

Molecular Modeling, SAR and *in silico* Toxicological Studies of Squalene Synthase Inhibitors, a promising target against Atherosclerosis

Esthefanie C. Ribeiro (IC)¹, Ilídio F. Afonso (PG)², Helena C. Castro (PQ)³, Carlos R. Rodrigues (PQ)², Monique A. de Brito (PQ)^{1*} (moniquebrito@vm.uff.br)

¹ Lab. de Química Medicinal Computacional, Faculdade de Farmácia, UFF. ² ModMolQSAR, Faculdade de Farmácia, UFRJ. ³ LaBioEMol, Instituto de Biologia, UFF.

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Introduction

LDL cholesterol when found in excess in human body is responsible for accumulation of arteriosclerosis deposits in blood vessels. Hyperlipidemias are metabolic changes that occur when levels of circulating lipids are elevated in the bloodstream. Atherosclerosis is a disease caused by the accumulation of atheromatous plaques in blood vessels. Squalene synthase catalyzes the biosynthesis of squalene, an important precursor of cholesterol.¹

Several inhibitors of squalene synthase have been reported, among them the 4,1-benzoxazepine derivatives, that showed a potent inhibition of this enzyme and therefore the synthesis of cholesterol, making it the subject of considerable interest.²

In this study, we decided to investigate the Structure-Activity Relationship (SAR) for the 17 inhibitors using descriptors came from molecular modeling calculations and also to access their pharmacokinetic and toxicological parameters.

Results and Discussion

The 4,1-benzoxazepine derivatives² (Figure 1), with the activities ranging from 15 nM to 471 nM, were constructed and minimized using Spartan Pro (Wavefunction Inc. Irvine, CA, 2000).

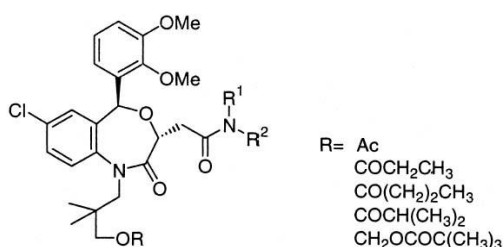


Figure 1. Structural profile of 4,1-benzoxazepine derivatives.

We have calculated electronic descriptors such as dipole moment (μ), and energies of HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital); and structural properties like molecular weight (M.W.),

area, volume, the number of atoms acceptors of hydrogen bond and the number of atoms donors of hydrogen bond. Our final goal was relate those properties with the activities of the compounds (IC_{50}).

Besides, pharmacokinetics and toxicological parameters was obtained with Osiris® Property Explorer (Actelion Pharmaceuticals Ltd.).

Our studies showed that structural properties, like the size of the molecules, were more correlated with activity, especially with **3a** and **3f**, the most active molecules ($IC_{50}=15$ nM) (Table 1).

Table 1. Structural properties related to the activities.

#	M.W. (g/mol)	Area (Å ²)	Volum (Å ³)	IC ₅₀ (nM)
3a	520,97	504,29	546,5	15
3f	534,99	537,27	569,69	15

The compounds showed good theoretical toxicity results, like mutagenic, tumorigenic, irritant and reproductive effects.

It is important to note that the compound **3f** had *drug-likeness* value, an important result.

Conclusion

A SAR, molecular modeling and *in silico* toxicological study were done with 17 inhibitors of squalene synthase.

The best relationships were found with structural descriptors like area, volume and molecular weight, and both of the two most active compounds had great results.

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