Study of novel pyrazolo[3,4-d]pyrimidine derivatives as selective TgCDPK1 inhibitors: molecular docking, structure-based 3D-QSAR and molecular dynamics simulation

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Electronic Supplementary Information

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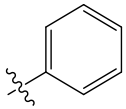
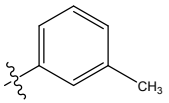
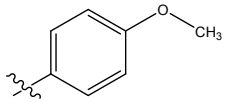
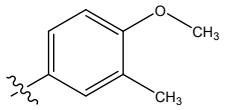
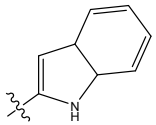
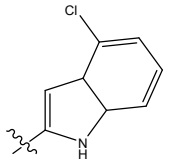
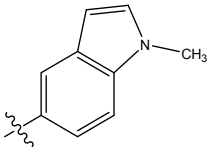
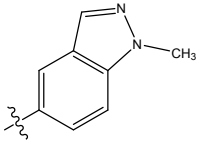
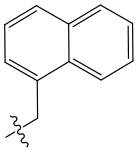
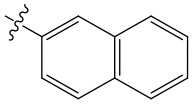
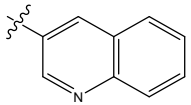
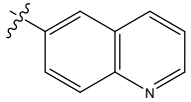
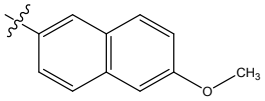
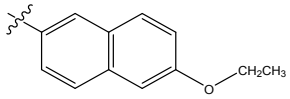
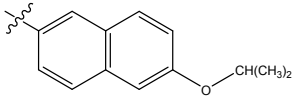
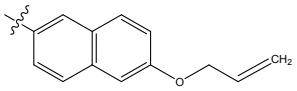
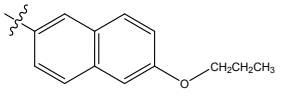
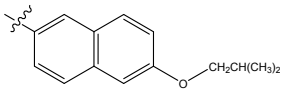
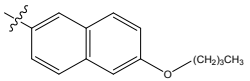
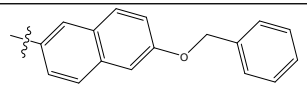
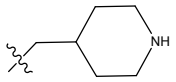
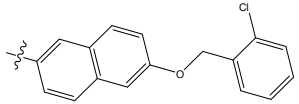
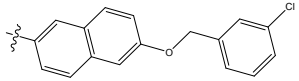
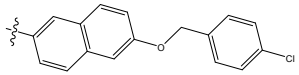
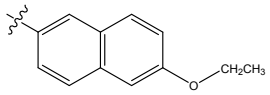
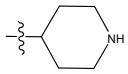
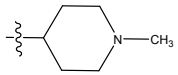
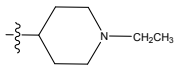
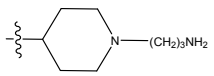
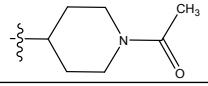
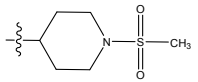
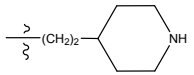
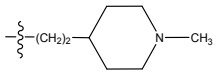
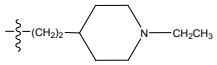
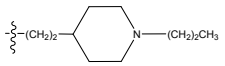
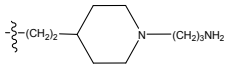
Table S1 Structures and experimental values IC_{50} (μM) of pyrazolo[3,4-d]pyrimidine derivatives

NO.		R_1	R_2	TgCDPK1		Src		Distance (APD=2.455)
				IC_{50}	pIC_{50}	IC_{50}	pIC_{50}	
1	2b		$-C(CH_3)_3$	0.0045	8.3468	0.13	6.8861	-
2*	3a		$-CH(CH_3)_2$	0.019	7.7212	1.3	5.8861	1.404
3*	3b	3	b	0.0073	8.1367	0.58	6.2366	1.813
4	4a		a	0.04	7.3979	5.1	5.2924	-
5	5a		a	0.005	8.3010	0.65	6.1871	-
6	5b	5	b	0.0041	8.3872	0.18	6.7447	-
7	6a		a	0.012	7.9208	1.5	5.8239	-

8	7a		a	0.0091	8.0410	1.2	5.9208	-
9	8a		a	0.0036	8.4437	0.29	6.5376	-
10*	8b	8	b	0.013	7.8861	0.52	6.2840	1.855
11	9b		b	0.0025	8.6021	2.1	5.6778	-
12*	10a		a	0.13	6.8861	8.8	5.0555	1.798
13	10b	10	b	0.031	7.5086	2.2	5.6576	-
14*	11a		a	0.005	8.3010	0.065	7.1871	1.578
15	11b	11	b	0.0079	8.1024	0.12	6.9208	-
16	12a		a	0.024	7.6198	0.2	6.6990	-

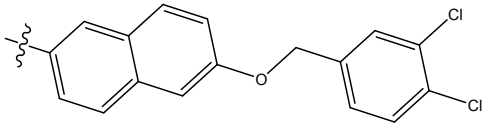
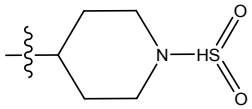
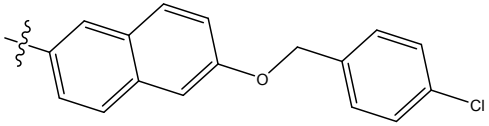
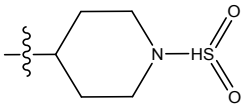
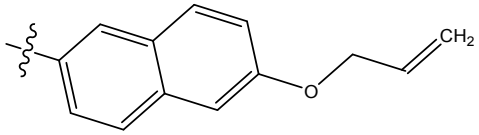
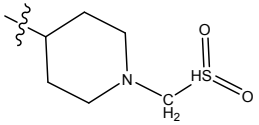
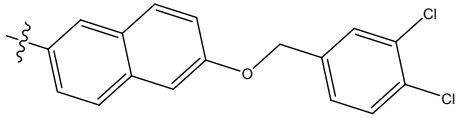
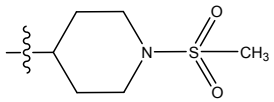
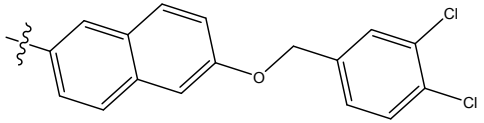
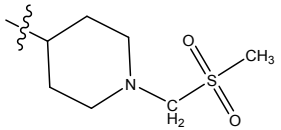
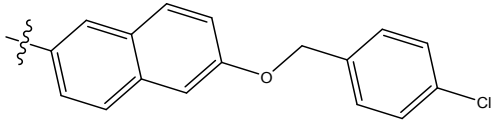
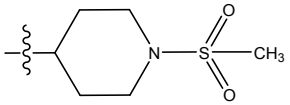
17*	13b		b	0.0031	8.5086	4.1	5.3872	1.539
18	14a		a	0.006	8.2218	0.67	6.1739	-
19	14b	14	b	0.02	7.6990	2	5.6990	-
20	15a		a	0.005	8.3010	0.38	6.4202	-
21	15b	15	b	0.033	7.4815	2.2	5.6576	-
22	17a		a	0.01	8.0000	0.55	6.2596	-
23	18a		a	0.0006	9.2218	0.2	6.6990	-
24	19a		a	0.0032	8.4949	0.3	6.5229	-
25	20a		a	0.0054	8.2676	0.26	6.5850	-
26	20b	20	b	0.2	6.6990	1.1	5.9586	-
27*	21a		a	0.0009	9.0458	0.78	6.1079	1.445

28*	22a		a	0.0008	9.0969	0.041	7.3872	1.388
29	22n	22		0.0023	8.6383	3.1	5.5086	-
30	23a		a	0.011	7.9586	0.28	6.5528	-
31	23n	23	n	0.0013	8.8861	1.8	5.7447	-
32	24a		a	0.0055	8.2596	0.28	6.5528	-
33	24n	24	n	0.0007	9.1549	0.38	6.4202	-
34*	25a		a	0.004	8.3979	0.27	6.5686	1.210
35	25n	25	n	0.0007	9.1549	1.6	5.7959	-
36	15g			0.0026	8.5850	5	5.3010	-
37	15h	15		0.0024	8.6198	5.6	5.2518	-
38	15i	15		0.0034	8.4685	8.7	5.0605	-
39*	15k	15		0.0043	8.3665	0.73	6.1367	1.612
40	15l	15		0.0061	8.2147	1.6	5.7959	-

41*	15m	15		0.0028	8.5528	0.81	6.0915	1.254
42	15s	15		0.0019	8.7212	3.3	5.4815	-
43	15t	15		0.0022	8.6576	5.2	5.2840	-
44*	15u	15		0.0027	8.5686	6.3	5.2007	1.380
45	15v	15		0.003	8.5229	6.7	5.1739	-
46	15w	15		0.0043	8.3665	8.2	5.0862	-

*Compounds in the test set

Table S2 Structure and predicted activities of new designed compounds

No.	R_1	R_2	Predicted pIC_{50}		Distance (APD=2.455)
			TgCDPK1	Src	
D1			9.4164	3.9511	0.799
D2			9.3971	3.8977	0.867
D3			9.3524	4.1102	0.798
D4			9.3514	3.8793	1.095
D5			9.3381	4.8057	0.781
D6			9.3226	3.8583	1.608

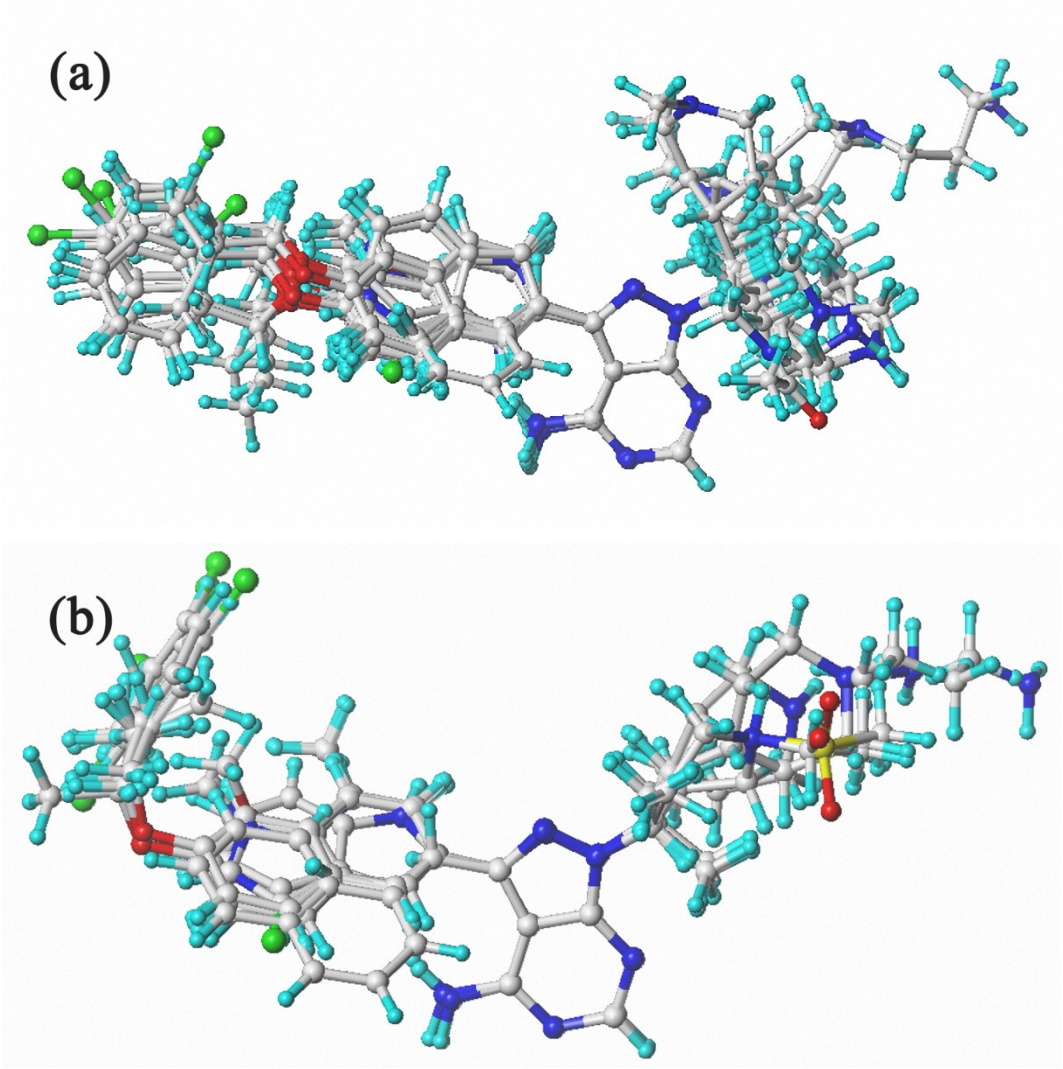


Fig.S1. (a) and (b), the alignment of the 34 studied compounds for TgCDPK1 and Src series.

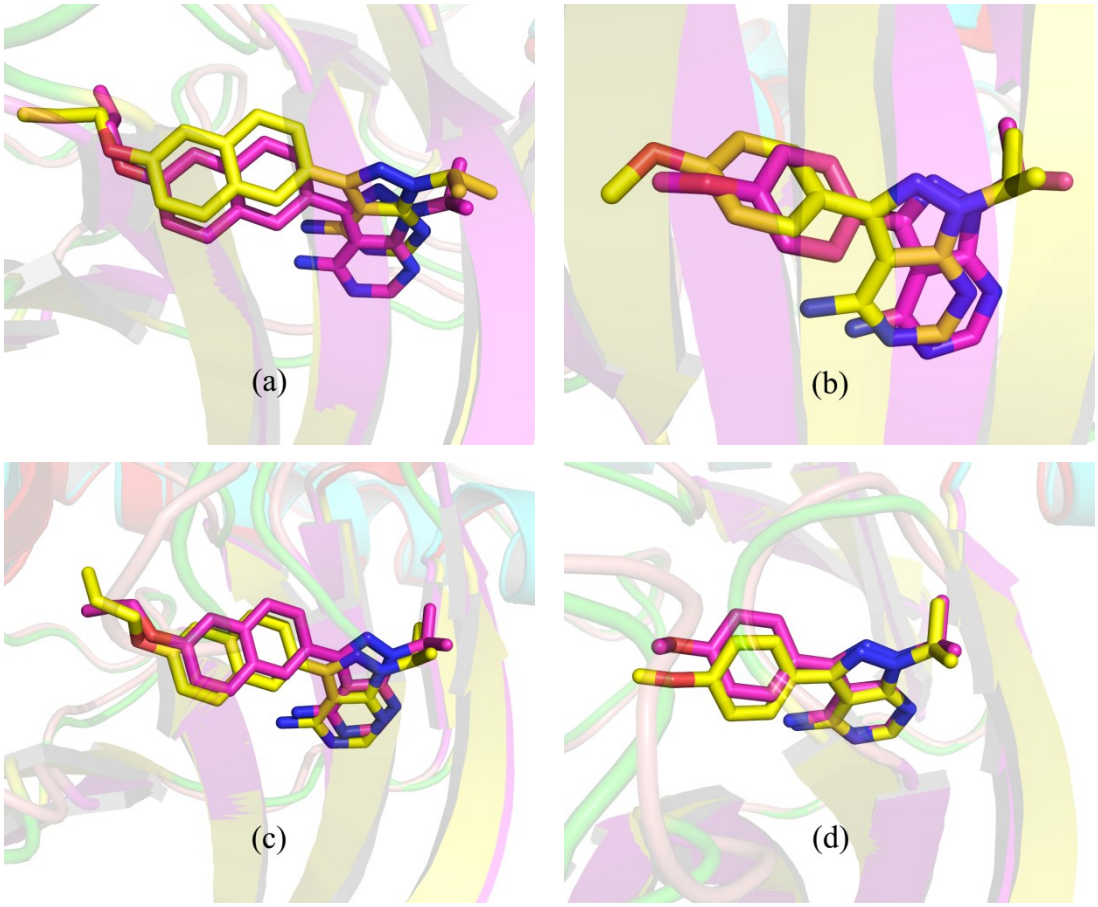


Fig.S2. Superimposition of the average structure from the last 2 ns of the MD simulation (magenta) and the initial structure (yellow). (a) 3SXF-**23** complex, (b) 3SXF-**4** complex, (c) 3UQF-**23** complex, (d) 3UQF-**4** complex.

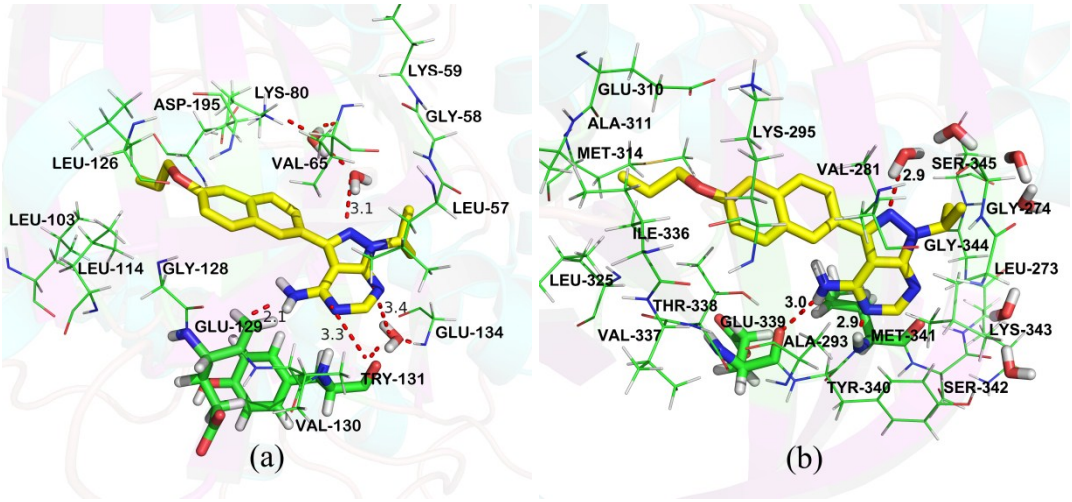


Fig.S3. The interaction of inhibitors with water molecules in **23-3SXF**(a) and **23-3UQF**(b) systems.