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Abstract of the thesis

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Title of the Thesis: DESIGN AND SYNTHESIS OF NEW ULK1/2 INHIBITORS AS ANTICANCER AGENTS

Abstract

Contents of the abstract: Autophagy initiation kinase 1 and 2 (also known as ULK1/2 in humans) is a protein kinase that plays a key role in the initiation of the autophagy process. Autophagy is a cellular process in which the cell breaks down and recycles its components, such as damaged or unnecessary proteins and organelles. This process helps the cell to maintain homeostasis and can also play a role in response to stress, such as starvation. In autophagy machinery various genes and enzymes are involved, among the most promising enzymes is ULK1 (Unc-51-like autophagy activating kinase 1). ULK1 is activated by various stress signals, such as nutrient deprivation, and phosphorylates other proteins to initiate the formation of the autophagosome, which is the membrane-bound structure that encloses the material to be degraded during autophagy. ULK1 has been found to play a role in the development and progression of non-small cell lung cancer (NSCLC). Research has shown that ULK1 is involved in promoting tumor cell proliferation, invasion, and resistance to chemotherapy and radiation therapy. ULK2 (Unc-51 like autophagy activating kinase 2) may have additional functions beyond autophagy regulation, such as cell migration, embryonic development, and neuronal survival. Inhibiting ULK1 has been found to sensitize NSCLC cells to chemotherapy and radiation, suggesting that targeting ULK1 may be a promising strategy for treating NSCLC. The present research proposal aims to design a new series of heterocyclic rings like Thiadiazole, quinazoline, benzimidazole, pyrimidine, and aniline derivatives as ULK ½ inhibitors. Initial *in-silico* studies of Ligand-based pharmacophore modeling, Molecular docking, Molecular dynamic simulation, DFT, and Drug-likeness assessment were done to strengthen the rationale of the study. Based on the literature review different synthetic routes were adopted to synthesize aforementioned heterocyclic compounds. A new series of nitrogen and sulfur-containing heterocyclic compounds were synthesized and characterized using spectral analysis such as IR, ^{1}H NMR, and MASS. The synthesized compounds were tested for *In-vitro* 96 well MTT assay on the A549 cell line (NSCLC) with Cisplatin as positive control. Compounds **12(b-IV), 12(c-II), 12(b-I), 12(d-IV), 12(f-IV)** and **12(a-II)** showed maximum inhibition IC_{50} values respectively (12.2 µM, 16.35 µM, 20.61 µM, 20.76 µM, 22.01 µM, and 32.04

μM) against Non-small cell lung cancer (A549) cell line, which is more potent or equivalent to Cisplatin (33.09 μM) as standard drug.

Keywords: Anticancer, Autophagy 1,3,4-Thiadiazole analogs, ULK inhibitors, MTT Assay.

Research Problem: Design and Synthesis of new Ulk1/2 Inhibitors as Anticancer agents.

Methodology followed for research: In this study, various investigations were conducted, including the computational assessment of proposed derivatives, and the synthesis and characterization of the proposed derivatives. Subsequently, a biological evaluation was carried out using the MTT assay method.

Outcome of the research: The descriptive result indicates that the synthesized derivatives have good binding energy, pharmacodynamic properties, and better anticancer activity as compared to standard drugs. From this result, we have inferred that the proposed derivatives help find the future potential anticancer agents.

Application: The author believes that the suggestions outlined in this thesis, derived from the study's results, will assist the pharmaceutical industry in developing a more efficient anticancer agent. The comprehensive findings are expected to provide valuable insights into the design, synthesis, characterization, and evaluation of novel entities.

This PhD Thesis would be useful for Research scholars, as well as Pharmaceutical industries

List of Publications:

1. Sidat PS, Jaber TMK, Vekaria SR, Mogal AM, Patel AM, Noolvi M. Anticancer Biological Profile of Some Heterocylic Moieties-Thiadiazole, Benzimidazole, Quinazoline, and Pyrimidine. Pharmacophore. 2022;13(4):59-71. https://doi.org/10.51847/rT6VE6gESu
2. Sidat P, Noolvi M, Patil R, Rathod S. ULK1/2 Inhibitor: Essential Component of Autophagic Cell Death Machinery. Journal of Pharmaceutical Research. 2022 Jul;21(3):56. https://doi.org/10.18579/jopcr/v21i3.4
3. N Noolvi Malleshappa*, Salim Sidat Parin, Rathod Sanket, Patil Rahul, Choudhari Prafulla, Wagh Raj and Beldar Vishal, Exploration of Virtually Designed and Developed Thiadiazole Derivatives as ULK1/2 Inhibitors: In silico Approach, Letters in Drug Design & Discovery 2023; 20 (x) . https://dx.doi.org/10.2174/1570180820666230825103609 https://dx.doi.org/10.2174/1570180820666230825103609
4. Synthesis, DFT Studies, and Biological Evaluation of new quinazoline-1,3,4-thiadiazole Derivatives as anti-proliferative agents", submitted to Chemistry Africa (Under Revision)

Poster Presentation:

1. Poster present at Chemchom-2023 on topic “Synthesis and Evaluation of ULK1/2 inhibitors as anticancer agents”.
2. Poster present at ICDD-2022 on topic “Design and synthesis of thiadiazole derivatives as a ULK1/2 inhibitor”.
3. Poster present at NCIP 2019 on topic “Design and synthesis of thiadiazole derivatives as a ULK1/2 inhibitor”.
4. Oral presentation present at one day national conference at BMCP on topic “Design and synthesis of thiadiazole derivatives as a ULK1/2 inhibitor”.
5. Poster present at AICTE sponsored national conference at SDPC on topic “*In silico* evaluation of thiadiazole derivatives”.