Implementation of computational methods for designing potential inhibitors against human p38α protein

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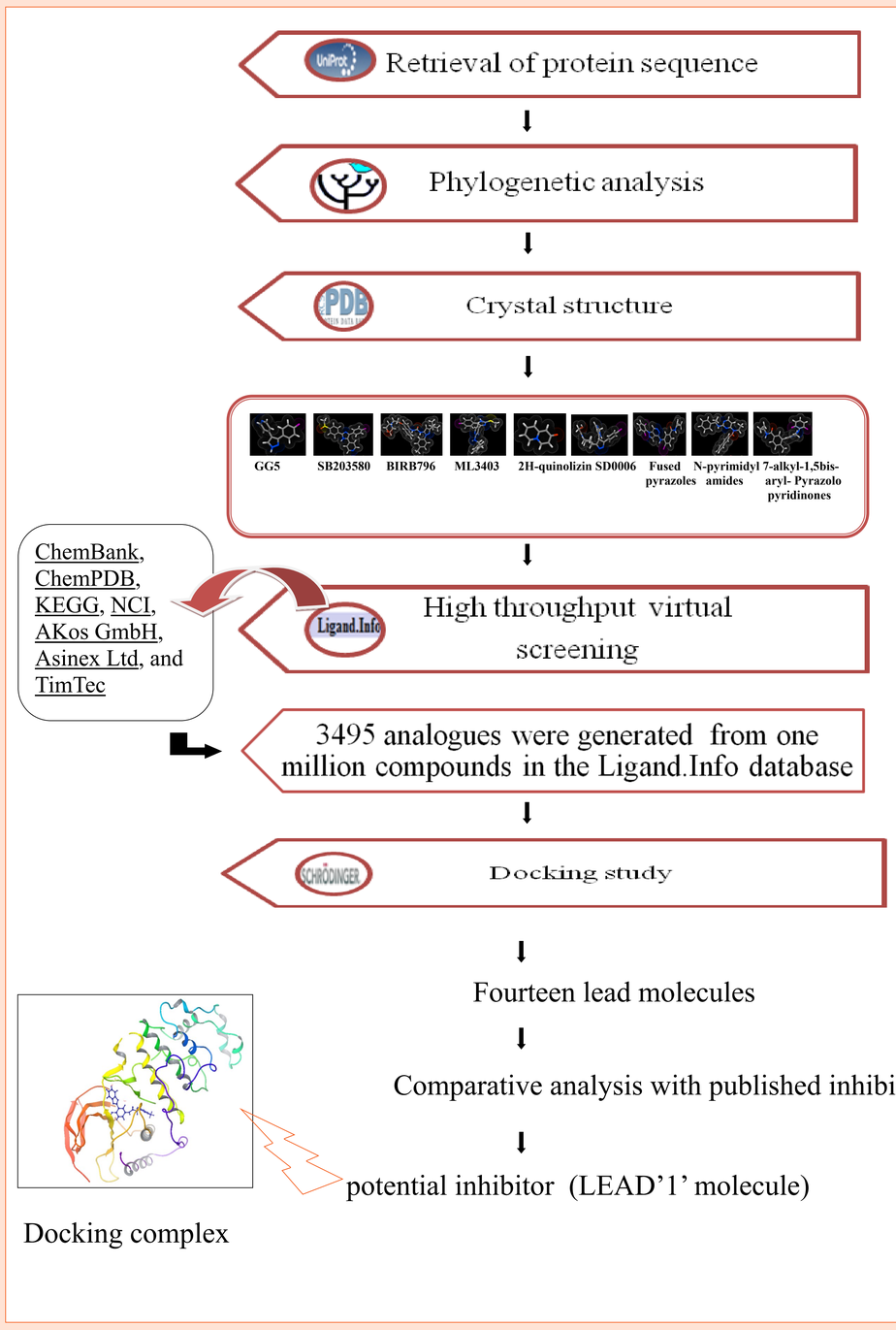
Key points

- p38α, a non-receptor serine/threonine kinase, plays an essential role in cell proliferation, cell differentiation, apoptosis, production of cytokines such as IL1β and TNFα, senescence and tumorigenesis.
- Over expression of p38α enhances the production of cytokines, leading to inflammation causing cancers. Therefore, the protein p38α selected as a target for the inhibition of progression of inflammatory cancers.
- Inhibitory drug molecules of human p38α reported till date are in preclinical stages. In these clinical studies, the drug molecules had shown side effects such as liver toxicity, development of lung tumors particularly in smokers.
- Virtual screening and docking techniques were utilized herein to gain insight on identifying a new potential inhibitors.

Materials and methods



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Results and discussion

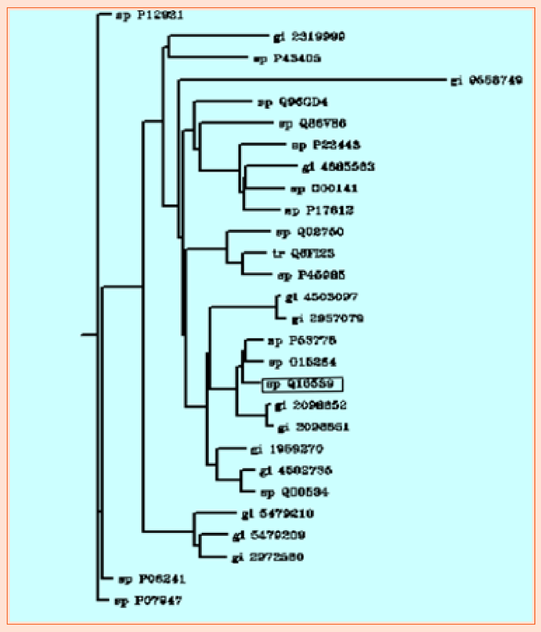

Figure1. Rooted tree was constructed by using the FITCH algorithm of Neighbor-joining method. p38γ and p38δ were closely related to p38α and is distantly related to eukaryotic elongation factor 2 kinase

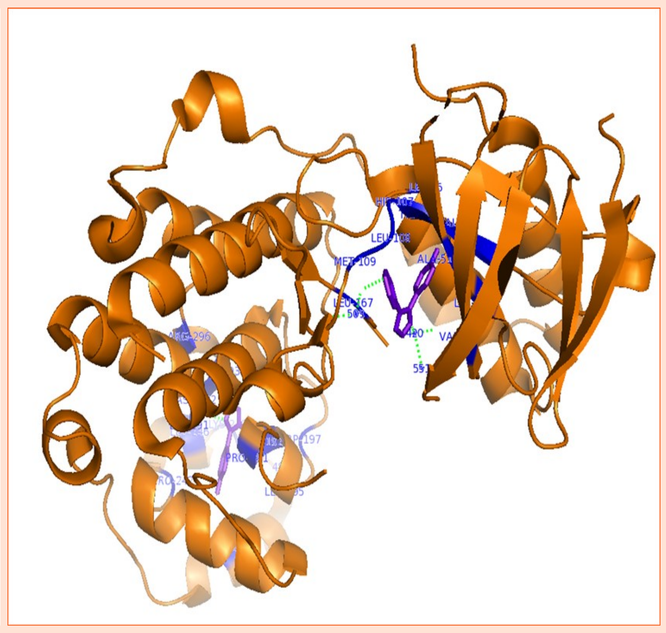

Figure 2.T he crystal structure of p38α (ID 3HVC) along with inhibitor GG5. The active site residues are Val30, Ser32, Val38, Ala51, Val52, Lys53, Leu75, Ile84, Gly85, Leu86, Leu104, Thr106, His107, Leu108, Met109, Val110, Leu167 and Asp168

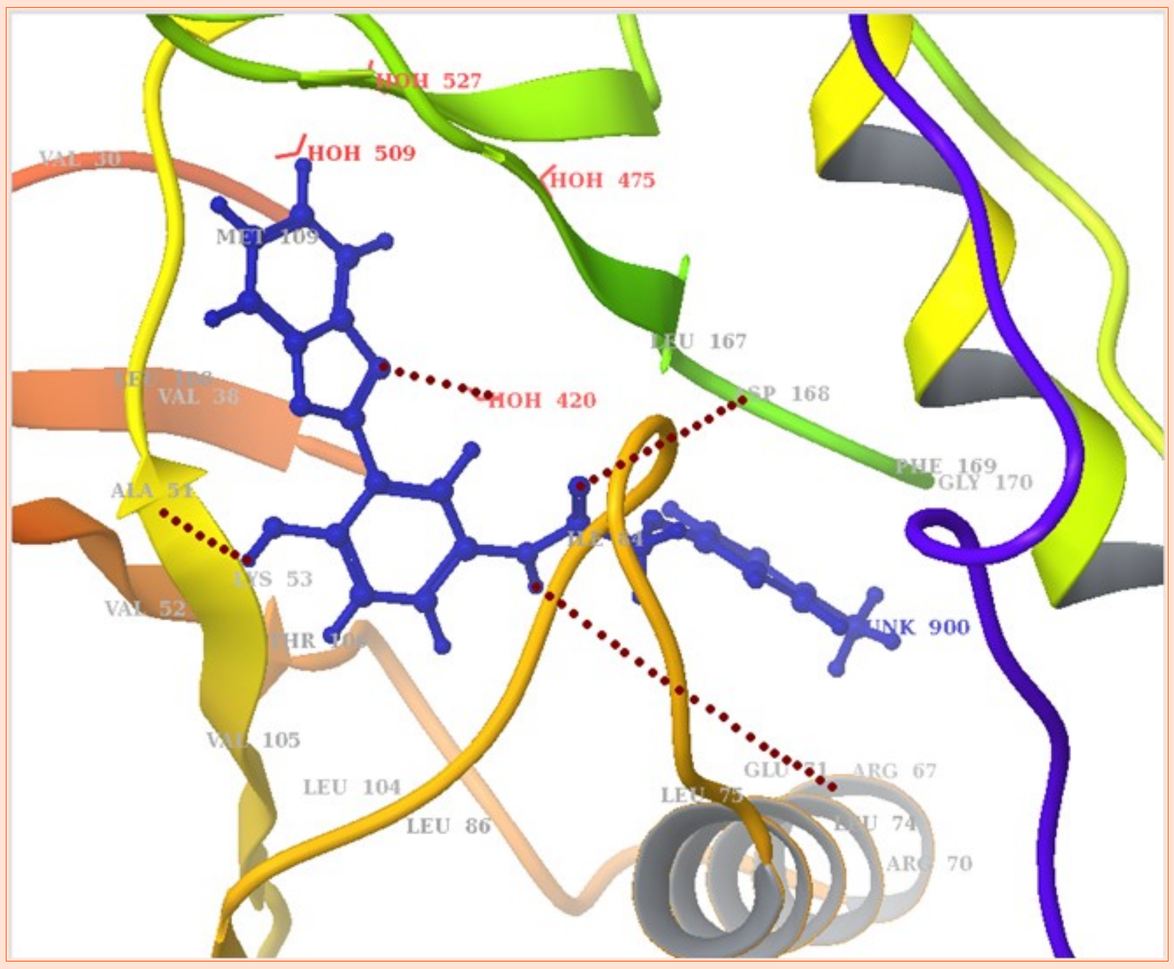

Figure 4 Docking complex of p38α and Lead'1'molecule

Conclusion

In comparison with the nine existing inhibitors, lead '1' (N-(3-Benzooxazol-2-yl-4-hydroxy-phenyl) 2ptolyloxyacetamide) has lowest binding affinity among the lead molecules with XP Gscore of -9.38 kcal/mol and forming four hydrogen bonds: one with each of Ala 51, Glu71 and Asp168 and one water bond (position 420) with a well complementing binding mode with the crystallographic data of human p38α. Therefore, Lead '1' can be raised into potential inhibitors after binding assays and passing several phases of clinical trials.