

Supplementary table S1: gene expression as measured by RT-PCR

Supplementary table 1: Changes in gene expression after treatment for 24h and 6 days with propiconazole (Pi) and tebuconazole (Te) in HepaRG cells. Fold changes, standard deviations and substance concentrations are given. Abbreviation: n.s., not significant.

gene	24 hours			6 days		
	Pi	Te	Pi + Te	Pi	Te	Pi + Te
<i>hABCB11</i>	0.47 ± 0.49 (40µM)	n.s.	0.08 ± 0.01 (40µM)	0.69 ± 0.08 (20µM)	n.s.	0.82 ± 0.08 (20µM)
<i>hABCC3</i>	0.82 ± 0.02 (40µM)	0.63 ± 0.28 (40µM)	0.84 ± 0.10 (40µM)	n.s.	n.s.	n.s.
<i>hABCG5</i>	0.18 ± 0.11 (40µM)	0.33 ± 0.23 (40µM)	0.10 ± 0.04 (40µM)	0.51 ± 0.26 (20µM)	n.s.	0.46 ± 0.05 (20µM)
<i>hCYP7A1</i>	0.09 ± 0.12 (40µM)	0.31 ± 0.01 (40µM)	0.23 ± 0.32 (20µM)	0.38 ± 0.02 (20µM)	0.88 ± 0.60 (20µM)	0.59 ± 0.16 (20µM)
<i>hCYP8B1</i>	0.11 ± 0.13 (40µM)	0.37 ± 0.21 (40µM)	0.28 ± 0.36 (20µM)	0.46 ± 0.12 (20µM)	n.s.	n.s.
<i>hACAT2</i>	1.96 ± 0.21 (20µM)	2.23 ± 0.26 (20µM)	2.15 ± 0.32 (10µM)	2.05 ± 0.34 (20µM)	2.16 ± 0.77 (10µM)	2.04 ± 0.53 (10µM)
<i>hHMGCR</i>	1.68 ± 0.07 (20µM)	2.05 ± 0.25 (20µM)	1.94 ± 0.42 (10µM)	3.06 ± 0.89 (20µM)	2.04 ± 0.51 (10µM)	1.94 ± 0.16 (5µM)
<i>hHMGCS1</i>	2.04 ± 0.26 (20µM)	2.56 ± 0.63 (20µM)	2.32 ± 0.34 (10µM)	3.30 ± 0.25 (10µM)	2.88 ± 0.69 (10µM)	2.43 ± 0.32 (5µM)
<i>hLSS</i>	1.97 ± 0.09 (20µM)	2.33 ± 0.46 (20µM)	2.10 ± 0.40 (10µM)	3.15 ± 0.98 (20µM)	5.26 ± 1.26 (10µM)	5.88 ± 0.22 (20µM)
<i>hOSTα</i>	0.36 ± 0.44 (40µM)	0.56 ± 0.13 (40µM)	n.s.	0.28 ± 0.12 (20µM)	n.s.	0.42 ± 0.09 (20µM)
<i>hOSTβ</i>	n.s.	n.s.	n.s.	2.50 ± 0.92 (20µM)	n.s.	n.s.
<i>hSC4mol</i>	1.60 ± 0.17 (20µM)	1.81 ± 0.11 (20µM)	1.65 ± 0.23 (10µM)	3.03 ± 0.92 (20µM)	1.51 ± 0.29 (10µM)	1.55 ± 0.21 (20µM)
<i>hSLC10A1</i>	0.08 ± 0.10 (40µM)	0.34 ± 0.28 (40µM)	0.34 ± 0.47 (20µM)	0.37 ± 0.11 (20µM)	n.s.	n.s.
<i>hSLCO1B1</i>	0.63 ± 0.24 (40µM)	n.s.	n.s.	n.s.	n.s.	n.s.

Supplementary table S2: Proteindata

Supplementary table 2: Changes in protein amount after treatment for 24h with propiconazole (Pi) and tebuconazole (Te) in HepaRG cells. Fold changes and standard deviations are given.

	protein amount		
	Pi [40 µM]	Te [40 µM]	Pi + Te [40 µM]
ABCC3	0.48 ± 0.02	0.42 ± 0.01	0.47 ± 0.06
CYP8B1	0.35 ± 0.07	0.27 ± 0.01	0.29 ± 0.03
SLC10A1	0.50 ± 0.19	0.39 ± 0.17	0.51 ± 0.19

Supplementary table S3: DLR data based on Knebel et al. 2019

Supplementary table 3: Propiconazole and tebuconazole interact with different nuclear receptors in HepG2 cells. Here data on CAR and PXR are presented. Substance, concentrations, fold changes ≥ 2 or ≤ 0.75 and significance ($p < 0.05$, Mann-Whitney rank sum test, n.s.), and are given. Abbreviation: n.s., not significant.

Reporter	Substance	Concentration	Response	Significance
CAR	Pi	5 μ M	2,76	n.s.
	Pi	10 μ M	4,51	n.s.
	Pi	20 μ M	6,62	$p < 0.05$
	Pi	40 μ M	6,76	$p < 0.05$
	Te	5 μ M	0,97	n.s.
	Te	10 μ M	0,95	n.s.
	Te	20 μ M	0,73	n.s.
	Te	40 μ M	0,70	n.s.
PXR	Pi	5 μ M	2,79	n.s.
	Pi	10 μ M	5,31	$p < 0.05$
	Pi	20 μ M	8,77	$p < 0.05$
	Pi	40 μ M	9,33	$p < 0.05$
	Te	5 μ M	3,12	n.s.
	Te	10 μ M	5,40	$p < 0.05$
	Te	20 μ M	6,23	$p < 0.05$
	Te	40 μ M	7,00	$p < 0.05$

Supplementary table S4: Sequences of primers used for RT-PCR analysis

gene	forward primer (5'-3')	reverse primer (5'-3')
<i>hABCB11</i>	ACCGAGGTTGGAAGGTTGT	CAGCCAACGACCCTGTGAAT
<i>hABCC3</i>	CTGGTGGTTCACAAAGATGGC	GGCATTTCCTCCAGGTGCTG
<i>hABCG5</i>	GGGTGCTTGTTGGATCTGGA	CATTGAGCTGCCACAAGTGA
<i>hCYP7A1</i>	CTTCTGCGAAGGCATTTGGG	GTCTGTCCCGCCTTGTAAGA
<i>hCYP8B1</i>	GGGAGGTTCTTTGCACTCAG	TAGTGGTGTGTCAGGGTC
<i>hACAT2</i>	TATGAGCAAGGCTCCTCACTTG	TCAAATGGCCAGCTTTCTGTG
<i>hHMGCR</i>	GACGTGAACCTATGCTGGTCAG	GGTATCTGTTTCAGCCACTAAGG
<i>hHMGCS1</i>	AAGTCACACAAGATGCTACACCG	TCAGCGAAGACATCTGGTGCCA
<i>hLSS</i>	CGTGGTATATGCGCTCCTCA	AGATCTGTGAGCCGTTGGTG
<i>hOSTα</i>	TGGAACCTGCCCTCACTAGC	GGCAAAGGGTGTTCTTGTA
<i>hOSTβ</i>	TGCTGGAAGAGATGCTTTGGT	CTGCTTGCCTGGATGCTTCT
<i>hSC4mol</i>	GCAAGATGCTTTGGTTGTGC	AATGGTCACCCATGCCAAA
<i>hSLC10A1</i>	TGCGCTATGTCATCAAGGGAG	GCCACATTGAGGATGGTGGA
<i>hSLCO1B1</i>	ACTGATTCTCGATGGGTTGG	TATTTGGAGTTTGGGGCA

Supplementary table S5: Used plasmids and positive controls for reporter gene assays.

	plasmid	positive control
<i>promoter assay</i>		
<i>CYP7A1</i>	pGL14- CYP7A1	5 μ M PMA (Sigma-Aldrich)
<i>transactivation assays</i>		
CAR	pGAL4/DBD-CAR/LBD(+3aa) pGAL4-(UAS)5-TK-Luc	10 μ M CITCO (Enzo life sciences)
FXR	pGAL4-FXR-LBD pGAL4-(UAS)5-TK-Luc	10 μ M GW4064 (Sigma-Aldrich)
PXR	pGAL4-PXR-LBD pGAL4-(UAS)5-TK-Luc	10 μ M SR12813 (Sigma-Aldrich) 10 μ M Rifampicin (Sigma-Aldrich)