Biol. Stud. 2025, 19(3), 21–32 • doi: https://doi.org/10.30970/sbi.1903.835
www.http://publications.lnu.edu.ua/journals/index.php/biology

UDC: 615.357:578.834.1]:577.322

ASSESSING THE BINDING AFFINITY OF GLUCOCORTICOIDS TO THE SARS-CoV-2 SPIKE PROTEIN – ANGIOTENSIN-CONVERTING ENZYME 2 COMPLEX: A MOLECULAR DOCKING SIMULATION STUDY

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Khmil, N., Shestopalova, A., & Kolesnikov, V. (2025). Assessing the binding affinity of glucocorticoids to the SARS-CoV-2 spike protein – angiotensin-converting enzyme 2 complex: a molecular docking simulation study. *Studia Biologica*, 19(3), 21–32. doi:10.30970/sbi.1903.835

Background. SARS-CoV-2 has been identified as the causative agent of COVID-19. Viral infection occurs through the interaction of the viral spike protein (S protein) with the host's angiotensin-converting enzyme 2 (ACE2). In moderate and severe cases of COVID-19, the therapeutic benefits of glucocorticoids are attributed to their ability to mitigate immune-mediated lung injury and suppress the cytokine storm. This study aims to evaluate the binding affinity of glucocorticoids to the S protein–ACE2 complex in two SARS-CoV-2 variants: the wild-type Wuhan strain and the JN.1 subvariant of Omicron, to identify potential glucocorticoid binding sites and the amino acid residues involved in ligand interactions.

Materials and Methods. Two crystal structures of the S protein–ACE2 complexes (PDB IDs: 6M0J and 8Y18 from the Protein Data Bank) were selected as docking targets. Molecular docking was performed to assess the binding affinity of dexamethasone (DEX), methylprednisolone (Medrol), and triamcinolone (TAC) to the S protein–ACE2 complex. Docking results were visualized using PyMol 2.5. The protein-ligand interaction profiler (PLIP) was employed to identify non-covalent interactions between proteins and ligands. The root mean square fluctuation (RMSF) of amino acid residue was quantified using CABS-flex 2.0 software.

Results and Discussion. Using a molecular docking approach, it has been demonstrated that DEX, Medrol, and TAC form energetically favorable interactions with both the 6M0J and 8Y18 structures, exhibiting low binding energy scores: 6M0J-DEX

-8.0 kcal/mol; 6M0J-Medrol -7.8 kcal/mol; 6M0J-TAC -8.3 kcal/mol; 8Y18-DEX -8.4 kcal/mol; 8Y18-Medrol -8.3 kcal/mol; 8Y18-TAC -8.7 kcal/mol. However, the binding affinities of these complexes differ due to mutations in the S protein, which alter the polarity distribution of its amino acid residues, particularly their ability to form hydrogen bonds.

Conclusion Studying the binding parameters of DEX, Medrol, and TAC with the S protein–ACE2 complex is essential, particularly given SARS-CoV-2's capacity for rapid mutation. Certain mutations can alter binding sites, potentially influencing drug efficacy. Docking studies that analyze the energetic and structural characteristics of glucocorticoid binding pockets on the S protein–ACE2 complex can help predict how molecular interactions may change as the virus mutates.

Keywords: SARS-CoV-2, spike protein, angiotensin-converting enzyme 2, glucocorticoids, molecular docking, health care

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly pathogenic strain of coronavirus that has rapidly spread worldwide over the past five years and is identified as the causative agent of coronavirus disease 2019 (COVID-19). As of April 2025, over 777 million confirmed cases and over 7.0 million deaths have been reported globally (https://www.who.int/emergencies/diseases/novel-coronavirus-2019).

SARS-CoV-2 is a positive-sense single-stranded RNA (ssRNA) virus with a 30 kb genome that encodes non-structural, structural, and accessory proteins (Kakavandi *et al.*, 2023; Gorkhali *et al.*, 2021). The S protein, a trimeric glycoprotein, facilitates viral fusion with host cells via the ACE2 receptor. Mutations in the S protein can alter its structure and function, impacting transmissibility, resistance, and potentially reducing the efficacy of therapies. (Huang *et al.*, 2020; Lomoio *et al.*, 2023).

SARS-CoV-2 has evolved significantly from the original Wuhan variant. The Omicron variant (B.1.1.529), now globally prevalent, has undergone key genomic changes (Fan *et al.*, 2022; Zaidi *et al.*, 2024; Kaku *et al.*, 2024). As of autumn 2024, the Omicron subvariant JN.1, which has over 30 mutations in the S protein, is classified as a variant under monitoring (https://data.who.int/dashboards/covid19/variants). Since SARS-CoV-2's infectivity depends on ACE2 receptor recognition, this receptor remains a primary target for vaccines and antiviral therapies (Shang *et al.*, 2020).

Systemic glucocorticoids, known for their anti-inflammatory and immune-suppressive effects, have been utilized in conditions related to COVID-19, such as SARS, MERS, and severe influenza (Prescott *et al.*, 2020). By inhibiting pro-inflammatory cytokines and suppressing immune cell activation, they help manage cytokine storms in severe COVID-19 cases, reducing lung damage and mortality (Okoye *et al.*, 2020; Horby *et al.*, 2021). Certain glucocorticoids have also been shown to inhibit the SARS-CoV-2 main protease (Mpro) and the S protein (Elmaaty *et al.*, 2021; Sarker *et al.*, 2022; Khmil *et al.*, 2024; Mishra *et al.*, 2023; Khmil *et al.*, 2025). The molecular mechanisms underlying their effects, including binding energy scores and ligand-protein interactions, remain unclear, complicating efforts to enhance their efficacy amid rapidly emerging viral mutations.

The study aims to assess the binding affinity of glucocorticoids to the SARS-CoV-2 spike protein–ACE2 complex of two different SARS-CoV-2 variants – Wuhan wild-type and the JN.1 Omicron subvariant, to identify the potential glucocorticoid binding sites and the amino acid residues involved in interaction with ligands.

MATERIALS AND METHODS

Computational modeling of the S protein–ACE2 complex with glucocorticoids (DEX, Medrol, and TAC) was conducted using molecular docking via AutoDock Vina. This tool predicts ligand interactions with the SARS-CoV-2 S protein–ACE2 complex and evaluates binding affinity to rank potential binding poses.

Glucocorticoid structures were downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov) and optimized using the Open Babel 3.1.1. The SARS-CoV-2 S protein-ACE2 crystal structures (6M0J for wild-type, 8Y18 for JN.1) were obtained from the Protein Data Bank. The key binding amino acid residues were identified: in 6M0J, the S protein (B chain Thr333-Gly526) interacts with the ACE2 (A chain Ser19-Asp615), while in 8Y18, the S protein (B chain Cys336-Ala520) binds to the ACE2 (A chain Ser19-Ala614) (www.rcsb.org). Protonation of amino acid residues at pH 7 was verified with Propka 3.1, water molecules were removed, and Kollman charges were added using AutoDock Tools. A grid with a volume of 126 Å³ and a spacing of 0.508 Å was centered at coordinates x = -26.858, y = 18.39, z = -13.832. The exhaustiveness parameter was set to 50. Ligand interactions were analyzed with PLIP (https://plip-tool.biotec.tu-dresden.de), docking results visualized with PyMol 2.5 (Schrödinger *et al.*, 2020), and RMSF values calculated using CABS-flex 2.0 (Kurcinski *et al.*, 2019). A paired sample *t*-test was used to compare the two groups (wild-type and mutated subvariant), with differences considered statistically significant at $p < 0.05$. The analysis was conducted using the online statistical calculator, Statistics Kingdom (https://www.statskingdom.com/index.html).

RESULTS AND DISCUSSION

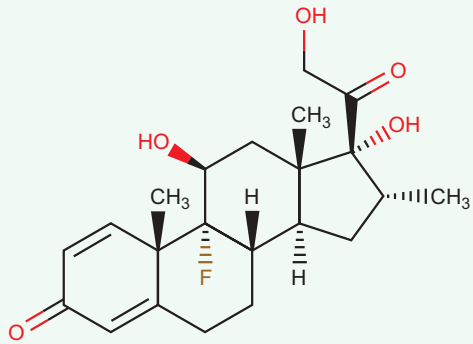
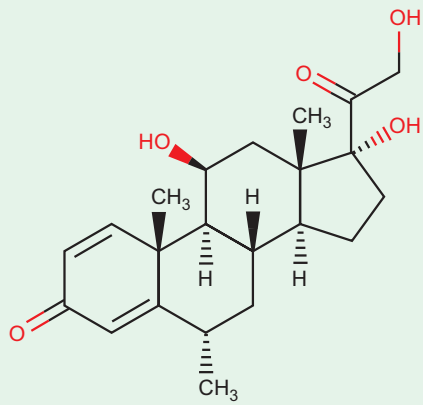
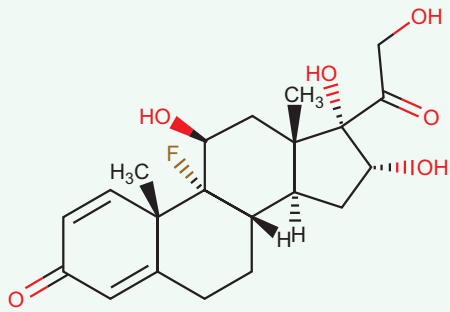
Docking studies showed that DEX, Medrol, and TAC can dock with the SARS-CoV-2 S protein–ACE2 complex, exhibiting high AutoDock Vina scores, which are presented in **Table**.

The docking analysis of the SARS-CoV-2 S protein–ACE2 complexes (6M0J and 8Y18) identified ligand-binding sites, focusing on the binding energy score, hydrogen bonds, and hydrophobic interactions. 3D contact maps were generated using the PLIP tool.

Molecular docking results of DEX and Medrol with the S protein–ACE2 complex. In complex with structure 6M0J, DEX exhibited a binding energy score of -8.0 kcal/mol and formed hydrogen bonds with Glu37, Gln96, Ala386, and Arg393 of chain A of the ACE2 receptor, as well as with Arg403 and Tyr505 of chain B of the S protein. The interaction of the ligand with Asn33 of chain A was through a halogen bond. For DEX in this structure, hydrophobic interactions occurred with Pro389 residue. In complex with 8Y18 structure, DEX displays hydrogen bonds with Gly205, Ala396, and Lys562 of chain A (**Fig. 1**). The other interactions were hydrophobic with residues Leu95, Gln98, Gln102, and Lys562 of chain A. The binding energy score in this complex is -8.4 kcal/mol.

Medrol exhibited a binding energy score of -7.8 kcal/mol when bound to the SARS-CoV-2 S protein–ACE2 complex (PDB ID: 6M0J). In this structure, Medrol formed hydrophobic interactions with the Asn33 and Pro389 residues of chain A. It also established hydrogen bonds between the amine hydrogens of Thr92, Gln96, Gln388, Phe390, and Arg393 of chain A, as well as Arg403 and Tyr505 of chain B, and the oxygen atoms of the ligand (**Fig. 2**).

List of the potential inhibitors of the S protein–ACE2 complex and their binding energy score (ΔG, kcal/mol)

Glucocorticoids interacting with the S protein–ACE2 complex	3D glucocorticoid structure	Binding energy score, ΔG, kcal/mol	
		6M0J	8Y18
Dexamethasone		-8.0	-8.4
Methylprednisolone		-7.8	-8.3
Triamcinolone		-8.3	-8.7

The binding energy score of Medrol with the S protein–ACE2 complex (PDB ID: 8Y18) was -8.3 kcal/mol. This interaction resulted in hydrogen bonds involving the Leu236 and Lys596 residues of chain A of ACE2 and the nitrogen atoms of the ligand. Additionally, the residues Leu236, Leu585, Glu589, and Phe592 of chain A formed hydrophobic interactions with the methyl hydrogens of the ligand.

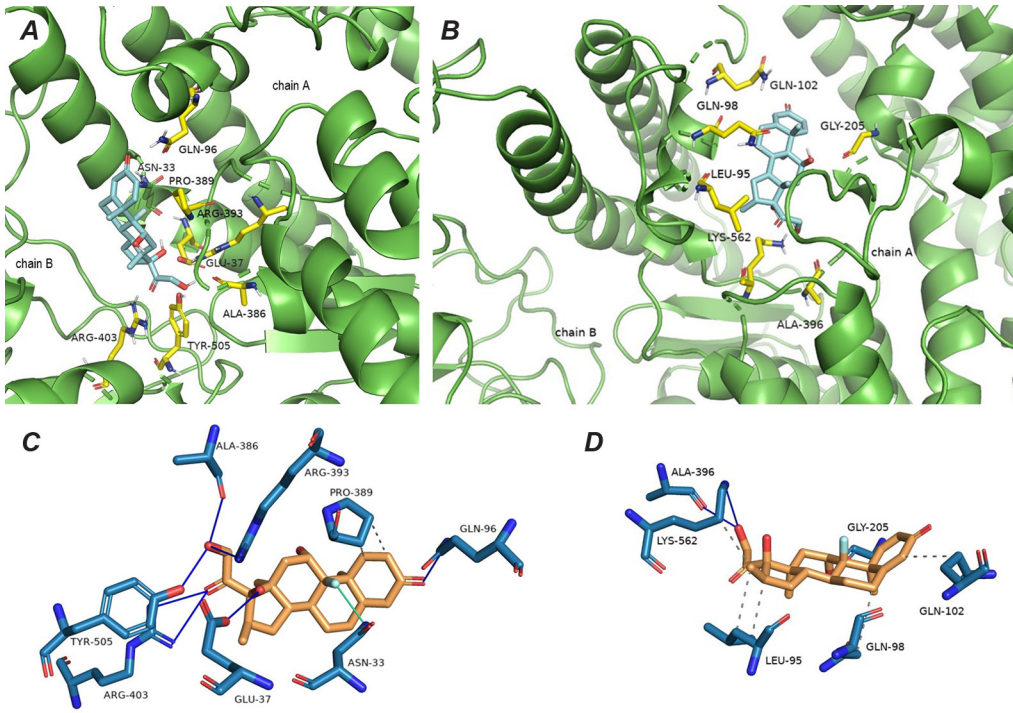


Fig. 1. The predicted docking position of DEX in the S protein–ACE2 complexes: ***A*** – PDB ID 6M0J; ***B*** – PDB ID 8Y18; the S protein–ACE2 complexes are represented as green ribbons, C atoms of the complex are shown in yellow, O – in red, N – in blue, H – in gray; the interacting amino acid residues are depicted as yellow sticks; atoms of DEX are shown (C – cyan, O – red, H – gray, F – dark gray); ***C–D*** – the 3D contact map of DEX with the S protein–ACE2 complexes (6M0J) and (8Y18), respectively; hydrogen bonds are represented by thin blue solid lines, hydrophobic interactions by gray dotted lines, halogen bonds by thin light green solid lines

Structural analysis reveals that the S protein features a tightly packed receptor-binding domain (RBD) and a flexible fusion peptide region (Gobeil *et al.*, 2022). Based on the crystal structures of 6M0J, the RBD core (composed of β-strands and α-helices) forms the receptor-binding motif (RBM, amino acid residues 438–506) (Lan *et al.*, 2020). Our findings suggest that DEX and Medrol exhibit a high binding affinity near the RBM, particularly through interactions with Arg403 and Tyr505 of chain B, which align with the molecular docking results reported by Y. Zhang (Zhang *et al.*, 2021). Molecular docking revealed that dexamethasone interacts with the active amino acid residue Lys353 of ACE2 and Gln498 of the RBD. Similarly, methylprednisolone forms interactions with Thr324, Gly354, and Arg357 of ACE2, as well as with Gln493, Gly496, and Tyr505 of the RBD.

Our docking studies confirm that the key RBD residues (Leu455, Phe486, Gln493, Ser494, Asn501, Tyr505) are crucial for ACE2 binding and interaction with glucocorticoids such as DEX and Medrol (Andersen *et al.*, 2020). It has been reported that many Omicron subvariants are characterized by unique and dynamic mutations in various motifs of the S protein (Fan *et al.*, 2022; Ma *et al.*, 2022). We observed that the mutation in JN.1 subvariant, such as Arg403Lys, may disrupt hydrogen bond formation with these ligands. This substitution reduces local polarity, as lysine's shorter, less flexible side chain forms fewer hydrogen bonds compared to arginine.

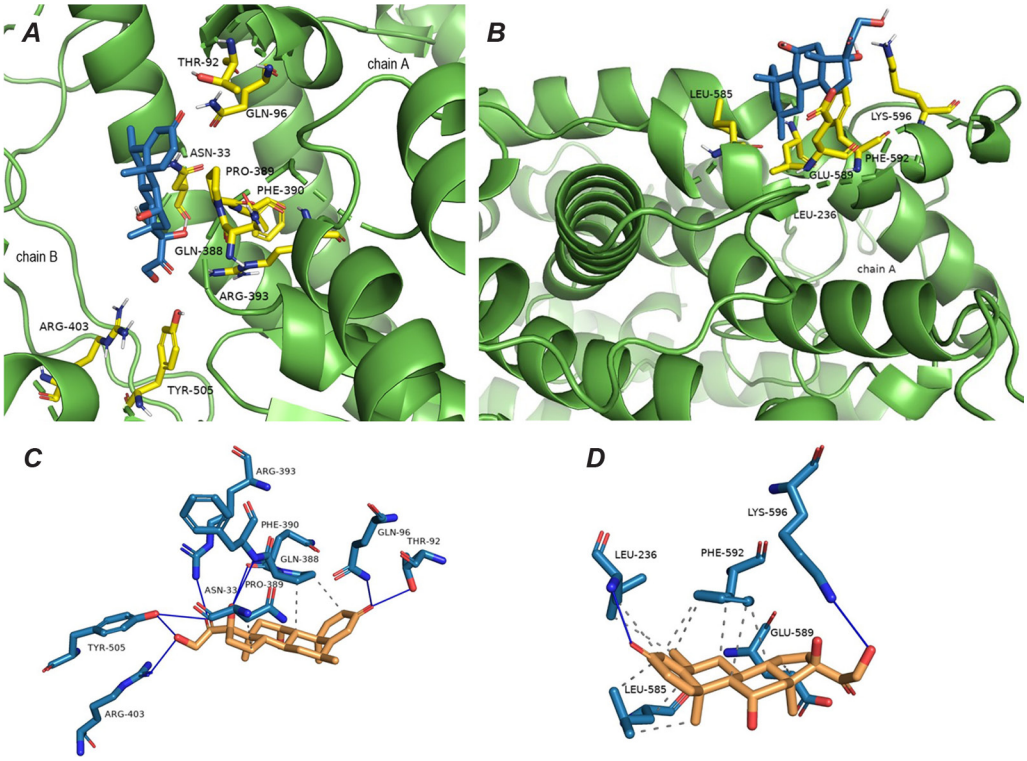


Fig. 2. The predicted docking position of Medrol in the S protein–ACE2 complexes: ***A –*** PDB ID 6M0J; ***B –*** PDB ID 8Y18; the S protein–ACE2 complexes are represented as green ribbons, C atoms of the complex are shown in yellow, O – in red, N – in blue, H – in gray; the interacting amino acid residues are depicted as yellow sticks; atoms of Medrol are shown (C – sky blue, O – red, H – gray); ***C–D*** – the 3D contact map of Medrol with the S protein–ACE2 complexes (6M0J) and (8Y18), respectively; hydrogen bonds are represented by thin blue solid lines, hydrophobic interactions by gray dotted lines

The substitution of polar tyrosine with nonpolar histidine at position 505 in the JN.1 subvariant reduces the S protein polarity and disrupts hydrogen bonds in the 8Y18-Dex and 8Y18-Medrol complexes. However, according to our data, this change does not reduce the binding affinity of DEX and Medrol.

The effect of TAC on the S protein–ACE2 complex. In complex with 6M0J structure, TAC exhibited a binding energy score of −8.3 kcal/mol and formed five hydrogen bonds between the oxygen atoms of the ligand and the amine hydrogens of the Gln81, Leu85, Gln86, Gln101, and Tyr196 residues of chain A. Hydrophobic interactions occurred with three amino acid residues, Gln81, Gln101, and Gln102 of chain A (**Fig. 3**).

The best binding affinity was observed for TAC with a binding energy score of -8.7 kcal/mol within the 8Y18 structure. There were five hydrogen bonds for this ligand with residues Gln98, Gln102, Tyr196, Tyr202, and Asn206 of chain A. Other interactions occurred whereby the residue Lys562 of chain A formed a π-cation interaction with the aromatic ligand group of the TAC structure. Additionally, hydrophobic interactions with the residues Leu95, Gln98, and Lys562 of chain A were observed. According to Y. Zhang, triamcinolone binds to Asp30 and Gln35 in ACE2 and to Tyr449 and Gly496

in the RBD of the S protein (Zhang *et al.*, 2021). Li and co-authors report that replacing hydrophobic leucine with neutral-polar serine at position 455 in the JN.1 variant's S protein enhances its binding affinity for human ACE2 compared to the Omicron BA.2.86 variant (Li *et al.*, 2024). Our study confirms that high affinity is maintained with ligands present, aligning with S. T. Selvavinayagam's findings of stronger ACE2 binding by mutated RBDs compared to the Wuhan wild-type (Selvavinayagam *et al.*, 2024).

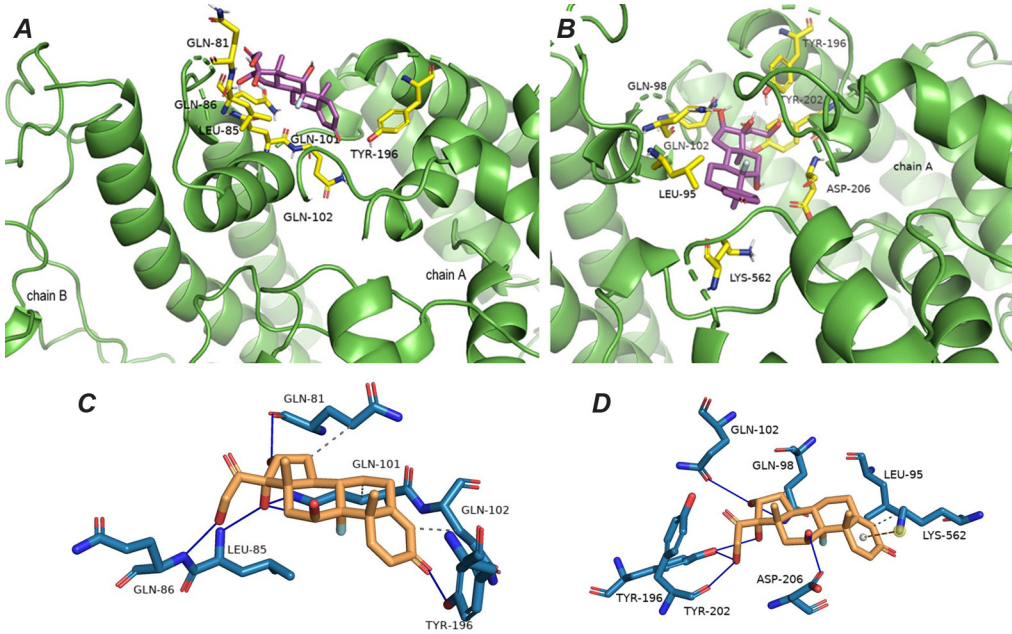


Fig. 3. The predicted docking position of TAC in the S protein–ACE2 complexes: ***A*** – PDB ID 6M0J; ***B*** – PDB ID 8Y18; the S protein–ACE2 complexes are represented as green ribbons, C atoms of the complex are shown in yellow, O – in red, N – in blue, H – in gray; the interacting amino acid residues are depicted as yellow sticks; atoms of DEX are shown (C – magenta, O – red, H – gray, and F – dark gray); ***C–D –*** the 3D contact map of TAC with the S protein–ACE2 complexes (6M0J) and (8Y18), respectively; hydrogen bonds are represented by thin blue solid lines, hydrophobic interactions by gray dotted lines, π-cation interaction by brown dotted lines

Hydrophobic interactions typically occur between nonpolar regions of molecules. In the case of TAC and the Gln81, Gln101, and Gln102 residues of ACE2, these polar amino acids usually engage in hydrogen bonding. However, TAC's hydrophobic steroid backbone may interact with nonpolar regions on the residues' side chains or nearby protein areas, enabling indirect hydrophobic interactions despite glutamine's polarity.

RMSF of the S protein–ACE2 complex. The study used CABS-flex 2.0 (https://biocomp.chem.uw.edu.pl/CABSflex2) to model the flexibility of S protein–ACE2 structures during glucocorticoid binding and calculate the RMSF of amino acid residues based on a coarse-grained model to predict protein dynamics. Regions with high RMSF are more flexible, while low RMSF indicates rigidity. As shown in **Figure 4**, moderate RMSF values (0.5–2.0 Å) favor ligand-protein binding by enabling conformational adjustments, which confirms the molecular docking results.

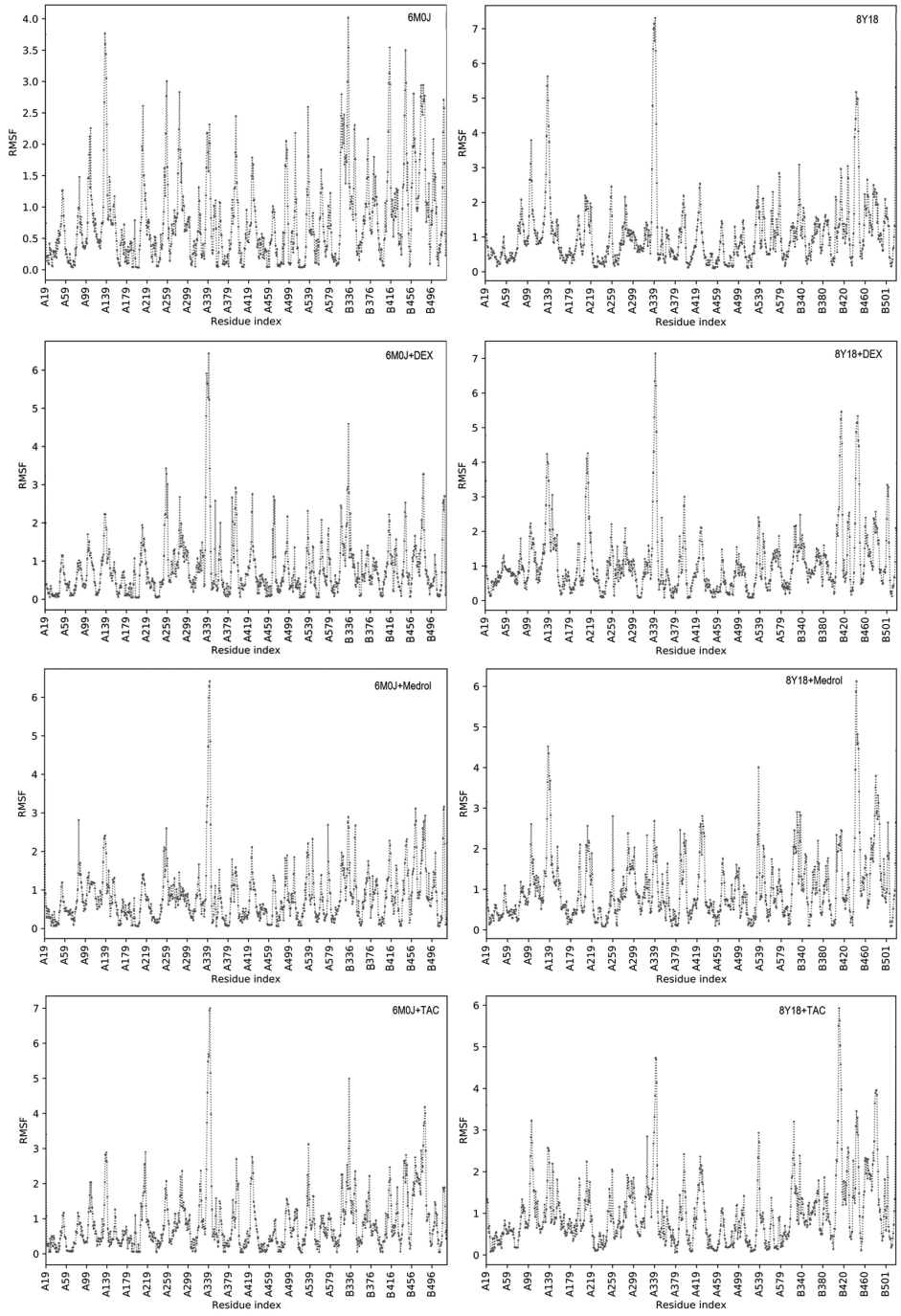


Fig. 4. RMSF of the amino acid residues in the S protein–ACE2 complexes (top two plots) and in the presence of glucocorticoids (bottom six plots): 6M0J-glucocorticoids – left column; 8Y18-glucocorticoids – right column. The abscissa axis shows the amino acid residue numbers and their association with the A chain of ACE2 (A19–A615 for 6M0J and A19–A614 for 8Y18) and the B chain of the S protein (B333–B526 for 6M0J and B336–B520 for 8Y18)

RMSF analysis showed deviations in specific amino acid residue ranges for the 6M0J and 8Y18 complexes with glucocorticoids. In 6M0J, DEX and Medrol increased rigidity in chain B and flexibility in chain A, while in 8Y18, TAC caused chain B to become more flexible and chain A more rigid relative to the crystal structure. These changes may result from hydrogen bond rearrangements, hydrophobic alterations, or allosteric effects of glucocorticoid binding. RMSF analysis and binding data indicate that DEX, Medrol, and TAC form energetically favorable interactions with the S protein–ACE2 complex without significant structural changes, though deviations vary by ligand.

CONCLUSION

This study has shown that DEX, Medrol, and TAC bind to specific sites on the S protein–ACE2 complex, involving both A and B chains in the wild type but only the A chain in the mutated JN.1 Omicron subvariant. These glucocorticoids may block viral entry along with their anti-inflammatory effects. Identifying these binding sites is key to developing antiviral strategies and designing drugs to disrupt S protein–ACE2 interactions or adapt to viral mutations.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest: the authors declare that they have no conflict of interest.

Human Rights: this article does not contain any studies with human subjects performed by any of the authors.

Animal Rights: this article does not contain any studies with animal subjects performed by any of the authors.

AUTHOR CONTRIBUTIONS

Conceptualization, [N.K.; A.S.]; methodology, [N.K.; A.S.]; validation, [N.K.; A.S.; V.K.]; formal analysis, [N.K.; A.S.].; investigation, [N.K.; A.S.; V.K.]; resources, [N.K.; A.S.; V.K.]; data curation, [N.K.; A.S.; V.K.]; writing – original draft preparation, [N.K.; A.S.; V.K.]; writing – review and editing, [N.K.; A.S.; V.K.]; visualization, [N.K.; A.S.]; supervision, [N.K.; A.S.]; project administration, [N.K.]; funding acquisition, [-].

All authors have read and agreed to the published version of the manuscript.

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ОЦІНКА СПОРІДНЕНОСТІ ЗВ'ЯЗУВАННЯ ГЛЮКОКОРТИКОЇДІВ ІЗ КОМПЛЕКСОМ СПАЙК-БІЛОК SARS-CoV-2 – АНГІОТЕНЗИНПЕРЕТВОРЮЮЧИЙ ФЕРМЕНТ 2: ДОСЛІДЖЕННЯ МОЛЕКУЛЯРНОГО ДОКІНГУ

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Обґрунтування. SARS-CoV-2 є збудником COVID-19. Вірусна інфекція виникає через взаємодію спайк білка (S-білка) з ангіотензинперетворюючим ферментом 2 (АПФ2) клітини-хазяїна. У лікуванні середніх і важких випадків COVID-19

переваги надаються глюкокортикоїдам, які пом'якшують імуноопосередковане ураження легень та пригнічують цитокіновий шторм. Це дослідження мало на меті оцінити спорідненість зв'язування глюкокортикоїдів безпосередньо з комплексом S білок–АПФ2 для двох варіантів SARS-CoV-2: дикого типу Ухань і субваріанта Omicron – JN.1. Дослідження також спрямоване на виявлення потенційних сайтів зв'язування глюкокортикоїдів і визначення амінокислотних залишків, залучених до взаємодії з лігандами.

Матеріали та методи. Дві кристалічні структури комплексів S білок–АПФ2 (PDB ID: 6M0J і 8Y18 з білкової бази даних) були обрані як док-мішені. Для оцінки спорідненості зв'язування дексаметазону (DEX), метилпреднізолону (Medrol) і триамцинолону (TAC) з комплексом S білок–АПФ2 застосували молекулярний докінг. Результати докінгу візуалізовано в PyMol 2.5. Нековалентні взаємодії між білками та лігандами визначали за допомогою веб-інструменту PLIP. Середньоквадратичні коливання амінокислотних залишків визначали у програмі CABS-flex 2.0.

Результати. За допомогою молекулярного докінгу продемонстровано здатність DEX, Medrol і TAC утворювати енергетично вигідні взаємодії зі структурами 6M0J і 8Y18, що підтверджено низькими показниками енергії зв'язування: 6M0J-DEX -8,0 ккал/моль; 6M0J-Medrol -7,8 ккал/моль; 6M0J-TAC -8,3 ккал/моль; 8Y18-DEX -8,4 ккал/моль; 8Y18-Medrol -8,3 ккал/моль; 8Y18-TAC -8,7 ккал/моль. Однак спорідненість зв'язування цих комплексів різниться через мутації в S білку, які призвели до зміни розподілу полярності амінокислотних залишків, зокрема, їхньої здатності утворювати водневі зв'язки.

Висновки. Дослідження параметрів зв'язування DEX, Medrol і TAC з комплексами S білок–АПФ2 є важливим, оскільки SARS-CoV-2 здатний до швидких мутацій. Певні мутації можуть змінювати сайти зв'язування та впливати на ефективність ліків. Аналіз результатів молекулярного докінгу – енергетичних і структурних характеристик сайтів зв'язування глюкокортикоїдів із комплексом S білок–АПФ2 – може передбачити зміну молекулярних взаємодій у разі мутації вірусу.

Ключові слова: SARS-CoV-2, спайк білок, ангіотензинперетворюючий фермент 2, глюкокортикоїди, молекулярний докінг, охорона здоров'я

Received / Одержано 26 October, 2024 | Revision / Доопрацьовано 05 February, 2025 | Accepted / Прийнято 17 September, 2025 | Published / Опубліковано 24 September, 2025