Supplementary Material

Polybrominated diphenyl ethers isolated from the marine sponge *Lendenfeldia chondrodes* collected in Mayotte

Charifat Saïd Hassane[a], Florent Tintillier[a], Pierre-Eric Campos[a, b], Gaëtan Herbette[c], Nicole J. de Voogd[d, e], Jamal Ouazzani[f], Mireille Fouillaud[a], Laurent Dufossé[a] and Anne Gauvin-Bialecki*[,a]

[a] *Laboratoire de Chimie et de Biotechnologie des Produits Naturels, Faculté des Sciences et Technologies, Université de La Réunion, Saint-Denis, La Réunion, France.*

[b] *Institut de Chimie Organique et Analytique, Université d'Orléans - Pôle de chimie, Orléans, France.*

[c] *Spectropole, FSCM CNRS, Centrale Marseille, Aix-Marseille University, Marseille, France.*

[d] *Naturalis Biodiversity Center, Leiden, The Netherlands.*

[e] *Institute of Environmental Sciences, Leiden University, Leiden, The Netherlands.*

[f] *Institut de Chimie des Substances Naturelles, CNRS UPR 2301, Université Paris-Saclay, Gif-sur-Yvette, France.*

***** *Correspondence: anne.bialecki@univ-reunion.fr; Tel.: +262 262 93 81 97*

CDK7 and FynB protein kinases have been recognized as relevant targets for cancer and brain diseases treatment due to their pivotal regulatory roles in cellular functions such as cell cycle and neural signal transduction. Several studies demonstrated that the inhibition of these proteins could be useful in altering the onset or progression of these diseases. Based on bioassay-guided approach, the extract of the marine sponge Lendenfeldia chondrodes (Thorectidae), which exhibited interesting kinase inhibitory activities, was fractionated. The investigation led to the isolation of five known 1-5 and one new 6 polybrominated diphenyl ethers (PBDEs). Their structure elucidation was established based on spectroscopic data (NMR and HRMS) and comparison with literature data.

List of content

Table S1. List of the isolated known compounds with their CAS Registry Number, synonyms in cited literature and IUPAC names.

Compound	CAS RN	Synonym used in literature and IUPAC names
1	934243-34-2	2-(3’,5’-dibromo-2′-hydroxyphenoxy)-3,5-dibromophenol
		3,5-dibromo-2-(3,5-dibromo-2-hydroxyphenoxy)phenol
2	170473-61-7	4,6-dibromo-2-(4’,5’,6’-tribromo-2’-hydroxyphenoxy)phenol
		3,4,5-tribromo-2-(3,5-dibromo-2-hydroxyphenoxy)phenol
3	170473-60-6	4,6-dibromo-2-(2’-methoxy-4’,6’-dibromophenoxy)phenol
		3,5-dibromo-2-(3,5-dibromo-2-methoxyphenoxy)phenol
4	661476-66-0	2-(4’,5’,6’-tribromo-2’-methoxyphenoxy)-4,6-dibromophenol
		2,4-dibromo-6-(2,3,4-tribromo-6-methoxyphenoxy)phenol
5	80246-27-1	3,4,4’,5,6,6’-Hexabromo-2,2’-oxydiphenol
		2,3,4,5-tetrabromo-6-(3,5-dibromo-2-hydroxyphenoxy)phenol

3,5-dibromo-2-(3’,5’-dibromo-2’-hydroxyphenoxy)phenol (**1**). White cristal. MS m/z 540.7 $[M+Na]^+$ and 516.7 [M-H]- ($C_{12}H_5Br_4O_3$).

Figure S1. Mass spectra for 3,5-dibromo-2-(3’,5’-dibromo-2’-hydroxyphenoxy)phenol (**1**)

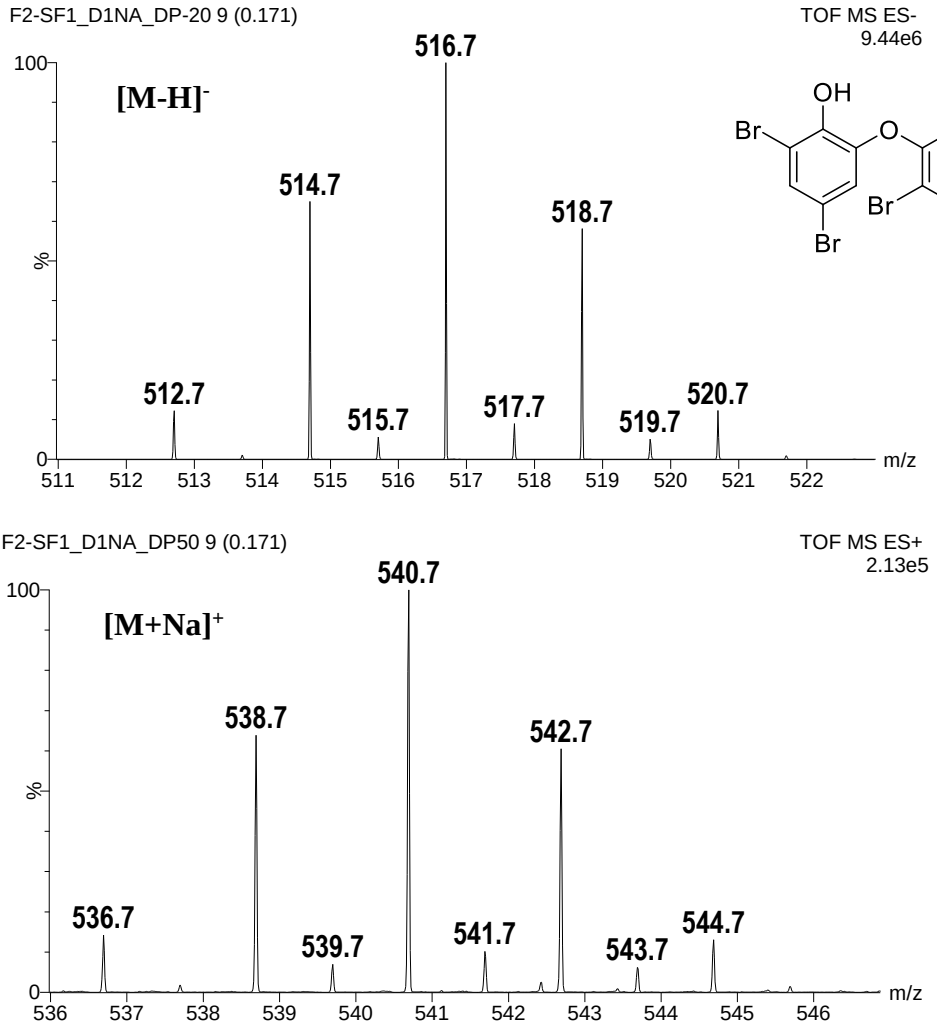


Figure S2. ^{1}H NMR (600 MHz, CD_3OD) spectrum for 3,5-dibromo-2-(3',5'-dibromo-2'-hydroxyphenoxy)phenol (**1**)

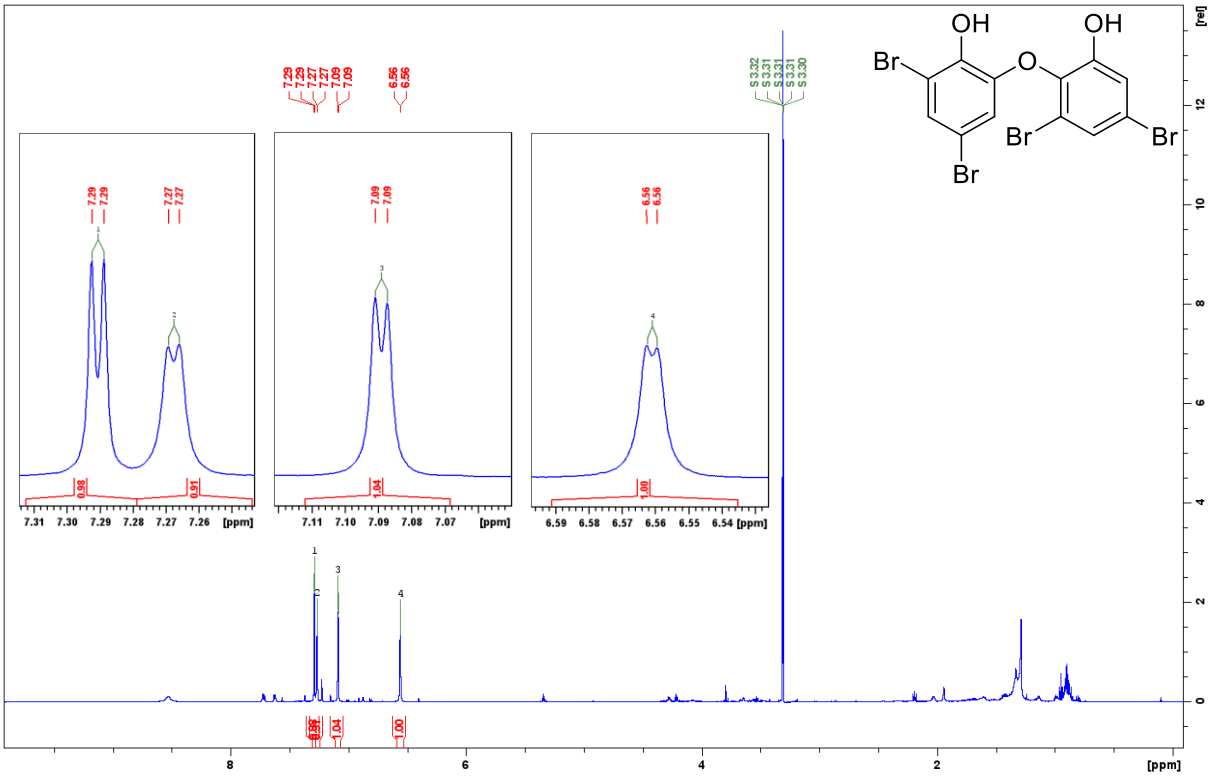


Figure S3. ^{13}C NMR (150 MHz, CD_3OD) spectrum for 3,5-dibromo-2-(3',5'-dibromo-2'-hydroxyphenoxy)phenol (**1**)

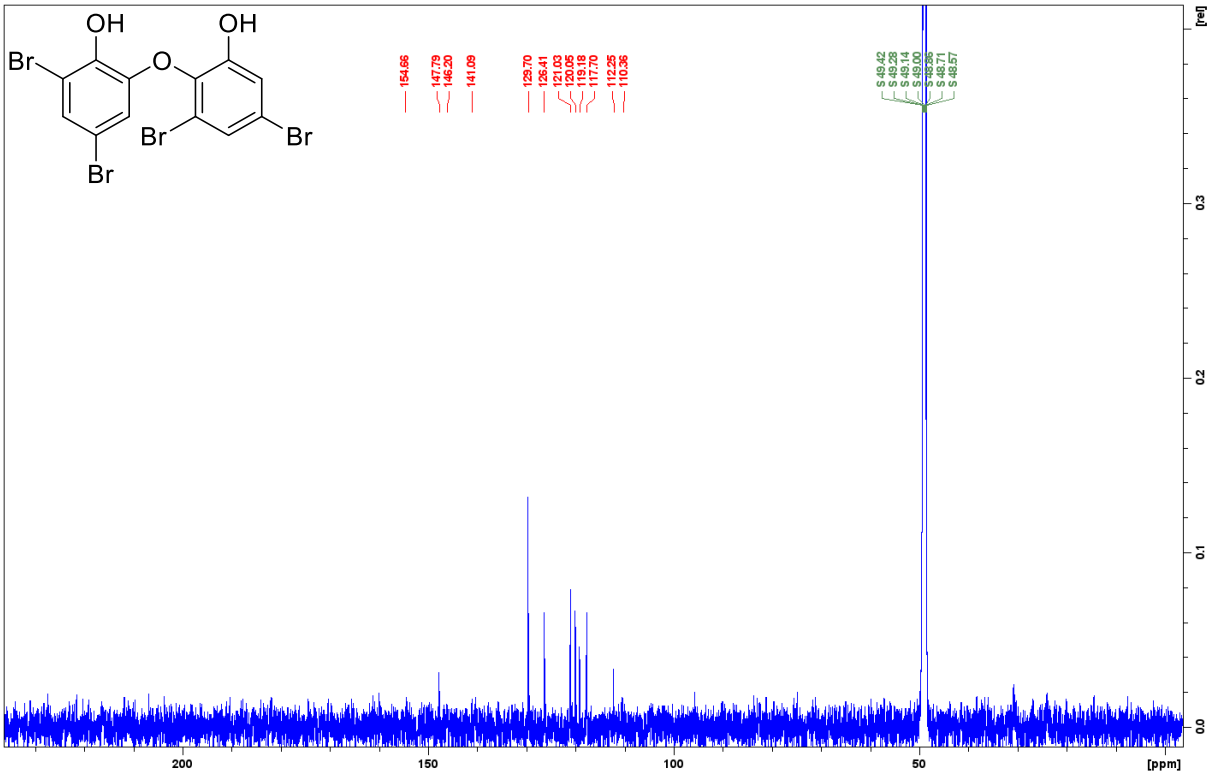


Table S2. Comparative ^{1}H and ^{13}C NMR spectral data of compound **1** and 2-(3',5'-dibromo-2'-hydroxyphenoxy)-3,5-dibromophenol[1].

	Compound 1 (^{1}H 600 MHz, ^{13}C 150 MHz, CD_3OD)		2-(3',5'-dibromo-2'-hydroxyphenoxy)-3,5-dibromophenol[1] (^{1}H 500 MHz, ^{13}C 125 MHz, acetone-d_6)	
Position	δ_H (H, mult., *J* in Hz)	δ_C	δ_H (mult., *J* in Hz)	δ_C
1		154.7		152.6
2		141.1		139.3
3		120.1		118.6
4	7.27 (1H, d, 2.2)	126.4	7.38 (d, 2.1)	126.8
5		119.2		119.6
6	7.09 (1H, d, 2.2)	121.0	7.24 (d, 2.1)	120.7
1'		147.8		146.7
2'		146.2		144.5
3'		112.3		111.2
4'	7.29 (1H, d, 2.2)	129.7	7.37 (d, 2.1)	129.1
5'		110.4		110.7
6'	6.56 (1H, d, 2.2)	117.7	6.64 (d, 2.1)	116.3

[1] [1] N. K. Utkina, V. A. Denisenko, 'New polybrominated diphenyl ether from the marine sponge *Dysidea herbacea*', *Chem. Nat. Compd.* **2006**, *42*, 606–607.

3,4,5-tribromo-2-(3’,5’-dibromo-2’-hydroxyphenoxy)phenol (**2**). White cristal. MS *m/z* 618.6 $[M+Na]^+$ and 594.6 $[M-H]^-$ ($C_{12}H_4Br_5O_3$).

Figure S4. Mass spectra for 3,4,5-tribromo-2-(3’,5’-dibromo-2’-hydroxyphenoxy)phenol (**2**)

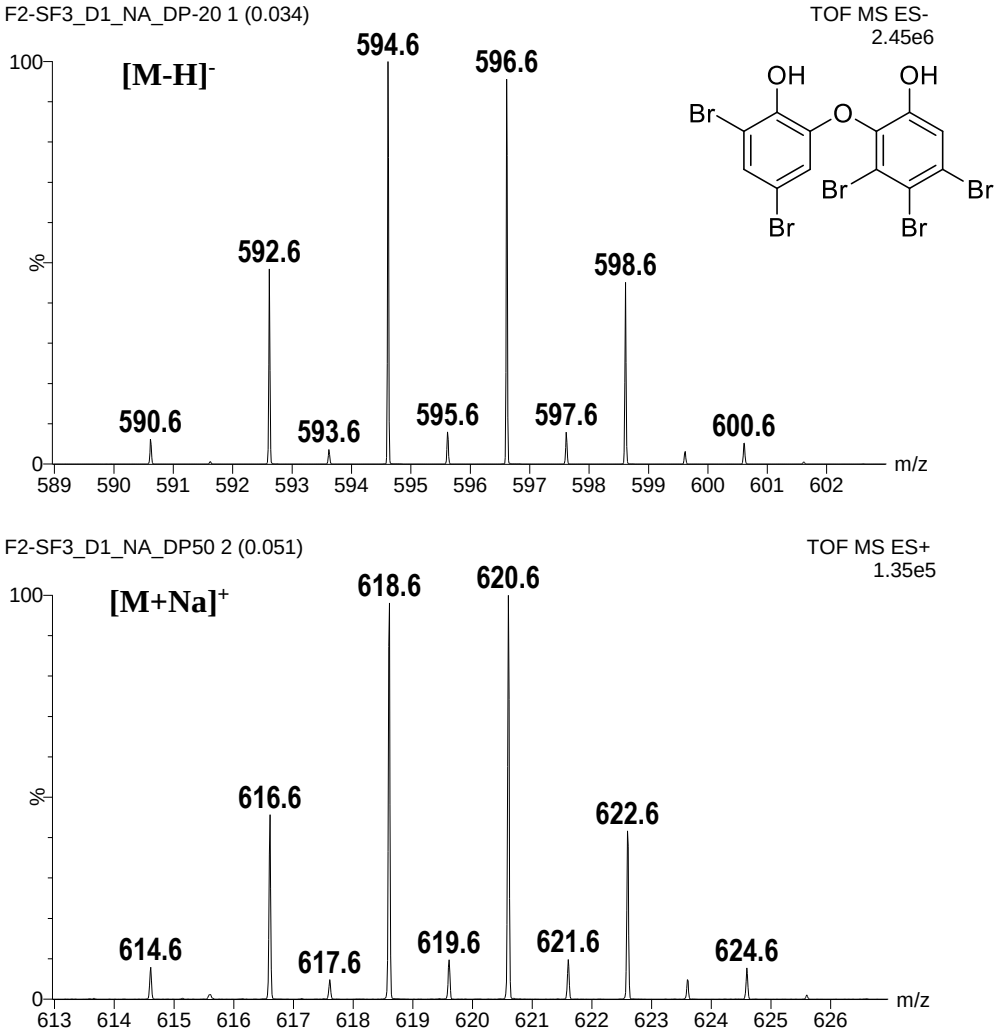


Figure S5. ^{1}H NMR (600 MHz, CD_3OD) spectrum for 3,4,5-tribromo-2-(3',5'-dibromo-2'-hydroxyphenoxy)phenol (**2**)

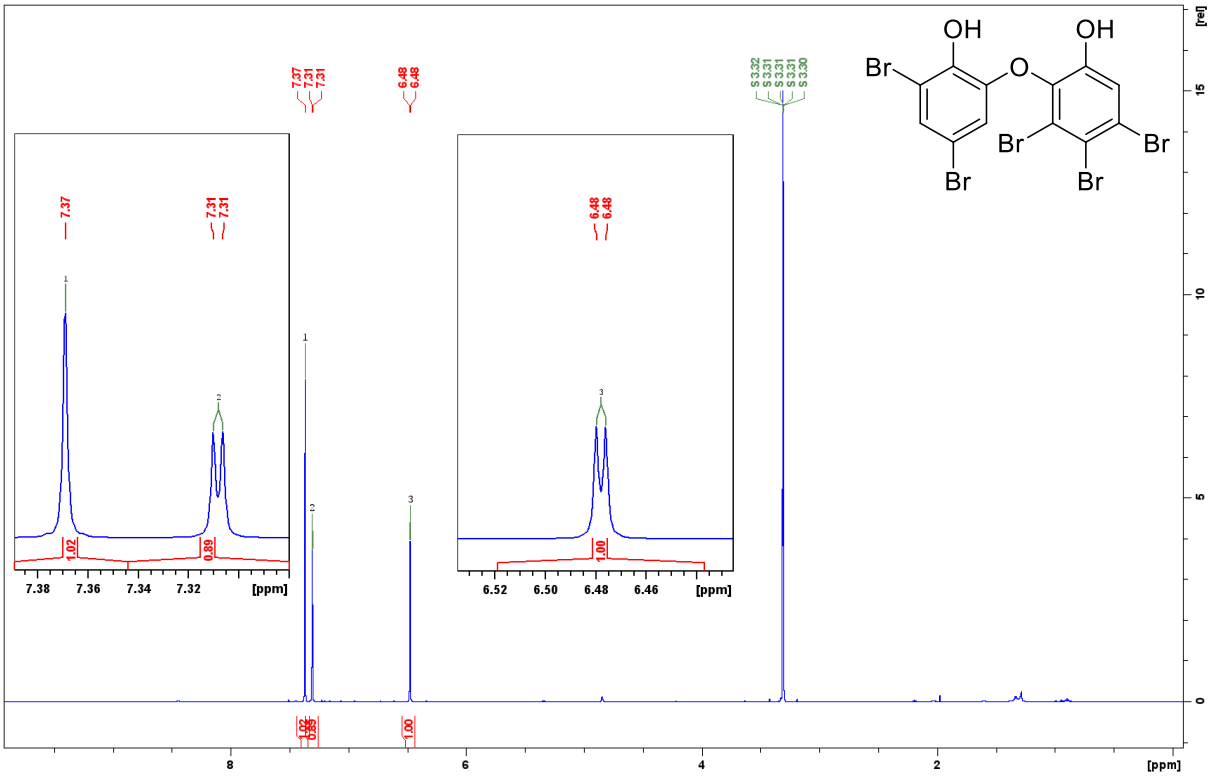


Figure S6. ^{13}C NMR (150 MHz, CD_3OD) spectrum for 3,4,5-tribromo-2-(3',5'-dibromo-2'-hydroxyphenoxy)phenol (**2**)

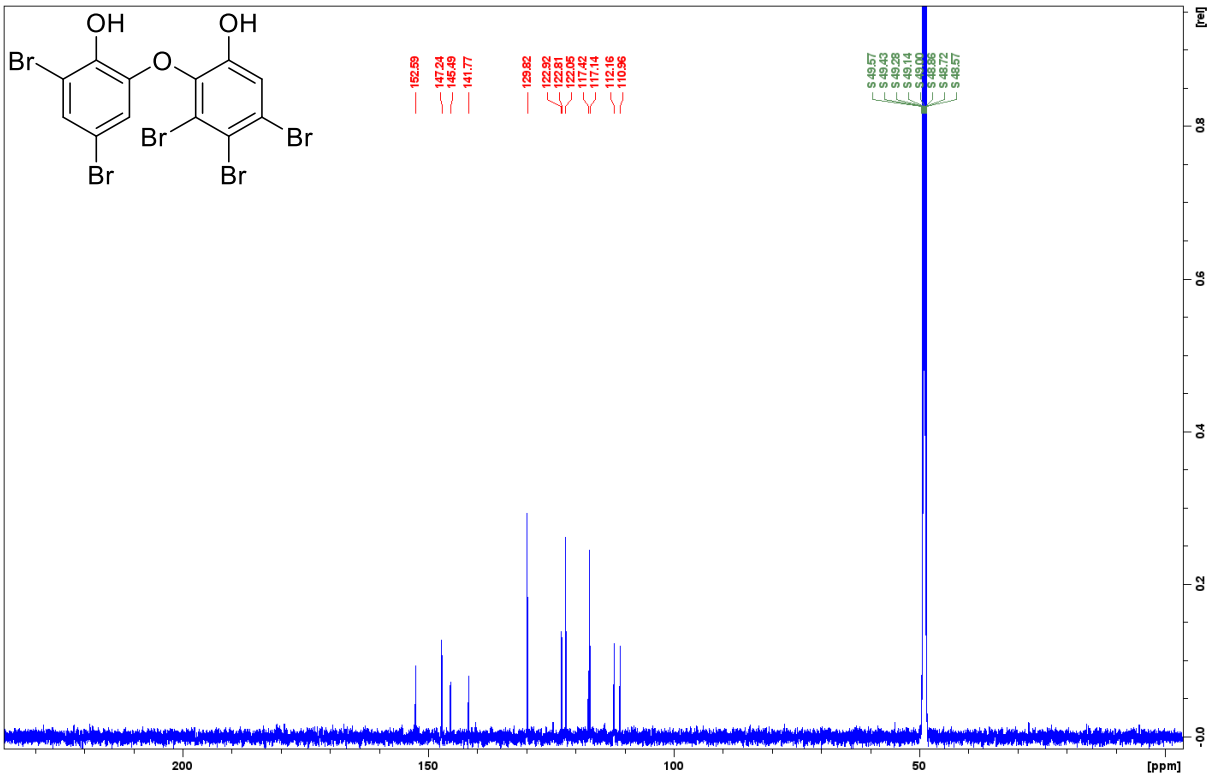


Table S3. Comparative ^{1}H and ^{13}C NMR spectral data of compound **2** and 4,6-dibromo-2-(4',5',6'-tribromo-2'-hydroxyphenoxy)phenol[2].

	Compound **2** (^{1}H 600 MHz, ^{13}C 150 MHz, CD_3OD)		4,6-dibromo-2-(4',5',6'-tribromo-2'-hydroxyphenoxy)phenol[2] (^{1}H 300Hz, CD_3OD)
Position	δ_H (H, mult., *J* in Hz)	δ_C	δ_H (H, mult., *J* in Hz)
1		152.6	
2		141.8	
3		122.8	
4		117.4	
5		122.9	
6	7.37 (1H, s)	122.1	7.26 (1H, s)
1'		147.2	
2'		145.5	
3'		111.0	
4'	7.31 (1H, d, 2.2)	129.8	7.23 (1H, d, 2)
5'		112.2	
6'	6.48 (1H, d, 2.2)	117.1	6.46 (1H, d, 2)

2 [2] X. Fu, F. J. Schmitz, M. Govindan, S. A. Abbas, K. M. Hanson, P. A. Horton, P. Crews, M. Laney, R. C. Schatzman, 'Enzyme inhibitors: new and known polybrominated phenols and diphenyl ethers from four Indo-Pacific *Dysidea* sponges', *J. Nat. Prod.* **1995**, *58*, 1384–1391.

3,5-dibromo-2-(3',5'-dibromo-2'-hydroxyphenoxy)anisole (**3**). White cristal. MS *m/z* 554.7 $[M+Na]^+$ and 530.7 $[M-H]^-$ ($C_{13}H_7Br_4O_3$).

Figure S7. Mass spectra for 3,5-dibromo-2-(3',5'-dibromo-2'-hydroxyphenoxy)anisole (**3**)

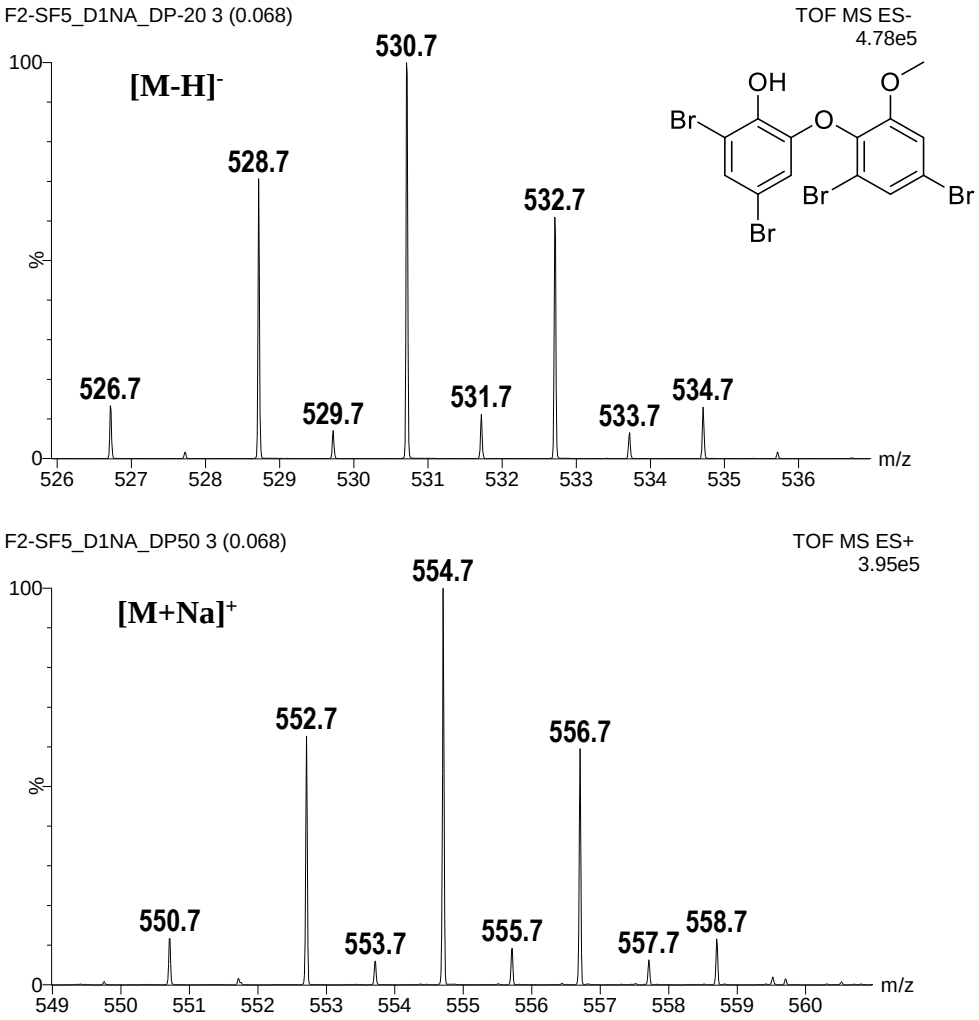


Figure S8. ^{1}H NMR (600 MHz, CD_3OD) spectrum for 3,5-dibromo-2-(3',5'-dibromo-2'-hydroxyphenoxy)anisole (**3**)

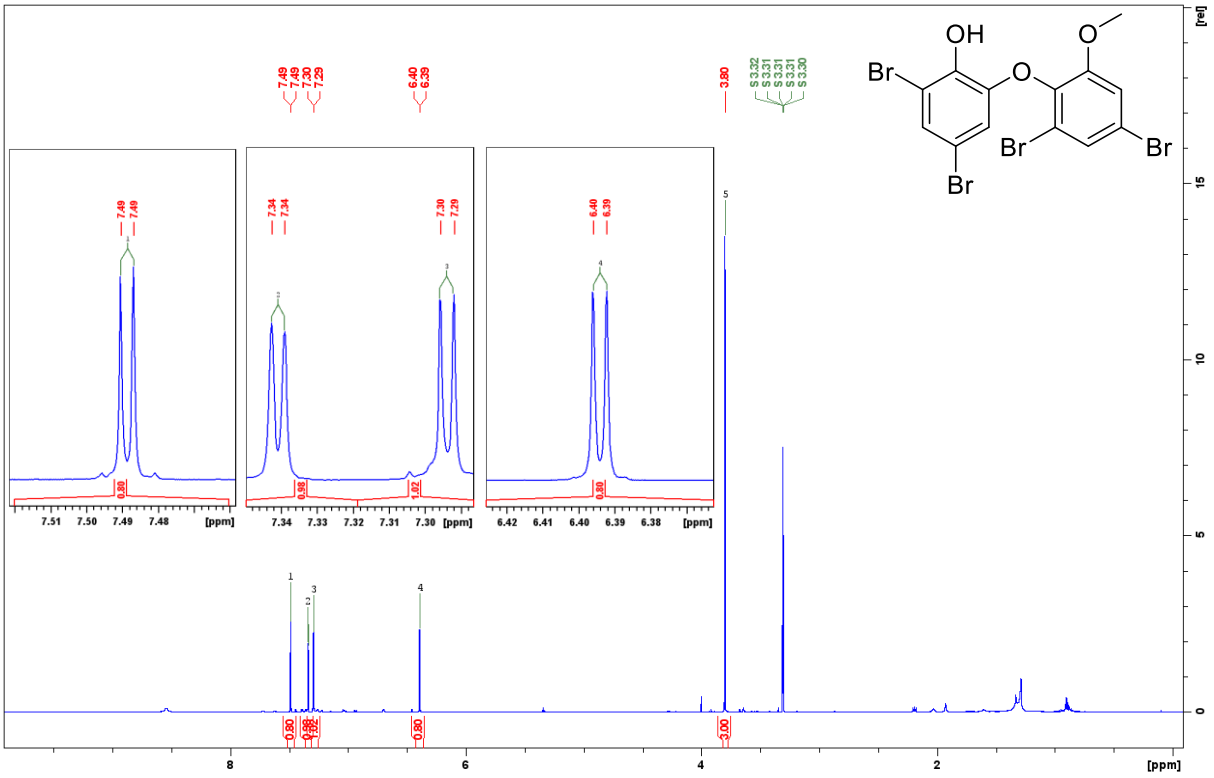


Figure S9. ^{13}C NMR (150 MHz, CD_3OD) spectrum for 3,5-dibromo-2-(3',5'-dibromo-2'-hydroxyphenoxy)anisole (**3**)

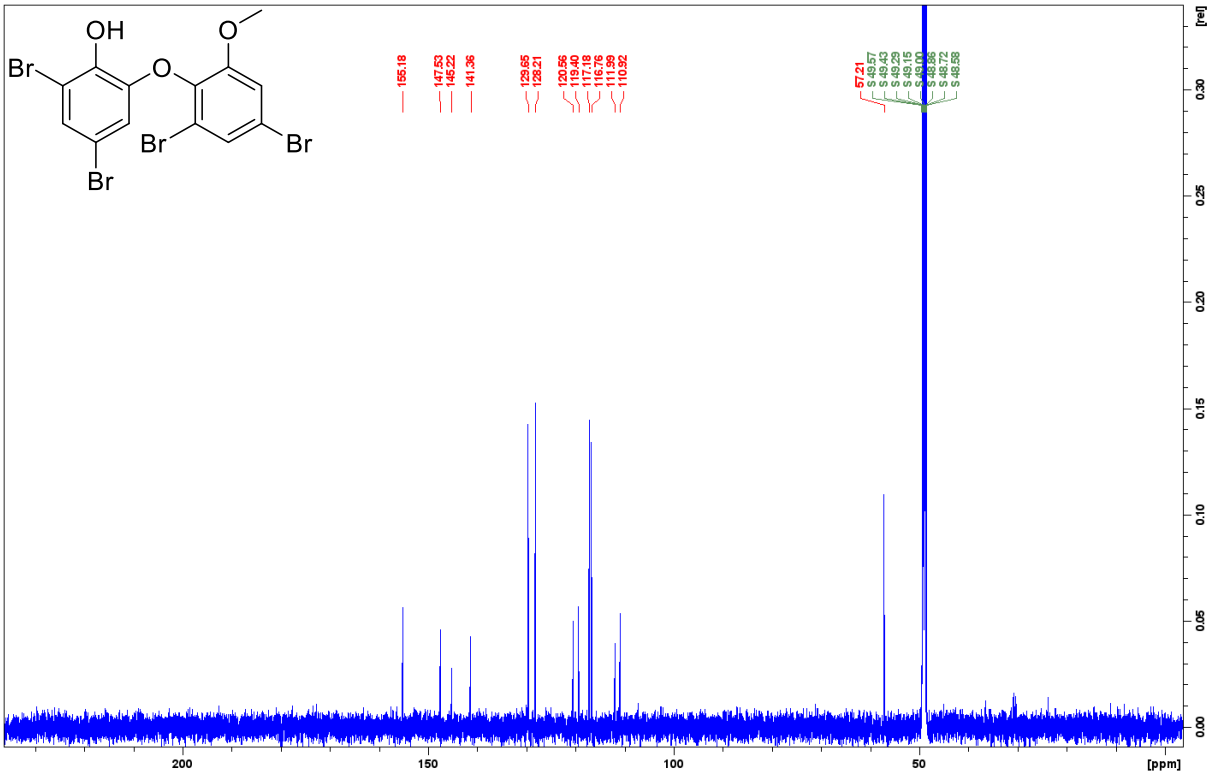


Table S4. Comparative ^{1}H and ^{13}C NMR spectral data of compound **3** and 4,6-dibromo-2-(2'-methoxy-4',6'-dibromophenoxy)phenol[3].

	Compound **3** (^{1}H 600 MHz, ^{13}C 150 MHz, CD_3OD)		4,6-dibromo-2-(2'-methoxy-4',6'-dibromophenoxy)phenol[2] (^{1}H, ^{13}C 300Hz, $CDCl_3$)	
Position	δ_H (H, mult., *J* in Hz)	δ_C	δ_H (H, mult., *J* in Hz)	δ_C
1		155.2		153.4
2		141.4		139.9
3		119.4		118.6
4	7.49 (1H, d, 2.2)	128.2	7.40 (1H, d, 2)	127.5
5		120.6		119.8
6	7.34 (1H, d, 2.2)	117.2	7.09 (1H, d, 2)	116.5
O-Me	3.80 (3H, s)	57.2	3.78 (3H, s)	56.6
1'		147.5		145.2
2'		145.2		142.8
3'		112.0		111.5
4'	7.29 (1H, d, 2.2)	129.6	7.33 (1H, d, 2)	129.2
5'		110.9		110
6'	6.39 (1H, d, 2.2)	116.8	6.54 (1H, d, 2)	115.7

[3] [2] X. Fu, F. J. Schmitz, M. Govindan, S. A. Abbas, K. M. Hanson, P. A. Horton, P. Crews, M. Laney, R. C. Schatzman, 'Enzyme inhibitors: new and known polybrominated phenols and diphenyl ethers from four Indo-Pacific *Dysidea* sponges', *J. Nat. Prod.* **1995**, *58*, 1384–1391.

3,4,5-tribromo-2-(3’,5’-dibromo-2’-hydroxyphenoxy)anisole (**4**). White cristal. MS *m/z* 632.6 $[M+Na]^+$ and 608.6 $[M-H]^-$ ($C_{13}H_6Br_5O_3$).

Figure S10. Mass spectrum for 3,4,5-tribromo-2-(3’,5’-dibromo-2’-hydroxyphenoxy)anisole (**4**)

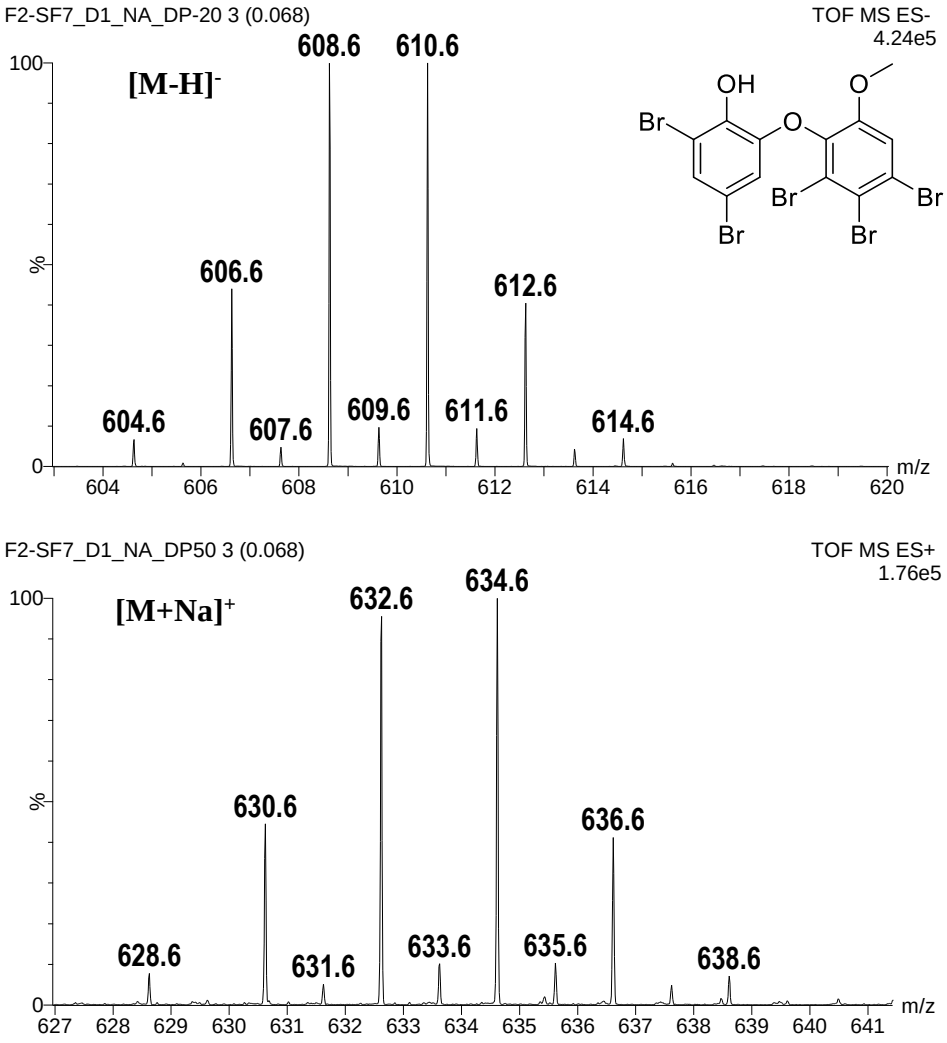


Figure S11. ^{1}H NMR (600 MHz, CD_3OD) spectrum for 3,4,5-tribromo-2-(3',5'-dibromo-2'-hydroxyphenoxy)anisole (**4**)

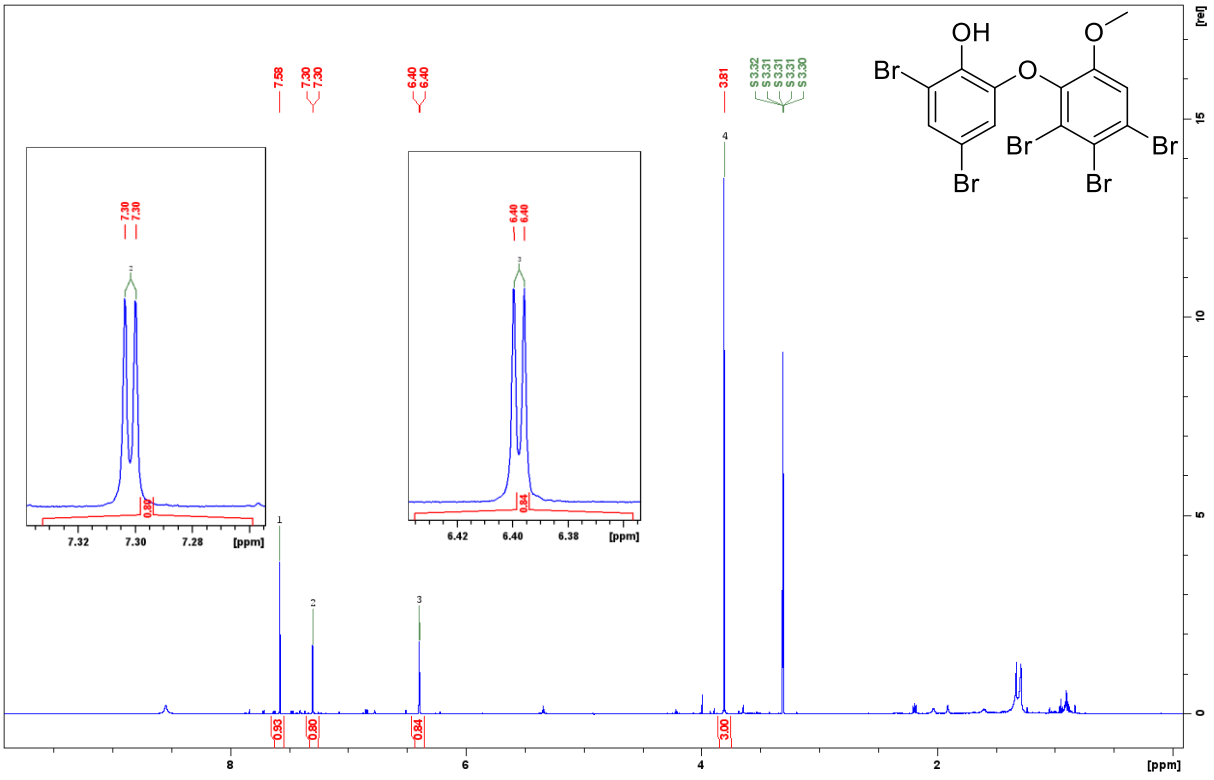


Figure S12. ^{13}C NMR (150 MHz, CD_3OD) spectrum for 3,4,5-tribromo-2-(3',5'-dibromo-2'-hydroxyphenoxy)anisole (**4**)

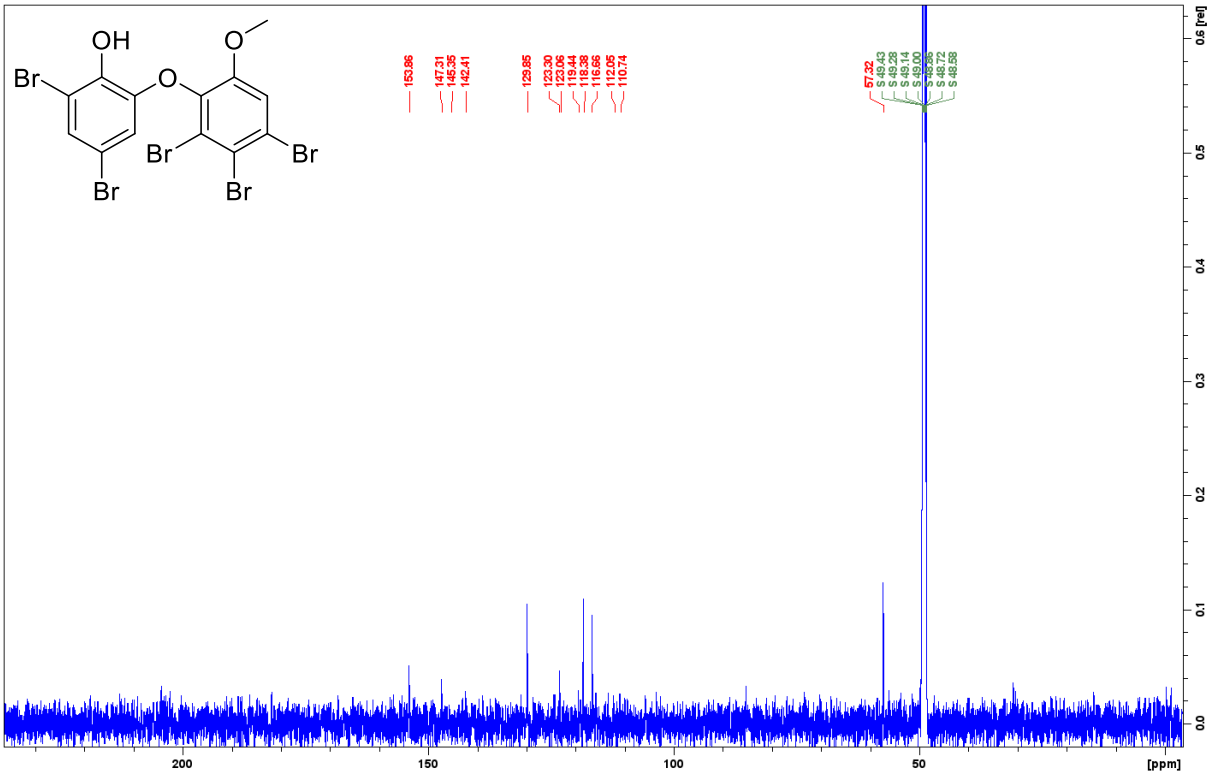


Table S5. Comparative ^{1}H and ^{13}C NMR spectral data of compound **4** and 2-(4',5',6'-tribromo-2'-methoxyphenoxy)-4,6-dibromophenol[4].

	Compound **4** (^{1}H 600 MHz, ^{13}C 150 MHz, CD_3OD)		2-(4',5',6'-tribromo-2'-methoxyphenoxy)-4,6-dibromophenol[3] (^{1}H 500 MHz, ^{13}C 125 MHz, $CDCl_3$)	
Position	δ_H (H, mult., *J* in Hz)	δ_C	δ_H (H, mult., *J* in Hz)	δ_C
1		153.9		152.0
2		142.4		140.8
3		123.1		122.4
4		119.4		122.8
5		123.3		119.1
6	7.58 (1H, s)	118.4	7.28 (1H, s)	116.6
O-Me	3.81(3H, s)	57.3	3.78 (3H, s)	56.7
1'		147.3		144.7
2'		145.9		142.7
3'		112.5		110.1
4'	7.30 (1H, d, 2.2)	129.9	7.34 (1H, d, 2.1)	129.3
5'		110.7		111.5
6'	6.40 (1H, d, 2.2)	116.7	6.51 (1H, d, 2.1)	116.3

4 [3] H. Liu, M. Namikoshi, S. Meguro, H. Nagai, H. Kobayashi, X. Yao, 'Isolation and Characterization of Polybrominated Diphenyl Ethers as Inhibitors of Microtubule Assembly from the Marine Sponge *Phyllospongia d endyi* Collected at Palau', *J. Nat. Prod.* **2004**, *67*, 472–474.

3,4,5,6-tetrabromo-2-(3',5'-dibromo-2'-hydroxyphenoxy)phenol (**5**). White cristal. HRMS *m/z* 674.5124 $[M-H]^-$ ($C_{12}H_3Br_6O_3$ calcd. for 674,5127).

Figure S13. HRMS mass spectrum for 3,4,5,6-tétrabromo-2-(3',5'-dibromo-2'-hydroxyphenoxy)phenol (**5**)

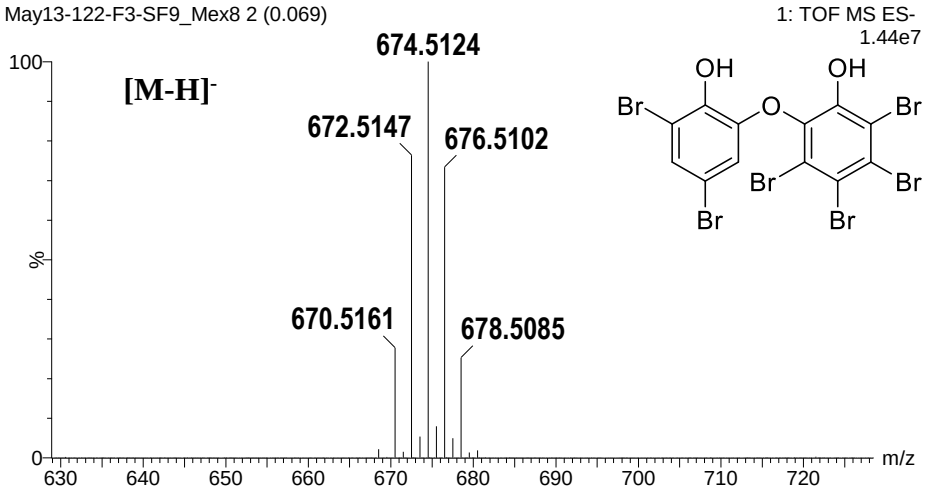


Figure S14. ^{1}H NMR (600 MHz, CD_3OD) spectrum for 3,4,5,6-tétrabromo-2-(3',5'-dibromo-2'-hydroxyphenoxy)phenol (**5**)

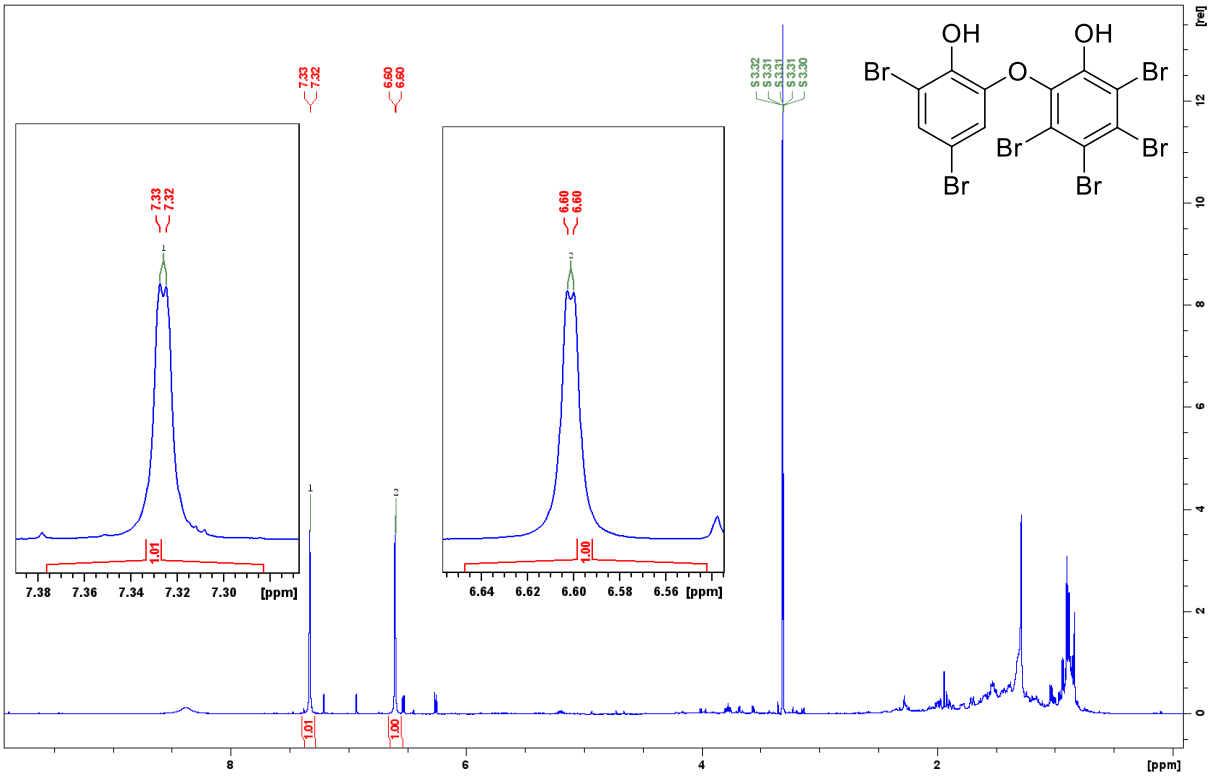


Figure S15. ^{13}C NMR (150 MHz, CD_3OD) spectrum for 3,4,5,6-tétrabromo-2-(3',5'-dibromo-2'-hydroxyphenoxy)phenol (**5**)

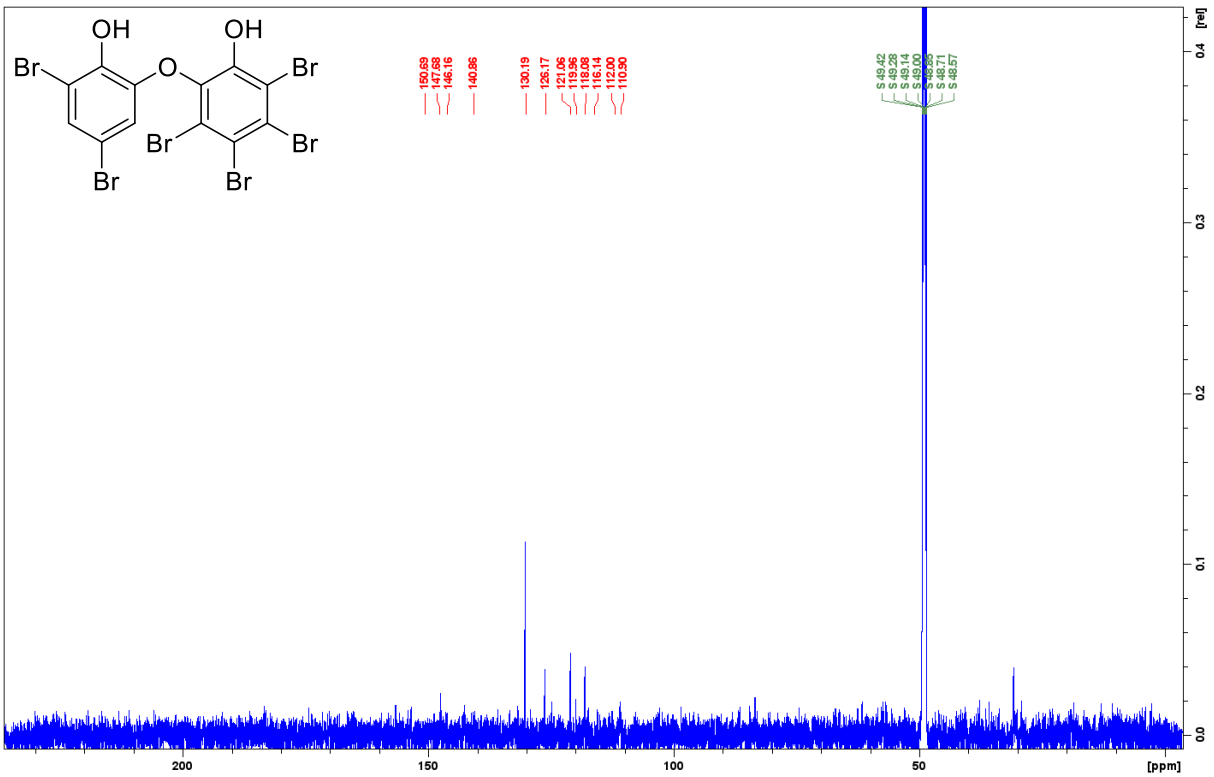


Table S6. Comparative ^{1}H and ^{13}C NMR spectral data of compound **5** and 3,4,4',5,6,6'-Hexabromo-2,2'-oxydiphenol[5].

	Compound 5 (^{1}H 600 MHz, ^{13}C 150 MHz, CD_3OD)		3,4,4',5,6'-Hexabromo-2,2'-oxydiphenol[4] (^{1}H 100 MHz, CD_3OD; ^{13}C 15.04 MHz, DMSO-d_6)	
Position	δ_H (H, mult., *J* in Hz)	δ_C	δ_H (H, mult., *J* in Hz)	δ_C
1		-		149.0
2		-		139.5
3		121.1		-
4		-		-
5		-		-
6		126.2		-
1'		147.7		145.6
2'		146.2		143.9
3'		112.0		111.2
4'	7.33 (1H, d, 1.7)	130.2	7.21 (1H, d, 2)	128.4
5'		110.9		109.5
6'	6.60 (1H, d, 1.7)	118.1	6.36 (1H, d, 2)	115.6

[5] [4] R. S. Norton, K. D. Croft, R. J. Wells, 'Polybrominated oxydiphenol derivatives from the sponge dysidea herbacea', *Tetrahedron* **1981**, *37*, 2341–2349.

Figure S16. HRMS mass spectrum for 3,5-dibromo-2-(3',4',5'-tribromo-2'-hydroxyphenoxy)phenol (**6**)

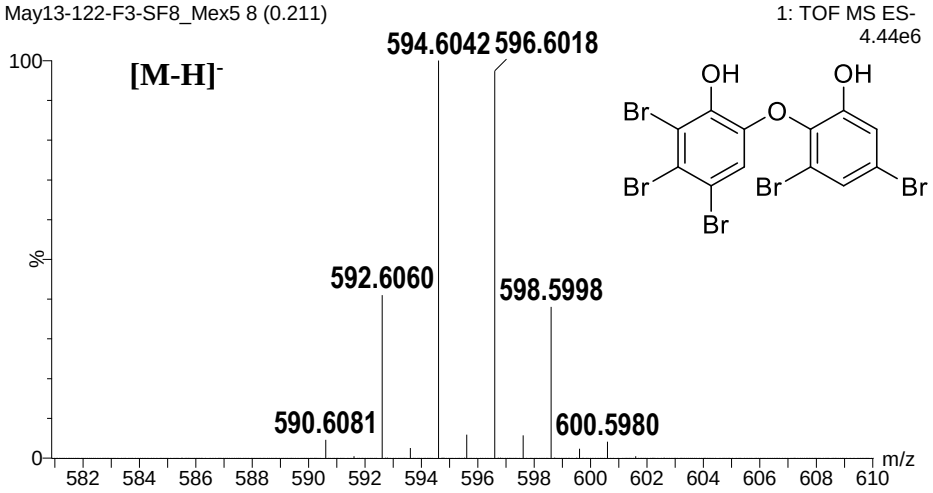


Table S7. 1D and 2D NMR spectroscopic data (^{1}H 600 MHz,^{13}C 150 MHz, CD_3OD) for 3,5-dibromo-2-(3',4',5'-tribromo-2'-hydroxyphenoxy)phenol (**6**) at 300 K. δ in ppm.

Position	**δ_H (*J* in Hz)**	**δ_C, type**	**HMBC (^{1}H -> ^{13}C)**
1		146.9, C	
2		147.9, C	
3		113.3, C	
4	7.46, 1H, d (2.2)	132.0, CH	2, 3, 5, 6
5		111.1, C	
6	7.02, 1H, d (2.2)	122.9, CH	1, 2, 4, 5
1'		146.2 C	
2'		149.6 C	
3'		116.7, C	
4'		123.4, C	
5'		113.1, C	
6'	7.15, 1H, s	123.0, CH	1', 2', (3'), 4', 5'

Figure S17. ^{1}H NMR (600 MHz, CD_3OD) spectrum for 3,5-dibromo-2-(3',4',5'-tribromo-2'-hydroxyphenoxy)phenol (**6**)

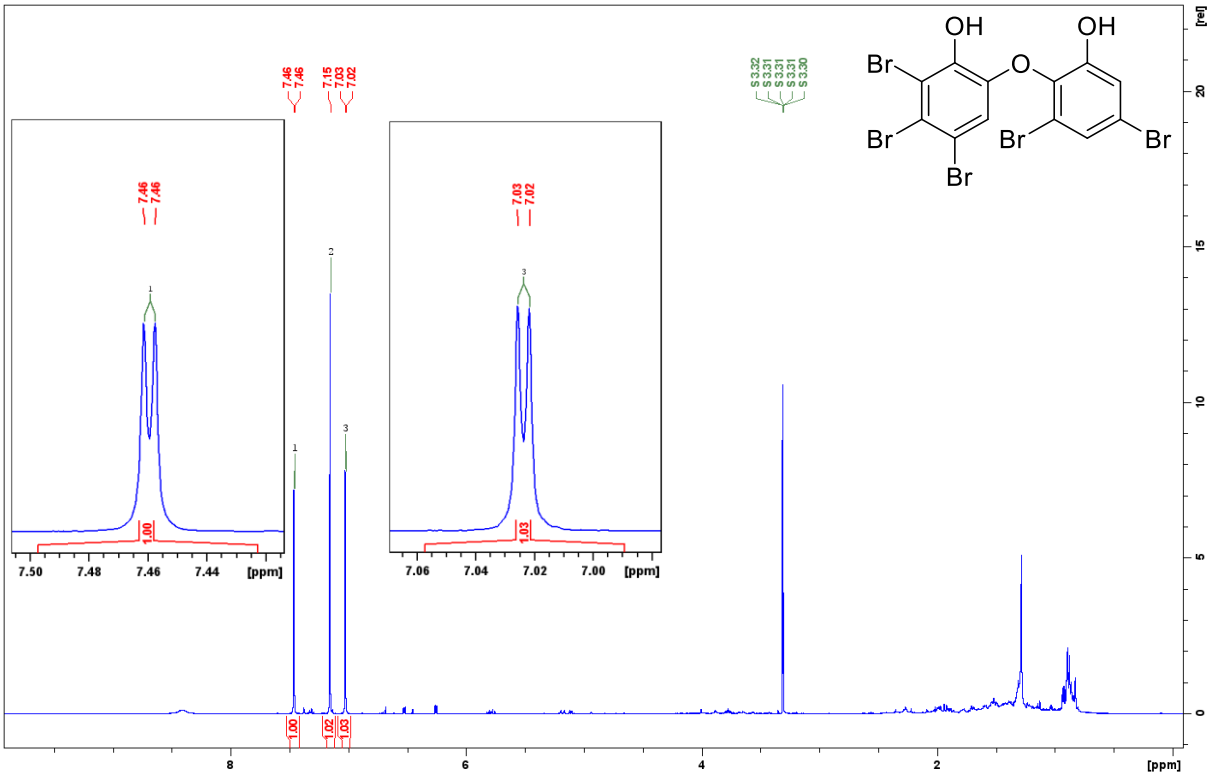


Figure S18. ^{13}C NMR (150 MHz, CD_3OD) spectrum for 3,5-dibromo-2-(3',4',5'-tribromo-2'-hydroxyphenoxy)phenol (**6**)

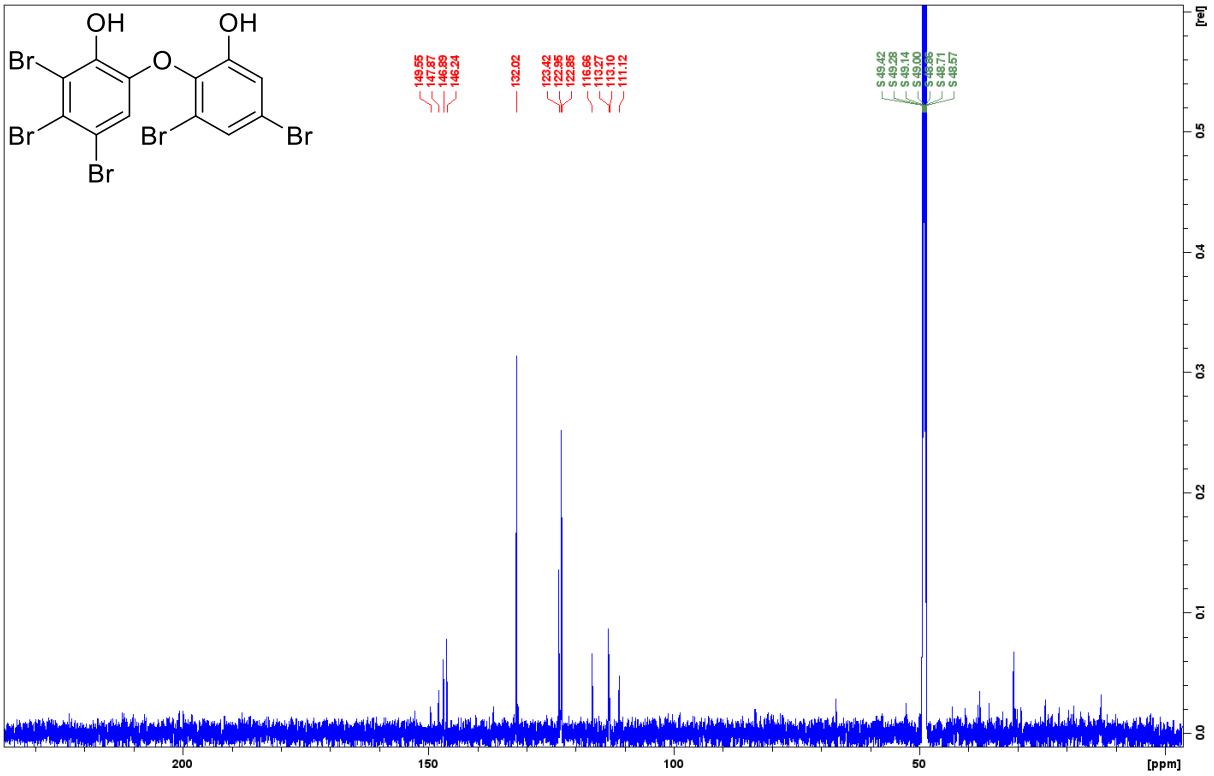


Figure S19. ^{1}H-^{13}C HSQC NMR (600 MHz) spectrum for 3,5-dibromo-2-(3',4',5'-tribromo-2'-hydroxyphenoxy)phenol (**6**)

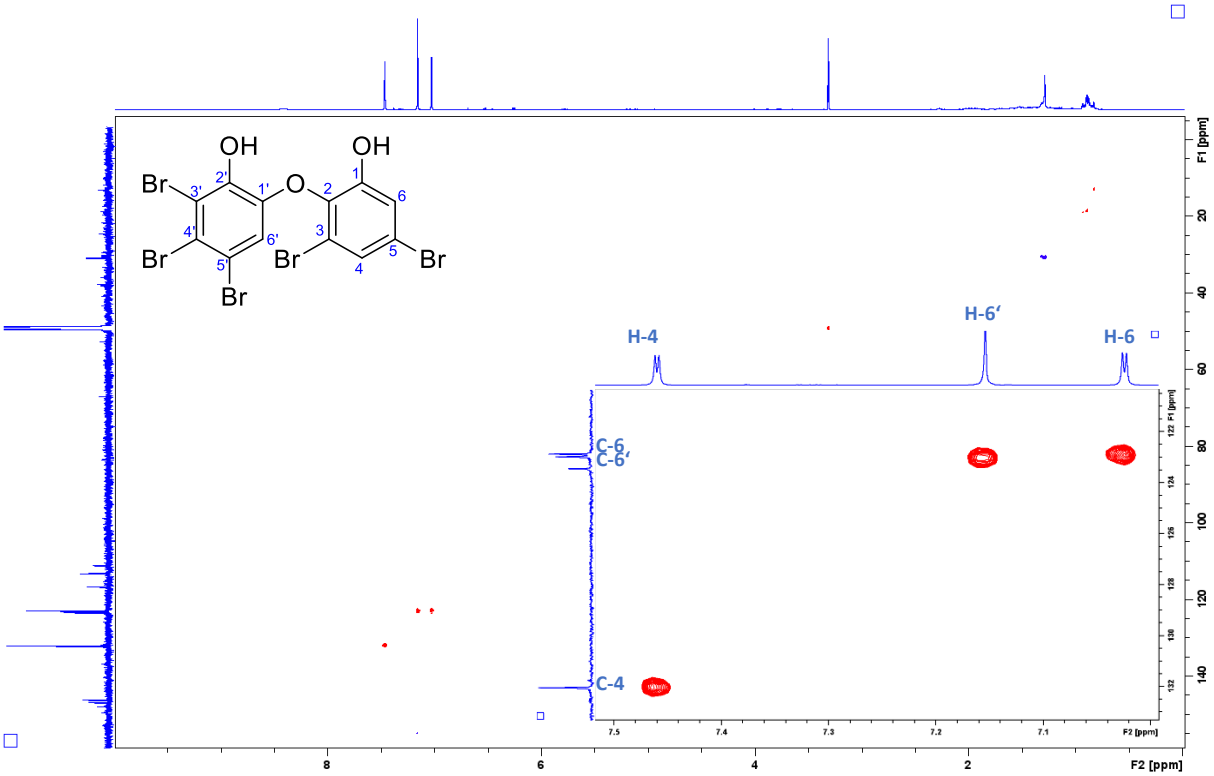


Figure S20. ^{1}H-^{13}C HMBC NMR (600 MHz) spectrum for 3,5-dibromo-2-(3',4',5'-tribromo-2'-hydroxyphenoxy)phenol (**6**)

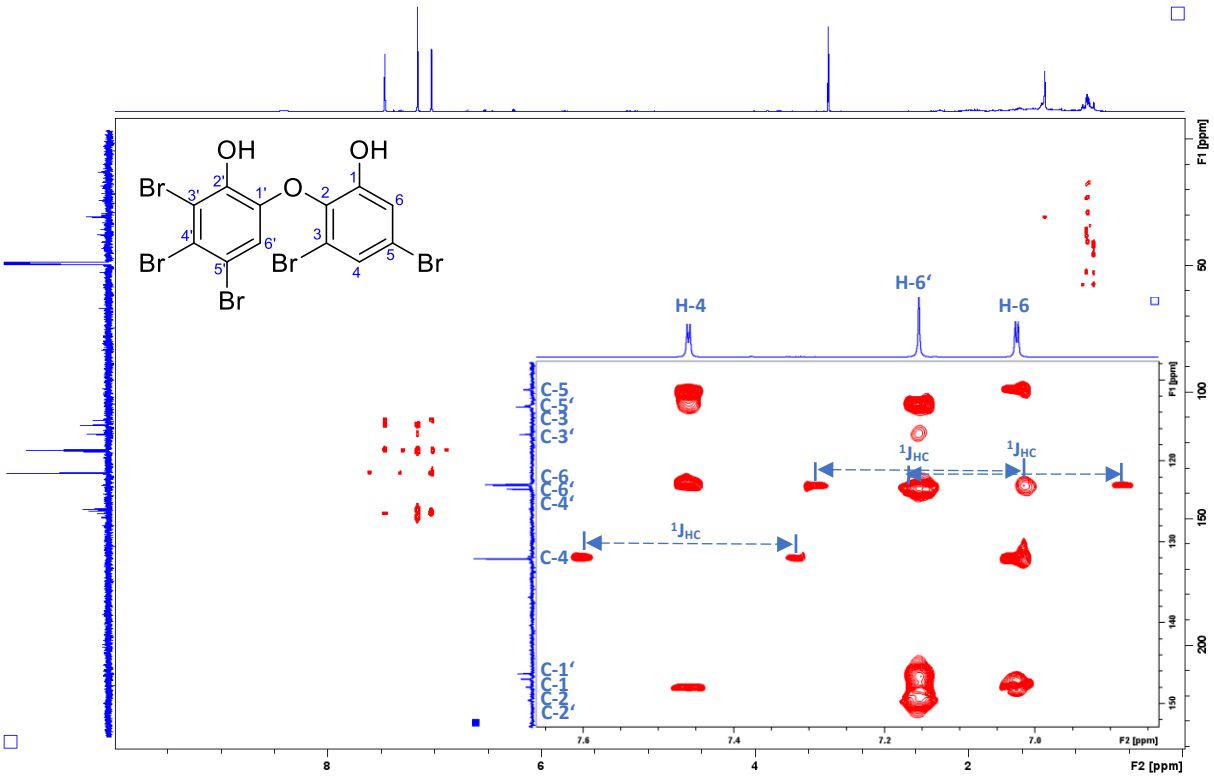
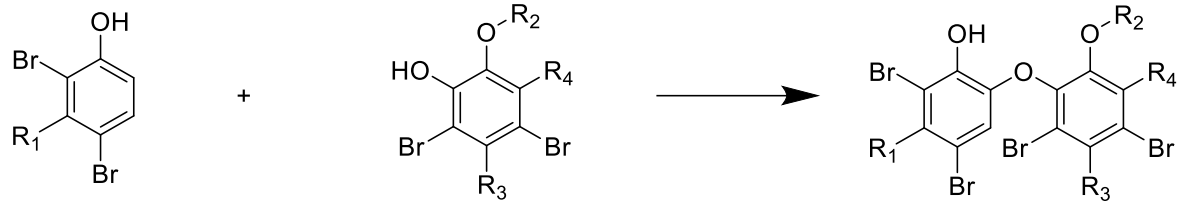


Figure S21. Biosynthetic scheme for purified compounds



2,4-dibromophenol: R_1 = H	3,5-dibromocatechol: $R_2 = R_3 = R_4$ = H	Compound **1**
2,4-dibromophenol: R_1 = H	3,4,5-tribromocatechol: $R_2 = R_4$ = H, R_3 = Br	Compound **2**
2,4-dibromophenol: R_1 = H	3,5-dibromocatechol-Me: R_2 = Me, $R_3 = R_4$ = H	Compound **3**
2,4-dibromophenol: R_1 = H	3,4,5-tribromocatechol-Me: R_2 = Me, R_3 = Br, R_4 = H	Compound **4**
2,4-dibromophenol: R_1 = H	3,4,5,6-tetrabromocatechol: R_2 = H, $R_3 = R_4$ = Br	Compound **5**
2,3,4-tribromophenol: R_1 = Br	3,5-dibromocatechol: $R_2 = R_3 = R_4$ = H	Compound **6**