

Table S1. List of known RdRp compounds with their Pubchem ID and IC50 taken for pharmacophore modelling.

S. no.	CID	IC50 (μM)	Reference
1.	6439576	0.85	[1]
2.	21672233	9.3	[1]
3.	44577154	37.8	[1]
4.	46898022	0.9	[2]
5.	49799036	NA	[2]
6.	49799133	4.2	[2]
7.	56834067	14.8	[3]
8.	56834069	4.2	[3]
9.	56834070	1.8	[3]
10.	56834169	2.9	[3]
11.	56834170	2.4	[3]
12.	56834171	15.3	[3]
13.	56834172	9	[3]
14.	56834173	27	[3]
15.	56834283	7.4	[3]
16.	57409245	23.8	[1]
17.	57409246	35.5	[1]
18.	57409247	13.4	[1]
19.	60165190	9.5	[1]
20.	70683874	24.3	[1]
21.	118717693	0.26	[1]
22.	118779901	1.7	[4]
23.	118797900	15	[4]
24.	118797902	0.34	[4]
25.	121232415	0.17	[4]
26.	127043014	2.3	[4]
27.	127043015	0.53	[4]
28.	127043016	2.4	[4]
29.	127043018	44	[4]
30.	127043019	2.5	[4]
31.	127043024	0.17	[4]
32.	127043025	0.25	[4]
33.	127043211	0.14	[4]
34.	127043212	0.023	[4]
35.	127043361	26	[4]
36.	127044830	29	[4]
37.	127044864	7.5	[4]
38.	127045349	39	[4]
39.	137243533	3.2	[4]
40.	57409350	39.8	[1]
41.	135434165	0.02	[3]

Table S2. IUPAC names of compounds used for pharmacophore model generation.

S. no.	PubChem ID	IUPAC
1	6439576	(1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-9-[(E)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxy-5a,5b,8,8,11a-pentamethyl-1-prop-1-en-2-yl-

		1,2,3,4,5,6,7,7a,9,10,11,11b,12,13,13a,13b-hexadecahydrocyclopenta[a]chrysene-3a-carboxylic acid
2	21672233	[(2R,3S,4S,5R,6S)-3,4,5-trihydroxy-6-(4-hydroxyphenoxy)oxan-2-yl]methyl benzoate
3	44577154	[2-[(2S,3R,4S,5S,6R)-6-(benzoyloxymethyl)-3,4,5-trihydroxyoxan-2-yl]oxy-5-hydroxyphenyl]methyl 2-hydroxybenzoate
4	46898022	4-[(2-morpholin-4-yl-7H-purin-6-yl)amino]benzenesulfonamide
5	49799036	4-[[2-[4-(2-hydroxyethyl)piperazin-1-yl]-7H-purin-6-yl]amino]benzenesulfonamide
6	49799133	2-[4-(6-anilino-7H-purin-2-yl)piperazin-1-yl]ethanol
7	56834067	(E,5R)-5-[(2R)-5,7-dihydroxy-4-oxo-2-phenyl-2,3-dihydrochromen-6-yl]-7-phenylhept-6-enoic acid
8	56834069	(E)-7-[8-[(E)-6-carboxy-1-phenylhex-2-enyl]-5,7-dihydroxy-4-oxo-2-phenyl-2,3-dihydrochromen-6-yl]-7-phenylhept-5-enoic acid
9	56834070	(E)-7-[8-[(E)-6-carboxy-1-phenylhex-1-en-3-yl]-5,7-dihydroxy-4-oxo-2-phenyl-2,3-dihydrochromen-6-yl]-7-phenylhept-5-enoic acid
10	56834169	(E)-7-[6-[(E)-6-carboxy-1-phenylhex-1-en-3-yl]-5,7-dihydroxy-4-oxo-2-phenyl-2,3-dihydrochromen-8-yl]-7-phenylhept-5-enoic acid
11	56834170	(E)-5-[8-[(E)-6-carboxy-1-phenylhex-1-en-3-yl]-5,7-dihydroxy-4-oxo-2-phenyl-2,3-dihydrochromen-6-yl]-7-phenylhept-6-enoic acid
12	56834171	(E,5R)-5-[(2R)-5,7-dihydroxy-4-oxo-2-phenyl-2,3-dihydrochromen-6-yl]-7-phenylhept-6-enoic acid
13	56834172	(E,5S)-5-[(2R)-5,7-dihydroxy-4-oxo-2-phenyl-2,3-dihydrochromen-6-yl]-7-phenylhept-6-enoic acid
14	56834173	(E,5R)-5-[(2S)-5,7-dihydroxy-4-oxo-2-phenyl-2,3-dihydrochromen-6-yl]-7-phenylhept-6-enoic acid
15	56834283	(E,5S)-5-[(2S)-5,7-dihydroxy-4-oxo-2-phenyl-2,3-dihydrochromen-6-yl]-7-phenylhept-6-enoic acid
16	57409245	[(2R,3S,4S,5R,6S)-6-[(2R,3R,4S,5R,6S)-2-(benzoyloxymethyl)-6-(2-formyl-4-hydroxyphenoxy)-3,5-dihydroxyoxan-4-yl]oxy-3,4,5-trihydroxyoxan-2-yl]methyl benzoate
17	57409246	[2-[(2S,3R,4S,5S,6R)-3-benzoyloxy-6-(benzoyloxymethyl)-4,5-dihydroxyoxan-2-yl]oxy-5-hydroxyphenyl]methyl (1S,2R,3S,4S)-1,2,3,4-tetrahydroxy-5-oxocyclohexane-1-carboxylate
18	57409247	[2-[(2S,3R,4S,5R,6R)-4-benzoyloxy-6-(benzoyloxymethyl)-3,5-dihydroxyoxan-2-yl]oxy-5-hydroxyphenyl]methyl (1R,2R,6R)-1,2,6-trihydroxy-5-oxocyclohex-3-ene-1-carboxylate
19	60165190	[2-[(2S,3R,4S,5S,6R)-3-benzoyloxy-6-(benzoyloxymethyl)-4,5-dihydroxyoxan-2-yl]oxy-5-hydroxyphenyl]methyl 2,3-dihydroxybenzoate
20	70683874	[2-[(2S,3R,4S,5S,6R)-3-benzoyloxy-6-(benzoyloxymethyl)-4,5-dihydroxyoxan-2-yl]oxy-5-hydroxyphenyl]methyl (1R,2R,6R)-1,2,6-trihydroxy-5-oxocyclohex-3-ene-1-carboxylate
21	118717693	6-[4-(5,7-dihydroxy-4-oxochromen-2-yl)phenoxy]-5,7-dihydroxy-3-(4-hydroxyphenyl)chromen-4-one
22	118779901	(5-hydroxypyridin-2-yl)-[(1S,9S)-8-oxa-2,3,4,12-tetrazatricyclo[7.4.0.0.02,6]trideca-3,5-dien-12-yl]methanone
23	118797900	2-[3-(carboxymethyl)-5-thiophen-2-ylphenyl]acetic acid
24	118797902	5-[5-(3-hydroxyprop-1-ynyl)thiophen-2-yl]-4-methoxy-2-methyl-N-methylsulfonylbenzamide
25	121232415	5-[5-(3-hydroxyprop-1-ynyl)thiophen-2-yl]-2,4-dimethoxy-N-(3-methoxyphenyl)sulfonylbenzamide
26	127043014	3-[5-(3-hydroxyprop-1-ynyl)thiophen-2-yl]-4-methoxybenzoic acid

27	127043015	5-[5-(3-hydroxyprop-1-ynyl)thiophen-2-yl]-4-methoxy-2-methylbenzoic acid
28	127043016	3-[5-[2-methoxy-5-(2H-tetrazol-5-yl)phenyl]thiophen-2-yl]prop-2-yn-1-ol
29	127043018	3-[5-[5-(1H-imidazol-2-yl)-2-methoxy-4-methylphenyl]thiophen-2-yl]prop-2-yn-1-ol
30	127043019	N-[5-[5-(3-hydroxyprop-1-ynyl)thiophen-2-yl]-4-methoxy-2-methylphenyl]sulfonylacetamide
31	127043024	N-(benzenesulfonyl)-5-[5-(3-hydroxyprop-1-ynyl)thiophen-2-yl]-4-methoxy-2-methylbenzamide
32	127043025	N-(benzenesulfonyl)-5-[5-(3-hydroxyprop-1-ynyl)thiophen-2-yl]-2,4-dimethoxybenzamide
33	127043211	4-chloro-5-[5-(3-hydroxyprop-1-ynyl)thiophen-2-yl]-2-methoxy-N-(3-methoxyphenyl)sulfonylbenzamide
34	127043212	N-[5-[5-(3-hydroxyprop-1-ynyl)thiophen-2-yl]-4-methoxy-2-methylphenyl]sulfonylquinoline-8-carboxamide
35	127043361	2-[3-(carboxymethyl)-5-(5-chlorothiophen-2-yl)phenyl]acetic acid
36	127044830	2-[2-[(3-chlorophenyl)methyl]-4,5-dihydroxyphenyl]-5,7-dihydroxychromen-4-one
37	127044864	2-[3-[5-(3-hydroxyprop-1-ynyl)thiophen-2-yl]-4-methoxyphenyl]acetic acid
38	127045349	2-[3-(5-bromothiophen-2-yl)-5-(carboxymethyl)phenyl]acetic acid
39	137243533	3-[5-[5-(3-hydroxyprop-1-ynyl)thiophen-2-yl]-4-methoxy-2-methylphenyl]-4H-1,2,4-oxadiazol-5-one
40	57409350	[2-[(2S,3R,4S,5S,6R)-3-benzoyloxy-6-(benzoyloxymethyl)-4,5-dihydroxyoxan-2-yl]oxy-5-hydroxyphenyl]methyl (1R,2R,6R)-6-benzoyloxy-1,2-dihydroxy-5-oxocyclohex-3-ene-1-carboxylate
41	135434165	[[[(2S,4R,5R)-5-(2-amino-6-oxo-1H-purin-9-yl)-4-hydroxyoxolan-2-yl]methoxy-hydroxyphosphoryl] phosphono hydrogen phosphate

Table S3. Number and type of pharmacophore points matched in ligand-based screening against approved drug compound library.

S.no	Title	Num Sites/points Matched	Type of Matched Ligand Sites
1	Sildenafil	4	A(3) A(5) R(13) R(14)
2	Trovaflaxacin	4	A(4) A(1) R(11) R(13)
3	Alatroflaxacin	4	A(5) A(1) R(18) R(17)
4	Fenolftaleina	4	A(3) A(1) R(6) R(8)
5	Merbromin	4	A(3) A(1) R(10) R(11)
6	Hmbp cpd	4	A(1) A(2) R(6) R(5)
7	2,2'-Dihydroxy-4-methoxybenzophenone	4	A(1) A(2) R(8) R(7)
8	2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4h-chromen-4-one	4	A(3) A(7) R(15) R(14)
9	3',6'-Dihydroxy-3-oxospiro(isobenzofuran-1(3h),9'-(9h)xanthene)-6-carboxylic acid	4	A(4) A(1) R(9) R(8)
10	Regadenoson	4	A(5) A(2) R(17) R(19)
11	Fenofibrate	4	A(2) A(4) R(8) R(7)
12	2-Hydroxy-4-methoxybenzophenone-5-sulfonic acid	4	A(1) A(2) R(7) R(6)
13	Mebendazole	4	A(1) A(4) R(9) R(8)
14	Tasmar	4	A(3) A(1) R(7) R(8)
15	Amiodarone	4	A(1) A(2) R(8) R(10)
16	bosentan	4	A(5) A(8) R(15) R(16)

17	Nepafenac	4	A(1) A(2) R(8) R(7)
18	Triiodothyronine	4	A(2) A(1) R(9) R(10)
19	Bisacodyl	4	A(3) A(1) R(6) R(7)
20	levofloxacin	4	A(4) A(1) R(10) R(11)
21	Fenofibric acid	4	A(1) A(2) R(6) R(5)
22	2-Methyl-1,4-naphthalenediol	4	A(3) A(2) R(9) R(8)
23	raloxifene	4	A(1) A(2) R(9) R(12)
24	Sulfadoxine	4	A(5) A(4) R(13) R(12)
25	Dronedarone	4	A(3) A(4) R(11) R(12)
26	Ofloxacin	4	A(3) A(1) R(10) R(11)
27	Rutin	4	A(13) A(4) R(30) R(28)
28	deferasirox	4	A(4) A(3) R(9) R(8)
29	Papaverine hydrochloride	4	A(3) A(1) R(10) R(12)
30	Picosulfate de sodium	4	A(3) A(1) R(6) R(7)
31	Levothyroxine	4	A(2) A(1) R(10) R(11)
32	riboflavin	4	A(5) A(2) R(16) R(18)
33	Clodronic Acid	4	A(1) A(3) R(11) R(10)
34	Gefitinib	4	A(1) A(4) R(13) R(11)
35	Permethrin	4	A(2) A(3) R(11) R(10)
36	Tinosorb s	4	A(8) A(7) R(16) R(17)
37	Ellagic acid	4	A(5) A(4) R(14) R(12)
38	Sulfaphenazole	4	A(3) A(1) R(9) R(7)
39	Daunorubicin	4	A(1) A(6) R(19) R(18)
40	Epirubicin	4	A(3) A(7) R(22) R(21)
41	doxorubicin	4	A(3) A(7) R(21) R(22)
42	Sulfadimethoxine	4	A(5) A(4) R(13) R(12)
43	Citalopram	4	A(1) A(2) R(7) R(6)
44	Thyroxine	4	A(2) A(1) R(11) R(10)
45	Ethaverine	4	A(3) A(1) R(10) R(12)
46	2-(4-Methoxyphenyl)-1h-indene-1,3(2h)-dione	4	A(1) A(2) R(6) R(5)
47	Dextrothyroxine	4	A(2) A(1) R(10) R(11)
48	Urispas	4	A(2) A(1) R(11) R(9)
49	Flavoxato	4	A(2) A(1) R(10) R(8)
50	colchicine	4	A(1) A(3) R(14) R(13)
51	Noscapine	4	A(6) A(2) R(13) R(14)
52	Hanegif	4	A(2) A(3) R(7) R(8)
53	Riboflavin phosphate	4	A(6) A(2) R(17) R(19)
54	lapatinib	4	A(2) A(5) R(15) R(14)
55	Sulfasalazine	4	A(2) A(4) R(12) R(11)
56	Sorafenib tosilate	4	A(1) A(3) R(12) R(11)
57	Warfarin	4	A(1) A(3) R(8) R(7)
58	Topotecan	4	A(2) A(5) R(13) R(12)
59	erlotinib	4	A(1) A(5) R(12) R(10)
60	Dicoumarol	4	A(5) A(4) R(11) R(8)
61	Valrubicin	4	A(3) A(10) R(25) R(24)
62	Sitaxentan	4	A(5) A(6) R(13) R(14)
63	Rifampin	4	A(3) A(13) R(31) R(32)
64	Protokylol	4	A(4) A(3) R(10) R(11)
65	zafirlukast	4	A(6) A(3) R(13) R(15)
66	Zolpidem	4	A(2) A(1) R(9) R(7)
67	Rifapentine	4	A(3) A(13) R(32) R(31)
68	Oxyphenbutazone	4	A(2) A(1) R(6) R(7)
69	Etravirine	4	A(2) A(5) R(13) R(12)

70	Idarubicin	4	A(5) A(8) R(16) R(15)
71	escitalopram	4	A(1) A(2) R(7) R(6)
72	Rifaximin	4	A(12) A(8) R(28) R(29)
73	Candesartan cilexetil	4	A(8) A(4) R(16) R(14)
74	(1,1'-Biphenyl)-3-carboxylic acid, 3'-((2z)-(1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4h-pyrazol-4-ylidene)hydrazino)-2'-hydroxy-	4	A(4) A(1) R(12) R(11)
75	Chlorophyll	4	A(6) A(1) R(28) R(26)
76	1,8-Dihydroxyanthraquinone	4	A(3) A(1) R(8) R(7)
77	Tolvaptan	4	A(2) A(3) R(12) R(11)
78	Dicloxacillin	4	A(5) A(1) R(15) R(14)
79	Tubocurarine	4	A(3) A(6) R(19) R(18)
80	Isobarbaloin	4	A(6) A(7) R(18) R(19)
81	letrozole	4	A(2) A(4) R(7) R(6)
82	Ad 810	4	A(3) A(4) R(8) R(7)
83	zaleplon	4	A(4) A(3) R(7) R(8)
84	celecoxib	4	A(3) A(1) R(9) R(10)
85	vinorelbine	4	A(6) A(4) R(21) R(22)
86	Glipizide	4	A(4) A(5) R(13) R(14)
87	7H-furo(3,2-g)(1)benzopyran-7-one, 9-methoxy-	4	A(2) A(1) R(6) R(8)
88	Deracoxib	4	A(2) A(1) R(12) R(13)
89	Vinblastine	4	A(7) A(4) R(22) R(23)
90	Zolazepam	4	A(3) A(2) R(10) R(9)
91	conivaptan	4	A(3) A(2) R(12) R(9)
92	vincristine	4	A(7) A(4) R(22) R(23)
93	omeprazole	4	A(3) A(2) R(12) R(11)
94	irinotecan	4	A(3) A(6) R(15) R(16)
95	telmisartan	4	A(2) A(1) R(9) R(11)
96	Pemirolast	4	A(2) A(1) R(9) R(8)
97	Rabeprazole	4	A(3) A(1) R(8) R(9)
98	1H-1,2,3-triazole-4-carboxamide, 1-((2,6-difluorophenyl)methyl)-	4	A(3) A(1) R(9) R(8)
99	Atracurium	4	A(11) A(2) R(27) R(28)
100	Olmesartan medoxomil	4	A(5) A(4) R(18) R(14)
101	Cerivastatin	4	A(3) A(1) R(13) R(14)
102	lansoprazole	4	A(2) A(1) R(9) R(8)
103	Indometacin	4	A(1) A(2) R(9) R(7)
104	Telithromycin	4	A(12) A(2) R(26) R(25)
105	dasatinib	4	A(5) A(2) R(14) R(13)
106	Novobiocin	4	A(5) A(7) R(24) R(23)
107	Imatinib	4	A(1) A(2) R(11) R(12)
108	Genestein	4	A(3) A(1) R(9) R(8)
109	ketoconazole	4	A(4) A(1) R(11) R(10)
110	1-(P-chlorophenoxy)-1-imidazol-1-yl-3,3-dimethyl-2-butanone	4	A(3) A(1) R(6) R(5)
111	Moracizine	4	A(4) A(2) R(11) R(10)
112	N-benzoyl-l-tyrosyl-paba	4	A(3) A(1) R(8) R(9)
113	posaconazole	4	A(5) A(7) R(17) R(15)
114	saquinavir	4	A(6) A(1) R(17) R(18)
115	Cisatracurium	4	A(3) A(2) R(27) R(28)
116	Metocurine	4	A(5) A(3) R(19) R(18)
117	Sincalide	4	A(4) A(2) R(35) R(33)
118	tadalafil	4	A(2) A(3) R(8) R(10)

119	Dipyridamolum	4	A(8) A(2) R(15) R(16)
120	Lypressin	4	A(4) A(12) R(34) R(33)
121	sennoside	4	A(15) A(13) R(31) R(30)
122	Dofetilide	4	A(1) A(5) R(10) R(9)
123	Mangafodipir	4	A(4) A(6) R(18) R(19)
124	Nicardipine	4	A(3) A(2) R(11) R(10)
125	Nedocromil	4	A(2) A(1) R(9) R(8)
126	Lanreotide	4	A(9) A(10) R(29) R(31)
127	Iotrolan	4	A(17) A(14) R(43) R(44)
128	itraconazole	4	A(6) A(2) R(17) R(13)
129	Meralein sodium	4	A(1) A(2) R(7) R(9)
130	Disodium 2,3,4,5-tetrachloro-6-(2,4,5,7-tetraiodo-6-oxido-3-oxo-3h-xanthen-9-yl)benzoate	4	A(1) A(2) R(15) R(16)
132	Iodixanol	4	A(12) A(13) R(36) R(35)
133	Terconazole	4	A(3) A(1) R(13) R(11)
134	Desmopressin	4	A(3) A(12) R(33) R(32)

Table S4. Type and name of residues involved in interaction with RdRp protein for the selected four compounds and the native ligand in their best docked poses with the protein.

Compound	H-bond	Hydrophobic	Polar	$\pi - \pi /$ * π -cat- ion	Salt bridge	Posi- tive	Negative
Demo- pressin	Asn ⁴⁹³ , Lys ⁴⁰² , Tyr ⁴⁵² , Glu ⁴⁸⁵ , Gly ⁶⁰⁰ , Ser ⁶⁶¹ , Asp ⁶⁶⁴	Phe ⁴⁵² , Tyr ⁴⁷⁴ , Phe ⁴⁸⁴ , Leu ⁵¹² , Leu ⁵¹⁵ , Tyr ⁵⁷³ , Tyr ⁶⁰⁷ , Cys ⁷⁰⁹ , Tyr ⁷⁵⁸ , Trp ⁷⁹⁵ Ile ⁷⁹⁷ ,	Asn ⁴⁹³ , Ser ⁶⁰¹ , Thr ⁶⁰⁶ , Ser ⁶⁶¹ , Ser ⁷¹⁰ , Ser ⁷¹¹ , Gln ⁷⁴² , Thr ⁷⁹³ , Thr ⁷⁹⁴ , Ser ⁷⁹⁶ , His ⁷⁹⁸	Arg ⁷³⁷	Glu ⁴⁸⁵	Lys ⁴⁰² , Arg ⁴⁷² , Arg ⁴⁸² , Arg ⁵⁹⁹ , Arg ⁷²⁹ , Arg ⁷³⁷ , Arg ⁷⁹²	Glu ⁴⁸⁵ , Glu ⁴⁹⁴ , Asp ⁵³⁴ , Asp ⁶⁶³ , Asp ⁶⁶⁴
Rutin	Val ⁴⁰³ , Asn ⁴⁰⁶ (2), Met ⁴⁷⁷ (2)	Phe ³⁹⁹ , Val ⁴⁰³ , Ala ⁴²² , Tyr ⁴⁷⁶ , Met ⁴⁷⁷ , Trp ⁴⁷⁸ , Leu ⁴⁷⁶ , Phe ⁴⁸⁶ , Trp ⁷⁶⁵	Ser ⁴⁰⁵ , Asn ⁴⁰⁶ , Ser ⁴²¹	--	--	Lys ⁴⁰² , Arg ⁴²³ , Arg ⁴⁸²	--
Lypres- sin	Lys ⁴⁰² , Asn ⁴⁰⁶ , Arg ⁴⁸² , Tyr ⁶⁰⁷ , Gly ⁶⁰⁰ , Asp ⁶⁶⁴ , Ser ⁷¹⁰ , Ile ⁷⁹⁷	Phe ³⁹⁹ , Val ⁴⁰³ , Trp ⁴⁵² , Trp ⁴⁷⁵ , Phe ⁴⁸⁶ , Leu ⁴⁷⁶ , Cys ⁷⁰⁹ , Trp ⁷⁹⁵ , Ile ⁷⁹⁷	Asn ⁴⁰⁶ , Ser ⁶⁰¹ , Thr ⁶⁰⁶ , Ser ⁶⁶¹ , Ser ⁷¹⁰ , Ser ⁷⁹⁷ ,	--	--	Lys ⁴⁰² , Arg ⁴⁷² , Arg ⁴⁸² , Arg ⁷⁹⁵	Glu ⁴⁸² , Asn ⁶⁶³ , Asp ⁹
Lanreo- tide	Lys ⁴⁰² , Asn ⁴⁰⁶ , Asn ⁴⁹³ , Glu ⁴⁹⁴ , Glu ⁵⁰⁸ , Ser ⁶⁶¹ , Asp ⁶⁶⁴	Val ⁴⁰³ , Ala ⁴²² , Ile ⁴⁷⁴ , Trp ⁴⁷⁵ , Tyr ⁴⁷⁶ , Met ⁴⁷⁷ , Tyr ⁶⁰⁷ , Cys ⁷⁰⁹ , Trp ⁷⁹⁵ , Ile ⁷⁹⁷	Ser ⁴⁰⁵ , Asn ⁴⁰⁶ , Ser ⁴²¹ , Asn ⁴⁹³ , Ser ⁶⁰¹ , Thr ⁶⁰⁶ , Ser ⁶⁶¹ , Ser ⁷⁹⁶ , His ⁷⁹⁸	Tyr ⁴⁷⁶	Asp ⁶⁶⁴	Lys ⁴⁰² , Arg ⁴²³ , Arg ⁴⁸² , Hip ⁴⁹⁶	Glu ⁴⁹⁴ , Glu ⁵⁰⁸ , Asp ⁶⁶³ , Asp ⁶⁶⁴
68T in- hibitor	Arg ⁷²⁹ , Lys ⁸⁰⁰ , Glu ⁸⁰²	Leu ⁵¹² , Leu ⁵¹⁵ , Cys ⁷⁰⁹ , Tyr ⁷⁵⁸ , Met ⁷⁶¹ , Leu ⁷⁶⁴ , Met ⁷⁶⁵ , Tyr ⁷⁶⁶ , Trp ⁸⁰³ , Trp ⁷⁹⁵ , Ala ⁷⁹⁹	His ⁵¹³ , Ser ⁷¹⁰ , His ⁷¹¹ , Gln ⁷⁴² , Thr ⁷⁹³ , Thr ⁷⁹⁴ , Ser ⁷⁹⁶ , His ⁷⁹⁸ , His ⁸⁰¹	--	--	Arg ⁷²⁹ , Arg ⁷³⁷ , Lys ⁸⁰⁰	Glu ⁸⁰²

Table S5. Calculated net binding free energy for the selected docked poses of DENV^{RdRp}-natural compounds snapshots from the last 10 ns interval of 100 ns MD simulation.

MM/GBSA components	Demopressin	Rutin	Lypressin	Lanreotide	68T inhibitor
ΔG_{Bind}	-74.72 ± 7.55	-39.94 ± 7.00	-99.32 ± 7.30	-88.87 ± 5.07	-72.71 ± 8.44
$\Delta G_{\text{Bind Coulomb}}$	-29.75 ± 14.36	-29.07 ± 7.14	-67.12 ± 7.64	-38.93 ± 12.14	-19.16 ± 9.79
$\Delta G_{\text{Bind Covalent}}$	10.50 ± 3.49	2.13 ± 1.58	1.50 ± 3.95	7.53 ± 2.95	4.58 ± 2.71
$\Delta G_{\text{Bind Hbond}}$	-7.10 ± 0.37	-3.02 ± 1.20	-6.34 ± 0.65	-3.29 ± 0.49	-2.29 ± 0.61
$\Delta G_{\text{Bind Lipo}}$	-15.33 ± 2.73	-9.36 ± 1.69	-21.33 ± 1.23	-29.63 ± 0.49	-22.53 ± 2.71
$\Delta G_{\text{Bind Packing}}$	-2.31 ± 0.59	-1.08 ± 0.68	-1.57 ± 0.66	-4.47 ± 0.77	-3.08 ± 1.15
$\Delta G_{\text{Bind Solv GB}}$	45.60 ± 8.66	38.74 ± 6.23	78.99 ± 7.25	78.82 ± 5.00	28.13 ± 7.54
$\Delta G_{\text{Bind vdW}}$	-76.30 ± 3.72	-38.27 ± 4.53	-83.42 ± 3.30	-93.89 ± 6.27	-58.36 ± 4.68

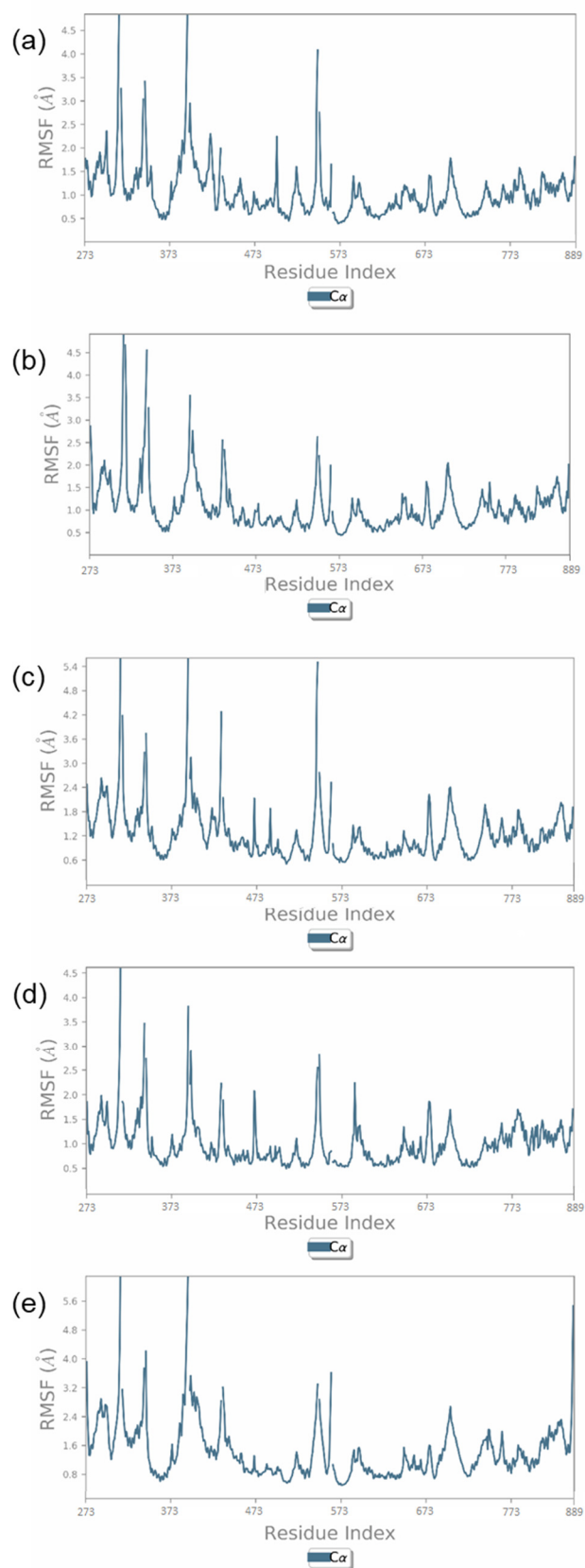


Figure S1. RMSF of RdRp protein complexed with (a) Demopressin, (b) Rutin, (c) Lypressin, and (d) Lanreotide and (e) Native Ligand- 68T . Herein, residue number 1 is 273 and end at 617 is 889 according to the crystal structure of the DENV^{RdRp}.

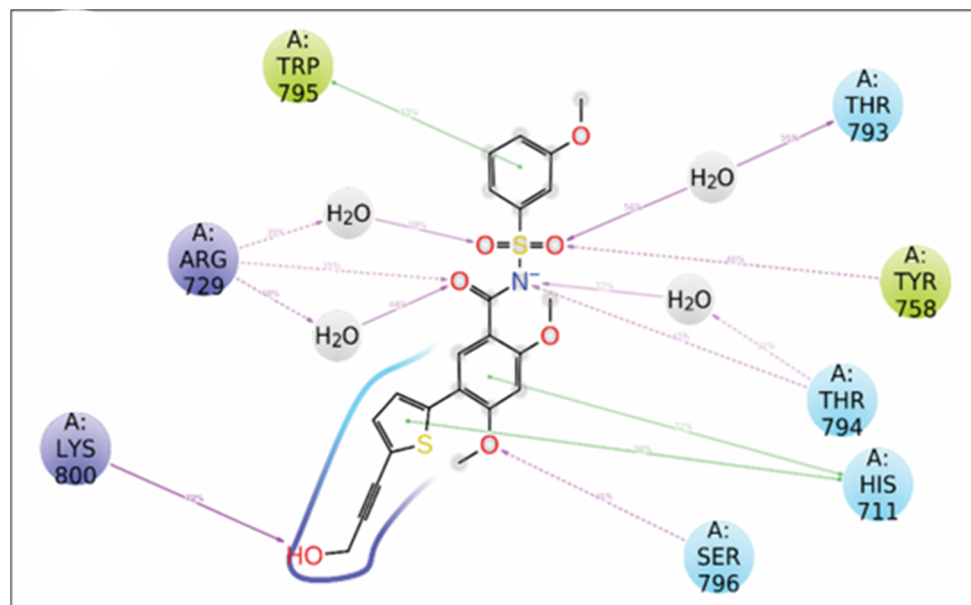


Figure S2. 2D interaction diagram of protein-ligand interactions maps for Dengue RdRp with the control Ligand- 68T extracted from the total 100 ns MD simulations.

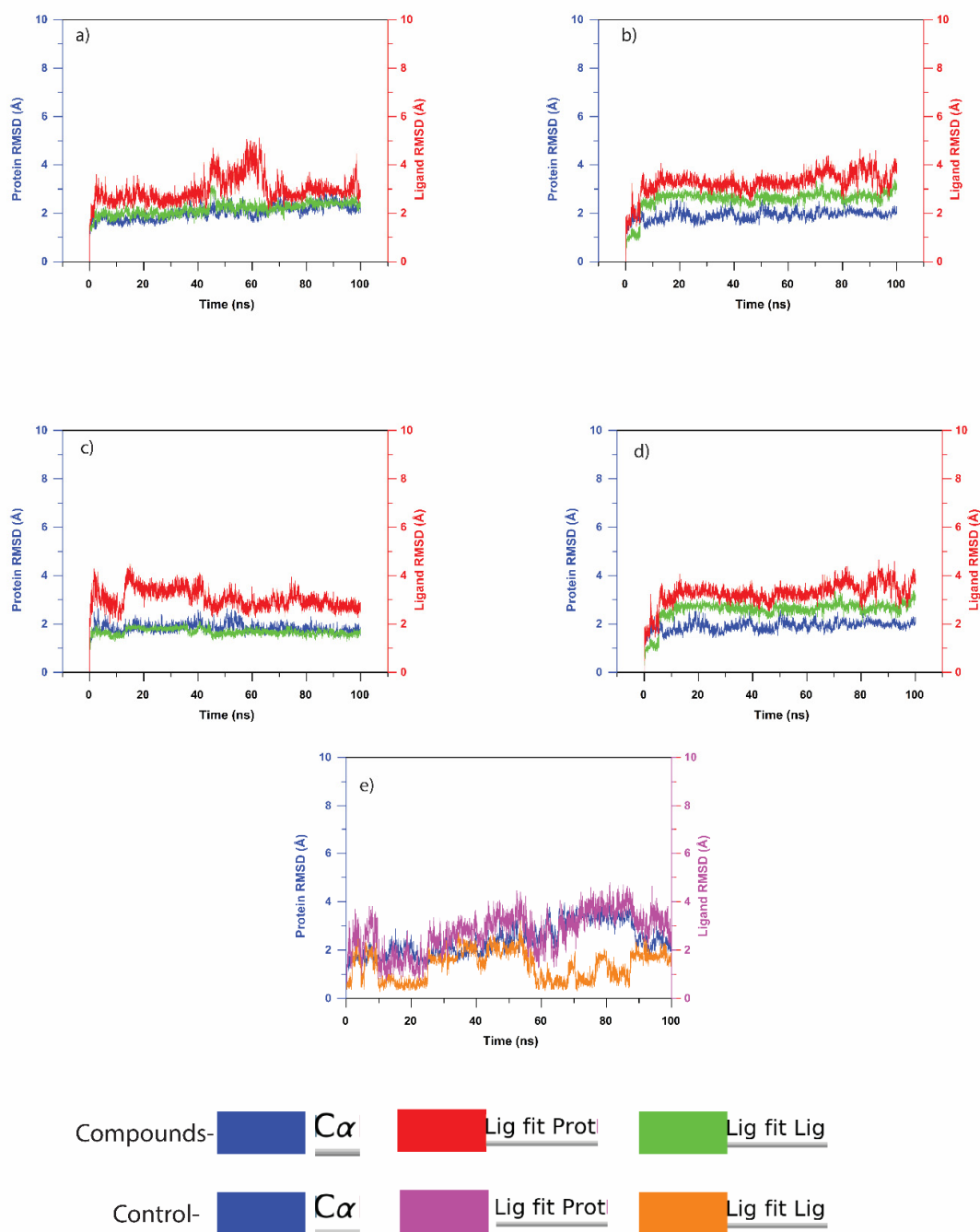


Figure S3. Root mean square deviation (RMSD) of protein and ligand and, ligand and ligand for the docked poses obtained from 100 ns MD simulation for (a) Desmopressin, (b) Rutin, (c) Lypressin, (d) Lanreotide and (e) 68T. $C\alpha$ atoms of protein is used for RMSD calculation (blue), Ligand RMSD (red) is calculated for heavy atoms by fitting the protein ligand complex, Ligand RMSD (green) is calculated for heavy atoms by fitting the ligand -ligand complex. In case of control $C\alpha$ atoms of protein is used for RMSD calculation (blue), Ligand RMSD (pink) is calculated for heavy atoms by fitting the protein ligand complex, Ligand RMSD (orange) is calculated for heavy atoms by fitting the ligand -ligand complex.

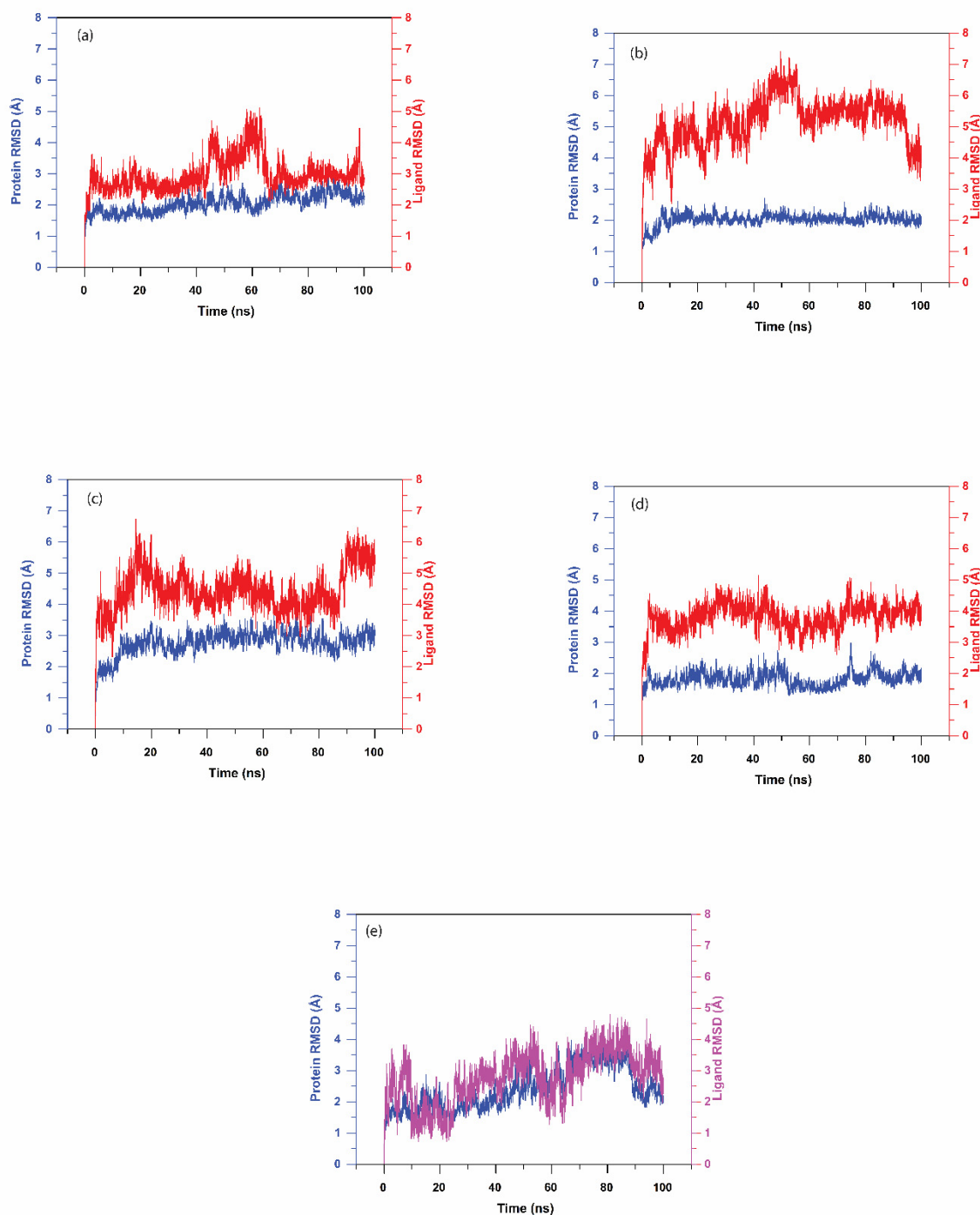


Figure S4. Root mean square deviation (RMSD) of protein and ligand and, ligand and ligand for the docked poses obtained from 100 ns MD simulation for (a) Desmopressin, (b) Rutin, (c) Lypressin, (d) Lanreotide and (e) 68T. $\text{C}\alpha$ atoms of protein is used for RMSD calculation (blue), Ligand RMSD (red) is calculated for heavy atoms by fitting the protein ligand complex. In case of control $\text{C}\alpha$ atoms of protein is used for RMSD calculation (blue), Ligand RMSD (pink) is calculated for heavy atoms by fitting the protein ligand complex.

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