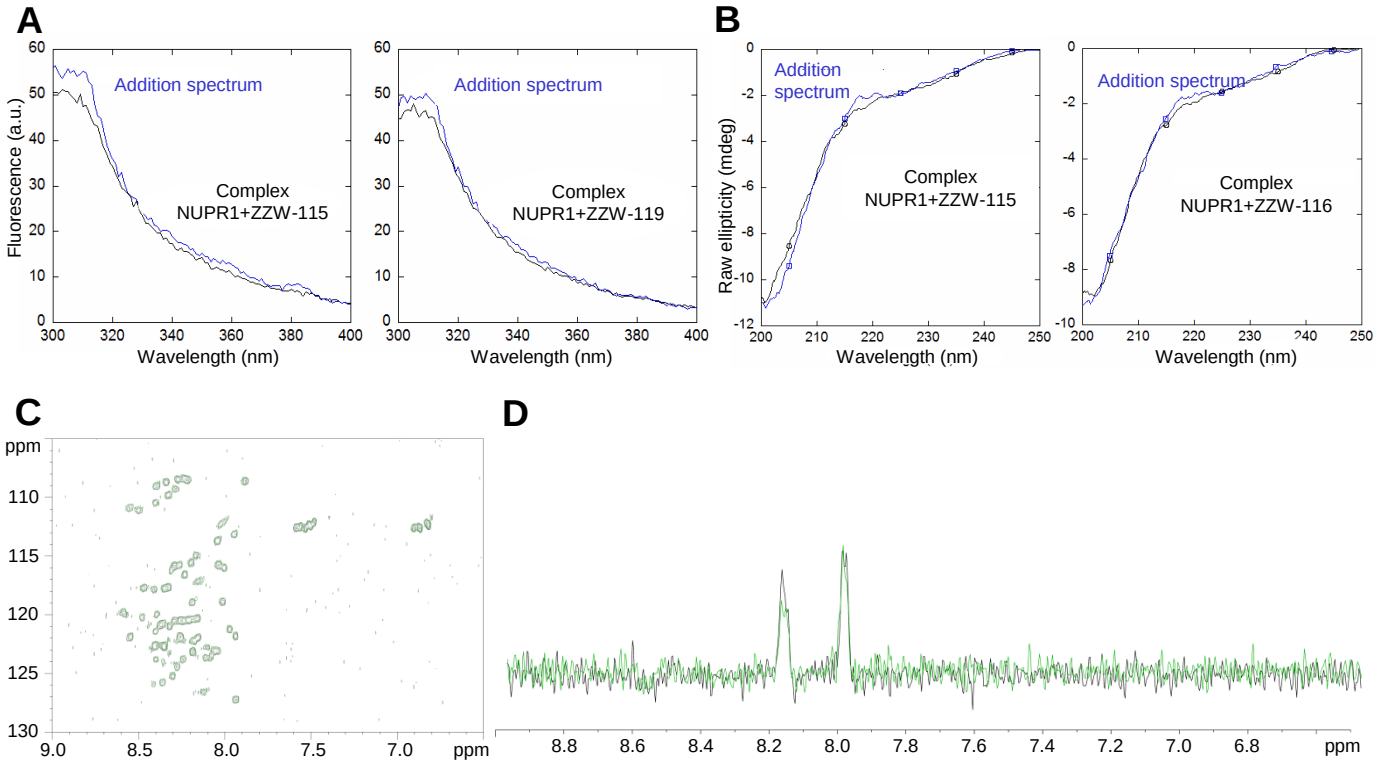

A
Addition spectrum
Complex
NUPR1+ZZW-115
Fluorescence (a.u.)
Wavelength (nm)
Addition spectrum
Complex
NUPR1+ZZW-119
Wavelength (nm)
B
Addition
spectrum
Complex
NUPR1+ZZW-115
Raw ellipticity (mdeg)
Wavelength (nm)
Addition spectrum
Complex
NUPR1+ZZW-116
Wavelength (nm)
C
ppm
D
ppm

Fig S1

Fig S2

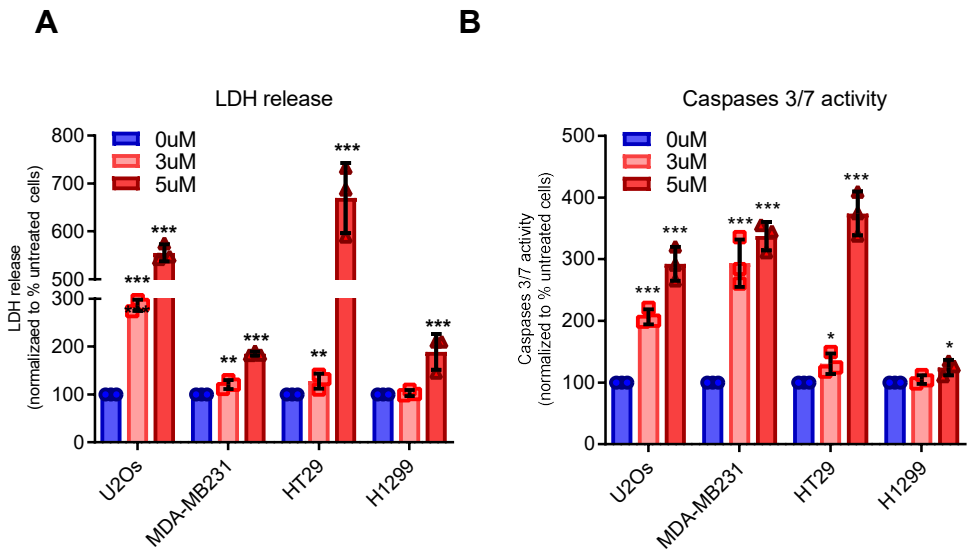
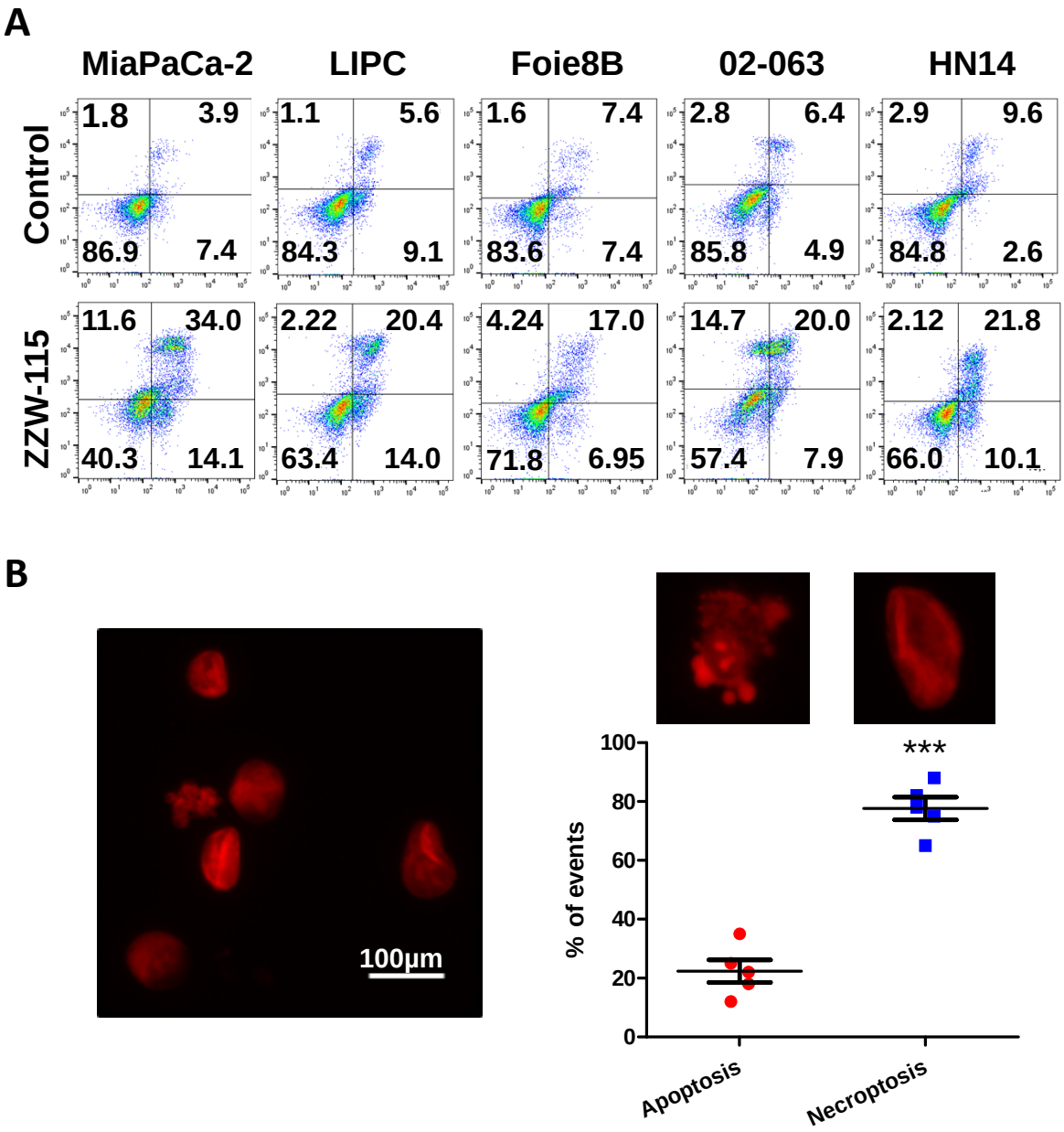

A
LDH release
LDH release (normalizaed to % untreated cells)
0uM
3uM
5uM
800
700
600
500
300
200
100
0
***
**
U2OS
MDA-MB231
HT29
H1299
B
Caspases 3/7 activity
Caspases 3/7 activity (normalized to % untreated cells)
500
400
300
200
100
0
*

Fig S3


A
MiaPaCa-2
LIPC
Foie8B
02-063
HN14
Control
ZZW-115
1.8
3.9
86.9
7.4
1.1
5.6
84.3
9.1
1.6
7.4
83.6
7.4
2.8
6.4
85.8
4.9
2.9
9.6
84.8
2.6
11.6
34.0
40.3
14.1
2.22
20.4
63.4
14.0
4.24
17.0
71.8
6.95
14.7
20.0
57.4
7.9
2.12
21.8
66.0
10.1
B
100μm
***
% of events
100
80
60
40
20
0
Apoptosis
Necroptosis

# Fig S4

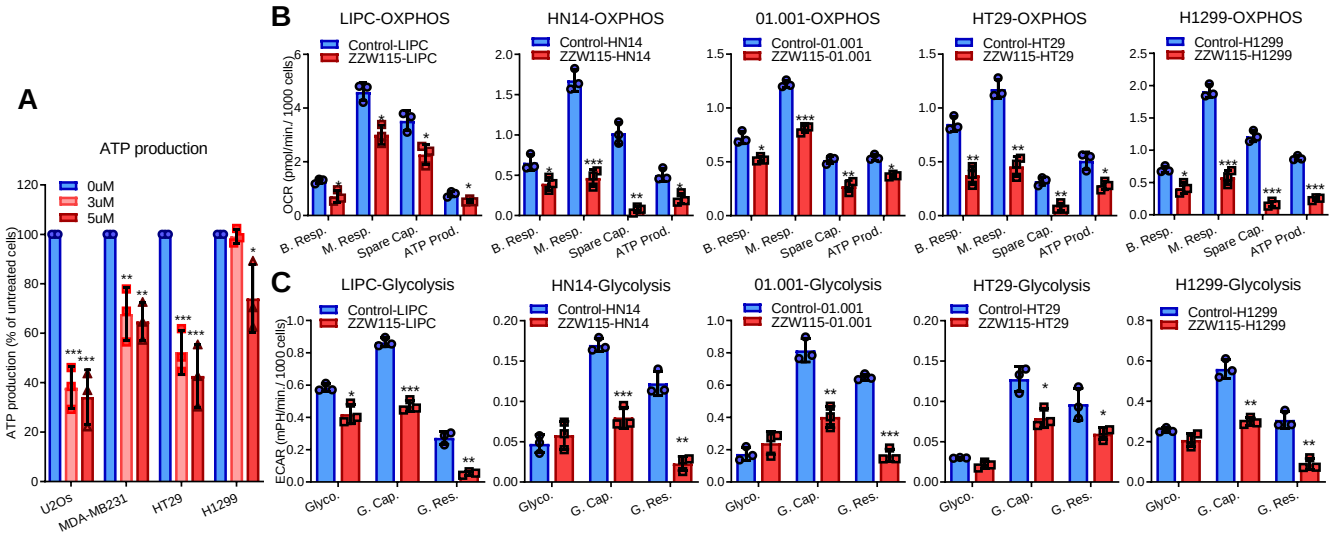

A
ATP production
0uM
3uM
5uM
ATP production (% of untreated cells)
U2OS
MDA-MB231
HT29
H1299
B
LIPC-OXPHOS
Control-LIPC
ZZW115-LIPC
HN14-OXPHOS
Control-HN14
ZZW115-HN14
01.001-OXPHOS
Control-01.001
ZZW115-01.001
HT29-OXPHOS
Control-HT29
ZZW115-HT29
H1299-OXPHOS
Control-H1299
ZZW115-H1299
OCR (pmol/min / 1000 cells)
B. Resp.
M. Resp.
Spare Cap.
ATP Prod.
C
LIPC-Glycolysis
HN14-Glycolysis
01.001-Glycolysis
HT29-Glycolysis
H1299-Glycolysis
ECAR (mPH/min / 1000 cells)
Glyco.
G. Cap.
G. Res.

Fig S5

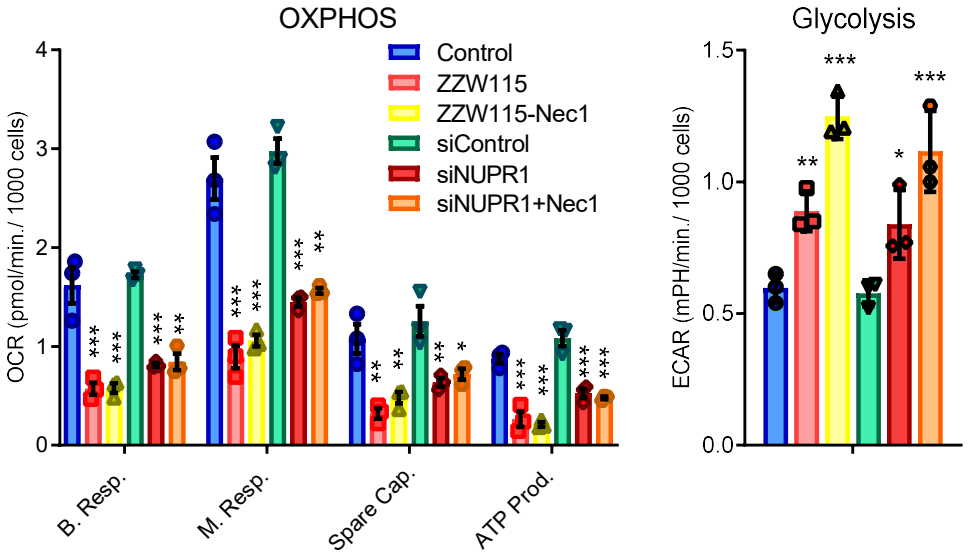

OXPHOS
Control
ZZW115
ZZW115-Nec1
siControl
siNUPR1
siNUPR1+Nec1
OCR (pmol/min./ 1000 cells)
B. Resp.
M. Resp.
Spare Cap.
ATP Prod.
Glycolysis
ECAR (mPH/min./ 1000 cells)

**Figure S1**

**Spectra of NUPR1 in the presence of selected compounds.** (A) Intrinsic fluorescence spectra of NUPR1 in the presence of **ZZW-115** (left) and **ZZW-119** (right). The addition spectra were obtained by the sum of the spectra of the isolated molecules. Experiments were carried out at pH 7.0 (50 mM, phosphate) at 25 °C; each experiment was repeated twice. (B) Far-UV CD spectra of NUPR1 in the presence of **ZZW-115** (left) and **ZZW-116** (right). The addition spectra were obtained by the sum of the spectra of the isolated molecules. Experiments were carried out at pH 7.0 (50 mM, phosphate) at 25 °C; (n=2), and the spectra were acquired by averaging 6 different scans. (C) HSQC spectra of isolated NUPR1 (black) and in the presence of **ZZW-112** (green). (D) Rows corresponding at the $^{15}$N chemical shift of Thr68 (appearing at 8.18 ppm in the $^{1}$H dimension) for isolated NUPR1 (black) and in the presence of **ZZW-112** (green). The signal appearing around 8.00 ppm (in the $^{1}$H dimension) belongs to Tyr30. It is important to note that the intensities show in both rows are raw ones, as obtained from the spectra. Experiments were acquired in acetate buffer (pH 4.5, 50 mM) at 25 °C.

**Figure S2**

**ZZW-115 induces cell death by necrosis and apoptosis in vitro in cancer cell lines.** A panel of cancer cell lines (U2OS, MEDA-MB231m HT29 and H1299) was incubated at either 3 or 5 µM of **ZZW-115** during 24 h and (A) LDH release and (B) Caspase 3/7 activity were measured. Statistical significance is *$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$ compared to 0 µM treated group (2-way ANOVA, Bonferroni post-hoc test). Data represent mean ± SEM, n=3.

**Figure S3**

**ZZW-115 induces cell death by necrosis and apoptosis in vitro. (A)** On a panel of pancreatic cancer cell lines flow cytometry analysis of annexin-V and PI staining following 8 h of treatment with 5 µM of **ZZW-115** compound, a representative experiment of the dot plot profile of cells is shown (n=3). The same panel of control cells as in Figure 4C is presented. (B) MiaPaCa-2 cells were treated with 5 µM of **ZZW-115** during 8 hours following annexin-V and PI staining. Double-positive cells were classified as apoptotic or necrotic cells. The percentage of events per field is shown, no less than 10 fields per sample were counted

(n=5). Statistical significance is ***p < 0.001 (Student's 2-tailed unpaired t test). Data represent mean ± SEM.

**Figure S4**

**ZZW-115 treatment induces a decrease in ATP production and mitochondrial failure in vitro.** A panel of cancer cell lines (U2OS, MEDA-MB231m HT29 and H1299) was incubated at 3 or 5 µM of **ZZW-115** compound during 24 h and (A) ATP content was measured. For each treatment, statistical significance is *p < 0.05, **p < 0.01 and ***p < 0.001 from 0 µM (2-way ANOVA, Bonferroni post-hoc test). (B) OXPHOS metabolism, reflected by oxygen consumption rate (OCR) levels for Basal respiration, Maximal respiration, Spare capacity and ATP production; and (C) Anaerobic glycolytic metabolism, reflected by extracellular acidification rate (ECAR) levels for glycolysis, glycolytic capacity and glycolysis reserve were measured in LIPC, HN14 and 01.001 (primary PDAC cells) as well as in HT29 and H1299 cancer cells treated with **ZZW-115** during 24 h. Statistical significance is *p < 0.05, **p < 0.01 and ***p < 0.001 from 0 µM (Student's 2-tailed unpaired t test). Data represent mean ± SEM, n=3.

**Figure S5**

**Nec-1 rescue ZZW-115 ATP production by glycolysis but not by OXPHOS.** (A) OXPHOS metabolism, reflected by oxygen consumption rate (OCR) levels for Basal respiration, Maximal respiration, Spare capacity and ATP production and (B) Anaerobic glycolytic metabolism reflected by extracellular acidification rate (ECAR) levels for Glycolysis were measured in MiaPaCa-2 cells treated with 3 µM of **ZZW-115** or **ZZW-115**+Nec-1 and siControl-MiaPaCa-2 cells, siNUPR1-MiaPaCa-2 cells and siNUPR1-MiaPaCa-2+Nec1. Statistical significance is *p < 0.05, **p < 0.01, and ***p < 0.001 (1-way ANOVA, Tukey's post-hoc test).