A

AHRR

Relative mRNA level

RBN-2397(100 nM)	-	+	-	+	-	+		-	+	-	+	-	+
CH-223191(1 μM)	-	-	+	+	-	-		-	-	+	+	-	-
Tapinarof (100 nM)	-	-	-	-	+	+		-	-	-	-	+	+

NCI-H1373 NCI-H1373 AHR KO

PARP7

Relative mRNA level

RBN-2397(100 nM)	-	+	-	+	-	+		-	+	-	+	-	+
CH-223191(1 μM)	-	-	+	+	-	-		-	-	+	+	-	-
Tapinarof (100 nM)	-	-	-	-	+	+		-	-	-	-	+	+

NCI-H1373 NCI-H1373 AHR KO

IL1A

Relative mRNA level

RBN-2397(100 nM)	-	+	-	+	-	+		-	+	-	+	-	+
CH-223191(1 μM)	-	-	+	+	-	-		-	-	+	+	-	-
Tapinarof (100 nM)	-	-	-	-	+	+		-	-	-	-	+	+

NCI-H1373 NCI-H1373 AHR KO

IL1B

Relative mRNA level

RBN-2397(100 nM)	-	+	-	+	-	+		-	+	-	+	-	+
CH-223191(1 μM)	-	-	+	+	-	-		-	-	+	+	-	-
Tapinarof (100 nM)	-	-	-	-	+	+		-	-	-	-	+	+

NCI-H1373 NCI-H1373 AHR KO

PAI2

Relative mRNA level

RBN-2397(100 nM)	-	+	-	+	-	+		-	+	-	+	-	+
CH-223191(1 μM)	-	-	+	+	-	-		-	-	+	+	-	-
Tapinarof (100 nM)	-	-	-	-	+	+		-	-	-	-	+	+

NCI-H1373 NCI-H1373 AHR KO

IL6

Relative mRNA level

RBN-2397(100 nM)	-	+	-	+	-	+		-	+	-	+	-	+
CH-223191(1 μM)	-	-	+	+	-	-		-	-	+	+	-	-
Tapinarof (100 nM)	-	-	-	-	+	+		-	-	-	-	+	+

NCI-H1373 NCI-H1373 AHR KO

B

AHR

Relative mRNA level

RBN-2397(100 nM)	-	+	-	+	-	+		-	+	-	+	-	+
CH-223191(1 μM)	-	-	+	+	-	-		-	-	+	+	-	-
Tapinarof (100 nM)	-	-	-	-	+	+		-	-	-	-	+	+

NCI-H1373 NCI-H1373 AHR KO

ARNT

Relative mRNA level

RBN-2397(100 nM)	-	+	-	+	-	+		-	+	-	+	-	+
CH-223191(1 μM)	-	-	+	+	-	-		-	-	+	+	-	-
Tapinarof (100 nM)	-	-	-	-	+	+		-	-	-	-	+	+

NCI-H1373 NCI-H1373 AHR KO

C

DMSO Tapinarof

RBN-2397 RBN-2397
+Tapinarof

D

Relative nuclear/cytoplasmic
Alexa 488 intensity ratio

P = 0.0009
P = 0.0217
P = 0.0036

RBN-2397(100 nM)	-	+	-	-	+
Olaparib (10 μM)	-	-	+	-	-
Tapinarof (100 nM)	-	-	-	+	+

NCI-H1373

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Supplementary Fig. 5 RBN-2397 activates the transcription of AHR target genes through AHR activity and localization but does not affect AHR/ARNT mRNA levels.

A, RT-qPCR showing relative mRNA levels of AHR target genes in NCI-H1373 and *AHR* knockout cells treated with the indicated drugs for 24 hours. **B,** RT-qPCR showing relative mRNA levels of *AHR* and *ARNT* in NCI-H1373 and *AHR* knockout cells treated with the indicated drugs for 24 hours. Data is shown as mean values ± SD; *n* = 2. **C,** Representative images of NCI-H1373 cells treated with RBN-2397, tapinarof or a combination of both drugs for 2 h and then stained with AhR Rabbit mAb and Goat anti-Rabbit IgG Alexa Fluor 488 secondary antibody and. DMSO treated cells are shown as a vehicle control. **D,** Relative nuclear/cytoplasmic Alexa 488 intensity ratio of cells from (**C**). Data shown as mean values ± SD; At least 25000 cells were analyzed each group, from triplicate wells.