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Planning of new heterocyclic compounds targeting class I PI3Ks for cancer therapy

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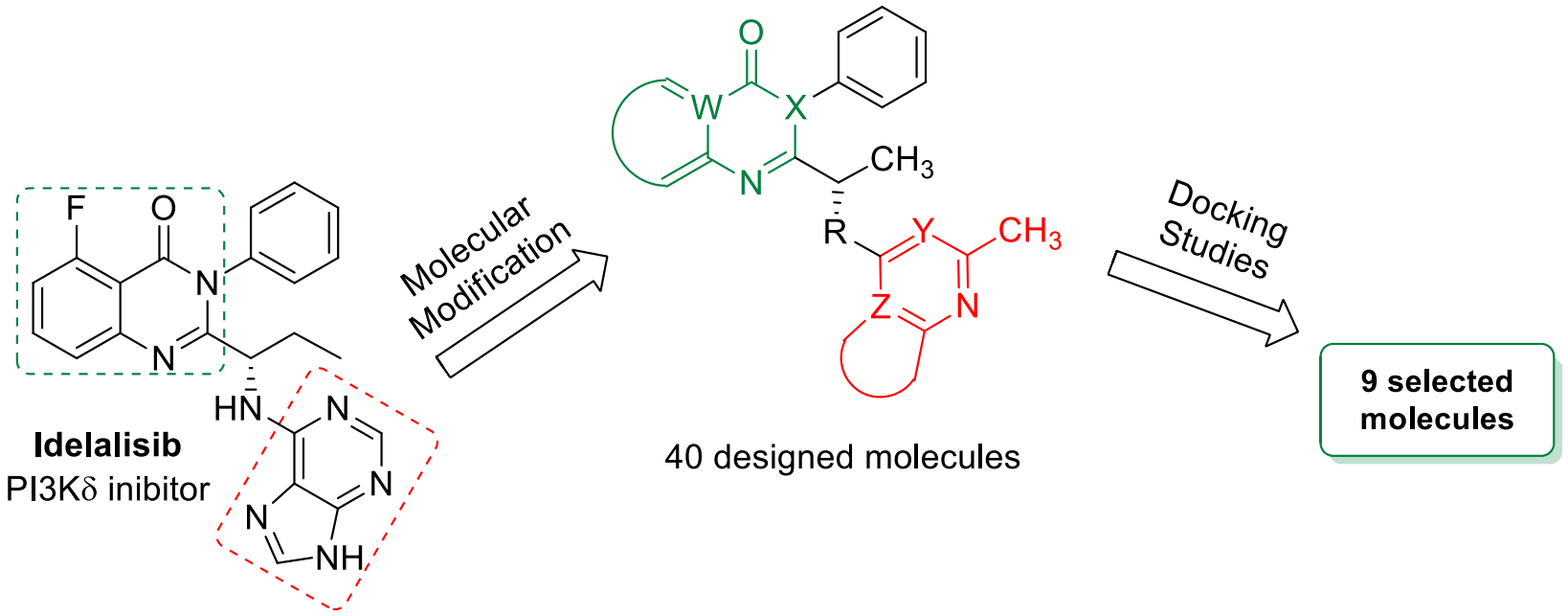
Graphical Abstract



Abstract: Class I phosphoinositide-3-kinase (PI3K-C1) are considered important therapeutical targets for cancer therapy since its four isoforms (PI3Kα, β, δ, and γ) are associated with diverse neoplastic manifestations. The first PI3K inhibitor approved by the FDA for cancer therapy, Idelalisib, has great selectivity over myeloid-restricted PI3Kδ. This selectivity is assigned to the Idelalisib propeller-shaped conformation on the active site, having a minimal effect over the ubiquitously expressed PI3Kα. This feature turns Idelalisib a lead compound for developing new PI3Kδ inhibitors. Based on that, this work aims to design and conduct preliminary virtual screening of new heterocyclic compounds for application in cancer therapy. In this sense, 40 compounds that are structurally related to Idelalisib were designed using the concept of bioisosterism. Afterward, the designed molecules were submitted to docking studies over PI3Kδ on Autodock 4.0. The docking protocol was validated with the redocking technique using the complexed ligand LASW1976. The Lowest Binding Energy (LBE) and H-bond profile on the active site were used as parameters for preliminary virtual screening. Idelalisib was also docked to be used as a positive control. 9 out of the 40 designed molecules presented LBE values (-8.10 to -9.95 Kcal/mol) close to Idelisib's (-9,54 Kcal/mol), and among them, 7 reproduced at least 1 H-bond observed on Idelalisib or LASW1976 on the active site. These results indicate the potential of these 9 compounds to inhibit PI3Kδ, which will be synthesized and biologically evaluated in follow-up studies.

Keywords: Cancer Therapy; Idelalisib; phosphoinositide-3-kinase.

Introduction

- Phosphoinositide-3-kinases (PI3Ks) convert PIP_2 to PIP_3, and are important second-messengers involved in cellular signal transduction.[1]
- PI3K is the first node of the PI3K-AKT-mTOR pathway, which leads to important cellular effects often associated with the Hallmarks of Cancer, and may be a trigger for the tumorigenesis process. [1, 2]
- The genetic alterations linked to PI3Ks overexpression or overactivity are also strongly associated with the diverse types of cancer.[3]
- Class I PI3K isoforms (α, β, δ, and γ) are viable targets in cancer targeted therapy.

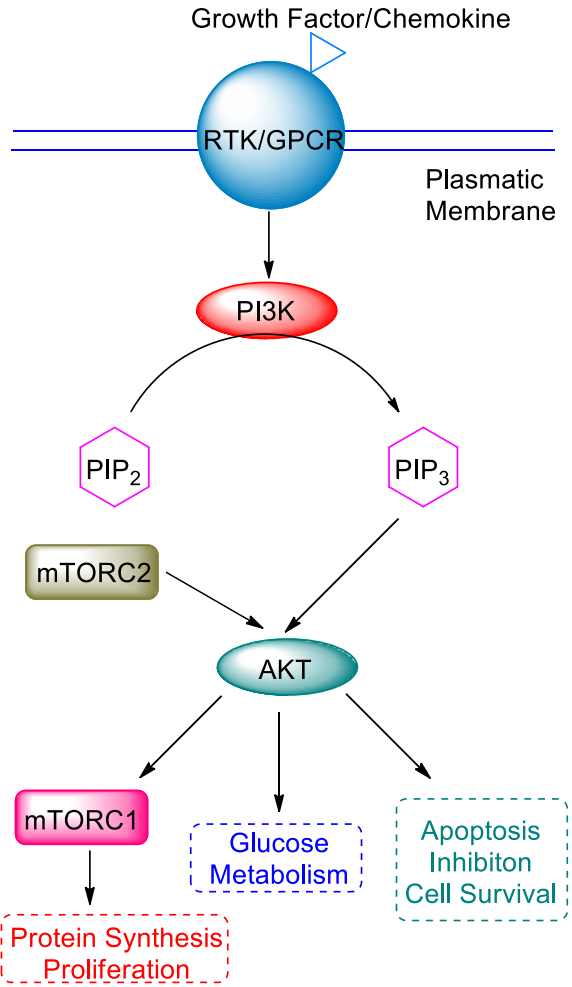


Fig.1. PI3K-AKT-mTOR pathway.

1- De Santis et al. Biochim. Biophys. Acta Rev. Cancer, 1871; (2):361, 2019;
2- Moses, C.; Garcia-Bloj, B.; Harvey, A. R..; Blancafort, P. Eur. J. Cancer, 93, 10, 2018;
3- Noorolyai, S. et al. Gene, 698(2019):120, 2018.

Introduction

- The PI3K inhibitors (PI3Ki) are divided into isoform-selective PI3Ki and pan-PI3Ki.[4]
- The pan-PI3Ki and the selective PI3Kαi showed on-target side effects due to their high activity over PI3Kα in normal cells, limiting the progress of these inhibitors in clinical trials.[4]
- Since the δ and γ isoforms are restricted to myeloid tissues and its inhibition may interfere minimally in the physiological activity of PI3Ks, the inhibition of these isoforms seem to be a more efficient approach for PI3Ki.[5]
- Idelalisib was the first isoform-selective PI3Ki FDA-approved for myeloid cell cancer treatment.

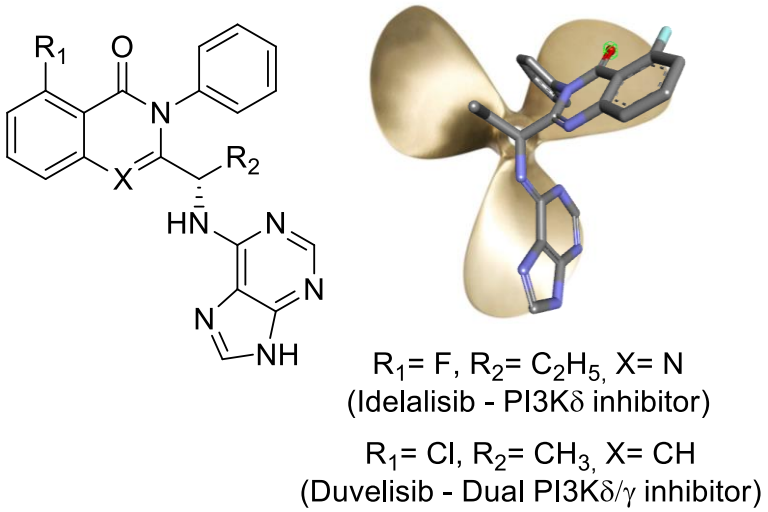
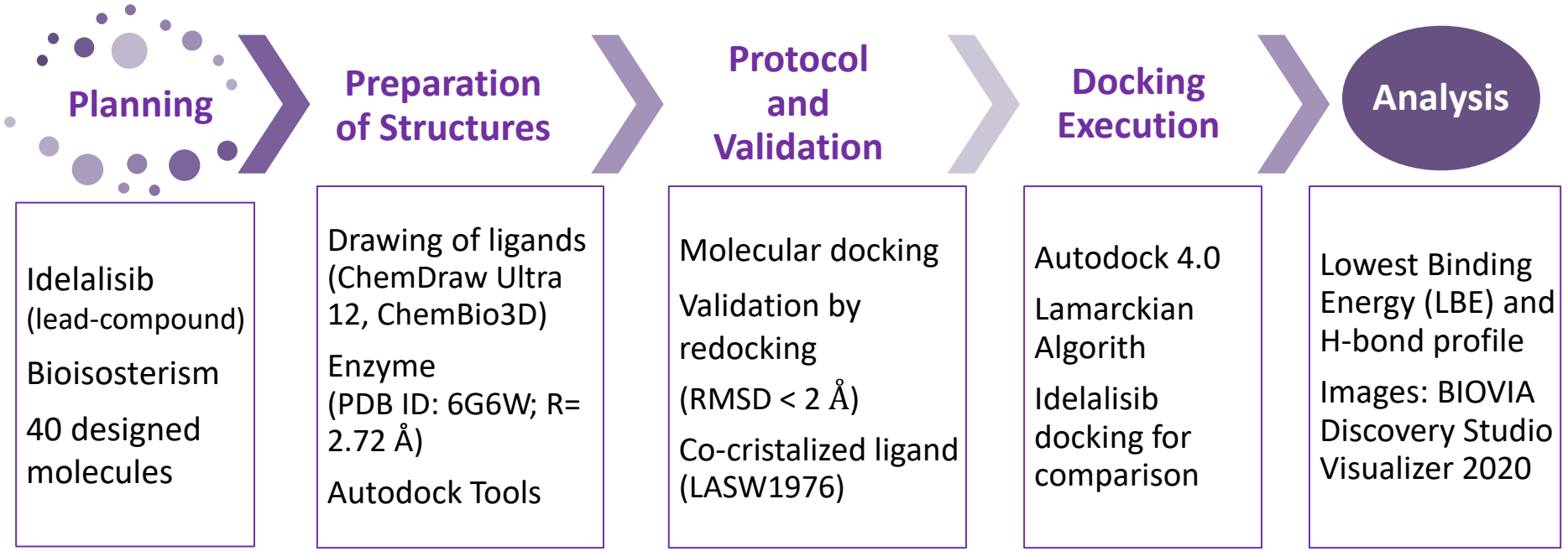


Fig.2. Propeller-shaped conformation of PI3Kδ and PI3Kδ/γ inhibitors when interacting with the ATP binding site of the enzyme. This conformation has a minimal effect over PI3Kα with minimal systemic on-target side effects.

4- Janku, F.; Yap, T. A.; Meric-Bernstam, F. Nat. Rev. Clin. Oncol., 15(5):273, 2018;
5- Miller, M. S.; Thompson, P. E.; Gabelli, S. B. Biomolecules, 9(3):82, 2019.

Introduction

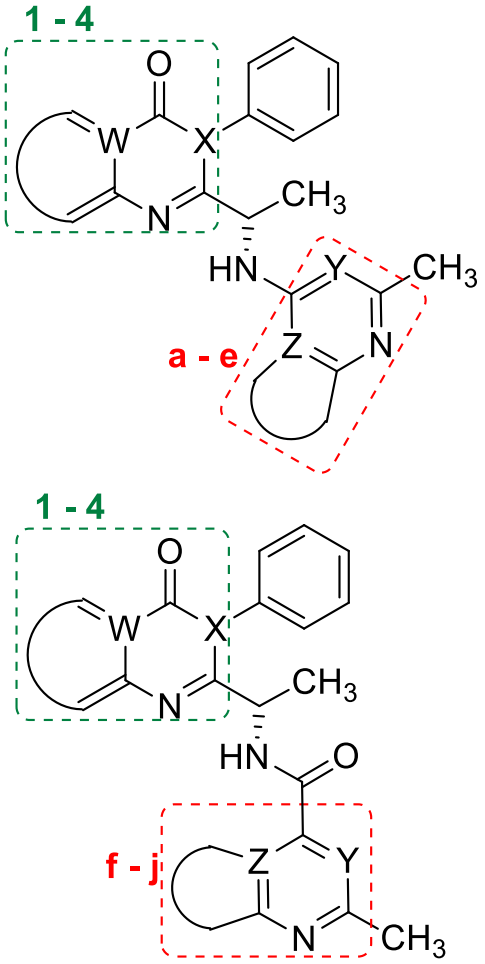
- In this work, a new series of heterocyclic compounds were designed through molecular modification techniques using Idelalisib, an FDA-approved drug for cancer therapy, as a lead-compound. Afterwards, a preliminary virtual screening of the planned compounds was conducted using molecular docking as a classification parameter.



Results and discussion

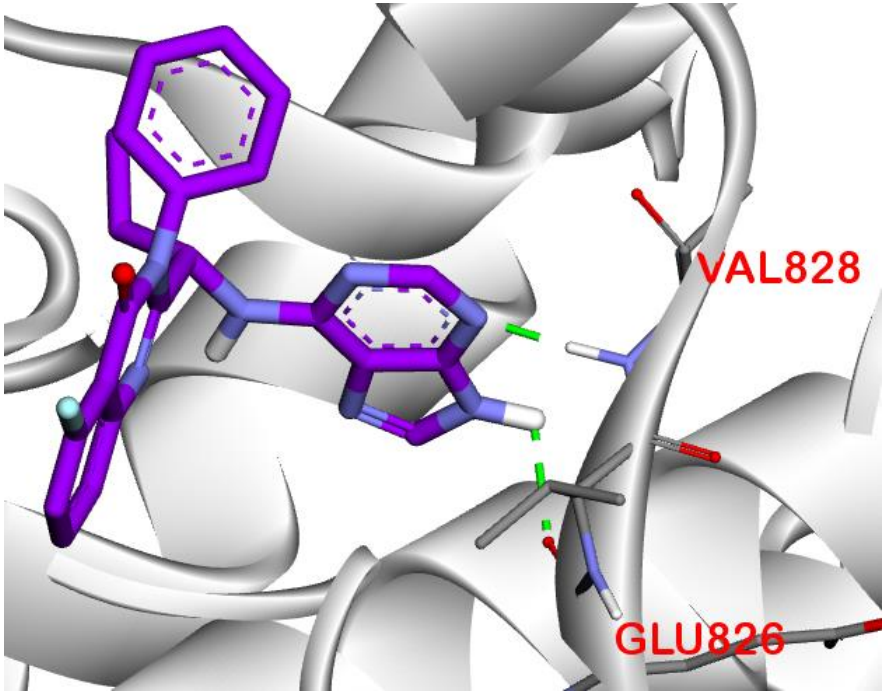
- Among the 40 designed molecules, 9 showed LBE values close to Idelisib's.

Ligante	LBE (kcal/mol)	Total H-bonds	Residues				
LASW1976 (redocking)	-13,32	5	Val828	Lys779	Asp787	Tyr813	Asp911
Idelalisib	-9,54	2	Val828	Glu826			
1a	-9,95	1	Val828				
2b	-9,39	1	Val828				
4d	-9,39	2		Lys779			Asp911
1b	-8,59	0					
4e	-8,49	2		Lys779			Asp911
4a	-8,48	0					
1i	-8,27	2				Tyr813	Asp911
3d	-8,13	1	Val828				
1g	-8,10	2				Tyr813	Asp911

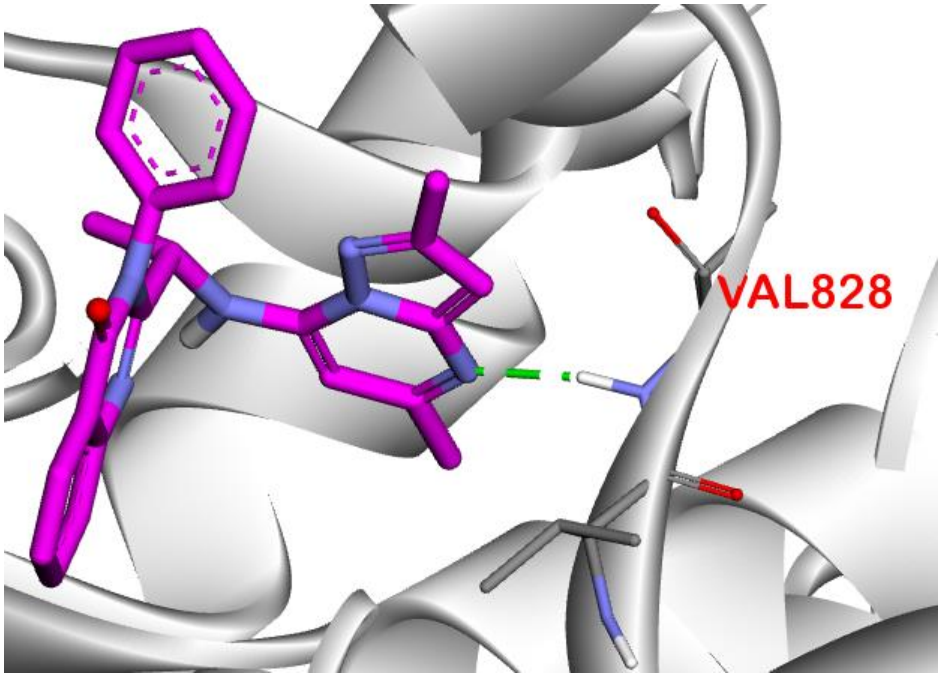


Results and discussion

- 7 out of the 9 selected molecules showed at least 1 H-bond in common with Idelalisib or LASW1976 bond interactions on the PI3Kδ active site.



Idelalisib interactions with Val828 and Glu825



Best performing compound **1a** interactions with Val828

H-bonds **(Dashed green lines)**

Conclusions

- The virtual screening protocol used lead to the planning of new heterocyclic compounds as PI3Kδ-selective inhibitors, reducing the number of potential inhibitors that are to be synthesized.
- The results indicated the potential of 9 designed molecules to inhibit the PI3Kδ enzyme. These molecules would then be sinthetisized and evaluated against cancer cell lines.
- Further *in sílico* studies will be carried out with the designed molecules, particularly docking studies with the PI3Kγ isoform.

Acknowledgments

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