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In silico tuning of binding selectivity for new SARS-CoV-2 main protease inhibitors

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ABSTRACT

Rapid identification of effective SARS-CoV-2 inhibitors is essential for managing the ongoing pandemic and preparing for future outbreaks. This study aims to develop an efficient computational framework to accelerate pre-screening and optimization of inhibitors through functional group modifications of FDA-approved drugs, Adrafinil and Baicalein, targeting the SARS-CoV-2 main protease (MPro). We introduce MDBinding, a computational drug optimization program designed to enhance the inhibitor screening process by integrating molecular dynamics (MD) simulations. MDBinding systematically identifies inhibitors with improved binding affinities to MPro through functional group modifications, refining lead compound design. Combined with the previously developed PerQMConf module, MDBinding provides a robust in silico framework for rapid drug discovery. This approach significantly reduces the time and cost of inhibitor development while identifying promising candidates for experimental validation. The findings highlight the potential of MDBinding to accelerate antiviral drug discovery and improve the efficiency of computational drug design.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of the COVID-19 pandemic, remains a significant global health challenge [1,2]. Despite the passage of nearly five years since the virus first emerged, new variants of the virus persist, posing ongoing risks. For instance, the Australian Government Department of Health and Aged Care (DHAC) reported over COVID-19 over 275,000 cases since the first confirmed case of COVID-19 was reported in Australia on 25 January 2020 [3,4]. Although the end of the emergency response was declared on 20 October 2023, COVID-19 remains an important issue, with a large wave occurring at the end of 2023 and into 2024 [3]. Fig. 1 reports the waves of outbreaks of COVID-19 impact on residential aged care homes in Australian from January 2022 to December 2024 based on the data from the Australian Government DHAC [3]. While vaccines have been effective in reducing severe disease, the ongoing emergence of variants and limitations of current antiviral therapies, such as remdesivir and molnupiravir, highlight the continued need for effective antiviral treatments [5,6].

Among the 29 proteins encoded by the SARS-CoV-2 genome, the main protease (Mpro) plays a critical role in viral replication, making it a prime target for drug development [7,8]. Its structural conservation across coronaviruses, combined with its distinct nature compared to human proteases, to make Mpro an ideal candidate for selective inhibition. However, challenges remain in developing effective Mpro inhibitors, such as weak inhibitory activity, suboptimal pharmacokinetics, and toxicity concerns [5,6].

Recent advances in computational techniques, including molecular docking, molecular dynamics (MD) simulations, and density functional theory (DFT) calculations, provide powerful tools for designing and optimizing novel inhibitors [9,10]. These in silico techniques not only streamline the pre-screening of drug candidates, reducing both costs and environmental impact, but also offer valuable into drug-target interactions, aiding in the design of more efficient and selective inhibitors. Notably, they provide detailed insights into drug-target interactions, enhancing our understanding of quantitative structure-activity relationships (QSAR) and facilitating rational drug design [5].

2. Objectives

The primary goal of this study is to develop a rapid computational drug improver program, MDBinding, that enhances the pre-screening and optimization of SARS-CoV-2 inhibitors. MDBinding uses molecular

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Glossary

COVID-19	coronavirus disease 2019
DFT	density function theory
FDA	food and drug administration
MD	molecular dynamics
MM/PBSA	molecular mechanics/Poisson–Boltzmann surface area model
MPro	main protease
QSRP	structure-activity relationship
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

dynamics (MD) simulations to identify new inhibitors with superior binding affinities for Mpro. By leveraging functional group modifications of FDA-approved drugs, such as Adrafinil and Baicalein, the study also aims to optimize lead compound design.

A secondary objective is to demonstrate how MDBinding can address existing gaps in current research, such as improving inhibitor specificity and reducing the reliance on labour-intensive *in silico* discovery process with computational intelligence. MDBinding's novel approach distinguishes itself from traditional methods by incorporating both functional group substitution and MD simulations to expedite the discovery process and optimize the pharmacological profiles of potential inhibitors. Through these advancements, this study aims to contribute to the rapid development of effective antiviral drugs for SARS-CoV-2 and similar viral threats.

2.1. Significance and innovation

Our study introduced and developed the MDBinding drug improver program, a novel and robust computational tool designed to enhance and expedite inhibitor pre-screening by integrating molecular dynamics (MD) simulations and functional group substitutions. Unlike conventional drug repurposing methods, which typically focus on testing pre-existing compounds/inhibitors with limited structural modifications, MDBinding enables a more systematic and dynamic exploration of novel derivatives, through scanning the extendable functional group database. This flexibility provides a more efficient pathway to discovering potent inhibitors against a target virus protein such as SARS-CoV-2 Mpro. Furthermore, MDBinding's unique approach allows for the optimization of existing high-performance inhibitors through systematic functional group modifications, a feature not commonly incorporated in traditional one inhibitor at a time computational drug discovery methods.

A key innovation of our study lies in the application of functional group substitutions to FDA-approved drugs, such as Adrafinil and Baicalein, to generate new potential inhibitors targeting the active sites SARS-CoV-2 Mpro [7,9,11] as a case study. These compounds were chosen due to their previously demonstrated inhibitory activity against SARS-CoV-2, with Baicalein being shown to inhibit Mpro with an IC_{50} value of 5.16 μM [12] and more recent studies reporting an improved IC_{50} of 0.94 μM [13,14]. By leveraging their known effectiveness as reference inhibitors, we can systematically modify and optimize their structures to enhance their binding affinity and therapeutic potential. The integration of the PrefQMConf program [15], which refines the conformational profiles of these identified new inhibitors using density functional theory (DFT), provides further insights into their stability and mechanism of action [16]. This robust PrefQMConf program [15] accelerates conformational landscape of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) from a four-year postgraduate project into approximately four weeks [15–17].

This study also addresses key gaps in the current computational drug discovery landscape. The MDBinding program significantly improves the efficiency of lead compound screening by offering a comprehensive in silico framework for inhibitor design. By incorporating MD simulations [10] with functional group modifications and conformational analysis, our method accelerates the identification of promising SARS-CoV-2 inhibitors and provides insights into structure-activity relationships (QSRP), paving the way for the rapid development of effective antiviral therapies. In this way, MDBinding enhances the drug discovery process by minimizing costs and reducing the time required to identify and optimize candidate drugs, a critical advantage in responding to ongoing and future viral threats.

Ultimately, this study not only contributes to the growing pool of potential COVID-19 inhibitors but also demonstrates the power of in silico methods in drug discovery. Through our innovative approach, we aim to advance antiviral drug development and provide a robust and reliable computational framework that could be applied to other viral diseases as well.

2.2. Method/program development

Adrafinil and Baicalein (Fig. 2) were selected as scaffolds in this study due to their relevance as repurposed SARS-CoV-2 Mpro inhibitors. Adrafinil, initially developed for narcolepsy and sleep disorder treatments over the past five decades [16], has potential antiviral

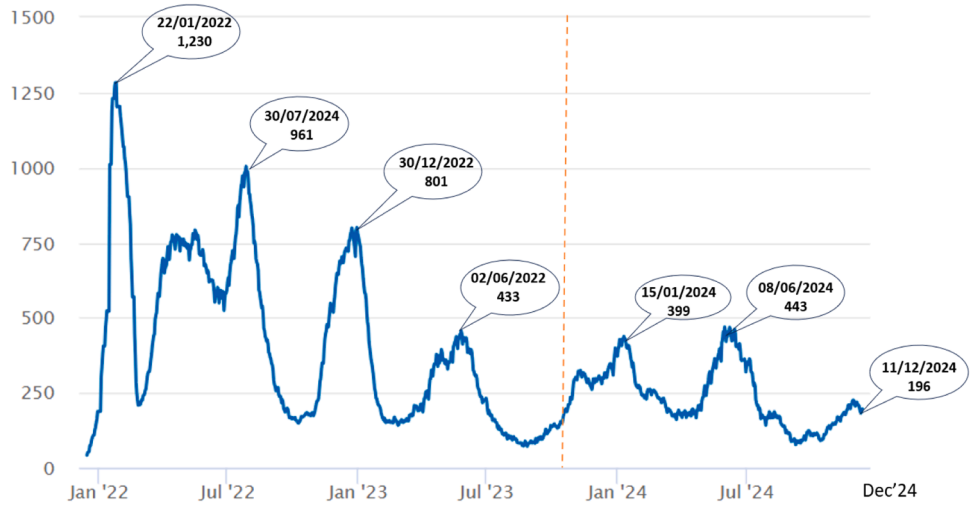
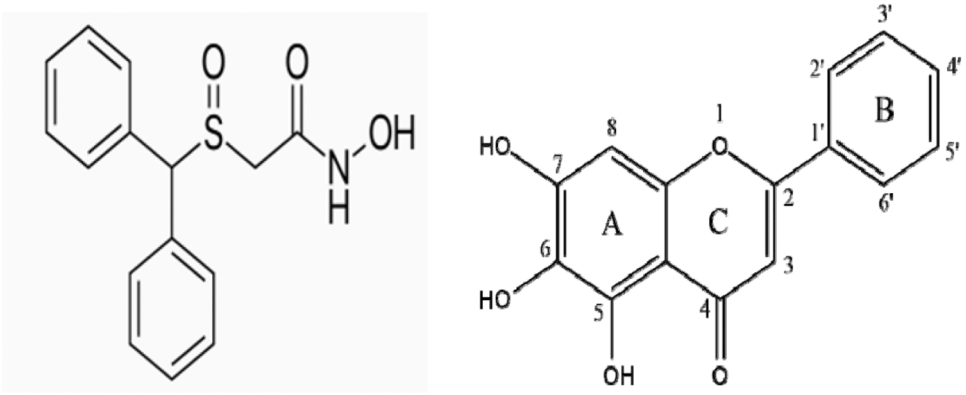


Fig. 1. Waves of outbreaks of COVID-19 impact on residential aged care homes in Australian (Jan 2022–Dec 2024) [1]. The orange vertical line is the end of the emergency response was declared by the Australian Government (DHAC).



(a) Adrafinil ($C_{15}H_{15}NO_3S$) (b) Baicalein ($C_{15}H_{10}O_5$)

Fig. 2. Chemical structures of Adrafinil (2-[(diphenylmethyl)sulfinyl]-N-hydroxy-acetamide, trade name, Olmifon) and of Baicalein (5,6,7-trihydroxy-2-phenyl-4H-1-benzopyran-4-one or 5,6,7-trihydroxyflavone, trade name, Noroxylin), respectively, as SARS-CoV-2 Mpro inhibitors.

applications when repurposed for COVID-19 [18], has shown potential for antiviral applications when repurposed for COVID-19 to bring the past to the future. Baicalein, a natural flavonoid derived from the roots of *Scutellaria baicalensis Georgi*, exhibits promising binding affinity to Mpro and residual interactions with RPS3, making it a viable candidate for COVID-19 treatment [19]. For instance, Baicalein inhibits Mpro with IC50 values ranging from 0.94 ± 0.20 μM to 5.158 ± 0.928 μM, depending on assay conditions [7,9,11–14]. These compounds serve as reference scaffolds for structural modifications, supporting the development of optimized inhibitors with enhanced efficacy.

The MDBinding program, developed in this study, serves as a drug discovery tool with a streamlined workflow, as outlined in the diagram in Fig. 3. This workflow is illustrated in five step in the section step by step.

Step 1: Selection of existing inhibitors **Step 1** involves downloading the structure of the ligand-protein complex for a known high-performance drug, inhibitor, or drug candidate. In this study, two crystal structures of SARS-CoV-2 Mpro complexes with ligands were obtained from the RCSB Protein Data Bank (https://www.rcsb.org/): SARS-CoV-2 Mpro with Adrafinil (7ANS) [6,20] and SARS-CoV-2 Mpro with Baicalein (6M2N) [21]. The structures of Adrafinil and Baicalein along with their positions in the active site of SARS-CoV-2 Mpro (7ANS) [6] and (6M2N) [14,21] are shown in Fig. 4, respectively.

Step 2: Selection of atoms on the reference scaffold During Step 2, Adrafinil and Baicalein structures are utilized as scaffolds for developing new inhibitors with improved binding affinities. Specific atoms, highlighted in pink in Fig. 5(a) for Adrafinil and Fig. 5(b) and (d) for Baicalein, are selected for substitution with functional groups from the database shown in Fig. 5(c). The MDBinding program automates this substitution process, systematically replacing the highlighted atoms with selected functional groups. The newly modified ligand structures are then built for further evaluation.

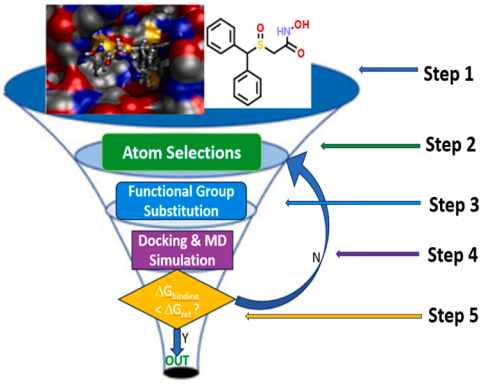


Fig. 3. The streamlined workflow of the MDBinding program developed for robust pre-screen for new inhibitors.

Up to four atoms on the scaffold can be selected for replacement. If M atoms (here $M \leq 4$) are chosen on the scaffold and the functional group database (FGD, eg Fig. 5(c)) contains N functional groups, the total number of possible new inhibitors (combinations), including repetitions, is calculated as $N_g = N^M$. This systematic substitution approach generates a diverse set of ligand variants, enabling the exploration of structural modifications and their effects on binding affinities, ultimately facilitating the identification of optimized inhibitors for further analysis. $N_g = C(M,N) = (N+M-1)!/(M!(N-1)!)$ where N_g can be a very large number for different combinations of multiple atomic site selections (M) and the size (N) of the FGD. In this study, the MDBinding program limits up to four atomic sites ($M \leq 4$) which can be substituted simultaneously. If $M = 4$ (select upto 4 atoms on the scaffold structure) and $N = 10$ (ten functional groups in the database), the total number of combinations (ie, new inhibitors) N_g is given by $N_g = C(4,10) = (10+4–1)!/(4!10–1)!) = 715$.

Step 3: Replacing the selected atoms on the reference scaffold with function groups In this study, three atoms ($M = 3$) were selected for Adrafinil, and two sets of four atoms ($M = 4$) each for Baicalein are selected as illustrated in Fig. 5(a), (b) and (d). Followed this, one needs to select the functional groups, for example, single atoms such as -H, -F, -Cl, -Br, -I, and function groups such as -CO—CH_3, Methyl-Cyano, -OH, etc. from the FGD (Fig. 5(c)), which will run through for all possible substitutions at the selected atom sites.

After the selection of atom sites and functional groups on the scaffold inhibitor, the MDBinding program begins to generate all N_g possible structures with each structure being subjected to partial optimization, i.e. only atoms of the added functional groups are optimised while other atoms of the scaffold are kept freezing at the structure of the unsubstituted inhibitor. This is done to preserve from the overall structure changes of the modified ligands. This is due to the assumption that the modified ligands will be situated in the active centre in the same manner as the scaffold (reference structure), i.e. the modified ligands are not subject to redocking calculations. It is noted that the reality may not fit such as assumption, we plan to add the option of redocking the modified ligands in the future.

Step 4.1 Docking The sequence of commands in ***Step 3*** is combined in a script designed to run for compatibility by a Unix bash-shell. The script in the MDBinding program operates in automated mode, takes the generated structures from ***Step 3*** one by one and executes the following commands:

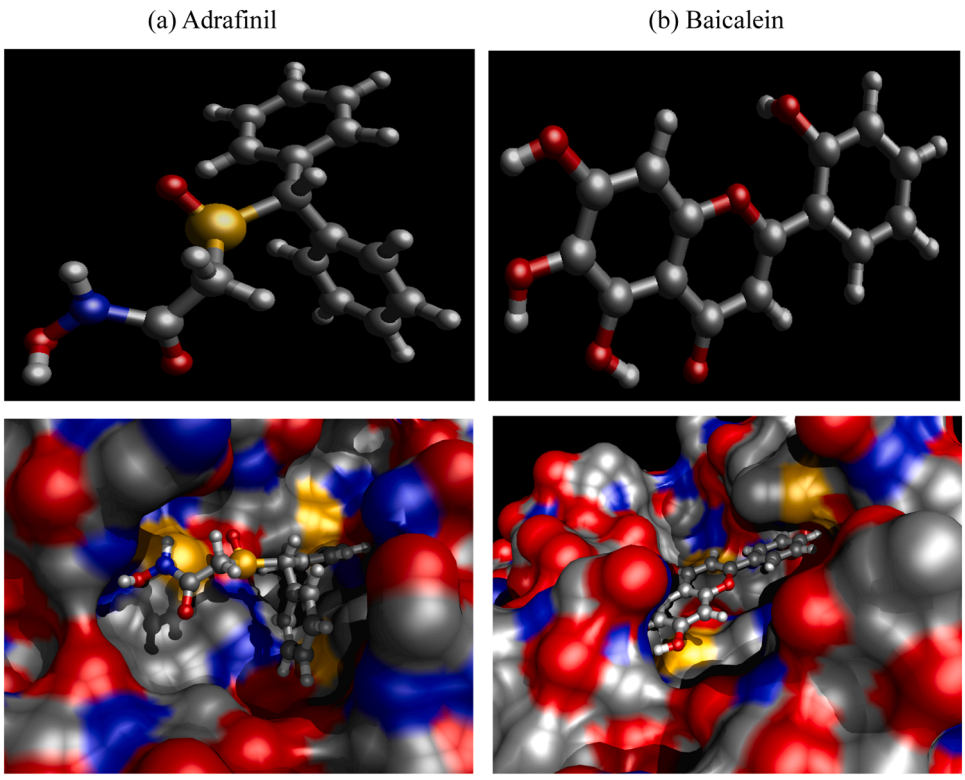


Fig. 4. (a) The structure of Adrafinil (a) and the 7ANS complex structure bound to the SARS-CoV-2 virus Mpro [2]; (b) The structure of Baicalein and the 6M2N complexed with the SARS-CoV-2 Mpro protein [3,4].

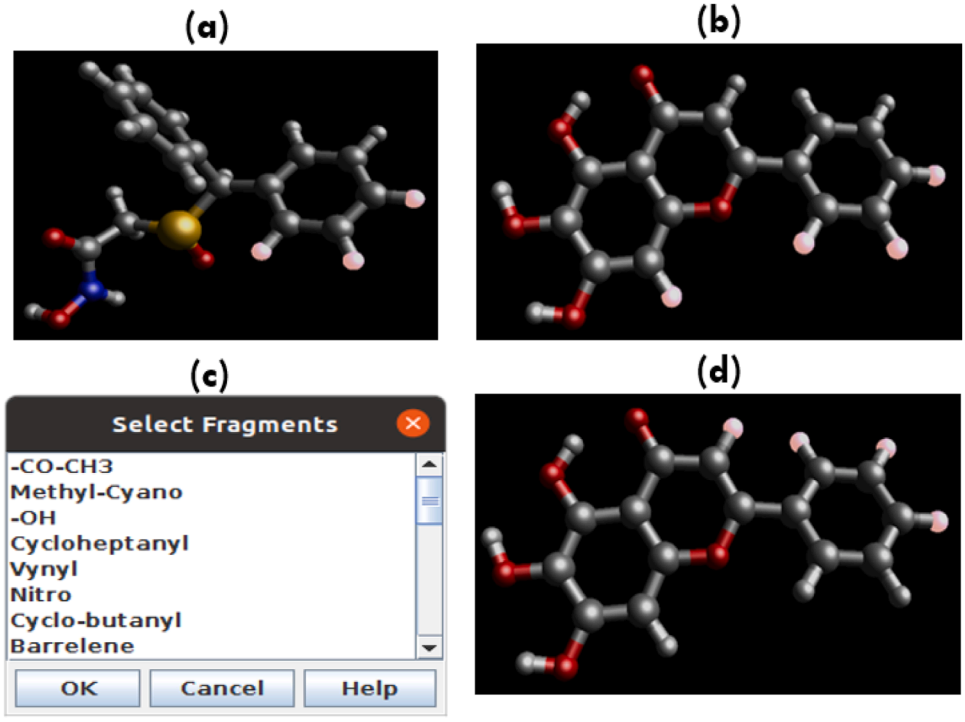


Fig. 5. The selected atom sites (highlighted) on the drug candidates (a) for Adrafinil (M = 3), (b) and (d) for Baicalein (M = 4), which are replaced with functional groups in the FGD (c) performed by the MDBinding automatically.

(1) Automatically generates GAFF2 [22] force field parameters for each modified ligand using Amber MD program [23] utilities, **antechamber, parmchk2**, and **tleap** as well as Gaussian program [24] for calculation of the partial charges;

(2) The MDBinding program substitutes an original ligand in the experimental ligand-protein complex with a modified ligand structure, solvates the system and generates Amber/GAFF2 [22, 23] parameters for a whole system using **tleap** Amber utility;

(3) Submission of a resulted inhibitor-complex system for the Amber optimization (using **sander** or **pmemd**) to remove bad steric contacts (it performs approximately 200–300 iterations, i.e. not until the full optimization convergence);
(4) If the optimization is unsuccessful, the MDBinding program will reduce a ligand **0.75** times and reoptimize the resulted system. If the second time optimization is again unsuccessful, the MDBinding will reduce the ligand **0.5** times and reoptimizes the resulted system again. If the third time the optimization is unsuccessful, the program generates an error message, discards the structure and moves to the next modified ligand;
(5) If the optimization is successful, the MDBinding program submits the resulted optimized system for further MD simulation using **pmemd**.

The ultimate task of this step (***Step 4.1***) is to produce an MD trajectory for each optimized ligand which will be used on the next step. All calculations for each ligand are performed in a separately created directory which will contain all data of the inhibitor, the input, output, and intermediate/temporary files which can be used for the future analysis and troubleshooting, if needed. This process is repeated until the last ligand (molecule) is produced and is in the queue.

Step 4.2 MD simulations of the binding free energy for each complex At this step the MD trajectories of each ligand-protein complex produced at ***Step 4.1*** are employed for the calculation of the binding free energies using the MM-PBSA [25] approach. The MDBinding program uses a Unix bash-shell to check for the completed MD simulations. If the MD simulation is already completed, it will a) extracts snapshots from the MD trajectory for the **MM-PBSA** calculation using the Amber **ante-MMPBSA.py** utility; or b) automatically creates topology files for the obtained complex, enzyme/protein, and ligand for further **MM-PBSA** calculations. Finally, it performs **MM-PBSA** calculation to obtain binding free energy ($\Delta G_{binding}$).

Step 5: Collecting and sorting the binding free energies for all complexes. At the final step, a specifically written program in MDBinding reads all the **MM-PBSA** outputs, collects all binding free energies and their components, places them into the interactive table and ranks the results according to their binding free energies. Giving the binding free energy (ΔG^0_{ref}) of the initial reference ligand, MDBinding program compares the obtained free binding energy ($\Delta G_{binding}$) of the new (modified) ligands. If the obtained free binding energy of the new ligand has a lower (more negative) binding energy $\Delta G_{binding}$ than the reference free binding energy ΔG_{ref}, the new inhibitor is considered as a good potential drug candidate, otherwise MDBinding discards the ligand and moves to the next one, as indicated in the flowchart in Fig. 3.

3. Results and case study

In the case study, the scaffold drugs are Adrafinil and Baicalein as shown in Fig. 2. Each new drug candidate was subjected to 200 steps in the optimization in the active site of enzyme followed by MD simulation calculations. In the case of Adrafinil, the MD simulation consisted of 1000,000 of 1fs steps at 298K°, with the coordinates being written to the MD trajectory file every 1000th steps, i.e. each MD trajectory consisted of 1000 MD snapshots. The first 300 MD snapshots (or 300,000 MD steps) were considered as the equilibration phase while the rest 700 snapshots were used for the estimation of binding free energy ($\Delta G_{binding}$) using the MM-PBSA approach. In the case of Baicalein, the MD simulation consisted of 300,000 of 1fs steps at 298K°, with the coordinates being written to the MD trajectory file every 1000th steps, i.e. each MD trajectory consisted of 300 MD snapshots. The first 100 MD snapshots (or 100,000 MD steps) were considered as the equilibration phase while the rest 200 snapshots were used for the estimation of binding free energy ($\Delta G_{binding}$) using the MM-PBSA approach.

For the Adrafinil (7ANS) scaffold, the MDBinding pre-screened the possible derivatives using the FGD (Fig. 5(c)). It identified several drug candidates showing better affinity to the target enzyme than the original Adrafinil, as they exhibit better (more negative) free binding energies, ΔG. Here only three such new ligands with the highest binding affinity are discussed in detail.

Three new Adrafinil (7ANS) derivatives, Ligand 458 (or Adrafinil_mA), Ligand 619 (or Adrafinil_mB) and Ligand 109 (or Adrafinil_mC) shown in Fig. 6, are among those which exhibit better binding than original Adrafinil, are selected for further discussions. These new inhibitors are produced by substitution of the three highlighted atomic sites as shown in Fig. 5(c). In the new inhibitor, Adrafinil_mA, the three highlighted atoms in the original scaffold (Fig. 5(a)) are replaced by halogens (X), two iodine atoms (I, in magenta color) and the middle one is a bromine atom (Br, in brown-red color) atom in Fig. 6(a). Ligand 619 (Adrafinil_mB) has three bromine (Br) atoms (Fig. 5(b)), while Ligand 109 (Adrafinil_mC) has no halogen atoms but a methyl (-CH_3) in the middle and two nitro (-NO_2) groups on the sides (Fig. 5(c)).

Halogens (X) play a very important role in drug development due to their unique electronic properties, which enhances binding interactions with target proteins [2,26–29]. The ability of halogens to form strong halogen bonds and their impact on hydrophobic interactions make them valuable in optimising drug potency and stability. The new inhibitors, Adrafinil_mA and Adrafinil_mB, can be potential better inhibitors for SARS-CoV-2 Mpro [2,26,29], as they exhibit more negative bonding free energies. This is supported by other studies, which have demonstrated that halogen substitution can significantly improve the efficacy of drug candidates, making halogens an essential consideration in our design strategy for effective COVID-19 therapies [27,29]. Certainly, they are merely pre-screen of new inhibitors, they need further experimental tests.

The FDA-approved ligand Adrafinil is not necessarily the top-ranked inhibitor. Interestingly, the nonmutated Adrafinil inhibitor (7ANS) ranks 627th based on free binding energy ($\Delta G_{ref} = -14.63$ kcal/mol), as calculated in this study. This aligns with previous MD with approximation of continuum solvent (ESMACS) simulation results of -13.20 ± 0.44 kcal/mol and -13.57 ± 0.44 kcal/mol [18,30]. Fig. 7 highlights the top 20 potent Adrafinil-derived candidates (out of a total of 903 ligands) with significantly lower binding energies ($\Delta G_{binding} = -24.0$ kcal/mol) compared to Adrafinil (blue colores). While promising, considerations like availability and toxicity remain crucial for drug development.

Details of the Adrafinil derivative inhibitors are given in Table S1 of the supplementary materials (SM). All the structures given in Fig. 7 report significantly lower (more negative) in free binding energy than the reference Adrafinil (7ANS) inhibitor ($\Delta G_{ref} = -14.63$ kcal/mol). These selected new inhibitors all exhibit significantly lower free binding energy than all the subset of 14 inhibitors (all above −23 kcal/mol) selected from the 37 compounds identified from drug libraries all of which bind to the SARS-CoV-2 main protease (Mpro) [30]. Noted that Wan et al. used ESMACS simulation [18,30]. However, properties other than free binding energy and issues must be considered in the drug development, such as availability and toxicity. The large binding free energy of the new ligand and protein complexes remains an important indicator in drug design.

The next case study of applying the MDBinding program developed in this study is from a flavone derivative Baicalein (6M2N). There are two sets of four mutations (atoms) on the Baicalein scaffold can be selected, which are indicated in the highlighted atoms in Fig. 8. As seen in the structures below, the manner of selecting of the group of four atoms will lead to a variety of different derivative ligands, and Fig. 8 reports two of such varieties.

The selection of atomic sites for mutation is not unique which will lead N_{total} sets of classes of derivative ligands. Each of the selected set, Baicalein-A and Baicalein-B, on Baicalein produces better binding inhibitors than the original scaffold. We discuss the top two ranked new inhibitors obtained from Fig. 8. The top couple of inhibitors from Baicalein-A are Ligand 0064 and Ligand 1684 as shown in Fig. 9(a) and

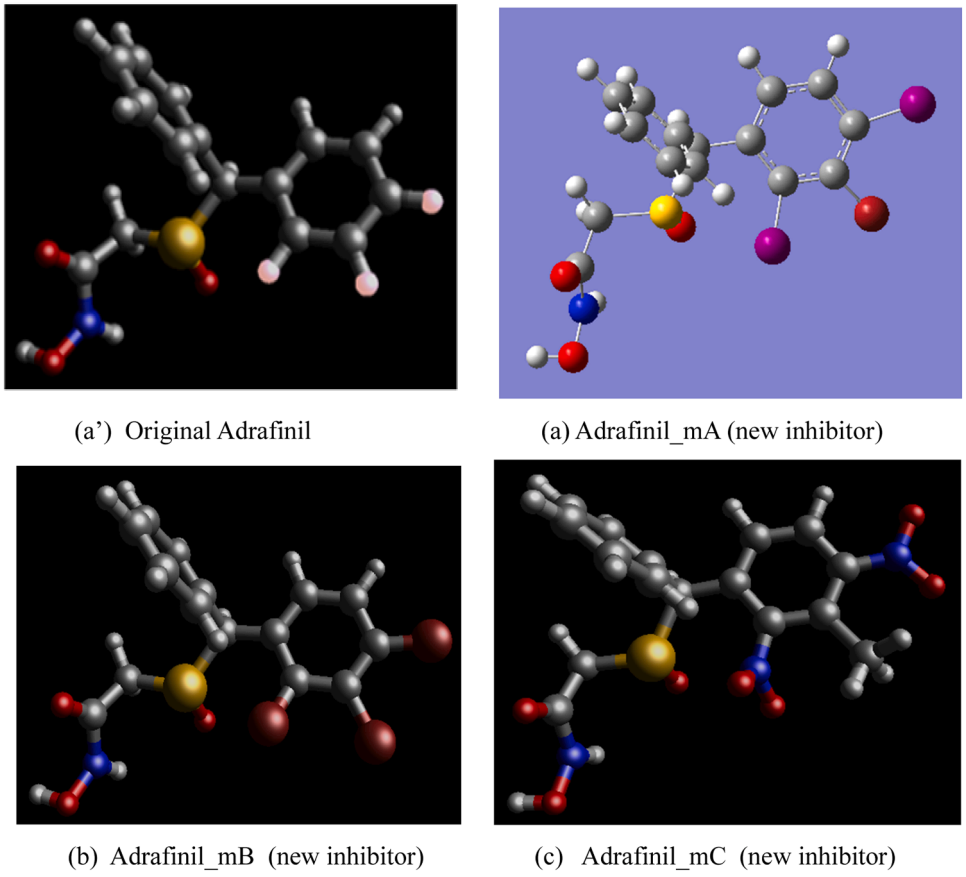


Fig. 6. The new inhibitors (a)–(c) produced from the modifications of the original Adrafinil (7ANS) (a'). Where Adrafinil_mA and Adrafinil_mB contain halogens but Adrafinil_mC contains other FGs.

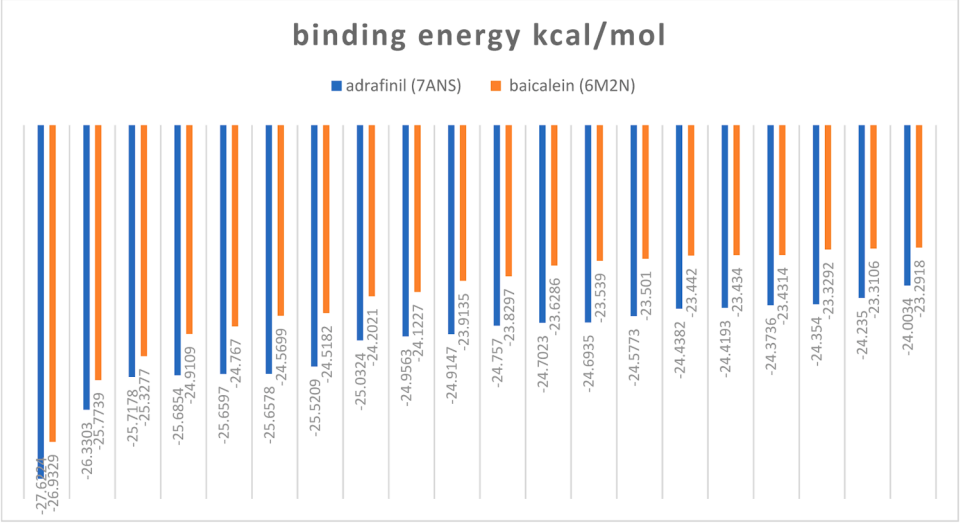


Fig. 7. Free binding energies of the 20 most potent drug candidates (out of a total of 903 ligands) derived from Adrafinil (7ANS) scaffold (blue) and the top 20 most potent drug candidates (out of a total of 3273 ligands) derived flavone derivative Baicalein (6M2N) scaffold (orange). All the new candidates exhibit better free binding energies than their reference ligand scaffolds.

(b), respectively, from a total of 3273 ligand conformers for the structures, Baicalein-A_a and Baicalein-A_b. In Baicalein-A_a (Ligand 0064), the hydrogen atom on $C_{2'}$ position of the phenyl ring (see Fig. 1) was replaced by an hydroxyl group (-OH) as shown in Baicalein-A_a of Fig. 9. The second best inhibitor is Baicalein-A_b, which has four substitutions relative to the original Baicalein-A, including two Br atoms on $C_{2'}$ and $C_{3'}$ respectively and a methyl (-CH_3) on $C_{4'}$ and -CHO group on carbon C_8 position in flavone (Baicalein-A_b) in Fig. 9.

Similarly, it is noted that the original ligand Baicalein compound (6M2N) is ranked at 3032th place. The top new ligand **Baicalein-A_a** ($\Delta G_{binding} = -26.93$ kcal/mol) is obtained by adding an -OH group. The second-best binding ligand **Baicalein-A_b** ($\Delta G_{binding} = -25.77$ kcal/

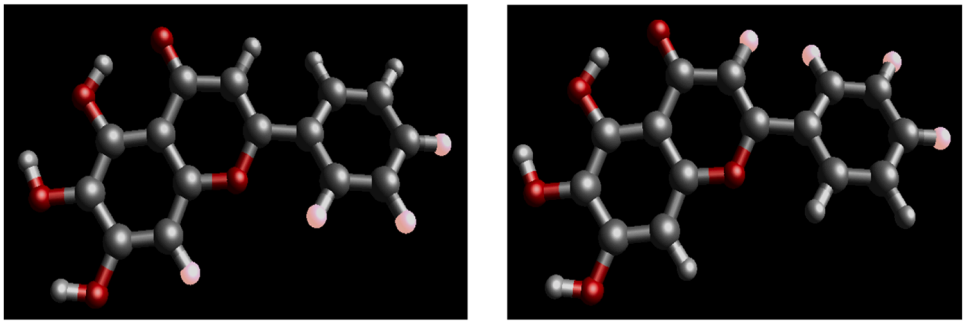


Fig. 8. Two sets of selected mutations on the structure of Baicalein. Among the four atoms selected, three are in the phenyl ring and the last ones are the hydrogens next to the ether oxygen atom on the flavone skeleton.

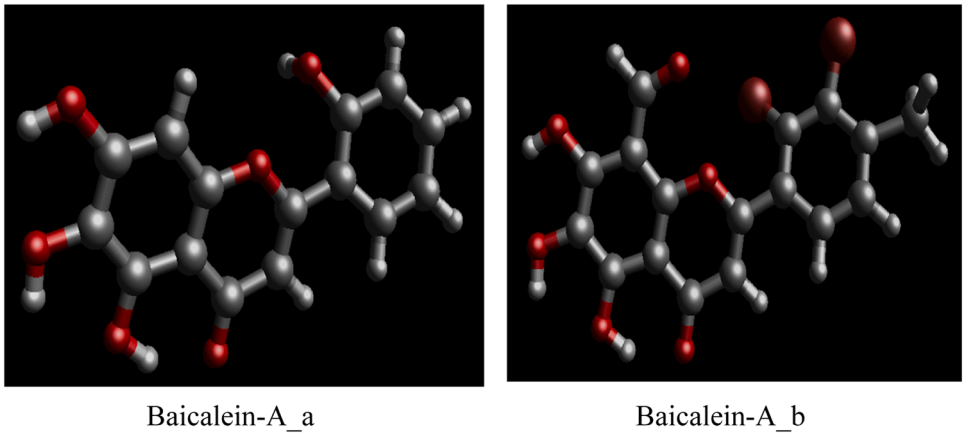


Fig. 9. New potential inhibitors obtained using MDBinding based on Baicalein-A (6M2N).

mol). The free binding energy depends on the force fields employed. For example, Hengphasatporn et al. obtained the free binding energy of Baicalein (6M2 N) at approximately −18 kcal/mol, −19 kcal/mol, −28 kcal/mol and −32 kcal/mol using various force fields such as MM-GBSA; MM/PBSA, PM6/MM-GBSA and PM3/MM-GBSA, respectively [7,27]. Similarly, the second set of Baicalein-B can also produce new potential inhibitors based on different set of atoms.

It is important to note that the present MM/PBSA method yields more reliable free binding energy estimates than many docking programs like Glide, DOCK, AutoDock, AutoDock Vina, FRED, and EnzyDock, which are primarily designed to reproduce correct ligand binding modes. While MM/PBSA is superior for ranking binding modes and predicting free binding energies, it is, however, more time-consuming.

4. Conclusions

This study highlights the robust capabilities of the MDBinding program in streamlining the lead optimization process for pre-screening new SARS-CoV-2 Mpro inhibitors. By automatically replacing selected atoms with functional groups from a built-in database and conducting docking and MD simulations, the program efficiently identifies new derivatives with improved binding affinities. Initial results show that scaffold modifications, such as those based on Adrafinil and Baicalein, can significantly enhance ligand binding free energies. The use of the MM/PBSA method further strengthens the accuracy of binding energy predictions, surpassing conventional docking programs, albeit with a greater computational cost. Additionally, the reduced human intervention during the process underscores the program's robustness and efficiency. MDBinding's versatility extends beyond antiviral drug design, making it a valuable tool for other drug classes, such as anticancer agents, and solidifying its broader impact in the field of medicinal chemistry.

Although different research groups have tried to investigate that Baicalein may act as ananti-SARS-CoV-2drugthroughinvitro analysis, its safety and efficacy in SARS-CoV-2-infected transgenic animals have not been studied yet [13,31,32]. However, Song et al. (2021) investigated the therapeutic effect of baicalein against SARS-CoV-2 both *in vivo* and *in vitro* (Song et al., 2021). Further experimental studies are recommended to prove that baicalein may act as an effective anti-COVID-19 molecule.

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Data availability statement

Data are contained within the article and Supplementary Materials.

Conflicts of interest

The authors declare no conflicts of interest in this research.

Ethics statement

Not applicable.

Declaration of interests

The authors to confirm at submission if their research needs an Ethics statement. Such statement will confirm that all procedures were performed in compliance with relevant laws and institutional guidelines and have been approved by the appropriate institutional committee(s). This statement should contain the date and reference number of the ethical approval(s) obtained. Authors should also include in the Ethics statement that informed consent was obtained for experimentation with human subjects. The privacy rights of human subjects must always be observed. In case their research does not need an Ethics statement they must state why.

The authors declare the research to be published in the manuscript entitled "Computer Methods and Programs in Biomedicine In Silico Tuning of Binding Selectivity for New SARS-CoV-2 Main Protease Inhibitors" co-authored by Feng Wang and Vladislav Vasilyev, with the manuscript ID CMPB-D-24–04427 does not contain any experimentation with human subjects, as the article is about a computer program to accelerate drug discovery process. As a result, an Ethics statement is not relevant to the research.

CRediT authorship contribution statement

Feng Wang: Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Vladislav Vasilyev:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Feng Wang reports a relationship with Swinburne University of Technology that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cmpb.2025.108678.

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