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Research paper

Identification of potential inhibitors of SARS-CoV-2 papain-like protease from tropane alkaloids from *Schizanthus porrigens*: A molecular docking study

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ABSTRACT

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This paper presents identification of potential inhibitors of SARS-CoV-2 papain-like protease from tropane alkaloids from *Schizanthus porrigens*, using molecular docking method. Binding affinities were compared with those obtained with Lopinavir as a SARS-CoV-2 papain-like protease inhibitor. Overall, our findings indicate that Schizanthine Z binds to the SARS-CoV-2 papain-like protease with relatively high affinity and favorable ADME properties. Therefore, Schizanthine Z may represent an appropriate compound for further evaluation in antiviral assays.

1. Introduction

Coronavirus disease 2019 COVID-19 causes severe acute respiratory syndrome (SARS), and therefore this new virus has been given the name severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1]. Coronavirus non-structural polyprotein is processed by two proteases, the main protease (Mpro) and the papain-like protease (PLpro), inhibition of PLpro affects virus replication through poor viral protein processing and can also affect activities of other PLpro [2]. Other PLpro that can be affected are desubiquitination proteases, which recognize ubiquitin through an enzymatic ubiquitin binding site and can specifically bind and cleave polyubiquitin by binding to diubiquitin through the ubiquitin active site, in contrast, SARS PLpro recognizes Lys48 bound polyubiquitin through ubiquitin binding sites and is, therefore, capable of directly removing Lys48 bound diubiquitin from substrates [3]. Maiti (2020) reports that the PLpro encoded by SARS-CoV-2 has a labile Zn site formed by the amino acids Cys189, Cys192, Cys224 and Cys226 and a classic catalytic site formed by the amino acids Cys111, His272 and Asp286, which play key functions for viral replication and represents promising drug targets, because sulfur-based drugs such as peptide-based inhibitors can block Cys residues at the catalytic site or Zn site of CoV-2-PLpro, which leads to CoV-2-PLpro dysfunction and thus stops viral replication [4]. Moreover, de-ISGylation proteases [5] and innate anti-host immunity reactions can also be affected, PLpro comprises a

central catalytic domain and the ubiquitin-like domain, which interferes with the host's antiviral pathways and modulates the immune response of the host, furthermore PLpro subdomains showed different reaction patterns in presence or absence of ubiquitin, lastly, it should be mentioned that PLpro was an important drug target against several Coronaviruses, including MERS CoV [2]. Freitas et al (2020) reported that naphthalene-based PLpro inhibitors are effective against SARS-CoV-2 [6], other researchers have also reported that a naphthalene derivative inhibited SARS-CoV-2 PLpro [3,7]. Due to the above, the search for new drug prospects is the most reliable option to design an efficient therapy for infected patients without delay [8], because the development of vaccines against the SARS-CoV-2 virus can take many months. Furthermore, virus-encoded peptide-based vaccines may not be effective against future coronavirus epidemics, as virus mutations could render them useless [9]. In the pharmaceutical industry the development and discovery of new drugs is the main driver of it. In the past, the design of drugs was directly related to Chemistry of natural products, which were later modified by organic synthesis. Currently, the development of more powerful and efficient computers has allowed the generation of methodologies and simulations that have optimized this process [10]. However, Natural Products Chemistry continues to be a source for obtaining drugs, for example, *S. porrigens* Graham is an herbaceous plant that grows only in humid soils in northern Chile (IV Region) [11]. Studies on *Schizanthus* have shown that a series of tropane-derived alkaloids

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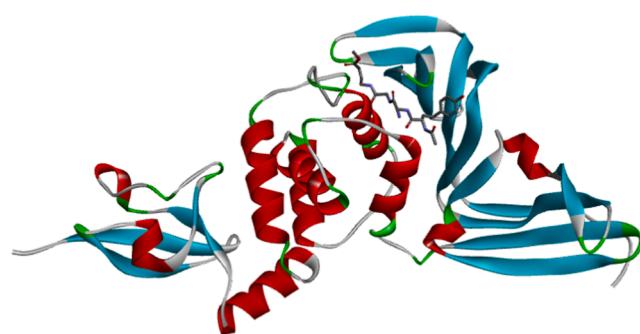


Fig. 1. Complex between the papain-like protease of SARS-CoV-2 and the crystallized inhibitor VIR251. Source Protein Data Bank (<https://www.rcsb.org/>) code 6WX4.

accumulate in this genus [12], which have anticholinergic activity [13], antiemetic [14], anesthetics [15], mydriatics [16], antispasmodics [17], bronchodilators [18] and antivirals [19]. Species *Schizanthus porrigens*, native to Chile and Argentina [20], was chosen as source of potential inhibitors for SARS-CoV-2 papain-like protease, which have not yet been investigated, choosing molecular docking for carry out the investigation in silico of tropane alkaloids of *Schizanthus porrigens* since this method predicts the orientation of a ligand that binds to a protein forming a stable complex and the strength of the bonds generated between them [21,22]. Molecular docking is one of the most frequently used methods in the design of structure-based drugs, due to the ability to predict the conformation of the ligand to the binding site [23]. Kandeel et al (2020) investigated PLpro use of SARS-CoV-2 to select virtually 1,697 FDA-approved clinical drugs, finding that Losartan, Montelukast Sodium, Quercitrin, Zanamivir, NAD1, Candesartan, Chlorhexidine chlorhydrate and Fostamatinib disodium exhibited binding energy superiors to -7.5 kcal/mol [2], and within the natural compounds Laskar and Choudhury (2020) repot Baicalin, Quercetin, Licoleafol, Biotperin, Luteolin and

Rutin with binding energy equal to or greater than -25 kcal/mol [24]. The characterization of the protein ligand bond in the cases of viral proteins plays an important role in the search for drugs [25]. Thus the objective of this work was the identification of potential inhibitors of SARS-CoV-2 papain-like protease from tropane alkaloids from Schizanthus porrigens using molecular docking.

2. Materials and methods

SARS-CoV-2 papain-like protease is essential for virus maturation and infectivity [26,27]. The crystalline structure of the papain-like protease was obtained from the Protein Data Bank (<https://www.rcsb.org/>) code 6WX4 [28]. The water molecules together with the VIR251 ligand were removed and then the hydrogen atoms were added to the protein to correct the ionization of the amino acid residues of the protein using the Discovery Studio 2020 Client program [29], in order to prepare the protein to effect molecular docking. The obtained protein was saved in pdb format and imported into the PyRx program [30] to perform the molecular docking, which was carried out with the Autodock Vina program [30]. Fig. 1 shows complex between SARS-CoV-2 papain-like protease and inhibitor VIR251. Fig. 2 shows the 2D structure of tropane alkaloids from Schizanthus porrigens, which were imported from the ChemDraw 3D program [31] in sdf format. The most stable conformer was determined with the PyPx program [30], then the ADME properties (Absorption, Distribution, Metabolism, and Excretion) were analyzed using the SwissADME database (<http://www.swissadme.ch/>) [32]. Since the main objective in molecular docking is to evaluate protein-ligand interactions to predict binding affinity [33], Autodock Vina [34] and PyRx [30] were used to determine the orientations of the ligands in the active site of SARS-CoV-2 papain-like protease, according to those reported by Rut et al. (2020), deep hydrophobic pocket formed by the residues Asp164, Met208, Pro247, Pro248, Tyr264, Tyr268, Tyr273 y Thr301 was considered as active site [28]. Discovery Studio 2020 Client software [29] was used to determine and illustrate the intermolecular interactions between tropane alkaloids and residues of active site SARS-CoV-2 papain-like protease. The molecular dynamics

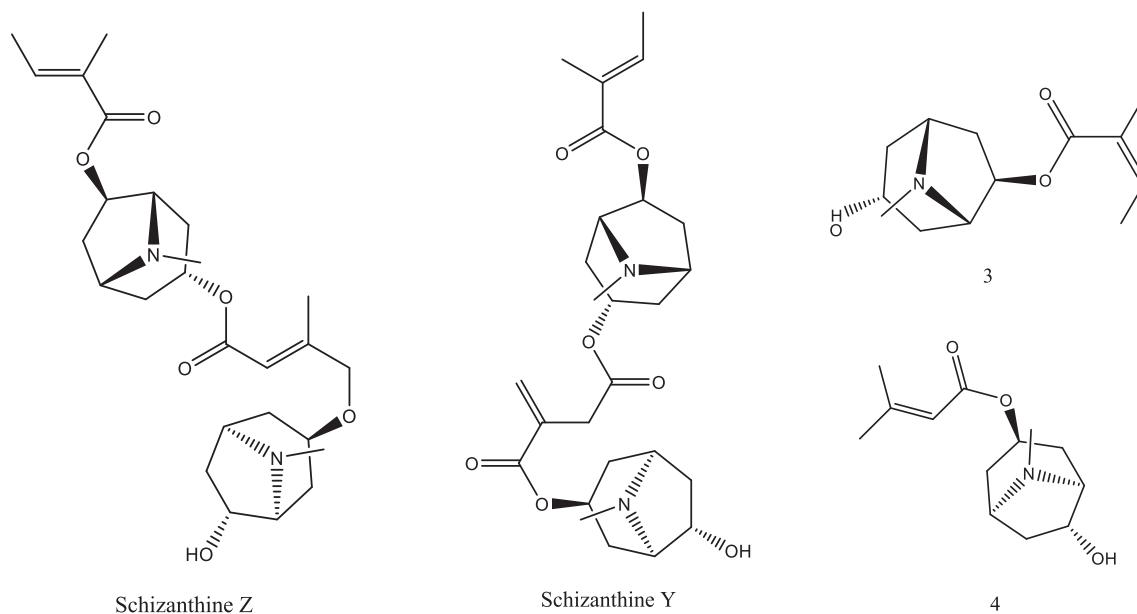


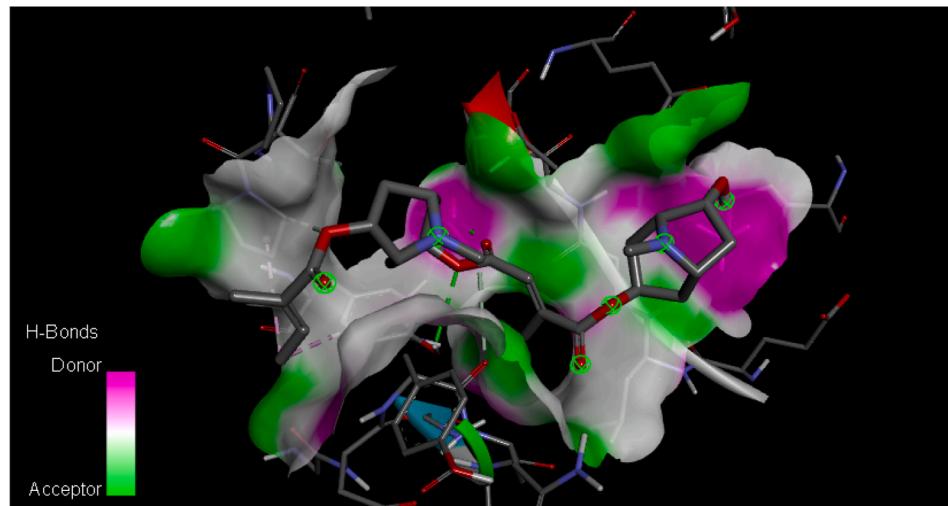
Fig. 2. 2D structure of tropane alkaloids from *Schizanthus porrigens*.

Table 1

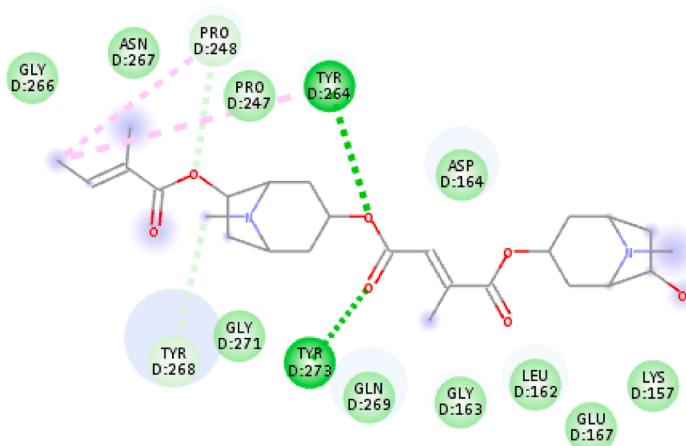
Binding affinity (kcal/mol) of 6WX4 and Ligands.

Receptor PDB ID	Ligands	Binding Affinity (ΔG in kcal/mol)
6WX4	Schizanthine Y	-7.1
	Schizanthine Z	-7.5
	3	-5.7
	4	-5.6
	Lopinavir (Ref. ligand)	-7.0

simulation was performed using NAMD v.2.14 [35,36] with CHARMM36 force field [37,38,39]. Then each structure was converted to a psf protein structure file by automatic psf generation plugin within the VMD v program. 1.9.3 [40]. The simulation was carried out with 5000 steps that were carried out for all the atoms of the system to ensure the elimination of any residual steric shock [41]. Then, the structure was simulated at a constant temperature of 310 K and a pressure of 1 atm using Langevin dynamics [42].



(a)

**Interactions**

- [Green square] van der Waals
- [Green square] Conventional Hydrogen Bond
- [Green square] Carbon Hydrogen Bond
- [Pink square] Alkyl
- [Pink square] Pi-Alkyl

(b)

Fig. 3. (a) H-bonding interactions between the Schizanthine Z with papain-like protease of SARS-CoV-2 target; (b) All types of interactions between the Schizanthine Z with papain-like protease of SARS-CoV-2.

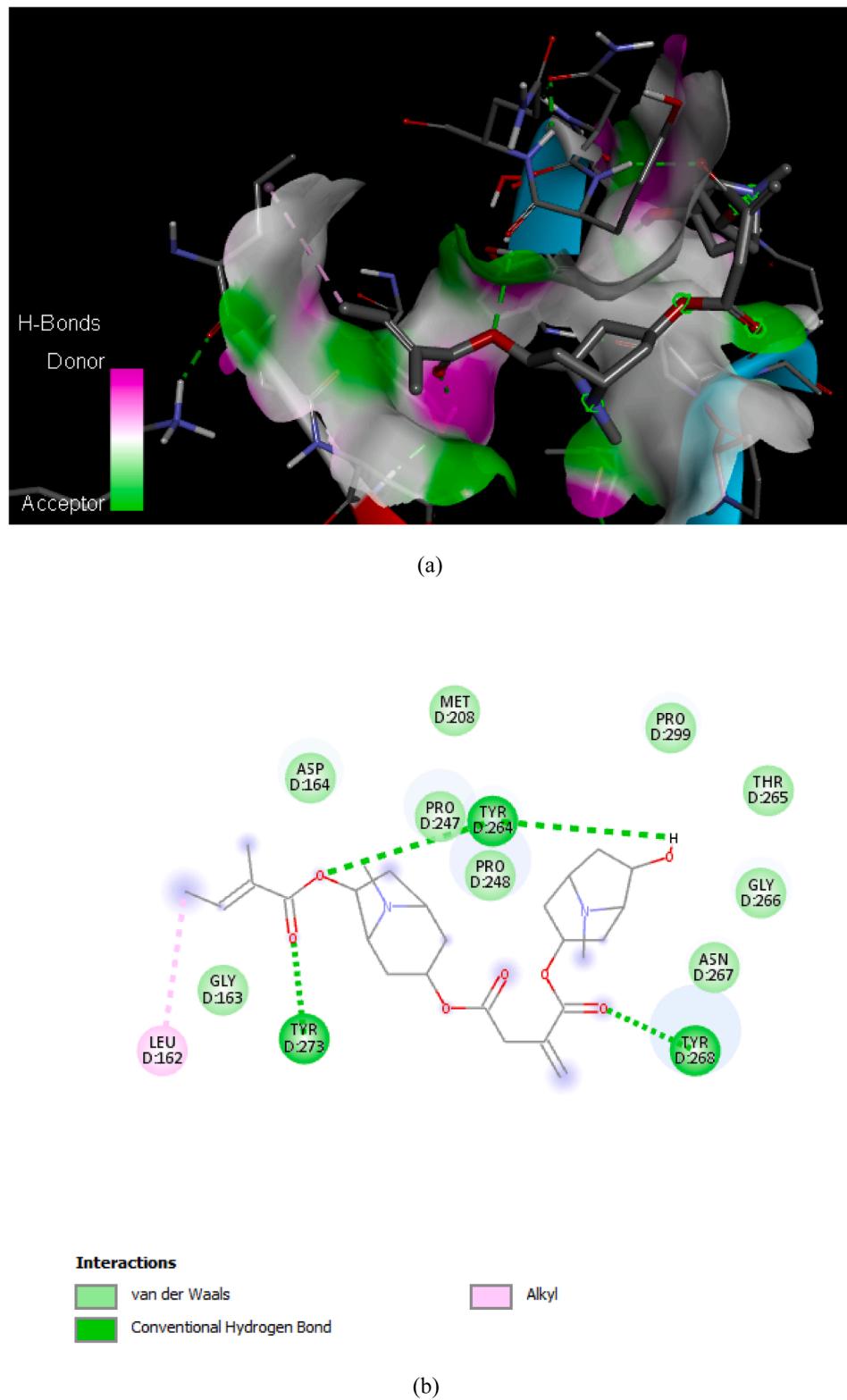
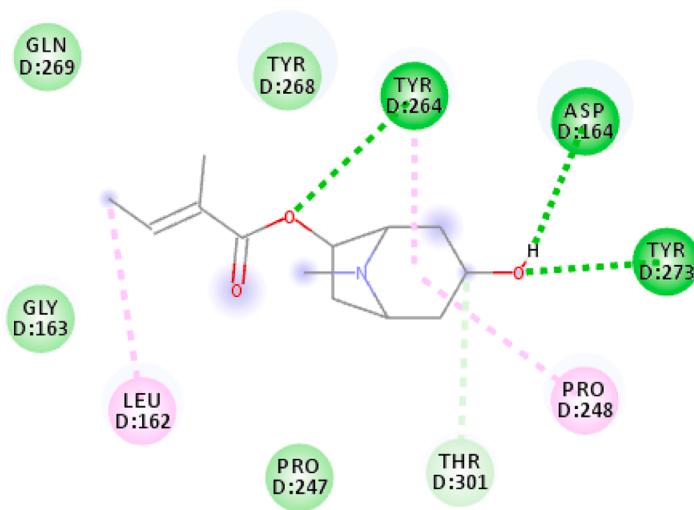
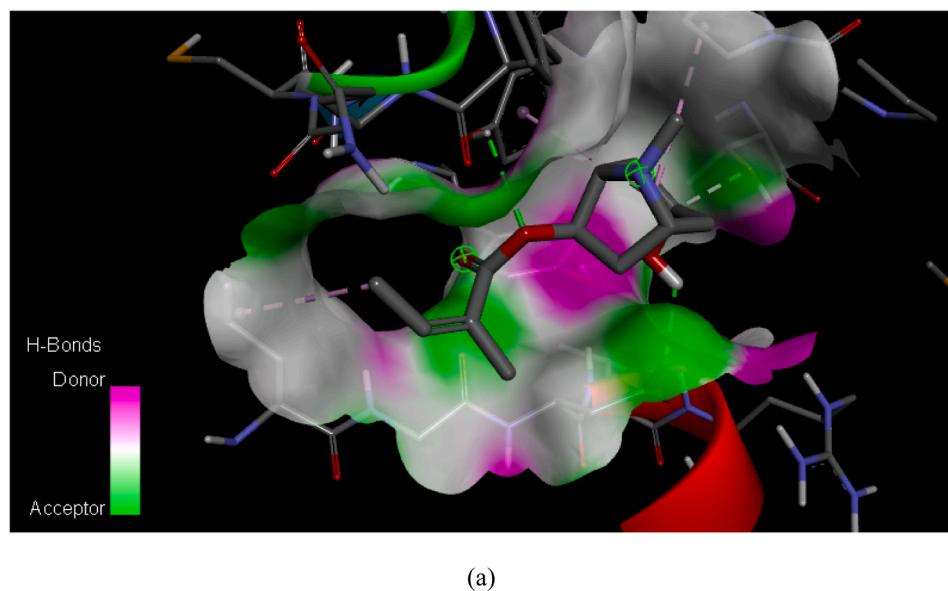


Fig. 4. (a) H-bonding interactions between the Schizanthine Y with papain-like protease of SARS-CoV-2 target; (b) All types of interactions between the Schizanthine Y with papain-like protease of SARS-CoV-2.



Interactions

	van der Waals
	Conventional Hydrogen Bond
	Carbon Hydrogen Bond

	Alkyl
	Pi-Alkyl

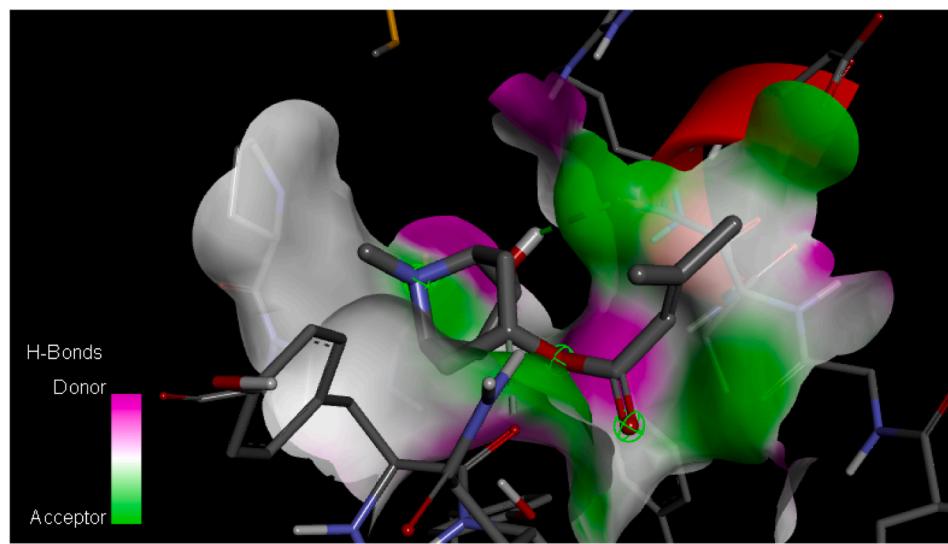
(b)

Fig. 5. (a) H-bonding interactions between the Compound 3 with papain-like protease of SARS-CoV-2 target; (b) All types of interactions between the Compound 3 with papain-like protease of SARS-CoV-2.

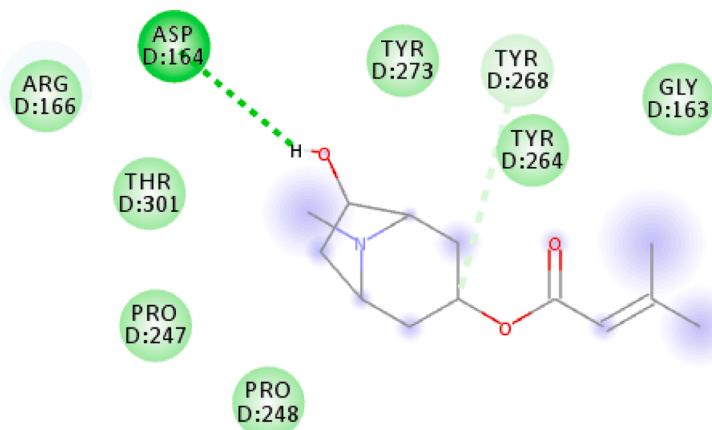
3. Results and discussion

Binding affinities and major interactions between SARS-CoV-2 papain-like protease and tropane alkaloids from Schizanthus porrigens were obtained using Autodock Vina. Binding affinities were compared with those obtained with Lopinavir as inhibitor of the SARS-CoV-2

papain-like protease. The binding affinity obtained from 6WX4 binding with the Lopinavir and tropane alkaloids from Schizanthus porrigens are shown in Table 1. The binding affinity values vary from -5.6 to -7.5 kcal/mol. Discovery Studio 2020 Client software was used to illustrate the molecular interactions between active site SARS-CoV-2 papain-like protease and the ligands. The ligands showed the expected



(a)

PRO
D:248**Interactions**

van der Waals

Conventional Hydrogen Bond

Carbon Hydrogen Bond

(b)

Fig. 6. (a) H-bonding interactions between the Compound 4 with papain-like protease of SARS-CoV-2 target; (b) All types of interactions between the Compound 4 with papain-like protease of SARS-CoV-2.

Table 2

Amino acids residues involved in H-bonds in both ligands and receptors.

Ligands	Amino acids with H-bonds
Schizanthine Y	TYR164, TYR168, TYR173
Schizanthine Z	TYR164, TYR173,
3	ASP164, TYR164, TYR173
4	ASP164
Lopinavir	TYR168, GLN269

interactions with the amino acids present in active site of protein, which implies powerful antagonistic properties towards SARS-CoV-2 papain-like protease. Exhibiting the highest binding affinity Schizantina Z with a value of -7.5 kcal/mol followed by Schizantina Y with a binding energy value of -7.1 kcal/mol. The ligands with the lowest values obtained in this study correspond to ligands 3 and 4 with binding affinity that -5.7 kcal/mol and -5.6 kcal/mol respectively. In general, the binding affinity values of Schizantin Z and Schizantin Y obtained from the set of 4 tropane alkaloids from Schizanthus porrigens suggest that they can be used as potential inhibitors of SARS-CoV-2 papain-like protease. The binding energies of all compounds are close to that of the reference ligand, except for compounds 3 and 4. As shown in Figs. 3–6 complexes between ligands and receptor are stabilized mainly by hydrogen bonds, where the ligand can act as electron acceptor, like in the case of Schizanthine Z or a simultaneous donor and acceptor as in the case of Schizanthine Y, however, other interactions such as hydrophobic interactions also contribute to the stability of the complexes [33]. Table 2 shows that all of tropane alkaloids from Schizanthus porrigens that form hydrogen bonds with the key amino acid residues of SARS-CoV-2 papain-like protease. Natural products provide a source for the development of new antiviral drugs [43]. Identifying the antiviral mechanisms of these natural agents has shed light on where they interact with the virus life cycle, such as viral entry, replication, assembly, and release, as well as on the goal of virus-specific interactions and host [33]. In the present work, we summarize the antiviral activity of tropane-derived alkaloids present in the shrub plant Schizanthus porrigens that grows in soils in northern Chile (IV Region) [11] and perform molecular docking of these compounds. (four ligands) with the SARS-CoV-2 papain-like protease to identify possible inhibitors of this, as well as the ADME analysis [32]. This is vital since several proteins have recently been described that play a key role in SARS-CoV-2 virus infection and that are considered possible pharmacological targets. These include in addition to the SARS-CoV-2 papain-like protease considered in the present study, the SARS-CoV-2 main protease Mpro [7], RNA-dependent RNA polymerase (NPS12) [44], spike glycoprotein (S) [16], transmembrane protease serine 2 (TMPRSS2) [45] and

angiotensin-converting enzyme 2 (ACE2) [46] among others. Therefore, it should be borne in mind that the best candidate for a drug against SARS-CoV-2 is the molecule that can specifically bind to one of the pharmacological targets mentioned above to form a thermodynamically stable complex, this is a compound with the energy of highest possible binding expressed in terms of Gibbs free energy variation (ΔG) [33]. Lipinski's rule of five [47] and ADME properties [47] which were obtained from SwissADME see Tables 3 and 4. The results of virtual detection of two tropane alkaloids from Schizanthus porrigens based on molecular docking scores, hydrogen bridge interactions, and Lipinski's rule of five suggest that they are potential inhibitors of the major protease SARS-CoV-2 papain-like protease, which is essential for virus maturation and infectivity [26,27]. Schizanthine Z is the best drug candidate between the two successes since, in addition to fully obeying Lipinski's rules, it exhibits the highest binding energy. Schizanthine Z, being the one with the highest docking score and the most favorable pharmacokinetics was subjected to a molecular dynamics simulation. Schizanthine Y was also subjected to a molecular dynamics simulation since it was the next best candidate. Fig. 7 shows a water box simulations using molecular dynamics simulation of Schizanthine Z and Schizanthine Y papain-like protease complexes of SARS-CoV-2 [2]. Fig. 8 shows the mean square deviation (RMSD), which was used to examine the structural changes of the Schizanthine Z and Schizanthine Y papain-like protease complexes of SARS-CoV-2, both graphs show a similar deviation and fluctuation, validating the consistency of the simulation trajectories [41].

4. Conclusions

The development of new drugs to treat COVID-19 is of vital importance to design an efficient therapy, because development of vaccines against SARS-CoV-2 virus can take many months. Furthermore, virus-encoded peptide-based vaccines may not be effective against future coronavirus epidemics, as virus mutations could render them useless. While researchers are looking for molecules with anti-SARS-CoV-2 activity using organic synthesis techniques, another way is to promote chemistry research on natural products. Considering the enormous amount of existing phytocomposites, we can refer to computational chemistry to help in the study of different plant activities such as Schizanthus porrigens candidates from the set of 4 tropane alkaloids from Schizanthus porrigens using molecular docking and ADME properties. The reactivity of SARS-CoV-2 papain-like protease with 4 tropane alkaloids from Schizanthus porrigens showed that the most stable complex is obtained with Schizanthine Z with a binding affinity value of -7.5 kcal/mol, followed by Schizanthine Y with -7.1 kcal/mol. Finally, Lipinski's rule of five based on ADME analysis and molecular dynamics

Table 3

Lipinski parameters for dataset from SwissADME.

Inhibitor	MW	Log P	HBD	HBA	Violation	Yes/No	Solubility	Log S
Schizanthine Y	490,59	4,52	1	9	0	Yes	M.S.	-4.62
Schizanthine Z	490,59	4,33	1	9	0	Yes	M.S.	-4,71
3	239,31	2,51	1	4	0	Yes	S	-2,20
4	239,31	2,51	1	4	0	Yes	S	-2,46

MW: Molecular weight (Da), Log P: Octanol-water partition coefficient, HBD: Hydrogen bond donors, HBA: Hydrogen bond acceptors Log S: 10-based logarithm of the solubility measured in mol/l unit.

Table 4

Pharmacokinetics of the four potential inhibitors.

Inhibitor	Gla	BBBp	P-gps	1A2	2C19	2C9	2D6	3A4	Log Kp
Schizanthine Y	High	No	No	No	No	No	No	No	-7,34
Schizanthine Z	High	No	No	No	No	No	No	No	-7,28
3	High	Yes	No	No	No	No	No	No	-6,65
4	High	Yes	No	No	No	No	No	No	-6,48

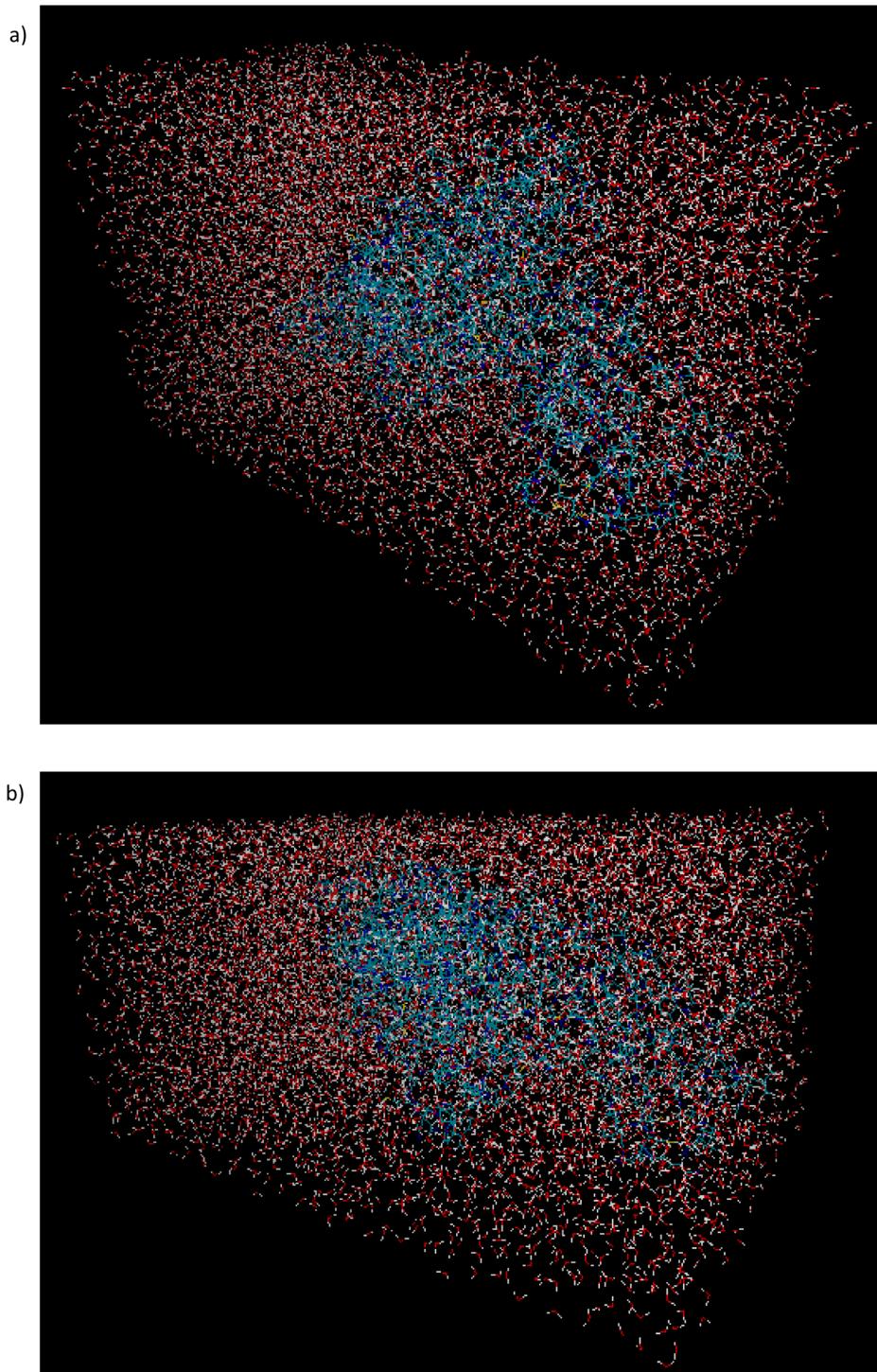


Fig. 7. (a) Water box simulation using molecular dynamics simulation of complex between the papain-like protease of SARS-CoV-2 and the Schizanthine Z. (b) Water box simulation using molecular dynamics simulation of complex between the papain-like protease of SARS-CoV-2 and the Schizanthine Y.

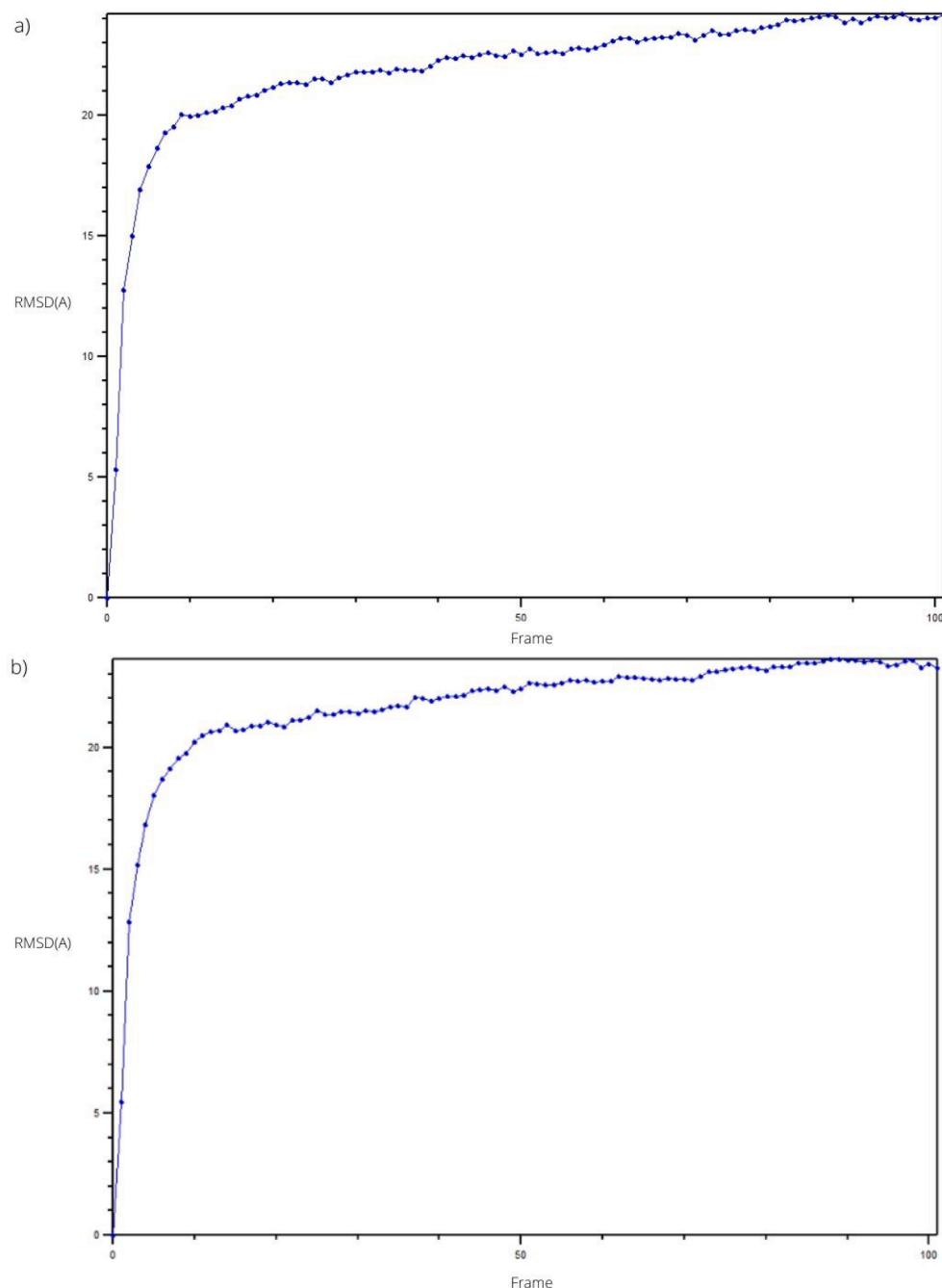


Fig. 8. (a) The Root Mean Square Deviation (RMSD) curve of complex between the papain-like protease of SARS-CoV-2 and the Schizanthine Z. (b) The Root Mean Square Deviation (RMSD) curve of complex between the papain-like protease of SARS-CoV-2 and the Schizanthine Y.

simulation confirms that Schizanthine Z is the best candidate for the drug, which is why it is recommended for in vitro tests.

CRediT authorship contribution statement

Marco Alfaro: Conceptualization, Data curation, Formal analysis, Methodology, Writing - original draft, Writing - review & editing. **Ignacio Alfaro:** Conceptualization, Data curation, Formal analysis, Methodology, Resources, Software, Writing - original draft, Writing - review & editing. **Constanza Angel:** Resources, Software, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cplett.2020.138068>.

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