Way2Drug
Understanding Chemical-Biological Interactions

XXXII Symposium on Bioinformatics
and Computer-Aided Drug Discovery
(BCADD-2026)

CIENTÍFICA
UNIVERSIDAD CIENTÍFICA DEL SUR

"IN SILICO EVALUATION OF MULTITARGET CANDIDATES AS POTENTIAL INHIBITORS OF ESSENTIAL DENGUE VIRUS TYPE 2 (DENV-2) PROTEINS USING MOLECULAR DOCKING, QUANTUM CHEMISTRY AND MOLECULAR DYNAMICS"

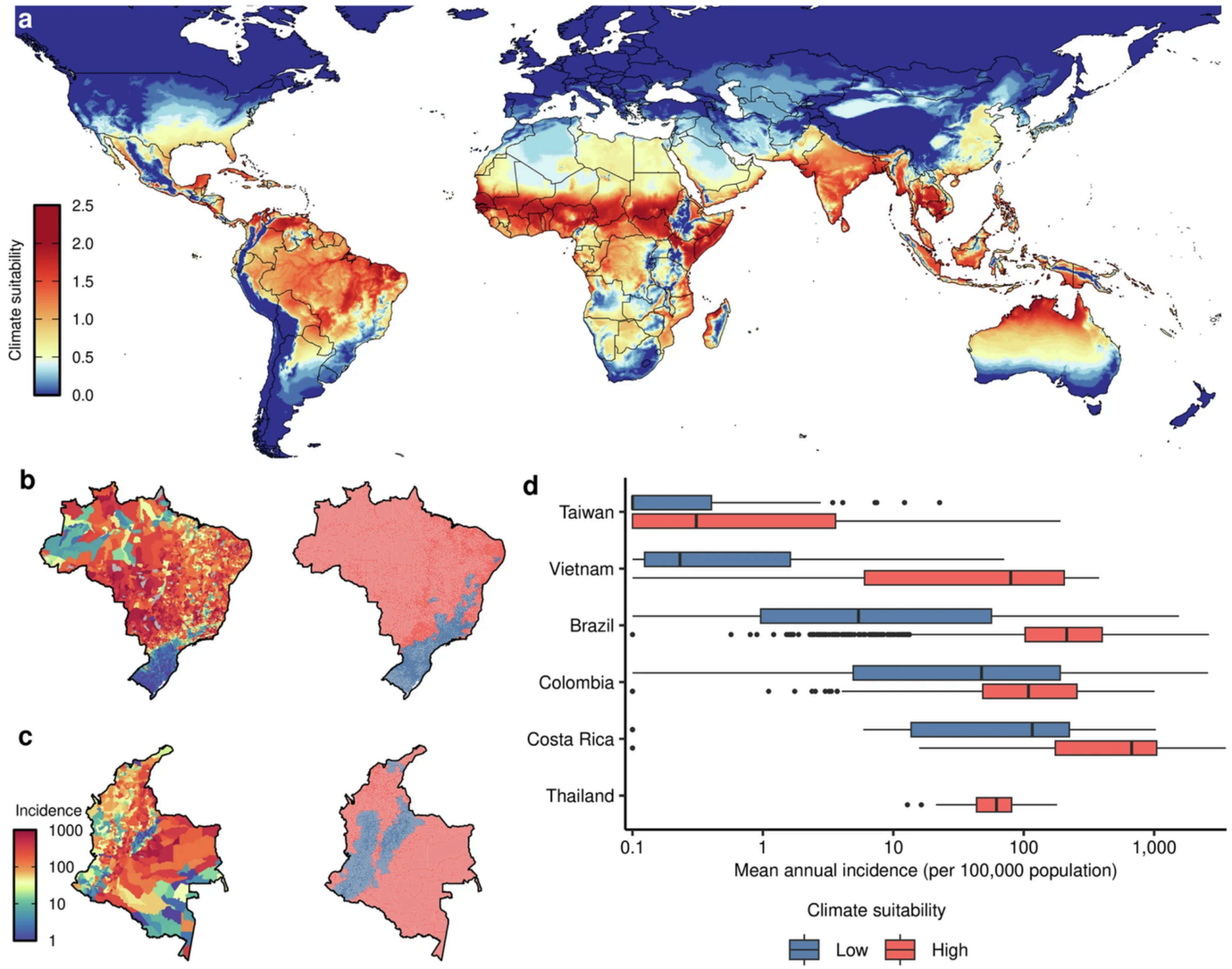
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Dengue: A challenge for antiviral development

Climatic conditions favorable for dengue transmission



Source: Nakase et al. (2024). Communications Earth & Environment, 5, 475.

Epidemiological source: World Health Organization (2025). Dengue and severe dengue.

100–400 million
Estimated infections per year

≈ 50%
Of the world's population at risk

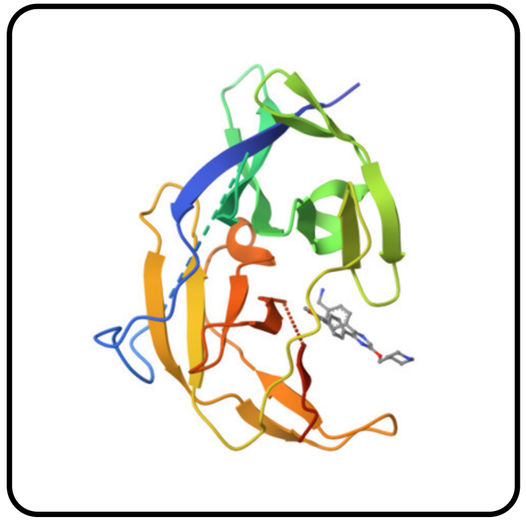
No specific antiviral treatment
Current care relies mainly on supportive measures.

STUDY OBJECTIVE

To design and evaluate in silico molecular candidates with favorable interaction profiles against three essential DENV-2 proteins using a multitarget strategy.

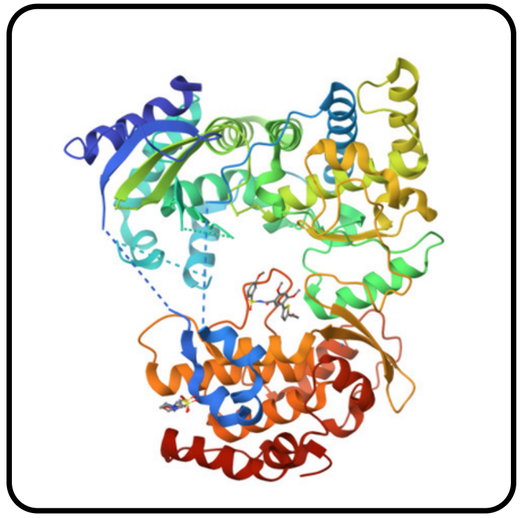
Three Essential therapeutic targets of DENV-2

DENV-2 requires different enzymatic activities to process its proteins and replicate its RNA. Therefore, we evaluated three targets: the NS2B-NS3 protease and two functional domains of NS5.



NS2B-NS3 Protease
PDB: 6MO0

Cleaves the viral polyprotein through serine protease activity, enabling the maturation of proteins required for the viral life cycle.



NS5 RNA Polymerase (RdRp)
PDB: 5K5M

Synthesizes viral RNA using an RNA template, generating replication intermediates and new copies of the viral genome.



NS5 Methyltransferase (MTase)
PDB: 2P3L

Catalyzes N7 and 2′-O methylation of the 5′ cap, promoting viral RNA translation and evasion of immune recognition.

Multitarget strategy: To evaluate candidates capable of interacting favorably with all three viral targets.

Luo et al., 2015; Lim et al., 2015; Sreekanth, 2023. Structures: RCSB PDB (6MO0, 5K5M, 2P3L).

Methodology: Rational design and multitarget 0ptimization

PHASE I · Rational candidate design

01. Drug Evaluation and Selection

15 drugs

⬇

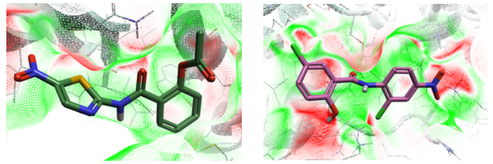
Docking + EC + Lipinski

⬇

Nitazoxanide
and
Niclosamide

02. Identification of modifiable regions

Flare + EC · 2 ligands × 3 targets
Green: favorable · Red: unfavorable
Unfavorable regions → targeted substitutions



Electrostatic complementarity (EC) of the protein–ligand complex.
Image generated using Cresset's Flare software

03. EC-Guided Structural Substitution

2 drugs × 3 targets × 3 searches × 3 subsearches = 18 searches
18 databases → 428,346 available fragments ≈ 7.71 million potential fragment–search combinations.
~18,000 proposed structures, preserving the original chemical scaffolds.

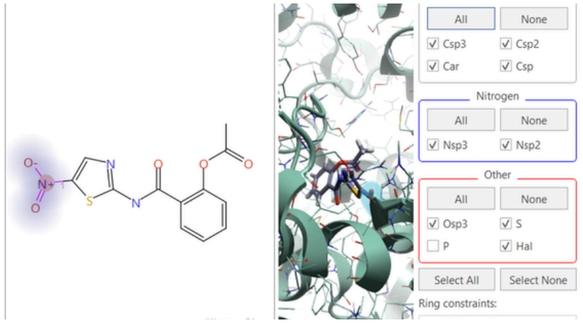


Image generated using Spark™ from Cresset®

PHASE II · Iterative screening and optimization

04. Library generation and virtual screening

MAKE_RECEPTOR + OMEGA

⬇

FRED

⬇

17,869 molecules evaluated per target

05. Second docking round and EC-based refinement

Top 50 per target

⬇

150 selections – distinct compounds

⬇

Flare + EC

⬇

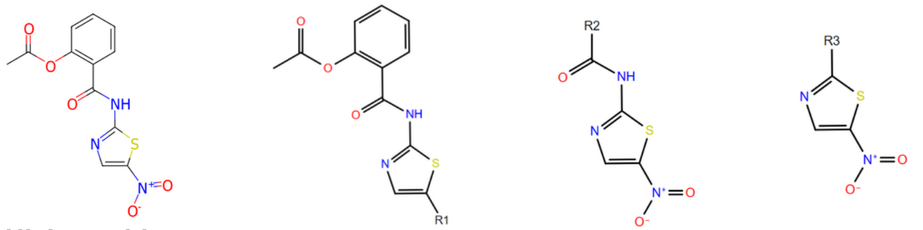
1 MTase · 2 RdRp · 18 proteasa
(Structures retained for recombination)

06. Substituent Recombination

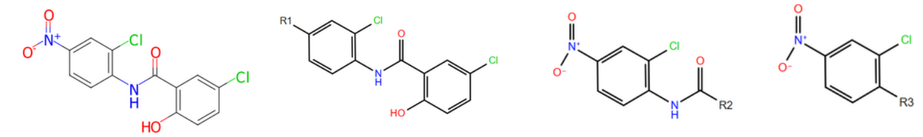
Combination of R1–R3 substituents ➡ **121 molecules**

New docking + EC ➡ **8 finalists**

Nitazoxanide



Niclosamide



PHASE III · Integrated computational evaluation

07. Characterization of the eight candidates

Preparation in Avogadro (pH 7.4) → Geometry optimization in ORCA → Quantum characterization and ADME prediction.

08. Prioritization and Molecular Dynamics

3_30_D · 100 ns

Simulations performed in UnoMD for complexes involving the three viral targets.

NS2B-NS3 complex – 3_30_D.

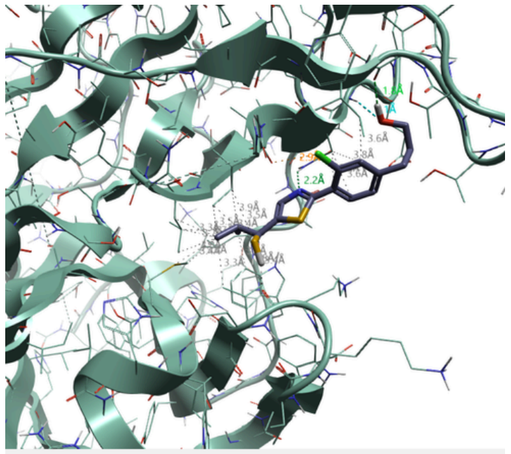


Image generated using Cresset's Flare software

Results: Selection of the multitarget candidate 3_30_D

A · Molecular docking comparison

LF dG (kcal/mol) · 4 of the 8 finalist candidates

Candidate	MTase	RdRp	Proteasa
3_30_D	**−10.246**	**−10.517**	**−10.244**
3_18_D	−9.155	−11.560	−9.308
3_32_D	−10.712	−10.103	−10.449
3_28_D	−9.815	−11.485	−11.551

LF dG: Estimated scoring function calculated by Lead Finder.

EC: Electrostatic complementarity index.

These values do not represent experimental measurements of binding affinity or inhibition.

B · Electrostatic complementarity comparison

EC Index · The same four candidates

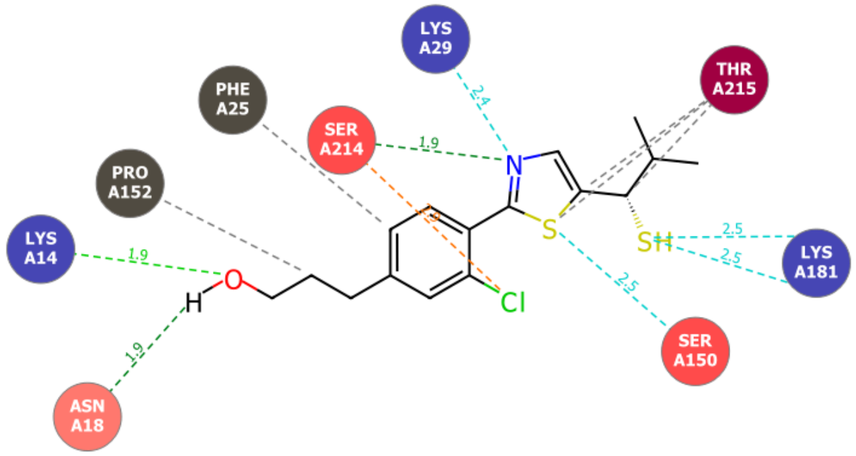
Candidate	MTase	RdRp	Proteasa
3_30_D	**0.238**	**0.279**	**0.251**
3_18_D	0.199	0.245	0.249
3_32_D	0.152	0.180	0.172
3_28_D	0.159	0.187	0.324

3_30_D: Relatively consistent LF dG scores and positive EC values across all three targets

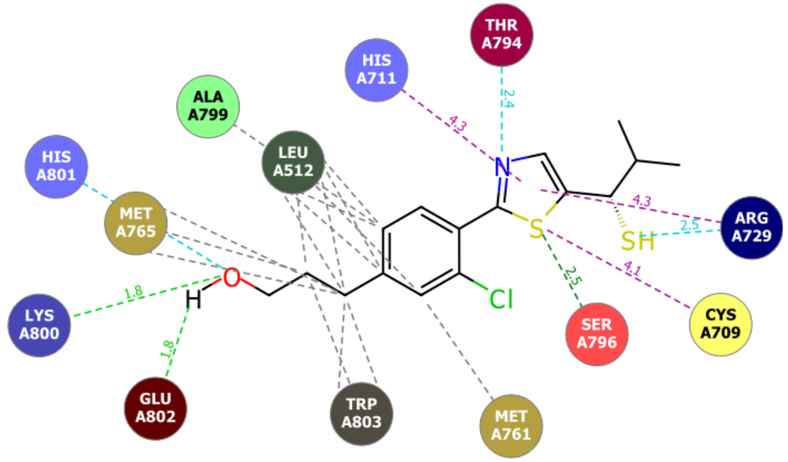
LF dG range: 0.273 kcal/mol · Minimum EC: 0.238

C · Structural evidence

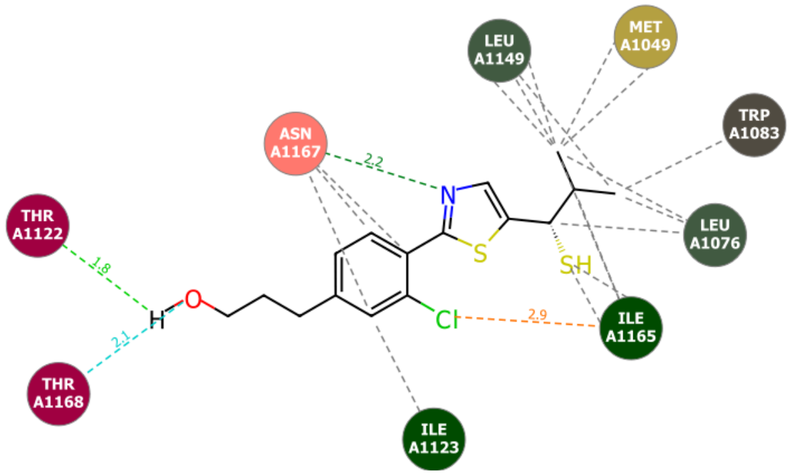
NS5-MTase (2P3L)



NS5-RdRp (5K5M)



NS2B-NS3 · 6MO0



Source: Images generated using Cresset's Flare™. Results from the present study.

Hydrogen bonds · Weak hydrogen bonds · Hydrophobic contacts · Aromatic interactions, cation–π interactions, and sulfur–lone pair interactions · Steric clashes

Results: Quantum chemistry and ADME profiles of eight candidates

A · Quantum characterization

ORCA · 8 candidates

Comparative table: HOMO | LUMO | GAP | Dipole Moment

Candidate	HOMO (eV)	LUMO (eV)	GAP (eV)	Dipolo (D)
3_10_D	−5.4339	−2.2075	3.2264	3.3541
3_18_D	−5.7874	−2.5809	3.2065	3.2198
3_20_D	−5.7754	−2.5258	3.2496	3.1146
3_24_D	−5.6852	−2.7067	2.9785	5.1076
3_28_D	−5.3917	−2.9881	2.4036	3.4033
3_30_D	−5.5381	−2.3464	3.1917	0.8559
3_32_D	−5.5313	−2.3384	3.1929	3.5421
3_33_D	−5.6666	−2.6559	3.0107	1.3419

8/8 optimizations completed successfully, with no imaginary frequencies.

B · ADME Evaluation

SwissADME · 8 candidates

Comparative table: MW | LogP | TPSA | GI Absorption | LogS | Lipinski

Candidate	MW (g/mol)	Consensus LogP	TPSA (Å²)	Log S (ESOL)	GI Absorption	P-gp Substrate
3_10_D	340.91	3.16	119.92	−4.37	High	No
3_18_D	340.89	3.55	123.02	−4.24	High	No
3_20_D	354.92	3.91	123.02	−4.66	Low	No
3_24_D	375.96	3.59	136.44	−4.10	Low	No
3_28_D	381.96	3.33	113.61	−4.64	High	Yes
3_30_D	341.92	4.47	100.16	−4.89	High	No
3_32_D	369.93	4.12	117.23	−4.67	High	No
3_33_D	369.93	4.03	120.39	−4.76	High	No

8 meet Lipinski criteria · 6 show high GI absorption

Solubility and CYP450: Areas requiring optimization

Complementary evaluation

Drug-likeness

8/8 meet Lipinski criteria (0 violations)
Bioavailability score: 0.55 (8/8)
PAINS: 0 alerts (8/8)

CYP450

CYP1A2 · CYP2C19 · CYP2C9 · CYP2D6 · CYP3A4
3_30_D: Predicted inhibition of all five CYP isoforms
P-gp: 1/8 predicted substrate

Medicinal Chemistry

Brenk: thiol_2 (8/8)
imina_1 and imina_2 (3_10_D)
Synthetic accessibility: 3.59–4.14

3_30_D: Complete Quantum Characterization and Identified ADME Limitations

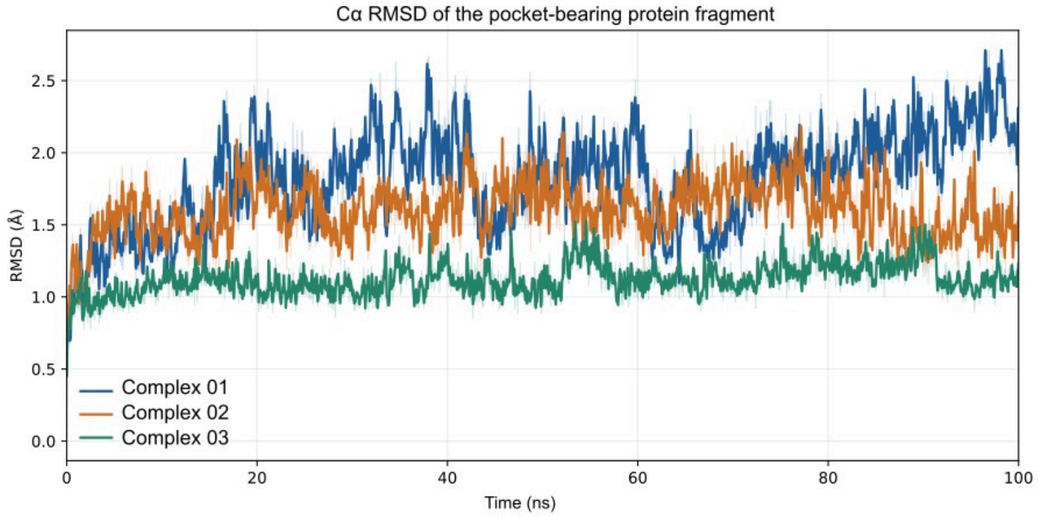
Prioritized based on multitarget docking and EC; quantum chemistry and ADME analyses provided complementary evidence to support further evaluation.

Results: Molecular dynamics of 3_30_D against three DENV-2 targets

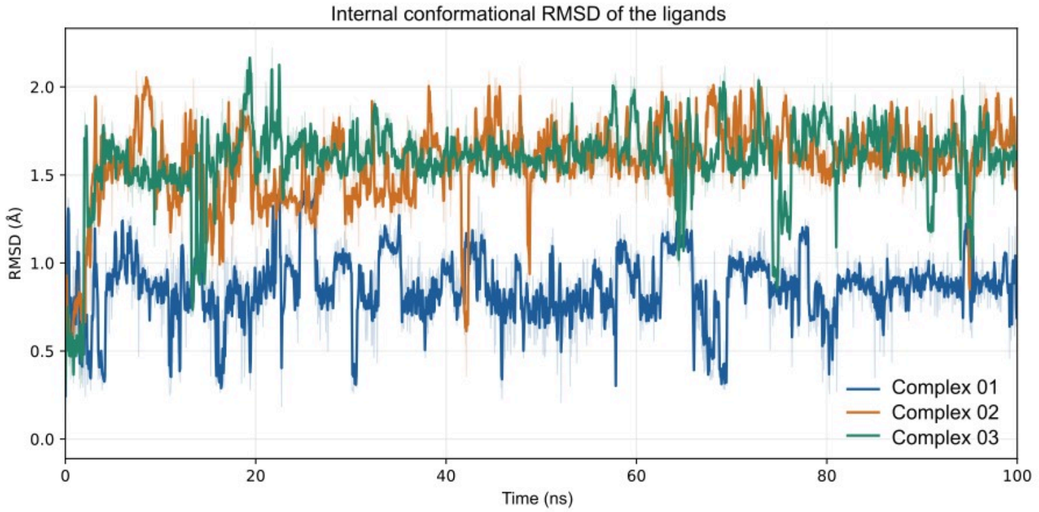
UnoMD · 100 ns per complex One candidate · Three systems

Complex 1: NS5-RdRp (5K5M) Complex 2: NS2B-NS3 Protease (6MO0) Complex 3: NS5-MTase (2P3L)

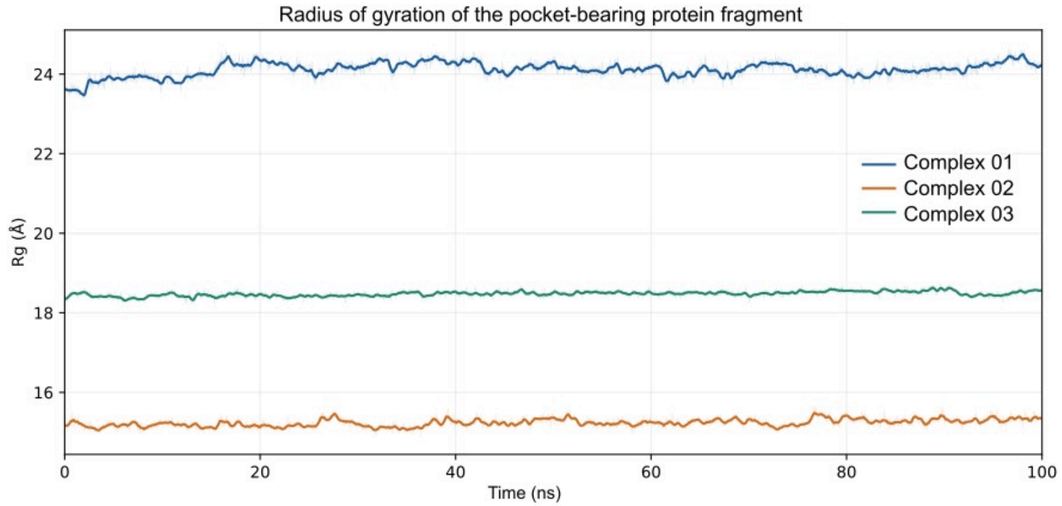
A · Binding pocket Cα RMSD



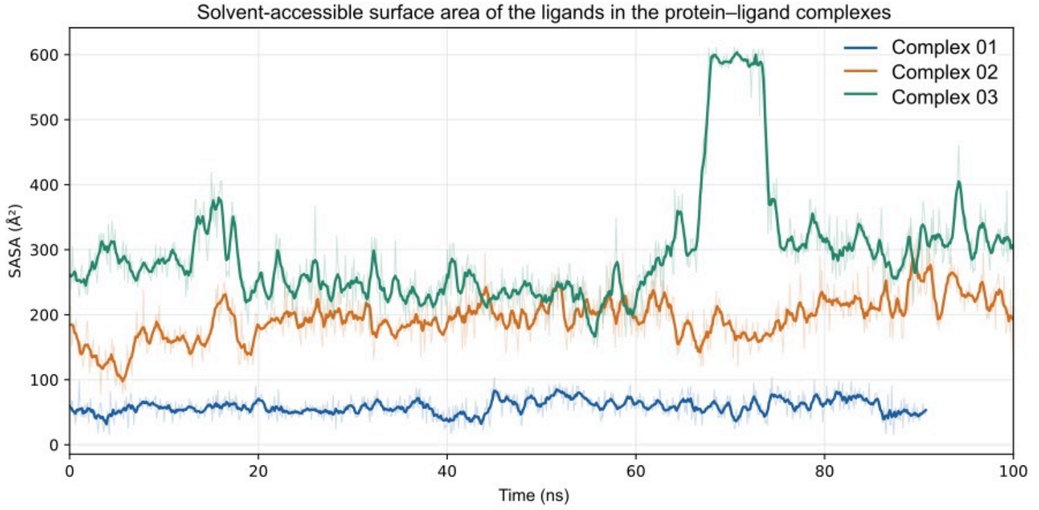
B · Ligand internal RMSD



C · Radius of Gyration of the Protein Fragment (Rg)



D · Ligand SASA



Trajectory observations

- A. Lower local fluctuations in Complex 03 (MTase).
- B. Lower conformational variability in Complex 01 (RdRp).
- C. Relatively stable values throughout the 100 ns simulations in all three systems.
- D. Greater solvent exposure in Complex 03, with a transient increase between 67 and 73 ns.

Note. Figure generated using UnoMD.

Conclusions and future perspectives

01 · Multitarget identification

Rational screening and optimization enabled the prioritization of 3_30_D based on its relatively consistent docking scores and positive electrostatic complementarity (EC) across all three DENV-2 targets.

02 · Molecular characterization

The eight candidates were characterized using quantum chemistry and ADME predictions, identifying physicochemical properties and potential pharmacokinetic limitations.

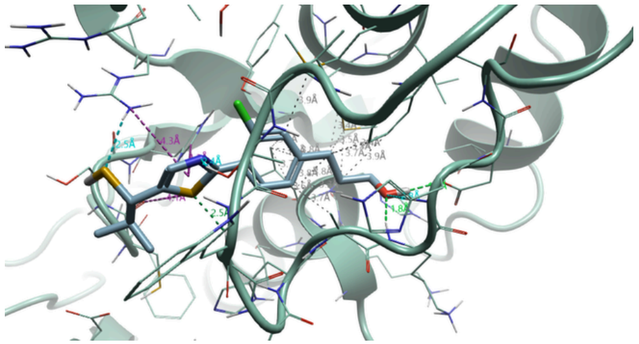
03 · Molecular Dynamics

The 100 ns simulations of 3_30_D revealed target-dependent differences in structural behavior and solvent exposure.

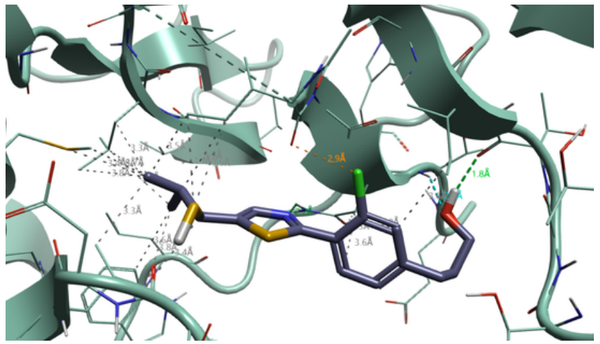
04 · Limitations and validation

The results are predictive and require biochemical assays, cell-based antiviral evaluation, and toxicity studies to determine antiviral activity and safety

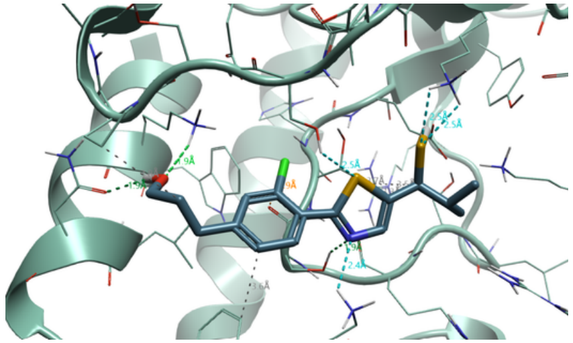
NS5-RdRp (5K5M)



NS2B-NS3 proteasa (6MO0)



NS5-MTase (2P3L)



Source: Images generated using Cresset's Flare™. Results from the present study.

3_30_D: Priority computational candidate for further experimental validation studies.

Acknowledgments and references

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Thank You!

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BCADD 2026

Acknowledgments

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Software and selected references

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