PREFACE

Natural products and their analogs comprise a major part of the approved drugs, mainly anticancer and anti-infectives, also in other therapeutic areas like cardiovascular diseases etc. Almost half of the approved drugs comprise either natural products, their semi-synthetic derivatives, or inspired from natural products. Natural products have a wide range of structural complexity and diversity. Despite the large number of successful drugs from natural sources, there is a declining trend in the number of NP-derived new drugs, raising renewed interest in the natural product-based drug discovery.

The present thesis work was aimed at the discovery of new anticancer lead molecules, derived from the natural products. In the present work, two plants were selected: *Ipomoea nil* (Convolvulaceae), and *Gloriosa superba* (Colchicaceae), based on degree of exploration and reported cytotoxic potential. These two plants were investigated for their phytochemistry and semi-synthetic derivatization of the major isolates.

This thesis consists of five chapters: (1) Introduction, (2) Isolation, synthesis, and *in-vitro* cytotoxic activity of compounds of *Ipomoea nil* seeds, (3) Isolation, semi-synthetic modification, and *in-vitro* cytotoxic evaluation of compounds of *Gloriosa superba* roots, (4) Conclusions and prospects, and References.

In the first chapter, the role of natural products in drug discovery is discussed, along with the examples and disadvantages of natural products. Semi-synthesis as an important tool to optimize the natural products in terms of biological activity as well as pharmacokinetic properties is discussed. The aims and objectives of the thesis and the plan of work is also discussed.

Chapter 2 describes the first objective: Isolation, total synthesis, and *in-vitro* cytotoxic activity of compounds of *Ipomoea nil* seeds. The phytochemical investigation

of *Ipomoea nil* seeds (commonly known as morning glory) is discussed. Eight compounds, including a novel diterpenoid containing bicyclo[3.2.1]octanone nucleus, were isolated from the acidified hydroalcoholic extract of *Ipomoea nil* seeds. All the isolated compounds were characterised on the basis of detailed NMR and mass spectral techniques. The novel compound, ipomone, showed structural similarity to the gibberellins that has been reported from the *I. nil* seeds. Ipomone was screened for cytotoxic activity in a panel of 12 cancer cell lines and found to have moderate activity (IC_{50} = 34 – 86 μM). The mechanistic investigation suggested that ipomone produced the cytotoxic activity mediated by apoptosis and autophagy.

We hypothesized, that ipomone is an acid-catalysed pinacol pinacolone type 1,2 alkyl rearrangement product of gibberellin, as it was obtained under acidic extraction conditions. Inspired by the fact that many gibberellins have already been reported from *I. nil* seeds, an efficient one-step method for the synthesis of ipomone was developed using commercially available gibberellic acid as a starting material and molecular iodine.

In the third chapter, the second objective i.e., isolation, semi-synthetic modification, and *in-vitro* cytotoxic evaluation of compounds of *Gloriosa superba* roots is discussed. The roots of *Gloriosa superba* were investigated for phytochemistry and 17 compounds were isolated including colchicine, gloriosine, and a new compound. All the known compounds were characterized by extensive NMR studies and comparing with reported data. The new compound was elucidated based on comprehensive spectroscopic analysis, including 1D, 2D NMR and HRMS.

Gloriosine has never been explored for its pharmacology, so we carried out its cytotoxic screening and found that gloriosine exhibited significant cytotoxicity (IC_{50} =32 to 100 nM) that was comparable with colchicine. Since C-10 amino derivatives of

colchicine produced potent compounds, twenty semi-synthetic C-10 amino and amide derivatives of gloriosine were synthesized. Usual methods like benzoylation of amines, EDC coupling reactions did not provided the amide derivatives in an isolable yield. So, a new synthetic method for the synthesis of amides directly from aldehydes and amines using a nickel catalyst was developed. This new amidation method was found suitable for the synthesis of desired amide derivatives of gloriosine in isolable good yields.

Chapter 4 describes the conclusion and future prospects of the thesis. A new natural product, ipomone, was isolated from the seeds of *Ipomoea nil*. The total synthesis of ipomone led to the discovery of an intermediate (iodomethyl derivative of ipomone) that could be used as starting material to synthesise additional analogs for the future prospects. An anticancer lead, gloriosine, having *in-vitro* cytotoxic activity in nanomolar range was isolated from the roots of *Gloriosa superba*. Further, C-10 amino and amide derivatives of gloriosine were synthesized. The study suggested that gloriosine might serve as an interesting lead for further *in-vivo* and preclinical studies and future anticancer therapeutics.