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Exploring molecular docking and electronic studies of [^{11}C]LY2795050 as a novel antagonist tracer for positron emission tomography (PET) scan of the kappa (κ) and mu (μ) opioid receptors (KOR and MOR)

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ABSTRACT

The main purpose of the present research article is the docking analysis of [^{11}C]LY2795050 radiopharmaceutical with kappa (κ) and mu (μ) opioid receptors (KOR and MOR) and comparison of MOR-ligand and KOR-ligand complexes. In the first step, the title compound was optimized using B3LYP/6-31+G(d,p) basis set of theory at room temperature by Gaussian 03 software. Its reactivity and stability was done by frontier molecular orbitals (FMOs) theory. The molecular orbitals calculations indicate that this molecule prefers to react only with powerful nucleophile agents. The second step of this study is related to the docking analysis of the Ligand [^{11}C]LY2795050 embedded in the active site of the kappa (κ) and mu (μ) opioid receptors. This work is done using Molegro Virtual Docker (MVD) software. The docking studies show that the possibility of the ligand-KOR complex formation is more than the ligand-MOR complex.

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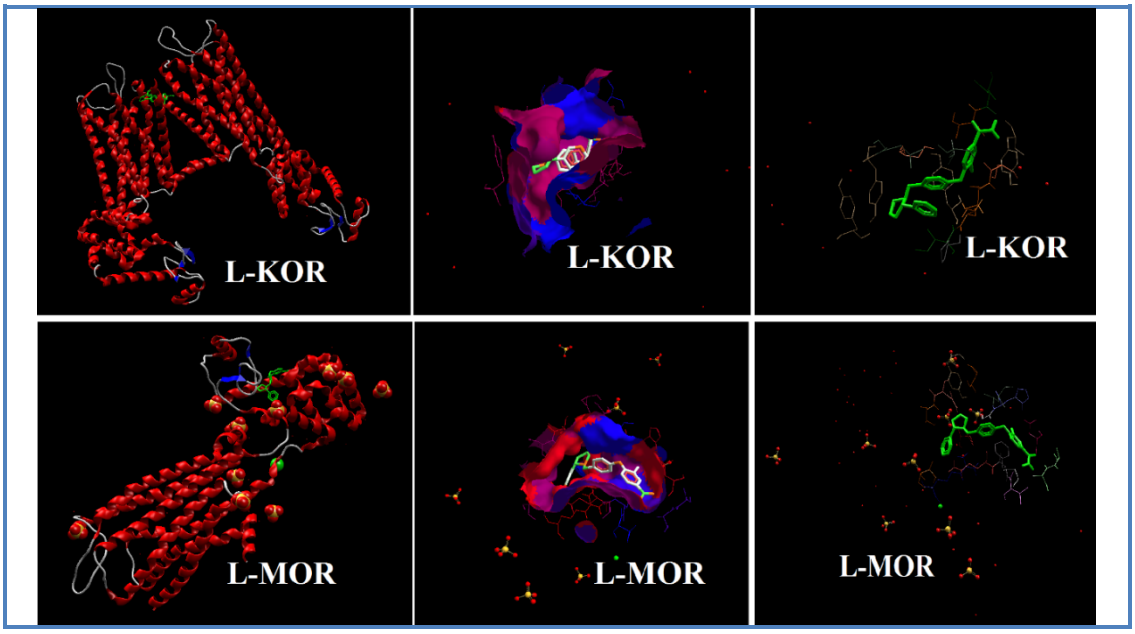
Graphical Abstract



Introduction

A receptor into the cells has two main operations when it makes complex with an agonist compound and or an antagonist molecule [1]. The agonist-receptor complex formation causes the receptor activation, but the binding of antagonist molecule to the receptor causes its blocking. In pharmacology, the antagonist compounds have tendency for their desired receptors and inhibit their function [2]. The antagonist-receptor complex formation happens by binding the small molecule to the active site or to the allosteric site on the receptor. Depending on the longevity of the antagonist-receptor complex, the activity of the antagonist compounds may be reversible or irreversible [3]. One main group of the receptors into the human cells is the opioid receptors (OR). These receptors belong to a various group of G protein coupled receptors with opioids as ligands. The endogenous opioids include nociceptin, endorphins, dynorphins, endomorphins and enkephalins. These receptors are mainly distributed in the brain, in the spinal cord, on peripheral neurons and digestive tract [4]. Mu and Kappa receptors are the most important opioid receptors. The μ-opioid receptors (MOR) have a high affinity for β-endorphin and enkephalins. In contrast, the κ-opioid receptors (KOR) like to make complex with dynorphins. High levels of the kappa opioid receptors have been detected in the solitary nucleus, prefrontal cortex, parabrachial nucleus, periaqueductal gray, spinal trigeminal nucleus, raphe nuclei, locus coeruleus, ventral tegmental area, midline thalamic nuclei, substantia nigra, hypothalamus, dorsal striatum (putamen, caudate), hippocampus, ventral striatum (nucleus accumbens, olfactory tubercle), bed nucleus stria terminalis and amygdala [5–8]. On the other hand, the Mu opioid receptors (MOR) exist presynaptically in the periaqueductal greay region and in the superficial dorsal horn of the spinal cord. Also, high levels of these receptors (MORs) have been detected in the external plexiform layer of the olfactory bulb, the nucleus accumbens, in several layers of the cerebral cortex, and in the nuclei of the amygdala [8–10].

[^{11}C]LY2795050 is a novel antagonist small molecule that uses for positron emission tomography (PET) scan. The different literatures have been showed that this antagonist radiopharmaceutical has high affinity to formation of the KOR-LY2795050 complex. These studies have been showed that this molecule binds to the receptor selectively [11–13].

From literature survey, it was found that the identification of the structural properties of the molecule under study had not been previously performed in the light of computational chemistry and hence the study was undertaken. The main aim of the present research is to give an electronic properties comprehensive description of this novel antagonist compound as a ligand for kappa opioid receptor (KOR) by quantum-mechanical (QM) and molecular docking methods. In parallel, the possibility of MOR-ligand formation will be studied too. After that, the docking of the antagonist radiolabeled tracer [^{11}C]LY2795050 into the active site of kappa opioid receptor will be compared with the possible formation of MOR-ligand complex. It is believed that the outputs of this study will provide a deep and accurate understanding of the possible biological activities of the said radiopharmaceutical.

Computational Methods

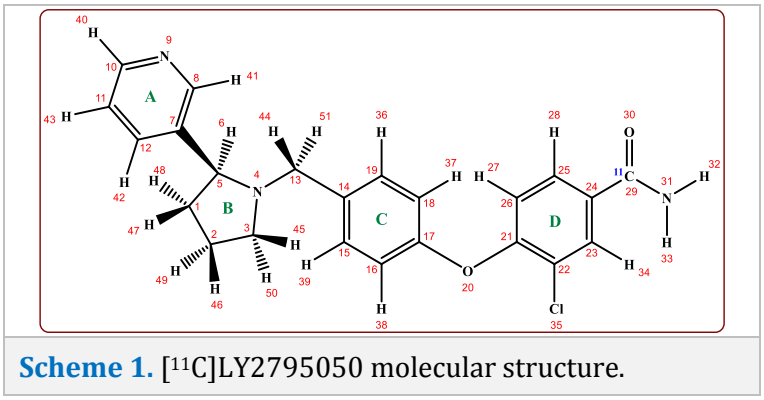
Quantum mechanics (QM) is a molecular simulation technique aided by computer for investigation on the physical movements of molecules and atoms [14]. The QM molecular simulation method covers all aspects of research related to the molecular modeling and simulation [15]. The molecular modeling aspects include informatics, theoretical and experimental work [14–16]. The main aim of this research field is study of applications of simulation methods and simulation methodology from biology, biochemistry, chemistry, chemical engineering, materials, nanomaterials, medicine, physics and information science [17]. In the present work, the structural and electronic properties of the novel antagonist small molecule [^{11}C]LY2795050 perform and study using density functional theory (DFT) method. The molecular structure of the title radiopharmaceutical optimizes using B3LYP/6-31+G(d, p) basis set of theory at room temperature. After the molecular structure optimization, the global reactivity indices use to understand the reactivity and stability of the said compound. These reactivity indices will be accessed using frontier molecular orbitals (FMOs) theory. On the other hand, one important field in the simulation of biomolecules is docking of the molecules into the active sites of the proteins or receptors. In fact, this method predicts the preferred orientation of one ligand to a receptor when bound to each other for a stable complex formation. In this study, we use Molegro Virtual Docker (MVD) software to predict the preferred orientations of the said antagonist compound in the ligand-receptor complexes.

Results and Discussion

[^{11}C]LY2795050 structural properties study

Scheme 1 shows the [^{11}C]LY2795050 molecular structure. This molecule has been constructed from three unsaturated rings and a saturated pirole ring. The C-29 element of this molecular structure is a radioisotope with mass number 11. So, this compound can be used as radiopharmaceutical to getting PET scan. For our future studies, the geometry of this compound was optimized using B3LYP/6-31+G(d,p) level of theory at room temperature by Gaussian 03 software. Figure 1 indicates the theoretical geometric structure of the title compound. The C-13 and O-20 elements cause

the rings of the molecule come near together. Being the various saturated and unsaturated rings induce, this molecule can react with different residues of natural proteins like receptors. Figure 2 indicates the dependence between the theoretical and experimental bond lengths of the radiopharmaceutical under study. This dependence is shown by the equation y=0.9374x+0.0694. The higher correlation coefficient (R^2=0.99817) for this equation shows a great convergence. So, the B3LYP/6-31+G(d,p) basis set of theory is a good method to compute the electronic properties of the title compound.



Scheme 1. [^{11}C]LY2795050 molecular structure.

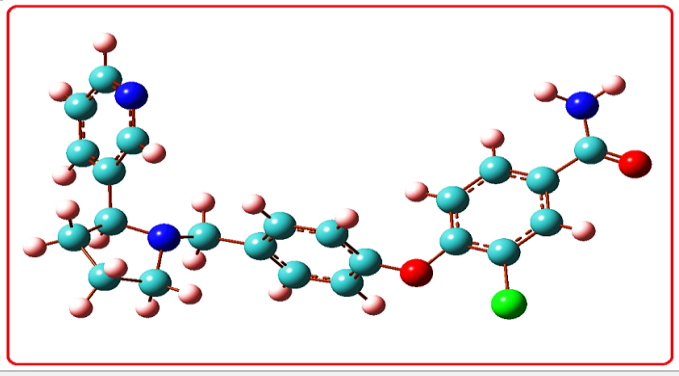


Figure 1. The theoretical geometric structure of [^{11}C]LY2795050.

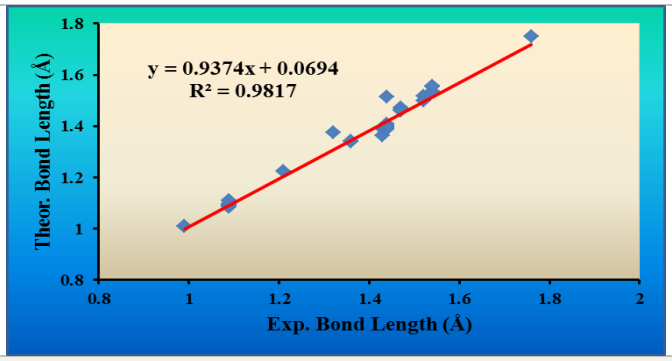


Figure 2. The experimental and theoretical bond lengths relationship of [^{11}C]LY2795050.

Stability and reactivity study of the compound irilone

The highest energy occupied and lowest energy unoccupied orbitals (HOMO and LUMO) are the frontier molecular orbitals of a chemical molecule [18]. The interactions between these orbitals (HOMO and LUMO) on one or more chemical compounds are used to explain the resonance and chemical reactions. So, the molecular structure and reactivity of the chemical compounds can be explained using frontier molecular orbitals (FMOs) theory [19–21]. Figure 3 shows the frontier molecular orbitals (the filled HOMO and the empty LUMO) of the radiopharmaceutical [^{11}C]LY2795050. We can see the highest energy occupied molecular orbital (filled HOMO) is mainly constructed by the elements of the rings pyridine (A) and pyrrolidine (B), while the lowest energy unoccupied molecular orbital (the empty LUMO) has been made by the atoms of the chlorobenzene ring and amide group. On the other hand, the atoms of the benzene ring (C) are participated in construction of both HOMO and LUMO. It can be deduced that the pyridine and pyrrolidine rings will show nucleophilic or electron donating property in interaction with the residues of a receptor. In contrast, the empty LUMO (chlorobenzene and amide group) will indicate the electrophilic or electron accepting property. The stability and global reactivity indices of a chemical molecule can be gained using FMO theory [22]. The global reactivity descriptors like energy gap (Eg), ionization potential (IP), electron affinity (EA), chemical hardness (η), chemical softness (S), electronegativity (χ), electronic chemical potential (μ) and electrophilicity index (ω) can be obtained from the energies of the frontier orbitals. These reactivity indices are achieved by following formulas [23]:

$$E_g = E_{LUMO} - E_{HOMO}$$

$$IP = -E_{HOMO}$$

$$EA = -E_{LUMO}$$

$$\eta = \frac{(\varepsilon_{LUMO} - \varepsilon_{HOMO})}{2}$$

$$\chi = \frac{-(\varepsilon_{LUMO} + \varepsilon_{HOMO})}{2}$$

$$\mu = \frac{(\varepsilon_{LUMO} + \varepsilon_{HOMO})}{2}$$

$$\omega = \frac{\mu^2}{2\eta}$$

$$S = \frac{1}{\eta}$$

Table 1 has been listed the global reactivity indices and frontier molecular orbitals energies of the labeled compound [^{11}C]LY2795050. As can be seen from the data, the energies of HOMO and LUMO are -6.489 eV and -1.425 eV, respectively. The HOMO/LUMO energies gap (Eg) is 5.064 eV. This high amount of HOMO/LUMO energies gap shows high stability of the said compound. Figure 4 indicates the density of states (DOS) graph of the title compound. It can be seen from this graph that the unoccupied molecular orbitals have more density than the occupied molecular orbitals. So, it can be deduced that the radiopharmaceutical [^{11}C]LY2795050 prefers to react with nucleophile agents. The low energy of the electron affinity (EA) and high energy of the ionization potential (IP) show the high electrophilic property of the molecule, too. The electrophilicity of this compound is 3.092 eV. On the other hand, the low chemical hardness and high amount of the chemical softness indicates this electron accepting property of the compound [24]. The electrostatic potentials negative, zero and positive have been shown by red, green and blue colors in molecular electrostatic potential (MEP) graph (Figure 5). It can be seen that all segments of the molecule except the nitrogen elements have electrostatic potential zero. So, this molecule prefers to react only with powerful nucleophile agents.

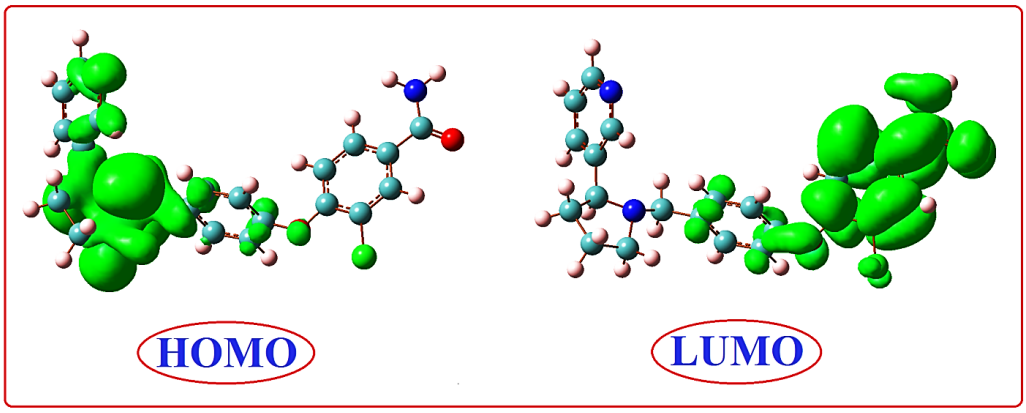


Figure 3. The frontier molecular orbitals of [^{11}C]LY2795050.

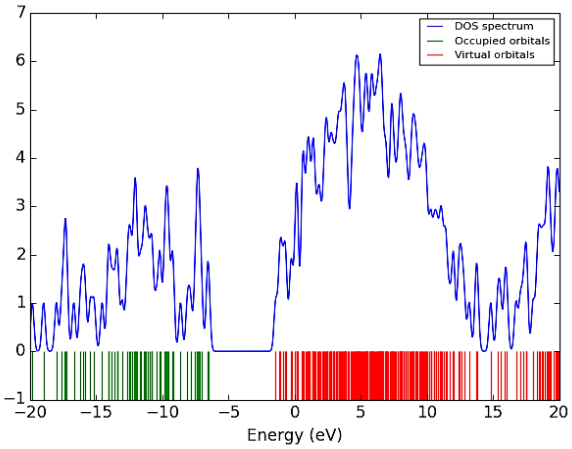


Figure 4. The density of states (DOS) graph of [^{11}C]LY2795050.

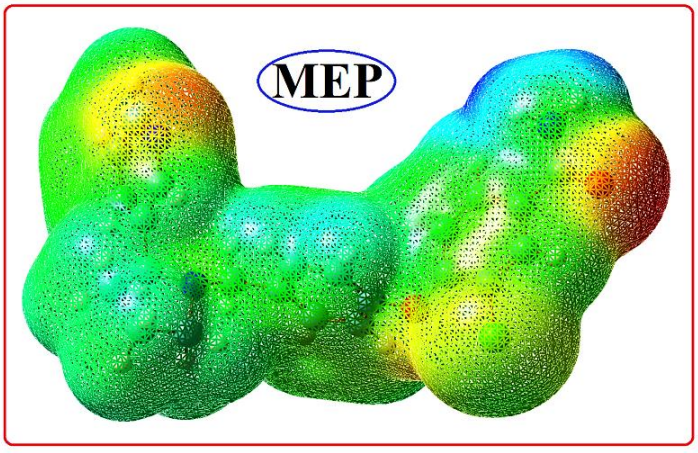


Figure 5. The molecular electrostatic potential (MEP) graph of [^{11}C]LY2795050.

Table 1. Global reactivity indices of [^{11}C]LY2795050.

Parameter	Energy value (eV)
HOMO	-6.489
LUMO	-1.425
Ionization Potential (IP)	6.489
Electron Affinity (EA)	1.425
Energy Gap (Eg)	5.064
Electronegativity (χ)	3.957
Chemical Potential (μ)	-3.957
Chemical Hardness (η)	2.532
Chemical Softness (S)	0.395
Electrophilicity index (ω)	3.092

Physicochemical descriptors and ADME parameters of the compound [^{11}C]LY2795050

The physicochemical descriptors computations and prediction of the ADME parameters and pharmacokinetic properties of the molecular structure under study are done using SwissADME web tool. Figure 6 indicates the predicted physicochemical graph of the title molecule. The colored zone shows the suitable physicochemical space for oral bioavailability. This compound has 6 rotatable bonds, 4 hydrogen bond acceptors and 1 hydrogen bond donor. Its molar refractivity is 117.24. The topological polar surface area (TPSA) of this compound is 68.45 Å^2. The computations show 3.24 as a lipophilicity index (Log $P_{O/W}$ or iLog P) for this radiopharmaceutical. On the other hand, Log S (ESOL) is a topological method for showing the water solubility of a chemical compound. The Log S scale is insoluble < -10 < poorly < -6 < moderately < -4 < soluble < -2 < very < 0 < highly. From the computational data, this index is -4.78 for the title compound. So, the radiopharmaceutical [^{11}C]LY2795050 is moderately soluble in water. The pharmacokinetic parameters prediction shows this molecule has BBB permeability and high gastrointestinal (GI) absorption. Also, it is a cytochrome P450 inhibitor (CYP1A2, CYP2C19, CYP2C9, CYP2D6 and CYP3A4). The skin permeation index (Log Kp) of this molecule is -6.82 cm/s. In overall, its bioavailability score is 055 due to its obeying from Lipinski rules (a: MW ≤ 500, b: MLOGP ≤ 4.15, c: N or O ≤ 10, d: NH or OH ≤ 5).

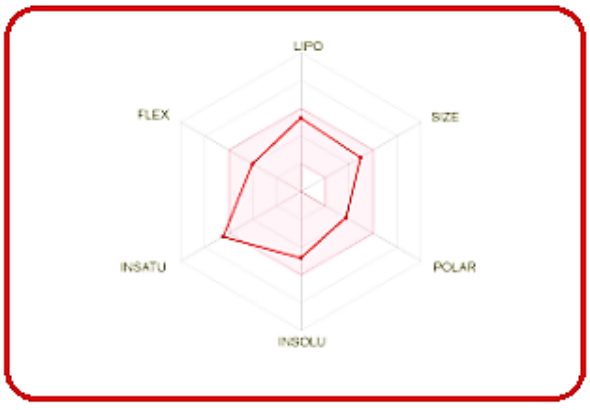


Figure 6. The physicochemical properties graph of [^{11}C]LY2795050.

Charge distribution and molecular docking

The Mulliken charge distribution on atoms of the radiopharmaceutical [^{11}C]LY2795050 is shown in Figure 7. In this graph, the red, black and green colors are related to the negative, zero and positive charges, respectively. The charge distribution amount on the atoms of the title compound has been shown in Figure 8. We can see the C-2, C-5, C-8, C-13, C-19, O-20, C-21, C-25, O-30 and N-31 atoms of the molecular structure have negative charge. So, these atoms can interact with the atoms containing positive charge. In contrast, the hydrogen atoms and C-7, C-14, C-23, C-29 and Cl-35 atoms show the positive charge on themselves. So, these atoms are responsible for interaction with the receptor residues with negative charge. On the other hand, Figure 9 indicates the two-dimensional electron localization graph of [^{11}C]LY2795050. This graph shows that the main charge localization is on the rings of the title compound. So, the saturated and unsaturated rings of the radiopharmaceutical can be participated in steric interactions with the residues of the receptors.

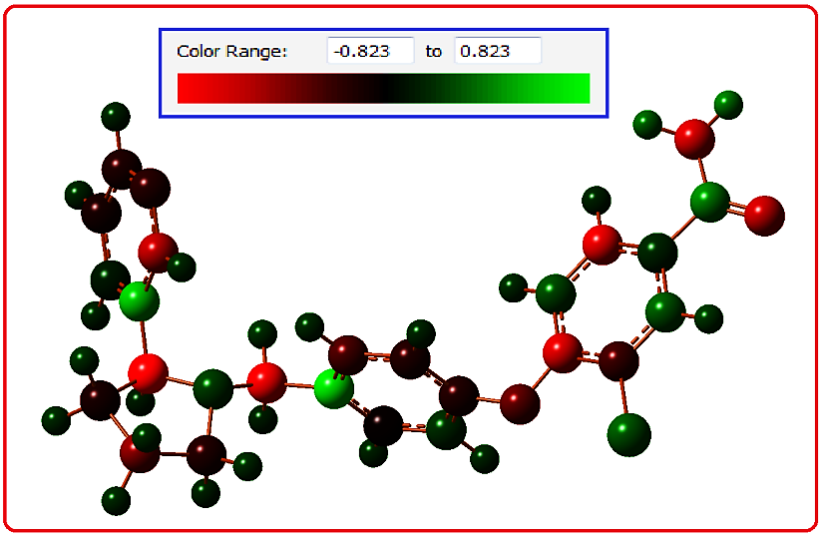


Figure 7. The charge distribution of [^{11}C]LY2795050.

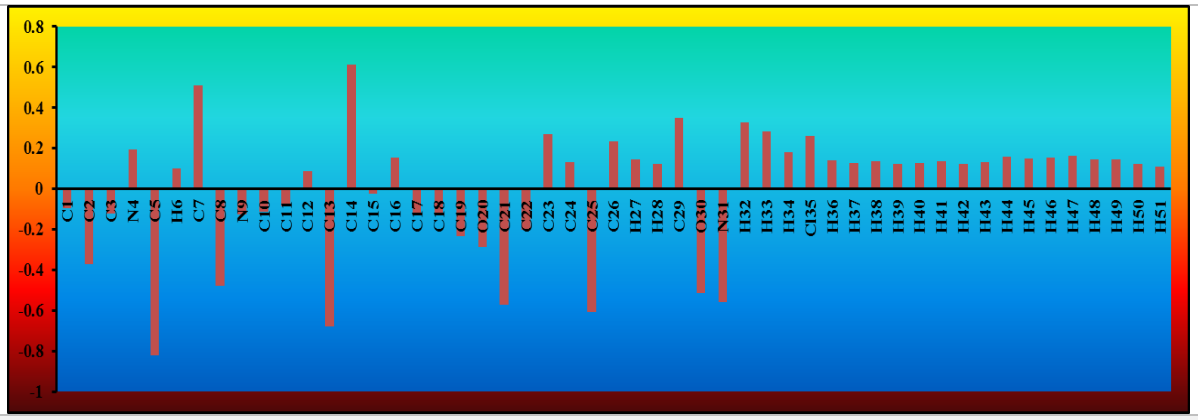


Figure 8. The charge distribution on the elements of [^{11}C]LY2795050.

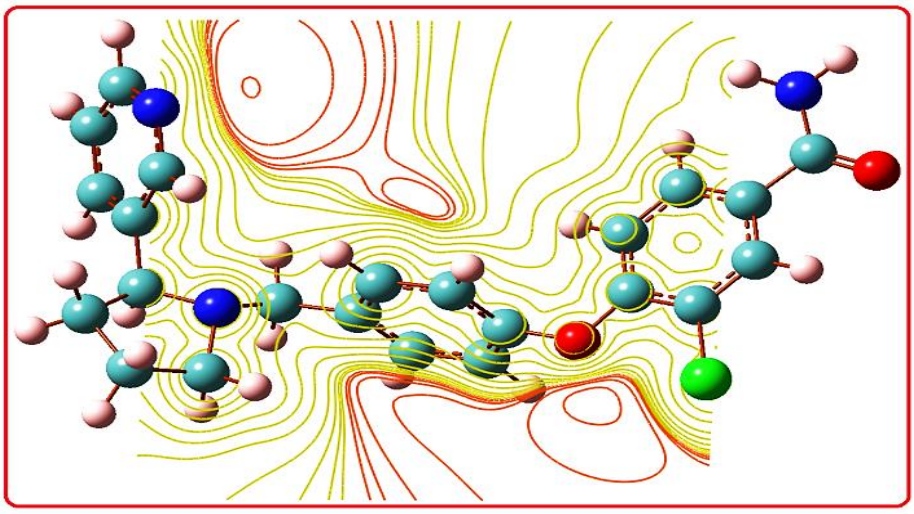


Figure 9. The two-dimensional electron localization graph of [^{11}C]LY2795050.

Literature review clearly shows that the medicinal radio-compound [^{11}C]LY2795050 has high affinity to formation of the KOR-LY2795050 complex [11]. On the other hand, some papers show that this radiopharmaceutical may be interacted with Mu opioid receptor (MOR) [25]. So, its interaction with these receptors will be analyzed using docking studies. The three dimensional crystal structures of the title receptors (KOR and MOR) were obtained from protein data bank (PDB) and the docking analyses were carried out using Molegro Virtual Docker (MVD) program. Figure 10 collects the graphs of the Ligand [^{11}C]LY2795050 embedded in the active site of the kappa (κ) and mu (μ) opioid receptors. These graphs show the second structure, hydrophobicity and pose state of the residues of the title receptors that they have been located around the ligand after ligand-receptor formation. From the data of the Table 2, the formation of the ligand-KOR complex is mainly done by steric interactions with moldock score -158.192. This score is -148.757 for the ligand-MOR complex formation (Table 3). In mu opioid receptor, the cofactor-ligand interactions are formed by steric interactions. On the other hand, the hydrogen bond interactions have not important role in complex formation of the said radiopharmaceutical with both receptors (KOR and MOR). It can be deduced from the moldock score amount of steric interactions, the possibility of the ligand-KOR complex formation is more than the ligand-MOR complex. Figure 11 shows the H-bond and steric interactions of title radiopharmaceutical embedded in the active site of the kappa (κ) and mu (μ) opioid receptors. It can be seen from the data of the Table 4 that the KOR residues containing Tyr [B] 119, Thr [B] 63, Tyr [A] 66, Thr [A] 63, Tyr [B] 66, Ile [B] 62, Ser [B] 116, Leu [B] 120, Ser [A] 116, Pro [B] 59 and Ile [A] 62 play main role in the ligand-receptor complex formation. In contrast, the MOR-ligand complex formation is mainly done by the residues Phe 1104, Gln 1105, Glu 1011, Leu 1032, Arg 1145, Asn 1020, Thr 1021, Val 1103, Gly 1030, His 1031 and Asp 1070. The cofactor 10 of mu opioid receptor interacts with the title ligand with the total energy score -3.384.

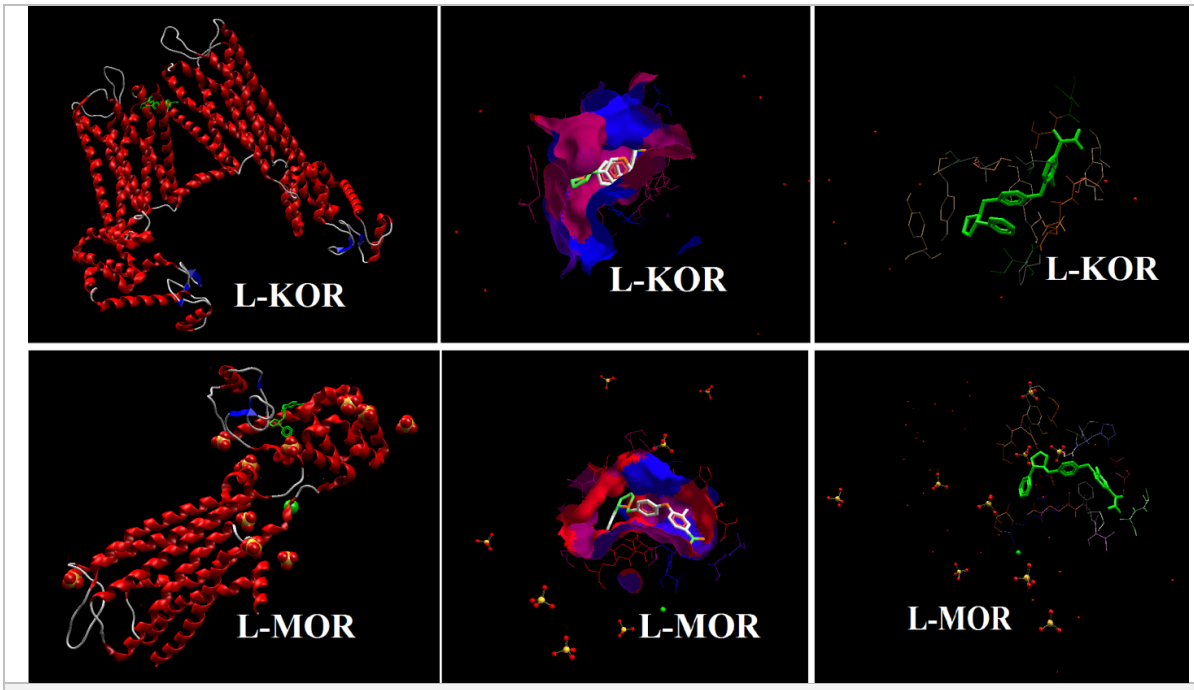


Figure 10. Ligand [^{11}C]LY2795050 embedded in the active site of the kappa (κ) and mu (μ) opioid receptors.

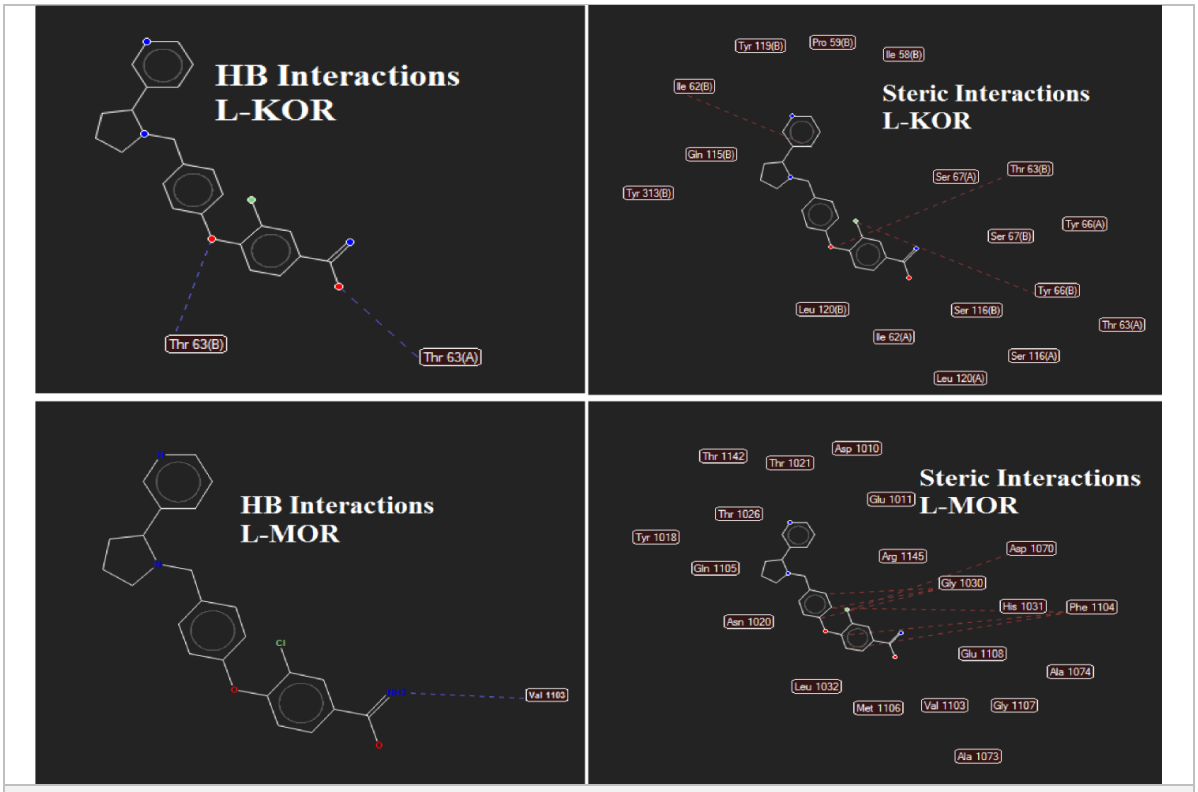


Figure 11. H-bond and steric interactions of ligand [^{11}C]LY2795050 embedded in the active site of the kappa (κ) and mu (μ) opioid receptors.

Table 2. The ligand-KOR interactions.

Interactions		MolDock Score
Protein-Ligand Interactions	Steric (by PLP)	-154.192
	Steric (by LJ12-6)	-46.926
	Hydrogen bonds	-3.863
	Hydrogen bonds (no directionality)	-5.278
Internal Ligand Interactions	Torsional strain	3.933
	Steric (by PLP)	-1.973
	Steric (by LJ12-6)	84.974

Table 3. The ligand-MOR interactions.

Interactions		MolDock Score
Protein-Ligand Interactions	Steric (by PLP)	-148.757
	Steric (by LJ12-6)	-51.635
	Hydrogen bonds	-2.368
	Hydrogen bonds (no directionality)	-6.924
Cofactor-Ligand Interactions	Steric (by PLP)	-3.384
	Steric (by LJ12-6)	-0.929
Water-Ligand Interactions		-0.323
Internal Ligand Interactions	Torsional strain	3.540
	Steric (by PLP)	15.722
	Steric (by LJ12-6)	97.155

Table 4. The participated KOR residues in ligand-receptor interactions.

Residue/HOH	Total energy score
Tyr [B] 119	-23.329
Thr [B] 63	-18.270
Tyr [A] 66	-18.175
Thr [A] 63	-16.443
Tyr [B] 66	-14.672
Ile [B] 62	-12.344
Ser [B] 116	-11.540
Leu [B] 120	-7.235
Ser [A] 116	-6.729
Pro [B] 59	-5.950
Ile [A] 62	-5.642
Leu [A] 120	-4.971
Tyr [B] 313	-3.657
Ser [A] 67	-1.251
Ser [B] 67	-0.974
Pro [A] 59	-0.618
Thr [A] 117	-0.574
Gln [B] 115	-0.394
Ile [B] 58	-0.342

Table 5. The participated MOR residues in ligand-receptor interactions.

Residue/HOH	Total energy score
Phe 1104	-24.646
Gln 1105	-20.906
Glu 1011	-13.440
Leu 1032	-11.248
Arg 1145	-10.286
Asn 1020	-9.104
Thr 1021	-9.088
Val 1103	-8.910
Gly 1030	-7.811
His 1031	-5.314
Asp 1070	-5.129
Thr 1142	-4.254
Ala 1074	-4.080
Gly 1107	-3.411
Cofactor (SO4) 10	-3.384
Ala 1073	-2.829
Thr 1026	-2.640
Tyr 1018	-1.986
Water (HOH) 27	-0.323
Glu 1022	-0.304

Conclusions

In the present research work, [^{11}C]LY2795050 radiopharmaceutical was optimized using B3LYP/6-31+G(d,p) basis set of theory at room temperature by Gaussian 03 software. Its docking analysis with kappa (κ) and mu (μ) opioid receptors (KOR and MOR) is done using Molegro Virtual Docker (MVD) software. The molecular orbitals calculations (global indices) indicate that this molecule prefers to react only with powerful nucleophile agents. On the other hand, the docking studies show that the possibility of the ligand-KOR complex formation is more than the ligand-MOR complex. The MOR residues containing Phe 1104, Gln 1105, Glu 1011, Leu 1032, Arg 1145, Asn 1020, Thr 1021, Val 1103, Gly 1030, His 1031 and Asp 1070 play the main role in the ligand-receptor complex formation. In contrast, the KOR-ligand complex formation is mainly done by the residues Tyr [B] 119, Thr [B] 63, Tyr [A] 66, Thr [A] 63, Tyr [B] 66, Ile [B] 62, Ser [B] 116, Leu [B] 120, Ser [A] 116, Pro [B] 59 and Ile [A] 62.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Disclosure statement

No potential conflict of interest was reported by the authors

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