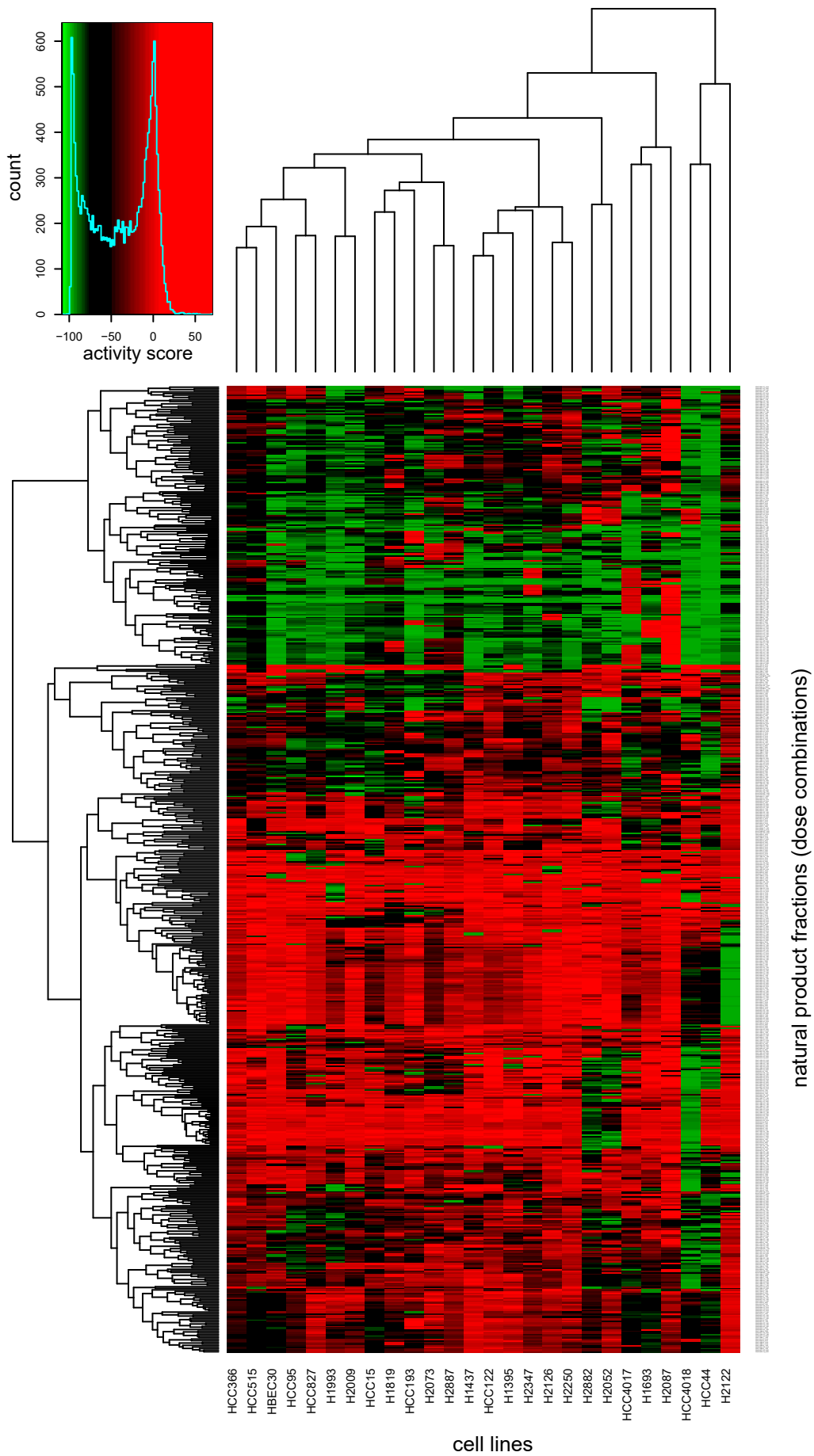
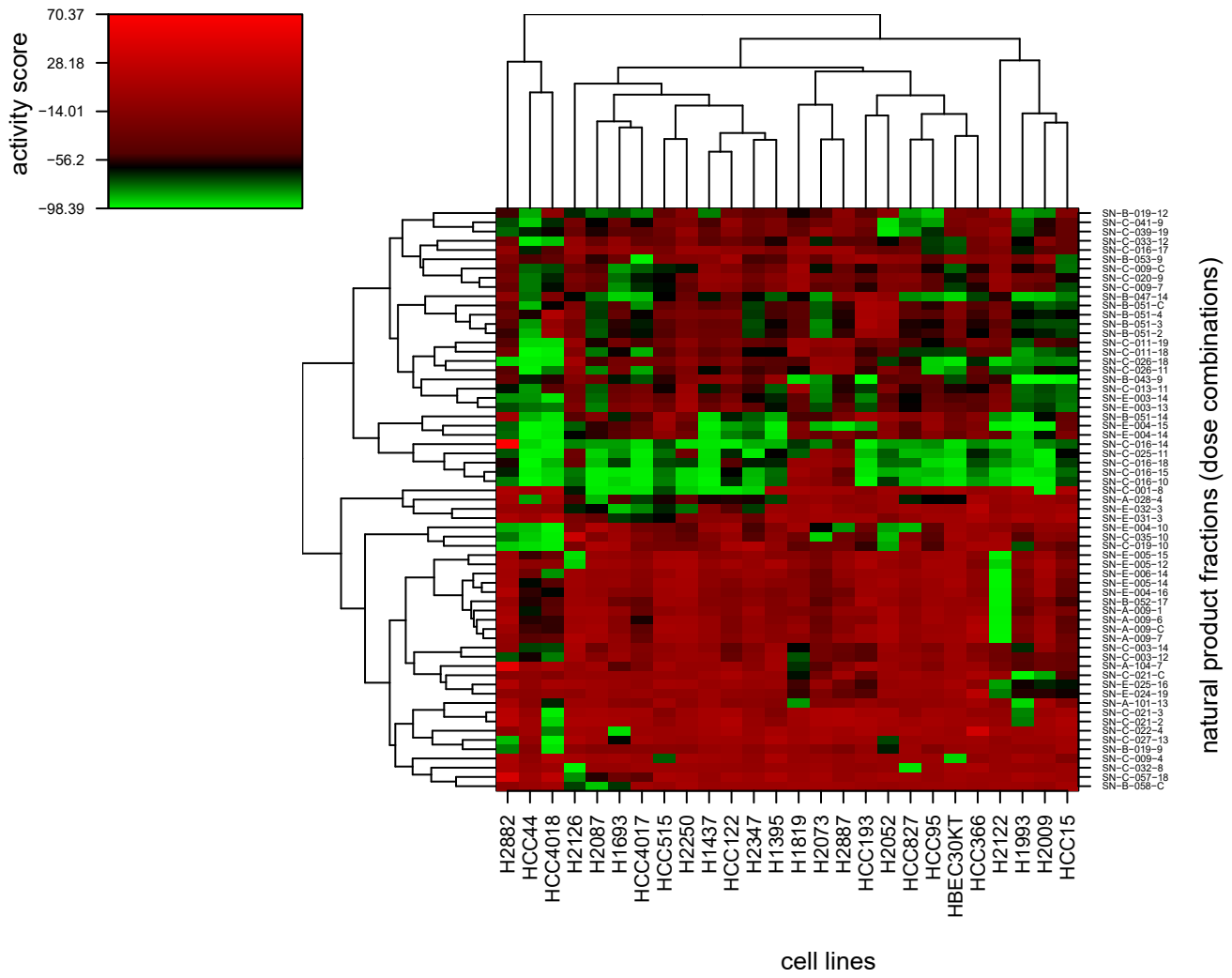


**Supplementary Figure 1. Piericidin A and HORMAD1 association identified by NPF screen.** (A) Heat map of the top 609 (out of 17,432) most selective (indicated by activity score) natural product fraction/dose combinations in 26 cell lines. (B) Heat map of 63 natural product/dose combinations that exhibited most selectivity (indicated by activity score) at lowest doses and also displayed favorable LC-MS profiles. (C) Heat map of selectivity (activity score) of natural product fraction SNB-051-14 in a panel of 26 cell lines. (D) LC-MS chromatograph of natural product subfraction SNB-051-F36. Seven individual peaks were collected at 254 nM absorption over 20 min. (E) Left: <sup>1</sup>H NMR analysis identifies piericidin A as the major metabolite for enriched natural product subfraction SNB-051-F36-H7. Right: chemical structure of piericidin A. (F) Expression profile for HORMAD1 gene expression across panel of tissues indicated (data accessed from GTEx Portal). (G) Whole cell lysates immunoblotted with indicated antibodies.

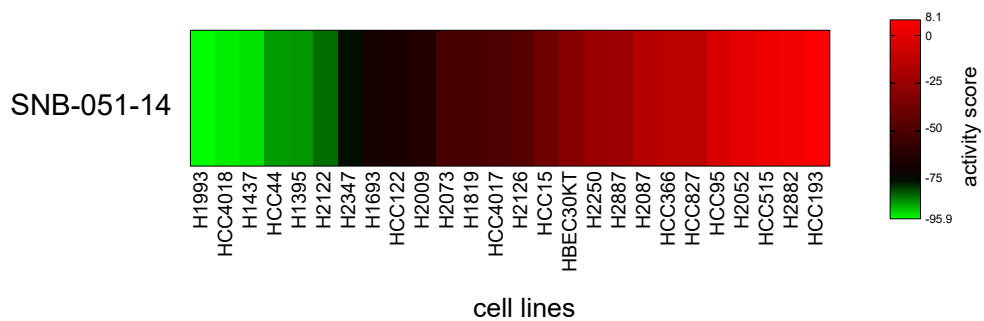
A.



B.

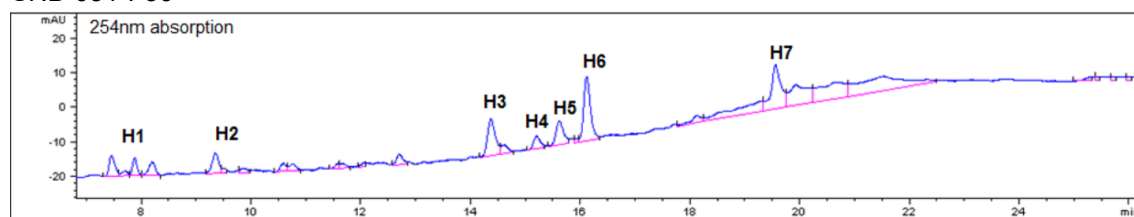


C.



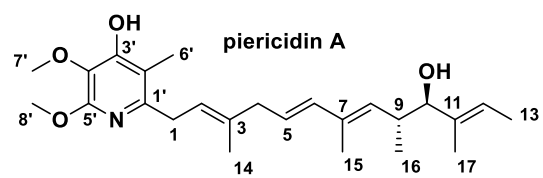
D.

SNB-051-F36

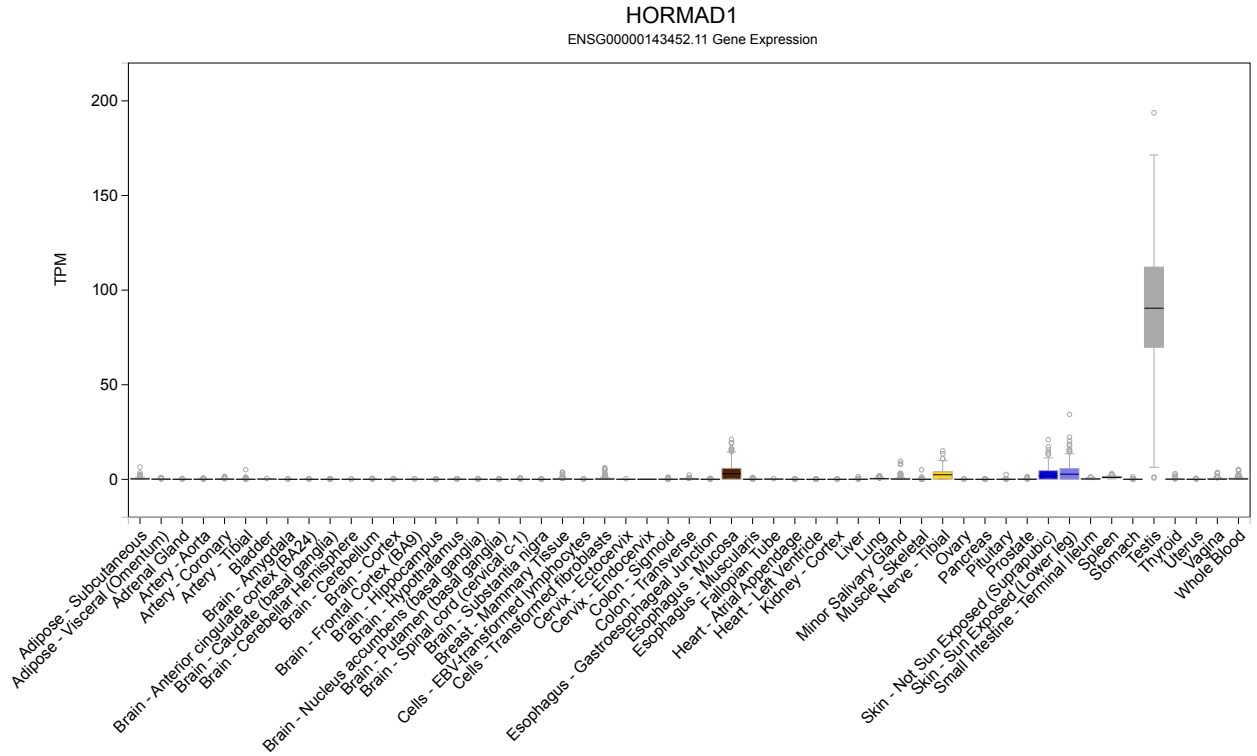


E.

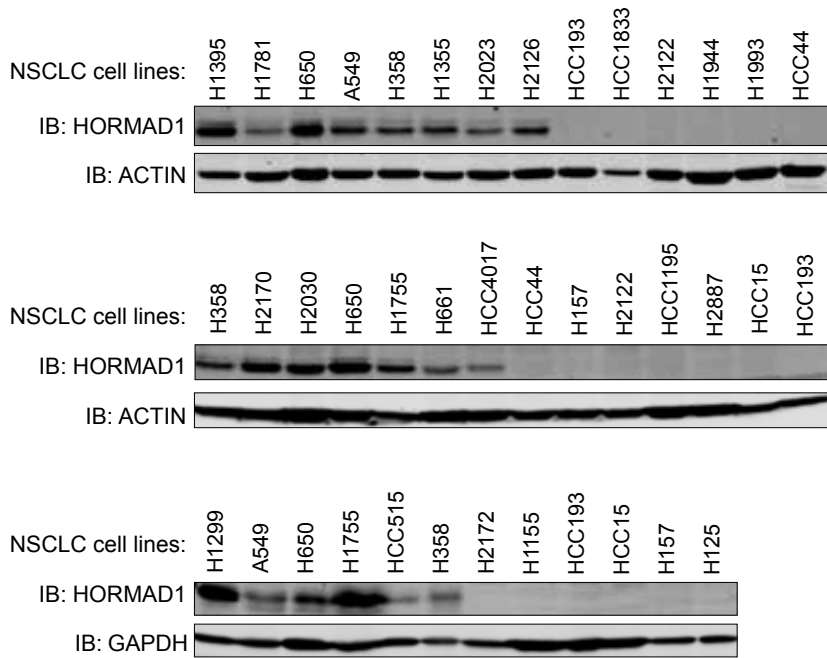
No.	$\delta_H$ , mult. (J in Hz) piericidin A (4.1)	No.	$\delta_H$ , mult. (J in Hz) piericidin A (4.1)
1	3.34 d (6.9)	1'	-
2	5.43 dd (13.0, 6.9)	2'	-
3	-	3'	-
4	2.76 d (6.9)	4'	-
5	5.52 dt (15.5, 6.9)	5'	-
6	6.07 d (15.5)	6'	2.03 s
7	-	7'	3.73 s
8	5.27 d (9.5)	8'	3.89 s
9	2.66 m		
10	3.68 d (8.3)		
11	-		
12	5.30 m		
13	1.61 d (7.5)		
14	1.73 s		
15	1.73 s		
16	0.79 d (6.9)		
17	1.59 s		



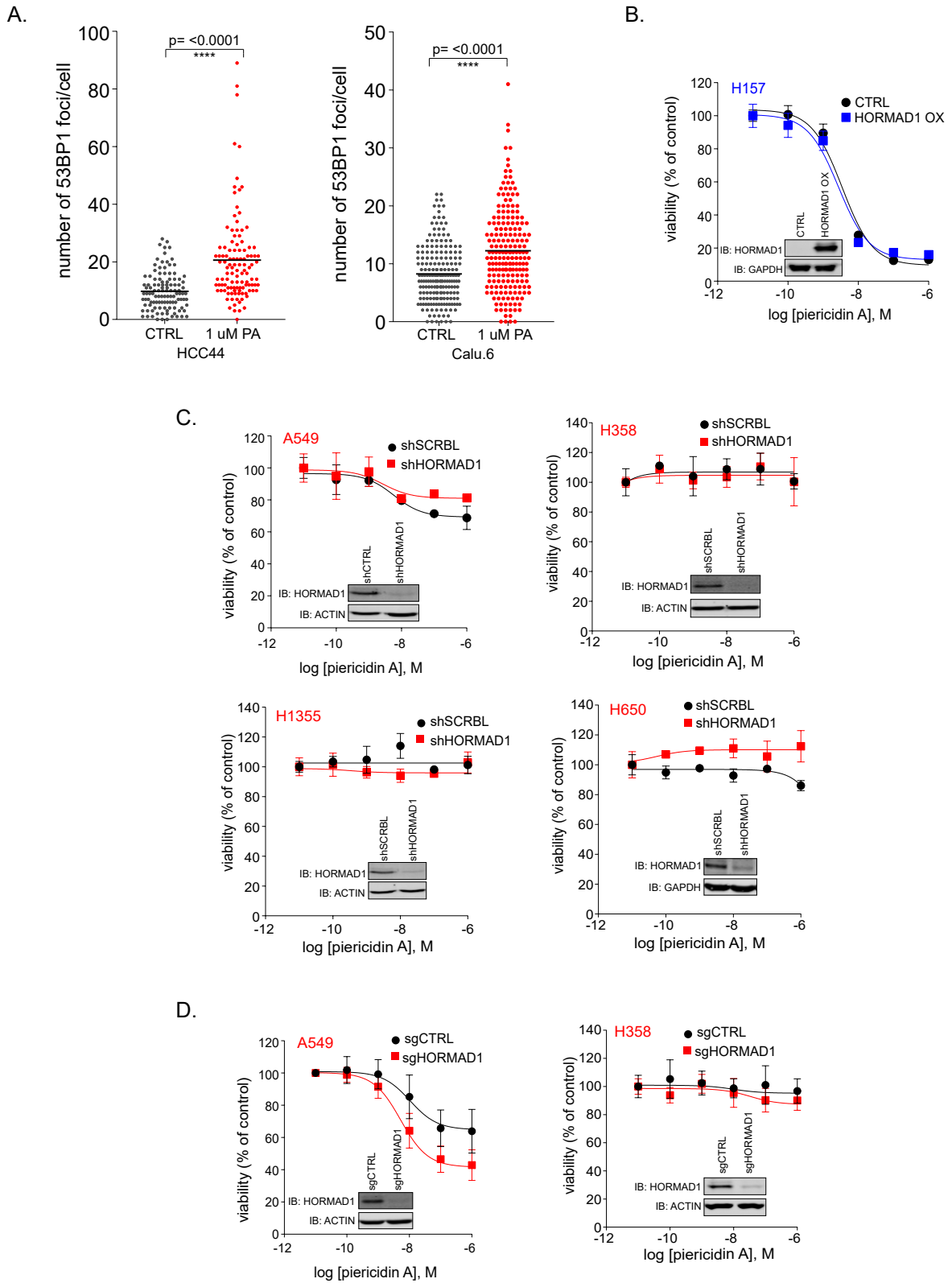
F.



G.



**Supplementary Figure 2. Piericidin A induces DNA damage in NSCLC lines.** (A) HCC44 and Calu.6 cells were exposed to piericidin A (PA) (1  $\mu$ M) for 48 h, then fixed and immunostained with 53BP1 antibody. Dots indicate individual cells, >100 cells quantified for each condition, and bar represents the mean. P-values calculated by Mann-Whitney test. (B) H157 cells lentivirally infected with HORMAD1 or control vector were exposed to escalating doses of piericidin A for 72 hours (h). Points indicate viability as measured by Cell-Titer Glo® (n=3) and bars indicate standard deviation (sd). Curves are non-linear fits to the respective data. Whole cell lysates were immunoblotted with indicated antibodies. (C) Indicated cell lines expressing shHORMAD1 and shSCRBL were exposed to escalating doses of piericidin A for 72 h. Points indicate viability as measured by Cell-Titer Glo® (n=3) and bars indicate sd. Curves are non-linear fits to the respective data. Whole cell lysates were immunoblotted with indicated antibodies. (D) Indicated cell lines expressing Cas9 and sgCTRL or sgHORMAD1 were exposed to escalating doses of piericidin A for 72 h. Points indicate viability as measured by Cell-Titer Glo® (n=3) and bars indicate sd. Curves are non-linear fits to the respective data. Whole cell lysates were immunoblotted with indicated antibodies.



**Supplementary Figure 3. S2N and geneset overlaps for HORMAD1 high LUAD tumors.**

(A) Descriptions of overlapping genes between top 10% of genes upregulated in HORMAD1 high tumors by Signal-2-Noise analysis (251 genes) and Hallmark Gene Sets (Molecular Signatures Database). (B) Descriptions of overlapping genes between top 10% of genes upregulated in HORMAD1 high tumors by Signal-2-Noise analysis (251 genes) and KEGG gene sets (Molecular Signatures Database).



A.

Hallmark Genes Sets and Associated Statistical Values

Gene Set Name [# Genes]	Description	# Genes in Overlap	p-value	FDR q-value	Genes
HALLMARK_E2F_TARGETS [200]	Genes encoding cell cycle related targets of E2F transcription factors.	51	1.14 e-72	2.86 e-71	AURKA, KIF2C, CCNB2, TOP2A, PLK1, CENPE, KIF4A, RACGAP1, BIRC5, BRCA2, ESPL1, CDKN3, CDC20, PLK4, MCM2, CDC25A, KPN2A, CKS1B, CHEK1, ORC6, UBE2S, MKI67, MYBL2, AURKB, DLGAP5, MCM4, RFC3, CCNE1, DEPDC1, BRCA1, SPAG5, RAD51AP1, CHEK2, KIF18B, SPC24, ATAD2, UBE2T, PSMC3IP, HELLS, CDCA8, SPC25, BUB1B, TK1, DSCC1, DIAPH3, CDCA3, GINS4, TIMELESS, TRIP13, MELK, GINS1
HALLMARK_G2M_CHECKPOINT [200]	Genes involved in the G2/M checkpoint, as in progression through the cell division cycle.	51	1.14 e-72	2.86 e-71	AURKA, KIF2C, CCNB2, TOP2A, PLK1, CENPE, KIF4A, RACGAP1, BIRC5, BRCA2, ESPL1, CDKN3, CDC20, PLK4, MCM2, CDC25A, KPN2A, CKS1B, CHEK1, ORC6, UBE2S, MKI67, MYBL2, AURKB, BUB1, NEK2, TTK, NDC80, CENPF, TPX2, FBXO5, KIF11, NUSAP1, KIF15, KIF23, DBF4, CDC6, STIL, CCNF, CDC45, CENPA, E2F1, E2F2, TROAP, TRAP1, POLQ, UBE2C, CASC5, RBL1, RAD54L, EXO1
HALLMARK_MITOTIC_SPINDLE [200]	Genes important for mitotic spindle assembly.	26	5.74 e-29	9.56 e-28	AURKA, KIF2C, CCNB2, TOP2A, PLK1, CENPE, KIF4A, RACGAP1, BIRC5, BRCA2, ESPL1, DLGAP5, BUB1, NEK2, TTK, NDC80, CENPF, TPX2, FBXO5, KIF11, NUSAP1, KIF15, KIF23, SASS6, ANLN, KNTC1
HALLMARK_SPERMATOGENESIS [135]	Genes up-regulated during production of male gametes (sperm), as in spermatogenesis.	12	5.24 e-12	6.55 e-11	AURKA, KIF2C, CCNB2, CDKN3, BUB1, NEK2, TTK, DBF4, YBX2, RPL39L, NCAPI, ACRV1
HALLMARK_ESTROGEN_RESPONSE_LATE [200]	Genes defining late response to estrogen.	7	7.44 e-5	6.2 e-4	TOP2A, CDC20, PLK4, CDC6, STIL, MEST, PLAC1
HALLMARK_MTORC1_SIGNALING [200]	Genes up-regulated through activation of mTORC1 complex.	7	7.44 e-5	6.2 e-4	AURKA, PLK1, MCM2, CDC25A, MCM4, BUB1, CCNF
HALLMARK_MYC_TARGETS_V1 [200]	A subgroup of genes regulated by MYC - version 1 (v1).	6	5.54 e-4	3.96 e-3	CDC20, MCM2, KPN2A, MCM4, CDC45, TYMS
HALLMARK_MYC_TARGETS_V2 [58]	A subgroup of genes regulated by MYC - version 2 (v2).	3	3.16 e-3	1.97 e-2	PLK1, PLK4, MCM4
HALLMARK_DNA_REPAIR [150]	Genes involved in DNA repair.	4	7.12 e-3	3.95 e-2	RFC3, TYMS, ZWINT, RAD51

B.

KEGG Genes Sets and Associated Statistical Values

Gene Set Name [# Genes]	Description	# Genes in Overlap	p-value	FDR q-value	Genes
KEGG_CELL_CYCLE [128]	Cell cycle	25	1.43 e-32	2.66 e-30	CCNB1, CCNB2, CCNE1, CCNE2, PLK1, BUB1, PKMYT1, CDC25C, CDC20, ESPL1, CHEK1, CHEK2, CDC25A, MCM2, MCM4, E2F1, E2F2, RBL1, DBF4, ORC6, ORC1, BUB1B, TTK, CDC45, CDC6
KEGG_OOCYTE_MEIOSIS [114]	Oocyte meiosis	13	2.58 e-14	2.4 e-12	CCNB1, CCNB2, CCNE1, CCNE2, PLK1, BUB1, PKMYT1, CDC25C, CDC20, ESPL1, SGOL1, FBXO5, AURKA
KEGG_HOMOLOGOUS_RECOMBINATION [28]	Homologous recombination	7	8.01 e-11	4.97 e-9	RAD51, BRCA2, EME1, RAD54B, BLM, XRCC2, RAD54L
KEGG_P53_SIGNALING_PATHWAY [69]	p53 signaling pathway	7	6.13 e-8	2.85 e-6	CCNB1, CCNB2, CCNE1, CCNE2, CHEK1, CHEK2, GTSE1
KEGG_PROGESTERONE_MEDIATED_OOCYTE_MATURATION [86]	Progesterone-mediated oocyte maturation	7	2.84 e-7	1.06 e-5	CCNB1, CCNB2, PLK1, BUB1, PKMYT1, CDC25C, CDC25A
KEGG_DNA_REPLICATION [36]	DNA replication	5	1.02 e-6	3.16 e-5	MCM2, MCM4, RFC3, POLE2, DNA2
KEGG_PANCREATIC_CANCER [70]	Pancreatic cancer	5	2.85 e-5	7.57 e-4	E2F1, E2F2, RAD51, BRCA2, RAC3
KEGG_PATHWAYS_IN_CANCER [328]	Pathways in cancer	9	4.76 e-5	1.11 e-3	CCNE1, CCNE2, E2F1, E2F2, RAD51, BRCA2, RAC3, CKS1B, BIRC5
KEGG_SMALL_CELL_LUNG_CANCER [84]	Small cell lung cancer	5	6.87 e-5	1.42 e-3	CCNE1, CCNE2, E2F1, E2F2, CKS1B
KEGG_PROSTATE_CANCER [89]	Prostate cancer	4	1.09 e-3	2.02 e-2	CCNE1, CCNE2, E2F1, E2F2
KEGG_NEUROACTIVE_LIGAND_RECEPTOR_INTERACTION [272]	Neuroactive ligand-receptor interaction	6	2.66 e-3	4.49 e-2	CHRM5, GRIN2D, HTR2C, GPR83, GABRR1, MCHR2