Phytochemistry, Medicinal Chemistry & *In-vitro* Cytotoxicity of *Ipomoea nil* and *Gloriosa superba*

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By

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Chapter 4

Conclusions and Future Perspectives

4. Conclusion and future perspectives

The objective of this thesis was to identify the NP-based anticancer lead molecules for further drug discovery. Two plants, *Ipomoea nil* seeds and *Gloriosa superba* roots were selected for the lead identification.

From the seeds of *I. nil*, one new gibberic acid diterpenoid, ipomone (**2.11**), along with seven known compounds (**2.12-2.18**) were isolated. Ipomone was characterized by extensive NMR and ECD analysis. This new compound appeared to be a process-generated product that might have resulted from acid-catalyzed pinacol-pinacolone rearrangement of allogibberic acid diterpenoids. A plausible mechanism; 1,2 alkyl shift: pinacol-pinacolone rearrangement, has been proposed to justify the conversion. Ipomone was further screened for cytotoxic activity against a panel of twelve human cancer cell lines. Although it exhibited weak cytotoxicity against all cell lines tested i.e., 34-86 μM (except HEK-293 cells) but mechanistic investigation suggested it as a lead that induces apoptosis and autophagy.

Since ipomone (**2.11**) showed structural similarities to pharbinilic acid (**2.2**), the total synthesis of ipomone starting from gibberellic acid (**2.1**) using molecular iodine was carried out. The reaction proceeded through aromatization and 1,2-alkyl rearrangement simultaneously. The total synthesis of ipomone led to the discovery of an intermediate (iodomethyl derivative of ipomone, **2.19**) that could be used as starting material to synthesize additional analogues with improved biological activity.

Another plant *G. superba* was selected based on its ethnopharmacological uses. From the roots of *G. superba*, 17 natural products, including a new compound glorigerine (**3.19**), were isolated. All the known compounds were characterized by comparing the NMR data with the literature. The new compound **3.19**, glorigerine, was characterized by

extensive 2D NMR and HRMS analyses. Since gloriosine (**3.3**) was an unexplored compound, it was screened for its anti-proliferative potential in fifteen human cancer cell lines of different tissue origin and one normal breast cell line. Gloriosine displayed significant cytotoxic activity in all the tested cancer cell lines with IC_{50} values of 32 – 100 nM. Gloriosine was found to be more active than colchicine in some of the cell lines. A mechanistic study revealed that gloriosine exhibited potential apoptotic and anti-migratory activities in A549 cells. Gloriosine (IC_{50}: 700 nM) appeared to be less toxic to normal breast cells as compared to colchicine (IC_{50}: 567.8 nM). Toxicity window in cancer cells and normal cells indicated that gloriosine is less toxic to normal cells and more selective towards the cancer cells than colchicine. Further, molecular docking studies were performed to explore the possible binding modes of gloriosine with colchicine binding site of tubulin protein. Our findings suggested that gloriosine might be a potential lead for anticancer drug discovery.

Gloriosine was further derivatized to synthesize C-10 amino (**3.20a-p**) and amide derivatives (**3.26a-d**). 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 reasonable for the synthesis of desired amide derivatives of gloriosine in isolable good yields.

The identified leads can be taken further for detailed investigation. As ipomone (**2.11**) was found to have moderate cytotoxicity, there is a scope for medicinal chemists to improve its activity. The iodinated derivative of ipomone (**2.19**) can be used as an interesting starting material to synthesize additional analogues for future prospects.

Gloriosine (**3.3**) has been scaled up to continue our work on detailed pharmacology (both *in vitro* and *in vivo*), including mechanism and pharmacokinetic studies. Semi-

synthetic derivatives of gloriosine (**3.20a-p**, **3.26a-d**) will be screened for anticancer potential in order to establish SAR and identified lead may be taken for pre-clinical studies. Since, the medicinal chemistry of gloriosine is unexplored, it may be investigated to synthesize library of novel derivatives. The identified new compound, glorigerine (**3.19**), isolated from *Gloriosa superba* roots, may have a lot of potential for medicinal chemistry.