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Theoretical evaluation losartan derivatives as ^{18}F-labeled radiopharmaceutical candidates for cancer diagnosis

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The losartan and its fluoro n-ethoxy-methyl-triazole losartan derivatives (FEM, n=0-3) were studied as potential candidates of ^{18}F-labeled radiopharmaceuticals. Each derivate is obtained by the reaction of a terminal alkyne with a substituted azide in presence of Cu(I) catalyst. The stability and association energy of four FEM to the AT1 receptor was evaluated. The Density Functional Theory with the base 6-31G(2d, 2p) was used to evaluate radiotracers stability. In order to determine the functional that provides the best description of FEM, the experimental X-ray diffraction structure of losartan potassium was compared with calculated using different functionals, been the M06-2X the most suitable. The vibrational frequencies of the FEM structures and the bond dissociation energy (BDE) were also calculated. In both, vacuum and water calculations, the stability of compounds decreased following the order: FTEMT(n = 3)>FDEMTL(n = 2)>FMTL (n = 0) > FEMTL(n = 1). When water as implicit solvent was considered in the model, the difference of BDE was only 6kJ/mol. The electron density analysis of atoms in molecules was performed in order to characterize the intramolecular interactions in each FEM derivative. There was an increase of van der Waals type interactions with the increase of the length of the chain, being the FDEMTL the only one with two hydrogen bonds. Molecular Docking study was performed to evaluate the interactions of the four FEM with the receptor. All evaluated derivatives have similar interaction energy with the receptor than losartan. The FMTL derivative can be considered the best candidate as radiotracer.

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