Molecular docking simulations to assess the estrogenic activity of lignin-derivable bisphenol A alternatives and their polymerization via additive manufacturing

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Lignin-derivable bisphenols could serve as potentially safer replacements to BPA, a suspected endocrine disruptor. This work focuses on fundamentally understanding the structure-activity relationships of lignin-derivable bisphenols to predict estrogenic activity (EA) and design safer alternatives to existing bisphenols. Binding affinities to estrogen receptor alpha (ERα) were calculated *via* molecular docking simulations, and a correlation between the median effective concentration (EC_{50}) values of commercially available (bis)phenols and their binding affinities was developed to predict the EC_{50} values of lignin-derivable bisphenols. On the basis of the correlation curve, lignin-based bisphenols with binding affinities weaker than -6.0 kcal/mol are expected to exhibit no EA. Two methoxy groups on the aromatic rings substantially weaken the binding affinities to ERα (~-6.0 kcal/mol) by blocking the binding pockets. Similarly, the bulkier bridging groups such as ethyl or methoxy on lignin-bisphenols reduce the binding affinities because of steric effects. Several of the lignin-derivable bisphenols with binding affinities weaker than -6.0 kcal/mol were synthesized and incorporated into additive manufacturing resins for stereolithography 3D printing. The thermal (*e.g.,* glass transition temperature, thermal decomposition behavior) and mechanical (*e.g.,* tensile strength, modulus) properties of the printed materials were characterized to elucidate key structure-property relationships. Together, the structure-activity and structure-property relationships developed in this work could be leveraged to design materials that can match or exceed the performance of existing bisphenol-based materials without endocrine disruption potential.