Abstract

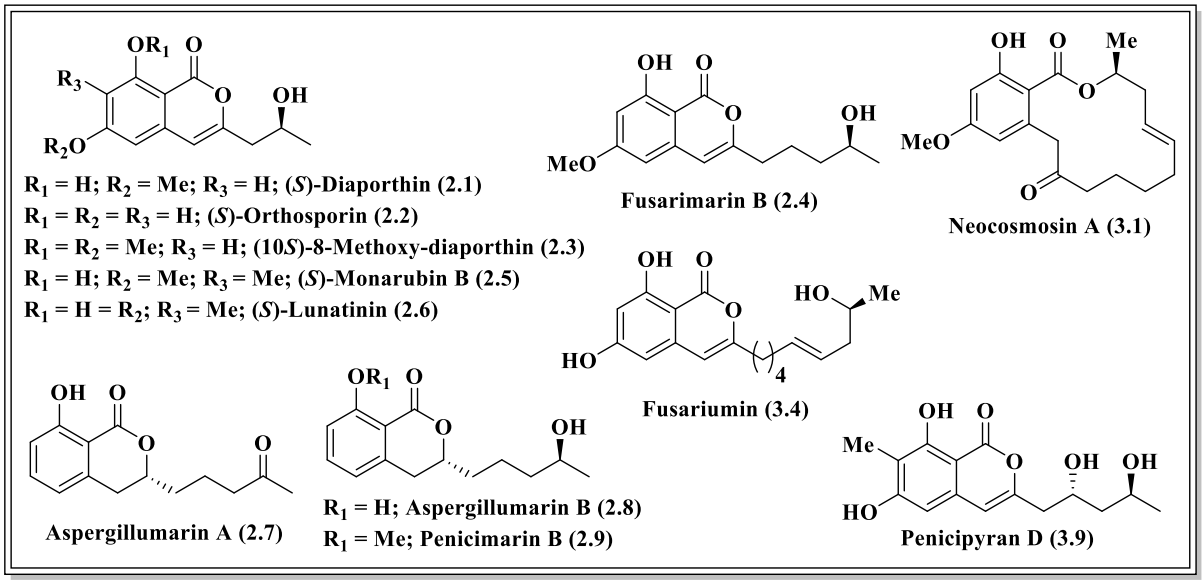
Thesis Title: Synthetic studies towards Naturally Occurring Isocoumarins and γ- Alkylidinebutenolides

Abstract: Natural products continue to play a central role in drug discovery owing to their remarkable structural diversity and wide range of biological activities. Among them, isocoumarins and γ-alkylidenebutenolides constitute important classes of oxygenated heterocyclic natural products, many of which are isolated from fungal, plant, and marine sources and exhibit significant antimicrobial, cytotoxic, anti-inflammatory, and enzyme-inhibitory properties. The structural complexity and stereochemical richness of these molecules present considerable synthetic challenges and, at the same time, offer opportunities for the development of efficient and asymmetric synthetic methodologies.

This thesis is broadly divided into two parts. Part A focuses on naturally occurring isocoumarins and related resorcylic acid lactones (RALs), while Part B is devoted to γ-alkylidenebutenolides and aporpinone derivatives. The introductory chapters provide a comprehensive overview of the occurrence, biosynthesis, biological significance, and existing synthetic strategies for these natural products.

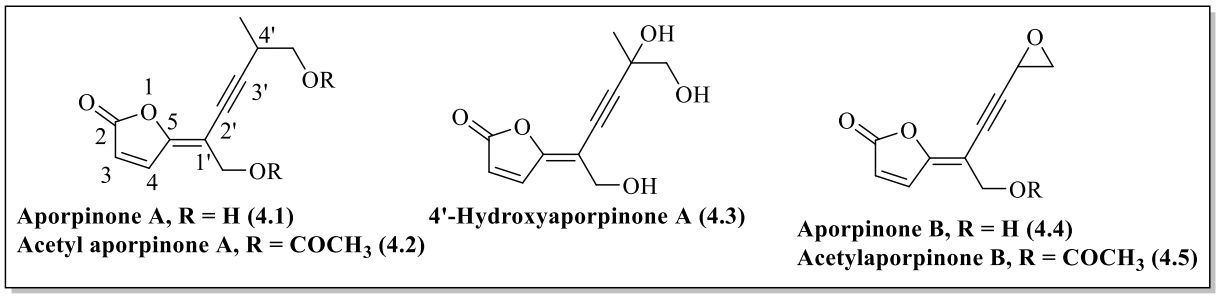
In Part A, an efficient Ag(I)-mediated 6-*endo*-*dig* cyclization strategy has been developed and successfully applied to the total synthesis of several naturally occurring isocoumarins and dihydroisocoumarins, including fusarimarin B, monarubin, lunatinin, peniciimarin B, aspergillumarin A and B, as well as optically active members such as (*S*)-diaporthin, (*S*)-orthosporin, and (10*S*)-8-methoxydiaporthin. The synthetic approach demonstrates high regioselectivity and functional group tolerance and enables access to both racemic and enantiomerically enriched targets through asymmetric hydrogenation.

Furthermore, an isocoumarin-based synthetic route has been strategically exploited for the asymmetric total synthesis of the resorcylic acid lactone neocosmosin A and the isocoumarin-containing natural product fusariumin. The developed methodology was also extended to accomplish the total synthesis of penicipyran D, another polyketide-derived isocoumarin-based natural product, highlighting the versatility of the isocoumarin intermediate in complex molecule construction.



Keywords: Sonogashira-coupling, 6-*endo-dig* cyclization and asymmetric hydrogenation

Part B describes synthetic studies toward naturally occurring γ-alkylidenebutenolides and aporpinones. An asymmetric synthetic route has been developed for the preparation of 1′-deshydroxymethyl analogues of aporpinone A, aporpinone B, and 4′-hydroxyaporpinone A, providing access to structurally simplified analogues for future biological evaluation.



Keywords: Bimetallic (Pd-Cu) cascade cyclization, asymmetric dihydroylation, bis-alkyne

Overall, this work demonstrates the power of metal-mediated cyclization and asymmetric strategies in the efficient synthesis of structurally diverse natural products and provides practical, scalable routes to several biologically significant isocoumarins and γ-alkylidenebutenolides, which may serve as valuable scaffolds for further medicinal chemistry and biological studies.