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 date 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 was accomplished. The X-ray crystallographic structure of human MEK1 was investigated to adjudicate unique inhibitor binding pocket. Four inhibitors (Crystal structure inhibitor: BBM; inhibitors under clinical trial: AZD6244; AZD6330; 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 lead molecules having lower XP Gscore compared to published inhibitors would open up new avenues for designing of potent MEK1 inhibitors.

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. The docking result endeavors potential of Lead 1 (Catechin) as a promising inhibitor for Melanoma. However, the first four lead molecules having lower XP Gscore compared to published inhibitors would open up new avenues for designing of potent 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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