Design, Synthesis, and Biological Evaluation of *N*-Substituted-7-Methyl-4-Hydroxy-2-Quinolone-3-Carboxamides as PI3Kα Inhibitors

By

Batool Mohammed Al-lahowani

Supervisor

Dr. Dima A. Sabbah

Co-supervisor

Dr. Rima Hajjo

AL-Zaytoonah University of Jordan, 2021

Abstract

Phosphoinositide-3-kinase α (PI3Kα) is assigned as a promising target for cancer treatment. A series of *N*-substituted-7-methyl-4-hydroxy-2-quinolone-3-carboxamides (**34-50**) was synthesized and characterized by FT-IR and NMR (^{1}H and ^{13}C). The series exhibited selective inhibitory activity against human colon carcinoma (HCT-116) epithelial and colorectal adenocarcinoma (Caco-2) cell lines. Compounds **48** (HCT-116 IC_{50} = 13 µM, Caco-2 IC_{50} = 82 µM), **38** (HCT-116 IC_{50} = 32 µM, Caco-2 IC_{50} = 105 µM), **49** (HCT-116 IC_{50} = 42 µM, Caco-2 IC_{50} = 149 µM), **42** (HCT-116 IC_{50} = 53 µM, Caco-2 IC_{50} = 100 µM), **41** (HCT-116 IC_{50} = 49 µM, Caco-2 IC_{50} = 105 µM) exhibited distinct inhibitory activity in HCT-116 cell line. The induced-fit docking (IFD) studies against PI3Kαs shows that the series occupies PI3Kα kinase domain and forms H-bonds with Asp933, Ser919, Tyr836, Tyr835, Asp810, Lys802, Ser774 of mutant PI3Kα

Keywords: HCT-116 cell line, Caco-2 cell line, PI3Kα**,** cancer**.**