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Role of QSAR in Filling in the Gaps of CoVID-19 Therapeutics

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Abstract

Background: QSAR modelling has been used extensively as an efficient method in the process of drug development against CoVID-19. The rapid spread and devastating impact of this viral disease across the globe required the speed and versatility of QSAR as a powerful approach for developing potential therapeutics, working upon massive datasets and harnessing collaborations between chemists, medical professionals and biologists.

Methodology: In this letter to the editor, we report examples of how QSAR has been successfully employed in the development of anti CoVID-19 drugs. It provides vital details on drug-target interaction which informs future drug design. Notably, various models in QSAR such as CoMSIA, HiT etc. allow for holistic evaluation, as well as adaptability to peptide-based or nano scale agents.

Conclusion: Challenges associated with vaccines, as well as shortcomings of traditional drug development processes which often take dozens of years, QSAR approach is a quick, data-intensive and effective alternative with promising instances of its application in different combinations.

Keywords: QSAR; CoVID-19; SARS-CoV-2; Coronavirus; CoVID-19 therapeutics; 3D QSAR

Introduction

Since initial reports from Wuhan, China in December 2019 and the subsequent declaration of global pandemic by the WHO in March 2020, CoVID-19 has precipitated the greatest health crisis in modern history. While exposing fundamental weaknesses in healthcare systems across the globe, this tragedy has also been an opportunity for scientists and researchers in different fields to collaborate and produce solutions to this multi dimensional problem in record times. Vaccines have become a reliable and efficient first line defence, yet improving patient outcomes remains a core objective as cases continue to rise periodically with the advent of new, mutated variants. With this aim, drug development and repurposing for a beneficial anti viral treatment against SARS-CoV-2 has been a vital thrust area. Quantitative Structure Activity Relationship (QSAR) modelling has played a revolutionary role in this regard. QSAR develops a mathematical/statistical relationship between a chemical moieties' structure and its pharmaceutical properties. As a result, the long, onerous hit and trial method of drug development which often stretches for decades is sped up drastically. With QSAR modelling, potential properties such as pharmacokinetics and pharmacodynamics of the drug candidate can be reliably predicted and linked with its structure. This, in turn, allows for the development of families of analogues based on the information obtained from a dataset of known active compounds. In this information technology era, massive amounts of data from numerous research groups worldwide, working in chemistry, biology, pharmaceutics etc. can thus be harnessed through the use of computer aided drug design tools such as QSAR.

Literature Review

QSAR in CoVID-19 therapeutics

Current scenario: The accessibility of novel and effective computational facilities has made it possible to produce authentic calculations to invent novel entities and fuel the growth and development of various industries [1]. Reportedly, the QSAR based techniques could screen even huge datasets. In a study, a few in house chemicals were sorted using various ligand based drug discovery techniques. And QSAR based methods were employed to screen the active compounds against SARS-CoV Papain Like protease (PLpro) enzyme [2]. The QSAR tools are used to locate the protein receptors and calculate the binding affinities between the drug and the protein. And the deep learning models are employed for guiding the descriptor databases to extract features that could help in discovering a drug to treat COVID-19 [3]. Various QSAR models were generated like the auto-QSAR algorithm, multi parametric model, multivariate image analysis QSAR, QSAR-MLR model and the genetic algorithm multi linear regression model for automatic aid in the COVID-19 drug discovery [4].

Seminal studies of QSAR in CoVID-19 therapeutics

There are numerous studies in which 3D QSAR assisted in identifying lead compounds that helped scientists all round the globe in designing novel inhibitors of the various proteins of the coronavirus. We have discussed some of the seminal studies here. For instance, using the 3D QSAR technique Saluja, et al. identified three compound series (Isatin (2,3-oxindole) Inhibitors, Biflavonoid and Flavonoid Derivatives and Ethacrynic Acid derivatives) which can act against COVID-19 [5]. 3D QSAR was also used by Ghaleb, et al. on a CoMSIA based model to demonstrate a family of 110 pyridine N-oxide having anti-viral properties with one lead compound showing better activity chloroquine and hydroxychloroquine against SARS-CoV-2, in inhibiting 3-chymotrypsin-like protease (3CLpro) of the virus [6]. The 3CLpro is a very important protease for SARS-CoV-2 replication. And using the 3D pharmacophore modelling and 2D-QSAR technique, Kumar, et al. recognized the structural characteristics accountable for the inhibition of this enzyme and also found new inhibitors for curing SARS-CoV-2. From 5 chemical datasets, CASAntiV-2043031-84-9, CASAntiV-865453-40-3, and CASAntiV-865453-58-3 were identified as efficacious drug agents for COVID-19 treatment. The same drug target was used by Roy, et al. in a 2D multiple linear regression model to evaluate over 50,000 heterocyclic compounds. And by employing QSAR-rooted virtual screening along with other techniques, Jawarkar, et al. evolved a hit molecule against HCoV SARS 3CLpro [8]. Similarly, CHEMBL210097, CHEMBL196635, and CHEMBL194398 were also recognized as potential 3CLpro inhibitors [9]. Another example of the ability of QSAR to tackle large datasets of compounds is a study of the AutoQSAR model with KPLS analysis of 69,000 compounds against 3CLpro. Some other scientists employed 59,363 compounds and out of them, 28 were selected to explain the pharmacophore of the virus. Amparo, et al. designed a QSAR model of secondary metabolites of Brazilian herbal medicines against multiple SARS-CoV-2 targets such as spike glycoprotein, PLpro and 3CLpro. Calculating inhibitory constants of 89 chemical compounds, QSAR technique along with genetic algorithm and support vector machine was also proved effective against SARS-CoV 3CLpro. Zhai, et al. used a docking approach to identify hits from a very huge dataset of bioactive chemicals. Further, a QSAR model was evolved to evaluate the inhibitory and physiochemical effects against the SARS-CoV-2 3CLpro target. As a result, two compounds were identified as potent inhibitors having quinoxaline and pyrimidinetrione as their basic structure, which are of great interest for the evolvement of future drugs [10]. Great efforts have been put in to recognize and examine various drug targets for COVID-19 drug development. Main protease (Mpro) is one of the major drug targets of SARS-CoV-2. And is inhibited by various phosphorus-rooted drugs, amongst them L24 compound is recognised as the finest one. QSAR studies show that the topology and polarity of these phosphonate derivatives greatly affect the blocking capability and binding energy of these compounds. HiT QSAR modelling with Random Forest algorithm was used by Alves, et al. to propose drug candidates for possible repurposing against CoVID-19. Three of the lead compounds identified in this study later demonstrated anti SARS-CoV-2 activity thus validating the model. Similarly, phosphoramides have also been assessed using QSAR modelling using genetic algorithm-artificial neural networks tandem. As phosphoramides remarkably inhibit Mpro and can prevent viral replication and transcription. In a study phospho-pyrazine and phospho-guanine derivatives were employed and it was observed that phosphoguanides that has amino benzimidazole displayed better interacting ability with the virus. Also, the QSAR studies revealed that the count of amide nitrogen atoms, aromatic rings and their potent in hydrogen interactions and π-staking with Mpro sites were prime contributing factors to the inhibition. Ghosh, et al. have collated data of 88 compounds (selected through activity criteria) and subjected these to a Structural and Physicochemical Interpretation (SPCI) analysis followed by Monte Carlo simulations based QSAR model. They recommended that pyridine, furan, and diazole display positive effects whereas pyrimidine, thiazole, and thiophen showed negative effects on the inhibition of SARS-CoV-2 Mpro. The inferences from this exercise were then used to predict possible natural Mpro inhibitors. The study was then extended to identify hits targeting the PLpro enzyme of the virus. Similarly, Afshar, et al. screened 2629 approved therapeutics mainly 5-hydroxy indanone derivatives. QSAR and docking studies found that deslanoside (DB01078) can efficaciously interact with both ACE2 and Mpro sites of the virus [11]. Both these sites were also targeted by benzothiazoles and benzimidazoles compounds using various computational studies and Plonka, et al. focused only ACE2 receptor which was targeted by 160 aminothiourea derivatives. For the drug discovery development, QSAR and docking calculations found 1-(cyclopentanoyl)-4-(3-iodophenyl)-thiosemicarbazide and 5-(pyrrol-2-yl)-2-(2-methoxy phenylamino)-1,3,4-thiadiazole as the leading candidates. In a research study, robust HQSAR and Topomer CoMFA models were employed to study 48 peptide molecules against the COVID-19 Mpro enzyme [12]. As result 24 novel inhibitors were discovered with high inhibition activity at nano-molar concentration. In a study, Ali, et al. identified the factors which improve the inhibitory actions of already reported COVID-19 inhibitors. And it was clear that the formation of covalent bonds, presence of peptidomimetic or amidic structure and presence of hydrophobic groups on the terminal plays a major role in influencing the inhibition. Generally, the QSAR findings were executed on SARS-CoV Mpro inhibitors and there is a scarcity of data on SARS-CoV-2 Mpro inhibitors. Considering this, a novel QSAR model was evolved recently that employed theoretical molecular descriptors which are entirely computed from the original COVID-19 structures. A 3D-QSAR model using CoMFA and CoMSIA geometric evaluation of antimalarial carboxamides sulphonamide derivatives was used to predict hits for anti-SARS-CoV-2 activity. Similarly, Azithromycin and Chloroquine, which are effective antibacterial and antimalarial drugs along with 25 iminoguanidine compounds, were treated against SARS-CoV-2 nucleocapsid phosphoprotein. And it was observed that among them a new compound possessed great binding affinity for the target molecule. From the database of 72 phytocompounds, Zothantluanga, et al. identified 2 antiviral drugs leucoanthocyanidin 4-(2-galloyl) of *Bergenia ciliata* plant and 6-O-vanilloylisotachioside of *Baccaurea ramiflora* plant for inhibiting SARS-CoV-2 Mpro. Norouzi, et al. also tested antiviral

drugs against the SARS-CoV-2 target from the huge database of natural compounds. The 3D pharmacophores along with the QSAR model evolved and verified for virtual screening. And further molecular docking and ADMET studies were performed on the hit compounds. In another study, 8 phytochemicals from *Ocimum sanctum*, *Azadirachta indica*, and *Aegle marmelos* medicinal plants were examined against SARS-CoV-2S spike protein, human ACE2 receptor, and SARS-CoV-2 Mpro. As a result of pharmacokinetic and QSAR studies, the C-5 compound was identified as an effective template for designing novel therapeutics to cure COVID-19 [13]. Also, some FDA-approved marine drugs that are clinically employed for the treatment of cancer have the potential to cure SARS-CoV-2 patients. Kalhotra, et al. suggested that Trabectedin, Plitidepsin, and Eribulin Mesylate have features similar to other Mpro inhibitors and so could be explored further. In another study, 1615 approved drugs were tested against SARS-CoV-2 Mpro and Tadalafil, Bromocriptine, Ergotamine, and Simeprevir were identified as suitable candidates for further computational calculations. Keretsu, et al. identified 32 molecules from the protease inhibitor datasets after the computational screening [14]. Amongst them, are aclarubicin (cancer chemotherapy drug), saquinavir (HIV-1 treatment drug), faldaprevir (a clinical trial drug for hepatitis C), and TMC-310911 (an antiviral drug) were recommended as potent 3CLpro inhibitors after their experimental validation. Drugs prescribed to CoVID-19 patients, including lopinavir, ritonavir, thalidomide, favipiravir, arbidol, chloroquine, hydroxychloroquine, ivermectine theaflavin and remdesivir were studied on QSAR model which linked their topological indices to activity. This is an excellent example of using QSAR as a powerful method to better understand the molecular basis of therapeutic activity. Over 10,000 existing drugs were evaluated by Tejera, et al. to identify drug repurposing possibilities using a QSAR model [15].

Discussion

Another fascinating and crucial aspect of QSAR modelling is that, unlike wet lab setups, it is readily adaptable [16,17]. This opens up the avenue of evaluating non small molecule agents. For instance, nano QSAR was used to assess the interaction of carbon nanoparticles with SARS-CoV-2 RNA fragment, which gives prima facie support to the exploration of medicinal nano materials against CoVID-19. Many important studies make use of these methods. Similarly, Masand, et al. used a genetic algorithm multi linear regression QSAR model to study peptide-type compounds for hits against Mpro of the virus [18,19]. Recently QSAR techniques are evolved with fragment recognition methods such as Laplacian-corrected Bayesian and SARpy models, to optimize the lead in the drug discovery process against SARS-CoV 3CLpro and PLpro. The ongoing scientific research is developing QSAR methods for intestinal administered therapeutics also. The QSAR tools were also employed in the COVID Moonshot project to anticipate the PAMPA effective permeability of various chemical compounds and thereby leading the drug discovery process. The transcription factor, NF-κB is responsible for the inflammatory response by the SARS-CoV-2 virus. And therefore, inhibiting NF-κB could be regarded as an effective approach to counter this pandemic. The QSAR model was developed, screening the anti-inflammatory therapeutics from three databases. From molecular dynamics simulations and further calculations, 5 hit compounds were discovered, which will be further examined for validation [20].

Conclusion

Vaccines, although a crucial preventive measure, have efficacies varying from person to person as well as from strain to strain. And due to considerable reduction in cost and time and authentic immunogenic results, the immunoinformatic technique is getting popularity in drug discovery and development. The structural proteins are comprehensively studied as COVID-19 drug targets. At the time of writing this paper, the Omicron variant is accelerating throughout the world and has been stated to be not only more contagious but may show antibody escape. Previous mutations have been known to lower vaccine efficacy. On the contrary, an anti viral drug is expected to be more reliable given that it actively targets the virus rather than relying on a passive immune system mediated response. Further, as a drug targets biological pathways and alleviates symptoms, it may be more resilient to future mutations. In light of other issues such as vaccine hesitancy, an anti viral drug, purpose built to tackle CoVID-19, would create a robust therapy portfolio against the disease. It is here that QSAR is already proving to be a vital resource, in both identifying new candidates but also informing drug repurposing. With greater sharing of information through large databases such as drug bank etc. and the inclusion of other technologies such as machine learning and other CADD techniques, it is undeniable that QSAR will remain a cornerstone in the journey to predict and produce an anti CoVID-19 drug.

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