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Materials Today: Proceedings xxx (xxxx) xxx

Contents lists available at ScienceDirect

Materials Today: Proceedings

journal homepage: www.elsevier.com/locate/matpr

Pyrazole, imidazole and triazole: In silico, docking and ADMET studies against SARS-CoV-2

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ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Pyrazole
Imidazole
Triazole
SARS-CoV-2
Theoretical study
AMET

ABSTRACT

The Coronavirus pandemic, Covid-19 and SARS-Cov-2 put multidisciplinary research by chemists, biologists, pharmacists and theorists necessary and primordial task to find new active biomolecules which will be beneficial for all humanity. The azoles drugs are electronic rich, they should be used with caution, and an understanding of their pharmacokinetic profile, safety, absorption, distribution, excretion, metabolism, toxicity, and drug-drug interaction profiles is important to provide effective and cure therapy. In these objectives and goals, twenty aromatic nitrogen heterocycle compounds were chosen for in silico, docking and AMET studies against SARS-CoV-2. In this paper with respect to the protein S of SARS-CoV-2 properties, the GAUSSIAN 09w program used in the semi-empirical method at the AM1 level with the optimization of the geometry of the structures. Then Toxicity and physicochemical properties were evaluated by AMET. Molecular docking investigations conducted; the binding affinities as well as interactions of the sieve compounds with the SRAS-CoV-2 protein Spike using PyRx software. In general, the preliminary results are fructuous and needs further in vitro testes.
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Selection and peer-review under responsibility of the scientific committee of the Fifth edition of the International Conference on Materials & Environmental Science.

1. Introduction

The theoretical calculation of bonding energy is important. It helps to screen the formulations to avoid many unnecessary lab reactions; eventually, it can save the chemical and time. Thus, it is highly beneficial for the environment by using only necessary chemicals as well as cost-effective by arranging the required chemicals only. The widely used theoretical calculation method of bonding is the density functional the (DFT) method. Especially, the hydrogen bond energy calculation by the DFT method has been proved an efficient tool [1–10]. The Nitrogen chemistry containing multimodal molecules is attracting current interest in the scientific world because of their specificity for biological targets [11]. These azole compounds are also appeared to play a key role since it is involved in several types of chelating ligands [12–16], which have been used in models that mimic the active sites of copper proteins [17–45]. Meanwhile, research into the properties of nitrogen ligand complexes has increased exponentially [46], largely due to their possible use as photo-catalysts during solar energy conversion, anti-inflammatory agents [47], cytotoxic agents [48], insecticides [49], herbicides [50], fungicides [51]. Aromatic nitrogen heterocyclic compounds and their derivatives represent an important class in metal coordination chemistry [52]. These complexes have been extensively studied generating increasing interest in coordination chemistry and medicinal chemistry [53]. In fact, several derivatives have been successfully prepared and marketed such as Celecoxib, Viagra, Rimonabant, Sulfaphenazole or Penthiopyrad (Fig. 1) [54].

Our study focuses on pyrazole, thiazole and imidazole derivate (Fig. 2) by evaluating their biological activity and interaction on SARS-CoV-2 protein Spike.

2. Materials and methods

2.1. Chemistry

We first undertook the synthesis of 1-hydroxymethyl-3, 5-dimethylpyrazole and 1-hydroxymethyl-pyrazole by the condensation of 3, 5-dimethylpyrazole with formaldehyde in aqueous

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https://doi.org/10.1016/j.matpr.2022.09.060
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Please cite this article as: M. Mohamed, F. Abrigach, S. El Kadiri et al., Pyrazole, imidazole and triazole: In silico, docking and ADMET studies against SARS-CoV-2, Materials Today: Proceedings, https://doi.org/10.1016/j.matpr.2022.09.060

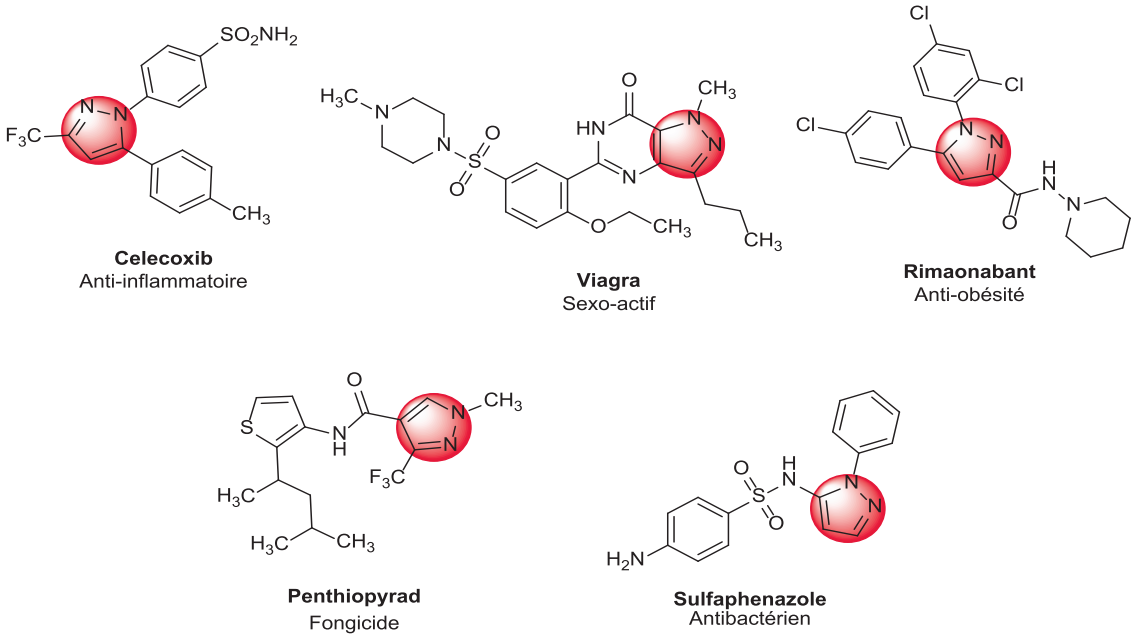

Fig. 1. Usual drug basis in pyrazole.

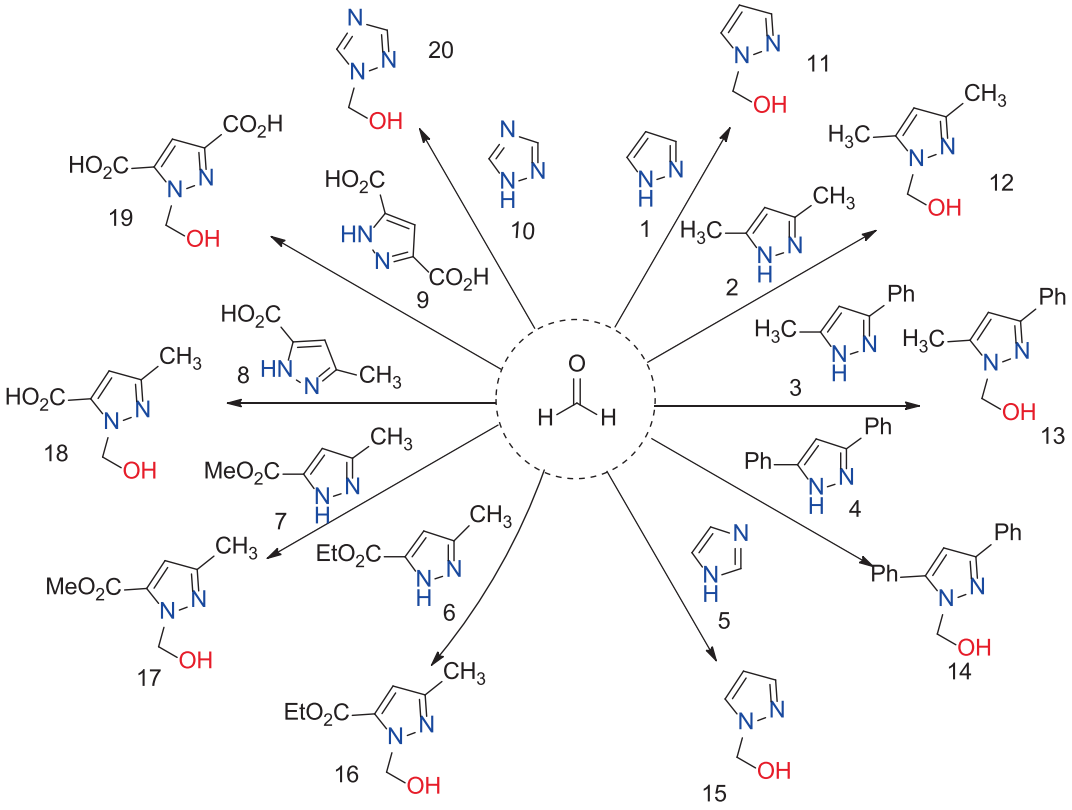

Fig. 2. Structure of 20 monodentate compounds based on pyrazole, triazole and imidazole.

solution (37 %), the same technique used for imidazole and triazole.

2.2. Theoretical calculations

Theoretical calculations evaluated using Gaussian 09w and Gaussview09 for optimization, Osiris for the toxicity risk of the molecules while Molinspiration calculates the physicochemical properties. The sieves compounds will be evaluated with ADME-Tlab.2.0 to determinate the ADMET properties before Docking in protein spike 6CS2. Molecular docking studies were performed by using Vina in PyRx docking tool to predict the protein–ligand interactions at molecular level. The crystal structure of COVID-19 main protease (6CS2) was used as targets. Target proteins were

downloaded from Protein Data Bank and prepared by Biovia discovery studio tool. The water molecules were removed and polar hydrogens were added to the protein. The ligand molecules and protein structures determined were imported into PyRx and converted into PDBQT format. The active sites of target molecules were identified from the existing ligand molecules in crystal structures. The docking simulations were performed after assigning grid box and grid centers in Vina wizard. The docking results were visualized by using Biovia Discovery Studio Visualizer.

3. Results and discussions

3.1. Lipinski rules

Lipinski's Rule of Five, also known as Pfizer's Rule of Five or simply the Rule of Five, is a basic rule for evaluating drug-likeness or determining whether a chemical compound with a certain pharmacological or biological activity has chemical properties and physical properties that would make it an orally active drug in humans [55] (Table 1).

Lipinski rules used for the screening of molecules in order to eliminate molecules that may cause problems of absorption, bioavailability and eventual toxicity on the human body. The rule describes molecular properties important for the pharmacokinetics of a drug in the human body, including its absorption, distribution, metabolism, excretion and toxicity (''ADME-Tox"). No compound violates Lipinski's rule, so none seem to cause absorption or solubility problems. However, this result does not mean that these molecules are active. The molecules that haven reproductive mutagenic and tumorigenic effects not consider such as a therapeutic compound. Three compounds (**3, 4,** and **9**) among twenty do not present any risk of toxicity to humans. This allows us to concentrate the effort of our work in only in these three compounds.

3.2. Geometry optimization:

The structures modelized and geometry optimized using the semi-empirical method at the le AM1 level with Gaussian 09w and Gausview 6.0.16 in the gas phase. The energy level of HOMO and LUMO determined. The HOMO (highest occupied molecular orbital) and LUMO (lowest occupied molecular orbital) of the frontier molecular orbital's (FMOs) play a key role in the reactivity of the molecular. Table 2 shows the HOMO And LUMO orbital molecular for the twenty following compounds.

The ionization potential, electron affinity, global hardness, chemical potential, electrophilicity index, hardness and softness values reported (atomic units) in Table 3.

3.3. Energy MEP

The molecular electrostatic potential (MEP) is used globally as a reactivity map displaying the most suitable region for the electrophilic and nucleophilic attack of charged point-like reagents on organic molecules. It helps to illustrate the biological recognition process and hydrogen bonding interaction. the energy MEP also used to visualize the reactivity area in molecule. It's informed the reaction may be haven with our molecules. The richest electronegativity shown by the red color in the molecular map (Fig. 3).

The importance of MEP lies in the fact that it simultaneously shows the molecular size and shape, as well as positive, negative and neutral electrostatic potential regions in terms of color grading, which is very useful in the research of molecular structure, along with the physicochemical properties' relationship. Molecular electrostatic potential (MEP) was calculated to forecast the reactive sites for the. electrophilic and nucleophilic attack of the optimized structure of electrostatic potential are represented by different colors, with potential increases in the order red < orange < yellow < green < blue. The red color displays the maximum negative area, which shows favorable sites for electrophilic attack; the blue color indicates the maximum positive area favorable for the nucleophilic attack, and the green color represents zero potential areas.

3.4. Molecular docking and simulation

Molecular docking is a type of bioinformatics modeling which deals with the interaction between two or more molecules to give a stable adduct. The key aim of molecular docking is to predict the potential binding geometries of a putative ligand of a known

Table 1
Lipinski's rule of the twenty compounds.

Lipinski rules						Toxicity risk			
Code	**MW(g/mol)**	**NHBA**	**NHBD**	**Log(P)**	**V**	**Mu**	**Tu**	**Ir**	**Re**
1	68.08	2	1	0.32	None	–	–	–	+++
2	96.13	2	1	0.76	None	–	+++	–	–
3	158.20	2	1	2.21	None	–	–	–	–
4	220.28	2	1	3.67	None	–	–	–	–
5	68.08	2	1	−0.07	None	+++	–	–	+++
6	154.17	4	1	0.99	None	–	+++	–	–
7	140.14	4	1	0.61	None	–	+++	–	–
8	126.11	4	2	0.35	None	–	+++	–	–
9	156.10	6	3	−0.06	None	–	–	–	–
10	69.07	3	1	−0.61	None	–	–	+++	–
11	98.11	3	1	−0.65	None	–	+++	+++	+++
12	126.16	3	1	0.18	None	–	+++	+++	+++
13	188.23	3	1	1.64	None	–	+++	+++	+++
14	250.30	3	1	3.09	None	–	+++	+++	+++
15	98.11	3	1	−0.65	None	–	+++	+++	+++
16	184.20	5	1	0.41	None	–	+++	+++	+++
17	170.17	5	1	0.04	None	–	+++	+++	+++
18	156.14	5	2	−0.23	None	–	+++	+++	+++
19	186.12	7	3	−0.64	None	–	+++	+++	+++
20	99.09	4	1	−1.19	None	–	+++	+++	+++

With (MW: Molecular weight**; NHBA**: Number of Hydrogen Bond Acceptors; **NHBD**: Number of Hydrogen Bond Donners; **Log (P)**: water/octanol partition coefficient, it measures the lipophilic character: **V**: Violation**;**
Mu: Mutagenic**; Tu:** Tumorigenic**; Ir:** Irritant**; Re:** Reproduction effective**).**

Table 2
Molecular orbital's of the twenty structures.

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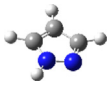
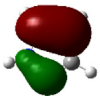
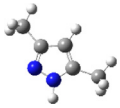
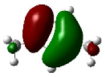
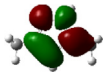
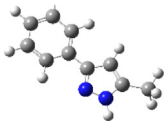
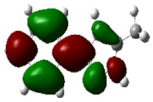
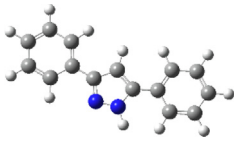
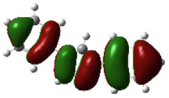
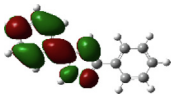
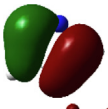
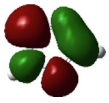
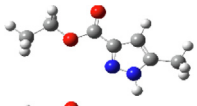
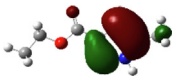
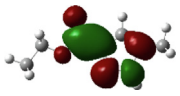
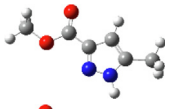
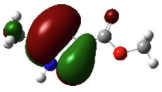
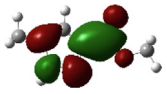
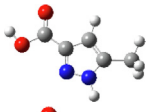
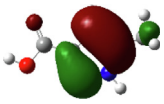
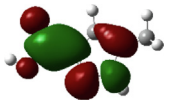
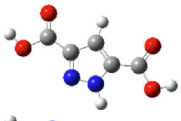
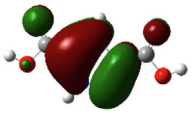
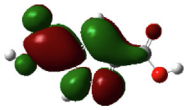
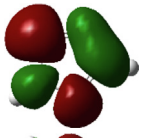
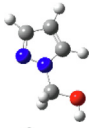
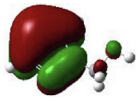
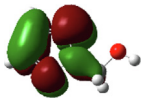
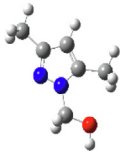
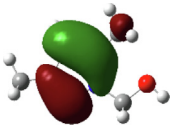
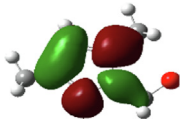
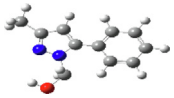
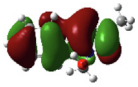
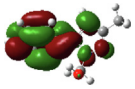
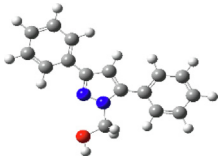
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			

Table 2 (*continued*)

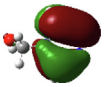
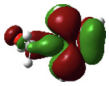
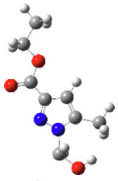
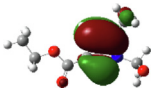
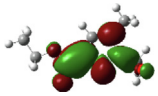
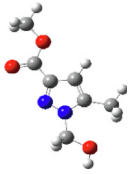
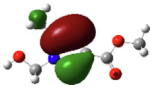
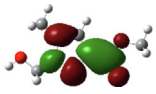
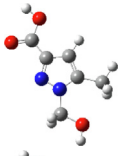
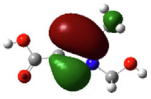
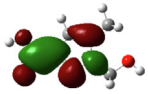
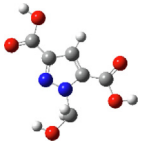
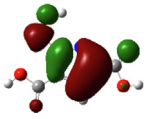
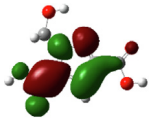
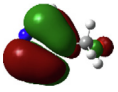
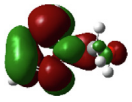
Code	Structure	HOMO	LUMO
15			
16			
17			
18			
19			
20			

Table 3
Values of chemical reactivity of the twenty compounds.

Code	E_{HOMO}	E_{LUMO}	ΔE	η	σ	χ	μ	ω
1	−0.3567	0.3508	0.7075	0.35375	2.82685512	0.00295	−0.00295	0.0000123004
2	−0.34179	0.3479	0.68969	0.344845	2.89985356	−0.00306	0.003055	0.0000135322
3	−0.32047	0.00625	0.32672	0.16336	6.12144956	0.15711	−0.15711	0.0755495596
4	−0.31997	−0.01217	0.3078	0.1539	6.4977258	0.16607	−0.16607	0.0896011855
5	−0.36333	0.0025	0.36583	0,0.182915	5.4670202	0.180415	−0.18042	0.0889745844
6	−0.39544	−0.02871	0.36673	0.183365	5.45360347	0.212075	−0.21208	0.1226401048
7	−0.36088	0.00603	0.36691	0.183455	5.45092802	0.177425	−0.17743	0.0857966003
8	−0.36005	0.00726	0.36731	0.183655	5.44499197	0.176395	−0.1764	0.0847109962
9	−0.37748	0.01986	0.39734	0.19867	5.03347259	0.17881	−0.17881	0.0804676501
10	−0.3366	0.03588	0.37248	0.18624	5.36941581	0.15036	−0.15036	0.0606962242
11	−0.34723	0.03691	0.38414	0.19207	5.20643515	0.15516	−0.15516	0.0626714885
12	−0.33633	0.03652	0.37285	0.186425	5.36408743	0.149905	−0.14991	0.0602695696
13	−0.33834	−0.00539	0.33295	0.166475	6.00690794	0.171865	−0.17187	0.0887147566
14	−0.32535	−0.00426	0.32109	0.160545	6.22878321	0.164805	−0.16481	0.0845890187
15	−0.33946	0.02793	0.36739	0.183695	5.44380631	0.155765	−0.15577	0.0660408156
16	−0.35919	0.00377	0.36296	0.18148	5.51024906	0.17771	−0.17771	0.0870091583
17	−0.35256	0.00775	0.36031	0.180155	5.55077572	0.172405	−0.17241	0.0824941967
18	−0.35481	0.00445	0.35926	0.17963	5.56699883	0.17518	−0.17518	0.0854201202
19	−0.38897	−0.03262	0.35635	0.178175	5.61245966	0.210795	−0.2108	0.1246935093
20	−0.37759	0.01416	0.39175	0.195875	5.10529675	0.181715	−0.18172	0.0842893203

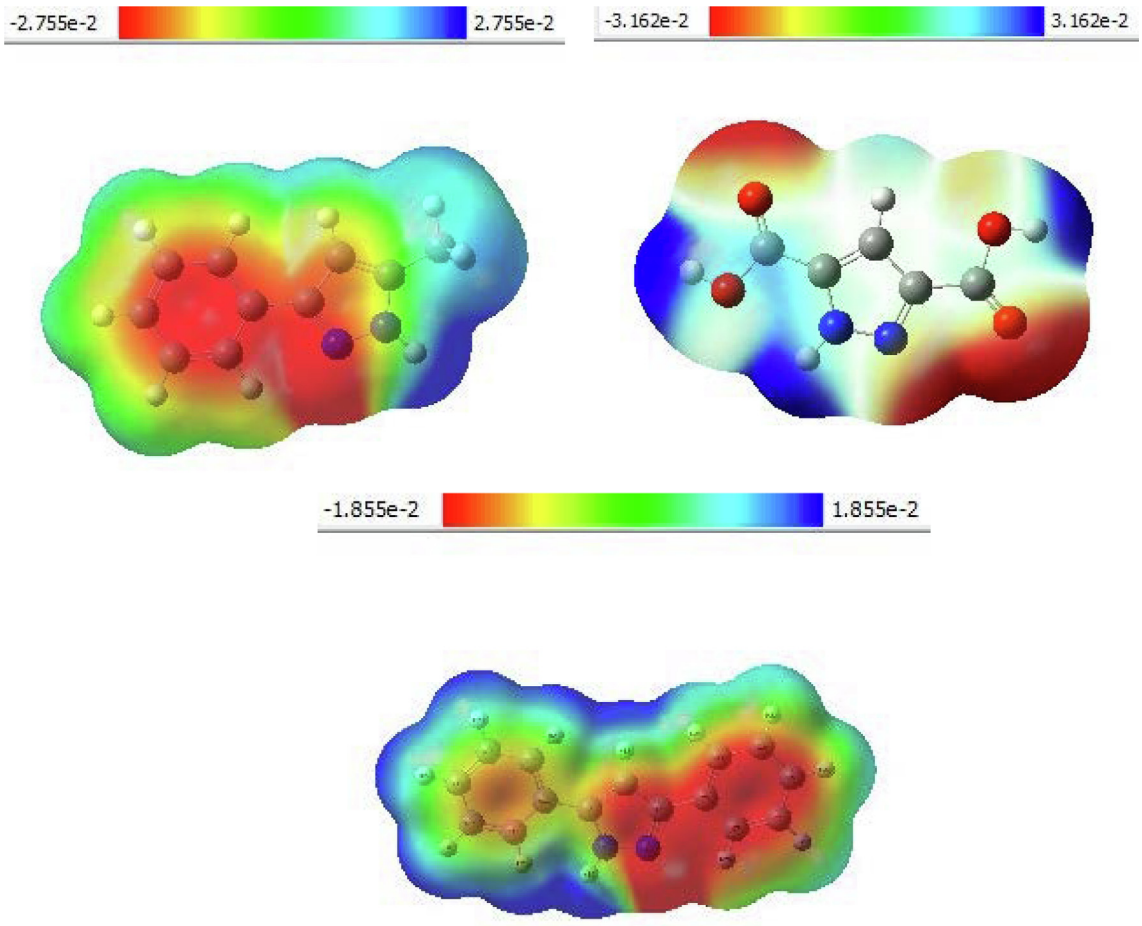


Fig. 3. The MEP map of the compounds **3**, **9** and **4.**

three-dimensional structure with a target protein. In this investigation, three molecular based on pyrazole were studied in silico to highlight their possible binding energy and interaction modes with the active site of SARS-CoV-2 main protease (Fig. 4), using the AutoDock Vina software. Then this three moleculars conduced to molecular docking study withe the proteine spike viral 6CS2. The molecular 9 illustred very interesting interaction with the proteine spike with the litle distance between ligand-proteine.

The distance of the ligands, along with the change in the accessible area of the two important catalytic residues (Cys145 and His41) within the active site of the protease, is shown in Fig. 4. It is noted that the analyzed of the active site of the main protease of SARS-CoV-2, like the standard drug hydroxychloroquine (HCQ), which is inevitable to prevent the protein mutarotation of the virus by minimizing the viral replication. The binding affinities calculated varied in the range of (-4.0 to − 8.6 kcal/mol), suggesting that the synthesized molecules can spontaneously interact within the binding site of the SARS-CoV-2 main protease.

Although the blind docking studies revealed that all the molecules can act as potential agents for the establishment of COVID-19 drugs, from the estimated free energy of binding values, it may be inferred that the analogs (**3**, **4** and **9**) with the highest negative minimum binding energy value amongst all the studied analogs could be the best possible SARS-CoV-2 inhibitors.

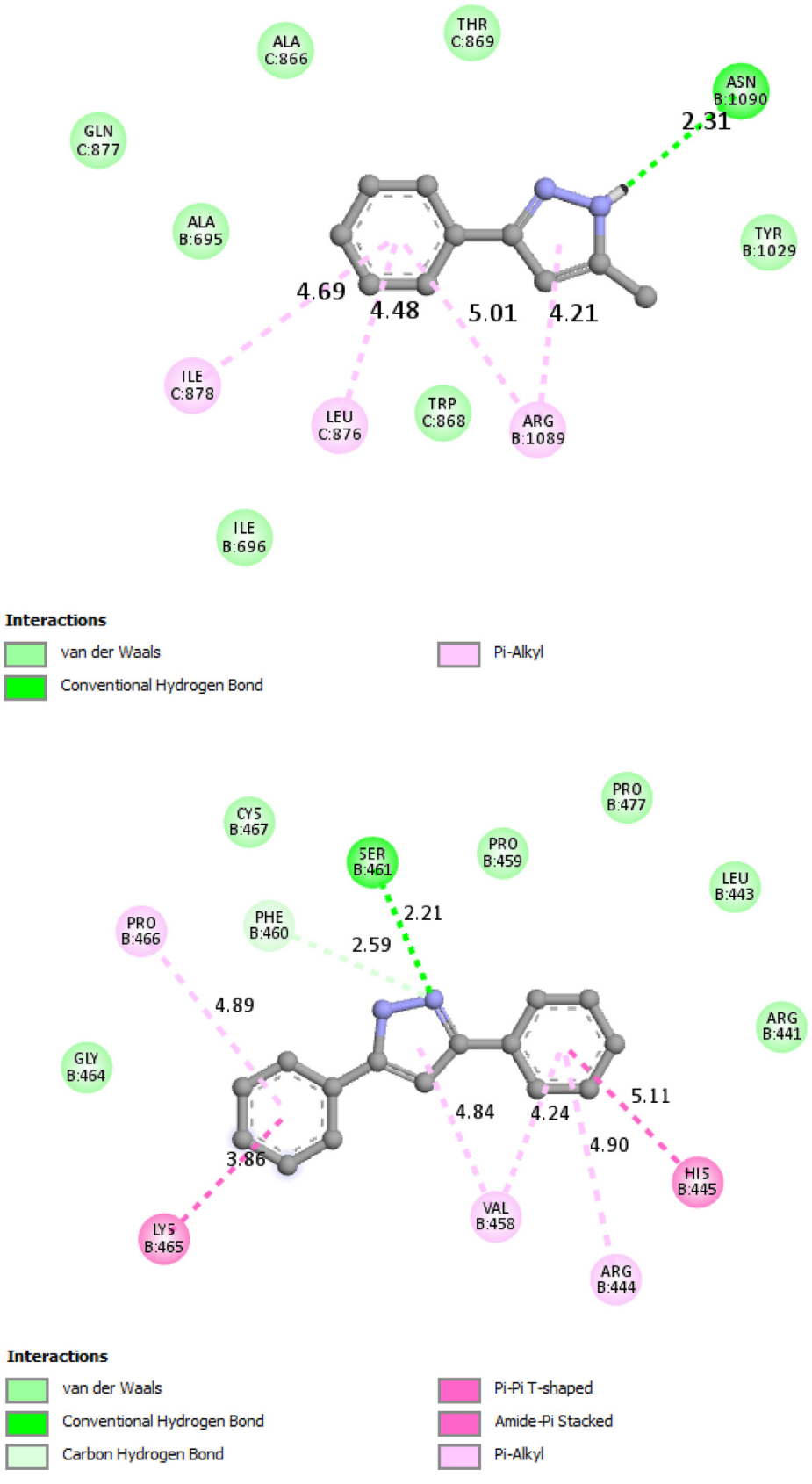


Fig. 4. Molecular docking interaction modes with SARS-CoV-2 main protease with compounds **3**, **4** and **9.**

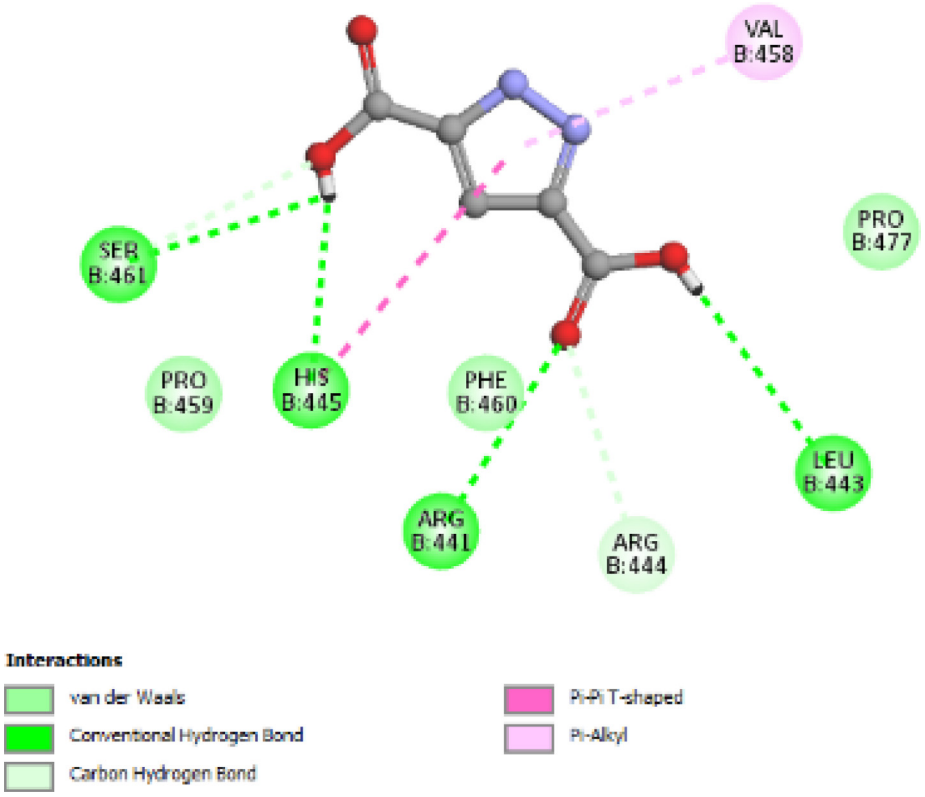


Fig. 4 (*continued*)

4. Conclusion

In this research, a series of ligands based on pyrazole analogs were analyzed in silico for their molecular docking, and drug likeness properties. In addition, these analogs were analyzed for their cytotoxicity and pharmacokinetic properties, which revealed that a combination of toxicity determination, in silico ADMET prediction, and drug-likeness has promising results because most of the designed molecules showed improved kinetic parameters, and maintained all drug-likeness rules as well as provided an interesting result in terms of biological activity. Most of the ligand's pyrazole analogs have a HOMO-LUMO gap lower than pyrazole. pyrazole analogs (**3, 4** and **9**) showed promising binding interactions and binding energy with SARS-CoV-2 main protease which revealed analogs (**3, 4** and **9**) showed an *in silico* potent ability to fight SARS-CoV-2. The molecular electrostatic potential study also showed the most negative and positive surface area of the investigated ligand, and thus, anticipated the most suitable areas for hydrogen bonding sites.

CRediT authorship contribution statement

Mounir Mohamed: Conceptualization, Methodology, Validation, Formal analysis, Data curation, Writing – original draft. **Farid Abrigach:** Data curation, Methodology, Supervision. **Sghir El Kadiri:** Conceptualization, Methodology, Supervision. **Said Omar Said Hassane:** Resources, Validation, Supervision. **Magda H. Abdellattif:** Formal analysis, Supervision, Validation. **Rachid Touzani:** Conceptualization, Investigation, Supervision.

Data availability

No data was used for the research described in the article.

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.

Acknowledgements

I would like to thank the Laboratory of Applied Chemistry and Environment (LCAE) of the Faculty of Sciences of Oujda, for providing a laboratory equipment. I would also like to thank the CNRST-Rabat for its analytical support and the IRC of Italy. Bilateral project between CNR Italy and CNRST Morocco (project 2020/2022, CUP B54I20000340001, IC-CNR Bari, Italy, A.M., and UMP Oujda, Morocco, R.T.).

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