Supplementary Figure 1

\[
\begin{align*}
\text{Cl}_2\text{N} & \rightarrow \text{Cl-N} \rightarrow \text{Cl-N} \\
\text{Cl-N} & \rightarrow \text{Cl-N} \rightarrow \text{Cl-N} \\
\text{Cl-N} & \rightarrow \text{Cl-N} \rightarrow \text{Cl-N} \\
\end{align*}
\]
Supplementary Figure 2

A

\[
\text{tert-butyl 2-(2-chloropyrimidin-4-yl)-1H-pyrrole-4-carboxylate (3)}
\]

B

\[
1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(3-nitrophenyl)urea (8)
\]
Supplementary Figure 2

C

1-(3-aminophenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (7)

D

1-(3-(4-(1H-pyrrol-2-yl)pyrimidin-2-yl)amino)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (SCT-1015)
Supplementary Figure 2

1-(O-(4-(1H-pyrrol-2-yl)pyrimidin-2-yl)amino)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea (STC-1015)
Supplementary Figure 4

PLC5

PP2A activity (pmol of Pi released)

DMSO  SCT-1015  DES

*
Supplementary Figure 5

PLC5

Cell death (%)

DMSO  2.5  5  10  15  20
SCT-1015 (µM)

**  **
Supplementary Figure 6

ATP

Conc. (μmol/g)

DMSO  
SCT-1015

**
Supplementary Figure 7

A

| Dose (μM) | PLC5 (SCT-1015) | Huh7 (SCT-1015) | SK-HEP-1 (SCT-1015) |
|-----------|------------------|------------------|---------------------|
| D         | 5                | 10               | 15                  | 20                  |
| p-ERK (42/44 kDa) |       |       |                     |
| ERK (42/44 kDa)   |       |       |                     |
| GAPDH (37 kDa)    |       |       |                     |

B

**C**

DMSO

SCT-1015

Roxadustat

HIF1α (120 kDa)

PHD3 (27 kDa)

IgG

HIF1α (120 kDa)

PHD3 (27 kDa)

GAPDH (37 kDa)
Supplementary Figure 8

A

| Dose (µM) | PLC5 SCT-1015 | Huh7 SCT-1015 | SK-HEP-1 SCT-1015 |
|-----------|----------------|----------------|---------------------|
| D         | 5 10 15 20     | 5 10 15 20     | 5 10 15 20          |
| p-4E-BP1  |                |                |                     |
| (T37/46, 15-20 kDa) |          |                |                     |
| p-4E-BP1  |                |                |                     |
| (S65, 15-20 kDa) |          |                |                     |
| 4E-BP1    |                |                |                     |
| (15-20 kDa) |          |                |                     |
| p-S6K     |                |                |                     |
| (T389, 70/85 kDa) |          |                |                     |
| S6K       |                |                |                     |
| (70/85 kDa) |          |                |                     |
| GAPDH     |                |                |                     |
| (37 kDa)  |          |                |                     |

B

[Bar graph showing Cyto-ID fold change for PLC5 with DMSO and SCT-1015 concentrations 2.5, 5, 10, 15, 20 µM, with significant differences indicated by **.]

**p-S6K (T389, 70/85 kDa)**

**p-4E-BP1 (S65, 15-20 kDa)**

**GAPDH (37 kDa)**
Supplementary Figure 9

A

Tumor size (mm$^3$)

Days

Vehicle
SCT-1015 25mg/kg/day

B

Body weight (g)

Days

Vehicle
SCT-1015 25mg/kg/day

C

Vehicle
SCT-1015

p-AMPK$\alpha$
(62 kDa)

AMPK$\alpha$
(62 kDa)

GAPDH
(37 kDa)

D

p-AMPK$\alpha$/GAPDH (relative to Vehicle)

Vehicle
SCT-1015

**
Supplementary Figure 10

A

- A-769662
  - IC\textsubscript{50}: >300 µM

- PX-478
  - IC\textsubscript{50}: >120 µM

- sorafenib
  - IC\textsubscript{50}: 4.1 µM

- rapamycin
  - IC\textsubscript{50}: 31.4 µM

- lenvatinib
  - IC\textsubscript{50}: >120 µM

B

- SCT-1015 (µM)
  - Cell viability (%)
  - Rapa 0µM
  - Rapa 5µM
  - Rapa 15µM

Legend:
- Rapa 0µM
- Rapa 5µM
- Rapa 15µM

Annotations:
- a
- # a
- † a
- b
- # b
- † b
- c
- # c
- † c
- d
- # d
- † d
- e
- # e
- † e
Supplementary Figure 11

A

Day 22

Rapa vs. Vehicle \( (p<0.0001) \)
SCT-1015 vs. Vehicle \( (p<0.0001) \)
Rapa+SCT-1015 vs. Vehicle \( (p<0.0001) \)
Rapa vs. Rapa+SCT-1015 \( (p=0.0107) \)
SCT-1015 vs. Rapa+SCT-1015 \( (p=0.0077) \)

B

Day 22

Rapa vs. Vehicle \( (p=0.048) \)
SCT-1015 vs. Vehicle (N.S.)
Rapa+SCT-1015 vs. Vehicle (N.S.)
Rapa vs. Rapa+SCT-1015 (N.S.)
SCT-1015 vs. Rapa+SCT-1015 (N.S.)
