DESIGN AND SYNTHESIS OF POTENTIAL ANTICANCER COMPOUNDS

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Introduction

Cancer is a group of diseases caused by uncontrolled cell growth and is among the leading causes of death worldwide. [1] In this study, we explore virtual screening to design new compounds targeting phosphatidylinositol-3-kinase (PI3K) enzymes, often overactive in cancer cells. By inhibiting PI3Kδ and PI3Kβ, the researchers aim to develop effective treatments for cancers with phosphatase and tensin homolog (PTEN) deficiencies. [2] This work presents the synthesis of new compounds designed as anticancer agents.

Material and Methods

We generated a virtual library of new chemical structures based on the idelalisib drug, a PI3Kδ-selective inhibitor. [3] The generated library was subjected to a virtual screening using molecular docking simulation on Autodock 4.2 software. The PI3Kδ crystal structure (PDB-ID: 6G6W, resolution: 2.72 Å) was obtained from the Protein Data Bank. The protocol was validated by redocking and had their best-scoring docked poses with RMSD<2Å. The analysis of intermolecular interactions of the generated complexes was performed by BIOVIA Discovery Studio Visualizer 2020.

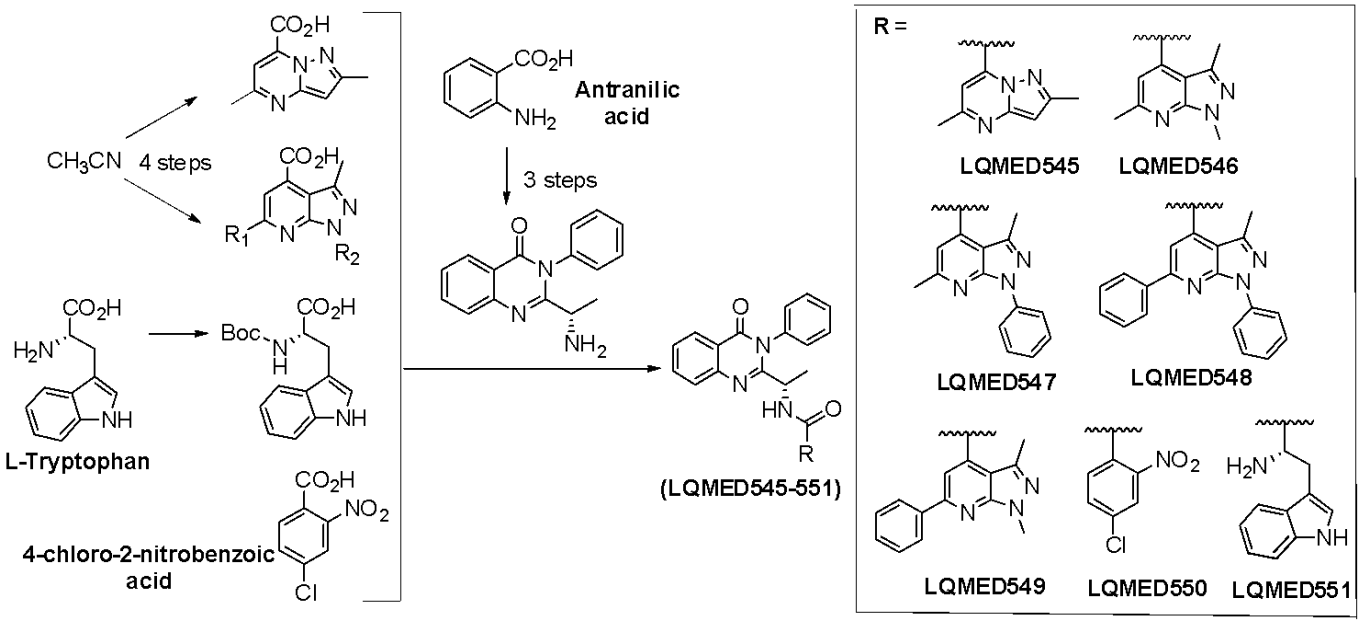
Reagents were obtained commercially or prepared by modifying functional groups for the synthesis. TLC monitored reactions on silica gel plates using a gradient eluent and UV visualization. Structural identification of synthesized compounds was carried out using the following spectroscopic analyses: FTIR by ATR on a Shimadzu IRTracer-100; ^{1}H NMR on Varian VNMRS 500 MHz and Bruker 500 MHz spectrometers; ^{13}C NMR, DEPTQ, HSQC, and HMBC on Bruker 500 and 400 MHz spectrometers; and HRMS on a Bruker ESI-Q20 TOF in positive ion mode.

Results and Discussion

We created a virtual library of chemical structures comprising 170 proposed molecular structures related to the idelalisib drug, exchanging the purine nucleus for pyrazolopyridine or pyrazolopyrimidine to prevent metabolic oxidation at C-8 of the purine. These structures were designed with the desired propeller shaped to perform H-bond interactions with the amino acid residues Glu826 and Val828 in the hinge region and present good values of minimal binding energy (MBE). [3,4]

The virtual library structures were evaluated *in silico* for the inhibition potential of the PI3Kδ and β isoforms and selected by virtual screening using the molecular docking technique in the active site of these enzymes. The selection of structures for the chemical synthesis step initially considered the PLP score of the molecular docking in the two targets, PI3Kδ and β, and the availability of reagents. It was considered indicative of potential inhibitors of PI3Kδ and β isoforms PLP score values greater than 90. [4] Seven new compounds (LQMED545-551, **Fig. 1**) consisting of combinations of an aromatic nucleus (1*H*-pyrazolo[3,4-*b*]pyridine, pyrazolo[1,5-*a*]pyrimidine e 1*H*-indole) interconnected with the quinazolin-4(3*H*)-one nucleus by an amide group were synthesized, purified and their structures elucidated by spectroscopic methods.

Fig. 1. Synthesis route of the designed compounds LQMED545-551.



Conclusion

This research used virtual screening to plan new heterocyclic compounds as potential anticancer agents, specifically targeting PI3Kδ and PI3Kβ enzymes. This approach presents a promising yet under-explored strategy for inhibiting PI3K and offers potential applications in treating tumors with PTEN deficiencies.

Seven compounds derived from the quinazolin-4(3*H*)-one core, incorporating subunits of the heterocycles 1*H*-pirazolo[3,4-*b*]pyridine, pyrazolo[1,5-*a*]pyrimidine, and 1*H*-indole, were synthesized with overall yields ranging from 17 to 76%. Their structures were confirmed using spectroscopic methods.

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