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FIRST REACTIONS

A Road to Profitability from Lignin via the Production of Bioactive Molecules

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A new study opens a route to convert lignin, the world largest natural source of aromatics, into valuable bioactive compounds.

Lignin, one of the three major components in lignocellulosic biomass, is by far the largest natural source of aromatic functionalities and as such is an obvious feedstock for the production of renewable chemicals or fuels. Industrial development of lignin depolymerization has long been contemplated but has remained limited to a few niche applications. A team lead by Katalin Barta has developed a novel route to convert lignin into tetrahydro-2-benzazepines, a class of compound with promising pharmacological activities, and high potential value, which could help add value to this feedstock that is notoriously difficult to valorize.[1]

A longstanding roadblock to lignin deconstruction and use has been the quality of the lignin available industrially, which has largely been produced by the pulp and paper industry and, to a lesser extent, by biorefineries. In traditional pulp and paper plant, lignin is a highly modified side product and burned directly to generate energy for the plant.[2] In most of the biorefinery strategies, polysaccharides are separated, deconstructed, and converted to fuels, chemicals, or materials, leaving behind a lignin with a completely altered structure as a byproduct. These technical lignins are almost impossible to valorize because any condition that is harsh enough to isolate them generally leads to condensation and the associated formation of interunit C−C linkages, which cannot be cleaved selectively with current chemical techniques. As a result, these lignins can barely be depolymerized into low molecular weight monomers and thus are a poor feedstock for producing platform molecules that could be upgraded to other products.[3]

Increasingly, there has been a realization that integrated utilization of biomass and associated lignin valorization is necessary for the development of a profitable biorefinery. Therefore, several researchers have been developing methods for depolymerizing lignin to a select group of molecules at high yields and selectivity as part of the integrated conversion of all fractions of biomass.[4−7] Reductive catalytic fractionation (RCF) is one of these methods and has been developed among others by Barta and her co-workers.[4,7] This method mixes untreated biomass and a catalyst to directly cleave the ethers of native lignin and rapidly hydrogenate its fragments in the presence of a hydrogen donor at high temperature (180−250 °C).[5] Because lignin is directly converted as it is being extracted, this process avoids the aforementioned condensation issues and allows the recovery of a select number of products at high yield and selectivity. The major products of RCF (and other isolation methods) are propylphenols and phenylpropanols, which do not have a market application as of yet. They can be deoxygenated and converted to phenol, benzene, or alkane derivatives, but the low market value of these bulk chemicals makes it very challenging to build a profitable process, especially for an emerging technology. For this reason, targeting higher value compounds such as pharmaceuticals could be interesting.

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Barta's group has developed a copper-doped porous metal oxide (Cu20-PMO) for the RCF process and achieved

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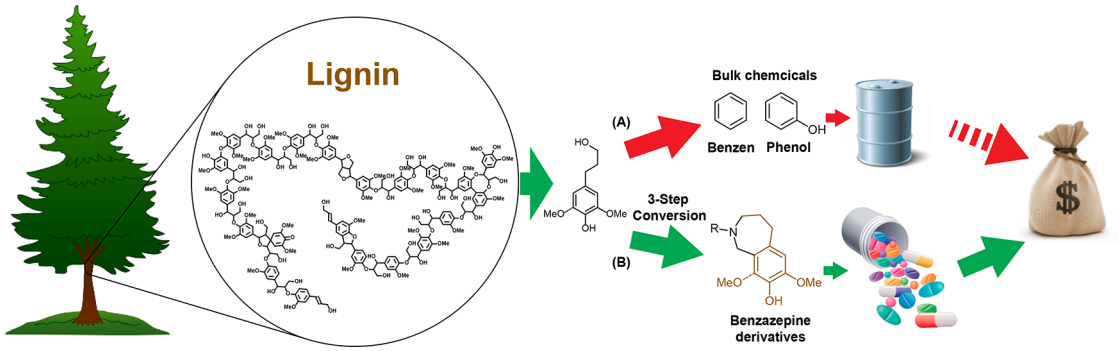

Figure 1. Reductive catalytic fractionation of lignin in biomass produces dihydroconiferyl and sinapyl alcohol. These phenylpropanols can be converted to bulk chemicals such as benzene and phenol which have relatively low market value (A). Barta's group reported an alternative green route to generate benzazepine derivatives from these intermediates (B), with the potential to increase the profitability of lignin valorization.

interesting aromatic monomer yields (10 wt % of lignin) with 86% selectivity toward phenylpropanol from pine (Figure 1, route B).[7] On the basis of this work, they further developed the transformation of phenylpropanol to pharmaceutical platform chemicals, 2-benzazepine derivatives, and the result is published in this issue of *ACS Central Science*.[1] The idea to produce benzazepines from lignin-based phenylpropanols is clever because the seven-membered *N*-heterocyclic benzazepine is synthetically challenging to produce from petroleum-based chemistry. The fossil-based route to benzazepines consists of multiple steps that produce stoichiometric quantities of waste and use toxic organic solvents. In contrast, the lignocellulosic-based scheme is environmentally friendly because it features a waste-free process and uses a bioderived green solvent. Furthermore, this biomass-derived route is able to integrate the entire structure of phenylpropanol, which leads to high atom economy.

The novel synthetic route included three steps (Figure 1): (1) reductive catalytic fractionation of biomass using Cu20-PMO to generate phenylpropanol, (2) Ru-catalyzed amination of dihydroconiferyl (**G**) and/or dihydrosinapyl alcohol (**S**) in the depolymerized mixture, and (3) cyclization of the secondary amine to generate the seven-membered *N*-heterocyclic ring. After hydrogenolysis of the biomass (step 1), **G** and **S** along with other aromatic monomers, dimers, oligomers, and carbohydrates (mainly from hemicellulose) were dissolved in the liquor. A direct amination of this raw mixture was possible but required much more reagent (4 equiv) and catalyst (10 mol %) and resulted in a lower yield (64% of theoretical yield) of the desired product, because the other OH-containing products in the RCF mixture also consumed the reagent and catalyst. A simple ethyl acetate extraction of the RCF mixture can remove the high molecular weight fractions and some of the carbohydrates to improve the amination process (84% yield of aminated dihydroconiferyl alcohol using 2 equiv of amines and 5 mol % catalyst). However, the consumption of reagents illustrates the challenges ahead for developing any transformation that starts with biomass-derived liquor. The last cyclization step was performed in deep eutectic solvent under mild conditions with up to 95% yield of tetrahydro-2-benzazepines depending on different types of amines used.

> Targeting a highly valuable pharmaceutical precursor such as the lignin-derived bioactive tetrahydro-2-benzazepines discussed here could add significant profitability to biomass deconstruction.

Tetrahydro-2-benzazepines are high value molecules due to their remarkable pharmacological properties. Compounds containing 2-benzazepines show strong neuroleptic and neurotropic activities.[8] Moreover, they are extractable from *Galanthus nivalis* and clinically used for the treatment of Alzheimer's disease.[9] The lignin-derived tetrahydro-2-benzazepines synthesized in this study also exhibited interesting biological activities. They were notably active against *Staphylococcus aureus* and inhibited the viability of HepG2 cells by >85%, indicating their promising anti-infective and anticancer activities.

Various biorefinery schemes have long suffered from limited profitability and the difficulty of competing against the petrochemical industry, which has had over a century to develop and optimize its technology. Valorization of lignin is regarded as a possible route to palliate this problem. However, as these new technologies emerge they will inherently cost more than mature and highly optimized petrochemical processes. Targeting a highly valuable pharmaceutical precursor such as the lignin-derived bioactive tetrahydro-2-benzazepines discussed here could add significant profitability to biomass deconstruction. The demand volume

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for such chemicals is likely to be small, which will limit large-scale implementation. However, a profitable small-scale demonstration plant could derisk lignin conversion technology and lower costs for a much larger scale production of lignin-derived bulk aromatic chemicals—paving the way for renewable chemical production.

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Notes

The authors declare no competing financial interest.

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