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Laboratory note

Action mechanisms and structure–activity relationships of PI3Kγ inhibitors on the enzyme: a molecular modeling study

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Abstract

Action mechanisms of four types of PI3Kγ inhibitors were investigated on the ligand-binding pocket (LBP) of PI3Kγ with molecular modeling method. At first five compounds whose complex structures with PI3Kγ were available experimentally were used to validate the reliability of docking program Autodock3.0. The results demonstrated that the program could reproduce the bound conformations of those compounds in crystal structures. Then the program was used to dock all the four types of PI3Kγ inhibitors into the LBP of the enzyme. The predicted activities of these compounds were in agreement with their experimental activities, and a pharmacophore model was hence derived for these compounds, which consisted of one hydrophobic portion flanked by two symmetric hydrophilic portions. Furthermore, the structure–activity relationships of PI3Kγ inhibitors were elucidated and the activity differences between them were discussed.

Keywords: PI3Kγ; Molecular docking; Pharmacophore; Structure–activity relationships

1. Introduction

Phosphoinositide 3-kinases (PI3Ks) catalyze the phosphorylation of 3-OH group of phosphatidyl myo-inositol (PtdIns) lipids to generate different 3′-phosphorylated lipid products that act as secondary messengers. PI3Ks are found to play important roles in a lot of biological processes, such as cell survival and proliferation, cell motility and adhesion, cytoskeletal rearrangement and vesicle trafficking [1,2]. There are three major classes of PI3Ks, namely Class I, II and III, based on their sequences and substrate specificities. Class I PI3Ks are further divided into Class IA and IB according to regulatory subunit. Class IA enzymes (α, β, and δ) have a p85 regulatory subunit containing two SH2 domains, whereas Class IB enzyme (PI3Kγ) has a p101 subunit, which is required for maximal Gβγ-stimulated formation of PIP_3 [3,4].

Macrophages and neutrophils from PI3Kγ knockout mice show reduced motility in vitro and in vivo models of inflammation, as well as an impaired respiratory burst [5–7]. PI3Kγ-deficient mice also show resistance to thromboembolism [8]. In addition, the lipid products resulting from PI3Kγ activity are elevated in certain tumors [9,10]. PI3Kγ/Akt signaling pathway not only involves in characteristic cancer processes but also contributes to resistance to chemotherapy and γ-irradiation therapy [11]. All these facts suggest that PI3Kγ is a potential target for cancer and inflammation treatments, and hence, spark great interests in the discovery and development of its inhibitors.

Docking method is a powerful tool to explore ligand-receptor interaction providing 3D structure of the target. Currently docking software mainly includes Autodock, Dock, FlexX and Gold [12–15]. Here Autodock was used for the study. Autodock uses three types of algorithms (Genetic Algorithm, SW algorithm and Lamarckian Genetic Algorithm) to place ligand into the active site of a target [12]. The scoring function of Autodock is used to estimate the free binding energy of the ligand-protein complex. Normally Autodock provides 10 can-

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didate conformations. Among them the conformation with the lowest binding energy could be regarded as the bound conformation to protein.

Program Grid22 is a computational procedure to determine energetically favorable binding sites on molecules with known structures [16]. The program works by defining a three-dimensional grid of points that contains the chosen ligand-binding pocket. The interaction of the Probe groups with the target is computed at sample positions (the grid points) distributed throughout and around the molecule. With the Probe at each Grid point in turn, the interaction is calculated from: $E_{total} = \sum E_{LJ} + \sum E_{HB} + \sum E_Q + S$, where E_{total}, E_{LJ}, E_{HB}, E_{Q} and S represent overall energy, Lennard–Jones interaction, hydrogen-bonding interaction, electrostatic interaction and entropic term, respectively.

In the last decade, four types of PI3Kγ inhibitors (benzopyrano, quinazoline, quinoline and caffeine analogs [17–21]) have been discovered, shown in Fig. 1. The first three types of compounds have a benzopyrano, quinazoline and quinoline moiety, respectively, and the last one is derived from caffeine. However, there are some common weaknesses for these inhibitors, such as low activities, low selectivity and low water-solubility. Therefore, it is necessary to explore the structure–activity relationships of known ligands and their action mechanisms on the enzyme in order to shed light on the search of new potent, selective and well water-soluble PI3Kγ inhibitors.

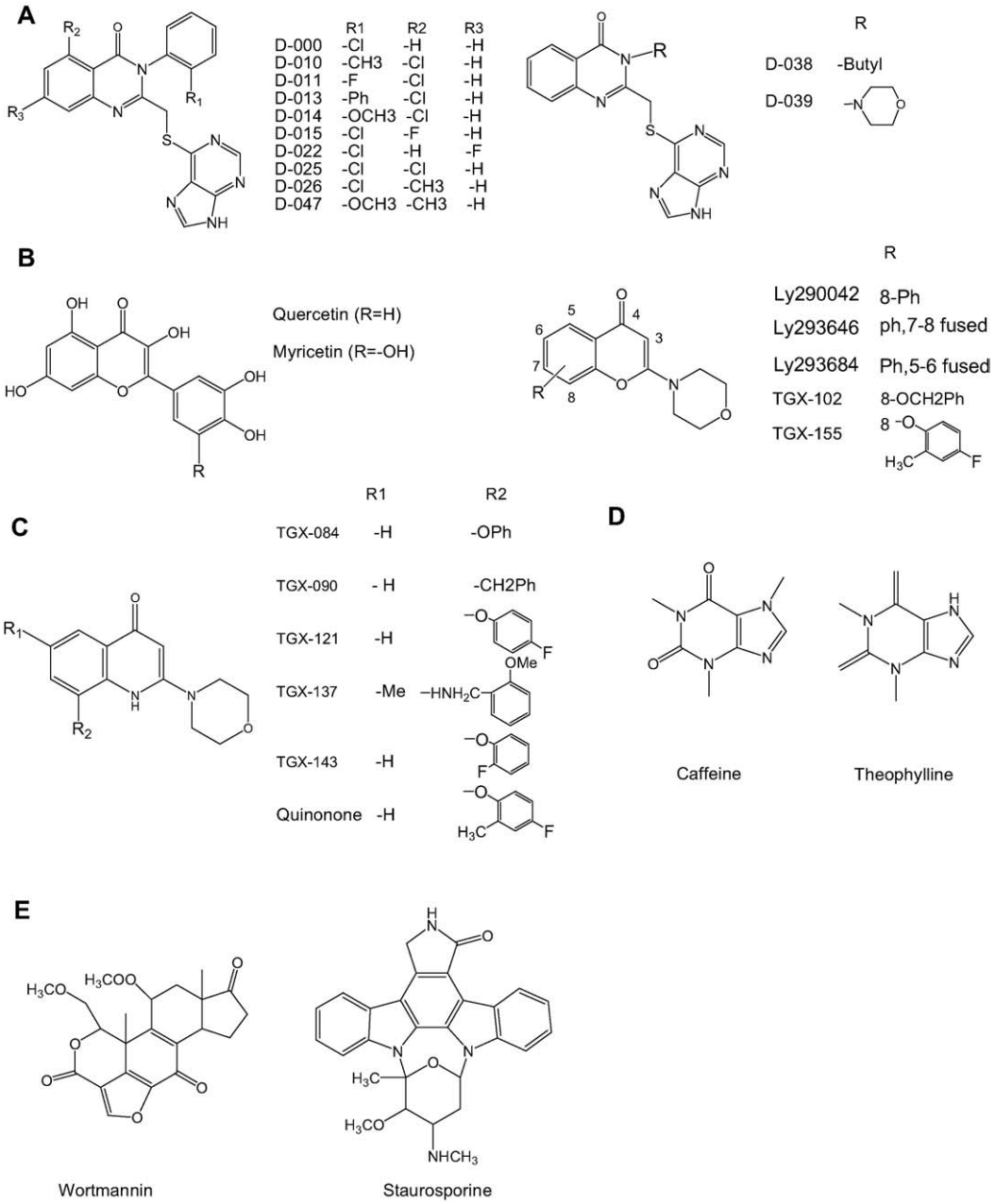

Fig. 1. Structures of 29 PI3Kγ inhibitors used in the study. (A) Quinazoline derivatives, (B) Benzopyrano derivatives, (C) Quinoline derivatives, (D) Caffeine analogs, (E) Wortmannin and Staurosporine.