Saadah LM, Abu Deiab GI, Al-Balas QA, Basheti IA. Computational medicinal chemistry role in clinical pharmacy education: Ingavirin for coronavirus disease 2019 (COVID-19) discovery model. Pharmacy Practice 2022 Oct-Dec;20(4):2746
https://doi.org/10.18549/PharmPract.2022.4.2746

Original Research

Computational medicinal chemistry role in clinical pharmacy education: Ingavirin for coronavirus disease 2019 (COVID-19) discovery model

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Received (first version): 14-Sep-2022 Accepted: 13-Oct-2022 Published online: 08-Nov-2022

Abstract

Objective: Given the major shift to patient-directed education, novel coronavirus (nCoV) provides a live example on how medicinal chemistry could be a key science to teach pharmacy students. In this paper, students and clinical pharmacy practitioners will find a stepwise primer on identifying new potential nCoV treatments mechanistically modulated through angiotensin-converting enzyme 2 (ACE2). **Methods:** First, we identified the maximum common pharmacophore between carnosine and melatonin as background ACE2 inhibitors. Second, we performed a similarity search to spot out structures containing the pharmacophore. Third, molinspiration bioactivity scoring enabled us to promote one of the newly identified molecules as the best next candidate for nCoV. Preliminary docking in SwissDock and visualization through University of California San Francisco (UCSF) chimera made it possible to qualify one of them for further detailed docking and experimental validation. **Results:** Ingavirin had the best docking results with full fitness of −3347.15 kcal/mol and estimated ΔG of −8.53 kcal/mol compared with melatonin (−6.57 kcal/mol) and carnosine (−6.29 kcal/mol). UCSF chimera showed viral spike protein elements binding to ACE2 retained in the best ingavirin pose in SwissDock at 1.75 Angstroms. **Conclusion:** Ingavirin has a promising inhibitory potential to host (ACE2 and nCoV spike protein) recognition, and hence could offer the next best mitigating effect against the current coronavirus disease (COVID-19) pandemic.

Keywords: Coronavirus disease (COVID-19); novel coronavirus (nCoV); ingavirin; angiotensin-converting enzyme 2 (ACE2); practitioner; molecular docking; modeling

INTRODUCTION

Confirmed novel coronavirus disease (COVID-19), first reported to the World Health Organization (WHO) in December 2019, is probably the most challenging out of the known coronavirus infections.[1-4] COVID-19 has evolved since 30 January 2020, into an unprecedented modern time worldwide pandemic.[5] By the time of writing this paper (14 September 2022), confirmed cases have reached close to 615 million people, with more than 6.52 million deaths globally.[6] Therefore, researchers and practitioners are under pressure to repurpose, identify, and develop new drugs for this insurgent healthcare emergency.[7] As such, COVID-19 presents a live example of how clinical literature may be enriched with repurposing, design, and/or drug-disease interaction studies on this evolving ailment story.[8,9]

Pharmacy education has evolved in the last 60 years towards more clinical and pharmacy practice-driven curricula with less emphasis on basic sciences, such as medicinal chemistry.[7,10,11] Nevertheless, medicinal chemistry remains a unique and important distinguishing foundational science for the pharmacy profession.[12] Particularly, scarcity in articles demonstrating the significance of computational medicinal chemistry to a pharmacy student or pharmacy practitioner is serene. Furthermore, it is unclear how could this rich source of knowledge be systematically incorporated into practice to further the development and need for clinical pharmacy expertise.[12,13] Now, COVID-19 seems like a real-life prototype, if appropriately described, which could serve as a model for implementing medicinal chemistry in clinical practice.

Several papers have discussed the potential role of melatonin in the management of COVID-19.[14,15] Our team has also shown that carnosine offers a better candidate for the management of COVID-19 based on molecular docking and chemical modeling[16]. Both drugs are antioxidants and possess organ protective and antiviral effects[17,18]. Researchers propose that angiotensin converting enzyme 2 (ACE2) mediates the antiviral effects of these molecules. Notably at this stage, both molecules are largely awaiting *in vitro*, animal, and human models validation research as potential COVID-19 treatments.

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www.pharmacypractice.org (eISSN: 1886-3655 ISSN: 1885-642X)

Some of this research is already underway.[19,20] Looking at the structures of both molecules and determining their common pharmacophore, we can expect a few other drugs would benefit patients with COVID-19 or at least modulate this disease. In this paper, we will build a computational medicinal chemistry model to predict the activity of multiple compounds against COVID-19. This model would be the first of its kind and scope to show how average practitioners can implement computational medicinal chemistry in clinical practice. It would also provide a most needed example of how medicinal chemistry can be taught to the new patient-directed pharmacy trainees.

AIMS

The aim of this study is to identify currently approved or known experimental compounds as potential ACE2 modulators based on what is chemically known about melatonin and carnosine. PubMed searches helped assess the current state of research pertaining to these new potential treatments for patients with COVID-19. Finally, the new identified molecules underwent preliminary molecular docking to the ACE2 with the viral spike protein to help determine if it is possible to modulate this protein–protein interaction.

METHODS

Figure 1 shows an overview of the methods used in this study. As a starting point, simple Google search made us elucidate the structure-activity relationship (SAR) of ACE2 inhibitors. It led to the scaffold general structure of ACE2 inhibitors that has been reported by Dales and Torres (Figure 2).[21,22] Considering the simplest chemical structure possible, R^1 and R^3 groups are replaced with hydrogen atoms, and R^2 is dropped. Carnosine, as shown before, has emerged as the most similar molecule to the resultant structure. While melatonin also provides another potential ACE2 inhibitor that has been studied in COVID-19.[14,15,17] Common pharmacophore was identified, as shaded in light green, based on comparing the structures of carnosine and melatonin.

Next step, chemical similarity searches were performed on DrugBank and Swiss similarity in a similar method as described in our previous paper.[16] Similarity or diversity search is a relatively new concept in chemo-informatics and there are numerous methods or equations to study it.[23] These include Euclidean, Manhattan, and Mahalanobis metrics.[24] However,

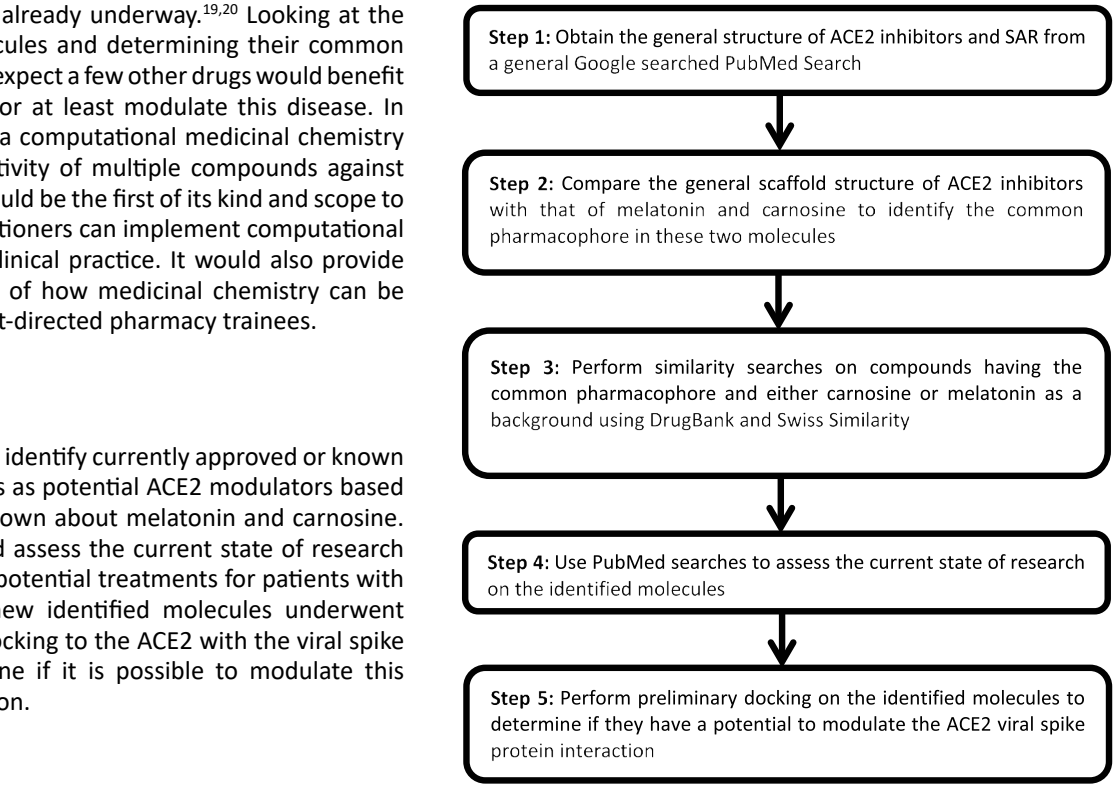
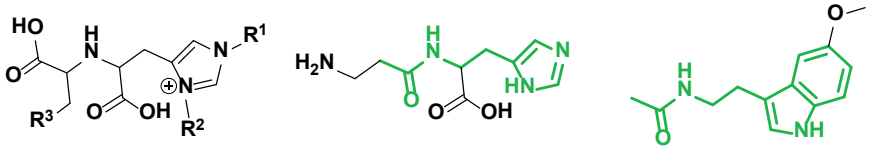


Figure 1. Overview of the study methodology

Tanimoto index is the simplest and most direct such distance measure which calculates the fraction shared bits between chemical fingerprints (also known as pharmacophores).[25] Using chemical similarity search we can then most likely find few new drugs to repurpose for COVID-19. Our strategy in similarity search was to use the common pharmacophore once each with carnosine and melatonin. Each time only drugs, which were more similar to these structures than carnosine and melatonin, were assessed. Just structures containing the pharmacophore were actually further preliminary docked.

Moreover, molinspiration bioactivity score calculator predicted the activity of the identified drug candidates at six important ligands; namely, 1: G-protein coupled receptor (GPCR) ligand, 2: ion channel modulator, 3: kinase inhibitor, 4: nuclear receptor ligand, 5: protease inhibitor, and 6: enzyme inhibitor.[26] Summed absolute differences from scaffold general structure at these six ligands enabled us to determine which molecule



A. Scaffold ACE2 inhibitor B. Carnosine C. Melatonin

Figure 2. (A) Scaffold structure for angiotensin converting enzyme 2 (ACE2) inhibitors from Dales and Torres (A), (B) Structure for carnosine, and (C) Structure for melatonin. Common pharmacophore is shaded in light green. Please note that the indole ring in the melatonin replaces the imidazole ring in carnosine (both are bioisosteres in the SwissBioisostere engine) and hence considered part of the pharmacophore.

may have the greatest potential as an ACE2 inhibitor. On the other hand, ChemMine similarity scoring was used to check how close the molecule to the general scaffold structure of ACE2 inhibitor was.[27] Obviously, similarity metrics, atom pair (AP) Tanimoto method, maximum common substructure (MCS), Tanimoto method, MCS Min, and MCS Max, were compared for the various agents. The higher values of these metrics, the closer the drug is to the general scaffold structure of ACE2 inhibitor. Bioactivity scoring was made on every new potential or reference molecule identified. Absolute differences between the binding scores of each molecule and the general scaffold structure were calculated. The differences for each of the six ligands were, then, summed up into a final total number. Hence, the lower this absolute summed total the closer supposedly the identified drug is to the general scaffold structure.

Preliminary molecular docking was performed using SwissDock server as described by other research groups.[28] ACE2 code in SwissDock server is 6M0J. Note this is the cocrystallized structure of ACE2 with nCoV spike protein. Our research team docked only identified molecules that were available in the ZINC database. Binding modes were visually presented with University of California San Francisco (UCSF) chimera version 1.14. To compare docking results of the various drugs both the lowest estimated Gibbs free delta G (ΔG) energy for cluster 0 first elements and the summary of all binding modes were considered.

Finally, searches on PubMed were conducted to check the current state of knowledge about identified molecules in the COVID-19 infection. The following strategies were used: ((@ Name of Molecule)[Title]) AND ((COVID)[Title] OR (nCoV)[Title] OR (SARS CoV-2)[Title] OR (ACE2)[Title]). Literature on each identified drug or its related molecules is presented. Proof of concept for this study should follow with *in vitro* or animal model experimentation and that will be our subsequent future step for all suggested COVID-19 treatments in this paper.

Statistical analysis

Taking all clusters and elements from SwissDock, data for both full fitness and estimated ΔG was not normally distributed. Therefore, nonparametric tests were performed comparing five molecules; namely, melatonin, carnosine and three new potential nCoV therapies. Sample sizes for the five molecules were 251, 253, 254, 257, and 257 elements, respectively, and these were determined by SwissDock engine. Of course, they represented the population of poses for each drug. Kruskal–Wallis test was used as a nonparametric alternative to the one-way ANOVA test and Mann–Whitney U test as an alternative to Student's *t*-test. At the two-sided, alpha level of significance of 0.05, *p*-values were generated to compare the five groups.

RESULTS AND DISCUSSION

As detailed in Section 3, Google search led us to the general scaffold structure of ACE2 inhibitors from Dales and Torres (Figure 2). Simplest form of this structure when R^1 and R^3 groups are replaced with hydrogen atoms, and R^2 is dropped, served as our reference in all subsequent bioactivity scoring searches. Moreover, figure 2 shows the common pharmacophore in carnosine and melatonin that we will use as the basis for similarity searches. Worth noting is that the pharmacophore may not be a mere simple structure similarity. The 3-substituted indole in melatonin is replaced by a 5-substituted imidazole in the carnosine structure. Replacing the second nitrogen atom in the carnosine imidazole ring with a fused benzene ring make the two structures similar in two aspects. First, both structures are aromatic at this end. Second, rings are electron rich. Now, this replacement of 3-substituted indole and 5-substituted imidazole is expected to yield molecules with similar activity at ACE2 on SwissBioisostere.[29]

Identifying new similar structures

Searching for drugs similar to the proposed pharmacophore, using carnosine as the background structure, three experimental or investigational drug candidates were observed (Figure 3). First, *N*-acetylhistamine (NAH) is 100% similar to the pharmacophore. Second, histamine glutarimide is 73.5% similar. Third, ingavirin is 72% similar. Only one PubMed indexed article suggested one of these; namely ingavirin, as a potential treatment for SARS CoV-2.[30] When melatonin is used as the background structure, one similar structure to the pharmacophore was found and that is *N*-acetylserotonin (NAS) (Figure 3). NAS is 86.1% similar to the pharmacophore. PubMed searches yielded no articles suggesting this drug as a potential treatment for COVID-19. Therefore, there are four potential ACE2 modulating drugs with only one of them being actually suggested as a potential treatment for COVID-19. However, this suggestion is not made on the basis of ACE2 modulation. Additionally, readers can see that the aliphatic amine group is chiral in NAH, NAS and ingavirin but not in the histamine glutarimide. Moreover, unlike the carnosine NAH, NAS and ingavirin all have a non-chiral carbon next to the aliphatic nitrogen atom. Having no chirality makes all the structures more flexible in 3-dimensional spaces than carnosine. 3D superimposition of the pharmacophore in these

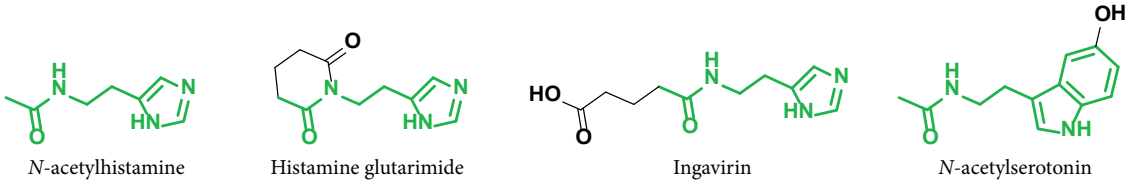


Figure 3. New drug candidates for COVID-19 disease on the basis of ACE2 modulation similarity

molecules is therefore possible and this is illustrated in figure 4 for carnosine and ingavirin.

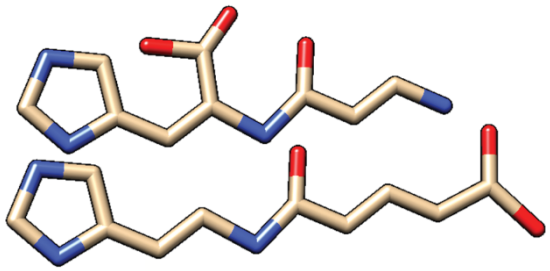


Figure 4. Top panel molecule (carnosine) superimposed on below panel (ingavirin)

Table 1 shows the molinspiration bioactivity scores for the general scaffold ACE2 inhibitor and the four new molecules. Clearly, bioactivity scoring lends ingavirin as the best drug candidate to test next only to carnosine (i.e. lowest total difference 2nd only to carnosine).

Table 2 shows the similarity scores from ChemMine for all these drugs. Herein, ingavirin seems to be a bit less similar to the general scaffold structure than anticipated by molinspiration bioactivity scores. Nevertheless, ingavirin is still closely related to carnosine and hence qualify for further preliminary docking on ACE2 and experimental validation for COVID-19 disease. Additionally, ingavirin has better similarity scores to the scaffold compared to melatonin that is currently widely investigated for COVID-19.

Preliminary molecular docking

Our team succeeded in preliminary docking of all the identified molecules except for histamine glutarimide. None of these new molecules were previously implicated as potential ACE2 modulators. However, our comparators; namely melatonin and carnosine, have been implicated as ACE2 inhibitors.[13-15] Furthermore, there are now multiple transgenic mouse models incorporating human ACE2 that can be used during the experimental validation phase for testing whether the new identified molecules are real ACE2 inhibitors.[31] Back to SwissDock, ingavirin had the best docking results (Table 3) for cluster 0 element 0 with full fitness of (−3347.15 kcal/mol) and estimated ΔG of (−8.53). Collectively, ingavirin had the next best results to carnosine and melatonin as an ACE2 modulator (Figure 5). Statistically, ingavirin were better than both NAH and NAS based on full fitness (p value < 0.05). It was statistically comparable to carnosine and melatonin based on estimated ΔG (p value > 0.05). Ingavirin best pose in UCSF chimera showed parts of the viral spike protein ligand binding with ACE2 retained at 1.75 Å, and as result, protein–protein interactions are vulnerable to inhibitory actions by ingavirin in this model. Therefore, further detailed docking and experimental validation are worth undertaking. Due to the limited time and lockdowns in our country, these steps would be pursued in future studies.

Table 1. Molinspiration bioactivity scores for the general scaffold structure of ACE2 inhibitors, *N*-acetylhistamine, histamine glutarimide, ingavirin, *N*-acetylserotonin, carnosine and melatonin

Drug	1 *	2	3	4	5	6	Total Difference **
General scaffold	0.46	0.47	−0.15	−1.25	0.52	0.58	0.00
N-acetylhistamine	−0.10	−0.03	−0.54	−2.43	−0.27	0.14	3.86
Histamine glutarimide	0.16	0.14	−0.32	−1.26	−0.06	0.27	1.70
Ingavirin	0.46	0.31	−0.20	−1.05	0.33	0.59	0.61
N-acetylserotonin	0.13	0.06	−0.06	−0.38	−0.21	0.10	2.91
Carnosine	0.61	0.48	−0.06	−1.20	0.65	0.73	0.58
Melatonin	0.06	−0.09	−0.10	−0.51	−0.24	−0.01	3.1

* 1: GPCR ligand 2: Ion channel modulator 3: Kinase inhibitor 4: Nuclear receptor ligand 5: Protease inhibitor 6: Enzyme inhibitor. ** Total sum of absolute difference at each of the six receptors between the drugs and the general scaffold structure value.

Table 2. ChemMine similarity scores for the general scaffold structure of ACE2 inhibitors, *N*-acetylhistamine, histamine glutarimide, ingavirin, N-acetylserotonin, carnosine and melatonin

Drug	AP Tanimoto	MCS Tanimoto	MCS Size	MCS Min	MCS Max
Scaffold	-	-	-	-	-
N-acetylhistamine	0.268	0.588	10	0.909	0.625
Histamine glutarimide	0.131	0.476	10	0.667	0.625
Ingavirin	0.206	0.455	10	0.625	0.625
N-acetylserotonin	0.212	0.391	9	0.563	0.563
Carnosine	0.283	0.684	13	0.813	0.813
Melatonin	0.185	0.375	9	0.563	0.529

Table 3. SwissDock results for *N*-acetylhistamine, ingavirin, *N*-acetylserotonin, carnosine and melatonin

Molecule	Clusters	Elements	Full Fitness (kcal/mol)	Estimated ΔG (kcal/mol)
N-acetylhistamine	54	254	−3301.33	−6.53
Ingavirin	53	251	−3347.15	−8.53
N-acetylserotonin	36	257	−3293.53	−6.53
Carnosine	42	253	−3416.81	−6.29
Melatonin	44	257	−3365.10	−6.57

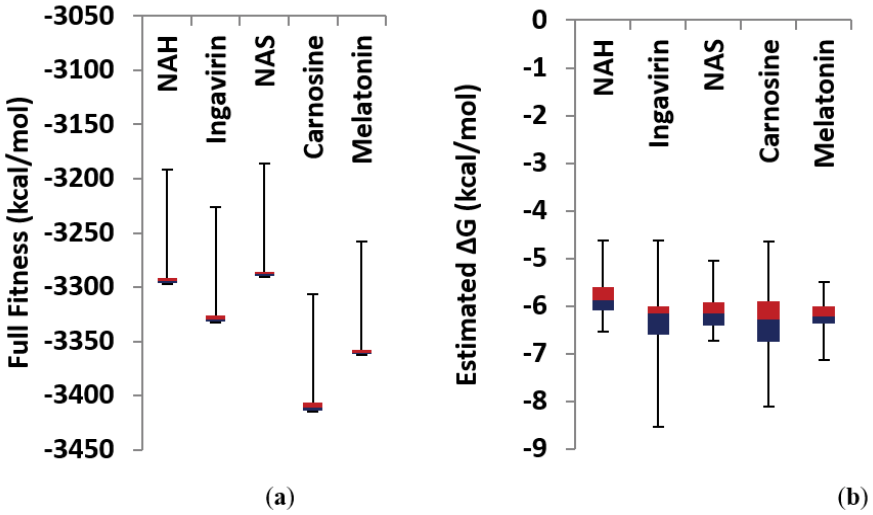


Figure 5. A full fitness (a) and an estimated ΔG (b) of all docking clusters to host ACE2 cocrystallized with nCoV viral spike protein. (* Comparisons of ingavirin with NAH and NAS were statistically significant for full fitness at alpha level of significance of 0.05, all p-values < 0.001. Ingavirin comparisons for estimated ΔG with carnosine and melatonin were statistically insignificant). Best cluster 0 element 0 ΔG was observed with ingavirin. Abbreviations: NAH; N-acetylhistamine, NAS; N-acetylserotonin.

Clearly, ingavirin is anticipated to be an inhibitor of the protein–protein interaction or at least a good starting point to design such potent ACE2 inhibitors. Based on a previous assessment of other drugs, one can infer that ingavirin is a better inhibitor of ACE2 than chloroquine (docking score −5.53 kcal/mol) and hydroxychloroquine (docking score of −5.99 kcal/mol) both initially implicated as good drug qualifiers for COVID-19.[32] Moreover, first element results of preliminary docking of ingavirin to ACE2 were better than both melatonin (−6.57 kcal/mol) and carnosine (−6.29 kcal/mol). Ingavirin is also more optimal than other ACE2 inhibitors from Chikhale et al. such as withanoside X with an estimated ΔG (−7.07 kcal/mol) and ashwagandhanolide (−6.50 kcal/mol).[33] However, ingavirin is still in the experimental phase and therefore caution should be exercised in mobilizing it in the fight of COVID-19 at this stage. Although like carnosine and melatonin, ingavirin is sold as a supplement on the World Wide Web, further approvals and studies are warranted before its wide application.

In summary, ingavirin seems to be a very promising drug candidate that could help mitigate the current COVID-19 pandemic by inhibiting ACE2, and further testing is recommended in this regard. These findings provide a live example from the COVID-19 pandemic on how practitioners and clinical pharmacists can repurpose well-established and/or experimental drugs with great potential. Computational medicinal chemistry tools may thus be employed by clinical pharmacy practitioners to come up with solutions for healthcare challenges.

Literature evaluation

Only one article has recommended ingavirin for COVID-19 but based on its effect on other viruses rather than its potential ACE2 modulation in SARS CoV-2. In particular, this broad-spectrum antiviral has been shown to be active on the nucleocapsid (N) protein of SARS CoV.[34]

LIMITATIONS

This research skipped *in vitro* or animal model validation due to the lockdowns in our country, Jordan, and the extra expense and expertise needed for these steps. Moreover, multiple receptor binding domain (RBD) variants with nCoV exist.[35-37] These may modify the nature, stability, and affinity of the protein–protein interaction. Current research had limited time to study all of them but the promising results we had should prompt extensive evaluation of ingavirin or any future ACE2

inhibitors with such variants.

CONCLUSIONS

This is the first, to our best knowledge, preliminary molecular docking study that shows ingavirin has a great potential as an inhibitor against ACE2, and its protein–protein interaction with the viral spike protein. It provides a stepwise approach for students and clinical pharmacy practitioners to repurpose known compounds recommending some of them in the fight against COVID-19 pandemic. If ingavirin or its derivatives live through the test of time to be shown effective on COVID-19, this study would prove that methods provided could be used by practitioners for proposing and solving other disastrous health patient–centered challenges. Hence, medicinal chemistry concepts and software can be a great asset to students and clinical practitioners in chemically identifying promising therapeutic candidates

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

FUNDING

This study has not received any funds.

AUTHOR CONTRIBUTIONS

Conceptualization, L.M.S. G.I.A.D., Q.A.B., I.A.B.; methodology, L.M.S., G.I.A.D., Q.A.B., I.A.B.; software, L.M.S.; validation, L.M.S., G.I.A.D., Q.A.B., I.A.B.; formal analysis, L.M.S., G.I.A.D., Q.A.B., I.A.B.; investigation, L.M.S., G.I.A.D., Q.A.B., I.A.B.; resources, L.M.S; data curation, L.M.S.; writing—original draft preparation, L.M.S.; writing, review and editing, G.I.A.D., Q.A.B., I.A.B.; visualization, L.M.S., G.I.A.D.; supervision, Q.A.B., I.A.B.; project administration, I.A.B.; funding acquisition, I.A.B. All authors have read and agreed to the published version of the manuscript.

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