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FELLOWSHIP FINAL REPORT

Design of ERK2 inhibitors for cancer therapy

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REPORT INFO

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ABSTRACT

Constitutive activation of ERK1/2 pathway drives the proliferation and survival of many cancer cell types. Therefore, the new approaches, i.e. small molecular weight compounds targeting directly hyperactivated ERK 1/2, are widely explored as anticancer compounds. Recently, new molecules based on a 1,1-dioxido-2,5-dihydrothiophen-3-yl 4-benzenesulfonate scaffold (targeting the FRS domain of ERK2) were synthesized. These new molecules, indicated as compounds 4 and 6, contain modifications of the arylamine substituent at the 4-position of the heterocyclic scaffold. To gain insight into molecular mechanisms of their activity, the study was focused on the exploration of potential interaction of these new compounds with ERK2 by means of in silico study, i.e. molecular docking. The docking procedure was carried out within both substrate docking sites, DRS and FRS, and ATP binding sites, and by means of Molecular Operating Environment (MOE) system. The 4gt3, high-resolution ERK2 structure available in the Protein Data Bank (RCSB PDB) was chosen for this purpose. The analysis indicated that both compounds 4 and 6 bound with similar efficiency within both substrate docking sites, DRS and FRS, but not in the ATP binding site.

1- Introduction

Extracellular signal–regulated kinases 1/2 (ERK1/2) as a one of core members of MAPK signaling pathways regulates the expression of genes implicated in control of cell proliferation and survival via phosphorylation of transcription factors and regulatory molecules. The disturbance of ERK1/2-mediated signaling caused, e.g. by mutations of upstream activator BRAF leads to excessive activation of ERK1/2 and tumorigenesis. Hence, in this case, the significant approach in the development of tumor treatment is the design of molecules that interfere with members of ERK1/2 pathway. There are several drugs used in clinic which inhibit ERK1/2 signaling via interactions with BRAF and MEK1/2 but the side effects associated with their use, e.g. toxicity and resistance development, force to the creation of new compounds directed towards other targets, i.e. ERK1/2 kinases. There are several potential targets for drugs in ERK1/2 molecules, i.e. ATP binding site or substrate docking domains. ERK1/2 has two distinct docking sites, i.e. the D-recruitment site (DRS) and the F-recruitment site (FRS) that mediate specific recognition of

substrate and kinase-substrate complex assembly. Compounds targeting substrate recruitment sites of ERK1/2 seem to be promising considering therapeutic purpose as they allow to bypass the detrimental outcomes on overall cell signaling caused by ATP-competitive inhibitors [1-4].

Recently, a set of compounds containing a 1,1 – dioxide - 2,5 – dihydrothiophen - 3 - yl 4 - benzenesulfonate scaffold and targeted to docking site for ERK/FXF (DEF) motif have been described by Martinez et al. These studies clearly indicated the anticancer potential of 1,1-dioxido-2,5-dihydrothiophen-3-yl 4-benzenesulfonate derivatives, including compound indicated as SF-3-027. This prompted us to design the new molecules based on SF-3-027 compound. A structure-activity relationship study carried out by the Martinez group determined that the presence of a double bond in the sulfur heterocycle was a key chemical feature required for the compound's biological activity [5]. For this reason, the modifications of SF-3-027 we performed were focused among others on the substituent at position 4 of the heterocycle by introducing an amino group. To gain insight into mechanisms of the activity of these new compounds, indicated as compound 4 and compound 6, the study was focused on the exploration of potential interaction of these new compounds with ERK2 by means of in silico study, i.e. molecular docking.

2- Experimental details

The docking procedure was performed by means of Molecular Operating Environment (MOE) system [6]. The 4gt3, high-resolution ERK2 structure available in the Protein Data Bank (RCSB PDB) was chosen for this purpose [7]. First, the structure of protein was validated and the docking sites were defined. Then, the database of ligands (compound 4 and compound 6) created. The docking procedure was carried out within both substrate docking sites, DRS and FRS, within ERK2 molecules with open and closed activation loop, with and without water molecules. The accuracy of docking was evaluated on the basis of S-score values.

3- Results and discussion

Concerning the docking of the ligand 4 in the DRS site, the best pose has a S-score value (affinity binding prediction) equal to -5.6. It was observed two hydrogen bonds with Glu79 and Gln130 and a hydrogen-Pi interaction with Glu79 within groove at protein surface. Whereas, the best pose of ligand 6 has a S-score value equal to -4.7. The 2D interaction map shows only one hydrogen bond with Lys162. Concerning the docking of ligand 4 in the FRS site, we found the two best poses with opposite orientations. Their values of the S-score were respectively -6.5 and -6.1. In this case, the binding site was a buried cavity inside the receptor. The observed interactions were as follow: for first of the two best poses, hydrogen bonds were made with residues in the bottom of the cavity (Glu195 and Pro296) whereas for the second best pose, the residues involved in hydrogen bonds are at the cavity entry (Thr204, Ser206 and His297). In case of ligand 6, the S-score value of the best pose is -5.8. Only a single interaction was observed, namely hydrogen bond with Thr204.

4- Conclusion

On the basis of the obtained results, it can be concluded that the positions of ligand 4 and 6 differ substantially because there is no similar poses between the two compounds in DRS and only one common, i.e. with Thr204, in FRS. This could resulted from the different steric and electronic properties of the substituents at the 4-positions of the sulfol-2-enes 4 and 6. The S-score values and number of interactions within DRS and FRS indicated that ligand 4 exerts better affinity binding within substrate docking sites of ERK2 and presumably inhibitory potential towards this kinase. However, these issues need further exploration.

5- Perspectives of future collaborations with the host laboratory

The future collaboration with laboratory Bio-informatique Structurale et Chémoinformatique, Institut de Chimie Organique et Analytique, Université d'Orléans will be focused on design further dervivatives of 1,1-dioxido-2,5-dihydrothiophen-3-yl 4-benzenesulfonate, their molecular docking into ERK2 kinase and SAR studies to choose the most promising compounds for biological evaluation.

6- Articles published in the framework of the fellowship

The analysis performed in the frame of the fellowship constitute the one of the preliminary stages of studies of the project on "Design of ERK2 inhibitors for cancer therapy". Currently, biological assays are carried out to evaluate the mechanisms of antiproliferative activity of tested compounds. Hence, there is no article published up to now.

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