Design, Synthesis, and Biological Evaluation of Naphthyridine Carboxamides as Potential Anticancer Agents

By

Taima Mohammad Odeh Alodat

Supervisor

Prof. Dr. Dima A. Sabbah

Co-supervisor

Prof. Dr. Kamal Sweidan

Al-Zaytoonah University of Jordan, 2023

Abstract

Cancer is a life-threatening polygenic disease accompanied with massive incidence and death rates. Changes in DNA sequence and abnormal signaling pathways proceed cancer development. Analogues of 4-hydroxy-1,8-naphthyridin-2-one-3-carboxamide were designed and synthesized as a surrogate for 4-hydroxy-2-quinolone-3-carboxamide. The synthesized compounds were characterized using FTIR, ^{1}H NMR, ^{13}C NMR, and elemental analysis.

Biological examinations against human colon carcinoma cell (HCT-116) and breast cancer cell (MCF-7) lines displayed that compounds induce potent and selective inhibitory activity. Derivatives with tailored benzyl motif illustrated by *m*-CF_3 (**36**) (IC_{50} HCT-116 = 22.9µM, IC_{50} MCF-7 = 42.0µM), *p*-CF_3 (**37**) (IC_{50} HCT-116 = 52.9µM, IC_{50} MCF-7 = 125.0µM), *o*-F (**38**) (IC_{50} HCT-116 = 55.6µM, IC_{50} MCF-7 =

98.0μM), *m*-F (**39**) (IC_{50} HCT-116 = 51.7μM, IC_{50} MCF-7 = 69.3μM), and *p*-F (**40**) (IC_{50} HCT-116 = 31.7μM, IC_{50} MCF-7 = 58.2μM) potentiate the activity interrogating that flexibility in carboxamide side chain and/or electron-withdrawing group are crucial for activity. However, analogues with substituted aniline moiety exemplified by *o*-CF_3 (**47**) (IC_{50} HCT-116 = 35.5μM, IC_{50} MCF-7 = 74.0μM), *m*-CF_3 (**48**) (IC_{50} HCT-116 = 37.5μM, IC_{50} MCF-7 = 64.0μM), and *p*-CF_3 (**49**) (IC_{50} HCT-116 = 39.3μM, IC_{50} MCF-7 = 72.0μM) incite the activity implying that steric features and/or electron-withdrawing group is/are essential for activity.

The induced-fit docking (IFD) studies against potential receptors such as phosphoinositide-3-kinase (PI3Kα), histone deacetylase (HDAC-II), and caspase-3 receptor disclosed distinctive docking scores against HDAC-II motivating us to explore the molecular level interaction of the verified series to better identify potential receptor.

Keywords: 4-Hydroxy-1,8-naphthyridin-2-one-3-carboxamide, Cancer, Docking, HCT-116, MCF-7.