In silico insights towards mPGES-1 inhibitors mechanism of action

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Introduction

The microsomal prostaglandin E synthase I (mPGES-1) is the last enzyme responsible for the synthesis of PGE_2, the main prostanoid involved in the inflammatory response, and for that reason it is considered a promising target for the development of anti-inflammatory and fever reducing drugs.[1] Previous virtual screening studies led to the acquisition of a series of molecules (Figure 1) which reduces the febrile response in rats.[2,3,4] However, it has not been possible to confirm the molecules mechanism of action (competitive/ uncompetitive /noncompetitive). In order to give a molecular perspective to ongoing in vitro studies, pharmacophore and chemical similarity studies were carried out.

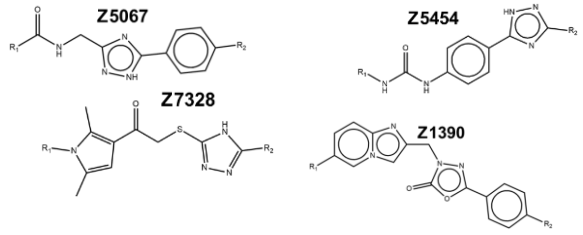

Figure 1. General structure of molecules with fever reducing activity, selected by virtual screening

Results and Discussion

Previous phenotypic assays have shown that the selected molecules significantly reduce ($P < 0.05$) fever caused by injection of LPS (50µg/kg, i.p.) (Table 1). However, this type of biological evaluation does not provide data on the interaction mode of the molecules with their macromolecular target. This information is crucial to elucidate the structure-activity relationships (SAR) that would guide the development of improved inhibitors.

mPGES-1 substrate (PGH_2) binds to a site different from the one in which the cofactor (glutathione-GSH) binds. Thus, molecules chemically similar to PGH_2 shall behave as competitive inhibitors, whereas those similar to GSH do not (non-competitive inhibitors). In order to assess this hypothesis, the morphological similarity (SIM) between the inhibitors and PGH_2/GSH was calculated through the SURFLEX-SIM software, using standard parameters (Table 2). This strategy suggests that bioactive molecules are competitive inhibitors.

Although chemical similarity to the substrate/cofactor gives some hints on the inhibition mechanism, what really defines the binding location is the interactions of pharmacophoric moieties towards the macromolecule.

Table 1. Effect (1 mg/kg) of selected molecules over the temperature shift, measured by the area under the curve (AUC), after LPS stimuli.

Mol_ID	AUC	Mol_ID	AUC
Control	8,0	7328	5,9
5454	3,0	5067	3,1
1390	2,7	----	----

Table 2. Morphological similarity of bioactive molecules towards PGH_2 and GSH

	5454	1390	5067	7328
SIM-PGH_2	6,15	5,64	5,81	6,03
SIM-GSH	4,92	4,76	5,12	5,43

In order to investigate this matter, the bioactive molecules were flexible aligned to each other, so that common pharmacophore points are identified, as available in GALAHAD program. Next, the pharmacophore model with highest MOL-QRY value (7.80) was superposed on the substrate analogue found in the crystal structure of mPGES-1 (PDB code: 4AL1) (Figure 2). Similar pharmacophore points are found at comparable distances/angles.

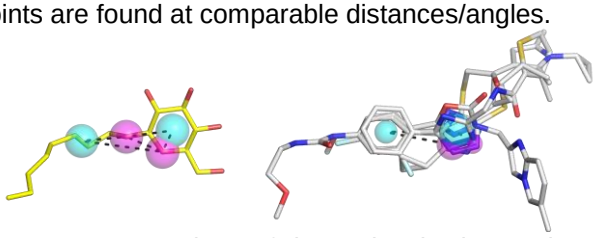

Figure 2. Comparison of the molecular interactions found in the substrate analogue (BOG) (left) and pharmacophoric points identified by the program GALAHAD (right)

Conclusion

Pharmacophore models and chemical similarity studies suggests that the bioactive molecules are competitive inhibitors of mPGES-1.

Acknowledgement

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