Ligand based virtual screening to design novel human MEK1 inhibitors for potential development of drugs against melanoma

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ABSTRACT

The Ras-dependent Raf/MEK/ERK signaling pathway is a major regulator of cell proliferation and survival. MEK inhibitors may have broad utility in the treatment of human cancers driven by activation of this pathway due to the selective phosphorylation of ERK by MEK and the highly selective inhibition of MEK displayed by this class of inhibitors. In view of its importance, identification of potent inhibitor against MEK1 may be valuable to design effective drugs against melanoma. Inhibitors for human MEK1 reported till dates have poor pharmacokinetic properties and some are under clinical trials. Therefore, with an objective to identify potent MEK1 inhibitors with good pharmacokinetic properties, computer assisted virtual screening method was accomplished. The X-ray crystallographic structure of human MEK1 was investigated to adjudge unique inhibitor binding pocket. Four inhibitors (Crystal structure inhibitor: BBM; inhibitors under clinical trial: AZD6244; AZD8330; RDEA119) of MEK1 were attained to search geometrically closely related chemical entities through Ligand.Info high throughput screening tool. The structural analogues (1549) were prepared using LigPrep applying flexible filter to generate fully customized ligand libraries that were optimized for further computational analysis. Glide v5.5 flexible docking procedures were then applied for screening ligands with good binding affinity towards the inhibitor binding pocket of MEK1 and nine lead molecules were proposed. The lead molecules were ranked based on XP Gscore and binding orientations were correlated with the four existing inhibitors. The docking result endeavors potential of Lead 1 (Catechin) as a promising inhibitor for Melanoma. However, four lead molecules having lower XP Gscore compared to published inhibitors would open up new avenues for designing of potent MEK1 inhibitors.

INTRODUCTION

Figure 1: Raf/MEK/ERK signaling pathway

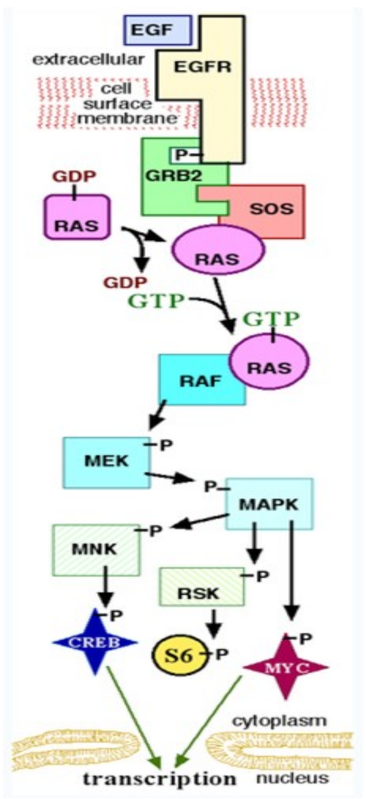
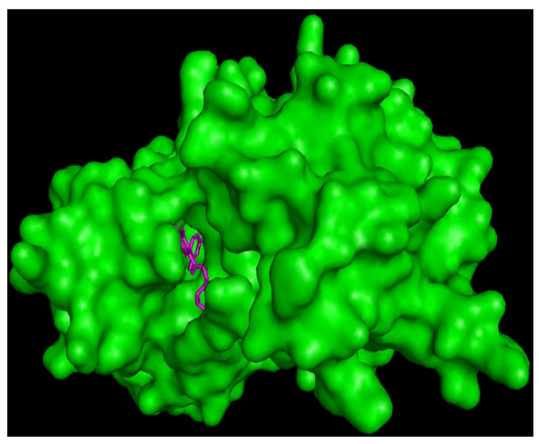


Figure 2: MEK1 XRC structure (1S9J) with inhibitor BBM binding at the unique inhibitor binding pocket



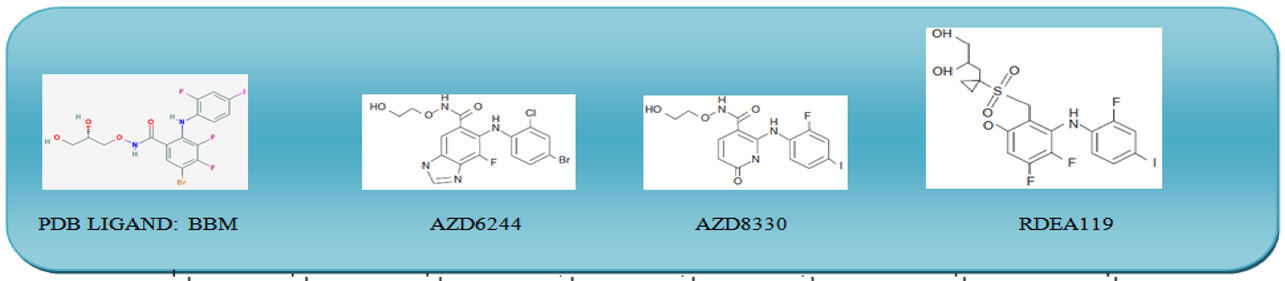
The unique inhibitor binding pocket of MEK1 contains the residues Gly77, Asn78, Lys97, Ile99, Leu115, Leu118, Val127, Ile141, Met143, Asp208, Phe209, Gly210, Val211, Ser212, Leu215, Ile216 and Met219 to which a ligand binds.

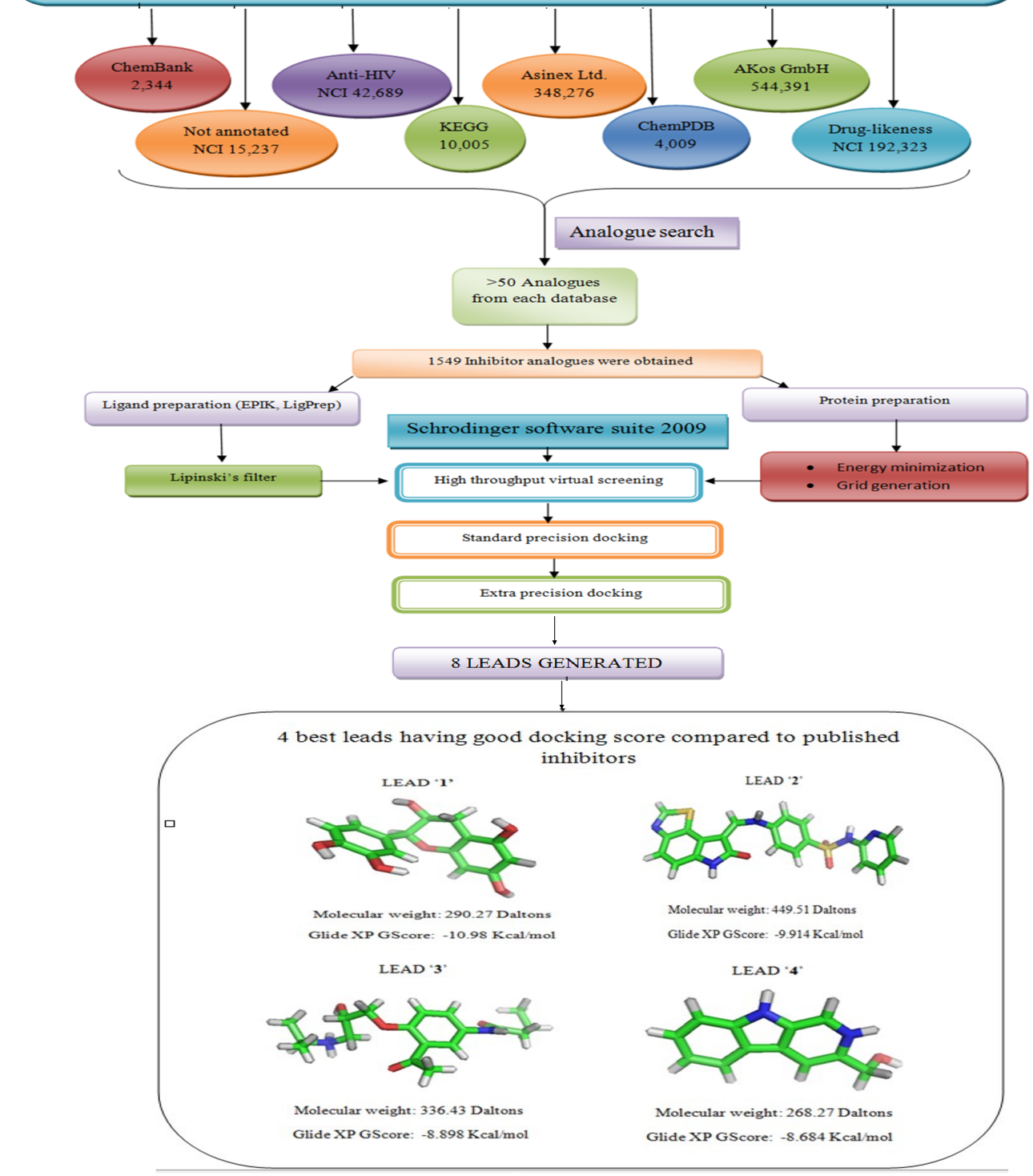
Figure 3: Current status of MEK1 inhibitors in

Mitogen activated Extra regulated Kinase 1 (MEK1) is the only acknowledged activator of extracellular signal-regulated kinase (ERK), making them attractive targets for therapeutic intervention. Defects in the RAS/RAF/MEK1/ERK signaling pathway (Figure 1) are closely associated with the development of human tumors such as melanoma. The MEK1 inhibitors have a unique inhibitor binding pocket (Figure 2). The latest 2010 review displayed the current status of MEK1 inhibitors clearly shown in the PIE chart (Figure 3). Ligand based virtual screening method was accomplished to identify potent inhibitors for MEK1 with good pharmacokinetic properties.

RESULTS

Four published MEK1 inhibitors





The four lead molecules bind at the same unique inhibitor pocket of MEK1 protein. Analysis of The MEK1-Lead 1 docking complex (Figure 4) had shown presence of two new residues Asp190 and Cys207, in addition to the inhibitor pocket observed in crystal structure. Binding orientations of four leads were corroborated well with the four existing inhibitors with lower XP Gscore (Figure 5).

Figure 4: Docking of lead 1 with MEK1

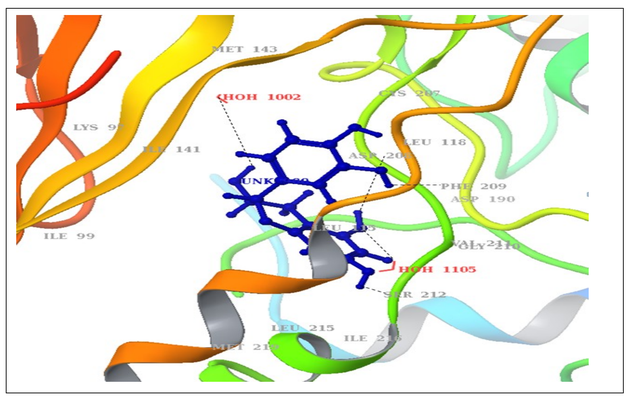
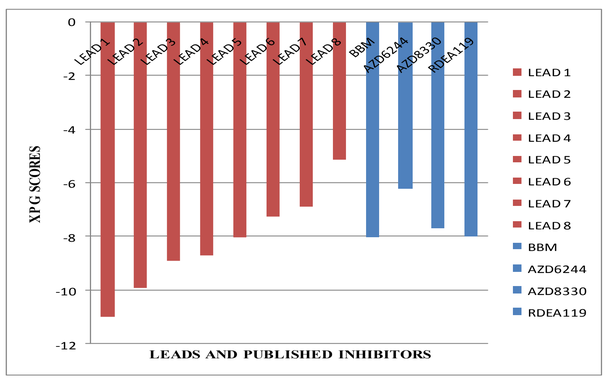


Figure 5: Comparison of XP Gscore of all 8 leads and 4 published MEK1 inhibitors



CONCLUSION

The docking result endeavors potential of Lead 1(Catechin) as a promising inhibitor for Melanoma. However, the first four lead molecules having better docking score than the published inhibitors, would open up new avenues for designing of potent MEK1 inhibitors if synthesized and tested in animal models.

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