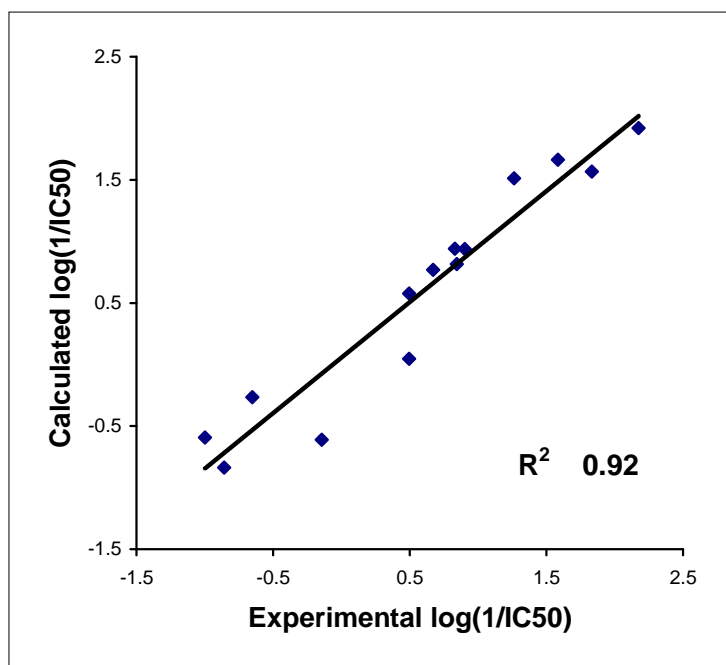


hERG QSAR for Cardiac Toxicity Assessment



This hERG QSAR model, developed by SciScout LLC using Partial Least Squares (PLS) and a diverse set of known hERG potassium channel blockers, uses a combination of WHIM (Weighted Holistic Invariant Molecular, *3D descriptors*) and functional group descriptors to accurately predict *in vitro* IC₅₀ values of virtual compounds for assessment of QT interval prolongation potential based on molecular structure.

$$\text{Calculated } \log(1/\text{IC}_{50}) = w_1(S(|q_i| \times |\text{WHIM Descriptors}_i|) + b_1) + w_2(S(|g_i| \times |\text{Functional Group Descriptors}_i|) + b_2)$$

hERG QSAR: Comparison of Calculated log (1/IC₅₀) versus Experimental log (1/IC₅₀)

Compound Name	Experimental <i>In Vitro</i> IC ₅₀	Experimental <i>In Vitro</i> log (1/IC ₅₀)	Calculated <i>In Vitro</i> log (1/IC ₅₀)	%Accuracy Relative to Experimental
amitriptyline	10	-1.000	-0.592	59.2
cocaine	7.2	-0.857	-0.837	97.7
n-desmethyl clozapine	4.49	-0.652	-0.265	40.6
desipramine	1.39	-0.143	-0.611	427.0
clozapine	0.32	0.495	0.046	9.2
mesoridazine	0.32	0.495	0.578	116.7
terfenadine	0.213	0.672	0.768	114.4
risperidone	0.148	0.830	0.939	113.2
verapamil	0.143	0.845	0.817	96.7
ziprasidone	0.125	0.903	0.937	103.7
pimozide	0.0546	1.263	1.513	119.8
haloperidol	0.026	1.585	1.663	104.9
sertindole	0.0147	1.833	1.567	85.5
cisapride	0.0067	2.174	1.920	88.3

Percentage of Compounds with %Accuracy of (100 ± 20)% = 71.4

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DRAGON[®]script Functional Descriptors, 14 hERG Compounds, Constant & Near-Constant Variables Excluded

Name	In Vitro IC50	log (1/IC50)	nCp	nCs	nCt	nCq	nCrH2	nCrHR	nCrR2	nCaH	nCaR	nCOOR	nCONR2	nCONN	nNHR	nNR2	nOH	nOHs	nOHt	nROR	nRORPh	nRSR	nPhX	nHDon	nHAcc
amitriptyline	10	-1.000	2	2	0	0	2	0	0	8	5	0	0	0	0	1	0	0	0	0	0	0	0	0	1
cocaine	7.2	-0.857	2	0	0	0	3	4	0	5	1	1	0	0	0	1	0	0	0	0	0	0	0	2	5
n-desmethyl clozapine	4.49	-0.652	0	0	0	0	4	0	0	7	6	0	0	0	2	1	0	0	0	0	0	0	1	2	4
desipramine	1.39	-0.143	1	3	0	0	2	0	0	8	4	0	0	0	1	1	0	0	0	0	0	0	0	1	2
clozapine	0.32	0.495	1	0	0	0	4	0	0	7	6	0	0	0	1	2	0	0	0	0	0	0	1	1	4
mesoridazine	0.32	0.495	2	2	0	0	4	1	0	7	5	0	0	0	0	2	0	0	0	0	0	1	0	0	3
terfenadine	0.213	0.672	3	3	1	2	4	1	0	14	4	0	0	0	0	1	2	1	1	0	0	0	0	4	3
risperidone	0.148	0.830	1	2	0	0	8	1	0	3	8	0	1	0	0	1	0	0	0	0	0	0	1	0	7
verapamil	0.143	0.845	7	5	1	1	0	0	0	6	6	0	0	0	0	1	0	0	0	0	4	0	0	0	6
ziprasidone	0.125	0.903	0	2	0	0	5	0	0	6	7	0	0	0	0	2	0	0	0	0	0	0	1	1	5
pimozide	0.0546	1.263	0	3	1	0	4	1	0	12	6	0	0	1	0	1	0	0	0	0	0	0	2	0	6
haloperidol	0.026	1.585	0	3	0	0	4	0	1	8	4	0	0	0	0	1	1	0	1	0	0	0	2	3	4
sertindole	0.0147	1.833	0	2	0	0	6	1	0	8	6	0	0	1	0	2	0	0	0	0	0	0	2	0	6
cisapride	0.0067	2.174	2	3	0	0	3	2	0	6	6	0	0	0	0	1	0	0	0	1	2	0	2	2	8

Regression Coefficients: -0.015020015 0.12264599 0.01833 0.015772 0.052611 0.027009 0.522594 0.006303 0.050556 -0.45053 -0.16034 0.337976 -0.28148 0.396385 0.119143 0.018231 0.292947 0.77284 0.090353 0.250349 0.308787 0.040786 0.126908
Y-intercept: -1.7225288

Weight Coefficient: 0.5 R-squared = 0.9502012

DRAGON°script WHIM Descriptors, 14 hERG Compounds, Constant & Near-Constant Variables Excluded

Name	In Vitro IC50	log (1/IC50)	L1u	L1m	L1v	L1e	L1p	L1s	Tu	Tm	Tv	Te	Tp	Ts
amitriptyline	10	-1.000	9.905	8.042	8.595	9.866	8.788	7.717	15.194	12.31	13.311	15.106	13.619	11.883
cocaine	7.2	-0.857	10.905	9.064	10.666	10.56	10.877	8.654	15.657	12.31	14.387	15.238	14.778	11.835
n-desmethyl clozapine	4.49	-0.652	9.446	9.774	8.579	9.397	8.87	8.25	15.518	14.762	14.131	15.458	14.636	13.073
desipramine	1.39	-0.143	9.089	6.997	7.738	9.017	7.964	6.692	14.588	11.544	12.752	14.453	13.092	11.19
clozapine	0.32	0.495	11.142	11.072	10.181	11.067	10.483	9.655	16.694	16.155	15.479	16.632	15.985	14.466
mesoridazine	0.32	0.495	9.97	9.944	9.728	9.959	9.894	9.846	18.14	17.57	17.123	18.174	17.489	17.526
terfenadine	0.213	0.672	19.532	19.438	19.51	19.512	19.538	20.137	27.442	25.7	26.317	27.39	26.527	26.21
risperidone	0.148	0.830	26.742	29.79	27.294	27.29	26.981	31.317	30.231	32.108	30.02	30.714	29.847	33.555
verapamil	0.143	0.845	24.1	24.82	23.179	24.489	23.159	25.242	30.479	29.582	28.585	30.777	28.75	30.02
ziprasidone	0.125	0.903	24.748	27.367	25.68	25.117	25.593	29.318	27.786	30.042	28.176	28.147	28.251	31.573
pimozide	0.0546	1.263	24.057	27.076	24.849	24.534	24.512	28.881	28.867	31.743	29.064	29.471	28.753	34.097
haloperidol	0.026	1.585	23.603	31.066	25.752	24.404	25.504	31.174	26.313	33.234	27.914	27.099	27.787	33.179
sertindole	0.0147	1.833	25.354	25.881	24.379	25.836	24.142	27.986	29.696	31.724	28.714	30.356	28.598	33.403
cisapride	0.0067	2.174	22.262	23.926	22.459	22.778	22.064	27.25	28.636	29.326	28.027	29.089	27.785	32.372

Regression Coefficients: -0.070637815 -0.002666397 -0.06084 -0.04981 -0.07424 0.037901 -0.01425 0.110157 0.023502 0.012255 0.013457 0.120665
Y-intercept: -1.7679948

Weight Coefficient: 0.5 R-squared = 0.852