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Comparative modelling of the kinase IKK-beta and prediction of inhibitors

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Introduction

The inhibitor κB kinase-β (IKK-β) phosphorylates the NF-κB inhibitor protein IκB leading to the translocation of the transcription factor NF-κB to the nucleus activating gene transcription involved in inflammation response and cellular proliferation.

The transcription factor NF-κB and consequently IKK-β are central to signal transduction pathways of mammalian cells. The aim of this research was to develop a 3D structural model of the IKK-β kinase domain and evaluate its performance for predicting inhibitors.

Methods

- Five-template comparative modelling was performed with Modeller v9.7 and explicit inclusion of the ATP cofactor.
- Model was refined with 20x simulated annealing molecular dynamics (SAMD) simulations in explicit water using GROMACS 4.07. The cluster central structure was chosen as the final model.
- The models were assessed with the Modeller DOPE z-score and Molprobity server.
- 40 inhibitors were selected from the **ChEMBL** database with $IC_{50} \leq 2.5$ μM.
- For each known inhibitor 40 decoys with similar molecular mass and water/butanol partition coefficient were selected (1600 decoys).
- Virtual screening was performed with AutoDock 4.0 and AutoDock Vina 1.02 consensus method (Kukol, 2011).
- Enrichment factors (EFs) were calculated.

Results

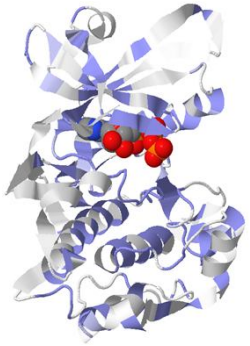

Fig. 1: 3-D structure of the IKK-β kinase domain with bound ATP included during model building. The shading corresponds to coverage by any of the five templates. Maximum sequence identity between target and any of the templates was 30% (Kalia & Kukol, 2011).

Table 1: Model assessment results and comparison with x-ray structures. For all scores 'smaller is better'.

Model	DOPE z-score	MolProbity score
IKK-β (Modeller)	-0.388	3.08
IKK-β (SAMD)	-0.779	0.98
1RDQE	-1.80	1.25
3HKOA	-1.28	1.77

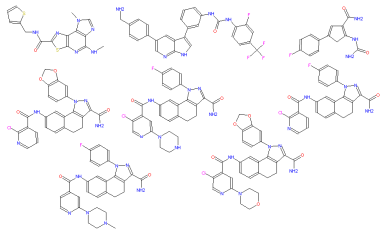

Fig. 2: A selection of known inhibitors from **ChEMBL.**

Table 2: Enrichment factors (EFs) from virtual screening with 40 known inhbitors from **ChEMBL** and 1600 decoys.

% of database	% of known ligands predicted
1%	18%
2%	23%
5%	33%
10%	36%

Conclusions

- A 3-D structural model of the IKK-β kinase domain was predicted.
- The SAMD refinement method resulted in improved model assessment scores.
- Virtual screening with the predicted protein structure was capable of recovering known inhibitors among physicochemical similar decoys.
- The $EF_{1\%}$ of 18% exceeded EFs reported in the literature of 12% averaged over nine protein kinases from x-ray crystallography.

References

Kalia, M., & Kukol, A. (2011). Structure and dynamics of the kinase IKK-β – A key regulator of the NF-kappa B transcription factor. Journal of Structural Biology, 176(2), 133-142.

Kukol, A. (2011). Consensus virtual screening approaches to predict protein ligands. European *Journal of Medicinal Chemistry*, 46(9), 4661-4664.

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