Journal of Cheminformatics

POSTER PRESENTATION Open Access

Evaluation of molecular model-based discovery of ecto-5'-nucleotidase inhibitors on the basis of X-ray structures

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From 9th German Conference on Chemoinformatics
Fulda, Germany. 10-12 November 2013

Ecto-5'-nucleotidase (e5NT) belongs to the family of metallophosphoesterases, hydrolyses AMP to adenosine, and is a regulator of the adenosine signaling pathway [1]. It has been shown, that free adenosine is involved in various diseases and cancer progression [2,3]. In a previous study, a molecular model of e5NT has been created and used for the identification of new sulfonamide inhibitors [4]. Recently, X-ray structures of human e5NT in complex with different inhibitors were published [5]. This made it possible to reevaluate the model building and virtual screening efforts in detail. An extensive analysis of the comparative e5NT model, built using a bacterial enzyme in the presence of 35% sequence identity as a template, showed that the model was topologically correct and had high accuracy within the active site region. Comparative docking studies were carried out to explore inhibitor binding characteristics within the X-ray structure and the model. The results provided plausible explanations for the successful identification of new e5NT inhibitors by model-based virtual screening and highlighted important parameters [6].

Published: 11 March 2014

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doi:10.1186/1758-2946-6-S1-P13
Cite this article as: Furtmann and Bajorath: **Evaluation of molecular model-based discovery of ecto-5'-nucleotidase inhibitors on the basis of X-ray structures.** *Journal of Cheminformatics* 2014 **6**(Suppl 1):P13.

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