Electronic Supplementary Material (ESI) for Molecular BioSystems.

Studies of N^9-arenthenyl purines as novel DFG-in and DFG-out dual Src/Abl inhibitors using 3D-QSAR, docking and molecular dynamics simulations

Shaojie Ma,[a] Guohua Zeng,[a] Danqing Fang,[b] Juping Wang,[a] Wenjuan Wu,*[a] Wenguo Xie,[a] Shepei Tan[a] and Kangcheng Zheng[c]

[a]: Department of Physical Chemistry,College of Pharmacy, Guangdong Pharmaceutical University, Guangzhou 510006, China. E-mail: wuwenjuan83@126.com; Tel: +86 20 39352119

[b]: Department of Cardiothoracic Surgery, Affiliated Second Hospital of Guangzhou Medical University, Guangzhou 510260, China

[c]: School of Chemistry and Chemical Engineering, Sun Yat-Sen University, Guangzhou 510275, China

Electronic Supplementary Information

Table of Contents

Supplementary tables (Table S1-S2) S2-S8

Supplementary figure (Figures S1) S9

Table S1 Structures and experimental values of purine derivatives

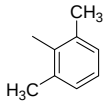
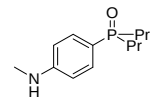
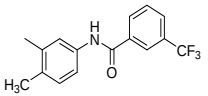
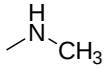
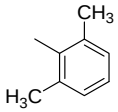
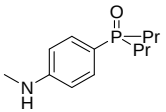
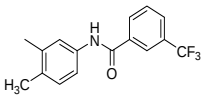
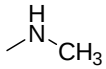
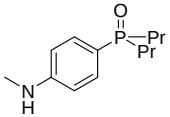
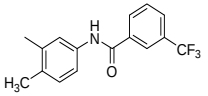
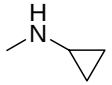
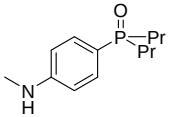
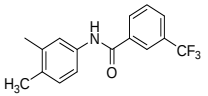
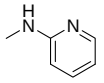
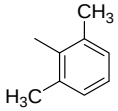
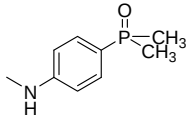
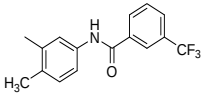
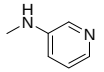
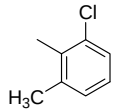
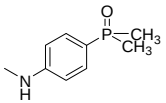
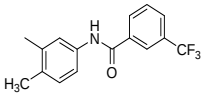
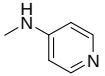
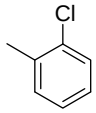
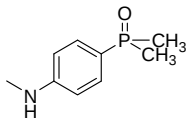
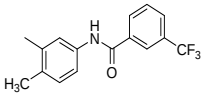
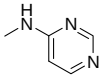
No.	R_1	R_2	R_3	L	IC_{50}(nM) of DFG-in		No.	R_1	R_2	R_3	L	IC_{50}(nM) of DFG-out	
					Src	Abl						Src	Abl
1			Isopropyl	Vinyl	1.78	5.93	**25***			H	Ethylidene	300	96
2			Isopropyl	Vinyl	6.58	54.3	**26**			H	Vinyl	52	25
3			Isopropyl	Vinyl	31.8	73.3	**27***			H	Vinyl	91	74
4			Isopropyl	Vinyl	376	626	**28***			H	Vinyl	201	243
5*			H	Vinyl	8.31	3.58	**29**			H	Vinyl	9.3	26
6			H	Vinyl	5.56	2.77	**30**			H	Vinyl	4.7	9.9
7			H	Vinyl	126	69.4	**31**			H	Vinyl	26	40

Table S1 (*continued*)

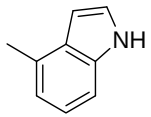
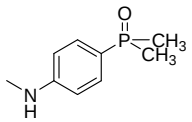
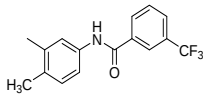
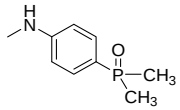
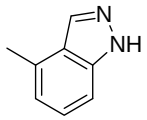
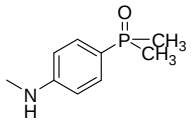
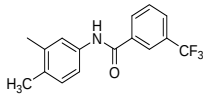
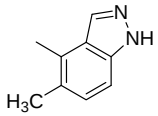
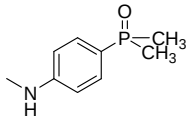
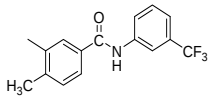
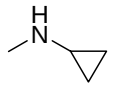
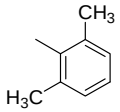
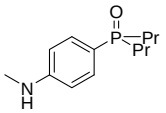
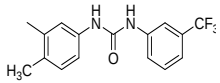
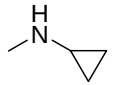
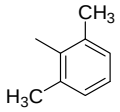
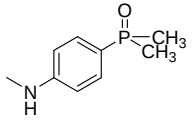
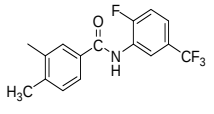
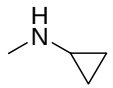
No.	R_1	R_2	R_3	L	IC_{50}(nM) of DFG-in		No.	R_1	R_2	R_3	L	IC_{50}(nM) of DFG-out	
					Src	Abl						Src	Abl
8			H	Vinyl	198	16.7	**32**			H	Vinyl	3.8	5.7
9			H	Vinyl	17	2.36	**33**		$NH(CH_2)_3N(CH_3)_2$	H	Vinyl	159	157
10			H	Vinyl	0.46	0.46	**34**			H	Vinyl	11	23
11			H	Vinyl	4	17.3	**35**			H	Vinyl	517	62
12[*]			NMe_2	Vinyl	3.74	17.6	**36**			H	Vinyl	86	236

Table S1 (*continued*)

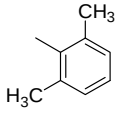
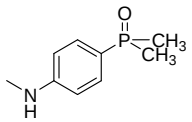
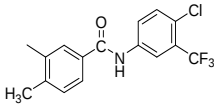
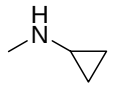
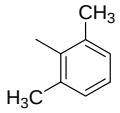
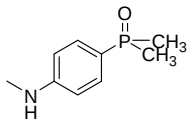
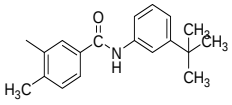
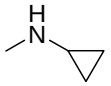
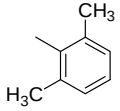
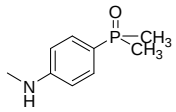
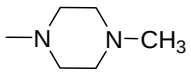
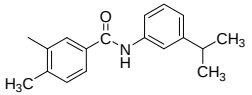
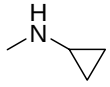
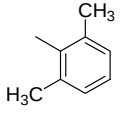
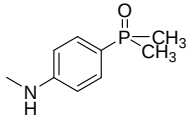
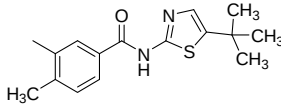
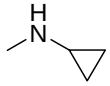
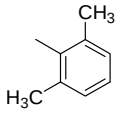
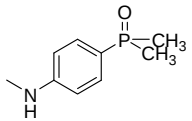
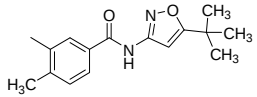
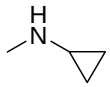
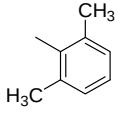
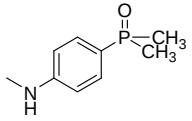
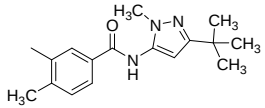
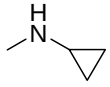
No.	R_1	R_2	R_3	L	IC_{50}(nM) of DFG-in		No.	R_1	R_2	R_3	L	IC_{50}(nM) of DFG-out	
					Src	Abl						Src	Abl
13			1-Pyrroldine	Vinyl	1.43	19.5	**37***			H	Vinyl	45	37
14*			1-Morpholine	Vinyl	0.23	3.02	**38**			H	Vinyl	4.8	59
15				Vinyl	0.23	6.8	**39**			H	Vinyl	46	60
16*			1-Imidazole	Vinyl	0.46	1.63	**40**			H	Vinyl	310	267
17			OMe	Vinyl	0.46	1.8	**41**			H	Vinyl	6.6	23
18*			Isopropyl	Vinyl	0.46	7.32	**42***			H	Vinyl	46	146

Table S1 (*continued*)

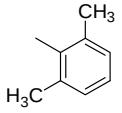
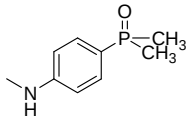
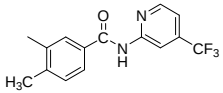
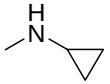
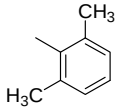
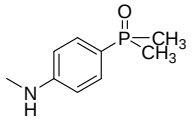
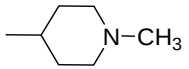
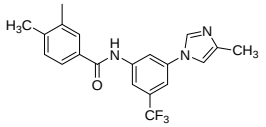
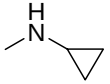
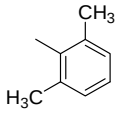
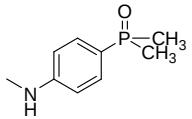
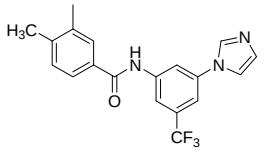
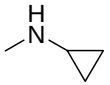
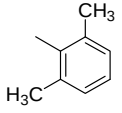
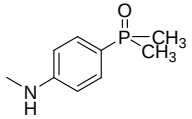
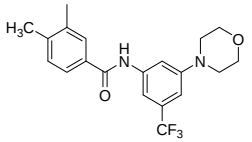
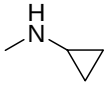
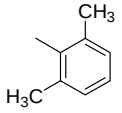
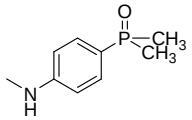
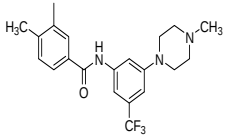
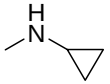
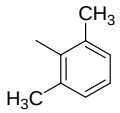
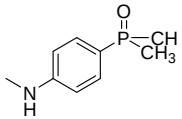
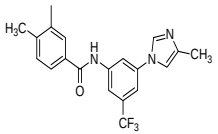
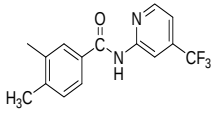
No.	R_1	R_2	R_3	L	IC_{50}(nM) of DFG-in		No.	R_1	R_2	R_3	L	IC_{50}(nM) of DFG-out	
					Src	Abl						Src	Abl
19			OCH_2CH_2OMe	Vinyl	0.46	1.57	**43**			H	Vinyl	7.0	20
20				Vinyl	0.46	0.46	**44**[*]			H	Vinyl	7.6	25
21[*]			3-PyO	Vinyl	0.46	0.5	**45**			H	Vinyl	8.0	13
22			Isopropyl	Vinyl	0.89	15.8	**46**			H	Vinyl	33	72
23[*]			Cyclopentyl	Vinyl	1.29	32.3	**47**[*]			H	Vinyl	41	24

Table S1 (*continued*)

No.	R_1	R_2	R_3	L	IC_{50}(nM) of DFG-in		**No.**	R_1	R_2	R_3	L	IC_{50}(nM) of DFG-out	
					Src	Abl						Src	Abl
24			$NCCH_2CH_2$	Vinyl	0.46	0.46	**48**		H	H	Vinyl	84	48
							49		H	H	Vinyl	307	38

* Compounds in the test set

Table S2 The actual pIC_{50}, predicted pIC_{50} and their residuals of the studied compounds for CoMFA analyses

No.	DFG-in						No.	DFG-out					
	Src			Abl				Src			Abl		
	Actual pIC_{50}	Pred. pIC_{50}	Res.	Actual pIC_{50}	Pred. pIC_{50}	Res.		Actual pIC_{50}	Pred. pIC_{50}	Res.	Actual pIC_{50}	Pred. pIC_{50}	Res.
Training set													
1	8.750	8.796	-0.046	8.227	8.222	0.005	**26**	7.284	7.232	0.052	7.602	7.586	0.016
2	8.182	8.160	0.022	7.265	7.259	0.006	**29**	8.032	8.127	-0.095	7.585	7.597	-0.012
3	7.498	7.477	0.021	7.134	7.137	-0.003	**30**	8.328	8.245	0.083	8.004	7.955	0.049
4	6.425	6.443	-0.018	6.203	6.177	0.026	**31**	7.585	7.627	-0.042	7.398	7.373	0.025
6	8.255	8.213	0.042	8.558	8.553	0.005	**32**	8.420	8.384	0.036	8.244	8.287	-0.043
7	6.900	6.920	-0.020	7.159	7.235	-0.076	**33**	6.799	6.785	0.014	6.804	6.827	-0.023
8	6.703	6.697	0.006	7.777	7.764	0.013	**34**	7.959	8.056	-0.097	7.638	7.595	0.043
9	7.770	7.756	0.014	8.627	8.623	0.004	**35**	6.287	6.338	-0.051	7.208	7.208	0.000
10	9.337	9.337	0.000	9.337	9.349	-0.012	**36**	7.066	7.061	0.005	6.627	6.649	-0.022
11	8.398	8.415	-0.017	7.762	7.770	-0.008	**38**	8.319	8.350	-0.031	7.229	7.281	-0.052
13	8.845	8.902	-0.057	7.710	7.616	0.094	**39**	7.337	7.359	-0.022	7.222	7.208	0.014
15	9.638	9.669	-0.031	7.710	8.149	-0.439	**40**	6.509	6.474	0.035	6.573	6.559	0.014
17	9.337	9.316	0.021	8.745	8.761	-0.016	**41**	8.180	8.169	0.011	7.638	7.624	0.014
19	9.337	9.352	-0.015	8.804	8.814	-0.010	**43**	8.155	8.104	0.051	7.699	7.690	0.009
20	9.337	9.301	0.036	9.337	9.319	0.018	**45**	8.097	8.082	0.015	7.886	7.913	-0.027
22	9.051	9.035	0.016	7.801	7.883	-0.082	**46**	7.481	7.458	0.023	7.143	7.116	0.027
24	9.337	9.310	0.027	9.337	9.320	0.017	**48**	7.076	7.045	0.031	7.319	7.312	0.007
							49	6.513	6.532	-0.019	7.420	7.457	-0.037
Test set													
5	8.080	7.605	0.475	8.446	8.542	-0.096	**25**	6.523	6.937	-0.414	7.018	6.846	0.172

Table S2 (*continued*)

No.	DFG-in						No.	DFG-out					
	Src			Abl				Src			Abl		
	Actual pIC_{50}	Pred. pIC_{50}	Res.	Actual pIC_{50}	Pred. pIC_{50}	Res.		Actual pIC_{50}	Pred. pIC_{50}	Res.	Actual pIC_{50}	Pred. pIC_{50}	Res.
12	8.427	8.774	-0.347	7.754	7.965	-0.211	**27**	7.041	7.347	-0.306	7.131	7.515	-0.384
14	9.638	9.265	0.373	8.520	8.112	0.408	**28**	6.697	7.388	-0.691	6.614	7.025	-0.411
16	9.337	9.693	-0.356	8.788	8.892	-0.104	**37**	7.347	7.145	0.202	7.432	7.591	-0.159
18	9.337	8.740	0.597	8.135	8.303	-0.168	**42**	7.337	7.062	0.275	6.836	6.907	-0.071
21	9.337	9.200	0.137	9.301	8.692	0.609	**44**	8.119	8.338	-0.219	7.602	7.364	0.238
23	8.889	8.697	0.192	7.491	8.021	-0.530	**47**	7.387	7.443	-0.056	7.620	7.385	0.235

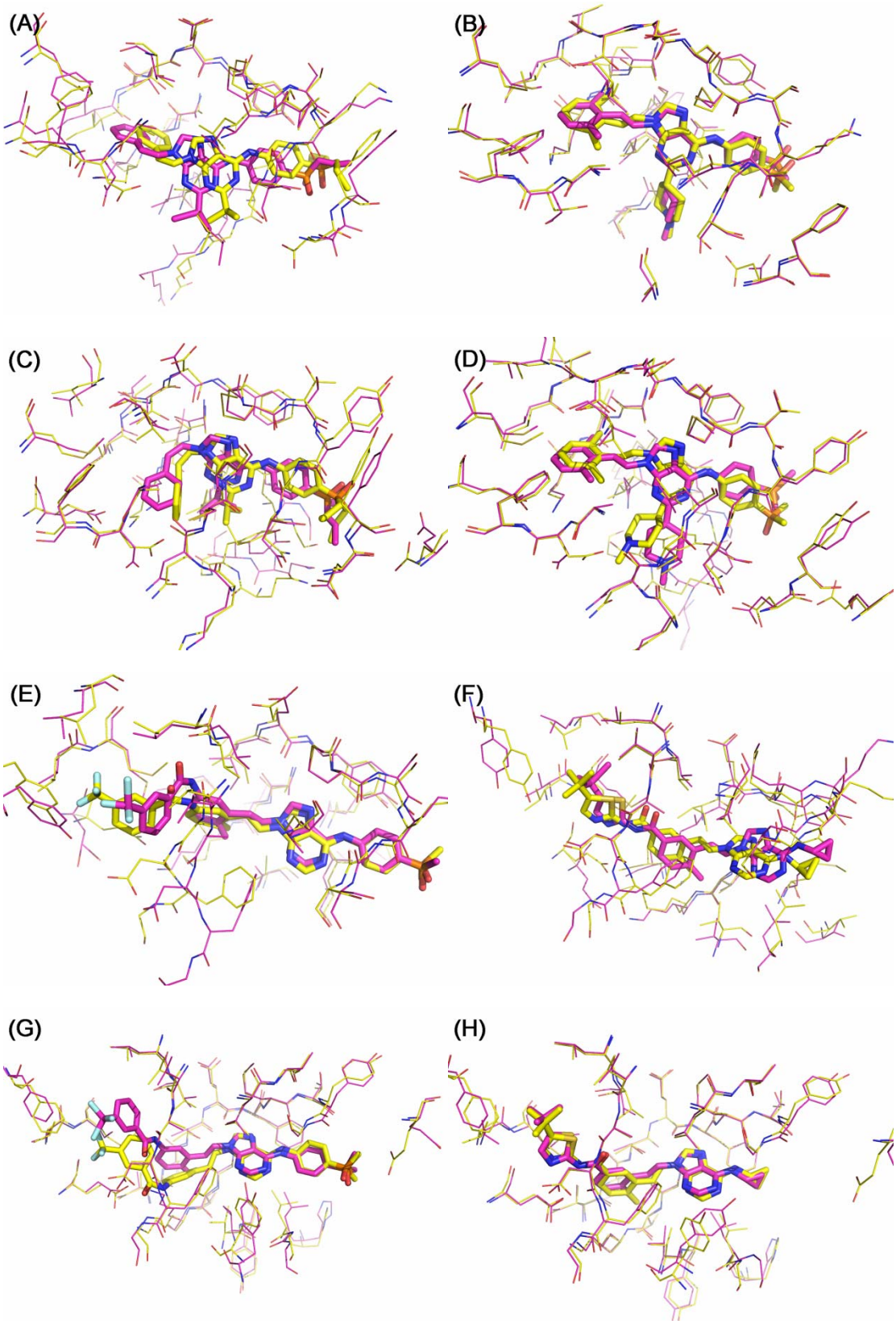


Fig.S1 Superimposition of the average structure from the last 2 ns of the MD simulation (magenta) and the initial structure (yellow). (A) **4**-2BDJ complex, (B) **20**-2BDJ complex, (C) **4**-3KF4 complex, (D) **20**-3KF4 complex, (E) **32**-3G6H complex, (F) **40**-3G6H complex, (G) **32**-3KFA complex, (H) **40**-3KFA complex.