New insights on the molecular recognition properties of insecticides through various molecular modeling approaches

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Introduction

- Nicotinic Acetylcholine Receptors (nAChRs) : involved in many physiological processes in the nervous system [1]

Important targets in modern crop protection

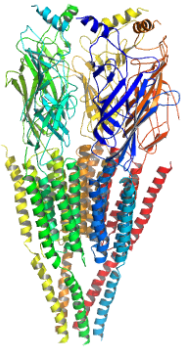
- Neonicotinoids : the most important and the fastest growing class of insecticides (efficiency, selectivity) [2]

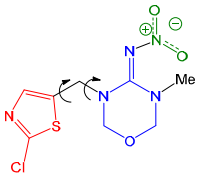
But : adverse effects on beneficial insect species such as honey bees

Quest for new compounds more selective, specific of pests and devoid of adverse effects

- **Thiamethoxam (THA)**: a neonicotinoid designed by Syngenta in 1998, banned of the European market in 2013 [3]
- *Aplysia californica* Acetylcholine binding protein (*Ac*-AChBP) : a recognized surrogate of the extra-cellular domain of insects nAChRs [4]

The rational design of nAChRs agonists requires a deep characterization of the structure and interactions in the receptor binding site





Objectives:

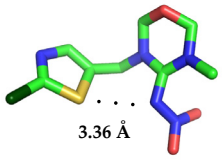
- To elucidate the binding mode of **THA** with *Ac*-AChBP
- To quantify the interactions of **THA** with *Ac*-AChBP and determine the key interacting residues
- To investigate the potential role of a chalcogen bonding interaction in the binding process

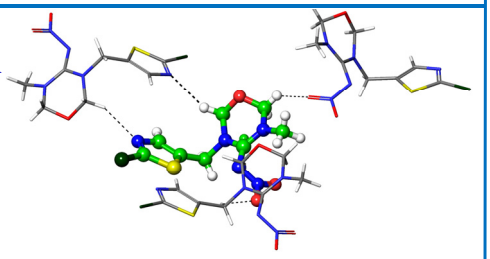
Methods

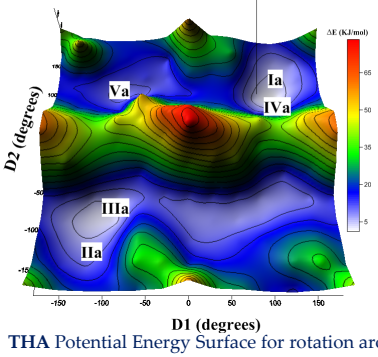
- **Conformational analysis** of **THA** using quantum chemistry methods (QM) in the isolated state and different solvent models **(M06-2X/6-311G(d))**
- **Docking** (Flexible) of **THA** with *Ac*-AChBP **(Glide 6.3, Prime 3.6)**
- **Molecular dynamics (MD)** of **THA-*Ac*-AChBP complexes (Desmond 3.8, CHARMM27, 40 ns)**
- **QM/QM' calculations of THA-*Ac*-AChBP complexes (Gaussian09, ONIOM)**

Results and discussion

I. Structural features of THA

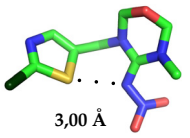




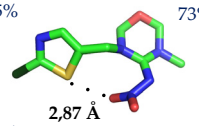


THA Potential Energy Surface for rotation around D1 (2-3-6-7) and D2 (3-6-7-12) dihedral angles

Gas phase **Water**



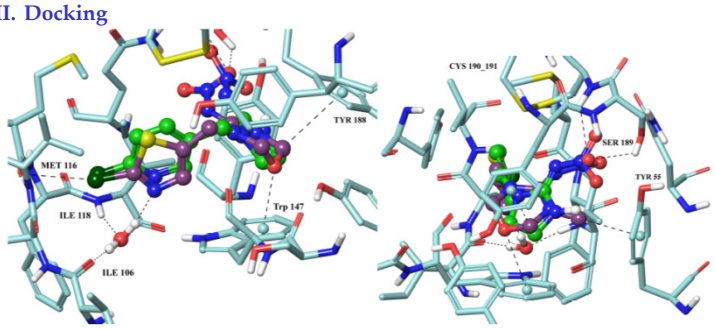
65% 73%



16% 17%

Main conformers of **THA** in the gas phase and water.

II. Docking

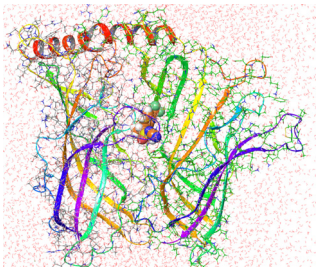


Superposition of the best pose of **THA** on the imidacloprid –*Ac*-AChBP complex crystallographic structure (3C79) according to two orientations

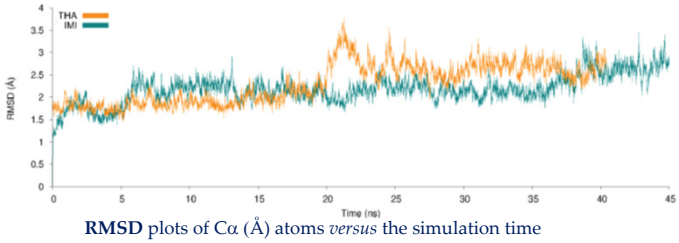
III. THA-*Ac*-AChBP MD simulations

III.1 Definition of the model system

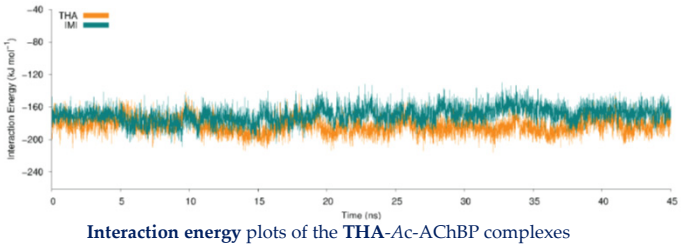
The Model system: THA-*Ac*-AChBP complex (dimer of two subunits) solvated wih water (TIP3P model)



III.2 MD simulations analyses

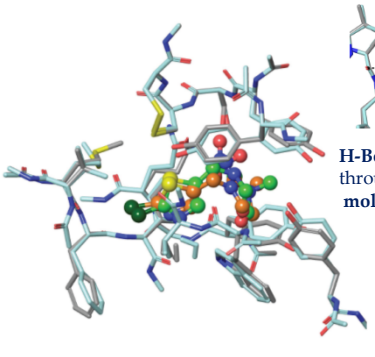


RMSD plots of Cα (Å) atoms *versus* the simulation time

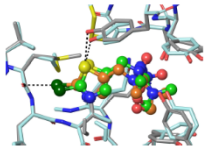


Interaction energy plots of the **THA**-*Ac*-AChBP complexes

IV. QM/QM' calculations

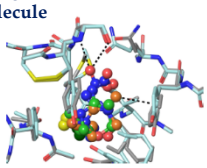


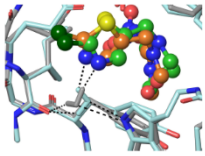
Model System
(ONIOM2 M062X/6-311G(d):PM6)



Halogen and **chalcogen** bonding (Met116, Tyr195)

H-Bond network mediated through a **conserved water molecule**





CH···π H-bonding (Tyr55, Tyr188)
OH···O (Ser189) and **NH···O** (Cys190)

Key components of the binding interactions (**SFX RS** stereoisomer)

Conclusion

- **Elucidation of the mode of action of THA with** *Ac*-AChBP
- **Significant contribution of weak intermolecular interactions** (chalcogen and halogen bonding, CH…π H-bonding)

Work in progress

- **Application of the same strategy to other nAChRs agonists acting as insecticides**
- **Comparison of the binding site properties (structures, energies) of the various systems.**
- **Investigation of the selectivity of the various compounds (pests with respect to non target species like honey bees)**

References

[1] P. Rucktooa, A.B. Smit, T.K. Sixma; Biochem. Pharmacol. **2009**, 78, 777-787.

[2] M. Jeschke, R. Nauen, M. Edmund Beck; Angew. Chem. Int. Ed. **2013**, 52, 9464-9485.

[3] G.B. Waston, M.R. Loso, J.M. Babock, J.M. Hasler, T.J. Letherer, C.D. Young, Y. Zhu, J.E. Casida, T.C. Sparks, Insect. Biochem. Molec. Biol. **2011**, 41, 432-439.

[4] A.B. Smit, K. Brejc, N. Syed, T. K. Sixma, Ann. N. Y. Acad. Sci. **2003**, 998, 81-92.