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# Synthesis, utility and medicinal importance of 1,2- & 1,4-dihydropyridines

Vivek K. Sharma<sup>a</sup> and Sunil K. Singh<sup>\*b</sup>

Dihydropyridine (DHP) is among the most beneficial scaffolds that have revolutionised pharmaceutical research with unprecedented biological properties. Over the years, metamorphosis of easily accessible 1,2- and 1,4-dihydropyridine (1,4-DHP) intermediates by synthetic chemists has generated several drug molecules and natural products such as alkaloids. The 1,4-dihydropyridine (1,4-DHP) moiety itself is the main fulcrum of several approved drugs. The present review aims to collate the literature of 1,2- and the 1,4-DHPs relevant to synthetic and medicinal chemists. We will describe various methodologies that have been used for the synthesis of this class of compounds, including the strategies which can furnish enantiopure DHPs, either by asymmetric synthesis or by chiral resolution. We will also elaborate the significance of DHPs towards the synthesis of natural products of medicinal merit.

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## 1. Introduction

Arthur Hantzsch added one of the most valuable scaffolds to the toolbox of medicinal chemists, reporting the synthesis of dihydropyridine (DHP) in 1882. Among five possible regioisomers only 1,2- and the 1,4-DHP (Fig. 1) have gained significant attention. The 1,4-DHP scaffold has served as a nucleus for several blockbuster drugs such as nifedipine and amlodipine.<sup>1</sup> Close resemblance to nicotinamide adenine dinucleotide (NADH) coenzyme, which has an important role in biological

oxidation–reduction reactions, has made the 1,4-DHP core even more lucrative. Perhaps less studied in the past, the potential of 1,2-dihydropyridines has recently been explored as a critical scaffold for the synthesis of alkaloids and other drugs. 1,2-DHPs are now popular as a precursor for the synthesis of the 2-azabicyclo[2.2.2]octanes (isoquinuclidines) ring system present in alkaloids, ibogaine and dioscorine. The anti-influenza drug, oseltamivir phosphate (Tamiflu), is also synthesised from 1,2-DHP *via* an isoquinuclidine intermediate (Fig. 1).<sup>2</sup>

Recently, we reviewed reactions of 1,2- and the 1,4-dihydropyridines.<sup>3a</sup> The present manuscript aims to highlight the importance of 1,2- and the 1,4-dihydropyridines relevant to both synthetic and medicinal chemists. We will describe various methodologies that have been used for the synthesis of this class of compounds. We then focus on strategies which can

<sup>a</sup>RNA Therapeutics Institute, University of Massachusetts Medical School, Worcester, MA 01605, USA

<sup>b</sup>Department of Chemistry, Kirori Mal College, University of Delhi, Delhi-110007, India. E-mail: chem.sunil@gmail.com



Vivek received his PhD degree in Chemistry in 2014 from University of Delhi, India. Currently he is working as Postdoctoral Fellow at RNA Therapeutics Institute, University of Massachusetts Medical School, USA. His current research interests include development of low-cost microfluidic gene synthesis, to improve in vivo delivery of peptide nucleic acid (PNA), and study the effect of neutral

linkage between conformationally locked nucleotides for gene silencing applications.



Sunil K. Singh has obtained his M.Sc and PhD in Chemistry from University of Delhi. He is currently working as Assistant Professor in Chemistry Department at Kirori Mal College (A constituent college), University of Delhi. His current research works include multicomponent synthesis and biocatalysis. He has 17 research publications in his credit.

