

## Supporting Information

### Adverse outcome pathway-driven analysis of liver steatosis *in vitro*: a case study with cyproconazole

Claudia Luckert<sup>†</sup>, Albert Braeuning<sup>†,\*</sup>, Georges de Sousa<sup>§</sup>, Sigrid Durinck<sup>||</sup>, Efrosini S. Katsanou<sup>‡</sup>, Parthena Konstantinidou<sup>‡</sup>, Kyriaki Machera<sup>‡</sup>, Emanuela S. Milani<sup>•</sup>, Ad A.C.M. Peijnenburg<sup>‡</sup>, Roger Rahmani<sup>§</sup>, Andreja Rajkovic<sup>||</sup>, Deborah Rijkers<sup>‡</sup>, Anastasia Spyropoulou<sup>‡</sup>, Marianna Stamou<sup>#,•</sup>, Geert Stoopen<sup>‡</sup>, Shana Sturla<sup>#</sup>, Bernd Wollscheid<sup>#,•</sup>, Nathalie Zucchini-Pascal<sup>§</sup>, Alfonso Lampen<sup>†</sup>

<sup>†</sup>German Federal Institute for Risk Assessment, Department Food Safety, Berlin, Germany

<sup>‡</sup>RIKILT Wageningen University & Research, Wageningen, The Netherlands

<sup>§</sup>French National Institute for Agricultural Research, INRA Unit 1331, TOXALIM, France

<sup>||</sup>Ghent University, Faculty of Bioscience Engineering, Department of Food Technology, Food Safety and Health, Ghent, Belgium

<sup>‡</sup>Benaki Phytopathological Institute, Athens, Greece

<sup>#</sup>ETH Zurich, Department of Health Sciences and Technology, Zurich, Switzerland

<sup>•</sup>ETH Zurich, BioMedical Proteomics Platform & Institute of Molecular Systems Biology, Zurich, Switzerland

\*Corresponding author:

Albert Braeuning

German Federal Institute for Risk Assessment

Dept. Food Safety

Max-Dohrn-Str. 8-10

10589 Berlin

Germany

Phone +49-(0)30-18412-3758

Fax +49-(0)30-18412-63758

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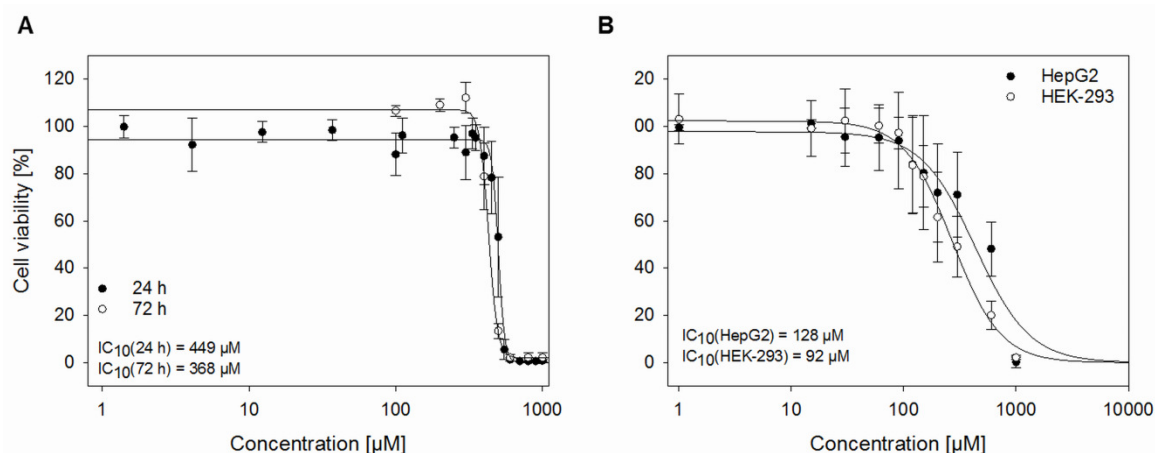
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**Figure S1:** Cytotoxicity of cyproconazole. Cytotoxic effects of cyproconazole on (A) differentiated HepaRG cells after 24 h and 72 h and (B) on HepG2 and HEK-293 cells after 24 h were assessed using the WST-1 assay. Data are expressed in percent of solvent control (0.5 % DMSO). Following dose response curve fitting (four parameter logistic curve) inhibitory concentration of 10% ( $\text{IC}_{10}$ ) values were determined.

**Table S1:** Plasmids, cell lines and positive controls used for the different reporter gene assays<sup>a</sup>

Reporter gene assay	Plasmid <sup>b</sup>	Plasmid amount	Cell line	Positive control
AhR	p3xDREC	80 ng/well	HepG2	5 $\mu\text{M}$ 3-Methylcholanthrene
CAR	pGAL4/DBD-hCAR/LBD(+3aa) pGAL4-(UAS)5-TK-Luc	40 ng/well 40 ng/well	HEK-293	10 $\mu\text{M}$ CITCO
CAR-CYP2B6	pGL3-CYP2B6-wt-luc pCR3-hCAR1+A	40 ng/well 40 ng/well	HepG2	10 $\mu\text{M}$ CITCO
FXR	pGAL4-(UAS)5-TK-LUC pGAL4-FXR-LBD	40 ng/well 40 ng/well	HEK-293	10 $\mu\text{M}$ GW 4064
GRE	pGRE-luc	200 ng/well	HepG2	10 $\mu\text{M}$ Dexamethasone
LXR $\alpha$	pGAL4-(UAS)5-TK-LUC pGAL4-LXR $\alpha$ -LBD	40 ng/well 40 ng/well	HEK-293	10 $\mu\text{M}$ GW 3965
PPAR $\alpha$	pGAL4-(UAS)5-TK-LUC pGAL4-hPPAR $\alpha$ -LBD	40 ng/well 40 ng/well	HEK-293	1 $\mu\text{M}$ GW 7647
PPAR $\gamma$	pGAL4-(UAS)5-TK-LUC pGAL4-hPPAR $\gamma$ -LBD	40 ng/well 40 ng/well	HEK-293	10 $\mu\text{M}$ Troglitazon
PPAR $\delta$	pGAL4-(UAS)5-TK-LUC pGAL4-hPPAR $\delta$ -LBD	40 ng/well 40 ng/well	HEK-293	1 $\mu\text{M}$ GW 501516
PXR	pGAL4-(UAS)5-TK-LUC pGAL4-PXR-LBD	40 ng/well 40 ng/well	HEK-293	10 $\mu\text{M}$ SR12813
PXR-CYP2B6	pGL3-CYP2B6-wt-luc pSG5-hPXR	40 ng/well 40 ng/well	HepG2	10 $\mu\text{M}$ SR12813
RAR $\alpha$	pGAL4-(UAS)5-TK-LUC pCMX-GAL4-hRAR $\alpha$	40 ng/well 40 ng/well	HEK-293	100 nM AM580
RXR $\alpha$	pGAL4-(UAS)5-TK-LUC pCMX-GAL4-hRXR $\alpha$	40 ng/well 40 ng/well	HEK-293	100 nM CD 2608
VDR-CYP2B6	pGL3-CYP2B6-wt-luc pSG5-hVDR	40 ng/well 40 ng/well	HepG2	100 nM Calcitriol

<sup>a</sup>Transfected cells were exposed to respective positive controls and test compounds for 24 h.

<sup>b</sup>For normalization purposes cells were always additionally transfected with 1 ng/well of *Renilla* luciferase expression plasmid pcDNA3-Rluc.

**Table S2:** List of selected genes linked to liver steatosis, nuclear receptor activation and hepatotoxicity

<b>Gene Name</b>	<b>Gene Symbol</b>	<b>TaqMan Assay ID</b>
acetyl-CoA carboxylase alpha	<i>ACACA</i>	Hs01046047_m1
acyl-CoA oxidase 1	<i>ACOX1</i>	Hs01074241_m1
adenosine kinase	<i>ADK</i>	Hs00417073_m1
aldehyde dehydrogenase 1 family member A1	<i>ALDH1A1</i>	Hs00946916_m1
aldehyde dehydrogenase 2 family (mitochondrial)	<i>ALDH2</i>	Hs01007998_m1
aquaporin 2	<i>AQP2</i>	Hs00292214_s1
ATPase phospholipid transporting 8B1	<i>ATP8B1</i>	Hs00900656_m1
C-C motif chemokine ligand 5	<i>CCL5</i>	Hs00982282_m1
CD36 molecule	<i>CD36</i>	Hs00169627_m1
CCAAT/enhancer binding protein delta	<i>CEBPD</i>	Hs00270931_s1
carboxylesterase 2	<i>CES2</i>	Hs01077945_m1
catechol-O-methyltransferase	<i>COMT</i>	Hs00241349_m1
cytochrome b-245 beta chain	<i>CYBB</i>	Hs00166163_m1
cytochrome P450 family 1 subfamily A member 2	<i>CYP1A2</i>	Hs00167927_m1
cytochrome P450 family 1 subfamily B member 1	<i>CYP1B1</i>	Hs02382916_s1
cytochrome P450 family 2 subfamily A member 6	<i>CYP2A6</i>	Hs00868409_s1
cytochrome P450 family 2 subfamily B member 6	<i>CYP2B6</i>	Hs04183483_g1
cytochrome P450 family 2 subfamily C member 19	<i>CYP2C19</i>	Hs00426380_m1
cytochrome P450 family 2 subfamily C member 9	<i>CYP2C9</i>	Hs02383631_s1
cytochrome P450 family 2 subfamily D member 6	<i>CYP2D6</i>	Hs02576167_m1
cytochrome P450 family 2 subfamily E member 1	<i>CYP2E1</i>	Hs00559367_m1
cytochrome P450 family 3 subfamily A member 4	<i>CYP3A4</i>	Hs00604506_m1
cytochrome P450 family 3 subfamily A member 5	<i>CYP3A5</i>	Hs00241417_m1
cytochrome P450 family 3 subfamily A member 7	<i>CYP3A7</i>	Hs00426361_m1
cytochrome P450 family 7 subfamily A member 1	<i>CYP7A1</i>	Hs00167982_m1
cytochrome P450 family 7 subfamily B member 1	<i>CYP7B1</i>	Hs00191385_m1
dynamin 1	<i>DNM1</i>	Hs00189369_m1
enolase 1	<i>ENO1</i>	Hs00361415_m1
Fas cell surface death receptor	<i>FAS</i>	Hs00163653_m1
fatty acid synthase	<i>FASN</i>	Hs01005622_m1
F-box protein 32	<i>FBXO32</i>	Hs01041408_m1
glucose-6-phosphatase catalytic subunit	<i>G6PC</i>	Hs02560787_s1
glucose-6-phosphate dehydrogenase	<i>G6PD</i>	Hs00166169_m1
glycerol-3-phosphate dehydrogenase 1	<i>GPD1</i>	Hs01100039_m1
3-hydroxyanthranilate 3,4-dioxygenase	<i>HAAO</i>	Hs00895712_m1
hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), beta subunit	<i>HADHB</i>	Hs01027271_m1
interleukin 6	<i>IL6</i>	Hs00985639_m1
insulin induced gene 1	<i>INSIG1</i>	Hs01650979_m1
Jun proto-oncogene, AP-1 transcription factor subunit	<i>JUN</i>	Hs01103582_s1
ketohexokinase	<i>KHK</i>	Hs00240827_m1
lamin A/C	<i>LMNA</i>	Hs00153462_m1
lipoprotein lipase	<i>LPL</i>	Hs00173425_m1
lymphocyte antigen 6 complex, locus D	<i>LY6D</i>	Hs00933261_g1
mitogen-activated protein kinase 8	<i>MAPK8</i>	Hs01548508_m1
MLX interacting protein like	<i>MLXIPL</i>	Hs00975714_m1
methylsterol monooxygenase 1	<i>MSMO1</i>	Hs00932159_m1
microsomal triglyceride transfer protein	<i>MTTP</i>	Hs00165177_m1
nitric oxide synthase 2	<i>NOS2</i>	Hs01075529_m1
NAD(P)H quinone dehydrogenase 1	<i>NQO1</i>	Hs02512143_s1
nuclear receptor subfamily 0 group B member 2	<i>NR0B2</i>	Hs00222677_m1
propionyl-CoA carboxylase alpha subunit	<i>PCCA</i>	Hs00165407_m1
pyruvate dehydrogenase kinase 4	<i>PDK4</i>	Hs01037712_m1
patatin like phospholipase domain containing 3	<i>PNPLA3</i>	Hs00228747_m1
cytochrome p450 oxidoreductase	<i>POR</i>	Hs01016332_m1

Gene Name	Gene Symbol	TaqMan Assay ID
peroxisome proliferator activated receptor alpha	<i>PPARA</i>	Hs00947536_m1
PPARG coactivator 1 alpha	<i>PPARGC1A</i>	Hs01016719_m1
resistin	<i>RETN</i>	Hs00220767_m1
regulator of cell cycle	<i>RGCC</i>	Hs00204129_m1
stearoyl-CoA desaturase	<i>SCD</i>	Hs01682761_m1
solute carrier organic anion transporter family member 4A1	<i>SLCO4A1</i>	Hs00983988_m1
sterol regulatory element binding transcription factor 1	<i>SREBF1</i>	Hs01088691_m1
starch binding domain 1	<i>STBD1</i>	Hs00187621_m1
sulfotransferase family 1B member 1	<i>SULT1B1</i>	Hs00234898_m1
sulfotransferase family 1C member 2	<i>SULT1C2</i>	Hs00602560_m1
synaptotagmin 1	<i>SYT1</i>	Hs00194572_m1
trefoil factor 3	<i>TFF3</i>	Hs00902278_m1
tubulin beta 2B class IIb	<i>TUBB2B</i>	Hs00603550_g1
UDP glucuronosyltransferase family 2 member B7	<i>UGT2B7</i>	Hs00426592_m1
valosin containing protein	<i>VCP</i>	Hs00997642_m1

**Table S3:** Quantotypic peptides used to compare protein level changes in cyproconazole-exposed HepaRG cells relative to untreated controls

Uniprot	Protein_ID	Gene_ID	Peptide	Charge
Q13085	ACACA	ACACA	DVDDGLQAAEEVGYPVMIK	2
Q13085	ACACA	ACACA	IGSFGPQEDLLFLR	2
Q15067	ACOX1	ACOX1	EVAWNLTSVDLVR	2
P55263	ADK	ADK	ELFDELVK	2
P55263	ADK	ADK	IFTLNLSAPFISQFYK	2
P00352	AL1A1	ALDH1A1	ANNTFYGLSAGVFTK	2
P00352	AL1A1	ALDH1A1	ILDLIESGK	2
P00352	AL1A1	ALDH1A1	QAFQIGSPWR	2
P05091	ALDH2	ALDH2	AAFQLGSPWR	2
P05091	ALDH2	ALDH2	ILGYINTGK	2
P05091	ALDH2	ALDH2	TIEEVVGR	2
O00748	EST2	CES2	FTEEEEQLSR	2
O00748	EST2	CES2	IQELEEPEER	2
P11509	CP2A6	CYP2A6	GTGGANIDPTFFLSR	2
P11509	CP2A6	CYP2A6	GYGVVFSNGER	2
P05181	CP2E1	CYP2E1	EALLDYKDEFSGR	3
P08684	CP3A4	CYP3A4	LGIPGPTPLPFLGNILSYHK	3
P08684	CP3A4	CYP3A4	LSLGGLLQPEKPVVLK	3
O75881	CP7B1	CYP7B1	SLDILLESMMQNLK	2
Q05193	DYN1	DNM1	LQSQLLSIEK	2
P06733	ENOA	ENO1	GNPTVEVDLFTSK	2
P25445	TNR6	FAS	DITSDSENSNFR	2
P25445	TNR6	FAS	IDEIKNDNVQDTAEQK	3
P49327	FAS	FASN	DNLEFFLAGIGR	2
P49327	FAS	FASN	VLEALLPLK	2
P11413	G6PD	G6PD	DGLLPENTFIVGYAR	2
P11413	G6PD	G6PD	LFYLALPPTVYEAVTK	3
P21695	GPDA	GPD1	ELYSILQHK	2
P21695	GPDA	GPD1	IVGGNAAQLAQFDPR	2
P46952	3HAO	HAAO	DLGTQLAPIIQEFFSSEQYR	3
P46952	3HAO	HAAO	TGKPIPDQLLK	2
P46952	3HAO	HAAO	TGKPIPDQLLK	3
P55084	ECHB	HADHB	AALTGLLHR	2
P55084	ECHB	HADHB	DQLLLGPTYATPK	2
P50053	KHK	KHK	HLGFQSAEEALR	2
P50053	KHK	KHK	SLPDVSATDFEK	2
P50053	KHK	KHK	VDLTQFK	2

Uniprot	Protein_ID	Gene_ID	Peptide	Charge
P02545	LMNA	LMNA	DLEALLNSK	2
P02545	LMNA	LMNA	EDLQELNDR	2
P02545	LMNA	LMNA	LAVYIDR	2
P06858	LIPL	LPL	ITGLDPAGPNFEYAEAPSR	2
P06858	LIPL	LPL	LSPDDADFVDVLHTFTR	3
P45983	MK08	MAPK8	NIIGLLNVFTPQK	2
Q15800	MSMO1	MSMO1	DKPETWENQWK	2
Q15800	MSMO1	MSMO1	IFGTDSQYNAYNEK	2
P55157	MTP	MTTP	KLILGGLEK	2
P15559	NQO1	NQO1	EGHLSPDIVAEQK	2
P05165	PCCA	PCCA	GVTHNIALLR	2
P05165	PCCA	PCCA	SFGLPSIGR	2
P05165	PCCA	PCCA	VTEDTSSVLR	2
P16435	NCPR	POR	FAVFGLGNK	2
O00767	ACOD	SCD	GSTLDLSDLEAEK	2
O00767	ACOD	SCD	PAHLLQDDISSSYTTTTTITAPPSR	3
O95210	STBD1	STBD1	HSSWGDVGVGGSLK	2
O95210	STBD1	STBD1	NESLESPMGEWGFQK	2
O95210	STBD1	STBD1	WNTYIPLHYNK	2
O43704	ST1B1	SULT1B1	THLPTDLLPK	2
O00338	ST1C2	SULT1C2	IVQETSFEK	2
O00338	ST1C2	SULT1C2	SILDQSISFMR	2
P16662	UD2B7	UGT2B7	ADVWLIR	2
P55072	TERA	VCP	DVDLEFLAK	2
P55072	TERA	VCP	GDDLSTAILK	2

**Table S4:** Gene expression analysis of genes linked to liver steatosis, nuclear receptor activation and hepatotoxicity<sup>a</sup>

Gene	25 µM cyproconazole				50 µM cyproconazole				100 µM cyproconazole				200 µM cyproconazole			
	Fold Regulation	RQ	SD	SEM	Fold Regulation	RQ	SD	SEM	Fold Regulation	RQ	SD	SEM	Fold Regulation	RQ	SD	SEM
ACACA	-1.06	0.94	0.29	0.12	-1.04	0.96	0.44	0.18	-1.18	0.85	0.25	0.10	-1.06	0.94	0.28	0.12
ADK	1.17	1.17	0.91	0.41	1.12	1.12	0.65	0.27	-1.09	0.92	0.54	0.22	-1.33	0.75	0.41	0.17
ATP8B1	-1.12	0.89	0.35	0.14	-1.11	0.90	0.38	0.16	-1.14	0.88	0.40	0.16	-1.15	0.87	0.38	0.16
CYP1A2	1.90	1.90	0.48	0.15	<b>2.51</b>	<b>2.51</b>	1.07	0.34	<b>3.34</b>	<b>3.34</b>	0.99	0.31	1.88	1.88	1.17	0.37
CYP1B1	1.58	1.58	0.53	0.22	1.87	1.87	1.07	0.44	1.84	1.84	0.27	0.11	1.69	1.69	0.86	0.35
CYP2B6	3.17	3.17	1.22	0.50	<b>3.23</b>	<b>3.23</b>	1.49	0.61	2.61	2.61	1.15	0.47	1.89	1.89	0.85	0.35
CYP2E1	-1.62	0.62	0.22	0.09	-2.92	0.34	0.08	0.03	<b>-6.33</b>	<b>0.16</b>	0.04	0.02	<b>-21.11</b>	<b>0.05</b>	0.01	0.00
CYP3A4	<b>4.90</b>	<b>4.90</b>	4.29	1.36	<b>5.47</b>	<b>5.47</b>	3.78	1.20	<b>4.71</b>	<b>4.71</b>	3.22	1.07	2.61	2.61	1.36	0.43
CYP3A5	1.22	1.22	0.78	0.32	1.16	1.16	0.84	0.34	1.06	1.06	0.69	0.28	-1.02	0.98	0.68	0.28
CYP3A7	3.81	3.81	3.40	1.08	3.76	3.76	3.26	1.03	<b>2.74</b>	<b>2.74</b>	1.62	0.51	2.24	2.24	1.45	0.46
CYP7A1	-1.09	0.92	0.69	0.22	-1.55	0.65	0.51	0.16	-2.05	0.49	0.29	0.09	<b>-15.57</b>	<b>0.06</b>	0.02	0.01
FASN	1.58	1.58	0.42	0.13	1.85	1.85	1.45	0.46	1.39	1.39	0.36	0.11	1.00	1.00	0.30	0.09
G6PC	-1.20	0.84	0.79	0.32	-1.32	0.76	0.70	0.29	-1.99	0.50	0.33	0.13	<b>-5.53</b>	<b>0.18</b>	0.09	0.04
INSIG1	2.02	2.02	1.19	0.49	2.27	2.27	1.13	0.46	2.47	2.47	1.60	0.65	1.19	1.19	0.60	0.24
LPL	1.05	1.05	0.48	0.20	-1.04	0.96	0.40	0.16	-1.15	0.87	0.39	0.16	1.01	1.01	0.50	0.20
LY6D	-1.21	0.83	0.30	0.12	-1.17	0.86	0.37	0.15	-1.29	0.78	0.27	0.11	-1.88	0.53	0.22	0.09
MAPK8	1.37	1.37	0.73	0.23	1.26	1.26	0.74	0.23	1.50	1.50	0.34	0.11	1.47	1.47	0.51	0.16
NQO1	1.22	1.22	0.98	0.40	1.10	1.10	0.55	0.23	1.00	1.00	0.53	0.22	-1.02	0.98	0.50	0.20
POR	1.02	1.02	0.58	0.24	1.12	1.12	0.57	0.23	1.17	1.17	0.67	0.27	1.11	1.11	0.65	0.26
PPARGC1A	1.03	1.03	0.45	0.18	1.06	1.06	0.53	0.22	-1.03	0.97	0.28	0.11	1.58	1.58	0.59	0.24
RGCC	-1.13	0.88	0.10	0.04	-1.36	0.73	0.07	0.03	-2.13	0.47	0.12	0.05	<b>-4.34</b>	<b>0.23</b>	0.01	0.01
SCD	1.05	1.05	0.42	0.17	1.37	1.37	0.73	0.30	1.23	1.23	0.62	0.25	-1.15	0.87	0.25	0.10
STBD1	-1.19	0.84	0.40	0.16	-1.02	0.98	0.45	0.18	-1.07	0.93	0.35	0.14	-1.30	0.77	0.28	0.11
SULT1B1	-1.19	0.84	0.15	0.06	-1.22	0.82	0.21	0.09	-1.67	0.60	0.09	0.04	<b>-3.67</b>	<b>0.27</b>	0.05	0.02
SULT1C2	1.32	1.32	0.62	0.25	1.30	1.30	0.36	0.15	1.24	1.24	0.16	0.07	<b>1.61</b>	<b>1.61</b>	0.40	0.16
TFF3	1.13	1.13	1.07	0.44	-1.11	0.90	0.87	0.36	-1.44	0.70	0.57	0.23	-2.23	0.45	0.40	0.16
UGT2B7	1.19	1.19	1.40	0.57	1.25	1.25	1.05	0.43	-1.34	0.75	0.71	0.29	-3.21	0.31	0.34	0.14

<sup>a</sup>HepaRG cells were treated with 25 µM, 50 µM, 100 µM and 200 µM cyproconazole or solvent control (0.5 % DMSO) for 24 h. Based on the screening by a PCR array containing 69 steatosis-related target genes with top dose cyproconazole samples, 27 genes deregulated with a |fold change| ≥ 2 (compared to solvent control) were selected for further single-gene PCR analysis with cDNA samples of cells treated with different

concentrations of cyproconazole. RQ: relative quantification, SD: standard deviation, SEM: standard error of the mean. Statistical significant fold regulations/relative quantifications are marked in bold ( $p < 0.05$ ).

**Table S5:** Protein abundance changes in cyproconazole-exposed HepaRG cells<sup>a</sup>

Uniprot ID	Gene ID	Protein name	25 µM cyproconazole			50 µM cyproconazole			100 µM cyproconazole			200 µM cyproconazole		
			log2 FC	SEM	p-value	log2 FC	SEM	p-value	log2 FC	SEM	p-value	log2 FC	SEM	p-value
Q13085	ACACA	Acetyl-CoA carboxylase 1	0.11	0.15	0.56	-0.08	0.11	0.53	0.11	0.13	0.48	-0.31	0.09	0.08
Q15067	ACOX1	Peroxisomal acyl-coenzyme A oxidase 1	<b>-0.57</b>	0.05	0.00	<b>-1.07</b>	0.23	0.04	<b>-1.63</b>	0.10	0.00	<b>-2.42</b>	0.14	0.00
P55263	ADK	Adenosine kinase	0.09	0.06	0.21	-0.34	0.23	0.32	-0.37	0.28	0.37	-1.03	0.46	0.15
P00352	ALDH1A1	Retinal dehydrogenase 1	-0.23	0.08	0.12	<b>-0.18</b>	0.02	0.01	-0.10	0.15	0.62	<b>-0.54</b>	0.07	0.02
P05091	ALDH2	Aldehyde dehydrogenase, mitochondrial	0.20	0.16	0.36	<b>0.32</b>	0.11	0.04	0.41	0.21	0.21	0.18	0.16	0.38
O00748	CES2	Cocaine esterase	<b>0.49</b>	0.07	0.01	<b>0.55</b>	0.09	0.02	<b>1.01</b>	0.08	0.00	<b>0.58</b>	0.04	0.00
P11509	CYP2A6	Cytochrome P450 2A6	<b>0.60</b>	0.14	0.02	0.43	0.14	0.06	-0.01	0.21	0.96	<b>-1.40</b>	0.11	0.01
P05181	CYP2E1	Cytochrome P450 2E1	-0.16	0.26	0.47	-0.38	0.41	0.47	-0.76	0.47	0.26	-0.80	0.34	0.14
P08684	CYP3A4	Cytochrome P450 3A4	<b>1.90</b>	0.36	0.02	<b>2.04</b>	0.39	0.02	<b>2.21</b>	0.40	0.02	-0.73	0.30	0.14
O75881	CYP7B1	Cytochrome P450 7B1	0.64	0.42	0.17	-0.43	0.53	0.49	0.11	0.59	0.88	-0.92	0.44	0.17
Q05193	DNM1	Dynamin-1	0.08	0.19	0.66	0.10	0.19	0.56	0.24	0.22	0.35	0.15	0.21	0.55
P06733	ENO1	Alpha-enolase	-0.03	0.35	0.93	0.10	0.34	0.75	-0.08	0.39	0.85	0.04	0.45	0.93
P25445	FAS	Tumor necrosis factor receptor superfamily member 6	0.41	0.24	0.16	0.08	0.24	0.75	0.23	0.21	0.27	0.34	0.34	0.43
P49327	FASN	Fatty acid synthase	-0.10	0.16	0.66	-0.23	0.19	0.42	<b>-0.78</b>	0.15	0.03	<b>-1.86</b>	0.22	0.01
P11413	G6PD	Glucose-6-phosphate 1-dehydrogenase	-0.06	0.20	0.83	-0.15	0.21	0.61	0.09	0.11	0.55	-0.19	0.12	0.25
P21695	GPD1	Glycerol-3-phosphate dehydrogenase [NAD+], cytoplasmic	-0.15	0.13	0.41	-0.22	0.14	0.28	-0.33	0.14	0.14	<b>-0.57</b>	0.09	0.03
P46952	HAAO	3-hydroxyanthranilate 3,4-dioxygenase	-0.06	0.15	0.74	-0.96	0.60	0.30	-0.50	0.21	0.15	<b>-1.81</b>	0.13	0.01
P55084	HADHB	Trifunctional enzyme subunit beta, mitochondrial	0.01	0.09	0.96	0.03	0.17	0.91	0.23	0.11	0.20	0.39	0.19	0.17
P50053	KHK	Ketohexokinase	-0.06	0.07	0.55	<b>-0.29</b>	0.04	0.01	-0.19	0.14	0.36	<b>-0.71</b>	0.11	0.02
P02545	LMNA	Prelamin-A/C	0.04	0.09	0.72	0.02	0.11	0.91	-0.04	0.08	0.72	0.05	0.11	0.73
P06858	LPL	Lipoprotein lipase	0.11	0.14	0.42	-0.07	0.18	0.74	0.30	0.24	0.36	0.48	0.31	0.26
P45983	MAPK8	Mitogen-activated protein kinase 8	0.10	0.06	0.23	-0.38	0.21	0.25	-0.36	0.21	0.28	<b>-1.32</b>	0.13	0.01
Q15800	MSMO1	Methylsterol monooxygenase 1	0.17	0.27	0.58	0.29	0.22	0.21	0.16	0.20	0.37	-0.23	0.30	0.52
P55157	MTPP	Microsomal triglyceride transfer protein large subunit	0.07	0.24	0.84	-3.55	3.87	0.53	0.15	0.17	0.55	<b>-0.40</b>	0.07	0.03
P15559	NQO1	NADPH dehydrogenase [quinone] 1	-0.07	0.46	0.91	0.22	0.20	0.37	0.41	0.26	0.26	0.58	0.35	0.24
P05165	PCCA	Propionyl-CoA carboxylase alpha chain, mitochondrial	0.05	0.12	0.76	0.15	0.14	0.47	0.29	0.12	0.15	0.19	0.07	0.10
P16435	POR	NADPH-cytochrome P450 reductase	0.29	0.16	0.25	0.25	0.10	0.13	0.14	0.12	0.41	-0.32	0.39	0.50
O00767	SCD	Acyl-CoA desaturase	0.04	0.43	0.93	0.25	0.42	0.57	0.30	0.39	0.44	-1.60	0.78	0.18
O95210	STBD1	Starch-binding domain-containing protein 1	-0.25	0.38	0.48	-1.05	0.72	0.31	-0.80	0.57	0.30	-0.39	0.42	0.45
O43704	SULT1B1	Sulfotransferase family cytosolic 1B member 1	-1.65	0.85	0.13	-1.28	1.86	0.61	-0.45	0.78	0.55	-1.98	1.11	0.21
O00338	SULT1C2	Sulfotransferase 1C2	0.75	0.25	0.08	0.22	0.28	0.57	0.05	0.13	0.67	-0.34	0.17	0.17
P16662	UGT2B7	UDP-glucuronosyltransferase 2B7	-0.20	0.17	0.34	-0.40	0.20	0.17	-0.94	0.26	0.05	<b>-2.16</b>	0.27	0.02
P55072	VCP	Transitional endoplasmic reticulum ATPase	0.15	0.21	0.49	0.24	0.20	0.24	0.03	0.38	0.95	0.36	0.29	0.35



<sup>a</sup>HepaRG cells were exposed for 72 h to increasing concentrations of cyproconazole or solvent control (0.5 % DMSO). Proteins which corresponded to the gene transcripts analyzed by TaqMan real-time PCR array analysis were uniquely identified by Parallel Reaction Monitoring (PRM) LC-MS/MS. Protein abundance changes are expressed as log<sub>2</sub> fold change (log<sub>2</sub> FC) relative to solvent control. Statistical significance was determined by unpaired t-test compared to solvent treated cells and marked in bold ( $p < 0.05$ ). SEM: standard error of the mean.