SUPPORTING INFORMATION

Fragment-Based Screening of a Natural Product Library against 62 Potential Malaria Drug Targets Employing Native Mass Spectrometry

Hoan Vu,[†] Liliana Pedro,[†] Tin Mak, [†] Brendan McCormick, [†] Jessica Rowley, [†] Miaomiao Liu,[†] Angela Di Capua,[†] Billy Williams-Noonan,[†] Ngoc B. Pham,[†] Rebecca Pouwer, [†] Bao Nguyen,[†] Katherine T. Andrews,[†] Tina Skinner-Adams,[†] Jessica Kim,[‡] Wim G. J. Hol,[‡] Raymond Hui,[§] Gregory J. Crowther,[⊥] Wesley C. Van Voorhis,[⊥] and Ronald J. Quinn*[,†]

[†]Griffith Institute for Drug Discovery, Griffith University, 170 Kessels Rd, Nathan, Queensland 4111, Australia

[‡]Department of Biochemistry, University of Washington, 1705 NE Pacific St., Seattle, Washington 98195-7350, United States

[§]Structural Genomics Consortium, University of Toronto, MaRS South Tower, 7th floor 101 College St. Toronto, Ontario M5G 1L7, Canada

[⊥]Department of Medicine, University of Washington, 1705 NE Pacific St., Seattle, Washington 98195-7350, United States

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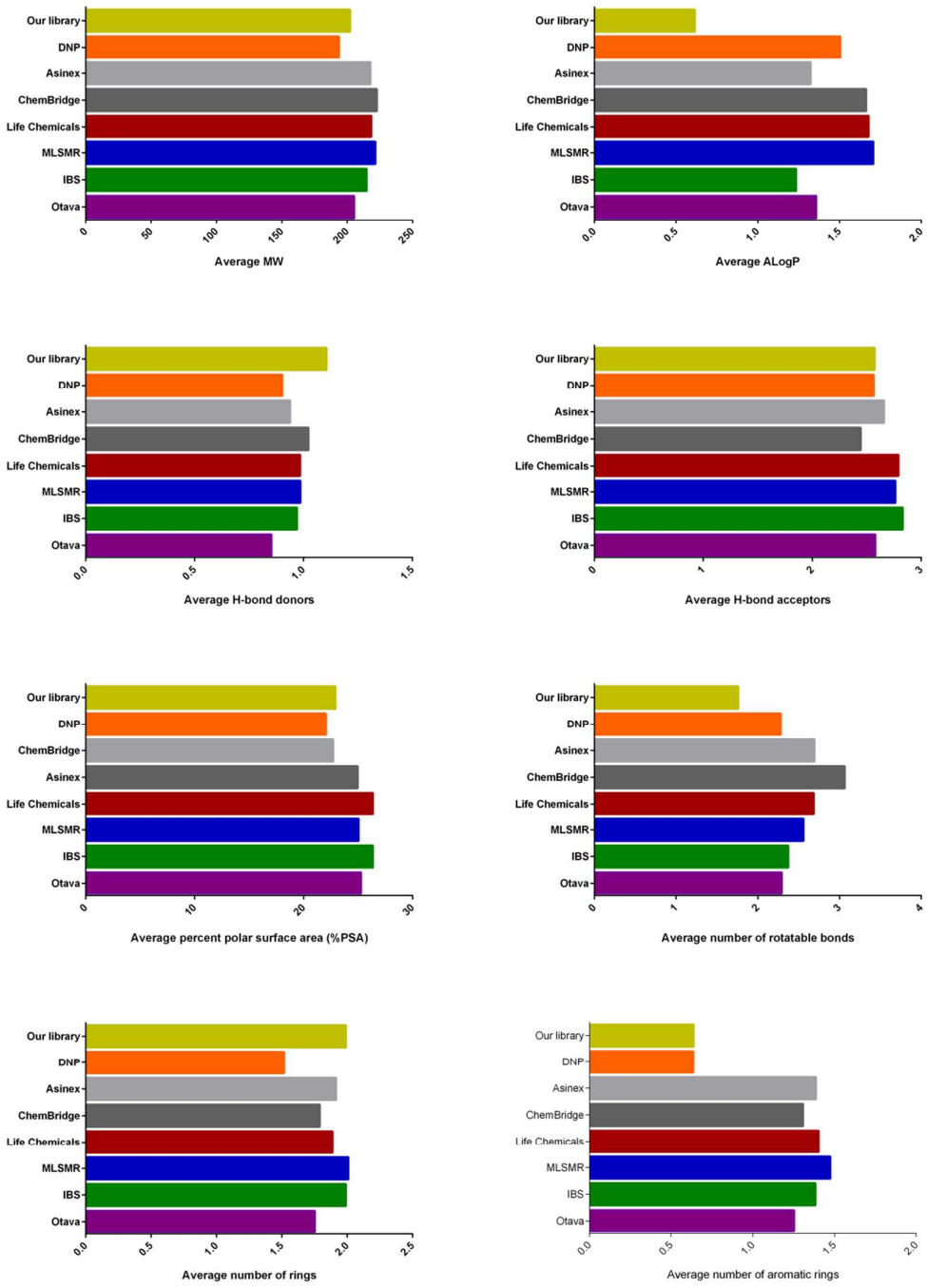


Figure S1. Mean physicochemical properties of different fragment libraries. Dictionary of Natural Products (DNP) and our fragment libraries are natural product-based fragment libraries. Asinex, ChemBridge, InterBioscreen (IBS), Life Chemicals and Otava fragment libraries are from commercially available libraries. Molecular Libraries Small Molecule Repository (MLSMR) fragment library is from the US national screening collection where most of the molecules are commercially sourced.

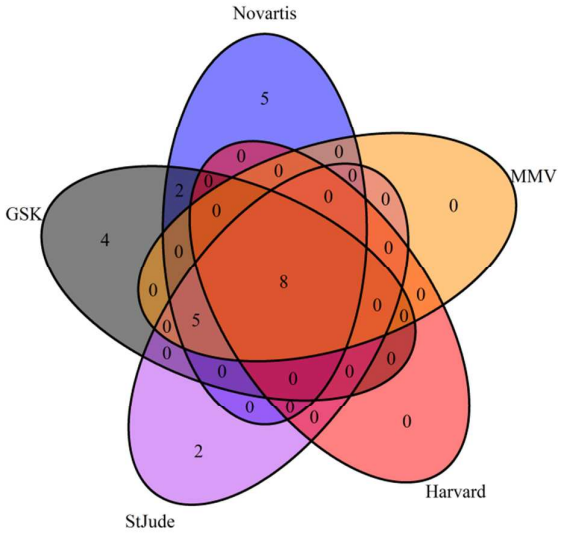


Figure S2. Venn diagram depicting the number of fragment hit scaffolds present within the molecular structures of GSK, Harvard Medical School (Harvard), St. Jude's Children's Research Hospital (StJude), MMV and Novartis library members. Diagram produced with R software (http://www.R-project.org/)[1], package "VennDiagram" (http://CRAN.R-project.org/package=VennDiagram) [2]

Table S1. List of forty-nine proteins studied for cloning and expression. Thirteen out of the forty-nine proteins were successfully cloned, expressed and purified.

Protein name/function	PlasmoDB ID	Purified
3-oxoacyl-(acyl-carrier-protein) reductase (FabG)	PF3D7_0922900	No
6-pyruvoyltetrahydropterin synthase (6PTPS)	PF3D7_0628000	Yes
Actin-related protein (ARP)	PF3D7_0103800	No
Adenylate cyclase-associated protein, putative (C-terminal actin binding domain)	PF3D7_0105300	No
ADP-ribosylation factor	PF3D7_1316200	No
Alpha-tubulin 2	PF3D7_0422300	No
ARK1	PF3D7_0605300	No
Beta-hydroxyacyl-ACP dehydratase precursor (FabZ)	PF3D7_1323000	No
Beta-ketoacyl-acyl carrier protein synthase III precursor (FabH/FabB/KASIII)	PF3D7_0211400	No
cAMP-dependent protein kinase (PKA)	PF3D7_0934800	No
Casein kinase 2	PF3D7_1108400	No
CDK-related protein kinase 6 (PfPK6)	PF3D7_1337100	Yes
CDP-DAG synthase (CDS)	PF3D7_1409900	No
CelTOS (cell traversal protein for ookinetes and sporozoites)	PF3D7_1216600	Yes
Chitinase	PF3D7_1252200	No
Conserved Plasmodium protein, unknown function	PF3D7_0818600	No
Conserved Plasmodium protein, unknown function (CITH; CAR-I/Trailer Hitch Homolog)	PF3D7_1474900	No
CSP (circumsporozoite surface protein)	PF3D7_0304600	Yes
Dihydrofolate reductase (DHFR)	PF3D7_0417200	Yes
Dihydroorotase	PF3D7_1472900	No
DOZI (development of zygote inhibited)	PF3D7_0320800	No
dUTPase	PF3D7_1127100	Yes
ETRAMP10.3	PF3D7_1016900	No
Fructose-bisphosphate aldolase	PF3D7_1444800	No
Glyceraldehyde-3-phosphate dehydrogenase	PF3D7_1462800	Yes
HMGB2 (high mobility group protein 2) -- transcription factor	PF3D7_0817900	Yes
HU homolog	PF3D7_0904700	Yes
Hypothetical protein	PF3D7_0313200	No
Hypothetical secreted protein	PF3D7_1360000	No
Hypoxanthine phosphoribosyltransferase (HXGPRT)	PF3D7_1012400	Yes
MDV-1/Peg3	PF3D7_1216500	Yes
Membrane-associated histidine-rich protein-2 (MAHRP2)	PF3D7_1353200	No
Methionine tRNA synthetase	PF3D7_1442300	No

Nek2 (NIMA-related kinase 2)	PF3D7_0525900	No
Nek4 (NIMA-related kinase 4)	PF3D7_0719200	No
Nucleosome assembly protein NapS	PF3D7_0919000	No
Orotate phosphoribosyltransferase	PF3D7_0512700	No
pbs36 homologue (P36)	PF3D7_0404400	No
PK7 (Serine/threonine protein kinase)	PF3D7_0213400	No
O-sialoglycoprotein endopeptidase	PF3D7_0708300	No
Protein kinase	PF3D7_1316000	No
Rhomboid protease ROM1	PF3D7_1114100	No
Secreted ookinete protein, putative (PSOP13, putative secreted ookinete protein 13)	PF3D7_0518800	No
Serine hydroxymethyltransferase	PF3D7_1235600	No
Sexual stage-specific precursor (Pfs16)	PF3D7_0406200	Yes
Signal Peptide Peptidase (SPP)	PF3D7_1457000	No
SPECT1 (sporozoite microneme protein essential for cell traversal)	PF3D7_1342500	No
Spermidine synthase	PF3D7_1129000	Yes
Thymidylate synthase	PF3D7_0417200	Yes*

*Same sequence with dihydrofolate reductase (DHFR).

Table S2. List of seventy-nine proteins studied by native mass spectrometry. Sixty-two out of the seventy-nine proteins were visible at native MS.

No	Protein Name	ID	EC number	MW
1	Thioredoxin peroxidase 2 (Trx-Px2)	PF3D7_1215000	1.11.1.15	18,526
2	Thioredoxin	PF3D7_1330000	1.8.1.8	24,275
3	NADP-specific glutamate dehydrogenase (GDH1)	PF3D7_1416500	1.4.1.4	50,240
4	Glycerol-3-phosphate dehydrogenase	PF3D7_1216200	1.1.1.8	42,133
5	Superoxide dismutase (SOD)	PKH_142350	1.15.1.1	24,976
6	Branched-chain alpha keto-acid dehydrogenase	PF3D7_1312600	1.2.4.4	55,125
7	Thioredoxin 1 (TRX1)	PF3D7_1457200	1.8.1.8	12,607
8	Glyceraldehyde-3-phosphate dehydrogenase	PF3D7_1462800	1.2.1.12	37,530
9	N-myristoyltransferase (NMT)	PF3D7_1412800	2.3.1.97	49,935
10	Ribosomal RNA methyltransferase	PF3D7_1309600	2.1.1.56	25,539
11	Phosphomethylpyrimidine kinase (PMPK)	PF3D7_0520500	2.7.4.7	35,861
12	Guanylate kinase	PVX_099895	2.7.4.8	23,544
13	Spermidine synthase	PF3D7_1129000	2.5.1.16	34,421
14	Uridine phosphorylase (purine nucleoside phosphorylase)	PF3D7_0513300	2.4.2.1	19,554
15	CDK-related protein kinase 6 (PfPK6)	PF3D7_1337100	2.7.11.22	37,995
16	Phosphoglycerate kinase (PGK)	PF3D7_0922500	2.7.2.3	46,325
17	Aspartate carbamoyltransferase	PVX_083135	2.1.3.2	47,102
18	RAB18 GTPase	PF3D7_0807300	3.6.5.2	21,757
19	Adenosine deaminase (ADA)	PVX_111245	3.5.4.4	42,816
20	dUTPase	PF3D7_1127100	3.6.1.23	20,340
21	6-phosphogluconolactonase	PF3D7_1453800	3.1.1.31	41,005
22	RAB11a GTPase	PF3D7_1320600	3.6.5.2	23,241
23	Ubiquitin carboxyl-terminal hydrolase isozyme L3(UCHL3)	PF3D7_1460400	3.4.19.12	27,790
24	Methionine aminopeptidase 1b (METAP1b, MAP1)	PF3D7_1015300	3.4.11.18	37,932
25	S-adenosylhomocysteine hydrolase (SAHH)	PF3D7_0520900	3.3.1.1	54,733
26	ATP-dependent DNA helicase Q1 (RECQ1)	PF3D7_0918600	3.6.4.12	12,576
27	Adenosine deaminase (ADA)	PF3D7_1029600	3.5.4.4	44,666
28	ATP-dependent Clp protease proteolytic subunit (ClpP)	PF3D7_0307400	3.4.21.92	23,552
29	Glyoxalase I	PF3D7_1113700	4.4.1.5	23,775
30	Adenylosuccinate lyase	PVX_003765	4.3.2.2	47,094
31	Deoxyribose-phosphate aldolase	PY02252	4.1.2.4	31,101
32	Orotidine 5' monophosphate decarboxylase (OMPDC)	PF3D7_1023200	4.1.1.23	38,760
33	6-pyruvoyltetrahydropterin synthase	PF3D7_0628000	4.2.3.12	20,953
34	2C-methyl-D erythritol 2,4-cyclodiphosphate synthase (IspF)	PVX_003920	4.6.1.12	22,388
35	Phosphoglycerate mutase (PGM)	PF3D7_1120100	5.4.2.1	29,662
36	Cyclophilin	PF3D7_0528700	5.2.1.8	24,263
37	Ribose 5-phosphate epimerase	PF3D7_0514600	5.3.1.6	27,072
38	D-ribulose- 5-phosphate 3-epimerase	PF3D7_1219900	5.1.3.1	25,780
39	Prolyl tRNA ligase (aPRS)	PF3D7_0925300	6.1.1.15	58,213
40	Ubiquitin conjugating enzyme E2	PF3D7_0305700	6.3.2.19	17,886
41	Adenylosuccinate synthetase (AdSS)	PF3D7_1354500	6.3.4.4	51,461
42	Tryptophan tRNA ligase	PF3D7_1336900	6.1.1.2	47,746
43	Ubiquitin conjugating enzyme E2	PF3D7_1203900	6.3.2.19	17,431
44	Ubiquitin conjugating enzyme E2 N	PF3D7_0527100	6.3.2.19	19,176
45	Ubiquitin conjugating enzyme	PF3D7_0812600	6.3.2.19	19,554
46	Ubiquitin conjugating enzyme	PF3D7_1033900	6.3.2.19	19,288
47	Ubiquitin conjugating enzyme	PF3D7_1356300	6.3.2.19	23,776
48	MTIP	PF3D7_1246400	NA	16,482
49	Bacterial histone-like protein (HU homolog)	PF3D7_0904700	NA	17,403
50	Phosphatidylethanolamine-binding protein	PVX_123630	NA	45,604
51	Dynein light chain 1	PF3D7_1213600	NA	11,544
52	CSP (circumsporozoite surface protein)	PF3D7_0304600	NA	26,787
53	Conserved protein, unknown function	PF3D7_1351100	NA	19,603
54	Vacuolar protein-sorting protein (VPS2)	PF3D7_0816200	NA	25,721
55	Eukaryotic translation initiation factor 5A (eIF5a)	PF3D7_1204300	NA	18,529
56	6-pyruvoyltetrahydropterin synthase	PVX_114505	4.2.3.12	21.975
57	Sexual stage-specific protein precursor (Pfs16)-PFD0310w	PF3D7_0406200	NA	9,200
58	Cell traversal protein for ookinetes and sporozoites (CelTOS)	PF3D7_1216600	NA	17,683
59	Hypoxanthine-guanine phosphoribosyltransferase (HGPRT)	PF3D7_1012400	2.4.2.8	26,660
60	High mobility group protein B2 (HMGB2)	PF3D7_0817900	NA	10,107
61	Orotate phosphoribosyltransferase, putative	PKNH_1020400	2.4.2.10	34,802
62	Serine/threonine-protein kinase NEK4, putative	PVX_096360	2.7.11.1	37,077
63	Eukaryotic translation initiation factor 2b (eIF2b), alpha subunit	PF3D7_0828500	NA	NA
64	Thioredoxin reductase	PF3D7_0923800	1.8.1.9	NA
65	Ribonucleotide reductase, small subunit	PVX_086155	1.17.4.1	NA
66	Pyrroline carboxylate reductase	PF3D7_1357900	1.5.1.2	NA
67	Dihydrofolate reductase (DHFR)	PF3D7_0417200	1.5. 1.3	NA

68	Superoxide dismutase [Fe] (SOD)	PBANKA_1422700	1.15.1.1	NA
69	S-adenosylmethionine synthetase (SAMS)	PF3D7_0922200	2.5.1.6	NA
70	Ornithine aminotransferase	PY00104	2.6.1.13	NA
71	Nucleoside diphosphate kinase B (NDK)	PF3D7_1366500	2.7.4.6	NA
72	Protein-L-isoaspartate O-methyltransferase	PF3D7_1432700	2.1.1.77	NA
73	Choline Kinase	PF3D7_1401800	2.7.1.32	NA
74	Geranylgeranyl pyrophosphate synthase (GGPPS)	PVX_092040	2.5.1.29	NA
75	Nucleosome assembly protein 1	PKNH_1303500	NA	NA
76	Conserved protein, unknown function	PF3D7_0618200	NA	NA
77	Male development gene 1 (MDV1/MDV-1/Peg3)	PF3D7_1216500	NA	NA
78	Male development gene 1 (MDV1/MDV-1/Peg3)	PVX_123505	NA	NA
79	Protein phosphatase 1, regulatory (inhibitor) subunit	PVX_111140	NA	NA

Table S3. List of 96 detected hits and their anti-malarial activity.

Compound	Name	*% Inh at 100* µM	IC_{50} (µM) *P. falciparum* asexual (3D7)	IC_{50} (µM) *P. falciparum*	Sources
1	Indole-3-butyric acid				Widespread in plants[3]
2	6-Acetamido-6-deoxy-castanospermine	*44*			*Castanospermum austral, Alexa leiopetala* (castanospermine)[4]
3	Patulin	*98*	*91.6*		*Aspergillus clavatus, Aspergillus terreus, Aspergillus varians, Penicillium patulum, Penicillium griseofulvum, Byssochlamys nivea*[5]
4	Santonin	*9*	-		*Artemisia* spp.[4, 6]
5	Piceatannol	*92*	*>100*	*120*	*Vouacapoua macropetala*, *Pericopsis angolensis Vaccinium* sp. *Picea abies*[7, 8]
6	Resveratrol	*60*	*>100*	*60*	*Veratrum grandiflorum*, *Pinus sibirica*, *Vitis vinifera*, *Arachis hypogaea, Polygonum* spp., *Nothofagus* spp., *Cudrania javanensis, Eucalyptus* spp.[9]
7	Acivicin	*94*	*5.4*		*Streptomyces sviceus*[10]
8	Citrinin	*63*	*>100*		*Penicillium citrinum, Guanomyces polythrix, Aspergillus terreus, Monascus* spp.[11]
9	Cantharidin	*61*	*>100*	*9*	*Epicauta* spp., *Lytta vesicatoria*[12]
10	trans-parthenolide	*96*	*>100*		*Chrysanthemum parthenium*, *Michelia champaca*, *Michelia nilagirica*, *Michelia compressa*[13-15]
11	(-)-Huperazine				*Lycopodium serratum (Huperzia serrata), Lycopodium selago, Lycopodium saururus, Lycopodium erythraeum, Lycopodium gnidioides, Paecilomyces tenuis*[16, 17]
12	2,5-Dihydro-4-hydroxy-5-oxo-3-phenyl-2-furanpropanoic acid	*9*	-		*Acremonium* sp., *Chaetomella raphigera*[18]
13	Phaeofuran B	*19*	-		*Phaeoacremonium* sp.[19]
14	Curcumenol	*66*	*>100*		*Curcuma zedoaria*, *Curcuma longa*[20]
15	2 – Hydroxyalantolactone	*98*	*44.3*		*Francoeuria crispa, Inula helenium*, *Inula royleana*[21]
16	(+)-reynosin	*98*	*32.3*		*Magnolia grandiflora, Tanacetum praeterium, Saussurea lappa, Ambrosia confertiflora*[22]
17	Asperilin	*98*	*23.2*		*Iva texensis, Telekia speciosa, Iva asperifolia,*[23]
18	Graveolide	*84*	*15.6*		*Inula graveolens*[21]
19	Xanthinosin (or tomentosin)	*65*	*62.8*		*Dittrichia* spp., *Inula* spp., *Pulicaria* spp., *Xanthium* spp.[24]
20	Pinnatifidin	*92*	*66.5*		*Helenium pinnatifidum*[25]
21	Homononactic acid	*30*	-		*Streptomyces* spp.[26]

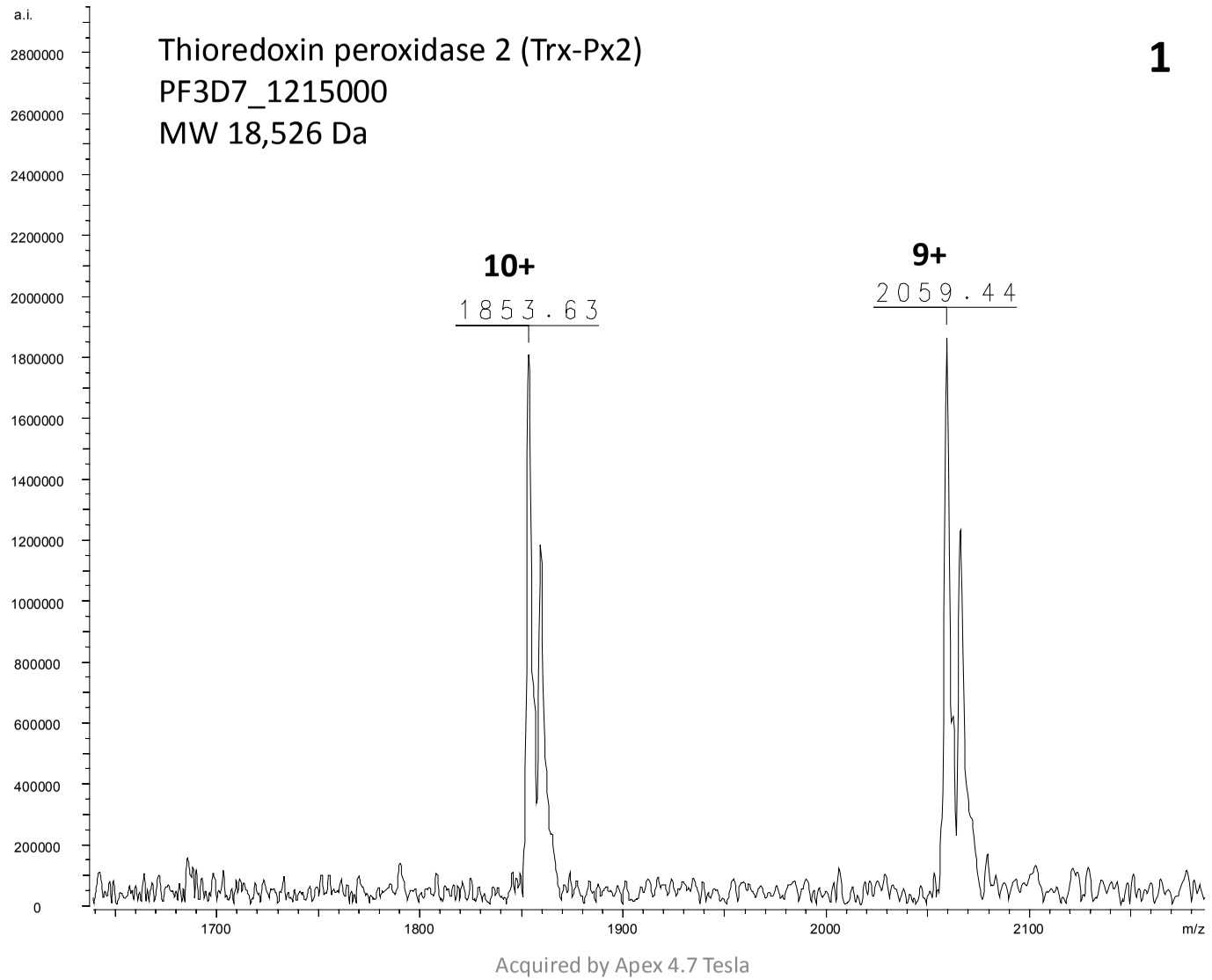
22	Curdionolide B	*42*	-		*Curcuma wenyujin*[27]
23	Neolitacumone B	*27*	-		*Neolitsea acuminatissima*[28]
24	*β*-Santonin	*37*	-		*Artemisia* spp.[29]
25	Acremine I	*43*	-		*Acremonium byssoides* strain A20[30]
26	Asteriscunolide A	*68*	*34.2*		*Asteriscus aquaticus, Asteriscus graveolens, Asteriscus vogelii*[31]
27	Arteannuin B	*98*	*6.6*		*Artemisia annua*[32]
28	Xerantholide	*96*	*38.3*		*Anthemis austriaca, Decachaeta thieleana, Xeranthemum cylindraceum*[33]
29	1-Epi-inuviscolide	*100*	*79.4*		*Dittrichia graveolens*[34]
30	Camphanic acid	*23*	-		*Fagaropsis glabra*[35]
31	Fraxinellonone	*31*	-		*Fagaropsis glabra*[35]
32	Dihydrokawain-5-ol	*14*	-		*Piper methysticum*[36]
33	Costunolide	*35*	-		*Saussurea lappa*, *Artemisia balchanorum*, *Talauma ovata*, *Talauma mexicana*, *Liriodendron tulipifera*, *Frullania tamarischii*, *Frullania nisquallensis*, *Michelia* spp., *Magnolia grandiflora*, *Magnolia sieboldii*, *Gochnatia foliosa*, *Chrysanthemum boreale*, *Cosmos caudatus*, *Cosmos sulphureus*[37-39]
34	Antibiotic 927A	*23*	-		*Streptomyces griseus*[40]
35	Methyl ester of 3-Chloro-1,5-dihydroxy-4-oxo-2-(1-propenyl)-2-cyclopentene-1-carboxylic acid	*98*	*67.3*		*Cryptosporiopsis* spp.[41]
36	Santamarine	*96*	*61.3*		*Magnolia grandiflora L.*[42]
37	Zaluzanin C	*99*	*93.6*		*Conocephalum conicum, Zaluzania* spp., *Zaluzania robinsonii*[43]
38	Derivative of Antibiotic EI 1941-2	*20*	-		Antibiotic EI 1941-2 was found in *Phomopsis* sp. (strain No. 7233)[44]
39	Alantolactone	*92*	*92.7*		*Inula helenium, Inula racemosa, Inula grandis, Inula magnifica, Saussurea lappa, Codonocephalum grande, Abutilon indicum*[45]
40	Isoalantolactone	*50*	*39.8*		*Inula helenium, Inula racemosa, Abutilon indicum, Telekia speciosa*[46]
41	5-Fluoro-3,4-dihydro-2,4-dioxo-1(2H)-pyrimidineacetic acid	*27*	-		*Phakellia fusca*[47]
42	Biotin	*44*	-		yeast, eggs, liver, various microorganisms, sweet corn seedlings, leaves of *Raphanus sativus*[48]
43	12-Methoxycarbonylcytisine				*Leontice watereri, Petteria ramentacea*[49]
44	Lepiotin C	*25*	-		*Macrolepiota neomastoidea*[50]
45	*N*-Benzoyl of 4-Piperidinone	*33*	-		*Dichilus strictus, Dichilus reflexus, Dichilus lebeckioides, Dichilus pilosus, Dichilus gracilis*[51]

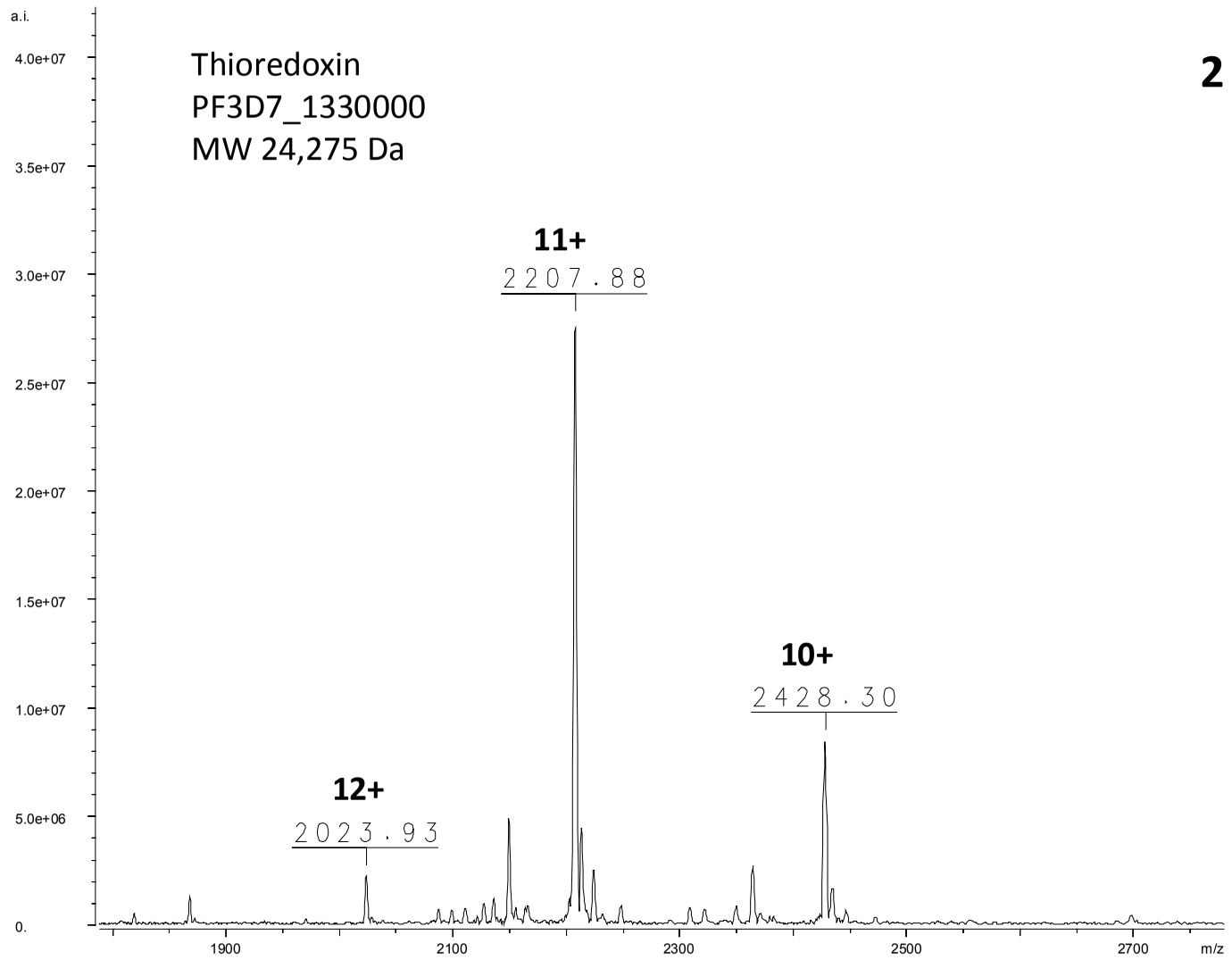
46	cis-parthenolide	*76*	*20.5*		*Chrysanthemum parthenium, Michelia champaca, Michelia nilagirica, Michelia compressa, Chrysanthemum parthenium, Ambrosia dymosa, Magnolia grandiflora, Artemisia* spp., *Tanacetum parthenianum, Paramichelia baillonii, Acanthopanax koreanum*[14]
47	Isofischeric acid				*Neolitsea fischeri*[52]
48	Thymidine	*34*	-		*Phaseolus vulgaris, Acanthaster planci, Cryptochiton stelleri, Pavonaria finmarchica*[53]
49	1-Aminocyclopropanecarboxylic acid				*Ethylene* spp.[54]
50	7-amino deacetoxy cephalosporanic acid	*40*	-		*Acremonium chrysogenum*[55]
51	Fenchone	*48*	-		*Foeniculum vulgare, Blumea lacera, Prunella vulgaris*[56, 57]
52	Eseroline	*100*	*20.2*		Physostigmine was found in *Physostigma venenosum, Streptomyces* sp. AH-4, *Streptomyces pseudogriseolus* [58]
53	*N*-tert-butyloxycarbonyl derivative of homoproline	*30*	-		*Arnica montana, Arnica chamissonis* ssp. *foliosa, Arnica amplexicaulis, Arnica sachalinensis, Tussilago farfara*[59]
54	*N*-tert-butyloxycarbonyl derivative of 2-piperidinecarboxylic acid	*22*	-		*Amphiroa beauvoisii, Acacia rigidula*[60]
55	Aloperine	*43*	-		*Sophora alopecuroides*[61]
56	Lycoperodine 1	*49*	-		*Aleurites fordii* , *Allium tuberosum. Asterias rollestoni, Lycopersicon esculentum* [62]
57	*N,N*-dipropylsuccinamic acid				
58	Derivative of matlystatins, 4-oxo-4-(piperidin-1-yl)butanoic acid	*24*	-		*Actinomadura atramentaria*[63]
59	Derivative of pyroglutamic acid, (*S*)-1-(2-amino-2-oxoethyl)-5-oxopyrrolidine-2-carboxamide	*24*	-		Ginseng (pyroglutamic acid)[64]
60	1,2,3,4-Tetrahydro-6,7-dihydroxy-3-isoquinolinecarboxylic acid	*26*	-		*Mucuna mutisiana* (Leguminosae), *Mucuna urens, Mucuna deeringiana, Mucuna andreana, Mucuna holtoni, Mucuna pruriens, Mucuna sloanei*, *Stizolobium hassjoo*[65]
61	Derivative of almazolone, (Z)-2-methyl-4-(4-methylbenzylidene)oxazol-5(4H)-one	*33*	-		Almazolone was found in *Haraldiophyllum* sp.[66]

62	*O*-Methyl-L-tyrosine				*Cylindrocladium scoparium*[67]
63	*N*,*N*-diethyl-4-hydroxy- benzamide				Synthetic?[68]
64	Diethylamide of 3-hydroxybenzoic acid				Synthetic?[69]
65	Derivative of dysinosin A, 5-(*S*)-acetyl-9-(*S*)-hydroxy- (3*R*, 7*R*)-octahydro-1*H*-Indole	*31*	-		Dysinosin A was found in *Citronia astra*[70]
66	*N,N*-diethylsuccinamic acid	*40*	-		*Candida tropicalis, Candida* sp., *Saccharomyces cerevisiae, Xanthomonas campestris, Pseudomonas putida, Xanthomonas campestris oryzae, Gerbera* sp.[71, 72]
67	Derivative of almazolone, 4-[(2-methyl-5-oxo-4(5H)-oxazolylidene)methyl]- benzoic acid	*41*	-		Almazolone was found in *Haraldiophyllum* sp.[66]
68	Derivative of almazolone, 4-methyl-2-(*p*-hydroxyphenylmethylene)-5(2*H*)-Oxazolone	*35*	-		Almazolone was found in *Haraldiophyllum* sp.[66]
69	Derivative of almazolone, (*E*)-methyl 4-((2-methyl-5-oxooxazol-4(5*H*)-ylidene)methyl)benzoate	*22*	-		Almazolone was found in *Haraldiophyllum* sp.[66]
70	Derivative of almazolone, (*E*)-4-(benzodioxol-5-ylmethylene)-2-methyloxazol-5(4*H*)-one	*15*	-		Almazolone was found in *Haraldiophyllum* sp.[66]
71	Derivative of almazolone, (*E*)-4-(4-chlorobenzylidene)-2-methyloxazol-5(4*H*)-one	*29*	-		Almazolone was found in *Haraldiophyllum* sp.[66]
72	Derivative of almazolone, (*E*)-4-(3,4-dimethoxybenzylidene)-2-methyloxazol-5(4*H*)-one	*41*	>100		Almazolone was found in *Haraldiophyllum* sp.[66]
73	5-Methoxytryptophan methyl ester	*65*	*>100*		*Griffonia simplicifolia, Panaeolus sphinctrinus*[73]
74	Derivative of cichorine, *N*-(2-(3-	*32*	-		Cichorine was found in *Aspergillus silvaticus, Alternaria cichorii*[74]

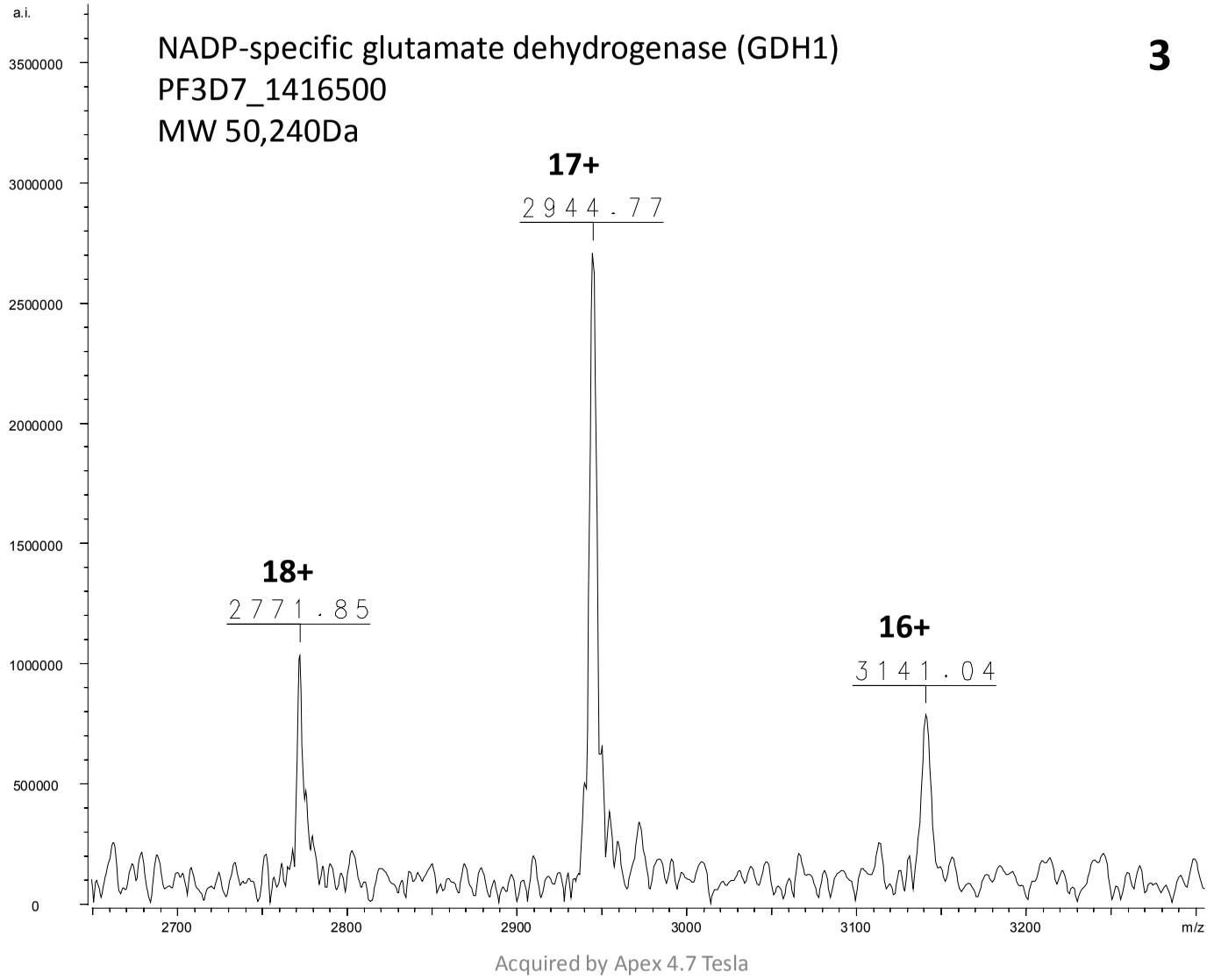
	oxoisoindolin-1-yl)ethyl)acetamide				
75	Derivative of astrocasine, 2,3-dihydro-1*H*-benzo[36]azepin-1-one	*42*	-		Astrocasine was found in *Astrocasia phyllanthoides*[75]
76	Derivative of astrocasine, 2-acetyl-7-methoxy-2,3,4,5-tetrahydro-1*H*-benzo[36]azepin-1-one	*45*	-		Astrocasine was found in *Astrocasia phyllanthoides*[75]
77	(S)-Stachydine	*26*	-		*Capparis tomentosa, Chrysanthemum* spp., *Citrus* spp., *Galeopsis grandiflora, Lagochilus hirtus, Medicago sativa, Stachys* spp., *Aspergillus oryzae*[76]
78	Preclathridine A	*100*	*24.5*		*Notodoris gardineri*[77]
79	*N*-Phenylmethylglutamine	*57*	*>100*		*Dysoxylum sp.*[78]
80	(-)-Norsecurinine	*25*	*40.3*		*Flueggea virosa*, Securinega virosa*[79, 80]
81	Allosecurinine				*Securinega* spp., *Securinega suffruticosa*[81, 82]
82	L-tryosine				Widespread in plants
83	N-(1-carboxyethyl)-5-oxoproline	*49*	-		*Timonius sp.*[78]
84	New compound 1	*30*	-		*Lindera gambleana**[78]
85	Methyl gallate	*18*	-	*38*	*Barklya syringifolia,* Koelreuteria paniculata*, *Euphorbia* spp., *Geranium* spp., *Sapium sebiferum*, *Acacia* spp., *Spirogyra* spp., *Rhus glabra, Pelargonium sidoides*[83]
86	Phyllanthine	*90*	*59.3*		*Margaritaria dubium-traceyi,* Margaritaria indica, Flueggea leucopyra, Securinega suffruticosa, Phyllanthus discoides*[84]
87	4-Hydroxyallosecurine	*51*	*>100*		*Margaritaria dubium-traceyi,* Phyllanthus niruri*[85]
88	Securinine	*39*	*20.6*		*Margaritaria dubium-traceyi,* Margaritaria indica, Securinega suffruticosa, Phyllanthus discoides*[86]
89	Securinine *N*-oxide				Natural Product Fragment Library[87]
90	*N*-Methyltryptophan	*41*	*79.2*		*Gastrolobium grandiflorum,* Erythrina caffra, Abrus precatorius, Desmodium tiliaefolium*[88]
91	1-Prenyl-6*N*-methyl-isoguanine (new)	*35*	-		*Glochidion zeylanicum*[78]
92	New compound 2				[78]
93	Gentianol				*Swertia* spp.[89]
94	Derivative of grandisine E				Grandisine E was found in *Elaeocarpus grandis*[90]
95	5-Methoxydictamnine				*Ruta chalepensis* var. *latifolia* (Rutaceae)[91]
96	2-Amino-1-phenylethanol				*Halostachys caspica* (Chenopodiaceae)[92]

Figure S3. Mass spectra of 62 *Plasmodium* proteins


Thioredoxin peroxidase 2 (Trx-Px2)
PF3D7_1215000
MW 18,526 Da
1
10+
1853.63
9+
2059.44
a.i.
2800000
2600000
2400000
2200000
2000000
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
1700
1800
1900
2000
2100
m/z
Acquired by Apex 4.7 Tesla

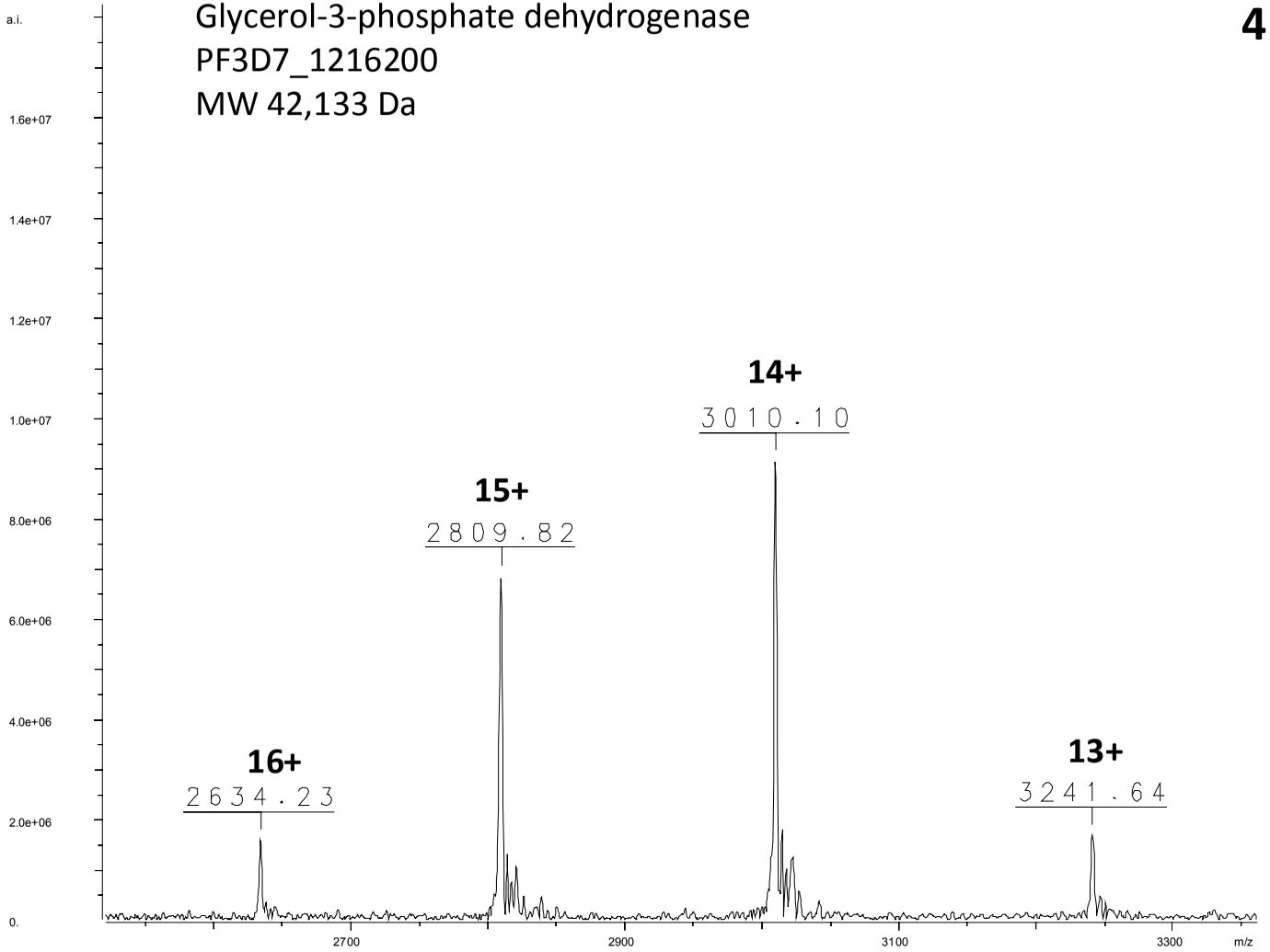


Acquired by Apex 4.7 Tesla


NADP-specific glutamate dehydrogenase (GDH1)
PF3D7_1416500
MW 50,240Da
3
17+
2944.77
18+
2771.85
16+
3141.04
a.i.
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
2700
2800
2900
3000
3100
3200
m/z
Acquired by Apex 4.7 Tesla

Glycerol-3-phosphate dehydrogenase
PF3D7_1216200
MW 42,133 Da

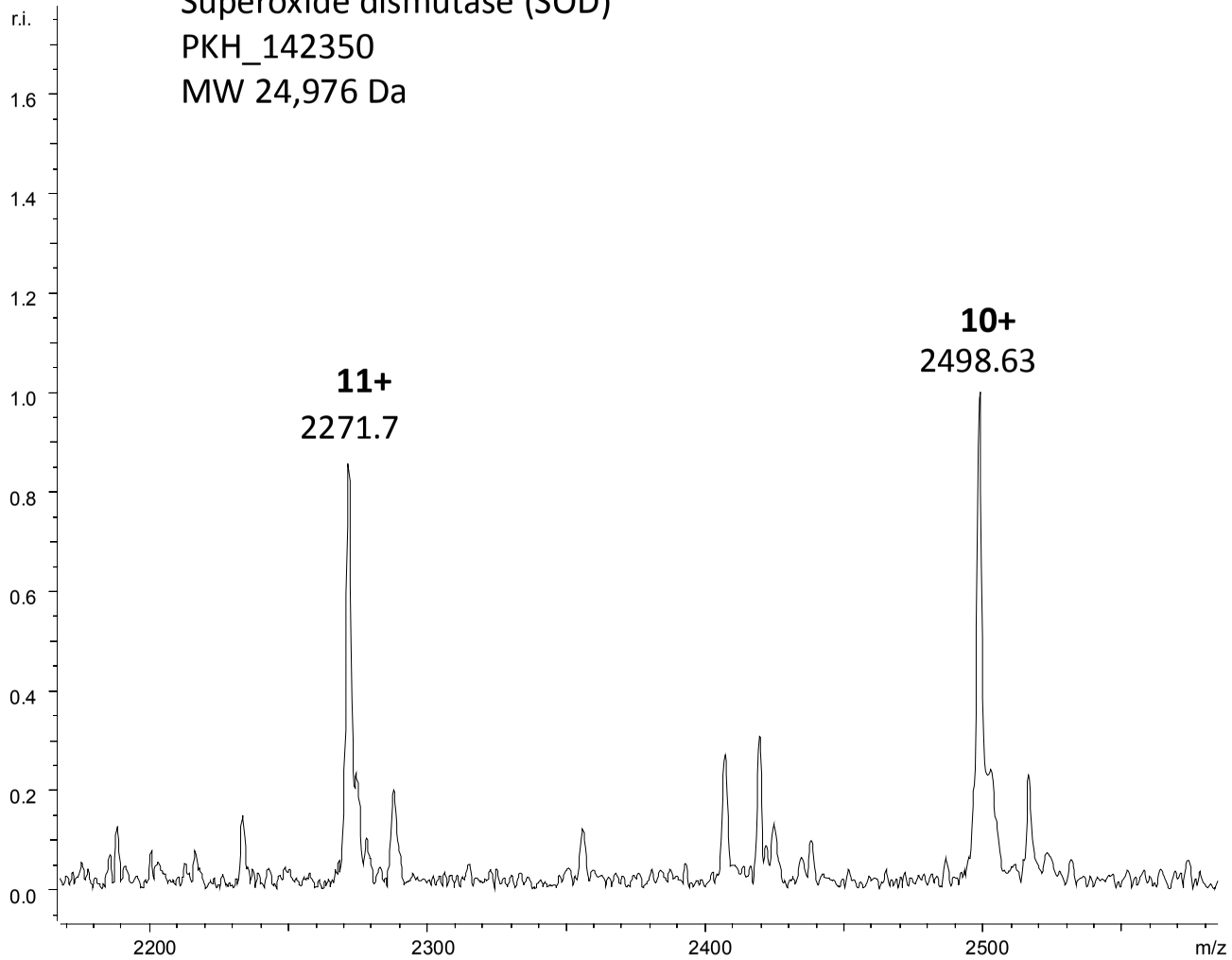
4



Acquired by Apex 4.7 Tesla

Superoxide dismutase (SOD)
PKH_142350
MW 24,976 Da

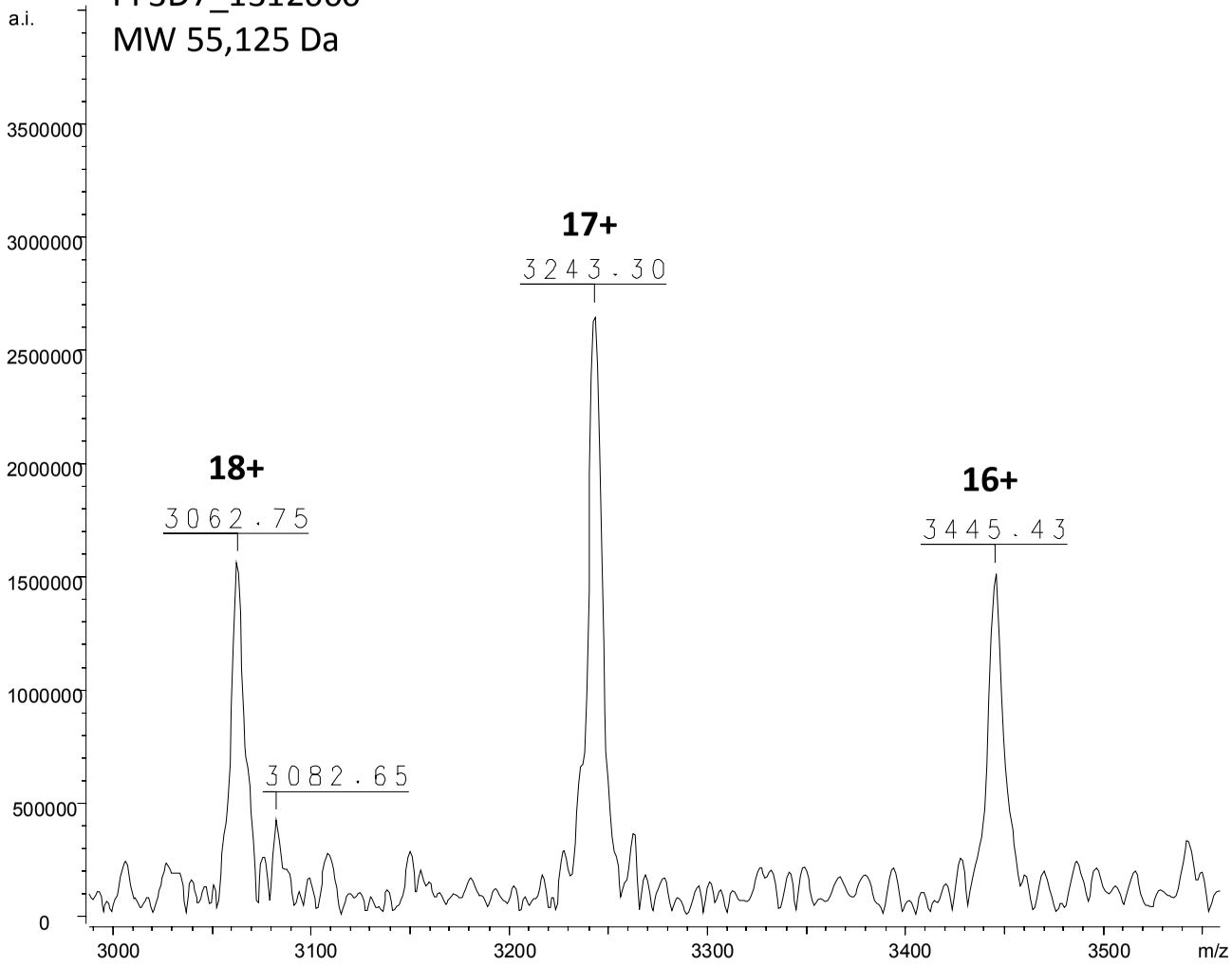
5



Acquired by Apex 4.7 Tesla

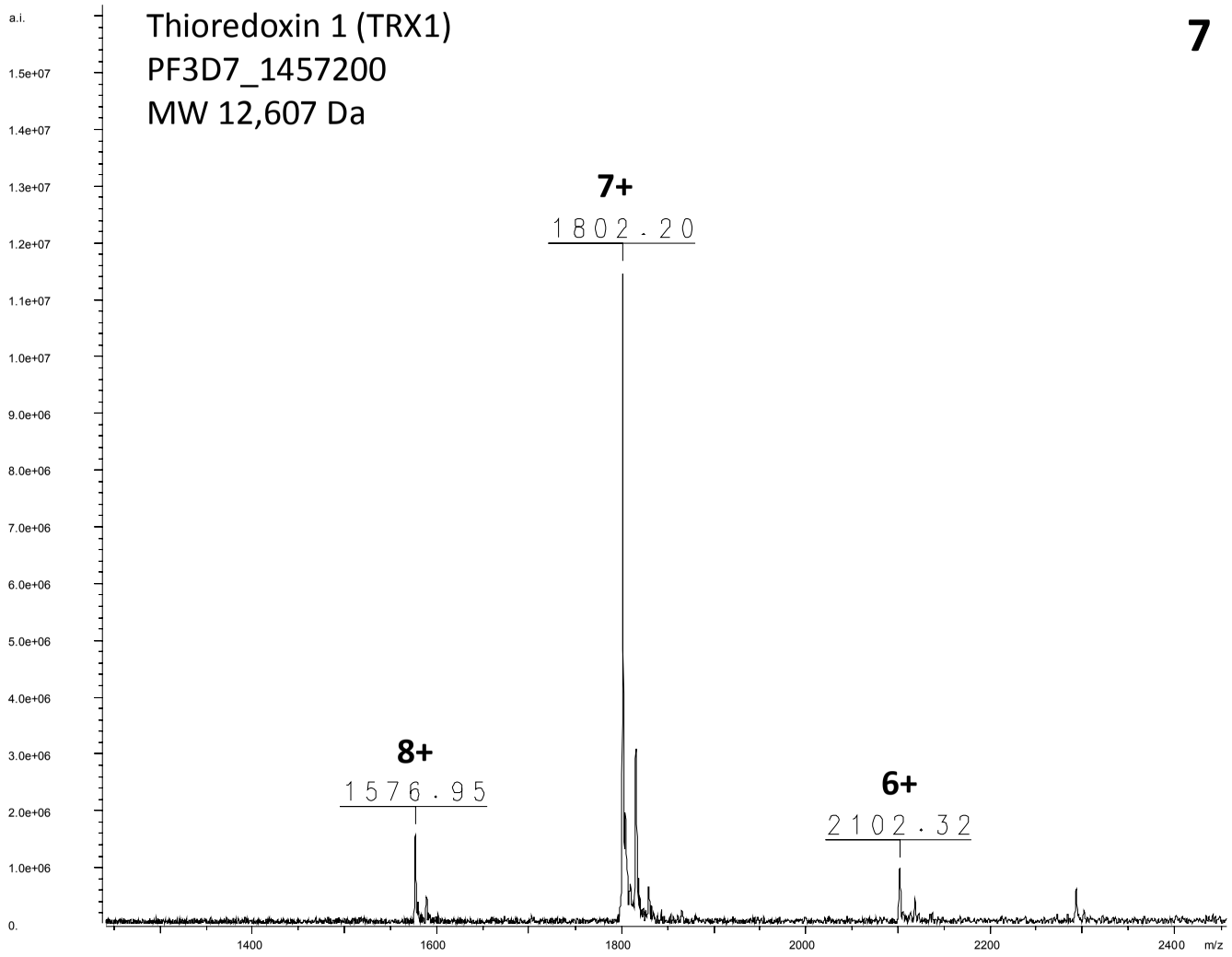
branched-chain alpha keto-acid dehydrogenase (BCKDHA)
PF3D7_1312600
MW 55,125 Da

6



Thioredoxin 1 (TRX1)
PF3D7_1457200
MW 12,607 Da

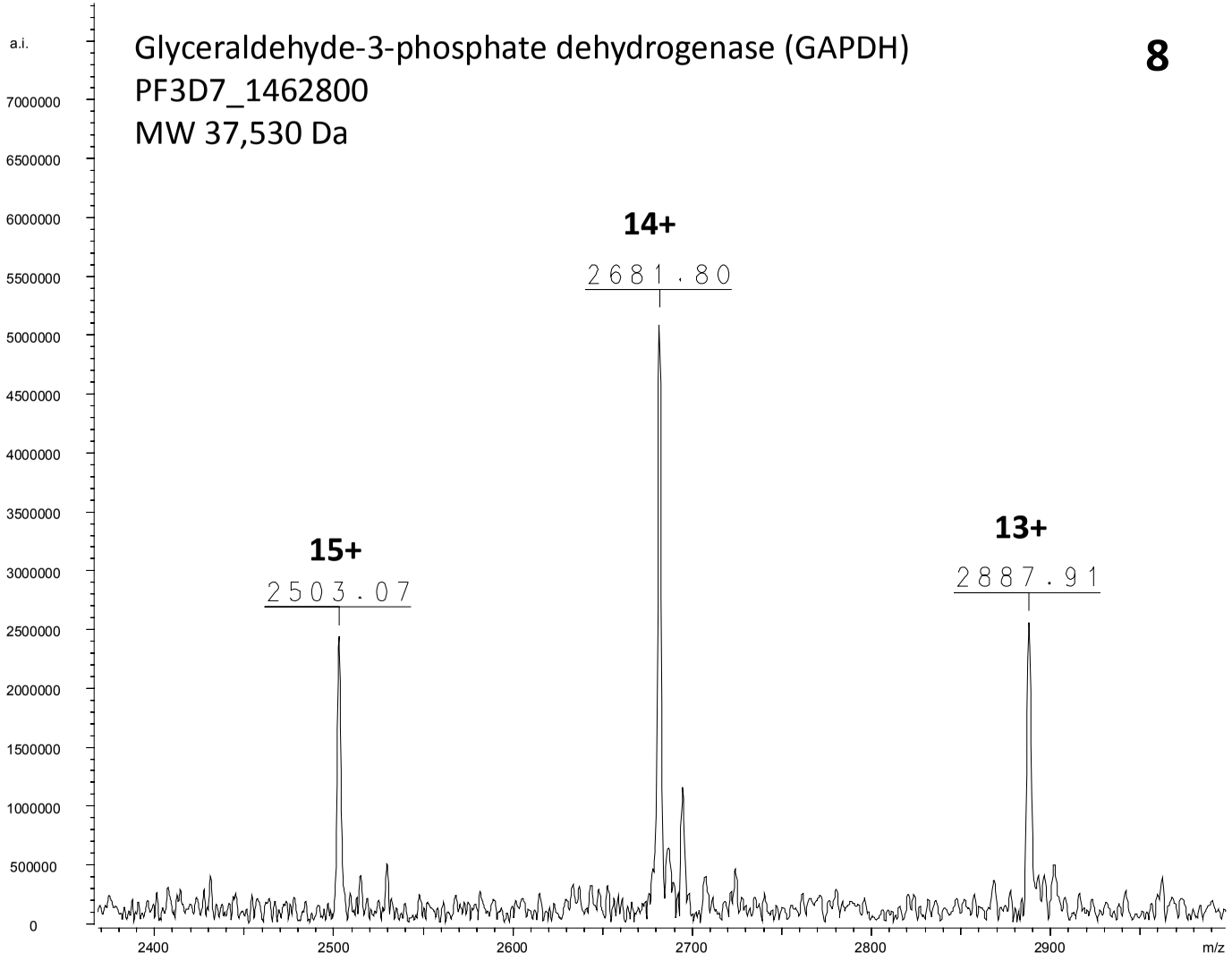
7



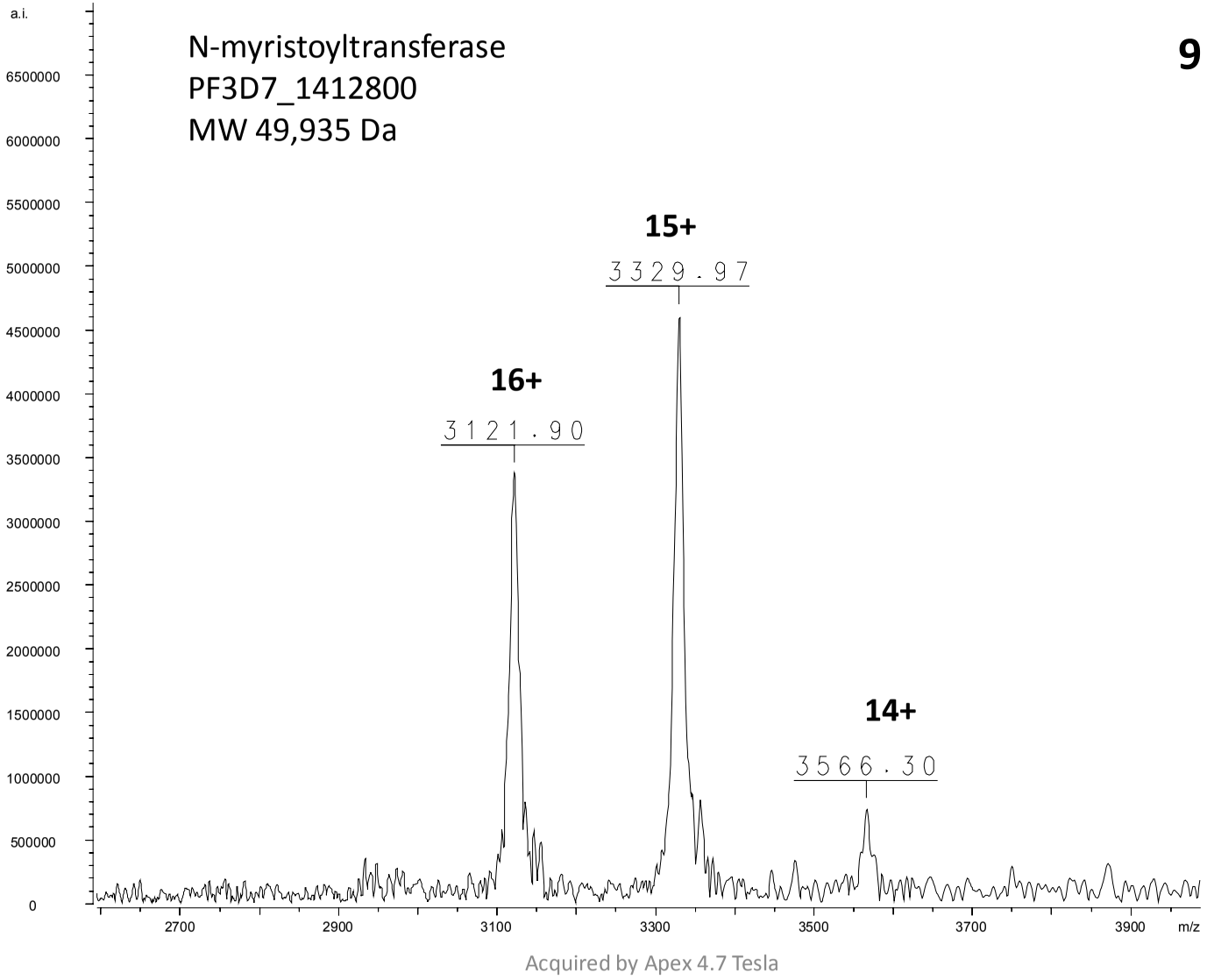
Acquired by Apex 4.7 Tesla

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH)
PF3D7_1462800
MW 37,530 Da

8

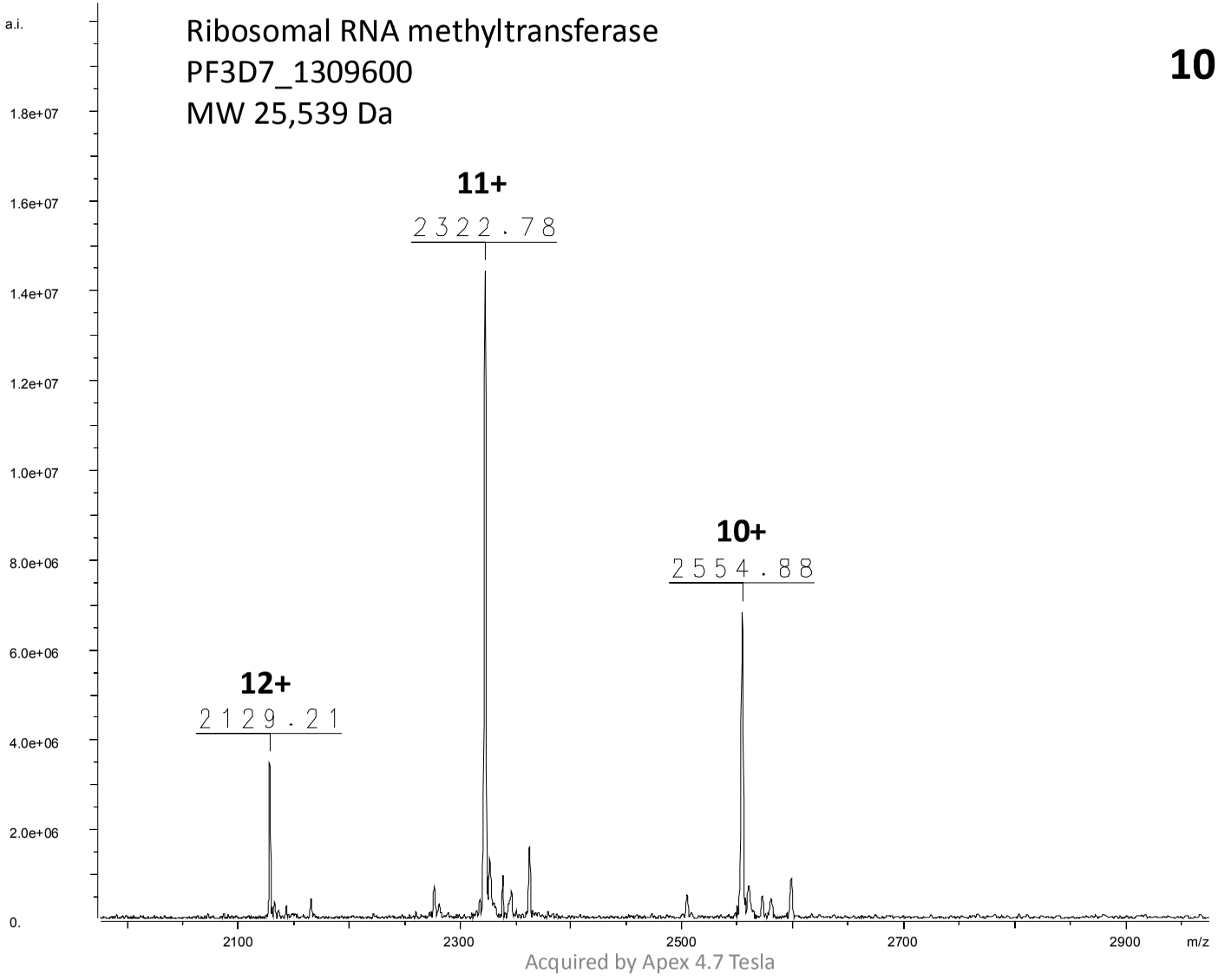


Acquired by Apex 4.7 Tesla


N-myristoyltransferase
PF3D7_1412800
MW 49,935 Da
9
a.i.
6500000
6000000
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
15+
3329.97
16+
3121.90
14+
3566.30
2700
2900
3100
3300
3500
3700
3900
m/z
Acquired by Apex 4.7 Tesla

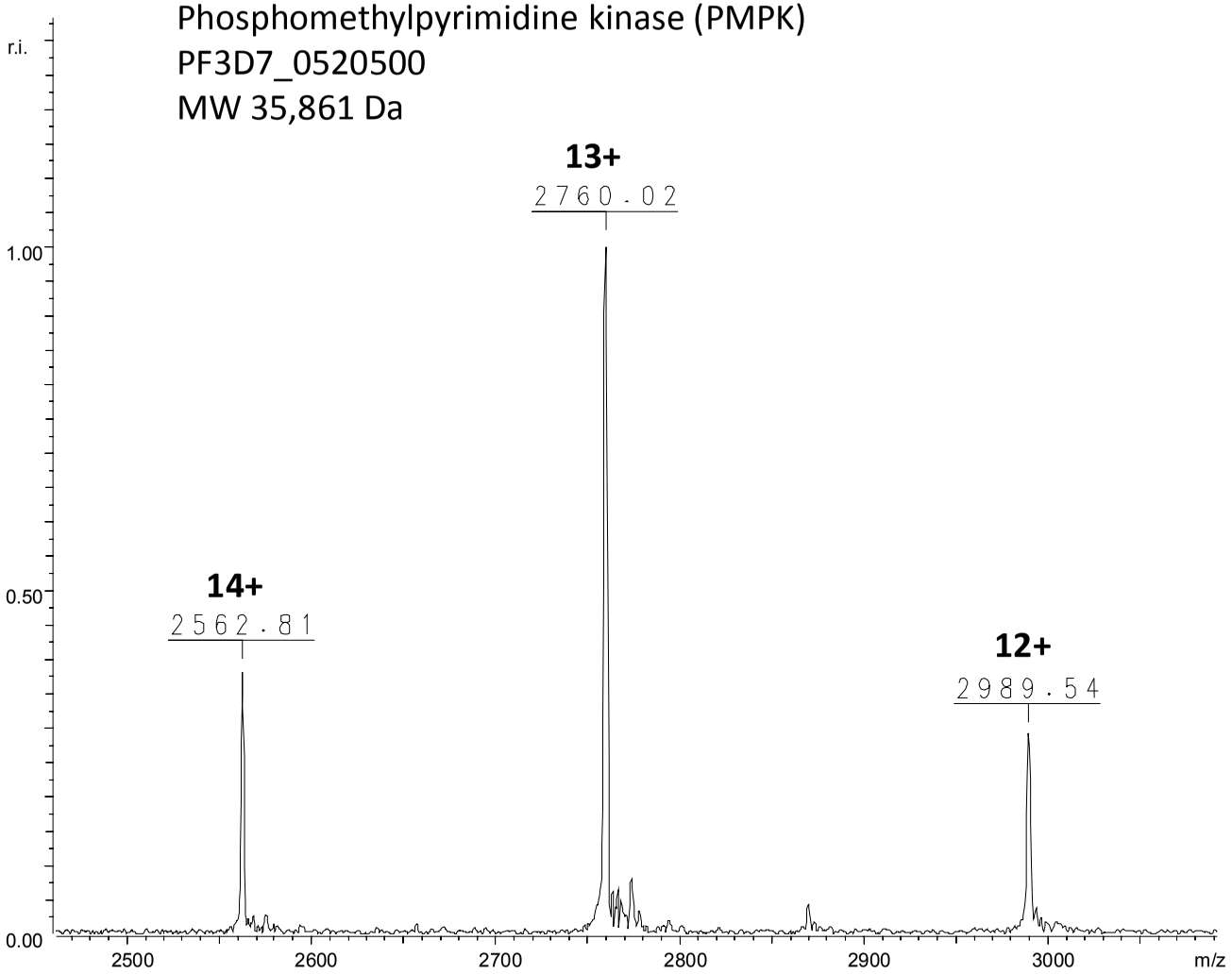
Ribosomal RNA methyltransferase
PF3D7_1309600
MW 25,539 Da

10



Phosphomethylpyrimidine kinase (PMPK)
PF3D7_0520500
MW 35,861 Da

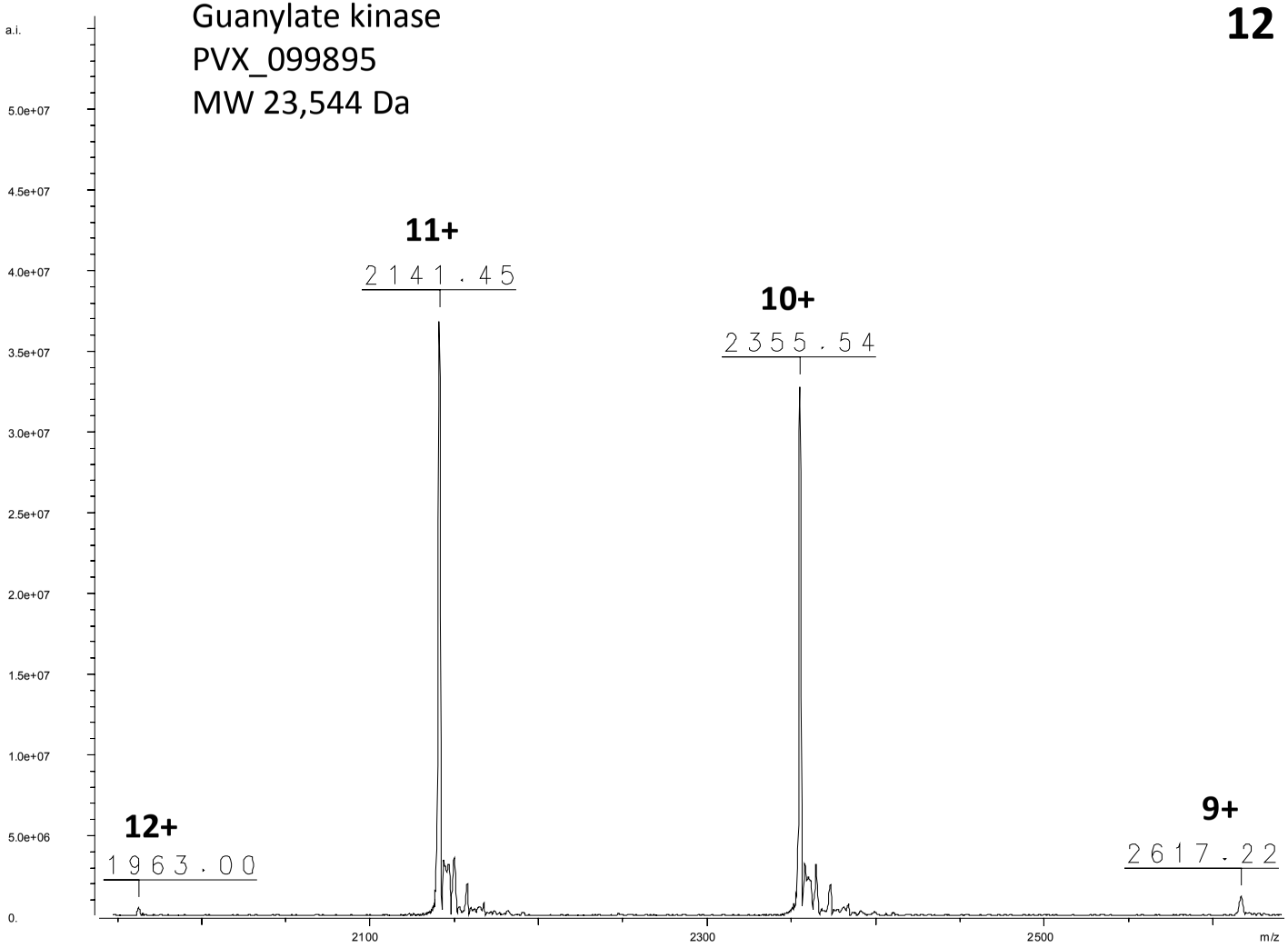
11



Acquired by Apex 4.7 Tesla

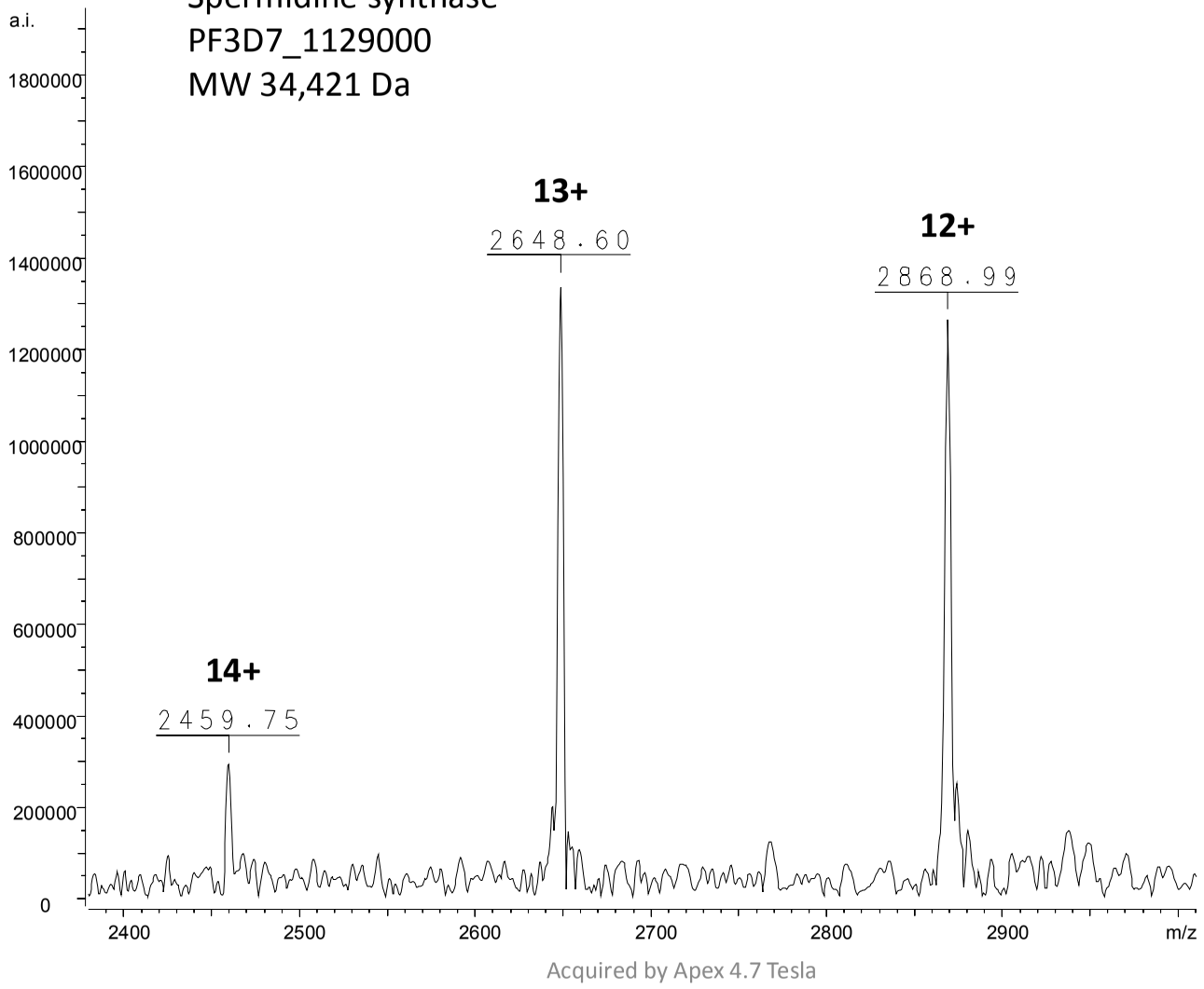
Guanylate kinase
PVX_099895
MW 23,544 Da

12



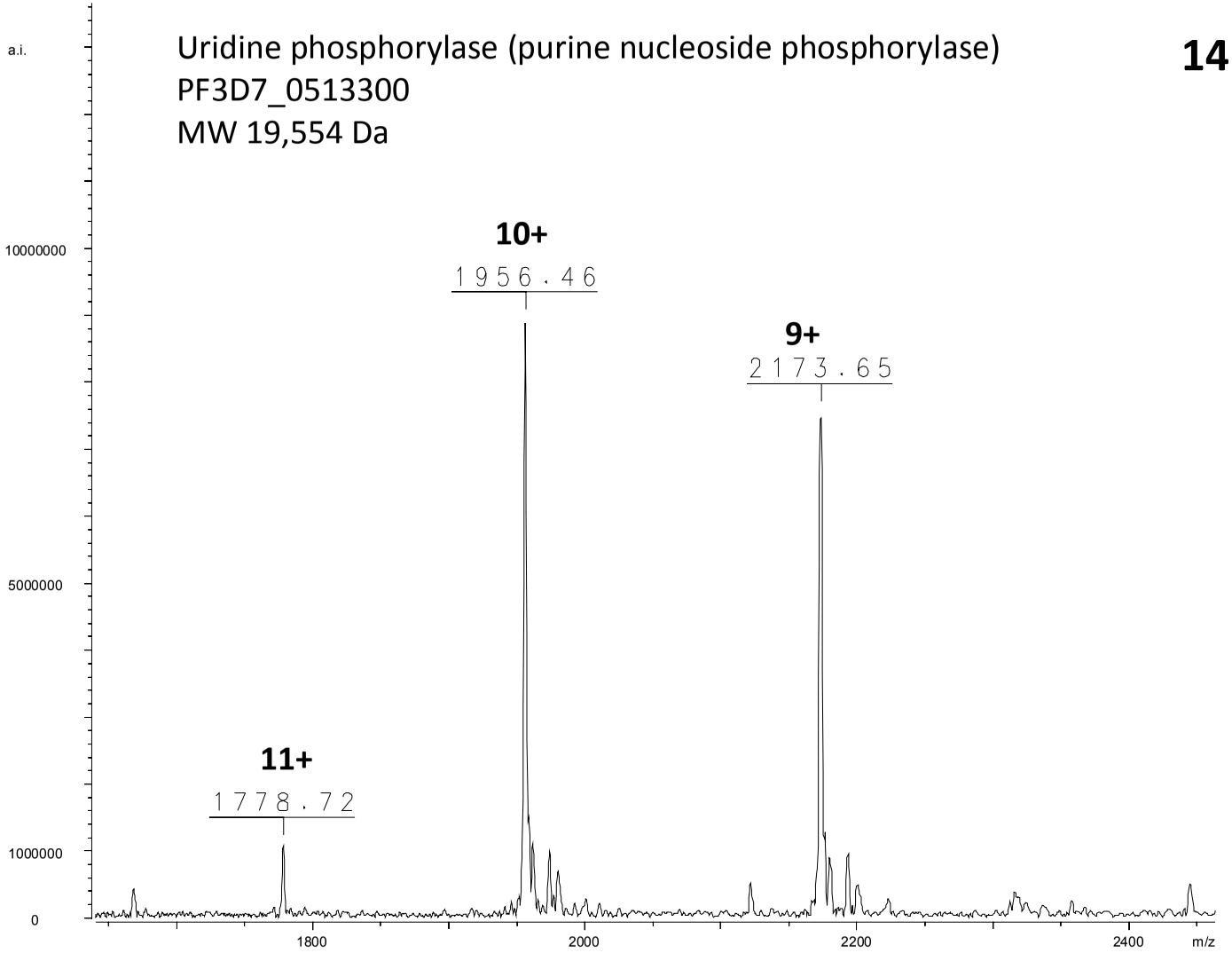
Acquired by Apex 4.7 Tesla

13


Spermidine synthase
PF3D7_1129000
MW 34,421 Da
a.i.
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
13+
2648.60
12+
2868.99
14+
2459.75
2400
2500
2600
2700
2800
2900
m/z
Acquired by Apex 4.7 Tesla

Uridine phosphorylase (purine nucleoside phosphorylase)
PF3D7_0513300
MW 19,554 Da

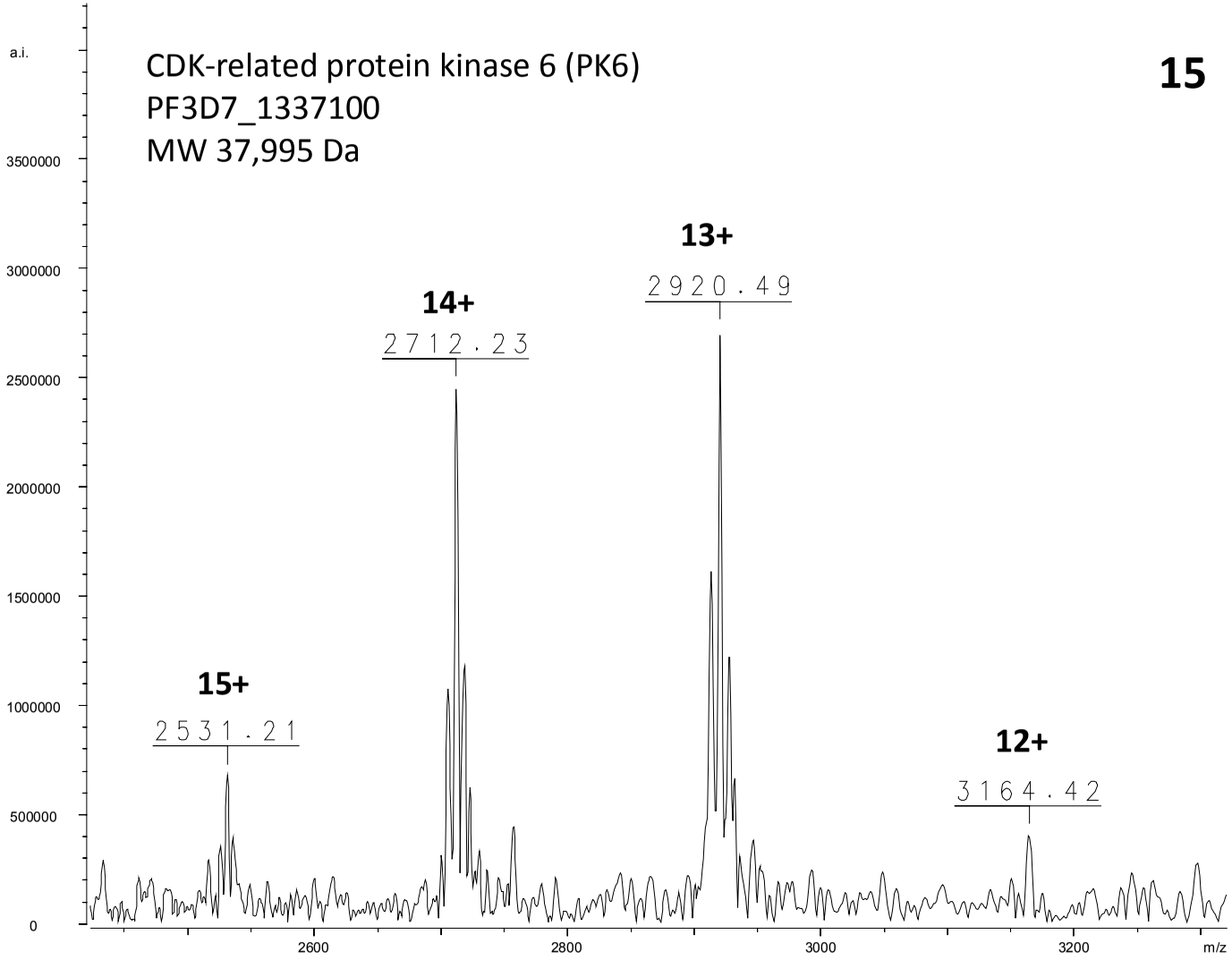
14



Acquired by Apex 4.7 Tesla

CDK-related protein kinase 6 (PK6)
PF3D7_1337100
MW 37,995 Da

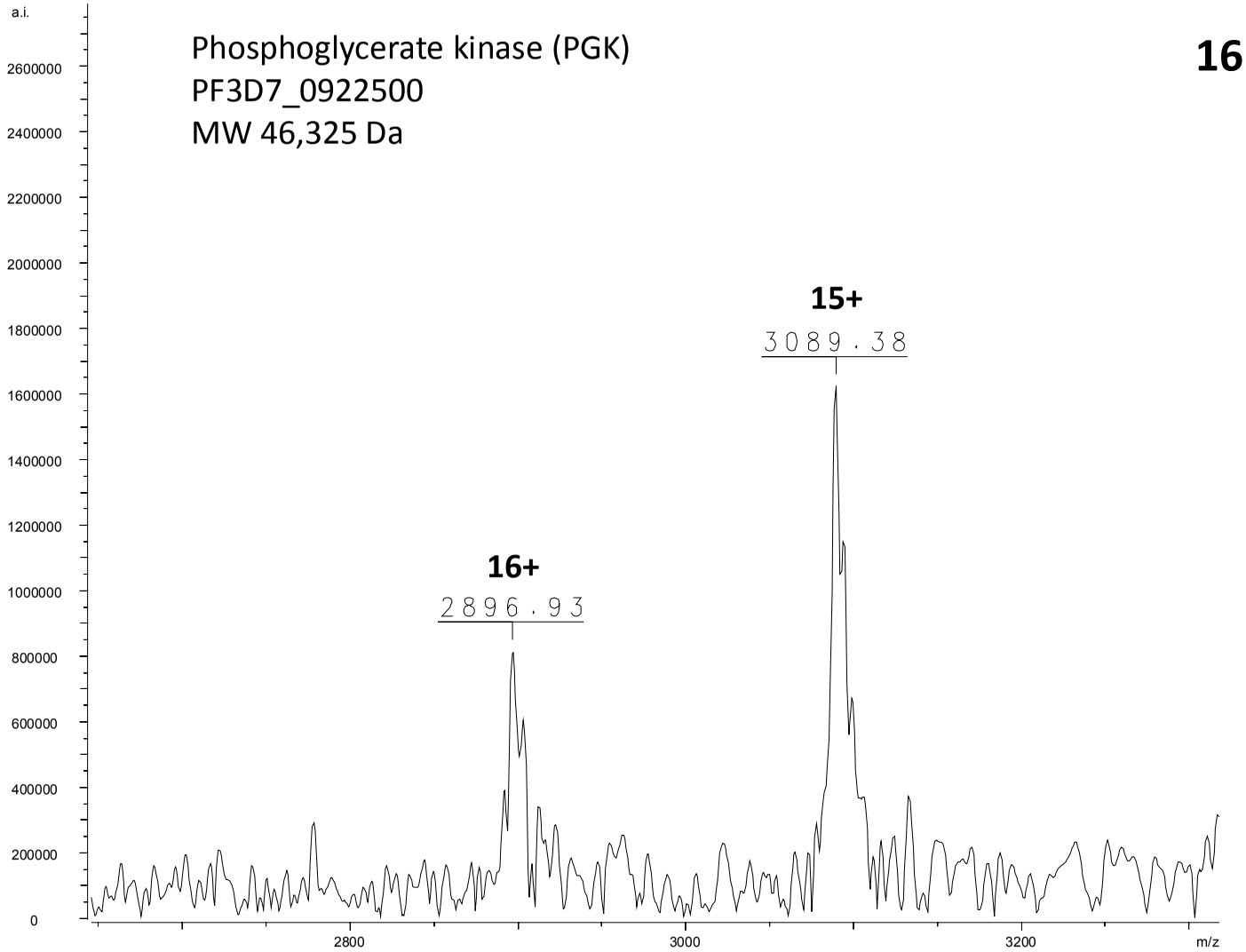
15



Acquired by Apex 4.7 Tesla

Phosphoglycerate kinase (PGK)
PF3D7_0922500
MW 46,325 Da

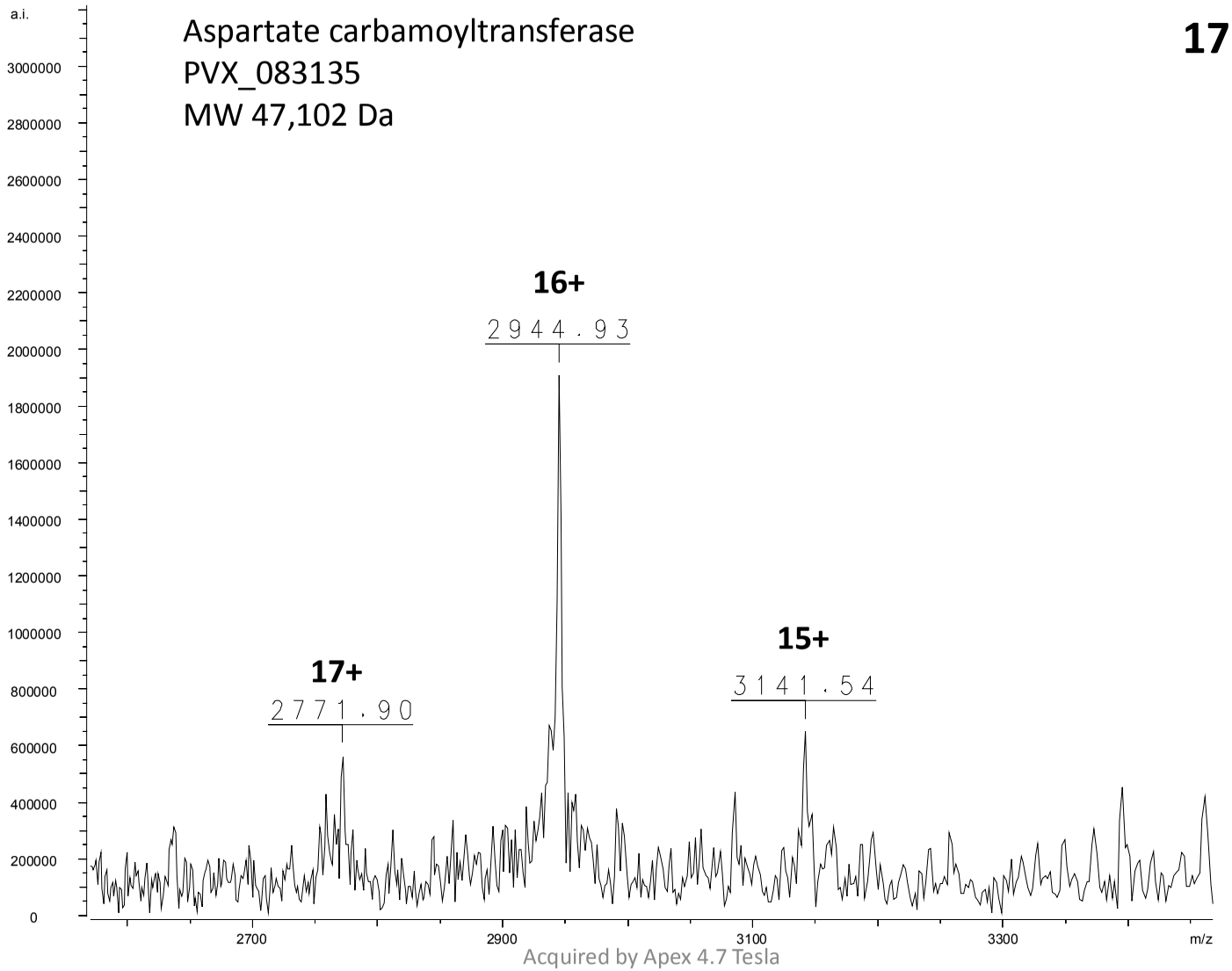
16



Acquired by Apex 4.7 Tesla

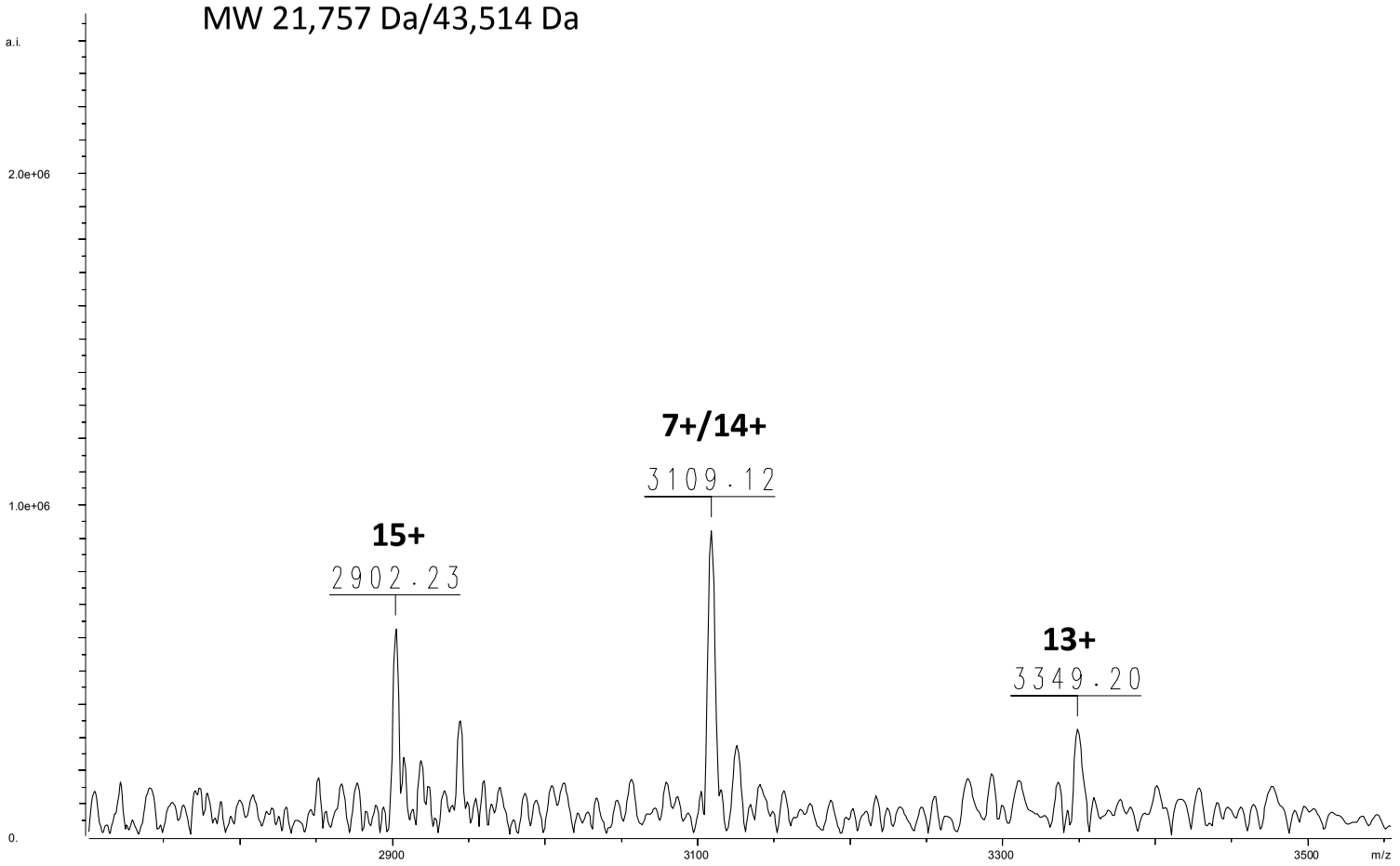
Aspartate carbamoyltransferase
PVX_083135
MW 47,102 Da

17



Rab18GTPase
PF3D7_0807300
MW 21,757 Da/43,514 Da

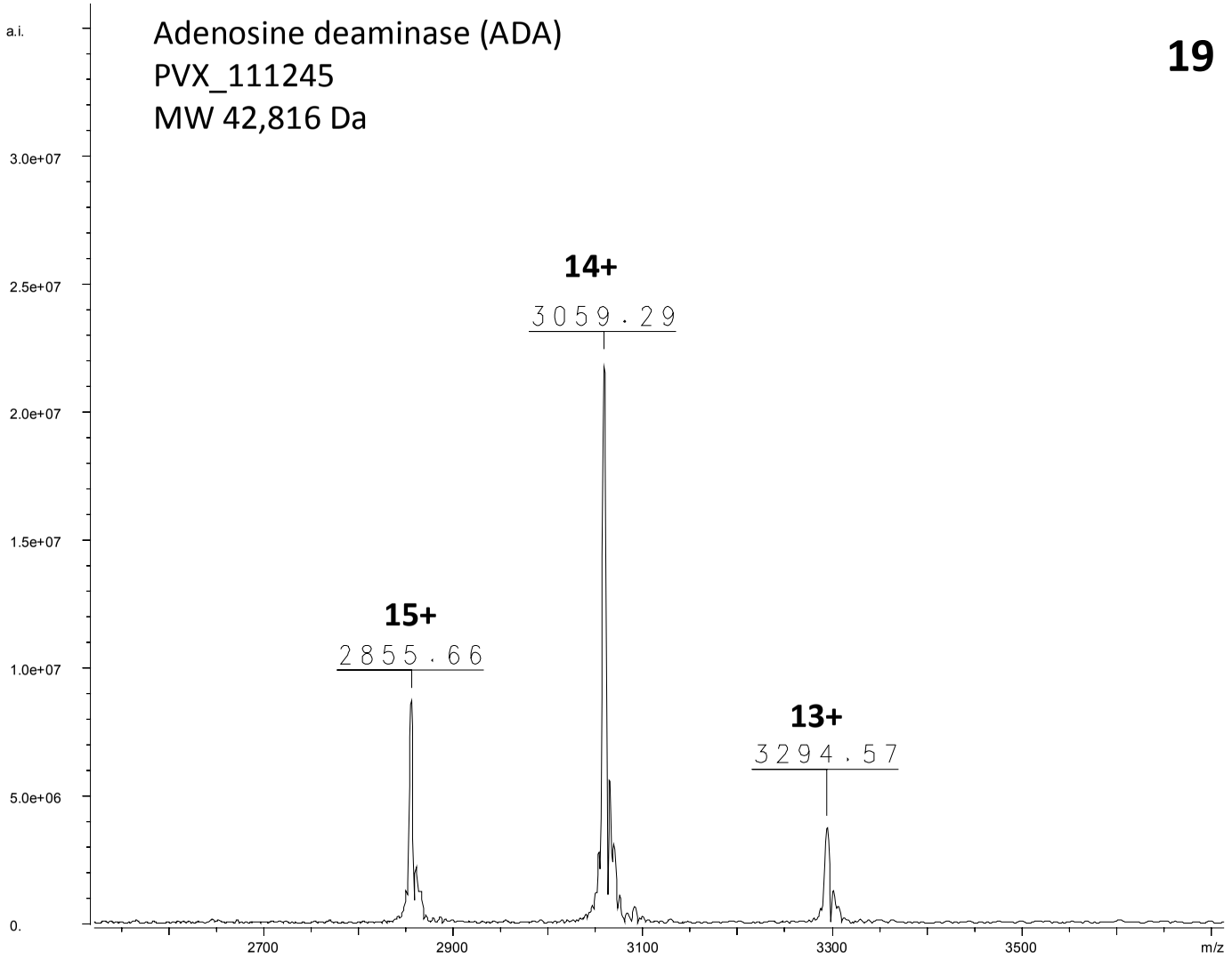
18



Acquired by Apex 4.7 Tesla

Adenosine deaminase (ADA)
PVX_111245
MW 42,816 Da

19



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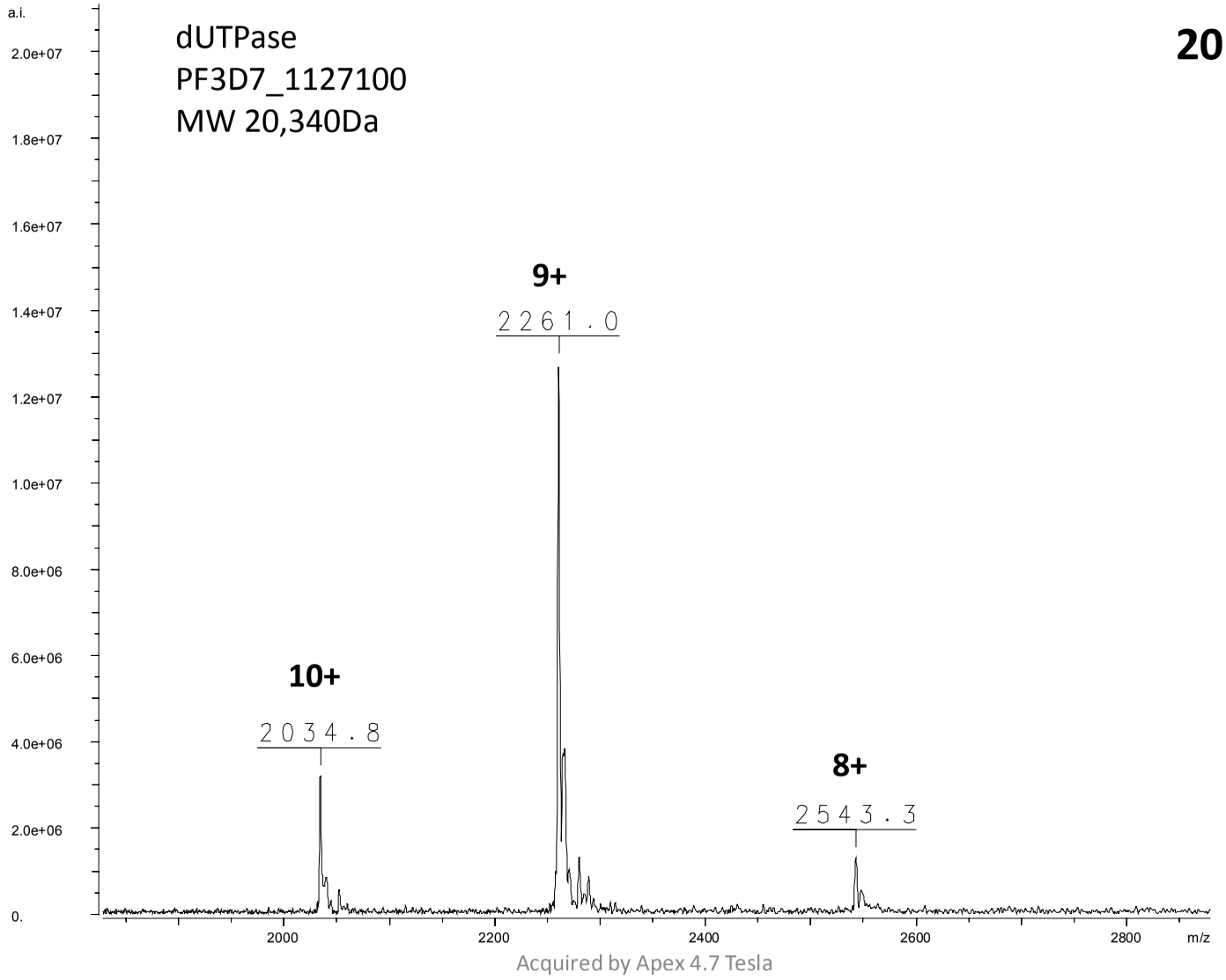
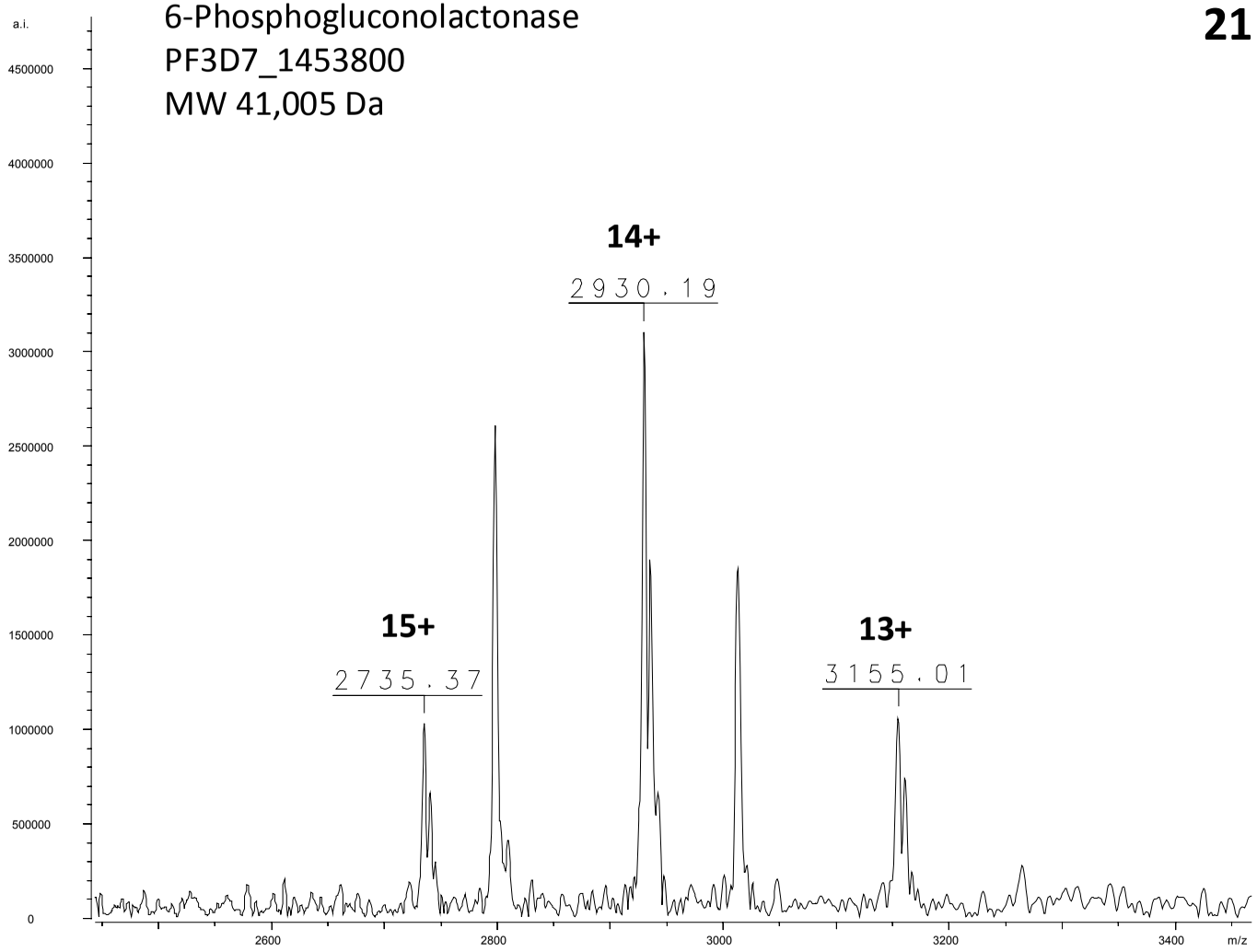

a.i.
2.0e+07
1.8e+07
1.6e+07
1.4e+07
1.2e+07
1.0e+07
8.0e+06
6.0e+06
4.0e+06
2.0e+06
0.
dUTPase
PF3D7_1127100
MW 20,340Da
20
9+
2261.0
10+
2034.8
8+
2543.3
2000
2200
2400
2600
2800
m/z
Acquired by Apex 4.7 Tesla

6-Phosphogluconolactonase
PF3D7_1453800
MW 41,005 Da

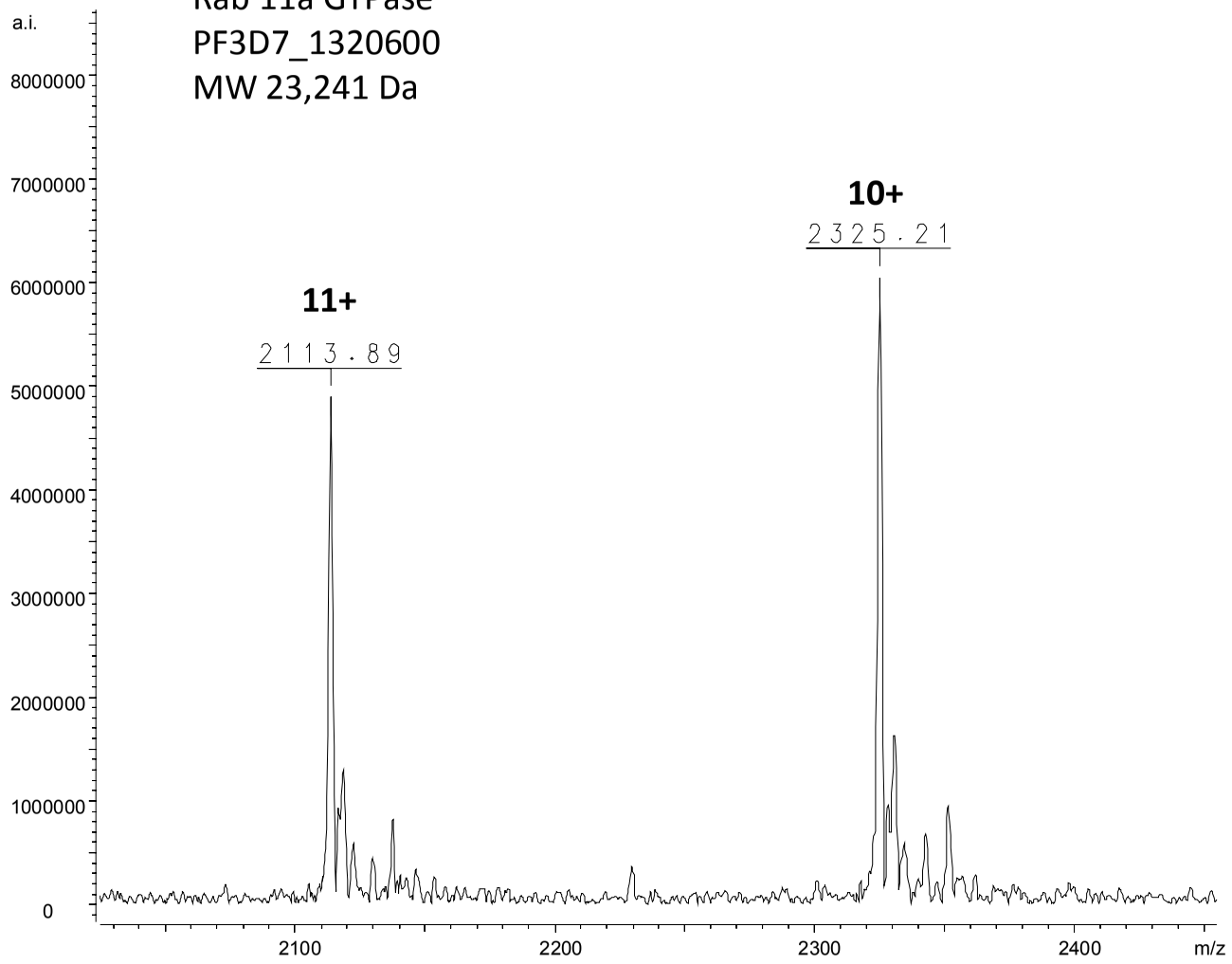
21



Acquired by Apex 4.7 Tesla

Rab 11a GTPase
PF3D7_1320600
MW 23,241 Da

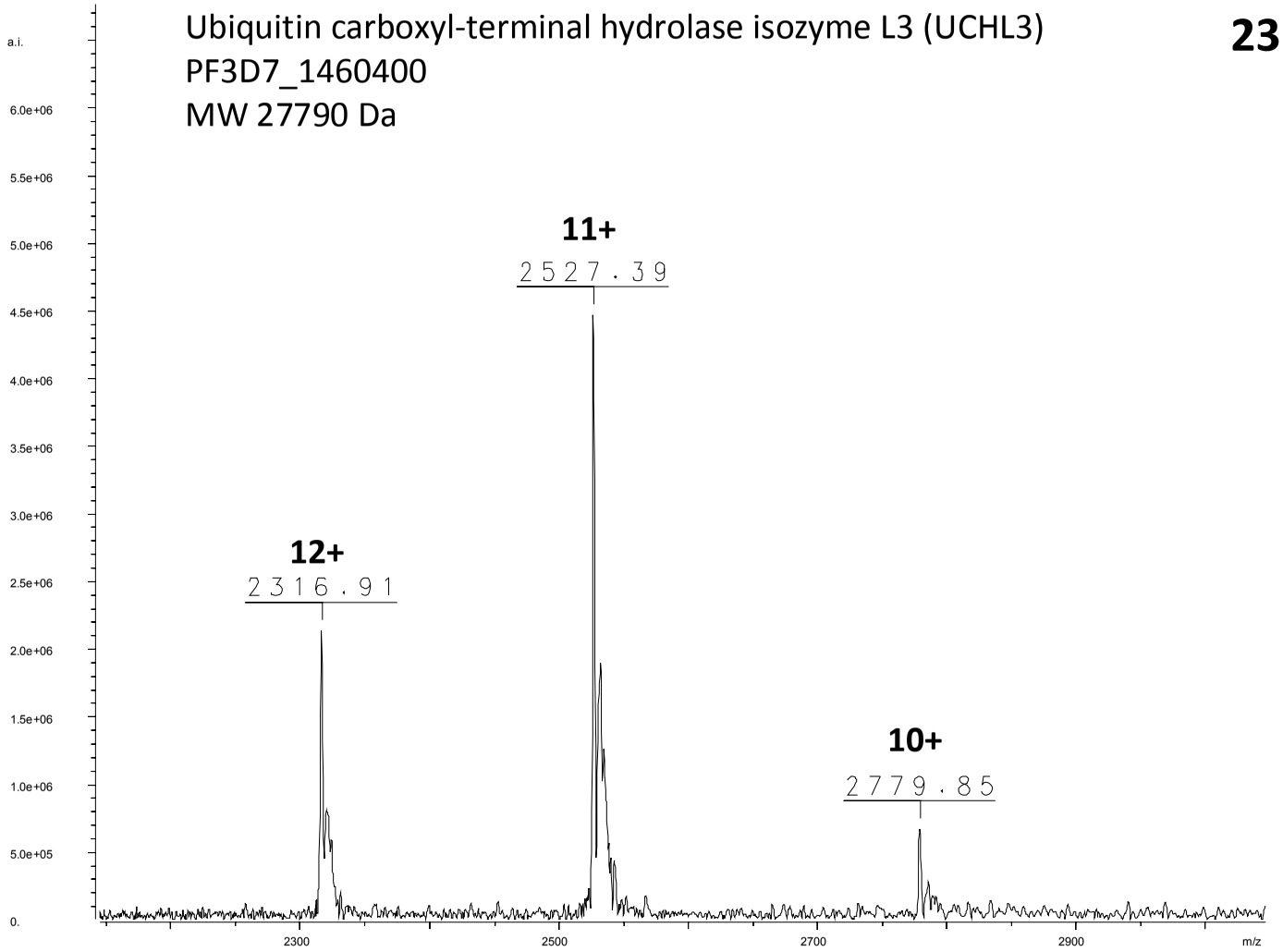
22



Acquired by Apex 4.7 Tesla

Ubiquitin carboxyl-terminal hydrolase isozyme L3 (UCHL3)
PF3D7_1460400
MW 27790 Da

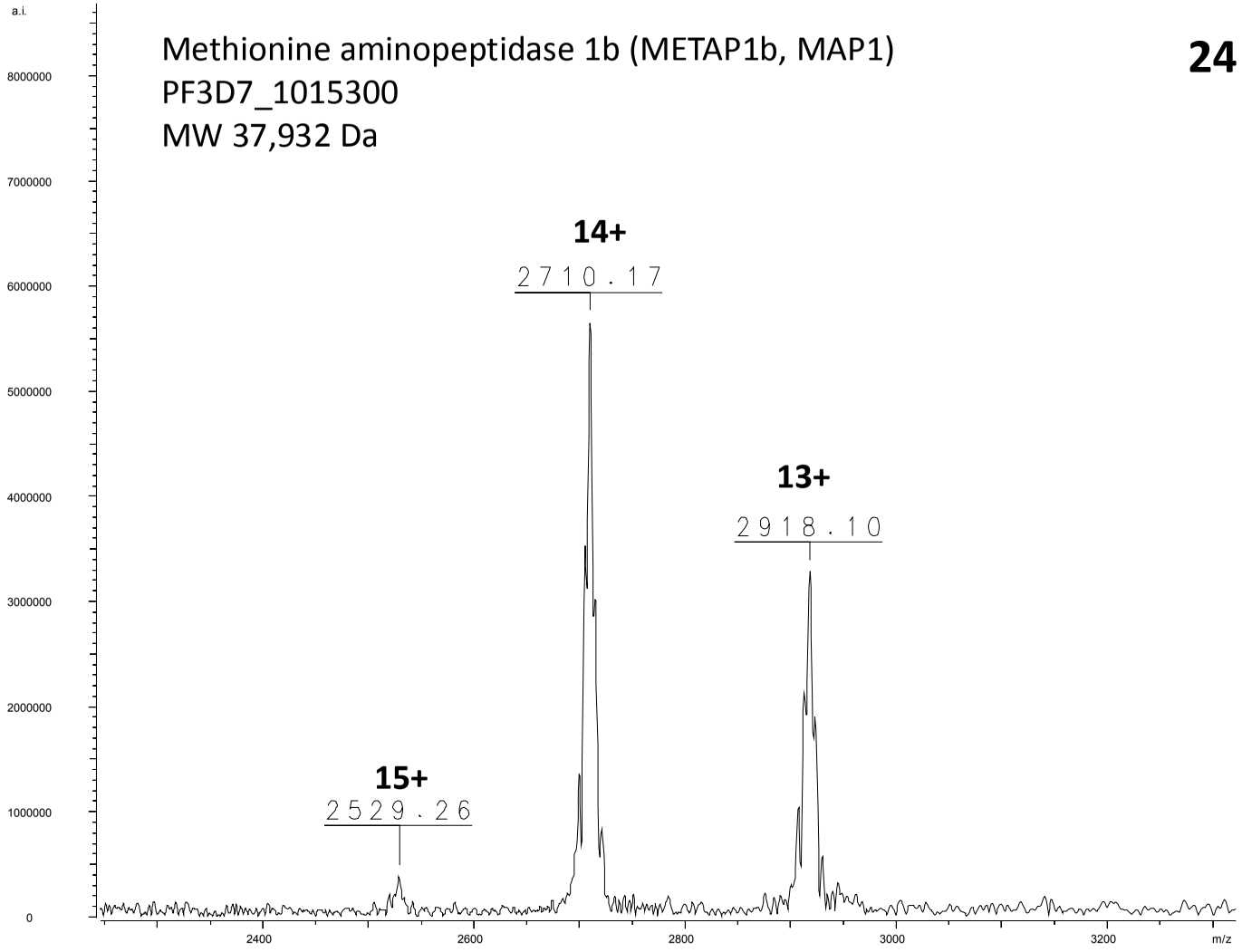
23



Acquired by Apex 4.7 Tesla

Methionine aminopeptidase 1b (METAP1b, MAP1)
PF3D7_1015300
MW 37,932 Da

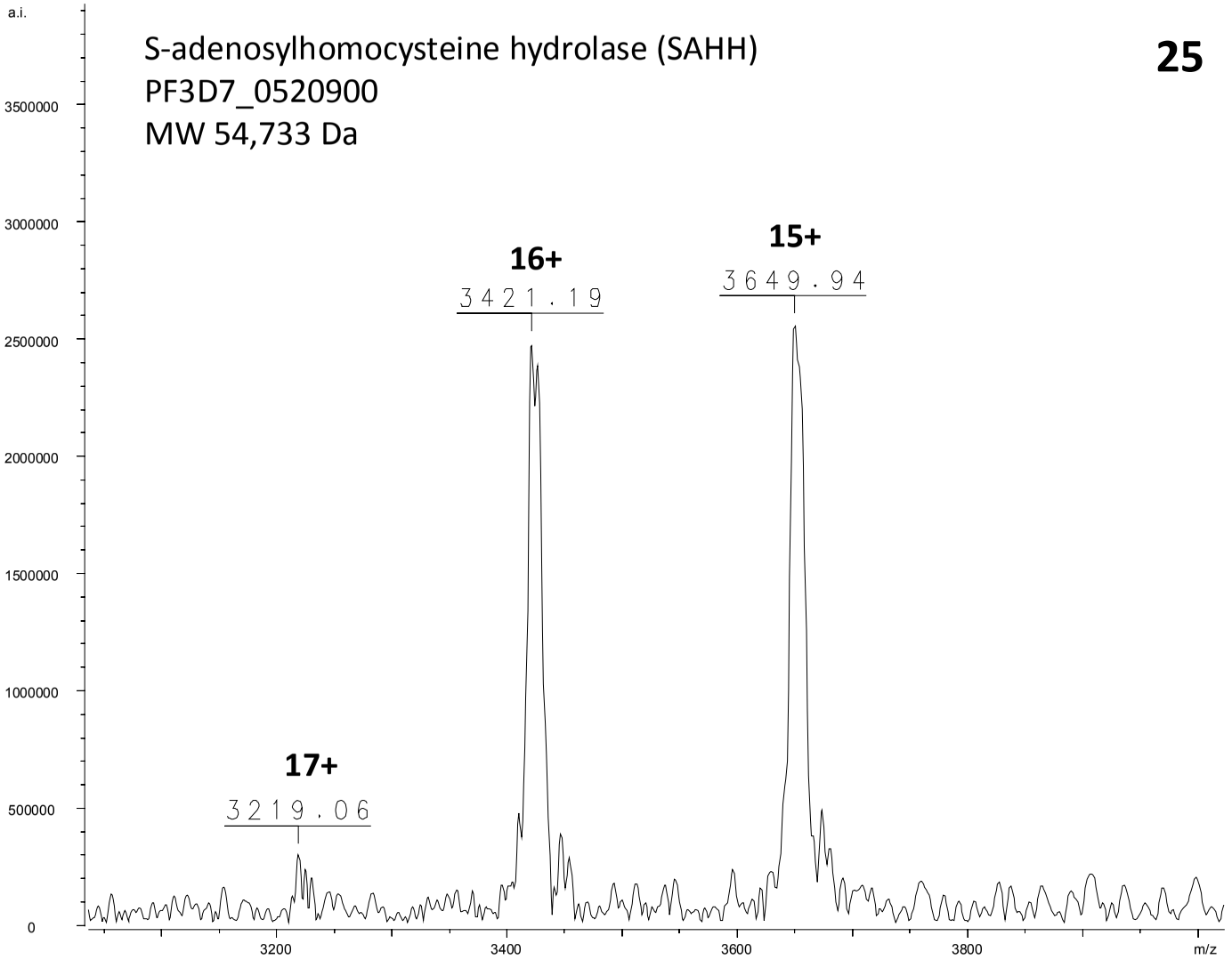
24



Acquired by Apex 4.7 Tesla

S-adenosylhomocysteine hydrolase (SAHH)
PF3D7_0520900
MW 54,733 Da

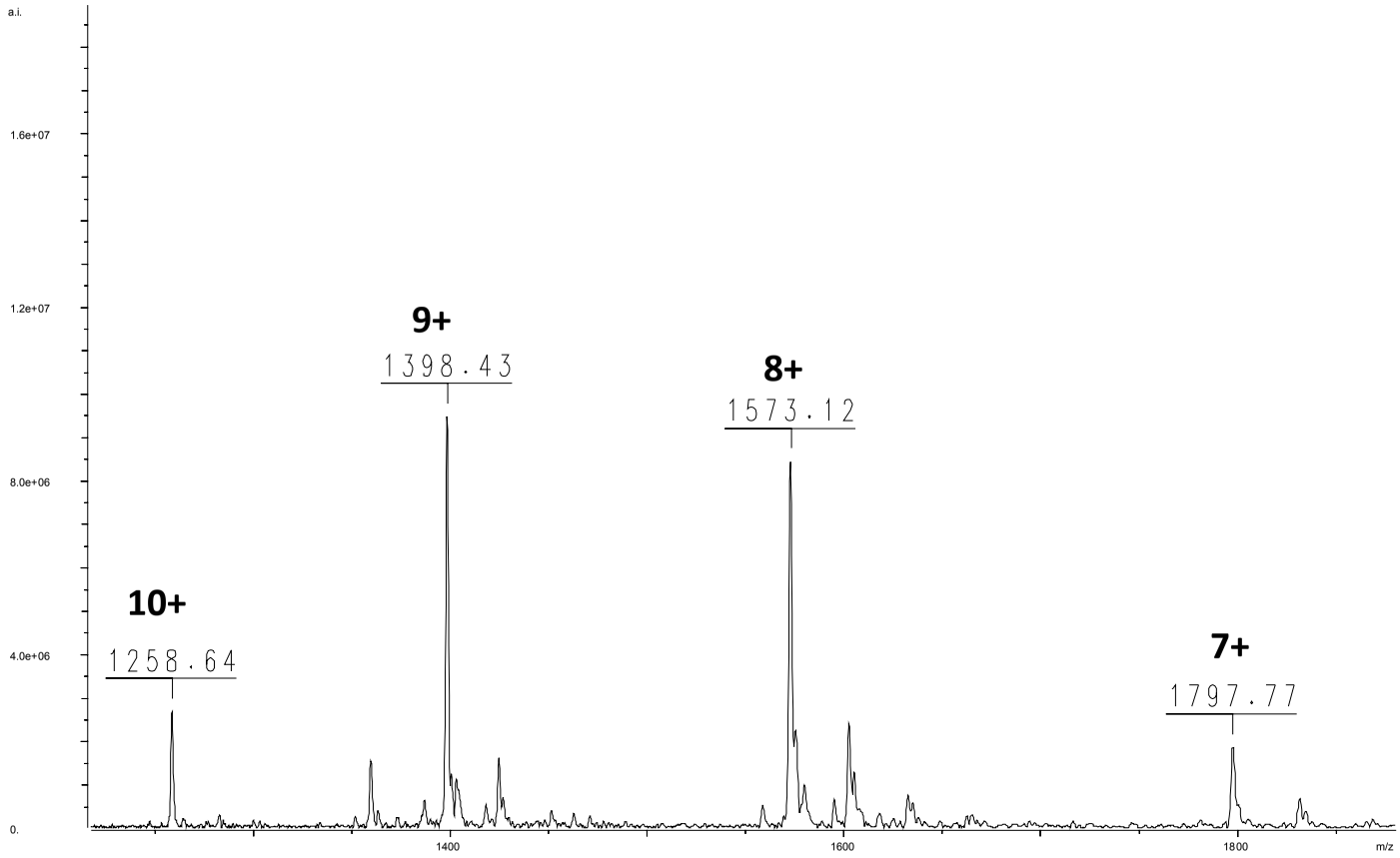
25



Acquired by Apex 4.7 Tesla

ATP-dependent DNA helicase Q1 (RECQ1)
PF3D7_0918600
MW 12,576 Da

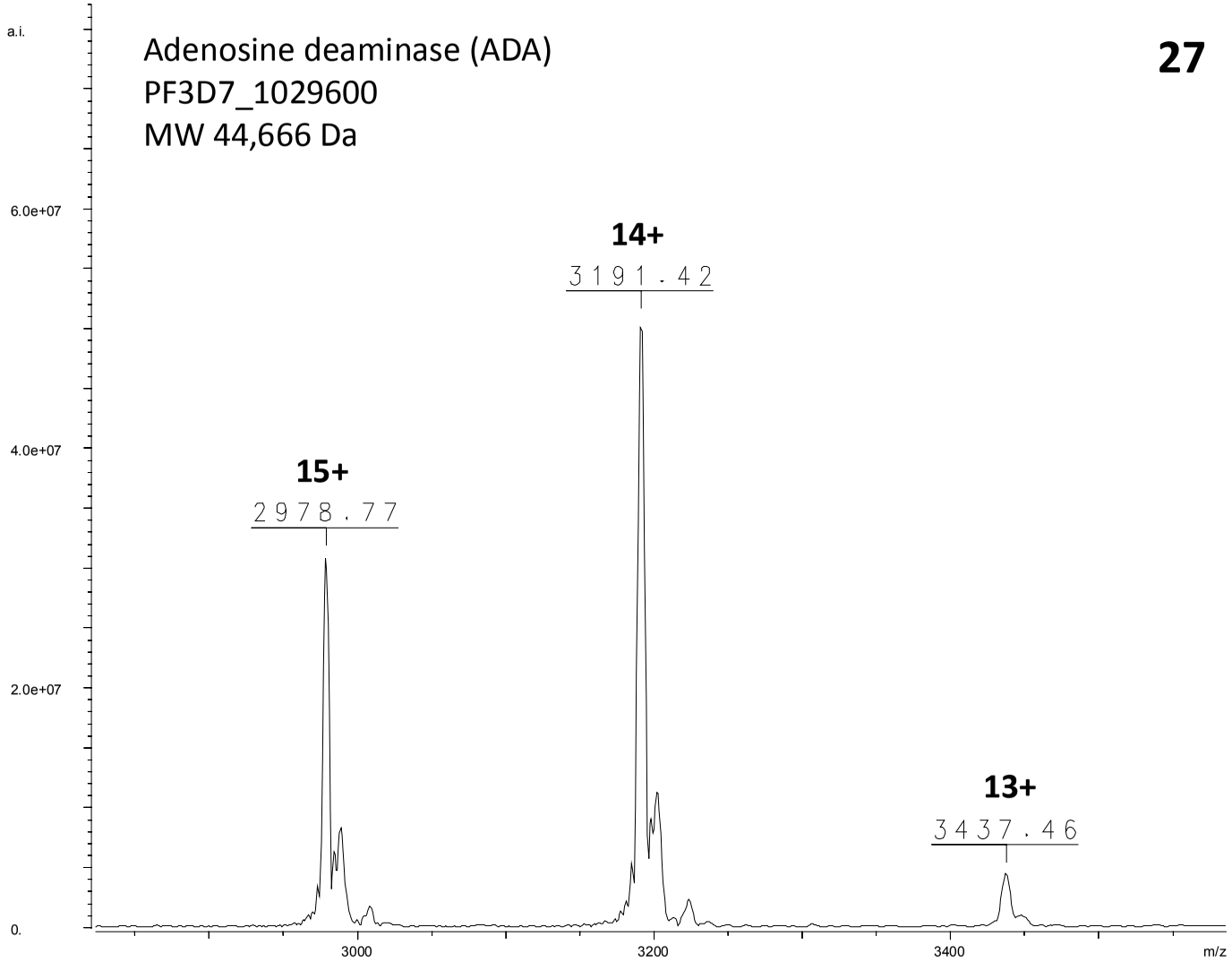
26



Acquired by Apex 4.7 Tesla

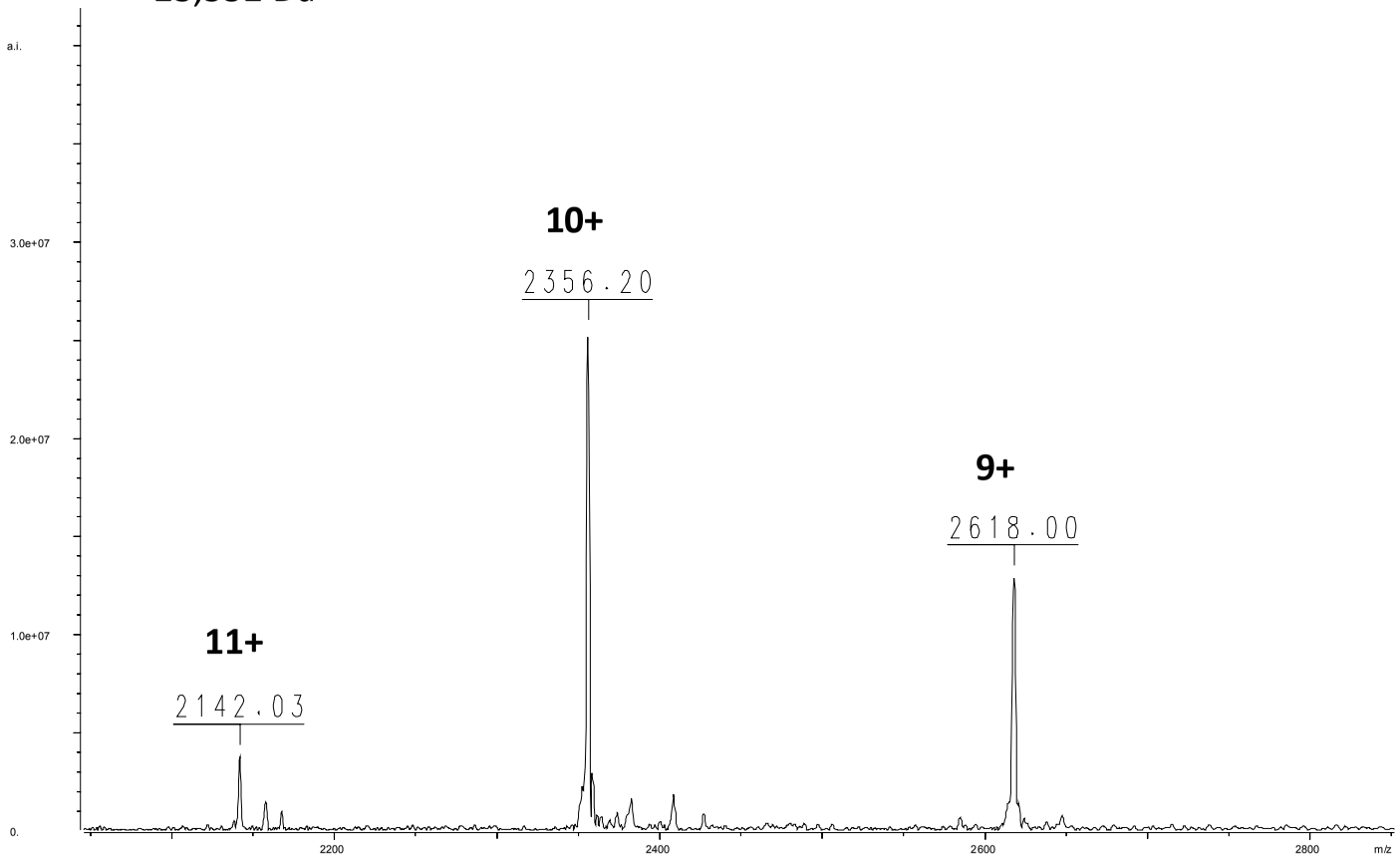
Adenosine deaminase (ADA)
PF3D7_1029600
MW 44,666 Da

27



Acquired by Apex 4.7 Tesla

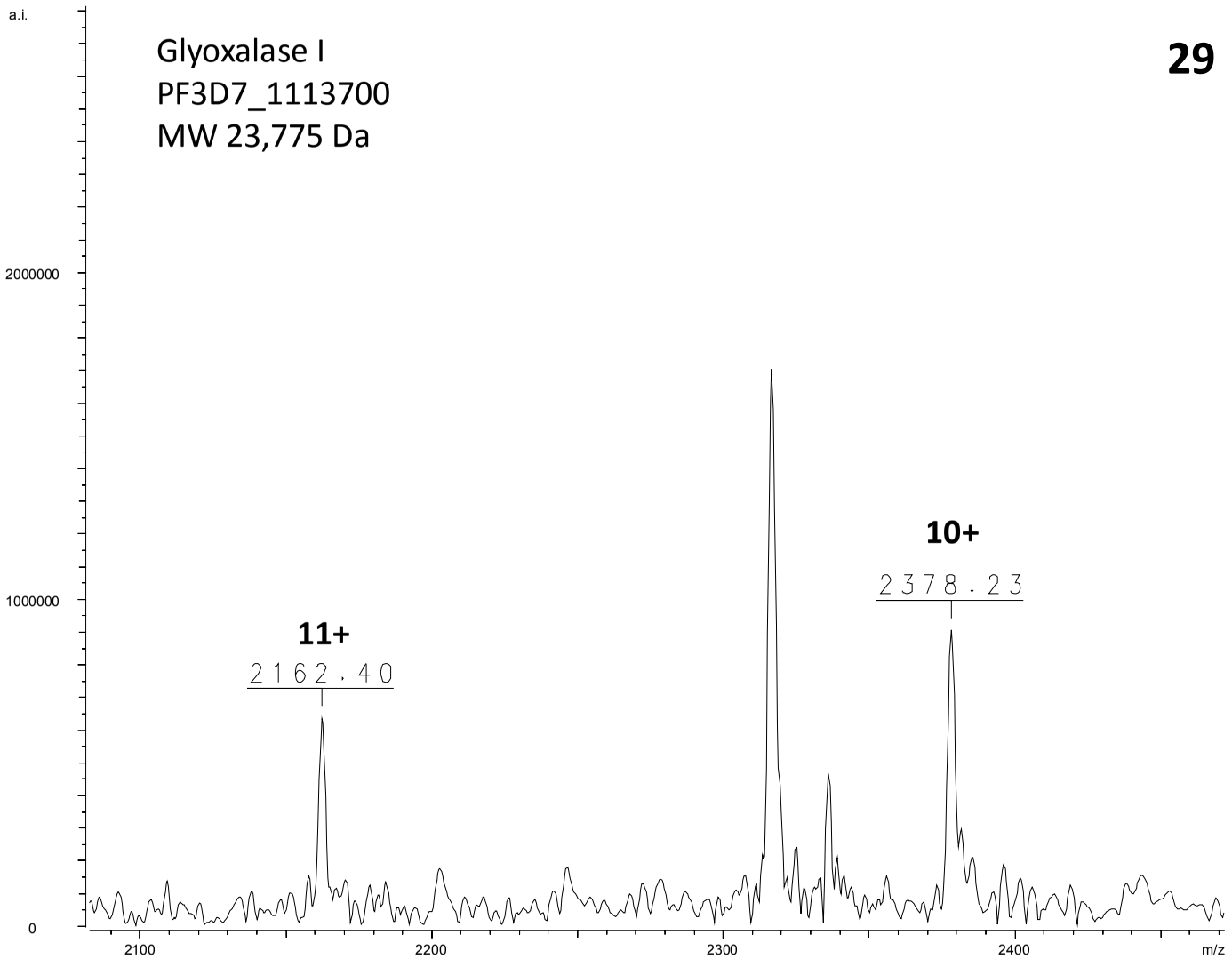
ATP-dependent Clp protease proteolytic subunit (ClpP)
PF3D7_0307400
23,552 Da



Acquired by Apex 4.7 Tesla

Glyoxalase I
PF3D7_1113700
MW 23,775 Da

29



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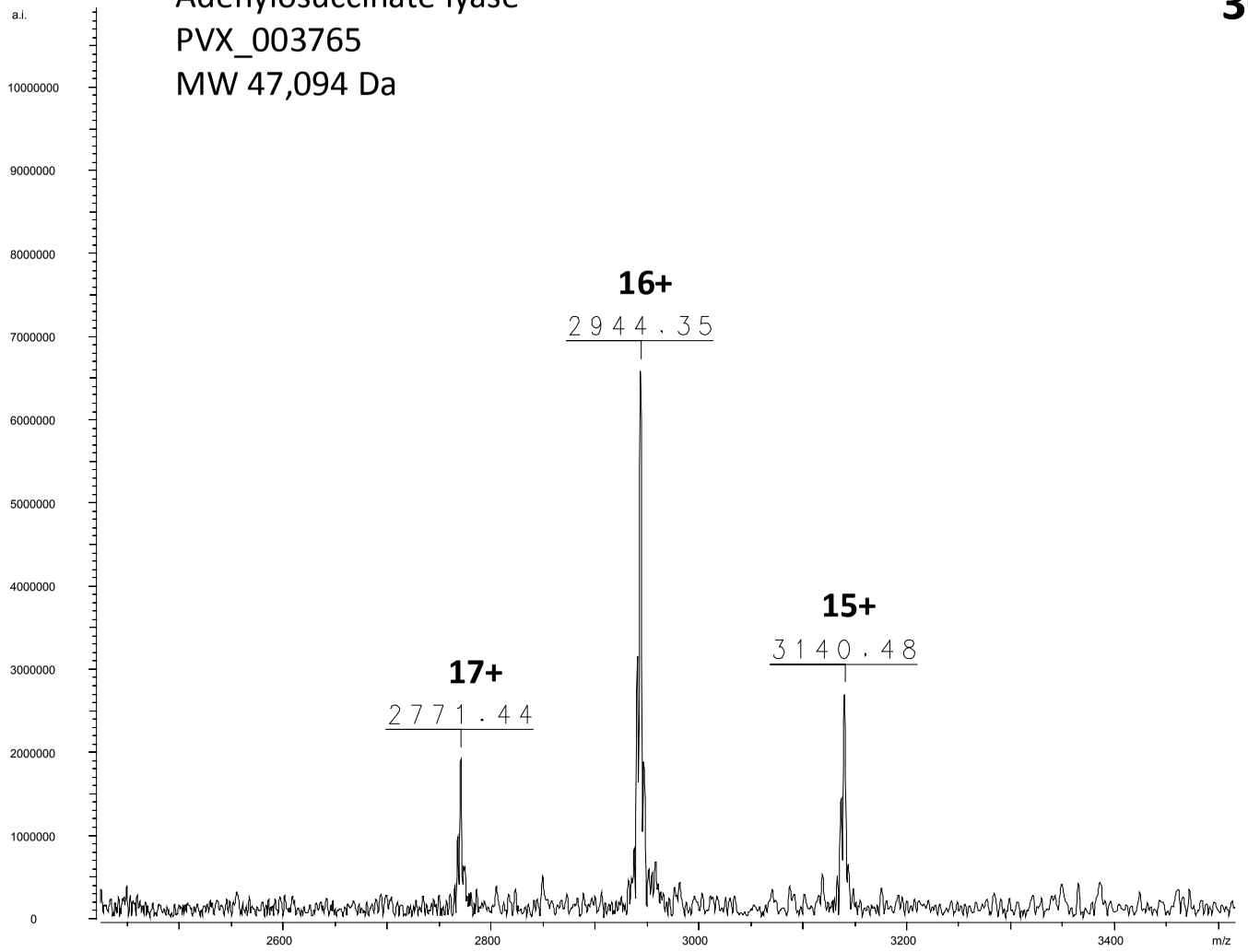
Adenylosuccinate lyase
PVX_003765
MW 47,094 Da

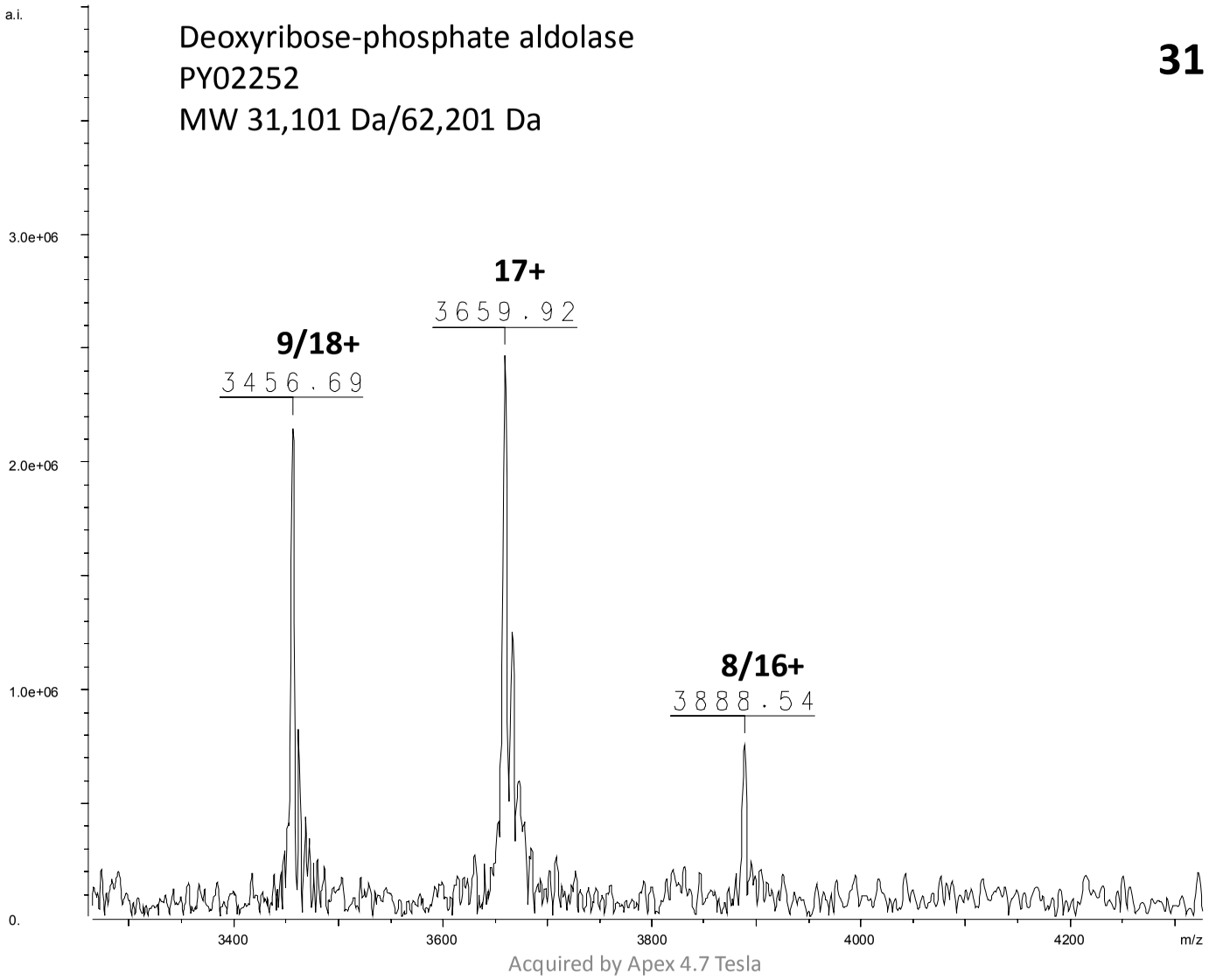
30



Acquired by Apex 4.7 Tesla

Deoxyribose-phosphate aldolase
PY02252
MW 31,101 Da/62,201 Da

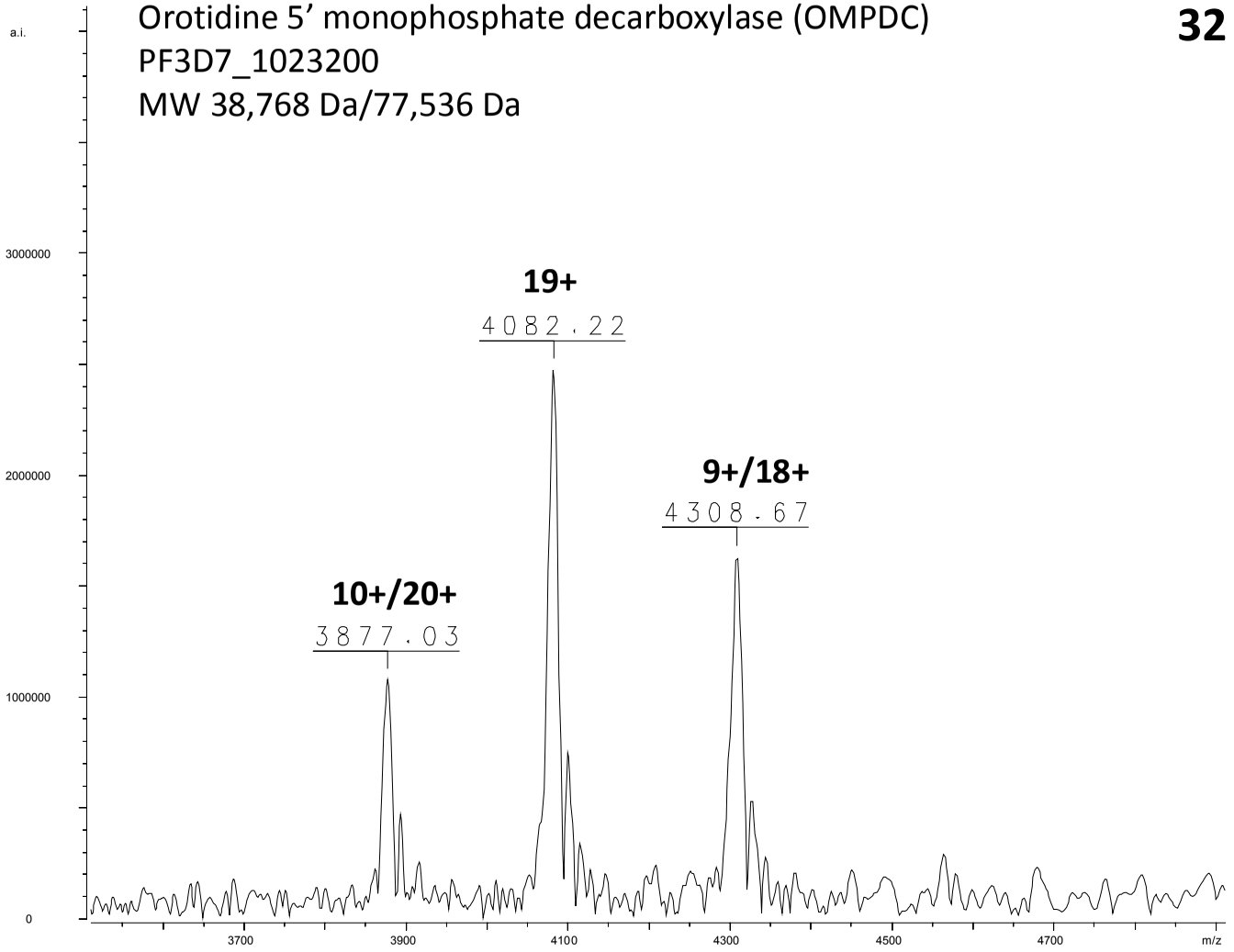
31



Acquired by Apex 4.7 Tesla

Orotidine 5’ monophosphate decarboxylase (OMPDC)
PF3D7_1023200
MW 38,768 Da/77,536 Da

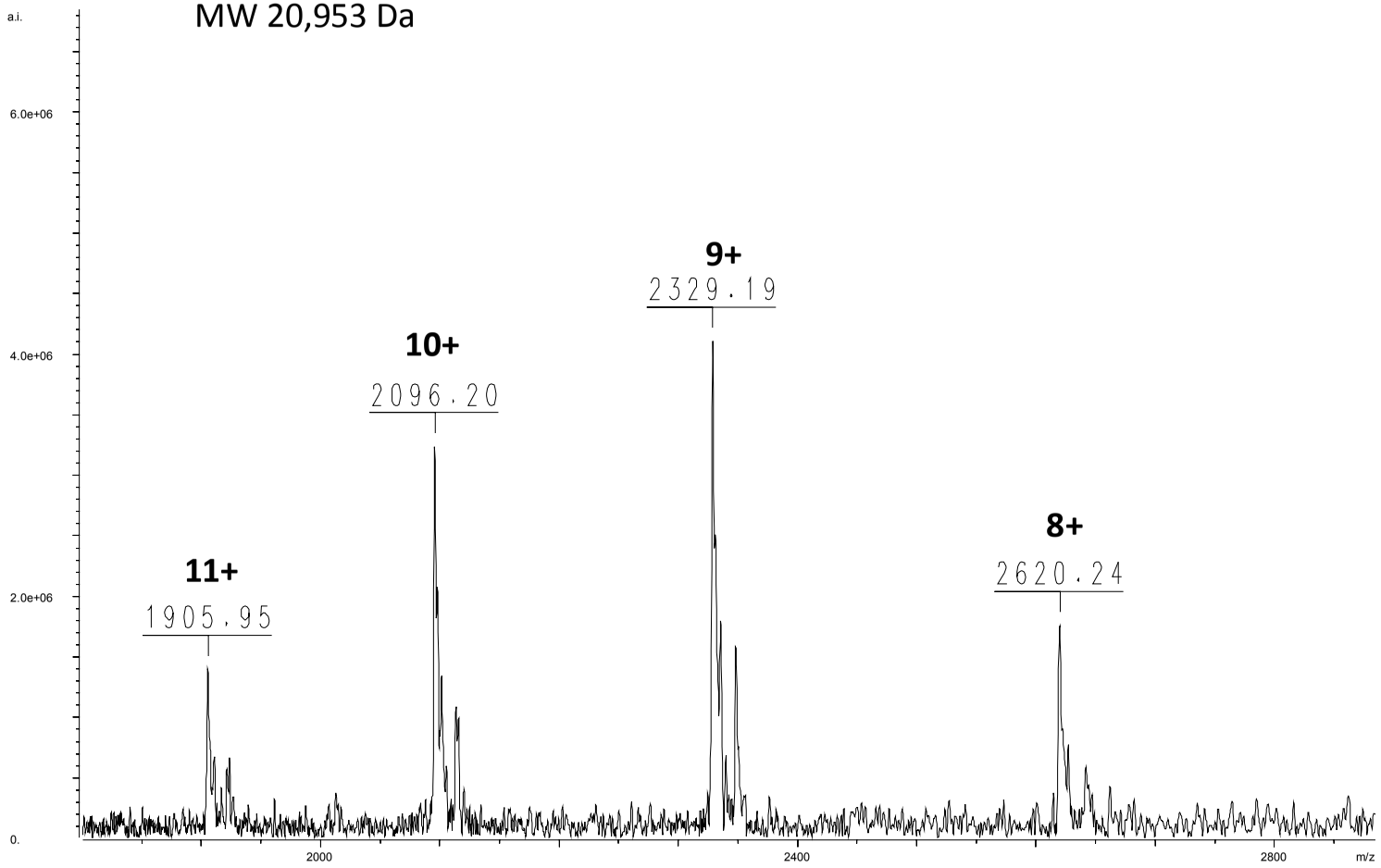
32



Acquired by Apex 4.7 Tesla

6-pyruvoyltetrahydroptern synthase
PF3D7_0628000
MW 20,953 Da

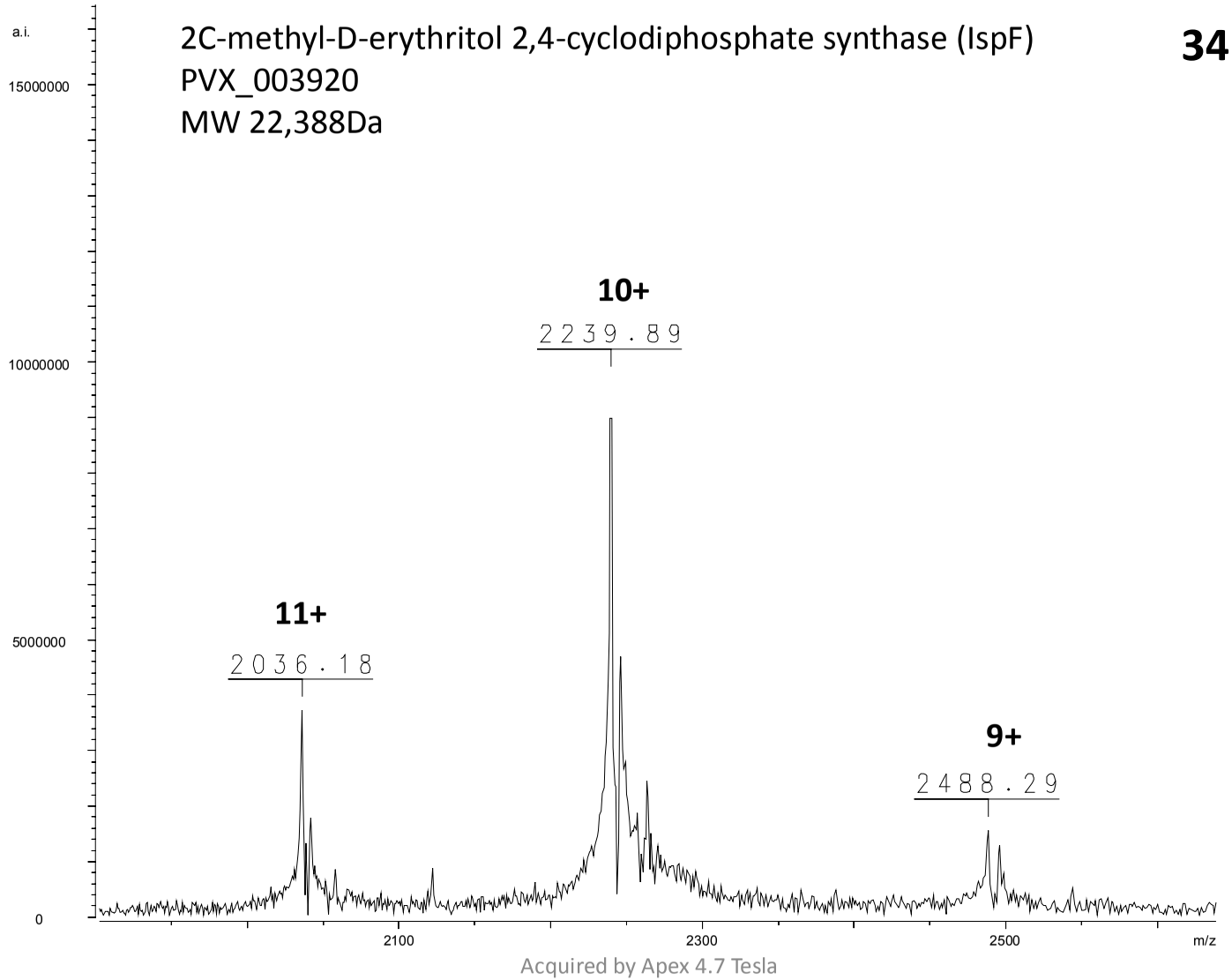
33



Acquired by Apex 4.7 Tesla

2C-methyl-D-erythritol 2,4-cyclodiphosphate synthase (IspF)
PVX_003920
MW 22,388Da

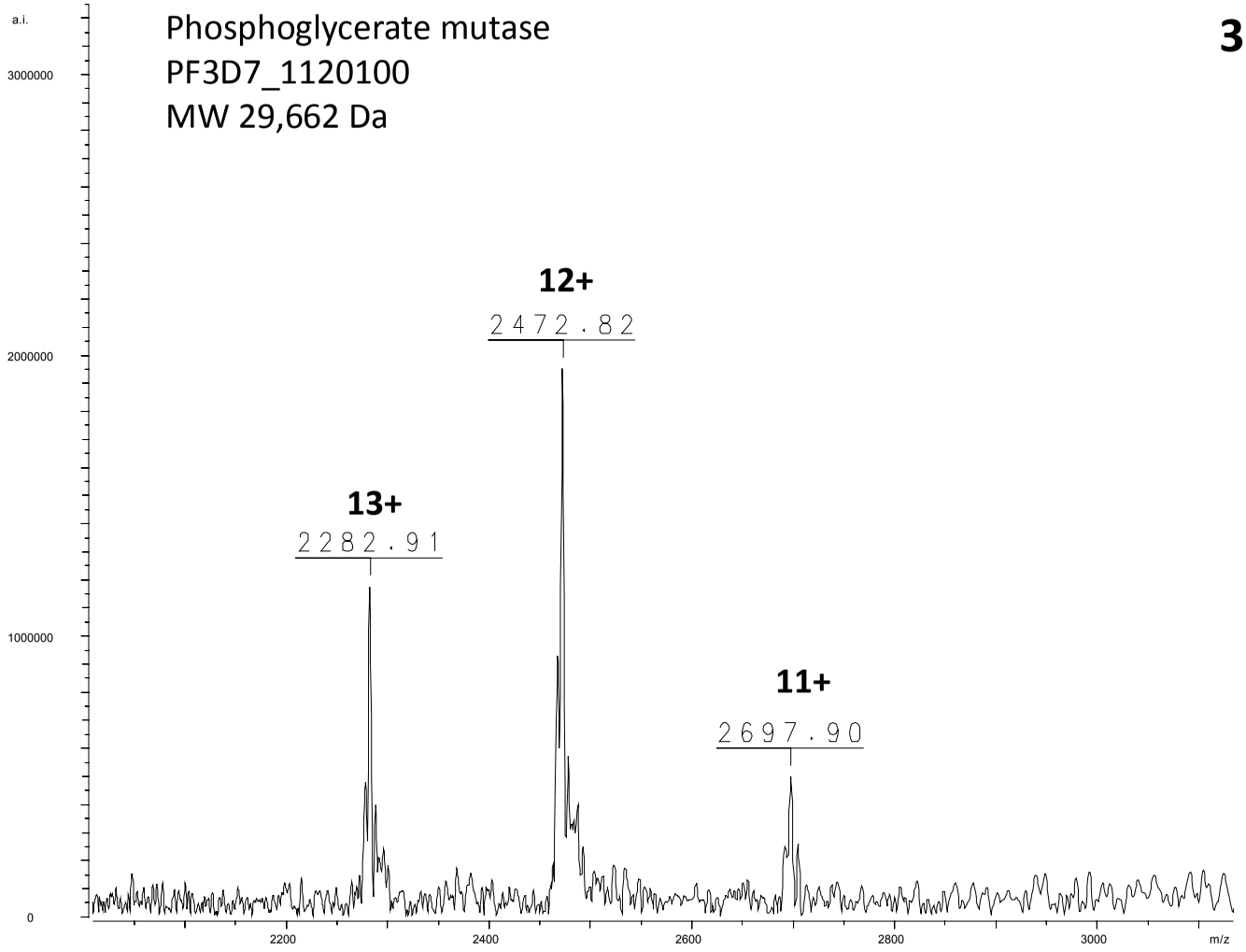
34



Acquired by Apex 4.7 Tesla

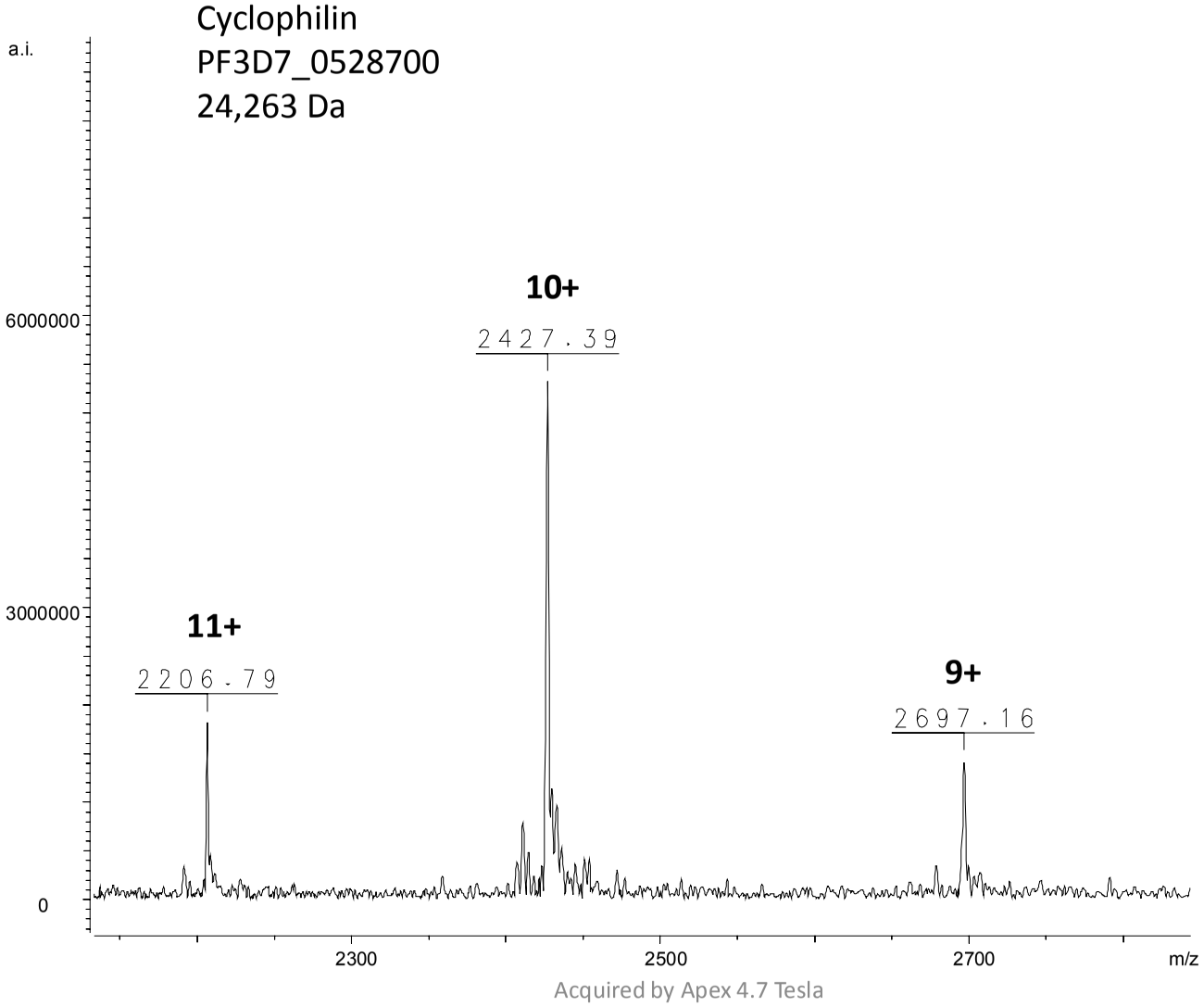
Phosphoglycerate mutase
PF3D7_1120100
MW 29,662 Da

35



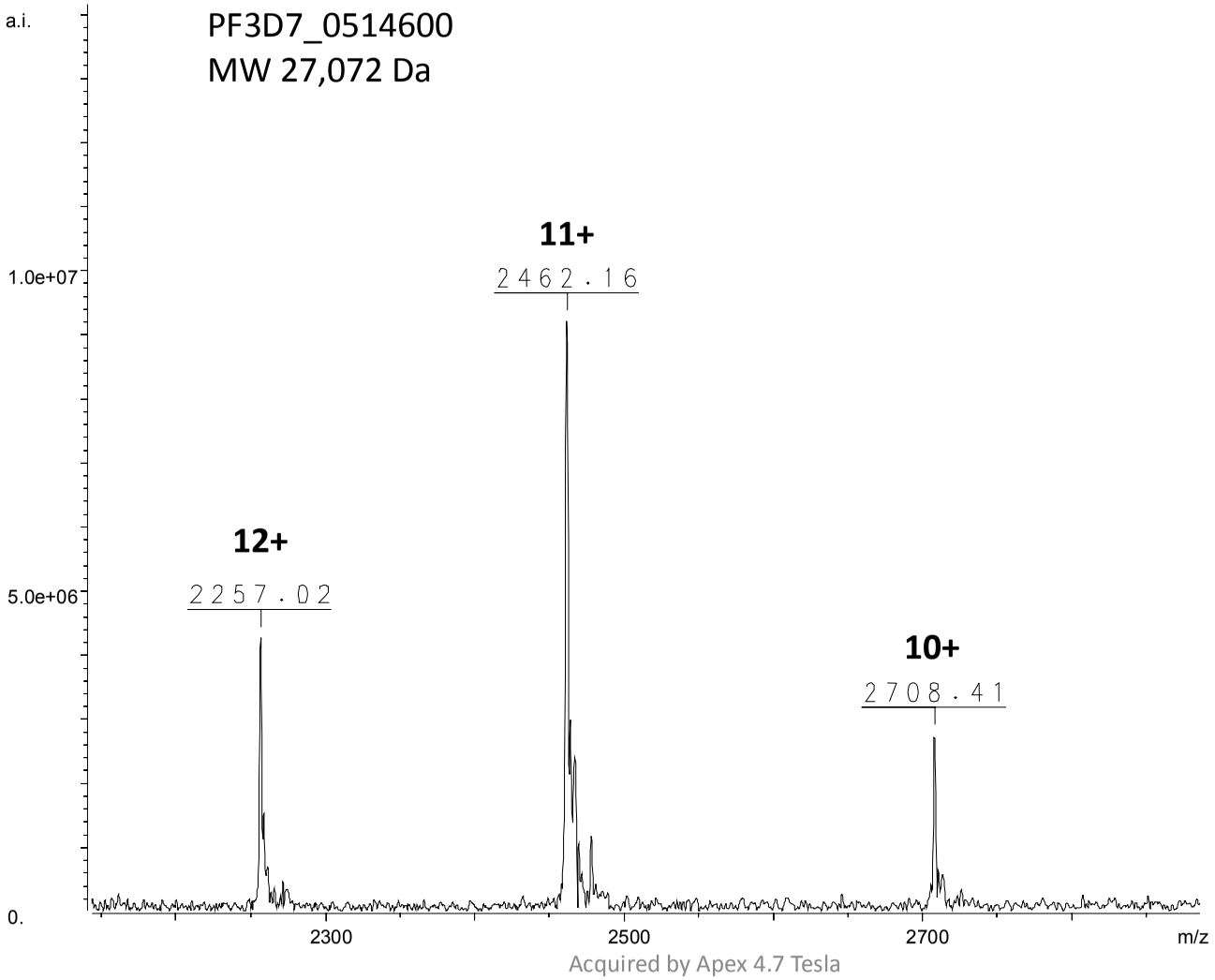
Acquired by Apex 4.7 Tesla

36


Cyclophilin
PF3D7_0528700
24,263 Da
a.i.
6000000
3000000
0
10+
2427.39
11+
2206.79
9+
2697.16
2300
2500
2700
m/z
Acquired by Apex 4.7 Tesla

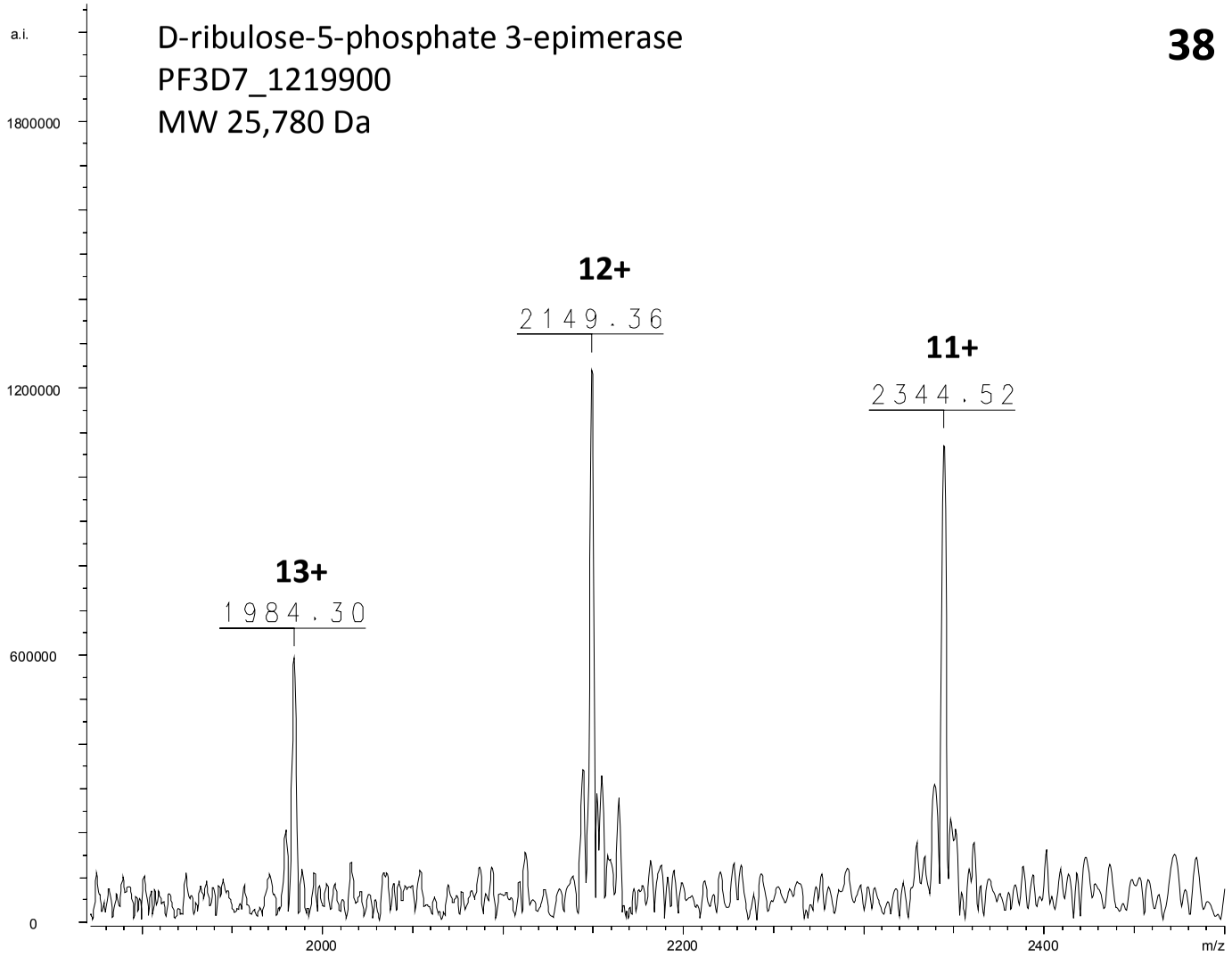
Ribose 5-phosphate isomerase
PF3D7_0514600
MW 27,072 Da

37



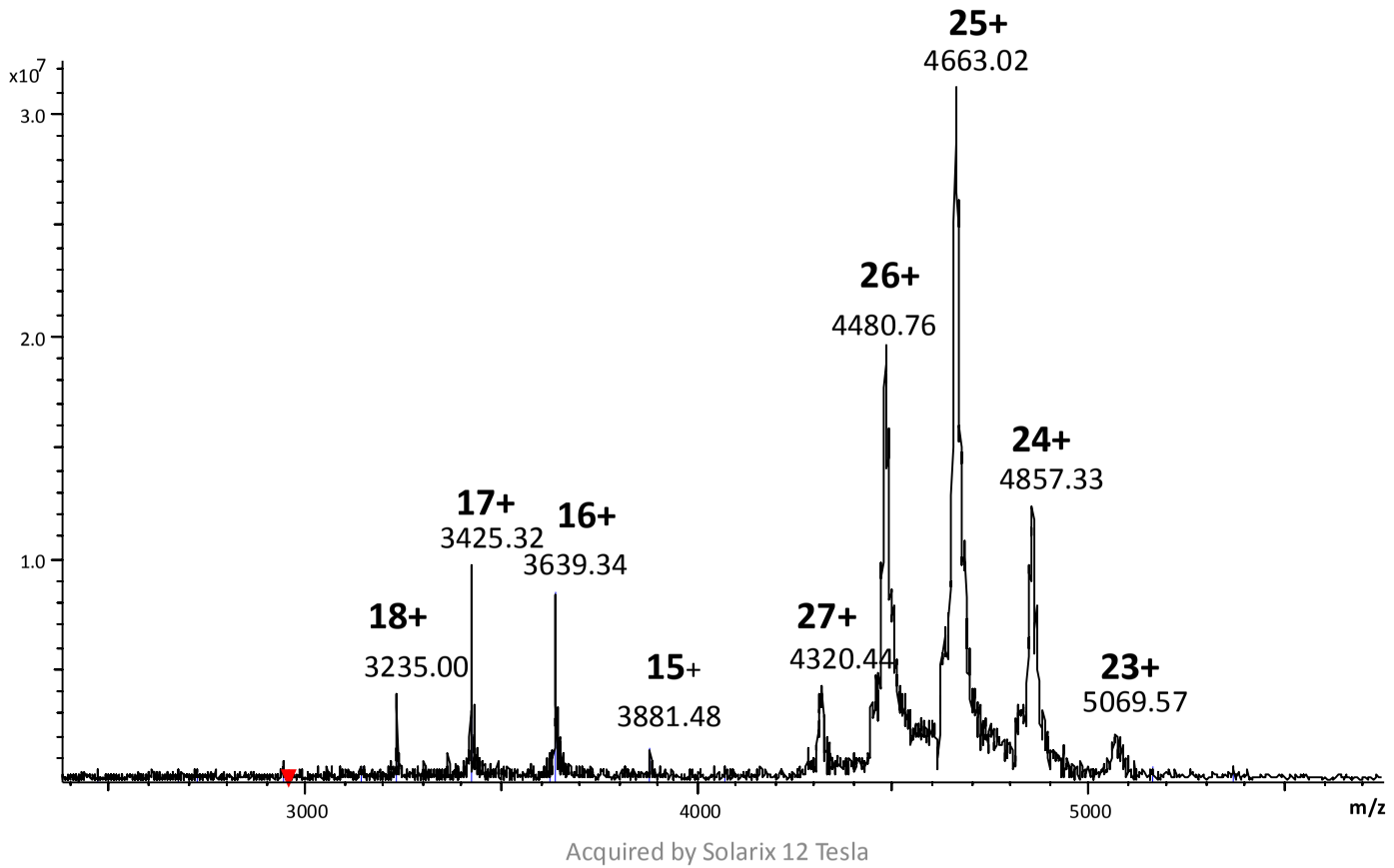
D-ribulose-5-phosphate 3-epimerase
PF3D7_1219900
MW 25,780 Da

38



Prolyl- tRNase
PF3D7_0925300
MW 58,213 Da/ 116,426 Da (dimer)

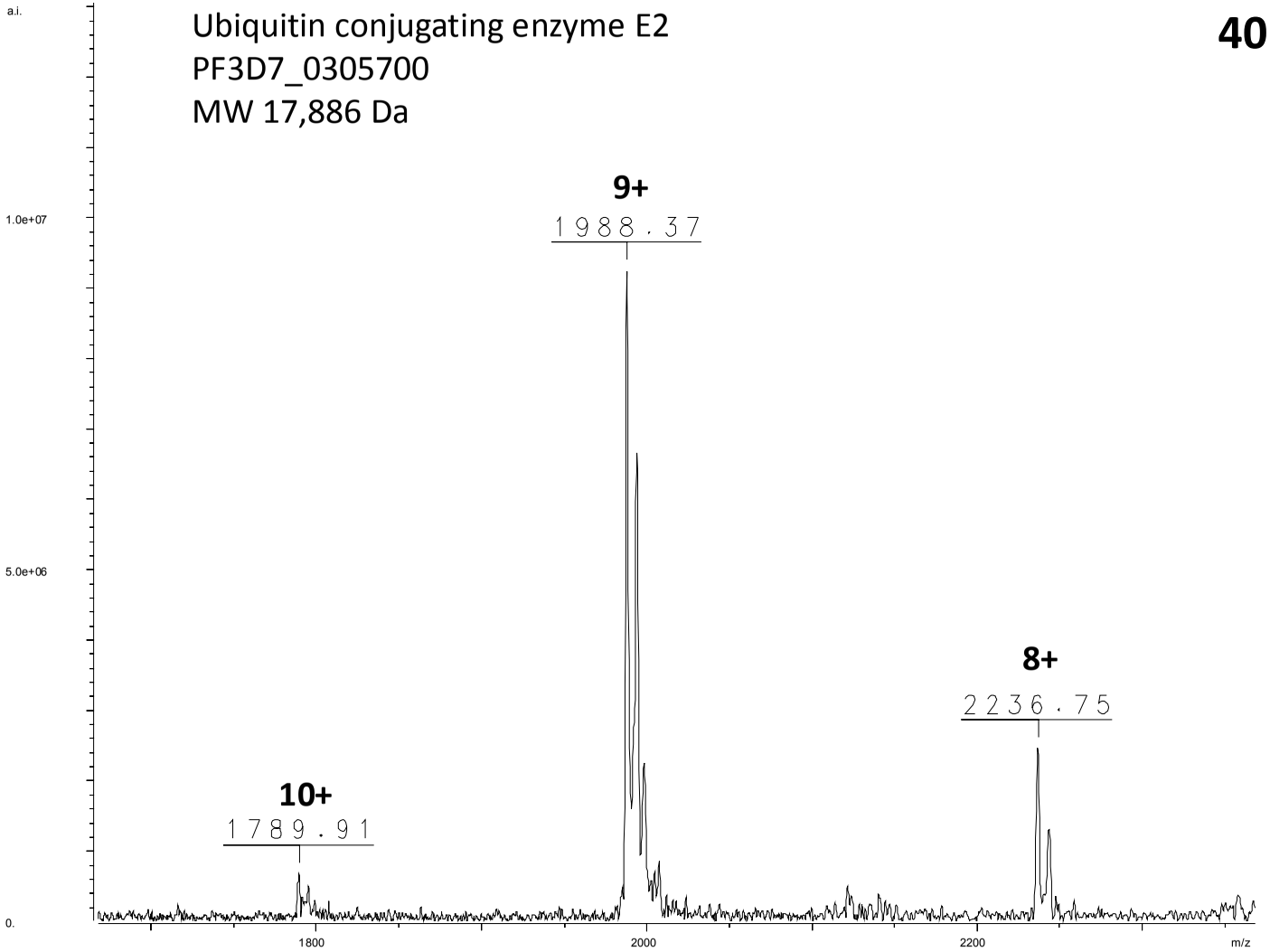
39



Acquired by Solarix 12 Tesla

Ubiquitin conjugating enzyme E2
PF3D7_0305700
MW 17,886 Da

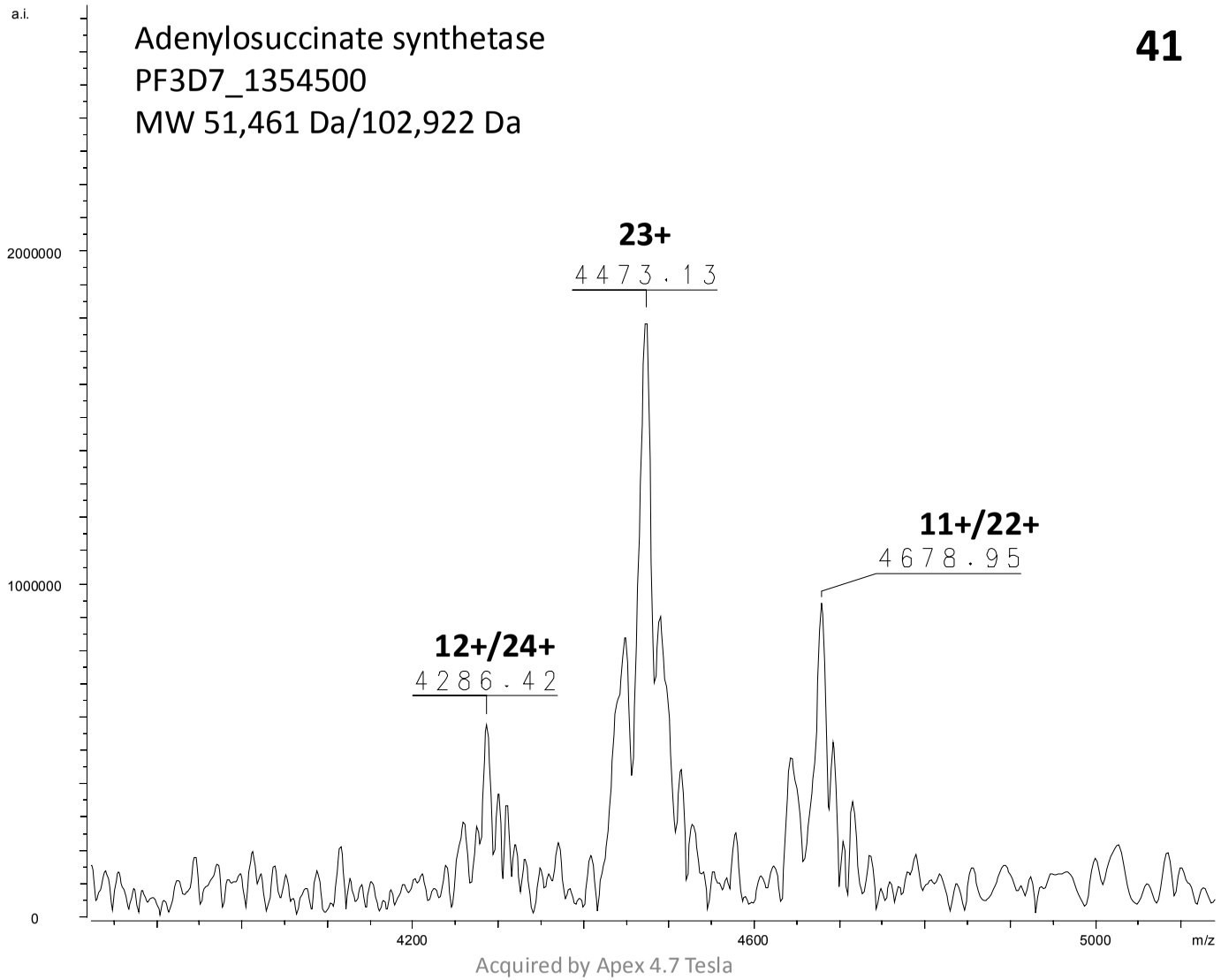
40



Acquired by Apex 4.7 Tesla

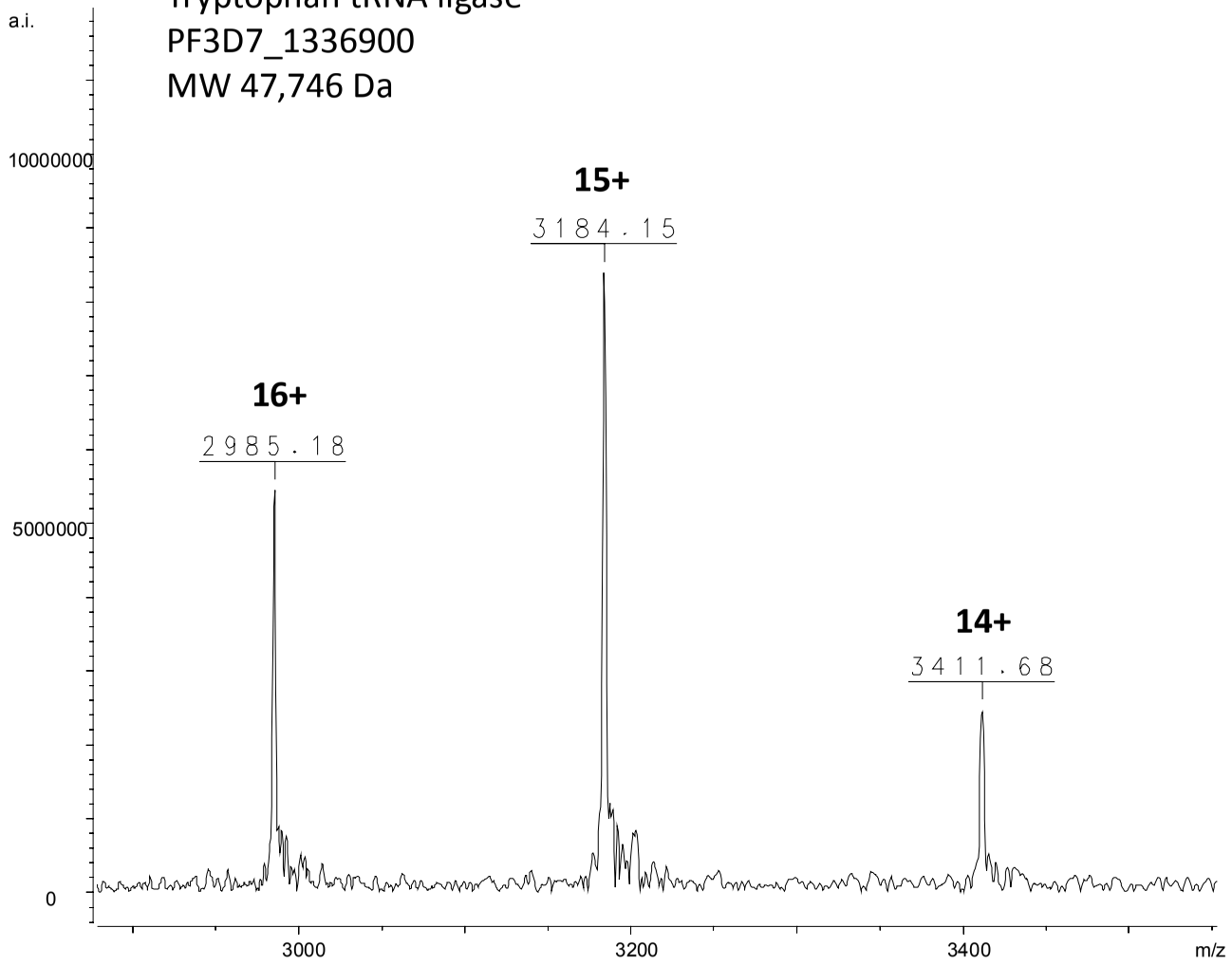
Adenylosuccinate synthetase
PF3D7_1354500
MW 51,461 Da/102,922 Da

41



Tryptophan tRNA ligase
PF3D7_1336900
MW 47,746 Da

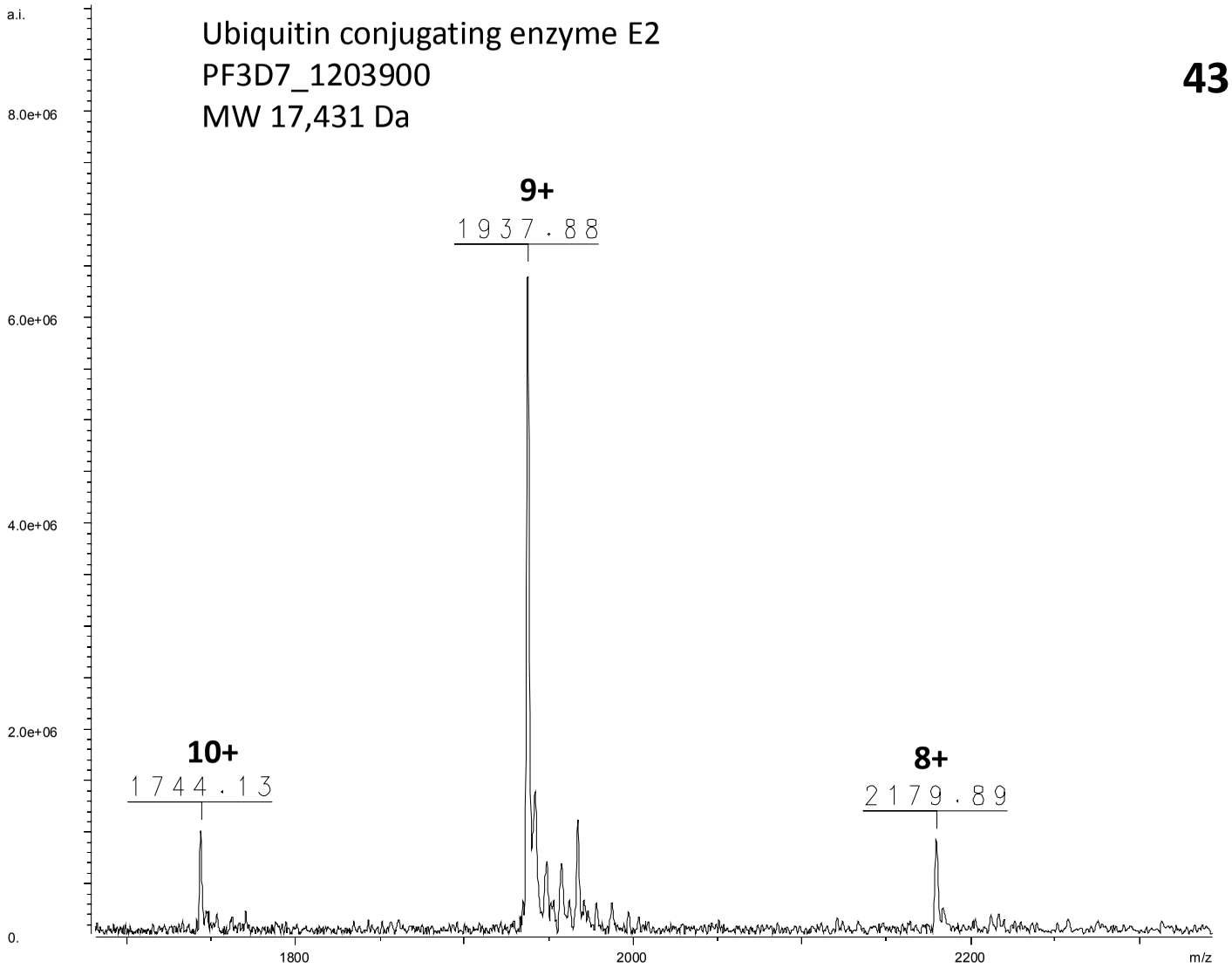
42



Acquired by Apex 4.7 Tesla

Ubiquitin conjugating enzyme E2
PF3D7_1203900
MW 17,431 Da

43



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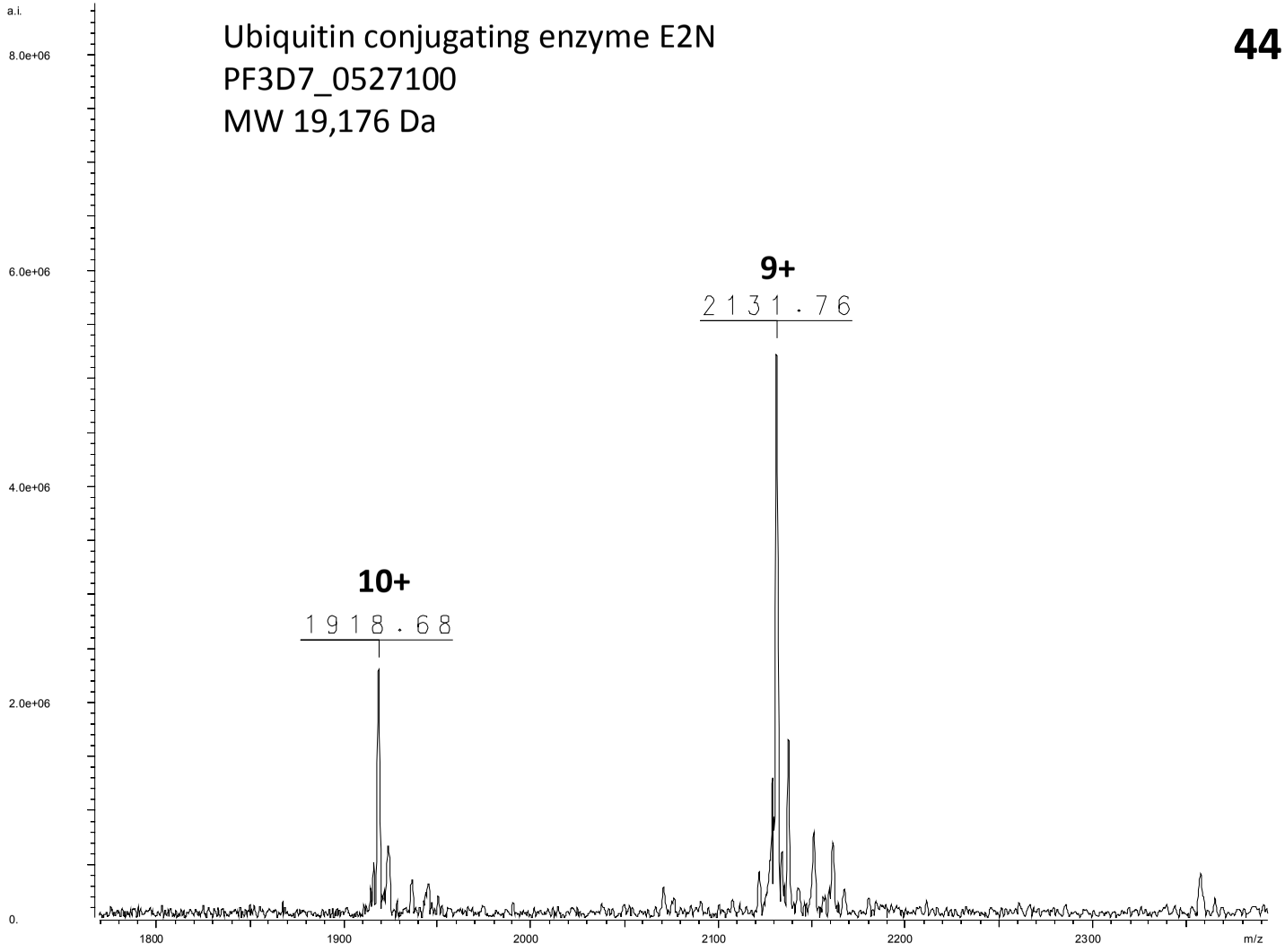
Ubiquitin conjugating enzyme E2N
PF3D7_0527100
MW 19,176 Da

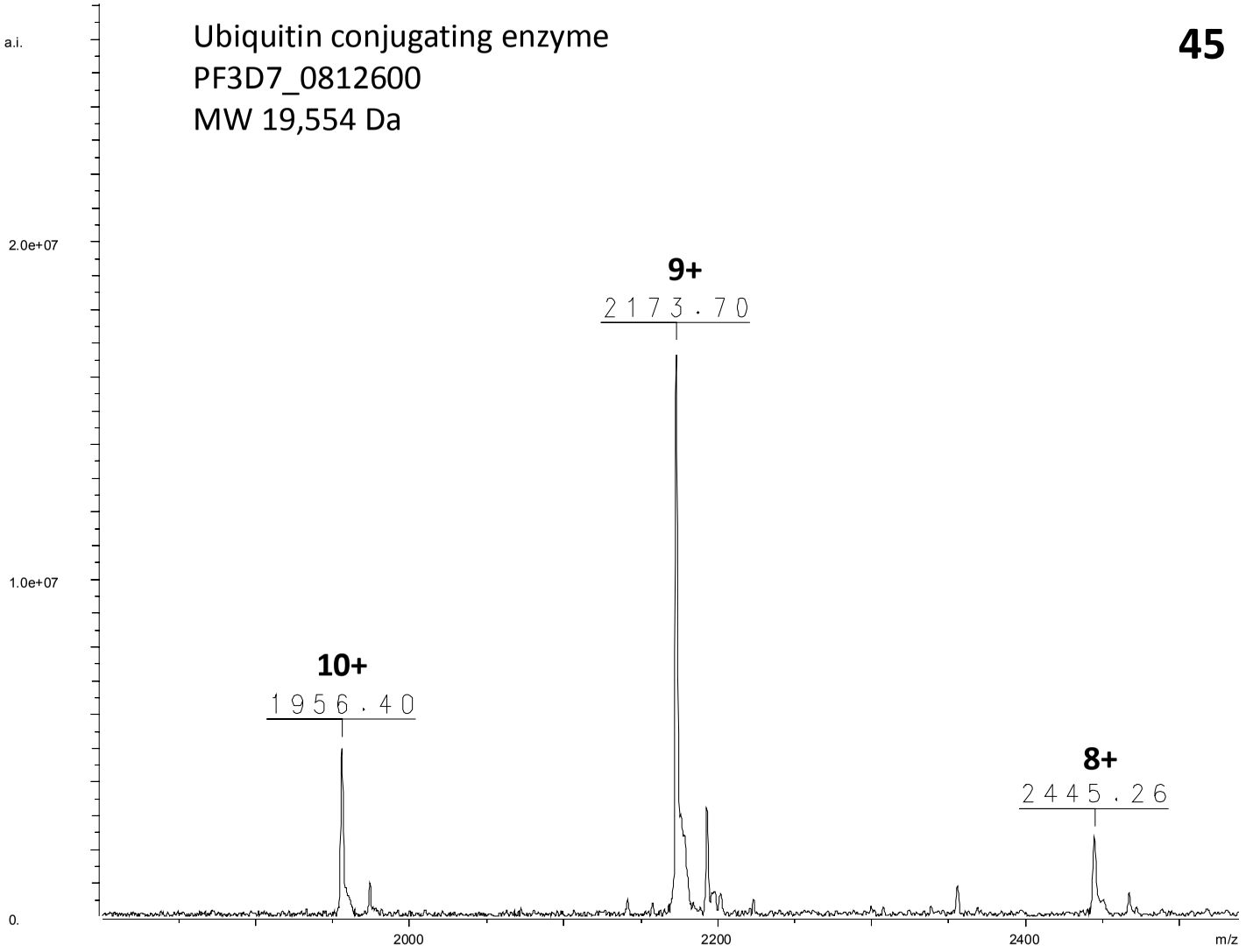
44



Acquired by Apex 4.7 Tesla

Ubiquitin conjugating enzyme
PF3D7_0812600
MW 19,554 Da

45



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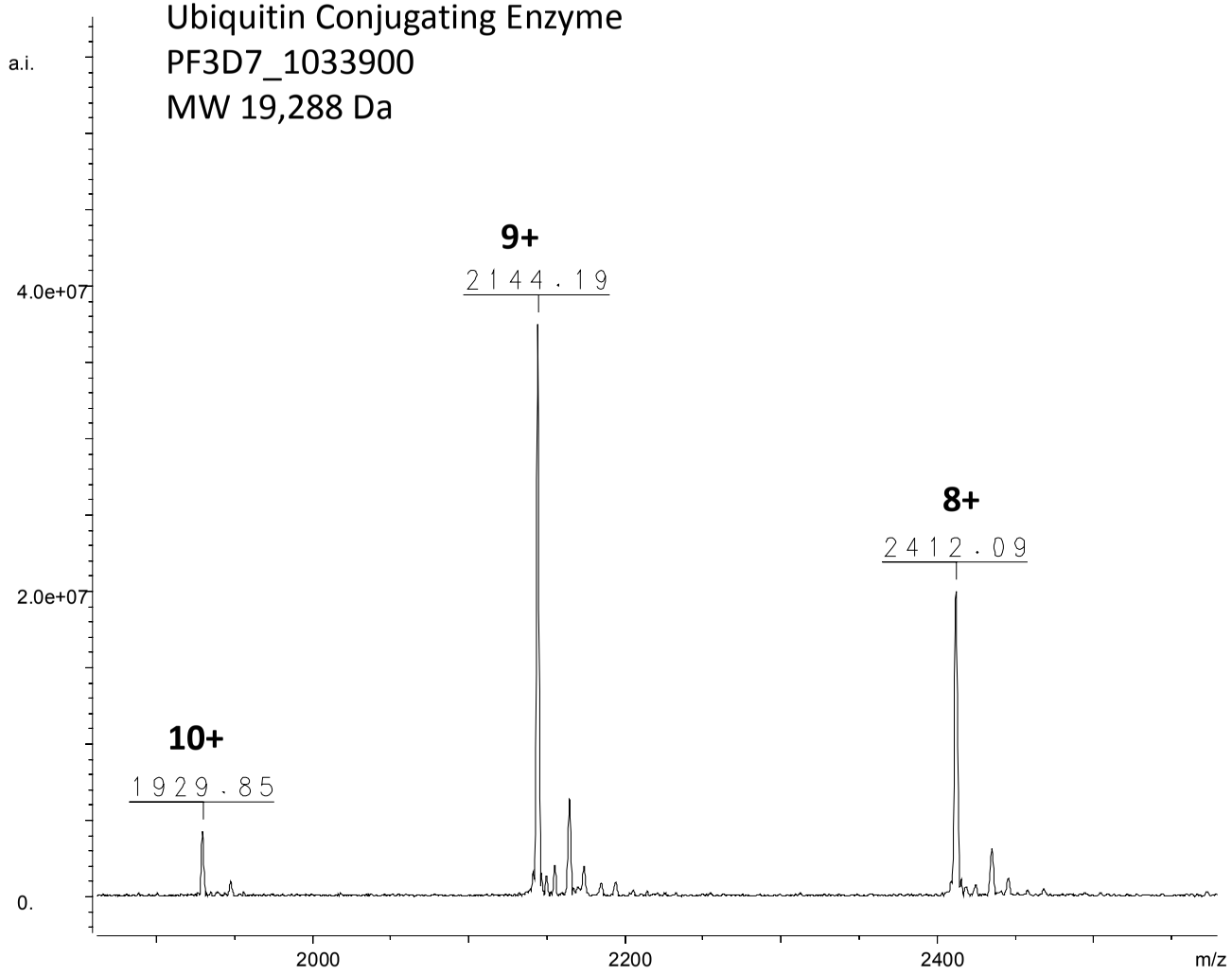
Ubiquitin Conjugating Enzyme
PF3D7_1033900
MW 19,288 Da

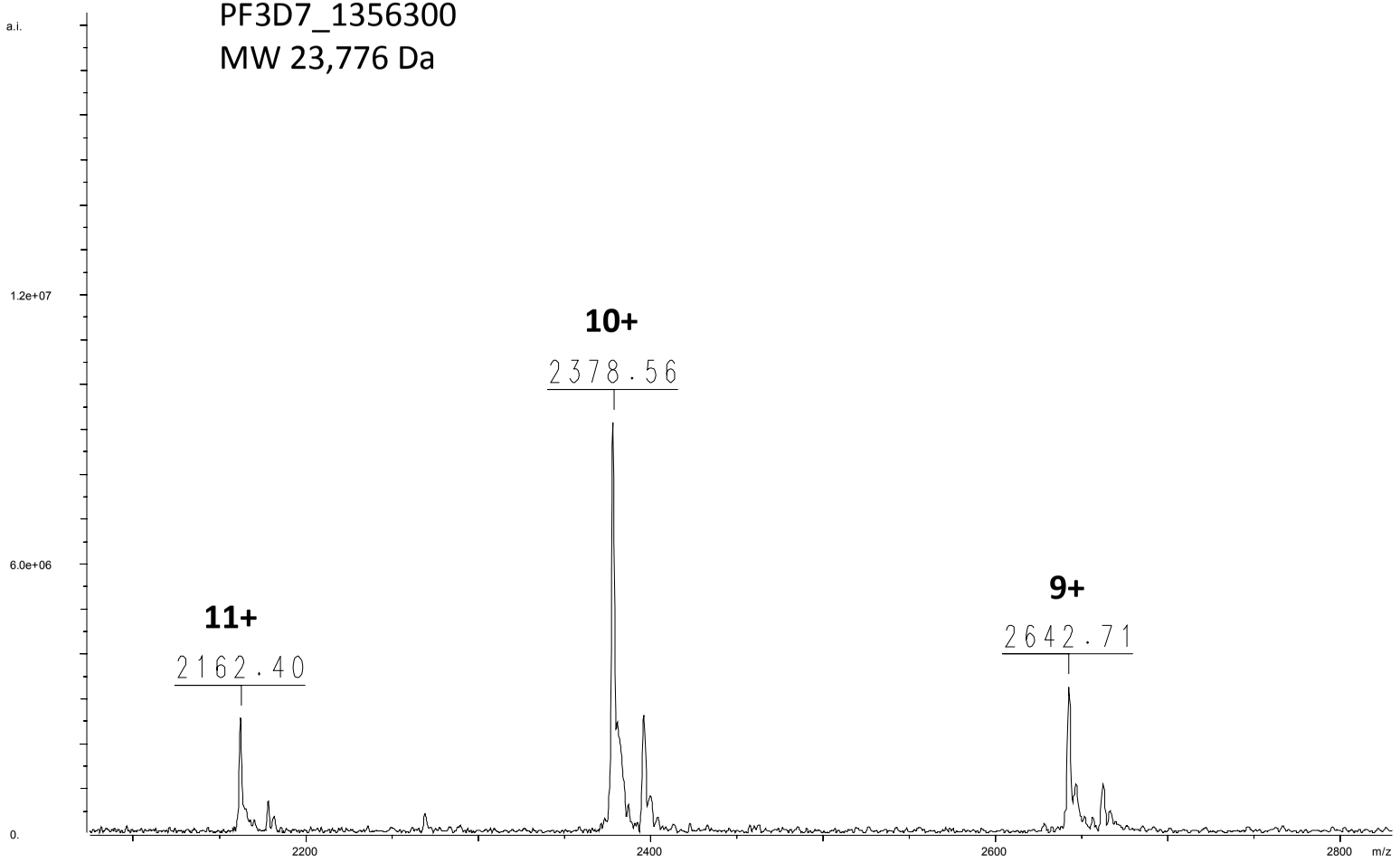
46



Acquired by Apex 4.7 Tesla

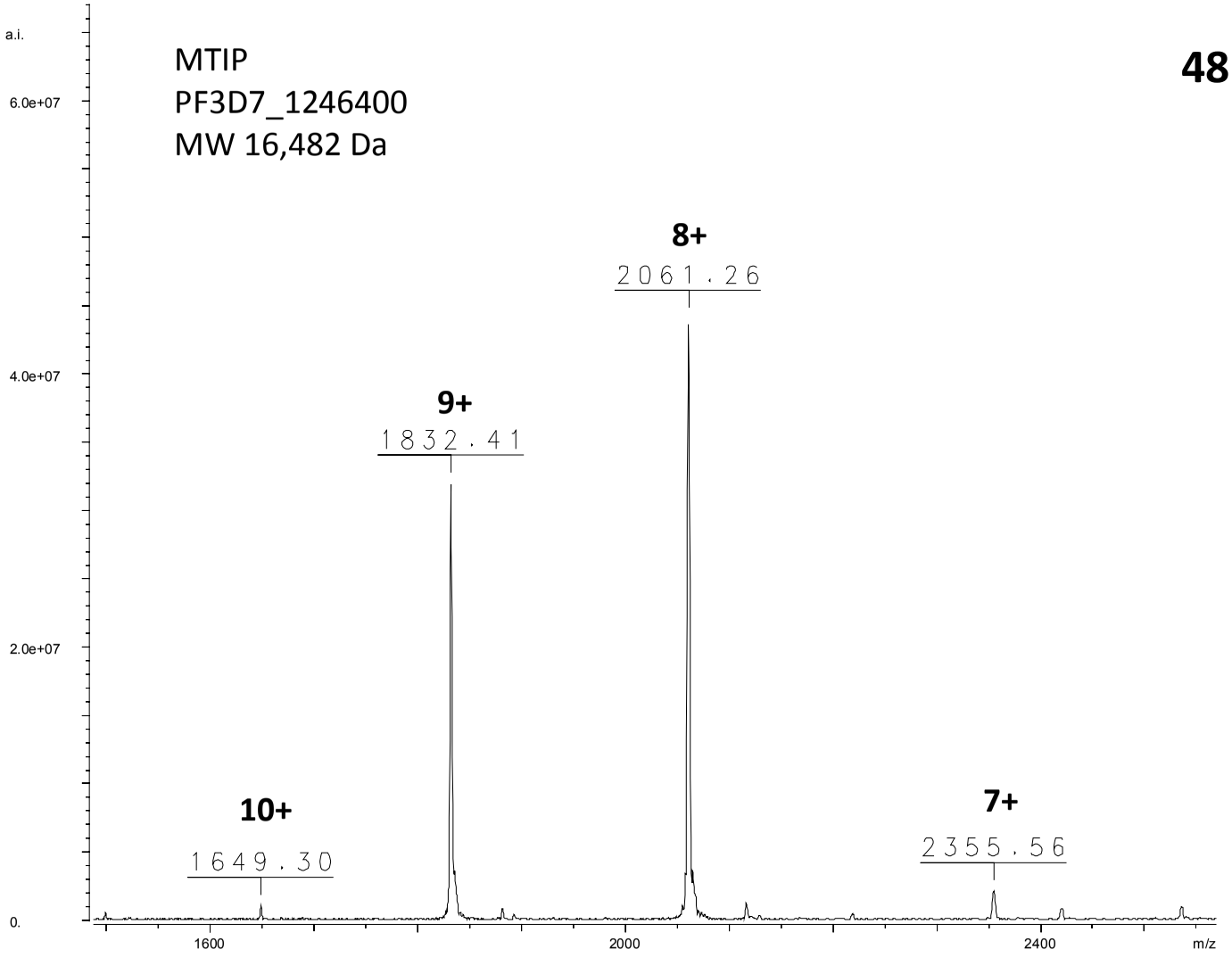
Ubiquitin conjugating enzyme
PF3D7_1356300
MW 23,776 Da

47



Acquired by Apex 4.7 Tesla

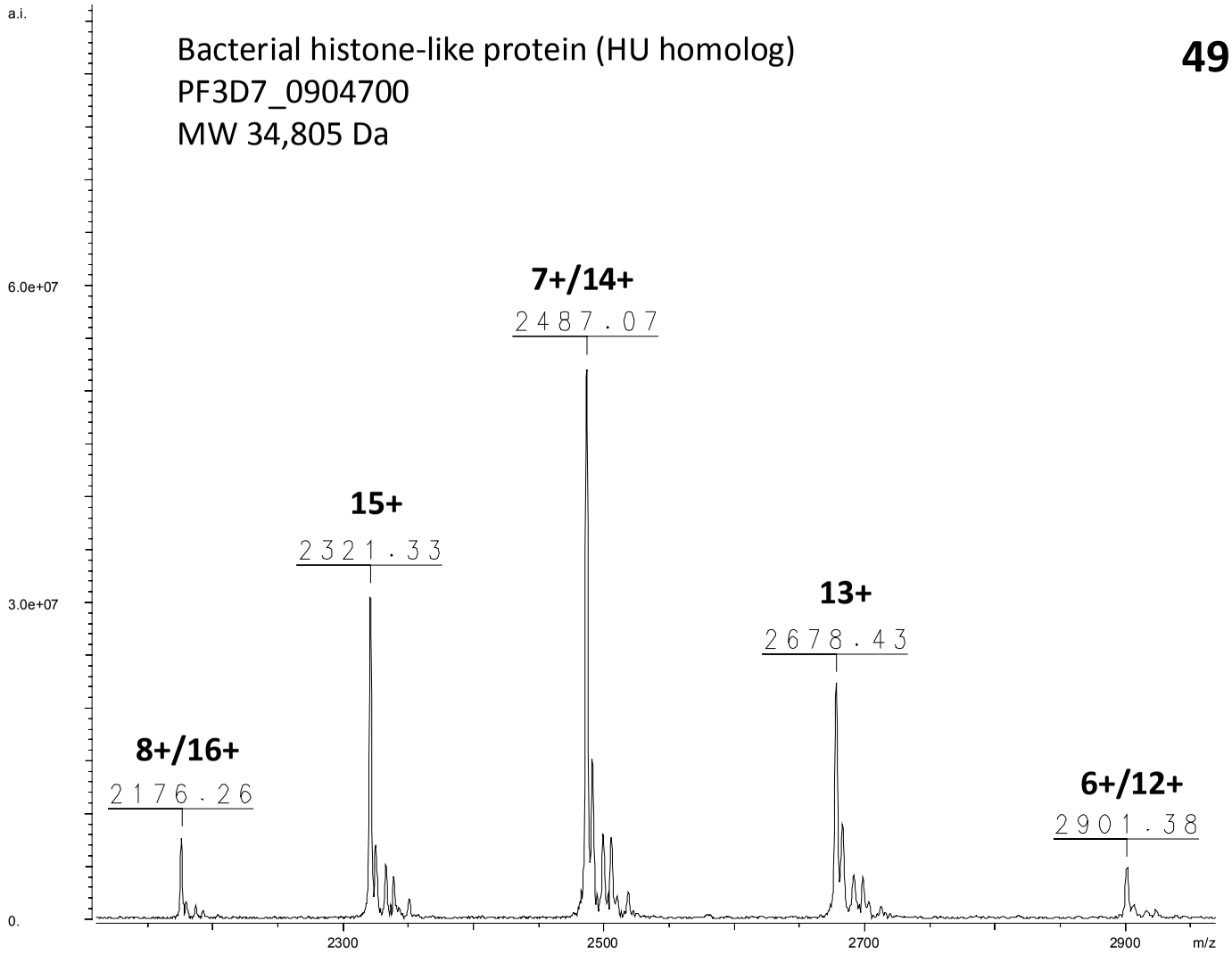
S60



Acquired by Apex 4.7 Tesla

Bacterial histone-like protein (HU homolog)
PF3D7_0904700
MW 34,805 Da

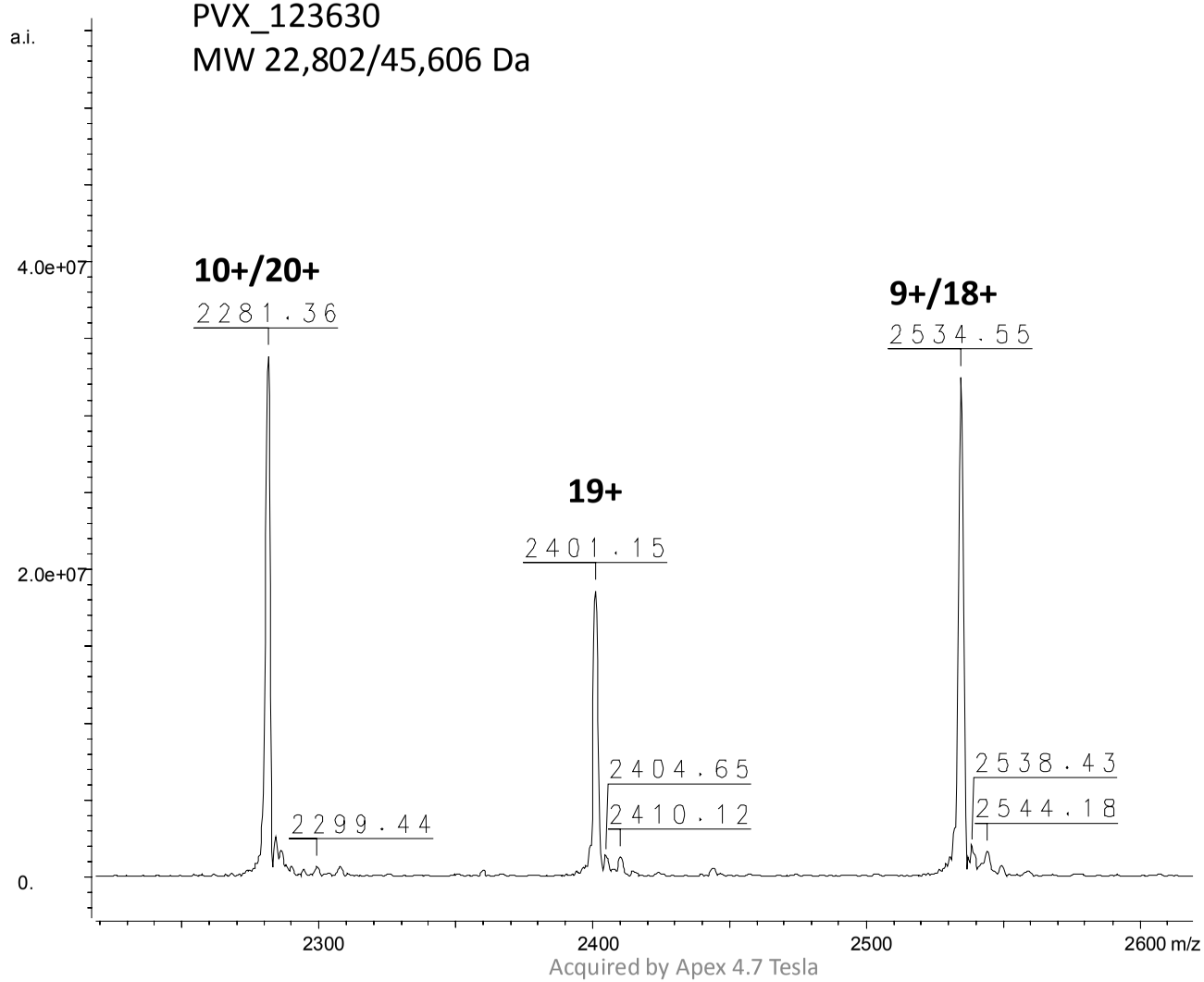
49



Acquired by Apex 4.7 Tesla

Phosphatidylethanolamine-binding protein
PVX_123630
MW 22,802/45,606 Da

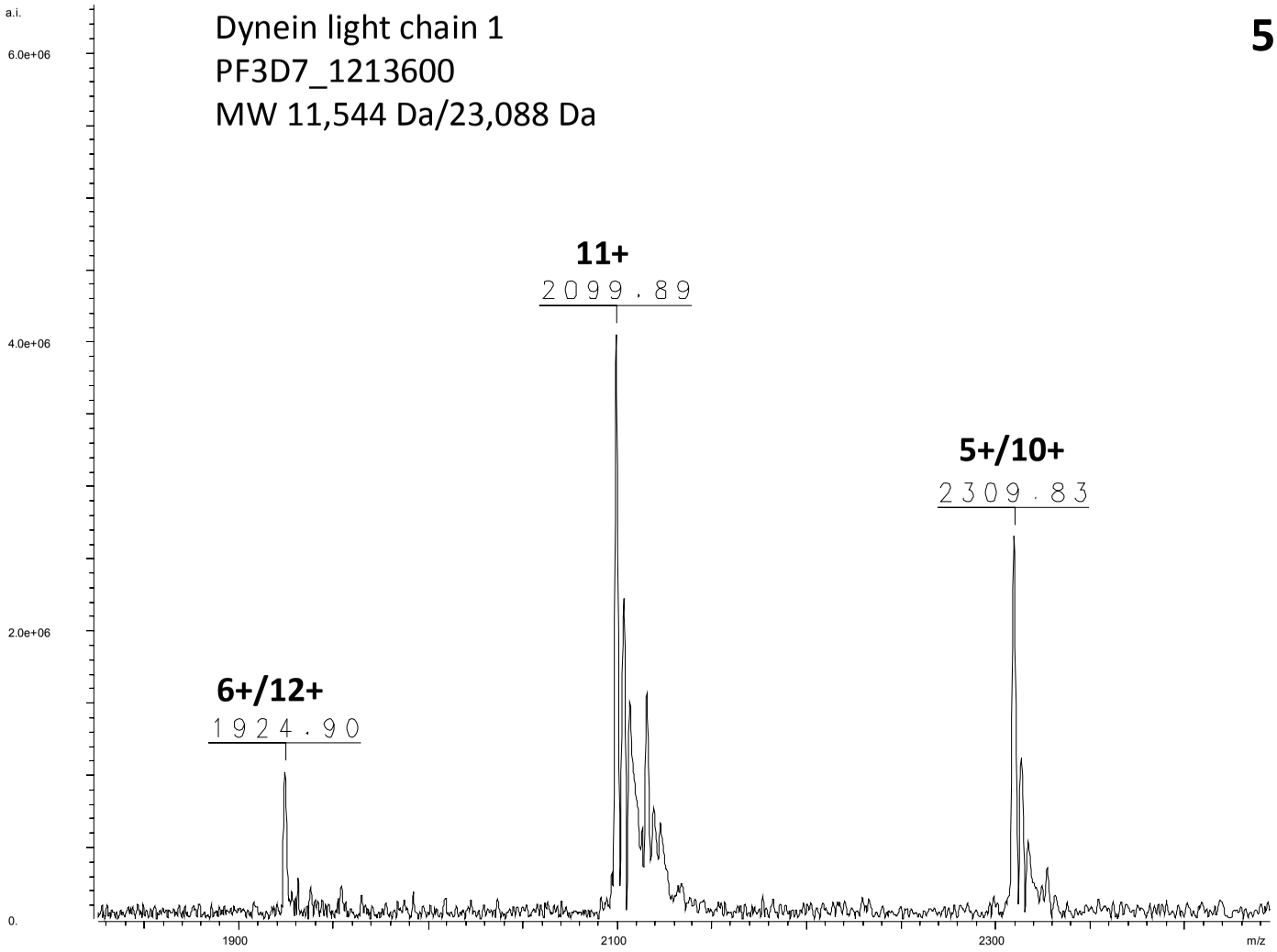
50



Acquired by Apex 4.7 Tesla

Dynein light chain 1
PF3D7_1213600
MW 11,544 Da/23,088 Da

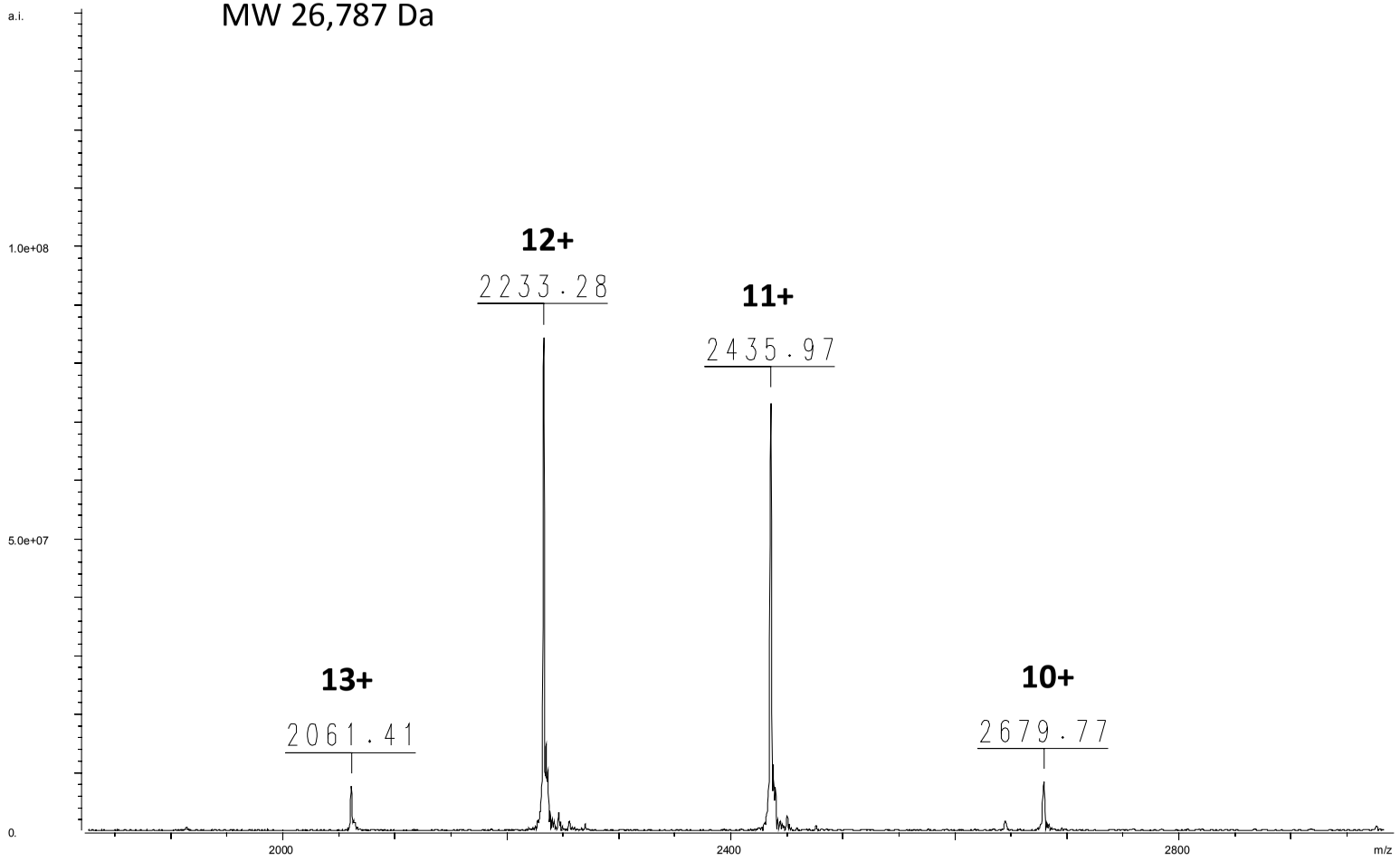
51



Acquired by Apex 4.7 Tesla

Circumsporozoite surface protein (CSP)
PF3D7_0304600
MW 26,787 Da

52

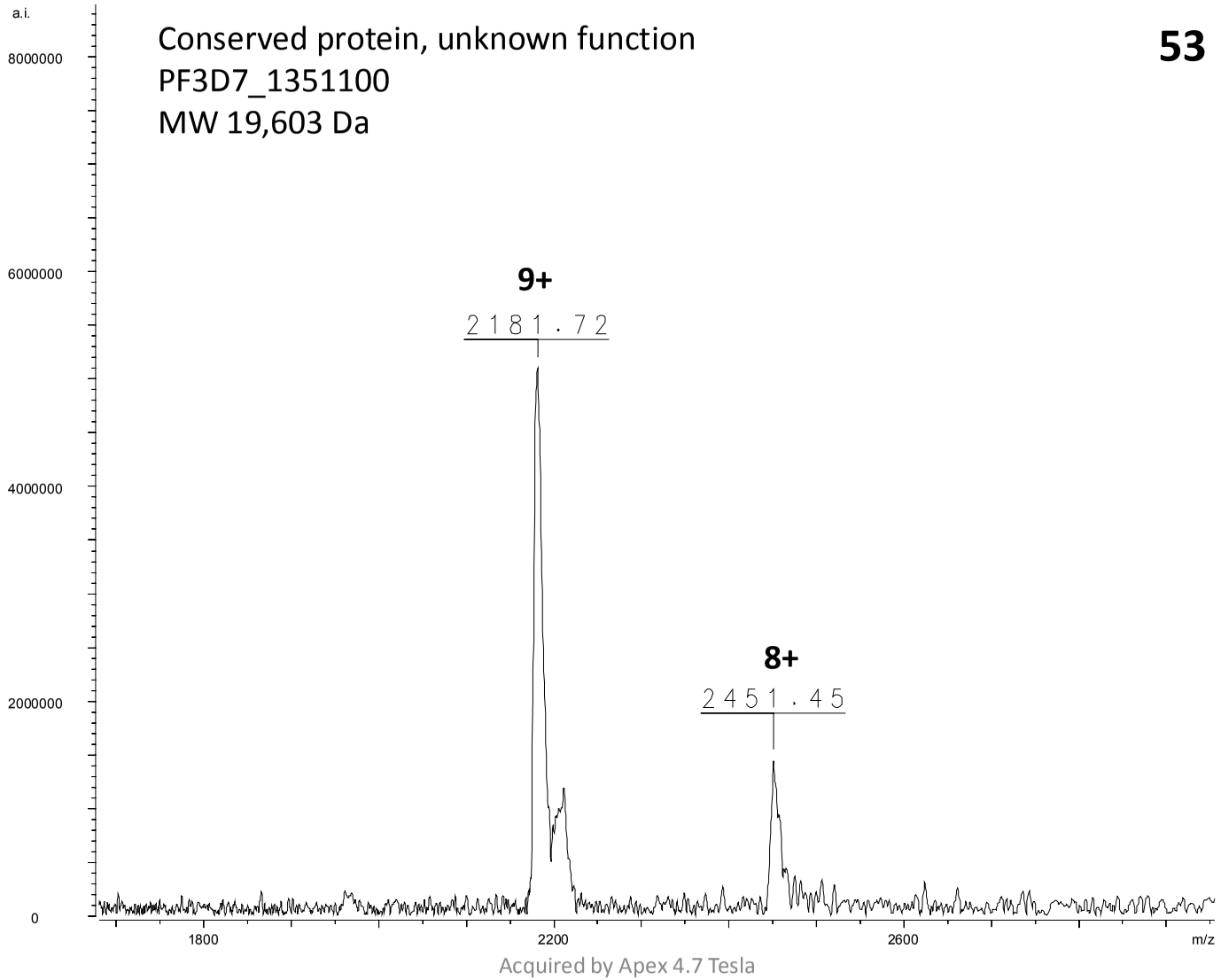


Acquired by Apex 4.7 Tesla

S65

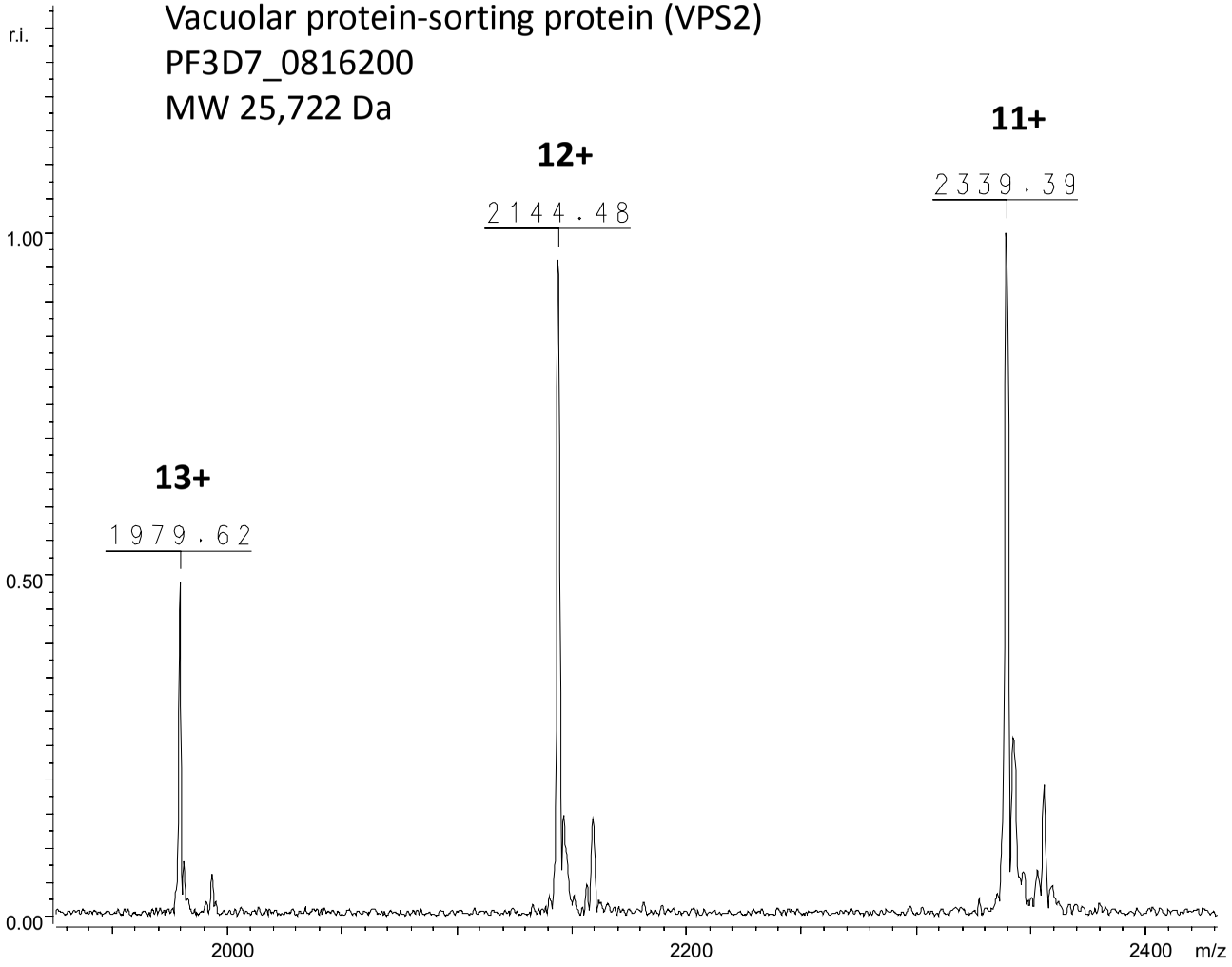
Conserved protein, unknown function
PF3D7_1351100
MW 19,603 Da

53



Vacuolar protein-sorting protein (VPS2)
PF3D7_0816200
MW 25,722 Da

54

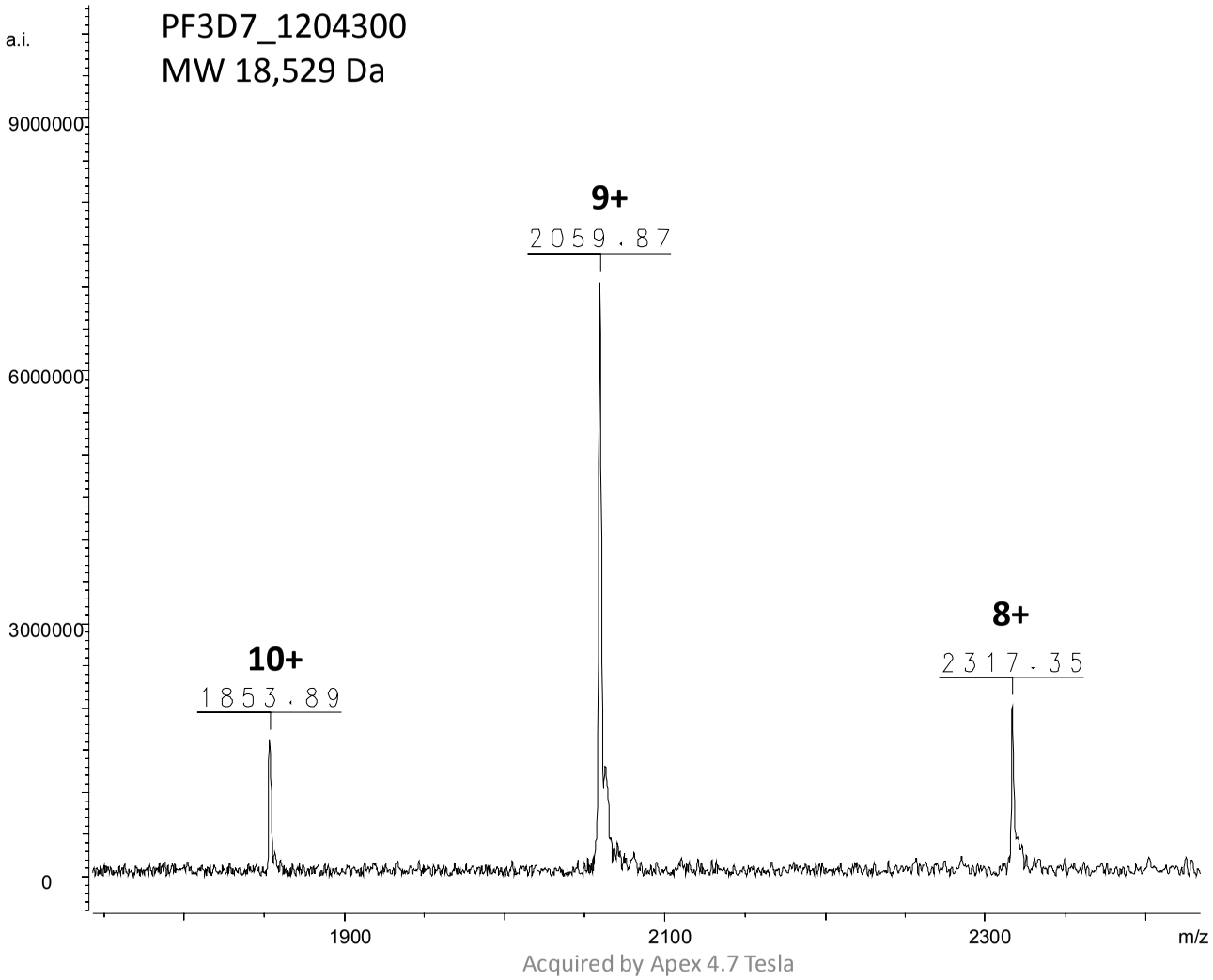


Acquired by Apex 4.7 Tesla

S67

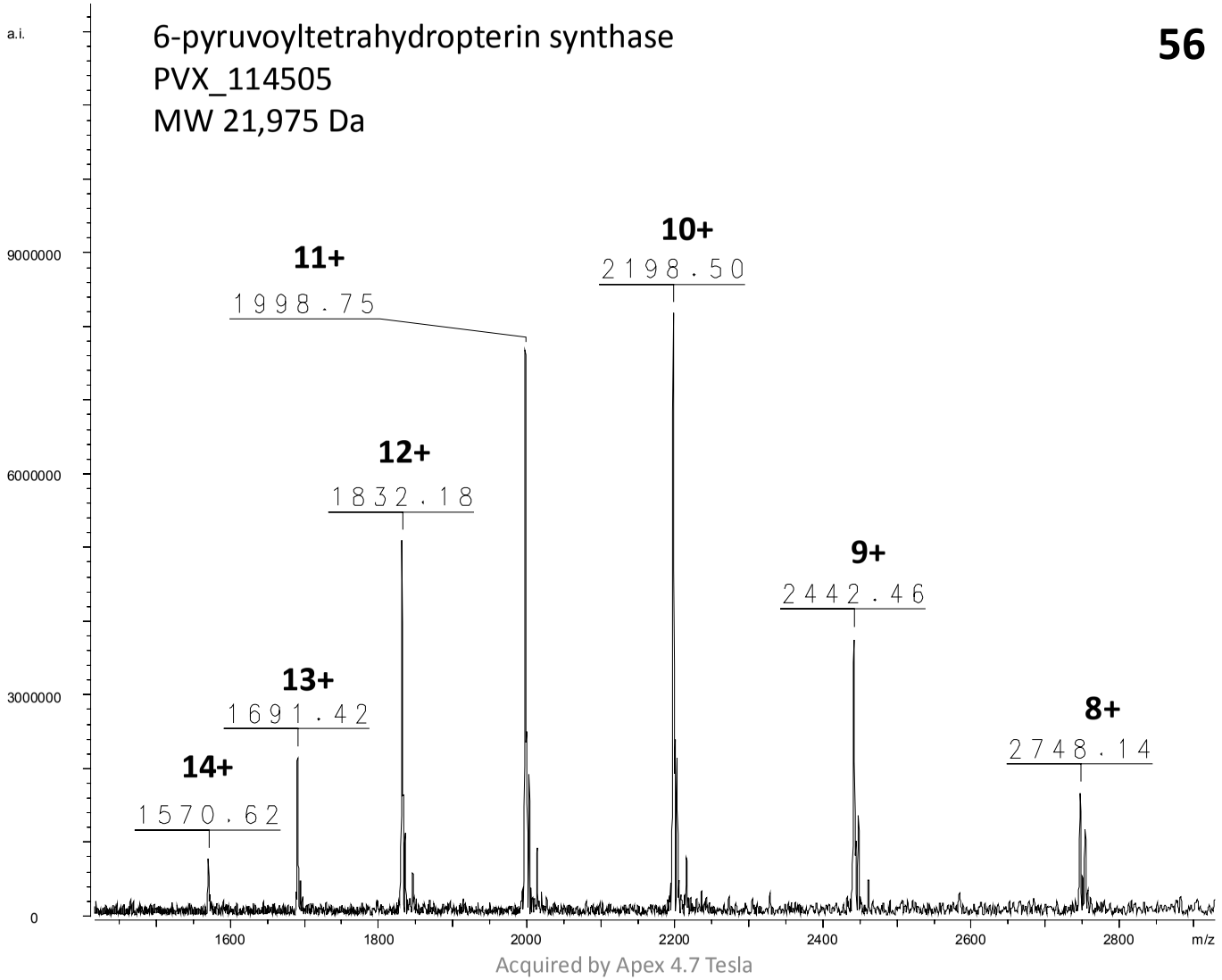
Eukaryotic translation initiation factor 5A (eIF5a)
PF3D7_1204300
MW 18,529 Da

55



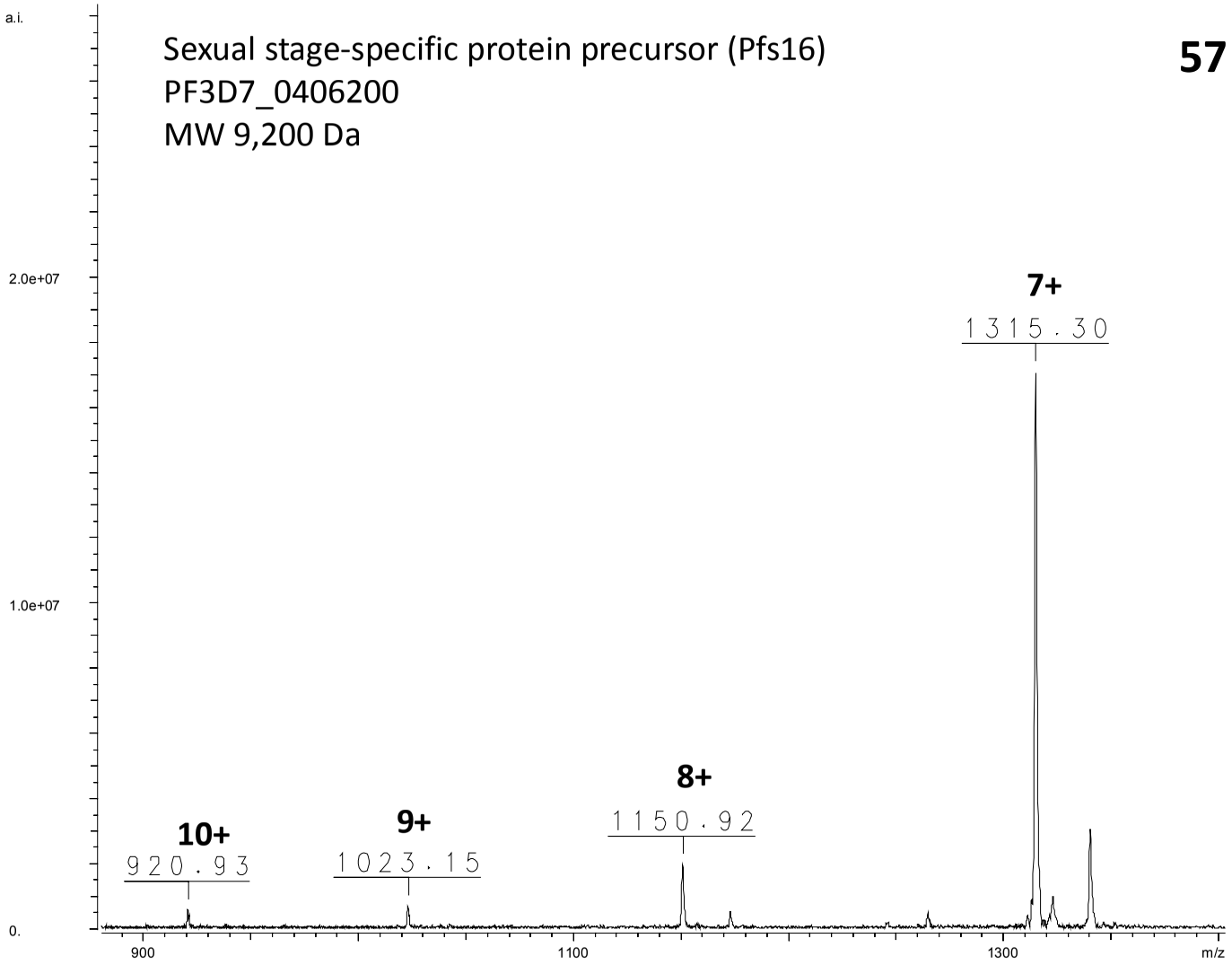
6-pyruvoyltetrahydropterin synthase
PVX_114505
MW 21,975 Da

56



Sexual stage-specific protein precursor (Pfs16)
PF3D7_0406200
MW 9,200 Da

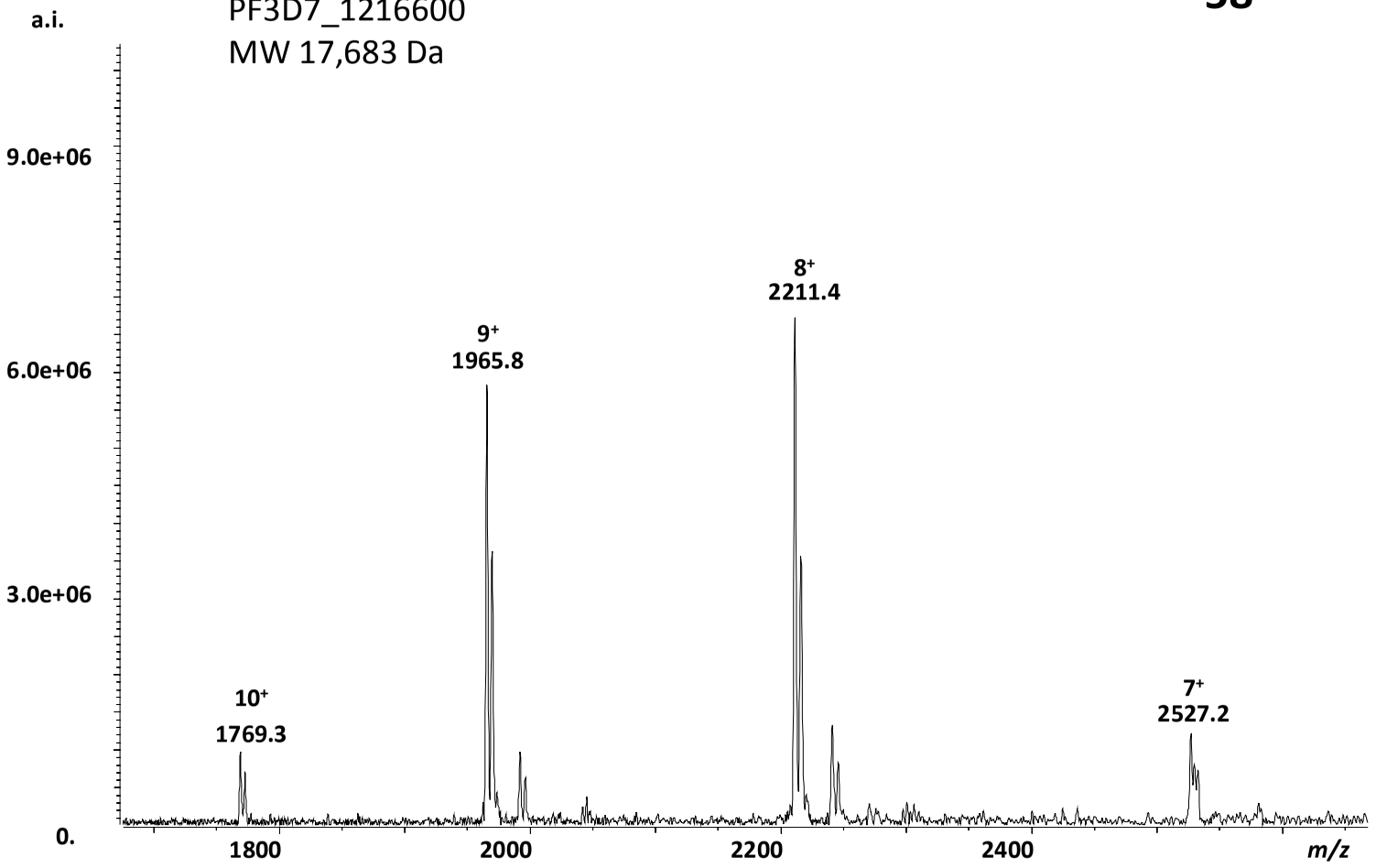
57



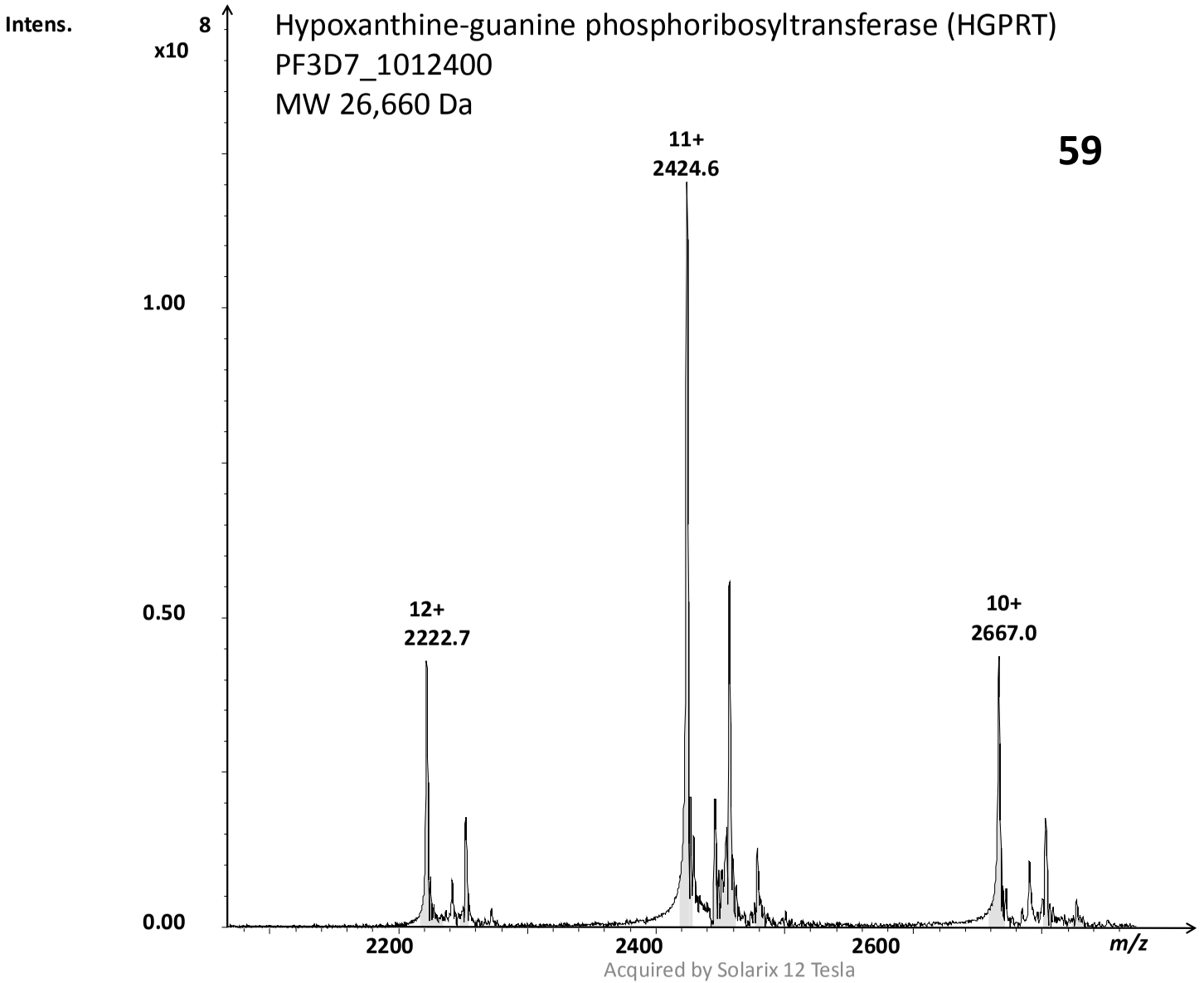
Acquired by Apex 4.7 Tesla

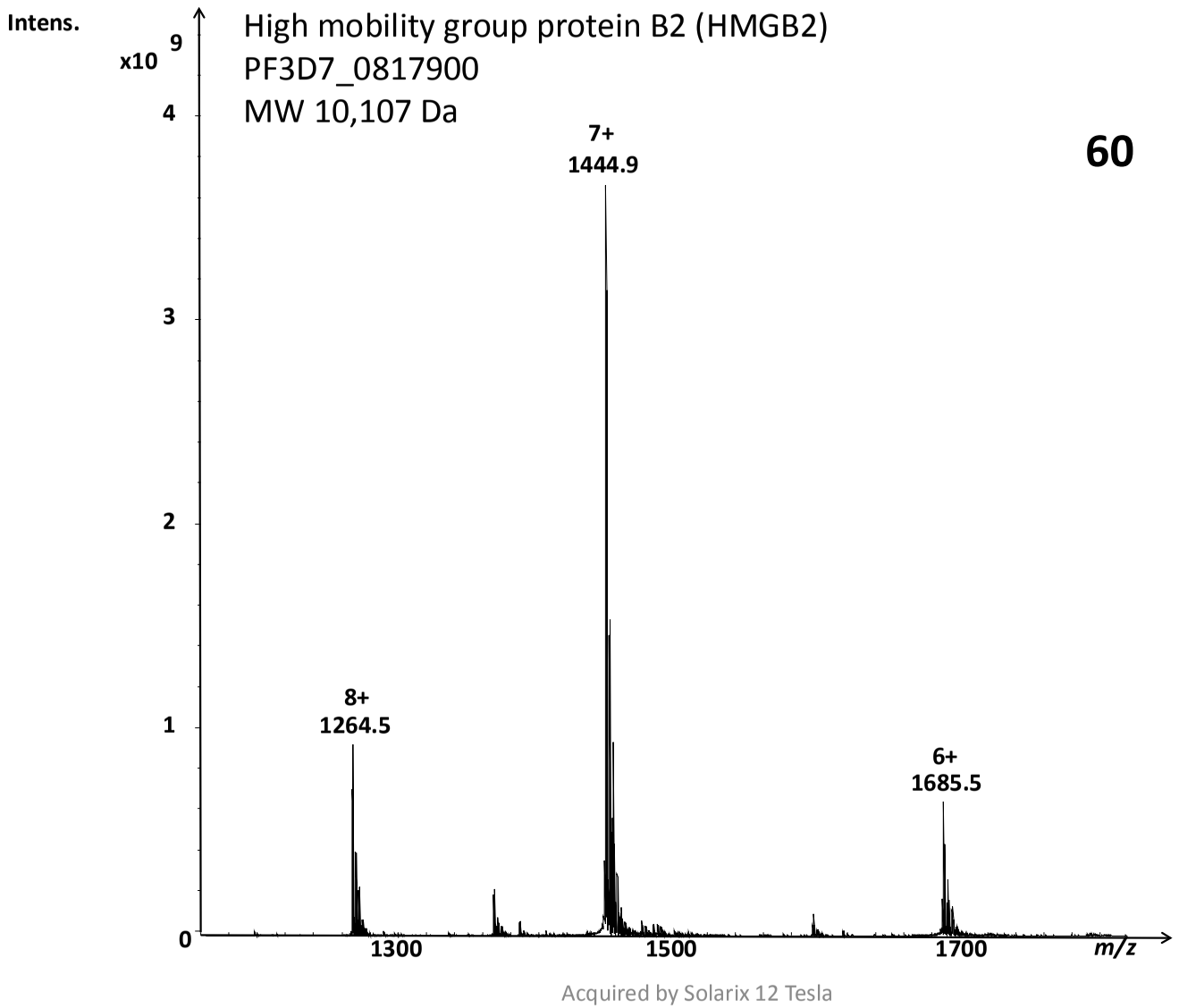
Cell traversal protein for ookinetes and sporozoites (CelTOS)
PF3D7_1216600
MW 17,683 Da

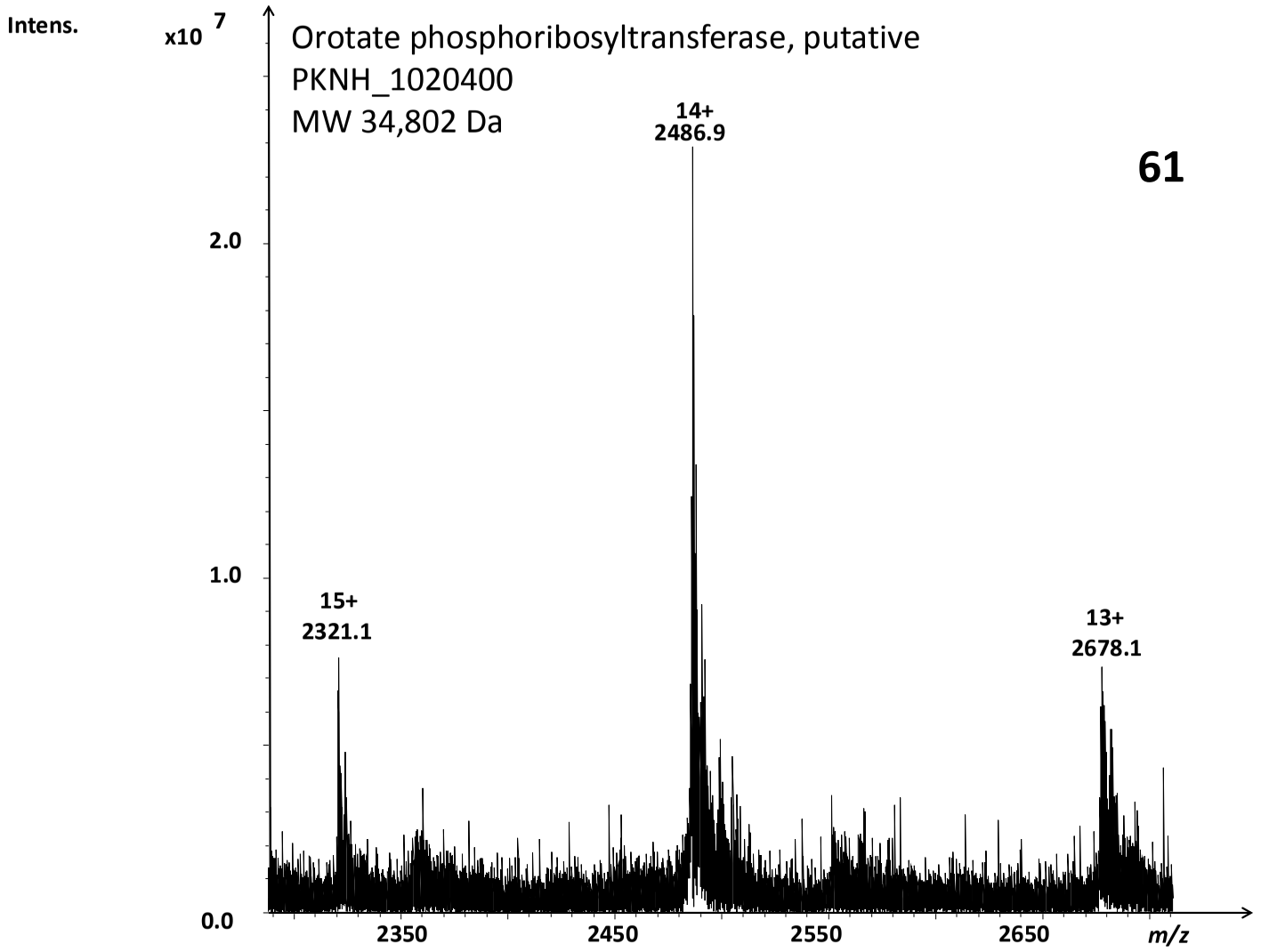
58



Acquired by Solarix 12 Tesla


Intens.
8
x10
1.00
0.50
0.00
Hypoxanthine-guanine phosphoribosyltransferase (HGPRT)
PF3D7_1012400
MW 26,660 Da
59
11+
2424.6
12+
2222.7
10+
2667.0
2200
2400
2600
m/z
Acquired by Solarix 12 Tesla


Intens.
x10 9
4
3
2
1
0
High mobility group protein B2 (HMGB2)
PF3D7_0817900
MW 10,107 Da
60
7+
1444.9
8+
1264.5
6+
1685.5
1300
1500
1700
m/z
Acquired by Solarix 12 Tesla



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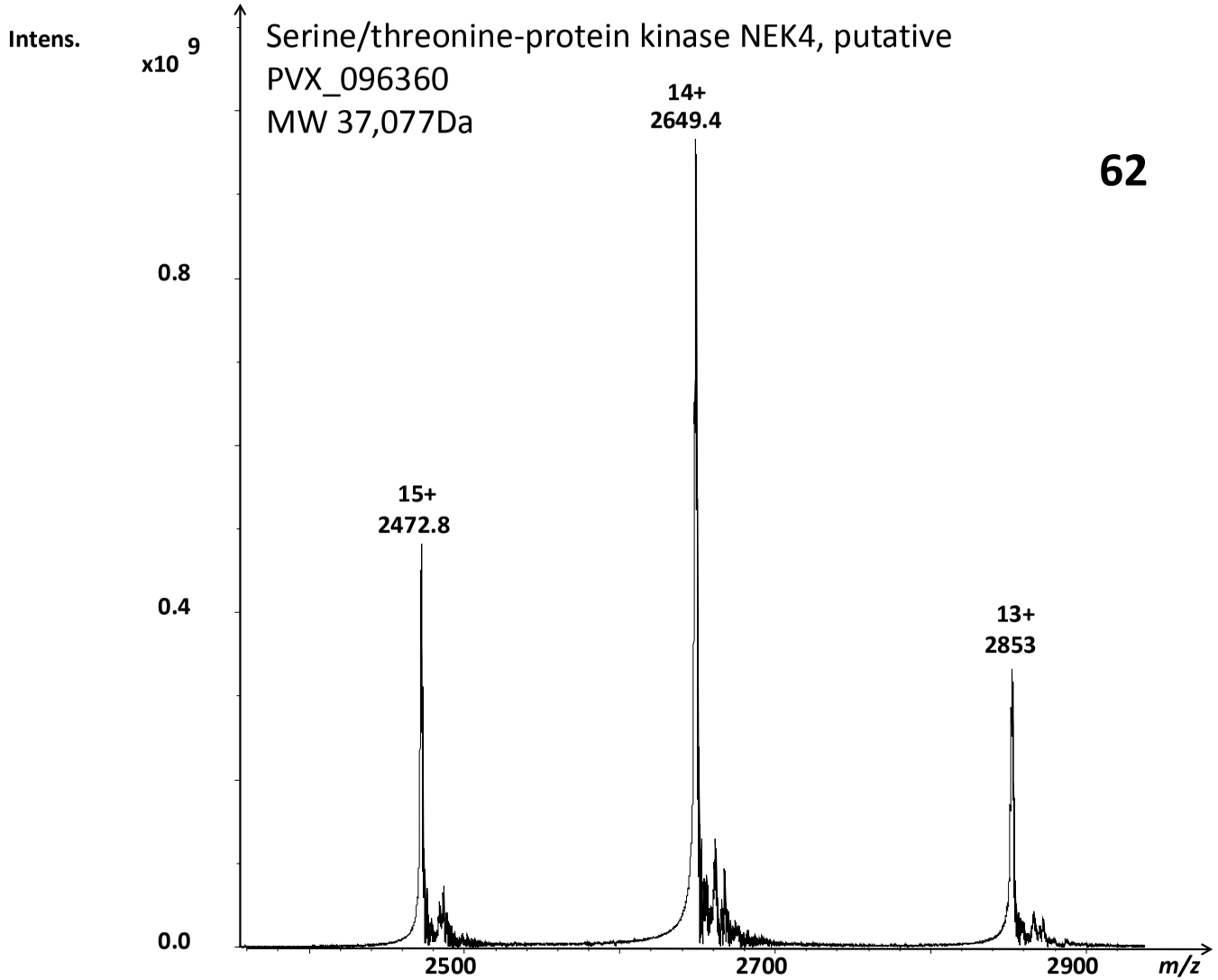

Acquired by Solarix 12 Tesla

REFERENCES

1. R. (2013) A Language and Environment for Statistical Computing, R Foundation for Statistical Computing: Vienna, Austria, 2013. http://www.R-project.org/.
2. Chen, H., and Boutros, P. C. (2011) VennDiagram: a package for the generation of highly-customizable Venn and Euler diagrams in R. *BMC Bioinformatics 12*, 35. DOI: 10.1186/1471-2105-12-35.
3. Wurst, M., Prikryl, Z., and Vokoun, J. (1984) High-performance liquid-chromatography of plant hormones: II. determination of plant hormones of the indole type. *J. Chromatogr. A 286*, 237-245. DOI: 10.1016/S0021-9673(01)99191-5.
4. Hohenschutz, L. D., Bell, E. A., Jewess, P. J., Leworthy, D. P., Pryce, R. J., Arnold, E., and Clardy, J. (1981) Castanospermine, a 1,6,7,8-tetrahydroxyoctahydroindolizine alkaloid, from seeds of *Castanospermum australe*. *Phytochemistry 20*, 811-814. DOI: 10.1016/0031-9422(81)85181-3.
5. Birkinshaw, J. H., Michael, S. E., Bracken, A., and Raistrick, H. (1943) Patulin in the common cold. Collaborative research on a derivative of *Penicillium patulum* Bainier. II. biochemistry and chemistry. *Lancet 242*, 625-630. DOI: 10.1016/S0140-6736(00)88176-3.
6. Pinhey, J. T., and Sternhell, S. (1965) Structure of α-hydroxysantonin and some aspects of the stereochemistry of related eudesmanolides and guaianolides. *Aust. J. Chem. 18*, 543-557. DOI: 0.1071/ch9650543.
7. Endres, H. (1959) Constitution of the coloring matter of spruce bark, a new class of condensable tannin. *Qualitas Plantarum et Materiae Vegetabiles 5*, 367-374.
8. Grassmann, W., and Endres, H. (1965) The constitution of piceatannol. Comment on a paper by Cunningham, Haslam, and Haworth. *J. Chem. Soc.*, 4579. DOI: 10.1039/jr9650004579.
9. Nakajima, K., Taguchi, H., Endo, T., and Yosioka, I. (1978) The constituents of *Scirpus fluviatilis* (Torr.) A. Gray. I. the structures of two new hydroxystilbene dimers, scirpusin A and B. *Chem. Pharm. Bull. 26*, 3050-3057. DOI: 10.1248/cpb.26.3050.
10. Martin, D. G., Duchamp, D. J., and Chidester, C. G. (1973) Isolation, structure, and absolute configuration of U-42,126 a novel antitumor antibiotic. *Tetrahedron Lett.*, 2549-2552. DOI: 10.1016/s0040-4039(01)96202-1.
11. Clark, B. R., Capon, R. J., Lacey, E., Tennant, S., and Gill, J. H. (2006) Citrinin revisited: from monomers to dimers and beyond. *Org. Biomol. Chem. 4*, 1520-1528. DOI: 10.1039/b600960c.
12. Frenzel, M., and Dettner, K. (1994) Quantification of cantharidin in *Canthariphilous ceratopogonidae* (Diptera), Anthomyiidae (Diptera) and cantharidin-producing Oedemeridae (Coleoptera). *J. Chem. Ecol. 20*, 1795-1812. DOI: 10.1007/Bf02066223.
13. Govindachari, T. R., Joshi, B. S., and Kamat, V. N. (1965) Structure of parthenolide. *Tetrahedron 21*, 1509-1519. DOI: 10.1016/s0040-4020(01)98314-0.
14. Heptinstall, S., Awang, D. V. C., Dawson, B. A., Kindack, D., Knight, D. W., and May, J. (1992) Parthenolide content and bioactivity of feverfew (*Tanacetum parthenium* (L.) Schultz-Bip). Estimation of commercial and authenticated feverfew products. *J. Pharm. Pharmacol. 44*, 391-395. DOI: 10.1111/j.2042-7158.1992.tb03631.x.
15. Hendriks, H., Anderson-Wildeboer, Y., Engels, G., Bos, R., and Woerdenbag, H. J. (1997) The content of parthenolide and its yield per plant during the growth of *Tanacetum parthenium*. *Planta Med. 63*, 356-359. DOI: 10.1055/s-2006-957700.
16. Yoshimura, H. V., Z.; Wiesner, K. (1960) A rigorous proof of the selegaine structure. *Tetrahedron Lett. 1*, 14-17. DOI: 10.1016/S0040-4039(01)99306-2.

17. Liu, J. S., Zhu, Y. L., Yu, C. M., Zhou, Y. Z., Han, Y. Y., Wu, F. W., and Qi, B. F. (1986) The structures of huperzine A and B, two new alkaloids exhibiting marked anticholinesterase activity. *Can. J. Chem. 64*, 837-839. DOI: 10.1139/v86-137.
18. Nishikawa, M., Tsurumi, Y., Namiki, T., Yoshida, K., and Okuhara, M. (1987) Studies on WF-3681, a novel aldose reductase inhibitor. I. Taxonomy, fermentation, isolation and characterization. *J. Antibiot. (Tokyo). 40*, 1394-1399. DOI: 10.7164/antibiotics.40.1394.
19. Reategui, R. F., Wicklow, D. T., and Gloer, J. B. (2006) Phaeofurans and sorbicillin analogues from a fungicolous *Phaeoacremonium* species (NRRL 32148). *J. Nat. Prod. 69*, 113-117. DOI: 10.1021/np0504199.
20. Hikino, H., Sakurai, Y., Numabe, S., and Takemoto, T. (1968) Structure of curcumenol. *Chem. Pharm. Bull. 16*, 39-42. DOI: 10.1248/cpb.16.39.
21. Bohlmann, F., Mahanta, P. K., Jakupovic, J., Rastogi, R. C., and Natu, A. A. (1978) Naturally occurring terpene derivatives. Part 142. New sesquiterpene lactones from *Inula* species. *Phytochemistry 17*, 1165-1172. DOI: 10.1016/s0031-9422(00)94308-5.
22. Yoshioka, H., Renold, W., Fischer, N. H., Higo, A., and Mabry, T. J. (1970) Sesquiterpene lactones from *Ambrosia confertiflora* (Compositae). *Phytochemistry 9*, 823-832. DOI: 10.1016/s0031-9422(00)85188-2.
23. Herz, W., and Viswanathan, N. (1964) Constituents of Iva species. II. The structures of asperilin and ivasperin, two new sesquiterpene lactones. *J. Org. Chem. 29*, 1022-1026. DOI: 10.1021/jo01028a009.
24. McMillan, C., Chavez, P. I., Plettman, S. G., and Mabry, T. J. (1975) Systematic implications of the sesquiterpene lactones in the strumarium morphological complex (Xanthium strumarium, Asteraceae) of Europe, Asia, and Africa. *Biochem. Syst. Ecol. 2*, 181-184. DOI: 10.1016/0305-1978(75)90059-9.
25. Herz, W., Mitra, R. B., Rabindran, K., and Viswanathan, N. (1962) Constituents of Helenium species. XI. The structure of pinnatifidin. *J. Org. Chem. 27*, 4041-4043. DOI: 10.1021/jo01058a068.
26. Beck, J., Gerlach, H., Prelog, V., and Voser, W. (1962) Metabolic products of actinomycetes. XXXV. Constitution of the macrotetrolides, monactin, dinactin, and trinactin. *Helv. Chim. Acta 45*, 620-630.
27. Lou, Y., Zhao, F., Wu, Z., Peng, K.-F., Wei, X.-C., Chen, L.-X., and Qiu, F. (2009) Germacrane-type sesquiterpenes from Curcuma wenyujin. *Helv. Chim. Acta 92*, 1665-1672. DOI: 10.1002/hlca.200900059.
28. Chang, F.-R., Hsieh, T.-J., Huang, T.-L., Chen, C.-Y., Kuo, R.-Y., Chang, Y.-C., Chiu, H.-F., and Wu, Y.-C. (2002) Cytotoxic constituents of the stem bark of Neolitsea acuminatissima. *J. Nat. Prod. 65*, 255-258. DOI: 10.1021/np010236w.
29. Khafagy, S. M., Gharbo, S. A., and Sarg, T. M. (1971) Phytochemical investigation of Artemisia herba alba. *Planta Med. 20*, 90-96. DOI: 10.1055/s-0028-1099670.
30. Arnone, A., Assante, G., Bava, A., Dallavalle, S., and Nasini, G. (2009) Acremines H-N, novel prenylated polyketide metabolites produced by a strain of *Acremonium byssoides*. *Tetrahedron 65*, 786-791. DOI: 10.1016/j.tet.2008.11.058.
31. San Feliciano, A., Barrero, A. F., Medarde, M., Miguel del Corral, J. M., Ledesma, E., and Sanchez-Ferrando, F. (1982) Asteriscunolide A: humulanolide from Asteriscus aquaticus. *Tetrahedron Lett. 23*, 3097-3100. DOI: 10.1016/s0040-4039(00)87542-5.
32. Jeremic, D., Jokic, A., Behbud, A., and Stefanovic, M. (1973) New type of sesquiterpene lactone isolated from Artemisia annua. Arteannuin B. *Tetrahedron Lett.*, 3039-3042. DOI: 10.1016/s0040-4039(01)96314-2.
33. Samek, Z., Holub, M., Drozdz, B., Grabarczyk, H., and Hladon, B. (1977) On terpenes. CCXLVIII. Xerantholide - a new cytotoxically active sesquiterpenic lactone from

Xeranthemum cylindraceum Sibth. et Smith. *Collect. Czech. Chem. Commun. 42*, 2441-2447. DOI: 10.1135/cccc19772441.
34. Bohlmann, F., Suwita, A., Natu, A. A., Czerson, H., and Suwita, A. (1977) Naturally occurring terpene derivatives, 106. Further Œ±-longipinene derivatives from Composites. *Chem. Ber. 110*, 3572-3581.
35. Boustie, J., Moulis, C., Gleye, J., Fouraste, I., Servin, P., and Bon, M. (1990) A degraded limonoid from Fagaropsis glabra. *Phytochemistry 29*, 1699-1701. DOI: 10.1016/0031-9422(90)80152-7.
36. Achenbach, H., and Wittmann, G. (1970) Dihydrokawain-5-ol, a new alcohol from smoke pepper, *Piper methysticum*. *Tetrahedron Lett.*, 3259-3262.
37. Robinson, A., Kumar, T. V., Sreedhar, E., Naidu, V. G., Krishna, S. R., Babu, K. S., Srinivas, P. V., and Rao, J. M. (2008) A new sesquiterpene lactone from the roots of Saussurea lappa: structure-anticancer activity study. *Bioorg. Med. Chem. Lett. 18*, 4015-4017. DOI: 10.1016/j.bmcl.2008.06.008.
38. Chen, W. M. R., M.; Helmuth, Z.; Gerhard, R. (1989) A non-oxidized melampolide and other germacranolides from Aristolochia yunnanensis. *Phytochemistry 28*, 3233-3234. DOI: 10.1016/0031-9422(89)80315-2.
39. Somasekar, A. R. K., G. R.; Bhattacharyya, S. C. (1960) Terpenoids—XXI : The structure of costunolide, a new sesquiterpene lactone from costus root oil. *Tetrahedron 9*, 275-283. DOI: 10.1016/0040-4020(60)80017-8.
40. Hirota, A., Higashinaka, Y., and Sakai, H. (1978) Isolation of indolmycin and its derivative as antagonists of L-tryptophan. *Agric. Biol. Chem. 42*, 147-151. DOI: 10.1271/bbb1961.42.147.
41. Strunz, G. M., Kazinoti, P. I., and Stillwell, M. A. (1974) New chlorinated cyclopentenone produced by a Cryptosporiopsis species. *Can. J. Chem. 52*, 3623-3625. DOI: 10.1139/v74-541.
42. el-Feraly, F. S., and Chan, Y. M. (1978) Isolation and characterization of the sesquiterpene lactones costunolide, parthenolide, costunolide diepoxide, santamarine, and reynosin from Magnolia grandiflora L. *J. Pharm. Sci. 67*, 347-350. DOI: 10.1002/jps.2600670319.
43. Devivar, A. R., Cabrera, A., Ortega, A., and Romo, J. (1967) Constituents of Zaluzania species .2. structures of zaluzanin C and zaluzanin D. *Tetrahedron 23*, 3903-&. DOI: 10.1016/S0040-4020(01)97900-1.
44. Koizumi, F., Ishiguro, H., Ando, K., Kondo, H., Yoshida, M., Matsuda, Y., and Nakanishi, S. (2003) EI-1941-1 and -2, novel interleukin-1 beta converting enzyme inhibitors Produced by Farrowia sp. E-1941. II. Taxonomy of producing strain, fermentation, isolation, physico-chemical properties, and biological properties. *J Antibiot 56*, 603-609. DOI: 10.7164/antibiotics.56.464.
45. Tsuda, K., Tanabe, K., Iwai, I., and Funakoshi, K. (1957) Structure of alantolactone. *J. Am. Chem. Soc. 79*, 5721-5724. DOI: 10.1021/ja01578a037.
46. Tan, R. X., Tang, H. Q., Hu, J., and Shuai, B. (1998) Lignans and sesquiterpene lactones from Artemisia sieversiana and Inula racemosa. *Phytochemistry 49*, 157-161.
47. Xu, X.-H., Yao, G.-M., Li, Y.-M., Lu, J.-H., Lin, C.-J., Wang, X., and Kong, C.-H. (2003) 5-Fluorouracil derivatives from the sponge Phakellia fusca. *J. Nat. Prod. 66*, 285-288. DOI: 10.1021/np020034f.
48. Stanton, A. H. D., E. W.; Ralph, M.; Anderson, R. C.; Glen, E. A.; Nelson, R. E.; Dorothea, H.; Andrew, N. W.; Karl, F. (1944) Biotin. II. synthesis of biotin. *Biochemistry 66*, 1756-1757.

49. Veen, G., Gunther, S., Greinwald, R., Bachmann, P., Witte, L., Kustrak, D., and Czygan, F. C. (1992) Quinolizidine alkaloids in Petteria ramentacea. *Phytochemistry 31*, 3487-3490. DOI: 10.1016/0031-9422(92)83712-8.
50. Kim, K. H., Lee, I. K., Park, K. M., Kim, W. K., and Lee, K. R. (2008) Isolation of Œ≥-lactam alkaloids from the Macrolepiota neomastoidea. *Bull. Korean Chem. Soc. 29*, 1591-1593. DOI: 10.5012/bkcs.2008.29.8.1591.
51. Van Wyk, B. E., Verdoorn, G. H., and Schutte, A. L. (1988) Chemotaxonomic value of alkaloids in the genus Dichilus. *Biochem. Syst. Ecol. 16*, 471-474. DOI: 10.1016/0305-1978(88)90046-4.
52. Joshi, B. S., and Kamat, V. N. (1971) Structures of fischeric acid and isofischeric acid, two new desquiterpenes from neolitsea-fischeri. *Indian J. Chem. 9*, 80-83.
53. Levene, P. A., and London, E. S. (1929) The structure of thymonucleic acid. *J. Biol. Chem. 83*, 793-802.
54. Pirrung, M. C., Cao, J., and Chen, J. (1995) Ethylene biosynthesis: analog approach to the active-site topography of the ethylene-forming enzyme - novel hydroxamate inhibitors. *J. Org. Chem. 60*, 5790-5794. DOI: 10.1021/jo00123a012.
55. Fukagawa, M., Isogai, T., Aramori, I., Iwami, M., Kojo, H., Ono, T., Kohsaka, M., and Imanaka, H. (1991) Direct production of 7-aminodeacetylcephalosporanic acid by Acremonium chrysogenum Hm178. *Agric. Biol. Chem. 55*, 2163-2165. DOI: 10.1271/bbb1961.55.2163.
56. Baslas, K. K. (1955) Essential oil from Prunella vulgaris. *J. Indian Chem. Soc. 32*, 228-230.
57. van Zyl, R. L., Seatlholo, S. T., van Vuuren, S. F., and Viljoen, A. M. (2006) The biological activities of 20 nature identical essential oil constituents. *J. Essent. Oil Res. 18*, 129-133.
58. Ehrenberg, A. Alkaloids of calabar beans. *Verh. Vers. deutsch. Naturf. u. Artze. ii*, 102.
59. Cassal, J. M. F., A.; Meier, W. (1976) Synthese der enantiomeren 2-Pyrrolidinessigsäuren. *Helv. Chim. Acta 59*, 1917-1924. DOI: 10.1002/hlca.19760590602.
60. Clement, B. A., Goff, C. M., and Forbes, T. D. A. (1998) Toxic amines and alkaloids from Acacia rigidula. *Phytochemistry 49*, 1377-1380. DOI: 10.1016/s0031-9422(97)01022-4.
61. Orekhov, A. P., Proskurnina, N., and Konovalova, R. (1935) Sophora alkaloids. VIII. Alkaloids from the seeds and the foliage of Sophora alopecuroides. *Berichte der Deutschen Chemischen Gesellschaft [Abteilung] B: Abhandlungen 68B*, 431-436.
62. Yahara, S., Uda, N., Yoshio, E., and Yae, E. (2004) Steroidal alkaloid glycosides from tomato (Lycopersicon esculentum). *J. Nat. Prod. 67*, 500-502. DOI: 10.1021/np030382x.
63. Ogita, T., Sato, A., Enokita, R., Suzuki, K., Ishii, M., Negishi, T., Okazaki, T., Tamaki, K., and Tanzawa, K. (1992) Matlystatins, new inhibitors of typeIV collagenases from Actinomadura atramentaria. I. Taxonomy, fermentation, isolation, and physico-chemical properties of matlystatin-group compounds. *J Antibiot 45*, 1723-1732. DOI: 10.7164/antibiotics.45.1723.
64. Takaku, T., Kameda, K., Matsuura, Y., Sekitani, K., Okuda, T., and Okai, H. (1988) Isolation and structure of insulin-like substances from ginseng. *Wakan Iyaku Gakkaishi 5*, 544-545.
65. Bell, E. A., Nulu, J. R., and Cone, C. (1971) L-Dopa and L-3-carboxy-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, a new imino acid, from seeds of Mucuna mutisiana. *Phytochemistry 10*, 2191-2194. DOI: 10.1016/s0031-9422(00)97217-0.
66. Guella, G., N'Diaye, I., Fofana, M., and Mancini, I. (2006) Isolation, synthesis and photochemical properties of almazolone, a new indole alkaloid from a red alga of Senegal. *Tetrahedron 62*, 1165-1170. DOI: 10.1016/j.tet.2005.10.072.

67. Behr, L. D. C., H. T. . (1932) l-p-Mehoxyphenylalanine. *J. Am. Chem. Soc. 54*, 1630-1634.
68. Canonica, L. B., B.; Bonati, A.; Tedeschi, C. (1955) Synthetic analeptics. I. Hydroxybenzoic acid diethylamides. *Annali di Chimica (Rome, Italy) 45*, 205-215.
69. Sperry, J., Gibson, J. S., Sejberg, J. J. P., and Brimble, M. A. (2008) Enantioselective synthesis of the dimeric pyranonaphthoquinone core of the cardinalins using a late-stage homocoupling strategy. *Organic & Biomolecular Chemistry 6*, 4261-4270. DOI: 10.1039/b813605j.
70. Carroll, A. R., Pierens, G. K., Fechner, G., de Leone, P., Ngo, A., Simpson, M., Hyde, E., Hooper, J. N. A., Bostroem, S.-L., Musil, D., and Quinn, R. J. (2002) Dysinosin A: A novel inhibitor of factor VIIa and thrombin from a new genus and species of Australian sponge of the family Dysideidae. *J. Am. Chem. Soc. 124*, 13340-13341. DOI: 10.1021/ja020814a.
71. Gu, L., Wang, S., Li, X., and Zhu, T. (1987) Antibacterial constituents from Gerbera anandria (L.) Sch. Bip. *Yaoxue Xuebao 22*, 272-277.
72. Xiao, Y., Li, J., and Ding, Y. (2002) Studies on chemical constituents in roots and rhizomes of Gerbera piloselloides. *Zhongguo Zhongyao Zazhi 27*, 594-596.
73. Tyler, V. E., Jr., and Groger, D. (1964) Occurrence of 5-hydroxytryptamine and 5-hydroxytryptophan in Panaeolus sphinctrinus. *J. Pharm. Sci. 53*, 462-463. DOI: 10.1002/jps.2600530433.
74. Kawahara, N., Nozawa, K., Nakajima, S., Udagawa, S., and Kawai, K. (1988) Studies on fungal products. XVI. New metabolites related to 3-methylorsellinate from Aspergillus silvaticus. *Chem. Pharm. Bull. 36*, 398-400. DOI: 10.1248/cpb.36.398.
75. Lloyd, H. A. (1965) Astrocasine, a new Euphorbiaceae alkaloid. *Tetrahedron Lett.*, 1761-1767. DOI: 10.1016/s0040-4039(00)90124-2.
76. Henry, A. J., and King, H. (1950) Isolation and identification of (-)-stachydrine ethyl ester periodide from the root of Courbonia virgata. *J. Chem. Soc.*, 2866-2868. DOI: 10.1039/jr9500002866.
77. Alvi, K. A., Peters, B. M., Hunter, L. M., and Crews, P. (1992) 2-Aminoimidazoles and their zinc complexes from indo-pacific Leucetta sponges and Notodoris nudibranchs. *Tetrahedron 49*, 329-336. DOI: 10.1016/s0040-4020(01)80302-1.
78. Quinn, R. J. (unpublished).
79. Iketubosin, G. O., and Mathieson, D. W. M. (1963) The isolation of hordenine and norsecurinine from Securinega virosa (Baill) - structure of norsecurinine. *J. Pharm. Pharmacol. 15*, 810-815. DOI: 10.1111/j.2042-7158.1963.tb12885.x.
80. Saito, S., Tanaka, T., Kotera, K., Nakai, H., Sugimoto, N., Horii, Z., Ikeda, M., and Tamura, Y. (1965) Absolute stereochemistry at C-9a of norsecurinine and dehydronorsecurinine. *Chem. Pharm. Bull. 13*, 614-616.
81. Saito, S., Tanaka, T., Iwamoto, T., Matsumura, C., Sugimoto, N., Horii, Z., Makita, M., Ikeda, M., and Tamura, Y. (1964) Determination of securinine and its stereoisomers in plants of the Securinega species, and isolation of viroallosecurinine and virosine. *Yakugaku Zasshi. 84*, 1126-1133.
82. Yuan, W., Zhu, P., Cheng, K. D., Meng, C., Ma, L., Wu, F., and Zhu, H. X. (2007) Callus of Securinega suffruticosa, a cell line accumulates dextro Securinega alkaloids. *Nat. Prod. Res. 21*, 234-242. DOI: 10.1080/14786410701189781.
83. Zhu, J. P., Chastanet, J., and Beugelmans, R. (1996) Selective hydroxy group protection of gallic acid. *Synth. Commun. 26*, 2479-2486. DOI: 10.1080/00397919608004560.
84. Parello, J. (1968) Structure of phyllanthine, a minor alkaloid from Phyllanthus discoides Meull. Arg. (Euphorbiacees). *Bull. Soc. Chim. Fr. 3*, 1117-1129.

85. Hassarajani, S. A., and Mulchandani, N. B. (1990) Securinine type of alkaloids from Phyllanthus niruri. *Indian Journal of Chemistry, Section B: Organic Chemistry Including Medicinal Chemistry 29B*, 801-803.
86. Nakano, T., Yang, T. H., and Terao, S. (1963) Alkaloids of Securinega virosa. I. Structure of virosecurinine. *Tetrahedron 19*, 609-619. DOI: 10.1016/s0040-4020(01)98547-3.
87. Vu, H., Roullier, C., Campitelli, M., Trenholme, K. R., Gardiner, D. L., Andrews, K. T., Skinner-Adams, T., Crowther, G. J., Van Voorhis, W. C., and Quinn, R. J. (2013) *Plasmodium* gametocyte inhibition Identified from a natural-product-based fragment library. *ACS Chem. Biol. 8*, 2654-2659. DOI: 10.1021/cb400582b.
88. El-Masry, S., Hammoda, H. M., Zaatout, H. H., Alqasoumi, S. I., and Abdel-Kader, M. S. (2010) Constituents of Erythrina caffra stem bark grown in Egypt. *Nat. Prod. Sci. 16*, 211-216.
89. Wang, Z. G., Wang, X. J., Sun, H., Chen, L., and Ma, C. M. (2012) Determination of novel nitrogen-containing metabolite after oral administration of swertiamarin to rats. *J. Asian Nat. Prod. Res. 14*, 176-181. DOI: 10.1080/10286020.2011.631132.
90. Katavic, P. L., Venables, D. A., Forster, P. I., Guymer, G., and Carroll, A. R. (2006) Grandisines C-G, indolizidine alkaloids from the Australian rainforest tree Elaeocarpus grandis. *J. Nat. Prod. 69*, 1295-1299. DOI: 10.1021/np060179c.
91. Ulubelen, A., Guner, H., and Cetindag, M. (1988) Alkaloids and coumarins from the roots of Ruta-chalepensis var latifolia. *Planta Med.*, 551-552.
92. Wehrli, H. (1980) Zur photocyclisierung von N-phenacylformamiden. *Helv. Chim. Acta 63*, 1915-1919. DOI: 10.1002/hlca.19800630718.