Synthesis of Polyfunctional Aromatic Ring Systems (Phloroglucide Analogs) under Microwave Irradiation

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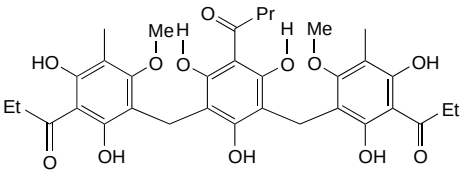
An efficient and rapid synthesis of phloroglucide analogs under microwave irradiation is described. The solid-phase condensation reaction of the 4-halo-2,6-bis(hydroxymethyl)phenols **1a**,**b** with other substituted phenols in the presence of $ZnCl_2$ afforded the target molecules in much higher yields than by classical solution-phase synthesis and allowed us to prepare new phloroglucide analogs possessing sensitive functional groups difficult to access by established means.

Introduction. – The presence of essential functional groups in a suitable spatial arrangement for chelating metal ions of enzymes is a feature common to several antibiotics [1], *e.g.*, triaspedinol (**I**) [2], cryptosporin (**II**) [3], and tetracycline (**III**) [4].



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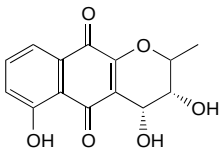

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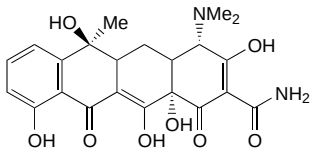


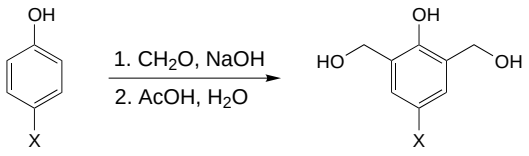
III

We have prepared several antibacterial phloroglucide analogs by classical methods, and the results were published in this journal [5–9].

The application of microwave technology in organic chemistry has been explored extensively within the last ten years. Microwave irradiation often leads to a remarkable decrease in reaction time, increased yields, easier workup, compliance with green-chemistry protocols, and may enhance the regio- and stereoselectivity of reactions. These advantages encouraged us to prepare phloroglucide analogs by this technique [10–14].

Herein, we report the solid-phase synthesis of phloroglucide analogs by condensation of 4-halo-2,6-bis(hydroxymethyl)phenols (**1**), prepared according to *Scheme 1*, with substituted phenols in the presence of $ZnCl_2$ under microwave irradiation.

Scheme 1

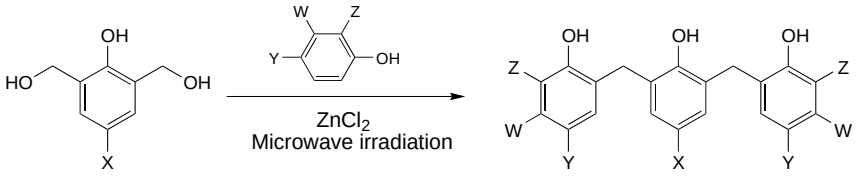


1a X = Cl
1b X = Br

Results and Discussion. – 4-Chloro- (**1a**) and 4-bromo-2,6-bis(hydroxymethyl)-phenol (**1b**), [8][15] are precursors for the synthesis of phloroglucide analogs of type **2** (*Scheme 2*). The halogen substituent in *para*-position of **1** was found to be essential for antimicrobial activity [17].

In the mortar, compounds **1a** or **1b** were mixed with substituted phenols, and $ZnCl_2$ was added as a *Lewis*-acid catalyst. The compounds were crushed to a 'homogeneous' solid mixture, which was then irradiated in a microwave oven at 400 – 700 W until a

Scheme 2



1a X = Cl
1b X = Br

2

	X	Y	Z	W
2a	Cl	Cl	H	H
2b	Br	Cl	H	H
2c	Cl	Br	H	H
2d	Cl	H	H	H
2e	Br	Br	H	H
2f	Cl	Cl	Cl	H
2g	Cl	Me	H	H

	X	Y	Z	W
2h	Cl	NO_2	H	H
2i	Cl	CHO	H	H
2j	Cl	OH	H	H
2k	Cl	Ph	H	H
2l	Cl	allyl	MeO	H
2m	Br	allyl	MeO	H
2n	Cl	Cl	H	Me

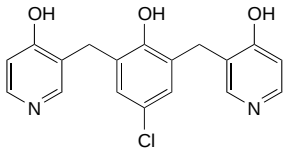


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Table 1. *Comparison of Solution-Phase and Microwave-Assisted Solid-Phase Syntheses of Phloroglucide Analogs*

Product	Conventional Method[a])		Microwave-Assisted Method[b])		
	Yield[c]) [%]	Reaction time [h]	Yield[c]) [%]	Reaction time [s]	Irradiation power [W]
2a	56[d])	12	92	40	600
2b	77[d])	12	92	45	500
2c	60[d])	12	90	42	600
2d	37[d])	18	73	40	400
2e	54	10	86	50	700
2f	20	24	95	35	500
2g	60	10	85	40	600
2h	0	72	96	25	500
2i	30	18	75	30	600
2j	71	9	93	50	600
2k	53	13	82	50	500
2l	43	10	85	50	500
2m	39	9	80	40	500
2n	36	15	84	40	400
3	0	72	90	40	500

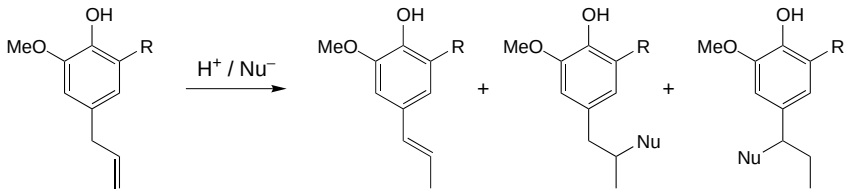
[a]) In HCl/MeOH solution [19]. [b]) In the solid phase with an excess of $ZnCl_2$. [c]) Isolated yields. [d]) Literature values [8].

color change was observed. The yields increased greatly with respect to the classical method [5–9], as shown in a comparative study (*Table 1*).

As substrates, substituted phenols with different electron-releasing and electron-withdrawing groups were subjected to the coupling, as well as phenols that showed biological activity to some extent. With regard to the data in *Table 1*, the isolated yields cannot be rationalized simply on the basis of substituent effects, since compounds with higher dipole moments generate more heat under microwave irradiation ('microwave effect') [10].

One remarkable advantage of microwave-assisted solid-phase synthesis of phloroglucide analogs is the possibility of introducing acid-sensitive functional groups. Compounds **2l** and **2m**, *e.g.*, are derived from eugenol (essential oil of clove [18]) and would be difficult to prepare by classical methods [19] in which the allyl moiety is altered. In the literature [19], electrophilic substitutions with eugenol are performed with a protected allyl group, which otherwise reacts with electrophiles, leading to loss of biological activity. Under 'classical' conditions (HCl/MeOH solution), side reactions dominate, as shown in *Scheme 3*.

Scheme 3



The solution-phase syntheses of **2i** and **2n** were also beset with problems. The formyl group of 4-hydroxybenzaldehyde is sensitive toward HCl (conc.) in MeOH and tends to polymerize.

4-Hydroxypyridine used for the preparation of the phloroglucide analog **3** was deactivated in HCl/MeOH solution (salt formation by protonation), but readily reacted in the solid phase under microwave irradiation.

Because of technical problems, concentrated HCl cannot be used under microwave conditions. However, suitable solid *Lewis* acids can be selected. We compared several *Lewis* acids in the solid-phase reaction leading to phloroglucide **2c** as a model compound [8]. The results are summarized in *Table 2*.

Table 2. *Effect of Different* Lewis *Acid Catalysts in the Microwave-Assisted Solid-Phase Reaction Leading to the Formation of Compound* **2c**

Catalyst	Yield [%]	Catalyst	Yield [%]	Catalyst	Yield [%]
TsOH	10	$CdCl_2$	22	$CoCl_3$	n.r.[a])
$CuCl_2$	n.r.[a])	LiBr	n.r.[a])	$HgCl_2$	10
$SnCl_2$	20	$MgCl_2$	n.r.[a])	$Zn(OAc)_2$	50
$SnCl_4$	10	$NiCl_2$	n.r.[a])	$ZnBr_2$	74
$FeCl_3$	n.i.[b])	$MnCl_2$	n.r.[a])	$ZnCl_2$	90

[a]) No reaction observed. [b]) Product(s) not identified.

Clearly, Zn^{2+} salts are especially versatile as *Lewis* acids in the synthesis of phloroglucide analogs under microwave irradiation. This may be due to the special chelating properties of Zn^{2+} with the reactants (suitable spatial arrangement, so-called *Symphoria* effect [21]). The phloroglucide analogs **2d** and **2n** are good examples to demonstrate the special role of Zn^{2+}. In the case of **2d**, there is a higher tendency for *ortho* rather than *para* condensation with respect to solution-phase synthesis (*Table 1*). In the condensation of **1a** with 4-chloro-3-methylphenol leading to **2n**, there are two nonequivalent *ortho* positions in the substrate, yet the less-hindered *ortho* position was preferred under microwave conditions, as confirmed by ^{1}H-NMR and ^{13}C-NMR spectroscopy. The observed regioselectivity was rationalized in the case of **2d** by means of consisted-valance-force-field (CVFF) calculations. The most-stable conformer exists in a *cis-syn-syn* geometry in front of the metal ion, forming a cavity (half-calix) [22]. We also used AM1 semi-empirical quantum-mechanic calculations to optimize the structure of **2a**, which also suggested 'cavity' formation in the presence of Zn^{2+}, as shown in the *Figure*.

Conclusions. – Microwave-assisted syntheses of phloroglucide analogs **2a**–**n** and **3** has several advantages over classical solution-phase methods. It reduces the reaction time and increases the yields considerably, even in the case of phenols that hardly react in solution. This seems to contradict the classical rule, according to which electrophilic aromatic substitution of phenols containing electron-withdrawing groups results in lower yields due to deactivation of the phenolic ring. Also, several acid-sensitive functional groups remain unchanged in the solid-phase reaction under microwave irradiation (**2f**, **2i**, **2l, 2m**, and **3**). As *Lewis* acid catalysts, Zn^{2+} salts seem to be crucial

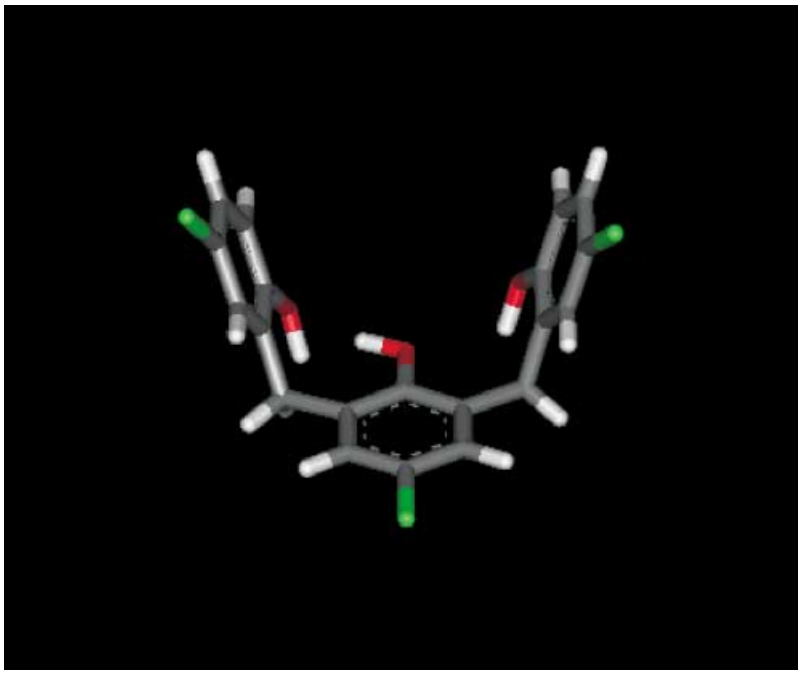


Fig. 1. cis-syn-cis *Conformer of the Phloroglucide Analog* **2a**

for the success of the reactions, probably due to their ability to form complexes with the reactants.

We appreciate financial support of the *Shiraz University Research Council*. We also thank *Sajedian Fard* for recording the NMR spectra.

Experimental Part

General. All chemicals were obtained from *Fluka or Merck*. Solvents were purified according to reported methods and stored over molecular sieves. Compounds **1a** and **1b** were prepared according to [8][15]. TLC: Silica gel *SILG/UV 254* plates. Melting points were recorded on a *Büchi 510* apparatus in open capillary tubes and are uncorrected. IR spectra were run on a *Perkin-Elmer 781* spectrophotometer; in cm^{-1}. ^1H- and ^{13}C-NMR Spectra were run on a *Bruker Advance DPX-250* spectrometer; δ in ppm, J in Hz. Mass spectra were recorded on a *Shimadzu GC MS-QP 1000EX* apparatus. Microanalyses were performed on a *Perkin-Elmer 240-B* microanalyzer. Microwave oven: *MB 245* from *Butane Industrial Co.*

General Procedure for the Preparation of Phloroglucide Analogs under Microwave Irradiation. In a mortar containing 2.7 mmol of **1** were added 4 equiv. of substituted phenol, and the mixture was crushed to a homogeneous mass. Then, $ZnCl_2$ (10 mmol) was added, and crushing was continued for one min. The mixture was transferred to a test tube and irradiated in the microwave oven for 25–50 s (*cf. Table 1*). The crude products were suspended in boiling H_2O to dissolve $ZnCl_2$ and unreacted phenols. The mixture was evaporated and purified as specified.

4-Chloro-2,6-bis[(5-chloro-2-hydroxyphenyl)methyl]phenol (**2a**). Sublimation at 200–210°, 0.01 Torr, gave white crystals (1.01 g, 92%). M.p. 232–234°. R_f (CH_2Cl_2) 0.2. IR (KBr): 3150*w*, 3010*m*, 2980*m*, 1610*s*, 1220*m*. ^1H-NMR ((D_6)DMSO, 250 MHz): 9.7 (br., 2 OH); 8.95 (br., OH); 7.75–6.54 (*m*, 8 arom. H); 3.88 (*s*, 2 CH_2). ^{13}C-NMR ((D_6)DMSO, 62.5 MHz): 154.85; 154.53; 129.60; 128.03; 127.62; 124.26; 123.01; 120.05; 118.02; 114.51;

15.58 (2 CH_2). MS (*m*/*z*): 409. Anal. calc. for $C_{20}H_{15}Cl_3O_3$: C 58.63, H 3.69, Cl 25.96; found: C 58.60, H 3.73, Cl 26.03.

4-Bromo-2,6-bis[(5-chloro-2-hydroxyphenyl)methyl]phenol (**2b**). CC on SiO_2 ($CHCl_3$/hexane 1:3) gave pale yellow crystals (1.10 g, 92%). M.p. 234–238° (dec.). R_f (CH_2Cl_2) 0.25. IR (KBr): 3150*w*, 3050*m*, 2950*m*, 1600*s*, 1220*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 9.84 (br., 2 OH); 8.88 (br., OH); 7.07–6.08 (*m*, 8 arom. H); 3.81 (*s*, 2 CH_2). ^{13}C-NMR ((D$_6$)DMSO, 62.5 MHz): 154.76; 154.23; 132.28; 129.57; 127.69; 124.03; 123.44; 118.03; 116.22; 112.27; 16.04 (2 CH_2). MS (*m*/*z*): 454. Anal. calc. for $C_{20}H_{15}BrCl_2O_3$: C 52.89, H 3.33, Br 17.59, Cl 15.61; found: C 52.83, H 3.32, Br 17.61, Cl 15.59.

4-Chloro-2,6-bis[(5-bromo-2-hydroxyphenyl)methyl]phenol (**2c**). Recrystallization from benzene (15 ml) or CH_2Cl_2 (20 ml) gave white crystals (1.2 g, 90%). M.p. >250°. R_f (CH_2Cl_2) 0.23. IR (KBr): 3150*w*, 3020*m*, 2990*m*, 1600*s*, 1220*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 9.91 (br., 2 OH); 8.78 (br., OH); 7.34–6.69 (*m*, 8 arom. H); 3.81 (*s*, 2 CH_2). ^{13}C-NMR ((D$_6$)DMSO, 62.5 MHz): 155.32; 152.09; 131.75; 131.40; 128.14; 124.55; 122.93; 122.43; 118.01; 100.66; 15.06 (2 CH_2); MS (*m*/*z*): 498. Anal. calc. for $C_{20}H_{15}Br_2ClO_3$: C 48.18, H 3.03, Br 32.05, Cl 7.11; found: C 48.20, H 3.05, Br 32.00, Cl 7.09.

4-Chloro-2,6-bis[(2-hydroxyphenyl)methyl]phenol (**2d**). CC on SiO_2 (AcOEt/hexane 1:3) gave white crystals (0.67 g, 73%). M.p. 180–182°. R_f (CH_2Cl_2) 0.28. IR (KBr): 3300*w*, 3010*m*, 2900*m*, 1600*s*, 1200*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 9.53 (*s*, 2 OH); 8.88 (*s*, OH); 7.33–6.65 (*m*, 10 arom. H); 3.84 (*s*, 2 CH_2). ^{13}C-NMR ((D$_6$)DMSO, 62.5 MHz): 155.34; 153.01; 133.44; 128.34; 127.80; 124.52; 121.02; 120.32; 119.23; 115.42; 16.02 (2 CH_2). MS (*m*/*z*): 340. Anal. calc. for $C_{20}H_{17}ClO_3$: C 70.49, H 5.03, Cl 10.40; found: C 70.52, H 5.05, Cl 10.37.

4-Bromo-2,6-bis[(5-bromo-2-hydroxyphenyl)methyl]phenol (**2e**). CC on SiO_2 ($CHCl_3$/hexane 1:3) gave yellow crystals (1 g, 86%). M.p. 235–236°. R_f (CH_2Cl_2) 0.27. IR (KBr): 3200*w*, 3010*m*, 2950*m*, 1600*s*, 1250*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 9.76–8.28 (br., 3 OH); 7.30–6.72 (*m*, 8 arom. H); 3.81 (*s*, 2 CH_2). ^{13}C-NMR ((D$_6$)DMSO, 62.5 MHz): 154.74; 153.02; 132.02; 131.98; 131.33; 124.52; 120.18; 117.41; 113.48; 100.72; 14.09 (2 CH_2). MS (*m*/*z*): 543. Anal. calc. for $C_{20}H_{15}Br_3O_3$: C 44.23, H 2.78, Br 44.14; found: C 44.21, H 2.76, Br 44.16.

4-Chloro-2,6-bis[(3,5-dichloro-2-hydroxyphenyl)methyl])phenol (**2f**). CC on SiO_2 (CH_2Cl_2) gave white pungent crystals (1.17 g, 95%). M.p. 156–160°. R_f (CH_2Cl_2) 0.33. IR (KBr): 3350*w*, 3100*w*, 2920*m*, 1490*s*, 1590*m*, 1180*s*, 1230*m*, 850*s*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 10.52–9.73 (br., 3 OH); 7.42–6.92 (*m*, 6 arom. H); 3.97 (*s*, 2 CH_2). ^{13}C-NMR ((D$_6$)DMSO, 62.5 MHz): 157.32; 150.21; 136.02; 129.23; 128.31; 127.66; 124.85; 124.23; 120.91; 116.32; 15.61 (2 CH_2). MS (*m*/*z*): 478. Anal. calc. for $C_{20}H_{13}Cl_5O_3$: C 50.19, H 2.74, Cl 37.04; found: C 50.16, H 2.78, Cl 37.05.

4-Chloro-2,6-bis[(2-hydroxy-5-methylphenyl)methyl]phenol (**2g**). Recrystallization from hexane (20 ml) gave white crystals (0.86 g, 85%). M.p. 136–140°. R_f (CH_2Cl_2) 0.45. IR (KBr): 3200*w*, 3020*m*, 2920*m*, 2880*m*, 1600*m*, 1450*m*, 1210*s*, 810*s*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 9.38 (*s*, 2 OH); 9.06 (*s*, OH); 7.04–6.41 (*m*, 8 arom. H); 4.02 (*s*, 2 CH_2); 2.15 (*s*, 2 Me). ^{13}C-NMR ((D$_6$)DMSO, 62.5 MHz): 155.02; 153.61; 133.61; 128.33; 127.70; 127.61; 123.61; 118.58; 114.31; 113.62; 31.48 (2 CH_2); 20.07 (2 Me). MS (*m*/*z*): 368. Anal. calc. for $C_{22}H_{21}ClO_3$: C 71.64, H 5.74, Cl 9.61; found: C 71.62, H 5.79, Cl 9.59.

4-Chloro-2,6-bis[(2-hydroxy-5-nitrophenyl)methyl]phenol (**2h**). CC on SiO_2 ($CHCl_3$) gave yellow-orange needles (1.12 g, 96%). M.p. 220–225° (dec.). R_f (CH_2Cl_2) 0.15. IR (KBr): 3400*w*, 3090*m*, 2920*m*, 1630*s*, 1590*s*, 1500*s*, 1300*s*, 1250*s*, 1300*m*, 1080*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 11.15 (br., 2 OH); 8.86 (br., OH); 8.77–6.67 (*m*, 8 arom. H); 3.86 (*s*, 2 CH_2). ^{13}C-NMR ((D$_6$)DMSO, 62.5 MHz): 161.56; 151.02; 140.91; 130.21; 129.61; 125.32; 123.40; 122.81; 117.21; 112.36; 17.65 (2 CH_2). MS (*m*/*z*): 430. Anal. calc. for $C_{20}H_{15}ClN_2O_7$: C 55.76, H 3.51, Cl 8.23, N 6.50; found: C 55.80, H 3.46, Cl 8.22, N 6.52.

4-Chloro-2,6-bis[(5-formyl-2-hydroxyphenyl)methyl]phenol (**2i**). CC on SiO_2 ($CHCl_3$) gave yellow crystals (0.8 g, 75%). M.p. 200–205°. R_f (CH_2Cl_2) 0.1. IR (KBr): 3200*w*, 3020*w*, 2950*w*, 2850*m*, 2750*m*, 1690*s*, 1600*s*, 1210*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 10.59–8.07 (br., 3 OH); 9.86 (*s*, 2 CHO); 7.87–6.65 (*m*, 8 arom. H); 3.90 (*s*, 2 CH_2). ^{13}C-NMR ((D$_6$)DMSO, 62.5 MHz): 196.63 (2 CHO); 156.22; 154.23; 132.61; 132.57; 128.01; 123.11; 118.32; 116.64; 114.62; 112.36; 18.62 (2 CH_2). MS (*m*/*z*): 396. Anal. calc. for $C_{22}H_{17}ClO_5$: C 66.59, H 4.32, Cl 8.93; found: C 66.53, H 4.36, Cl 8.90.

4-Chloro-2,6-bis[(2,5-dihydroxyphenyl)methyl]phenol (**2j**). Recrystallization from MeOH/H_2O 1:5 gave light-brown crystals (0.94 g, 93%). M.p. 178–180° (dec.). R_f (CH_2Cl_2) 0.05. IR (KBr): 3200*w*, 3020*m*, 2990*m*, 1600*s*, 1610*s*, 1500*s*, 1450*m*, 1250*m*, 850*s*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 8.93–8.62 (br., 5 OH); 6.79–6.32 (*m*, 8 arom. H); 3.76 (*s*, 2 CH_2). ^{13}C-NMR ((D$_6$)DMSO, 62.5 MHz): 156.23; 150.56; 150.31; 132.01; 128.36; 125.91; 123.91; 116.36; 116.21; 114.61; 15.73 (2 CH_2). MS (*m*/*z*): 372. Anal. calc. for $C_{20}H_{17}ClO_5$: C 64.44, H 4.60, Cl 9.51; found: C 64.44, H 4.65, Cl 9.48.

4-Chloro-2,6-bis[(4-hydroxy-1,1′-biphenyl-3-yl)methyl]phenol (**2k**). CC on SiO_2 (AcOEt/hexane 1:5) gave white crystals (1.1 g, 82%). M.p. 143–145°. R_f (CH_2Cl_2) 0.64. IR (KBr): 3200*w*, 3030*m*, 2910*m*, 1610*s*, 1600*s*, 1520*s*, 1490*m*, 1220*s*, 820*s*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 9.79 (*s*, 2 OH); 8.82 (*s*, OH); 7.59–6.84 (*m*, 18 arom. H); 3.91 (*s*, 2 CH_2). ^{13}C-NMR ((D$_6$)DMSO, 62.5 MHz): 158.62; 154.32; 149.21; 135.39; 134.01; 133.62; 128.71; 128.31, 125.60; 123.31; 120.45; 117.61; 116.62; 114.35; 31.41 (2 CH_2). MS (*m*/*z*): 492. Anal. calc. for $C_{32}H_{25}ClO_3$: C 77.96, H 5.11, Cl 7.19; found: C 78.02, H 5.08, Cl 7.22.

4-Chloro-2,6-bis{[2-hydroxy-3-methoxy-5-(prop-2-en-1-yl)phenyl]methyl}phenol (**2l**). CC on SiO_2 (AcOEt/hexane 1:3) gave light-yellow crystals (1.1 g, 85%). M.p. 54–56°. R_f ($CHCl_3$) 0.66. IR (KBr): 3450*w*, 3090*m*, 2950*m*, 2985*m*, 1600*m*, 1510*m*, 1450*m*, 1410*m*, 1210*w*, 1200*s*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.49–6.54 (*m*, 6 arom. H); 5.70 (*m*, 2 H, =C(H)–C); 5.16 (br., 3 OH); 4.81 (*dd*, *J* = 10.3, 16.5, 2 H_2C=C); 3.67 (*s*, MeO); 3.61 (*s*, 2 CH_2); 3.11 (*d*, *J* = 6.6, 2 CH_2). ^{13}C-NMR ((D$_6$)DMSO, 62.5 MHz): 156.37; 143.02; 141.69; 138.81; 134.01; 128.65; 125.81; 122.67; 124.61; 117.52; 115.36; 111.36; 56.34 (MeO); 40.01 (2 CH_2); 30.02 (2 CH_2). MS (*m*/*z*): 480. Anal. calc. for $C_{28}H_{29}ClO_5$: C 69.92, H 6.08, Cl 7.37; found: C 69.96, H 6.12, Cl 7.40.

4-Bromo-2,6-bis{[2-hydroxy-3-methoxy-5-(prop-2-en-1-yl)phenyl]methyl}phenol (**2m**). CC on SiO_2 (AcOEt/hexane 1:3) gave light-brown crystals (0.92 g, 80%); M.p. 58–60°. R_f ($CHCl_3$) 0.67. IR (KBr): 3450*w*, 3090*m*, 2950*m*, 2985*m*, 1600*m*, 1520*m*, 1430*s*, 1420*m*, 1200*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.28–6.46 (*m*, 6 arom. H); 5.90 (*m*, 2 =C(H)–C); 5.10 (br., 3 OH); 4.97 (*dd*, *J* = 10.3, 16.8, 2 H_2C=C); 43.8 (*s*, 2 MeO); 3.84 (*s*, 2 CH_2); 3.34 (*d*, *J* = 6.3, 4 H, 2 CH_2). ^{13}C-NMR ((D$_6$)DMSO, 62.5 MHz): 154.33; 143.19; 142.21; 138.23; 134.51; 128.68; 125.75; 124.33; 122.63; 117.65; 115.33; 111.39; 56.41 (MeO); 40.32 (2 CH_2; 29.63 (2 CH_2). MS (*m*/*z*): 525. Anal. calc. for $C_{28}H_{29}BrO_5$: C 64.00, H 5.56, Br 15.21; found: C 64.05, H 5.58, Br 15.19.

4-Chloro-2,6-bis[(5-chloro-2-hydroxy-4-methylphenyl)methyl]phenol (**2n**). CC on SiO_2 (AcOEt/hexane 1:3) gave white crystals (0.99 g, 84%). M.p. 178–180°. R_f (CH_2Cl_2) 0.66. IR (KBr): 3350*w*, 3100*m*, 2950*m*, 1650*m*, 1620*m*, 1460*s*, 1225*m*, 1170*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 9.75 (br., 2 OH); 8.88 (br., OH); 7.19–6.27 (*m*, 6 arom. H); 3.89 (*s*, 2 CH_2); 2.12 (*s*, 2 Me). ^{13}C-NMR ((D$_6$)DMSO, 62.5 MHz): 154.61; 153.22; 136.32; 130.81; 128.46; 126.21; 124.61; 120.01; 116.32; 112.22; 31.21 (2 CH_2), 20.06 (2 Me). MS (*m*/*z*): 437. Anal. calc. for $C_{22}H_{19}Cl_3O_3$: C 60.36, H 4.37, Cl 24.30; found: C 60.40, H 4.41, Cl 24.27.

4-Chloro-2,6-bis[(4-hydroxypyridin-3-yl)methyl]phenol (**3**). Recrystallization from MeOH (20 ml) afforded orange crystals (0.83 g, 90%). M.p. >270°. R_f (CH_2Cl_2) 0.07. IR (KBr): 3200*w*, 3030*m*, 2910*m*, 1650*s*, 1550*s*, 1220*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 9.91 (br., 2 OH); 8.78 (br., OH); 7.34–6.69 (*m*, 8 arom. H); 3.89 (*s*, 2 CH_2). ^{13}C-NMR ((D$_6$)DMSO, 62.5 MHz): 156.96; 156.35; 150.01; 147.02; 132.61; 126.02; 123.92; 122.02; 114.54; 29.36 (2 CH_2). MS (*m*/*z*): 342. Anal. calc. for $C_{18}H_{15}ClN_2O_3$: C 63.07, H 4.41, Cl 10.34, N 8.17; found: C 63.08, H 4.36, Cl 10.35, N 8.13.

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