

Nucleoside Chemistry

Integrated, innovative approaches for promising drugs

Nucleoside chemistry plays an important role in the development of some of the most important drugs used to combat cancer and viral diseases.

Archimica has developed nucleoside chemistry as a core area of expertise for nearly two decades, and today, offers one of the industry's broadest and most in-depth resources for route and process development and commercial scale manufacturing of nucleoside analogs. These strengths are available at virtually any stage of the drug commercialization process. At the same time, Archimica has extensive experience in producing APIs based on nucleoside technology. This experience allows Archimica to offer insight and perspective throughout the commercialization process.

Nucleoside strengths

- Creation of building blocks (pseudosugars and bases)
- Coupling and modification of both sugar moiety and base
- Modification of the coupled nucleoside

State of the art coupling

In the development of nucleosides, coupling is critical because it will almost entirely determine the enantiomeric purity and the syn/anti ratio of the final compound. Changing the purity characteristics of these compounds after synthesis is cost intensive. Archimica has a substantial body of expertise in the area of coupling of different bases and pseudosugars, and on the modification of both sugar and base moiety of nucleosides.

Modification

A prominent variation of the pseudo-sugar/base-coupling sequence is the chemical or enzymatic functionalization that can occur after the coupling step. Nucleoside molecules, which are extremely sensitive and contain chiral structures, require highly selective and very mild further processing. Archimica has developed addition/elimination-type and halogenation/elimination-type procedures as well as selective mono- or bis-dehalogenations for this situation. Since all of these steps are very close to the final API structure, they require cGMP manufacture and the corresponding process development, process robustness, quality control and scalability standards.

The ability to perform some of the required modifications for a nucleoside molecule after ring formation means that Archimica's technology team can choose the highest quality and economically most attractive option for specific syntheses.

One part of this ongoing success story is the regular production of Ribavirine (Figure 1). Also, Archimica has developed a proprietary technology for the preparation of 2',3'-Dideoxy- and 2',3'-Dideoxy-didehydro nucleosides which can be applied for the production of several nucleosides of these classes.

Pseudosugars and bases

The ability to create tailored bases and pseudosugars and couple them in effective ways is central to nucleoside analog production – offering the opportunity for specialized and enhanced efficacy, reduction in side effects, enhanced bioavailability and increased stability.

Excellence in heterocycles

Bases and the modification of bases result from Archimica's expertise in heterocyclic chemistry – specifically nitrogen-containing heterocycle chemistry (Figure 2). Archimica has experience in synthesis, functionalization and transformation of a broad range of substitution patterns of pyridines, pyrimidines, purines, indoles, chinolines, isochinolines, oxazoles and isoxazoles as well as annellated compounds. Since such nucleoside bases require heterocycles in readily functionalized forms, Archimica offers a broad toolbox in this area.

Archimica produces pyrimidine base derivatives including compounds such as 5-fluorocytosine (Figure 3).

Archimica's strengths in halogenation and halogen compounds have been applied to both the formation of sugar moieties and the development of selectively reactable centers for coupling. This aspect of synthesis includes the creation of oxygen-containing leaving groups. In this area, chloro, bromo, iodo as well as mesyl or phosphate leaving groups are the most common.

Glyoxylic chemistry

Archimica applies expertise in glyoxal and glyoxylic chemistry to sophisticated pseudosugar ring formation, providing higher yields, enhanced selectivity, cost effective commercial manufacturing and eliminating extensive purification. This technology is particularly relevant when a non-oxygen heteroatom is included in the sugar ring. For example, sulphur can be introduced in the 3' position of the ribose ring, thus obtaining 3'-

Figure 1

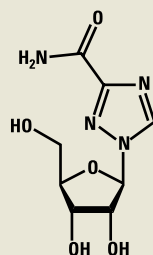


Figure 2

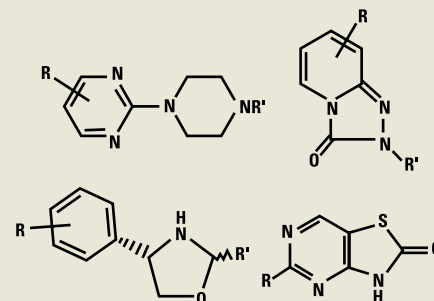


Figure 3

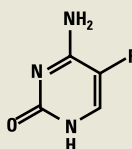
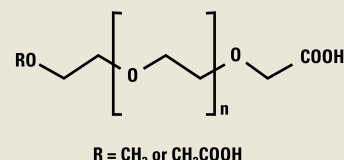


Figure 4



thionucleosides. Glyoxal and glyoxylic technology also allow the design of industrial scale synthesis routes for oxygen-containing pseudo-sugars that offer efficient isolation and purification solutions.

Expanding horizons

Archimica offers other technologies for pseudosugar tailoring. Oxa acids (Figure 4) (polyglycol mono- or di-acids with defined chain lengths) are used for chain modifications and for modifying the bioavailability properties of the final nucleoside. Phosphorous-based reagents and building blocks are used to add phosphoryl groups. The primary opportunity addressed with these capabilities is to provide orally administrable compounds, such as prodrugs.

Purification

Purification is an important issue in the production of nucleosides. Archimica has developed non-chromatographic purifications based solely on process development, mainly through crystallizations. In specific cases, particularly in situations where timelines play a major role during clinical development and fast-track launches, innovative specialized purification and separation technology is required.

Archimica has developed alliances with best-in-class specialist partners for both crystallizations and chromatographic methods of purification. These partnerships allow fast, seamless and reliable technology transfers and problem solving. Archimica customers can benefit both short- and long-term from this complete portfolio of options, acquiring speed and excellence and economics.