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Table 1 Drug-specific input parameters from in vitro experiments and prediction

Drug	LogP	pKa[1]	fu_{ob}[2]	fu_{pr}	BP[3]	$Caco2_{ob}$[4]	$Caco2_{pr}$	CLi
Acetaminophen	0.91	9.46(a)	0.52	0.34	1.04	100	19.2	1
Alprazolam	3.02	5.01(b)	0.29	0.17	0.78	25.5	51.7	1
Amitriptyline	4.81	9.76(b)	0.07	0.07	0.86	54.7	23.1	1
Atenolol	0.43	9.67(b)	0.94	0.58	1.12	1.60	1.00	1
Betaxolol	2.54	9.67(b)	0.22	0.36	1.03	53.9	44.8	1
Bosentan	4.94	5.8(a)	0.04	0.07	0.55	1.05	21.0	1
Caffeine	-0.07	0(n)	0.64	0.46	1.00	40.1	33.6	0
Chlorpromazine	5.40	9.40(b)	0.06	0.06	1.19	17.8	10.5	4
Cimetidine	-0.11	6.91(~~a~~b)	0.78	0.76	0.97	4.48	3.00	8
Clozapine	3.40	7.35(b)	0.06	0.04	0.81	30.7	31.5	1
Desipramine	3.90	10.01(b)	0.16	0.14	0.93	29.5	14.5	1
Dexamethasone	1.68	12.42(a)	0.198	0.25	0.93	15.0	16.5	8
Diazepam	2.82	3.4(b)	0.02	0.05	0.81	41.0	50.1	1
Diclofenac	4.26	4(a)	0.01	0.004	0.60	20.2	39.8	1
Diltiazem	2.73	~~8.18(~~12.86(a)-8.18(b)	0.18	0.15	0.99	38.7	20.2	2
Furosemide	1.75	4.25(a)	0.01	0.13	0.90	1.60	1.60	2
Ibuprofen	3.97	5.53(a)	0.006	0.05	0.55	48.1	46.2	3
Imipramine	4.28	9.2(b)	0.08	0.12	0.99	30.0	13.2	2
Ketoprofen	3.10	4.45(a)	0.008	0.01	1.09	40.3	48.3	6
Lidocaine	2.84	7.75(b)	0.33	0.28	0.74	18.5	21.5	1
Methylprednisolone	1.80	0(n)	0.23	0.17	0.88	9.59	11.8	2
Metoprolol	1.76	9.67(b)	0.88	0.61	1.15	34.2	12.3	3
Midazolam	2.90	~~9.16~~6.19(b)	0.02	0.04	0.68	39.8	42.6	3
Montelukast	8.49	4.40(a)-3.12(b)	0.002	0.003	0.55	76.0	5.20	9
Morphine	0.89	8.21(b)	0.65	0.57	1.00	6.27	10.2	6
Nadolol	0.81	9.76(b)	0.14	0.65	1.00	1.17	2.90	1
Naloxone	1.67	~~7.84(~~10.07(a)-7.84(b)	0.54	0.49	1.43	21.5	21.9	1
Naproxen	3.18	4.15(a)	0.002	0.01	0.51	52.8	41.9	1
Nifedipine	2.20	0(n)	0.04	0.04	0.74	42.0	29.0	8
Omeprazole	2.23	~~9.29(~~4.47(b)-9.29(a)	0.05	0.03	0.61	54.8	12.4	1
Ondansetron	2.80	7.34(b)	0.27	0.24	0.79	110	107	2
Prazosin	1.30	6.54(b)	0.06	0.15	0.70	7.72	10.8	6
Propranolol	2.58	9.67(b)	0.13	0.17	0.89	45.0	31.8	1
~~Ranitidine~~Quinidine	~~0.20~~ 2.51	~~7.8~~9.05(b)	~~0.95~~ 0.26	~~0.59~~0.09	~~1.00~~ 1.02	~~4.45~~21.0	~~0.70~~ 5.70	~~3~~
~~Quinidine~~Ranitidine	~~2.51~~ 0.20	~~9.05~~7.8(b)	~~0.26~~ 0.95	~~0.09~~0.59	~~1.02~~ 1.00	~~21.0~~4.45	~~5.70~~ 0.70	~~21~~
Sildenafil	1.87	11.14(a)-5.59(b)	0.04	0.06	0.81	55.0	43.9	5
Theophylline	-0.02	8.81(a)	0.61	0.34	0.92	44.1	14.5	2
Triazolam	3.63	4.26(b)	0.10	0.16	0.62	28.0	29.9	4
Verapamil	3.79	8.92(b)	0.09	0.14	0.817	9.02	4.30	1
Vinorelbine	4.80	8.66(b)	0.87	0.09	0.58	1.30	2.90	1

[1]a=acid,b=base,n=neutral

[2]pr=predicted,ob=observed.Experimental Plasma protein fraction unbound from Lombardo et.al[1, 2].

[3]Experimental Blood:Plasma ratio obtained from previous studies[3, 4].

[4]Experimental Caco-2 cell permeability(10^{-6}cm/s) obtained from previous publications[5–7].

[5]Experimental Intrinsic hepatic clearance(ml/min/kg) from literature[2, 8, 9].

[6]Total plasma clearance(L/hr/kg) for drugs obtained from Lombardo et.al[1].

Table 2 Prediction results for in vitro and ML input parameters

Drug	In Vitro[1]				ML[2]				Reference[4]
	$RT_{1/2}$[3]	RAUC	RCL	RV	$RT_{1/2}$	RAUC	RCL	RV	
Acetaminophen	0.34	1.47	0.68	0.21	0.45	0.71	1.40	0.49	[10]
Alprazolam	2.05	0.24	4.10	8.50	1.72	0.36	2.77	4.92	[11]
Amitriptyline	0.43	1.24	0.81	0.26	1.01	0.17	5.87	3.49	[12]
Atenolol	2.36	0.58	1.74	1.92	0.64	0.40	2.53	0.88	[13]
Betaxolol	0.34	0.61	1.65	0.42	0.64	0.43	2.34	1.36	[14]
Bosentan	10.2	0.92	1.09	10.1	7.59	0.45	2.23	27.5	[15]
Caffeine	0.60	1.48	0.68	0.36	0.50	0.74	1.35	0.67	[16]
Chlorpromazine	2.43	5.95	0.17	0.34	4.64	1.78	0.56	2.59	[17]
Cimetidine	0.83	~~1.77 0.56 0.22~~ 0.81	0.81	0.97	1.23	~~0.60~~1.03	0.64	0.59	[18]
Clozapine	3.04	3.24	0.31	1.12	2.81	13.3	0.07	0.20	[19]
Desipramine	0.41	2.20	0.45	0.13	1.90	0.60	1.65	1.91	[20]
Dexamethasone	0.49	0.45	2.21	0.44	0.46	0.26	3.89	0.57	[21]
Diazepam	1.52	4.33	0.23	0.42	0.71	0.65	1.54	1.23	[22]
Diclofenac	2.88	5.76	0.17	0.34	2.77	3.81	0.26	0.52	[23]
Diltiazem	2.55	3.01	0.33	0.75	2.72	1.85	0.54	1.08	[24]
Furosemide	1.63	4.20	0.24	1.29	0.80	2.68	0.37	1.03	[25]
Ibuprofen	1.14	1.61	0.62	0.78	3.13	0.65	1.54	5.39	[26]
Imipramine	0.60	2.52	0.40	0.15	1.98	0.54	1.85	2.12	[20]
Ketoprofen	5.35	9.18	0.11	0.59	1.54	1.70	0.59	1.01	[27]
Lidocaine	2.26	2.94	0.34	0.55	3.67	1.12	0.89	2.68	[28]
Methylprednisolone	1.38	1.05	0.95	0.42	1.37	0.85	1.18	0.49	[29]
Metoprolol	3.13	5.91	0.17	0.52	1.96	2.63	0.38	0.62	[30]
Midazolam	2.99	0.74	1.36	1.77	9.85	1.37	0.73	5.51	[31]
Montelukast	7.73	0.05	20.6	58.3	0.85	0.29	3.48	0.93	[32]
Morphine	1.41	3.73	0.27	0.22	0.30	0.57	1.77	0.38	[33]
Nadolol	0.98	1.34	0.75	0.38	0.30	0.51	1.95	0.43	[34]
Naloxone	2.60	0.62	1.62	2.92	1.30	1.12	0.89	0.89	[35]
Naproxen	0.73	0.50	2.00	1.55	0.35	0.18	5.52	1.68	[36]
Nifedipine	0.81	1.95	0.51	0.36	1.36	0.60	1.67	0.59	[37]
Omeprazole	4.59	5.92	0.17	1.12	1.47	0.98	1.03	1.76	[38]
Ondansetron	1.44	0.88	1.13	1.45	7.01	1.71	0.58	4.90	[39]
Prazosin	1.20	2.35	0.43	0.49	0.68	0.98	1.02	0.45	[40]
Propranolol	1.78	5.39	0.19	0.39	1.49	1.68	0.59	0.93	[41]
Quinidine	0.82	0.55	1.83	1.03	1.05	0.50	2.00	0.87	[42]
Ranitidine	1.48	1.33	0.75	0.85	1.85	1.58	0.63	0.66	[18]
Sildenafil	1.13	1.33	0.75	0.32	1.33	0.65	1.55	0.45	[43]
Theophylline	0.22	0.43	2.31	0.50	0.21	0.22	4.51	0.92	[44]
Triazolam	3.46	0.24	4.25	8.38	7.45	0.39	2.54	16.6	[45]
Verapamil	1.32	1.51	0.66	0.47	2.00	0.92	1.09	1.58	[46]
Vinorelbine	0.99	0.13	7.72	6.15	1.14	1.00	1.00	1.03	[47]

[1]Drug-specific input parameters from in vitro experiments

[2]Drug-specific input parameters from ML prediction

[3]R=Ratio of Predicted/Observed

[3]References for drugs clinical pharmacokinetics

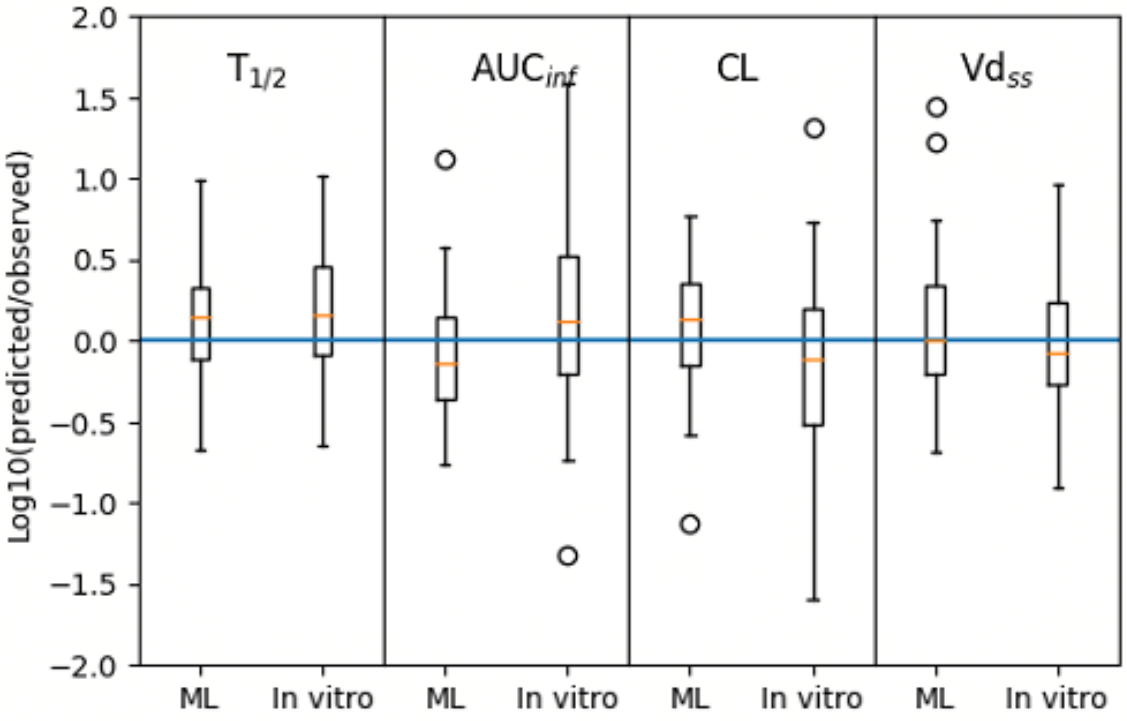

Fig. 1 Box plots present log ratios of predicted/observed PK parameter values. Positive values indicate overprediction, and negative values indicate underprediction. The blue line refers to the equal value between prediction and observation.

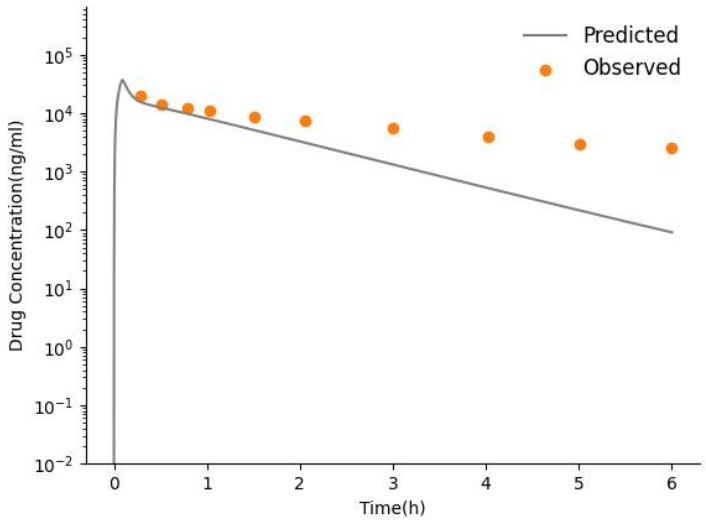

Fig. 2 Predicted vs. Observed Plot For Concentration-time Curve of Acetaminophen

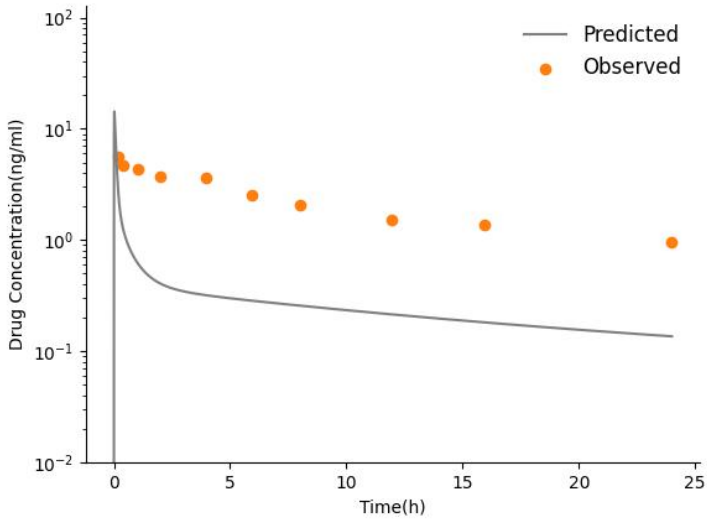

Fig. 3 Predicted vs. Observed Plot For Concentration-time Curve of Alprazolam

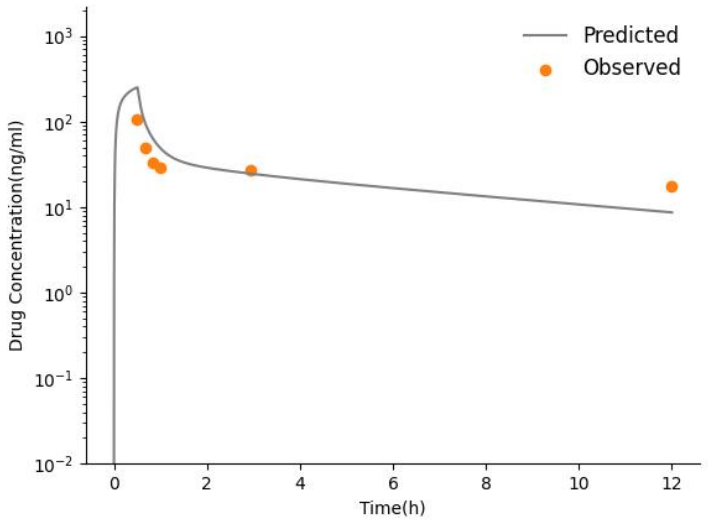

Fig. 4 Predicted vs. Observed Plot For Concentration-time Curve of Amitriptyline

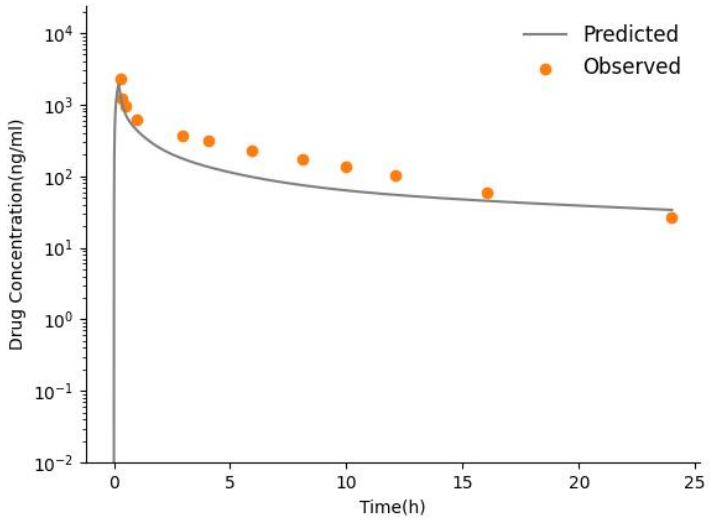

Fig. 5 Predicted vs. Observed Plot For Concentration-time Curve of Atenolol

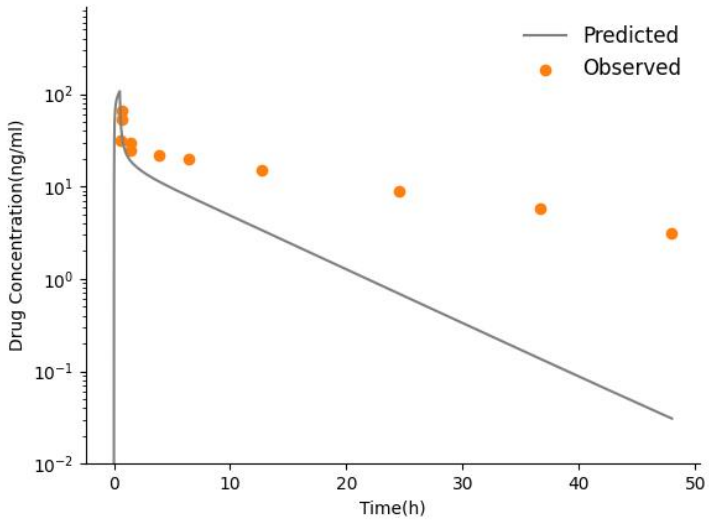

Fig. 6 Predicted vs. Observed Plot For Concentration-time Curve of Betaxolol

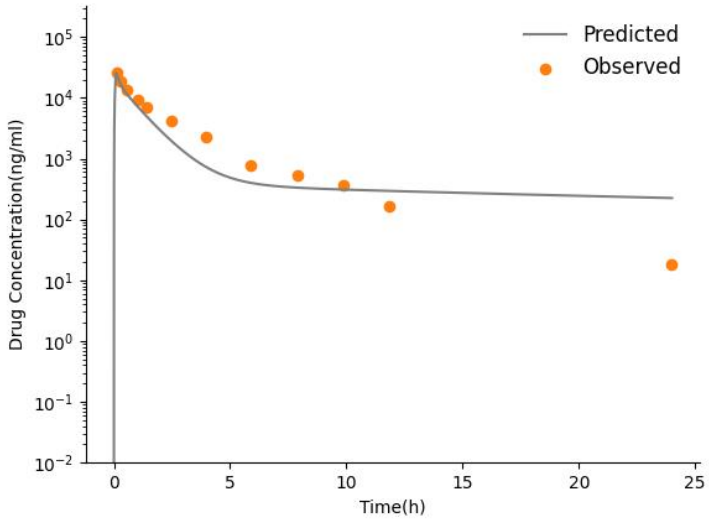

Fig. 7 Predicted vs. Observed Plot For Concentration-time Curve of Bosentan

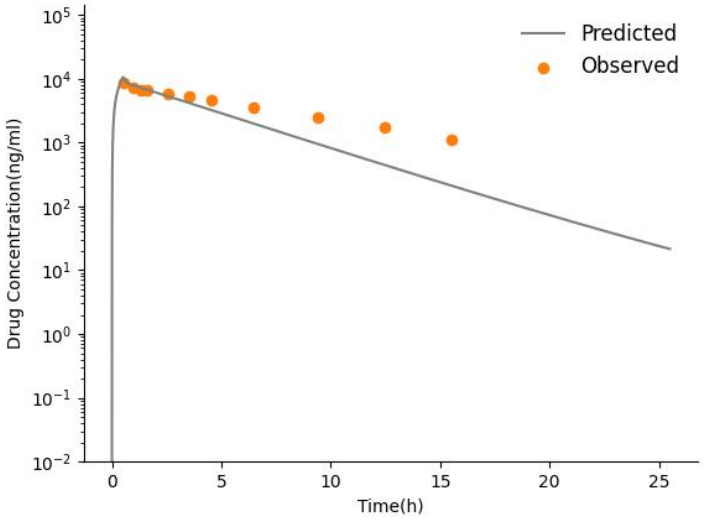

Fig. 8 Predicted vs. Observed Plot For Concentration-time Curve of Caffeine

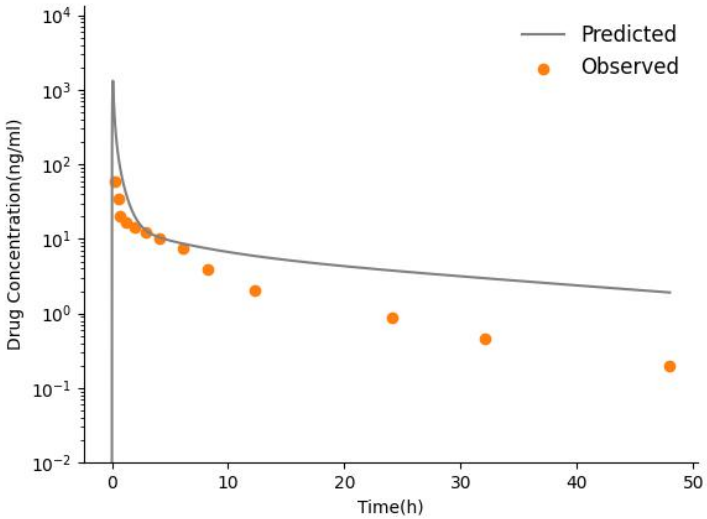

Fig. 9 Predicted vs. Observed Plot For Concentration-time Curve of Chlorpromazine

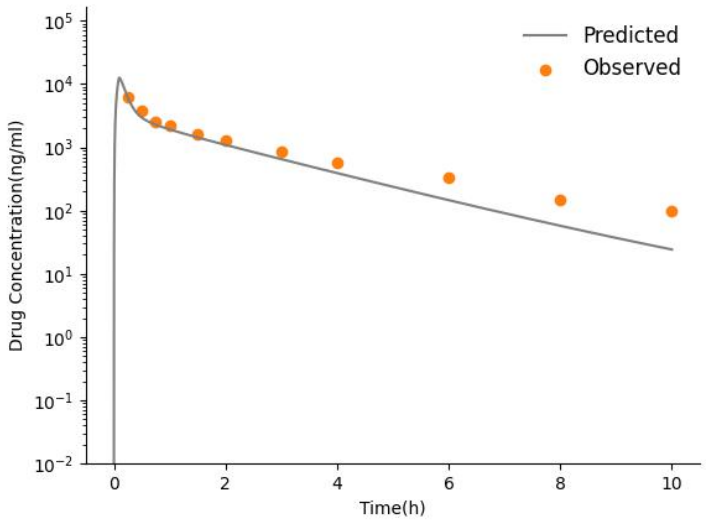

Fig. 10 Predicted vs. Observed Plot For Concentration-time Curve of Cimetidine

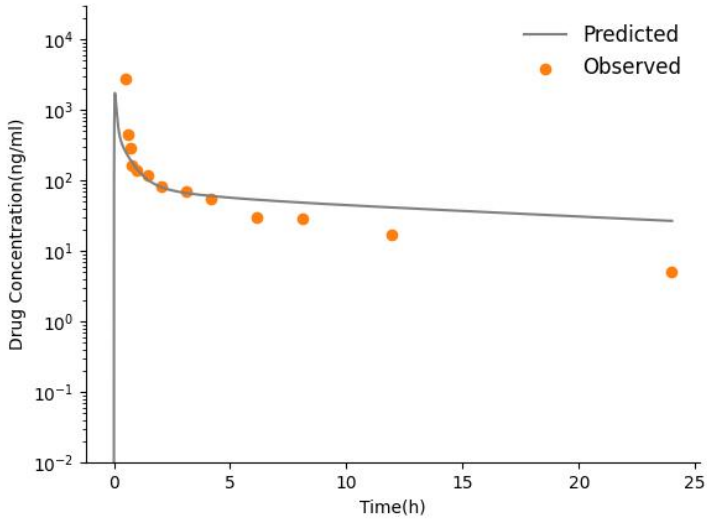

Fig. 11 Predicted vs. Observed Plot For Concentration-time Curve of Clozapine

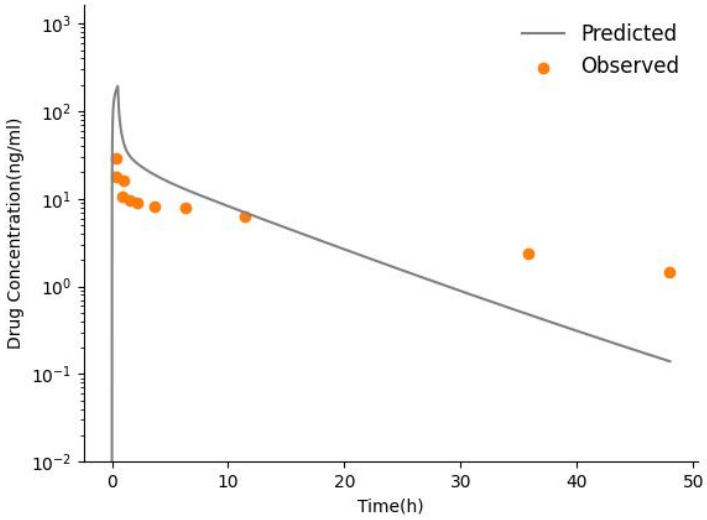

Fig. 12 Predicted vs. Observed Plot For Concentration-time Curve of Desipramine

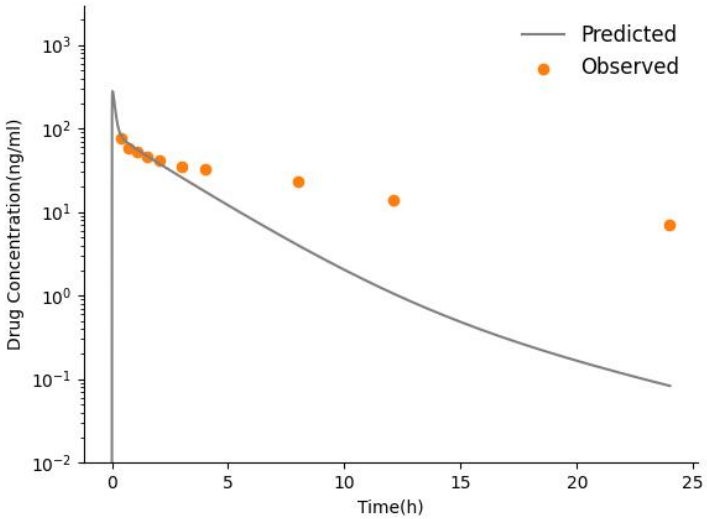

Fig. 13 Predicted vs. Observed Plot For Concentration-time Curve of Dexamethasone

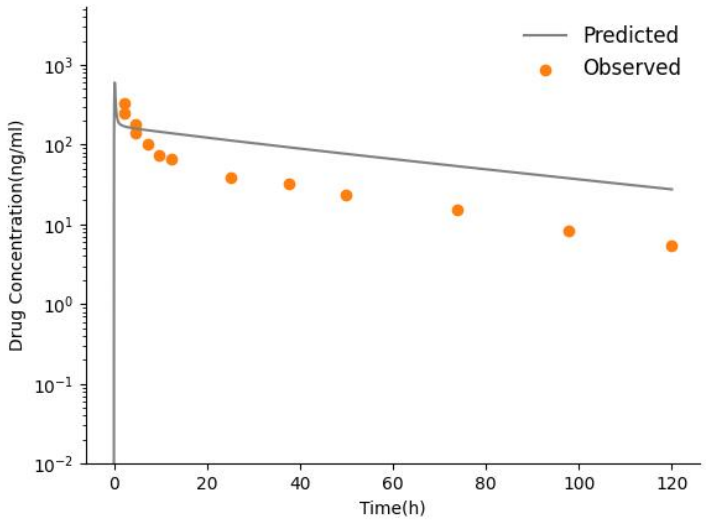

Fig. 14 Predicted vs. Observed Plot For Concentration-time Curve of Diazepam

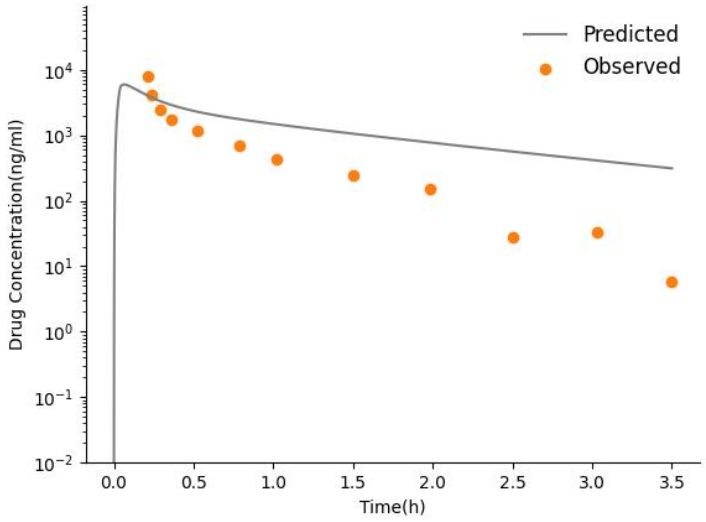

Fig. 15 Predicted vs. Observed Plot For Concentration-time Curve of Diclofenac

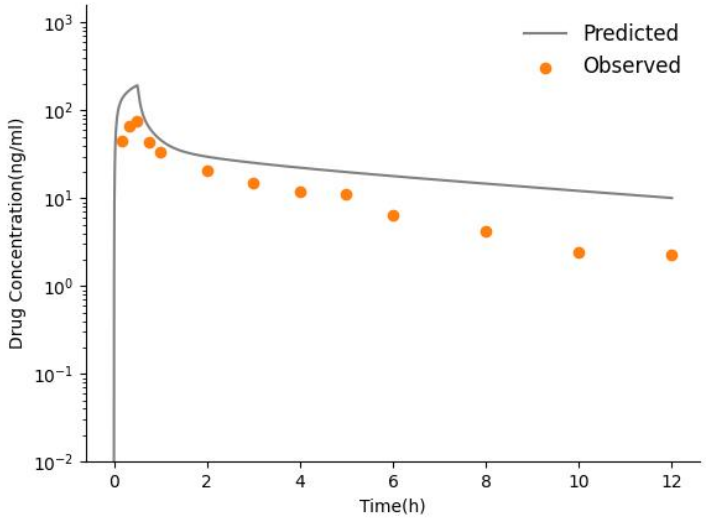

Fig. 16 Predicted vs. Observed Plot For Concentration-time Curve of Diltiazem

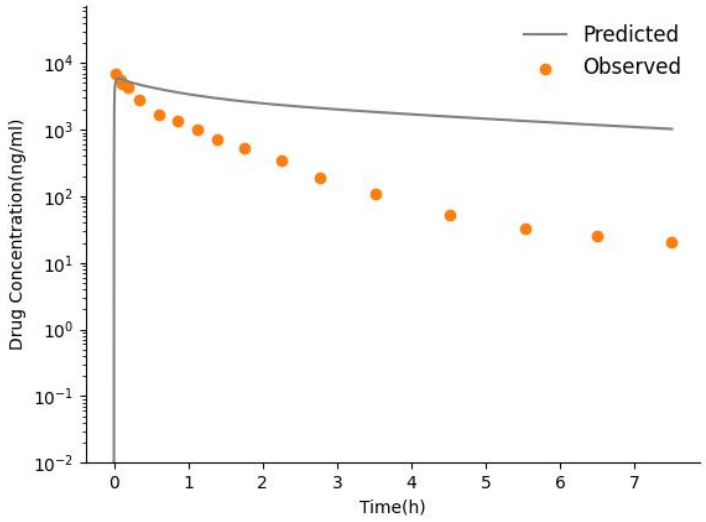

Fig. 17 Predicted vs. Observed Plot For Concentration-time Curve of Furosemide

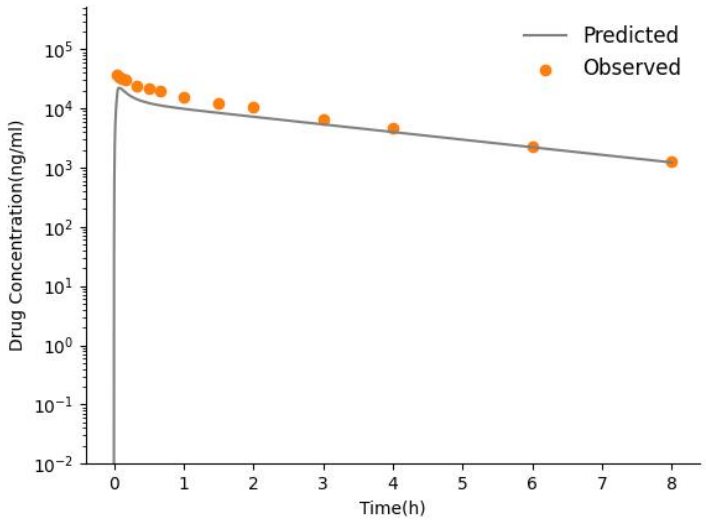

Fig. 18 Predicted vs. Observed Plot For Concentration-time Curve of Ibuprofen

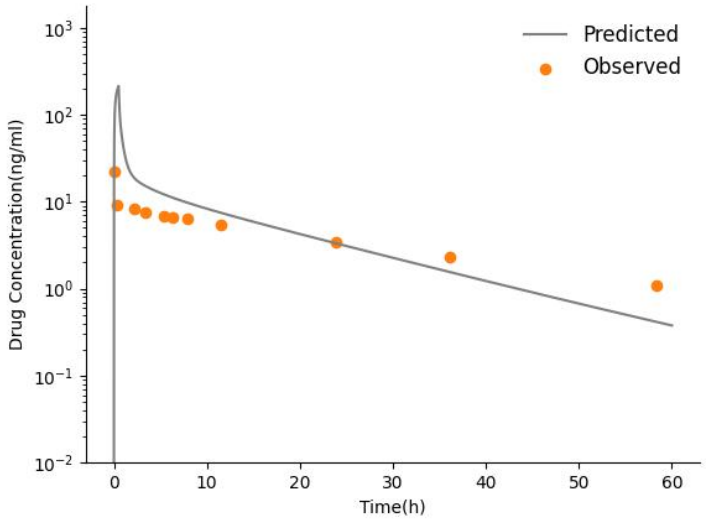

Fig. 19 Predicted vs. Observed Plot For Concentration-time Curve of Imipramine

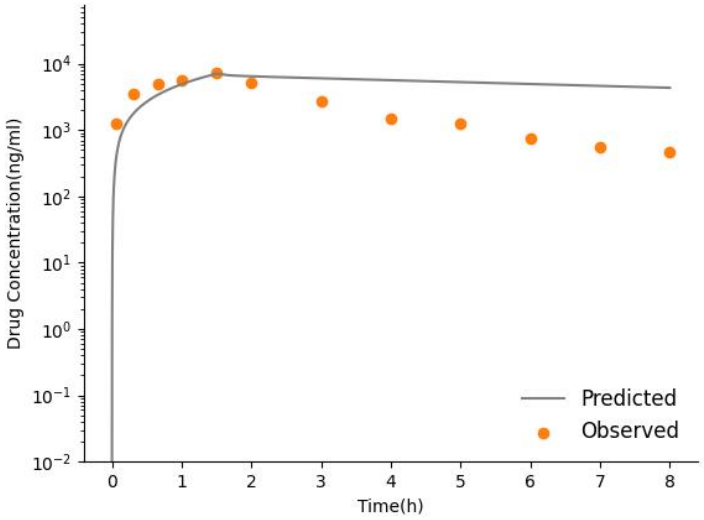

Fig. 20 Predicted vs. Observed Plot For Concentration-time Curve of Ketoprofen

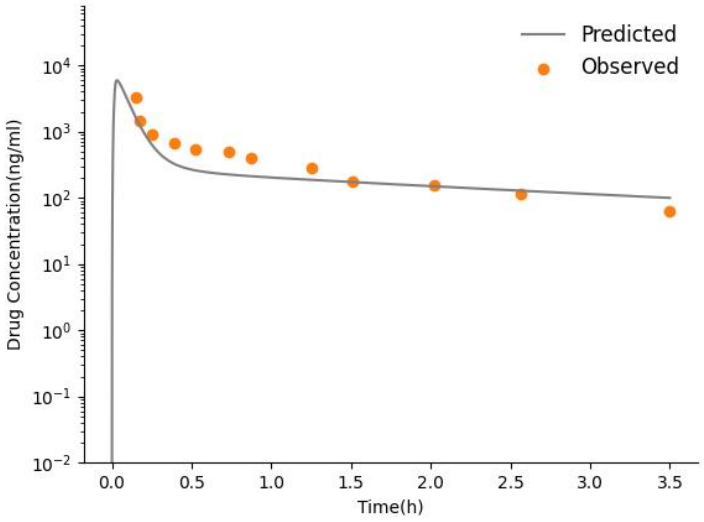

Fig. 21 Predicted vs. Observed Plot For Concentration-time Curve of Lidocaine

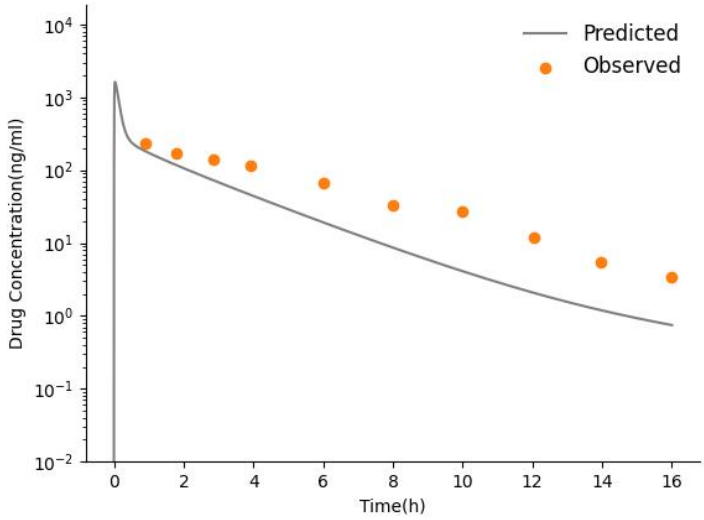

Fig. 22 Predicted vs. Observed Plot For Concentration-time Curve of Methylprednisolone

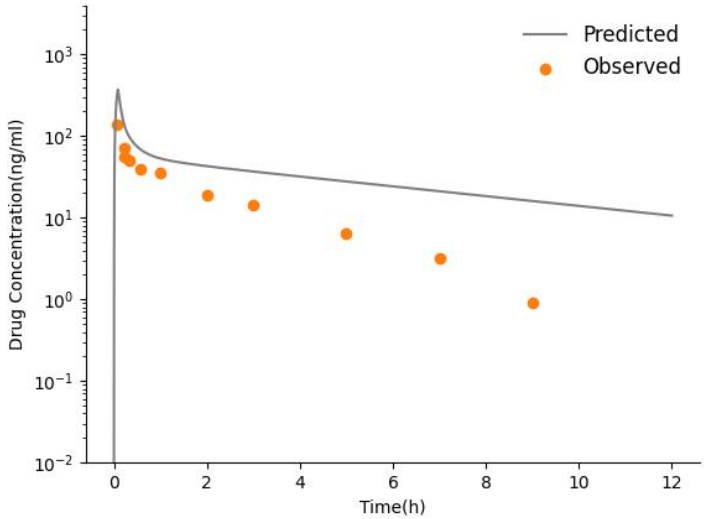

Fig. 23 Predicted vs. Observed Plot For Concentration-time Curve of Metoprolol

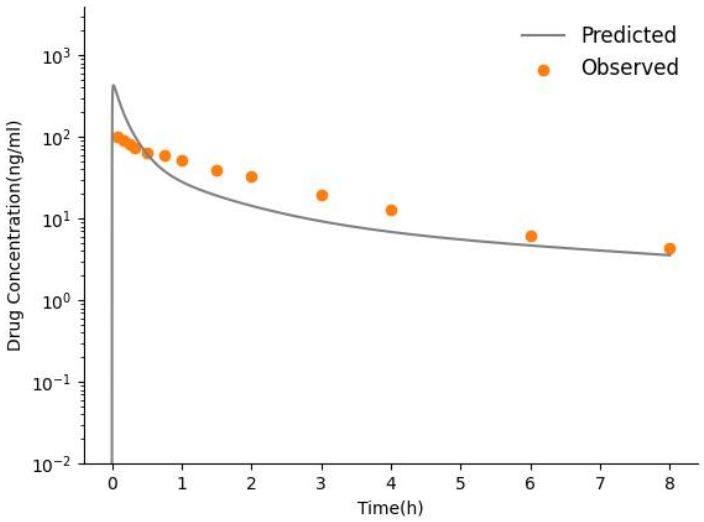

Fig. 24 Predicted vs. Observed Plot For Concentration-time Curve of Midazolam

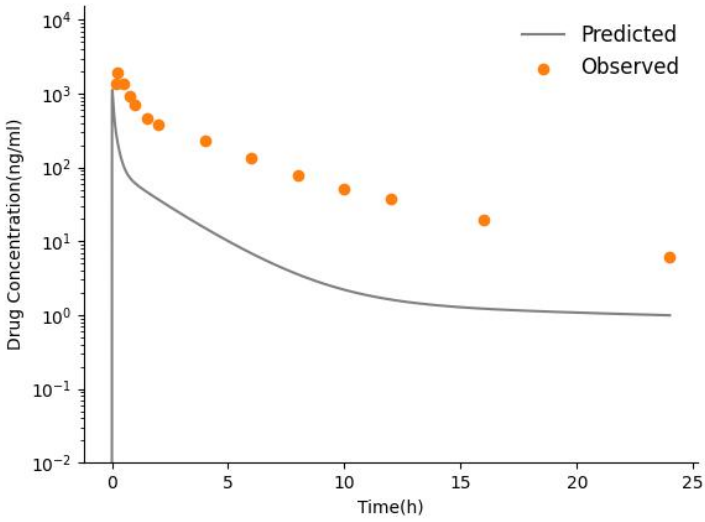

Fig. 25 Predicted vs. Observed Plot For Concentration-time Curve of Montelukast

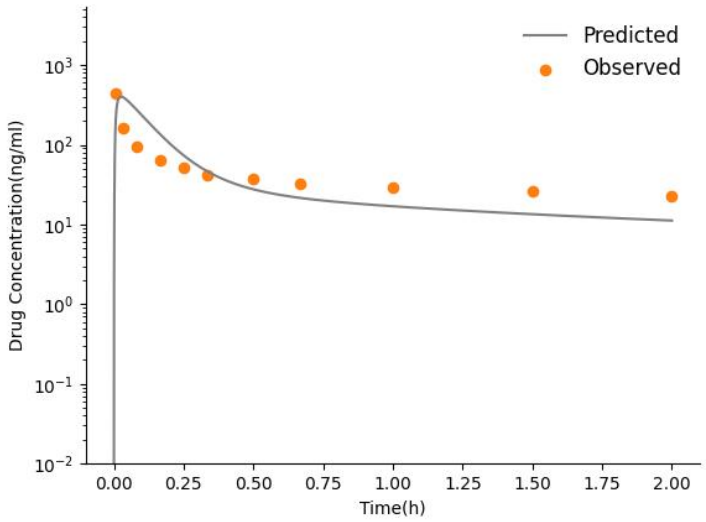

Fig. 26 Predicted vs. Observed Plot For Concentration-time Curve of Morphine

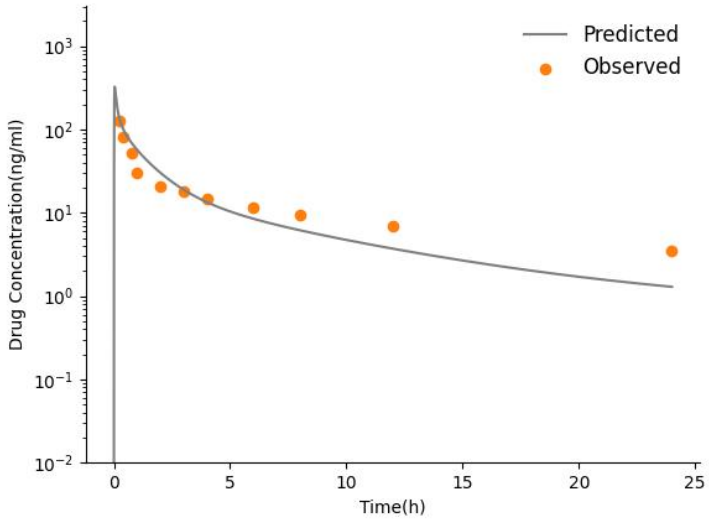

Fig. 27 Predicted vs. Observed Plot For Concentration-time Curve of Nadolol

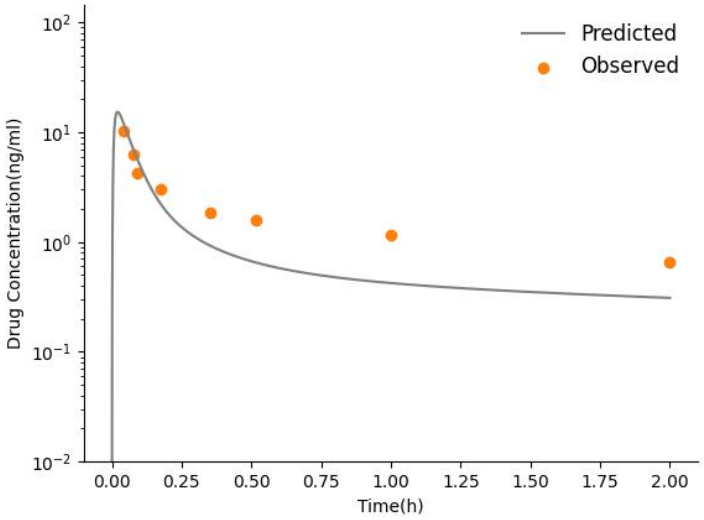

Fig. 28 Predicted vs. Observed Plot For Concentration-time Curve of Naloxone

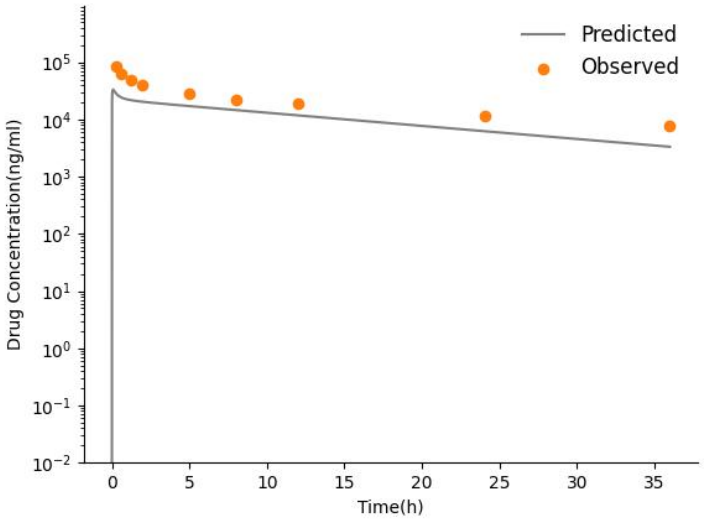

Fig. 29 Predicted vs. Observed Plot For Concentration-time Curve of Naproxen

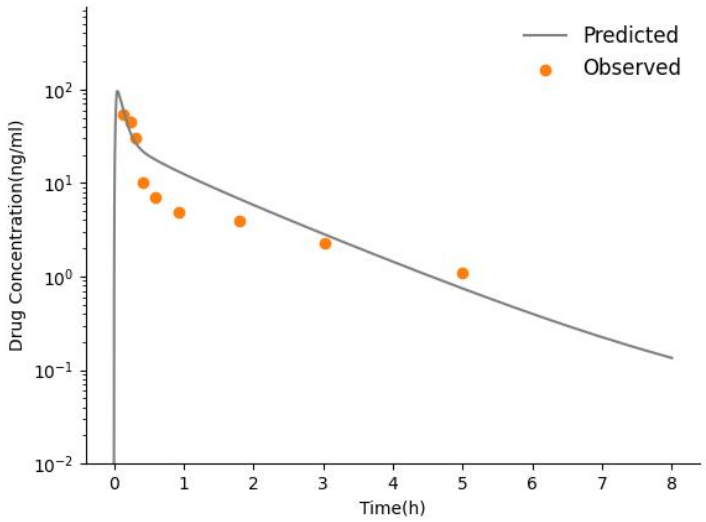

Fig. 30 Predicted vs. Observed Plot For Concentration-time Curve of Nifedipine

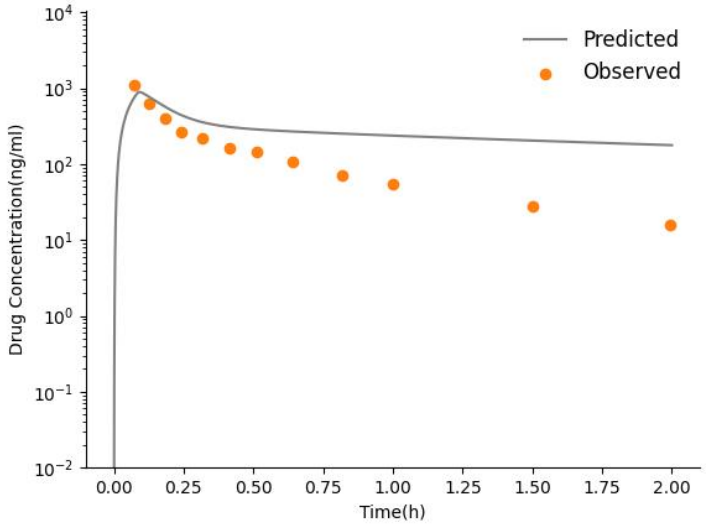

Fig. 31 Predicted vs. Observed Plot For Concentration-time Curve of Omeprazole

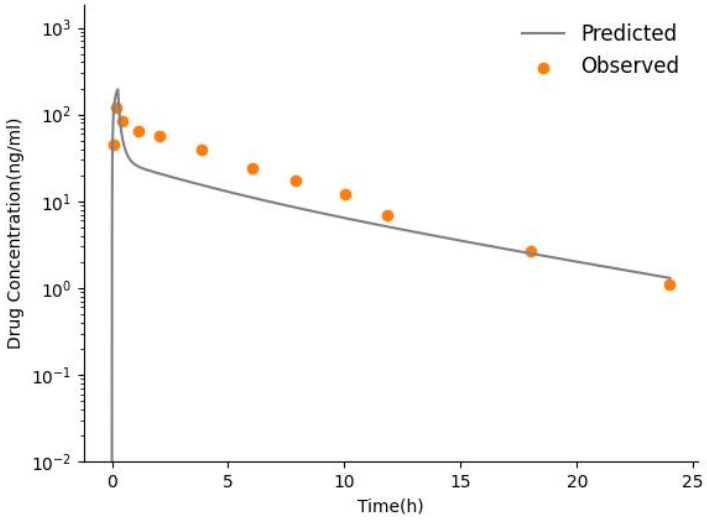

Fig. 32 Predicted vs. Observed Plot For Concentration-time Curve of Ondansetron

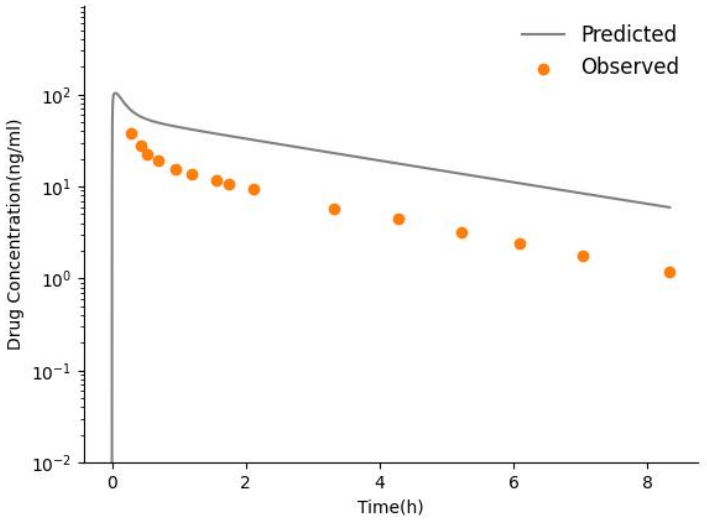

Fig. 33 Predicted vs. Observed Plot For Concentration-time Curve of Prazosin

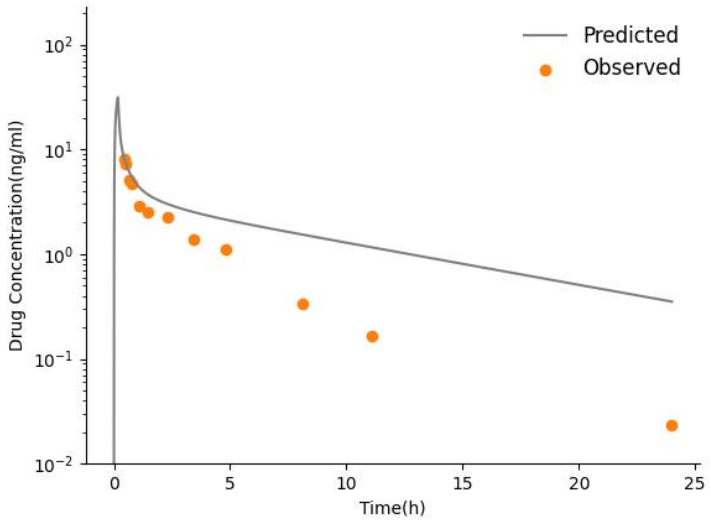

Fig. 34 Predicted vs. Observed Plot For Concentration-time Curve of Propranolol

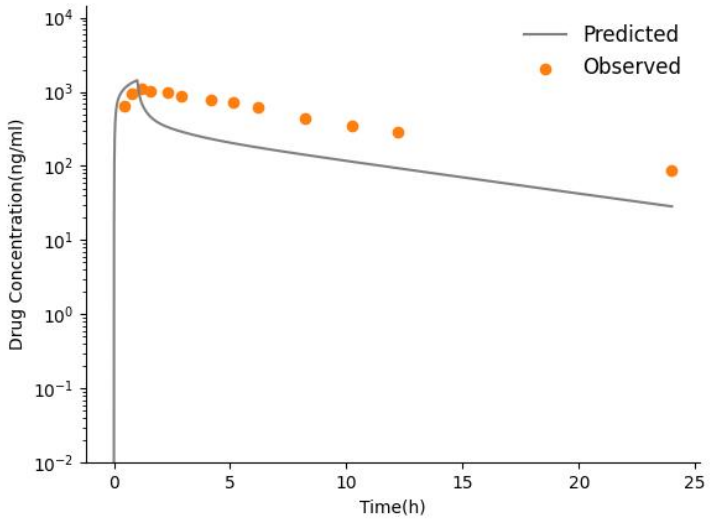

Fig. 35 Predicted vs. Observed Plot For Concentration-time Curve of Quinidine

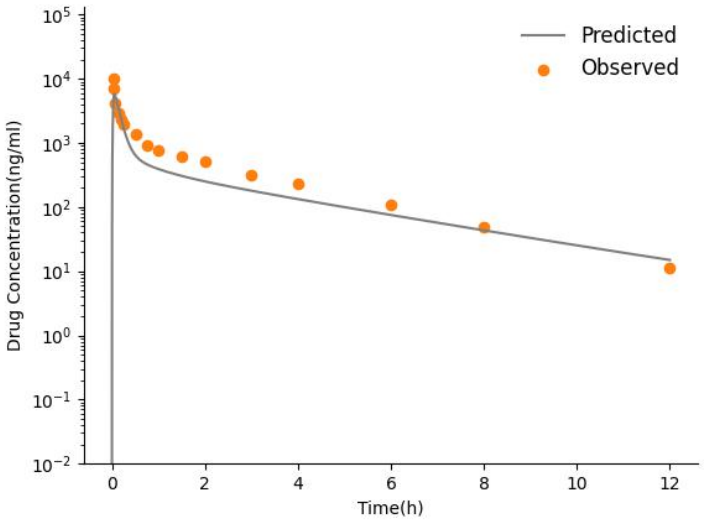

Fig. 36 Predicted vs. Observed Plot For Concentration-time Curve of Ranitidine

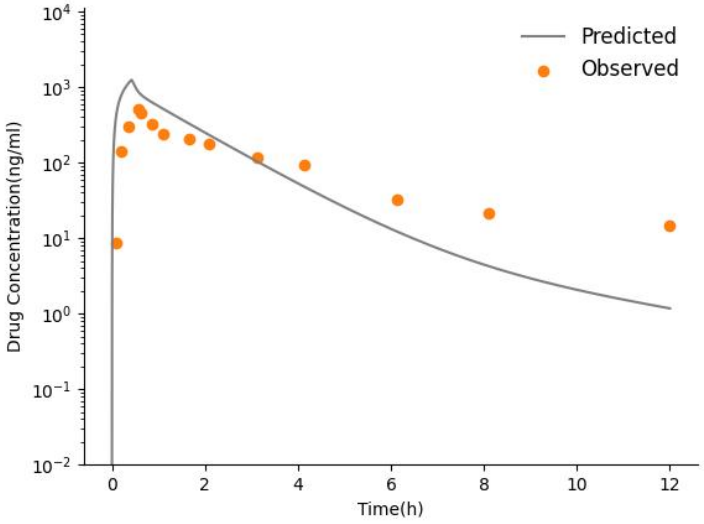

Fig. 37 Predicted vs. Observed Plot For Concentration-time Curve of Sildenafil

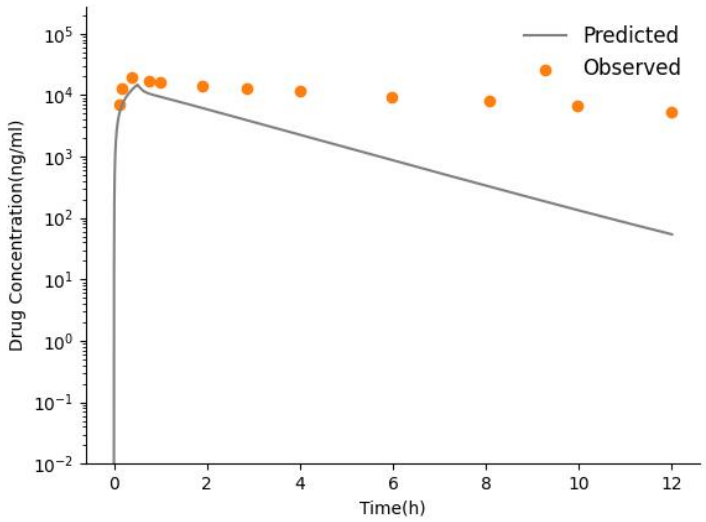

Fig. 38 Predicted vs. Observed Plot For Concentration-time Curve of Theophylline

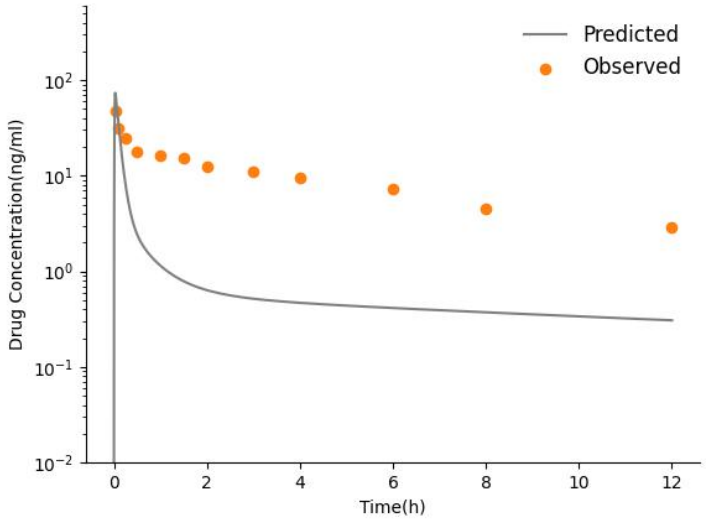

Fig. 39 Predicted vs. Observed Plot For Concentration-time Curve of Triazolam

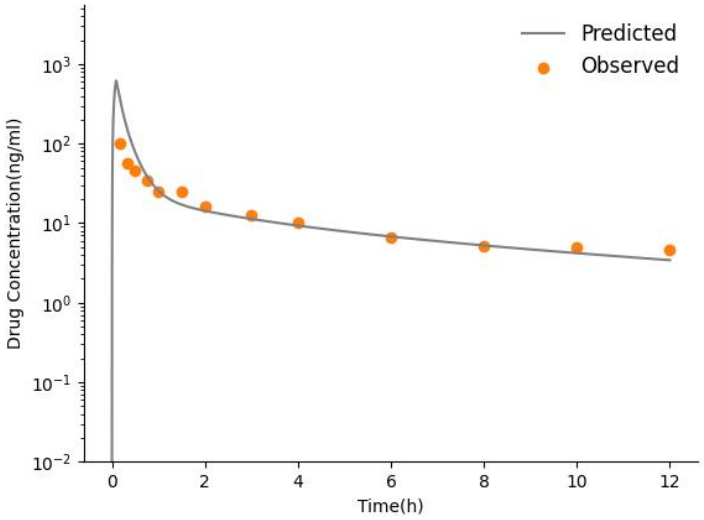

Fig. 40 Predicted vs. Observed Plot For Concentration-time Curve of Verapamil

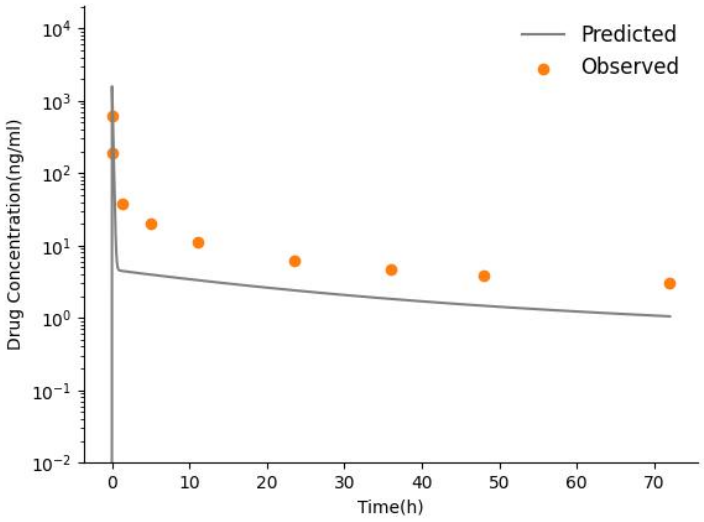

Fig. 41 Predicted vs. Observed Plot For Concentration-time Curve of Vinorelbine