

Supplementary Materials: Pharmacokinetic Characterization of Supinixin and its Physiologically Based Pharmacokinetic Modeling in Rats

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Table S1. Plasma concentrations of supinixin after intravenous injection of 0.5, 1 and 5 mg/kg in fasted male SD rats.

(A) 0.5 mg/kg.

Time (h)	Plasma concentration (µg/mL)					Mean	S.D.
	#1	#2	#3	#4	#5		
0.083	0.3220	0.3380	0.3850	0.2300	0.2910	0.3132	0.0576
0.25	0.2580	0.2990	0.3100	0.1780	0.2290	0.2548	0.0538
0.5	0.2320	0.2370	0.2450	0.1260	0.1920	0.2064	0.0494
1	0.1080	0.1400	0.1930	0.0982	0.1590	0.1396	0.0385
3	0.0812	0.0773	0.1140	0.0483	0.0758	0.0793	0.0234
7	0.0204	0.0220	0.0290	0.0200	0.0128	0.0208	0.0058
10	0.0072	0.0074	0.0126	0.0092	0.0049	0.0082	0.0029
24	BQL	BQL	0.0007	0.0008	BQL	0.0003	0.0004

BQL, Below the quantification limit, treated as "0".

(B) 1 mg/kg.

Time (h)	Plasma concentration (µg/mL)					Mean	S.D.
	#1	#2	#3	#4	#5		
0.083	0.7870	0.7620	0.9920	0.8510	0.9090	0.8602	0.0933
0.25	0.5420	0.5750	0.7960	0.7480	0.7500	0.6822	0.1151
0.5	0.5020	0.4890	0.5230	0.4180	0.5760	0.5016	0.0573
1	0.2080	0.3190	0.2330	0.3180	0.3840	0.2924	0.0714
3	0.1640	0.2060	0.3080	0.1660	0.1270	0.1942	0.0695
7	0.0451	0.0699	0.0759	0.0266	0.0440	0.0523	0.0203

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10	0.0170	0.0330	0.0211	0.0246	0.0081	0.0208	0.0092
24	0.0006	0.0007	0.0005	BQL	0.0005	0.0005	0.0003

BQL, Below the quantification limit, treated as "0".

(C) 5 mg/kg.

Time (h)	Plasma concentration (µg/mL)					Mean	S.D.
	#1	#2	#3	#4	#5		
0.083	1.1300	3.0400	3.5000	1.8400	2.3775	1.0869	1.1300
0.25	0.9410	2.2800	2.1700	1.1600	1.6378	0.6854	0.9410
0.5	0.6340	1.7400	1.9100	0.9740	1.3145	0.6096	0.6340
1	0.5580	1.3100	1.0800	0.6810	0.9073	0.3489	0.5580
3	0.4870	0.7050	0.7800	0.4270	0.5998	0.1694	0.4870
7	0.3350	0.1360	0.3290	0.1350	0.2338	0.1135	0.3350
10	0.1810	0.0497	0.1990	0.0891	0.1297	0.0718	0.1810
24	0.0074	BQL	0.0140	0.0020	0.0058	0.0063	0.0074

BQL, Below the quantification limit, treated as "0".

Table S2. Plasma concentrations of supinoxin after oral administration of 0.5, 1 and 5 mg/kg in fasted male SD rats.

(A) 0.5 mg/kg.

Time (h)	Plasma concentration (µg/mL)					Mean	S.D.
	#1	#2	#3	#4	#5		
0.25	0.0382	0.0699	0.0525	0.0484	0.0459	0.0510	0.0118
0.5	0.1280	0.1230	0.0776	0.0843	0.0853	0.0996	0.0239
1	0.0946	0.1610	0.0696	0.0849	0.0880	0.0996	0.0355
3	0.0734	0.0864	0.0452	0.0276	0.0575	0.0580	0.0231
7	0.0185	0.0142	0.0156	0.0027	0.0144	0.0131	0.0061
10	0.0069	0.0047	0.0052	0.0008	0.0076	0.0050	0.0027
24	BQL	BQL	BQL	BQL	BQL	0.0000	0.0000

BQL, Below the quantification limit, treated as "0".

(B) 1 mg/kg.

Time (h)	Plasma concentration (µg/mL)					Mean	S.D.
	#1	#2	#3	#4	#5		
0.25	0.0846	0.1850	0.2460	0.3710	0.1730	0.2119	0.1060
0.5	0.1680	0.1590	0.2860	0.3870	0.1680	0.2336	0.1006
1	0.1620	0.1660	0.2150	0.3950	0.2180	0.2312	0.0953
3	0.0708	0.1270	0.0944	0.2110	0.1080	0.1222	0.0537
7	0.0042	0.0467	0.0118	0.0526	0.0590	0.0349	0.0250
10	0.0012	0.0170	0.0036	0.0168	0.0298	0.0137	0.0116
24	BQL	BQL	BQL	BQL	0.0016	0.0003	0.0007

BQL, Below the quantification limit, treated as "0".

(C) 5 mg/kg.

Time (h)	Plasma concentration (µg/mL)					Mean	S.D.
	#1	#2	#3	#4	#5		
0.25	0.1860	0.5240	0.1150	1.0700	0.4738	0.4357	
0.5	0.3310	0.6210	0.5100	1.2400	0.6755	0.3948	
1	0.4820	0.6110	0.9490	1.1600	0.8005	0.3102	
3	0.3510	0.3300	0.6310	0.6070	0.4798	0.1613	
7	0.0722	0.0767	0.1420	0.1600	0.1127	0.0448	
10	0.0178	0.0244	0.0587	0.0607	0.0404	0.0225	

24	BQL	BQL	0.0008	0.0014	0.0005	0.0007
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BQL, Below the quantification limit, treated as "0".

Table S3. Unbound fractions of supinoxin in rat plasma and liver microsomes.

Time (h)	Unbound fraction (%) ^a	
	Plasma	Liver microsomes
4	2.30 ± 0.25	51.8 ± 2.5
8	2.83 ± 0.19	57.0 ± 1.7
18	3.63 ± 0.25	62.3 ± 1.6
24	3.54 ± 0.55	61.5 ± 4.6

^aThe data are represented as mean ± SD of triplicate or quadruplicate runs

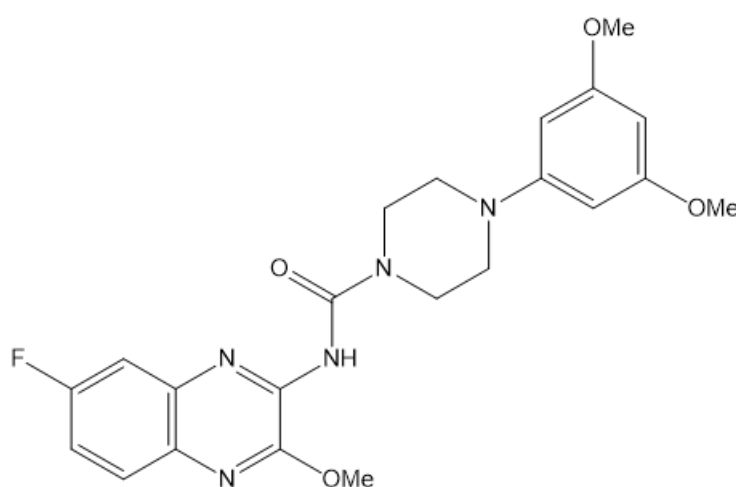


Figure S1. Chemical structure of supinoxin.

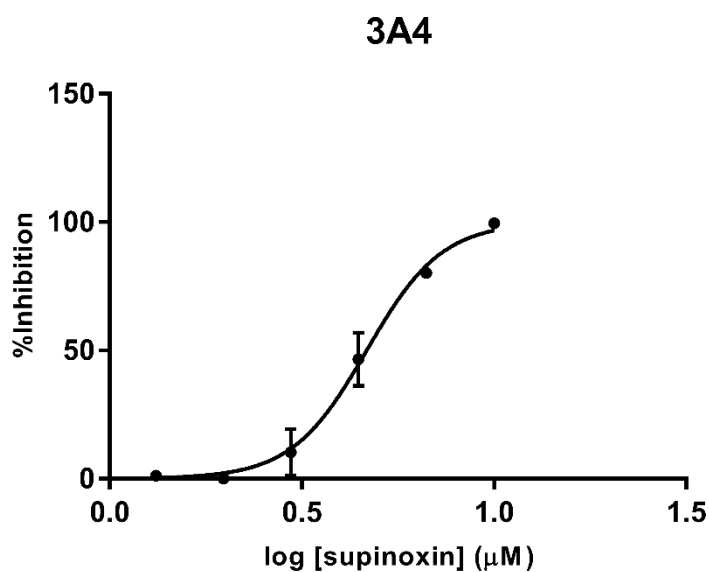


Figure S2. Inhibitory effects of supinoxin on the CYP3A4 activity in human recombinant enzymes. Each point represents the mean ± standard deviation ($n = 3$).

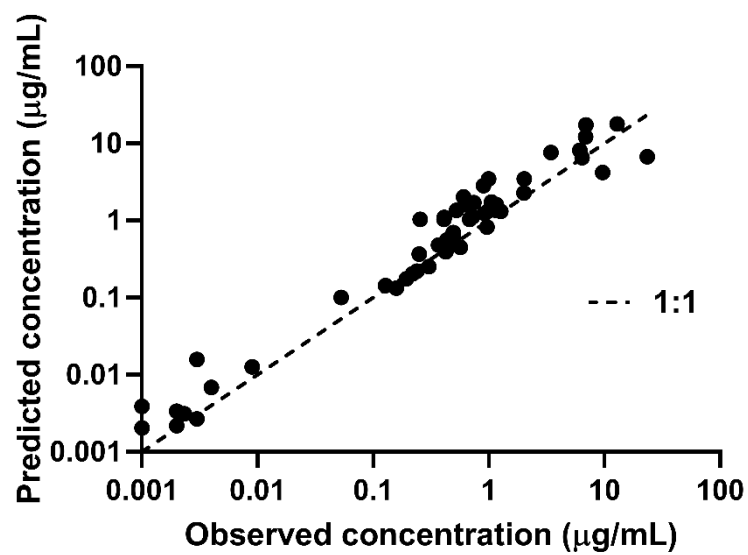


Figure S3. Relationship between observed and predicted concentration.