Design, Synthesis, and Biological Evaluation of *N*'-(Diphenylmethylene) Benzohydrazide Derivatives as PI3Kα Inhibitors

By

Qutaiba Salah Jasim

Supervisor

Dr. Dima A. Sabbah

AL-Zaytoonah University of Jordan, 2021

Abstract

Phosphoinositide 3-Kinase α (PI3Kα) has been defined as a substantial target for the design and development of anticancer agents. Derivatives of *N'*-(diphenyl methylene)-1H-indole-2-carbohydrazides, *N*-phenyl-1H-indole-2-carboxamides, and *N*-benzyl-1H-indole-2-carboxamides (**35-48**) were synthesized, the present yield was (40%-91%), and characterized using FT-IR, ^{1}H and ^{13}C-NMR. The derivatives displayed distinguishable inhibitory activity in human epithelial colorectal adenocarcinoma (Caco-2) and colon carcinoma (HCT-116) cell lines. Compounds (**35)** (Caco-2 IC_{50} = 131.3 µM, HCT-116 IC_{50} = 230.2 µM), **36** (Caco-2 IC_{50} = 54.41 µM, HCT-116 IC_{50} = 419.7 µM), **37** (Caco-2 IC_{50} = 161.2 µM, HCT-116 IC_{50} = 600 µM), and **40** (Caco-2 IC_{50} = 1807 µM, HCT-116 IC_{50} = 91.83 µM) exerted distinct inhibitory effect in HCT-116 cell line. The induced-fit docking (IFD) studies showed that the derivatives accommodate PI3Kα kinase domain and bind to the backbones of key binding residues.

Keywords: Cancer, PI3Kα inhibitors, kinase domain, Caco-2, HCT-116.