Lead identification and docking studies of human mitogen activated protein kinase kinase4 (MAP2K4)

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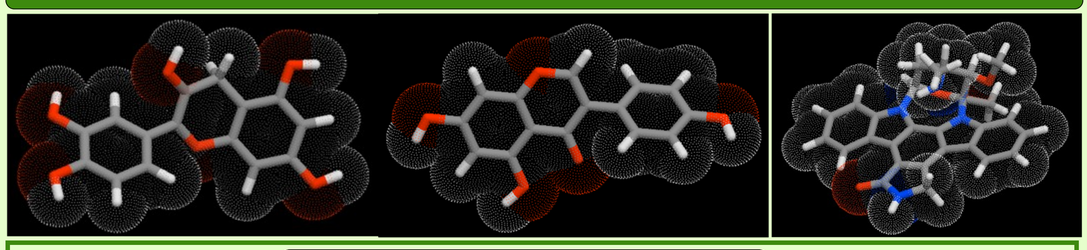
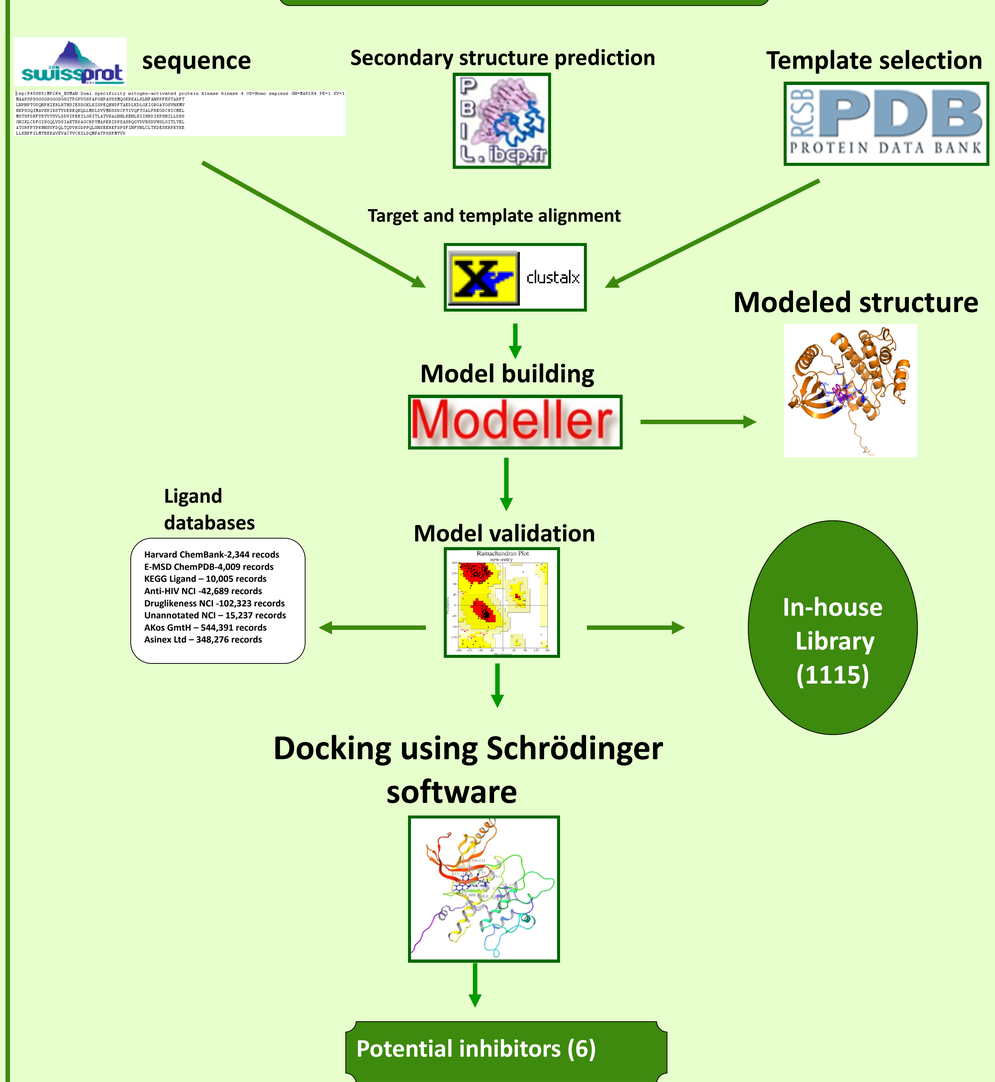
Introduction

- Dual specificity Mitogen-activated protein kinase kinase 4 (MAP2K4) is an enzyme encoded by the MAP2K4 gene. The protein belongs to Ser/Thr protein ki nase family and located at Chromosome 17p11.2.
- Three published inhibitors (staurosporine, genistein, cyanidin) of human MAP2K4 protein searched through the PubMed, PubChem and literature search.
- Over expression of MAP2K4 leads to carcinogenic effect such as prostate cancer, ovarian cancer, skin cancer and lung cancer. Thus, MAP2K4 would be highly useful as cancer drug target.
- Potential drug molecules of human MAP2K4 reported till date are under clinical trials and associated with side effects.
- Molecular modeling, ligand based virtual screening and computational docking techniques were applied here in to find potential inhibitors against MAP2K4 without ADMET (Absorption, Disruption, Metabolism, Excretion and Toxicity) violations.

Three published inhibitors for MAP2K4 CYANIDINE, GENESTINE, STAUROSPORINE



Materials and methods



Results and discussion

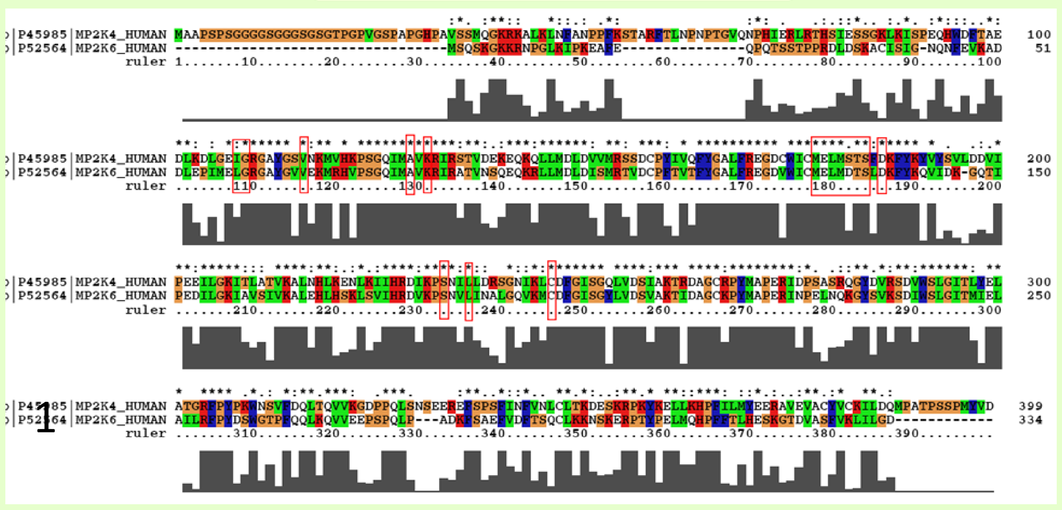
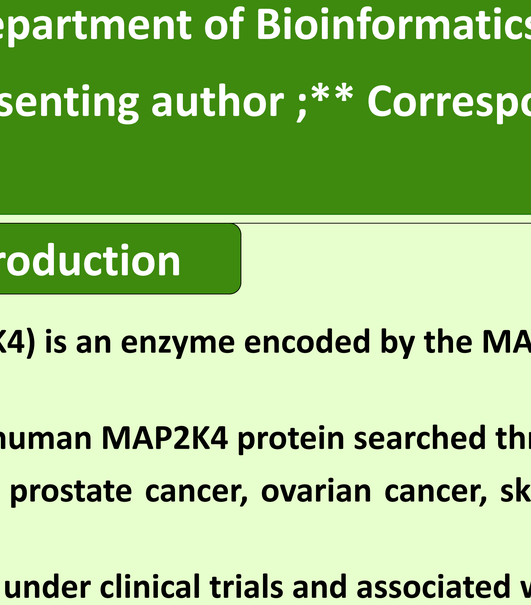


Figure: (1) Target (MAP2K4) - template (MEK6) alignment revealing active site residues were conserved in target and template except Ile108 and Ser182 replaced by similar residues Leu59 and Asp133, respectively.



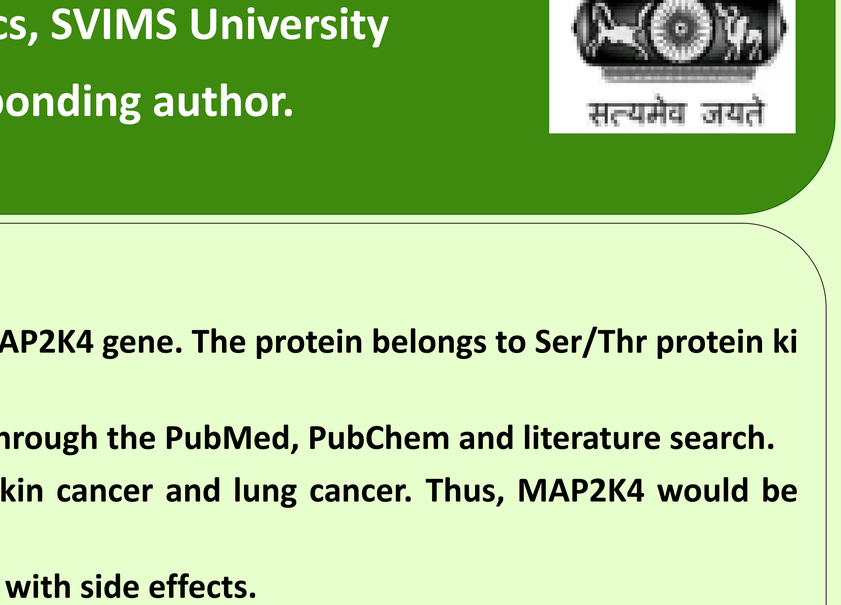


Figure : (2) PROCHECK analysis for modeled human MAP2K4 (3) predicted structure of human MAP2K4 with STAUROSPORINE (4) MAP2K4 with STAUROSPORINE model highlighting potential active site residues : ILE-108, GLY-109, VAL-116, ALA-129, LYS-131, MET-178, GLU-179, LEU-180, MET-181, SER-182, THR-183, SER-184, ASP-186, SER-233, LEU-236 AND CYS-246 (5) CASTp confirmed predicted active site residues constitutes the largest binding pocket of MAP2K4 (6) Predicted 10 lead molecules and published inhibitors .

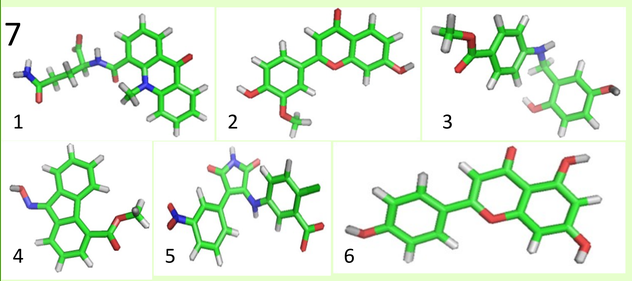


Figure : (7) Six potential inhibitors for human MAP2K4 based on XP Gscore and comparative analysis with published inhibitors

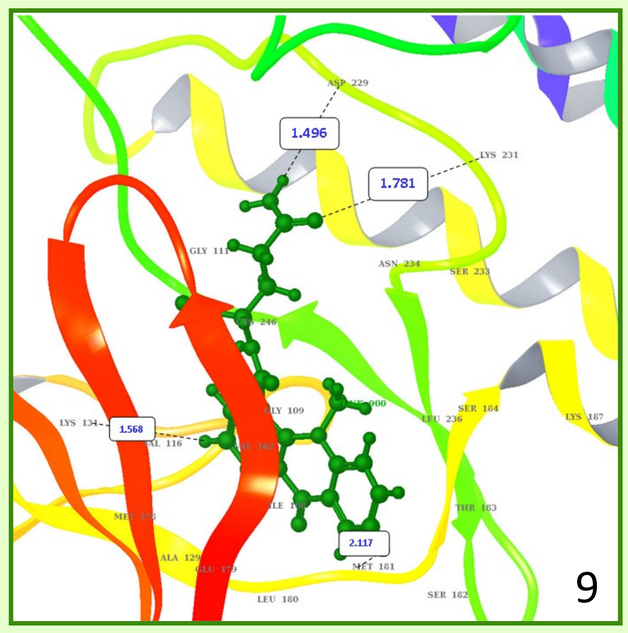


Figure : (9) Lead 1 - MAP2K4 docking complex displaying docking interaction with hydrogen bonds and good van der Waal contacts

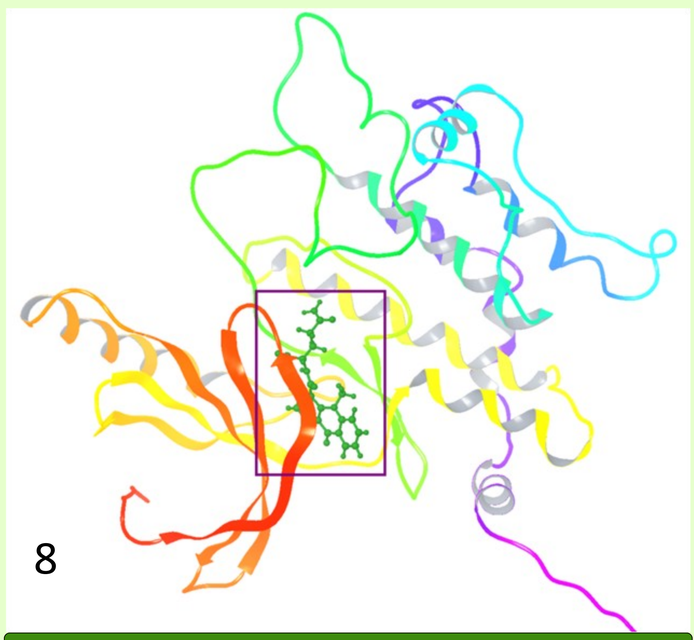


Figure : (8) Docking complex of human MAP2K4 with lead '1' molecule

Conclusion

- A reliable three dimensional structure for human MAP2K4 was predicted with good stereochemistry. The structure would be used for structure function analysis, protein—protein interaction studies and structure based drug discovery.
- Ten lead molecules were identified through ligand based virtual screening and computational docking. These leads had good binding affinity towards MAP2K4. Through comparative analysis with published inhibitor binding affinity and docking orientation six potential inhibitors were proposed.
- All potential inhibitors had good ADMET properties. Lead 1 belongs to Quinazolinones, lead2 belongs to flavonoids while lead3 (AG957) is an established kinase inhibitor used for cancer treatment.
- Analysis of binging orientation of Lead1-MAP2K4 docking complex had revealed that The active site residues such as LYS-131, MET-181, LYS-231 and ASP-229 are directly getting blocked by lead '1' through hydrogen bonds and other active site residues through good van der Waal contacts. Hence, lead1 with docking score -8.75kcal/mol would be useful for designing inhibitory drug molecule for cancer treatment.

Acknowledgements

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