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MDPI

Supplementary Materials

Virtual Screening and Molecular Docking Studies for Discovery of Potential RNA-Dependent RNA Polymerase Inhibitors

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Table S1. Molecular docking interaction between RdRp and selected compounds.

Compound	Binding Affinity (kcal/mol)	Docking Score	Ligand	Receptor	Interaction	Distance
ZINC000014944915	−20.37	−5.93	O 27	OD1 ASP 760 (A)	H-donor	2.05
			C–H 30	O5 POP 1003 (A)	H-donor	2.38
			O–H 38	O5 POP 1003 (A)	H-donor	1.91
			O 27	ND2 ASN 691 (A)	H-acceptor	2.28
			O 37	Mg Mg 1005 (A)	metal	2.49
			C 48	6-ring U 20 (P)	H-pi	4.03
			O 27	OD1 ASP 760 (A)	H-donor	2.8
ZINC000027556215	−20.19	−5.59	O 59	OD2 ASP 760 (A)	H-donor	1.9
			O 44	NE ARG 555 (A)	H-acceptor	1.97
			O 44	NH2 ARG 555 (A)	H-acceptor	2.5
ZINC000013556344	−17.91	−6.95	C 3	OD1 ASP 760 (A)	H-donor	3.29
			C 3	O5 POP 1003 (A)	H-donor	3.21
			O 14	O2 POP 1003 (A)	H-donor	2.13
			O 51	O6 POP 1003 (A)	H-donor	1.87
			O 1	NH2 ARG 555 (A)	H-acceptor	2.46
ZINC000003833965	−17.02	−5.079	C 28	O5 POP 1003 (A)	H-donor	3.34
			O 36	OD2 ASP 760 (A)	H-donor	2.75
			6-ring	CB SER 682 (A)	pi-H	3.89
ZINC000001642252	−16.86	−5.104	C 3	OD2 ASP 760 (A)	H-donor	3.46
			C 3	O5 POP 1003 (A)	H-donor	3.1
			O 20	O3' U 20 (P)	H-donor	2.01
			O 1	OG SER 759 (A)	H-acceptor	2.36
			O 1	O2' U 20 (P)	H-acceptor	1.83
			6-ring	CB SER 682 (A)	pi-H	3.82
ZINC000028525778	−16.78	−6.41	O 3	OD1 ASP 760 (A)	H-donor	3.22
			C 5	OD2 ASP 760 (A)	H-donor	3.51
			O 27	OG1 THR 556 (A)	H-donor	2.92

			O 1	MG Mg 1005 (A)	metal	2.42
ZINC000027557701	−16.63	−5.979	C 37	OD1 ASP 760 (A)	H-donor	3.23
			C 37	O5 POP 1003 (A)	H-donor	3.22
			O 51	O HOH 1104 (A)	H-donor	2.68
			O 1	N3 U 10 (T)	H-acceptor	3.11
			O 36	NH2 ARG 555 (A)	H-acceptor	3.1
			C 37	OD1 ASP 760 (A)	H-donor	3.23
ZINC000003589958	−16.29	−6.07	O 17	OD2 ASP 760 (A)	H-donor	2.06
			O 41	SD MET 542 (A)	H-donor	2.82
			O 30	ND2 ASN 691 (A)	H-acceptor	2.17
ZINC000001651128	−16.27	−6.749	C 3	OD2 ASP 760 (A)	H-donor	3.29
			C 3	O5 POP 1003 (A)	H-donor	3.1
			O 17	O HOH 1104 (A)	H-donor	2.87
			O 36	O4 U 20 (P)	H-donor	3.2
			O 1	OG SER 759 (A)	H-acceptor	3.02
			O 1	O2' U 20 (P)	H-acceptor	2.67
			O 25	ND2 ASN 691 (A)	H-acceptor	2.89
ZINC000013781295	−15.41	−3.574	C 3	OD1 ASP 760 (A)	H-donor	3.12
			O 13	O2 POP 1003 (A)	H-donor	2.85
			C 18	OD2 ASP 760 (A)	H-donor	3.48
			O 36	O4 U 10 (T)	H-donor	2.68
			O 1	ND2 ASN 691 (A)	H-acceptor	2.18
			O 1	OG SER 759 (A)	H-acceptor	1.82
			S 23	NH2 ARG 555 (A)	H-acceptor	2.30
ZINC000013473324	−13.41	−5.812	C 36	OD2 ASP 760 (A)	H-donor	2.36
			O 10	OG1 THR 680 (A)	H-acceptor	2.28
			C 36	O5 POP 1003 (A)	H-donor	2.18
			O 35	OG SER 759 (A)	H-acceptor	2.33
			O 35	O2' U 20 (P)	H-acceptor	1.85

Table S2. The average of gyration scores and RMSD as well as the number of H-bond for selected compounds.

Compounds	The Average of Gyration Score	The Average Hydrogen Bonding Interaction	Number of H-bond	The Average of RMSD
ZINC000028525778	31.31 ± 0.086	3.01	27	1.976 ± 0.377
ZINC000001642252	31.4 ± 0.141	0.43	17	2.141 ± 0.425
ZINC000001651128	31.36 ± 0.121	3.93	20	2.002 ± 0.297
ZINC000003589958	31.29 ± 0.134	4.81	38	1.854 ± 0.312
ZINC000003833965	31.08 ± 0.066	1.65	26	1.81 ± 0.305
ZINC000013473324	31.3 ± 0.151	3.54	32	1.943 ± 0.394
ZINC000013556344	31.37 ± 0.124	4.95	35	2.023 ± 0.369
ZINC000013781295	31.14 ± 0.09	4.37	14	2.022 ± 0.368
ZINC000014944915	31.21 ± 0.111	3.98	19	1.825 ± 0.288
ZINC000027556215	31.3 ± 0.103	2.69	22	1.986 ± 0.249

ZINC000027557701	91.52 ± 0.204	1.93	23	5.306 ± 0.89
Protein Backbone	31.17 ± 0.073		-	1.947 ± 0.31

Table S3. Physicochemical properties of the hit compounds based on Lipinski's rule-of-five.

	logP	Molecular Weight	Num_H_ Acceptors	Num_ H_ Donors	Molecular Fractional Polar Surface Area	Num. Ring	Num_ Rotatable onds	logD
ZINC000001642252	3.331	300.306	5	3	0.287	2	6	3.325
ZINC000001651128	3.103	340.327	6	4	0.339	2	6	3.065
ZINC000003589958	2.126	429.377	9	6	0.414	2	9	0.636
ZINC000003833965	−0.52	360.447	5	3	0.262	2	8	−0.493
ZINC000013473324	1.72	400.425	6	2	0.256	3	9	1.72
ZINC000013556344	4.193	440.443	8	4	0.311	3	8	4.155
ZINC000013781295	3.414	356.392	6	4	0.361	3	2	3.376
ZINC000014944915	−2.417	311.377	5	4	0.354	1	6	−2.367
ZINC000027556215	1.687	516.451	12	7	0.431	3	9	0.194
ZINC000027557701	4.193	440.443	8	4	0.311	3	8	4.155
ZINC000028525778	2.535	356.283	8	4	0.411	3	4	0.367

Table S4. ADMET values of selected hit compounds.

	Absorption Level	CYP2D6	Hepatotoxicity	PPB	Solubility Level	BBB Level	AlogP98	PSA_2D
ZINC000001642252	0	0	false	1	3	3	3.331	88.677
ZINC000001651128	1	0	false	1	3	4	3.103	117.863
ZINC000003589958	3	0	false	0	3	4	2.126	177.72
ZINC000003833965	0	0	false	0	3	3	1.959	103.697
ZINC000013473324	0	0	false	1	3	3	1.72	104.313
ZINC000013556344	2	0	false	1	2	4	4.194	135.723
ZINC000013781295	0	0	false	0	3	4	3.414	100.562
ZINC000014944915	0	0	true	0	4	4	0.062	124.878
ZINC000027556215	3	0	false	0	2	4	1.687	215.471
ZINC000027557701	2	0	false	1	2	4	4.194	135.723
ZINC000028525778	1	0	true	1	3	4	2.535	135.723

AlogP98: must be less than 5 for good absorption through BBB. **Absorption level**: 0 = good, 1 = moderate, 2 = low, 3 = very low and 4 = Undefined. **Hepatotoxicity**: False = non-toxic and True = toxic. **CYP 2D6 inhibitory effect**: 0 = non-inhibitor and 1 = inhibitor. **PPB (plasma protein binding)**: 1 = binding and 0 = non-binding. **Solubility level** is the prediction of molar solubility of drugs: level 0 = Extremely low solubility; level 1 = No, very low; level 2 = Yes, low solubility; level 3 = Good solubility; level 4 = optimal solubility; level 5 = No, too soluble.

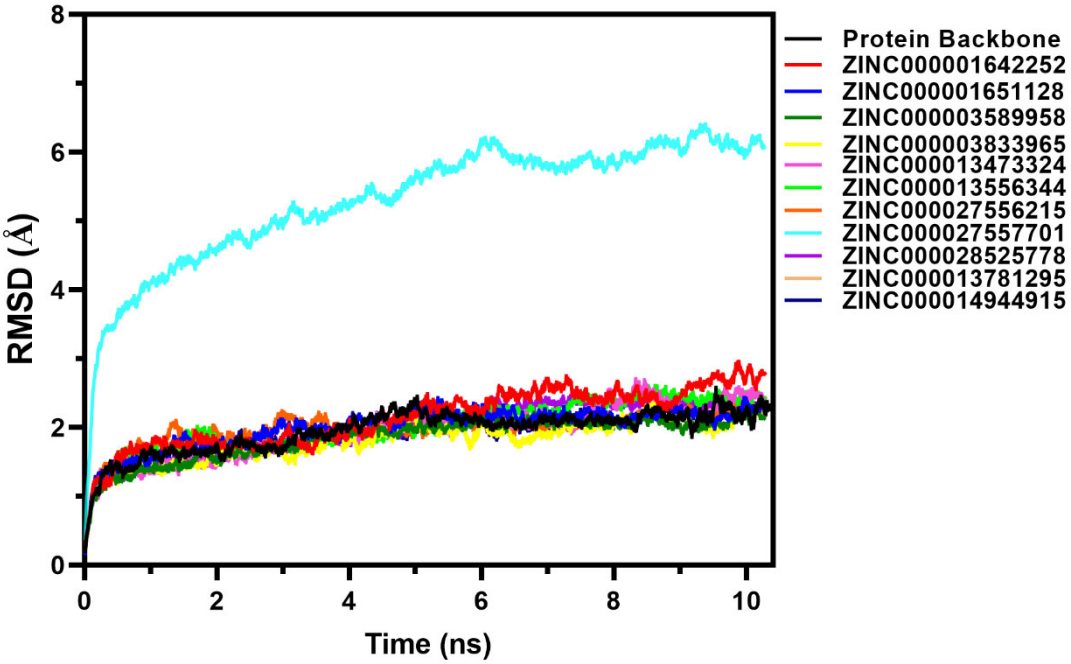
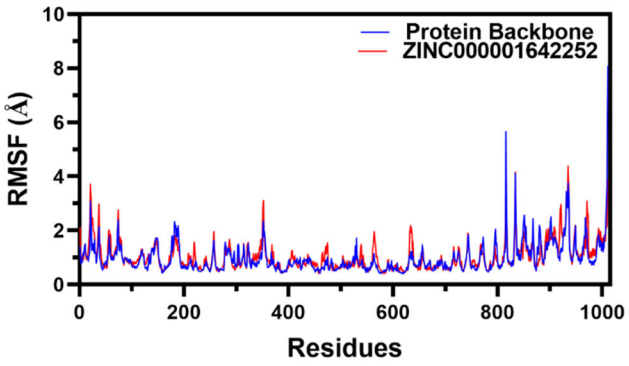
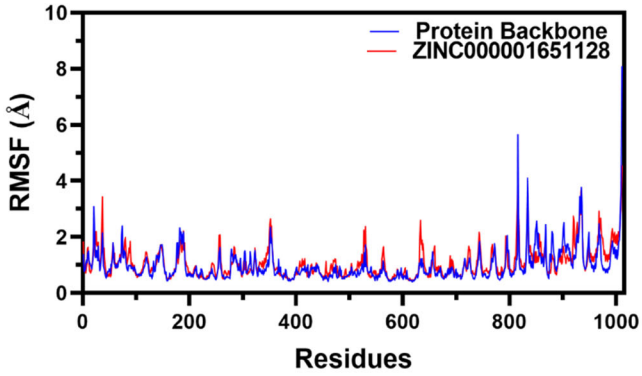
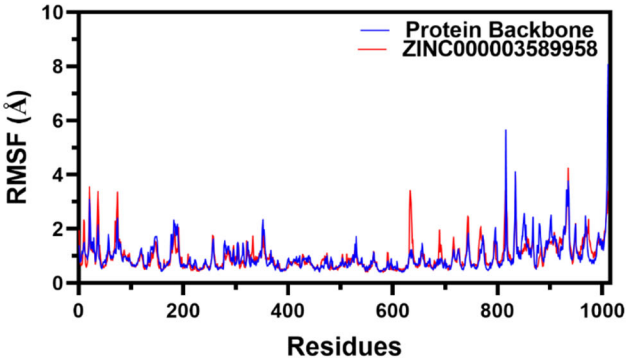
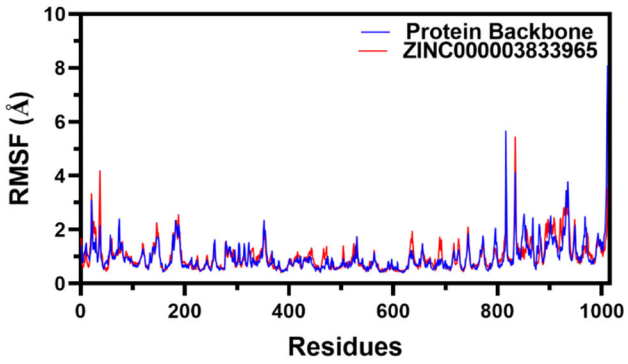


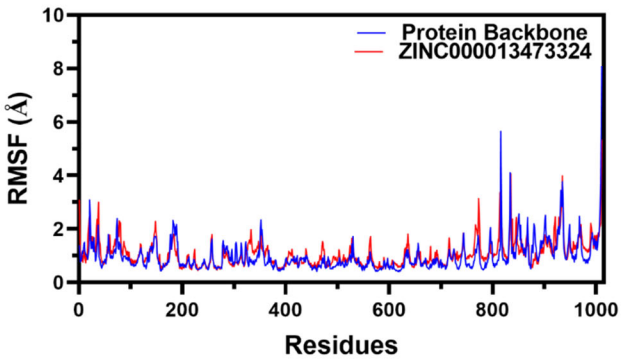
Figure S1. RMSD of the hit compounds and the protein calculated as a function of time over a 10 ns run.

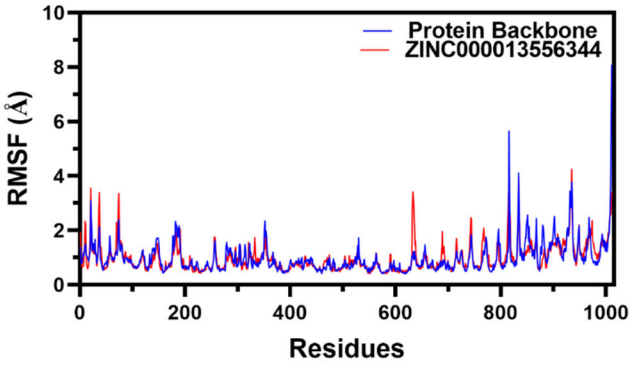

Protein Backbone
ZINC000001642252
RMSF (Å)
Residues


Protein Backbone
ZINC000001651128
RMSF (Å)
Residues


Protein Backbone
ZINC000003589958
RMSF (Å)
Residues


Protein Backbone
ZINC000003833965
RMSF (Å)
Residues


Protein Backbone
ZINC000013473324
RMSF (Å)
Residues


Protein Backbone
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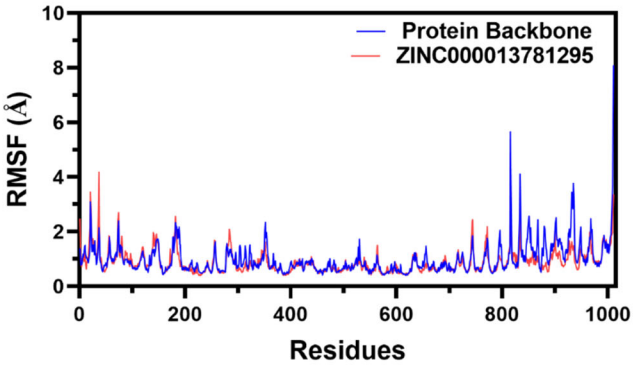
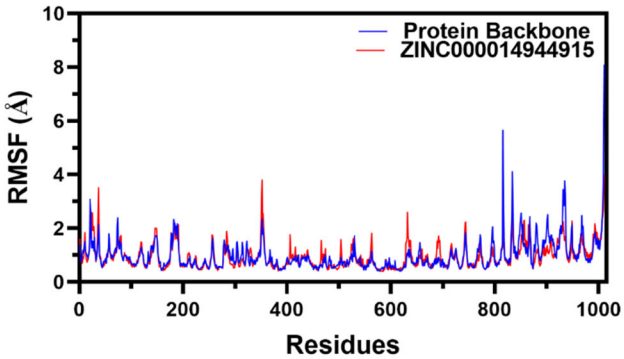
RMSF (Å)
Residues


Protein Backbone
ZINC000013781295
RMSF (Å)
Residues


Protein Backbone
ZINC000014944915
RMSF (Å)
Residues

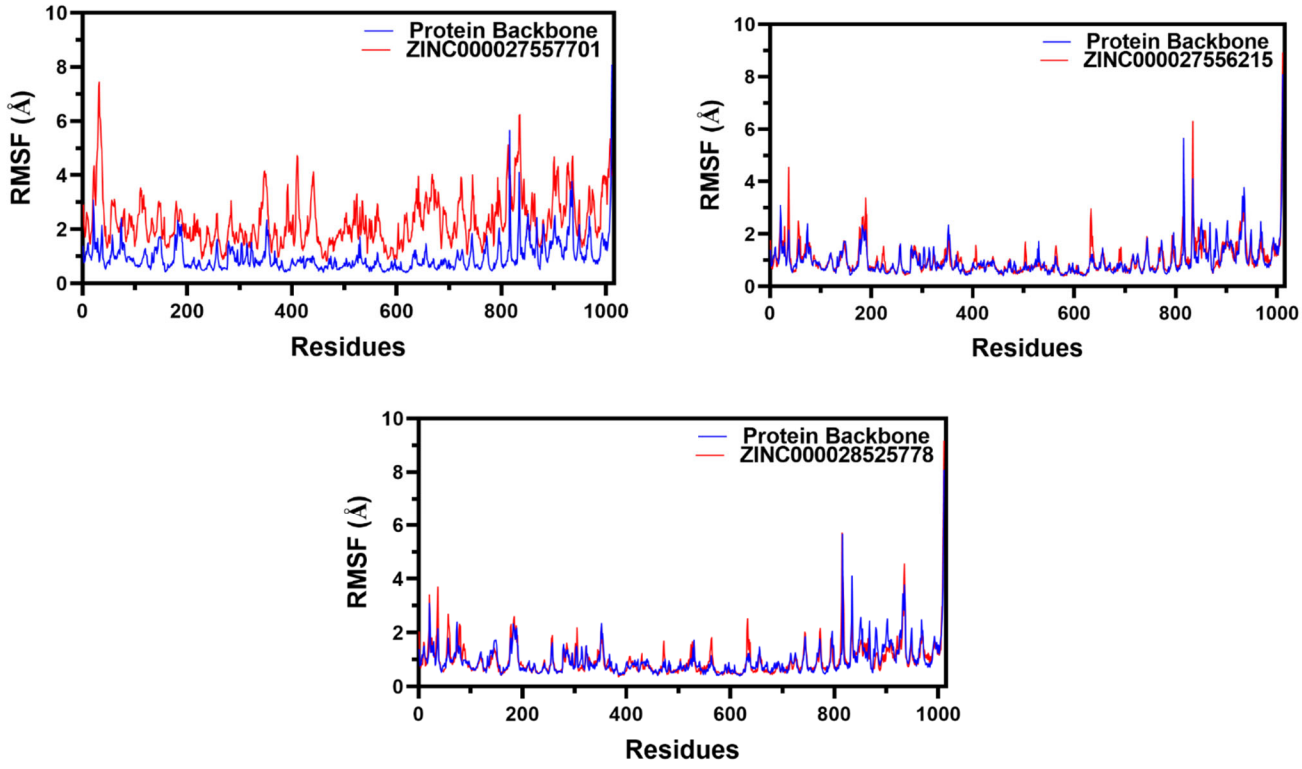


Figure S2. RMSF of the hit compounds and amino acid residues calculated as a function of time over a 10 ns run.

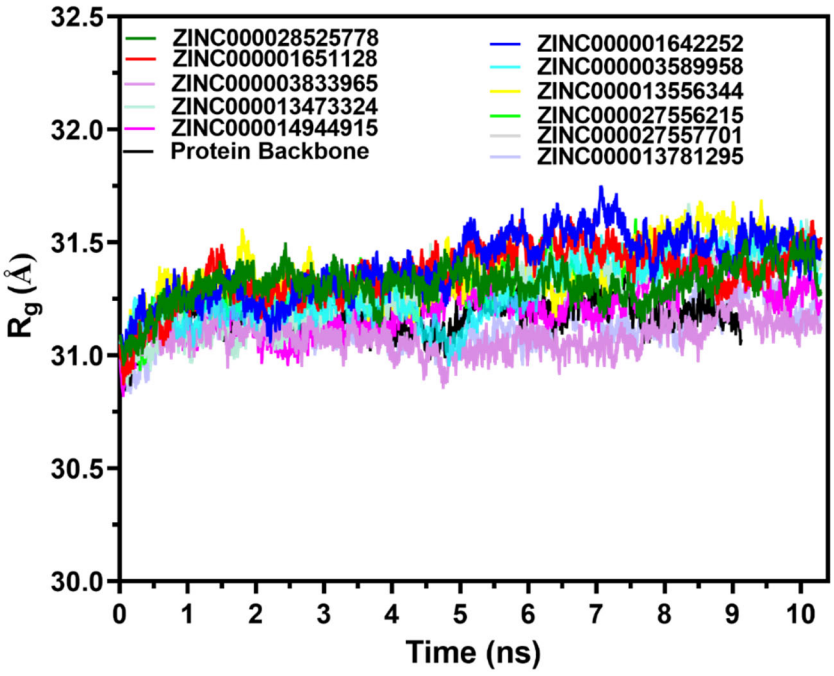
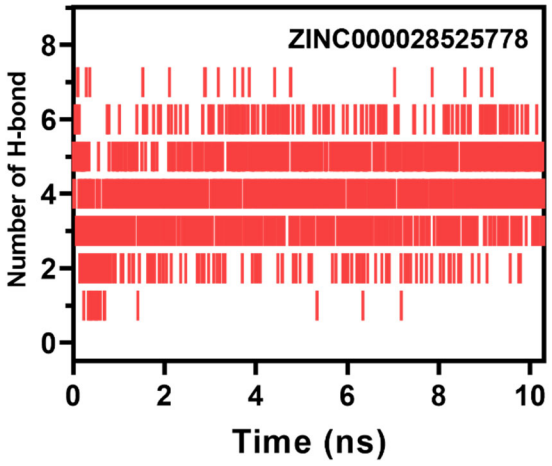
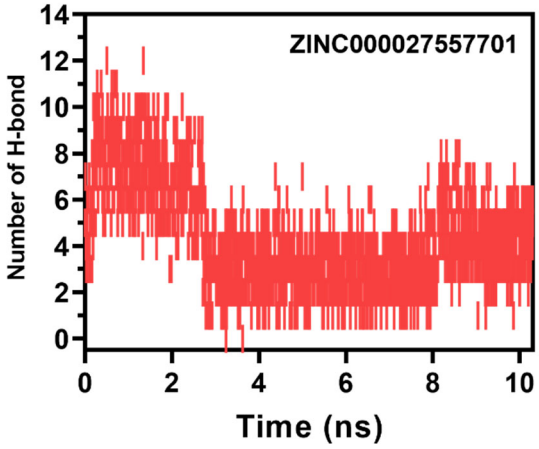


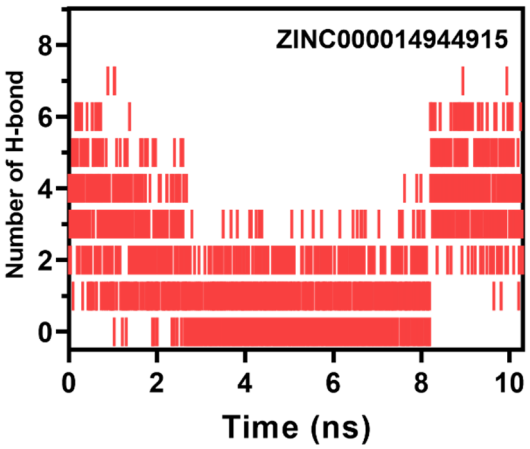
Figure S3. Radius of gyration of the protein and the 11 compounds calculated as a function of time over a 10 ns run.


ZINC000028525778
Number of H-bond
Time (ns)

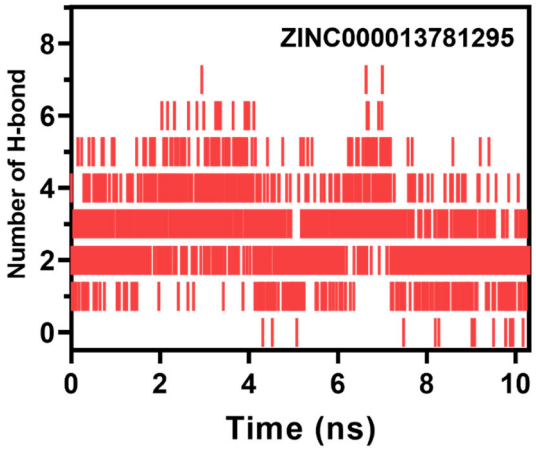
(**a**)


ZINC000027557701
Number of H-bond
Time (ns)

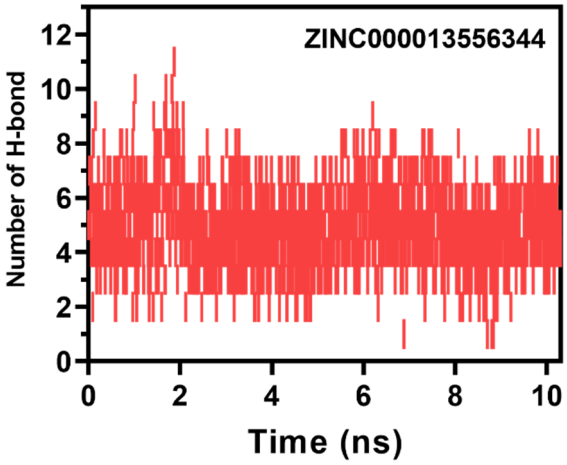
(**b**)


ZINC000014944915
Number of H-bond
Time (ns)

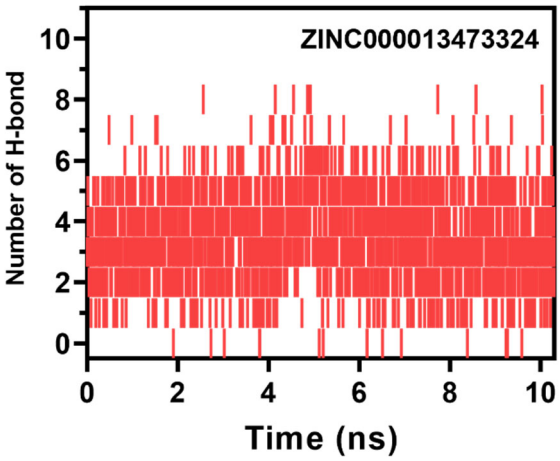
(**c**)


ZINC000013781295
Number of H-bond
Time (ns)

(**d**)


ZINC000013556344
Number of H-bond
Time (ns)

(**e**)


ZINC000013473324
Number of H-bond
Time (ns)

(**f**)

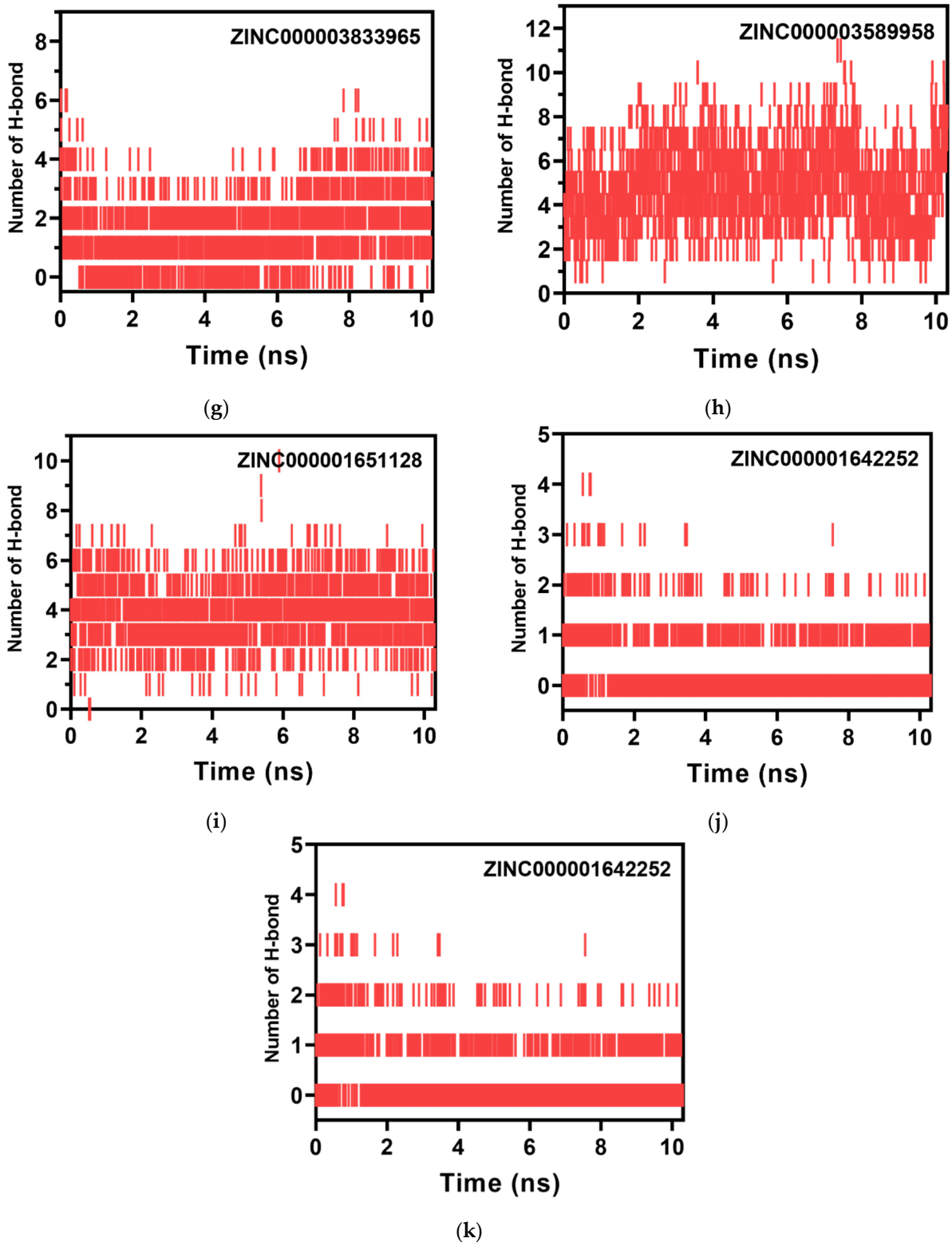


Figure S4. (**a**)–(**k**) Hydrogen bond stabilization of the 11 compounds over 10 ns production run.

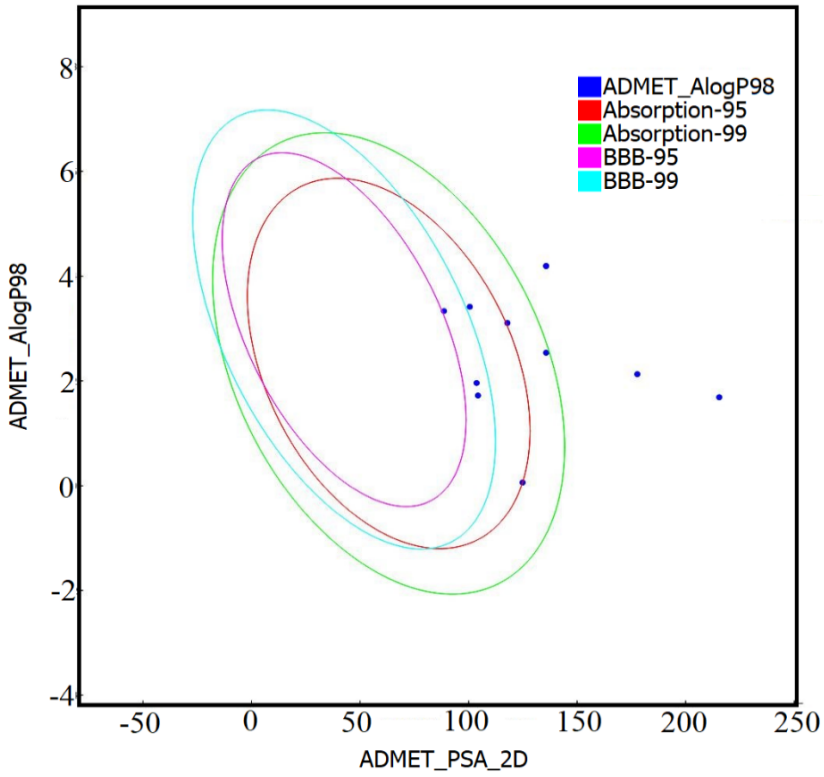


Figure S5. ADMET plot for the selected hits. The 95% and 99% confidence limit ellipses are shown which are corresponding BBB and HIA models.