ICHEC Class B Application

PPARγ Tiered Virtual Screening- Development of an Improved Post-Hit Scoring Process

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Abstract

Peroxisome Proliferating Activated Receptors (PPAR's) have long been established as validated targets for therapeutic intervention in multiple disease states, including type II diabetes and dyslipidemia. Recent literature has provided a large collection of evidence implicating a novel regulatory role for PPARγ in clinical conditions associated with inflammatory components. At present, no marketed therapeutics exist that attenuate inflammatory responses through specific modulation of PPARγ. vHTS (virtual High Throughput Screening) is a computational process that involves the rapid *in silico* assessment of large libraries of chemical structures in order to rationally predict their activities against a biological target of interest. In conjunction with initial virtual screening protocols, retrospective analysis is frequently used to further validate computational techniques. At present, rational computational screening methods have been implemented in the successful identification of novel small molecule modulators of PPARγ. In order to further progress the validity of computational techniques employed, this application will focus on developing an investigational procedure by which virtual hit scoring can be optimally parameterised to decrease the disparity between *predicted* and *biologically validated* hits. Through iterative adjustment of screening tool parameters, it is believed that a quantifiable means by which to separate false positives/negative hits will be deciphered. Also, the computational resources available to this project would pave an allowance for larger database screening to be carried out, thus increasing the possibility of identifying suitable PPARγ targeting compounds.