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Evaluation of [^{18}F]- Evaluation of [^{18}F]FPTT Molecular structure and its binding to progesterone receptor (PR) for PET scan of breast cancer FPTT Molecular structure and its binding to progesterone receptor (PR) for PET scan of breast cancer

Mehdi Nabati*, Vida Bodaghi-Namileh and Mohammad Mazidi

Synthesis and Molecular Simulation Laboratory, Chemistry Department, Pars Isotope Company, P.O. Box: 1437663181, Tehran, Iran

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ABSTRACT

Breast cancer is a complicated disease that it is accompanied by different symptoms. Diagnosis of this disease is performed by various techniques. Using Radiopharmaceuticals is a new method to diagnose the said tumors. [^{18}F]-FPTT is one of these nuclear medicines for detection of breast cancer. It seems that the binding of the title radiopharmaceutical to the progesterone receptor is the main cause of the breast cancer diagnosis. Studying the electronic properties, stability, reactivity and binding of the title compound to the progesterone receptor are the main purposes of the present research work. In first step, [^{18}F]-FPTT molecular structure is optimized at B3LYP/6-311++G(d,p) level of theory at room temperature. Then, its stability and reactivity properties are calculated by frontier molecular orbitals (FMOs) energies. The global reactivity indices show this medicinal molecule may be interacted with active reagents into the cell such as free radicals. Also, this radiopharmaceutical has a molecular structure with high reactivity and it prefers to interact with nucleophile agents or residues. Analyzing the molecular electrostatic potential (MEP) graph of the compound indicates it prefers to interact with the residues of a receptor by its oxygen atoms. On the other hand, the docking analysis of the ligand-receptor complex shows the steric interactions play the main role in this complex formation. The docking analysis data shows the progesterone receptor (PR) residues containing Arg 899 [B], Phe 895 [A], Phe 895 [B], Ser 898 [B], Ser 910 [A], Ile 896 [A], Ser 898 [A], Ile 896 [B], Val 903 [B], Glu 911 [A], Ser 902 [B], Arg 899 [A] and Glu 904 [B] are the major amino acids participating in the ligand-receptor complex formation.

Keywords: Breast cancer; FPTT; Molecular docking; Molecular simulation; Progesterone receptor

INTRODUCTION

Breast cancer is a complicated, heterogeneous disease, mostly accompanied by symptoms such as a mass in the breast, changes in breast shape, size and color, pain in breast or nipple, fluid discharge from the nipple, inverted nipple, dimpling or irritation of the skin, etc. [1-5]. Age, sex, alcohol consumption, dietary factors, ionizing radiation, genetic factors and prior history of cancers are all among various factors affecting an individual's predisposition to breast cancer [6-17]. Breast cancers are put into different categories based on several grading systems which determine their prognosis and treatment [18, 19]. There are several well established approaches in treatment of breast cancer namely, radiation therapy,

*Corresponding author: mnabati@ymail.com

surgery, hormone therapy, chemotherapy and targeted therapy as well as a combination of these options [20]. Breast cancers are either ductal or lobular carcinoma (classified by their histopathology and origin) and could be in situ and limited to one specific tissue without invading the surrounding tissues or could be invasive and spread to other tissue compartments in different regions of the body [21]. In addition, assessment of differentiation degree defined as histological tumor grade categorizes breast cancer into low grade (well differentiated cells), intermediate grade (moderately differentiated) and high grade (poorly differentiated). The main stages of breast cancer based on TNM system (Tumor, Node, Metastasis) include stage 0 (pre-cancerous), stages 1-3 (limited to the breast or surrounding lymph nodes) and stage 4 (metastatic) [22-27]. Breast cancers are further determined by the manifestation of three major receptors including estrogen receptor (ER), progesterone receptor (PR), and HER2. Accordingly, in ER positive cancer cells, treatments target estrogen receptors whereas HER2 positive cancers respond to monoclonal antibodies [28-38]. Progesterone is a steroid and sex hormone involved in hormone response regulation in the reproductive tract and breast tissues. Progesterone collaborates with estrogen to induce proliferation in the breast. Consequently, over-expression of PR in breast cells contributes to pathogenesis of breast cancer and is a subject of focus in many breast cancer treatment regimens [39-43]. Early detection of breast cancer is of significant importance in management of this disease and greatly affects prognosis and survival rate as well as patient's quality of life. Over the past few years, molecular imaging as a non-invasive and safe procedure has been considered for detection and early treatment of breast cancer [44-46]. Furthermore, the utilization of a PR targeting probing agent in detection and PR positive breast cancers has come into attention in several studies [47, 48]. In a study by Fei Gao et al., a novel probing agent 1-(17-[18F]fluoro-3, 6, 9, 12, 15-pentaoxaheptadecyl-1 H-1, 2, 3-triazole) testosterone ([^{18}F]-FPTT) constituted of modified ethisterone, a progestin with naturally high affinity for PR, labelled with ^{18}F, a convenient radionuclide for PET imaging, was synthesized and evaluated in detection of PR-positive breast cancer [49]. Although, the synthesis procedure and tumor uptake has been extensively elucidated in this study, the exact structural interaction between this compound and progesterone receptor is yet to be analyzed. The aim of the present study was to comprehensively investigate molecular compound-receptor interactions using computational chemistry and docking methods. The pharmacokinetic behavior and physiochemical attributes of the title compound was further predicted utilizing swissADME web tool.

COMPUTATIONAL METHODS

Quantum chemical calculations were carried out within the Gaussian 03 package of programs [50]. All calculations were performed within the density functional theory (DFT) with a hybrid exchange-correlation functional, B3LYP (the three-parameter exchange functional of Beck B3 [51] combined with the Lee–Yang–Parr correlation functional LYP [52]), using the extended basis set 6-311++G(d,p). After molecular geometry optimization, the stability and reactivity properties of the title radiopharmaceutical will be discussed using global reactivity indices. These parameters are calculated using the energy levels of the frontier molecular orbitals (FMOs). Finally, the complex formation between [^{18}F]-FPTT and progesterone receptor (PR) will be analyzed by

molecular docking analysis. Our docking analysis is performed by Molegro Virtual Docker (MVD) program.

RESULTS AND DISCUSSION

[^{18}F]-FPTT structural properties study

[^{18}F]-FPTT is a radiopharmaceutical for scanning of the breast cancer. Its molecular structure is shown in Figure 1. We can see this nuclear medicine has been composed from a testosterone backbone with a triazole ring and a long aliphatic chain. The radionuclide fluorine-18 has been attached to the end of the aliphatic ring. Due to the testosterone backbone, it is predicted that the title nuclear medicine can be interacted with the progesterone receptor (PR). To study the ligand-receptor interaction, it is needed to survey the reactivity and stability of this molecular structure. So, the said molecular structure was optimized at B3LYP/6-311++G(d,p) level of theory. The optimized molecular geometry can be seen in Figure 1 and it shows the molecular structure has been bended in the attachment point of the aliphatic chain to the testosterone backbone. This molecular structure bending will probably help the compound to insert into the active site of the receptor. Figure 2 indicates the dependence between the theoretical and experimental bond lengths [49] of the medicinal compound [^{18}F]-FPTT. This dependence is shown by the equation y=0.9541x+0.0655. The higher correlation coefficient (R^2=0.996) for this equation shows a great convergence. So, the B3LYP/6-311++G(d,p) basis set of theory is a good method to compute the electronic properties of the title medicinal compound.

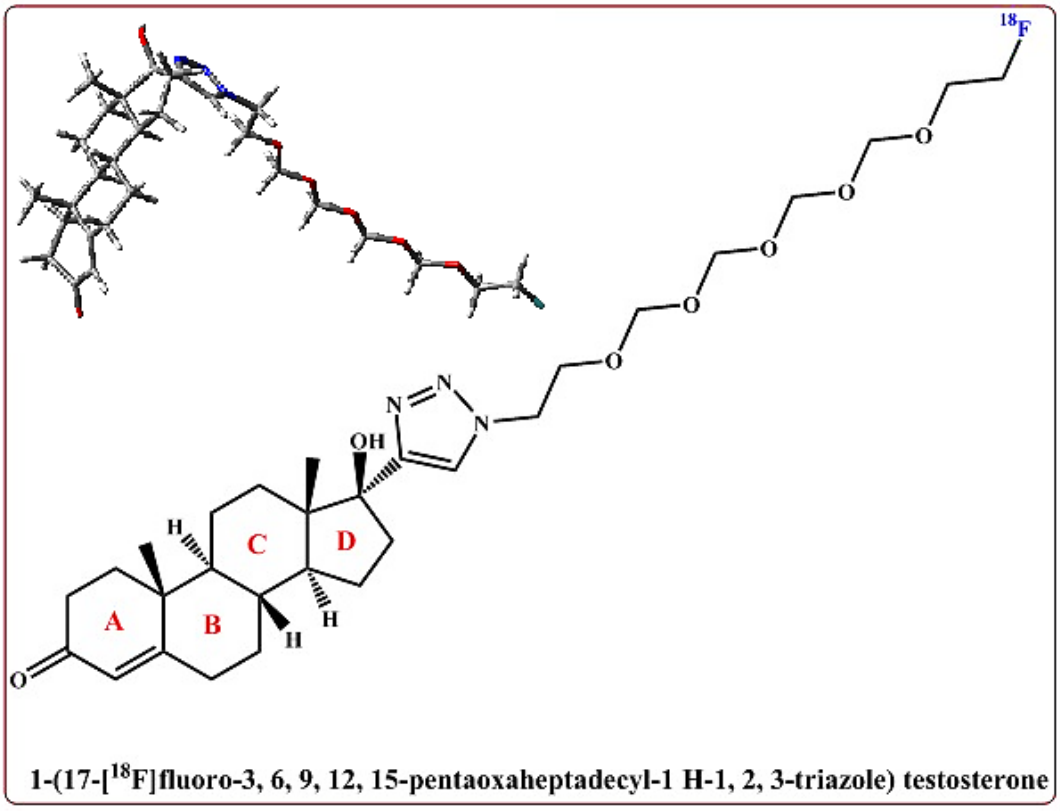

Fig. 1. The theoretical geometric structure of [^{18}F]-FPTT.

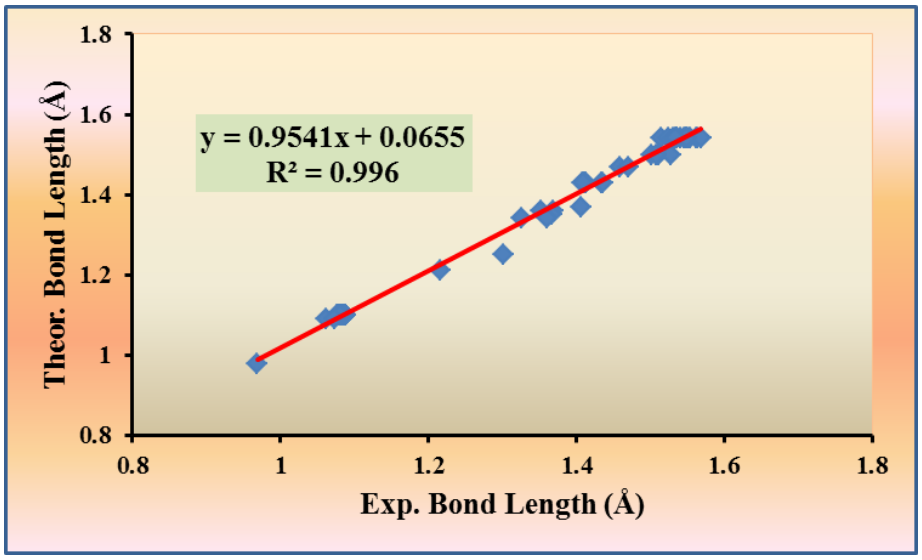

Fig. 2. The experimental and theoretical bond lengths relationship of [^{18}F]-FPTT.

Stability and reactivity study of the medicinal nuclear compound [^{18}F]-FPTT

Before interaction of a drug with a receptor or a protein, the medicinal compound sees two types of metabolism in its absorption phase. The molecular structure of the medicinal compound should have high stability due to avoid the destroying in metabolisms process. On the other hand, it should be reactive due to its insertion into the receptor. So, stability and reactivity are two important parameters to describe a medicinal active compound. These chemical properties are gained using the frontier molecular orbitals (FMOs) calculations. The highest occupied and the lowest unoccupied molecular orbitals (HOMO and LUMO) are the frontier molecular orbitals of a chemical compound. The HOMO is filled with electrons and in contrast the LUMO is empty of electron. The title properties of a medicinal substance can be studied using the global reactivity indices [53-57]. 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 [58]:

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

$$IP = -E_{HOMO}$$

$$EA = -E_{LUMO}$$

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

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

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

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

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

Figure 3 shows the graph of the frontier molecular orbitals (HOMO and LUMO) of

[^{18}F]-FPTT. We can see both of the frontier molecular orbitals are composed by the atoms of the ring A. So, the nucleophilic and electrophilic reactions prefer to do on this ring. It happens due to the α,β-unsaturated carbonyl system of this ring. From the data of the Table 1, the HOMO and LUMO energy levels are -6.27 eV and -1.09, respectively. The low energy gap of the frontier molecular orbitals (5.18 eV) makes easy the electronic transition from occupied orbitals to virtual orbitals. It means that the oxidation/reduction reactions can be performed on this molecular structure. It can be deduced that the title radiopharmaceutical may be interacted with active reagents into the cell such as free radicals. This energy gap of the FMOs is seen in Figure 4. Also, the density of states graph shows the importance of the virtual orbitals. So, it can be said the title compound prefers to interact with nucleophile agents or residues. On the other hand, the low chemical hardness (2.59 eV) and high chemical softness (0.386 eV) indices show the said compound has a molecular structure with high reactivity. The molecular electrostatic potential (MEP) graph of [^{18}F]-FPTT can be shown in Figure 5. The red, green and blue colors in this graph show the regions of the molecules with negative, zero and positive charges, respectively. It seems the charge density of the entire of molecule except the oxygen elements equals to zero. So, it can be deduced that the molecule under study prefers to interact with the residues of a receptor by its oxygen atoms.

Physicochemical descriptors and ADME parameters of the compound [^{18}F]-FPTT

Evaluation of absorption, distribution, metabolism and excretion (ADME) has long been considered an important step in the process of drug discovery and drug development. Assessment of physicochemical and pharmacokinetic attributes of the lead compound is now performed at early stages of drug discovery to lower the chance of failure in later stages [59-63]. ADME prediction and

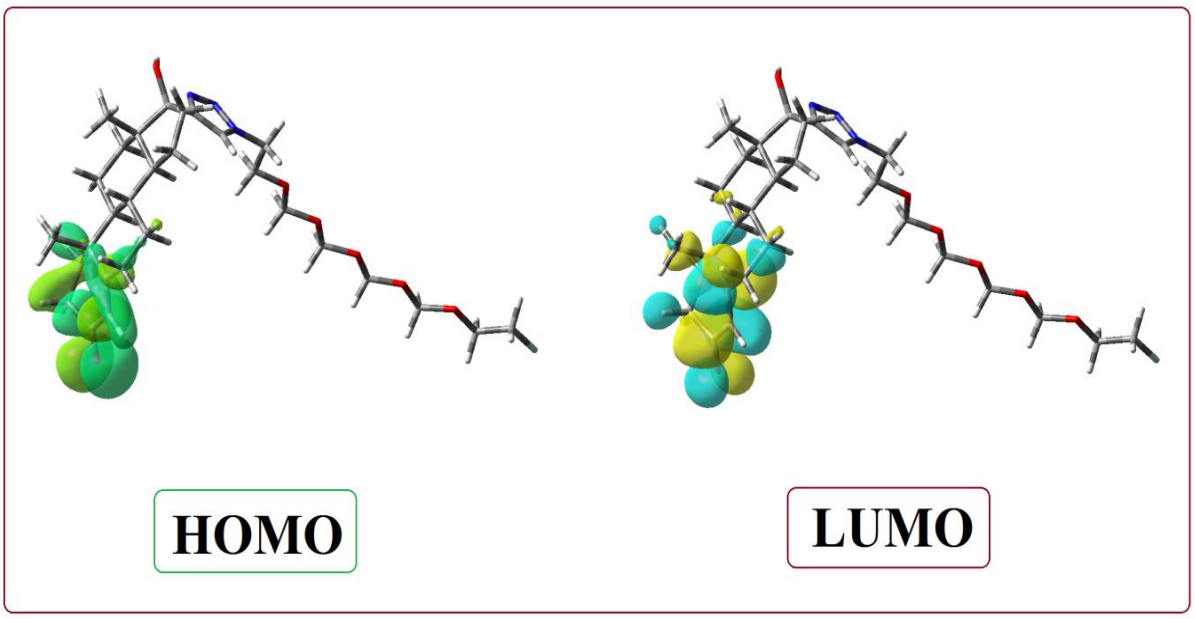

Fig. 3. The frontier molecular orbitals of [^{18}F]-FPTT.

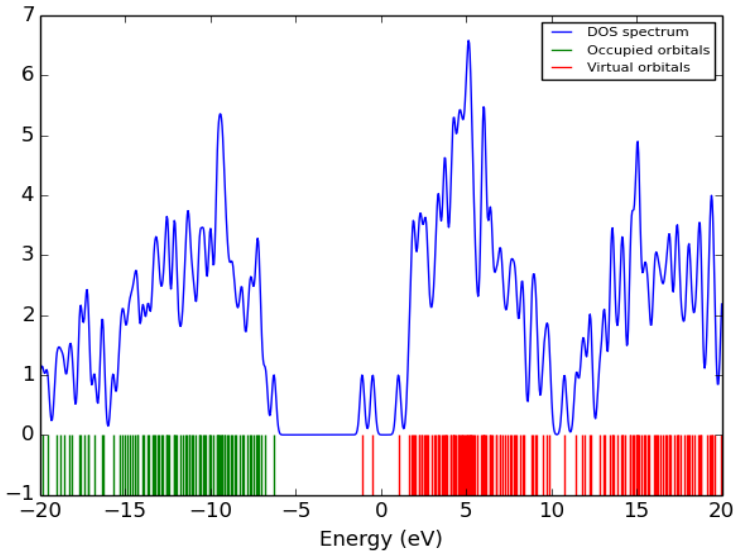

Fig. 4. The density of states (DOS) graph of [^{18}F]-FPTT.

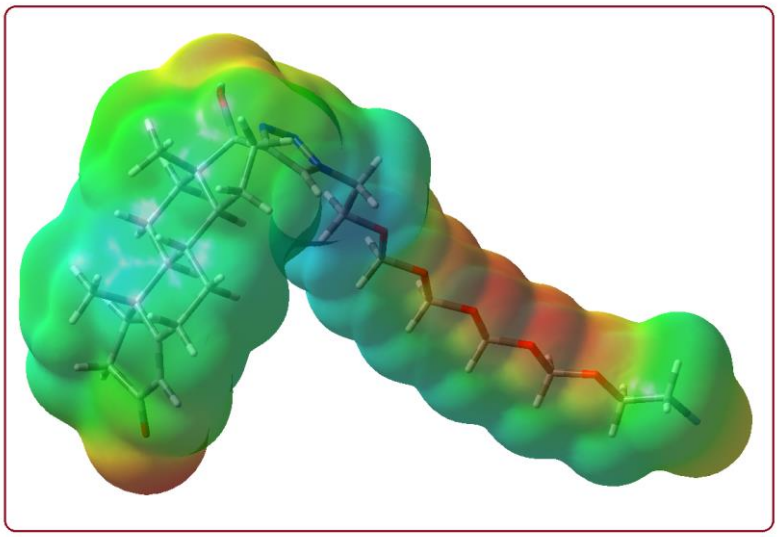

Fig. 5. The molecular electrostatic potential (MEP) graph of [^{18}F]-FPTT.

Table 1. Global reactivity indices of [^{18}F]-FPTT

Parameter	Energy value (eV)
HOMO	-6.27
LUMO	-1.09
Ionization Potential (IP)	6.27
Electron Affinity (EA)	1.09
Energy Gap (Eg)	5.18
Electronegativity (χ)	3.68
Chemical Potential (μ)	-3.68
Chemical Hardness (η)	2.59
Chemical Softness (S)	0.386
Electrophilicity index (ω)	2.61

computational analysis of the compound [^{18}F]-FPTT was conducted using SwissADME web tool. The predicted physicochemical graph of the investigated compound is presented in Figure 6. The evaluation of the compound's *physiochemical properties* in the first section showed a molecular weight of 565.67 g/mol, 40 heavy atoms, 5 aromatic heavy atoms, the fraction Csp3 of 0.83, 14 rotatable bonds, 10 hydrogen bond acceptors and 1 hydrogen bond donor. Moreover, the calculated topological polar surface area (TPSA) is 114.16 A^2 and the molar refractivity is 143.70. The next factor examined is lipophilicity. The role of lipophilicity in determining the lead compound's solubility, permeability through biological membranes, toxicological profile, selectivity, potency and metabolism is of significant importance. Lipophilicity values are determined by measurement of the partition coefficient between n-octanol and water (log PO/W). ADME utilizes five predictive models regarding lipophilicity of the compounds (iLOGP, XLOGP, WLOGP, MLOGP and SILICOS-IT). Based on calculations, iLog P of the compound is 4.40, XLog P3 is 2.22, WLog P is 4.19, MLog P is 2.30, SILICOS-IT is 3.79 and the consensus log PO/W is 3.38. Water solubility significantly influences the drug's bioavailability and absorption from gastrointestinal tract (GIT) and therefore is of central importance in drug discovery and design, specifically in oral dosage forms. Water solubility of the title compound was determined using ESOL model, a topical method to evaluate Log S. In this regard, the compounds are placed into six categories: 1) Insoluble (Log S < -10), 2) Poorly soluble (-10 < Log S < -6), 3) Moderately soluble (-6 < Log S < -4), 4) Soluble (-4 < Log S < -2), 5) Very soluble (-2 < Log S < 0) and 6) Highly soluble (Log S > 0). The measured Log S is -3.91, determining the compound soluble. Individual ADME behaviors of the molecule are predicted in pharmacokinetics section. The investigated compound has a high gastrointestinal (GI) absorption and is neither blood-brain barrier (BBB) permeant nor a P-gp efflux pump substrate. Identifying CYP 450 inhibitory potential of the compound is important in predicting any drug-drug interactions and adverse effects since drug biotransformation is heavily dependent on CYP 450 isoenzyme family. The compound shows an inhibitory effect on CYP3A4 isoform. The skin permeation index (Log Kp) is calculated using lipophilicity and molecular weight of the compound and the more negative values are indicative of lower skin permeability. The calculated Log Kp for this molecule is -8.17 cm/s. The compound's drug likeness was determined based on its compliance with Lipinski's rule of five and bioavailability score. The investigated molecule follows Lipinski's rule (MLOGP $\leq$ 4.15, relative MW $\leq$ 500, N or O $\leq$ 10, NH or OH $\leq$ 5) and has a bioavailability score of 0.55.

Molecular docking analysis of the ligand-receptor complex

The survey through previous studies determines the diagnostically effects of [^{18}F]-FPTT in detection of breast cancer [49]. It seems that the binding of the title radiopharmaceutical to the progesterone receptor is the main cause of the breast cancer diagnosis [64]. Therefore, the binding of the said medicinal compound to the progesterone receptor and drug-receptor interactions were investigated in the present article. It needs to say that the three dimensional crystal structure of progesterone receptor was obtained from protein data bank (PDB) and the docking analysis was performed using Molegro Virtual Docker (MVD) program. Figure 7

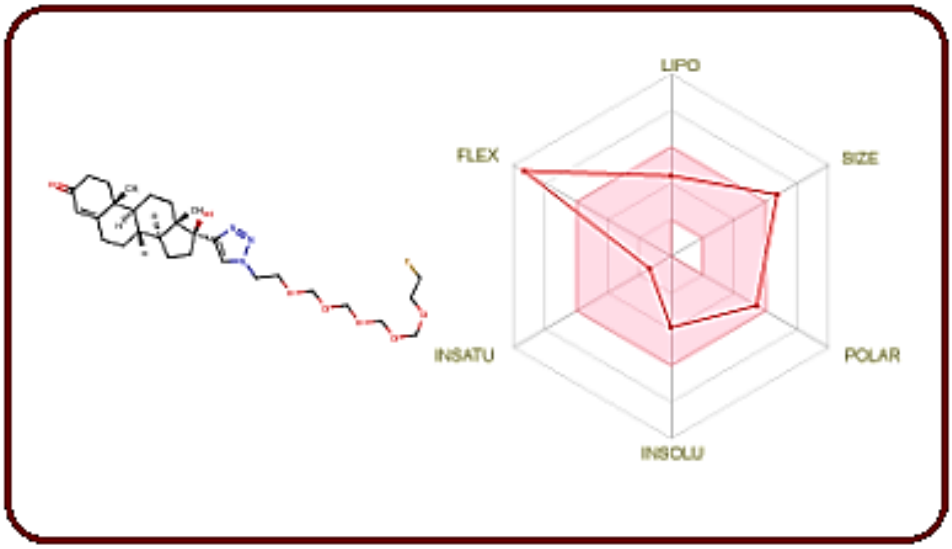

Fig. 6. The physicochemical parameters graph graph of [^{18}F]-FPTT.

indicates [^{18}F]-FPTT embedded in the active site of the progesterone receptor (PR). The interactions score data of the drug-receptor complex is presented in Table 2. It is deduced from the data that the FPTT-PR complex formation is mainly done via steric interaction with Moldock score of -129.932. The receptor residues Glu 904 [B], Ser 902 [B], Ser 898 [B], Val 903 [B], Phe 905 [B], Phe 895 [B], Ile 896 [B], Ile 896 [A], Ser 898 [A], Arg 899 [B], Arg 899 [A], Phe 905 [A], Phe 895 [A], Ser 910 [A], Glu 907 [A], Ala 914 [A] and Glu 911 [A] make steric interactions with the radiopharmaceutical (Figure 8). On the other hand, some hydrogen bond (HB) interactions are done between FPTT and the cofactors (Score = -5.787). Therefore, hydrogen bond interactions play a minor role in the FPTT-PR complex formation. Five water molecules and Ser 898 (A and B) residues make hydrogen bond with the title compound (Figure 9). Furthermore, the internal ligand interactions (torsional strain and steric interaction) scores are 12.833 and 60.315, respectively. With regards to both internal and external interactions of the FPTT-PR complex, the total energy score of the system is -96.644. It can be observed from the data presented in Table 3 that the progesterone receptor (PR) residues containing Arg 899 [B], Phe 895 [A], Phe 895 [B], Ser 898 [B], Ser 910 [A], Ile 896 [A], Ser 898 [A], Ile 896 [B], Val 903 [B], Glu 911 [A], Ser 902 [B], Arg 899 [A] and Glu 904 [B] are the major amino acids participating in the ligand-receptor complex formation (Figure 7).

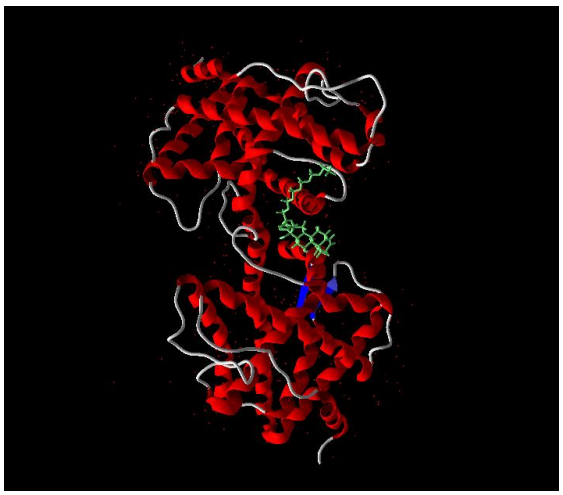

Fig. 7. Ligand [^{18}F]-FPTT embedded in the active site of the progesterone receptor.

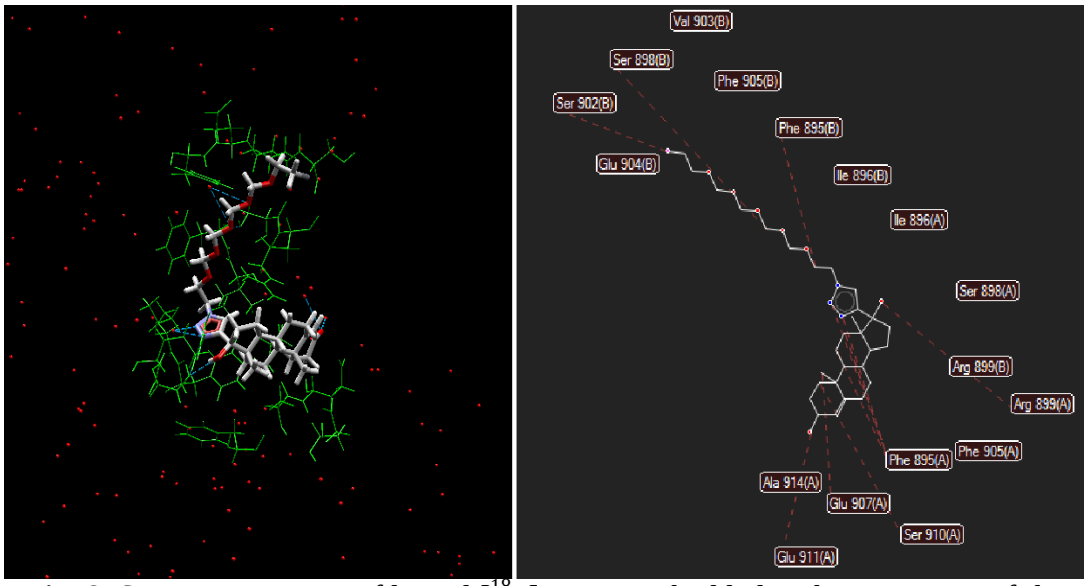

Fig. 8. Steric interactions of ligand [^{18}F]-FPTT embedded in the active site of the progesterone receptor.

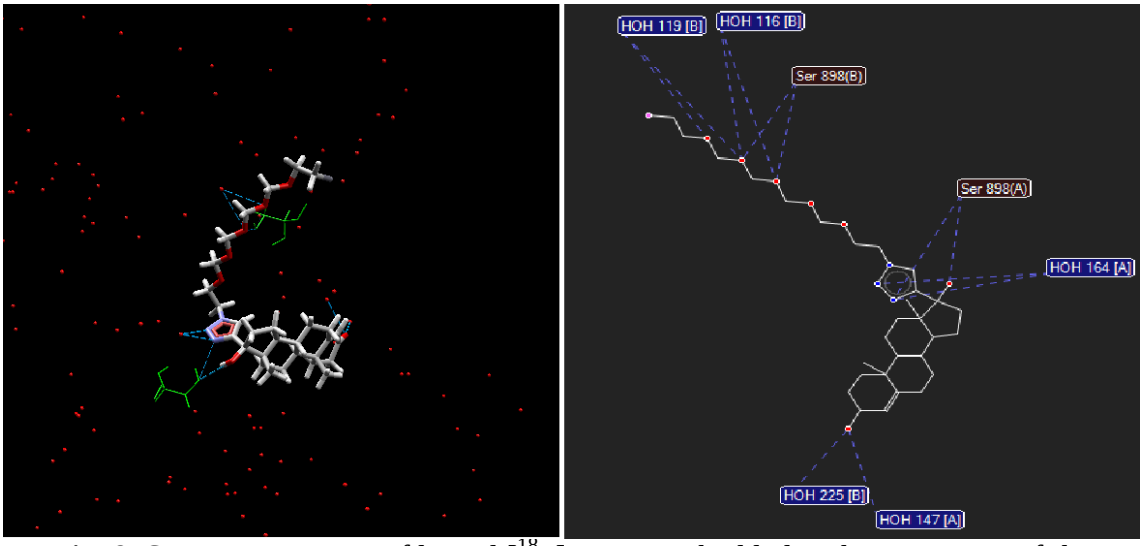

Fig. 9. Steric interactions of ligand [^{18}F]-FPTT embedded in the active site of the progesterone receptor.

Table 2. The ligand-progesterone interactions

	Interactions	**MolDock Score**
Protein-Ligand Interactions	Steric (by PLP)	-129.932
	Steric (by LJ12-6)	-46.237
	Hydrogen bonds	-5.787
	Hydrogen bonds (no directionality)	-9.871
Water-Ligand Interactions		26.672
Internal Ligand Interactions	Torsional strain	12.833
	Steric (by PLP)	-0.430
	Steric (by LJ12-6)	60.315
External and Internal Ligand Interactions	Total Energy	-96.644

Table 3. The participated progesterone residues in ligand-receptor interactions

Residue/HOH	Total energy score
Arg [B] 899	-21.2466
Phe [A] 895	-14.4523
Phe [B] 895	-13.2774
Ser [B] 898	-11.6588
Ser [A] 910	-11.0083
Ile [A] 896	-9.22667
Ser [A] 898	-8.51690
Water (HOH)	-7.09327
Ile [B] 896	-6.91424
Val [B] 903	-6.27488
Glu [A] 911	-6.07751
Ser [B] 902	-5.65716
Arg [A] 899	-5.61858
Glu [B] 904	-5.24722
Water (HOH)	-3.42448
Water (HOH)	-3.19808
Water (HOH)	-2.52345
Ala [A] 914	-2.37140
Glu [A] 907	-2.23884
Water (HOH)	-1.64276
Water (HOH)	-1.33975
Phe [A] 905	-1.03181
Water (HOH)	-0.804795
Water (HOH)	-0.542902
Phe [B] 905	-0.480482
Water (HOH)	1.27167
Water (HOH)	45.9649

The main purpose of the present study is discussing about the electronic properties, stability, reactivity and binding of the title compound to the progesterone receptor (PR). The following results were obtained from our computations:

- The medicinal molecule may be interacted with active reagents into the cell such as free radicals.
- This medicinal compound has a molecular structure with high reactivity.
- It prefers to interact with nucleophile agents or residues.
- It prefers to interact with the residues of a receptor by its oxygen atoms.
- The steric interactions play the main role in the ligand-receptor complex formation.
- The progesterone receptor (PR) residues containing Arg 899 [B], Phe 895 [A], Phe 895 [B], Ser 898 [B], Ser 910 [A], Ile 896 [A], Ser 898 [A], Ile 896 [B], Val 903 [B], Glu 911 [A], Ser 902 [B], Arg 899 [A] and Glu 904 [B] are the major amino acids participating in the ligand-receptor complex formation.

CONFLICT OF INTERESTS

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

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