

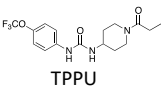
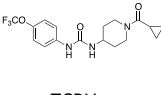
JPET # 265330

**Simultaneous Target-Mediated Drug Disposition (TMDD) Model for Two
Small-Molecule Compounds Competing for Their Pharmacological Target:
Soluble Epoxide Hydrolase**

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Supplemental Table 1. Physical properties and human, mouse, and rat kinetics parameters of TPPU and TCPU. (Liu et al., 2012; Lee et al., 2013; Lee et al., 2014; Lee et al., 2019)

Structure	Physical Properties				Human								Mouse		Rat	
	Mol. Weight	Sol ^c (ug/mL)	Melting Point (°C)	Log P	IC ₅₀ (nM) (sEH)	K _i (nM) (sEH)	IC ₅₀ (nM) sEH tDPP O	k _{off} / t _{1/2} (x10 ⁻⁴ s ⁻¹ / min) (sEH) ^d	HERG Inhibition at 50 μM (%)	Plasma Protein Binding at 1μM (%)	CYP 2J Remaining activity at 10 μM (%)	CYP2C Remaining activity at 10 μM (%)	K _i (nM) (sEH)	k _{off} / t _{1/2} (x10 ⁻⁴ s ⁻¹ / min) (sEH) ^d	IC ₅₀ (nM) (sEH)	k _{off} / t _{1/2} (x10 ⁻⁴ s ⁻¹ / min) (sEH) ^d
 TPPU	359.34	60	198.2-200.8 (199.5)	3.23	3.7	0.64±0.09 0.91±0.13	34	10.5±0.2/ 11.0±0.2	26±1	79±1	91.9±2.2	118±2.4	2.50±0.38	5.84±0.05/ 19.8±0.2	29.1±4.5	8.52±0.47/ 13.6±0.8
 TCPU	371.35	4.6	193.4-194.2 (193.8)	3.28	2	0.55±0.10	20.3	6.67±0.45/ 17.4±1.2		90.0±0.5			0.92±0.09	4.89±0.54/ 23.8±2.7	9.9±0.1	7.30±0.55/ 15.89±1.21

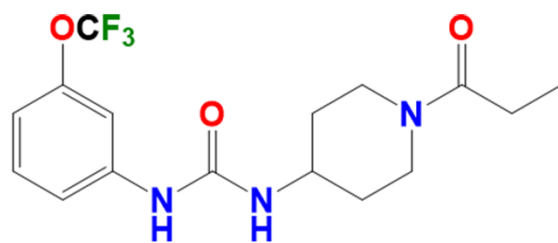
Supplemental Table2. Model building history

No.	Dataset	Description	Model fit process	OFV
1	Data only from experiment 1	5 compartmental model; Only TPPU shows TMDD; TPPU k_{off} was affected by TCPU plasma concentration;	Minimization successfully; Fit well with high RSE	3013.497
2	Data only from group experiment 1	6 compartmental model; TPPU and TCPU both show TMDD binding with R1 competitively;	Minimization successfully; Fit well with high RSE	2992.667
3	Data from group experiment 1 and 2 (experiment 2 group 3 was excluded)	6 compartmental model; TPPU and TCPU both show TMDD binding with R1 competitively;	Minimization successfully; Did not capture TCPU high dose	5811.443
4	Data from group experiment 1 and 2 (experiment 2 group 3 was excluded)	7 compartmental model; TPPU and TCPU both show TMDD binding with R1 competitively; TCPU and TPPU could also bind with each other's receptor complex; TCPU has another specific binding pool R2;	Terminated	
5	Data from group experiment 1 and 2 (experiment 2 group 3 was excluded)	6 compartmental model; TPPU and TCPU both show TMDD binding with R1 competitively; TCPU and TPPU could also bind with each other's receptor complex;	Terminated	
6	Data from group experiment 1 and 2 (experiment 2 group 3 was excluded)	7 compartmental model; TPPU and TCPU both show TMDD binding with R1 competitively; TCPU has peripheral compartment;	Minimization successfully; Did not capture TCPU high dose with high RSE	5770.227

7	Data from group experiment 1 and 2 (experiment 2 group 3 was excluded)	6 compartmental model; TPPU and TCPU both show TMDD binding with R1 competitively; TCPU also have M-M elimination;	Minimization successfully; Fit well with high RSE	5921.653
8	Data from group experiment 1 and 2	7 compartmental model; TPPU and TCPU both show TMDD binding with R1 competitively; TCPU has another specific binding pool R2;	Minimization successfully; Did not capture TCPU high dose with high RSE	6227.922
Final Model	Data from group experiment 1 and 2 (experiment 2 group 3 was excluded)	7 compartmental model; TPPU and TCPU both show TMDD binding with R1 competitively; TCPU has another specific binding pool R2;	Minimization successfully; Good	5744.069

OFV, objective function value; RSE, relative standard errors.

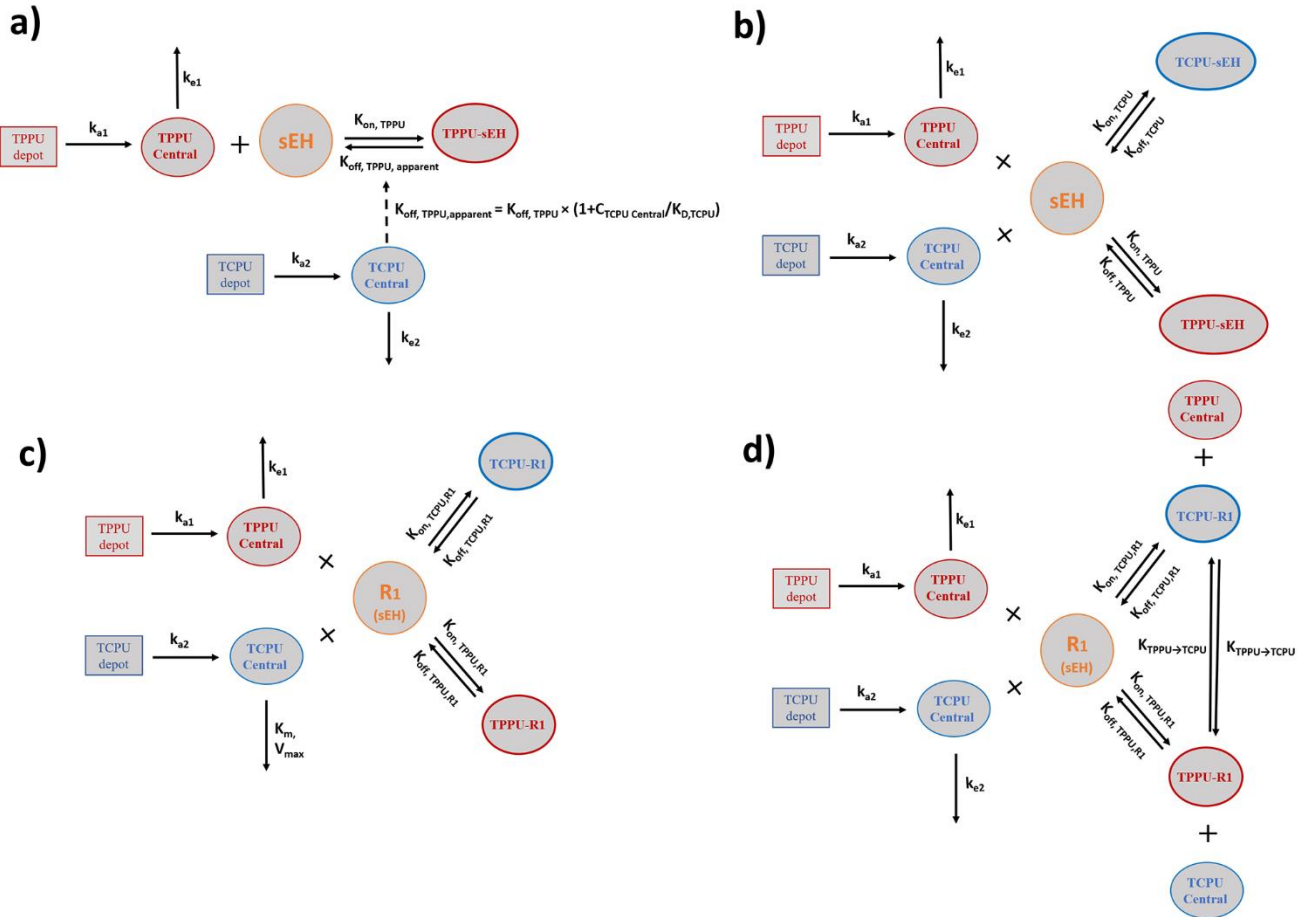
Supplemental Figure 1. Chemical structure of mTPPU.



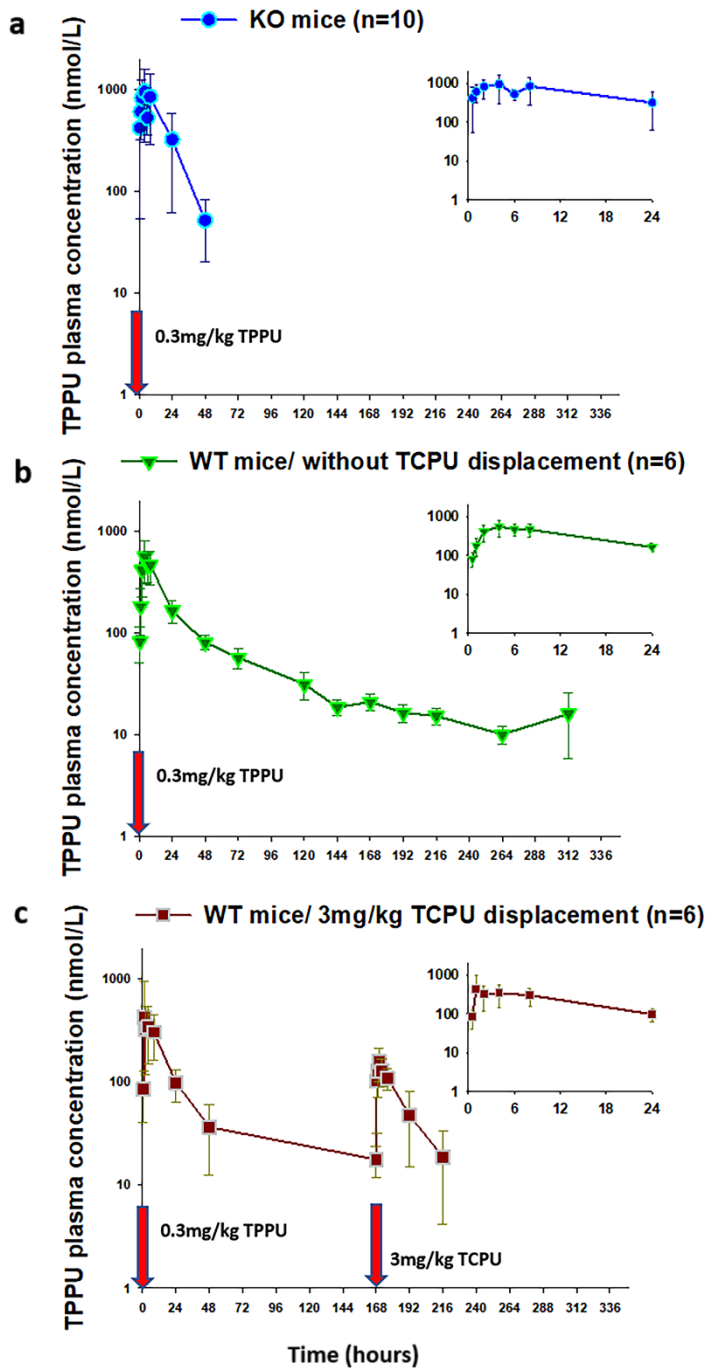
mTPPU

3-(3-trifluoromethoxy)-1-(propionlpiperidin-4-yl)-phenyl)urea

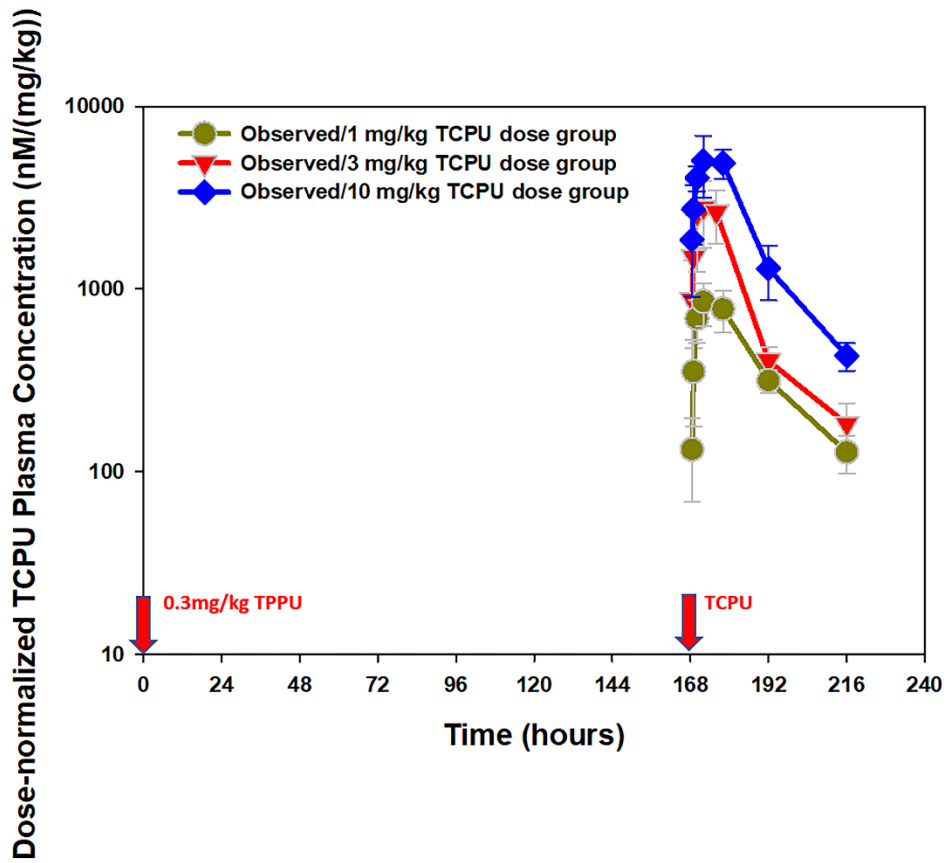
Supplemental Figure 2. Four model structures proposed during model development phase. Model with one TMDD component. b) Model with two TMDD components. c) Model with two TMDD components plus MM process. d) Model with two TMDD components mixing with competitive and non-competitive mechanism.



Supplemental Figure 3. Time courses of mean observed TPPU plasma concentrations following 0.3 mg/kg TPPU at time 0 in a) sEH deficient mice without TCPU displacement; b) wild-type mice without TCPU displacement; and c) wild-type mice with 3 mg/kg TCPU displacement at 168 hours.



Supplemental Figure 4. Time courses of mean observed TCPU plasma concentrations following 0.3 mg/kg TPPU at time 0 in wild-type mice with 1,3, 10mg/kg TCPU displacement at 168 hours.



Supplemental Figure 5. Visual Predictive Check (VPC) for a) TPPU in sEH knockout mic; b) TPPU in wild-type mice; and c) TCPU in wild-type mice. The open triangles represent the observed concentrations, the dashed lines represent the 5th, 50th, and 95th percentiles for the observed data, and the solid lines represent the 5th, 50th, and 95th of the prediction percentiles

