Understanding the Enantioselectivity of Fenamiphos as Endocrine Disrupter

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Introduction

Endocrine disrupting chemicals (EDC) are compounds that alter the normal functioning of the endocrine system of humans. Many chemicals that have been identified as endocrine disruptors are pesticides. They can bind and active various hormone receptors. Peroxisome proliferator activated receptors (PPARγ) is one of the nuclear receptor family. In recent years chiral pesticides have attracted great attention and there is an urgent need to develop computational methods to determine the stereoselective bioactivity, and environmental behavior of these. The aim of the current study was to investigate the different interaction behavior of fenamiphos enantiomers with PPARγ by molecular docking and molecular dynamic simulation.

fig. 1. Structure of (R,S)fenamiphos

Method

The docking calculation was conducted with the Autodock software4.2 on the ligand-binding domain (LBD) of PPARγ (PDB ID:3VOS). The docking calculation utilized the Lamarckian Genetic Algorithm. The lowest free-binding energy conformation of each complex was selected as the initial conformation for the molecular dynamics (MD) studies. All MD studies were carried out using GROMACS4.5.6 and GROMOS96 43a1 force field. The complex was located in a cubic box and filled with extended simple-point charge (SPC) water molecules with the periodic boundary conditions. The solvated systems were neutralised by adding 6 sodium ions. Energy minimisation was performed using the steepest descent method. Next, the system was equilibrated for 200 ps at a temperature of 300 K by Nose-Hoover-thermostat and a 200 ps NPT equilibration was performed using the Parrinello-Rahman barostat to maintain a pressure of 1.0 bar. Finally, a 14 ns MD simulation was carried out at 1.0 bar and

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300 K. The particle mesh Ewald (PME) method for long-range electrostatics, a 0.9 nm cutoff for Coulomb interactions and 1.4 nm for the van der Waals interactions were used.

Result and Discussion

In this study, the binding mode of (R, S) fenamiphos on the ligand-binding domain (LBD) of PPARγ was examined. The docking results show in Table1.

Table 1. Docking parameters and amino acide residues near components

component	ΔG (kcal.mol^{-1})	Residues
R-Fenamiphos	-7.0	PRO227, PHE226, LEU228, ARG288, ALA292, GLU295, ILE328, MET329, SER332, LEU333, GLU343
S-Fenamiphos	-6.46	ILE281, PHE282, CYS285, ILE341, LEU356, PHE360, PHE363, HIS449

The analysis of root mean square fluctuations (*RMSF*) of backbone atoms of PPARγ in the absence and presence of ligands can be used as a reference for evaluating the local protein mobility (Fig. 2). H12 (470-476) of PPARγ have less fluctuation in presents of R-fenamiphos while residues number339-347 and 355-362 have less fluctuation in presents of S-fenamiphos. This results show stereoselective bioactivity of this pesticide.

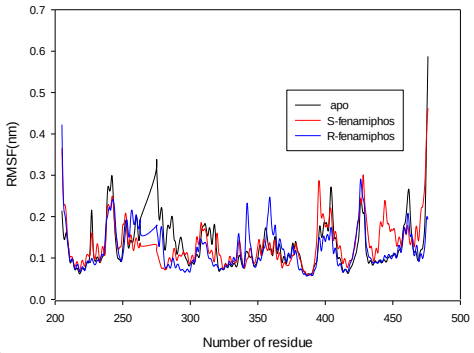

Fig. 2. *RMSF* of backbone atom of PPAR in absence and in presents of S-fenamiphos (red) and R-fenamiphos(blue)

Conclusion

The molecular docking and molecular dynamic simulation are competent approach for predicting the enantioselective interaction between Chiral fenamiphos and PPARγ. Chiral fenamiphos showed significant enantioselectivity in interaction with PPARγ and the order of their potential was R>S.

References

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