Supplementary Information

Hybrid 2D/3D-QSAR Study of Methylamine Derivatives as Dopamine Transporter Inhibitors

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Table S1. Statistical parameters used in internal validation

Definition	Parameter	Equation
Determination coefficient[a]	R^2	$R^2 = 1 - \frac{\sum(y_{ei} - y_{ci})^2}{\sum(y_{ei} - \bar{y}_e)^2}$
F-test (with 95% confidence, $\alpha = 0.05$)[b]	F	$F = \frac{\sum(y_{ci} - \bar{y}_e)^2/p}{\sum(y_{ei} - y_{ci})^2/(n - p - 1)}$
Cross-validation determination coefficient[c,d]	Q^2_{LOO}	$Q^2_{LOO} = 1 - \frac{\sum(y_{ei} - y_{vi})^2}{\sum(y_{ei} - \bar{y}_e)^2}$
Root mean square error of calibration[a]	RMSEC	$RMSEC = \sqrt{\frac{\sum(y_{ei} - y_{ci})^2}{n - p - 1}}$
Root mean square error of cross-validation	RMSECV	$RMSECV = \sqrt{\frac{\sum(y_{ei} - y_{vi})^2}{n}}$

[a]Adjustment quality; [b]significance; [c]cross-validation, if n = 1, and leave-N-out robustness test, if n > 1; [d]internal prediction quality; i = summation index; y_e = experimental values of biological activity; y_c = calculated values of biological activity; y_v = calculated values of biological activity from an internal validation (LOO, LNO or **y**-randomization); $\bar{y}_e$= average value of y_e; n = number of samples (training set); p = number of latent variables.

Table S2. Statistical parameters used in external validation

Definition	Parameter	Equation
Determination coefficient of external validation	R^2_{ext}	$R^2_{ext} = \left(\frac{\sum_{i=1}^{n_{EXT}} (y_i - \bar{y})(\hat{y}_i - \bar{\hat{y}})}{\sqrt{\sum_{i=1}^{n_{EXT}} (y_i - \bar{y})^2 \sum_{i=1}^{n_{EXT}} (\hat{y}_i - \bar{\hat{y}})^2}} \right)^2 \approx 1$
Slope of the regression lines	k, k'	$k = \frac{\sum_{i=1}^{n_{EXT}} y_i \hat{y}_i}{\sum_{i=1}^{n_{EXT}} \hat{y}_i^2} \approx 1$ $k' = \frac{\sum_{i=1}^{n_{EXT}} y_i \hat{y}_i}{\sum_{i=1}^{n_{EXT}} y_i^2} \approx 1$
Correlation coefficient (r^2) of regression through origin	$R_0^2, R_0'^2$	$R_0^2 = 1 - \frac{\sum_{i=1}^{n_{EXT}} (\hat{y}_i - \hat{y}_i^{r0})^2}{\sum_{i=1}^{n_{EXT}} (\hat{y}_i - \bar{\hat{y}})^2} \approx R^2$ $R_0'^2 = 1 - \frac{\sum_{i=1}^{n_{EXT}} (y_i - \hat{y}_i^{r0'})^2}{\sum_{i=1}^{n_{EXT}} (y_i - \bar{y})^2} \approx R^2$
Modified r^2 [a]	r_m^2	$r_m^2 = r^2 \left(1 - \sqrt{r^2 - r_0^2}\right) > 0.5$
Average modified r^2 [a]	$\bar{r_m^2}$	$\bar{r_m^2} = \frac{r_m^2 + r_m'^2}{2}$
Modified r^2 variation[a]	Δr_m^2	$\Delta r_m^2 = \lvert r_m^2 - r_m'^2 \rvert < 0.2$
Root mean square error of prediction	RMSEP	$RMSEP = \sqrt{\frac{\sum_{i=1}^{n_{EXT}} (y_i - \hat{y}_i)^2}{n_{EXT}}}$
Mean absolute error	MAE	$MAE = \frac{\sum_{i=1}^{n_{EXT}} \lvert y_i - \hat{y}_i \rvert}{n_{EXT}}$

[a]Used with scaled values, as recommended by Roy *et al*.[1] EXT = external set; y_i = experimental data values; $\hat{y}_i$ = predicted data values; $\bar{y}$ = average of the experimental data values; $\bar{\hat{y}}$ = average of the predicted data values; $r^2$and r_0^2 = determination coefficients of the regression function; r_m^2 = modified correlation coefficient obtained from regression with observed and predicted data; $r_m'^2$ = modified correlation coefficient obtained from regression with the axes swapped.

Table S3. Predicted values in the LOO cross-validation step for the three models obtained

Compound	pIC_{50} real	pIC_{50} pred		
		Model 1	Model 2	Model 3
1	7.678	7.612	7.342	7.352
2	6.824	6.577	7.072	7.053
3	8.398	8.443	8.337	8.113
4	8.699	8.500	8.573	8.512
5	9.000	9.246	8.718	8.962
6	9.000	9.012	9.361	9.052
7	9.000	8.901	9.479	9.254
8	8.699	8.387	8.539	8.530
9	7.921	7.901	8.433	8.253
10	8.699	8.962	8.928	9.267
11	9.000	8.738	9.029	9.208
12	7.125	6.639	7.090	7.004
13	8.046	8.367	7.771	7.839
14	7.086	6.733	7.713	7.134
15	7.585	7.567	7.830	7.647
16	6.403	6.116	6.403	6.381
17	7.377	7.558	7.273	7.411
18	6.054	6.905	5.694	6.225
19	7.770	8.004	7.666	7.790
20	7.959	7.910	7.600	7.741
21	6.770	6.572	6.497	6.451
22	7.244	7.277	6.860	7.132
23	5.439	5.661	5.585	5.586
24	6.263	6.701	6.457	6.683
25	6.903	6.450	6.987	6.797
26	6.416	6.538	6.425	6.510
27	6.204	6.066	6.799	6.545
28	6.572	6.142	6.688	6.097
29	5.219	5.516	5.395	5.712
30	5.750	5.765	5.595	6.113
31	9.000	7.937	8.055	7.932
32	7.081	6.881	7.072	6.935
33	7.046	7.295	7.288	7.213
34	8.523	8.998	8.484	8.094
35	6.002	6.121	6.332	5.670
36	6.131	6.729	5.872	5.859

pIC50: negative logarithmic of concentration required to inhibit dopamine reuptake by 50%.

Table S4. Descriptors selected for model 1. All descriptors were generated using Dragon 6

Compound	TDB06p	Mor09s	RDF095m	Eig06_EA(ri)	Mor10u	SPAM	CATS2D_07_DL	Mor08p
1	0.365	1.086	0.000	1.000	–0.347	0.412	1	–0.49
2	0.327	0.570	0.000	1.000	–0.144	0.391	1	–0.65
3	0.367	0.392	0.035	1.191	–0.624	0.423	1	–0.566
4	0.381	1.075	0.046	1.196	–0.712	0.387	1	–0.718
5	0.379	1.777	0.000	1.194	–0.835	0.385	0	–0.693
6	0.372	1.569	0.215	1.194	–0.58	0.389	0	–0.685
7	0.364	2.480	0.496	1.195	–0.818	0.367	0	–0.733
8	0.383	2.071	0.000	1.197	–0.341	0.359	0	–0.547
9	0.359	1.240	0.156	1.294	–0.074	0.362	0	–0.502
10	0.369	–0.221	0.003	1.201	–1.327	0.354	0	–0.923
11	0.327	1.584	0.221	1.359	–1.212	0.365	0	–0.936
12	0.334	2.318	0.133	1.196	0.865	0.384	1	–0.677
13	0.379	2.025	0.000	1.157	0.687	0.379	0	–0.700
14	0.355	3.030	0.000	0.849	0.335	0.386	0	–0.232
15	0.342	0.338	0.000	1.000	–0.374	0.370	0	–0.806
16	0.322	–0.773	0.000	1.000	–0.208	0.400	1	–0.433
17	0.354	0.834	0.000	1.095	–0.462	0.367	0	–0.468
18	0.336	–0.500	0.000	1.000	–0.176	0.394	0	–0.27
19	0.340	–1.055	0.000	1.251	–0.258	0.378	0	–0.845
20	0.353	–1.184	0.255	1.217	–0.497	0.375	0	–0.599
21	0.334	–2.888	0.131	1.000	–0.112	0.403	0	–0.331
22	0.314	–1.202	0.258	1.308	–0.277	0.368	0	–0.716
23	0.289	–3.056	0.132	1.000	0.069	0.396	0	–0.404
24	0.315	–0.950	0.000	1.102	–0.463	0.357	0	–0.643
25	0.316	–1.349	0.257	1.000	–0.405	0.359	0	–0.684
26	0.317	0.033	0.000	1.000	–0.345	0.36	0	–0.602
27	0.318	–10.512	0.042	1.191	–0.513	0.368	0	–0.842
28	0.295	–11.612	3.013	1.217	–0.41	0.375	0	–0.831
29	0.282	–1.131	0.019	1.333	–0.153	0.387	2	–0.593
30	0.309	–0.947	0.077	1.350	–0.292	0.379	2	–0.436
31	0.320	–0.100	1.156	1.483	–0.663	0.373	0	–0.625
32	0.326	–0.017	0.007	1.261	–0.405	0.364	1	–0.732
33	0.349	–0.669	0.018	1.263	–0.489	0.36	1	–0.722
34	0.357	0.915	0.014	1.460	–0.783	0.346	0	–0.905
35	0.242	–1.608	3.713	1.093	0.132	0.407	1	–0.796
36	0.266	–1.692	3.965	1.124	–0.095	0.399	1	–0.634

Table S5. Selected molecular interaction field (MIF) descriptors for model 2 (C: Columb descriptors; LJ: Lenard-Jones descriptors)

Compound	-2_2_0_C	-1_0_0_C	2_0_1_C	-6_2_2_LJ	-5_2_2_LJ	-3_-1_-3_LJ	-3_0_2_LJ	-3_6_4_LJ	-2_1_3_LJ	-2_3_-2_LJ	3_-4_-4_LJ	5_-5_3_LJ	6_-3_0_LJ
1	–72.162	130.543	–110.693	–1.957	–3.099979	128.373077	40.323238	–0.802633	133.101578	140.131927	–2.156911	–1.526344	135.747147
2	–140.092	132.399	–48.536	–1.156	–1.816556	–1.230848	72.853455	–0.693878	106.748131	144.564346	–2.075556	–1.549182	136.493866
3	–72.354	130.705	–78.326	135.645	136.680939	8.086535	133.013611	–0.793834	131.428879	141.120407	–2.134984	–1.536935	136.052948
4	118.500	–381.488	–124.417	–1.976	–3.106671	131.594269	133.359009	–0.790951	132.212158	135.846619	–2.252889	–1.519641	133.458588
5	–9.365	132.049	–55.176	22.155	134.2332	128.635284	157.985931	–0.884232	133.656708	139.670517	–2.170067	–1.525184	135.693787
6	–35.526	131.466	–91.019	141.911	152.204224	124.985199	161.916779	–0.944164	133.117538	141.90094	–2.137108	–1.54312	136.12738
7	–45.063	131.754	–55.498	141.712	158.439056	131.469055	148.510544	–1.04512	139.017944	144.537201	–2.119797	–1.557022	136.437469
8	126.193	–271.077	–162.939	–2.058	3.416551	137.378052	151.295715	–0.852615	137.23378	134.990479	–2.328509	–1.52839	132.546158
9	131.873	–253.336	–210.856	–0.139	126.221298	142.169327	144.731445	–2.181191	135.153793	137.091965	–2.340841	–1.471475	131.891937
10	128.663	–125.308	–34.599	–2.703	24.584545	131.34343	144.969376	–0.782792	130.443359	136.841507	–2.310004	–1.539558	133.494003
11	128.570	–141.473	–37.830	–2.720	27.014124	146.763229	153.857468	–0.774317	129.575531	137.858963	–2.291923	–1.519118	133.558853
12	–68.012	133.825	–3.423	–1.018	–2.190987	143.322495	133.235703	–0.190141	40.694942	134.49234	–1.409997	–1.238284	23.196608
13	38.300	130.637	–36.374	–1.391	–1.477719	158.571411	133.780624	–0.752668	157.916748	138.86142	–1.179256	–1.501236	132.501297
14	–56.375	132.074	–26.858	–1.144	–2.725202	158.904556	131.546509	–0.843633	139.548248	138.567871	–1.094408	–1.492549	114.332024
15	–26.254	132.208	–213.824	39.018	136.551788	114.657234	156.089081	–0.813792	133.502884	141.959442	–2.05887	–0.677289	136.403076
16	–71.251	131.254	–236.468	–2.112	–1.988704	13.321682	131.639359	–0.778996	132.201843	140.57045	–2.067774	–0.667923	136.222504
17	–26.541	132.297	–66.725	39.936	136.811279	95.199318	156.373108	–0.807514	133.822357	142.826096	–1.337802	–1.276968	–0.286326
18	–72.383	130.627	–156.931	–2.102	–1.763247	10.707056	132.166061	–0.764831	131.863724	140.76268	–1.339298	–1.274383	–0.385314
19	5.399	132.354	–278.919	32.702	135.894882	122.424133	157.555542	–0.838253	133.406693	140.956177	–2.086618	–0.881368	136.412735
20	–28.238	132.040	–78.344	67.224	139.427933	53.319233	150.771011	–0.748011	136.363739	145.879074	–1.535758	–1.35137	66.492744
21	–59.630	131.003	–64.192	–2.105	–1.800674	10.368579	132.312622	–0.76192	131.677856	140.851852	–1.573508	–1.346963	52.450699
22	–1.408	132.254	–241.554	30.336	135.644669	121.912773	158.280853	–0.848259	133.461792	140.604858	–1.544906	–0.669091	56.7766
23	–50.611	131.728	–261.086	–2.102	–1.835456	10.842827	132.188004	–0.773098	132.115601	140.575012	–1.535488	–0.666395	57.202278
24	–22.080	132.764	–204.124	62.809	138.817001	68.889221	151.094498	–0.756383	135.634476	145.401642	–1.282163	–0.592083	0.761817
25	–29.271	131.953	–161.909	51.558	137.842819	85.996529	153.504929	–0.780902	134.523468	143.777313	–1.497019	–0.462679	61.491329
26	–41.721	131.758	–211.752	40.043	136.653931	114.871414	155.911179	–0.817278	133.546234	142.443298	–1.285799	–0.389946	0.349867
27	–35.261	132.565	–129.356	63.304	139.096146	60.99538	150.981903	–0.765319	136.02919	145.351501	–1.371358	–0.563195	4.953867
28	–30.170	132.304	–131.347	57.514	138.476044	74.32518	152.176682	–0.764789	135.26033	144.794052	–0.249415	–1.10593	137.910324
29	–715.058	132.272	–138.932	–1.150	–0.607149	148.226395	43.207043	–0.209081	11.112493	56.391499	–1.773634	–0.576582	75.887505
30	–531.553	40.626	–137.614	–1.829	59.732391	153.277802	42.688549	–0.820238	16.53437	82.354431	–1.774651	–0.590157	92.132706
31	–159.477	94.191	–137.353	98.076	146.109161	154.648132	160.764236	–0.673542	137.134277	145.795837	–1.768599	–0.593691	94.91777
32	–440.472	4.955	–119.315	–1.272	–2.221098	133.509064	148.545227	–0.215025	132.826477	131.766129	–2.134508	–0.418478	–1.962493
33	–406.394	–174.871	–99.682	–1.915	–3.080193	134.414413	146.378571	–0.404625	130.487289	146.019501	–2.029557	–0.422581	–1.948773
34	–38.985	–1093.237	–123.138	–0.545	131.348877	133.733383	147.918457	–0.705644	132.642258	149.298553	–2.095311	–0.422519	–1.982142
35	–898.853	133.293	–132.963	–1.150	–1.816282	138.576859	137.731964	–0.204361	5.081602	126.805946	–1.927298	–0.776108	57.313019
36	–644.771	47.340	–107.893	–2.066	11.197556	141.734818	53.715343	–0.760725	2.498762	61.143394	–1.66103	–1.600234	146.319138

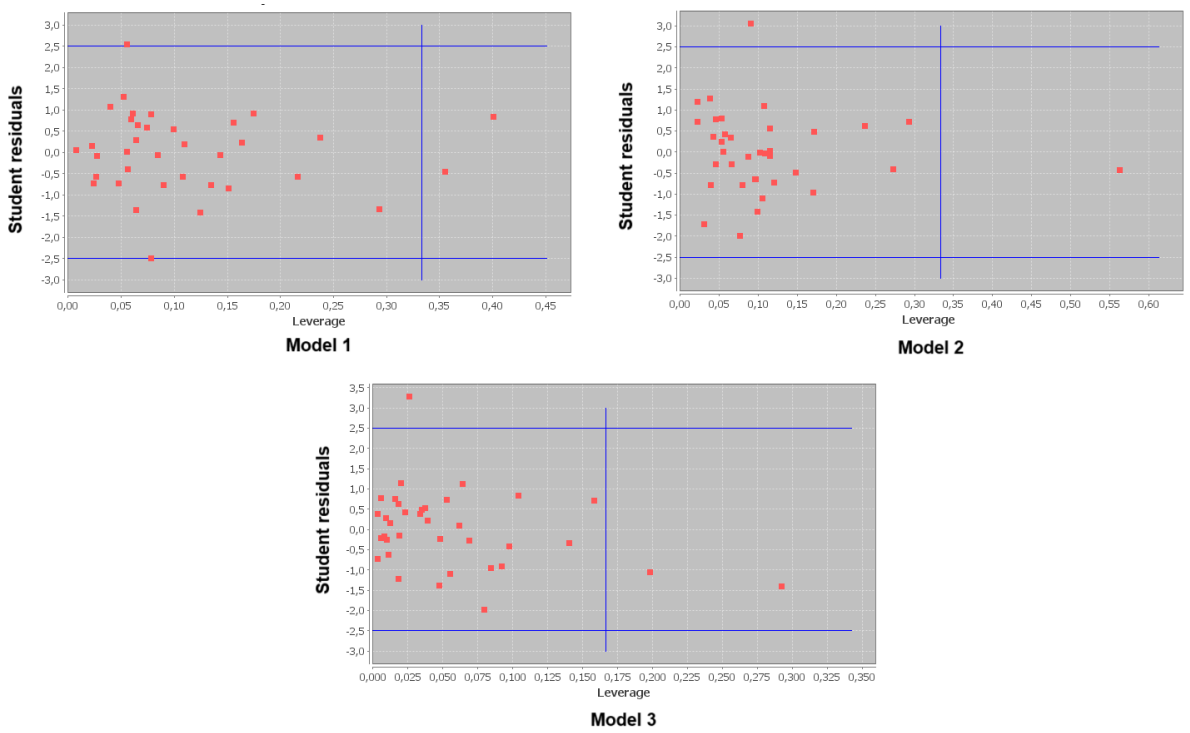

Figure S1. Williams plots used for outlier detection in Models 1–3. Model 1 shows that 88.89% of the samples lie within the applicability domain (h* = 0.340), with two molecules exhibiting |σ| ≈ 2.5 and two others exhibiting leverage values above h*. Model 2 contains 94.44% of the samples within the applicability domain (h* = 0.340), with one preditiva outlier (σ ≈ +3) and one structurally influential compound (h ≈ 0.550). Model 3 shows 91.67% of the samples within the applicability domain (h* = 0.170), with one molecule exhibiting σ ≈ +3 and two compounds presenting leverage values above h*.

Reference

1. Roy, K.; Kar, S.; Das, R. N.; *Understanding the Basics of QSAR for Applications in Pharmaceutical Sciences and Risk Assessment*; Elsevier: London, UK, 2015.

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