DESIGN OF NEW HETEROCYCLIC COMPOUNDS AS POTENTIAL PI3K INHIBITORS FOR CANCER THERAPY

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Introduction

The phosphoinositide-3-kinase (PI3K) family represents an important molecular target for cancer targeted therapy since genetic alteration related to this enzyme family is strongly associated with some types of cancer (Noorolyai *et al.*, 2019). Class I PI3Kα, β, δ, and γ are the main isoforms associated with cancer, among which isoforms α and β are expressed ubiquitously and isoforms δ and γ remain restricted to myeloid cells (De Santis *et al.*, 2019). The PI3K inhibitors (PI3Ki) that have been developed for application in cancer therapy can be divided in two main groups: isoform-selective PI3Ki and pan-PI3Ki. Although pan-PI3Ki have an efficient antitumor activity, they also have important on-target side effects due to their high activity over PI3Kα in normal cells, limiting the progress of these inhibitors in clinical trials. This is also observed in specific PI3Kαi (Janku; Yap; Meric-Bernstam, 2018). Thus, inhibition of the isoforms δ and γ may represent a more efficient approach for developing PI3Ki, since the first specific PI3Kδi (Idelalisib) was approved by the FDA in 2014 (Evans *et al.*, 2016). Based on structural features of isoform-selective PI3Ki, it was possible to note the adoption of a propeller-shaped conformation when interacting with the ATP binding site of this enzyme from some inhibitor such as Idelalisib. Since the propeller-shaped PI3Ki have minimal effect over PI3Kα, they offer a good way for the development of selective PI3Kδ and/or γ inhibitors with minimal systemic on-target side effects (Garces; Stocks, 2019; Miller; Thompson; Gabelli, 2019). In this work, we design a new series of heterocyclic compounds by molecular modification techniques from propeller-shaped PI3Ki on available literature.

Method

Information about the structure and properties of isoform-selective PI3Ki were selected from Scopus and Google Scholar databases from which original and review articles with relevant information about propeller-shaped PI3Ki were selected. Structural modifications proposed were based on classical molecular modification techniques, such as bioisosterism (Meanwell, 2011).

Results / Discussion

Comparative analysis of propeller-shaped PI3Ki structure shows that, in general, this kind of inhibitor is composed of two heterocyclic subunits (A and B, Fig. 1) connected by an alkyl group (C). Affinity for the ATP-binding site and specificity for isoforms δ, γ, or β can be modulated depending on the substituents. Crystallographic information shows that class I PI3K has a highly homologous ATP-binding site, differing only by some key residues on its periphery (Miller; Thompson; Gabelli, 2019). Thus, it was possible to divide the ATP-binding site of PI3K into five regions, depending on their contribution to specificity or affinity: Affinity pocket, specificity pocket, hinge region, and non-conserved regions I and II (Garces; Stocks, 2019; Miller; Thompson; Gabelli, 2019). In this work, we propose a new series of heterocyclic compounds as potential PI3Ki planned by molecular modifications from the general structure of propeller-shaped PI3Ki, such as Idelalisib (Figure 1). Since propeller-shaped inhibitors are the only class

of PI3Ki that interact with the specificity pocket, we aim to explore the influence of this interaction for the inhibitory activity. Thus, based on the bioisosterism concept, we propose the substitution of the quinazolin-4(3*H*)-one present in Idelalisib for pyrazole condensed heterocycles. Another modification proposed is the extension of Region II through the addition of long and/or hydrophobic groups (R_1) to the heterocycle A, since the available literature (Evans *et al.*, 2016) has shown that this kind of modification provides high specificity for PI3Kγ over other isoforms. Consequently, this modification could provide the assessment to new propeller-shaped PI3Kγi, which are still rare. Molecular modifications of the phenyl group attached to the position 3 of the quinazolin-4(3*H*)-one on Idelalisib are also proposed. The addition of 2-substituted phenyl groups (R_2) can cause a rotational restriction that can allow an increase in biological activity (Lodola *et al.*, 2017). The change of the purine ring present in Idelalisib by pyrazole condensed heterocycles was also based on the bioisosterism concept aiming to avoid the metabolic oxidation of the carbon C-8 by aldehyde oxidase. We have also suggested the extension of heterocycle B through the addition of new substituents (R_4), in order to assess the affinity pocket, since the interaction with this region of the binding site is known to provide an increase in the inhibitors' potency (Miller; Thompson; Gabelli, 2019).

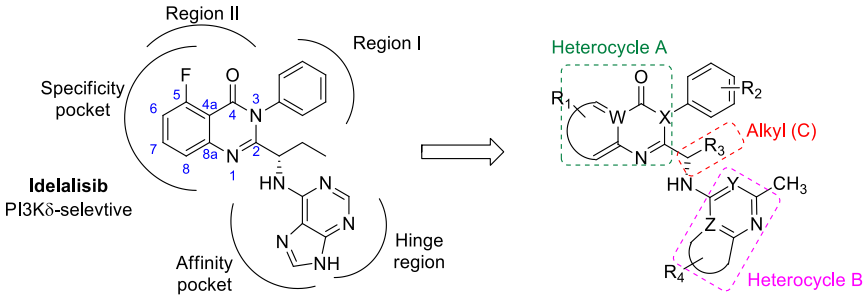

Figure 1: General structure of the new series of heterocycles based on the main regions of interaction with PI3K ATP-binding site exemplified in the Idelalisib structure.

Conclusion

Since the propeller-shaped PI3Ki chemotype represent a higher specificity over PI3Kα, avoiding the emergence of systemic on-target side-effects, they provide a good way for planning new isoform-selective PI3Ki. Analyzing the available literature about propeller-shaped PI3Ki, we were able to suggest a new series of heterocyclic compounds with potential activity on this target. From this point, we can start the next research steps by proceeding to the synthesis and biological evaluation of the planned compounds.

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