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SUPPLEMENTARY MATERIAL TO

Optimization of chromatographic separation of aripiprazole and impurities: Quantitative structure–retention relationship approach

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TABLE S-I. Values of log *P* and log *D* for the tested analytes*

Compound	pK_a	log *P*	log *D*		Amount of ionization form, %			
			pH 3.0	pH 4.7	at pH 3.0		at pH 4.7	
					Neutral	Cation	Neutral	Cation
IMP A	9.21	1.21	1.21	1.21	100	0	100	0
IMP B	8.82	2.75	-0.49	-0.43	0	100	0	100
IMP C	13.21; 13.81	3.12	3.12	3.12	100	0	100	0
IMP D	13.51	2.60	2.60	2.60	100	0	100	0
IMP E	3.73; 13.51	3.78	3.71	3.77	16	84	90	10
Aripiprazole	7.46; 13.51	4.90	1.45	2.21	0	100	0	100

* Values obtained with MarvinView 6.1.6 software

TABLE S-II. Values of the molecular descriptors for the tested analytes**

pH 4.7	Aripiprazole	ImpA	ImpB	ImpC	ImpD	ImpE	Average	SD	RSD
SAS, Å^2	634.862	273.278	341.850	5606.222	416.452	645.140	1319.634	1922.037	145.649
MS, Å^2	406.347	155.716	206.327	378.030	250.729	413.149	301.716	101.820	33.747
SEV, Å^3	360.380	120.307	178.063	310.906	201.820	366.442	256.320	94.454	36.850
Mass, g mol^{-1}	448.156	163.063	231.046	380.174	253.087	463.143	323.112	113.649	35.173
Charge	1.526 10^{-5}	0	1.526 10^{-5}	0	0	0	5.087 10^{-6}	7.194 10^{-6}	141.421
MW / AMU	449.402	163.177	232.133	380.446	253.730	464.394	323.880	113.918	35.173
O	1.659	1.321	1.348	1.703	1.507	1.668	1.535	0.154	10.060
PMIX / g mol^{-1} Å^2	2194.300	230.895	445.371	533.635	275.057	2047.790	954.508	832.063	87.172
PMIY / g mol^{-1} Å^2	12786.400	816.627	1585.570	17237.400	4849.740	17033.500	9051.540	6902.642	76.259
PMIZ /g mol^{-1} Å^2	14054.500	1031.900	1831	17709.300	5081.160	17982.500	9615.060	7188.624	74.764
MR	12.225	4.460	5.998	10.598	6.807	12.378	8.744	3.200	35.679
C log *P*	5.219	0.629	3.072	3.107	2.671	4.790	3.248	1.500	46.192
Eb / Kcal mol^{-1}	6.463	1.588	1.243	6.129	4.149	8.440	4.669	2.617	56.042
Ev / Kcal mol^{-1}	-0.028	-1.882	-4.103	-3.683	1.790	1.693	-1.036	2.366	228.459
Es / Kcal mol^{-1}	27.752	6.071	21.131	0.778	6.290	32.686	15.785	12.022	76.162
Esb / Kcal mol^{-1}	0.443	-0.053	0.093	0.228	-0.267	-0.008	0.073	0.223	308.010
Et / Kcal mol^{-1}	0.297	0.065	0.010	0.012	0.085	0.082	0.092	0.097	105.222

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pH 4.7	Aripiprazole	ImpA	ImpB	ImpC	ImpD	ImpE	Average	SD	RSD
E / Kcal mol^{-1}	55.387	7.436	28.203	11.329	20.545	65.551	31.408	21.782	69.352
E14 / Kcal mol^{-1}	20.460	1.647	9.828	7.866	8.499	22.659	11.826	7.374	62.350
DPLL, eV	5.369	3.771	3.449	0.184	2.576	2.206	2.926	1.587	54.255
ElcE, eV	-41611.200	-10471.300	-14473	-33306	-17685.500	-42828.200	-26729.200	13039.864	48.785
HOMO , eV	-1.729	-8.881	-1.319	-8.834	-8.873	-8.874	-6.418	3.463	53.955
LUMO, eV	-0.044	0.084	0.133	0.077	0.098	-0.405	-0.009	0.185	1988.073
NRE, eV	36274.100	8346.990	11854.900	28464.200	14578.400	37185.600	22784.032	11668.033	51.211
TotE, eV	-5337.090	-2124.320	-2618.11	-4841.810	-3107.070	-5642.670	-3945.178	1378.520	34.942
BIndx	1258736	19099	40414	914045	118842	1421449.000	628764.167	589415.962	93.742
ClsC	30	12	14	28	17	31	22	7.853	35.695
Diam	18	6	7	17	11	18	12.833	5.080	39.584
TIndx	22957	1387	2120	19444	4174	23847	12321.500	9888.517	80.254
Rad	9	3	4	9	6	9	6.667	2.494	37.417
ShpA	28.033	10.083	12.071	26.036	15.059	29.032	20.052	7.833	39.063
ShpC	1	1	0.75	0.889	0.833	1	0.912	0.097	10.611
SDeg	66	26	30	62	36	68	48	17.663	36.799
SVDe	92.556	44	38.5556	98	53.778	99.556	71.074	26.100	36.722
TCon	1.392 10^{-5}	0.014	0.007	2.411 10^{-5}	0.002	1.206 10^{-5}	0.004	0.005	131.245
TVCon	2.166 10^{-7}	0.001	0.002	6.279 10^{-8}	1.421 10^{-4}	7.910 10^{-8}	4.480 10^{-4}	0.001	160.538
WIndx	3204	185	291	2652	590	3400	1720.333	1388.551	80.714

**Values obtained using Chem3D Ultra 7.0 software

TABLE S-III. Weight values for QSRR-ANN

Neuron unit	*h1#01*	*h1#02*	*h1#03*	*h1#04*	log t_r
Threshold	-0.1495	-0.3591	2.18358	0.3097661	-0.1003
s_{MeOH}	-0.405927	-0.6614	-0.3095	0.3783298	
e_{MeOH}	0.5581015	-0.09984	-1.592106	-0.1448	
F	-0.2832	0.851204	-0.5773	0.3834429	
O	1.034471	-0.3111	1.131429	-7.023405	
Ev	0.6841513	0.0851934	0.09666	0.2688041	
Et	0.3471714	-0.2554	1.808066	1.602358	
h1#01					0.7634846
h1#02					-0.01301
h1#03					3.178396
h1#04					-6.083286

TABLE S-IV. Values of *RMSE* for ANNs trained during LOO-CV for log s_{B-A} and log s_{C-D}

Test case No.	log s_{B-A}			log s_{C-D}		
	Training *RMSE*	Verification *RMSE*	Test *RMSE*	Training *RMSE*	Verification *RMSE*	Test *RMSE*
1	0.0292	0.0357	0.0274	0.1232	0.0261	0.0024
2	0.0352	0.0630	0.0513	0.0944	0.0141	0.0528
3	0.0295	0.0525	0.0621	0.0939	0.0031	0.1638
4	0.0378	0.0611	0.0653	0.1613	0.0020	0.0038
5	0.0513	0.0740	0.0127	0.0878	0.0520	0.0223
6	0.0617	0.0193	0.2480	0.0763	0.0953	0.0171
7	0.0573	0.0686	0.0218	0.1243	0.0282	0.0393
8	0.0802	0.0811	0.0853	0.1153	0.0145	0.0274
9	0.0640	0.0892	0.0066	0.0581	0.0056	0.2760
10	0.0764	0.0207	0.0877	0.0763	0.0464	0.0279
11	0.0998	0.0703	0.0695	0.0693	0.0354	0.0594
12	0.0895	0.0603	0.0538	0.0765	0.0386	0.0315

TABLE S-IV. Continued

Test case No.	log s_{B-A}			log s_{C-D}		
	Training *RMSE*	Verification *RMSE*	Test *RMSE*	Training *RMSE*	Verification *RMSE*	Test *RMSE*
13	0.0908	0.0192	0.0510	0.0688	0.0351	0.0049
Average *RMSE*	0.0617	0.0550	0.0648	0.0943	0.0305	0.0560

TABLE S-V. Weight values for ANN to optimized log s_{B-A}

Neuron unit	*h1#01*	*h1#02*	log s_{B-A}
Threshold	-1.405131	-1.756968	3.721817
s_{MeOH}	-0.0548	-5.093693	
e_{MeOH}	0.1236208	-0.1554	
F	-4.129496	0.8476573	
h1#01			4.327358
h1#02			6.393134