Supplementary material

First Report on Predictive Comparative Ligand-based Multi-QSAR Modeling Analysis of 4-pyrimidinone and 2-pyridinone based APJ inhibitors

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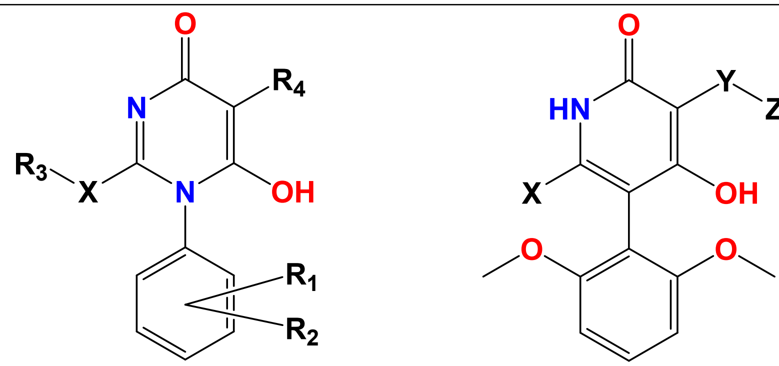
Supplementary Table S1. Structures of APJ inhibitors with their activity



Scaffold A   Scaffold B

Scaffold A							
Cpd No.	R_1	R_2	***X***	R_3	R_4	***APJ*** EC_{50} ***(nM)***	pEC_{50}
1	H	NA	s	*n*-Propyl	H	5000	5.301
2	2-OCH_3	NA	s	*n*-Propyl	H	64	7.194
3#	3-OCH_3	NA	s	*n*-Propyl	H	940	6.027
4	4-OCH_3	NA	s	*n*-Propyl	H	6800	5.167
5	2-CH_3	NA	s	*n*-Propyl	H	100	7.000
6*	3-CH_3	NA	s	*n*-Propyl	H	2900	5.538
7	4-CH_3	NA	s	*n*-Propyl	H	2600	5.585
8	2-Cl	NA	s	*n*-Propyl	H	250	6.602
9	2-F	NA	s	*n*-Propyl	H	160	6.796
10*	2-Br	NA	s	*n*-Propyl	H	155	6.810
11	2-CF_3	NA	s	*n*-Propyl	H	90	7.046
12	2-C_2H_5	NA	s	*n*-Propyl	H	140	6.854
13#	2-OC_2H_5	NA	s	*n*-Propyl	H	100	7.000
14	2-OCH_3	NA	s	*iso*-Propyl	H	23	7.638
15*	2-OCH_3	NA	s	*iso*-Butyl	H	78	7.108
16	2-OCH_3	NA	s	Butyl	H	200	6.699
17	2-OCH_3	NA	s	*n*-Propyl	Methyl	1400	5.854
18*#	2-OCH_3	NA	s	*n*-Propyl	Ethyl	860	6.066
19#	2-OCH_3	NA	s	*n*-Propyl	Butyl	1700	5.770
20	2-OCH_3	NA	s	*n*-Propyl	Benzyl	340	6.469
21	2-OCH_3	NA	s	*n*-Propyl	Allyl	570	6.244
22	2-OCH_3	NA	s	*n*-Propyl	*iso*-Propyl	450	6.347
23	2-OCH_3	H	-CH_2-	*n*-Propyl	H	22	7.658
24*	2-OCH_3	Methyl	-CH_2-	*n*-Propyl	H	5	8.301
25#	2-OCH_3	Methoxy	-CH_2-	*n*-Propyl	H	11	7.959
26	2-OCH_3	Methoxy	-CH_2-	*n*-Propyl	4-Methoxy Benzyl	13	7.886

Scaffold B					
Cpd No.	***X***	***Y***	***Z***	***APJ EC_{50} (nM)***	***pEC_{50}***
27	*n*-Butyl	Ethoxy carbonyl	--	450	6.347
28*[#]	*n*-Butyl	5-benzyl-1*H*-1,2,4-triazole-3-yl	--	330	6.481
29	*n*-Butyl	3-benzyl-1,2,4-oxadiazole-5-yl	--	43	7.367
30*	*n*-Butyl	5-benzyl-1,3,4-oxadiazole-2-yl	--	13	7.886
31[#]	*n*-Butyl	5-benzyl-1,3,4-oxadiazole-2-yl	2-Chloro Benzyl	8.6	8.066
32	*n*-Butyl	5-benzyl-1,3,4-oxadiazole-2-yl	3-Chloro Benzyl	2.6	8.585
33	*n*-Butyl	5-benzyl-1,3,4-oxadiazole-2-yl	4-Chloro Benzyl	0.4	9.398
34	*n*-Butyl	5-benzyl-1,3,4-oxadiazole-2-yl	4-Chloro Phenyl	180	6.745
35	*c*-Propyl	5-benzyl-1,3,4-oxadiazole-2-yl	4-Chloro Benzyl	11	7.959
36	*c*-Pentyl	5-benzyl-1,3,4-oxadiazole-2-yl	4-Chloro Benzyl	0.24	9.620
37	Methoxy ethyl	5-benzyl-1,3,4-oxadiazole-2-yl	4-Chloro Benzyl	0.94	9.027
38[#]	Ethoxy methyl	5-benzyl-1,3,4-oxadiazole-2-yl	4-Chloro Benzyl	0.12	9.921
39*	Ethoxy methyl	5-benzyl-1,3,4-oxadiazole-2-yl	2-Chloro-5-pyridylmethyl	0.17	9.770
40	Ethoxy methyl	5-benzyl-1,3,4-oxadiazole-2-yl	3-Chloro-6-pyridylmethyl	0.023	10.638

* Marked molecules were considered as the Y-based test set.

[#] Marked molecules were considered as the k-Medoid-based test set.

Supplementary Table S2. Performance summary for the SW-MLR models developed on the two different training and test sets using various correlation cutoff values

parameters	***Correlation cutoff***							
	0.6		***0.7***		***0.8***		***0.9***	
	Y-based MLR	***k-Medoid-based MLR***	***Y-based MLR***	***k-Medoid-based MLR***	***Y-based MLR***	***k-Medoid-based MLR***	***Y-based MLR***	***k-Medoid-based MLR***
No. Features	4	4	3	4	4	4	4	4
R^2	0.805	0.800	0.777	0.815	0.812	0.837	0.843	0.903
SEE	0.644	0.645	0.675	0.622	0.633	0.583	0.579	0.451
R^2_{Adj}	0.776	0.771	0.754	0.787	0.784	0.813	0.819	0.888
Q^2	0.739	0.722	0.687	0.735	0.687	0.771	0.796	0.854
PRESS	11.209	11.250	12.766	10.445	10.817	9.165	9.050	5.485
$F(4, 27)$	27.868	27.083	32.692[a]	29.690	29.119	34.779	36.122	62.636
R^2_{Pred}	0.353	0.650	0.457	0.743	0.414	0.727	0.679	0.834

Supplementary Table S3. Feature values and the predicted activity of SW-MLR model (***Equation 1***), MIA-QSAR (***PLS-1***), CoMFA and CoMSIA models for the Y-based training and the test sets

Cpd No	*GATS8v*	*VE1_Dze*	*nHBAcc*	*SHBd*	*pEC_{50}*	*Y_{Pred}(Equation 1)*	*Y_{Pred}(PLS 1)*	*CoMFA*	*CoMSIA*
1	1.119196	0.29821	4	0.506276	5.301	6.695	5.969	5.825	5.983
2	1.127332	0.290414	4	0.485868	7.194	6.673	6.952	6.877	6.855
3	1.248227	0.193783	4	0.490651	6.027	5.545	5.960	5.818	6.024
4	1.144883	0.093632	4	0.493931	5.167	5.668	5.151	4.988	5.022
5	1.067947	0.296701	4	0.478499	7	7.057	6.869	6.710	6.327
7	1.241512	0.173521	4	0.490651	5.585	5.492	5.500	5.587	5.759
8	1.178432	0.311345	4	0.477813	6.602	6.503	6.563	6.683	6.712
9	1.15357	0.318411	4	0.520165	6.796	6.552	6.774	6.673	6.689
11	1.123266	0.241642	4	0.509111	7.046	6.410	7.205	7.068	7.159
12	1.082206	0.234577	4	0.458091	6.854	6.757	7.223	6.761	6.554
13	1.1817	0.202989	4	0.470243	7	6.020	7.051	6.976	6.984
14	0.923227	0.171792	4	0.481085	7.638	7.303	7.309	7.796	7.778
16	1.144359	0.468239	4	0.473523	6.699	7.411	6.727	6.890	6.798
17	1.193742	0.283776	4	0.423368	5.854	6.451	6.083	6.114	6.228
19	1.249027	0.302498	4	0.335182	5.77	6.480	5.535	5.893	6.118
20	1.138087	0.169759	4	0.309371	6.469	6.583	6.608	6.511	6.360
21	1.263577	0.254752	4	0.372535	6.244	6.076	5.886	6.205	6.248
22	1.285064	0.252482	4	0.343368	6.347	6.029	6.030	6.362	6.059
23	1.040235	0.331288	4	0.491794	7.658	7.329	7.478	7.490	7.583
25	0.917617	0.363005	4	0.471386	7.959	8.221	7.995	8.075	8.056
26	1.005717	0.295367	4	0.284888	7.886	7.963	8.182	7.940	7.789
27	1.000761	0.132099	5	0.798041	6.347	6.733	6.431	6.335	6.297
29	0.914906	0.322586	4	0.703349	7.367	7.382	8.139	7.316	7.243
31	0.884386	0.27595	5	0.687856	8.066	8.353	8.258	8.186	8.193
32	0.896757	0.300227	5	0.690545	8.585	8.385	8.240	8.503	8.655
33	0.893769	0.326931	5	0.69259	9.398	8.515	9.275	9.360	9.383
34	0.914028	0.108786	5	0.703388	6.745	7.391	6.630	6.690	6.761
35	0.935072	0.363737	5	0.703484	7.959	8.417	7.926	7.892	7.962
36	0.961103	0.378237	5	0.622668	9.62	8.570	9.447	9.640	9.689
37	0.865594	0.343738	6	0.752998	9.027	9.538	8.943	8.986	9.050
38	0.827901	0.354349	6	0.782868	9.921	9.711	10.079	9.995	9.827
40	0.823258	0.329798	7	0.795213	10.638	10.556	10.351	10.623	10.625
6	1.125066	0.240234	4	0.485868	5.538	6.46071355	5.967	5.905	5.963
10	1.182603	0.30701	4	0.477213	6.81	6.461812956	6.486	6.827	6.511
15	1.230156	0.366781	4	0.470243	7.108	6.482750062	7.059	7.386	7.485
18	1.245981	0.275892	4	0.383368	6.066	6.237937826	6.019	6.312	6.273
24	1.02138	0.351176	4	0.464016	8.301	7.605326908	7.609	7.523	7.599
28	0.931102	0.322091	6	1.203981	6.481	7.763908083	8.206	8.384	7.255

30	0.915863	0.300965	5	0.703349	7.886	8.243353046	8.262	9.129	8.723
39	0.840049	0.335257	7	0.792868	9.77	10.49251318	9.866	9.622	9.137

Supplementary Table S4. Feature values and the predicted activity of SW-MLR model (***Equation 2***), MIA-QSAR (***PLS-2***), CoMFA and CoMSIA models for the k-medoid-based training and the test sets

Cpd No	*SpMax6_Bhm*	*GATS8i*	*VE1_Dze*	*maxdssC*	*pEC$_{50}$*	*Y$_{Pred}$(Equation 2)*	*Y$_{Pred}$(PLS 2)*	*CoMFA*	*CoMSIA*
1	2.637785	0.800901	0.29821	0.817639	5.301	5.476	5.909	5.709	5.920
2	2.915377	0.859709	0.290414	0.75588	7.194	6.913	6.974	6.893	6.835
4	2.822754	0.950736	0.093632	0.784275	5.167	4.829	5.132	5.005	5.002
5	2.861315	0.767374	0.296701	0.825139	7.000	7.038	6.875	6.815	6.431
6	2.820824	0.877384	0.240234	0.821713	5.538	5.863	5.535	5.544	5.830
7	2.761186	0.910768	0.173521	0.820095	5.585	4.989	5.460	5.514	5.678
8	2.918526	0.803597	0.311345	0.851312	6.602	7.185	6.607	6.571	6.662
9	2.789834	0.829646	0.318411	0.585139	6.796	6.786	6.738	6.647	6.708
10	2.92016	0.815402	0.30701	0.862546	6.810	7.080	6.575	6.967	6.750
11	2.919568	0.901344	0.241642	0.327361	7.046	7.302	7.286	7.1	7.169
12	2.918285	0.840818	0.234577	0.83588	6.854	6.634	7.272	6.798	6.522
14	2.907384	0.697039	0.171792	0.735648	7.638	7.357	7.369	7.697	7.705
15	2.915609	0.94879	0.366781	0.752963	7.108	6.724	7.124	7.15	7.216
16	2.915734	0.956273	0.468239	0.76662	6.699	7.116	6.805	6.85	6.737
17	2.916494	0.942335	0.283776	0.76338	5.854	6.369	6.082	6.014	6.199
20	2.985631	0.945215	0.169759	0.755242	6.469	6.272	6.390	6.507	6.402
21	2.985603	1.039032	0.254752	0.746909	6.244	6.102	5.802	6.199	6.244
22	2.956689	1.026625	0.252482	0.771528	6.347	5.941	5.841	6.311	6.133
23	2.9127	0.834827	0.331288	0.542917	7.658	7.654	7.700	7.672	7.795
24	2.925733	0.814441	0.351176	0.550417	8.301	7.935	8.295	8.203	8.326
26	3.079396	0.903429	0.295367	0.463547	7.886	8.253	8.206	7.995	7.845
27	3.014573	0.953564	0.132099	0.509443	6.347	6.709	6.545	6.317	6.337
29	3.079396	0.971259	0.322586	0.583263	7.367	7.727	8.074	7.357	7.259
30	3.079396	0.97291	0.300965	0.583263	7.886	7.618	8.180	7.832	8.140
32	3.277436	0.976858	0.300227	0.588247	8.585	8.802	8.224	8.543	8.555
33	3.282642	0.979863	0.326931	0.587477	9.398	8.939	9.179	9.389	9.434
34	3.188512	0.960653	0.108786	0.582482	6.745	7.488	6.630	6.739	6.678
35	3.295235	1.018535	0.363737	0.650579	7.959	8.824	8.092	7.978	7.965
36	3.302244	1.040539	0.378237	0.671413	9.620	8.758	9.489	9.687	9.711
37	3.250415	0.962315	0.343738	0.462477	9.027	9.170	8.902	9.044	8.877
39	3.250694	0.91831	0.335257	0.356991	9.770	9.609	9.935	9.787	9.920
40	3.24619	0.849971	0.329798	0.355255	10.638	9.979	10.213	10.606	10.454
3	2.87482	0.917422	0.193783	0.773244	6.027	5.833	5.793	5.559	6.096
13	2.920457	0.910434	0.202989	0.762966	7.000	6.220	7.042	6.876	6.979
18	2.920877	0.988892	0.275892	0.77412	6.066	6.053	5.984	6.329	6.251
19	2.985625	1.059052	0.302498	0.786202	5.770	6.121	5.770	6.175	6.504
25	2.933138	0.764988	0.363005	0.481157	7.959	8.474	8.048	8.838	8.580
28	3.079396	1.004629	0.322091	0.607356	6.481	7.473	8.121	8.753	7.118
31	3.261997	0.971999	0.27595	0.589249	8.066	8.623	8.378	8.709	7.768

38	3.251207	0.902659	0.354349	0.365255	9.921	9.780	9.933	9.547	10.663

Supplementary Table S5. Detailed summary of SW-MLR model (***Equation 1***) for the Y-based dataset division method.

Regression Summary for Dependent Variable: pEC_{50} (Y-based SW-MLR Equation 1) R= .91790830 R²= .84255564 Adjusted R²= .81923055 F(4,27)=36.122 p<.00000 Std.Error of estimate: .57895						
	Beta	**Std.Err.**	**B**	**Std.Err.**	**t(27)**	**p-level**
Intercept			9.26493	2.061315	4.49467	0.000118
GATS8v	-0.589053	0.126204	-5.62583	1.205333	-4.66745	0.000074
VE1_Dze	0.277965	0.080212	4.48776	1.295027	3.46538	0.001785
nHBAcc	0.537723	0.133909	0.96426	0.240129	4.01559	0.000425
SHBd	-0.315141	0.144253	-2.90190	1.328320	-2.18464	0.037772

Supplementary Table S6. Detailed summary of SW-MLR model (***Equation 2***) for the k-medoid-based -based dataset division method.

Regression Summary for Dependent Variable: *pEC_{50}* (004_k-Medoid-based SW-MLR Equation 2) R= .95011445 R²= .90271746 Adjusted R²= .88830523 F(4,27)=62.636 p<.00000 Std.Error of estimate: .45074						
	Beta	**Std.Err.**	**B**	**Std.Err.**	**t(27)**	**p-level**
Intercept			-5.64028	1.942545	-2.90355	0.007268
SpMax6_Bhm	0.808594	0.089087	6.16569	0.679307	9.07644	0.000000
GATS8i	-0.384499	0.072647	-6.12614	1.157468	-5.29271	0.000014
VE1_Dze	0.281433	0.062384	4.57326	1.013726	4.51133	0.000113
maxdssC	-0.227529	0.074401	-1.96263	0.641767	-3.05817	0.004980

Supplementary Table S7. Detailed summary of SW-MLR model (***Equation 1***) for the k-medoid-based-based dataset division method.

Equation 1				***Equation 2***			
Model Type	***R***	***R^2***	***Q^2(LOO)***	***Model Type***	***R***	***R^2***	***Q^2(LOO)***
Original	0.917908	0.842556	0.796337	Original	0.950114	0.902717	0.854371
Random 1	0.376041	0.141407	-0.17356	Random 1	0.360832	0.1302	-0.21735
Random 2	0.397835	0.158273	-0.15633	Random 2	0.438829	0.19257	-0.14956
Random 3	0.445661	0.198614	-0.28324	Random 3	0.409615	0.167784	-0.16015
Random 4	0.356204	0.126881	-0.24145	Random 4	0.46516	0.216373	-0.10002
Random 5	0.36812	0.135512	-0.24435	Random 5	0.382932	0.146637	-0.18408
Random 6	0.141327	0.019973	-0.32574	Random 6	0.17255	0.029773	-0.55269
Random 7	0.370879	0.137551	-0.34505	Random 7	0.377326	0.142375	-0.27264
Random 8	0.28186	0.079445	-0.28115	Random 8	0.172029	0.029594	-0.44062
Random 9	0.139305	0.019406	-0.37919	Random 9	0.371957	0.138352	-0.32177
Random 10	0.342797	0.11751	-0.32936	Random 10	0.241188	0.058172	-0.27312
Random 11	0.385715	0.148776	-0.2483	Random 11	0.265274	0.070371	-0.2466
Random 12	0.362452	0.131371	-0.30337	Random 12	0.424699	0.180369	-0.16888
Random 13	0.23074	0.053241	-0.21509	Random 13	0.344625	0.118767	-0.30115
Random 14	0.634012	0.401971	0.108131	Random 14	0.549483	0.301932	0.035059
Random 15	0.359919	0.129542	-0.26069	Random 15	0.413452	0.170942	-0.13475
Random 16	0.236816	0.056082	-0.34069	Random 16	0.259479	0.067329	-0.34643
Random 17	0.351411	0.123489	-0.21933	Random 17	0.140377	0.019706	-0.40212
Random 18	0.311395	0.096967	-0.18014	Random 18	0.452136	0.204427	-0.17723
Random 19	0.330382	0.109152	-0.18735	Random 19	0.368105	0.135502	-0.20943
Random 20	0.383558	0.147117	-0.19294	Random 20	0.459212	0.210876	-0.14046
Random 21	0.274253	0.075215	-0.21276	Random 21	0.266633	0.071093	-0.30134
Random 22	0.367058	0.134732	-0.22867	Random 22	0.365204	0.133374	-0.15912
Random 23	0.436234	0.1903	-0.08498	Random 23	0.339342	0.115153	-0.27219
Random 24	0.364171	0.132621	-0.28761	Random 24	0.318595	0.101503	-0.25046
Random 25	0.317792	0.100992	-0.20634	Random 25	0.125693	0.015799	-0.48744
Random 26	0.455467	0.20745	-0.05875	Random 26	0.382545	0.146341	-0.21154
Random 27	0.606437	0.367766	0.083009	Random 27	0.276622	0.07652	-0.31583
Random 28	0.214059	0.045821	-0.62875	Random 28	0.371149	0.137751	-0.13164
Random 29	0.398996	0.159198	-0.14556	Random 29	0.241972	0.058551	-0.26436
Random 30	0.230546	0.053151	-0.25307	Random 30	0.376017	0.141389	-0.21743
Random 31	0.252456	0.063734	-0.25196	Random 31	0.127127	0.016161	-0.3897
Random 32	0.237798	0.056548	-0.26808	Random 32	0.453498	0.20566	-0.13012
Random 33	0.537429	0.28883	-0.16068	Random 33	0.490119	0.240217	-0.09953
Random 34	0.399712	0.159769	-0.26869	Random 34	0.097789	0.009563	-0.43003
Random 35	0.315261	0.09939	-0.22974	Random 35	0.164736	0.027138	-0.35385
Random 36	0.249517	0.062259	-0.32364	Random 36	0.203548	0.041432	-0.43699
Random 37	0.30203	0.091222	-0.28416	Random 37	0.413726	0.171169	-0.14606

Random 38	0.24414	0.059605	-0.2153	Random 38	0.423607	0.179443	-0.15927
Random 39	0.719334	0.517441	0.365838	Random 39	0.460145	0.211734	-0.14512
Random 40	0.271324	0.073617	-0.20078	Random 40	0.32791	0.107525	-0.33514
Random 41	0.285283	0.081387	-0.47815	Random 41	0.393034	0.154476	-0.1302
Random 42	0.333272	0.11107	-0.3855	Random 42	0.278144	0.077364	-0.36992
Random 43	0.190123	0.036147	-0.40415	Random 43	0.372053	0.138423	-0.18563
Random 44	0.399579	0.159664	-0.1929	Random 44	0.286692	0.082192	-0.33758
Random 45	0.202534	0.04102	-0.43864	Random 45	0.262917	0.069125	-0.36092
Random 46	0.174132	0.030322	-0.31375	Random 46	0.29606	0.087652	-0.28867
Random 47	0.311221	0.096858	-0.31967	Random 47	0.120313	0.014475	-0.35229
Random 48	0.350317	0.122722	-0.25747	Random 48	0.281385	0.079178	-0.29157
Random 49	0.219899	0.048355	-0.32574	Random 49	0.242419	0.058767	-0.34537
Random 50	0.264212	0.069808	-0.51079	Random 50	0.302617	0.091577	-0.35148
Random Models Parameters				***Random Models Parameters***			
Average R	0.346057			***Average R***	0.334921		
Average R^2	0.139448			***Average R^2***	0.131285		
Average Q^2(LOO)	-0.2253			***Average Q^2(LOO)***	-0.23844		
cRp^2	0.784575			***cRp^2***	0.849083		