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# Are Lignin-Derived Monomers and Polymers truly sustainable? An In-Depth Green Metrics Calculations Approach

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**ABSTRACT:** The usage of renewable resources has become a hot topic upon the rising global awareness against fossil feedstock consumption. Lignin, the 2<sup>nd</sup> most abundant natural polymer on Earth, is an aromatic biomacromolecule that holds a tremendous potential for the synthesis of biobased materials. The production of monomers and polymers from lignin has been investigated for years and keeps on-expanding, as proven by the flourishing literature. However, the sustainability of the synthesis reactions has not been systematically analyzed. Herein, green chemistry plays a vital role in this area and provides several tools to design eco-friendly production methods. This critical review first describes the preeminent approaches for the synthesis of biobased monomers and polymers from lignin-derived compounds. In the second part, the “greenness” aspects of the 175 key monomer synthesis methods and 32 polymerization methods are evaluated based on selected criteria, including waste generation, atom efficiency, energy efficiency, usage of safer solvents and biocatalytic methodology. The accessible green metrics, such as environmental factor (*E* factor) and atom economy are calculated to measure the greenness and to provide a quantitative base for strategic decisions. Furthermore, this study provides insights for the improvement opportunities and lights up the room for further developments. This review, aiming at scientists, industries and investors, strives to provide a critical outlook for the existing synthetic methods and motivates researchers to call for the integration of sustainability factors.

## 1. INTRODUCTION

### 1.1. Green and sustainable chemistry

Green chemistry was developed in the 1990s as an indispensable approach to eliminate or reduce pollution by improved organic synthesis design.<sup>1,2</sup> It seeks to provide environmentally-friendly methods for the manufacture and application of chemicals by using renewable raw materials, and avoiding hazardous substances.<sup>3-6</sup> Nevertheless, the

balance between environmental impact, social integrity and economic development is precluded in green chemistry. This led to the concept of sustainable development that essentially “*meets the needs of the present generation without compromising the ability of future generations to meet their own needs*”.<sup>7</sup> A fully sustainable process relies on three pillars: environmental, social and economic and it is the region where the three of them intersect. This can be represented with a Venn diagram of three overlapping sustainability circles each has its own metrics (Figure 1). S. K. Sikdar, AIChE J., 2003, 49 (8), 1928-1932.

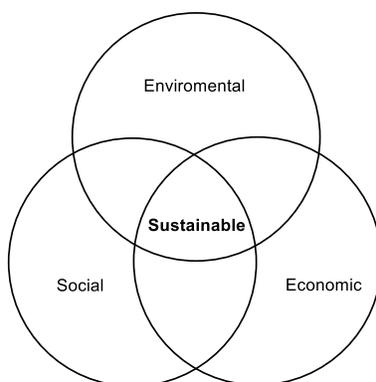


Figure 1. Sustainability Venn diagram

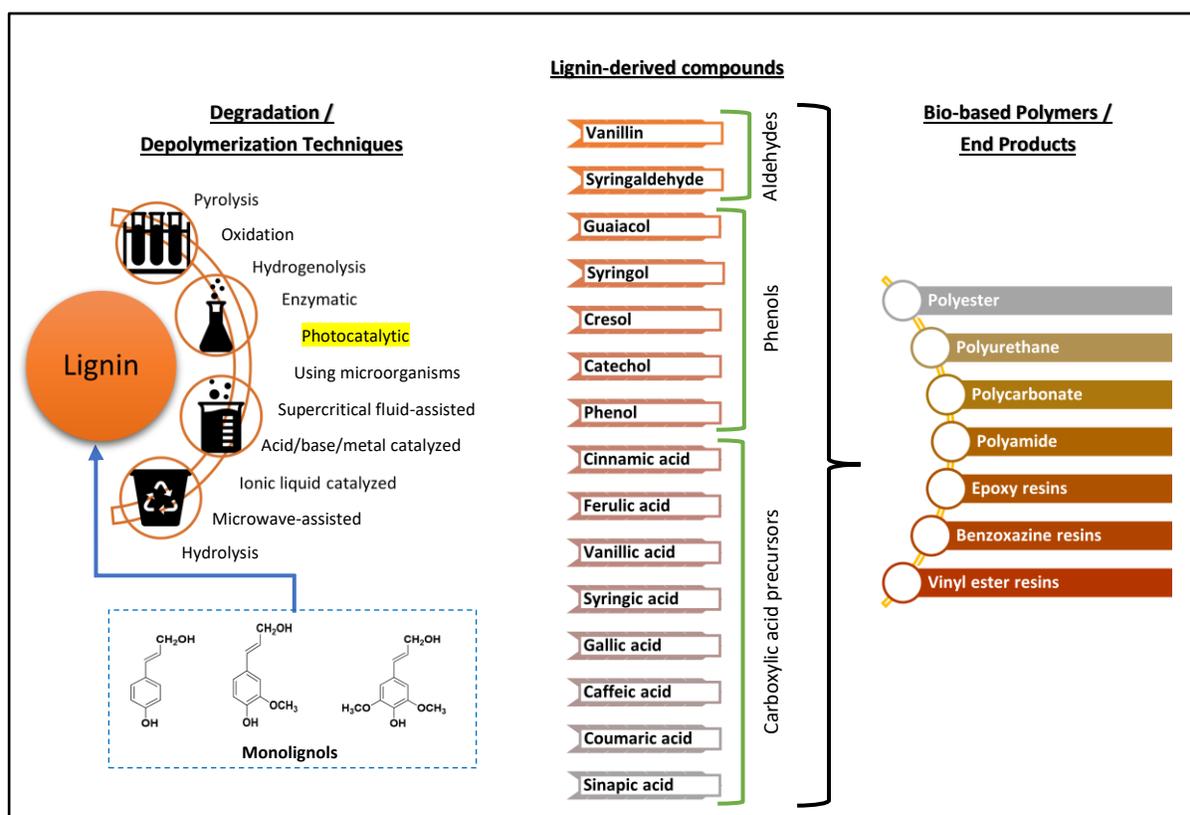
## 1.2. Renewable vs. fossil resources

Fossil resources (coal, oil, and natural gas) are violating the sustainable development due to our high consumption rate which leads to their irrevocable depletion within several hundred years.<sup>8</sup> Another major issue is the residues generated from the manufacturing process. Indeed, the rate of production of these residues is higher than the natural assimilation rate of the environment, which causes greenhouse gas emission (*e.g.* CO<sub>2</sub>) and originates climate change.<sup>9</sup> Therefore, non-renewable fossil resources should be replaced by renewable biomass – organic material derived from plants and animals – especially when dealing with products with colossal worldwide demand such as polymers.<sup>10</sup>

Polymers are inevitable, versatile, durable, and highly tunable materials that are massively employed in everyday life.<sup>11</sup> The predominant portion of all industrial polymers, such as polyethylene terephthalate (PET) and polystyrene, (PS), are mainly produced from fossil feedstock.<sup>12,13</sup> This leads to environmental damage due to greenhouse gas emission.<sup>14</sup> In the context of the 2<sup>nd</sup> generation biorefinery and circular bioeconomy, special considerations were directed to make polymers from waste (byproducts)<sup>15</sup> such as lignin. Markedly, this plant-based material,<sup>16,17,18</sup> is produced in a large quantity (5-36 x 10<sup>8</sup> tons annually) as a waste from paper and pulp industries.<sup>19</sup>

### 1.3. Lignin: composition and degradation techniques

Lignin is a promising source for developing renewable versions of fossil-derived Benzene Toluene Xylene (BTX) that are used in massive amounts to produce polymers such as PET and PS.<sup>20</sup> It is made up of three types of aromatic and crosslinked structural units (H, G and S), also known as monolignols, *p*-coumaryl alcohol, coniferyl alcohol and sinapyl alcohol.<sup>18,21</sup> Upon oxidative polymerization, these monolignols connect through different C-C and C-O-C linkages, which increase the complexity of the structure and make it more resistant to chemical actions. Lignin can be used in combination with other materials as a blend, grafted to different structures,<sup>22</sup> or broken down to smaller molecules *via* depolymerization or degradation techniques.<sup>23</sup> Different degradation methods are constantly explored to obtain smaller fragments of lignin. Some of the main techniques are pyrolysis,<sup>23</sup> J. Am. Chem. Soc. 2010, 132, 12554-12555, J. Am. Chem. Soc. 2016, 138, 8900-8911, J. Org. Chem. 2018, 83, 11019-11027, Sci. Adv. 2020; 6, 45, 1951, hydrogenolysis,<sup>23</sup> hydrolysis,<sup>24</sup> oxidative degradation,<sup>25</sup> Nature, 2014, 515, 249-252, Angew. Chem. Int. Ed. 2015, 54, 258-262, Green Chem., 2017, 19, 3135-3141, Green Chem., 2018, 20, 3318-3326 enzymatic degradation,<sup>26</sup> photocatalytic degradation, ACS Catal. 2019, 9, 8843-8851; Science Bulletin 2019,64,1658-1666; ACS Catal. 2020, 10, 800-805; CCS Chem. 2020, 2, 107-117 depolymerization using ionic liquids,<sup>27,28</sup> microwave,<sup>29</sup> and supercritical fluids<sup>30,31</sup> (Figure 2). Lignin-based guaiacol, syringol and catechol can be obtained by a neat pyrolysis method, also



**Figure 2.** Lignin degradation or depolymerization techniques and potential derived monomers and polymers from lignin

known as thermolysis, and most efficiently by hydrogenolysis, which is a pyrolysis method in the presence of hydrogen.<sup>23</sup> Oxidative degradation of lignin generates aromatic compounds, such as vanillin, syringaldehyde, *p*-hydroxybenzaldehyde, vanillic acid and syringic acid. Furthermore, ferulic acid, coumaric acid and sinapic acid can be obtained from the corresponding benzaldehydes, *i.e.* vanillin, *p*-hydroxybenzaldehyde, and syringaldehyde, respectively.<sup>32,33</sup> All the aforementioned phenolics can be used for the production of numerous polymers, *e.g.* epoxy resins, polyurethanes, polyesters, phenolic resins, to name a few.<sup>34,35</sup>

#### 1.4. Green metrics: *E* factor and atom economy

Renewable carbon should not be the only consideration while designing biobased alternative products. Indeed, it is an oversimplification to consider the greenness of a process only by the renewability of the starting materials.<sup>36–39</sup> Complementary factors are needed to evaluate the greenness and the efficiency of synthetic processes and to assign values to waste and toxic/hazardous materials.<sup>40,41</sup> Various green metrics were developed during the last two decades.<sup>40,41</sup> Among them the environmental factor (*E* factor)<sup>42,43</sup> and atom economy (AE)<sup>44</sup> are largely accepted as simple, accessible and useful measures of the greenness of a chemical reaction. *E* factor measures the amount of waste generated from a process and it is expressed as kg of waste/kg of product (Equation 1).<sup>42,43</sup> Waste is everything except the desired product and the ideal *E* factor of a process is 0. In contrast, a higher *E* factor implies a higher amount of waste generated and, in turn, a greater negative environmental impact. Typically, a major portion of the discharged waste corresponds to the large volume of solvent used in a chemical reaction. Besides, most of these solvents are non-renewable, toxic and can cause environmental damaging. This necessitates considering replacement strategies according to selection guides, *e.g.* that of Pfizer, to eliminate the usage of undesirable solvents. In an attempt to address the solvent issue, the tools and techniques for green solvent selection guides are markedly reviewed by Clark *et al.* REF: Tools and techniques for solvent selection: green solvent selection guides.

*E* factor differs from the AE in an important aspect that it considers the chemical yields and the experimental weights of all solvents and reagents used. On the other hand, AE is a theoretical number based on stoichiometric quantities of raw materials and assuming a 100% yield. It is commonly used for rapid evaluation to calculate how many atoms of the raw materials entered into a reactor ends up in the desired product.<sup>41–43</sup>

$$E \text{ factor} = \frac{\sum m(\text{raw materials}) + \sum m(\text{reagents}) + \sum m(\text{solvents}) - m(\text{desired product})}{m(\text{desired product})} \quad \text{Equation (1)}$$

In this review we strive to attain three main objectives. First, to measure – using *E* factor and AE – the greenness of lignin-derived monomers and polymers reported in a plethora of authoritative published studies. Second, to highlight from our findings how lignin can be more efficiently transformed through greener processes to provide genuine sustainable polymers. Finally, more importantly, we want to: *i*) convince researchers to consider the green aspects of the available synthetic methods, *ii*) redesign the current methods towards more efficient ones, and *iii*) include the sustainability factors along with the renewability in their future investigations.

## 2. METHODOLOGY

The main body of the paragraph starts with describing briefly the main strategies selected to produce polymers from lignin (Section 3). However, for the discussion and comparison of different reports, only lignin-derived monomer precursors are considered. The assessment of the synthetic procedures was carried out based on specific criteria of green chemistry: the generation of waste, the usage of safer solvents and chemicals, the atom efficient reactions, energy efficiency, and the usage of biocatalysts. The green metrics, such as AE, *E* factor, and the simple *E* factor (sEF, Equation 2), were calculated for all the monomer syntheses and some of the polymerization processes wherever required.

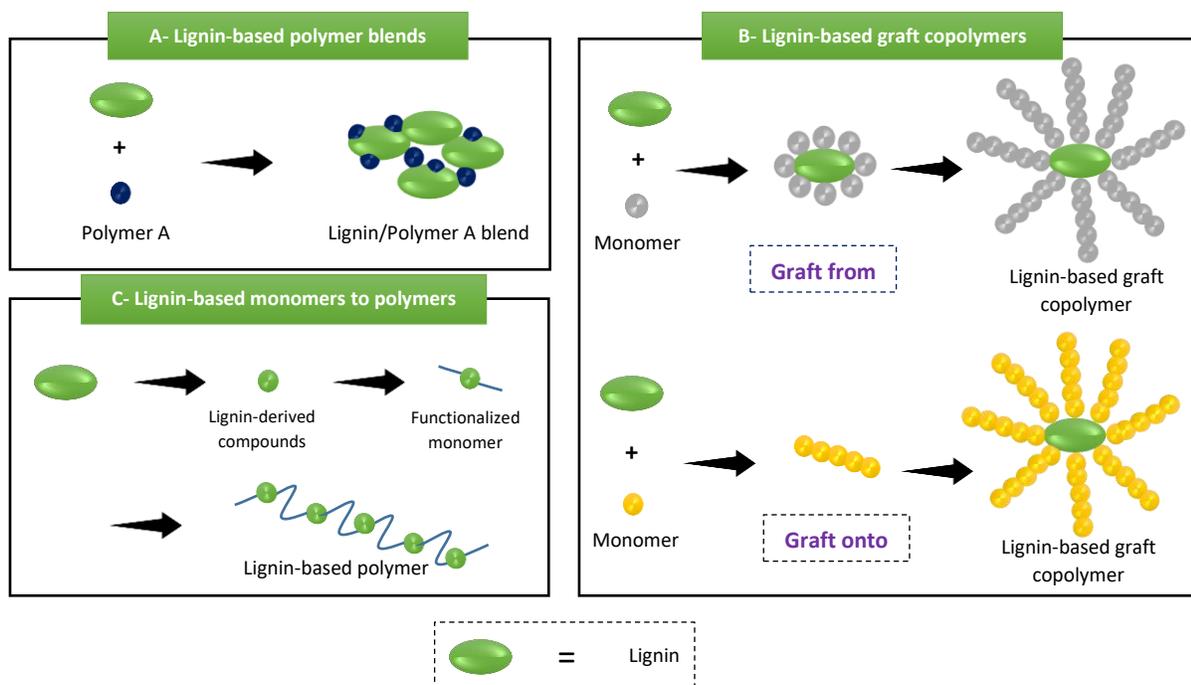
$$\text{sEF} = \frac{\sum m(\text{raw materials}) + \sum m(\text{reagents}) - m(\text{desired product})}{m(\text{desired product})} \quad \text{Equation (2)}$$

It is important to note that sEF excludes solvents while calculating the waste generated, and it is useful for the primary evaluation and comparison of different processes. On the contrary, the traditional *E* factor takes into consideration the waste analysis of all reagents including solvents used in a reaction mixture.<sup>43</sup> Nonetheless, it does not address the toxicity of the reagents and solvents, *e.g.* tetrahydrofuran (THF) vs. a green solvent 2-methyl tetrahydrofuran. Indeed, a more detailed analysis, such as life cycle assessment, is necessary to evaluate the full sustainability of a given chemical synthesis. Unfortunately, the data required for such studies are rarely available, which renders difficult the comparison between the different reports on this basis.

Most of the articles do not provide the amount of solvent used during the work-up process. Hence, herein, the *E* factor is exclusively calculated with reaction solvents to allow meaningful comparison. Nevertheless, the work-up step will have to be revisited at the manufacturing stage. Since cleaning contaminated water is tough, *E* factor calculation includes water wherever used in the chemical synthesis. Solvents contribution to the *E* factor was also calculated in percentage to have a better understanding of their usage during the reaction. The overall *E* factor of a multistep reaction is calculated including all raw materials except the generated intermediate, which is expected to be totally consumed during the next subsequent step. Many of the reported multi-step procedures isolate the intermediate and use it in different amount in the next step. Thus, to calculate the overall *E* factor, the amount of the intermediate for the next step is adjusted according to the same amount produced during the previous step. In addition, other raw materials: reagents and solvents, are also readjusted using the equivalent ratios reported in the original publications. Two tables presenting all data/calculations are available in the Supplementary Information. Table S1 shows the amounts of raw materials, reagents, solvents, and products with readjusted values along with the green metric calculations of the monomer syntheses and Table S2 allows to evaluate the polymerization processes.

## 3. STRATEGIES OF POLYMER SYNTHESIS FROM LIGNIN

The direct use of lignin as a polymer material is restricted due to its complex structure and its wide range of chemical and physical properties.<sup>32</sup> Nonetheless, lignin has active functional sites, *e.g.* hydroxyl and carbonyl groups, that can undergo structural modifications.<sup>16,32</sup> Different strategies are described to produce high-performance polymers from lignin (Figure 3).



**Figure 3.** Different approaches for lignin-based polymer synthesis

### 3.1. Direct use of Lignin

Several methods are industrialized to separate lignin from other woody components. Among them, kraft lignin, liginosulfonates, soda lignin, organosolv lignin are the most popular and investigated ones.<sup>32</sup> Using lignin directly without any modification comes with its pros and cons. Unmodified lignin is a low-cost material, ideal for fossil replacement. However, it varies in structure, chemical composition and properties and there is no standard method across all kinds of lignin. Constant experimentations have evolved to overcome these challenges and synthesize value-added chemicals and polymers from this material.<sup>32,45</sup> The direct use of lignin can be achieved by blending or grafting lignin with other materials (Figure 3A, B).

#### 3.1.1. Lignin in blends

Polymer blends can increase the suitability of lignin for specific applications. Fernandes *et al.* investigated the photo-degradation and thermal stability of polyvinyl alcohol (PVA) films blended with kraft lignin.<sup>46</sup> PVA is a water-soluble and biocompatible polymer often used for outdoor applications. By blending with lignin, the degradation of the PVA films was improved.<sup>46</sup> In other study, lignin was blended with polyvinylpyrrolidone (PVP), which is also a water-

soluble FDA (Food and Drug Administration)-approved polymer, to enhance its mechanical properties and performance as electrode materials in rechargeable batteries.<sup>47</sup> Lignin was successfully blended with polyhydroxybutyrate (PHB), a promising biodegradable polymer, to increase its thermal stability and reduce its cost.<sup>48,49</sup> It has also been extensively used as a filler to improve biodegradability of polyolefins.<sup>50</sup> Blending lignin can significantly improve the thermal, mechanical, and degradation properties of polymeric materials while reducing cost.

### 3.1.2. Lignin-based graft polymers

Another way to utilize lignin is *via* graft polymerization (Figure 3B). This is one of the most effective methods to functionalize and incorporate lignin into a polymeric structure. This leads to interesting materials combining features of both lignin and polymer matrix.<sup>51</sup> There are mainly two approaches to synthesize lignin-grafted copolymers: graft-from and graft-onto (Figure 3B). In the graft-from method, lignin hydroxyl groups are first modified and then the polymerization process starts. While, in the graft-onto method, polymer chains are formed first and then grafted onto the lignin. Lignin grafted with acrylic acid was explored for water treatment to improve biosorption capacity.<sup>52</sup> Since lignin has high UV absorption properties, UV-absorbent films were prepared from graft copolymers synthesized from lignin modified with acryloyl chloride and copolymerized with acrylate derivatives.<sup>53</sup> Improvement in thermal and mechanical properties of lignin grafted with polylactic acid (PLA) were studied by Kim and coworkers.<sup>54</sup> Lignin-based PLA materials *via* graft polymerization techniques showed new functions such as self-healing and conductivity.<sup>51</sup>

### 3.2. Lignin-derived monomers to polymers

The depolymerization techniques mentioned earlier have great potential to produce numerous monomer precursors, such as alcohols, aldehydes and acid, from lignin (Figure 2). Vanillin, an oxidation product of lignin, is one of the best investigated compounds.<sup>16</sup> Other lignin-derived compounds are syringaldehyde, guaiacol, syringol, phenol, cresol, catechol, vanillic acid, syringic acid, caffeic acid, cinnamic acid, coumaric acid, ferulic acid and sinapic acid.<sup>32,33</sup> These molecules can be used as building blocks for numerous polymers (Figure 3C), *e.g.* polyurethane, polyester, phenolic resins, polycarbonates, and epoxy resins.<sup>16,55,56,57</sup> Several reviews describe the synthesis of lignin-derived compounds and their use in the production of biobased polymers.<sup>20,58–63</sup> Nonetheless, to the best of our knowledge, no comparative study based on the green metric calculations has assessed the sustainability of the reactions.

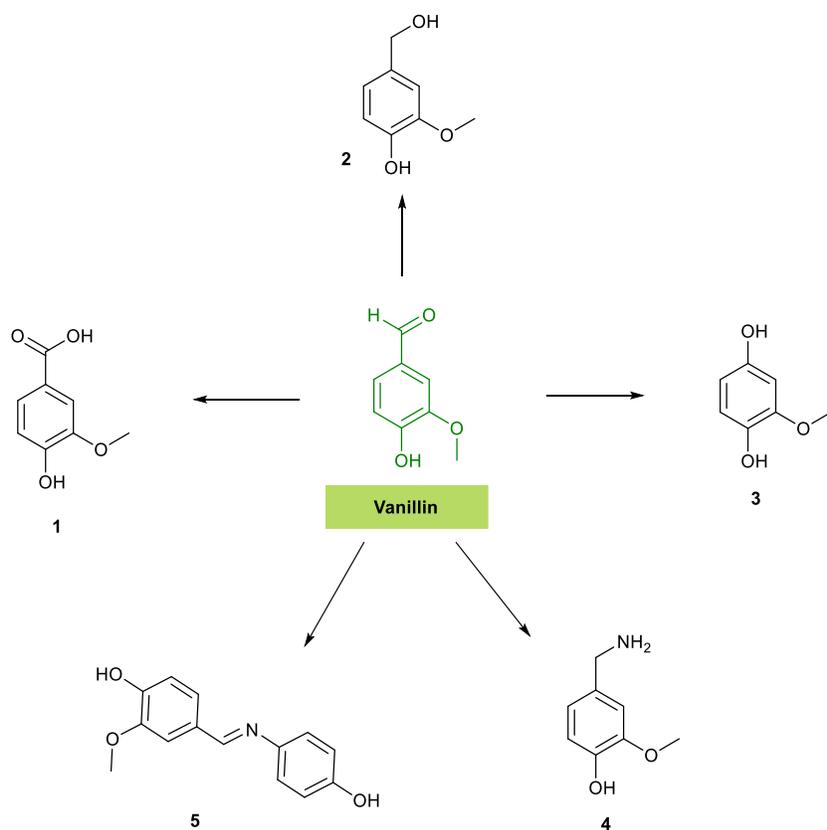
## 4. VANILLIN: AN AROMATIC CHEMICAL PRODUCED FROM LIGNIN ON A COMMERCIAL SCALE

The production cost of vanillin is lower than those of the other lignin-derived compounds. Accordingly, it is currently the only aromatic molecule that is extracted from lignin on a commercial scale. This molecule is of high interest due

to its multiple usages in a wide range of applications, such as flavoring agent (most demanded flavor after saffron) and polymer precursor.<sup>64</sup> The aromatic ring of vanillin has two important functionalities: a hydroxy and an aldehyde - so-called a phenolic aldehyde or *p*-hydroxybenzaldehyde. These inherent groups can be modified to lead to a large array of vanillin-derived monomers and polymers.<sup>65</sup>

#### 4.1. Vanillin: monomeric derivatives

A variety of versatile monomeric derivatives of vanillin are reported in the literature. Vanillic acid **1** and vanillyl alcohol **2** (Scheme 1) being the most known as they are commercially available. The direct synthesis of **1** from vanillin can be readily achieved in water through the Cannizzaro reaction.<sup>66</sup> The green metrics of this reaction are: 81% AE and *E* factor equal to 3.89 kg of waste/kg of product with only 8% of water contribution to the value (Table 1). When **2** is considered, we register an increase of *E* factor to 15.8 for the reduction of vanillin in methanol, where 90% of the waste corresponds to the solvent. A relatively large sEF of 3.48 was registered for **1** compared to the sEF (0.64) of **2** (Table 1).<sup>67</sup> Such remarkable difference in sEF is due to the large excess amount of KOH (7.5 equivalent (eq)) used to form the acid analogue, whereas, in the case of **2**, only 1.1 eq of KBH<sub>4</sub> was required to reduce the aldehyde moiety. Another interesting molecule is 2-methoxyhydroquinone **3** (Scheme 1). It can be prepared from vanillin through the Dakin reaction in 97% yield using sodium percarbonate that readily dissociates in solution into H<sub>2</sub>O<sub>2</sub>.<sup>68</sup> The reaction results in one carbon loss and a high *E* factor (38.0) with 94% of solvents (THF and water) contribution (Table 1). Nevertheless, the usage of sodium percarbonate rather than commercial H<sub>2</sub>O<sub>2</sub> solution, is considered more sustainable in terms of efficiency and easy handling. Vanillyl amine **4** (Scheme 1) was synthesized from vanillin by a three-step reaction involving two intermediates, vanillyl oxime and vanillyl ammonium chloride.<sup>69</sup> This widely enlarged the process *E* factor (161) as shown in Table 1. An imine-embedded bisphenol **5** (Scheme 1), with 93% AE and very low sEF (0.13) (Table 1), was prepared from the reaction between vanillin and aminophenol in water.<sup>70</sup> Although water was used as a solvent, we estimate the total waste *E* factor from this reaction (including the mass of the water) as 13.7. This confirms the necessity of using the least amount of reaction water, as cleaning polluted water is a difficult and tedious task to achieve.



**Scheme 1.** Valuable vanillin-derived monomers for versatile precursors

**Table 1.** Green metrics of the vanillin-derived monomer precursors represented in Scheme 1

Monomer	Steps	Yield (%)	AE (%)	sEF	E factor	Solvent Contribution (%)	Ref
1	1	76	81	3.48	3.89	8	66
2	1	84	75	0.64	15.8	90	67
3	1	97	92	1.41	38.0	94	68
4	3	57	60	4.20	161	97	69
5	1	95	93	0.13	13.7	92	70

#### 4.1.1. Glycidyl ether

Caillol *et al.* reported the synthesis of vanillin-based epoxide monomers **6**,<sup>68</sup> **8**,<sup>68</sup> **9**,<sup>68</sup> **10**<sup>71</sup> and **11**<sup>70</sup> with ~70% AE through the glycidylation of **1**, **2**, **3**, **4** and **5**, respectively (Scheme 2). A comprehensive explanation of the glycidylation mechanism was reported by Caillol *et al.* including the reaction schemes.<sup>71</sup> The same procedure was followed by the authors to prepare the five aforementioned epoxide monomers: *i*) epichlorohydrin, derived from

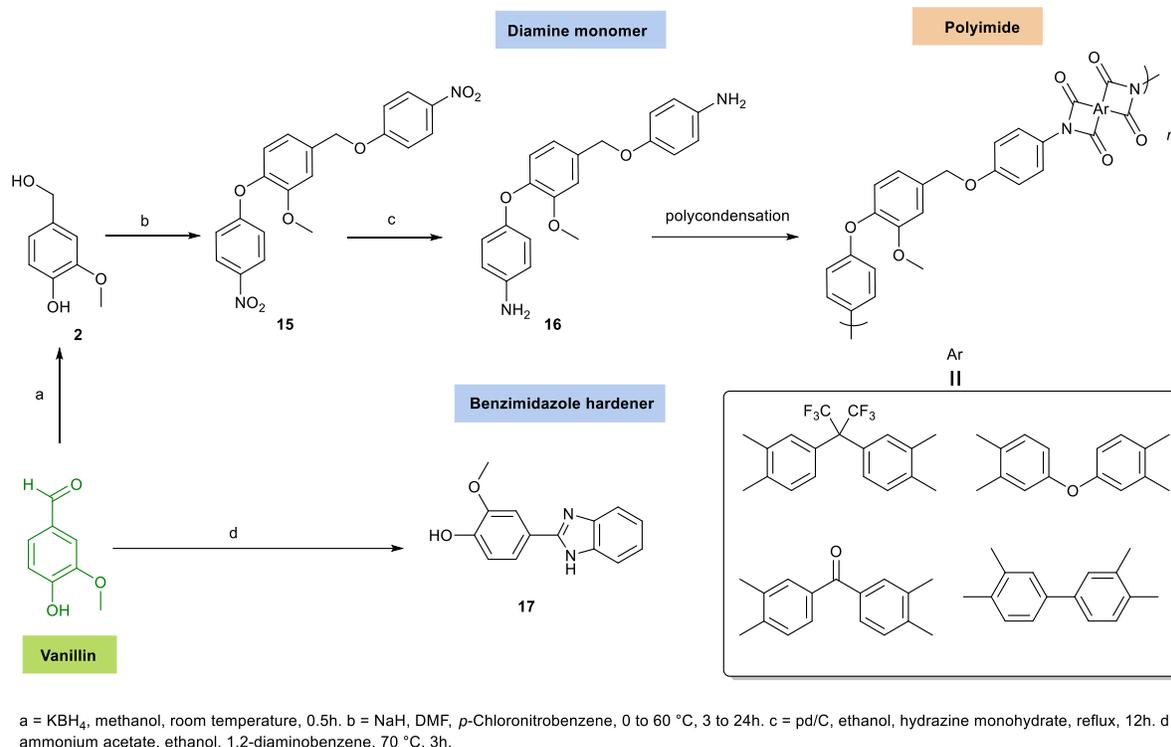
the Epicerol® process, as a reactive solvent, *ii*) triethylbenzylammonium chloride (TEBAC) as a phase transfer catalyst, and *iii*) aqueous solution of NaOH to close the intermediate formed from the ring-opening of the epoxy. We observe a remarkable variation in the amount of waste produced depending on the number of epichlorohydrin equivalents. The recorded sEF are 4.46, 6.18, 4.79, 10.7, 6.95 for **6**, **8**, **9**, **10** and **11**, respectively (Table S1, entries 2, 7, 10, 15 and 17). When 30 eq of epichlorohydrin was used instead of 10 eq, sEF increases from 4.46 to 10.7 (Table S1, entries 2 vs. entry 15). This raises the possibility of using the least amount of epichlorohydrin for such glycidylation reactions to occur. We studied the effect of the reaction yield in the case of glycidyl ether **7**. An increase in sEF from 4.46 to 10.0 is recorded for reaction yields of 85% and 55%, respectively (Table S1, entry 2 vs. 4). This highlights the importance of recovering the unreacted monomers at the end of the reaction, if possible by using solvent-free techniques such as sublimation. Such approach decreases both the negative impact on the environment and the cost of reaction. The epoxy resins and composites prepared from monomers **6-11** (Scheme 2) show interesting performance in comparison to the fossil-based bisphenol A (BPA).<sup>71</sup> **6-11** were also used for the synthesis of other monomers such as dual-functional **12**,<sup>72</sup> dihydroxyaminopropane of vanillyl alcohol **13**<sup>73</sup> and cyclic carbonate **14**<sup>71</sup> (Scheme 2). Although **12**, **13**, and **14** were obtained in good yields, their process sEF is relatively high, especially for the preparation of **12** (15.3) (Table S1, entries 3-5).



#### 4.1.2. Amine and curing agent

An asymmetric diamine **16** was recently synthesized by Qi *et al.* through a three-step reaction.<sup>67</sup> Firstly **2** was obtained from the reduction of vanillin as described previously, followed by the reaction with *p*-chloronitrobenzene to yield molecule **15**. Monomer **16** was then prepared from **15** using hydrazine monohydrate as a source of hydrogen. The process *E* factor of this multistep synthesis is 98.8 (Table S1, entries 18-20) for the following three reasons. **2** was prepared with waste production of 15.8 (step *E* factor) (Table S1, entry 18). This can be avoided as **2** is commercially available. The second step was conducted in 108.8 eq of dimethylformamide (DMF) which leads to a step *E* factor of 24.5 with 94% solvent contribution (Table S1, entry 19). Lastly, the reduction of **15** to **16** using 41.2 eq of hydrazine monohydrate, thus leading to 58.0 kg of waste/ kg of product, with 86% of the solvent (ethanol) contribution (Table S1, entry 20). The step *E* factors of the last two steps can be diminished if the reaction conditions are optimized to use the minimal amounts of DMF and hydrazine monohydrate. Monomer **16** was polymerized by polycondensation with four commercial dianhydrides to yield high-performance polyimide with good thermal properties (Scheme 3). The glass transition ( $T_g$ ) and degradation temperatures for 5% mass loss ( $T_{d5\%}$ ) are in the range of 241-262 °C and 448-478 °C, respectively.<sup>67</sup>

Recently, **17** a benzimidazole-containing hardener, was synthesized by Zhao *et al.* from vanillin in only 6.9 eq of ethanol, using 1 eq of diaminobenzene and 0.05 eq of ammonium acetate.<sup>74</sup> This leads to low sEF and *E* factor of 0.37 and 2.03, respectively (Table S1, entry 20). The solvent contribution is 55% solvent. **17** was used to cure bisepoxide renewable molecules derived from eugenol and commercial epoxide diglycidyl ether of bisphenol F. The resulting epoxy thermosets showed good thermal stability with  $T_g = 77$ -140 °C and  $T_{d5\%}$  up to 421 °C.<sup>74</sup>



**Scheme 3.** The synthesis of asymmetric diamine and benzimidazole-containing curing agents from vanillin (detailed reaction conditions are available in Table S1, entry 18-21)

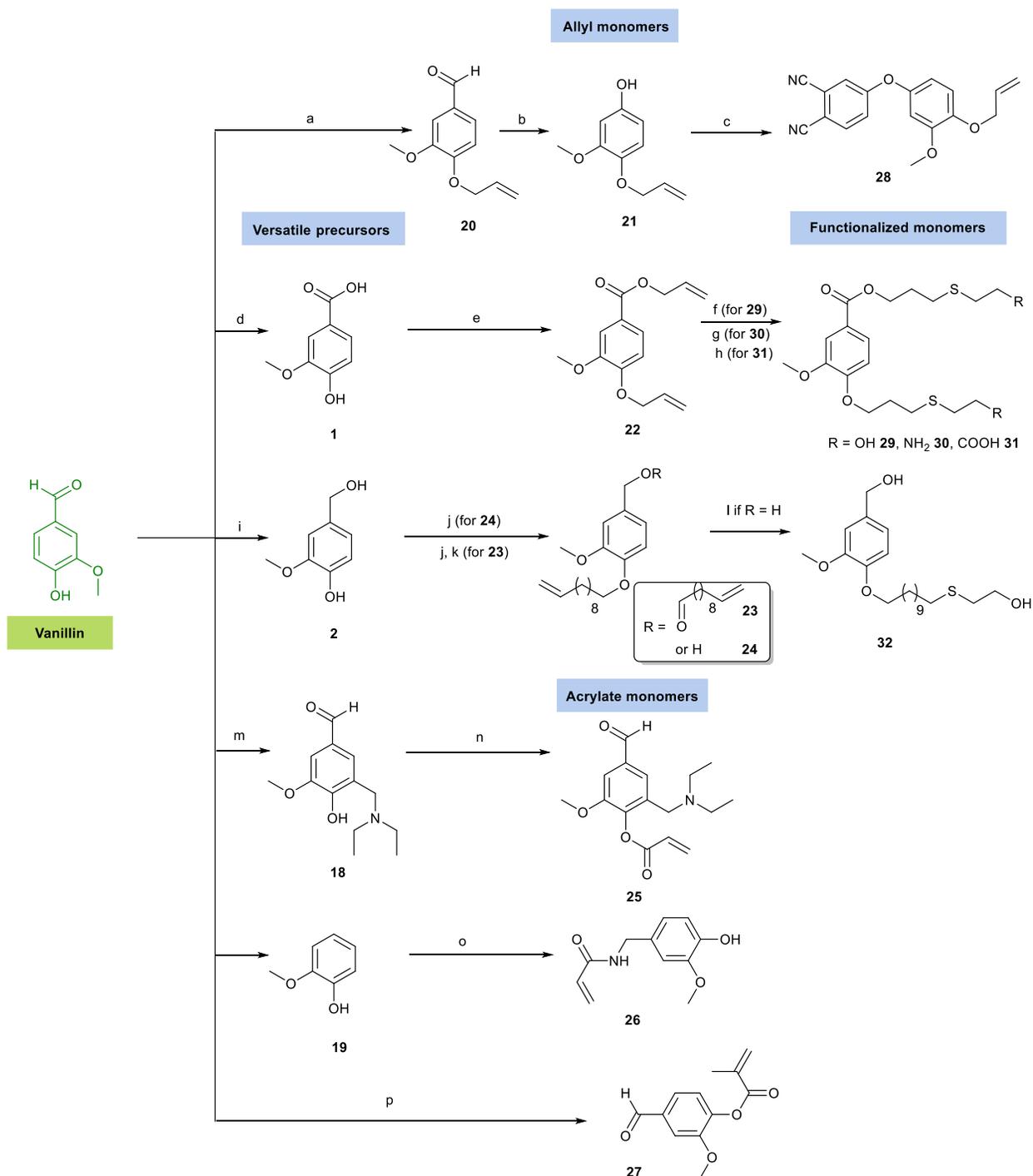
#### 4.1.3. Allyl and acrylate compounds

Recently, Zhao, Qiu *et al.* reported a successful synthesis of a stable dual-functional phthalonitrile allylated monomer (**28**) (Scheme 4).<sup>75</sup> This three-step synthetic process started with the allyloxy functionalization of vanillin using allyl bromide, followed by one carbon loss to yield **21**. The phthalonitrile functionalization of **21** using CaO@AC-catalyzed nucleophilic substitution (Scheme 4), produced **28** in good yield (67%) and high purity.<sup>75</sup> Apart from the second step, the step *sEF* and step *E* factor are relatively low for the allyl and phthalonitrile functionalization steps, 1.42 and 4.33 (Table S1, entry 22), 1.06 and 3.84 (Table S1, entry 24), respectively. The authors used low amounts of solvents for the whole process and the process *E* factor is 15.4 with 67% contribution to the value (Table S1, entries 22-23). They also attempted different routes to access **28**, where phthalonitrile was introduced first followed by the allylation. This however led to an unstable compound and complicated purification, preventing the scalable synthesis and increasing the waste.<sup>75</sup> Monomer **28** and its propargyl analogue were thermally cured through self-catalytic thermal process at different temperatures in the range 170-375 °C. A comprehensive mechanism of curing process is reported in the original publication. In the case of **28**, the cured polymer exhibited the lowest melting point ( $T_m = 94.5$  °C) compared to the propargyl analogue ( $T_m = 130.4$  °C) and  $T_g$  higher than 500 °C and  $T_{d5\%}$  up to 482 °C.<sup>75</sup> Interestingly, the authors tried to green up the curing process by avoiding the usage of catalysts thus leading to a 0 process *E* factor.

Monomers **22**, **23** and **24** - allylated analogues of **1** and **2** - were also synthesized by Caillol *et al.* (Scheme 4).<sup>71</sup> The *E* factor depends on the allylation procedure. The synthesis of **23** was performed in solvent-free conditions using catalytic amount of triazabicyclodecene (0.05 eq with respect to **2**) and only 0.9 eq of methyl 10-undecenoate with 94% AE. This leads to the lowest step *E* factor (0.14) with 0% solvent contribution to the waste. On the other hand, the *E* factor for the formation of **22** and **24** are 10.2 and 2.43 with solvent contribution of 57% and 37%, respectively (Table S1, entries 25 and 30). Such difference in *E* factor is due to the larger amount of solvents used in the case of **22** (34 eq of ethanol vs. 9.6 eq of acetonitrile for **24**) and also to the excessive quantities of reagents (*e.g.* 4 eq of allyl bromide vs. 1.3 eq of 11-bromo-1-undecene) (Table S1, entries 25 and 30). The same authors reported the alcohol, amine and acid functionalization of the allyl moieties of **22**, **23** and **24** in addition to other analogues using thiol-ene click chemistry with almost 100% AE. Some of the functionalized products are illustrated in Scheme 4 (**29-32**). Products **29** and **31** were prepared in neat conditions, the *E* factor is 0.85 (Table S1, entry 26). When methanol (product **30**) or ethanol (product **32**) were used, the *E* factor increased to 2.33 (Table S1, entry 27) and 1.59 (Table S1, entry 32), respectively. **22-24** and **29-32** are useful building blocks for biobased polymers<sup>65</sup> prepared by acrylic diene metathesis polymerization (ADMET) and polycondensation.<sup>76</sup>

Three acrylate monomers **25**, **26**, and **27** were prepared from product **18**,<sup>77</sup> guaiacol **19**<sup>78</sup> and vanillin,<sup>79</sup> respectively. The different reagents and conditions used to access **25-27** are recorded in Table S1. We have noticed a large difference of the *E* factor of the acrylation procedures, 22.3, 17.7, and 0.41 for the synthesis of **25**, **26**, and **27**, respectively (Table S1, entries 34-36). The low *E* factor (0.41) in the case of **27** is due to two reasons: *i*) a catalytic amount of 4-dimethylaminopyridine (0.02 eq) was used, and *ii*) the reaction was performed in solvent-free conditions, thus zero solvent contribution to the waste. This was not the case for monomer **25** where 90% solvent contribution to *E* factor (22.3) is estimated. Furthermore, in the latter, 54 eq of dichloromethane (DCM) was employed as the solvent, which is known for its toxicity and bad effect on the health and environment. In addition, a non-renewable acryloyl chloride was used for the substitution reaction. Indeed, methacrylic anhydride can be used as potential renewable acrylating reagent (as in the case of **27**). Different types of polymers,<sup>80-88</sup> *e.g.* thermostable polymers ( $T_g = 155$  °C and  $T_{d50\%} = 405$  °C) were prepared from **27** through free-radical polymerization. Interestingly, with 100% AE and *E* factor almost equal to 0.<sup>85</sup> The acrylate guaiacol-based monomer **26** was also polymerized *via* free radical polymerization with azobisisobutyronitrile (AIBN) as initiator.<sup>78</sup> Different parameters were studied including the influence of reaction time (1-24h) and AIBN concentration (0.25-4 wt%) to afford polymers having  $T_g$  around 101 °C. However, no study on the effect of monomer concentration was reported.<sup>78</sup> Indeed, the monomer concentration can greatly increase the amount of waste generated from a polymerization reaction. <https://www.sciencedirect.com/science/article/abs/pii/S0014305720316943>, <https://pubs.rsc.org/-/content/articlelanding/2020/py/d0py01471k#!divAbstract>. We calculated the *E* factor of two polymerization reactions performed using 0.25 wt% and 4 wt% of AIBN. *E* factors are respectively 99.6 and 41.1 (Table S2, entries 1 and 2). This difference is due to monomer conversion, which is nearly complete when 4 wt% of AIBN was loaded whereas in the presence of 0.25 wt% of AIBN only 10% of the monomers was polymerized. In both cases, the *E* factor

is very high due to the diluted conditions in toluene and DMF (90% of the waste corresponds to the solvents). The sEF are 9.0 for 1 wt% AIBN (Table S2, entry 1) and 0.1 for 4 wt% AIBN (Table S2, entry 2).



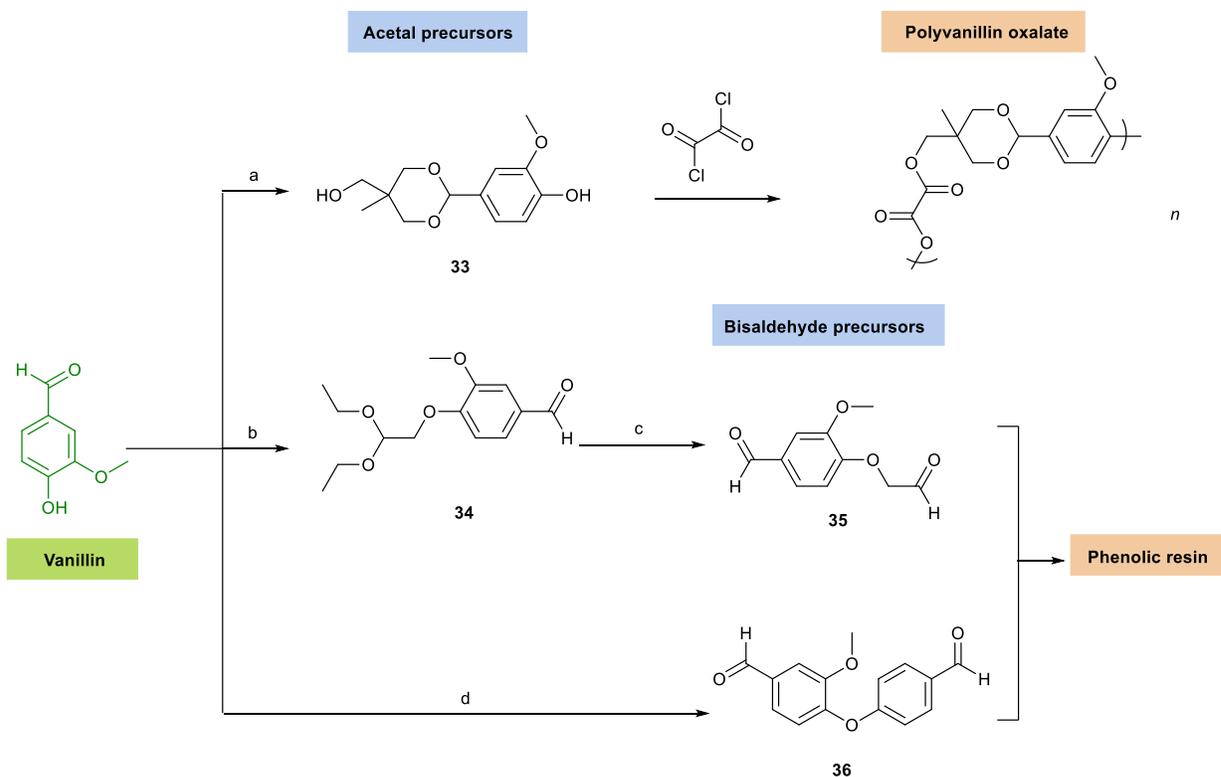
a =  $K_2CO_3$ , ethanol, allyl bromide, reflux, 6h. b = boric acid, THF, sulfuric acid,  $H_2O_2$ ,  $-10\text{ }^\circ\text{C}$ . c = 4-nitrophthalonitrile,  $CaO@AC$ , acetonitrile,  $80\text{ }^\circ\text{C}$ , 6h. d = KOH, water. e = ethanol,  $K_2CO_3$ , allyl bromide. f = mercapto-ethanol. g = allyl vanillic acid, cysteamine, methanol. h = 3-mercaptopropionic acid. i =  $KBH_4$ , methanol, room temperature, 0.5h. j = 11-bromo-1-undecene, acetonitrile, tetrabutylammonium iodide,  $K_2CO_3$ , reflux, 16h. k = methyl 10-undecenoate, Triazabicyclodecene,  $80\text{ }^\circ\text{C}$ . l = 2-mercapto-ethanol, ethanol, reflux, 3h. m = formaldehyde,  $Et_2NH$ , ethanol, reflux, 3h. n =  $CH_2Cl_2$ , NaOH, acryloyl chloride,  $5\text{ }^\circ\text{C}$  to room temperature, 6h. o = N-hydroxymethylacrylamide, ethanol, sulfuric acid,  $35\text{ }^\circ\text{C}$ , 96h. p = 4-(dimethylamino)pyridine, methacrylic anhydride,  $50\text{ }^\circ\text{C}$ , 24h.

**Scheme 4.** The synthesis of allylated monomers from vanillin (detailed reaction conditions are available in Table S1, entry 22-36)

#### 4.1.4. Acetal and aldehyde monomers precursors

A vanillin-derived acetal (**33**) was synthesized by Lee *et al.* (Scheme 5) with 93% AE using stoichiometric equivalents of vanillin and 2-(hydroxymethyl)-2-methylpropane-1,3-diol in THF in the presence of a catalytic amount of *p*-toluenesulfonic acid (0.004 eq).<sup>89</sup> The sEF of this reaction is 0.34 (Table S1, entry 37). We were not able to calculate the *E* factor of the process as the volume of THF is not provided in the original work. Nevertheless, if we assume 10 eq of the solvent, the *E* factor is 3.88 (Table S1, entry 37). Polyvanillin oxalate having H<sub>2</sub>O<sub>2</sub>-responsive peroxalate ester and acid-acetal linkages was synthesized by the polycondensation of **33** and oxalyl chloride in DCM in the presence of pyridine. The data related to the polymerization condition, such as monomer concentration and conversion, are not provided,<sup>89</sup> thus, we were not able to calculate the sEF and *E* factor. However, in general considerations, polycondensation methods are accompanied with some drawbacks including the loss of small molecules as by-products (*e.g.* acid) upon each condensation reaction. This generally increases the amount of waste generated compared to catalytic polymerization methods.<sup>90</sup>

In an attempt to prepare biobased and formaldehyde-free phenolic resin, vanillin-based aliphatic aldehyde precursor **35** was synthesized by Caillol *et al.* through a two-step reaction (Scheme 5).<sup>91</sup> The first step of the grafting reaction of the aliphatic aldehyde is the Williamson etherification of vanillin with a halogenated diethyl ketal. This was followed by the deprotection of the ketal moiety to yield **35**.<sup>91</sup> The overall *E* factor of these two steps is 51.5 with 88% solvent contribution (Table S1, entries 38 and 39). The step *E* factor of the functionalization step is 5.98 (Table S1, entry 38). A much larger *E* factor (51.5) was registered for the deprotection step due to the larger amounts of solvents used (Table S1, entry 39). A difunctional dialdehyde precursor **36** was also synthesized from vanillin.<sup>92</sup> A one-step reaction with 4-fluorobenzaldehyde was employed. Thus, leading to much better *E* factor (6.02) compared to the aforementioned two-step synthesis of **35** (Table S1, entry 40) (Scheme 5). The solvent (DMF) contribution to the previous value is 60%, sEF is 1.78 and AE is 93% (Table S1, entry 40). This highlights the necessity of avoiding the deprotection steps while designing a chemical reaction (whenever it is possible). **35** and **36** were used to prepare highly thermally stable biobased phenolic resins, which have the potential to substitute the commercial phenolic resins obtained from phenol and formaldehyde, a highly toxic and volatile reagent.<sup>91,92</sup>



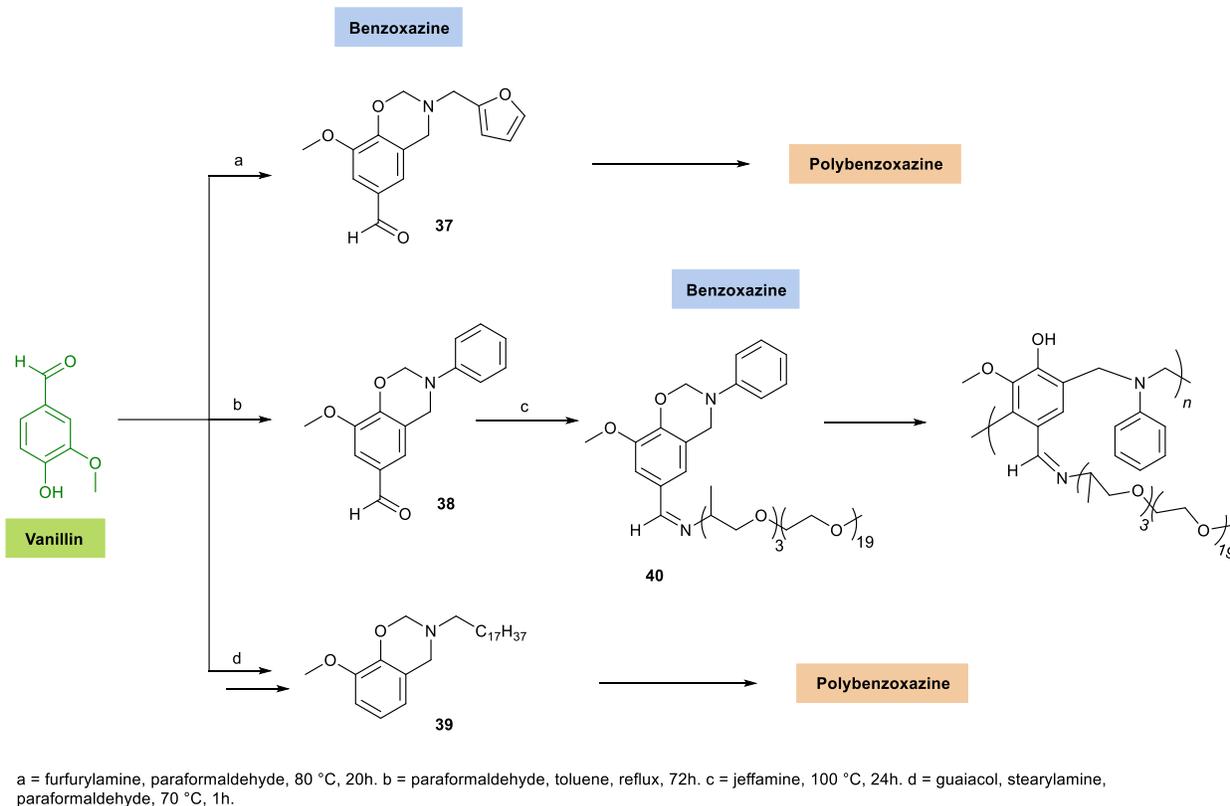
a = 2-(hydroxymethyl)-2-methylpropane-1,3-diol, THF, *p*-toluenesulfonic acid, 85 °C, overnight. b = vanillin, 2-bromo-1,1-diethoxyethane,  $K_2CO_3$ , acetone, reflux. c = THF, HCl, water, 60 °C, 5h. d = 4-fluorobenzaldehyde,  $K_2CO_3$ , dimethylsulfoxide, 110 °C.

**Scheme 5.** Acetal/aldehyde monomers synthesized from vanillin (detailed reaction conditions are available in Table S1, entry 37-40)

#### 4.1.5. Benzoxazine

Benzoxazine-based polymers are considered as a class of high-performance material due to their excellent chemical and mechanical properties including high  $T_d$  and  $T_g$ , in addition to flame retardance effect and many other properties.<sup>93</sup> Biobased benzoxazine monomers such as **37** and **39** were prepared from vanillin<sup>94</sup> and guaiacol,<sup>95</sup> respectively (Scheme 6). Interestingly, **37** and **39** are fully biobased benzoxazine that use biobased amine in their syntheses instead of the petroleum-based ones.<sup>94,95</sup> Notably, **37** and **39** were synthesized by Varma *et al.* and Endo *et al.*, respectively, under solvent-free conditions with almost 100% AE and *E* factor as less as 0.13 and 0.33, respectively (Table S1, entries 41 and 44). The *E* factor of the (co-)polymers of these monomers is equal to zero where only heat was required to open the benzoxazine ring. We will not discuss the interesting properties of the resulting polybenzoxazine as they are already reported elsewhere.<sup>65,93</sup>

Benzoxazine aniline **38** was synthesized by Ishida *et al.* following similar conditions to those of **37** and **39**, however using toluene as a solvent which led to an increase of the waste produced from the process (Table S1, entry 42).<sup>96</sup> **38** was used to form **40**,<sup>96</sup> a benzoxazine jeffamine monomer, without using any solvent and with 99% AE (Table S1, entry 43). The process sEF and *E* factor of **40** are 0.53 and 1.71, respectively (Table S1, entries 42-44).



**Scheme 6.** Synthesis of biobased benzoxazine monomers from vanillin (detailed reaction conditions are available in Table S1, entry 41-44)

## 4.2. Vanillin: dimeric derivatives

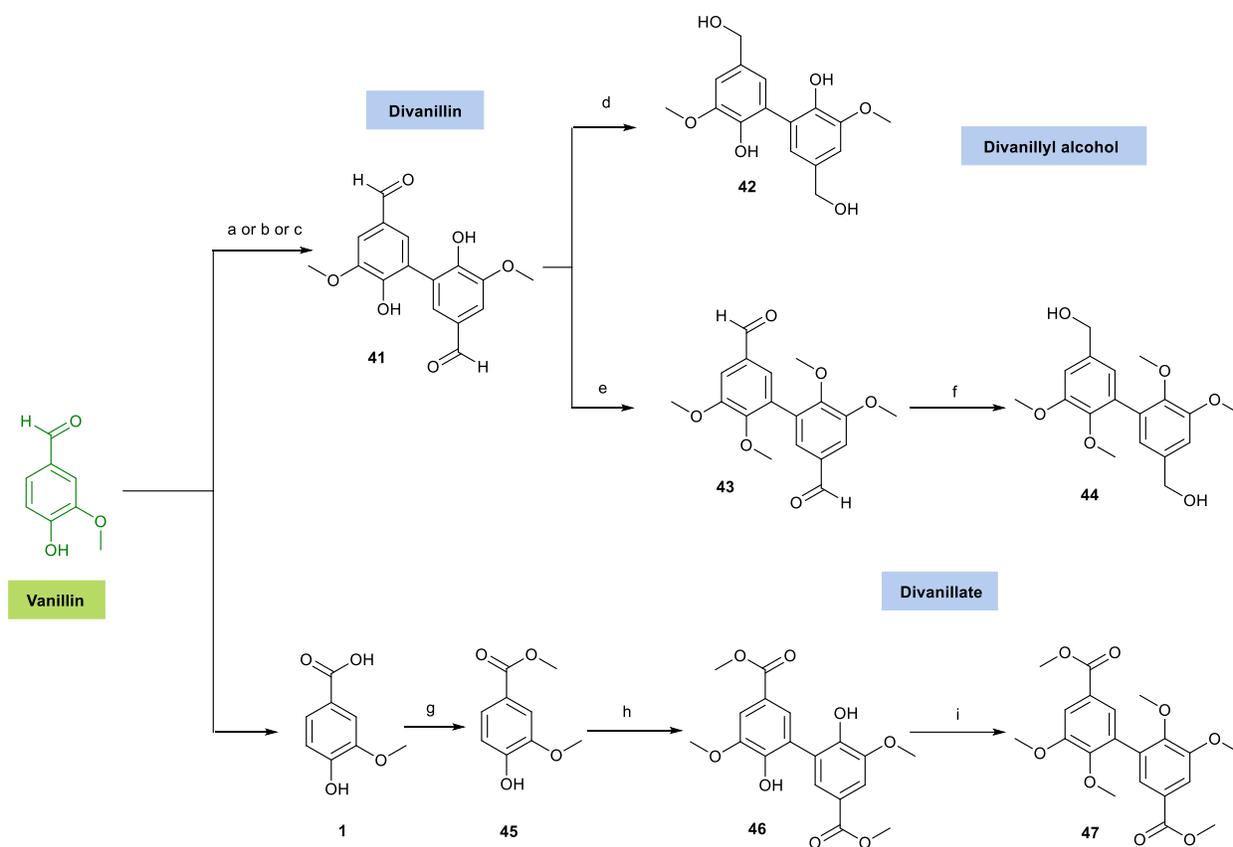
### 4.2.1. Aromatic-aromatic coupling

Divanillin **41** is a molecule of high interest that can be used to produce highly valuable monomers and polymers (Scheme 7). It can be synthesized by chemical or enzymatic oxidative coupling of two molecules of vanillin.<sup>97</sup> The chemical oxidative coupling usually requires the stoichiometric use of a metal-based complex, such as iron(III) chloride ( $\text{FeCl}_3$ ), that oxidizes the phenol group into the aryloxy radical.<sup>98-101</sup> The sEF of the dimerization reaction of vanillin using 1.1 eq of  $\text{FeCl}_3$  is relatively high (*i.e.* 4.22). If the solvent water is included in the calculation, the *E* factor is then equal to 62.4 (Table S1, entry 46). Indeed, a major drawback of vanillin is its very low solubility in water; 100 g of water is required to solubilize 1 g of vanillin. especially when it is contaminated with high amounts of metal residues. In an attempt to minimize the amount of metal residues in the contaminated water, Nègre-Salvayre *et al.* showed that a catalytic amount, as less as 2 mol%, of iron sulfate is enough to make the reaction.<sup>102</sup>

Horseradish peroxidase (HRP) was reported as an efficient catalytic enzyme to perform the enzymatic oxidative coupling of vanillin in the presence of hydrogen peroxide.<sup>103,104</sup> The coupling mechanism is already reported elsewhere.<sup>97</sup> The sEF of this process is 2.62 (Table S1, entry 45) which is less than that recorded for the

chemical method (4.22) (Table S1, entry 46). However, if the water is considered in the calculation<sup>104</sup> the *E* factor of the enzymatic catalyzed process is 108 (97% solvent contribution) which is higher than the *E* factor of the iron-catalyzed coupling (62.4 with 92% solvent contribution) (Table S1, entries 45 and 46). Nevertheless, an enzymatic method is characterized with some general interesting green aspects. A low enzyme loading is required to access the dimer product at room temperature under oxygen or air. The catalyst can be easily separated from the reaction mixture and reused with no or slight loss of activity. If a co-solvent is needed with water, acetone can be used which is known for its low toxicity. Furthermore, the product extraction and purification are easy and lead usually to high yield.

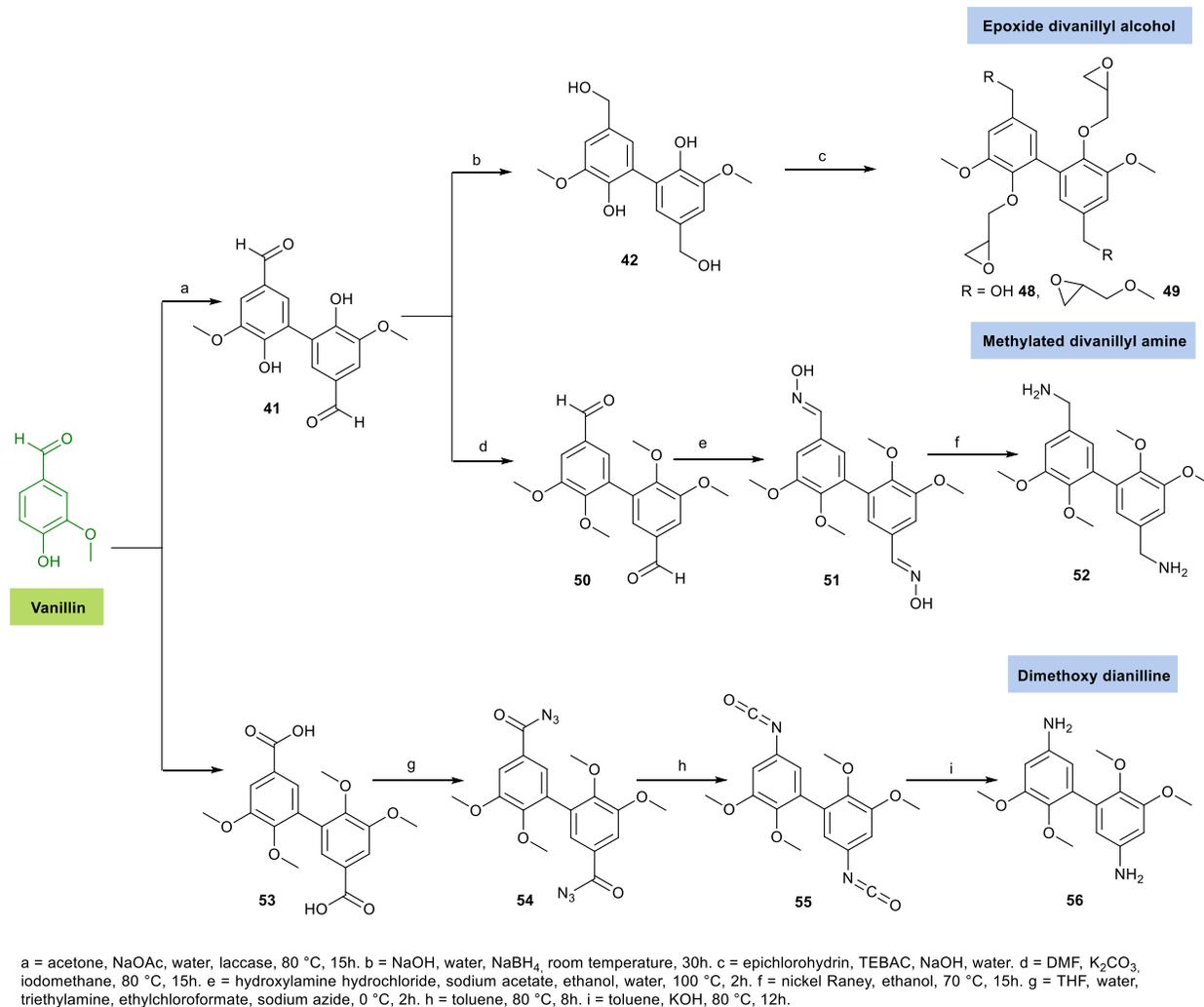
The enzymatic oxidative coupling of vanillin was also achieved by Cramail *et al.* using laccase in an acetone/water mixture.<sup>105</sup> The sEF of this route is 1.09 (Table S1, entry 47) and it is the lowest compared to the peroxidase- and iron-catalyzed dimerization of vanillin. Nevertheless, the *E* factor is higher (138) (Table S1, entry 47). The reduction of **41** was performed in water using NaBH<sub>4</sub> to yield **42**<sup>106</sup> (Scheme 7) with sEF 1.15 and *E* factor 19.3 (Table S1, entry 48). A methylated analogue to **42**, *i.e.* **44**, was also prepared by the reduction of the methylated product **43** using NaBH<sub>4</sub> in ethanol.<sup>105</sup> The process *E* factor of the three-step synthesis of **44** from vanillin is extremely high, 277 kg of waste/kg of product with 99% of solvents (acetone, water, DMF and ethanol) contribution (Table S1, entries 49-51). The enzymatic synthesis of dimethyl divanillate **47** was also achieved by Cramail *et al.* from vanillic acid as shown in Scheme 7 leading to similar results as discussed previously (Table S1, entries 52-54).<sup>105</sup>



a = water, acetic acid, horseradish peroxidase (Type I) 1000 units, hydrogen peroxide (3% in water). b =  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ , water, 50 °C, 4h. c = acetone, NaOAc, water, laccase, 80 °C, 15h. d = NaOH, water,  $\text{NaBH}_4$ , room temperature, 30h. e = DMF,  $\text{K}_2\text{CO}_3$ , iodomethane, 80 °C, 15h. f = ethanol,  $\text{NaBH}_4$ , water, room temperature, 30h. g = methanol, sulfuric acid, reflux, 8h. h = acetone, NaOAc, water, laccase, . i = DMF,  $\text{K}_2\text{CO}_3$ , iodomethane, room temperature, 24h.

**Scheme 7.** Synthesis of divanillin derivatives from vanillin (detailed reaction conditions are available in Table S1, entry 45-54)

The direct glycidylation of divanillyl alcohol **42** to form **49** was then performed with a large excess of epichlorohydrin (20 eq with respect to **42**) to prevent the formation of oligomers.<sup>106</sup> Epichlorohydrin was used as both reactant and solvent, nevertheless, it must be noted that epichlorohydrin is classified as carcinogenic, mutagenic and reprotoxic (CMR). The process sEF is 7.34 (Table S1, entries 55-57), where the larger amount of the produced waste is found for the glycidylation, step sEF = 5.64 (Table S1, entry 57). Two other glycidylated analogues were prepared from this reaction, *i.e.* diglycidylether and triglycidylether of vanillyl alcohol (the structures are not shown in Scheme 7). The parameters to control this reaction towards one type of glycidylated product are the equivalents of sodium hydroxide and the reaction duration.<sup>106</sup> The reactivity of **42** and its analogues was examined in the preparation of epoxy thermosets in the presence of isophorone diamine as a curing agent. The  $T_g$  of the epoxy resins increased as the degree of epoxidation of the monomer increased. For example, 138 °C vs. 198 °C for diglycidylether vs. tetraglycidylether of vanillyl alcohol.<sup>106</sup>

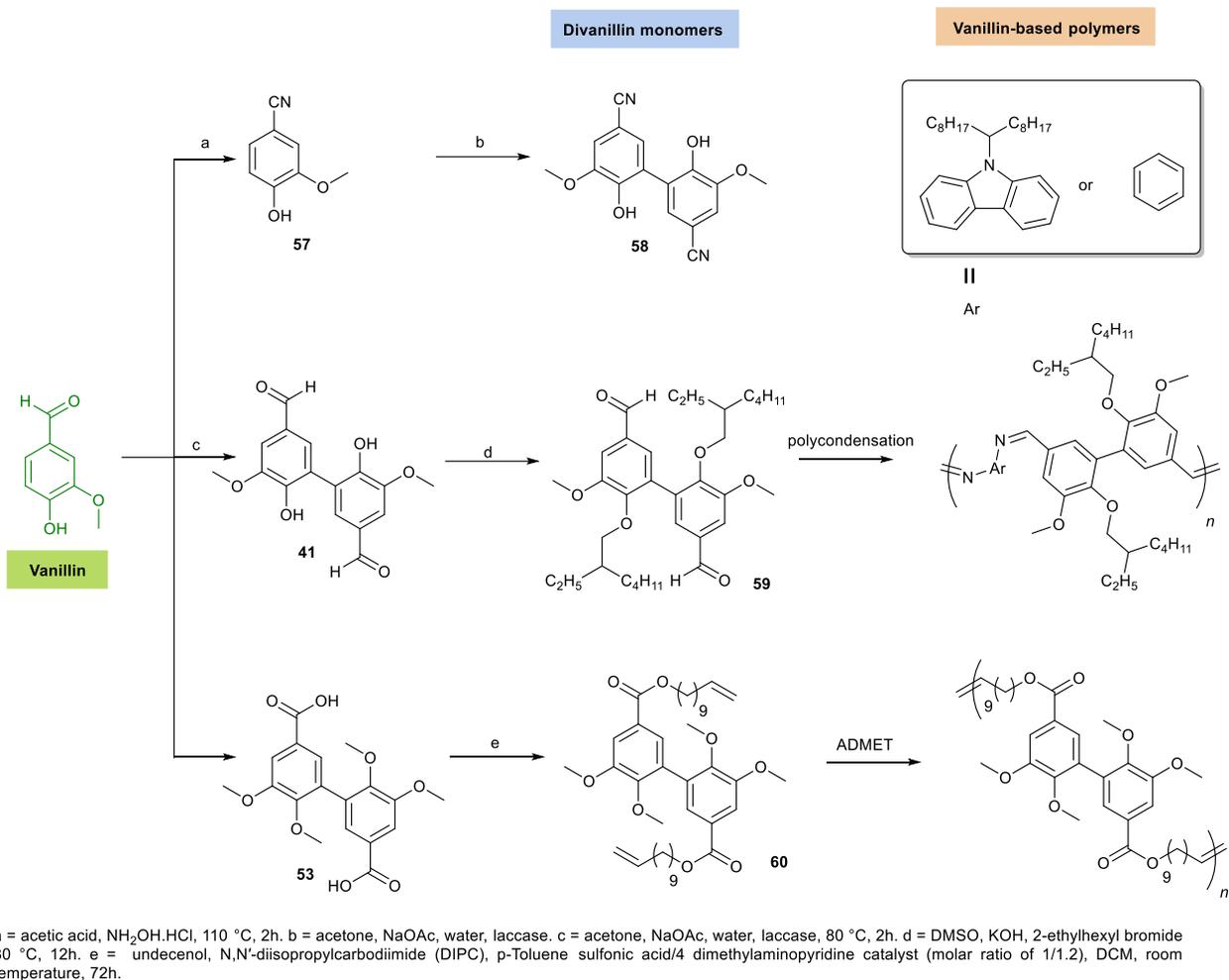


**Scheme 8.** Synthesis of tetraglycidylether of divanillyl alcohol, methylated divanillyl amine and 3,4-dimethoxyaniline from vanillin (detailed reaction conditions are available in Table S1, entry 55-62)

Recently, aromatic diamines derived from vanillin, *i.e.* methylated divanillyl amine **52** and 3,4-dimethoxydianiline **56**, were synthesized (Scheme 8).<sup>107</sup> These fully biobased molecules were used as curing agent for the synthesis of fully vanillin-based epoxy resins having promising thermal properties.<sup>107</sup> Although, these molecules constitute a useful addition to the biobased curing agent, especially that they are fully derived from vanillin, we decided to approach the synthetic processes in relation to the amounts of waste generated. The dimerization of methyl vanillate then hydrolysis to form the acid, is not considered in the calculations. Nonetheless, the sEF and *E* factor for the formation of **56** from **53** were found extremely high and indeed the highest reported in this critical review. The process sEF and *E* factor for the aforementioned three steps are equal to 146 and 1070 kg of waste/kg of product with 86% solvents (THF, water, and toluene) contribution to the waste (Table S1 entries 60-62). The main two reasons for such a high release of waste are the too low yield (<10%) for the isocyanate **55** hydrolysis

to form the amine product **56** and the excess amounts of reactants and reagents during the first and third steps (Table S1, entries 60 and 62 respectively).<sup>107,108</sup>

The enzymatic coupling of 4-hydroxy-3-methoxybenzonitrile **57** to yield **58** was also performed by Cramail *et al.* using the same previously described procedure<sup>109</sup> (Scheme 9), thus the calculations of the green metrics led almost to the same results as described previously for the other divanillin derivatives (Table S1, entry 64). The same research group described the preparation of **60** from vanillic acid by a four-step synthesis (only the last step is showed in Scheme 9) (Table S1, entry 67). They then polymerized **60** through ADMET in Polarclean in diluted conditions (0.22 M).<sup>110</sup> Polarclean is a green solvent with high boiling point and good compatibility with Grubbs' catalyst. ADMET polymerization can be optimized by using a more concentrated solution to reduce the solvent contribution to the waste from the process. **59** was synthesized from the alkylation of divanillin **41** with 2-ethylhexyl side chains (Table S1, entries 65 and 66).<sup>111</sup> It was then polymerized by microwave-assisted polycondensation at 130 °C in toluene using stoichiometric amounts of *p*-phenylenediamine or diamino carbazole (Scheme 9).<sup>111</sup> The resulting polyazomethine exhibited interesting thermal stability  $T_{d20\%}$  up to 401 °C and no thermal transition was observed by differential scanning calorimetry (DSC) indicating a very rigid and most likely an amorphous structure.<sup>111</sup>

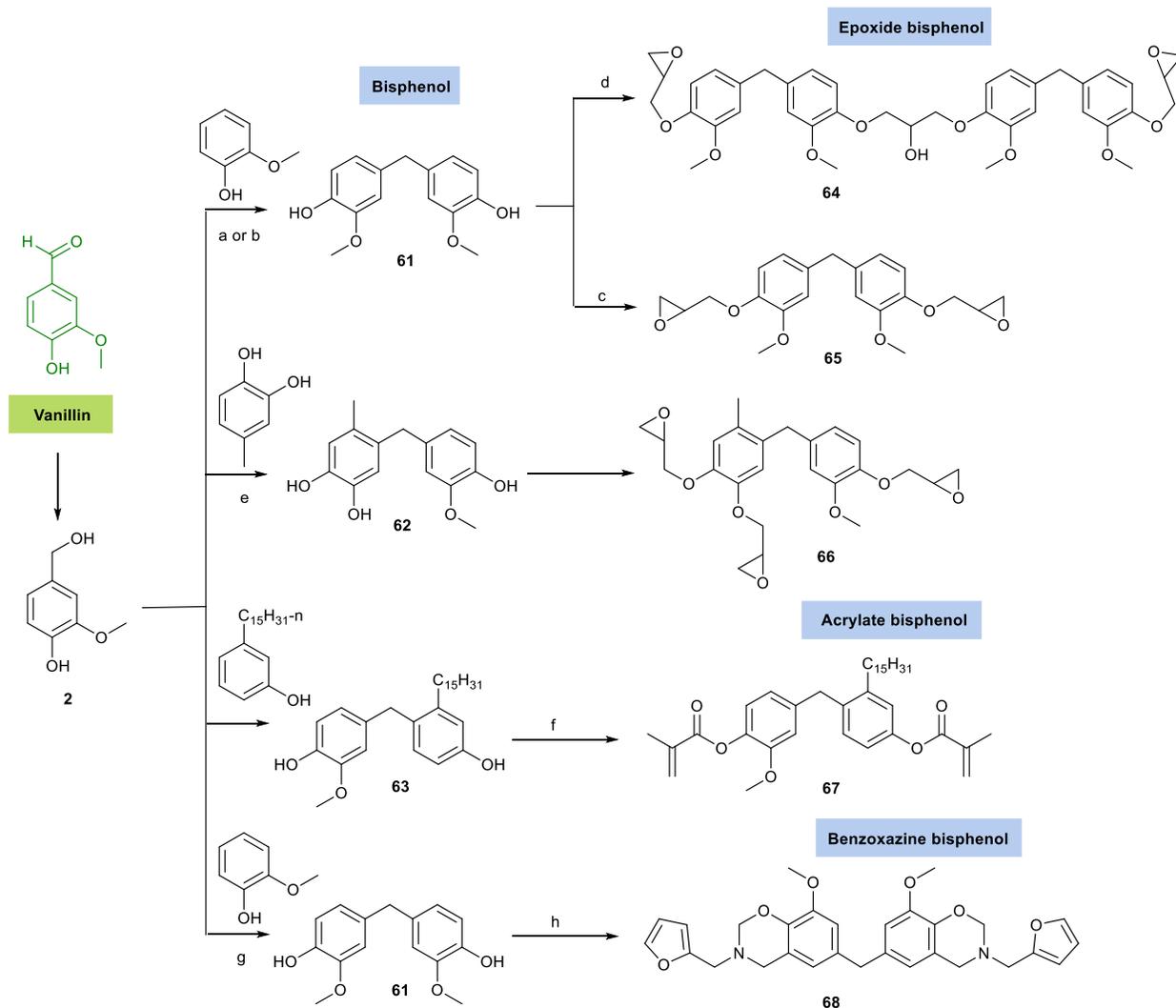


**Scheme 9.** Selected derivatives of divanillin monomers and polymers (detailed reaction conditions are available in Table S1, entry 63-67)

#### 4.2.2. Electrophilic aromatic condensation

Bisguaiacol **61**, synthesized from vanillyl alcohol and guaiacol is considered as a green alternative to the fossil-fuel-based bisphenol A (BPA) produced annually on industrial multi-ton scale (Scheme 10).<sup>112</sup> BPA is a highly valuable monomer used in the production of certain plastics and epoxy resins. However, its molecular structure leads to the disruption of our natural hormones, in particular estrogen.<sup>113,114</sup> In contrast to BPA, **61** exhibits no endocrine disruptive activity, in addition, it preserves the desirable thermal and mechanical properties of BPA due to the similar structure. In addition, **61** is produced from vanillyl alcohol **2** and guaiacol **19** as already introduced in this review. We calculated the green metrics of two different synthetic procedures of **61**. First, Stanzione *et al.*<sup>115</sup> employed an ion-exchange acid catalyst resin and the electrophilic aromatic condensation of **2** and **19** occurred in solvent-free conditions. The step  $\text{sEF} = E$  factor = 1.80 (Table S1 entry 68). Another procedure was reported by Kim *et al.*<sup>116</sup> where stoichiometric amounts of **2** and **19** were reacted however using 171 eq of ethanol as a solvent, which enlarged the

step *E* factor to 37.4 with 97% solvent contribution (Table S1, entry 74). Recently, Stanzione *et al.* used **61** as a monomer to prepare biobased copolyesters with different types of comonomers such as adipoyl chloride and succinyl chloride.<sup>117</sup> Interestingly, the polyesterification reactions were carried out at room temperature in an aqueous-organic biphasic system using a phase transfer catalyst (benzyltriethylammonium chloride). Nevertheless, DCM was used as a solvent to accommodate the resulting polymer. The thermal properties of the polyesters formed were dependent on the comonomer structure where the  $T_g$  can be tuned accordingly. Besides, the polymers formed showed high thermal stability exceeding 300 °C in air.<sup>117</sup> Biobased glycidyl ethers **64** and **65** were prepared from **61** by Stanzione *et al.*<sup>115</sup> and Epps *et al.*,<sup>118</sup> respectively. In both cases, epichlorohydrin was used in similar amount as described earlier in this review. Thus, the sEF and *E* factor fall in the previously reported range (Table S1, entries 69 and 71 for the glycidyl ethers **65** and **64** respectively). Notably, other studies like the recent work of Zhu *et al.* reported the synthesis of fully biobased diepoxy *via* acetalization<sup>119</sup> and partially biobased monomers by Schiff base condensation<sup>120</sup> reactions. However, the reactions are not discussed herein to avoid repetition as the obtained values of green metrics fall in the aforementioned range. Kim *et al.*<sup>116</sup> showed the ability of **61** to substitute BPA in the synthesis of polybenzoxazines using environmentally friendly reagents (furfuryl amine and paraformaldehyde) and solvent-free synthesis. This leads to a step *E* factor of 0.13 (Table S1, entries 75). In recent times, Abu-Omar *et al.* reported the synthesis of tri-epoxide glycidyl ether **66** from **62**.<sup>121</sup> The latter was prepared from the reaction between **2** and *p*-methyl catechol (Scheme 10).<sup>121</sup> The *E* factor of the synthesis of **62** lies between the two values calculated for **61**, *i.e.* 8.00 compared to 1.80 and 37.4 (Table S1, entries 72, 69 and 74) due to the moderate amount of solvent ethanol (25.7 vs. 0 and 171.3 eq, respectively). A single epoxide derivative from **62** was also produced in the same work (the structure is not shown in Scheme 10). This derivative was used in combination with **62** with different ratios to prepare different vitrimers/polymers that showed interesting properties such as high strain, excellent self-healing and fast stress relaxation.<sup>121</sup> Not long ago, Stanzione *et al.* reported the synthesis of methacrylated bisphenol **67** from **63**, that in turn can be prepared starting from electrophilic aromatic condensation of vanillyl alcohol and cardanol (Scheme 10).<sup>122</sup> The sEF of the methacrylation procedure is 1.12 and if solvent (DCM) is considered in the calculation, the *E* factor is 9.14 with 79.1% solvent contribution (Table S1, entry 73). **67** blended with reactive diluent (35 wt% styrene) was then cured to prepare interesting thermoset resins (a comprehensive comparison with commercial thermosets is well described in the original work).<sup>122</sup>

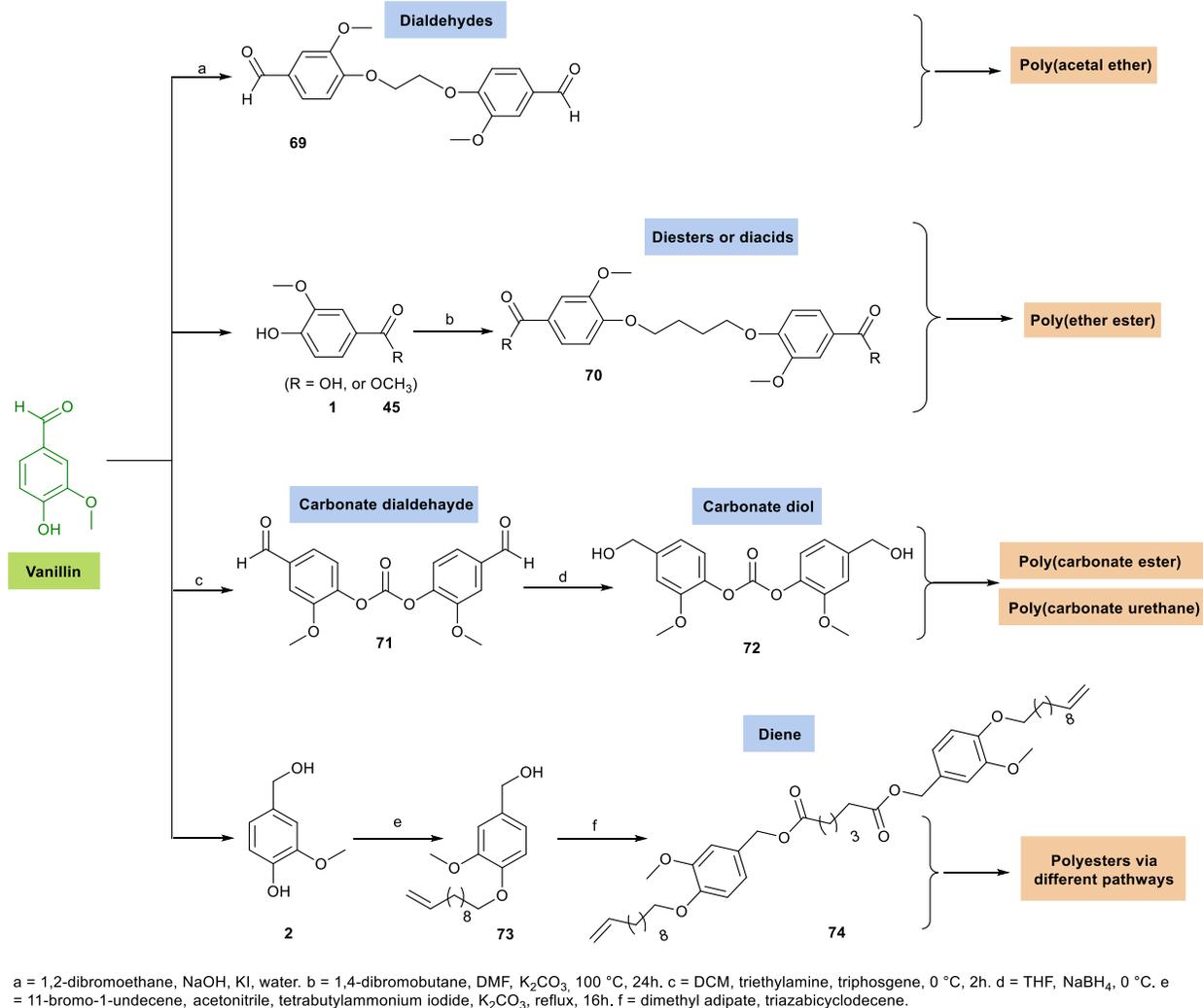


**Scheme 10.** Electrophilic aromatic condensation of vanillin and phenol compounds (detailed reaction conditions are available in Table S1, entry 68-75)

#### 4.2.3. Esterification and Etherification

Two molecules of vanillin or methyl vanillate **46** were reacted with dibromoalkane to afford the dialdehyde or diester **69**<sup>123</sup> and **70**<sup>124</sup> respectively (Scheme 11). A dicarboxylic acid analogue of **70** was also synthesized using **1** as starting material.<sup>125</sup> Water (205.8 eq with respect to vanillin) was used as a solvent for the synthesis of **69** in the presence of 2.2 eq of sodium hydroxide and 0.01 eq of sodium iodide.<sup>123</sup> On the other hand, when **70** was targeted, DMF (51.6 eq with respect to vanillin) was employed with 1 eq of sodium carbonate.<sup>124</sup> We evaluate the *E* factor of this synthesis of **69** as 22.2 kg of waste/kg of product (Table S1, entry 76). This is greater than the *E* factor (14.3) calculated for **70**. Indeed, we realized that water is usually used in huge excess regardless the extent of solubility of the starting

materials. Probably, the rationale behind such excessive usage of water is its green nature.<sup>126</sup> Monomers **69** and **70** (in addition to its diacid analogue) were used in the production of poly(acetal ether)<sup>123</sup> and poly(ether ester),<sup>124,125</sup> respectively. These polymers are described in another review.<sup>65</sup> Recently, Xie *et al.* used triphosgene (bis(trichloromethyl) carbonate) to link two molecules of vanillin and form a carbonate dialdehyde **71** (Scheme 11).<sup>127</sup> Triphosgene is a renewable chemical as it is derived from CO<sub>2</sub> and it is considered as a greener and safer crystalline easy-handled molecule when compared to phosgene which is a poisonous gas. Thus, using triphosgene as a safer alternative to phosgene is highly encouraged. The authors chose to perform the reactions using 6 eq of vanillin and 9 eq of triethylamine with respect to 1 eq of triphosgene which leads to a step sEF of 5.91 (Table S1, entry 78). If the solvent (391.5 eq of DCM) is considered, regardless its toxicity, we recorded a high amount of waste generated, *E* factor = 114. The same work reported the reduction of **71** using sodium borohydride in THF to afford an interesting aromatic carbonate diol molecule **72**.<sup>127</sup> The process *E* factor of the latter is 140 with 94% solvent contribution to the waste. Such a huge value of waste of this two-step synthesis is due to the first step as discussed previously. Notably, Xie *et al.* employed monomers **71** and **72** to design new biobased synthetic poly(carbonate ester) and poly(carbonate urethane) with *T<sub>g</sub>* and *T<sub>d5%</sub>* in the range of 37-138 °C and 130-256 °C, respectively.<sup>127</sup> The same authors calculated the *E* factor of the polymerizations performed and different values were obtained ranging from 4.30 to 8.90 depending on the monomer and the comonomer used (whether it is diacid, acyl chloride or diisocyanate). Meier *et al.* reported the synthesis of the monomers **73** and **74** (in addition to other monomers reported in the same work) from vanillin.<sup>76</sup> These monomers were polymerized *via* different and well-established polymerization strategies (Scheme 11).<sup>76</sup> We will not discuss the monomer and polymer syntheses as they are already well reviewed elsewhere.<sup>65</sup> The step *E* factor of **73** is 2.43 with 38% of solvent contribution (Table S1, entry 8) and it is the lowest recorded for Scheme 11, due to the low amount of solvent used (9.6 eq of acetonitrile). The synthesis of **74** was conducted in bulk, thus leading to further lower *E* factor of 0.48 (Table S1, entry 81).

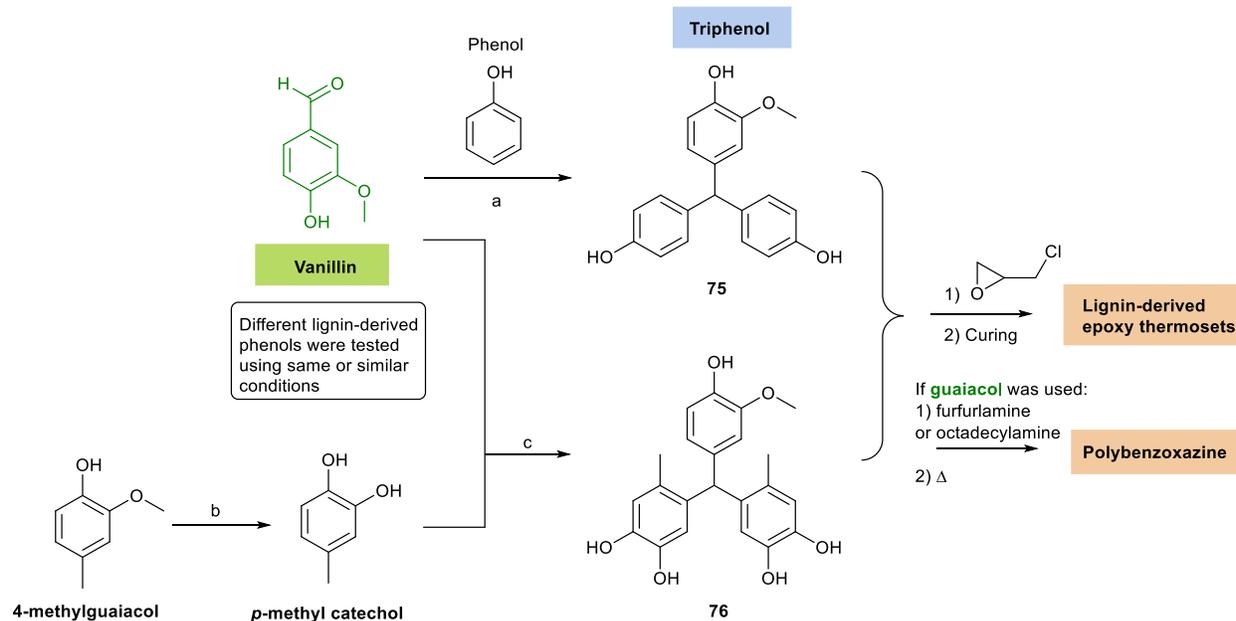


**Scheme 11.** Versatile dimers of vanillin with different linkages (detailed reaction conditions are available in Table S1, entry 76-81)

#### 4.3. Vanillin: trimeric derivative

Polyphenols molecules are valuable precursors for polymers such as epoxy resins and polybenzoxazine. They are generally produced by condensation of phenol with ketone or aldehyde in acidic conditions (Scheme 12). In 2015, Wu *et al.* described the synthesis of fully renewable benzoxazine monomers from triphenol to prepare pH-responsive polybenzoxazine having good thermal properties such as  $T_{d5\%} = 284-335$  °C.<sup>128</sup> In 2017, a series of renewable triphenylmethane-type polyphenols, such as **75** and **76**, were synthesized by Abu-Omar *et al.* from vanillin and catechol derivatives (Scheme 12).<sup>129</sup> The triphenol molecule **75** was prepared using a one-step condensation reaction of vanillin and phenol<sup>130</sup> (Scheme 12). The sEF is 3.14 (Table S1, entry 84). In order to prepare **76**, the synthesis of *p*-methyl catechol was first performed from 4-methylguaiacol in neat conditions at 120 °C using 10.3 eq of hydrobromic acid. Then the condensation reaction of 4 eq of *p*-methyl catechol and vanillin was conducted in

ethanol (11 eq) in the presence of 3 eq of sulfuric acid in 88% yield. The AE is 95% and *E* factor is 3.31 of **76** with 35% solvent contribution (Table S1, entry 83). The process sEF and *E* factor of the synthesis are 11.7 and 13.2, respectively (Table S1, entries 82 and 83).

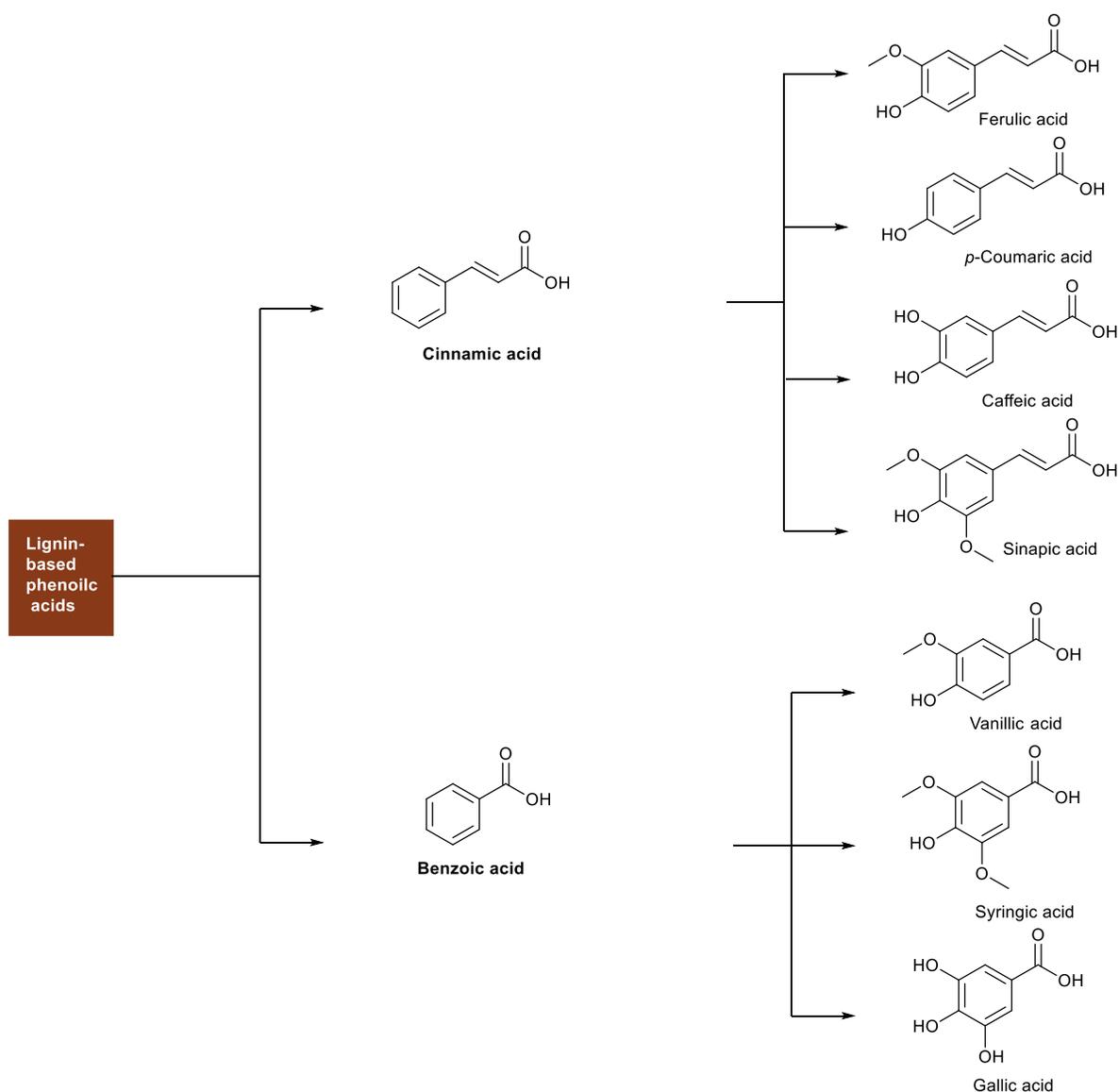


a = ethanol, sulfuric acid, 65 °C, 48h. b = hydrobromic acid 48% aqueous, 120 °C, 20h. c = *p*-methyl catechol, ethanol, sulfuric acid, room temperature, 48h.

**Scheme 12.** The synthesis of triphenol and polyphenol by the condensation of vanillin and phenolic derivatives (detailed reaction conditions are available in Table S1, entry 82-84)

## 5. LIGNIN-BASED PHENOLIC ACID DERIVATIVES

Another important class of lignin-based compounds, other than vanillin, are the phenolic acids, generally categorized as cinnamic acid derivatives and benzoic acid derivatives. The cinnamic acid derivatives include ferulic acid, *p*-coumaric acid, caffeic acid, and sinapic acid, also called hydroxycinnamic acids,<sup>131</sup> whereas vanillic acid, syringic acid, and gallic acid are considered as benzoic acid derivatives (Scheme 13).



**Scheme 13.** Lignin-based phenolic acids and their derivatives

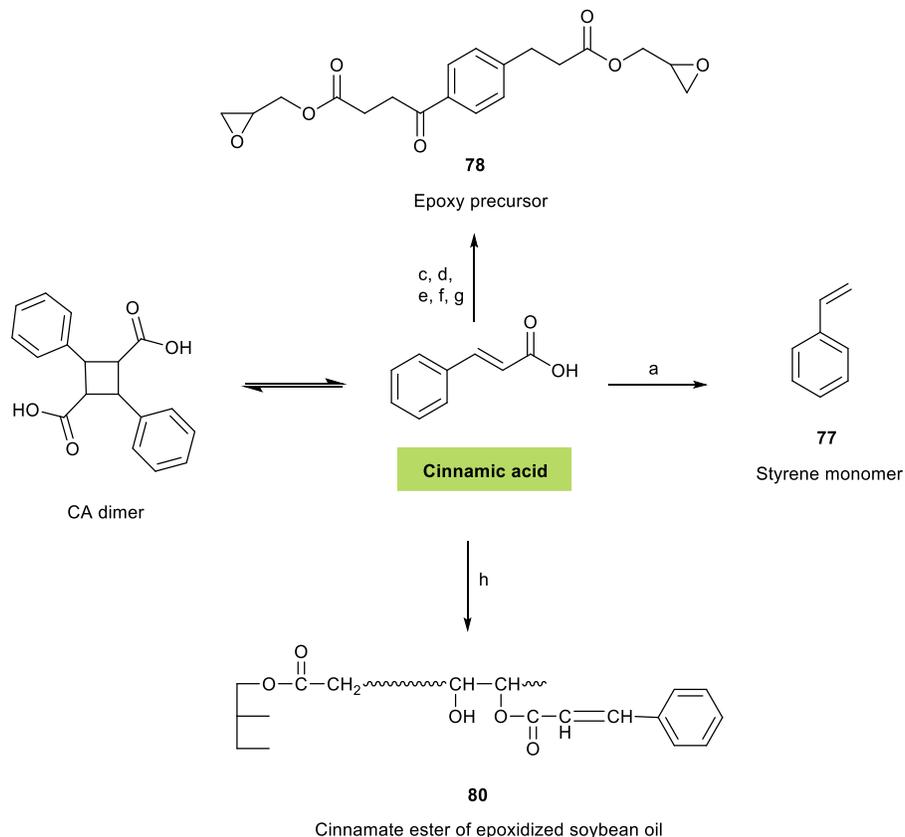
### 5.1. Cinnamic acid and its derivatives

Cinnamic acid is a phenyl ring substituted acrylic acid, which happens to be the first metabolite of the lignin-biosynthesis process.<sup>132,133</sup> Polymers obtained from cinnamic acid can be used in advanced fields, such as electronics, photo-responsive coatings, shape-memory polymers, and many more.<sup>134</sup> Different methods of cinnamic acid synthesis from aldehydes are developed over the years, in which Perkin reaction, Knoevenagel-Doebner condensation, and Heck reaction are the popular ones.<sup>134</sup>

Synthesis of polystyrenes from cinnamic acid is extensively investigated in terms of the feasibility of production and sustainability. In one such example, styrene monomer **77** was obtained from cinnamic acid by

catalytic decarboxylation using a one-step synthesis process, where polyethylene glycol (PEG) 6000 was used as a green solvent (Scheme 14).<sup>135</sup> The calculated value of the *E* factor is 23.3, sEF value is 1.64 and AE is 70% (Table S1, entry 85). Such a huge difference between the sEF and *E* factor value is due to the higher amount of the solvent used, the numerical value of which is 89% solvent contribution to the *E* factor. The use of biocompatible solvent works in favor of this particular reaction. Moreover, both the solvent and catalyst can be recovered from the process by distillation, and the copper catalyst can be reused for several cycles without any deactivation and thus satisfy the requirements of a greener synthesis method. In another similar study, the decarboxylation reaction of cinnamic acid was carried out in dimethylsulfoxide under mild and metal-free conditions, where ionic liquid (1-ethyl-3-methylimidazolium acetate) was used to generate *N*-heterocyclic carbene (NHC) by self-deprotonation that acted as a strong base catalyst and probably the reason for the reaction to take place under milder conditions.<sup>136</sup> This reaction showed promising results for several other carboxylic acids, however, no decarboxylation was observed with cinnamic acid with no phenolic -OH group, whereas when caffeic acid was used that has two phenolic groups, decarboxylation happened rapidly.

A work reported by Zhang *et al.*, where an epoxy precursor **78** was produced from cinnamic acid and a renewable curing agent **79**, was also produced from dipentene and maleic anhydride. To produce the epoxy precursor, cinnamic acid was first hydrogenated and then converted to a diacid by Friedel-Craft reaction. It is then subsequently allylated, epoxidized, and cured with the synthesized anhydride curing agent. This synthesis method apparently led to high process sEF and process *E* factor values, 21.5 and 95.0, respectively, mainly because of five reaction steps (Table S1, entry 86-90).<sup>137</sup> The use of DCM and DMF as solvents during the hydrogenation, allylation, and epoxidation reactions can also be a matter of concern in order to consider a green synthesis method. However, the renewable curing agent **79** was synthesized without any solvent, in presence of a catalytic amount of iodine, and the reaction method delivers 100% AE, and both the calculated sEF and *E* factor is found to be 0.30 kg of waste/kg of product (Table S1, entry 91) and thus, have the characteristics of a sustainable synthesis method. Another study on cinnamate esters of epoxidized soybean oil **80** was reported, which shows 100% AE, sEF value 0.58. Triphenyl phosphine was used as a catalyst and no solvent was used which means the *E* factor value is also 0.58 (Table S1, entry 92).<sup>138</sup> This renewable monomer can undergo photo-polymerization and free-radical polymerization to produce valuable polymers, and also can be effectively copolymerized with styrene, vinyl acetate and methyl methacrylate.



**Scheme 14.** Monomers and dimers synthesized from cinnamic acid (detailed reaction conditions are available in Table S1, entry 85-92)

Due to the presence of the  $\alpha,\beta$ -unsaturated ester in cinnamic acid and its derivatives, the latter can undergo photo-reversible [2+2] cycloaddition reactions under the specific wavelength of UV radiations.<sup>139</sup> This interesting property of cinnamic and hydroxycinnamic compounds makes them valuable candidates for producing photo-responsive materials, that can have potential applications in drug delivery, shape-memory systems, and also to produce photo-crosslinking and self-healing polymers.<sup>140,141</sup> Different monomers and polymers synthesized from other cinnamic acid derivatives and their sustainability factors are discussed below.

#### 5.1.1. Ferulic acid

Ferulic acid, also known as 4-hydroxy-3-methoxycinnamic acid, is a naturally occurring phenolic compound, which can commonly be found in lignocellulosic plants, fruits, vegetables, seeds, and grains, hardly in the free form but mostly as the ester linkage.<sup>142,143</sup> It shows antioxidant, anti-inflammatory activities and it is a renewable non-toxic chemical that finds increasing application in biobased polymer synthesis, foods, and cosmetics.<sup>144,145</sup> It can be extracted from hardwood or lignosulfonates by alkaline degradation and can be effectively synthesized from renewable aldehydes.<sup>146</sup> Synthesis of this compound from vanillin by Knoevenagel condensation was first reported

in the year 1925.<sup>147</sup> It can also be synthesized from vanillin by Perkin condensation reaction.<sup>145</sup> Recently, a sustainable procedure for the synthesis of ferulic acid (**81**) from vanillin was developed by Allais *et al.* following a simple proline-mediated single-step procedure that was employed with a sEF value 2.10 and 76% AE, where ethanol was used as solvent to replace the toxic solvent pyridine (Table S1, entry 93).<sup>148</sup>

Many research groups are actively searching for a replacement for the existing fossil-based compounds with a renewable one, and simultaneously the whole process has to be sustainable. BPA is such a compound widely used in the manufacturing of polycarbonates, polyurethanes, epoxy resins, and is a known carcinogen and suspected endocrine disruptor.<sup>149</sup> Chemo-enzymatic synthesis of biobased bisphenols and tris-phenols from ferulic acid were explored to replace fossil-based BPA. They were produced *via* a two-step synthetic process, where ferulic acid was first converted to ethyl dihydroferulate *via* Fisher esterification followed by palladium-catalyzed hydrogenation reaction, and in the second step biobased polyols were reacted with ethyl dihydroferulate using lipase-catalyzed transesterification.<sup>150</sup> The resulting bisphenols and trisphenols, bis-*O*-dihydroferuloyl isosorbide (IDF) **82**, bis-*O*-dihydroferuloyl 1,4-butanediol (BDF) **85**, bis-*O*-dihydroferuloyl 1,3-propanediol (PDF) **88** and tris-*O*-dihydroferuloyl glycerol (GTF) **91** were then subjected to acrylation and allylation to allow access to various polymerization reactions. The two-step synthesis of these bisphenols and trisphenol shows both process sEF and *E* factor values as 5.59, 5.64, 6.05 and 6.03 for **82**, **85**, **88** and **91**, respectively and non-toxic solvent ethanol was used for the esterification reaction with a solvent contribution of 68-70% to the process *E* factor, whereas the transesterification reaction was carried out without any solvent. Three acrylated bisphenols, **83**, **86** and **89**, were then produced from **82**, **85** and **88**, which show sEF value 1.09, 1.01 and 0.70, AE values are 89%, 88% and 88%, and the *E* factor values are 7.35, 7.60 and 6.57, respectively (Table S1, entries 98, 106 and 114). The high *E* factor values are mainly due to a large amount of solvent used (31-33 eq with respect to the bisphenol). The bisphenols were also exposed to the allylation step to produce monomers **84**, **87** and **90**. In this case, the calculated sEF values are 1.73, 2.02 and 1.74, *E* factor values are 5.76, 7.74 and 6.15 and the atom economy values are 78%, 76% and 76% for **84**, **87** and **90**, respectively (Table S1, entries 101, 109 and 117). A triphenol **91** produced using glycerol was subsequently acrylated and allylated to produce **92** and **93** with process sEF value 9.80 and 8.80, and process *E* factor 15.8 and 11.8, respectively (Table S1, entries 120-122 and 123-125). These high waste values are again associated with the solvent used in the esterification, acrylation and allylation steps. For all the reactions (for **82-93**), the transesterification step for the conversion of ethyldihydroferulate to the corresponding bisphenol or trisphenols shows sEF and *E* factor values in the range of 0.98-1.30 (Table S1, entry 95, 97, 100, 103, 105, 108, 111, 113, 116, 119, 121 and 124). The use of enzymes eliminates the need for the solvents in the reaction thereby reducing the *E* factor value drastically. The synthesis methods of biobased bisphenols **82**, **85**, **88** and **91** (Table S1, entries 94-95, 102-103, 110-111 and 118-119) were also successfully upscaled from lab to kilo lab production, which is extremely important, and the carbon footprint, environmental stability, solvent intensity parameters were compared, evaluated and reported in the literature<sup>151</sup>. Solvent resistant nanofiltration (SRNF) step was incorporated into the process to deal with the major

drawback of the membrane filtration, *i.e.* excessive solvent consumption. Almost 90% of the solvent recovery was possible with only 1% impurity.

These sustainably synthesized biobased bisphenols were taken forward to study the properties of the corresponding polymers. Co-polyesters were synthesized by thermal polycondensation of the bisphenols along with two renewable diacyl chlorides in bulk as well as in solution and their thermal properties were assessed.<sup>152</sup> This polymerization method follows acyl chloride pathway to avoid the use of metal catalysts. The sEF and *E* factors are calculated for the bulk polymerization of **82** and **85** with succinyl chloride and azelaoyl chloride and in all the cases, sEF and *E* factor are found to be in the range of 0.04-0.06 kg of waste/kg of product (Table S2, entries 3-6). Since no solvent or metal catalyst was used, the only waste generated was due to some unreacted monomers. Most importantly, these polymers are biocompatible and have no metal catalyst residue, thus, can be employed for biomedical applications. Polyurethanes were also produced *via* catalyst-free polyaddition with the biobased bisphenols **82**, **85** and **88** and commercially available isocyanates, 1,6-hexamethylene diisocyanate (HDI) and 1,4-toluene diisocyanate (TDI).<sup>153</sup> The polyadditions were carried out in bulk and in solvent at 100-140 °C temperature range. For the bulk polymerization methods, the sEF and *E* factor values are in the range of 0.01 to 0.36 as no solvent was present (Table S2, entries 7-12), whereas for the solvent polymerization method, the sEF values are in the range of 0.05 to 0.19 and *E* factor values are in between 0.90 to 1.15 with 45% solvent contribution to the *E* factor (Table S2, entries 13-18). The bulk polymerization method for all the bisphenols with 1,4-toluene diisocyanate (TDI) provided excellent yield of 98-99% and considering the above mentioned sEF and *E* factor values, this method can definitely be the best for polyurethane synthesis (Table S2, entries 8, 10 and 12). These polyurethanes showed interesting thermal properties, such as  $T_g$  ranging from 28 to 128 °C and thermal stability up to 180 °C. However, considering the toxicity of the isocyanate compounds, another study was conducted where an isocyanate-free polyurethane synthesis method from ferulic acid derivatives was developed.<sup>154</sup> C<sub>5</sub>-cyclocarbonate precursors were synthesized from ferulic acid derivatives by epoxidation and subsequent carbonation under high-pressure carbon dioxide and it was then reacted with diamine to prepare non-isocyanate polyurethanes (NIPUs), which are renewable and produced *via* chemo-enzymatic synthesis procedure. In addition,  $\alpha,\omega$ -diene monomers were produced from ferulic acid and biobased diols by chemo-enzymatic method, and then subjected to ADMET polymerization in bulk and in solvent in the presence of second-generation Hoveyda–Grubbs catalyst to prepare poly(ester-alkenamer)s, whose thermal properties were studied and discussed.<sup>155,156</sup> These polymers are stable at around 280-370 °C, and notably, their  $T_g$  can be finely tuned by adjusting the monomer diester nature and alkene length. Another study in which, laccase catalyzed oxidative oligomerization process of the ferulic acid-based bisphenols **82**, **85** and **88** were described and their thermal and anti-oxidant properties were evaluated.<sup>157</sup> In addition, the antioxidant activity for these bisphenols and triphenol for the polypropylene and polybutylene succinate polymer processing were demonstrated and compared with the commercial antioxidant generally used for these polymers.<sup>158</sup> Epoxy-amine resins produced from these plant-derived bisphenols **82**, **85**, **88** and **91** were investigated for thermal and mechanical properties and structure-property relationship of the renewable epoxy resins was also established.<sup>56,159</sup>

A recent study based on the use of monomers **94**, **95** and **96** for the synthesis of epoxy-amine resins was conducted with biobased trisphenols along with other fatty acids, such as lauric acid, palmitic acid and stearic acid, which provides process sEF values 3.82, 3.70, 3.26 and process *E* factor values 33.3, 31.8, 28.4 respectively (Table S1, entries 126-134).<sup>160</sup> The solvent contribution to *E* factor is 86% for each cases, which justifies the higher wastage values associated with this reaction. The estrogenic activity of these monomers was studied and they showed no significant activity and therefore, they appear suitable to replace BPA. These trisphenols were then subjected to TEBAC-mediated glycidylation to produce the epoxy precursors and cured with diamines. High thermal stability with  $T_{d5\%}$  ranging from 282 to 310 °C and  $T_g$  between 3 to 62 °C were observed and can be once again finely tuned by changing the diamine linker.



Another extensively explored ferulic acid-based polymers are polystyrenes. Similar to the synthetic method of styrene monomer from cinnamic acid, ferulic acid was also studied for the synthesis of styrene mimics **98** using PEG-6000 as a solvent by copper-catalyzed decarboxylation reaction in a single-step synthesis process with a high yield of 96% and low waste values, *i.e.* sEF value 0.44 and *E* factor value 9.69 (Table S1, entry 136).<sup>135</sup> PEG-6000 was used as a green solvent and it can be recovered and reused. Thus, the high *E* factor, which is mainly due to the use of solvent, can be ignored. Therefore, this decarboxylation reaction to produce styrene monomers from ferulic acid shows the characteristics of a sustainable synthetic process. Another study conducted on the styrene-like monomers **99**, **100**, **101** and **102** produced from ferulic acid by the incorporation of different alkylene spacers, and for **100**, an additional step of hydrogenation of the double bond was included to increase the flexibility of the polymer chain.<sup>161</sup> These monomers **99**, **100**, **101** and **102** show sEF values 1.42, 2.74, 1.64 and 1.73, respectively (Table S1, entries 137-141). The high *E* factor values 13.2, 32.6, 13.8 and 10.0 are associated with the high amount of solvent used, which is water in this case. However, such chemical reaction requires 100 °C and takes almost 3-4 days to complete which is not viable from the energy efficiency perspective. The polystyrenes produced from these monomers in presence of antimony trioxide as catalyst, have very low sEF and *E* factors 0.13, 0.16, 0.09 and 0.09 for **99**, **100**, **101** and **102**, respectively (Table S2, entries 19-22). In an alternative two-step synthetic process employed for styrene monomers, ferulic acid is first converted to 4-vinylguaiaicol by decarboxylation and then protected by silyl groups. The resulting four monomers **103**, **104**, **105** and **106** were then subjected to reversible addition-fragmentation chain-transfer (RAFT) polymerization with or without AIBN initiator.<sup>162</sup> The process sEF values obtained are 2.20, 2.00, 2.40 and 2.20 and process *E* factors values are 6.40, 5.70, 7.50 and 7.60, respectively, with 56-63% solvent contribution (Table S1, entries 142-149). The solvents used for these reactions are DMF, pyridine, THF and toluene. Pfizer scientists in their solvent selection guide mentioned DMF and pyridine as 'toxic' solvents, whereas THF and toluene, were termed as 'usable' solvents.<sup>163, 164</sup> The usage of proper non-toxic solvents is a major criterion in the green chemistry evaluation process.

Attempts were made to produce monomers for poly(carbonate-amide)s **107**, **108**, **109** and **110** from renewable resources and the *E* factor values for all these monomers are extremely high 21.5, 105, 68.7 and 135, respectively with 82-92% solvent contribution (Table S1, entries 150-161).<sup>165</sup> These synthetic methods used DCM, THF, and pyridine as solvents and none of them are green solvents. Monomers **108** and **110** have high process sEF values 9.83 and 16.7, very high *E* factor values 105 and 135, and very low overall yield, 41% and 39%, respectively, mainly because of a greater number of reaction steps. Ferulic acid-containing poly(anhydride-ester)s were prepared for controlled release application in the skincare products due to the UV absorption properties of ferulic acid. Diacid **111** was synthesized using *t*-butyl ferulic acid and adipoyl chloride and then subjected to solution polymerization.<sup>166</sup> This three-step synthesis of **111** has high process sEF and process *E* factor values of 14.6 and 129 with 88% solvent contribution (Table S1, entries 162-164). In an extended study, monomers **112** and **113** were also prepared with glycol functionality for the rapid release of ferulic acid.<sup>167</sup> The calculated process sEF value for **112** is 12.6, the process *E* factor is 105 and the solvent contribution to is 87% (Table S1, entries 165-166). The high amount of trifluoroacetic

acid (40 eq) and a large amount of solvent used are the main reasons for such high sEF and *E* factor values. In addition to these monomers, ferulic acid-based homopolymer was produced *via* thermal polycondensation using 1 mol% of sodium acetate as a catalyst and offers sEF and *E* factor values of 2.78, which is because of the use of 6.2 eq of anhydride acetic acid as condensation agent (Table S2, entry 27).<sup>168</sup> Liquid crystalline hyperbranched copolymers were produced in a one-pot two-step process *via* thermal acidolysis and polycondensation of caffeic acid and ferulic acid using disodium phosphate as a catalyst with 77-87% yield for applications in adhesives and environmental-friendly plastics.<sup>169</sup>

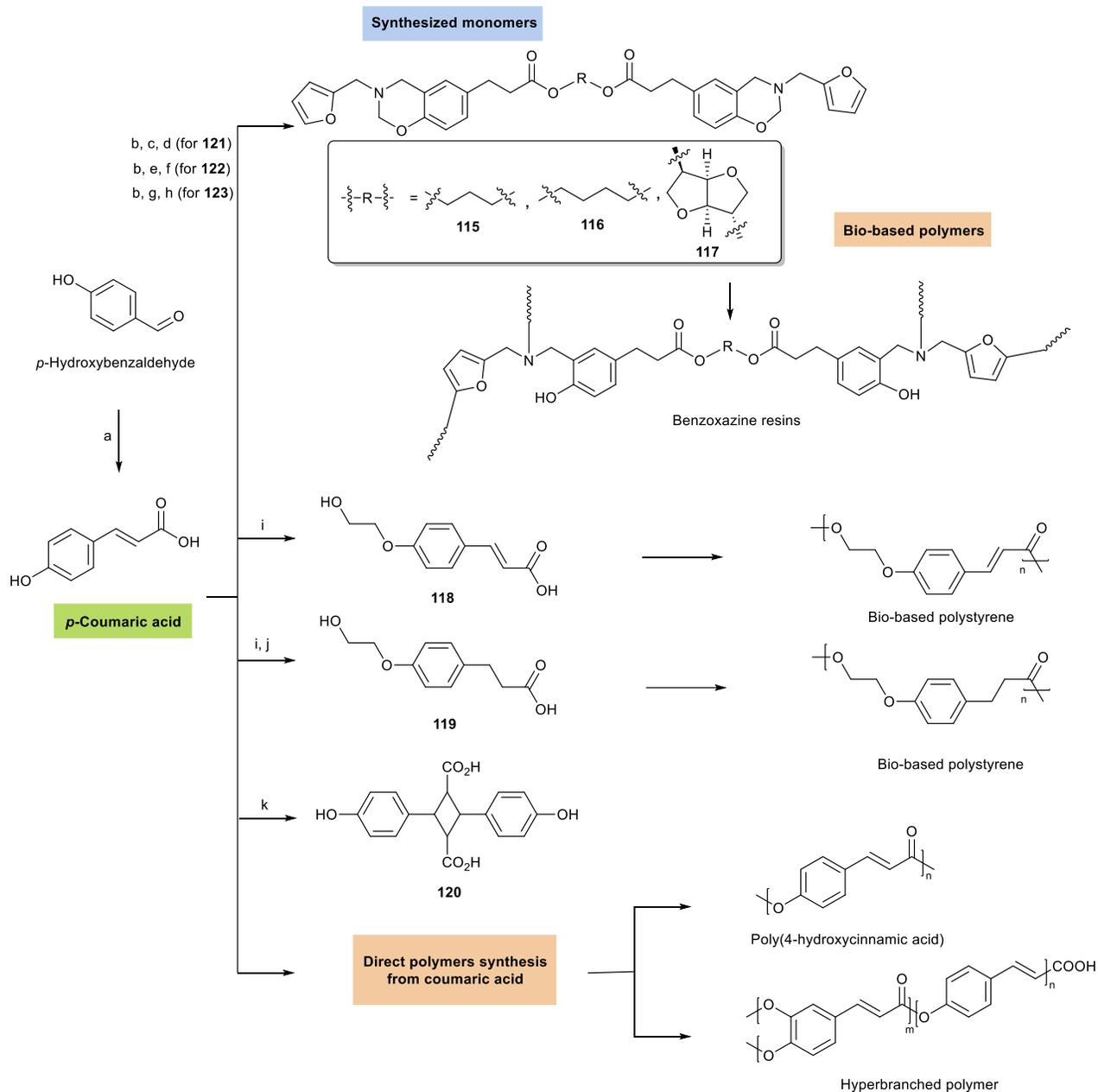


### 5.1.2. *p*-Coumaric acid

*p*-Coumaric acid, also known as 4-hydroxycinnamic acid, is one of the most readily available natural monomers obtained from lignocellulose.<sup>135,170</sup> It can form ester linkages with hemicellulose, and ester or ether linkages with lignin.<sup>171,172,173</sup> *p*-Coumaric acid **114** can be also chemically produced by a simple single-step process from *p*-hydroxybenzaldehyde in 50% yield, 73% AE and sEF value 3.66 using ethanol as solvent/reagent *via* Knoevenagel condensation reaction (Table S1, entry 169).<sup>148</sup>

Many studies have evolved with efficient processing conditions to produce value-added polymers, such as polystyrene, benzoxazine resins, polyesters using *p*-coumaric acid. The precursors for benzoxazine resins **115**, **116**, and **117** were synthesized from *p*-coumaric acid by one-pot Fischer esterification and a palladium-catalyzed hydrogenation process followed by solvent-free lipase-mediated transesterifications to afford the bisphenols with three different biobased diols.<sup>174</sup> These bisphenols were then taken forward to synthesize the benzoxazine precursors using furfurylamine and paraformaldehyde. The first step of the reaction has a high *E* factor value 10.5, 92% of which is contributed by the solvent, which is ethanol in this case (Table S1, entry 170). The second step is the lipase-mediated step, which is solvent-free and provides sEF and *E* factor values 1.66, 1.34 and 18.8 for **115**, **116**, and **117**, respectively (Table S1, entries 171, 174 and 177). The monomer **117** has a yield of only 11% in the second step, which is the reason for the higher value of sEF and *E* factor for this particular monomer. The third step includes 1,4-dioxane, which is a potential carcinogen. The sEF values for the third step for the three monomers are 0.34, 0.32, 0.25 and *E* factor values are 1.22, 1.48 and 1.40 for **115**, **116**, and **117**, respectively (Table S1, entries 172, 175 and 178). Despite having three steps of the reaction, these monomer syntheses are having low wastages and have the potential to be a green synthetic process, if some of the solvent systems are altered and the amounts used are reduced. Also, because of the low boiling point of ethanol, it can be removed from the system easily by vacuum distillation after the first step and it can be reused again and recyclability is undeniably an important facet in the green chemistry.

In an attempt to synthesize polystyrenes from *p*-coumaric acid, the monomers were produced with two strategies, one is, keeping the double bond of the coumaric acid as it is, and another consists of the hydrogenation of the double bond to incorporate flexibility into the structure.<sup>161</sup> Monomer **118** was synthesized by introducing an alkylene spacer into the structure and monomer **119** was synthesized with an additional hydrogenation step. Water was used as a solvent for monomer **118** and the calculated sEF value is 2.11 and *E* factor is 18.1 with 84% solvent contribution (Table S1, entry 179 and 180). The hydrogenation step for **119** shows an sEF value of 0.29 and *E* factor 3.44 with a 100% atom economy (Table S1, entry 181). The *E* factor has a solvent contribution of 71%, which is clearly the reason for higher wastage value. Another work on the synthesis of *p*-coumaric acid dimer **120** was investigated using a fluorescent light with 96% yield, 100% AE, and with an *E* factor value of 0.04 due to its well-known photo-dimerization property (Table S1, entry 182).<sup>175</sup>



**Scheme 17.** Monomers and polymers synthesized from *p*-coumaric acid (detailed reaction conditions are available in Table S1, entry 169-182)

Adhesive polymers were produced from the naturally available compounds with catechol groups which shows strong adhesion properties towards metal surfaces. Caffeic acid and *p*-coumaric acid was copolymerized and modified *via* transesterification to produce these natural adhesive polymers.<sup>176</sup> In addition, hyperbranched polymers with defined structure were also synthesized by co-polycondensation of caffeic and *p*-coumaric acid using various catalysts with 75-85% yield. These polymers can find applications as environmental materials, biodegradable polymers and also in biomedical fields.<sup>177</sup> Furthermore, hyperbranched polyarylates were also prepared by

copolymerizing with caffeic acid and the resultant polymer shows liquid crystalline properties and biodegradability.<sup>178</sup> *p*-Coumaric acid-based homopolymer was also prepared by polycondensation using sodium acetate as a catalyst.<sup>168</sup> This homopolymer production process has a high yield of 90%, sEF and *E* factor value 3.17 (Table S2, entry 26). This higher value is due to the 6.2 eq of anhydride acetic acid used as a condensation agent for the polymerization. These *p*-coumaric acid-based homopolymers possess cell-adhesion properties suitable for biomedical applications.

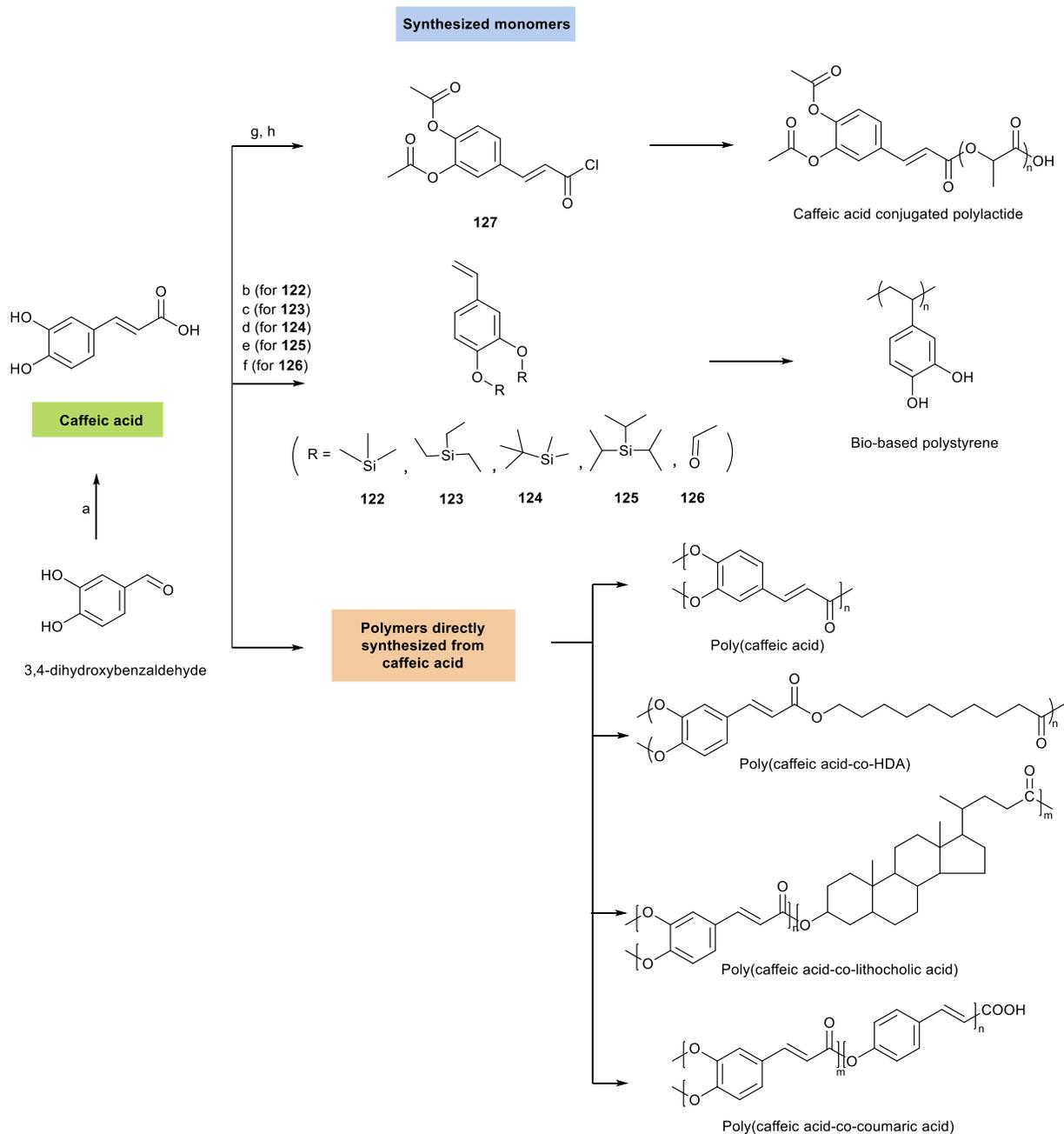
### 5.1.3. Caffeic acid

3,4-Dihydrocinnamic acid, popularly known as caffeic acid, is an aromatic compound naturally available in the plant cells and is mostly known for its antioxidant properties.<sup>179,180</sup> It is a crucial intermediate formed during the biosynthetic process of lignin.<sup>181</sup> Caffeic acid can be chemically produced from biobased aldehydes. Recently an efficient method of synthesizing caffeic acid **121** from phenolic aldehyde was developed with a 74% AE and sEF value 2.25 using pyridine- and piperidine-free Knoevenagel–Doebner condensation (Table S1, entry 183).<sup>148</sup> Several biobased polymers can be produced using caffeic acid either directly or by synthesizing intermediate monomers due to the presence of multiple reactive functional groups.

A styrene mimic monomer synthesis from caffeic acid was developed by Takeshima *et al.* via a one-pot two-step decarboxylation and protection reaction.<sup>182</sup> The resulting protected vinyl catechol derivatives were then subjected to RAFT polymerization, nitroxide-mediated radical polymerization (NMP) and anionic polymerization, and subsequently deprotected to produce poly(vinylcatechol)s, that can be used in many applications, such as adhesives, epoxy curing agent, photo-resists to name a few. Five different monomers **122**, **123**, **124**, **125** and **126** were synthesized for this study. Monomers **122** and **126** show waste values higher than the rest of the monomers. The sEF values for **122** and **126** are 2.30 and 3.21, *E* factor values are 8.50 and 11.3, yield 76% and 74%, respectively (Table S1, entries 184 and 188). In addition, monomer **126** has a lower AE value of 57%. For monomers **123**, **124** and **125**, the sEF values were in the range 1.12 to 1.37, has high yield 91 to 98% (Table S1, entries 185-187). Monomer **125** shows the lowest value of the *E* factor (3.08) among these five monomers mainly because of the lesser amount of solvent used, around 11 eq of DMF with respect to **121**, whereas for the rest of the monomers 18 eq were used. In another study, photo-reactive caffeic acid conjugated polylactide with improved thermal properties, that can find its application in biomedical fields, was synthesized following a two-step monomer (3,4-diacetoxycinnamoyl chloride **127**) synthesis procedure followed by a conjugation with poly(L-lactide).<sup>183</sup> The monomer synthesis method, however, shows process sEF value 6.45, *E* factor 11.7, with a solvent contribution of 41% (Table S1, entries 189-190). The solvents used for this study were DMF and DCM, which can also be a matter of consideration as far as green chemistry is concerned.

The synthesis of homopolymers from caffeic acid was carried out *via* polycondensation using sodium acetate as a catalyst.<sup>168</sup> The sEF and *E* factor for a single step polymerization process shows a higher value of 4.08 kg

of waste/kg of product (Table S2, entry 25). 6.2 eq of anhydride acetic acid was used here as a condensation reagent and the yield of the polymerization was 69%, which certainly contributed towards high waste generation. However, this plant-derived polymer showed the highest cell adhesion properties as compared to the homopolymers produced from other *p*-hydroxycinnamic acids and is indeed suitable for biomedical application. Monomer **121** was utilized to produce biodegradable copolyesters, which demonstrated high solubility and thermal stability, through polycondensation along with lithocolic acid in 78-91% yield.<sup>184</sup> Melt-spinnable caffeic acid homopolymer was synthesized by acetylation followed by transesterification and subjected to melt spinning to produce fine fibers. However, the mechanical strength of the fiber was on the lower side and needs to be improved to use these biomass-derived polymers into melt-spinning, the area mostly dominated by synthetic polymers.<sup>185</sup> Polycondensation of caffeic acid and castor oil-derived 10-hydroxycapric acid (HDA) provided a biodegradable and photo-crosslinkable co-polyester with a flexibility that ensured higher mobility of the macromolecular chain and higher photo-reactivity, thus increasing the mechanical strength after photo-crosslinking.<sup>186</sup>

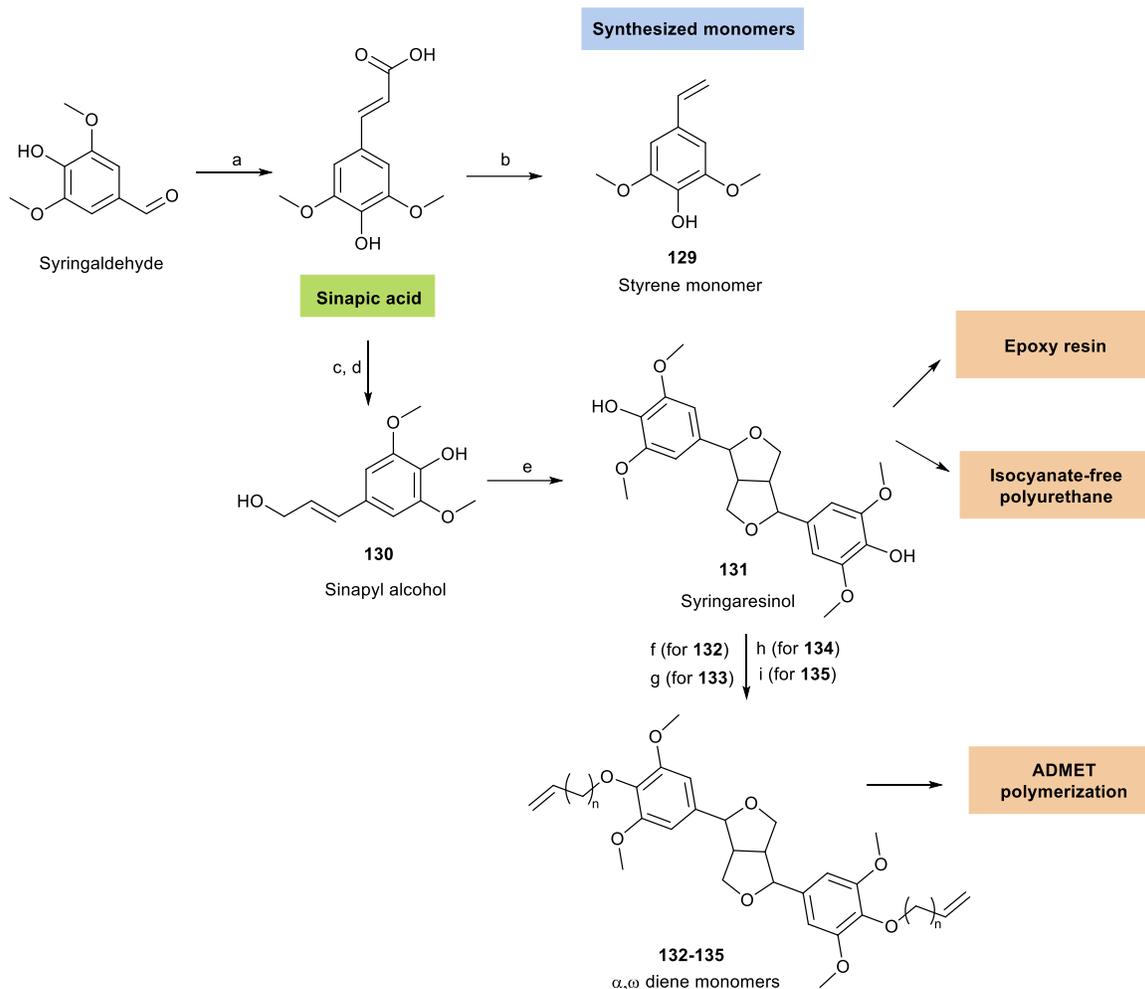


**Scheme 18.** Monomers and polymers synthesized from caffeic acid (detailed reaction conditions are available in Table S1, entry 183-190)

#### 5.1.4. Sinapic acid

Sinapic acid, also known as 3,5-dimethoxy-4-hydroxycinnamic acid, can be found in various fruits, vegetables, grains, and in oilseed crops, either in the free form or in the form of esters.<sup>187</sup> This compound can be obtained through the hydrolysis of sinapine (the choline ester of sinapic acid) contained in *Brassicaceae* species.<sup>188,189</sup> Sinapic acid is

available abundantly in nature and consists 9-10% of all phenolic acid and it can be also chemically synthesized from syringaldehyde.<sup>190</sup> Sinapic acid **128** can be efficiently produced using a proline-mediated Knoevenagel-Doebner condensation, where a non-hazardous solvent, ethanol, was used with sEF value 0.54, 78% AE and *E* factor 5.96 (Table S1, entry 191). This method avoids the use of toxic solvent, pyridine (generally used in Knoevenagel-Doebner condensation reaction) and uses ethanol instead, which can be recovered and reused also.<sup>148</sup>



**Scheme 19.** Monomers and polymers synthesized from sinapic acid (detailed reaction conditions are available in Table S1, entry 191-213)

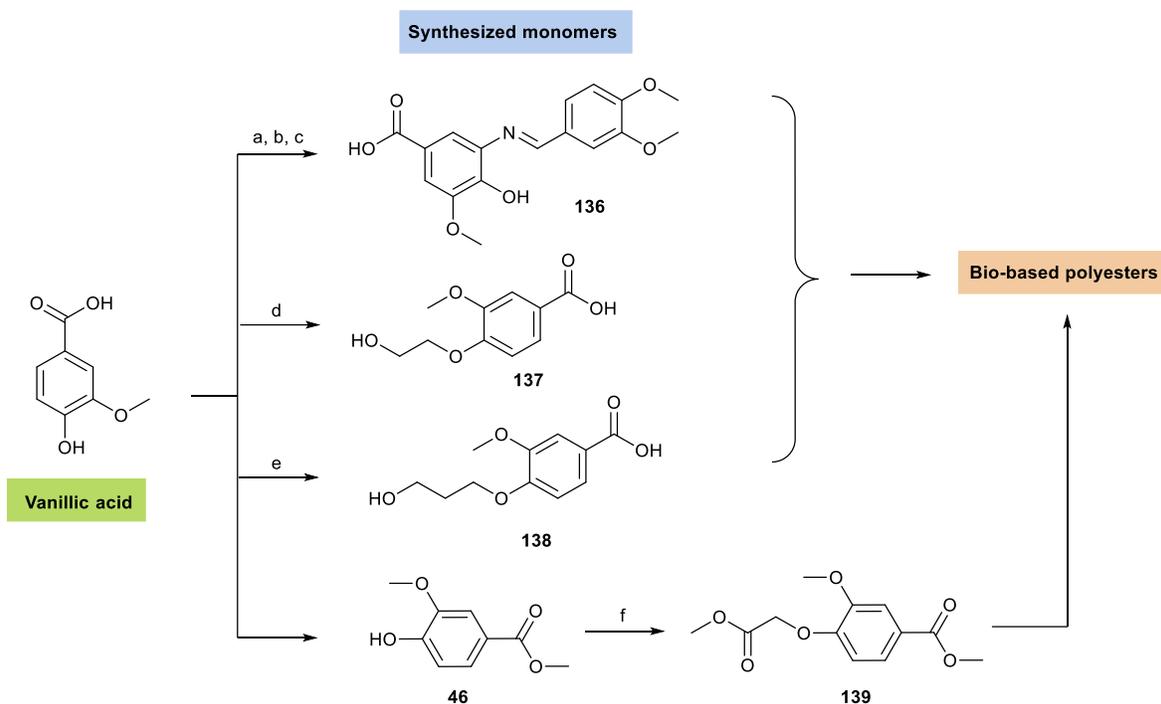
Similar to other *p*-hydroxycinnamic acids, sinapic acid also was utilized to produce functional styrene monomer **129** by decarboxylation with PEG used as a solvent.<sup>135</sup> This particular reaction shows an 80 % AE, sEF value 3.26 and *E* factor 27.1 with 85% solvent contribution (Table S1, entry 192). However, the solvent can be recovered and copper catalysts also can be reused for up to three cycles without deactivation, and hence the high *E* factor value should not be an issue while considering utilization of this method. In another study based on sinapic acid, a two-step reaction was carried out to synthesize sinapyl alcohol **130** from **128**, which was then subjected to a highly

regioselective laccase-catalyzed radical-radical dimerization in order to produce syringaresinol **131**.<sup>191</sup> Synthesizing this compound from sinapic acid thus takes three steps to complete, while it takes only a single enzymatic reaction step from sinapyl alcohol. **131** produced from sinapyl alcohol shows that the sEF value is only 0.09, while the *E* factor value is 117 with 99% solvent contribution (Table S1, entry 197) due to a large amount of buffer solvent used for the enzymatic reaction, which can be optimized in order to reduce the *E* factor value. Syringaresinol is thus a biobased compound that can be effectively used as an alternative to fossil-based BPA and has the capability of producing a number of polymers through slight structural modifications. One good example is the synthesis of  $\alpha,\omega$ -diene monomers **132**, **133**, **134**, **135** from **131** using bromo-alkenes that provide AE values 75%, 76%, 78% and 81%, sEF values 7.52, 7.03, 7.52, 6.42 and *E* factor values 13.5, 12.5, 13.1, 10.9, respectively (Table S1, entries 201, 205, 209, 213).<sup>192</sup> Almost 5 eq of inorganic salt and 15-16.5 eq of solvent were used for the allylation process, which is the reason for such higher values of green metrics. Compound **131** was also utilized to produce epoxy-amine resins using renewable diamine and the resultant resins showed thermal properties similar to that of the commercial BPA-epoxy based resins.<sup>193</sup> Furthermore, the epoxidized syringaresinol was converted to cyclic carbonate under high pressure CO<sub>2</sub> and further polymerized with different diamines to prepare NIPUs.<sup>57</sup>

## 5.2. Benzoic acid derivatives

Vanillic acid, syringic acid, and gallic acid are categorized as lignin-based benzoic acid derivatives. Vanillic acid **1** (3-methoxy-4-hydroxybenzoic acid) is the oxidized form of vanillin<sup>194</sup> and due to its bifunctional nature, it has become a building block of interest to produce biobased polymers.<sup>195,196</sup> One of the first polyester synthesis processes from this compound was investigated in the 1960s.<sup>197</sup> Since then, several types of research were carried out to access polyesters, polyamides, and epoxy resins. There are a few examples available of vanillic acid-based monomers for synthesizing polyesters, one of which is **136** that is obtained through a three-step synthetic pathway involving nitration, amination and finally condensation with veratraldehyde using acetic acid and ethanol as a solvent. The latter then gives access to biobased polyesters *via* transesterification.<sup>66</sup> Undoubtedly, this multi-step pathway produces high wastages and provides a process sEF value 10.1 and process *E* factor value of 283 with a 96% solvent contribution (Table S1, entries 214-216). However, as more attention was given to bio-based polyester synthesis, the monomers were efficiently produced by following a single or two-step reaction procedure with lower wastages. One good example is the synthesis of hydroxy-acid monomers **137** and **138**, produced *via* a one-step reaction using ethanol and water as solvents.<sup>197</sup> Monomer **137** shows 72% yield, sEF value 2.23, *E* factor value 5.76 with 52% solvent contribution, and AE value of 85% (Table S1, entry 217). Monomer **138**, however, showed only 46% yield with high sEF and *E* factor values 3.06 and 9.69, respectively with a solvent contribution of 62% (Table S1, entry 218). The higher wastage in the latter was attributed to lower yield as compared to **137**. These monomers were found suitable for polyesterification and the polymers were produced using 1 mol% of antimony trioxide as a catalyst. The polymerization process shows both sEF and *E* factor value of 0.41 for **137** and 0.78 for **138** (Table S2, entries 29-30). Another investigation of lignin-based vanillic acid along with castor oil-based 10-undecenoic acid was demonstrated

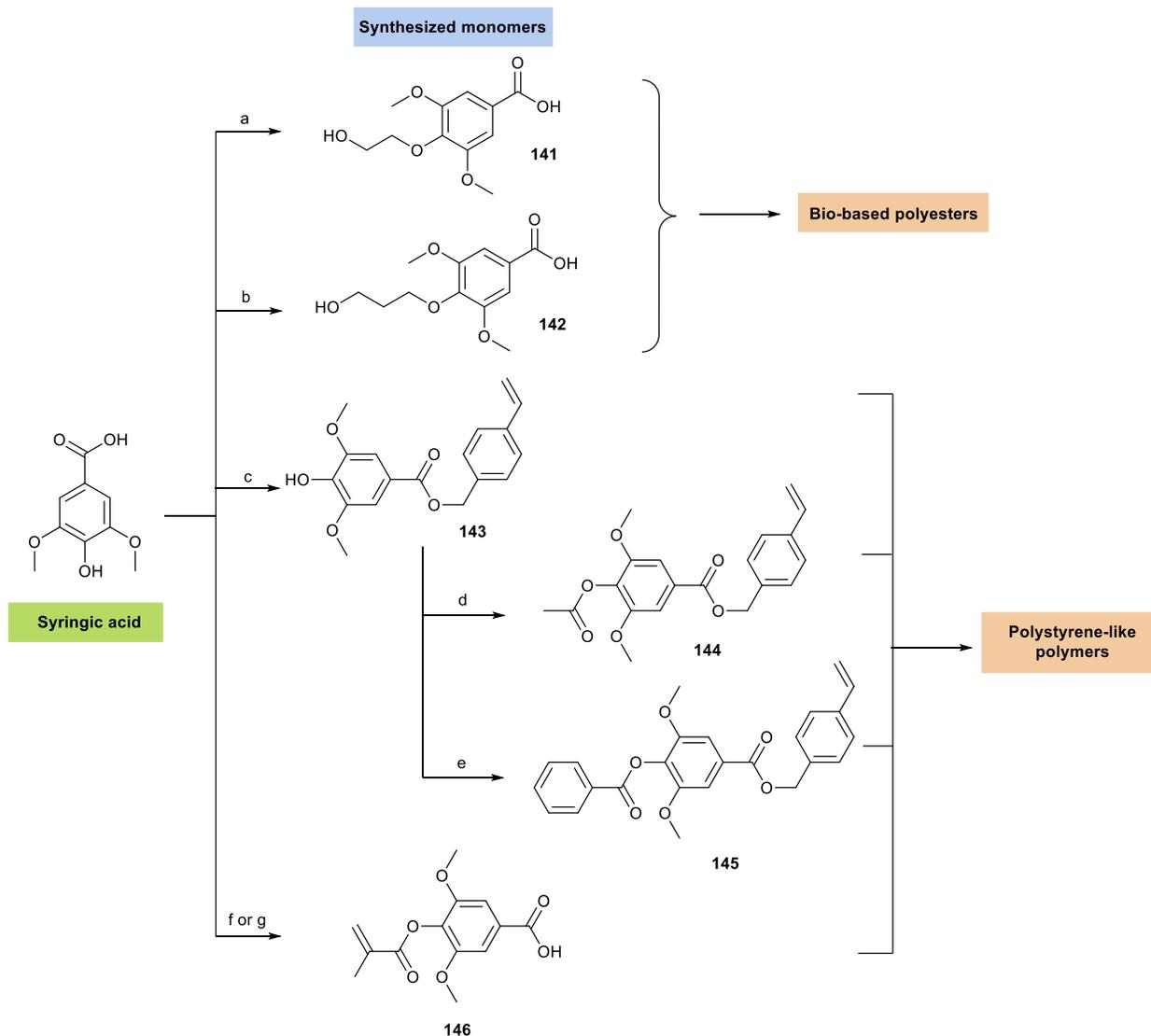
for producing aliphatic-aromatic polyesters.<sup>198</sup> The aromatic diester **139** was produced *via* Williamson etherification and the aliphatic component from 10-undecenoic acid was incorporated into the structure *via* polycondensation to provide aliphatic-aromatic polyesters. Monomer **139** was synthesized from methyl vanillate **46** by using a simple one-step process, which shows 76% yield, 87% AE and sEF value 3.42 (Table S1, entry 219). However, a high value of *E* factor values was recorded, around 44.1 with 90% solvent contribution for **139**. The use of acetonitrile in this synthesis is still considered as 'usable' as per the green chemistry solvent selection guide.<sup>163</sup>



**Scheme 20.** Monomers and polymers synthesized from vanillic acid (detailed reaction conditions are available in Table S1, entry 214-220)

Another lignin-derived benzoic acid derivative is the syringic acid, also known as 4-hydroxy-3,5-dimethoxybenzoic acid, that can be found in hardwoods, leaves of many plant species and grains.<sup>199,200</sup> Degradation of S-unit-rich lignin can result in the production of syringic acid.<sup>201</sup> This compound can also be extracted from lignin using wood-rotting fungi.<sup>202</sup> Recently, researchers have shown marked attention towards this compound and different biobased polymer, such as polyesters, polyamide, high molecular weight water-soluble polymers were produced using syringic acid. Hydroxy-acid monomers **141** and **142** were synthesized with subsequent reaction with chloroalkanols and then subjected to polyesterification.<sup>197</sup> The yields for the monomers **141** and **142** were 41% and 52%, respectively, AE values are 87% and 88%, sEF values 3.44 and 2.10 and the *E* factor values are very high 24.9 and 14.0 with 83% and 79% water contribution, respectively (Table S1, entries 221-222). The higher wastages for these monomer syntheses were largely due to the low yield and high solvent usage. The polymerization process, however, shows very low wastage with sEF and *E* factor values for the polymerization of **141** and **142** being 0.42 and

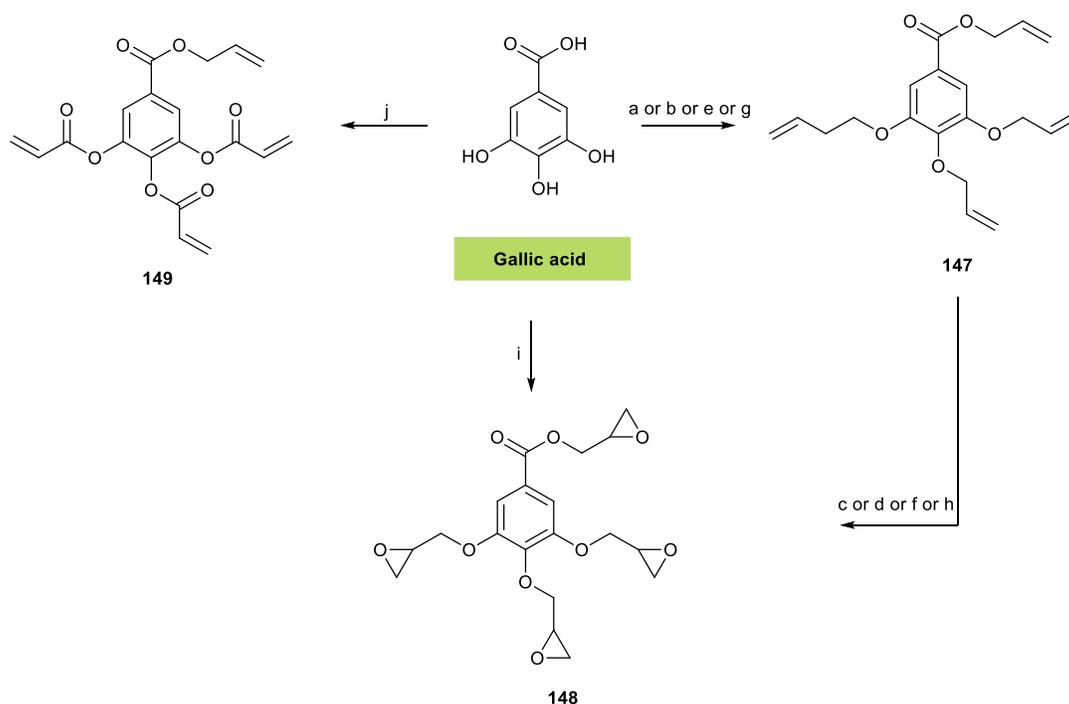
0.23, respectively (Table S2, entries 31-32). Synthesis of polystyrene-like polymers were also explored using syringic acid by functionalization, protection and radical polymerization.<sup>201</sup> Monomer **143** was produced from syringic acid functionalized with vinyl benzyl chloride in DMF, which shows 90% AE, sEF value 18.5 and 52% yield (Table S1, entry 223). Additionally, this monomer was less effective and the polymerization terminated quickly after initiation step, most probably because of the radical capture by the phenol groups. To overcome this issue, two new monomers (**144** and **145**) were synthesized from monomer **143** with benzoate and acetate protection, respectively. The protection step provides sEF values 0.24 and 0.28 and *E* factor value 9.05 and 8.53 with 88% and 87% solvent contribution for **144** and **145**, respectively (Table S1, entries 225 and 227). Furthermore, monomer **146** was synthesized from syringic acid through the concomitant functionalization and protection step using methacryloyl chloride or methacrylic anhydride. The sEF values are found to be 2.14 and 1.38, *E* factor values 7.40 and 6.55, respectively (Table S1, entries 228 and 229). Lower yield and higher amount of solvent were behind this high *E* factor values. It is interesting to note here, due to the presence of free carboxyl group in monomer **146**, it is polymerizable in water and produces a water-soluble polymer.



**Scheme 21.** Monomers and polymers synthesized from syringic acid (detailed reaction conditions are available in Table S1, entry 221-229)

3,4,5- Trihydroxybenzoic acid, also known as gallic acid, is another benzoic acid derivative that can be derived from lignin.<sup>203</sup> Gallic acid can be found freely available or in the form of esters in tea leaves and also in the mature seeds and roots of Norway spruce.<sup>204,205</sup> Effluent from paper and pulp industry treated with *Bacillus* sp. of bacteria shows the presence of gallic acid in the treated samples.<sup>206</sup> Although little information is available about the direct extraction method of gallic acid from lignin, syringic acid derived from lignin can be demethylated by sulfate or nitrate-reducing agents to produce gallic acid.<sup>207</sup> It shows antibacterial activity against different bacteria as well as excellent antioxidant activity.<sup>205,204</sup> Mostly, gallic acid was explored to produce epoxy resins owing to its large number of phenolic groups. Several single and two-step reactions were reported to produce epoxy precursors *via* two-step process (allylation and epoxidation) or by direct one-step epoxidation method. One example to access

allylated gallic acid **147** consists in the use of allyl bromide and DMF that shows a high yield of 84% and sEF value 3.17 (Table S1, entry 230).<sup>208</sup> However, due to the use of a large amount solvent, the *E* factor value is increased to 22.4 where 82% is the solvent contribution. Gallic acid can be epoxidized by different methods to afford **148**.<sup>209,210</sup> Synthesis of **148** from **147** with *m*-chloroperoxybenzoic acid (*m*-CPBA) provides 38% AE and 60-62% yield and used DCM as solvent (Table S1, entries 232 and 236). Another direct epoxidation method of synthesizing **148** using epichlorohydrin in the presence of phase transfer catalyst was studied by Patil *et al.* which shows 73% AE (Table S1, entry 239).<sup>211</sup> Nevertheless, most of the allylation and epoxidation reactions use either DMF or DCM as solvents that do not fall under the category of green solvents. In effort to replace the solvent to a green one, monomer **147** was synthesized in presence of acetone with a high yield of 90%.<sup>212</sup> The sEF value for this reaction is 7.40 and *E* factor value is 14.9 (Table S1, entry 237). The higher wastage is due to the use of 10 eq of inorganic salt and 38 eq of acetone. If the sEF and *E* factor values are reduced by dropping the amount of solvent and by optimizing the amount of inorganic salt, this reaction has the potential to be a green method for the synthesis of compound **147**. A crosslinking agent **149** was also developed for UV-cured coatings, where acetone was used as a solvent. However, its AE is 66% and also the reaction has high sEF and *E* factor values of 3.12 and 43.9 respectively (Table S1, entry 240).<sup>213</sup> In this case also, the wastage is mainly associated with the high amount of inorganic salt and the solvent (91% is the solvent contribution).



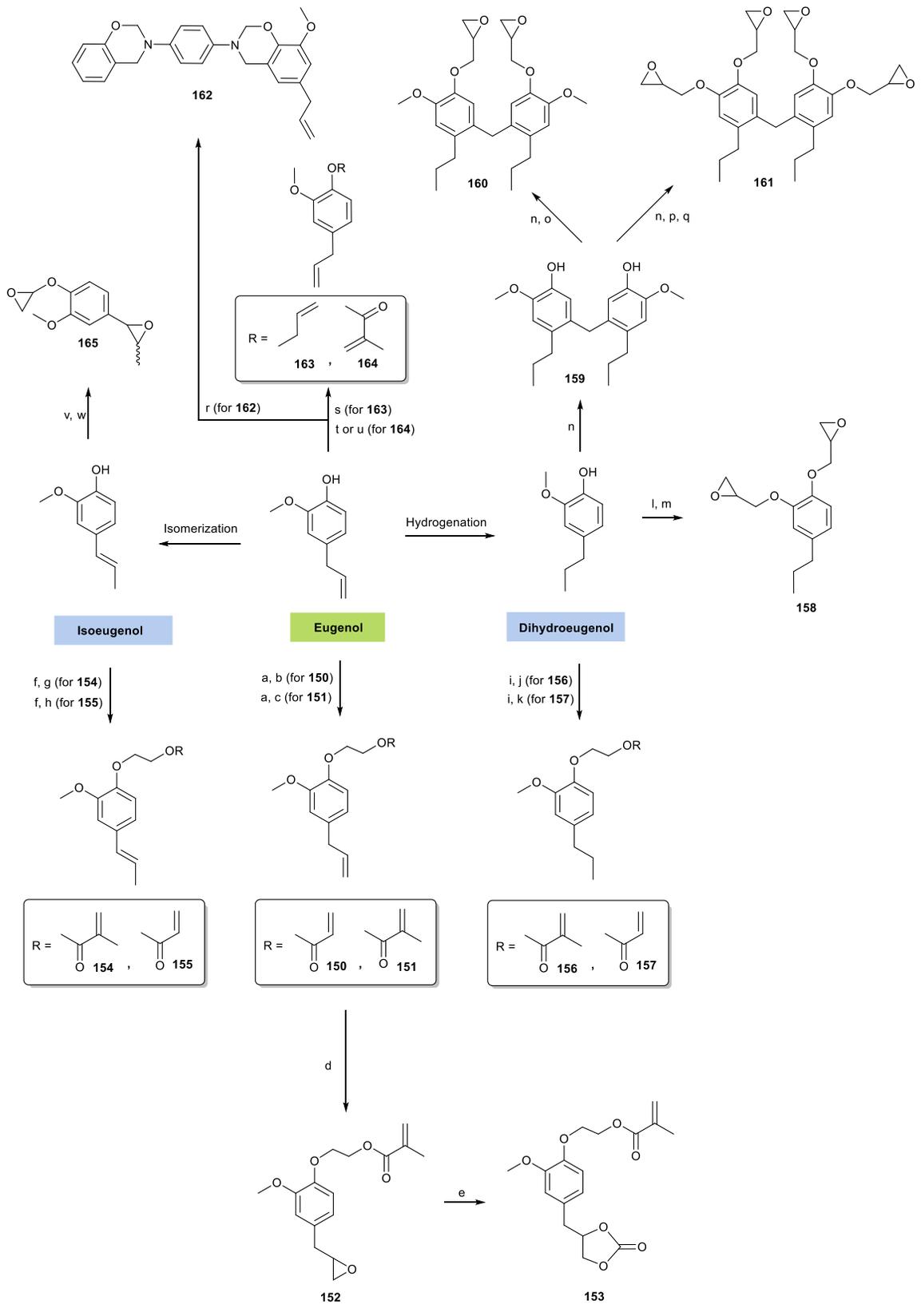
**Scheme 22.** Monomers synthesized from gallic acid (detailed reaction conditions are available in Table S1, entry 230-240)

## 6. EUGENOL: LIGNIN-DERIVED COMPOUND WITH MEDICINAL VALUE

4-Allyl-2-methoxyphenol, which is commonly known as eugenol, can be obtained from lignin by thermo-chemical degradation or fast pyrolysis method.<sup>214</sup> This aromatic compound possesses several crucial functional groups, such as hydroxy, methoxy, and allyl group along with the phenyl component.<sup>215</sup> It shows different key activities, which makes it popular in medicinal applications, for example, it shows anti-inflammatory actions and can be used to produce local anesthesia for the dental applications.<sup>216</sup> Apart from its medicinal applications, it can be used to produce different biopolymers, such as epoxy resins, benzoxazines, and other thermally stable polymers due to the presence of multiple functional groups for reaction.

Eugenol, as well as its derivatives isoeugenol and dihydroeugenol, the isomerized and hydrogenated form of eugenol respectively, are fascinating compounds and can be easily modified to produce biobased polymers. In one such approach, acrylate and methacrylate derivatives of these three compounds were produced and further epoxidized or carbonated to synthesize polymeric materials.<sup>217,218</sup> Acrylate **150** and methacrylate **151** of eugenol were synthesized in a two-step process involving the addition of an ethyl spacer on the phenol to move the hydroxyl group apart and to increase its accessibility, and the introduction of the acrylate or methacrylate group. The resultant process sEF values for **150** and **151** are 2.06 and 2.37 and process *E* factor values are 17.6 and 4.54, respectively (Table S1, entries 241-244). The solvent (DCM) contribution to process *E* factor of **150** is 84% whereas for **151**, it is 39%, and this drastic difference is also evident in the *E* factor values. **151** was then taken forward to synthesize **152** and **153**, epoxidized and carbonate form of **151**, respectively. Synthesis of **153** from eugenol proceeds *via* four steps and provides sEF value of 8.29 and *E* factor value of 105 with 91% solvent contribution (Table S1, entries 245-248). This large wastage value is definitely due to the four reaction steps and the huge amount of solvent used. Similarly, methacrylates **154** and acrylates **155** were also produced from isoeugenol *via* similar two-step synthesis process, which provides process sEF values 2.59 and 3.17 and process *E* factor values 5.44 and 24.3 with solvent contribution 44% and 84%, respectively (Table S1, entries 249-252). Furthermore, monomers **156** and **157**, methacrylate and acrylate of dihydroeugenol, were also synthesized in a similar manner, which offers process sEF values 1.79 and 1.54 and process *E* factor values 4.05 and 14.5 (in the latter case, 32 eq of dichloromethane was used vs. 6.5 eq in the former) (Table S1, entries 253-256). In another work, epoxy precursor **158** was produced from eugenol *via* two-step synthesis process, demethylation followed by epoxidation.<sup>219</sup> The demethylation step has a low atom economy 62% and the epoxidation with epichlorohydrin shows an AE value of 78% (Table S1, entries 257-258). The sEF and *E* factor for the demethylation is 2.04 and 5.96 respectively and a 56% of the solvent contribution, which is water in this case. Dihydroeugenol dimer **159** can be produced with 83% yield, 78% AE, sEF value 2.80 and *E* factor 9.14 with water as solvent (Table S1, entries 259). This dimer can be subjected to epoxidation to produce **160** and **161**.<sup>220</sup> Epoxidized dimer **160** was produced from **159** with 86% AE (Table S1, entries 260). For synthesizing **161** from **159**, a two-step method was followed, i.e., demethylation and epoxidation, which offer AE values 62% and 79% respectively (Table S1, entries 262 and 263). Unfortunately, the yield of the epoxidation step was not provided; thus, the *E* factor was

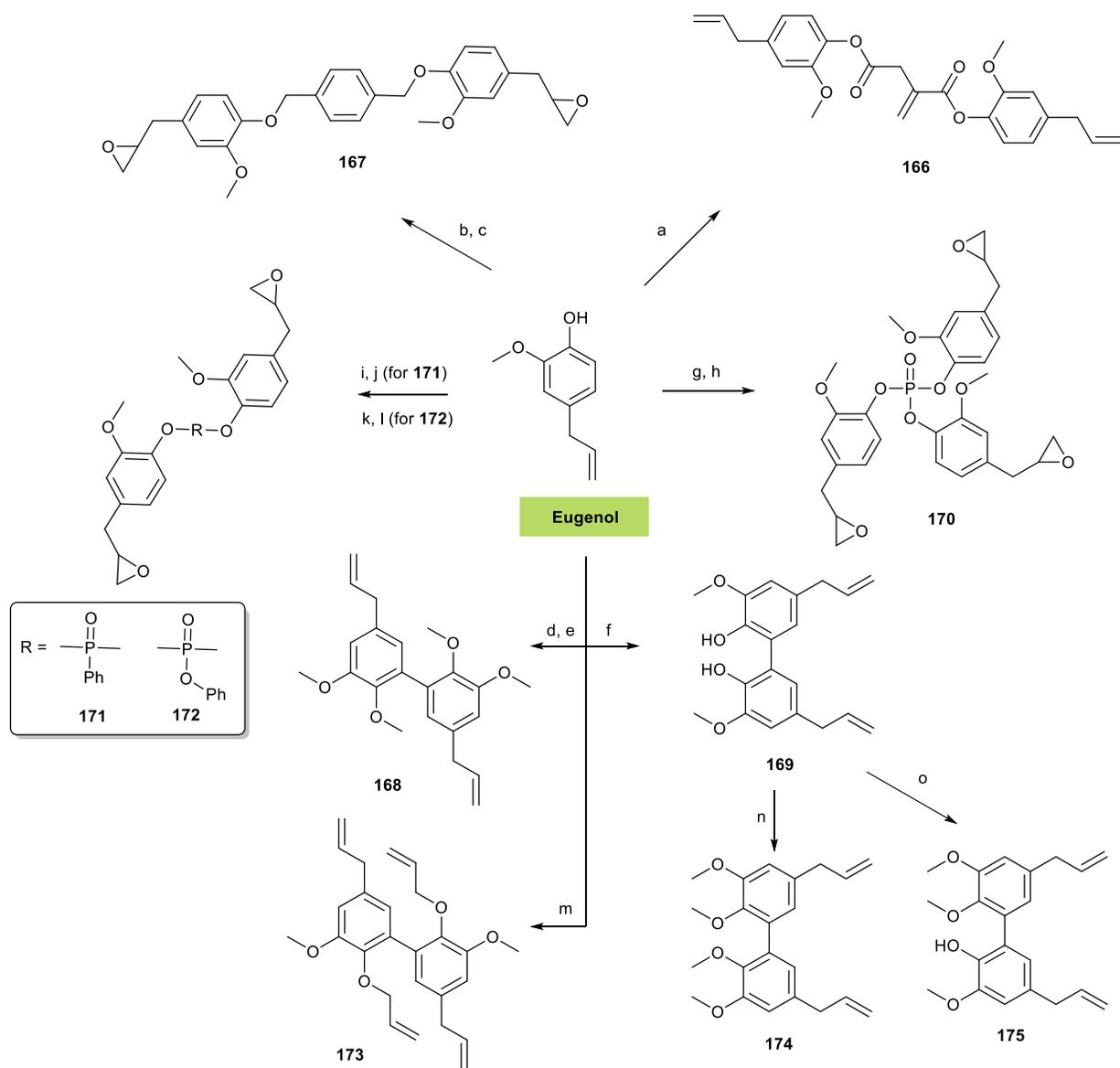
not calculated for these monomers. Hybrid monomer **162** was synthesized using phenol and eugenol to have both moieties in the monomer to facilitate effective polymerization and was used to produce benzoxazine resins.<sup>221</sup> This solvent-free reaction shows an sEF and *E* factor value 0.29, 93% yield and 97% AE. Although this reaction can be termed as green by looking at these values, the reagents used in this reaction certainly cannot be considered as safe (Table S1, entry 264). Thermoset resins were prepared by using *o*-allyl-eugenol **163**, which shows sEF value 0.74 and *E* factor 3.55 with 62% solvent contribution (Table S1, entry 265).<sup>222</sup> Dimethyl sulfoxide (DMSO) was used as a solvent, which is termed as 'usable' in the solvent selection guide and the reaction also proceeds in high yield (96%). Another methacrylate monomer of eugenol **164** was produced from eugenol in a solvent-free environment, which provides both sEF and *E* factor values in the range of 0.61-0.77 (Table S1, entry 266 and 267).<sup>79,223</sup> This monomer was utilized to produce thermoset resin and vinyl ester resin in two separate studies. Epoxy thermoset resins were produced from isoeugenol using two distinct steps of epoxidation followed by curing with several curing agents.<sup>224</sup> The epoxidized monomer **165** offers a process sEF value 7.11 and process *E* factor 82.9 (90% of which is contributed by the solvent) (Table S1, entries 268-269). While most of the solvent used here is water, 60 eq of DCM was also used in the second step, which is not acceptable in terms of green chemistry.



**Scheme 23.** Strategic compounds synthesized from eugenol and its derivatives (detailed reaction conditions are available in Table S1, entry 241-269)

A sustainable synthesis method was designed to produce biodegradable thermoset *via* thiol-ene click chemistry from eugenol.<sup>225</sup> The synthesis of eugenol dimer **166** took place in a solvent-free and catalyst-free environment, which is indeed reflected by the sEF and *E* factor value of 0.47 (Table S1, entry 270). An epoxy precursor **167** was also synthesized from eugenol through a two-step process, followed by curing in the presence of diamine curing agent to produce the epoxy resins.<sup>226</sup> The synthesis of **167** shows sEF value of 7.43 and *E* factor 54.4 (Table S1, entries 271-272). The epoxidation step has a low yield (ca.44%), which contributed to the high wastage and also 85% of the waste value was contributed by the solvent (DCM and DMSO). Another dimer **168** was produced from eugenol *via* a two-step reaction, i.e. enzymatic dimerization and subsequent allylation, led to the production of  $\alpha,\omega$ -dienes, which are then subjected to ADMET polymerization.<sup>227</sup> The synthesis of **168** provides high *E* factor value 314, 96% of which is the solvent contribution (Table S1, entries 273-274). A huge amount of buffer solvent was used in the enzymatic synthesis step, which apparently increased the waste value drastically. A one-step synthesis of dehydrodieugenol **169** was achieved under mild condition and using water and acetone as solvents.<sup>228</sup> The reaction proceeds at room temperature overnight and has an AE value 99%. However, the sEF and *E* factor values are high 7.54 and 55.2 with 85% solvent contribution (Table S1, entry 275).

Interesting fire-retardant epoxy resins were produced by using phosphorylated bis and tris-eugenol **170**, **171** and **172**.<sup>229,230</sup> The sEF values associated with these syntheses are 1.85, 10.1 and 5.77 and *E* factor values are 32.2, 108 and 82.4 with 91%, 90% and 92% solvent contribution, respectively (Table S1, entries 276-281). The higher wastage is due to the number of steps of the reaction and the amount of solvent used. In another method, an allylated eugenol dimer **173** was produced using 96% of the DMSO solvent which apparently provided a very high *E* factor (54.6) for this method (Table S1, entry 282).<sup>222</sup> A study on the development of new drugs was conducted using eugenol, where **169** was synthesized by oxidative coupling reaction and further transformed into dimers **174** and **175** through partial or per-methylation using methyl iodide.<sup>231</sup> The methylation reaction was carried out in DMF, and the *E* factor values obtained are 92.3 and 27.3 where 81% of these values were contributed by the amount of solvent used (Table S1, entries 283-284). Looking at these available synthetic methods, it is evident that there are plenty of scopes available for improvement via process optimization, solvent system alteration or reduction in the solvent amounts, to achieve greener pathways for most of the reactions in order to truly achieve sustainable green synthesis procedures.



**Scheme 24.** Dimers and trimers from eugenol (detailed reaction conditions are available in Table S1, entry 270-284)

## 7. CONCLUSION

Lignin has been extensively explored as a renewable resource to produce biobased value-added chemicals and polymers. However, despite having fruitful results in terms of properties, the usage of carbon from renewable resources should not be the only criterion in assessing alternatives to fossil-derived materials. Indeed, the assessment of synthesis methods by

calculating the green metrics helps in designing greener approaches for more sustainable future. We have strategically analyzed 175 monomer synthesis methods and 32 polymerization procedures through 24 reaction schemes by following the 12 principles of green chemistry. In addition, the sustainability factors were numerically quantified using simple *E* factor (sEF), *E* factor, atom economy and solvent contribution calculations.

Our analysis provides important insight regarding the procedures available for the conversion of lignin-based compounds into different value materials in terms of green chemistry. For example, the synthesis of styrene monomer **77** was achieved from cinnamic acids in PEG as a green solvent that can even be recovered and reused. Moreover, the catalyst can also be reused many times without deactivation. In addition, no harmful chemicals were used. Another synthesis method is the production of *p*-hydrocinnamic acids from the corresponding aldehydes at the lab scale. Notably, toxic solvent pyridine used in Knoevenagel-doebner condensation reaction was replaced by ethanol, that can also be recovered easily using vacuum distillation and reused back again. A cinnamate ester of epoxidized soybean oil **80** was synthesized with 100% atom economy and *E* factor value 0.58 through a one-step procedure. A dimer of eugenol **166** was synthesized by a single step catalyst- and solvent-free reaction method, which provides *E* factor value of 0.47 and 85% atom economy.

Our analysis portrays that applying the green chemistry tools is very simple and yet effective to highlight the sustainability of a process and further improvements can be taken care accordingly. Usage of excess solvents or reagents, multi-step reactions, low atom utilization, high temperature and time-consuming synthetic process have undeniable effects on the sustainability.

Apparently, many available potential processes can be considered for industrial scale application. However, to the best of our knowledge, we have found only one study on biobased bisphenols **82**, **85**, **88** and **91**, where the reaction conditions were actually optimized for pilot scale production. Certainly, the *E* factor values of an industrial scale process may largely differ from those performed in the lab scale. Nonetheless, researchers can consider optimizing the conditions by using minimal quantities of solvents and reagents, that can be improved further in

the pilot scale. Additional solvent recovery methods can be implemented depending on the type of solvents and can be reused back in the process. This can reduce the impact of high  $E$  factor on the environment as well as the cost of the process. On the other hand, recovery of reagents is a difficult task and can be impossible in some cases. Hence, proper optimization of the reagent quantities needs to be carried in the lab scale; large excess could lead to a socio-economic challenge for industrial scale production.

Although many of the reaction methods in this review show relatively high  $E$  factor values, the decision for sustainable development cannot be taken merely looking at these numbers. A thoughtful analysis for each factor contributing to the generated waste needs to be considered. Indeed, we have noticed that the reagent quantity and the amount of solvent used were not always optimized in the lab scale and for most of the cases, these are the reasons for higher wastage values. On the other hand, if one process has low wastage, but has high energy consumption, this can also affect the socio-economic development process. Generally, the time and temperature for any reaction process are optimized in the lab scale and high energy, time-consuming or/and costly processes have less opportunity for further improvement in pilot or industrial scale.

Due to the increasing awareness of the green chemical synthesis methods, this study could be a major research foundation in the field of biomass-derived monomers and polymers. The calculated green metrics and the sustainable overview provided in this work will conclusively help future researchers to develop and design more sustainable and green synthesis procedures.

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