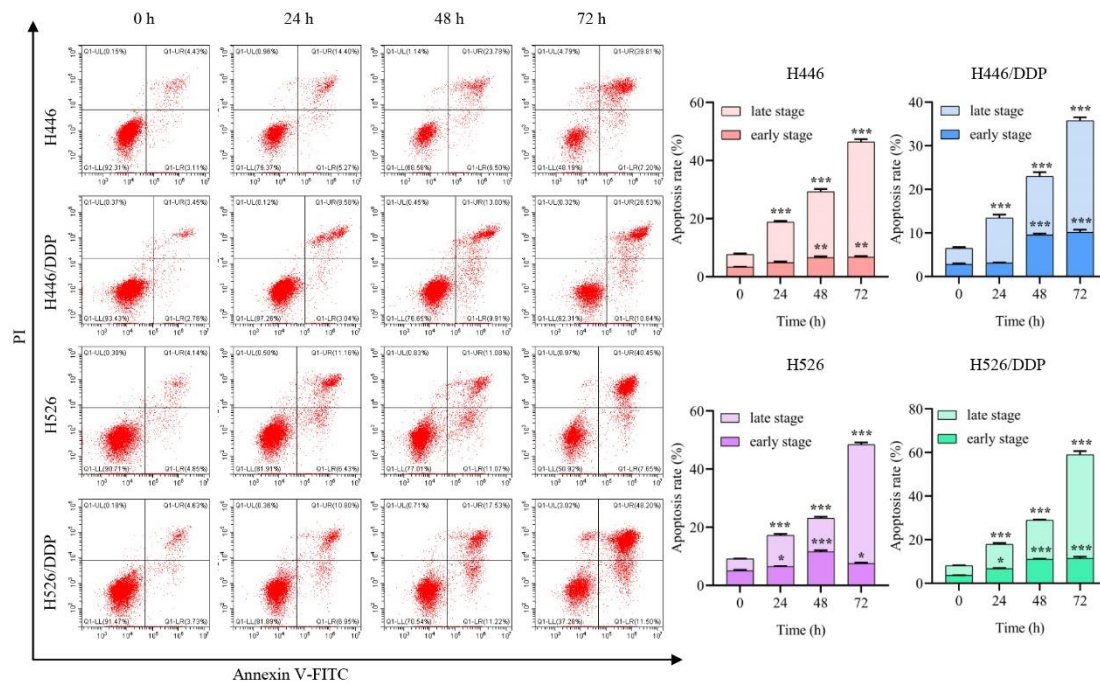


Abbreviations:

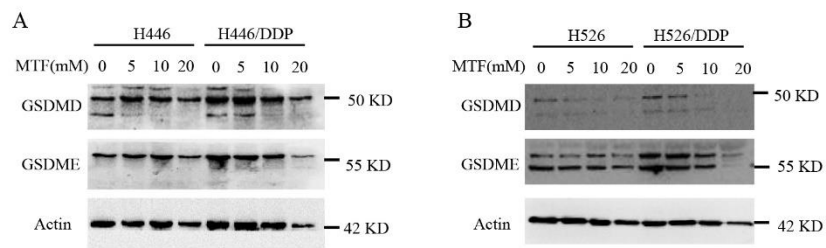
SCLC, small cell lung cancer; MDR, acquired multidrug resistance; OS, overall survival; PFS, progression-free survival; MTF, metformin; T2D, type 2 diabetes; AMPK, adenosine monophosphate-activated protein kinase; 3-MA, 3-methyladenine; CCK-8, Cell Counting Kit-8; HE, haematoxylin and eosin; IHC, immunohistochemistry.

Supplementary Figure. S1.



Supplementary Figure S1. Metformin promotes SCLC cell apoptosis in a time-dependent manner. Apoptosis rates were measured via flow cytometry via an Annexin V-FITC Apoptosis Detection Kit. The cells were treated with 10 mM metformin for 0, 24, 48, and 72 h. The data are shown as the means $\pm$ SDs of values from triplicate experiments. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ versus the control group.

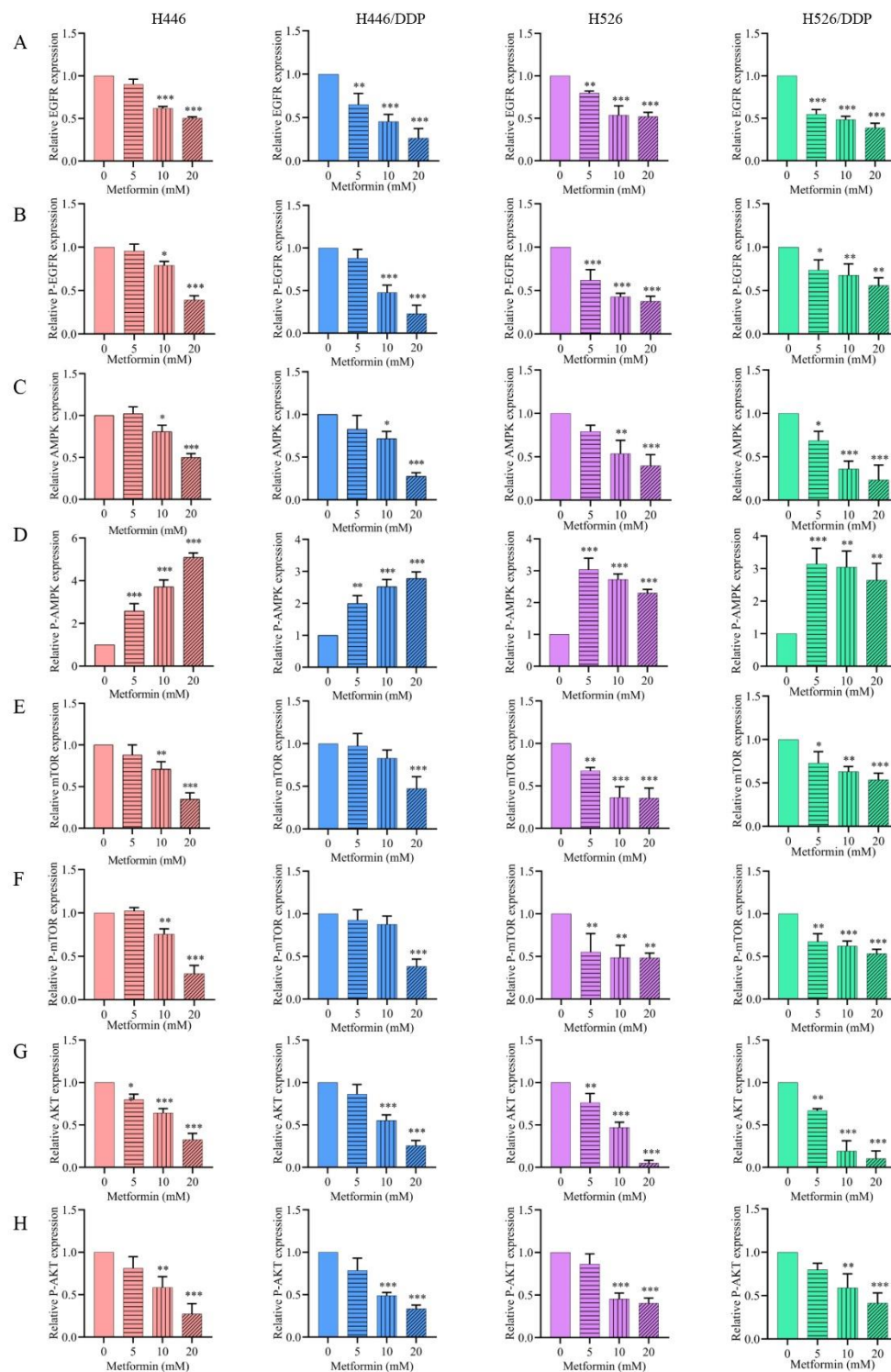
Supplementary Fig. S2



Supplementary Figure S2. The expression of pyroptosis-related proteins in metformin-treated SCLC cells.

(A, B) The protein levels of GSDMD and GSDME were measured in H446, H446/DDP (A) H526, and H526/DDP (B) cells treated with different concentrations of metformin (MTF) for 48 h via western blotting.

Supplementary Figure. S3.

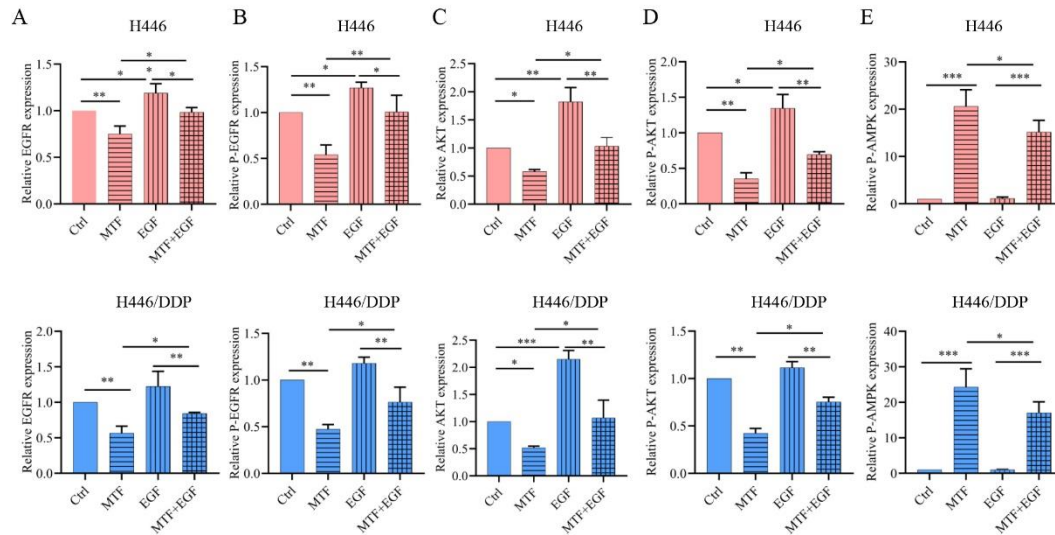


Supplementary Figure S3. Quantification of the western blot data in Figure 5A

(A-H) Densitometric analysis of western blot signals of EGFR (A), p-EGFR (B), AMPK (C), p-AMPK (D), mTOR (E), p-mTOR (F), AKT (G), and p-AKT (H) were normalized to the loading control actin. Pixel density analysis of protein expression compared with that in the untreated control

groups (set to 1). Significant difference compared with the untreated control: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. n=3.

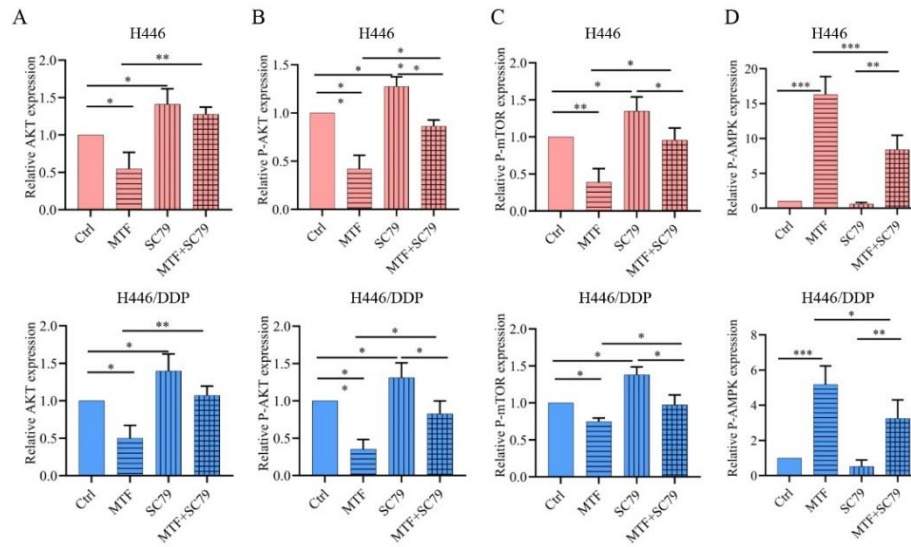
Supplementary Figure. S4.



Supplementary Figure S4. Quantification of the western blot data in Figure 5D

(A-E) Densitometric analysis of western blot signals of EGFR (A), p-EGFR (B), AKT (C), p-AKT (D), and p-AMPK (E) were normalized to the loading control actin. Pixel density analysis of protein expression compared with that in the untreated control groups (set to 1). Significant difference compared with the untreated control: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. n=3.

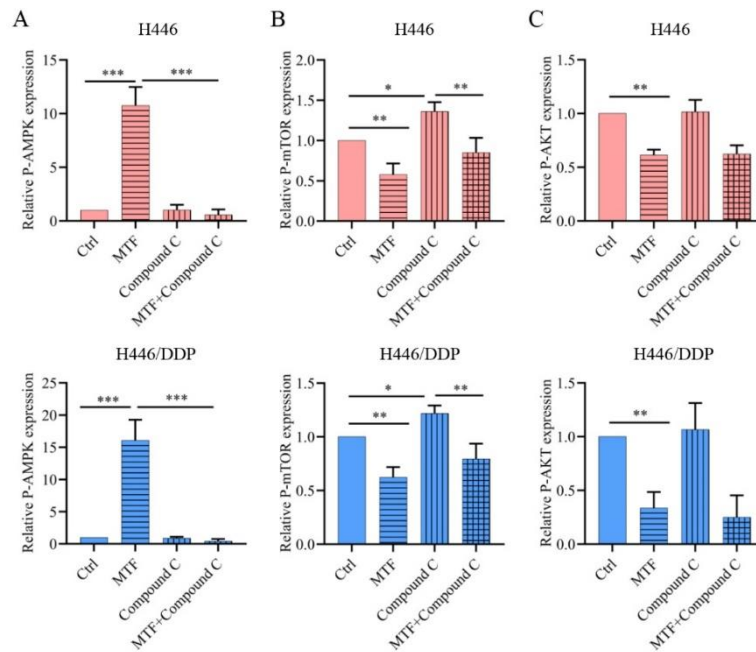
Supplementary Figure. S5.



Supplementary Figure S5. Quantification of the western blot data in Figure 5E

(A-D) Densitometric analysis of western blot signals of AKT (A), p-AKT (B), p-MTOR (C), and p-AMPK (D) were normalized to the loading control actin. Pixel density analysis of protein expression compared with that in the untreated control groups (set to 1). Significant difference compared with the untreated control: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. $n=3$.

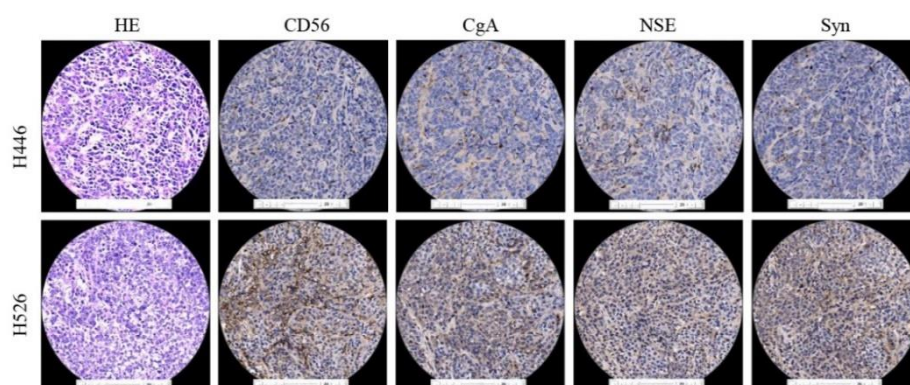
Supplementary Figure. S6.



Supplementary Figure S6. Quantification of the western blot data in Figure 5F

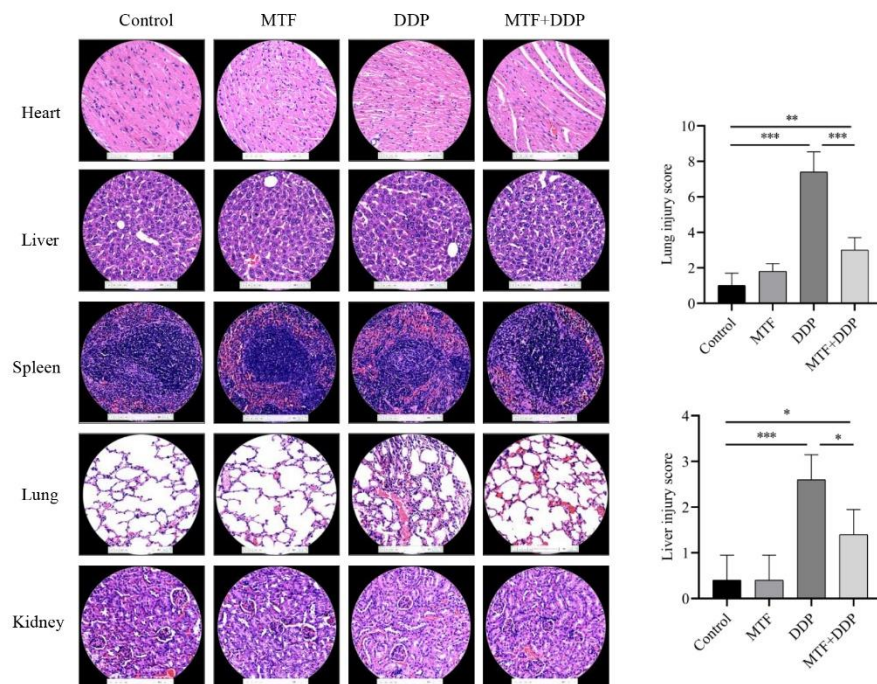
(A-C) Densitometric analysis of western blot signals of p-AMPK (A), p-mTOR (B), and p-AKT (C) were normalized to the loading control actin. Pixel density analysis of protein expression compared with that in the untreated control groups (set to 1). Significant difference compared with the untreated control: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. n=3.

Supplementary Fig. S7



Supplementary Figure S7. H&E staining and IHC staining of SCLC biomarkers (CD56, CgA, NSE, and Syn) in the tumour tissues of xenograft models.

Supplementary Fig. S8



Supplementary Figure S8. HE staining was used to assess the toxicity of metformin, cisplatin, and metformin+cisplatin to the major organs (heart, liver, spleen, lung, and kidney) of the mice (magnification: 200×). Histopathological injury scores in the lung and liver are shown for different groups. Statistical analyses were performed via ANOVA, which revealed significant differences compared with the untreated control: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. $n=5$.

These are original western blot for three repeats. All the blots were cut according to the molecular weight marker prior to hybridization with primary antibody for the corresponding protein.

Fig 2B

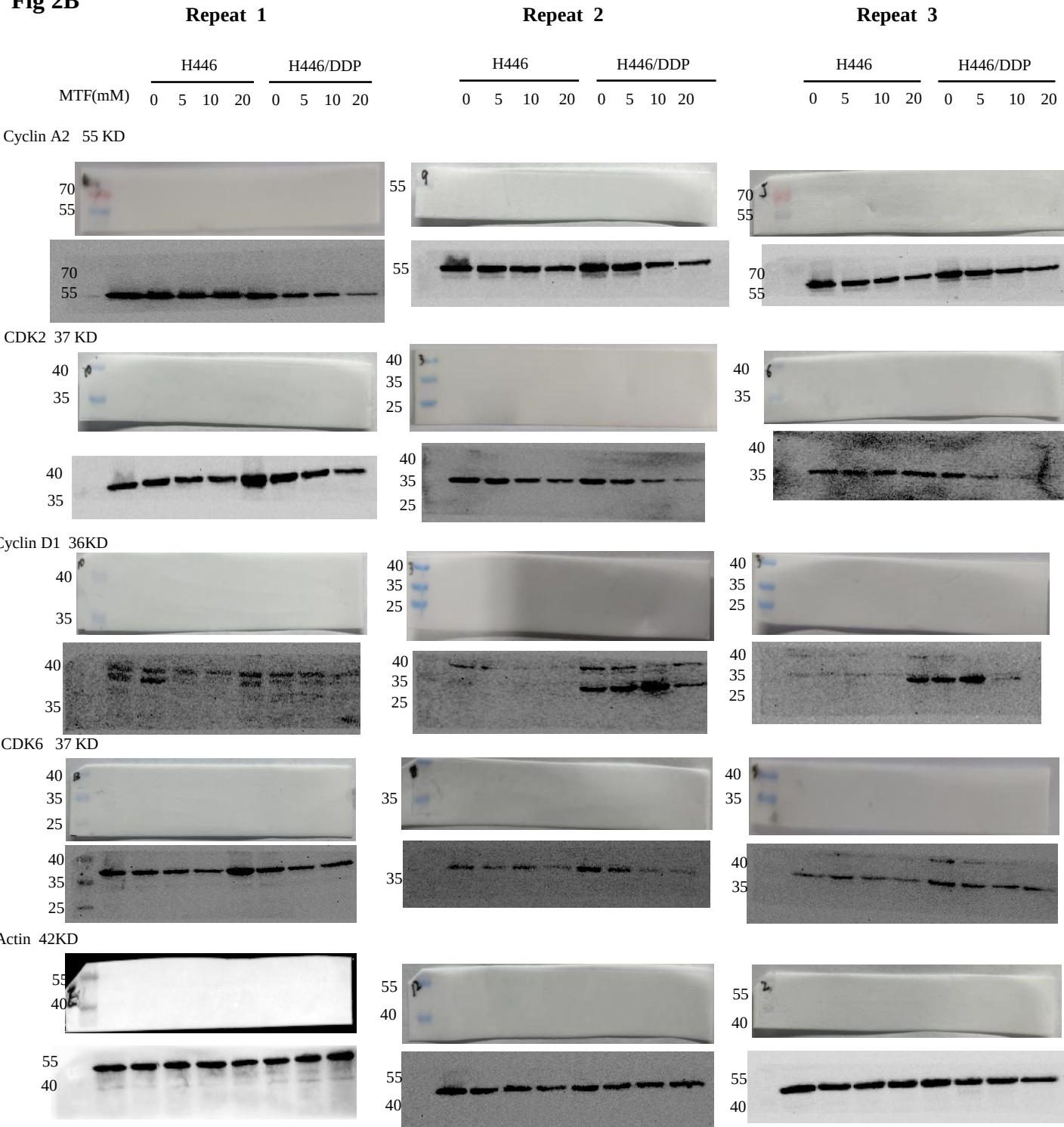


Fig 2C

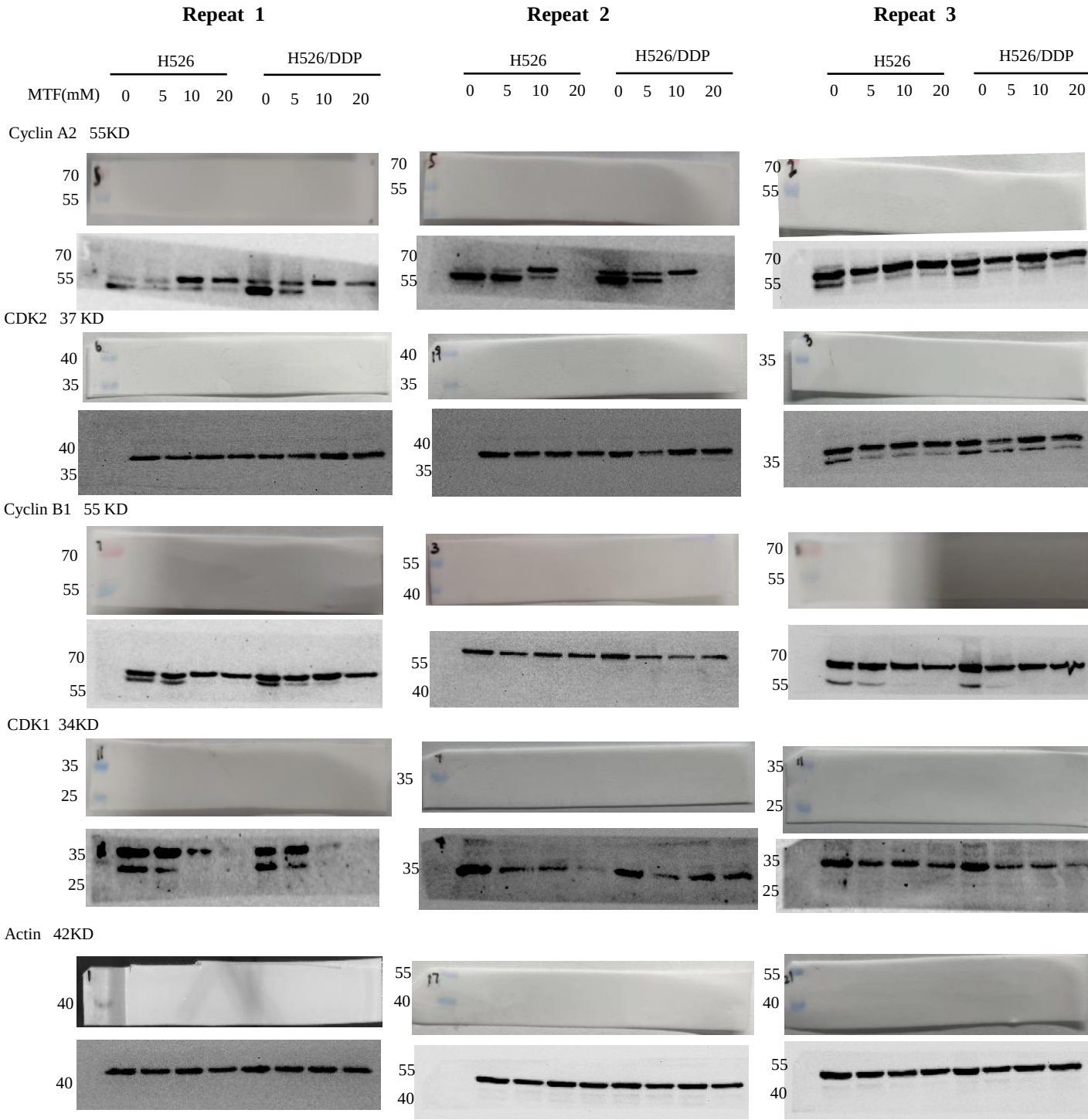


Fig 3B

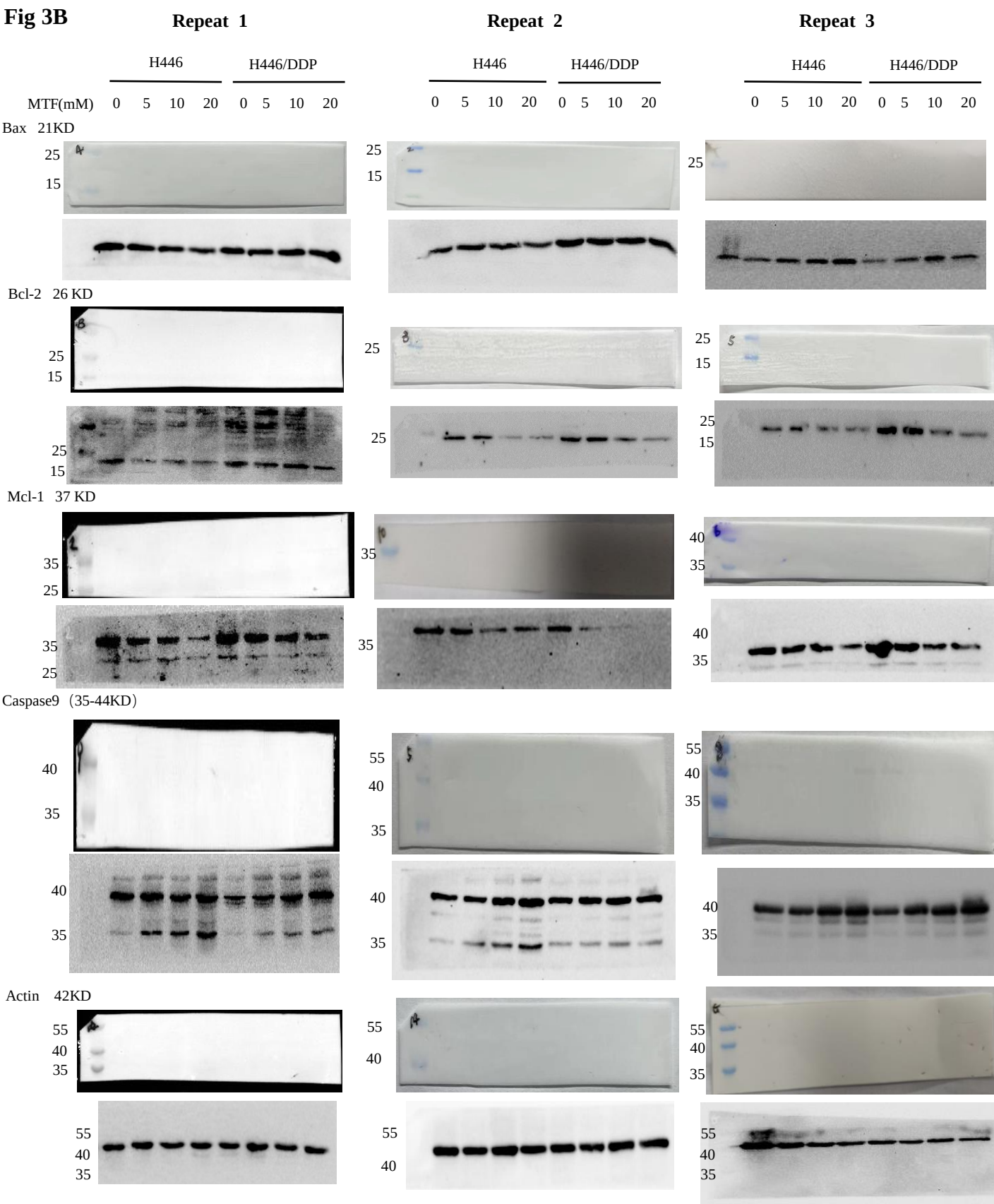


Fig 3C

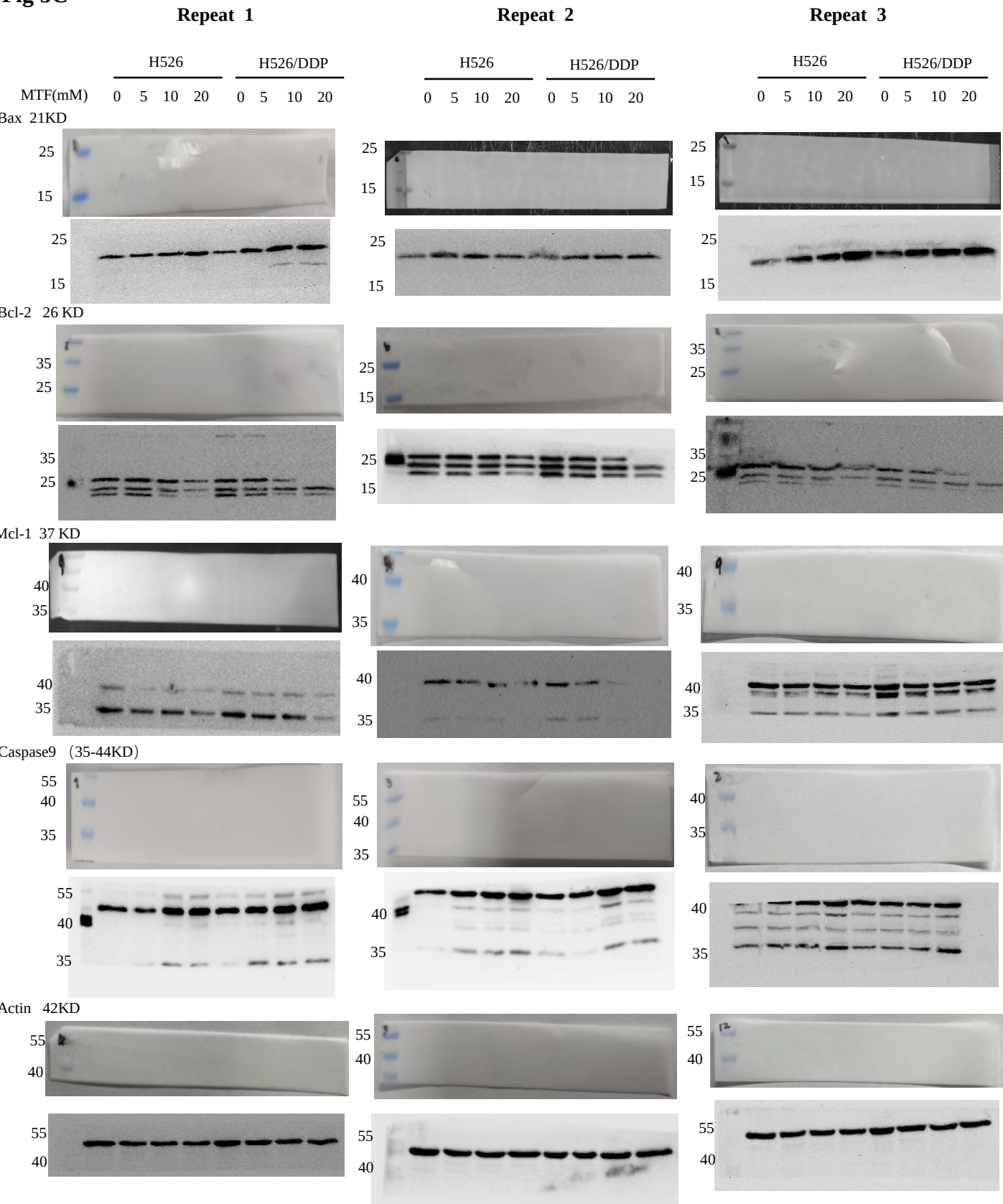


Fig 4A

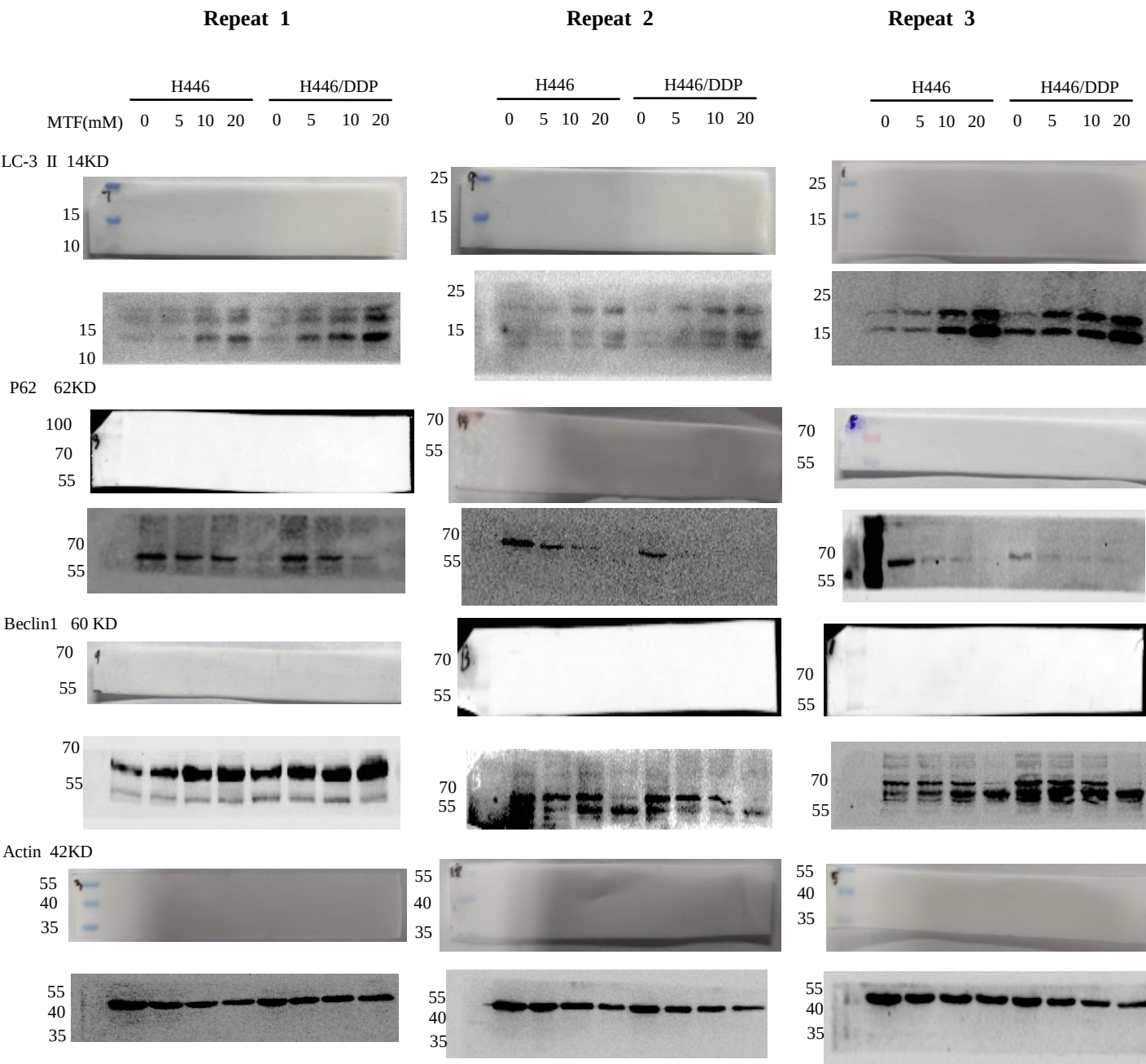
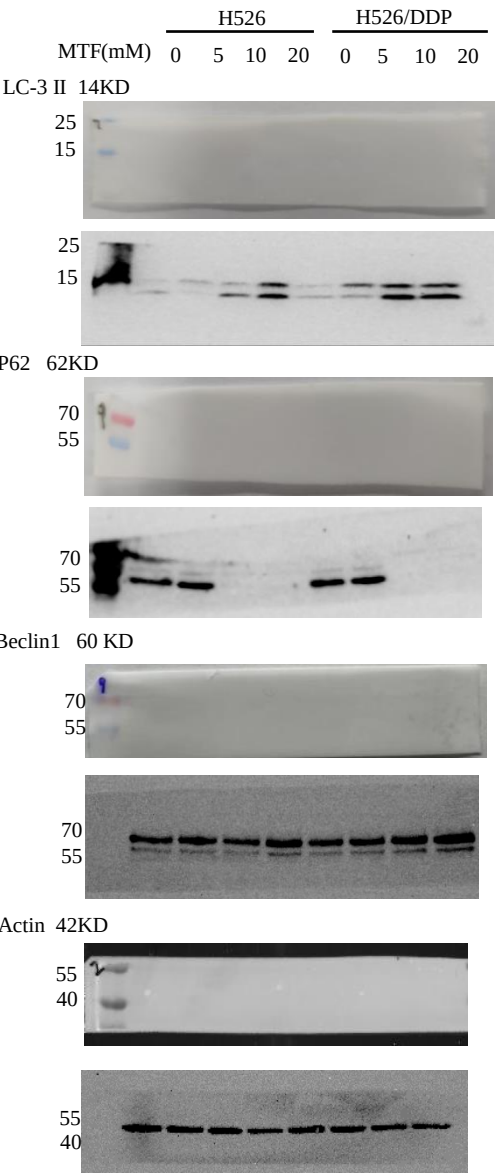
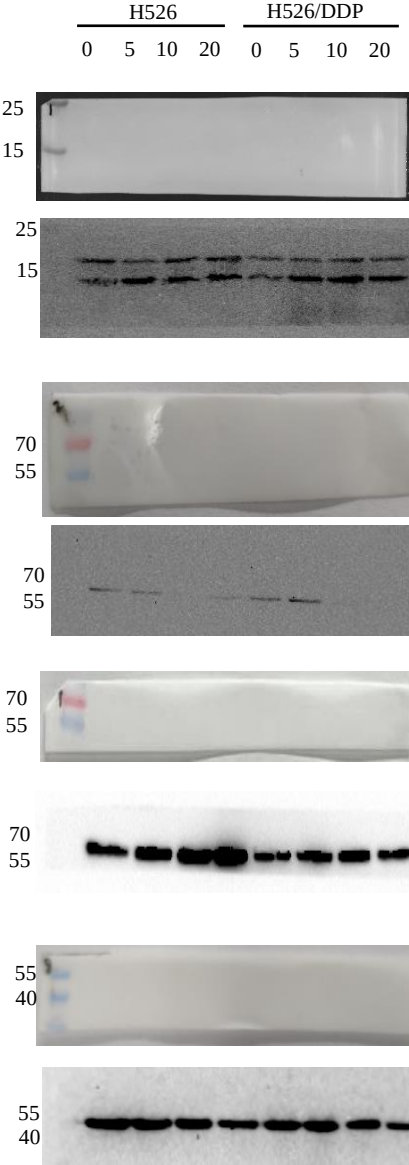


Fig 4A

Repeat 1



Repeat 2



Repeat 3

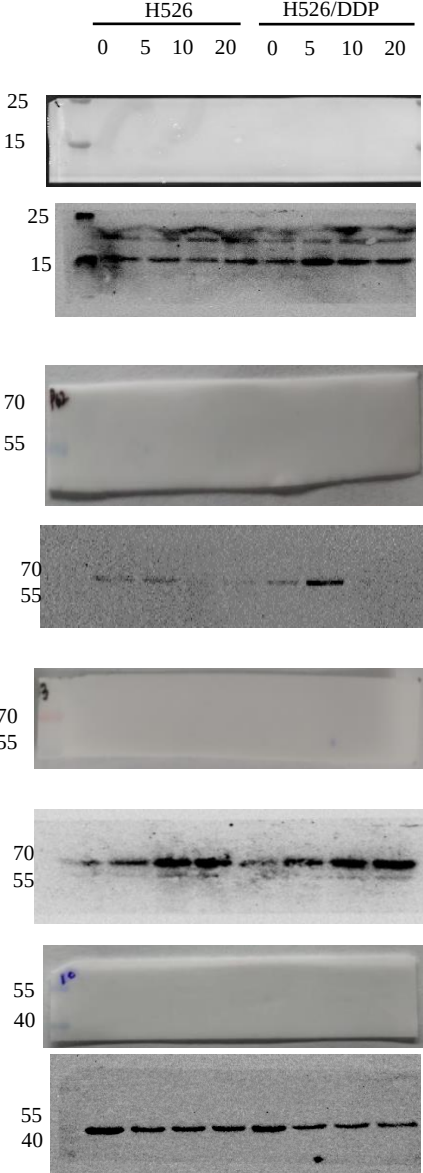


Fig 4B

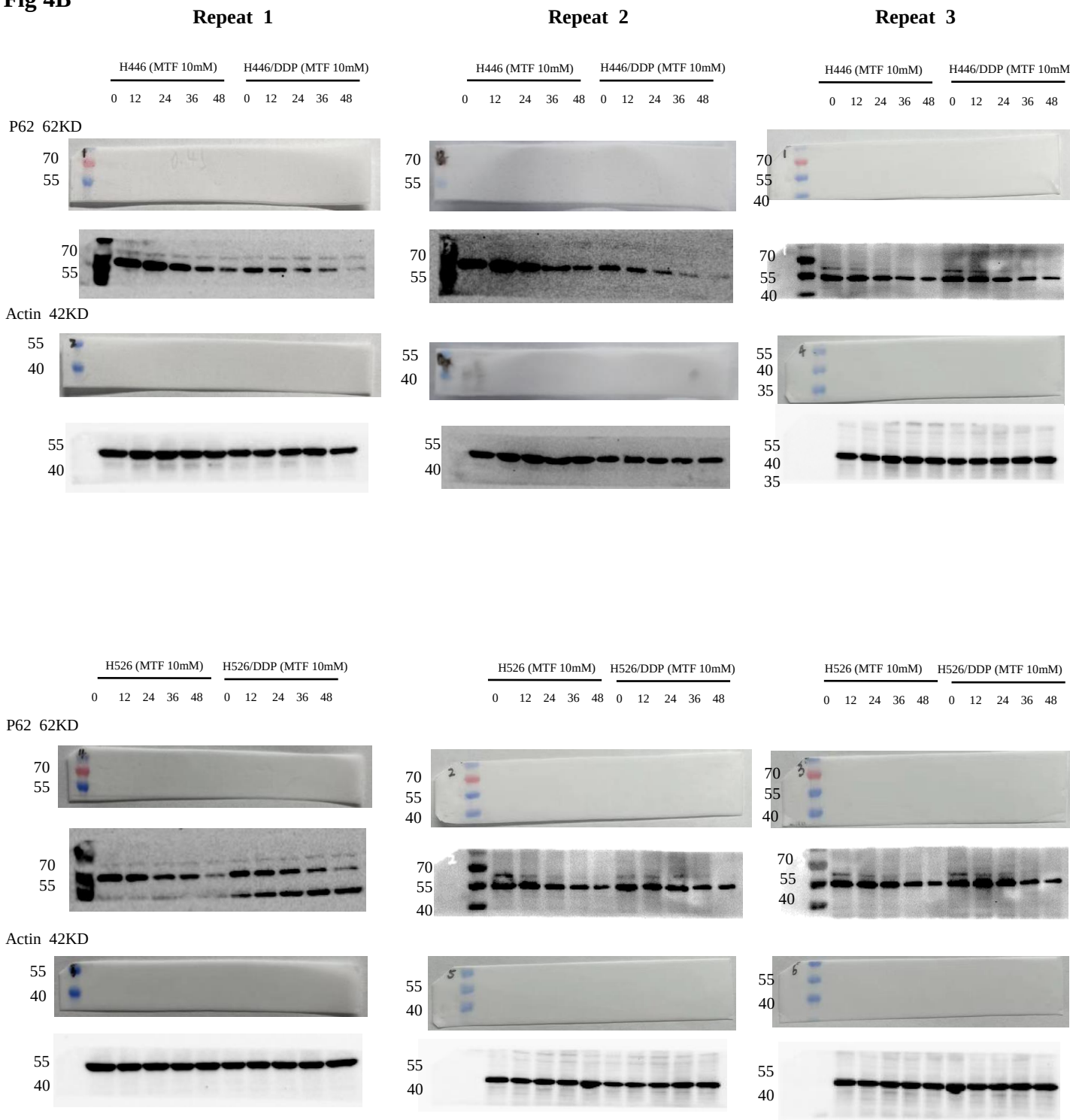


Fig 4D

Repeat 1

	H446				H446/DDP			
MTF	-	+	-	+	-	+	-	+
3-MA	-	-	+	+	-	-	+	+

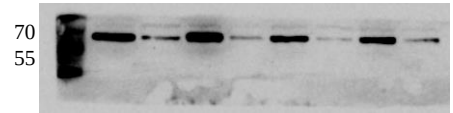
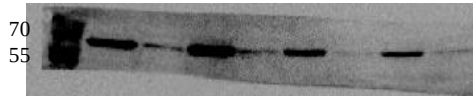
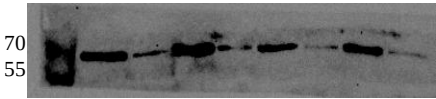
Repeat 2

	H446				H446/DDP			
MTF	-	+	-	+	-	+	-	+
3-MA	-	-	+	+	-	-	+	+

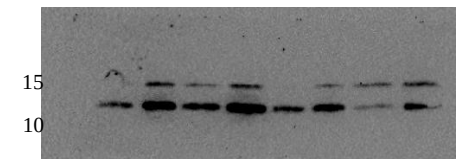
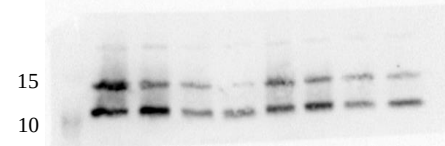
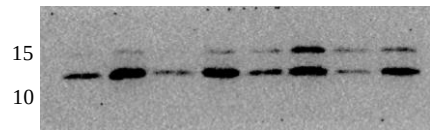
Repeat 3

	H446				H446/DDP			
MTF	-	+	-	+	-	+	-	+
3-MA	-	-	+	+	-	-	+	+

P62 62KD



LC-3 II 14KD



Actin 42KD

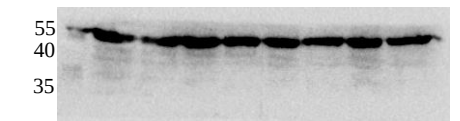
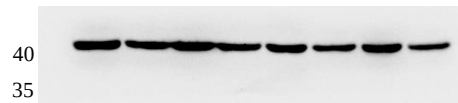
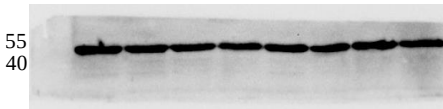


Fig 5A

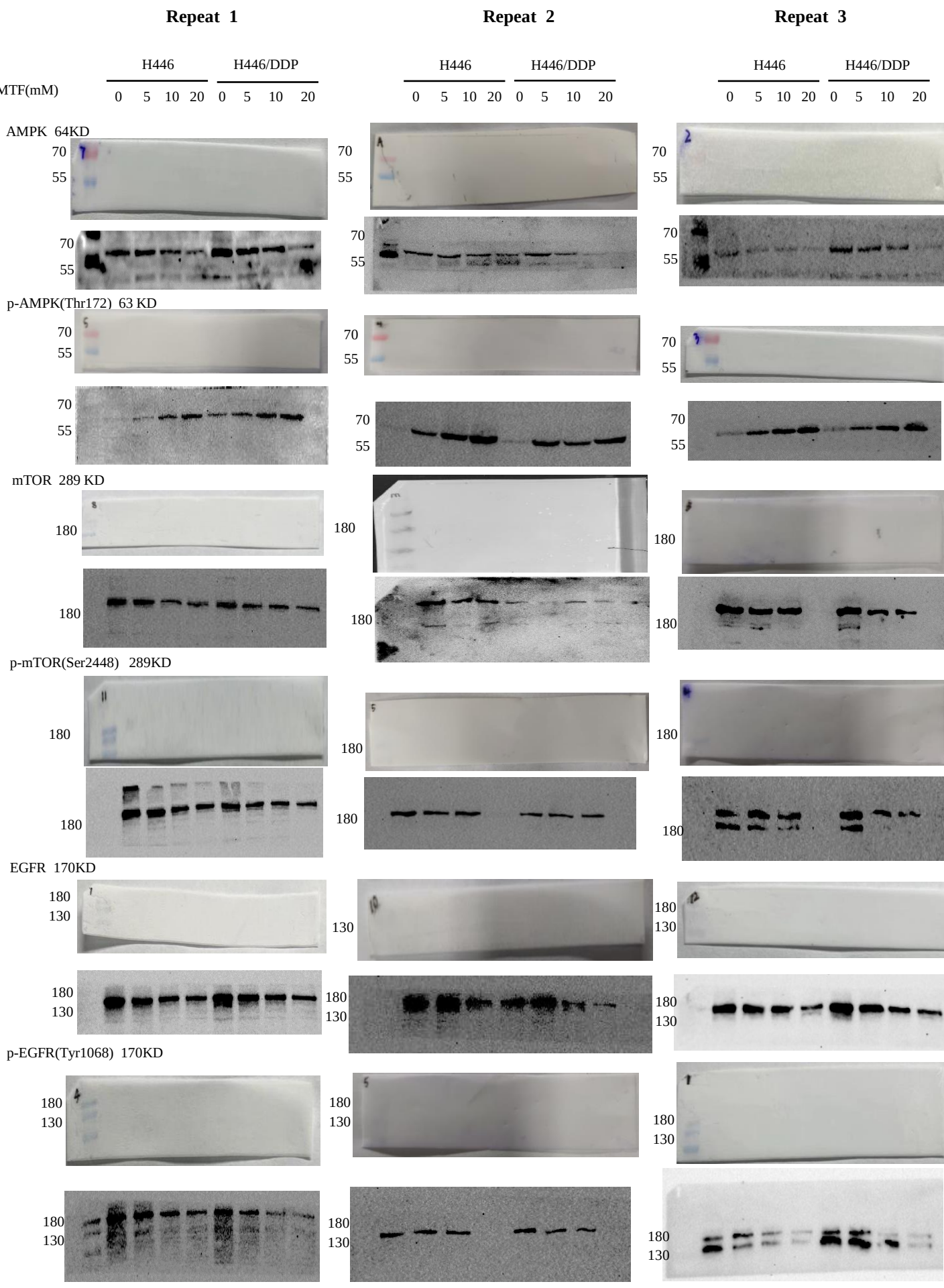


Fig 5A

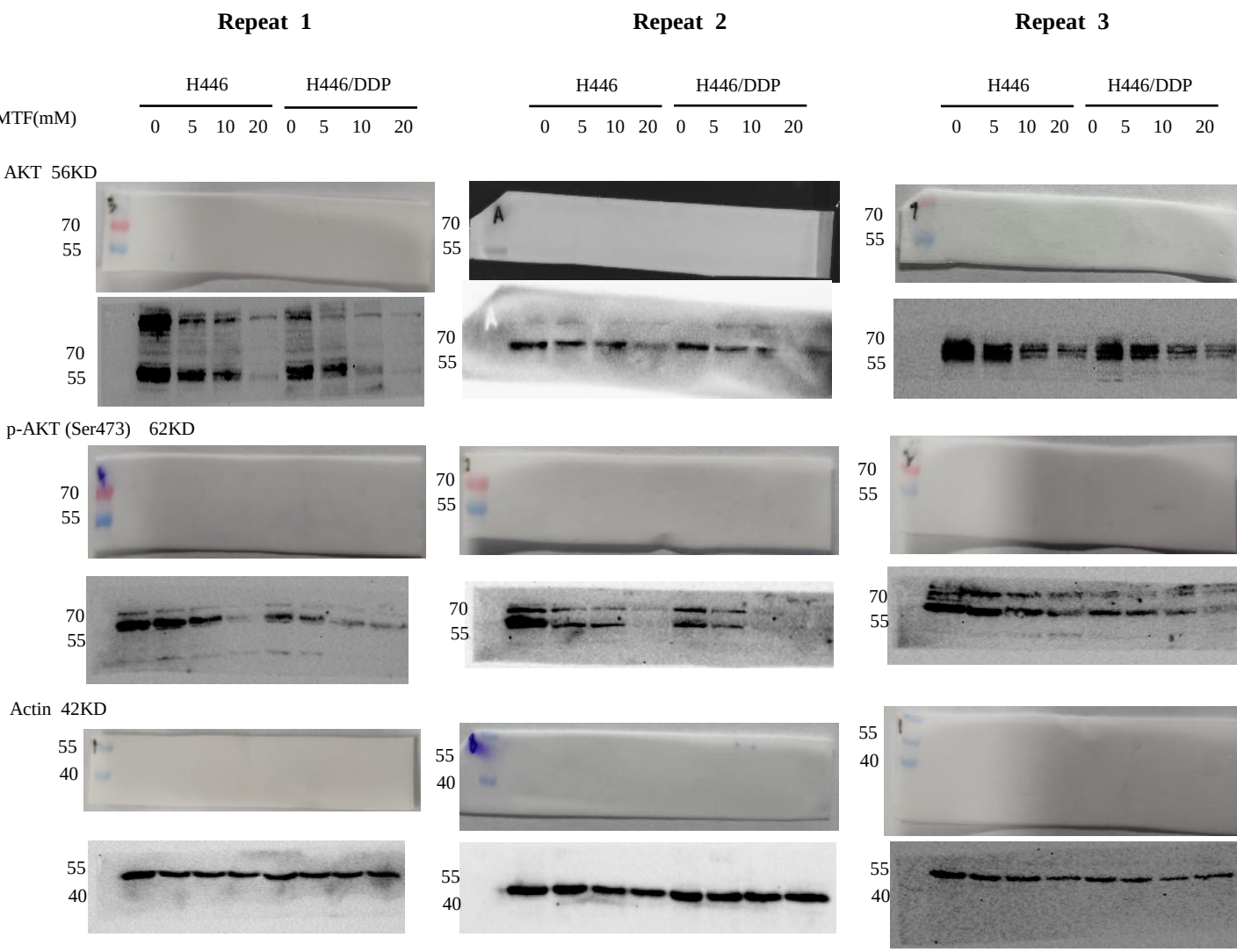


Fig 5A

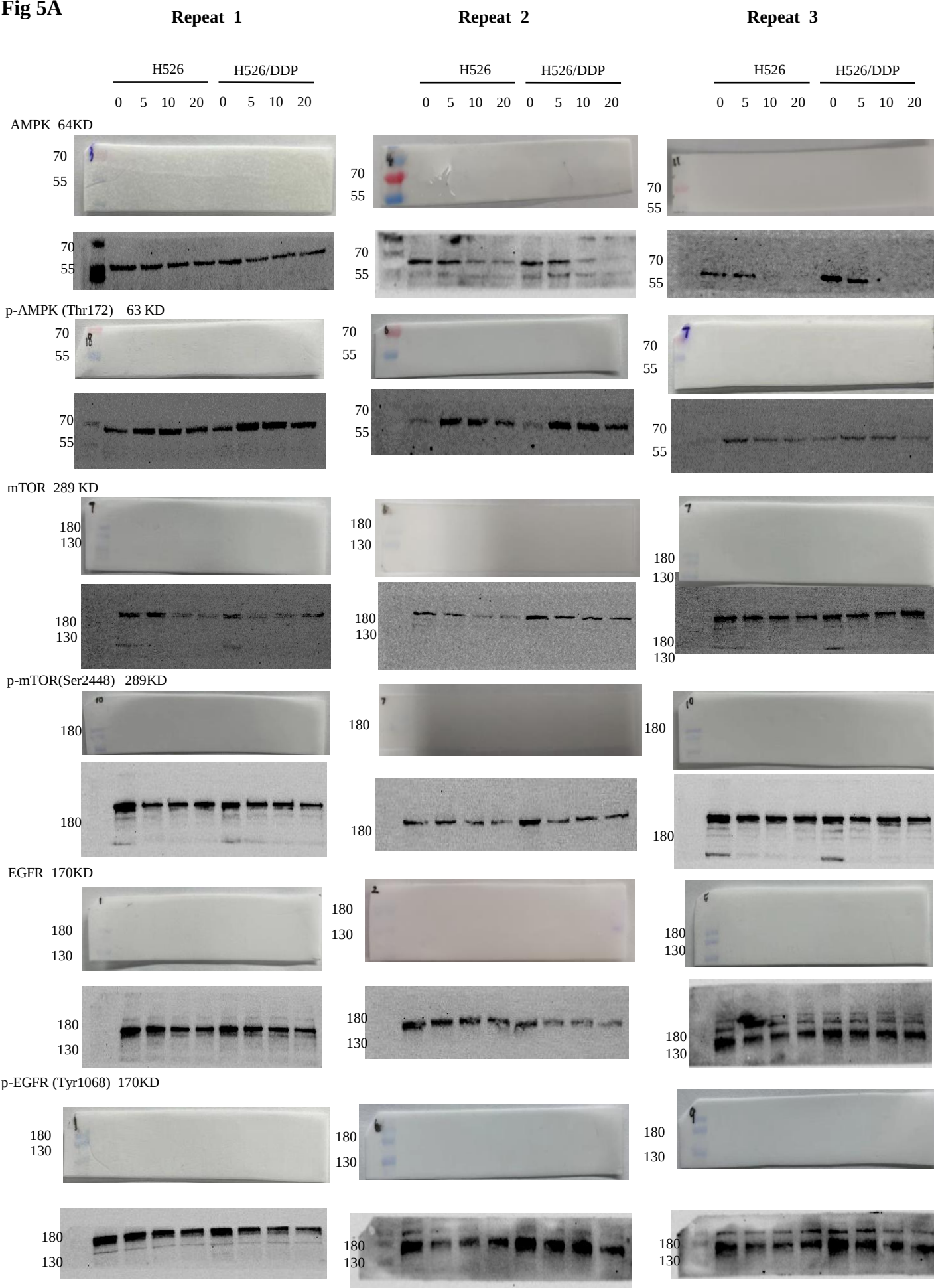


Fig 5A

Repeat 1

Repeat 2

Repeat 3

H526

H526/DDP

H526

H526/DDP

H526

H526/DDP

AKT 56KD

0 5 10 20 0 5 10 20

0 5 10 20 0 5 10 20

0 5 10 20 0 5 10 20

70
55

70

70
55

70
55

70
5570
55

p-AKT(Ser473) 62KD

70
55

70
5570
5570
55

70
55

70
55

Actin 42KD

55
40

55
40

55
40

55
40

55
40

55
40

Fig 5D

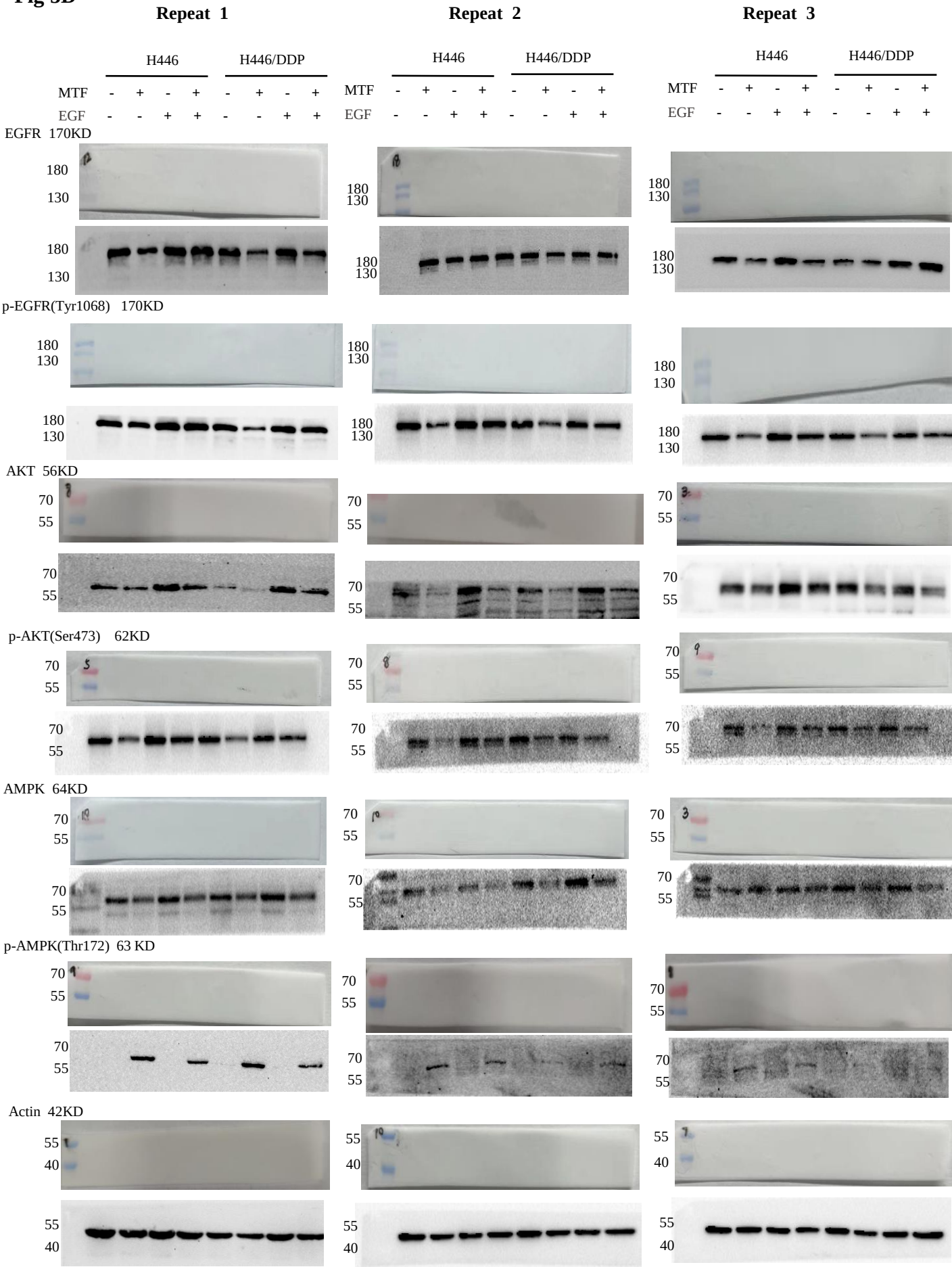


Fig 5E

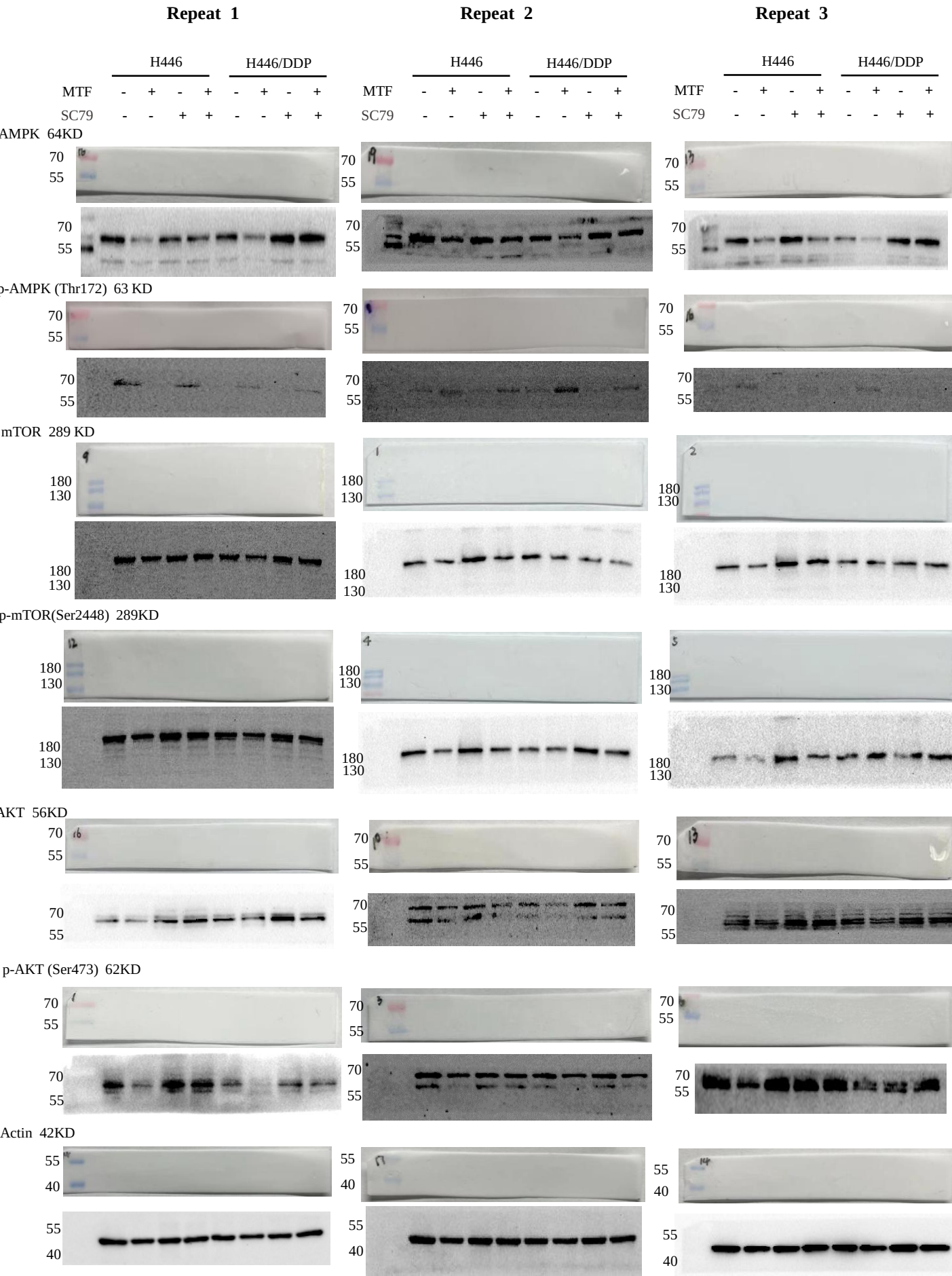
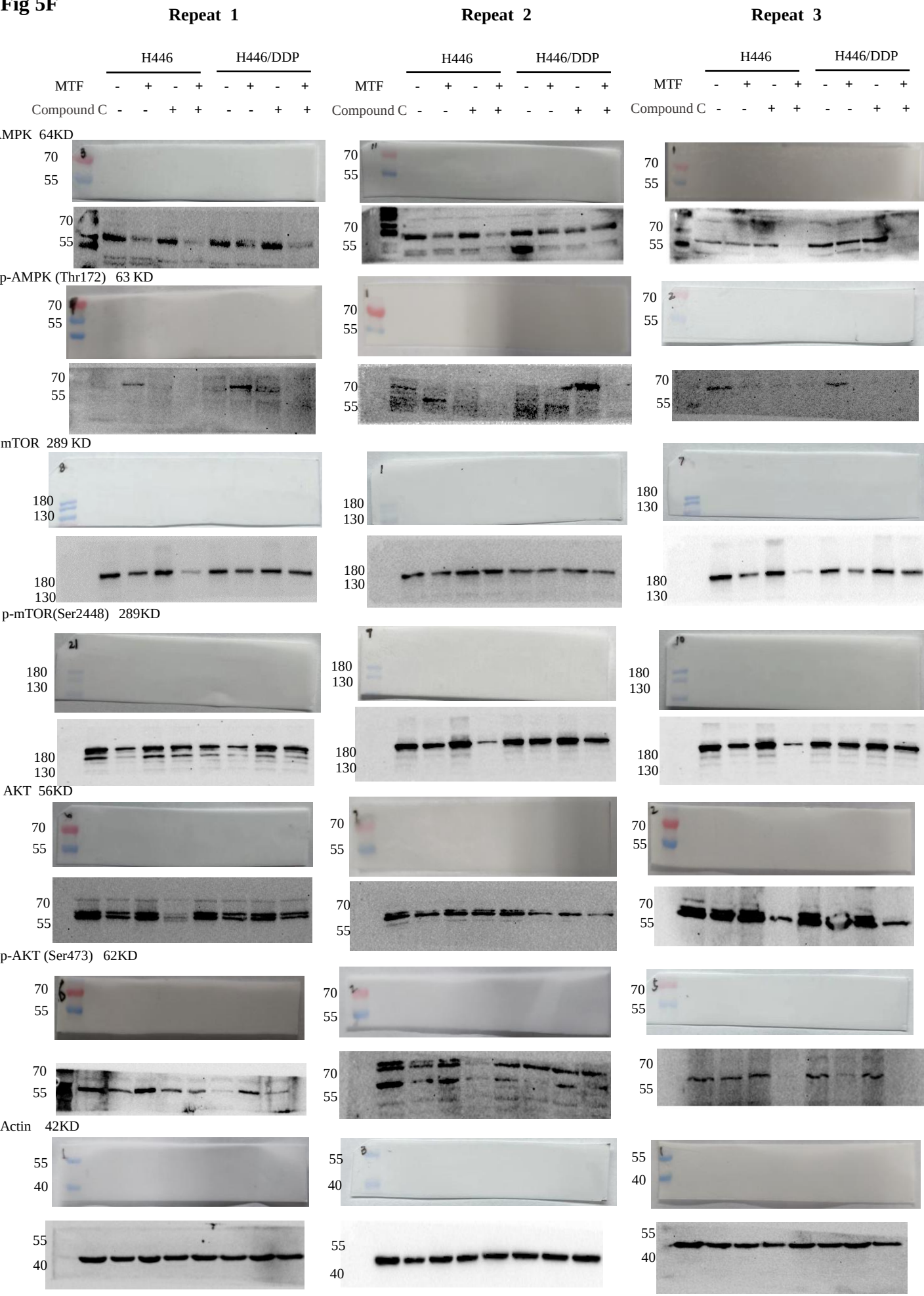


Fig 5F



Supplementary Fig. S2

