Key points:

- Oncogenic constitutive enzyme human p38γ is a serine/threonine protein kinase, activated through phosphorylation by environmental stress and pro-inflammatory cytokines responses (Lechner et al., 1996). Over expression of the protein leads to formation of tumorigenesis effectors.

- Human p38γ protein is highly expressed in several human malignant cell lines (Wang et al., 2000; Pillaire et al., 2000), indicating its possible role in tumorigenesis. Human p38γ specifically integrates their antagonistic activity to stimulate cell invasion. Human p38γ over expression increases invasion that is the spread of malignant cells to new sites of the body in ER+ and higher levels in ER breast cancer cells (Qi et al., 2006).

- Computational method for drug designing was practiced here to explore lead molecules targeting human p38γ protein.

Materials and Methods:

- Docking of the generated lead molecules with the human p38γ protein using Schrodinger software suite 2009 (Maestro 9.0) produced 18 lead molecules, among the 18 lead molecules, Lead 1 directly blocking five residues forming hydrogen bond with lowest XP G Score: -10.224 kcal /Mol.

- Analysis of binding orientations of the docking complex revealed that four amino acid residues Pro110, Met112, Asp115 (two Hydrogen bonds), Asn158 and W2039 of active site were directly involved in formation of hydrogen bond network for human p38γ protein functional activity inhibition with Lead 1 that complements well with previous crystallographic reports of human p38γ–ANP inhibitor complex.

- 3-DEAZA-ADENOSINE (Lead 1’) was involved in good van der Waal interaction with Lys56 that is highly important for ATP binding and subsequent activation of human p38γ.

3-DEAZA-ADENOSINE (Lead 1’) was involved in good van der Waal interaction with Lys56 that is highly important for ATP binding and subsequent activation of human p38γ.

Conclusion:

- 3-DEAZA-ADENOSINE reports with good docking energy, docking score, stable conformation, orientation and exhibits functional activity inhibition. Thus it might be encouraging for new directions as a drug for human p38γ protein for the novel class treatment of breast cancer.

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