Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

SUPPORTING INFORMATION

Design of vilazodone-donepezil chimeric derivatives as Acetylcholinesterase inhibitors by QSAR, molecular docking and molecular dynamics simulations

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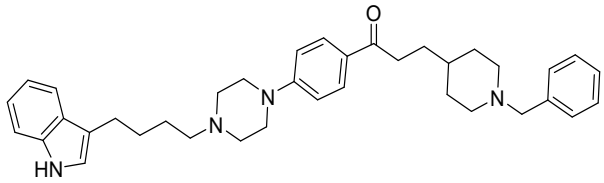
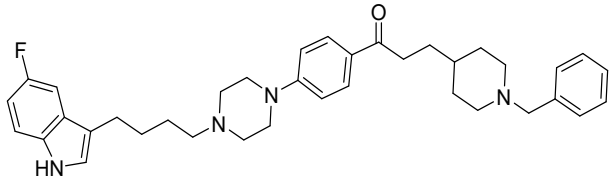
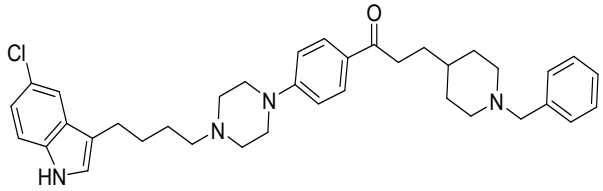
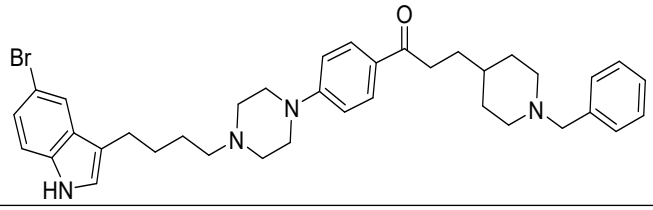
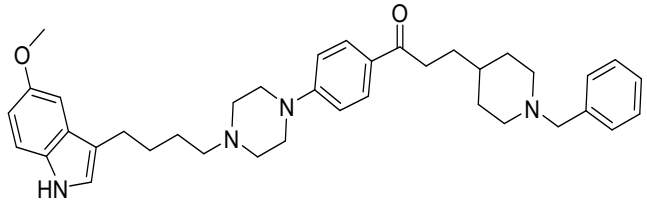
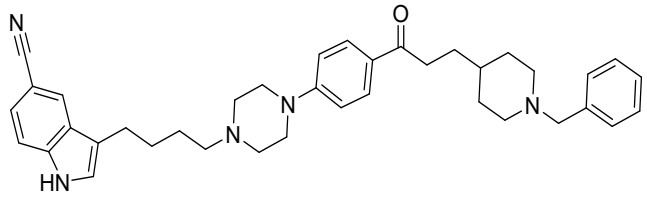
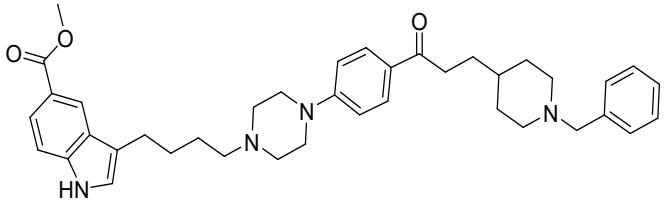
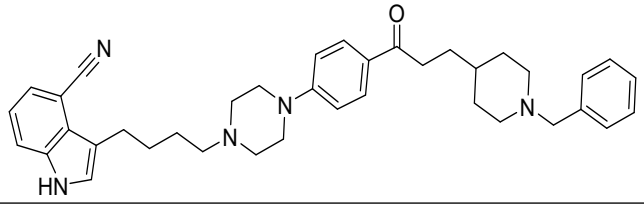
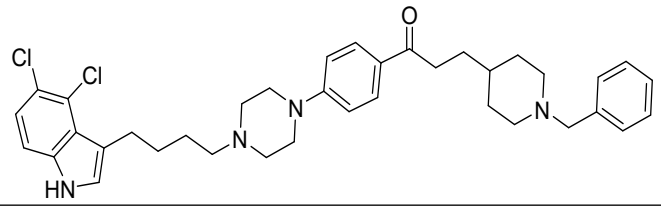
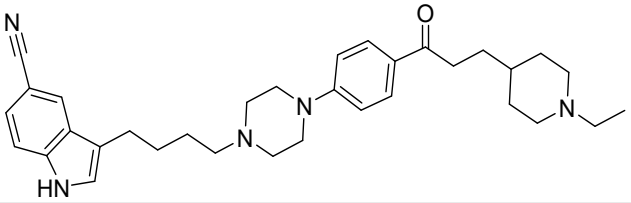
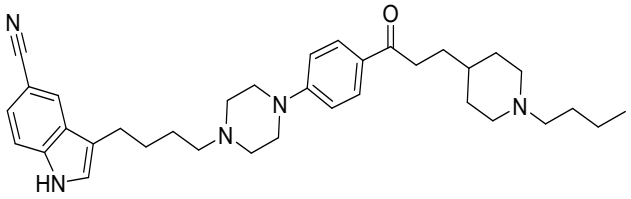
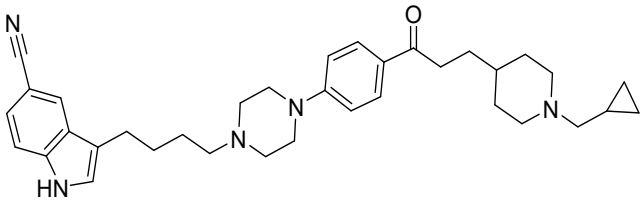
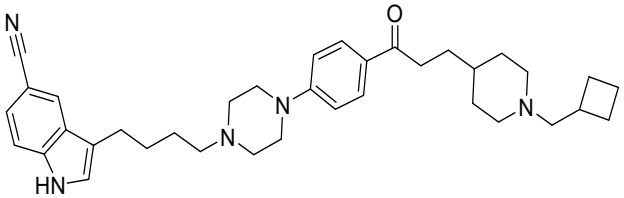
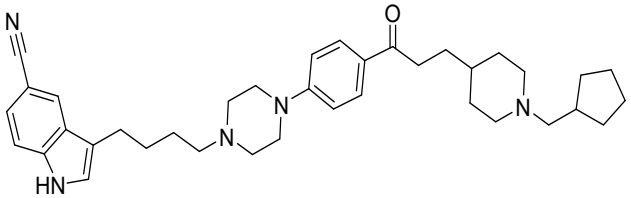
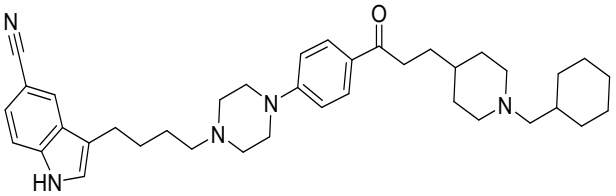
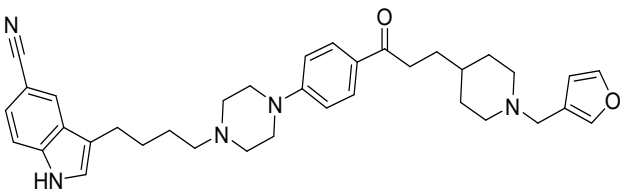
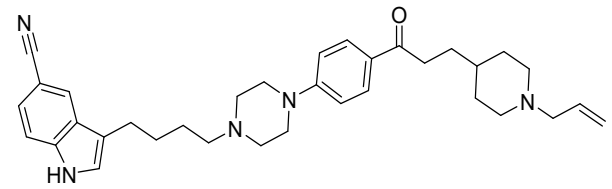
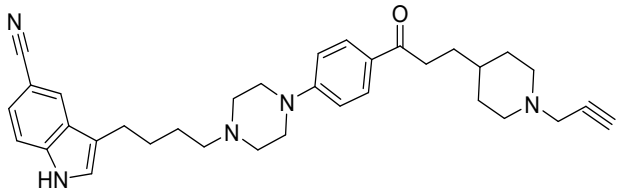
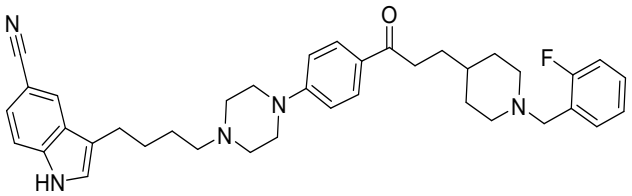
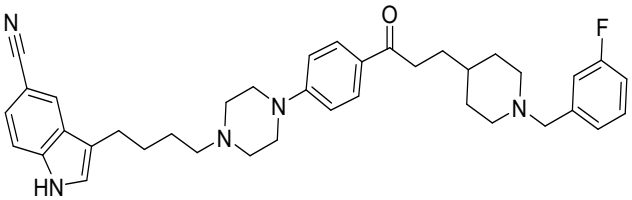
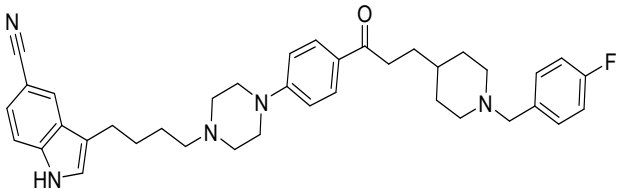
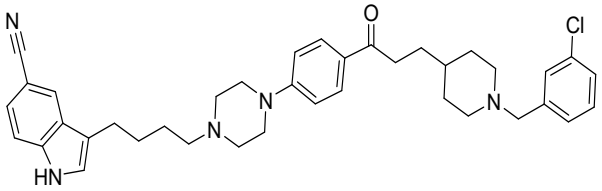
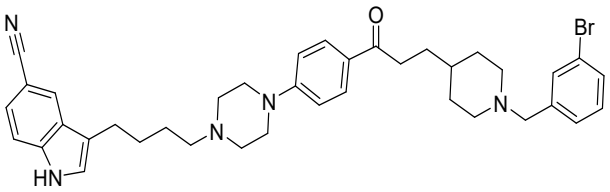
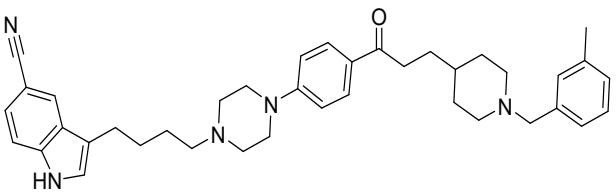
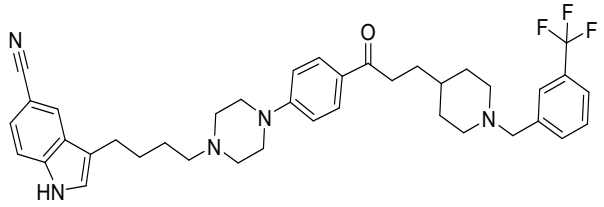
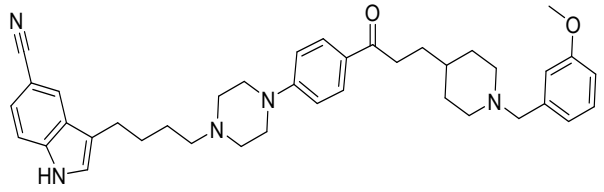
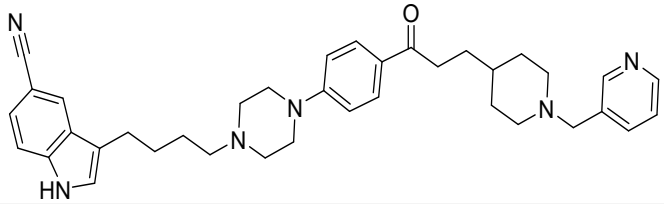
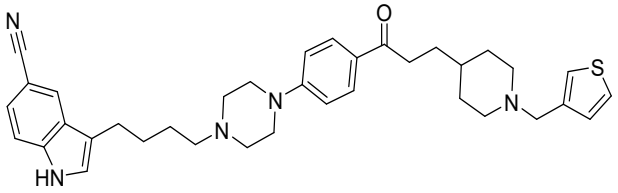
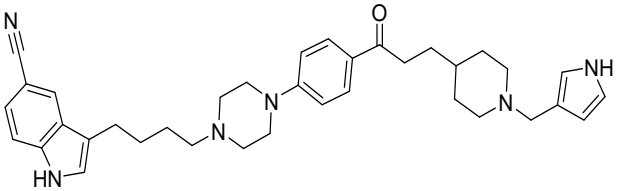
Table S1. Compound structure and activity values

Comp.	Structure	IC_{50}(nM)	pIC_{50}
1		1.51	8.82
2		2.43	8.61
3*		3.52	8.45
4		7.75	8.11
5*		2.42	8.62
6		2.28	8.64
7		3.28	8.48
8		3.71	8.43

9*		11.18	7.95
10*		392.8	6.41
11		123.5	6.91
12		366.1	6.44
13*		249.2	6.60
14*		40.4	7.39
15		76.5	7.12
16		8.95	8.05

17		267	6.57
18		1138	5.94
19		12.0	7.92
20		10.9	7.96
21		32.4	7.49
22		27.0	7.57
23		91.5	7.04
24		18.3	7.74

25		294	6.53
26		644	6.19
27*		7.98	8.10
28		3.01	8.52
29		3.94	8.40

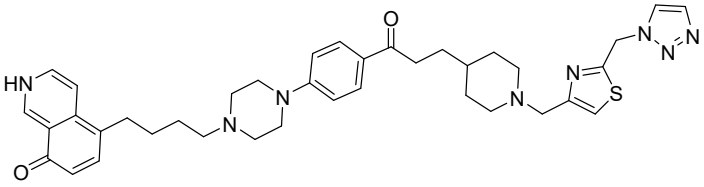
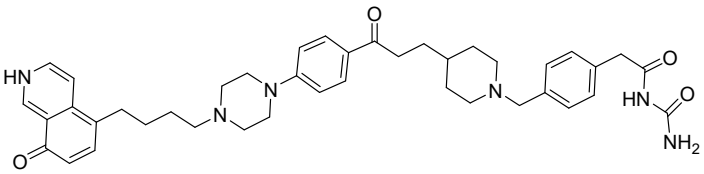
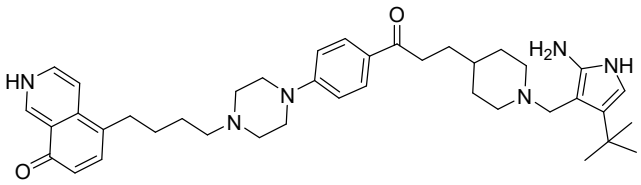
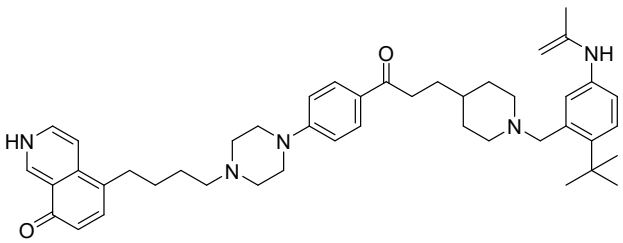
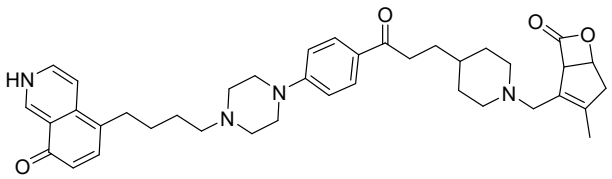
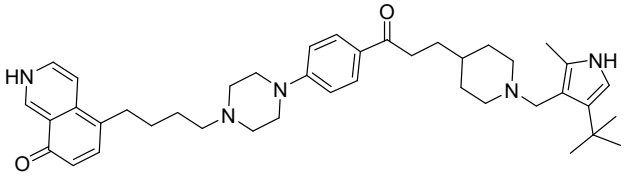
* selected as test set

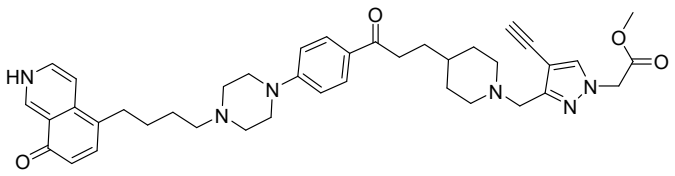
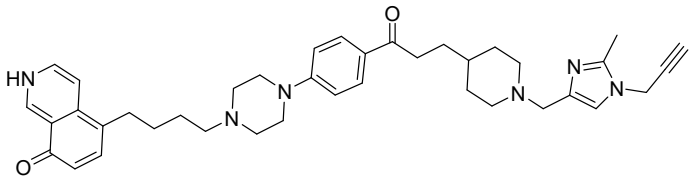
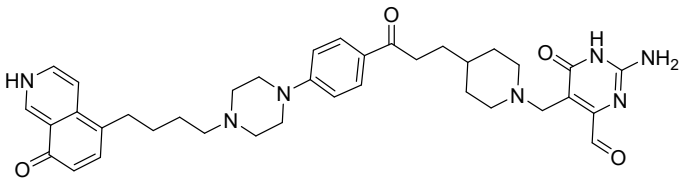
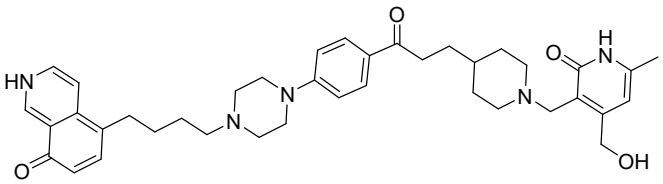
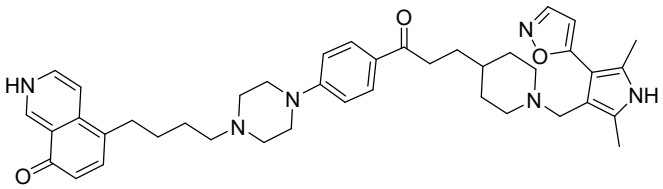
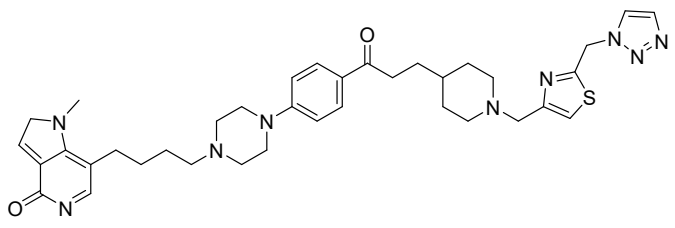
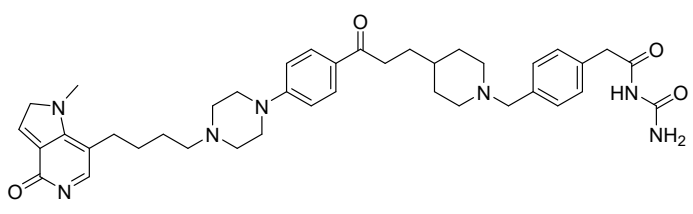
Table S2. Actual and predicted activity of compounds in training and test sets

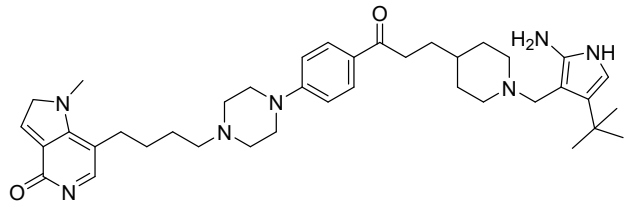
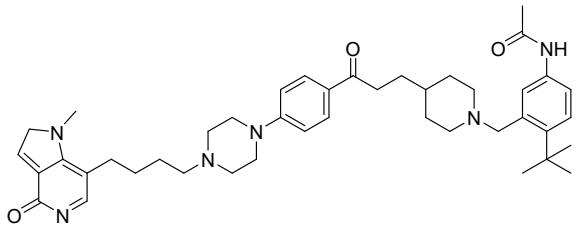
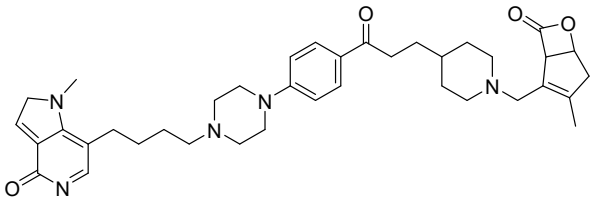
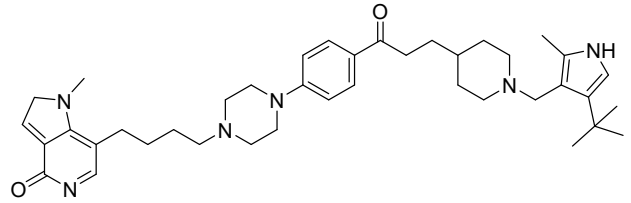
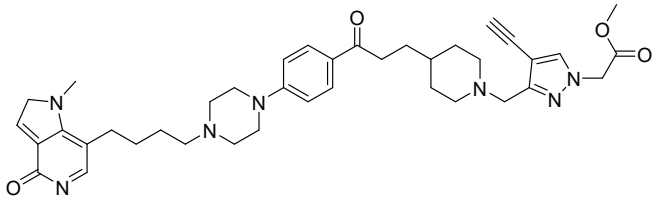
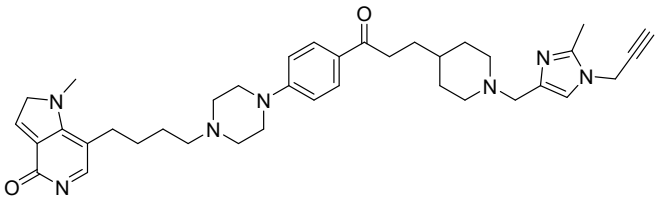
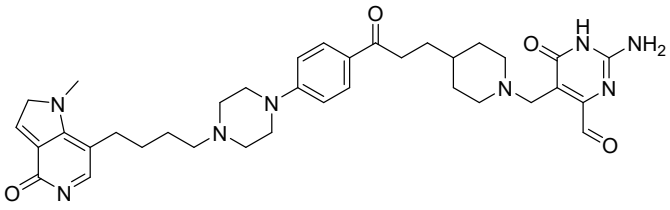
NO.	Actual pIC_{50}	Topomer CoMFA model			
		Predicted pIC_{50}	Residual	Fragment contribution	
				R1	R2
1	8.82	8.89	-0.07	0.05	1.70
2	8.61	8.59	0.02	-0.25	1.70
3*	8.45	8.46	-0.01	-0.38	1.70
4	8.11	8.19	-0.08	-0.65	1.70
5*	8.62	8.74	-0.12	-0.11	1.70
6	8.64	8.54	0.10	-0.30	1.70
7	8.48	8.56	-0.08	-0.28	1.70
8	8.43	8.41	0.02	-0.43	1.70
9*	7.95	8.28	-0.33	-0.56	1.70
10*	6.41	6.45	-0.04	-0.86	1.70
11	6.91	7.00	-0.09	-0.86	0.72
12	6.44	6.44	0.00	-0.86	0.16
13*	6.60	6.99	-0.39	-0.86	0.71
14*	7.39	6.90	0.49	-0.86	0.62
15	7.12	7.17	-0.05	-0.86	0.89
16	8.05	8.16	-0.11	-0.86	1.89
17	6.57	6.55	0.02	-0.86	0.27
18	5.94	5.87	0.07	-0.86	-0.41
19	7.92	7.80	0.12	-0.86	1.53
20	7.96	7.86	0.10	-0.86	1.58
21	7.49	7.47	0.02	-0.86	1.19
22	7.57	7.48	0.09	-0.86	1.20
23	7.04	7.23	-0.19	-0.86	0.96
24	7.74	7.63	0.11	-0.86	1.36
25	6.53	6.54	-0.01	-0.86	0.26
26	6.19	6.22	-0.03	-0.86	-0.05
27*	8.10	8.04	0.06	-0.86	1.76
28	8.52	8.46	0.06	-0.86	2.18
29	8.40	8.40	0.00	-0.86	2.12

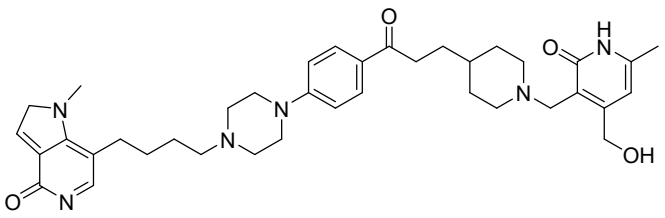
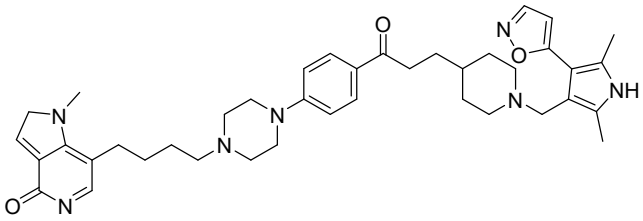
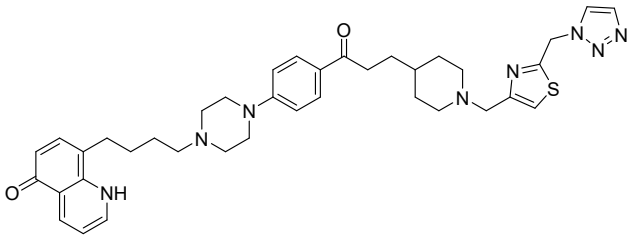
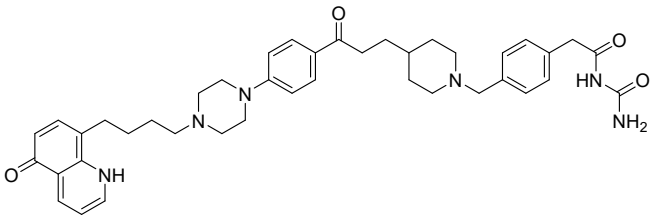
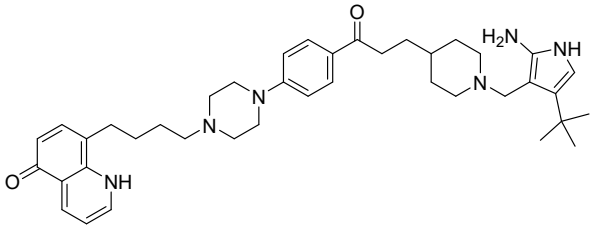
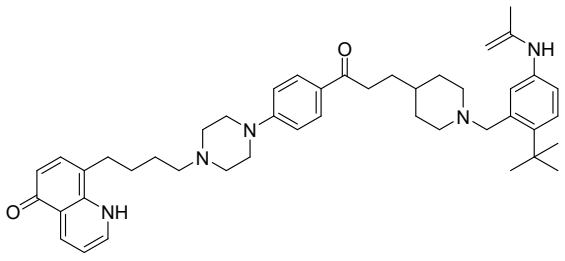
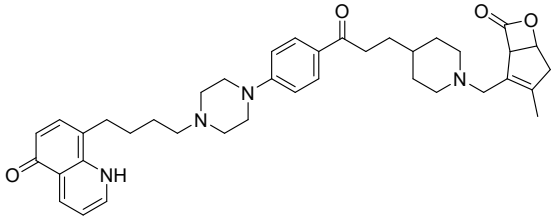
* were selected as test set

Table S3. Structures and predicted pIC_{50} values of newly designed molecules

Comp.	Structure	pIC_{50}(Pred)	R1	R2
N01		10.23	0.76	2.33
N02		10.79	0.76	2.89
N03		11.16	0.76	3.27
N04		10.75	0.76	2.85
N05		11.13	0.76	3.24
N06		10.67	0.76	2.77

N07		10.17	0.76	2.28
N08		10.18	0.76	2,28
N09		11.00	0.76	3.10
N10		10.99	0.76	3.09
N11		10.60	0.76	2.70
N12		10.21	0.74	2.33
N13		10.77	0.74	2.89

N14		11.14	0.74	3.27
N15		10.73	0.74	2.85
N16		10.81	0.43	3.24
N17		10.64	0.74	2.77
N18		10.13	0.71	2.28
N19		10.16	0.74	2.28
N20		10.98	0.74	3.10

N21		10.97	0.74	3.09
N22		10.57	0.74	2.70
N23		10.14	0.67	2.33
N24		10.70	0.67	2.89
N25		11.07	0.67	3.27
N26		9.67	0.67	1.87
N27		11.04	0.67	3.24

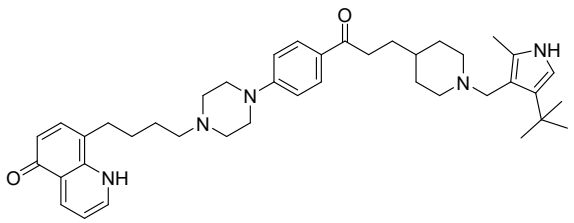
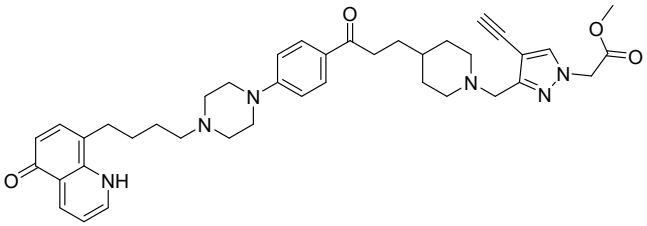
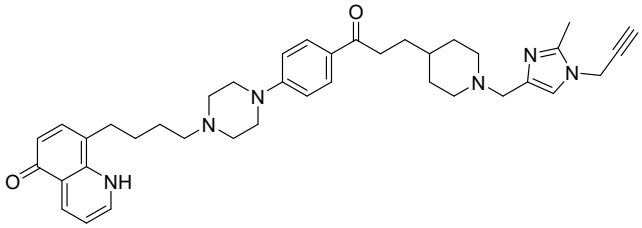
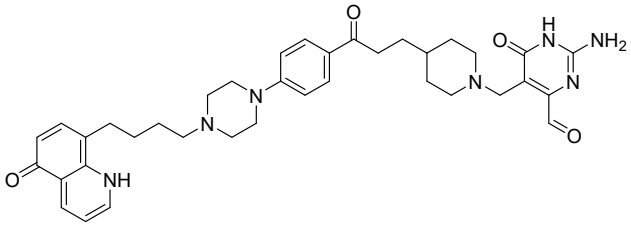
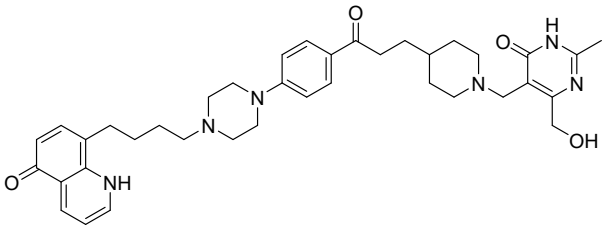
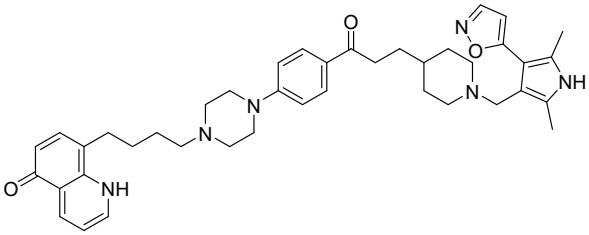
N28		10.58	0.67	2.77
N29		10.08	0.67	2.28
N30		10.09	0.67	2.28
N31		10.91	0.67	3.10
N32		10.90	0.67	3.09
N33		10.51	0.67	2.70

Table S4. Docking scores and amino acid interactions of newly designed compounds in Autodock Vina

Comp.	Binding energy score (Kcal/mol)	Hydrogen bond interacting residues	Hydrophobic interactions
N01	-11.7	Ser293、Tyr124	Tyr337、Trp286
N02	-12.0	Ala343、Phe346、Val340、Tyr72、Tyr124	His447、Trp286、Tyr337、Phe338
N03	-11.4	Ser125、Ser293、Tyr124	Trp86、Trp286、Tyr337、Gly121、Phe338
N04	-11.6	Ser125、Tyr124	Tyr337、Trp86、Trp286、Gly121、Phe338
N05	-12.2	Ser203、Ser293、Phe295	Trp286、Tyr124、Tyr337、Tyr341、Phe297、Phe338
N06	-11.2	Ser125、Trp286	Trp86、Phe338、Tyr337、Leu289
N07	-11.6	Tyr72、Tyr124	Leu289、Tyr337、Tyr341、Phe338、Trp286、His447、Val294
N08	-10.0	Tyr72、Tyr124、Tyr133	Phe338、His447、Tyr337、Trp286
N09	-11.1	Tyr72、Tyr124、Ser125	Trp86、Trp286、Tyr337
N10	-11.3	Gln291、Ser293、Tyr72	Tyr337、Tyr341、Phe338、Tyr124、Trp86、Trp286、His447
N11	-12.5	Gln291、Ser293、Tyr341	Tyr124、Trp86、Trp286、Tyr337、Phe338
N12	-11.3	Tyr72、Tyr124	Trp286、Phe338、Tyr337、His447
N13	-10.6	Tyr133、Tyr341、Ser203、Glu202	Trp286、Leu289、Phe338
N14	-10.9	Glu202、Tyr133	Trp86、Trp286、Tyr341、Phe338
N15	-12.2	Ser125、Ser293	Trp86、Trp286、Leu289、Phe338、Tyr337、Tyr341
N16	-11.6	Ser125、Ser293	Trp86、Trp286、Leu289、Phe338、His287
N17	-10.8	Tyr124	Phe338、Tyr337、His447
N18	-10.7	Trp286、Tyr124	Leu76、Tyr337、Tyr341、Trp286、His447、Phe338
N19	-10.4	Tyr124	Trp86、Trp286、Phe338、Tyr337
N20	-10.8	Trp286、Tyr124、Ser293	Tyr337、Tyr341、Phe338、His447
N21	-11.3	Tyr72、Tyr124、Ser125、Tyr341	Trp86、Trp286、Tyr337、Gly121
N22	-11.4	Gln291、Ser293、Tyr124	Trp286、Tyr337、Tyr341、Phe338、His447

N23	-11.3	Tyr124	Gly120、Tyr72、Tyr337、Trp286、Phe338、Tyr341、Val294
N24	-12.5	Ans87、Ser293	Leu289、Trp86、Trp286、Tyr337、Tyr341、Phe338
N25	-11.7	Ans87、Ser293、Leu289	Trp86、Trp286、Phe338、Tyr337、Tyr341、His447
N26	-11.4	Phe296、Trp286	Tyr337、Trp86、Phe338
N27	-12.3	Trp86、Tyr124、Tyr72、Phe295	Trp286、Tyr337、Phe338
N28	-12.7	Tyr124、Ser125、Ser293	Leu289、Tyr337、Trp86、Phe338、Trp286
N29	-11.2	Asp74、Trp86	Tyr124、Tyr337、Tyr341、Phe338、Trp286、His447
N30	-9.6	Tyr133、Gly120、Ser293、Arg296、His447	Trp86、Trp286、Tyr72、Tyr341、Phe338
N31	-12.0	Tyr133、Ser125、Ser293	Trp86、Trp286、Tyr337
N32	-11.5	Tyr124、Ser125、Ser293、Trp286	Trp86、Phe338
N33	-12.6	Tyr124、Gly120、Gln291、Ser293	Trp86、Trp286、Tyr337、Phe338、Leu289

Table S5. Prediction of ADMET properties of newly designed compounds

Comp.	Absorption			Distribution	Metabolism		Excretion	Toxicity
	HIA(%)	OB(%)	Caco2(nm/sec)	PPB(%)	CYP2D6 substrate	CYP3A4 substrate	Total Clearance(ml/min/kg)	AMES toxicity
N01	99.29	61.43	83.60	70.29	-	+	6.012	-
N02	97.18	54.29	84.25	70.56	-	+	5.527	-
N03	99.00	55.71	83.52	79.13	-	+	6.172	-
N04	93.16	52.86	83.06	88.23	-	+	4.177	-
N05	98.11	55.71	82.99	77.01	-	+	5.699	-
N06	98.66	50.00	82.31	90.94	-	+	5.110	-
N07	97.25	60.00	83.50	85.29	-	+	7.480	-
N08	99.71	52.86	83.00	90.60	-	+	4.674	-
N09	96.96	68.57	85.05	57.13	-	+	5.347	-
N10	92.78	52.86	84.18	62.61	-	+	4.794	-
N11	98.41	57.14	83.24	95.93	-	+	3.686	-
N12	96.80	60.00	83.31	66.06	-	+	4.285	-
N13	96.94	57.14	83.86	64.88	-	+	3.081	-
N14	97.98	57.14	83.17	69.34	-	+	5.261	-
N15	95.37	54.29	82.64	81.40	-	+	2.665	-
N16	92.28	51.43	81.85	81.16	-	+	4.816	-
N17	98.19	55.71	81.97	81.20	-	+	4.283	-
N18	91.80	60.00	83.53	77.01	-	+	6.646	-
N19	98.89	50.00	82.76	84.62	-	+	3.035	-
N20	97.94	65.71	83.45	60.77	-	+	4.089	-
N21	95.53	50.00	83.12	62.68	-	+	3.776	-
N22	97.29	54.29	83.26	91.43	-	+	3.019	-

N23	97.99	58.57	84.73	91.86	-	+	6.017	-
N24	98.67	65.71	84.65	60.95	-	+	5.587	-
N25	98.60	58.57	84.43	57.99	-	+	5.778	-
N26	98.47	57.14	83.82	66.61	-	+	6.316	-
N27	97.80	54.29	82.83	79.56	-	+	3.923	-
N28	97.65	57.14	80.86	70.57	-	+	5.405	-
N29	96.46	62.86	84.14	78.46	-	+	7.087	-
N30	98.99	52.86	83.70	81.03	-	+	4.686	-
N31	98.58	72.86	85.02	55.67	-	+	4.935	-
N32	98.06	54.29	84.58	58.89	-	+	5.072	-
N33	98.66	52.86	84.00	83.87	-	+	4.132	-

Classification: (HIA%) 0–20% (poorly absorbed), 20–70% (moderately absorbed), 70–100% (well absorbed); (HOB%) > 50 (moderately utilised); caco2 cell permeability: < 4 (low permeability), 4–70 (moderate permeability), and >70 (higher permeability); plasma protein binding. > 0.9 (strongly bound), and <0.9 (weakly bound). (Total clearance). > 15 mL min^{-1} kg^{-1}: high, 5 mL min^{-1} kg^{-1} < Cl < 15 mL min^{-1} kg^{-1}: moderate, < 5 min^{-1} kg^{-1}: low.