# PREFACE

Cancer is a major public health problem worldwide, fastest developing and second driving reason of death after cardiovascular diseases. Basically it is abnormal cellular growth, division without control and invades other tissues. It is predicted that the number of new cancer patient would reach 21 million by 2030.American cancer society reported the flux of disease as about 4750 new malignant and 1670 death cases on daily basis. The invasiveness of cancer and its metastatic behavior makes its unpredictable for treatment, but it can be addressed by identifying the biological pathway which participates in the progression of cancer. Researchers focus on the new approach for cancer treatment that involves the specific target of the cancer disease. The premise of targeted therapy in oncology is the fundamental reliance of tumor cells on biological pathways to which drug inhibit their pathway.

Tyrosine kinases play essential role in initiating various signal transduction pathways inside the cell and are associated with Differentiation, cellular proliferation and numerous monitoring mechanisms. These are a family of enzymes that catalyses phosphorylation of tyrosine residues in target protein using ATP. It is an important mediator of signally cascade and participate in diverse biological processes i.e. cell growth, differentiation, metabolism, and apoptosis in respone to external and internal stimuli. Recent advances have implicated the role of tyrosine kinases in path physiology of cancer. Though their activity is highly regulated in normal cells, they may acquire transforming functions due to mutations, overexpressive and autocrine and paracrine stimulation leading to malignancy sequence both on the N and C terminal ends. Tyrosine kinases possess an extracellular ligand- binding domain, typically glycosylated, which conveys ligand specificity. The ligand binding induces activation of the intracellular tyrosine kinase domain, leading to receptor dimerization.

The conformational change as a result from ligand binding and receptor dimerization leads to interactions between adjacent cytoplasmic domains and activation of the tyrosine kinase. Tyrosine kinases are classified as receptor tyrosine kinase (RTK) e.g. EGFR, PDGFR, VEGFR and non EGFR receptor tyrosine kinase. The Epithelial growth factor receptor is a type of tyrosine kinase receptor which is a transmembrane glycoprotein responsible for the migration, cell growth, proliferation, differentiation, and adhesion under typical physiological conditions. Binding of EGFR to its cognate ligands leads to autophosphorylation of receptor tyrosine kinase and subsequent activation of signal transduction pathways that are involved in cellular proliferation, differentiation and survival. Moreover, EGFR is over expressed in a variety of tumor (cancers) i.e. brain cancer, pancreatic cancer, lung cancer and neck cancer. Thus, EGFR is an alluring focus for the finding of novel anticancer agents. The controlling of EGFR has been esteemed as a vital methodology for the improvement of cancer therapy. Currently US FDA approved Tagrisso (Osimertinib) as first line treatment for EGFR mutated non-small cell Lung cancer. These drugs exhibit several side effects, such as papulopustular rash, diarrhoea, moderate alopecia, hypomagnesimia, hypokalemia, which limit their use. Therefore the ultimate goal is to develop novel anticancer agents that will impede EGFR function and help in decelerate tumor progression. In search of new chemical entities (NCE's) for the treatment of cancer, several derivatives with 1, 4 Naphthoquinone nucleuses have been explored. Like 2-methyl-1, 4-naphthoquinone, which is both a redox-cycling and an alkylating quinone, lead to the activation of the extracellular signal-regulated kinase (ERK) 1 and ERK 2, which are well known for their prominent role in the regulation of cellular proliferation. The activation of ERK was blocked by inhibitors of the direct upstream kinases of ERK 1/2, MAPK/ERK kinase (MEK) 1, and MEK 2 and by inhibitors of the epithelial growth factor receptor

(EGFR) tyrosine kinase. Thus 1,4-naphthoquinone moiety is regarded as a privileged framework in medicinal chemistry. In the designing of novel anticancer molecules the 1,4-naphthoquinone is treated with carbon chain linked with piperazines as the scaffold has been frequently found as naturally active substances across a variety of different therapeutic drugs. The piperazine scaffold has been regarded as a core and is frequently found in naturally active substances across a variety of different therapeutic drugs. The piperazine core has two primary nitrogen atoms which exert the improvement in pharmacokinetic features of drug candidates because of their appropriate pKa. For this purpose, the characteristics of the piperazine template make this molecular subunit a useful and well-positioned system in the rational design of drugs. We hypothesized that the designing of a molecule with 1,4-naphthoquinone tethered with carbon chain linked piperazines for better anticancer activity.

Besides, the quinone derivatives, recently, the oxadiazole chemistry have been explored for the development of new anticancer agents. The Oxadiazoles are an important type of oxygen and nitrogen containing aromatic heterocyclic compounds, which possess desirable electronic and charge-transport properties and the various functional groups are easily introduced into the structurally rigid oxadiazole ring. These characteristics resulted in the extensive potential applications of oxadiazole based derivatives in the field of medicinal chemistry.

Considering the reported postulations, in the design of new anticancer agent and based on hybrid pharmacophore approach, we have developed two novel series of compounds **(1) -** the 1,4-naphthoquinone moiety was tethered to substituted piperazine nucleuses, **(2)** - the 1,4-naphthoquinone moiety tethered with substituted 1, 3, 4-oxadiazole nucleuses with an aim to develop tyrosine kinase inhibitors as anticancer agents. The

chemical structure of compounds was confirmed using FT-IR, $^{1}$H-NMR, $^{13}$C-NMR and elemental analysis. The log P values were determined by QikProp analysis.

The synthesized compounds were evaluated for *in vitro* cytotoxicity assay i.e. MTT Assay and tyrosine kinase enzyme inhibition. The *in-silico* study was performed on vLife MDS software where inhibitors were docked on tyrosine kinase enzyme (PDB id: 2GS6) and binding interactions were observed. The favorable compounds were further subjected to *in vivo* N-methyl-N-nitrosourea induced breast cancer model. The outcome of these studies substantiated the designing for the treatment of cancer.

The studies have been performed and published in different refereed international journals, and also presented in different international conferences. However, the studies presented in this dissertation comprise a small part of the broad spectrum of envisaged work. Considering the predetermined time limit, only some representative and significant studies could be performed. Many other interesting aspects arising out of this work could have been investigated in a more meaningful way, which might be planned in future prospects.

The work has been presented in this dissertation under the following sections:

**Chapter 1:** The first chapter provides basic information about cancer, the pathology of cancer, physiological mechanisms associated with it, available drug therapy and drug design approaches to develop the potential lead molecules.

**Chapter 2:** This chapter is focused on a detailed literature survey on 1, 4-Naphthoquinones, piperazines and 1, 3, 4-oxadiazoles to inhibit elevated tyrosine kinase activity.

**Chapter 3:** This chapter summarizes the overall rationale for carrying out this investigation for designing of the compounds, the research objectives, and plan of work as embodied in this thesis.

**Chapter 4:** This chapter describes the experimental procedure used in the synthesis, characterization, biological evaluation, and computational studies.

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

**Chapter 6:** This chapter outlines the summary and conclusion.

**Chapter 7:** This section includes references as a source of information to carry out the research work in a helpful manner.

**Chapter 8:** An appendix consisting of the NMR ($^{1}H$ and $^{13}C$) spectra of the representative compounds.