ABSTRACT

Investigations embodied in this thesis entitled "Natural and Non-Natural Pyridine Alkaloids: Synthesis of Conformationally Restricted Tobacco Alkaloids, Nicotine and Anabasine, and Naturally Occurring Cerpegin" have been presented in two parts. Part 1 includes non-natural pyridine alkaloids and describes the efforts towards synthesis and biological evaluation of conformationally restricted analogues of nicotine and anabasine. Part 2 covers the studies on aerobic oxidation of carbon-silicon σ-bond and synthesis of naturally occurring cerpegin.

Part 1: This part has been further divided into two chapters.

Chapter 1: In this chapter, a novel synthetic route to bridged anabasines is described based on a domino intramolecular [4+2]-cycloaddition / ring opening-elimination sequence of 3-amino substituted furo[3,4-*c*]pyridines. Incidentally, this is the first example of an intramolecular Diels-Alder reaction involving a transient furo[3,4-*c*]pyridine. Extension of this route to bridged nicotines proved abortive even when the dienophile tether is activated by a *p*-tolylsulfonyl group or when the diene moiety is activated by an electron-releasing methoxy substituent. A detailed density functional theoretical study (B3LYP/6-31+G**) was undertaken to provide insight into the factors that facilitate intramolecular Diels-Alder reaction in the former case. Heats of reaction calculated for two closely related reactions with DFT were used as a qualitative tool for explaining Diels-Alder reactivity of furo[3,4-*c*]pyridines.

Chapter 2: In this chapter, generation of pyridine-*o*-quinodimethanes by a phenylsulfanyl group assisted formal imine-tautomerization protocol has been demonstrated for the first time.This provides a rapid synthesis of both conformationally constrained nicotine and anabasine analogues. This route offers new possibilities in drug development because of its considerable flexibility for the synthesis of a variety of constrained nicotine and anabasine analogues. Biological evaluation of some of the restricted analogues on immobilized α4β2 nicotinic receptors column has been done and

three of our synthetic conformationally restricted analogues are found to be more potent than nicotine itself in binding assay on $\alpha4\beta2$ nAChRs. In addition, we have also illustrated an interesting and novel rearrangement by which conformationally constrained nicotines can be converted into the potent anticancer drug ellipticine and analogues.

Part 2: This part has also been further divided into two chapters.

Chapter 1: This chapter deals with a mechanistic investigation of oxidation of a carbon-silicon σ–bond with air. Here, we proposed a novel 1,3-radical Brook type rearrangement (also may be looked upon as a 1,3-homolytic translocation reaction) pathway and designed some silylated azaphthalans as suitable probes for the mechanistic study. This study is still ongoing, but the results so far obtained from ESR studies suggest that a 1,3-radical Brook rearrangement may be operating in our cases. Currently, low temparature ESR (as well as simulation experiments) and synthesis of geminally substituted silylated azaphthalans are being carried out to substantiate our mechanistic proposal.

Chapter 2: This chapter describes the development of a route to geminally dialkylated azaphthalans based on consequtive double desilylation-alkylation reaction. Furthermore, this chemistry proved useful in a synthesis of cerpegin, an alkaloid which has been used in traditional Indian medicine for its tranquilizing, anti-inflammatory, analgesic, and antiulcer properties.