# **Pharmaceuticals** from renewables come closer

**Dr Jason E. Camp**, CTO at **Circa Group**, discusses commercialising biobased platform chemicals, the company's investment in renewable chemistry and EU projects


The ReSolute plant will be built at Carling-St Avold in northern France

Pharmaceutical manufacturing generates more waste per kilogram of product than any other chemical manufacturing sector. Despite significant advances in green chemistry, more can be done to improve the sustainability of pharmaceutical production.

Part of the answer lies in using millions of tonnes of renewable cellulosic biomass waste to create biobased platform molecules that allow for more efficient syntheses. When combined with advances in new technology, these innovations can deliver better medicines more sustainably. There is clear evidence that biobased starting materials provide more sustainable routes to pharmaceutical production.

## Sustainability

Circa is bringing new intermediates to market with its patented Furacell technology that converts non-food biomass into the platform chemical levoglucosenone (LGO). The company has refined the technology at a series of plants and the next, ReSolute, will produce 1,000 tonnes/year. ReSolute will be commissioned at the end of 2023 in the northeast of France.

The production of LGO is conducted via a dehydration protocol using a standardised process from cellulose waste, such as wood chips. The co-products are water and biochar, which can be used to make the ReSolute plant virtually energy self-sufficient. The clean conversion means that the downstream purification, separation and waste disposal processes are reduced, making the process close to carbon-neutral.

ReSolute is the first commercial-scale LGO production facility on a roadmap to build a series of plants worldwide that will produce 80,000 tonnes by 2030. Locating production near markets increases the sustainability of the product profile and builds short-responsive supply chains decoupled from petroleum.

## LGO

Biobased platform molecules have distinct advantages over their petroleum-based counterparts. In addition to being fossil-free, their inherent complexity (chirality) allows for efficient production of existing drugs and candidates, as well as access to novel chemicals. Research has proved that LGO is an excellent platform molecule for the production and discovery of pharmaceuticals (Figure 1).

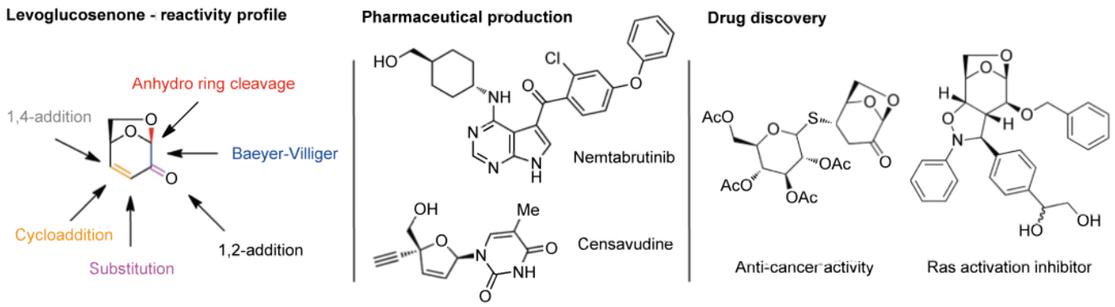
This chiral building block has been converted via well-established chemical processes into previously difficult-to-synthesise building blocks.[1] Research over the past half century has demonstrated the stereochemical control offered by the bicyclic ring-system and high degree of orthogonality in the reactive functional groups.

The chiral nature of LGO offers significant advantages over achiral biobased chemicals, such as furfural, while it is easier to derivatise than monosaccharides. Its chemical reactivity is well understood, but until recently its potential to produce pharmaceuticals more sustainably was untapped due to lack of production at scale.

## Pharmaceutical production

Recent work by MSD highlights how using the bio-based platform molecule LGO in combination with advances in chemical technology can result in more sustainable production of pharmaceuticals.[2]

Figure 1 – Levoglucosone as a pharmaceutical building block




An LGO derivative was used for the production of an investigational drug for the treatment of leukaemia. The initial manufacturing process relied on an 11-step synthesis. The development team was able to reduce this to two, thereby reducing energy use, carbon emissions and wastewater generation. One of the key transformations was the enzymatic reductive amination of the carbonyl group to form the required chiral amine.

Oncolys Bipharma has used the LGO platform to synthesise Censavudine, which has been investigated as a novel drug therapy for HIV with greater activity against the less common HIV-2 variant[3] Its patented route allowed for the synthesis of the API in a simpler way, at lower cost and in larger quantities than previous methods. The company used the inherent chirality of the LGO platform as well as the well-established chemical reactivity pattern to increase the sustainability of its production process.

Despite these recent advances in the sustainable manufacturing of pharmaceuticals using the LGO platform, there are still significant opportunities to use it more widely to intercept key intermediates. For example, straightforward protocols have been developed for the facile conversion of LGO to substituted butanolides, which are key building blocks for the synthesis of the COVID-19 anti-infective drug Remdesivir and the HIV protease inhibitor Indinavir.[3] These have the potential to increase the sustainable production of not only these drugs but a range of related compounds.

## Drug discovery

Beyond pharmaceutical production, LGO has been used extensively for the synthesis of novel, biologically active compounds. These studies take advantage of the rigid, highly functionalised nature of LGO and its well understood chemical reactivity.[1]

A series of recent papers has shown that the 1,4-addition of a range of nucleophiles, including thiols, amines, azides and alcohols, to the enone of LGO resulted in a range of biologically active compounds that had anti-cancer properties. Simple variations in the structure of the nucleophile gave control over both the specific cancer target and the activity of the molecules. In related work, Banwell introduced a 2-nitropyridine motif at the alpha position of LGO to afford a series of compounds with anti-microbial and anti-cancer activities.

Cycloaddition reactions are commonly used to selectively functionalise LGO for the synthesis of biologically active compounds. The cycloaddition of nitrones with LGO proceeds in a highly selective manner due to the polarisation of the double bond as well as the 1,6-anhydro bridge. This reactivity has been used to synthesise a series of carbonic anhydrase and RAS activation inhibitors.

## Outlook

Continued innovation in drug development, primarily driven by specialty drugs, is driving an expected CAGR of 8% from 2021 to 2025.[4] There is also increasing demands from customers and governments for more sustainable pharmaceutical manufacturing.

Against this backdrop, Circa is delivering biomass-derived LGO platform molecules, and developing new products and technologies to support the integration of our products into the sustainable production of pharmaceuticals. The Circa Renewable Chemistry Institute at the University of York has been established for this purpose. Circa is also a partner on the EU Horizon-funded project TransPharm, which seeks to develop sustainable production methods for pharmaceuticals products. ●

***References:***

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***4:*** *. Future of US healthcare post-COVID-19 | McKinsey*

**Dr Jason E. Camp**
CTO
**CIRCA GROUP**
jason.camp@circa-group.com
www.circa-group.com