Predicted stereoselectivity of the inhibition of Aldosterone Synthase and Cortisol Synthase

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Introduction

In the past years, it has become apparent that elevated levels of aldosterone play an important role during the development of congestive heart failure, vascular remodelling and reactive fibrosis in the heart. 1

During the previous FIGON Dutch Medicine Days (October 2004), we have postulated that inhibiting aldosterone synthesis could decrease the detrimental action of the mineralocorticoid on the heart. To facilitate inhibitor design, we constructed 3D models of aldosterone synthase (Cyp11B2) as well as its close family member cortisol synthase (Cyp11B1, 97% similarity), and showed that we could predict both substrate selectivity and regioselectivity of the hydroxylation performed by the Cyps.

Method

The 3D architectures of the two enzymes have been constructed by use of comparative modelling and molecular dynamics (figure 1). In order to validate and optimise the resulting 3D in silico models we have used a subset of 20 drug candidates, for which in vitro screening has been conducted in Cyp11B1 and Cyp11B2 transfected V79 cells.

The compounds have been docked in the active site of the 3D models using the GOLD 2.2 docking suite, after which docking values were correlated with the in vitro IC50 data.

Results

The correlation diagram between in vitro and in silico (figure 2) is being used as a screening tool for compound selection for synthesis and testing.

Conclusions

The correlation between in vitro and in silico data and the predicted (inverse) stereoselectivity of the Cyps towards the fadrazole enantiomers suggests that the GOLD docking models may provide a valuable tool for virtual screening. This may contribute to designing selective inhibitors for aldosterone synthase. However, future model refinement is necessary to improve the correlation.

Currently we are performing in silico screening of compound databases utilising our 3D models. Several compounds have already been selected for synthesis and in vitro testing.

Literature: