

Table S1. Observed and predicted values of AUC_{0-t} and C_{max} of enalapril and enalaprilat following oral enalapril maleate to healthy (HT) subjects and liver cirrhosis patients

Drug	Dose	Subjects	AUC _{0-t} ($\mu\text{g}\times\text{h}/\text{mL}$)			C _{max} (ng/mL)		
			Obs	Pre	Obs/Pre	Obs	Pre	Obs/Pre
Enalapril	10mg[1]	HT	0.1229	0.1470	0.84	66.9	45.6	1.47
	10mg[2]	HT	NR	0.1152	/	NR	45.6	/
	10mg[3]	HT	0.1600	0.1531	1.05	72.1	45.6	1.58
	10mg[3]	HT	0.1480	0.1552	0.95	65.4	45.6	1.43
	10mg[4]	HT	NR	0.1470	/	NR	45.6	/
	10mg[5]	CP-B	0.1761	0.2208	0.80	110.1	61.0	1.80
Enalaprilat	10mg[1]	CP-C	0.2769	0.3205	0.86	123.4	80.9	1.53
	10mg[1]	HT	0.3754	0.3705	1.01	46.1	40.2	1.15
	10mg[2]	HT	NR	0.3705	/	NR	40.2	/
	10mg[3]	HT	0.2170	0.3705	0.59	29.3	40.2	0.73
	10mg[3]	HT	0.2600	0.3705	0.70	37.3	40.2	0.93
	10mg[4]	HT	NR	0.2797	/	NR	40.2	/
	10mg[5]	CP-B	0.3812	0.5223	0.73	36.8	35.4	1.04
	10mg[1]	CP-C	0.1733	0.2476	0.70	16.8	20.1	0.84

NR: Not reported

Table S2. Observed and predicted values of AUC_{0-t} and C_{max} of benazepril and benazeprilat following benazepril hydrochloric to healthy(HT) subjects and cirrhosis

Drug	Dose	Subjects	AUC _{0-t} ($\mu\text{g}\times\text{h}/\text{mL}$)			C _{max} (ng/mL)		
			Obs	Pre	Obs/Pre	Obs	Pre	Obs/Pre
Benazepril	10mg[6]	HT	0.1390	0.2583	0.54	139.139	114.189	1.22
	10mg[7]	HT	0.1380	0.2678	0.52	78.957	114.189	0.69
	20mg[8]	HT	0.2195	0.4635	0.47	265.313	228.378	1.16
	20mg[9]	HT	NR	0.4635	/	252.98	228.378	1.11
	20mg[10]	CP-B	0.6159	0.5777	1.07	543.472	265.237	2.05
Benazeprilat	10mg[11]	HT	1.5330	1.6847	0.91	188.704	207.60	0.91
	10mg[6]	HT	1.0787	1.3741	0.79	200.410	207.60	0.97
	10mg[7]	HT	1.1039	1.3741	0.80	164.520	207.60	0.79
	20mg[8]	HT	2.3800	2.7482	0.87	463.830	415.20	1.12
	20mg[9]	HT	NR	2.7482	/	342.164	415.20	0.82
	20mg[10]	CP-B	2.1650	2.3238	0.93	345.010	338.93	1.02

Table S3. Observed and predicted values of AUC_{0-t} and C_{max} of cilazapril following oral cilazapril to healthy(HT) subjects and LC patients

Drug	Dose	Subjects	AUC _{0-t} ($\mu\text{g}\times\text{h}/\text{mL}$)			C _{max} (ng/mL)		
			Obs	Pre	Obs/Pre	Obs	Pre	Obs/Pre
Cilazapril	1mg[12]	HT	0.0998	0.1030	0.97	33.9	26.2	1.29
	2.5mg[12]	HT	0.2560	0.2574	0.99	82.7	65.6	1.26
	5mg[12]	HT	0.4960	0.5148	0.96	182.0	131.1	1.39
	2.5mg[13]	HT	0.1830	0.2423	0.76	75.7	65.6	1.15
	1mg[14]	HT	0.0657	0.0880	0.75	25.2	26.2	0.96
	1mg[14]	CP-B	0.1840	0.1201	1.53	40.0	28.5	1.40
Cilazaprilat	1mg[12]	HT	0.0791	0.07114	1.11	12.4	10.0	1.24
	1mg[15]	HT	NR	0.1143	/	8.3	10.0	0.83
	2.5mg[12]	HT	0.175	0.17784	0.98	37.7	24.9	1.51
	5mg[12]	HT	0.342	0.3557	0.96	94.2	49.9	1.89
	2.5mg[13]	HT	0.178	0.3324	0.54	39.3	24.9	1.58
	5mg[16]	HT	0.398	0.6648	0.60	83.4	49.9	1.67
	1.25mg[17]	HT	0.070	0.0889	0.79	13.0	12.5	1.04
	2.5mg[17]	HT	0.170	0.1778	0.96	36.0	24.9	1.45
	5mg[17]	HT	0.280	0.3557	0.79	74.0	49.9	1.48
	10mg[17]	HT	0.550	0.7114	0.77	165.0	99.7	1.65
	1mg[14]	HT	0.053	0.0711	0.75	7.96	10.0	0.80
	1mg[14]	CP-B	0.0775	0.0688	1.13	10.2	8.3	1.23

Table S4. Observed and predicted values of AUC_{0-t} and C_{max} of perindopril following oral perindopril tert-butylamine to healthy(HT) subjects and LC patients

Drug	Dose	Subjects	AUC _{0-t} (µg×h/mL)			C _{max} (ng/mL)		
			Obs	Pre	Obs/Pre	Obs	Pre	Obs/Pre
Perindopril	4mg[18]	HT	0.121	0.120	1.01	64.2	34.8	1.84
	8mg[19]	CP-A	0.377	0.240	1.57	NR	70.7	/
	8mg[20]	CP-B	0.602	0.275	2.19	NR	75.3	/
Perindoprilat	4mg[18]	HT	0.0520	0.0680	0.76	4.7	4.3	1.09
	8mg[21]	HT	0.1197	0.1361	0.88	NR	8.5	/
	8mg[19]	CP-A	0.3210	0.2676	1.20	29	8.7	3.33
	8mg[20]	CP-B	0.1340	0.2759	0.49	NR	8.5	/

Table S5. Observed and predicted values of AUC_{0-t} and C_{max} of temocapril and temocaprilat following oral temocapril hydrochloride to healthy (HT) subjects and LC patients

Drug	Dose	subjects	AUC _{0-t} (µg×h/mL)			C _{max} (ng/mL)		
			Obs	Pre	Obs/Ore	Obs	Pre	Obs/Ore
Temocapril	1mg[22]	HT	NR	0.0254	/	NR	10.9	/
	1mg[22]	CP-B	NR	0.0272	/	NR	11.6	/
Temocaprilat	1mg[22]	HT	0.1230	0.1199	1.03	15.8	11.3	1.40
	1mg[22]	CP-B	0.1714	0.0797	2.15	14.3	7.4	1.93

Table S6. Observed and predicted values of AUC_{0-t} and C_{max} of oseltamivir and oseltamivir carboxylate (OC) following oral oseltamivir phosphate to healthy (HT) subjects and cirrhosis

Drug	Dose	subjects	AUC _{0-t} (µg×h/mL)			C _{max} (ng/mL)		
			Obs	Pre	Obs/Pre	Obs	Pre	Obs/Pre
Oseltamivir	75mg[23]	HT	0.1590	0.1438	1.11	74.4	60.2	1.24
	75mg[24]	HT	0.1240	0.1438	0.86	75.1	60.2	1.25
	75mg[24]	HT	0.1140	0.1438	0.79	67.6	60.2	1.12
	75mg[25]	HT	0.1188	0.1450	0.82	61.0	60.2	1.01
	150mg[23]	HT	0.3130	0.2876	1.09	192.0	120.4	1.59
	75mg[26]	CP-B	0.2100	0.2006	1.05	100.0	86.0	1.16
OC	75mg[23]	HT	3.0200	2.5000	1.21	291.00	264.80	1.10
	75mg[24]	HT	2.6500	2.5000	1.06	276.00	264.80	1.04
	75mg[24]	HT	2.5600	2.5000	1.02	278.00	264.80	1.05
	75mg[25]	HT	3.1763	3.0867	1.03	360.31	264.80	1.36
	150mg[23]	HT	6.3100	5.0000	1.26	550.00	529.60	1.04
	75mg[26]	CP-B	3.1000	4.3154	0.72	260.00	281.30	0.92

Table S7. Observed and predicted values of AUC_{0-t} (μg×h/mL) or CL(L/min) and C_{max}(ng/mL) of flumazenil to healthy(HT) subjects and LC patients

Dose	Subjects	AUC _{0-t} or CL			C _{max}		
		Obs	Pre	Obs/Pre	Obs	Pre	Obs/Pre
10mg, 1min, i.v.[27]	HT	0.9000 ^a	0.4486 ^a	2.01			
10mg, 10min, i.v.[28]	HT	0.8967 ^a	0.4540 ^a	1.98			
2.5mg, 0.5min, i.v.[29]	HT	0.7160 ^a	0.4767 ^a	1.50			
2mg, 5min, i.v.[30]	CP-B	0.4932 ^a	0.4969 ^a	0.99			
2mg, 5min, i.v.[30]	CP-C	0.3165 ^a	0.4032 ^a	0.78			
2mg, 1min, i.v.[31]	CP-C	0.7050 ^a	0.4299 ^a	1.67			
30mg, p.o.[31]	HT	NR	0.1721 ^b	/	70.1	70.1	1.00
30mg, p.o.[31]	CP-C	NR	0.5122 ^b	/	258.0	173.5	1.49

a: represent CL; b: represent AUC

Table S8. Observed and predicted values of AUC_{0-t}(μg×h/mL) or CL(L/min) and C_{max}(ng/mL) of pethidine following oral and intravenous pethidine HCL to healthy (HT) subjects and LC patients

Dose	Subjects	AUC _{0-t} or CL			C _{max}		
		Obs	Pre	Obs/Pre	Obs	Pre	Obs/Pre
25mg, 1min, i.v.[32]	HT	0.5624 ^a	0.4875 ^a	1.15			
50mg, 1min, i.v.[33]	HT	1.0200 ^a	0.7766 ^a	1.31			
50mg, 1min, i.v.[34]	HT	0.9640 ^a	0.8523 ^a	1.13			
70mg, 2min, i.v.[35]	HT	0.7505 ^a	0.4871 ^a	1.54			
70mg, 2min, i.v.[36]	HT	0.7226 ^a	0.4871 ^a	1.48			
0.8mg/kg, 1min, i.v.[37]	HT	1.3160 ^a	0.7808 ^a	1.69			
0.8mg/kg, 5min, i.v.[38]	HT	0.9000 ^a	0.6933 ^a	1.30			
0.8mg/kg, 1min, i.v.[39]	CP-A	0.3920 ^a	0.5260 ^a	0.75			
0.8mg/kg, 1min, i.v.[37]	CP-A	0.6640 ^a	0.7312 ^a	0.91			
0.8mg/kg, 5min, i.v. [38]	CP-A	0.5730 ^a	0.7472 ^a	0.77			
0.8mg/kg, 1min, i.v.[40]	CP-B	0.3730 ^a	0.5598 ^a	0.67			
25mg, p.o.[32]	HT	0.9270 ^a	0.8402 ^a	1.10	NR	31.5	/
100mg, p.o.[41]	HT	0.8600 ^b	0.6096 ^b	1.41	170.0	143.7	1.18
0.8mg/kg, p.o. [38]	HT	NR	0.4652 ^b	/	NR	80.48	/
1.6mg/kg, p.o. [39]	CP-A	NR	1.2817 ^b	/	NR	139.8	/
0.8mg/kg, p.o. [38]	CP-A	NR	0.4511 ^b	/	NR	79.75	/
1.6mg/kg, p.o. [40]	CP-B	NR	1.2091 ^b	/	NR	129.5	/

a: represent CL; b: represent AUC

Table S9. Observed and predicted values of AUC_{0-t} of remimazolam following intravenous remimazolam besylate to healthy (HT) subjects and LC patients

Dose	Subjects	AUC _{0-t} (μg×h/mL)		
		Obs	Pre	Obs/Pre
0.05mg/kg[42]	HT	0.0447	0.0509	0.88
0.075mg/kg	HT	0.0665	0.0748	0.89
0.1mg/kg	HT	0.0860	0.0996	0.86
0.2mg/kg	HT	0.1683	0.2137	0.79
0.3mg/kg	HT	0.2517	0.2949	0.85
0.4mg/kg	HT	0.3317	0.3964	0.84
10.4mg[43]	CP-B	NR	0.1274	/
8.2mg	CP-C	NR	0.0803	/

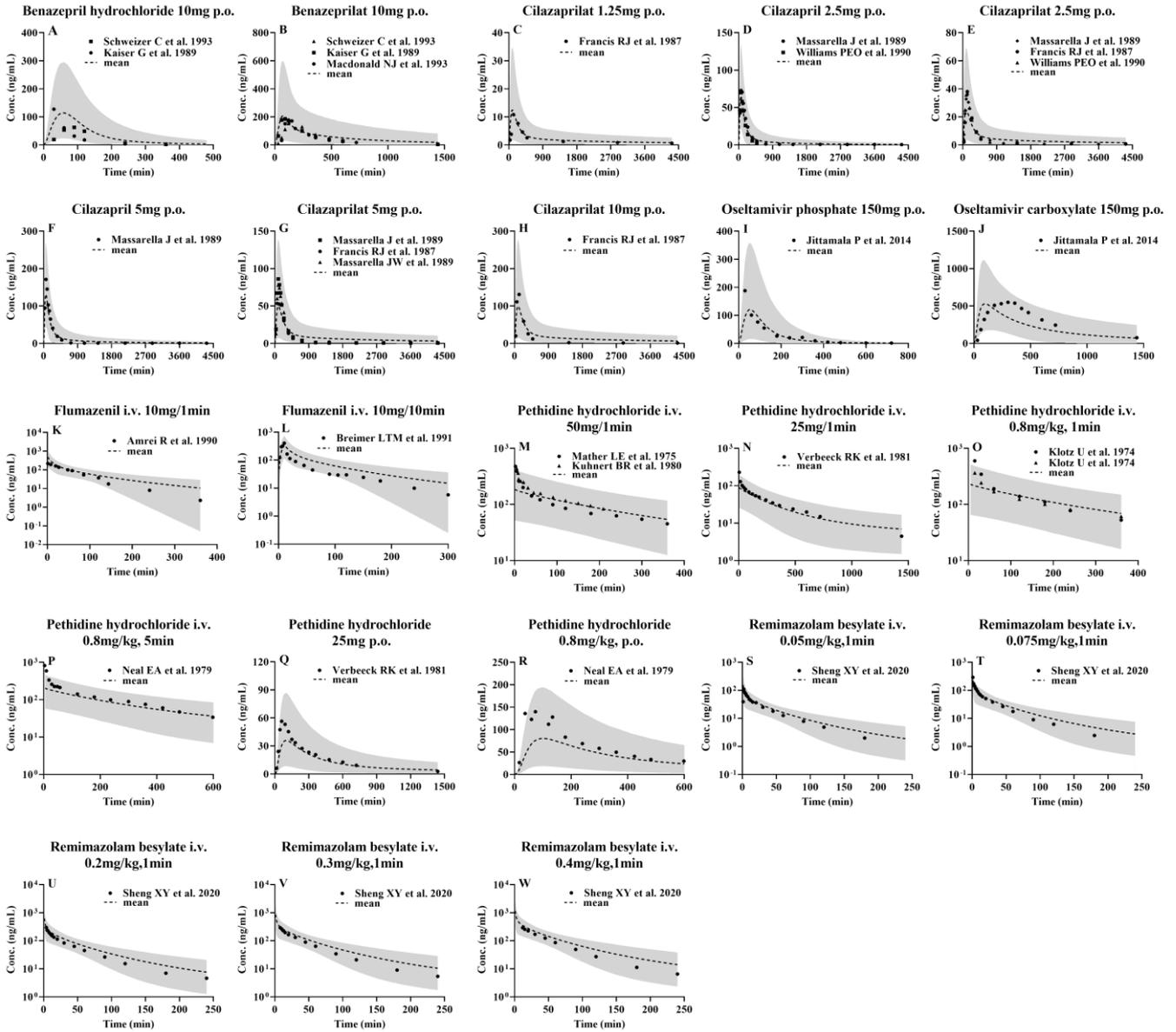


Figure S1. The observed(points) and predicted(lines) plasma concentrations of the tested CES1 substrates and their active metabolites following intravenous or oral administration to healthy subjects. Benazepril(A) and benazeprilat(B) following oral 10 mg benazepril hydrochloride; cilazapril(D,F) and cilazaprilat(C,E,G,H) following oral 1.25, 2.5, 5, 10 mg cilazapril; osetamivir(I) and osetamivir carboxylate(J) following oral 150 mg osetamivir phosphate; flumazenil following intravenous 10 mg/1 min(K) and 10mg/10min(L); pethidine following intravenous 50 mg/1min(M), 25mg/1min(N), 0.8mg/kg,1min(O) and 0.8mg/kg,5min(P) pethidine hydrochloride and oral 25 mg(Q), 0.8mg/kg(R) pethidine hydrochloride; remimazolam following intravenous 0.05(S), 0.075(T), 0.2(U), 0.3(V), 0.4(W)mg/kg remimazolam besylate. Shaded areas indicate the 5% and 95% quantile of simulations derived from 100 virtual individuals. The dashed lines indicate the mean of the simulated profiles.

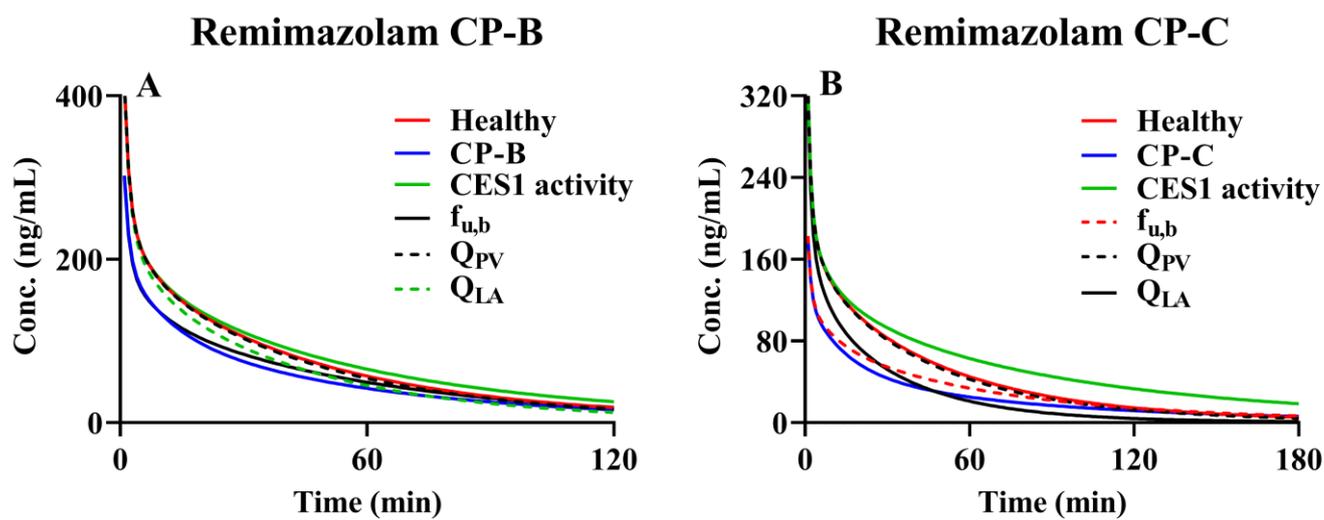


Figure S2. Contributions of alterations in $f_{u,b}$, CES1 activity, Q_{LA} and Q_{PV} by LC to plasma concentration of remimazolam following 10.4mg(CP-B, A) and 8.2mg(CP-C, B) to healthy human and LC patients.

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