Perspective

Pharmaceutically relevant (hetero)cyclic compounds and natural products from lignin-derived monomers: Present and perspectives

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SUMMARY

Lignin, the richest source of renewable aromatics on the planet, is an intriguing raw material for the construction of value-added aromatics. In the past decade, much progress has been made regarding the development of efficient lignin depolymerization methods, able to produce specific monophenol derivatives in high-enough selectivity and yields. This now serves as an excellent basis for developing powerful downstream conversion strategies toward a wide range of products, including fine chemical building blocks. The inherent structural features of lignin-derived platform chemicals undoubtedly inspire the development of novel, creative, atom-economic synthetic routes toward biologically active molecules or natural products. In this perspective we attempt to bridge the structural features of lignin-derived platform chemicals with existing synthetic strategies toward the construction of heterocycles and provide a summary of efforts for the production of natural products from aromatics that can be, in principle, obtained from lignin. Last, we comment on the latest efforts that present entire value-chains from wood to valuable pharmaceutically relevant compounds.

INTRODUCTION

Lignocellulose is a promising raw material for future biorefineries providing access to a wide variety of chemical products, ranging from fuels, bulk chemicals, and pharmaceuticals (Christopher et al., 2012; Tuck et al., 2012; Nicholas, 2014). Although biofuels (Love and Bryant, 2017) and drop-in chemicals (Liao et al., 2020; Sun et al., 2020; Wong et al., 2020) are frequent targets due to their widespread utility and importance in the chemical industry, obtaining these from the structurally complex lignocellulose constituents ((hemi)cellulose and lignin) requires extensive defunctionalization strategies (Schutyser et al., 2018; Sun et al., 2018b). In comparison, the construction of fine chemical building blocks and biologically active molecules from renewable resources would allow for more direct routes (Dusselie et al., 2014; Elangovan et al., 2019). Surprisingly, this approach has received much less attention (Blondiaux et al., 2019; Elangovan et al., 2019; Natte et al., 2020), although straightforward pathways to gain medicinally relevant compounds from renewables would have several advantages. The construction of high-value products in addition to other product platforms would increase the profitability of biorefineries (Lan and Luterbacher, 2019), and taking advantage of the inherent functionality of bio-based platform chemicals would lead to more efficient and sustainable synthesis strategies compared with the multi-step processes required from low-functionality petrochemicals (Elangovan et al., 2019; Shi et al., 2019; Natte et al., 2020). The latter is a crucially important aspect for the pharmaceutical industry, where reduction of E-factors, limiting hazardous waste and extensive solvent use, and overall, the incorporation of the principles of green chemistry into manufacturing protocols is of prime importance (Bryan et al., 2013; Peterson and Manley, 2015).

Perhaps the biggest challenge in this regard, in our view, is to optimally harness the natural structural complexity displayed in renewables (Afanasenko and Barta, 2019). That is, to find creative strategies starting from bio-based platform chemicals as defined by nature and shaped by the type of depolymerization method, to arrive to a final product of a specific and desired structure that will be suitable as pharmaceutical or biologically active molecule. There is certainly a lot of potential, because biologically active natural products frequently originate from the same building blocks as plant structural material (i.e., lignocellulose) (Vanholme et al., 2010, 2019), thus several moieties already existing in platform chemicals are in principle advantageous for displaying biological activities (Vardanyan and Hruby, 2016; Kühlborn et al., 2020). In

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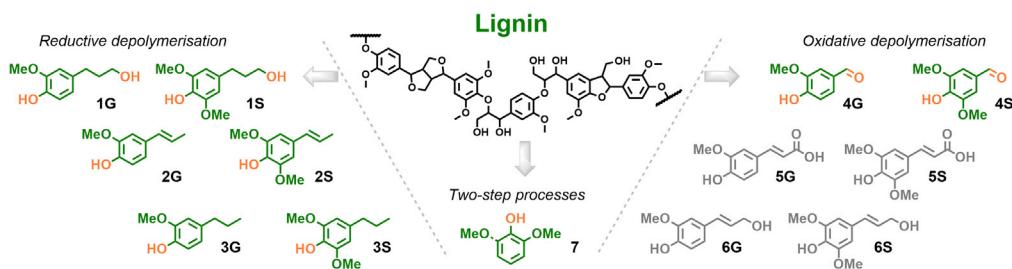
Figure 1. Overview of selected key platform chemicals obtained from different lignin depolymerization processes

Compounds in gray do not belong to a pool of typical platform chemicals that are directly obtained by catalytic depolymerization.

addition, the highly oxygenated nature of renewable building blocks is a good basis for developing waste-free catalytic functionalization or cyclization strategies, for example, routes toward higher value primary or secondary amines (Bariwal and Van Der Eycken, 2013; Corma et al., 2018; Irrgang and Kempe, 2020), as well as *N*-heterocycles (Bhusal and Sperry, 2016), and/or *O*-heterocycles (Lichtenthaler, 2002; Hülsey et al., 2018) omnipresent in medicinal chemistry. Undoubtedly, chemical catalysis will play a key role both in biomass depolymerization and shifting toward atom-economic and waste-free routes from the obtained platform chemicals to fine chemical building blocks (Sun et al., 2018a; Elangovan et al., 2019; Shi et al., 2019).

Here we summarize the recent developments related to this area, while focusing specifically on *lignin* as starting material. Lignin is the most abundant source of aromatic moieties in nature and is highly oxygen rich, thus it already carries an appreciable degree of aromaticity and functionalization already present in biologically active compounds (Vardanyan and Hruby, 2016; Kühlborn et al., 2020). Alternatively, its intrinsic structure can be utilized for the development of catalytic strategies to create new biologically active scaffolds (e.g., those including N or heterocycles) or existing pharmaceutically relevant molecules and natural products.

In this perspective, we focus on establishing pathways/connections between lignin-derived platform chemicals that recently became available in higher yields and selectivities by utilizing cutting-edge depolymerization strategies and selected potential target products that could be obtained from these structures. The suggested pathways are literature-based, although full value-chains have not necessarily been established from lignin itself. In addition, we separately discuss already reported, recent systematic approaches that focus on establishing transformations to value-added chemicals. Starting from lignocellulose or lignin as raw material, these methods allow to access biologically active compounds or pharmaceuticals.

In the past decade, several powerful catalytic methods have been developed to obtain aromatic building blocks from lignin in high selectivity (Figure 1) (Schutyser et al., 2018; Sun et al., 2018b; Wong et al., 2020). For example, vanillin and syringaldehyde are produced by oxidative depolymerization of lignin as also demonstrated in the paper and pulp industry (Heitner et al., 2010), and recently novel strategies have focused on increasing the yield of the desired aldehydes (Mobley, 2020). Beside oxidation, various reductive methods have been introduced (Song, 2020). The recently developed stabilization strategies (Abu-Omar et al., 2020; Questell-Santiago et al., 2020), such as reductive catalytic fractionation (RCF) (Renders et al., 2019) or aldehyde-assisted fractionation (Shuai et al., 2016), start directly from lignocellulose and are able to achieve near-theoretical yields of monoaromatics and high selectivity for 4-propylguaiacol and 4-propyl syringol (Song et al., 2013) as well as dihydroconiferyl (Sun et al., 2018a) and/or dihydrosinapyl alcohols (Lan et al., 2018), whereas product distribution depends on the catalytic system and specific reaction conditions. Alternatively, these methods may also result in the formation of 4-(1-propenyl)-guaiacols and syringols as main products (Galkin and Samec, 2014).

CONSTRUCTION OF CORE HETERO- AND POLYCYCLIC SCAFFOLDS BY ATOM-EFFICIENT STRATEGIES

The lignin-derived platform chemicals that are all monophenol derivatives, displayed in Figure 1, were collected to different categories based on their side-chain functionality. These molecules could, in
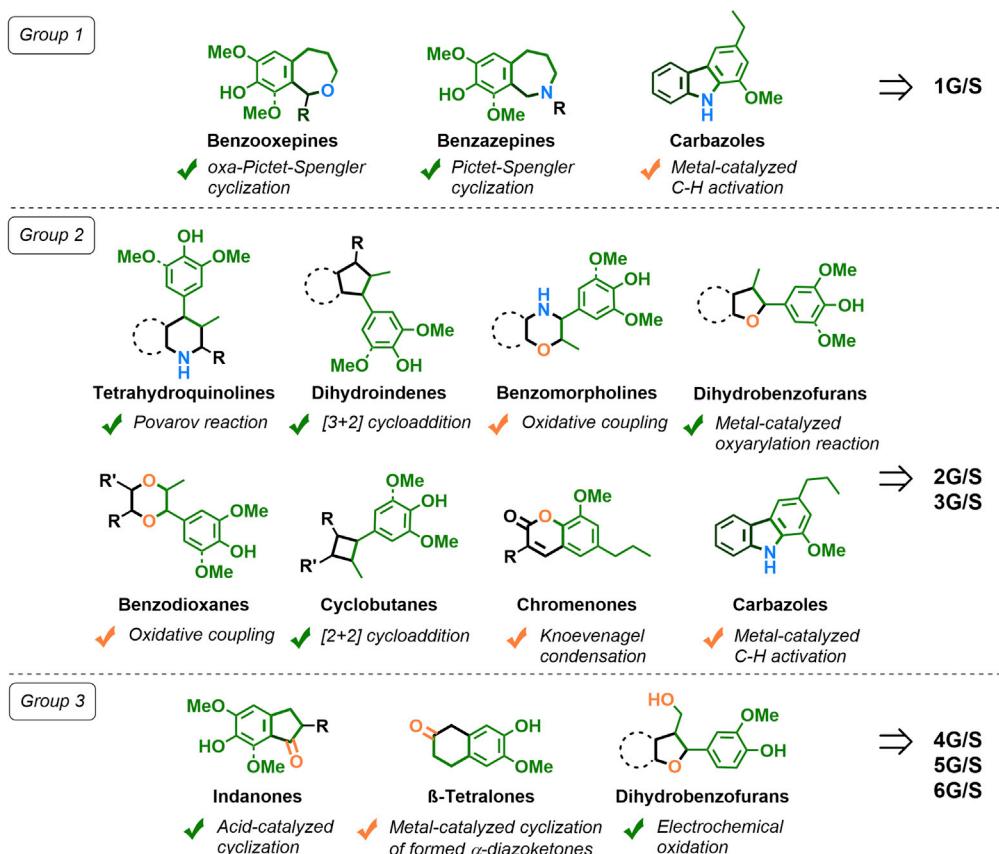
Figure 2. Various classes of (hetero)cyclic compounds that could be potentially obtained through the functionalization of key lignin-derived platform chemicals (for more details see the supplemental information, Scheme S1)

principle, serve as starting material for the construction of attractive heterocyclic and/or polycyclic compounds for application in medicinal chemistry (Figure 2). In fact, synthetic pathways starting from these or similar scaffolds, not necessarily originating from lignin depolymerization studies, have already been reported. Here we highlight such possibilities, divided by the different compound groups. After an extensive literature search, the pathways were selected based on the following criteria: synthetic utility and atom economy, the preservation of the inherent chemical functionality of the lignin-derived substrate, and sufficient molecular complexity of the final product. In addition, focus is devoted to the formation of heterocycles or cyclic structures. Key catalytic methodologies that are able to implicate both the phenol moiety and the side chain into core heterocyclic structure will be consequently discussed (for more details see the supplemental information, Scheme S1).

Group 1: Dihydroconiferyl and dihydrosinapyl alcohols

We have assigned dihydroconiferyl and dihydrosinapyl alcohols to belong to the first group of lignin-derived monomers that may originate from specific lignin depolymerization methods (Lan et al., 2018; Sun et al., 2018a; for more details see the supplemental information, Scheme S1A).

Having electron-donating substituents such as phenolic hydroxyl and methoxy groups as well as a free *ortho* position next to the alkyl side chain in their structures, these alkyl-phenol derivatives (1G, 1S) could appear as excellent starting material for the construction of the *benzooxepine* scaffold via the *oxa*-Pictet-Spengler reaction (Duan et al., 2007). *Benzazepines* could also be synthesized via amination of the corresponding phenyl-propyl alcohols followed by the Pictet-Spengler cyclization (Elangovan et al., 2019); more details regarding the three-step synthesis of a variety of benzazepine derivatives from wood are specified in

the section "High-value chemicals from raw lignocellulose or lignin: construction of sustainable catalytic pathways".

Another intriguing class of nitrogen-containing heterocycles, namely, *carbazoles*, could be potentially obtained in three steps starting from dihydroconiferyl alcohol (1G). The latter was shown to undergo reductive defunctionalization to produce 4-ethylguaiacol (Sun et al., 2018a), which serves as starting material for the construction of the carbazole core by the metal-free oxidative coupling with 2-bromo-*N*-phenylpropanamide (Yu et al., 2013) followed by a palladium-catalyzed oxidative biaryl coupling (Liégault et al., 2008) to arrive to naturally occurring carbazole alkaloids.

Group 2: Alkyl- and alkenyl-guaiacol and syringol derivatives

trans-Isoeugenol and *trans*-4-propenylsyringol (2G, 2S) are the main products of several reductive catalytic depolymerization methods (Galkin and Samec, 2014; Galkin et al., 2016). Comprising an electron-rich double bond in their structure, phenylpropenoid derivatives are utilized as dienophiles in the acid-catalyzed imino Diels-Alder reaction (also known as Povarov reaction) (Kouznetsov et al., 2008; He et al., 2012) for the construction of *tetrahydroquinolines*, a typical scaffold in a myriad of natural products (for more details see the supplemental information, Scheme S1B).

Dimerization reaction of two phenylpropanoid units via a [3 + 2] cycloaddition reaction (Kouznetsov and Merchan Arenas, 2009) supplies polyfunctional *dihydro(1H)indene* derivatives (lignan-like molecules). The employment of the environmentally benign solvent (PEG-400) and Lewis acid as a catalyst makes the entire process highly attractive.

Benzomorpholines are another important class of benzoheterocycles that could be accessed via oxidative coupling between 2-aminophenols and aryl alkenes (Dong et al., 2020). As well as the previous methodology, this visible light-promoted reaction features a high atom economy.

Dihydrobenzofuran and *benzodioxane* skeletons are prominent structural motifs in lignin itself and are a remarkable subgroup of the naturally occurring *O*-heterocycles owing to their complex biological activities (Teponno et al., 2016). The former unit could be easily constructed from *o*-aminophenol and arylpropene via diazotization and palladium-catalyzed oxyarylation reaction in a "one-pot" process (Coy et al., 2010), whereas the latter is a result of the coupling between *trans*-4-propenylsyringol or *trans*-isoeugenol and the 3,4-dihydroxy aryl substrate in the presence of an oxidizing agent (for instance, silver oxide) (She et al., 1999; Jing et al., 2004).

Organocatalytic, stepwise [2 + 2] cycloaddition (Nielsen et al., 2016) converts α,β-unsaturated aldehydes and alkenylphenols in a regiospecific manner to *tetra*-substituted *cyclobutanes*. It is worth mentioning that both last-described methodologies could utilize coniferyl and sinapyl alcohols (6G, 6S) as starting material as well.

Besides side chain functionality, the free phenolic hydroxyl group of the propyl phenol derivatives (3G, 3S) could also be used for the construction of heterocycles. Thus, the hexamine aromatic formylation (Duff reaction) of 4-propylguaiacol followed by Knoevenagel condensation with ethyl acetoacetate (Brancaglion et al., 2018) furnishes the formation of *chromenones (coumarins)*, ubiquitous components in plant species, possessing a wide range of pharmacological activities (anti-inflammatory, antioxidant). The synthesis of *carbazoles* from 4-propylguaiacol is described in details in section "High-value chemicals from raw lignocellulose or lignin: construction of sustainable catalytic pathways".

Group 3: Vanillin, syringaldehyde, and its derivatives

Vanillin and sinapyl aldehydes (4G, 4S) are typical products of lignin depolymerization, whereas ferulic and sinapinic acids (5G, 5S) are generally obtained from agricultural biomass by extraction methods (Faulds et al., 1997); however, they are also known to be detected as products of lignin depolymerization mixtures (Karp et al., 2016). Although 5G and 5S are not typical monomers obtained upon catalytic depolymerization, herein we will include a brief discussion of possible transformations starting from these building blocks as well (for more details see the supplemental information, Scheme S1C). In fact, numerous procedures for the synthesis of hetero- and polycycles commonly require the transformation of vanillin or sinapyl aldehyde to ferulic or sinapinic acid by Knoevenagel condensation with malonic acid at the first step.
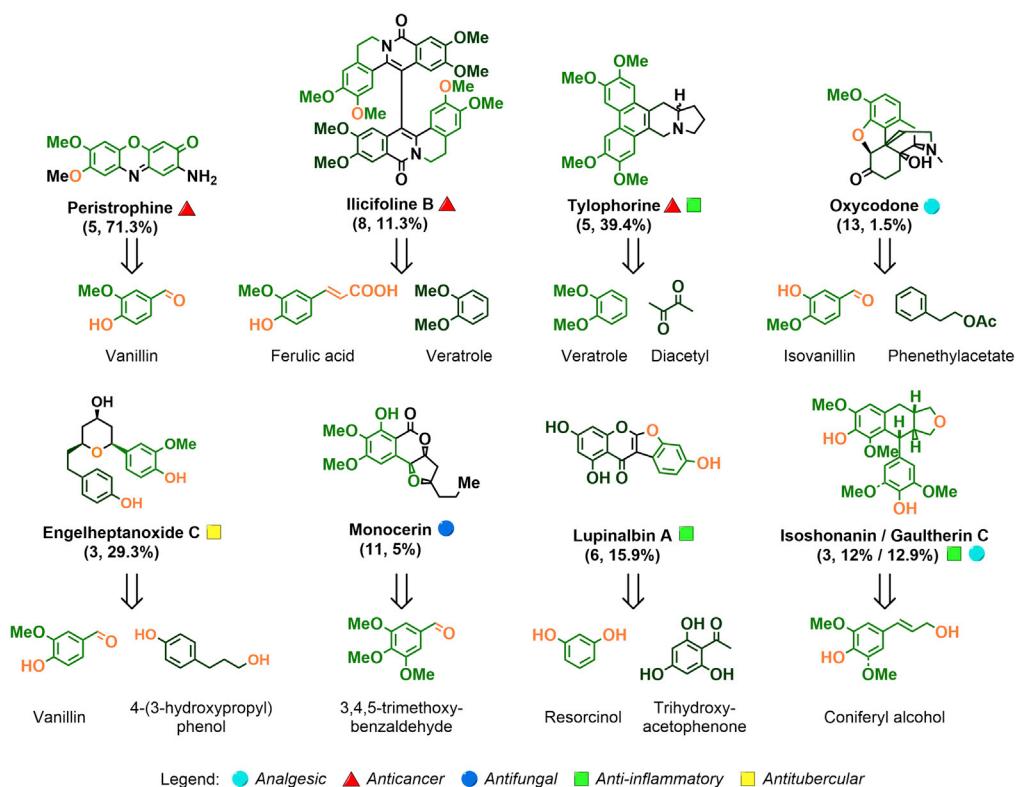
Figure 3. Selected examples of natural products that could be in principle obtained from lignin-derived platform chemicals (besides neolignanes and lignans)

In parenthesis the number of steps required to synthesize the target products and overall yields are specified. The corresponding biological activities are color coded.

Indanones could be synthesized from ferulic acid in two steps by Pd-catalyzed hydrogenation followed by acid-catalyzed cyclization (Hu et al., 2015).

Catalytic hydrogenation of ferulic acid and its transformation to acid chlorides followed by reaction with (trimethylsilyl)diazomethane and subsequent rhodium(II) acetate-catalyzed cyclization of the formed diazoketones provides the substituted *beta-tetralones* (Li et al., 2003).

Interestingly, subjecting coniferyl alcohol to electrochemical oxidation at low potential in the presence of 2,6-lutidine affords the formation of *dihydrobenzofuran* scaffold of the natural product (±)-Hierochin D (Romero et al., 2018). Besides the latter approach, the dihydrobenzofuran moiety can be constructed from ferulic acid following an oxidative dimerization strategy (Lahive et al., 2016).

In summary to this section, here we summarized a number of atom-economic approaches for the synthesis of diverse hetero- and polycyclic scaffolds that could be potentially obtained from abundant lignin-derived monomers. It is worth mentioning that the displayed methodologies are based on cycloaddition, acid-catalyzed cyclization, electrochemical oxidation, nucleophilic addition, and metal-mediated coupling reactions that allow preserving the innate functionality of platform chemicals and meanwhile achieving the target value-added products, typically in waste-free and energy-efficient way. In the next section, we will review successful examples of pharmaceutically relevant and biologically active molecules.

CONSTRUCTION OF NATURAL PRODUCTS FROM POTENTIALLY LIGNIN-DERIVED BUILDING BLOCKS

Several aromatic monomers can be obtained or will be, in the future, potentially accessible from lignin by depolymerization and appropriate defunctionalization strategies. These building blocks have been reported as starting materials for the synthesis of a number of natural products (displayed in Figure 3). As
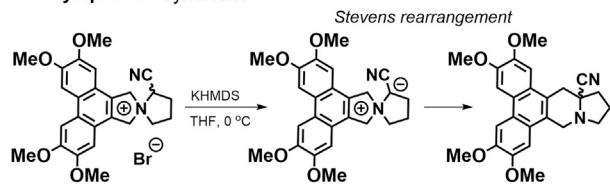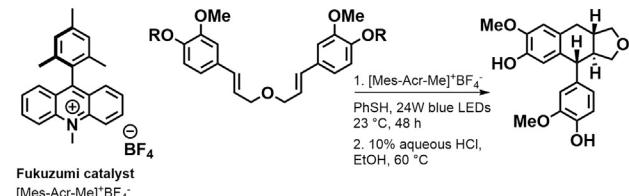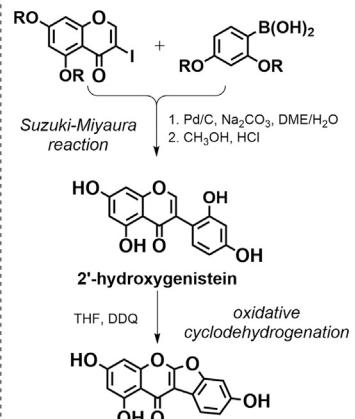
Scheme 1. Key steps in the synthesis of selected natural products
(A) Tylophorine.
(B) Lupinalbin A.
(C) Isoshonanin.

our group (Sun et al., 2018b) as well as Jagadeesh and co-workers (Natte et al., 2020) recently thoroughly reviewed this subject, hereafter we shortly discuss selected complex structures, emphasize bio-precursors for their synthesis, and summarize pharmacological activities.

An elegant approach for the synthesis of 2-aminophenoxazinone natural product, *peristrophine*, exhibiting pronounced antiproliferative properties, was introduced by Opatz and co-workers using potentially wood-derived chemicals such as vanillin and phenols (Kühlborn et al., 2019). Besides the utilization of bio-sourced substrates in this protocol, the authors implemented the use of mild and ecofriendly oxidant—H_2O_2—instead of the commonly utilized benzoquinone that allowed selective cross-coupling between two aminophenol units.

The same group reported the first total synthesis of the dimeric berberine alkaloid *Ilicifoline (Ilicifoline B)* (Stubba et al., 2015) as well as a short synthesis of the phenanthroindolizine alkaloid, *tylophorine* (Lahm et al., 2012), employing in principle bio-derived starting materials such as ferulic acid, veratrole, and diacetyl. Interestingly, the latter synthetic approach is based on the Stevens rearrangement of the formed nitrile-stabilized ammonium ylide and requires only five linear steps, three of which could be performed in one-pot without intermediate purification (Scheme 1A).

A potent analgesic, *oxycodone* (Endoma-Arias et al., 2019), and *engelheptanoxide C*, the natural product recently isolated from stems of *Engelhardia roxburghiana* (Klucznik et al., 2018), possessing antitubercular activity, are prominent examples of biologically active compounds that could be readily available from iso-vanillin/vanillin and phenethylacetate/4-(3-hydroxypropyl)phenol. Remarkably, despite the fact that the oxycodone synthesis is entirely based on classical organic chemistry methodologies, the utilization of lignin platform chemicals allows shortening the number of reaction steps from 24 to 13, significantly improving the total yield of the target compound (from 0.016% to 1.5%).

The 4-oxyisochroman-1-one skeleton of the fungal metabolite *monocerin* could be efficiently constructed from potentially bio-based 3,4,5-trimethoxybenzaldehyde over the sequence of 11 reactions with an overall yield of 5% (Fang et al., 2013).

van Heerden and co-workers demonstrated a highly convergent route for the synthesis of naturally occurring phytoestrogen, *Lupinalbin A* (Selepe et al., 2011), starting from resorcinol and trihydroxyacetophenone, in two major steps that involve the preparation of 2′-hydroxygenistein by the Suzuki-Miyaura reaction, followed by oxidative cyclodehydrogenation (Scheme 1B).

The aryltetralin cyclic ether lignans (Xiang et al., 2020), namely, *isoshonanin* and *gaultherin C* have been synthesized by Zhu and co-workers from monolignols in three steps in the presence of Fukuzumi's
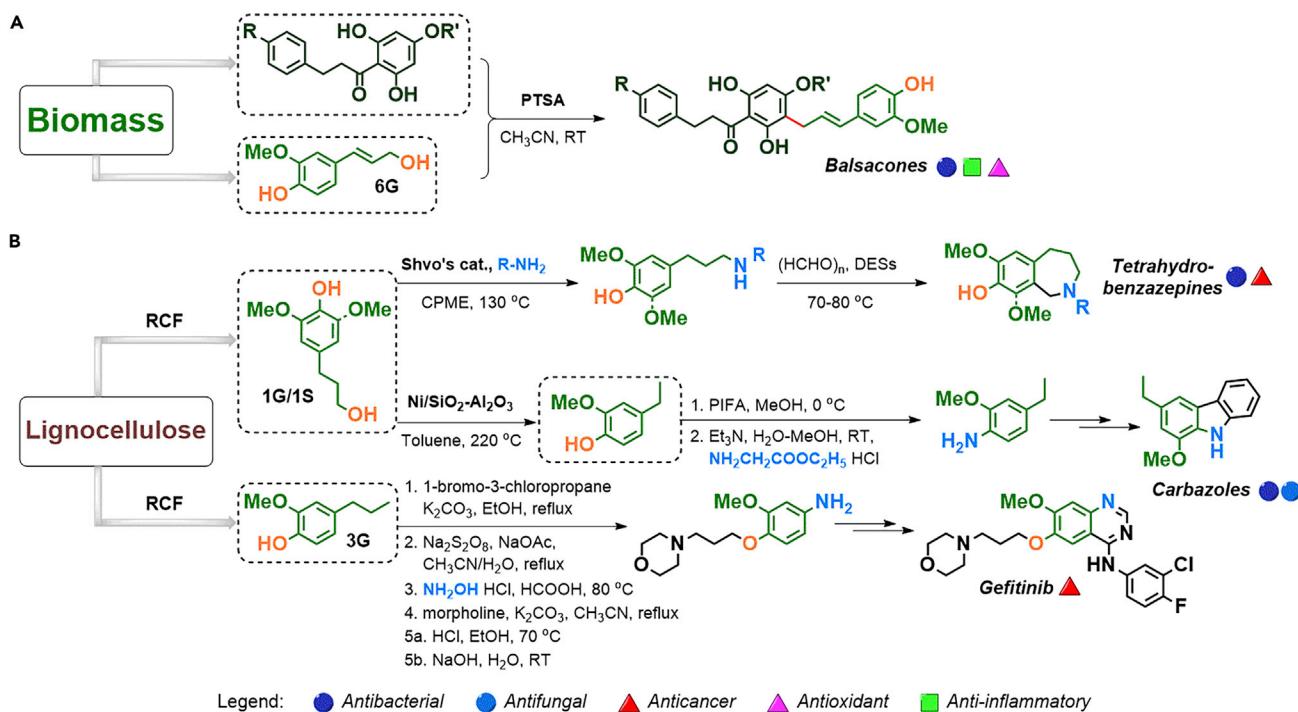
Figure 4. Various strategies to obtain pharmaceutically relevant compounds from lignocellulose
(A) Example of a sustainable synthesis strategy of a biologically active molecule from bio-sourced precursors.
(B) Overview of known pathways for the production of nitrogen-containing chemicals from lignin-derived platform chemicals obtained upon reductive catalytic fractionation (RCF).

acridinium salt under blue LED irradiation (Scheme 1C). The obtained members of this family of natural products display analgetic and anti-inflammatory properties.

HIGH-VALUE CHEMICALS FROM RAW LIGNOCELLULOSE OR LIGNIN: CONSTRUCTION OF SUSTAINABLE CATALYTIC PATHWAYS

The utilization of building blocks originating from wood, for the synthesis of functional materials such as dyes (Kühlborn et al., 2017), adhesives (Wang et al., 2018), and polymers (Isikgor and Becer, 2015; Sun et al., 2018b; Questell-Santiago et al., 2020), as sustainable and renewable replacement of petrochemical building blocks has been accomplished and widespread activities are ongoing. More recently, a few groups have also focused on the production of high-value compounds such as natural products (Alsarraf et al., 2020), pharmaceuticals (Blondiaux et al., 2019), or biologically active compounds (Elangovan et al., 2019) starting from wood. These methods focus on obtaining the starting materials from lignocellulose either by extraction methods or by catalytic depolymerization, in particular, the recently introduced RCF, a prominent method that leads to high yield and selectivity of aromatic monomers. In this section, we will summarize these efforts in more detail, also focusing on overall value-chains as well as isolation/product separation strategies and current challenges in these areas.

The one-step synthesis of *balcasones*, a promising class of bioactive molecules, displaying attractive antimicrobial and antipsoriatic activities, has been recently introduced by Alsarraf and co-workers following a Brønsted acid-catalyzed Friedel-Crafts alkylation methodology (Figure 4A) (Alsarraf et al., 2020). In this protocol dihydrochalcone, which was directly isolated from the buds of *Populus balsamifera,* and coniferyl alcohol (6G), which could be potentially derived from lignin, have been used for the one-step synthesis of the target product. The method does not use any protecting groups, and dehydration yields water as a side product, which renders the entire process 100% carbon economic (CE) and 96% atom economic (AE). The studies of biological properties of balcasones revealed that the obtained cinnamylated dihydrochalcones are active against gram-positive *Staphylococcus aureus*. Compared with gentamycin that was used as a positive control, about 83-fold higher MIC (minimum inhibitory concentration) was observed for the best obtained bio-derived inhibitor.

Our group recently accomplished the waste-free synthesis of a library of seven-membered *N*-heterocycles from wood in three straightforward steps. The first step consisted of RCF of various wood lignocelluloses to afford the platform chemicals dihydroconiferyl (1G) and dihydrosinapyl (1S) alcohol (depending on wood type) in high selectivity using a copper-doped porous metal oxide (Cu20-PMO) as catalyst in methanol, taking advantage of our previously developed "LignoFlex" process (Sun et al., 2018a). Second, capturing the aliphatic alcohol moieties in these alcohols by Ru-catalyzed direct amination via the borrowing hydrogen methodology resulted in a library of secondary amines in very high selectivity (up to >95% depending on the amine coupling partner). The reactions were accomplished in the non-toxic solvent cyclopentyl methyl ether. Finally, the target *tetrahydro-2-benzazepines* were subsequently constructed via a Pictet-Spengler cyclization (Figure 4B) (Elangovan et al., 2019). This last step, namely, the challenging construction of the seven-membered *N*-heterocyclic scaffold, was carried out using the non-toxic, biodegradable, recyclable, and potentially bio-derived deep eutectic solvent, consisting of oxalic acid (OA) and choline chloride (ChCl), which acted both as solvent and catalyst and rendered the use of strong inorganic acids and conventional solvents obsolete. Considering the use of lignocellulose as substrate in this work, the earlier mentioned ruthenium-catalyzed highly selective amination protocol was shown to tolerate the multicomponent crude depolymerization mixture that commonly contains besides 1G, also 4-ethylguaiacol, and 4-propylguaiacol (3G), residual sugars, and lignin oligomers. This allowed accomplishing the one-step conversion of 1G using *p*-chloroaniline as coupling partner, directly in crude product mixtures obtained from reductive depolymerization of pine and poplar lignocellulose, without the need for separation of 1G.

The viability of the modular amination/cyclization protocol has been demonstrated by the discovery of a number of promising biologically active structures in the obtained compound libraries. Several structures have displayed an effect on a human hepatoma cell line (Hep G2) by >85% at 100 μM with IC_{50} values ranging from 30 to 50 μM for the best inhibitors (compare with doxorubicin—44-fold activity gap) and against gram-positive *Staphylococcus aureus* (compare with erythromycin about 10-fold higher MIC for the best lignin-derived inhibitor), indicating their anti-infective and anticancer activities.

Describing the "Lignoflex" process in 2018, our group also reported the diversification of 1G obtained from pine lignocellulose to access a wide array of amines and other value-added compounds to be used as fine chemical or polymer building blocks (Sun et al., 2018a). Among these, the formation of 4-ethylguaiacol through defunctionalization of 1G over a commercially available Ni/SiO$_2$-Al$_2$O$_3$ catalyst (Figure 4B) was reported. Subsequently, this compound was subjected to phenol-to-aniline transformation through an *ipso*-oxidative aromatic substitution process (St Amant et al., 2016) to yield 4-ethyl-2-methoxyaniline, which could in principle undergo a palladium-catalyzed direct arylation (Ackermann and Althammer, 2007) to yield carbazoles such as murrayafoline A (Martin and Moody, 1985). The synthesis of the latter is particularly relevant due to its strong fungicidal activity against *Cladosporium cucumerinum* and growth inhibitory activity on human fibrosarcoma HT-1080 cells (Cui et al., 2002).

In a separate, elegant strategy, Maes and co-workers demonstrated the synthesis of valuable 3,4-dialkoxyanilines and pharmaceuticals, namely, *gefitinib*, using hydroxylamine hydrochloride as an amine source and 4-propylguiacol (3G) as starting material (Figure 4B) (Blondiaux et al., 2019). As it was shown by many groups (Song et al., 2013; Van Den Bosch et al., 2015; Galkin et al., 2016; Renders et al., 2017), 3G could be obtained through RCF using external or *in situ*-generated H$_2$ over Ni/C, Pd/C, and Ru/C as catalysts. The creative strategy to access 3,4-dialkoxyanilines from 4-propylguaiacol (3G) is based on its *O*-alkylation followed by benzylic oxidation, Beckmann rearrangement (crucial step for the nitrogen introduction), and amide alcoholysis. Notably, this method uses the propyl side chain, which in this case, does not participate in the construction of any structural moiety that would be present in the final product, to introduce a valuable aniline moiety, in *para* position to the existing phenol. Although the presented approach is mainly based on stoichiometric reactions, all reaction steps are characterized by excellent regio- and chemoselectively, excluding the need for column chromatography to purify reaction products. In fact, the study also provided an in-depth analysis of the developed novel pathways in terms of green chemistry metrics as well as detailed comparison with classical organic chemistry approaches.

The synthesis method for the construction of novel benzazepines discussed in the previous sections focused on developing modular catalytic methods for easily creating a library of novel structures for facile evaluation of biological activities in essays, and thus serve potential drug development purposes, whereas the current approach focused on creating novel pathways to access already existing important pharmaceutical products, drug precursors. The authors demonstrated that the obtained 3,4-dialkoxyanilines can be used as precursors for the synthesis

of several drug molecules, such as the anticancer drug *gefitinib*. This can be prepared in 10 steps starting from 3G with an overall yield of 22% (and in five steps from 3-methoxy-4-(3-morpholinopropoxy)aniline). The fungicide *diethofencarb* can be obtained in five steps from 3G and in one step by coupling 3,4-diethoxyaniline with isopropyl chloroformate (Xu et al., 2010) delivering the target compound in an overall 48% yield from 3G.

CONCLUSION

For the past decades, significant efforts have been directed to the development of efficient catalytic depolymerization methodologies—ranging from oxidation to reduction, acid or base catalysis—to obtain diverse aromatic monomers with high selectivity (Schutyser et al., 2018; Sun et al., 2018b). Fundamentally important concepts, such as the stabilization of reactive intermediates during fractionation or depolymerization, for preventing recondensation processes have been introduced, which markedly reduced the formation of recalcitrant side products, thereby increasing selectivity toward desired products in near theoretical yields (Abu-Omar et al., 2020; Questell-Santiago et al., 2020). Having access to diverse lignin platform chemicals, the search for catalytic downstream processing approaches has been initiated, and several important product classes, such as fuels, bulk chemicals, or drop-in intermediates, became accessible (Sun et al., 2020; Wong et al., 2020). However, upgrading of the obtained lignin-derived building blocks to high-value end products, namely, pharmaceuticals and specialty chemicals, remained still underrepresented despite its obvious advantages. The success of converting biomass into the target complex products is highly dependent on the development of novel preferably catalytic atom-efficient methodologies. As we highlighted in this perspective, various atom-economic strategies are already found in the literature or could be newly constructed, which take advantage of the inherent functionalities of lignin-derived monomers, introduce heteroatom elements, and finally convert them to value-added products in a highly sustainable way.

Some of the remarkable synthesis routes presented here show ample possibilities for the construction of valuable structural moieties using atom-economic, green transformations, even considering the use of alternative solvents. By doing so, the number of reaction steps needed to arrive at the target products will be significantly shortened. All these aspects are extremely important for the pharmaceutical industry during the manufacture of pharmaceutical products, and the easy, efficient, and highly modular synthesis of novel compound libraries based on bio-based platform chemicals is invaluable for drug discovery purposes.

Beside the immense benefits for the medicinal and pharmaceutical branches, the development of novel more sustainable and green routes from renewable building blocks would significantly increase the profitability of existing biorefineries where—beside other larger volume product classes—a portion of the platform chemicals could be converted to higher added value products depending on market demand. We hope that this perspective will inspire researchers to create their unique strategies, which will provide access to products of increased complexity and added value from already inherently functionalized bio-based materials. We are confident that plenty of new discoveries will be made in this research area, in the coming decade.

METHODS

All methods can be found in the accompanying Transparent Methods supplemental file.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2021.102211.

AUTHOR CONTRIBUTIONS

A.A. and K.B. wrote the manuscript. A.A. conceived the idea of the figures and constructed all the figures based on comments of K.B. who supervised the overall project.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Supplemental information

Pharmaceutically relevant (hetero)cyclic compounds

and natural products from lignin-derived

monomers: Present and perspectives

Anastasiia Afanasenko and Katalin Barta

Scheme S1: Construction of core hetero- and polycyclic scaffolds by atom-efficient strategies; Related to **Figure 2**.

### A Group 1: dihydroconiferyl and dihydrosinapyl alcohols

a) Benzooxepines (Duan *et al.*, 2007)

Overall AE = 94%
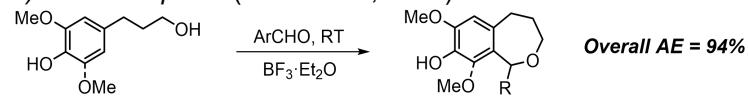
b) Benzazepines (Elangovan *et al.*, 2019)

Overall AE = 89%
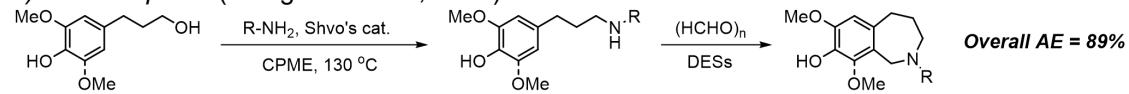
c) Carbazoles (Liégault *et al.*, 2008; Yu *et al.*, 2013; Sun *et al.*,

Overall AE = 55%

2018)
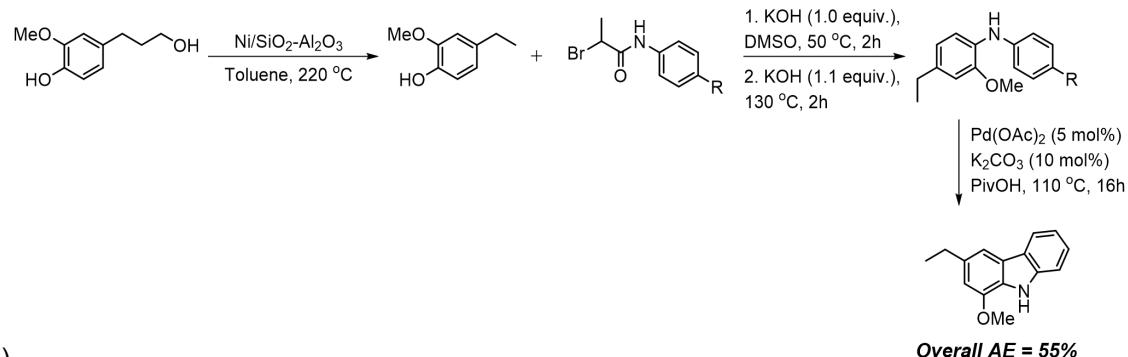
B Group 2: alkyl- and alkenyl- guaiacol and syringol derivatives

*a) Tetrahydroquinolines* (He *et al.*, 2012)

Overall AE = 95%
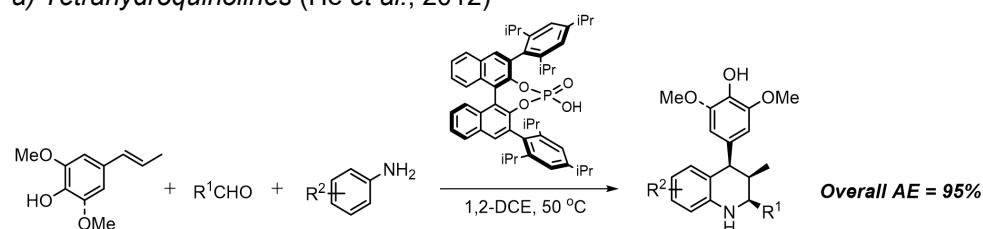
b) Dihydro(1H)indenes (Kouznetsov and Merchan Arenas, 2009)

Overall AE = 100%
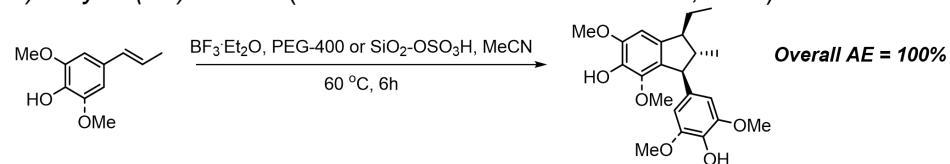
c) Benzomorpholines (Dong *et al.*, 2020)

Overall AE = 99%
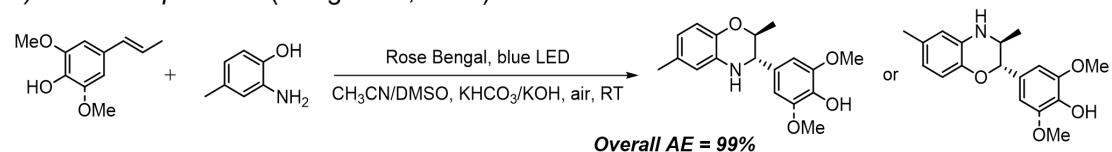
d) Dihydrobenzofurans (Coy B., Jovanovic and Sefkow, 2010)

Overall AE = 66%
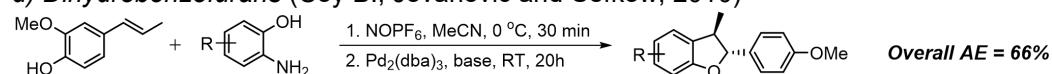
e) Benzodioxanes (Jing et al., 2004)

Overall AE = 99%
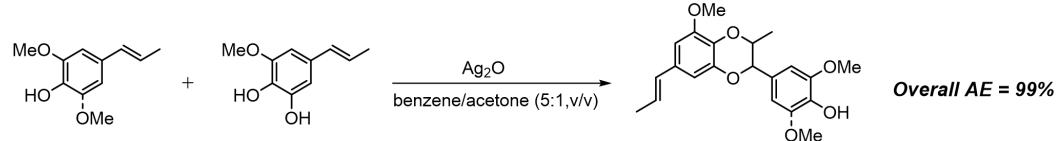
f) Cyclobutanes (Nielsen, Jenkins and McNulty, 2016)

Overall AE = 100%
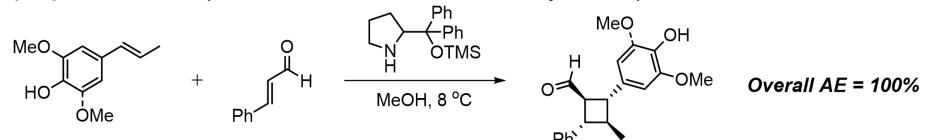
g) Chromenones (coumarins) (Brancaglion et al., 2018)

1. Hexamine, glacial AcOH, 125 °C, 5h
2. HCl 2M, 0.5 h

ethyl acetoacetate, L-proline, 90 °C, 1h

Overall AE = 64%
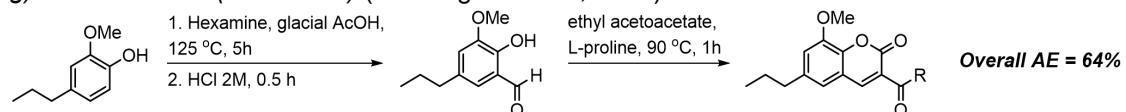
h) Carbazoles (Ackermann and Althammer, 2007; St Amant et al., 2016)

1. PIDA, MeOH
2. Et₃N, H₂O
NH₂CH₂COOEt·HCl

Pd(OAc)₂, PCy₃, K₃PO₄, NMP

Overall AE = 48%
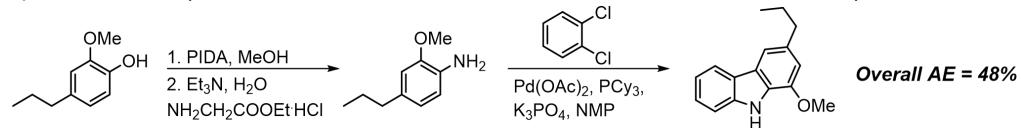
C Group 3: vanillin, syringaldehyde and its derivatives

a) Indanones (Hu et al., 2015)

malonic acid piperidine/pyridine

Pd/C, H₂ MeOH, 40 °C

1:10 P₂O₅-MsOH, 50 °C

Overall AE = 69%

b) beta-Tetralones (Li et al., 2003)

malonic acid piperidine/pyridine

Pd/C, H₂ 40 psi

1. BnBr, K₂CO₃
2. KOH, H₂O, CH₃OH

(COCl)₂

Rh(OAc)₂

TMSCHN₂

Overall AE = 42%
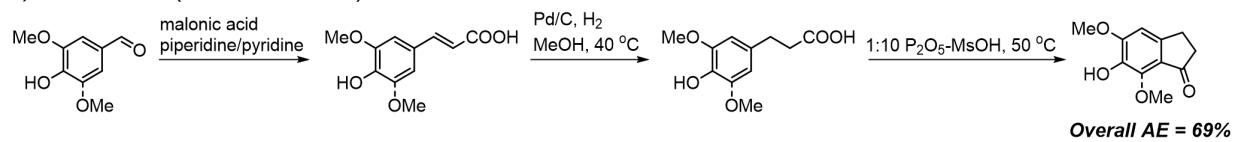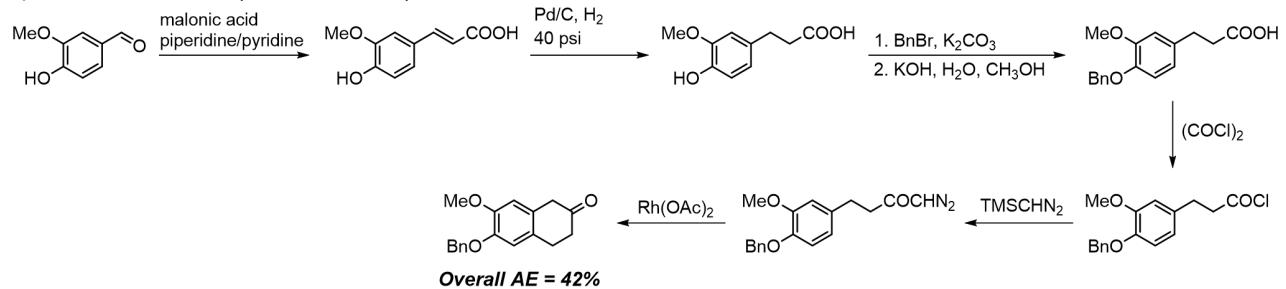
c) Dihydrobenzofurans (Lahive et al., 2016; Romero et al., 2018)

2,6-lutidine
MeCN, 0.6 V

Overall AE = 99%

Ag₂O
DCM, 24h

Overall AE = 99%