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Structural Analysis of Some Pyrrolopyrimidine Derivatives and Examining their Binding Affinity against the Cyclooxygenase-2 Enzyme

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Abstract: This work was performed to investigate structural features of ten models (L1-1L10) of pyrrolopyrimidine derivatives in addition to evaluating their activity against the cyclooxygenase-2 (COX-2) enzyme target. In this regard, celecoxib (CEL) was employed as a reference model for evaluating features of the investigated models. Frontier molecular orbitals features were evaluated for the models including the highest occupied and the lowest unoccupied molecular orbitals (HOMO and LUMO) in addition to evaluating chemical hardness and softness (H and S) features. Afterwards, molecular docking (MD) simulations were performed for examining the contribution of each compound against the COX-2 enzyme for formation of ligand-target complexes. The models showed that the investigated structures could work as efficient ligands for building string complexes with the COX-2 target, in which some of them with CN, F, and OMe functional groups were also more efficient than the reference CEL drug. As a consequence, details of ligand-target complex formations including types of interactions and surrounding amino acids were all recognized for the models systems.

Keywords: *Pyrrolopyrimidine; Celecoxib; COX-2; Anti-inflammatory; DFT; In silico.*

1. Introduction

Pyrrolopyrimidine bicyclic compounds (Fig. 1) play important roles in biological systems regarding their activity against enzymatic targets [1]. In addition to the original structures, several other derivatives have been also available for such compounds based on their specified features and activity for the desired goals [2]. Earlier works showed therapeutic activities in living systems such as anti-cancer, anti-diabetic, anti-microbial, anti-viral, and anti-inflammatory for pyrrolopyrimidine based compounds [3-7]. Therefore, characterizing chemical and biochemical features of these compounds could help to innovate novel pharmaceutical applications based on employing heterocyclic compounds in living systems [8]. To this aim, some pyrrolopyrimidine derivatives (Table 1) were investigated in this work for characterizing their features in addition to examining their binding affinity against cyclooxygenase-2 (COX-2) enzyme target.

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The importance of this topic is related to evaluation of anti-inflammatory activity for the investigated pyrrolopyrimidine derivatives by inhibition of COX-2 activity. Overexpression of COX-2 could initiate the formations of prostaglandins, which are reasons of inflammation in the tissues [9]. Nonsteroidal anti-inflammatory drugs (NSAIDs) could block the activity of COX-2 and consequently preventing prostaglandins formations [10]. However, efficient inhibition of enzyme activity has been still a challenging task for NSAIDs prescription besides their serious side effects [11]. Therefore, several attempts have been dedicated to investigate more efficient compounds for inhibiting activity of COX-2 enzyme in comparison with the available NSAIDs [12-14].

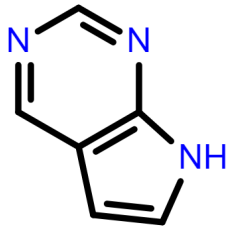


Fig. 1: The original pyrrolopyrimidine.

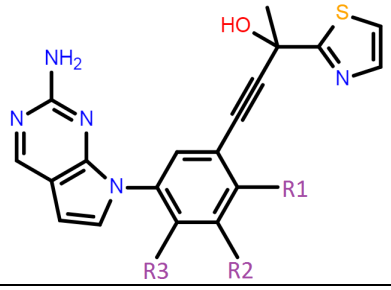
Based on an earlier work about pyrrolopyrimidine derivatives [15], ten compounds with similarity of main scaffold were selected for analyzing their chemical features besides examining their binding affinity against COX-2 enzyme target (Table 1). The models were optimized employing density functional theory (DFT) calculations and their features were evaluated accordingly. Next, their interactions with the enzyme target were investigated through performing molecular docking (MD) simulations. In this case, celecoxib was considered as a reference compound of known selective inhibitor for COX-2 enzyme target. As a consequence, the main goal of this work was investigated employing computer-based in silico tools for analyzing single standing structures and examining their interactions among ligand-target complexes formations [16-21].

2. In Silico Details

Within this work, ten models of pyrrolopyrimidine derivatives (L1-L10) were investigated by assistance of performing computer-based in silico calculations, in which the models were described in Table 1. The major criteria of selecting such models were similarity of the original skeleton and putting small modification for them. The model were optimized by performing DFT calculations at the B3LYP/6-31G* level as implemented in the Gaussian program [22-24]. By obtaining the minimized energy structures, molecular features including energy levels of the highest occupied and the lowest unoccupied molecular orbitals (HOMO and LUMO), chemical hardness and softness (H and S), and dipole moment were evaluated for the models as listed in Table 1. Each of molecular orbitals levels could help to determine reactivity indexes for contributing to reactions with other substances [25-29]. Moreover, graphical representations of HOMO and LUMO distribution patterns and electrostatic potential (ESP) surfaces were visualized in Fig. 2 for the optimized models of pyrrolopyrimidine derivatives. By doing such steps, ligand models were prepared for examining their binding affinity against the COX-2 enzyme target. To this aim, celecoxib (CEL) was used as a reference ligand for selective inhibition of COX-2

activity [30]. 3D macromolecular structures of COX-2 (Code: 3LN1) was obtained from the Protein Data Bank (PDB) [31] and it was prepared as the target for involving in molecular interactions with the investigated ligands. Molecular docking (MD) simulations were performed to examine binding affinity of each of ligand compounds against the COX-2 enzyme target. To do this, the models were submitted to the SwissDock webserver [32] for performing accurate MD simulations by defining a grid box of 40*40*40. As a consequence, the ligand-target complexes were obtained for achieving the goal of this work to show binding affinity of ligands against the enzyme target. The results of ΔG and RMSD were evaluated for the complex models as listed in Table 2 besides the graphical representations of interacting complexes as shown in Fig. 3. Types of surrounding amino acids and their interactions with the central ligand structure could be seen by complex representations of Fig. 3. On the other hand, the quantitative scoring of binding affinity could be achievable by the obtained values of ΔG and RMSD for each complex in comparison with other complexes.

Table 1: Models descriptions and optimized results.



Result	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	CEL
R1	H	F	H	F	OMe	H	Me	H	CN	H	n/a
R2	H	H	H	H	H	H	H	H	H	CN	n/a
R3	H	H	F	F	H	OMe	H	Me	H	H	n/a
HOMO	-5.39	-5.43	-5.41	-5.46	-5.26	-5.22	-5.32	-5.32	-5.68	-5.64	-6.52
LUMO	-1.93	-1.16	-1.11	-1.21	-0.94	-0.98	-0.96	-1.04	-1.76	-1.66	-1.62
H	1.73	2.14	2.15	2.12	2.16	2.12	2.18	2.14	1.96	1.99	2.45
S	0.58	0.47	0.46	0.47	0.46	0.47	0.46	0.47	0.51	0.50	0.41
DM	2.55	1.73	3.26	2.61	3.62	3.66	2.89	2.84	2.81	4.81	7.21

H = (LUMO – HOMO)/2
S= 1/H
HOMO, LUMO, and H are in eV and S is in eV^{-1}. DM is in Debye.

3. Results and discussion

The main goal of this work was to investigate structural features of some pyrrolopyrimidine derivatives and examining their binding affinity against the COX-2 enzyme for evaluating any anti-inflammatory activity. To this aim, ten compounds (L1-L10) were investigated based on similarity of the main scaffold and attaching some functional groups to an intermediate ring, in which their specifications were summarized in Table 1. All of them were optimized based on performing DFT calculations and the optimized features were obtained for them for doing a chemical recognition. In addition to such compounds, celecoxib (CEL) was also investigated as a reference compound with selective inhibition of CPX-2 enzyme. Frontier molecular orbital features including the energy levels of HOMO and LUMO in addition to H and S

were evaluated for the models systems to show their chemical reactivity features. As could be seen by the models specifications, the functionalized groups were changed among the sites of intermediate ring yielding variations in molecular orbital features. To this point, the levels of HOMO and LUMO detected the effects of existence of such functional groups, in which both of them underwent more or less significant fluctuations in comparison with each other. Indeed, HOMO and LUMO could imply for tendencies of molecules for participating in electron transferring processes, in which HOMO could imply for electron donating process and LUMO could imply for electron accepting process. In this regard, these features could be designated for electron transferring between substances besides internal electron transition systems. Therefore, both of them are important features for analyzing a structure regarding its participation in electron transferring processes especially in interactions with other substances. Each of H and S features, designating chemical hardness and softness, are also derived from the already known HOMO and LUMO levels, in which such features could imply for the contribution of a structure to chemical reactions somehow. In this regard, analyzing such features could help for describing next activities of a structure especially for the ligand-based drug design process.

Comparing the results of investigated compounds could show that HOMO levels for the models including F and CN functional groups were in lower levels in comparison with those models including Me and OMe groups. Bases on atomic features of F and CN groups, it could be interpreted that the electron reach valence shells could help the models to be in better mode of electron containing. On the other hand, HOMO levels of those of Me and OMe included models were located in upper levels. However, comparing to CEL showed that the HOMO level of all of L1-L10 compounds were located in upper levels and that of CEL was indeed in the lowest level. Analyzing LUMO levels of L1-L10 compounds and the reference CEL also showed that the models were in different modes of electron accepting feature, in which those of CN group included, L9 and L10, were in better levels even than the reference CEL. Here it is important to mention that the process of lead optimization of drug design could show benefits of employing structural modifications by evaluating the related descriptors, in which such results could help for making filtration of the structures for the specified purposes. Indeed, quantum-chemical approaches could reveal insightful information about the chemical compounds proposing further application for them based on such characteristic features [33-37]. For L1-L10 compounds, it could be expected that the activity for L9 and L10 should be in a characteristic mode in comparison with the reference CEL, in which such features could provide information for making filtration of the investigated compounds. As a consequence, the models including F and CN groups could be considered as compatible structures in features in comparison with the already known CEL drug, which make them candidates for involving in further investigations.

Comparing the visualized representations of HOMO and LUMO distribution patterns for the investigated compounds (Fig. 2) shows that the main localization of each pattern has been concentrated in opposite directions, in which HOMO and LUMO were localized in two separated sides of molecules. However, such localization is completely different for the references CEL with localizations of both of HOMO and LUMO almost at the whole molecular surface. In this regard, it could be mentioned that the characteristic feature of distribution patterns for the investigated L1-L10 modes and that of the reference CEL are completely different. To this point, the investigated L1-L10 models could be expected for participating in various types of interactions even more than the reference CEL drug, in which the earlier results of energy levels of such molecular orbitals could also approve such varieties of features.

Table 2: Molecular docking results.

Result	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	CEL
ΔG	-8.13	-8.42	-8.39	-8.62	-8.44	-8.66	-8.35	-8.12	-8.64	-8.63	-8.41
ΔΔG	0.28	-0.01	0.02	-0.21	-0.03	-0.25	0.06	0.29	-0.23	-0.22	0
RMSD	46.81	46.87	46.91	49.72	47.15	46.99	46.64	47.84	47.02	47.06	47.65

ΔG and Δ ΔG are in kcal.mol^{-1} and RMSD is unitless.

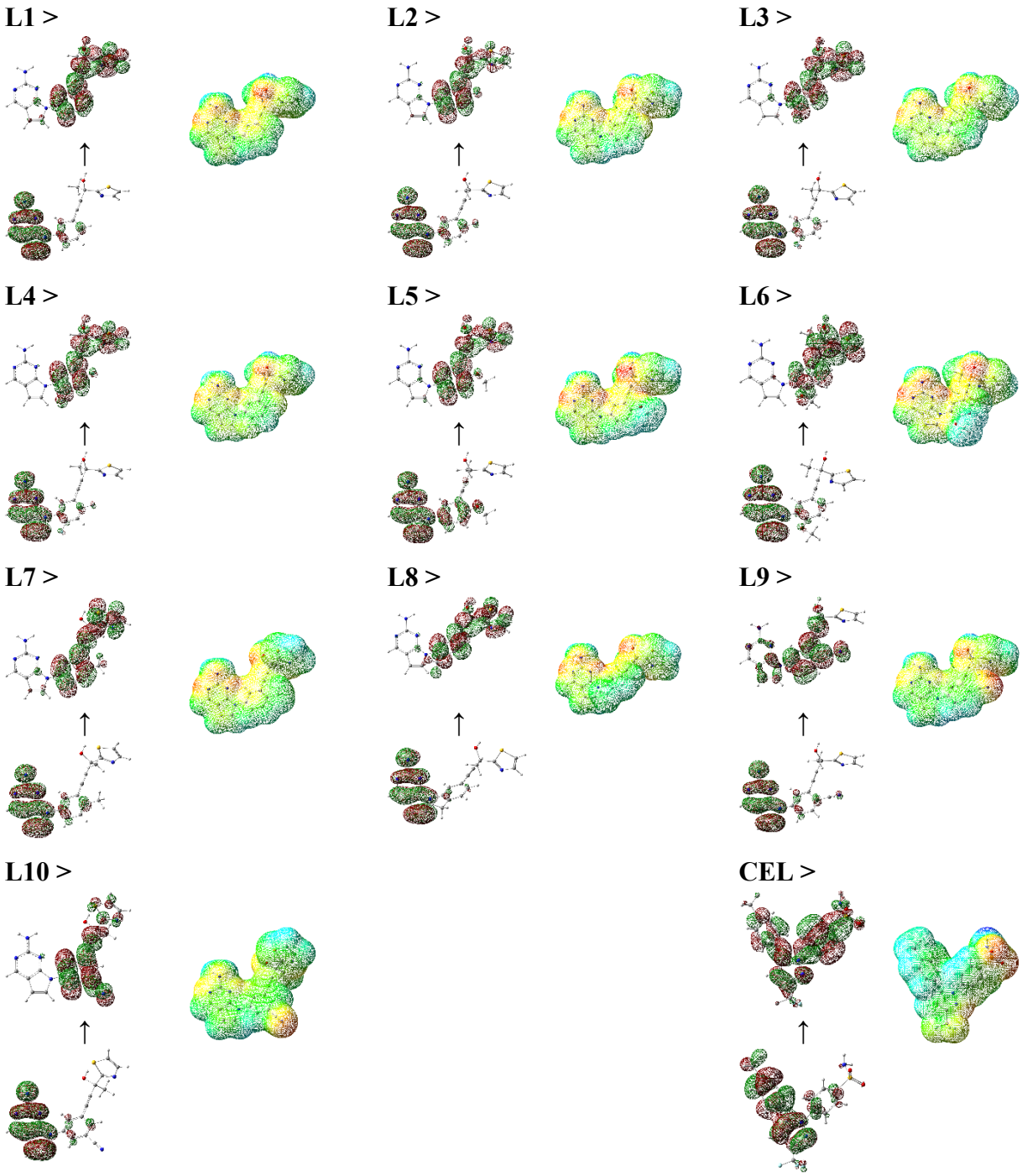


Fig. 2: HOMO (bottom) → LUMO (top) distribution patterns and ESP surfaces.

Based on the obtained features for the L1-L10 compounds and the reference CEL drug, the investigated models were expected to show functions for interactions with other substances more or less significant than the reference model. In this regard, performing molecular docking (MD) simulations could help to examine such hypothesis of obtaining desired formations of ligand-target complex systems based on evaluating features between the inetracting substances.

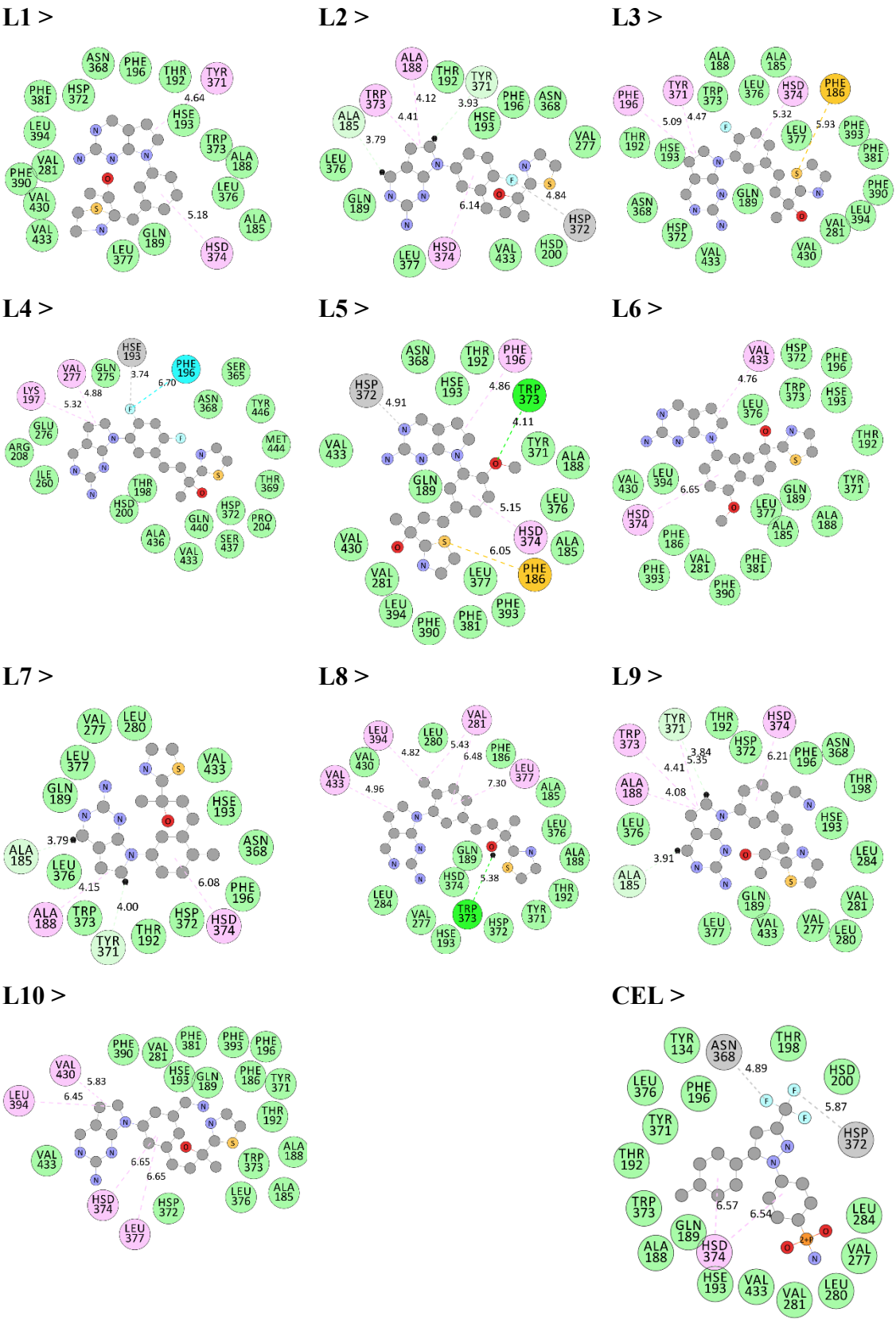


Fig. 3: Interacting Ligand-Target complexes.

The obtained results of Table 2 could show the strength of formations of ligand-target complexes based on the evaluated ΔG values, in which the obtained ΔG values indicated the difference between each complexes of L-Target in comparison with the CEL-Target complex. The target molecule of this work was the COX-2 enzyme, in which its overexpression could lead to inflammatory symptoms for the patients. Therefore, designing efficient COX-2 inhibitors could help to reduce such inflammations in the tissues in the case of anti-inflammatory drugs developments. To this aim, the current work was performed to achieve results on proposing efficient COX-2 inhibitors by employing L1-L10 pyrrolopyrimidine derivatives.

Each ligand model was participated in interaction with the target through performing MD simulations, in which the results were obtained in both of quantitative and qualitative modes (Table 2 and Fig. 3). Indeed, this is an important step for recognition of structures for working as possible inhibitors based on evaluating their own features and examining their interactions with the specified target.

The obtained results from performed MD simulations could show that the predicated ligands with the CN functional group could also show characteristic features in activity against the enzymatic target. As could be seen by the values of ΔΔG, showing the difference of values of ΔG between each Ligand-Target complex and that of reference CEL-Target complex in kcal/mol, L9 and L10 were placed at the highest ranking of complex formations among the investigated models systems. Moreover, those of F and OMe functionalized models were also seen suitable for participating in stronger interactions with the enzymatic target in comparison with the reference CEL ligand.

As a quick result of this work, it could be mentioned that the structural modification of original pyrrolopyrimidine derivatives could lead to development of more efficient ligand structures in comparison with the original structure and also the reference CEL structure. Analyzing values of RMSD, showing the magnitude of structural deformation of a ligand from the starting point of MD simulation up to the finishing point, could show that the changes of investigated structures were more or less significant in comparison with each other and also the reference model. Interestingly, the changes of L9 and L10 were less significant than those of other ligands and also the reference model making them as characteristic ligands for participating in interactions with the target. In addition to the obtained quantitative values, qualitative representations results of performed MD simulations were exhibited in Fig. 3. As could be seen for different models, all ligands were involved in interactions with amino acids of the target showing possibility of complex formation for all investigated ligands against the target. However, types of interactions and localization of ligands in the center of complexes were different. Existences of hydrogen bond and non-hydrogen bond interactions were seen for the complex models. As a consequence, the hypothesis of participation of each of L1-L10 ligands with the COX-2 target was affirmed based on the obtained quantitative and qualitative results, in which some of them were seen to work better than the reference CEL drug. Hence, the models could be proposed for performing further investigations on them to achieve desired results for inhibition of COX-2 enzyme in an anti-inflammatory activity process.

4. Conclusion

Within this work, L1-L10 models of pyrrolopyrimidine derivatives were investigated for analyzing their structural features besides their binding affinity against the COX-2 enzyme target for evaluating anti-inflammatory activities. In this regard, some achievements could be summarized. Molecular orbital features indicated significant effects of structural modification on the investigated structures, in which additional of F and CN functional group leaded to introduction of ligands with features even better than the reference CEL drug. In this regard, the models were expected to show better features than the reference CEL drug. Examining further features of the models by performing MD simulations on the formation of ligand-target complexes indicated that some of pyrrolopyrimidine derivatives could work better than the reference CEL for interacting with the COX-2 enzyme target. In this case, L9 and L1o with the CN functional group worked as the best ligands among all L1-L10 and reference CEL models. Moreover, those ligands with F and OMe functional

groups also showed significant features for formations of ligand-target complexes. As a final note, the investigated pyrrolopyrimidine derivatives could be proposed for performing further investigations for the purpose of development of COX-2 enzyme inhibitors.

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Conflict of Interests

There is no conflict of interests for the authors.

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