Biointerface Research in Applied Chemistry
Open-Access Journal (ISSN: 2069-5837)

Article
Volume 13, Issue 3, 2023, 208
https://doi.org/10.33263/BRIAC133.208

In Silico Interactions of Morphine Opioids with TLR4 and TRPV1 Targets

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Scopus Author ID 13204227300
Received: 30.04.2022; Accepted: 21.05.2022; Published: 5.06.2022

Abstract: By the importance of exploring new inhibitors or antagonists for the over-activity of each of Toll-Like Receptor 4 (TLR4) and Transient Receptor Potential Vanilloid 1 (TRPV1) targets, derivatives of morphine opioid were investigated in this work using the *in silico* methodology. The original morphine and three derivatives of oxymorphone, naloxone, and naltrexone were considered the parent ligands (L1-L4), and the C-3-O-Alky functionalized models were considered as functionalized ligands (L5-L8). The singular models of ligands were optimized to obtain the minimized energy structures, and molecular docking simulations were performed to examine their interactions with the targets. The optimizations indicated significant variations of the frontier electronic molecular orbital levels proposing different activities for the ligands. Next, molecular docking simulations showed that L1 (the original morphine) was at the lowest suitability of complex formation and L8 was at the highest suitability of complex formation with both TLR4 and TRPV1 targets. Consequently, optimizing the morphine lead compound for obtaining more suitable ligands was achieved for proposing new inhibitors or antagonists for the investigated TLR4 and TRPV1 targets.

Keywords: TLR4; TRPV1; morphine; opioid; *in silico*.

1. Introduction

The Toll-Like Receptor (TLR) belongs to a class of pattern recognition receptors with significant importance in immune responses [1]. TLR4 was indeed the first recognized member of the TLR family with a protective role in self-defense mechanisms [2]. In the case of Gram-negative bacteria infection, inflammatory cytokines and type I interferon will be released for such a protective mechanism of TLR4; however, serious inflammatory reactions could appear after an over-release condition [3]. Consequently, the harmful impacts of over-activation of TLR4 made it a target for exploring new interacting ligands for regulating its activity [4-6]. On the other hand, the Transient Receptor Potential Vanilloid 1 (TRPV1), a member of the TRP family, has been supposed to participate in many biological functions and pain transmissions [7]. In this regard, the pain transmitting signals from the periphery to the central nervous system could be inhibited by the TRPV1 antagonists yielding analgesic effects for inflammatory and neuropathic pains [8]. However, the appearance of side effects such as hyperthermia made

TRPV1 a target for exploring new interacting ligands for working in antagonist functions [9-11]. To this aim, a series of morphine derivatives were investigated for interacting with each of the TLR4 and TRPV1 targets to see details of interactions employing the *in silico* approach.

Morphine, a member of opioids, could be administrated orally or by injection to directly act on the central nervous system to induce analgesia and resistant responses against the pain [12]. However, morphine has its negative side effects lowering blood pressure besides addicting and abusing misfunctions [13-15]. In this regard, a careful prescription of morphine is necessary, and the wanted and unwanted effects of morphine medication made it a lead compound for exploring new optimized derivative compounds [16]. Morphine has also been a source of producing other opioids by availability on the World Health Organization's List of Essential Medicines [17]. Consequently, both exploring new derivative compounds and examining new biological functions are important in the case of developing morphine medications. Accordingly, the structural modification of morphine was investigated in this work by adding O-alkyl groups to the C-3 atomic site to produce other derivative compounds [18]. It has already been proposed that such structural modification could provide analgesic activity for the morphine derivatives analgesic to moderate pain besides possessing antitussive activity [19]. In this regard, considerable efforts have been dedicated to synthesizing O-alkylated derivatives of morphine besides characterizing their functions in biological systems [20-22].

Within this research work, the O-functionalization of the C-3 atomic site was investigated for the original morphine and three of its derivatives, including oxymorphone, naloxone, and naltrexone. Next, interactions of each pre/post functionalized compound were examined against each of the TLR4 and TRPV1 targets. The main goal of this work was to learn details of interactions of such ligand-target complexes besides exploring a more potent ligand for this purpose. Indeed, the non-stop field of drug design and development has been found important for dealing with diseases in different conditions. The *in silico* drug design could help approach such purposes more efficiently, avoiding the existence of interference [23-28]. To approach the goal of this work, the required information was provided using the *in silico* methodology as an appropriate tool for exploring complicated systems in biology [29-33].

2. Materials and Methods

The ligand materials of this work were 3D molecular structures of morphine, oxymorphone, naloxone, and naltrexone in the pre/post-C-3 O-functionalized forms, a total of eight ligands of Figure 1, obtained from an already experimental synthesized work [34]. The target materials were 3D macromolecular structures of TLR4 and TRPV1, a total of two targets in Figure 2, obtained with the codes of 3FXI and 5IS0 from the protein data bank (PDB), respectively [35]. First, the ligand materials were optimized to achieve the energy minimized structures using the B3LYP/6-31G* density functional theory (DFT) level of quantum chemical calculations as implemented in the Gaussian program [36]. Next, the target materials were prepared by cleaning the macromolecular structure using the Discovery Studio program [37]. Subsequently, the molecular docking simulations of interacting ligand-target complexes were done using the HDOCK web server [38].

Consequently, the interaction strength and configuration of ligand-target complexes (Figures 3 and 4) were found to learn about the impacts of C-3 O-alkylation of morphine derivatives on their function against the investigated targets. All the obtained results of ligand

descriptors and docking scores were summarized in Table 1, and the visualized representations are exhibited in Figures 1-4. It is important to mention here that the methodology of this work was based on performing computational assessments for evaluating chemical and biological features of the specified compounds, as indicated as a useful methodology of an investigation by earlier works [39-43]. This work was done by combining quantum chemical calculations and molecular docking simulations [44-48].

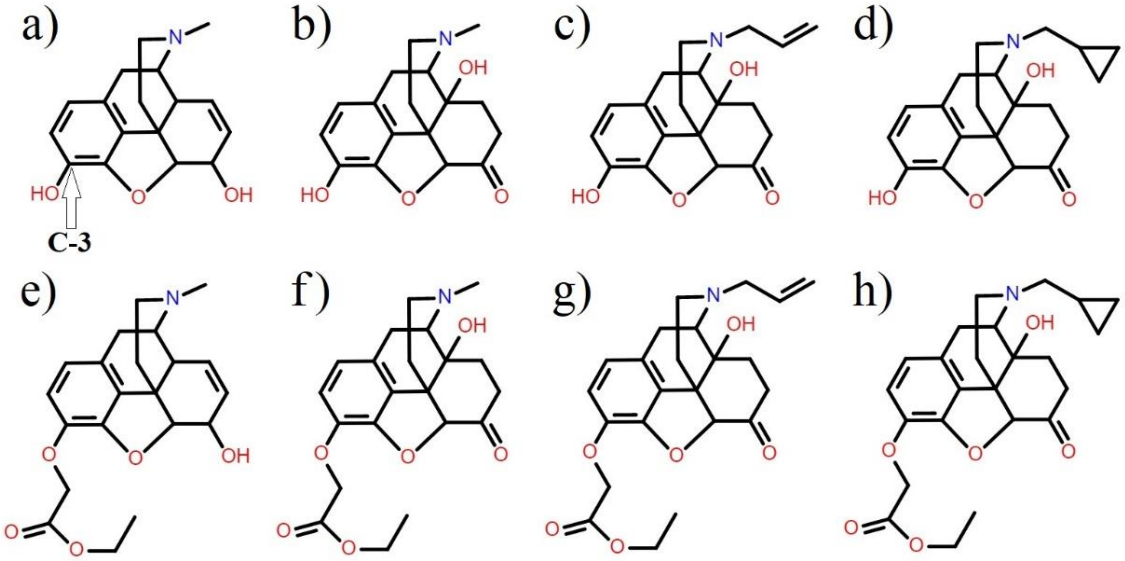

Figure 1. (a) L1; Morphine; (**b**) L2; Oxymorphone; (**c**) L3; Naloxone; (**d**) L4; Naltrexone; (**e-h**) L5-L8; C-3-O-Alkylated models.

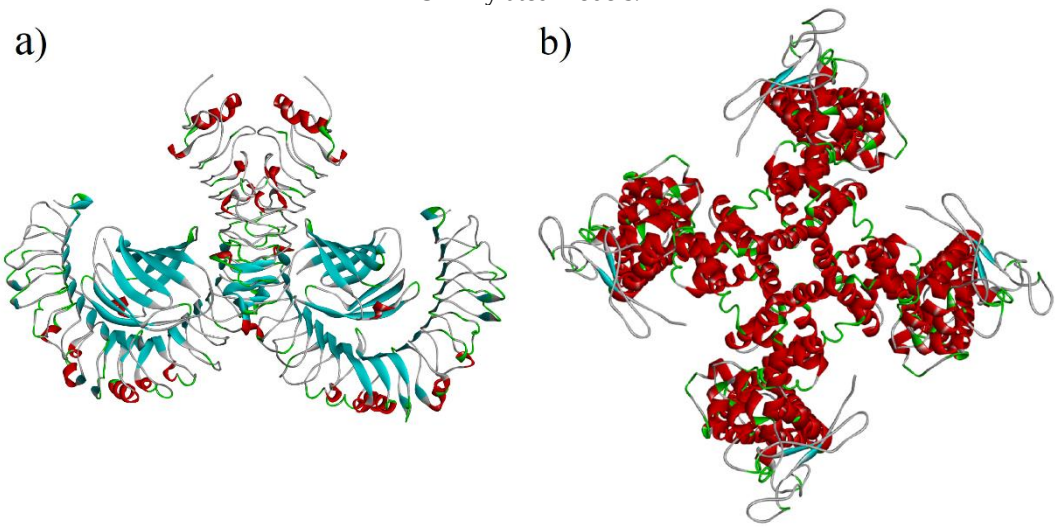

Figure 2. (a) T1; TLR4 (PDB: 3FXI); (**b**) T2; TRPV1 (PDB: 5IS0).

3. Results and Discussion

In accordance with the main goal of this work to investigate interactions of the morphine derivatives opioids with each of the TLR4 and TRPV1 targets, the required information was prepared using the in silico methodology. As shown in Figure 1, eight models of morphine derivatives, including the original morphine, oxymorphone, naloxone, and naltrexone and their C-3-O-alkylated, were investigated in this work for playing the ligand roles; Li-L8. In these structures, L5-L8 are the C-3 functionalized models of L1-L4. First, the singular ligand models were optimized by performing DFT calculations to obtain the energy minimized structures. The results of energy levels of frontier electronic molecular orbitals, the highest occupied and the lowest unoccupied molecular orbitals (HOMO and LUMO) were summarized in Table 1 for the optimized ligand models. These results were indeed among the

most important electronic features of the chemical structures to show their electron transmission behavior. Accordingly, the values of energy gap (EG) indicating energy differences of HOMO and LUMO levels were listed in Table 1 to show the variations of electronic features among the investigated ligand models. It could be learned from such results that the derivatives of morphine show different frontier electronic molecular orbital features, in which such variations could have significant impacts on their next behaviors. The level of HOMO is characteristic of the electron-donating, and the level of LUMO is characteristic of the electron-accepting. Hence, variations of such features could directly impact the interaction systems with the variations of the tendency of electron-donating and accepting. Additional functionalized groups are one of the main reasons for such electronic variations in the chemical structures.

Table 1. The obtained features of investigated models.[1]

Ligand		HOMO	LUMO	EG	DS: TLR4 (T1)	DS: TRPV1 (T2)
Morphine	(L1)	-5.48	0.08	5.56	-127.54	-152.94
C-3-O-Morphine	(L5)	-5.58	-0.05	5.53	-140.99	-182.09
Oxymorphone	(L2)	-5.55	-0.82	4.73	-130.09	-160.09
C-3-O-Oxymorphone	(L6)	-5.56	-0.82	4.74	-138.81	-186.89
Naloxone	(L3)	-5.54	-0.79	4.75	-137.47	-173.11
C-3-O-Naloxone	(L7)	-5.75	-0.84	4.91	-138.99	-194.21
Naltrexone	(L4)	-5.52	-0.79	4.73	-142.95	-176.73
C-3-O-Naltrexone	(L8)	-5.56	-0.79	4.77	-148.99	-209.44

[1]The models are represented in Figures 1-4. HOMO, LUMO, and EG are in eV. DS is arranged in kcal/mol.

Careful analyses of the HOMO and LUMO results in Table 1 could reveal that the levels of HOMO and LUMO were moved to lower achievable energy levels in three related compounds of L2-L4 compared with the original morphine, L1. Moreover, the C-3-O-Alkyl functionalization moved the orbital levels of all L5-L8 models to lower energy levels compared to the parent L1-L4 models. In this regard, it could be found that both of structural modification of morphine to have each L2-L4 compounds and the C-3-O-Alky functionalization had significant impacts on the electronic transmission features. Then, it could be found that the lead optimization of morphine could yield more suitable molecular structures, L2-L8, in accordance with their more achievable frontier electronic molecular orbitals. Additionally, the values of EG of L2-L8 models were also smaller than that of the L1 model revealing higher overall activity of derivatives than with the original morphine compound. It is worth mentioning that the chemical hardness, as a resistance of chemical structure for contributing to other reactions or interactions, would be decreased in the case of shorter distances of HOMO and LUMO levels (EG). As a consequence, more activated derivatives of morphine could be proposed for participating in the interactions with each of the target compounds.

Figure 2 represents the TLR4 (T1) and TRPV1 (T2) target compounds, which were cleaned to work as the targets of molecular docking simulations. In this regard, molecular docking simulations were performed to examine formations of interacting ligand-target complexes for each of the L1-L8 ligands against each of the T1 and T2 targets. The docking scores (DS) results were listed in Table 1, and the visualized L-T complexes were exhibited in Figures 3 and 4. It is worth mentioning that smaller negative values of DS are more suitable for forming stronger complexes. The derivatives showed more suitability of formations of stronger complexes according to their already proposed higher activity than the original morphine. Looking at the panels of Figure 3 could reveal that the surrounding amino acids are more or less similar in the formations of interacting L1-L8 ligands with the T1 target.

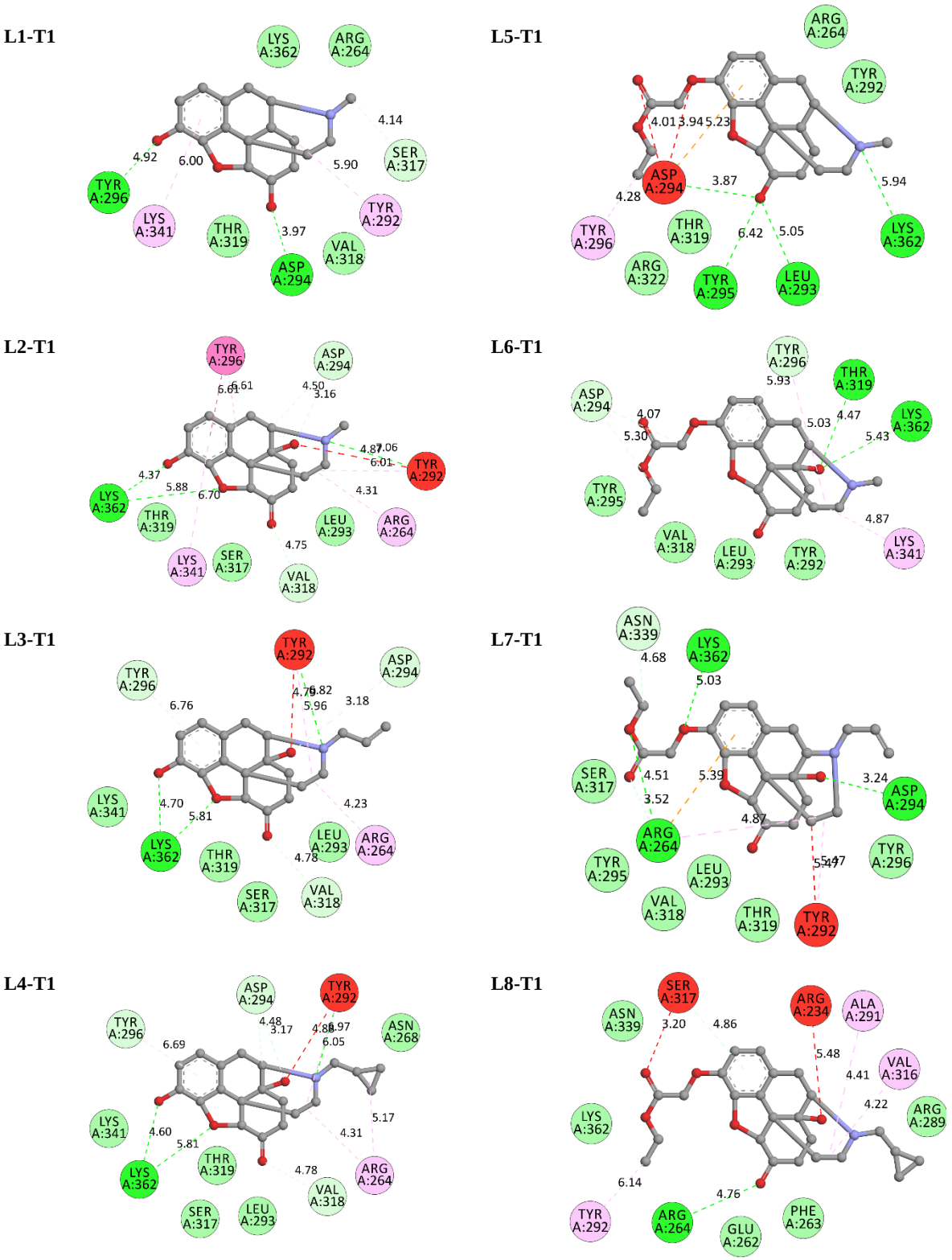

Figure 3. The interacting L1-L8 and T1 complexes.

It is important to know that the interacting sites were almost similar, including ARG264 and ASP294; however, the types and numbers of interactions were different, resulting in different levels of complex strength. As could be seen by the DS values of Table 1, the weakest strength of the complex was observed for the L1-T1 complex among all eight complexes. Subsequently, structural modifications yielded stronger complexes in L2-L4 and L5-L8 complex model systems. In this regard, the role of C-3-O-Alkyl functionalization for L5-L8 ligands was highlighted by producing stronger complexes than the parent L1-L4 ligands.

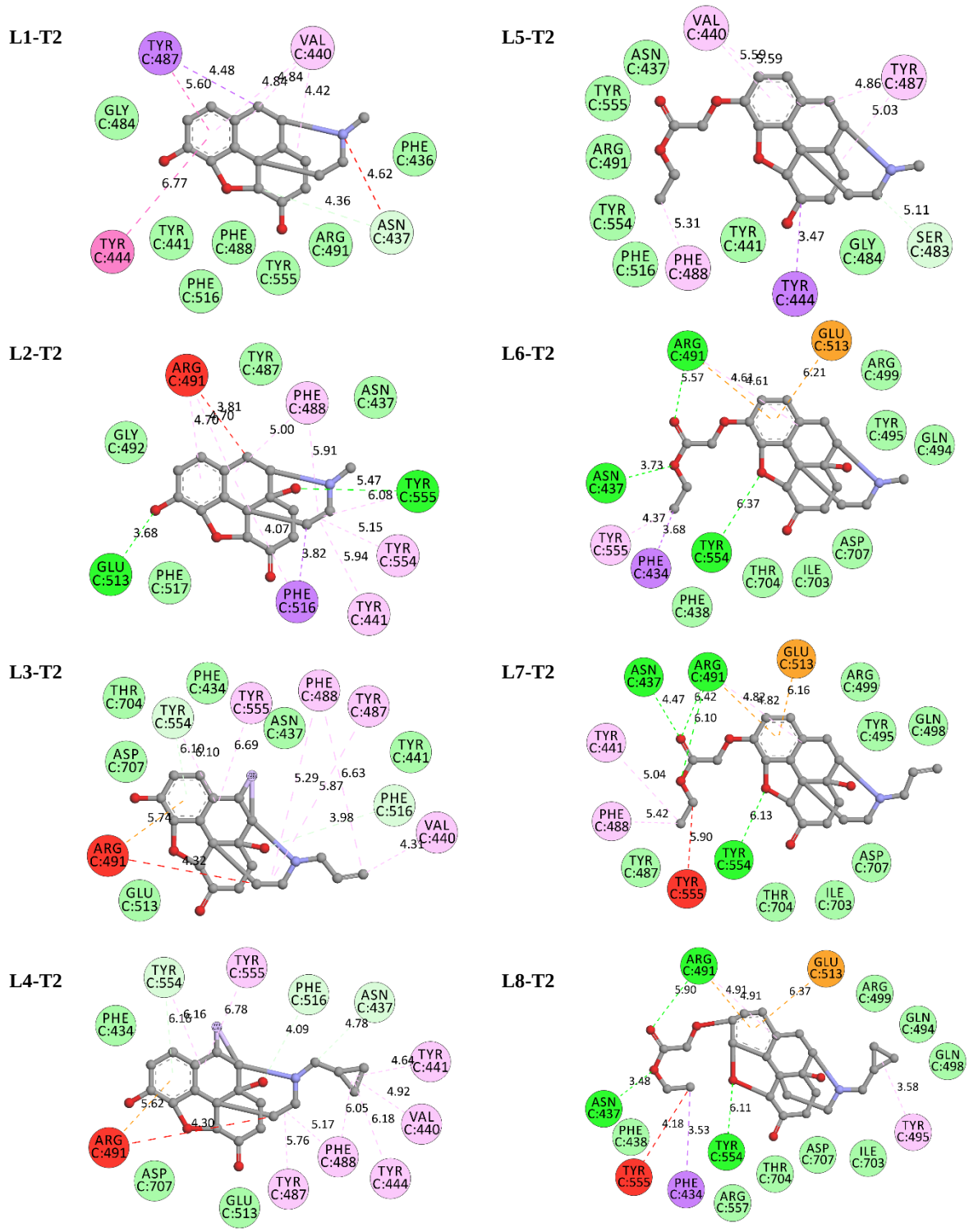

Figure 4. The interacting L1-L8 and T2 complexes.

Parallel situations were observed for the complexes of L1-L8 and T2 interactions (Figure 4), in which the original morphine was at the lowest tendency of formation of a strong complex with T2 target. It is worth noting that stronger complex formations are preferred over weaker complexes for providing antagonist ligands. In this regard, for both T1 and T2 targets, the C-3-O-Alkyl functionalized models were more suitable ligands for participating in stronger interactions with each of the T1 and T2 targets. In this regard, L8 was indeed the most favorable ligand for forming strong complexes with both T1 and T2 targets.

4. Conclusions

The main goal of this work was to examine interactions of morphine derivatives with TLR4 (T1) and TPRV1 (T2) targets to show their complex strength in accordance with exploring new inhibitors or antagonists or over-activity of the targets. In this regard, eight ligands were examined against each of the T1 and T2 targets, in which the C-3-O-Alkyl functionalized models were seen as better interacting ligands than the parent ligand structures. Accordingly, stronger complexes were found for the functionalized ligands, and L8 was found to work as the best ligand for participating in interactions with both T1 and T2 targets, whereas the original morphine was found as the worst ligand for the formation of interacting L-T complexes.

Funding

This research was funded by Isfahan University of Medical Sciences, grant number 299179.

Acknowledgments

Support of the Applied Physiology Research Center of Isfahan University of Medical Sciences for approving the research proposal of this work is acknowledged.

Conflicts of Interest

The authors declare no conflict of interest.

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