

Potentials Mu Receptor Ligands to Avoid Fentanyl Interactions by Molecular Docking

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Abstract: In this study, we propose a repositioning of Food and Drug Administration (FDA) approved drugs for treating fentanyl addiction; these approved drugs could be adjuvants with the habitual treatment, like naloxone, and in this way, try to improve the response against this addiction. Where these FDA-drugs potentially will be selective to Mu Opioid Receptor (MOR). Thus, these could avoid the fentanyl interactions. We used data from FDA-approved drugs to perform molecular docking using the structure of MOR (Protein Data Bank: 8EF5). It was performed using the region for fentanyl interactions with MOR; thus, the potential site of interaction was the region between Asp149, Lys211, Glu231, Lys235, Phe291, Trp295, His299, Lys305, Glu312, and His321 amino acids in MOR. We determined ten compounds from the FDA-approved drugs list. These drugs probably have better interactions with MOR than fentanyl. The main amino acids in MOR for interactions are Asp149, Asp218, Glu231, Lys305, and Glu312, and this region is specifically for MOR and different in Kappa Opioid Receptor (KOR) and Delta Opioid Receptor (DOR). We propose ten FDA drugs as adjuvants against fentanyl addiction; these molecules/drugs probably have better interactions with MOR than fentanyl. In addition, these drugs are potentially safe for humans. Therefore, in vitro or in vivo experiments will be required to determine the effect and even a probable synergy with traditional anti-addiction drugs like naloxone.

Keywords: substance-related disorders; drug repositioning; fentanyl; mu opioid receptor.

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1. Introduction

The use of drugs and current derivatives of Opioids have generated addictions, and this causes death due to overdose. According to World Health Organization (WHO) estimates, approximately 125,000 people die of opioid overdose per year [1]. Thus, there is an urgent need to discover molecules or drugs with anti-opioid effects that have adverse side effects [2]. To understand the opioid effects, it is necessary to identify which receptor is more important in regulating the opioid effects [2]. The opioid receptors known are Mu, Delta, Kappa, and nociceptive (MOR, DOR, KOR, and NOPR, respectively) [2-4].

Opioid addiction could be considered a problem for public health because, in the last decades, there have been reports that suggested that fentanyl was being abused by healthcare professionals and people too. These excesses have increased the surge in fentanyl-related overdose deaths and are a signal for the Drug Enforcement Agency (DEA) to attend the illicitly

manufactured fentanyl in the United States of America [5]. It has become relevant over time. Since 2016, estimates of overdoses and deaths from fentanyl and analogs (e.g., acetyl fentanyl, furanyl fentanyl, and carfentanil) have contributed to almost half of opioid overdose deaths. The concern is that the number of overdoses and deaths from fentanyl will continue to rise in the coming years [6,7]. It has been identified that the Opioid Receptors (ORs) are highly related to fentanyl, and the Or are widely expressed in the human brain. The main effects associated with drugs with these receptors are difficulties in emotional learning, emotion regulation, and anhedonia, which have been linked to endogenous opioid signaling. Specifically, the mu receptor has dysfunction in the mu-opioid system, and the specific mechanisms are not well understood yet [8]. For addictions, agonist opioid receptors such as morphine, oxycodone, and fentanyl, among others. The mu receptor has relevance for addictions, as well, as there are anti-addiction medications such as mu-opioid receptor ligands (methadone, buprenorphine, and naloxone), each one with pharmacologic features and therapeutic effects [9], where there are different affinity grade and signaling between ORs; particularly, MOR has a higher affinity for opioids [9, 10], and the KOR is associated with several types of cancer and may influence cancer progression [11]. Thereby, there are anti-addiction drugs, which are drugs against the different opioid receptors (mu, delta, and kappa) [9], but there is still a high necessity to attend to people with some addiction regulating the ORs. Opioid receptors characteristics

The identity between ORs is almost 61 %, UniProt code: P35372-Mu, P41145-Kappa, and P41143-Delta [12], and their Gene ID: 4988, 4986, and 4985, respectively [13], which shows the possibility to identify molecules selective against a specific region on the opioid receptor. Despite the identity, it is reported that structural comparisons indicated that opioid receptors have a highly conserved activation site [14], and it has relevance to the possibility of determining a new selective molecule/drug.

1.1. Mu opioid receptor.

The Mu Opioid Receptor (MOR) has an important analgesic effect, and there are powerful agonists for analgesic medications, but they are among the most addictive. Currently, the opioid crisis has energized a quest to develop opioid analgesics, where MOR agonists produce euphoria, promote stress coping, and even addictions [4,10]. MOR could be more relevant because studies indicate that MOR has rich expression in the human brain, mainly in the thalamus, insulae, amygdala, anterior cingulate cortex, and in the locus coeruleus, where MOR has effects on stress, and contributes to the regulation of reward and threat processing. Thus, agonists MOR develop symptoms associated with opioid use disorder, such as anhedonia and depression/anxiety [8], and the agonist's knowledge users are morphine, fentanyl, lofentanil, and mitragynine pseudoindoxyl, where these have different effects and affinities with MOR [10], as we mentioned, by the structural analysis is proposed that fentanyl binds to an additional pocket of MOR that is not occupied by endomorphin and b-endorphin, it could providing a higher effect of fentanyl to MOR [14].

1.2. Fentanyl.

As we mentioned, fentanyl addiction is a condition that, in some countries, could be a serious public health problem due to there being approximately 60 million consumers of opioid drugs (WHO-World Drug Report 2024). Fentanyl is a potent synthetic opioid, MOR agonist, mainly to mu than kappa receptors. It was introduced into medical practice in the 1960s. It is a

potent synthetic opioid agonist derived from phenylpiperidine, and it is soluble in lipids. Fentanyl is used to aid the induction and maintenance of general anesthesia and to complement regional and spinal analgesia. Fentanyl is preferred over morphine in anesthesia due to its ability to attenuate hemodynamic responses and maintain cardiac stability [3, 5, 15-19]. For those who abuse fentanyl, it is illicitly combined with other substances of the same origin. Furthermore, fentanyl has different forms of administration, such as parenteral, transdermal, transmucosal, topical, intravenous, intramuscular, and epidural, and all of them are more stable than anti-addiction medications (naloxone and nalmefene), and have fewer forms of administration [19], but these could be to improve due to their pharmacologic characteristic e interactions [19,20].

1.3. Ligands interact with the Mu opioid receptor.

Studies of agonist and antagonist ligands with the Mu receptor show different affinities between the ligands and opioid receptors [14,21]. This demonstrates that a pharmacophore ligand could be developed to limit the response of this receptor specifically. An example is fentanyl, which has a better interaction with MOR, for which the residues in MOR are important, and it will be important to analyze the simulations that could be linked to the differences in ligand-dependent efficacy with respect to receptor intracellular signaling events to determine small changes in the interactions ligand–residue [22,23] and to propose an important region in MOR to develop a quest for new ligands. So, there are drug studies related to developing anti-fentanyl drugs [24-26]. Where the MOR as a therapeutic target has relevance due to its interaction with fentanyl, therefore, all these show us the necessity to propose other drugs that could be adjuvant anti-addiction drugs and, in this way, improve the treatment for fentanyl addiction.

1.4. Drug repositioning for MOR.

Developing repositioning of drugs in different diseases (such as cancer) [27] could have the ability to provide more effective and more affordable treatment options than traditional drug development methods [28]. In this way, it is possible to propose drugs to be used against diseases, such as cancer or Alzheimer's disease; this has had a notable increase during the last decade [29], and *in silico* methods have been used as molecular docking [30,31]. Therefore, this study promotes ligands from FDA-approved drugs [32,33] for MOR by repositioning and molecular docking on MOR, with the aim of blocking the fentanyl interactions, and these FDA drugs could be used as adjuvants to treat fentanyl addictions.

2. Materials and Methods

2.1. Preparation of receptor protein and definition of binding site.

The X-ray crystallographic structure of the Mu opioid receptor (from *Homo sapiens*) was obtained from the Protein Data Bank (PDB) [34], PDB code 8EF5 (PDB:8EF5 has a -2 numbering of the amino acids in the sequence; PDB shows Asp149 instead of Asp147). The structure was used as a protein target for a molecular docking directed to the region between Asp149, Lys211, Glu231, Lys235, Phe291, Trp295, His299, Lys305, Glu312, His321 amino acids [22,23]. Each PDB file's protonation and energy minimization were performed using

Molecular Operating Environment (MOE) software with the default parameters, and the CHARMM27 Force Field was used [35].

2.2. Screening library.

The drug repurposing strategy was performed using a dataset of FDA-approved drugs (3019 drugs) from the Selleckchem.com database, which was downloaded from Selleckchem.com (accessed May 2024) [36], as well as the fentanyl and naloxone molecules. The conformer module in MOE [37] was applied for the generation of conformers of each drug/molecule, and up to 100 conformers of each drug/molecule were generated for molecular docking.

2.3. Molecular docking.

MOE carried out molecular docking, the potential binding site for the docking directed to the amino acids docking directed to the region between Asp149, Lys211, Glu231, Lys235, Phe291, Trp295, His299, Lys305, Glu312, His321 amino acids [22,23], and up to 100 conformers of each molecule were used for molecular docking. A flexible ligand-rigid receptor molecular docking was performed in the Dock module with MOE, as we reported [38-41]. Later, the values of up to 15 conformers of each compound were analyzed, and the average $\Delta G_{\text{binding}}$ of each molecule was determined, as previously reported [38,39]. The analysis of ligand interaction per amino acid was conducted using a Protein-Ligand Interaction Profiler (PLIP) [42].

2.4. Selection of the best ten molecules.

From the docking results, up to 15 conformers for each FDA drug were analyzed to determine their $\Delta G_{\text{binding}}$ averages in order to select the best 10 drugs as previously reported [40,43,44] as well, and the standard deviation was determined (using Excel Microsoft-365 software), with these results, the best $\Delta G_{\text{binding}}$ averages were determined for interactions of each drug/molecule with MOR.

2.5. Statistical analysis.

Data were expressed as mean \pm standard deviation (SD), averages, and standard deviations were calculated in Excel (Microsoft).

3. Results and Discussion

3.1. This selection of the best ten molecules by molecular docking.

We used the FDA-approved drug library from selleckchem.com [36] comprising 3109 drugs/molecules, and with them generated up to 100 conformers of each one for molecular docking [40] at the potential site between Asp149, Lys211, Glu231, Lys235, Phe291, Trp295, His299, Lys305, Glu312, His321 amino acids in MOR (using PDB code 8EF5, Figure 1). The best ten drugs/molecules were selected based on their average binding affinity ($\Delta G_{\text{binding}}$), calculated with the $\Delta G_{\text{binding}}$ of all conformers. After classifying and analyzing all molecules, we determined a range between ~ 11.37 to ~ 10.03 kcal/mol for the best ten FDA drugs (Table 1; the details are provided in the Table S1 in the supplementary files). The 10 FDA drugs were selected and labeled L-MOR1 to L-MOR10. Each molecule's interaction with MOR was

analyzed using its interaction report (Table 2; the details are provided in Tables S2–S11). All calculated $\Delta G_{\text{binding}}$ averages are related to the number of interactions generated from the conformers analyzed by molecular docking (Table S2 – S11).

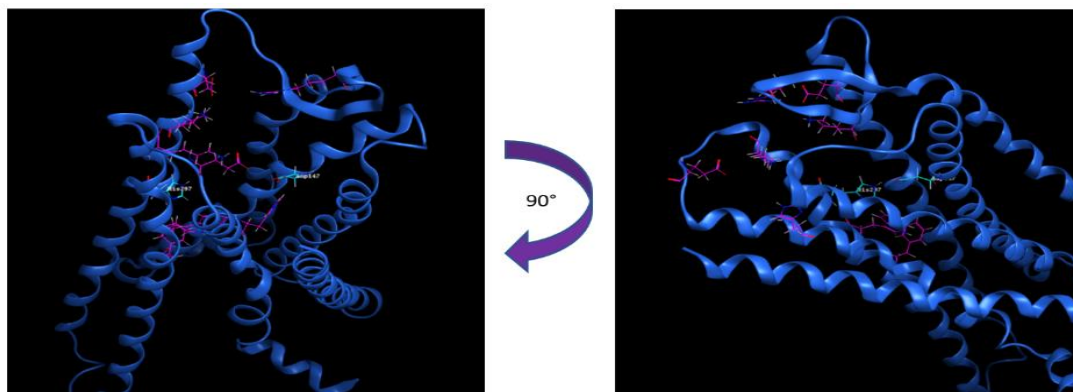
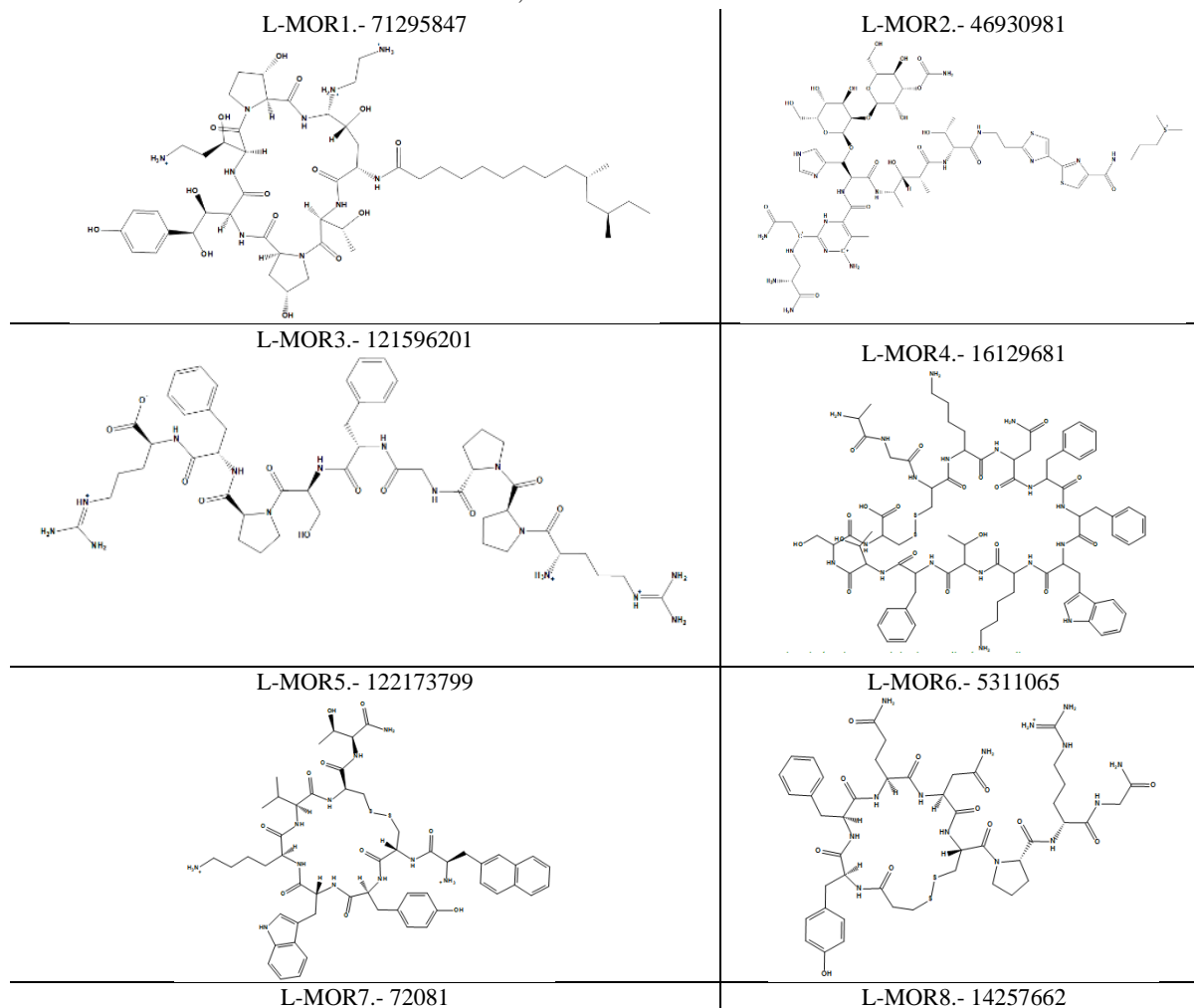


Figure 1. Potential site interaction in Mu Opioid Receptor (MOR). MOR (blue), potential site is between Asp149, His299 (cyan), Lys211, Glu231, Lys235, Phe291, Trp295, Lys305, Glu312, His321, amino acids (pink).

Table 1. PubChem CID, and structure of L-MOR1 to L-MOR10.



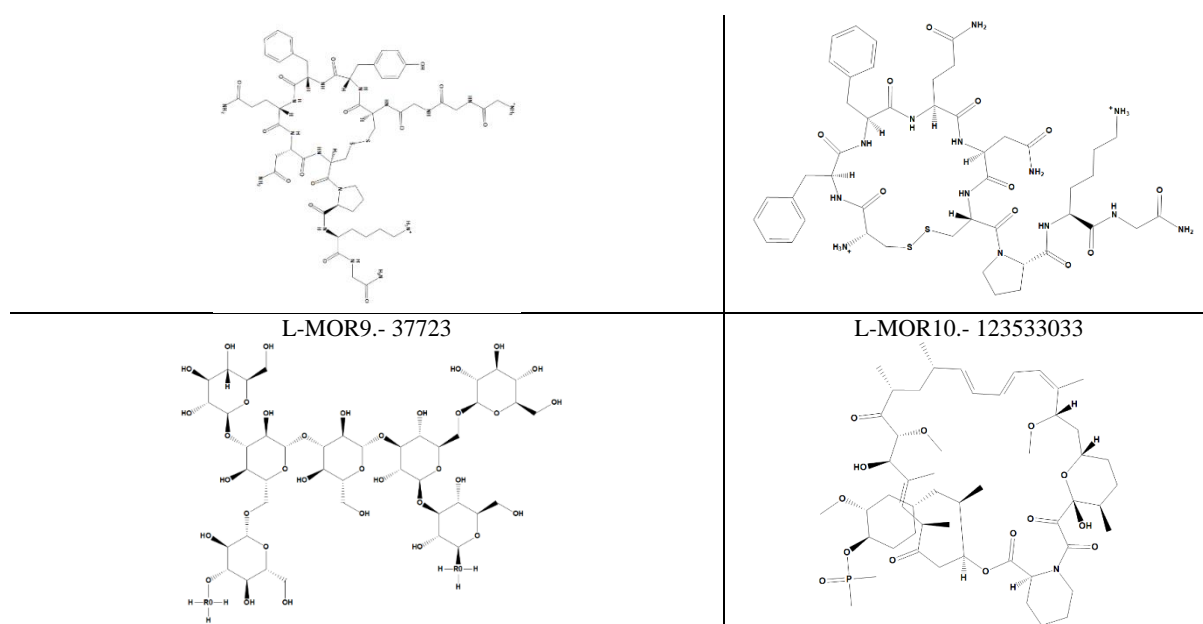
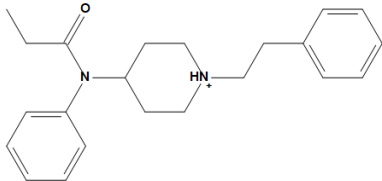
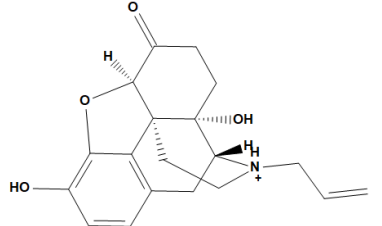


Table 2. Compound ID, PubChem CID, Canonical SMILES, interaction with amino acids in MOR, number of conformers used, and $\Delta G_{\text{binding}}$ average (kcal/mol) with standard deviation.

Compound ID and PubChem CID	Canonical SMILES	Interaction with residues in MOR (Table S2 – S11)	Number of conformers	Average of $\Delta G_{\text{binding}}$ and SD
L-MOR1 71295847	<chem>CCC(C)CC(C)CCCCCCCC(=O)NC1CC(C(NC(=O)C2C(CCN2C(=O)C(NC(=O)C(NC(=O)C3CC(CN3C(=O)C(NC1=O)C(C(O)O)C(C(C4=CC=C(C=C4)O)O)O)C(CCN)O)O)NCCN)O</chem>	Asp218, Lue221, Glu231, Lys305, Glu312	15	-11.37 ± 0.56
L-MOR2 46930981	<chem>CC1=C(N=C(N=C1N)C(CC(=O)N)NCC(C(=O)N)N)C(=O)NC(C(C2=CN=CN2)OC3C(C(C(C(O3)CO)O)O)OC4C(C(C(C(O4)CO)O)OC(=O)N)O)C(=O)NC(C(C(C(C(=O)NC(C(C)O)C(=O)NCCC5=NC(=CS5)C6=NC(=CS6)C(=O)NCCC[S+](C)CO.OS(=O)(=O)[O-])</chem>	Asn129, Asp149, Met153, Asp218, Thr220, Glu231, Lys305, Ile310, Glu312, Trp320	15	-10.86 ± 1.47
L-MOR3 121596201	<chem>C1CC(N(C1)C(=O)C2CCCN2C(=O)C(CCC[NH+]=C(N)N)[NH3+])C(=O)NCC(=O)NC(CC3=CC=CC=C3)C(=O)NC(CO)C(=O)N4CCCC4C(=O)NC(CC5=CC=CC=C5)C(=O)NC(CCC[NH+]=C(N)N)C(=O)[O-]</chem>	Asp149, Met153, Arg213, Asp218, Glu231, Lys235, Lys305, Glu312	15	-10.81 ± 0.48
L-MOR4 16129681	<chem>CC(C1C(=O)NC(C(=O)NC(C(=O)NC(C(=O)NC(CSSCC(C(=O)NC(C(=O)NC(C(=O)NC(C(=O)NC(C(=O)NC(C(=O)N1)CCCCN)CC2=CNC3=CC=CC=C32)CC4=CC=CC=C4)CC5=CC=CC=C5)CC(=O)N)CCCCN)NC(=O)CNC(=O)C(C)N)C(=O)O)CO)C(C)O)CC6=CC=CC=C6)O</chem>	Asn129, Asp149, Arg213, Gln214, Asp218, Leu221, Glu231, Lys235, Lys305, Glu312	15	-10.53 ± 1.41
L-MOR5 122173799	<chem>CC(C)C1C(=O)NC(CSSCC(C(=O)NC(C(=O)NC(C(=O)NC(C(=O)N1)CCCCN)CC2=CNC3=CC=CC=C32)CC4=CC=C(C=C4)O)NC(=O)C(CC5=CC6=CC=CC=C6=C5)N)C(=O)NC(C(C)O)C(=O)N</chem>	Asp149, Ser216, Asp218, Cys219, Thr220, Glu231, Lys235, Lys305, Glu312	15	-10.39 ± 0.90
L-MOR6 5311065	<chem>C1CC(N(C1)C(=O)C2CSSCCC(=O)NC(C(=O)NC(C(=O)NC(C(=O)N2)C(C(=O)N)CCC(=O)N)CC3=CC=CC=C3)C4=CC=C(C=C4)O)C(=O)NC(CCCN=C(N)N)C(=O)NCC(=O)N</chem>	Asn129, Asp149, Asp218, Glu231, Lys235, Lys305, Glu312	15	-10.22 ± 1.28
L-MOR7 72081	<chem>C1CC(N(C1)C(=O)C2CSSCC(C(=O)NC(C(=O)NC(C(=O)NC(C(=O)N2)CC(=O)N)CCC(=O)N)CC3=CC=CC=C3)CC4=CC=C(C=C4)O)NC(=O)CNC(=O)C</chem>	Asn129, Asp149, Arg213, Asp218, Cys219, Thr220, Glu231, Lys305, Glu312,	15	-10.20 ± 1.13

3), according to amino acids reported [22,23]. For these amino acids, the ten conformers showed greater interactions with the potential site (Figure 1), particularly with Asp149 and Val302 (Figure S11).

Table 3. PubChem CID, interaction with amino acids in MOR, number of conformers used, and $\Delta G_{\text{binding}}$ average (kcal/mol) with standard deviation.

PubChem CID	Interaction with residues in MOR (Table S12, S13)	Number of conformers	Average of $\Delta G_{\text{binding}}$ and SD
 Fentanyl, 3345	Gln126, Asp149, Val302, Ile324	10	-6.74 ± 0.29
 Naloxone, 5284596	Asp149, Met153, Val302	10	-6.02 ± 0.23

3.4. Naloxone's interactions with MOR.

Results of naloxone's interactions showed an average of -6.02 kcal/mol (Table 3; the details are provided in Table S13). Naloxone's interactions with MOR were analyzed using 10 conformers (Table S13). Based on the molecular docking results (Table 3), we determined the primary amino acids in MOR that interact with naloxone: Asp149, Met153, and Val302 (Table 3). For these amino acids, the ten conformers showed greater interactions with the potential site (Figure 1), particularly with Asp149 and Val302 (Figure S12).

In this study, we propose ten FDA drugs that could block the region of fentanyl interaction (Figure 1). We performed a molecular docking using an FDA-approved drug library [36] comprising >3,000 molecules directed in the potential site between Asp149, Asp218, Glu231, Lys305, and Glu312 amino acids in MOR (Figure 1), which is the similar region reported for interaction with fentanyl [22,23]. The molecular docking results showed that each molecule's interactions (L-MOR1 to L-MOR10) with MOR (mainly between Asp149, Asp218, Glu231, Lys305, and Glu312 (Table 2, Tables S2–S11), and similar results for fentanyl and naloxone molecules in the same potential site in MOR (Figure 2). The molecular docking results showed that fentanyl and naloxone have lower averages of $\Delta G_{\text{binding}}$ (-6.74 and -6.02 kcal/mol, respectively, Table 3) than L-MOR1 – L-MOR10 (-11.37 to -10.03 kcal/mol, Table 2), as well as the main amino acids for interactions are similar for all drugs/molecules (Table 2 and 3). Also, we compared the interaction results of fentanyl and naloxone with the MOR, and we determined better interactions for the FDA drugs (L-MOR1 – L-MOR10). These ten drugs showed greater interactions with the potential site (Figure 2), particularly with Asp218, Glu231, and Glu312 amino acids (mainly through hydrogen bonding and hydrophobic interactions, Table S2-S11).

Thus, in this study, we propose a repurposing of 10 FDA drugs as potential MOR ligands, such as naloxone. We compared the interactions reported by the MOR with fentanyl and naloxone [22,23,45]. These interactions were important to determine the potential

interactions of these ten FDA drugs selected. They could block/hinder the cavity near Asp149, Asp218, Glu231, Lys305, and Glu312 amino acids, and in this way, avoid access to the binding pocket in MOR for fentanyl [22,23]. This blocking by some of these ten FDA-drugs could be because there are more interactions with the region near Asp218, Glu231, and Glu312 amino acids in MOR. Therefore, the probable interactions of these ten FDA-Drugs (Table 2) are similar to the main amino acids reported for fentanyl interactions [22,23,45], and these interactions were confirmed in the molecular docking performed (Table 2, 3), as we already mentioned is reported that the interactions near of Asp149 and His299 amino acids are important to get the probable inhibition effect on the MOR (Figure 2), due to these results, the L-MOR1 – L-MOR10 could generate interactions for blocking/hindering the cavity/space for fentanyl [22,23,45].

We keenly recognize that the above interactions are highly speculative, and it is necessary to validate their interactions and selectivity with MOR by experimental assays. We propose these ten molecules that could interact with this therapeutic target (MOR) to repurpose an FDA drug to treat fentanyl addictions, even to try combinations with other anti-addiction drugs.

4. Conclusions

In conclusion, fentanyl addictions are a public health problem in many countries due to fentanyl being abused and seizures of illicitly manufactured [1,5-7]. It is clear that the necessity to increase the treatments or adjuvants seems to be naloxone, which increases the MOR ligands drugs. We propose ten FDA drugs (L-MOR1 to L-MOR10) that correspond to the CID number in PubChem: 71295847, 46930981, 121596201, 16129681, 122173799, 5311065, 72081, 14257662, 37723, 123533033 respectively, as potential MOR ligands that could be interacting in the region of access to fentanyl and other ligands that could interact with fentanyl's site interaction between Asp147, Trp293, and His297 in MOR [22,23]. These FDA drugs could be tested like anti-addiction drugs related to MOR; thus, this study demonstrates another approach to treating addictions by regulating MOR ligands.

Author Contributions

All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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Supplementary materials

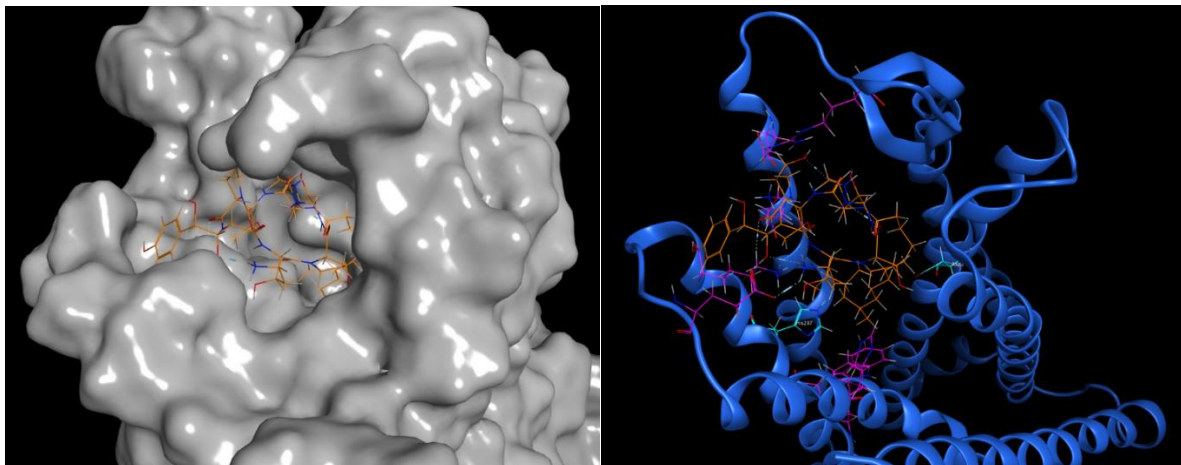


Figure S1. Mu Opioid Receptor (blue), potential site is between Asp149, His299 (cyan), Lys211, Glu231, Lys235, Phe291, Trp295, Lys305, Glu312, His321, amino acids (pink) with 15 conformers of L-MOR1 compound (orange), from docking results.

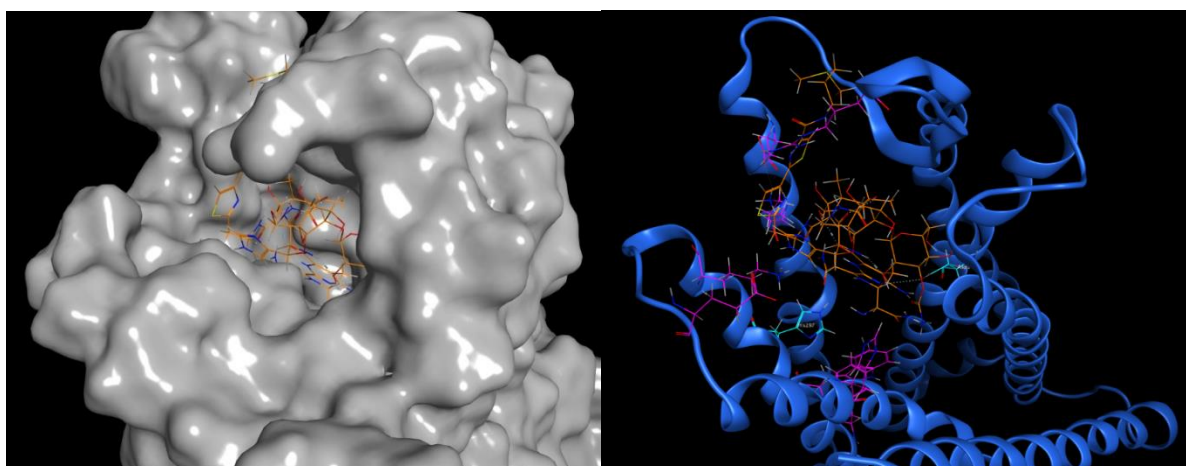


Figure S2. Mu Opioid Receptor (blue), potential site is between Asp149, His299 (cyan), Lys211, Glu231, Lys235, Phe291, Trp295, Lys305, Glu312, His321, amino acids (pink) with 15 conformers of L-MOR2 compound (orange), from docking results.

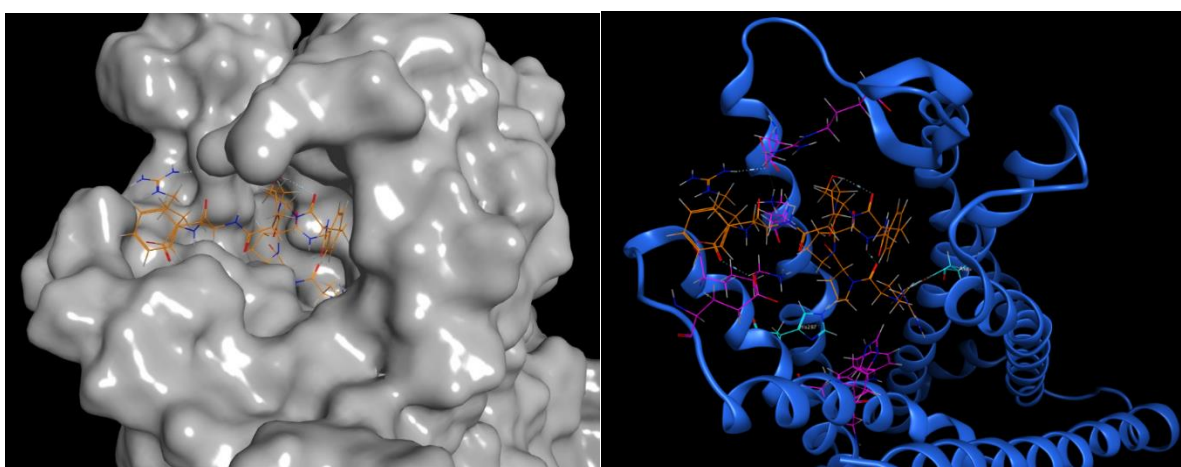


Figure S3. Mu Opioid Receptor (blue), potential site is between Asp149, His299 (cyan), Lys211, Glu231, Lys235, Phe291, Trp295, Lys305, Glu312, His321, amino acids (pink) with 15 conformers of L-MOR3 compound (orange), from docking results.

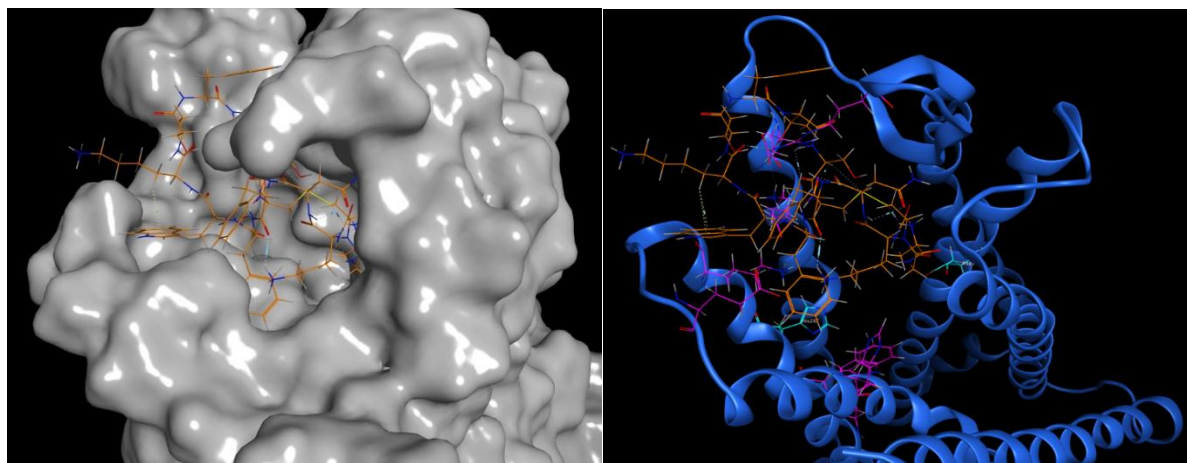


Figure S4. Mu Opioid Receptor (blue), potential site is between Asp149, His299 (cyan), Lys211, Glu231, Lys235, Phe291, Trp295, Lys305, Glu312, His321, amino acids (pink) with 15 conformers of L-MOR4 compound (orange), from docking results.

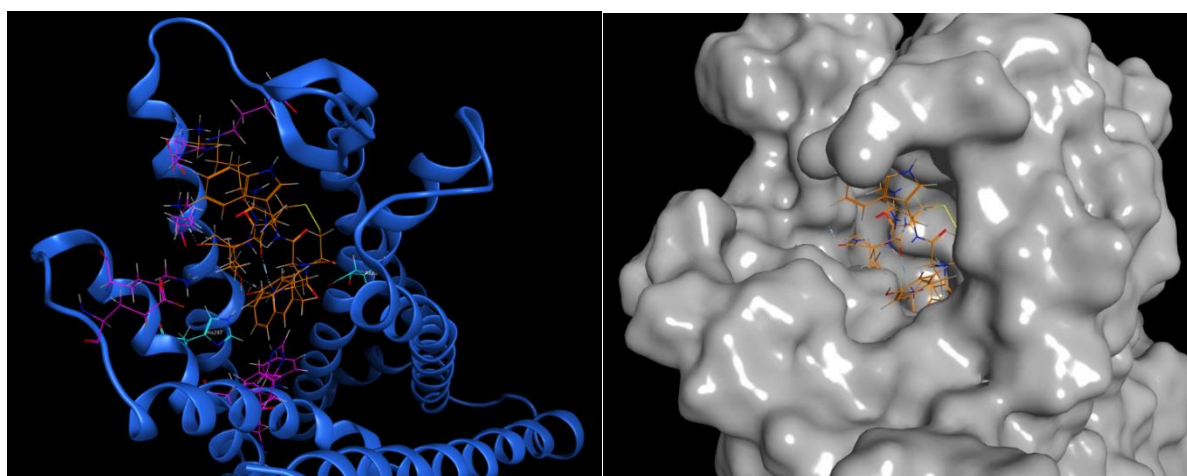


Figure S5. Mu Opioid Receptor (blue), potential site is between Asp149, His299 (cyan), Lys211, Glu231, Lys235, Phe291, Trp295, Lys305, Glu312, His321, amino acids (pink) with 15 conformers of L-MOR5 compound (orange), from docking results.

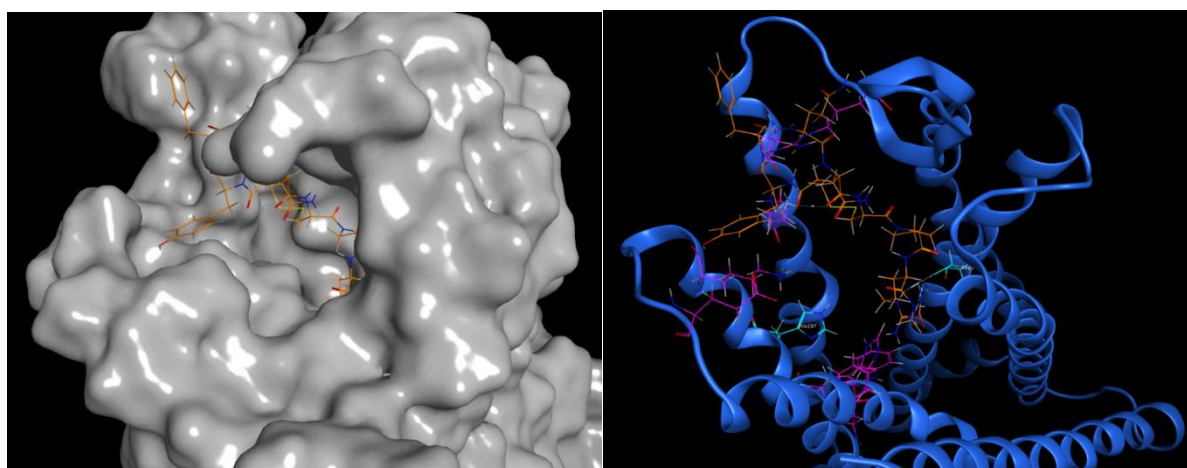


Figure S6. Mu Opioid Receptor (blue), potential site is between Asp149, His299 (cyan), Lys211, Glu231, Lys235, Phe291, Trp295, Lys305, Glu312, His321, amino acids (pink) with 15 conformers of L-MOR6 compound (orange), from docking results.

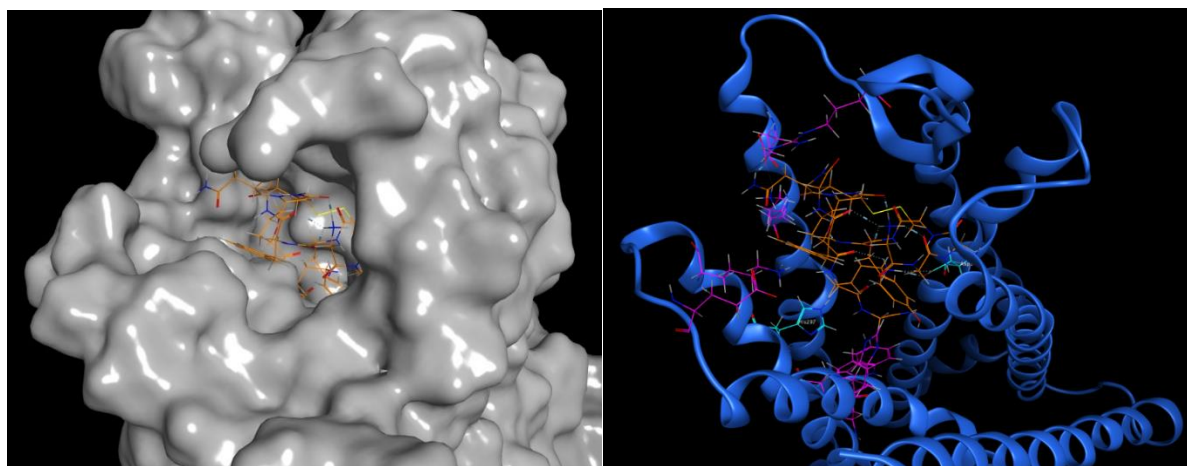


Figure S7. Mu Opioid Receptor (blue), potential site is between Asp149, His299 (cyan), Lys211, Glu231, Lys235, Phe291, Trp295, Lys305, Glu312, His321, amino acids (pink) with 15 conformers of L-MOR7 compound (orange), from docking results.

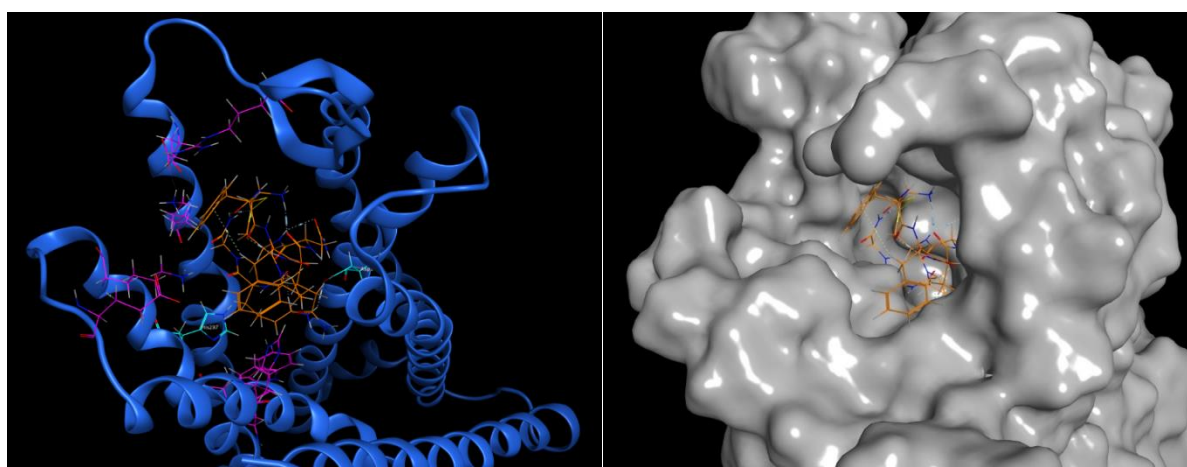


Figure S8. Mu Opioid Receptor (blue), potential site is between Asp149, His299 (cyan), Lys211, Glu231, Lys235, Phe291, Trp295, Lys305, Glu312, His321, amino acids (pink) with 15 conformers of L-MOR8 compound (orange), from docking results.

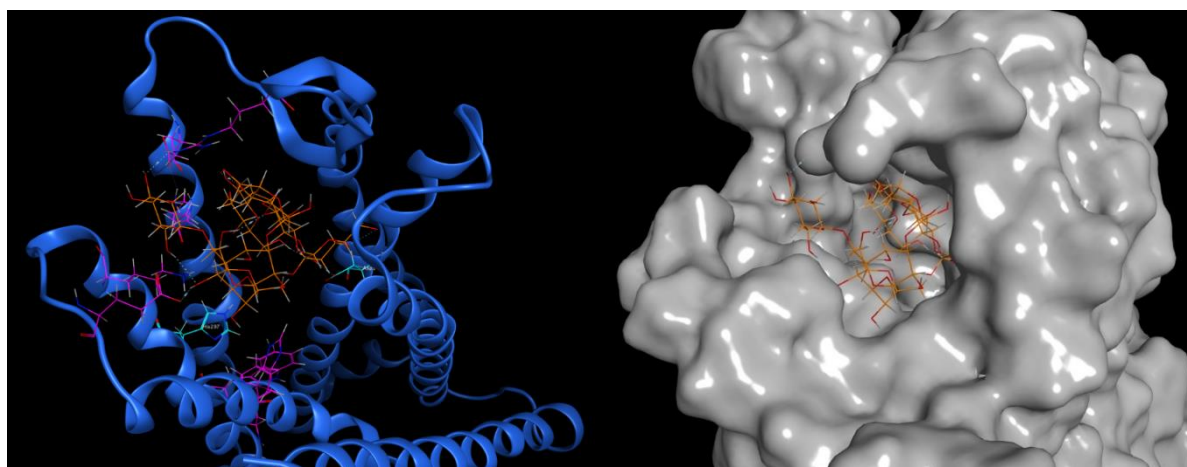


Figure S9. Mu Opioid Receptor (blue), potential site is between Asp149, His299 (cyan), Lys211, Glu231, Lys235, Phe291, Trp295, Lys305, Glu312, His321, amino acids (pink) with 15 conformers of L-MOR9 compound (orange), from docking results.

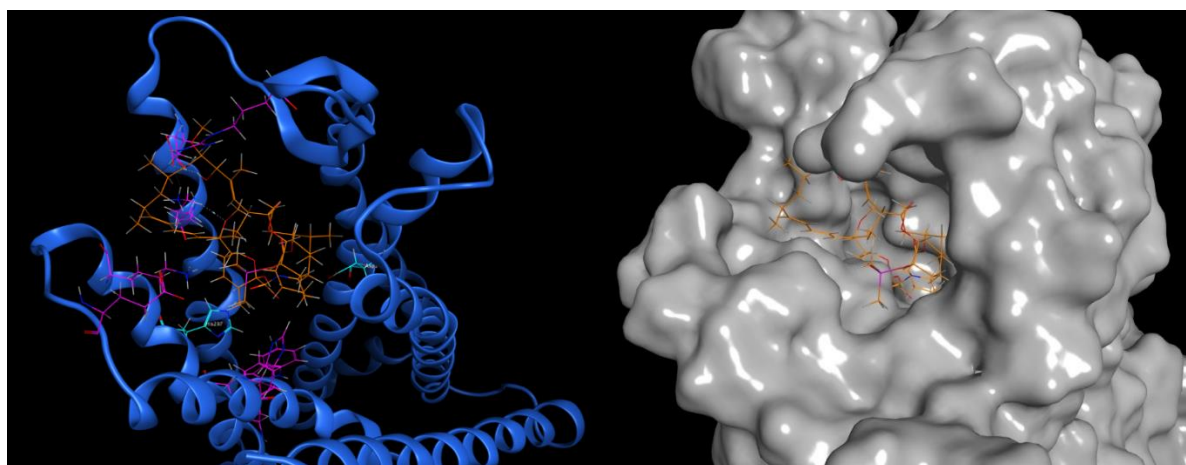


Figure S10. Mu Opioid Receptor (blue), potential site is between Asp149, His299 (cyan), Lys211, Glu231, Lys235, Phe291, Trp295, Lys305, Glu312, His321, amino acids (pink) with 15 conformers of L-MOR10 compound (orange), from docking results.

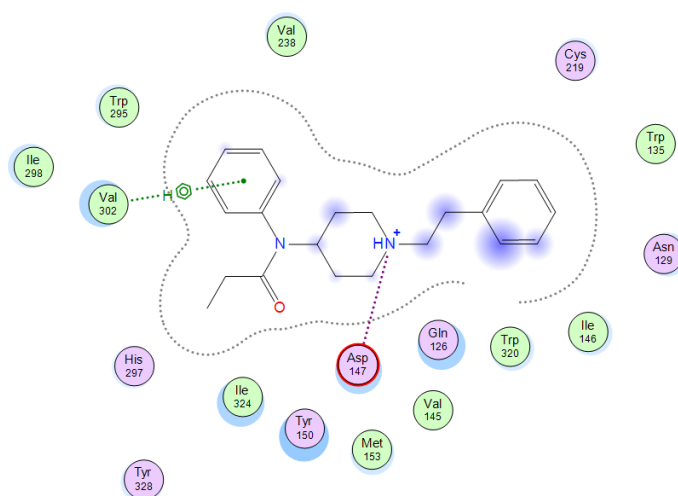


Figure S11. Interactions between MOR and the best conformer of fentanyl.

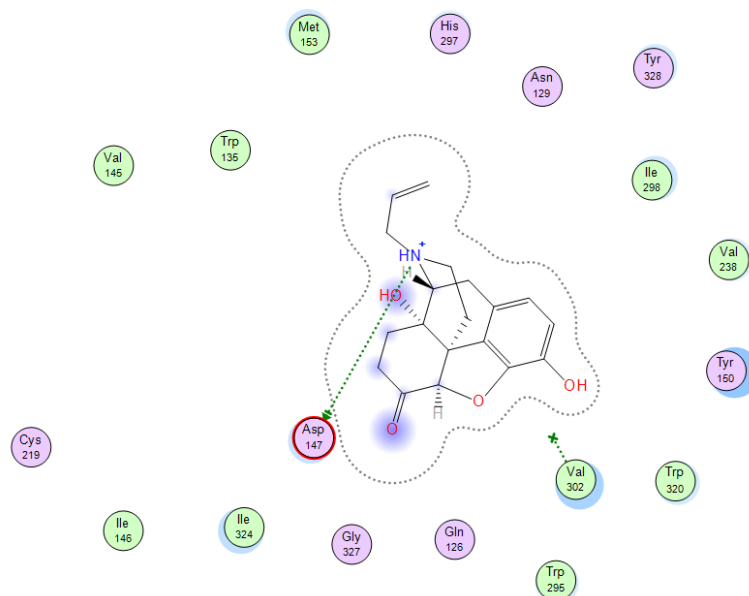


Figure S12. Interactions between MOR and the best conformer of naloxone.

Table S1. $\Delta G_{\text{binding}}$ of 10 to 15 conformers from each Drug/molecule, average $\Delta G_{\text{binding}}$ and SD.

Compound	Conformer	$\Delta G_{\text{binding}}$
L-MOR1	1	-12.4393
L-MOR1	2	-11.993081
L-MOR1	3	-11.960096
L-MOR1	4	-11.843637
L-MOR1	5	-11.705959
L-MOR1	6	-11.451163
L-MOR1	7	-11.3868
L-MOR1	8	-11.331926
L-MOR1	9	-11.259407
L-MOR1	10	-11.210739
L-MOR1	11	-11.196198
L-MOR1	12	-11.066356
L-MOR1	13	-10.913364
L-MOR1	14	-10.413323
L-MOR1	15	-10.403589
	Average $\Delta G_{\text{binding}}$	-11.37166253
	SD	0.563346077
L-MOR2	1	-13.313896
L-MOR2	2	-12.933618
L-MOR2	3	-12.589929
L-MOR2	4	-12.322167
L-MOR2	5	-11.734794
L-MOR2	6	-11.224293
L-MOR2	7	-11.052252
L-MOR2	8	-10.970574
L-MOR2	9	-10.359142
L-MOR2	10	-10.147148
L-MOR2	11	-9.8167057
L-MOR2	12	-9.4084826
L-MOR2	13	-9.0798788
L-MOR2	14	-9.0051079
L-MOR2	15	-8.9932156
	Average $\Delta G_{\text{binding}}$	-10.86341357
	SD	1.474734676
L-MOR3	1	-11.74179
L-MOR3	2	-11.294454
L-MOR3	3	-11.176023
L-MOR3	4	-11.118619
L-MOR3	5	-11.048621
L-MOR3	6	-11.030716
L-MOR3	7	-11.030202
L-MOR3	8	-10.884291
L-MOR3	9	-10.862567

L-MOR3	10	-10.776647
L-MOR3	11	-10.560395
L-MOR3	12	-10.232785
L-MOR3	13	-10.225716
L-MOR3	14	-10.135461
L-MOR3	15	-10.0684
	Average $\Delta G_{\text{binding}}$	-10.8124458
	SD	0.480879954
L-MOR4	1	-13.363445
L-MOR4	2	-12.465529
L-MOR4	3	-12.037615
L-MOR4	4	-11.896293
L-MOR4	5	-10.710623
L-MOR4	6	-10.703691
L-MOR4	7	-10.6802
L-MOR4	8	-10.296678
L-MOR4	9	-10.266088
L-MOR4	10	-10.218131
L-MOR4	11	-9.6141415
L-MOR4	12	-9.4630146
L-MOR4	13	-9.225668
L-MOR4	14	-8.5759916
L-MOR4	15	-8.4553423
	Average $\Delta G_{\text{binding}}$	-10.53149673
	SD	1.414766595
L-MOR5	1	-11.913193
L-MOR5	2	-11.848376
L-MOR5	3	-11.741557
L-MOR5	4	-11.300964
L-MOR5	5	-10.915608
L-MOR5	6	-10.536916
L-MOR5	7	-10.034949
L-MOR5	8	-9.9911861
L-MOR5	9	-9.9004164
L-MOR5	10	-9.7956543
L-MOR5	11	-9.7304535
L-MOR5	12	-9.6745749
L-MOR5	13	-9.6357565
L-MOR5	14	-9.545661
L-MOR5	15	-9.3954248
	Average $\Delta G_{\text{binding}}$	-10.39737937
	SD	0.906186247
L-MOR6	1	-13.115589
L-MOR6	2	-12.180578

L-MOR6	3	-11.388666
L-MOR6	4	-10.878213
L-MOR6	5	-10.864018
L-MOR6	6	-10.786431
L-MOR6	7	-10.221839
L-MOR6	8	-9.7577333
L-MOR6	9	-9.6675158
L-MOR6	10	-9.341239
L-MOR6	11	-9.1427498
L-MOR6	12	-9.1256895
L-MOR6	13	-8.9800215
L-MOR6	14	-8.9485884
L-MOR6	15	-8.9439459
	Average $\Delta G_{\text{binding}}$	-10.22285448
	SD	1.287142255
L-MOR7	1	-12.41503
L-MOR7	2	-11.246712
L-MOR7	3	-11.120336
L-MOR7	4	-11.08731
L-MOR7	5	-10.98572
L-MOR7	6	-10.932474
L-MOR7	7	-10.773968
L-MOR7	8	-10.228906
L-MOR7	9	-10.211429
L-MOR7	10	-9.5636082
L-MOR7	11	-9.2517929
L-MOR7	12	-8.9718866
L-MOR7	13	-8.8822317
L-MOR7	14	-8.815196
L-MOR7	15	-8.6470251
	Average $\Delta G_{\text{binding}}$	-10.20890837
	SD	1.133820049
L-MOR8	1	-12.721801
L-MOR8	2	-11.447378
L-MOR8	3	-11.333591
L-MOR8	4	-11.32437
L-MOR8	5	-10.9265
L-MOR8	6	-10.698387
L-MOR8	7	-10.378998
L-MOR8	8	-10.088764
L-MOR8	9	-9.7034988
L-MOR8	10	-9.320756
L-MOR8	11	-9.2210169
L-MOR8	12	-9.1229897
L-MOR8	13	-9.0361013

L-MOR8	14	-8.8090677
L-MOR8	15	-8.8007431
	Average $\Delta G_{\text{binding}}$	-10.1955975
	SD	1.185332947
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L-MOR9	1	-11.724644
L-MOR9	2	-10.949849
L-MOR9	3	-10.647851
L-MOR9	4	-10.520026
L-MOR9	5	-10.491909
L-MOR9	6	-10.391362
L-MOR9	7	-10.058987
L-MOR9	8	-10.041899
L-MOR9	9	-9.9990129
L-MOR9	10	-9.9604549
L-MOR9	11	-9.8482208
L-MOR9	12	-9.8302717
L-MOR9	13	-9.7299156
L-MOR9	14	-9.4649973
L-MOR9	15	-9.2540112
	Average $\Delta G_{\text{binding}}$	-10.19422743
	SD	0.619351011
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L-MOR10	1	-11.055427
L-MOR10	2	-10.761396
L-MOR10	3	-10.754389
L-MOR10	4	-10.702752
L-MOR10	5	-10.517179
L-MOR10	6	-10.309683
L-MOR10	7	-10.114244
L-MOR10	8	-9.8014908
L-MOR10	9	-9.6838655
L-MOR10	10	-9.5668612
L-MOR10	11	-9.522274
L-MOR10	12	-9.5079107
L-MOR10	13	-9.4540281
L-MOR10	14	-9.3792582
L-MOR10	15	-9.3420401
	Average $\Delta G_{\text{binding}}$	-10.03151991
	SD	0.599510934
<hr/>		
Fentanyl	1	-7.3065267
Fentanyl	2	-7.2126346
Fentanyl	3	-6.8692665
Fentanyl	4	-6.6636348

Fentanyl	5	-6.6312523
Fentanyl	6	-6.6293144
Fentanyl	7	-6.598177
Fentanyl	8	-6.5828199
Fentanyl	9	-6.5123854
Fentanyl	10	-6.4442387
	Average $\Delta G_{\text{binding}}$	-6.74502503
	SD	0.293409989
Naloxone	1	-6.3772607
Naloxone	2	-6.2988982
Naloxone	3	-6.1914015
Naloxone	4	-6.174098
Naloxone	5	-6.061646
Naloxone	6	-5.9286389
Naloxone	7	-5.9067736
Naloxone	8	-5.8789387
Naloxone	9	-5.7344995
Naloxone	10	-5.7083893
	Average $\Delta G_{\text{binding}}$	-6.02605444
	SD	0.230841223

Table S2. Interaction report of each conformer of L-MOR1. Number of conformer, Atom of compound, Amino acid in MOR, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in MOR		Interaction	Distance
1	C	ASP	218	H-donor	3.24
	O	THR	220	H-donor	2.98
	C	ASP	218	H-donor	3.34
	C	ASP	218	H-donor	2.98
	N	ASP	218	H-donor	2.89
	N	GLU	312	H-donor	2.8
	O	GLU	312	H-donor	2.75
	O	LYS	305	H-donor	3.08
	O	LYS	305	H-acceptor	3.18
	N	ASP	218	Ionic	3.7
	N	ASP	218	Ionic	3.94
	N	ASP	218	Ionic	2.89
	N	GLU	312	Ionic	3.36
	N	GLU	312	Ionic	2.8
2	C	ASP	218	H-donor	2.88
	N	ASP	218	H-donor	3.01
	O	GLU	312	H-donor	3.21
	O	GLU	312	H-donor	2.95
	O	GLU	312	H-donor	2.77

	O	LYS	305	H-donor	2.83
	O	LYS	305	H-acceptor	3.26
	N	ASP	218	Ionic	3.01
	N	ASP	218	Ionic	3.4
	N	ASP	218	Ionic	3.27
	N	GLU	312	Ionic	3.18
3	C	ASP	218	H-donor	3.46
	N	GLU	312	H-donor	2.94
	O	GLU	312	H-donor	2.78
	O	LYS	305	H-donor	2.89
	O	LYS	305	H-acceptor	3.25
	N	ASP	218	Ionic	3.8
	N	ASP	218	Ionic	3.33
	N	GLU	312	Ionic	2.94
4	C	ASP	218	H-donor	3.09
	N	ASP	218	H-donor	2.92
	N	ASP	218	H-donor	2.87
	O	LYS	305	H-donor	2.86
	O	LYS	305	H-acceptor	3.33
	N	ASP	218	Ionic	3.68
	N	ASP	218	Ionic	2.92
	N	ASP	218	Ionic	2.87
	N	GLU	312	Ionic	3.34
5	C	GLU	231	H-donor	3.36
	C	ASP	218	H-donor	3.02
	O	ASP	218	H-donor	2.96
	N	ASP	218	H-donor	2.8
	O	GLU	312	H-donor	3.13
	O	GLU	312	H-donor	3.16
	O	GLU	312	H-donor	2.79
	O	LYS	305	H-donor	2.85
	O	LYS	305	H-acceptor	3.26
	O	ARG	213	H-acceptor	3.07
	O	ASN	129	H-acceptor	3.22
	N	ASP	218	Ionic	3.49
	N	ASP	218	Ionic	2.8
	N	GLU	312	Ionic	3.07
6	O	CYS	219	H-donor	2.86
	N	ASP	218	H-donor	2.67
	N	SER	216	H-donor	3
	N	ASP	218	H-donor	2.96
	O	GLU	312	H-donor	2.86
	O	GLU	312	H-donor	2.93
	O	GLU	312	H-donor	2.83
	O	LYS	305	H-donor	2.79
	O	LYS	305	H-acceptor	3.28
	O	ARG	213	H-acceptor	3.02

	N	ASP	218	Ionic	2.67
	N	ASP	218	Ionic	3.43
	N	ASP	218	Ionic	2.96
	N	GLU	312	Ionic	2.95
7	N	CYS	219	H-donor	2.71
	N	ASP	218	H-donor	2.81
	N	GLU	312	H-donor	3.12
	O	GLU	231	H-donor	3.25
	O	LEU	221	H-acceptor	3.15
	O	TRP	320	H-acceptor	2.77
	N	ASP	218	Ionic	2.81
	N	GLU	312	Ionic	3.12
8	C	ASP	218	H-donor	3.33
	C	ASP	218	H-donor	3.06
	N	ASP	218	H-donor	2.79
	N	GLU	312	H-donor	2.91
	N	GLU	312	H-donor	2.97
	O	LYS	305	H-donor	2.82
	O	LYS	305	H-acceptor	3.2
	O	LYS	305	H-acceptor	3.24
	N	ASP	218	Ionic	3.31
	N	ASP	218	Ionic	3.94
	N	ASP	218	Ionic	3.92
	N	ASP	218	Ionic	2.79
	N	GLU	312	Ionic	2.91
	N	GLU	312	Ionic	2.97
9	O	THR	220	H-donor	3.03
	N	ASP	218	H-donor	2.95
	O	GLU	231	H-donor	3.12
	O	LEU	221	H-acceptor	3.19
	N	ASP	218	Ionic	2.95
	N	ASP	218	Ionic	3.61
	N	ASP	218	Ionic	3.18
	N	GLU	312	Ionic	2.88
	C	TRP	320	H-pi	4.63
10	C	ASN	129	H-donor	3.37
	N	ASP	218	H-donor	2.87
	N	ILE	217	H-donor	3.34
	N	GLU	312	H-donor	2.92
	O	GLU	231	H-donor	2.96
	O	LYS	235	H-acceptor	3.18
	O	LEU	221	H-acceptor	3.1
	O	TYR	150	H-acceptor	3.3
	N	ASP	218	Ionic	2.87
	N	ASP	218	Ionic	4
	N	GLU	312	Ionic	2.92
	N	GLU	312	Ionic	3.93

Table S3. Interaction report of each conformer of L-MOR2. Number of conformer, Atom of compound, Amino acid in MOR, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in MOR		Interaction	Distance
1	O	ASP	218	H-donor	2.84
	O	ASN	129	H-donor	3.18
	C	ASP	149	H-donor	3.23
	C	MET	153	H-donor	3.78
	N	MET	153	H-donor	3.63
	O	ASN	129	H-acceptor	3.04
	O	GLN	126	H-acceptor	3.28
	C	ASP	149	Ionic	3.64
2	O	GLU	231	H-donor	2.9
	S	THR	220	H-donor	3.01
	S	LEU	221	H-donor	3.84
	C	MET	153	H-donor	3.65
	N	TYR	130	H-donor	3.13
	N	GLU	312	H-donor	3.69
	N	GLU	312	H-donor	3.64
	O	LYS	305	H-acceptor	2.84
	O	TYR	150	H-acceptor	2.89
	S	ASP	149	Ionic	3.01
	5-ring	THR	220	pi-H	4.17
3	S	GLN	126	H-donor	3.46
	N	MET	153	H-donor	3.25
	C	GLU	231	H-donor	3.2
	N	GLU	312	H-donor	3.02
	O	TRP	320	H-acceptor	2.96
	C	GLU	312	Ionic	3.85
	C	GLU	312	Ionic	3.29
	4	S	ASP	218	H-donor
O		GLU	312	H-donor	3.15
N		TYR	130	H-donor	3.22
N		ILE	310	H-donor	3.56
O		LYS	305	H-acceptor	3.3
S		ASP	149	Ionic	3.04
C		GLU	312	Ionic	3.48
C		GLU	312	Ionic	3.64
5-ring		THR	220	pi-H	3.91
5		N	GLU	312	H-donor
	N	GLU	312	H-donor	3.05
	O	ASP	218	H-donor	3.47
	N	THR	220	H-donor	2.78
	C	GLN	214	H-donor	3.53
	N	LYS	235	H-donor	3.56
	O	TRP	320	H-acceptor	3.24
	C	TRP	320	H-pi	4.36
	6	O	ASP	218	H-donor

	N	ILE	310	H-donor	2.95
	O	LYS	305	H-acceptor	3.04
	S	ASP	149	Ionic	3.04
	C	GLU	312	Ionic	3.81
	C	GLU	312	Ionic	3.52
	5-ring	LYS	305	pi-cation	3.46
	6-ring	GLU	312	pi-H	4.17
	5-ring	TRP	320	pi-pi	4
7	N	GLU	312	H-donor	3.35
	C	GLU	231	H-donor	3.19
	C	GLU	312	H-donor	3.34
	S	GLN	316	H-donor	4.3
	O	ASP	218	H-donor	3.38
	O	CYS	219	H-donor	2.62
	N	LYS	305	H-acceptor	3.08
	O	ARG	213	H-acceptor	2.82
	O	ASN	129	H-acceptor	2.95
8	S	SER	216	H-donor	3.71
	N	ILE	310	H-donor	3.1
	O	LYS	305	H-acceptor	3.1
	N	LYS	235	H-acceptor	3.39
	O	LEU	221	H-acceptor	3.19
	5-ring	ASN	129	pi-H	3.53
	5-ring	GLY	133	pi-H	3.58
9	O	LYS	305	H-acceptor	3.42
	O	LYS	305	H-acceptor	3.35
	O	ARG	213	H-acceptor	3.08
	S	ASP	149	Ionic	3.08
	5-ring	ASN	129	pi-H	4.67
10	C	CYS	219	H-donor	3.53
	C	CYS	219	H-donor	3.37
	O	GLU	312	H-donor	3.24
	O	LYS	305	H-acceptor	3.28
	O	ARG	213	H-acceptor	3.15
	O	HIS	321	H-acceptor	3.33
	C	GLU	312	Ionic	3.37

Table S4. Interaction report of each conformer of L-MOR3. Number of conformer, Atom of compound, Amino acid in MOR, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in MOR		Interaction	Distance
1	N	ASP	149	H-donor	2.86
	N	ASP	149	H-donor	3.11
	N	ALA	306	H-donor	3.23
	N	GLU	231	H-donor	2.99
	N	ASN	232	H-donor	3.46
	O	TYR	150	H-acceptor	2.89
	O	LYS	305	H-acceptor	3

	N	ASP	149	Ionic	2.86
	N	ASP	149	Ionic	3.11
	N	GLU	231	Ionic	3.44
	N	GLU	231	Ionic	2.99
2	N	GLN	126	H-donor	2.99
	N	GLU	231	H-donor	3.15
	N	MET	153	H-donor	3.37
	N	ASP	218	H-donor	3.06
	N	ASP	218	H-donor	2.96
	N	ASP	149	Ionic	3.85
	N	ASP	218	Ionic	3.99
	N	ASP	218	Ionic	3.06
	N	ASP	218	Ionic	3.41
	N	ASP	218	Ionic	2.96
	6-ring	THR	317	pi-H	4.46
3	N	SER	216	H-donor	2.95
	N	ASP	218	H-donor	2.98
	N	SER	216	H-donor	3.19
	N	LEU	221	H-donor	3.5
	N	GLU	312	Ionic	3.25
	N	ASP	218	Ionic	2.98
	N	GLU	231	Ionic	3.22
4	N	ASP	149	H-donor	2.86
	N	MET	153	H-donor	3.28
	N	MET	153	H-donor	3.32
	N	GLU	231	H-donor	2.98
	N	ASN	232	H-donor	2.96
	O	LYS	305	H-acceptor	3.4
	O	ARG	213	H-acceptor	3.13
	N	ASP	149	Ionic	2.86
	N	ASP	149	Ionic	3.68
	N	GLU	231	Ionic	3.91
	N	GLU	231	Ionic	2.98
	N	GLU	231	Ionic	3.78
5	O	TRP	320	H-acceptor	2.95
	O	LYS	305	H-acceptor	2.93
	O	LYS	235	H-acceptor	3.54
	O	LYS	235	Ionic	3.54
	O	LYS	305	Ionic	3.72
	N	ASP	218	Ionic	2.73
	N	TRP	135	cation-pi	3.62
6	N	MET	153	H-donor	3.25
	N	GLU	231	H-donor	2.99
	N	GLU	231	H-donor	3.16
	N	GLU	231	H-donor	2.96
	C	ASP	149	H-donor	3.71
	O	LEU	221	H-acceptor	3.45

	O	LYS	305	H-acceptor	3.15
	O	GLN	316	H-acceptor	2.99
	O	ARG	213	H-acceptor	3.24
	O	ARG	213	H-acceptor	3.01
	O	ARG	213	Ionic	3.01
	N	GLU	231	Ionic	2.99
	N	GLU	231	Ionic	3.16
	N	GLU	231	Ionic	2.96
7	N	ASP	149	H-donor	2.84
	N	MET	153	H-donor	4.05
	N	GLU	231	H-donor	2.92
	N	GLU	231	H-donor	3.29
	O	LYS	305	H-acceptor	2.96
	N	ASP	149	Ionic	2.84
	N	ASP	149	Ionic	3.8
	N	GLU	231	Ionic	2.92
	N	GLU	231	Ionic	3.97
	N	GLU	231	Ionic	3.29
8	N	ASP	149	H-donor	2.88
	N	MET	153	H-donor	3.17
	N	ASP	149	H-donor	3.05
	N	GLU	231	H-donor	3.03
	N	GLU	231	H-donor	3.02
	O	TRP	320	H-acceptor	2.85
	O	THR	220	H-acceptor	3.18
	O	LYS	305	H-acceptor	2.79
	O	LYS	305	Ionic	3.89
	O	LYS	305	Ionic	2.79
	N	ASP	149	Ionic	2.88
	N	ASP	149	Ionic	3.05
	N	GLU	231	Ionic	3.03
	N	GLU	231	Ionic	3.02
9	O	ASP	218	H-donor	3.26
	O	ASP	218	H-donor	3.03
	N	GLN	126	H-donor	2.91
	N	ASP	218	H-donor	3.24
	N	GLU	312	H-donor	3.02
	C	ASN	129	H-donor	3.35
	C	ASP	218	H-donor	3.33
	O	LYS	305	H-acceptor	3.07
	O	LYS	235	H-acceptor	2.88
	O	LYS	235	Ionic	2.88
	N	GLU	312	Ionic	3.02
10	N	GLU	312	H-donor	2.81
	O	TRP	320	H-acceptor	3.18
	O	LYS	235	H-acceptor	2.91
	O	LYS	305	H-acceptor	3

	O	LYS	235	Ionic	2.91
	O	LYS	305	Ionic	3
	N	GLU	312	Ionic	3.91
	N	GLU	312	Ionic	2.81

Table S5. Interaction report of each conformer of L-MOR4. Number of conformer, Atom of compound, Amino acid in MOR, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in MOR		Interaction	Distance	
1	S	THR	220	H-donor	3.4	
	O	GLU	231	H-donor	2.91	
	O	GLU	231	H-donor	3.02	
	O	ASP	218	H-donor	2.84	
	S	THR	220	H-acceptor	4	
	S	LEU	221	H-acceptor	4.47	
	O	ARG	213	H-acceptor	3.01	
	O	ASN	129	H-acceptor	3.04	
	O	ARG	213	H-acceptor	3.06	
	O	LYS	235	H-acceptor	2.99	
	O	LYS	235	Ionic	2.99	
	N	GLU	312	Ionic	3.07	
	2	O	ASP	218	H-donor	2.86
		O	ASP	218	H-donor	3.01
N		GLN	214	H-donor	3.34	
N		GLU	231	H-donor	3.42	
N		GLN	214	H-donor	3.54	
N		GLY	215	H-donor	3.29	
N		ASP	218	H-donor	3.26	
C		LEU	131	H-donor	3.48	
O		LYS	305	H-acceptor	3.11	
O		ARG	213	H-acceptor	3.15	
O		ARG	213	H-acceptor	3.13	
O		ASN	129	H-acceptor	3.18	
O		LYS	305	Ionic	3.25	
N		GLU	231	Ionic	3.42	
N		GLU	231	Ionic	3.19	
3		O	ASP	218	H-donor	3.08
	N	GLU	312	H-donor	2.92	
	N	GLU	231	H-donor	3.18	
	N	GLU	312	H-donor	3.16	
	N	GLU	231	H-donor	3.18	
	N	ALA	306	H-donor	3.22	
	S	LYS	235	H-acceptor	3.21	
	S	ALA	306	H-acceptor	3.72	
	O	TRP	320	H-acceptor	3.11	
	O	LYS	305	H-acceptor	3.13	
	O	ASN	129	H-acceptor	2.94	
	O	LYS	235	H-acceptor	3.05	

	O	LYS	305	H-acceptor	3.07
	O	LYS	235	H-acceptor	3.22
	O	LYS	305	Ionic	3.07
	O	LYS	235	Ionic	3.22
	N	GLU	312	Ionic	2.92
	6-ring	GLN	126	pi-H	3.65
	6-ring	TYR	150	pi-H	3.25
4	O	GLU	231	H-donor	2.81
	N	ILE	310	H-donor	2.85
	N	ASP	218	H-donor	3.36
	N	ASP	149	H-donor	2.88
	C	GLU	231	H-donor	3.2
	C	ASP	149	H-donor	3.18
	S	LYS	235	H-acceptor	3.57
	O	LYS	305	H-acceptor	3.3
	O	THR	309	H-acceptor	3.17
	O	LYS	305	H-acceptor	2.79
	O	ARG	213	H-acceptor	2.89
	O	LYS	235	Ionic	2.94
	N	ASP	149	Ionic	2.88
	N	ASP	149	Ionic	3.62
	6-ring	GLU	312	pi-H	4.13
	5-ring	GLU	312	pi-H	4.45
	6-ring	THR	317	pi-H	4.04
5	N	GLU	312	H-donor	3.19
	N	GLU	312	H-donor	3.36
	N	GLU	312	H-donor	3.32
	N	GLN	214	H-donor	3.32
	N	GLY	215	H-donor	3.07
	N	ASP	218	H-donor	3.44
	S	GLN	214	H-acceptor	3.44
6	N	GLU	231	H-donor	2.9
	N	ASP	218	H-donor	2.96
	N	ASP	218	H-donor	2.98
	N	ASP	149	H-donor	3.1
	N	ASP	149	H-donor	2.95
	S	LYS	235	H-acceptor	4.29
	O	ARG	213	H-acceptor	3.32
	O	LYS	305	H-acceptor	3.4
	O	TYR	150	H-acceptor	2.94
	N	GLU	231	Ionic	2.9
	N	GLU	231	Ionic	3.91
	N	ASP	218	Ionic	2.96
	N	ASP	218	Ionic	2.98
	N	ASP	149	Ionic	3.1
	N	ASP	149	Ionic	2.95
	N	TYR	150	cation-pi	4.73

7	N	GLU	312	H-donor	2.84
	N	GLY	133	H-donor	3.11
	N	CYS	219	H-donor	2.95
	O	ARG	213	H-acceptor	2.96
	O	ARG	213	H-acceptor	3.06
	O	LEU	221	H-acceptor	3.32
	N	GLU	312	Ionic	3.31
	N	GLU	312	Ionic	2.84
8	S	GLU	231	H-donor	3.42
	O	GLU	312	H-donor	2.91
	N	LEU	221	H-donor	2.92
	N	PHE	223	H-donor	3.12
	N	ASP	218	H-donor	2.89
	C	GLU	312	H-donor	3.37
	S	ARG	213	H-acceptor	3.47
	O	LYS	305	H-acceptor	3.09
	O	LYS	305	Ionic	3.09
	N	ASP	218	Ionic	2.89
	N	ASP	218	Ionic	3.49
	9	S	THR	220	H-donor
O		LEU	221	H-donor	2.91
N		ILE	310	H-donor	2.95
N		GLU	312	H-donor	2.83
O		PHE	223	H-acceptor	3.43
O		ARG	213	H-acceptor	2.86
O		LYS	305	H-acceptor	2.93
O		ARG	213	Ionic	3.95
O		ARG	213	Ionic	2.86
N		GLU	312	Ionic	3.74
N		GLU	312	Ionic	2.83
		6-ring	LYS	235	pi-cation
10	O	GLU	312	H-donor	3.16
	O	ILE	310	H-donor	2.98
	N	GLU	312	H-donor	3.16
	N	SER	216	H-donor	3.06
	N	ASP	218	H-donor	2.88
	N	TYR	130	H-donor	2.98
	N	ASN	129	H-donor	2.88
	N	CYS	219	H-donor	3.19
	O	ARG	213	H-acceptor	3.14
	O	ARG	213	H-acceptor	2.87
	O	ARG	213	Ionic	3.31
	O	ARG	213	Ionic	2.92
O	ARG	213	Ionic	2.87	
N	ASP	218	Ionic	2.88	

Table S6. Interaction report of each conformer of L-MOR5. Number of conformer, Atom of compound, Amino acid in MOR, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in MOR		Interaction	Distance	
1	N	ASP	218	H-donor	3.01	
	N	GLU	231	H-donor	2.97	
	S	CYS	219	H-donor	3.15	
	S	THR	220	H-acceptor	3.6	
	O	LYS	235	H-acceptor	3.17	
	N	GLU	231	Ionic	2.97	
	N	GLU	231	Ionic	3.74	
	C	HIS	299	H-pi	4.51	
	6-ring	TYR	130	pi-H	3.53	
	2	N	ASP	218	H-donor	3
N		GLU	231	H-donor	3.19	
S		CYS	219	H-donor	3.15	
S		THR	220	H-acceptor	3.6	
O		LYS	235	H-acceptor	3.16	
N		GLU	231	Ionic	3.19	
N		GLU	231	Ionic	3.37	
C		HIS	299	H-pi	4.51	
3		N	SER	216	H-donor	2.94
		N	ASP	218	H-donor	3.11
	N	GLU	231	H-donor	3.03	
	N	TYR	150	H-donor	3.14	
	N	GLU	231	Ionic	3.03	
	N	GLU	231	Ionic	3.93	
	4	N	SER	216	H-donor	2.95
N		ASP	218	H-donor	2.98	
S		CYS	219	H-donor	3.1	
N		GLU	231	H-donor	2.98	
N		GLU	231	Ionic	2.98	
N		GLU	231	Ionic	3.7	
C		HIS	299	H-pi	4.43	
5	N	ASP	218	H-donor	3.21	
	N	GLU	231	H-donor	2.98	
	O	GLU	312	H-donor	2.78	
	S	THR	220	H-acceptor	3.58	
	N	GLU	231	Ionic	2.98	
	N	GLU	231	Ionic	3.55	
	6	N	SER	216	H-donor	2.93
N		ASP	218	H-donor	3.08	
N		GLU	231	H-donor	3.01	
C		ASP	149	H-donor	3.33	
N		ASP	149	H-donor	3.47	
S		TYR	150	H-acceptor	4.41	
S		THR	220	H-acceptor	4.27	
S		LEU	221	H-acceptor	4.2	

	O	LYS	235	H-acceptor	3.43
	O	LYS	305	H-acceptor	3.37
	N	GLU	231	Ionic	3.01
	N	GLU	231	Ionic	3.45
	N	ASP	149	Ionic	3.47
	6-ring	VAL	302	pi-H	4.09
7	N	GLN	126	H-donor	3.36
	S	THR	220	H-donor	3.68
	N	SER	216	H-donor	2.85
	N	ILE	217	H-donor	3.13
	O	ASP	149	H-donor	3.28
	S	ASP	218	H-donor	4.23
	N	GLU	231	H-donor	2.87
	N	GLU	312	H-donor	3.24
	O	TRP	320	H-acceptor	3.28
	O	GLN	316	H-acceptor	2.87
	N	GLU	231	Ionic	2.87
	C	TRP	320	H-pi	4.49
8	O	LYS	305	H-donor	2.91
	N	GLU	312	H-donor	2.93
	O	LYS	305	H-acceptor	2.89
	N	GLU	312	Ionic	3.7
	N	GLU	312	Ionic	2.93
9	N	THR	220	H-donor	3.06
	N	GLN	316	H-donor	3.42
	N	CYS	219	H-donor	2.86
	O	ARG	213	H-acceptor	3.14
	O	LEU	221	H-acceptor	3.03
	S	LYS	235	H-acceptor	3.24
	O	LYS	305	H-acceptor	2.72
	N	GLU	312	Ionic	3.79
10	N	THR	220	H-donor	3.17
	N	GLU	231	H-donor	3.25
	N	TYR	150	H-donor	2.94
	S	LYS	235	H-acceptor	3.98
	S	LYS	305	H-acceptor	4.06
	O	LYS	305	H-acceptor	3.11
	O	ARG	213	H-acceptor	3.08
	O	ARG	213	H-acceptor	2.96
	N	GLU	312	Ionic	3.16

Table S7. Interaction report of each conformer of L-MOR6. Number of conformer, Atom of compound, Amino acid in MOR, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in MOR		Interaction	Distance
1	N	GLN	126	H-donor	3.2
	N	ASP	149	H-donor	2.93
	N	ASP	149	H-donor	3.3

	N	ASP	218	H-donor	2.92
	N	ASP	218	H-donor	3.27
	N	ASP	149	H-donor	2.9
	N	GLU	231	H-donor	3.06
	S	LYS	235	H-acceptor	3.84
	O	LYS	235	H-acceptor	2.87
	O	PHE	223	H-acceptor	3.4
	N	ASP	149	Ionic	2.93
	N	ASP	149	Ionic	3.3
	N	ASP	149	Ionic	2.9
2	N	MET	153	H-donor	3.78
	N	LYS	235	H-donor	3.01
	N	HIS	299	H-donor	3.21
	N	ASN	129	H-donor	3.33
	O	GLU	312	H-donor	2.91
	O	TYR	150	H-acceptor	2.83
3	N	ASP	149	H-donor	3.14
	C	GLU	231	H-donor	3.32
	N	GLU	231	H-donor	3.07
	S	LYS	235	H-acceptor	3.72
	N	TYR	328	H-pi	3.78
4	N	GLN	126	H-donor	3.11
	N	ASP	149	H-donor	3.02
	O	ILE	310	H-donor	3.03
	O	LYS	305	H-acceptor	2.76
	N	ASP	149	Ionic	3.02
5	S	GLU	231	H-donor	3.39
	N	ASP	149	H-donor	3.09
	N	ILE	324	H-donor	3.01
	N	ASP	218	H-donor	3.32
	S	LYS	235	H-acceptor	3.5
	O	ARG	213	H-acceptor	3.14
6	N	GLU	312	H-donor	2.92
	N	LEU	131	H-donor	3.33
	S	ASN	129	H-acceptor	3.11
	6-ring	LEU	221	pi-H	3.83
7	N	GLU	312	H-donor	3.15
	C	GLU	312	H-donor	3.46
	N	GLN	214	H-donor	2.98
	N	LEU	131	H-donor	3
	N	GLY	133	H-donor	2.98
	N	ILE	310	H-donor	3.02
	O	LYS	305	H-acceptor	3
	O	THR	317	H-acceptor	3.46
	6-ring	LYS	235	pi-cation	3.43
	6-ring	LYS	305	pi-H	3.93
8	S	GLU	312	H-donor	3.88

	N	ASP	218	H-donor	3.06
	N	ASP	218	H-donor	3.55
	N	GLY	133	H-donor	2.99
	N	SER	216	H-donor	3.09
	N	ASP	218	H-donor	3.1
	N	ASN	129	H-donor	3.18
	S	HIS	321	H-acceptor	3.95
	O	LYS	305	H-acceptor	2.9
9	S	GLU	312	H-donor	3.43
	S	GLU	312	H-donor	3.37
	N	GLN	214	H-donor	3.25
	N	GLU	312	H-donor	2.96
	O	ASN	129	H-acceptor	2.98
	S	LYS	305	H-acceptor	3.71
	S	LYS	305	H-acceptor	3.94
	O	LYS	305	H-acceptor	3.17
	O	LYS	235	H-acceptor	3.22
	N	GLU	312	Ionic	3.99
	N	GLU	312	Ionic	2.96
10	N	GLU	312	H-donor	2.97
	N	GLU	312	H-donor	3.14
	N	GLU	312	H-donor	3.11
	N	GLU	231	H-donor	2.95
	O	LYS	305	H-acceptor	2.88
	N	GLU	231	Ionic	3.8
	N	GLU	231	Ionic	2.95

Table S8. Interaction report of each conformer of L-MOR7. Number of conformer, Atom of compound, Amino acid in MOR, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in MOR		Interaction	Distance
1	C	MET	153	H-donor	3.6
	N	GLU	231	H-donor	3.06
	N	ASP	149	H-donor	2.81
	N	ASP	149	H-donor	3.36
	O	TYR	150	H-acceptor	2.79
	N	ASP	149	Ionic	2.81
	N	ASP	149	Ionic	3.36
	C	TYR	150	H-pi	3.4
2	N	GLU	231	H-donor	2.96
	N	GLU	231	H-donor	2.95
	S	LYS	305	H-acceptor	3.3
	O	TRP	320	H-acceptor	3.14
	O	HIS	321	H-acceptor	3.45
	N	GLU	231	Ionic	2.96
	N	GLU	231	Ionic	2.95
3	C	LYS	305	H-donor	3.29
	N	GLU	312	H-donor	2.98

	N	GLU	231	H-donor	2.94
	N	GLU	231	H-donor	3.01
	N	SER	216	H-donor	2.95
	O	LYS	305	H-acceptor	3.29
	S	ARG	213	H-acceptor	4.49
	O	LEU	221	H-acceptor	3.08
	O	ASN	129	H-acceptor	3.27
	N	GLU	231	Ionic	2.94
	N	GLU	231	Ionic	3.01
	N	ASP	218	Ionic	2.85
4	N	GLU	231	H-donor	2.93
	N	GLN	126	H-donor	3.09
	S	LYS	305	H-acceptor	3.63
	S	LYS	305	H-acceptor	3.15
	O	LYS	305	H-acceptor	3.1
	N	GLU	231	Ionic	2.93
5	S	THR	220	H-donor	3.63
	N	GLU	312	H-donor	2.89
	N	MET	153	H-donor	4.33
	N	CYS	219	H-donor	3.14
	O	ASP	149	H-donor	2.83
	N	ASP	218	H-donor	3.07
	N	CYS	219	H-donor	3.17
	O	LYS	305	H-acceptor	2.9
	O	LYS	235	H-acceptor	3.11
	O	LYS	305	H-acceptor	3.19
	O	THR	220	H-acceptor	3.56
	O	ASN	129	H-acceptor	3.37
	O	GLN	126	H-acceptor	3.15
	N	GLU	231	Ionic	3.52
	N	ASP	218	Ionic	3.07
6	N	LYS	305	H-donor	3.08
	N	GLU	231	H-donor	2.97
	N	GLU	231	H-donor	3.08
	N	CYS	219	H-donor	2.95
	C	CYS	219	H-donor	3.22
	S	ARG	213	H-acceptor	4.02
	S	ARG	213	H-acceptor	3.37
	O	ASN	129	H-acceptor	3.3
	N	GLU	231	Ionic	2.97
	N	GLU	231	Ionic	3.08
	N	ASP	218	Ionic	2.92
7	N	GLU	312	H-donor	3.21
	S	ASP	218	H-donor	3.48
	S	ASP	218	H-donor	3.31
	N	LYS	305	H-donor	3.04
	N	GLU	231	H-donor	2.82

	N	GLU	231	H-donor	2.92
	N	GLU	231	H-donor	3.24
	N	ASN	232	H-donor	3.11
	S	ARG	213	H-acceptor	3.33
	O	TRP	320	H-acceptor	3.02
	N	GLU	231	Ionic	3.24
	N	GLU	231	Ionic	3.41
8	S	THR	220	H-donor	2.97
	N	GLU	312	H-donor	3.04
	N	GLU	312	H-donor	2.9
	N	ASP	149	H-donor	2.99
	N	SER	216	H-donor	3.12
	N	ASN	129	H-donor	2.86
	N	ASN	129	H-donor	3.19
	N	ASP	218	H-donor	3.15
	N	CYS	219	H-donor	2.9
	O	LYS	305	H-acceptor	3.44
	O	TYR	150	H-acceptor	2.9
	O	LEU	221	H-acceptor	3.29
	N	GLU	231	Ionic	3.68
	N	ASP	218	Ionic	3.15
9	S	ASP	218	H-donor	3.42
	S	ASP	218	H-donor	3.05
	C	ASP	218	H-donor	3.34
	N	GLN	126	H-donor	3.02
	N	CYS	219	H-donor	2.91
	N	LEU	221	H-donor	3.01
	N	THR	220	H-donor	2.92
	O	LYS	305	H-acceptor	3.16
	O	TRP	320	H-acceptor	2.95
	O	ARG	213	H-acceptor	3.12
10	N	GLU	312	H-donor	2.9
	C	CYS	219	H-donor	3.4
	O	LYS	305	H-acceptor	3.2
	S	LYS	305	H-acceptor	3.81
	O	ARG	213	H-acceptor	3.53
	O	TRP	320	H-acceptor	2.82
	N	GLU	312	Ionic	2.9

Table S9. Interaction report of each conformer of L-MOR8. Number of conformer, Atom of compound, Amino acid in MOR, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in MOR		Interaction	Distance
1	N	ASP	149	H-donor	2.91
	N	ASP	218	H-donor	2.98
	N	ASP	218	H-donor	3.08
	N	ASP	218	H-donor	2.91
	N	GLN	126	H-donor	3.25

	C	MET	153	H-donor	3.58
	S	THR	220	H-acceptor	3.84
	S	LEU	221	H-acceptor	4
	O	TYR	150	H-acceptor	2.92
	O	ASN	129	H-acceptor	2.94
	O	TYR	130	H-acceptor	3.34
	N	ASP	149	Ionic	2.91
	N	ASP	149	Ionic	3.76
	N	ASP	218	Ionic	2.91
2	S	GLN	126	H-donor	3.62
	N	GLU	312	H-donor	2.98
	N	ASN	129	H-donor	3.15
	N	ASP	218	H-donor	2.94
	N	THR	317	H-donor	3.03
	N	GLU	312	Ionic	2.98
3	S	THR	220	H-donor	3.98
	N	ASP	149	H-donor	2.79
	N	MET	153	H-donor	4.27
	N	THR	220	H-donor	3.01
	N	LYS	235	H-donor	2.98
	S	LYS	235	H-acceptor	3.51
	N	ASP	149	Ionic	2.79
4	C	HIS	299	H-pi	4.28
	N	ASP	218	H-donor	3.49
5	O	ASN	129	H-acceptor	3.23
	S	ASP	218	H-donor	4.22
	N	ASN	232	H-donor	3.03
	N	ASP	218	H-donor	2.84
	N	CYS	219	H-donor	3.11
	N	GLU	312	H-donor	3.07
	O	TYR	150	H-acceptor	2.93
	O	LYS	235	H-acceptor	3.14
	N	ASP	218	Ionic	2.84
6	N	ILE	310	H-donor	2.91
	N	ASP	149	H-donor	2.93
	N	ASP	218	H-donor	2.78
	N	GLU	312	H-donor	3.1
	O	LYS	305	H-acceptor	2.88
	O	HIS	321	H-acceptor	2.92
	6-ring	TYR	328	pi-pi	3.92
7	N	ASP	218	H-donor	2.83
	N	CYS	219	H-donor	3.26
	C	MET	153	H-donor	3.43
	S	ASN	129	H-acceptor	3.09
	S	ASP	218	H-acceptor	3.84
	S	CYS	219	H-acceptor	3.64
	O	LEU	221	H-acceptor	2.99

	O	LYS	305	H-acceptor	3.16
	N	ASP	218	Ionic	2.83
8	N	ILE	310	H-donor	2.97
	N	ASP	218	H-donor	2.94
	N	ASP	218	H-donor	3.38
	N	GLU	312	H-donor	2.99
	C	GLU	312	H-donor	3.11
	C	ASP	149	H-donor	3.23
	O	LYS	305	H-acceptor	2.89
	O	TYR	150	H-acceptor	2.71
	O	HIS	321	H-acceptor	2.89
	O	LYS	235	H-acceptor	3.2
9	S	GLU	312	H-donor	3.55
	N	ASP	218	H-donor	2.99
	N	ASP	218	H-donor	3.09
	N	GLU	312	H-donor	3.03
	N	GLY	133	H-donor	3.07
	N	SER	216	H-donor	3.28
	O	ARG	213	H-acceptor	3.09
	6-ring	GLN	126	pi-H	3.63
10	N	GLU	312	H-donor	3.01
	N	SER	66	H-donor	2.99
	N	GLU	312	H-donor	3.07
	C	GLU	312	H-donor	3.54
	S	GLY	133	H-acceptor	3.88
	O	THR	314	H-acceptor	3.27
	6-ring	LYS	235	pi-cation	3.47

Table S10. Interaction report of each conformer of L-MOR9. Number of conformer, Atom of compound, Amino acid in MOR, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in MOR		Interaction	Distance
1	O	CYS	219	H-donor	3.27
	O	ASP	149	H-donor	3.15
	O	CYS	219	H-donor	3.46
	O	GLU	312	H-donor	3.04
	O	ASN	129	H-acceptor	3.28
	O	GLN	126	H-acceptor	2.92
	O	ARG	213	H-acceptor	3.16
2	O	ASP	218	H-donor	2.85
	O	GLU	312	H-donor	3.05
	O	ASP	149	H-donor	2.95
	O	ASP	149	H-donor	2.71
	O	GLN	316	H-acceptor	3.36
	O	TYR	150	H-acceptor	3.1
3	O	ASP	218	H-donor	2.87
	O	GLU	231	H-donor	2.75
	O	GLU	312	H-donor	2.87

	O	GLN	214	H-donor	3.36
	O	GLN	126	H-acceptor	3.03
	O	ARG	213	H-acceptor	3.05
4	C	ASP	218	H-donor	3.31
	O	CYS	219	H-donor	2.97
	O	GLU	312	H-donor	2.97
	O	LYS	235	H-acceptor	3.03
	O	LYS	305	H-acceptor	3.42
	O	ARG	213	H-acceptor	3.12
5	O	ASP	218	H-donor	2.97
	O	CYS	219	H-donor	3
	O	CYS	219	H-donor	2.92
	O	GLU	312	H-donor	3.18
	C	GLU	312	H-donor	3.24
	O	ASN	129	H-acceptor	2.96
	O	ARG	213	H-acceptor	3.1
	O	LYS	235	H-acceptor	3.18
6	O	GLU	231	H-donor	3.25
	C	GLU	231	H-donor	3.28
	O	GLU	231	H-donor	3.03
	O	ALA	306	H-donor	3
	O	GLU	312	H-donor	2.77
	O	PHE	223	H-acceptor	3.25
	O	THR	309	H-acceptor	3.11
	O	LYS	211	H-acceptor	3.43
	O	TRP	320	H-acceptor	3.15
7	O	ASP	218	H-donor	2.74
	O	CYS	219	H-donor	2.88
	C	GLU	312	H-donor	3.31
	O	GLU	312	H-donor	2.99
	O	ARG	213	H-acceptor	3.15
8	C	ASP	218	H-donor	3.35
	O	ASP	218	H-donor	2.67
	C	GLU	312	H-donor	3.18
	C	GLU	312	H-donor	3.48
	O	GLU	312	H-donor	2.88
	O	GLU	312	H-donor	3.38
	O	LEU	221	H-acceptor	3.12
	O	HIS	321	H-acceptor	3.12
	O	LYS	305	H-acceptor	3.26
	O	ARG	213	H-acceptor	2.99
9	O	CYS	219	H-donor	3.11
	O	GLU	312	H-donor	2.83
	O	GLU	312	H-donor	3.03
	O	LYS	235	H-acceptor	3.08
	O	ARG	213	H-acceptor	3.06
10	O	ASP	218	H-donor	2.76

	O	CYS	219	H-donor	2.92
	O	GLU	231	H-donor	3.1
	O	GLU	231	H-donor	2.94
	O	GLU	312	H-donor	2.9
	O	GLU	312	H-donor	2.78
	O	ASN	129	H-acceptor	2.94
	O	LEU	221	H-acceptor	3.25
	O	ARG	213	H-acceptor	3.12

Table S11. Interaction report of each conformer of L-MOR10 . Number of conformer, Atom of compound, Amino acid in MOR, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in MOR		Interaction	Distance
1	O	GLU	231	H-donor	2.97
	O	MET	153	H-donor	3.02
	O	LYS	235	H-acceptor	3.26
	O	ARG	213	H-acceptor	2.95
2	O	GLU	231	H-donor	2.92
	O	TYR	150	H-acceptor	2.83
	O	ARG	213	H-acceptor	3.39
	O	ARG	213	H-acceptor	3.52
3	O	GLU	231	H-donor	2.82
	O	ASP	149	H-donor	3.03
	O	GLY	133	H-acceptor	3.36
	O	ARG	213	H-acceptor	3.17
4	O	GLU	231	H-donor	2.93
	O	TRP	320	H-acceptor	3.13
	O	ARG	213	H-acceptor	2.98
	O	ARG	213	H-acceptor	2.96
5	O	LEU	221	H-acceptor	3.2
6	O	LYS	305	H-acceptor	3.14
7	O	TRP	320	H-acceptor	2.85
8	O	GLU	231	H-donor	2.67
	O	MET	153	H-donor	3.89
	O	ASN	129	H-acceptor	2.88
	O	GLY	133	H-acceptor	3.34
	O	ARG	213	H-acceptor	3.35
9	O	THR	220	H-acceptor	3.55
10	O	ARG	213	H-acceptor	3.29
	O	ARG	213	H-acceptor	3.29

Table S12. Interaction report of each conformer of Fentanyl. Number of conformer, Atom of compound, Amino acid in MOR, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in MOR		Interaction	Distance
1	N	ASP	149	Ionic	3.84
	6-ring	GLN	126	pi-H	3.69
	6-ring	VAL	302	pi-H	4.43
	6-ring	VAL	302	pi-H	3.94
2	C	ASP	149	H-donor	3.39

	C	ASP	149	H-donor	3.33
	N	ASP	149	Ionic	3.81
	6-ring	VAL	302	pi-H	3.62
3	C	ASP	149	H-donor	3.37
	N	ASP	149	H-donor	2.95
	N	ASP	149	Ionic	2.95
	6-ring	VAL	302	pi-H	3.86
4	N	ASP	149	H-donor	2.79
	O	TYR	150	H-acceptor	3.13
	N	ASP	149	Ionic	2.79
	6-ring	GLN	126	pi-H	3.78
5	C	ASP	149	H-donor	3.25
	C	TYR	328	H-pi	3.78
6	6-ring	GLN	126	pi-H	3.64
	6-ring	ILE	324	pi-H	4.57
7	N	ASP	149	Ionic	3.64
8	C	ASP	149	H-donor	3.56
9	6-ring	GLN	126	pi-H	4.03
	6-ring	VAL	302	pi-H	4.6
	6-ring	ILE	324	pi-H	4.18

Table S13. Interaction report of each conformer of Naloxone. Number of conformer, Atom of compound, Amino acid in MOR, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in MOR		Interaction	Distance
1	N	ASP	149	H-donor	3.6
	N	ASP	149	Ionic	2.83
	N	ASP	149	Ionic	3.6
2	N	ASP	149	H-donor	3.64
	N	ASP	149	Ionic	2.81
	N	ASP	149	Ionic	3.64
	6-ring	VAL	302	pi-H	4.14
3	N	ASP	149	H-donor	3.57
	N	ASP	149	Ionic	2.81
	N	ASP	149	Ionic	3.57
4	N	ASP	149	H-donor	2.84
	O	ASP	149	H-donor	2.94
	N	ASP	149	Ionic	2.84
	N	ASP	149	Ionic	3.84
	6-ring	VAL	302	pi-H	4.3
5	N	ASP	149	H-donor	3.6
	N	ASP	149	Ionic	2.77
	N	ASP	149	Ionic	3.6
	C	HIS	299	H-pi	3.45
	6-ring	VAL	302	pi-H	4.35
6	C	ASP	149	H-donor	2.94
	C	ASP	149	H-donor	2.92
	N	ASP	149	Ionic	3.05

	N	ASP	149	Ionic	3.49
7	N	ASP	149	H-donor	2.87
	N	ASP	149	Ionic	2.87
	N	ASP	149	Ionic	3.85
	6-ring	VAL	302	pi-H	4.25
8	C	MET	153	H-donor	3.36
	C	ASP	149	H-donor	2.94
	C	MET	153	H-donor	3.2
	N	ASP	149	Ionic	3.07
9	C	MET	153	H-donor	4.45
10	N	MET	153	H-donor	4.26
	C	MET	153	H-donor	3.74
	C	ASP	149	H-donor	3.03
	O	GLN	126	H-donor	2.99