



CONCEPT LIFE SCIENCES

a spectris company

NUCLEOSIDES AND NUCLEOTIDES IN DRUG DISCOVERY

Nucleosides and Nucleotides receive extensive synthetic attention due to their numerous uses in therapeutic and biotechnology applications. Examples include Sofosbuvir¹, an important antiviral medication for the treatment of the hepatitis C virus (HCV) which works as a selective inhibitor of HCV NS5B polymerase with a high barrier to viral resistance, and more recently Remdesivir² for its potential use in the treatment of Covid-19. Concept Life Sciences has unrivalled expertise in the synthesis of nucleosides and nucleotides from route development to synthesis of mg to kg scale.



CAPABILITIES AND EXPERIENCE

Scientists at Concept Life Sciences have significant hands-on experience in the synthesis of nucleosides and nucleotides and have published or presented a wide variety of this work³⁻⁴. Projects have included collaborations and partnerships relating to milligram scale discovery chemistry through to kilogram scale process development as well as GMP and RSM manufacture in order to support our clients' drug discovery programmes. Our teams have extensive experience in the synthesis, purification and scale up of:

- ▶ Novel sugars and nucleosides
- ▶ Novel purine and pyrimidine derived bases
- ▶ Novel nucleotide monophosphates and triphosphates
- ▶ Novel nucleotide phosphoramidate and phosphate prodrugs

Synthesis, purification and characterisation are achieved by:

- ▶ UPLC / ion exchange systems using methods specifically designed for nucleosides and nucleotides
- ▶ Fully automated normal and reverse phase Isolera chromatography systems
- ▶ ELS and mass-directed prep HPLC detectors for the purification of UV-inactive sugars

- ▶ Lyophilisation for convenient isolation of purified material
- ▶ Multinuclear NMR for stereochemistry determination experiments and structure elucidation
- ▶ State-of-the-art scale up facilities for route optimisation and process development including 10-50L jacketed vessels, flow chemistry and fully compliant GMP and RSM manufacturing capabilities

Our project teams have a demonstrated track record of producing robust nucleoside and nucleotide candidates suitable for 'proof-of-concept' testing and have made key contributions to compounds undergoing clinical development. We have extensive experience in the complexities involved in the nucleotide prodrug strategies common to the marketed antivirals, Sofosbuvir², Tenofovir disoproxil⁵ and Remdesivir³. Our long-established history of scaling up complex chemistry delivers increased yields, safety and process improvements and shorter time-frames resulting in more cost effective projects for our clients.

Our personalised approach is provided with complete confidentiality and is underpinned by clear and regular communication from a dedicated project team while ensuring complete protection of Intellectual Property.



Our Expert team at Concept Life Sciences have undertaken numerous successful client collaborations and partnerships involving the synthesis of nucleosides and nucleotides where our project teams have made vital contributions, several of which are exemplified in Figure 1.

Our scientists have successfully delivered the synthesis of several complex bridged nucleosides including the 17 chemical step synthesis of >1 g of **2'-C-Me-LNA-G**. Key to this synthesis was the optimisation and scale up of a multigram 1-pot oxidation-Grignard protocol for the stereoselective introduction of the 2'-C-methyl substituent to provide access to key intermediate **2** starting from >500 g of **1**.

On other occasions we have provided synthetic expertise towards triphosphate type compounds including an array of acetylene functionalised clickable nucleotide phosphates, as well as a huge array of variously modified nucleosides and nucleotides for a client over the course of a multi-year FTE collaboration.

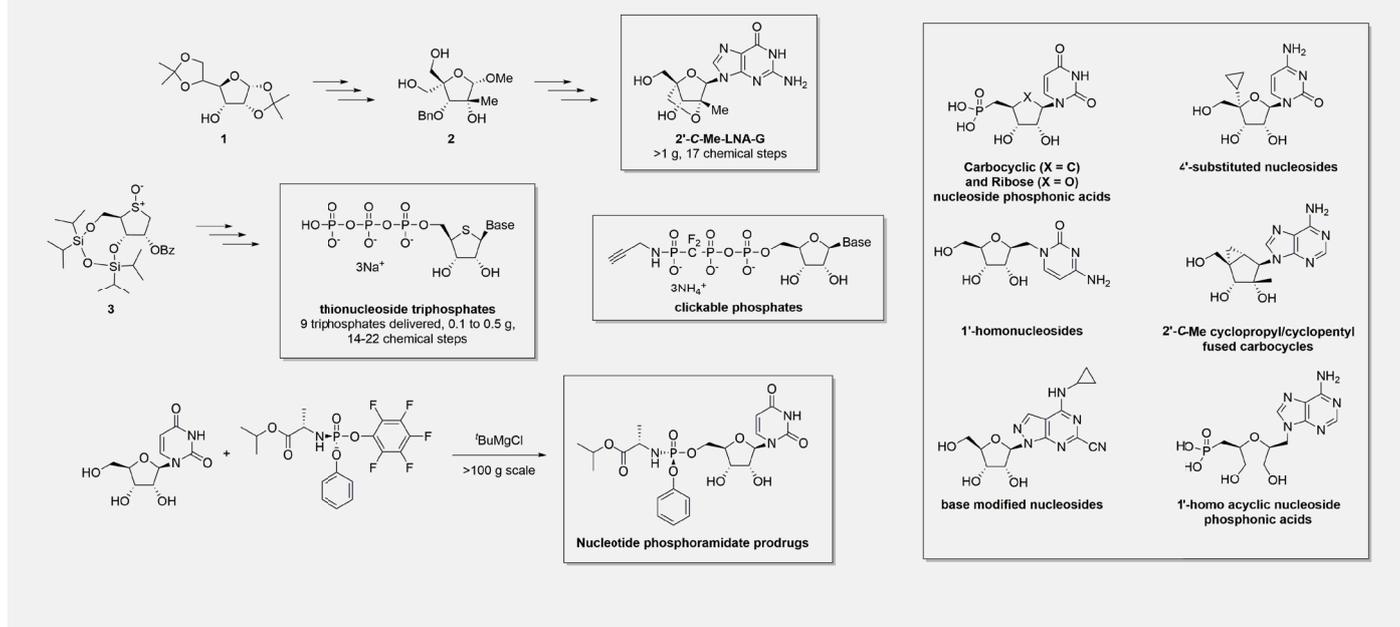
Additionally, we have gained extensive experience of prodrug strategies working collaboratively with several clients over many years to prepare and purify a large array of highly sensitive nucleotide phosphoramidate and phosphate prodrugs on milligram to >100 g scale.

Selecting the right CRO and CDMO partner is an important investment in the ever-changing landscape of today's industry. Housed in state-of-the-art facilities, scientists at Concept Life Sciences have extensive experience in the preparation of novel modified nucleosides and nucleotides. With a demonstrable history of successful client collaborations on a wide variety of project types from discovery chemistry through to process development, we pride ourselves in delivering a world class synthetic chemistry service underpinned by clear communication and confidentiality. We are the perfect partner to support your investment, sharing your passion for delivering science.


REFERENCES

- Sofia M. J. et al, *J. Med. Chem.*, **2010**, 53, 7202.
- Eastman R. T., et al, *ACS Cent. Sci.* **2020**, 6, 672.
- (a) Wainwright P., et al, *Synlett* **2005**, 765. (b) Maddaford A., et al, *Synlett* **2007**, 3149. (c) Maddaford A., et al, *Synthesis* **2007**, 1378. (d) Wainwright et al, *Synlett* **2011**, 1900. (e) Pryde D. C., et al *Tetrahedron Lett.*, **2011**, 52, 6415. (f) Wainwright P., et al *Nucleosides, Nucleotides and Nucleic Acids* **2013**, 32, 477 (g) Betson M., et al, *Org. Biomol. Chem.*, **2014**, 12, 9291.
- Chapron C., et al, *Bioorg. Med. Chem. Lett.*, **2014**, 24, 2699.
- Deeks S. G., et al, *Antimicrob. Agents. Chemother.*, **1998**, 42, 2380.

Figure 1: Example nucleosides and nucleotides that have been prepared by Concept Life Sciences scientists



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