C(=O)NC(CC1=CC=CC=C1)C(CN(CC2=CC=C(C=C2)C3=CC=CC=N3)NC(=O)C(C(C)(C)C)NC(=O)OC)O)NC(=O)OC	229975-97-7
Atomoxetine	Atm	CC1=CC=CC=C1OC(CCNC)C2=CC=CC=C2	83015-26-3
Atovaquone	Atv	C1CC(CCC1C2=CC=C(C=C2)Cl)C3=C(C4=CC=CC=C4C(=O)C3=O)O	95233-18-4
Budesonide	Bud	CCCC1OC2CC3C4CCC5=CC(=O)C=CC5(C4C(CC3(C2(O1)C(=O)CO)C)O)C	51333-22-3
Canagliflozin hydrate	Can	CC1=C(C=C(C=C1)C2C(C(C(C(O2)CO)O)O)O)CC3=CC=C(S3)C4=CC=C(C=C4)F	842133-18-0
Ceritinib	Cer	CC1=CC(=C(C=C1C2CCNCC2)OC(C)C)NC3=NC=C(C(=N3)NC4=CC=CC=C4S(=O)(=O)C(C)C)Cl	1032900-25-6
Clopidogrel bisulfate	Clp	COC(=O)C(C1=CC=CC=C1Cl)N2CCC3=C(C2)C=CS3	120202-66-6
Clotrimazol	Clt	C1=CC=C(C=C1)C(C2=CC=CC=C2)(C3=CC=CC=C3Cl)N4C=CN=C4	23593-75-1
Dapagliflozin	Dap	CCOC1=CC=C(C=C1)CC2=C(C=CC(=C2)C3C(C(C(C(O3)CO)O)O)O)Cl	461432-26-8
Dasatinib	Das	CC1=C(C(=CC=C1)Cl)NC(=O)C2=CN=C(S2)NC3=CC(=NC(=N3)C)N4CCN(CC4)CCO	302962-49-8
Dienogest	Die	CC12CCC3=C4CCC(=O)C=C4CCC3C1CCC2(CC#N)O	65928-58-7
Dolutegravir sodium	Dol	CC1CCOC2N1C(=O)C3=C(C(=O)C(=CN3C2)C(=O)NCC4=C(C=C(C=C4)F)F)O	1051375-16-6
Duloxetine	Dul	CNCCC(C1=CC=CS1)OC2=CC=CC3=CC=CC=C32	116539-59-4
Efavirenz	Efa	C1CC1C#CC2(C3=C(C=CC(=C3)Cl)NC(=O)O2)C(F)(F)F	154598-52-4

Ezetimibe	Eze	C1=CC(=CC=C1C2C(C(=O)N2C3=CC=C(C=C3)F)CCC(C4=CC=C(C=C4)F)O)O	439081-02-4
Fexofenadine	Fex	CC(C)(C1=CC=C(C=C1)C(CCCN2CCC(CC2)C(C3=CC=CC=C3)(C4=CC=CC=C4)O)O)C(=O)O	83799-24-0
Fingolimod hydrochloride	Fin	CCCCCCCCC1=CC=C(C=C1)CCC(CO)(CO)N	162359-55-9
Hydrochlorothiazide	Hyd	C1NC2=CC(=C(C=C2S(=O)(=O)N1)S(=O)(=O)N)Cl	58-93-5
Irbesartan	Irb	CCCCC1=NC2(CCCC2)C(=O)N1CC3=CC=C(C=C3)C4=CC=CC=C4C5=NNN=N5	138402-11-6
Keto-desogestrel/ Etonogestrel	Ket	CCC12CC(=C)C3C(C1CCC2(C#C)O)CCC4=CC(=O)CCC34	54048-10-1
Lumiracoxib	Lum	CC1=CC(=C(C=C1)NC2=C(C=CC=C2Cl)F)CC(=O)O	220991-20-8
Metformin hydrochloride	Met	CN(C)C(=N)N=C(N)N	1115-70-4
Mirtazapine	Mir	CN1CCN2C(C1)C3=CC=CC=C3CC4=C2N=CC=C4	85650-52-8
Mometasone furoate	Mom	CC1CC2C3CCC4=CC(=O)C=CC4(C3(C(CC2(C1(C(=O)CCl)OC(=O)C5=CC=CO5)C)O)Cl)C	83919-23-7
Naloxegol	Nal	COCCOCCOCCOCCOCCOCCOCCOCC1CCC2(C3CC4=C5C2(C1OC5=C(C=C4)O)CCN3CC=C)O	854601-70-0
Nilotinib	Nil	CC1=C(C=C(C=C1)C(=O)NC2=CC(=CC(=C2)C(F)(F)F)N3C=C(N=C3)C)NC4=NC=CC(=N4)C5=CN=CC=C5	641571-10-0
Olanzapine	Ola	CC1=CC2=C(S1)NC3=CC=CC=C3N=C2N4CCN(CC4)C	132539-06-1
Omeprazole	Ome	CC1=CN=C(C(=C1OC)C)CS(=O)C2=NC3=C(N2)C=C(C=C3)OC	73590-58-6
Orlistat	Orl	CCCCCCCCCCCCC(CC1C(C(=O)O1)CCCCCC)OC(=O)C(CC(C)C)NC=O	96829-58-2
Panobinostat lactate	Pan	CC1=C(C2=CC=CC=C2N1)CCNCC3=CC=C(C=C3)C=CC(=O)NO	404950-80-7
Pemetrexed	Pem	C1=CC(=CC=C1CCC2=CNC3=C2C(=O)NC(=N3)N)C(=O)NC(CCC(=O)O)C(=O)O	137281-23-3
Pioglitazone hydrochloride	Pio	CCC1=CN=C(C=C1)CCOC2=CC=C(C=C2)CC3C(=O)NC(=O)S3	112529-15-4
Quetiapine fumarate	Que	C1CN(CCN1CCOCCO)C2=NC3=CC=CC=C3SC4=CC=CC=C42	111974-72-2
Regorafenib	Reg	CNC(=O)C1=NC=CC(=C1)OC2=CC(=C(C=C2)NC(=O)NC3=CC(=C(C=C3)Cl)C(F)(F)F)F	755037-03-7

Ridaforolimus	Rid	CC1CCC2CC(C(=CC=CC=CC(CC(C(=O)C(C(C(=CC(C(=O)CC(OC(=O)C3CCCCN3C(=O)C(=O)C1(O2)O)C(C)CC4CCC(C(C4)OC)OP(=O)(C)C)C)C)O)OC)C)C)C)OC	572924-54-0
Rivastigmine hydrochloride	Riv	CCN(C)C(=O)OC1=CC=CC(=C1)C(C)N(C)C	123441-03-2
Rosuvastatin calcium	Ros	CC(C)C1=NC(=NC(=C1C=CC(CC(CC(=O)O)O)O)C2=CC=C(C=C2)F)N(C)S(=O)(=O)C	147098-20-2
Tadalafil	Tad	CN1CC(=O)N2C(C1=O)CC3=C(C2C4=CC5=C(C=C4)OCO5)NC6=CC=CC=C36	171596-29-5
Terbinafine hydrochloride	Ter	CC(C)(C)C#CC=CCN(C)CC1=CC=CC2=CC=CC=C21	91161-71-6
Ticagrelor	Tic	CCCSC1=NC(=C2C(=N1)N(N=N2)C3CC(C(C3O)O)OCCO)NC4CC4C5=CC(=C(C=C5)F)F	274693-27-5
Valsartan	Val	CCCCC(=O)N(CC1=CC=C(C=C1)C2=CC=CC=C2C3=NNN=N3)C(C(C)C)C(=O)O	137862-53-4
Vildagliptin	Vil	C1CC(N(C1)C(=O)CNC23CC4CC(C2)CC(C4)(C3)O)C#N	274901-16-5
Vorinostat	Vor	C1=CC=C(C=C1)NC(=O)CCCCCCC(=O)NO	149647-78-9

S2. Data Table for Identified TPs

The reported SMILES corresponds to the predicted structure and does not necessarily represent the found structural information.

Supplementary Table S2: List of tentatively identified TPs

Name	SMILES	CAS Number(s)
12_TP_Ali	COc1ccc(CC(CC(N)C(O)CC(C(=O)NCC(C)(C)C(N)=O)C(C)C)C(C)C)cc1OCCC(=O)O	949925-75-1
Aml_TP_12	CCOC(=O)C1=C(COCC(=O)O)NC(C)=C(C(=O)OC)C1c1ccccc1Cl	90445-14-0
Atm_TP_9	CNCCC(Oc1ccccc1C(=O)O)c1ccccc1	540729-11-1
Can_TP_7	Cc1ccc(C(O)C(O)C(O)C(O)C(=O)C(=O)O)cc1Cc1ccc(-c2ccc(F)cc2)s1	Not found
Clp_TP_10	O=Cc1ccsc1CCNC(C(=O)O)c1ccccc1Cl	Not found
Clp_TP_5	O=C(O)C(c1ccccc1Cl)N1CCc2sccc2C1	1246814-52-7, 324757-50-8, 144457-28-3, 90055-55-3
TP_Clp_16	O=C(O)c1ccsc1CCNC(C(=O)O)c1ccccc1Cl	Not found
Clp_TP_3	COC(=O)C(NCCc1sccc1C=O)c1ccccc1Cl	Not found
Clp_TP_11	COC(=O)C(NCCc1sccc1C(=O)O)c1ccccc1Cl	Not found
TP_Dap_14	CCOc1ccc(Cc2cc(C(=O)C(O)C(O)C(O)C(O)C(=O)O)ccc2Cl)cc1	Not found
TP_Das_8	Cc1nc(Nc2ncc(C(=O)Nc3c(C)cccc3Cl)s2)cc(N2CCN(CC(=O)O)CC2)n1	910297-53-9
Dol_TP_4	CC1CCOC(C=O)N1C(=O)c1[nH]cc(C(=O)NCc2ccc(F)cc2F)c(=O)c1O	Not found
Eze_TP_2	O=C1C(CCC(O)c2ccc(F)cc2)C(c2ccc(O)c(O)c2)N1c1ccc(F)cc1	Not found
Eze_TP_15	O=C(CCC1C(=O)N(c2ccc(F)cc2)C1c1ccc(O)cc1)c1ccc(F)cc1	191330-56-0
TP_Fex_22	CC(C)(C(=O)O)c1ccc(C(=O)CCCNCCC(CC=O)C(O)(c2ccccc2)c2ccccc2)cc1	Not found
Fex_TP_3	OC(c1ccccc1)(c1ccccc1)C1CCNCC1	115-46-8
Fex_TP_13	CC(C)(C(=O)O)c1ccc(C(=O)CCCN2CCC(C(O)(c3ccccc3)c3ccccc3)CC2)cc1	76811-98-8
Fex_TP_4	CC(C)(C(=O)O)c1ccc(C(O)CCC(=O)O)cc1	Not found
Val_TP_7	O=C(O)c1ccc(-c2ccccc2-c2nn[nH]n2)cc1	164265-78-5
Irb_TP_1	CCCCC(=NC1(C(=O)O)CCCC1)NCc1ccc(-c2ccccc2-c2nn[nH]n2)cc1	Not found
Val_TP_12	CCCCC(=O)NCc1ccc(-c2ccccc2-c2nn[nH]n2)cc1	Not found
Val_TP_5	NCc1ccc(-c2ccccc2-c2nn[nH]n2)cc1	147225-68-1
Ket_TP_2	C=C1CC2(CC)C(CCC2(O)CC=O)C2CCC3=CC(=O)CCC3C12	Not found
TP_Lum_11	Cc1ccc(Nc2c(F)cccc2Cl)c(C(O)C(=O)O)c1	Not found
TP_Mir_34	CN(CC(=O)O)CC(=O)c1ccccc1Cc1cccnc1N	Not found
Mir_TP_1	CN(CC=O)CC1Nc2ncccc2Cc2ccccc21	Not found
TP_Mir_27	CNCCNc1ncccc1Cc1ccccc1C(=O)C(=O)O	Not found
Ola_TP_2	Cc1cc2c(s1)Nc1ccccc1N=C2NCCN(C)CC=O	Not found

TP_Ola_6	CNCCN(CC(=O)O)C1=Nc2ccccc2Nc2sc(C)cc21	Not found
Ome_TP_1	COc1ccc2nc(S(=O)(=O)Cc3ncc(C)c(OC)c3C)[nH]c2c1	1261393-28-5, 1189891-71-1, 88546-55-8
Pan_TP_1	O=Cc1ccc(C=CC(=O)NO)cc1	Not found
Pan_TP_4	NCc1ccc(C=CC(=O)NO)cc1	Not found
TP_Pan_14	Cc1[nH]c2ccccc2c1C(O)CN	926196-01-2
TP_Pem_42	Nc1nc2[nH]cc(CC(O)c3ccc(O)c(O)c3)c2c(=O)[nH]1	Not found
TP_Pem_14	Nc1nc2[nH]cc(CCc3ccc(O)c(O)c3)c2c(=O)[nH]1	Not found
Pem_TP_2	Nc1nc2[nH]cc(CCc3ccc(C(=O)O)cc3)c2c(=O)[nH]1	137281-39-1
Pio_TP_9	CCc1ccc(CCOc2ccc(CC3C(=O)NC(=O)S3=O)cc2)nc1	Not found
Pio_TP_8	CCc1ccc(CCOc2ccc(CC(=O)C(=O)NC(=O)S)cc2)nc1	Not found
16_TP_Pio	O=C1NC(=O)C(Cc2ccc(OCCc3ccc(CCO)cn3)cc2)S1	625853-72-7
14_TP_Pio	O=CCc1ccc(CCOc2ccc(CC3SC(=O)NC3=O)cc2)nc1	Not found
19_TP_Que	Nc1ccccc1Sc1ccccc1C(=O)N1CCN(CC(=O)O)CC1	Not found
TP_Que_35	Nc1ccccc1Sc1ccccc1C(=O)N1CCN(CC=O)CC1	Not found
TP_Que_32	Nc1ccccc1S(=O)c1ccccc1C(=O)N1CCNCC1	Not found
Que_TP_1	O=CCN(CCNC1=Nc2ccccc2Sc2ccccc21)CCOCCO	Not found
Que_TP_3	c1ccc2c(c1)N=C(N1CCNCC1)c1ccccc1S2	1189866-35-0, 5747-48-8
13_TP_Que	O=C(O)COCCN1CCN(C2=Nc3ccccc3Sc3ccccc32)CC1	Not found
18_TP_Que	O=C(O)CN1CCN(C2=Nc3ccccc3Sc3ccccc32)CC1	Not found
Riv_TP_1	CC(c1cccc(O)c1)N(C)C	1217706-31-4, 194930-03-5, 851086-95-8, 139306-10-8, 105601-04-5
Riv_TP_5	CCN(C)C(=O)Oc1cccc(C(C)NC)c1	948051-93-2, 923035-05-6
Riv_TP_6	CC(c1ccc(O)c(O)c1)N(C)C	Not found
Ros_TP_15	CC(C)c1nc(N(C)S(C)(=O)=O)nc(-c2ccc(F)cc2)c1C=CC(O)CC(=O)O	Not found
Ros_TP_12	CC(C)c1nc(N(C)S(C)(=O)=O)nc(-c2ccc(F)cc2)c1C=CC(=O)O	Not found
Ros_TP_2	CC(C)c1nc(N(C)S(C)(=O)=O)nc(-c2ccc(F)cc2)c1C=CC(=O)CC(O)CC(=O)O	1422619-13-3
TP_Ros_12	CC(=O)C=Cc1c(-c2ccc(F)cc2)nc(N(C)S(C)(=O)=O)nc1C(C)C	Not found
Tad_TP_4	CN1CC(=O)N2C(c3ccc4c(c3)OCO4)c3[nH]c4ccccc4c3C(O)C2C1=O	Not found
TP_Ter_33	CC(C)(C)C#CC=CCNCc1cccc2c(O)c(O)ccc12	Not found
Ter_TP_2	CNCc1cccc2ccccc12	1189686-07-4, 1033720-13-6, 14489-75-9
Ter_TP_11	CN(CC=CC#CC(C)(C)CO)Cc1cccc2ccccc12	162227-13-6, 162227-13-6, 162227-13-6
TP_Ter_15	CN(CC=CC#CC(C)(C)C(=O)O)Cc1cccc2ccccc12	1246833-21-5, 99473-14-0
Ter_TP_12	CNCC=CC#CC(C)(C)CO	Not found
TP_Ter_24	CC(C)(C#CC=CCNCc1cccc2ccccc12)C(=O)O	1185238-58-7, 99473-15-1
TP_Tic_34	CCCS(=O)c1nc(NC2CC2c2ccc(F)c(F)c2)c2nnn(C3CC(OCC(=O)O)C(O)C3O)c2n1	Not found
Tic_TP_4	CCCSc1nc(NC2CC2c2ccc(F)c(F)c2)c2nnn(C3CC(OCC(=O)O)C(O)C3O)c2n1	Not found
Val_TP_5	NCc1ccc(-c2ccccc2-c2nn[nH]n2)cc1	147225-68-1

Val_TP_12	CCCCC(=O)NCc1ccc(-c2ccccc2-c2nn[nH]n2)cc1	Not found
Val_TP_7	O=C(O)c1ccc(-c2ccccc2-c2nn[nH]n2)cc1	164265-78-5
Vil_TP_1	O=C(O)CNC12CC3CC(CC(O)(C3)C1)C2	1032564-18-3
Legend: 1 = EAWAG/BBD-PPS, 2 = enviPath-BBD, 3 = enviPath-BBD+SOIL, 4 = enviPath-BBD+SLUDGE, 5 =		
Manual Predictions		
3_TP_Aml	ClC1=CC=CC=C1C2=C(C(OCC)=O)C(COCC(O)=O)=NC(C)=C2C(OC)=O	113994-45-9
9_TP_Hyd	ClC1=C(S(N)(=O)=O)C=C(S(NC=N2)(=O)=O)C2=C1	58-94-6
10_TP_Riv	CC([N+](C)([O-])C)C1=CC(OC(N(C)CC)=O)=CC=C1	NA
15_TP_Pio	O=C(C(S1)CC(C=C2)=CC=C2OCCC3=CC=C(CC(O)=O)C=N3)NC1=O	146062-48-8
20_TP_Met	NC(/N=C(N)/N)=O	141-83-3
21_TP_Ter	CC(C)(C)C#C/C=C/CN(CO)CC1=CC=CC2=C1C=CC=C2	162227-13-6
22_TP_Ter	CC(C)(C)C#C/C=C/CN(CO)C(O)C1=CC=CC2=C1C=CC=C2	NA
Bud_TP_9	CCCC1OC2CC3C4CCC5=CC(=O)CC(O)C5(C)C4C(=O)CC3(C)C2(C(=O)C(=O)O)O1	Not found
TPs from Conjugation Reactions		
Aml_TP_ace	ClC1=CC=CC=C1C2C(C(OCC)=O)=C(COCCNC(C)=O)NC(C)=C2C(OC)=O	Not found
Aml_TP_succ	ClC1=CC=CC=C1C2C(C(OCC)=O)=C(COCCNC(CCC(O)=O)=O)=O)NC(C)=C2C(OC)=O	Not found
Atm_TP_succ	CC1=CC=CC=C1O[C@@H](C2=CC=CC=C2)CCN(C(CCC(O)=O)=O)C	Not found
Dul_TP_succ	CN(C(CCC(O)=O)=O)CCC(C1=CC=CS1)OC2=CC=CC3=CC=CC=C32	Not found

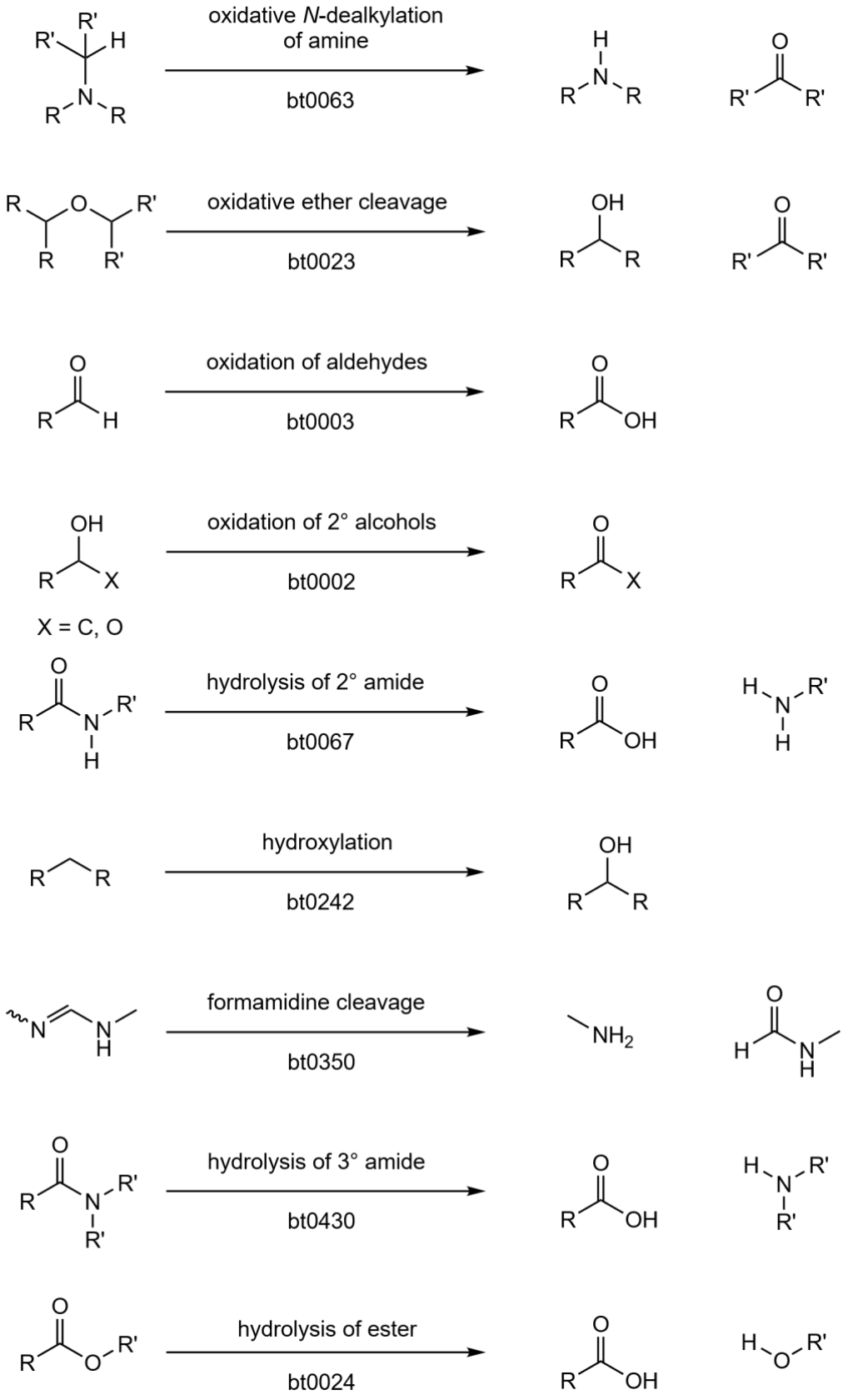
S3. Biotransformation pathways and Structure Elucidation

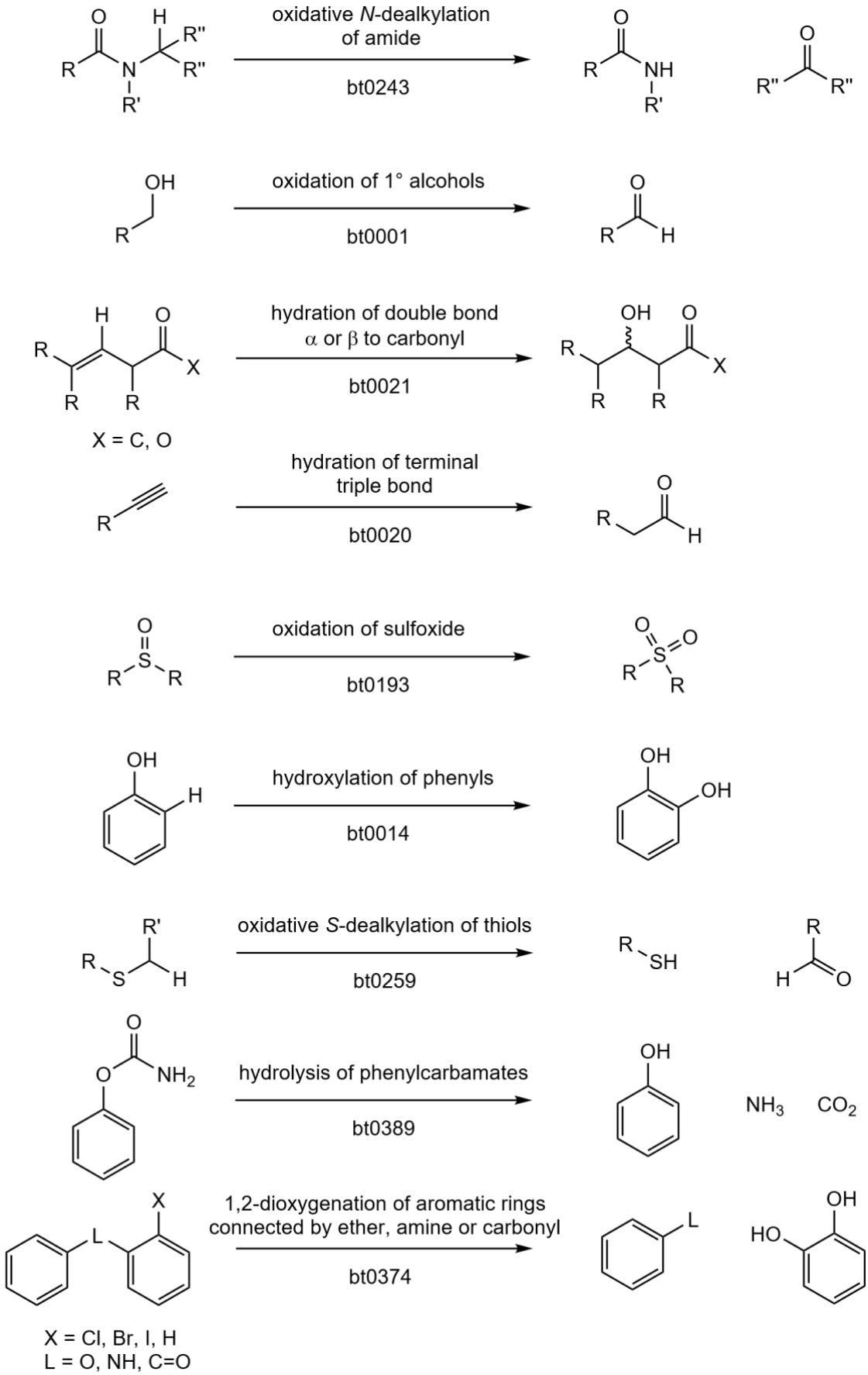
The biotransformation pathways for all found TPs are shown in this section. The used bt rules are indicated next to reaction arrow. Further information about the rules can be found in the biotransformation section and on the EAWAG-PPS/BBD website (http://eawag-bbd.ethz.ch/servlets/pageservlet?ptype=allrules). Exact mass corresponds to the monoisotopic mass of the uncharged molecule. Brackets in pathway indicate unobserved hypothetical intermediates to improve readability. Unidentified isomeric structures were reported as brackets with added modification.

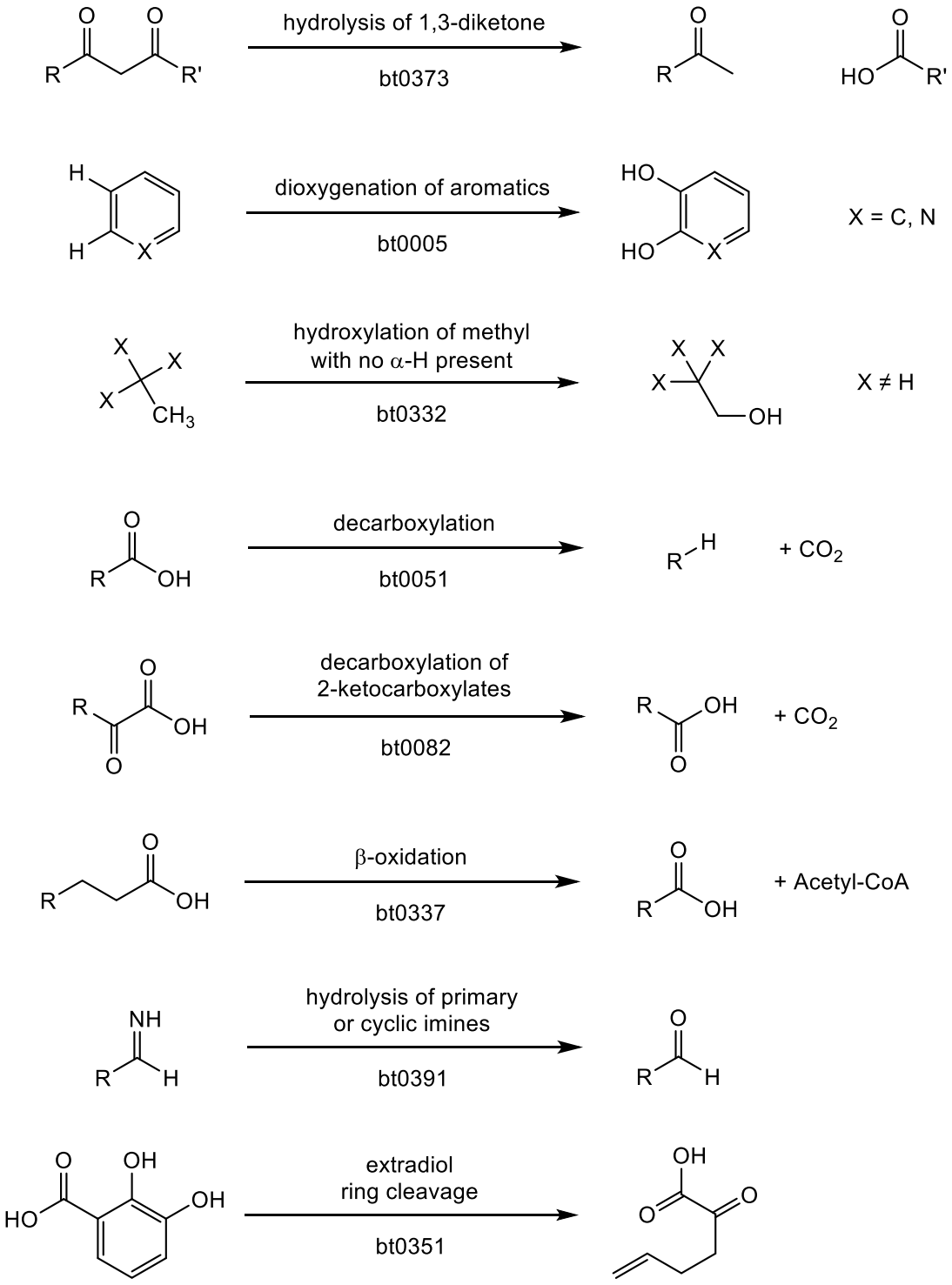
The pathways are followed by time series plots of a given parent and its corresponding TPs in biotransformation (BT) reactors and unspiked (UC), sorption (SC) and abiotic (AB) control reactors.

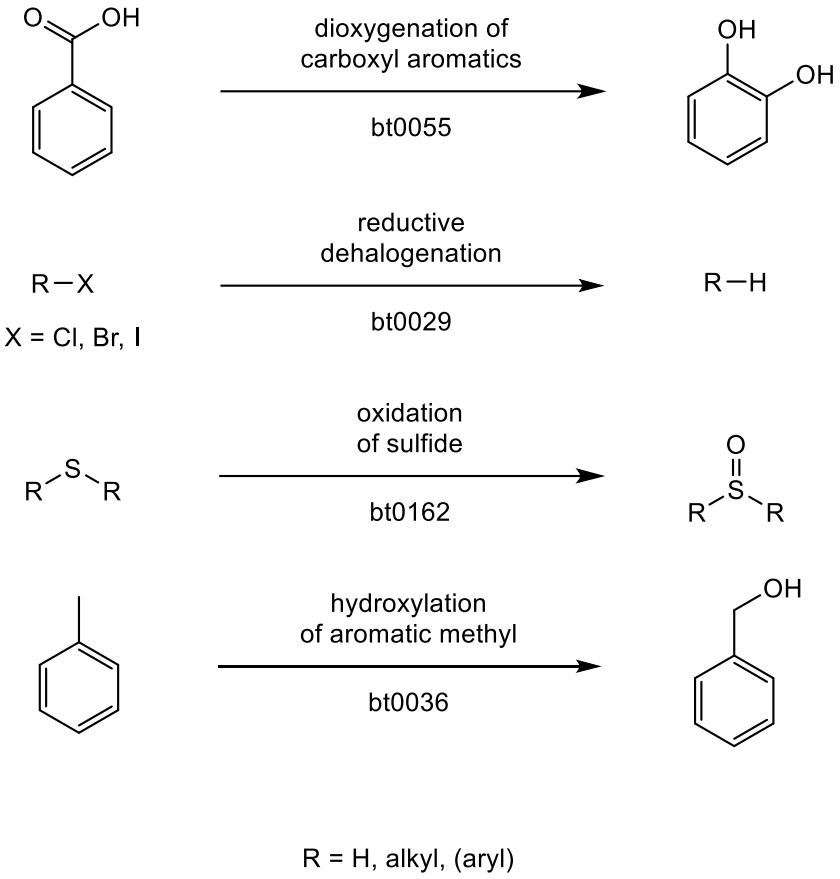
This section reports structural evidence for found transformation products, which was obtained by the interpretation of MS^2 spectra. Spectra are shown as mirror plot with the corresponding parent compound or *mzCloud* match. NCE of TP and parent are not necessarily identical. If data was obtained by second measurements using stepped collision energies, it was indicated in the suffix of the name. Confidence levels were assigned independently from plausible isomers; however, potential structural isomers were mentioned. Fragments were annotated with structure and chemical formula using Fish scoring (based on *MassFrontier* using default parameters) of *Compound Discoverer*. Manually annotated fragments were reported with mass difference in ppm to calculated mass of given composition. Plausible neutral losses were indicated with arrows.

S3.1 Biotransformation rules

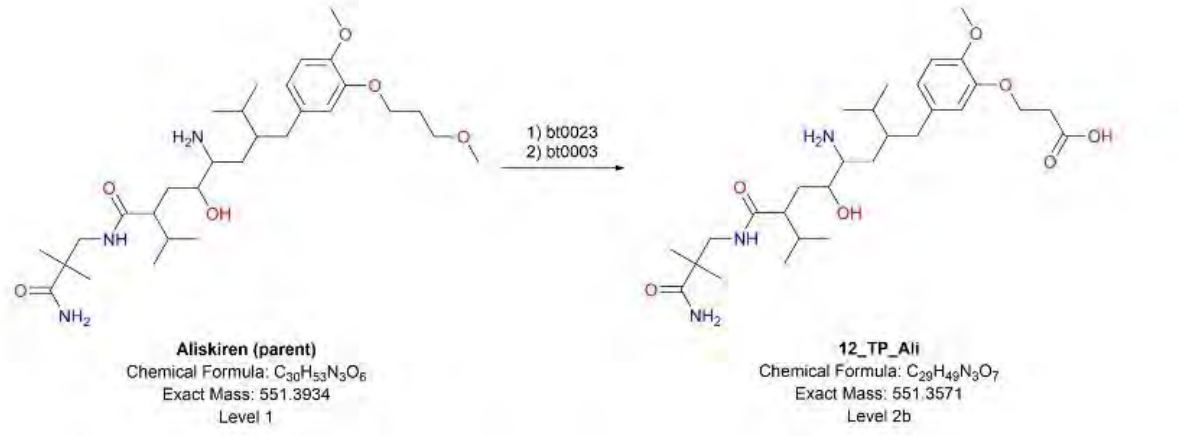


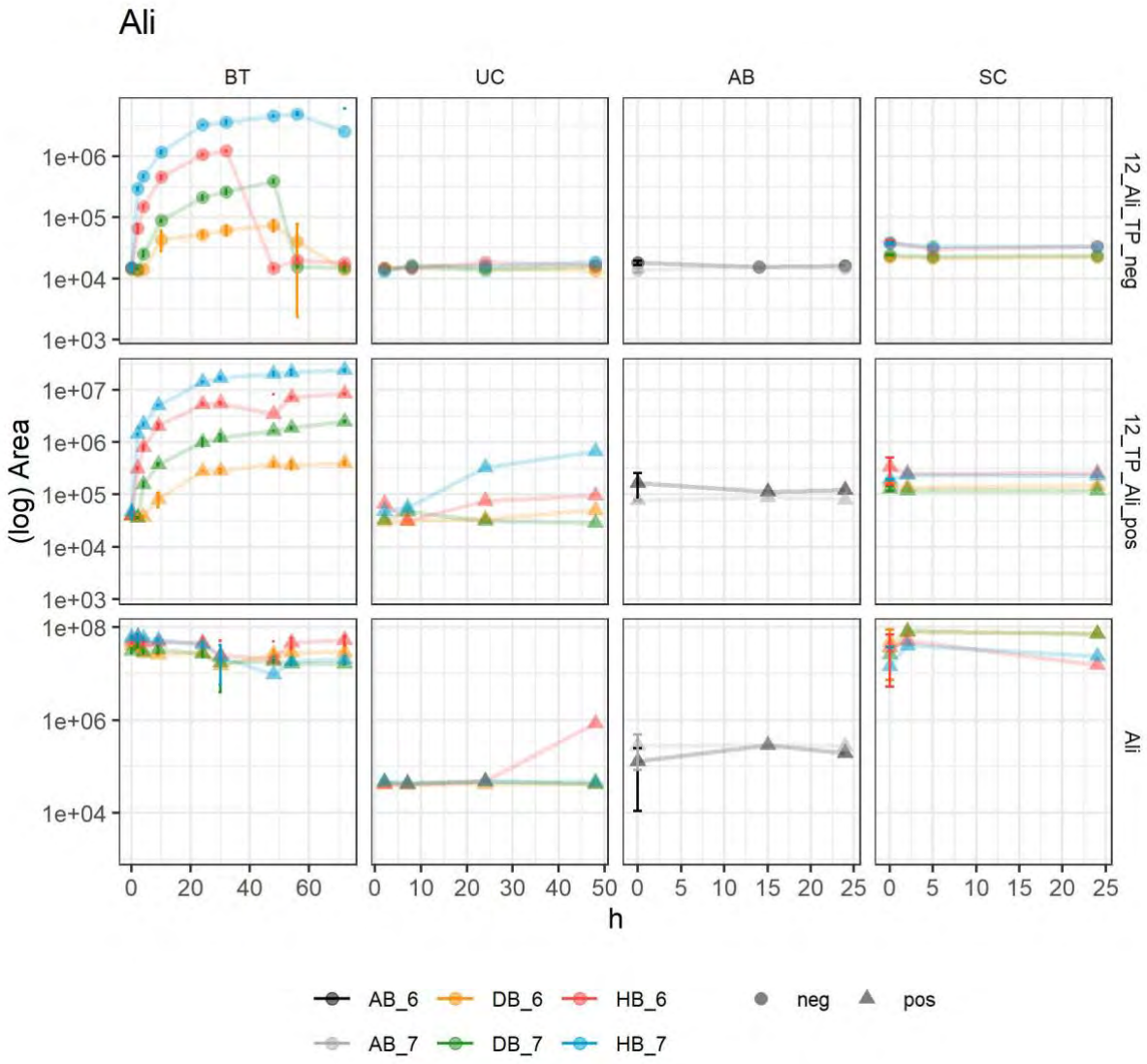

oxidative N-dealkylation of amide
bt0243
oxidation of 1° alcohols
bt0001
hydration of double bond α or β to carbonyl
bt0021
X = C, O
hydration of terminal triple bond
bt0020
oxidation of sulfoxide
bt0193
hydroxylation of phenyls
bt0014
oxidative S-dealkylation of thiols
bt0259
hydrolysis of phenylcarbamates
bt0389
1,2-dioxygenation of aromatic rings connected by ether, amine or carbonyl
bt0374
X = Cl, Br, I, H
L = O, NH, C=O


hydrolysis of 1,3-diketone
bt0373
dioxygenation of aromatics
bt0005
X = C, N
hydroxylation of methyl
with no α-H present
bt0332
X ≠ H
decarboxylation
bt0051
+ CO2
decarboxylation of
2-ketocarboxylates
bt0082
+ CO2
β-oxidation
bt0337
+ Acetyl-CoA
hydrolysis of primary
or cyclic imines
bt0391
extradiol
ring cleavage
bt0351

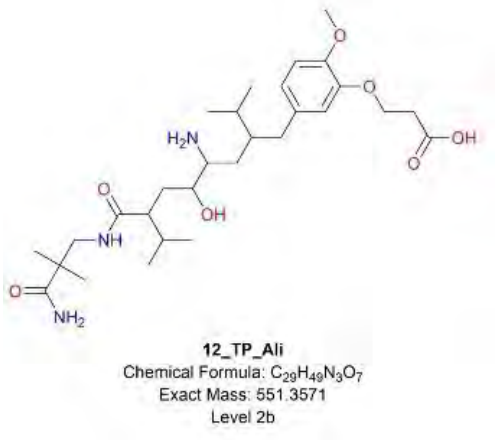

O
OH
dioxygenation of
carboxyl aromatics
bt0055
OH
OH
reductive
dehalogenation
R—X
X = Cl, Br, I
bt0029
R—H
oxidation
of sulfide
S
R
R
bt0162
O
S
R
R
hydroxylation
of aromatic methyl
bt0036
OH
R = H, alkyl, (aryl)

S3.2 Aliskiren



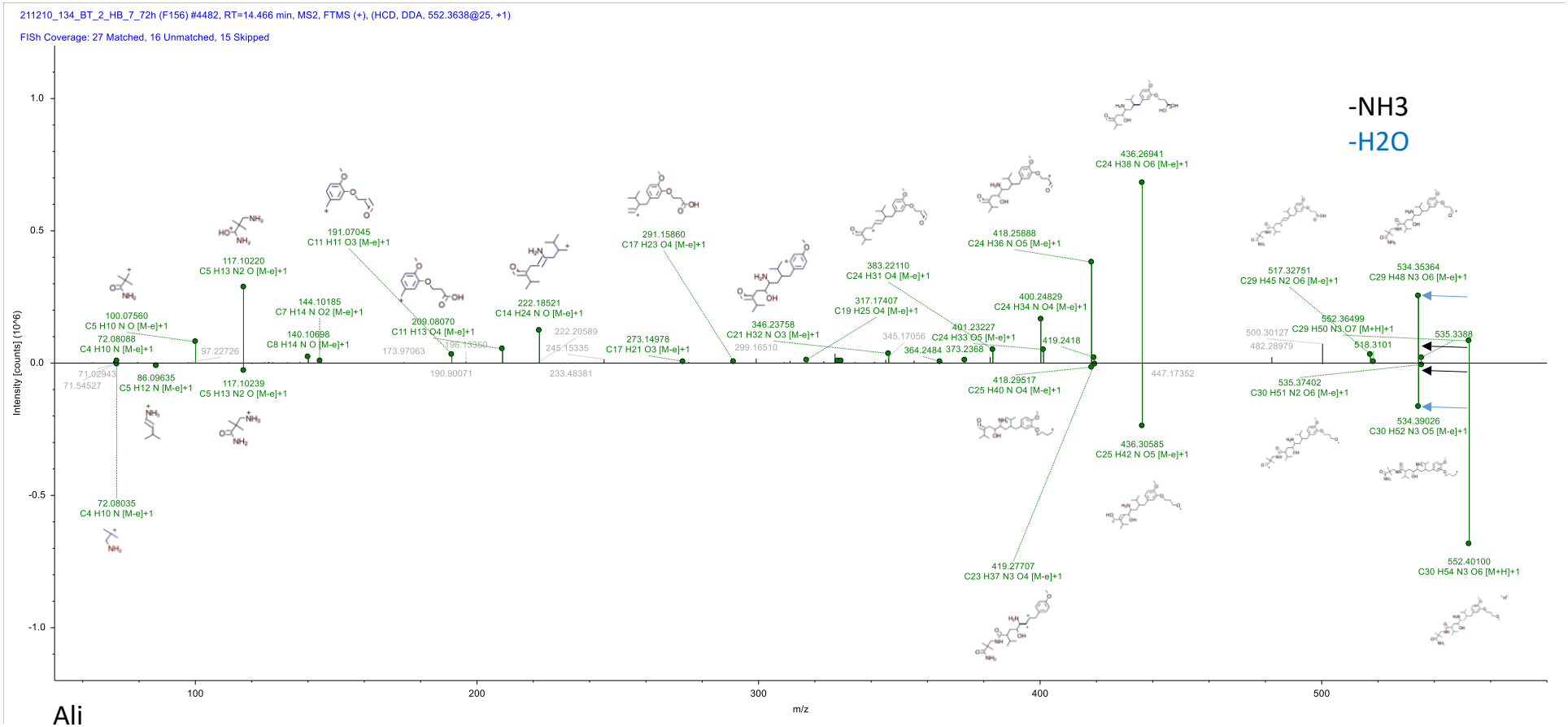


S3.2.1. 12 TP Ali



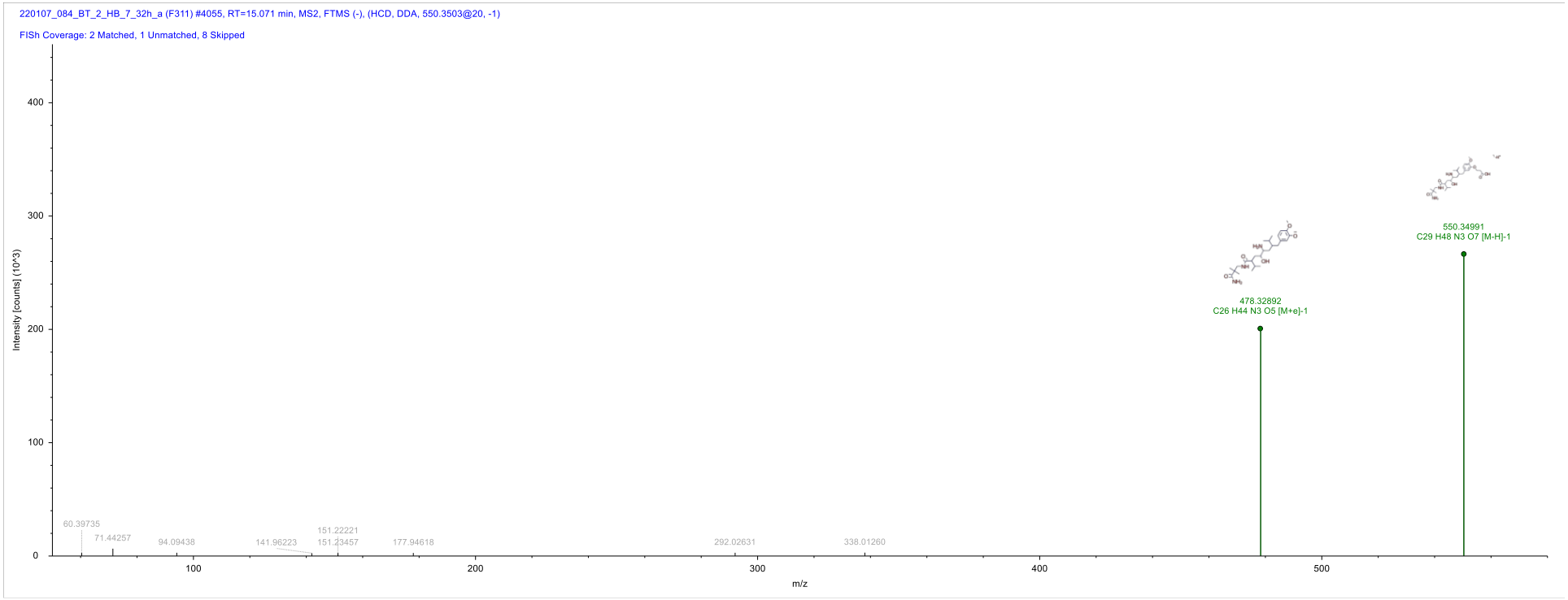
35 fragment ions with identical nominal masses and chemical composition were observed in both parent and TP positive MS^2 spectra. The neutral loss of water and ammonia was also observed for both. Additionally, $[M-H]^-$ ion was detected, which supports the transformation to a carboxylate. However, no comparison with parent compound was possible since it was only detected in positive mode.

12_TP_Ali

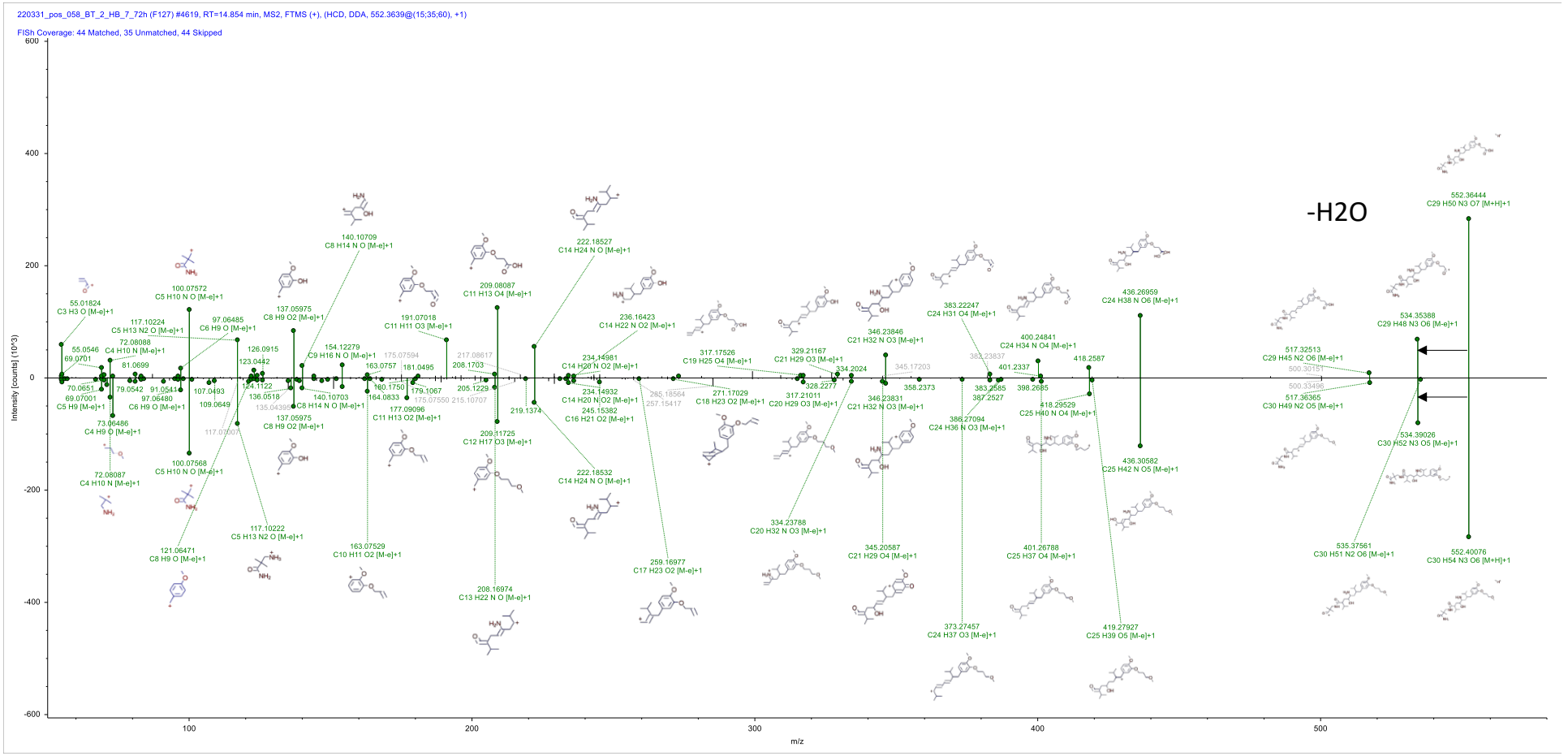

211210_134_BT_2_HB_7_72h (F156) #4482, RT=14.466 min, MS2, FTMS (+), (HCD, DDA, 552.3638@25, +1)
FISh Coverage: 27 Matched, 16 Unmatched, 15 Skipped
-NH3
-H2O
Intensity [counts] (10^6)
m/z
72.08088
C4 H10 N [M-e]+1
100.07560
C5 H10 N O [M-e]+1
117.10220
C5 H13 N2 O [M-e]+1
191.07045
C11 H11 O3 [M-e]+1
144.10185
C7 H14 N O2 [M-e]+1
140.10698
C8 H14 N O [M-e]+1
209.08070
C11 H13 O4 [M-e]+1
222.18521
C14 H24 N O [M-e]+1
291.15860
C17 H23 O4 [M-e]+1
273.14978
C17 H21 O3 [M-e]+1
346.23758
C21 H32 N O3 [M-e]+1
383.22110
C24 H31 O4 [M-e]+1
317.17407
C19 H25 O4 [M-e]+1
401.23227
C24 H33 O5 [M-e]+1
400.24829
C24 H34 N O4 [M-e]+1
418.25888
C24 H36 N O5 [M-e]+1
436.26941
C24 H38 N O6 [M-e]+1
517.32751
C29 H45 N2 O6 [M-e]+1
534.35364
C29 H48 N3 O6 [M-e]+1
552.36499
C29 H50 N3 O7 [M+H]+1
535.3388
72.08035
C4 H10 N [M-e]+1
86.09635
C5 H12 N [M-e]+1
117.10239
C5 H13 N2 O [M-e]+1
418.29517
C25 H40 N O4 [M-e]+1
436.30585
C25 H42 N O5 [M-e]+1
419.27707
C23 H37 N3 O4 [M-e]+1
535.37402
C30 H51 N2 O6 [M-e]+1
534.39026
C30 H52 N3 O5 [M-e]+1
552.40100
C30 H54 N3 O6 [M+H]+1

Ali

12_TP_Ali_neg

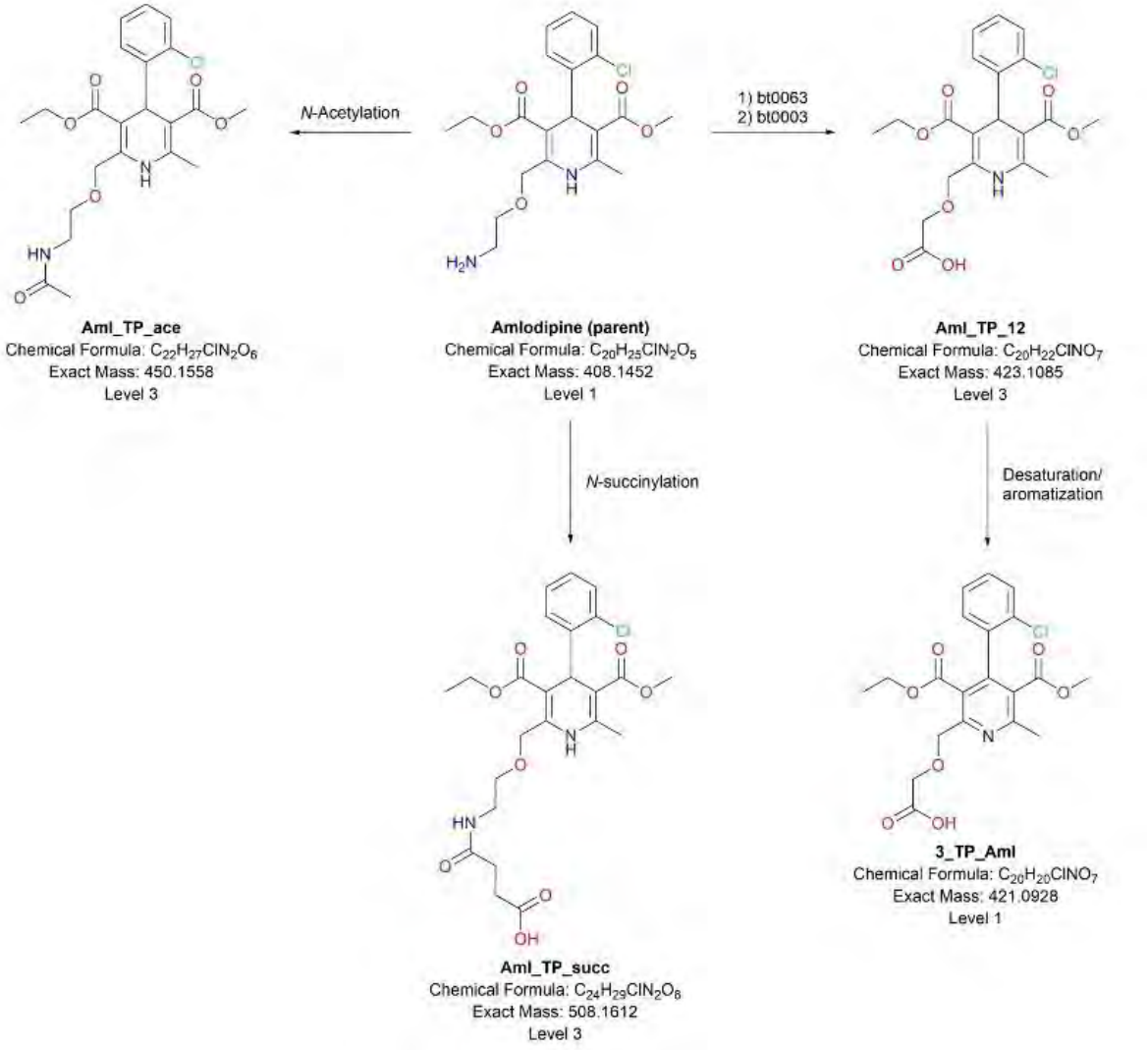

220107_084_BT_2_HB_7_32h_a (F311) #4055, RT=15.071 min, MS2, FTMS (-), (HCD, DDA, 550.3503@20, -1)
FISh Coverage: 2 Matched, 1 Unmatched, 8 Skipped
Intensity [counts] (10^3)
m/z
478.32892
C26 H44 N3 O5 [M+e]-1
550.34991
C29 H48 N3 O7 [M-H]-1
60.39735
71.44257
94.09438
141.96223
151.22221
151.23457
177.94618
292.02631
338.01260

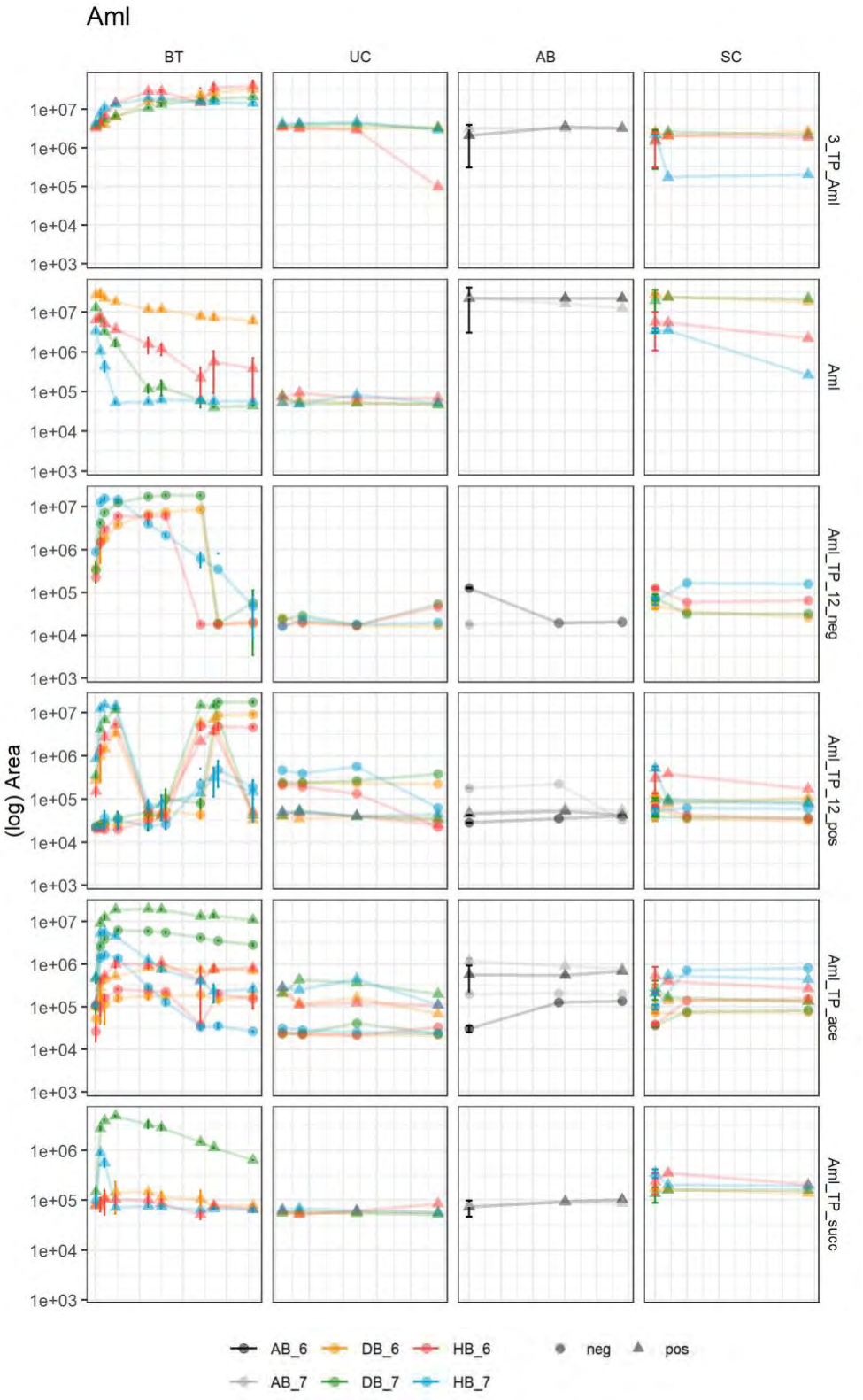
12_TP_Ali_remeas



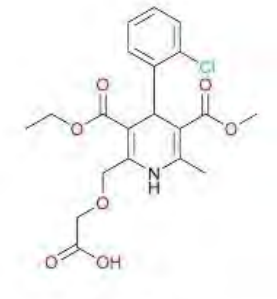
Ali_remeas

S3.3 Amlodipine




Aml
BT
UC
AB
SC
3_TP_Aml
Aml
Aml_TP_12_neg
Aml_TP_12_pos
Aml_TP_ace
Aml_TP_succ
(log) Area
1e+07
1e+06
1e+05
1e+04
1e+03
AB_6
DB_6
HB_6
AB_7
DB_7
HB_7
neg
pos

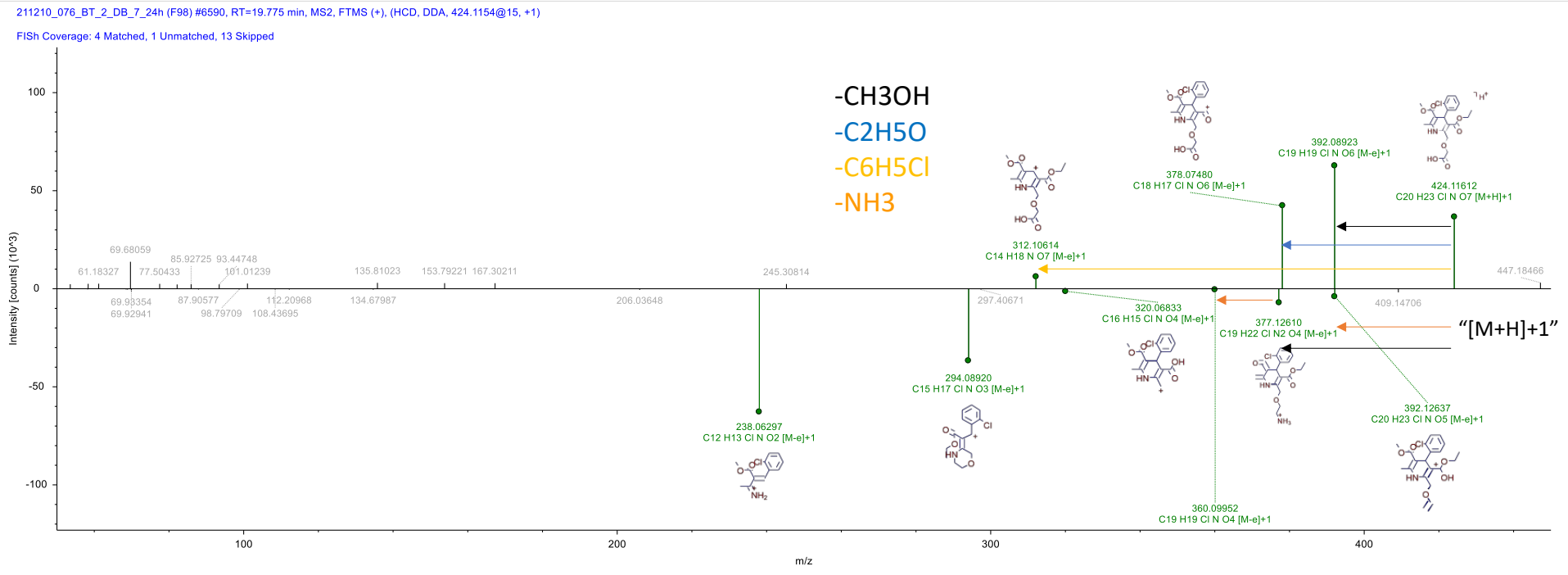
S3.3.1. Aml TP 12



Aml_TP_12
Chemical Formula: $C_{20}H_{22}ClNO_7$
Exact Mass: 423.1085
Level 3

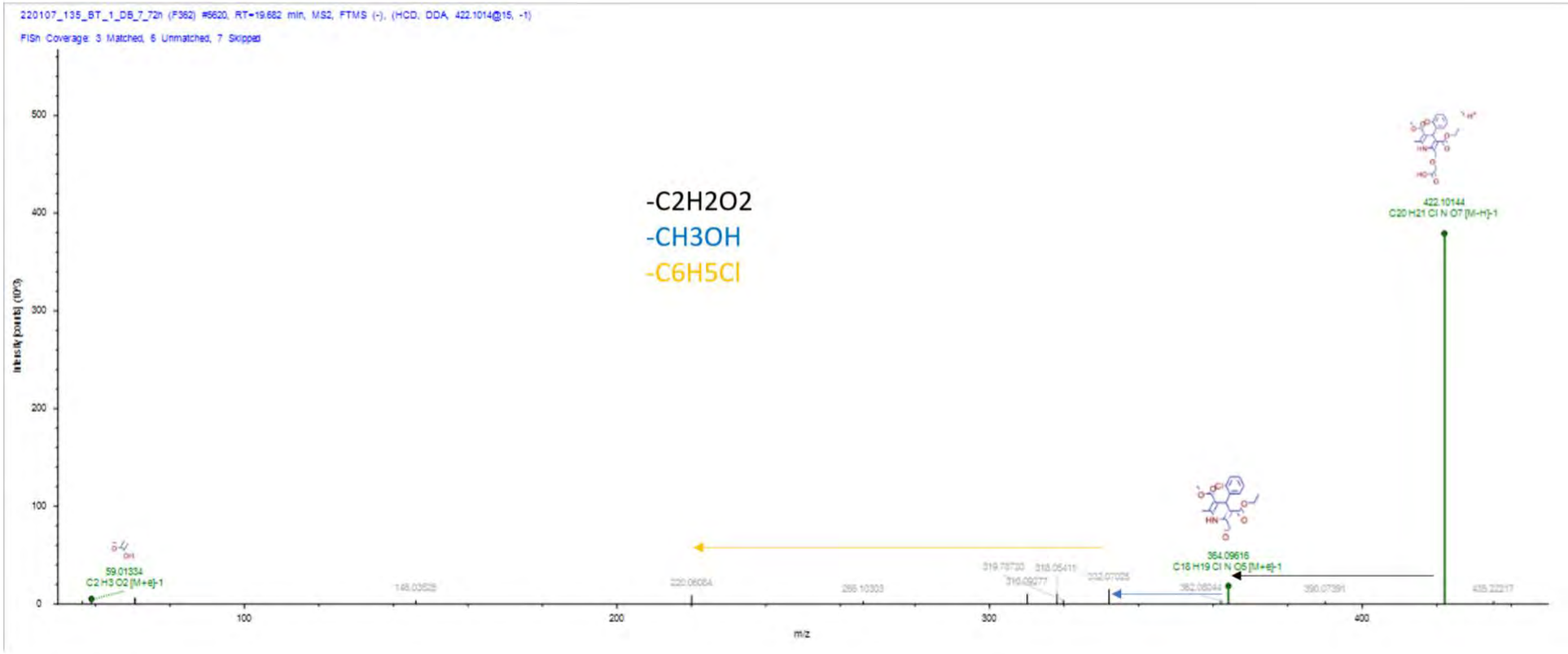
MS^2 fragments at 149, 176 and 208 m/z were observed for both the parent and the TP. Ion at nominal mass 409 in parent MS^2 is not the $[M+H]^+$ ion, because of large mass error (12.54 ppm). Ion at nominal mass 447 in TP MS^2 is probably an interfering ion, resulting in fragments below 200 m/z. No chlorobenzene loss was observed for the parent. Absence of ammonia loss in TP spectrum indicates the modification of terminal amine in parent. In negative measured spectrum, $[M-H]^-$ indicates carboxylic acid moiety. First fragmentation of $[M-H]^-$ is confirmed by $C_2H_3O_2$ fragment. Two other fragmentation patterns, which were observed for $[M+H]^+$ ion, are feasible.

Aml_TP_12

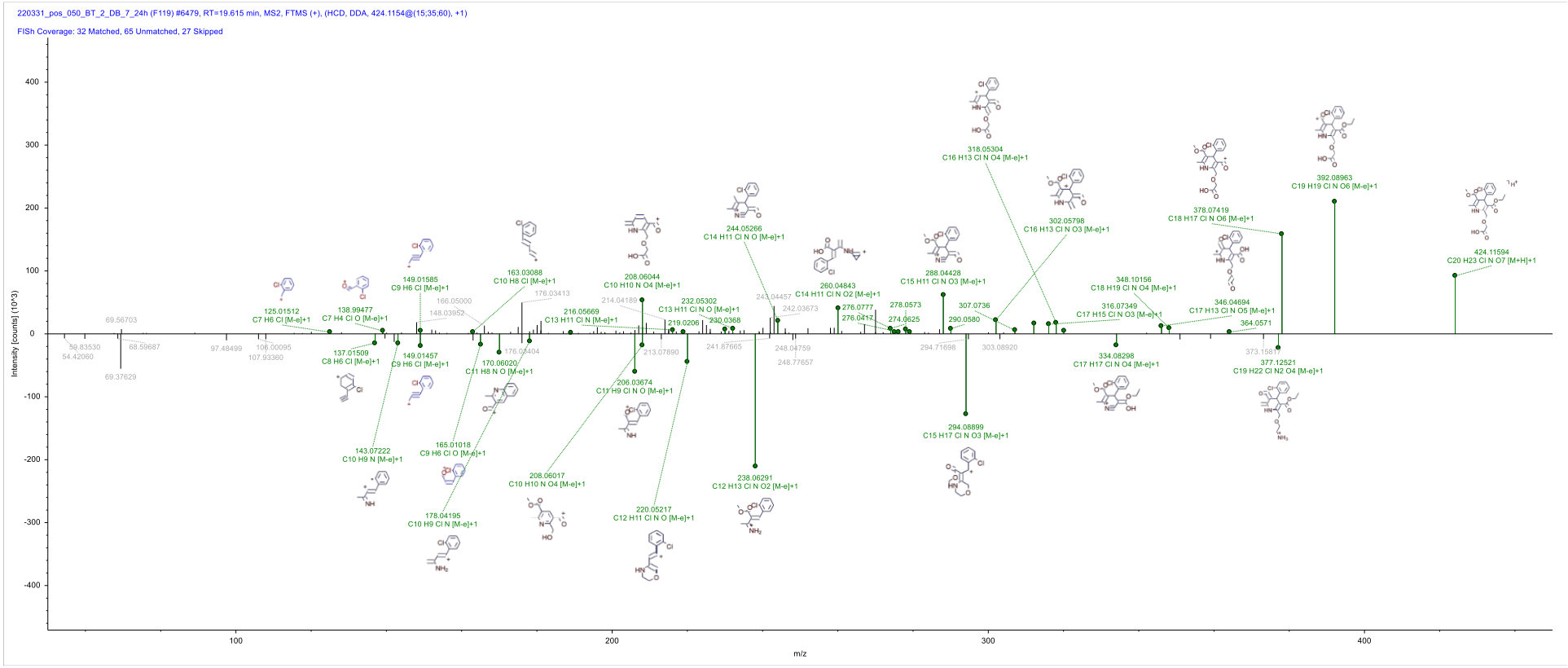

211210_076_BT_2_DB_7_24h (F98) #6590, RT=19.775 min, MS2, FTMS (+), (HCD, DDA, 424.1154@15, +1)
FISh Coverage: 4 Matched, 1 Unmatched, 13 Skipped
-CH3OH
-C2H5O
-C6H5Cl
-NH3
"[M+H]+1"
Intensity [counts] (10^3)
m/z
238.06297
C12 H13 Cl N O2 [M-e]+1
294.08920
C15 H17 Cl N O3 [M-e]+1
312.10614
C14 H18 N O7 [M-e]+1
320.06833
C16 H15 Cl N O4 [M-e]+1
360.09952
C19 H19 Cl N O4 [M-e]+1
377.12610
C19 H22 Cl N2 O4 [M-e]+1
378.07480
C18 H17 Cl N O6 [M-e]+1
392.08923
C19 H19 Cl N O6 [M-e]+1
392.12637
C20 H23 Cl N O5 [M-e]+1
424.11612
C20 H23 Cl N O7 [M+H]+1

Aml

Aml_TP_12

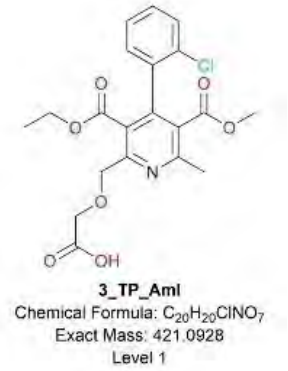

220107_135_BT_1_DB_7_72h (F362) #6620, RT=19.682 min, MS2, FTMS (-), (HCD, DDA, 422.1014@15, -1)
FISh Coverage: 3 Matched, 6 Unmatched, 7 Skipped
-C2H2O2
-CH3OH
-C6H5Cl
422.10144
C20 H21 Cl N O7 [M-H]-1
364.09616
C18 H19 Cl N O5 [M+e]-1
59.01334
C2 H3 O2 [M+e]-1
m/z

Aml_TP_12_remeas



Aml_remeas

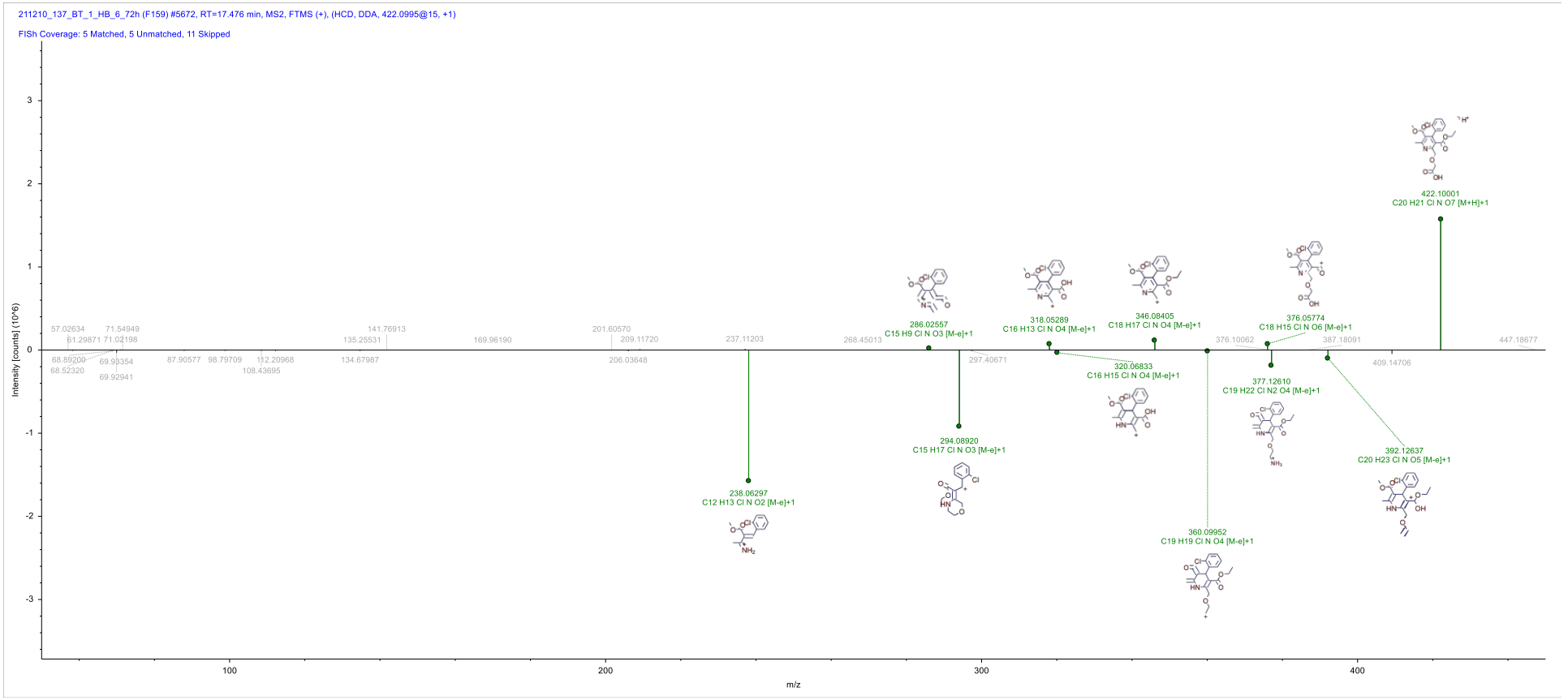
S3.3.2. 3 TP Aml



3_TP_Aml
Chemical Formula: $C_{20}H_{20}ClNO_7$
Exact Mass: 421.0928
Level 1

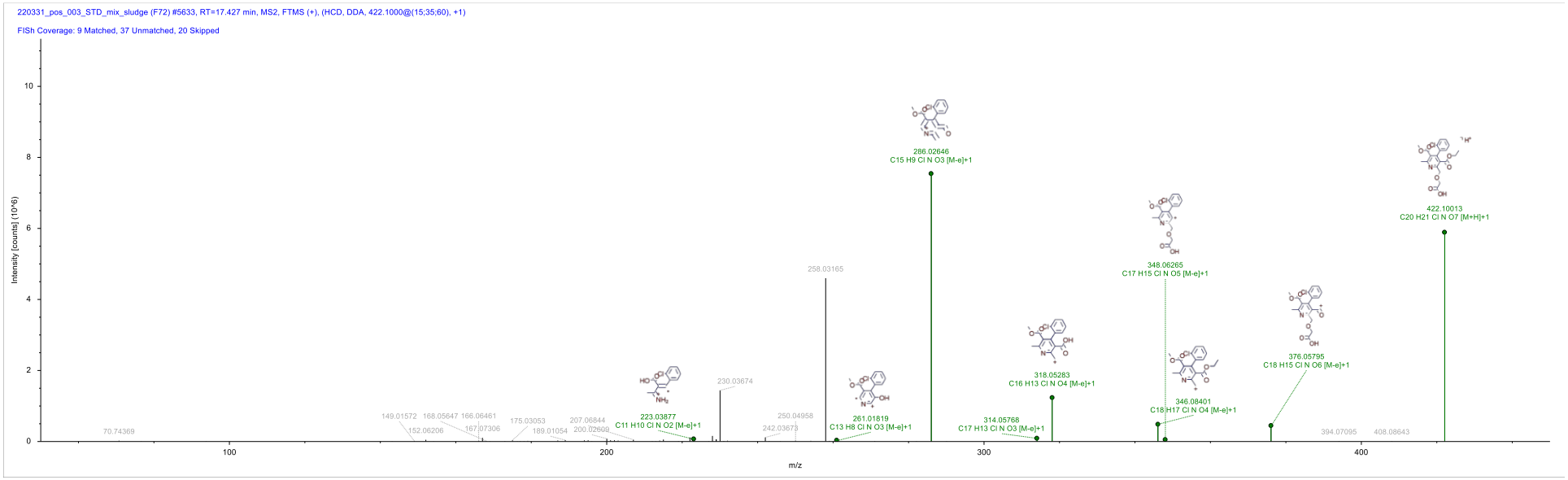
This TP was confirmed by reference standard.

3_Aml_TP

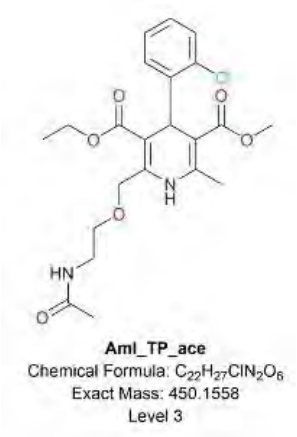

211210_137_BT_1_HB_6_72h (F159) #5672, RT=17.476 min, MS2, FTMS (+), (HCD, DDA, 422.0995@15, +1)
FISh Coverage: 5 Matched, 5 Unmatched, 11 Skipped
Intensity [counts] (10^6)
m/z
422.10001
C20 H21 Cl N O7 [M+H]+1
376.05774
C18 H15 Cl N O6 [M-e]+1
346.08405
C18 H17 Cl N O4 [M-e]+1
318.05289
C16 H13 Cl N O4 [M-e]+1
286.02557
C15 H9 Cl N O3 [M-e]+1
238.06297
C12 H13 Cl N O2 [M-e]+1
294.08920
C15 H17 Cl N O3 [M-e]+1
320.06833
C16 H15 Cl N O4 [M-e]+1
360.09952
C19 H19 Cl N O4 [M-e]+1
377.12610
C19 H22 Cl N2 O4 [M-e]+1
392.12637
C20 H23 Cl N O5 [M-e]+1

Aml

3_Aml_TP_remeas_reference_standard

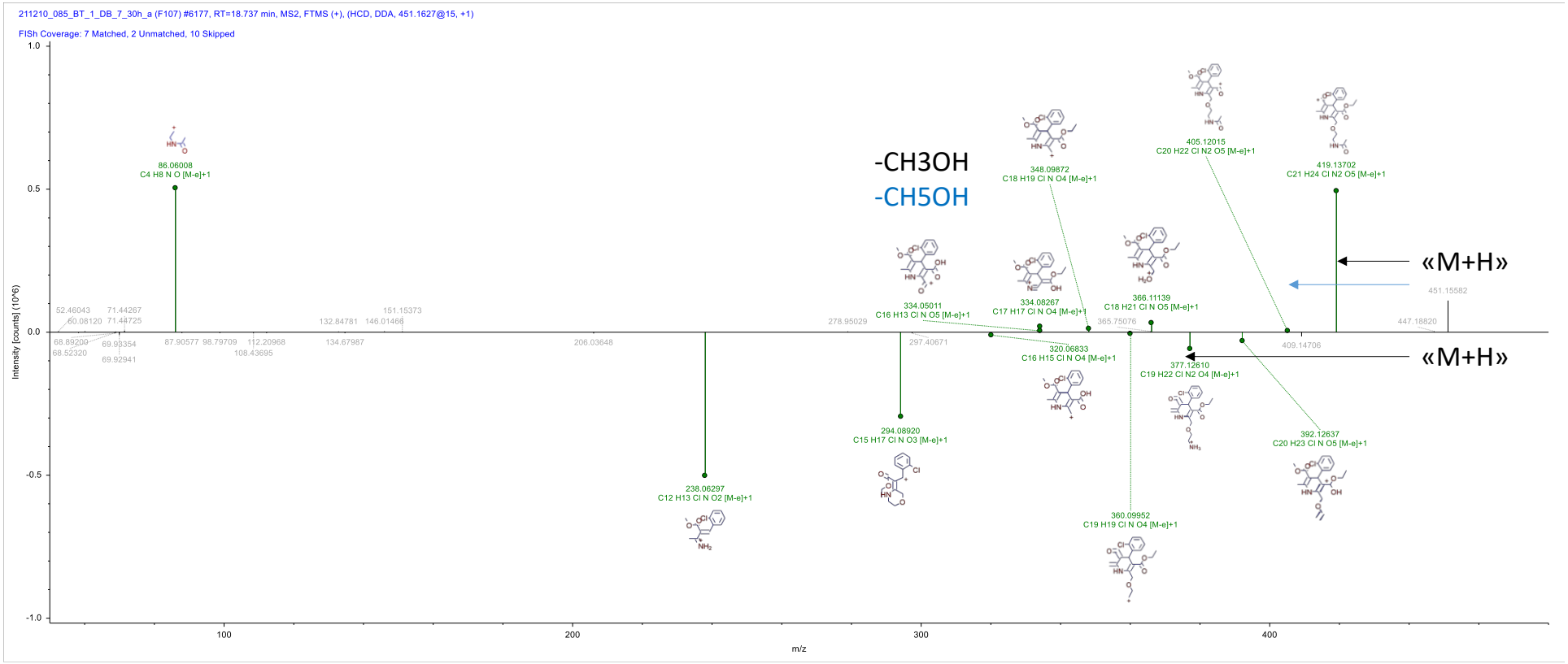


S3.3.3. Aml TP ace



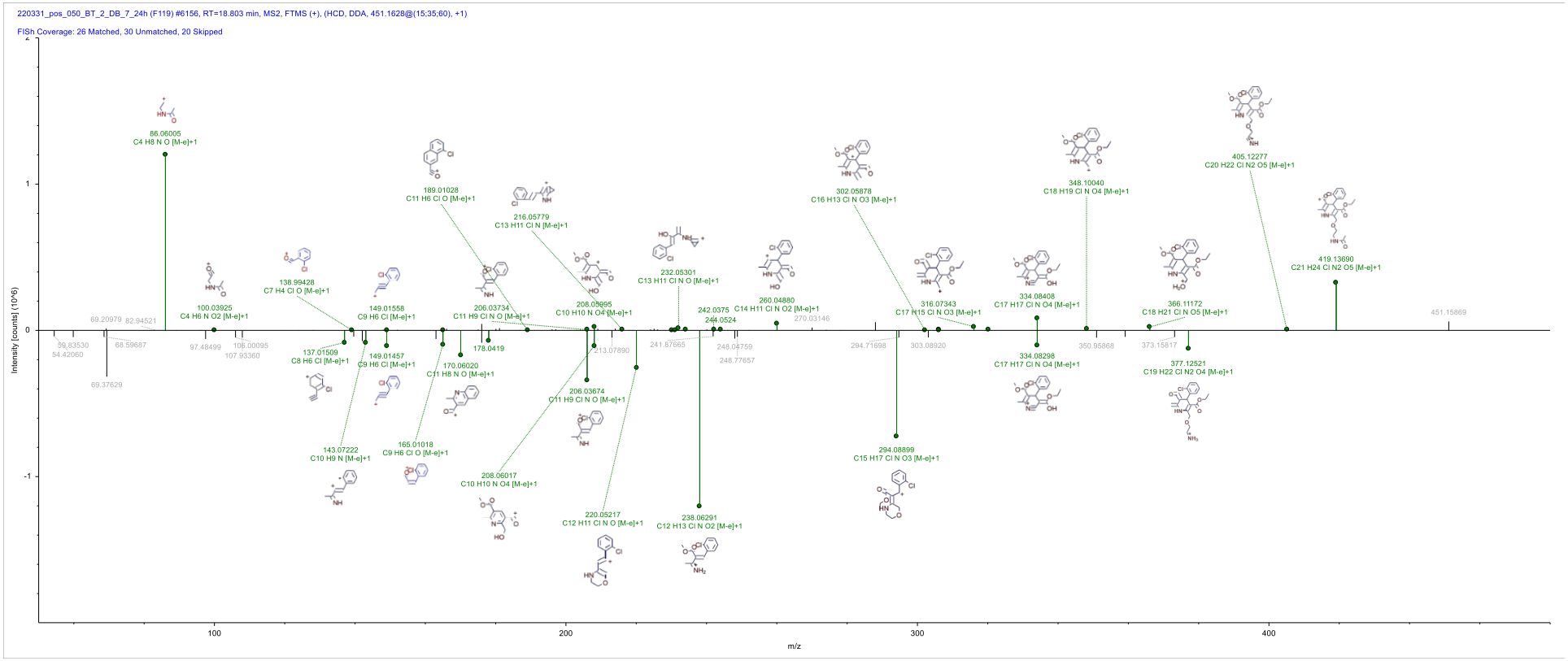
The TP and the parent compound share fragments at 149, 165, 176, 206, 208 and 334 m/z. and show methanol loss. The absence of neutral ammonia loss suggests the transformation to an amide.

Aml_TP_ace



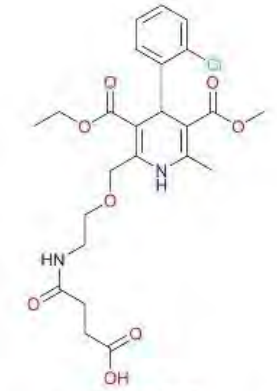
Aml

Aml_TP_ace_remeas



Aml_remeas

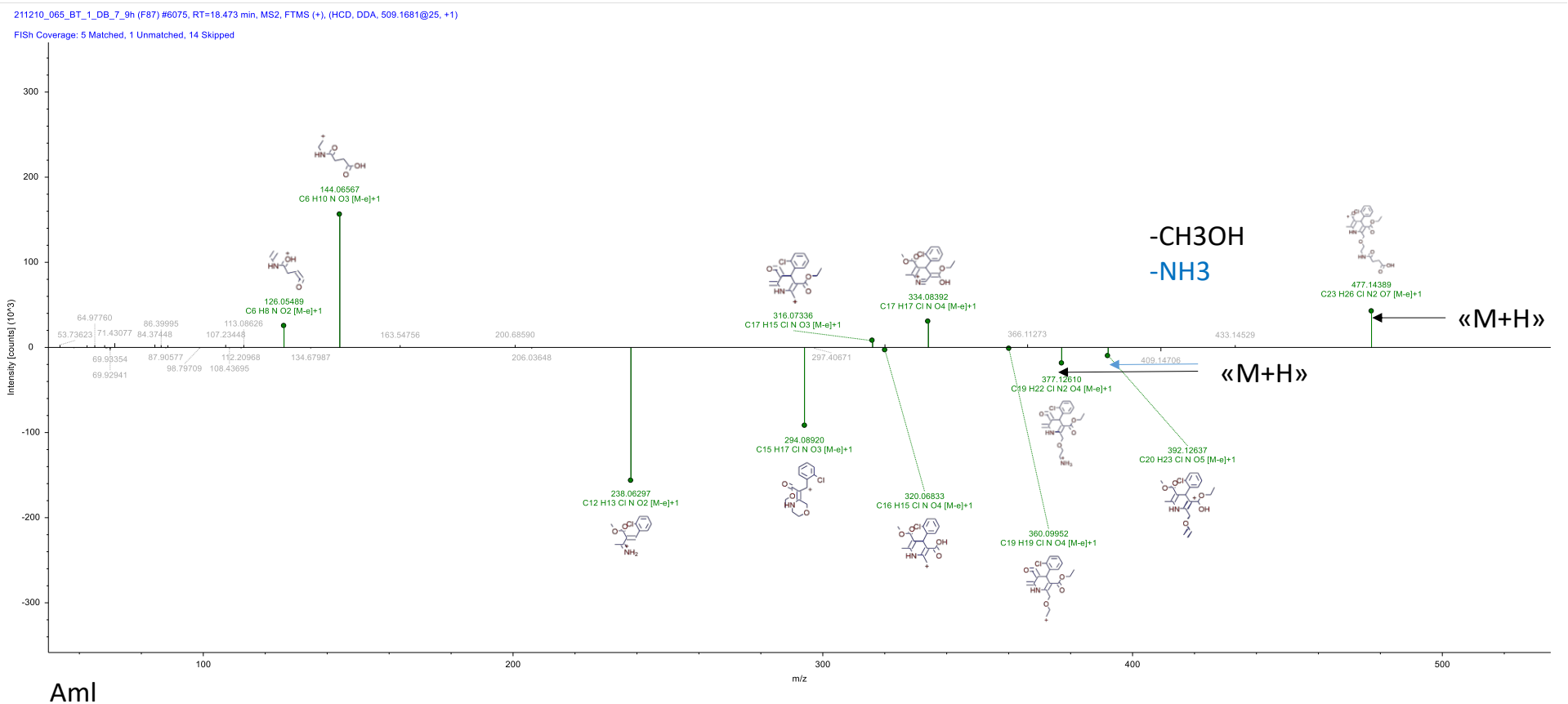
S3.3.4. Aml TP succ



Aml_TP_succ
Chemical Formula: $C_{24}H_{29}ClN_2O_8$
Exact Mass: 508.1612
Level 3

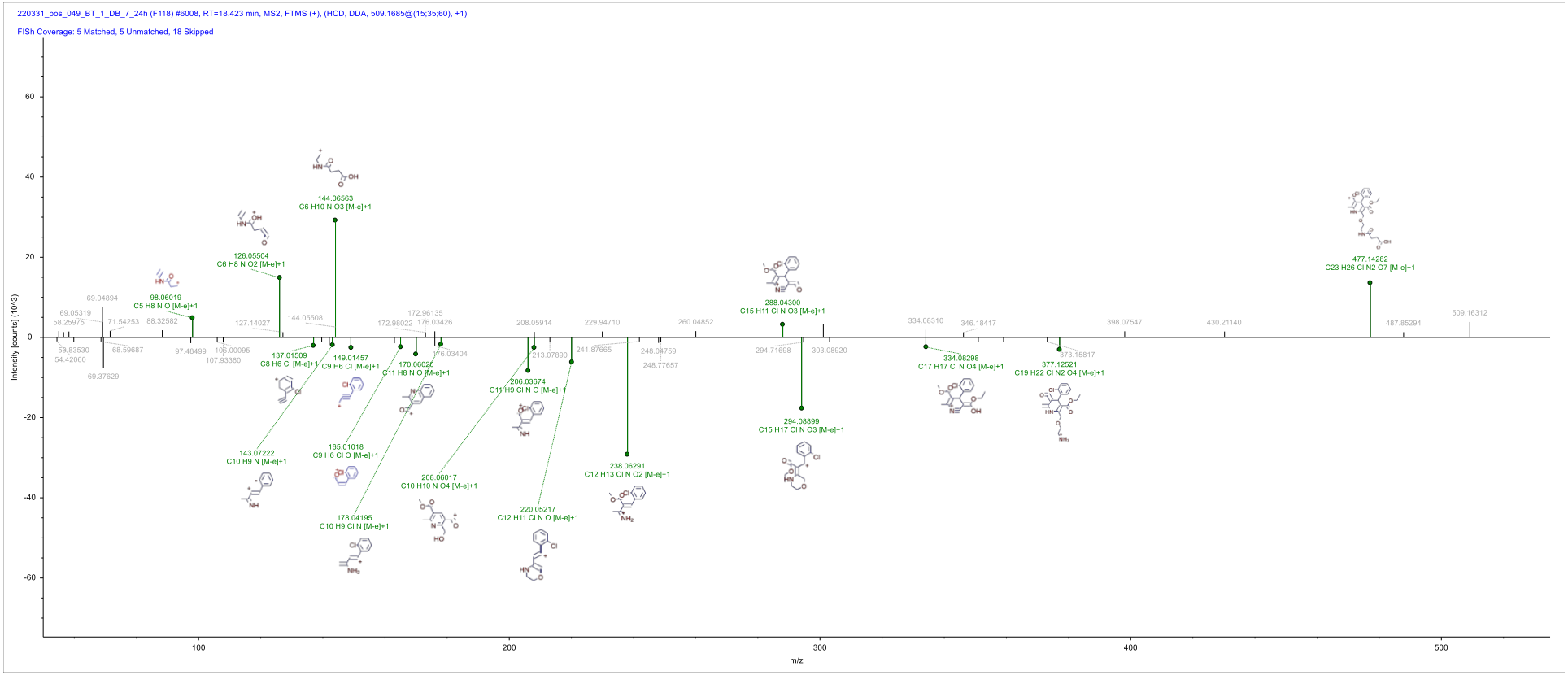
The TP and the parent compound share fragments at 176, 208 and 334 m/z and also both show methanol loss. The absence of neutral ammonia loss suggests the transformation to an amide.

Aml_TP_succ



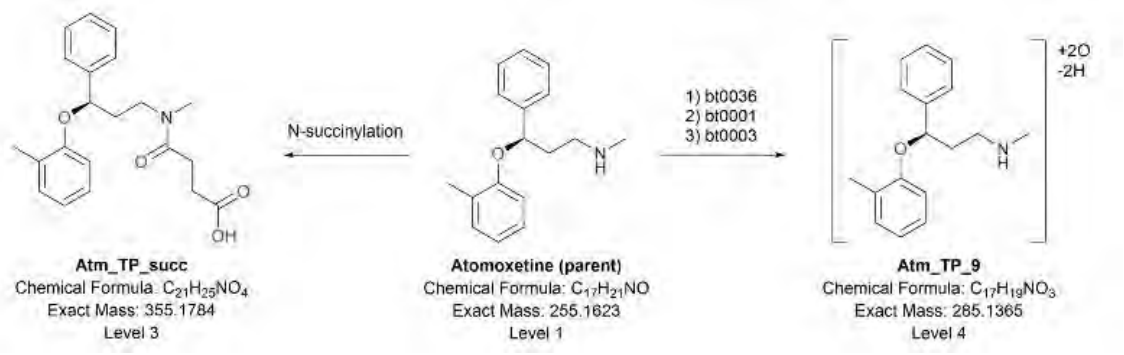
Aml

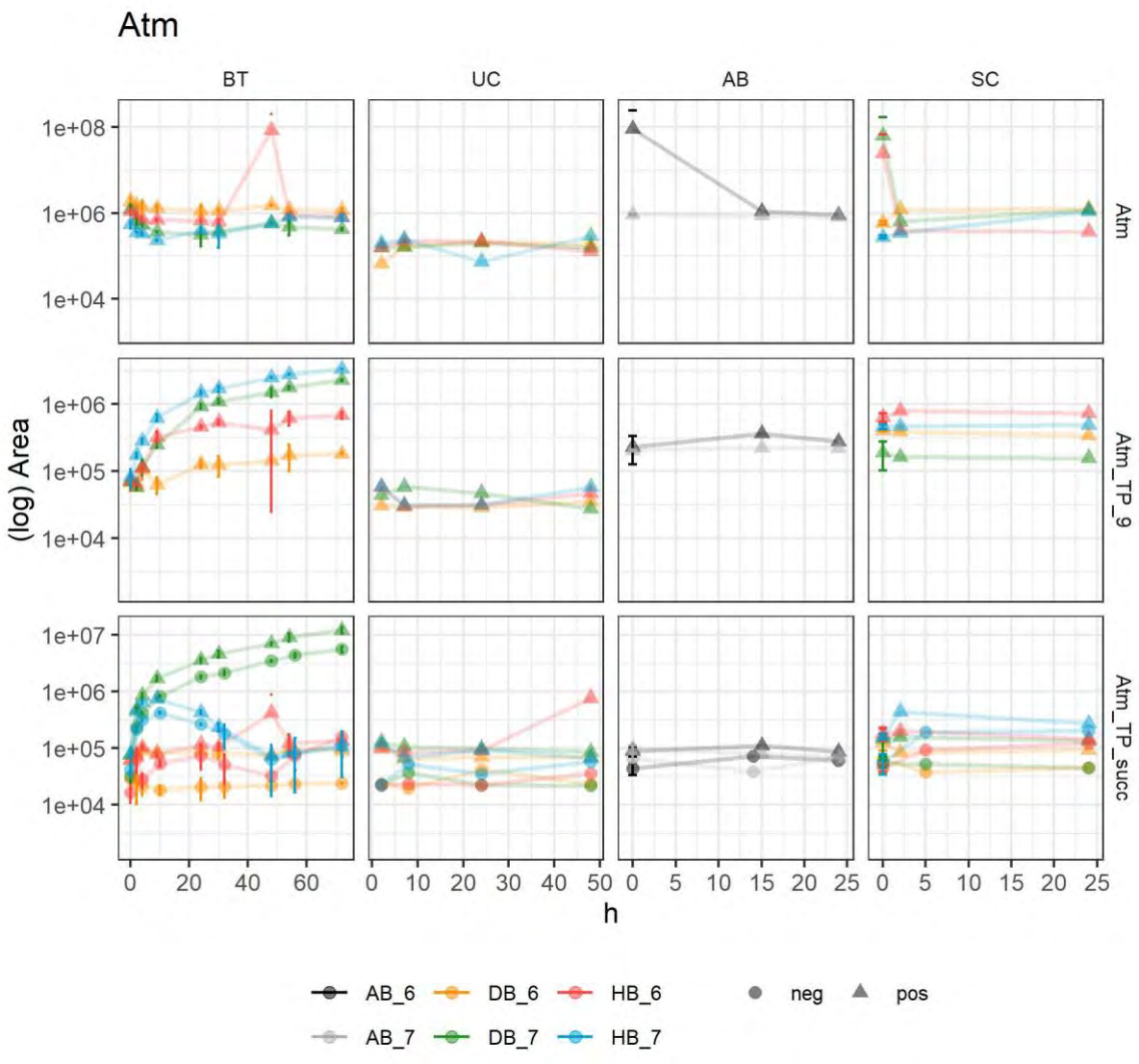
Aml_TP_succ_remeas



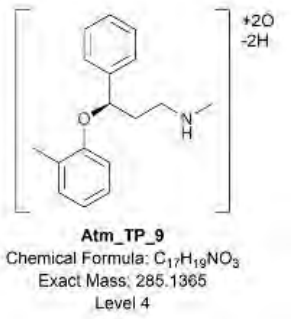
Aml_remeas

S3.4 Atomoxetine



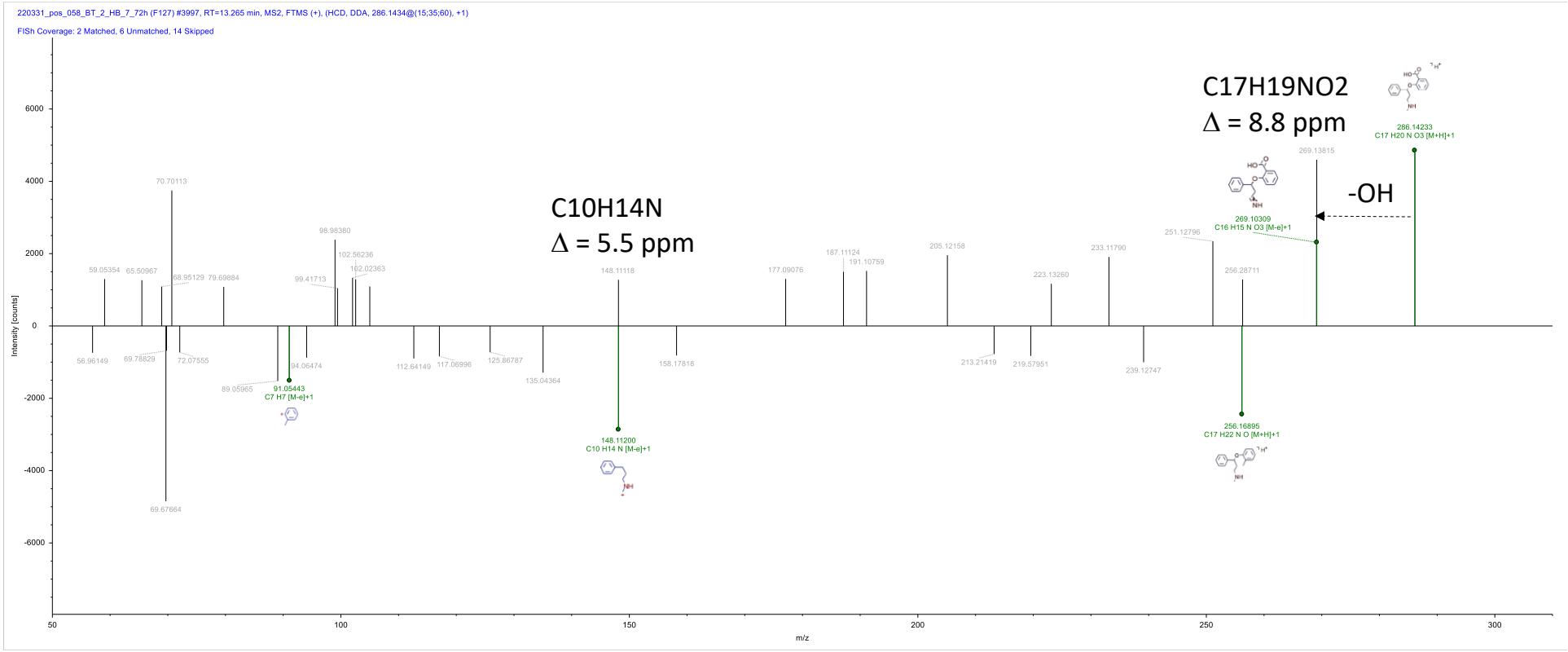


S3.4.1. Atm TP 9



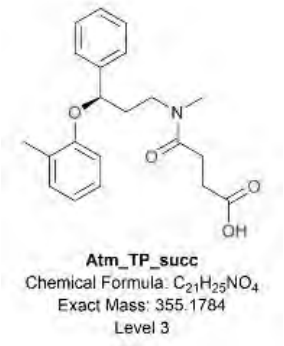
No matching fragments with parent compound, except for nominal mass 148, which shows a large mass difference of 5.5 ppm. Potential OH loss, but with large mass difference of 8.8 ppm. COOH modification could not be confirmed by scan in negative mode.

Atm_TP_9_remeas



Atm_remeas

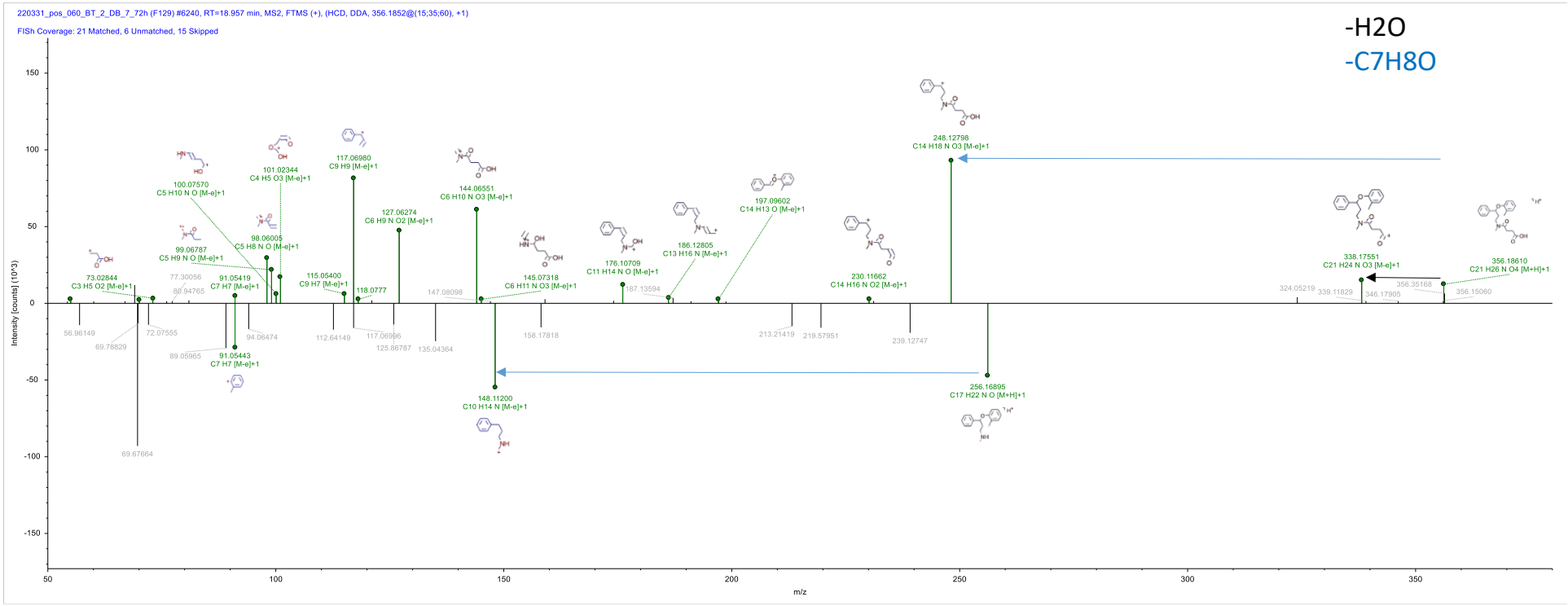
S3.4.2. Atm TP succ



Atm_TP_succ
Chemical Formula: $C_{21}H_{25}NO_4$
Exact Mass: 355.1784
Level 3

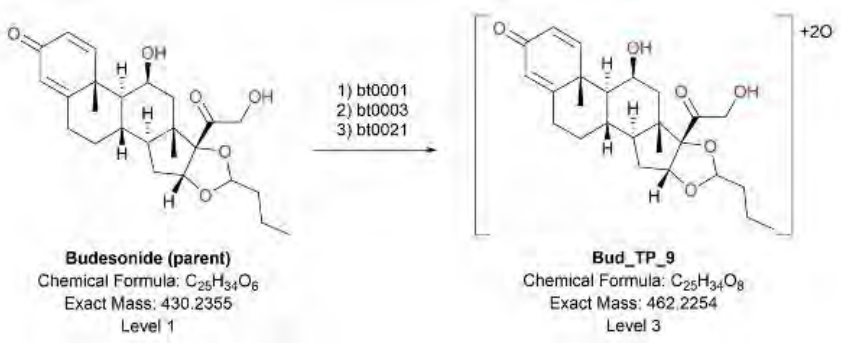
Fragment matches with parent compound at 91 and 117 m/z. Neutral loss of water indicates *N*-succinylation of parent. Both show loss of C_7H_8O. $[M-H]^-$ ion for further confirmation of the carboxylate could not be found.

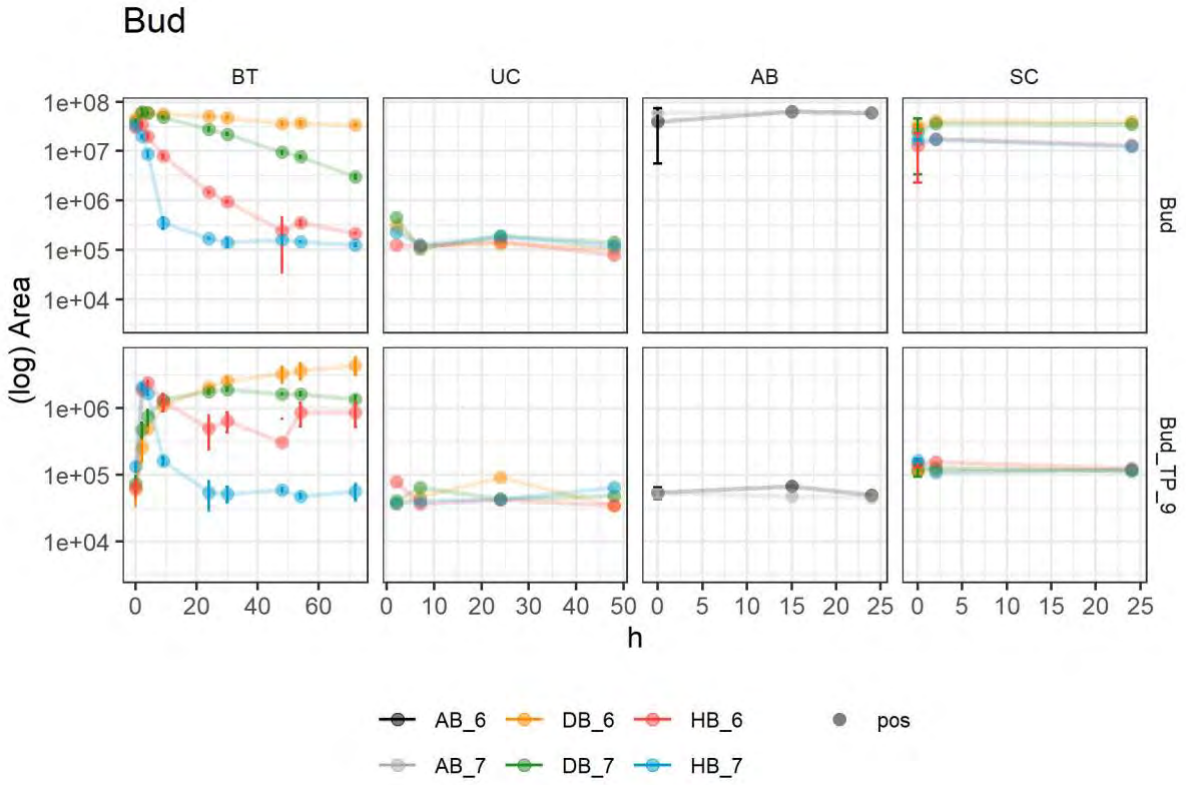
Atm_TP_succ_remeas



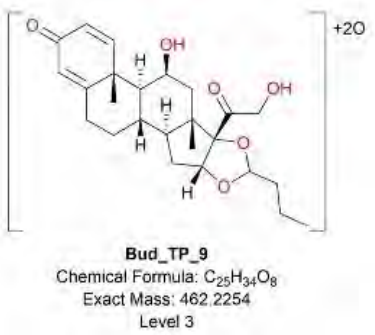
Atm_remeas

S3.5 Budesonide



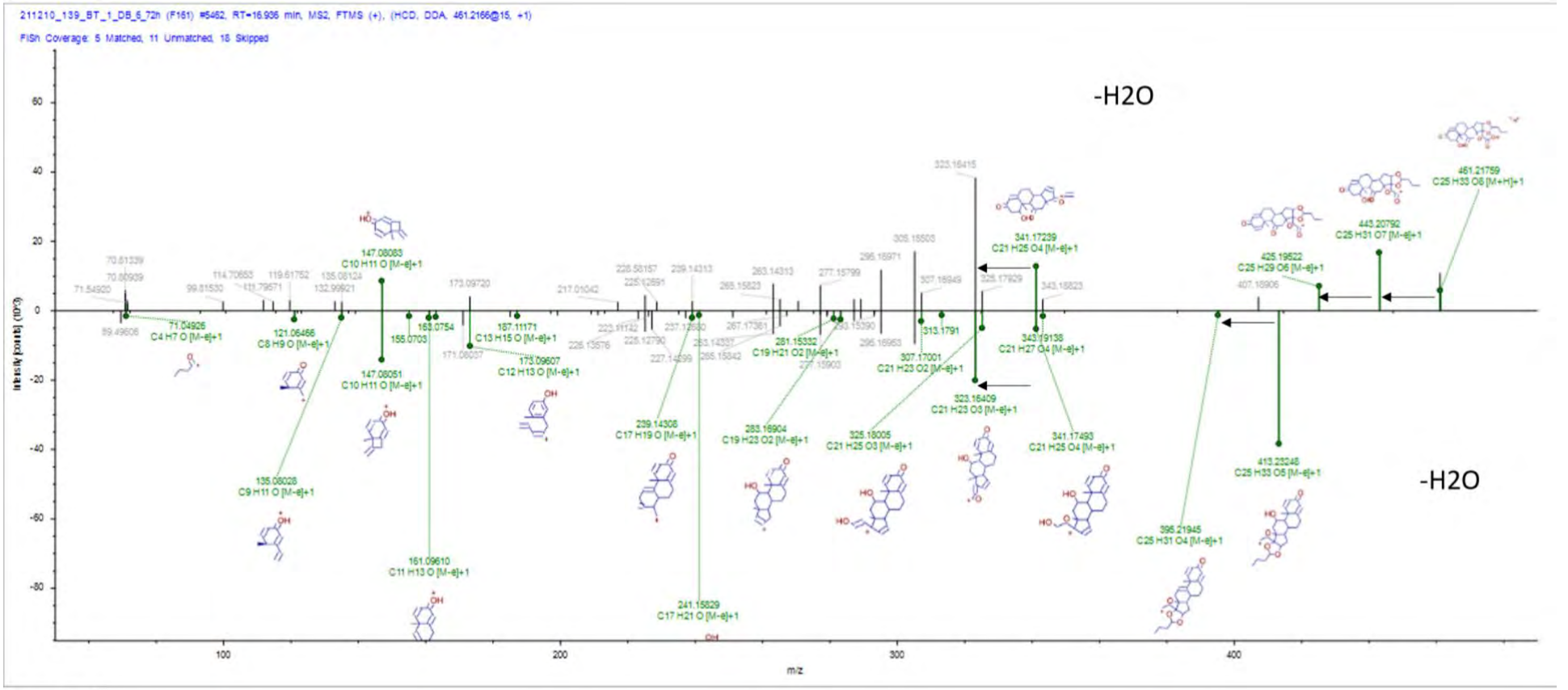


S3.5.1. Bud TP 9



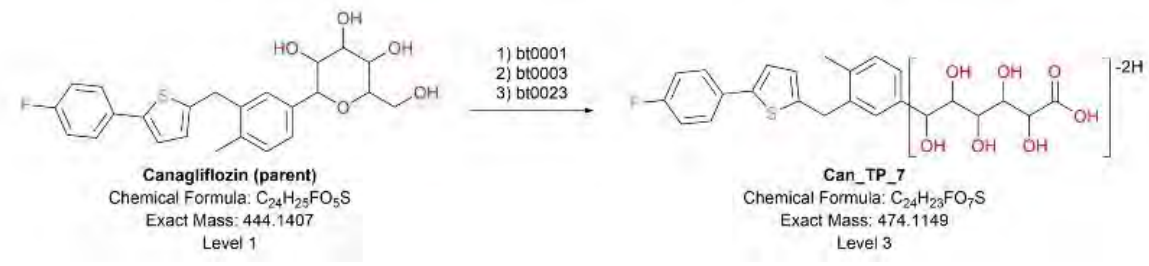
Many fragment-matches between TP and parent confirm the steroid backbone. The loss of water can be observed twice for the parent, whereas for the TP it can be observed 3 times, suggesting the TP is the product of hydroxylation and oxidation of terminal alcohol to carboxylate. The COOH moiety could not be confirmed by an $[M-H]^-$ ion.

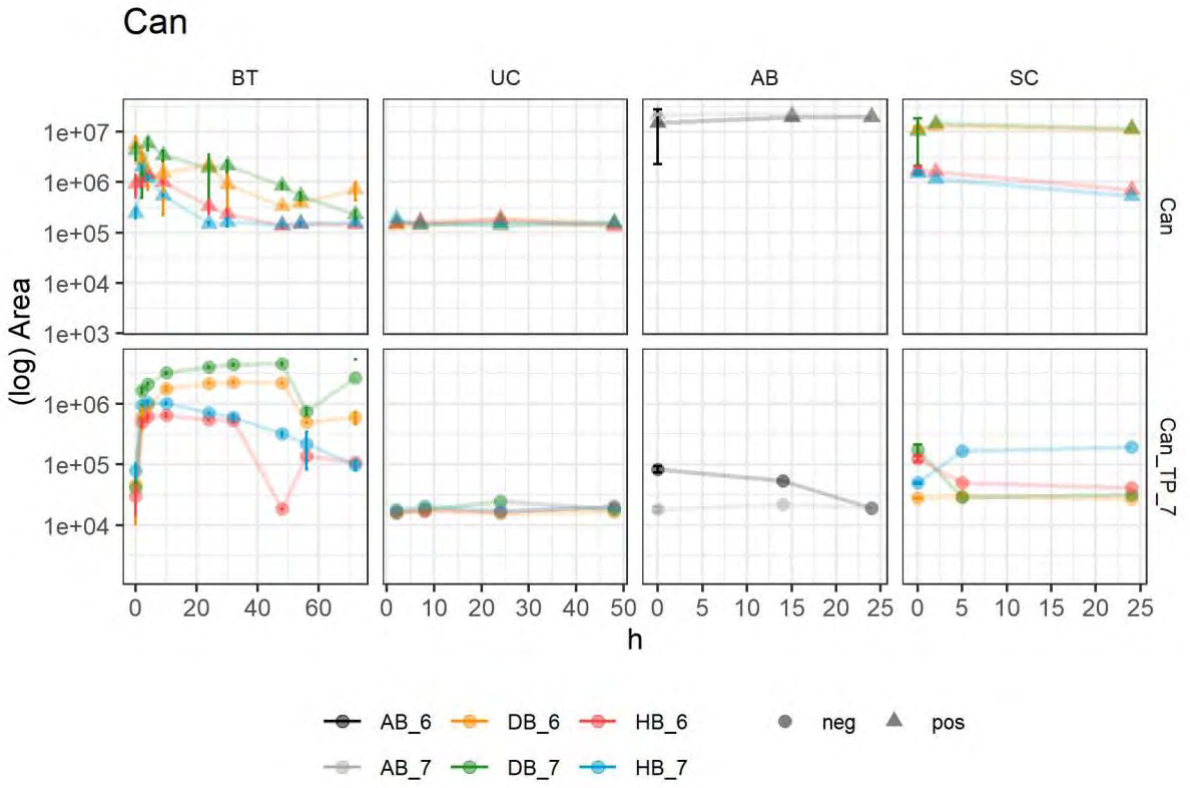
Bud_TP_9


211210_139_BT_1_DB_6_72h (F161) #5462, RT=16.936 min, MS2, FTMS (+), (HCD, DDA, 461.2166@15, +1)
FISh Coverage: 5 Matched, 11 Unmatched, 18 Skipped
-H2O
-H2O
147.08083
C10 H11 O [M-e]+1
341.17239
C21 H25 O4 [M-e]+1
461.21759
C25 H33 O6 [M+H]+1
443.20792
C25 H31 O7 [M-e]+1
425.19522
C25 H29 O6 [M-e]+1
71.04926
C4 H7 O [M-e]+1
121.06466
C8 H9 O [M-e]+1
147.08051
C10 H11 O [M-e]+1
155.0703
163.0754
187.11171
C13 H15 O [M-e]+1
173.09607
C12 H13 O [M-e]+1
135.08028
C9 H11 O [M-e]+1
161.09610
C11 H13 O [M-e]+1
239.14306
C17 H19 O [M-e]+1
241.15529
C17 H21 O [M-e]+1
281.15332
C19 H21 O2 [M-e]+1
283.16904
C19 H23 O2 [M-e]+1
307.17001
C21 H23 O2 [M-e]+1
313.1791
323.16409
C21 H23 O3 [M-e]+1
325.18005
C21 H25 O3 [M-e]+1
343.19138
C21 H27 O4 [M-e]+1
341.17493
C21 H25 O4 [M-e]+1
395.21945
C25 H31 O4 [M-e]+1
413.23246
C25 H33 O5 [M-e]+1
Intensity [10^3]
m/z

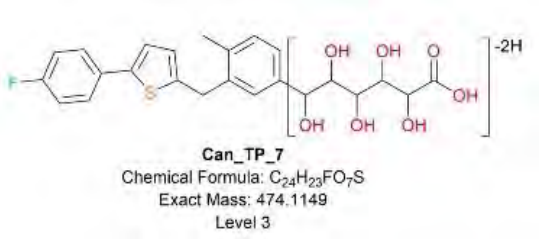
Bud

S3.6 Canagliflozin





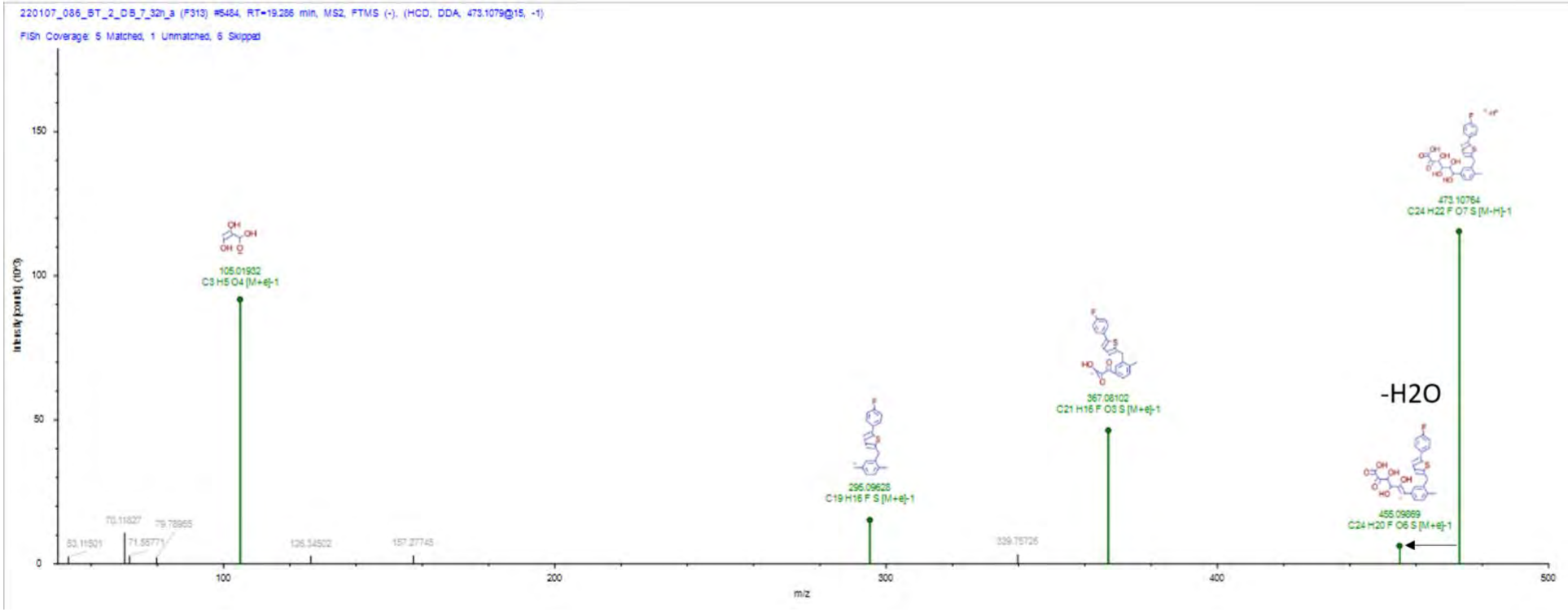
S3.6.1. Can TP 7



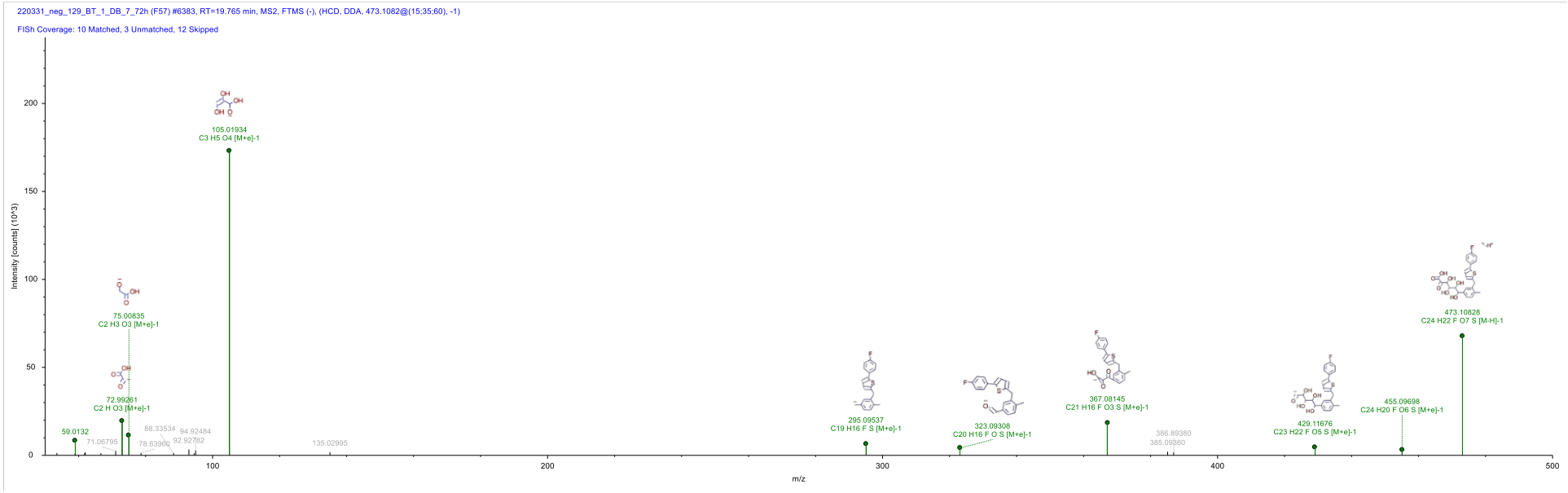
Can_TP_7
Chemical Formula: $C_{24}H_{23}FO_7S$
Exact Mass: 474.1149
Level 3

MS spectra of parent could only be acquired in positive mode, whereas TP only in negative mode. $[M-H]^-$ ion of TP suggests the presence of a carboxylate, which supports the oxidation of the primary alcohol. Oxidative cleavage of the ether bond is supported by fragments of nominal mass 473 and 455.

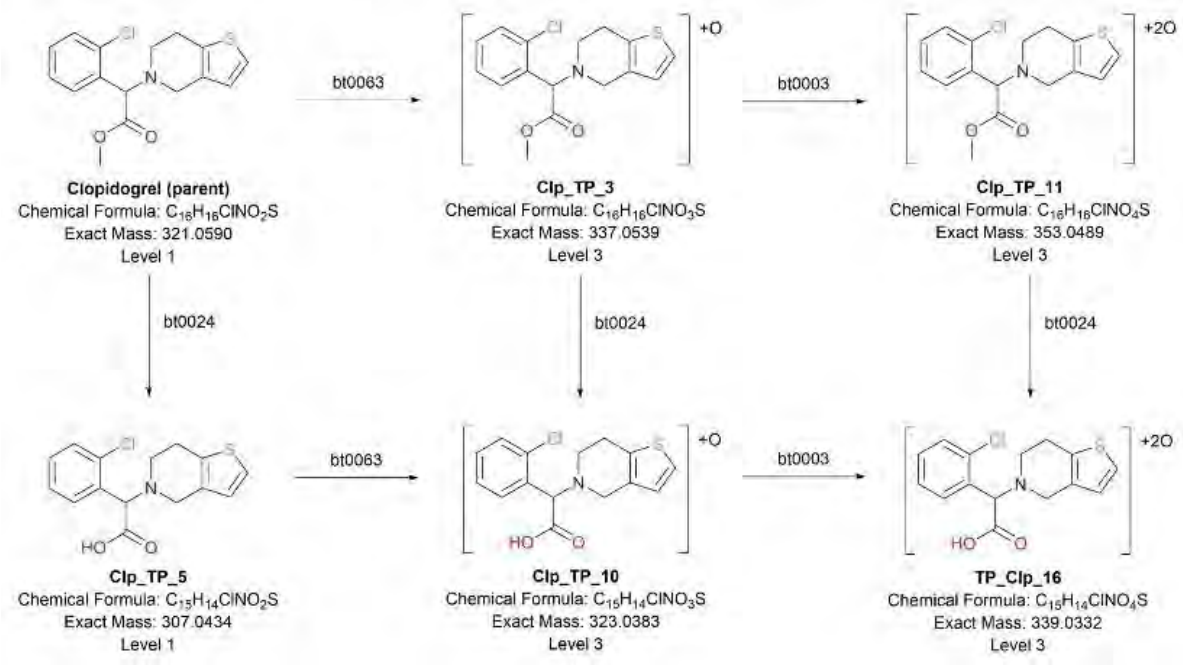
Can_TP_7

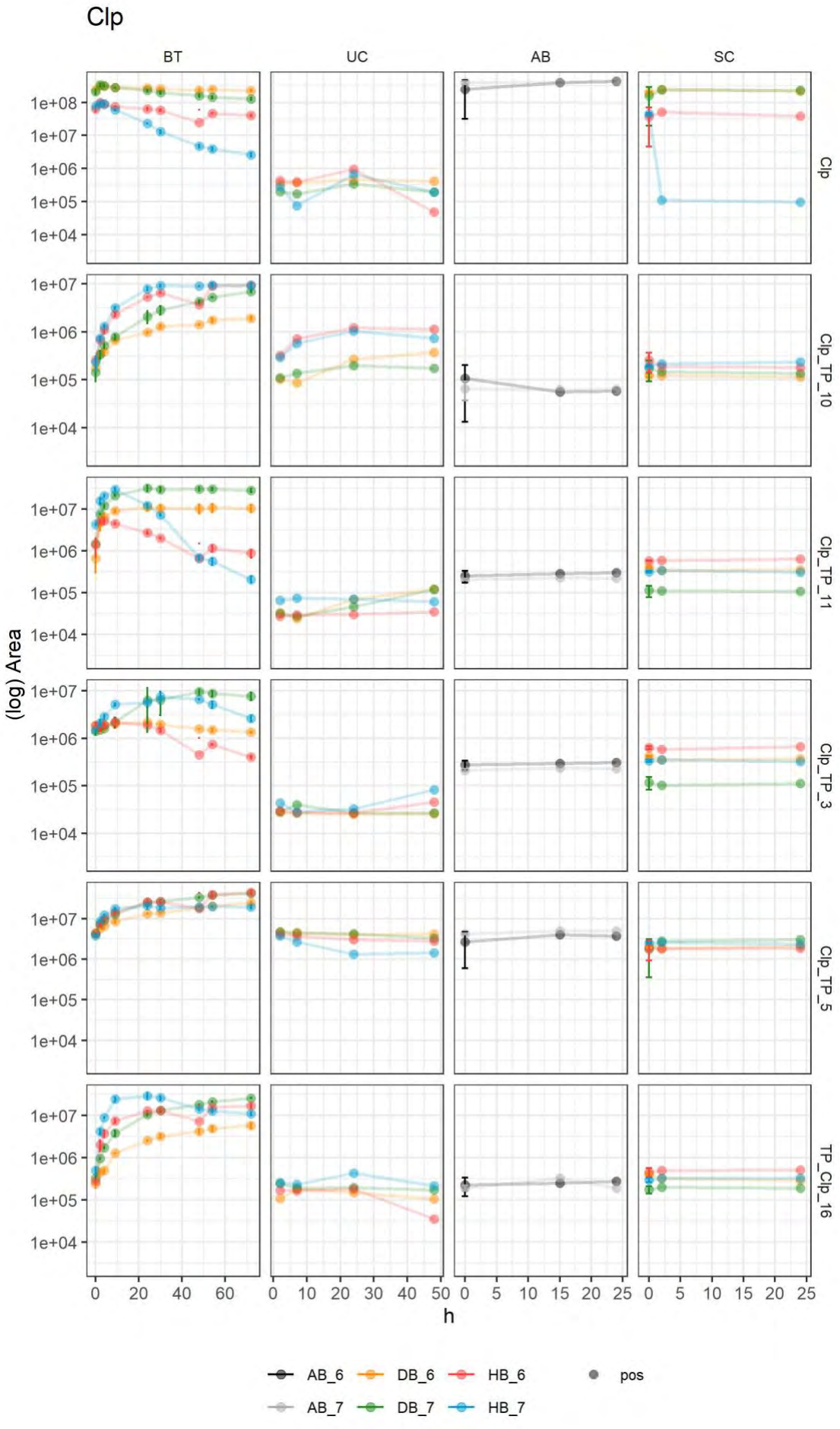

220107_086_ST_2_DB_7_32h_a (F313) #5484, RT=19.286 min, MS2, FTMS (-), (HCD, DDA, 473.1079@15, -1)
FISh Coverage: 5 Matched, 1 Unmatched, 6 Skipped
Intensity [100%]
m/z
105.01932
C3 H5 O4 [M+e]-1
296.09628
C19 H16 F S [M+e]-1
367.06102
C21 H16 F O3 S [M+e]-1
455.09869
C24 H20 F O6 S [M+e]-1
473.10764
C24 H22 F O7 S [M-H]-1
-H2O
83.11501
70.11827
71.55771
79.78965
126.54502
157.27745
339.75726

Can_TP_7_remeas

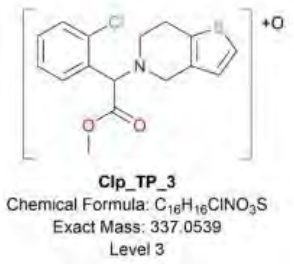


S3.7 Clopidogrel




Clp
BT
UC
AB
SC
Clp
Clp_TP_10
Clp_TP_11
Clp_TP_3
Clp_TP_5
TP_Clp_16
(log) Area
1e+08
1e+07
1e+06
1e+05
1e+04
0 20 40 60
0 10 20 30 40 50
0 5 10 15 20 25
h
AB_6
DB_6
HB_6
pos
AB_7
DB_7
HB_7

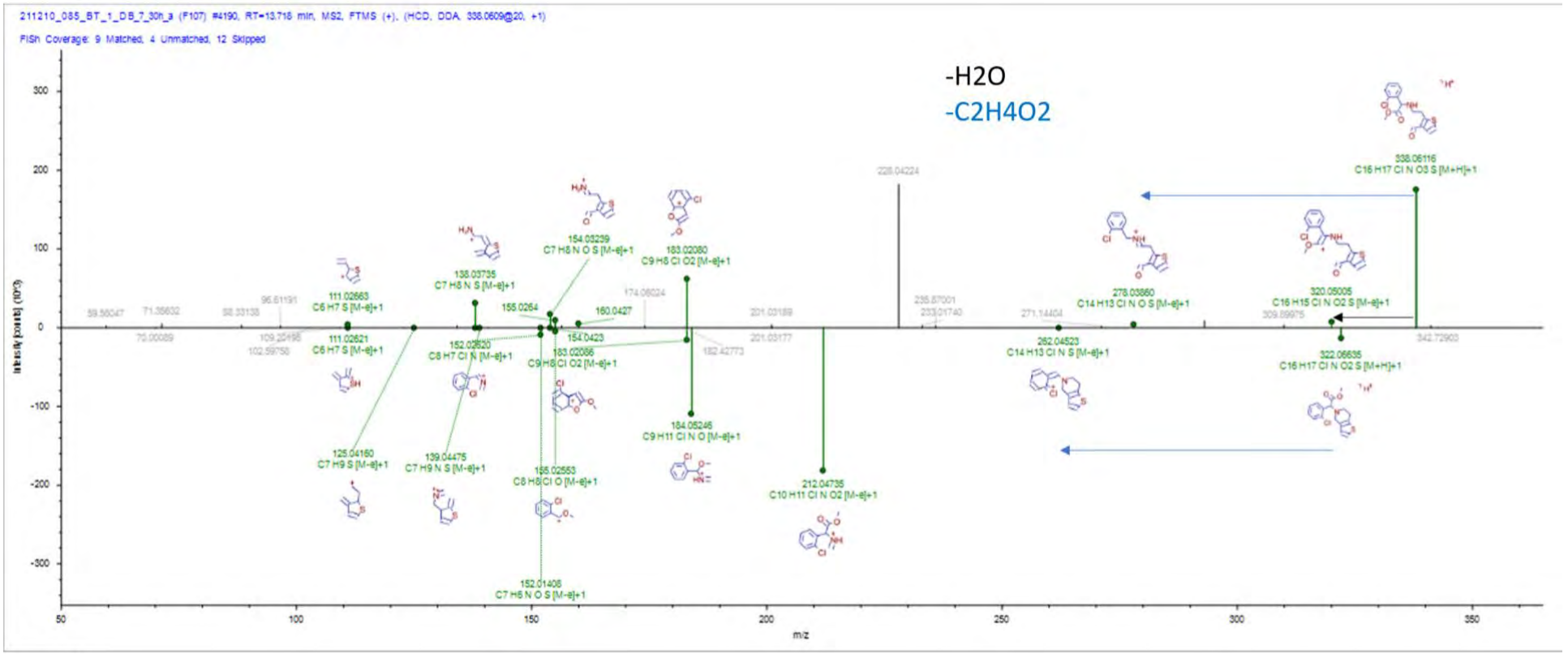
S3.7.1. Clp TP 3



Clp_TP_3
Chemical Formula: $C_{16}H_{16}ClNO_3S$
Exact Mass: 337.0539
Level 3

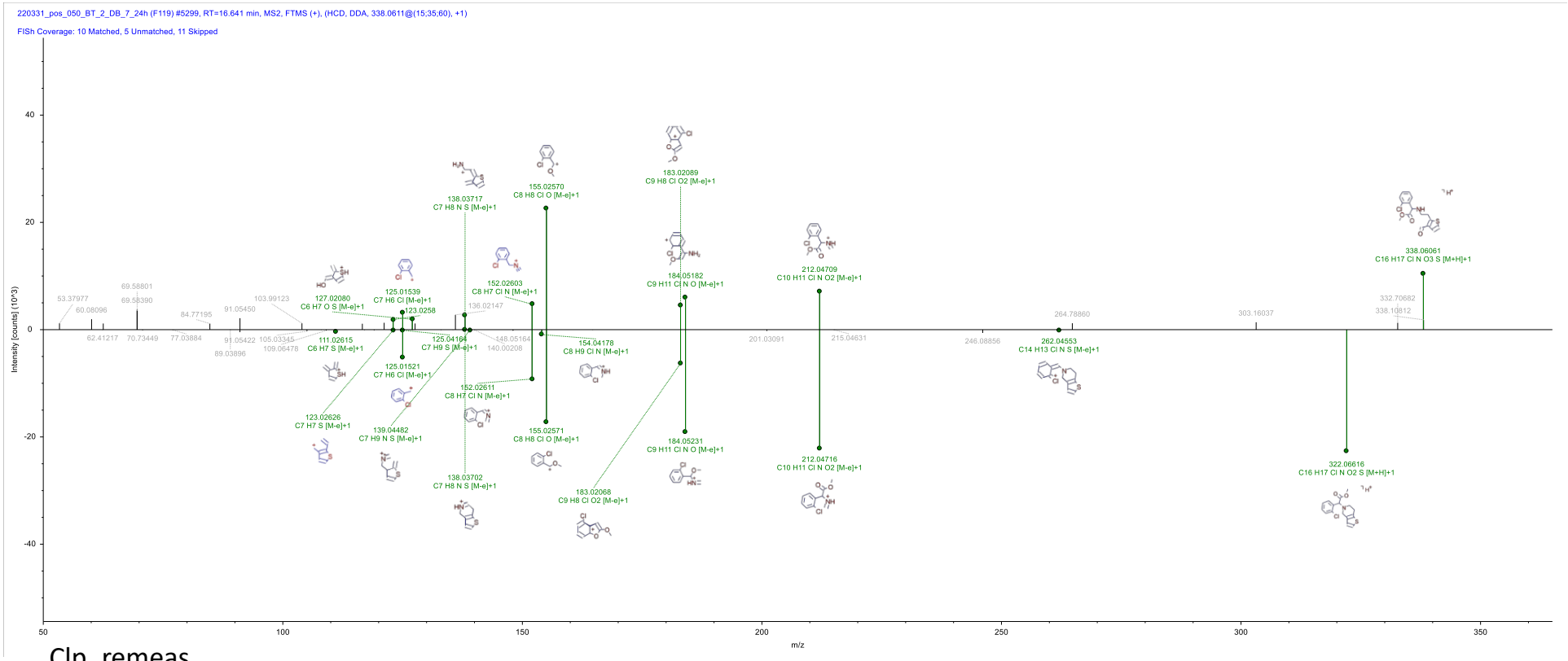
Many fragment-matches in lower m/z range support substructure. Both parent and TP show loss of methyl formate (-$C_2H_4O_2$). The absence of nominal masses 322 and 262 – structures with bicyclic ring intact – in TP spectrum indicate oxidative *N*-dealkylation. The human metabolite 2-oxo-clopidogrel as reported by Loer et al.[8] shares the same mass and cannot be excluded as a possible candidate.

Clp_TP_3


211210_085_BT_1_DB_7_30h_a (F107) #4190, RT=13.718 min, MS2, FTMS (+), (HCD, DDA, 338.0609@20, +1)
FISh Coverage: 9 Matched, 4 Unmatched, 12 Skipped
-H2O
-C2H4O2
338.06116
C16 H17 Cl N O3 S [M+H]+1
228.04224
278.03860
C14 H13 Cl N O S [M-e]+1
320.05005
C16 H15 Cl N O2 S [M-e]+1
262.04523
C14 H13 Cl N S [M-e]+1
322.06635
C16 H17 Cl N O2 S [M+H]+1
154.03239
C7 H8 N O S [M-e]+1
183.02080
C9 H8 Cl O2 [M-e]+1
138.03735
C7 H8 N S [M-e]+1
111.02663
C6 H7 S [M-e]+1
111.02621
C6 H7 S [M-e]+1
152.02620
C8 H7 Cl N [M-e]+1
155.0264
160.0427
154.0423
183.02086
C9 H8 Cl O2 [M-e]+1
184.05246
C9 H11 Cl N O [M-e]+1
125.04160
C7 H9 S [M-e]+1
139.04475
C7 H9 N S [M-e]+1
155.02553
C8 H8 Cl O [M-e]+1
212.04735
C10 H11 Cl N O2 [M-e]+1
152.01408
C7 H6 N O S [M-e]+1
Intensity (%)
m/z

Clp

Clp_TP_3_remeas

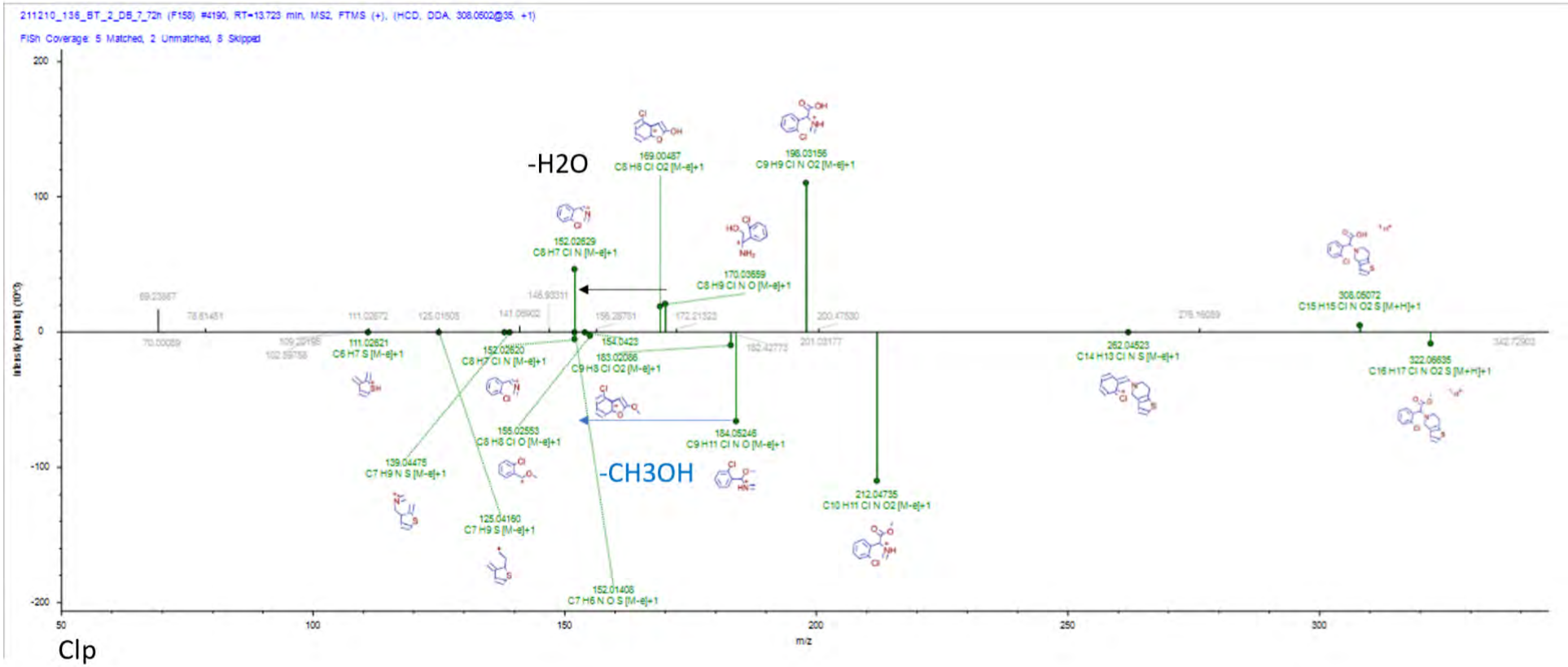


Clp_remeas

S3.7.2. Clp TP 5

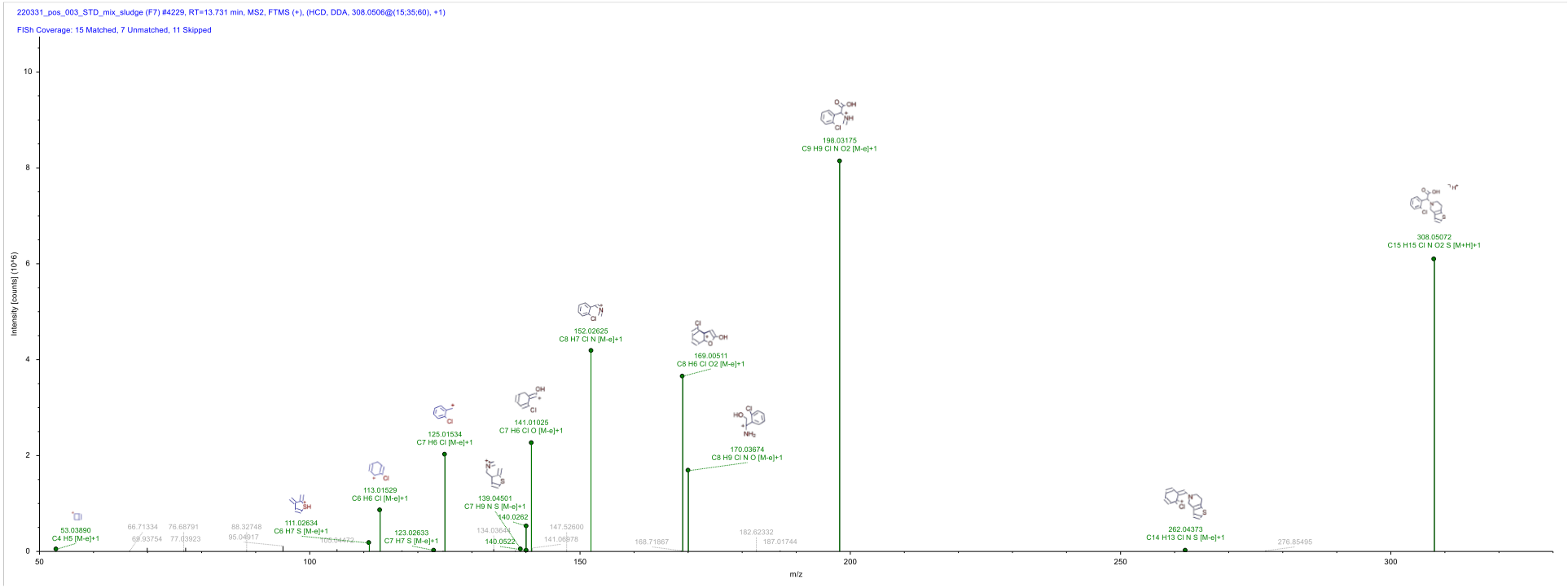
Many fragment-matches in lower m/z range support substructure of parent. Parent spectrum shows methanol loss, whereas TP spectrum shows water loss. This indicates the hydrolysis of the ester parent compound. No $[M-H]^-$ ion could be detected for this TP to increase confidence of carboxylate moiety. Furthermore, MS^2 of TP showed full match with *mzCloud* database and reference standard.

Clp_TP_5

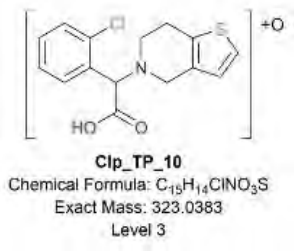

211210_136_BT_2_DB_7_72h (F158) #4190, RT=13.723 min, MS2, FTMS (+), (HCD, DDA, 308.0502@35, +1)
FISh Coverage: 5 Matched, 2 Unmatched, 8 Skipped
-H2O
169.00487
C8 H6 Cl O2 [M-e]+1
196.03156
C9 H9 Cl N O2 [M-e]+1
152.02629
C8 H7 Cl N [M-e]+1
170.03659
C8 H9 Cl N O [M-e]+1
308.05072
C15 H15 Cl N O2 S [M+H]+1
111.02621
C6 H7 S [M-e]+1
152.02620
C8 H7 Cl N [M-e]+1
154.0423
183.02066
C9 H8 Cl O2 [M-e]+1
262.04523
C14 H13 Cl N S [M-e]+1
322.06635
C16 H17 Cl N O2 S [M+H]+1
155.02553
C8 H8 Cl O [M-e]+1
184.05246
C9 H11 Cl N O [M-e]+1
139.04475
C7 H9 N S [M-e]+1
-CH3OH
212.04735
C10 H11 Cl N O2 [M-e]+1
125.04160
C7 H9 S [M-e]+1
152.01408
C7 H6 N O S [M-e]+1
Intensity (%)
m/z

Clp

Clp_TP_5 (reference standard)



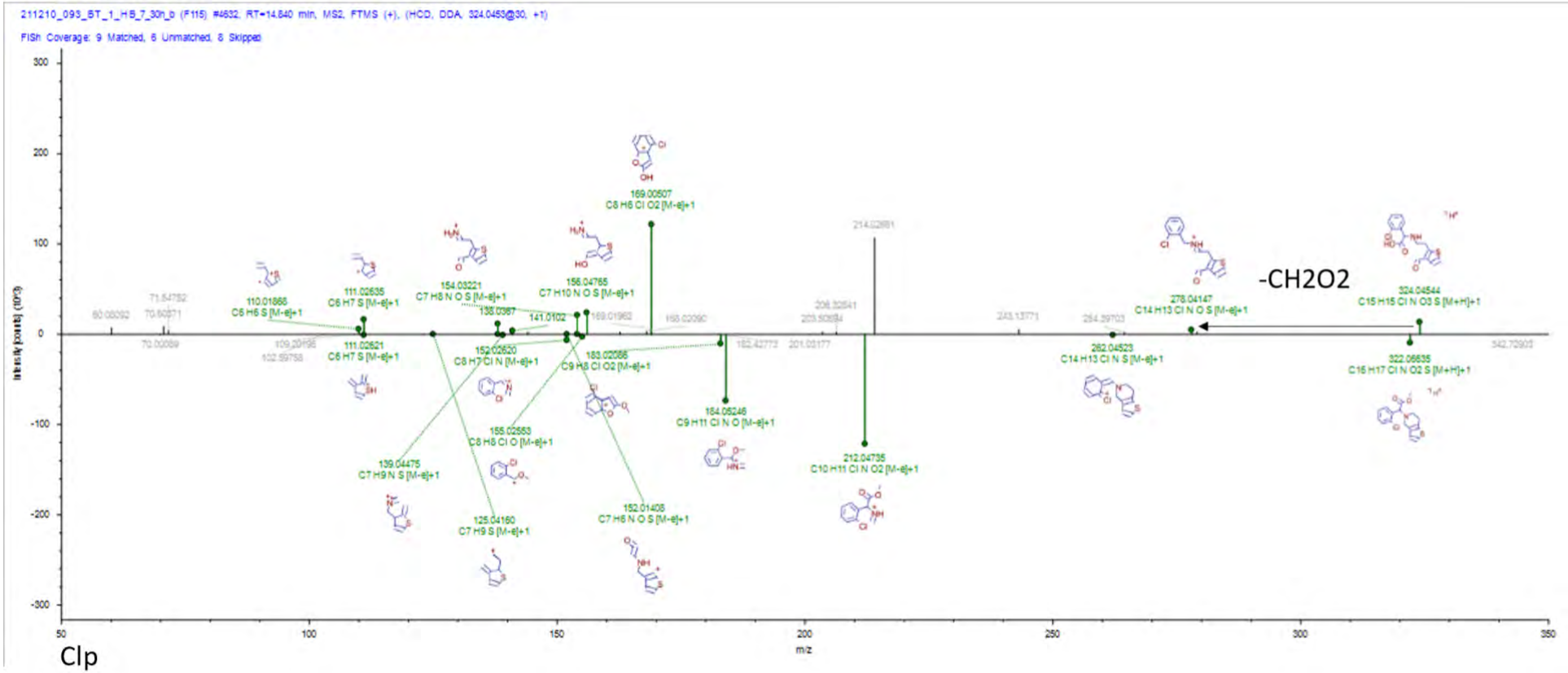
S3.7.3. Clp TP 10



Clp_TP_10
Chemical Formula: $C_{15}H_{14}ClNO_3S$
Exact Mass: 323.0383
Level 3

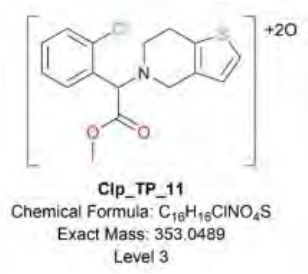
Many fragment-matches in lower m/z range support substructure of parent. Loss of formic acid and absence of methyl formate loss (nominal mass 264 does not correspond to correct molecular formula due to large mass error of 0.37 u) support hydrolysis of ester. No $[M-H]^-$ ion could be detected for this TP to increase confidence of carboxylate moiety.

Clp_TP_10


211210_093_ST_1_HS_7_30h_b (F115) #4632, RT=14.640 min, MS2, FTMS (+), (HCD, DDA, 324.0453@30, +1)
FISh Coverage: 9 Matched, 6 Unmatched, 8 Skipped
Intensity [cps] (10^3)
m/z
-CH2O2
169.00507
C8 H6 Cl O2 [M-e]+1
156.04765
C7 H10 N O S [M-e]+1
154.03221
C7 H8 N O S [M-e]+1
111.02635
C6 H7 S [M-e]+1
110.01866
C6 H6 S [M-e]+1
111.02621
C6 H7 S [M-e]+1
152.02620
C8 H7 Cl N [M-e]+1
183.02066
C9 H8 Cl O2 [M-e]+1
164.05246
C9 H11 Cl N O [M-e]+1
155.02553
C8 H8 Cl O [M-e]+1
139.04475
C7 H9 N S [M-e]+1
125.04160
C7 H9 S [M-e]+1
152.01408
C7 H6 N O S [M-e]+1
212.04735
C10 H11 Cl N O2 [M-e]+1
282.04523
C14 H13 Cl N S [M-e]+1
278.04147
C14 H13 Cl N O S [M-e]+1
324.04544
C15 H15 Cl N O3 S [M+H]+1
322.06535
C16 H17 Cl N O2 S [M+H]+1

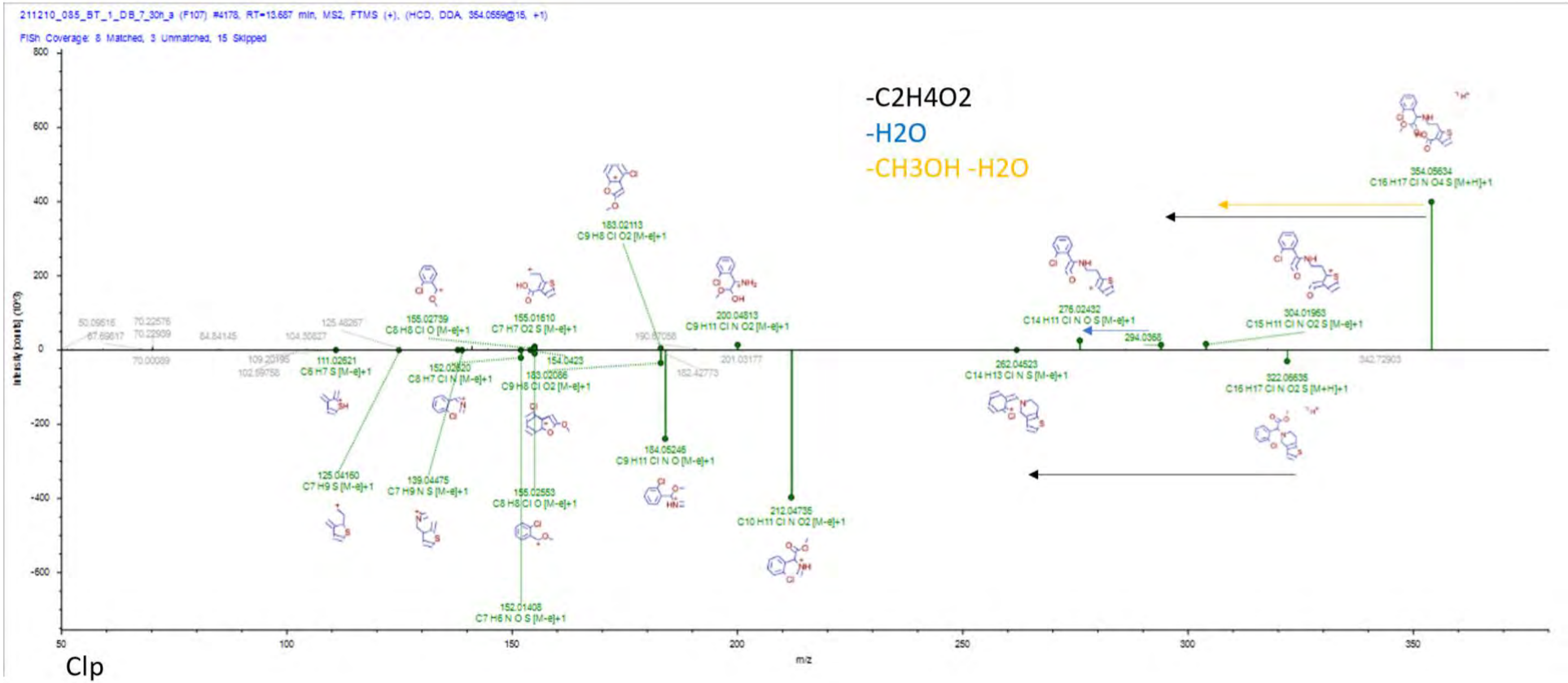
Clp

S3.7.4. Clp TP 11



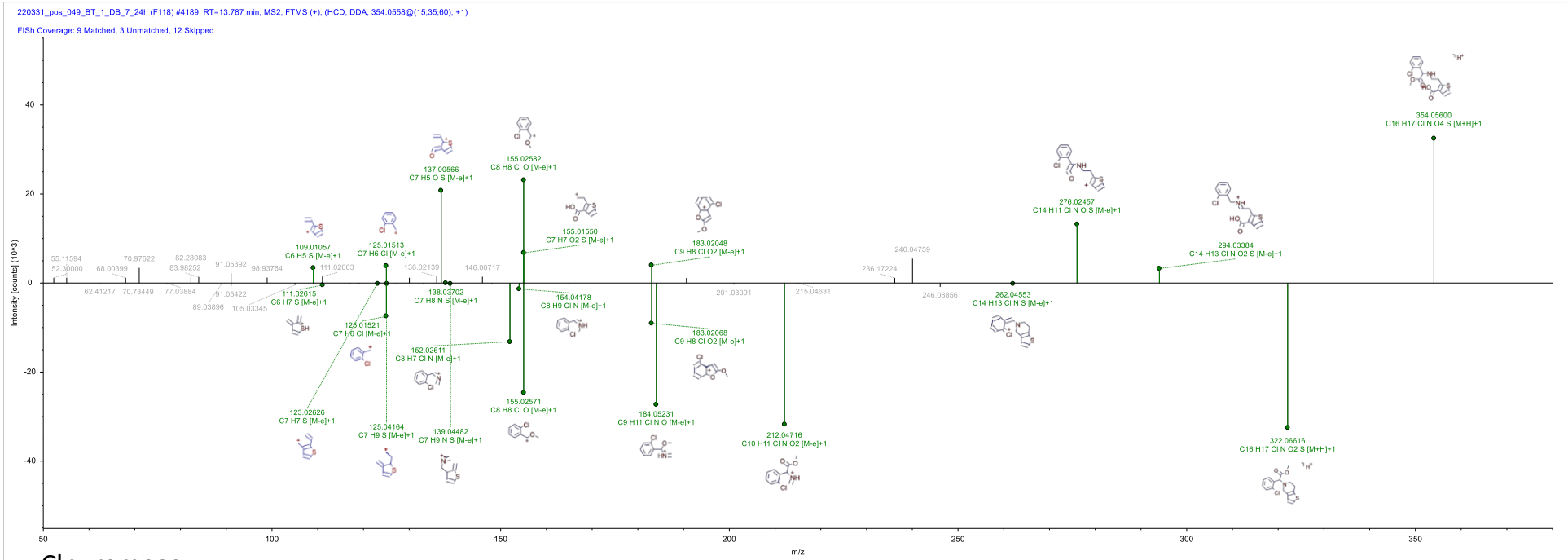
Many fragment-matches in lower m/z range support substructure of parent. Parent and TP show loss of methyl formate (-$C_2H_4O_2$). The absence of nominal masses 322 and 262 (structures with bicyclic ring intact) in TP spectrum indicate oxidative *N*-dealkylation. The loss of methanol together with water is only present in TP spectra, which could support carboxylate. No $[M-H]^-$ ion was detected.

Clp_TP_11


211210_085_BT_1_DB_7_30h_a (F107) #4178, RT=13.667 min, MS2, FTMS (+), (HCD, DDA, 354.0559@15, +1)
FISh Coverage: 8 Matched, 3 Unmatched, 15 Skipped
-C2H4O2
-H2O
-CH3OH -H2O
Intensity [10^3]
m/z
354.05634
C16 H17 Cl N O4 S [M+H]+1
304.01963
C15 H11 Cl N O2 S [M-e]+1
276.02432
C14 H11 Cl N O S [M-e]+1
262.04523
C14 H13 Cl N S [M-e]+1
322.06635
C16 H17 Cl N O2 S [M+H]+1
294.0368
200.04813
C9 H11 Cl N O2 [M-e]+1
183.02113
C9 H8 Cl O2 [M-e]+1
155.02739
C8 H8 Cl O [M-e]+1
155.01610
C7 H7 O2 S [M-e]+1
154.0423
183.02086
C9 H8 Cl O2 [M-e]+1
184.05246
C9 H11 Cl N O [M-e]+1
212.04735
C10 H11 Cl N O2 [M-e]+1
155.02553
C8 H8 Cl O [M-e]+1
152.01408
C7 H6 N O S [M-e]+1
111.02621
C6 H7 S [M-e]+1
125.04160
C7 H9 S [M-e]+1
139.04475
C7 H9 N S [M-e]+1
152.02330
C8 H7 Cl N [M-e]+1

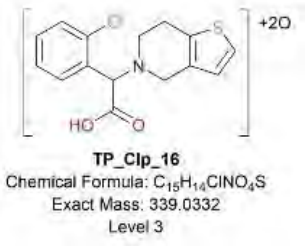
Clp

Clp_TP_11_remeas



Clp_remeas

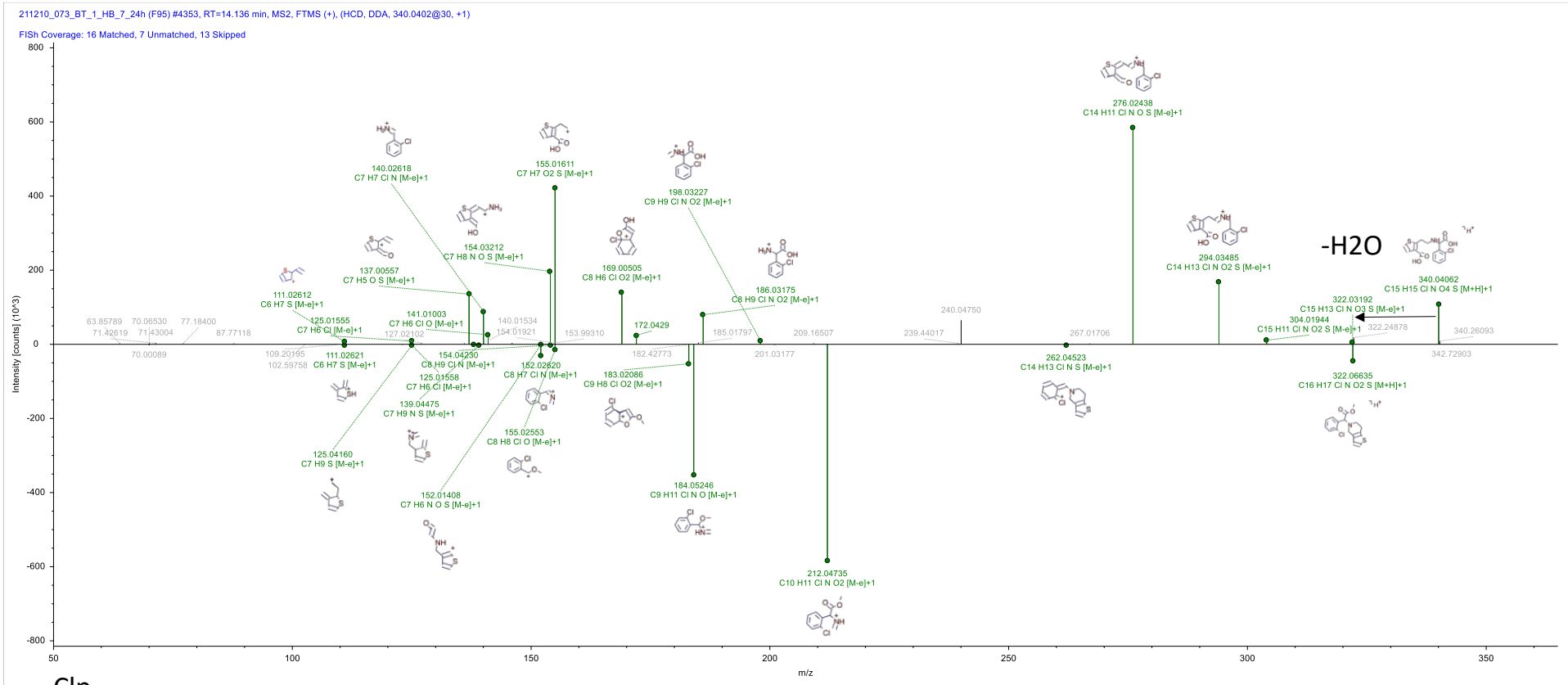
S3.7.5. TP Clp 16



TP_Clp_16
Chemical Formula: $C_{15}H_{14}ClNO_4S$
Exact Mass: 339.0332
Level 3

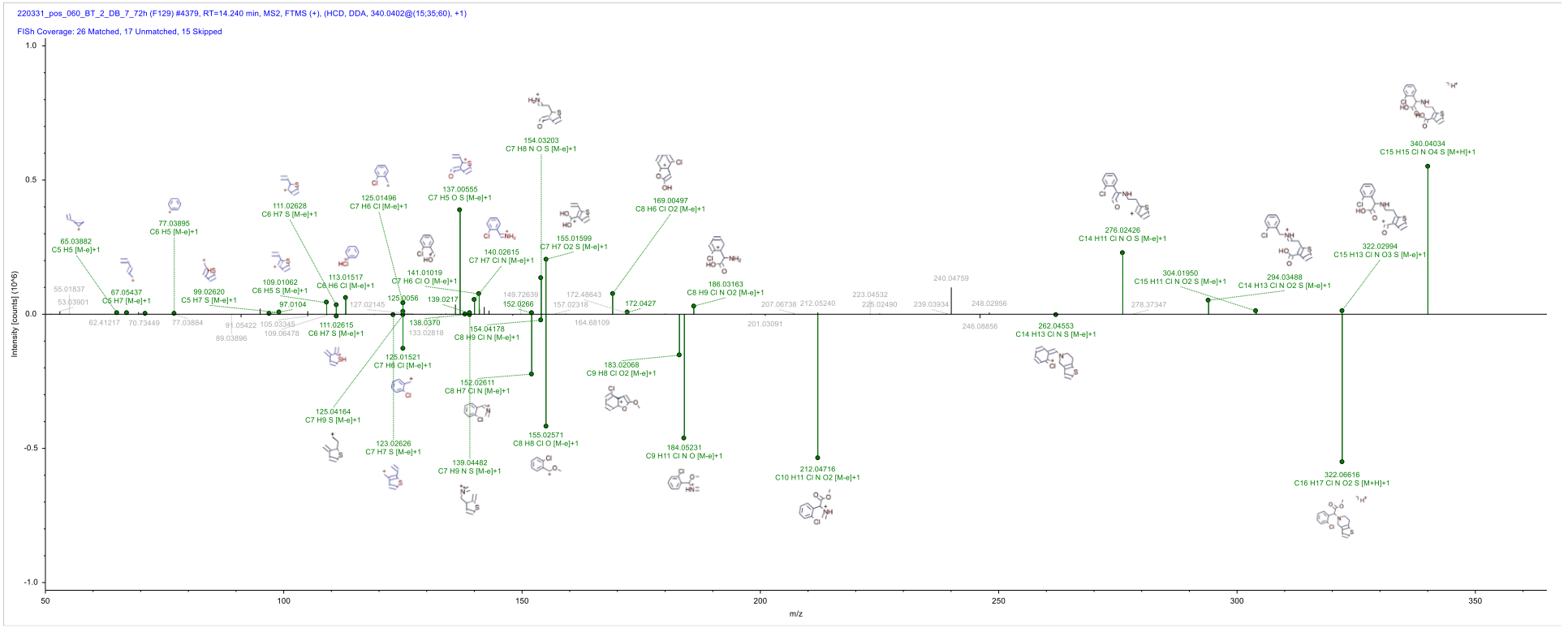
Nominal masses 111, 125 and 152 were also observed for parent comound. Absence of methanol loss, which was observed for Clp TP 11, indicates full hydrolysis of both ester bonds.

TP_Clp_16


211210_073_BT_1_HB_7_24h (F95) #4353, RT=14.136 min, MS2, FTMS (+), (HCD, DDA, 340.0402@30, +1)
FISh Coverage: 16 Matched, 7 Unmatched, 13 Skipped
Intensity [counts] (10^3)
m/z
276.02438
C14 H11 Cl N O S [M-e]+1
140.02618
C7 H7 Cl N [M-e]+1
155.01611
C7 H7 O2 S [M-e]+1
198.03227
C9 H9 Cl N O2 [M-e]+1
154.03212
C7 H8 N O S [M-e]+1
137.00557
C7 H5 O S [M-e]+1
169.00505
C8 H6 Cl O2 [M-e]+1
186.03175
C8 H9 Cl N O2 [M-e]+1
294.03485
C14 H13 Cl N O2 S [M-e]+1
-H2O
340.04062
C15 H15 Cl N O4 S [M+H]+1
322.03192
C15 H13 Cl N O3 S [M-e]+1
304.01944
C15 H11 Cl N O2 S [M-e]+1
111.02612
C6 H7 S [M-e]+1
125.01555
C7 H6 Cl [M-e]+1
141.01003
C7 H6 Cl O [M-e]+1
172.0429
111.02621
C6 H7 S [M-e]+1
154.04230
C8 H9 Cl N [M-e]+1
152.02620
C8 H7 Cl N [M-e]+1
125.01558
C7 H6 Cl [M-e]+1
183.02086
C9 H8 Cl O2 [M-e]+1
262.04523
C14 H13 Cl N S [M-e]+1
322.06635
C16 H17 Cl N O2 S [M+H]+1
139.04475
C7 H9 N S [M-e]+1
155.02553
C8 H8 Cl O [M-e]+1
125.04160
C7 H9 S [M-e]+1
184.05246
C9 H11 Cl N O [M-e]+1
152.01408
C7 H6 N O S [M-e]+1
212.04735
C10 H11 Cl N O2 [M-e]+1

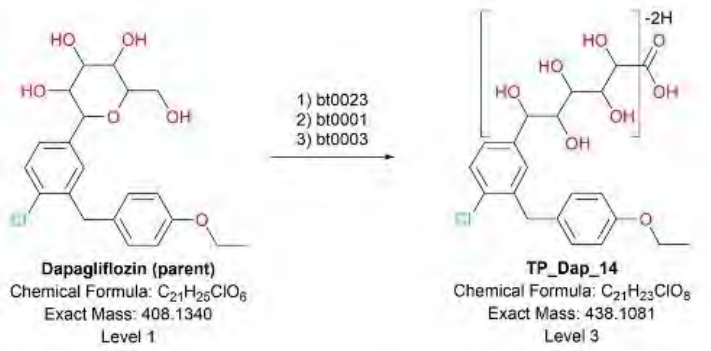
Clp

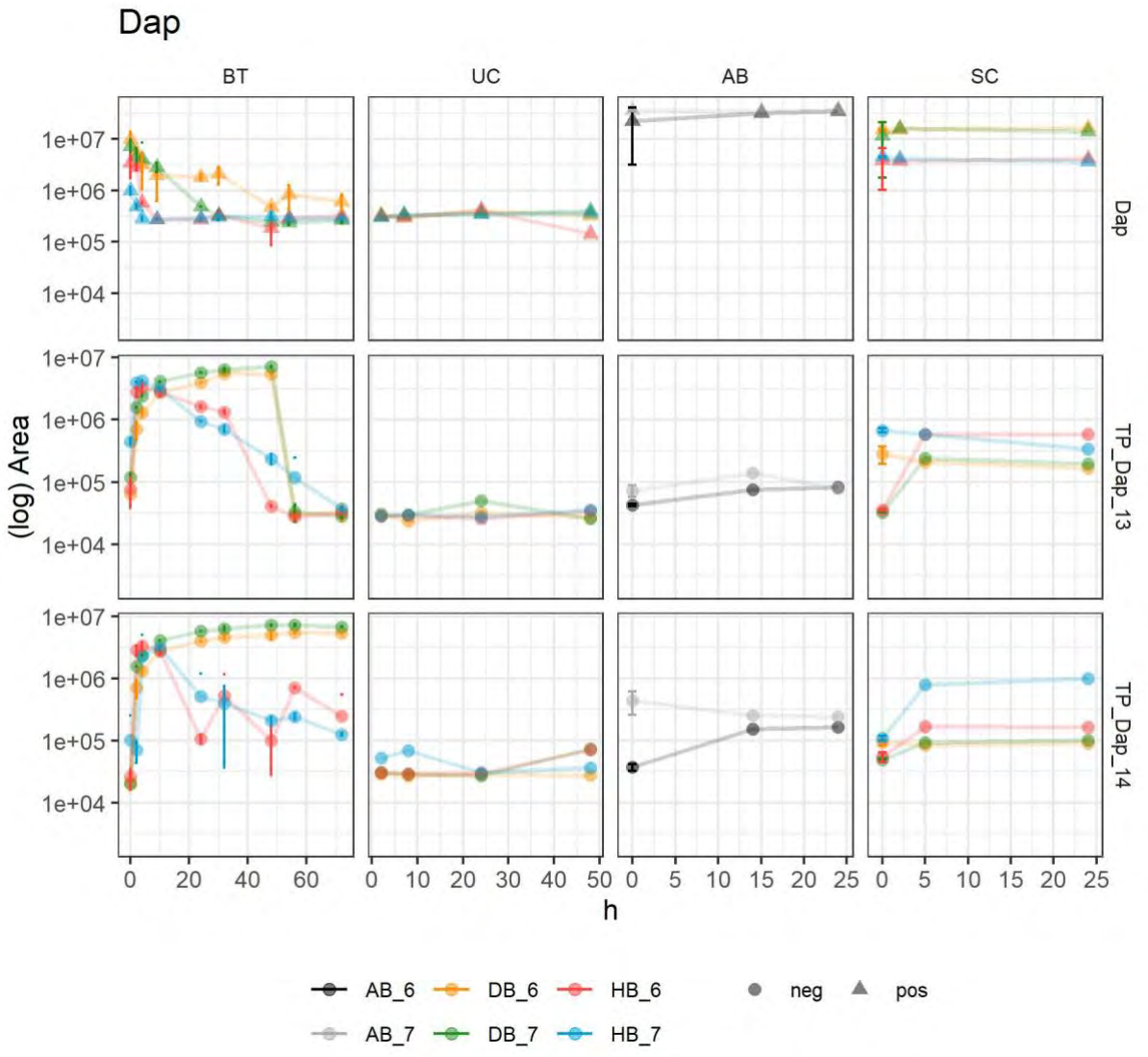
TP_Clp_16_remeas



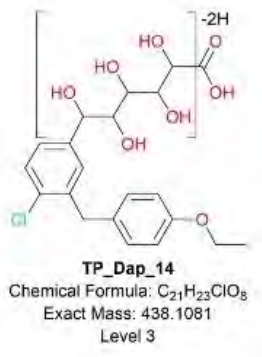
Clp_remeas

S3.8 Dapagliflozin



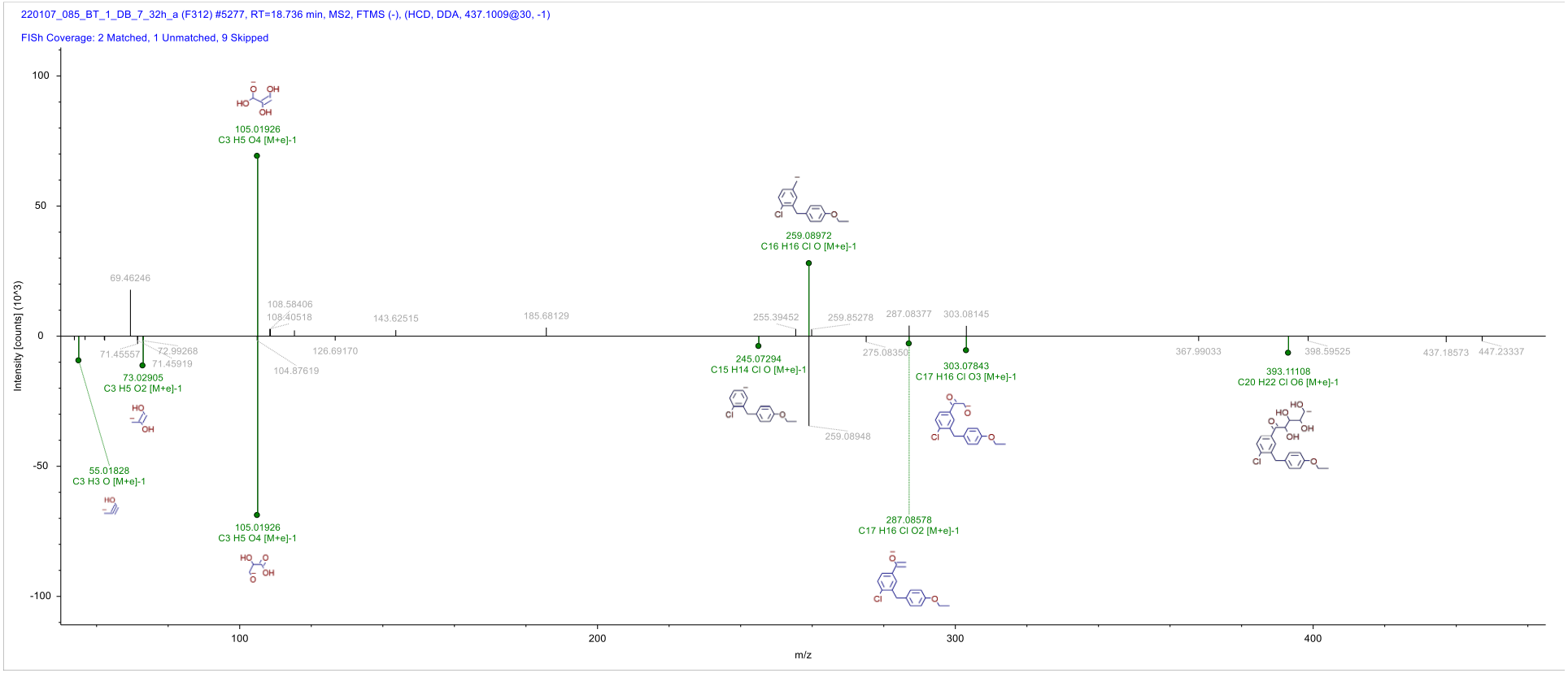


S3.8.1. TP Dap 14



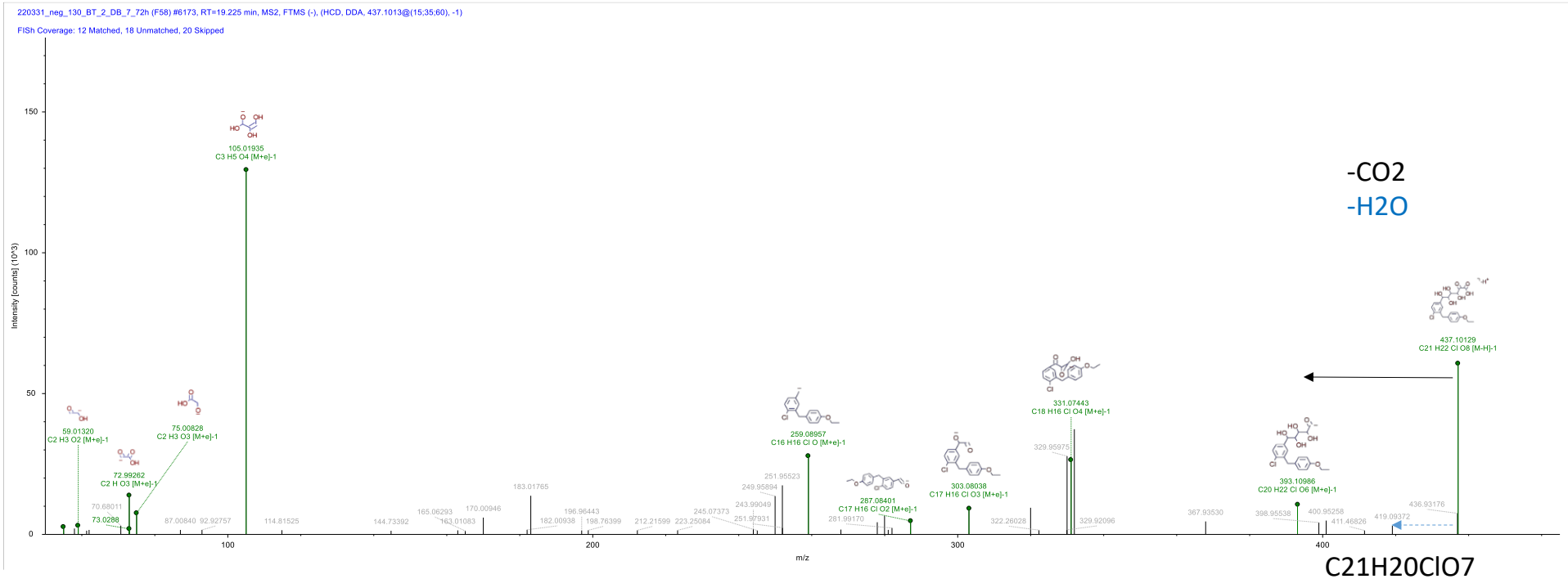
Two distinct peaks in chromatogram at RT 18.6 and 18.8. These could be two isomers or the RT alignment failed. MS^2 spectra of both look very similar. Parent was only found in positive mode, so no comparison was possible. CO_2 loss from $[M-H]^-$ ion indicates COOH moiety after ring opening.

TP_Dap_13_(14)

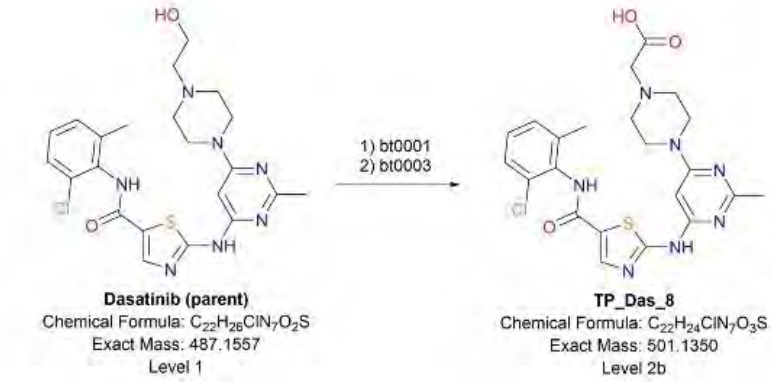


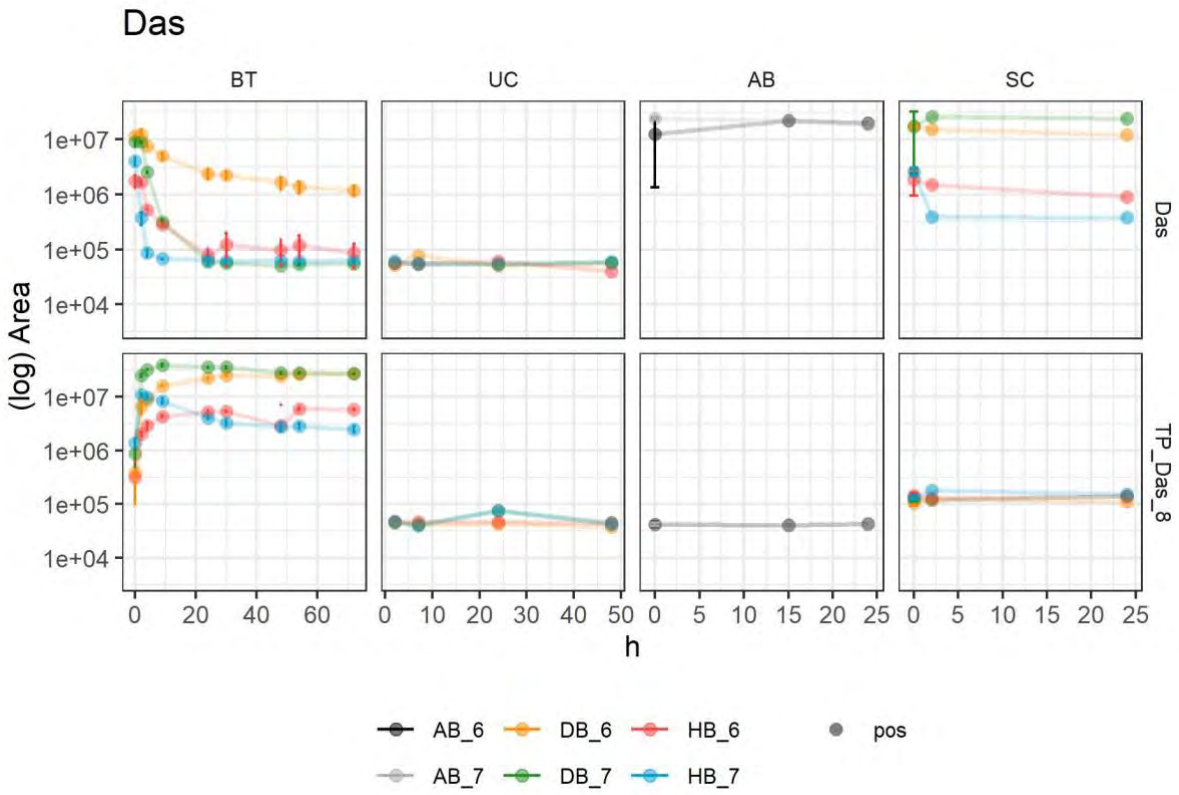
TP_Dap_14_(13)

TP_Dap_13_(14)_remeas



S3.9 Dasatinib

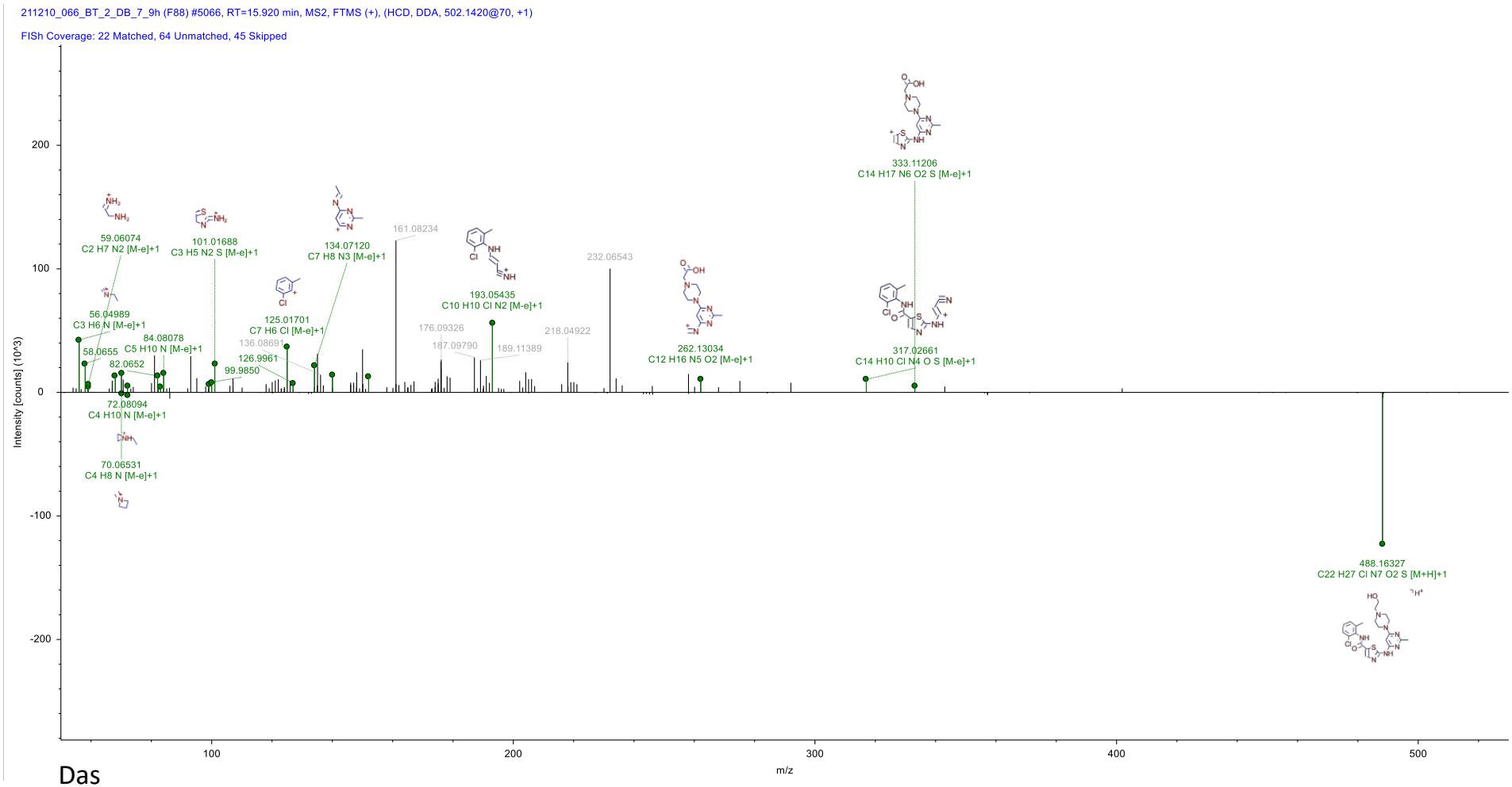




S3.9.1. TP Das 8

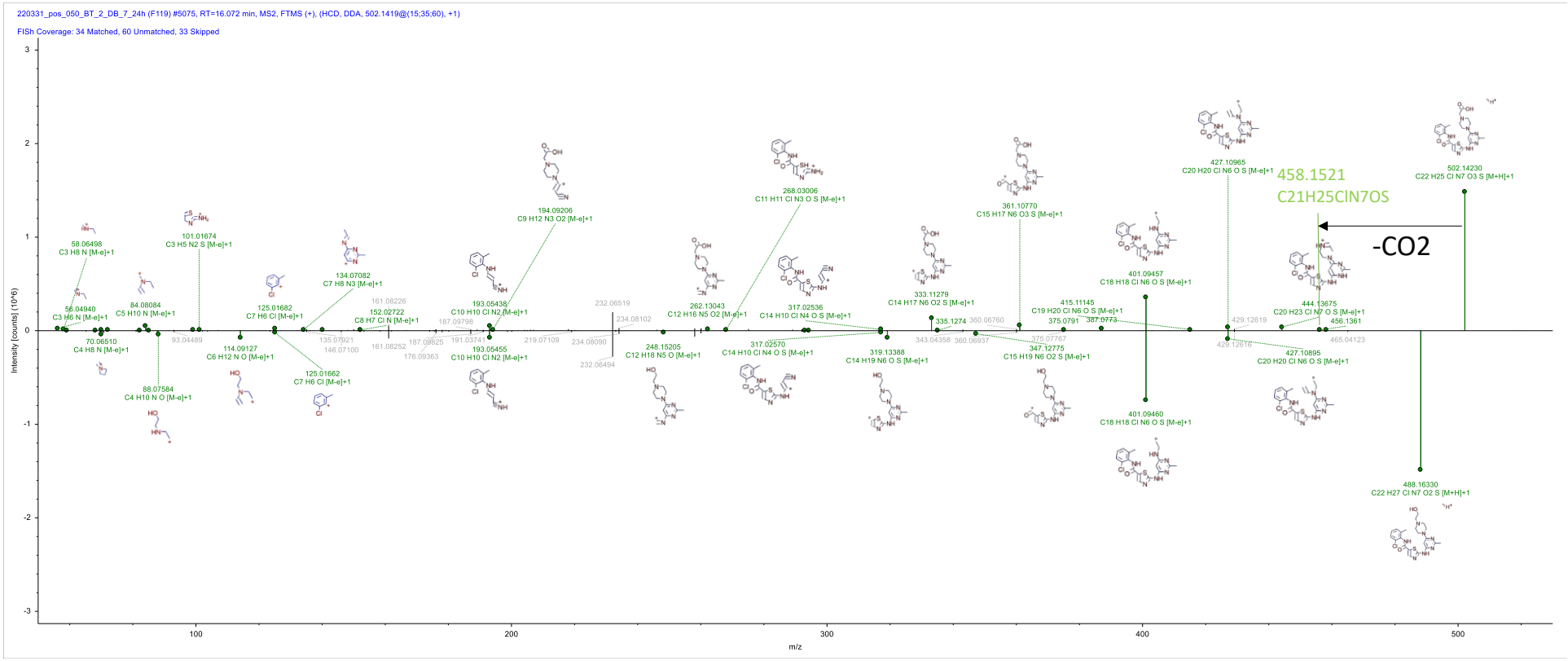
19 Ions with identical nominal masses and chemical composition were found for the TP and the parent. Especially, fragments at 317, 401 and 427 m/z confirm the same backbone for both. Neutral loss of CO_2 supports the oxidation of the terminal alcohol.

TP_Das_8


211210_066_BT_2_DB_7_9h (F88) #5066, RT=15.920 min, MS2, FTMS (+), (HCD, DDA, 502.1420@70, +1)
FISh Coverage: 22 Matched, 64 Unmatched, 45 Skipped
Intensity [counts] (10^3)
m/z
59.06074
C2 H7 N2 [M-e]+1
101.01688
C3 H5 N2 S [M-e]+1
134.07120
C7 H8 N3 [M-e]+1
161.08234
193.05435
C10 H10 Cl N2 [M-e]+1
232.06543
333.11206
C14 H17 N6 O2 S [M-e]+1
56.04989
C3 H6 N [M-e]+1
84.08078
C5 H10 N [M-e]+1
58.0655
82.0652
125.01701
C7 H6 Cl [M-e]+1
136.08691
126.9961
99.9850
176.09326
187.09790
189.11389
218.04922
262.13034
C12 H16 N5 O2 [M-e]+1
317.02661
C14 H10 Cl N4 O S [M-e]+1
72.08094
C4 H10 N [M-e]+1
70.06531
C4 H8 N [M-e]+1
488.16327
C22 H27 Cl N7 O2 S [M+H]+1

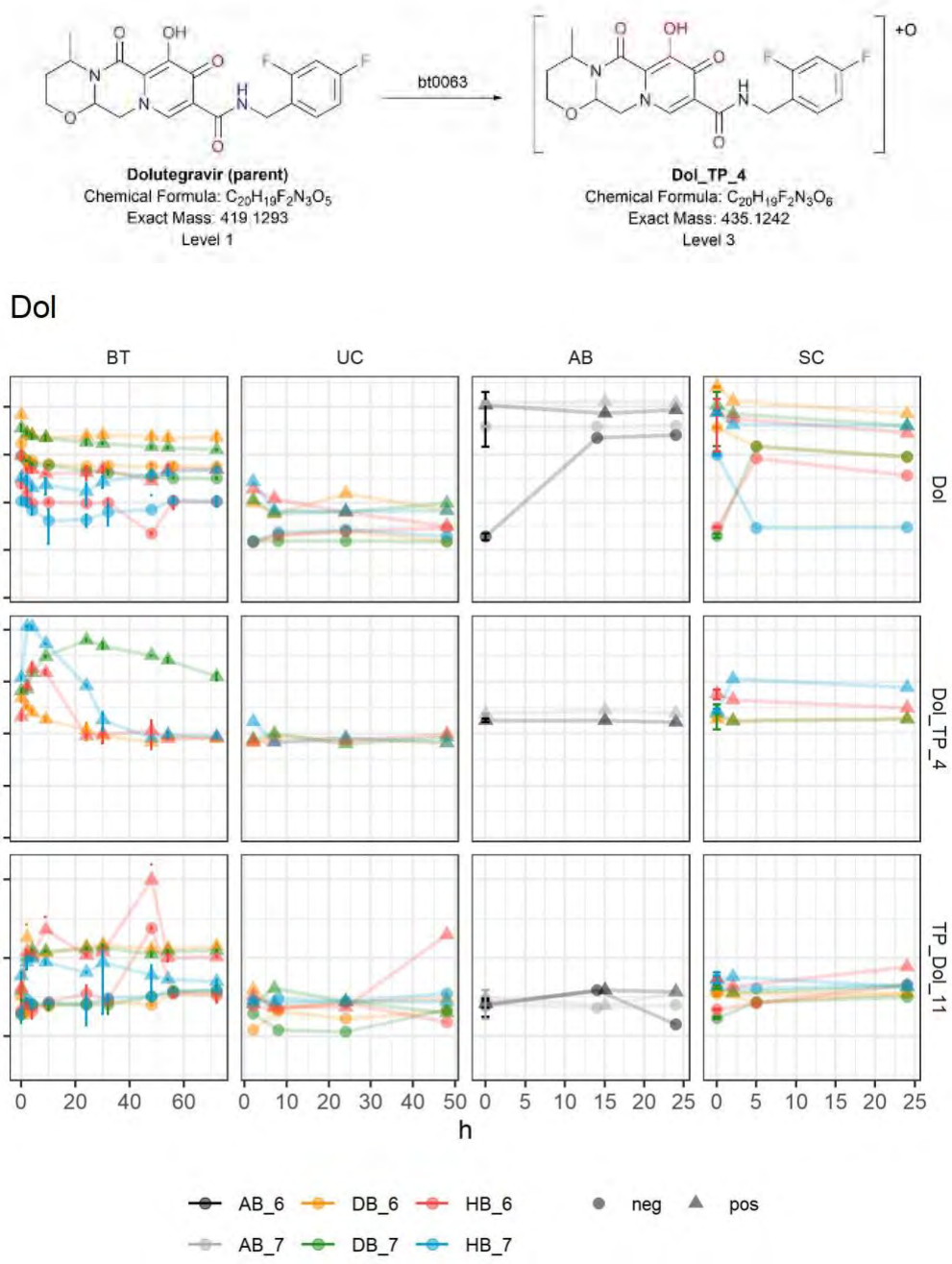
Das

TP_Das_8_remeas

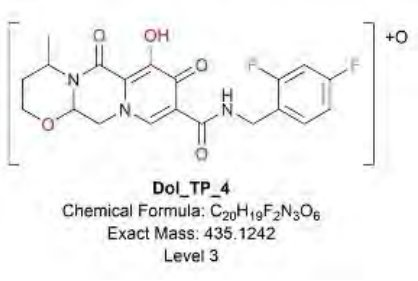


Das_remeas

S3.10 Dolutegravir



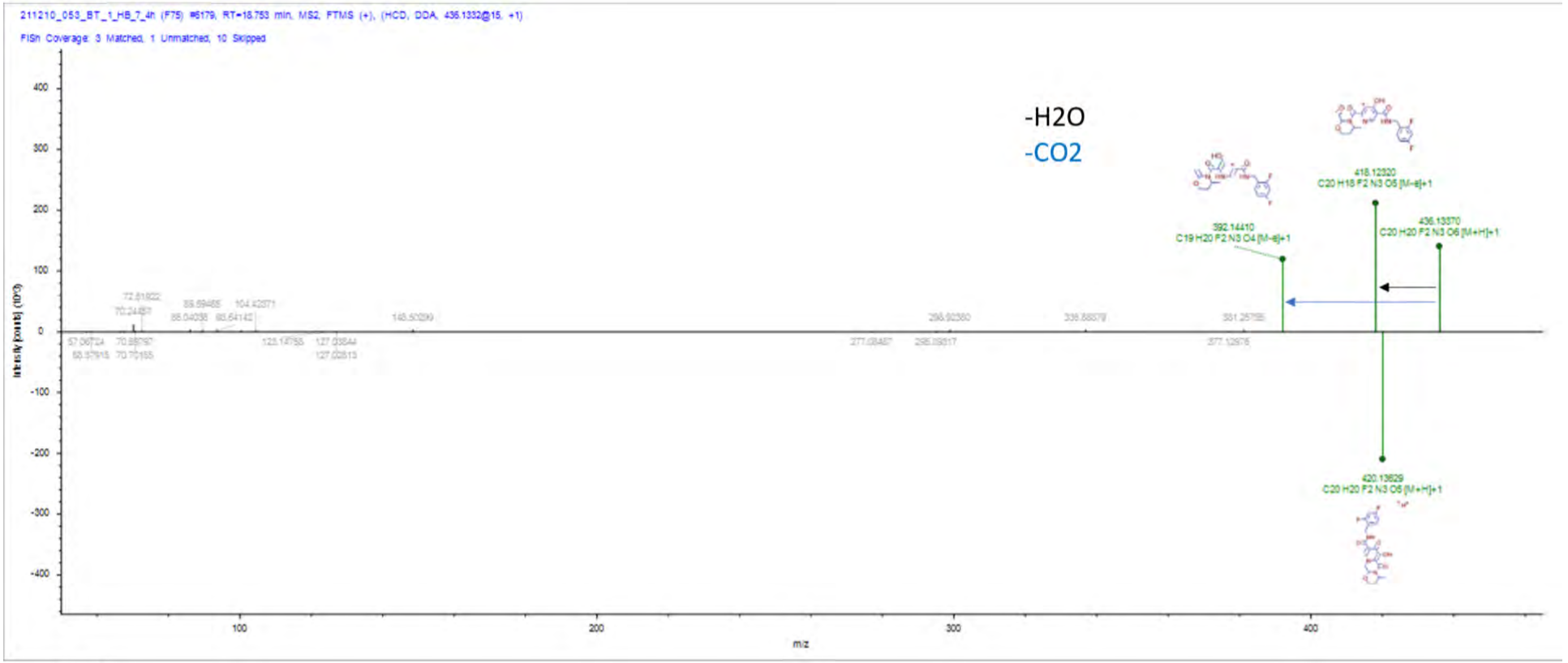
S3.10.1. Dol TP 4



Dol_TP_4
Chemical Formula: $C_{20}H_{19}F_2N_3O_6$
Exact Mass: 435.1242
Level 3

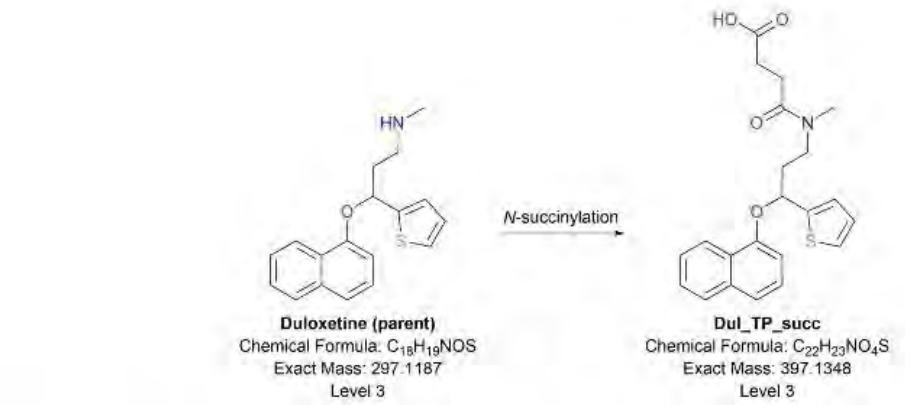
Only 3 annotations with *in silico* fragmentation tool due to low NCE, but covers all high intensity peaks. No additional information could be obtained in the remeasured scans.

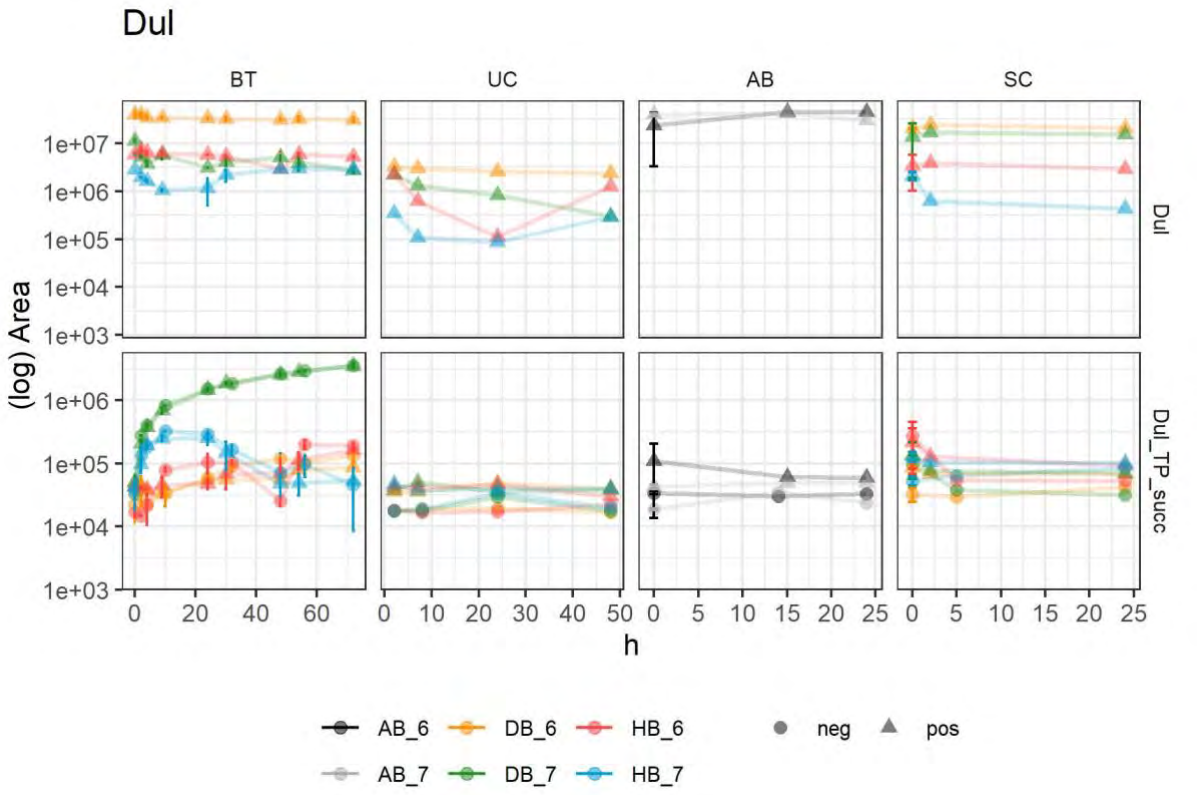
Dol_TP_4


211210_053_BT_1_HB_7_4h (F75) #6179, RT=18.753 min, MS2, FTMS (+), (HCD, DDA, 436.1332@15, +1)
FISh Coverage: 3 Matched, 1 Unmatched, 10 Skipped
-H2O
-CO2
418.12320
C20 H18 F2 N3 O5 [M-e]+1
436.13370
C20 H20 F2 N3 O6 [M+H]+1
392.14410
C19 H20 F2 N3 O4 [M-e]+1
420.13929
C20 H20 F2 N3 O5 [M+H]+1
Intensity [counts] (10^3)
m/z

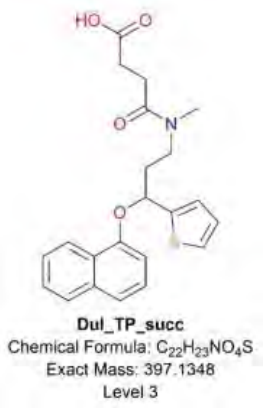
Dol

S3.11 Duloxetine



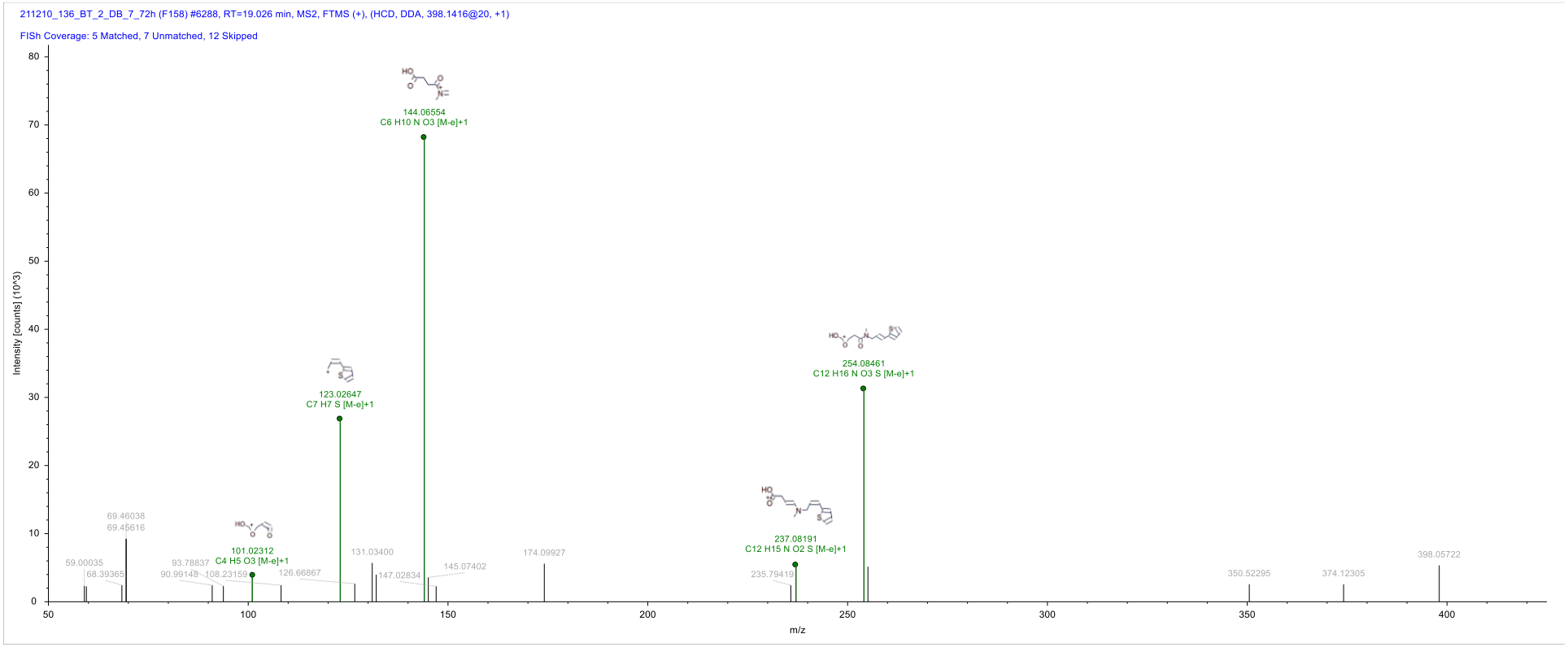


S3.11.1. Dul TP succ

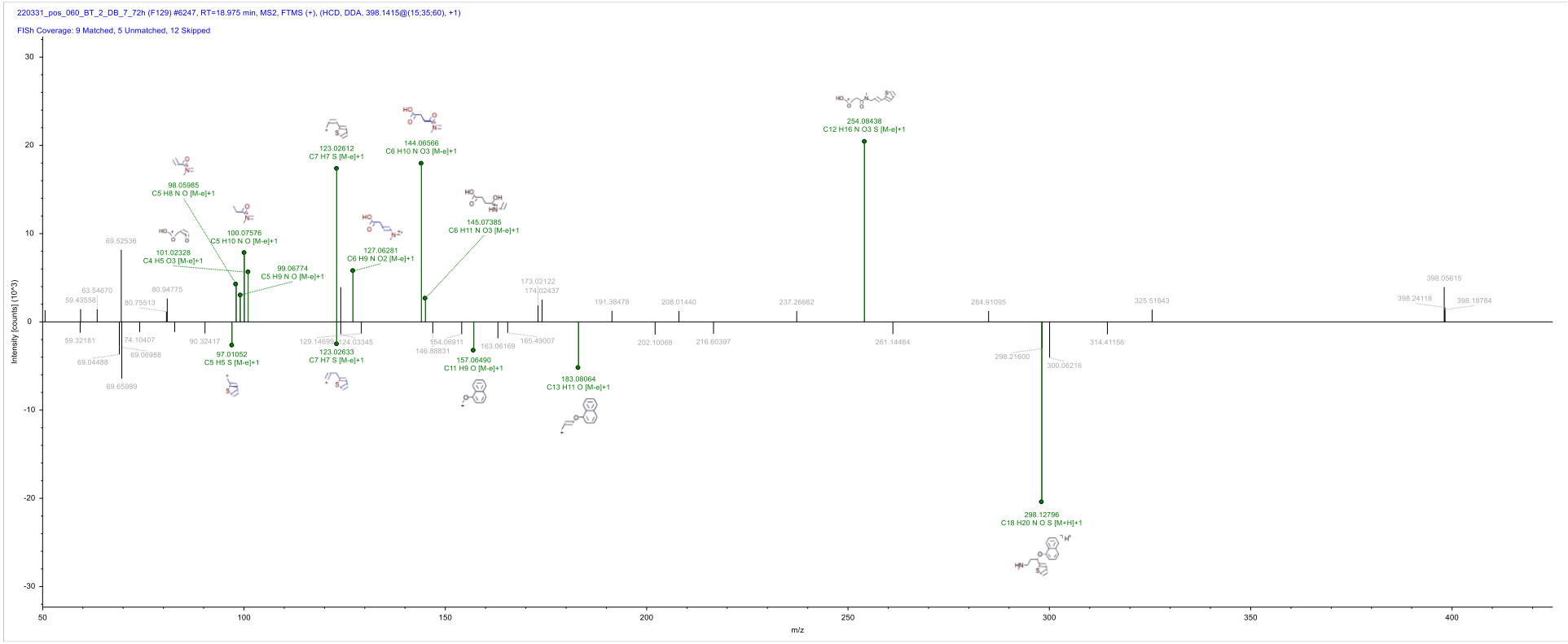


Ion with nominal mass 398 does not correspond to $[M+H]^+$ of TP. Fragment with 123 m/z was found for both TP and parent. Fragments derived from succinyl group are absent in MS^2 of parent compound.

Dul_TP_succ

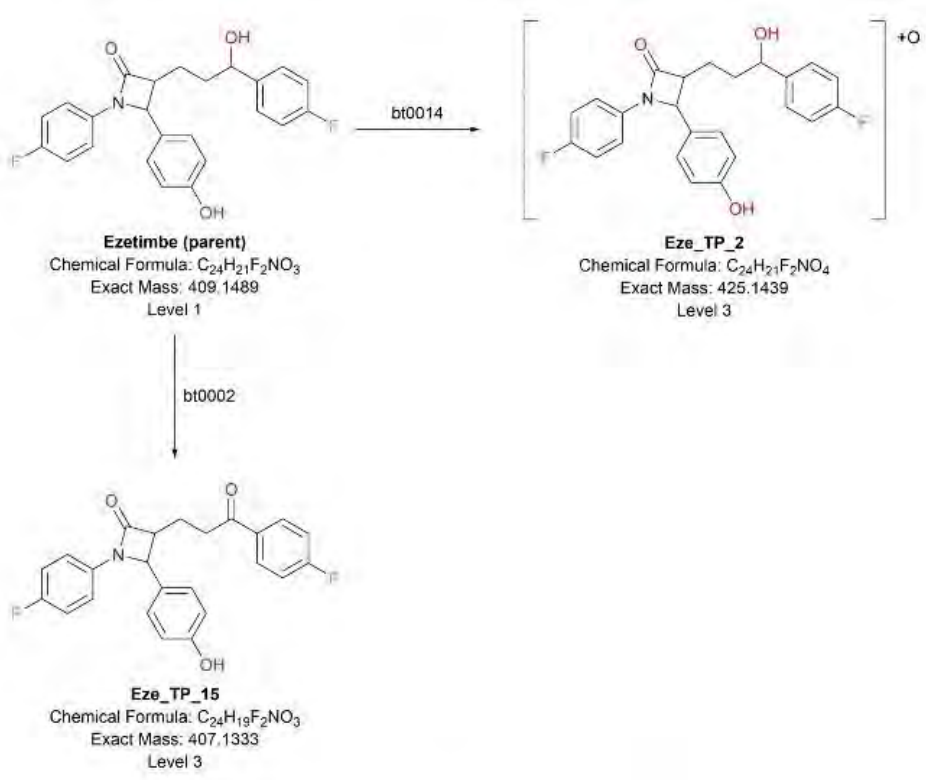

211210_136_BT_2_DB_7_72h (F158) #6288, RT=19.026 min, MS2, FTMS (+), (HCD, DDA, 398.1416@20, +1)
FISh Coverage: 5 Matched, 7 Unmatched, 12 Skipped
Intensity [counts] (10^3)
m/z
144.06554
C6 H10 N O3 [M-e]+1
123.02647
C7 H7 S [M-e]+1
101.02312
C4 H5 O3 [M-e]+1
254.08461
C12 H16 N O3 S [M-e]+1
237.08191
C12 H15 N O2 S [M-e]+1
69.46038
69.45616
59.00035
68.39365
93.78837
90.99148
108.23159
126.66867
131.03400
147.02834
145.07402
174.09927
235.79419
350.52295
374.12305
398.05722

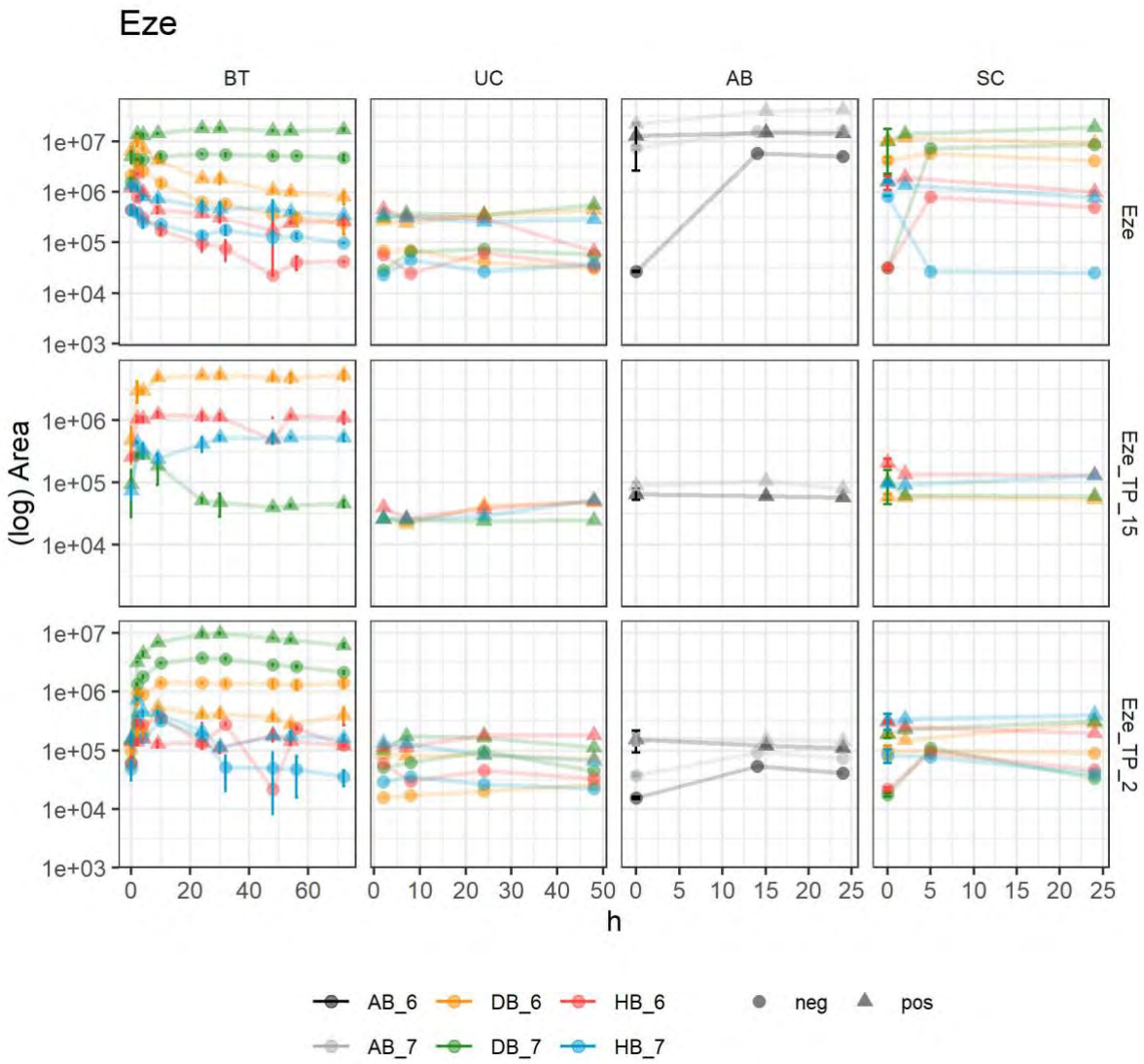
Dul_TP_succ_remeas



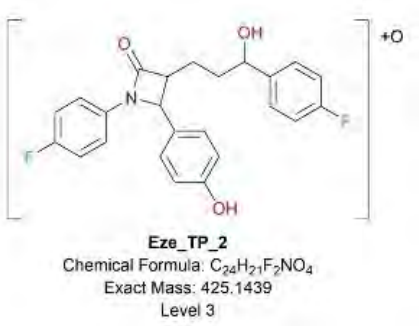
Dul_remeas

S3.12 Ezetimbe



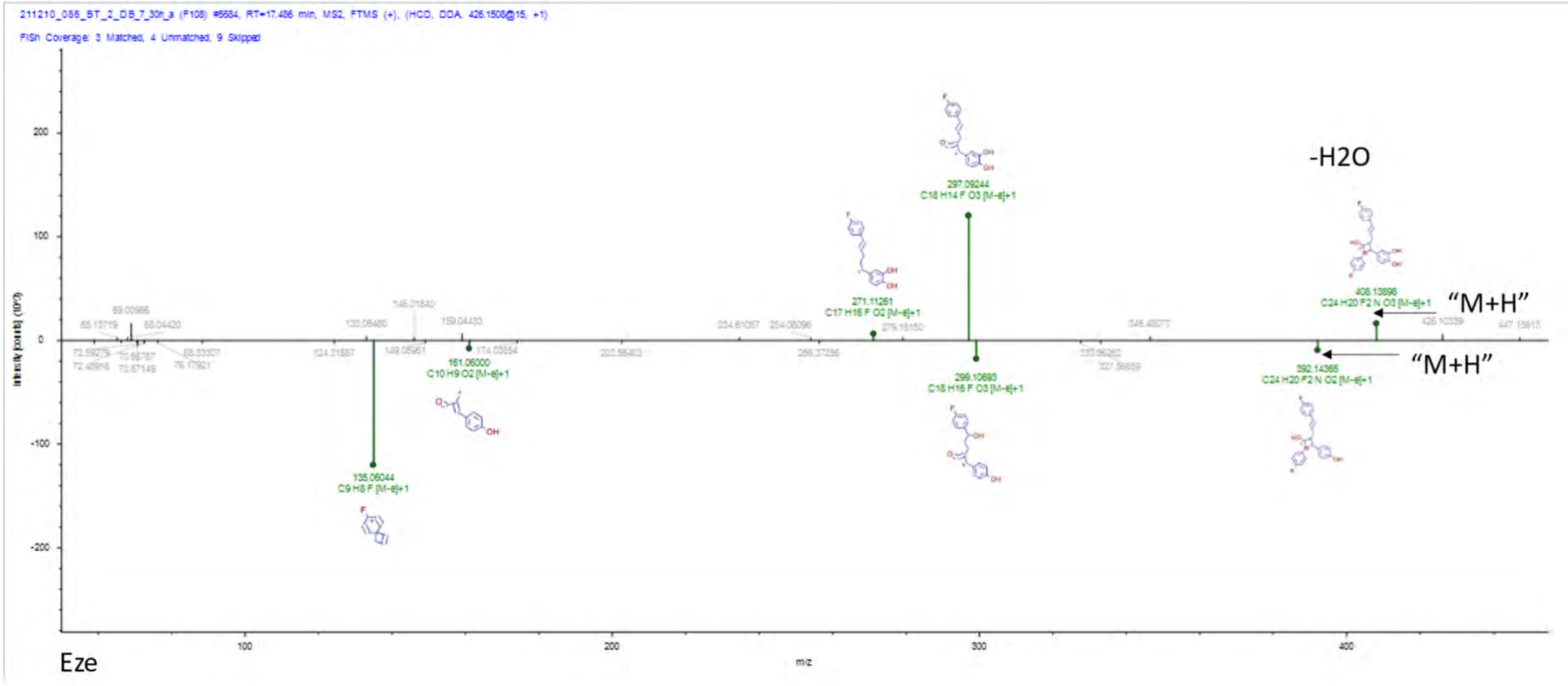

Eze
BT
UC
AB
SC
Eze
Eze_TP_15
Eze_TP_2
(log) Area
1e+07
1e+06
1e+05
1e+04
1e+03
0 20 40 60
0 10 20 30 40 50
0 5 10 15 20 25
h
AB_6
DB_6
HB_6
AB_7
DB_7
HB_7
neg
pos

S3.12.1. Eze TP 2



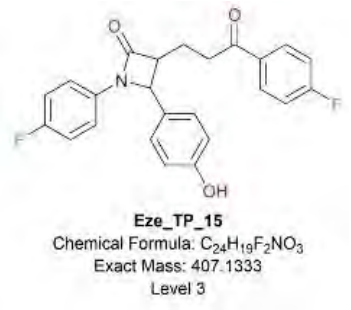
No $[M+H]^+$ ion found for neither parent nor TP. Ion with highest m/z corresponds to fragment after water loss. Comparison of ions at nominal masses 297 and 299 indicate hydroxylation in TP and parent spectra, respectively. No additional information could be obtained in the remeasured scans.

Eze_TP_2


211210_086_BT_2_DB_7_30h_a (F108) #6684, RT=17.486 min, MS2, FTMS (+), (HCD, DDA, 426.1508@15, +1)
FISh Coverage: 3 Matched, 4 Unmatched, 9 Skipped
-H2O
"M+H"
"M+H"
297.09244
C18 H14 F O3 [M-e]+1
271.11261
C17 H16 F O2 [M-e]+1
299.10693
C18 H16 F O3 [M-e]+1
161.06000
C10 H9 O2 [M-e]+1
135.06044
C9 H8 F [M-e]+1
406.13896
C24 H20 F2 N O3 [M-e]+1
392.14365
C24 H20 F2 N O2 [M-e]+1
Intensity [counts] (10^3)
m/z

Eze

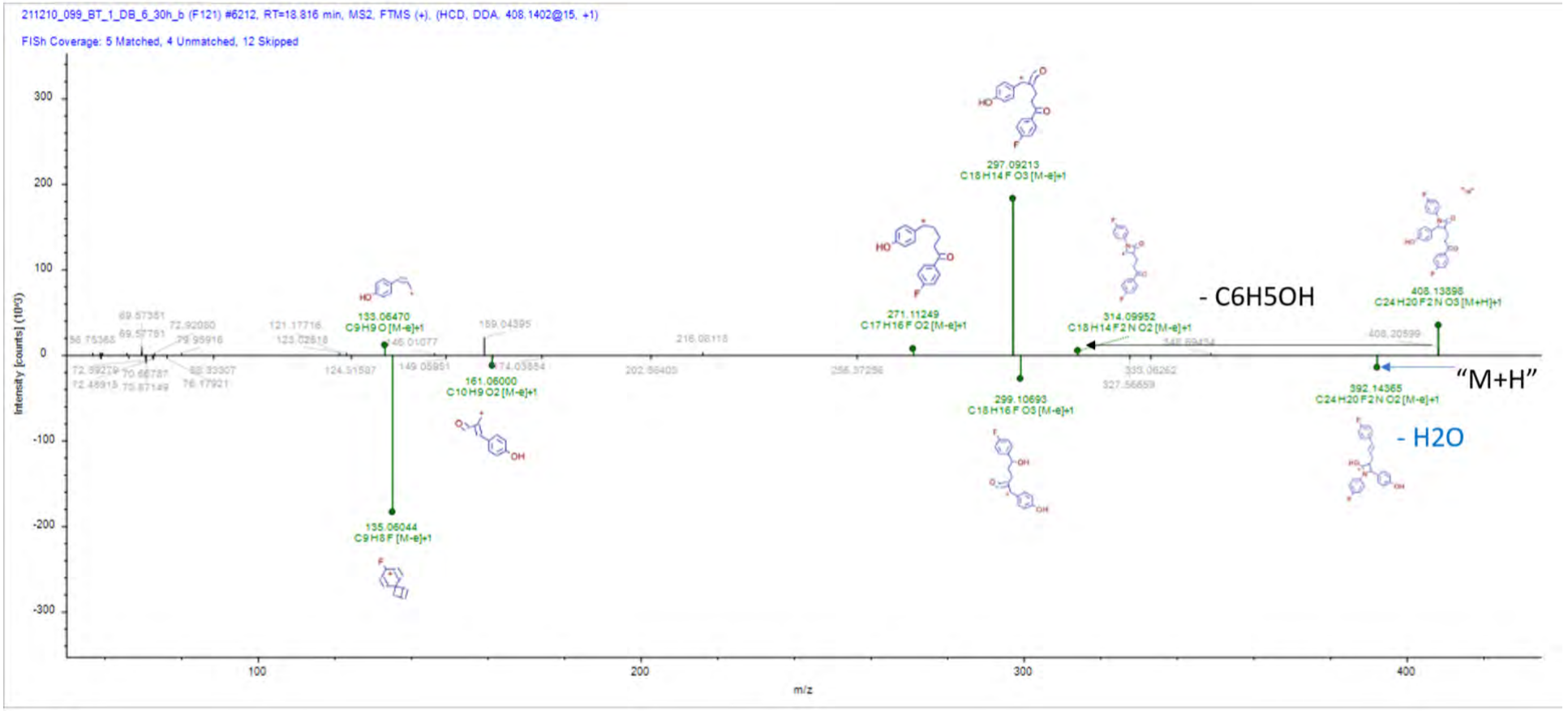
S3.12.2. Eze TP 15



Eze_TP_15
Chemical Formula: $C_{24}H_{19}F_2NO_3$
Exact Mass: 407.1333
Level 3

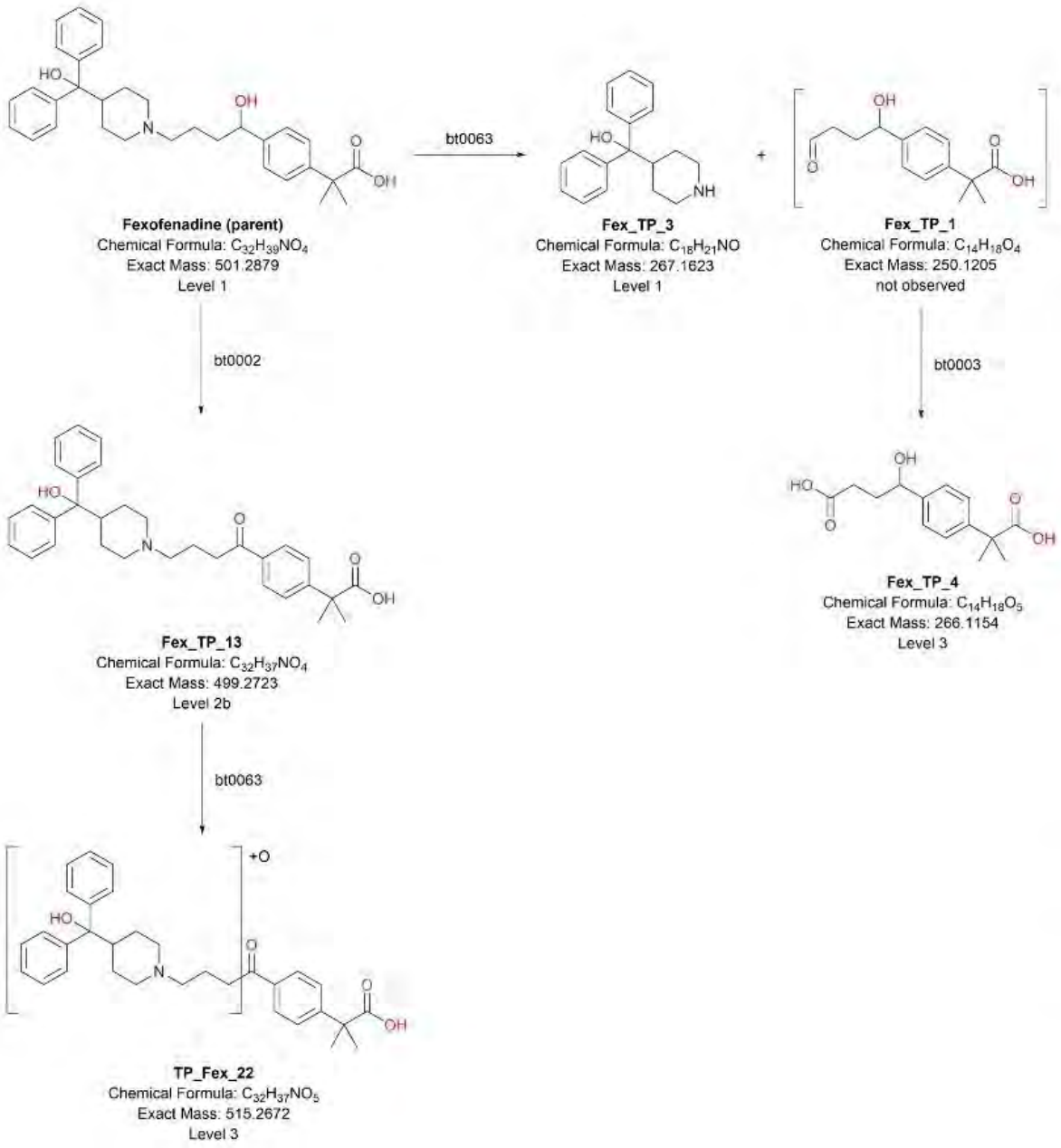
The absence of water loss in TP and comparison of nominal masses 297 and 299 (difference of H_2) indicate oxidation of hydroxyl group to ketone.

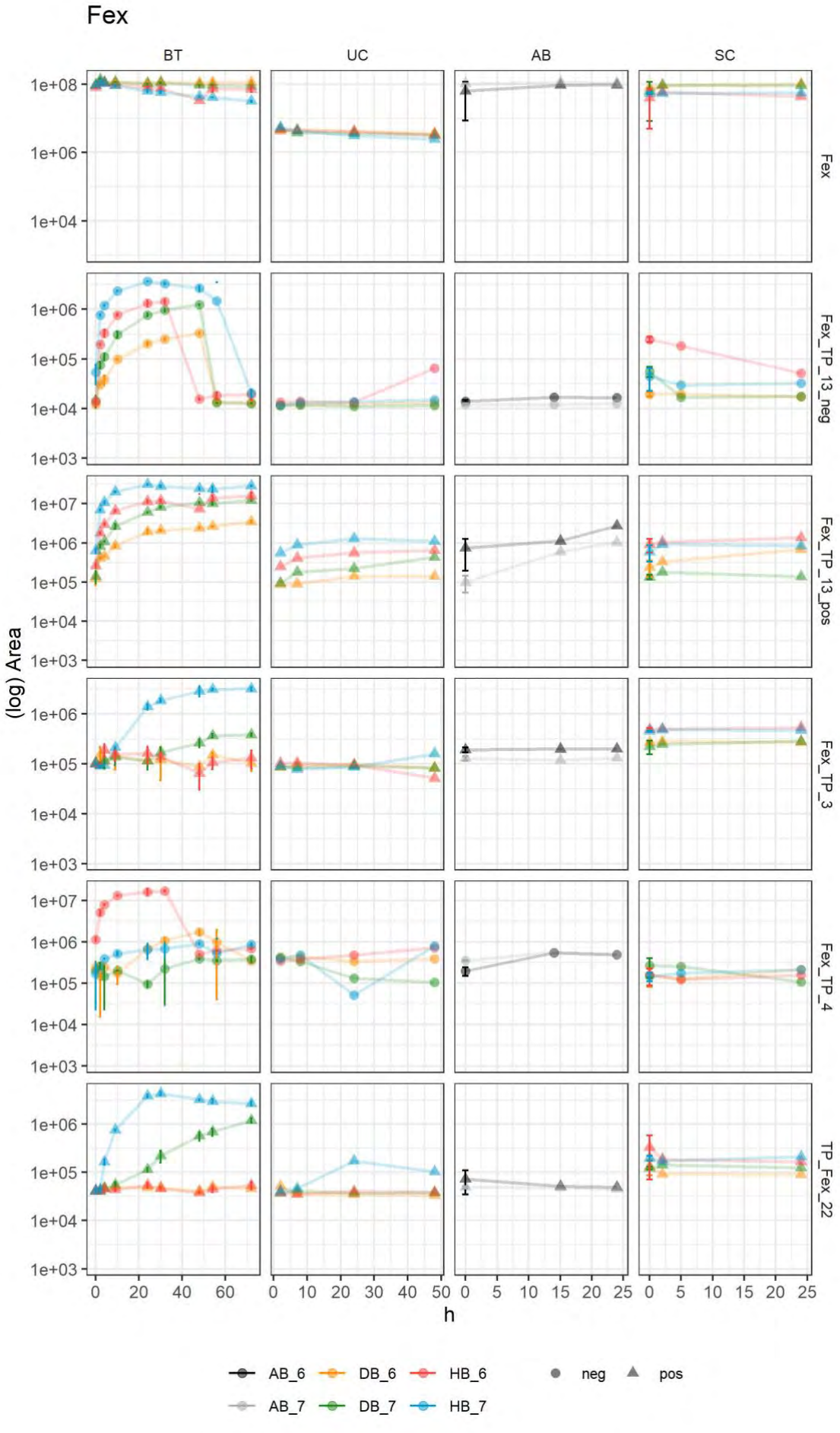
Eze_TP_15


211210_099_BT_1_DB_6_30h_b (F121) #6212, RT=18.816 min, MS2, FTMS (+), (HCD, DDA, 408.1402@15, +1)
FISh Coverage: 5 Matched, 4 Unmatched, 12 Skipped
Intensity [counts] (10^3)
m/z
133.06470
C9H9O [M-e]+1
135.06044
C9H8F [M-e]+1
161.06000
C10H9O2 [M-e]+1
271.11249
C17H16FO2 [M-e]+1
297.09213
C18H14FO3 [M-e]+1
299.10693
C18H16FO3 [M-e]+1
314.09952
C18H14F2NO2 [M-e]+1
392.14365
C24H20F2NO2 [M-e]+1
408.13896
C24H20F2NO3 [M+H]+1
- C6H5OH
- H2O
"M+H"

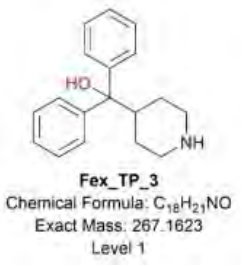
Eze

S3.13 Fexofenadine



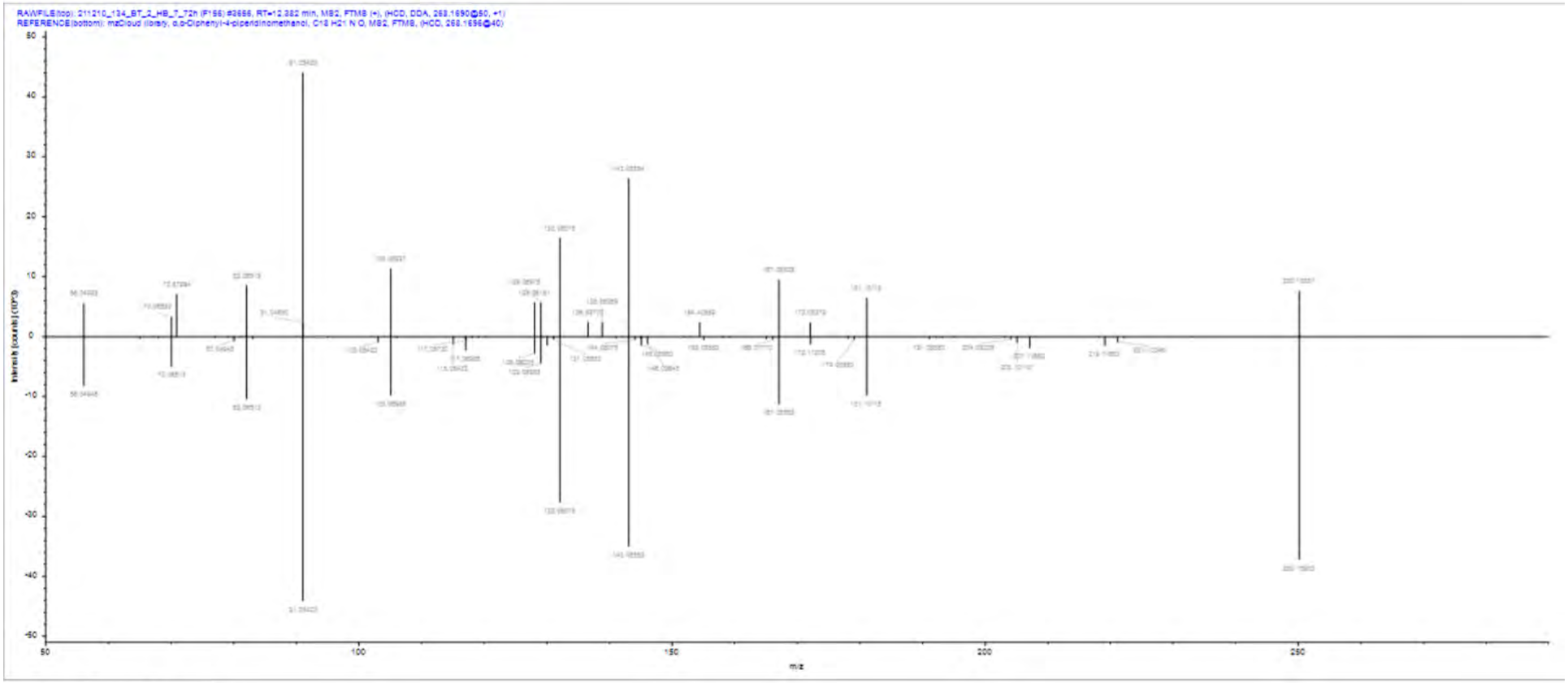

Fex
BT
UC
AB
SC
Fex
Fex_TP_13_neg
Fex_TP_13_pos
Fex_TP_3
Fex_TP_4
TP_Fex_22
(log) Area
h
AB_6
DB_6
HB_6
AB_7
DB_7
HB_7
neg
pos

S3.13.1. Fex TP 3



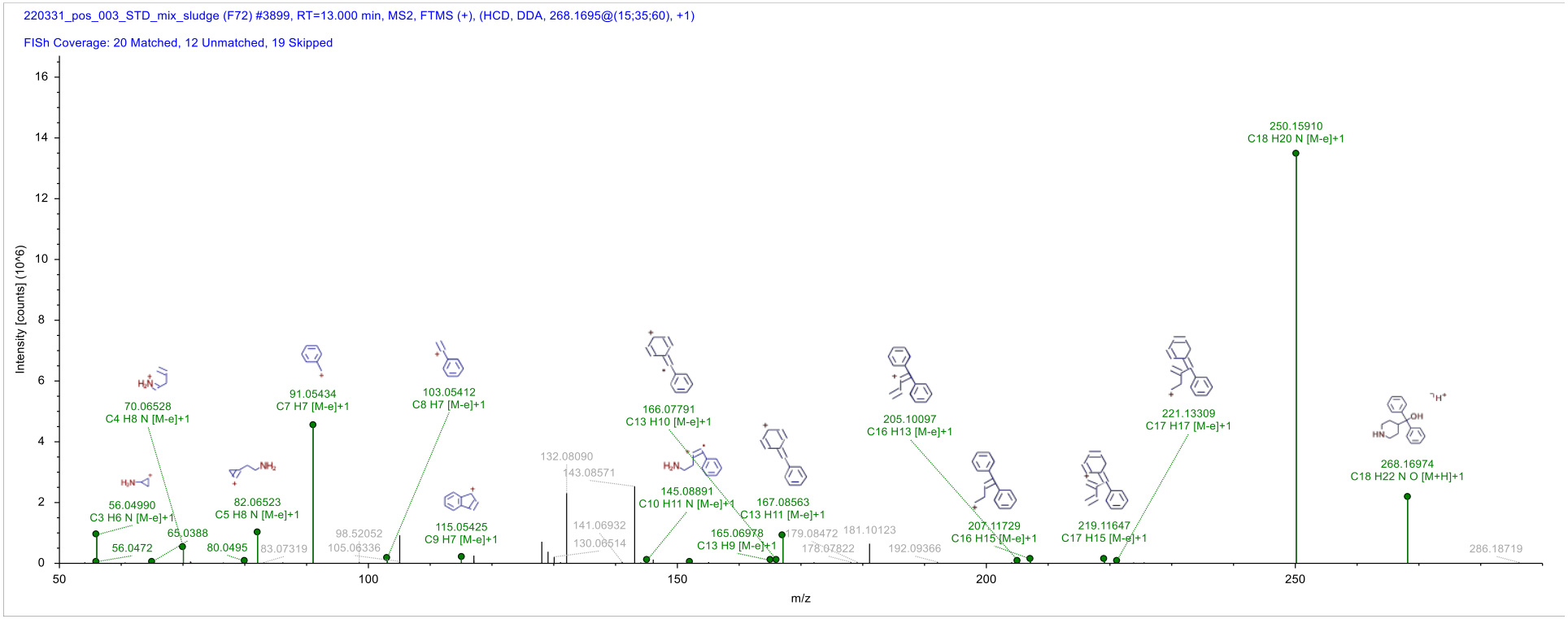
Structure of TP could be confirmed with *mzCloud* library match and with reference standard after remeasuring.

Fex_TP_3

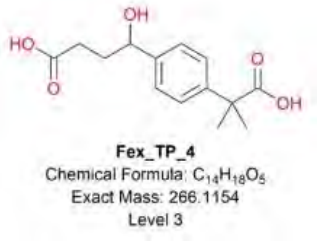


mzCloud library

Fex_TP_3_remeas_ref_std

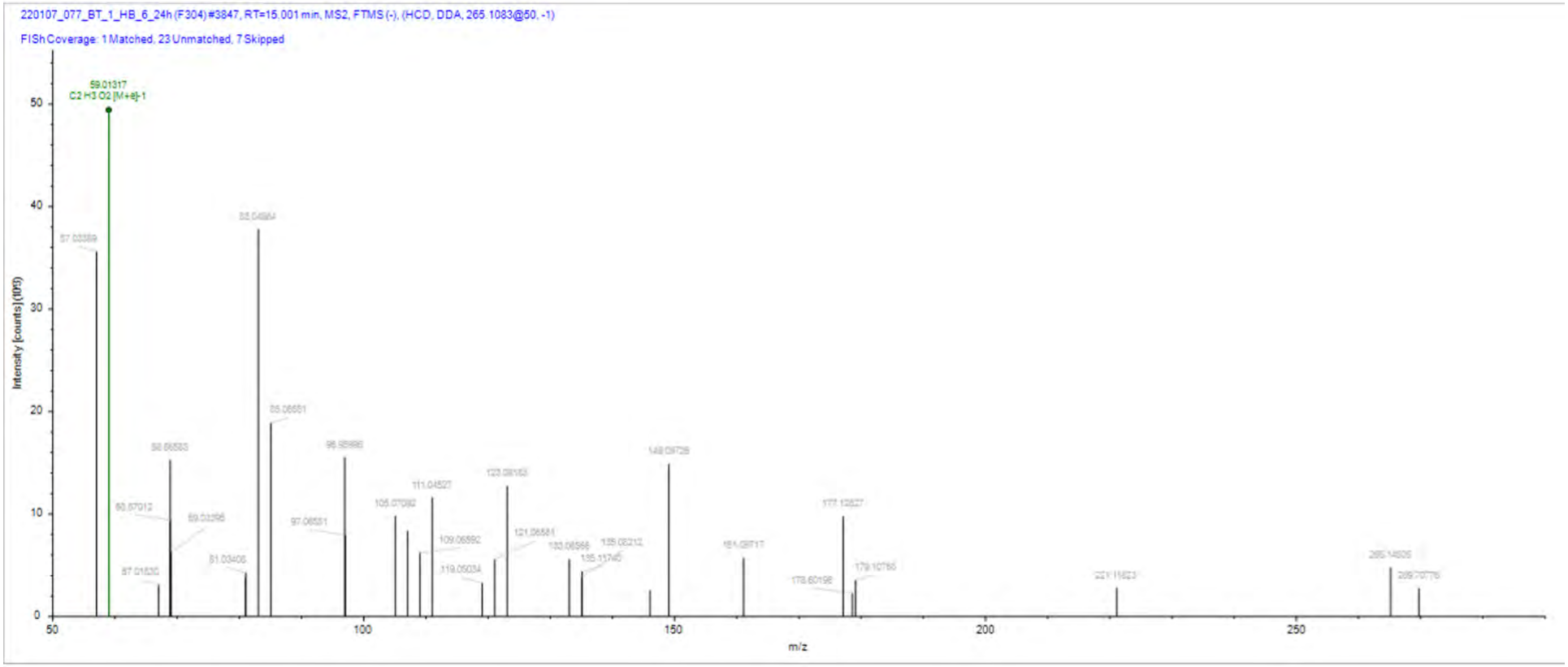


S3.13.2. Fex TP 4

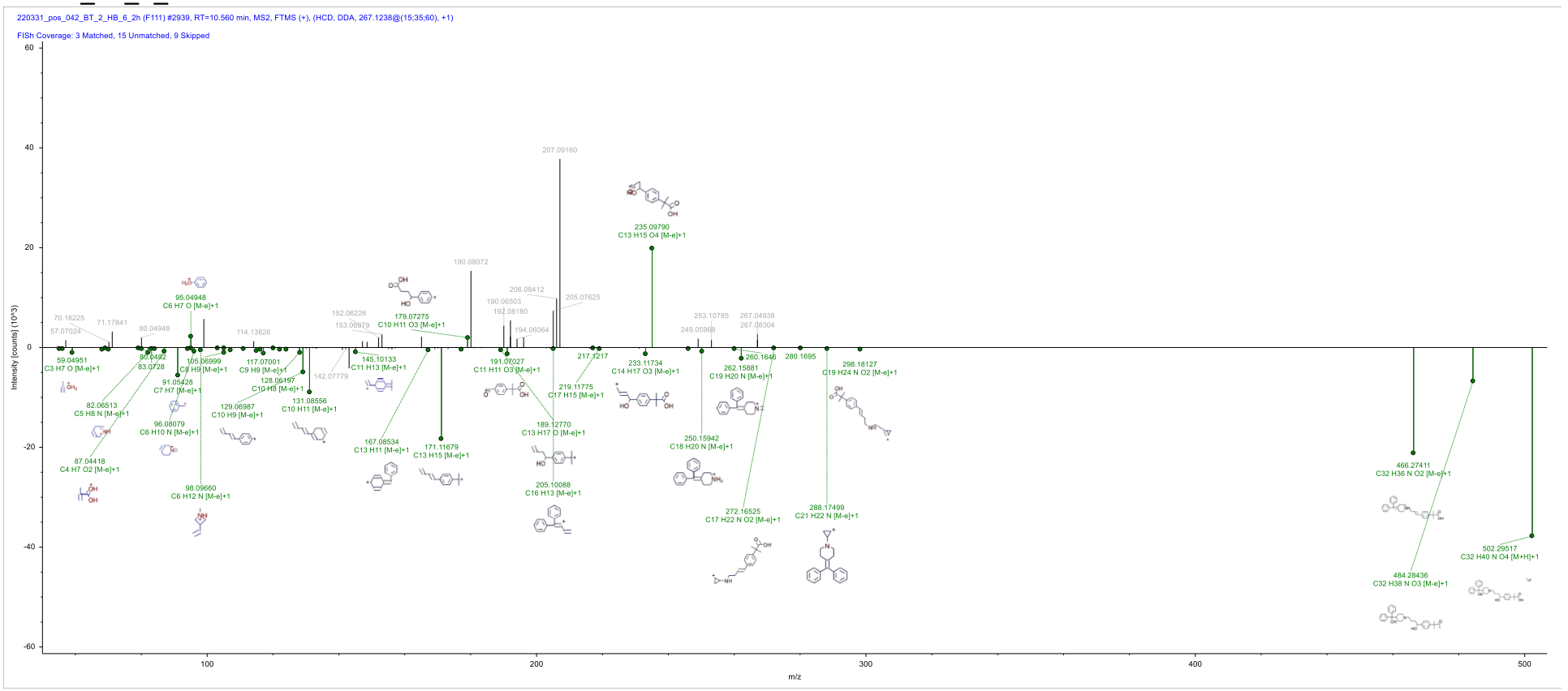


Ions with nominal masses 55, 79, 133, 153 were observed in both parental and TP positive MS^2 spectra. $[M-H]^-$ ion and CO_2 loss indicate carboxylic acid.

Fex_TP_4

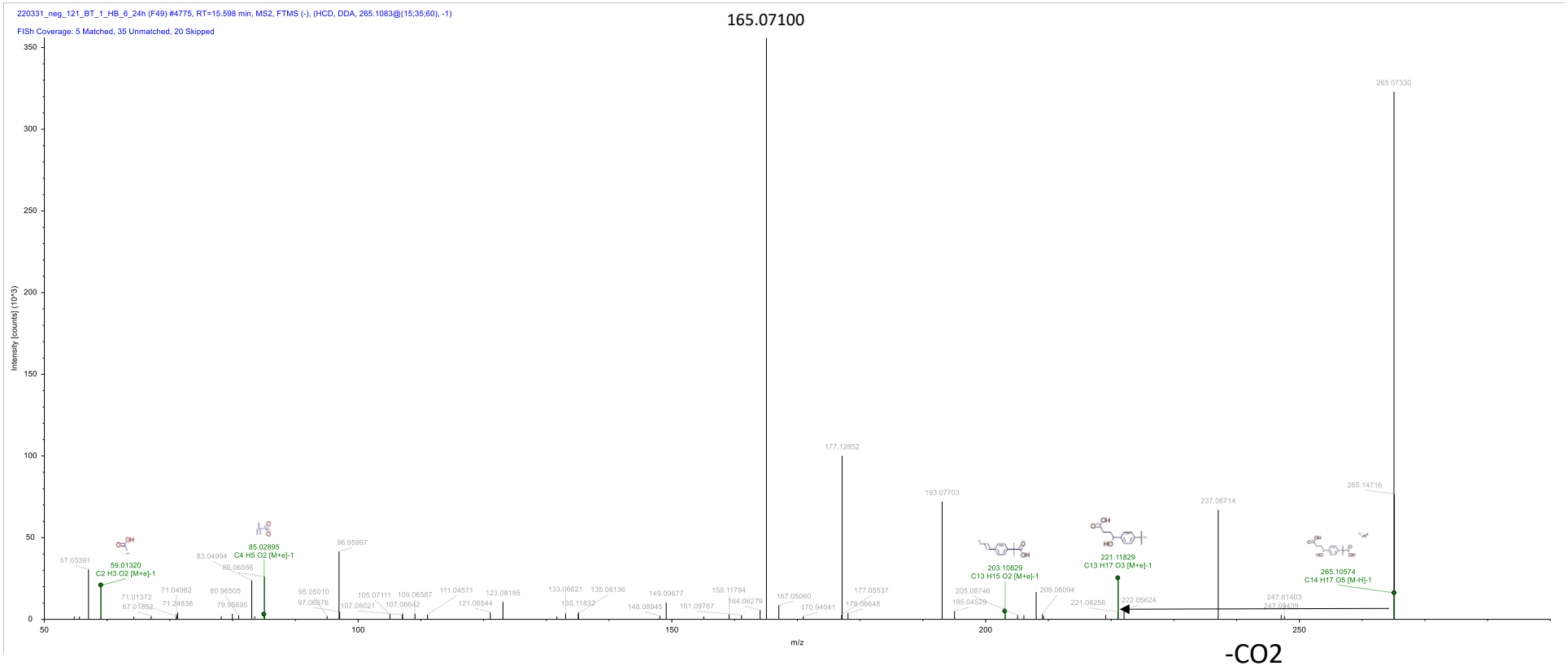

220107_077_BT_1_HB_6_24h (F304) #3847, RT=15.001 min, MS2, FTMS (-), (HCD, DDA, 265.1083@50, -1)
FISh Coverage: 1 Matched, 23 Unmatched, 7 Skipped
59.01317
C2 H3 O2 [M+e]-1
Intensity [counts] (105)
m/z

Fex_TP_4_remeas

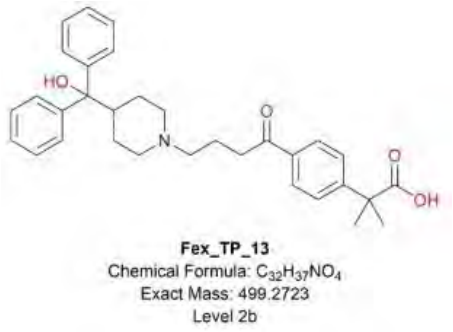


Fex_remeas

Fex_TP_4_remeas



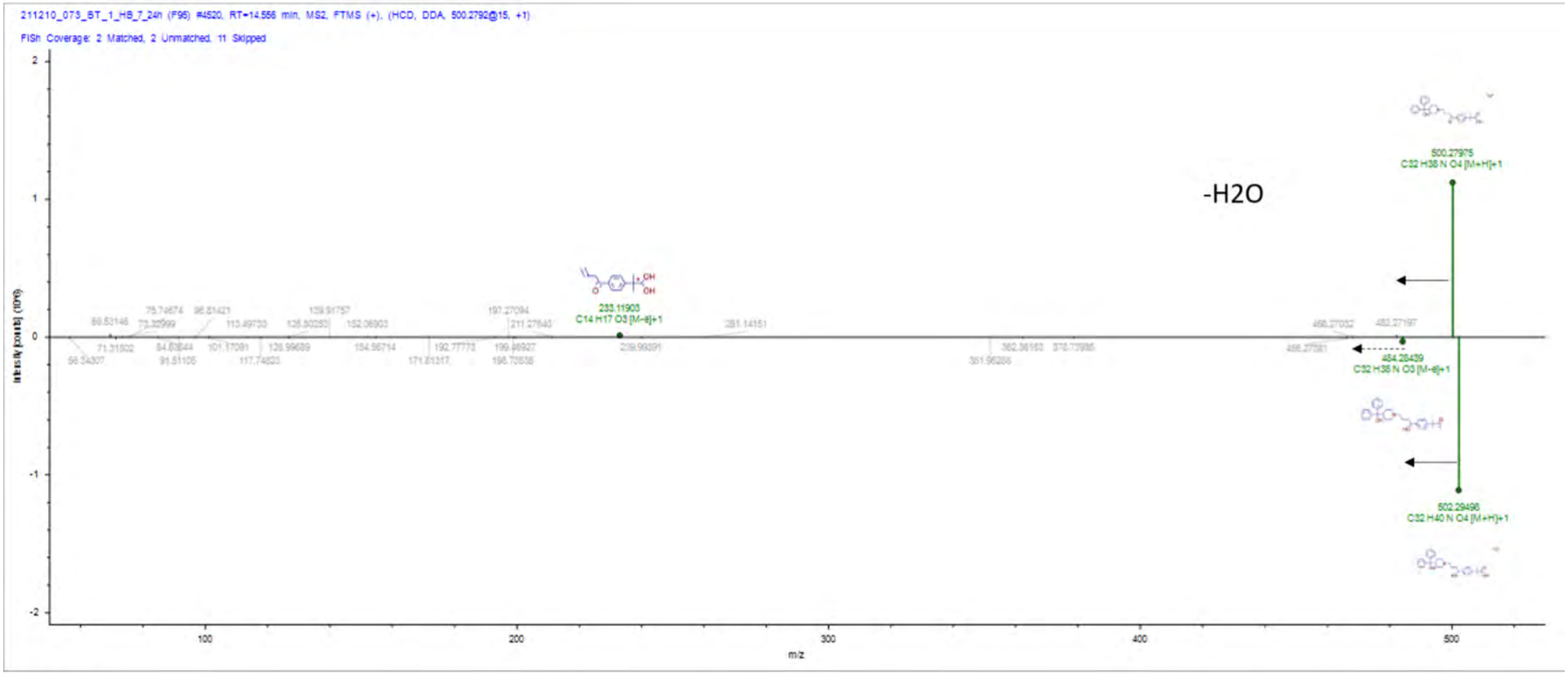
S3.13.3. Fex TP 13



Fex_TP_13
Chemical Formula: $C_{32}H_{37}NO_4$
Exact Mass: 499.2723
Level 2b

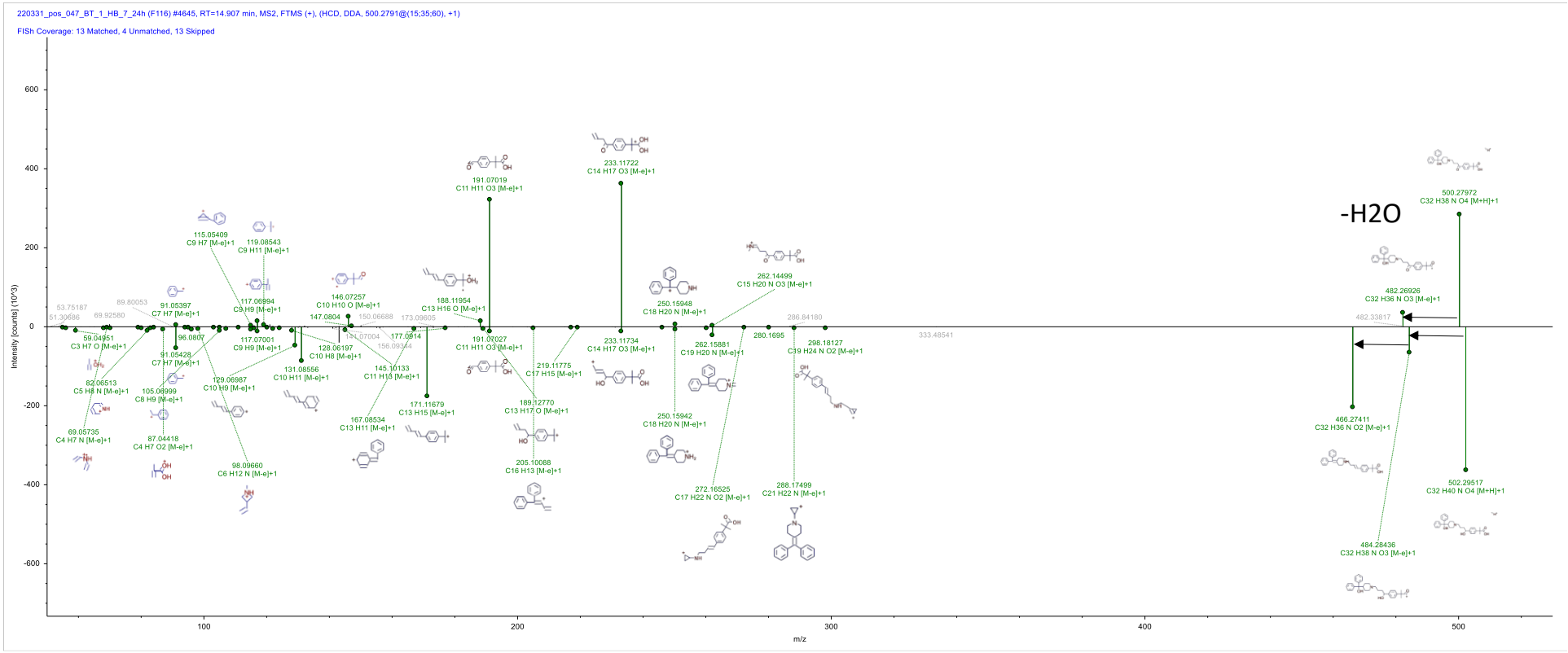
Both parent and TP show loss of water. Absence of second water loss for TP could suggests the oxidation of secondary alcohol. Fragments with nominal masses 82, 91, 111, 115, 117, 143, 191, 233 and 250 were observed for parent as well as TP. Especially, ions at 233 and 250 m/z confirm substructure and by their fragmentation support the oxidation of secondary alcohol. $[M-H]^-$ ion for TP and CO_2 loss in MS^1 were identified, which supports carboxylic acid group.

Fex_TP_13


211210_073_ST_1_HB_7_24h (F96) #4520, RT=14.556 min, MS2, FTMS (+), (HCD, DDA, 500.2792@15, +1)
FISh Coverage: 2 Matched, 2 Unmatched, 11 Skipped
Intensity [10^6]
m/z
-H2O
500.27975
C32 H38 N O4 [M+H]+1
233.11903
C14 H17 O3 [M-e]+1
484.28439
C32 H38 N O3 [M-e]+1
502.29496
C32 H40 N O4 [M+H]+1

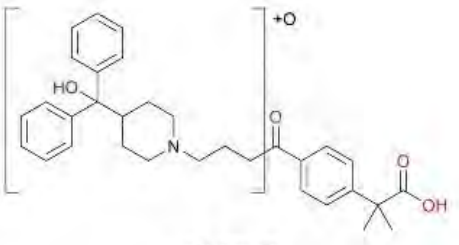
Fex

Fex_TP_13_remeas



Fex_remeas

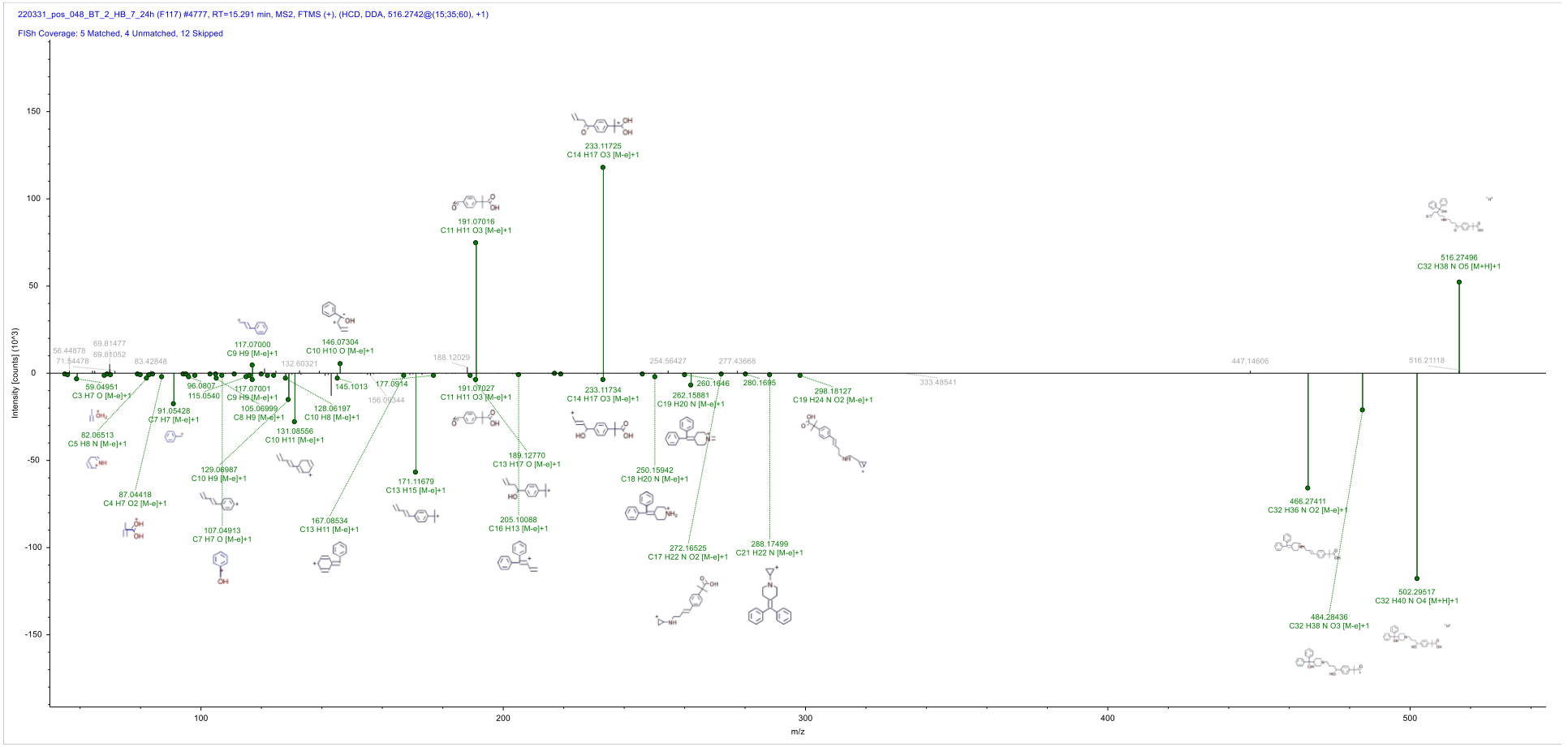
S3.13.4. TP Fex 22



TP_Fex_22
Chemical Formula: $C_{32}H_{37}NO_5$
Exact Mass: 515.2672
Level 3

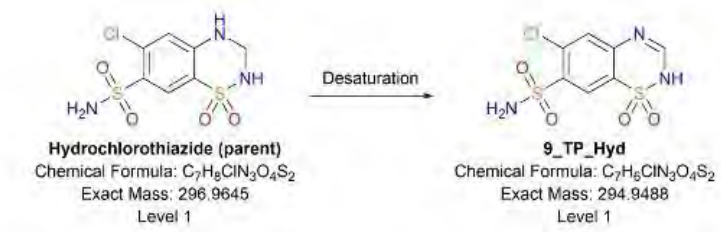
Fragment ions with nominal mass 117, 191 and 233 were also observed for parent compound. Hydroxylation could also have occurred to tertiary amine, leading either to another ring opening or stable hemiaminal. *N*-oxidation would also be possible.

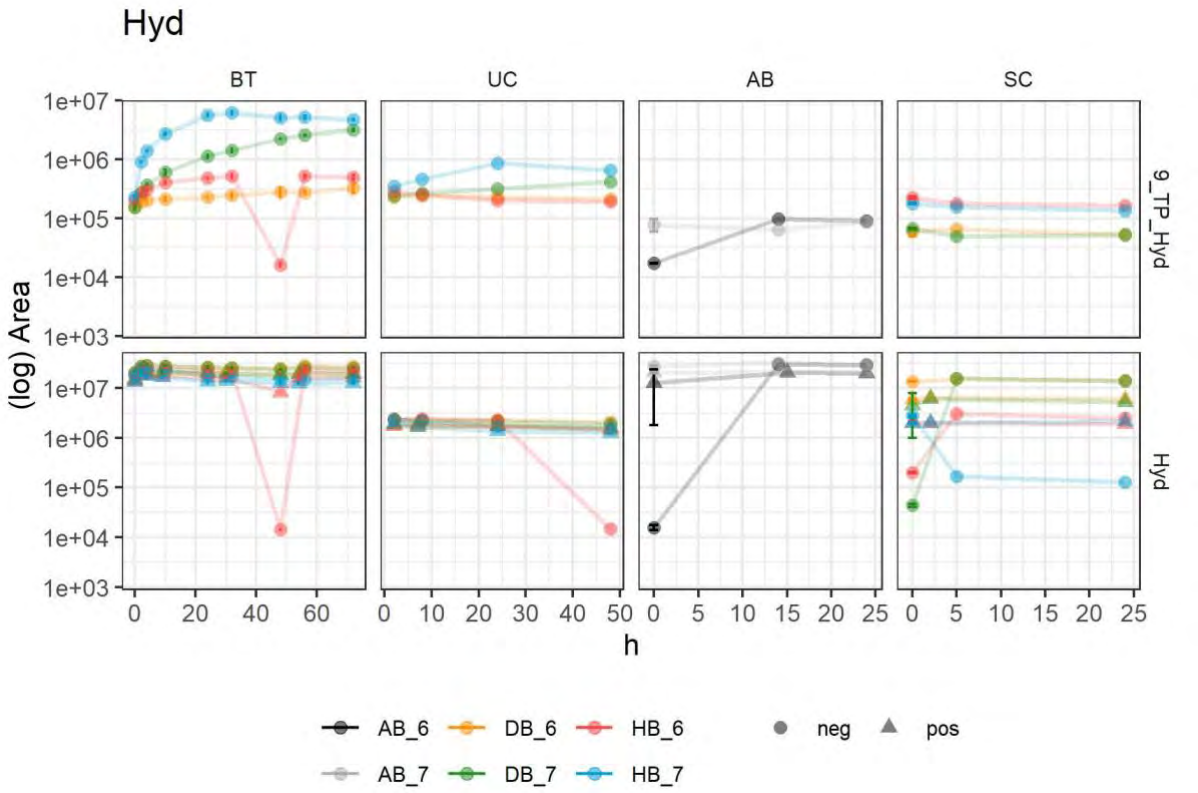
Fex_TP_22_remeas



Fex_remeas

S3.14 Hydrochlorothiazide

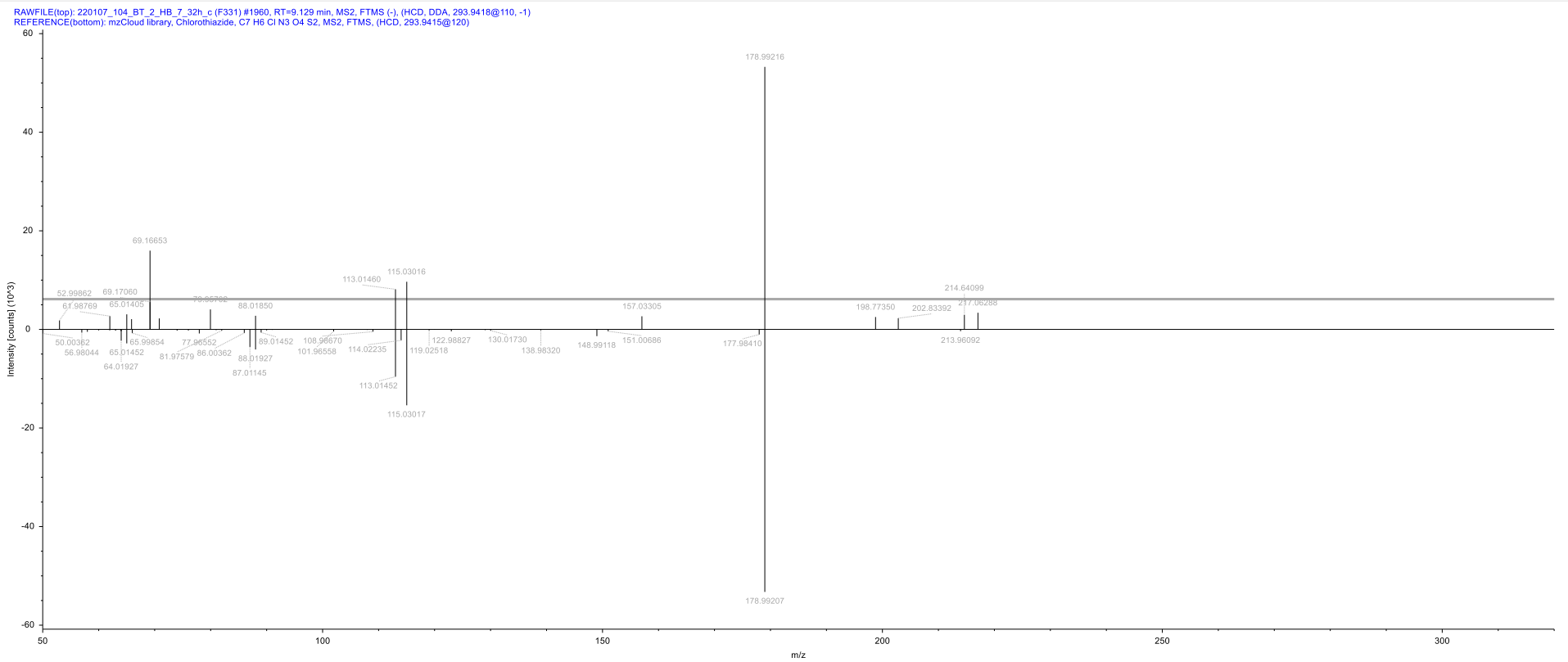




S3.14.1. 9 TP Hyd

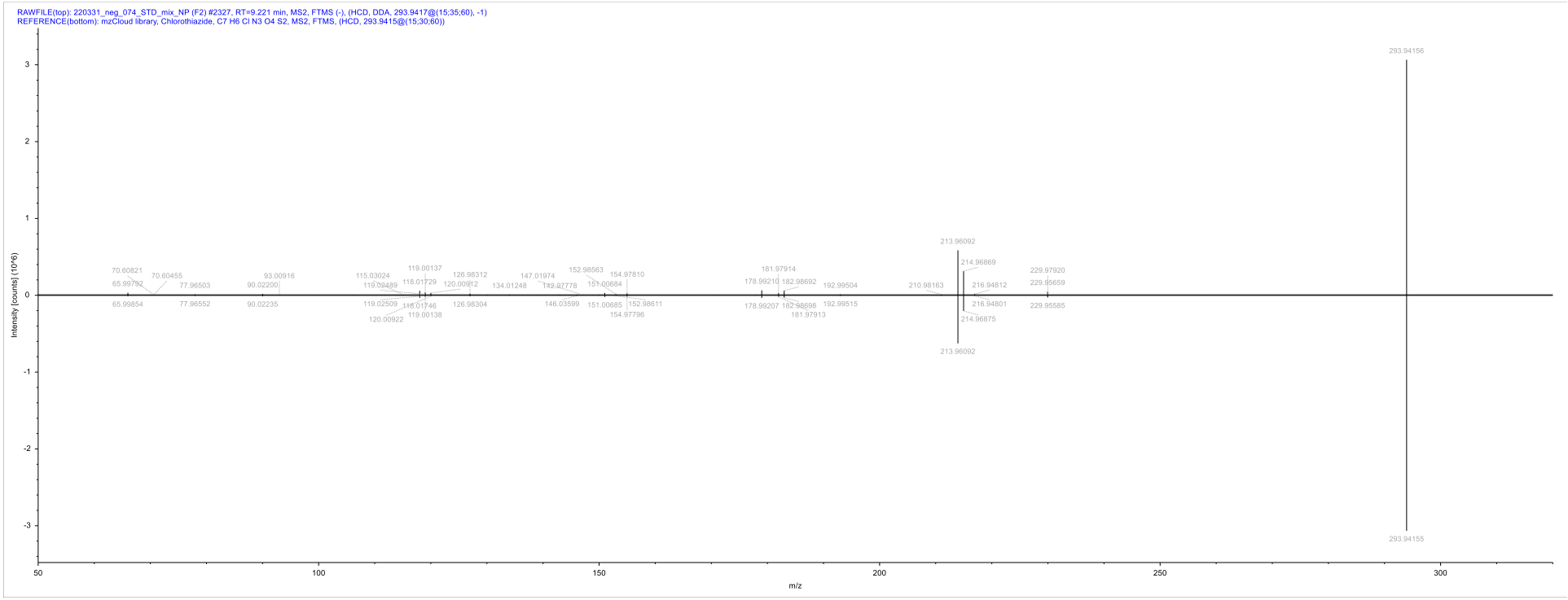
This TP was confirmed by a full *mzCloud* spectrum library match and by reference standard. This TP was not predicted by any prediction method.

9_TP_Hyd



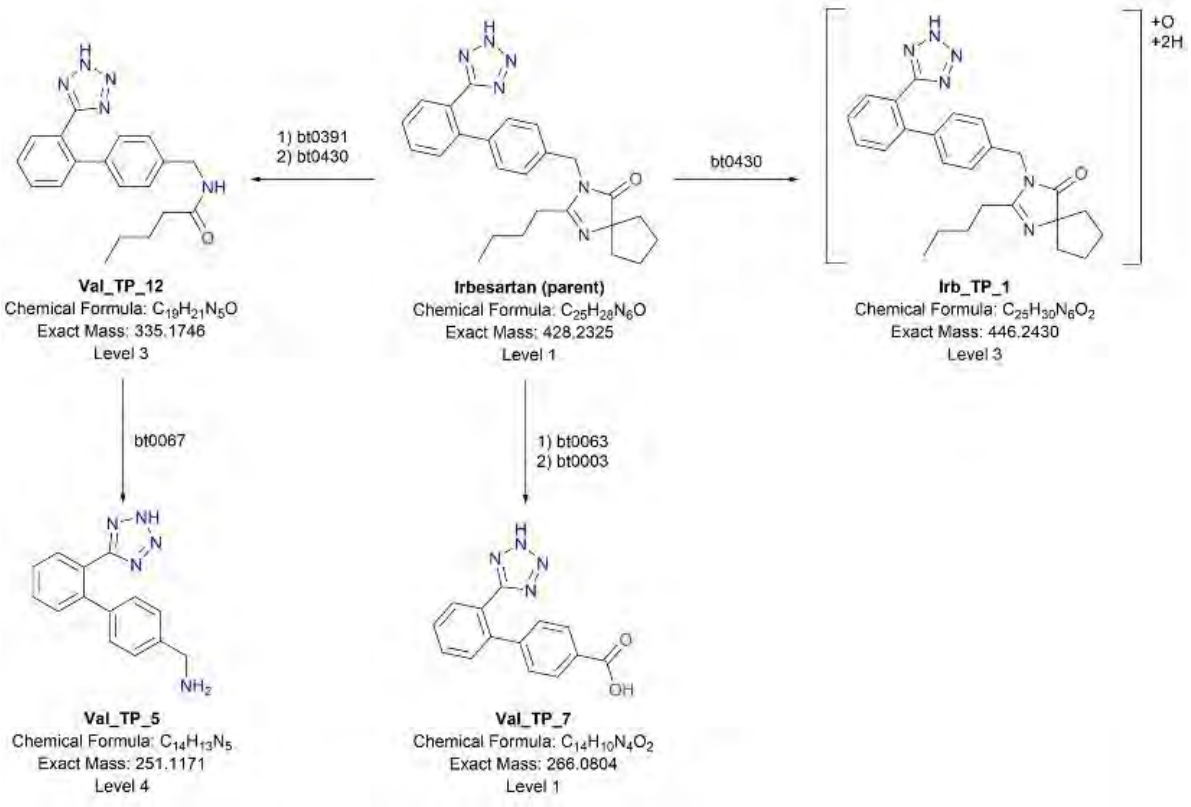
mzCloud

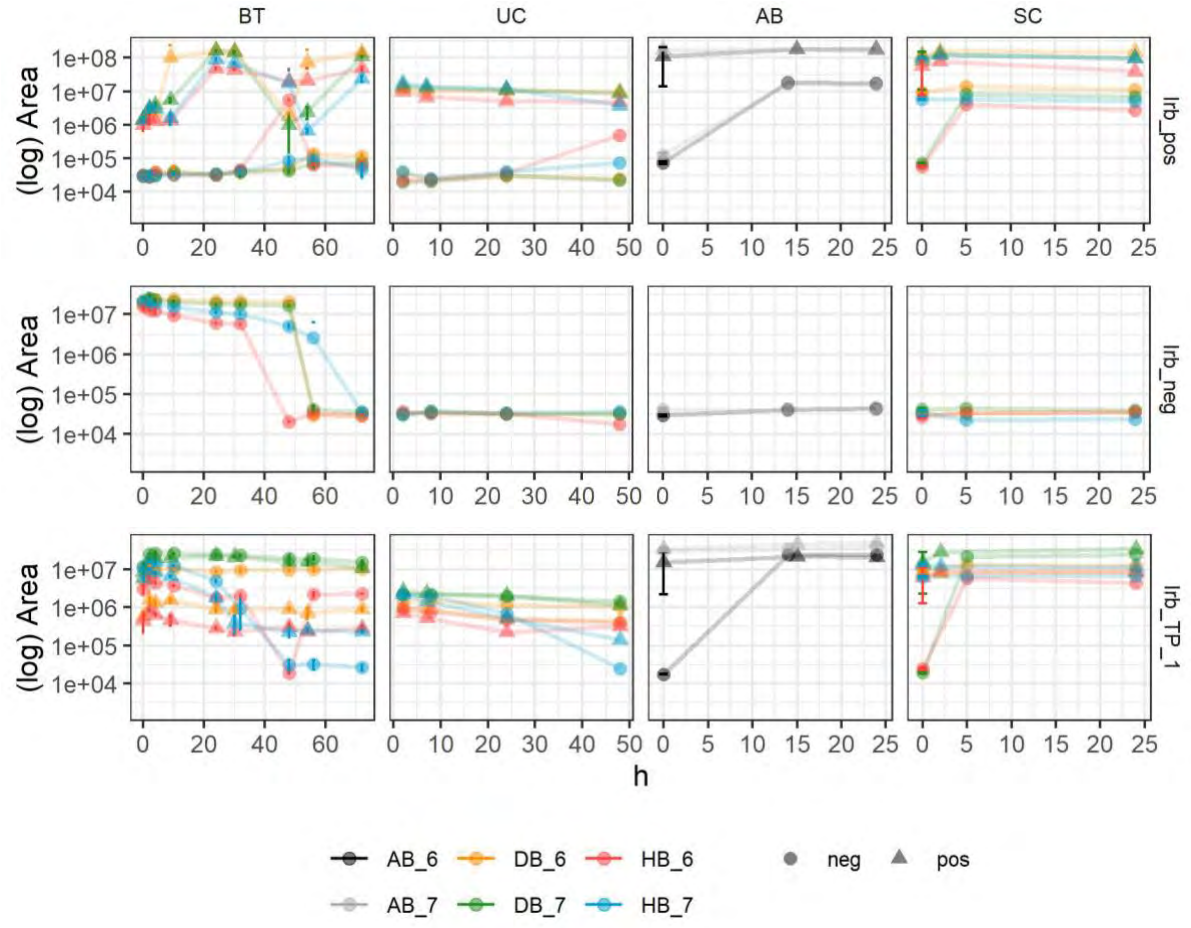
9_TP_Hyd_remeas_ref_standard



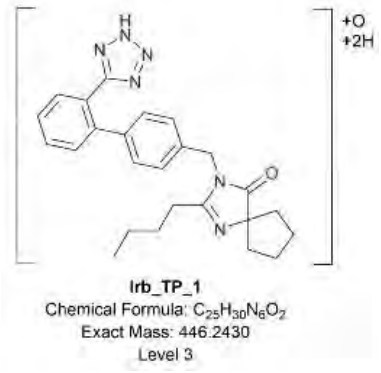
mzCloud

S3.15 Irbesartan



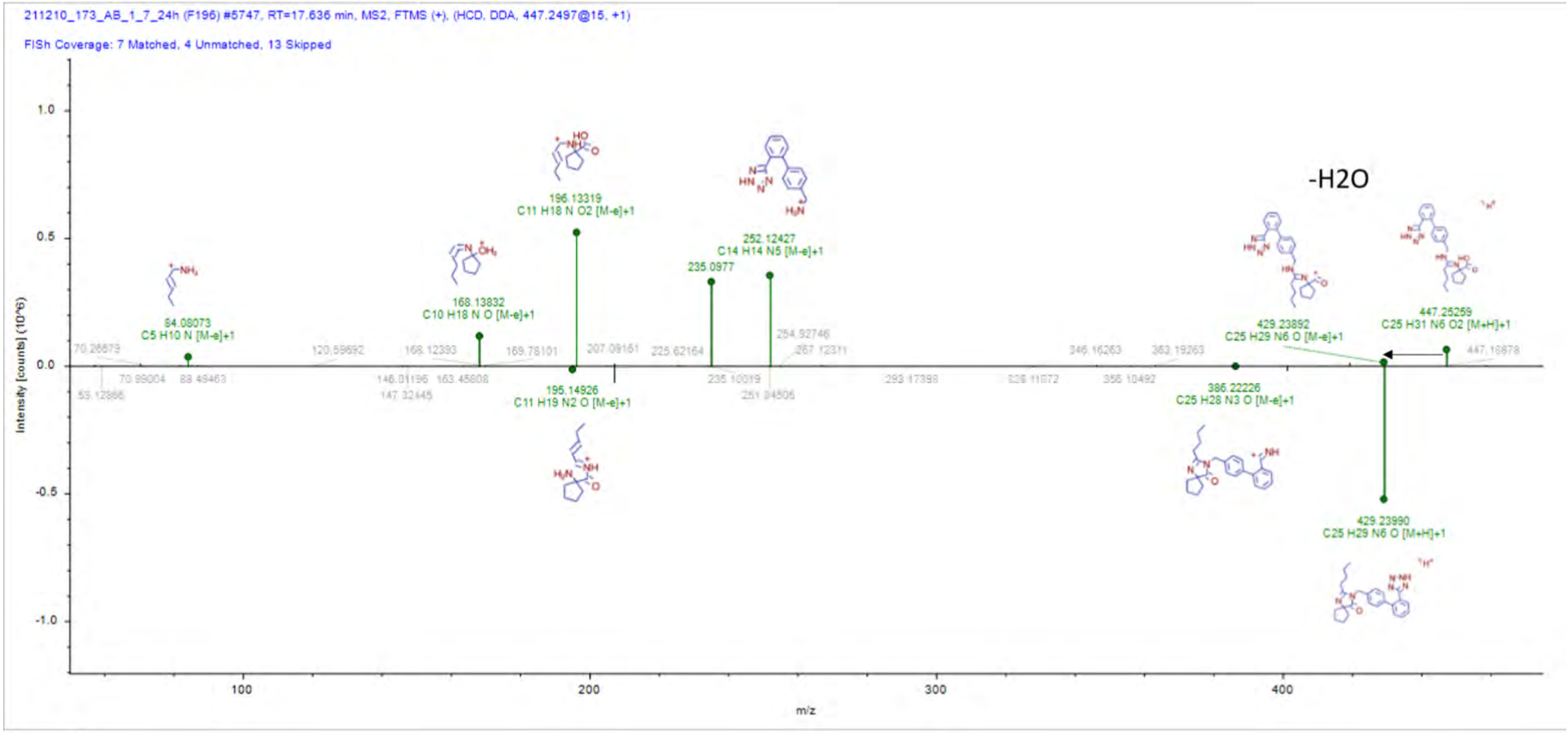


S3.15.1. Irb TP 1



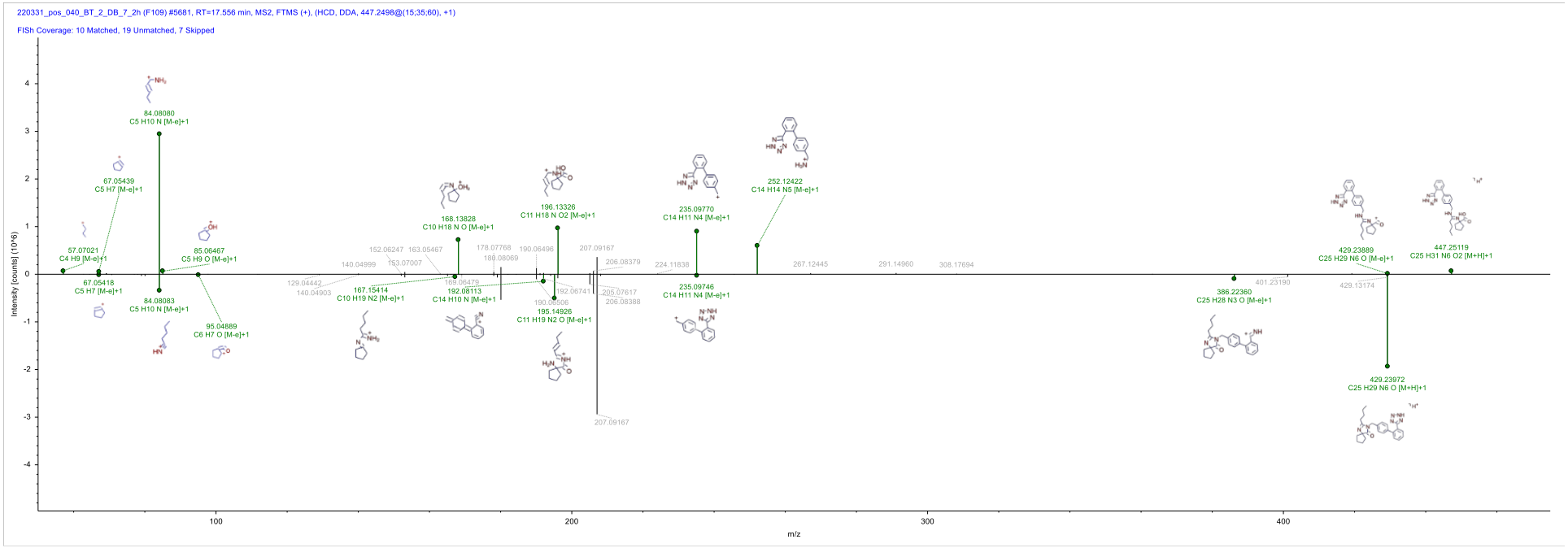
Water loss of $[M+H]^+$ ion in TP spectrum therefor – without considering electrons – has same mass as parent compound and supports hydrolysis of lactam. $[M-H]^-$ ion could not be identified, which could indicate carboxylate function. Ion with nominal mass 235 in mass spectrum of the TP corresponds to fragment after benzyl cleavage and was detected for both compounds. This TP was also found in the abiotic control and may therefore also be an abiotic reaction in lower pH range. The hydrolysis of lactam reliefs strain from 5-membered *spiro* ring system, which supports spontaneous reaction. Nevertheless, the chromatogram intensity was higher in biotransformation samples. Val TP 5, 7 and 12 were also counted as detected TPs for this parent, but data is found in valsartan section.

Irb_TP_1


211210_173_AB_1_7_24h (F196) #5747, RT=17.636 min, MS2, FTMS (+), (HCD, DDA, 447.2497@15, +1)
FISh Coverage: 7 Matched, 4 Unmatched, 13 Skipped
Intensity [counts] (10^6)
m/z
-H2O
84.08073
C5 H10 N [M-e]+1
168.13832
C10 H18 N O [M-e]+1
196.13319
C11 H18 N O2 [M-e]+1
195.14926
C11 H19 N2 O [M-e]+1
235.0977
252.12427
C14 H14 N5 [M-e]+1
429.23892
C25 H29 N6 O [M-e]+1
447.25259
C25 H31 N6 O2 [M+H]+1
386.22226
C25 H28 N3 O [M-e]+1
429.23990
C25 H29 N6 O [M+H]+1

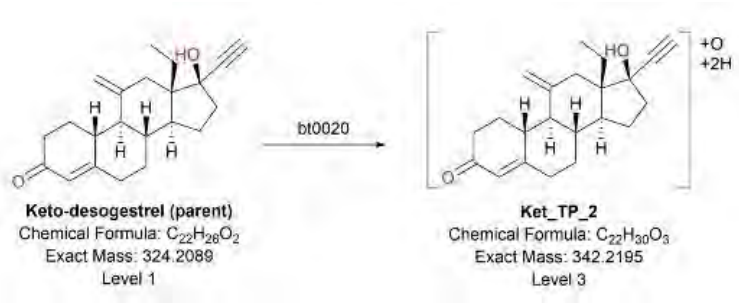
Irb

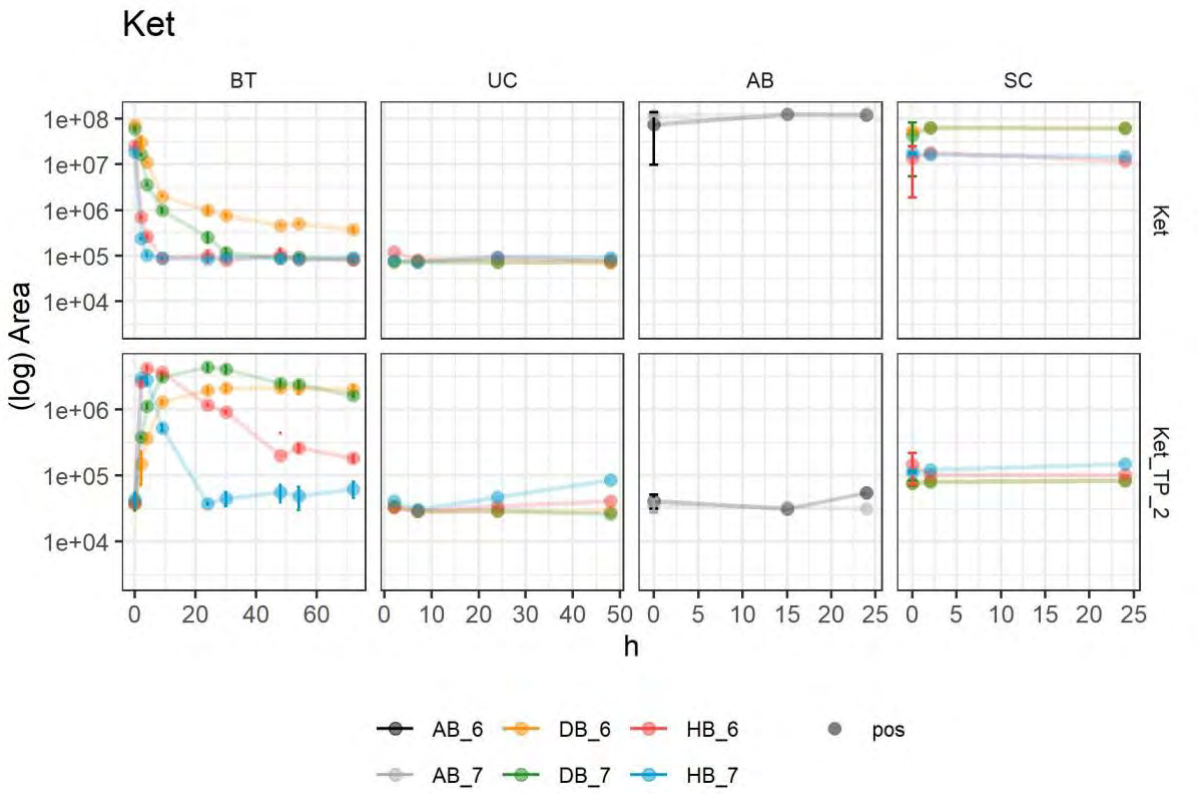
Irb_TP_1_remeas



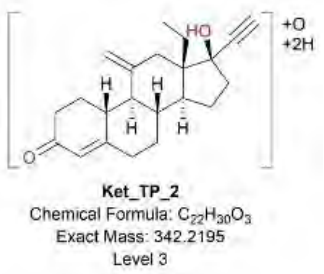
Irb_remeas

S3.16 Keto-desogestrel



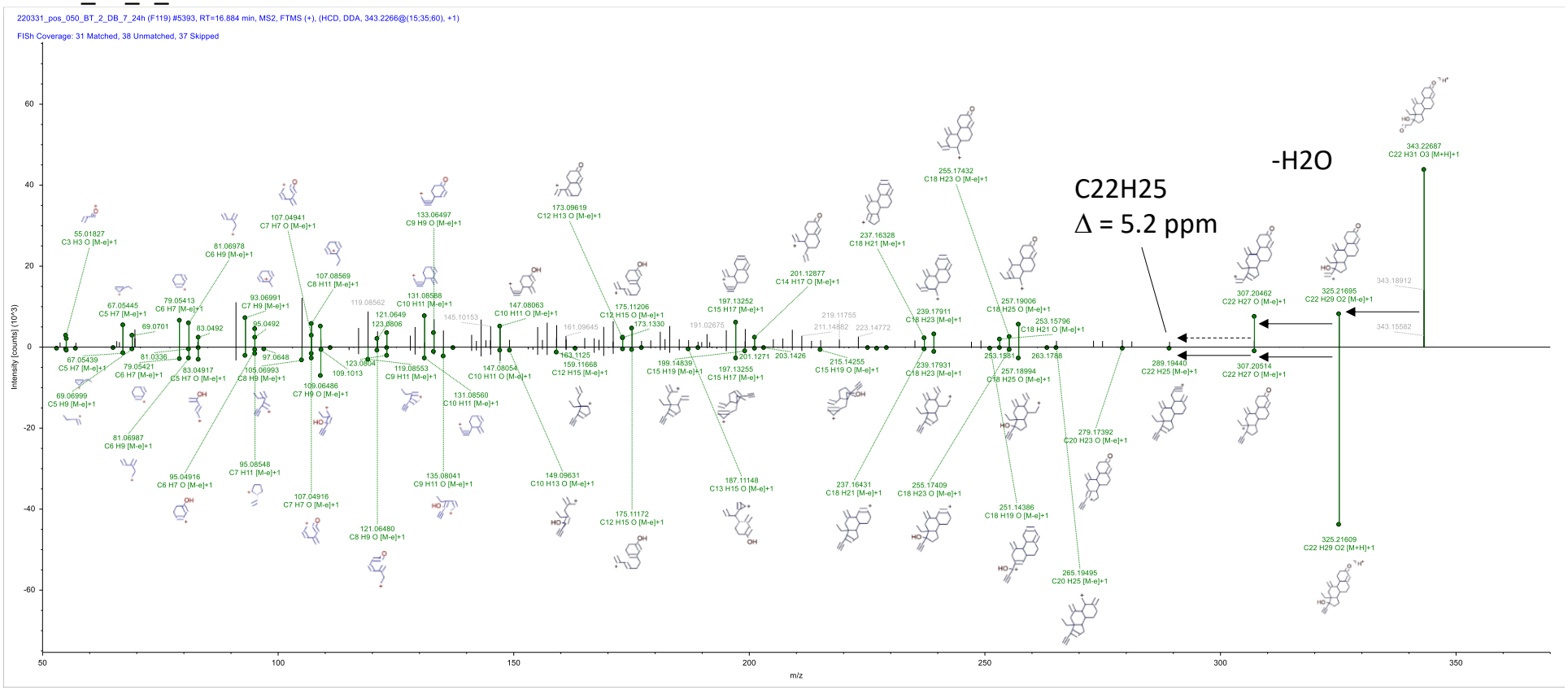


S3.16.1. Ket TP 2



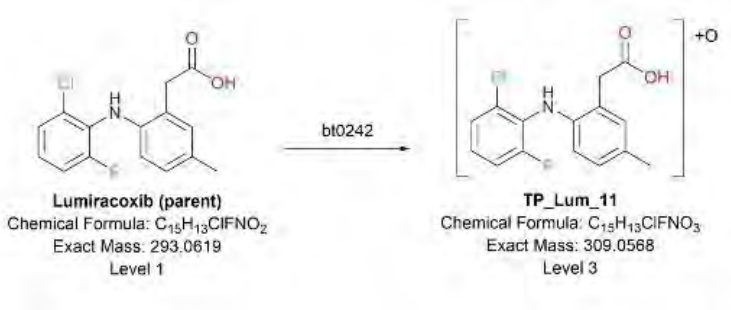
79 matching fragments with parent (but possibly with different proposed structure) fully confirm the steroid backbone. Parent $[M+H]^+$ ion shows successive water loss twice, whereas the TP $[M+H]^+$ ion probably loses H_2O three times. The expected intermediates show larger mass difference than 5 ppm and may be due to an interfering ion.

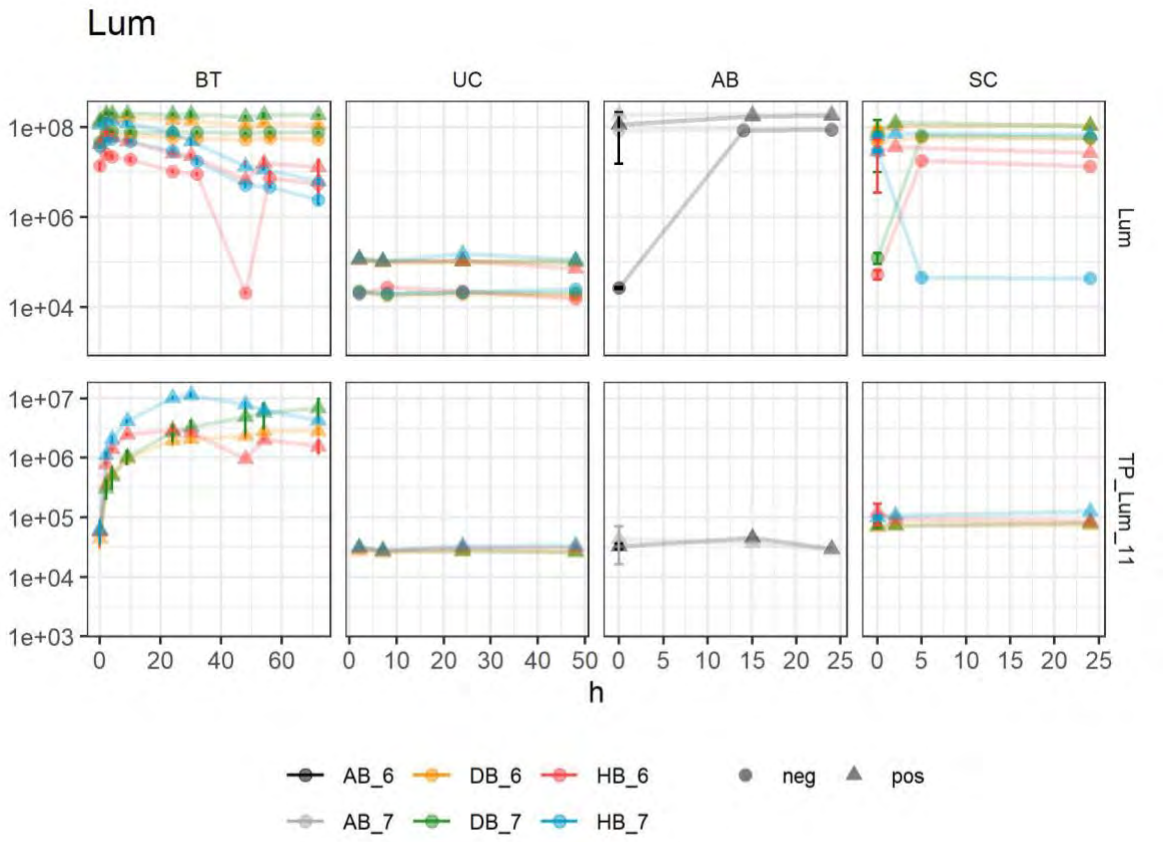
Ket_TP_2_remeas



Ket_remeas

S3.17 Lumiracoxib

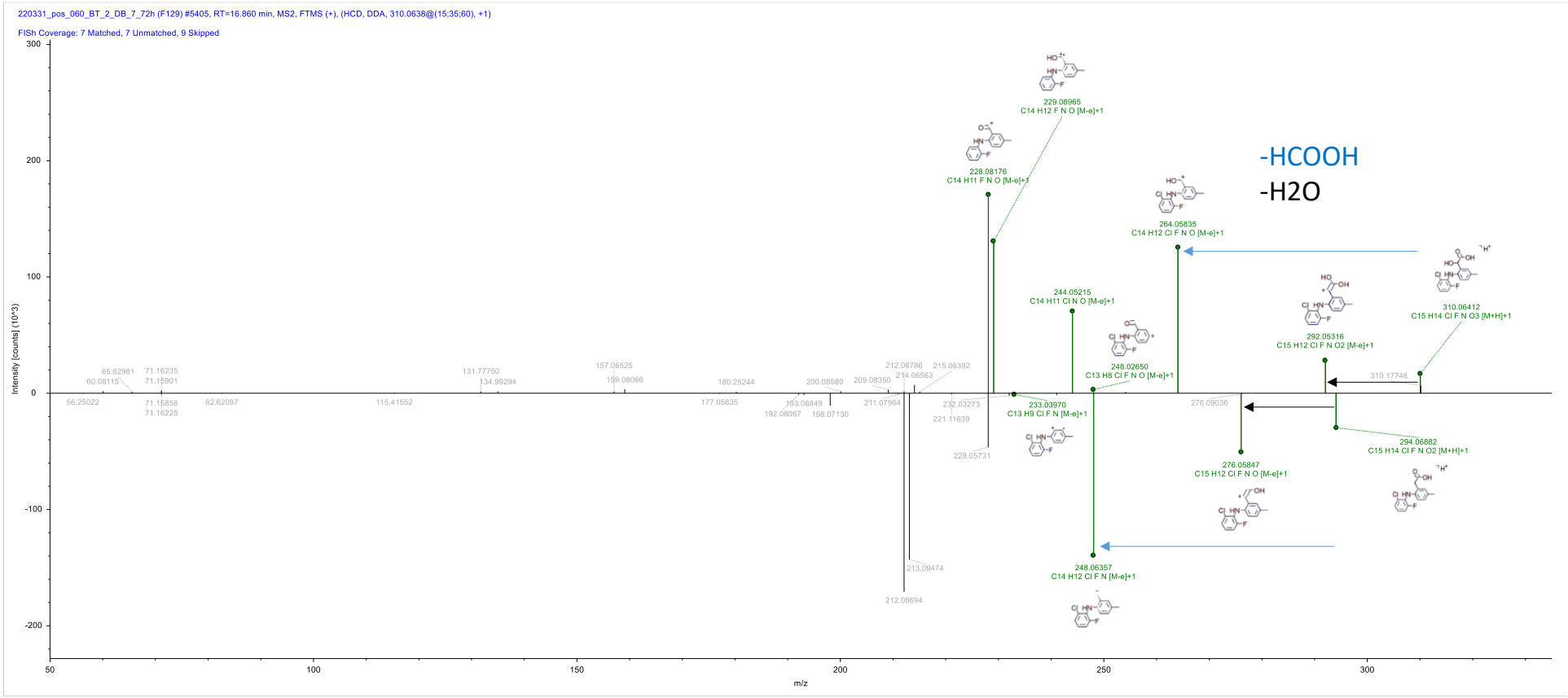




S3.17.1. TP Lum 11

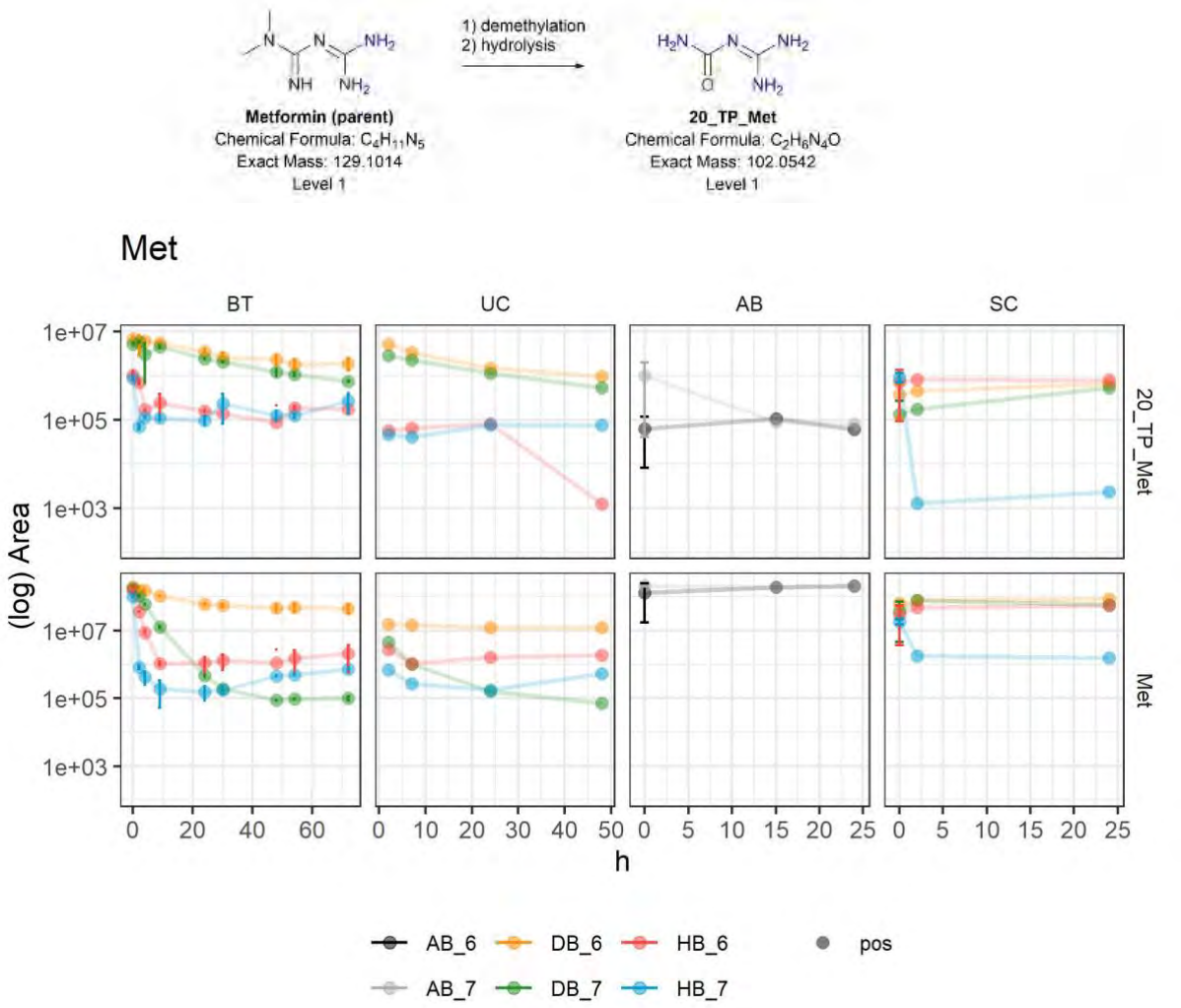
Fragments with nominal masses 71 (2x) and 212 were observed in parent and TP spectra, however no structural annotation from *MassFrontier* was made. Neutral loss of water and formic acid was also detected for both, which indicates carboxylic acid functionality. Further, water loss suggest hydroxylation to COOH or on methyl group. 4'-hydroxyl-lumiracoxib could also fit the obtained data.

TP_Lum_11_remeas

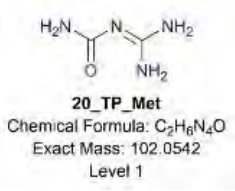


Lum_remeas

S3.18 Metformin

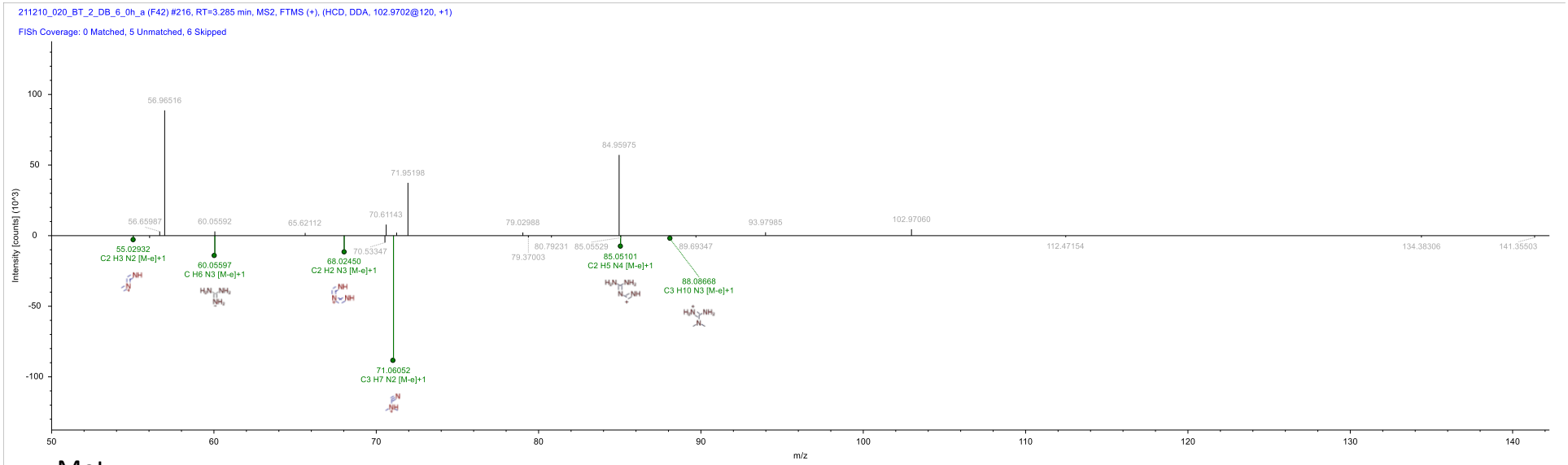


S3.18.1. 20 TP Met



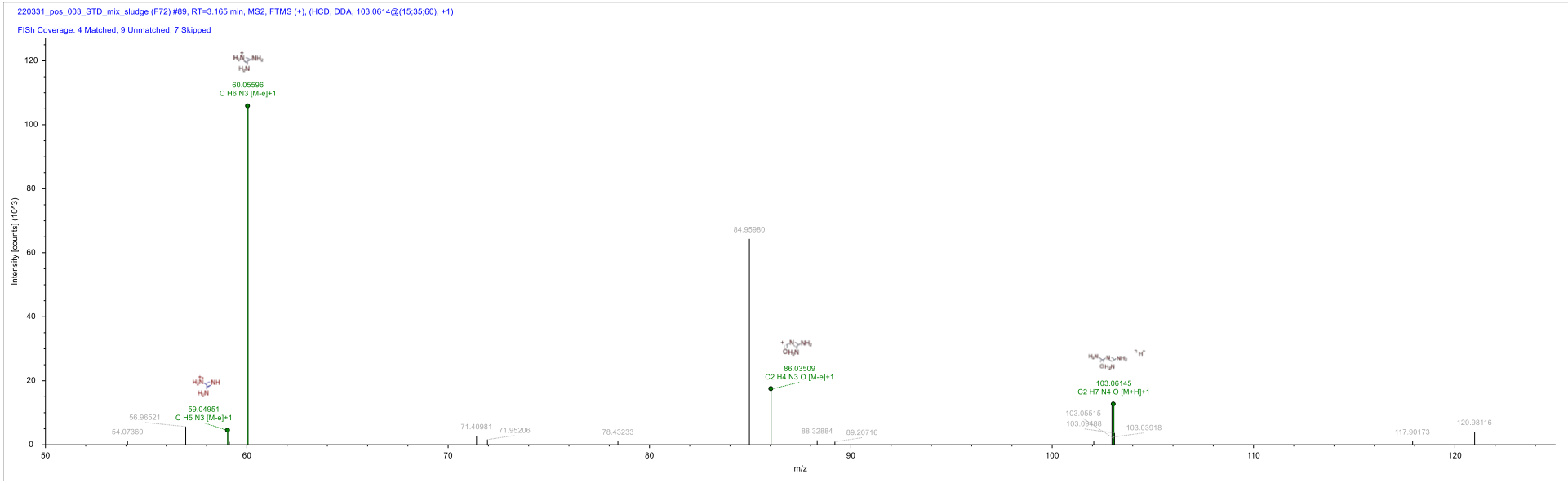
This TP was confirmed by reference standard. This TP was also found in the unspiked control reactors, but this was expected since metformin is used in a large scale and has a high concentration in wastewater. The samples taken from the biotransformation reactors showed higher areas in the chromatogram. However, this could also be due to higher activity of microorganism as a result of additional nutrition.

20_TP_Met

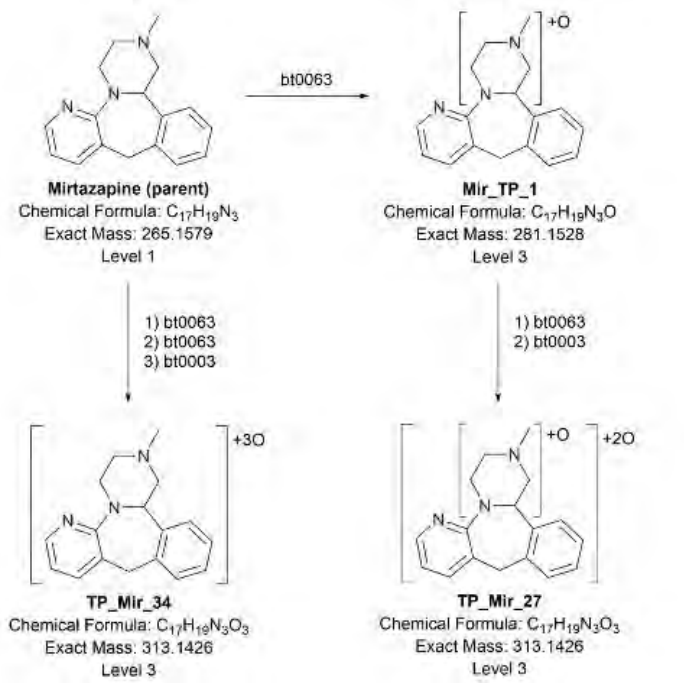

211210_020_BT_2_DB_6_0h_a (F42) #216, RT=3.285 min, MS2, FTMS (+), (HCD, DDA, 102.9702@120, +1)
FISh Coverage: 0 Matched, 5 Unmatched, 6 Skipped
Intensity (counts) (10^3)
m/z
56.96516
84.95975
71.95198
56.65987
60.05592
65.62112
70.61143
79.02988
93.97985
102.97060
55.02932
C2 H3 N2 [M-e]+1
60.05597
C H6 N3 [M-e]+1
68.02450
C2 H2 N3 [M-e]+1
70.53347
80.79231
79.37003
85.05529
85.05101
C2 H5 N4 [M-e]+1
89.69347
88.08668
C3 H10 N3 [M-e]+1
112.47154
134.38306
141.35503
71.06052
C3 H7 N2 [M-e]+1

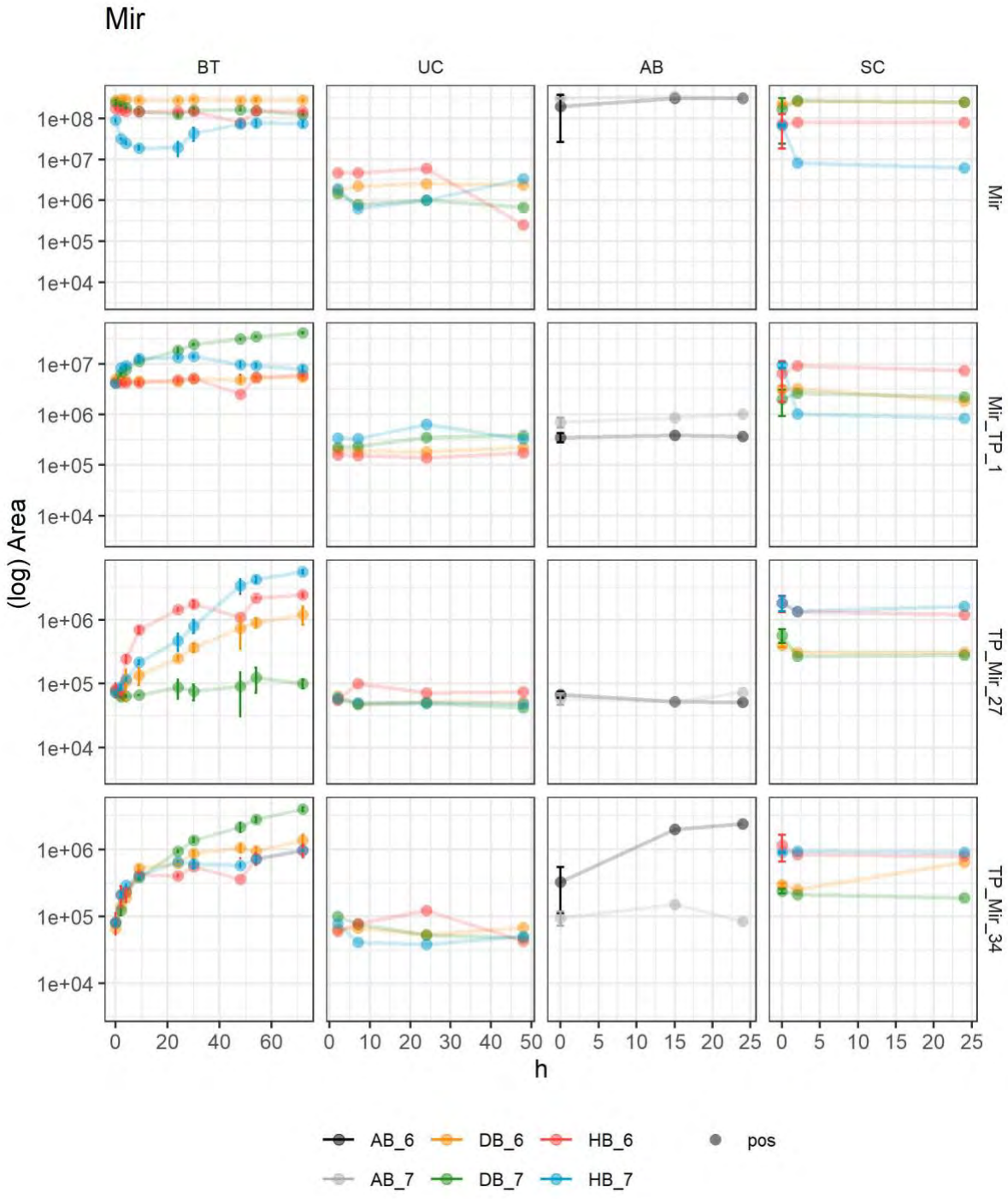
Met

20_TP_Met_remeas_reference_standard

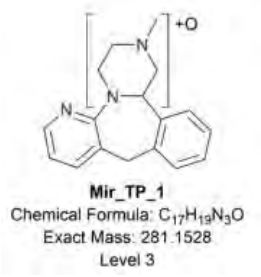


S3.19 Mirtazapine



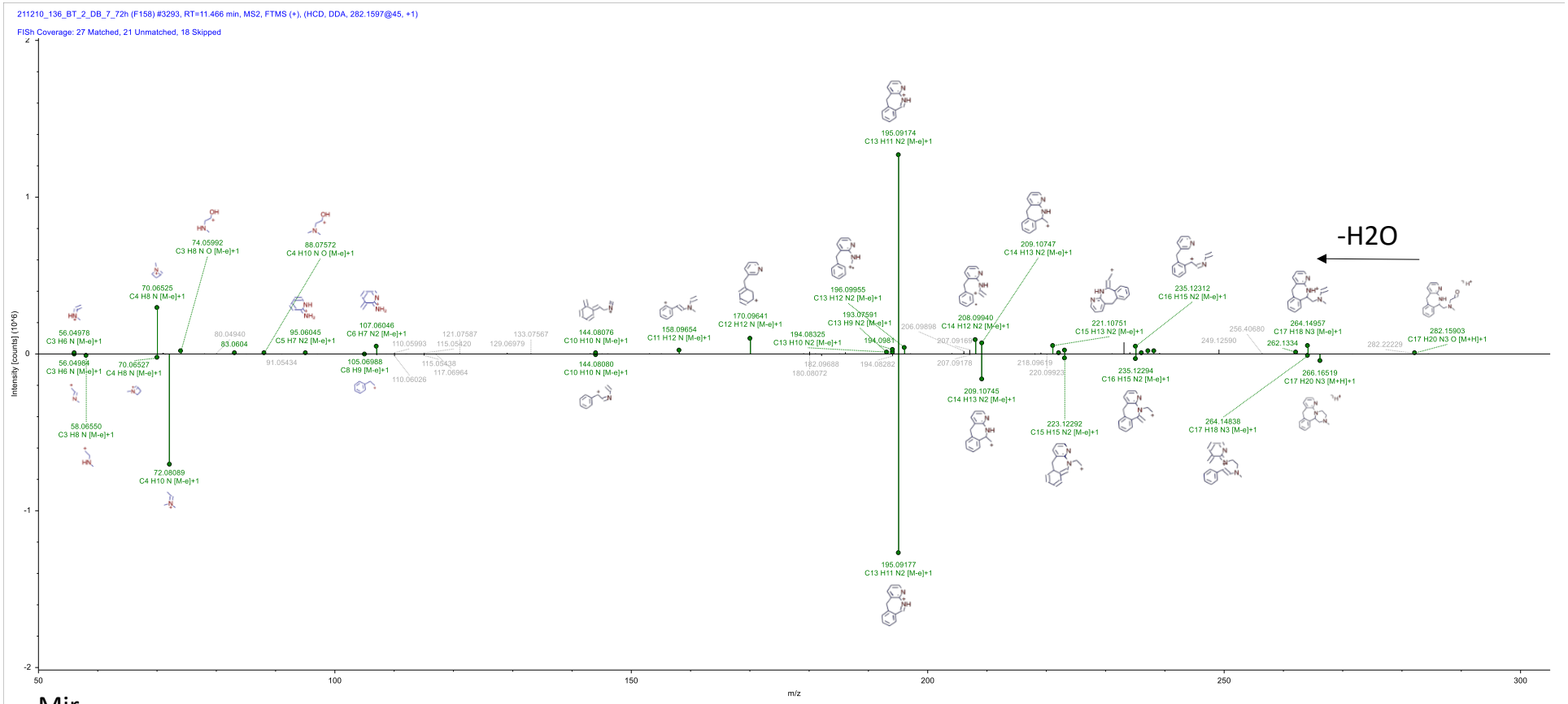

Mir
BT
UC
AB
SC
Mir
Mir_TP_1
TP_Mir_27
TP_Mir_34
(log) Area
1e+08
1e+07
1e+06
1e+05
1e+04
0 20 40 60
0 10 20 30 40 50
0 5 10 15 20 25
h
AB_6
DB_6
HB_6
pos
AB_7
DB_7
HB_7

S3.19.1. Mir TP 1



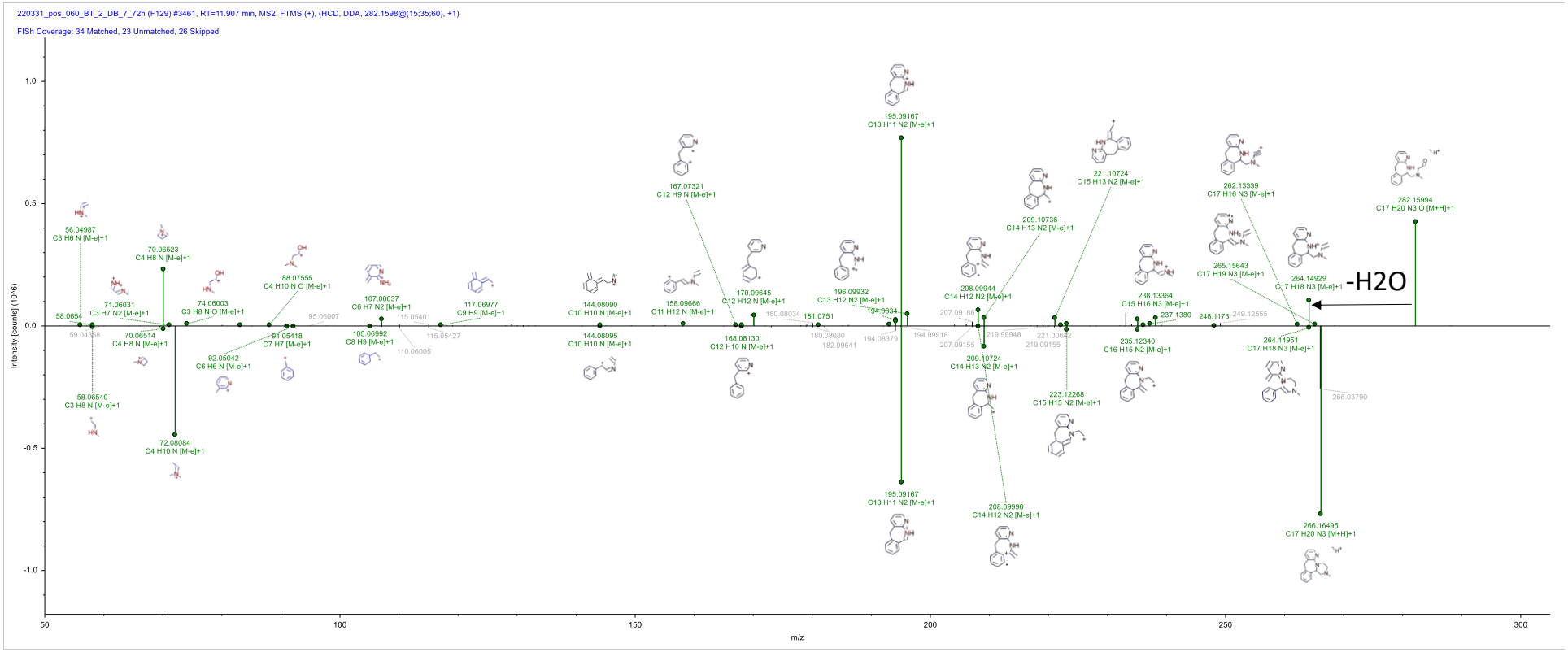
Nominal masses 56, 58, 70, 107, 110, 115, 117, 144, 167, 168, 180, 194, 195, 208, 209, 223, 235 and 264 were also observed for the parent compound, where especially mass 195 confirms substructure. The water loss was only present in TP not in parent spectrum, which supports the formation of an aldehyde. The TP shares the chemical formula of 8-Hydroxymirtazapine, however fragments with m/z 195, 208, 209, 264 suggest no hydroxylation of aromatic of 7-membered ring system and the library spectrum of 8-Hydroxymirtazapine is no good match. Multiple structural isomers are possible leading to the same chemical formula, therefore only confidence level 3 was chosen.

Mir_TP_1


211210_136_BT_2_DB_7_72h (F158) #3293, RT=11.466 min, MS2, FTMS (+), (HCD, DDA, 282.1597@45, +1)
FISh Coverage: 27 Matched, 21 Unmatched, 18 Skipped
Intensity [counts] (10^6)
m/z
-H2O
56.04978 C3 H6 N [M-e]+1
56.04984 C3 H6 N [M-e]+1
58.06550 C3 H8 N [M-e]+1
70.06525 C4 H8 N [M-e]+1
70.06527 C4 H8 N [M-e]+1
72.08089 C4 H10 N [M-e]+1
74.05992 C3 H8 N O [M-e]+1
80.04940
83.0604
88.07572 C4 H10 N O [M-e]+1
91.05434
95.06045 C5 H7 N2 [M-e]+1
105.06988 C8 H9 [M-e]+1
107.06046 C6 H7 N2 [M-e]+1
110.05993
110.06026
115.05438
115.05420
117.06964
121.07587
129.06979
133.07567
144.08076 C10 H10 N [M-e]+1
144.08080 C10 H10 N [M-e]+1
158.09654 C11 H12 N [M-e]+1
170.09641 C12 H12 N [M-e]+1
180.08072
182.09688
194.08325 C13 H10 N2 [M-e]+1
193.07591 C13 H9 N2 [M-e]+1
194.0981
194.08282
195.09174 C13 H11 N2 [M-e]+1
195.09177 C13 H11 N2 [M-e]+1
196.09955 C13 H12 N2 [M-e]+1
206.09898
207.09169
207.09178
208.09940 C14 H12 N2 [M-e]+1
209.10745 C14 H13 N2 [M-e]+1
209.10747 C14 H13 N2 [M-e]+1
218.09619
220.09923
221.10751 C15 H13 N2 [M-e]+1
223.12292 C15 H15 N2 [M-e]+1
235.12294 C16 H15 N2 [M-e]+1
235.12312 C16 H15 N2 [M-e]+1
249.12590
256.40680
262.1334
264.14838 C17 H18 N3 [M-e]+1
264.14957 C17 H18 N3 [M-e]+1
266.16519 C17 H20 N3 [M+H]+1
282.22229
282.15903 C17 H20 N3 O [M+H]+1

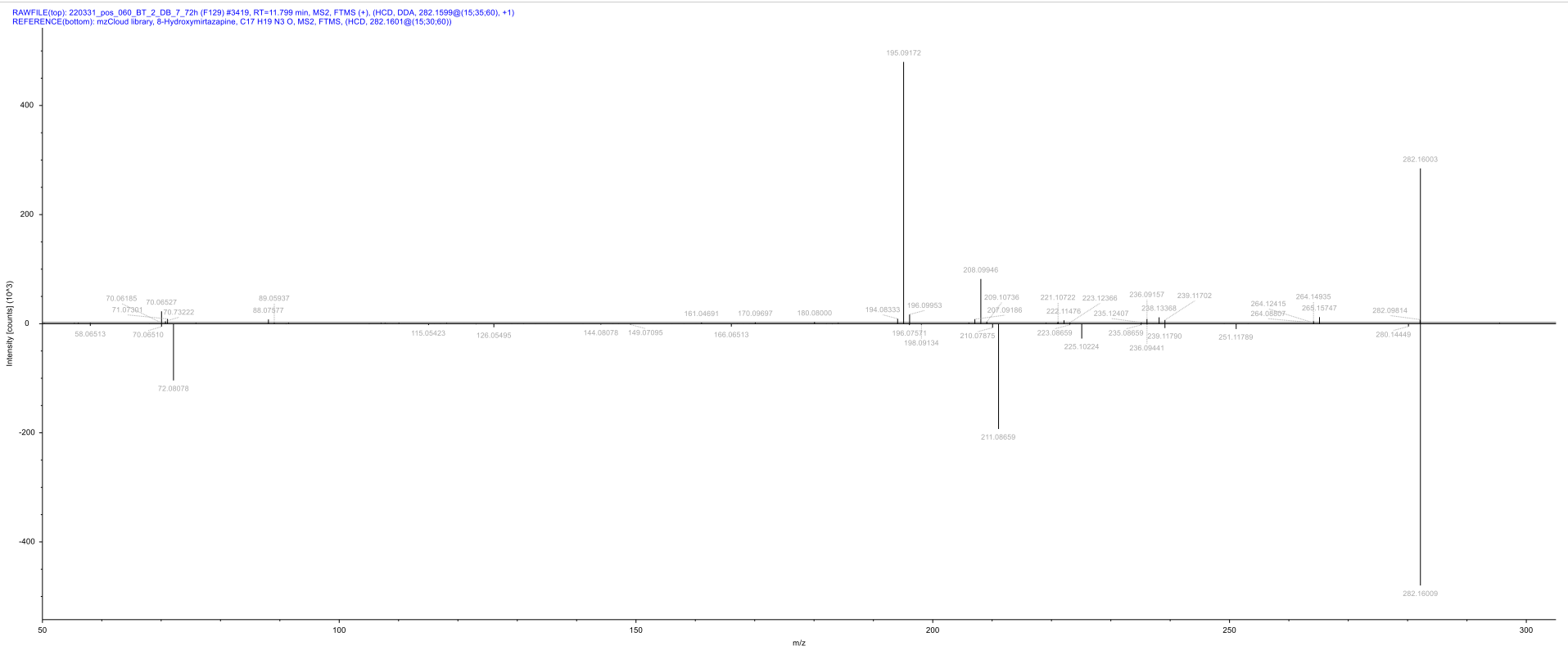
Mir

Mir_TP_1_remeas



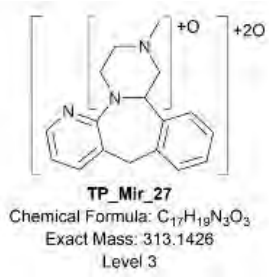
Mir_remeas

Mir_TP_1_remeas



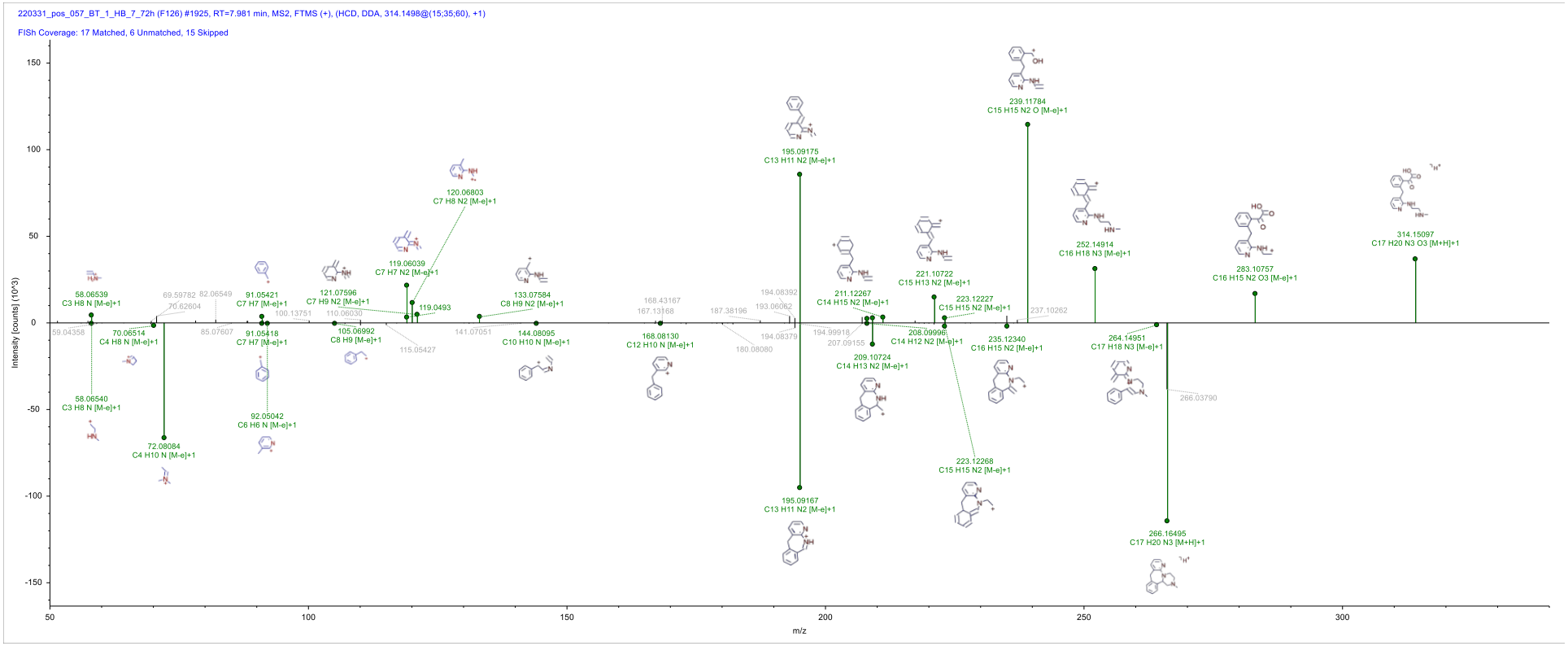
mzCloud (8-Hydroxymirtazapine)

S3.19.2. TP Mir 27



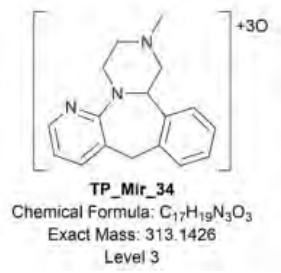
Two compounds with identical molecular formula at RT 7.7 (TP Mir 27) and 10.3 (TP Mir 34) were found. 8 structural isomers were predicted. Fragments with m/z 195, 208 and 209 suggest no hydroxylation of aromatic of 7-membered ring system.

TP_Mir_27_remeas



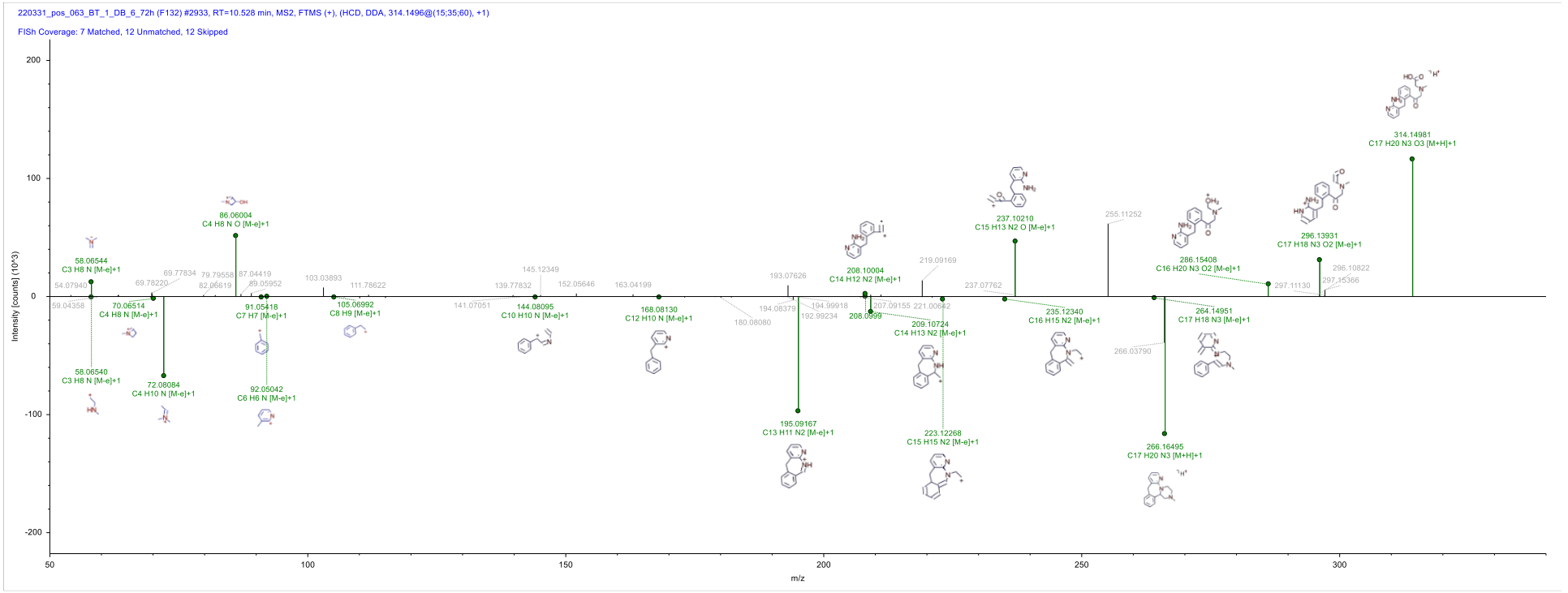
Mir_remeas

S3.19.3. TP Mir 34



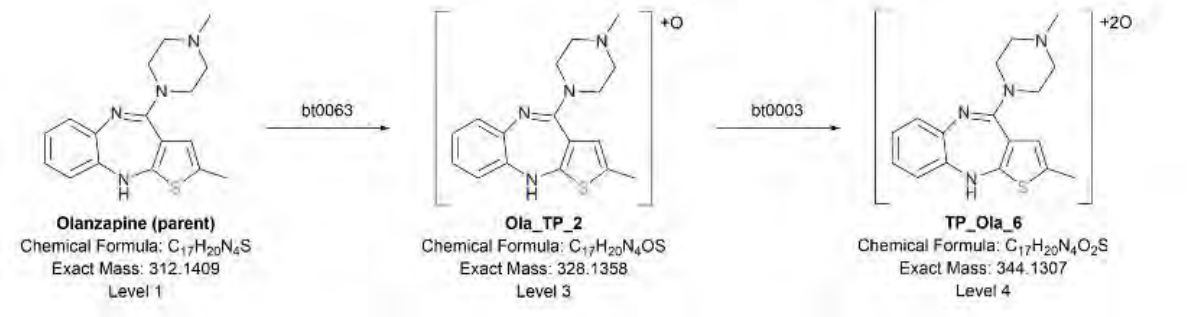
Two compounds with identical molecular formula at RT 7.7 (TP Mir 27) and 10.3 (TP Mir 34) were found. 8 structural isomers were predicted.

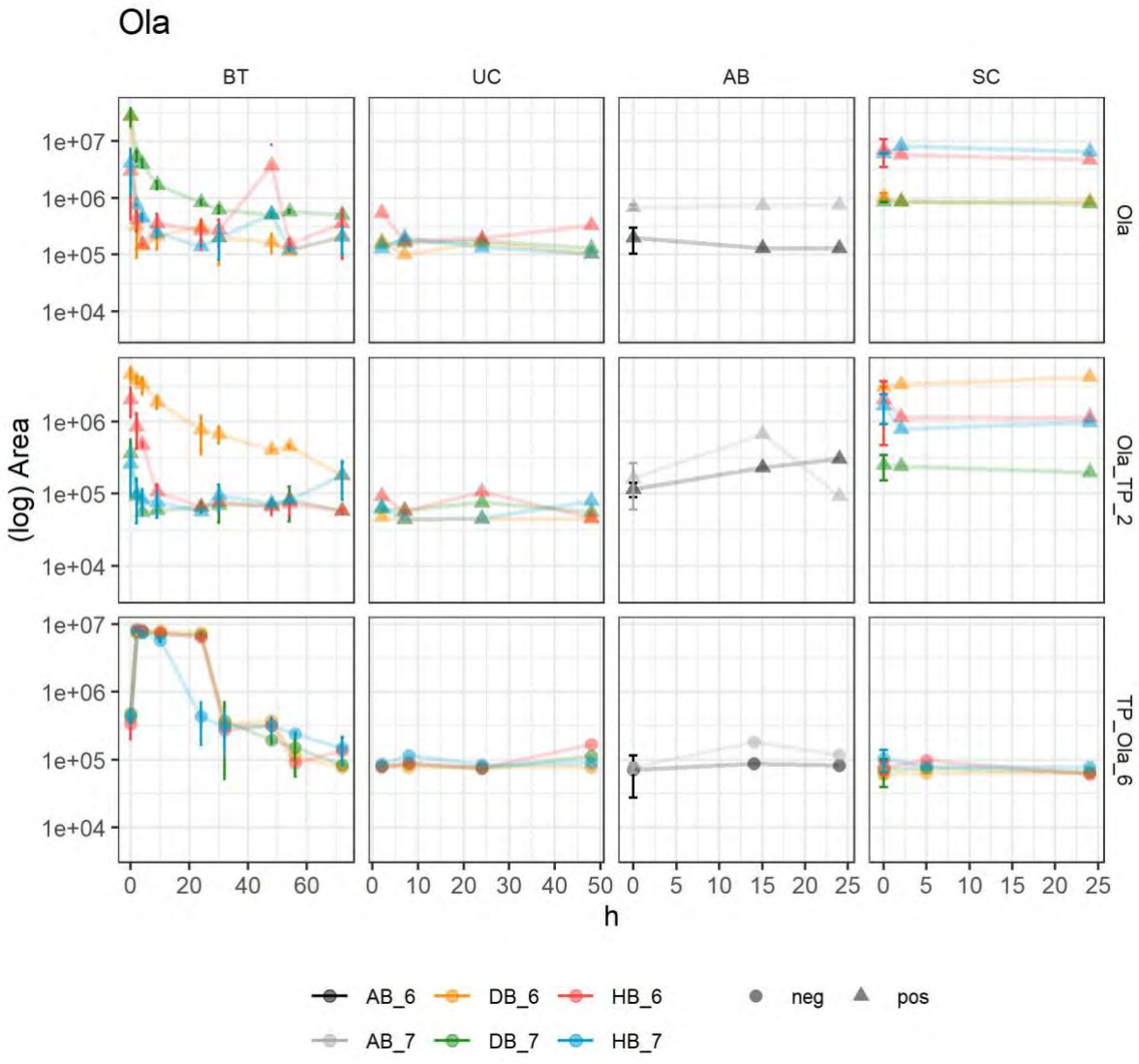
TP_Mir_34_remeas



Mir_remeas

S3.20 Olanzapine

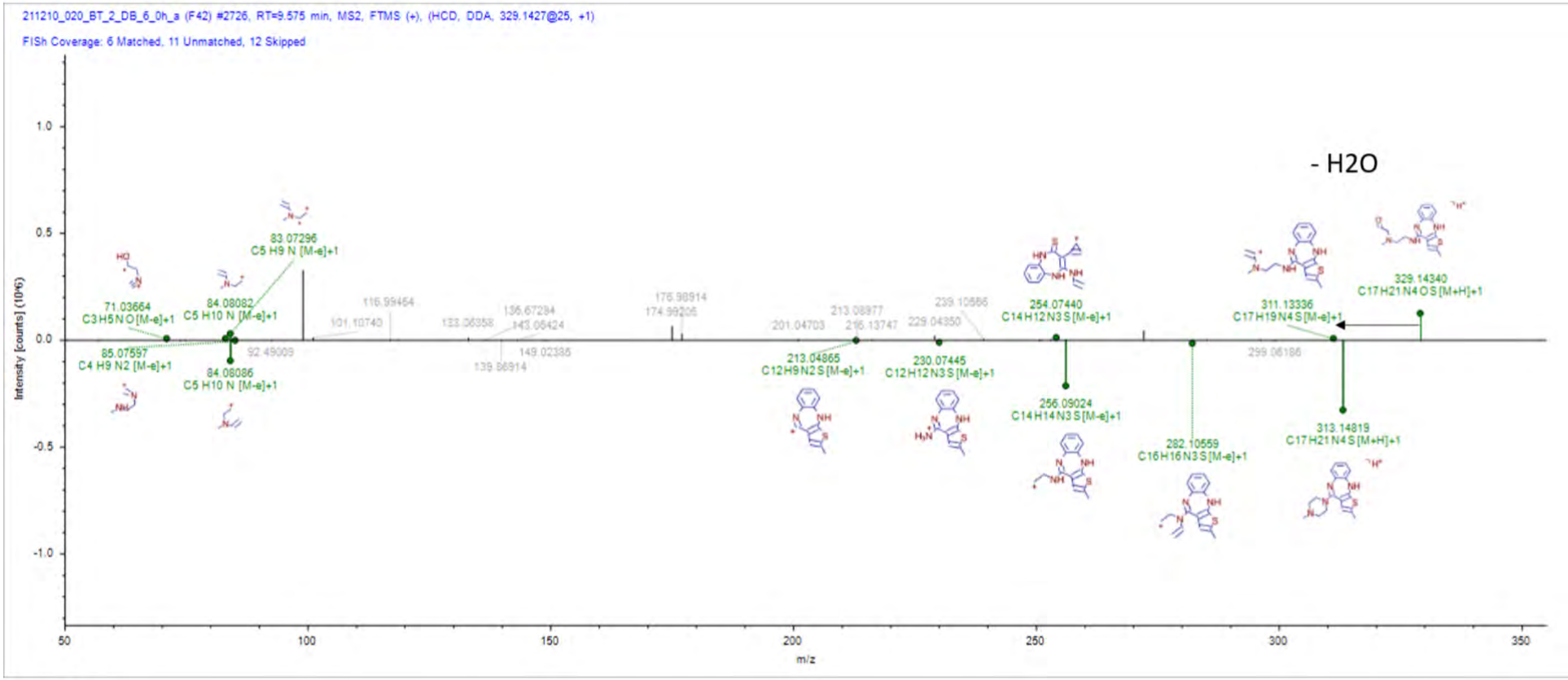




S3.20.1. Ola TP 2

Nominal mass 84 was also observed for parent compound. Water loss, which is only present in TP MS^2 scan, indicates oxidation.

Ola_TP_2

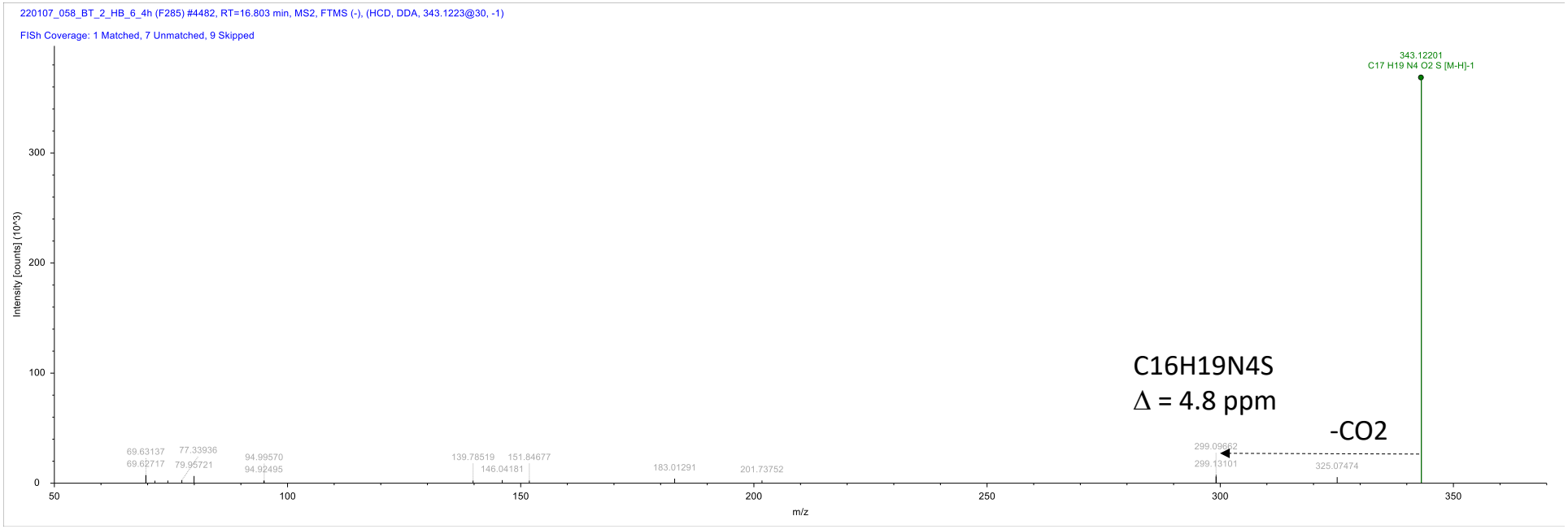

211210_020_BT_2_DB_6_0h_a (F42) #2726, RT=9.575 min, MS2, FTMS (+), (HCD, DDA, 329.1427@25, +1)
FISh Coverage: 6 Matched, 11 Unmatched, 12 Skipped
- H2O
83.07296
C5 H9 N [M-e]+1
71.03664
C3 H5 N O [M-e]+1
84.08082
C5 H10 N [M-e]+1
85.07597
C4 H9 N2 [M-e]+1
84.08086
C5 H10 N [M-e]+1
116.99464
101.10740
133.06358
136.67284
143.05424
149.02385
139.86914
175.98914
174.99206
213.08977
201.04703
216.13747
239.10586
229.04350
213.04865
C12H9N2S[M-e]+1
230.07445
C12H12N3S[M-e]+1
254.07440
C14H12N3S[M-e]+1
256.09024
C14H14N3S[M-e]+1
282.10559
C16H16N3S[M-e]+1
311.13336
C17H19N4S[M-e]+1
299.06186
329.14340
C17H21N4OS[M+H]+1
313.14819
C17H21N4S[M+H]+1
Intensity [counts] (10^6)
m/z

Ola

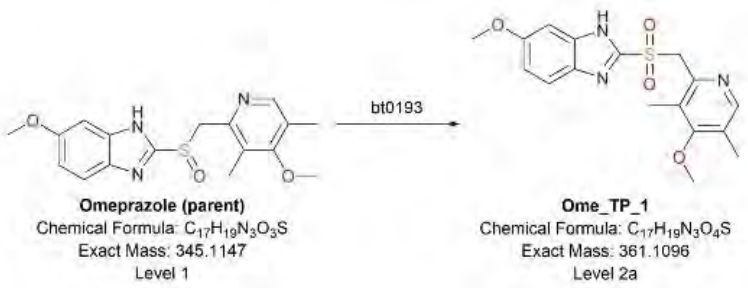
S3.20.2. TP Ola 6

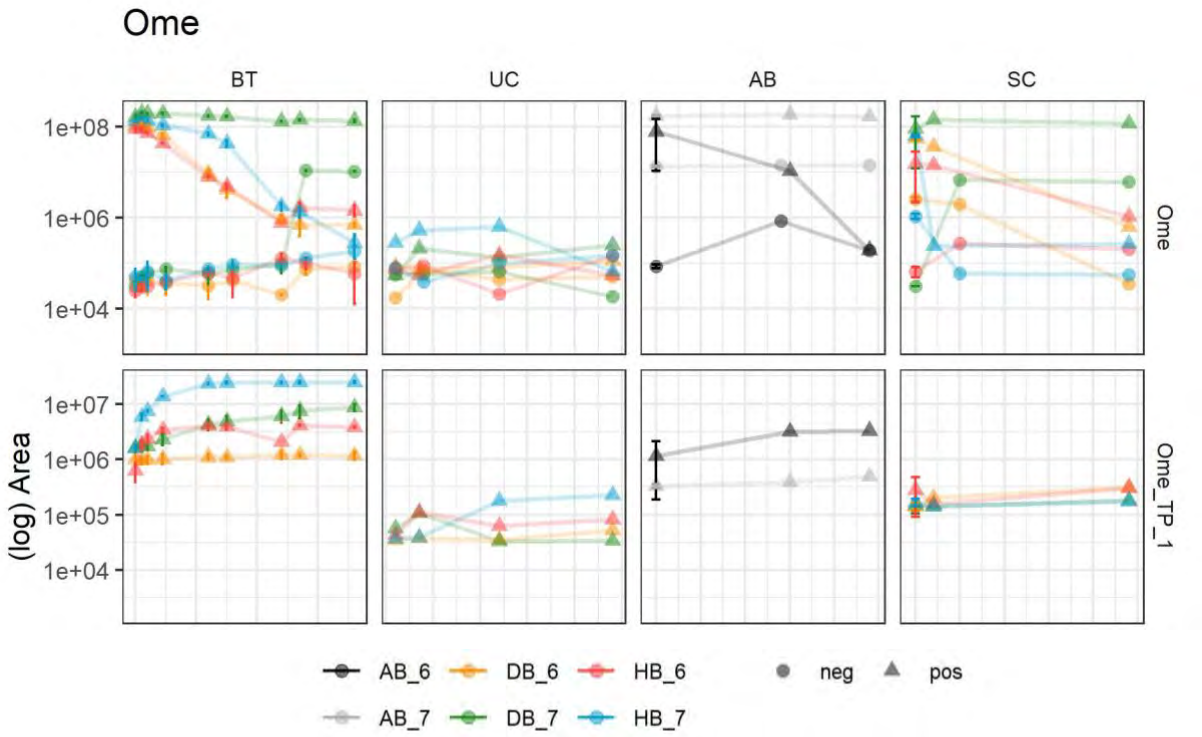
Only $[M-H]^-$ and plausible CO_2 loss detected. No further information could be obtained in the remeasured sample.

TP_Ola_6


220107_058_BT_2_HB_6_4h (F285) #4482, RT=16.803 min, MS2, FTMS (-), (HCD, DDA, 343.1223@30, -1)
FISh Coverage: 1 Matched, 7 Unmatched, 9 Skipped
343.12201
C17 H19 N4 O2 S [M-H]-1
C16H19N4S
Δ = 4.8 ppm
-CO2
Intensity [counts] (10^3)
m/z
69.63137
69.62717
77.33936
79.95721
94.99570
94.92495
139.78519
146.04181
151.84677
183.01291
201.73752
299.09582
299.13101
325.07474

S3.21 Omeprazole

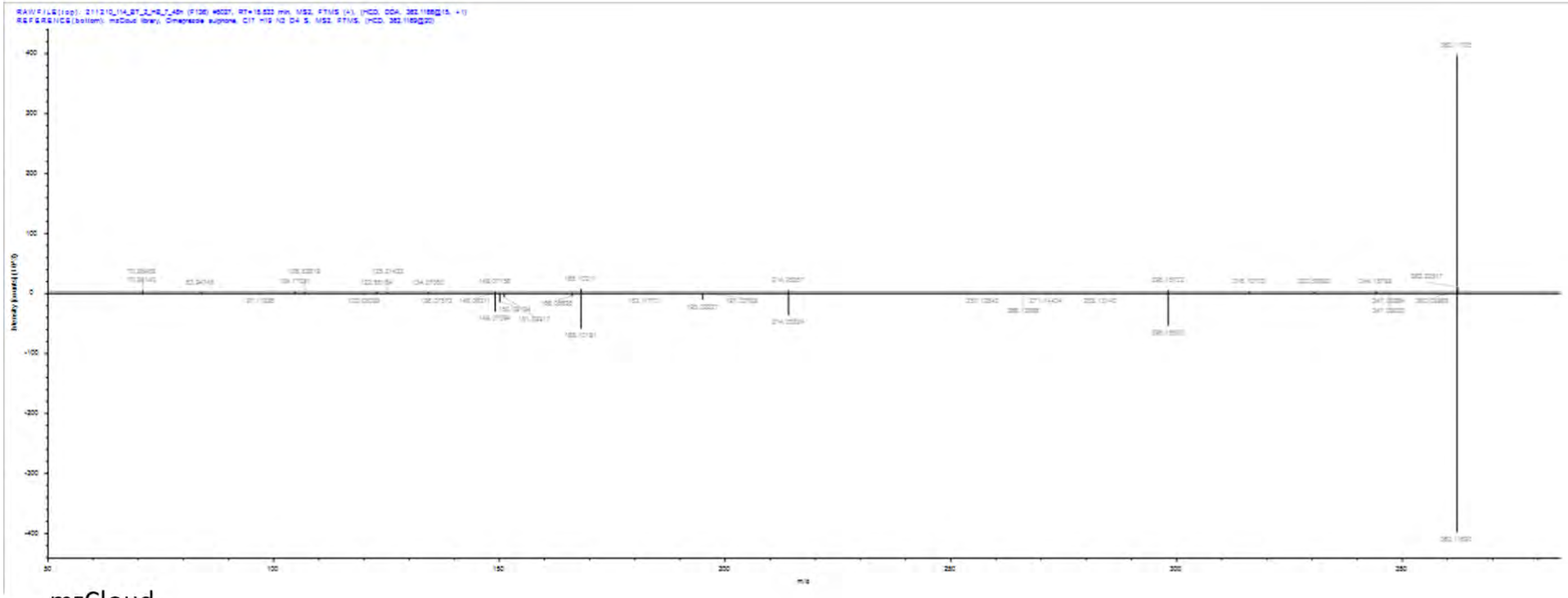




S3.21.1. Ome TP 1

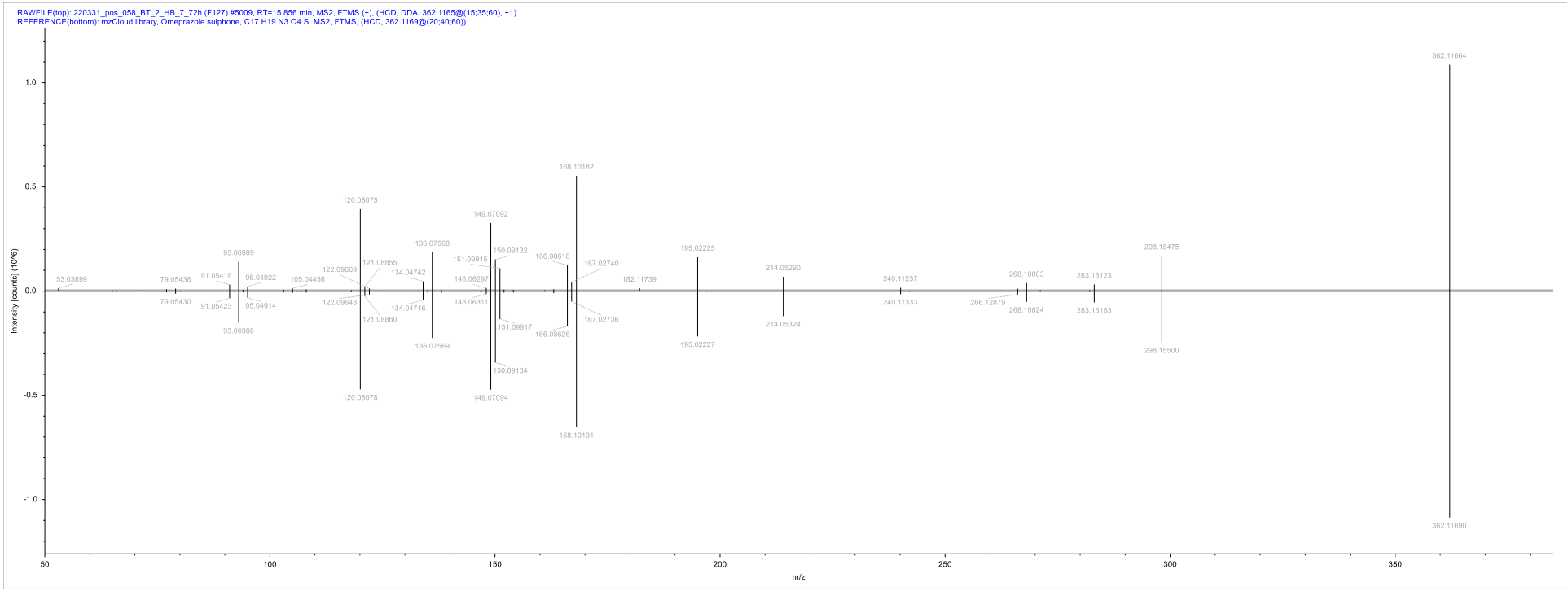
Structure of TP could be confirmed with *mzCloud* library match. Fragment with nominal mass 214 corresponds to □-cleavage of sulfone group. Additionally, SO_2 loss was observed, which further supports the oxidation of the sulfur atom.

Ome_TP_1



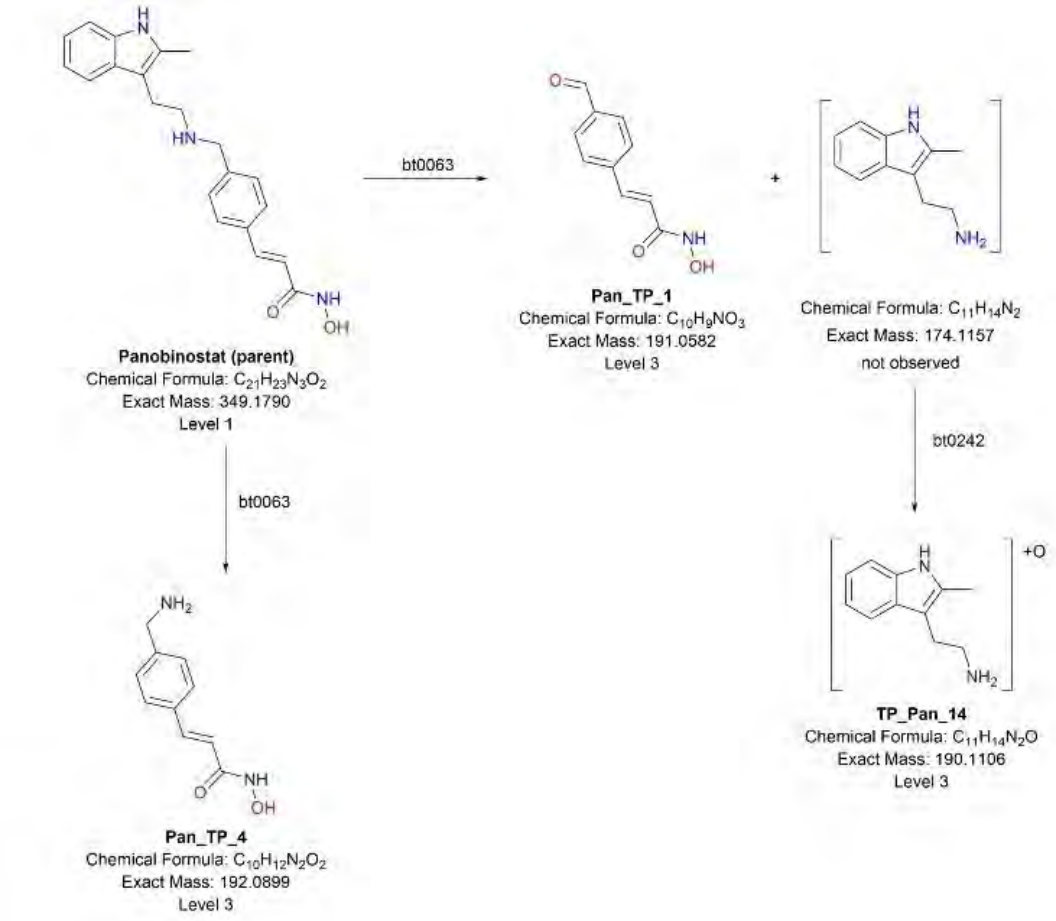
mzCloud

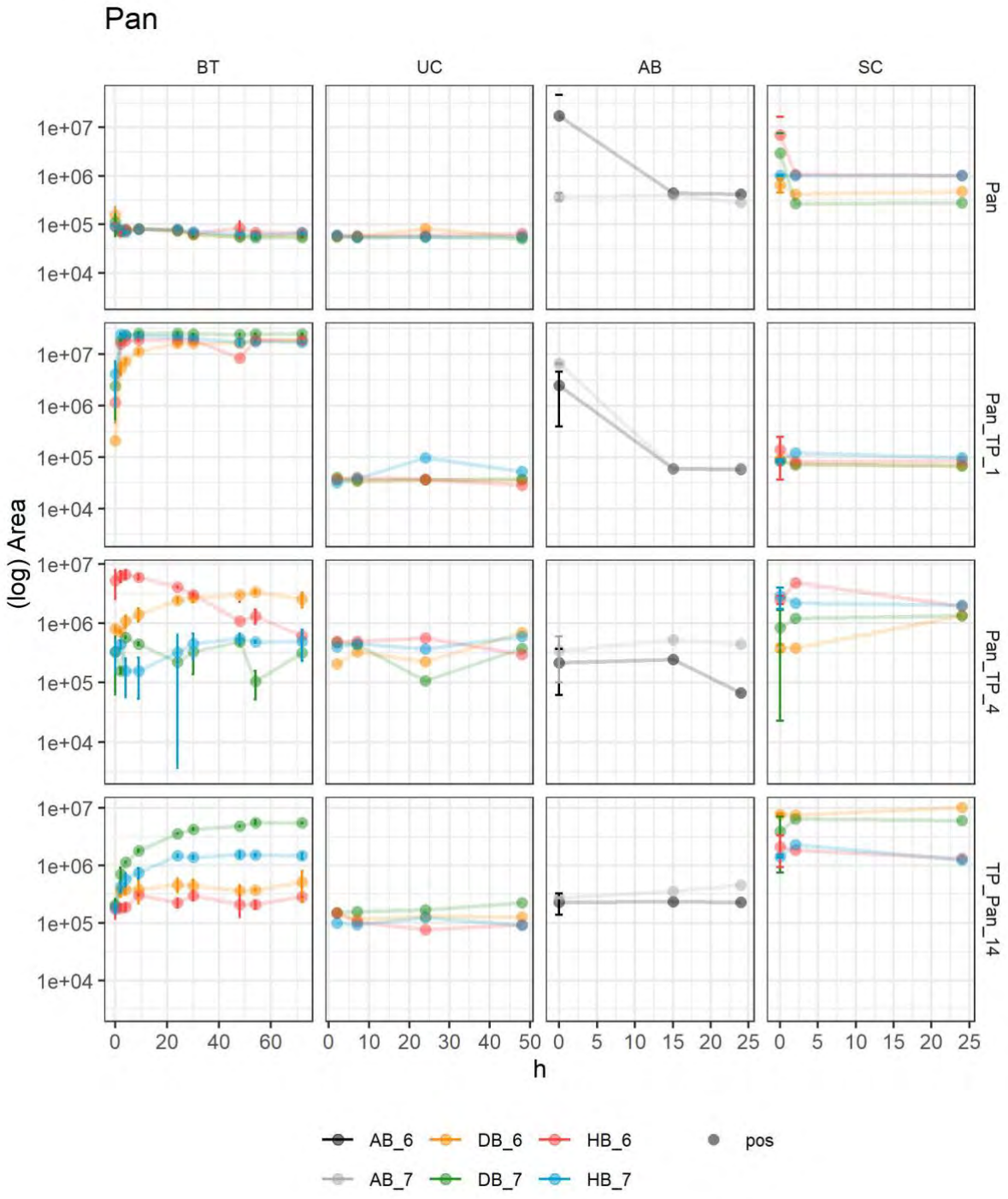
Ome_TP_1_remeas



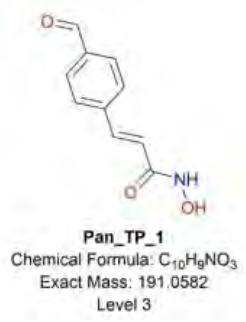
mzCloud

S3.22 Panobinostat



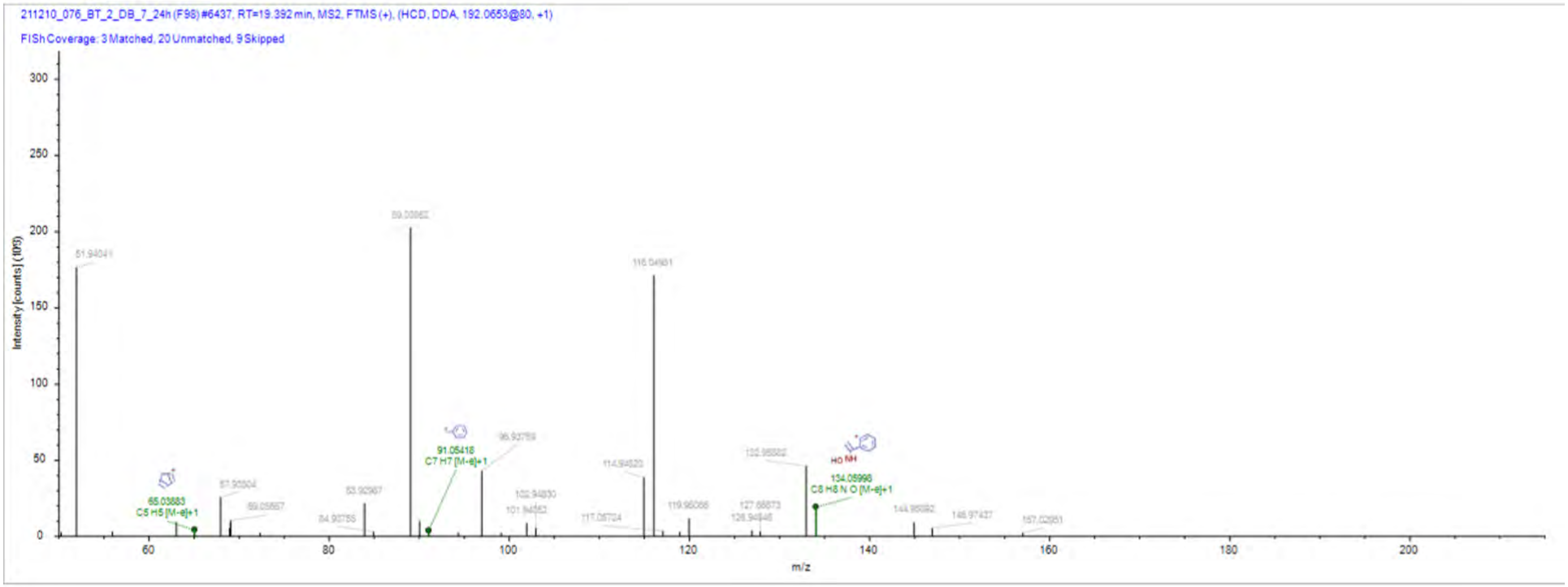

Pan
BT
UC
AB
SC
Pan
Pan_TP_1
Pan_TP_4
TP_Pan_14
(log) Area
1e+07
1e+06
1e+05
1e+04
0 20 40 60
0 10 20 30 40 50
0 5 10 15 20 25
h
AB_6
DB_6
HB_6
pos
AB_7
DB_7
HB_7

S3.22.1. Pan TP 1

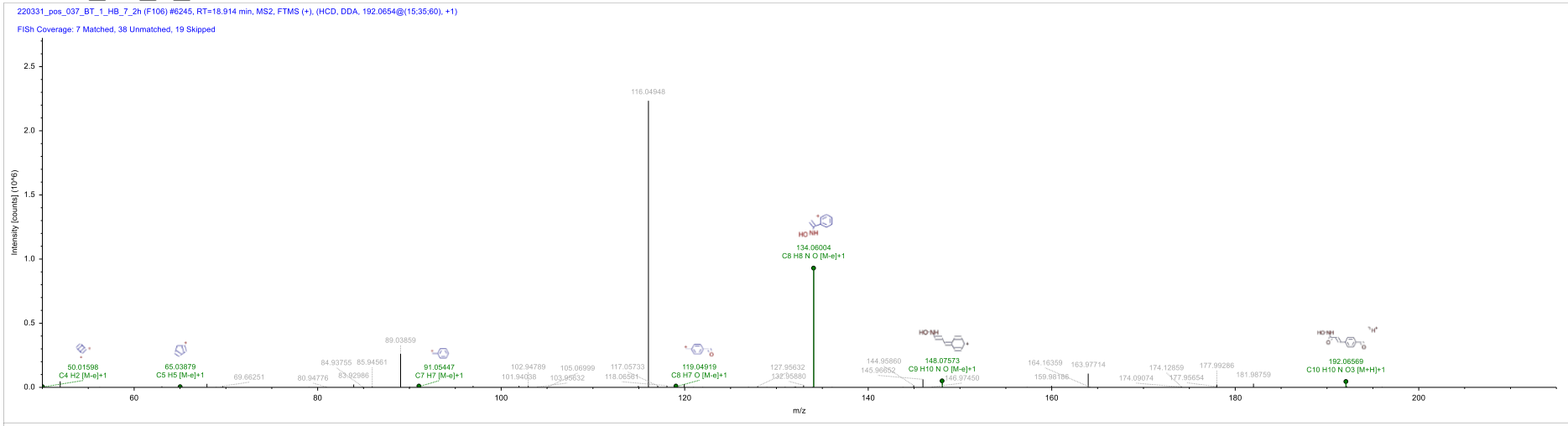


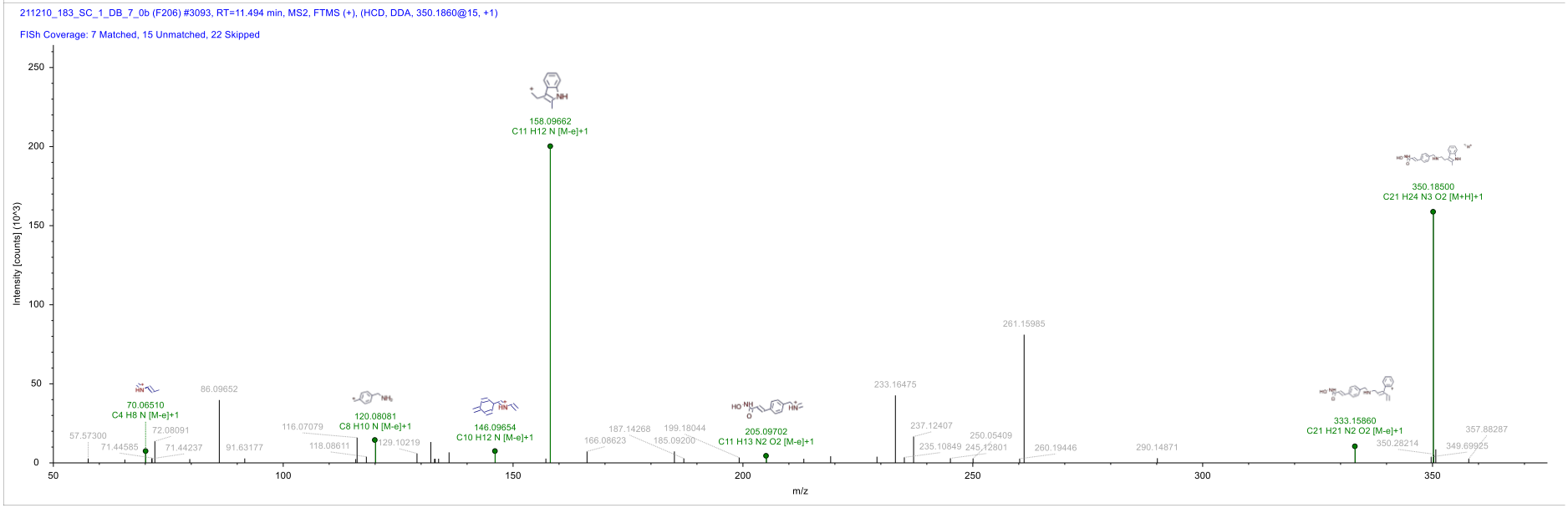
TP shows no matches with parent spectra. Fragments at nominal masses 91 and 65 suggest toluene substructure, whereas mass 134 hints at hydroxylamide group. Parent compound was only observed in original measurement.

Pan_TP_1


211210_076_BT_2_DB_7_24h (F98) #6437, RT=19.392 min, MS2, FTMS (+), (HCD, DDA, 192.0653@80, +1)
FISh Coverage: 3 Matched, 20 Unmatched, 9 Skipped
Intensity [counts] (10^3)
m/z
65.03883
C5 H5 [M-e]+1
91.05418
C7 H7 [M-e]+1
134.05998
C8 H8 N O [M-e]+1
HO NH

Pan_TP_1_remeas



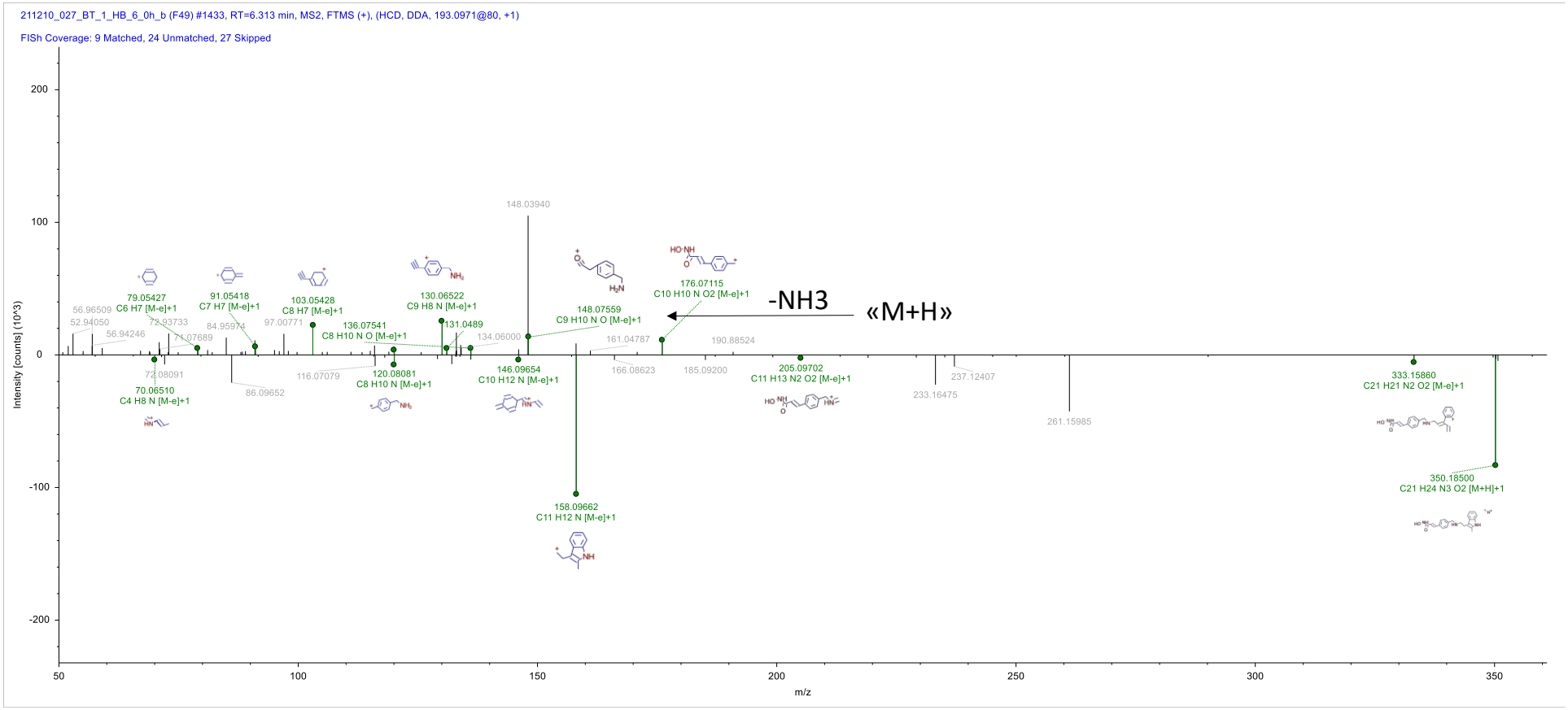


Pan

S3.22.2. Pan TP 4

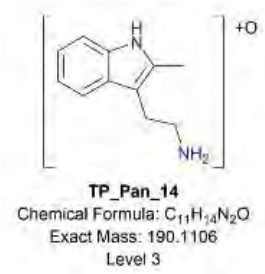
Nominal mass 120 was also observed for the parent compound. Fragments at nominal mass 91 supports toluene substructure. The neutral loss of ammonia supports the oxidative *N*-dealkylation to the methyl-indole moiety and not to the benzyl as in Pan TP 1.

Pan_TP_4


211210_027_BT_1_HB_6_0h_b (F49) #1433, RT=6.313 min, MS2, FTMS (+), (HCD, DDA, 193.0971@80, +1)
FISh Coverage: 9 Matched, 24 Unmatched, 27 Skipped
Intensity [counts] (10^3)
m/z
-NH3
«M+H»
148.03940
79.05427 C6 H7 [M-e]+1
91.05418 C7 H7 [M-e]+1
103.05428 C8 H7 [M-e]+1
130.06522 C9 H8 N [M-e]+1
148.07559 C9 H10 N O [M-e]+1
176.07115 C10 H10 N O2 [M-e]+1
136.07541 C8 H10 N O [M-e]+1
131.0489
70.06510 C4 H8 N [M-e]+1
120.08081 C8 H10 N [M-e]+1
146.09654 C10 H12 N [M-e]+1
158.09662 C11 H12 N [M-e]+1
205.09702 C11 H13 N2 O2 [M-e]+1
333.15860 C21 H21 N2 O2 [M-e]+1
350.18500 C21 H24 N3 O2 [M+H]+1
56.96509
52.94050
56.94246
72.93733
77.07689
84.95974
97.00771
134.06000
161.04787
190.88524
72.08091
116.07079
86.09652
166.08623
185.09200
237.12407
233.16475
261.15985

Pan

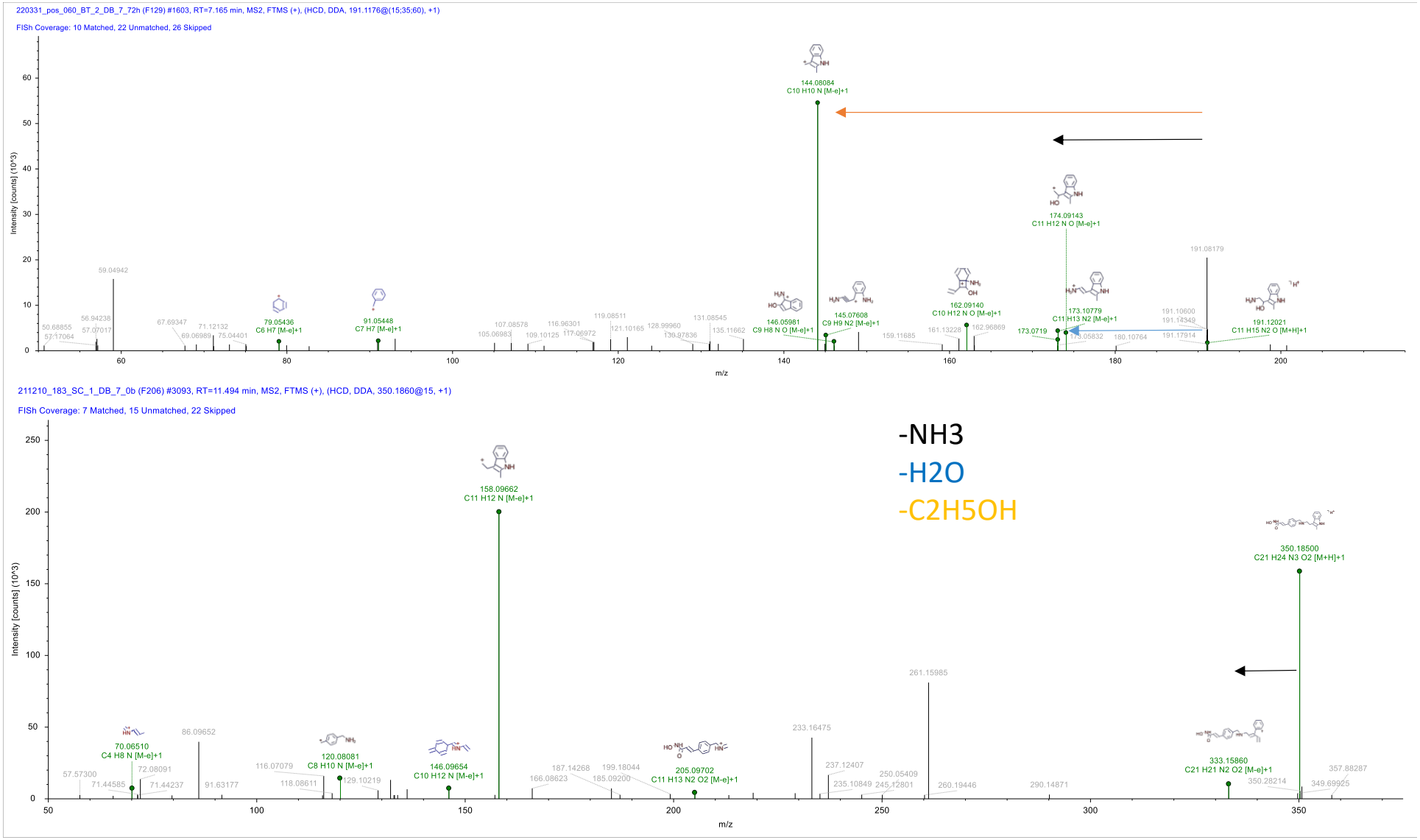
S3.22.3. TP Pan 14



TP_Pan_14
Chemical Formula: $C_{11}H_{14}N_2O$
Exact Mass: 190.1106
Level 3

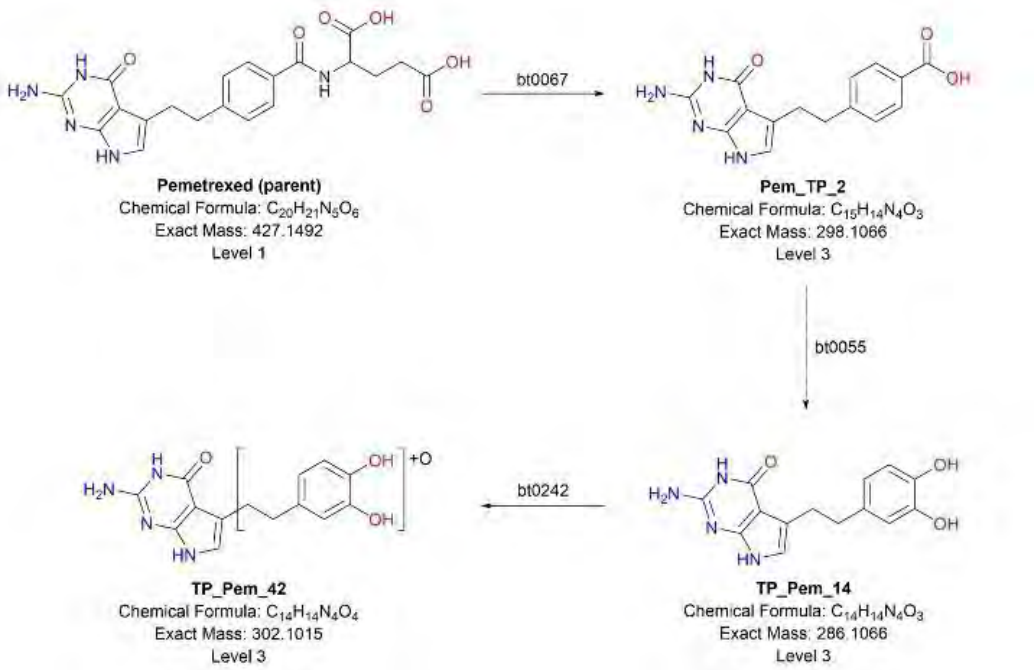
No fragments were shared between TP and parent. Neutral loss of ammonia was observed for both.

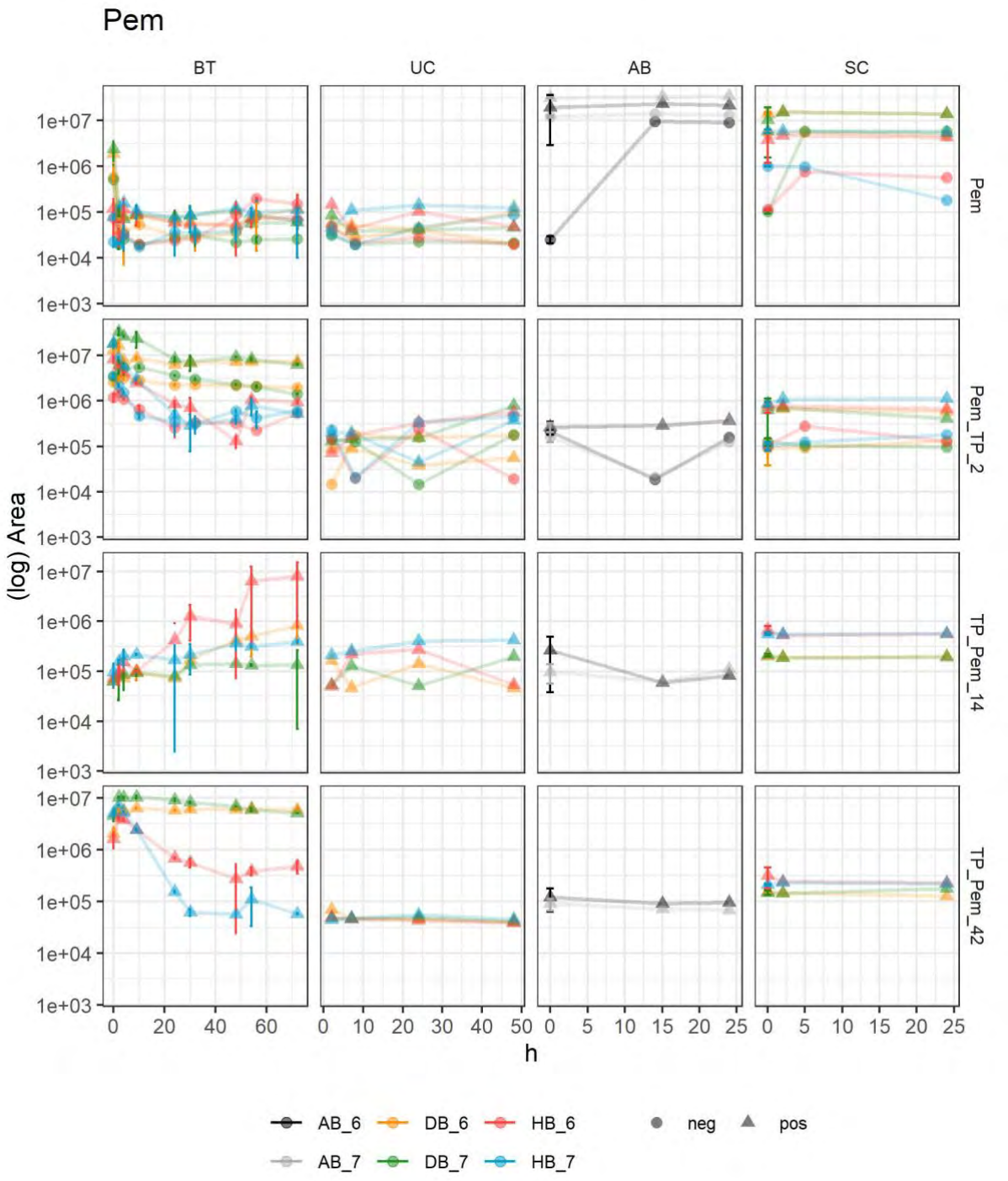
TP_Pan_14_remeas



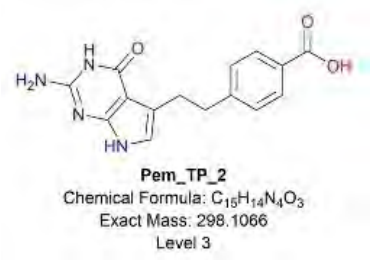
Pan

S3.23 Pemetrexed



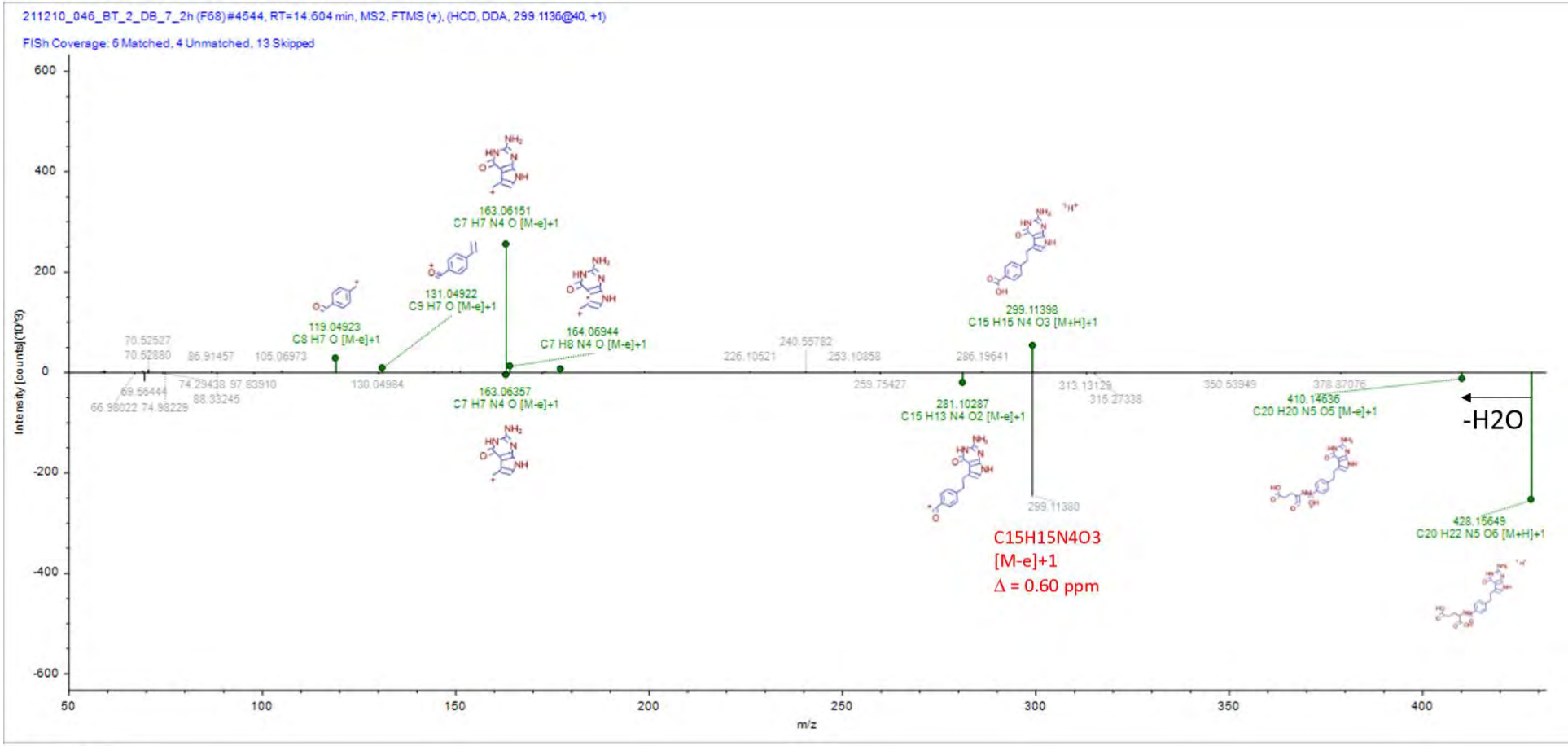

Pem
BT
UC
AB
SC
Pem
Pem_TP_2
TP_Pem_14
TP_Pem_42
(log) Area
1e+07
1e+06
1e+05
1e+04
1e+03
0 20 40 60
0 10 20 30 40 50
0 5 10 15 20 25
h
AB_6
DB_6
HB_6
AB_7
DB_7
HB_7
neg
pos

S3.23.1. Pem TP 2



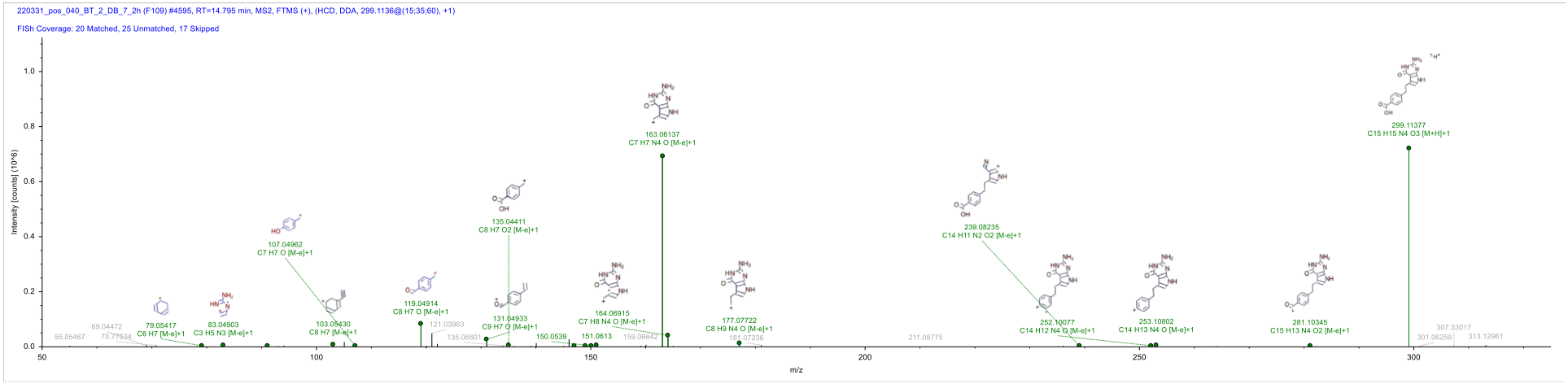
Nominal masses 163 and 281 was also observed for parent compound, which corresponds to allyl cleavage, and water loss respectively. $[M-H]^-$ ion could not be identified, which could indicate carboxylate function. Ion with nominal mass 299 was not present in parental MS^1 scan. The mass could shares the same value as $[M+H]^+$ ion of TP, but no feasible fragmentation reaction was found. The parent was not detected in the stepped NCE measurements.

Pem_TP_2

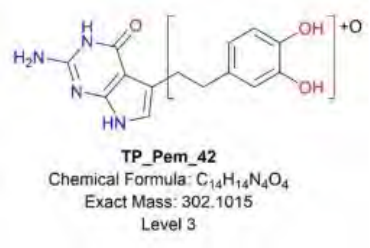

211210_046_BT_2_DB_7_2h (F68)#4544, RT=14.604 min, MS2, FTMS (+), (HCD, DDA, 299.1136@40, +1)
FISh Coverage: 6 Matched, 4 Unmatched, 13 Skipped
Intensity [counts](10^3)
m/z
163.06151
C7 H7 N4 O [M-e]+1
131.04922
C9 H7 O [M-e]+1
119.04923
C8 H7 O [M-e]+1
164.06944
C7 H8 N4 O [M-e]+1
163.06357
C7 H7 N4 O [M-e]+1
299.11398
C15 H15 N4 O3 [M+H]+1
281.10287
C15 H13 N4 O2 [M-e]+1
299.11380
C15H15N4O3
[M-e]+1
Δ = 0.60 ppm
410.14636
C20 H20 N5 O5 [M-e]+1
-H2O
428.15649
C20 H22 N5 O6 [M+H]+1

Pem

Pem_TP_2_remeas

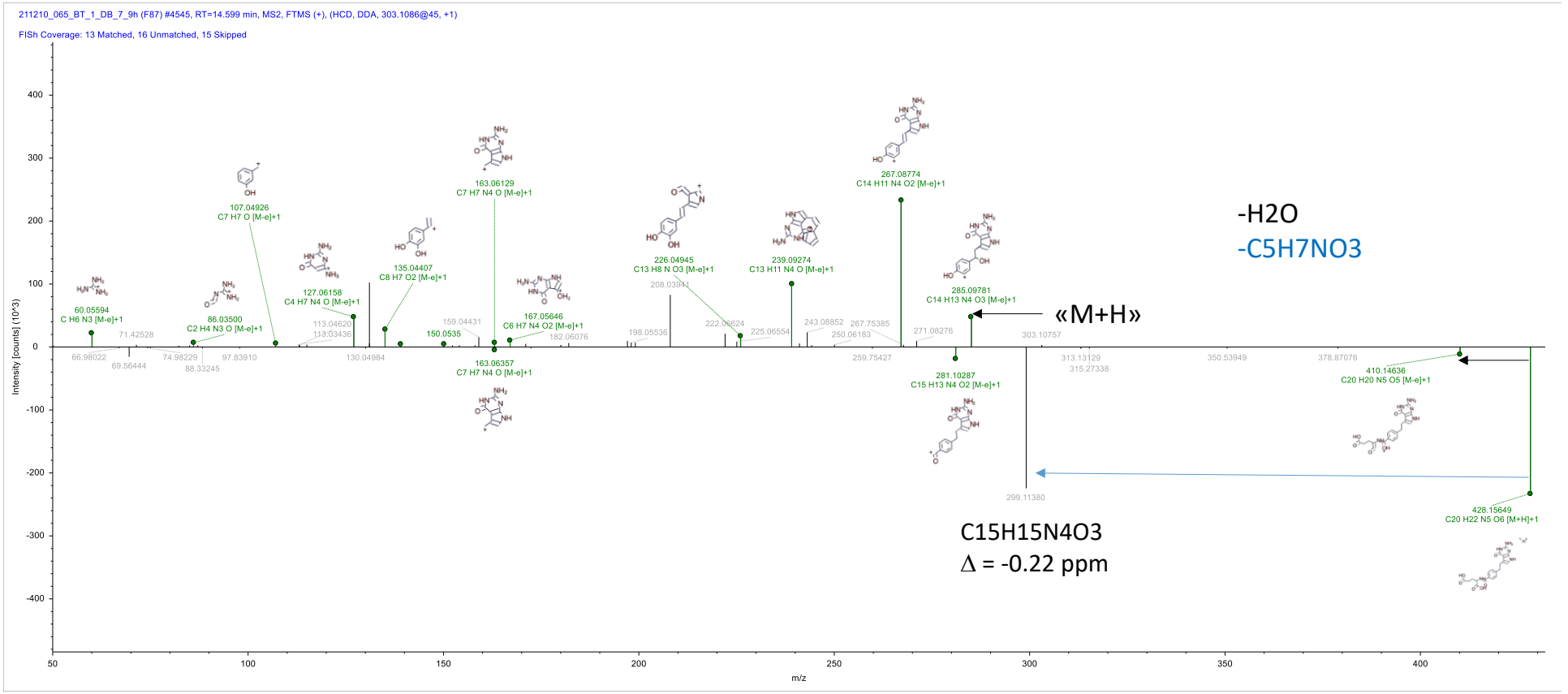


S3.23.2. TP Pem 42



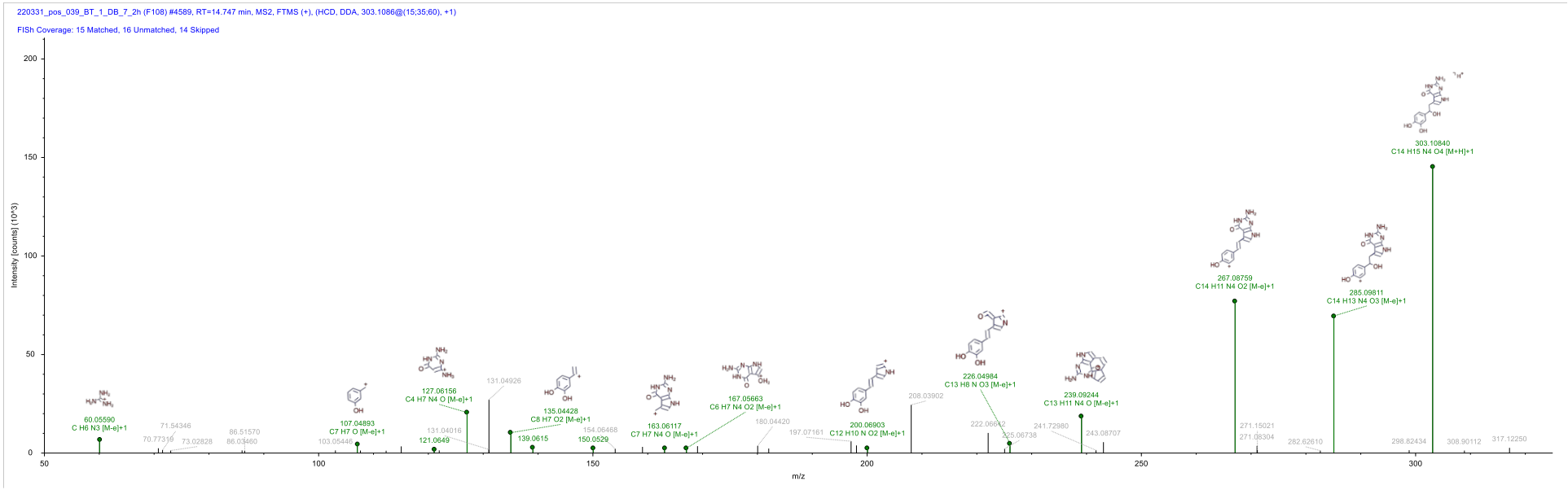
Fragments with nominal mass 163 were observed in the MS^2 for parent and TP compounds, which indicates hydroxylation of either benzene or methylene. Fragmentation or neutral loss of $C_5H_7NO_3$ (pyroglutamic acid) was not observed for TP, which indicates cleavage of side chain.

TP_Pem_42

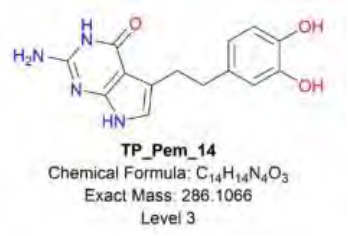

211210_065_BT_1_DB_7_9h (F87) #4545, RT=14.599 min, MS2, FTMS (+), (HCD, DDA, 303.1086@45, +1)
FISh Coverage: 13 Matched, 16 Unmatched, 15 Skipped
Intensity [counts] (10^3)
m/z
60.05594
C H6 N3 [M-e]+1
86.03500
C2 H4 N3 O [M-e]+1
107.04926
C7 H7 O [M-e]+1
127.06158
C4 H7 N4 O [M-e]+1
135.04407
C8 H7 O2 [M-e]+1
163.06129
C7 H7 N4 O [M-e]+1
167.05646
C6 H7 N4 O2 [M-e]+1
163.06357
C7 H7 N4 O [M-e]+1
226.04945
C13 H8 N O3 [M-e]+1
239.09274
C13 H11 N4 O [M-e]+1
267.08774
C14 H11 N4 O2 [M-e]+1
285.09781
C14 H13 N4 O3 [M-e]+1
281.10287
C15 H13 N4 O2 [M-e]+1
«M+H»
-H2O
-C5H7NO3
410.14636
C20 H20 N5 O5 [M-e]+1
428.15649
C20 H22 N5 O6 [M+H]+1
C15H15N4O3
Δ = -0.22 ppm

Pem

TP_Pem_42_remeas

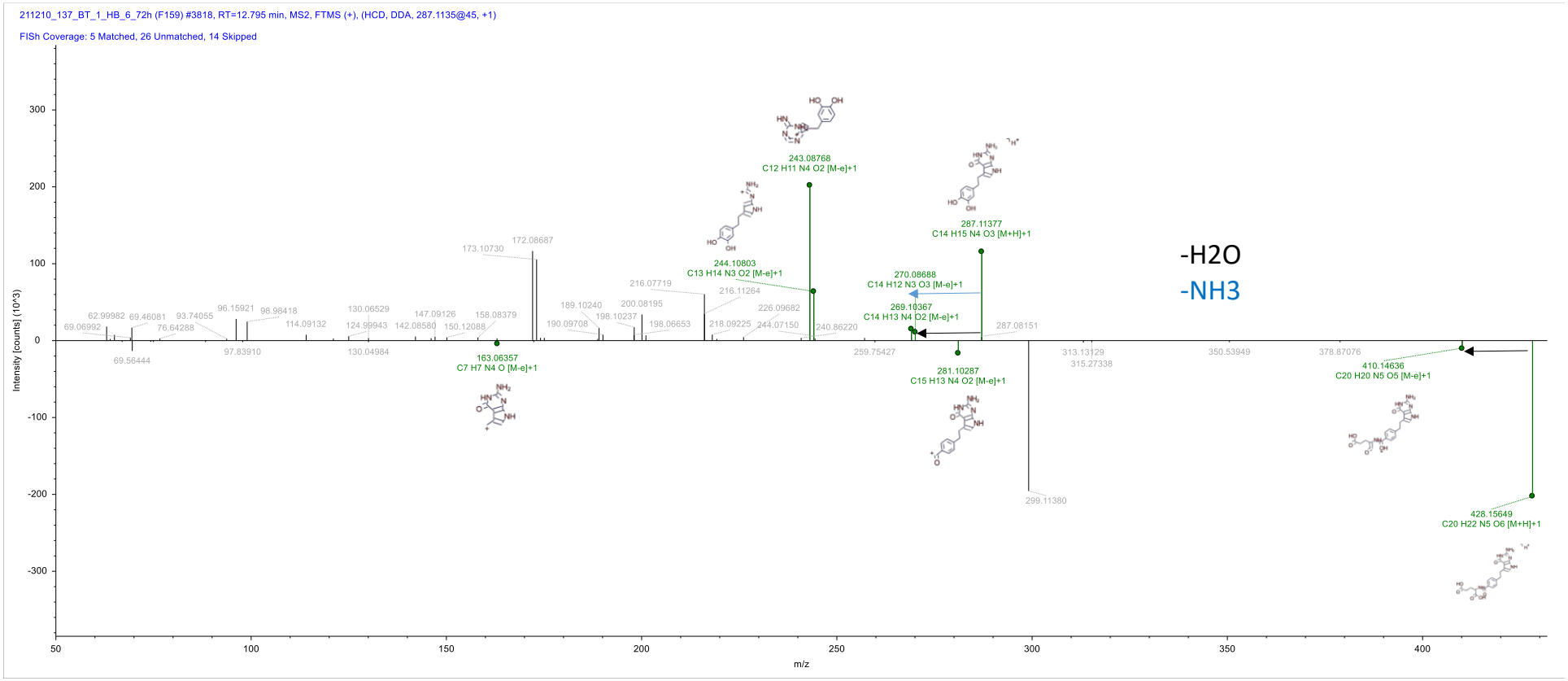


S3.23.3. TP Pem 14



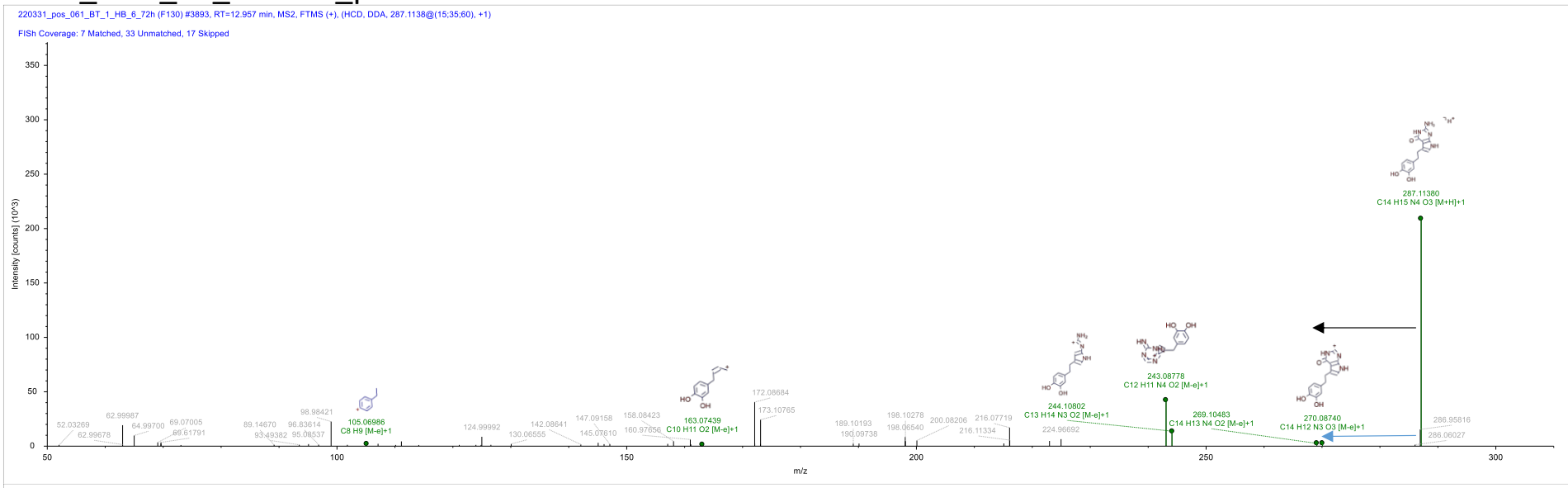
No matches with parent compound. Water loss was detected for both, while ammonia loss was only detected for TP.

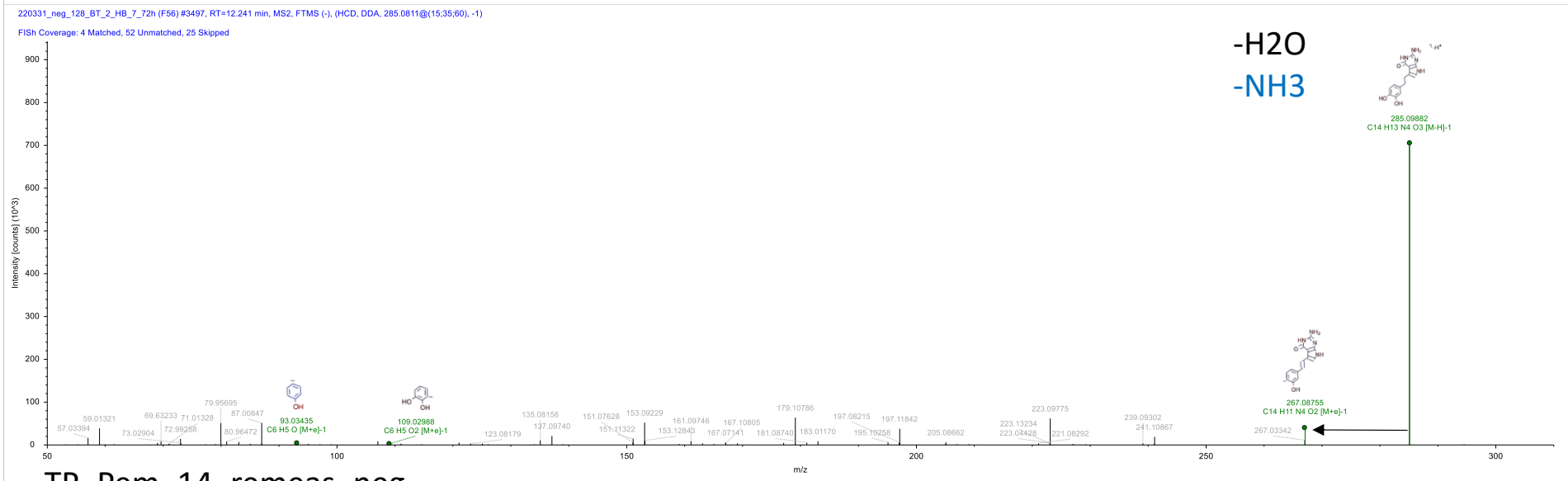
TP_Pem_14


211210_137_BT_1_HB_6_72h (F159) #3818, RT=12.795 min, MS2, FTMS (+), (HCD, DDA, 287.1135@45, +1)
FISh Coverage: 5 Matched, 26 Unmatched, 14 Skipped
Intensity [counts] (10^3)
m/z
243.08768
C12 H11 N4 O2 [M-e]+1
287.11377
C14 H15 N4 O3 [M+H]+1
244.10803
C13 H14 N3 O2 [M-e]+1
270.08688
C14 H12 N3 O3 [M-e]+1
269.10367
C14 H13 N4 O2 [M-e]+1
163.06357
C7 H7 N4 O [M-e]+1
281.10287
C15 H13 N4 O2 [M-e]+1
410.14636
C20 H20 N5 O5 [M-e]+1
428.15649
C20 H22 N5 O6 [M+H]+1
-H2O
-NH3

Pem

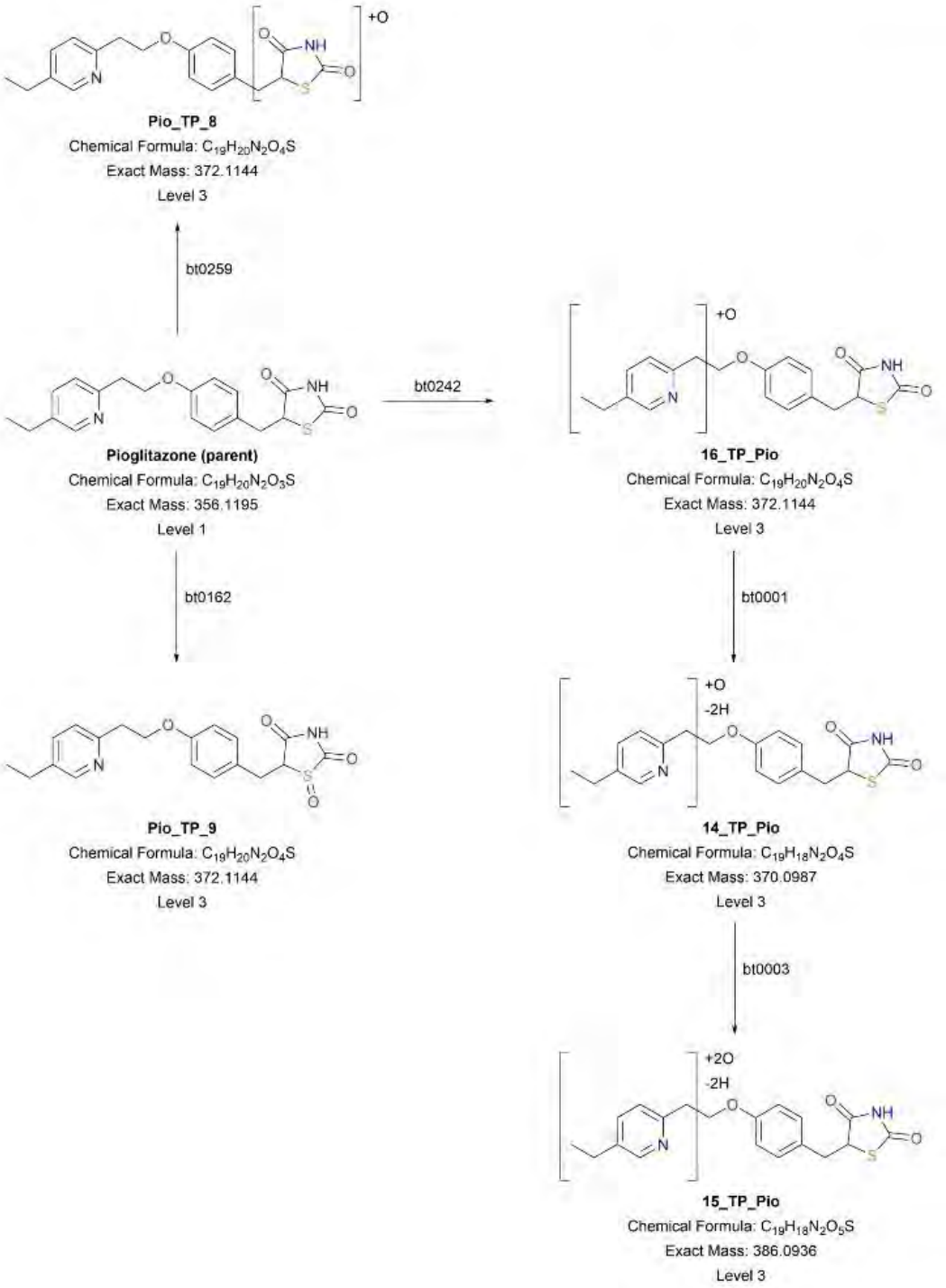
TP_Pem_14_remeas_pos

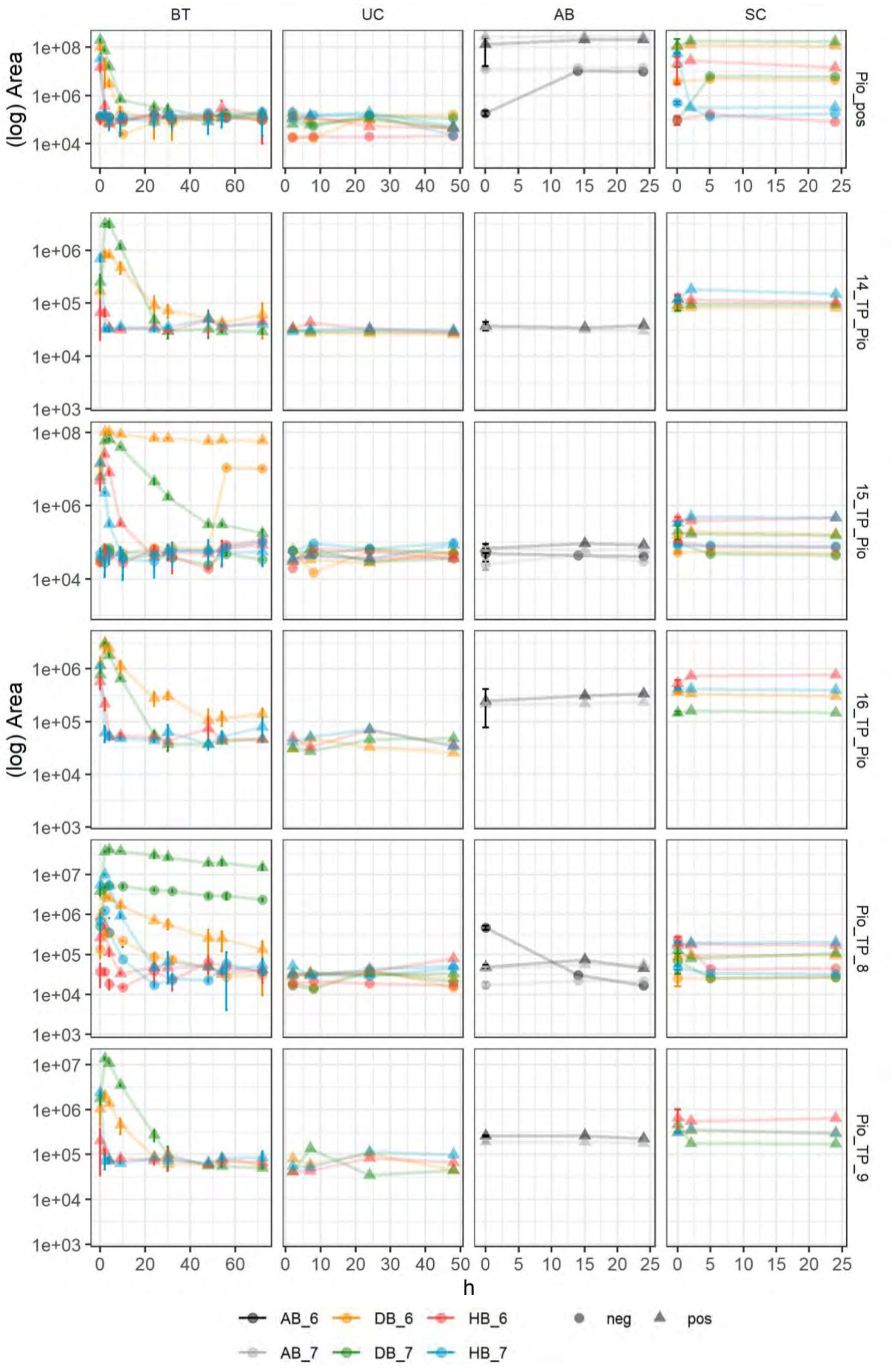




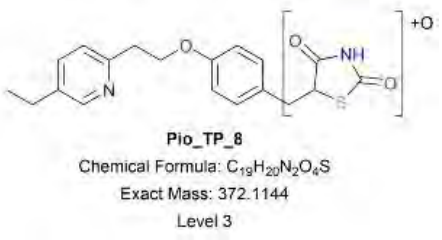
TP_Pem_14_remeas_neg

S3.24 Pioglitazone




BT
UC
AB
SC
(log) Area
Pio_pos
14_TP_Pio
15_TP_Pio
16_TP_Pio
Pio_TP_8
Pio_TP_9
h
AB_6
DB_6
HB_6
AB_7
DB_7
HB_7
neg
pos

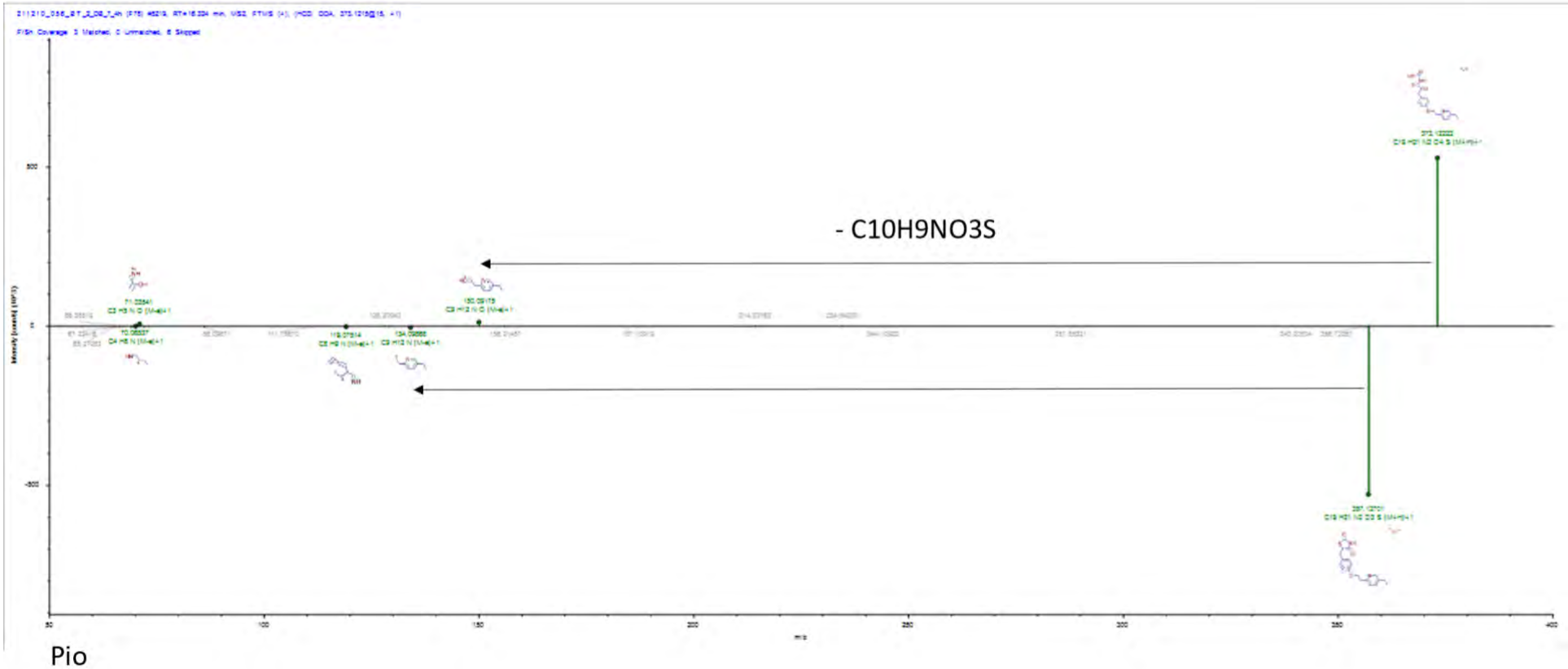
S3.24.1. Pio TP 8



Pio_TP_8
Chemical Formula: $C_{19}H_{20}N_2O_4S$
Exact Mass: 372.1144
Level 3

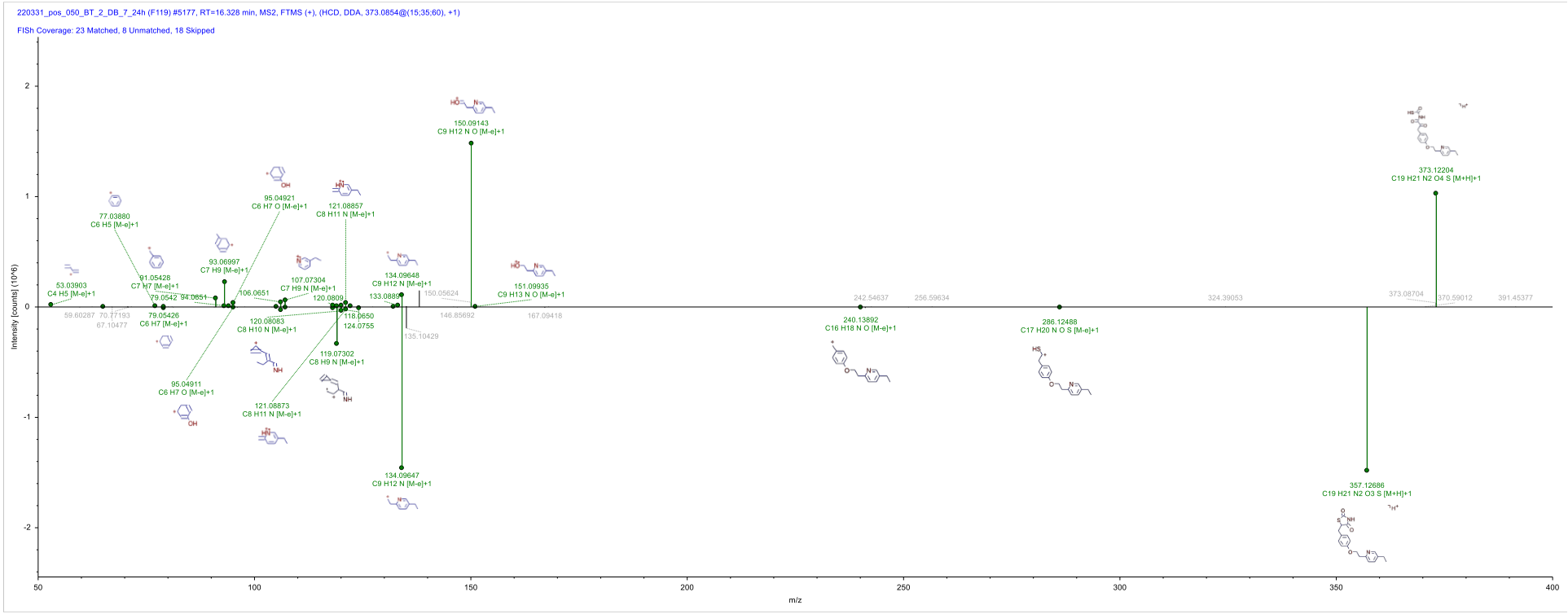
Three isomers were found with RT 12.8 (16 TP Pio), RT 14.0 (Pio TP 9) and 16.3 (Pio TP 8). Chemical formula could possibly arise from oxidative *S*-dealkylation (Pio TP 8), hydroxylation (16 TP Pio) or oxidation to sulfoxide (Pio TP 9). Structures were assigned according to best match with MS^2 spectrum. TP shows matches with parent spectra for ions at 79, 91, 95, 106, 107, 118, 119, 120, 121 and 134. However, fragments with nominal masses 95 and 134 support no hydroxylation on benzyl or pyridine moiety respectively. Similar fragmentation pattern (–$C_{10}H_9NO_3S$) was observed for both. Neutral water loss was observed in a different MS^2 scan.

Pio_TP_8



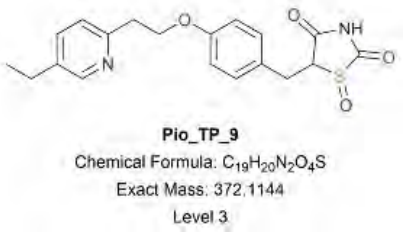
Pio

Pio_TP_8_remeas



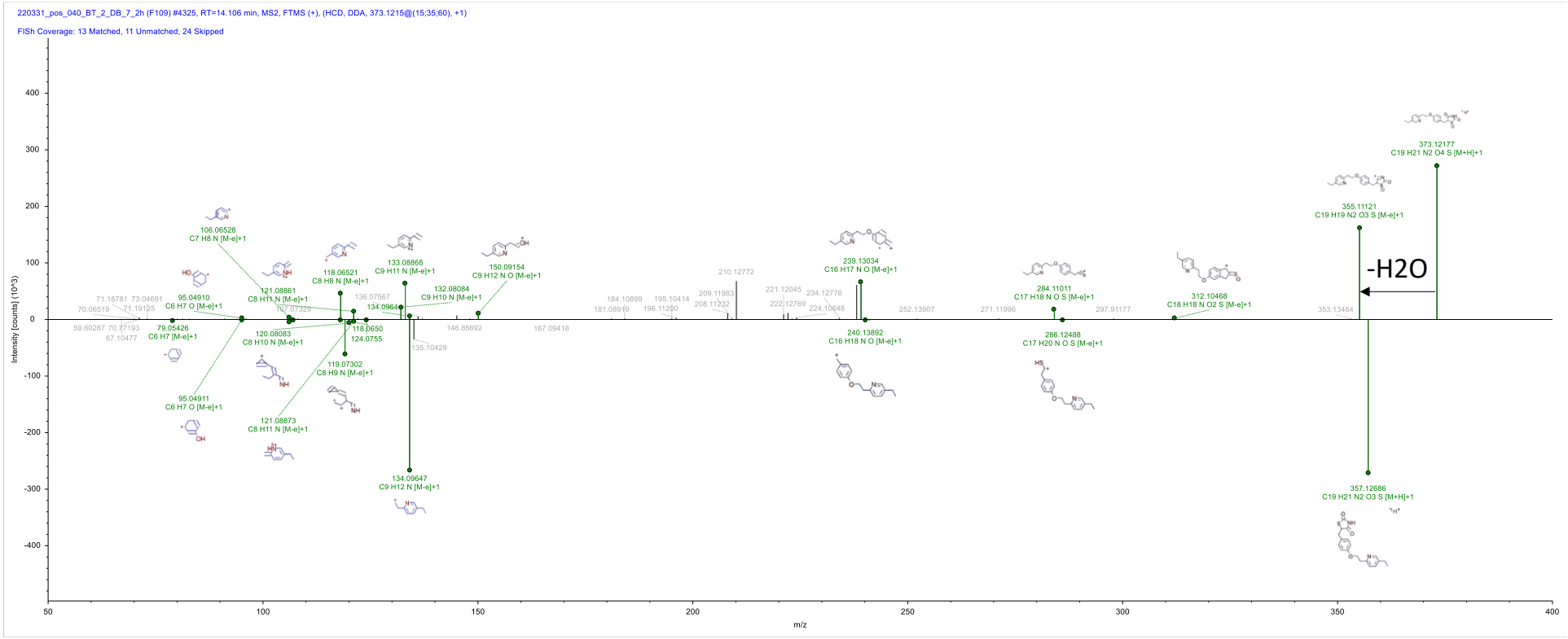
Pio_remeas

S3.24.2. Pio TP 9



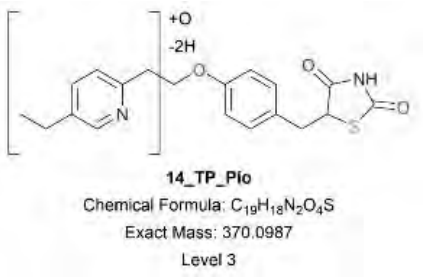
Three isomers were found with RT 12.8 (16 TP Pio), RT 14.0 (Pio TP 9) and 16.3 (Pio TP 8). Chemical formula could possibly arise from oxidative *S*-dealkylation (Pio TP 8), hydroxylation (16 TP Pio) or oxidation to sulfoxide (Pio TP 9). Structures were assigned according to best match with MS^2 spectrum. Fragment matches at m/z 95, 106, 118, 121 and 134, where 106, 121 and 134 indicate no hydroxylation of terminal carbon.

Pio_TP_9_remeas



Pio_remeas

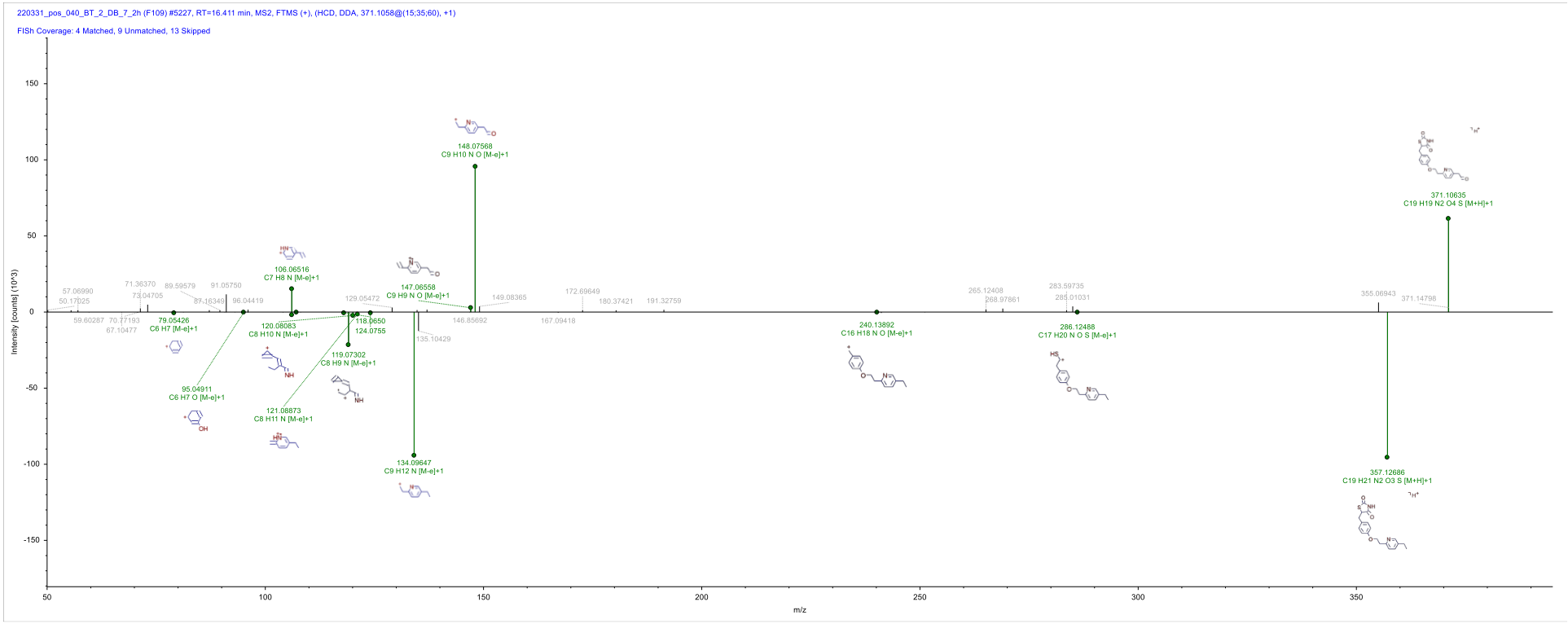
S3.24.3. 14 TP Pio



14_TP_Pio
Chemical Formula: $C_{19}H_{18}N_2O_4S$
Exact Mass: 370.0987
Level 3

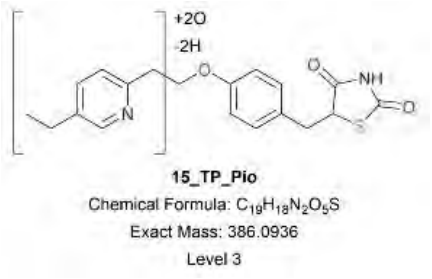
Fragment at 106 m/z was observed for both parent and TP. Ion with mass 148, which is absent in parental MS^2, support oxidation of terminal carbon. Ketone derived from secondary alcohol as reported in Jaakkola et al.[5] is also possible.

14_TP_Pio_remeas



Pio_remeas

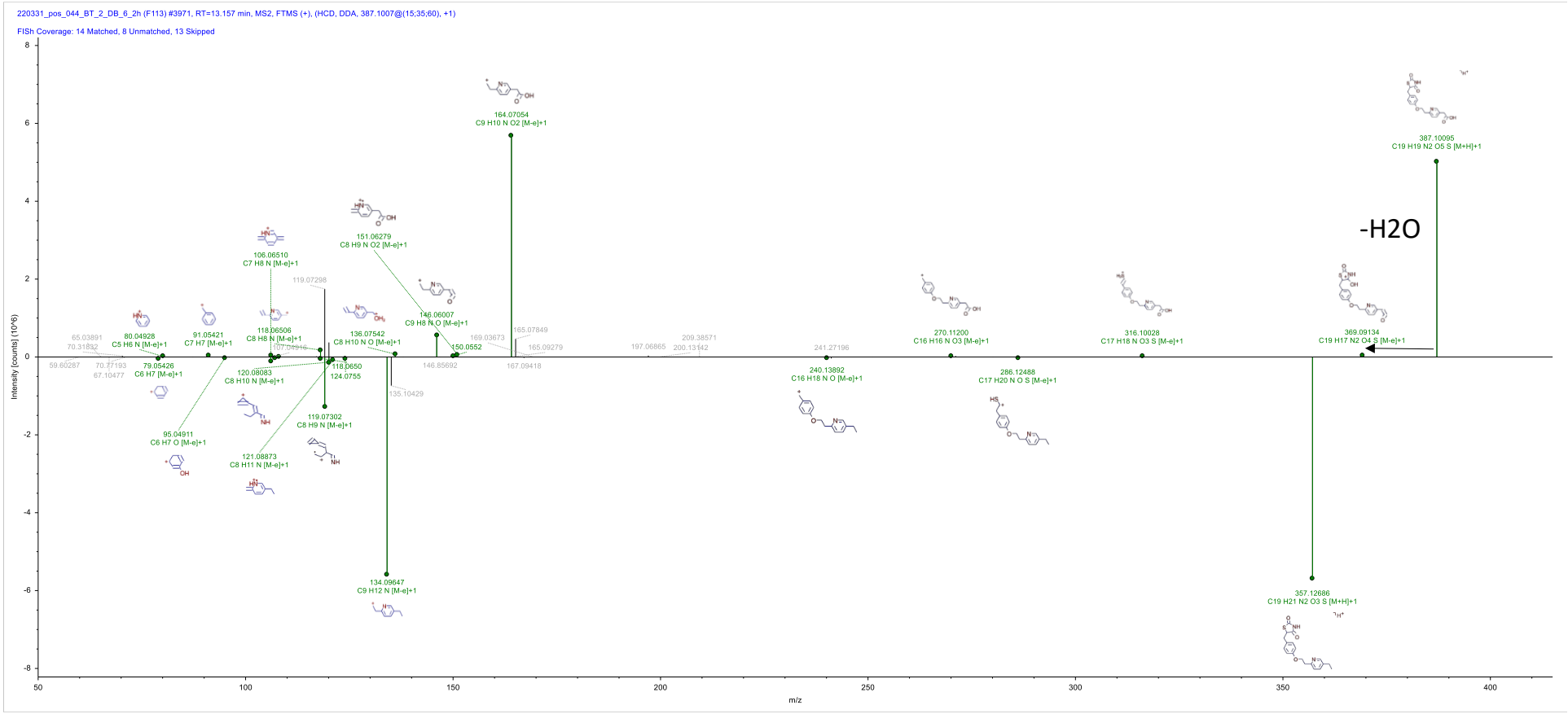
S3.24.4. 15 TP Pio



15_TP_Pio
Chemical Formula: $C_{19}H_{18}N_2O_5S$
Exact Mass: 386.0936
Level 3

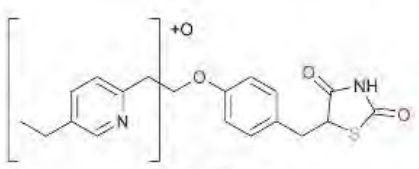
Fragments with nominal masses 91, 106, 118, 119 and 120 were also observed for parent compound. Water loss from M+H ion, which was not present in 14 TP Pio, could indicate oxidation to carboxylic acid.

15_TP_Pio_remeas



Pio_remeas

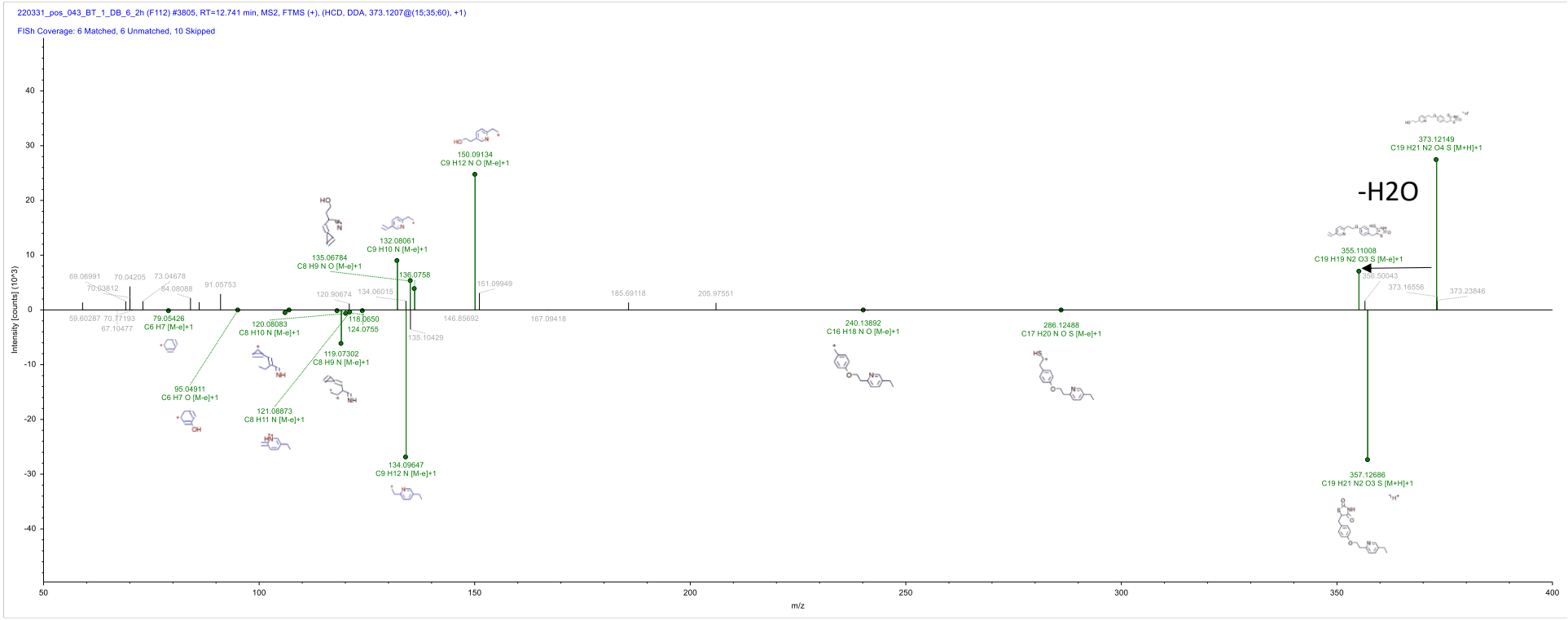
S3.24.5. 16 TP Pio



16_TP_Pio
Chemical Formula: $C_{19}H_{20}N_2O_4S$
Exact Mass: 372.1144
Level 3

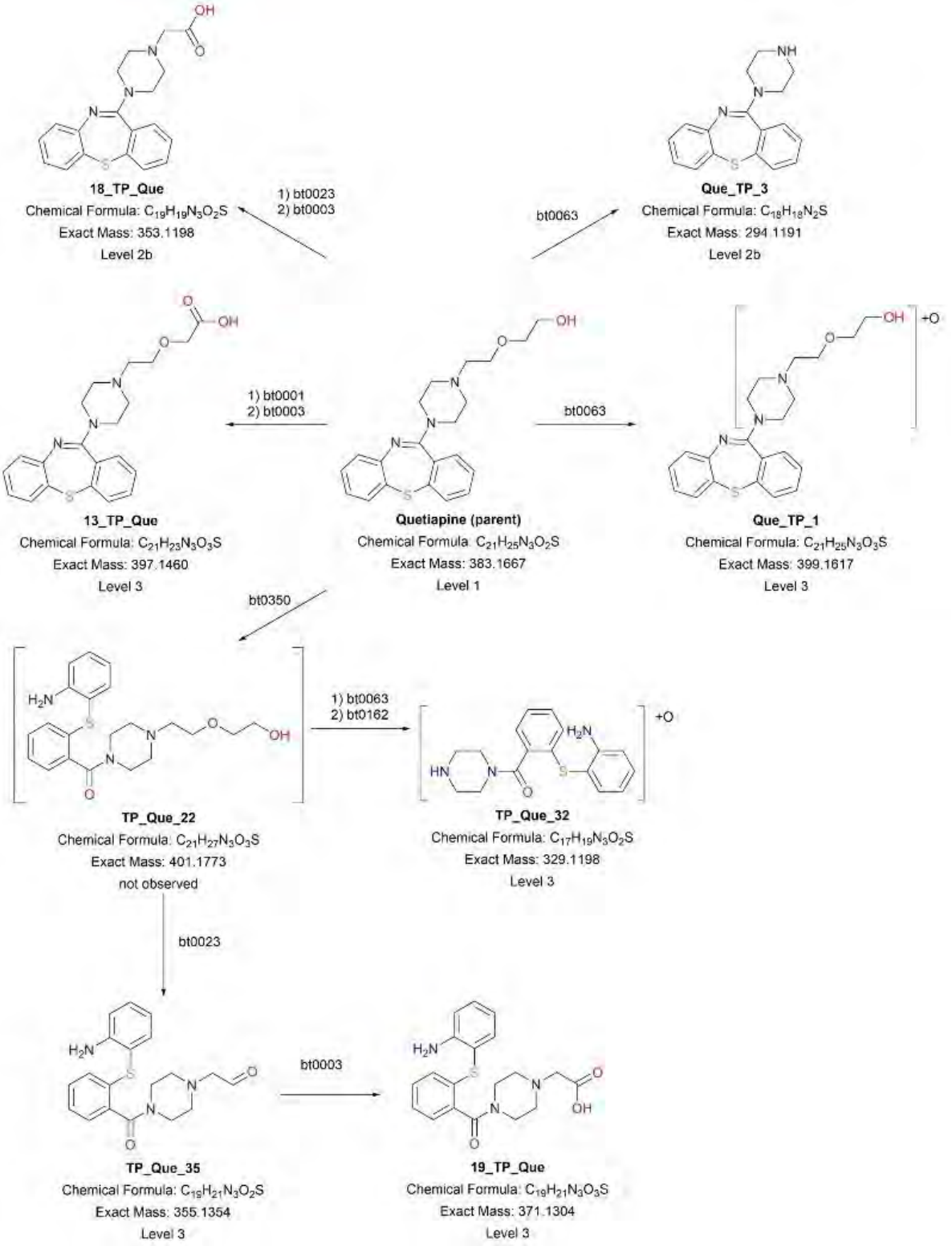
Three isomers were found with RT 12.8 (16 TP Pio), RT 14.0 (Pio TP 9) and 16.3 (Pio TP 8). Chemical formula could possibly arise from oxidative *S*-dealkylation (Pio TP 8), hydroxylation (16 TP Pio) or oxidation to sulfoxide (Pio TP 9). Structures were assigned according to best match with MS^2 spectrum. No matches detected between parent compound and TP. Fragment with masses 150 and 134 for TP and parent respectively, show mass difference of one oxygen atom, which could suggest hydroxylation of terminal ethyl moiety. Formation of secondary alcohol instead of terminal is also plausible and was reported by Jaakkola et al.[5]

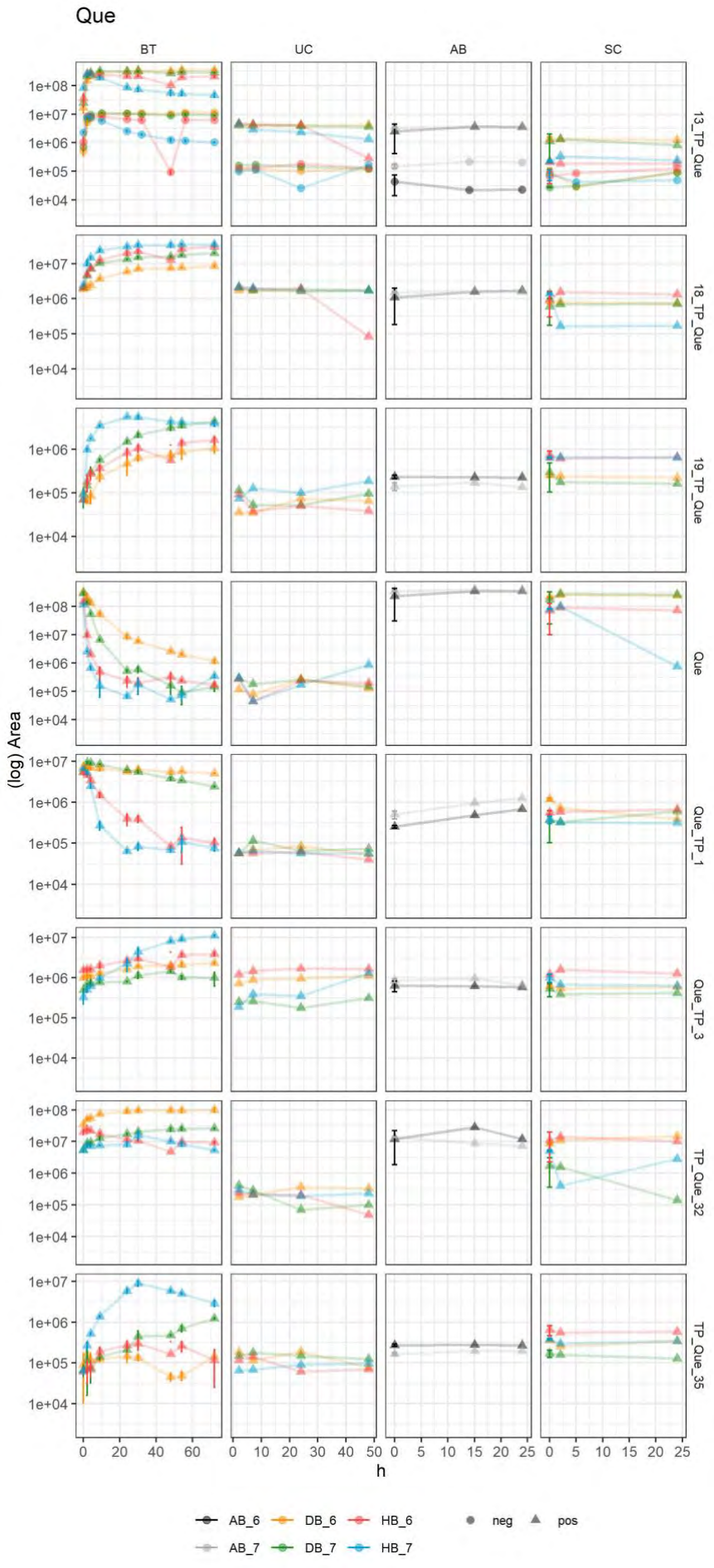
16_TP_Pio_remeas



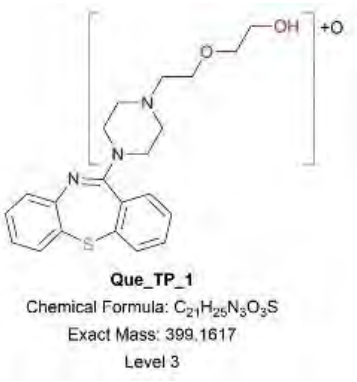
Pio_remeas

S3.25 Quetiapine



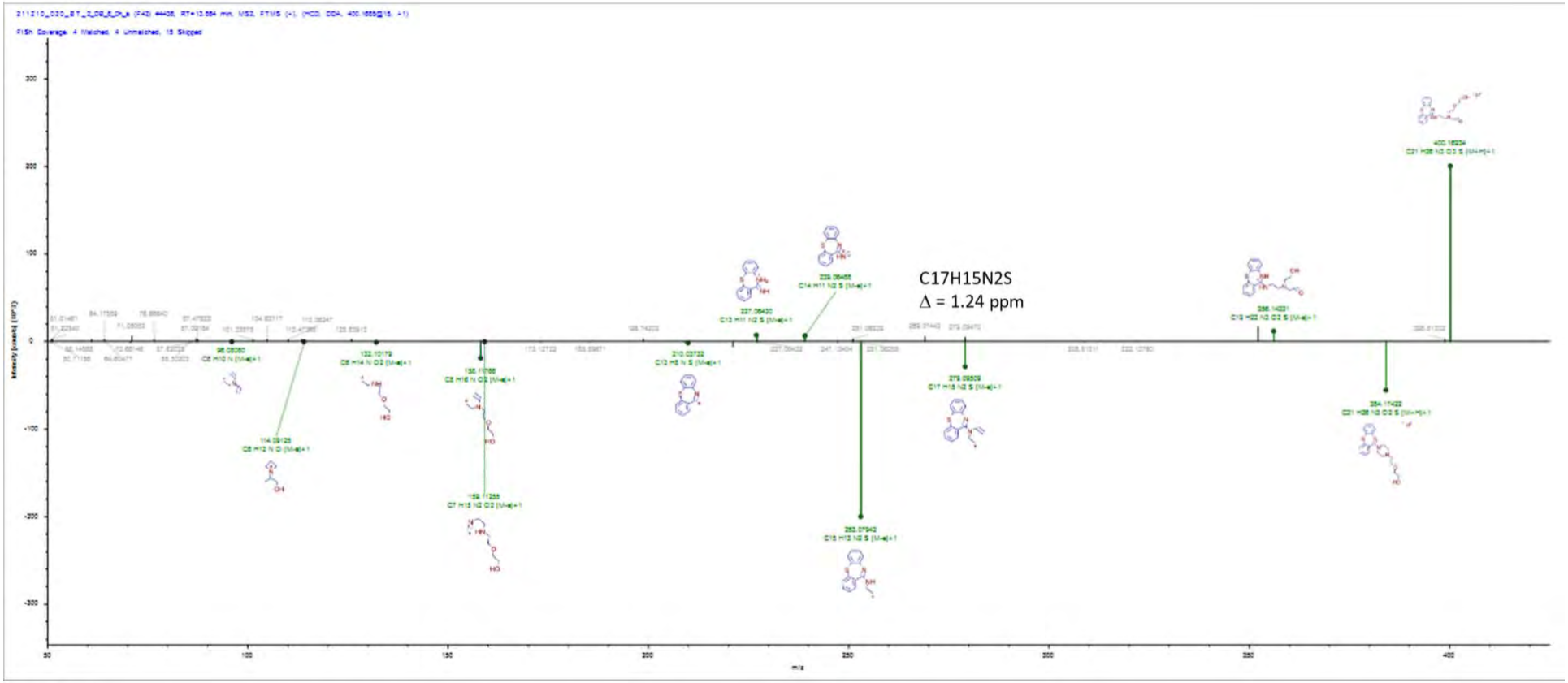

Que
BT
UC
AB
SC
13_TP_Que
18_TP_Que
19_TP_Que
Que
Que_TP_1
Que_TP_3
TP_Que_32
TP_Que_35
(log) Area
h
AB_6
DB_6
HB_6
AB_7
DB_7
HB_7
neg
pos

S3.25.1. Que TP 1



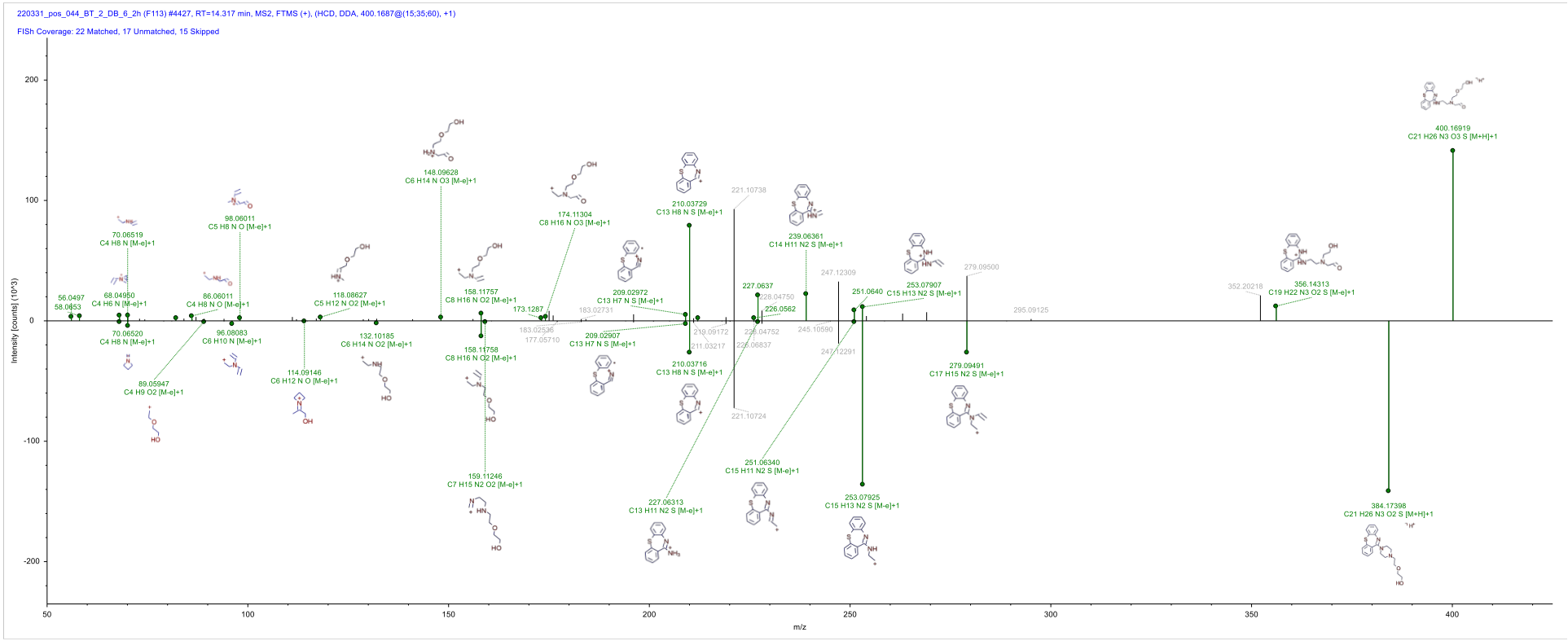
Nominal masses 68, 70, 89, 94, 132, 158, 196, 209, 210, 212, 219, 221, 227, 247, 251, 253 and 279 were also observed for the parent compound. Because of the many matches, it is unlikely that the oxidation occurred on the ring system. Thus, hydroxylation on the piperazine ring is probable and after cleavage leads to an aldehyde.

Que_TP_1



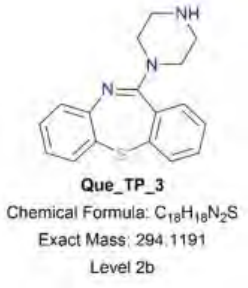
Que

Que_TP_1_remeas



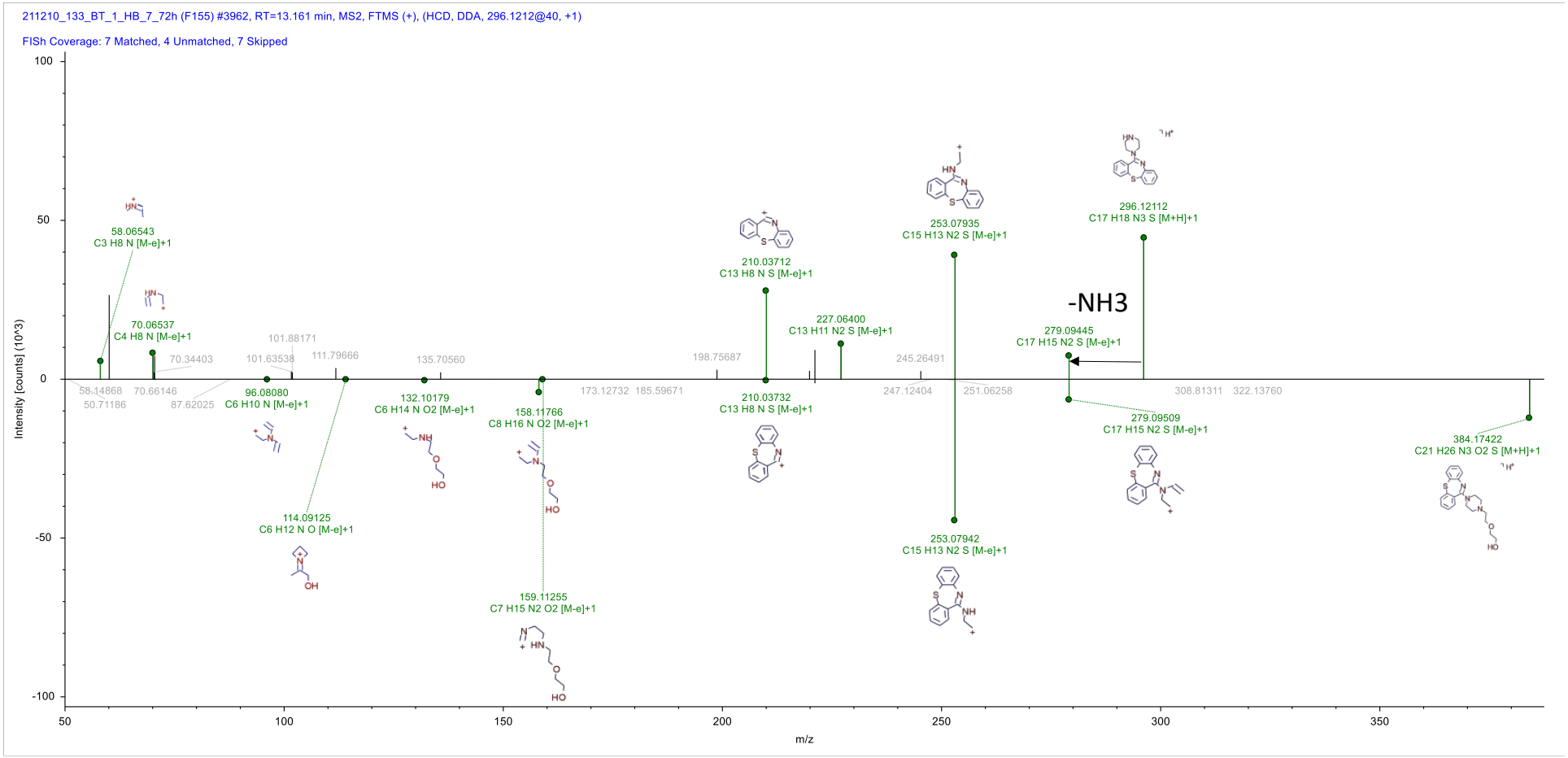
Que_remeas

S3.25.2. Que TP 3



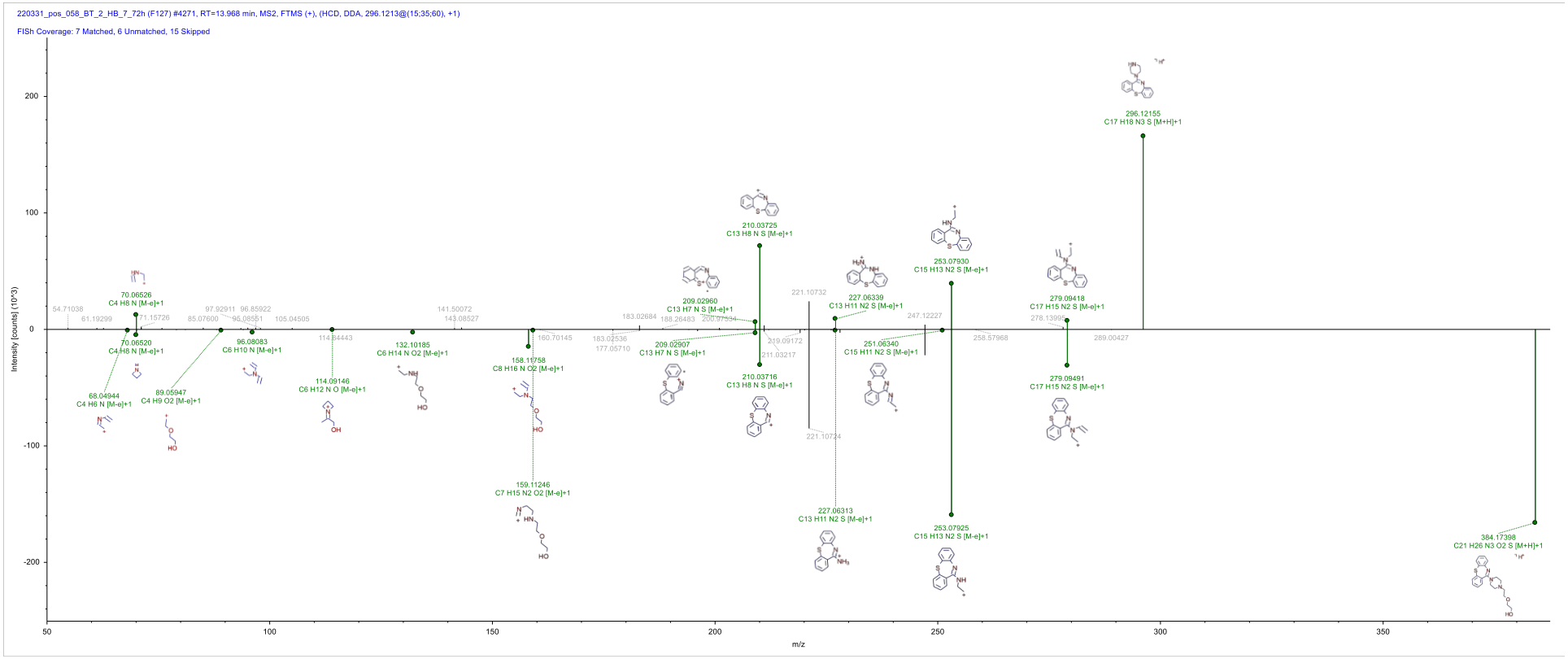
Nominal masses 70, 209, 210, 221, 227, 247, 253 and 279 were also observed for the parent compound. Fragments in the MS^2 of the parent containing oxygen were absent in the MS^2 of the TP, which indicates deamination.

Que_TP_3


211210_133_BT_1_HB_7_72h (F155) #3962, RT=13.161 min, MS2, FTMS (+), (HCD, DDA, 296.1212@40, +1)
FISh Coverage: 7 Matched, 4 Unmatched, 7 Skipped
Intensity [counts] (10^3)
m/z
58.06543
C3 H8 N [M-e]+1
70.06537
C4 H8 N [M-e]+1
96.08080
C6 H10 N [M-e]+1
114.09125
C6 H12 N O [M-e]+1
132.10179
C6 H14 N O2 [M-e]+1
158.11766
C8 H16 N O2 [M-e]+1
159.11255
C7 H15 N2 O2 [M-e]+1
210.03712
C13 H8 N S [M-e]+1
210.03732
C13 H8 N S [M-e]+1
227.06400
C13 H11 N2 S [M-e]+1
253.07935
C15 H13 N2 S [M-e]+1
253.07942
C15 H13 N2 S [M-e]+1
279.09445
C17 H15 N2 S [M-e]+1
279.09509
C17 H15 N2 S [M-e]+1
296.12112
C17 H18 N3 S [M+H]+1
-NH3
384.17422
C21 H26 N3 O2 S [M+H]+1

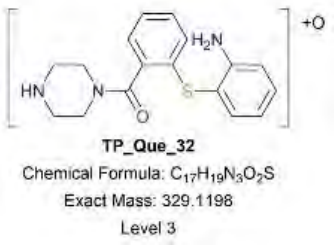
Que

Que_TP_3_remeas



Que_remeas

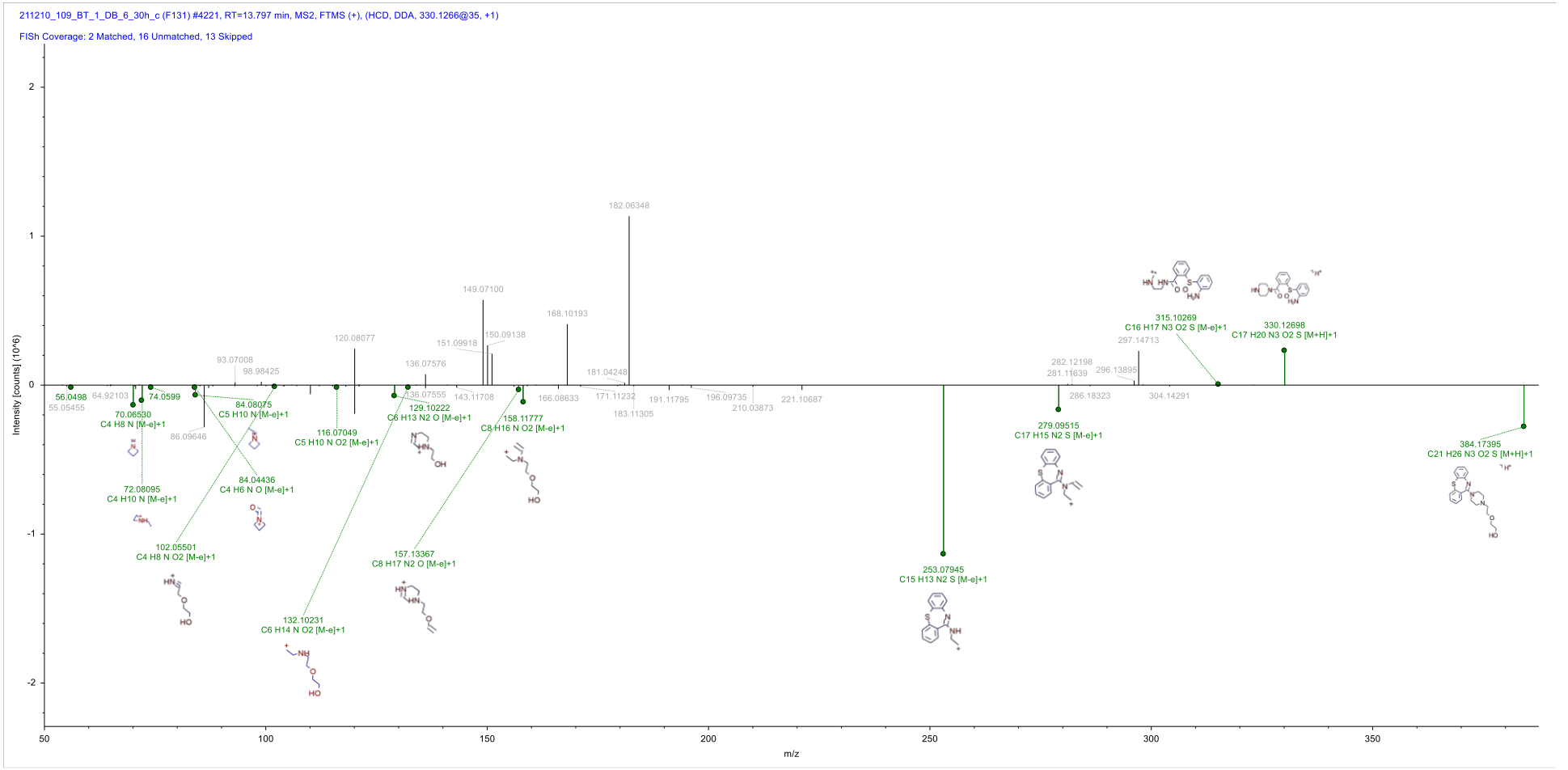
S3.25.3. TP Que 32



TP_Que_32
Chemical Formula: $C_{17}H_{19}N_3O_2S$
Exact Mass: 329.1198
Level 3

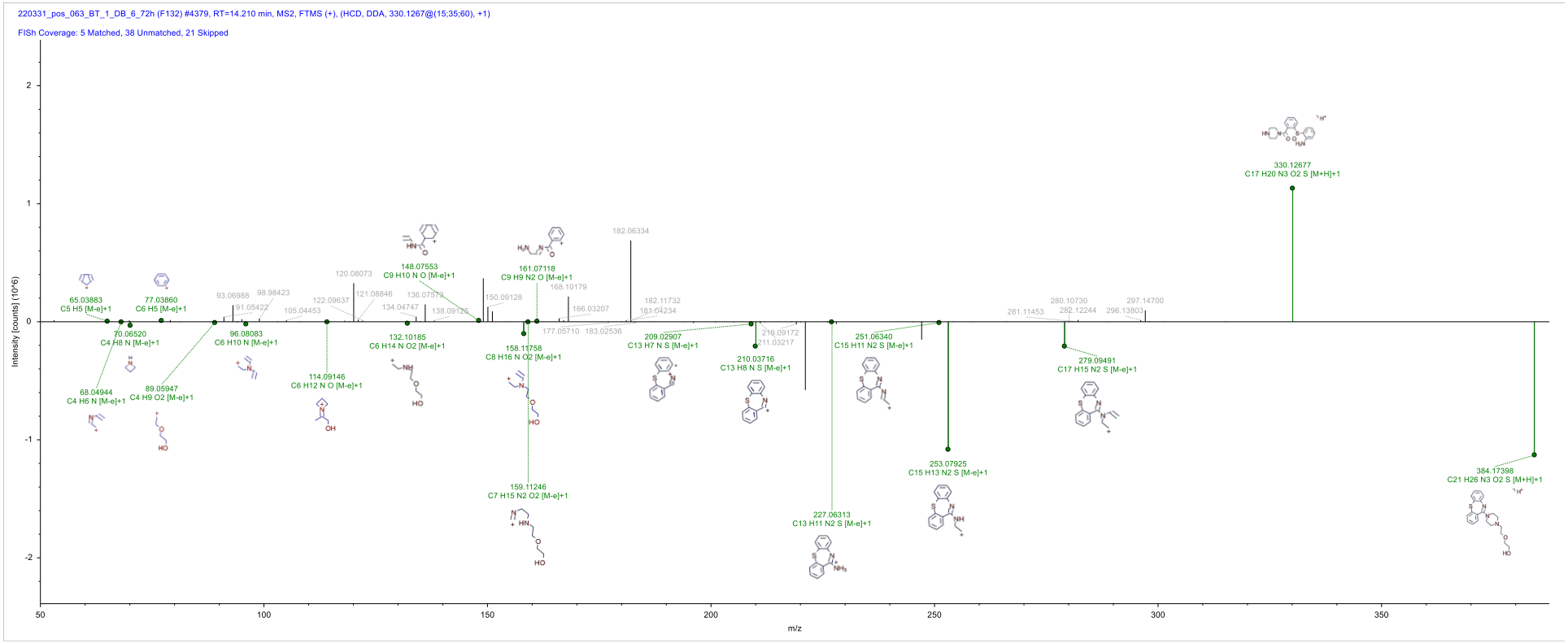
Ions at m/z 79, 94, 120 and 136 were also observed for parent, but without structural annotation. Hydroxylation and/or subsequent ring opening leads to the same chemical formula.

TP_Que_32


211210_109_BT_1_DB_6_30h_c (F131) #4221, RT=13.797 min, MS2, FTMS (+), (HCD, DDA, 330.1266@35, +1)
FISh Coverage: 2 Matched, 16 Unmatched, 13 Skipped
Intensity [counts] (10^6)
m/z
56.0498
C4 H8 N [M-e]+1
70.06530
C4 H10 N [M-e]+1
72.08095
C4 H10 N [M-e]+1
84.08075
C5 H10 N [M-e]+1
84.04436
C4 H6 N O [M-e]+1
102.05501
C4 H8 N O2 [M-e]+1
116.07049
C5 H10 N O2 [M-e]+1
129.10222
C6 H13 N2 O [M-e]+1
132.10231
C6 H14 N O2 [M-e]+1
157.13367
C8 H17 N2 O [M-e]+1
158.11777
C8 H16 N O2 [M-e]+1
253.07945
C15 H13 N2 S [M-e]+1
279.09515
C17 H15 N2 S [M-e]+1
315.10269
C16 H17 N3 O2 S [M-e]+1
330.12698
C17 H20 N3 O2 S [M+H]+1
384.17395
C21 H26 N3 O2 S [M+H]+1

Que

TP_Que_32_remeas

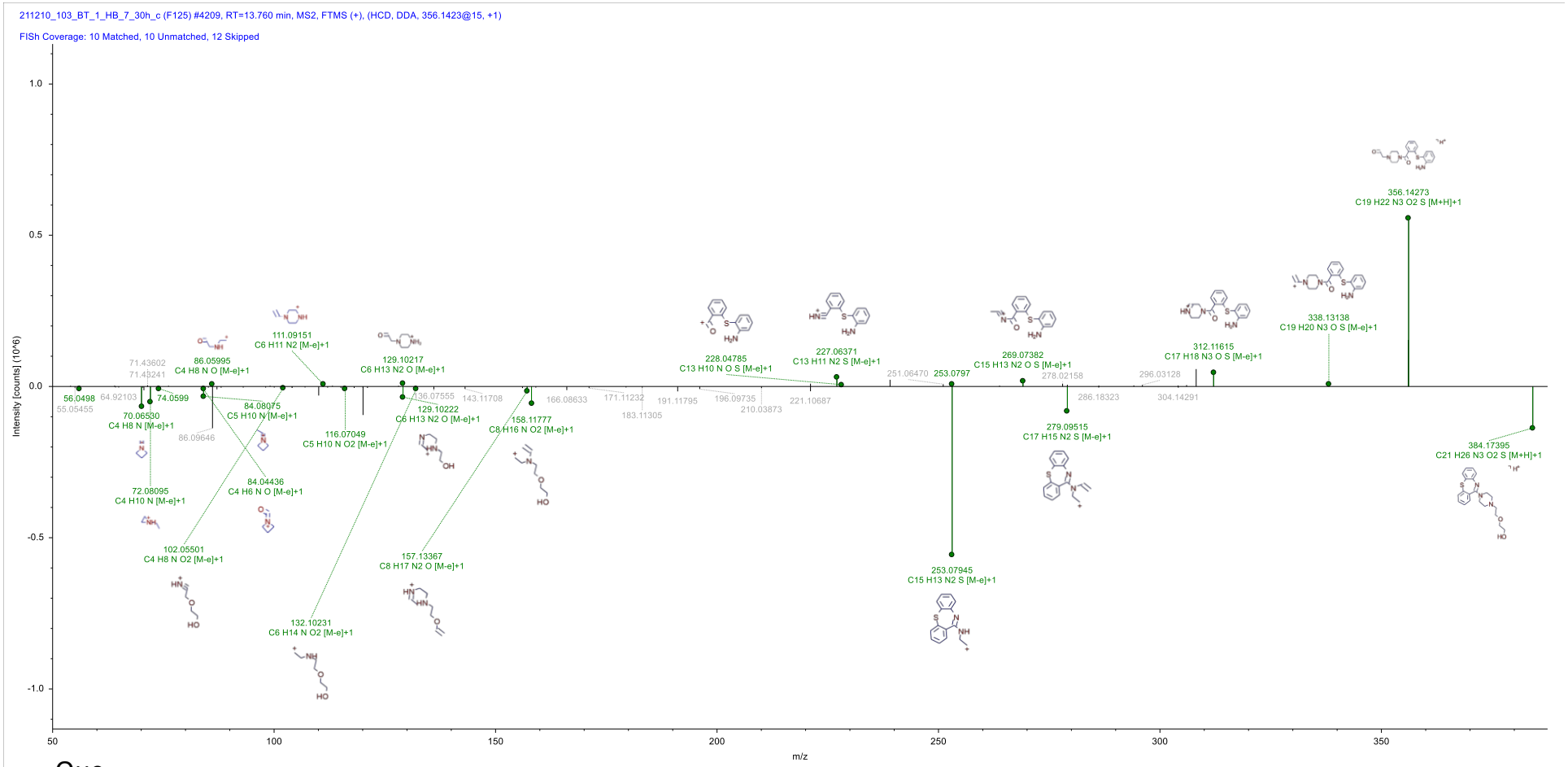


Que_remeas

S3.25.4. TP Que 35

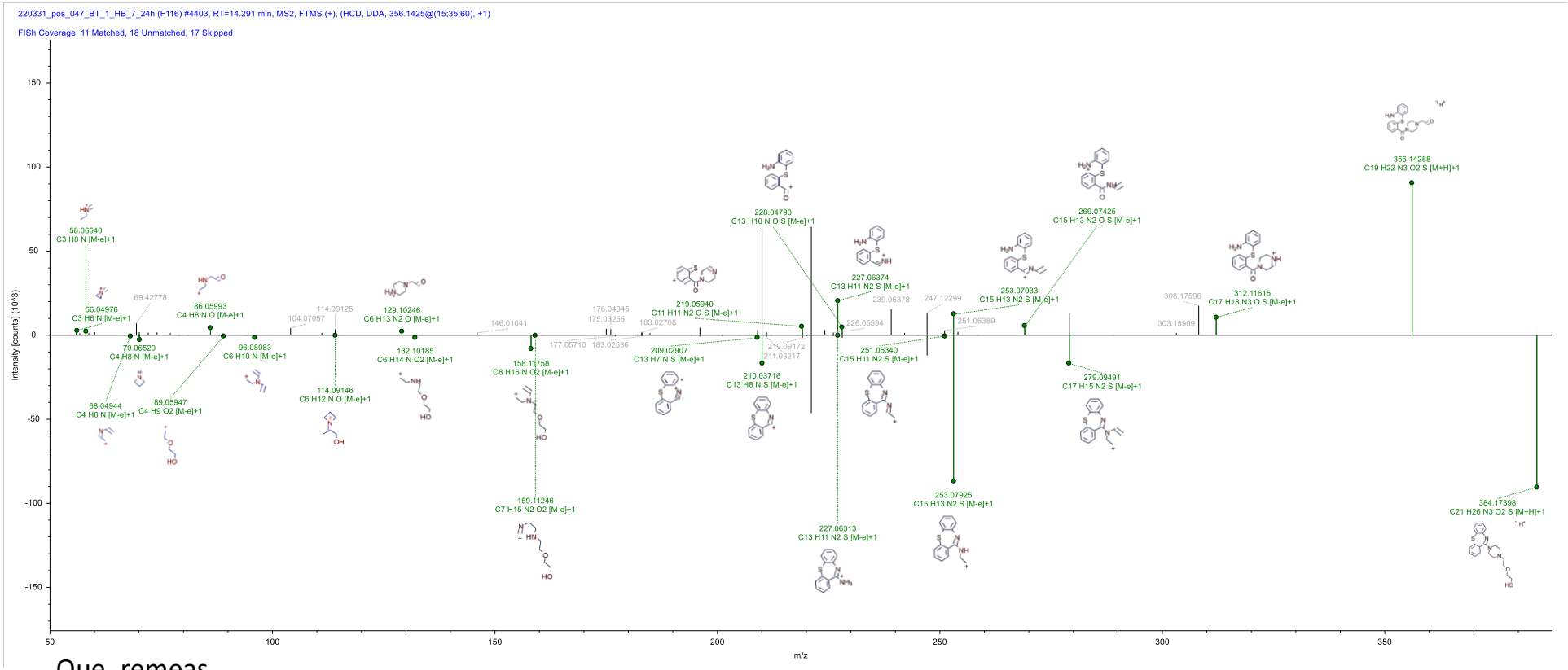
Ions at m/z 70, 114, 196, 209, 210, 221, 227, 247, 253 and 279 were also observed for parent compound.

TP_Que_35


211210_103_BT_1_HB_7_30h_c (F125) #4209, RT=13.760 min, MS2, FTMS (+), (HCD, DDA, 356.1423@15, +1)
FISh Coverage: 10 Matched, 10 Unmatched, 12 Skipped
Intensity [counts] (10^6)
m/z
1.0
0.5
0.0
-0.5
-1.0
50
100
150
200
250
300
350
356.14273
C19 H22 N3 O2 S [M+H]+1
338.13138
C19 H20 N3 O S [M-e]+1
312.11615
C17 H18 N3 O S [M-e]+1
384.17395
C21 H26 N3 O2 S [M+H]+1
269.07382
C15 H13 N2 O S [M-e]+1
279.09515
C17 H15 N2 S [M-e]+1
253.07945
C15 H13 N2 S [M-e]+1
253.0797
251.06470
278.02158
286.18323
296.03128
304.14291
228.04785
C13 H10 N O S [M-e]+1
227.06371
C13 H11 N2 S [M-e]+1
221.10687
210.03873
196.09735
191.11795
183.11305
171.11232
166.08633
143.11708
136.07555
129.10222
C6 H13 N2 O [M-e]+1
129.10217
C6 H13 N2 O [M-e]+1
116.07049
C5 H10 N O2 [M-e]+1
111.09151
C6 H11 N2 [M-e]+1
86.05995
C4 H8 N O [M-e]+1
86.09646
84.08075
C5 H10 N [M-e]+1
84.04436
C4 H6 N O [M-e]+1
74.0599
71.43602
71.43241
70.06530
C4 H8 N [M-e]+1
72.08095
C4 H10 N [M-e]+1
64.92103
56.0498
55.05455
158.11777
C8 H16 N O2 [M-e]+1
157.13367
C8 H17 N2 O [M-e]+1
132.10231
C6 H14 N O2 [M-e]+1
102.05501
C4 H8 N O2 [M-e]+1

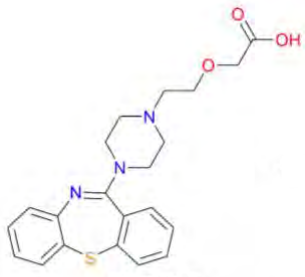
Que

TP_Que_35_remeas



Que_remeas

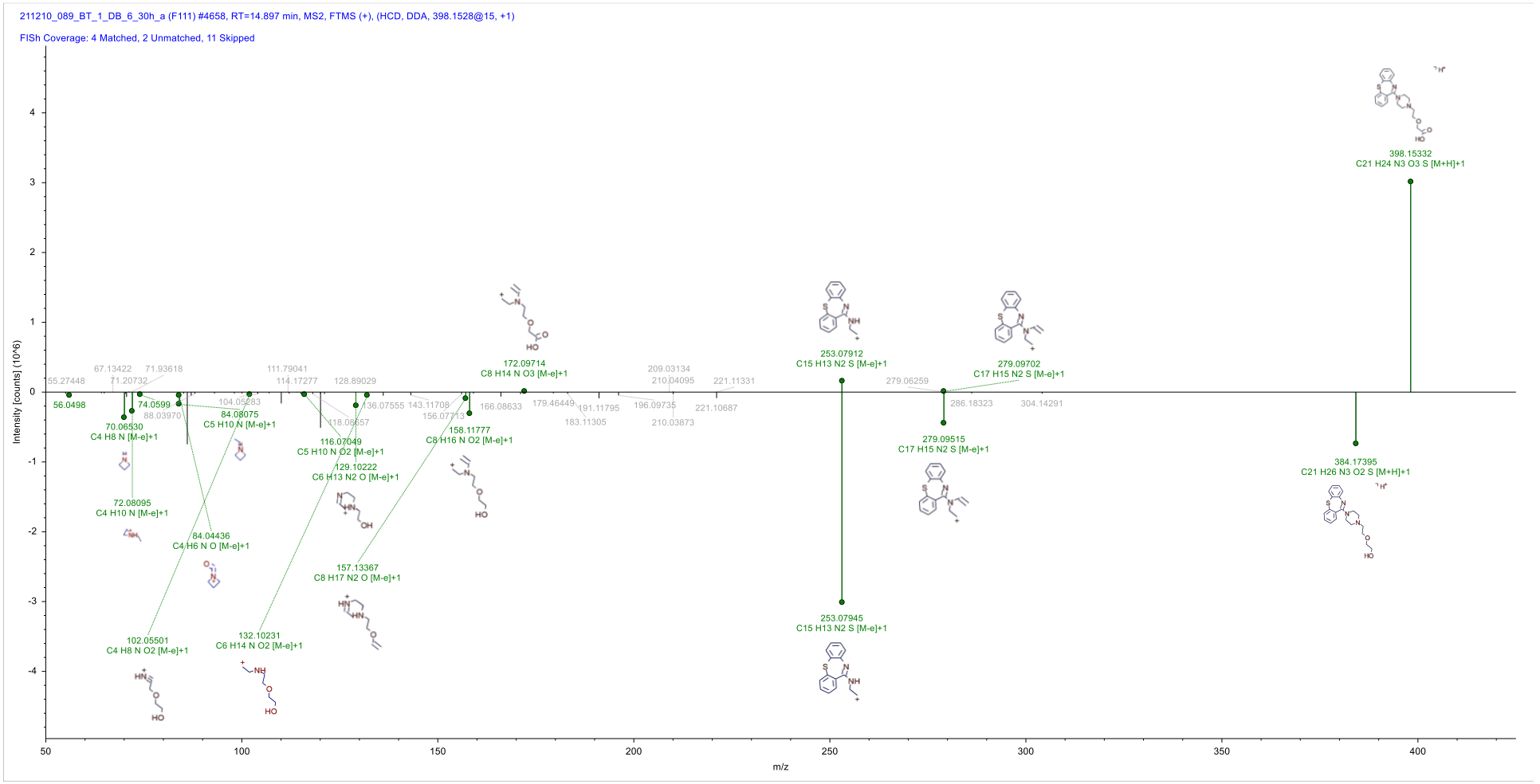
S3.25.5. 13 TP Que



13_TP_Que
Chemical Formula: $C_{21}H_{23}N_3O_3S$
Exact Mass: 397.1460
Level 3

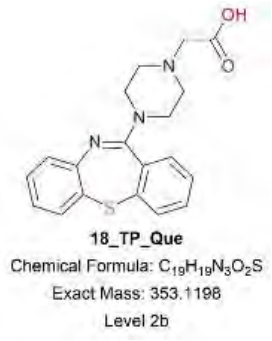
Nominal masses 253 and 279 were also observed in parent MS^2 spectra. Ion with m/z ratio of 172 is only present in TP scan, which indicates that the transformation occurred on the terminal alcohol. This TP was not predicted by any prediction method.

13_TP_Que


211210_089_BT_1_DB_6_30h_a (F111) #4658, RT=14.897 min, MS2, FTMS (+), (HCD, DDA, 398.1528@15, +1)
FISh Coverage: 4 Matched, 2 Unmatched, 11 Skipped
Intensity [counts] (10^6)
m/z
398.15332
C21 H24 N3 O3 S [M+H]+1
384.17395
C21 H26 N3 O2 S [M+H]+1
279.09702
C17 H15 N2 S [M-e]+1
279.09515
C17 H15 N2 S [M-e]+1
253.07912
C15 H13 N2 S [M-e]+1
253.07945
C15 H13 N2 S [M-e]+1
172.09714
C8 H14 N O3 [M-e]+1
158.11777
C8 H16 N O2 [M-e]+1
157.13367
C8 H17 N2 O [M-e]+1
132.10231
C6 H14 N O2 [M-e]+1
129.10222
C6 H13 N2 O [M-e]+1
116.07049
C5 H10 N O2 [M-e]+1
102.05501
C4 H8 N O2 [M-e]+1
84.08075
C5 H10 N [M-e]+1
84.04436
C4 H6 N O [M-e]+1
72.08095
C4 H10 N [M-e]+1
70.06530
C4 H8 N [M-e]+1
56.0498

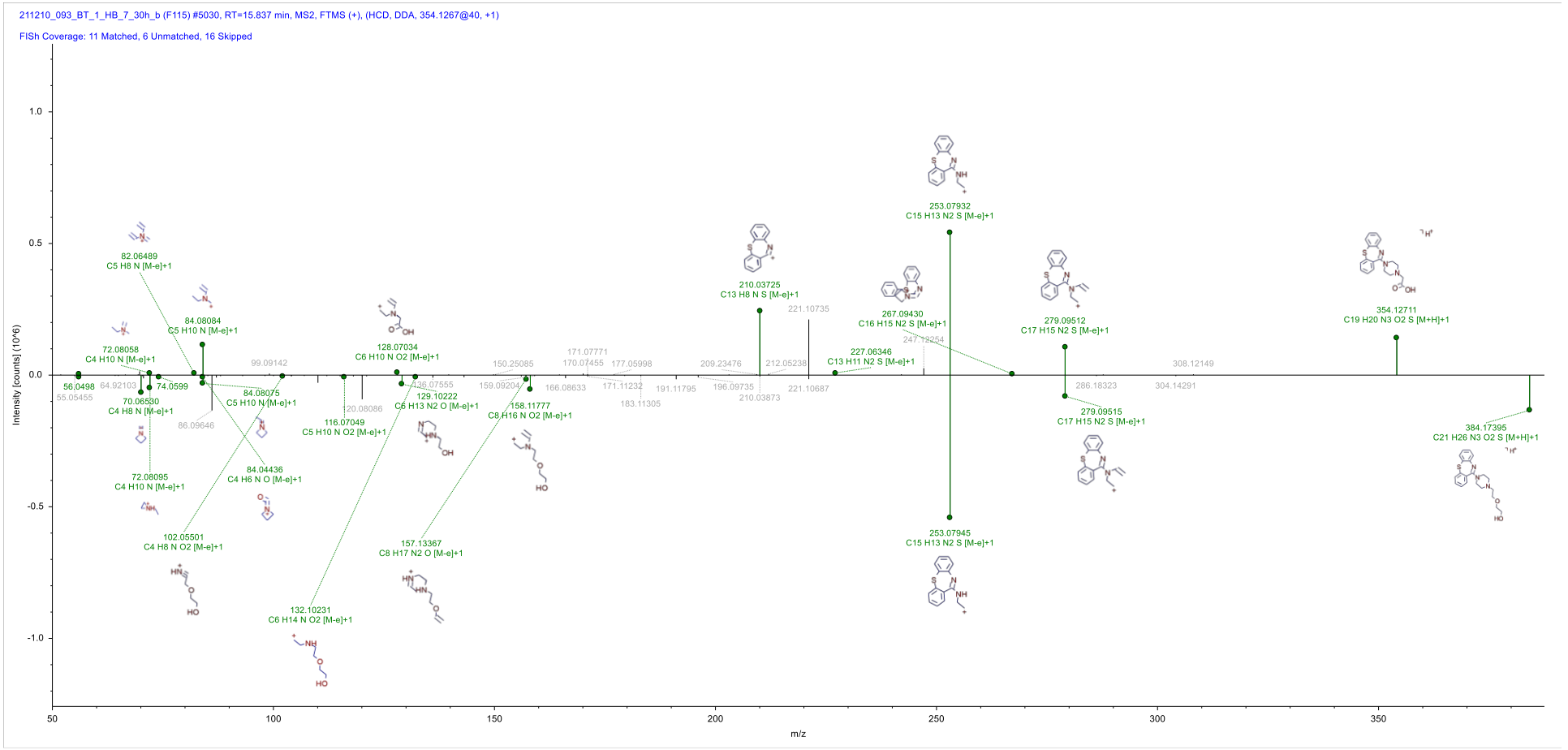
Que

S3.25.6. 18 TP Que



Nominal masses 56, 72, 84, 253 and 279 were also observed in parent MS^2 spectra. Ion with m/z ratio of 128 is only present in TP scan, which indicates oxidation after *N*-dealkylation. No $[M-H]^-$ ion was detected for this TP. This TP was not predicted by any prediction method.

18_TP_Que

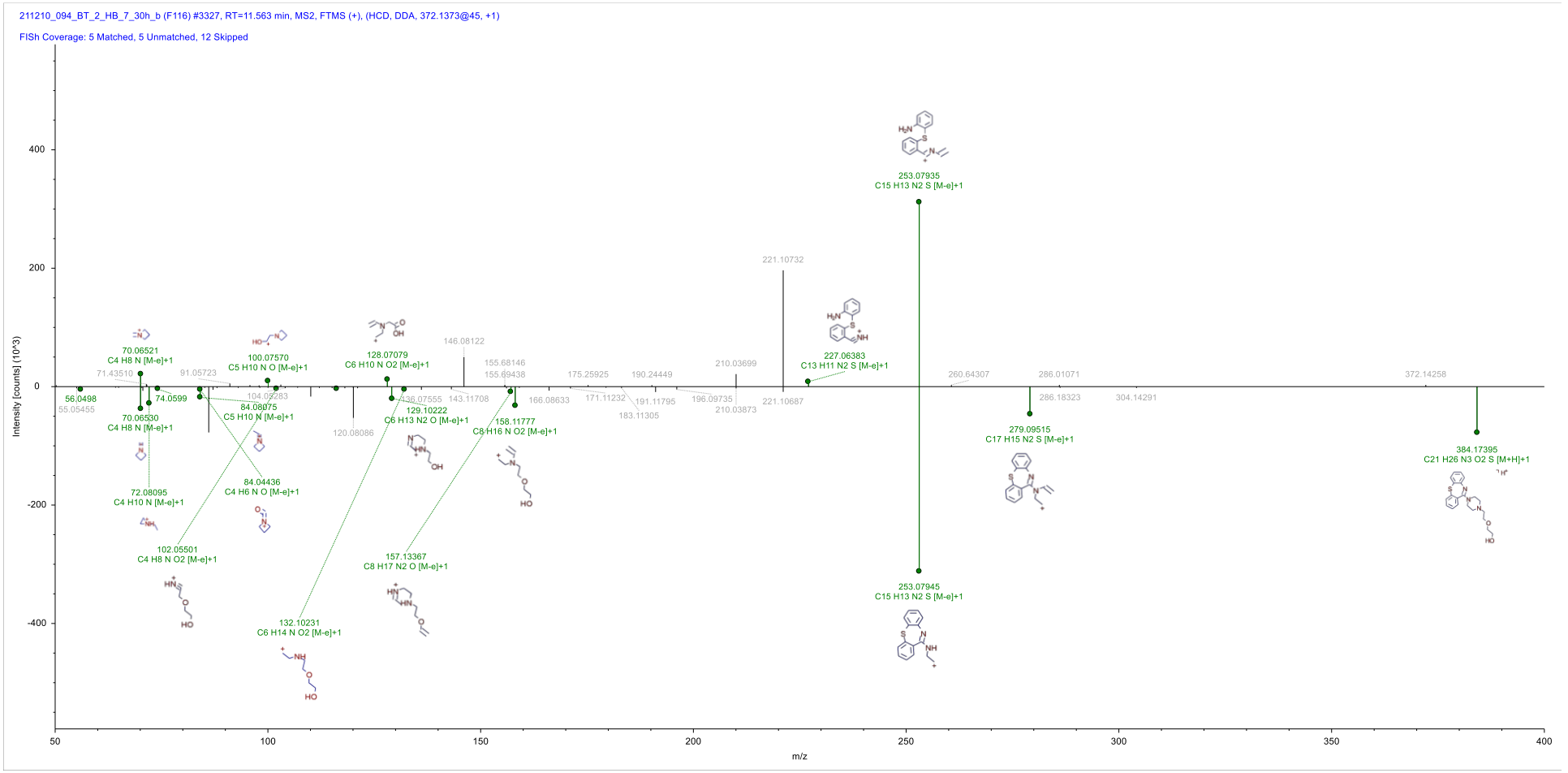

211210_093_BT_1_HB_7_30h_b (F115) #5030, RT=15.837 min, MS2, FTMS (+), (HCD, DDA, 354.1267@40, +1)
FISh Coverage: 11 Matched, 6 Unmatched, 16 Skipped
Intensity [counts] (10^6)
m/z
82.06489
C5 H8 N [M-e]+1
84.08084
C5 H10 N [M-e]+1
72.08058
C4 H10 N [M-e]+1
56.0498
64.92103
74.0599
55.05455
70.06530
C4 H8 N [M-e]+1
86.09646
84.08075
C5 H10 N [M-e]+1
72.08095
C4 H10 N [M-e]+1
84.04436
C4 H6 N O [M-e]+1
102.05501
C4 H8 N O2 [M-e]+1
132.10231
C6 H14 N O2 [M-e]+1
99.09142
128.07034
C6 H10 N O2 [M-e]+1
120.08086
116.07049
C5 H10 N O2 [M-e]+1
136.07555
129.10222
C6 H13 N2 O [M-e]+1
157.13367
C8 H17 N2 O [M-e]+1
150.25085
159.09204
166.08633
158.11777
C8 H16 N O2 [M-e]+1
171.07771
170.07455
177.05998
171.11232
183.11305
191.11795
209.23476
210.03725
C13 H8 N S [M-e]+1
196.09735
210.03873
212.05238
221.10735
221.10687
227.06346
C13 H11 N2 S [M-e]+1
253.07932
C15 H13 N2 S [M-e]+1
267.09430
C16 H15 N2 S [M-e]+1
247.13254
253.07945
C15 H13 N2 S [M-e]+1
279.09512
C17 H15 N2 S [M-e]+1
279.09515
C17 H15 N2 S [M-e]+1
286.18323
304.14291
308.12149
354.12711
C19 H20 N3 O2 S [M+H]+1
384.17395
C21 H26 N3 O2 S [M+H]+1

Que

S3.25.7. 19 TP Que

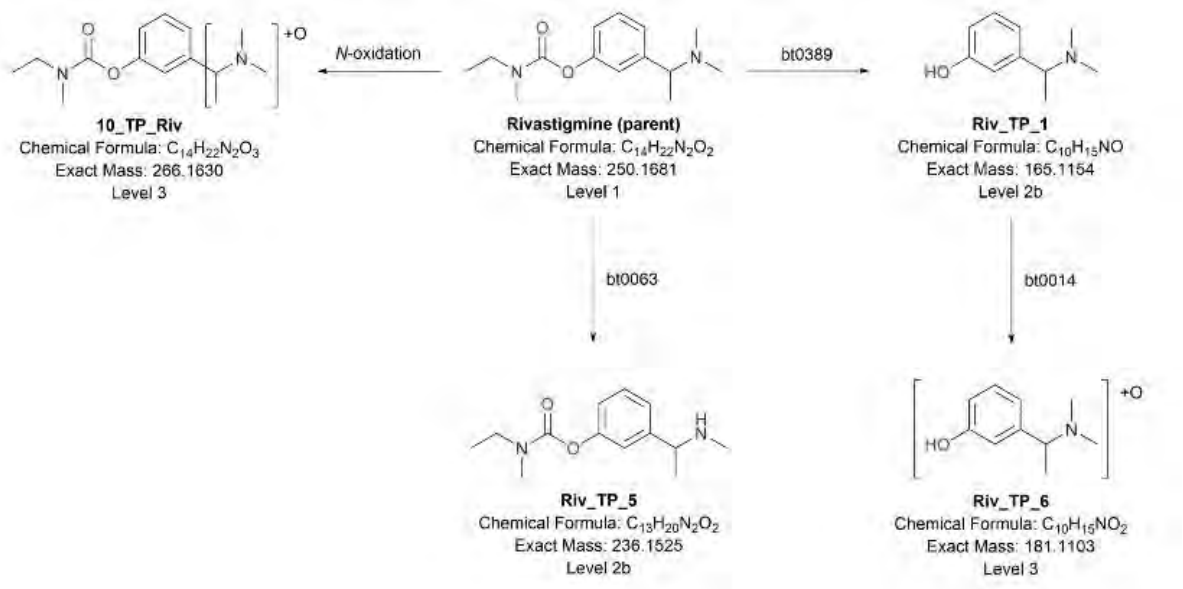
Fragments with nominal masses 70, 210, 221 and 253 were also observed for parent compound. Ion at 253 m/z had different structure proposal.

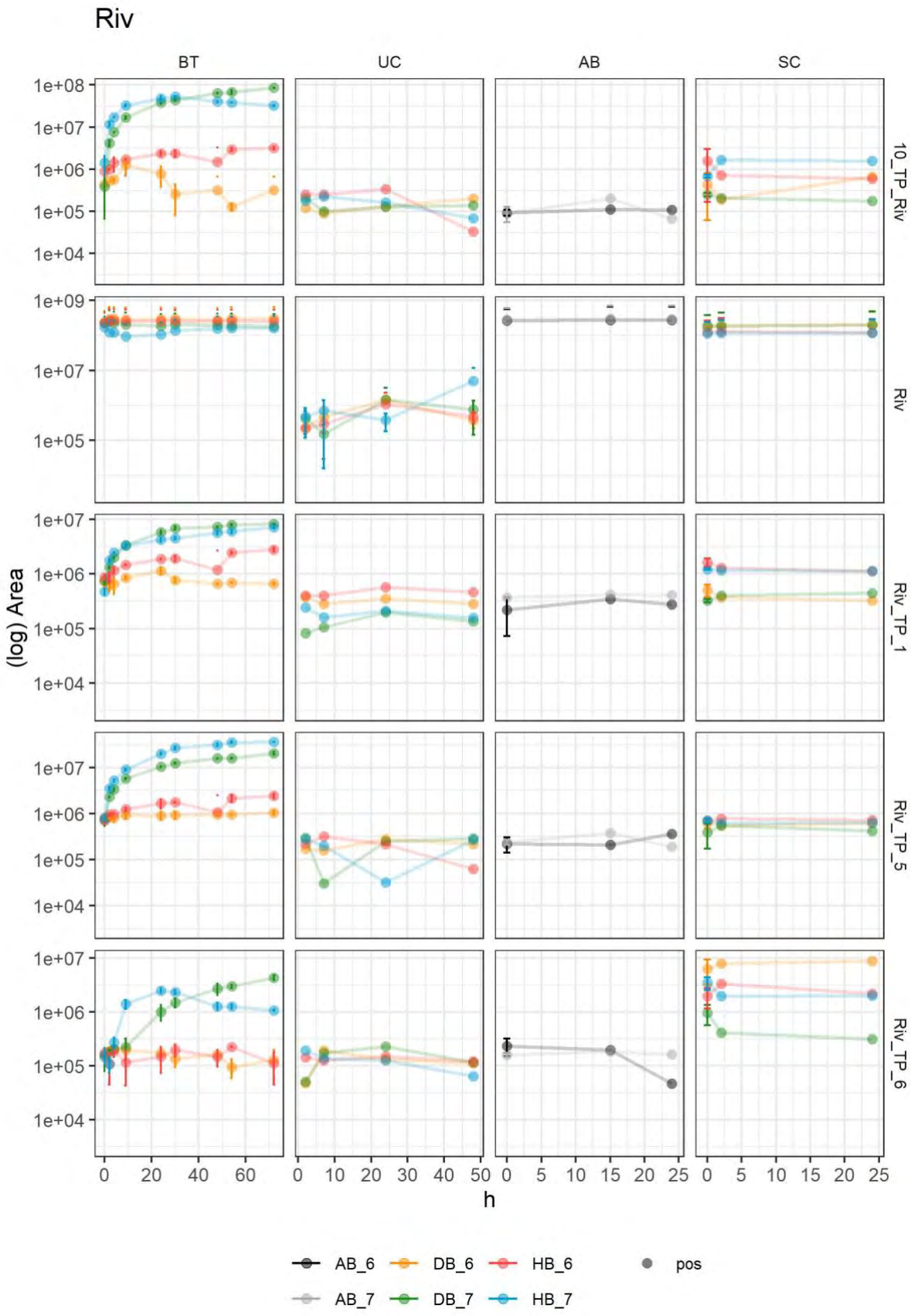
19_TP_Que


211210_094_BT_2_HB_7_30h_b (F116) #3327, RT=11.563 min, MS2, FTMS (+), (HCD, DDA, 372.1373@45, +1)
FISh Coverage: 5 Matched, 5 Unmatched, 12 Skipped
Intensity [counts] (10^3)
m/z
253.07935
C15 H13 N2 S [M-e]+1
221.10732
227.06383
C13 H11 N2 S [M-e]+1
128.07079
C6 H10 N O2 [M-e]+1
146.08122
100.07570
C5 H10 N O [M-e]+1
70.06521
C4 H8 N [M-e]+1
279.09515
C17 H15 N2 S [M-e]+1
384.17395
C21 H26 N3 O2 S [M+H]+1
253.07945
C15 H13 N2 S [M-e]+1
129.10222
C6 H13 N2 O [M-e]+1
158.11777
C8 H16 N O2 [M-e]+1
84.08075
C5 H10 N [M-e]+1
84.04436
C4 H6 N O [M-e]+1
72.08095
C4 H10 N [M-e]+1
102.05501
C4 H8 N O2 [M-e]+1
157.13367
C8 H17 N2 O [M-e]+1
132.10231
C6 H14 N O2 [M-e]+1

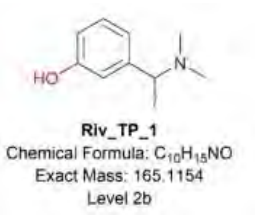
Que

S3.26 Rivastigmine



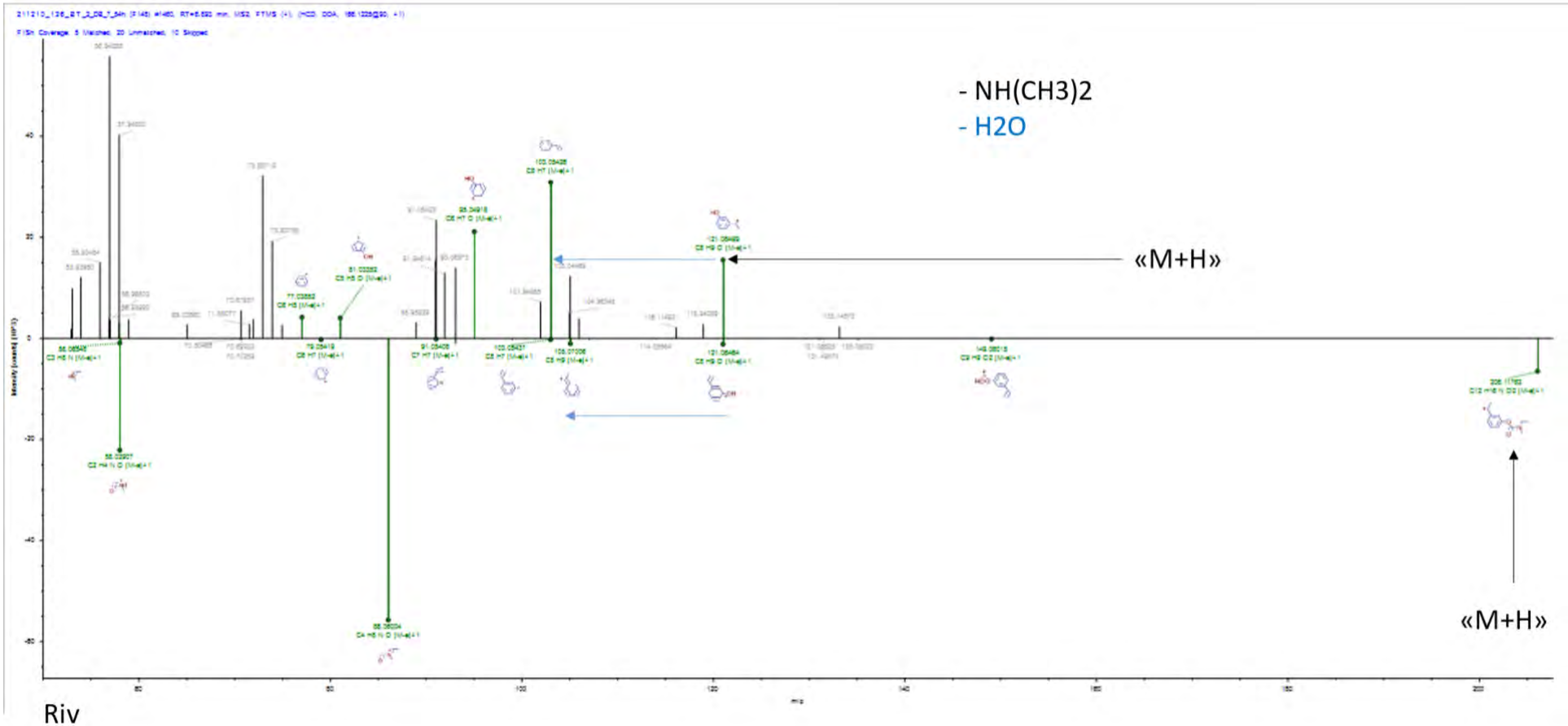

Riv
BT
UC
AB
SC
10_TP_Riv
Riv
Riv_TP_1
Riv_TP_5
Riv_TP_6
(log) Area
h
AB_6
DB_6
HB_6
pos
AB_7
DB_7
HB_7

S3.26.1. Riv TP 1



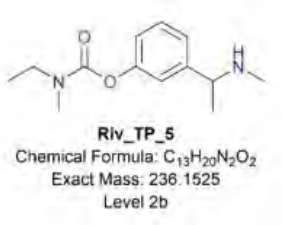
Nominal masses 121, 103 and 91 were also observed for the parent compound, where especially mass 91 supports substructure. Ions with the highest m/z ratio of both parent and TP are obtained by dimethylamine loss, which is then followed by the loss of water. The absence of nominal mass 149 in TP MS^2 suggests transformation.

Riv_TP_1



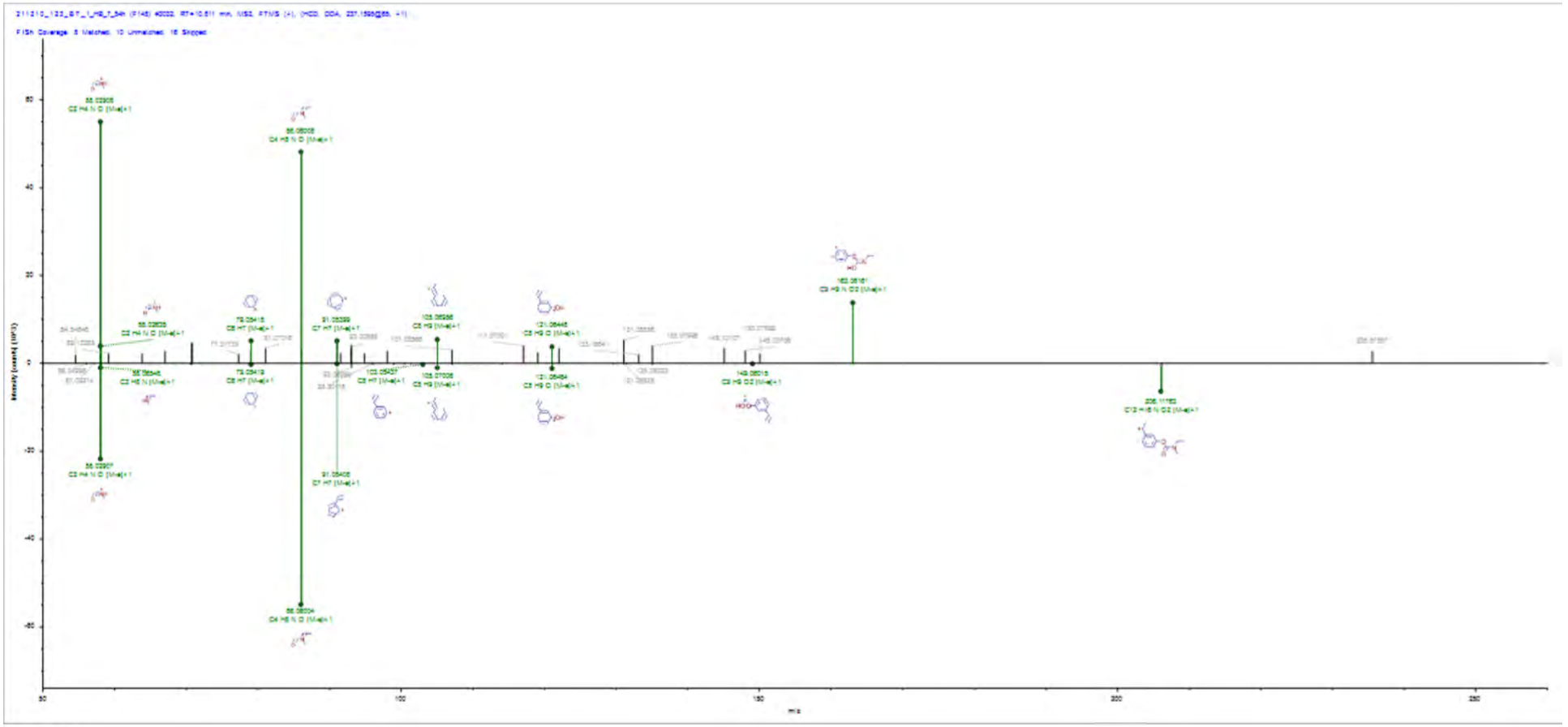
Riv

S3.26.2. Riv TP 5



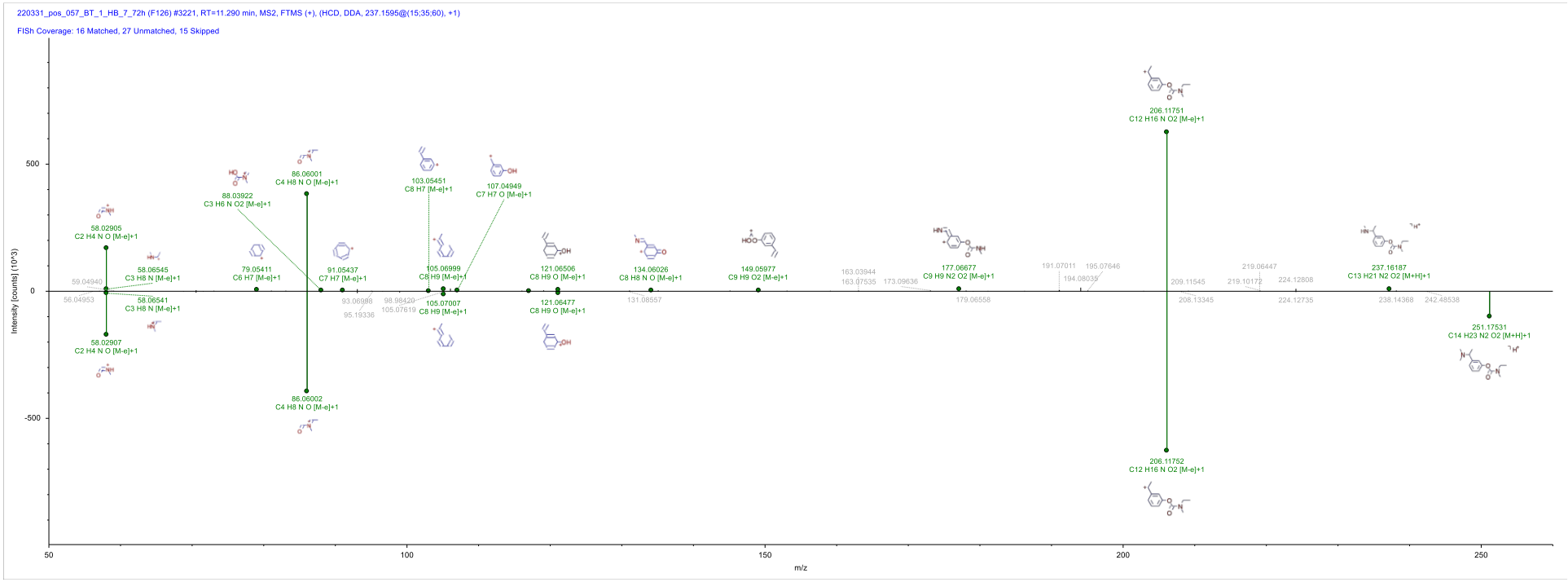
Nominal masses 58 (2x), 79, 86, 91, 105 and 121 (2x), 131 and 206 were also observed for the parent compound, where especially the ion at 206 supports the demethylation on the amine.

Riv_TP_5



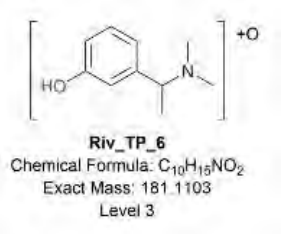
Riv

Riv_TP_5_remeas



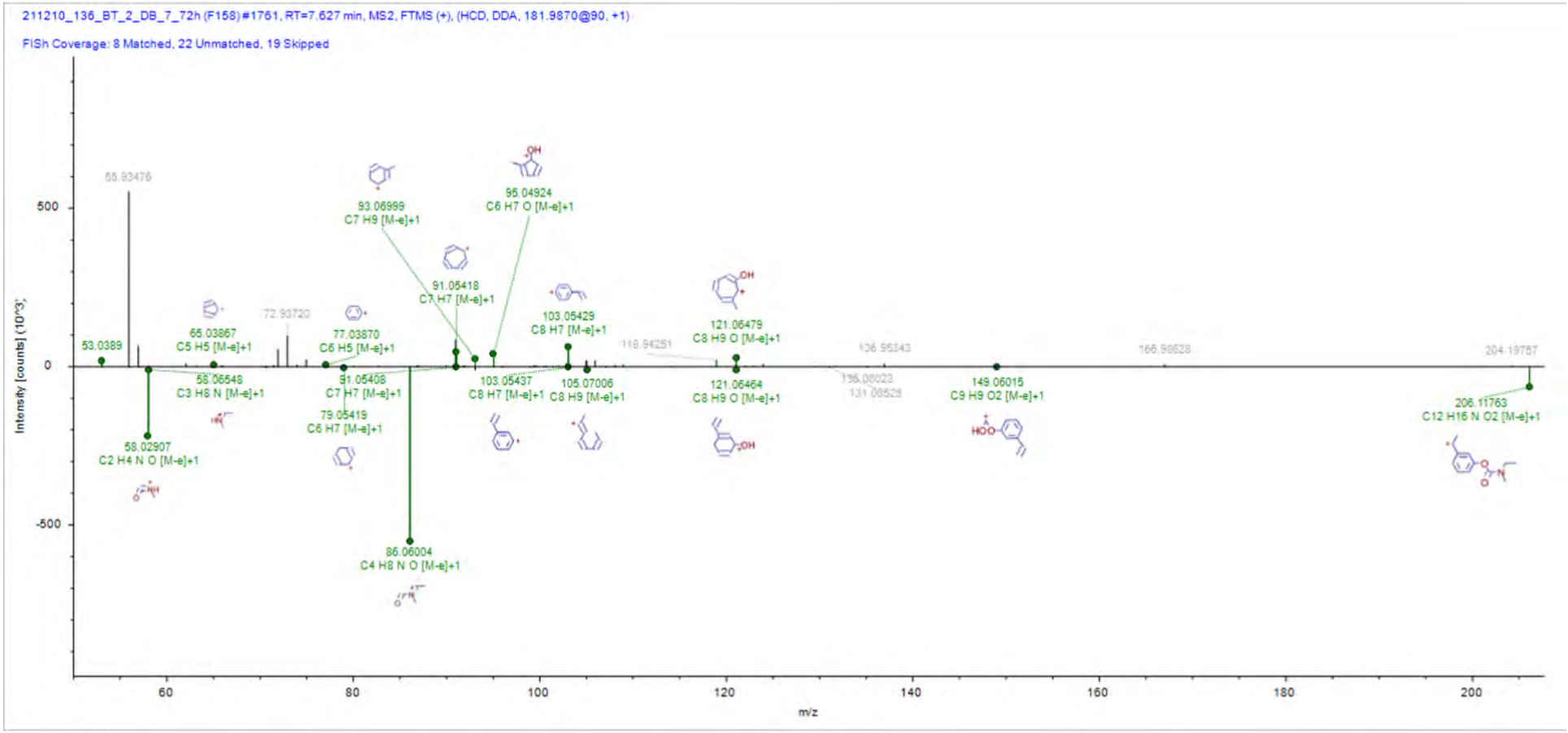
Riv_remeas

S3.26.3. Riv TP 6



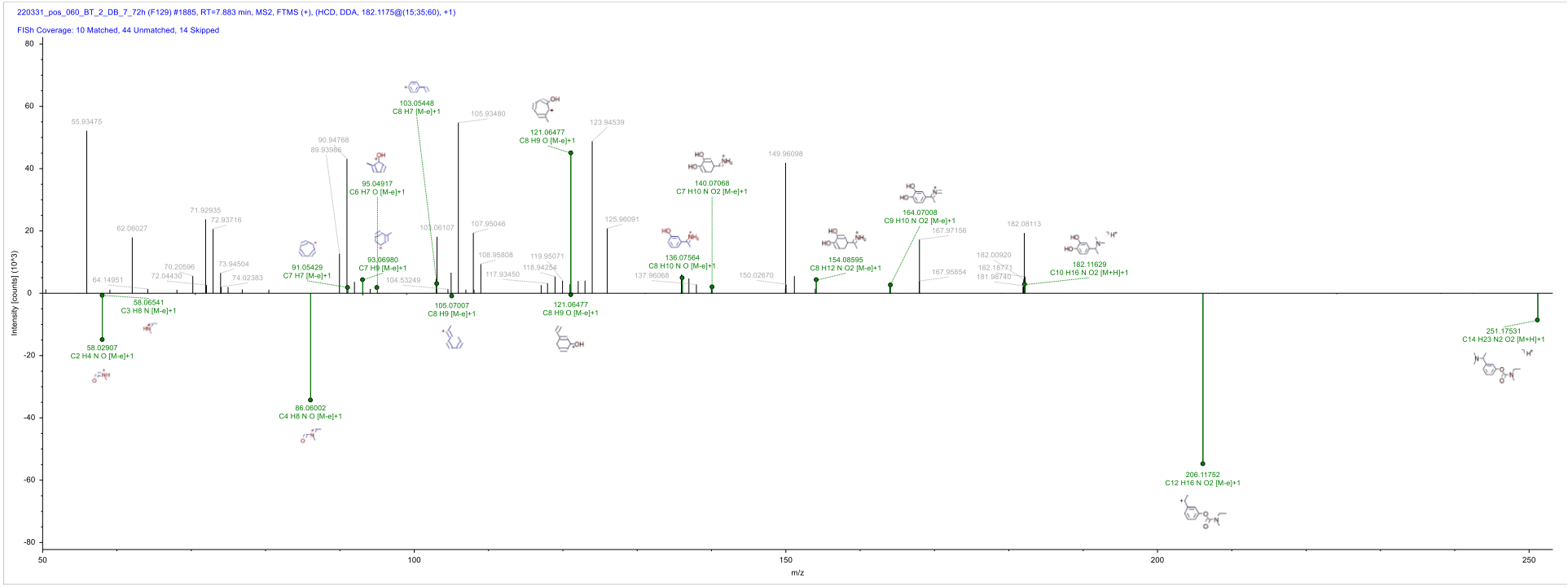
Nominal masses 91, 93, 103 and 121 were also observed for the parent compound, which confirms the benzene ring with its substituents and supports the hydrolysis transformation. The absence of water loss and the proposed structures of m/z 140, 154 and 164 in TP MS^2 could support the hydroxylation of the aromatic ring. However, isomers with OH *para* to carbon substituent or *ortho* can't be distinguished.

Riv_TP_6


211210_136_BT_2_DB_7_72h (F158) #1761, RT=7.627 min, MS2, FTMS (+), (HCD, DDA, 181.9870@90, +1)
FISh Coverage: 8 Matched, 22 Unmatched, 19 Skipped
Intensity [counts] (10^3)
m/z
55.93476
53.0389
58.02907
C2 H4 N O [M-e]+1
65.03867
C5 H5 [M-e]+1
58.06548
C3 H8 N [M-e]+1
72.93720
77.03870
C6 H5 [M-e]+1
79.05419
C6 H7 [M-e]+1
91.05408
C7 H7 [M-e]+1
86.06004
C4 H8 N O [M-e]+1
93.06999
C7 H9 [M-e]+1
91.05418
C7 H7 [M-e]+1
95.04924
C6 H7 O [M-e]+1
103.05429
C8 H7 [M-e]+1
103.05437
C8 H7 [M-e]+1
105.07006
C8 H9 [M-e]+1
118.94251
121.06479
C8 H9 O [M-e]+1
121.06464
C8 H9 O [M-e]+1
136.95343
136.08023
131.08528
149.06015
C9 H9 O2 [M-e]+1
166.96528
204.19757
206.11763
C12 H16 N O2 [M-e]+1

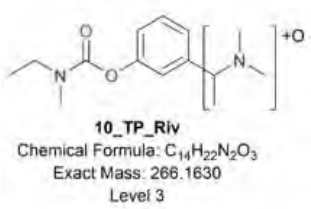
Riv

Riv_TP_6_remeas



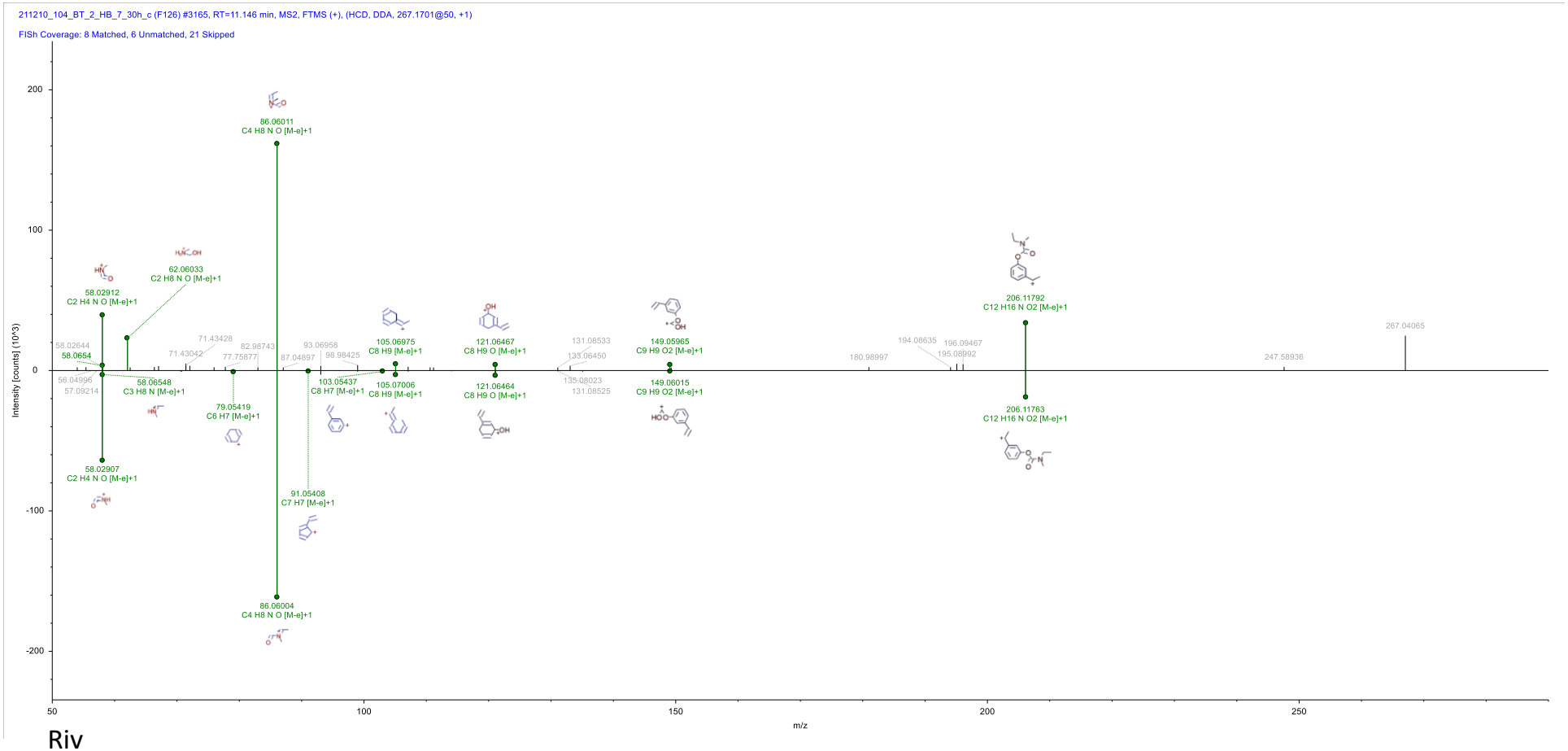
Riv_remeas

S3.26.4. 10 TP Riv



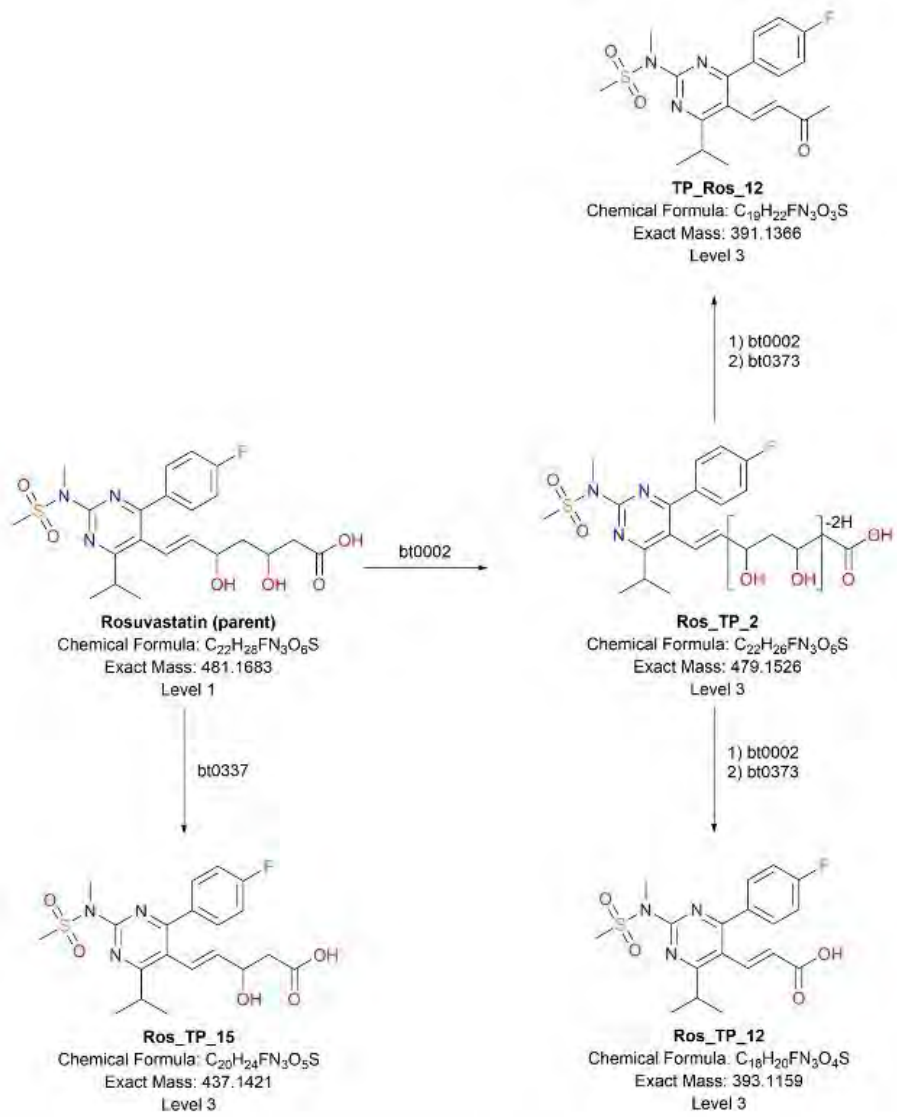
Nominal masses 58, 86, 105, 121, 149 and 206 were also observed for the parent compound. MS^2 spectra from parent and TP are very similar. Structure of mass 206 from *in silico* fragmentation tool suggests that modification occurred on or in close proximity of tertiary amine group. It is not possible to distinguish if TP is the product of *N*-oxidation or hydroxylation. However, tertiary amines tend to form *N*-oxides.[19] This TP was not predicted by any prediction method.

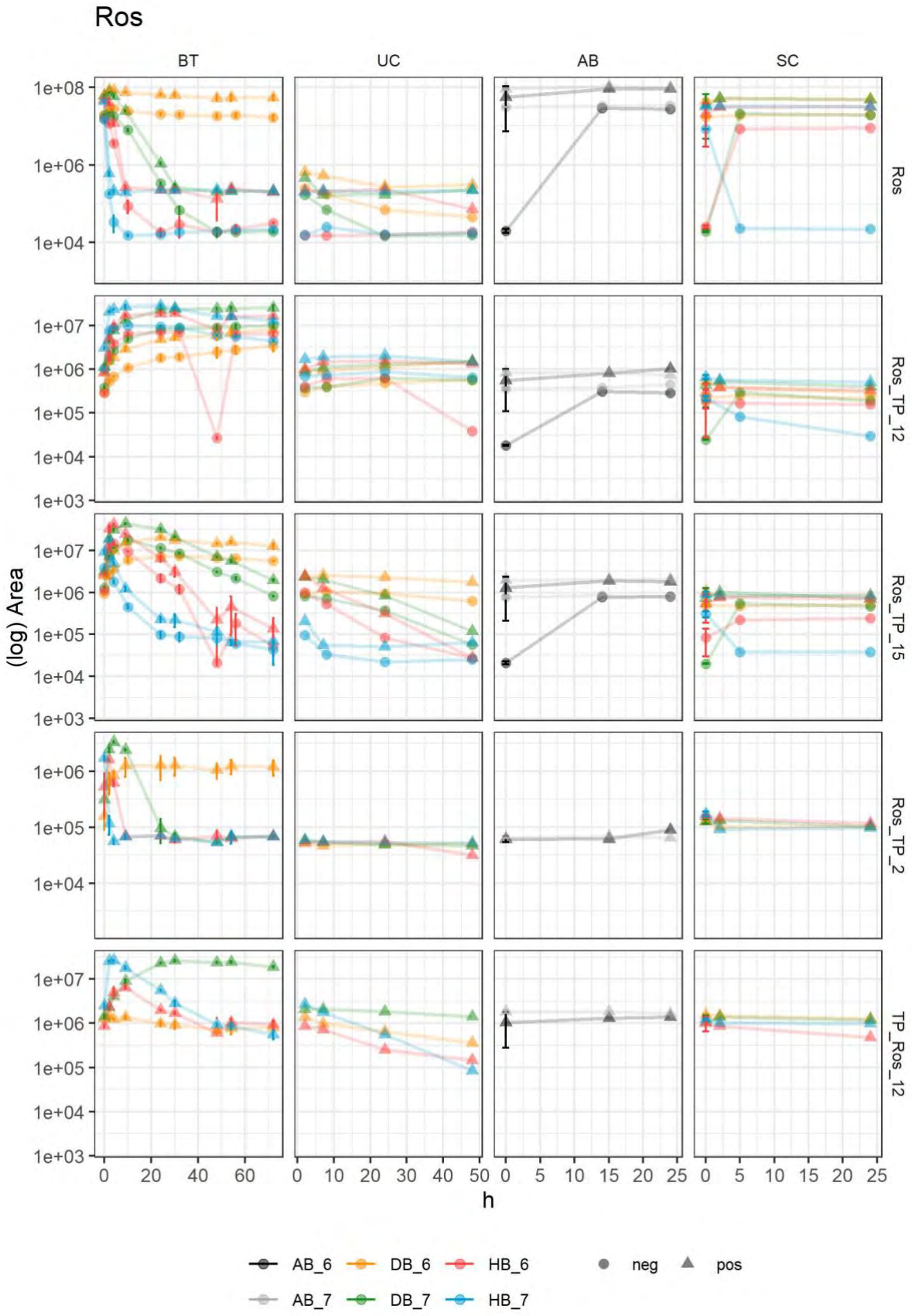
10_TP_Riv


211210_104_BT_2_HB_7_30h_c (F126) #3165, RT=11.146 min, MS2, FTMS (+), (HCD, DDA, 267.1701@50, +1)
FISh Coverage: 8 Matched, 6 Unmatched, 21 Skipped
Intensity [counts] (10^3)
m/z
86.06011
C4 H8 N O [M-e]+1
62.06033
C2 H8 N O [M-e]+1
58.02912
C2 H4 N O [M-e]+1
58.02644
58.0654
56.04996
57.09214
58.06548
C3 H8 N [M-e]+1
71.43428
71.43042
77.75877
79.05419
C6 H7 [M-e]+1
82.98743
87.04897
93.06958
98.98425
103.05437
C8 H7 [M-e]+1
105.06975
C8 H9 [M-e]+1
105.07006
C8 H9 [M-e]+1
121.06467
C8 H9 O [M-e]+1
121.06464
C8 H9 O [M-e]+1
131.08533
133.06450
135.08023
131.08525
149.05965
C9 H9 O2 [M-e]+1
149.06015
C9 H9 O2 [M-e]+1
180.98997
194.08635
196.09467
195.08992
206.11792
C12 H16 N O2 [M-e]+1
206.11763
C12 H16 N O2 [M-e]+1
247.58936
267.04065
58.02907
C2 H4 N O [M-e]+1
91.05408
C7 H7 [M-e]+1
86.06004
C4 H8 N O [M-e]+1

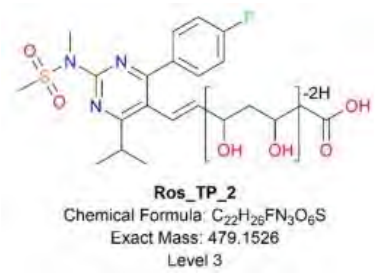
Riv

S3.27 Rosuvastatin



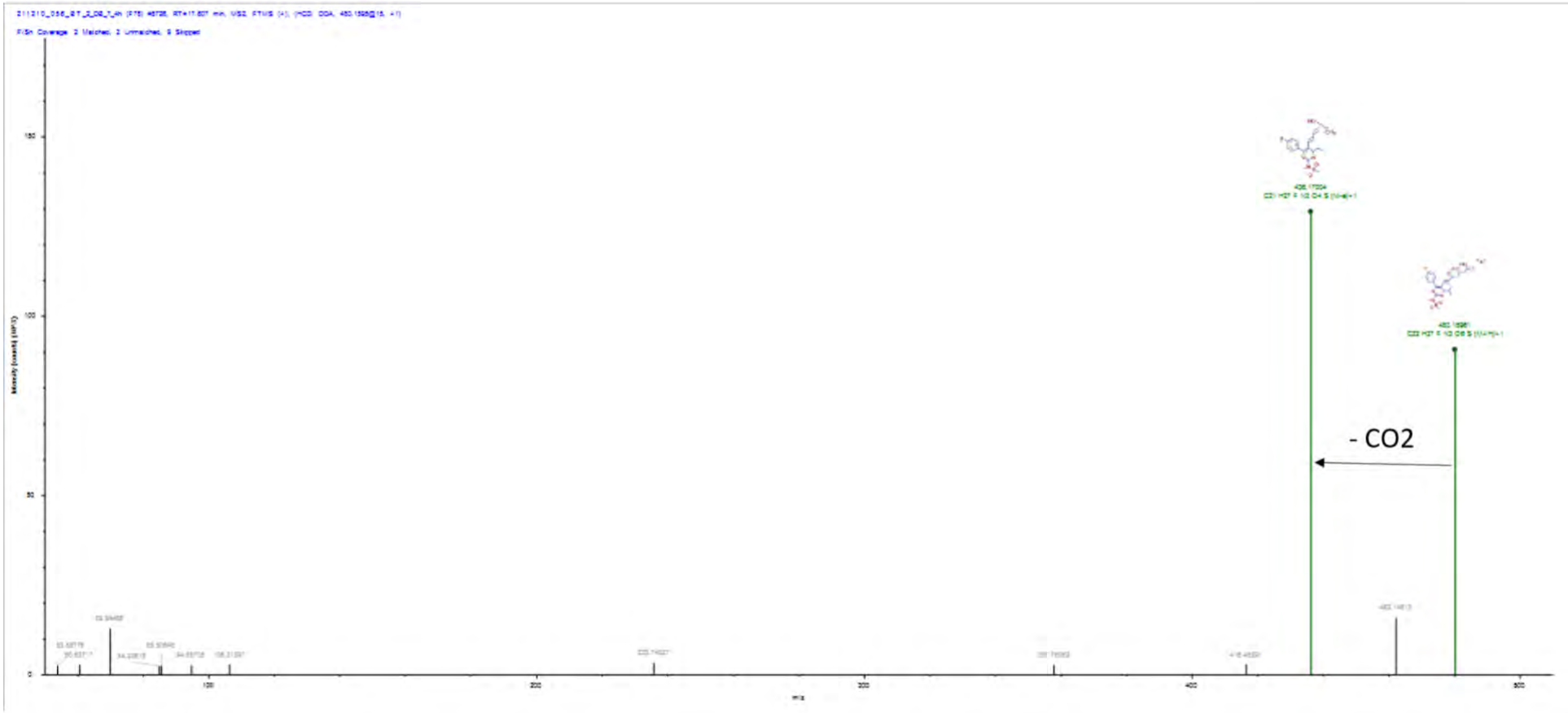

Ros
BT
UC
AB
SC
Ros
Ros_TP_12
Ros_TP_15
Ros_TP_2
TP_Ros_12
(log) Area
h
AB_6
DB_6
HB_6
AB_7
DB_7
HB_7
neg
pos

S3.27.1. Ros TP 2

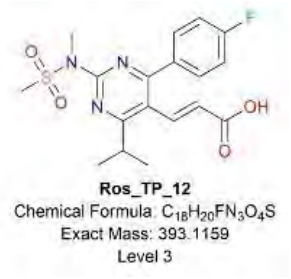


No matches were found with the parent compound, even though they are structurally very similar. The cause may be the lower NCE of 15 in comparison to the parent with a value of 35. Carbon dioxide loss could be observed in the MS^2 scan.

Ros_TP_2

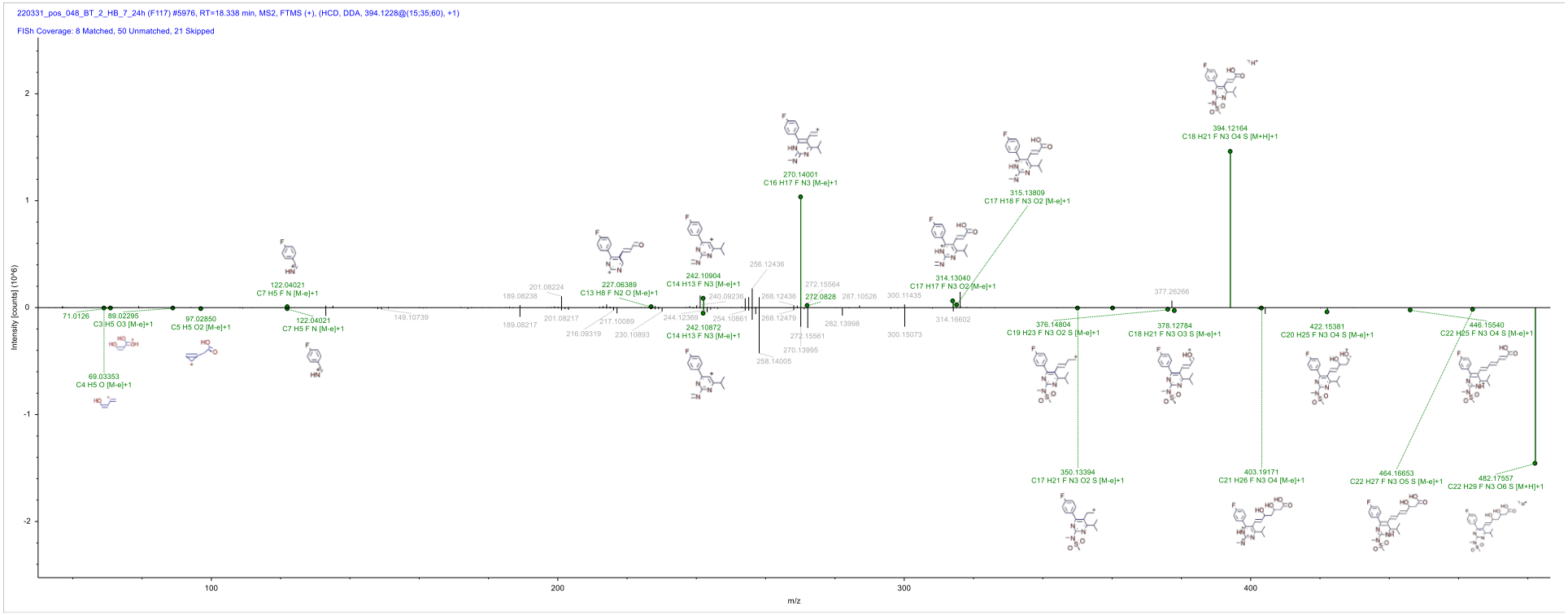


S3.27.2. Ros TP 12



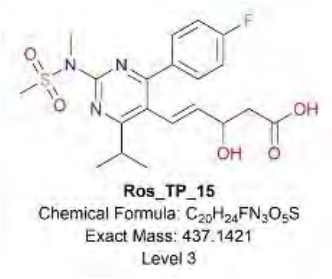
Fragments with nominal masses 79, 122, 133, 135, 149, 189, 201, 212, 216, 242, 243, 254, 256, 258 and 270 were also observed in the parental MS^2 spectrum. However, only masses 122, 242 and 270 could be annotated with a predicted structure. The absence of ions at 89 and 97 m/z suggest oxidation followed by a hydrolysis reaction of the 1,3-diketone intermediate.

Ros_TP_12_remeas



Ros_remeas

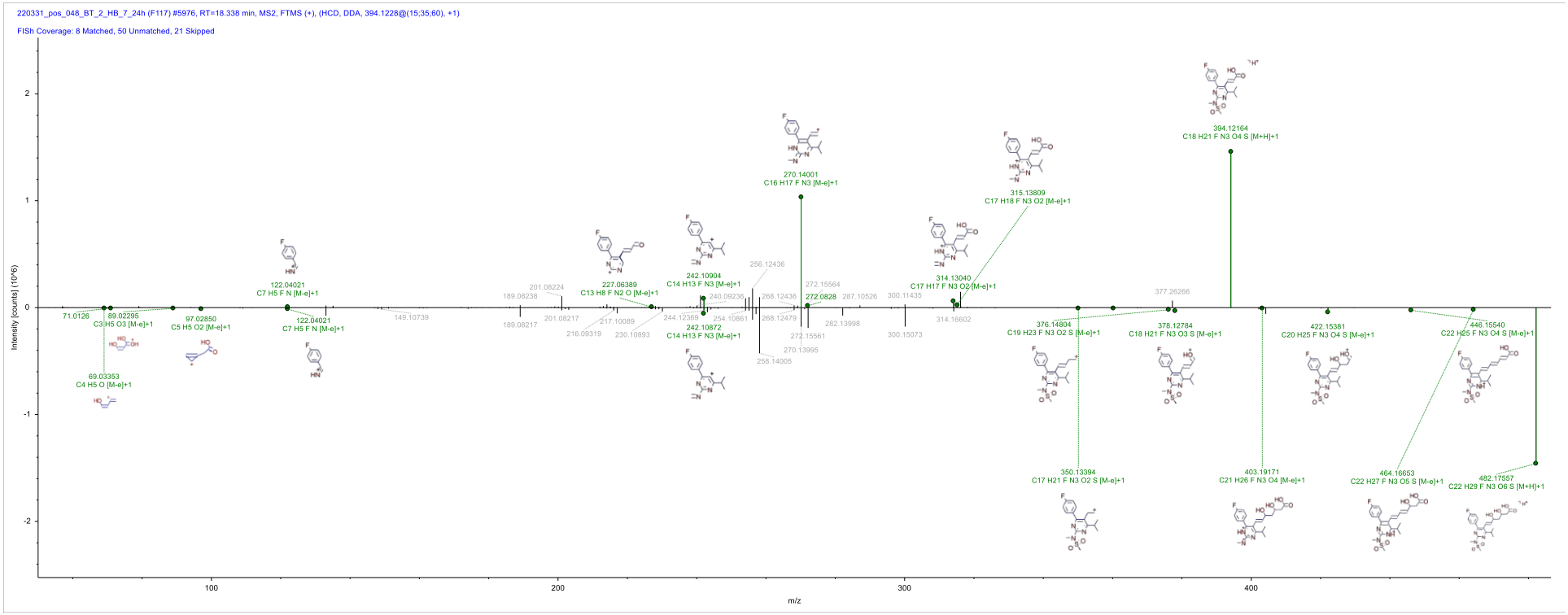
S3.27.3. Ros TP 15



Ros_TP_15
Chemical Formula: $C_{20}H_{24}FN_3O_5S$
Exact Mass: 437.1421
Level 3

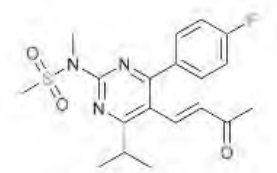
56 fragment ions were observed in MS^2 of both TP and parent, which indicates modification on side chain. Structures of m/z 242 and 378 confirm structural backbone.

Ros_TP_15_remeas



Ros_remeas

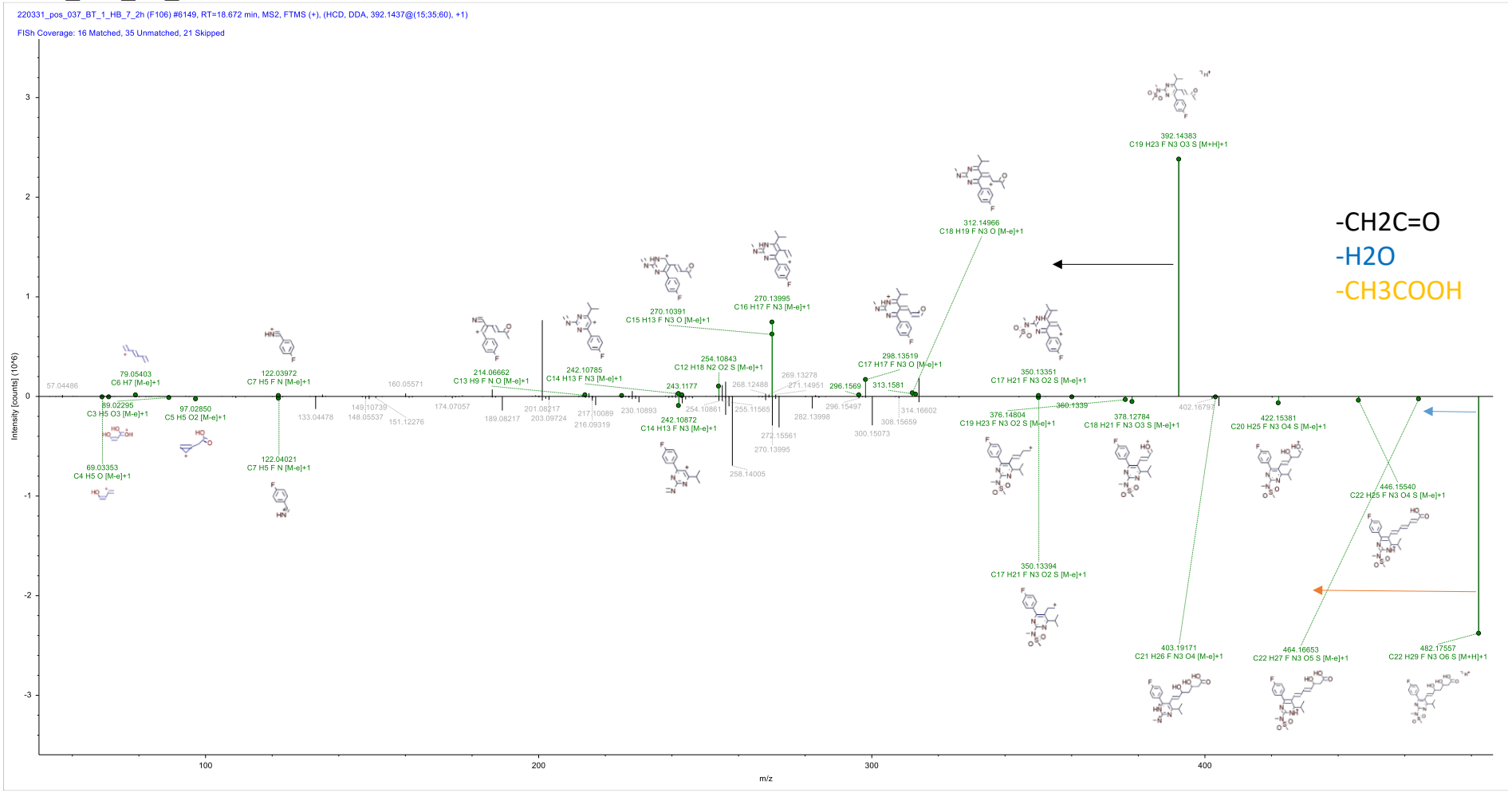
S3.27.4. TP Ros 12



TP_Ros_12
Chemical Formula: $C_{19}H_{22}FN_3O_3S$
Exact Mass: 391.1366
Level 3

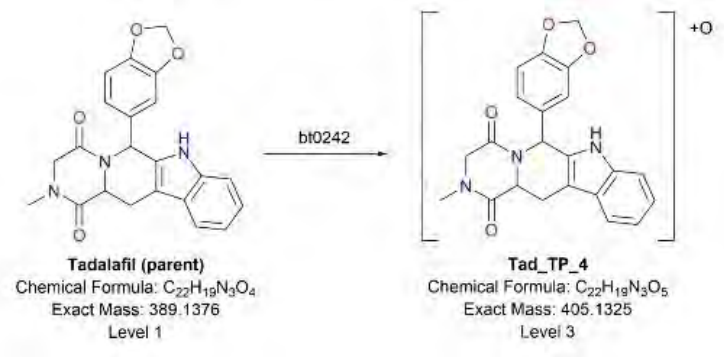
Ions at m/z 79, 122, 133, 135, 149, 160, 201, 215, 228, 239, 240, 242, 254, 256, 270, 298, 314 and 350 were also observed for parent compound. Mass 350 supports that the TP and parent share the same structural backbone. In TP spectrum $CH_2C{=}O$ loss was observed instead of water and acetic acid loss as in parental spectrum. Similar to Ros TP 12, this TP is the other possible product after oxidation and hydrolysis of 1,3-diketone.

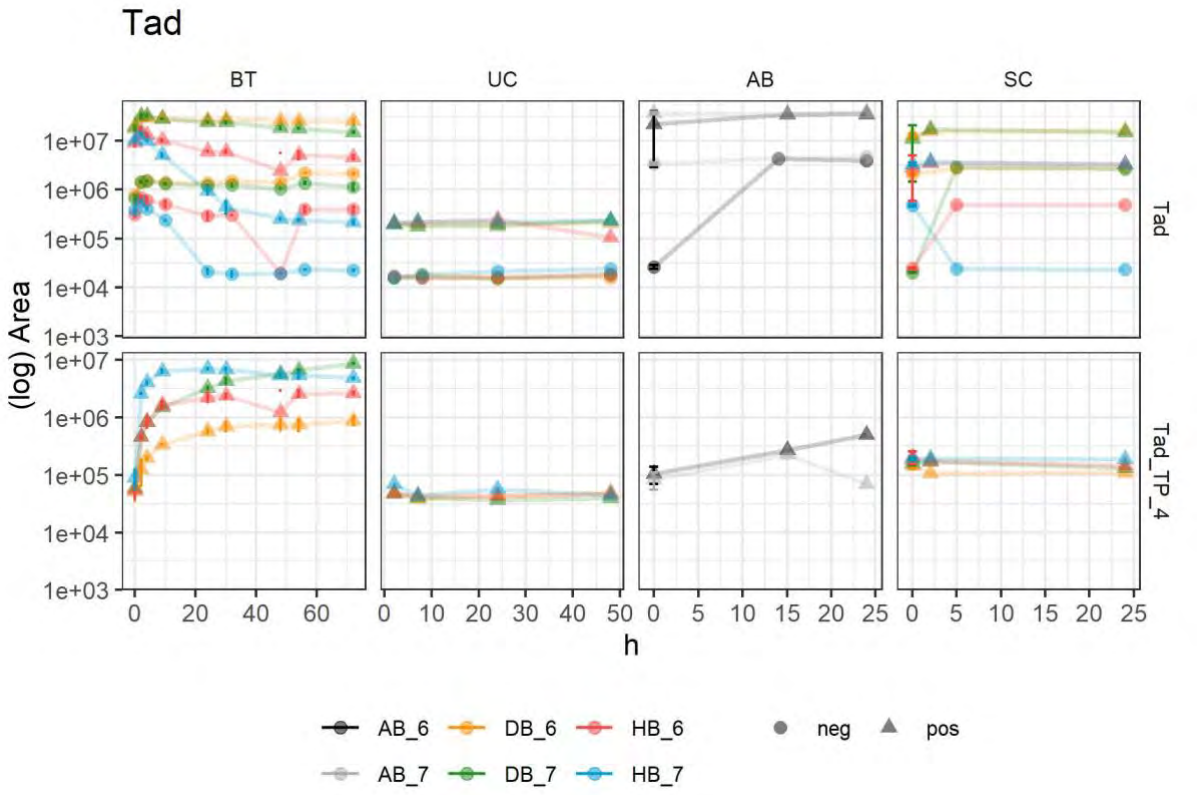
TP_Ros_12_remeas



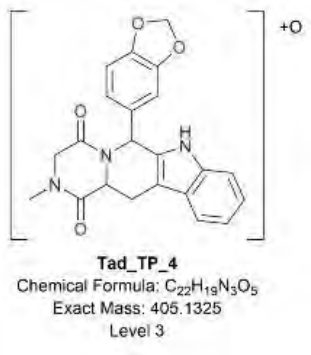
Ros_remeas

S3.28 Tadalafil



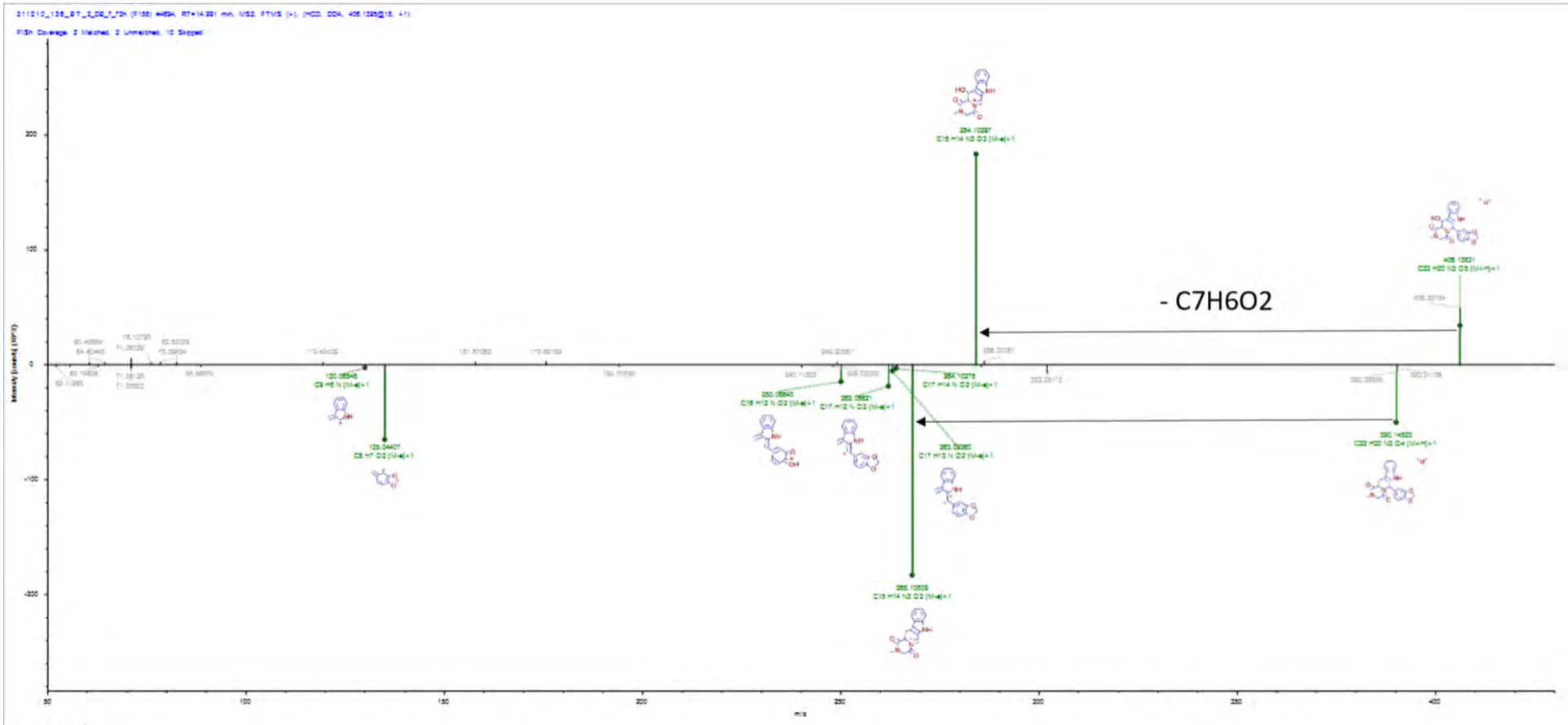


S3.28.1. Tad TP 4



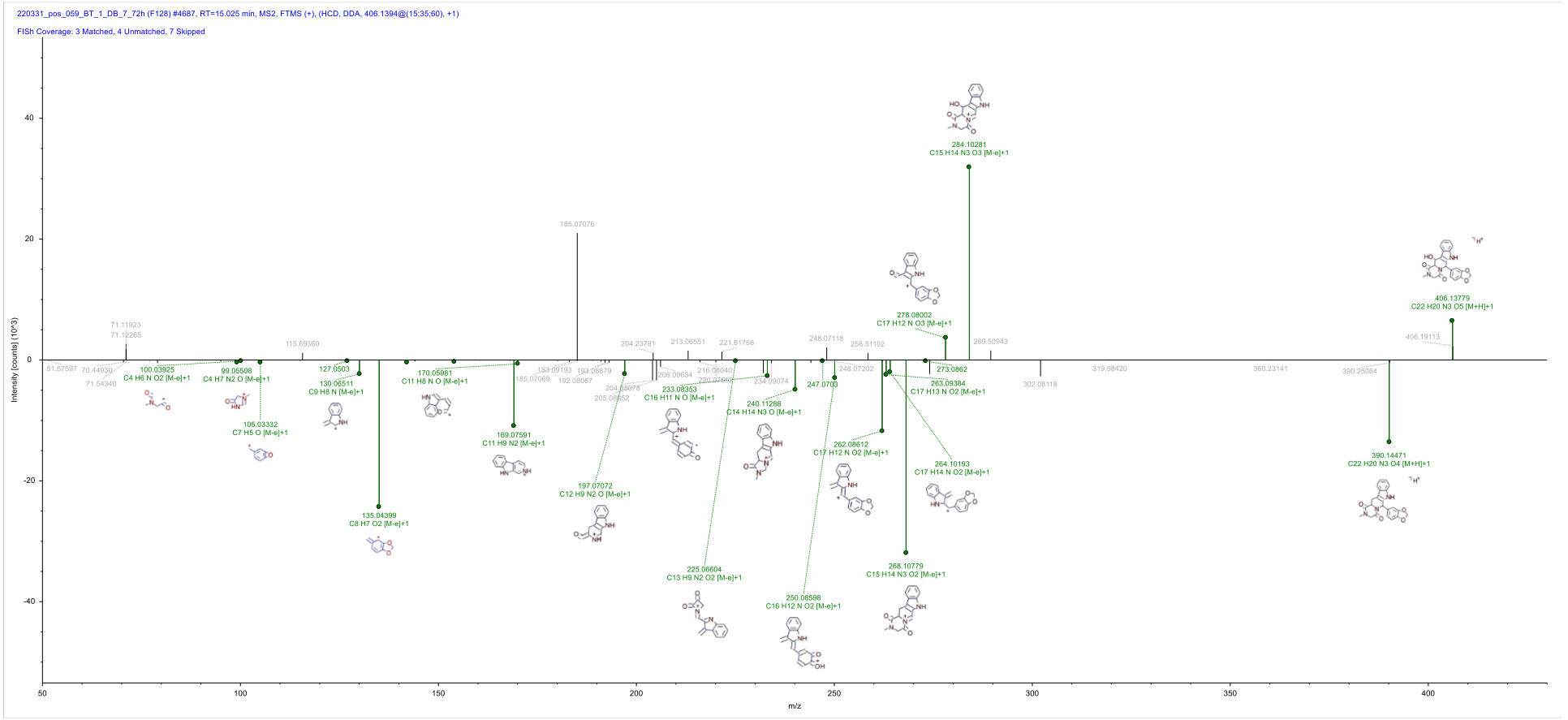
No matches were found with the parent compound except ion at m/z 185, even though they are structurally very similar. Same $C_7H_6O_2$ loss in parent and TP could be observed.

Tad_TP_4



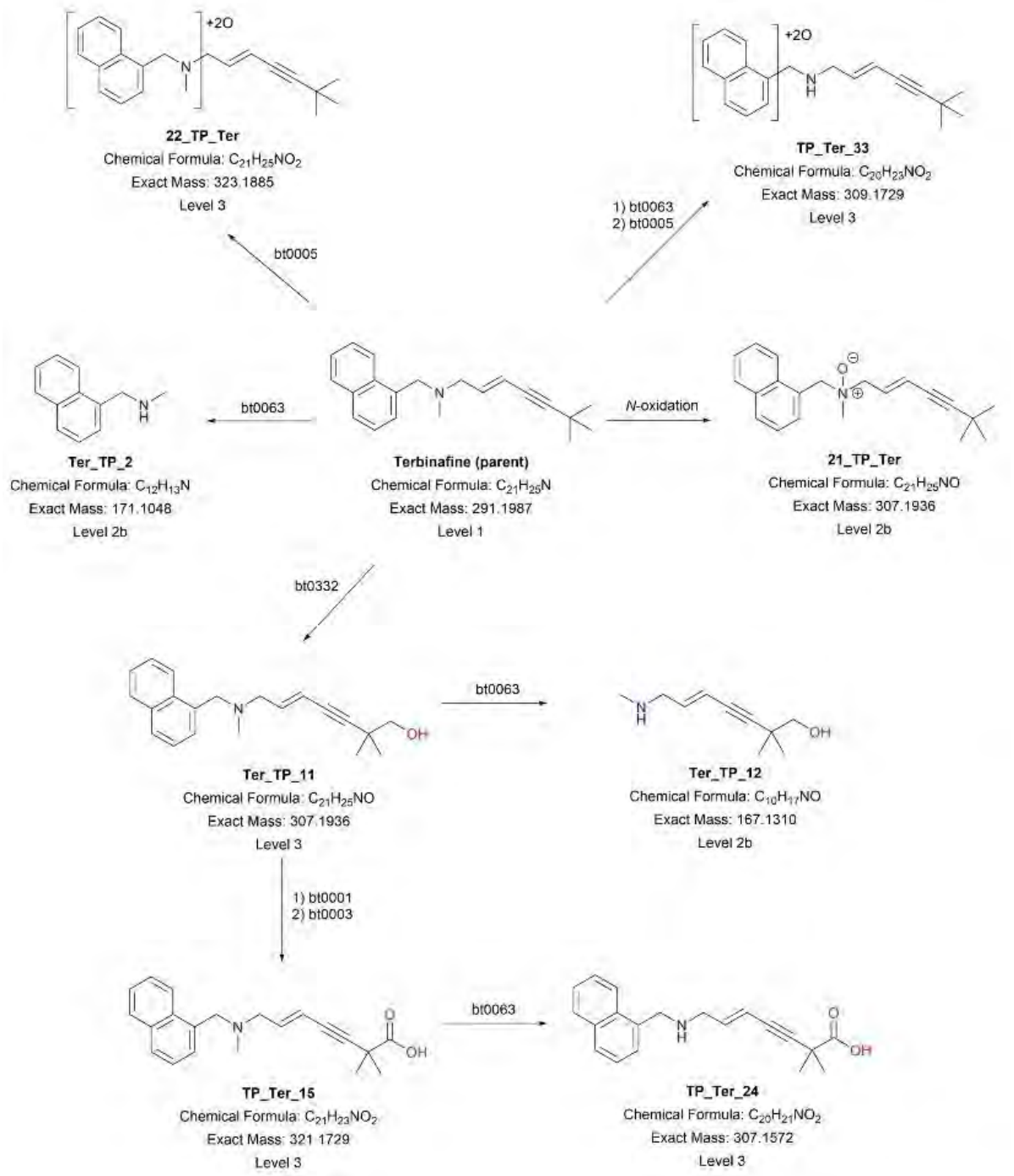
Tad

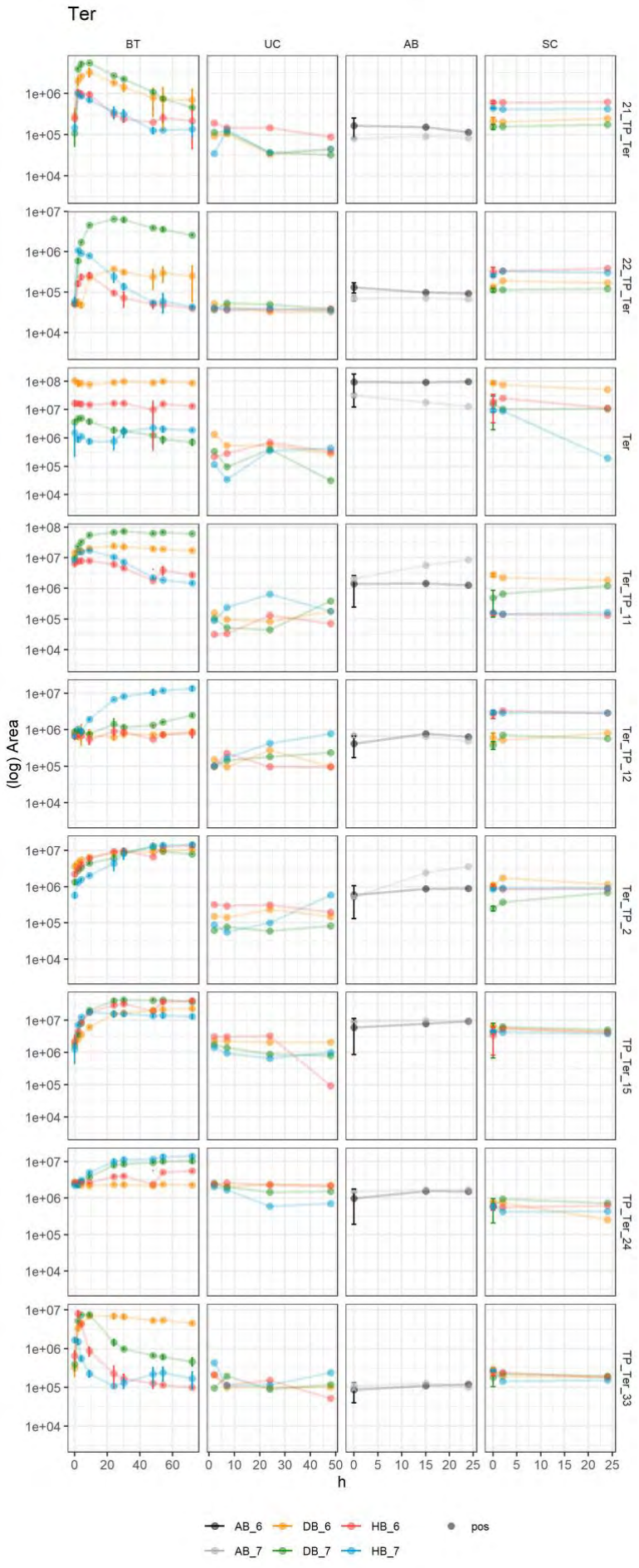
Tad_TP_4_remeas



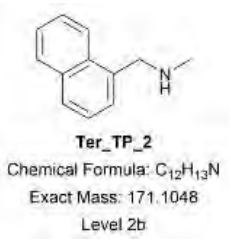
Tad_remeas

S3.29 Terbinafine



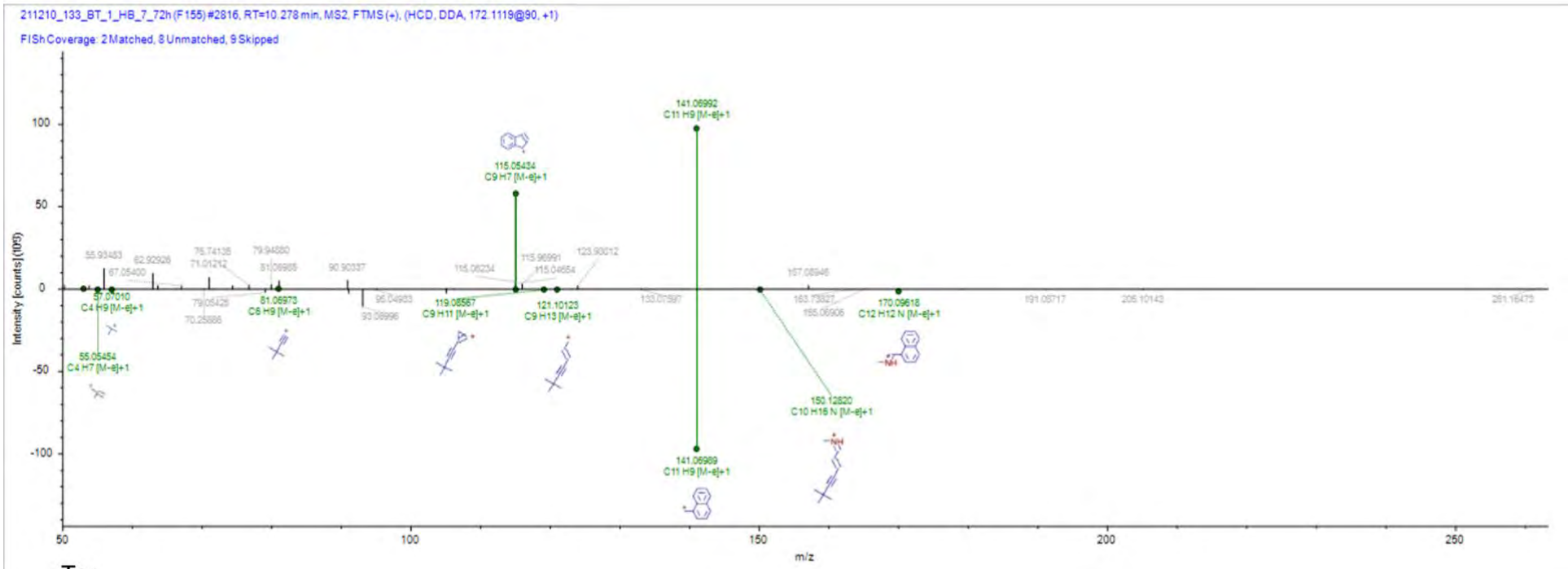

Ter
BT
UC
AB
SC
21_TP_Ter
22_TP_Ter
Ter
Ter_TP_11
Ter_TP_12
Ter_TP_2
TP_Ter_15
TP_Ter_24
TP_Ter_33
(log) Area
h
AB_6
DB_6
HB_6
pos
AB_7
DB_7
HB_7

S3.29.1. Ter TP 2



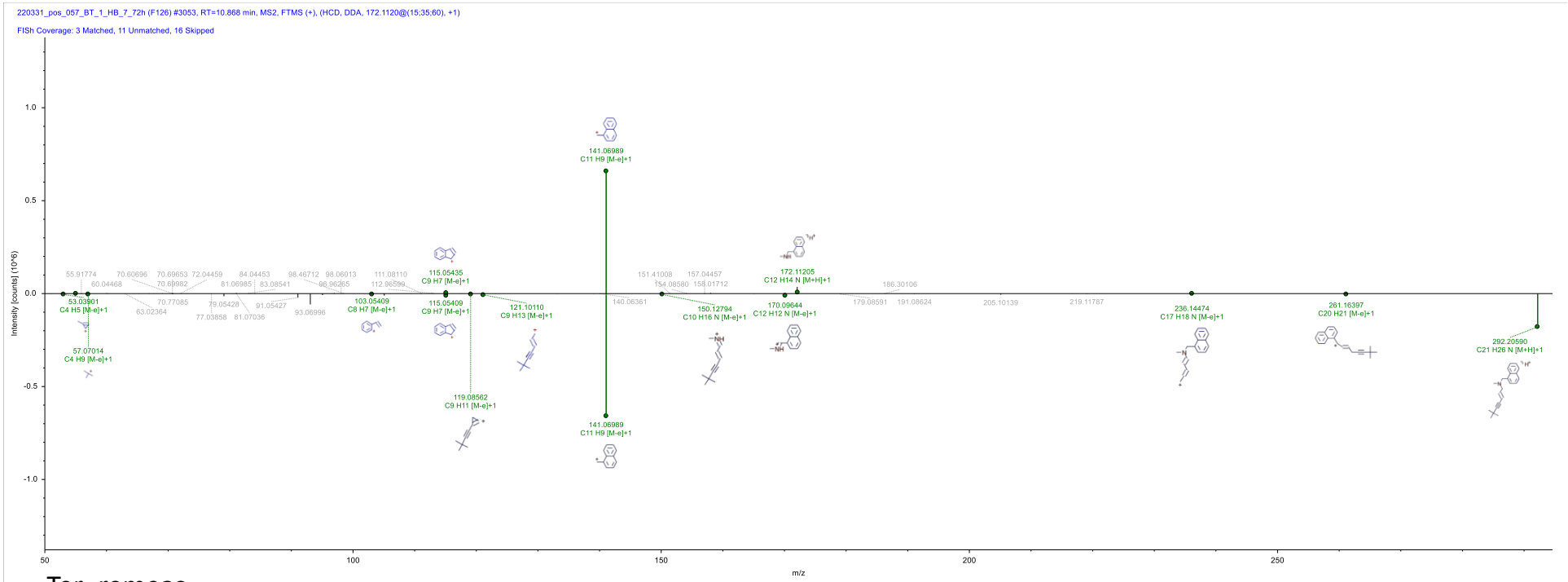
Fragments at nominal masses 141 and 115 were also observed for the parent compound. Absence of mass 119 and 121 indicates loss of carbon chain moiety.

Ter_TP_2


211210_133_BT_1_HB_7_72h (F155) #2816, RT=10.278 min, MS2, FTMS (+), (HCD, DDA, 172.1119@90, +1)
FISh Coverage: 2 Matched, 8 Unmatched, 9 Skipped
Intensity [counts] (100)
m/z
141.06992
C11 H9 [M-e]+1
115.05434
C9 H7 [M-e]+1
141.06989
C11 H9 [M-e]+1
170.09618
C12 H12 N [M-e]+1
150.12820
C10 H16 N [M-e]+1
121.10123
C9 H13 [M-e]+1
119.08567
C9 H11 [M-e]+1
81.06973
C6 H9 [M-e]+1
57.07010
C4 H9 [M-e]+1
55.05454
C4 H7 [M-e]+1

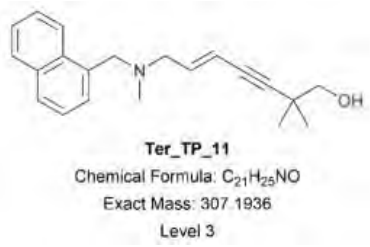
Ter

Ter_TP_2_remeas



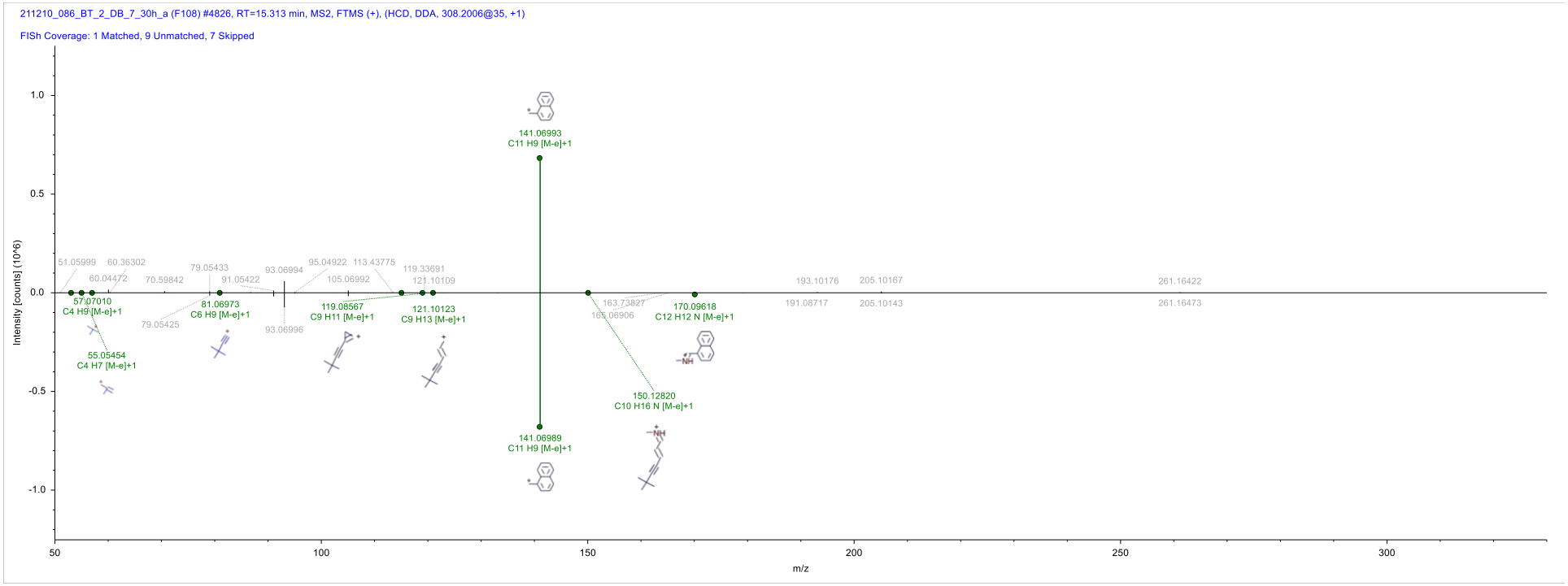
Ter_remeas

S3.29.2. Ter TP 11



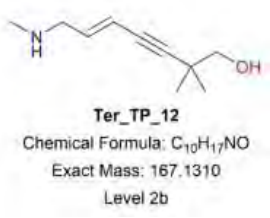
Two compounds with the same chemical formula were found at RT 13.2 (Ter TP 11, intensity in chromatogram around 10^6) and 15.4 (21 TP Ter, intensity in chromatogram around 10^7), which suggests two distinct structural isomers. Matching fragments at nominal mass 141 confirming naphthalene subunit, but no water loss was observable. No further information for structure elucidation was found. This TP serves as intermediate for TP Ter 15.

Ter_TP_11


211210_086_BT_2_DB_7_30h_a (F108) #4826, RT=15.313 min, MS2, FTMS (+), (HCD, DDA, 308.2006@35, +1)
FISh Coverage: 1 Matched, 9 Unmatched, 7 Skipped
Intensity [counts] (10^6)
m/z
141.06993
C11 H9 [M-e]+1
141.06989
C11 H9 [M-e]+1
57.07010
C4 H9 [M-e]+1
55.05454
C4 H7 [M-e]+1
81.06973
C6 H9 [M-e]+1
119.08567
C9 H11 [M-e]+1
121.10123
C9 H13 [M-e]+1
170.09618
C12 H12 N [M-e]+1
150.12820
C10 H16 N [M-e]+1
51.05999
60.36302
60.04472
70.59842
79.05433
91.05422
93.06994
95.04922
113.43775
105.06992
119.33691
121.10109
79.05425
93.06996
163.73827
163.06906
193.10176
191.08717
205.10167
205.10143
261.16422
261.16473

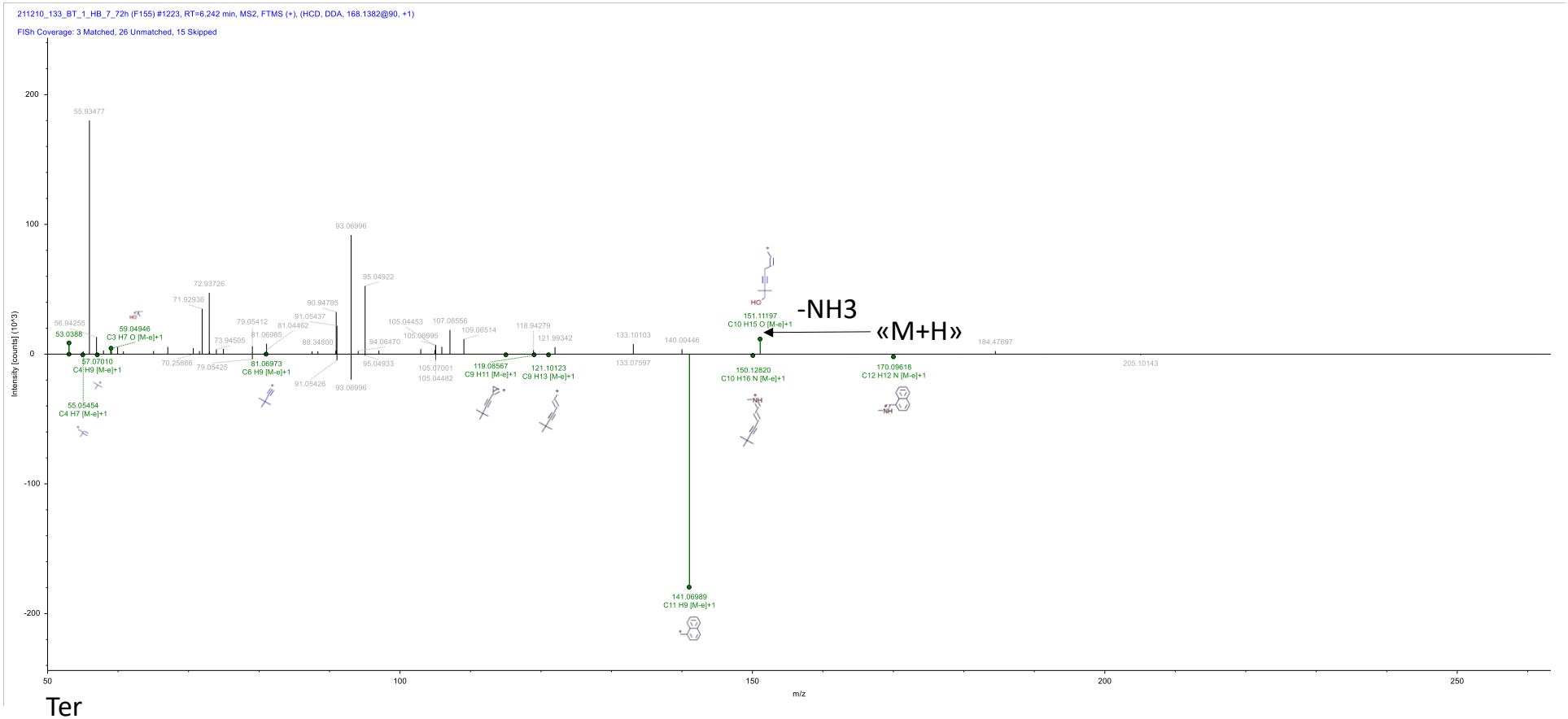
Ter

S3.29.3. Ter TP 12



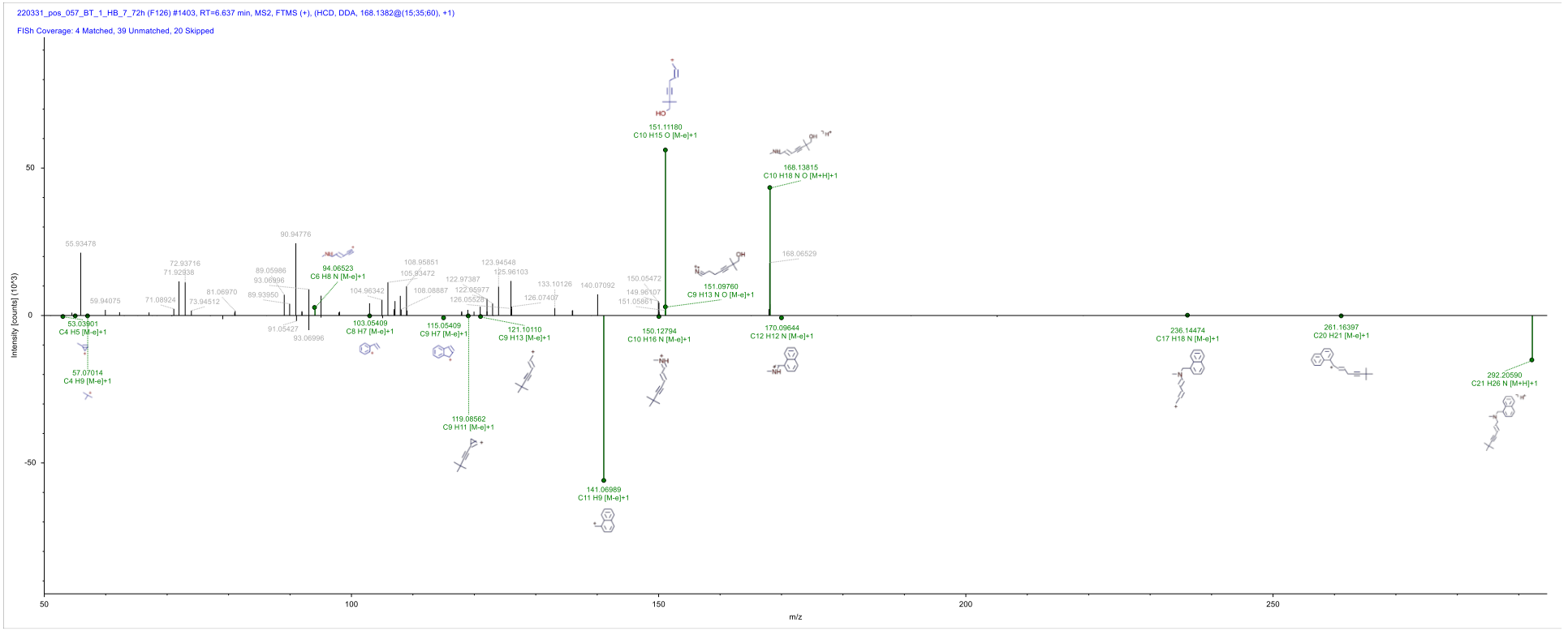
Matching fragments at nominal masses 53, 55, 79, 81, 91, 93, 95 and 105 supporting chain-like substructure. These fragments were not annotated by *MassFrontier* due to their low intensity. Absence of masses 141 and 170 suggest cleavage of naphthalene unit. High mass fragments are obtained by allyl cleavage in TP as opposed to benzyl cleavage in parent spectrum. No water loss was observed to support hydroxy moiety. The loss of ammonia was only observed for the TP and not for the parent, which indicates the transformation from a 3° amine to a 2° amine.

Ter_TP_12


211210_133_BT_1_HB_7_72h (F155) #1223, RT=6.242 min, MS2, FTMS (+), (HCD, DDA, 168.1382@90, +1)
FISh Coverage: 3 Matched, 26 Unmatched, 15 Skipped
Intensity [counts] (10^3)
m/z
-NH3
«M+H»
55.93477
93.06996
95.04922
72.93726
71.92936
90.94785
91.05437
79.05412
81.04462
81.06985
73.94505
88.34800
56.94255
53.0388
59.04946
C3 H7 O [M-e]+1
57.07010
C4 H9 [M-e]+1
55.05454
C4 H7 [M-e]+1
70.25886
79.05425
81.06973
C6 H9 [M-e]+1
91.05426
93.06996
94.06470
95.04933
105.04453
105.06995
107.08556
109.06514
105.07001
105.04482
119.08567
C9 H11 [M-e]+1
118.94279
121.99342
121.10123
C9 H13 [M-e]+1
133.10103
133.07597
140.00446
141.06989
C11 H9 [M-e]+1
151.11197
C10 H15 O [M-e]+1
150.12820
C10 H16 N [M-e]+1
170.09618
C12 H12 N [M-e]+1
184.47697
205.10143

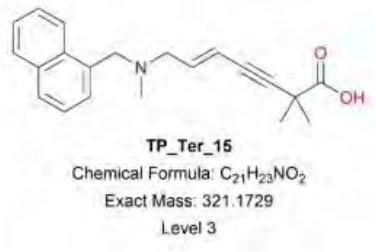
Ter

Ter_TP_12_remeas



Ter_remeas

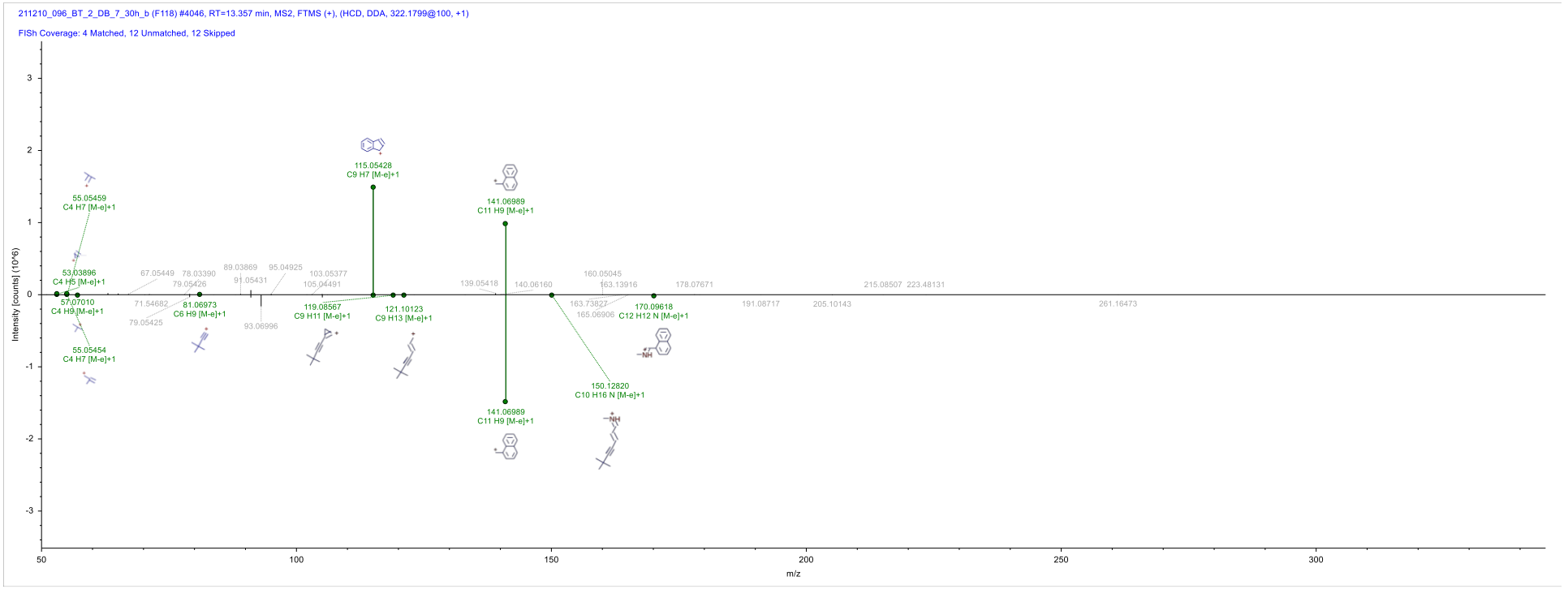
S3.29.4. TP Ter 15



TP_Ter_15
Chemical Formula: $C_{21}H_{23}NO_2$
Exact Mass: 321.1729
Level 3

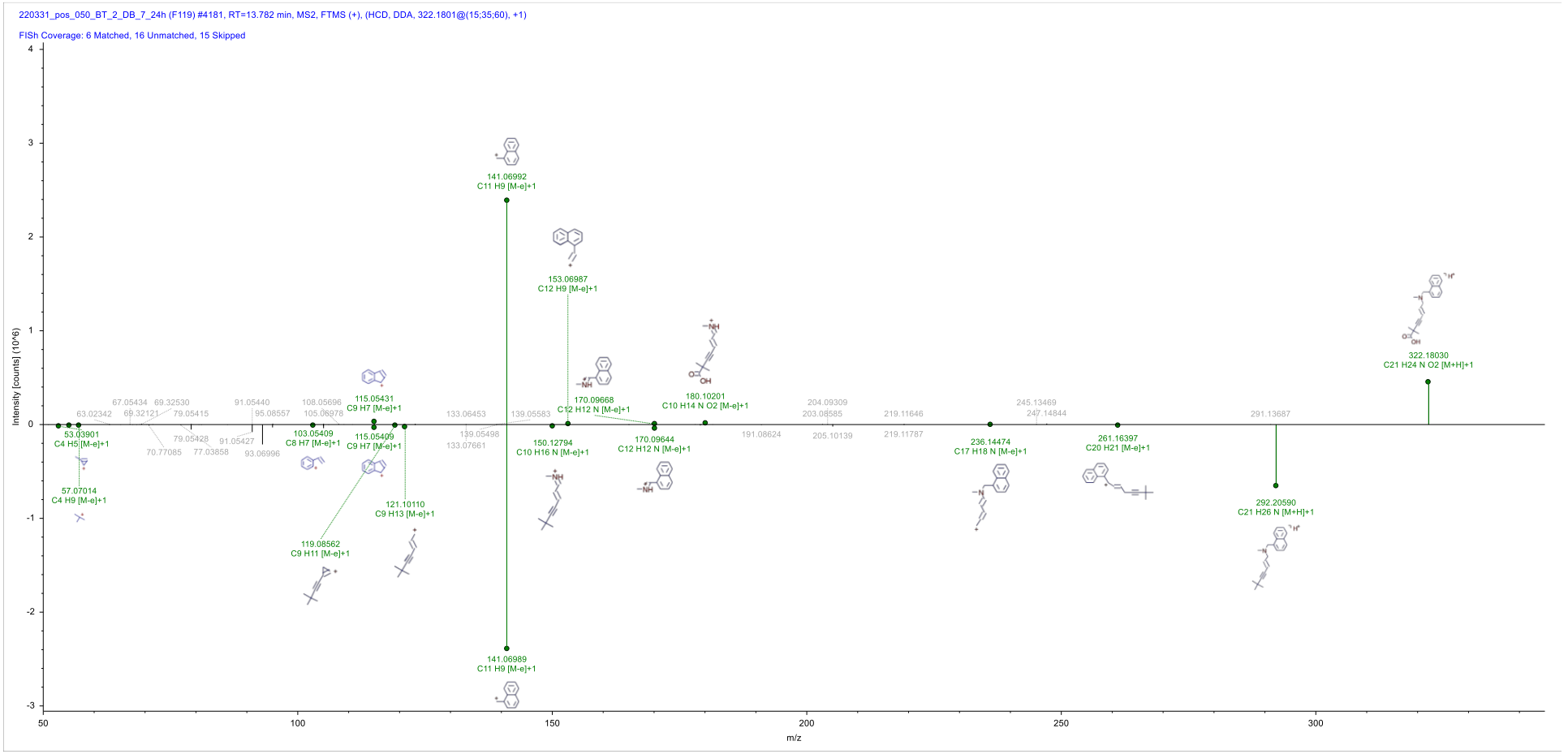
Matching fragments at nominal masses 53, 55, 63, 79, 91, 105, 115, 123, 139, 141, 170, 179 and 205 confirming that backbone of parent is conserved. Missing signals of m/z 119 and 121 in TP MS^2 indicates oxidation of methyl to carboxylic acid. No $[M-H]^-$ ion or CO_2 loss was observed.

TP_Ter_15


211210_096_BT_2_DB_7_30h_b (F118) #4046, RT=13.357 min, MS2, FTMS (+), (HCD, DDA, 322.1799@100, +1)
FISh Coverage: 4 Matched, 12 Unmatched, 12 Skipped
Intensity [counts] (10^6)
m/z
115.05428
C9 H7 [M-e]+1
141.06989
C11 H9 [M-e]+1
55.05459
C4 H7 [M-e]+1
53.03896
C4 H5 [M-e]+1
57.07010
C4 H9 [M-e]+1
55.05454
C4 H7 [M-e]+1
81.06973
C6 H9 [M-e]+1
119.08567
C9 H11 [M-e]+1
121.10123
C9 H13 [M-e]+1
170.09618
C12 H12 N [M-e]+1
150.12820
C10 H16 N [M-e]+1
141.06989
C11 H9 [M-e]+1
67.05449
78.03390
79.05426
89.03869
91.05431
95.04925
103.05377
105.04491
139.05418
140.06160
160.05045
163.13916
178.07671
215.08507
223.48131
71.54682
79.05425
93.06996
163.73827
165.06906
191.08717
205.10143
261.16473

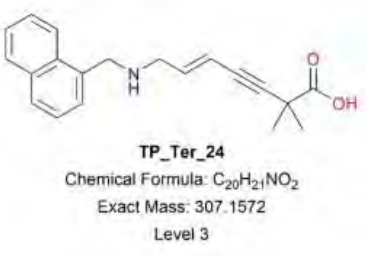
Ter

TP_Ter_15_remeas



Ter_remeas

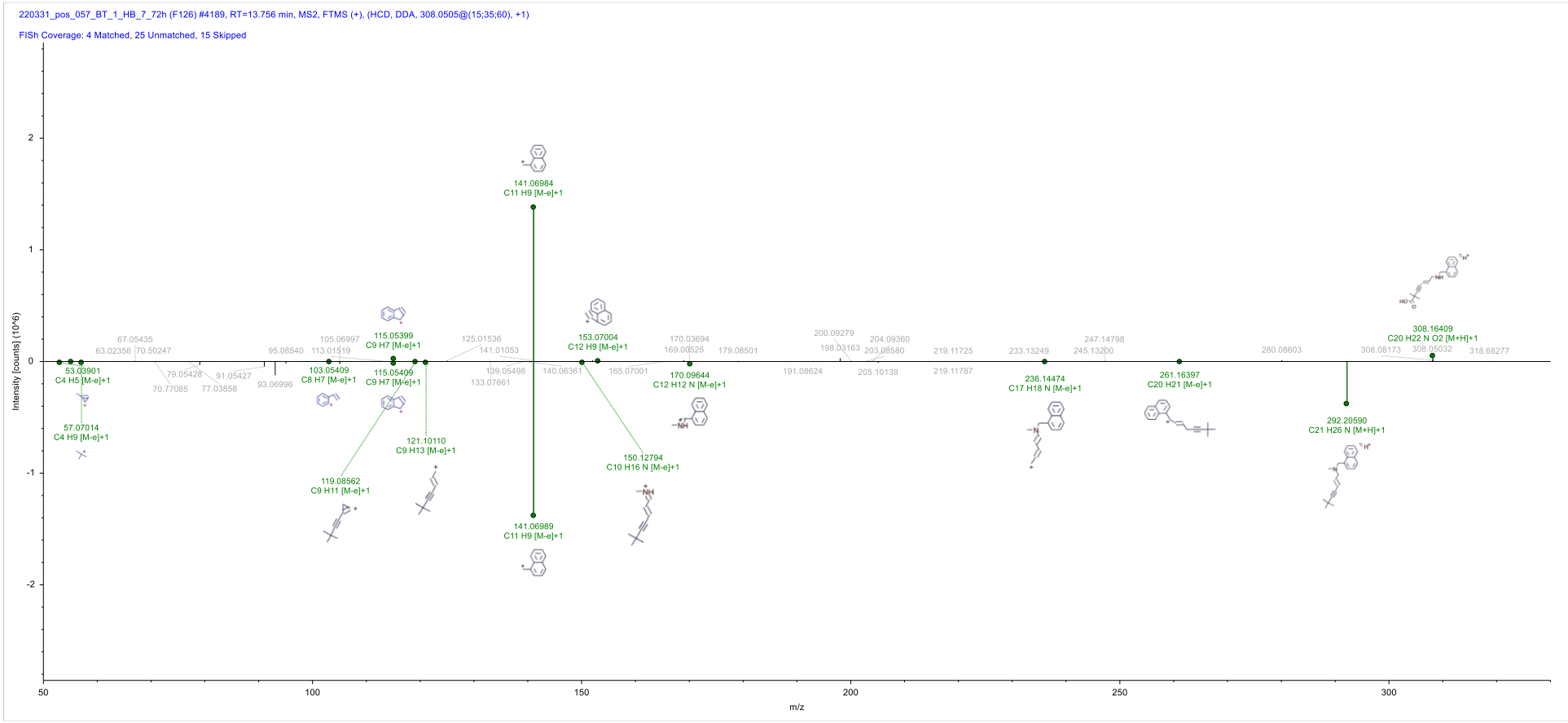
S3.29.5. TP Ter 24



TP_Ter_24
Chemical Formula: $C_{20}H_{21}NO_2$
Exact Mass: 307.1572
Level 3

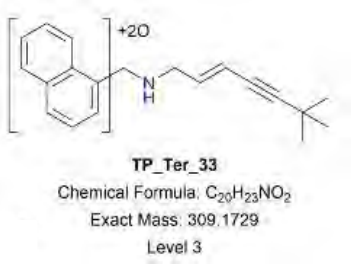
Fragments with nominal masses 63, 105, 115, 123, 141, 179, 205 and 219 were also observed for parent compound. As for TP Ter 15, Missing signals of m/z 119 and 121 in TP MS^2 indicates oxidation of methyl to carboxylic acid. No $[M-H]^-$ ion or CO_2 loss was observed. Additionally, missing parent fragments with masses 150 and 170 indicate demethylation of amine.

TP_Ter_24_remeas



Ter_remeas

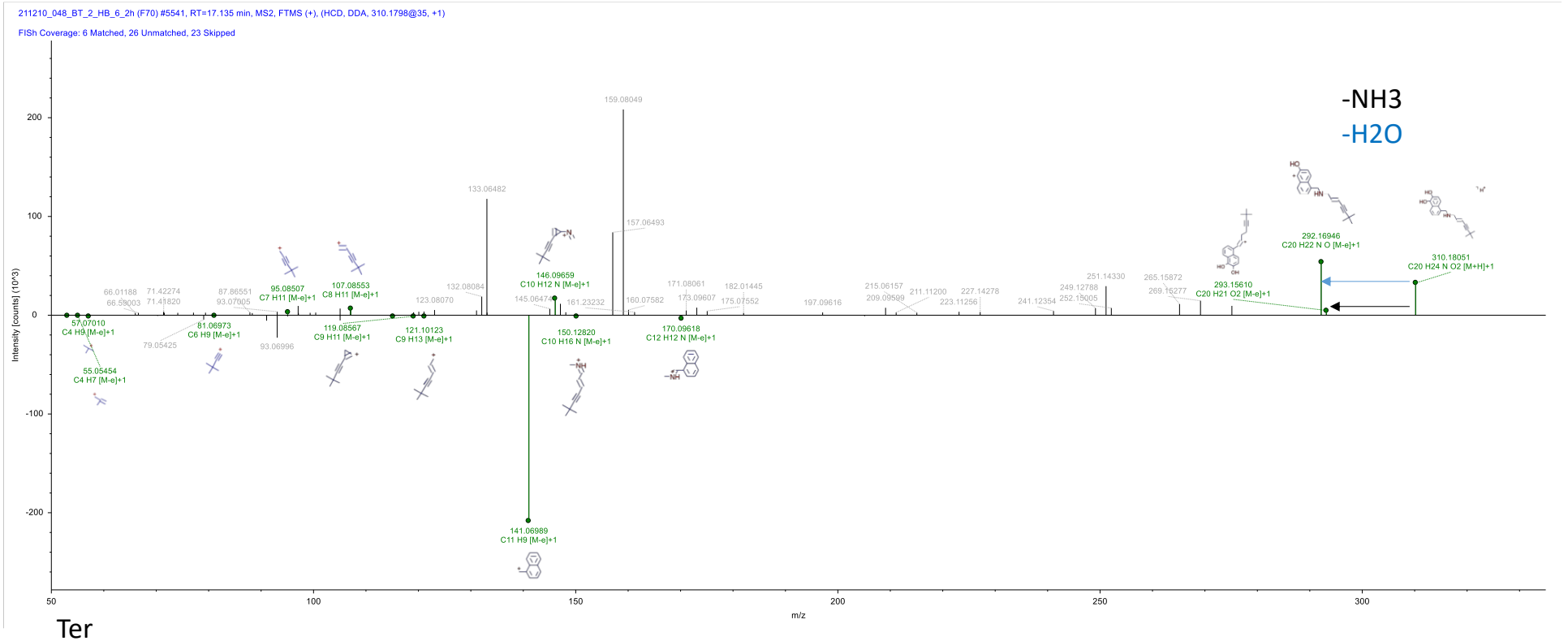
S3.29.6. TP Ter 33



TP_Ter_33
Chemical Formula: $C_{20}H_{23}NO_2$
Exact Mass: 309.1729
Level 3

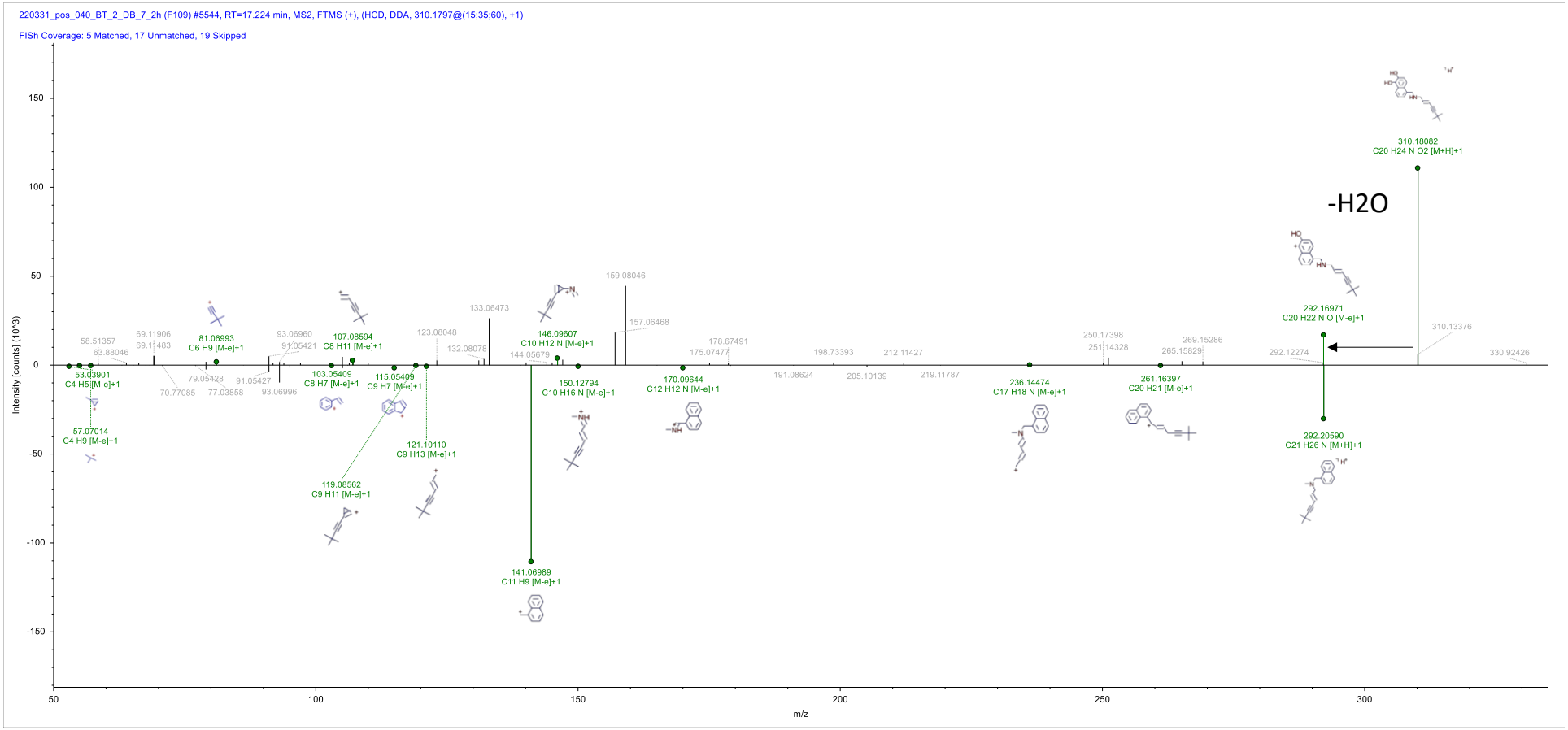
Parent and TP MS^2 spectra show matching fragments with m/z 79, 81, 91, 93, 105, 119 and 123. Water loss indicates oxidation and matching fragment with mass 119, as well as absence of masses 141 and 170 supports dioxidation of naphthalene unit and thus conversion to a chatechol derivative.

TP_Ter_33


211210_048_BT_2_HB_6_2h (F70) #5541, RT=17.135 min, MS2, FTMS (+), (HCD, DDA, 310.1798@35, +1)
FISh Coverage: 6 Matched, 26 Unmatched, 23 Skipped
-NH3
-H2O
Intensity [counts] (10^3)
m/z
57.07010 C4 H9 [M-e]+1
55.05454 C4 H7 [M-e]+1
81.06973 C6 H9 [M-e]+1
95.08507 C7 H11 [M-e]+1
107.08553 C8 H11 [M-e]+1
119.08567 C9 H11 [M-e]+1
121.10123 C9 H13 [M-e]+1
133.06482
141.06989 C11 H9 [M-e]+1
146.09659 C10 H12 N [M-e]+1
150.12820 C10 H16 N [M-e]+1
157.06493
159.08049
170.09618 C12 H12 N [M-e]+1
292.16946 C20 H22 N O [M-e]+1
293.15610 C20 H21 O2 [M-e]+1
310.18051 C20 H24 N O2 [M+H]+1

Ter

TP_Ter_33_remeas

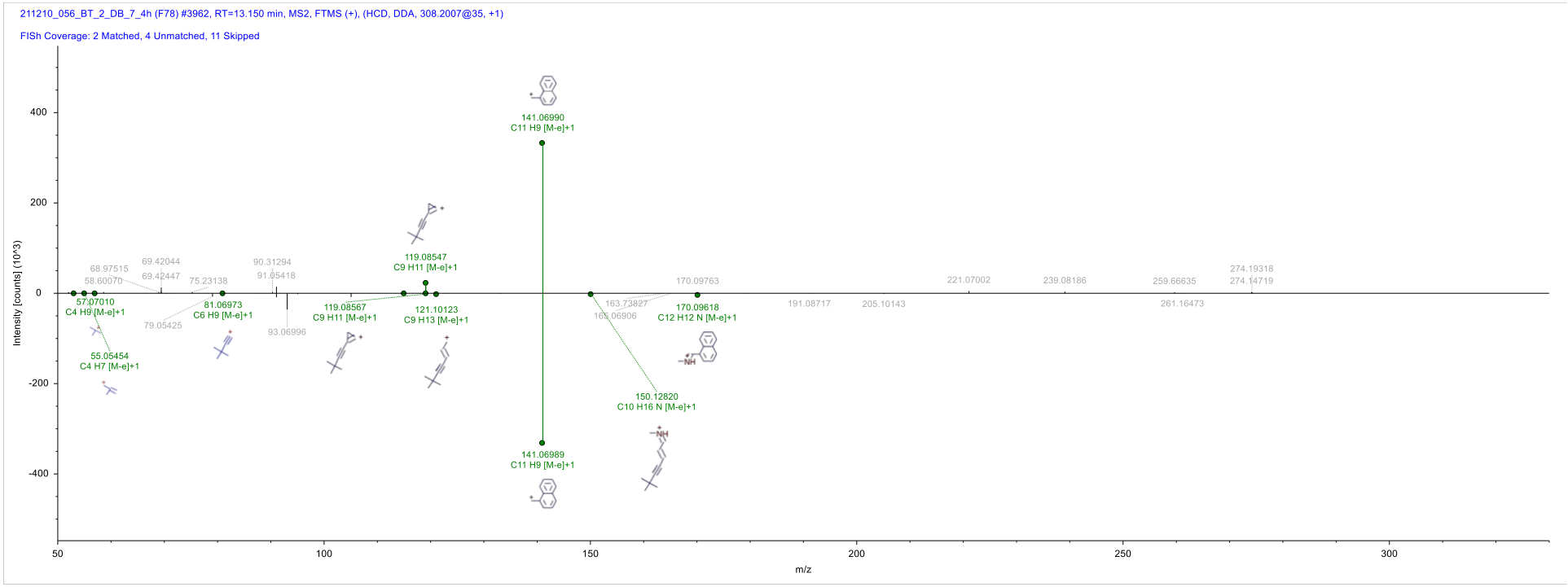


Ter_remeas

S3.29.7. 21 TP Ter

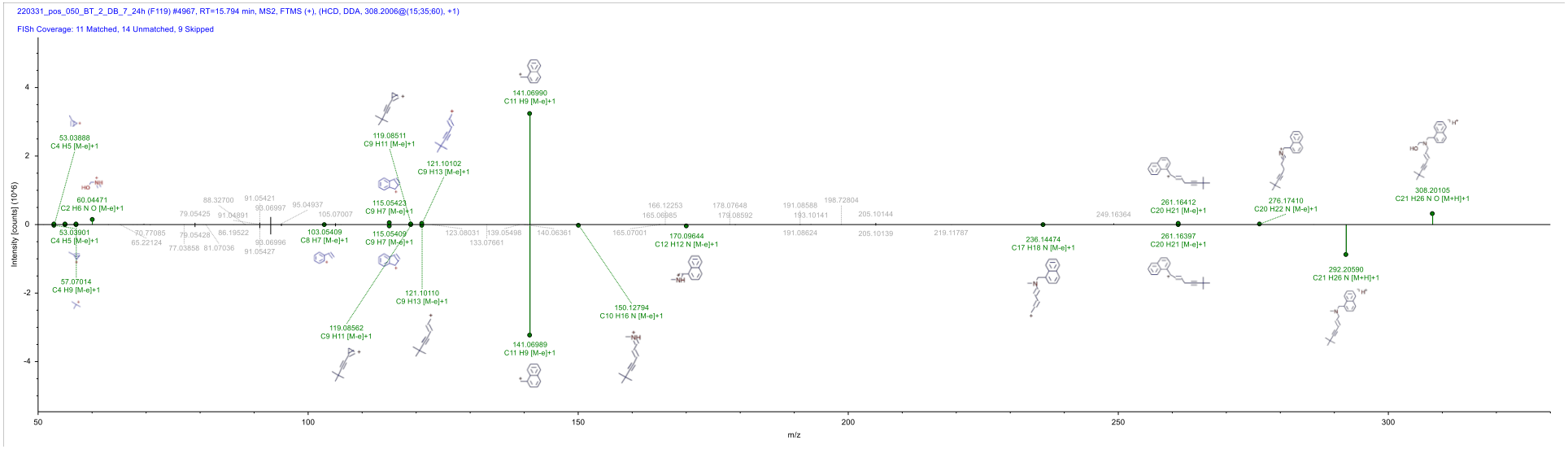
Two compounds with the same chemical formula were found at RT 13.2 (Ter TP 11, intensity in chromatogram around 10^6) and 15.4 (21 TP Ter, intensity in chromatogram around 10^7), which suggests two distinct structural isomers. Matching fragments between parent and TP were found at m/z 53, 55, 57, 63, 79, 91, 93, 95, 103, 105, 115, 119, 121, 141, 205 and 261, where especially fragments 119, 121 and 261 exclude terminal hydroxylation and support the transformation on the tertiary amine. However, this compound could also be the hydroxylated intermediate for TP Ter 33 and TP Ter 24.

21_TP_Ter


211210_056_BT_2_DB_7_4h (F78) #3962, RT=13.150 min, MS2, FTMS (+), (HCD, DDA, 308.2007@35, +1)
FISh Coverage: 2 Matched, 4 Unmatched, 11 Skipped
Intensity [counts] (10^3)
m/z
141.06990
C11 H9 [M-e]+1
119.08547
C9 H11 [M-e]+1
57.07010
C4 H9 [M-e]+1
55.05454
C4 H7 [M-e]+1
81.06973
C6 H9 [M-e]+1
119.08567
C9 H11 [M-e]+1
121.10123
C9 H13 [M-e]+1
170.09618
C12 H12 N [M-e]+1
150.12820
C10 H16 N [M-e]+1
141.06989
C11 H9 [M-e]+1

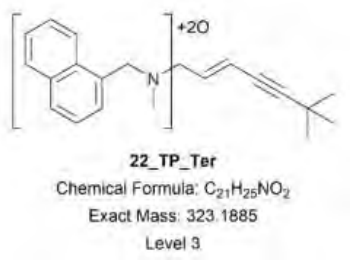
Ter

21_TP_Ter_remeas



Ter_remeas

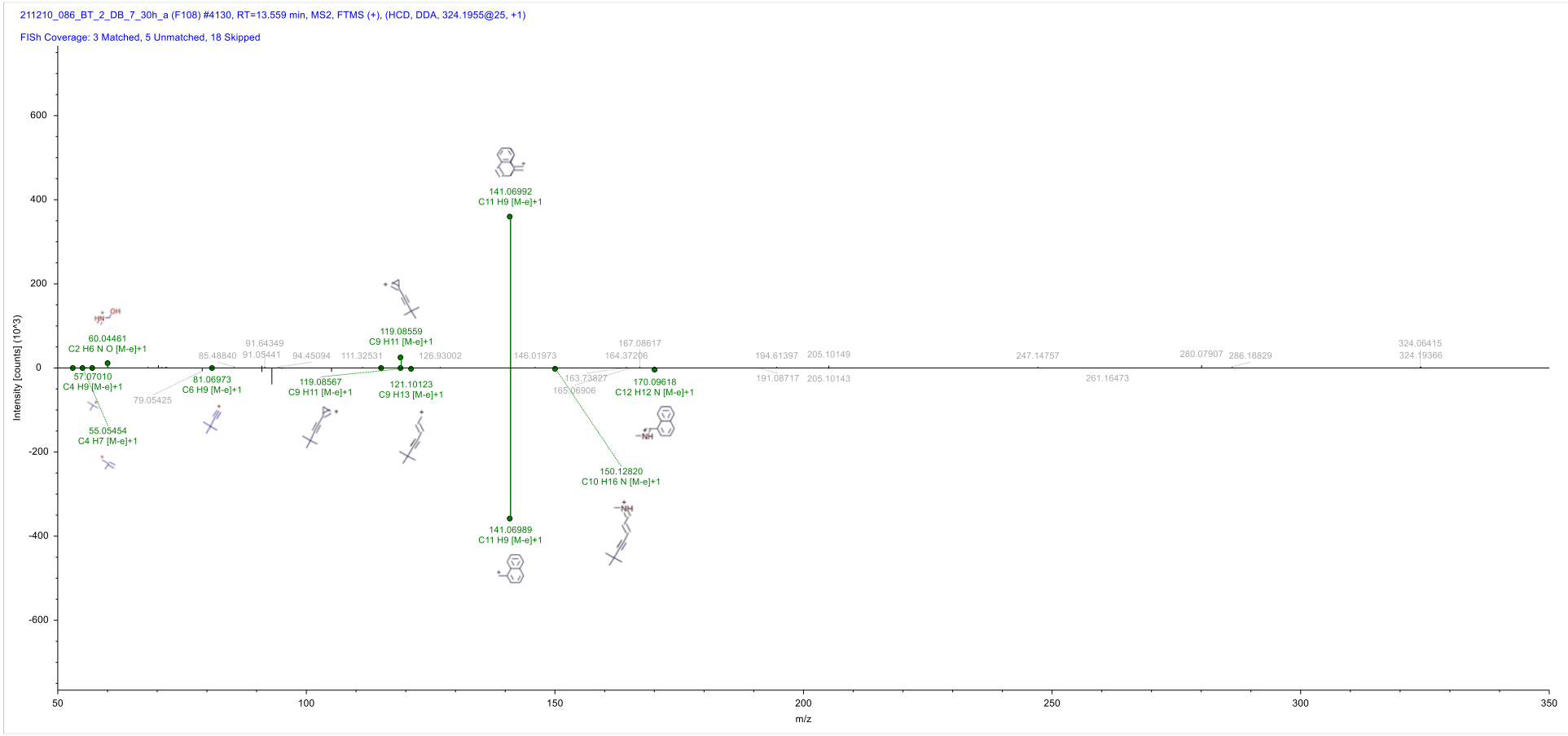
S3.29.8. 22 TP Ter



Matching fragments at nominal masses 91, 93, 115, 119 and 141 confirming substructure. Ion at m/z 141 suggests no hydroxylation of aromatic ring system. Ion at m/z 119 suggests no hydroxylation of terminal *tert*-butyl group.

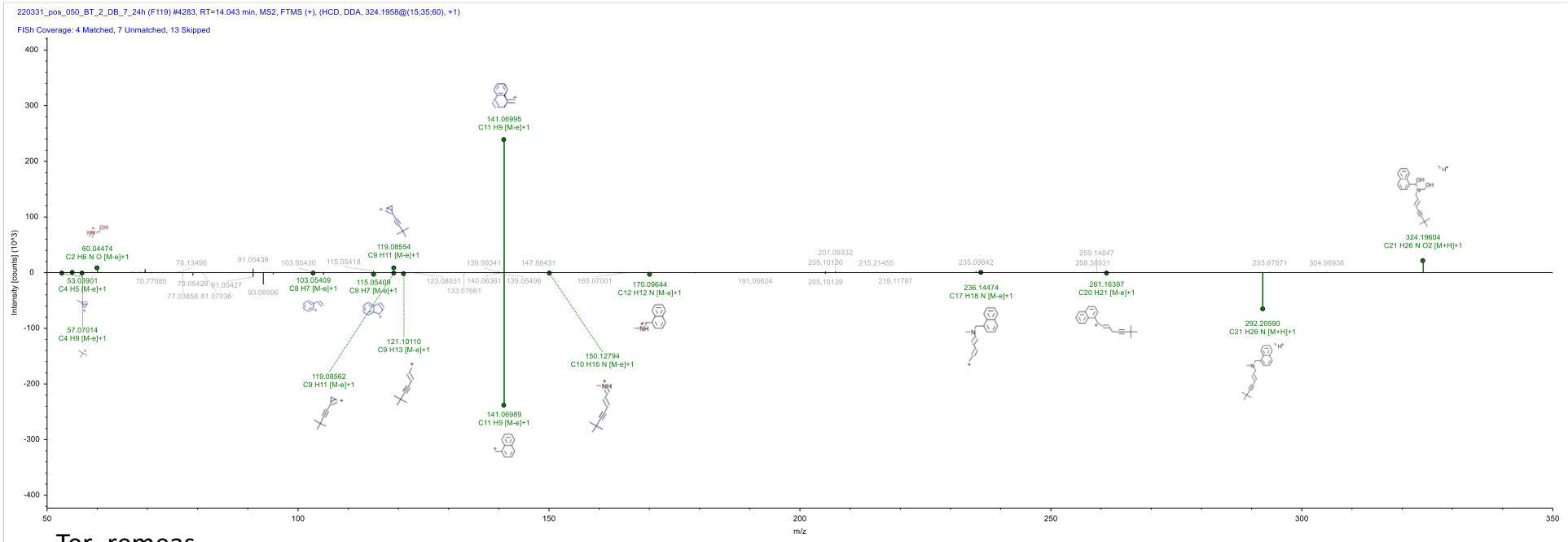
The first oxidation step was proposed as an *N*-oxidation and the second as hydroxylation. However, dihydroxylation would be possible and lead to multiple potential structural isomers. The formation of germinal alcohols is unlikely, because they should spontaneously form ketones or aldehydes.

22_TP_Ter


211210_086_BT_2_DB_7_30h_a (F108) #4130, RT=13.559 min, MS2, FTMS (+), (HCD, DDA, 324.1955@25, +1)
FISh Coverage: 3 Matched, 5 Unmatched, 18 Skipped
Intensity [counts] (10^3)
m/z
600
400
200
0
-200
-400
-600
50
100
150
200
250
300
350
141.06992
C11 H9 [M-e]+1
119.08559
C9 H11 [M-e]+1
60.04461
C2 H6 N O [M-e]+1
57.07010
C4 H9 [M-e]+1
81.06973
C6 H9 [M-e]+1
119.08567
C9 H11 [M-e]+1
121.10123
C9 H13 [M-e]+1
170.09618
C12 H12 N [M-e]+1
55.05454
C4 H7 [M-e]+1
150.12820
C10 H16 N [M-e]+1
141.06989
C11 H9 [M-e]+1
85.48840
91.64349
91.05441
94.45094
111.32531
126.93002
146.01973
167.08617
164.37206
194.61397
205.10149
247.14757
280.07907
286.18829
324.06415
324.19366
79.05425
163.73827
165.06906
191.08717
205.10143
261.16473

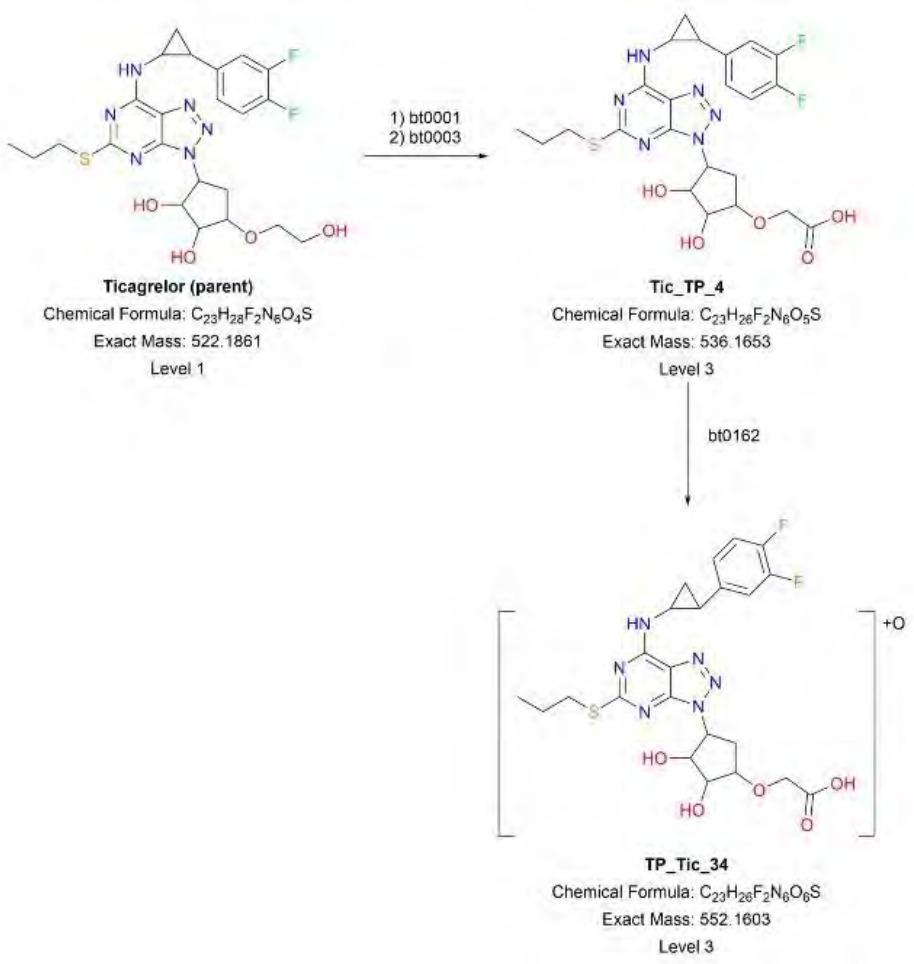
Ter

22_TP_Ter_remeas



Ter_remeas

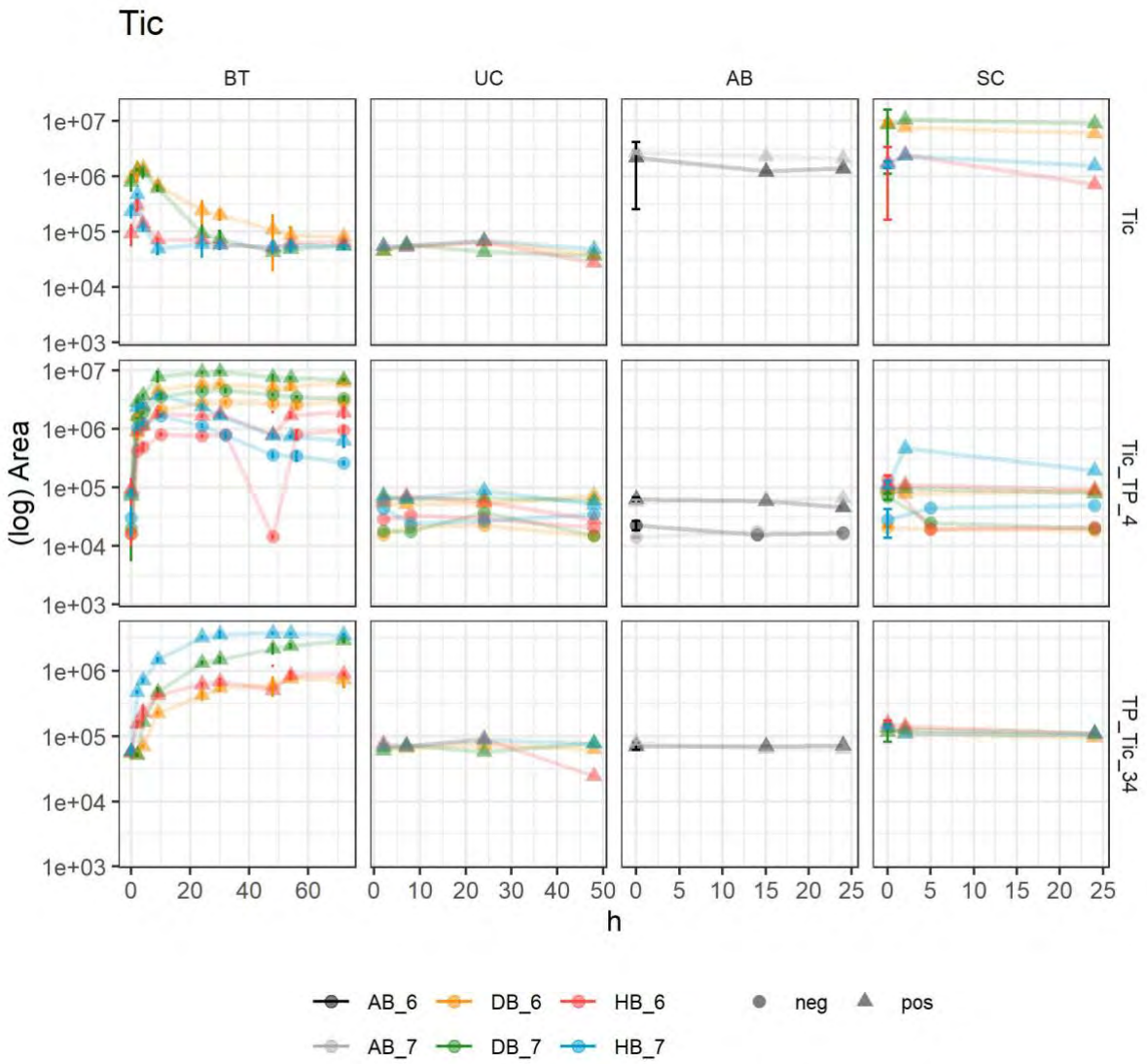
S3.30 Ticagrelor



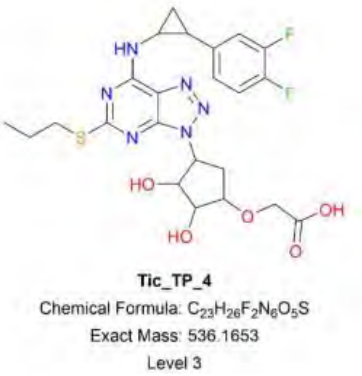
Ticagrelor (parent)
Chemical Formula: $C_{23}H_{28}F_2N_6O_4S$
Exact Mass: 522.1861
Level 1

Tic_TP_4
Chemical Formula: $C_{23}H_{26}F_2N_6O_5S$
Exact Mass: 536.1653
Level 3

TP_Tic_34
Chemical Formula: $C_{23}H_{26}F_2N_6O_6S$
Exact Mass: 552.1603
Level 3


Tic
BT
UC
AB
SC
Tic
Tic_TP_4
TP_Tic_34
(log) Area
1e+07
1e+06
1e+05
1e+04
1e+03
0 20 40 60
0 10 20 30 40 50
0 5 10 15 20 25
h
AB_6
DB_6
HB_6
AB_7
DB_7
HB_7
neg
pos

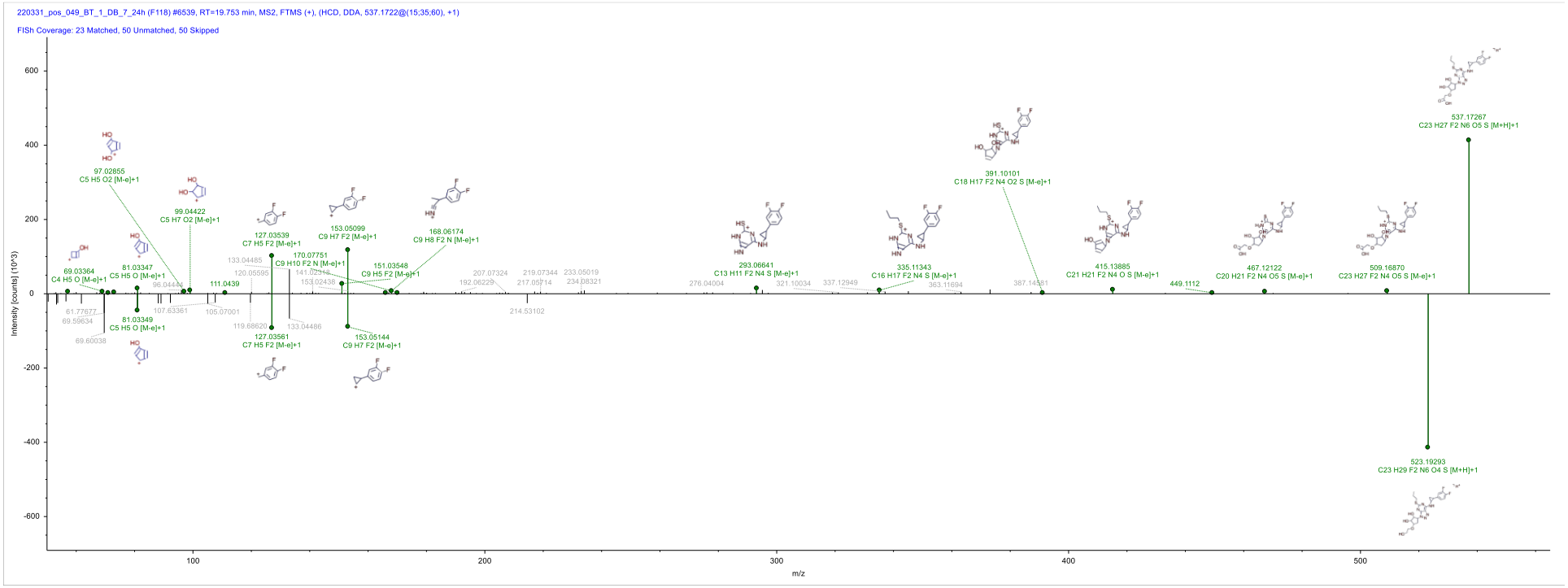
S3.30.1. Tic TP 4



Tic_TP_4
Chemical Formula: $C_{23}H_{26}F_2N_6O_5S$
Exact Mass: 536.1653
Level 3

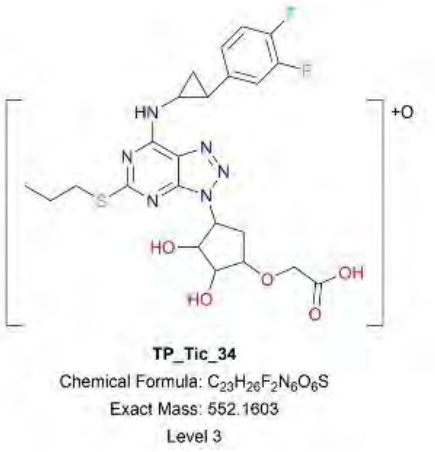
Ions at m/z 81, 105, 127, 133 and 153 were also detected for parent compound, where especially 127 and 153 confirm benzyl moiety together with its substituents.

Tic_TP_4_remeas



Tic_remeas

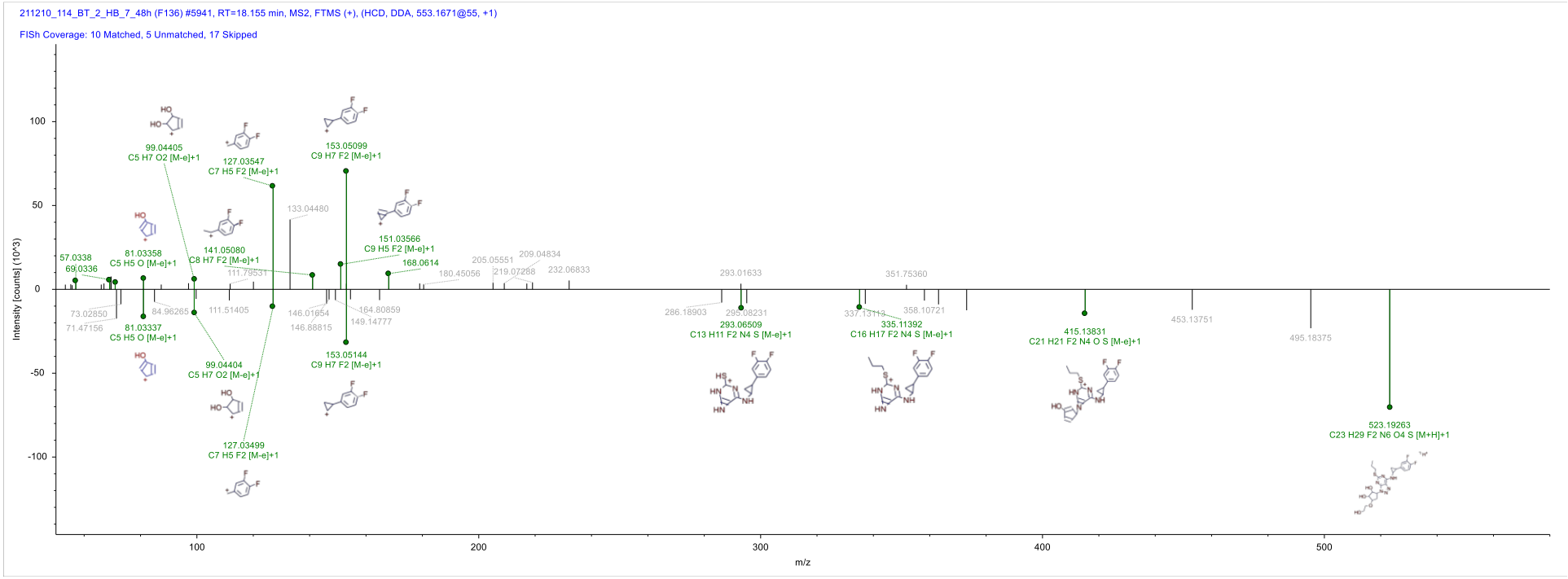
S3.30.2. TP Tic 34



TP_Tic_34
Chemical Formula: $C_{23}H_{26}F_2N_6O_6S$
Exact Mass: 552.1603
Level 3

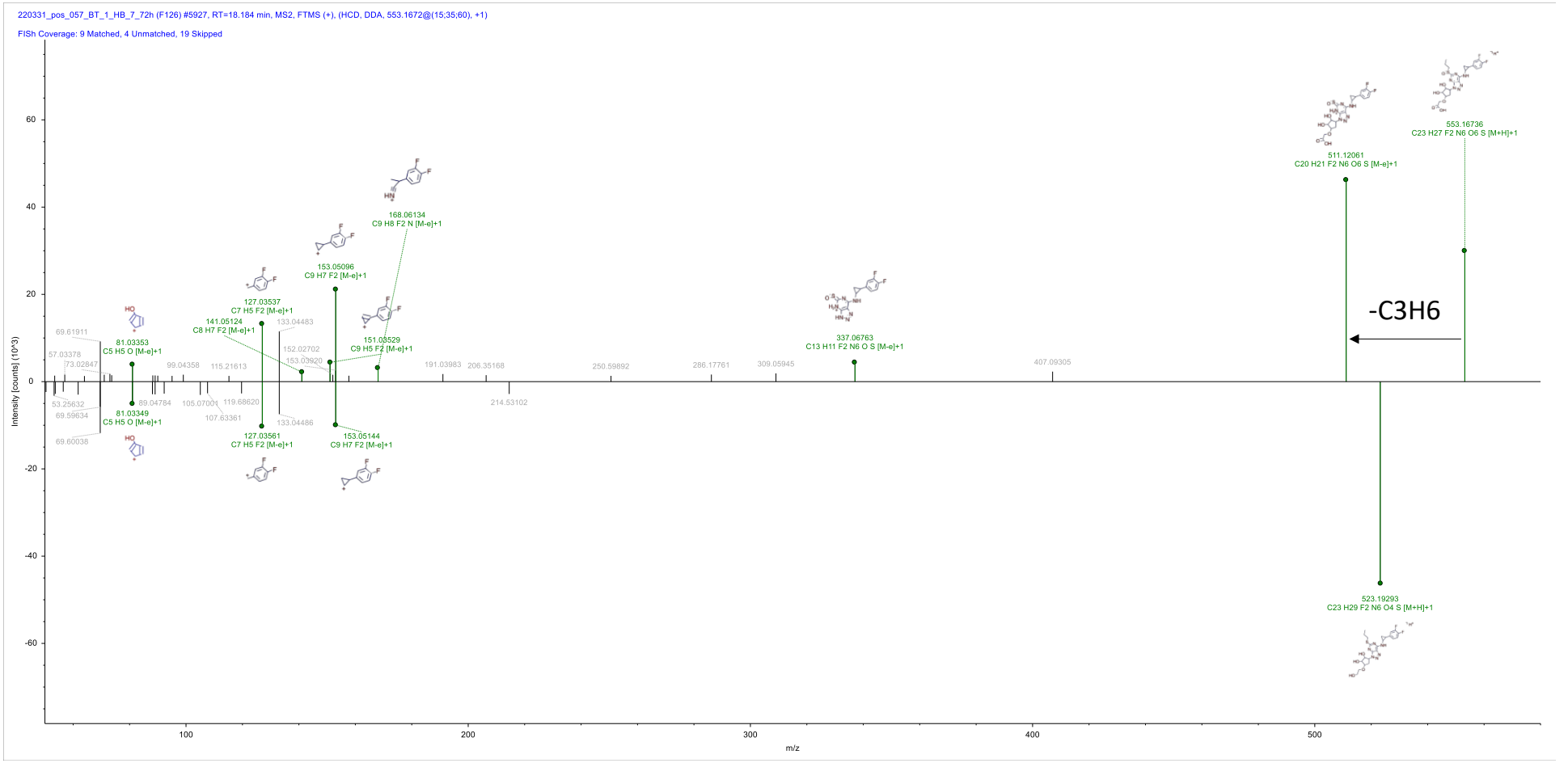
Ions at m/z 81, 99, 127, 133 and 153 were also detected for parent compound, where especially 127 and 153 confirm benzyl moiety together with its substituents. These also suggest no hydroxylation of benzene of 3-membered ring. Fragment with mass 511 is the result of □-cleavage of sulfoxide, which was observed neither in parent nor Tic TP 4.

TP_Tic_34


211210_114_BT_2_HB_7_48h (F136) #5941, RT=18.155 min, MS2, FTMS (+), (HCD, DDA, 553.1671@55, +1)
FISh Coverage: 10 Matched, 5 Unmatched, 17 Skipped
Intensity [counts] (10^3)
m/z
99.04405
C5 H7 O2 [M-e]+1
127.03547
C7 H5 F2 [M-e]+1
153.05099
C9 H7 F2 [M-e]+1
133.04480
151.03566
C9 H5 F2 [M-e]+1
168.0614
141.05080
C8 H7 F2 [M-e]+1
111.79531
81.03358
C5 H5 O [M-e]+1
57.0338
69.0336
205.05551
209.04834
219.07258
232.06833
180.45056
293.01633
351.75360
73.02850
71.47156
84.96265
111.51405
146.01654
146.88815
164.80859
149.14777
286.18903
295.08231
337.13113
358.10721
81.03337
C5 H5 O [M-e]+1
293.06509
C13 H11 F2 N4 S [M-e]+1
335.11392
C16 H17 F2 N4 S [M-e]+1
415.13831
C21 H21 F2 N4 O S [M-e]+1
453.13751
495.18375
99.04404
C5 H7 O2 [M-e]+1
153.05144
C9 H7 F2 [M-e]+1
127.03499
C7 H5 F2 [M-e]+1
523.19263
C23 H29 F2 N6 O4 S [M+H]+1

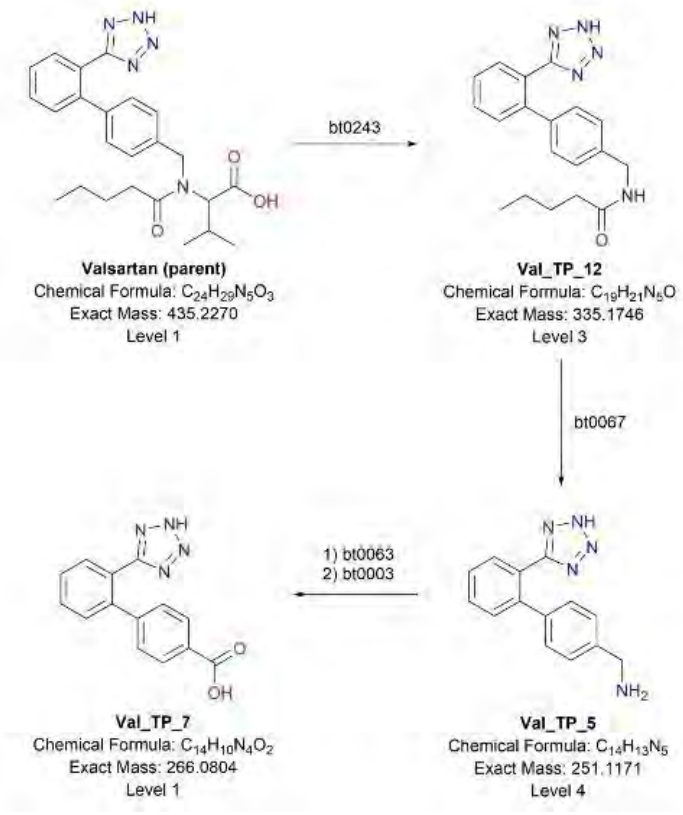
Tic

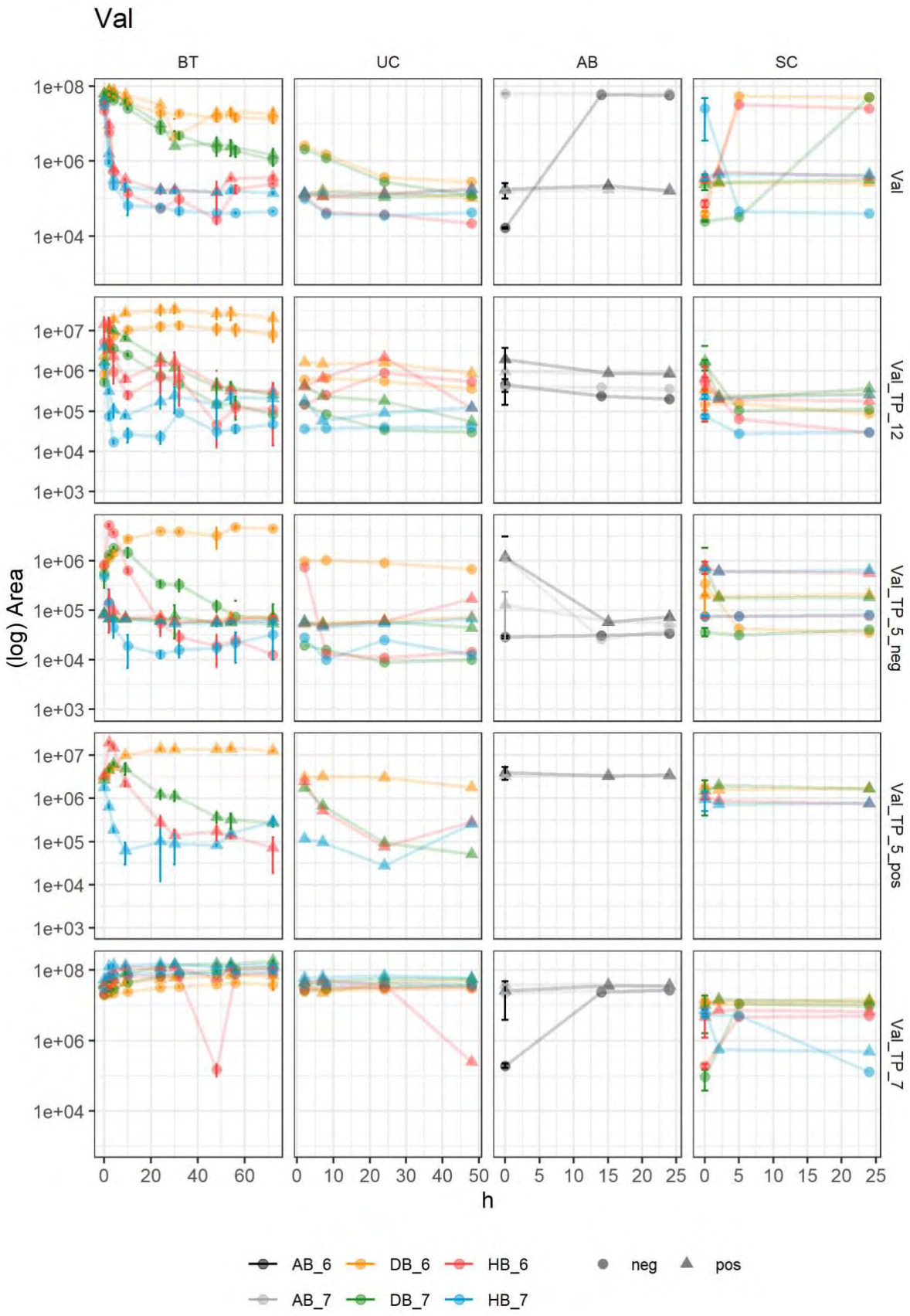
TP_Tic_34_remeas



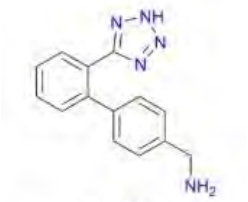
Tic_remeas

S3.31 Valsartan




Val
BT
UC
AB
SC
Val
Val_TP_12
Val_TP_5_neg
Val_TP_5_pos
Val_TP_7
(log) Area
h
AB_6
DB_6
HB_6
AB_7
DB_7
HB_7
neg
pos

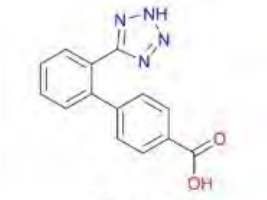
S3.31.1. Val TP 5



Val_TP_5
Chemical Formula: $C_{14}H_{13}N_5$
Exact Mass: 251.1171
Level 4

MS^2 scan of TP was not informative, because it only showed $[M-H]^-$ ion. Furthermore, comparison with parent was not possible due to polarity difference.

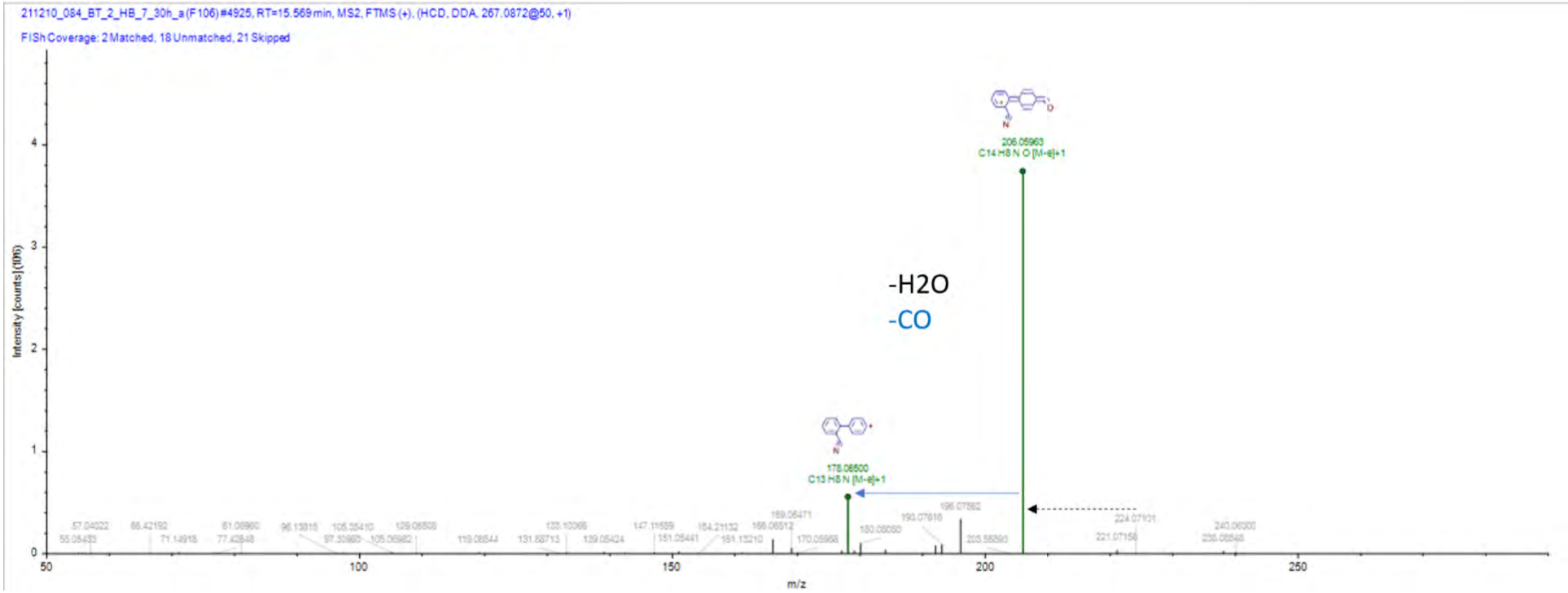
S3.31.2. Val TP 7



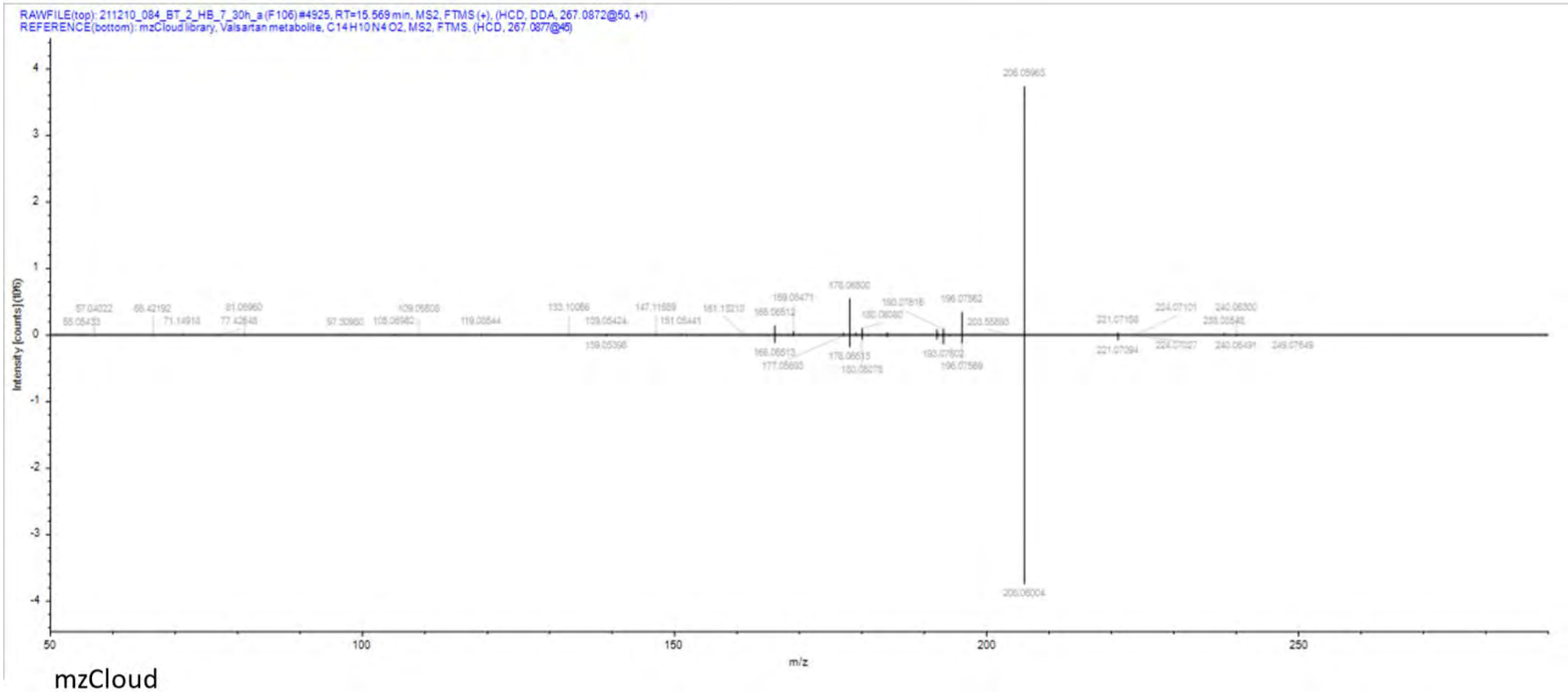
Val_TP_7
Chemical Formula: $C_{14}H_{10}N_4O_2$
Exact Mass: 266.0804
Level 1

The structure was confirmed by library match and by reference standard.

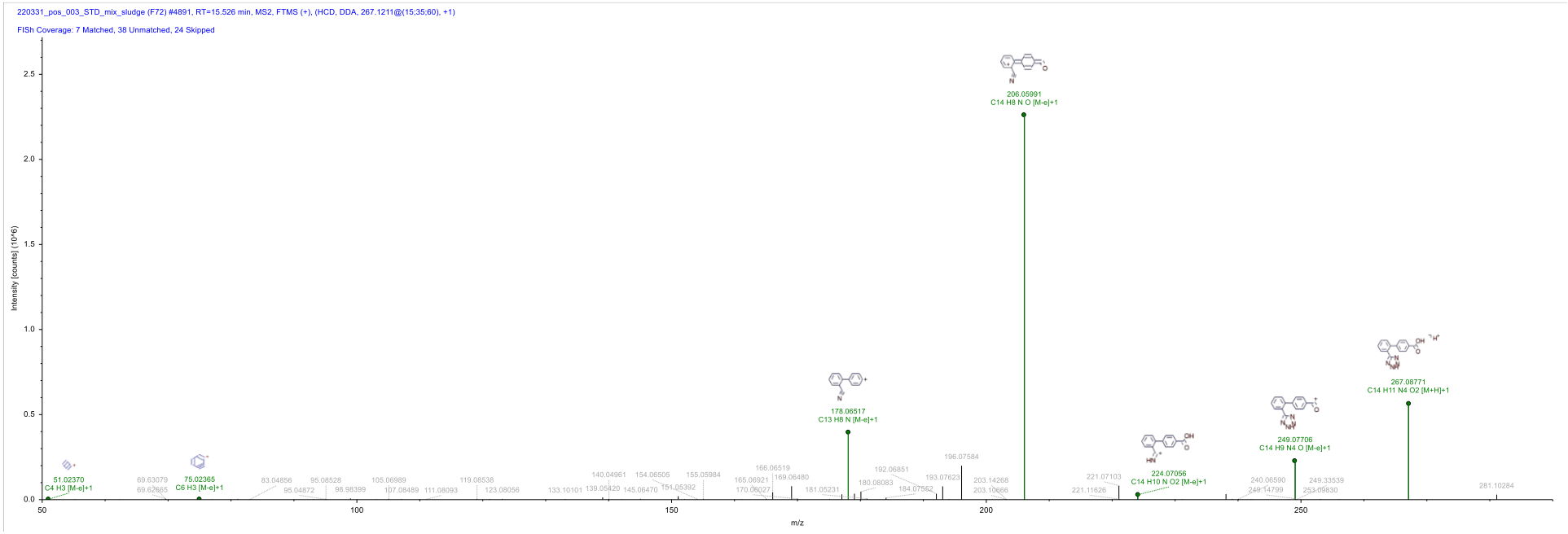
Val_TP_7


211210_084_BT_2_HB_7_30h_a (F106) #4925, RT=15.569 min, MS2, FTMS (+), (HCD, DDA, 267.0872@50, +1)
FISh Coverage: 2 Matched, 18 Unmatched, 21 Skipped
206.05963
C14 H8 N O [M+e]+1
-H2O
-CO
178.06500
C13 H8 N [M-e]+1
Intensity [counts] (10^6)
m/z

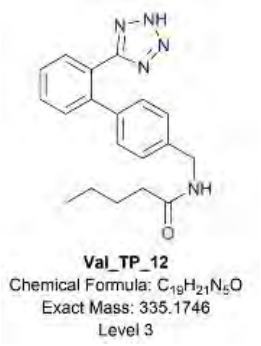
Val TP 7


RAWFILE(top): 211210_084_BT_2_HB_7_30h_a (F106) #4925, RT=15.569 min, MS2, FTMS (+), (HCD, DDA, 267.0872@50, +1)
REFERENCE(bottom): mzCloud library, Valsartan metabolite, C14 H10 N4 O2, MS2, FTMS, (HCD, 267.0877@45)
Intensity [counts] (10^6)
m/z
mzCloud

Val_TP_7_reference_standard



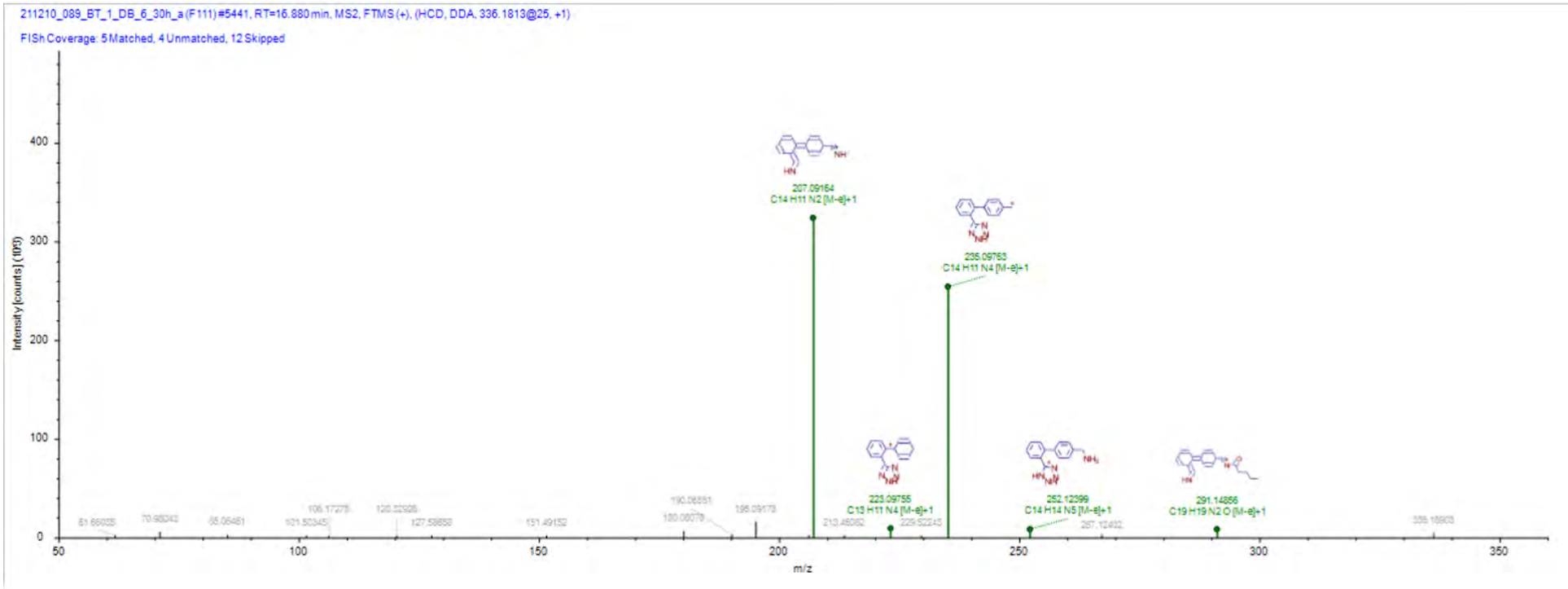
S3.31.3. Val TP 12



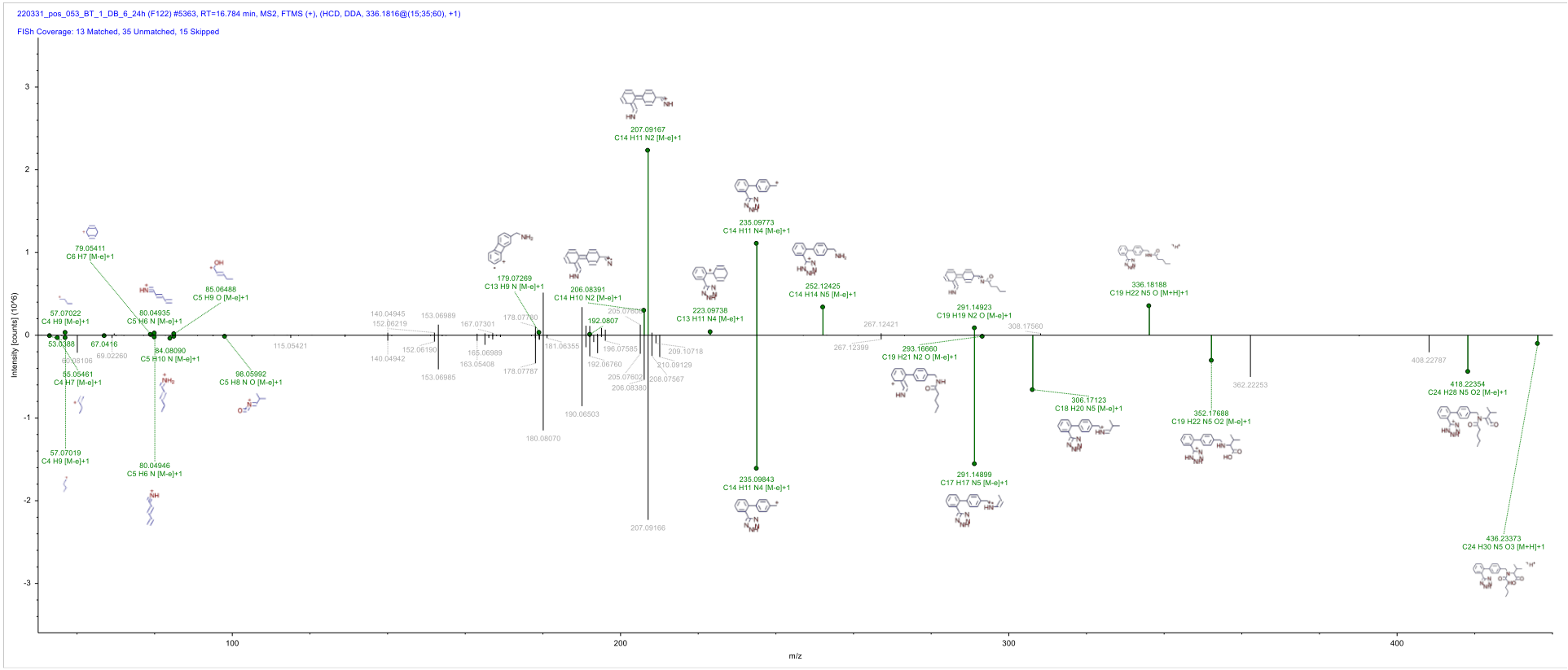
Val_TP_12
Chemical Formula: $C_{16}H_{21}N_5O$
Exact Mass: 335.1746
Level 3

30 matches with MS^2 scans of parent, but many without structure annotation. Ion with nominal mass 235 confirms structural backbone.

Val_TP_12

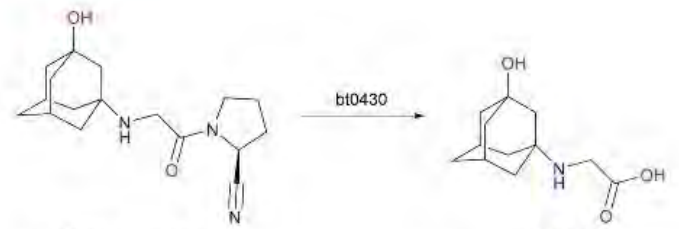

211210_089_BT_1_DB_6_30h_a (F111) #5441, RT=16.880 min, MS2, FTMS (+), (HCD, DDA, 336.1813@25, +1)
FISh Coverage: 5 Matched, 4 Unmatched, 12 Skipped
Intensity [counts] (109)
m/z
207.09164
C14 H11 N2 [M-e]+1
235.09763
C14 H11 N4 [M-e]+1
223.09755
C13 H11 N4 [M-e]+1
252.12399
C14 H14 N5 [M-e]+1
291.14866
C19 H19 N2 O [M-e]+1

Val_TP_12_remeas



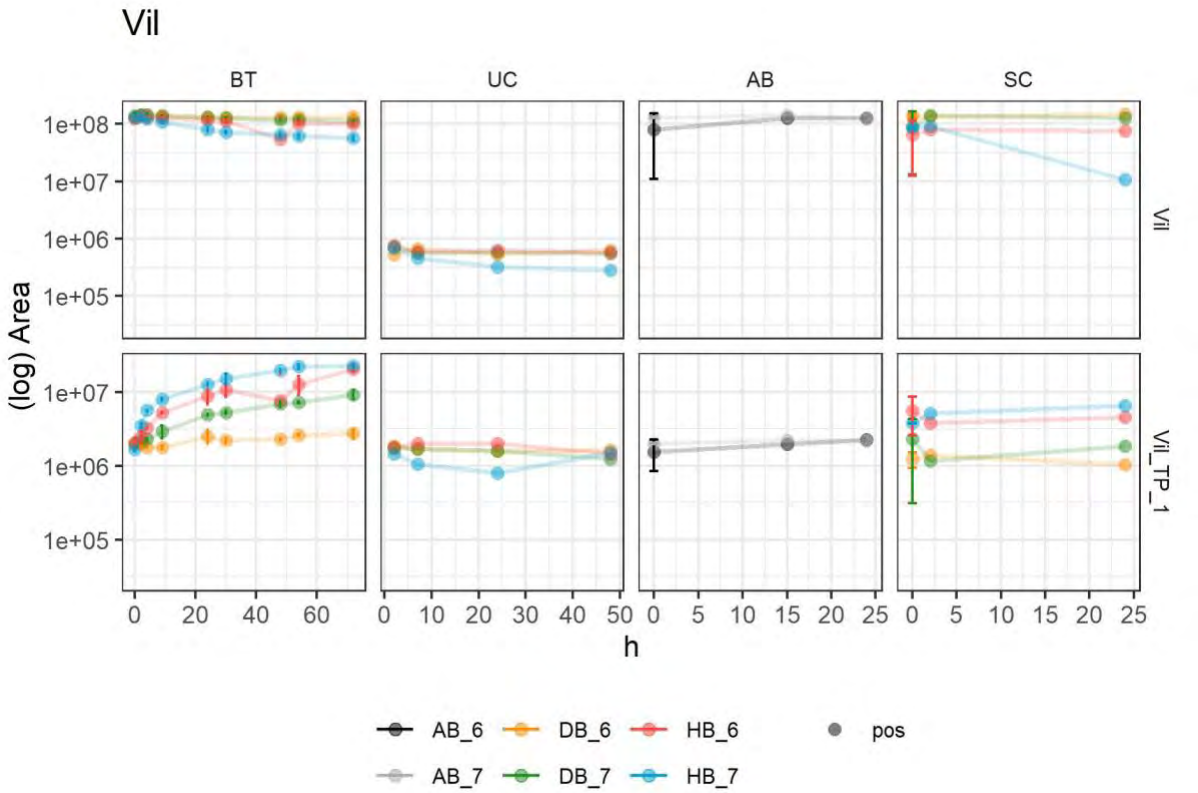
Val_remeas

S3.32 Vildagliptin

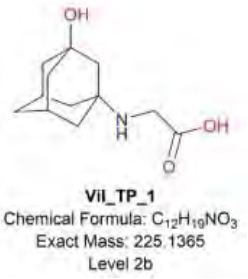


Vildagliptin (parent)
Chemical Formula: $C_{17}H_{25}N_3O_2$
Exact Mass: 303.1947
Level 1

Vil_TP_1
Chemical Formula: $C_{12}H_{19}NO_3$
Exact Mass: 225.1365
Level 2b

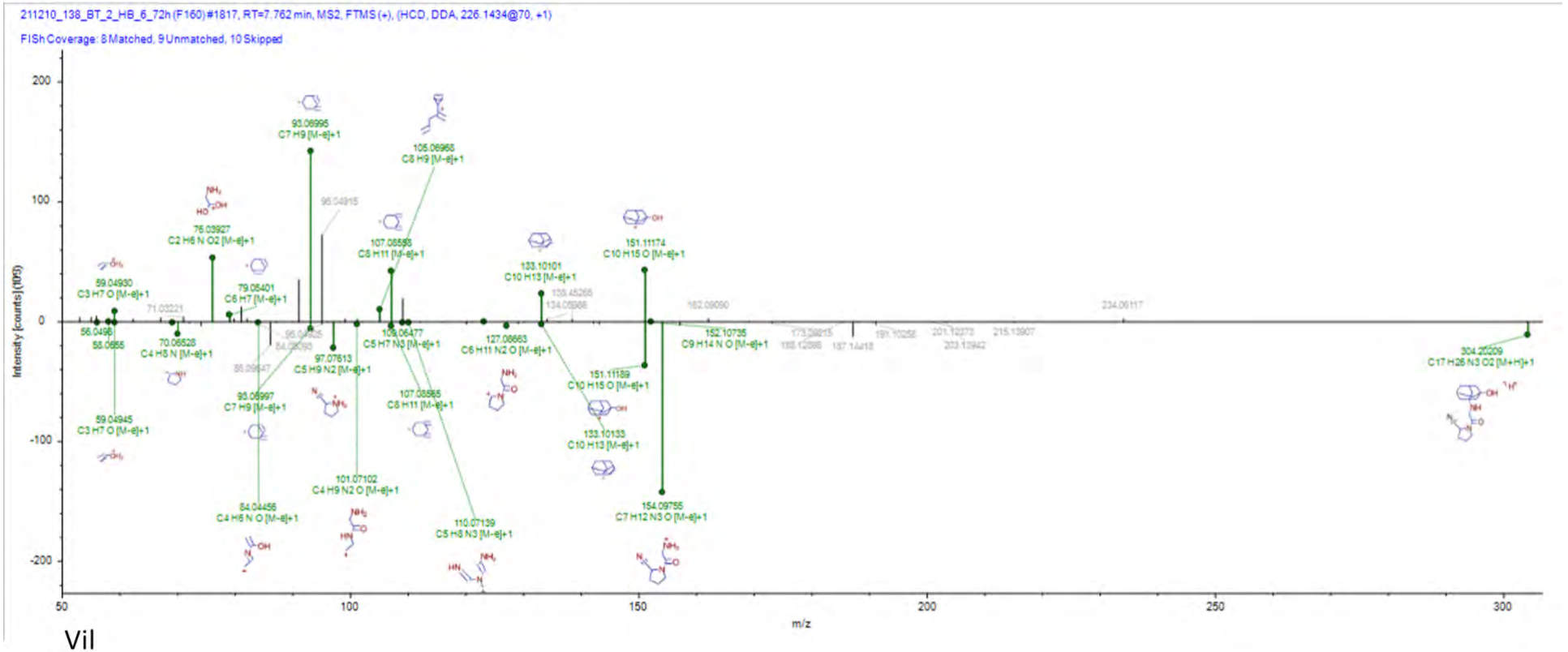


S3.32.1. Vil TP 1



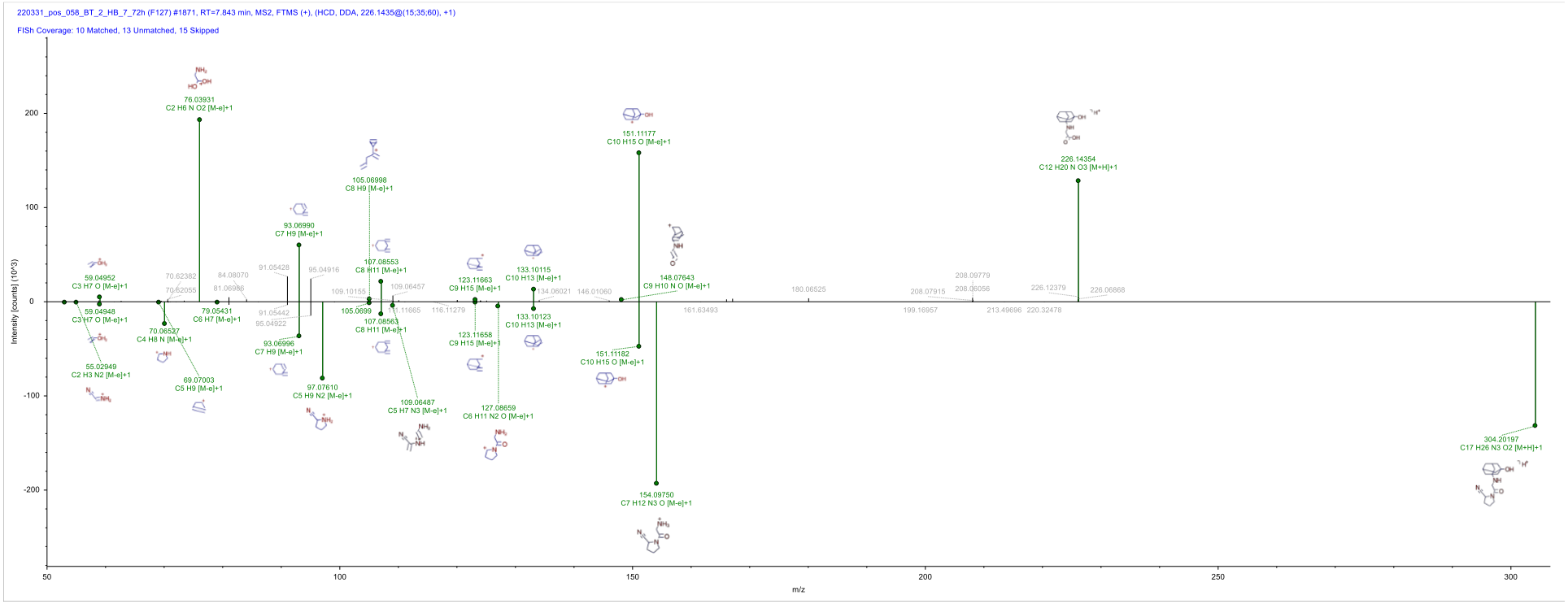
Comparison of TP and parent MS^2 scan shows matching fragments at m/z 59, 81, 91, 93, 95, 105, 107, 123, 133 and 151. Thus, confirming adamantane moiety with m/z 133 and 151. Absence of pyrrolidine fragments (m/z 55, 97, 127 and 154) in TP supports hydrolysis, but no $[M-H]^-$ ion was observed. Ion with nominal mass 76 can only be achieved by hydrolysis of amide.

Vil_TP_1


211210_138_BT_2_HB_6_72h (F160) #1817, RT=7.762 min, MS2, FTMS (+), (HCD, DDA, 226.1434@70, +1)
FISh Coverage: 8 Matched, 9 Unmatched, 10 Skipped
Intensity [counts] (100)
m/z
93.06995 C7 H9 [M-e]+1
105.06968 C8 H9 [M-e]+1
76.03927 C2 H6 N O2 [M-e]+1
107.08593 C8 H11 [M-e]+1
133.10101 C10 H13 [M-e]+1
151.11174 C10 H15 O [M-e]+1
59.04930 C3 H7 O [M-e]+1
79.05401 C6 H7 [M-e]+1
109.06477 C5 H7 N3 [M-e]+1
127.08663 C6 H11 N2 O [M-e]+1
152.10735 C9 H14 N O [M-e]+1
304.20209 C17 H26 N3 O2 [M+H]+1
70.06528 C4 H8 N [M-e]+1
97.07613 C5 H9 N2 [M-e]+1
151.11189 C10 H15 O [M-e]+1
59.04945 C3 H7 O [M-e]+1
107.08585 C8 H11 [M-e]+1
133.10133 C10 H13 [M-e]+1
101.07102 C4 H9 N2 O [M-e]+1
84.04456 C4 H6 N O [M-e]+1
110.07139 C5 H8 N3 [M-e]+1
154.09755 C7 H12 N3 O [M-e]+1

Vil

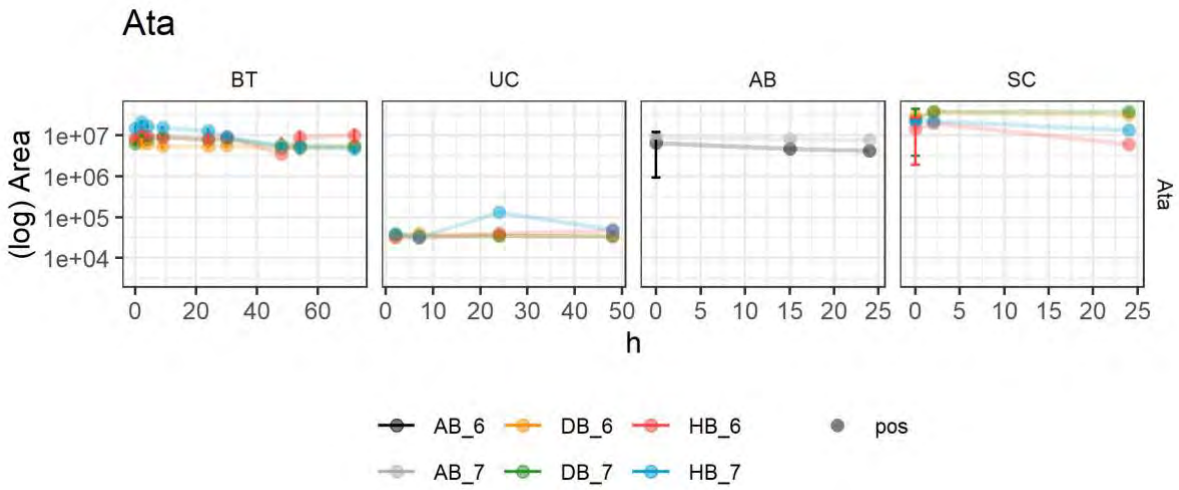
Vil_TP_1_remeas



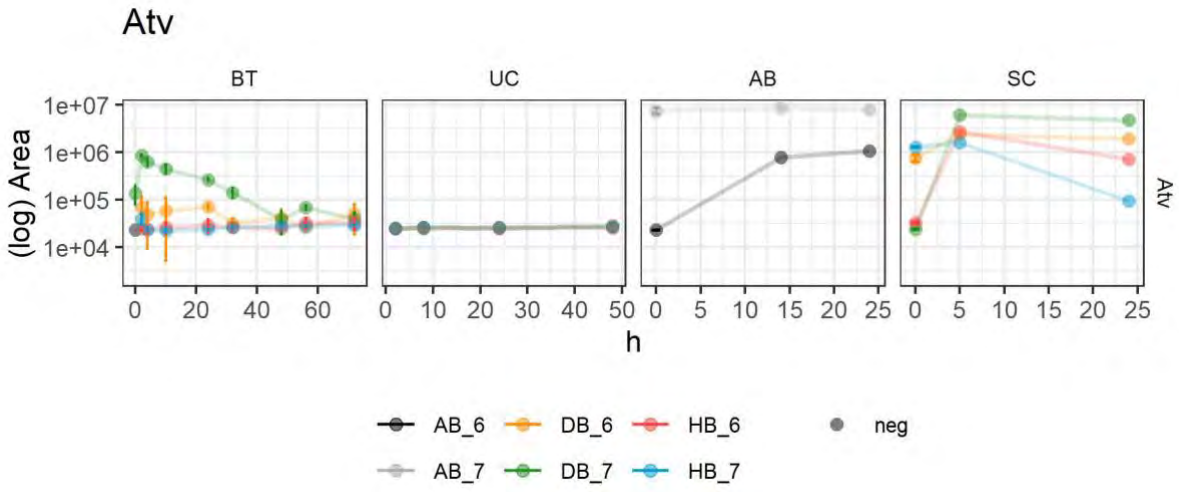
Vil_remeas

S4. Parents without identified TPs

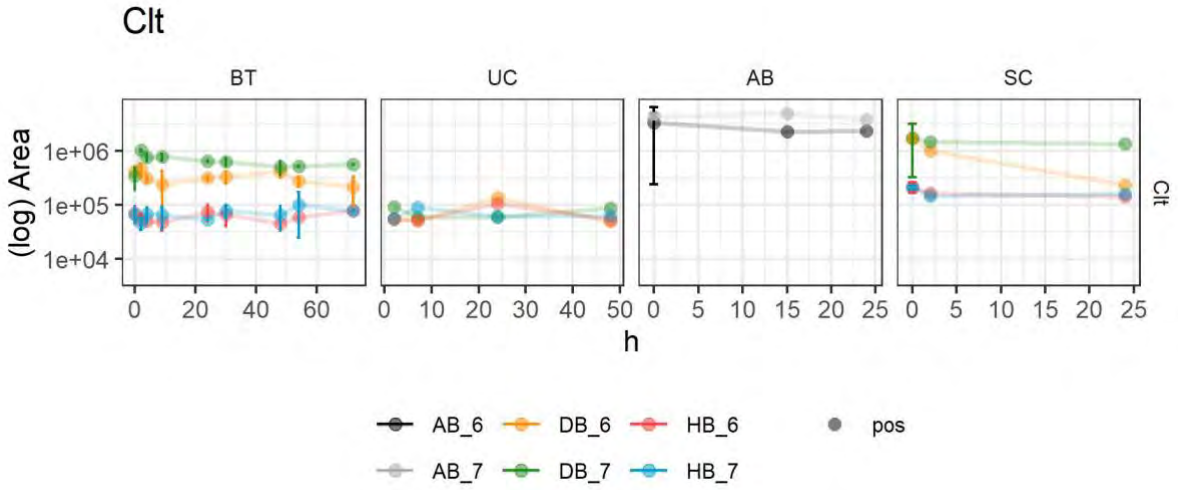
S4.1 Atazanavir



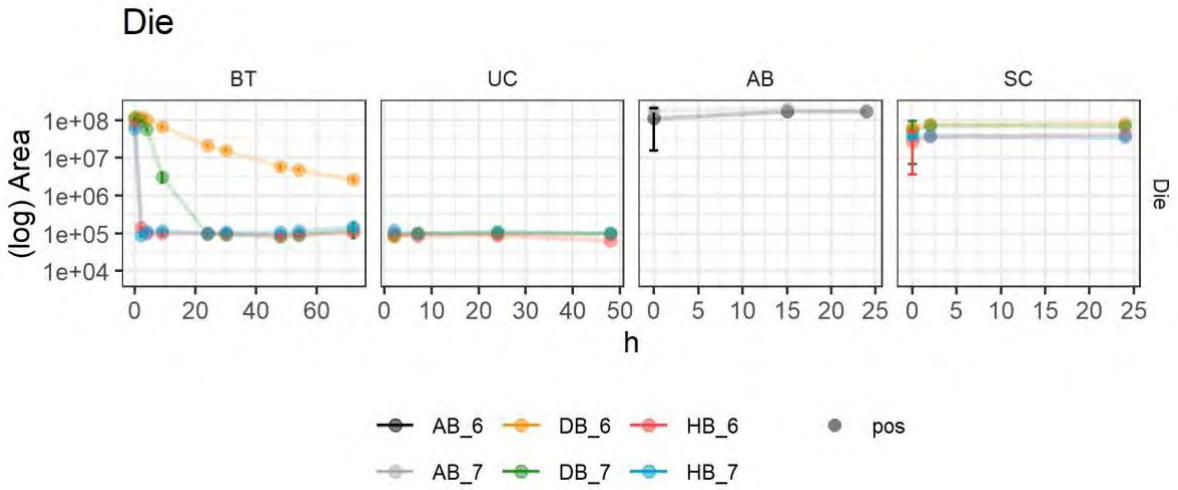
S4.2 Atovaquone



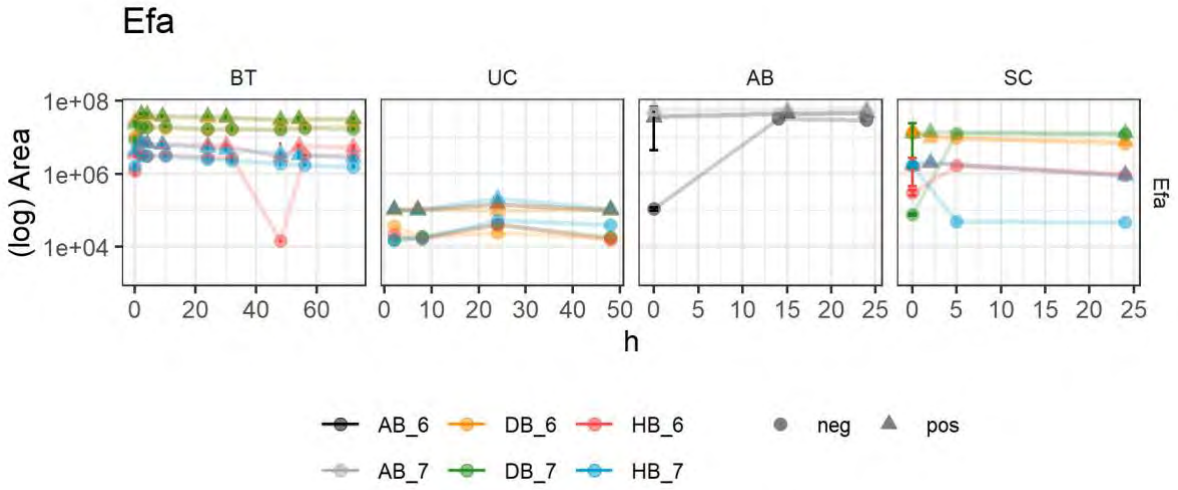
S4.3 Clotrimazol



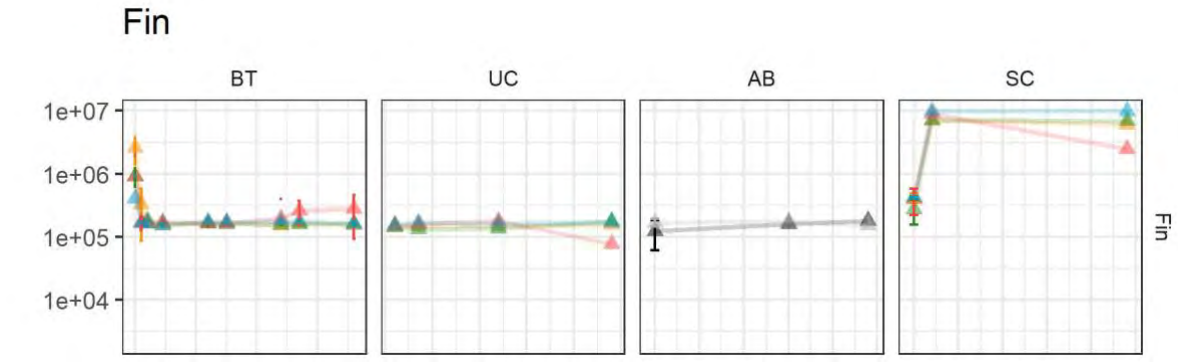
S4.4 Dienogest



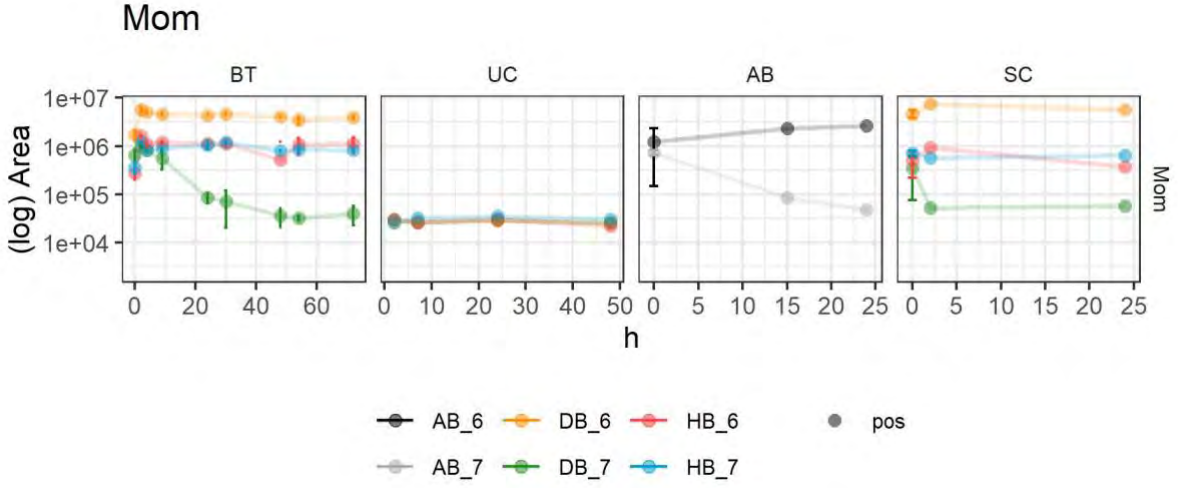
S4.5 Efavirenz



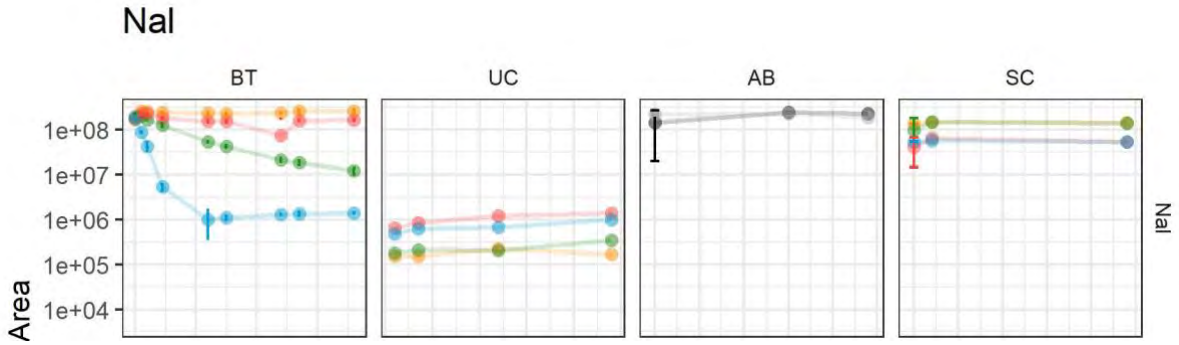
S4.6 Fingolimod



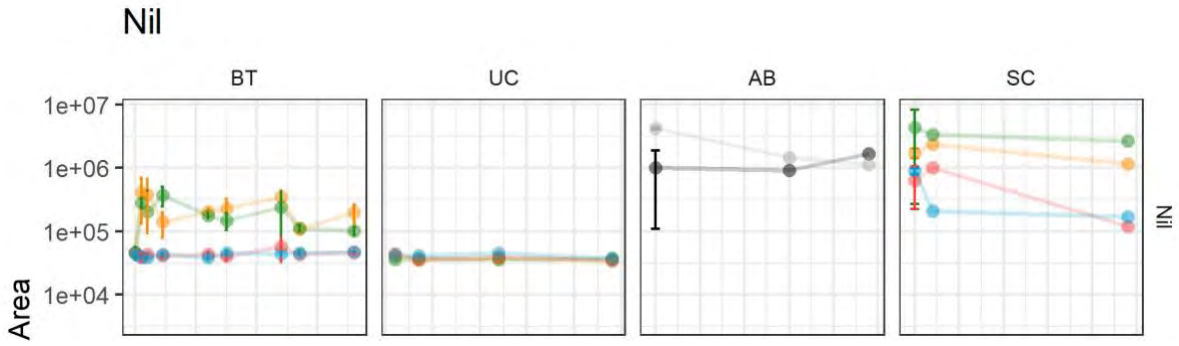
S4.7 Mometasone



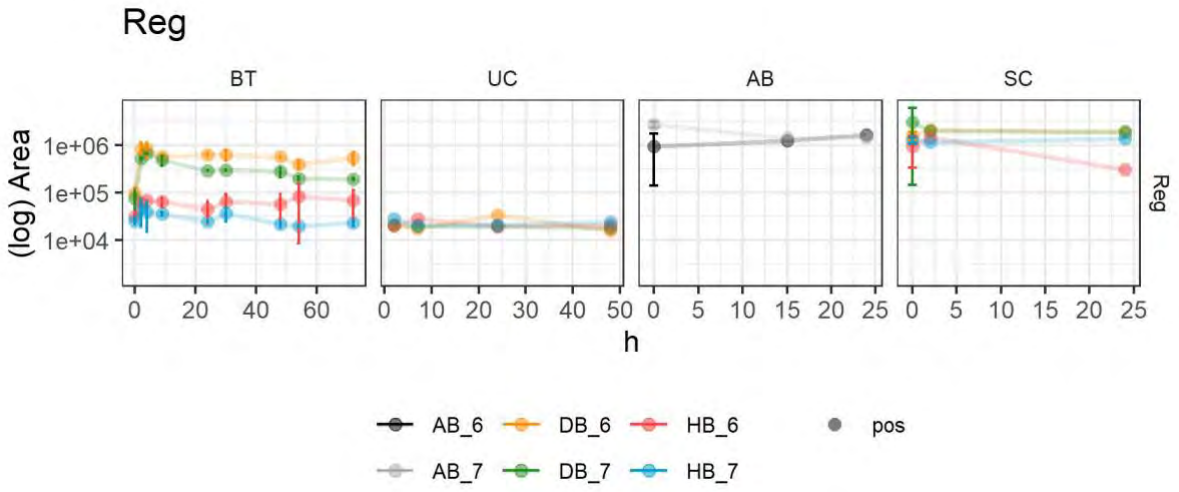
S4.8 Naloxegol



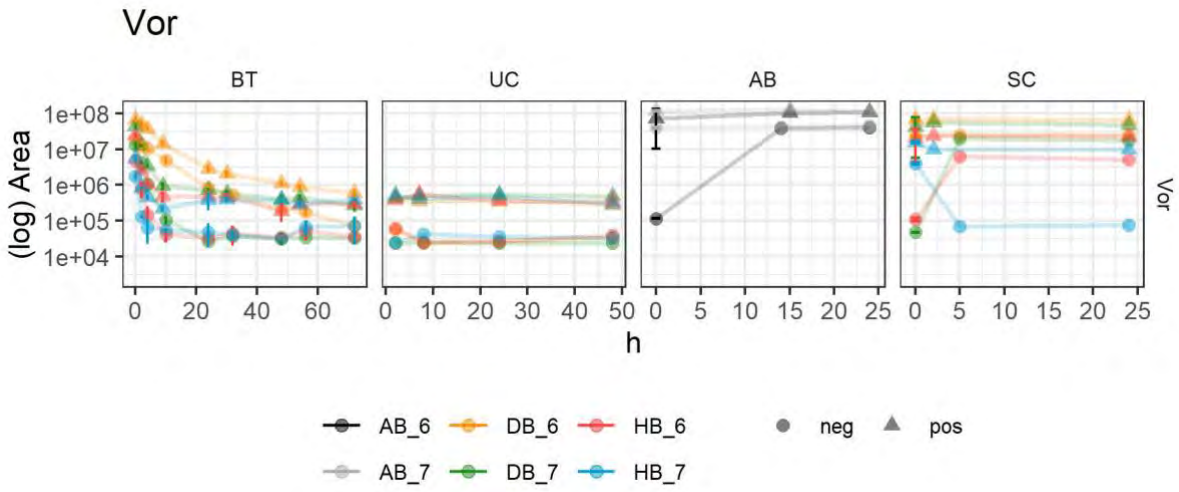
S4.9 Nilotinib



S4.10 Regorafenib



S4.11 Vorinostat



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