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Synthesis of bio-based epoxy monomers from natural allyl- and vinyl phenols and the estimation of their affinity to the estrogen receptor α by molecular docking.

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ABSTRACT:

Diepoxydized diphenyls from eugenol, 4-vinyl guaiacol and 4-vinyl syringol (canolol) were synthesized as sustainable alternatives to the diglycidyl ether of bisphenol A (DGEBA). In a first step, glycidylated derivatives were produced by reaction with epichlorohydrin. Then, the dimerization of these derivatives was performed by cross metathesis (CM) reaction in the presence of Grubbs II catalyst. From the CM reaction, a set of epoxy phenolic dimers was obtained in good yields with a high diastereoselectivity. Estimation by molecular docking calculations of the affinity of the synthesized products and their hydrolysed structures to the intranuclear estrogen receptor ERα showed that the epoxy forms presented a moderate affinity to the antagonistic conformation of the receptor (six to forty times lower than bisphenol A and in the same order of magnitude as DGEBA) and mostly no binding in the agonist conformation. The hydrolysed forms of the epoxy products, which are expected to be predominant in the human body cells, exhibited a relatively weak affinity to the ERα LBD in its both agonistic and antagonistic conformations.

KEYWORDS: epoxy monomers, natural polyphenols, cross metathesis, bioactivity.

INTRODUCTION

Bisphenol A (BPA) is one of the highest volume chemicals produced worldwide, with 6.3 million metric tons produced in 2010 and a 6-10% growth in demand expected per year[1]. This petroleum-based product is classified as an endocrine-disruptor. It can interact with the ligand binding domain (LBD) of several nuclear hormone receptors such as estrogen, androgen and thyroid hormone receptors[2], giving rise to disorders in downstream signalling pathways. Because

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nuclear receptors regulate the expression of a large number of genes, BPA is suspected to have profound effects on organisms. Indeed, this chemical has been associated to diseases such as cancer, osteoporosis and obesity[2, 3] The current concerns surrounding BPA began in the early 1990s when researchers from Stanford University realized that the chemical was migrating from the plastic laboratory bottles into the water they were using[4]. Nowadays, exposure to bisphenol A is proven to be nearly universal. Indeed, a recent study has reported that BPA was detected in the urine samples from 92.6% of the population in USA[5] .Consequently, responding to expressions of public concern and pressure from certain media, some countries such as Canada, France and some US states decided to ban BPA from baby bottles and to extend this prohibition to all food and beverage containers[6, 7].

However, no one can overlook the excellent properties of BPA which allowed it to become a key ingredient in several polymer and non-polymer processes. Indeed, this compound is mainly used for the production of polycarbonate resins (71%), epoxy resins (27%), unsaturated polyesters, polysulfone, polyetherimide and polyarylate resins[8, 9]. In the epoxy resins industry, manufacturers are producing a very large variety of products bearing different properties from a single molecule, the diglycidyl ether of BPA (DGEBA). Indeed, in combination with a judicious selection of curing agents and appropriate modifiers, epoxy resins can be specifically tailored to fit a broad range of applications[10-13]. For example, cured epoxy resin is used for coatings such as corrosion protectors, lacquers in the automotive industry, housings for electrical equipment, laminates, industrial floorings, construction parts, adhesives as well as in dental products[14-16] . This broad range of applications is related to the characteristic properties that BPA chemical structure provides. Indeed, this aromatic, bulky diol affords excellent thermal, mechanical, optical and electrical properties, especially upon incorporation into polymers[11, 17].

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Therefore, scientists face a dilemma as, on one hand they need to substitute this hazardous fossil-based product, and on the other hand, the high performance of BPA must be preserved. In the present work, we describe the synthesis of some epoxidized phenolic compounds, which could represent a bio-based alternative to DGEBA. Thus, natural phenolic compounds bearing alkenyl chain on their aromatic ring have first undergone a glycidylation reaction to introduce the epoxy group. Then, the resulting products were dimerized through the cross metathesis (CM) coupling, producing diglycidylated diphenyl compounds. The resulting epoxy monomers exhibit a structural similarity with DGEBA, which will undoubtedly lead to approach the versatile properties of this latter. However, care must be taken to ensure that these new compounds do not show comparable health effects as BPA. Hence, the second part of this work was dedicated to the assessment of the affinity of the synthesized diphenyls and some of their derivatives to the intranuclear estrogen receptor ERα by means of molecular docking simulations. This would give indications on the potential relative risks associated to the various structures obtained and represent a crucial step before epoxy resins production. Three natural phenolic compounds were selected for this study: eugenol (4-allyl guaiacol) **1**, 4-vinylguaiacol **2** and canolol (4-vinylsyringol) **3** (scheme 1). Eugenol **1** is a phenylpropene, mainly extracted from clove oil (80%)[18] and widely used in food, pharmaceutical, cosmetic and active packaging applications [18, 19]. 4-vinyl guaiacol **2**, a styrene type molecule, is a valuable starting material for fragrances, flavours, oxygenated biodegradable polymers and is an intermediate for organic synthesis[20]. This molecule is produced by the either bio-catalytic or thermal decarboxylation of ferulic acid[21, 22], a hydroxycinnamic acid widely present in the cell wall of several cereal grains[23, 24]. A few years ago, canolol **3** was isolated from crude rapeseed oil and identified as the decarboxylation product

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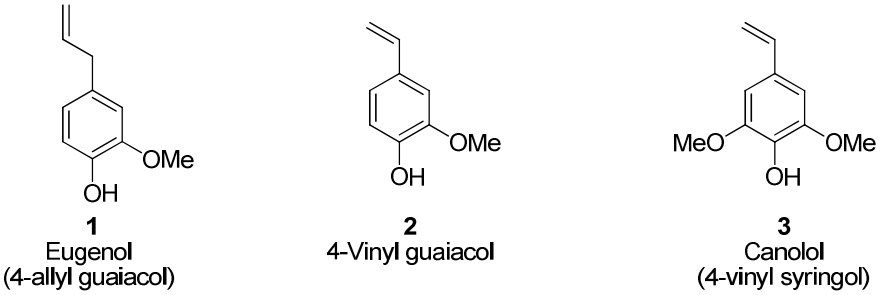
of sinapic acid[25, 26]. Canolol **3** is mainly formed under high temperatures arising during rapeseed processing [27] and is of interest for the food industry due to its flavour and antioxidant property[28].

The relative abundance of the biomass-derived compounds **1**, **2** and **3** prompted us to consider them as starting materials in the synthesis of bio-based epoxy monomers.



Scheme 1: Chemical structures of compounds **1**, **2** and **3**.

EXPERIMENTAL

Chemicals

Eugenol (99%), syringaldehyde (≥98%), vanillin (99%), malonic acid (99%), piperidine (≥99.5%), sodium carbonate (≥99.5%), epichlorohydrin (99%), sodium hydroxide (≥98%), benzyltriethylammonium chloride (≥98.0%), Grubbs II catalyst, dichloromethane (≥99.5)%, N,N-dimethylformamide (99.8%) were purchased from Sigma-Aldrich France.

Methods

All the reactions were monitored by TLC performed on pre-coated silica gel 60 F254 plates purchased from Merck (Germany).

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Excepted for **3**, all compounds were dissolved in DMSO-d_6 and analysed using an Agilent VNRMS DD2 500MHz spectrometer, operating at 500.05 MHz for ^{1}H and 125.75 MHz for ^{13}C, using a 5mm indirect detection Z-gradient probe. The chemical shifts were reported to that of internal DMSO at 2.5 ppm and 39.5 ppm for ^{1}H and ^{13}C respectively. Assignments of both proton and carbon resonances, identification and structure characterization of products were performed using 1D and 2D NMR spectrum analyses using homonuclear ^{1}H and heteronuclear $^{1}H/^{13}C$ experiments. Data were processed and analysed using both VNMRJ and ACD/Labs software. Compound **3** in solution in $CDCl_3$ was analysed on a Bruker 600 MHz spectrometer, operating at 600 MHz for ^{1}H and 150 MHz for ^{13}C. Chemical shifts were referenced using residual internal $CHCl_3$ signals at 7.26 ppm and 77.0 ppm for ^{1}H and ^{13}C respectively.

Melting points were measured on Stuart SMP10 apparatus. Samples were heated with a rate of 20 °C per minute to plateau, then 2 °C per minute to melt.

Computational structural analysis of interactions with estrogen receptors

The protein structure of the complex of the human estrogen receptor alpha (hER alpha) ligand-binding domain recognition bound either to agonist diethylstilbestrol and a peptide derived from the NR box II region of the coactivator GRIP1 (PDB accession code: 3ERD) or to the antagonist 4-hydroxytamoxifen (PDB accession code: 3ERT) were downloaded from the RCSB Protein Data Bank [http://www.pdb.org]. Ligands were drawn and converted to 3D structures using Marvin Sketch 15.4.6.0 [ChemAxon (2015) http://www.chemaxon.com]. Docking simulations were carried out using Autodock Vina 1.1.2[29] within UCSF Chimera version 1.10.1[30] , using the default options for receptor's and ligand's preparation scripts and for docking parameters. The maximum number of binding modes was set to 10, with a maximum energy difference of 3 kcal•mol^{-1}.

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Docking coordinates were determined through a centered grid box enclosing the whole ligand-binding domain. Interactive visualization, analysis and imaging of molecular structures were performed using UCSF Chimera. The computations were performed on a PC with a 17-4650U Intel CPU and 8 GB RAM, running 64 bits Windows 8.1 Professional.

Synthesis of 4-vinylguaiacol 2 and canolol 3

Vanillin (3-methoxy-4-hydroxybenzaldehyde) and syringaldehyde (3,5-dimethoxy-4-hydroxybenzaldehyde) were used as 4-vinyl-guaiacol and canolol precursors respectively. In a 100 mL round bottom flask were added 20 mL of toluene, 5 mmol of 4-hydroxybenzaldehyde derivative, 7.5 mmol of malonic acid and 25 mmol of piperidine. The reaction medium was kept under stirring and heated to reflux (115 °C) until the total solubilisation of the reagents. The kinetics of the reactions were followed by TLC-densitometry at 280 nm, using a CAMAG TLC scanner 3 (Muttenz, Switzerland). The conversion of vanillin into 4-vinyl guaiacol and syringaldehyde into canolol required respectively 100 min and 240 min. After completion of the reaction, the medium was cooled down to room temperature and the solvent was evaporated at reduced pressure. In order to eliminate any trace of piperidine, the crude product was washed twice with 20 mL of toluene followed by vacuum drying until complete solvent removal.

The products were purified by silica gel chromatography using petroleum ether/ethyl acetate (70:30, v/v) as the mobile phase to yield:

2-methoxy-4-vinylphenol (4-vinylguaiacol) **2**: dark yellow oil, 74% yield (3.70 mmol). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 3.79 (s, 3H, Me), 5.06 (d, *J*= 11.1 Hz, 1H, H8), 6.63 (d, *J*= 16.8 Hz, 1H, H8), 6.61 (dd, *J*= 17.6, 10.9 Hz, 1H, H7), 6.72 (d, *J*= 8.1 Hz, 1H, H5), 6.85 (d, *J*= 8.1 Hz, 1H, H6), 7.04 (s, 1H, H3), 9.07 (s, 1H, OH) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ = 55.3

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(Me), 109.4 (C3), 110.7 (C8), 115.02 (C6), 119.4 (C5), 128.5 (C4), 136.3 (C7), 146.3 (C1), 147.6 (C2) ppm. $C_9H_{10}O_2$ calcd. C 71.98, H 6.71; found. C 72.08, H 6.60.

2,6-dimethoxy-4-vinylphenol (canolol) **3**: dark green oil, 47% yield (2.35 mmol). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 3.91 (s, 6H, Me), 5.15 (d, *J*= 10.9 Hz, 1H, H8), 5.53 (s, 1H, OH), 5.60 (d, *J*= 17.5 Hz, 1H, H8), 6.62 (dd, *J*= 17.5, 10.9 Hz, 1H, H7), 6.65 (s, 1H, H3,H5) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ = 56.7 (Me), 103.3 (2C, C3 and C5), 112.0 (C8), 129.5 (C4), 135.3 (C1), 137.1 (C7), 147.5 (2C, C2 and C6) ppm.$C_{10}H_{12}O_3$ calcd. C 66.65, H 6.54; found. C 66.42, H 6.54.

General procedure for the glycidylation of phenolic compounds

A 250 mL two-necked round bottom flask equipped with a condenser, a Teflon septum cap and a magnetic stirring bar was charged with 1 g of **1**, **2** or **3** in epichlorohydrin (4 molar eq). The suspension was then heated to 100°C and benzyltriethylammonium chloride ($BnEt_3NCl$, 0.05 molar eq) was added. After 90 min, the resulting mixture was cooled down to 30°C and an aqueous solution of NaOH 200 g•L^{-1} (2 molar eq) containing the same previous amount of phase transfer catalyst ($BnEt_3NCl$) was added. The reaction medium was stirred vigorously for 90 min. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under vacuum. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (70:30, v/v) to yield the following products:

From **1:**

2-((4-allyl-2-methoxyphenoxy)methyl)oxirane **4**: colourless oil, 84% yield (5.12 mmol). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 2.67 (dd, *J*= 5.1, 2.7 Hz, 1H, Hγ'), 2.82 (m, 1H, Hγ), 3.29-3.30 (m, 2H, H7 and Hβ), 3.75 (s, 3H, Me), 3.77 (m, 1H, Hα'), 4.24 (dd, *J*= 11.3, 2.7 Hz, 1H, Hα), 5.04 (dd, *J*= 12.5, 8.0 Hz, 2H, H9), 5.93 (tdd, *J*= 16.8, 10.0, 6.8 Hz, 1H, H8), 6.68 (d, *J*= 8.1 Hz, 1H,

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H5), 6.80 (s, 1H, H3), 6.87 (d, *J*=8.1 Hz, 1H, H6) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ = 39.3(C7), 44.0 (Cγ), 50.0 (Cβ), 55.6 (Me), 70.2 (Cα), 112.7 (C3), 113.9 (C6), 115.7 (C9), 120.3 (C5), 133.1 (C4), 138.0 (C8), 146.2 (C1), 149.1 (C2) ppm. $C_{13}H_{16}O_3$ calcd. C 70.89, H 7.32; found. C 70.57, H 7.21.

From **2:**

2-((2-methoxy-4-vinylphenoxy)methyl)oxirane **5**: light yellow solid (MP = 129°C), 80% yield (5.32 mmol). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 2.68 (dd, *J*= 5.0, 2.6 Hz, 1H, Hγ'), 2.83 (m, 1H, Hγ), 3.32 (qd, *J*= 6.8, 3.1 Hz, 1H,Hβ), 3.78-3.82 (m, 1H, Hα'), 3.71 (s, 3H, Me), 4.27 (dd, *J*= 11.3, 2.7 Hz, 1H, Hα), 5.13 (d, *J*= 11.0 Hz, 1H, H8), 5.74 (d, *J*= 17.6 Hz, 1H, H8), 6.65 (dd, *J*= 17.6, 11.0 Hz, 1H, H7), 6.92 (d, *J*= 8.3 Hz, 1H, H5), 6.94 (d, *J*=8.3 Hz, 1H, H6), 7.11 (s, 1H, H3) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ = 43.8 (Cγ), 49.7 (Cβ), 55.4 (Me), 69.8 (Cα), 109.3 (C3), 112.2 (C8), 113.1 (C6), 119.1 (C5), 130.7 (C4), 136.4 (C7), 147.7 (C1), 149.0 (C2) ppm. $C_{12}H_{14}O_3$ calcd. C 69.88, H 6.84; found. C 69.98, H 6.96.

From **3:**

2-((2,6-dimethoxy-4-vinylphenoxy)methyl)oxirane **6**: light green solid (MP = 138°C), 90% yield (5.0 mmol). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 2.56 (dd, *J*= 5.1, 2.7 Hz, 1H, Hγ'), 2.73 (m, 1H, Hγ), 3.24 (dt, *J*= 6.8, 2.9 Hz, 1H,Hβ), 3.74 (dd, *J*= 11.5, 6.5 Hz, 1H, Hα'), 3.80 (s, 6H, Me), 4.07 (dd, *J*= 11.5, 3.0 Hz, 1H, Hα), 5.21 (d, *J*= 11.0 Hz, 1H, H8), 5.80 (d, *J*= 17.6 Hz, 1H, H8), 6.66 (dd, *J*= 17.6, 11.0 Hz, 1H, H7), 6.79 (s, 2H, H5 and H3) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ = 43.3 (Cγ), 50.3 (Cβ), 56.0 (Me), 63.9 (Cα), 103.5 (2C, C3 and C5), 113.7 (C8), 133.0 (C4), 136.3 (C7), 136.7 (C1), 153.0 (2C, C2 and C6) ppm. $C_{13}H_{16}O_4$ calcd. C 66.09, H 6.83; found. C 65.88, H 6.62.

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General procedure for 4, 5 and 6 dimerization by cross metathesis

A mixture of **4**, **5** or **6** (1 mmol) and Grubbs II catalyst (5 mol%, 0.05 mmol) in CH_2Cl_2 (1 mL) was heated at 42°C under argon for 48 h. The mixture was concentrated under vacuum. The residue was purified by silica gel chromatography using petroleum ether/ethyl acetate (50:50, v/v) to give the following products:

From **4:**

4,4'-(but-2-ene-1,4-diyl)bis(2-methoxyphenol) **7**: light yellow solid (MP = 234°C), 56% yield (0.28 mmol). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 2.67 (dd, *J*= 5.1, 2.7 Hz, 1H, Hγ'), 2.82 (m, 1H, Hγ), 3.26 (d, *J*= 4.8 Hz, 2H,H7), 3.30 (td, *J*= 9.4, 4.8 Hz, 1H, Hβ), 3.73 (s, 3H, Me), 3.76 (dd, *J*= 11.0, 6.4 Hz, 1H, Hα´),4.23 (dd, *J*= 11.4, 2.7 Hz, 1H, Hα), 5.63 (t, *J*= 3.8 Hz, 1H, H8), 6.66 (d, *J*= 8.2 Hz, 1H, H5), 6.79 (s, 1H, H3), 6.86 (d, *J*= 8.2 Hz, 1H, H6) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ = 37.8 (C7), 43.9 (Cγ), 50.0 (Cβ), 55.5 (Me), 70.2 (Cα), 112.6 (C3), 114.0 (C6), 120.2 (C5), 130.4 (C8), 133.9 (C4), 146.1 (C1), 149.1 (C2) ppm. $C_{24}H_{28}O_6$ calcd. C 69.88, H 6.84; found. C 69.73, H 6.68.

4,4'-(ethene-1,2-diyl)bis(2-methoxyphenol) **8**: light yellow solid (MP = 263°C), 10% yield (0.05 mmol). ^{1}HNMR (500 MHz, DMSO-d_6) δ = 2.70 (dd, *J*= 5.0, 2.6 Hz, 1H, Hγ'), 2.85 (m, 1H, Hγ), 3.34 (m, 1H,Hβ), 3.82 (dd, *J*= 10.0, 5.1 Hz, 1H, Hα´), 3.84 (s, 3H, Me), 4.30 (dd, *J*= 11.4, 2.7 Hz, 1H, Hα), 6.95 (d, *J*= 8.3 Hz, 1H, H6), 7.05 (d, *J*= 8.3 Hz, 1H, H5), 7.08 (s, 1H, H7), 7.23 (s, 1H, H3) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ = 43.0 (Cγ), 49.3 (Cβ), 54.9 (Me), 69.3 (Cα), 109.0 (C3), 112.7 (C6), 118.8 (C5), 125.8 (C7), 130.3 (C4), 146.7 (C1), 148.6 (C2) ppm. $C_{22}H_{24}O_6$ calcd. C 68.74, H 6.29; found. C 68.52, H 6.18.

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2,2'-(4,4'-(prop-1-ene-1,3-diyl)bis(2-methoxy-4,1-phenylene))bis(oxy)bis(methylene)dioxirane **9**: yellow solid (MP = 237°C), 14% yield (0.07 mmol). ^{1}HNMR (500 MHz, DMSO-d_6) δ = 2.67 (m, 2H, Hγ′), 2.83 (m, 1H, Hγ), 3.32 (m, 2H,Hβ), 3.43 (d, *J*= 6.4 Hz, 2H, H9), 3.75 (m, 2H, Hα´), 3.77 (s, 3H, Me),3.78 (s, 3H, Me), 4.26 (dd, *J*= 11.0, 2.7 Hz, 1H, Hα), 6.31 (m, 1H, H8), 6.37 (d, *J*= 15.8 Hz, 1H, H7), 6.74 (d, *J*= 8.0 Hz, 1H, $H5_B$), 6.87-6.91 (m, 4H, $H5_A$, $H6_A$, $H6_B$ and $H3_B$), 7.05 (s, 1H, $H3_A$) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ = 38.0 (C9), 43.5 (2C, Cγ), 49.5 (2C, Cβ), 55.2 (2C, Me), 69.5 (2C, Cα), 108.9 ($C3_A$), 112.2 ($C3_B$), 113.0 ($C6_A$), 113.4 ($C6_B$), 118.6 ($C5_A$), 120.0 ($C5_B$), 127.5 (C8), 129.5 (C7), 133.2 (2C, $C4_A$ and $C4_B$), 145.8 ($C1_B$), 146.8 ($C1_A$), 148.7 ($C2_B$), 148.8 ($C2_A$) ppm. $C_{23}H_{26}O_6$ calcd. C 69.33, H 6.58; found. C 69.08, H 6.13.

From **5**:

8: 76% yield (0.38 mmol).

From **6**:

4,4'-(ethene-1,2-diyl)bis(2,6-dimethoxyphenol) **10**: light yellow solid (MP = 291°C), 78% yield (0.39 mmol). ^{1}HNMR (500 MHz, DMSO-d_6) δ = 2.58 (dd, *J*= 5.0, 2.7 Hz, 1H, Hγ′), 2.75 (m, 1H, Hγ), 3.25 (dt, *J*= 6.8, 2.9 Hz, 1H,Hβ), 3.76 (dd, *J*= 11.5, 6.5 Hz, 1H, Hα´), 3.84 (s, 6H, Me), 4.10 (dd, *J*= 11.5, 2.9 Hz, 1H, Hα), 6.92 (s, 2H, H3 and H5), 7.18 (s, 1H, H7) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ = 43.3 (Cγ), 50.3 (Cβ), 55.9 (Me), 74.0 (Cα), 103.6 (2C, C3 and C5), 127.9 (C7), 133.0 (C4), 136.0 (C1), 153.0 (C2) ppm. $C_{24}H_{28}O_8$ calcd. C 64.85, H 6.35; found. C 65.06, H 6.19.

Coupling of 4 with 5, 4 with 6 and 5 with 6 by cross metathesis

A mixture (0.5 mmol each) of **4** and **5**, **4** and **6** or **5** and **6** with 0.025 mmol (5 mol%) Grubbs II catalyst in 1 mL CH_2Cl_2 was heated at 42°C under argon for 48 h. The solvent was evaporated

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under vacuum. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (45:55, v/v) mixture to give the following products:

From **4** + **5**:

9 (36% yield, 0.09 mmol) and **7** (10% yield, 0.025 mmol) and **8** (44% yield, 0.11 mmol).

From **4** + **6**:

((2,6-dimethoxy-4-(3-(3-methoxy-4-(oxiran-2-ylmethoxy)phenyl)prop-1-enyl)phenoxy)methyl)oxirane **11**: light yellow solid (MP = 234°C), 48% yield (0.12 mmol). ^{1}HNMR (500 MHz, DMSO-d_6) δ = 2.55 (dd, *J*= 5.2, 2.7 Hz, 1H, Hγ'), 2.67 (dd, *J*= 5.0, 2.6 Hz, 1H, Hγ´), 2.72 (m, 1H,Hγ), 2.82 (m, 1H, Hγ), 3.23 (m, 1H, Hβ), 3.30 (m, 1H, Hβ), 3.44 (d, *J*= 5.1 Hz, 2H, H9), 3.71 (dd, 2H, Hα´), 3.76 (s, 3H, Me), 3.77 (s, 6H, Me), 4.05 (dd, *J*= 11.4, 3.0 Hz, 1H, Hα), 4.24 (dd, *J*= 11.3, 2.5 Hz, 1H, Hα), 6.38 (s, 2H, H7 and H8), 6.71 (s, 2H, $H3_A$ and $H5_A$), 6.73 (d, *J*= 8.2 Hz, 1H, $H5_B$), 6.86 (s, 1H, $H3_B$), 6.90 (d, *J*= 8.2 Hz, 1H, $H6_B$) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ = 37.8 (C9), 42.8 ($Cγ_A$), 43.2 ($Cγ_B$), 49.4 ($Cβ_A$), 49.7 ($Cβ_B$), 55.3 (Me_B), 69.5 ($Cα_B$), 73.4 ($Cα_A$), 55.3 (2C, Me_A), 103.0 (2C, $C3_A$ and $C5_A$), 112.4 ($C3_B$), 113.2 ($C6_B$), 120.0 ($C5_B$), 128.7 (C8), 129.8 (C7), 132.7 ($C4_A$), 132.8 ($C4_B$), 145.2 ($C1_A$), 145.7 ($C1_B$), 148.5 ($C2_B$), 152.4 (2C, $C2_A$ and $C6_A$)ppm. $C_{24}H_{28}O_7$ calcd. C 67.28, H 6.59; found. C 66.90, H 6.28.

7 (16% yield, 0.04 mmol) and **10** (16% yield, 0.04mmol)

2-((2,6-dimethoxy-4-(3-methoxy-4-(oxiran-2-ylmethoxy)styryl)phenoxy)methyl)oxirane **12**: light yellow solid (MP = 278°C), 5% yield (0.012 mmol). ^{1}HNMR (500 MHz, DMSO-d_6) δ = 2.57 (dd, *J*= 5.0, 2.6 Hz, 1H, $Hγ'_A$), 2.70 (dd, *J*= 5.0, 2.6 Hz, 1H, $Hγ´_B$), 2.74 (m, 1H,$Hγ_A$), 2.84 (m,

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1H, Hγ_B), 3.25 (m, 1H, Hβ_A), 3.34 (m, 1H, Hβ_B), 3.75 (dd, *J*= 11.5, 6.5 Hz, 1H, Hα'_A),3.82 (m, 1H, Hα'_B), 3.83 (s, 6H, Me$_A$), 3.85 (s, 3H, Me$_B$), 4.10 (dd, *J*= 11.6, 3.0 Hz, 1H, Hα_A), 4.30 (dd, *J*= 11.4, 2.7 Hz, 1H, Hα_B), 6.90 (s, 2H, H5$_A$ and H3$_A$), 6.96 (d, *J*= 8.3 Hz, 1H, H6$_B$), 7.07 (d, *J*= 8.7 Hz, 1H, H5$_B$), 7.10 (d, *J*= 16.3Hz, 2H, H7 and H8), 7.24 (s, 1H, H3$_A$) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ = 43.0 (Cγ_A), 43.5 (Cγ_B), 49.3 (Cβ_B), 50.0 (Cβ_A), 55.1 (Me$_B$), 55.5 (2C, Me$_A$), 69.6 (Cα_B), 73.6 (Cα_B), 103.1 (2C, C3$_A$ and C5$_A$), 108.9 (C3$_B$), 112.9 (C6$_B$), 119.2 (C5$_B$), 126.1 (C7), 127.5 (C8), 130.3 (C4$_B$), 132.8 (C4$_A$), 135.4 (C1$_A$), 147.1 (C1$_B$), 148.3 (C2$_B$), 152.6 (2C, C2$_A$ and C6$_A$) ppm. $C_{23}H_{26}O_7$ calcd. C 66.65, H 6.32; found. C 67.02, H 6.63.

From **5** + **6**:

12 (30% yield, 0.075 mmol) and **10** (33% yield, 0.082 mmol) and **8** (24% yield, 0.06 mmol).

RESULTS AND DISCUSSION

Diglycidyl ether of BPA (DGEBA) is synthesized by reaction of bisphenol A with epichlorohydrin. Structurally, it consists of two aromatic derivatives each bearing a methyl oxirane group. In order to reach a similar chemical structure and to synthesize a wide range of potential DGEBA substitutes, the following synthetic strategy was adopted: i) the *O*-glycidylation of compounds **1**, **2** and **3** by epichlorohydrin. ii) the homo- and heterodimerization of compounds **4**, **5** and **6** assisted by the cross metathesis (CM) reaction.

Synthesis of 4-vinyl guaiacol 2 and canolol 3

Contrary to eugenol **2**, which is commercially available with a relatively low price ($ 5 Kg^{-1})[31], 4-vinyl guaiacol **2** and canolol **3** had to be prepared. To avoid the time-consuming extraction and purification from biomass for this laboratory-scale study, these compounds were synthesized

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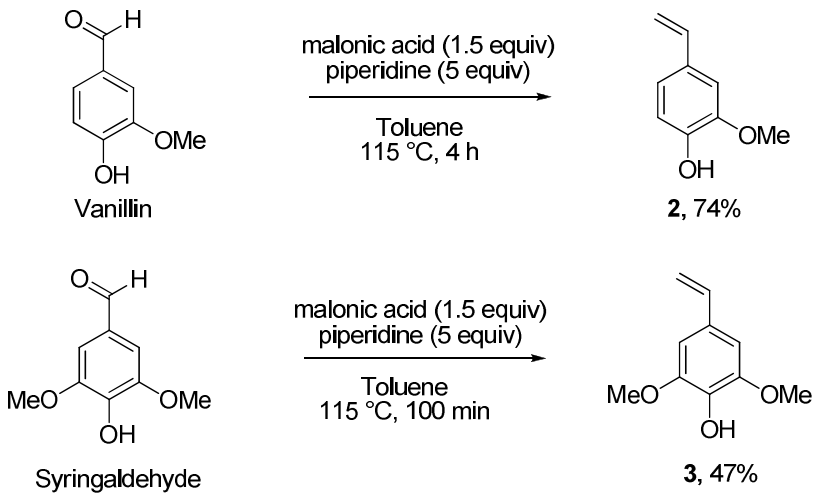
according to the procedure described by Simpson *et al*[32], using vanillin and syringaldehyde as precursors respectively. The reported reaction based on Knoevenagel-Doebner condensation afforded 4-vinyl guaiacol **2** and canolol **3** in 74% and 47% yields respectively (scheme 2). In spite of the total conversion of syringaldehyde into canolol **3,** the latter was isolated in relatively low yield. This arose from the rapid degradation of the canolol crude product during the purification step, as indeed this product has proved to be air and light sensitive.



Scheme 2: 4-vinyl guaiacol **2** and canolol **3** synthesis.

O-glycidylation reaction of compounds 1, 2 and 3

Based on our previous studies related to the production of bio-based epoxy polymers[33, 34]; the *O*-glycidylation reaction of compounds **1**, **2** and **3** was carried out using epichlorohydrin in alkaline medium. It is worth mentioning that the use of bio-based epichlorohydrin, commercially available from DOW or Solvay[35] might strengthen the sustainability of the process.

In alkaline medium and in the presence of a catalytic amount of $BnEt_3NCl$, a large excess of epichlorohydrin was reacted with compounds **1**, **2** and **3** to give the glycidylated derivatives **4**, **5**

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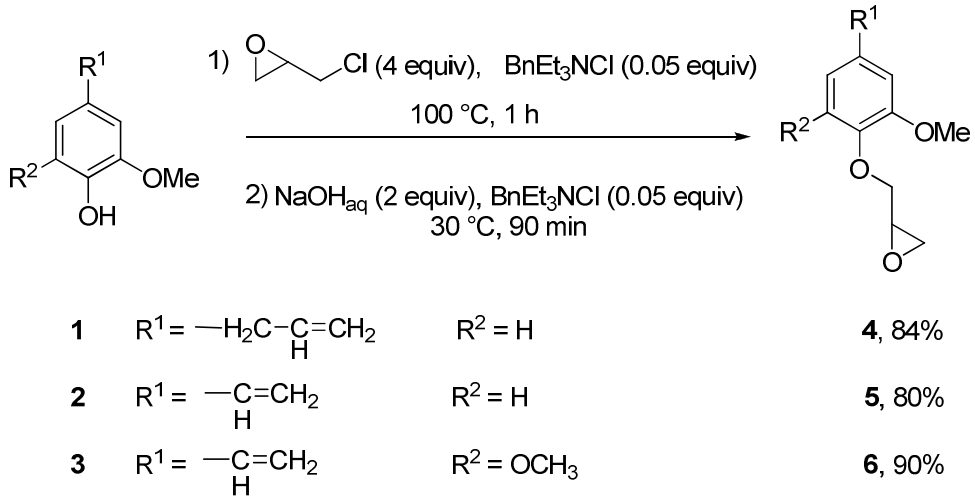
and **6** respectively (scheme 3). The substitution of the phenolic hydroxyl proton by the methyl oxirane group was clearly established by ^{1}H NMR analysis. Indeed, the disappearance of signals corresponding to the phenolic hydroxyl protons was accompanied by the occurrence of several aliphatic signals arising from the glycidyl group. The methylene and methyne ring proton signals appear in the 2.55-2.84 ppm and 3.23-3.32 ppm ranges respectively and the C<u>H$_2$</u>–O protons give resonance signals in the 3.67-4.30 ppm spectral range.



1	$R^1 = -H_2C-\underset{H}{C}=CH_2$	$R^2 = H$	**4**, 84%
2	$R^1 = -\underset{H}{C}=CH_2$	$R^2 = H$	**5**, 80%
3	$R^1 = -\underset{H}{C}=CH_2$	$R^2 = OCH_3$	**6**, 90%

Scheme 3: The O-glycidylation reaction of compounds **1**, **2** and **3**.

Cross metathesis reactions of compounds 4, 5 and 6

The CM dimerization of the glycidylated derivatives **4**, **5** and **6** was carried out in refluxing CH_2Cl_2, in the presence of 5 mol% of Grubbs II catalyst ($C_{46}H_{65}Cl_2N_2PRu$) during 48 h. In order to produce differently substituted diphenyls, CM reactions of **4** with **5**, **4** with **6** and **5** with **6** were also performed under the same reaction conditions. The reaction products are summarised in both table 1 and scheme 4.

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As shown in scheme 4, three kinds of linkages resulted from the CM reactions of **4**, **5** and **6**: "allyl-allyl" (compound **7**), "vinyl-vinyl" (compounds **8**, **10** and **12**) and "vinyl-allyl" (compounds **9** and **11**).

Depending on the linkage type, the ^{1}H NMR signals arising from the olefinic protons of the intercyclic chain exhibited different patterns and chemical shifts. The structural characterisation of all dimer products was performed from several NMR 1D and 2D analyses which allowed all ^{1}H and ^{13}C resonances to be assigned. The spectra showed that, for each dimer, only one stereoisomer was formed since only one set of signals could be observed. The determination of the double bond relative configuration was only possible for dimers **9, 11** and **12,** for which the olefinic proton coupling constants were found to be equal to ~16Hz, a value characteristic of an *E* configuration. In molecules **7**, **8** and **10**, the olefinic protons are chemically and magnetically equivalent, precluding the olefinic coupling constant measurements and consequently the determination of the geometric configuration of the double bond. According to the computational study of Bahri-Laleh *et al.*[36] on the origin of the *Z*-*E* selectivity of the CM reaction, it has been established that the (*E*)-stereoisomers are preferentially formed. Indeed, the transition state leading to the formation of the (*Z*)-stereoisomer is of similar energy or even favoured, relative to that leading to the (*E*)-stereoisomer. Thus, the CM reaction should kinetically lead first to the formation of the (*Z*)-stereoisomer, which is gradually converted into the more stable (*E*)-stereoisomer. However, the key step to rationalize the preferential formation of the (*E*)-stereoisomer is the product releasing step, since the (*E*)-stereoisomer has a higher tendency to be released from the catalyst at the end of the CM reaction. In other words, all the (*Z*)-stereoisomers remain linked to the catalyst until they are converted to (*E*)-stereoisomers and eventually

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released. Based on this study, it could be assumed that compounds **7**, **8** and **10** were (*E*)-stereoisomers.

Table 1: Products of the cross metathesis of the glycidylated derivatives **4**, **5** and **6**.

Entry	Monomers	CM products		Yield (%)
		Homodimers	Heterodimers	
i	**4**	**7**		56
		8		10
			9	14
ii	**5**	**8**		76
iii	**6**	**10**		78
iv	**4+5**	**8**		44
		7		10
			9	36
v	**4+6**	**7**		16
		10		16
			11	48
			12	5
vi	**5+6**	**10**		33
		8		24
			12	30

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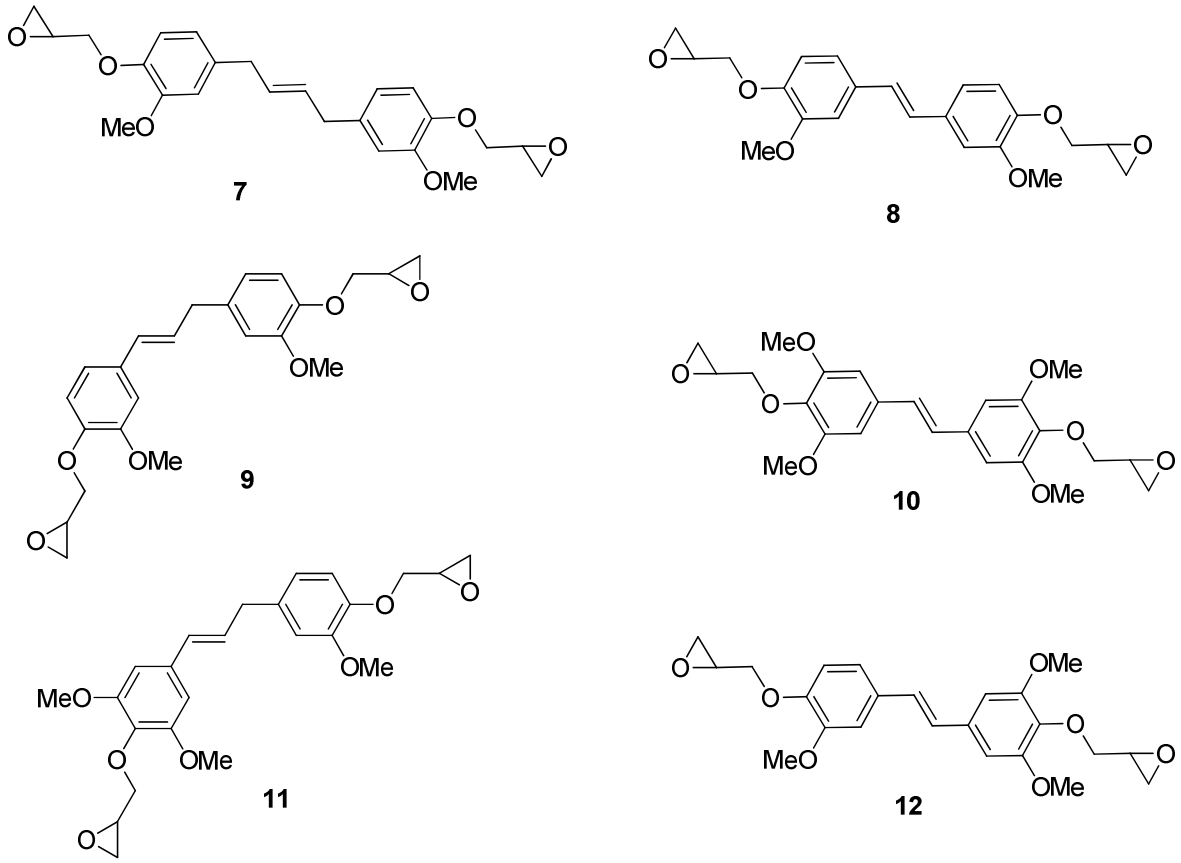

Scheme 4: cross metathesis products obtained from **4**, **5** and **6**.

As displayed in table 1 (entries ii and iii), the CM dimerization of **5** and **6** led to the diglycidylated diphenyl products **8** and **10** respectively with approximately same yields (76% and 78%). In the case of compound **4** (entry i), the CM reaction gave the expected homodimer **7** in the highest yield (56%) along with two dimers identified as **8** (10%) and **9** (14%). The formation of these two unexpected dimers is very likely related to the double bound isomerization of compound **4**. Indeed, it is well known that ruthenium-based olefin metathesis catalysts can isomerise double bonds[37, 38]. The mechanism leading to the formation of the ruthenium-hydride species that are responsible for this isomerisation is discussed in detail in the

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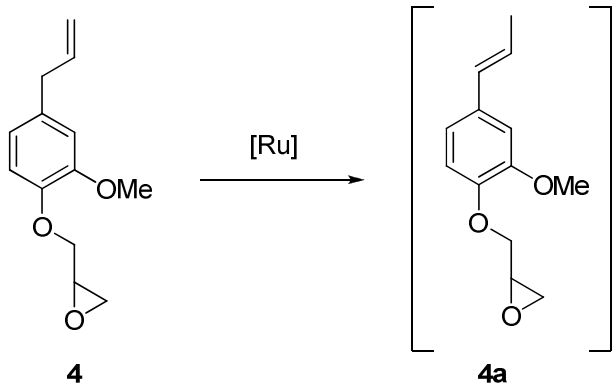
literature[39]. Furthermore, this isomerisation activity is not specific to ruthenium; it may be catalysed by several transition-metal complexes[40]. In the case of compound **4**, the action of the ruthenium catalyst, associated to the conjugated system created by the migration of the double bond, favoured the partial conversion of **4** into **4a** (scheme 5). The homodimerization of the latter led to the formation of product **8,** whereas diphenyl **9** was the heterodimer product arising from the reaction of **4** and **4a**. In both cases, prop-1-ene molecules are released.



4 **4a**

Scheme 5: The partial isomerisation of **4** in the presence of the Ru-based catalyst.

In spite of this side reaction, the higher yield of homodimer **7** compared to those of diphenyls **8** and **9** implies that dimerization reaction occurs faster than double bond migration.

In addition to the homodimerization of **4**, **5** and **6**, each compound reacted with the other under the CM reaction conditions cited above. Generally, the cross metathesis of two different alkenes proceeds to yield three unique products: one desired heterodimeric product and two undesired homodimeric products. This pattern was reproduced during the CM reaction of **5** with **6** (entry vi) which produced heterodimer **12** in 30% yield along with homodimers **10** and **8** in 33% and 24% yield respectively. It was observed that both homodimer **10** and heterodimer **12** were obtained with a similar yield, suggesting that the CM reaction was not very selective in this case.

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The cross coupling of **4** and **5** (entry iv) led to the formation of products **7**, **8** and **9**, *i.e.* the same as those obtained from the CM reaction of **4**, in 10%, 44% and 36% yield respectively. The homodimer **8** was the most abundant product formed. This can be explained by the increase of the proportion of **4a**in the reaction medium due to the isomerization of compound **4** as explained above.

The cross metathesis reaction between **4** and **6** gave the heterodimer product **11** in 48% yield, beside homodimers **7** and **10** which were obtained in equal amounts (16% yield each). The recovery of heterodimer **11** in the highest yield was in accordance with the literature data which have shown that cross metathesis of alkenes bearing allylic (or more distant) groups gives mainly unsymmetrical coupling products[41]. On the other hand, the isomerisation phenomenon did not seem to be very significant in this case. Indeed, dimer **12** was formed in very low yield (5%) and the product arising from the reaction of **4** with **4a** (compound **9**) was not observed.

In summary, the homodimerization of the glycidylated derivatives **4**, **5** and **6** led to the corresponding symmetrical dimers **7**, **8** and **10** respectively in good yields and high diastereoselectivity. During the CM of compound **4**, double bond isomerisation occurred, leading also to the heterodimer **9**. By cross coupling **6** with both **4** and **5,** two new dimers (**11** and **12** respectively) were obtained in fair yields. Before envisioning the epoxy resins production from the synthesized diphenyl (which will be a subject of a future study), it seems worth to assess their safety. Indeed, the structural similarities between DGEBA and the synthesized epoxy precursors bring up questions about the possible bioactivity of the latter. Hence, we conducted a computational study to estimate the affinity of these compounds and the substrates that they originated from (phenols **1** to **3** and their glycidylated derivatives **4** to **6**) toward the ligand binding domain (LBD) of one of the most studied estrogen receptor for such cases, ERα.

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The affinity of the synthesized diphenyl ethers and some of their derivatives to the ERα LBD

Estrogen receptor α (ERα), with 17-β-estradiol as a natural endogen ligand, regulates the differentiation and maintenance of neural, skeletal, cardiovascular and reproductive tissues. All ERα ligands bind exclusively to the C-terminal ligand binding domain. The LBD recognizes a variety of compounds, diverse in their sizes, shapes and chemical properties. Some of these ligands function as agonist, whereas others are antagonist[42]. When an agonist binds to ERα LBD, the positioning of helix 12 (H12, in brown on figure 1) allows the formation of the coactivator binding surface. In contrast, when an antagonist binds to LBD, the coactivator binding surface is not formed because H12 is preventing from reaching its correct position[43].

Using available three-dimensional structures of ERα LBD, estimates of the binding affinity of the compounds of interest were calculated from the binding energy of best ligand-receptor configurations obtained by molecular docking with either agonistic or antagonistic conformations of the receptor. The study included phenolic compounds **1** to **3**, their glycidylated derivatives **4** to **6**, as well as the CM products **7** to **12**. It also involved all the structures resulting from the hydrolysis of the glycidylated derivatives. Indeed, it is well known that, once penetrated in the organism, epoxy groups are converted into diols by the action of epoxide hydrolases[44, 45]. Hence, epoxidized structures are supposed to be practically inexistent in the human body cells.

The chemical structures arising from the hydrolysis of the glycidylated compounds are depicted in scheme 6. The hydrolysis of compounds **4**, **5** and **6** would lead to derivatives **13**, **14** and **15** respectively. Structures **16** to **21** correspond to the hydrolysis products of diglycidylated diphenyls **7** to **12**.

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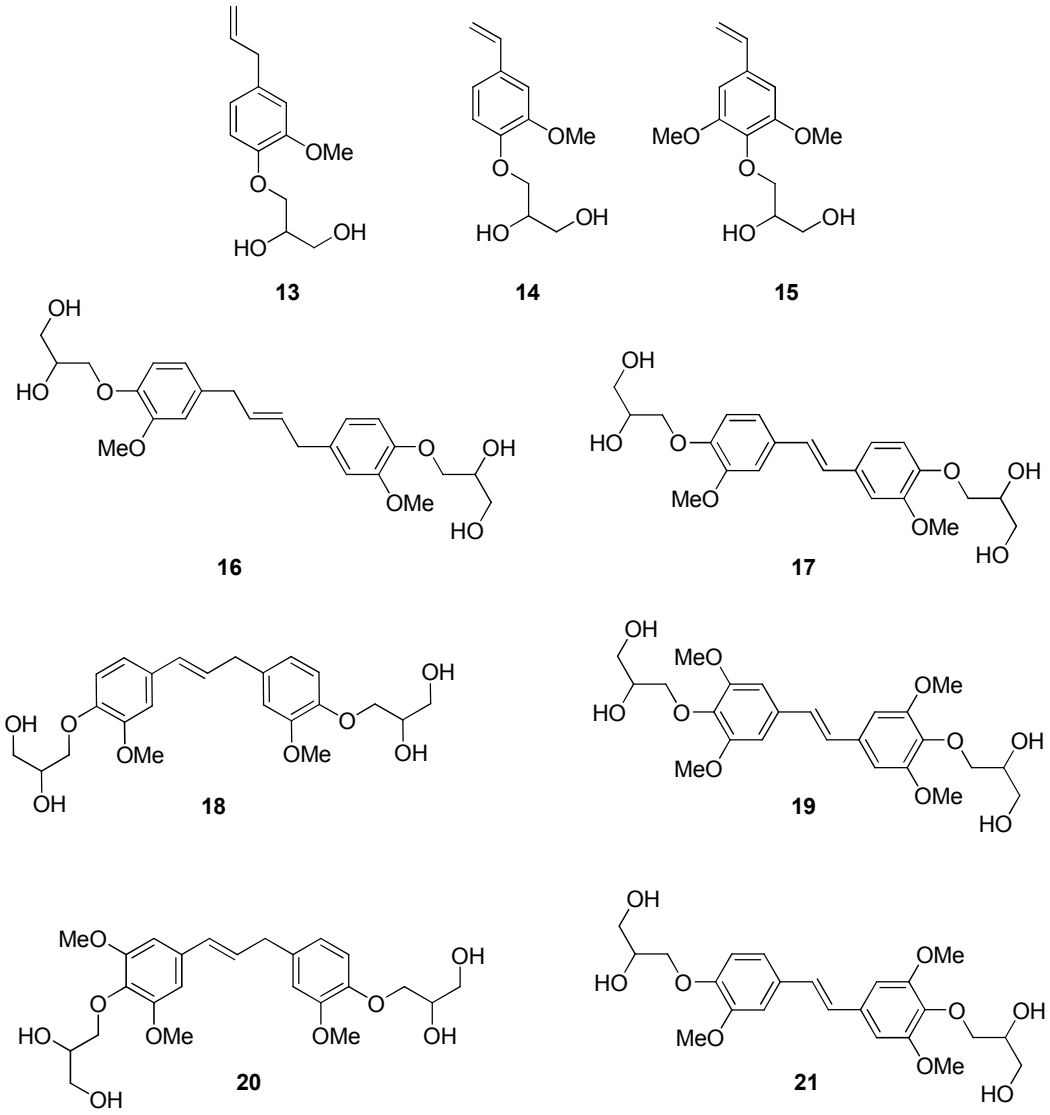

Scheme 6: hydrolysis products of the glycidylated compounds.

Dissociation constants (Kd) of all the structures cited above are summarized in table 2. BPA which has been proven to have an estrogenic effect was included in the calculations as a reference. Interactions of DGEBA and its hydrolysis product with receptor LBD were also evaluated.

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Table 2: the binding affinity of the different ligands to ERα LBD. Agonist and antagonist interactions were computed using PDB structures 3ERD and 3ERT, respectively. Empty cells indicated the absence of binding poses interfering with the ligand binding pocket or helix H12.

Compound	Dissociation constant Kd (µM)	
	Antagonist	**Agonist**
BPA	1	2
DGEBA	20	*50**
7	7	40
8	10	-
9	7	-
10	*30**	-
11	6	*20**
12	40	-
Hydrolysed DGEBA	10	*40**
16	30	-
17	*50**	-
18	10	-
19	*50**	-
20	40	*100**
21	20	-
1	*260**	110
2	220	40
3	130	40
4	30	40
5	*300**	40
6	60	30
13	70	40
14	100	50
15	*130**	40

*: these ligands are predicted to interact with helix H12 but not inside the ligand-binding pocket.

The results displayed in table 2 show that, except for compound **7**, the diglycidylated diphenyls (**8** to **12**) and their hydrolysed derivatives (**17** to **21**) are not predicted to bind to the agonistic conformation of ERα LBD. In contrast, BPA shows a dual action as agonist and antagonist with the same affinity (which is in accordance with literature data[46]).

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Compound **10** resulting from the CM reaction of the glycidylated canolol did not show a significant affinity neither to the agonistic nor to the antagonistic conformations of the receptor. Indeed, binding poses were predicted by the docking calculations with an affinity constant of 30 μM for the antagonistic conformation, but the molecule did not fit within the ligand-binding pocket and was located between Helix 12 and the pocket. Docking the glycidylated compounds **8**, **9**, **11** and **12** showed a certain affinity as antagonists but weaker than that of BPA. For instance, compounds **9** and **12** should be respectively 7-fold and 35-fold more concentrated than BPA to reach a similar effect, according to these estimations.

Compound **7**, produced from the glycidylated eugenol metathesis, exhibits a binding affinity to both agonistic and antagonistic conformations of the receptor LBD, with a marked preference for the antagonistic one. Compared to compound **10** (for which no relevant binding pose was found), compound **7** shows a less hindered and a less constrained structure that may contribute to facilitate its penetration in the ligand binding pocket of the receptor.

According to this computational study, the hydrolysis of the glycidylated diphenyls would modify their respective binding affinities to the antagonistic conformation of the receptor. Indeed, the binding affinities of compounds **8** and **11** become weaker after hydrolysis of their epoxy groups, especially for compound **11**, whereas, the oxirane ring opening of compound **12** would enhance its affinity (as antagonist) to the receptor. Interestingly, the tetrahydroxy derivative generated from the hydrolysis of compound **7** was not found to bind to the agonistic conformation of the receptor, while requiring a concentration 25 times higher than that of BPA to bind to the receptor antagonist form. The only diphenyl that preserved its strong affinity to the receptor antagonistic form after hydrolysis was compound **9**. Indeed, as depicted in figures 1a and 1b, the resulting compound **18** would partially penetrate the receptor binding pocket,

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adopting a similar configuration than that of 4-hydroxytamoxyfen (which is well known for its ERα antagonistic activity). Excluding compound **18**, if we assume that the diglycidylated diphenyls are transformed into tetrahydroxy derivatives when penetrating the human organism, these latter would show a weak activity towards ERα. On the other hand, the antagonistic dissociation constant of compounds **17** and **19** (Kd = 50 µM) perfectly matches with the *in vitro* estimated IC_{50} value of resveratrol[47] (IC_{50} = 58.5 µM), a phenolic diphenyl with a similar chemical structure as **17** and **19**. This brings solid evidence on the computational study efficiency.

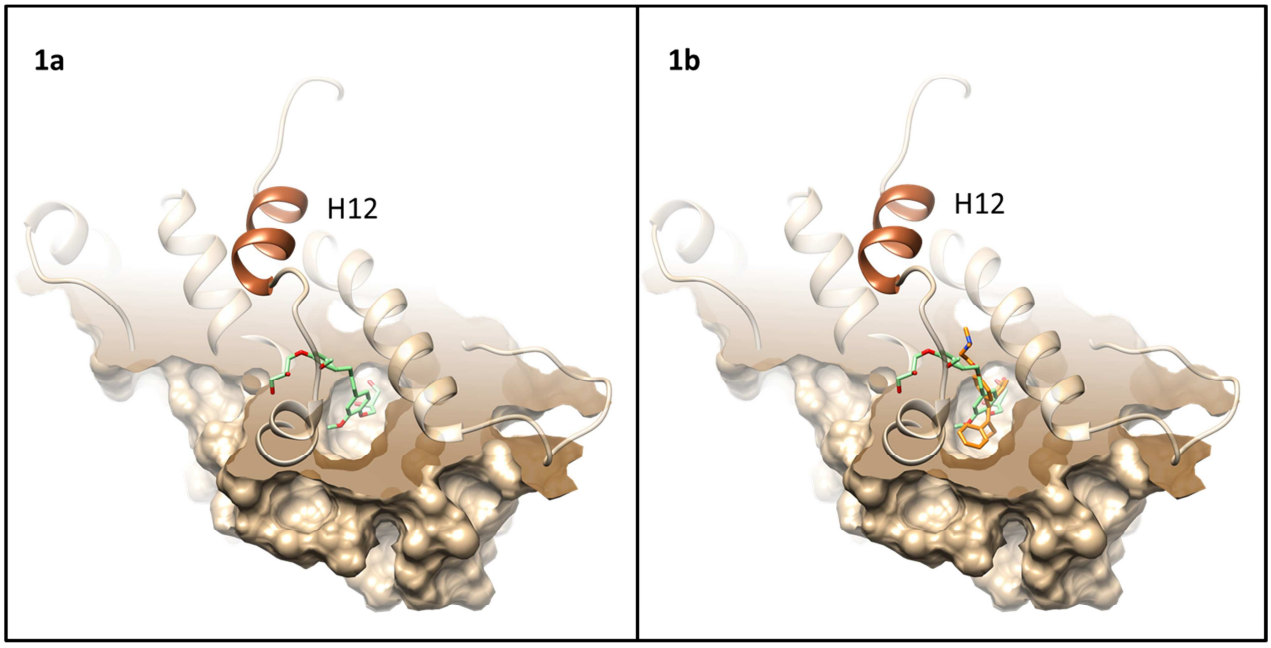

Figure 1: a) antagonist configuration of human estrogen receptor ERα ligand-binding domain (pdb structure 3ERT) in complex with compound **18**. b) antagonist configuration of human estrogen receptor ERa ligand-binding domain (pdb structure 3ERT) in complex with 4-hydroxytamoxifen (orange) and compound 18 (green). Helix 12 is depicted in brown.

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Besides the final products, it was also worth evaluating the potential risk associated to the exposure to the reactants (phenolic compounds **1** to **3)**, intermediates (glycidylated derivatives **4** to **6**) and their hydrolysis products (**13** to **15**).

As shown in table 2, all these compounds display a potential agonist interaction with ERα LBD but with binding affinities 15 to 50 times lower than that of BPA.

The same way, their predicted affinity for the receptor in the antagonist conformation is more than 100 times lower than that of BPA, with the exception of the O-glycidylation products of eugenol **1** (product **4**) and canolol **3** (product **6**) and the hydrolysis product of **4** (compound **13**), which affinities are higher but still 30 to 70 times lower than that of BPA.

CONCLUSIONS

In this work, we have provided a facile synthetic strategy for producing diglycidylated diphenyls from renewable resources. The epichlorohydrin-assisted glycidylation of eugenol **1**, 4-vinyl guaiacol **2** and canolol **3**, followed by the cross metathesis reaction of the glycidylated derivatives converted the three natural phenolic compounds into a set of homo- and hetero-phenolic dimers (**7**-**12**) in good yields and with a high diastereoselectivity. The bio-based synthetized diphenyls comprise two aromatic rings each bearing a methyl oxirane group, which make them good candidates for the substitution of DGEBA.

Molecular docking calculations of their binding to the ligand-binding domain of ERα suggested that diglycidylated diphenyls **7** to **12** present a moderate affinity to the antagonistic conformation of the receptor (6-40 times lower than that of BPA) . However, their hydrolysed forms, which are expected to be predominant in the human organism, exhibit a relatively weak affinity towards ERα LBD in its both agonistic and antagonistic conformations. Obviously, this computational

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approach could be used to give a first indication on the potential risk associated to the synthesized dimers towards the endocrine receptor and must be consolidated and completed through *in vitro* and *in vivo* tests. Compared to DGEBA, which is synthesised from BPA, all the potential substitutes **7** to **12** proposed here are synthesised using reactants or intermediates with a predicted affinity for the ERα LBD much lower than that of BPA. Although this has to be confirmed by *in vivo* studies, this is, besides its bio-based character, another advantage of the proposed synthesis.

Supporting information

1D and 2 D NMR spectra of all the synthesized products. This material is available free of charge via the internet

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REFERENCES

1. E. Burridge, *European Chemical News*, 2003, 17.
2. L. Li, Q. Wang, Y. Zhang, Y. Niu, X. Yao and H. Liu, *Plos One*, 2015, **10**.
3. D. Montes-Grajales and J. Olivero-Verbel, *Toxicology Letters*, 2013, **222**, 312-320.
4. A. V. Krishnan, P. Stathis, S. F. Permuth, L. Tokes and D. Feldman, *Endocrinology*, 1993, **132**, 2279-2286.
5. X. Ye, L.-Y. Wong, A. M. Bishop and A. M. Calafat, *Environ. Health Persp.*, 2011, **119**, 983-988.
6. R. Lofstedt, *Risk Anal.*, 2013, **33**, 192-202.
7. X. Audran, *Glob. Agri. Info. Network*, 2013.
8. A. M. Nelson and T. E. Long, *Polym. Int.*, 2012, **61**, 1485-1491.
9. S. K. Ritter and R. Bryson, *Chem. Eng. News*, 2011, **89**, 13-16.
10. J. R. M. dAlmeida and S. N. Monteiro, *Polym. Test.*, 1996, **15**, 329-339.
11. G. Odian, ed., *Principles of Polymerization*, John Wiley, Hoboken, New Jersey, 2004.
12. B. Ellis, *Chemistry and Technology of Epoxy Resins*, Blackie Academic & Professional, London, 1993.
13. E. C. Dearborn, R. M. Fuoss, A. K. MacKenzie and R. G. Shepherd, *Ind. Eng. Chem.*, 1953, **47**, 2715-2721.
14. S. V. Levchik and E. D. Weil, *Polym. Int.*, 2004, **53**, 1901-1929.
15. L. V. McAdams and J. A. Gannon, *Encyclopedia of Polymer Science and Engineering*, Wiley, New York, 1988.
16. N. Olea, R. Pulgar, P. Perez, F. OleaSerrano, A. Rivas, A. NovilloFertrell, V. Pedraza, A. M. Soto and C. Sonnenschein, *Environ. Health Persp.*, 1996, **104**, 298-305.
17. M. Ueda, *Polym. Eng. Sci.*, 2004, **44**, 1877-1884.
18. K. P. Devi, S. A. Nisha, R. Sakthivel and S. K. Pandian, *J. Etnopharmacol.*, 2010, **130**, 107-115.
19. Y. Baskaran, V. Periyasamy and A. C. Venkatraman, *Toxicology*, 2010, **268**, 204-212.
20. L. V. Mabinya, T. Mafunga and J. M. Brand, *Afr. J. Biotechnol.*, 2010, **9**, 1955-1958.
21. D. Callemien, S. Dasnoy and S. Collin, *J. Agri. Food Chem.*, 2006, **54**, 1409-1413.
22. N. Vanbeneden, F. Gils, F. Delvaux and F. R. Delvaux, *Food Chem.*, 2008, **107**, 221-230.
23. B. Bartolome, C. B. Faulds and G. Williamson, *J. Cereal Sci.*, 1997, **25**, 285-288.
24. C. Brezillon, P. A. Kroon, C. B. Faulds, G. M. Brett and G. Williamson, *Appl. Microbiol. Biotechnol.*, 1996, **45**, 371-376.
25. A. Koski, S. Pekkarinen, A. Hopia, K. Wahala and M. Heinonen, *Eur. Food Res. Technol.*, 2003, **217**, 110-114.
26. D. Wakamatsu, S. Morimura, T. Sawa, K. Kida, C. Nakai and H. Maeda, *Biosci. Biotechnol. Biochem.*, 2005, **69**, 1568-1574.
27. E. Zago, J. Lecomte, N. Barouh, C. Aouf, P. Carre, F. Fine and P. Villeneuve, *Ind. Crops Prod.*, 2015, **76**, 1061-1070.
28. B. Harbaum-Piayda, K. Oehlke, F. D. Soennichsen, P. Zacchi, R. Eggers and K. Schwarz, *Food Chem.*, 2010, **123**, 607-615.
29. O. Trott and A. J. Olson, *J. Comput. Chem.*, 2010, **31**, 455-461.
30. E. F. Pettersen, T. D. Goddard, C. C. Huang, G. S. Couch, D. M. Greenblatt, E. C. Meng and T. E. Ferrin, *J. Comput. Chem.*, 2004, **25**, 1605-1612.
31. N. J. Walton, A. Narbad, C. B. Faulds and G. Williamson, *Curr. Opin. Biotechnol.*, 2000, **11**, 490-496.

View Article Online
DOI: 10.1039/C6NJ00782A

32. C. J. Simpson, M. J. Fitzhenry and N. P. J. Stamford, *Tetrahedron Lett.*, 2005, **46**, 6893-6896.
33. C. Aouf, C. Le Guerneve, S. Caillol and H. Fulcrand, *Tetrahedron*, 2013, 69, 1345-1353.
34. H. Nouailhas, C. Aouf, C. Le Guerneve, S. Caillol, B. Boutevin and H. Fulcrand, *J. Polym. Sci. Part a-Polym. Chem.*, 2011, **49**, 2261-2270.
35. *http://www.solvaychemicals.com/EN/products/chlorinated/*

Allylicproducts/Epichlorohydrin.aspx, Accessed 26.01.2013.

36. N. Bahri-Laleh, R. Credendino and L. Cavallo, *Beilstein J. Org. Chem.*, 2011, **7**, 40-45.
37. F. C. Courchay, J. C. Sworen and K. B. Wagener, *Macromolecules*, 2003, **36**, 8231-8239.
38. S. E. Lehman, J. E. Schwendeman, P. M. O'Donnell and K. B. Wagener, *Inorg. Chim. Acta*, 2003, **345**, 190-198.
39. B. Schmidt, *Eur. J. Org. Chem.*, 2004, 1865-1880.
40. T. C. Morrill and C. A. D'Souza, *Organometallics*, 2003, **22**, 1626-1629.
41. D. Forget-Champagne, M. Mondon, N. Fonteneau and J. P. Gesson, *Tetrahedron Lett.*, 2001, **42**, 7229-7231.
42. A. K. Shiau, D. Barstad, P. M. Loria, L. Cheng, P. J. Kushner, D. A. Agard and G. L. Greene, *Cell*, 1998, **95**, 927-937.
43. K. Fukuzawa, K. Kitaura, M. Uebayasi, K. Nakata, T. Kaminuma and T. Nakano, *J. Comput. Chem.*, 2005, **26**, 1-10.
44. V. A. Oneill, M. D. Rawlins and P. H. Chapman, *Brit. J. Clin. Pharmacol.*, 1981, **12**, 517-521.
45. P. L. Podolin, B. J. Bolognese, J. F. Foley, E. Long, III, B. Peck, S. Umbrecht, X. Zhang, P. Zhu, B. Schwartz, W. Xie, C. Quinn, H. Qi, S. Sweitzer, S. Chen, M. Galop, Y. Ding, S. L. Belyanskaya, D. I. Israel, B. A. Morgan, D. J. Behm, J. P. Marino, Jr., E. Kurali, M. S. Barnette, R. J. Mayer, C. L. Booth-Genthe and J. F. Callahan, *Prostag. Oth. Lipid M.*, 2013, **104**, 25-31.
46. T. Kurosawa, H. Hiroi, O. Tsutsumi, T. Ishikawa, Y. Osuga, T. Fujiwara, S. Inoue, M. Muramatsu, M. Momoeda and Y. Taketani, *Endocr. J.*, 2002, **49**, 465-471.
47. J. L. Bowers, V. V. Tyulmenkov, S. C. Jernigan and C. M. Klinge, *Endocrinology*, 2000, **141**, 3657-3667.

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Graphical abstract

Potential substitutes of diglycidyl ether of bisphenol A (DGEBA) were synthesized by the metathesis reaction of glycidylated biobased phenolic compounds.