

Identification of novel Src, Bcl-2 dual inhibitors by Pharmacophore Model, Molecular Docking, and Molecular Dynamics Simulations

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Table S1. Information about small molecules in the Src active validation set

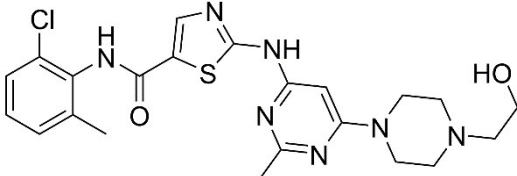
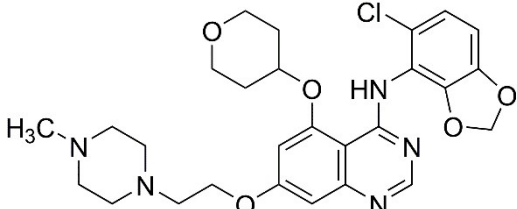
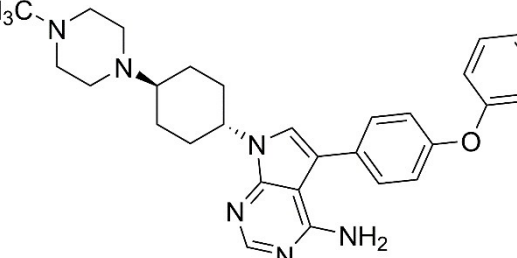
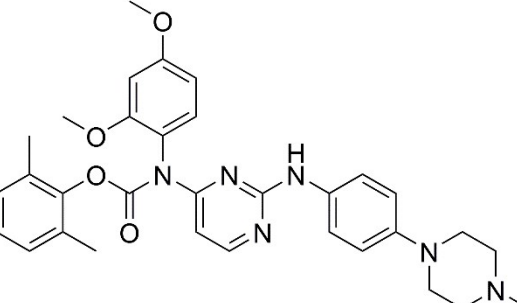
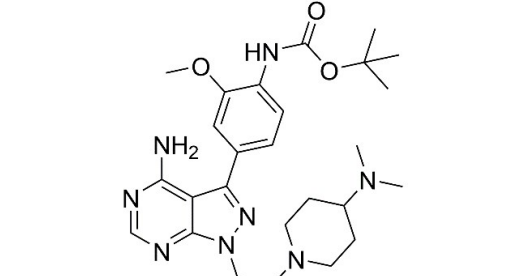
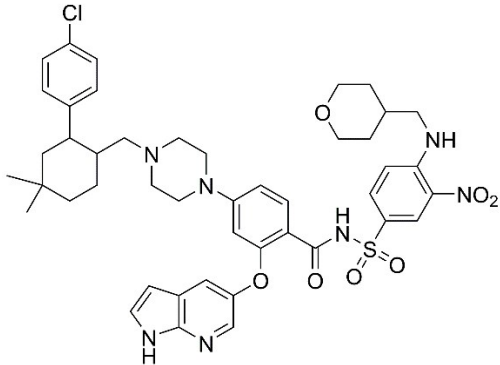
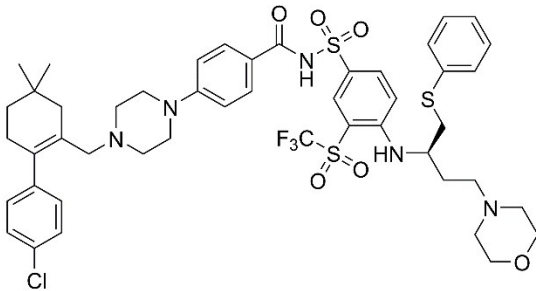
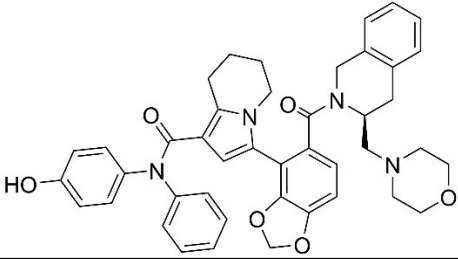
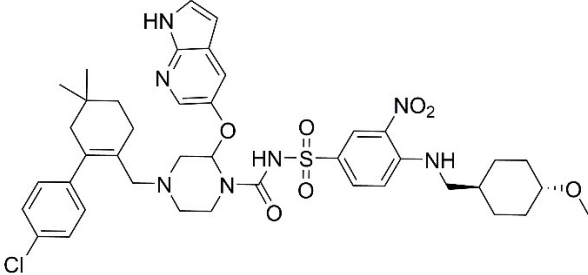
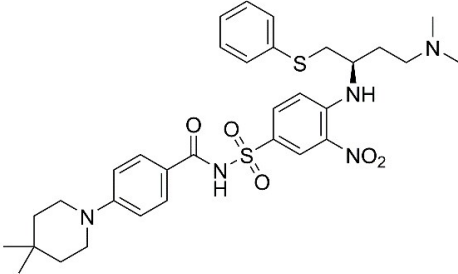
No.	Structure	Active
Dasatinib CAS 302962-49-8	 <p>The structure of Dasatinib features a central pyrimidopyrimidine core. It is substituted with a 2-chloro-3-methylphenyl group, a 2-hydroxyethylpiperazine ring, and a 2-thiazolyl group. The thiazole ring is further substituted with a 2-(3-chloro-4-(2-hydroxyethyl)piperazin-1-yl)phenyl group.</p>	Ki = 16pM
Saracatinib CAS 379231-04-6	 <p>The structure of Saracatinib consists of a central pyrimidopyrimidine core. It is substituted with a 2-(2-(2-methylpiperazin-1-yl)ethoxy)phenyl group, a 2-(2-chloro-4-(2-hydroxyethyl)piperazin-1-yl)phenyl group, and a 2-(2-(2-hydroxyethyl)piperazin-1-yl)phenyl group.</p>	IC50 = 2.7nM
A 419259 CAS 364042-47-7	 <p>The structure of A 419259 features a central pyrimidopyrimidine core. It is substituted with a 2-(2-(2-methylpiperazin-1-yl)cyclohexyl)phenyl group, a 2-(2-(2-hydroxyethyl)piperazin-1-yl)phenyl group, and a 2-(2-(2-hydroxyethyl)piperazin-1-yl)phenyl group.</p>	IC50 = 9nM
WH-4-023 CAS 837422-57-8	 <p>The structure of WH-4-023 consists of a central pyrimidopyrimidine core. It is substituted with a 2-(2-(2-methylpiperazin-1-yl)ethoxy)phenyl group, a 2-(2-(2-hydroxyethyl)piperazin-1-yl)phenyl group, and a 2-(2-(2-hydroxyethyl)piperazin-1-yl)phenyl group.</p>	IC50 = 6nM
eCF506 CAS 1914078-41-3	 <p>The structure of eCF506 features a central pyrimidopyrimidine core. It is substituted with a 2-(2-(2-methylpiperazin-1-yl)ethoxy)phenyl group, a 2-(2-(2-hydroxyethyl)piperazin-1-yl)phenyl group, and a 2-(2-(2-hydroxyethyl)piperazin-1-yl)phenyl group.</p>	IC50 < 0.5nM

Table S2. Information about small molecules in the Bcl-2 active validation set

No.	Structure	Active
Venetoclax CAS 1257044-40-8	 <p>The structure of Venetoclax features a central benzene ring substituted with a 4-chlorophenyl group, a piperazine ring, a 2-oxo-1,2,3,4-tetrahydroquinoline-5-yl group, and a sulfonamide group. The sulfonamide group is further substituted with a morpholine ring and a 2-nitrophenyl group.</p>	Ki = 0.01 nM
Navitoclax CAS 923564-51-6	 <p>The structure of Navitoclax consists of a central benzene ring with a 4-chlorophenyl group, a piperazine ring, a sulfonamide group, and a sulfonamide group substituted with a trifluoromethyl group and a morpholine ring. A thioether bridge connects the central benzene ring to a phenyl ring, which is further substituted with a morpholine ring.</p>	Ki = 1 nM
S55746 CAS 1448584-12-0	 <p>The structure of S55746 is a complex polycyclic molecule featuring a central benzene ring with a hydroxyphenyl group, a piperazine ring, a morpholine ring, and a morpholine ring. It also includes a piperidine ring and a morpholine ring.</p>	Ki = 1.3 nM
BCL2-IN-1 CAS 1257044-75-9	 <p>The structure of BCL2-IN-1 features a central benzene ring with a 4-chlorophenyl group, a piperazine ring, a morpholine ring, a sulfonamide group, and a morpholine ring. It also includes a morpholine ring and a morpholine ring.</p>	Ki = 0.01 nM
A-385358 CAS 406228-55-5	 <p>The structure of A-385358 consists of a central benzene ring with a piperazine ring, a sulfonamide group, and a sulfonamide group. It also includes a morpholine ring and a morpholine ring.</p>	Ki = 67 nM.

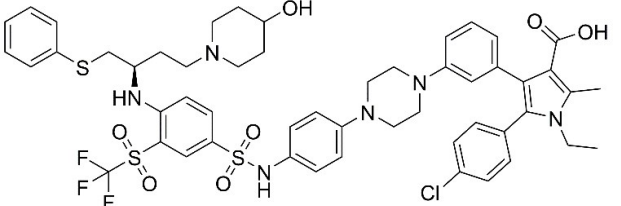
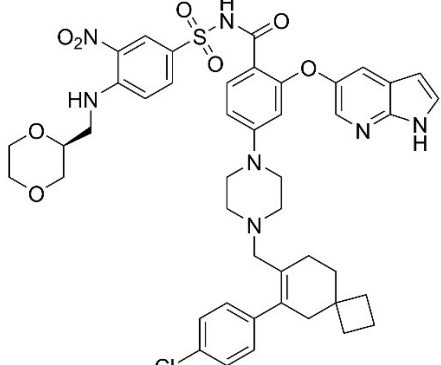
<p>BM 957 CAS 1391107-54-2</p>	 <p>The structure of BM 957 is a complex molecule featuring a central benzimidazole ring system. It is substituted with a 4-chlorophenyl group, a 4-(4-hydroxypiperidin-1-yl)phenyl group, a 4-(4-(2-phenylpropan-2-ylamino)phenyl)phenyl group, and a 4-(4-(trifluoromethyl)sulfonyl)phenyl group. The benzimidazole ring also has a methyl group and a carboxylic acid group attached to it.</p>	<p>IC50 = 5.4nM</p>
<p>Bcl-2/Bcl-xl inhibitor 1 CAS 2180923-05-9</p>	 <p>The structure of Bcl-2/Bcl-xl inhibitor 1 is a complex molecule featuring a central benzimidazole ring system. It is substituted with a 4-(4-chlorophenyl)phenyl group, a 4-(4-(2-(4-chlorophenyl)cyclohexyl)methyl)piperidin-1-yl)phenyl group, a 4-(4-nitrophenyl)phenyl group, and a 4-(4-(2-(4-methoxyphenyl)phenyl)phenyl)phenyl group. The benzimidazole ring also has a methyl group and a carboxylic acid group attached to it.</p>	<p>IC50 = 2 nM</p>

Table S3. The hydrogen bonding analysis of the last 10ns of MD simulation(T=300K)

Complex	Donor	Acceptor	Distance/Å	Angle/°	Occupancy/%
Compound1- Src	Compound1 (N41-H42)	GLU339(O)	2.883	14.29	90.54%
	Compound1 (N41-H42)	MET341(O)	3.152	14.95	0.03%
QTZ101-Src	QTZ101 (N41-H42)	GLU339(O)	3.023	13.45	0.01%
	QTZ101 (N41-H42)	MET341(O)	2.879	14.17	59.20%

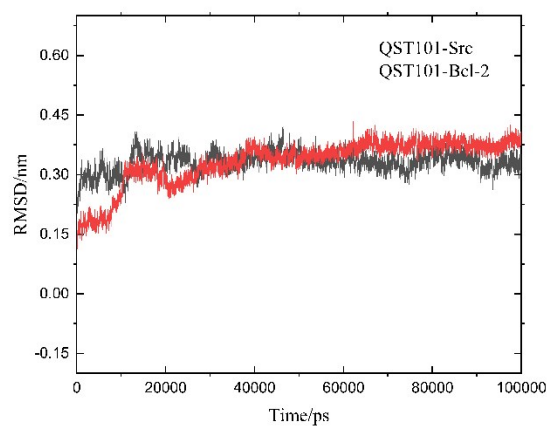


Figure S1. Root mean square deviation of protein backbone atoms ($T = 310\text{K}$).