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Title of Thesis - Synthesis, Characterization and Biological Evaluation of Some Heterocyclic Based Compounds

Abstract

The present research work deals with the synthesis, characterization and biological evaluation of some heterocyclic compounds. The thesis comprises of six chapters. The first chapter deals with the general introduction, literature reviews of heterocyclic compounds. The applications of heterocycles in medicinal chemistry have become very important area of research with constant growth. General synthesis and medicinal importance of three heterocycles viz, quinolines, imidazole and indole have been discussed in brief. The second chapter deals with the synthesis of 3-[4-(7-chloro-quinolin-4-yl)-piperazin-1-yl]-propionic acid hydrazones as antiprotozoal agents. Thirty three compounds have been synthesized and characterized by various spectroscopic techniques like ^{1}H NMR, ^{13} C NMR, IR and mass spectroscopy. The compounds were evaluated for blood-stage of *P. falciparum* and *E. histolytica* trophozoites. An analysis of the antiplasmodial and antiamoebic properties for the compounds (F1–F33) revealed a potency enhancement of antiparasitic activity when compared to the hydrazide. This work has confirmed that *N*-acylhydrazones are antiparasitic agents, and also suggested that converting antiparasitic agents in *N*-acylhydrazones derivatives is an appealing synthetic tool for the antiparasitic drug discovery.

In an endeavor to develop efficacious antiprotozoal agents 2-[4-(7-chloroquinolin-4-yl)piperazin-1-yl]acetamide derivatives were synthesized and screened *in vitro* against the HM1:IMSS strain of *E. histolytica* and 3D7 strain of *P. falciparum.* Among the twenty-seven synthesized compounds, eleven evinced propitious anti-amoebic activity with IC_{50} values ranging from 0.41 to 1.80 µM) lower than the standard drug metronidazole (IC_{50} 1.80 µM). All the compounds inhibited the *in vitro* growth of *P. falciparum* (IC_{50} range: 0.30-33.52 µM). The molecular docking of crystal resolved inhibitors with *Pf*DHFR allowed identification of stabilizing interactions within enzyme active site. These compounds affirm potential for further derivatives to enhance antiprotozoal activity whilst retaining their safety profile.

Two series of compounds bearing 5-nitroimidazole and indole scaffolds linked via hydrazone were designed, synthesized and screened against *E. histolytica*. Thirty compounds bearing acetamide group {15 aldehydes (C1-C15) & 15 hydrazones (RC1-RC15)} and eighteen comprising of sulfonamide group {9aldehydes (S1-S9) & 9hydrazones (MS1-MS9)} were synthesized and characterized by spectroscopic techniques. *In vitro* antiamoebic activity was performed for all the compounds. An analysis of the antiamoebic properties for the *N*-acylhydrazones showed an impressive potency enhancement when compared to the hydrazide and the aldehydes in both the series. The compounds endowed with activities were then evaluated for their cell viability through MTT assay. The *in vitro* antiamoebic results and cytotoxicity profile revealed that the compounds can further be explored and can turn out to be better future.

The last chapter deals with a series of thirty hydrazones (H1-H30) synthesized and characterized by different spectroscopic techniques such as ^{1}HNMR, IR, mass and CHNS elemental analysis and evaluated for *in vitro* antiamoebic activity. The structure was further confirmed by X-ray crystallographic studies for compound H23. Out of thirty compounds fourteen showed promising results against the HM1: ISS strain of *E. histolytica*. Cytotoxicity of the 14 compounds on lung cancer cell line (A549 cells) was measured by MTT assay.

It can be concluded that a total of **138 compounds** have been synthesized, characterized and evaluated for antiprotozoal activities. Molecular docking studies have been performed for various compounds. X-ray crystallographic studies were also performed for the compounds whose crystal was obtained. A number of new compounds endowed with remarkable potency have been established which can be appraised further and can turn out to be future drugs.

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