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Synthesis and Toxicity of Halogenated Bisphenol Monosubstituted-Ethers: Establishing a Library for Potential Environmental Transformation Products of Emerging Contaminant

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As an important branch of halogenated bisphenol compounds, the halogenated bisphenol monosubstituted-ether compounds have received a lot of attention in environmental health science because of their toxicity and variability. In this study, a synthetic method for bisphenol monosubstituted-ether byproduct libraries was developed. By using the versatile and efficient method, tetrachlorobisphenol A, tetrabromobisphenol A, and tetrabromobisphenol S monosubstituted alkyl-ether compounds were accessed in 39–82% yield. Subsequently, the cytotoxicity of 27 compounds were screened using three different cell lines (HepG2, mouse primary astrocytes and Chang liver cells). Compound 2,6-dibromo-4-[3,5-dibromo-4-(2-hydroxyethoxy)benzene-1-sulfonyl]phenol was more toxic than other compounds in various cells, and the sensitivity of this compound to the normal hepatocytes and cancer cells was inconsistent. The compounds 2,6-dichloro-4-(2-{3,5-dichloro-4-[(prop-2-en-1-yl)oxy]phenyl}propan-2-yl)phenol and 2,6-dibromo-4-(2-{3,5-dibromo-4-[(prop-2-en-1-yl)oxy]-phenyl}propan-2-yl)phenol were the most toxic to HepG2 cells, and most of the other compounds inhibited cell proliferation. Moreover, typical compounds were also reproductive and developmental toxic to zebrafish embryos at different concentrations. The synthetic byproduct libraries could be used as pure standard compounds and applied in research on environmental behavior and the transformation of halogenated flame retardants.

Keywords: halogenated bisphenol, versatile synthetic method, standard compounds, new derivatives, toxicology studies.

Introduction

Tetrachlorobisphenol A (TCBPA), tetrabromobisphenol A (TBBPA), and TBBPA's alternative-tetrabromobisphenol S (TBBPS) are three main types of bisphenol compounds that have been utilized widely as halogenated flame retardants (HFRs). These compounds can be applied in various items, including building materials, synthetic textiles, electronic products, plastic products, and printed circuit boards. For instance, TBBPA bis(allyl) ether (TBBPA-BAE) and TBBPA bis(2,3-dibromopropyl) ether (TBBPA-BDBPE) are used as

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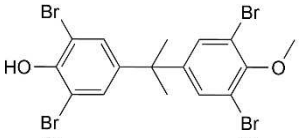
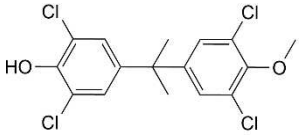
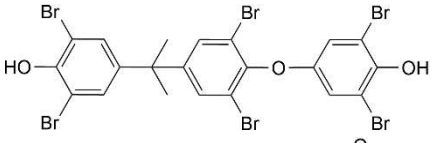
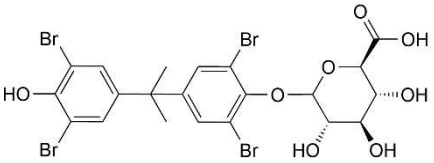
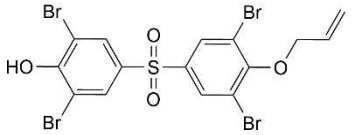
additive flame retardants in polymers.[1,2] They can be released into the environment during the production, usage, and disposal of HFRs-containing products. Thus, HFRs have become ubiquitous environmental contaminants and are detected frequently in various matrices, such as air, sewage sludge, sediment, soil, mankind and animal tissues.[3–15] The levels of TCBPA, TBBPA/S, and their derivatives and transformations are increasing year by year in the environment, which leads to potential environmental and human-health risks.[1,16–23] For instance, they have been detected in umbilical-cord serum and in breast milk with concentrations up to 649.45 ng/g and 11 ng/g, respectively.[24,25] Evidence suggests that HFRs exhibit potential neurotoxicity, endocrine disruption effects on bio-organisms, and reproductive-development toxicity.[20,26–33]

As an important branch of HFRs, the halogenated bisphenol monosubstituted-ether compounds have received a lot of attention in environmental and health effects because of their toxicity and ubiquity (*Table 1*).[34–40] Meanwhile, these compounds result from HFR production, and various derivatives are generated by environmental transformation through oxidation or biological processes. An incomplete reaction is the main mechanism by which diverse byproducts are generated.[41,42] Therefore, hydroxy-group compounds could be used as starting materials to produce polymers and to react halogenated flame retardants according to the mechanism used to extinguish a fire.[43,44] The amount of these compounds in use as byproducts cannot be ignored.

The degradation of TBBPA derivatives from bis-hydroxy substitution compounds to monohydroxy substitution compounds have been predicted by the University of Minnesota Pathway Prediction System (UM-PPS).[18] And the transformed compounds are of particular concern, because they may be more toxic to the environment and organisms.[44–46] For instance, the debromination of tetrabromobisphenol A could yield partial TBBPA derivatives under specific conditions.[47–51] TriBBPA mono(allyl ether) (TriBBPA-MAE) and dibromobisphenol mono(allyl ether)(DBBPA-MAE) as less-brominated bisphenol derivatives have been identified through environmental debromination transformation.[52] It is imperative to identify the byproducts and environmental transformation derivatives, to clarify the fate of halogenated bisphenol monosubstituted-ether compounds, and to reduce the risk of environmental hazards.

In our previous studies, a portion of the products such as TBBPA allyl ether had been identified consis-

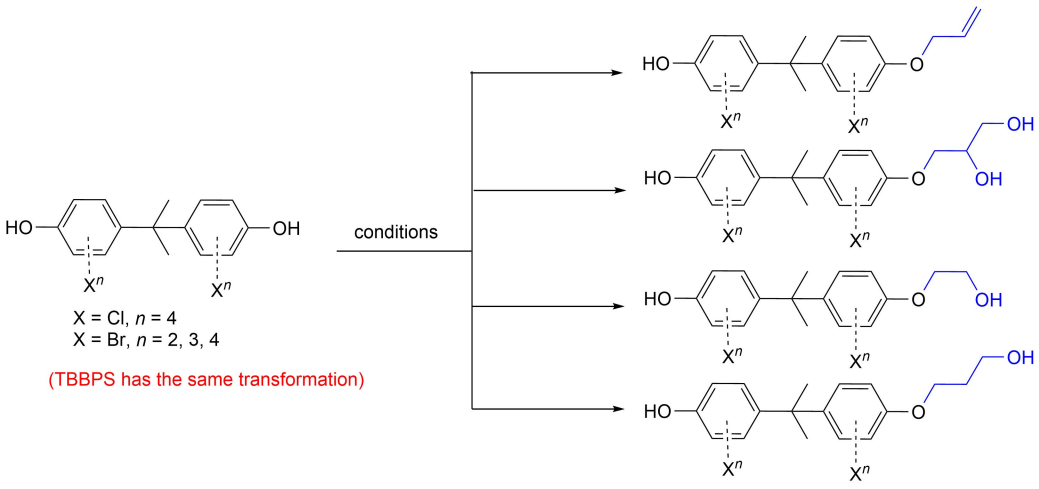
Table 1. Study on the methylation and toxicity of some bisphenol-substituted ether compounds.

Entry	Compounds	Research contents	Reference
1		Microbial *O*-methylation	[34]
2		Microbial *O*-methylation	[34]
3		Study on toxic metabolism	[35,36]
4		Plasma toxicology study	[37–39]
5		Toxic effects	[40]

tently with environmental samples.[18] Because TBBPA/S analogs are produced with TBBPA/S as a raw material, while the reaction of commercial BFR products with the corresponding reagents is not complete, they will contain hypothetical monomodified compounds as impurities. TBBPA mono(allyl ether) (TBBPA-MAE) has been identified as a byproduct of commercial TBBPA disubstituted products.[53] TBBPS mono(allyl ether) was also identified with the same appearance.[54–56] TBBPA mono (3-hydroxypropyl ether), TBBPA mono(2,3-dihydroxypropyl ether),[52] and TBBPA mono(2-hydroxyethyl ether) have been identified as transformation products or byproducts of their derivatives.[41]

TBBPA acting as thyroid hormones can disrupt cell function and ultimately affect health, researchers have shown. To date, understanding the potential health effects of TBBPA has been limited to the results of in vitro testing. In vitro assays have been used to identify human cells with different reactive oxygen species (ROS), such as normal cells, lung cancer cells, and cellular immune cells. Until now, detailed toxicity studies have been conducted on TBBPA or other halogenated flame retardants,[57,58] it has been studied that TBBPA can cause acute toxicity, endocrine disrupting activity, animal immunotoxicity, neurotoxicity, nephrotoxicity and hepatotoxicity. However, monosubstituted derivatives are indeed generated by the side reactions of the flame retardant production process and through further derivatization during environmental transformation, and the toxicity of these compounds have not been systematically studied until now. Due to the lack of convenient synthetic methods to provide the standard compounds, little is known about the environmental behavior, toxicity, and transformation of bisphenol monosubstituted-ether compounds. To date, no examples exist to synthesize the less-brominated bisphenol directly, or to substitute with the hydroxy group as monosubstituted standard compounds. The orientation synthesis of their monohydroxy substitution compounds is urgently needed to study the occurrence, environmental health effect and transformation of TCBPA, TBBPA/S, and their derivatives in the environment. At the same time, systematic analysis of the cytotoxicity of such monosubstituted derivatives provides a reliable environmental impact and health risk assessment data for further research and evaluation of the promotion and use of flame retardants, which has great environmental significance.

We have developed a simple and efficient method to synthesize the monohydroxy substitution byproducts, including TBBPA-MHPE and TBBPA-MDHPE. Mono-, di-, and tribromobisphenol standard compounds were also synthesized using bisphenol A (*Scheme 1*). Using TCBPA, TBBPA/S, and their derivatives as reaction starting materials, the corresponding products were obtained with very high yields as standard compounds to study the environmental behavior and transformation of these chemicals. Based on the novel monosubstituted derivatives, we assayed for cytotoxicity of these compounds in three different lines of cells (HepG2, mouse primary astrocytes and Chang liver cells), and zebrafish embryo toxicity for typical compounds at different concentrations, providing basic data for environmental risk assessment of these compounds.



Scheme 1. Synthesis of halogenated bisphenol monosubstituted-ethers library.

Results and Discussion

Synthesis

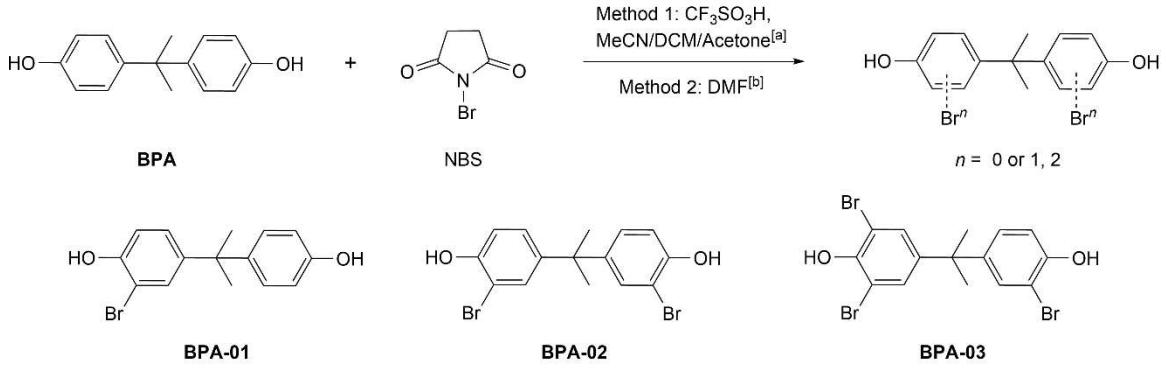
Synthesis of Brominated Bisphenol Compounds

The common method for obtaining different brominated phenolic compounds is mainly to remove bromine under specific conditions using TBBPA, but did not obtain this product using organic-reagent methodology.[59] So we attempted to develop a simple method to obtain bisphenol compounds with different bromine numbers. As illustrated in *Table 2*, our initial studies began with the attempted reaction of BPA with *N*-bromosuccinimide (NBS) using trifluoromethanesulfonic acid as an additive reagent in component solvents at room temperature (r.t.) for 12 h, and the expected product was obtained. According to this method, mono-, di-, and trichlorobisphenol standard compounds can be obtained as derivatives using bisphenol A and *N*-chlorosuccinimide (NCS). The reaction activity of this method was examined with different equivalents in the system that contained NBS, and obtained the target compounds up to in 85% yield (see the *Supporting Information* for more details). Another method which using *N*,*N*-dimethylformamide (DMF) as the solvent was also developed to complete the conversions without trifluoromethanesulfonic acid.

Synthesis of 1,2-Diol Compounds

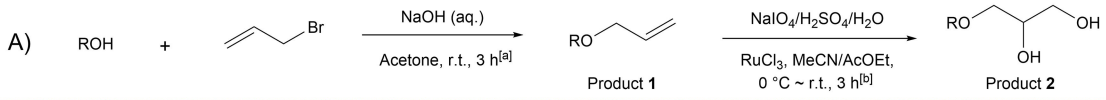
In the synthesis of TBBPA-MDHPE and TBBPS-MDHPE, deleterious and strongly oxidizing reagents, such as 4-methylmorpholine *N*-oxide (NMO) and osmium tetroxide (OsO_4), were used in previous study.[52] To overcome these shortcomings and optimize the reaction conditions, we require an efficient method to synthesize diol-compounds from olefin. Catalyst use has been achieved and has enhanced the conversion reaction; some substrates completed their reaction in 5 min with an 85% yield.[60] We used a versatile method to obtain bisphenol-monoalkyl-diol compounds from bisphenol mono(allyl ether). Initial studies began with the attempted reaction of BPA-02 with 3-bromoprop-1-ene using sodium hydroxide as an alkali in acetone at r.t. for 3 h, and the title product BPA mono(allyl ether) (**1a**) was obtained in a 78% yield (*Scheme 2*, entry 1). The title product 3-{2-bromo-4-[2-(3-bromo-4-hydroxyphenyl)propan-2-yl]phenoxy}-propane-1,2-diol (**2a**) was obtained by using **1a** as the starting material in moderate to good yields (*Scheme 2*, entry 1). Using optimized conditions, we investigated the substrate scope for TCBPA, TBBPA/S, and other derivatives shown in *Scheme 2* (entries 3–5). All starting materials reacted smoothly and afforded corresponding products in moderate to high yields. It is worth mentioning that two product types exist when using BPA-03, because of the unsymmetrical structure of this compound (*Scheme 2*, entry 2).

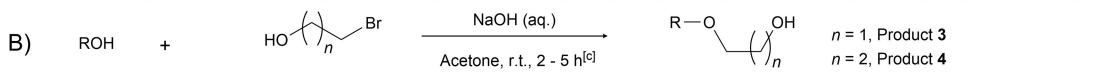
Table 2. Optimizing bromination reaction conditions.

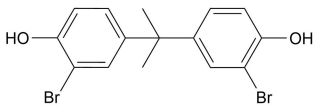
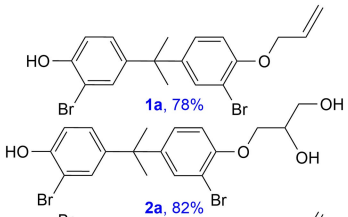
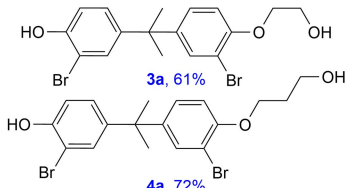
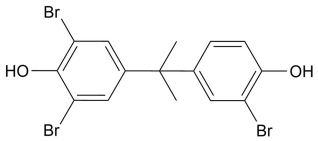
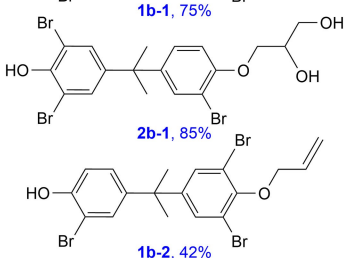
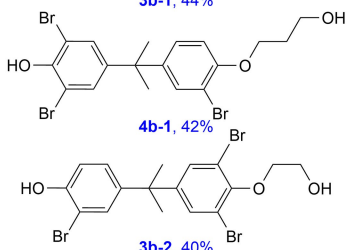
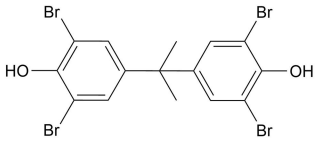
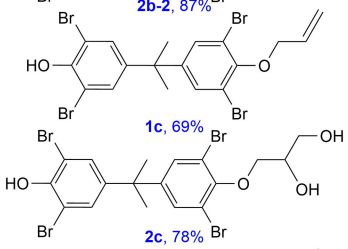
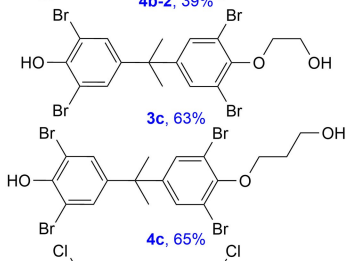
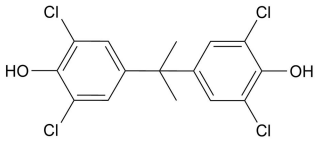
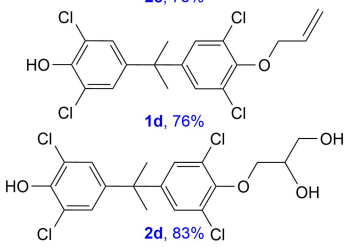
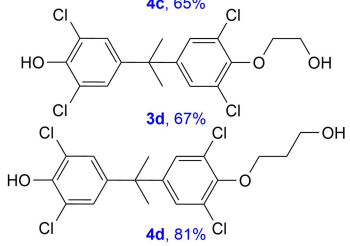
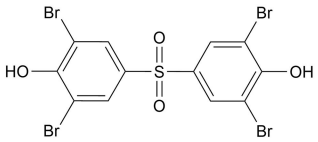
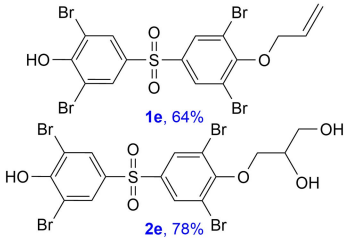
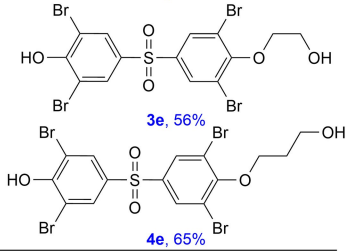


Entry	Equivalent of NBS	Product	Yield[a]	Yield[b]
1	1.0	BPA-01	78%	75%
2	2.5	BPA-02	85%	76%
3	3.0	BPA-03	60%	65%

[a] BPA (1.0 equiv.), NBS (0.8–4.0 equiv.), CF_3SO_3H (3.3 equiv.). [b] BPA (1.0 equiv.), NBS (0.8–4.0 equiv.).





Entry	ROH	Product **1**/Product **2**	Product **3**/Product **4**
1		 **1a**, 78% **2a**, 82%	 **3a**, 61% **4a**, 72%
2		 **1b-1**, 75% **2b-1**, 85% **1b-2**, 42% **2b-2**, 87%	 **3b-1**, 44% **4b-1**, 42% **3b-2**, 40% **4b-2**, 39%
3		 **1c**, 69% **2c**, 78%	 **3c**, 63% **4c**, 65%
4		 **1d**, 76% **2d**, 83%	 **3d**, 67% **4d**, 81%
5		 **1e**, 64% **2e**, 78%	 **3e**, 56% **4e**, 65%

[a] ROH (1.0 equiv.), allyl bromide (1.0 equiv.), NaOH (1.5 equiv.); [b] Olefine (1.0 equiv.), $RuCl_3$ (0.5% mol equiv.), $NaIO_4$ (1.5 equiv.), H_2SO_4 (0.2 equiv.); [c] ROH (1.0 equiv.), bromhydrin (1.5 equiv.), NaOH (2.2 equiv.).

Scheme 2. Synthesis of bisphenol-monoalkene, bisphenol-monoalkyl-diol and bisphenol-monoalkyl alcohol compounds.

Synthesis of Mono-Ol Compounds

As an extension of the above bisphenol-monoalkyl dialcohol, a different chain length bisphenol-monoalkyl alcohol reaction was implemented as displayed in *Scheme 2*. A simpler and shorter reaction condition with atom economy was implemented instead of the former experimental program that used 9-borabicyclo [3.3.1]nonane (9-BBN), anhydrous furanidine, NaOH and H_2O_2 as the reagents. Mono-ethanol and propanol ether compounds were obtained from TCBPA, TBBPA/S, and the derivatives with isolated yields from 39% to 81% (*Scheme 2*, entries 3–5). Corresponding products were obtained for compound BPA-03 in 84% yield in a reaction (for example, the yield of compounds **3b–1** and **3b–2** in a reaction system) (*Scheme 2*, entry 2). The highly efficient synthesis of the bisphenol-monoalkyl-diol compounds was achieved by using a catalyst without deleterious and strongly oxidizing reagents, and more atom economy was implemented instead of the complicated experimental procedures that were used to yield bisphenol-monoalkyl-alcohol compounds (*Scheme 1*). With its operational simplicity, this method could find practical application in polymer research and in the development of the synthesis of other bisphenol compounds.

Toxic Effects of Halogenated Bisphenol Monosubstituted-Ethers Compounds

The results showed that different compounds had different cytotoxicity in *Figure 1*. Generally, most compounds had low cytotoxicity in HepG2, mouse primary astrocytes and Chang liver cells after 24 h exposure compared with that of TBBPA. From the data, IC_{50} values of Compound **3e** were 332.7 μM (HepG2 cells), 455.8 μM (mouse primary astrocytes) and 1593 μM (Chang liver cells), respectively. Compound **3e** was insensitive to two hepatocyte models (HepG2 and Chang liver cells). Compounds **1c** and **1d** were highly toxic in HepG2 cells with IC_{50} values of 991 μM and 588.8 μM, respectively, and the 24-h IC_{50} of compound **1d** to mouse primary astrocytes was 1478 μM. Most of the other compounds induced cell proliferation and the fitting curve was like the trend of compound **3c** (*Figure 1,c*). The 24-h IC_{50} of BPA to ZFL

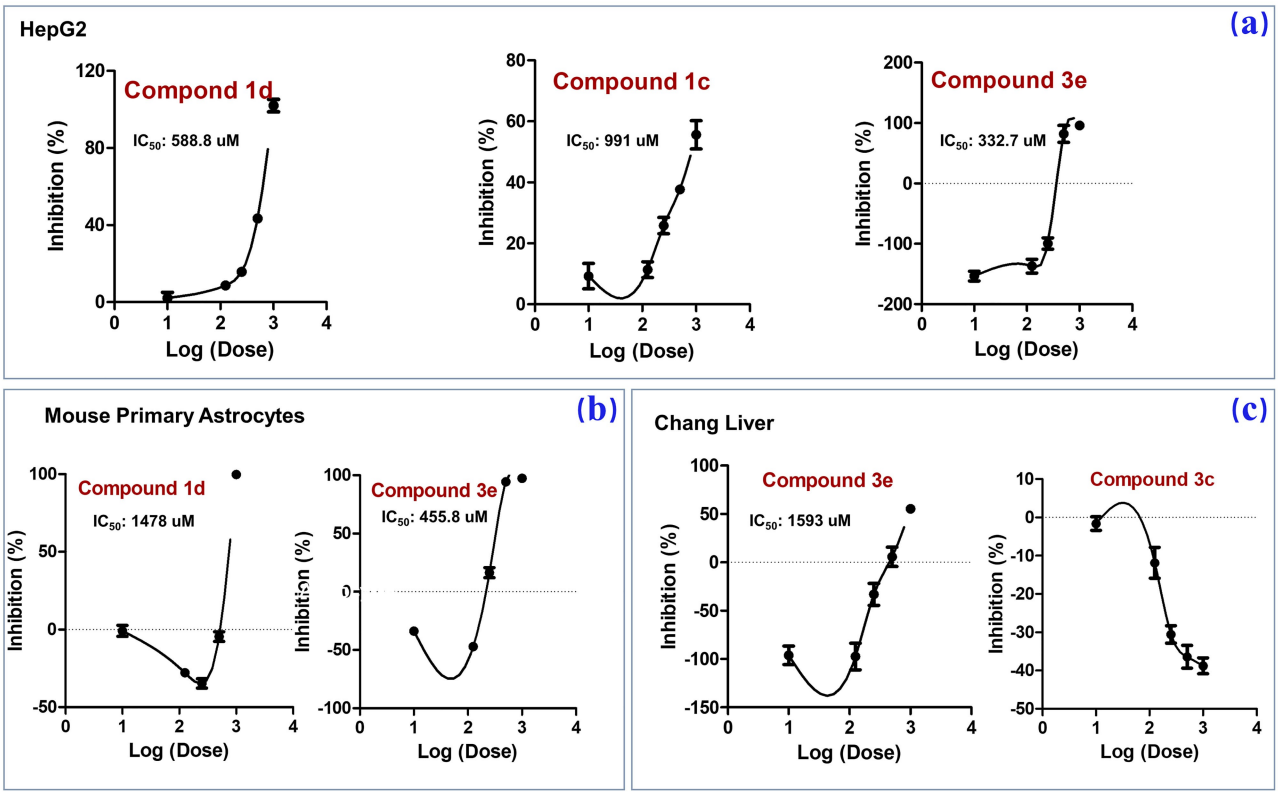


Figure 1. Concentration-response relationship for the inhibitory/stimulating effect of individual bisphenol monosubstituted ether compounds on HepG2 (a), mouse primary astrocytes (b) and Chang Liver (c) cell lines after 24 h of exposure. '•' refers to the experimental data, the solid line (–) is the fitted concentration response curve (standard deviation, $n = 6$).

cell lines was 367.1 μM.[61] A549 cell lines showed decreased cell viability when treated by TBBPA with a concentration of 29.42 μM for 48 h.[62] The in vitro toxicity of TBBPA has been shown to differ between cell lines with IC_{50} ranging from 50 to 200 μM.[63] Our results, in combination with these studies, indicated low acute cell toxicity of bisphenol monosubstituted-ether byproducts compared with TBBPA, in particular, they could be used as a supplement and enhancement of the cytotoxicity studies for TCBPA and TBBPS monosubstituted derivatives. Further studies of the long term toxicity with low concentration exposure of these compounds are needed.

Study of Zebrafish Embryo Toxicity for Typical Bisphenol Monosubstituted Ether Compounds

The results showed that compounds **1c** and **2c** had zebrafish embryo toxicity in *Figure 2*. Generally, the two compounds had reproductive and developmental toxic to zebrafish embryos at different concentrations. The toxicity of compound **1c** to zebrafish embryos was the greatest at 1×10^{-4} mol/L, 2×10^{-5} mol/L concentration, but lower at 2×10^{-4} mol/L concentration (*Figure 2*,*a*). Compound **2c** was highly toxic to zebrafish embryos at 2×10^{-4} mol/L and 1×10^{-4} mol/L concentrations (*Figure 2*,*b*). The embryotoxicity to zebrafish were mainly manifested in the presence of pericardial edema, spinal curvature, tail deformity and delayed hatch in zebrafish (*Figure 2*,*c*–*f*), and more details were also shown in the *Supporting Information*. All studies were conducted in accordance with the guidelines for the care and use of experimental animals at Jianghan University.

By comparison with the reported synthetic methods, the newly synthesized mono-substituted derivatives are used as standard compounds for bisphenol compound byproducts or environmental transformation compounds, providing new insight into environmental-contaminants identification. The synthetic method could also provide and establish reliable technical guarantee for the determination and quantification of TCBPA and TBBPA/S derivatives. Furthermore, research on the cytotoxicity and zebrafish embryo toxicity of a series of compounds provides a scientific basis to evaluate comprehensively the environmental and health risks of related HFRs.

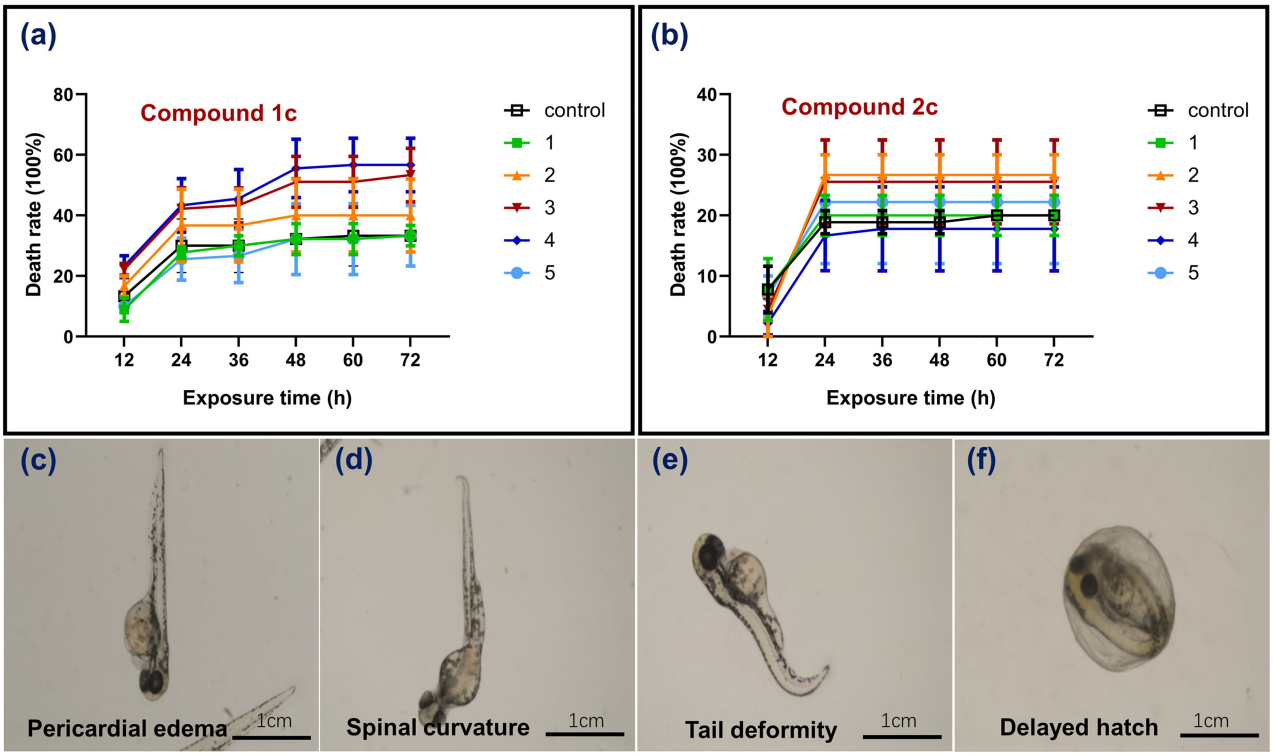


Figure 2. Zebrafish embryotoxicity study of typical bisphenol monosubstituted ether compounds. The death rate of compound **1c** (a) and compound **2c** (b) exposure. '1', '2', '3', '4' and '5' refers to 10, 125, 250, 500, and 1000 μM, respectively. The malformation of embryos included (c) pericardial edema, (d) spinal curvature, (e) tail deformity and (f) delayed hatch.

Conclusions

In this study, we developed the simple methods to obtain brominated bisphenol compounds, then, synthesized TBBPA, TCBPA and TBBPA/S derivatives substituted with different functional groups to build the halogenated bisphenol monosubstituted-ethers compound libraries, finally evaluated the cytotoxicity of these derivative compounds and the zebrafish embryo toxicity of typical compounds. And we anticipate that a simple method to obtain TCBPA, TBBPA/S derivatives will find wide application in organic synthesis, environmental and toxicology studies. The novel study route suggested the generation of new derivatives and probable research on the exposure, absorption and transformation pathways, and degradation products of commercial TCBPA and TBBPA/S derivatives. The cytotoxicity study showed that the cytotoxicity of the compounds with different structures was quite different, and the sensitivity of normal hepatocytes and cancer cells were inconsistent after exposure to the same compound. Compounds **1c** and **2c** had a certain degree of toxicity to zebrafish embryos at different concentrations and had a variety of teratogenic effects on their embryonic development. Cytotoxicity and zebrafish embryos toxicity assays enhanced the understanding of the potential risks of these derivatives exposure to ecological and human health. Subsequent research on environmental transformation, degradation or toxicity will continue to be implemented in our laboratory. The study also contributed to understand the fate, risk assessment, and the resulting health impacts of the transformation products of their derivatives in a detailed investigation in the environment.

Experimental Section

General

Unless otherwise noted, all the starting materials and solvents were purchased from commercial suppliers and directly used. MeOH was purchased from Alfa Aesar. $CDCl_3$, (D_6)acetone, dimethyl sulfoxide (DMSO) and CD_3OD were purchased from Sigma-Aldrich. Reactions were monitored by thin layer chromatography (TLC). Silica gel (200–300 mesh) was purchased from Qingdao Haiyang Chemical Co., China. Cell Counting Kit-8 (CCK-8) were purchased from Biosharp (Beijing, China). Cell culture medium and fetal calf serum were obtained from Gibco (Glasgow, UK). ^{1}H- and ^{13}C-NMR were recorded on a Bruker AVANCE AV 400 (400 MHz and 101 MHz). All NMR chemical shifts were reported with the solvent resonance as internal standard. All cell culture and toxicity test procedures in the experiments were performed according to standardized protocols according to the literature. Laboratory animal handling and animal welfare meet the requirements of the Jianghan University Ethics Committee, and the experimental animal use license number is SYXK2012-0042.

General Procedure for Preparation of Bisphenol Mono(Allyl Ether)

To a solution of bisphenol compound (1.00 equiv.) and allyl bromide (1.10 equiv.) in acetone, a sodium hydroxide aqueous solution (1.80 equiv.) was added dropwise at room temperature. The reaction mixture was stirred for 3 h. Then, the mixture was diluted with dichloromethane, washed with water, filtered and dried over $MgSO_4$. The residue was purified by column chromatography on silica gel after removing the solvent, eluting with hexanes/AcOEt (v/v) to afford the title product **1**. 2-Bromo-4-(2-{3-bromo-4-[(prop-2-en-1-yl)oxy]phenyl}propan-2-yl)phenol (**1a**) as the representative. **1a** was prepared following Method A from 4,4′-(propane-2,2-diyl)bis(2-bromophenol) (3.84 g, 10.0 mmol) as a pale white oil (3.30 g, 78%).[52] R_f = 0.40 (hexanes/AcOEt 5:1 (v/v)). ^{1}H-NMR (400 MHz, CD_3OD): 7.34 (d, J = 4.8, 1H), 7.28 (d, J = 4.8, 1H), 7.04 (d, J = 6.4, 1H), 6.96 (d, J = 6.4, 1H), 6.80 (s, 1H), 6.78 (s, 1H), 5.97–6.03 (m, J = 4.9, 1H), 5.45–5.42 (dd, J = 6.4, 1.8, 1H), 5.19–5.23 (dd, J = 12.4, 4.8, 1H), 4.52–4.50 (d, J = 6.4, 2H), 1.53 (s, 6H). ^{13}C-NMR (101 MHz, CD_3OD): 153.9, 152.8, 145.4, 143.9, 133.9, 132.2, 131.8, 127.8, 127.6, 117.3, 116.6, 114.1, 112.3, 110.2, 70.3, 42.2, 31.1. HR-ESI-MS (*m/z*): calc. for $C_{18}H_{17}Br_2O_2$ $[M-H]^-$, 424.95748; found 424.95810.

General Procedure for Preparation of Bisphenol Monoalkyl-Diol Compounds

To a solution of 1.5 mL of H_2O and 2 N H_2SO_4 (400 μL, 0.4 mmol, 0.200 equiv.), $NaIO_4$ (642 mg, 3 mmol, 1.50 equiv.) was added. After all solids were dissolved, the solution was cooled to 0 °C. A 0.1 M solution of $RuCl_3$ (100 μL, 0.01 mmol, 0.005 equiv.) was added, and the mixture was stirred until the color turned bright yellow, then, followed by adding AcOEt (6 mL) and acetonitrile (6 mL). Continue stirring for another 5 min. The olefin (2 mmol, 1.00 equiv.) was added to the mixture, and the slurry was stirred until all starting material was exhausted. A saturated $NaHCO_3$ solution

(15 mL) and a saturated $Na_2S_2O_3$ solution (20 mL) were added to quench the reaction. The aqueous layer was extracted with AcOEt (3×30 mL). After the combined organic layer was dried over $MgSO_4$, the solvent was evaporated in vacuum. The crude product was purified by flash chromatography, furnishing the title product **2. 3-{2-Bromo-4-[2-(3-bromo-4-hydroxyphenyl)-propan-2-yl]phenoxy}propane-1,2-diol** (**2a**) as the representative. **2a** was prepared following Method B from 2-bromo-4-(2-{3-bromo-4-[(prop-2-en-1-yl)oxy] phenyl}propan-2-yl)phenol (**1a**; 2.12 g, 5.0 mmol) as a pale yellow solid (1.87 g, 82%). R_f=0.40 (hexanes/AcOEt 3:1 (v/v)). ^{1}H-NMR (400 MHz, CD_3OD): 7.33 (d, *J*=8.4, 1H), 7.26 (d, *J*=8.4, 1H), 7.10–7.06 (dd, *J*=6.4, 1.8, 1H), 6.89–6.94 (dd, *J*=12.6, 6.4, 1H), 6.90 (d, *J*=12.4, 1H), 6.80 (d, *J*=12.4, 1H), 4.06–4.02 (m, *J*=4.8, 1H), 4.04–3.98 (m, *J*=4.8, 2H), 3.79–3.76 (dd, *J*=6.4, 1.8, 1H), 3.72–3.68 (dd, *J*=6.4, 1.8, 1H), 1.54 (s, 6H). ^{13}C-NMR (101 MHz, CD_3OD): 154.2, 152.8, 145.6, 144.0, 132.2, 131.9, 128.0, 127.7, 116.6, 113.9, 112.3, 110.2, 71.3, 70.9, 63.9, 42.2, 31.0. HR-ESI-MS (*m/z*): calc. for $C_{18}H_{19}Br_2O_4$ $[M-H]^-$, 458.96296; found 458.96390. Melting range: 122.8~132.0 °C, melting point: 127.1 °C.

General Procedure for Preparation of Bisphenol Mono(2-Hydroxyethyl Ether)

To a solution of bisphenol compound (1.00 equiv.) and 2-bromoethanol (1.05 equiv.) in acetone, a sodium hydroxide aqueous solution (1.80 equiv.) was added dropwise at r.t. The system was stirred for 2–5 h, then, diluted with dichloromethane and washed with water. The organic layer was dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel, eluting with hexanes/AcOEt (v/v) to afford the title product **3. 2-Bromo-4-{2-[3-bromo-4-(2-hydroxyethoxy)phenyl]propan-2-yl}phenol** (**3a**) as the representative. **3a** was prepared following Method C from 4,4′-(propane-2,2-diyl)bis(2-bromophenol) (3.84 g, 10.0 mmol) as a pale yellow solid (2.61 g, 61%). R_f=0.40 (hexanes/AcOEt 3:1 (v/v)). ^{1}H-NMR (400 MHz, CD_3OD): 7.36–7.35 (d, *J*=4.8, 1H), 7.27–7.26 (d, *J*=4.8, 1H), 7.15–7.12 (dd, *J*=12.4, 4.8, 1H), 7.01–6.98 (dd, *J* =12.4, 4.8, 1H), 6.96–6.94 (d, *J*=12.4, 1H), 6.81–6.79 (d, *J*=12.4, 1H), 4.10–4.08 (t, *J*=4.8, 2H), 3.91–3.89 (t, *J*=4.8, 2H), 1.59 (s, 6H). ^{13}C-NMR (101 MHz, CD_3OD): 154.8, 153.2, 145.9, 144.3, 132.6, 132.2, 128.04, 128.02, 116.8, 114.5, 112.7, 110.4, 71.9, 61.6, 42.5, 31.2. HR-ESI-MS (*m/z*): calc. for $C_{17}H_{17}Br_2O_3$ $[M-H]^-$, 428.95240; found 428.95303. Melting range: 122.5~125.5 °C, melting point: 123.8 °C.

General Procedure for Preparation of Bisphenol Mono(3-Hydroxypropyl Ether)

To a solution of bisphenol compound (1.00 equiv.) and 3-bromo-1-propanol (1.05 equiv.) in acetone, a sodium hydroxide aqueous solution (1.80 equiv.) was added dropwise at r.t. The system was stirred for 2–5 h. The reaction mixture was diluted with dichloromethane and washed with water. The organic layer was dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel, eluting with hexanes/AcOEt (v/v) to afford the title product **4. 2-Bromo-4-{2-[3-bromo-4-(3-hydroxypropoxy)phenyl]propan-2-yl}phenol** (**4a**) as the representative. **4a** was prepared following Method D from 4,4′-(propane-2,2-diyl)bis(2-bromophenol) (3.84 g, 10.0 mmol) as a pale yellow solid (3.18 g, 72%). R_f= 0.40 (hexanes/AcOEt 3:1 (v/v)). ^{1}H-NMR (400 MHz, CD_3OD): 7.35–7.34 (d, *J*=4.8, 1H), 7.28–7.27 (d, *J*=4.8, 1H), 7.14–7.12 (dd, *J*=12.4, 4.8, 1H), 7.01–7.68 (dd, *J* =12.4, 4.8, 1H), 6.94–6.92 (d, *J*=8.4, 1H), 6.81–6.79 (d, *J*=8.4, 1H), 4.14–4.11 (t, *J*=4.8, 2H), 3.81–3.78 (t, *J*= 4.8, 2H), 2.04–1.98 (m, *J*=4.8, 2H), 1.59 (s, 6H). ^{13}C-NMR (101 MHz, CD_3OD): 154.7, 153.2, 145.6, 144.3, 132.5, 132.2, 128.04, 128.01, 116.8, 113.9, 112.5, 110.4, 66.9, 59.6, 42.5, 33.2, 31.2. HR-ESI-MS (*m/z*): calc. for $C_{18}H_{19}Br_2O_3$ $[M–H]^-$, 442.96805; found 442.96890. Melting range: 102.7~107.6 °C, melting point: 103.6 °C.

Cell Viability Assay

To evaluate toxicity of HFR compounds in vitro, the cell viability assay was used to screen the toxicity of 27 compounds (including all synthetic compounds, TBBPA, TCBPA and TBBPS) in HepG2 cells, mouse primary astrocytes and Chang liver cells. The chemicals' solutions were made as stock solutions and prepared freshly before exposure experiment. We dissolved TBBPA, TCBPA and the other compounds in serum-free medium and the final concentration of DMSO was less than 0.1%. HepG2 cells, mouse primary astrocytes and Chang liver cells were seeded into 96-well plates at a cell density of 10,000 cells/well. After culturing overnight, the medium were changed to 100 μL serum-free medium containing different concentrations of bisphenol derivatives (diluted to 10, 125, 250, 500, and 1000 μM, respectively). Reagent blank and control group (0.1% DMSO, V/V) of 6 parallel were conducted. After exposure for 24 h, the exposed solution was aspirated, and 100 μL of the medium diluted CCK-8 reagent (10%) were added in the dark, and the incubation was continued to 2 h in a

carbon dioxide incubator, and the absorbance at 450 nm was measured by a microplate reader (SpectraMax i3x, Molecular Device, USA). The mean and standard deviation of each set of data were calculated and further converted to a percentage relative to the control group. Cell viability = $(OD_{Drug} - OD_{Blank})/(OD_{Control} - OD_{Blank}) \times 100\,\%$. Cell inhibition = 1 − cell viability. Regression analysis was performed using nonlinear least-squares fit, and the IC_{50} (half inhibitory concentration) value was obtained using GraphPad Prism 5.0 software.

Zebrafish Embryo Cultivation and Drug Exposure

To evaluate zebrafish embryotoxicity of compounds **1c** and **2c**, zebrafish embryos were exposed to different concentrations of each compound. Zebrafish of AB strain obtained from the China Zebrafish Resource Center (Wuhan, China) was used in the exposure experiment. The embryos were collected and cultured in a six-well plate with 30 eggs per well and 2 ml of exposure solution. The exposure experiments consisted of five concentration gradients (1×10^{-3} mol/L, 2×10^{-4} mol/L, 1×10^{-4} mol/L, 2×10^{-5} mol/L, 1×10^{-5} mol/L, respectively) and one control group with three replicates of each group. The drugs were dissolved in DMSO and diluted to each concentration with fresh fish culture water. The final concentration of DMSO of exposure group and control group was 0.1 %. The embryo exposure was performed in a constant temperature incubator at 28 °C. The dead embryos and exposed solution were removed and changed twice a day. The mortality rate was recorded at 12 hpf (hour post fertilization), 24 hpf, 36 hpf, 48 hpf, 60 hpf, 72 hpf. The malformation was recorded at 72 hpf. The embryos with malformation were imaged by a microscope (SteREO Discovery.V20, Zeiss) and a color CCD (506 color, Zeiss).

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Author Contribution Statement

R. Guo, M. Hu, and W. Deng performed the organic synthesis experiments. R. Guo, M. Cao, S. Ye, and W. Zhou performed the biological experiments, contributed samples and analysis tools. Y. Gao and W. Zhang analyzed the data. R. Guo analyzed the data and wrote the article. R. Guo and J. Shi conceived and designed the experiments.

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