Binary-QSAR guided virtual screening of FDA approved drugs and compounds in clinical investigation against SARS-CoV-2 main protease

Lalehan Oktay¹, Ece Erdemoğlu^{1,2}, İlayda Tolu¹, Yeşim Yumak^{1,3}, Ayşenur Özcan^{1,4}, Elif Acar^{1,4}, Şehriban Büyükkılıç^{1,5}, Alpsu Olkan^{1,6}, Serdar Durdağı^{1,*}

¹ Computational Biology and Molecular Simulations Laboratory, Department of Biophysics, School of Medicine, Bahcesehir University, Istanbul, Turkey; ² School of Medicine, Mersin University, Mersin, Turkey; ³ Faculty of Science and Letters, Tokat Gaziosmanpasa University, Tokat, Turkey; ⁴ Faculty of Medicine, Istanbul Medeniyet University, Istanbul, Turkey; ⁵ Faculty of Science, Necmettin Erbakan University, Konya, Turkey; ⁶ School of Medicine, Bahcesehir University, Istanbul, Turkey

Author	ORCID ID	Email
Lalehan Oktay	0000-0002-3293-5551	oktaylalehan@gmail.com
Ece Erdemoğlu	0000-0002-6084-2037	eceerdemoglu@gmail.com
İlayda Tolu	0000-0002-0106-5426	ilaydatolu.01@gmail.com
Yeşim Yumak	0000-0001-5227-0932	yumakyesim@gmail.com
Ayşenur Özcan	0000-0002-8493-7380	aysenur.ozcan@live.com
Elif Acar	0000-0002-8180-227X	elifacar5665@gmail.com
Şehriban Büyükkılıç	0000-0003-2390-3379	buyuk35sehiban@gmail.com
Alpsu Olkan	0000-0002-8938-6952	alpsuolkan@hotmail.com
Serdar Durdağı	0000-0002-0426-0905	serdar.durdagi@med.bau.edu.tr

***Corresponding Author: Prof. Dr. Serdar DURDAĞI (E-mail: serdar.durdagi@med.bau.edu.tr)**

Acknowledgment

This study was supported by the TÜBİTAK 2247-C STAR program.

Conflict of Interest

The authors declare that there is not any conflict of interest.

Abstract

With the emergence of the new SARS-CoV-2 virus, drug repurposing studies have gained substantial importance. Combined with the efficacy of recent improvements in ligand- and target-based virtual screening approaches, virtual screening has become faster and more productive than ever. In the current study, an FDA library of approved drugs and compounds under clinical investigation were screened for their antiviral activity using the MetaCore™/MetaDrug™ (<https://portal.genego.com>) platform's antiviral therapeutic activity binary QSAR model. In the 6733-compound collection, we found 370 compounds with a normalized therapeutic activity value greater than a cutoff of 0.75. Only these selected compounds were used for molecular docking studies against the SARS-CoV-2 Main Protease (M^{pro}). After initial short (10 ns) molecular dynamics (MD) simulations with the top-50 docked compounds and following Molecular Mechanics Generalized Born Surface Area (MM/GBSA) calculations, top-10 compounds were subjected to longer (100 ns) MD simulations and end-point MM/GBSA estimations. Our virtual screening protocol yielded Cefuroxime pivotexil, an ester prodrug of second-generation cephalosporin antibiotic Cefuroxime, as being a considerable molecule for drug repurposing against the SARS-CoV-2 M^{pro}.

Key words: Binary QSAR, virtual screening, drug repurposing, SARS-CoV-2

1. Introduction

In December 2019, a local outbreak of pneumonia with unknown origin was reported in Wuhan (Hubei, China), and a novel coronavirus was soon found to be the underlying cause (Dong et al., 2020). It has quickly become a global pandemic and has spread to other countries, affecting around 180 million people worldwide (WHO, 2021). Consequently, it has now become the biggest public health emergency all around the world. Shortly after the World Health Organization (WHO) denominated the disease as ‘Coronavirus disease-2019’ or COVID-19 (Ghosh et al., 2020). The International Committee on Taxonomy of Viruses defined the virus as SARS-CoV-2 (Wu et al., 2020). The severity of the disease ranges from asymptomatic cases to multi-organ failure deaths. Although most of the patients experience some mild prodromal symptoms 5 days after the incubation period, such as fever, fatigue, cough and shortness of breath, in some cases, the ‘cytokine storm’ following the acute respiratory distress syndrome induced septic shock, pulmonary embolism and multi-organ failure associated with an increased risk of death (Ruano-Gallego et al., 2021). Some studies claim the incidence of deep venous thrombosis and pulmonary embolism in hospitalized COVID-19 patients is 25% to 58% (Erben et al., 2021). The disease mortality is 10% overall, with 34% of the patients who need intensive care units and 83% who are subjected to invasive ventilation (Potere et al., 2020). This disease with its wide clinical spectrum has suddenly become more than a global healthcare problem with its economic and social consequences. These consequences alarmed the world to find an urgent treatment. Unfortunately, there are currently no globally accepted medicine for COVID-19 despite a great number of research (Han et al., 2021).

SARS CoV-2 is a single stranded positive-sense RNA virus that is a member of the β -coronaviruses family (Kirtipal et al., 2020). SARS-CoV-2 contains approximately 30,000 nucleotide RNA sequences responsible for encoding the entire viral proteome. The viral genome is divided into a non-structural protein (NSP) coding region, a helper protein coding region and a structural protein coding region (Kirtipal et al., 2020). Furthermore, multiple open reading frames (ORF) are present. Structural proteins such as spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins are produced from the ORF's close to the 3'-terminus of the genome and also non-structural proteins such as the main protease is encoded in the 5'-terminus region (Chen et al., 2020).

The main protease (M^{pro}) or 3CLpro (also called chymotrypsin-like protease or Nsp5) enzyme is the pivotal point of drug discovery research for COVID-19. The enzyme plays an important role in the processing of polyproteins translated from the viral RNA and their separation into different functional components. The inactivation of this enzyme blocks processes such as viral replication and transcription, stopping the virus from reproducing in the host (Ahmed et al., 2021; Molavi et al., 2021). The most important assignment of the M^{pro} is to cleave pp1a and pp1ab, replicase 1a and replicase 1ab, respectively. The pp1a and pp1ab are the polyproteins of SARS CoV-2 resulting from the codification of the ORFs, ORF1a and ORF1b. Coding these ORFs is crucial for the virus to form its structural and non-structural proteins. After the production of these polyproteins, the M^{pro} takes the scene and starts to cleave these polyproteins at 11 sites with papain-like protease to create the functional proteins of SARS CoV-2 (Shitrit et al., 2020; Guedes et al., 2021).

M^{pro} is a homodimeric proteolytic enzyme which is crucial for the life cycle of SARS CoV-2. While M^{pro} monomers are enzymatically inactive when separated from each other, they become active in dimeric structure (Silvestrini et al., 2021). Histidine at the 41st position and Cysteine at the 145th position on monomer 'A' of the M^{pro} constitute the catalytic domain of the enzyme for the binding of substrates (Shitrit et al., 2020). Targeting the M^{pro} responsible for the virus-induced apoptotic signal is the most favorable option in inhibiting viral replication and dysregulation of signaling cascades in infected cells (Han et al., 2021; Rothan and Teoh, 2021).

In most studies on the catalytic activity of cysteine protease (Nsp5), it has been reported that it mainly depends on the interaction between Glu166 and Ser1 amino acids, and the proximity of the two protomers' S1 sub pocket and N-terminal residues, thus their connection with dimer structures (Behnam, 2021).

Targeting the SARS CoV-2 M^{pro} may be a safer option, since this protease has a cleavage site which has no similarity with any human proteases and is special from the standpoint of its recognition sequence Leu-Gln (Ser, Ala, Gly) on polyprotein 1ab (Zhang et al., 2020). Additionally, the proposed drugs that are identified/developed against the M^{pro} have a very low risk of mutation-mediated drug resistance. The M^{pro} sequence is protected amongst CoV's because M^{pro} mutations are highly mortal for the virus (Silvestrini et al., 2021). When we consider all of these features of SARS CoV-2 M^{pro} such as (i) its key role in the viral cycle, (ii) its targetable active zone in terms of both its perishable dimer structure and blockable catalytic dyad, (iii) its resistance against mutations, and (iv)

specific recognition site, a drug aiming M^{pro} can be a convenient and secure option to tackle the SARS-CoV-2 virus.

Currently, in silico studies with computational simulations are the first step for developing a new drug, since this kind of virtual screening approaches make it possible to scan huge databases in a very short time at a very low cost for a chosen target. (Durdagi et al., 2020; Tutumlu et al., 2020; Kanan et al., 2021; Durdağı 2020). With the advantage of innovative in silico drug-discovery techniques, it is possible to integrate and mine a wide variety of high-throughput biological data developed globally for drug repurposing, to find new indications for existing drugs (Akhoon et al., 2019). The use of existing drugs which have already been approved to treat different diseases is another advantage of drug repurposing since they have already been studied in vivo and completed clinical trials. Therefore, their use in pandemics such as the COVID-19 is more suitable than new molecules that have never been tested.

In the current study, a binary QSAR model-guided virtual screening of FDA approved compounds and compounds in clinical investigation library which includes around 7000 compounds are performed.

2. Methods

2.1 Ligand Preparation. 7922 ligands were downloaded from NPC library (<https://tripod.nih.gov/npc/>). In order to avoid misleading results and decrease the non-specificity, some filtration criteria on library is conducted: (i) Compounds that

have molecular weight between 100-1000 g/mol are considered; (ii) compounds that have more than 100 rotatable bonds are not considered; (iii) compounds that have more than 10 hydrogen bond donor and acceptor are not considered. Thus, the total number of molecules were decreased to 6654 before the docking simulations. These compounds were prepared with LigPrep module (LigPrep, Schrodinger v.2017) of Maestro molecular modeling package. After the ligand preparation total number of compounds was 6733.

2.2 Protein Preparation. Crystal structure of SARS-CoV-2 Main Protease was downloaded from the Protein Data Bank with ID of 7CWC. The structure in apo form was prepared using the *Protein Preparation* tool in the Maestro molecular modeling suite. Initially, hydrogens were added, side chains and loops were mended, and disulfide bonds were created. Protonation states of the residues at physiological pH (7.4) were assigned using PROPKA. Conformational optimization was performed via the OPLS3e forcefield. Homodimer stoichiometry was kept for all molecular simulations.

2.3 Binary QSAR Model. Our pre-filtered ligand library was subjected to the antiviral therapeutic activity binary QSAR model in the MetaCore™/MetaDrug™ platform from Clarivate Analytics. (<https://portal.genego.com>) The MetaCore™/MetaDrug™ platform uses QSAR predictions for pharmacokinetic and pharmacodynamic characterization of small molecules (Dogan and Durdagi 2020). Viral binary QSAR model is used for the therapeutic activity predictions of the screened compounds, (model description: Training set, N=206; Test set, N=35; Sensitivity= 0.92; Specificity=0.95; Accuracy=0.94; Matthews correlation coefficient (MCC)=0.88). In the therapeutic activity prediction by

the Viral binary QSAR model, predicted activity values are normalized between 0 and 1 (a value of more than 0.5 may be interpreted as potential therapeutic activity). Here, we used a higher cutoff (0.75). There were 370 compounds among screened library.

2.4 Molecular Docking. Molecular docking simulations were performed on the surviving 370 compounds from binary QSAR screen using the Glide/SP docking algorithm. Crucial residues at the catalytic site of the M^{pro} such as His41, Cys145, and Glu166 were used to define the grid box. The thiol and hydroxyl groups of the residues enclosed in this box were allowed to rotate. Glide offers an optimization where van der Waals radii can be scaled for softening potentials of non-polar parts of the ligands. Scaling factor was selected as 0.80 Å for ligand atoms having less than 0.15 partial charge. Flexible ligand sampling was used. Post-docking minimizations were also performed as part of Glide's docking algorithm.

2.5 Molecular Dynamics Simulations. Molecular dynamics (MD) simulations are used to explore the structural and dynamical features once the compounds bind to the infamous binding pocket of the main protease. The Desmond program was used for this purpose. Best scoring docked complexes were initially submerged in an orthorhombic water box of TIP3P water models and ions for neutralization. Salt concentration of 0.15 M was defined to the water box. As for all the previous experiments conducted, OPLS3e forcefield was employed for assigning parameters. NPT ensemble was used and controlled by the Martyna-Tobias-Klein barostat and Nosé-Hoover thermostat, respectively. RESPA integrator is used with 2 fs time steps. Simulations are conducted at 310 K and 1 bar. Two different length of MD simulations are conducted: (i) short MD

simulations (10 ns); (ii) long MD simulations (100 ns). While 100 trajectory frames are collected throughout the simulations in short MD simulations, 1000 frames are collected in long MD simulations.

2.6 Molecular Mechanics the Generalized Born Surface Area (MM/GBSA)

Calculations. Average binding free energies of screened compounds were studied with MM/GBSA method. The OPLS3e force field for molecular mechanical energy and the surface-generalized Born model for polar solvation energy (VSGB), as well as the apolar solvation factor (G_{SA}), were used to calculate the endpoint energy. 100 frames throughout the simulations are extracted, then MM/GBSA was calculated for the complexes. An average calculation of all the frames was considered.

3. Results and Discussion

Considering the off-target binding, high costs, and slow pace of new drug discovery and development, drug repurposing - also known as drug repositioning - has become a more appealing method with the coronavirus pandemic, since it involves the use of relatively safe compounds, which could result in lower overall costs and faster maturation timelines, which is crucial for mass pandemics, like SARS-CoV-2. Our study aims to screen FDA approved drugs and compounds in clinical trials for anti-viral activity and use these filtered compounds against the SARS-CoV-2 M^{pro} target.

Among the 6733 compounds, 370 compounds had normalized therapeutic activity prediction value of 0.75 or higher (Table S1). A histogram of the therapeutic activity

prediction of the 6733-compound library revealed that the normalized predicted activity was mostly between 0.4-0.5 (Figure 1). The 370 identified compounds based on used QSAR model were used in the docking simulations.

Previously reported crucial residues, His41, Cys145 and Glu166 (Yoshino et al., 2020) were used to define the grid-box. The thiol and hydroxyl groups of the residues enclosed in this box were allowed to rotate. The Glide/SP docking score ranged between -7.60 kcal/mol to -2.66 kcal/mol (Figure S1). Docking scores of identified 370 compounds are reported in Table S1. The best docking score was obtained from compound Cefuroxime axetil, which is the ester prodrug of second-generation cephalosporin antibiotic Cefuroxime. The 3rd best scoring compound, Cefuroxime pivoxetil is also an ester pro-drug of Cefuroxime (Scott et al., 2001).

Top-50 high docking scored compounds (Table 1) were used in short (10 ns) MD simulations. Figures S2 shows the protein backbone atoms RMSD versus time plot of the selected top-10 compounds throughout 100 ns. In Figure S3, 'Lig fit Prot' RMSD versus time plot for the same top-10 molecules is given. The RMSD of a ligand is displayed in 'Lig fit Prot' when the protein-ligand complex is first fitted on the protein backbone and the RMSD of the ligand heavy atoms is calculated. Among the top-10 hit compounds, Ibutamoren showed the lowest Lig fit Prot RMSD, while Cilostamide has the most deviation. Cilostamide shows high deviation because it loses its initial contact with Thr24 and Thr25, instead to make interaction with Glu166 and Pro168 for last half of the 100 ns MD simulation (see Figure S7).

233 Average MM/GBSA scores of these 50 hit compounds are sorted and top-10 compounds
234 were used in long (100 ns) MD simulations. MM/GBSA analysis of the trajectories for
235 10 ns indicates Ibutamoren as being the ideal binder. However, for a 100 ns trajectory
236 energy analysis, Cefuroxime pivoxetil, shows better average free energy of binding than
237 the other compounds as it can be seen in the Box and Whisker plots of the MM/GBSA
238 scores for the top-10 compounds in Figure 2. Given that Cefuroxime pivoxetil has one of
239 the top docking scores, this compound may yield promising results. Extending MD
240 simulations to 100 ns has given further insight into the changing binding energies and
241 further fortified the results. Figure 3 shows 2-Dimensional and 3-Dimensional ligand
242 interaction diagrams of Cefuroxime pivoxetil. Crucial residues were found as His41,
243 His164, Glu166, Gln189, and Gln192. 2-Dimensional and 3-Dimensional interaction
244 diagrams of the remaining top-10 compounds are given in the Supplementary Materials
245 Figures S4-S12). Glu166 residue was crucial for ligand binding in Ibutamoren, which is
246 selective ghrelin receptor and a growth hormone secretagogue agonist, and this
247 interaction is sustained throughout the simulations. (Figure S4) Corresponding residues
248 were His41, Glu166, Asp187, and Gln189 in Atevirdine which is studied in the treatment
249 of HIV. (Figure S5) Figure S6 shows binding mode of another identified hit compound
250 Ambamustine an antineoplastic agent. A selective PDE3 inhibitor Cilostamide showed a
251 dramatic conformational change during the simulations. Its interactions with Thr24 and
252 Thr25 break off and new contacts are established with Glu166, and Gln189. (Figure S7)
253 Among the identified hit, Tafenoquine, which is an antimalaria drug (Haston et al., 2019)
254 forms residue interactions mainly from Ser46, Glu166, and Gln189. (Figure S8)
255 Montirelin is a thyrotropin releasing hormone analog (Sugimoto et al. 1996) constructs
256 crucial interactions with Thr26, Cys44, and Glu166. (Figure S9) Ritonavir was also found

as hit compound among identified molecules. Its interactions mainly form from Thr26, Ser46, Tyr118, and Glu166. (Figure S10) Corresponding main contacts were from Met49, Asn142, Gly143, Glu166, and Gln189 for Amlodipine which is calcium channel blocker. (Figure S11) The importance of hydrogen bonding in ligand binding cannot be overstated. Because of their considerable influence on drug selectivity, metabolism, and adsorption, hydrogen-bonding properties should be considered in drug design. Compounds Ambamustine, Cefuroxime axetil, Cefuroxime pivoxetil and Ateviridine maintain hydrogen bonding interactions with Gln189 throughout the 100 ns MD simulations. (Figure 3, and Supplementary Figures S5, S6, S12)

In geriatric patients admitted with SARS-CoV-2 infection, amlodipine, which is a dihydropyridine calcium channel blocker, was found to be related with significantly lower mortality and a lower probability of intubation and mechanical breathing (Solaimanzadeh 2020). Ateviridine, as the name implies, acts as an antiviral agent by inhibiting non-nucleoside reverse transcriptase (Reichman et al., 1995) Construction of hydrogen bonds with crucial residue Glu166 at the SARS-CoV-2 M^{pro} and compounds Ambamustine, Amlodipine, Cefuroxime pivoxetil, Cefuroxime axetil, Ibutamoren, Montirelin and Ritonavir must be also highlighted (Figures S2-S11). Notably, Ibutamoren, an agonist of the growth hormone secretagogue receptor, has also been reported as having antiviral activity against Ebola virus-like particles (Yoon et al., 2020). Treatment with Ritonavir or Ritonavir in combination with Lopinavir against hospitalized SARS-CoV-2 patients, however, resulted in no significant effect in clinical improvement, mortality rates or decrease in SARS-CoV-2 viral RNA levels (Dalerba et al., 2020; Horby

et al., 2020). Furthermore, hydrophobic interactions were assembled between His41 and Ateverdine and between Tyr118 and Montirelin.

4. Conclusions

The reported study focuses on the binary QSAR screening of the FDA library of approved and under clinical investigation compounds for potential antiviral drug candidates against the SARS-CoV-2 Main protease by drug repurposing. Initial filtering of potential antiviral compounds using the therapeutic activity binary QSAR models available in the MetaCore™/MetaDrug™ platform aimed to pick only use molecules with potential antiviral activity, which would hamper virus development. Our screen yielded 370 compounds among the 6733-compound library, having normalized therapeutic activity value over the cutoff of 0.75. These 370 compounds were docked to SARS-CoV-2 M^{pro} and the top-50 scoring complexes were subjected to short 10 ns MD simulations. The MD simulations were followed by MM/GBSA calculations and the 10-top complexes with best average MM/GBSA scores were simulated for 100 ns and average MM/GBSA scores were calculated from their trajectories. End-point energy calculations from MD simulations revealed Cefuroxime pivoxil, second-generation cephalosporin antibiotic, as being a considerable compound for drug repurposing against the SARS-CoV-2 M^{pro}.

References

Ahmed MZ, Zia Q, Haque A, Alqahtani AS, Almarfadi OM, Banawas S, Alqahtani MS, Ameta KL, Haque S. (2021). Aminoglycosides as potential inhibitors of SARS-CoV-2

304 main protease: an in silico drug repurposing study on FDA-approved antiviral and anti-
 305 infection agents. *Journal of Infection and Public Health*. 14(5):611–619.
 306 doi:10.1016/j.jiph.2021.01.016.

307 Akhoun BA, Tiwari H, Nargotra A. (2019). In Silico Drug Design Methods for Drug
 308 Repurposing. In: *In Silico Drug Design*. Elsevier. p. 47–84. [accessed 2021 Jun 23].
 309 <https://linkinghub.elsevier.com/retrieve/pii/B9780128161258000031>.

310 Behnam MAM. (2021). Protein structural heterogeneity: A hypothesis for the basis of
 311 proteolytic recognition by the main protease of SARS-CoV and SARS-CoV-2.
 312 *Biochimie*. 182:177–184. doi:10.1016/j.biochi.2021.01.010.

313 Chen Y, Liu Q, Guo D. (2020). Emerging coronaviruses: Genome structure, replication,
 314 and pathogenesis. *J Med Virol*. 92(4):418–423. doi:10.1002/jmv.25681.

315 Dalerba P, Levin B, Thompson JL. (2020). A Trial of Lopinavir-Ritonavir in Covid-19.
 316 *The New England journal of medicine*. 382 (21).

317 Dogan B, Durdagi S. (2020). Drug Re-Positioning Studies for Novel HIV-1 Inhibitors
 318 Using Binary QSAR Models and Multi-Target-Driven *In Silico* Studies. *Mol*
 319 *Inf.:minf*.202000012. doi:10.1002/minf.202000012.

320 Dong L, Tian J, He S, Zhu C, Wang J, Liu C, Yang J. (2020). Possible Vertical
 321 Transmission of SARS-CoV-2 From an Infected Mother to Her Newborn. *JAMA*.
 322 doi:10.1001/jama.2020.4621. [accessed 2021 Jun 23].
 323 <https://jamanetwork.com/journals/jama/fullarticle/2763853>.

324 Durdağı S. (2020) Virtual drug repurposing study against SARS-CoV-2 TMPRSS2
 325 target. Turk. J. Biol. 44: 185-191.
 326

327 Durdagi S, Aksoydan B, Dogan B, Sahin K, Shahraki A. (2020). Screening of Clinically
 328 Approved and Investigation Drugs as Potential Inhibitors of COVID-19 Main Protease:
 329 A Virtual Drug Repurposing Study. [accessed 2020 Dec 8].
 330 [https://chemrxiv.org/articles/Screening_of_Clinically_Approved_and_Investigation_Dr](https://chemrxiv.org/articles/Screening_of_Clinically_Approved_and_Investigation_Drugs_as_Potential_Inhibitors_of_COVID-19_Main_Protease_A_Virtual_Drug_Repurposing_Study/12032712/1)
 331 [ugs_as_Potential_Inhibitors_of_COVID-](https://chemrxiv.org/articles/Screening_of_Clinically_Approved_and_Investigation_Drugs_as_Potential_Inhibitors_of_COVID-19_Main_Protease_A_Virtual_Drug_Repurposing_Study/12032712/1)
 332 [19_Main_Protease_A_Virtual_Drug_Repurposing_Study/12032712/1](https://chemrxiv.org/articles/Screening_of_Clinically_Approved_and_Investigation_Drugs_as_Potential_Inhibitors_of_COVID-19_Main_Protease_A_Virtual_Drug_Repurposing_Study/12032712/1).

333 Erben Y, Franco-Mesa C, Gloviczki P, Stone W, Quinones-Hinojoas A, Meltzer AJ, Lin
 334 M, Greenway MRF, Hamid O, Devcic Z, et al. (2021). Deep vein thrombosis and
 335 pulmonary embolism among hospitalized coronavirus disease 2019–positive patients
 336 predicted for higher mortality and prolonged intensive care unit and hospital stays in a
 337 multisite healthcare system. Journal of Vascular Surgery: Venous and Lymphatic
 338 Disorders.:S2213333X2100175X. doi:10.1016/j.jvsv.2021.03.009.

339 Ghosh AK, Brindisi M, Shahabi D, Chapman ME, Mesecar AD. (2020). Drug
 340 Development and Medicinal Chemistry Efforts toward SARS-Coronavirus and Covid-19
 341 Therapeutics. ChemMedChem. 15(11):907–932. doi:10.1002/cmdc.202000223.

342 Guedes IA, Costa LSC, dos Santos KB, Karl ALM, Rocha GK, Teixeira IM, Galheigo
 343 MM, Medeiros V, Krempser E, Custódio FL, et al. (2021). Drug design and repurposing
 344 with DockThor-VS web server focusing on SARS-CoV-2 therapeutic targets and their
 345 non-synonym variants. Scientific Reports. 11(1):5543. doi:10.1038/s41598-021-84700-
 346 0.

347 Han YJ, Lee KH, Yoon S, Nam SW, Ryu S, Seong D, Kim JS, Lee JY, Yang JW, Lee
 348 JH, et al. (2021). Treatment of severe acute respiratory syndrome (SARS), Middle East
 349 respiratory syndrome (MERS), and coronavirus disease 2019 (COVID-19): a systematic
 350 review of *in vitro* , *in vivo* , and clinical trials. *Theranostics*. 11(3):1207–1231.
 351 doi:10.7150/thno.48342.

352 Haston JC, Hwang J, Tan KR. (2019). Guidance for Using Tafenoquine for Prevention
 353 and Antirelapse Therapy for Malaria — United States, 2019. *MMWR Morb Mortal Wkly*
 354 *Rep*. 68(46):1062–1068. doi:10.15585/mmwr.mm6846a4.

355 Horby PW, Mafham M, Bell JL, Linsell L, Staplin N, Emberson J, Palfreeman A, Raw J,
 356 Elmahi E, Prudon B, et al. (2020). Lopinavir–ritonavir in patients admitted to hospital
 357 with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *The*
 358 *Lancet*. 396(10259):1345–1352.

359 Kanan D, Kanan T, Dogan B, Orhan MD, Avsar T, Durdagi S. (2021). An Integrated in
 360 silico Approach and in vitro Study for the Discovery of Small-Molecule USP7 Inhibitors
 361 as Potential Cancer Therapies. *ChemMedChem*. 16(3):555–567.
 362 doi:10.1002/cmdc.202000675.

363 Kirtipal N, Bharadwaj S, Kang SG. (2020). From SARS to SARS-CoV-2, insights on
 364 structure, pathogenicity and immunity aspects of pandemic human coronaviruses.
 365 *Infection, Genetics and Evolution*. 85:104502. doi:10.1016/j.meegid.2020.104502.

366 Molavi Z, Razi S, Mirmotalebisohi SA, Adibi A, Sameni M, Karami F, Niazi V, Niknam
 367 Z, Aliashrafi M, Taheri M, et al. (2021). Identification of FDA approved drugs against
 368 SARS-CoV-2 RNA dependent RNA polymerase (RdRp) and 3-chymotrypsin-like

369 protease (3CLpro), drug repurposing approach. *Biomedicine & Pharmacotherapy*.
 370 138:111544. doi:10.1016/j.biopha.2021.111544.

371 Potere N, Valeriani E, Candeloro M, Tana M, Porreca E, Abbate A, Spoto S, Rutjes AWS,
 372 Di Nisio M. (2020). Acute complications and mortality in hospitalized patients with
 373 coronavirus disease 2019: a systematic review and meta-analysis. *Crit Care*. 24(1):389.
 374 doi:10.1186/s13054-020-03022-1.

375 Reichman RC, Morse GD, Demeter LM, Resnick L, Bassiakos Y, Fischl M, Para M,
 376 Powderly W, Leedom J, Greisberger C, et al. (1995). Phase I study of atevirdine, a
 377 nonnucleoside reverse transcriptase inhibitor, in combination with zidovudine for human
 378 immunodeficiency virus type 1 infection. *Journal of Infectious Diseases*. 171(2):297–
 379 304.

380 Rothan HA, Teoh TC. (2021). Cell-Based High-Throughput Screening Protocol for
 381 Discovering Antiviral Inhibitors Against SARS-COV-2 Main Protease (3CLpro). *Mol*
 382 *Biotechnol*. 63(3):240–248. doi:10.1007/s12033-021-00299-7.

383 Ruano-Gallego D, García-Villadangos M, Moreno-Paz M, Gómez-Elvira J, Postigo M,
 384 Simón-Sacristán M, Reyburn HT, Carolis C, Rodrigo N, Codeseira YB, et al. (2021). A
 385 multiplex antigen microarray for simultaneous IgG and IgM detection against SARS-
 386 CoV-2 reveals higher seroprevalence than reported. *Microb Biotechnol*. 14(3):1228–
 387 1236. doi:10.1111/1751-7915.13801.

388 Scott LJ, Ormrod D, Goa KL. (2001). Cefuroxime axetil: an updated review of its use in
 389 the management of bacterial infections. *Drugs*. 61(10):1455–1500.
 390 doi:10.2165/00003495-200161100-00008.

391 Shitrit A, Zaidman D, Kalid O, Bloch I, Doron D, Yarnizky T, Buch I, Segev I, Ben-Zeev
 392 E, Segev E, et al. (2020). Conserved interactions required for inhibition of the main
 393 protease of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Sci Rep.*
 394 10(1):20808. doi:10.1038/s41598-020-77794-5.

395 Silvestrini L, Belhaj N, Comez L, Gerelli Y, Lauria A, Libera V, Mariani P, Marzullo P,
 396 Ortore MG, Palumbo Piccionello A, et al. (2021). The dimer-monomer equilibrium of
 397 SARS-CoV-2 main protease is affected by small molecule inhibitors. *Sci Rep.*
 398 11(1):9283. doi:10.1038/s41598-021-88630-9.

399 Singh R, Gautam A, Chandel S, Sharma V, Ghosh A, Dey D, Roy S, Ravichandiran V,
 400 Ghosh D. (2021). Computational screening of FDA approved drugs of fungal origin that
 401 may interfere with SARS-CoV-2 spike protein activation, viral RNA replication, and
 402 post-translational modification: a multiple target approach. *In Silico Pharmacol.* 9(1):27.
 403 doi:10.1007/s40203-021-00089-8.

404 Solaimanzadeh I. (2020). Nifedipine and Amlodipine Are Associated With Improved
 405 Mortality and Decreased Risk for Intubation and Mechanical Ventilation in Elderly
 406 Patients Hospitalized for COVID-19. *Cureus.* doi:10.7759/cureus.8069. [accessed 2021
 407 Jun 24]. [https://www.cureus.com/articles/31377-nifedipine-and-amlodipine-are-](https://www.cureus.com/articles/31377-nifedipine-and-amlodipine-are-associated-with-improved-mortality-and-decreased-risk-for-intubation-and-mechanical-ventilation-in-elderly-patients-hospitalized-for-covid-19)
 408 [associated-with-improved-mortality-and-decreased-risk-for-intubation-and-mechanical-](https://www.cureus.com/articles/31377-nifedipine-and-amlodipine-are-associated-with-improved-mortality-and-decreased-risk-for-intubation-and-mechanical-ventilation-in-elderly-patients-hospitalized-for-covid-19)
 409 [ventilation-in-elderly-patients-hospitalized-for-covid-19.](https://www.cureus.com/articles/31377-nifedipine-and-amlodipine-are-associated-with-improved-mortality-and-decreased-risk-for-intubation-and-mechanical-ventilation-in-elderly-patients-hospitalized-for-covid-19)

410 Sugimoto T, Hayashi T, Okita A, Morino A. (1996). Pharmacokinetics of the new
 411 thyrotropin releasing hormone analogue montirelin hydrate. 3rd communication:
 412 identification of metabolites in rat urine. *Arzneimittel-forschung.* 46(2):127–133.

413 Tutumlu G, Dogan B, Avsar T, Orhan MD, Calis S, Durdagi S. (2020). Integrating Ligand
414 and Target-Driven Based Virtual Screening Approaches With in vitro Human Cell Line
415 Models and Time-Resolved Fluorescence Resonance Energy Transfer Assay to Identify
416 Novel Hit Compounds Against BCL-2. Front Chem. 8:167.
417 doi:10.3389/fchem.2020.00167.

418 Wu Y, Ho W, Huang Y, Jin D-Y, Li S, Liu S-L, Liu X, Qiu J, Sang Y, Wang Q, et al.
419 (2020). SARS-CoV-2 is an appropriate name for the new coronavirus. The Lancet.
420 395(10228):949–950. doi:10.1016/S0140-6736(20)30557-2.

421 Yoon Y-S, Jang Y, Hoenen T, Shin H, Lee Y, Kim M. (2020). Antiviral activity of
422 sertindole, raloxifene and ibutamoren against transcription and replication-competent
423 Ebola virus-like particles. BMB reports. 53(3):166.

424 Yoshino R, Yasuo N, Sekijima M. (2020). Identification of key interactions between
425 SARS-CoV-2 main protease and inhibitor drug candidates. Sci Rep. 10(1):12493.
426 doi:10.1038/s41598-020-69337-9.

427 Zhang L, Lin D, Sun X, Curth U, Drosten C, Sauerhering L, Becker S, Rox K, Hilgenfeld
428 R. (2020). Crystal structure of SARS-CoV-2 main protease provides a basis for design of
429 improved α -ketoamide inhibitors. Science. 368(6489):409–412.
430 doi:10.1126/science.abb3405.

431

432

433

434

Figure 1. Histogram of therapeutic activity predictions from the MetaCore™/MetaDrug™ anti-viral QSAR model for all 6733 compounds.

439

440

441 **Figure 2.** MM/GBSA score Box and Whisker plots for the selected top-10 compounds.

442 MM/GBSA scores of 100 frames extracted from 100 ns simulations trajectories was

443 considered.

444

445

446

447

448

449

450

451

452

453

454

455

456

457

A

B

C

Figure 3. (A) 3D representation of the Cefuroxime Pivoxetil at binding site. The average frame from 100 ns trajectory was used. (B) 2D interaction diagram of Cefuroxime Pivoxetil at M^{pro} binding site with residues around 3 Angstrom. (C) Time-dependent protein-ligand contact panel throughout 100 ns simulation. Top-panel shows total contacts, while bottom-panel shows formed/broken interaction between the protein and ligand.

474 **Table 1.** Docking scores of top-10 compounds at the M^{pro} binding site. These compounds
 475 were initially used in short (10-ns) MD simulations. Table also shows average
 476 MM/GBSA scores of these compounds from derived 100-trajectories throughout the
 477 simulations. Prediction of antiviral therapeutic activity for the selected hit molecules
 478 using MetaCoreTM/MetaDrugTM was also reported in the table. Values in parenthesis -
 479 Tanimato Prioritization (TP) - indicates similarity of the analyzed structure to the most
 480 similar compound in the training set.

Compound Name	Glide/SP Docking Score (kcal/mol)	AntiViral (TP)	10 ns		100 ns	
			MM/GBSA (kcal/mol)	SD	MM/GBSA (kcal/mol)	SD
Ibutamoren	-7.27	0.85 (49.84)	-80.07	7.34	-59.77	12.75
Cefuroxime pivoxetil	-7.42	0.79 (33.60)	-74.63	7.88	-75.08	7.31
Cefuroxime axetil	-7.60	0.79 (33.27)	-63.80	5.62	-58.40	7.15
Ambamustine	-7.23	0.79 (58.30)	-61.89	9.00	-69.17	11.52
Montirelin	-7.47	0.75 (54.38)	-59.39	3.60	-49.88	6.36
Atevirdine	-6.35	0.75 (100.00)	-58.09	4.82	-56.93	5.99

Ritonavir	-6.37	0.79 (100.00)	-54.38	11.18	-51.97	9.37
Cilostamidum	-6.45	0.77 (39.83)	-53.68	4.80	-52.13	4.76
Amlodipine	-6.60	0.78 (34.10)	-53.63	4.63	-43.80	10.42
Tafenoquine	-6.66	0.83 (40.28)	-53.40	4.98	-49.60	6.73

481

482

483

484

485

486

487

488

489

490

491

492

493

494

495

496

497 **Table 2.** Docking scores of top-50 compounds at the M^{pro} binding site. These compounds
 498 were initially used in short (10 ns) MD simulations. Table also shows average MM/GBSA
 499 scores of these compounds from derived 100-trajectories throughout the simulations.
 500 Prediction of antiviral therapeutic activity for the selected hit molecules using
 501 MetaCoreTM/MetaDrugTM was also reported in the table. Values in parenthesis - Tanimato
 502 Prioritization (TP) - indicates similarity of the analyzed structure to the most similar
 503 compound in the training set.

Compound Name	Glide/SP Docking Score (kcal/mol)	Viral (TP)	10 ns	
			MM/GBSA (kcal/mol)	SD
Ibutamoren	-7.27	0.85 (49.84)	-80.07	7.34
Cefuroxime pivoxetil	-7.42	0.79 (33.60)	-74.63	7.88
Cefuroxime axetil	-7.60	0.79 (33.27)	-63.80	5.62
Ambamustine	-7.23	0.79 (58.30)	-61.89	9.00
Montirelin	-7.47	0.75 (54.38)	-59.39	3.60
Atevirdine	-6.35	0.75 (100.00)	-58.09	4.82
Ritonavir	-6.37	0.79 (100.00)	-54.38	11.18

Cilostamide	-6.45	0.77 (39.83)	-53.68	4.80
Amlodipine	-6.60	0.78 (34.10)	-53.63	4.63
Tafenoquine	-6.66	0.83 (40.28)	-53.40	4.98
Regadenoson	-6.47	0.88 (71.08)	-52.93	7.22
Opanixilum	-6.70	0.77 (48.40)	-51.07	4.45
Cefsumide	-6.98	0.80 (35.26)	-49.70	3.26
Cephaloglycin	-6.47	0.79 (38.26)	-48.96	7.75
Cefdinir	-6.44	0.75 (35.16)	-48.30	4.74
Triciribine	-6.39	0.91 (70.24)	-48.20	5.17
Piritrexim	-6.41	0.81 (37.67)	-47.16	5.65
Acadesine	-6.63	0.98 (60.38)	-47.12	3.95
Glibutimine	-6.41	0.80 (34.67)	-44.01	9.47

Loxoribine	-6.80	0.89 (64.73)	-42.87	5.89
Decitabine	-6.59	0.94 (72.83)	-42.46	5.70
Amdoxovir	-6.60	0.95 (100.00)	-40.80	5.80
Acrinol	-6.80	0.86 (34.88)	-40.44	6.46
Fludarabine	-6.36	0.91 (78.16)	-40.28	5.55
Tiamiprine	-6.84	0.79 (46.23)	-39.09	4.09
Penciclovir	-6.45	0.99 (100.00)	-38.81	4.82
Sulfacitine	-6.39	0.76 (40.00)	-36.94	5.66
Tiazofurine	-6.65	0.89 (37.20)	-36.46	6.67
Ampyrimine phosphate	-6.49	0.84 (38.79)	-36.08	3.29
Edoxudine	-6.81	0.99 (100.00)	-35.99	5.73
Omaciclovir	-6.42	0.99 (93.33)	-35.92	6.36

Clevudine	-6.57	0.98 (100.00)	-35.64	4.88
Floxuridine	-6.56	0.99 (100.00)	-33.97	9.89
Fluorocytidine	-7.35	0.95 (52.00)	-33.71	9.02
Mitoxantrone	-6.54	0.82 (33.33)	-33.68	9.73
Ancitidine	-6.42	0.95 (52.08)	-33.24	8.14
Zidovudine	-6.40	0.99 (100.00)	-32.65	4.48
Nelarabine	-6.38	0.95 (75.00)	-32.52	5.69
Entecavir	-6.86	0.99 (100.00)	-30.53	7.43
Inosine	-6.43	0.90 (87.50)	-30.51	6.10
Mitomycin	-7.40	0.85 (35.99)	-30.26	7.36
Clofarabine	-7.25	0.93 (87.45)	-29.92	13.01
Ly 163502	-6.46	0.85 (47.51)	-29.78	3.66

Gemcitabine	-6.38	0.99 (86.50)	-28.71	8.21
Mizoribine	-6.39	0.98 (55.80)	-26.26	5.26
Temodar	-6.61	0.80 (34.93)	-23.88	9.46
Navuridine	-6.38	0.99 (91.74)	-21.89	5.10
Ribavirin	-6.59	0.89 (100.00)	-20.08	13.37
Dametralast	-6.66	0.83 (37.91)	-17.46	5.51
6-Methoxy-1h-Purin-2-Ylamine	-6.51	0.80 (53.89)	-13.49	6.45

504

505

506

507

508

509

510

511

512

513

Supplementary Materials

Table S1. MetaCore™/MetaDrug™ results of therapeutic activity prediction for the screened compounds which have normalized activity value of 0.75 or higher along with Glide/SP docking scores.

Compound Name	Glide/SP Docking Score (kcal/mol)	AntiViral (TP)
Cefuroxime axetil	-7.60	0.79 (33.27)
Montirelin	-7.47	0.75 (54.38)
Cefuroxime pivoxetil	-7.42	0.79 (33.60)
Mitomycin	-7.40	0.85 (35.99)
Fluorocitabine	-7.35	0.95 (52.00)
Ibutamoren	-7.27	0.85 (49.84)
clofarabine	-7.25	0.93 (87.45)
Ambamustine	-7.23	0.79 (58.30)
Cefsumide	-6.98	0.80 (35.26)
Entecavir	-6.86	0.99 (100.00)
Tiamiprine	-6.84	0.79 (46.23)
Edoxudine	-6.81	0.99 (100.00)
Loxoribine	-6.80	0.89 (64.73)
Acrinol	-6.80	0.86 (34.88)
Opanixilum	-6.70	0.77 (48.40)

Compound Name	Glide/SP Docking Score (kcal/mol)	AntiViral (TP)
Dametralast	-6.66	0.83 (37.91)
Tafenoquine	-6.66	0.83 (40.28)
Tiazofurine	-6.65	0.89 (37.20)
acadesine	-6.63	0.98 (60.38)
Temodar	-6.61	0.80 (34.93)
Amdoxovir	-6.60	0.95 (100.00)
Amlodipine	-6.60	0.78 (34.10)
decitabine	-6.59	0.94 (72.83)
Ribavirin	-6.59	0.89 (100.00)
Clevudine	-6.57	0.98 (100.00)
Floxuridine	-6.56	0.99 (100.00)
Mitozolomide	-6.54	0.82 (33.33)
6-Methoxy-1h-purin-2-ylamine	-6.51	0.80 (53.89)
Ampyrimine phosphate	-6.49	0.84 (38.79)
Regadenoson	-6.47	0.88 (71.08)
Cephaloglycin	-6.47	0.79 (38.26)
Ly 163502	-6.46	0.85 (47.51)

Compound Name	Glide/SP Docking Score (kcal/mol)	AntiViral (TP)
Penciclovir	-6.45	0.99 (100.00)
Cilostamidum	-6.45	0.77 (39.83)
Cefdinir	-6.44	0.75 (35.16)
Inosine	-6.43	0.90 (87.50)
Ancitabine	-6.42	0.95 (52.08)
Omaciclovir	-6.42	0.99 (93.33)
Piritrexim	-6.41	0.81 (37.67)
Glibutimine	-6.41	0.80 (34.67)
Zidovudine	-6.40	0.99 (100.00)
Triciribine	-6.39	0.91 (70.24)
Mizoribine	-6.39	0.98 (55.80)
Sulfacitine	-6.39	0.76 (40.00)
Navuridine	-6.38	0.99 (91.74)
Gemcitabine	-6.38	0.99 (86.50)
nelarabine	-6.38	0.95 (75.00)
ritonavir	-6.37	0.79 (100.00)
Fludarabine	-6.36	0.91 (78.16)

Compound Name	Glide/SP Docking Score (kcal/mol)	AntiViral (TP)
Atevirdine	-6.35	0.75 (100.00)
cladribine	-6.33	0.93 (87.27)
Lobucavir	-6.32	0.99 (84.15)
Leminoprazole	-6.32	0.76 (32.70)
Netivudine	-6.31	0.99 (100.00)
peldesine	-6.31	0.76 (45.45)
Vidarabine_1	-6.30	0.91 (85.71)
Isatoribine	-6.30	0.98 (52.48)
Arabinosylthymine	-6.28	0.98 (93.27)
telbivudine	-6.28	0.99 (100.00)
Alovudine	-6.27	0.99 (100.00)
azacitidine	-6.26	0.94 (69.39)
Batracylin	-6.26	0.76 (34.89)
Buciclovir	-6.25	0.99 (100.00)
Tanaprogetum	-6.24	0.87 (36.88)
Sapropterin	-6.23	0.81 (49.21)
Rabeprazole	-6.22	0.79 (29.94)

Compound Name	Glide/SP Docking Score (kcal/mol)	AntiViral (TP)
Uk-52,046	-6.20	0.80 (47.79)
Etryptamine	-6.20	0.77 (36.88)
Azepexolum	-6.17	0.84 (24.77)
Binodenoson	-6.16	0.78 (80.00)
7-Amino-cephalosporanic acid	-6.16	0.75 (31.33)
Azelnidipine	-6.15	0.75 (34.26)
Milacainide	-6.15	0.76 (44.91)
Mioflazinum	-6.15	0.75 (46.93)
Capromorelin	-6.14	0.75 (50.59)
Dacopafant	-6.14	0.78 (31.79)
Monophosphothiamine	-6.14	0.85 (28.72)
Cycotiamine	-6.13	0.83 (29.58)
Protionamidum	-6.11	0.77 (29.88)
emtricitabine	-6.11	0.99 (62.50)
Cytarabine	-6.10	0.99 (92.97)
Amprolio	-6.06	0.88 (40.11)
Cefadroxil	-6.06	0.76 (36.90)
Triamterene	-6.06	0.84 (40.16)
Cefoxitin	-6.05	0.79 (34.69)
Cipamfylline	-6.05	0.91 (100.00)

Compound Name	Glide/SP Docking Score (kcal/mol)	AntiViral (TP)
Aditoprim	-6.05	0.76 (43.11)
Enviradene	-6.04	0.89 (100.00)
lansoprazole	-6.04	0.78 (29.58)
Evandamine	-6.03	0.83 (29.28)
Euprocine	-6.03	0.75 (49.44)
Tioguanine	-6.02	0.81 (44.52)
Cefradine	-6.01	0.77 (36.09)
Fialuridine	-6.01	0.98 (100.00)
Etricitrat	-6.00	0.80 (35.21)
Adenosine_1	-6.00	0.91 (83.88)
(+/-)-5-(.Alpha.-imidazol-1-ylbenzyl)-2-methylbenzimidazole	-6.00	0.76 (41.90)
Raluridine	-5.99	0.99 (100.00)
Resiquimod	-5.99	0.83 (70.98)
Chloroethyl thiamine	-5.98	0.84 (30.00)
Ethyl loflazepate	-5.97	0.88 (38.11)
Cifostodine	-5.96	0.99 (69.64)
Coccarboxylase	-5.95	0.85 (33.16)

Compound Name	Glide/SP Docking Score (kcal/mol)	AntiViral (TP)
Airomate	-5.93	0.87 (38.70)
Lamivudine_1	-5.93	0.76 (100.00)
alprazolam	-5.93	0.75 (31.71)
Ecenofloxacin	-5.93	0.80 (38.51)
Rocepagant	-5.93	0.76 (34.89)
Ethyl dirazepate	-5.92	0.88 (31.20)
Zalcitabine	-5.92	0.99 (100.00)
N-cyclopropylmelamine	-5.92	0.76 (24.22)
Diaveridine	-5.91	0.75 (47.48)
zaleplon	-5.91	0.83 (34.33)
Torcitabine	-5.90	0.99 (100.00)
Girodazole	-5.90	0.77 (30.17)
Oseltamivir	-5.90	0.81 (47.24)
Famciclovir	-5.89	0.99 (100.00)
Cefetamet	-5.88	0.76 (35.04)
Tomeglovir	-5.87	0.82 (100.00)
Acetiamine	-5.87	0.82 (29.03)

Compound Name	Glide/SP Docking Score (kcal/mol)	AntiViral (TP)
Cefoxazole	-5.87	0.77 (38.05)
Brivudine	-5.87	0.99 (100.00)
Arpocox	-5.87	0.77 (56.63)
Emorfazone	-5.87	0.82 (34.38)
Pirolate	-5.87	0.75 (38.36)
Trimetrexate	-5.87	0.88 (41.02)
Enecadinum	-5.87	0.80 (33.33)
N acetyl d galactosamin	-5.86	0.77 (69.14)
Nolatrexed	-5.86	0.79 (35.38)
Azalanstat	-5.85	0.75 (37.96)
abacavir	-5.85	0.94 (100.00)
Pancopride	-5.85	0.80 (48.21)
Sr 57227a	-5.85	0.75 (38.46)
Cns-1102	-5.85	0.86 (30.51)
Colfenamate	-5.85	0.77 (34.12)
Epiroprim	-5.84	0.87 (39.51)
Isoprazone	-5.84	0.75 (34.39)
Sorivudine	-5.84	0.99 (100.00)

Compound Name	Glide/SP Docking Score (kcal/mol)	AntiViral (TP)
Esafloxacin	-5.84	0.75 (36.65)
Lenampicillin_1	-5.83	0.76 (41.23)
ganciclovir	-5.82	0.98 (100.00)
Lemildipine	-5.82	0.81 (35.02)
Metioprim	-5.82	0.78 (39.19)
2-Amino-6-chloropurine	-5.82	0.79 (44.37)
Mepacrine	-5.82	0.75 (45.41)
Ibacinabine	-5.81	0.99 (100.00)
valganciclovir	-5.81	0.96 (78.50)
Triazolam	-5.81	0.75 (31.10)
Tezacitabine	-5.81	0.99 (77.13)
Nsc-98700	-5.80	0.95 (87.75)
Trimethoprim	-5.80	0.75 (45.83)
Tiquinamide	-5.80	0.77 (37.19)
Epervudine	-5.79	0.99 (100.00)
Nsc-4911	-5.76	0.81 (82.33)
Fradafiban	-5.76	0.75 (47.96)

Compound Name	Glide/SP Docking Score (kcal/mol)	AntiViral (TP)
Maribavir	-5.75	0.91 (100.00)
Vintiamol	-5.75	0.78 (32.67)
Cefalexin	-5.74	0.77 (37.85)
Amoxicillin	-5.74	0.78 (45.24)
4-(4-Fluorobenzoyl)pyridinium p- toluenesulfonate 4-fluorobenzyl-1h- benzimidazol-2-ylamine	-5.74	0.82 (42.35)
Xenazoic acid	-5.73	0.86 (100.00)
4-Nitrobenzyl 6-(2- phenoxyacetamido)penicillanate 1-oxide	-5.73	0.77 (38.10)
Lodenosine	-5.73	0.95 (100.00)
Clavulanic acid	-5.73	0.77 (35.83)
Ethoxazolamide	-5.72	0.76 (25.85)
Sulfadimethoxine	-5.72	0.75 (38.96)
Zaltidine	-5.72	0.83 (34.19)
valaciclovir	-5.71	0.96 (78.42)
6-Amino-5-formamido-1,3-dimethyluracil	-5.71	0.75 (38.50)
Lenampicillin	-5.70	0.76 (41.23)

Compound Name	Glide/SP Docking Score (kcal/mol)	AntiViral (TP)
Adenosine	-5.70	0.95 (100.00)
Spirgetine	-5.69	0.76 (36.67)
bropirimine	-5.69	0.75 (30.84)
Trifluridine	-5.68	0.99 (100.00)
Talviraline	-5.68	0.80 (100.00)
Tenatoprazole	-5.65	0.76 (31.70)
Aciclovir	-5.65	0.98 (100.00)
Disuprazole	-5.64	0.79 (31.09)
Tetroxoprim	-5.64	0.75 (42.14)
Adenosine cyclic 3',5'-phosphate	-5.64	0.91 (85.71)
Ronidazole	-5.64	0.83 (27.08)
Fenacetinol	-5.64	0.75 (50.85)
Iclaprim	-5.64	0.75 (36.51)
Stavudine	-5.63	0.97 (100.00)
Brecanavir	-5.62	0.79 (100.00)

Compound Name	Glide/SP Docking Score (kcal/mol)	AntiViral (TP)
Etravirine	-5.62	0.92 (100.00)
Stibamini glucosidum	-5.61	0.76 (39.56)
Cefpodoxime	-5.60	0.81 (35.07)
B 4, vitamini	-5.60	0.76 (47.26)
Benzyl (1-carbamoyl-2-hydroxypropyl)carbamate	-5.60	0.83 (38.83)
Tegafur	-5.60	0.88 (81.91)
4-Amino-neu5ac2en	-5.59	0.92 (89.00)
Opavirine	-5.59	0.83 (100.00)
Sc-33643	-5.58	0.94 (36.68)
Mosapride	-5.57	0.85 (41.11)
Didanosine	-5.57	0.93 (100.00)
Pyrimidine, 4-methoxy-2-(5-methoxy-3-methyl-1H-pyrazol-1-yl)-6-methyl-	-5.55	0.84 (32.63)
Epetirimoxyloside	-5.55	0.93 (82.76)
Imatinib	-5.54	0.79 (47.29)
Emivirine	-5.54	0.93 (100.00)
Fursultiamine	-5.54	0.77 (28.38)

Compound Name	Glide/SP Docking Score (kcal/mol)	AntiViral (TP)
Ormetoprim	-5.53	0.79 (45.21)
Pleconaril	-5.53	0.83 (100.00)
Idoxuridine	-5.52	0.99 (77.63)
Cefuroxime pivoxetil	-5.51	0.80 (33.33)
Lirexapride	-5.51	0.78 (45.61)
Pyrazinamidum	-5.51	0.75 (25.12)
Darunavir	-5.51	0.84 (87.90)
Lamotrigine	-5.50	0.76 (51.87)
Tolonium	-5.50	0.76 (25.00)
Amprenavir	-5.49	0.96 (100.00)
Imexon	-5.47	0.79 (22.29)
Adefovir	-5.46	0.96 (100.00)
Isotiquimide	-5.45	0.78 (37.37)
epinastine	-5.45	0.81 (36.59)
Quinazosin	-5.45	0.80 (53.48)
Lomeguatribum	-5.45	0.91 (40.91)
1-(α -D-arabinofuranosyl)pyrimidine- 2,4(1h,3h)-dione	-5.42	0.97 (84.30)

Compound Name	Glide/SP Docking Score (kcal/mol)	AntiViral (TP)
Roxifiban	-5.42	0.75 (47.06)
Troxacitabine	-5.42	0.99 (61.34)
(S)-tetrahydro-3-furyl (m-(3-(3-methoxy-4-(5-oxazolyl)phenyl)ureido)benzyl)carbamate	-5.41	0.77 (100.00)
Pentisomide	-5.41	0.75 (53.08)
6-Chloro-2-ethylamino-4-methyl-4-phenyl-4h-3,1-benzoxazine hydrochloride	-5.40	0.81 (42.80)
Lanoconazole	-5.40	0.75 (28.81)
Aditeren	-5.40	0.76 (44.94)
Pramipexole	-5.38	0.82 (32.40)
Minoxidil	-5.38	0.76 (37.57)
Saprisartan	-5.36	0.84 (32.37)
Loviride	-5.36	0.88 (100.00)
Sch-42495	-5.36	0.80 (53.62)
alfuzosin	-5.35	0.79 (53.88)
Bamnidazole	-5.34	0.84 (33.33)
Azanidazole	-5.34	0.82 (26.15)
Brodimoprim	-5.33	0.78 (43.06)
4H-thiazolo(4,5-d)azepin-2-amine, 5,6,7,8-tetrahydro-6-(2-propenyl)-, dihydrochloride	-5.33	0.82 (27.86)

Compound Name	Glide/SP Docking Score (kcal/mol)	AntiViral (TP)
Cefixime	-5.32	0.84 (35.11)
Sulfacecole	-5.31	0.78 (47.37)
Guanethidine	-5.30	0.76 (44.44)
Orbutopril	-5.29	0.77 (64.14)
Darodipine	-5.29	0.77 (30.72)
Adefovir_1	-5.27	0.95 (100.00)
Nepicastat	-5.27	0.77 (36.40)
Ampicillin	-5.27	0.79 (46.81)
Carbubarb	-5.26	0.81 (68.32)
Freselestat	-5.26	0.78 (32.02)
Vardenafil	-5.25	0.76 (36.72)
Benzoic acid, 4-(acetylamino)-2-ethoxy-, methyl ester	-5.25	0.77 (51.72)
imiquimod	-5.24	0.95 (100.00)
4-Amino-2-chloro-6,7-dimethoxyquinazoline	-5.24	0.78 (46.51)
Batanopride	-5.24	0.76 (44.71)
Vidarabine	-5.23	0.95 (100.00)
5-Methyl-2-(2-nitroanilino)thiophene-3- carbonitrile	-5.22	0.79 (28.08)

Compound Name	Glide/SP Docking Score (kcal/mol)	AntiViral (TP)
Enviroxime	-5.22	0.90 (100.00)
Amanozinum	-5.22	0.77 (43.97)
Cinitapride	-5.21	0.84 (41.71)
Diphenylguanidine	-5.20	0.77 (31.31)
Zanamivir	-5.19	0.97 (84.58)
2-Cyano-3-morpholinoacrylamide	-5.19	0.79 (31.82)
Cefdaloximum	-5.18	0.81 (35.16)
Febuxostat	-5.18	0.81 (35.59)
Guabenxan	-5.18	0.75 (46.26)
Palatrigine hydrochloride	-5.18	0.81 (48.83)
Fiacitabine	-5.18	0.99 (100.00)
Lamivudine	-5.16	0.99 (57.00)
Fludarabine_1	-5.16	0.95 (89.87)
4,6-Diamino-1-(p-chlorophenyl)-1,2-dihydro- 2,2-dimethyl-s-triazine salt of 4,4'-methylene- bis(3-hydroxy-2-naphthoic acid)	-5.15	0.78 (26.11)
Metahexamide	-5.15	0.78 (39.46)
Epicillin	-5.15	0.79 (41.42)
Luliconazole	-5.15	0.75 (28.99)

Compound Name	Glide/SP Docking Score (kcal/mol)	AntiViral (TP)
Besipirdine	-5.14	0.76 (34.97)
Tolycaine	-5.14	0.75 (42.86)
Ethyl 2-(2-amino-1,3-thiazol-4-yl)-2-hydroxyiminoacetate	-5.13	0.80 (25.07)
2,6-Pyridinediamine, 3-(phenylazo)-, monohydrochloride	-5.12	0.75 (27.81)
Mapinastine	-5.11	0.75 (43.56)
5'-Inosinic acid, homopolymer, complex with 5'-cytidylic acid homopolymer (1:1)	-5.08	0.86 (75.60)
Prosultiamine	-5.06	0.81 (29.66)
Antramycin	-5.06	0.79 (38.27)
amisulpride	-5.05	0.79 (43.70)
Hoe 757	-5.05	0.77 (40.95)
Chlorazanyl	-5.04	0.77 (40.31)
Desciclovir	-5.04	0.93 (100.00)
Primaquine	-5.03	0.77 (45.41)
Baquiloprim	-5.03	0.80 (45.09)
Ubenimex	-5.03	0.79 (66.44)
Alepride	-5.02	0.84 (43.69)
Dazopride	-5.01	0.81 (44.91)

Compound Name	Glide/SP Docking Score (kcal/mol)	AntiViral (TP)
Sildenafil	-5.01	0.76 (39.01)
Ethyl (z)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetate	-5.01	0.82 (24.57)
Sulfacloamide	-4.99	0.78 (38.26)
Quinocide	-4.98	0.79 (45.16)
Spirotriazine hydrochloride	-4.98	0.85 (30.30)
Sulfaperin	-4.97	0.77 (38.42)
Sulfalene	-4.96	0.76 (39.91)
Furterenum	-4.96	0.88 (37.91)
3H-1,2-dithiole-3-thione, 4-methyl-5-pyrazinyl-	-4.94	0.75 (100.00)
Taprizosinum	-4.94	0.84 (40.96)
Rociclovir	-4.94	0.99 (100.00)
Xylamidine	-4.93	0.78 (47.77)
Disoxaril	-4.93	0.89 (100.00)
Percodan	-4.92	0.77 (54.21)
Alamifovir	-4.91	0.85 (95.42)
Dimoxyline	-4.91	0.76 (39.75)
Romazarit	-4.91	0.77 (31.22)

Compound Name	Glide/SP Docking Score (kcal/mol)	AntiViral (TP)
3-(Cyanoimino)-3-piperidinopropiononitrile	-4.90	0.78 (28.95)
Naminidil	-4.87	0.87 (30.56)
Fosamprenavir	-4.87	0.96 (100.00)
Pyrimitate	-4.87	0.76 (29.91)
Sk&f 9267	-4.87	0.76 (28.22)
Midamor	-4.86	0.77 (29.50)
Tenofovir	-4.84	0.92 (100.00)
dacarbazine	-4.83	0.76 (26.80)
Sulfamerazine sodium	-4.82	0.75 (39.83)
Pyrimethamine	-4.81	0.81 (55.81)
Ci 994	-4.81	0.76 (68.22)
Santoquin	-4.80	0.75 (35.16)
Phenacainum	-4.80	0.78 (34.51)
Bm 41332	-4.78	0.77 (31.28)
Moroxydine	-4.78	0.92 (58.44)
erlotinib	-4.77	0.77 (53.78)
repaglinide	-4.74	0.78 (47.08)
Sulfasymazine	-4.74	0.85 (37.31)
Timegadinum	-4.73	0.76 (32.52)

Compound Name	Glide/SP Docking Score (kcal/mol)	AntiViral (TP)
Ontazolast	-4.73	0.77 (31.58)
Sulfametomidine	-4.72	0.80 (37.72)
Tivirapine	-4.69	0.79 (79.13)
Guanclofine	-4.67	0.76 (30.77)
Etocarlidum	-4.66	0.76 (43.36)
Apraclonidine	-4.64	0.78 (28.14)
cetotiamine	-4.63	0.77 (29.25)
Midaxifylline	-4.63	0.76 (50.60)
Ioxotrizoic acid	-4.62	0.77 (36.69)
Poly c	-4.61	0.95 (77.83)
Tromantadine	-4.59	0.85 (100.00)
Sulfamerazine_1	-4.58	0.84 (37.76)
Bw 1970	-4.57	0.76 (63.35)
Sulfabromomethazine sodium	-4.55	0.82 (35.55)
Lapudrine	-4.55	0.85 (28.42)
8-Chloroadenosine 3',5'-monophosphate	-4.54	0.93 (73.12)
Isamoxol	-4.52	0.86 (27.11)
Sulfaguanole	-4.52	0.79 (32.09)
Zaprinast	-4.51	0.78 (37.80)
Sulfametoxydiazine	-4.48	0.76 (37.76)

Compound Name	Glide/SP Docking Score (kcal/mol)	AntiViral (TP)
Bentiamine	-4.46	0.82 (29.71)
Aminoquinol	-4.43	0.75 (36.50)
Pinacidil	-4.37	0.84 (28.57)
Lauroguadinum	-4.35	0.85 (42.86)
1-(4-Chlorophenyl)-5-isopropyl-biguanide hydrochloride	-4.30	0.85 (28.83)
Terofenamate	-4.28	0.78 (39.80)
Eclazolast	-4.26	0.83 (24.14)
Trapencaine	-4.21	0.75 (46.60)
Sopromidinum	-4.18	0.79 (30.45)
Sulfisomidine	-4.15	0.84 (41.35)
Benoxafos	-4.10	0.85 (23.32)
Adenosine triphosphate	-4.07	0.95 (80.95)
Tiamenidine	-4.06	0.75 (22.43)
Carbantel	-4.06	0.82 (41.61)
N'-a-(tert-butyloxycarbonyl)-n'-omega-nitro-l- arginine	-4.04	0.76 (38.51)
Tigemonam	-4.01	0.85 (33.25)
Benphothiamine	-3.91	0.79 (31.37)
Nisobamate	-3.83	0.77 (32.21)
Silver sulfadiazine	-3.82	0.75 (39.83)

Compound Name	Glide/SP Docking Score (kcal/mol)	AntiViral (TP)
Sulfamerazine	-3.82	0.84 (37.56)
Atolide	-3.70	0.77 (58.40)
Carisoprodol	-3.69	0.77 (32.65)
Carbocloralum	-3.41	0.76 (18.88)
Cidofovir	-3.39	0.93 (100.00)
Lorbamate	-3.33	0.84 (33.01)
maraviroc	-3.30	0.79 (100.00)
Fuladectin gapromidine	-2.91	0.80 (41.04)
Amidantel	-2.66	0.76 (33.80)

519

520

521

522

Glide/SP Docking Scores of 370 Identified Compounds

Figure S1. Glide/SP docking scores of identified 374 compounds from 6733-compound library from the NPC database.

529

530 **Figure S2.** Protein backbone RMSD of selected top-10 compounds for 100 ns.

531

532 **Figure S3.** Lig Fit Prot RMSD of selected top-10 compounds for 100 ns.

Figure S4. (A) 3D representation of the Ibutamoren at binding site. The average frame from 100 ns trajectory was used. (B) 2D interaction diagram of Ibutamoren at M^{pro} binding site with residues around 3 Å. (C) Time-dependent protein-ligand contact panel throughout 100 ns simulation. Top-panel shows total contacts, while bottom-panel shows formed/broken interaction between the protein and ligand.

Figure S5. (A) 3D representation of the Atevirdine at binding site. The average frame from 100 ns trajectory was used. (B) 2D interaction diagram of Atevirdine at M^{pro} binding site with residues around 3 Å. (C) Time-dependent protein-ligand contact panel throughout 100 ns simulation. Top-panel shows total contacts, while bottom-panel shows formed/broken interaction between the protein and ligand.

A

B

C

Figure S6. (A) 3D representation of the Ambamustine at binding site. The average frame from 100 ns trajectory was used. (B) 2D interaction diagram of Ambamustine at M^{pro} binding site with residues around 3 Å. (C) Time-dependent protein-ligand contact panel throughout 100 ns simulation. Top-panel shows total contacts, while bottom-panel shows formed/broken interaction between the protein and ligand.

Figure S7. (A) 3D representation of Cilostamide at binding site. The average frame from 100 ns trajectory was used. (B) 2D interaction diagram of Cilostamidum at M^{pro} binding site with residues around 3 Å. (C) Time-dependent protein-ligand contact panel throughout 100 ns simulation. Top-panel shows total contacts, while bottom-panel shows formed/broken interaction between

Figure S8. (A) 3D representation of the Tafenoquine at binding site. The average frame from 100 ns trajectory was used. (B) 2D interaction diagram of Tafenoquine at M^{pro} binding site with residues around 3 Å. (C) Time-dependent protein-ligand contact panel throughout 100 ns simulation. Top-panel shows total contacts, while bottom-panel shows formed/broken interaction between the protein and ligand.

Figure S9. (A) 3D representation of the Montirelin at binding site. The average frame from 100 ns trajectory was used. (B) 2D interaction diagram of Montirelin at M^{pro} binding site with residues around 3 Å. (C) Time-dependent protein-ligand contact panel throughout 100 ns simulation. Top-panel shows total contacts, while bottom-panel shows formed/broken interaction between the protein and ligand.

Figure S10. (A) 3D representation of the Ritonavir at binding site. The average frame from 100 ns trajectory was used. (B) 2D interaction diagram of Ritonavir at M^{PRO} binding site with residues around 3 Å. (C) Time-dependent protein-ligand contact panel throughout 100 ns simulation. Top-panel shows total contacts, while bottom-panel shows formed/broken interaction between the protein and ligand.

Figure S11. (A) 3D representation of the Amlodipine at binding site. The average frame from 100 ns trajectory was used. (B) 2D interaction diagram of Amlodipine at M^{pro} binding site with residues around 3 Å. (C) Time-dependent protein-ligand contact panel throughout 100 ns simulation. Top-panel shows total contacts, while bottom-panel shows formed/broken interaction between the protein and ligand.

Figure S12. (A) 3D representation of the Cefuroxime Axetil at binding site. The average frame from 100 ns trajectory was used. (B) 2D interaction diagram of Cefuroxime Axetil at M^{pro} binding site with residues around 3 Å. (C) Time-dependent protein-ligand contact panel throughout 100 ns simulation. Top-panel shows total contacts, while bottom-panel shows formed/broken interaction between the protein and ligand.

556

557