Supplementary Material

In silico design of novel HIV-1 NNRTIs based on combined modeling studies of dihydrofuro[3,4-d]pyrimidines

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Table S1. Classical statistical parameters of the CoMFA and CoMSIA models.

	Model	q^2	ONC	R^2	SEE	F	r_{pred}^2	Field contributions (%)				
								S	E	A	D	H
CoMFA	**S+E**	**0.647**	**8**	**0.970**	**0.094**	**121.235**	**0.751**	**42.9**	**57.1**			
	S+E+A+D+H	**0.735**	**10**	**0.982**	**0.076**	**151.015**	**0.672**	**4.1**	**19.7**	**29**	**33.4**	**13.8**
	A+H	0.562	6	0.919	0.149	60.902	0.542			60.8		39.2
	S+H	0.593	7	0.916	0.154	48.294	0.432	22.1				77.9
	A+D+H	0.684	11	0.982	0.076	136.118	0.346			34.8	44.1	21.1
	E+D+H	0.711	8	0.947	0.125	66.611	0.389		34.2		21.3	44.5
CoMSIA	E+A+H	0.605	5	0.905	0.159	63.062	0.538		35.2	42.3		22.5
	S+A+H	0.632	12	0.974	0.094	80.698	0.657	12.7		48.9		38.4
	E+A+D+H	0.723	11	0.983	0.074	143.976	0.601		20.9	29.4	35.1	14.6
	S+A+D+H	0.685	11	0.983	0.074	144.841	0.379	5.1		34.1	41.5	19.3
	S+E+D+H	0.705	8	0.947	0.125	66.748	0.453	4.9	32.1		43.2	19.8
	S+E+A+H	0.634	5	0.913	0.152	69.200	0.616	46.7	32.4	39.8		21.2

Table S2. Statistical parameters of the pharmacophore models.

Name	SPECIFITY	N_HITS	FEATS	PARETO	ENERGY	STERICS	HBOND	MOL_QRY
Model_01	5.346	7	10	0	268.32	5458.10	601.20	156.74
Model_02	2.914	10	10	0	19056660	5442.80	700.90	186.64
Model_03	5.785	10	8	0	655334.44	5379.40	636.50	207.01
Model_04	4.231	10	9	0	1814494.5	5292.30	667.70	142.97
Model_05	5.334	10	10	0	2932319	5707.10	602.80	129.35
Model_06	4.423	7	8	0	247.97	4924.60	595.30	124.69
Model_07	5.302	7	9	0	1831234.8	5550.00	612.90	99.63
Model_08	5.413	7	9	0	332.48	4682.30	602.30	156.71
Model_09	5.400	10	9	0	261107.9	4982.00	656.90	93.39
Model_10	4.550	9	8	0	10088992	5325.90	667.20	104.94
Model_11	4.693	10	8	0	457813.1	5434.80	617.10	92.35
Model_12	5.443	7	9	0	1421060	5237.60	676.30	84.12
Model_13	5.576	10	8	0	18232012	5511.30	659.90	81.53
Model_14	5.658	7	8	0	5499636	5733.70	653.50	76.31
Model_15	4.537	7	9	0	355631.6	4983.10	619.90	92.48
Model_16	4.498	5	10	0	1718275.7	5461.00	558.50	121.01
Model_17	5.673	10	8	0	1843.74	5338.30	608.50	65.64
Model_18	4.498	7	8	0	496847.31	5149.30	646.80	66.92
Model_19	4.554	8	8	0	37.30	4663.60	526.90	85.87
Model_20*	**5.746**	**9**	**8**	**0**	**62.29**	**4521.80**	**568.20**	**70.88**

Table S3. Hydrophobic, hydrogen bond, and π-π stacking interactions of the screened hits as potential HIV-1 NNRTI in the RT protein (PDB ID:6C0J).

Compounds	Hydrophobic	Hydrogen bonds	π-π
ZINC_57841658	Val106, Tyr181, Tyr188, Phe227, Trp229	Lys101 with O of NH Lys101 with OH of N Lys101 with NH of C=O	Tyr188, Tyr181, Phe227, Trp229
ZINC_60381334	Val106, Tyr181, Tyr188, Phe227, Trp229	Lys101 with O of NH Lys101 with OH of N	Tyr188, Tyr181, Phe227, Trp229
ZINC_63070905	Val106, Tyr181, Tyr188, Phe227, Trp229	Lys101 with O of NH Glu138 with OH of OH	Trp229
ZINC_69532225	Val106, Tyr181, Tyr188, Phe227, Trp229	Lys101 with O of NH Lys101 with OH of N Lys101 with NH of C=O	Tyr188, Tyr181, Phe227, Trp229
ZINC_71894576	Val106, Tyr181, Tyr188, Phe227, Trp229	Lys101 with O of NH Lys101 with OH of N Lys101 with NH of C=O	Tyr188, Tyr181, Phe227
ZINC_73709240	Val106, Tyr181, Tyr188, Phe227, Trp229	Ile180 with OH of C=O Ile180 with NH of C=O Glu138 with OH of C=O	Tyr188, Tyr181, Phe227, Trp229
ZINC_89506228	Val106, Tyr181, Tyr188, Phe227, Trp229	Lys101 with O of NH Lys101 with OH of N Lys101 with NH of C=O	Tyr188, Tyr181, Phe227, Trp229
ZINC_91409938	Val106, Tyr181, Tyr188, Phe227, Trp229	A network between Pro236 and Lys103 by a water molecule (W936)	Tyr188, Tyr181, Phe227, Trp229
ZINC_97995063	Val106, Tyr181, Tyr188, Phe227, Trp229	Lys101 with O of NH Lys101 with OH of N Lys101 with NH of C=O	Tyr188, Tyr181, Phe227, Trp229

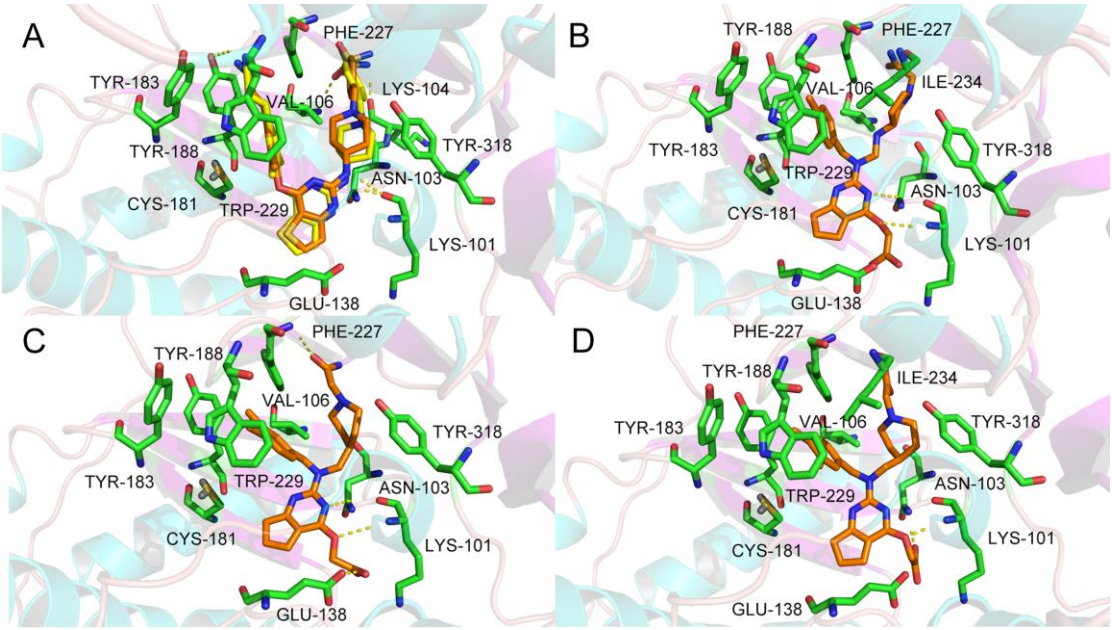

Figure S1. The docked results of compounds **25a**, **N1**, **N2**, and **N3** in the binding pocket of the mutant HIV-1 RT (PDB ID: 6C0R). (**A**) The re-docked co-crystallizing ligand (**25a**). The original and re-docked conformation were colored in yellow and orange, respectively. (**B**) The docking mode of compound **N1**. (**C**) The docking mode of compound **N2**. (**D**) The docking mode of compound **N3**.

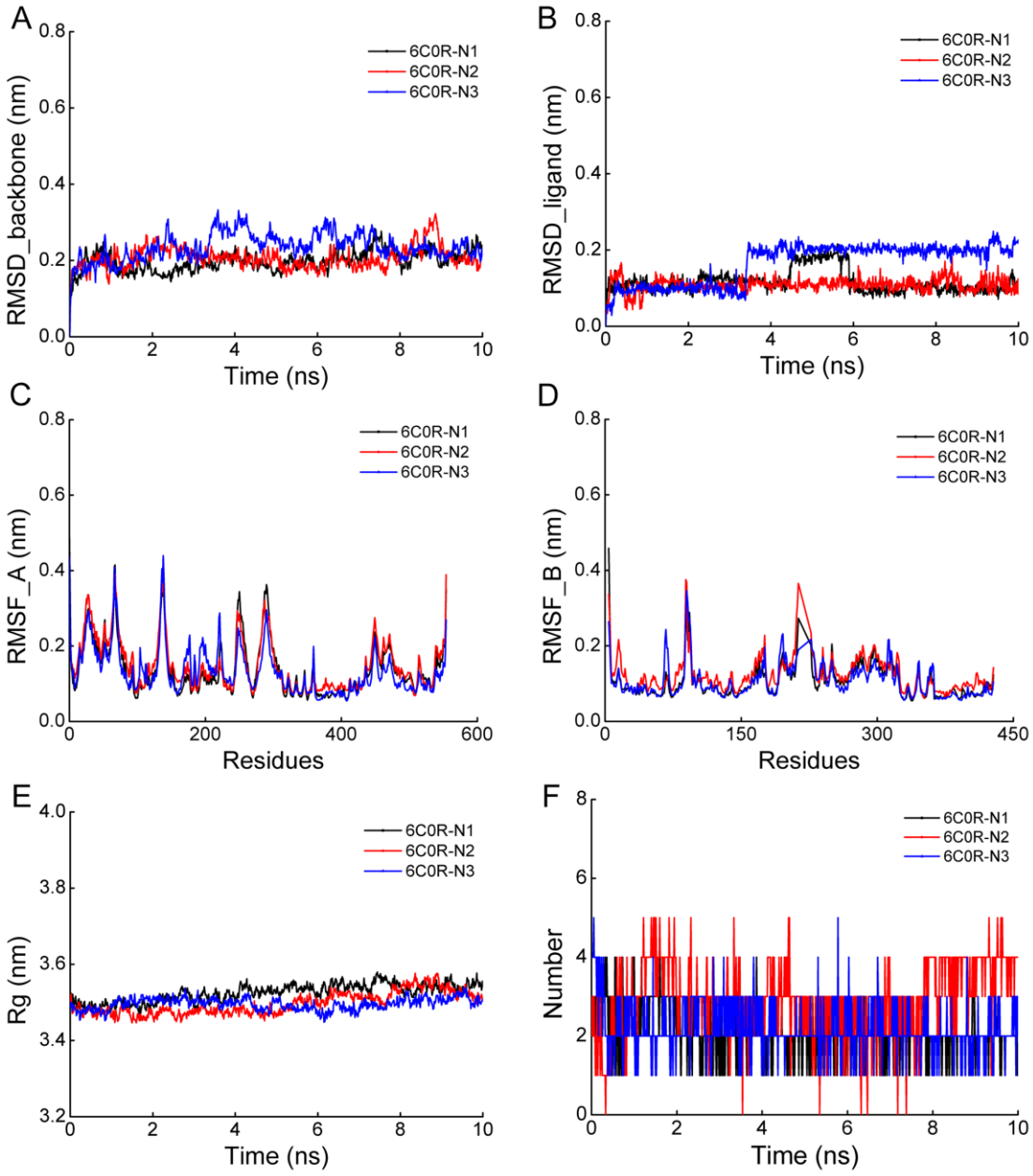

Figure S2. The 10 ns MD results of compounds **N1**, **N2**, and **N3** in the mutant HIV-1 RT (PDB ID: 6C0R). (**A**) RMSD values of backbone atoms of the protein. (**B**) RMSD values of the ligands. (**C**) RMSF values of the chain A. (**D**) RMSF values of the chain B. (**E**) Rg values of backbone atoms. (**F**) The total number of hydrogen bonds between the ligands and the protein.