RESEARCH PAPER

Design, Synthesis and Bio Evaluation of Novel 2-Chloropyrimidin-4-Yl-2,3-Dimethylindazol-6-Amine Derivatives as Anti-Covid and Anti-HIV Agent

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ABSTRACT
HIV AND COVID-19 are of great concern that the global healthcare system have to be treated with new antiviral drugs for the epidemic. While Protease inhibitors and Remdesivir help to fight HIV and COVID-19 infection, drug resistance and side effects are on the rise. In this work, a hybrid molecule Derivatives was added to indazole and pyrimidine scaffolds. Bounding by molecular docking and QSAR modelling, our compound achieved excellent antiviral binds with HIV-1 protease, reverse transcriptase, SARS-CoV-2 main and RNA-dependent RNA polymerase in contrast to the standard drugs with good ADMET results. Atazanavir (-8.3), darunavir (-8.9) and remdesivir (-9.8) docking scores were well above that of our compounds (M1: -11.0 for COVID-19, -9.6 for HIV; M2: -10.5, -10.1) suggesting the possibility that both drugs show antiviral activity, although of course, further validation will take place in the in vivo and in vitro settings [5, 6].

Keywords: *Medicinal chemistry, bio evaluation, RNA-dependent, dual-action antiviral agent, Anti-HIV and Anti-Covid*
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INTRODUCTION

The global epidemic of viral diseases, such as HIV and COVID-19, has presented major threats to health and these drugs have to be efficiently and effectively developed into antiviral therapy. The various antiviral drugs have been introduced to the global health community for decades for which viral replication is the primary cause of treatment with the largest clinical benefit to the public health community. Protein inhibitors -- the most commonly used HIV therapy - like Atazanavir and Darunavir have the inhibitor of HIV-1 protease which are a very crucial factor in the production of virus polyproteins and the formation of infection vectors in humans. Antiviral therapies like these drugs have shown substantial efficacy in providing an important combination antiretroviral therapy (cART) in some of Africa; but the problem of drug resistance and high cost and drug development are ongoing and always requiring novel drugs with a better pharmacokinetic and safety profile. Following the COVID-19 pandemic caused by SARS-CoV-2 drugs like Remdesivir was quickly repurposed, a nucleoside agent derived for Ebola [9,10]. Remdesivir inhibits RNA dependent RNA polymerase (RdRp) involved in gene replication of viruses so RNA can be effectively produced from the nucleus for re-expression for another fluency.

Although it has received emergency use approval, its clinical effectiveness is still modest, there are concerns about the clinical effectiveness of it in cases of severe COVID-19. From the limitations of existing antiviral therapy but because resistant viral species are found and a variety of anti-cancer activity is evolving, novel antiviral agents with better inhibitory effects that last over the long term, broad range of targets and safety is important. Computational approaches (i.e. QSAR modelling and molecular docking) for drug discovery in silico have advanced drug discovery process and fast drug screening in laboratory, as long as new drugs are targeted at viral targets. We show here what is a newly developed derivative, a hybrid structure consisting of indazole and pyrimidine moieties that is characterized as a heterocyclic scaffold and has good antiviral properties. We obtained docking and QSAR figures that our synthetic drug has good binding (and the effect of our compound on absorption, distribution, metabolism and excretion, and toxicity of metabolism) and good absorb and excretion (ADMET) results compared to common drugs, such as Atazanavir, Darunavir and Remdesivir. They also showed very high interaction energies, good hydrogen bonding and strong binding in and near the active enzymes. These promising in silico results underline a dual-agent therapy for HIV and SARS-CoV-2 in the future. The chemical structures and docking score of all the drugs related to the treatment of COVID-19 and HIV have been shown in figure. Remdesivir proposed for treatment of COVID-19 showed -9.8 auto docking. So it has a promising biologics.

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We had included two compounds, M1 and M2, of which auto vina was present to both COVID-19 and HIV activity, so that M1 is -11.0 for COVID-19 and anti-HIV activity and M2 is -10.5 and -10.1 for anti-HIV. We also tested the anti-HIV drugs Atazanavir and Darunavir and obtained auto-dock scores of -8.3 and -8.9, respectively. These results imply double-activity of both COVID-19, HIV for some of our drugs including M1 and M2 and also showed promising result in the docking computation and simulations for both, and our chemical carriers:

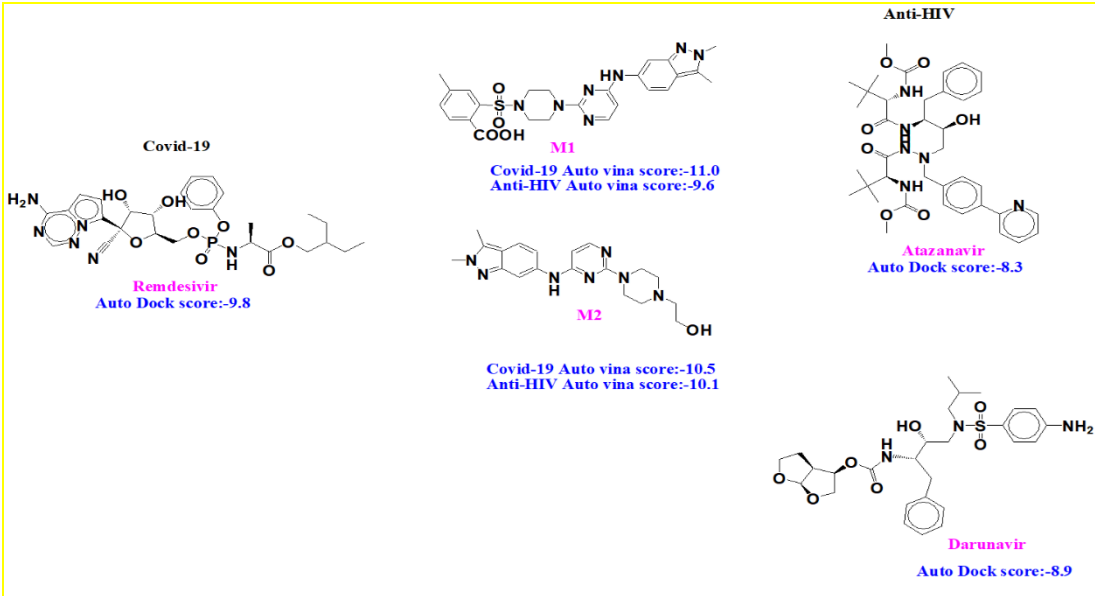
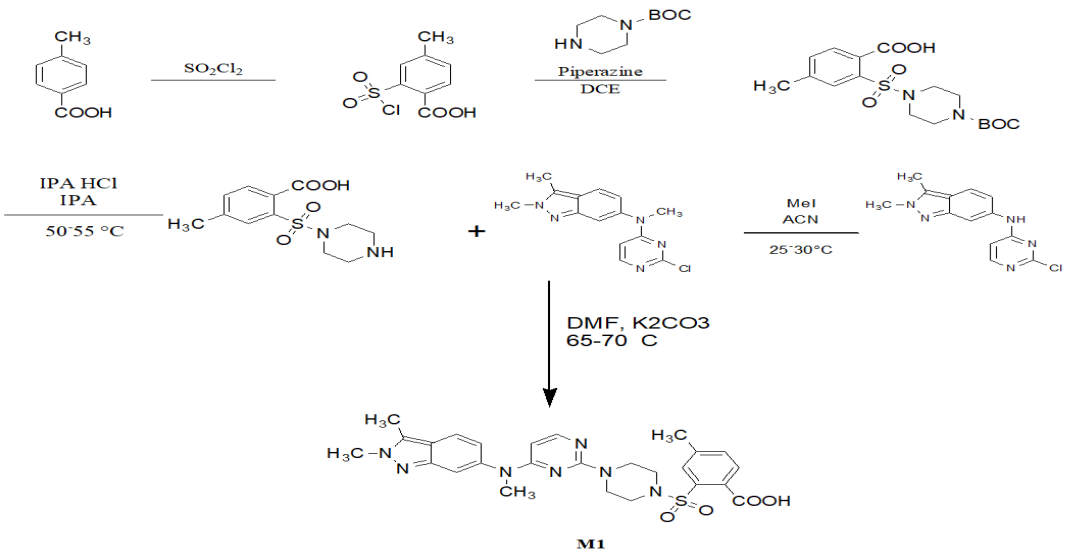


Figure:01 Auto dock score of already marketed drug for HIV and Covid-19, our synthesized molecules is more binding efficiency than the marketed molecules.

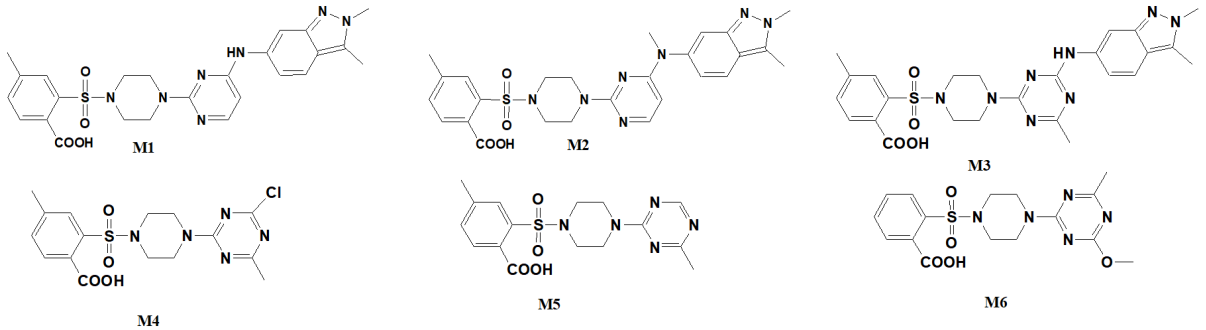
outperforming the existing commercial drugs. These findings warrant further in vitro and in vivo investigation to fully assess their pharmacological potential and therapeutic suitability. These promising in silico results support the potential of derivatives as dual-action antiviral agents with improved efficacy against both HIV and SARS-CoV-2, outperforming the existing commercial drugs. These findings warrant further in vitro and in vivo investigations to fully assess their pharmacological potential and therapeutic suitability[19].

MATERIALS AND METHODS:

All chemicals purchased from sigma Aldrich and solvents from local vendors, Analytical chemistry support got from SATHI-BHU facility. Insilco evaluation by Swiss ADME, CLICK 2 DRUG like online tools.



MOLECULE SYNTHESIS DERIVATIVES:



Structure Elucidation of Synthesized Derivatives:

M1: ^{1}HNMR:δ:1.27-1.30(1H),2.10(6H),2.59-2.64(5H),3.02-3.29(2.5H),3.92(1.6H),4.12(5H), 6.01(0.77H),6.70-6.90(2H),7.28(2H),7.50-7.60(2H),8.11(1H) , ^{13}C NMR: δ 9.90(1C) 21.6 (1C), 37.4(1C), 41.4 (2C), 45.3 (2C) ,102.41(1C), 109.3(1C), 117.8 (2C), 121.3(2C), 131.1(1C), 132.5(3C),134.5(2C),148.2(2C)158.7(1C),158.7(1C),163.0(1C),Mass Spectra (MW:521.89):522.89(M+1),520.10,504.10,478.20,295.20, 266.10,228.4,79.05

M2: ^{1}H NMR: δ 2.38-2.57 (6H), 3.00 (3H), 3.42-3.69 (8H), 3.81 (3H), 5.96 (1H), 6.96 (1H), 7.12 (1H), 7.58-7.75 (2H),7.76-7.96 (2H), 8.11 (1H). ^{13}C NMR: δ 11.2 (1C), 20.5 (1C), 36.9 (1C), 40.2 (1C), 45.4 (2C), 49.1 (2C), 102.6 (1C), 118.3 (1C), 120.0 (1C), 120.8 (1C), 121.6 (1C), 121.8 (1C), 123.6 (1C), 125.3 (1C), 128.0 (1C), 131.8 (1C), 136.1-136.4 (2C),144.8 (1C), 145.1 (1C), 148.9 (1C), 159.9 (1C), 162.6 (1C), 168.2 (1C).

M3: ^{1}H NMR: δ 2.49-2.60 (9H),2.94-3.01 (11H),6.94-7.11 (2H), 7.64 (1H), 7.76-7.96 (2H), 8.14 (1H). ^{13}C NMR: δ 11.2 (1C), 20.5 (1C), 24.9 (1C), 36.9 (1C), 45.4 (2C), 49.1 (2C), 117.0 (1C), 118.3 (1C), 118.6 (1C), 121.6 (1C), 121.8 (1C), 123.6 (1C), 125.3 (1C), 128.0 (1C), 131.8 (1C), 136.1-136.4 (2C), 136.6 (1C), 145.1 (1C), 159.9 (1C), 164.8 (1C), 165.6 (1C), 168.2 (1C).

M4:- ^{1}H NMR: δ 2.52 (3H), 3.47 (4H), 3.59-3.79 (10H), 7.64 (1H), 7.76-7.96 (2H), ^{13}C NMR: δ 20.5 (1C), 24.9 (1C), 44.4 (2C), 45.1 (2C), 121.6 (1C), 123.6 (1C), 125.3 (1C), 128.0 (1C), 131.8 (1C), 136.2 (1C), 161.6 (1C), 164.8 (1C), 165.6 (1C), 168.2 (1C). Mass Spectra (MW:411.12):413.42 (M+2).

M5: ^{1}H NMR: δ 2.49 (3H), 3.50 (4H), 3.60-3.79 (10H), 7.64 (1H), 7.76-7.96 (2H). ^{13}C NMR: δ 20.5 (1C), 43.4 (2C), 45.1 (2C), 55.4 (2C), 121.7 (1C), 123.7 (1C), 126.1 (1C), 128.1 (1C), 130.8 (1C), 130.2 (1C), 164.8 (2C), 166.8 (1C), 172.2 (1C). Mass Spectra (MW:387.42):389.41(M+2).

M6: ^{1}H NMR: δ 2.49 (3H), 3.40(4H), 3.71-3.79 (10H), 7.64 (1H), 7.79-7.96 (2H). ^{13}C NMR: δ 20.5 (1C), 45.4 (2C), 49.1 (2C), 54.5 (2C), 121.6 (1C), 123.6 (1C), 125.3 (1C), 128.0 (1C), 131.8 (1C), 136.2 (1C), 163.8 (2C), 164.8 (1C), 168.2 (1C), Mass Spectra (MW:423.12):424.45(M+2).

BIOLOGICAL STUDY:

In Silico Analysis Using Swiss ADME

In silico pharmacokinetic and drug-likeness evaluation of the studied small molecules was performed using the Swiss ADME web tool (http://www.swissadme.ch/), a widely recognized free resource for early drug discovery and development [20,21]. Swiss ADME predicts key Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties, medicinal chemistry friendliness, and pharmacokinetic parameters based on the molecular structures of compounds. This tool integrates multiple predictive models and rules to enable the efficient prioritization of potential drug candidates prior to experimental testing [22,23].

Pre-ADMET (PREADME) Study

Our ADMET profile was initially assessed by using Swiss-ADME pre-ADMET predictions to characterize biological assays and drug absorption, distribution, metabolism, excretion and toxicity for the drug compounds. This preliminary screening helps us identify compounds with suboptimal pharmacokinetic quality early, making it easier to exclude the few remaining poor candidates [24]. Toxicity Prediction Our risk of the drugs was evaluated by Brenk & PAINS (Pan-Assay Interference compound) filters in Swiss-ADME in terms of toxicology. PAINS targets for a class of chemical motifs known to interfere non-specifically with biological assays while Brenk looks for non-specific features that will lead to a toxic or metabolic issue. The compounds we identified by these filters would be put into a drug-likeness analysis. For the drug-likeness analysis, we followed a range of established empirical rules including Lipinski's Rule of Five, Ghose, Veber's, Egan's and Muegge's rules which are applied in Swiss ADME. For any molecular parameters that are linked to the criteria as described to them, Lipophilicity (LogP), topological polar area (TPSA), number of hydrogen bond donors and acceptors along with number of rotatable bonds were found on the molecular levels. Drug-likeness can be defined based on these factors and as such, these compounds are considered drug-like such that they may be more biologically beneficial in terms of oral bioavailability. Pharmacokinetic Properties. Pharmaceutical pharmacokinetic parameters such as GI

absorption, BBB permeability, P-gp substrate susceptibility, CYP enzyme inhibition rates and pharmacokinetics were predicted by Swiss ADME integrated models that are integrated prediction models, which would allow for the estimation of absorption efficiency, the risk of exposure to the central nervous system, efflux of drugs and drug-drug interaction risks [27].

Lipophilicity Assessment

Lipophilicity (LogP) for five different computations (XLOGP3 and WLOGP, MLOGP, SILICOS-IT and iLOGP) were achieved and a consensus value was used to make a reasonable estimate of Lipophilicity. Lipophilicity influences membrane permeability, solubility and pharmacodynamic interactions. It is often below five, based on Lipinski's criteria.

BOILED-Egg Model

The BOILED-Egg graphical model was used to predict the intestinal absorption and BBB permeation. Compounds were mapped onto the plot; those probably absorbed by the GI tract (white region) and those that could pass across the BBB (yellow region) giving insights into their probable biodistribution and CNS exposure[29].

Application to target validation and molecular docking. Swiss ADME and Swiss Dock can efficiently sample on the selected cell lines to check these ADMET and drug phenotype profiles, for in vitro experiments with HIV and SARS-CoV-2 cell lines to determine binding ability and ability of those compounds with HIV protease and SARS-CoV-2 main protease in the respective cell-line. For molecular docking, compounds with best ADMET profiles were selected for their docking by modelling and docking with the targets in the in vitro and in vivo experiments against the respective molecular docking and pre-screened drugs to monitor their affinity, toxicity and binding characteristics.

RESULTS AND DISCUSSION:

Swiss ADME study						
Name of test	M1	M2	M3	M4	M5	M6
Molecular weight	521.59 g/mol	535.62 g/mol	536.61 g/mol	411.86 g/mol	411.86 g/mol	423.44 g/mol
Num. heavy atoms	37	38	38	27	27	29
Num. arom. heavy atoms	21	21	21	12	12	12
Fraction Csp3	0.28	0.31	0.32	0.38	0.38	0.41
Num. rotatable bonds	6	6	6	4	4	6
Num. H-bond acceptors	8	8	9	8	8	10
Num. H-bond donors	2	1	2	1	1	1
Molar Refractivity	147.09	151.99	149.85	105.8	105.8	108.8
TPSA	141.93 Å²	133.14 Å²	154.82 Å²	124.97 Å²	124.97 Å²	143.43 Å²

1. Molecular Weight (g/mol): represents the mass one mole of molecules. When it comes to oral drugs, Lipinski's rule has a weight limit of no more than 500 g/mol. The M4, M5 and M6 have weight less than that of M1, M2 and M3 to help our oral drug absorb more quickly. 2. It gives an indication of drug-likeness, complexity and molecular size for the molecule. Number of Aromatic Heavy Atoms: Number of non-hydrogen atoms in aromatic systems that affect stability and binding, toxicity. Fraction Csp3: In sp3 hybridization state, the carbon atoms are fractionally distributed. With higher values, it showed that overall three dimensions are of higher quality since good oral bioavailability. Values near 0.4 are very good. 5. Number of Rotatable Bonds, a number of single non-ring bonds in the body excluding those with terminal bond points that can be rotated. The lower the number of non-rings to the end is positive for oral bioavailability. Number of Hydrogen Bond Acceptors: Atoms that accept protons in hydrogen bonds. A compound with ≤ 10 acceptors had acceptable oral character. Drug-like molecules are usually made up of less than 5 donors. Molar reactivity-both volumes of molecules, and polarizability-both of which affect binding affinity and solubility. Topological polar surface area (TPSA, Å²), i.e. sum of polar atoms in the cell. Solutions which were lower than 140 Å² in membrane permeation and bioavailability were more "drug-like". Drug-likeness properties are important when examining drug-likeness: lighter molecular weight of the molecule with good donor/acceptor for hydrogen bond and more rotatable

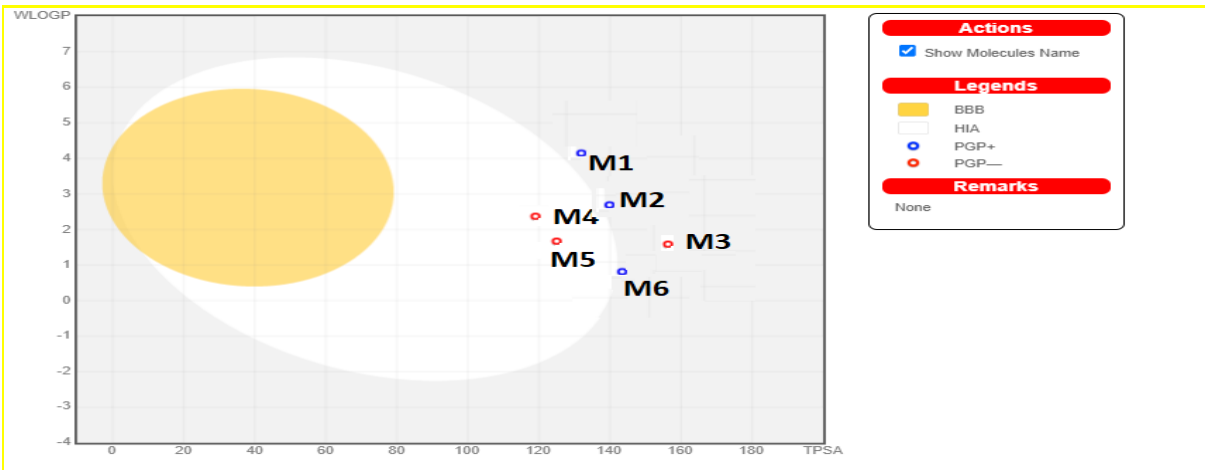
bonds. In oral molecule M4–M6 with weight (400 g/mol to 80 mg/mol), TPSA of medium. M1 & M3, for example, both heavier and above 140 mg were better at oral drugs. Medicinal Chemistry: Good aromatic content and Csp3 fraction indicated in comparison to other candidates that are very diverse planarity and three dimensionality. Such parameters must also be assessed along with ADME, toxicity and docking studies and some of the promising compounds will be tested experimentally. [31,32,33,34,35,36]

Parameter Descriptions and Significance

Lipophilicity						
Namw of test	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**
Log $P_{o/w}$ (iLOGP)	2.49	2.1	3.48	2.21	2.21	••▪•
Log $P_{o/w}$ (XLOGP3)	3.09	3.23	3.26	2.3	2.3	••▪•
Log $P_{o/w}$ (WLOGP)	3.25	3.28	2.96	1.67	1.67	••▪•
Log $P_{o/w}$ (MLOGP)	1.68	1.88	0.92	0.31	0.31	••▪••
Log $P_{o/w}$ (SILICOS-IT)	0.89	0.85	0.86	0.79	0.79	••▪••
Consensus Log $P_{o/w}$	2.28	2.27	2.3	1.45	1.45	••▪•

Early Toxicity Filtering Structural Alerts: The material reports toxicity predictions (PAINS and Brenk alerts) in terms of substructures and potentially hazardous compounds. Tracking on the basis of data-driven screening helps to differentiate safer candidates. It is then possible to stop all worrying for more likely failures in clinical trial. Drug-Likeness: The file reports, molecular weight, hydrogen bonds, rotatable bonds, TPSA and the other ingredients that are important in the assessment of its rate of drug absorption and distribution. Chemical compounds meeting the drug-likeness criteria without toxicity alerts can become the basis to move on with greater trust on them; clinical studies on human clinical drugs in the absence of toxicity alerts are available in a systematic manner and have been proven clinical to be in evidence. Data collected in silico can be used to obtain transparent data about drug-likeness selection and respond to regulatory demands that require toxicity screening. It supports the communication of chemists, pharmacologists and toxicologists. Data is also useful for resource optimization—and the computational analysis helps optimize the experimental toxicology studies to select drugs to follow, reducing animal testing and cost. An integrated approach to safety assessment has been done in silico studies, with more testing done on those high-risk compounds; multiple analyses have been performed to provide a prediction for drug safety assessment.

Boiled Egg Study



The plot comprises two fundamental measurements: 1. TPSA (x-axis): The polarity of molecule, and a higher average absorption value, than a lower one. 2. WLOGP (y-axis): lipophilicity of molecule. The plot details two important regions: White egg white - Molecules in this area are said to be efficient in gastrointestinal absorption. Yellow egg white - Molecules in this area are likely to easily penetrate the brain's blood tissue-sheaths. We plot the examples of molecules (M1-M6) with blue circles denoting some of the molecules in the material which could be expelled from cells whereas red with the molecules in the medium being released. Molecules M1 and M2 are best placed for absorption and even brain entry. In contrast molecular M3 and M6 show poor absorption. Molecular M4 and M5 are very promising for absorption. Thus, in order for drug development to take place as fast as possible, it is a relevant tool to quickly and efficiently analyze and improve proposed drugs that would leave any chance of no absorption ability or no brain entry [39,40].

MOLECULAR DOCKING STUDY:

1) Anti-HIV

Candidate Drug	Best Docking Score (kcal/mol)	Relative Binding Compared to Reference Drugs
M2	-10.1	Much better
M1, M3	-9.6	Better
M4	-8.4	Comparable
M5, M6	-8.3	Comparable
Atazanavir	-8.3	Reference
Darunavir	-8.9	Reference

Thus, this method can be used for targeting candidates before clinical development to allow for better understanding of the compounds in question. Candidate molecules were selected based on the molecule structure and predicted binding function. The table summarizes an in silico analysis of six candidates (M1–M6) with anti-HIV drugs Atazanavir and Darunavir by means of molecular docking simulations. Docking simulations were conducted to assess drug binding affinity to HIV virus protein to identify antiviral drugs that could inhibit viral activity. The "Vina score" (in kcal/mol) is calculated and shows binding affinity; lower values indicate stronger likely binding to the virus proteins. M2 had the lowest docking score (-10.1) indicating the strongest predicted binding. Both M1 and M3 showed similar binding scores or better with reference drugs and similar signals for M4, M5, M6. These candidates also had docking poses that were better than atazanavir and matched or exceeded darunavir's docking poses. This modelling study has shown that various promising M2 as potential HIV inhibitors have potential to reach biologic lab trials in the future, but we are waiting for feedback[41,42].

Molecule	Top Docking Score (Best)	Other Scores	Relative to Remdesivir
M1	-11	-10, -9.2	Much better
M2	-10.5	-10.1, -9.4	Better
M3	-10.9	-10.7, -9.5	Much better
M4	-9	-8.2, -7.5	Close
M5	-8.4	-8.2, -8.1	Slightly worse
M6	-8.5	-8.4, -7.2	Slightly worse
Remdesivir	**-9.8**	-9, -8.8	Reference

2) Anti-Covid19

With molecular docking studies of the binding of COVID-19 protein to the most commonly used drug for COVID-19 Remdesivir, we found M1 (-11), M2 (-10.5), and M3 (-10.9) to have better (negative) docking scores than Remdesivir (-9.8). This is consistent with a better binding with the protein, i.e. stronger binding affinity of the COVID-19 with Remdesivir drug which suggests high potential for antiviral activity. Molecule M4 had good binding affinity but weaker (better than Remdesivir) with molecular docking poses, but the molecules M5 and M6 stayed weak. We also presented secondary docked poses (of other possible binding pathway) for all the molecules which almost all of the molecule have the same binding affinity, or at least the same binding affinity. The three most efficient binding routes are M1, M2 and M3, and the best Binders always have to do with the high binding affinity to the CoVID-19 protein: the binding affinity of M2 and the one of M3. -Potential: Molecules with higher potential for comparison in silico to remdesivir do not seem to be approved enough. Caveat: Docking scores only provide some indication of how drug development is going on. More experiments to evaluate remdesivir on its safety, effectiveness and as a therapeutic candidate need to

be carried out to determine if remdesivir turns out to be effective on these new molecules: M1, M2, M3. Based on findings of this docking study we will know whether these drugs have improved likelihood of interaction with COVID-19 targets compared with remdesivir.

CONCLUSION

We also see that global pathogens such as HIV and COVID-19 present a global challenge which demands effective (ultrasensely) antiviral drugs. These drugs, with Protease Inhibitors and Remdesivir among them, have limited therapeutic benefit but their drug resistance is good but limited and they do not perform as well as the new drugs. The in silico design and evaluation of the novel hybrid molecule derivatives has shown the potential of this dual-active antiviral for HIV and SARS-CoV-2 on an HIV/SARS enzyme level, for which increased docking score for the drug and favourable binding affinity to the drug has been noted. As such there is potential for an ability that this drug could overcome all the existing treatment challenges it is overcoming and contribute to the next generation antivirals. But, extensive in vitro and in vivo studies are still needed to document our computational results and determine if they can be applied in medicine. Combining computational drug design with empirical validation could accelerate the development of broad-spectrum antiviral drugs which would serve as a much bigger public health mission for the future against the persistent viruses and the emergence as they emerged out of the virus' outbreak environment.

REFERENCE

1) Balasubramaniam, M., & Shmookler Reis, R. J. (2020). Computational target-based drug repurposing of elbasvir, an antiviral drug predicted to bind multiple SARS-CoV-2 proteins. In *ChemRxiv : the preprint server for chemistry* (Vol. 52, Issue 1). Chemrxiv. https://doi.org/10.26434/chemrxiv.12084822

2) Elfiky, A. A., Azzam, E. B., & Shafaa, M. W. (2021). The anti-HCV, Sofosbuvir, versus the anti-EBOV Remdesivir against SARS-CoV-2 RNA dependent RNA polymerase in silico. *Molecular Diversity*, *26*(1), 171–181. https://doi.org/10.1007/s11030-020-10178-z

3) Bhardwaj, V. K., Singh, R., Sharma, J., Rajendran, V., Purohit, R., & Kumar, S. (2021). Bioactive Molecules of Tea as Potential Inhibitors for RNA-Dependent RNA Polymerase of SARS-CoV-2. *Frontiers in Medicine*, *8*. https://doi.org/10.3389/fmed.2021.684020

4) Zhu, W., Chen, C. Z., Gorshkov, K., Xu, M., Lo, D. C., & Zheng, W. (2020). RNA-Dependent RNA Polymerase as a Target for COVID-19 Drug Discovery. *Slas Discovery*, *25*(10), 1141–1151. https://doi.org/10.1177/2472555220942123

5) Azeem, M., Mustafa, G., Ahmed, S., Mushtaq, A., Arshad, M., Usama, M., & Farooq, M. (2024). Structure based screening and molecular docking with dynamic simulation of natural secondary metabolites to target RNA-dependent RNA polymerase of five different retroviruses. *PloS One*, *19*(8), e0307615. https://doi.org/10.1371/journal.pone.0307615

6) Mishra, S., Chauhan, A. J., & Mahida, J. (2025). Exploring Biosensors: Distinctive Features and Emerging Applications. *Analytical Biochemistry*, 115993.

7) Nguyen, K. V. (2021). Problems associated with antiviral drugs and vaccines development for COVID-19: approach to intervention using expression vectors via GPI anchor. *Nucleosides, Nucleotides & Nucleic Acids*, *40*(6), 665–706. https://doi.org/10.1080/15257770.2021.1914851

8) Gudima, G., Kofiadi, I., Shilovskiy, I., Kudlay, D., & Khaitov, M. (2023). Antiviral Therapy of COVID-19. *International Journal of Molecular Sciences*, *24*(10), 8867. https://doi.org/10.3390/ijms24108867

9) Gudima, G., Kofiadi, I., Shilovskiy, I., Kudlay, D., & Khaitov, M. (2023). Antiviral Therapy of COVID-19. *International Journal of Molecular Sciences*, *24*(10), 8867. https://doi.org/10.3390/ijms24108867

10) Gudima, G., Kofiadi, I., Shilovskiy, I., Kudlay, D., & Khaitov, M. (2023). Antiviral Therapy of COVID-19. *International Journal of Molecular Sciences*, *24*(10), 8867. https://doi.org/10.3390/ijms24108867

11) Leung, A. K. L., Griffin, D. E., Bosch, J., & Fehr, A. R. (2022). The Conserved Macrodomain Is a Potential Therapeutic Target for Coronaviruses and Alphaviruses. *Pathogens*, *11*(1), 94. https://doi.org/10.3390/pathogens11010094

12) Tripathi, N., Tripathi, N., & Goshisht, M. K. (2021). COVID-19: inflammatory responses, structure-based drug design and potential therapeutics. *Molecular Diversity*, *26*(1), 629–645. https://doi.org/10.1007/s11030-020-10176-1

13) Flier, J. S., Underhill, L. H., & Crumpacker, C. S. (1989). Molecular Targets of Antiviral Therapy. *New England Journal of Medicine*, *321*(3), 163–172. https://doi.org/10.1056/nejm198907203210306

14) Magden, J., Kääriäinen, L., & Ahola, T. (2004). Inhibitors of virus replication: recent developments and prospects. *Applied Microbiology and Biotechnology*, *66*(6), 612–621. https://doi.org/10.1007/s00253-004-1783-3

15) Qayed, W. S., Ferreira, R. S., & Silva, J. R. A. (2022). In Silico Study towards Repositioning of FDA-Approved Drug Candidates for Anticoronaviral Therapy: Molecular Docking, Molecular Dynamics

and Binding Free Energy Calculations. *Molecules*, *27*(18), 5988. https://doi.org/10.3390/molecules27185988

16) Swain, S. S., Singh, S. R., Sahoo, A., Hussain, T., & Pati, S. (2021). Anti-HIV-drug and phyto-flavonoid combination against SARS-CoV-2: a molecular docking-simulation base assessment. *Journal of Biomolecular Structure and Dynamics*, *40*(14), 6463–6476. https://doi.org/10.1080/07391102.2021.1885495

17) Saravanan, K., Elavarasi, S., Revathi, G., Karuppannan, P., Ashokkumar, M., Muthusamy, C., & Ram Kumar, A. (2024). Targeting SARS-CoV2 spike glycoprotein: molecular insights into phytocompounds binding interactions – in-silico molecular docking. *Journal of Biomaterials Science, Polymer Edition*, *36*(3), 315–332. https://doi.org/10.1080/09205063.2024.2399395

18) Ahmed, S., Mahtarin, R., Ahmed, S. S., Akter, S., Islam, M. S., Mamun, A. A., Islam, R., Hossain, M. N., Ali, M. A., Sultana, M. U. C., Parves, M. R., Ullah, M. O., & Halim, M. A. (2020). Investigating the binding affinity, interaction, and structure-activity-relationship of 76 prescription antiviral drugs targeting RdRp and Mpro of SARS-CoV-2. *Journal of Biomolecular Structure and Dynamics*, *39*(16), 6290–6305. https://doi.org/10.1080/07391102.2020.1796804

19) Lin, J., Sahakian, D., De Morais, S., Xu, J., Polzer, R., & Winter, S. (2003). The role of absorption, distribution, metabolism, excretion and toxicity in drug discovery. *Current Topics in Medicinal Chemistry*, *3*(10), 1125–1154. https://doi.org/10.2174/1568026033452096

20) Matter, H., Barighaus, K.-H., Naumann, T., Klabunde, T., & Pirard, B. (2001). Computational approaches towards the rational design of drug-like compound libraries. *Combinatorial Chemistry & High Throughput Screening*, *4*(6), 453–475. https://doi.org/10.2174/1386207013330896

21) Moda, T. L., Torres, L. G., Carrara, A. E., & Andricopulo, A. D. (2008). PK/DB: database for pharmacokinetic properties and predictive *in silico* ADME models. *Bioinformatics*, *24*(19), 2270–2271. https://doi.org/10.1093/bioinformatics/btn415

22) Komura, H., Watanabe, R., & Mizuguchi, K. (2023). The Trends and Future Prospective of In Silico Models from the Viewpoint of ADME Evaluation in Drug Discovery. *Pharmaceutics*, *15*(11), 2619. https://doi.org/10.3390/pharmaceutics15112619

23) M Honorio, K., L Moda, T., & D Andricopulo, A. (2013). Pharmacokinetic Properties and In Silico ADME Modeling in Drug Discovery. *Medicinal Chemistry*, *9*(2), 163–176. https://doi.org/10.2174/1573406411309020002

24) Sindhu, M. S., Poonkothai, M., & Thirumalaisamy, R. (2022). Phenolic and terpene compounds from Plectranthus amboinicus (Lour.) Spreng. Act as promising hepatic anticancer agents screened through in silico and in vitro approaches. *South African Journal of Botany*, *149*, 145–159. https://doi.org/10.1016/j.sajb.2022.06.001

25) Sadeghian, Z., Bayat, M., & Gheidari, D. (2025). Synthesis, molecular docking, pharmacological evaluation, MD simulation, and DFT calculations of quinazolin-12-one derivatives as PDK1 inhibitors†. *Nanoscale Advances*, *7*(18), 5760–5783. https://doi.org/10.1039/d5na00182j

26) Lakhani, K. G., Hamid, R., Gupta, S., Prajapati, P., Prabha, R., Patel, S., & Suthar, K. P. (2024). Exploring the therapeutic mechanisms of millet in obesity through molecular docking, pharmacokinetics, and dynamic simulation. *Frontiers in Nutrition*, *11*. https://doi.org/10.3389/fnut.2024.1453819

27) Alotaibi, B. S. (2023). Targeting Filamenting temperature-sensitive mutant Z (FtsZ) with bioactive phytoconstituents: An emerging strategy for antibacterial therapy. *PLOS ONE*, *18*(8), e0290852. https://doi.org/10.1371/journal.pone.0290852

28) Wadood, A., Shareef, A., Ur Rehman, A., Muhammad, S., Khurshid, B., Khan, R. S., Shams, S., & Afridi, S. G. (2021). In Silico Drug Designing for ala438 Deleted Ribosomal Protein S1 (RpsA) on the Basis of the Active Compound Zrl15. *ACS Omega*, *7*(1), 397–408. https://doi.org/10.1021/acsomega.1c04764

29) Yang, Q., Fan, L., Hao, E., Hou, X., Deng, J., Xia, Z., & Du, Z. (2024). Machine Learning Exploration of the Relationship Between Drugs and the Blood-Brain Barrier: Guiding Molecular Modification. *Pharmaceutical Research*, *41*(5), 863–875. https://doi.org/10.1007/s11095-024-03686-2

30) Sharma, G., Kumar, N., Sharma, C. S., Alqahtani, T., Tiruneh, Y. K., Sultana, S., Rolim Silva, G. V., De Lima Menezes, G., Zaki, M. E. A., & Nobre Oliveira, J. I. (2025). Identification of promising SARS-CoV-2 main protease inhibitor through molecular docking, dynamics simulation, and ADMET analysis. *Scientific Reports*, *15*(1). https://doi.org/10.1038/s41598-025-86016-9

31) Nowroozi, G., Rahmani, S., Jalali, P., Zareie, A., Asvar, Z., & Nowroozi, A. (2025). Natural Marine-derived Compounds as Potential Inhibitors of SARS-CoV-2 Main Protease: A Comprehensive Computational Study. *Journal of Reports in Pharmaceutical Sciences*, *13*(1). https://doi.org/10.5812/jrps-159451

32) Veber, D. F., Johnson, S. R., Cheng, H.-Y., Smith, B. R., Ward, K. W., & Kopple, K. D. (2002). Molecular

properties that influence the oral bioavailability of drug candidates. *Journal of Medicinal Chemistry*, *45*(12), 2615–2623. https://doi.org/10.1021/jm020017n

33) O' Donovan, D. H., De Fusco, C., Kuhnke, L., & Reichel, A. (2023). Trends in Molecular Properties, Bioavailability, and Permeability across the Bayer Compound Collection. *Journal of Medicinal Chemistry*, *66*(4), 2347–2360. https://doi.org/10.1021/acs.jmedchem.2c01577

34) Veber, D. F., Johnson, S. R., Cheng, H.-Y., Smith, B. R., Ward, K. W., & Kopple, K. D. (2002). Molecular properties that influence the oral bioavailability of drug candidates. *Journal of Medicinal Chemistry*, *45*(12), 2615–2623. https://doi.org/10.1021/jm020017n

35) Baell, J., Congreve, M., Leeson, P., & Abad-Zapatero, C. (2013). Ask the Experts: Past, Present and Future of the Rule of Five. *Future Medicinal Chemistry*, *5*(7), 745–752. https://doi.org/10.4155/fmc.13.61

36) O' Donovan, D. H., De Fusco, C., Kuhnke, L., & Reichel, A. (2023). Trends in Molecular Properties, Bioavailability, and Permeability across the Bayer Compound Collection. *Journal of Medicinal Chemistry*, *66*(4), 2347–2360. https://doi.org/10.1021/acs.jmedchem.2c01577

37) Caminero Gomes Soares, A., Marques Sousa, G. H., Calil, R. L., & Goulart Trossini, G. H. (2023). Absorption matters: A closer look at popular oral bioavailability rules for drug approvals. *Molecular Informatics*, *42*(11). https://doi.org/10.1002/minf.202300115

38) Miteva, M. A., Violas, S., Montes, M., Gomez, D., Tuffery, P., & Villoutreix, B. O. (2006). FAF-Drugs: free ADME/tox filtering of compound collections. *Nucleic Acids Research*, *34*(Web Server issue), W738–W744. https://doi.org/10.1093/nar/gkl065

39) Janicka, M., Sztanke, M., & Sztanke, K. (2020). Predicting the Blood-Brain Barrier Permeability of New Drug-Like Compounds via HPLC with Various Stationary Phases. *Molecules*, *25*(3), 487. https://doi.org/10.3390/molecules25030487

40) Sardar, H., Shareef, U., & Khan, H. (2024). Molecular Docking & In Silico ADME Analysis of 5-O-Methyl-11-O-Acetylalkannin. *Phytopharmacological Communications*, *4*(01), 17–28. https://doi.org/10.55627/ppc.004.001.0523

41) Jia, Q., Ni, Y., Liu, Z., Gu, X., Cui, Z., Fan, M., Zhu, Q., Wang, Y., & Ma, J. (2022). Fast Prediction of Lipophilicity of Organofluorine Molecules: Deep Learning-Derived Polarity Characters and Experimental Tests. *Journal of Chemical Information and Modeling*, *62*(20), 4928–4936. https://doi.org/10.1021/acs.jcim.2c01201