PART B

SYNTHETIC MODIFICATIONS OF VASICINE, AN ALKALOID FROM ADHATODA VASICA NEES. FOR SAR STUDIES
INTRODUCTION

1. Review of *Adhatoda vasica* Nees.

*Adhatoda vasica* Nees. (Acanthaceae) leaves have been used in Indian Systems of Medicine for more than 2,000 years. The Ayurvedic system of medicine describes the use of this plant for treatment of respiratory ailments, particularly for the treatment of cough, bronchitis, asthma and tuberculosis. It is also claimed that it causes thinning of sputum and phlegm in bronchitis and asthma. The Ayurvedic literature and folklore drugs also mention the use of this drug by traditional midwives at the time of delivery to check post-partum haemorrhage.

In order to discover actual active principles in *Adhatoda vasica*, the plant was investigated in 18th and 19th centuries. Vasicine was first isolated as pure alkaloid by Hopper in 1888 from leaves of *Adhatoda vasica*. The chemical investigations of this alkaloid were done after it was again isolated by Sen et al. in 1924. After a lot of contradiction the structure of vasicine (13) was finally established after more than a decade.

![Diagram of vasicine](image_url)

Vasicine was found to have bronchodilatory activity. It was reported to cause relaxation of tracheal muscle at low concentrations and contraction at high concentrations. It also exhibited protection against histamine induced bronchospasm.
Another alkaloid vasicinone (14), an auto-oxidation product of vasicine, was also reported to cause bronchodilatory effect both *in vitro* and *in vivo*.\textsuperscript{102} Bhide *et al.*\textsuperscript{103,104} reported that vasicinone was more potent than vasicine and possessed antiasthmatic activity comparable to that of sodium cromoglycate.

![Structure of vasicinone](image)

A semisynthetic analog of vasicine, bromohexine (15), has been reported\textsuperscript{105} to reduce the viscosity of tracheal secretions.

![Structure of bromohexine](image)

Atal *et al.*\textsuperscript{91} after an in depth study on pharmacological, toxicological and pharmacokinetic studies, reported that vasicine and not the vasicinone is highly active as bronchodilatory agent both *in vitro* and *in vivo*, and its activity is comparable to theophylline. Vasicine was also highlighted as potential oxytocic and abortifacient agent.
2. Review of the work done on Vasicine Analogues and Structure Activity Relationship Studies done by other workers

Based on observations in previous section, a programme was started at Regional Research Laboratory, Jammu to synthesize vasicine analogues so that the effect of substitutions could be correlated with pharmacological activity. The aim was to synthesize a more active bronchodilatory and oxytocic molecule than vasicine.

Compounds with different substituents in ring A were synthesized. The 5,6-methylenedioxyvasicine (16) showed uterine stimulant activity comparable to vasicine but the hypotensive and cardiac depressant effect were more marked.\textsuperscript{106} Dhar et al.\textsuperscript{107} reported SAR studies indicating that the presence of only one oxygen function (either at C-3 or C-9) is an essential for the retention of activity as presence of both leads to the loss of activity. The deoxyvasicinone is found to possess bronchodilatory activity suggesting thereby that OH and CO groups in the vasicinone

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\begin{align*}
\text{16} & \\
\text{17} & \quad R = \text{O, H}_2 \quad n = 3-9
\end{align*}
\]

molecule are perhaps competing with each other. The bronchodilatory activity of the compounds (17) increases with increase in size of ring C upto ring size seven and
gradually decreases thereafter. No uterotonic or oxytocic activity was found in these compounds. Reduction of oxygen function at C-9 resulted in a drop in activity thus indicating that oxygen function is essential for activity. The 2,3-dialkyl derivatives were found to be devoid of bronchodilatory activity. Introduction of bromine group in ring A resulted in decrease in bronchodilatory activity. These compounds were also found to have antiinflammatory activity.108

These results encouraged us to work further on the structure activity relationship and decided to make derivatives with changes in ring A and ring C. The compounds without the ring A and ring C with different substituents were also prepared and are discussed under Results and Discussion.

3. Quinazolines and Microwave Mediated Synthesis

Quinazolines have been reported to have wide variety of biological activities. A number of reviews have appeared from time to time on this topic covering both chemistry and biological activity.109-114

The quinazolines have been reported to possess a number of therapeutic applications such as narcotic antagonists, antihypertensives, blood platelet aggregation inhibitors, antidiabetics, bronchodilators, antidepressants, CNS stimulants, tranquilizers, analeptics, gastric secretion inhibitors, cancer metastasis inhibitors, analgesics, cardiotonics, vasodilators, anticonvulsants, antithrombotics, PDE inhibitors, cardiovascular agents and antibacterials.114

In recent times there has been a tremendous interest in the microwave mediated organic synthesis. The main advantages are: a shorter reaction time, cleaner reaction, better yields, ease of workup after reaction, reduction in thermal degradation, better selectivity and environment friendly conditions.115-120
reactions can be carried out from a few milligram to 500 gram quantities in a simple household microwave oven.121

Microwave ovens can range from simple household multimode ovens to largescale batch as well as continuous multimode ovens. In batch closed reactor, vessels or turntables having a capacity to contain a number of reaction vessels, have been applied. Specifically in food industry large-scale (continuous mode) ovens are used frequently.122,123 Thus it is possible to scale up the reactions to industrial scale.

4. Synthetic approaches to 1,4-Dihydropyridines of Medicinal Interest

1,4-Dihydropyridines as calcium entry blockers, have rapidly emerged as one of the most important class of nitrogen heterocycles that are being used for the management of cardiovascular diseases. These compounds have occupied an important role as therapeutic agents among the various types of the calcium entry blockers. The interest in the dihydropyridines chemistry can be traced back to the co-enzyme reduced nicotinamide adenine dinucleotide and the unique ability of this compound in the biological systems to reduce unsaturated functionalities (carbonyls, conjugated olefins, etc.). Thus, a considerable portion of today’s efforts in dihydropyridine chemistry is extended to synthesizing NADH mimics, exploring the
reactions and mechanisms of these compounds and utilizing these compounds in a variety of synthetic reactions.

The clinical usefulness of nifedipine (18), a prototype of dihydropyridines, in the management of cardiovascular diseases,\textsuperscript{124} stimulated extensive research in this area leading to the discovery of a large number of 1,4-dihydropyridines which have been found to be even more potent than the nifedipine. 1,4-Dihydropyridines have been found to be of utmost importance in the biological systems and the superior calcium antagonistic dihydropyridines have initiated the development of large number of analogues as primary antianginal/anti-hypertensive agents.\textsuperscript{125,126}

Dihydropyridines are of utmost importance in the biological systems, especially NADH is involved in the biological redox reactions. The pharmacological properties of dihydropyridines also include antitumour activity.\textsuperscript{127,128} 1,4-Dihydropyridines have also been reported to possess some analgesic and curare properties.\textsuperscript{129} This type of compounds also possess CNS depressant (anticonvulsant and analgesic) activity.\textsuperscript{130} There are also reports of this class of compounds possessing antiasthmatic activity by reducing \textit{in vitro} lipoperoxidation and \textit{in vivo} experimental hyper-reactivity and cell infiltration.\textsuperscript{131} Donkor \textit{et al.}\textsuperscript{132} have recently reported the radioprotective effects of 1,4-dihydropyridines. The 6-phenyl-4-phenylethyl-1,4-dihydropyridines have been shown to be highly selective A\textsubscript{3} adenosine receptor antagonists,\textsuperscript{133} the 4$S$ isomer being thirty five times stereoselectivity in binding.\textsuperscript{134}

Dihydropyridine chemistry began in 1882 when Hantzsch\textsuperscript{135} published its synthesis, which bears his name. In the following fifty years, modifications of the original synthesis were developed and some reactions of dihydropyridines were studied. The interest in improved synthesis of 1,4-dihydropyridines has increased in
view of the wide biological profile of these compounds. Palacios et al.\textsuperscript{136} have recently reported synthesis of 1,4-dihydropyridines from phosphazene and their derivatives (Scheme 1). The reaction takes approximately 24 hr. and gives good yields of desired compounds. Another method (Scheme 2)\textsuperscript{137} via a regio and chemoselective addition of Ph\textsubscript{3}Cu(CN)Li\textsubscript{2} to β-substituted N-alkylpyridine salts followed by acylation of the intermediate 1,4-dihydropyridine with trichloroacetic anhydride and subsequent
haloform reaction has been reported for the synthesis of 3,5-diacyl-4-phenyl-1,4-
dihydropyridines. The cage dimeric N-acyl- and N-acyloxy-4-aryl-1,4-
dihydropyridines have been reported as first representatives of a novel class of HIV-1 
protease inhibitors.\textsuperscript{138}

Breitenbucher \textit{et al.}\textsuperscript{139} have reported an solid-phase synthesis of 4-aryl-1,4-
dihydropyridines \textit{via} the Hantzsch three component condensation. They prepared a 
272 compound library. Unwanted reaction impurities were removed by selective 
cleavage from solid support. In a Hantzsch-type Domino reaction illustrated by 
Gordeev \textit{et al.}\textsuperscript{140}, an enamide is generated by condensation of a resin bound amine 
with two $\beta$-keto esters and an aldehyde.

Marzabadi \textit{et al.}\textsuperscript{141} have reported a double protection strategy for the synthesis 
of biologically important dihydropyridines. Deprotection followed by independent 
chemical manipulation of the C$_3$- and C$_5$-substituents allows synthesis of a variety of 
derivatives not available using traditional routes. The compounds show good affinity 
and selectivity for the $\alpha_1$ adrenoceptor.\textsuperscript{142}

1,4-Dihydropyridines have also been synthesized \textit{via} Diels-Alder reaction of 
2-pyrrolidinones and 4-silylated 1-aza-1,3-butadienes with dimethyl acetylene 
dicarboxylate.\textsuperscript{143}

Dihydropyridines are readily convertible to pyridines and are important 
intermediates in the synthesis of the latter. A detailed survey of the synthetic reactions 
covering the literature has been published.\textsuperscript{144} Dihydropyridines also play an important 
role as intermediates in the reactions of pyridines, for example, in nucleophilic 
substitutions\textsuperscript{145} and reductions\textsuperscript{146} as well as acylations in the presence of pyridine.\textsuperscript{147}
5. Research Envisaged

Leaves of *Adhatoda vasica* Nees. have been used in Indian System of Medicine for more than 2000 years. This plant and its constituents vasicine and vasicinone have drawn attention of a number of workers for their various activities such as bronchodilatory and uterine stimulant.

Encouraged by the biological profile of these compounds, a modified structure of vasicinone named RLX (deoxydihomo-'C' vasicinone) has been synthesized which has shown 6 to 10 times more activity as compared to known bronchodilatory compounds. Various compounds with ring A modifications, 2,3-disubstituted quinazolines, 2,4- and 2,3,4-substituted, 3,4-dihydroquinazolines have been synthesized and subjected to pharmacological studies.

In continuation of these studies, which are based on structure activity relationship, it was envisaged to carry out further modifications in ring A, removal of ring A and carry out substitutions in ring B and changes in ring C. It was also envisaged to carry out evaluation of the synthesized compounds for bronchodilatory activity, so as to build up the structure activity relationship further.

Designing a microwave mediated synthesis for the above compounds was also contemplated so as to reduce the reaction time and simplify the processing.