https://adv-j-sci-eng.com eISSN: 2717-0705

Advanced Journal of Science and Engineering

Original Research

Molecular Analysis of 5-COR Derivatives of Uracil and Evaluating their Affinity Against the MPro Target of COVID-19

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Received: 02 June 2021 / ***Revised***: 25 June 2021 / ***Accepted***: 27 June 2021 / ***Published Online***: 30 June 2021

ABSTRACT

Molecular analysis of 5-COR (R: H, CH_3, NH_2, OH, F, Cl, Br, I) functionalized derivatives of uracil (U) were explored in this work using computational procedures. Next, binding affinity of each U compound was examined against the main protease (MPro) target of COVID-19 pandemic to maybe inhibit it from further growth. The results indicated that the models of U detected effects of structural modifications by showing variations in their molecular features. Molecular orbital properties indicated that the electronic features of models were changed through functionalization processes. Further analysis of performing molecular docking (MD) simulations also indicated that the models could contribute to different types of interactions with the MPro target, in which the model with 5-COI additional group was highlighted for strong contribution to make the strongest complex of ligand-target system. As a consequence, such structural modification of U helped the models for proper interaction with MPro to maybe inhibit the growth of COVID-19 pandemic.

KEYWORDS Uracil, Coronavirus, COVID-19, Main protease, Computational, Docking.

CITE Ashjaee Y, Zandi H. Molecular Analysis of 5-COR Derivatives of Uracil and Evaluating their Affinity Against the MPro Target of COVID-19. Advanced Journal of Science and Engineering. 2021;2(2):79-85.

DOI https://doi.org/10.22034/advjscieng21022079

URL https://sciengpub.com/adv-j-sci-eng/article/view/advjscieng21022079

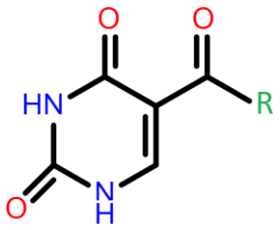
INTRODUCTION

Pioneering work of Watson and Crick for characterizing nucleic acids has yielded to perform huge number of research works on developing further features for these building blocks of life.[1-5] In addition to the original functions in living systems, several other applications have been developed for nucleobases; the main components of nucleic acids.[6-10] Pharmaceutical related applications have been always expected for nucleobases relatives with high level of importance.[11, 12] In this regard, considerable efforts have been dedicated to explore such important applications for each of nucleobases including adenine (A), guanine (G), cytosine (C), thymine (T), and uracil (U) employing various methods in computers and laboratories.[13-17] The significant feature of U is its originality for ribonucleic acids (RNA) instead of T of deoxyribonucleic acids (DNA); therefore, it has been always seen as a typical nucleobase for showing characteristic functions related to living systems.[18] Atom number 5 of heterocyclic ring of U has been introduced as a proper atomic site for functionalization with other substances, in which 5-fluoro U has been an example of such functionalized U with characteristic pharmaceutical functions.[19] Further 5-derivatives have been also developed for U with more or less significant effects in pharmacotherapy of living systems.[20] Therefore, such advantageous potential of U could be seen important for developing new compounds with possible pharmaceutical functions by performing targeted investigations on characterizing various features for this wonderful biological compound.[21]

Since the late days of the year 2019, coronavirus diseases (COVID-19) has been distributed all around the world with harmful impacts on all sides of human life.[22] To this time, no certain therapeutic procedure has been introduced for such deathful pandemic and considerable efforts have been still under examining to reach a success to overcome COVID-19.[23-25] Realizing crystalline structure of main protease (MPro) helped researches very much to examine ability of available or predicted chemical compounds to inhibit function of the enzyme to prevent growth of COVID-19.[26] In earlier works, such examinations have been reported with more or less significant success to overcome the deathful pandemic but without certain result yet.[27-30] Hence, performing further investigations are still required to see the effects of proposed compounds for showing activity against COVID-19. One of the advantageous methods for making sense such ideas is computational procedure employing theoretical backgrounds to analyze features of 3D molecular structures to achieve a response for hypotheses.[31-33]

In this work, 5-COR derivatives of U were analyzed by computational procedures for showing structural features and affinity against MPro of COVID-19. To this aim, R was replaced by H, CH_3, NH_2, OH, F, Cl, Br, and I substances to provide functionalized derivatives in addition to the original U (Table 1). All models were optimized to reach the minimum energy structures to be ready for further examination in interaction with the enzymatic target. Required results were evaluated for both of singular ligands and interacting complexes to show the structural features of 5-COR U compounds and their affinity against MPro of COVID-19. All results were summarized in Table 1 and Figs. 1 and 2 to be discussed to achieve the purpose of this work. It is worth to note that computer-based works could show insightful information about details of bio-chemical systems in addition to their own advantage of providing possibility of scientific exploration in computers.[34]

Table 1: Evaluated molecular features for 5-COR ligands and affinity.



Ligand	R	DM	HOMO	LUMO	EG	FE	ΔG
L1	n/a; Uracil	3.99	-9.71	-0.51	9.21	-5.11	-6.35
L2	-H	5.48	-9.95	-1.09	8.85	-5.52	-6.39
L3	$-CH_3$	2.75	-9.97	-0.93	9.04	-5.45	-6.68
L4	$-NH_2$	1.95	-10.03	-0.99	9.04	-5.51	-6.23
L5	-OH	3.06	-10.08	-1.04	9.03	-5.56	-6.31
L6	-F	5.02	-10.29	-1.43	8.86	-5.86	-6.26
L7	-Cl	4.46	-10.22	-1.35	8.88	-5.79	-6.24
L8	-Br	4.22	-10.42	-1.59	8.83	-6.01	-6.49
L9	-I	4.18	-9.94	-1.57	8.37	-5.75	-6.59

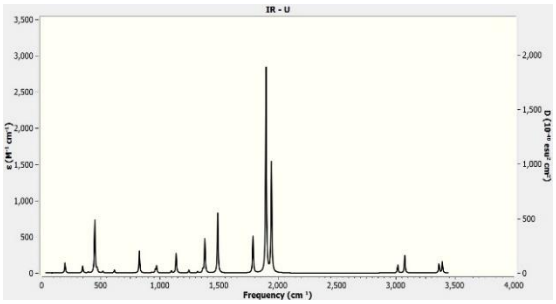
DM is in Debye. HOMO, LUMO, EG and FE are in eV. ΔG is in kcal/mol.

MATERIALS & METHODS

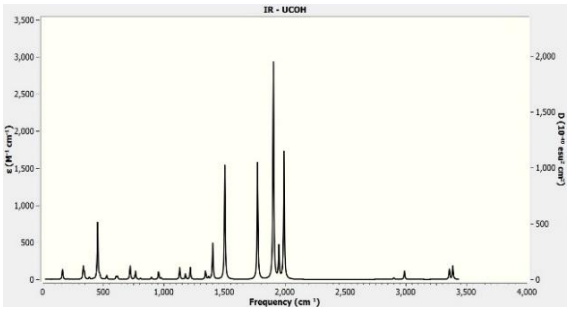
3D models of 5-COX derivatives of U were prepared by optimizing at the level of PM3 semi-empirical method as implemented in the Gaussian program.[35] There were nine models (L1-L9) as described in Table 1 with details of functionalized substance and molecular descriptors. Dipole moments (DM), energy values of the highest occupied and the lowest unoccupied molecule orbitals (HOMO and LUMO), energy gaps (EG) and Fermi energy (FE) were all evaluated for the optimized structures of 5-COX U derivatives as ligands of this work. All structures were confirmed by performing frequency calculations and the evaluated infrared (IR) spectra were visualized in Fig. 1. Next, 3D macromolecular structure of MPro was obtained from the protein data bank (PDB) with the id of 6lu7 and it was prepared as target for participating in interactions with each of the ligand structures.[36, 37] To make possible formation of interacting ligand-target complexes, each of U ligands were interacted with the MPro target through performing molecular docking (MD) simulations. The obtained quantities of ΔG (kcal/mol) and qualitative representations of interacting amino acids of the target with the ligand in complexes were evaluated for the investigated systems as

summarized in Table 1 and Fig. 2. To perform MD simulations, ligand and target structures were submitted to SwissDock webserver for providing interacting complexes at the accurate level.[38] In this step, the most proper configuration of ligand could be relaxed towards the target to obtain the minimized energy ligand-target complex.

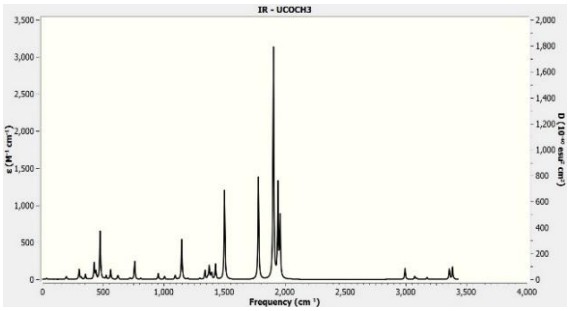
L1: R(n/a; Uracil)



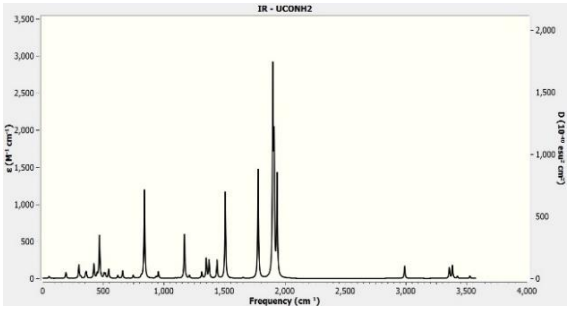
L2: R(-H)



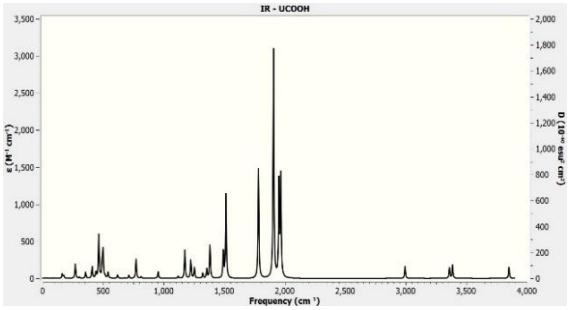
L3: R(-CH3)



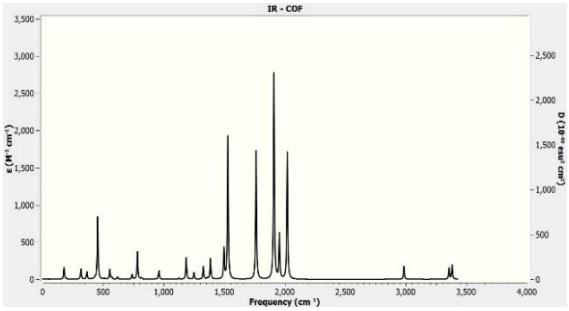
L4: R(-NH2)



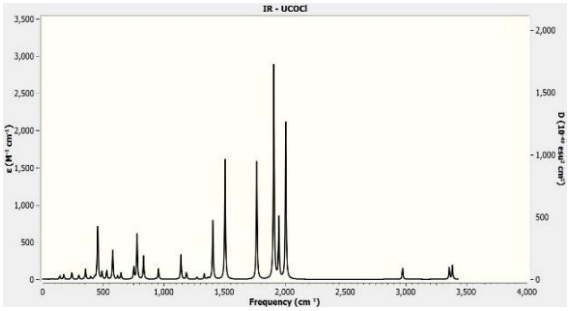
L5: R(-OH)



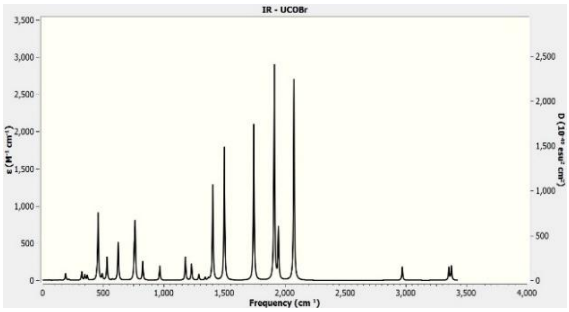
L6: R(-F)



L7: R(-Cl)



L8: R(-Br)



L9: R(-I)

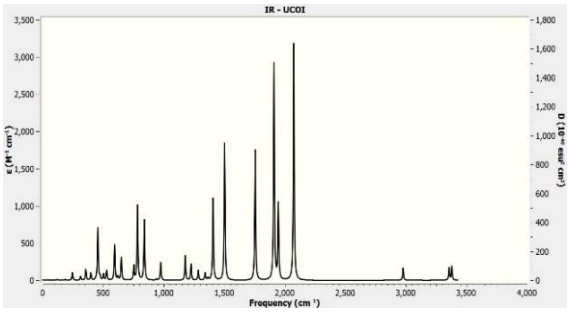


Fig. 1: IR spectrum for the singular form of 5-COR ligands.

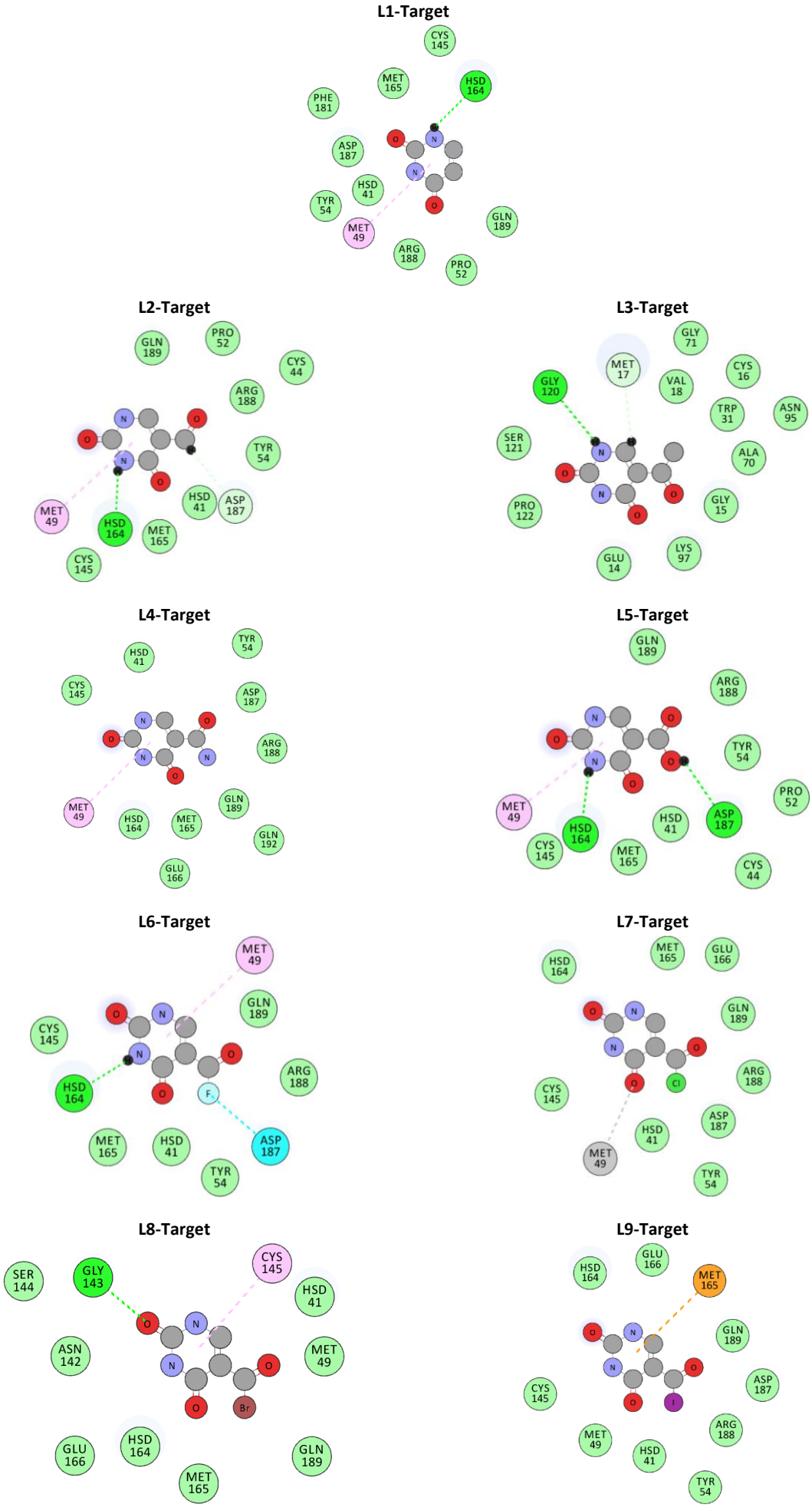


Fig. 2: The interacting forms of ligand-target complexes; Ligands: L1-L9 derivatives of 5-COR U, Target: Mpro of COVID-19.

RESULTS & DISCUSSION

This work was performed for obtaining two purposes; the first one was performing molecular analysis on 5-COR derivatives of U, and the second one was examining binding affinity against the MPro target. For qualifying the first purpose, optimizations at the PM3 semi-empirical levels were done to yield geometrically optimized structures. Additionally, molecular descriptors including DM, HOMO, LUMO, EG and FE were calculated for the optimized structures (Table 1). IR spectra were also exhibited in Fig. 1 for all the optimized structures. In this step, there were nine structures (L1-L9), in which then defined as the ligands of this work for participating in complex formations with the enzymatic target. U was the original compound, in which its atomic site number 5 was functionalized by carbonyl group (CO) and additional R substance including H, CH_3, NH_2, OH, F, Cl, Br, and I to provide 5-COR derivatives of U. The results of optimization processes indicated that the structures could be stabilized based on total energy features and the evaluated IR spectra indicated that the functionalized models could show different modes of vibrations based on addition of substance to the 5-atomic site. By such modifications, different vibrations could predict different sights of occurring interactions between ligand and target complex systems. Other molecular descriptors revealed that the electronic properties of structures would be changed by the employed modification, in which the results indicated that each descriptor was significantly changed from one molecule to another one. DM could show variation of electric distribution of molecular surface, in which the results indicated such changes of surfaces for the molecules. Other molecular orbital based components such as HOMO and LUMO showed changes of such energy levels based on the existence of functioning substances. It is important to note that each of HOMO and LUMO could play significant roles in electron transferring processes with the role of HOMO for electron donating and the role of LUMO for electron accepting. Ionization potential and electron affinity could be defined by such HOMO and LUMO levels, in which their variations could lead to changes of such features for the model systems. Moreover, differences of levels of HOMO and LUMO in EG values and their average in FE values could help to achieve better insight about electron transferring possibilities for the molecular structures. As a consequence, small modification of 5-atomic site yielded significant effects for the molecular properties of the models.

MD simulations were performed for providing complex formations of interacting ligand-target systems to investigate effects of such 5-COR modification of U on the interacting features with the target. Nine ligands of U (Table 1) interacted with MPro target to provide interacting systems as exhibited in Fig. 2. As expected with the ligand results, different interacting situations were observed for the ligand-target systems in either binding strength or binding description. In this regard, L9 (R: I) was the best ligand for interacting with the target to make the strongest complex among other models. To this point, it could be mentioned that he model modification helped the ligand to contribute to more powerful interaction with the target as designated by the 5-COI U model as the best one for the purpose. It was an interesting achievement that the original U itself was not the ligand with lowest binding affinity against the target revealing the importance of structural features characterizations for achieving insights about the complicated molecular systems complexes. Furthermore, types of interacting amino acids of Fig. 2 were more or less different from one complex to another one showing variation of interacting modes in both quantity and quality for the 5-COR and original U compounds.

CONCLUSION

Computational procedure was employed to perform molecular analysis of 5-COR derivatives of U to examine their binding affinity against MPro target of COVID-19. The results yielded stabilized structures through optimization processes with more or less significant features in structures and molecular orbital properties. Performing further analyses indicated that the model systems could show variations of 5-atomic site functionalization in different modes. MD simulations also indicated different quantitative and qualitative features, in which binding strengths and descriptions were very well recognized for the models. In this step, 5-COI derivative of U was seen to contribute to provide the strongest complex of interacting ligand-target system. As a consequence, such structural modification of U yielded more proper ligand for participating in strong interaction with the MPro target to maybe prevent COVID-19 from further growth.

DISCLOSURE STATEMENT

The author(s) did not report any potential conflict of interest.

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