ABSTRACT

Heterocyclic compounds have become highly important in medicinal chemistry due to their exceptional biological activities and potential therapeutic uses. In drug design, indole, benzothiazole, and triazole-based molecules have gained prominence due to their ability to provide various biological properties, including anticancer, antimicrobial, antimalarial, and antidiabetic activities. This thesis focuses on the design, synthesis, characterization, and biological evaluation of novel heterocyclic compounds for potential applications in medicinal chemistry.

Indole-containing cyanoacetamide chains were synthesized and tested for their antimalarial properties in the first series. Indole, a highly valuable compound in medicinal chemistry, is renowned for its broad range of biological activity, especially in the creation of antimalarial drugs. The antimalarial properties were improved by adding the cyanoacetamide functionality, which interacts with biological targets. Various spectroscopic techniques, such as ^{1}H NMR, ^{13}C NMR, mass spectrometry, and IR, were used to characterize the compounds. The in vitro antimalarial evaluation demonstrated promising activity against Plasmodium falciparum, with molecular docking studies revealing strong binding affinities to the dihydrofolate reductase (DHFR) enzyme, a key target in malaria treatment. These findings showcase the potential of indole-cyanoacetamide derivatives as starting points for the development of new antimalarial drugs.

The second series consists of benzothiazole-tethered 1,2,4-triazole derivatives bearing acetamide chains. Benzothiazole and triazole are pharmacophores known for their diverse bioactivities, including anti-cancer effects. The synthesized compounds in this series underwent thorough biological evaluations, including anticancer tests against various cancer cell lines at the National Cancer Institute's Developmental Therapeutics Program. Selective cytotoxicity was observed in the compounds, especially against the triple-negative breast cancer cell line (MDA-MB-231), with IC_{50} values in the micromolar range. Analysis of the cell cycle indicated arrest in the G2/M phase, while studies on apoptosis demonstrated a rise in early apoptotic populations. Molecular docking studies and MD simulations confirmed that these compounds significantly inhibited the antiapoptotic protein Bcl-2, indicating further investigation into the mechanism of action. MD simulations revealed the stability of the compound-protein complex, while MM-PBSA calculations assessed binding free energies. These benzothiazole-triazole derivatives have demonstrated potential in fighting cancer by

disrupting crucial cancer pathways, providing a promising option for targeted cancer treatments.

The third series explored benzothiazole-tethered 1,2,4-triazole compounds with Schiff bases. The synthesis and characterization of these compounds were achieved using spectroscopic techniques such as ^{1}H NMR, ^{13}C NMR, mass spectrometry, and IR. These compounds were mainly examined for their antimicrobial activity against a range of bacterial and fungal strains, including Acinetobacter baumannii, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pyogenes, Candida albicans, Aspergillus clavatus, and Aspergillus niger. The MIC test results demonstrated that these derivatives inhibited E. Coli, P. aeruginosa and Candida albicans effectively. Molecular docking studies were conducted to explore this selectivity, and it was found that there are favorable interactions with their respective target protein. The Schiff base derivatives thus represent potential candidates for the development of novel antibacterial and antifungal agents.

In the fourth series, dual triazole moieties (1,2,4- and 1,2,3-triazole) were tethered to the benzothiazole scaffold. This series was synthesized and characterized using spectroscopic techniques, and the compounds were screened for antidiabetic and anticancer activity. The synthesized compounds showed moderate activity against alpha amylase and alpha glucosidase. Therefore, we further evaluated these compounds against cancer cells. Preliminary results indicated high levels of cytotoxicity across several cancer cell lines. The dual triazole linkage was designed to explore the synergistic effects of both triazole isomers on the biological activity of the compounds. The incorporation of two triazole rings was hypothesized to improve the interaction with multiple biological targets simultaneously, thereby enhancing the anticancer potential of the compounds.

The fifth series combined indole, benzothiazole, and 1,2,3-triazole frameworks to explore their antimicrobial properties. These hybrid molecules were synthesized and characterized by ^{1}H NMR, ^{13}C NMR, mass spectrometry, and IR. The antimicrobial screening targeted Candida albicans and showed notable inhibition at concentrations similar to clinical antifungal drugs. In silico studies confirmed the specific activity against Candida albicans, revealing insights into the mechanism of action through molecular docking against ergosterol. The incorporation of indole, benzothiazole, and triazole in these compounds underscores their potential as antimicrobial therapeutic agents. To gain more insights into the interactions between the synthesized compounds and their biological targets, computational studies like molecular docking, simulations, and MM-PBSA calculations were conducted, alongside the synthesis and biological evaluations. Valuable insights into the binding modes and stability of

compound-protein complexes were gained through these in silico studies, especially in relation to antifungal activities. These studies will provide a basis for developing more powerful and targeted therapeutic drugs in the future. This thesis provides a thorough examination of novel heterocyclic compounds using indole, benzothiazole, and triazole structures, highlighting their potential as versatile therapeutic agents. The successful synthesis, detailed characterization, and extensive biological evaluations of these compounds demonstrate their significance in medicinal chemistry. The findings from these studies demonstrate encouraging antimalarial, anticancer, and antimicrobial activities, suggesting that these heterocyclic frameworks have potential as lead compounds in drug discovery.