Identification of potent inhibitors for p38δ protein of *human* through *in silico* analysis

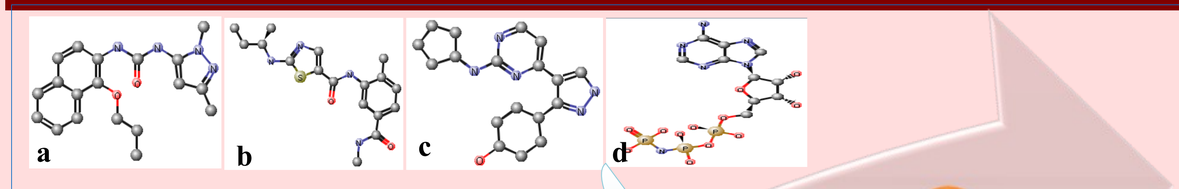
M Naga Lakshmi*, Dibyabhaba Pradhan, Manne Munikumar and Amineni Umamahwari**

SVIMS Bioinformatics Centre, Department of Bioinformatics, SVIMS University, Tirupati
Pin-517507, India, Email: svims.btisnet@nic.in
Presenting author ; Corresponding author*

Key points

- p38δ Mitogen activated protein kinase is a serine/threonine protein kinase.
- It mediats the signaling process activated by the MKK6 and MKK and acts as positive regulator in phosphorylating the cytoskeleton protein Tau, Stathmin and eEF_2K along with keratinocyte differentiation.
- Over-expression leads to tumor development by impairing the ERK1/2 –AP1 pathway.
- Herein an *in silico* approach was practiced to hit upon more potent inhibitors for human p38δ protein.

Materials & Methods

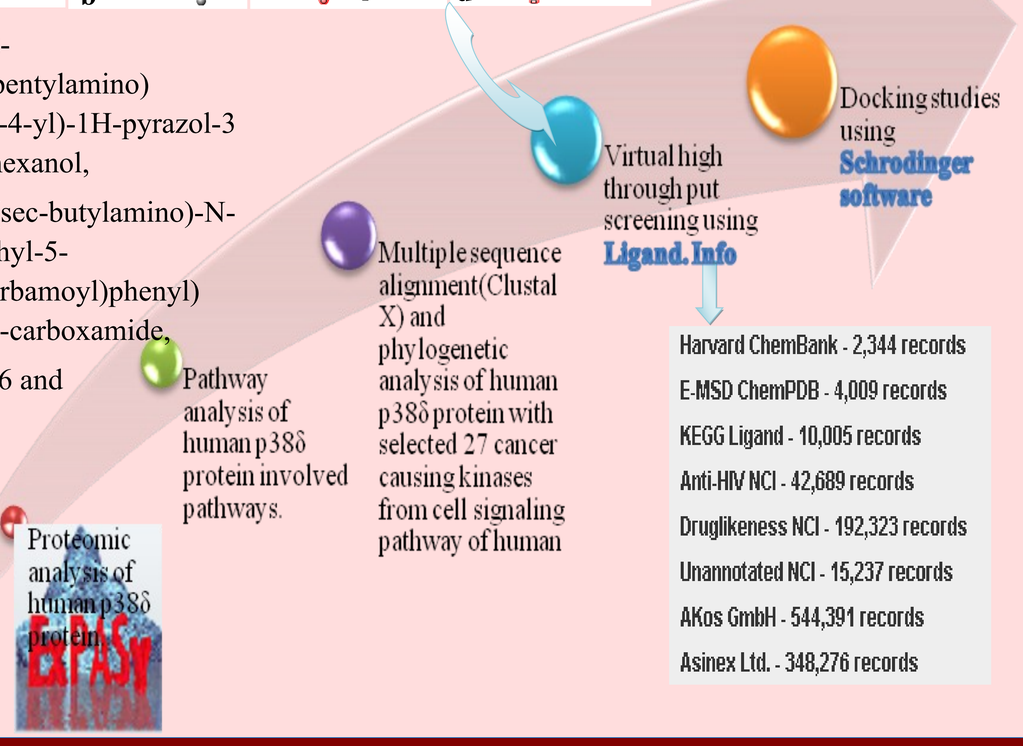


a 4-(4-(2-(cyclopentylamino) pyrimidin-4-yl)-1H-pyrazol-3-yl)cyclohexanol,

b (R)-2-(sec-butylamino)-N-(2-methyl-5-(methylcarbamoyl)phenyl) thiazole-5-carboxamide,

c BIRB796 and

d ANP



Results & Discussion

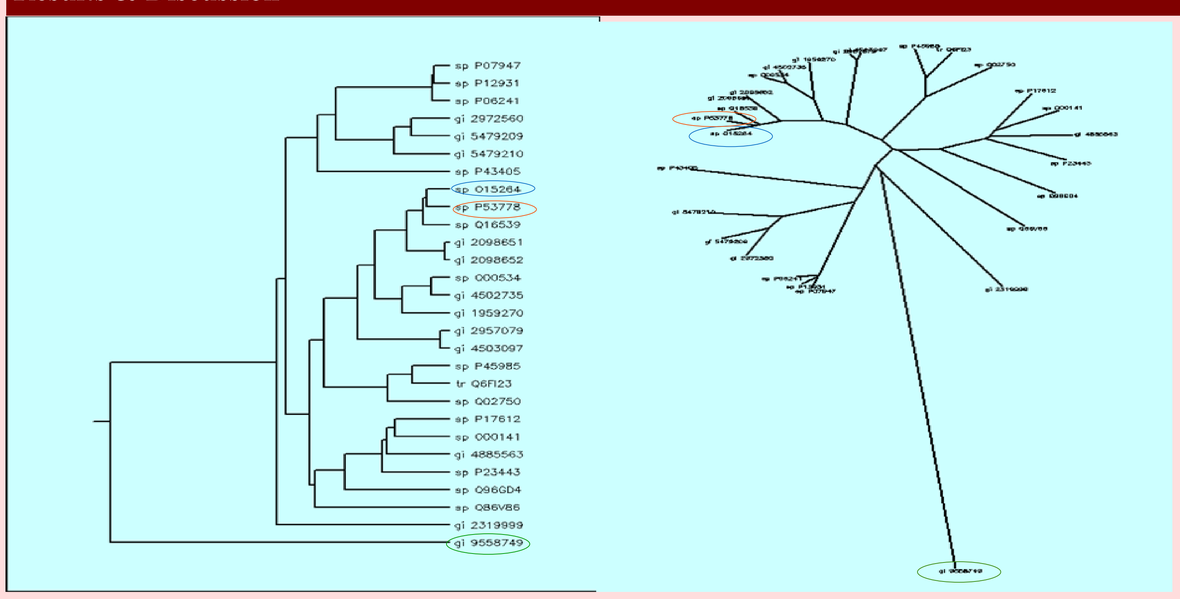


Figure 1: Rooted and unrooted representation of human p38δ protein with 27 selected cancer causing kinases from cell signaling pathway of human proteins in human.
Human p38δ is closely related to p38γ and distantly related to eukaryotic elongation factor 2 kinase of human.
Blue color: out group, Red color: closely related, Green color: distantly related

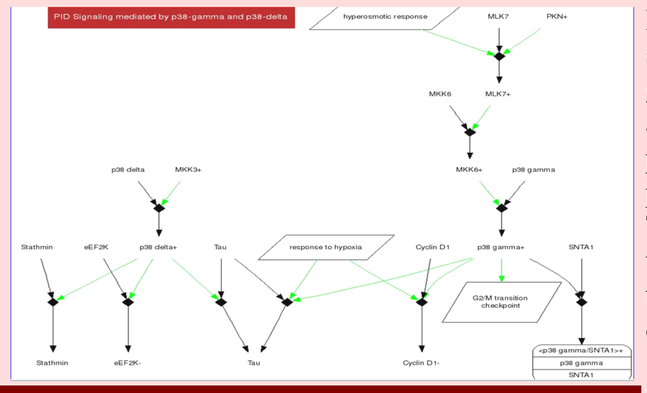
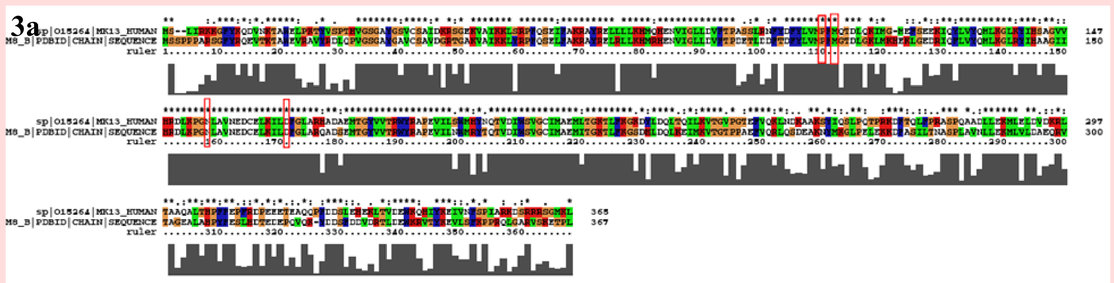


Figure 2: In response to hyper osmotic stress both the isoforms p38 delta and gamma mediates the signaling course of action activated by the MKK6 and MKK3. p38delta$^+$ acts as encouraging regulator in phosphorylating the cytoskeleton protein Tau, Stathmin and eEF_2K. Modification takes place in the protein substrates in retort to hypoxia involved reactions by p38 delta along with p38gamma.

Acknowledgement

Authors are highly thankful to DBT, Ministry of science and technology, Govt. of India for supporting research activities at SVIMS Bioinformatics centre. We are also thankful to Dr. B. Vengamma, Director, SVIMS, for her constant encouragement and support.

3a



3b

Active site of the p38δ protein were predicted through comparative analysis with closely related co-crystal structure p38γ (94% identity). The active site residues are Pro108, Met110, Asn155 and Asp168.

Figure 3:(a) Post Script file of multiple aligned p38δ with p38γ.**(b)** Crystal Structure of p38δ (RCSB)

Leads

4

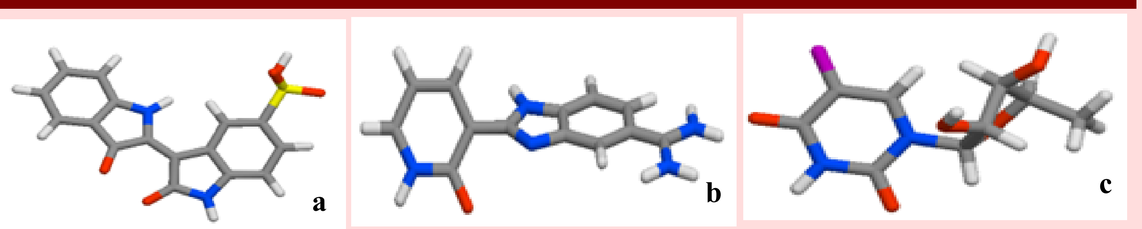
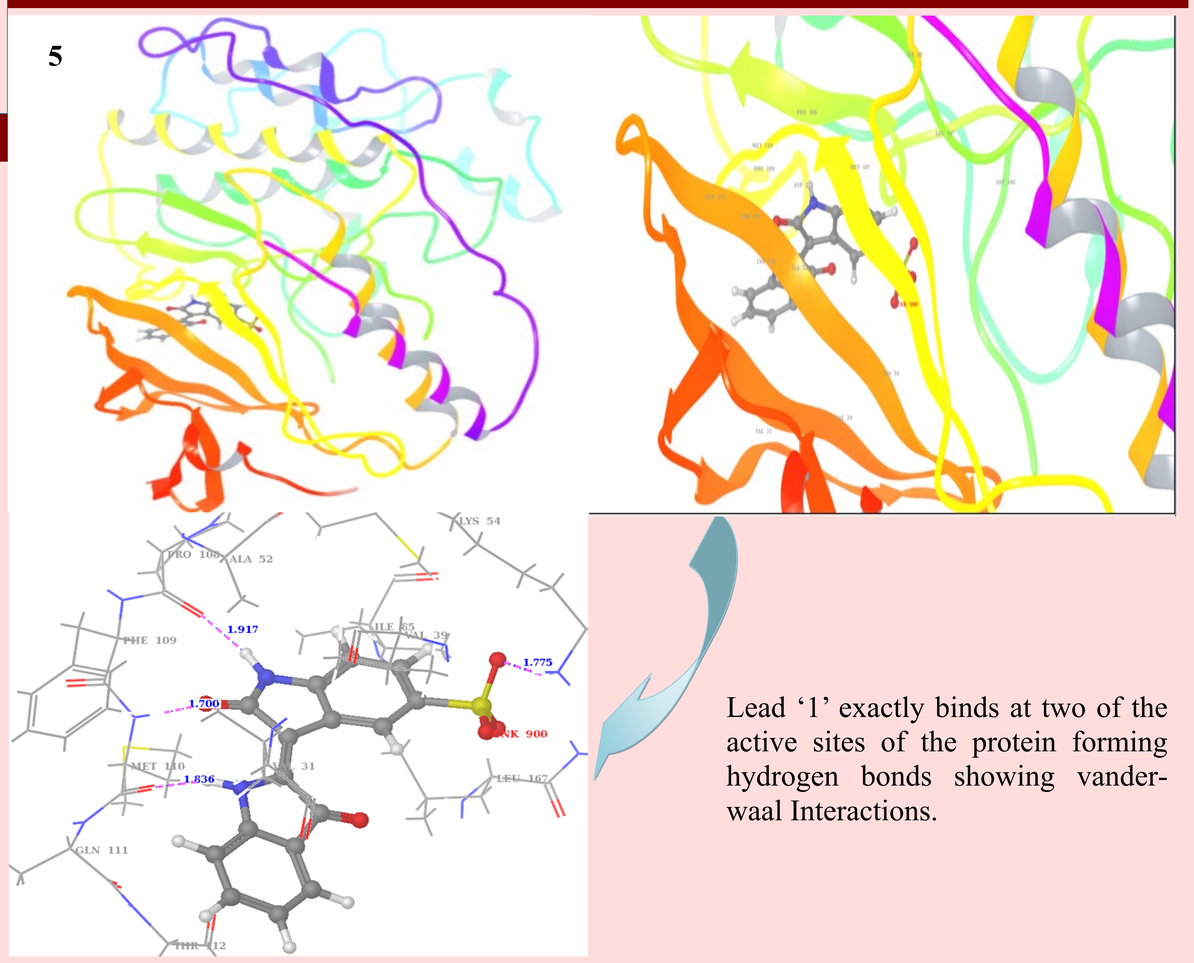


Figure 4: Molecular weight and Docking score for the Optimized leads
(a) 342.33,- 12.1226172726768
(b) 252.26, -10.0625979536364
(c)246.2, -9.47862315267917 (Drug-Doxifluridin)
(d) 398.47, -9.36607016324726

Docking Interaction with the Lead '1'

5



Lead '1' exactly binds at two of the active sites of the protein forming hydrogen bonds showing vander-waal Interactions.

Figure 5: Docking interface of lead '1'with the p38δ

Conclusion

The computational conduit presented in this work is a useful tool for the design of structurally stable leads with altered affinity for ligand binding, considerably reducing the number of ligands to be experimentally tested. Ligands are screened by docking simulation and stability evaluation followed by a rationally driven selection of those presenting the requisite characteristics. Through computational analysis four lead molecules were suggested as potential inhibitor of p38 delta. Lead1 with lowest docking score and good correlation with published inhibitor would be proposed for synthesis and clinical trial for p38 delta inhibition.