Revue des Sciences de la Santé (Rev. Sci. Sant.)
ISSN: 3078-6959 (Online); 3078-8226 (Print)
Volume-5 Issue-1, 2026

In Silico Investigation of the Interactions of Piflufolastat F-18 and Flotufolastat F-18 Radiopharmaceuticals with Biological Targets Relevant to Prostate Cancer Diagnosis

Etude in silico des interactions des radiopharmaceutiques Piflufolastat F-18 et Flotufolastat F-18 avec des cibles biologiques pertinentes pour le diagnostic du cancer de la prostate.

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RESUME:

Le cancer de la prostate constitue l'un des principaux problèmes de santé publique chez l'homme à l'échelle mondiale. Le diagnostic précoce et précis demeure un défi majeur, en particulier pour la détection des lésions de faible volume et des récidives précoces. L'imagerie par tomographie par émission de positons (TEP) utilisant des radiopharmaceutiques ciblant l'antigène de membrane spécifique de la prostate (PSMA) a considérablement amélioré la prise en charge diagnostique. Dans cette étude, une approche de modélisation moléculaire in silico a été employée afin d'analyser et de comparer les interactions entre deux radiopharmaceutiques marqués au fluor-18, le Piflufolastat F-18 et le Flotufolastat F-18, et plusieurs cibles biologiques impliquées dans le cancer de la prostate, notamment le récepteur des androgènes (AR), HIF-1α, HER2 et le PSMA. Le docking moléculaire a permis d'évaluer les affinités de liaison et d'identifier les interactions stabilisantes au niveau atomique. Les résultats montrent que les deux radiopharmaceutiques présentent une forte affinité pour le PSMA, avec des énergies de liaison particulièrement favorables, confirmant leur pertinence en imagerie diagnostique. Par ailleurs, le Piflufolastat F-18 est un ligand multi-cible, ce qui peut limiter sa sélectivité, tandis que le Flotufolastat F-18 est très sélectif. Cette étude met en évidence l'intérêt de la modélisation moléculaire comme outil complémentaire pour la compréhension des interactions ligand-récepteur et pour l'optimisation future des radiotraceurs PSMA-ciblés.

Mots clés : Médecine nucléaire, Tomographie par Emission de Positons, PSMA, radiopharmaceutiques, docking moléculaire.

ABSTRACT :

Prostate cancer is one of the major public health concerns among men worldwide. Early and accurate diagnosis remains a significant challenge, particularly for the detection of small-volume lesions and early recurrences. Positron emission tomography (PET) imaging using radiopharmaceuticals targeting the Prostate-Specific Membrane Antigen (PSMA) has considerably improved diagnostic management. In this study, an in silico molecular modeling approach was employed to analyze and compare the interactions between two fluorine-18–labeled radiopharmaceuticals, Piflufolastat F-18 and Flotufolastat F-18, and several biological targets involved in prostate cancer, including the androgen receptor (AR), HIF-1α, HER2, and PSMA. Molecular docking was used to evaluate binding affinities and to identify stabilizing interactions at the atomic level. The results show that both radiopharmaceuticals exhibit strong affinity for PSMA, with particularly favorable binding energies, confirming their relevance in diagnostic imaging. Furthermore, Piflufolastat F-18 behaves as a multi-target ligand, which may reduce its selectivity, whereas Flotufolastat F-18 appears highly selective This study highlights the value of molecular modeling as a complementary tool for understanding ligand–receptor interactions and for the future optimization of PSMA-targeted radiotracers.

Keywords : Nuclear medicine, Positron Emission Tomography, PSMA, radiopharmaceuticals, molecular docking.

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DOI: *https://doi.org/10.71004/rss.026.v5.i1.50*
Journal Website: *www.rss-istm.net*
Reçu le 15/12/2025 ; Révisé le 12/01/2026 ; Accepté le 02/02/2026

Publié Par: Institut Supérieur des Techniques Médicales de Kinshasa (ISTM/KIN)

I. INTRODUCTION

Prostate cancer currently represents one of the major challenges in oncology, because of its high prevalence and the complexity of its diagnosis and therapeutic management [1]. It is the most frequently diagnosed cancer in men and one of the leading causes of cancer-related mortality worldwide. It's often slow and asymptomatic progression in the early stages makes the development of sensitive and specific diagnostic strategies essential, particularly those capable of detecting primary and metastatic lesions at an early stage [1].

In this context, nuclear medicine, and more specifically the use of targeted radiopharmaceuticals, has profoundly transformed oncological imaging [2-5]. Radiopharmaceutical therapy (Radiopharmaceutical Therapy, RPT), also referred to as molecular radiotherapy or a theranostic approach, is based on the administration of radioligands capable of selectively binding to tumor cells or accumulating in them through specific physiological mechanisms [5]. These agents enable both non-invasive visualization of tumor biodistribution and, in some cases, targeted therapeutic action with limited systemic toxicity.

Among the biological targets exploited in prostate cancer, the Prostate-Specific Membrane Antigen (PSMA) occupies a central role due to its strong overexpression in prostate tumor cells, including metastatic forms and those resistant to conventional treatments [6]. This characteristic has led to the development of fluorine-18 (^{18}F)-labeled radiopharmaceuticals widely used in positron emission tomography (PET), particularly Piflufolastat F-18 (^{18}F-DCFPyL) and Flotufolastat F-18 (^{18}F-RhPSMA-7.3) [6,7]. These next-generation radiotracers exhibit high affinity for PSMA, good metabolic stability, and favorable biodistribution, enabling high-resolution imaging of prostate lesions [8].

Although these radiopharmaceuticals are designed to preferentially target PSMA, the possibility of interactions with other biological targets involved in tumor progression cannot be excluded, such as human androgen receptor [9], human epidermal growth factor receptor 2 [10], or proteins associated with angiogenesis [9]. The exploration of secondary targets is of particular interest, especially for understanding the molecular mechanisms of ligand–receptor recognition and for addressing biological resistance phenomena [11].

In this context, in silico molecular modeling appears to be a powerful tool for studying, at the atomic level, the interactions between radiopharmaceuticals and their biological targets. Computer-aided design approaches, including molecular docking and energetic analysis of the complexes formed, make it possible to predict binding modes, identify stabilizing interactions (hydrogen bonds, hydrophobic, electrostatic, and π–π interactions), and evaluate the molecular selectivity of ligands [12,13].

The present study therefore aims to model and compare the molecular interactions of Piflufolastat F-18 and Flotufolastat F-18 with several key biological targets associated with prostate cancer diagnosis, using PSMA as the reference target. This comparative approach seeks to provide a better understanding of the binding mechanisms of these radiopharmaceuticals, their potential multi-target activity, and their molecular performance, thereby contributing to the optimization of PSMA-targeted imaging agents and the future development of more effective radiotracers. The results of this research could also pave the way for polypharmacology studies of the radioligands under investigation [11].

II. MATERIALS AND METHODS

II.1. Selection and preparation of ligands

Piflufolastat F-18 is a radioligand that specifically targets the Prostate-Specific Membrane Antigen (PSMA), a transmembrane glycoprotein overexpressed in the majority of prostate tumor cells.

From a structural standpoint, Piflufolastat F-18 offers several possibilities for interactions, including hydrogen bonding, halogen bonding, chalcogen bonding, and interactions involving π-electrons thanks to its aromatic ring [14]. Figure 1 shows the chemical structure of Piflufolastat F-18.

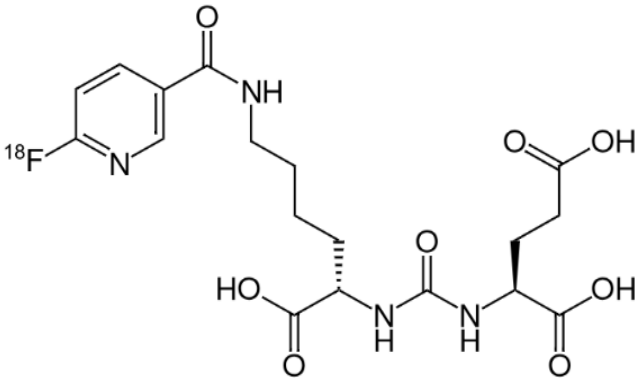

Figure 1. 2D chemical structure of Piflufolastat F-18

Flotufolastat F-18 is a more recent generation of PSMA-targeted radiopharmaceuticals, developed to improve biodistribution and reduce background interference observed with earlier generations. Its chemical structure, displayed in

DOI: https://doi.org/10.71004/rss.026.v5.i1.50
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Revue des Sciences de la Santé (Rev. Sci. Sant.)
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Volume-5 Issue-1, 2026

Figure 2, allows multiple electrostatic interactions as well as interactions involving π-electrons

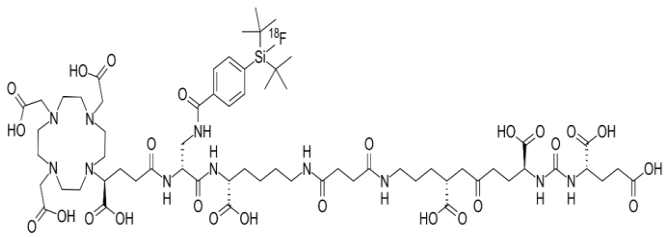


Figure 2. 2D chemical structure of Flotufolastat F-18

The 3D chemical structures of the two radiopharmaceuticals used were obtained from the PubChem database and subsequently geometrically optimized using Chem3D software. The SMILES codes of the two radioligands are listed in Table 1.

Table 1. SMILES codes of Flotufolastat F-18 and Piflufolastat F-18

Flotufolastat F-18
CC(C)(C)(Si](C1=CC=C(C=C1)C(=O)NC[C@H](C(=O)N[C@H](CCCCNC(=O)CCC(=O)NCCC[C@H](C(=O)O)NC(=O)CC[C@@H](C(=O)O)NC(=O)N[C@@H](CCC(=O)O)C(=O)O)C(=O)O)NC(=O)CC[C@@H](C(=O)O)N2CCN(CCN(CCN(CC2)CC(=O)O)CC(=O)O)CC(=O)O)(C(C)(C)C)(18F]
Piflufolastat F-18
C1=CC(=NC=C1C(=O)NCCCC[C@@H](C(=O)O)NC(=O)N[C@@H](CCC(=O)O)C(=O)O)[18F]

II.2. Selection and preparation of biological targets

The androgen receptor (AR) is a nuclear transcription factor activated by androgens (testosterone or dihydrotestosterone) and plays an essential role in the differentiation and survival of prostate epithelial cells. It is widely used in research as a primary target for evaluating the anticancer potential of compounds [9].

Hypoxia-inducible factor 1-alpha (HIF-1α) is a subunit of the HIF-1 complex. In the context of prostate cancer diagnosis, its high expression may indicate a more aggressive or resistant form of the disease, which justifies its inclusion in molecular target analyses [9].

Human epidermal growth factor receptor 2 (HER2) is a tyrosine kinase receptor belonging to the epidermal growth factor (EGF) family. Although its role is well documented in breast cancer, it has also been observed in oral and prostate cancers in the form of overexpression or activation, particularly in aggressive tumor subpopulations or those resistant to hormonal therapy [10, 15].

The Prostate-Specific Membrane Antigen (PSMA) is a membrane glycoprotein highly expressed in the majority of prostate adenocarcinomas (up to 95%) and weakly expressed in normal prostate tissue or other non-prostatic tissues. It constitutes a primary target for fluorine-18–labeled radiopharmaceuticals (such as the probes investigated in this study) [6].

Protein structures were downloaded from the Protein Data Bank (PDB). Each protein underwent a preparation process consisting of cleaning the structures by removing water molecules and non-essential heteroatoms, defining the active site based on the co-crystallized ligand, and performing energy minimization to obtain stable conformations free of steric constraints. Figure 3 shows the structures of the four targets used along with their PDB codes.

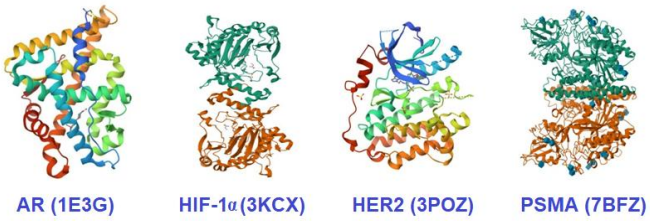


Figure 3. Structures of the four targets used and their PDB codes

II.3. Molecular docking

AutoDock Vina and PyRx [16]. were used to generate the bioactive binding poses of the ligand set within the active sites of the biological targets.

The binding pocket of the target protein was defined using a grid box of 50 × 50 × 50 Å³, generated with AutoGrid and centered at coordinates x = 43.730, y = 12.702, and z = 59.371.

Binding affinities were expressed in terms of binding free energy (ΔG, kcal/mol). Ligand–protein interactions were analyzed and visualized using Discovery Studio Visualizer, enabling the identification of hydrogen bonds, hydrophobic interactions, electrostatic interactions, and van der Waals interactions.

III. RESULTS AND DISCUSSION

III.1. Binding energy

DOI: https://doi.org/10.71004/rss.026.v5.i1.50
Journal Website: www.rss-istm.net
Reçu le 15/12/2025 ; Révisé le 12/01/2026 ; Accepté le 02/02/2026
Publié Par: Institut Supérieur des Techniques Médicales de Kinshasa (ISTM/KIN)

The binding affinities of Flotufolastat F-18 and Piflufolastat F-18 toward the selected targets were evaluated by calculating the binding free energies (ΔG), expressed in kcal/mol. These values reflect the thermodynamic stability of the ligand–macromolecule complexes. More negative ΔG values indicate stronger and more stable binding, corresponding to more favorable interactions. The binding energies obtained for each complex are summarized in Figure 4.

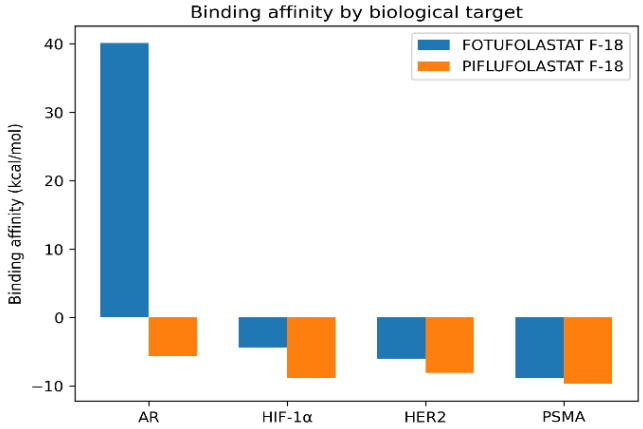


Figure 4. Binding affinity by biological target with the two radioligands

The binding energy values obtained reveal notable variations between the two radiotracers, indicating distinct affinity profiles depending on the target. Binding energies ranged from +40.1 to −8.9 kcal/mol and from −5.7 to −9.7 kcal/mol for Flotufolastat F-18 and Piflufolastat F-18, respectively.

First, these results indicate that both radiopharmaceuticals preferentially bind to the PSMA target, providing an in silico validation of previously reported experimental findings.

Second, Piflufolastat F-18 showed stronger interactions with all four macromolecules compared with Flotufolastat F-18, which interacted with only three targets; no affinity was observed for the AR receptor (+40.1 kcal/mol).

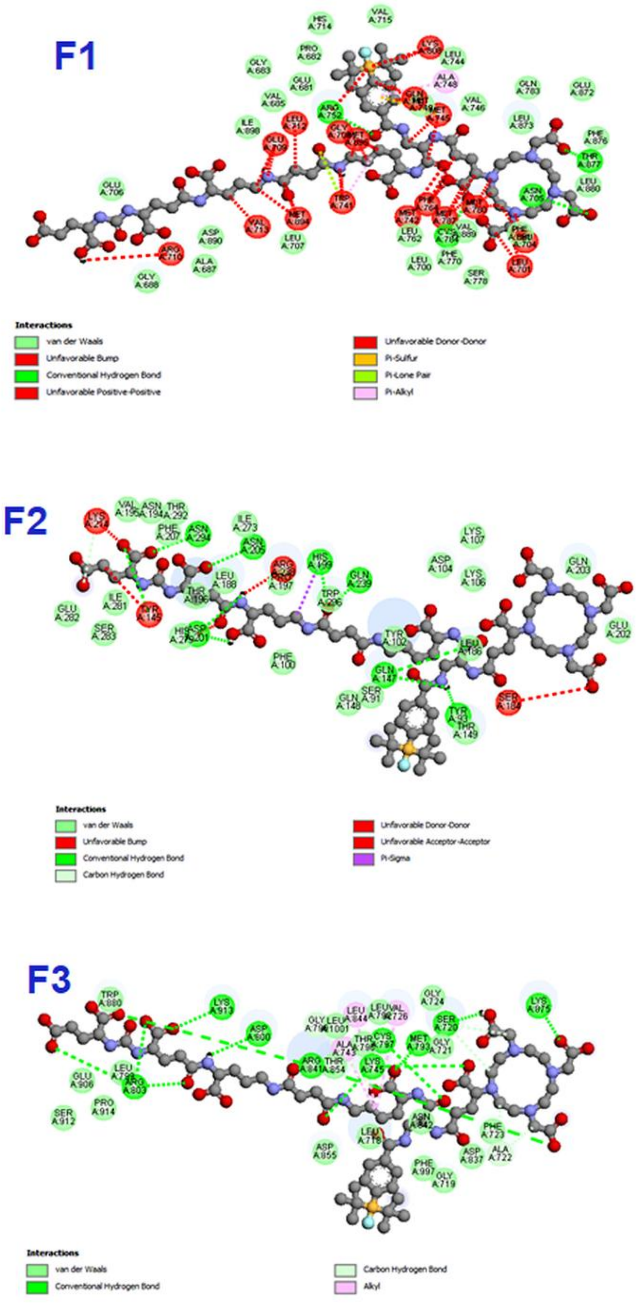
Third, beyond the preferred target PSMA, Piflufolastat F-18 exhibited the highest affinity for HIF-1α (−8.9 kcal/mol), followed by HER2 (−8.1 kcal/mol), and finally AR (−5.7 kcal/mol). In contrast, Flotufolastat F-18 interacted with only two secondary targets after PSMA, showing moderate binding affinity for HER2 (−6.0 kcal/mol) and weaker affinity for HIF-1α (−4.4 kcal/mol).

III.2. Geometry of the formed complexes

The geometries of the complexes obtained between the four targets and Flotufolastat F-18 (F1–F4) are presented in Figure 5, whereas those obtained between Piflufolastat F-18 and the four targets (P1–P4) are shown in Figure 6.

- **Flotufolastat–AR (F1): +40.1 kcal/mol**

Although Flotufolastat forms four hydrogen bonds with amino acid residues ARG752, CYS784, ASN705, and THR877, these contacts are insufficient to stabilize the ligand within the receptor pocket. The highly positive energy indicates poor overall fitting; the ligand geometry appears incompatible with the cavity, resulting in steric repulsion or unfavorable orientation that counteracts favorable interactions. Consequently, the resulting complex is unstable.



DOI: https://doi.org/10.71004/rss.026.v5.i1.50
Journal Website: www.rss-istm.net
Reçu le 15/12/2025 ; Révisé le 12/01/2026 ; Accepté le 02/02/2026
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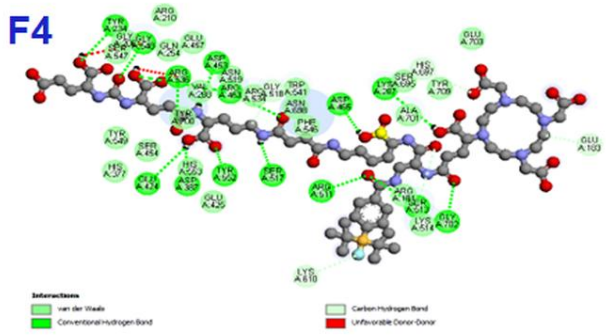


Figure 5. Complexes between Flotufolastat F-18 and biological targets

- **Flotufolastat–HIF-1α (F2): −4.4 kcal/mol**

The eight hydrogen bonds detected indicate a real interaction between the ligand and the HIF-1α binding pocket. The complex is also characterized by several non-conventional hydrogen bonds, multiple van der Waals (vdW) interactions, and a single hydrophobic interaction with residue HIS199. However, the affinity remains relatively weak, suggesting that although several contacts are formed, they likely lack optimal orientation or sufficient hydrophobic reinforcement around the ligand core. The complex is therefore stabilized, but only moderately.

- **Flotufolastat–HER2 (F3): −6.0 kcal/mol**

With several conventional and non-conventional hydrogen bonds, a number of vdW interactions, and three alkyl interactions, Flotufolastat demonstrates a good ability to establish both polar and nonpolar contacts with HER2. These interactions contribute to ligand stabilization, although the energy value suggests only moderate binding. It is likely that the environment surrounding the ligand does not provide perfect complementarity, limiting interaction strength despite the relatively high number of hydrogen bonds.

- **Flotufolastat–PSMA (F4): −8.9 kcal/mol**

This complex is characterized by fourteen conventional hydrogen bonds, nearly six non-conventional hydrogen bonds, and several vdW interactions. The radioligand benefits from very strong anchoring within the PSMA pocket. Numerous polar and charged residues create a coherent and well-distributed interaction network around the ligand. This accumulation of hydrogen bonds results in significantly stronger affinity than observed for other targets, despite the absence of π–π stacking or π-alkyl interactions.

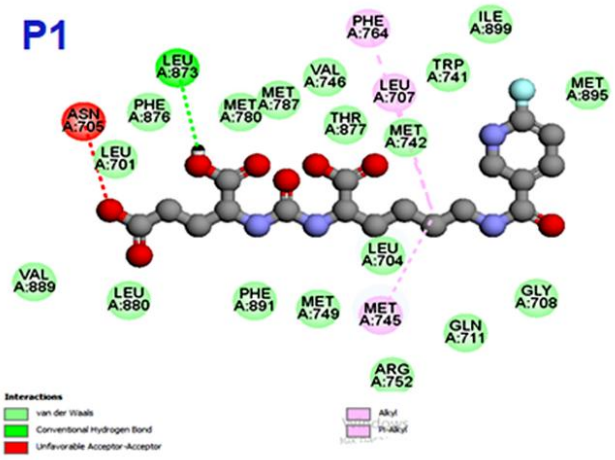
Let us turn next to the interactions obtained between Piflufolastat F-18 and the four biological targets (Figure 6).

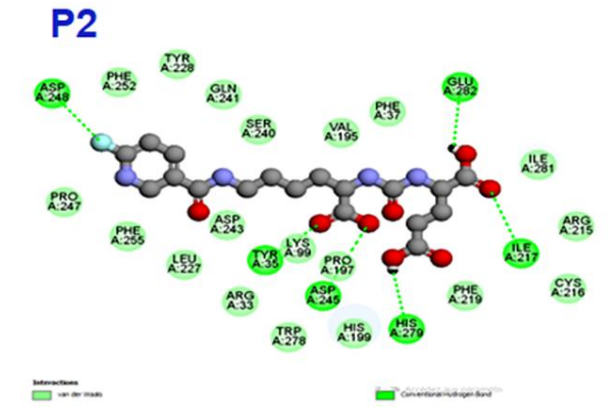
- **Piflufolastat–AR (P1): −5.7 kcal/mol**

This complex is characterized by a single conventional hydrogen bond involving residue LEU873, indicating relatively limited anchoring. The slightly negative energy suggests that the ligand adopts an acceptable orientation in the binding pocket, probably supported by a few hydrophobic contacts. However, the interaction remains weak, explaining the modest affinity observed for AR.

- **Piflufolastat–HIF-1α (P2): −8.9 kcal/mol**

This complex is mainly stabilized by conventional hydrogen bonds and several vdW interactions. The six hydrogen bonds provide a well-distributed set of anchoring points. Combined with ligand positioning in a favorably polarized region, these interactions allow strong stabilization of the complex. The high affinity obtained suggests that the ligand is well adapted to the geometry of the HIF-1α binding pocket.





DOI: https://doi.org/10.71004/rss.026.v5.i1.50
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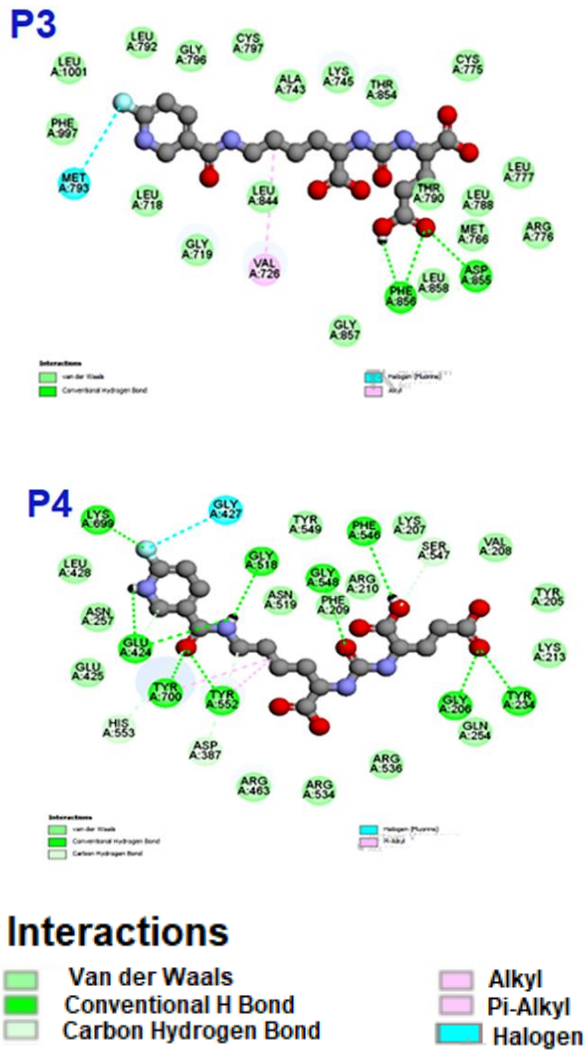

Figure 6. Complexes between Piflufolastat F-18 and biological targets

- **Piflufolastat–HER2 (P3): −8.1 kcal/mol**

The P3 complex formed with HER2 is characterized by strong interaction energy and stabilization through four types of interactions: hydrogen bonds, vdW interactions, halogen bonding, and alkyl–alkyl interactions. The halogen bond contributes significantly to stabilization. It is also noteworthy that two bifurcated hydrogen bonds are formed with residues PHE856 and ASP855 on the same oxygen atom, involving both lone electron pairs in anti and syn orientations [17].

- **Piflufolastat–PSMA (P4): −9.7 kcal/mol**

This complex, which exhibits the most favorable interaction energy among all complexes, is stabilized by the same types of interactions observed in the previous complex. In addition to conventional hydrogen bonds, several non-conventional hydrogen bonds contribute to stabilization. As in P3, the P4 complex is also stabilized by a halogen bond and two π-alkyl interactions with residues TYR700 and TYR552. Two oxygen atoms participate in bifurcated hydrogen bonds: one with residues TYR700 and TYR552, and the other with residues GLY206 and TYR234.

The results obtained in this study confirm that PSMA is the preferred biological target of both Piflufolastat F-18 and Flotufolastat F-18, consistent with their clinical use in PET imaging of prostate cancer. The strong affinity observed is mainly due to structural complementarity between the ligands and the PSMA active site, as well as the multiplicity of stabilizing non-covalent interactions, particularly hydrogen bonds, halogen bonding, and vdW interactions.

When examining other targets in the panel, Piflufolastat F-18 shows higher affinity than Flotufolastat F-18 for several proteins, suggesting that it may interact more readily with additional proteins expressed in certain tumor contexts.

Flotufolastat F-18, on the other hand, exhibits weaker affinity for secondary targets, which may be interpreted as improved selectivity toward PSMA. The highly positive energy obtained for Flotufolastat F-18 with the AR receptor is likely due to poor geometric fitting within the binding pocket. Thus, although both molecules function effectively as PSMA tracers, their overall interaction profiles differ.

Overall, Piflufolastat F-18 appears to be the more versatile ligand, showing strong binding to PSMA and other proteins associated with tumor mechanisms. This has several advantages because it can target multiple tumor mechanisms and is useful for understanding biodistribution or off-target effects. However, binding to multiple targets can reduce selectivity and may generate background noise in imaging or side effects in pharmacology [11]. As for Flotufolastat F-18, it appears slightly more selective. These differences may guide future experimental validation and tracer selection depending on the diagnostic objective.

IV. CONCLUSION

This study explored, through an in silico molecular modeling approach, the interactions between two recently developed radiopharmaceuticals, Flotufolastat F-18 and Piflufolastat F-18, and several biological targets involved in prostate cancer diagnosis. Docking simulations revealed variable affinities depending on the targets, with a marked preference for PSMA, consistent with clinical experimental observations.

The results showed that Piflufolastat F-18 exhibits more favorable binding energies and is capable of interacting with additional targets beyond PSMA, whereas Flotufolastat F-18

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appears highly selective and interacts with only three biological targets, completely avoiding the AR receptor.

Although the relatively large structure of Flotufolastat F-18 allows multiple interactions with targets, these interactions are generally weaker due to steric constraints and unfavorable contacts compared with those established by Piflufolastat F-18.

This study confirms the value of molecular modeling as a complementary and predictive tool to experimental data, helping to elucidate ligand–receptor recognition mechanisms and guide the rational design of new PSMA-targeted diagnostic agents.

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DOI: https://doi.org/10.71004/rss.026.v5.i1.50
Journal Website: www.rss-istm.net
Reçu le 15/12/2025 ; Révisé le 12/01/2026 ; Accepté le 02/02/2026
Publié Par: Institut Supérieur des Techniques Médicales de Kinshasa (ISTM/KIN)

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DOI: *https://doi.org/10.71004/rss.026.v5.i1.50*
Journal Website: ***www.rss-istm.net***
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