

## **Supplementary Material**

**Assessing and Predicting Drug-Induced Anticholinergic Risks: An Integrated  
Computational Approach**

## QSAR Model for Overall ADE Risk Prediction

MLR Regression Statistics:

S.D.	R-Squared	F(8.0,16.0)	P
0.0893	0.8336	10.0	6.014e-05

MLR Regression Coefficients and T-Values:

Variable	Coefficient	Std. Err.	T
Intercept	3.4186e+00	5.6869e-01	6.0113
volume	-4.5464e-03	9.0792e-04	5.0075
accptHB	3.7660e-01	8.0138e-02	4.6995
QPpolrz	3.7735e-02	1.5051e-02	2.5071
QPPCaco	-2.4387e-04	4.5767e-05	5.3285
PSA	-2.1764e-02	3.8609e-03	5.6369
CNS	-4.3910e-01	9.9107e-02	4.4306
QPlogKhsa	1.0647e+00	2.4502e-01	4.3455
ATS	-6.8080e-03	1.6991e-02	0.4007

Cross Validation leave-1-out Results Over 500 Cycles

q <sup>2</sup>	RMS
0.6350	0.1094

Predicted Results:

	ADE	Prediction
1	0.2449	0.2613
2	0.2050	0.2269
3	0.0580	0.0597
4	0.0203	0.0496
5	0.0443	0.0536
6	0.0920	0.0808
7	0.3067	0.4924
8	0.3995	0.4397
9	0.1812	0.2199
10	0.3501	0.4047
11	0.4308	0.3603
12	0.2278	0.2192
13	0.2645	0.3003
14	0.7273	0.7586
15	0.1387	0.1432
16	0.1543	0.1530
17	0.1129	0.0713
18	0.1067	0.1103
19	0.2576	0.1319
20	0.0743	0.1218
21	0.2245	0.1765
22	0.3011	0.0688
23	0.1305	0.1657
24	0.0951	0.0715
25	0.4960	0.5031

RMS 0.0715

## QSAR Model for M2 Receptor Subtype Specific Tachycardia Risks Prediction

MLR Regression Statistics:

S.D.	R-Squared	F(8.0,16.0)	P
0.9049	0.6756	4.2	7.342e-03

MLR Regression Coefficients and T-Values:

Variable	Coefficient	Std. Err.	T
Intercept	1.8798e+01	5.7595e+00	3.2638
volume	-2.7489e-02	9.3569e-03	2.9378
accptHB	2.5330e+00	8.0712e-01	3.1384
QPpolrz	1.5014e-01	1.5769e-01	0.9521
QPPCaco	-1.2016e-03	4.5880e-04	2.6190
PSA	-9.2798e-02	3.9071e-02	2.3751
CNS	-1.8692e+00	9.8024e-01	1.9069
QPlogKhsa	8.7303e+00	2.4858e+00	3.5120
M2	-2.0588e-01	7.9704e-01	0.2583

Cross Validation leave-1-out Results Over 500 Cycles

q <sup>2</sup>	RMS
0.2864	1.2757

Predicted Results:

	Tachycardia	Prediction
1	1.7982	1.9703
2	1.4119	1.1620
3	0.3971	0.1415
4	-0.0993	0.0990
5	0.2418	0.0999
6	0.1483	0.2697
7	1.8223	3.8799
8	2.3141	2.5209
9	1.2079	1.9685
10	2.7498	3.8099
11	3.2106	3.9140
12	2.1043	1.4592
13	2.3036	2.4788
14	4.2419	3.1312
15	1.5700	1.0782
16	0.8103	1.2951
17	0.9425	0.4199
18	0.5431	0.4203
19	1.6383	0.5073
20	0.4398	0.4792
21	1.5460	1.0486
22	1.7526	0.3073
23	0.8639	0.9009
24	0.3371	0.3584
25	2.7128	3.2891

RMS 0.7239

## Adsorption and Distribution Parameter Definitions

**volume** - Total solvent-accessible volume in cubic angstroms using a probe with a 1.4 Å radius. 500.0 – 2000.0.

**accptHB** - Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution. Values are averages taken over a number of configurations, 2.0 – 20.0.

**QPpolrz** - Predicted polarizability in cubic angstroms. 13.0 – 70.0.

**QPPCaco** - Predicted apparent Caco-2 cell permeability in nm/sec. Caco-2 cells are a model for the gut-blood barrier. <25 poor, >500 great.

**PSA** - Van der Waals surface area of polar nitrogen and oxygen atoms and carbonyl carbon atoms. 7.0 – 200.0.

**CNS** - Predicted central nervous system activity on a –2 (inactive) to +2 (active) scale. –2 to +2.

**QPlogKhsa** - Prediction of binding to human serum albumin. –1.5 – 1.5.

Table S1. Parameters used in the QSAR models.

Drug	volume	accptHB	QPpolrz	QPPCaco	PSA	CNS	QPlogKhsa	M2	ATS	ADE	Tachycardia
Amitriptyline	1000.87	2	34.818	2409.037	4.935	2	0.861	1	5	0.261278	1.970250877
Imipramine	1008.659	2.5	34.425	2285.564	7.008	2	0.708	1	5	0.226893	1.16196066
Brompheniramine	951.545	3	31.319	2144.512	14.401	2	0.366	0.43	3.11	0.059741	0.141500628
Carbinoxamine	995.114	4.7	32.55	1833.004	23.882	2	-0.005	0.65	3.25	0.049562	0.098988995
Chlorpheniramine	942.788	3	30.975	2144.569	14.4	2	0.34	1	5	0.053644	0.099911521
Diphenhydramine	952.578	3.7	31.4	2266.311	11.817	2	0.139	1	5	0.080826	0.269693488
Benztropine	1064.23	3.7	36.995	2206.8125	9.005	2	0.548	1	5	0.492372	3.879938204
Trihexyphenidyl	1080.575	2.75	34.759	1436.145	21.074	1	0.778	1	5	0.439721	2.520863805
Chlorpromazine	986.932	2.5	33.056	2439.532	5.413	2	0.644	1	5	0.219905	1.96849806
Haloperidol	1182.367	4.75	40.017	621.387	48.905	1	0.647	0.39	3.78	0.404702	3.809857219
Perphenazine	1248.073	6.2	41.661	157	36.479	2	0.485	0.78	3.9	0.360327	3.91397275
Risperidone	1302.939	7.5	45.503	344.703	70.564	1	0.267	1	5	0.219176	1.459168537
Thioridazine	1205.652	3	42.097	2174.905	7.745	2	1.146	1	5	0.300272	2.478849408
Trifluoperazine	1193.702	4.5	41.136	529.451	10.741	2	0.71	0.7	3.83	0.758583	3.1311782
Alprazolam	929.865	3	33.562	1896.1	50.144	1	0.515	0	0.6	0.14316	1.078197909
Clorazepate	893.072	3.5	31.591	69.655	101.1	-1	0.071	0.34	1.7	0.152955	1.295072344
Diazepam	886.914	4	31.878	2677.188	46.321	1	0.123	0.4	2	0.071299	0.419851718
Atropine	964.6708	4.7	30.58375	453.4595	55.69775	1	-0.051	1	5	0.110323	0.420257806
Dicyclomine	1140.826	4	35.649	1482.264	29.197	1	0.605	1	5	0.131856	0.507304269
Hyoscyamine	973.172	4.7	30.891	441.2675	57.2995	1	-0.026	1	5	0.12182	0.47921721
Loperamide	1478.331	5.75	52.584	594.462	44.257	1	0.884	0.49	2.45	0.176487	1.048567097
Promethazine	935.069	2.5	32.126	2096.845	7.678	2	0.536	1	5	0.068759	0.30730484
Ranitidine	1085.084	6	31.887	194.381	78.44	0	-0.051	0.65	1.3	0.16574	0.900897948
Orphenadrine	993.702	3.7	32.754	2115.505	12.939	2	0.258	1	5	0.071464	0.358387866
Fentanyl	1193.35	5	41.056	1082.641	33.745	1	0.49	0.42	1.99	0.503057	3.289068717