

TABLE OF CONTENTS

| CONTENTS | Page No. |
|---|----------|
| Certificates | ii |
| Acknowledgments | v |
| Table of contents | viii |
| List of figures | xi |
| List of tables | xiv |
| List of abbreviations | xv |
| Preface | xvii |
| Chapter 1. Introduction | |
| 1. Introduction | 1 |
| 1.1. Natural products as potential sources of drugs | 1 |
| 1.2. Semi-synthesis as an important tool in natural products-based drug discovery | 3 |
| 1.3. Total synthesis | 5 |
| 1.4. Diverted total synthesis (DTS) | 7 |
| 1.5. Function-oriented synthesis (FOS) | 7 |
| 1.6. Biology-oriented synthesis (BIOS) | 8 |
| 1.7. Biosynthesis inspired synthesis | 8 |
| 1.8. Aims and objectives | 9 |
| 1.9. Plan of work | 10 |
| 1.9.1. Isolation, total synthesis, and cytotoxic activity of compounds of <i>Ipomoea nil</i> seeds | 10 |
| 1.9.2. Isolation, semi-synthetic modification, and cytotoxic evaluation of compounds of <i>Gloriosa superba</i> roots | 11 |
| Chapter 2. Isolation, total synthesis, and cytotoxic activity of compounds of <i>Ipomoea nil</i> seeds | |
| 2. Isolation, total synthesis, and cytotoxic activity of compounds of <i>Ipomoea nil</i> seeds | 13 |
| 2.1. Literature review | 13 |
| 2.2. Results and discussion | 16 |
| 2.2.1. Phytochemical investigation of <i>I. nil</i> seeds | 16 |
| 2.2.2. Structure elucidation of new compound 2.11 | 18 |
| 2.2.3. Ipomone (2.11): An unusual bicyclo[3.2.1]octanone, perhaps a process generated product | 22 |
| 2.2.4. <i>In-vitro</i> cytotoxic activity of ipomone (2.11) | 23 |
| 2.2.4.1. Cytotoxicity of ipomone (2.11) against cancer cells | 23 |
| 2.2.4.2. Ipomone (2.11) causes A549 cell death by apoptosis | 24 |
| 2.2.4.3. Ipomone (2.11) induces autophagy | 25 |
| 2.2.4.4. Immunoblot analysis | 25 |
| 2.2.4.5. Molecular docking studies with caspase-3, p110 α , and PARP-1 proteins | 27 |

| | |
|--|----|
| 2.2.5. Total synthesis of ipomone (2.11) | 28 |
| 2.2.5.1. Mechanism of formation of ipomone from gibberellic acid | 30 |
| 2.3. Experimental section | 35 |
| 2.3.1. General experimental procedures | 35 |
| 2.3.2. Plant material | 36 |
| 2.3.3. Extraction and isolation | 36 |
| 2.3.4. Cell line and cell culture | 38 |
| 2.3.5. Cell viability assay | 38 |
| 2.3.6. Fluorescence microscopy | 39 |
| 2.3.7. Acridine orange staining | 39 |
| 2.3.8. Preparation of whole-cell lysates for immunoblotting | 39 |
| 2.3.9. Molecular docking | 40 |
| 2.3.10. Procedure for the synthesis of ipomone (2.11) | 41 |
| 2.3.11. Procedure for the synthesis of compounds 2.19 and 2.20 | 41 |
| Chapter 3. Isolation, semi-synthetic modification, and cytotoxic evaluation of compounds of <i>Gloriosa superba</i> roots | |
| 3. Isolation, semi-synthetic modification, and cytotoxic evaluation of compounds of <i>Gloriosa superba</i> roots | 43 |
| 3.1. Literature review | 43 |
| 3.1.1. SAR of colchinoids | 45 |
| 3.2. Results and discussion | 48 |
| 3.2.1. Phytochemistry of <i>Gloriosa superba</i> roots | 48 |
| 3.2.2. Structure elucidation of new compound (3.19) | 55 |
| 3.2.3. Biological activity of gloriosine | 58 |
| 3.2.3.1. In-vitro cytotoxicity screening of gloriosine | 58 |
| 3.2.3.2. Nuclear staining and fluorescence microscopy | 59 |
| 3.2.3.3. Scratch assay for cell migration study | 61 |
| 3.2.4. <i>In-silico</i> investigation of binding modes of gloriosine against tubulin protein | 62 |
| 3.2.4.1. Molecular docking studies of gloriosine with tubulin protein | 62 |
| 3.2.4.2. Molecular dynamic simulation of gloriosine with tubulin protein | 63 |
| 3.2.5. Synthetic modifications of gloriosine | 65 |
| 3.2.5.1. Series 1: Synthesis of C-10 amine derivatives of gloriosine | 66 |
| 3.2.5.2. Series 2: Synthesis of C-10 amide derivatives of gloriosine | 68 |
| 3.3. Experimental section | 75 |
| 3.3.1. General experimental procedures | 75 |
| 3.3.2. Plant material | 76 |
| 3.3.3. Extraction and isolation | 76 |
| 3.3.4. Synthetic modifications on gloriosine and new synthetic | 81 |

| | |
|--|------------|
| method | |
| 3.3.4.1. Synthesis of C-10 amino derivatives of gloriosine | 81 |
| 3.3.4.2. Synthesis of amides by new synthetic methodology | 87 |
| 3.3.4.3. Synthesis of C-10 amide derivatives of gloriosine | 92 |
| 3.3.5. <i>In-vitro</i> cytotoxicity studies | 93 |
| 3.3.5.1. General procedure for cytotoxicity (MTT) assay | 94 |
| 3.3.5.2. Nuclear staining and fluorescence microscopy | 94 |
| 3.3.5.3. Scratch assay for migration studies | 95 |
| 3.3.6. Molecular docking studies | 95 |
| 3.3.7. Molecular dynamics simulation of gloriosine-tubulin complex | 96 |
| Chapter 4. Conclusion and future perspectives | 98 |
| References | 101 |
| Appendix | 118 |
| List of publications | 120 |