

SUPPLEMENTARY MATERIAL

Anti-influenza and anti-inflammatory activity of bisabolane-type sesquiterpenoids from *Curcuma longa* L. and their mechanisms of action

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Abstract

Influenza is a viral respiratory illness that causes seasonal epidemics and occasional pandemics. Disease severity may be contributed by influenza virus-induced cytokine dysregulation. The study was designed to investigate the isolation and identification bisabolane-type sesquiterpenoids from *Curcuma longa* L. and their antiviral and anti-inflammatory activities against H1N1 and their potential effect in regulating host immune response *in vitro*. A pair of new bisabolane-type sesquiterpenoids, (6S,7S)-3-hydroxy-3-hydroxymethylbisabola-1,10-diene-9-one (**18**) together with seventeen known analogs (**1–17**) were isolated and elucidated from *Curcuma longa* L. Compounds **2**, **11** and **14** could significantly inhibit A/PR/8/34 (H1N1) replication in MDCK cells, and compound **2** could significantly inhibit A/PR/8/34 (H1N1) replication in A549 cells. Compounds **4**, **8**, **9**, **13** and **17** could markedly reduce pro-inflammatory cytokines (TNF- α , IL-6, IL-8 and IP-10) production at the mRNA and protein levels in A549 cells. Compound **4** regulated the levels of steroid biosynthesis, oxidative phosphorylation and protein processing in the endoplasmic reticulum, thereby inhibiting immune responses by a proteomics analysis. Furthermore, compound **4** could inhibit the expression of p-NF- κ B p65, NF- κ B p65, I κ B α , p-p38 MAPK, p-I κ B α , RIG-1, STAT-1/2 and p-STAT-1/2 in the signaling pathways. These findings indicate that bisabolane-type sesquiterpenoids of *C. longa* could inhibit the expression of inflammatory cytokines induced by virus and regulating the activity of NF- κ B/MAPK and RIG-1/STAT-1/2 signaling pathways *in vitro*.

Key words: *Curcuma longa* L.; bisabolane-type sesquiterpenoids; anti-inflammatory

activities; anti-influenza; proteomics analysis; NF- κ B/MAPK; RIG-1/STAT-1/2

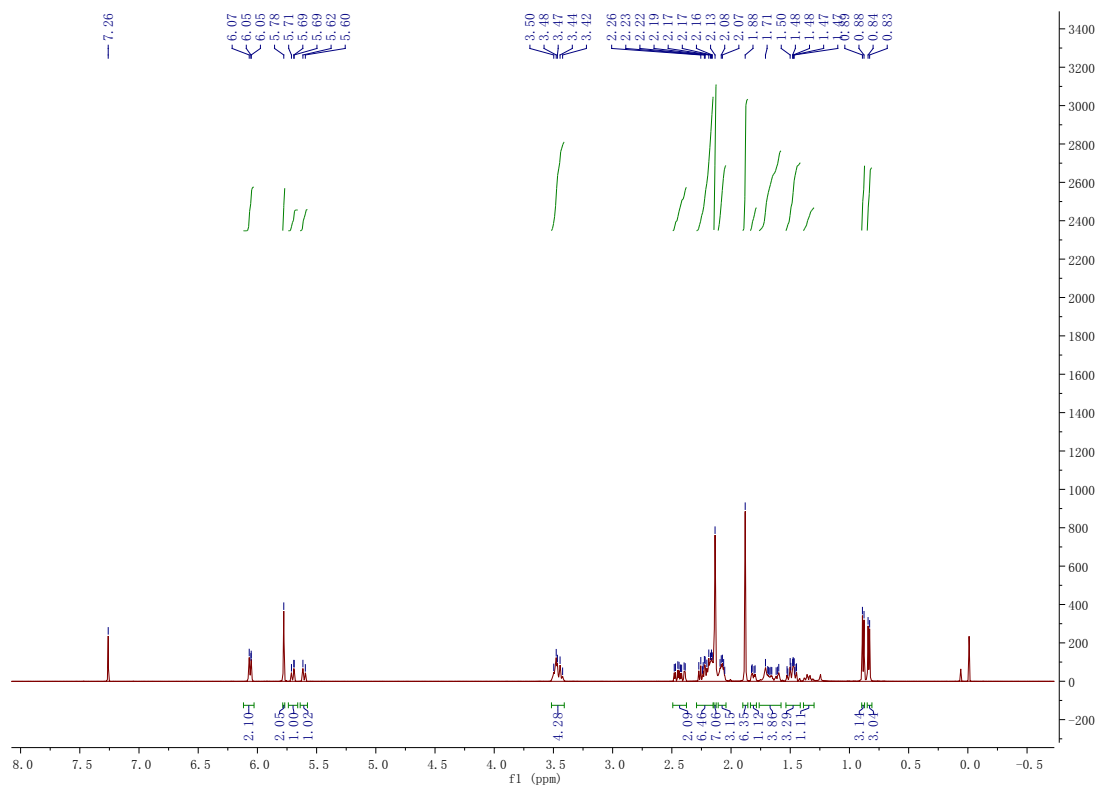


Figure S1 ^1H NMR spectrum of compound 18



Figure S2 ^{13}C NMR spectrum of compound 18

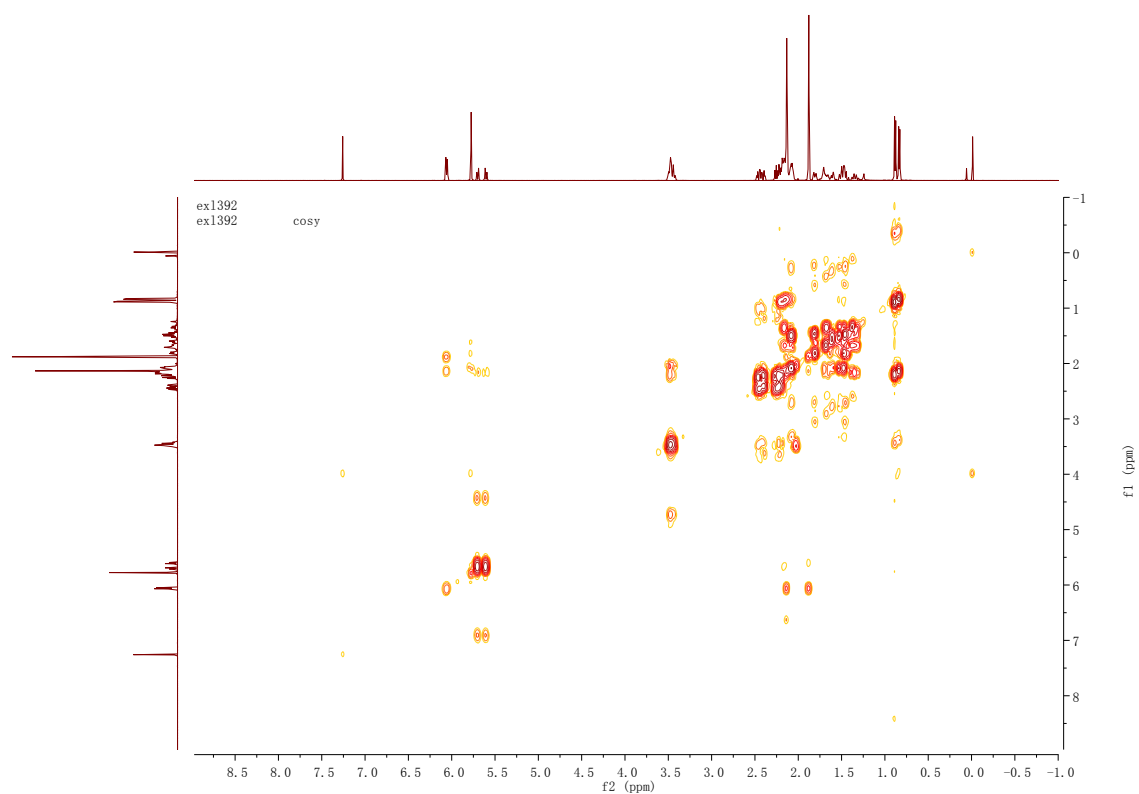


Figure S3 H-HCOSY spectrum of compound **18**

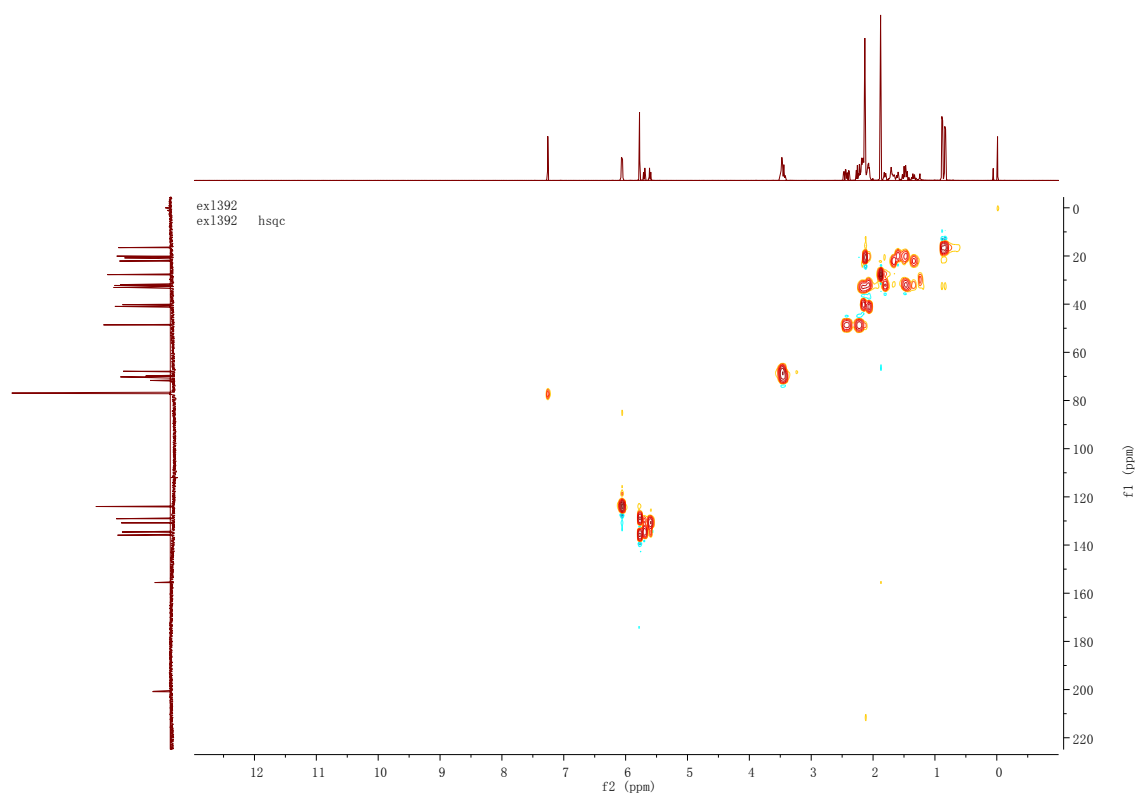


Figure S4 HSQC spectrum of compound **18**

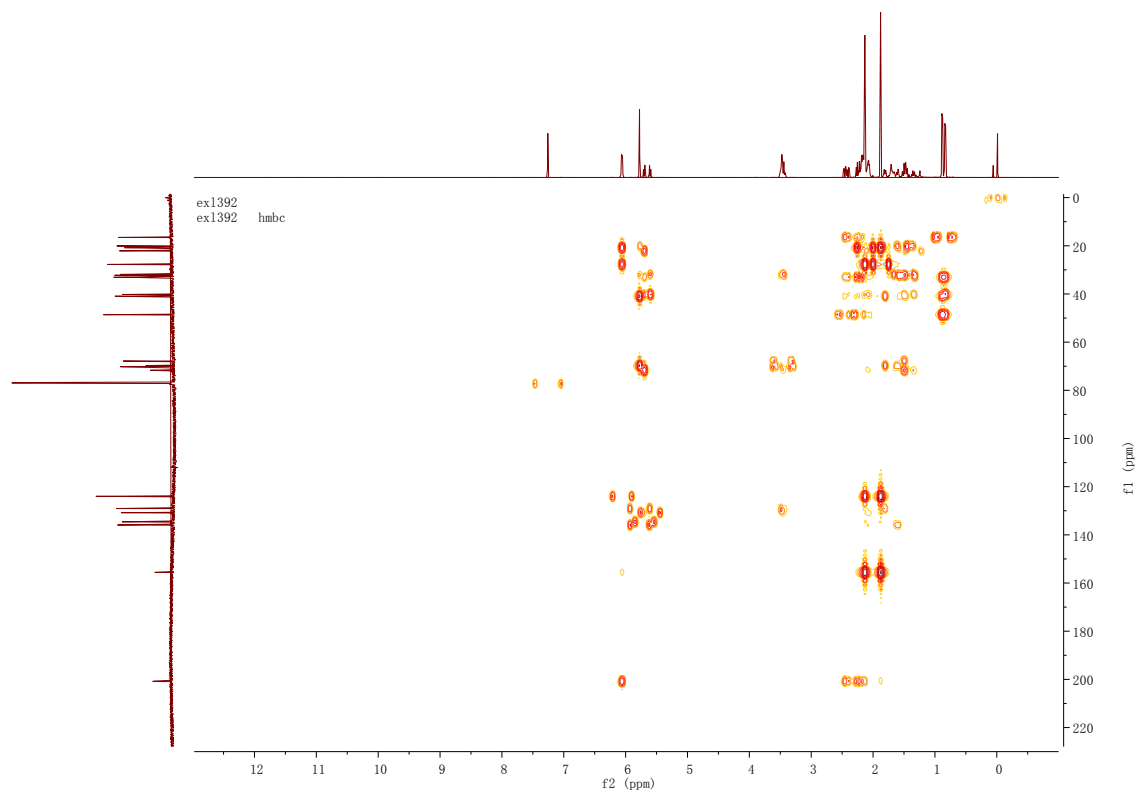


Figure S5 HMBC spectrum of compound **18**

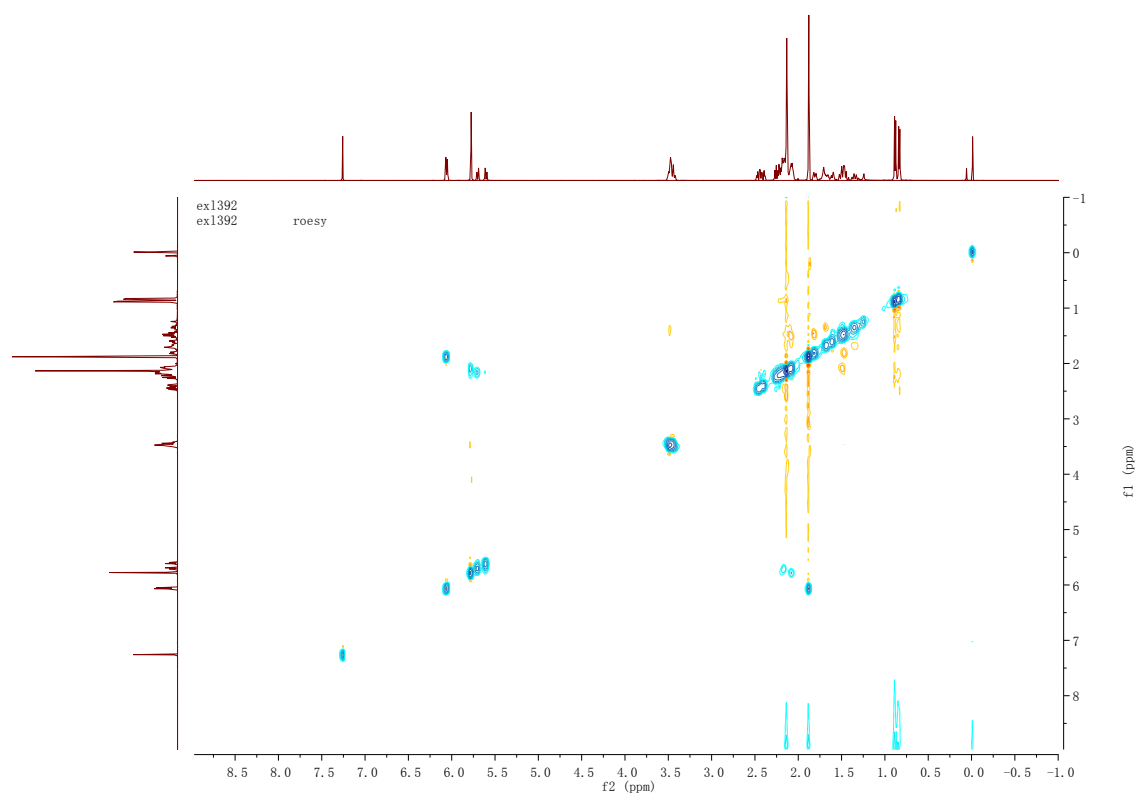
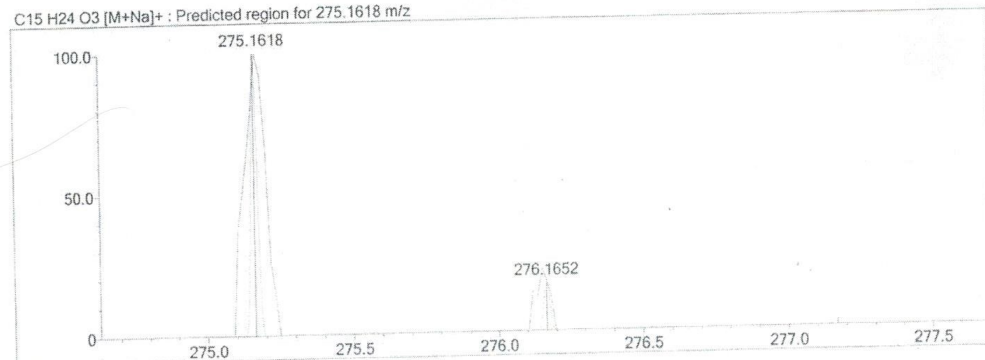
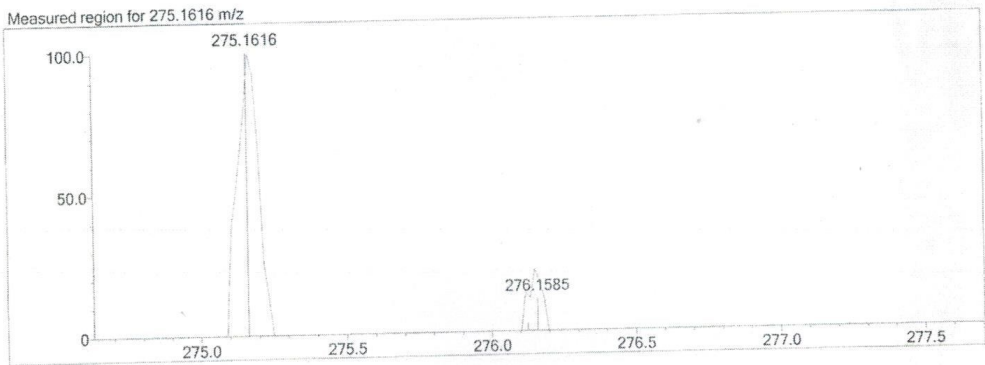
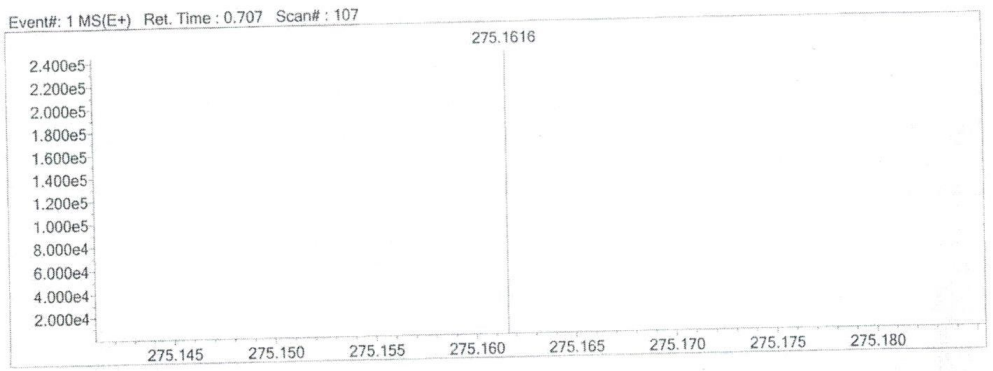


Figure S6 ROESY spectrum of compound **18**



Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	DBE
C15 H24 O3	[M+Na]+	275.1616	275.1618	-0.2	-0.73	4.0

Figure S7 HRESIMS spectrum of compound **18**

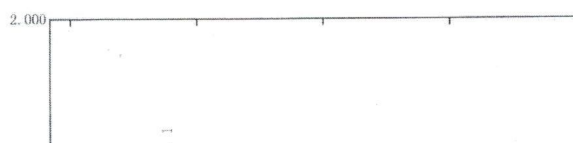
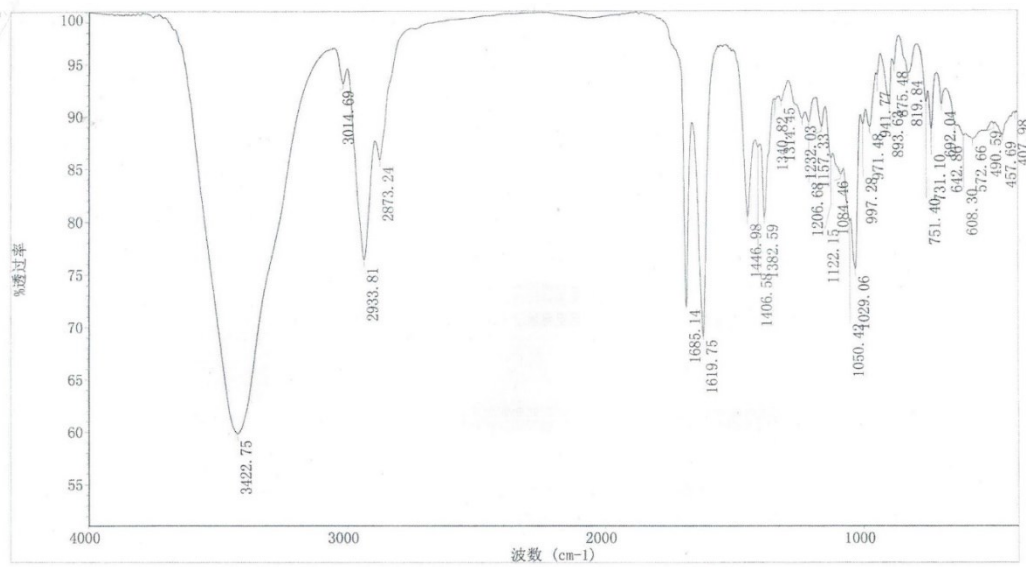


Figure S8 UV spectrum of compound **18**

Figure S9 IR spectrum of compound **18**

Position	δ_{H} , mult. J in Hz	δ_{C} , mult.
1	5.70/5.78, d, $J=10.0$	134.5/135.9
2	5.70/5.78, d, $J=10.0$	130.8/129.0
3		71.6/69.7
4	2.08, 1.49/1.81, 1.47, m	31.8/32.2
5	1.35/1.48, m	67.1/60.1
6	2.17/2.07, d, $J=10.0$, 5.1	40.2/40.9
7	2.12/2.17, m	33
8	2.41, 2.21/2.46, 2.25, dd, $J=15.3$, 7.2	48.5/48.6
9		200.8/200.7
10	6.05/6.07, br s	124
11		155.6/155.5
12	1.88, br s	27.7
13	2.13, br s	20.7
14	0.84/0.88, d, $J=6.5$	16.3/16.5
15	3.47/3.49, 3.43	67.8/70.2

Table S1 ^1H NMR (500 MHz) and ^{13}C NMR data (125 MHz) for Compounds **18** in CDCl_3 .

Number	Compound Name	TC50 ($\mu\text{g/ml}$)	IC50 ($\mu\text{g/ml}$)
Compound 2	Bisabola-3,10-dien-2-one	158.50 \pm 19.50	16.79 \pm 4.03
Compound 11	4-(6-Methyl-4-oxohept-5-en-yl)cyclohex-2-en-1-one	32.47 \pm 7.47	23.10 \pm 2.06
Compound 14	1,4-Epidioxybisabola-2,10-dien-9-one	11.97 \pm 5.72	11.43 \pm 0.31
Positive control	OSE	>1000	0.04

(A)

Number	Compound Name	TC50 ($\mu\text{g/ml}$)	IC50 ($\mu\text{g/ml}$)
Compound 2	Bisabola-3,10-dien-2-one	>100	47.65 \pm 2.3
Positive control	OSE	>1000	0.04

(B)

Table S2 The anti-influenza (A/PR/8/34 (H1N1)) activity of effective compounds in MDCK (A) and A549 (B) cells

Gene	Primer Sequence (5'→3')
IL-6	F: CGGGAACGAAAGAGAAGCTCTA R: CGCTTGTGGAGAAGGAGTTCA
IL-8	F: TTGGCAGCCTTCCTGATTTC R: TATGCACTGACATCTAAGTTCTTTAGCA
TNF- α	F: GAAATTATTCCTGCAAGCCAATTT R: TCACCCTTCTTTTTCAT-TGTAGCA
IP-10	F: AACATCCAACCTTCCCAAACG R: GACCCTAAGCCCCCAATTCTC

Table S3 Sequences of Primer Used for qRT-PCR

Gene.names	Unique.peptides	Symbol	fc CV	fc CV _{L_H}	fc CV _{L_L}
Upregulated proteins by Compound 1 (Number: 122)					
TAB1	2	TAB1	0.042062489	58.02664532	36.73034458
CCDC93	3	CCDC93	0.771552541	33.6974171	20.6611417
AKAP9	3	AKAP9	0.051444579	23.68075131	9.486007122
PTGES2	6	PTGES2	0.045168548	23.1736519	7.699158364
HPGD	7	HPGD	0.042461212	12.02093101	6.511043138
HMG2	3	HMG2	0.141407787	9.86313727	4.450404412
CLPP	3	CLPP	0.12632066	6.134334075	4.260557087
PTRH2	3	PTRH2	0.602920651	4.450269038	3.999180303
MYO5A	5	MYO5A	0.614268526	4.009540382	3.652053168
RPL26L1	2	RPL26L1	1.040213291	3.967774566	3.63428545
SYNE1	5	SYNE1	1.027311801	3.868977339	3.351678654
SLC35A4	4	SLC35A4	1.251708788	3.410383285	3.108385402
MCAT	2	MCAT	0.448979895	3.381733339	3.049545301
FLNA	2	Q60FE5	0.545258212	3.290964249	3.018172832
DYNLRB1;DYNLRB2	4	DYNLRB1	0.418580622	3.28711686	3.016330386
OSTF1	3	OSTF1	0.821932346	3.10559571	2.954041468
PRPF4B	3	PRPF4B	0.38513721	3.050703257	2.868951684
AP1S2	2	AP1S2	0.211208026	3.009184137	2.816567111
TGFBI	2	TGFBI	0.477488228	2.821214483	2.705630802
CSRP2	4	CSRP2	0.432085361	2.766477095	2.635825421
FADS1	3	FADS1	0.091442288	2.733964826	2.5988444
KPNA3	3	KPNA3	0.363311247	2.598462753	2.406194423
APP	3	APP	0.456545176	2.522835709	2.366754363

ABCC2	7	ABCC2	0.338565581	2.520961834	2.261095129
SQLE	5	SQLE	0.187527413	2.490045918	2.25294876
TRIM47	3	TRIM47	0.34801889	2.483144404	2.187650478
UBE2D1;UBE2D4	2	UBE2D1	0.612563481	2.467898572	1.989696883
LSM12	3	LSM12	6.025531946	2.361391879	1.988212961
NFYB	2	NFYB	0.726211478	2.332357482	1.983867275
EMG1	4	EMG1	1.187179143	2.324933777	1.983366632
DHRS1	2	DHRS1	0.301661895	2.256865849	1.966022326
NPM3	2	NPM3	0.538762386	2.253866589	1.961826206
PPP2CB;PPP2CA	2	PPP2CB	0.404819615	2.220969094	1.950247357
UQCRQ	5	UQCRQ	0.617057209	2.214327852	1.916276434
MRPS5	2	MRPS5	0.460944326	2.177831962	1.892860539
VKORC1L1	2	VKORC1L1	0.333684301	2.167804917	1.877790376
PREB	2	PREB	0.748180983	2.142226689	1.784779472
COQ6	2	COQ6	0.39945443	2.139634065	1.777182442
CSNK2A1;CSNK2A3	6	CSNK2A1	0.941324072	2.13605707	1.766305917
GINS4	3	GINS4	0.57005326	2.132320547	1.758592266
RPL21	8	RPL21	1.020769189	2.117198293	1.695277892
PPP1R9B	2	PPP1R9B	0.453647586	2.114423437	1.676814288
PFDN1	6	PFDN1	0.594564536	2.109178974	1.65532667
HDGFRP3	2	HDGFRP3	0.611590933	2.100154046	1.643482033
PDLIM2	2	PDLIM2	0.379824617	2.063269391	1.637197676
SNRPD1	3	SNRPD1	0.972322932	2.063131456	1.622530796
PSMG1	3	PSMG1	0.623461102	2.034672973	1.617898359
ALDH3B1	7	ALDH3B1	0.338584627	2.02824795	1.612389492
NUP160	8	NUP160	0.538291254	2.019003333	1.566850797

IQGAP3	2	IQGAP3	0.102506095	2.016445701	1.560651705
CHAMP1	2	CHAMP1	0.773945802	2.00629286	1.553702424
ZNF598	2	ZNF598	0.544675592	1.988715171	
CTR9	2	CTR9	0.58282293	1.986533603	
PTP4A1;PTP4A2	2	PTP4A1	0.551708342	1.962856709	
CARM1	5	CARM1	0.704666074	1.961731068	
MKI67	17	MKI67	0.941707437	1.956037052	
GALNS	3	GALNS	0.311285711	1.939545574	
KDM3B	4	KDM3B	0.495602577	1.934867804	
BRIX1	5	BRIX1	1.681591641	1.902747877	
DDRGK1	2	DDRGK1	0.706158884	1.899815292	
LIMCH1	4	LIMCH1	0.536981814	1.885896401	
IKBKB	2	IKBKB	0.329165799	1.876402286	
LMCD1	9	LMCD1	0.565800031	1.873963908	
SLC33A1	3	SLC33A1	0.68882025	1.870758123	
DAZAP1	5	DAZAP1	0.920438454	1.86345679	
DNAJC9	6	DNAJC9	1.275234552	1.85556703	
RPL10A	10	RPL10A	1.028977246	1.855406174	
GMPPB	2	GMPPB	0.756872724	1.853295979	
PSPC1	5	PSPC1	1.607076467	1.84141812	
CFDP1	3	CFDP1	0.469233397	1.832221423	
PREP	7	PREP	0.718254441	1.820617965	
DHODH	5	DHODH	0.702472446	1.80266302	
EMC4	2	EMC4	0.70643321	1.797687509	
VPS28	4	VPS28	0.60481214	1.789914079	
MKKS	2	MKKS	0.849133549	1.785730806	

SIL1	3	SIL1	0.469770679	1.785520011
HIRIP3	3	HIRIP3	0.382735541	1.784285413
PSMD8	4	PSMD8	0.774256566	1.764557463
DNMT1	4	DNMT1	1.248847317	1.763298216
SLC7A5	6	SLC7A5	0.651320935	1.757524534
PPWD1	4	PPWD1	0.784599863	1.744710757
NQO2	3	NQO2	0.620421754	1.737058657
DIMT1	5	DIMT1	1.395863091	1.726583853
IKBIP	5	Q70UQ0-4	0.807187085	1.723676404
CYP51A1	4	CYP51A1	0.40511068	1.707221808
SEC23B	4	SEC23B	0.460363742	1.69139259
SRSF5	2	SRSF5	0.854322635	1.689302137
CDK2;CDK3	3	CDK2	0.714776236	1.680526401
LDAH;C2orf43;FLJ21820	2	LDAH	0.706746369	1.668307103
SYVN1	3	SYVN1	0.386448771	1.661354054
HSPA1B;HSPA1A	15	HSPA1B	1.023541362	1.660523758
YBX1	6	YBX1	0.819628574	1.659968599
AP3S1	2	AP3S1	0.76963047	1.653563636
POLRMT	2	POLRMT	0.418574165	1.644907817
HADH	6	HADH	0.837622612	1.64034885
TMEM167A	2	TMEM167A	0.54979922	1.63825998
IKBKG	3	IKBKG	0.593803134	1.638169282
PCCA	4	PCCA	1.011025318	1.635834579
LARP7	2	LARP7	1.128120794	1.630956207
RFC4	5	RFC4	0.820710068	1.630710744
ABHD10	4	ABHD10	0.912531373	1.629744408

PLCH1	2	PLCH1	1.019789283	1.629635853
EXOSC8	3	EXOSC8	0.863537933	1.624108262
LYPLAL1	4	LYPLAL1	0.882736003	1.621594063
SMARCC1	3	SMARCC1	0.585174723	1.617468967
YBX3	2	YBX3	0.622261986	1.61268073
CDC73	8	CDC73	0.58045319	1.612074381
LAMB1	5	LAMB1	0.758474027	1.611954327
ESD	6	ESD	0.782728919	1.606574546
VPS52	2	VPS52	0.429302762	1.603762571
LAMP2	5	LAMP2	0.607490012	1.603298504
PABPC4	10	PABPC4	0.65467952	1.602358752
THEM6	7	THEM6	0.715549003	1.585398275
CDS2	3	CDS2	0.772716284	1.585196419
SNAP23	4	SNAP23	0.897690457	1.581908488
OGT	6	OGT	0.61798311	1.581161991
DCPS	8	DCPS	0.720133594	1.578764678
SF3A3	9	SF3A3	0.962270446	1.577212198
UBE2I	6	UBE2I	1.170788064	1.569029123
GCLM	5	GCLM	0.742845815	1.566086734
GRPEL1	3	GRPEL1	1.021442061	1.563669187
ACOX1	6	ACOX1	0.890236977	1.559582149

Downregulated proteins by Compound 1 (Number: 298)

GBE1	10	GBE1	0.885447811	0.666140846
ARL1	2	ARL1	1.311104416	0.664318923
ADAR	20	ADAR	1.270068676	0.663826357
PPP4R2	4	PPP4R2	1.604296455	0.662945233

ITGB1	16	ITGB1	0.840994866	0.662080499
ERLIN2	7	ERLIN2	0.962135196	0.661039096
TAF15	6	TAF15	1.063868775	0.659692744
BCAP31	15	BCAP31	1.134251186	0.656448089
C5orf51	2	C5orf51	0.644017854	0.655419903
ERO1L	12	ERO1L	1.100579036	0.655367398
OAS3	10	OAS3	1.541990353	0.655075355
NDUFS5	4	NDUFS5	0.74826907	0.6535495
WDR75	3	WDR75	2.431160492	0.65284129
ATP6V1A	10	ATP6V1A	1.072559508	0.652811412
CYP24A1	7	CYP24A1	0.089175286	0.65262416
ACBD3	6	ACBD3	1.232145476	0.652280069
FERMT2	8	FERMT2	1.108513288	0.652116587
IDI1	6	IDI1	0.538169815	0.651689102
KDELRL1;KDELRL2	2	KDELRL1	1.102624937	0.649165146
CNN3	5	CNN3	1.257945284	0.64903705
SBDS	8	SBDS	1.293331308	0.648402631
SMAP1	2	SMAP1	1.152837387	0.647918821
HIST1H1D	5	HIST1H1D	3.031549262	0.647244255
RRP1	3	RRP1	1.778797517	0.646145478
EHD1	11	EHD1	1.329165494	0.64554754
CHMP5	4	CHMP5	1.241583716	0.644909527
TMEM179B	2	TMEM179B	0.624417412	0.643715193
AP1M1	7	AP1M1	1.36524257	0.640381109
TGM2	23	TGM2	1.776769011	0.638010591
TBC1D15	10	TBC1D15	0.650948448	0.635900385

DDX20	2	DDX20	0.647785959	0.635210624
CNTN1	3	CNTN1	0.602926917	0.634762748
MAGED2	13	MAGED2	0.977931205	0.634675879
S100A16	5	S100A16	0.926468297	0.634331035
TCEAL4	2	TCEAL4	0.493143109	0.632372979
TIPRL	7	TIPRL	0.964277657	0.63164093
GSTK1	7	GSTK1	0.99853729	0.631510198
CNN2	8	CNN2	0.892278019	0.630142516
NDUFB9	4	NDUFB9	0.581102554	0.629389361
TPD52L1	2	TPD52L1	1.239488901	0.626239673
DENND4C	3	DENND4C	1.241082633	0.624715993
SMC6	2	SMC6	1.30518384	0.622010836
NDUFA4	4	NDUFA4	0.858532473	0.621893648
PARP4	8	PARP4	0.764250685	0.620746824
UTP20	3	UTP20	4.508549141	0.620658089
STUB1	3	STUB1	1.04427844	0.619907514
NDUFB1	2	NDUFB1	0.931497131	0.619318461
TNFAIP2	12	TNFAIP2	1.083219972	0.617592669
HECTD1	2	HECTD1	1.045675484	0.616385
FAM136A	5	FAM136A	0.977181148	0.615965736
SUMO1	5	SUMO1	1.438900361	0.615772384
RALA	4	RALA	1.203527651	0.615663866
VPS33B	3	VPS33B	0.778003064	0.613990036
RAB31;RAB22A	2	RAB31	1.340871523	0.612644399
PIGU	2	PIGU	0.863314689	0.609698657
DNAJC3	3	DNAJC3	1.345984113	0.609640098

NAMPT	13	NAMPT	1.263565692	0.607045336
SERPINB9	7	SERPINB9	1.9192941	0.606167508
CLPX	8	CLPX	0.727774864	0.605771102
UBE2T	2	UBE2T	0.466761504	0.605114211
UBLCP1	7	UBLCP1	0.820598432	0.604975404
YY2;YY1	2	YY2	1.812445981	0.604541027
JUP	16	JUP	0.59211699	0.601185722
PNPT1	10	PNPT1	1.858902444	0.600876115
LRPAP1	5	LRPAP1	1.016903715	0.600755078
ATP5EP2;ATP5E	3	ATP5EP2	1.407925697	0.596651714
SEC62	3	SEC62	1.065677327	0.596415111
NR3C1	9	NR3C1	0.921111595	0.593900688
TMPO	13	P42166	0.97813867	0.593018492
CIAO1	4	CIAO1	1.176516178	0.590021481
PPP2R5C	2	PPP2R5C	0.770434384	0.588838816
DNAJA1	10	DNAJA1	1.885383403	0.588471754
LMAN2	4	LMAN2	1.016202455	0.585552403
SDCBP	3	SDCBP	0.738483495	0.583561356
GFPT2	4	GFPT2	1.735596866	0.583451359
CCDC55;NSRP1	3	CCDC55	1.225723753	0.5820583
SLC30A1	2	SLC30A1	1.452895628	0.581922315
RANBP3	4	RANBP3	1.210481883	0.578109281
CD99	2	CD99	0.796213526	0.577674283
SAP18	4	SAP18	1.454603827	0.57715446
CHMP2B	5	CHMP2B	1.368741044	0.57630229
PDCD4	3	PDCD4	0.265516398	0.575063238

HMGCS1	14	HMGCS1	0.395909121	0.574664834
PLD3	3	PLD3	0.392513803	0.573877946
BZW1	12	BZW1	1.191685838	0.572543236
PLA2G4A	8	PLA2G4A	0.983345449	0.571540416
VPS4B	4	VPS4B	1.383518779	0.571247211
RRM2B	2	RRM2B	1.092963437	0.570546942
OCIAD2	6	OCIAD2	0.675332855	0.569276043
TMEM2	3	TMEM2	0.610866753	0.567781164
POLD1	10	POLD1	0.753962757	0.567160105
GLG1	15	GLG1	0.65397199	0.565122412
NUCB2;Nucb2	5	NUCB2	0.855805317	0.563110564
NDUFS3	8	NDUFS3	0.905687915	0.56236475
PTGFRN	2	PTGFRN	0.67261828	0.561769867
HELZ2	3	HELZ2	6.515608213	0.561705284
FUBP3	6	FUBP3	1.284924671	0.55926454
ARFGAP2	4	ARFGAP2	0.70741371	0.558635416
NUDT4	3	NUDT4	0.54451316	0.55815794
DSP	16	DSP	1.50902654	0.556477537
HSPB1	12	HSPB1	0.810817868	0.555422648
PXN	10	PXN	1.28992735	0.554975483
DPY30	2	DPY30	5.621647122	0.554403961
COX6B1	6	COX6B1	0.802358252	0.553249037
TMEM263	2	TMEM263	0.513198988	0.553125206
TMA7;hCG_2014768	3	TMA7	1.599323611	0.552290827
BTF3	3	BTF3	1.498693464	0.55212563
IDH3B	8	IDH3B	0.969192173	0.551843641

ABCF3	4	ABCF3	0.51059413	0.551819539
UBE2H	2	UBE2H	0.97786576	0.548127588
MINOS1;MINOS1-NBL1	2	MINOS1	1.208485628	0.546502533
RNF114	2	RNF114	1.183252139	0.544312112
NDUFS4	2	NDUFS4	0.869149203	0.543332249
MIF	3	MIF	1.132913817	0.541658617
NDUFV1	9	NDUFV1	0.843166644	0.537209114
PELO	4	PELO	1.175438858	0.534909938
S100P	2	S100P	1.984231505	0.533198156
PML	4	PML	2.200882704	0.530609922
GRSF1	3	GRSF1	0.523769968	0.529142285
GIT1	4	GIT1	1.335058185	0.529130095
NDUFC2	3	NDUFC2	0.931754638	0.527353943
NDUFS1	21	NDUFS1	0.859536172	0.525898482
LGMN	2	LGMN	0.390581592	0.525346082
EHD4	9	EHD4	1.482851755	0.524703536
C17orf49;RNASEK-C17orf49;BAP18	3	C17orf49	0.274640731	0.523991073
MRPS31	5	MRPS31	0.687719866	0.523831845
NDUFB3	2	NDUFB3	0.811997655	0.518538221
SDF4	4	SDF4	0.646949742	0.517897849
KPNA2	12	KPNA2	1.498768624	0.517379828
AKT1	3	AKT1	0.750625985	0.517189649
ITGA5	2	ITGA5	1.404313887	0.516050157
MYBBP1A	26	MYBBP1A	1.32298211	0.513093031
MRPS18B	2	MRPS18B	0.584251034	0.508675665
CPD	7	CPD	0.760805345	0.506267423

CLPTM1L	2	CLPTM1L	1.012478128	0.50589096
NDUFA2	6	NDUFA2	0.873449473	0.505726978
RBMS2	2	RBMS2	1.08887251	0.505377091
NLRP2	6	NLRP2	0.424414177	0.504703349
RRP12	11	RRP12	1.373565497	0.502441628
NDUFA5	4	NDUFA5	0.778426666	0.500553751
TRIM25	10	TRIM25	0.652137174	0.500291621
MAPK15	2	MAPK15	1.375375122	0.49293024
RPL37	3	RPL37	2.600760152	0.492328491
CA12	4	CA12	0.618763949	0.490847519
SNX3	8	SNX3	0.906121154	0.490193028
RBM3	5	RBM3	0.604343412	0.488843562
MRPL38	5	MRPL38	0.662899781	0.488534701
LAP3	18	LAP3	2.190660494	0.485220369
MRPL18	2	MRPL18	0.59402002	0.484864578
AGR2	5	AGR2	1.427527932	0.48307749
MPP5	2	MPP5	0.865639424	0.481833471
ASMTL	4	ASMTL	1.058308937	0.479066665
DSG2	6	DSG2	1.407135461	0.478008612
AQR	2	AQR	0.871527698	0.476940952
ENSA	4	ENSA	1.03195319	0.473958316
IPO4	15	IPO4	0.79513467	0.469442764
NDUFS2	6	NDUFS2	0.881388571	0.467595217
MRPS2	7	MRPS2	0.591367619	0.462226293
AFAP1L2	2	AFAP1L2	1.029096055	0.459172729
RSAD2	10	RSAD2	3.434645105	0.457500499

YTHDC1	3	YTHDC1	1.814230377	0.457436449	
NDUFS6	3	NDUFS6	0.920757	0.45400438	
NDUFA12	4	NDUFA12	1.035010321	0.453157277	
B2M	2	B2M	2.161880224	0.453007488	
EPHA2	11	EPHA2	2.133838081	0.452896923	
MRPL47	5	MRPL47	0.472505265	0.452663356	
MTUS1	6	MTUS1	0.600170681	0.452631484	
SAMHD1	9	SAMHD1	1.922100343	0.447088051	
TGOLN2	4	TGOLN2	0.386238485	0.445870903	
LGALS3BP	6	LGALS3BP	1.880551004	0.444846632	
CRYZL1	2	CRYZL1	1.119934201	0.443546202	
DAP3	6	DAP3	0.55629526	0.440561407	
FANCI	5	FANCI	1.000168384	0.433436692	
IFT80;TRIM59	2	IFT80	9.749575416	0.433301601	
MRPL19	4	MRPL19	0.709869968	0.431321898	
CASP8	5	CASP8	0.776151555	0.426793651	
DTX3L	2	DTX3L	1.830667339	0.425072959	
STAT3	8	STAT3	0.760092065	0.424672053	0.665798311
NUB1	2	NUB1	0.803156424	0.422171269	0.665084236
MRPL21	2	MRPL21	0.664016522	0.41641198	0.664795898
MRPS6	4	MRPS6	0.947671394	0.415643581	0.663895784
CDC2;CDK1	7	CDC2	0.660843858	0.414266976	0.663725983
OGFR	7	OGFR	1.583578244	0.410570152	0.662982085
PRNP	2	PRNP	0.702354987	0.410161763	0.661680295
WARS	20	WARS	3.049295724	0.409514241	0.661449642
BRAT1	2	BRAT1	0.861255936	0.408472843	0.660749402

UBE2G1	2	UBE2G1	2.882185952	0.406358844	0.658498825
NDUFB8	2	NDUFB8	0.711445714	0.405789325	0.654024627
UBE3C	3	UBE3C	1.095924393	0.404608564	0.652754952
MRPL44	3	MRPL44	0.551589963	0.401987147	0.649515478
AAMP	2	AAMP	0.942125079	0.39910945	0.645972897
MAP1LC3B;MAP1LC3B2;MAP1LC3A	2	MAP1LC3B	3.13115664	0.398924101	0.644653072
NMI	3	NMI	1.2005914	0.394301089	0.644592424
FAM208A	3	FAM208A	0.825446688	0.393161591	0.644326405
GSTM3	3	GSTM3	1.070265254	0.392655857	0.643178037
EARS2	6	EARS2	0.84380997	0.392375823	0.638452862
NDUFA10	8	NDUFA10	0.745094967	0.391728779	0.638407624
MRPS22	8	MRPS22	0.685620535	0.3896581	0.638205338
MRPS23	2	MRPS23	0.832695198	0.387071969	0.63761458
GADD45GIP1	2	GADD45GIP1	0.594479341	0.3861962	0.636746267
PRMT3	6	PRMT3	1.400726696	0.384295804	0.629032258
TSR2	2	TSR2	0.836054046	0.383435499	0.626348085
GULP1	2	GULP1	0.575953322	0.381613558	0.623967774
HCCS	2	HCCS	3.813782999	0.381239805	0.617660475
NDUFS8	4	NDUFS8	1.024792805	0.380612537	0.616872592
NDUFA7	2	NDUFA7	0.888705137	0.378972964	0.616408619
TRAM1	6	TRAM1	0.980316712	0.378434323	0.614710738
AGPAT5	3	AGPAT5	1.265989699	0.377063744	0.6137739
PHLDA2	2	PHLDA2	2.435677726	0.375611322	0.61375761
NDUFA13	5	NDUFA13	1.087272394	0.37514718	0.606503946
ZC3HAV1	21	ZC3HAV1	2.59416205	0.372786423	0.600887984
EIF1;EIF1B	3	EIF1	0.779662908	0.362161509	0.600482603

SUSD2	2	SUSD2	0.460816892	0.360430076	0.598130528
ITGA2	5	ITGA2	1.486854549	0.358794634	0.592716943
PTCD3	4	PTCD3	0.495700049	0.351335199	0.591892527
USP24	3	USP24	1.437850609	0.346846292	0.591657124
CUX1	2	CUX1	1.381337376	0.344506815	0.591376852
BCL10	3	BCL10	1.380985947	0.339853894	0.589925214
MRPL22	2	MRPL22	0.693467946	0.339576302	0.589047156
PDXDC1	8	PDXDC1	1.04074407	0.339441616	0.58569752
CHCHD2;CHCHD2P9	3	CHCHD2	1.065159813	0.336550048	0.583268022
CXorf38	2	CXorf38	2.58293731	0.33279555	0.580507268
IFIT5	3	IFIT5	1.055734762	0.330907956	0.580032526
WDR55	3	WDR55	0.969278948	0.326836526	0.577002635
MRPL24	3	MRPL24	0.57023427	0.325029541	0.576966702
GHITM	4	GHITM	0.607116725	0.322027959	0.575942493
GOPC	2	GOPC	2.581445744	0.313632832	0.567774046
NFKB2	7	NFKB2	1.812224981	0.31114312	0.564487172
SCD	2	SCD	0.086394161	0.309539877	0.562388445
MSRA	2	MSRA	1.013209521	0.300915608	0.561379049
NDUFB4	2	NDUFB4	0.835248373	0.296172791	0.560849692
SULT1A4;SULT1A3;SULT1A1	5	SULT1A4	0.784979248	0.28857158	0.560564936
CRELD2	2	CRELD2	0.841962839	0.282461119	0.55785816
IRF9	2	IRF9	1.749790347	0.282237676	0.555962631
PTGS2	11	PTGS2	5.830992886	0.282198858	0.555952851
C12orf57	4	C12orf57	0.669988714	0.278439162	0.554170967
HERC4	3	HERC4	0.791913954	0.274652098	0.5517394
STRA6	2	STRA6	0.609476133	0.27156632	0.551144653

POLD2	3	POLD2	0.788680872	0.269381333	0.551021618
MRPL23	3	MRPL23	0.4090822	0.26702656	0.549343568
INTS3	3	INTS3	1.242986103	0.266195305	0.549010177
ZFP36	2	ZFP36	19.40242954	0.26540432	0.547345737
RNF213	47	RNF213	0.988765628	0.264448877	0.546250182
NFKB1	2	NFKB1	1.923328148	0.263647724	0.539062827
GLS	6	GLS	0.464853744	0.258289162	0.53821667
PZP	2	PZP	1.213259992	0.252938982	0.537434411
HLA-E	2	HLA-E	2.368624568	0.241413679	0.53662846
VEZT	2	VEZT	134.8430744	0.240775302	0.535917313
PTDSS1	4	PTDSS1	1.910190802	0.238419593	0.520649057
JUNB	2	JUNB	2.811559088	0.235226479	0.520558686
DHCR7	7	DHCR7	0.405684707	0.229934241	0.519270711
VPS36	4	VPS36	0.726482526	0.225089334	0.518606845
UBE2L6	2	UBE2L6	1.611984832	0.218466712	0.518482152
SEL1L	2	SEL1L	0.826509539	0.217637423	0.515277544
IFI35	3	IFI35	3.463234936	0.216046128	0.514242993
TIAL1	2	TIAL1	0.8089979	0.206904257	0.509497704
LACTB	5	LACTB	0.738915761	0.203657235	0.509180066
MSMO1	2	MSMO1	0.428965847	0.20342458	0.506426032
POMP	2	POMP	1.087241721	0.194082381	0.499713561
FADS2	5	FADS2	0.014932883	0.193520401	0.494410183
CD55	2	CD55	1.877405052	0.190184508	0.492061426
HLA-B	2	Q2L6G2	9.255838534	0.186989407	0.487593166
LMF2	2	LMF2	1.336610137	0.175045474	0.487142625
TAP1	7	TAP1	4.166435057	0.169680707	0.483589409

AIDA	2	AIDA	1.661823668	0.163680933	0.480127088
MRPL37	8	MRPL37	0.477335165	0.160196784	0.475701417
NXF1	2	NXF1	1.135412984	0.154474174	0.473516999
GBP1	2	GBP1	3.974316677	0.154165716	0.464060824
ZFP36L1	2	ZFP36L1	4.224953455	0.147588855	0.461828631
CHID1	2	CHID1	1.330154199	0.146557606	0.452635259
MAFF	3	MAFF	3.875398584	0.139267511	0.451269037
SAMD9	2	SAMD9	7.009919972	0.136668757	0.44154585
FDFT1	9	FDFT1	0.194068963	0.136410488	0.4377276
MRPS21	2	MRPS21	0.926369847	0.127915616	0.435864491
GPX8	3	GPX8	1.321061879	0.124709991	0.435641506
EIF1AY	2	EIF1AY	1.65619681	0.117152512	0.426088643
APOL2	8	APOL2	5.217365274	0.115069711	0.419933923
TRIM21	3	TRIM21	1.982081309	0.111527612	0.412288758
IFI16	4	IFI16	7.934035532	0.099582165	0.402339328
NT5C3A	7	NT5C3A	6.868700799	0.093653685	0.397367377
UBE2S	4	UBE2S	1.414362253	0.092467352	0.394778409
LIMA1	2	LIMA1	1.825496763	0.090244791	0.375561542
NEB	3	NEB	26.07065879	0.082055867	0.36893342
ARPP19	2	ARPP19	1.033896571	0.065462088	0.360977318
NUCB1	14	NUCB1	0.585333772	0.064138202	0.358959151
ISG20	2	ISG20	18.63910532	0.062937345	0.341222925
PLAUR	3	PLAUR	24.66865392	0.054873278	0.337331291
ISG15	7	ISG15	474.2451443	0.050521826	0.332020186
CENPF	2	CENPF	1.756731763	0.047549731	0.305031331
DDX58	13	DDX58	16.34520759	0.040617565	0.28747866

HERC5	11	HERC5	37.05493772	0.039155656	0.286787011
IFIT1	16	IFIT1	93.01794185	0.035385391	0.246011891
OASL	18	OASL	76.25999546	0.024750595	0.181035056
MRPL14	2	MRPL14	0.693115589	0.021932152	0.098596208
MX1	15	MX1	85.20509118	0.006292461	0.095852461
IFIT3	13	IFIT3	269.7862583	0.004540579	0.08008024
IFIT2	17	IFIT2	649.560989	0.003790188	0.031540097
BAZ1A	3	BAZ1A	9.119539669	0.002043703	0.001608679

Table S4 All of the detailed parameters of target proteins obviously decreased or increased among experimental groups in influenza A-infected A549 cell model

ID	Pathway name	GeneRatio	pvalue	qvalue	Count	type
GO:0006120	mitochondrial electron transport, NADH to ubiquinone	21 367	2.85E-22	1.07E-18	21	Biological process
GO:0042775	mitochondrial ATP synthesis coupled electron transport	24 367	1.03E-19	1.68E-16	24	Biological process
GO:0042773	ATP synthesis coupled electron transport	24 367	1.34E-19	1.68E-16	24	Biological process
GO:0022904	respiratory electron transport chain	25 367	5.75E-19	5.39E-16	25	Biological process
GO:0010257	NADH dehydrogenase complex assembly	20 367	1.16E-18	7.24E-16	20	Biological process
GO:0032981	mitochondrial respiratory chain complex I assembly	20 367	1.16E-18	7.24E-16	20	Biological process
GO:0006119	oxidative phosphorylation	26 367	2.48E-18	1.33E-15	26	Biological process
GO:0022900	electron transport chain	28 367	8.15E-17	3.82E-14	28	Biological process
GO:0070125	mitochondrial translational elongation	20 367	9.07E-16	3.78E-13	20	Biological process
GO:0045333	cellular respiration	27 367	1.16E-15	4.33E-13	27	Biological process
GO:0070126	mitochondrial translational termination	20 367	1.46E-15	4.97E-13	20	Biological process
GO:0046034	ATP metabolic process	32 367	4.07E-15	1.27E-12	32	Biological process
GO:0033108	mitochondrial respiratory chain complex assembly	20 367	1.06E-14	3.06E-12	20	Biological process
GO:0015980	energy derivation by oxidation of organic compounds	31 367	2.20E-14	5.59E-12	31	Biological process
GO:0009144	purine nucleoside triphosphate metabolic process	33 367	2.30E-14	5.59E-12	33	Biological process
GO:0006415	translational termination	20 367	2.39E-14	5.59E-12	20	Biological process
GO:0009141	nucleoside triphosphate metabolic process	34 367	2.53E-14	5.59E-12	34	Biological process
GO:0032543	mitochondrial translation	22 367	2.95E-14	6.15E-12	22	Biological process

GO:0009205	purine ribonucleoside triphosphate metabolic process	32 367	7.34E-14	1.45E-11	32	Biological process
GO:0009199	ribonucleoside triphosphate metabolic process	32 367	1.25E-13	2.35E-11	32	Biological process
GO:0009161	ribonucleoside monophosphate metabolic process	33 367	1.33E-13	2.38E-11	33	Biological process
GO:0140053	mitochondrial gene expression	23 367	1.40E-13	2.39E-11	23	Biological process
GO:0009167	purine ribonucleoside monophosphate metabolic process	32 367	2.51E-13	4.09E-11	32	Biological process
GO:0009126	purine nucleoside monophosphate metabolic process	32 367	2.73E-13	4.27E-11	32	Biological process
GO:0009123	nucleoside monophosphate metabolic process	33 367	4.95E-13	7.43E-11	33	Biological process
GO:0006414	translational elongation	20 367	5.05E-12	7.29E-10	20	Biological process
GO:0032984	protein-containing complex disassembly	29 367	1.96E-11	2.73E-09	29	Biological process
GO:1903901	negative regulation of viral life cycle	15 367	7.10E-11	9.52E-09	15	Biological process
GO:0048525	negative regulation of viral process	16 367	1.09E-10	1.41E-08	16	Biological process
GO:0051607	defense response to virus	23 367	3.13E-10	3.91E-08	23	Biological process
GO:0043624	cellular protein complex disassembly	22 367	4.76E-10	5.76E-08	22	Biological process
GO:0019058	viral life cycle	27 367	5.72E-10	6.70E-08	27	Biological process
GO:1903900	regulation of viral life cycle	17 367	3.82E-09	4.34E-07	17	Biological process
GO:0060337	type I interferon signaling pathway	14 367	4.10E-09	4.39E-07	14	Biological process
GO:0071357	cellular response to type I interferon	14 367	4.10E-09	4.39E-07	14	Biological process
GO:0034340	response to type I interferon	14 367	8.52E-09	8.87E-07	14	Biological process
GO:0045071	negative regulation of viral genome replication	11 367	1.42E-08	1.44E-06	11	Biological process
GO:0009615	response to virus	24 367	3.60E-08	3.55E-06	24	Biological process
GO:0050792	regulation of viral process	18 367	1.53E-07	1.47E-05	18	Biological process

GO:0045540	regulation of cholesterol biosynthetic process	9 367	1.60E-07	1.50E-05	9	Biological process
GO:0051701	interaction with host	18 367	4.60E-07	4.20E-05	18	Biological process
GO:0043901	negative regulation of multi-organism process	16 367	6.32E-07	5.64E-05	16	Biological process
GO:1902930	regulation of alcohol biosynthetic process	10 367	7.45E-07	6.50E-05	10	Biological process
GO:0043903	regulation of symbiosis, encompassing mutualism through parasitism	18 367	9.68E-07	8.25E-05	18	Biological process
GO:0050810	regulation of steroid biosynthetic process	11 367	1.01E-06	8.42E-05	11	Biological process
GO:0006695	cholesterol biosynthetic process	10 367	1.15E-06	9.41E-05	10	Biological process
GO:0090181	regulation of cholesterol metabolic process	9 367	1.30E-06	0.000104	9	Biological process
GO:1902653	secondary alcohol biosynthetic process	10 367	1.52E-06	0.000119	10	Biological process
GO:0045069	regulation of viral genome replication	11 367	2.07E-06	0.000158	11	Biological process
GO:0060333	interferon-gamma-mediated signaling pathway	11 367	2.31E-06	0.000174	11	Biological process
GO:0019218	regulation of steroid metabolic process	12 367	2.53E-06	0.000186	12	Biological process
GO:0016126	sterol biosynthetic process	10 367	2.94E-06	0.000212	10	Biological process
GO:2001243	negative regulation of intrinsic apoptotic signaling pathway	11 367	4.91E-06	0.000347	11	Biological process
GO:0043900	regulation of multi-organism process	23 367	8.09E-06	0.000562	23	Biological process
GO:0008203	cholesterol metabolic process	12 367	2.54E-05	0.001732	12	Biological process
GO:0006636	unsaturated fatty acid biosynthetic process	7 367	2.68E-05	0.001795	7	Biological process
GO:0019079	viral genome replication	11 367	2.79E-05	0.001833	11	Biological process
GO:0046165	alcohol biosynthetic process	12 367	3.65E-05	0.002359	12	Biological process
GO:1903311	regulation of mRNA metabolic process	18 367	3.73E-05	0.002371	18	Biological process
GO:1903320	regulation of protein modification by small protein conjugation or removal	15 367	3.91E-05	0.002407	15	Biological process
GO:1902652	secondary alcohol metabolic process	12 367	3.91E-05	0.002407	12	Biological process

GO:0006979	response to oxidative stress	23 367	4.53E-05	0.00274	23	Biological process
GO:0046890	regulation of lipid biosynthetic process	13 367	4.80E-05	0.002856	13	Biological process
GO:0016125	sterol metabolic process	12 367	8.68E-05	0.005086	12	Biological process
GO:0008202	steroid metabolic process	18 367	9.60E-05	0.005539	18	Biological process
GO:0061013	regulation of mRNA catabolic process	13 367	0.000109	0.006216	13	Biological process
GO:2001242	regulation of intrinsic apoptotic signaling pathway	12 367	0.000125	0.007014	12	Biological process
GO:0097193	intrinsic apoptotic signaling pathway	17 367	0.000128	0.007014	17	Biological process
GO:0031396	regulation of protein ubiquitination	13 367	0.000129	0.007014	13	Biological process
GO:0006694	steroid biosynthetic process	13 367	0.000144	0.007703	13	Biological process
GO:0006402	mRNA catabolic process	19 367	0.000149	0.007845	19	Biological process
GO:0086004	regulation of cardiac muscle cell contraction	6 367	0.000164	0.008508	6	Biological process
GO:0006401	RNA catabolic process	20 367	0.000168	0.008508	20	Biological process
GO:0032020	ISG15-protein conjugation	3 367	0.00017	0.008508	3	Biological process
GO:0086073	bundle of His cell-Purkinje myocyte adhesion involved in cell communication	3 367	0.00017	0.008508	3	Biological process
GO:0032434	regulation of proteasomal ubiquitin-dependent protein catabolic process	10 367	0.00019	0.009275	10	Biological process
GO:0046718	viral entry into host cell	10 367	0.00019	0.009275	10	Biological process
GO:1903321	negative regulation of protein modification by small protein conjugation or removal	8 367	0.000195	0.009375	8	Biological process
GO:2000058	regulation of ubiquitin-dependent protein catabolic process	11 367	0.000202	0.009576	11	Biological process
GO:0019985	translesion synthesis	6 367	0.000216	0.010127	6	Biological process
GO:0032479	regulation of type I interferon production	10 367	0.00025	0.011555	10	Biological process
GO:0032606	type I interferon production	10 367	0.000267	0.01219	10	Biological process

GO:0086042	cardiac muscle cell-cardiac muscle cell adhesion	3 367	0.000293	0.013217	3	Biological process
GO:0033559	unsaturated fatty acid metabolic process	9 367	0.000296	0.013217	9	Biological process
GO:0043161	proteasome-mediated ubiquitin-dependent protein catabolic process	20 367	0.000315	0.013722	20	Biological process
GO:0045646	regulation of erythrocyte differentiation	6 367	0.000318	0.013722	6	Biological process
GO:1903115	regulation of actin filament-based movement	6 367	0.000318	0.013722	6	Biological process
GO:0031397	negative regulation of protein ubiquitination	7 367	0.000392	0.016689	7	Biological process
GO:1902186	regulation of viral release from host cell	5 367	0.000411	0.017327	5	Biological process
GO:0022613	ribonucleoprotein complex biogenesis	22 367	0.000416	0.017327	22	Biological process
GO:1904580	regulation of intracellular mRNA localization	2 367	0.000431	0.017573	2	Biological process
GO:1904582	positive regulation of intracellular mRNA localization	2 367	0.000431	0.017573	2	Biological process
GO:0046456	icosanoid biosynthetic process	6 367	0.000455	0.018354	6	Biological process
GO:0002483	antigen processing and presentation of endogenous peptide antigen	3 367	0.000462	0.018426	3	Biological process
GO:0043276	anoikis	5 367	0.000479	0.018925	5	Biological process
GO:0032480	negative regulation of type I interferon production	6 367	0.00051	0.019679	6	Biological process
GO:0030260	entry into host cell	10 367	0.000526	0.019679	10	Biological process
GO:0044409	entry into host	10 367	0.000526	0.019679	10	Biological process
GO:0051806	entry into cell of other organism involved in symbiotic interaction	10 367	0.000526	0.019679	10	Biological process
GO:0051828	entry into other organism involved in symbiotic interaction	10 367	0.000526	0.019679	10	Biological process

GO:0043488	regulation of mRNA stability	11 367	0.00053	0.019679	11	Biological process
GO:2001234	negative regulation of apoptotic signaling pathway	13 367	0.000536	0.019721	13	Biological process
GO:0098901	regulation of cardiac muscle cell action potential	5 367	0.000555	0.019759	5	Biological process
GO:1901673	regulation of mitotic spindle assembly	4 367	0.000556	0.019759	4	Biological process
GO:0006633	fatty acid biosynthetic process	10 367	0.000558	0.019759	10	Biological process
GO:0007565	female pregnancy	12 367	0.000558	0.019759	12	Biological process
GO:0051170	import into nucleus	11 367	0.000652	0.022847	11	Biological process
GO:0044706	multi-multicellular organism process	13 367	0.000667	0.023157	13	Biological process
GO:0034341	response to interferon-gamma	12 367	0.000674	0.023187	12	Biological process
GO:0060700	regulation of ribonuclease activity	3 367	0.000682	0.023255	3	Biological process
GO:0019216	regulation of lipid metabolic process	18 367	0.000691	0.023351	18	Biological process
GO:0019076	viral release from host cell	5 367	0.000734	0.023742	5	Biological process
GO:0035890	exit from host	5 367	0.000734	0.023742	5	Biological process
GO:0035891	exit from host cell	5 367	0.000734	0.023742	5	Biological process
GO:0052126	movement in host environment	5 367	0.000734	0.023742	5	Biological process
GO:0052192	movement in environment of other organism involved in symbiotic interaction	5 367	0.000734	0.023742	5	Biological process
GO:0006301	postreplication repair	6 367	0.00078	0.024805	6	Biological process
GO:0098900	regulation of action potential	6 367	0.00078	0.024805	6	Biological process
GO:0043487	regulation of RNA stability	11 367	0.000796	0.025092	11	Biological process
GO:0006631	fatty acid metabolic process	18 367	0.000833	0.025774	18	Biological process
GO:0006692	prostanoid metabolic process	5 367	0.000838	0.025774	5	Biological process
GO:0006693	prostaglandin metabolic process	5 367	0.000838	0.025774	5	Biological process
GO:0001701	in utero embryonic development	16 367	0.000872	0.026591	16	Biological process

GO:0071346	cellular response to interferon-gamma	11 367	0.000921	0.027722	11	Biological process
GO:0017038	protein import	12 367	0.000924	0.027722	12	Biological process
GO:0002934	desmosome organization	3 367	0.000959	0.028111	3	Biological process
GO:1904896	ESCRT complex disassembly	3 367	0.000959	0.028111	3	Biological process
GO:1904903	ESCRT III complex disassembly	3 367	0.000959	0.028111	3	Biological process
GO:0007249	I-kappaB kinase/NF-kappaB signaling	14 367	0.000981	0.028509	14	Biological process
GO:0032469	endoplasmic reticulum calcium ion homeostasis	4 367	0.000999	0.028828	4	Biological process
GO:0014074	response to purine-containing compound	10 367	0.001019	0.029183	10	Biological process
GO:0045862	positive regulation of proteolysis	17 367	0.001106	0.031426	17	Biological process
GO:0071260	cellular response to mechanical stimulus	7 367	0.001181	0.033292	7	Biological process
GO:2000209	regulation of anoikis	4 367	0.00119	0.033305	4	Biological process
GO:0002428	antigen processing and presentation of peptide antigen via MHC class Ib	2 367	0.001275	0.034112	2	Biological process
GO:0035928	rRNA import into mitochondrion	2 367	0.001275	0.034112	2	Biological process
GO:0042270	protection from natural killer cell mediated cytotoxicity	2 367	0.001275	0.034112	2	Biological process
GO:1903719	regulation of I-kappaB phosphorylation	2 367	0.001275	0.034112	2	Biological process
GO:1903721	positive regulation of I-kappaB phosphorylation	2 367	0.001275	0.034112	2	Biological process
GO:0072659	protein localization to plasma membrane	13 367	0.001277	0.034112	13	Biological process
GO:0006066	alcohol metabolic process	16 367	0.001294	0.034112	16	Biological process
GO:0019883	antigen processing and presentation of endogenous antigen	3 367	0.001299	0.034112	3	Biological process
GO:0043312	neutrophil degranulation	21 367	0.00131	0.034112	21	Biological process
GO:0062012	regulation of small molecule metabolic	21 367	0.00131	0.034112	21	Biological process

	process					
GO:0010498	proteasomal protein catabolic process	20 367	0.001346	0.034814	20	Biological process
GO:0060135	maternal process involved in female pregnancy	6 367	0.00138	0.035451	6	Biological process
GO:0002283	neutrophil activation involved in immune response	21 367	0.001413	0.036045	21	Biological process
GO:0007568	aging	15 367	0.001505	0.038151	15	Biological process
GO:0032436	positive regulation of proteasomal ubiquitin-dependent protein catabolic process	7 367	0.001583	0.039848	7	Biological process
GO:1901617	organic hydroxy compound biosynthetic process	13 367	0.001603	0.040075	13	Biological process
GO:0090169	regulation of spindle assembly	4 367	0.001645	0.040862	4	Biological process
GO:0006397	mRNA processing	21 367	0.001681	0.041467	21	Biological process
GO:0098798	mitochondrial protein complex	47 372	3.55E-31	1.72E-28	47	Cellular component
GO:0005747	mitochondrial respiratory chain complex I	21 372	7.10E-23	8.58E-21	21	Cellular component
GO:0030964	NADH dehydrogenase complex	21 372	7.10E-23	8.58E-21	21	Cellular component
GO:0045271	respiratory chain complex I	21 372	7.10E-23	8.58E-21	21	Cellular component
GO:0098800	inner mitochondrial membrane protein complex	27 372	3.97E-19	3.84E-17	27	Cellular component
GO:0098803	respiratory chain complex	22 372	8.12E-19	6.54E-17	22	Cellular component
GO:0005746	mitochondrial respiratory chain	22 372	6.72E-18	4.64E-16	22	Cellular component
GO:1990204	oxidoreductase complex	23 372	3.48E-17	1.93E-15	23	Cellular component
GO:0070469	respiratory chain	22 372	3.59E-17	1.93E-15	22	Cellular component
GO:0005759	mitochondrial matrix	42 372	8.74E-17	4.22E-15	42	Cellular component
GO:0000313	organellar ribosome	19 372	3.86E-15	1.55E-13	19	Cellular component
GO:0005761	mitochondrial ribosome	19 372	3.86E-15	1.55E-13	19	Cellular component

GO:0005840	ribosome	29 372	8.88E-15	3.30E-13	29	Cellular component
GO:0044455	mitochondrial membrane part	27 372	4.26E-14	1.47E-12	27	Cellular component
GO:0044391	ribosomal subunit	23 372	6.34E-12	2.04E-10	23	Cellular component
GO:0015934	large ribosomal subunit	16 372	2.34E-09	7.07E-08	16	Cellular component
GO:0000315	organellar large ribosomal subunit	11 372	4.85E-09	1.30E-07	11	Cellular component
GO:0005762	mitochondrial large ribosomal subunit	11 372	4.85E-09	1.30E-07	11	Cellular component
GO:0005925	focal adhesion	24 372	1.28E-06	3.25E-05	24	Cellular component
GO:0005924	cell-substrate adherens junction	24 372	1.46E-06	3.53E-05	24	Cellular component
GO:0030055	cell-substrate junction	24 372	1.82E-06	4.19E-05	24	Cellular component
GO:0000314	organellar small ribosomal subunit	6 372	1.55E-05	0.000325	6	Cellular component
GO:0005763	mitochondrial small ribosomal subunit	6 372	1.55E-05	0.000325	6	Cellular component
GO:0005635	nuclear envelope	22 372	0.000125	0.002521	22	Cellular component
GO:0016607	nuclear speck	19 372	0.000244	0.004712	19	Cellular component
GO:0009368	endopeptidase Clp complex	2 372	0.000395	0.007336	2	Cellular component
GO:0015935	small ribosomal subunit	7 372	0.000615	0.011011	7	Cellular component
GO:0034666	integrin alpha2-beta1 complex	2 372	0.001169	0.020167	2	Cellular component
GO:0000803	sex chromosome	4 372	0.00163	0.027152	4	Cellular component
GO:0005791	rough endoplasmic reticulum	7 372	0.002117	0.034096	7	Cellular component
GO:0043625	delta DNA polymerase complex	2 372	0.002307	0.03595	2	Cellular component
GO:0008137	NADH dehydrogenase (ubiquinone) activity	21 363	1.04E-23	2.37E-21	21	Molecular function
GO:0050136	NADH dehydrogenase (quinone) activity	21 363	1.04E-23	2.37E-21	21	Molecular function
GO:0016655	oxidoreductase activity, acting on NAD(P)H, quinone or similar compound as acceptor	23 363	1.06E-23	2.37E-21	23	Molecular function
GO:0003954	NADH dehydrogenase activity	21 363	3.21E-23	5.39E-21	21	Molecular function
GO:0016651	oxidoreductase activity, acting on NAD(P)H	23 363	9.72E-17	1.31E-14	23	Molecular function
GO:0003735	structural constituent of ribosome	22 363	2.72E-12	3.05E-10	22	Molecular function

GO:0044389	ubiquitin-like protein ligase binding	20 363	1.40E-05	0.001348	20	Molecular function
GO:0009055	electron transfer activity	11 363	2.45E-05	0.002056	11	Molecular function
GO:0031625	ubiquitin protein ligase binding	18 363	8.29E-05	0.004964	18	Molecular function
GO:0016717	oxidoreductase activity, acting on paired donors, with oxidation of a pair of donors resulting in	3 363	8.51E-05	0.004964	3	Molecular function
GO:0086083	cell adhesive protein binding involved in bundle of His cell-Purkinje myocyte communication	3 363	8.51E-05	0.004964	3	Molecular function
GO:0050839	cell adhesion molecule binding	24 363	8.87E-05	0.004964	24	Molecular function
GO:0045296	cadherin binding	18 363	0.000151	0.007641	18	Molecular function
GO:0098631	cell adhesion mediator activity	6 363	0.000159	0.007641	6	Molecular function
GO:0051539	4 iron, 4 sulfur cluster binding	6 363	0.000183	0.00821	6	Molecular function
GO:0048037	cofactor binding	23 363	0.000237	0.009968	23	Molecular function
GO:0008266	poly(U) RNA binding	4 363	0.000546	0.021561	4	Molecular function
GO:0001618	virus receptor activity	7 363	0.000838	0.029623	7	Molecular function
GO:0104005	hijacked molecular function	7 363	0.000838	0.029623	7	Molecular function
GO:0086080	protein binding involved in heterotypic cell-cell adhesion	3 363	0.000946	0.031483	3	Molecular function
GO:0031072	heat shock protein binding	9 363	0.000984	0.031483	9	Molecular function
GO:0008187	poly-pyrimidine tract binding	4 363	0.001168	0.035334	4	Molecular function
GO:0004768	stearoyl-CoA 9-desaturase activity	2 363	0.001263	0.035334	2	Molecular function
GO:0016215	acyl-CoA desaturase activity	2 363	0.001263	0.035334	2	Molecular function
GO:0019843	rRNA binding	6 363	0.001345	0.036134	6	Molecular function
GO:0017091	AU-rich element binding	4 363	0.001615	0.04172	4	Molecular function

Table S5 Enriched GO pathway of differentially expressed proteins in compound 8 treatment at 100 µg/mL in influenza A-infected A549 cell model

Pathway name	GeneRatio	BgRatio	pvalue	qvalue	Count
Oxidative phosphorylation	26 237	133 8034	7.82E-15	1.84E-12	26
Non-alcoholic fatty liver disease (NAFLD)	26 237	149 8034	1.34E-13	1.57E-11	26
Parkinson disease	30 237	249 8034	3.33E-11	2.62E-09	30
Retrograde endocannabinoid signaling	22 237	148 8034	2.92E-10	1.72E-08	22
Thermogenesis	27 237	231 8034	6.93E-10	3.27E-08	27
Huntington disease	31 237	306 8034	1.27E-09	4.98E-08	31
Alzheimer disease	34 237	369 8034	2.29E-09	7.71E-08	34
Ribosome	15 237	158 8034	6.16E-05	0.001815151	15
Influenza A	15 237	170 8034	0.000141691	0.003712128	15
Steroid biosynthesis	5 237	20 8034	0.000230959	0.005445774	5
Epstein-Barr virus infection	16 237	201 8034	0.000282087	0.006046654	16
Measles	12 237	138 8034	0.000748085	0.01469921	12
Protein processing in endoplasmic reticulum	13 237	167 8034	0.001284616	0.023299915	13

Table S6 Enriched KEGG pathway of differentially expressed proteins in compound 8 treatment at 100 µg/mL in influenza A-infected A549 cell model