[P46] New IL-36 cytokine receptor inhibitors

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A number of potential small molecule antagonists of IL-36 cytokine receptor were identified using in silico screening method.

IL-36 family cytokines (α, β and γ) have been implicated to play a key role in skin inflammatory diseases, such as psoriasis. Upon activation, IL-36 cytokines interact with their receptor and initiate the production of a range of pro-inflammatory cytokines and chemokines. Similar to most members of the IL-1 family, IL-36 cytokines require proteolytic processing for activation [1]. Thus, one therapeutic approach for blocking IL-36 activation is to inhibit the proteases responsible for activating IL-36 family cytokines, but unfortunately they are not identified yet. An alternative approach is to antagonize the interaction between IL-36 and the IL-36 receptor. Earlier it was shown that IL-36β and IL-36α bind the same receptor (IL-1RII) as its family member IL-1β.

In current work in silico screening for small molecule IL-1RII antagonist identification was made with LeadFinder (LF) and AutoDock (AD) packages under default computation parameters. The D3 domain from 3O4O.pdb structure of the IL-1RII was used for screening (the structure is resolved by X-ray diffraction at 2.50 Å resolution). D3 domain is responsible for interaction with the processed part of IL-1 family proteins. The water molecules and co-crystallized anions were removed from the protein model. Hydrogens were added to the resolved structure and their positions refined using Gromacs software package. The 20×20×20 Å box centered to the coordinates of the IL-1−IL-1RII binding interface was used for energy grid maps calculation with 0.300 Å grid spacing. Small molecules were treated as flexible and protein − as rigid.

A set of approximately 50000 compounds from the high diversity St. Petersburg State Technological Institute library was screened using *in silico* method. The ligand protonation states were accounted at the pH 7.0. For the accuracy increase each compound was represented in 15 most favored conformations generated by Omega with mmff94 force field.

A set of 20 promising IL-1RII antagonist molecules were identified during VS with the calculated inhibition constant K_i in the range of $1 \div 8 \cdot 10^{-8}$. The binding specificity and their physico-chemical properties of the representative compounds are discussed in the report.

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[1] M. Gresnigt; F.L. Veerdonk. Semin. Immunol. 25 (2013) 458-465.