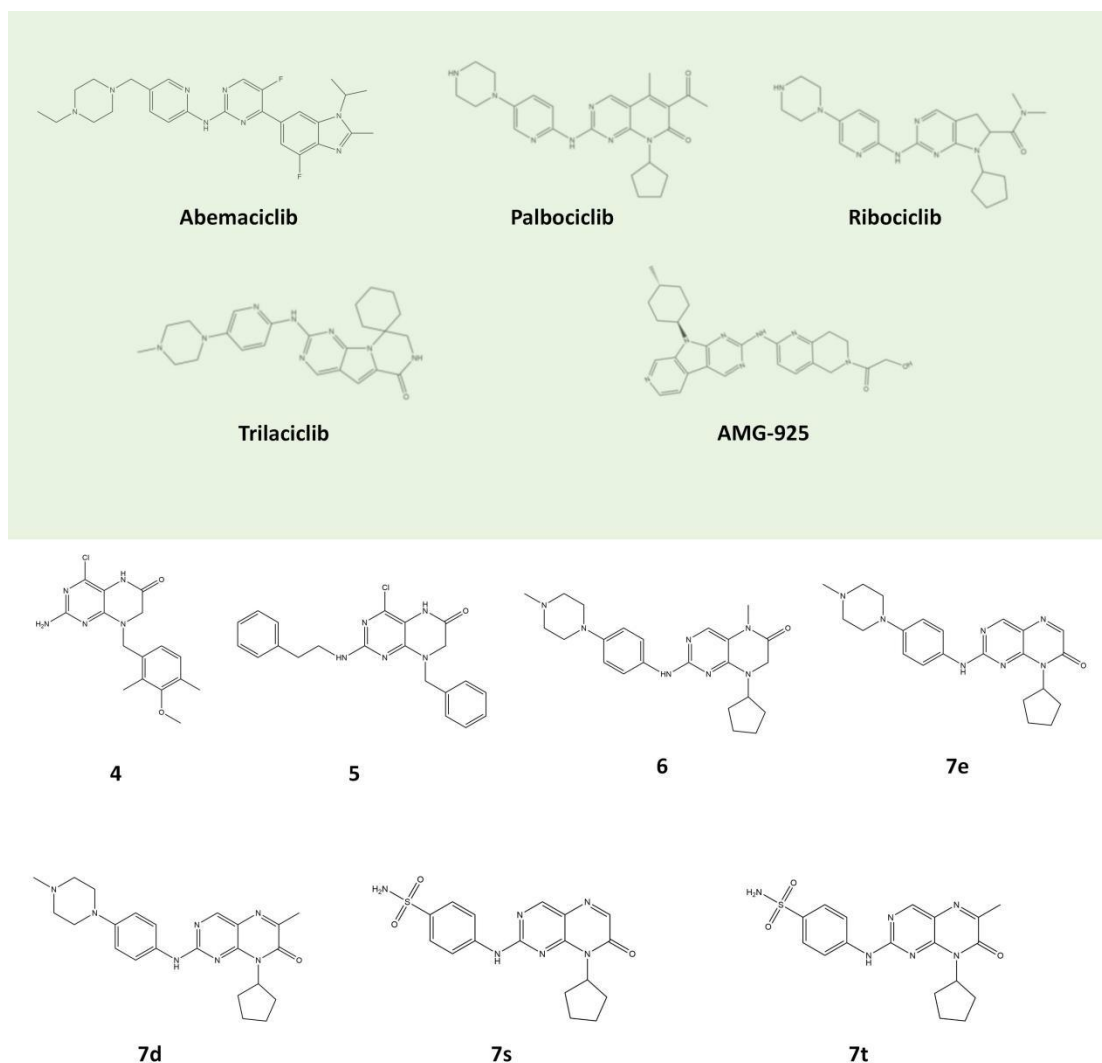


**Figure S1.** The Crystal structure and Ramachandran plot of CDK4/6. (A) CDK4 (PDB ID:2W96). (B) CKD6 (PDB ID:5L2S). (C) The Ramachandran plot of CDK4. (D) The Ramachandran plot of CKD6.



**Figure S2.** Five marketed and seven newly published inhibitor structures used to construct/test the pharmacophore.

**Table S1.** The 12 inactive decoy molecule's smile formula in the test set.

Smile	
Decoy molecules	<chem>CC1CCC(CC1)n2c3cnccc3c4c2nc(nc4)Nc5ccc6c(n5)CCN(C6)C(=O)CO</chem>
	<chem>Cc1cc(nn1C)C(=O)N[C@H]2C[C@H]3C(=O)Nc4ccc(cc4C(=O)N3C2)c5cccc(c5)C(F)(F)F</chem>
	<chem>Cc1cccc1n2c(=O)c(c([nH]c2=O)O)/C=C\3/C(=NN(C3=O)c4cccc(c4)Cl)C</chem>
	<chem>Cc1cc2c(cc1NC(=S)NC(=O)c3ccc4c(c3)OCCO4)nn(n2)c5ccc(cc5)F</chem>
	<chem>Cc1ccc(cc1)S(=O)(=O)Nc2nc(c(s2)C(=O)Nc3ccc4c(c3)OCCO4)C</chem>
	<chem>COc1cccc(c1)NC(=O)[C@@H]2CCCC3c2nc(s3)NC(=O)c4ccc5c(c4)OCO5</chem>
	<chem>c1ccc2c(c1)C=C(CO2)C(=O)Nc3ccc(cc3)NS(=O)(=O)c4ccc5c(c4)OCCCO5</chem>
	<chem>c1cc(cc(c1)NS(=O)(=O)c2cccc(c2)C(=O)Nc3ccc4c(c3)OCCCO4)C#N</chem>
	<chem>Cc1cc(cc(c1)NC(=O)c2cc(=O)[nH]c3c2cc(cc3)S(=O)(=O)N4CCOCC4)C</chem>
	<chem>CC(=O)Nc1ccc(cc1)S(=O)(=O)Nc2ccc3c(c2)S(=O)(=O)c4cccc4O3</chem>
	<chem>Cc1cc(c2c(c1)sc(n2)NC(=O)c3ccc(=O)n(c3)CC(=O)Nc4nccs4)C</chem>
	<chem>c1ccc(c(c1)C#N)NC(=O)Nc2cc(ccc2N3CCCC3)S(=O)(=O)N4CCCC4</chem>