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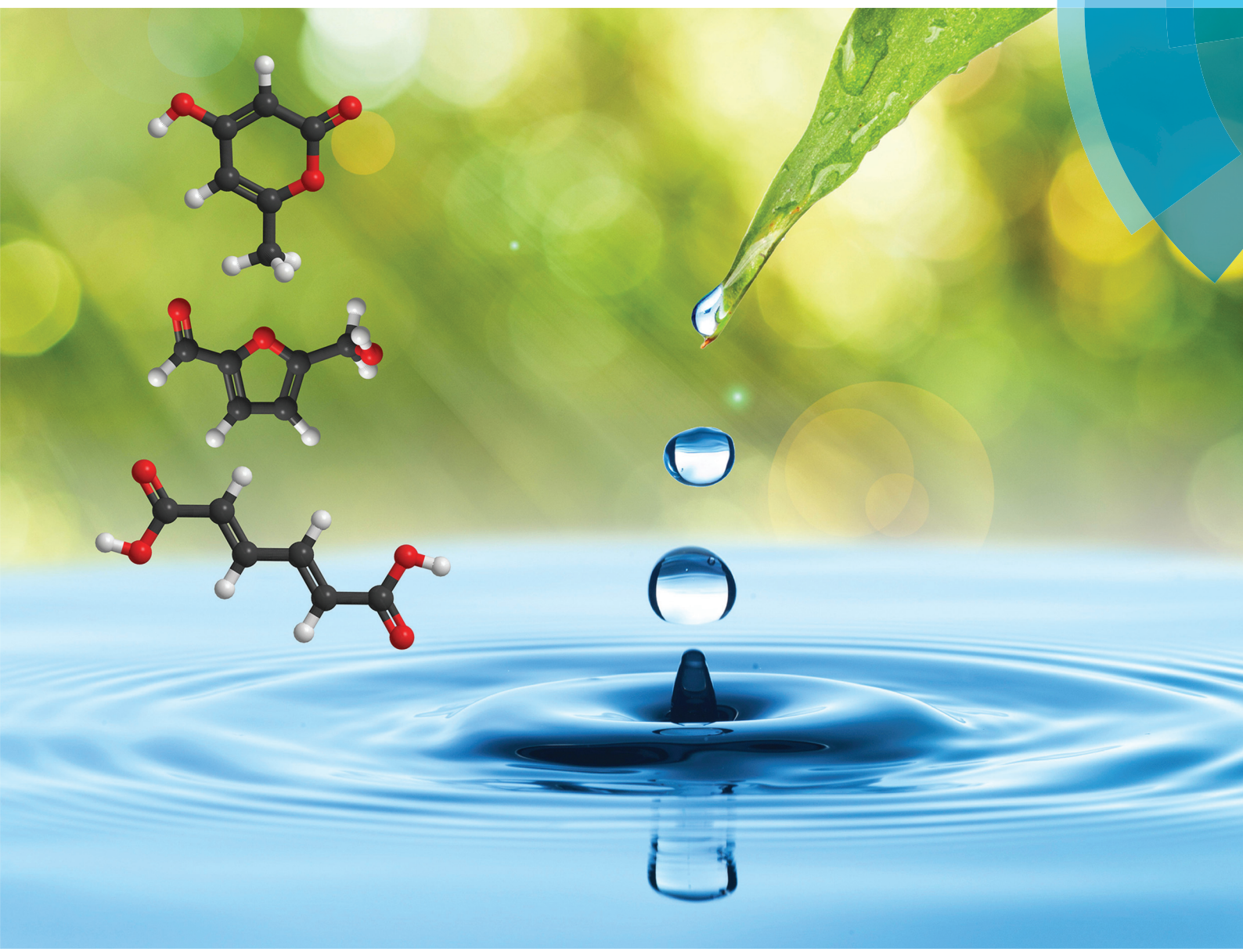

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Bioprivileged molecules: creating value from biomass

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The petrochemical industry is built on C_2–C_4 alkenes and aromatics as intermediate molecules, which are converted to a range of products. This industry is highly developed with little opportunity for new chemical products. In comparison biological-derived intermediates from biomass have the potential to introduce a new set of intermediate molecules, which can be converted to molecules that directly replace petrochemicals. Even more promising is the potential to convert biological-derived intermediates to novel chemical species that impart enhanced performance properties in their end use. Here the concept of bioprivileged molecules is introduced as a useful new paradigm for developing biobased chemicals. Included are muconic acid, 5-hydroxymethylfurfural and triacetic acid lactone as example bioprivileged molecules. Also, discussed is the research needed to move this concept forward.

Introduction

The birth and growth of the petrochemical industry was driven by low cost carbon available as a byproduct from the crude oil refining industry. Light gases from the refineries are thermally cracked to generate C_2–C_4 alkenes and aromatics (benzene, toluene and xylenes): intermediates that are subsequently converted to the broad range of petrochemicals in use today. This exquisitely efficient infrastructure has been advanced and optimized for more than a century to create cost-effective processes that produce low-cost petrochemicals. Importantly, the productivity of the chemical industry grew over that time period through a combination of improved production efficiencies and the introduction of new chemical products. However, the well-established petrochemical intermediates available today ultimately constrain the potential for new product chemicals. As such, it seems likely that future innovations in the now mature petrochemical industry will continue to involve further enhancements to processing efficiency and incorporation of cost-advantaged feedstocks such as shale gas. An important question to be asked is whether it is possible to identify viable routes to overcome product stagnation by developing innovative chemical species and products that address new market needs.

Such new market needs are driving an interest in next-generation nutraceuticals, antimicrobials, insecticides, herbicides, pharmaceuticals, consumer goods, specialty chemicals, materials, *etc.*, which can only be accomplished by identifying new chemical products. One upshot of this opportunity to reinvigorate the development of new chemical products, is to consider alternative carbon sources that can diversify the set of accessible and desirable intermediate chemical species beyond those available in the petrochemical industry. In this regard, biomass-derived feedstocks hold particular promise for dramatically increasing the pool of possible intermediates because they provide a rich array of chemical complexity. In 2004 Werpy *et al.* developed a set of criteria that led to the identification of a "Top 10" chemicals list that could be derived from carbohydrate-based feedstocks.[1] This list of potentially valuable biobased intermediates was later refined into a "Top 10 + 4" list[2] that has generated considerable research and development efforts as summarized in multiple recent review articles.[3–8] These chemicals were all classified as attractive because they had received significant attention in the literature. Most notable in the criteria was their ability to serve as potential platform chemicals that could be transformed into multiple chemical derivatives with multiple downstream applications. However, an important attribute of the identified intermediates was their ability to be converted into chemicals that were direct "drop-in" replacements for petrochemicals, *i.e.*, the same chemical species with just a different starting material. Additionally, the intermediates were already known to be readily accessible from carbohydrates. The lists were essentially retrosynthetic and did not consider how to identify more challenging forward-synthesis approaches to novel intermediates that might provide access to new chemical products.

Despite the upside potential for novel chemical products, a significant challenge in their identification and development

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is the relative dearth of structure–function understanding between chemical species and final product performance attributes in end use applications. This lack of structure–function insight creates a dilemma as the precise chemical target for improved product performance cannot be easily defined and as such no single novel target chemical species can be identified. Without a target-chemical-species, it is not possible to define a retrosynthetic pathway. The pharmaceutical industry has confronted the same challenge in their search for new bioactive compounds. In their evolution away from a target-based retrosynthetic approach two concepts emerged that could be combined into approaches to new intermediate chemical species, namely (i) privileged structures,[9,10] and (ii) diversity oriented synthesis.[11,12] Privileged structures are defined as "molecular frameworks that are capable of providing useful ligands for more than one type of receptor or enzyme target by judicious structural modifications". The key advantage of privileged structures combined with diversity-oriented synthesis is its ability to rapidly generate a large array of novel molecules based on "distinct molecular scaffolds" and "organic-chemical navigator" molecules having a high expectation of being bioactive.[13–15] This privileged-structure concept in combination with diversity-oriented synthesis[16–18] is able to deliver a library of molecules because of known chemical transformations that are possible with synthetic organic chemistry.

Translating this pharmaceutical-led vision of a broader bioactive molecule universe based on privileged structures into a bioproduct-led vision, there is an opportunity to rethink the retrosynthetic approach to biobased chemicals and build a broader bioproduct universe built on biological-derived intermediate chemicals rather than bioactive privileged structures. Specifically, we posit a new bioproducts paradigm that is focused around the objective of creating novel "bioprivileged molecules". Bioprivileged molecules are defined as "biology-derived chemical intermediates that can be efficiently converted to a diversity of chemical products including both novel molecules and drop-in replacements". There are several important components to this definition. First, a bioprivileged molecule is an intermediate chemical species that can be generated from a biological feedstock, but cannot be effectively accessed from petrochemical feedstocks. Second, while a bioprivileged molecule represents a unique intermediate, it must still allow for ready transformation to a number of valuable chemicals. Third, being efficiently transformable requires conversions delineated by minimal subsequent conversion steps, which can be achieved with high atomic utilization for carbon and hydrogen Finally, a bioprivileged molecule provides a pathway to a number of chemical products encompassing both existing chemical products as well as novel chemical species that can impart new product properties. A key attribute of novel molecules is that they cannot be effectively synthesized from petrochemical building blocks, so their properties in product applications have received little or no attention. This dual potentiality of a bioprivileged molecule is vital since innovation in bioproducts represents a powerful driver for the development of biobased chemicals beyond just replacing fossil carbon with renewable carbon.

The important conceptual evolution of bioprivileged molecules from biobased platform chemicals is the objective that a bioprivileged molecule provides a basis for diversity-oriented synthesis leading to novel bioproducts. This evolution of platform chemicals to bioprivileged molecules can be further clarified by comparing the previously proposed criteria for platform biobased chemicals[2] with newly proposed attributes for bioprivileged molecules as shown in Table 1.

The development of the petrochemical industry was essentially an exercise in diversity-oriented chemical synthesis on a highly constrained set of alkene and aromatic molecules leading to a limited number of possible transformations. In contrast, bioprivileged molecules by their origin from biological-derived molecules and concomitant plethora of functionalities have the potential to greatly expand the bioproduct horizon beyond the scope of petrochemicals.

Bioprivileged molecule examples

Although not explicitly labeled as such, there are a number of biobased chemical targets that demonstrate aspects of the bioprivileged molecules concept. While it is not the intent of this discussion to comprehensively list these molecules, several can be used as illustrative examples. The first molecule discussed is muconic acid, which was generally explored from a platform chemical perspective wherein the commercial targets involved synthesizing direct replacements to petrochemicals. However, there is also the potential to expand its product targets to include novel molecules and an example of that is described below. The next example is 5-hydroxymethylfurfural (HMF), which has been shown to be converted to both direct replacement as well as novel molecules. While not formally presented as such, HMF and its derivatives represent a utilization of diversity-oriented synthesis from a bioprivileged molecule. Finally, triacetic acid lactone (TAL) is presented as an emerging example demonstrating a more complete example of the development of the bioprivileged molecule concept.

Muconic acid

Muconic acid has been found with some organisms during the catabolism and detoxification of aromatic compounds, but is not produced endogenously by any known organism from carbohydrates. This molecule was postulated as a potential platform chemical (Fig. 1) when bioengineering enabled it to be produced from glucose in *E. coli*[19] and yeast[20,21] through the introduction of a heterologous synthetic pathway designed from a naturally occurring intermediate in the shikimate pathway, reviewed by Xie.[22] Additional opportunities exist to produce muconic acid from other sources of biomass, such as lignin.[23] Muconic acid can be converted to a range of large-volume commodity chemicals currently produced in the petrochemical industry (Fig. 1), including adipic acid,[24,25] capro-

Table 1 Bioprivileged molecule attributes relative to critera presented for platform biobased chemicals[2]

Platform biobased chemical criteria	Bioprivileged molecule attributes
The compound or technology has received significant attention in the literature. A high level of reported research identifies both broad technology areas and structures of importance to the biorefinery	The molecules may or may not have received significant attention in the literature
The compound illustrates a broad technology applicable to multiple products. As in the petrochemical industry, the most valuable technologies are those that can be adapted to the production of several different structures	The molecules illustrate the potential to be applicable to multiple product applications. This includes new functionalities that had previously not been identified
The technology provides direct substitutes for existing petrochemicals. Products recognized by the chemical industry provide a valuable interface with existing infrastructure and utility	The technology provides a novelty of applications for breakthrough developments that are not possible from previously recognized molecules in the chemical industry and a potential for direct substitutes for existing petrochemicals
The technology is applicable to high volume products. Conversion processes leading to high volume functional equivalents or utility within key industrial segments will have particular impact.	The technology may or may not be applicable to high volume products. The technology may require significant investment in synthetic biology to realize the potential for high volume products
A compound exhibits strong potential as a platform. Compounds that serve as starting materials for the production of derivatives offer important flexibility and breadth to the biorefinery	The molecule exhibits strong potential as a platform as well as for innovative product diversification. Novel higher-value molecules may serve as important starting materials for the production of derivatives that offer important added value, flexibilityand breadth to the biorefinery
Scale up of the product or a technology to pilot, demo, or full scale is underway. The impact of a biobased product and the technology for its production is greatly enhanced upon scale up	Scale up of the technology may not be the most immediate challenge as the initial markets may be lower volume yet higher value. The eventual impact of a bioprivileged molecule towards a diversity of applications is greatly enhanced by scale up, permitting further step-by-step market penetration towards commodity markets
The biobased compound is an existing commercial product, prepared at intermediate or commodity levels. Research leading to production improvements or new uses for existing biobased chemicals improves their utility	The bioproduct molecules are commonly not existing commercial products. Chemical diversification to existing commercial products can be a future larger volume opportunity
The compound may serve as a primary building block of the biorefinery. The petrochemical refinery is built on a small number of initial building blocks: olefins, BTX, methane, CO. Those compounds that are able to serve an analogous role in the biorefinery will be of high importance	The molecule may serve as a primary building block of the future biorefinery. Those bioprivileged molecules that offer the greatest potential to build upon a small number of advantaged intermediates will offer the greatest potential for commercialization in an analogous role relative to the petrochemical refinery
Commercial production of the compound from renewable carbon is well established. The potential utility of a given compound is improved if its manufacturing process is already recognized within the industry	Commercial production of the molecule from renewable carbon may or may not be well established. The potential utilization of any given molecule is dependent on its novelty and new added-value applications. Such molecules act as a bridgehead for longer term investment towards a diversity of molecules with larger market volumes

lactam,[26] caprolactone, unsaturated polyesters,[27] hexamethylene diamine[28] and terephthalic acid, has been demonstrated.[29]

The aspect of muconic acid that makes it a bioprivileged molecule is its ability to be efficiently converted to novel molecules such as 3-hexenedioic acid (HDA). The fully hydrogenated diacid, adipic acid, is produced in the petrochemical industry through the ketone-alcohol (KA) oil process, which converts a mixture of cyclohexanol and cyclohexanone, so HDA cannot be generated through a perturbation to the existing conversion approach. In contrast, HDA has been shown to be efficiently produced under appropriate reaction conditions from the partial hydrogenation of muconic acid.[30] HDA can be used in place of adipic acid as a monomer in the synthesis of nylons that now contain an unsaturated C–C bond in the polymer chain, which can be used for introducing novel polymer properties through further chemical modification.[31]

The generation and subsequent use of the HDA molecule is a clear demonstration of how diversity-oriented synthesis from bioprivileged molecules can lead to new chemical species that can potentially impart new functionality in bioproducts. HDA was not a widely known "target molecule" that was driving its retrosynthesis research, but instead is a novel chemical that became available when muconic acid was considered as an intermediate species. The primary focus of previous studies was converting muconic acid to drop-ion chemical product, so although HDA is one possible novel molecule that can be produced other possible novel bioproducts might be achievable from muconic acid if it is subjected to diversity-oriented synthesis.

5-Hydroxymethylfurfural

While muconic acid is an example in which biological catalysis can lead to bioprivileged molecules, these molecules can also result from the chemical conversion of biomass-derived molecules. The selective dehydration of fructose (or glucose *via* isomerization to fructose) can be used to produce HMF. The pro-

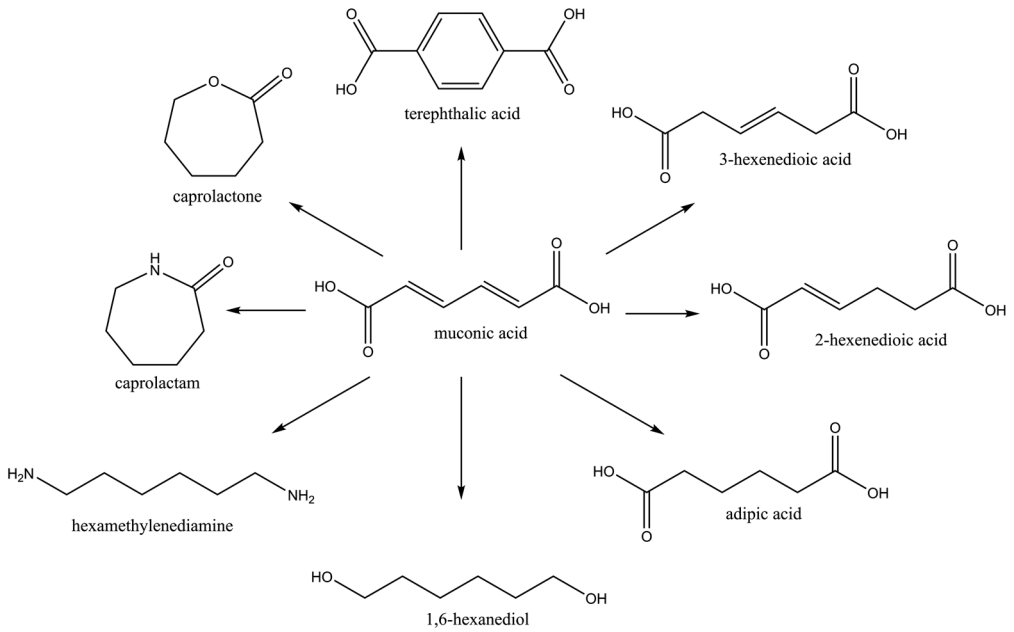

Fig. 1 Muconic acid diversification (adapted[31]).

duction of HMF has received a great deal of attention,[32] since HMF has been identified as a promising bio-based intermediate molecules that could be converted to a number of direct replacements for petrochemicals.[33] Importantly, HMF (as shown in Fig. 2) can also be converted into a number of furanic molecules with novel chemical properties. For example, 2,5-dimethylfuran, which in addition to having a high energy density and research octane number,[34] imparts improved antifriction and antiwear properties when used as a lubricant additive in gasoline[35] and 2,5-bis(hydroxymethyl) furan allows synthesis of a rigid polyurethane foam with improved flame hazard properties.[36]

Receiving particular attention is the oxidation product, 2,5-furandicarboxylic acid (FDCA). This molecule can be used as a replacement monomer for terephthalic acid in polycondensation polymerization with ethylene glycol thereby changing the polyester synthesis product from polyethylene terephthalate (PET) to polyethylene 2,5-furandicarboxylate (PEF). While the production of PEF has been touted as a completely biobased packaging material, the even more interesting characteristic of PEF relative to PET is its enhanced barrier properties when used in applications such as bottles.[37]

HMF represents a quite well-developed bioprivileged molecule as both its synthesis and subsequent conversion have

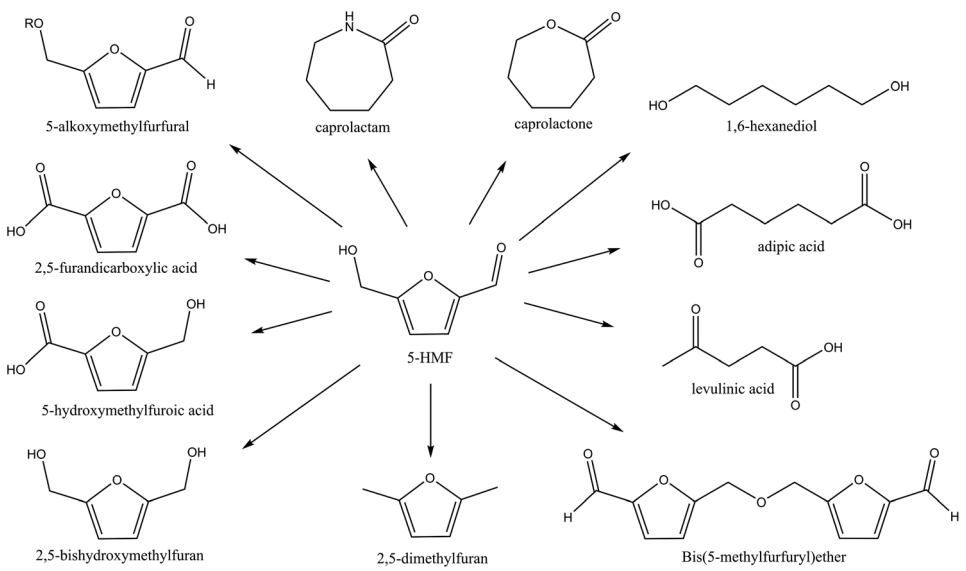

Fig. 2 HMF diversification (adapted[33]).

been the focus of numerous studies. Additionally, HMF has been the subject of a number of industrial announcements regarding its commercial development. The progression of a specific bioprivileged molecule is clearly demonstrated with HMF development. HMF was first shown to be generated through the dehydration of C_6 carbohydrates and then researchers effectively practiced diversity-oriented synthesis to determine both direct replacement and novel molecules that could be efficiently produced from it. It is important to note that some of the challenges associated with bioprivileged molecules are also demonstrated with HMF, which has been targeted for development for a number of decades with only limited progress towards commercialization.

Triacetic acid lactone

An example of a more recent emerging bioprivileged molecule is TAL. A secondary metabolite found in some plants, the microbial production of TAL has been demonstrated utilizing bioengineering efforts that led to introduction of a heterologous synthetic pathway designed from a type III polyketide synthase, 2-pyrone synthase (2-PS), first isolated from Gerbera hybrida.[38–40] TAL can be converted to range of molecules spanning commodity to specialty chemicals as shown in Fig. 3 [41–44] and can be used as an alternative synthetic intermediate to high value compounds such as styrenylpyrones, 4-amino-2-pyrones, and 4-hydroxy-2-pyridones.[45,46]

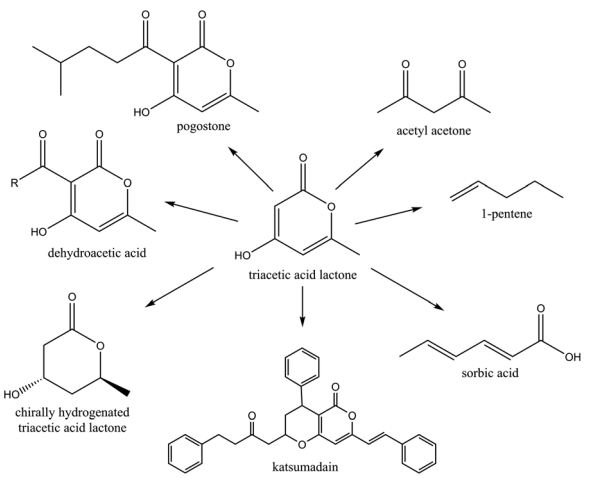

Fig. 3 Triacetic acid lactone diversification (adapted[41]).

TAL demonstrates the power of the bioprivileged molecule concept as it would typically not be considered a valuable target for engineered microbes due to its limited direct utility. However, as an intermediate subjected to diversity-oriented synthesis products as apparently disparate as sorbic acid (food preservative activity) and styrenylpyrones (anti-obesity activity) can be synthesized from the same chemical platform. Pursuing a merely retrosynthetic approach for either of these products would not likely coalesce on TAL as an important synthetic precursor.

A second valuable aspect of TAL as a bioprivileged molecule can be illustrated (Fig. 4) by considering pogostone (A) and dehydroacetic acid (B). These known molecules, which differ only by the carbon chain length of the keto-containing branch, have been demonstrated to both have antimicrobial activity. This commonality leads to the logical question about the performance of analogous species that contain something other than 2 or 6 carbons in the keto-branch. Using the same synthesis approach as with pogostone in which C–C coupling can be achieved with TAL and carboxylic acids, a family of molecules as shown in Fig. 4 were produced.[47] These compounds were then screened in a simple minimum inhibitory concentration (MIC) test for their antifungal activity against a range of organisms (Table 2). While pogostone, the known molecule, had better activity than many of the compounds there was one compound (species C) with similar antimicrobial activity and a second (species G) with broader activity. There has been no reported synthesis or efficacy testing of compound G, so it would never receive attention as a retrosynthesis target.

Path forward

Shifting our emphasis away from the retro-synthesis approach of known target molecules towards the forward-synthesis approach using diversity-oriented synthesis intrinsic in the bioprivileged molecule concept will require an improved understanding of the connectivity between bioproduct properties and candidate bioprivileged molecules. This connec-

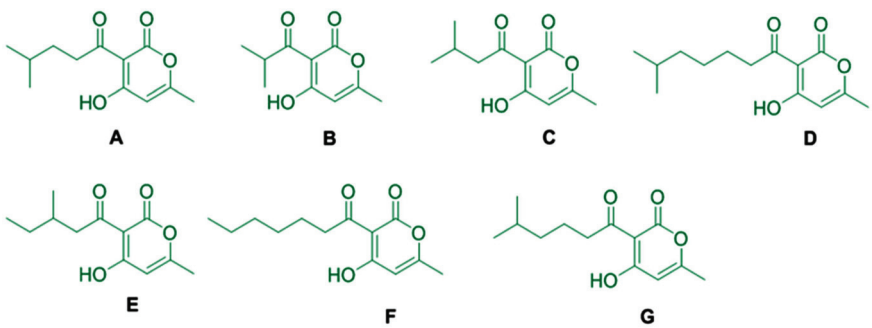

Fig. 4 Family of molecules derived from TAL and carboxylic acids.

Table 2 Minimum inhibitory concentration (MIC) test for antifungal activity with the Fig. 4 compounds (+ represents antifungal activity)

Organisms	A	B	C	D	E	F	G
Cryptococcus neoformans	+						+
Geotrichum capitatum	+		+				+
Candida kefyr	+					+	
Candida geochares	+						+
Candida krusei	+		+				+
Yarrowia lipolytica	+		+				+
Trichosporon mucoides			+	+			+
Prototheca wickehamii	+	+	+	+	+	+	+
Ogataea polymorpha	+		+				+
Candida intermedia	+		+				
Candida dubliniensis	+		+				
Cyberlindnera fabianii	+		+				+
Candida tropicalis	+		+				+
Rhodotorula mucilaginosa							+
Candida glabrata	+		+				
Candida parapsilosis							
Saccharomyces bayanus	+		+				+
Hanseniaspora guilliermondii	+		+				+
Cornebacterium glutamicum							+
Staphylococcus saprophyticus							+
Staphylococcus haemolyticus							+
Enterobacter cloacae							+
Chryseobacterium indologenes							+

tivity for the intermediates in the petrochemical industry was constrained by the limited number of available molecular species. The attractiveness of relatively unconstrained potential bioprivileged molecules is offset by the challenge in systematically identifying what are the most promising bioprivileged molecules. Of the three example molecules discussed above, the identification of muconic acid and TAL as potential bioprivileged molecules was serendipitous. When considered from a chemical conversion perspective, a common trait of each of the carbon atoms in the bioprivileged molecules is distinctly different chemical linkages, which contrasts with the somewhat similar chemical linkages available from the original carbohydrate feedstocks. This characteristic is particularly notable in TAL where each of the carbon atoms has significantly different bonding environments and as such have distinctly different reactivity patterns. Therefore, it can be envisioned that particularly promising chemical species are those having fewer and functionally differentiated groups (in terms of chemical reactivity) than are present in a carbohydrate molecule.[5,48] While this provides a notional direction for identifying bioprivileged molecules, there remains a significant challenge and opportunity to create a more systematic methodology.

One approach would be to choose metabolic products that organisms have already evolved to produce at high efficiency such as ethanol, lactic acid, fatty acids, *etc*. However, these "metabolic endpoints" typically have few functionally differentiated groups, thereby limiting their ability to be selectively diversified to novel bioproducts. An alternative to this would be first removing most of the molecular functionality and then putting it back in. However, this approach would be intrinsically flawed due to the high energetic penalty. Putatively more attractive than metabolic endpoints would be metabolic intermediates such as succinic acid (TCA cycle) or muconic acid (Shikimate pathway). Advances in synthetic and systems biology have improved bioengineering capability such that these intermediate species can be more easily considered.[49–53] This has the potential to significantly increase the number of prospective bioprivileged molecules. Given the remarkable diversity of biological-derived species and the state of bioengineering tool development, it is realistic to expand the metabolite candidates beyond these intermediates to almost any organic chemical that one could envision. With so many possibilities, the challenge remains how to choose the most promising bioprivileged molecules because bioengineering by forward-synthesis still requires the identification of target compounds.

A biological-derived intermediate is only valuable as a bioprivileged molecules if it can be efficiently converted to a range of useful chemical products. Therefore, understanding the target applications of the product molecules is a vital aspect of identifying bioprivileged molecules. If there was extensive structure–function understanding between chemical products and their applications, it might be possible to use performance criteria for the end use applications to predict desirable chemical products. Unfortunately, for many applications such as polymers, anti-oxidants, nutraceuticals, antimicrobials, *etc*. this structure–function understanding is relatively limited. As discussed above, FDCA is one example of this challenge as it was well known that plastic bottles with improved barrier resistance was a desirable property, but this knowledge did not lead to the prediction that replacing terephthalic acid with FDCA would lead to a polymer with better barrier properties. While detailed structure–function predictions for end-use applications of chemical species remains a work in progress, there is valuable knowledge that can provide some guidance to molecule selection. Again, considering the FDCA example where the FDCA-derived polymer could not be completely predicted, it could certainly be expected that FDCA could be substituted for terephthalic acid as they are diacids with aromatic carbons. Fortunately, sufficient application knowledge exists to at least suggest what could be interesting new chemical species for many applications.

Ultimately, the value of a new chemical species can only be validated by testing it in the end-use application. The types of testing required will vary by the application and as such the quantity of the novel chemical species that needs to be synthesized will also vary. For polymer applications, some initial polymer properties, melt temperature, polydispersity, *etc*., can be determined with quantities of less than a gram, but other properties such as gas barrier characteristics will require more than a kilogram of the polymer. For antimicrobial candidates, early-stage screening will require only milligram quantities of the chemical species. In any case, the development of bioprivileged molecules will require that sufficient quantities of the potential intermediate can be produced and subsequently converted to product molecules so that end use efficacy testing can be performed.

There is no direct current strategy for the identification and development of bioprivileged molecules. However, there are

emerging reports,[54–66] both computational and experimental, that look promising when effectively combined. For example:

1. Advanced synthetic and system biology tools,
2. Chemoinformatics for chemical transformations,
3. Advanced computational methods for determining structure–function relationships,
4. High-throughput screening and informatics technology for bioengineering, chemical conversions and performance/application testing.

There is no doubt that biomass-derived molecules hold great promise for generating products with enhanced properties. However, this promise can be most rapidly achieved if a more systematic approach was developed for finding and generating the chemical species that will provide improved properties. The bioprivileged molecule concept creates a paradigm with which to establish a rational structure for the search. The challenge is to integrate complimentary technological advances to achieve this vision.

Acknowledgements

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