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Synthesis S. Kumar et al. Short Review

Advances in the Synthesis of Spirocyclic Nucleosides

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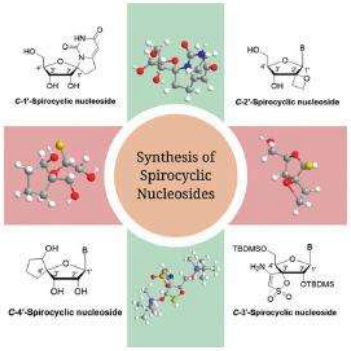

Dedicated to Late Professor Ashok K. Prasad, Department of Chemistry, University of Delhi, India.

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Abstract The nucleosides are the building blocks for nucleic acids and composed of a five-carbon sugar bearing either pyrimidine or purine nucleobase. The biological properties of nucleosides can be tailored by chemically modifying the five-carbon sugar to influence its sugar pucker. The spirocyclic scaffold is an indispensable scaffold in more than ten approved drugs, and its inherent three-dimensionality makes it an ideal modification to influence the sugar pucker and biological properties of nucleosides. However, the introduction of spirocyclic scaffold is often synthetically challenging due to increase in synthetic steps and stereocenters. The present review highlights the advances in synthetic methodologies developed during the past decades for accessing various members of the spiro-functionalized nucleoside family.

Key words sugar-modified nucleoside, hydantocidin, spironucleoside, spirocyclic scaffold, Vorbrüggen glycosylation, chemoenzymatic synthesis

1 Introduction

Since the critical function of nucleic acids in cells was recognized in the 1950s, the study of the chemistry and biology of nucleosides has been a fundamental research area. The interest in nucleoside analogues increased as the metabolic functions of nucleic acids were better understood.[1]

The nucleoside analogues display great anti-tumor and antiviral activities and have become cornerstones of treatment for cancer and viral infections (Figure 1, Table 1).[2–11] Numerous bioactive modified nucleosides have been produced as a result of the extended quest for clinically relevant nucleoside derivatives. Recent years have seen a lot of research on the conformational restriction of the ribose or deoxyribose furanose ring in the nucleosides, nucleotides, and oligonucleotides. This research has been stimulated by the possible medicinal use of these compounds.[12,13] The Food and Drug Administration (FDA) approval of the use of

Table 1 Anti-tumor and Antiviral Nucleoside Drugs

Bioactivity	Modified nucleoside drug
anti-tumor	6-mercaptopurine, 6-mercaptoguanine, fludarabine, clofarabine, cladribine, adenine arabinoside, cytarabine, nelarabine, decitabine, 5-FU, enocitabine, troxacitabine, gemcitabine, zalcitabine, capecitabine, CNDAC
antiviral broad-spectrum	ribavirin
antiviral	
anti-HIV	zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, tenofovir, emtricitabine
anti-HBV	lamivudine, adefovir dipivoxil, telbivudine, emtricitabine, tenofovir disoproxil, entecavir, clevudine
anti-HCV	sofosbuvir
antiherpes virus	idoxuridine, trifluorothymidine, brivudine, acyclovir, valacyclovir, penciclovir, famciclovir, ganciclovir, formimivir, cidofovir
anti-COVID-19	remdesivir, molnupiravir

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