Safe-and-Sustainable-by-Design Approach to Non-Toxic Bisphenol Polymers

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Abstract: The majority of contemporary chemical processes rely on non-renewable resources and reagents associated with negative impact on environment and human health. For this reason, the Safe-and-Sustainable-by-Design (SSbD) framework was launched by the European Commission to guide the innovation process towards green and safe chemical products. In this work, we demonstrate how SSbD guided a multidisciplinary study for facile identification of non-toxic bisphenol A (BPA) analogues suitable for incorporation into high-performance polymeric materials. Toxicological evaluation of a library of bisphenols with an *in silico* model identified promising candidates that were synthesized from renewable lignin-sourced feedstocks using benign catalytic routes. Subsequently, *in vitro* evaluation identified an optimal BPA analogue, that was successfully incorporated into a polyester with attractive properties for future consumer products. As such, the work showcases how the combination of synthetic chemistry, toxicology, and computational modelling enables an effective workflow towards renewable and inherently safe chemicals.

Introduction

Chemical synthesis of both bulk and fine chemicals is indispensable to the functioning of modern society. The associated industries are among the major contributors to the European Union's economy, with a workforce of more than 3 million people and annual sales reaching €760 billion (2022).[1] However, the majority of contemporary industrial chemical processes rely on non-renewable energy and raw materials associated with negative impact on human health and environment, leading to detrimental consequences. Additionally, the annual costs associated with the use of hazardous chemicals in the EU are counted in billions of euros.[2] To address these issues, the European Commission launched the Safe-and-Sustainable-by-Design (SSbD) framework in 2022.[3] This voluntary framework is intended to guide the innovation process in academia and chemical industry towards green production practices, which minimize the use of substances with adverse effects on health, climate, and environment. Toxicological studies constitute a fundamental part of SSbD by evaluating potential adverse effects of chemicals and materials throughout their lifecycle. By integrating toxicological assessments early in the design process, it is possible to identify and mitigate hazards, thereby enabling the development of safer and more sustainable products. However, such assessments traditionally include time-consuming and labor-intensive hazard screening of numerous compounds. Therefore, shifting the workflow from reliance on morphological endpoints in animal testing to a mechanism-driven approach is highly attractive, including incorporation of computational modelling as well as molecular, human, and high-throughput *in vitro* data.[4] At the stage of synthetic method development, the 12 principles of Green Chemistry can effectively guide the workflow towards sustainable processes.[5] These principles include the use of renewable feedstocks together with safe and environmentally-benign reagents and solvents in chemical processes that minimize formation of waste and by-products, ultimately leading to production of inherently safe products without compromising their consumer properties. Employing catalytic processes is a key in this endeavor, as it enables more atom-efficient synthesis by using a continuously regenerated mediator, which serves as a substitute for stoichiometric reagents and minimizes formation of chemical waste. Nevertheless, many catalytic transformations suffer from catalyst deactivation or degradation, and further development of robust and recyclable catalysts remains to be of great interest.

Bisphenols represent a prominent class of chemical compounds used in production of polymeric materials with excellent thermal, mechanical, and optical properties.[6] Bisphenol A (BPA) is the most widely-used member of this class of compounds, and is currently produced on multi-million ton scale per year.[7] BPA is used in manufacturing of materials for consumer products, such as packaging in food industry and epoxy resins in construction and furniture industries.[8] It has been known for a long time that BPA can activate estrogen receptors (ER), mimicking the biological activity of endogenous estrogens, such as 17β-estradiol (E2),[9] and a number of studies have linked BPA to adverse effects on both human health and the environment.[7,10] The use of BPA in food contact materials (FCM) is therefore highly regulated, with a complete ban for use in nursing bottles since 2011 in the EU. The adverse effects of

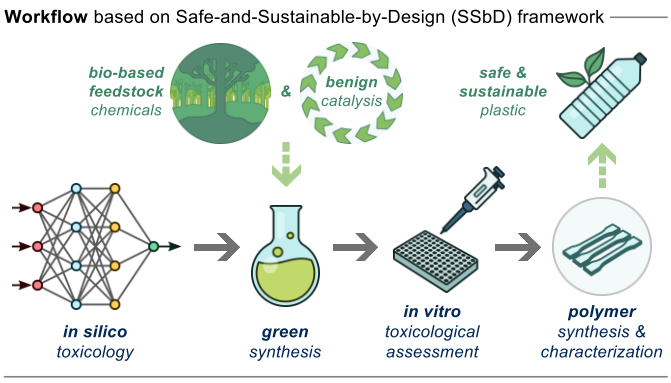

Figure 3. Safe-and-Sustainable-by-Design (SSbD) workflow towards non-toxic bisphenol polymers.

BPA have initiated a wide quest for the development of benign alternatives.[11] Despite extensive efforts, the majority of the proposed BPA substitutes display similar endocrine disruptive effects[12] with only a few exceptions.[13] Notably, introduction of methoxy groups onto the aryl backbone of BPA analogues was recently shown to significantly reduce the adverse exposure effects, while maintaining applicability of such compounds for the production of high-performance polymeric materials.[14] Another advantage of this class of compounds stems from the high abundance of methoxylated phenols in lignin — a widely available side-stream product from the pulp and paper industries, generated on multi-million ton scale per year.[15] Renewable phenolic compounds, such as guaiacol and syringol, can be derived from lignin, making them the ideal candidates for selection of safe and sustainable BPA analogs.[16]

Herein, we showcase a Safe-and-Sustainable-by-Design approach for the development of non-toxic bisphenol-based polymers. This multidisciplinary work demonstrates how *in silico* assessment can reliably predict toxicological profiles of the envisioned bio-based monomers, thereby minimizing the synthetic efforts towards assembling compound libraries for *in vitro* toxicological assessments. The *in vitro* toxicological studies are then used as a primary guide for selection of suitable monomers to yield sustainable polymeric materials with suitable consumer properties, minimized hazards during production and environmental impact.

Results and discussion

Guided by the SSbD principles, we implemented the following workflow towards non-toxic bisphenol-based polymers (Figure 1): (1) Assessment of toxicological properties for a library of bisphenol candidates with an *in silico* model. (2) Catalytic synthesis of the most attractive candidates, guided by the Green Chemistry principles. (3) Assessment of toxicological properties of the synthesized bisphenols with *in vitro* assays. (4) Large-scale synthesis of the prime bisphenol candidate, its incorporation into a polyester chain, and assessment of the material properties. Additionally, the corresponding BPA-derived polyester was synthesized for comparison.

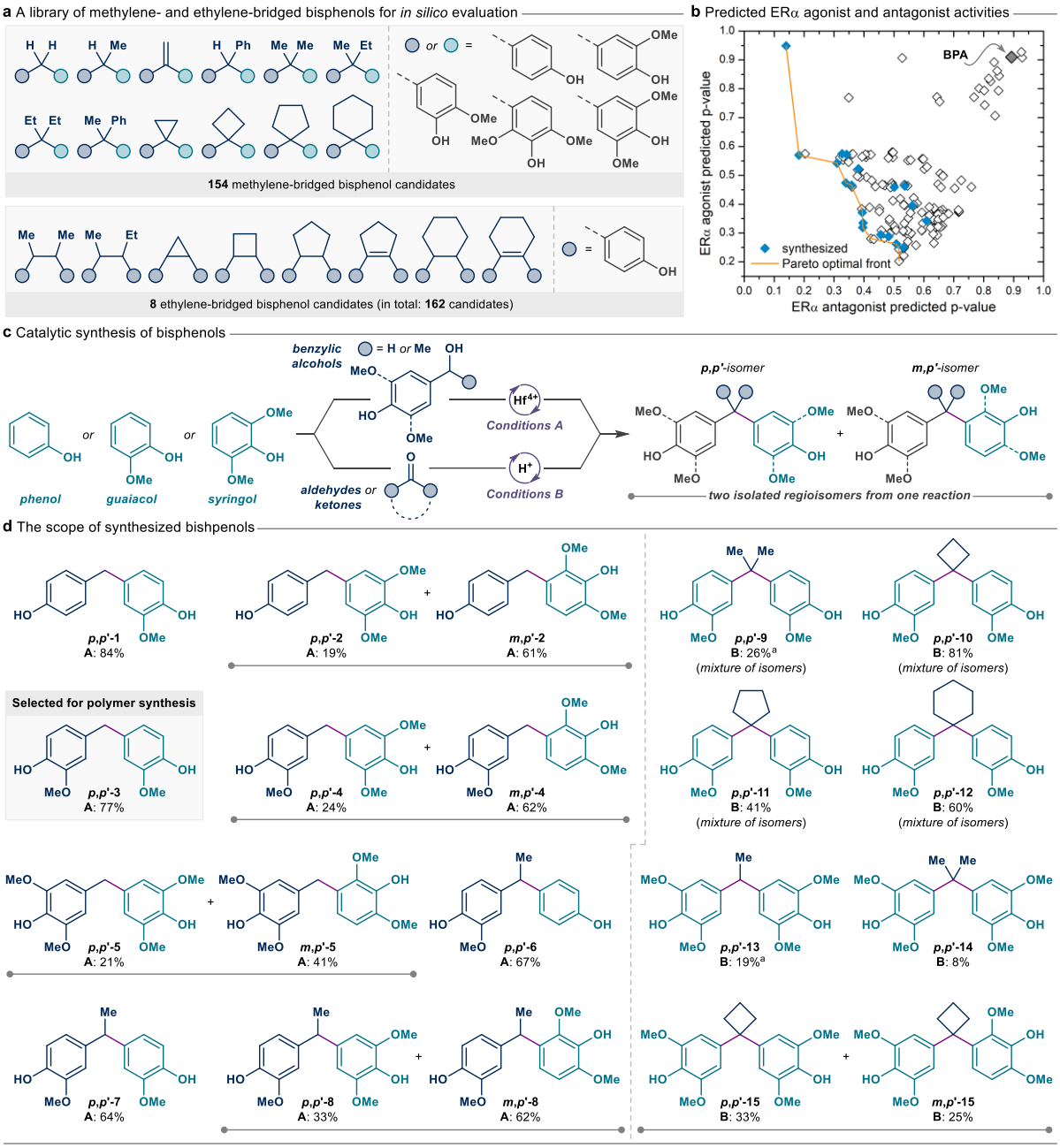

Figure 2. Assembling a library of bisphenol candidates. **a**, A general overview of the bisphenol candidate structures for *in silico* evaluation. **b**, Results of the *in silico* evaluation as conformal prediction p-values for ERα agonist and antagonist activities. **c**, The scope of synthesized bisphenol candidates for *in vitro* evaluation. **Conditions A:** benzylic alcohol (1 equiv.), phenol (16 equiv.), $Hf(OTf)_4$ (16 mol%), room temperature, 0.5–2 h, air. **Conditions B:** ketone or aldehyde (1 equiv.), phenol (4 equiv.), 3-mercaptopropionic acid (11 mol%), AcOH (5.2 equiv.), HCl ($37\%_{(aq.)}$, 24.5 equiv.), room temperature, 24 h, air. [a] modified conditions B (see the ESI for details)

Inspired by previous studies that indicated that electron-rich bisphenols display low endocrine-disrupting activity,[14] we aimed to systematically assess a library of methoxylated bisphenols, which could be potentially produced from renewable sources. An *in silico* model trained on PubChem ER-alpha (ERα) agonist and antagonist assay data was employed for evaluation of a

library of 162 bisphenol candidates (Figure 2a, see the ESI for details). As a result, the Conformal Prediction p-values for ERα agonist and antagonist activities for each of the bisphenol candidates were assessed (Figure 2b), and synthetically-accessible bisphenols with the lowest activity (on or close to the Pareto optimal front) were selected for further evaluation.

The selected bisphenol candidates based on phenol, guaiacol, and syringol were synthesized using Lewis or Brønsted acid catalysis (Figure 2c). For accessing bisphenols with up to one carbon substituent on the bridging methylene carbon, we adapted a procedure from our previous work on deoxygenative functionalization of benzylic alcohols.[17] In this catalytic approach, Friedel-Crafts-type alkylation of benzylic alcohols is catalyzed by moisture-tolerant zirconium- or hafnium-based metal salts under close to ambient conditions. Optimization of the reaction conditions for the synthesis of targeted bisphenol candidates included selection of the optimal catalyst, transition to 2-methyltetrahydrofuran (2-MeTHF) as a renewable solvent, and optimization of the catalyst and reactant concentrations for efficient and selective formation of the desired products. The bisphenols with up to two substituents on the bridging methylene carbon were synthesized with a more conventional Brønsted acid-catalyzed approach. Both protocols provided the expected products in reasonable yields, while several of the bisphenols were formed as a mixture of *p,p*'/*m,p*'-regioisomers (Figure 2d). The latter were separated as individual compounds by column chromatography prior to the *in vitro* toxicological assays, unless otherwise noted.

The endocrine-disrupting activity of the synthesized bisphenols was assessed with two *in vitro* assays employing the MCF-7 and VM7LucE2 human mammary adenocarcinoma cell lines, expressing both human ER forms, ERα and ERβ (Figures 3a and 3b). The MCF-7 proliferation assay gauges the ability of evaluated bisphenols to mimic the activity of native 17β-estradiol (E2) in stimulating cell proliferation, while VM7LucE2 assay evaluates the affinity of bisphenols to the estrogen receptors relative to E2. In the first of the assays, the MCF-7 cells were treated with E2, BPA or the targeted bisphenols for 72 h at the concentrations covering the median bisphenols exposure levels in the population (10^{-12} to 10^{-4} M), and the estrogenic activities were determined as half-maximal effective concentration (EC50) for each of the evaluated compounds (Figure S3). Additionally, a qualitative assessment of the influence of the tested bisphenols on cells proliferation and viability was used to visualize the endocrine-disrupting activity at each concentration (Figure 3a). Six of the evaluated bisphenols had minimal effect on cell proliferation (***p,p'*-3**, ***p,p'*/*m,p'*-4**, ***p,p'*/*m,p'*-5**, and ***p,p'*-14**), while the others displayed EC50 values that were either higher or on par with BPA, that is promoting significant estrogen-driven cell proliferation. Subsequently, MCF7-derived VM7Luc4E2 cells, stably transfected with a human ER-responsive luciferase reporter gene, were used to evaluate binding and activation of ERα and ERβ by the bisphenol candidates. The estrogenic activity of bisphenols was calculated as the relative maximum %E2 (%RME2, a measure of response amplitude), *i.e.*, the relative luminescence observed with the tested compound at a specific concentration relative to the maximum luminescence observed with E2 at the same concentration.[18] According to the OECD test guideline No. 455, the %RME2 values less than 20% were considered insignificant.[19] In this assay, BPA demonstrated a detectable response at

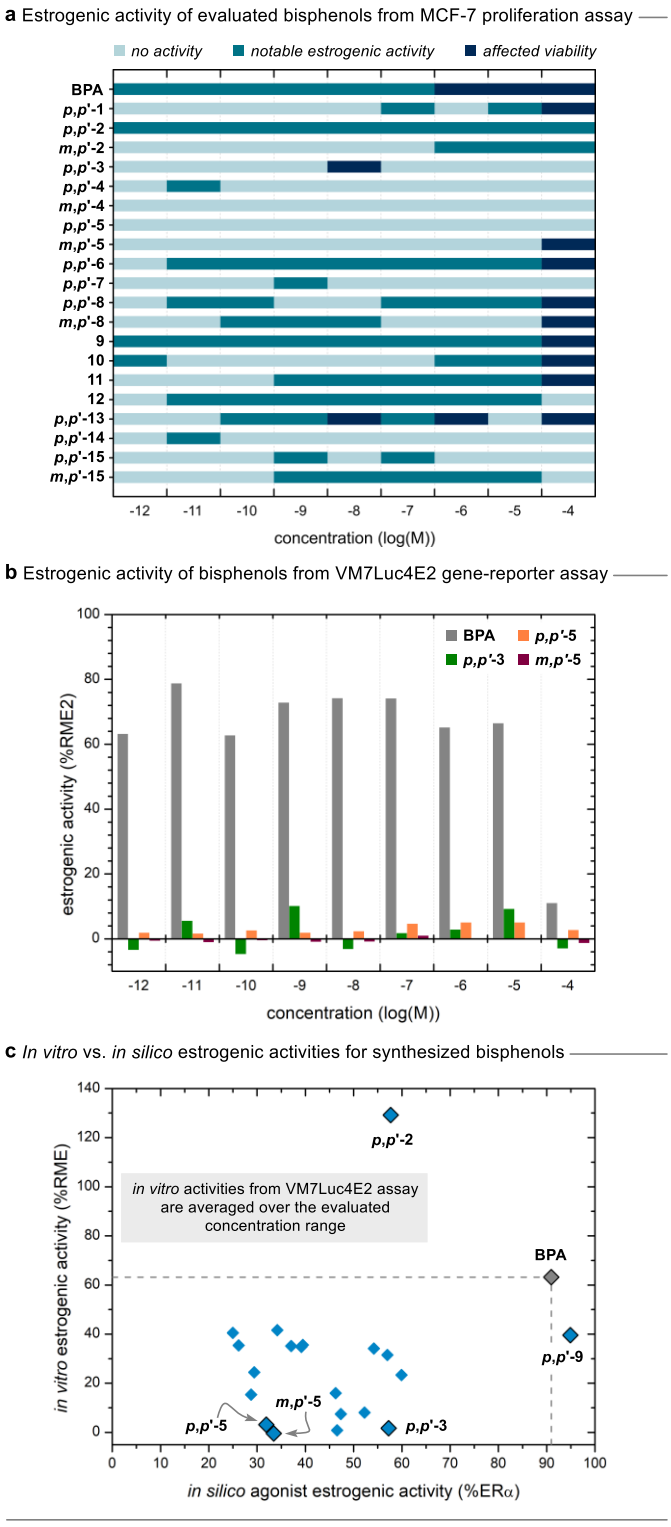

Figure 3. Evaluation of the endocrine-disrupting activity of the synthesized bisphenol candidates. **a**, Assessment of the estrogenic activity for all of the synthesized bisphenols from the MCF-7 proliferation assay. **b**, Estrogenic activity for selected bisphenols from the VM7Luc4E2 gene-reporter assay. **c**, Comparison of predicted *in silico* and measured estrogen activity (VM7Luc4E2 assay) for all evaluated bisphenol candidates (for compounds **9**–**12** isolated as isomer mixtures, the predicted values for *p,p'*-isomers were used).

almost all tested concentrations, whereas the majority of bisphenol candidates displayed lower estrogenic activity. Notably, three bisphenols displayed no estrogenic activity at any concentration: ***p,p'*-3**, ***p,p'*-5** and ***m,p'*-5** (Figure 3b). An overlay of estrogenic activities from *in silico* and *in vitro* studies with the VM7LucE2 assay (using averaged values over the assessed concentration range) demonstrated that 18 out of 20 synthesized bisphenols were both predicted and experimentally measured to have lower activity compared to BPA (Figure 3c). This excellent correlation clearly demonstrates the capacity of the *in silico* model to provide valid predictions for this compound class, despite being a general model trained on a dataset with 6754 compounds of wide structural diversity including only 60 bisphenols. Only two bisphenols — ***p,p'*-2** and ***p,p'*-9** — stood out as outliers, demonstrating higher and lower predicted activities relative to BPA, respectively, while displaying opposite trend for activities in the *in vitro* assay.

The data obtained from both *in vitro* assays identified bisphenols ***p,p'*-3** and ***p,p'*-5** as exhibiting minimal to no estrogenic activity. Among these, bisphenol ***p,p'*-3** could be accessed with significantly higher yield and regioselectivity relative to ***p,p'*-5**, thereby, the former was selected for scaled-up synthesis and subsequent incorporation into a polymer matrix. The scaled-up synthesis was performed under modified conditions in order to reduce the amount of excess reagents and lower the catalyst loading, delivering the desired bisphenol **3** in high yield (72%), but as a mixture of regioisomers (***p,p'*/*m,p'*-3** 7.5:1). Notably, previous reports indicated that the minor ***m,p'*-3** regioisomer displays even lower estrogenic activity compared to ***p,p'*-3**,[14d] thus the regioisomeric mixture **3** was used for polymer synthesis without further separation. While bisphenol **3** was previously incorporated into polycarbonate and epoxy resins,[14b,d] in this work we sought to incorporate **3** into a polyester, as this class of polymers is more attractive from the sustainability and circular material flow perspectives.[20] To overcome the lower reactivity of phenolic alcohol groups for polycondensation, bisphenol **3** was first functionalized as bisglycol ether derivative **3-G** with ethylene carbonate (Figure 4a). A bisglycolated BPA derivative **BPA-G** was synthesized using the same procedure for comparison. The bisglycolated bisphenols were each polymerized by reaction with dimethyl succinate (DMS) — a potentially biobased aliphatic diester — to furnish two polyester materials, **3-G-DMS** and **BPA-G-DMS**. The number and weight average molar masses ($\bar{M}_n$ and $\bar{M}_w$, respectively) and dispersities ($Đ$) of the purified materials were determined by size-exclusion chromatography (SEC) analysis, displaying higher molar masses and dispersity for **3-G-DMS** relative to **BPA-G-DMS** ($\bar{M}_n$ = 21.7 *vs.* 15.2 kDa, $\bar{M}_w$ = 92.1 *vs.* 33.2 kDa and $Đ$ = 4.2 *vs.* 2.2). The higher $\bar{M}_n$, $\bar{M}_w$, and $Đ$ values for **3-G-DMS** presumably stem from the higher flexibility of **3-G** monomer, which bears no substituents at the bridging methylene carbon, unlike **BPA-G**. This could facilitate the polymerization leading to higher molar mass. Furthermore, the 7.5:1 mixture of the *p,p'*/*m,p'*-regioisomers in **3** may contribute to the higher $Đ$ and more supple nature of the resulting polymer. The higher flexibility of the **3-G** monomer compared to **BPA-G** was further illustrated by the corresponding properties of the **3-G-DMS** and **BPA-G-DMS** polymers (Figure 4b). Dynamic mechanical analysis (DMA), using films with dimensions of 30 mm × 5 mm × 0.5 mm (length × width × thickness), demonstrated that

the storage modulus (E') of the glassy plateau was observed at 24 °C for the **3-G-DMS** polyester and at 34 °C for its BPA analogue. These observations correlate well with glass transition temperatures (T_g) of 22 °C and 33 °C for **3-G-DMS** and **BPA-G-DMS**, respectively, as determined from the temperatures at which the curves of E'' reached local maxima (tan δ max). This trend was further verified when assessing the T_g values by differential scanning calorimetry (DSC) (Figure S54, Table S4). While polymer materials are typically rigid and glassy-like below T_g, an elastic and rubbery behavior is observed when the temperature is above T_g. Similarly, a lower T_g reflects a more flexible chain structure that can retain the ability to rotate even at lower temperatures. As such, the lower T_g of the **3-G-DMS** polymer suggested that this material was more supple compared to the more rigid BPA analogue. In agreement, the mechanical properties of the two polyesters determined by tensile testing at room temperature**,** demonstrated that **BPA-G-DMS** exhibits higher elastic modulus and lower elongation at break, *i.e.*, it is stiffer and less flexible compared to **3-G-DMS** (478.2 *vs.* 185.1 MPa and 65% vs. 237%, respectively). Interestingly, both polyesters displayed very good thermal stability, as evaluated by thermogravimetric analysis (TGA), with thermal degradation onsets (T_5) at ~345–370 °C and degradation maxima (T_d) at ~390–400 °C. As expected, both polyesters were thermally more stable (~60 °C higher T_5 values) compared to the corresponding glycolated bisphenol monomers as a result of their higher molar masses and decreased content of end groups after polymerization. The char yields (CY) of both polymers after TGA pyrolysis at 600 °C were determined to be 26–28%, which is typical for polymer with high content of aromatic structures. Finally, the DSC analysis confirmed that both polyesters were completely amorphous.

Compared to previously reported polyesters based on methoxylated BPA analogs and aliphatic linkers,[21] the **3-G-DMS** polyester displayed similar T_g and tensile stress at break (~3 MPa). However, while the former produced brittle films with only ~1% elongation at break, **3-G-DMS** formed flexible films with elongation at break of more than 200%. In addition, **3-G-DMS** displayed a significantly improved thermal stability (~100 °C higher). This thermal stability is also on par with the previously reported methoxylated bisphenol-based polyterephthalate.[14b] This is noteworthy, since thermal stability of a polymer is typically proportional to its aromatic content, and **3-G-DMS** features only a limited amount of aromatic constituents.

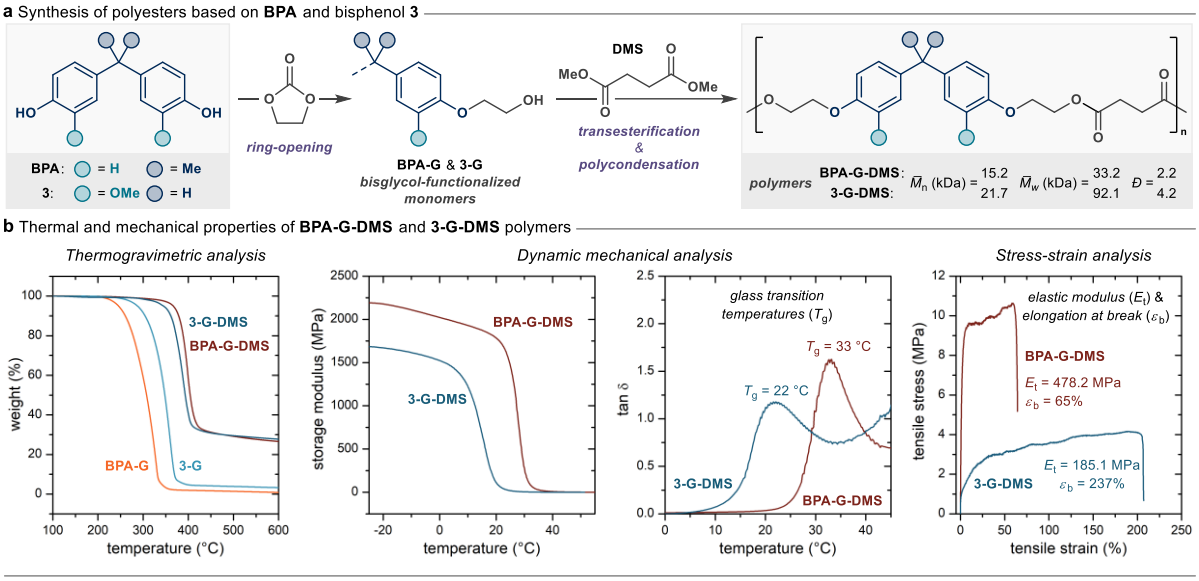

Figure 4. Synthesis of bisphenol-based polymers and evaluation of their properties. **a**, General reaction scheme for the synthesis of monomers (**BPA-G** and **3-G**) and polyesters (**BPA-G-DMS** and **3-G-DMS**). **b**, Thermogravimetric analysis (TGA), dynamic mechanical analysis (DMA), and stress-strain analysis for the synthesized polymers.

Conclusions

A multidisciplinary Safe-and-Sustainable-by-Design (SSbD) framework enabled synthesis of a non-toxic bisphenol-based polyester with attractive mechanical and thermal properties. We implemented a workflow that minimized synthetic efforts and associated chemical exposure by initial evaluation of endocrine disruptive effects for a library of bisphenols using an *in silico* model. This predictive evaluation resulted in the selection of a limited number of promising candidates that were synthesized from lignin-sourced reagents using renewable solvent and non-toxic catalysts. These candidates were evaluated for estrogenic activity by an *in vitro* toxicity assessment, which resulted in the selection of one non-estrogenic bisphenol that was successfully incorporated into a polyester matrix. As such, the present study demonstrates how the SSbD principles can guide the development of sustainable and safe materials with attractive properties for future applications in consumer products.

Data availability

The data that support the findings of this study are reported within the Article and its Supplementary Information and are available from the corresponding authors upon request.

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Author contributions

Conceptualization and methodology: H. L., C. M., U. N., M. H., S. S., O. K., P. P. *In silico* studies: U. N. Synthesis and characterization of bisphenol candidates: C. M., D. P., A. F., E. L., V. C., H. H., A. S. *In vitro* toxicological assessment: P. P., O. K. Synthesis and characterization of polymers: S. S., M. H. Writing and visualization, original draft: C. M., A. S., H. L., M. H., U. N., O. K., S. S., P. P. Supervision, project administration and funding acquisition: H. L., M. H., U. N., O. K. All authors contributed to discussing the results, as well as reviewing and editing the manuscript.

Competing interests

The authors declare no competing interests.

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