

SUPPORTING INFORMATION

1,3-Thiazolbenzamide Derivatives as Chikungunya Virus nsP2 Protease Inhibitors

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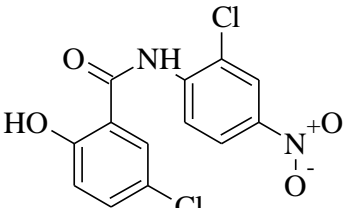
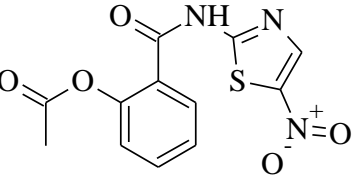
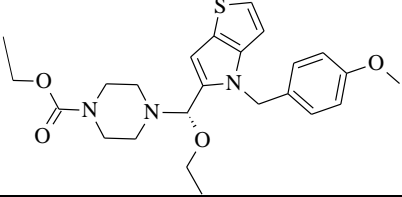
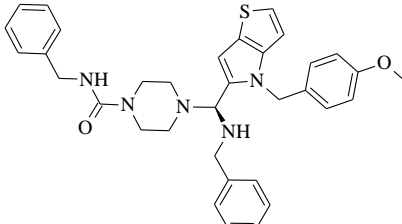
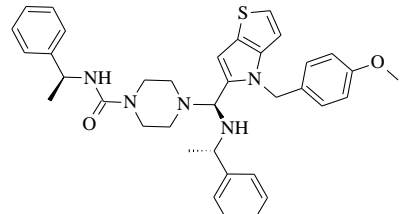
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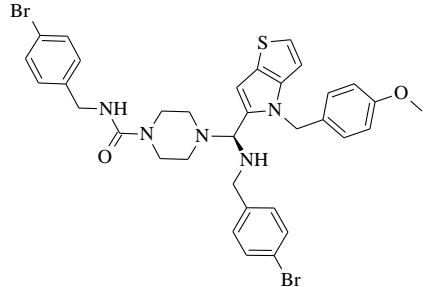
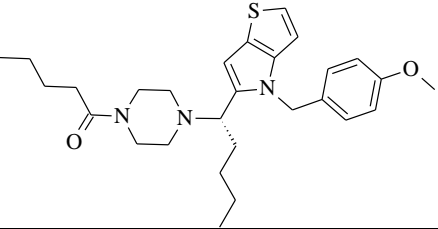
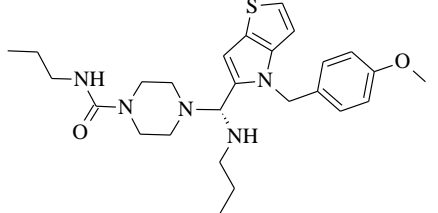
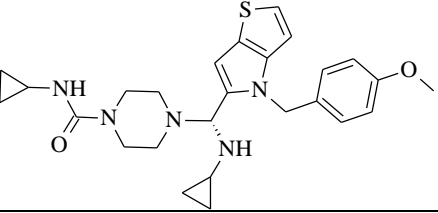
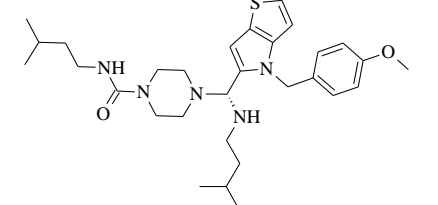
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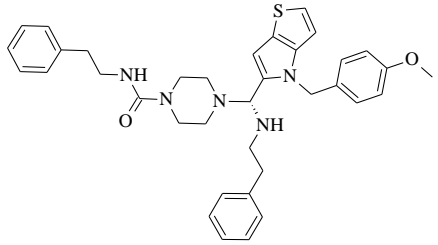
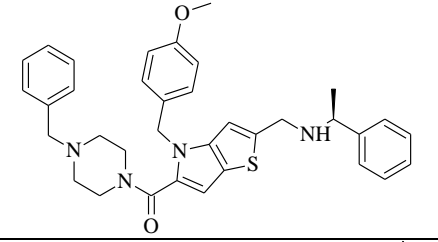
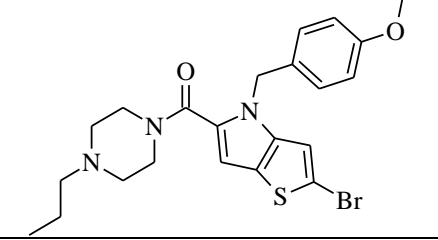
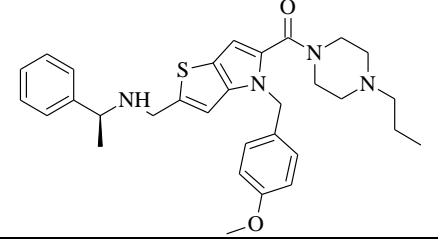
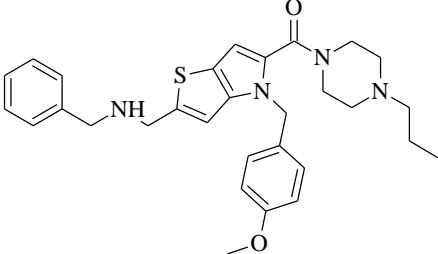
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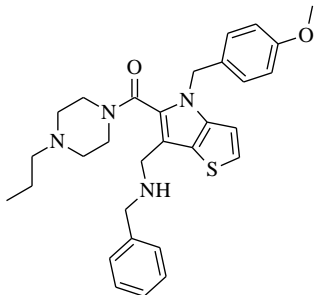
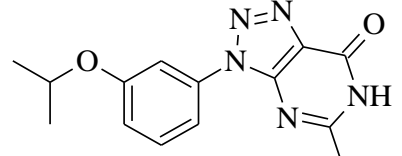
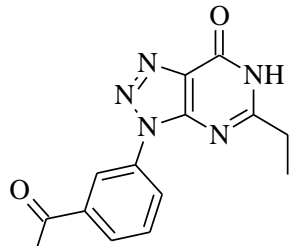
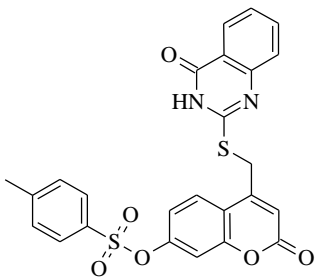
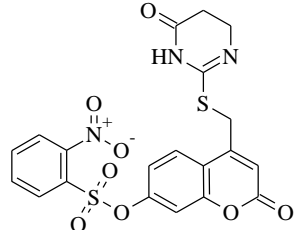
Table S1. Calculated Binding Energies, Ligand Efficiencies, and Interactions of CHIKV Inhibitors with IC₅₀ up to 15 μM with CHIKV nsP2

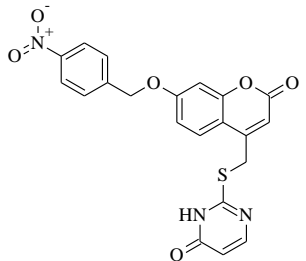
N₂	structure	virus strain	IC₅₀ (μM)	binding energy ΔG (kcal/mol)	ligand efficiency	interactions (H-bonds)	ref.
104		CHIKV	0.95 ± 0.22	-6.9	0.33	Lys1045, Gly1176, Pro1191, Glu1204, Ile1221, Lys1239	[1]
		CHIKV 0611aTw	0.85 ± 0.12				
		CHIKV 0810bTw	0.9 ± 0.12				
105		CHIKV	2.96 ± 0.18	-6.1	0.29	Lys1045, Pro1191, Leu1203, Ile1221, Lys1239	[1]
		CHIKV 0611aTw	1.96 ± 0.48				
		CHIKV 0810bTw	4.95 ± 0.23				
154		CHIKV-Gluc	13.1 ± 1.1	-7.2	0.23	Lys1045, Gly1176, Tyr1177, Leu1203, His1222, Lys1239	[1]
157		CHIKV-Gluc	12.3 ± 0.6	-8.2	0.19	Gln1039, Glu1043, Lys1045, Pro1191, Leu1192, Asn1202, Leu1203, Ile1221, His1222, Thr1223, Pro1224, Asp1235, Lys1239, Leu1243	[1]
158		CHIKV-Gluc	13.0 ± 2.8	-8.3	0.19	Lys1045, Gly1176, Tyr1177, Leu1203, His1222, Lys1239	[1]

159		CHIKV- Gluc	10.9 ± 1.3	-8.7	0.20	Gln1039, Glu1043, Lys1045, Gly1176, Tyr1177, Pro1191, Leu1203, His1222, Pro1224, Lys1239 ($NH_3^+ \dots O(ether)$)	[1]
160		CHIKV- Gluc	13.3 ± 0.1	-7.2	0.21	Lys1045, Tyr1177, Leu1203, Ile1221, His1222, Lys1239	[1]
162		CHIKV- Gluc	7.59 ± 2.17	-7.1	0.21	Lys1045, Gly1176, Leu1203, Ile1221, His1222, Lys1239	[1]
163		CHIKV- Gluc	10.4 ± 0.8	-7.6	0.22	Gly1176, Leu1203, Ile1221, His1222, Lys1239	[1]
164		CHIKV- Gluc	11.0 ± 0.4	-7.3	0.19	Lys1045, Gly1176, Tyr1177, Leu1203, Ile1221, Lys1239	[1]

165		CHIKV-Gluc	11.1 ± 0.1	-8.2	0.18	Lys1045, Gly1176, Tyr1177, Leu1203, Ile1221, His1222, Lys1239	[1]
169		CHIKV-Gluc	9.44 ± 0.06	-8.7	0.21	Lys1045, Tyr1177, Pro1191, Leu1203, Ile1221, Pro1224, Lys1239 ($NH_3^+ \dots O(ether)$)	[1]
175		CHIKV-Gluc	3.1 ± 0.71	-7.3	0.25	Gly1176, Tyr1177, Pro1191, Asn1202, Leu1203, Ile1221, His1222, Lys1239	[1]
177		CHIKV-Gluc	8.44 ± 2.21	-8.0	0.21	Gly1176, Pro1191, Leu1192, Asn1202 ($O \dots HN$), Leu1203, Glu1204, Ile1221, His1222, Lys1239	[1]
178		CHIKV-Gluc	11.2 ± 3.4	-7.9	0.21	Tyr1177, Pro1191, Leu1192, Asn1202, Leu1203, Glu1204, His1222, Lys1239	[1]

179		CHIKV- Gluc	4.33 ± 0.86	-7.7	0.26	Tyr1177, Pro1191, <i>Leu1192</i> (NH...OH), Asn1202, Leu1203, Ile1221, His1222, Lys1239	[1]
180		CHIKV- Gluc	3.6 ± 0.41	-7.6	0.26	Gly1176, Tyr1177, Pro1191, Asn1202, Leu1203, Ile1221, His1222, Lys1239	[1]
181		CHIKV- Gluc	3.85 ± 0.06	-7.7	0.23	Pro1191, Leu1192, Leu1203, Ile1221, His1222	[1]
182		CHIKV- Gluc	4.9 ± 0.16	-7.4	0.25	Gly1176, Tyr1177, Pro1191, Leu1203, Ile1221, His1222, Lys1239	[1]
183		CHIKV- Gluc	7.75 ± 0.23	-7.6	0.26	Pro1191, Leu1203, Ile1221, His1222, Lys1239	[1]

186		CHIKV- Gluc	11.9 ± 1.9	-7.5	0.20	Lys1045, Tyr1177, Pro1191, Leu1203, Ile1221, His1222, Lys1239	[1]
242		CHIKV 899	12 ± 4	-7.0	0.33	Lys1045, Glu1204, Ile1221, Lys1239	[1]
253		CHIKV 899	3 ± 1	-7.2	0.34	Pro1191, Leu1192, Leu1203, Glu1204, Lys1239, Leu1243	[1]
262		CHIKV 899	10.2	-8.6	0.24	Lys1045, Gly1176 (NH...O(sulfur)), Tyr1177, Leu1203, Ile1221, His1222 (NH...O(sulfur)), Lys1239, Leu1243	[1]
275		CHIKV 899	13	-8.5	0.26	Lys1155 (NH ₃ ⁺ ...O), Arg1158, Tyr1177, Leu1179, His1222, Phe1225, Gln1232, Arg1260, Thr1292, Glu1296	[1]

282		CHIKV 899	4.6	-8.1	0.26	His1151, Lys1155, <i>Gly1156</i> (<i>NH...O</i>), Tyr1177, Phe1225, <i>Gln1232</i> (<i>NH₂...O₂N</i>), <i>Arg1260</i> (<i>NH₂...O</i>), Thr1292, Ser1293	[1]
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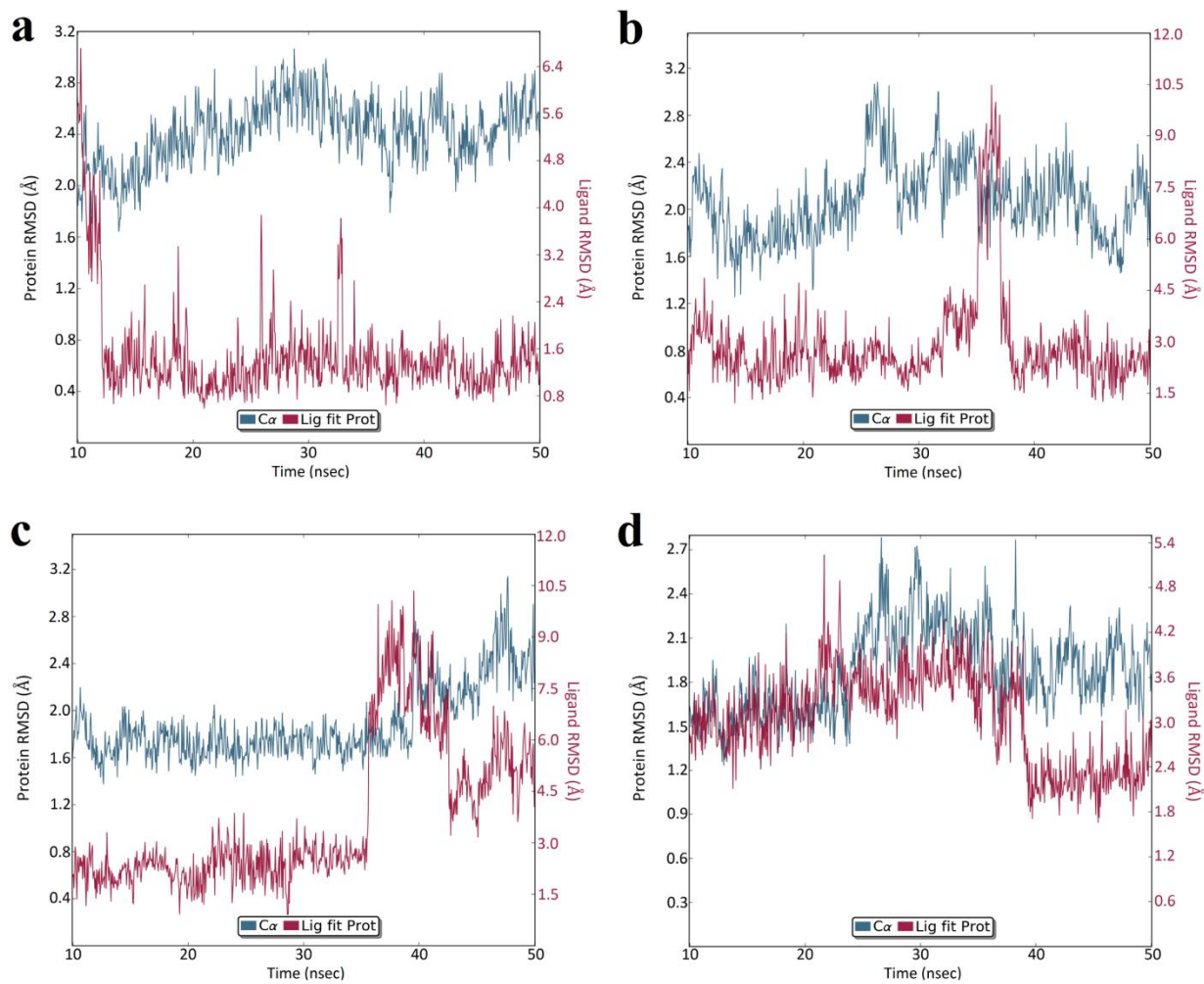


Figure S1. RMSD of the atomic positions for compounds **1**, **10**, **10b**, and **10c** (in red, Lig fit Prot) and CHIKV nsP2 ($C\alpha$ positions in blue) of the 50 ns molecular dynamics simulations using Desmond package: CHIKV nsP2 – compound **1** (a); CHIKV nsP2 – compound **10** (b); CHIKV nsP2 – compound **10b** (c); CHIKV nsP2 – compound **10c** (d). Protein PDB ID: 3TRK.

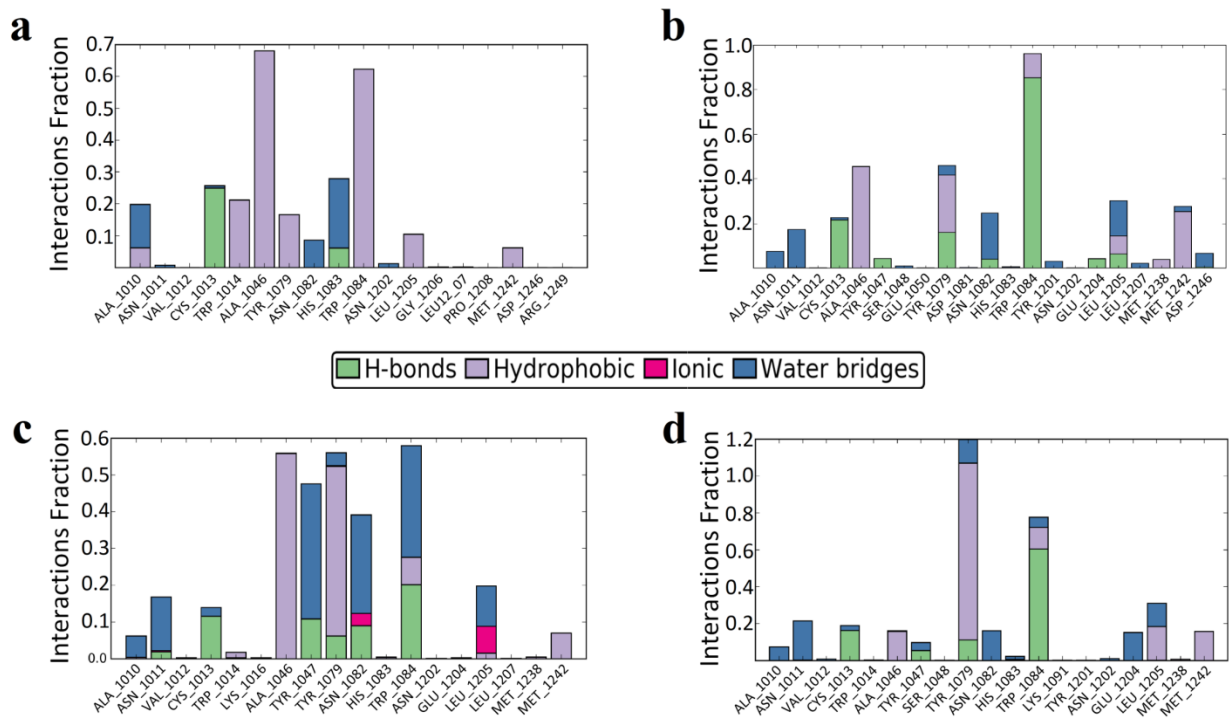


Figure S2. MD-calculated contacts for the complexes of CHIKV nsP2 with compounds **1** (a), **10** (b), **10b** (c), and **10c** (d).

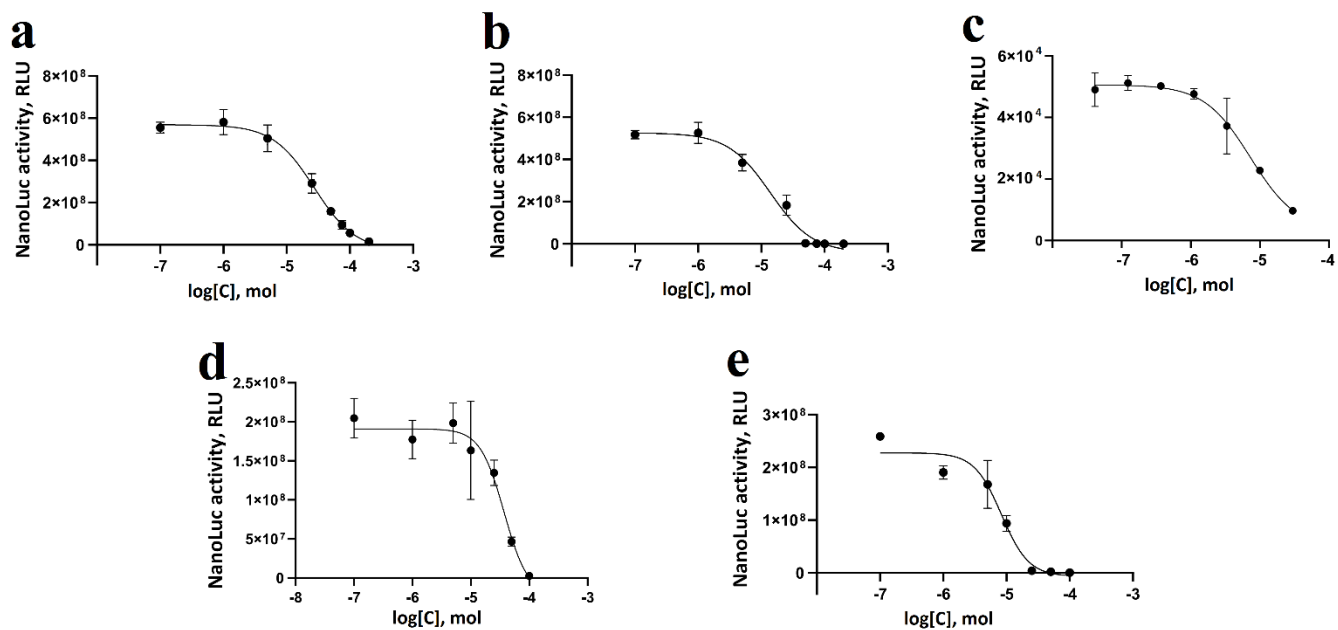


Figure S3. Determination of IC_{50} of compounds **1** (a – BHK-21 cells), **10** (b – BHK-21 cells, c – RPE cells), **10b** (d – BHK-21 cells), and **10c** (e – BHK-21 cells).

REFERENCES

(1) da Silva-Júnior, E. F.; Leoncini, G. O.; Rodrigues, É. E. S.; Aquino, T. M.; Araújo-Júnior, J. X. The medicinal chemistry of Chikungunya virus. *Bioorg. Med. Chem.* **2017**, *25*, 4219-4244.