Supplementary Figures

Supplementary Figure 1. Protein binding of MPOL_B_1 in human and mouse plasma. Scatter plot of the fraction unbound of MPOL_B_1 (2 µM) and Warfarin (2 µM) in both human and mouse (CD1) plasma. The y-axis represents the fraction unbound. Each data point is from an individual measurement. Warfarin serves as a reference compound with known protein binding properties.

Supplementary Figure 2. LogD measurements of MPOL_B_1 and reference compounds. Scatter plot showing the LogD (distribution coefficient) of MPOL_B_1 compared to several reference compounds: Warfarin, Chlorpromazine, Atenolol, and Pemetrexed. The y-axis is the LogD value, which is a measure of the compound's lipophilicity (see Materials and Methods). The x-axis lists the compounds tested. Each data point indicates an individual measurement.

Supplementary Figure 3. *In vitro* stability of MPOL_B_1 in human and mouse plasma and liver microsomes. Panel of scatter plots showing the *in vitro* stability of the compound MPOL_B_1 and two reference compounds, propantheline and Verapamil. The stability was assessed in four different matrices: mouse (CD1) liver microsomes, mouse (CD1) plasma, human liver microsomes, and human plasma. The natural logarithm of the percent remaining of the compound over time (Ln(%Remaining)) is on the y-axis, while the x-axis represents the incubation time in h.

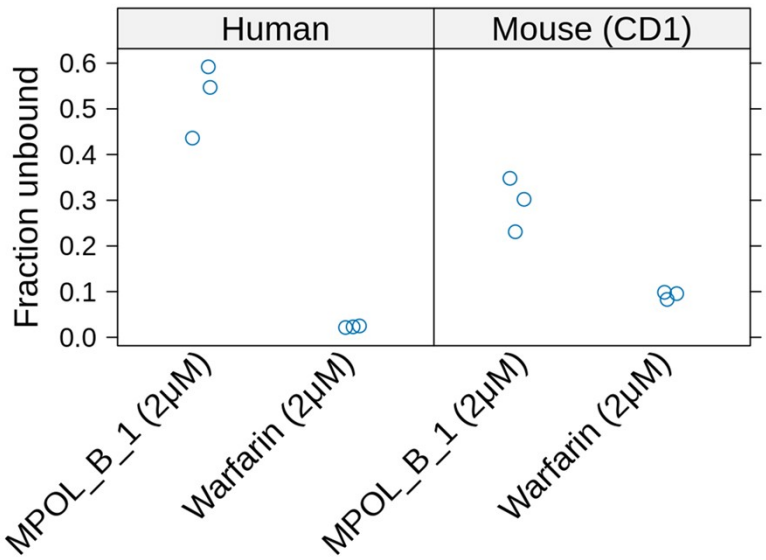
Supplementary Figure 4. Bidirectional permeability of MPOL_B_1 in Caco-2 Cells. Scatter plots displaying the apparent permeability (Papp) of MPOL_B_1 and several reference compounds. The y-axis represents the apparent permeability in units of 10^{-6} cm/s. The x-axis shows the different compounds and their concentrations. The data is divided into two panels: A2B (apical to basolateral) representing absorption, and B2A (basolateral to apical) representing efflux. The A2B panel includes MPOL_B_1 (10 µM), Warfarin (10 µM), Ranitidine

(10 µM), and Talinolol (10 µM), as well as a co-incubation of Talinolol (10 µM) with Verapamil (25 µM) to assess potential efflux transporter inhibition. The B2A panel includes the same set of compounds and concentrations.

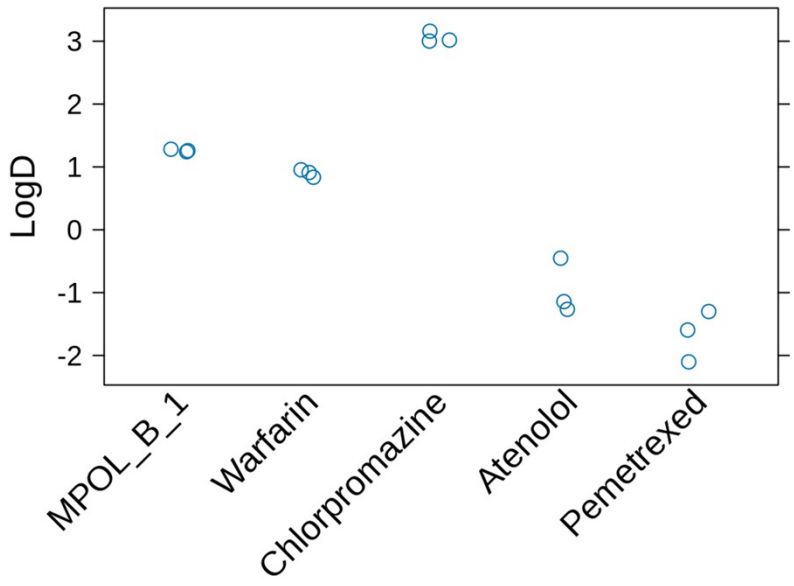
Supplementary Figure 5. In vitro cytochrome P450 (CYP) inhibition by MPOL_B_1 and reference inhibitors. The y-axis on the scatter plots lists the CYP substrates, with the corresponding enzyme in parentheses. The x-axis represents the percent inhibition (see Materials and Methods). The plot is divided into six sub-panels, each showing the inhibitory effect of a different compound at a specific concentration, as indicated. Each data point represents the inhibition of a particular CYP enzyme by the respective inhibitor.

Supplementary Figure 6. Cytotoxicity of MPOL_B_1 in HepG2 cells. Scatter plots displaying the *in vitro* cytotoxicity of MPOL_B_1 and the reference compound Terfenadine in human liver carcinoma (HepG2) cells. The percent cytotoxicity (see Materials and Methods) is on the y-axis, while the concentration of the compounds (in µM) is on the x-axis. Each data point represents the cytotoxicity measured at the indicated concentration.

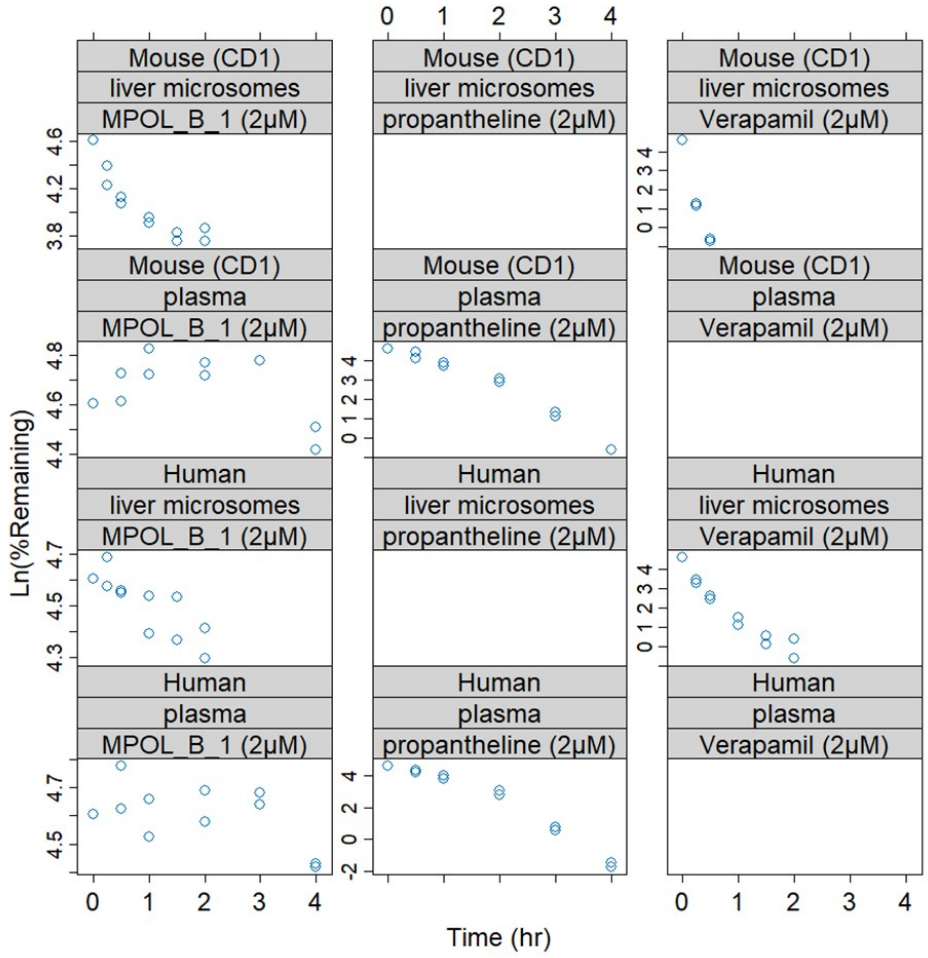
Supplementary Figure 1



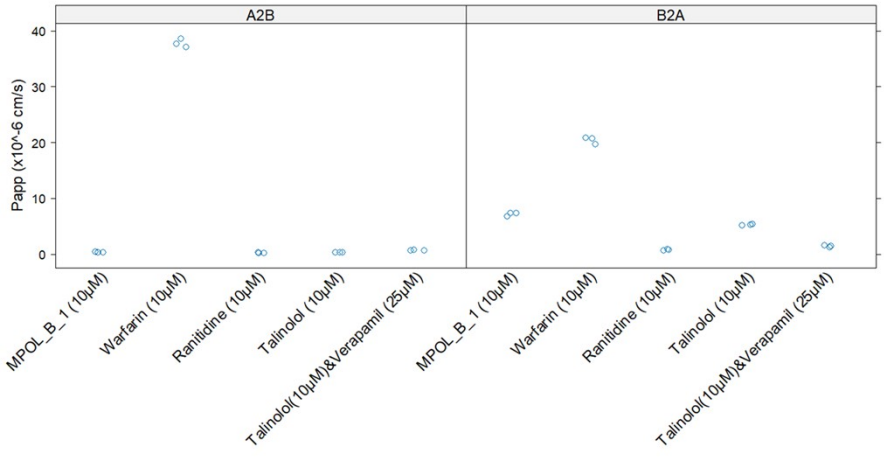
Supplementary Figure 2



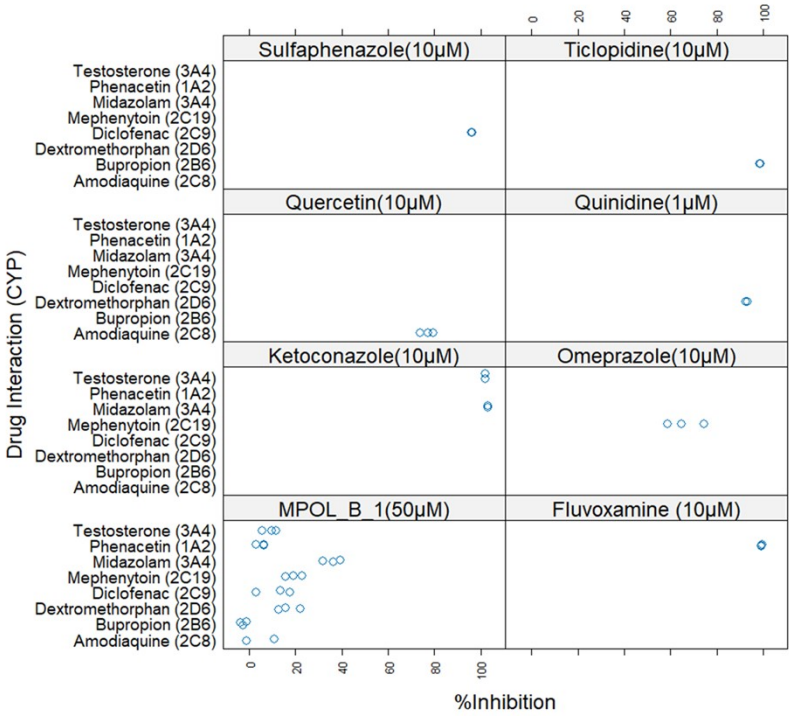
Supplementary Figure 3



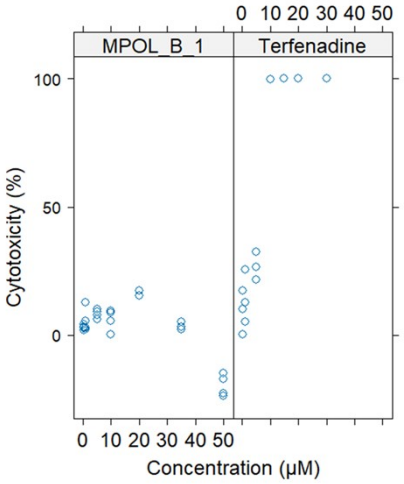
Supplementary Figure 4



Supplementary Figure 5



Supplementary Figure 6



Supplementary Table 1. Effects of MPOL_B_1 on hERG ion channel current

Compound	IC_{50} (μM)	Conc (μM)	Mean % hERG Inhibition	Standard Deviation	Standard Error	n	Individual Data Points (% Inhibition)
MPOL_B_1	86.997	0.1	2.6	7.9	4.6	3	11.6

							-0.8
							-3.2
		1	5.6	13.1	7.6	3	20.5
							-4.1
							0.4
		10	4.0	2.5	1.0	6	4.4
							3.4
							4.5
							0.4
							3.2
							8.3
		100	56.8	11.0	5.5	4	62.6
							40.4
							62.7
							61.6
Cisapride	NA	0.05	60.7	12.4	6.2	4	77.6
							52.0
							50.9
							62.2

Supplementary Table 2. Results of Ames test without metabolic activation

Strain	Treatment	Final Conc. (µg/plate)	Mean Revertants Per Plate	Standard Deviation	Fold Response	Revertant Counts Per Plate
TA100	DMSO	-	89.0	5.7	-	85 N NP, 93 N NP
	MPOL_B_1	1.58	93.5	14.8	1.1	83, 104
		5.0	92.5	6.4	1.0	97, 88
		15.8	88.0	9.9	1.0	81, 95
		50	94.0	12.7	1.1	103, 85
		158	93.0	1.4	1.0	94, 92
		500	103.5	2.1	1.2	105, 102
		1581	102.0	7.1	1.1	97, 107
		5000	90.0	2.8	1.0	88 N NP, 92 N NP
	NaAz	0.5	408.5 +	38.9	4.6	381, 436
TA1535	DMSO	-	25.0	15.6	-	14 N NP, 36 N NP
	MPOL_B_1	1.58	26.5[a]	4.9	1.1	23, 30
		5.0	12.0 L	4.2	0.5	15, 9
		15.8	14.5	0.7	0.6	14, 15
		50	12.5 L	0.7	0.5	12, 13
		158	25.0	8.5	1.0	31, 19
		500	18.5	4.9	0.7	15, 22
		1581	17.0	0.0	0.7	17, 17
		5000	19.0	0.0	0.8	19 N NP, 19 N NP
	NaAz	0.5	440.0 +	43.8	17.6	409, 471
TA1537	DMSO	-	11.0	2.8	-	9 N NP, 13 N NP
	MPOL_B_1	1.58	12.5	0.7	1.1	12, 13
		5.0	10.5	2.1	1.0	9, 12
		15.8	14.0	7.1	1.3	9, 19
		50	14.0	2.8	1.3	12, 16
		158	7.5	3.5	0.7	5, 10
		500	13.0	1.4	1.2	12, 14
		1581	10.5	3.5	1.0	8, 13
		5000	19.5	6.4	1.8	15 N NP, 24 N NP
	9AC	50	255.0 +	49.5	23.2	220, 290

Strain	Treatment	Final Conc. (µg/plate)	Mean Revertants Per Plate	Standard Deviation	Fold Response	Revertant Counts Per Plate
TA98	DMSO	-	29.5	3.5	-	27 N NP, 32 N NP
	MPOL_B_1	1.58	41.0[a]	1.4	1.4	40 CNOC, 42 CNOC
		5.0	32.5	4.9	1.1	36 CNOC, 29 CNOC
		15.8	27.0	0.0	0.9	27 CNOC, 27 CNOC
		50	25.5	2.1	0.9	24 CNOC, 27 CNOC
		158	25.5	3.5	0.9	28 CNOC, 23 CNOC
		500	36.5	0.7	1.2	36 CNOC, 37 CNOC
		1581	42.5[a]	17.7	1.4	30 CNOC, 55 CNOC
		5000	30.5	4.9	1.0	27 CNOC N NP, 34 CNOC N NP
	2NF	1	193.0 +	2.8	6.5	195, 191
WP2 uvrA	DMSO	-	23.5	2.1	-	22 N NP, 25 N NP
	MPOL_B_1	1.58	23.5	0.7	1.0	23, 24
		5.0	21.5	7.8	0.9	27, 16
		15.8	18.5	4.9	0.8	22, 15
		50	23.0	8.5	1.0	17, 29
		158	26.0	5.7	1.1	22, 30
		500	20.5	2.1	0.9	19, 22
		1581	31.0	4.2	1.3	28, 34
		5000	20.5	4.9	0.9	24 N NP, 17 N NP
	NQO	0.5	145.5 +	47.4	6.2	179, 112

Vehicles & Positive Controls

DMSO	Dimethyl sulfoxide
2NF	2-Nitrofluorene
9AC	9-Aminoacridine Hemihydrate
NQO	4-Nitroquinoline N-oxide
NaAz	Sodium azide

Observations

CNOC	Contamination did not obscure count
N	normal background lawn
NP	no precipitate
+	Substantially higher (≥ 2-fold for TA98, TA100, WP2uvra, and ≥ 3-fold for TA1535, TA1537) than the mean number of revertant colonies for its respective negative control
L	Low count considered due to normal variation rather than toxicity since not clearly dose-related and not outside normal limits based on historical negative control values
[a]	Revertant colony counts above the 95% tolerance limits of the negative historical control data

Supplementary Table 3. Results of Ames test with metabolic activation

Strain	Treatment	Final Conc. (µg/plate)	Mean Revertants Per Plate	Standard Deviation	Fold Response	Revertant Counts Per Plate
TA100	DMSO	-	119.0	5.7	-	115 N NP, 123 N NP
	MPOL_B_1	1.58	113.0	5.7	0.9	109, 117
		5.0	112.0	2.8	0.9	110, 114
		15.8	118.5	9.2	1.0	112, 125
		50	108.5	29.0	0.9	88, 129
		158	108.5	12.0	0.9	100, 117
		500	116.0	8.5	1.0	110, 122
		1581	107.0	2.8	0.9	105, 109
		5000	112.0	21.2	0.9	97 N NP, 127 N NP
	BaP	5	533.0 +	41.0	4.5	562, 504
TA1535	DMSO	-	14.0	1.4	-	13 N NP, 15 N NP
	MPOL_B_1	1.58	15.5	2.1	1.1	14, 17
		5.0	15.0	1.4	1.1	16, 14
		15.8	22.0[a]	2.8	1.6	24, 20
		50	16.5	10.6	1.2	9, 24
		158	8.5	2.1	0.6	10, 7
		500	22.0[a]	2.8	1.6	20, 24
		1581	15.5	2.1	1.1	14, 17
		5000	15.5	9.2	1.1	9 N NP, 22 N NP
	2AA	5	355.5 +	20.5	25.4	341, 370
TA1537	DMSO	-	12.5	6.4	-	8 N NP, 17 N NP
	MPOL_B_1	1.58	29.0[a]	8.5	2.3	35, 23
		5.0	20.0	1.4	1.6	19, 21
		15.8	17.0	4.2	1.4	14, 20
		50	16.5	4.9	1.3	13, 20
		158	15.0	1.4	1.2	16, 14
		500	24.0[a]	0.0	1.9	24, 24
		1581	21.5	0.7	1.7	21, 22
		5000	16.0	4.2	1.3	13 N NP, 19 N NP
	2AA	5	355.5 +	12.0	28.4	364, 347

Strain	Treatment	Final Conc. (µg/plate)	Mean Revertants Per Plate	Standard Deviation	Fold Response	Revertant Counts Per Plate
TA98	DMSO	-	40.5	6.4	-	36 N NP, 45 N NP
	MPOL_B_1	1.58	48.0[a]	0.0	1.2	48, 48
		5.0	33.5	3.5	0.8	36, 31
		15.8	40.0	1.4	1.0	39, 41
		50	43.0	11.3	1.1	35, 51
		158	39.5	3.5	1.0	42, 37
		500	42.5	16.3	1.0	31, 54
		1581	37.0	11.3	0.9	29, 45
		5000	45.5	3.5	1.1	43 N NP, 48 N NP
	BaP	5	175.0 +	17.0	4.3	163, 187
WP2 uvrA	DMSO	-	33.0	1.4	-	32 N NP, 34 N NP
	MPOL_B_1	1.58	27.5	6.4	0.8	23, 32
		5.0	41.0	5.7	1.2	37, 45
		15.8	31.0	4.2	0.9	28, 34
		50	42.5	2.1	1.3	41, 44
		158	26.0	2.8	0.8	24, 28
		500	38.0	5.7	1.2	34, 42
		1581	31.0	4.2	0.9	28, 34
		5000	34.5	9.2	1.0	28 N NP, 41 N NP
	2AA	20	181.0 +	11.3	5.5	189, 173

Vehicles & Positive Controls		Observations	
DMSO	Dimethyl sulfoxide	N	normal background lawn
2AA	2-Aminoanthracene (2-Anthramin	NP	no precipitate
BaP	Benzo(a)pyrene	+	Substantially higher (≥ 2-fold for TA98, TA100, WP2uvra, and ≥ 3-fold for TA1535, TA1537) than the mean number of revertant colonies for its respective negative control
		[a]	Revertant colony counts above the 95% tolerance limits of the negative historical control data

Supplementary Table 4. Lifespan results in worms

Treatment	Dose (μM)	Mean	Median	n
Mock (DMSO)	NA	21.8	23	86
MPOL_B_1	100	28.2	29	112
	50	26.5	27	120
	25	20.8	19	123
	12.5	19.5	19	116
	6.25	18.8	17	140
	3.125	19.2	17	111
	1.56	20.5	21	125
MPOL_D_1	100	18.6	17	95
	50	21.1	21	116
	25	22.3	21	117
	12.5	22.5	21	114
	6.25	21.2	21	126
	3.125	21.2	21	115
	1.56	20.7	21	137