Designing mitophagy-targeted robustine- and 4-acridinol-rhodium(III) coordination compounds to overcome cisplatin resistance in A549/DDP lung cancer cells

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Table S1. Crystal data and structure refinement for AcRh.	
Empirical formula	$C_{44}H_{31}ClN_2O_2PRh$
Formula weight	789.04
Temperature/K	293(2)
Crystal system	monoclinic
Space group	I2/a
a/Å	15.946(3)
b/Å	18.321(3)
c/Å	24.503(6)
α/°	90
β/°	90.963(19)
γ/°	90
Volume/Å^3	7157(3)
Z	8
ρ_{calc}mg/mm^3	1.465
m/mm^{-1}	0.638
F(000)	3216.0
Crystal size/mm^3	0.25 × 0.12 × 0.08
2Θ range for data collection	4.446 to 50.054°
Index ranges	$-18 \le h \le 18$, $-21 \le k \le 20$, $-17 \le l \le 29$
Reflections collected	12087
Independent reflections	6319[R(int) = 0.1765]
Data/restraints/parameters	6319/205/425
Goodness-of-fit on F^2	1.010
Final R indexes [I>=2σ (I)]	R_1 = 0.1450, wR_2 = 0.3346
Final R indexes [all data]	R_1 = 0.2715, wR_2 = 0.4498
Largest diff. peak/hole / e Å^{-3}	2.54/-1.65

Table S2. Bond Lengths for AcRh.					
Atom	**Atom**	**Length/Å**	**Atom**	**Atom**	**Length/Å**
Rh1	P1	2.297(5)	C15	C16	1.3900
Rh1	Cl1	2.393(4)	C16	C17	1.3900
Rh1	O1	2.020(13)	C17	C18	1.3900
Rh1	N2	2.109(12)	C18	C19	1.3900
Rh1	N1	2.077(16)	C3	C2	1.42(3)
Rh1	O2	2.035(14)	C3	C4	1.40(3)
P1	C26	1.844(11)	C20	C21	1.3900
P1	C14	1.848(13)	C20	C25	1.3900
P1	C20	1.824(10)	C21	C22	1.3900
O1	C2	1.354(19)	C22	C23	1.3900
N2	C1	1.27(2)	C23	C24	1.3900
N2	C9	1.42(2)	C24	C25	1.3900
N1	C40	1.34(2)	C8	C9	1.42(2)
N1	C37	1.27(2)	C8	C13	1.39(3)
C7	C6	1.37(3)	C12	C13	1.34(3)
C7	C8	1.36(3)	C37	C36	1.51(3)
C6	C1	1.42(2)	C37	C32	1.39(3)
C6	C5	1.44(3)	C9	C10	1.41(3)
C26	C31	1.3900	C36	C38	1.27(3)
C26	C27	1.3900	C36	C35	1.54(3)
C31	C30	1.3900	C39	C38	1.48(3)
C30	C29	1.3900	C39	C44	1.35(3)
C29	C28	1.3900	C5	C4	1.30(3)
C28	C27	1.3900	C41	C42	1.35(3)
C11	C12	1.29(3)	C43	C42	1.32(3)
C11	C10	1.32(3)	C43	C44	1.29(3)
C1	C2	1.43(3)	C34	C33	1.36(3)
C40	C39	1.42(3)	C34	C35	1.31(3)
C40	C41	1.38(2)	C33	C32	1.39(3)
C14	C15	1.3900	O2	C32	1.38(2)
C14	C19	1.3900			

Table S3. Bond Angles for AcRh.							
Atom	**Atom**	**Atom**	**Angle/°**	**Atom**	**Atom**	**Atom**	**Angle/°**
P1	Rh1	Cl1	177.22(17)	C16	C15	C14	120.0
O1	Rh1	P1	84.1(4)	C15	C16	C17	120.0
O1	Rh1	Cl1	93.4(4)	C16	C17	C18	120.0
O1	Rh1	N2	78.4(5)	C19	C18	C17	120.0
O1	Rh1	N1	98.9(6)	C18	C19	C14	120.0
O1	Rh1	O2	175.3(5)	C4	C3	C2	117(2)
N2	Rh1	P1	94.1(3)	C21	C20	P1	115.3(7)
N2	Rh1	Cl1	84.4(3)	C21	C20	C25	120.0
N1	Rh1	P1	95.2(4)	C25	C20	P1	124.6(7)
N1	Rh1	Cl1	86.2(4)	C22	C21	C20	120.0
N1	Rh1	N2	170.0(5)	C21	C22	C23	120.0
O2	Rh1	P1	91.3(4)	C24	C23	C22	120.0
O2	Rh1	Cl1	91.3(4)	C25	C24	C23	120.0
O2	Rh1	N2	102.8(6)	C24	C25	C20	120.0
O2	Rh1	N1	80.7(6)	C7	C8	C9	123.7(19)
C26	P1	Rh1	108.2(4)	C7	C8	C13	122.7(17)
C26	P1	C14	107.2(7)	C13	C8	C9	114(2)
C14	P1	Rh1	117.7(6)	C11	C12	C13	120(3)
C20	P1	Rh1	114.0(4)	N1	C37	C36	123(2)
C20	P1	C26	105.8(6)	N1	C37	C32	117.9(19)
C20	P1	C14	103.1(7)	C32	C37	C36	119(2)
C2	O1	Rh1	114.9(11)	O1	C2	C1	114.3(17)
C1	N2	Rh1	112.7(13)	O1	C2	C3	124.3(19)
C1	N2	C9	122.0(14)	C3	C2	C1	121.1(17)
C9	N2	Rh1	125.2(11)	N2	C9	C8	113.4(17)
C40	N1	Rh1	126.8(13)	C10	C9	N2	125.0(17)
C37	N1	Rh1	111.5(14)	C10	C9	C8	121(2)
C37	N1	C40	121.6(18)	C37	C36	C35	115(2)
C8	C7	C6	119.6(15)	C38	C36	C37	116(2)
C7	C6	C1	116.1(18)	C38	C36	C35	129(2)
C7	C6	C5	122.6(18)	C40	C39	C38	115.6(19)
C1	C6	C5	121(2)	C44	C39	C40	121(2)
C31	C26	P1	120.8(8)	C44	C39	C38	123(2)
C31	C26	C27	120.0	C4	C5	C6	120(2)
C27	C26	P1	119.1(8)	C5	C4	C3	125(3)

C30	C31	C26	120.0	C11	C10	C9	117(2)
C31	C30	C29	120.0	C42	C41	C40	119.8(18)
C28	C29	C30	120.0	C12	C13	C8	123(2)
C27	C28	C29	120.0	C44	C43	C42	116(3)
C28	C27	C26	120.0	C35	C34	C33	127(3)
C12	C11	C10	125(3)	C34	C33	C32	120(3)
N2	C1	C6	124.1(19)	C36	C38	C39	123(2)
N2	C1	C2	118.9(16)	C43	C42	C41	125(2)
C6	C1	C2	116.9(19)	C43	C44	C39	124(2)
N1	C40	C39	121.2(18)	C32	O2	Rh1	107.6(14)
N1	C40	C41	125.2(17)	C34	C35	C36	116(2)
C41	C40	C39	113.6(19)	C37	C32	C33	121(2)
C15	C14	P1	126.4(12)	O2	C32	C37	119(2)
C15	C14	C19	120.0	O2	C32	C33	120(2)
C19	C14	P1	113.6(12)				

Table S4. Crystal data and structure refinement for RoRh·3MeOH.	
Identification code	
Empirical formula	$C_{63}H_{58}ClN_2O_9P_2Rh$
Formula weight	1187.41
Temperature/K	150.0
Crystal system	triclinic
Space group	P-1
a/Å	11.7749(4)
b/Å	13.8665(4)
c/Å	18.1394(7)
α/°	96.8680(10)
β/°	99.566(2)
γ/°	107.8630(10)
Volume/Å^3	2733.48(16)
Z	2
ρ_{calc}mg/mm^3	1.443
m/mm^{-1}	0.481
F(000)	1228.0
Crystal size/mm^3	0.54 × 0.45 × 0.41
2Θ range for data collection	4.226 to 52.88°
Index ranges	-14 ≤ h ≤ 14, -17 ≤ k ≤ 17, -22 ≤ l ≤ 22

Reflections collected	97217
Independent reflections	11211[R(int) = 0.0706]
Data/restraints/parameters	11211/0/711
Goodness-of-fit on F^2	1.018
Final R indexes [I>=2σ (I)]	R_1 = 0.0405, wR_2 = 0.1055
Final R indexes [all data]	R_1 = 0.0535, wR_2 = 0.1176
Largest diff. peak/hole / e $Å^{-3}$	0.38/-1.03

Table S5. Bond Lengths for RoRh·3MeOH.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
Rh1	P1	2.3988(7)	C25	P2	1.820(3)
Rh1	O5	2.0217(19)	C58	C59	1.388(4)
Rh1	O2	2.0228(19)	C58	C57	1.405(5)
Rh1	N1	2.071(2)	C59	C53	1.423(4)
Rh1	N2	2.063(2)	C51	C52	1.418(4)
Rh1	P2	2.3875(7)	C51	C50	1.452(4)
P1	C7	1.826(3)	C51	C55	1.389(4)
P1	C1	1.824(3)	C42	C43	1.418(4)
P1	C13	1.832(3)	C42	C44	1.427(4)
O5	C59	1.328(3)	C23	C24	1.390(4)
O1	C40	1.350(3)	C23	C22	1.380(4)
O1	C37	1.395(3)	C24	C19	1.394(4)
O2	C47	1.333(3)	C43	C39	1.387(4)
O3	C43	1.345(3)	C10	C9	1.379(5)
O3	C48	1.441(4)	C26	C27	1.391(4)
O4	C52	1.348(3)	C46	C47	1.376(4)
O4	C49	1.393(4)	C46	C45	1.410(4)
O6	C55	1.337(3)	C19	C20	1.390(4)
O6	C60	1.442(4)	C19	P2	1.825(3)
N1	C41	1.389(3)	C35	C34	1.378(5)
N1	C40	1.312(4)	C53	C54	1.406(4)
N2	C52	1.314(4)	C44	C45	1.365(4)
N2	C53	1.378(3)	C34	C33	1.371(5)
O9	C63	1.407(4)	C38	C39	1.450(4)
O8	C62	1.412(5)	C21	C20	1.383(4)
C12	C7	1.383(4)	C21	C22	1.381(5)
C12	C11	1.390(4)	C8	C9	1.381(4)
C7	C8	1.398(4)	C50	C49	1.333(4)

C31	C36	1.387(4)	C13	C18	1.393(4)
C31	C32	1.392(4)	C13	C14	1.390(4)
C31	P2	1.824(3)	C5	C4	1.392(5)
C6	C1	1.395(4)	C18	C17	1.381(4)
C6	C5	1.392(4)	C30	C29	1.388(4)
O7	C61	1.400(6)	C27	C28	1.391(5)
C36	C35	1.394(4)	C57	C56	1.364(5)
C41	C42	1.403(4)	C55	C54	1.424(4)
C41	C47	1.425(4)	C2	C3	1.388(4)
C11	C10	1.381(4)	C28	C29	1.374(5)
C1	C2	1.397(4)	C14	C15	1.389(4)
C40	C39	1.421(4)	C17	C16	1.383(5)
C37	C38	1.332(4)	C56	C54	1.420(4)
C32	C33	1.384(4)	C16	C15	1.381(5)
C25	C26	1.392(4)	C4	C3	1.377(5)
C25	C30	1.395(4)			

Table S6. Bond Angles for RoRh·3MeOH.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O5	Rh1	P1	90.58(6)	C22	C23	C24	120.6(3)
O5	Rh1	O2	91.71(8)	C23	C24	C19	119.9(3)
O5	Rh1	N1	170.32(8)	O4	C52	C51	110.9(2)
O5	Rh1	N2	79.92(8)	N2	C52	O4	121.4(2)
O5	Rh1	P2	87.26(6)	N2	C52	C51	127.8(3)
O2	Rh1	P1	87.98(6)	O3	C43	C42	115.8(2)
O2	Rh1	N1	79.74(8)	O3	C43	C39	125.7(3)
O2	Rh1	N2	170.56(8)	C39	C43	C42	118.5(2)
O2	Rh1	P2	91.86(6)	C9	C10	C11	120.0(3)
N1	Rh1	P1	93.62(6)	C27	C26	C25	120.3(3)
N1	Rh1	P2	88.48(6)	C47	C46	C45	119.8(3)
N2	Rh1	P1	87.75(6)	C24	C19	P2	124.8(2)
N2	Rh1	N1	108.94(9)	C20	C19	C24	119.0(3)
N2	Rh1	P2	92.09(6)	C20	C19	P2	116.2(2)
P2	Rh1	P1	177.83(2)	C34	C35	C36	120.5(3)
C7	P1	Rh1	115.03(9)	N2	C53	C59	114.6(2)
C7	P1	C13	99.89(13)	N2	C53	C54	123.3(3)
C1	P1	Rh1	112.99(9)	C54	C53	C59	122.0(3)

C1	P1	C7	106.50(13)	C45	C44	C42	119.7(3)
C1	P1	C13	106.29(13)	C33	C34	C35	120.2(3)
C13	P1	Rh1	114.91(9)	C34	C33	C32	120.2(3)
C59	O5	Rh1	113.04(17)	C37	C38	C39	107.3(3)
C40	O1	C37	106.0(2)	C40	C39	C38	104.0(2)
C47	O2	Rh1	113.07(16)	C43	C39	C40	116.9(3)
C43	O3	C48	117.9(2)	C43	C39	C38	139.1(3)
C52	O4	C49	106.1(2)	C22	C21	C20	120.4(3)
C55	O6	C60	119.3(2)	C9	C8	C7	120.4(3)
C41	N1	Rh1	111.47(17)	C49	C50	C51	107.0(3)
C40	N1	Rh1	134.01(18)	C50	C49	O4	111.9(3)
C40	N1	C41	114.3(2)	C18	C13	P1	116.7(2)
C52	N2	Rh1	133.69(18)	C14	C13	P1	124.3(2)
C52	N2	C53	114.3(2)	C14	C13	C18	118.9(3)
C53	N2	Rh1	111.89(18)	C4	C5	C6	119.0(3)
C7	C12	C11	119.4(3)	C17	C18	C13	120.8(3)
C12	C7	P1	121.6(2)	C29	C30	C25	119.9(3)
C12	C7	C8	119.6(3)	C26	C27	C28	119.4(3)
C8	C7	P1	118.7(2)	C56	C57	C58	122.3(3)
C36	C31	C32	119.6(3)	C21	C20	C19	120.5(3)
C36	C31	P2	122.5(2)	O6	C55	C51	127.2(3)
C32	C31	P2	117.9(2)	O6	C55	C54	114.9(3)
C5	C6	C1	120.6(3)	C51	C55	C54	117.9(3)
C31	C36	C35	119.4(3)	O2	C47	C41	117.6(2)
N1	C41	C42	123.4(2)	O2	C47	C46	123.8(3)
N1	C41	C47	114.6(2)	C46	C47	C41	118.5(2)
C42	C41	C47	121.6(2)	C3	C2	C1	119.6(3)
C10	C11	C12	120.7(3)	C10	C9	C8	119.9(3)
C6	C1	P1	118.7(2)	C44	C45	C46	122.1(3)
C6	C1	C2	119.5(3)	C29	C28	C27	120.6(3)
C2	C1	P1	121.6(2)	C23	C22	C21	119.6(3)
O1	C40	C39	110.9(2)	C15	C14	C13	120.0(3)
N1	C40	O1	121.5(2)	C18	C17	C16	119.9(3)
N1	C40	C39	127.6(2)	C57	C56	C54	119.9(3)
C38	C37	O1	111.7(3)	C28	C29	C30	120.2(3)
C33	C32	C31	120.2(3)	C53	C54	C55	119.2(3)
C26	C25	C30	119.5(3)	C53	C54	C56	117.7(3)
C26	C25	P2	120.6(2)	C56	C54	C55	123.1(3)
C30	C25	P2	119.6(2)	C15	C16	C17	119.8(3)

C59	C58	C57	119.8(3)	C3	C4	C5	120.7(3)
O5	C59	C58	123.7(3)	C16	C15	C14	120.6(3)
O5	C59	C53	118.1(2)	C4	C3	C2	120.5(3)
C58	C59	C53	118.1(3)	C31	P2	Rh1	116.18(10)
C52	C51	C50	104.2(2)	C31	P2	C19	101.54(13)
C55	C51	C52	116.8(3)	C25	P2	Rh1	111.69(9)
C55	C51	C50	139.0(3)	C25	P2	C31	105.22(13)
C41	C42	C43	118.8(2)	C25	P2	C19	107.72(13)
C41	C42	C44	117.8(3)	C19	P2	Rh1	113.57(9)
C43	C42	C44	123.2(3)				

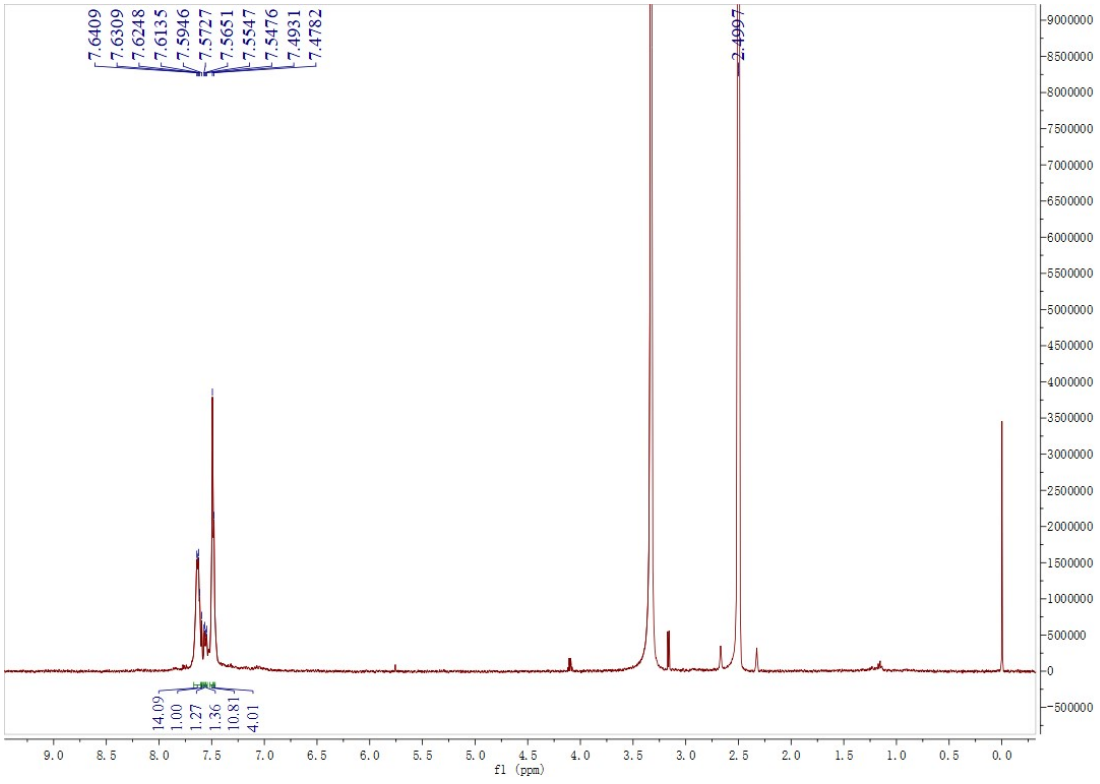


Figure S1. ^{1}H NMR of **AcRh**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.64 – 7.61 (m, 14H), 7.59 (s, 1H), 7.57 (m, 1H), 7.55 (m, 1H), 7.49 (m, 10H), 7.48 (m, 4H).

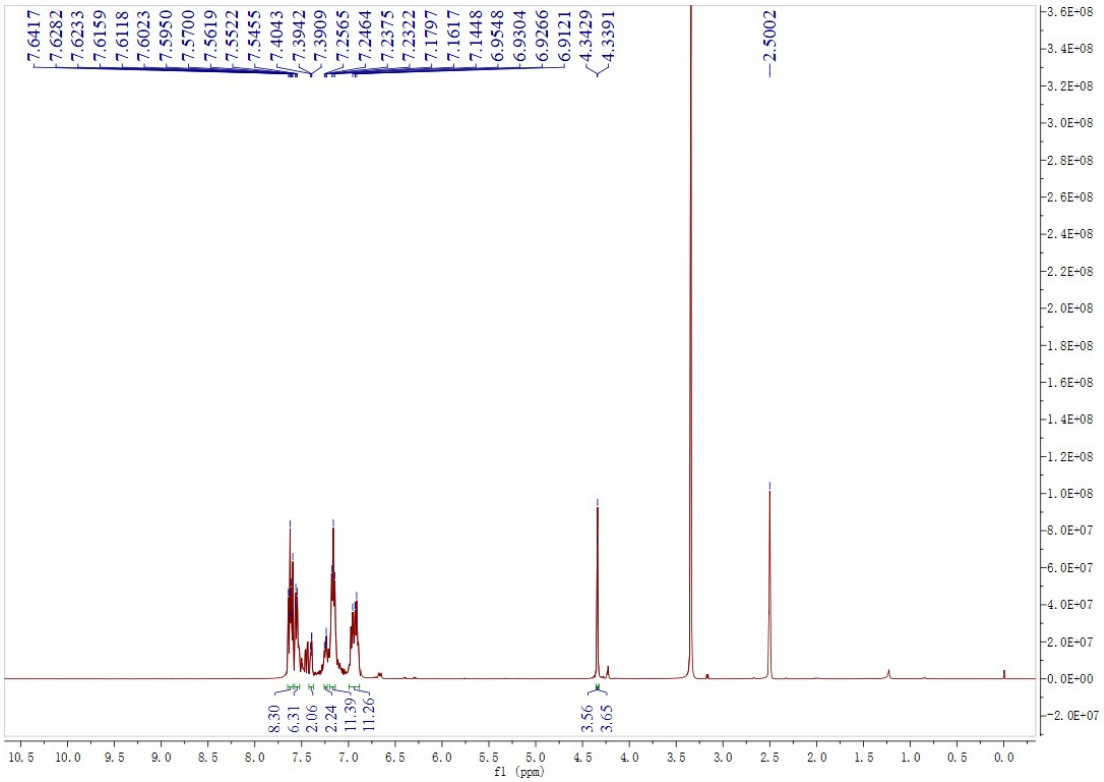


Figure S2. ^{1}H NMR of **RoRh**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.66 – 7.59 (m, 8H), 7.54 (m, 6H), 7.42 – 7.38 (m, 2H), 7.24 (m, 2H), 7.16 (m, 11H), 6.98 – 6.88 (m, 11H), 4.34 (s, 6H).

Table S7. The level of Rc1 in A549/DDP cells after incubation with **RoRh** (2.39 μM) and **AcRh** (20.00 μM) for 48 h (n= 3).

Group	ΔA	Cpr	Rc1 (U/mg prot)	Mean	SD
untreated cells	0.0691	1.333	83.39	89.46	5.97
	0.0643	1.153	89.66		
	0.0842	1.420	95.33		
AcRh	0.0552	1.308	67.85	63.67	3.91
	0.0438	1.172	60.12		
	0.0345	0.880	63.04		
RoRh	0.0052	0.456	18.35	18.98	1.27
	0.0164	1.290	20.45		
	0.0043	0.381	18.14		

ΔA: Measured value for each sample; Cpr: The protein concentration of each sample; All assays and calculation process were performed according to the manufacturer's instructions

(mitochondrial respiratory chain complexes I (Rc1) and IV (Rc4), Solarbio Life Sciences, Beijing, China).

Table S8. The level of Rc4 in A549/DDP cells after incubation with **RoRh** (2.39 μM) and **AcRh** (20.00 μM) for 48 h (n= 3).

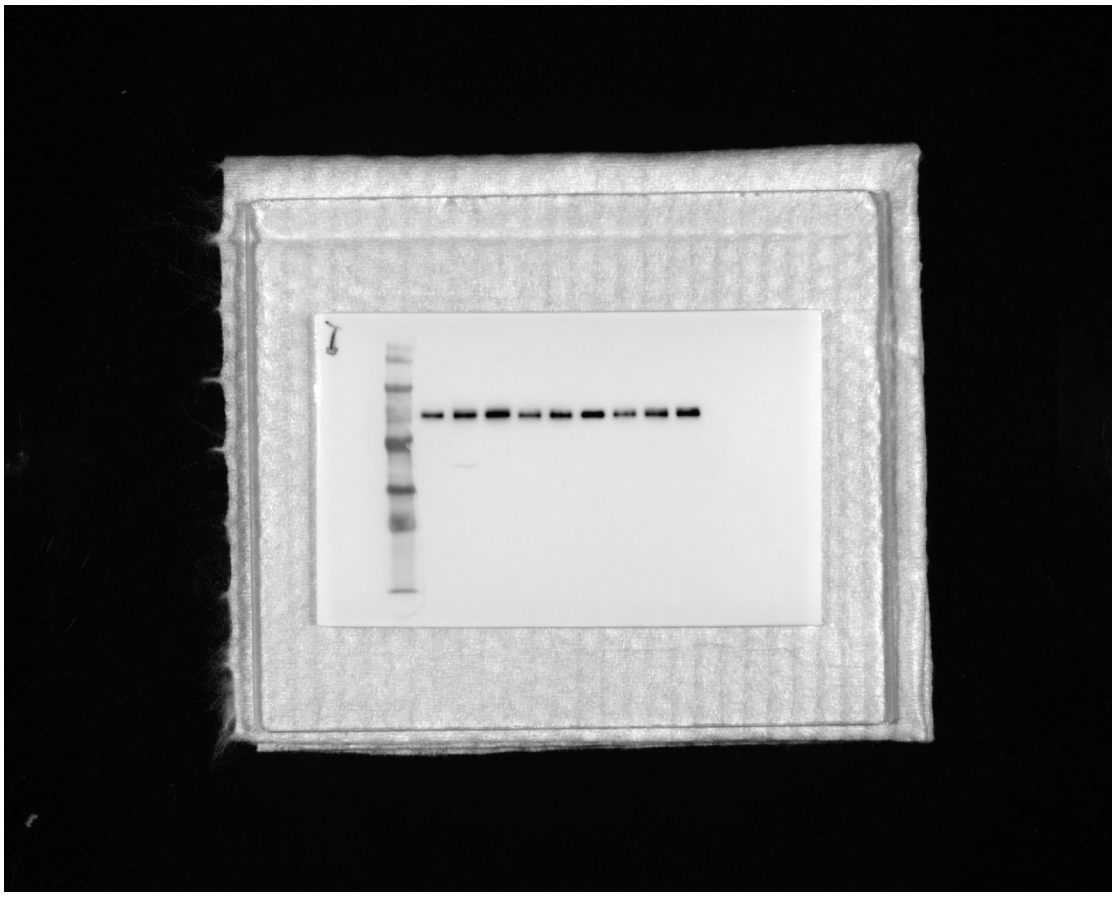
Group	ΔA	Cpr	Rc4 (U/mg prot)	Mean	SD
untreated cells	0.1409	2.046	75.68	73.23	4.66
	0.1038	1.681	67.85		
	0.1105	1.595	76.15		
AcRh	0.0333	0.685	53.44	56.52	2.91
	0.0321	0.596	59.21		
	0.0419	0.809	56.90		
RoRh	0.0071	0.463	16.86	17.88	1.06
	0.0062	0.382	17.82		
	0.013	0.753	18.97		

Table S9. The level of ATP in A549/DDP cells after incubation with **RoRh** (2.39 μM) and **AcRh** (20.00 μM) for 48 h (n= 3).

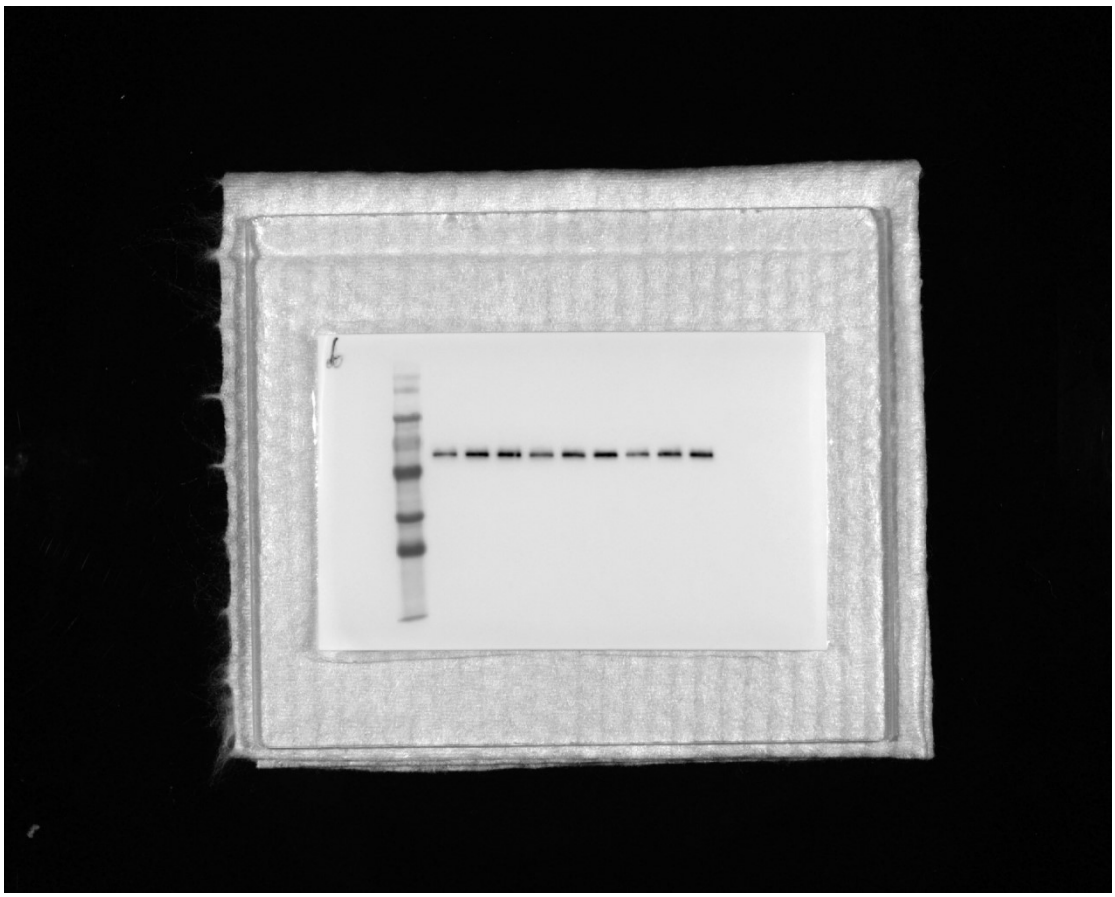
	untreated cells	**AcRh**	**RoRh**
OD	69411	53258	10629
	76135	62631	10313
	68685	62053	9987
corrected OD value	69393	53240	10611
	76117	62613	10295
	68667	62035	9969
the level of ATP (μM)	6.21	4.75	0.92
	6.81	5.60	0.89
	6.14	5.54	0.86
Mean	6.39	5.30	0.89
SD	0.37	0.47	0.03

The original drawing of WB experiment

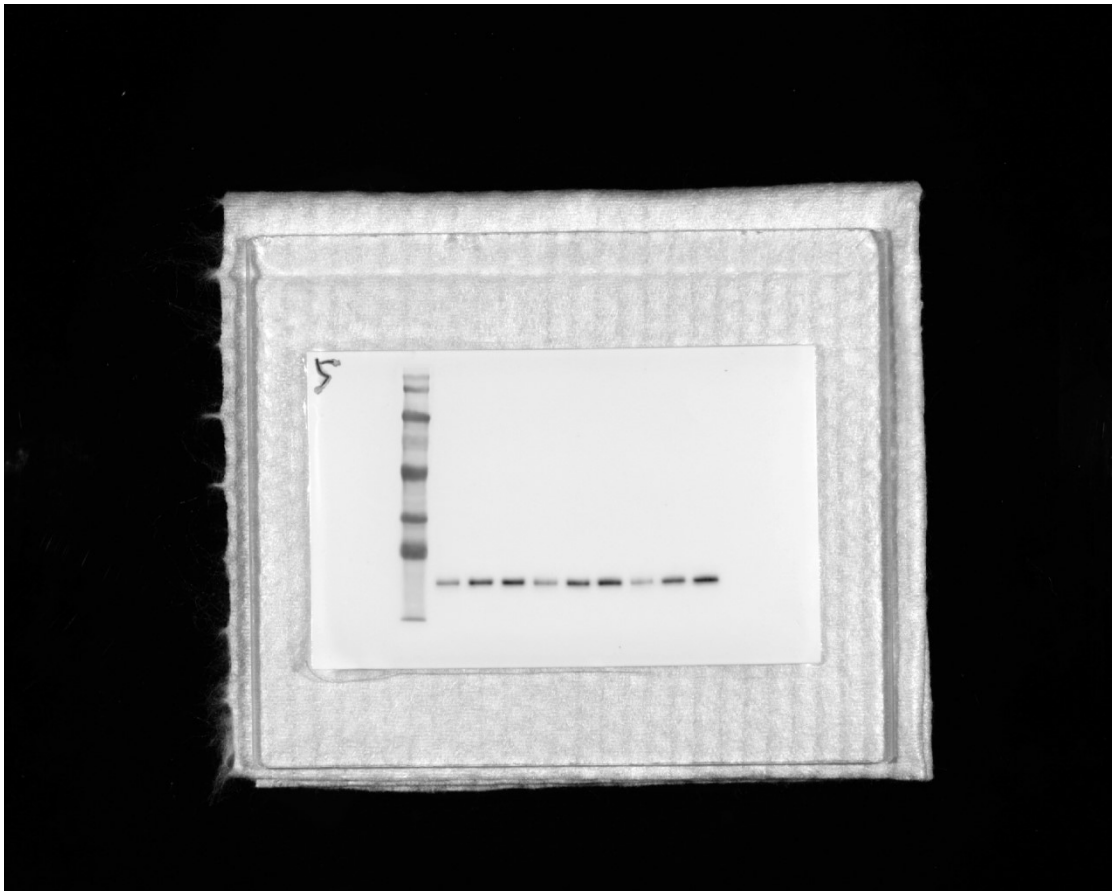
Anti-Beclin-1



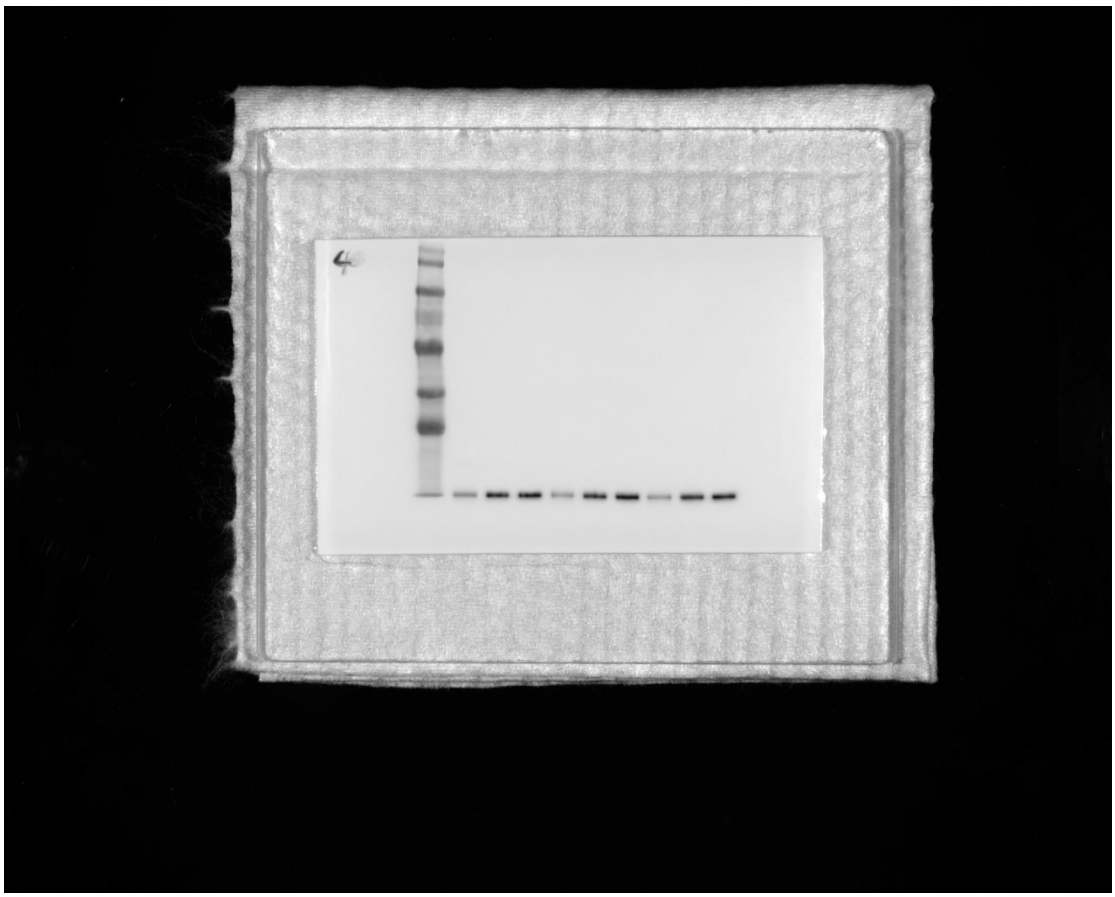
caspase9



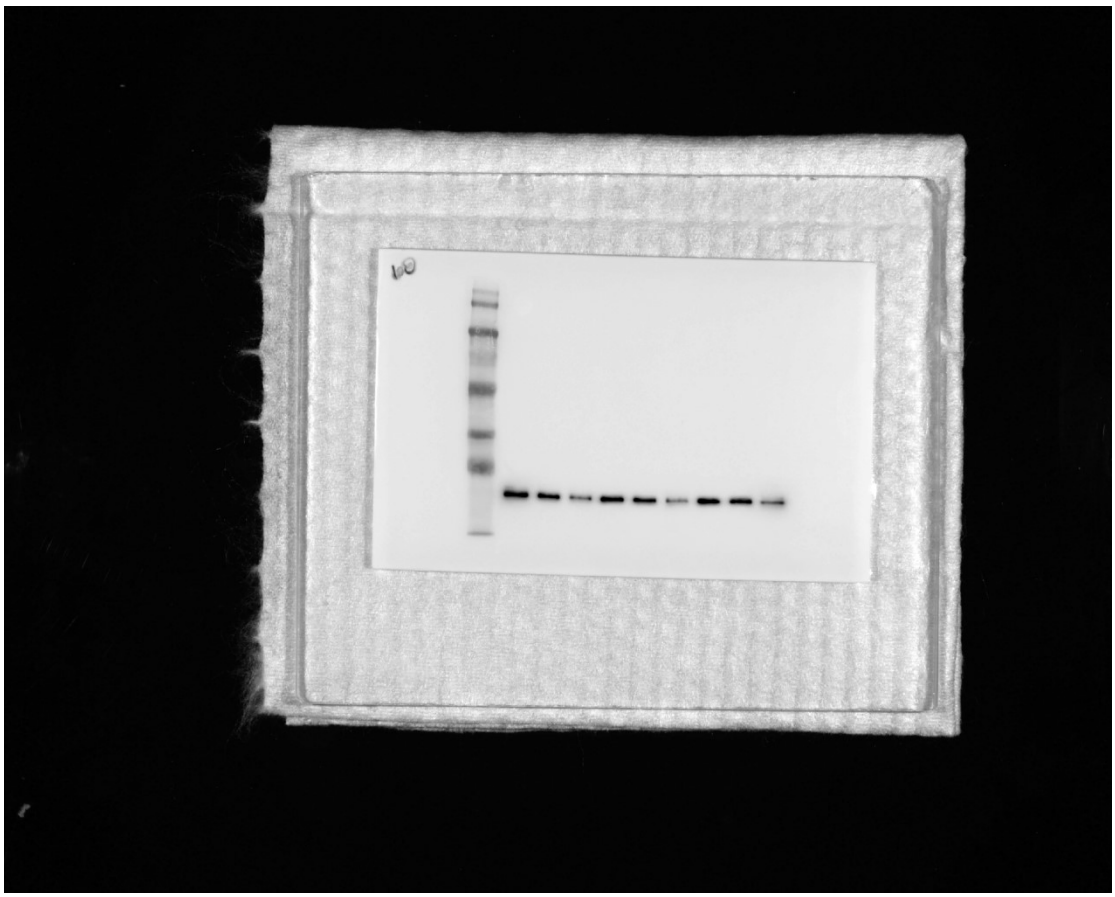
Anti-cleaved-caspase3



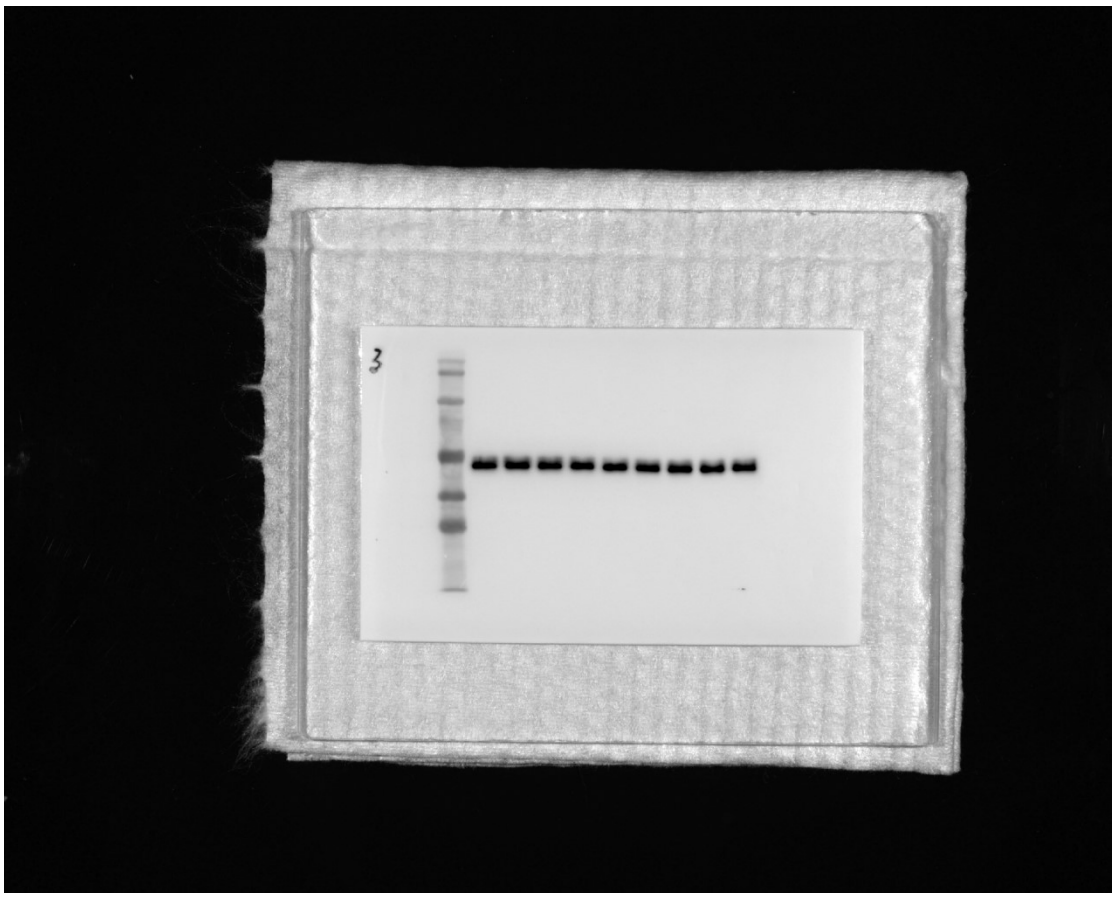
Anti-Cyto C

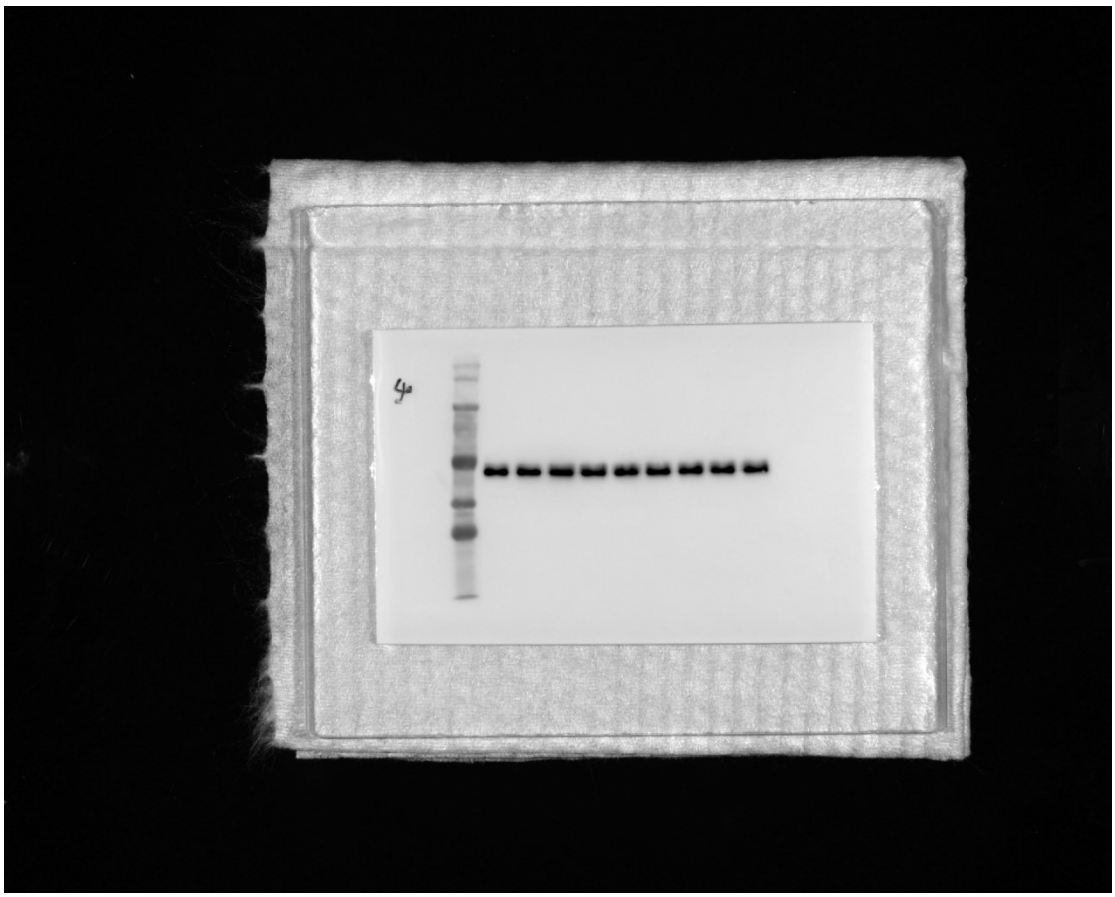


Anti-FUNDC1

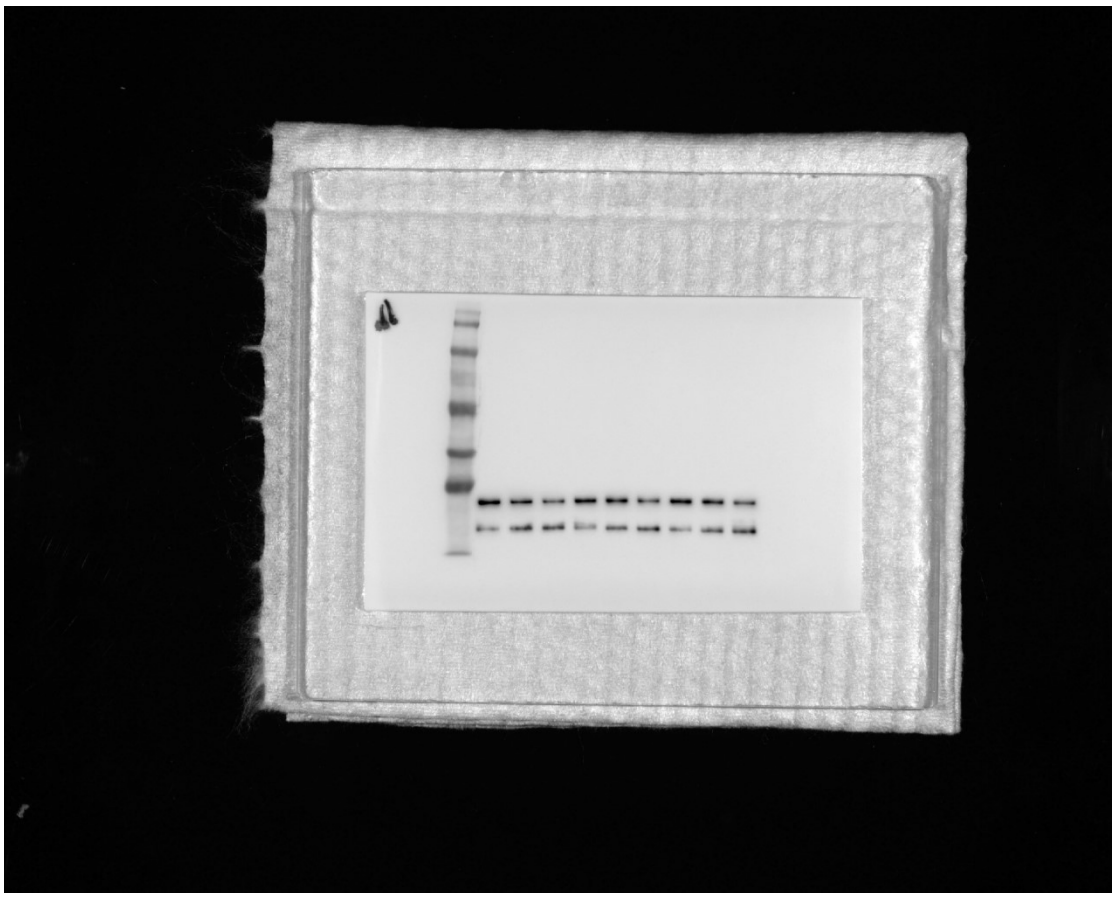


Anti-GAPDH

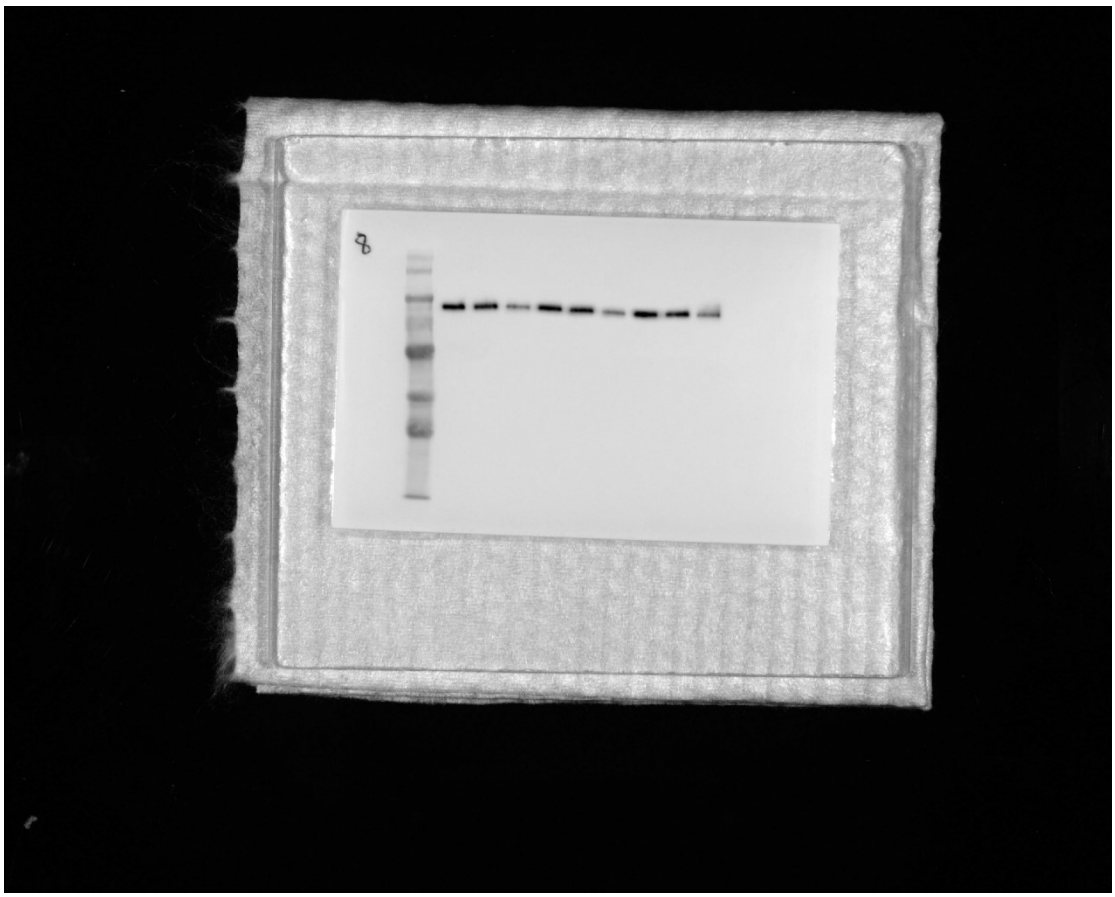



4

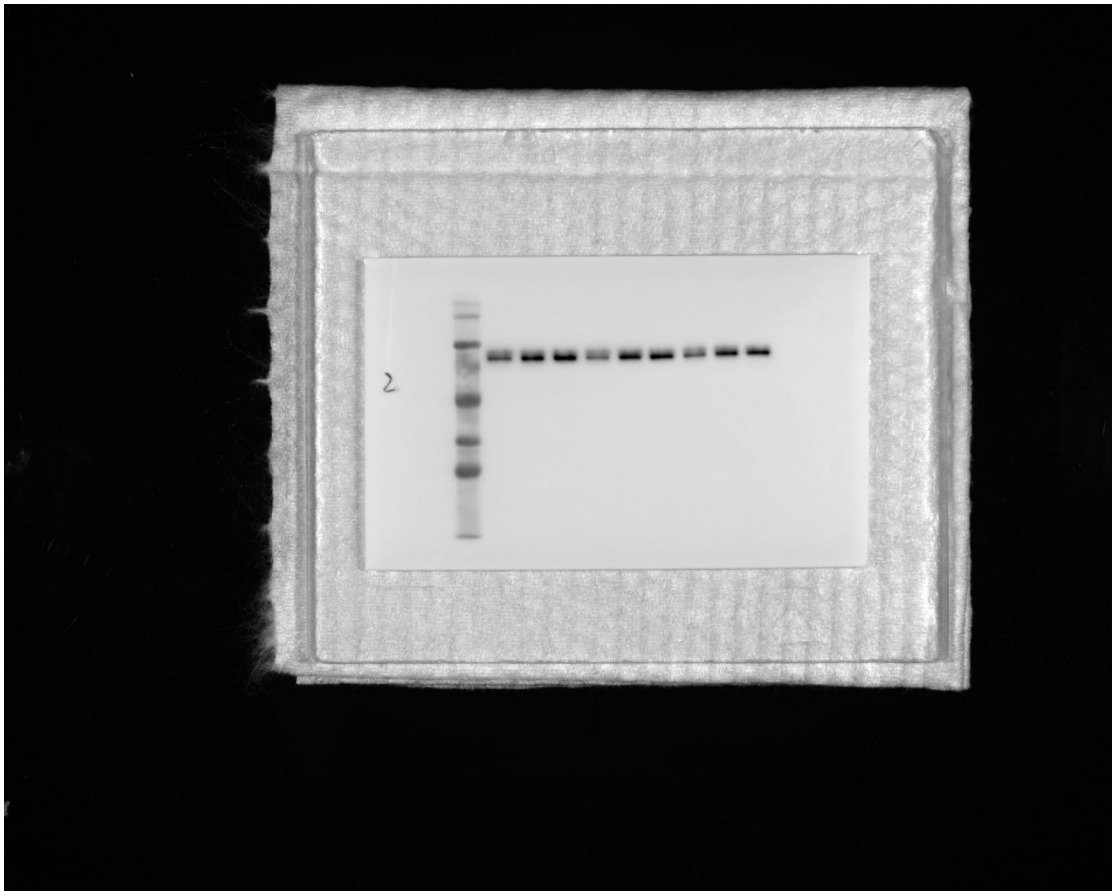
Anti-LC3B



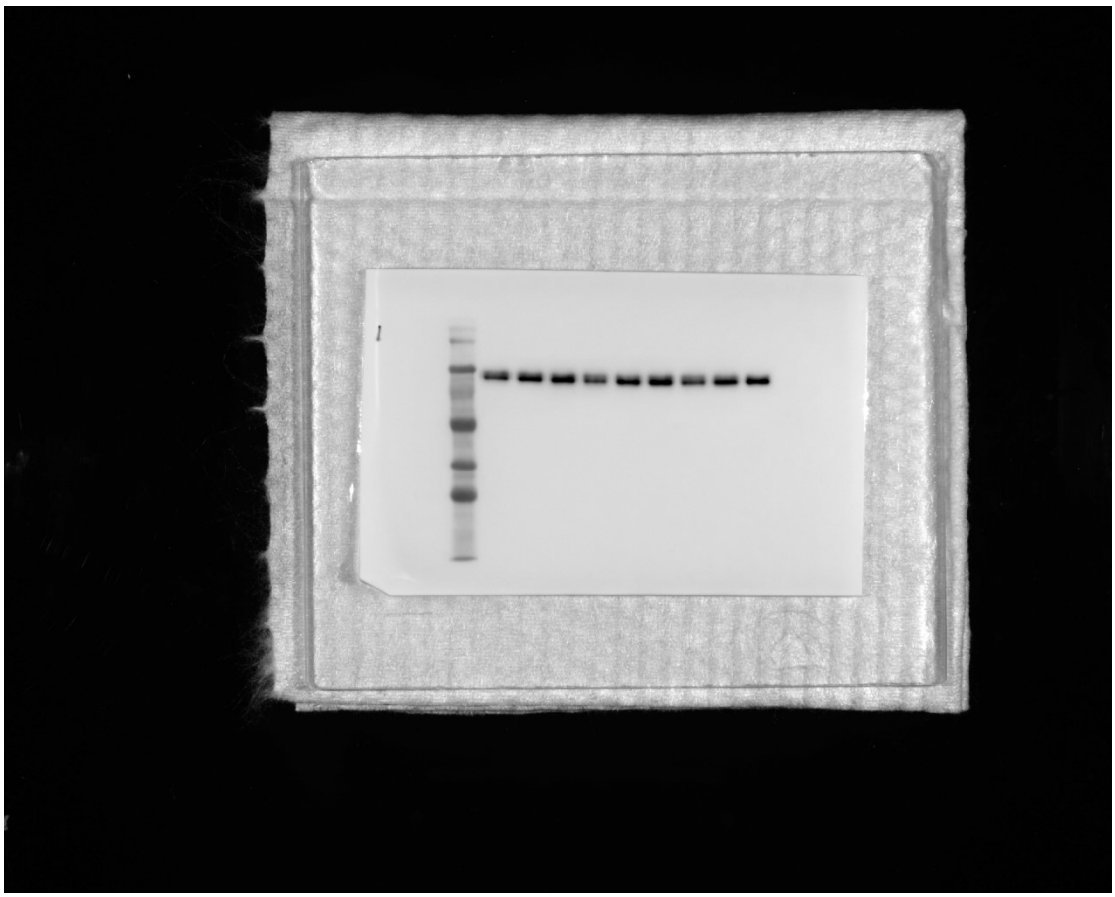
Anti-P62



Anti-Parkin



Anti-PINK1



Experimental methods

Furthermore, the other tests for **RoRh** (2.39 μM) and **AcRh** (20.00 μM) on the A549cisPt cells were conducted according to reported procedures[1-3].

Instrumentation

NMR spectra were recorded on a Bruker AV-400 NMR spectrometer. Elemental analyses (C, H, N) were carried out on a PerkinElmer series II CHNS/O 2400 elemental analyzer. The CCK-8, ATP, Rc1 and Rc4 experiments were obtained on a multifunctional microplate reader (Swiss, TECAN SPARK). The analysis results of Annexin V-APC/7-AAD probe (10.0 μL), DCFH-DA (10.0 μM), JC-1 (5 mg/mL, v : v = 1.0 : 500.0), and Fluo-3AM (1.0 μM) assays were recorded on flow cytometer (BECKMAN COULTER CytoFLEX). Western blotting assay were performed on electrophoresis apparatus (Bio-rad Power Supplies Basic, USA), Trans-Blot Turbo Universal Protein Transfer System (Bio-rad 170-4150, USA) and Gel imaging system (SYNGENE G:BOXChemiXR5, Britain), respectively.

CCK-8 assay

The A549cisPt and HL2 cells were seeded into 96-well plates (5.0×10^3 cells per well) and incubated overnight. The cells were then treated with H-Acr, H-Rob, cisPt, **RoRh** and **AcRh**. After incubation for 48 h, freshly diluted CCK-8 (10.0 μL per well) was added and the cells were incubated for an additional 2.0 h at 37 °C in a humidified atmosphere containing 5% CO_2. The absorbance was determined by measuring the optical density at 450 nm using a multifunctional enzyme marker (n= 5, Switzerland, TECAN SPARK).

Measurement of cell apoptosis, MMP, ROS, Ca^{2+}, ATP, and mitochondrial complexes I and IV (Rc1 and Rc4)

The A549cisPt cells were seeded into a 6-well plate and incubated with **RoRh** (2.39 μM) and **AcRh** (20.00 μM) for 48 h. The cells were then washed and added to a solution containing Annexin V-APC/7-AAD probe (10 μL), JC-1 (5 mg/mL, v : v = 1 : 500), DCFH-DA (10.0 μM), and Fluo-3AM (1.0 μM) and incubated for approximately 30.0 min at 37 °C in the dark. Cell staining was detected using FCM.

The levels of ATP and mitochondrial complexes I and IV (Rc1 and Rc4) were

determined using an enhanced ATP assay kit (Abcam, United Kingdom, Abcam ab113849), and Rc1 and Rc4 assay kits (Beijing Solarbio, China, BC0515 and BC0945, Beijing Solarbio Science & Technology Co., Ltd) in accordance with the manufacturer's instructions.

Single-crystal X-ray crystallography

Diffraction data for the complex were collected on a Bruker SMART CCD diffractometer (CuKα radiation and λ = 1.54 Å) in Φ and ω scan modes. The structures were solved by direct methods, followed by difference Fourier syntheses, and then refined by full-matrix least-squares techniques on F2 using SHELXL[4]. All other non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were placed at calculated positions and isotopically refined using a riding model. Tables S1-S6 summarizes X-ray crystallographic data and refinement details for the complexes. The CCDC numbers of **AcRh** and **RoRh** were 2466152 and 2466153, respectively.

Western blotting

The A549cisPt cells were treated with **RoRh** (2.39 μM) and **AcRh** (20.00 μM) for 48 h, and then this cells harvested from each well of the culture plates were lysed in 150μL of extraction buffer consisting of 149μL of RIPA lysis buffer and 1μL of PMSF (100.0 mM). The suspension was centrifuged at 10000 rpm at 4.0 °C for 25.0 min, and the supernatant (10μL for each sample) was loaded onto 10% polyacrylamide gel and then transferred to a microporous polyvinylidene difluoride (PVDF) membrane. Western blotting was performed by anti-apoptotic antibody or anti-β-actin primary antibody and horseradish-peroxidase-conjugated anti-mouse or anti-rabbit secondary antibody. In additon, all these protein bands were visualized by chemiluminescence substrate.

References

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