Indian Journal of Biochemistry & Biophysics
Vol. 63, October 2026, pp. 1187-1190
DOI: 10.56042/ijbb.v63i10.29816

In silico screening of Chromeno-pyrano-oxazole derivatives as dengue virus protease inhibitors using CB-dock

Prasanna Bhalchandra Ranade[1]*, Dinesh Nivrutti Navale[1], Santosh Waghu Zote[2], Dnyaneshwar Kisan Kulal[3], Swapnil Jagannath Wagh[4] & Saurabh Anil Shete[5]

[1]Department of Chemistry, Vivekanand Education Society's College of Arts, Science and Commerce (Autonomous), Sindhi Society, Chembur, Mumbai-400 071, Maharashtra, India

[2]Department of Chemistry, P.T.V.A.'s Sathaye College (Autonomous), Dixit Road, Vile Parle (East), Mumbai-400 057, Maharashtra, India

[3]Department of Chemistry, Ramnarain Ruia Autonomous College, L. N. Road, Matunga, Mumbai-400 019, Maharashtra, India

[4]Department of Chemistry, RSS Prasarak Mandal's Nanasaheb Yashvantrao Narayanrao Chavan, Arts, Science & Commerce College Chalisgaon, Jalgaon-424 101, Maharashtra, India

[5]Department of Chemistry, K J Somaiya College of Science and Commerce, Vidyanagar, Vidyavihar, Mumbai-400 077, Maharashtra, India

Received 17 March 2026; *revised 02 July 2026*

Dengue virus infection is globally a challenge, with extremely limited antiviral treatments available. Due to the important role of NS2B–NS3 protease in dengue viral replication, it is targeted for development of new antiviral entities. In current work, Chromeno-Pyrano-oxazole derivatives were evaluated as potential inhibitors using blind molecular docking through the CB-Dock web server. The docking results showed the binding interactions with His51 and Asp75 mainly suggesting that Chromeno-Pyrano-oxazole derivatives may serve as encouraging for developing dengue virus protease inhibitors.

Keywords: 2FOM, ADMET, Amino acid, NS2B–NS3 protease, Structure-based drug design

Dengue[1] is a mosquito-borne viral disease. The Dengue virus belongs to a *flaviviridae* family[1,2] having positive sense single stranded RNA with spherical and envelope shape . It is primarily transmitted by aedes aegypti type mosquitoes[3]. Dengue viruses exist in four serotypes DEN-1, DEN-2,DEN-3, and DEN-4.[4] Three structural proteins[4,5] namely envelope, capsid, membrane and seven non structural proteins *viz*., NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5[5] found in dengue viruses[4]. Millions of people worldwide each year get infected by dengue, particularly in tropical and subtropical regions, leading to mild fever, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS)[5].

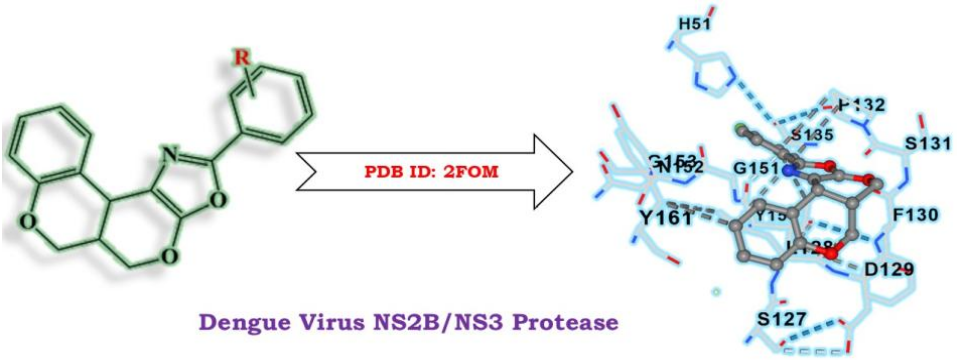
The NS2B–NS3 complex acts as a two-component serine protease that processes the viral polyprotein by cleaving it into separate functional proteins such as NS2A/NS2B, NS2B/NS3, NS3/NS4A, and NS4B/NS5.[5] When the activity of this protease is inhibited, the formation of essential viral proteins is prevented, which disrupts the viral life cycle and ultimately stops replication. The active site[6] of the NS2B–NS3 protease contains a catalytic triad[6] consisting of His51, Asp75, and Ser135, which facilitates the cleavage of peptide bonds. Because of its essential role in viral protein processing, targeting and inhibiting this protease represents a good route for developing antiviral drugs against dengue.

Currently there is no specific antidengue treatment available which highlights the urgent need for the development of effective antidengue therapeutic agents.

Substituted chromeno pyrano derivatives show anticancer,[7] antiCOVID,[8] antibacterial,[9] anti-proliferative[10] activities. Certain tetracyclic compounds[11] are known for their antidengue activities.

Though the biological properties of chromene-, pyran-, and oxazole-related compounds have been known[7-10], the anti-dengue efficacy of fused chromeno-pyrano-oxazole derivatives is still mostly uninvestigated. Specifically, their engagement with the dengue virus NS2B–NS3 protease and their potential as drug candidates have not been thoroughly assessed. Consequently, this research intends to fill

*Correspondence:
E-mail: prasannabranade@gmail.com
Suppl. data available on respective page of NOPR



Graphical abstract

this void by conducting an *in silico* analysis of these new derivatives.

Computer aided drug designing[12] is an important tool in cheminformatics[13]. A web base server is used to perform the docking between dengue virus protease and Chromeno-Pyrano-oxazole derivatives. The obtained docking results were encouraging and suggested the potential for designing new entities against dengue virus.

In current work we have designed tetracyclic Chromeno-Pyrano-oxazole derivatives for docking and ADME study along with structure activity relationship

Materials and Methods

In silico studies were carried out on a Dell desktop with an Intel (R) Core™ i3-4150 processor running Windows 10 Education.

Docking studies

On CB-Dock (AutoDock Vina, v1.1.2) web server[14] docking between designed molecules and protein were performed. (https://cadd.labshare.cn/cb-dock2/php/index.php)

Docking protocol

Docking was performed with the standard AutoDock Vina settings (exhaustiveness = 8, maximum binding modes = 9, and energy range = 3 kcal/mol), with the docking search area automatically established according to the anticipated binding pocket. The binding pose exhibiting the least binding free energy (highest negative Vina score) from the top-ranked cavity was chosen for subsequent interaction analysis.

Selection of target Dengue virus NS2B/NS3

The target is well-validated and highly conserved drug target across dengue serotypes, making it suitable for broad-spectrum inhibitor design.

Protein preparation

The crystal structure of the dengue virus NS2B/NS3 protease[15] (PDB ID: 2FOM)[15] was sourced from the Protein Data Bank (www.rcsb.org) and processed utilizing the CB-Dock2 web server. Hydrogen atoms were added automatically, and the protonation states of ionizable residues were determined at physiological pH (~7.4). The protein structure underwent energy minimization via the built-in preprocessing module to enhance its geometry. CB-Dock2 autonomously detected possible ligand-binding sites and created the docking search area. Blind docking was executed utilizing the highest-ranked anticipated cavity for ligand interaction.

Ligands preparation

Ligands i.e. designed molecules were drawn and saved in *.mol* file format using Chem Draw software (Chemdraw Ultra 12.0.2) Addition of hydrogens, and partial atomic charges were automatically added in CB dock2 web server upon uploading the ligand file.

SWISS ADME

A SWISS ADME[16] web-based server is used for knowing ADME properties of designed molecules.

Results and Discussion

A CB-Dock web server is used for docking of designed 2-substituted -phenyl-5,5a,6,11b-tetrahydrochromeno [4',3':4,5] pyrano[3,2-d] oxazole analogs for their binding interaction toward dengue virus NS2B/NS3 protease.

The docking score of each designed compound is comparable with the reported antidengue compounds[17] including Pinostrobin[17], Pinocembrin[17], Panduratin[17], Luteolin[18], Quercetin,[19] etc. Drugs including Chloroquine[20], Ribavirin[21], Doxycycline[22] used for treatment of dengue are also docked against dengue virus protease. The docking score fall in

between -5.8 to -7.5 which is comparable to designed compounds.

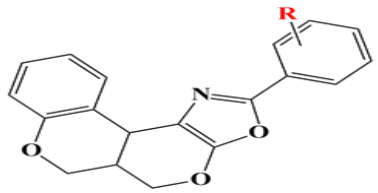
In the literature potent anti-dengue compounds interact with catalytic triad[17] residues His51, Asp75, and Ser135 along with other important amino acid residues[23-25] such as Trp50, Arg54 Val72 Lys73 Lys74, Leu76, Trp83, Gly87 Glu88 Trp89 Lys90 Glu91 Leu115 Thr118 Asn119 Thr120 Gly121 Thr122 Ile123 Val147 Gly148, Leu149, Asn152 Gly153 Val154 Val155 Ala164 Ile165 Ala166, Asn167[25].

His51 and Asp75, located in the active site[17] of the dengue virus protease, found to interact with designed chromeno-pyrano-oxazole derivatives by either hydrogen bonding or hydrophobic interactions[17]. Designed compounds show interaction[17] with Lys74 residue which is directly attached to Asp75 that is active site.

The structure–activity relationship (SAR)

The dock score of the virtually designed chromeno–pyrano–oxazole derivatives markedly influenced due to substitution on phenyl ring. The compound 1 exhibited a dock score of −6.3. The docking score performance is improved upon derivatizing phenyl ring with different substituents like alkyl or halogen. The compound 3 is 4-chloro-substituted analogue show -7.7 dock score. The compound 3 provides hydrophobic and steric interactions with the receptor binding pocket. Compounds bearing other electron-withdrawing groups, such as 4-cyano, 4-nitro, and 4-trifluoromethyl, also exhibited improved dock scores (−7.0 to −6.9), suggesting that electron-withdrawing substituents at the para position favor ligand–receptor interactions. Hydrogen-bonding interactions are observed in compound 5 due to hydroxyl substituent. In contrast, compounds with electron-donating substituents including 4-methyl, 4-methoxy, and 3,4-dimethoxy resulted in only minor improvements in dock score. Furthermore, the lower dock score of the 2-fluoro analogue compared to the 4-fluoro derivative highlights the importance of substituent position in achieving favorable binding. Overall, the SAR findings suggest that para-substituted electron-withdrawing groups, particularly chlorine, significantly enhance the dock score of the chromeno–pyrano–oxazole scaffold and may serve as promising structural modifications for further lead optimization (Table 1).

These findings suggest that the designed chromeno–pyrano–oxazole derivatives exhibit favorable predicted interactions with the dengue virus target protein and may serve as promising lead compound.



Substituted-2-phenyl-5,5a,6,11b-tetrahydrochromeno [4',3':4,5]pyrano[3,2-d]oxazole derivatives

Table 1 — Docking scores of chromeno–pyrano–oxazole scaffold

S. No	Compound No.	R	Dock score
1	Compound 1	H	-6.3
2	Compound 2	4-methyl	-6.5
3	Compound 3	4-chloro	-7.7
4	Compound 4	4-fluoro	-6.7
5	Compound 5	4-hydroxy	-6.9
6	Compound 6	4-bromo	-6.4
7	Compound 7	4-CF_3	-6.9
8	Compound 8	4-cyano	-7.0
9	Compound 9	3,4-dimethoxy	-6.6
10	Compound 10	4-nitro	-6.9
11	Compound 11	2-fluoro	-6.4
12	Compound 12	4- methoxy	-6.5
13	Ribavirin	-	-6.5
14	Chloroquine	-	-5.8
15	Doxycycline	-	-6.8
16	Luteolin	-	-7.3
17	Pinostrobin	-	-7.2
18	Pinocembrin	-	-7.0
19	Panduratin	-	-7.3
20	Quercetin	-	-7.4

ADME analysis reveals those pharmacokinetic characteristics of the designed chromeno–pyrano–oxazole derivatives are in acceptable range. These findings indicate that the compounds are promising candidates for further biological evaluation. The docking poses of interactions between the Chromeno-Pyrano-oxazole designed compounds and the amino acid residues of the protein, ADME parameters are provided in the Supporting Information.

Conclusion

The docking score reveals that designed tetracyclic chromeno pyrano derivatives have potential antidengue characteristics *in silico*. ADME parameter suggesting designed tetracyclic chromeno pyrano derivatives have drug likeness properties. A CB-Dock web server helps in predicting potential anti-dengue characteristics of designed compounds.

Acknowledgement

The authors, Prasanna Ranade and Dinesh Navale, gratefully acknowledge the support and access to the Central Instrumentation Facilities funded by DST-FIST at Vivekanand Education Society's College of Arts, Science and Commerce (Autonomous). The authors also acknowledge the financial and infrastructural support provided under the DBT STAR College Scheme. Further, the authors sincerely thank the RUSA grant under PM-USHA for their support in facilitating this work.

Conflict of interest

All authors declare no conflicts of interest.

1 Diamond MS & Pierson TC, Molecular insight into dengue virus pathogenesis and its implications for disease control. *Cell*, 162 (2015) 488.
2 Murugesan A & Manoharan M, Dengue virus. *Emerg Reemerg Viral Pathog*, (2020) 281.
3 Abbasi E, Aedes aegypti and dengue: insights into transmission dynamics and viral lifecycle. *Epidemiol Infect*, 153 (2025) e88.
4 Hannemann H, Sung PY, Chiu HC, Yousuf A, Bird J, Lim SP & Davidson AD, Serotype-specific differences in dengue virus non-structural protein 5 nuclear localization. *J Biol Chem*, 288 (2013) 22621.
5 Stevens AJ, Gahan ME, Mahalingam S & Keller PA, The medicinal chemistry of dengue fever. *J Med Chem*, 52 (2009) 7911.
6 Noble CG, Seh CC, Chao AT & Shi PY, Ligand-bound structures of the dengue virus protease reveal the active conformation. *J Virol*, 86 (2012) 438.
7 Bejjanki NK, Venkatesham A, Madda J, Kommu N, Pombala S, Kumar CG, Prasad KR & Nanubolu JB, Synthesis of new chromeno-annulated cis-fused pyrano[4,3-c]isoxazole derivatives via intramolecular nitrone cycloaddition and their cytotoxicity evaluation. *Bioorg Med Chem Lett*, 23 (2013) 4061.
8 Motamedi R, Soufian S, Rostami Ghalhar Z, Jalali M & Rahimi H, Synthesis and docking study of some novel chromeno[4',3'-b]pyrano[6,5-d]pyrimidine derivatives against COVID-19 main protease. *Curr Comput Aided Drug Des*, 20 (2024) 551.
9 Prasad JV, Kumar NR, Solomon KA, Nilaventhan KRS, Sudar LRC, Saisubramanian N & Gopikrishna G, One pot synthesis of fused chromeno-pyrano-pyrimidines and evaluation of their antimicrobial activity. *Indian J Chem B*, 53 (2014) 345.
10 Venkatesham A, Srinivasa Rao R, Nagaiah K, Yadav JS, Roopa Jones G, Basha SJ, Sridhar B & Addlagatta A, Synthesis of new chromeno-annulated cis-fused pyrano[3,4-c]pyran derivatives via domino Knoevenagel-hetero-Diels–Alder reactions and their biological evaluation towards antiproliferative activity. *Med Chem Commun*, 3 (2012) 652.
11 Rothan HA, Buckle MJ, Ammar YA, Mohammadjavad Y, Shatrah P, Noorsaadah AR & Rohana Y, Study the antiviral activity of some derivatives of tetracycline and non-steroid anti-inflammatory drugs towards dengue virus. *Trop Biomed*, 30 (2013) 681.
12 Niazi SK & Mariam Z, Computer-aided drug design and drug discovery: a prospective analysis. *Pharmaceuticals*, 17 (2024) 22.
13 Xu J & Hagler A, Chemoinformatics and drug discovery. *Molecules*, 7 (2002) 566.
14 Liu Y, Grimm M, Dai WT, Hou MC, Xiao ZX & Cao Y, CB-Dock: a web server for cavity detection-guided protein-ligand blind docking. *Acta Pharmacol Sin*, 41 (2020) 138.
15 Chiuan HN, Leow CH, Ezleen KE, Wahab HA, Vignesh R, Rasul A & Lai NS, Assessing the potential of NS2B/NS3 protease inhibitors biomarker in curbing dengue virus infections: in silico vs in vitro approach. *Front Cell Infect Microbiol*, 13 (2023) 1061937.
16 Daina A, Michielin O & Zoete V, SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Sci Rep*, 7 (2017) 42717.
17 Othman R, Kiat TS, Khalid N, Yusof R, Newhouse EI, Newhouse JS, Alam M & Rahman NA, Docking of noncompetitive inhibitors into dengue virus type 2 protease: understanding the interactions with allosteric binding sites. *J Chem Inf Model*, 48 (2008) 1582.
18 Peng M, Watanabe S, Chan KWK, He Q, Zhao Y, Zhang Z, Lai X, Luo D, Vasudevan SG & Li G, Luteolin restricts dengue virus replication through inhibition of the proprotein convertase furin. *Antiviral Res*, 143 (2017) 176.
19 Shimu MSS, Mahmud S, Tallei TE, Sami SA, Adam AA, Acharjee UK, Paul GK, Emran TB, Zaman S, Uddin MS, Saleh MA, Alshehri S, Ghoneim MM, Alruwali M, Obaidullah AJ, Jui NR, Kim J & Kim B, Phytochemical compound screening to identify novel small molecules against dengue virus: a docking and dynamics study. *Molecules*, 27 (2022) 653.
20 Farias KJS, Machado PRL, Almeida Junior RF, Aquino AA & Fonseca BAL, Dengue virus infection and host immune response. *Microbiol Immunol*, 58 (2014) 318.
21 Koff WC, Elm JL Jr & Halstead SB, Antiviral effects of ribavirin and 6-mercapto-9-tetrahydro-2-furylpurine against dengue viruses in vitro. *Antiviral Res*, 2 (1982) 69.
22 Rothan HA, Mohamed Z, Paydar M, Rahman NA & Yusof R, Inhibitory effect of doxycycline against dengue virus replication in vitro. *Arch Virol*, 159 (2014) 711.
23 Rhakho M, Potential inhibitor of DENV-2 virus protease (NS2B-NS3): an in-silico study of anti-viral plants. *J Drug Deliv Ther*, 14 (2024) 10.
24 Frimayanti N, Chee CF, Zain SM & Rahman NA, Design of new competitive dengue NS2B/NS3 protease inhibitors—A computational approach. *Int J Mol Sci*, 12 (2011) 1089.
25 Starvaggi J, Di Chio C, Lang J, Belgiovine V, Trisciuzzi D, Previti S, Klein C, Nicolotti O, Di Maro S, Zappalà M & Ettari R, Development of novel proline- and pipecolic acid-based allosteric inhibitors of dengue and Zika virus NS2B/NS3 protease. *Pharmaceuticals*, 19 (2026) 1.