Optimizing of core structure of 4-hydroxy-2-quinolone as potential anticancer agent.

By

Hana Kassim Al-Sawaf

Supervisor

Prof. Dr. Dima A. Sabbah

Co-supervisor

Prof. Dr. Kamal Sweidan

Al-Zaytoonah University of Jordan, 2023

Abstract

Cancer is a complex of deadliest heterogeneous diseases associated with a vast incidence and death rates. Genetic mutations and aberrant signaling pathways are considered as one of numerous factors predisposing cancer development. Derivatives of 4-hydroxy-1,6-naphthyridin-2-one-3-carboxamide were designed and synthesized in order to optimize the scaffold of 4-hydroxy-2-quinolone-3-carboxamide. The identity of the synthesized analogues was characterized using FT-IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis. Biological investigations against human colon carcinoma cell (HCT-116) and breast cancer cell (MCF-7) lines showed that analogues exhibit potent and selective inhibitory activity. Analogues tailored with benzyl moiety (**47**) (IC_{50} HCT-116 = 43.30 μM, IC_{50} MCF-7 = 88.98 μM) exerted promising activity implying that flexibility of carboxamide side chain assists in orientating the core structure deeply

in the binding domain. Derivatives with substituted benzyl motif exemplified by *o*-F (**49**) (IC_{50} HCT-116 = 62.32 μM, IC_{50} MCF-7 = 89.27 μM), *m*-F (**50**) (IC_{50} HCT-116 = 52.34 μM, IC_{50} MCF-7 = 37.06 μM), *p*-F (**51**) (IC_{50} HCT-116 = 50.48 μM, IC_{50} MCF-7 = 20.0 μM), *m*-CF_3 (**53**) (IC_{50} HCT-116 = 88.50 μM, IC_{50} MCF-7 = 33.0 μM), and *p*-CF_3 (**53**) (IC_{50} HCT-116 = 81.04 μM, IC_{50} MCF-7 = 54.0 μM) confirmed that flexibility of the side chain along with introducing -F and/or -CF_3 induce the activity. Results anticipate that electronegativity and/or hydrophobicity improves ligand/receptor binding interaction. The induced-fit docking (IFD) studies against potential receptors such as phosphoinositide-3-kinase (PI3Kα), histone deacetylase (HDAC-II), and estrogen receptor (ER) revealed distinguishable binding scores against HDAC-II encouraging us to dip deeply into the molecular level to better retrieve potential receptor (s).

Keywords: Cancer, Docking, 4-Hydroxy-1,6-naphthyridin-2-one-3-carboxamide, HCT-116, MCF-7.