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Identification of new anti-SARS-CoV-2 agents through virtual screening of phytoconstituents extracted from Moroccan plants

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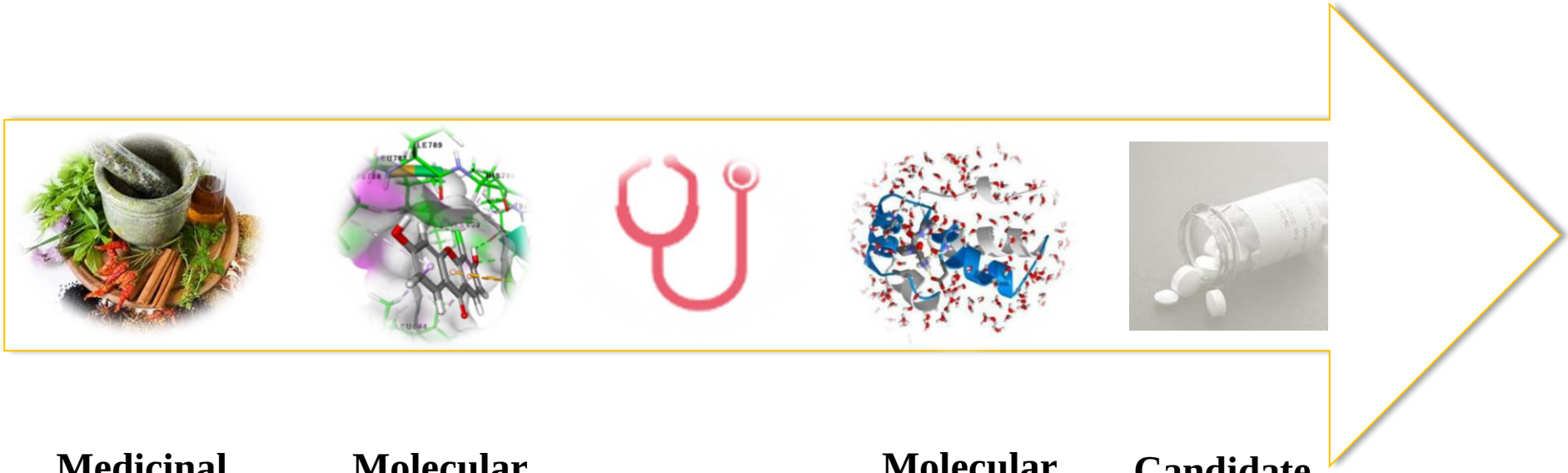
Identification of new anti-SARS-CoV-2 agents through virtual screening of phytoconstituents extracted from Moroccan plants

Graphical Abstract



Medicinal plants | **Molecular docking** | **ADMET** | **Molecular dynamics** | **Candidate drug**

Abstract:

The fast spread of deadly viruses like SARS-CoV-2 and the ineffectiveness of the available vaccinations push us to look for alternative medications that can stop the development of like SARS-CoV-2 cases around the world. Moroccan traditional medicine may hold the key, given how well it treats even the most prevalent local illnesses. For this reason, a virtual screening was conducted on a collection of phytoconstituents from Moroccan medicinal plants in order to identify any potential inhibitors of SARS-CoV-2 activity.

Molecular docking of studied compounds was done in the active site of 6lu7 and 6m0j proteins to assess their binding affinity towards the target proteins. The structural stability of the target protein models was validated by redocking of ACE2 and N3 ligands in the active pockets of 6m0J and 6lu7 receptors. The compounds with good values of binding affinity were further subjected to Lipinski's rule of five, chemical absorption and toxicity analysis to gain insight into their oral bioavailability and safety. The molecular dynamics results in this computational analysis to support the optimum stability of the complex obtained.

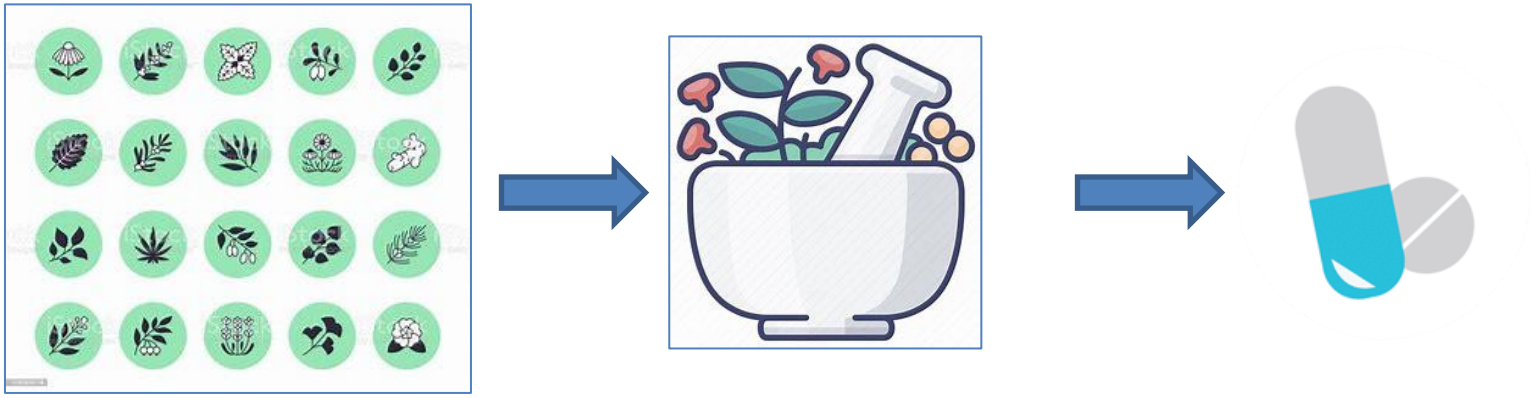
Keywords: ADMET; Drugs; Medicinal plants; Molecular Docking; SARS-CoV-2;

As known in the worldwide, the SARS-CoV-2 is an infectious virus has got its start in Wuhan and has spread over the rest of the world. The rapid progress of COVID19 cases occurred the WHO to announce a global health emergency.

Considering the rapid proliferation SARS-CoV-2 and survival are dependent on the replication process, it’s critical to discover a strategy to stop the progression of virus replication.

Introduction

A deep research was done in the previous literature to collect the phytoconstituents of Moroccan plants used in traditional medicine.
To determine that it has the ability to inhibit the SARS-CoV-2 activity, the virtual screening was done by using molecular docking study where we define the stability of the complex formed between the studied ligands and protein.



Drug design

Drug is a chemical substance used in the treatment, cure, prevention, or diagnosis of disease enhance physical or mental well-being.

Drug design (traditional): trial and error as molecular mechanisms of disease not known.

Cost and time consuming, laborious.

Computer-assisted drug design (CADD)

CADD is divided into two strategies:

Ligand-based:

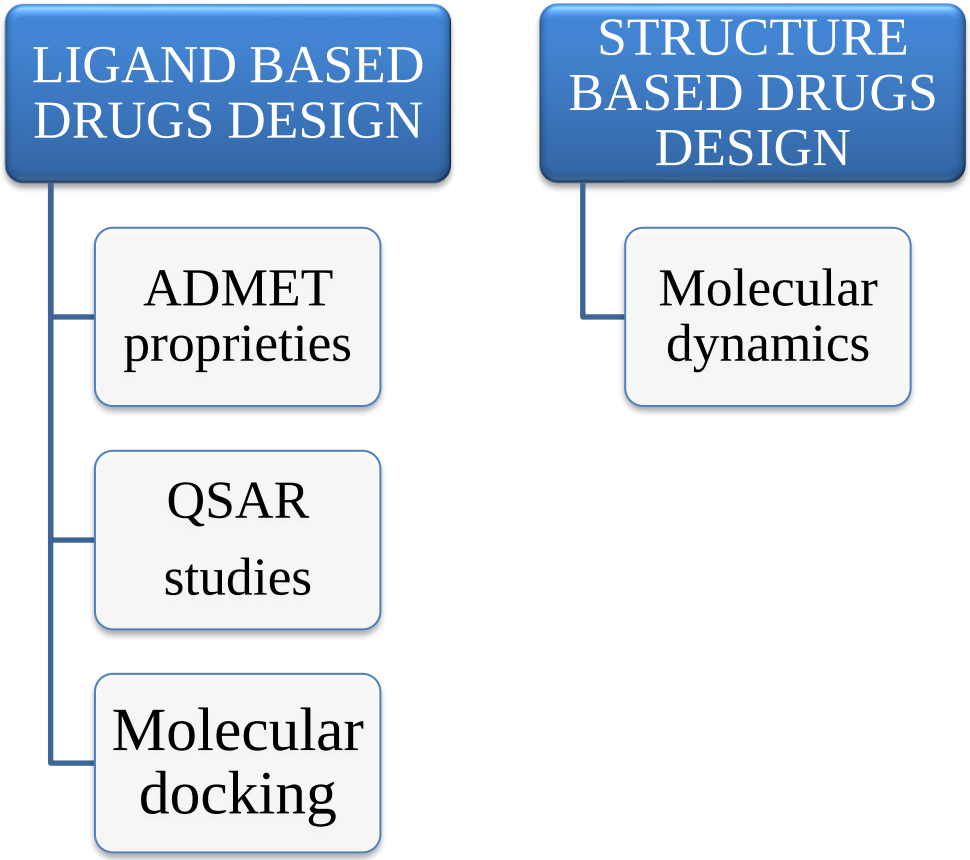
- Is about findings ligands for a given target.
- A large number of potential ligand molecules are screened.
- It saves synthetic effort to obtain new hit/lead compounds.

Structure-based:

- Relies on knowledge of the three dimensional structure of the biological target obtained through:

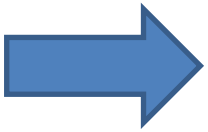
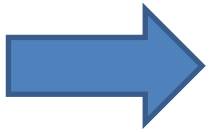
1. X-ray crystallography
2. Nuclear magnetic resonance (NMR) spectroscopy.

Computer assisted drug-design



Material and methods

Database

8 Families  27 Medicinal plants  297 Compounds

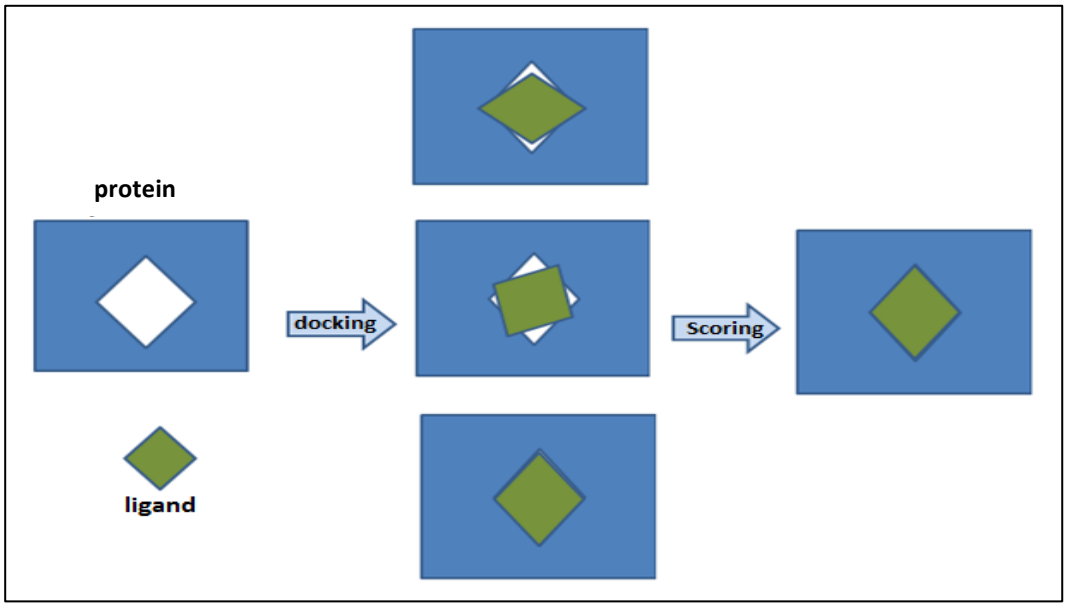
The database was formed after a deep research in previous works, where we collected the phytoconstituents of Moroccan plants used in traditional medicine. The chosen plants were listed in following table:

	Plants	Family	Plants	Family	Plants
Lamiaceae	Mentha pulegium	*Apiaceae*	Foeniculum vulgare	*Myrtaceae*	Syzygium aromaticum
	Lavandula angustifolia		Ammi visnaga		Eucalyptus globulus
	Origanum compactum		Pimpinella anisum		Myrtus communis
	Majorana hortensis moench	*Fabaceae*	Cassia absus	*Lauraceae*	Cinnamomum burmanni
	Rosmarinus officinalis		Acacia raddiana		Laurus nobilis
	Teucrium polium		Glycyrrhiza glabra	*Zingiberoside*	Alpinia officinarum hance
	Mentha spicata	*Asteraceae*	Artemisia herba alba		Curcuma longa
	Salvia officinalis		Matricaria camomilla	*Rosaceae*	Malus domestica
	Marrubium vulgare		Anacyclus pyrethrum		Rosa damascena

Molecular docking

Molecular docking is a method that predicts the preferred orientation of a molecule in a second when it is linked to each other to form a stable complex.

Knowledge of the preferred orientation, in turn, can be used to predict the binding force or affinity between two molecules.

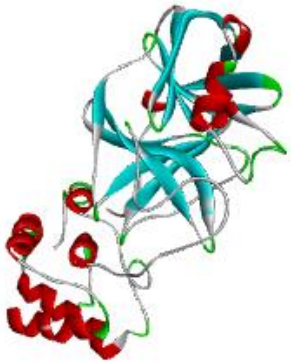


A target is a structure that generally consists of a protein and comprises the active site.

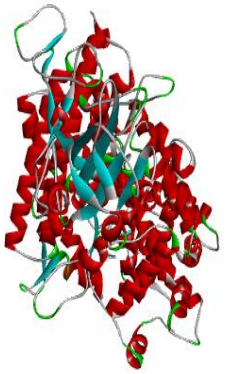
A ligand is a structure that binds to a liaison site, often a tiny molecule.

Molecular docking

We conducted molecular docking analysis of the candidates ligand with SARS-CoV-2 main protease (coded PDB ID: 6lu7) and spike protein (coded PDB ID: 6m0j), which represents potential therapeutic targets for the inhibition of SARS-CoV-2 replication.



6lu7

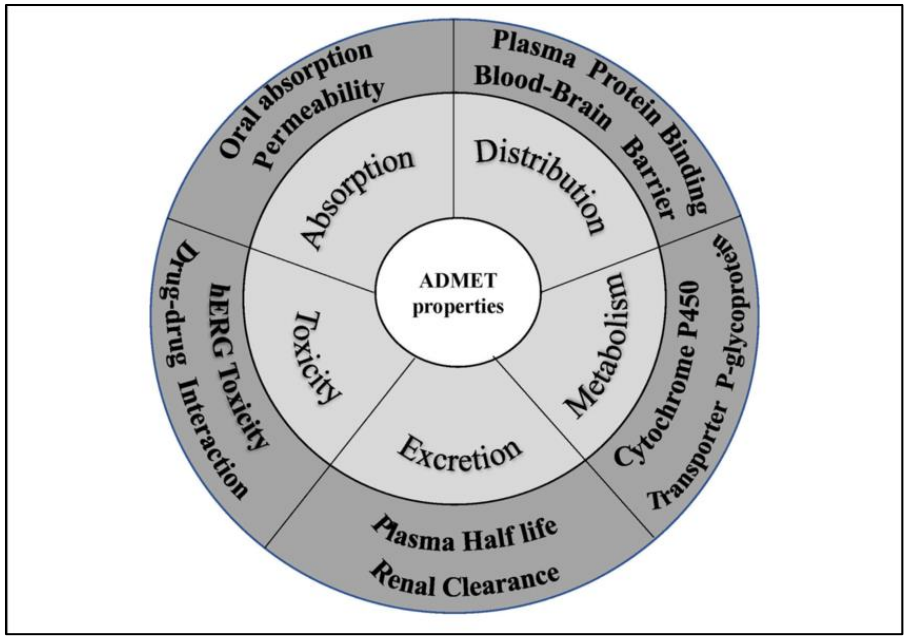


6m0j

ADME/Tox proprieties

ADME/Tox properties are important parameters for the selection of drug candidates to develop and investigate the level and kinetics of drug exposure to the tissues and hence influences the performance and pharmacological activity of the compound as a drug:

- Absorption
- Distribution
- Metabolism
- Excretion
- Toxicity

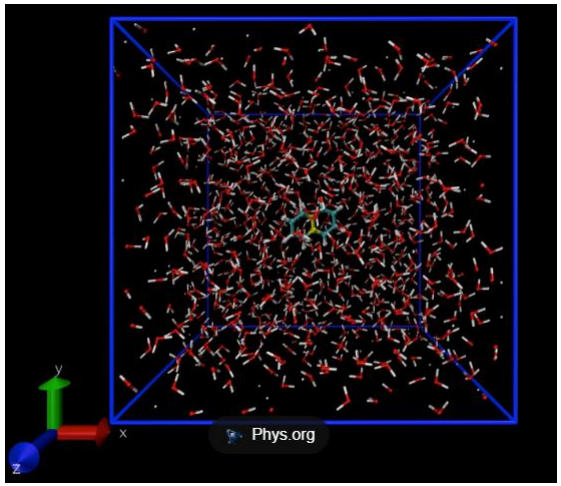


Molecular dynamics

Molecular dynamics is a computer simulation method for studying the physical movements of atoms and molecules and is thus a type of N-body simulation. Molecular dynamics simulation relies on a robust rule of nature: newton's Second Law of Motion. where the force equals mass multiplied by acceleration helps predict how the particles move.

The particles in the simulation will interact by two potential function terms:

- The force field in chemistry and biology.
- Interatomic potential in materials physics.



Results and discussion

The database (297 ligands) and the two studied proteins were prepared and downloaded as PDBQT format. AutoDockTools-1.5.6 was used to configure the coordinate grid box of the docking and the molecular docking simulations was perform using Autodock 4.

6lu7 receptor						6m0j receptor	
Compounds	Score	Compounds	Score	Compounds	Score	Compounds	Score
24	-8.1	108	-8	200	-7.4	109	-7
26	-7.6	109	-8.1	221	-7.8	126	-7.9
32	-8.7	123	-7	233	-7	139	-7.1
36	-7.8	126	-9.4	234	-7.7	143	-7.5
37	-7.8	139	-7.6	241	-9.2	144	-7.2
44	-8.5	140	-8.1	245	-7.3	177	-7.1
45	-9	143	-8.3	248	-7.4	189	-7.2
50	-7.6	148	-8.4	249	-7.2	221	-7.4
52	-7.3	154	-7.1	250	-8.3	24	-7.1
60	-7.3	164	-7.3	253	-7.5	241	-7.1
62	-7	166	-8.2	257	-7.7	270	-8.2
66	-7.3	167	-7.2	260	-8.1	312	-7.7
73	-7.3	176	-7.9	268	-7	32	-7.6
75	-7.2	177	-7.5	270	-8.6	323	-7.9
86	-8.4	178	-7.4	312	-8	50	-8.3
97	-7	189	-7.2	323	-7.6	86	-7.4
101	-7.2	190	-7.1	339	-8.4	-	-

Lipinski's and veber's rules

- Molecular weight (MW ≤ 500 Da),
- Number of hydrogen bond acceptor (HBA ≤10),
- Number of hydrogen bond donor (HBD ≤5),
- Octane-water partition coefficient (log P ≤5),
- Rotatable bonds(RB ≤5), Polar surface area (PSA ≤140 Å)

Lipinski's rule					Veber's rules	
N	Molecular Weight	LogP	Donors (HBD)	Acceptors (HBA)	Rotatable Bonds	PSA (Å)
26	340.284	-1.3227	5	9	3	134.461
123	302.282	2.1709	3	6	2	125.714
164	300.266	2.5854	3	6	2	123.998
178	286.239	2.2824	4	6	1	117.313
245	302.238	1.988	5	7	1	122.108
36	270.24	2.5768	3	5	1	112.519
249	300.266	2.5854	3	6	2	123.998
248	316.265	2.291	4	7	2	128.792
233	274.272	2.3245	4	5	4	114.922
154	274.272	2.2029	3	5	4	115.241
140	324.376	4.0007	2	4	1	140.522

Absorption and toxicity

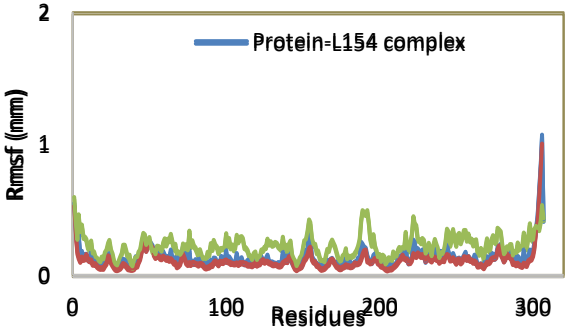
Cpd	AMES toxicity	Max. tolerated dose (human)	hERG I inhibitor	hERG II inhibitor	Hepatotoxicity	Skin Sensitization	Minnow toxicity
26	No	0.32	No	No	Yes	No	2.501
36	No	0.713	No	Yes	No	No	0.95
123	No	-0.132	No	No	No	No	1.59
140	Yes	-0.238	No	Yes	No	No	0.06
154	No	-0.044	No	No	No	No	1.04
164	No	0.896	No	No	No	No	0.576
178	No	0.801	No	Yes	No	No	1.545
233	No	0.346	No	No	No	No	-0.041
245	No	0.742	No	No	No	No	1.999
248	Yes	0.727	No	Yes	No	No	1.397
249	No	0.539	No	Yes	No	No	1.353

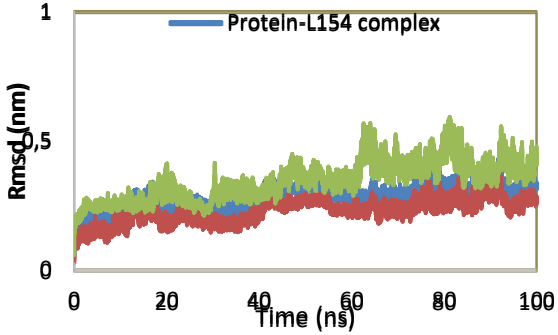
N	164	154
Caco-2 permeability	1.273	1.139
Intestinal absorption (human)	80.538	89.092
Skin permeability	-2.735	-3.139
P-glycoprotein substrate	Yes	Yes
P-glycoprotein I inhibitor	No	No
P-glycoprotein II inhibitor	No	No

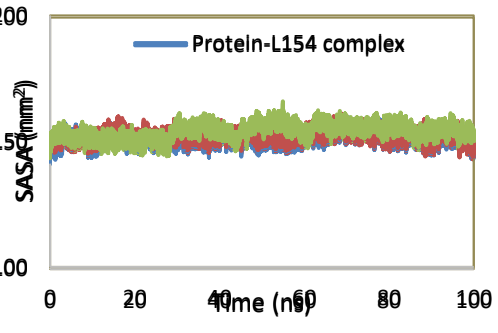
Molecular dynamics

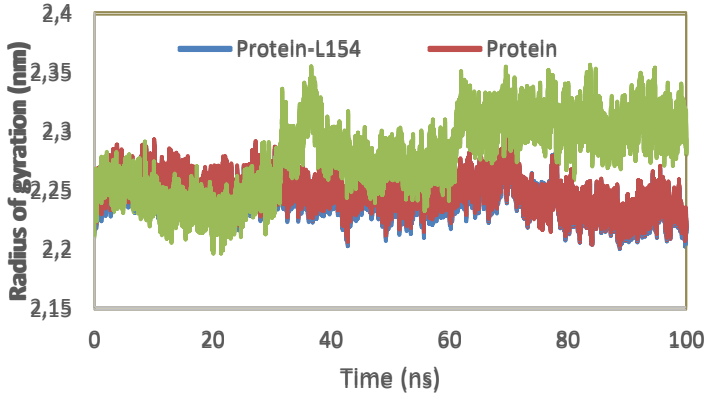
The obtained results highlight that the molecular recognition of L154 and 6lu7 lead to a stable complex.

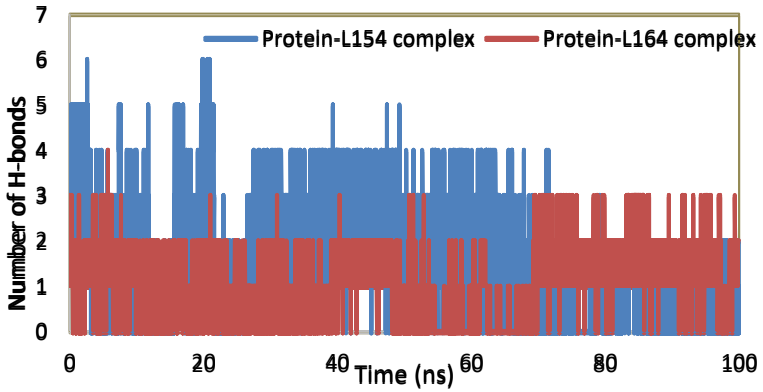
Complex	RMSD (nm)	RMSF (nm)	ROG (nm)	SASA (nm²)
6LU7	0.230	0.117	2.247	151.984
6LU7-154	0.283	0.142	2.245	151.354
6LU7-164	0.341	0.255	2.278	153.866











Conclusion

The virtual screening of a set of 297 compounds extracted from 27 Moroccan plants used in traditional medicine by using the ADMET , molecular dynamics and docking methods to predict the molecules that can be used as a drug and with no side effect, the results suggested 3 molecules that could form a stable complex with SARS-CoV-2, Adding to their good predicted pharmacokinetics properties.
Finally the molecular dynamics method supported the optimum stability of the complex obtained.
In vitro, then in vivo study may confirm the obtained results.