## PREFACE

The thesis entitled **"Design, Synthesis and Biological Evaluation of Some Novel Benzothiazole derivatives"** submitted for the award of the degree of Doctor of Philosophy (Ph.D.) contains the research work carried out during the period of March 2011 to March 2016, at the Department of Pharmaceutics, Indian Institute of Technology, Banaras Hindu University, Varanasi, India under the supervision of Prof. Sushil Kumar Singh. This thesis contains introduction, literature review, the detailed procedures for the synthesis of designed compounds, their characterization by physico-chemical and spectroscopic methods and finally biological evaluation.

The antimicrobial and antitumor potential of benzothiazole compounds prompted us to design and synthesize five different series 2-(4'-aminophenyl)benzothiazole analogues by various rationally based structural modifications. Synthesized compounds were evaluated by agar disc diffusion method against various pathogenic bacterial species (Gram-negative and Gram-positive) viz., *Escherichia coli, Staphylococcus aureus, Salmonella typhi, Enterococcus faecalis, Pseudomonas aeruginosa and Klebsiella pneumonia* and different fungal strains of *Candida* according to the guidelines of National Committee for Clinical Laboratory Standards (NCCLS, 1997). The antimicrobial results were presented with MIC values. To establish the possible antimicrobial mode of action, experiments were performed with the potent analogues in *E.coli and S.aureus* microbial strains by using techniques such as Bactericidal kinetics, Cytoplasmic membrane permeabilization assay, Fluorescence assisted cell cytometer and DNA binding/cleavage assay.

The synthesized compounds were also evaluated for *in-vitro* anticancer activity by standard MTT assay against two human ovarian cancer cell lines i.e. SKOV3 (endometroid adenocarcinoma) & A2780-S (undifferentiated EOC cell) and also on its cellular chemoresistant model (cisplatin resistant model, A2780-CR and paclitaxel resistant model, A2780-PR). The synthesized compounds were also evaluated on two human cervical cancer cell lines SiHa (HPV+ve) and C-33A (HPV-ve). Some of the potent compounds were further evaluated for cytotoxicity against normal ovarian surface cell line IOSE 364 and normal human embryonic kidney cell line HEK-293 to check their safety profile. Compounds having significant anticancer activity and good safety profile were evaluated for their ability to induce apoptosis triggered pathway in cancer cells and was determined by staining the cells with the AnnexinV-AlexaFlor488 and PI. Further, cell cycle distribution was analyzed using FACS Calibur flow cytometer in conjunction with PI staining and finally, the DNA fragmentation of synthesized compounds was observed to examine the molecular mechanisms.

Docking studies were also performed to find a correlation between the results of wet lab finding and dry lab findings. Compounds were subjected to *in-silico* pharmacokinetic prediction studies to check their ability of moving in next phases of drug development.

In summary, this study allows us to conclude that desirable improvement in antimicrobial and anticancer activity of synthesized compounds requires electron releasing groups such as methoxy, hydroxy and electronegative groups such as chloro, fluoro for achieving the best biological spectrum. These studies are expected to provide useful insights into the roles of various substitution patterns on the benzothiazole derivative and also help to design more potent compounds in near future.

In the end relevant references are included along with list of papers presented & published and reprint of publications from the present study is also included. The contents of this thesis may be useful for medicinal chemists working on benzothiazole analogues and open new vista in firmament of designing and developing novel antimicrobial and anticancer agents. The whole thesis was divided into six chapters as follows:

**Chapter-1:** The first chapter describes introduction and basic concepts about microbial infections and clinical approaches for the treatment of cancer. This chapter also presents the brief review of benzothiazole containing antimicrobial and anticancer drugs along with their possible mode of action.

**Chapter-2:** This chapter is focused on detailed literature survey of benzothiazole analogues and their diverse biological activities. It also comprises chemistry of benzothiazole and brief review on targets especially, Glucosamine-6-phosphate synthase (Glc-6-PS) and Epidermal Growth factor Receptor-Tyrosine Kinase (EGFR-TK).

**Chapter-3:** This chapter summarizes the research objectives, the overall rationale for conducting this research, design of 2-(4-aminophenyl)benzothiazole derivatives and plan of work as embodied in the thesis.

**Chapter-4:** This chapter deals with the experimental procedure used in the synthesis, characterization, biological evaluation, mechanism of action, docking and *in-silico* pharmacokinetic prediction of 2-(4-aminophenyl)benzothiazole derivatives.

**Chapter-5:** This chapter covers the results and discussion part of the research work.

**Chapter-6:** This chapter outlines the main findings of this research work with conclusions drawn from them.