ISSN 2075-3810 (Print), ISSN 2075-3829 (Online)

БІОФІЗИЧНИЙ ВІСНИК, 2024, Вип. 51 BIOPHYSICAL BULLETIN, 2024, Iss. 51

MOLECULAR BIOPHYSICS

Original article

https://doi.org/10.26565/2075-3810-2024-51-04

UDC 577.322:[578.834.1:615.2]

IDENTIFICATION OF POTENTIAL CORTICOSTEROID BINDING SITES ON THE SARS COV-2 MAIN PROTEASE MPRO — *IN SILICO* DOCKING STUDY

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Submitted December 14, 2023; Revised February 19, 2024;
Accepted May 1, 2024

Background: Currently, an increase in the number of new cases of Covid-19 caused by the severe acute respiratory syndrome virus (SARS-CoV-2) is recorded in Ukraine and the world. SARS-CoV-2 provokes exacerbation of chronic diseases and activates inflammatory and allergic reactions. A severe course of Covid-19 increases the duration of hospitalization and the mortality rate among the population. Pathogenetic therapy is carried out with systemic corticosteroids, which suppress the cytokine storm by mitigating the SARS-CoV-2-induced systemic inflammatory response and inhibit SARS-CoV-2 main protease Mpro, a key component of viral replication.

Objectives: The aim of this study is to identify the potential corticosteroid binding sites on SARS CoV-2 main protease Mpro based on the analysis of the energetic and topological characteristics of the complexes as well as to investigate the inhibitory activity of selected corticosteroids against Mpro.

Material and Methods: The crystal structure of Mpro (ID: 6LU7 from Protein Data Bank) (www.rcsb.org) was chosen as a docking target. Molecular docking methods (AutoDock Tools 1.5.7, AutoDock Vina 1.1.2) were used to gain insight into the binding affinity Mpro with systemic corticosteroids such as dexamethasone (DEX), prednisone (PRED), prednisolone (PNL), methylprednisolone (Medrol), triamcinolone (TAC), and hydrocortisone (HCT). Visualization of docking results was done in PyMol 2.5. The protein-ligand interaction profiler (PLIP) and the LigPlot+ web tool were used to identify non-covalent interactions between Mpro and ligands (https://plip-tool.biotec.tu-dresden.de).

Results: *In silico* docking study demonstrated that all selected corticosteroids bound with amino acid residues of II and III domains of Mpro with binding energy in the range -7.8…-6.6 kcal/mol. The high binding affinity is found for dexamethasone-Mpro (-7.8 kcal/mol); for prednisone, prednisolone, methylprednisolone, triamcinolone, and hydrocortisone the binding energies were -7.4, -7.0, -7.5, -7.6 and -6.6 kcal/mol, respectively. It was shown that hydrogen bonds and hydrophobic interactions were involved in the formation of ligand-protein complexes mainly through residues such as Arg131, Lys137, Thr199, Asp289, Leu272, Leu286, Leu287, Tyr239, and Gly275, which formed the catalytic and distal sites for ligand binding. The inhibition constant of corticosteroids has ranged from 1.90×10^{-6} to 14.4×10^{-6} M.

Conclusion: Our results showed that the favorable binding sites for dexamethasone, prednisone, methylprednisolone, and triamcinolone are located in the catalytic site of domain II and the distal site of domain III of SARS-CoV-2 main protease Mpro with high binding affinities confirming the stability of

In cites: Khmil NV, Shestopalova AV, Kolesnikov VG, Boiechko-Nemovcha AO. Identification of potential corticosteroid binding sites on the SARS CoV-2 main protease Mpro — *in silico* docking study. Biophysical Bulletin. 2024;51:53–63. https://doi.org/10.26565/2075-3810-2024-51-04

the complexes. The low inhibition constants values for dexamethasone, prednisone, methylprednisolone, and triamcinolone further confirm the effectiveness of the selected corticosteroids as inhibitors of Mpro activity. Based on the binding energy as well as inhibition constants values dexamethasone, prednisone, methylprednisolone, and triamcinolone were identified as potential inhibitors for Mpro.
KEY WORDS: Covid-19; SARS CoV-2 main protease Mpro; systemic corticosteroids; molecular docking; human health.

Since the summer of 2023, COVID-19 infections and hospitalizations have been on the rise worldwide. While they have remained below previous peaks, the World Health Organization has reported over 1.4 million new COVID-19 cases and over 1800 deaths. The Omicron variant is responsible for the recent rise in infection cases; its several subvariants such as BA.2.86 (Pirola), EG.5 (Eris), FL.1.5.1 (Fornax) are spreading significantly faster than the Delta variant B.1.617.2 [1].

Severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2) is the etiological agent of COVID-19 that causes respiratory illness ranging in severity from the common cold to fatal pneumonia. SARS-CoV-2 is a positive-sense single-stranded genomic RNA virus (+ssRNA) that uses +ssRNA to store and replicate its genetic information [2]. The SARS-CoV-2 genome comprises about 30,000 nucleotides flanked by two untranslated regions (UTR) at the 5′- and 3′- ends. The 5′ UTR contains the 5′ cap structure as well as 3′ UTR consists of the poly(A) tail. SARS-CoV-2 RNA genome contains at least 14 open reading frames (ORFs) and encodes 29 viral proteins, among which sixteen non-structural proteins (NSPs), four structural proteins including spike glycoprotein (S), envelope protein (E), membrane protein (M), nucleocapsid (N) protein, and eight accessory proteins [3]. The +ssRNA genome expression starts with the 5′ cap end of two ORFs (ORF1a and ORF1b) which comprise about two-thirds of the genome [4]. As a result, the synthesis of two large overlapping precursor polyproteins pp1a and pp1ab (molecular weights of 486 kDa and 790 kDa, respectively), is realized on cellular ribosomes. Differences exist in the translation of the SARS-CoV-2 +ssRNA due to a programmed −1 ribosomal frameshifting (−1 PRF) between ORF1a and ORF1b [5]. Thereby, an overexpression of ORF1a-encoded pp1a protein relative to ORF1b-encoded pp1ab protein occurs.

Then polyproteins pp1a and pp1ab undergo the proteolytic processing into 16 NSPs by two viral proteases — a papain-like protease (PLpro) and a 3-chymotrypsin-like cysteine protease (3CLpro) also known as main protease Mpro. Among the two, the main protease Mpro is a key protease of SARS-CoV-2 involved in viral RNA replication and transcription and is important in the life cycle of COVID-19. The crystal structures revealed that Mpro is a dimer, formed by two monomers. Each monomer consists of three domains — domain I (amino acid residues 8–101) and domain II (amino acid residues 102–184) have an antiparallel β-barrel structure. Domain III (amino acid residues 201–303) contains five α-helices connected to domain II by a long loop (amino acid residues 185–200) [6, 7]. The Mpro is highly conserved in its amino acid sequence and three-dimensional structure, making it a suitable drug target, especially for small molecules that have an inhibitory effect [8]. Most inhibitors targeted the enzyme catalytic site, which has four sub-pockets (S1, S1', S2, S3) and located in a cleft between domain I (amino acid residues 10-99) and domain II (amino acid residues 102-182). Cysteine (Cys145) and histidine (His41) compose the catalytic dyad and are two key residues of the catalytic site. In addition, in stabilizing the catalytic site of the SARS-CoV-2 Mpro and in the binding of ligands are involved amino acid residues such as Ser10, Gly11, Glu14, Thr24, Asn28, Ser139, Phe140, Ser147, His163, Met165, Glu166, His172, Gln189, and Gln192. However, there are distal sites on the SARS CoV-2 Mpro for inhibitors binding through an allosteric mechanism, especially non-covalent inhibitors with high selectivity for Mpro [9, 10].

Corticosteroids have been considered the effective inhibitors of the replication of influenza A and B viruses, herpes simplex virus as well as SARS-CoV-2 by binding and inhibiting the catalytic activity of Mpro [11]. In the case of COVID-19, pathogenetic therapy is carried out in the middle and severe course of the disease with systemic corticosteroids, which suppress the cytokine storm by mitigating the SARS-CoV-2-induced systemic inflammatory response. At the same time, systemic corticosteroids inhibit SARS-CoV-2 main protease Mpro, which is a key component of viral replication. The cytokine storm has been suggested to be associated with high levels of several key pro-inflammatory cytokines, such as IL-1, IL-2, IL-6, TNF-α, IFN-γ, IP-10, GM-CSF, MCP-1, IL-10, and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXC [12, 13, 14]. However, the mechanism of corticosteroid inhibitory action against Mpro is currently unclear due to insufficient study of ligand-binding sites of the main protease Mpro.

The aim of this study is to identify the potential corticosteroid binding sites on SARS CoV-2 main protease Mpro based on the analysis of the energetic and topological characteristics of the complexes as well as to investigate the inhibitory activity of selected corticosteroids against Mpro.

MATERIALS AND METHODS

As a docking target was the SARS-CoV-2 main protease Mpro. The 3-dimensional (3D) structure of Mpro was downloaded from the Protein Data Bank (www.rcsb.org) (ID: 6LU7), which is the result of X-ray diffraction at 2.16 Å resolution. After deleting water molecules and adding missing hydrogens, the protein in PDB format was converted to PDBQT format using AutoDock Tools 1.5.7. Six well-known corticosteroids — dexamethasone (DEX), prednisone (PRED), prednisolone (PNL), methylprednisolone (Medrol), triamcinolone (TAC), and hydrocortisone (HCT) were downloaded in SDF format from an open chemistry database PubChem at the National Institutes of Health and were subjected for molecular docking studies as ligands. The ligands in SDF format were converted to PDB format using the Open Babel 3.1.1 computer program. The structures of corticosteroids were optimized using the Open Babel 3.1.1. The Gasteiger-Marsili partial charges were computed using the UFF force field [15]. Protonation of amino acid residues at pH=7 was checked using Propka 3.1 [16]. First, the blind docking with the grid box dimensions set of 126 Å x 126 Å x 126 Å was performed. The center grid box had fixed coordinates x = -25.995, y = 12.591, and z = 59.151. The exhaustiveness parameter was 50; the distance between the grid points was 0.503 Å. Following this, sequential docking was performed to explore whether any allosteric mechanism of inhibition of the main protease among the considered ligands. AutoDock Vina (version 1.1.2) was used to calculate the predicted docking poses and binding energies [17]. For the identification of non-covalent interactions between Mpro and ligands, the protein-ligand interaction profiler (PLIP) and the LigPlot+ web tool were applied (https://plip-tool.biotec.tu-dresden.de) [18]. DoGSiteScorer from Proteins Plus was used to detect some characteristics of potential binding pockets such as the surface area, volume, and depth of binding pocket [19]. Visualization of docking results was done in PyMol 2.5 [20]. To convert PyMol files to PDB format, the interactive converter MichelaNGLo was used (https://michelanglo.sgc.ox.ac.uk/pymol).

RESULTS AND DISCUSSION

The molecular docking methods are being used to predict energetically favorable conformations and the orientations of ligands within the binding site of the protein as well as to assess the binding affinity at the molecular level. The AutoDock Vina program searches the topological space of the ligand relative to the receptor until a scoring function is minimized.

The result is an affinity score. Then an affinity score is used to rank ligand poses; the top-ranked conformation is selected as the predicted ligand-protein complex. In our recent work, we have demonstrated the efficiency and accuracy of the AutoDock Vina tool to determine the binding energies and amino acid residues involved in the interaction of penicillin G determinants with human serum albumin [21].

In this study, corticosteroids — DEX, PRED, PNL, Medrol, TAC, and HCT were subjected to docking studies. Autodock results demonstrated that DEX, PRED, PNL, Medrol, TAC, and HCT can dock SARS-CoV-2 main protease Mpro by AutoDock Vina scores of -7.8, -7.4, -7.0, -7.5, -7.6, -6.6 kcal/mol, respectively (Tabl. 1). The inhibition constant (k_i) was calculated to evaluate the inhibition potency of systemic corticosteroids toward Mpro using Van't Hoff equation:

$$k_i = \exp(\frac{\Delta G}{RT})$$

where ΔG is the binding energy in kcal/mol; R is the universal gas constant (1.987 cal·K^{-1}·mol^{-1}); T is the temperature (298 K).

It has been shown that the inhibition constants of six corticosteroids ranged from 1.9×10^{-6} to 14.4×10^{-6} M (Table 1).

The highest affinity was reported for DEX-Mpro with AutoDock Vina score of -7.8 kcal/mol and interacting amino acids of Arg131, Lys137, Thr199, and Asp289 through hydrogen bonds and Leu272, Leu286, Leu287, Tyr239, and Gly275 through hydrophobic interactions. For DEX is predicted to sit in the domains II and III of Mpro (Fig. 1). Therefore, DEX showed favorable interactions with several residues of the catalytic pocket of domain II and several residues of the distal site of domain III.

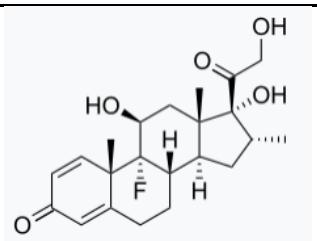
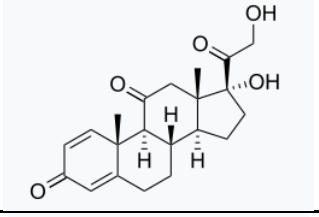
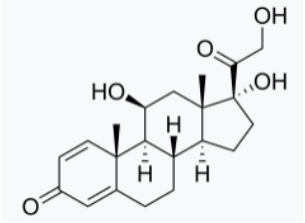
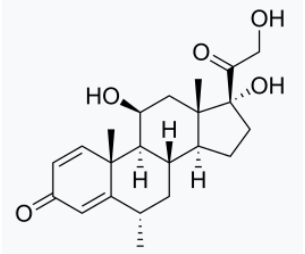
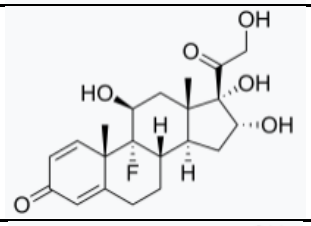
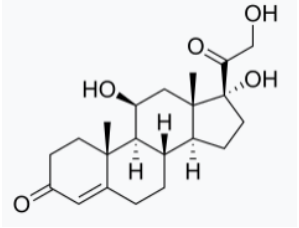
Recently Ghosh R. and colleagues have reported that dexamethasone exhibits a high binding affinity of -7.9 kcal/mol toward Mpro; k_i value at 298 K was 1.6×10^{-6} M [22]. Therefore, it can be considered as a high-quality drug to reduce the mortality rate of COVID-19 patients [23]. According to our calculations, the inhibition constant for DEX was 1.9×10^{-6} M. It was evidenced that DEX efficiently interacted with different amino acid residues of domain I as well as domain II of Mpro. Ghosh R. et al. [22] showed that DEX formed hydrogen bonds with His163, His164, and Cys145 of domain II of Mpro. In contrast to R. Ghosh's findings, our results suggested that DEX was docked to the distal active site of Mpro with high binding energy (-7.8 kcal/mol). Our results align with the general trend identified in [22], although with some notable distinctions that are primarily connected to the different preparation and optimization of corticosteroids. While there are similarities between our results and those of R. Ghosh, concerning the binding energy, it's important to note that high binding energy can indicate the importance of the involvement of the distal domain in dexamethasone binding to inhibit Mpro through an allosteric regulation.

From our molecular docking simulation, Medrol also demonstrated strong interactions with Mpro. The binding energy of Medrol was found to be -7.5 kcal/mol, which was lower compared to Ghosh R. et al. data which ranged from -5.1 to -5.5 kcal/mol [22]. The Medrol formed hydrogen bonds and had hydrophobic interaction with the identical residues of the catalytic pocket of domain II and the distal site of domain III of Mpro as DEX. In addition, in the case of Medrol, the carbonyl oxygen of Leu287 was involved in the interaction through the hydrogen bond.

In general, the binding energies of different amino acid residues that bind the same ligand can vary due to specific interactions and contributions of each residue in the binding site. However, if the binding energies are observed to be relatively similar for different residues binding the same ligand, it might be attributed to the following factors.

- *Conservation of binding motifs*: proteins often exhibit conservation in their binding sites or motifs. If different amino acid residues are part of a conserved motif that interacts with a specific ligand, the overall binding energy may be similar because the essential interactions are maintained.

Table 1. List of the potential inhibitors against the main protease SARS-CoV-2 Mpro with their binding energy and inhibition constant

Corticosteroids interacting with Mpro	2D corticosteroid structure	Binding energy, ΔG, kcal/mol	Inhibition constant, $k_i \times 10^{-6}$, M
Dexamethasone		-7.8	1.90
Prednisone		-7.4	3.74
Prednisolone		-7.0	7.35
Methylprednisolone		-7.5	3.16
Triamcinolone		-7.6	2.66
Hydrocortisone		-6.6	14.4

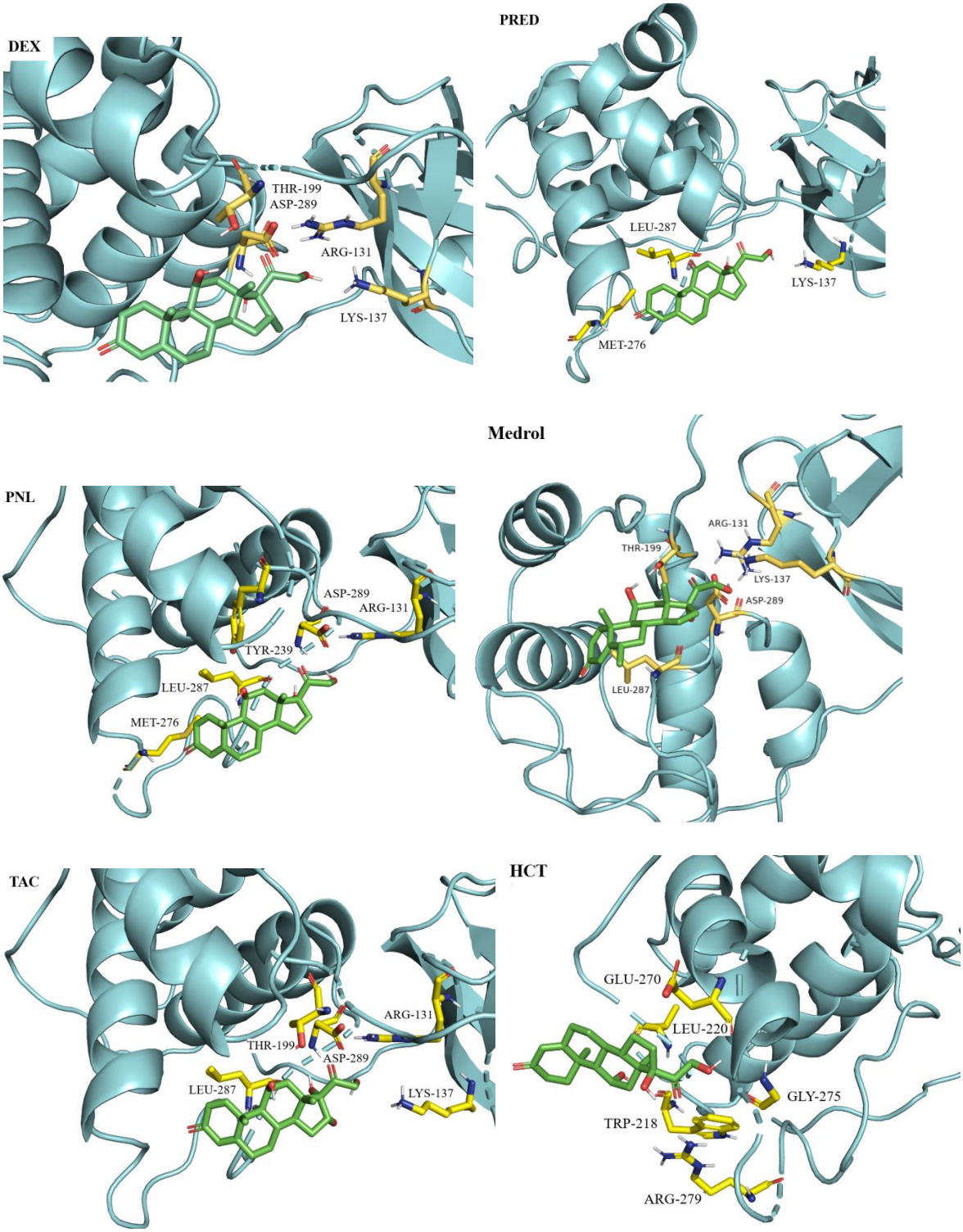


Fig. 1. The predicted docking poses of different corticosteroids in cyan cartoons rendering (coloring by element, all C atoms of ligands are in green, red — O, gray — H, dark gray — F). Cyan ribbons represent SARS-CoV-2 main protease Mpro; yellow-orange sticks are interacting amino acid residues (coloring by element, all C atoms of Mpro are in yellow-orange, red — O, blue — N, gray — H). The amino acid residues of Mpro forming hydrogen bonds with the ligand are colored in yellow-orange.

- *Structural constraints*: the three-dimensional structure of the binding site can impose constraints on the types of interactions that can occur. If the ligand interacts with a protein's specific region, the available amino acid side chains in this region may be limited, leading to similar binding energies.

- *Functional requirements*: different amino acids can have similar physicochemical properties. If the binding site requires specific characteristics, such as a particular charge or hydrophobicity, different residues with similar properties may contribute similarly to the binding energy.

- *Adaptability of proteins:* proteins can exhibit a degree of adaptability in their structures. This adaptability allows different amino acids to fulfill similar roles in terms of ligand binding, resulting in comparable binding energies.

- *Compensatory changes*: even if individual amino acid residues change in the binding site, compensatory changes in neighboring residues may occur to maintain overall binding energy. This compensation can lead to similar net effects on ligand binding. It's important to note that while the binding energies may be similar, the specific contributions and details of the interactions can still differ among different amino acids. Additionally, experimental techniques, such as site-directed mutagenesis combined with biophysical methods, are often used to study and quantify the contributions of individual residues to binding affinity.

Among all ligands, TAC showed a sufficient binding affinity energy of -7.6 kcal/mol and an inhibition constant of $k_i = 2.66 \times 10^{-6}$ M. These data are consistent with the findings about the binding affinity and stability reported by Mishra A. et al. [24]. The high affinity of TAC with Mpro is associated with the presence of hydrogen bonds with Arg131, Lys137, Thr199, Leu287, and Asp289. There are also hydrophobic interactions with Tyr239, Leu272, and Leu286, which are responsible for the conformational stability of TAC-Mpro complex.

The prednisone interacts with the Mpro with a binding energy of -7.4 kcal/mol and an inhibition constant of 3.74×10^{-6} M. In the case of PRED, the molecular binding stabilized through hydrogen bonds with Lys137, Met276, and Leu287 as well as hydrophobic interactions through four residues such as Leu286, Tyr239, Leu271, Gly275. The prednisolone interacts with SARS-CoV-2 Mpro with a binding energy of -7.0 kcal/mol and an inhibition constant of 7.35×10^{-6} M. The molecular interaction is facilitated through hydrogen bonds with Arg131, Tyr239, Met276, Asp289, Leu287, and hydrophobic interactions through residues (Gly286, Leu286, and Thr199).

Mpro showed the least binding affinity with HCT at -6.6 kcal/mol. For HCT is predicted to sit in the domain III of Mpro; there is a hydrogen bond with Trp218, Glu270, Gly275, Leu220 and Arg279. Tiwari G. et al. [25] performed screening of several anti-inflammatory drugs, including hydrocortisone and dexamethasone as the SARS-CoV-2 inhibitors, and reported higher binding energy compared to our study. At the same time, Fadaka A. O. et al. [26] reported that three amino acid residues (Asn142, Glu166, and Cys44) in the Mpro active site were involved in the formation of hydrogen bonds with DEX atoms with a binding energy of -6.7 kcal/mol.

Our study offers additional insights beyond the scope of publication [22] work by estimating the surface area, volume, and depth of the ligand binding pockets that have high binding affinity, such as dexamethasone, prednisone, methylprednisolone, and triamcinolone (Fig. 2).

In general, the difference in binding pocket surface area, volume, and depth is due to several factors. The first is steric hindrance, as even minor structural differences can lead to variations in how the ligand fits into the binding pocket. Differences in the arrangement of functional groups can result in steric hindrance, where certain parts of one ligand may come into contact with residues lining the pocket, influencing its effective surface area and volume.

Second, ligands with similar structures may interact differently with residues within the binding pocket due to hydrogen bonding or hydrophobic interactions. These differences can lead to alterations in the conformation of the ligand or the surrounding protein residues, affecting the overall shape and size of the binding pocket. In addition, ligands may exhibit inherent flexibility, allowing them to adopt different conformations upon binding to the protein. Small structural differences can influence the preferred conformation of the ligand within the binding pocket, leading to variations in the surface area and volume occupied by the ligand-protein complex.

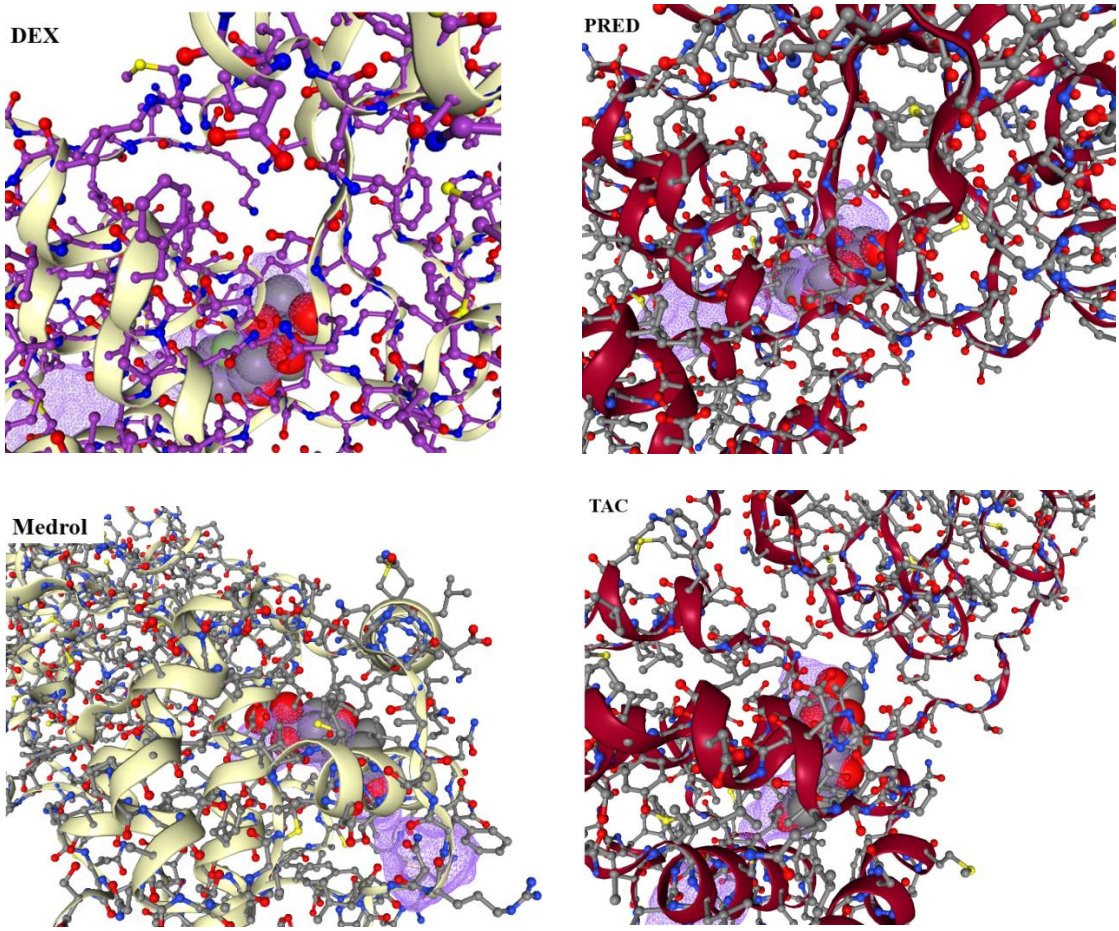


Fig. 2. The Mpro-ligand complexes. The ligand binding pocket of Mpro is marked in pale purple. The structure of Mpro is represented by ribbons; the ligand is represented as balls. The Mpro-dexamethasone ligand binding pocket has a depth of 20.59 Å, the surface area and volume of the binding site are 595.23 $Å^2$ and 416.19 $Å^3$, respectively. The Mpro-prednisone ligand binding pocket has a depth of 19.86 Å, the surface area and volume of the binding site are 582.67 $Å^2$ and 425.15 $Å^3$, respectively. The Mpro-methylprednisolone ligand binding pocket has a depth of 19.45 Å, the surface area and volume of the binding site are 578.47 $Å^2$ and 439.25 $Å^3$, respectively. The Mpro-triamcinolone ligand binding pocket has a depth of 20.45 Å, the surface area and volume of the binding site are 586.77 $Å^2$ and 420.34 $Å^3$, respectively.

Our results show the significance of distal sites in the ligand–Mpro affinity, especially domain III, through an allosteric mechanism. Domain II (Asp153-Asp155 and Leu167-Val171) and III (Asn277-Thr292) exhibit high flexibility and elasticity compared to the stable catalytic residues, His41 (from domain I) and Cys145 (from domain II) as was found by Weng Y.L. et al. [27]. We showed that the amino acid residue such as Thr199 is included in the Phe185-Thr201 linker loop (domain II-III) and can also cover the catalytic site in Mpro beside the Cys44-Pro52 loop. Dexamethasone, prednisone, methylprednisolone, and

triamcinolone were more stable due to the favorable packing and hydrophobic interaction with Thy239, Leu272, and Leu286. Hydrocortisone was quite stable in domain III with a well-packed hydrophobic structure formed by Phe223, Phe219, Val227, and Gly275.

CONCLUSIONS

In this study, the potential binding sites of systemic corticosteroids on SARS CoV-2 main protease Mpro were investigated. In silico docking studies were performed in the blind and sequential docking mode using the AutoDock Vina program. Screening of six systemic corticosteroids revealed that dexamethasone, prednisone, methylprednisolone, and triamcinolone had the best interaction with the Mpro among all others. Dexamethasone, prednisone, methylprednisolone, and triamcinolone showed promising results with binding affinities -7.8, -7.4, -7.5, and -7.6 kcal/mol, respectively, confirming the stability of the complexes. The low inhibition constants values for dexamethasone, prednisone, methylprednisolone, and triamcinolone confirm the effectiveness of the selected corticosteroids as inhibitors of Mpro activity. Considering the findings in [22], our research provides further evidence that the favorable binding sites for dexamethasone, prednisone, methylprednisolone, and triamcinolone may be located in the catalytic site of domain II and especially in the distal site of domain III of the SARS-CoV-2 main protease Mpro. The results of our study complement R. Ghosh's conclusions that dexamethasone, prednisone, methylprednisolone, and triamcinolone are promising inhibitors of the main protease Mpro and can be potential candidates for the treatment of COVID-19 or drug development against SARS-CoV-2.

ACKNOWLEDGEMENTS

The authors are thankful to Miroshnichenko E. V. for useful consultation and practical advice.

CONFLICT OF INTEREST

The authors report that there is no conflict of interest.

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ВИЗНАЧЕННЯ ПОТЕНЦІЙНИХ МІСЦЬ ЗВ'ЯЗУВАННЯ КОРТИКОСТЕРОЇДІВ НА ОСНОВНІЙ ПРОТЕАЗІ SARS COV-2 MPRO — *IN SILICO* ДОКІНГ ДОСЛІДЖЕННЯ

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Надійшла до редакції 14 грудня 2023 р. Переглянута 19 лютого 2024 р.
Прийнята до друку 1 травня 2024 р.

Актуальність. Наразі в Україні та світі фіксується зростання кількості нових випадків Covid-19, спричинених вірусом тяжкого гострого респіраторного синдрому (SARS-CoV-2). SARS-CoV-2 провокує загострення хронічних захворювань та активізує запальні й алергічні реакції. Важкий перебіг Covid-19 збільшує тривалість госпіталізації та смертність серед населення. Патогенетичну терапію проводять системними кортикостероїдами, які пригнічують цитокіновий шторм шляхом пом'якшення системної запальної відповіді, спричиненої SARS-CoV-2, а також пригнічують основну протеазу Mpro SARS-CoV-2, яка є ключовим компонентом реплікації вірусу.
Мета роботи. Метою цього дослідження є визначення потенційних сайтів зв'язування кортикостероїдів на головній протеазі SARS CoV-2 Mpro на основі аналізу енергетичних і топологічних характеристик комплексів, а також дослідження інгібіторної активності вибраних кортикостероїдів проти Mpro.
Матеріали та методи. Кристалічна структура Mpro (ID: 6LU7 з Protein Data Bank) (www.rcsb.org) була обрана в якості док-мішені. Методи молекулярного докінгу (AutoDock Tools 1.5.7, AutoDock Vina 1.1.2) були застосовані для отримання інформації про спорідненість зв'язування Mpro з системними кортикостероїдами, такими як дексаметазон, преднізон, преднізолон, метилпреднізолон, тріамцинолон і гідрокортизон. Візуалізація результатів докінгу була реалізована в PyMol 2.5. Для визначення нековалентних взаємодій між Mpro та лігандами були застосовані веб-засоби PLIP та LigPlot+ (https://plip-tool.biotec.tu-dresden.de).
Результати. Результати моделювання методом молекулярного докінгу (*in silico*) показали, що вибрані кортикостероїди зв'язувалися з амінокислотними залишками II і III доменів Mpro з енергією зв'язування -7,8…-6,6 ккал/моль. Була виявлена висока афінність зв'язування комплексу дексаметазон-Mpro (-7,8 ккал/моль); для преднізону, преднізолону, метилпреднізолону, тріамцинолону й гідрокортизону енергії зв'язку становили -7,4, -7,0, -7,5, -7,6 і -6,6 ккал/моль, відповідно. Було показано, що водневі зв'язки та гідрофобні взаємодії головним чином беруть участь в утворенні ліганд-білкових комплексів через такі залишки, як Arg131, Lys137, Thr199, Asp289, Leu272, Leu286, Leu287, Tyr239 і Gly275, які утворюють каталітичні та дистальні сайти для зв'язування ліганду. Константа інгібування кортикостероїдів коливалася в межах від $1{,}90 \times 10^{-6}$ до $14{,}4 \times 10^{-6}$ М.
Висновки. Результати дослідження показали, що сприятливі сайти зв'язування для дексаметазону, преднізону, метилпреднізолону та тріамцинолону розташовані в каталітичному сайті домену II та дистальному сайті домену III основної протеази SARS-CoV-2 Mpro; вони мають високу спорідненість зв'язування, що підтверджує стабільність комплексів. Низькі значення констант інгібування для дексаметазону, преднізону, метилпреднізолону та тріамцинолону додатково підтверджують ефективність вибраних кортикостероїдів як інгібіторів активності Mpro. На основі енергій зв'язування, а також значень констант інгібування, дексаметазон, преднізон, метилпреднізолон і тріамцинолон були визначені як потенційні інгібітори Mpro.
КЛЮЧОВІ СЛОВА: Covid-19; головна протеаза SARS CoV-2 Mpro; системні кортикостероїди; молекулярний докінг; здоров'я людини.