

Three-dimensional-QSAR and Relative Binding Affinity Estimation of Focal Adhesion Kinase Inhibitors

Suparna Ghosh ¹ and Seung Joo Cho ^{1,2,*}

¹Department of Biomedical Sciences, College of Medicine, Chosun University, Gwangju 501-759, Republic of Korea

²Department of Cellular Molecular Medicine, College of Medicine, Chosun University, Gwangju 501-759, Republic of Korea

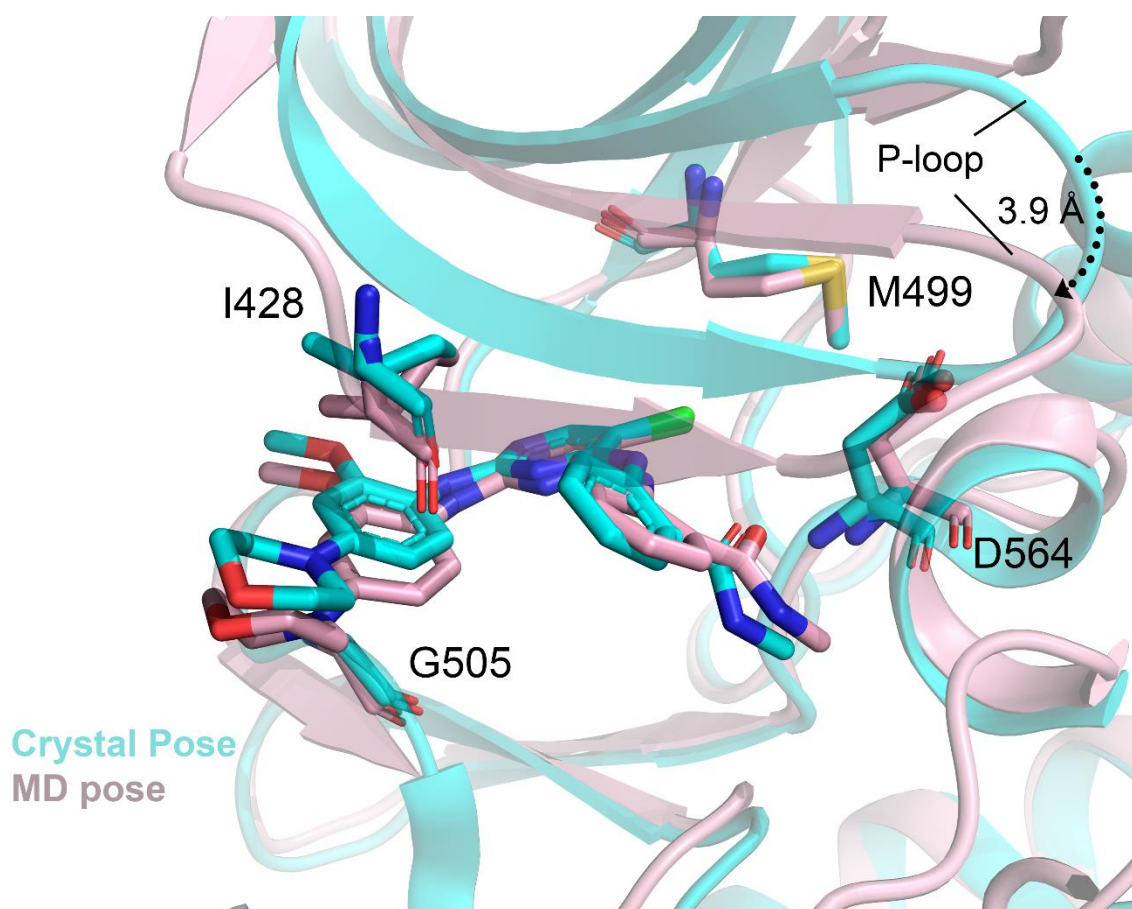


Figure S1. Binding poses comparison of TAE226 compound between MD and crystal form. The original crystal complex comprises homodimer of chain A and B. TAE226 is missing from Chain A, although it is present in Chain B. For the MD study, only TAE226 bound was considered.

Table S1. MM-PB/GBSA binding energy terms

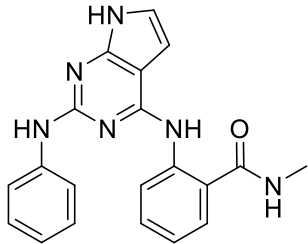
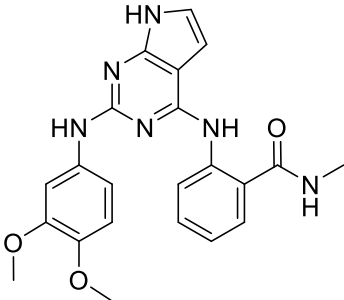
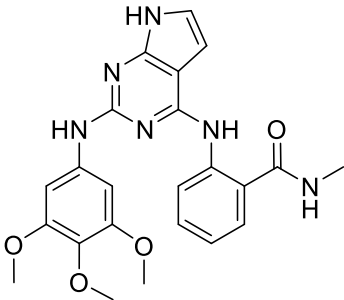
Binding energy terms	BE in kcal/mol
VDW	-58.85 ± 2.34
EEL	-16.96 ± 2.78
EGB	29.54 ± 1.89
ESURF	-6.49 ± 0.16
ΔG_{gas}	-75.81 ± 3.70
ΔG_{solv}	23.05 ± 1.82

ΔT_{TOTAL}	-52.76 ± 2.95
T_{AS}	7.51 ± 0.04
ΔG_{bind}	-45.25 ± 2.95

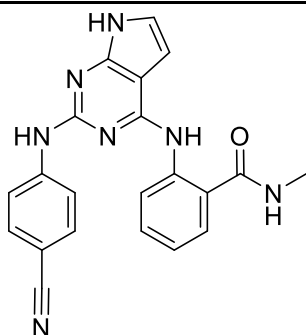
Table S2. Residue-specific MM-PB/GBSA binding energy decomposition in kcal/mol.

Residues	BE
I428	-3.25 ± 0.44
V436	-1.43 ± 0.26
V484	-0.70 ± 0.15
M499	-0.69 ± 0.14
L501	-2.37 ± 0.34
C502	-1.97 ± 0.53
G505	-2.25 ± 0.34
L553	-2.87 ± 0.38
G563	-1.04 ± 0.42
D564	-2.61 ± 0.44
L567	-2.18 ± 0.30

Table S3. Dataset compounds and their corresponding pIC_{50} values.

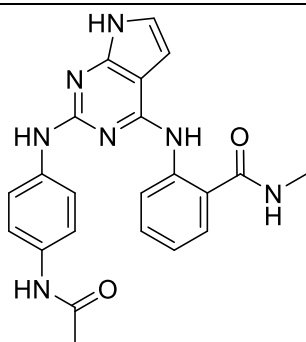
#Cpd	Structure	pIC_{50}
01		6.76
02		7.22
03		7.17

04



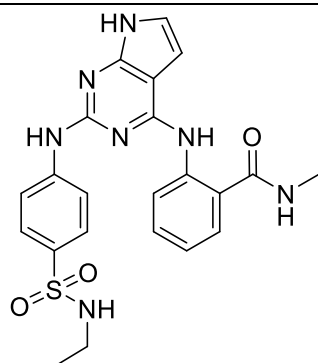
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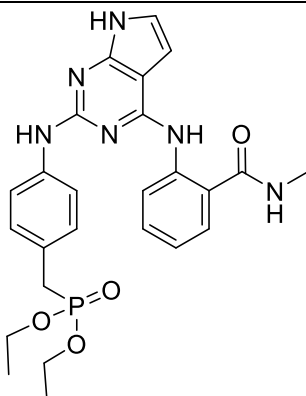
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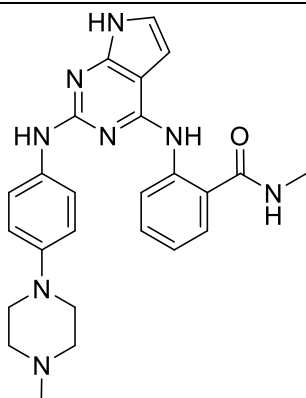
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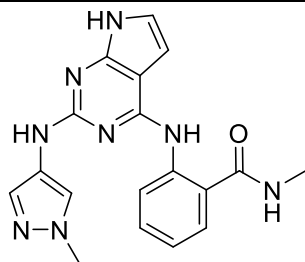
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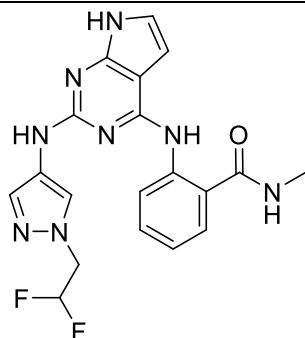
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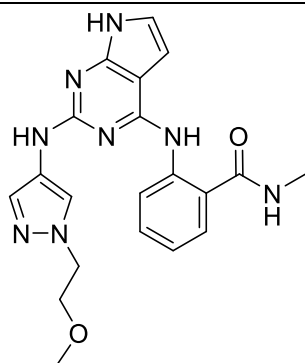
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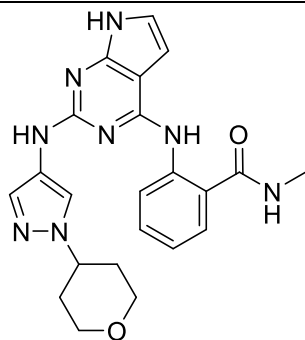
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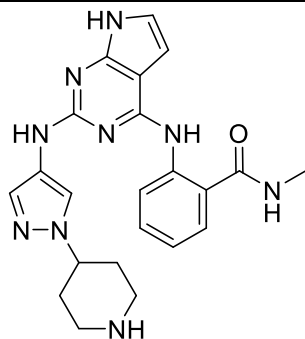
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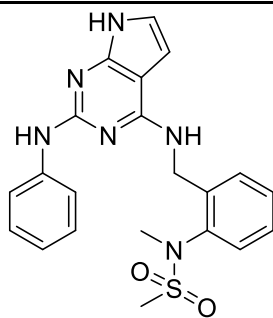
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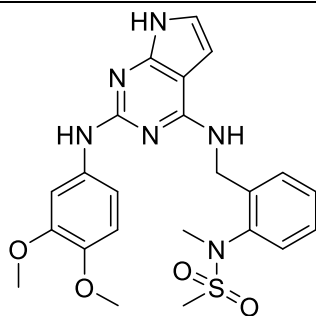
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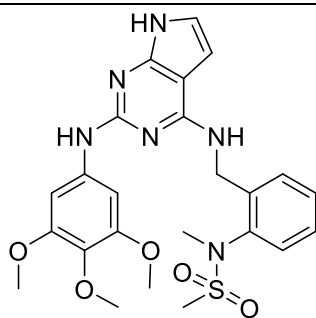
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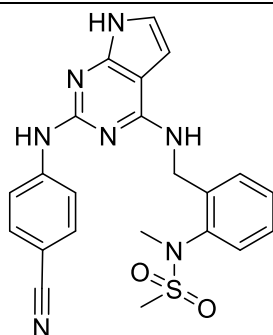
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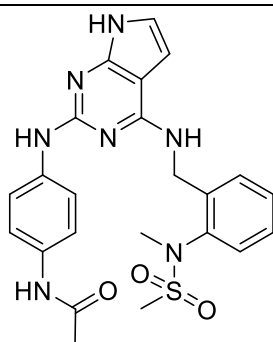
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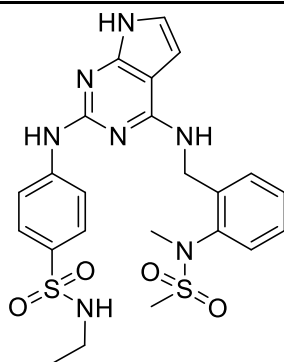
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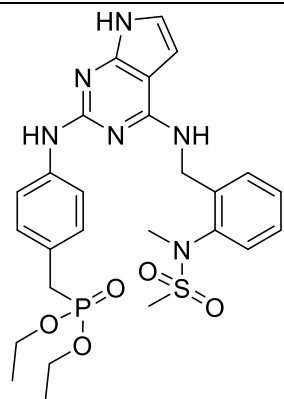
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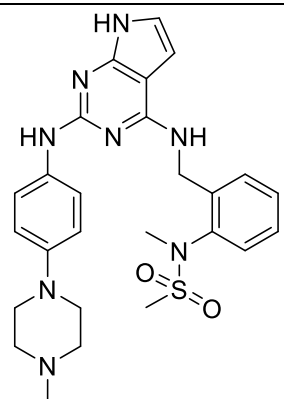
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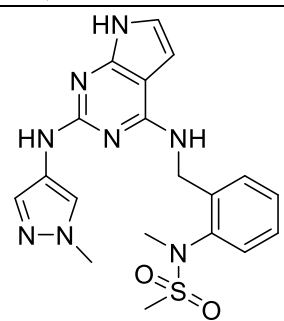
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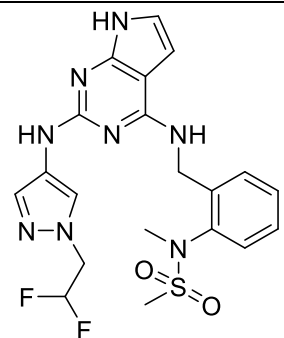
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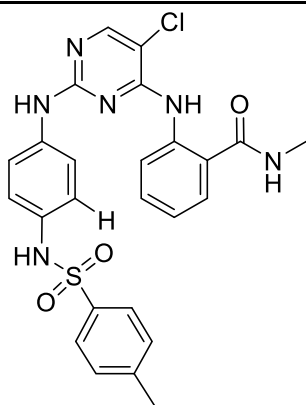
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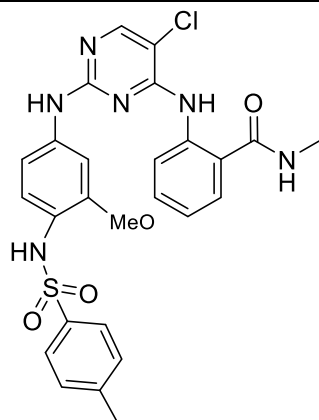
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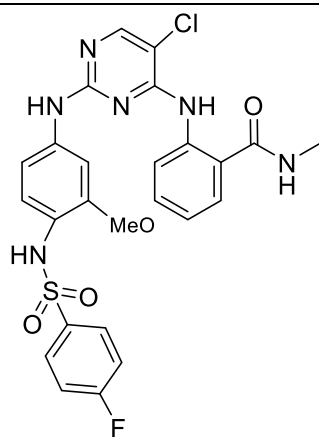
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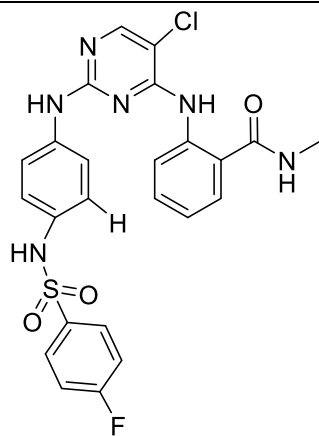
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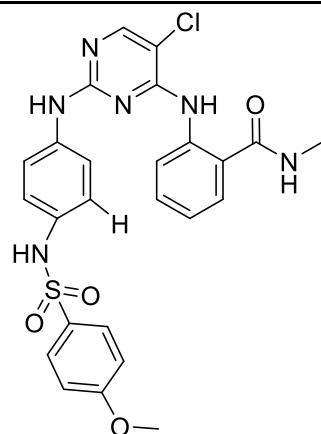
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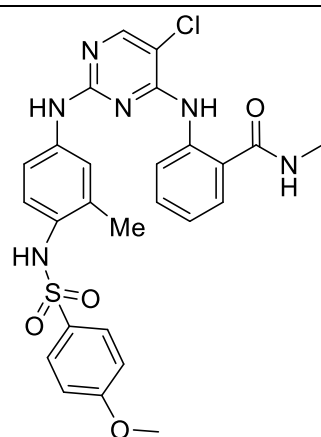
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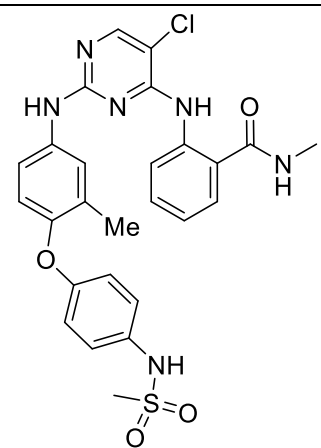
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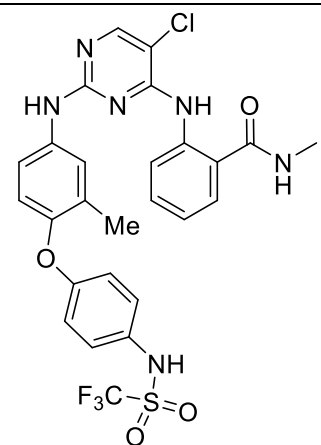
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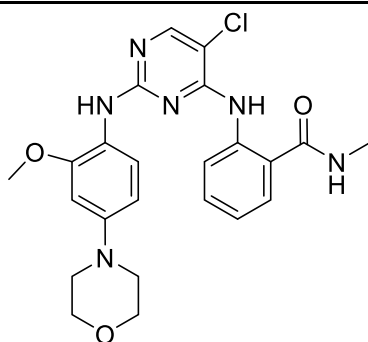
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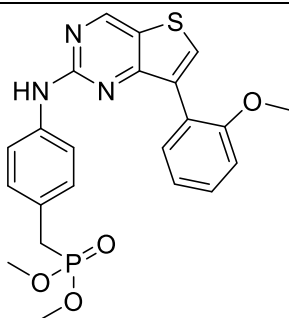
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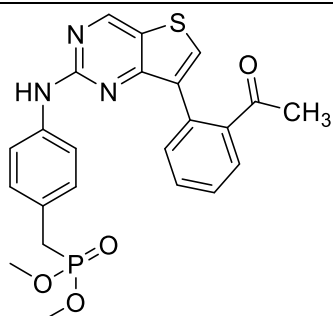
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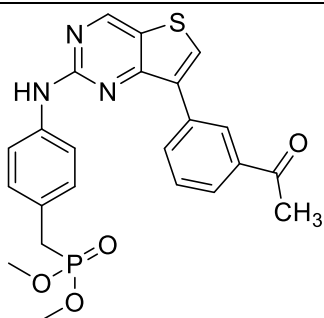
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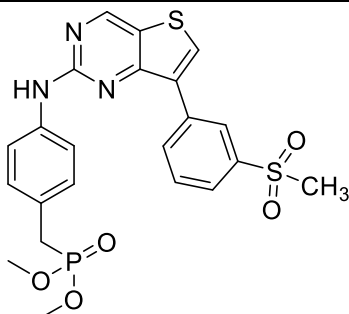
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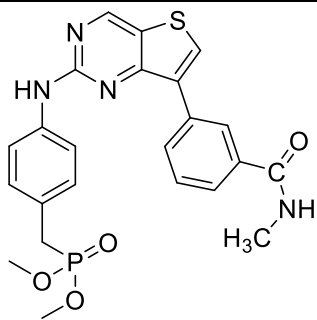
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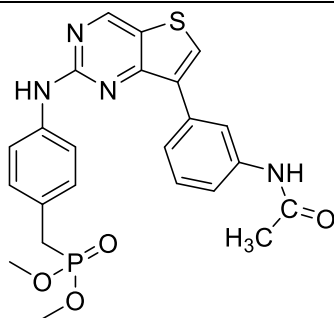
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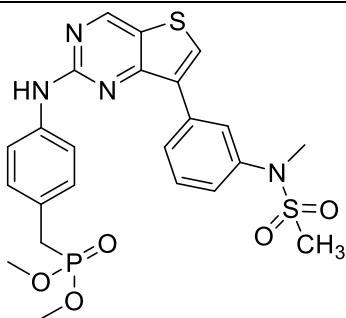
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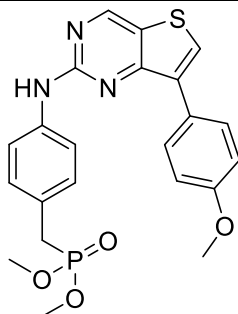
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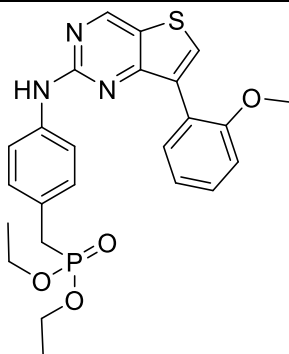
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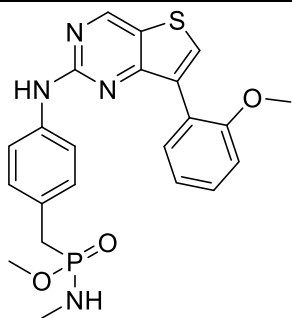
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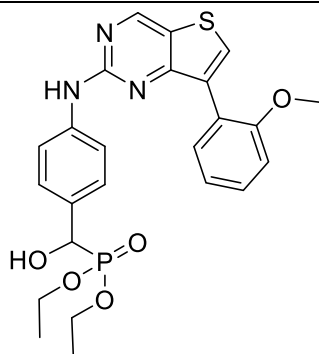
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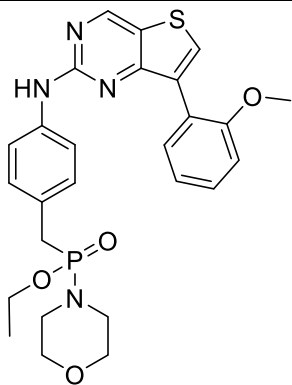
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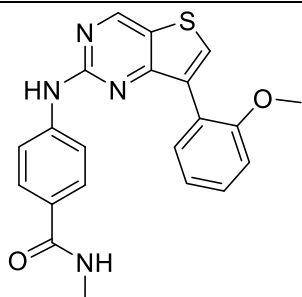
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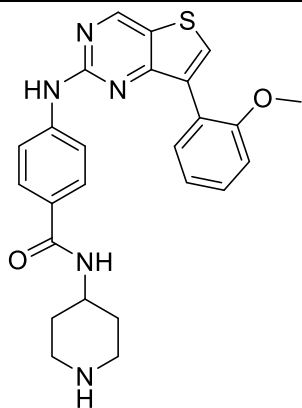
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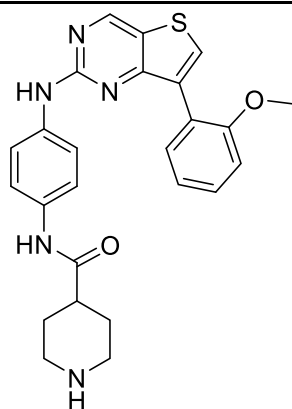
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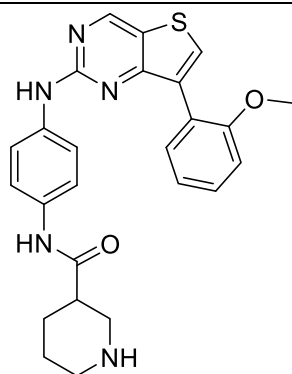
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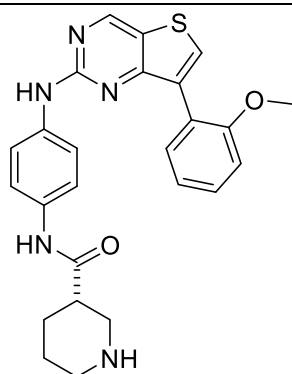
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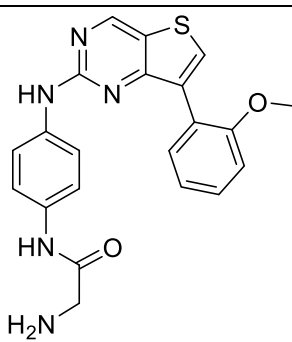
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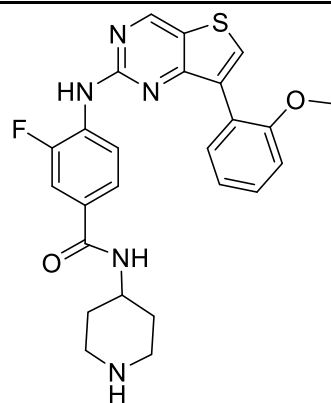
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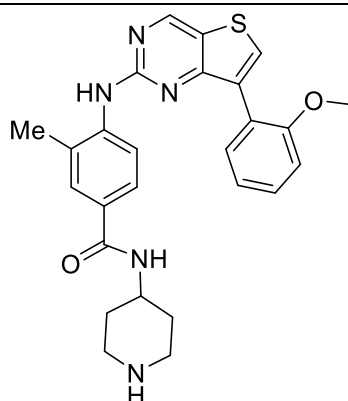
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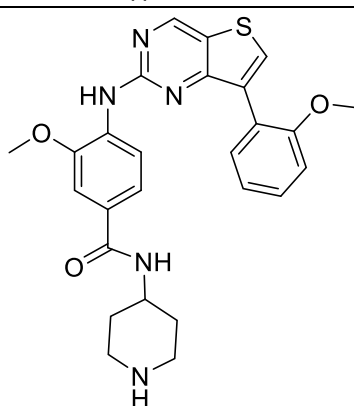
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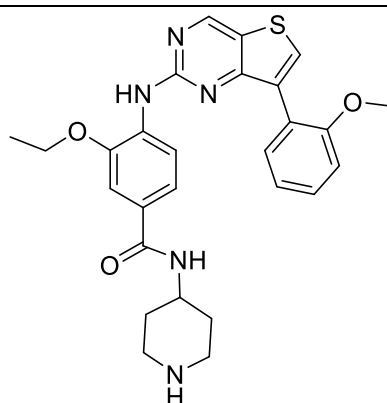
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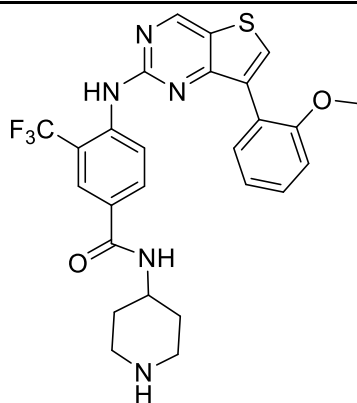
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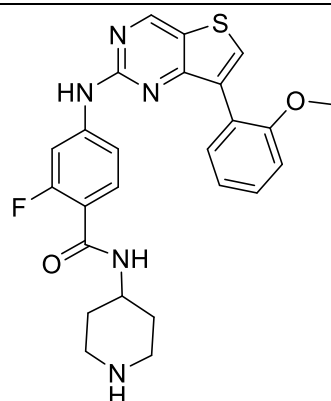
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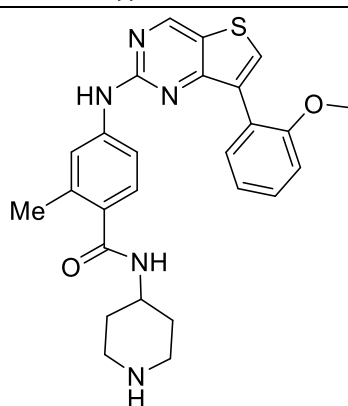
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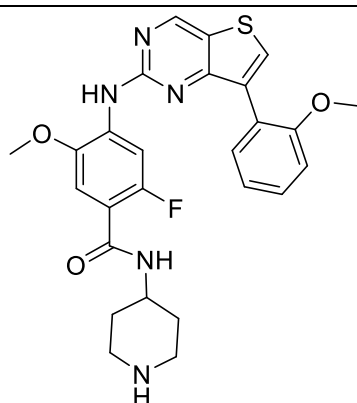
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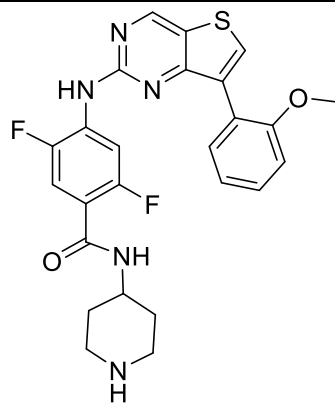
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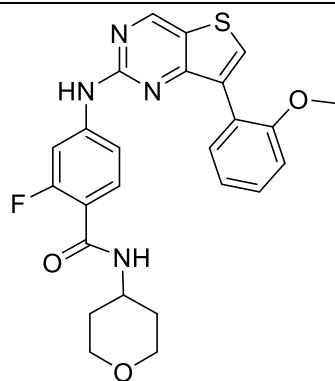
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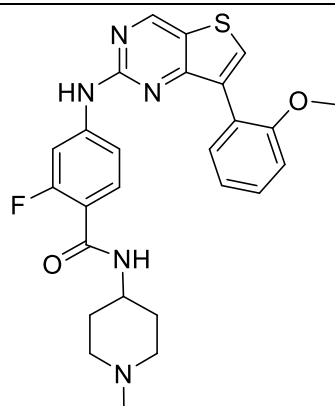
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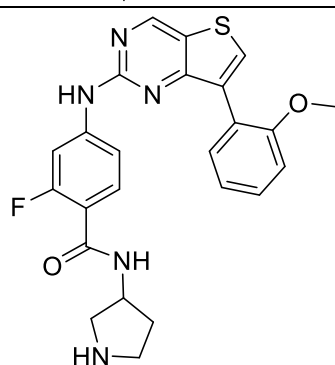
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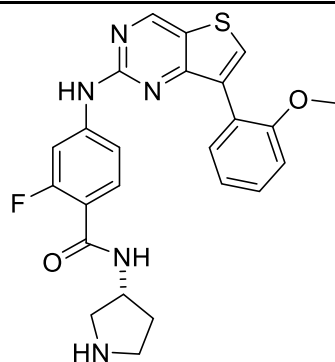
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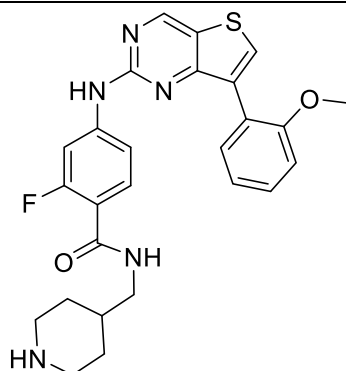
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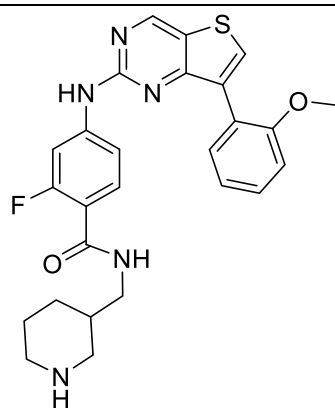
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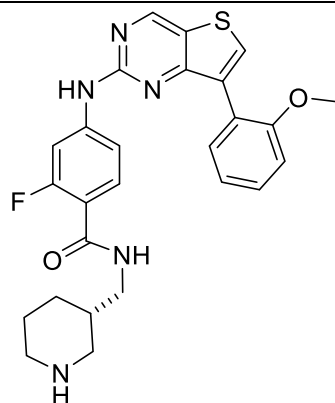
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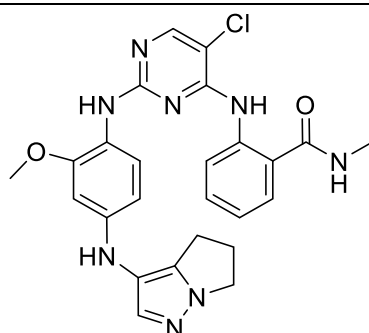
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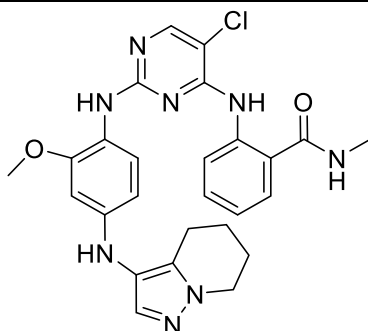
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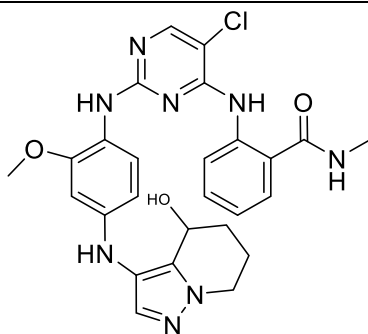
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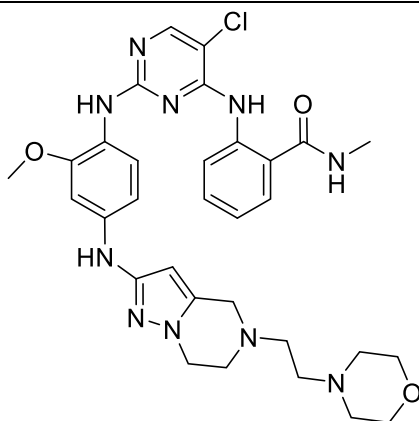
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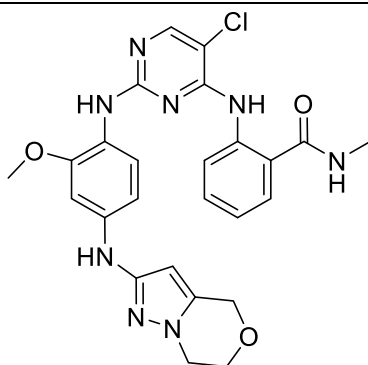
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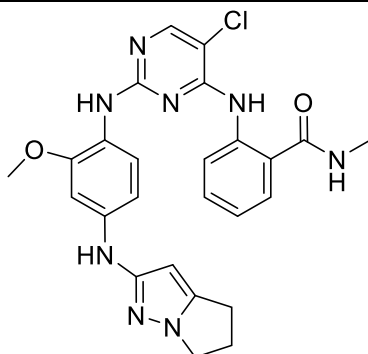
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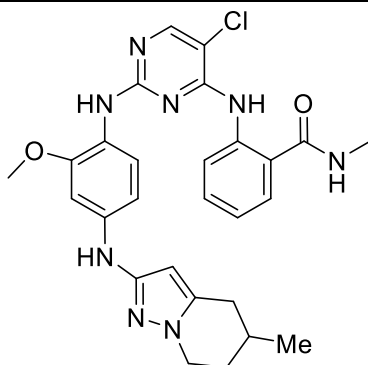
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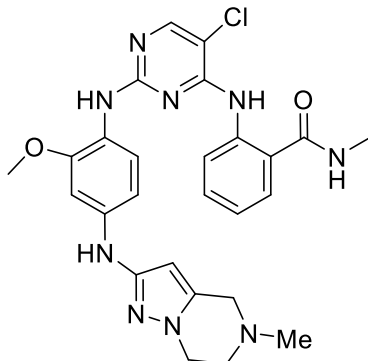
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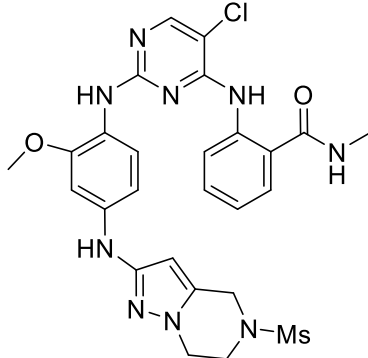
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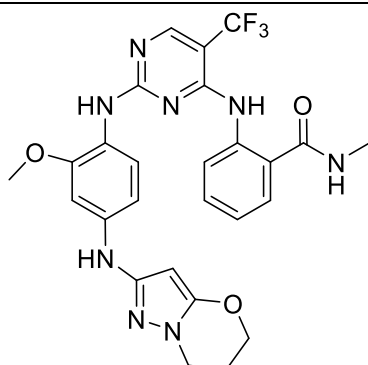
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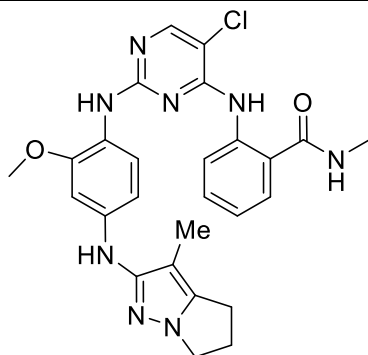
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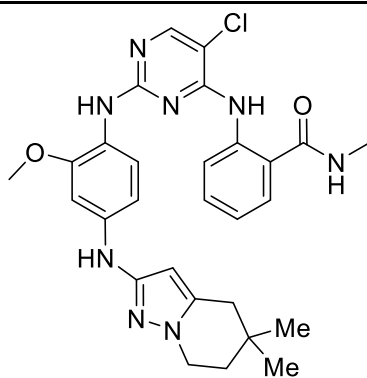
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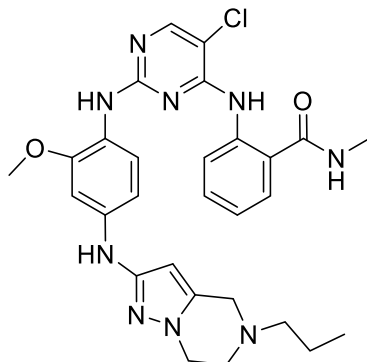
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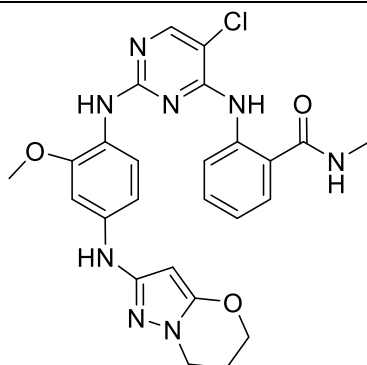
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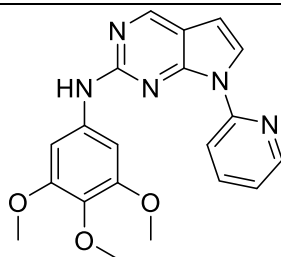
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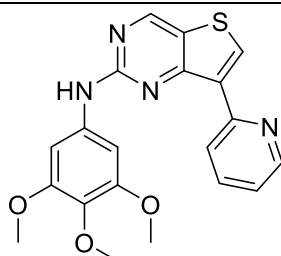
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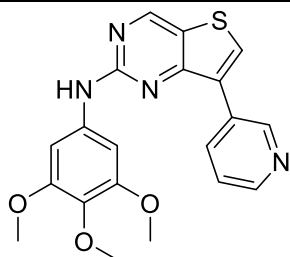
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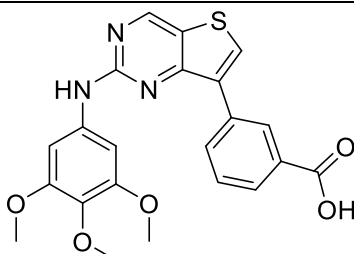
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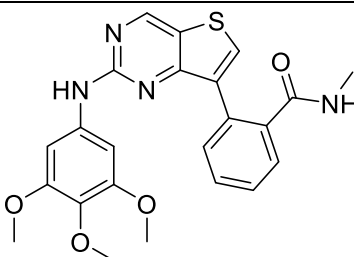
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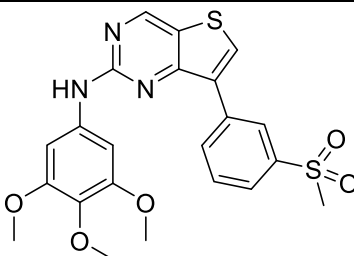
90



pyrimidine

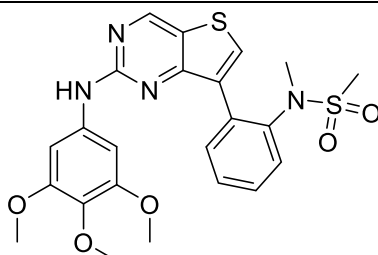
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91



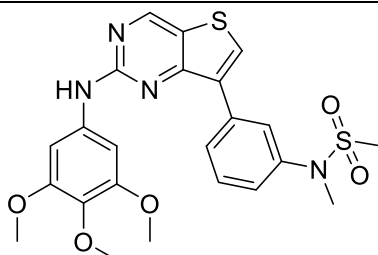
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92



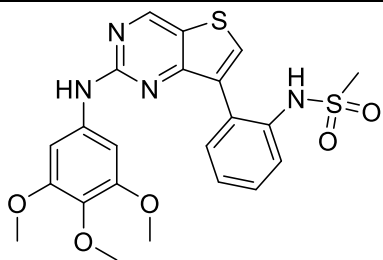
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93



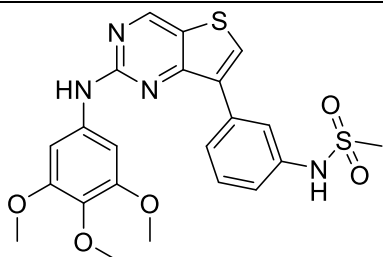
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94



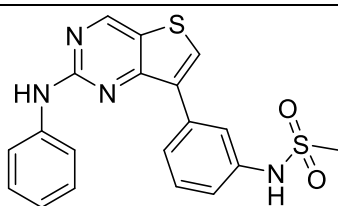
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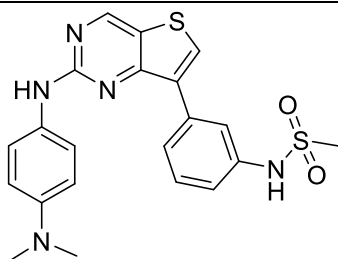
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96



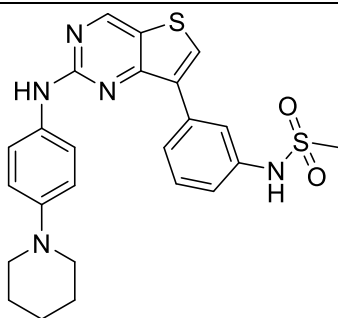
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97



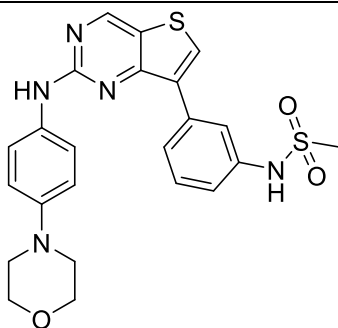
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98



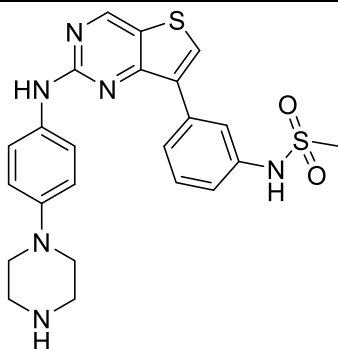
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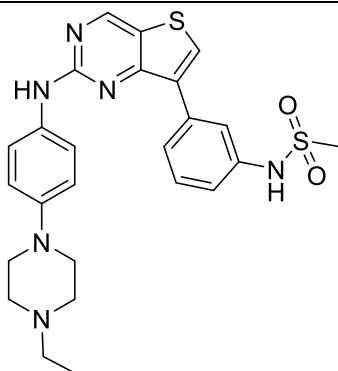
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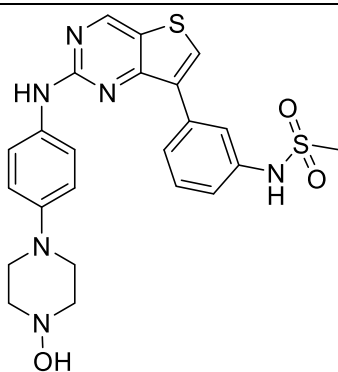
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101



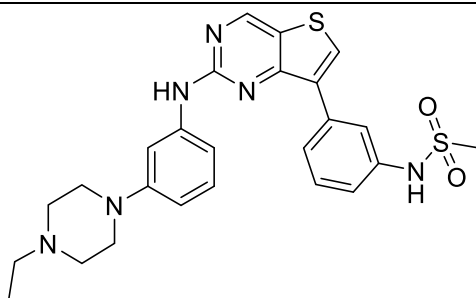
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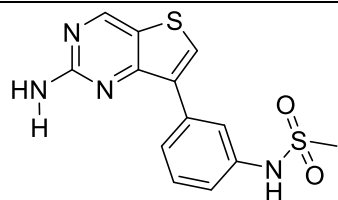
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103



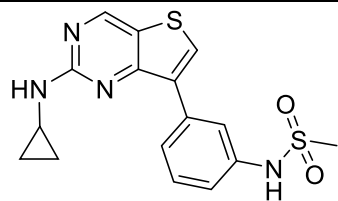
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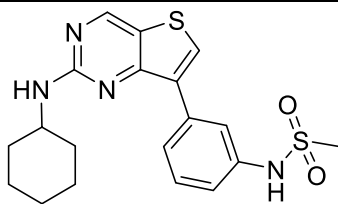
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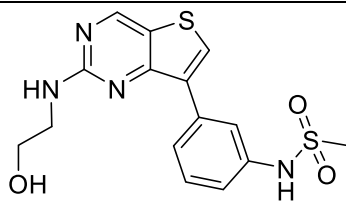
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106



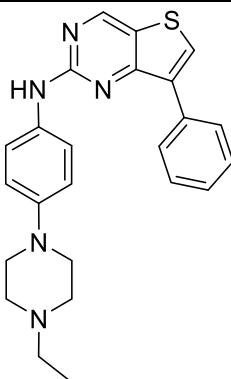
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107



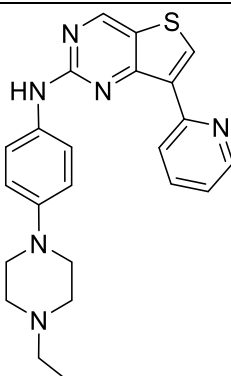
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108



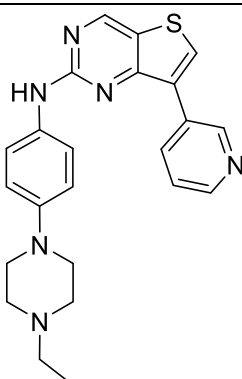
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109



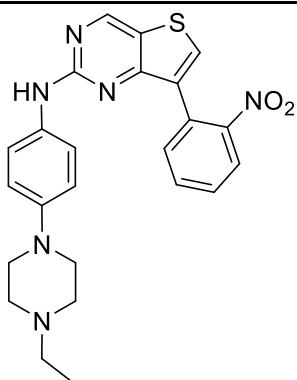
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110



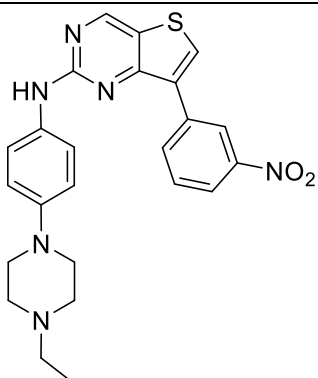
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111



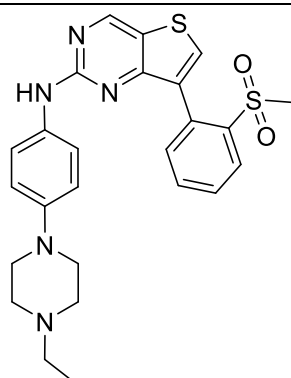
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112



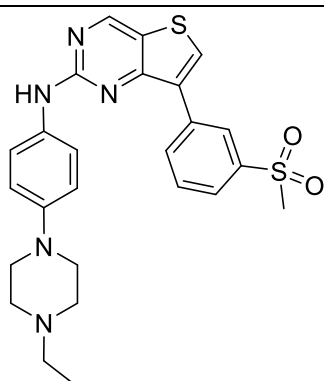
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113



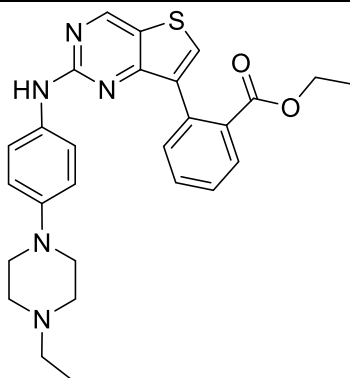
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114



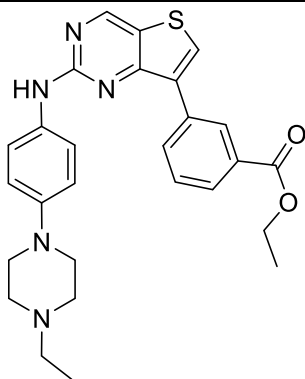
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115



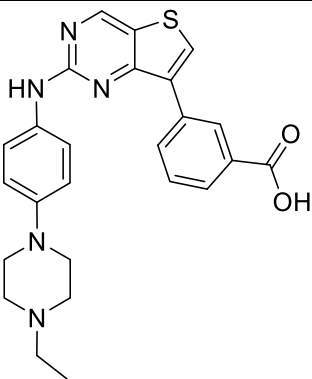
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116



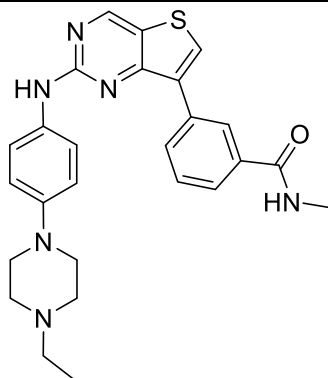
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117



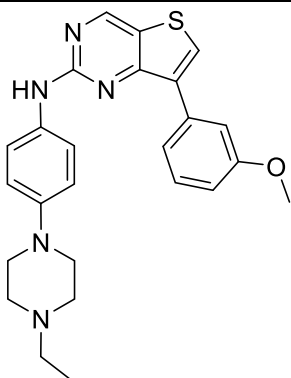
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118



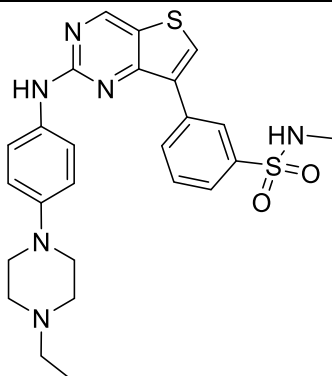
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119



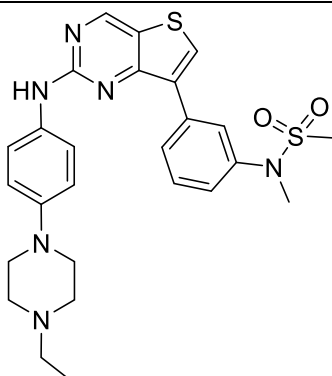
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120



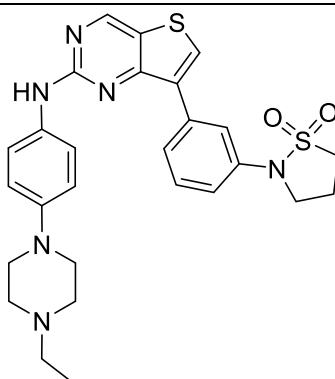
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121



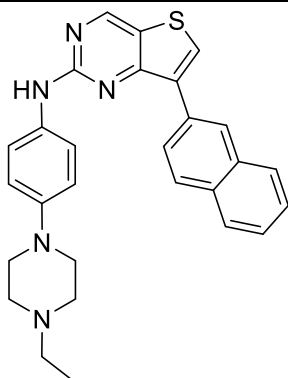
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122



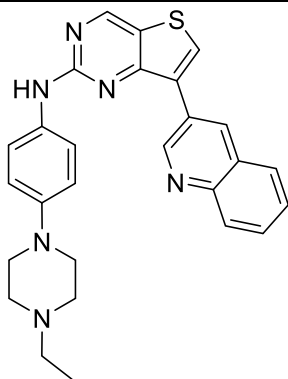
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123



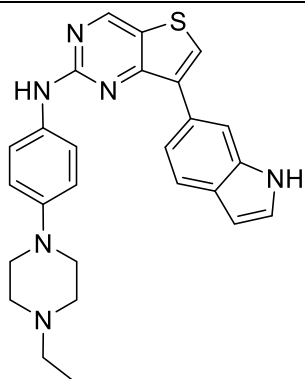
6.89

124



7.53

125



7.26

Table S4. Random draw table for test set compounds.

High activity			Low activity			Medium activity			
C99	8.09	0.046511	C91	7.04	0.047715	C94	7.1	0.067219	SET-A
C95	8.15	0.056668	C10	7.05	0.092258	C56	7.57	0.070681	
C22	7.81	0.119098	C66	6.87	0.115795	C50	7.41	0.094359	
C74	8.88	0.135938	C01	6.76	0.124531	C110	7.5	0.11626	
C112	7.67	0.142158	C64	6.92	0.156929	C93	7.45	0.146571	
C97	7.74	0.154044	C123	6.89	0.205567	C51	7.23	0.160988	SET-B
C120	7.95	0.170794	C59	6.14	0.222062	C118	7.44	0.185591	
C119	7.92	0.184314	C45	6.8	0.224221	C122	7.48	0.200651	
C82	8.29	0.188492	C48	6.45	0.238903	C04	7.2	0.217415	
C36	8.2	0.188558	C07	6.94	0.246183	C15	7.54	0.245775	
C76	9.24	0.19125	C40	6.85	0.247239	C62	7.14	0.251774	SET-C
C19	7.94	0.270151	C46	6.73	0.396101	C73	7.53	0.263063	
C26	7.98	0.27297	C54	6.48	0.418428	C03	7.17	0.288624	
C83	8.49	0.285854	C116	6.49	0.425414	C49	7.1	0.318349	
C121	7.67	0.291042	C39	6.45	0.427529	C27	7.07	0.329871	
C16	7.64	0.32477	C105	5.62	0.433339	C11	7.26	0.334799	SET-D
C75	8.74	0.366041	C44	5.97	0.449833	C124	7.53	0.338937	
C108	8	0.373527	C58	6.78	0.464327	C12	7.32	0.3417	
C63	7.61	0.374259	C70	6.82	0.490395	C14	7.23	0.368718	
C114	7.74	0.416158	C85	6.69	0.493984	C89	7.25	0.375657	
C86	7.74	0.429647	C42	6.42	0.498409	C98	7.16	0.476172	SET-A
C101	8.15	0.495314	C69	6.95	0.547368	C65	7.31	0.484069	
C18	7.62	0.519801	C47	6.49	0.606051	C25	7.31	0.484779	
C71	9.55	0.53617	C38	5.96	0.642058	C57	7.56	0.557927	
C72	9.35	0.559578	C52	6.77	0.659376	C28	7.08	0.574669	
C17	7.64	0.625503	C35	6.62	0.669621	C20	7.36	0.596315	SET-B
C80	9.46	0.633174	C68	6.92	0.694384	C125	7.26	0.598507	
C24	8.14	0.750463	C111	6.44	0.700532	C87	7.58	0.63906	
C84	9.37	0.75299	C53	6.7	0.702626	C60	7.54	0.681378	
C13	7.65	0.805919	C90	6.17	0.753446	C06	7.48	0.694101	
C109	7.92	0.817795	C115	5.78	0.758656	C96	7.52	0.722374	SET-C
C102	7.79	0.849353	C32	6.95	0.798334	C21	7.58	0.770724	
C61	7.59	0.852992	C104	5.39	0.800923	C117	7.22	0.820879	
C78	8.6	0.909932	C33	6.94	0.810285	C23	7.42	0.844675	
C81	10.04	0.922773	C34	6.96	0.823336	C31	7.06	0.849694	
C92	7.82	0.926264	C37	6.87	0.827899	C05	7.23	0.855154	SET-D
C100	7.92	0.930799	C113	6.71	0.847475	C02	7.22	0.855431	
C103	7.88	0.958278	C29	6.96	0.848348	C67	7.14	0.870785	
C08	7.71	0.980281	C43	6.19	0.866393	C30	7.07	0.922571	
C79	9.35	0.981901	C106	6.14	0.985245	C55	7.31	0.937029	
C77	9.95	0.987713	C41	6.48	0.994829	C88	7.3	0.940625	SET-A
						C09	7.19	0.94266	

Table S5. Statistics of CoMSIA model development.

CoMSIA	q^2	ONC	SEP	r^2	SEE	F-value	Field Contribution				
							S	E	H	A	D
S	0.476	2	0.615	0.608	0.532	69.815	100	-	-	-	-
E	0.543	3	0.577	0.672	0.489	60.786	-	100	-	-	-
H	0.462	4	0.630	0.710	0.463	53.777	-	-	100	-	-
A	0.412	2	0.651	0.527	0.584	50.123	-	-	-	100	-
D	0.475	5	0.626	0.711	0.465	42.738	-	-	-	-	100
SE	0.552	6	0.582	0.853	0.333	82.997	31.2	68.8	-	-	-
EH	0.533	6	0.594	0.854	0.332	83.767	-	62.7	37.3	-	-
EA	0.531	2	0.582	0.656	0.498	85.688	-	59.1	-	40.9	-
ED	0.626	6	0.531	0.838	0.352	73.143	-	59.4	-	-	40.6
SH	0.488	2	0.608	0.641	0.509	80.493	49.9	-	50.1	-	-
SA	0.476	5	0.626	0.786	0.400	63.954	41.1	-	-	59.9	-
SD	0.544	4	0.580	0.749	0.430	65.747	42.8	-	-	-	57.2
HA	0.426	5	0.654	0.760	0.423	55.022	-	-	46.9	53.1	-
HD	0.575	4	0.560	0.768	0.414	72.690	-	-	48.1	-	51.9
AD	0.487	3	0.612	0.666	0.494	59.212	-	-	-	54.6	45.4
SHE	0.556	6	0.579	0.877	0.305	102.032	21.2	49.9	29.3	-	-
SEA	0.561	6	0.576	0.864	0.320	91.420	20.4	47.0	-	32.6	-
SED	0.656	6	0.510	0.862	0.323	89.719	18.7	46.1	-	-	35.2
EHA	0.543	6	0.588	0.853	0.333	83.432	-	44.6	25.0	30.3	-

EHD	0.631	6	0.528	0.863	0.322	90.298	-	42.7	23.2	-	34.1
SHA	0.490	5	0.617	0.811	0.376	74.442	25.6	-	33.9	40.6	-
SHD	0.574	4	0.561	0.783	0.400	79.243	23.9	-	34.9	-	41.2
EAD	0.602	5	0.545	0.817	0.369	77.741	-	43.6	-	26.5	29.9
HAD	0.540	5	0.586	0.801	0.385	70.045	-	-	32.9	32.2	34.9
SEHD	0.639	6	0.522	0.874	0.309	99.200	14.2	35.8	19.3	-	30.6
SEHA	0.559	6	0.577	0.873	0.310	98.318	15.5	37.0	20.5	27.0	-
SEAD	0.639	6	0.522	0.863	0.321	90.442	14.9	34.9	-	23.9	26.3
EHAD	0.620	6	0.536	0.863	0.322	90.308	-	33.8	18.9	21.6	25.8
SHAD	0.584	5	0.557	0.827	0.359	83.193	18.0	-	25.3	27.2	29.6
SEHAD	0.639	6	0.522	0.875	0.307	100.545	12.0	28.7	15.7	19.9	23.7

(S: Steric; E: Electrostatic; H: Hydrophobic; A: H-bond acceptor; D: H-bond donor).

Table S6. Actual vs. predicted pIC₅₀ values of CoMFA and CoMSIA (SET-D) models.

#Cpd	CoMFA			CoMSIA (SED)		
	Actual pIC50	Predicted pIC50	Residuals	Actual pIC50	Predicted pIC50	Residuals
C105	5.62	5.777	-0.157	5.62	5.962	-0.342
C115	5.78	6.415	-0.635	5.78	6.592	-0.812
C38	5.96	6.966	-1.006	5.96	6.105	-0.145
C44	5.97	7.492	-1.522	5.97	6.622	-0.652
C59	6.14	7.428	-1.288	6.14	7.506	-1.366
C90	6.17	6.305	-0.135	6.17	6.658	-0.488
C42	6.42	6.604	-0.184	6.42	6.466	-0.046
C111	6.44	6.381	0.059	6.44	6.702	-0.262
C39	6.45	6.251	0.199	6.45	6.402	0.048
C48	6.45	6.5	-0.05	6.45	6.165	0.285
C54	6.48	6.29	0.19	6.48	6.832	-0.352
C47	6.49	6.683	-0.193	6.49	6.237	0.253
C116	6.49	6.626	-0.136	6.49	7.074	-0.584
C35	6.62	6.863	-0.243	6.62	6.789	-0.169
C85	6.69	7.065	-0.375	6.69	7.414	-0.724
C53	6.7	6.555	0.145	6.7	6.84	-0.14
C46	6.73	6.657	0.073	6.73	6.727	0.003
C01	6.76	7.08	-0.32	6.76	6.815	-0.055
C52	6.77	6.887	-0.117	6.77	6.878	-0.108
C58	6.78	7.869	-1.089	6.78	8.052	-1.272
C45	6.8	6.796	0.004	6.8	6.363	0.437
C70	6.82	7.204	-0.384	6.82	7.105	-0.285
C40	6.85	6.623	0.227	6.85	6.442	0.408
C66	6.87	7	-0.13	6.87	7.131	-0.261
C123	6.89	7.283	-0.393	6.89	7.339	-0.449
C64	6.92	7.152	-0.232	6.92	7.001	-0.081
C68	6.92	6.898	0.022	6.92	6.846	0.074
C07	6.94	7.044	-0.104	6.94	7.192	-0.252
C69	6.95	6.904	0.046	6.95	6.706	0.244
C91	7.04	6.999	0.041	7.04	6.954	0.086
C10	7.05	7.255	-0.205	7.05	7.154	-0.104
C27	7.07	7.168	-0.098	7.07	7.123	-0.053
C28	7.08	7	0.08	7.08	6.984	0.096
C94	7.1	6.95	0.15	7.1	7.024	0.076
C49	7.1	7.022	0.078	7.1	6.841	0.259
C62	7.14	7.77	-0.63	7.14	7.611	-0.471
C98	7.16	7.924	-0.764	7.16	7.33	-0.17
C03	7.17	7.562	-0.392	7.17	7.407	-0.237
C09	7.19	7.374	-0.184	7.19	7.229	-0.039
C04	7.2	7.146	0.054	7.2	7.089	0.111
C51	7.23	6.982	0.248	7.23	7.11	0.12
C14	7.23	7.206	0.024	7.23	7.128	0.102
C89	7.25	6.607	0.643	7.25	6.59	0.66
C125	7.26	7.408	-0.148	7.26	7.382	-0.122
C11	7.26	7.403	-0.143	7.26	6.856	0.404

C25	7.31	7.478	-0.168	7.31	7.529	-0.219
C65	7.31	7.24	0.07	7.31	7.064	0.246
C12	7.32	7.163	0.157	7.32	7.498	-0.178
C20	7.36	7.365	-0.005	7.36	7.333	0.027
C50	7.41	7.182	0.228	7.41	7.406	0.004
C118	7.44	7.75	-0.31	7.44	7.338	0.102
C93	7.45	8.25	-0.8	7.45	7.67	-0.22
C06	7.48	7.416	0.064	7.48	7.745	-0.265
C122	7.48	6.718	0.762	7.48	7.295	0.185
C110	7.5	7.654	-0.154	7.5	7.532	-0.032
C96	7.52	8.198	-0.678	7.52	7.227	0.293
C73	7.53	9.3	-1.77	7.53	9.108	-1.578
C124	7.53	7.418	0.112	7.53	7.177	0.353
C60	7.54	7.236	0.304	7.54	7.453	0.087
C15	7.54	7.5	0.04	7.54	7.469	0.071
C57	7.56	7.976	-0.416	7.56	8.009	-0.449
C56	7.57	7.527	0.043	7.57	7.759	-0.189
C87	7.58	7.637	-0.057	7.58	7.529	0.051
C63	7.61	7.079	0.531	7.61	7.275	0.335
C18	7.62	7.411	0.209	7.62	7.647	-0.027
C17	7.64	7.21	0.43	7.64	7.174	0.466
C16	7.64	7.542	0.098	7.64	7.518	0.122
C13	7.65	7.328	0.322	7.65	7.461	0.189
C112	7.67	7.415	0.255	7.67	7.065	0.605
C121	7.67	7.618	0.052	7.67	7.683	-0.013
C114	7.74	7.707	0.033	7.74	7.38	0.36
C86	7.74	7.286	0.454	7.74	7.484	0.256
C97	7.74	7.55	0.19	7.74	7.839	-0.099
C22	7.81	7.383	0.427	7.81	7.232	0.578
C119	7.92	7.839	0.081	7.92	7.553	0.367
C109	7.92	7.279	0.641	7.92	7.488	0.432
C19	7.94	7.496	0.444	7.94	7.266	0.674
C120	7.95	7.512	0.438	7.95	7.897	0.053
C26	7.98	7.616	0.364	7.98	7.918	0.062
C108	8	7.576	0.424	8	7.355	0.645
C99	8.09	7.995	0.095	8.09	7.817	0.273
C24	8.14	7.249	0.891	8.14	7.425	0.715
C101	8.15	8.236	-0.086	8.15	7.869	0.281
C95	8.15	8.35	-0.2	8.15	8.458	-0.308
C36	8.2	8.332	-0.132	8.2	7.951	0.249
C82	8.29	8.845	-0.555	8.29	9.14	-0.85
C83	8.49	8.409	0.081	8.49	8.613	-0.123
C75	8.74	8.846	-0.106	8.74	8.593	0.147
C74	8.88	8.911	-0.031	8.88	8.989	-0.109
C76	9.24	8.916	0.324	9.24	8.836	0.404
C72	9.35	9.362	-0.012	9.35	9.248	0.102
C84	9.37	9.363	0.007	9.37	9.237	0.133
C80	9.46	9.475	-0.015	9.46	9.262	0.198
C71	9.55	8.86	0.69	9.55	8.774	0.776
C104	5.39	5.672	-0.282	5.39	5.403	-0.013
C106	6.14	6.452	-0.312	6.14	6.272	-0.132
C43	6.19	6.276	-0.086	6.19	6.416	-0.226
C41	6.48	6.752	-0.272	6.48	6.434	0.046
C113	6.71	6.471	0.239	6.71	6.641	0.069
C37	6.87	6.544	0.326	6.87	6.402	0.468
C33	6.94	7.027	-0.087	6.94	7.089	-0.149
C32	6.95	6.848	0.102	6.95	6.932	0.018
C34	6.96	6.948	0.012	6.96	6.828	0.132
C29	6.96	7.258	-0.298	6.96	7.068	-0.108
C31	7.06	6.936	0.124	7.06	6.859	0.201
C30	7.07	7.164	-0.094	7.07	6.921	0.149
C67	7.14	7.198	-0.058	7.14	7.195	-0.055

C117	7.22	7.115	0.105	7.22	7.435	-0.215
C02	7.22	7.164	0.056	7.22	7.208	0.012
C05	7.23	7.36	-0.13	7.23	7.685	-0.455
C88	7.3	7.427	-0.127	7.3	7.081	0.219
C55	7.31	7.241	0.069	7.31	7.549	-0.239
C23	7.42	7.379	0.041	7.42	7.376	0.044
C21	7.58	7.716	-0.136	7.58	8.157	-0.577
C61	7.59	7.487	0.103	7.59	7.747	-0.157
C08	7.71	7.798	-0.088	7.71	8.06	-0.35
C102	7.79	8.102	-0.312	7.79	7.827	-0.037
C92	7.82	6.909	0.911	7.82	7.033	0.787
C103	7.88	7.74	0.14	7.88	6.659	1.221
C100	7.92	8.022	-0.102	7.92	7.808	0.112
C78	8.6	8.596	0.004	8.6	8.673	-0.073
C79	9.35	9.123	0.227	9.35	9.132	0.218
C77	9.95	9.02	0.93	9.95	9.152	0.798
C81	10.04	9.695	0.345	10.04	9.277	0.763

Test set data are shown in blue.

Table S7. λ parameters to gradually change the ligand interaction from state-A to state-B.

λ	Parameter id											
	1	2	3	4	5	6	7	8	9	10	11	12
lambljA	1.0	0.909	0.818	0.727	0.636	0.545	0.455	0.364	0.273	0.182	0.091	0.0
lambljB	0.0	0.091	0.182	0.273	0.364	0.455	0.545	0.636	0.727	0.818	0.909	1.0
lambelA	1.0	0.909	0.818	0.727	0.636	0.545	0.455	0.364	0.273	0.182	0.091	0.0
lambelB	0.0	0.091	0.182	0.273	0.364	0.455	0.545	0.636	0.727	0.818	0.909	1.0
lambbondA	1.0	0.909	0.818	0.727	0.636	0.545	0.455	0.364	0.273	0.182	0.091	0.0
lambbondB	0.0	0.091	0.182	0.273	0.364	0.455	0.545	0.636	0.727	0.818	0.909	1.0

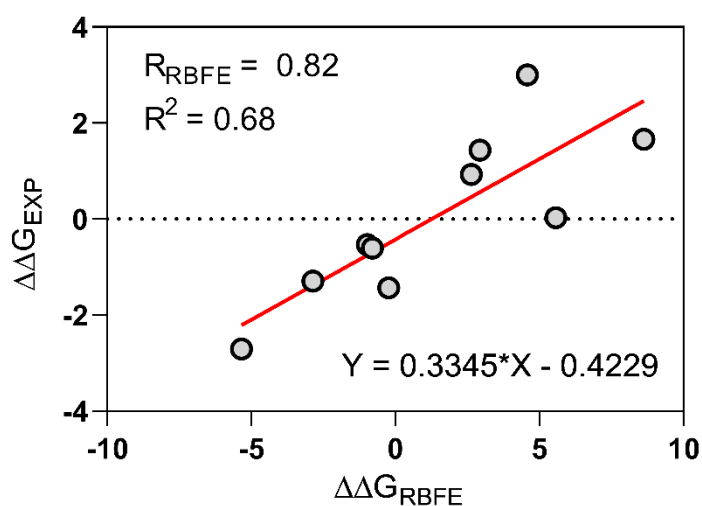


Figure S2. Correlation plot between experimental and computed relative binding free energies.