Preface

Natural products (NPs) are and have remained a rich source of inspiration in drug discovery and development. They exhibit a broad spectrum of structural diversity and complexity with vast pharmacological potential. A significant portion of approved anticancer and anti-infective drugs have natural origins. Till now, nearly one-third of the approved drugs and two-thirds of small-molecule drugs had some connection to NPs, whether in their original form, as derivatives, or mimetics. While successful drugs have historically emerged from NPs, there has recently been a noticeable decline in the number of new drugs derived from them, but despite the challenges, the significant impact of NPs on drug discovery remains evident.

Plant-derived cyclic esters, known as lactones, are abundant in nature's chemical reservoir and offer a wide range of structural diversity, thus serving as unique frameworks for lead compounds. Among naturally occurring lactones, γ- and δ-lactones are the most abundant. The present thesis work was aimed at the discovery of new lead molecules with cytotoxic and anti-inflammatory potential derived from natural lactones. The thesis consists of ten chapters in which the natural lactones were explored for their biological potential using a multitude of approaches that included computational screenings, phytochemical investigations, semi-synthetic derivatization, and pharmacological screenings.

Chapter 1 initiates a comprehensive exploration of NPs, encompassing their role in drug discovery, their precedence over synthetic molecules, their limitations and challenges, and their contribution toward approved drugs. It also discusses about natural lactones in drug discovery and their current therapeutic landscape. Additionally, the role of computational approaches in NP-based drug discovery and the advantages of amalgamating them are discussed.

In **Chapter 2**, the objectives of the study and plan of work are enumerated.

Chapter 3 describes the identification of natural coumarin compounds from the COCONUT database as potential VEGFR-2 inhibitors (anti-angiogenic). By developing a pharmacophore of lenvatinib and applying pharmacophore-based virtual screening and molecular modeling, the chapter identifies promising candidates associated with VEGFR-2 inhibition, contributing to the development of inhibitors of cancer-related angiogenesis.

Chapter 4 mentions the computational exploration of coumestans (type of lactone-containing phytoconstituents) of *Psoralea corylifolia* (L.) through molecular modeling studies for their EGFR (an important target for anticancer therapies) inhibitory potential and subsequent lead identification. The chapter then proceeds to extraction, isolation, and *in vitro* cytotoxicity screening of identified coumestan hit from *P. corylifolia*.

Chapter 5 describes the phytochemical investigations of leaves and seed of *P. corylifolia* (L.) for the presence of potential coumarin (benzenoid δ-lactones) phytoconstituents. The study proceeds through extraction of *P. corylifolia* leaves and seeds, followed by isolation and purification of various fractions for pure compounds. Later, the chapter mentions the evaluation of cytotoxic potential of isolated phytoconstituents and molecular modeling studies of the compounds that possessed potent cytotoxicity.

Chapter 6 explores a network pharmacology-based approach to identify anti-inflammatory lactones from a NP database and their possible mechanism of action. The study then proceeds to docking studies of selected lactone candidates with the inflammatory targets and identification of potential lactone hit and its potential targets. Later, the section describes molecular dynamic studies, extraction, isolation and purification of lactone hit and *in vitro* validation of its target inhibitory potential.

Chapter 7 mentions the semi-synthetic modification of lactone hit identified in Chapter 6. The chapter describes the development of naproxen-like analogs from santonin, a

sesquiterpene lactone identified through network pharmacology-based approach. The section then describes the evaluation of the anti-inflammatory potential of synthesized analogs through enzyme inhibition assay and later evaluation of the *in vivo* anti-inflammatory potential of the best analog.

Chapter 8 describes the phytochemical exploration of *Vitex negundo* (L.) leaves for potential phytoconstituents. The chapter encompasses the extraction of *V. negundo* leaves, resin-based fractionation, and repeated purification of fractions to obtain pure phytoconstituents. The section mentions the isolation of 2,3-Dehydrosilychristin, a silymarin flavonolignan, from the leaf extract of *V. negundo* along with 12 other phytoconstituents. It also describes the pharmacological exploration of 2,3-Dehydrosilychristin through *in vitro* and *in vivo* studies.

Chapter 9 outlines the summary and conclusions of the research work undertaken.

In **Chapter 10**, the references used to carry out the research work are enumerated.

An appendix containing additional supporting information, spectral data of representative compounds and a bibliography of publications during the course of the Ph.D. is included.