TESTING THE ACTIVITY OF BIGUANIDES AND SOME NOVEL DESIGEND MOLECULES AGAINST SARS-COV-2 PROTIENS, *IN SILICO* STUDY

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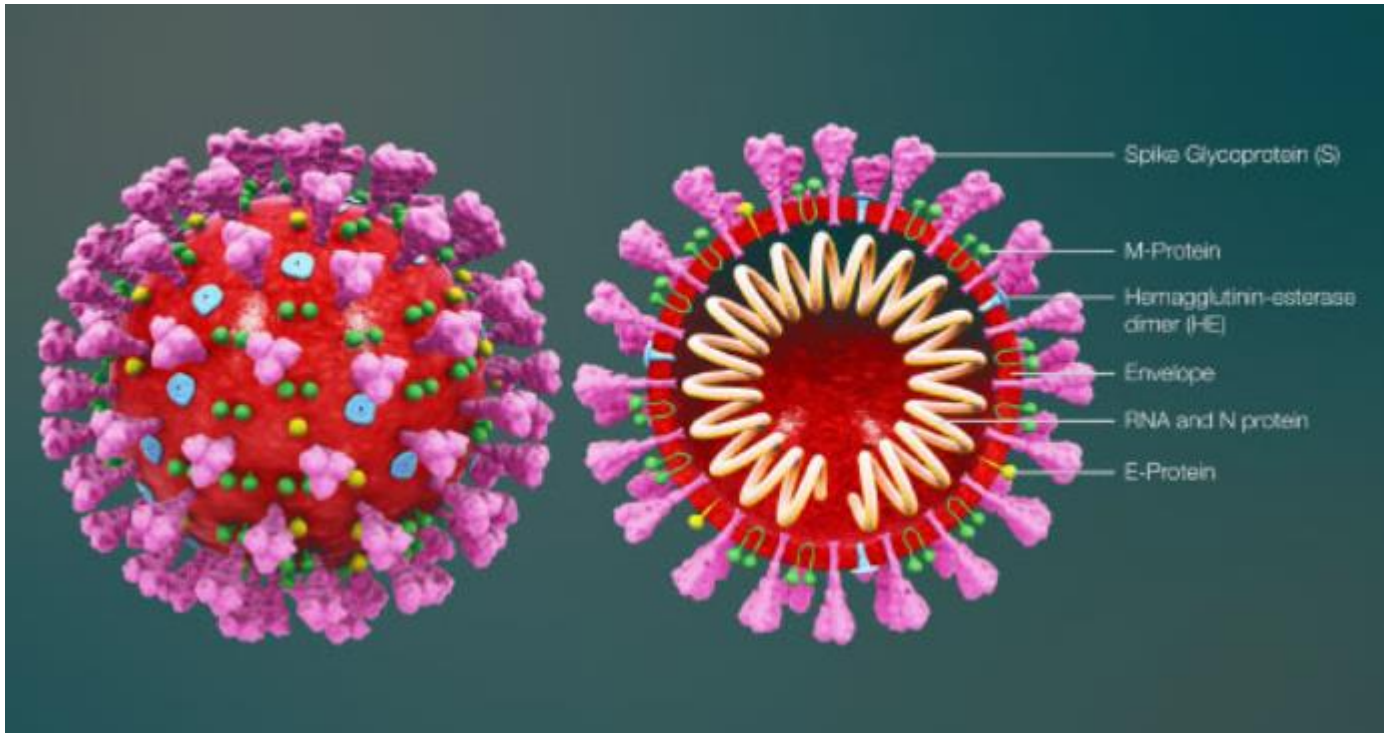
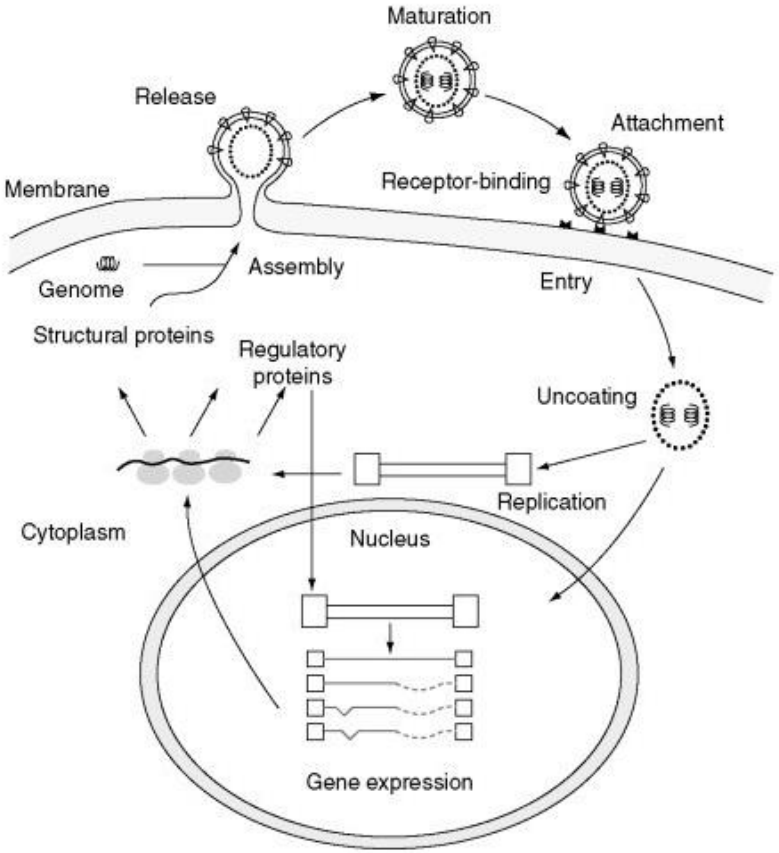
SARS-CoV-2 is the main pathogen which caused Corona Virus Disease 2019 (**COVID-19**)



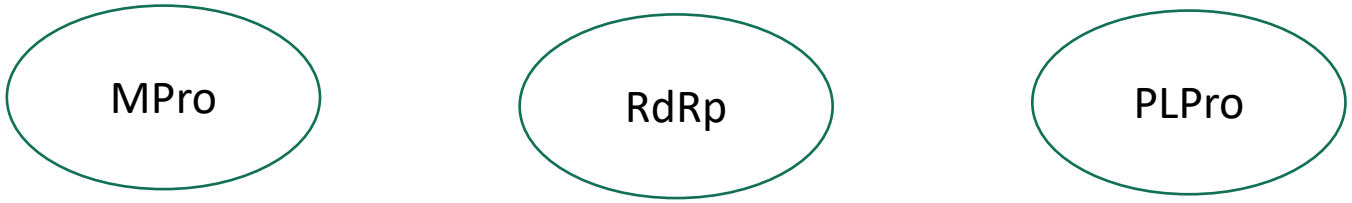
Overview

COVID-19 Spreading

After hijacking human cell, this virus gets inside it, then the replication and copying processes are initiated to form new copies of this virus, which attack new cell, and so the infection occurs.



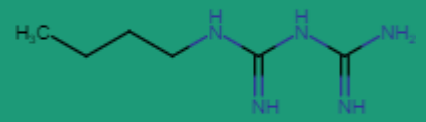
Some viral proteins responsible for Corona virus 2 replication



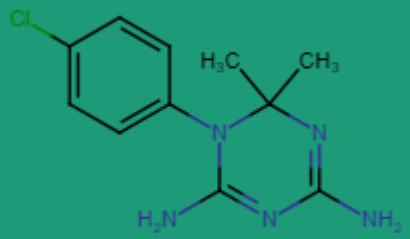
Purpose of the study

We aimed to investigate the activity of biguanides against these proteins to inhibit the growth of SARS-CoV-2

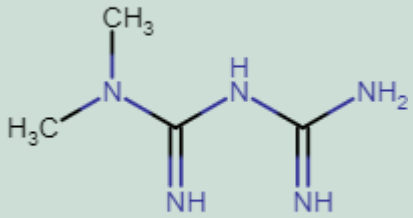
Buformin



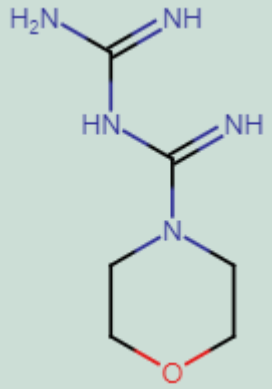
Cycloguanil



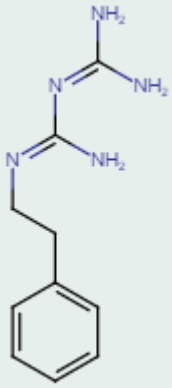
Metformin



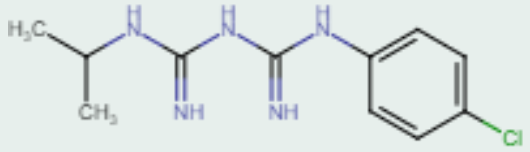
Moroxydine



Phenformin



Proguanil



Main derivatives of biguanides

The protocol of the study

We used three methods:

1- Molecular docking

In which we test the binding affinity of each compound with every single protein

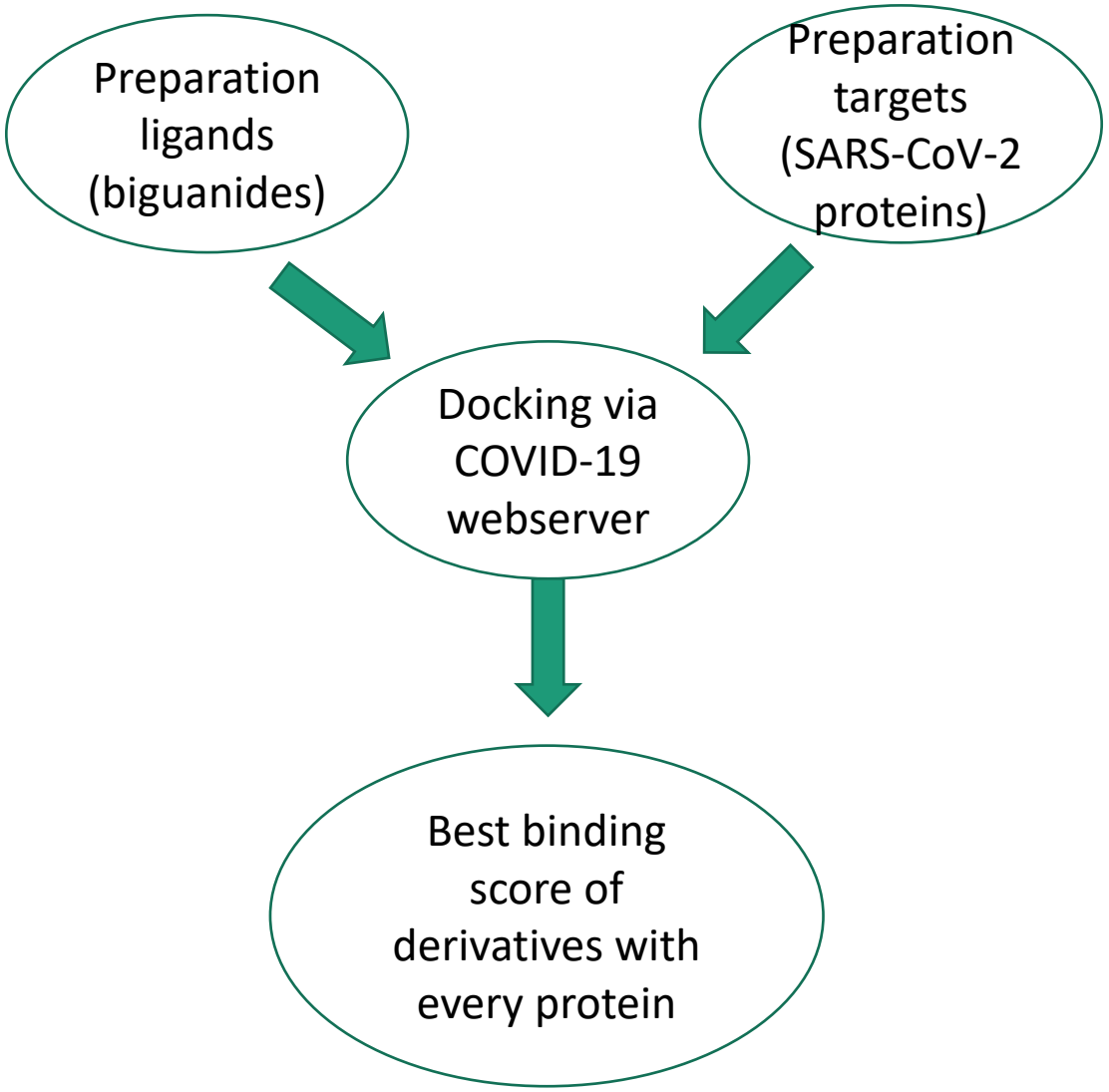
2- ADMET analysis

The physical properties of the new 30 created compounds and bioavailability were tested

3- Molecular dynamic simulation

Investigate the stability of the compounds upon the proteins

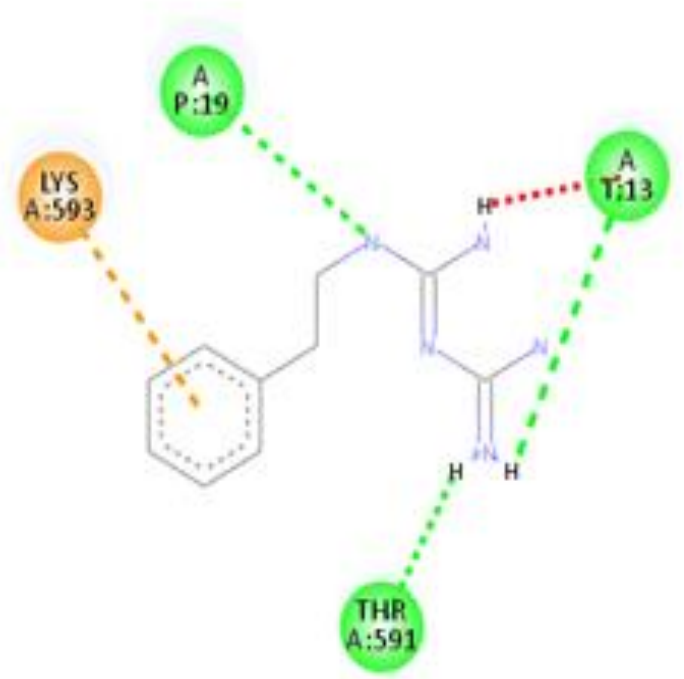
1- Molecular Docking

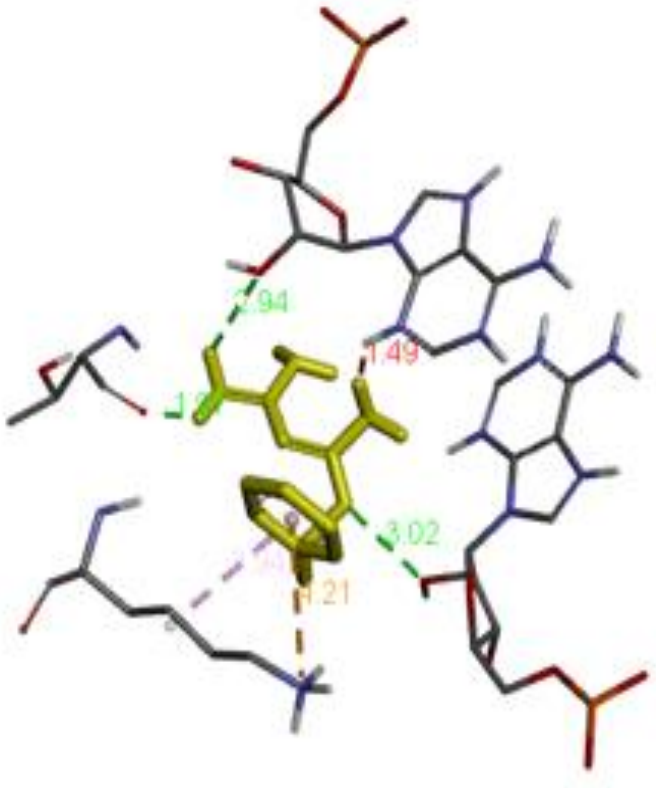


RESULT AND DISCUSSIONS

Molecular docking results of main derivatives against RdRp SARS-CoV-2

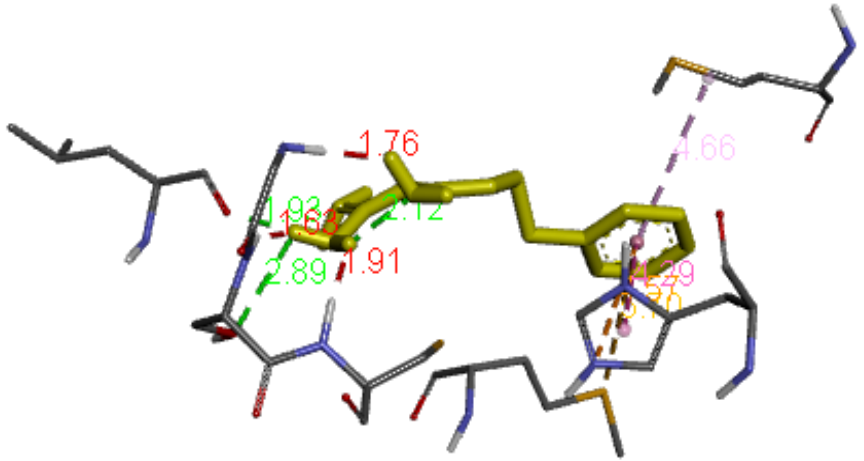
Docking results of RdRp	
Derivative name	Score value (kcal/mol)
Buformin	-6.7
Cycloguanil	-8.6
Metformin	-6.3
Moroxydine	-7.9
Phenformin	-9.1
Proguanil	-8

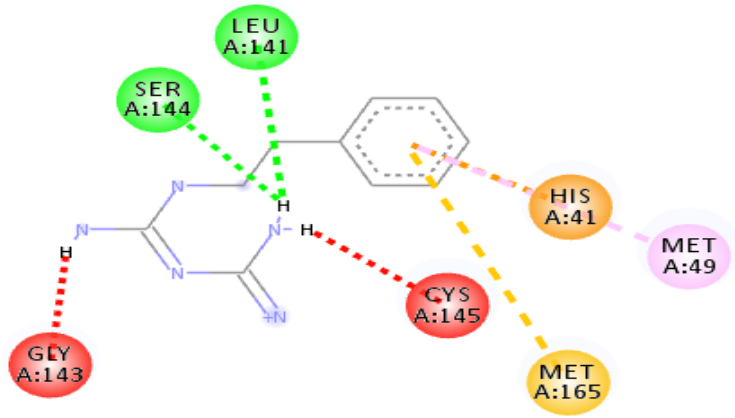




Molecular docking results of main derivatives against Main protease SARS-CoV-2:

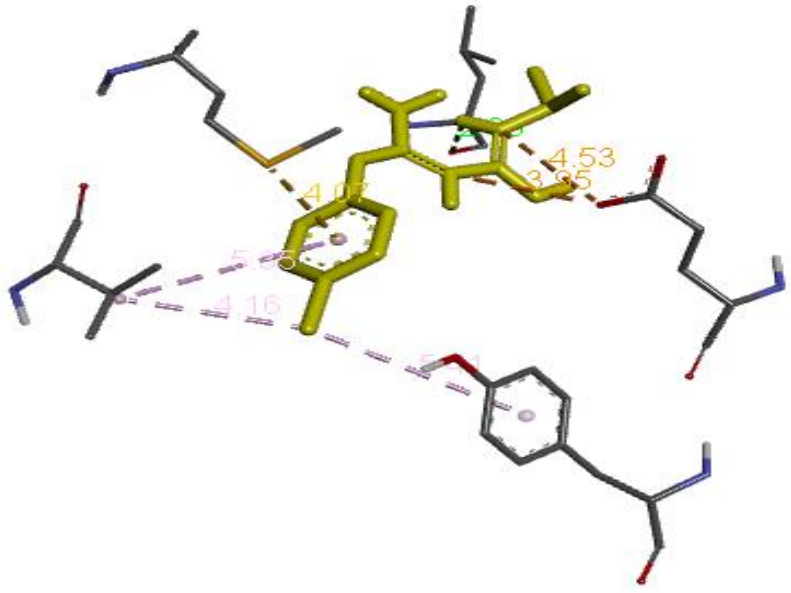
Docking results of MPro	
Derivative name	Score value (kcal/mol)
Buformin	-5.4
Cycloguanil	-6.5
Metformin	-5.3
Moroxydine	-6.3
Phenformin	-6.7
Proguanil	-6.7

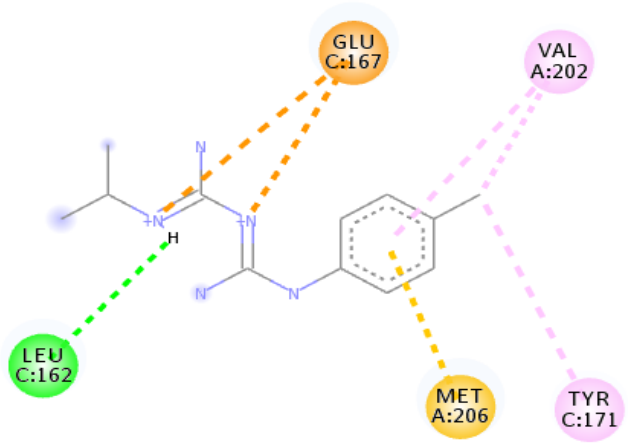




Molecular docking results of main derivatives against PLPro SARS-CoV-2:

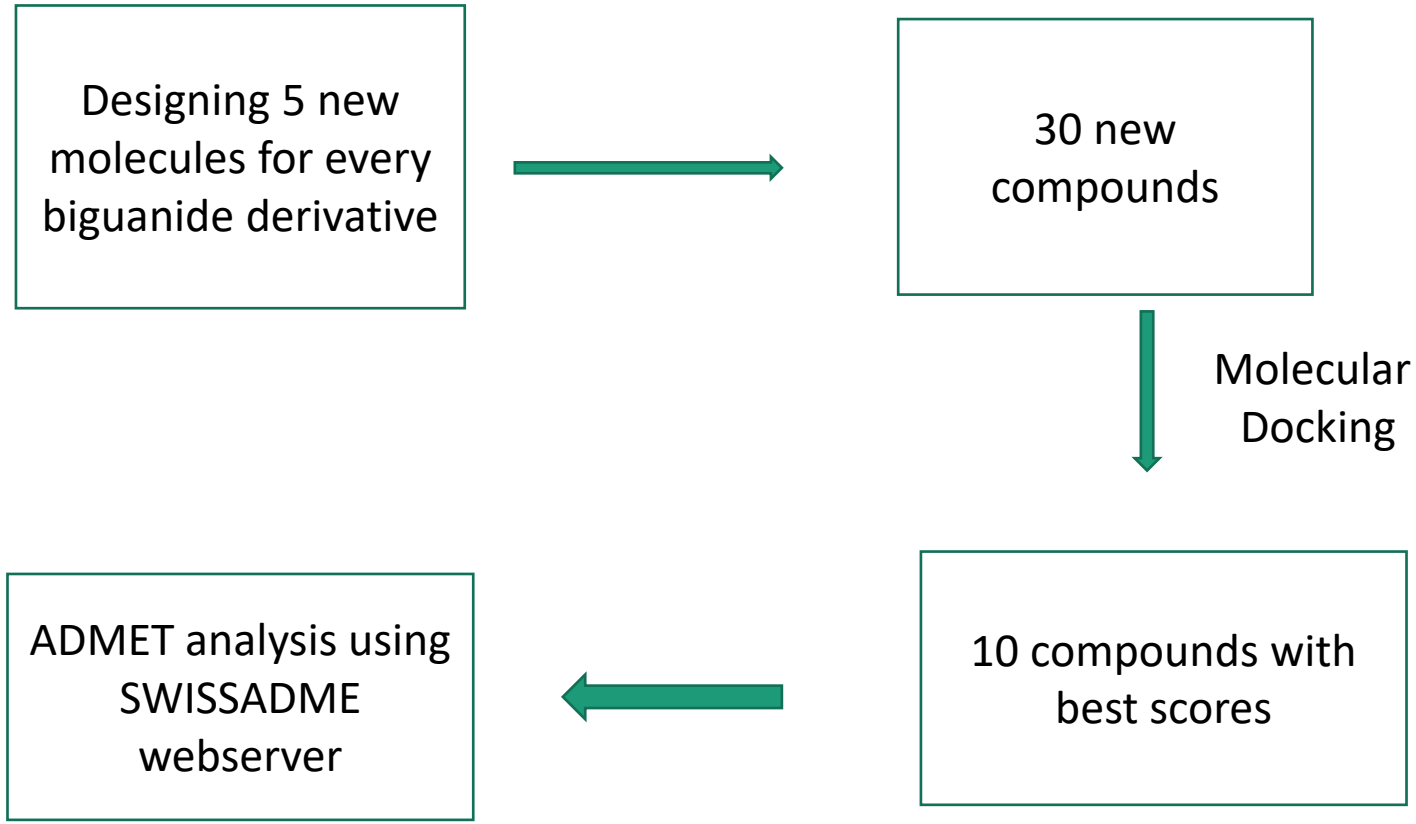
Docking results of PLPro	
Derivative name	Score value (kcal/mol)
Buformin	-5.8
Cycloguanil	-7
Metformin	-5.8
Moroxydine	-6.7
Phenformin	-6.9
Proguanil	-7.1





2- ADMET analysis

Investigating drug properties such; physicochemical properties, water solubility, pharmacokinetics, and drug likeness properties.

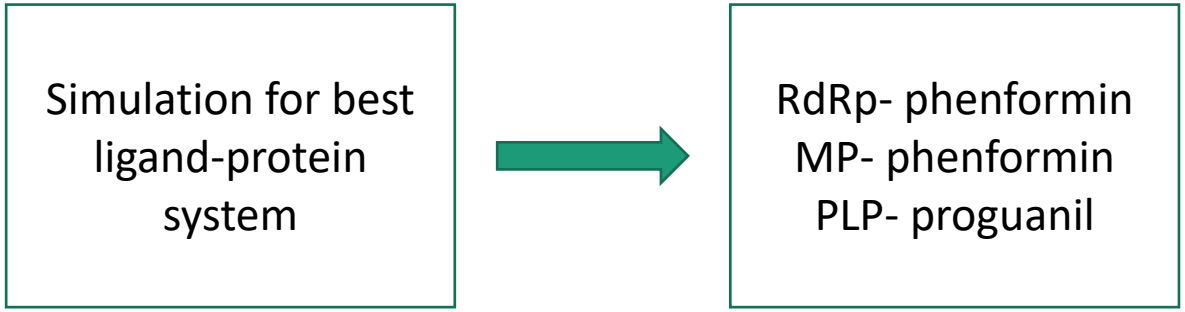


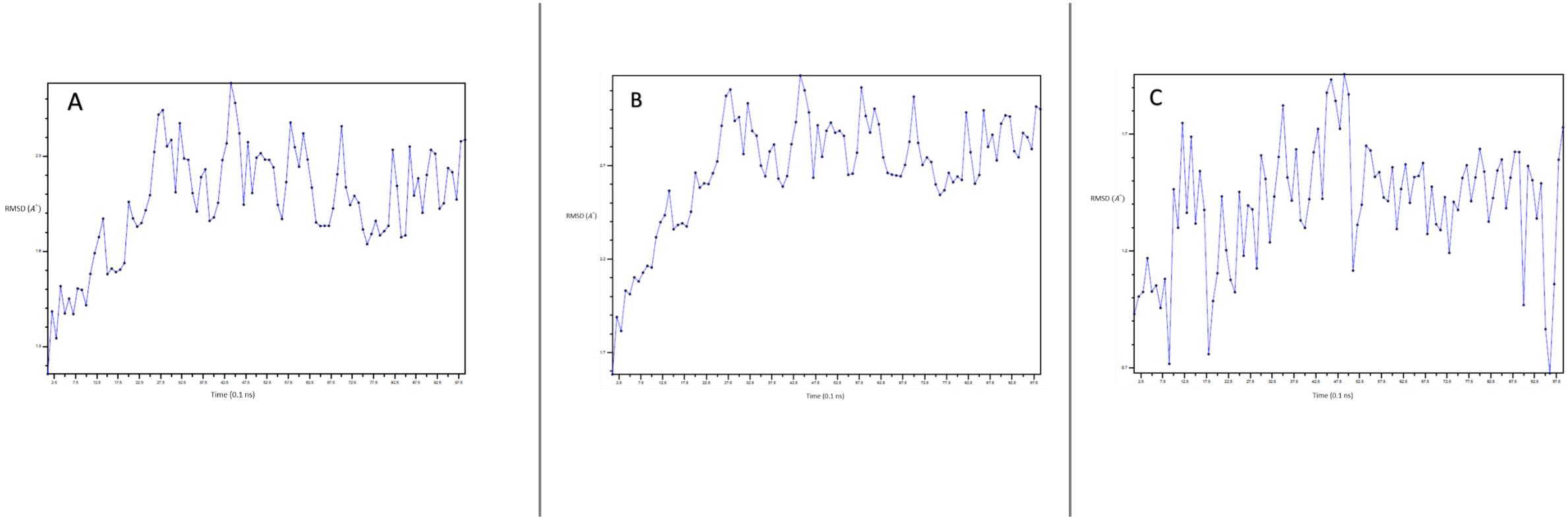
Modified drug name	Physiological properties						
	Formula	MW	Heavy atoms	Rotatable bonds	H-bond acceptors	H-bond donors	TPSA (A^2)
BUF3	C5H10N6O4	218,17	15	7	6	7	175,62
BUF4	C5H11N5O3	189,17	13	7	5	6	130,32
BUF 5	C9H17N5O4	259,26	18	9	6	4	129,81
MET 1	C4H9N5O3	175,15	12	5	5	6	146,52
MET 2	C4H10N6O2	174,16	12	5	4	6	152,31
MET 4	C6H15N5O2	189,22	13	6	4	5	106,67
MET 5	C6H7N5O8	277,15	19	8	10	7	215,41
PHEN 2	C12H17N5O3	279,3	20	7	5	4	137,53
PHEN 3	C12H18N6O2	278,31	20	7	4	4	143,32
PROG 1	C9H12ClN5O2	257,68	17	4	2	6	129,31

Modified drug name	Pharmacokinetics properties				Drug-likeness filters	
	GI absorption	BBB penetration	Pgp substrate	log Kp (cm/s)	Lipinski's violations	Bioavialability score
BUF3	Low	No	No	-8,79	Yes, 1 violation	0,55
BUF4	Low	No	No	-7,94	Yes, 1 violation	0,55
BUF 5	High	No	No	-7,28	Yes	0,55
MET 1	Low	No	No	-8,25	Yes, 1 violation	0,55
MET 2	Low	NO	NO	-8,7	Yes, 1 violation	0,55
MET 4	High	No	No	-8,63	Yes	0,55
MET 5	Low	No	No	-7,17	No	0,11
PHEN 2	High	No	No	-7,63	Yes	0,55
PHEN 3	Low	No	No	-8,08	Yes	0,55
PROG 1	Low	No	No	-6,93	Yes, 1 violation	0,55

3- Molecular dynamic simulation

To Investigate the stability of the compounds upon the proteins





A) RMSD values of PLPro backbone during 10 ns MD simulation. B) RMSD values of PLPro- proguanil complex. C) RMSD values for proguanil atoms during 10 ns MD simulation.

CONCLUSION

This study revealed that, **phenformin** could be used to inhibit the action of both RdRp and MPro proteins, also **proguanil** could be used against PLPro. At the same time, after validation of their properties using ADMET analysis; Buf 3, Buf 4, Buf 5, Met 1, Met 2, Met 4, Phen 2, Phen 3, and Pro 1 could be used for RdRp, Mpro, and PLPro inhibition, and so for treating COVID-19.

Thank you for listening