Overall Conclusion and Perspective

Present dissertation describes our concise and efficient approaches for the synthesis of various bioactive maleic anhydrides and their derivatives based natural and unnatural products implementing novel synthetic strategies along with the concise account of the relevant contemporary literature. Maleic anhydrides, maleimides and butenolides containing natural products bear the fascinating structures and their remarkable bioactivity has incited a lot of activity in the organic chemist’s community towards their isolation, characterization, total synthesis and biological screening. Metal catalyzed cross-coupling reactions have gained nobel attention in recent years. A brief re-materialization of the concise literature account on the metal catalyzed cross-coupling reactions of halomaleic anhydrides and halomaleimides leading to bioactive natural and unnatural products has been portrayed. (+)-Paeonilide is most promising anti-PAF agent and a schematic summary of previously reported four elegant synthetic approaches for this eminent natural product has been described in detail. A large number of alkyl(methyl)maleic anhydrides with a broad range of bioactivities have been isolated as the natural products since 1950. Novel synthetic approaches to biologically active natural/synthetic maleic anhydrides have been reported by various research groups. A composed literature report on the various synthetic approaches for alkyl(methyl)maleic anhydrides along with their promising biological activities has been presented.

In the present dissertation work, we have demonstrated an efficient approach to the various monoalkyl substituted maleimides, maleic anhydrides and butenolides for the first time by employing Sonogashira cross-coupling reaction on halomaleimides. The present general approach has been successfully utilized for the synthesis of several alkylnyl, alkenyl and alkyl substituted maleimides involving the chemo-, regio-, and stereoselective reduction reactions. This protocol has been further extended to accomplish the first total synthesis of two natural butenolides namely, luffarin X and cacosponganolide C. The serendipitously witnessed intramolecular nucleophilic oxygen insertion at the γ-position of 3,4-disubstituted butenolide with unusual double bond isomerisation led us the new reactivity in butenolides. The redox-neutral protocol with the insertion of oxygen at the electron rich position in butenolide coupled with reduction of internal carbon–carbon double bond provided the paeonilide skeleton in highly diastereoselective fashion. We have successfully explored this newly
developed reactivity umpolung conception to accomplish simple and efficient total synthesis of (±)-paeonilide with a very good overall yield. We have also presented the first total synthesis of natural 2,3-didehydrotafieric anhydride and unnatural alkenyl(methyl)maleic anhydrides starting from simple substrate, the dimethyl maleate. The Wittig reaction, methylation followed by innovative 1,2-, 1,4- and 1,6-elimination reactions and HWE-reaction strategy were the key points in accessing this intriguing class of compounds. The 1,2-eliminations in cyclic carbonate/sulfite by regioselective abstraction of methine proton with release of CO₂/SO₂ provided a conjugated ketone product. The characteristic 1,4-elimination in cyclic ketal with release of acetone and the 1,6-elimination of remotely placed mesylate in open chain system lead to the corresponding allylic alcohols. Both the allylic alcohols were systematically transformed into conjugative alkenyl(methyl)maleic anhydrides via oxidation followed by HWE reactions pathway. Although the biological screening of these fascinating structures have been not reported yet, we feel that the conjugative alkenyl(methyl)maleic anhydrides will exhibit strong RFTase inhibitory activity.

All above specified studies provided us an excellent opportunity for learning lot of new basic and applied chemistry not just from our research work point of view but also from the vast literature in this field. We also feel that the approaches which we have developed are quite general and biogenetic in nature and would be useful in designing several structurally similar important natural products and natural product hybrids for structure activity relationship studies. A look at the recent literature also revealed that the histogram of the maleic anhydride, maleimide and butenolide chemistry is in escalating slope and increasing medicinal and pharmaceutical demands for natural and designed maleic anhydride/imides and butenolides would maintain the high positive slope in the present day world of medicinal and synthetic chemistry. In our opinion, a combination of natural and hybrid anhydrides and their derivatives would serve as a launching pad to fight against new generation diseases. Finally, on the basis of exposure to the literature of anhydride chemistry and our contribution to the same, it can be said with assurance that, in future, this significant discipline will spread the wings still wider in the field of organic and pharmaceutical chemistry.