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Synthesis and antimicrobial activity of brominated resorcinol dimers

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ABSTRACT

Dibrominated resorcinol dimers were synthesized by reaction of 4-bromoresorcinol with aldehydes under reflux in ethanol in the presence of HCl. Subsequent dehalogenation yielded the corresponding monobrominated compounds and a fully dehalogenated dimer. Of the dimers, 6,6′-((4-hydroxyphenyl)methylene)bis(4-bromobenzene-1,3-diol) (**4**) displayed potent antibacterial activity and inhibitory activity against isocitrate lyase *Candida albicans*.

The isolation of bromophenolic dimers, of general structures **1** and **2** (Fig. 1) from marine red algae of the Rhodomelaceae family such as *Odonthalia corymbifera*,[1,2] *Symphyocladia latiuscula*,[3,4] *Rhodomela confervoide*,[5–7] *Rhodomela larix*[8,9] and *Polysiphonia brodiaei*[10] and brown algae of the Leatesiaceae family including *Leathesia nana*[11] has been accompanied by their evaluation as aldose-reductase inhibitors,[2] antibacterial and antifungal compounds,[1] feeding deterrent molecules and for their free-radical scavenging ability.[3]

Building on the observed activity of **1a** against isocitrate lyase[1] a component of the glyoxylate cycle present in prokatyotes and plants, we have investigated the synthesis of a range of halogenated diphenolic compounds to determine the structure–activity requirements for antifungal and antimicrobial activity.[12–14] In contrast, Zhao et al.[15] have considered similar molecules for their antioxidant effects.

Whilst the natural products and previous synthetic derivatives feature catechol motifs, early research, on alkyl resorcinol derivatives[16,17] and their halogenated derivatives[18] has indicated that this arrangement of phenolic units also shows significant antibacterial activity.

Resorcinol dimers, formed from the reaction of aldehydes with resorcinol under acid-catalysed conditions have been shown to be reaction intermediates[19] in the synthesis of the popular macrocyclic host molecules resorcin[4]arenes.[20,21] Through choice of reaction conditions, for example, by the use of an excess of resorcinol,[22] a less reactive resorcinol derivative[23] or by blocking the second reactive position by introducing a substituent, generally a halogen, at position 4,[24] the cyclisation reaction can be halted at the dimer stage. Such dimers have subsequently been exploited for the formation of hybrid calixarene-resorcin[4]arene structures,[24] resorcin[4]arenes with alternate bridging substituents,[25] xanthene dyes[26,27] and visual sensors for saccharides.[28] In light of the positive results obtained with catechol dimers we now report the synthesis of a family of halogenated and nonhalogenated resorcinol dimers and their biological evaluation as inhibitors of isocitrate lyase

4-Bromoresorcinol **3** was prepared from dihydroxy-5-bromobenzoic acid using a modification of a two step procedure developed by Sandin and McKee[29] in which bromination using bromine is followed by a heat induced decarboxylation. Dimerisation

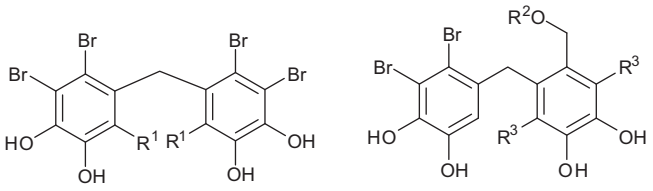

Figure 1. Natural bromophenolic dimers.

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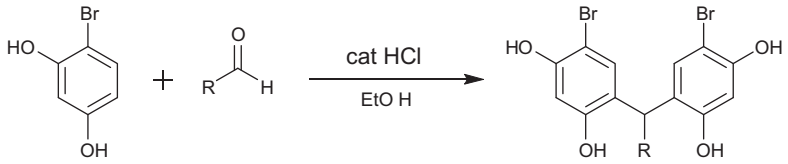
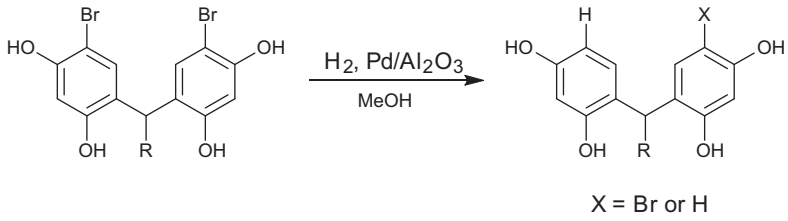


Scheme 1. Synthesis of resorcinol dimers.



Scheme 2. Catalytic hydrogenations of bromophenols.

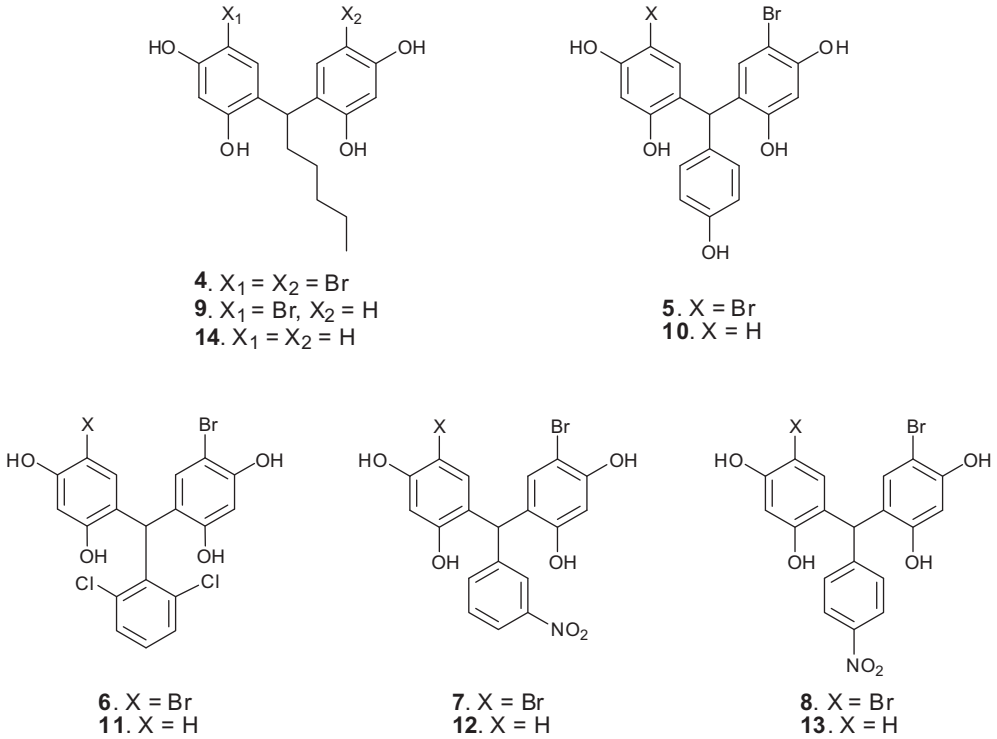


Figure 2. Synthesised resorcinol dimers.

was achieved simply by reaction of 2 equiv of **3** with the desired aldehyde under reflux in ethanol in the presence of HCl.[30] Purification by column chromatography gave the five dibrominated dimers **4–8** in moderate to good yields of up to 75% (Scheme 1). The choice of aldehydes was based on both synthetic and structure–activity objectives, allowing exploration of the constraints of the condensation reaction and an insight into the effect of substituent at the bridging position on inhibitory activity.

Although nonhalogenated resorcinol dimers could be accessed through using a large excess of resorcinol we instead used sequential catalytic hydrogenation reactions to allow the isolation of both the mono brominated derivatives **9**–**13**[31] and a fully dehalogenated dimer **14**[31] for comparison. The dibromoresorcinol dimers **4**–**8** were debrominated using H_2 in the presence of 10% Pd/Al_2O_3 in methanol at room temperature for 4 h[12] (Scheme 2). The debrominated phenolic compounds **9**–**14** were obtained from the corresponding reaction mixture by HPLC techniques in satisfactory yields.

All compounds (Fig. 2) were fully characterised using ^{1}H NMR, ^{13}C NMR, IR and mass spectra.

The in vitro antibacterial activity of the new dimers **4–14** and compound **1a**[13] were assessed against three representative Gram positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis* and *Micrococcus luteus*) and three representive Gram negative bacteria (*Salmonella typhimurium*, *Proteus vulgaris* and *Escherichia coli*) using our previously described method (Table 1).[14] In all cases activity against *E. coli* was low, however, no general selectivity between Gram positive and negative bacteria was observed. The most effective compounds featured two bromo substituents with compound **5** showing particularly high activity comparable with ampicillin. It is interesting to note that low activities were observed with **8** and **13** featuring a *para*-NO_2 substituent. Compared with previously

Table 1
Antibacterial activity

Compounds	Antibacterial activity (MIC, μg/ml)					
	S. aureus	*B. subtilis*	*M. luteus*	*S. typhimurium*	*P. vulgaris*	*E. coli*
1a[13]	25	25	25	25	25	50
4	3.12	1.56	1.56	3.12	1.56	50
5	0.78	0.78	0.78	1.56	0.78	>100
6	6.25	1.56	1.56	6.25	1.56	100
7	3.12	1.56	1.56	3.12	1.56	>100
8	25	12.5	12.5	25	25	>100
9	6.25	3.12	3.12	3.12	3.12	100
10	6.25	3.12	3.12	6.25	3.12	>100
11	12.5	6.25	12.5	12.5	12.5	>100
12	12.5	6.25	12.5	6.25	6.25	>100
13	100	50	50	100	100	>100
14	12.5	6.25	12.5	12.5	12.5	100
Ampicillin	0.39	0.39	1.56	0.78	0.78	6.25

Microorganisms: *Staphylococcus aureus* ATCC6538p; *Bacillus subtilis* ATCC6633; *Micrococcus luteus* IFC12708; *Salmonella typhimurium* ATCC14028; *Proteus vulgaris* ATCC3851; *Escherichia coli* ATCC25922.

Table 2
Antifungal activity

Compounds	Antifungal activity (MIC, μg/ml)			
	A. fumigatus	*T. rubrum*	*T. mentagrophytes*	*C. albicans*
1a[13]	12.5	12.5	1.56	25
4	12.5	12.5	25	25
5	50	100	100	50
6	100	>100	100	100
7	100	100	100	50
8	>100	>100	>100	>100
9	50	50	50	50
10	>100	>100	>100	>100
11	>100	>100	>100	>100
12	>100	>100	>100	100
13	>100	>100	>100	>100
14	>100	>100	>100	>100
Ampicillin	1.56	1.56	1.56	0.78

Microorganisms: *Aspergillus fumigates* HIC6094; *Trichophyton rubrum* IFO9185; *Trichrophton mentagrophytes* IFO40996; *Candida albicans* ATCC10231

Table 3
Inhibitory effect of **4**–**14** on the activity of isocitrate lyase (ICL)

Compounds	ICL IC_{50} μg/ml (μM)
1a[13]	10.1 (18.4)
4	12.9 (28.0)
5	12.5 (25.9)
6	9.6 (17.9)
7	13.7 (26.8)
8	10.6 (20.7)
9	17.8 (46.6)
10	36.5 (90.5)
11	35.9 (78.7)
12	30.2 (69.9)
13	17.8 (41.2)
14	50.5 (167.0)
3-Nitropropionate	4.7 (6.0)

synthesised catechol dimers[12–14] and the natural product **1a** activity is high.

In contrast, antifungal activity, against a panel of fungi (*Aspergillus fumigates*, *Trichophyton rubrum*, *Trichrophton mentagrophytes* and *Candida albicans*) of the new brominated resorcinol dimers is generally lower than the natural product **1a** and comparable with brominated catechol dimers,[12,13] with good activity only being observed in the case of **4** (Table 2).

Inhibition of isocitrate lyase, from *C. albicans*, was assessed, in comparison with the known inhibitor 3-nitropropionate, using our previously described method[32] (Table 3). All new dimers showed inhibition of the glyoxalate pathway enzyme. The importance of halogen substitution in achieving high inhibitory values for isocitrate lyase is clear, with the dibrominated compounds **4**–**8** being more active than the monobrominated **9**–**13** or the non-halogenated control molecule **14**. This is particularly apparent in the case of **6**, which features additional chlorine atoms. It is interesting to note that the inhibitory activity of the dibrominated compounds is comparable with the natural lead bromophenol **1a**, demonstrating that resorcinol derivatives bind well to isocitrate lyase. Unlike the natural products and catechol dimers all of the compounds under study also incorporate a bridging substituent, however, the excellent IC_{50} values show that such a substituent, whether aromatic or aliphatic, can be accommodated easily in the binding site allowing the possibility of further structural diversification and optimisation of binding.

In conclusion, a new series of brominated resorcinol dimers was synthesized and their antimicrobial activities were investigated. Among the synthesized resorcinol dimers, 6,6′-((4-hydroxyphenyl)methylene)bis(4-bromobenzene-1,3-diol) (**4**) displayed potent antibacterial activity and inhibitory activity against isocitrate lyase (ICL) of *C. albicans*. Since the enzymes of the glyoxylate cycle are not present in mammals, the readily prepared brominated resorcinol dimers tested in this study are good starting candidates for antimicrobial drug design. Future work will investigate further the constraints surrounding substituents at the bridging position and the effect of higher levels of halogenations on activity.

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30. *Experimental:* All reagents for synthesis were commercial (highest purity available for reagent grade compounds) and used without further purification. All reactions were performed under an Argon atmosphere. NMR solvents were purchased from Apollo. NMR spectra were recorded at 293 K, expect where stated, using a 500 MHz or a 400 MHz spectrometer. Shifts are referenced relative to deuterated solvent residual peaks. Melting points were determined using MelTemp digital melting point apparatus and are uncorrected. *General method for the synthesis of dibromoresorcinol dimers* **4**–**8**: concentrated hydrochloric acid (7.5 ml) was added to a solution of aldehyde (2.6 mM) and 4-bromo resorcinol (5.2 mM) in 15 cm^3 of ethanol. The mixture was heated at 70 °C for 3 h and then cooled. The solution was neutralised by addition of $NaHCO_3$ and then extracted into ethylacetate. The product was purified by column chromatography as shown. Compound **4**: column chromatography hexane/ethyl acetate 7:3 yield = 22%, ^{1}H NMR (500 MHz, CD_3OD-d_4) δ 7.10 (s, 2H, Ar), 6.40 (s, 2H, Ar), 4.33 (t, J = 8.0 Hz, 1H, $CH_{bridging}$), 1.88 (q, J = 7.5 Hz, 2H, $1CH_2$), 1.28 (m, 6H, $3CH_2$), 0.88 (t, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR (500 MHz, CD_3OD-d_4) δ 156.3, 153.7, 132.6, 126.3, 104.7, 100.4, 36.9, 35.1, 33.0, 28.8, 23.8, 14.6; IR 3350, 2928, 1614, 1487, 1429, 1260 cm^{-1}; Mpt 107–109 °C; MS (LRESI) 458.98 (M−H). Compound **5** column chromatography DCM/MeOH 9:1 yield = 63% ^{1}H NMR (500 MHz, CD_3OD-d_4) δ 6.81 (d, J = 8.5 Hz, 2H, Ar), 6.69 (d, J = 8 Hz, 2H, Ar), 6.64 (s, 2H, Ar), 6.42 (s, 2H, Ar), 5.75 (s, 1H, $CH_{bridging}$); ^{13}C NMR (500 MHz, CD_3OD-d_4) δ 156.6, 156.4, 154.0, 136.0, 134.4, 131.2, 126.2, 116.0, 104.6, 99.8, 42.9; IR 3426, 2922, 1734, 1614, 1511, 1427, 1242, 1054 cm^{-1}; Mpt 201–202 °C; MS (LRESI) 480.95 (M−H). Compound **6**: column chromatography DCM/MeOH 9:1 yield 36%, ^{1}H NMR (500 MHz, CD_3OD-d_4) 7.29 (d, J = 8.0 Hz, 2H, Ar) δ 7.14 (t, J = 8.0 Hz, 1H, Ar), 6.78 (s, 2H, Ar), 6.42 (s, 2H, Ar), 6.36 (s, 1H, $CH_{bridging}$); ^{13}C NMR (500 MHz, CD_3OD-d_4) δ 156.8, 154.4, 140.3, 137.6, 134.9, 130.4, 129.0, 122.1, 104.2, 99.7, 43.0; IR 3481, 2923, 1610, 1502, 1426, 1338, 1173, 1122, 1011 cm^{-1}; Mpt 162–164 °C; MS (LRESI) 533.02 (M−H). Compound **7**: column chromatography DCM/MeOH 9:1 yield 75%, ^{1}H NMR (500 MHz, CD_3OD-d_4) δ 8.07 (d, J = 8.5 Hz, 1H, Ar) 7.84 (s, 1H, Ar), 7.50 (t, J = 8.0 Hz, 1H, Ar), 7.43 (d, J = 7.5 Hz, 1H, Ar), 6.67 (s, 2H, Ar), 6.48 (s, 2H, Ar), 5.94 (s, 1H, $CH_{bridging}$); ^{13}C NMR (500 MHz, CD_3OD-d_4) δ 156.7, 154.9, 149.8, 148.3, 136.6, 134.4, 130.3, 124.5, 123.9, 122.1, 104.8, 100.0, 44.0; IR 3348, 2973, 1617, 1524, 1426, 1350, 1201, 1123, 1055 cm^{-1}; Mpt 218–220 °C; MS (LRESI) 509.92 (M−H). Compound **8**: column chromatography DCM/MeOH 9:1 yield = 72% ^{1}H NMR (500 MHz, CD_3OD-d_4) δ 8.14 (d, J = 9.0 Hz, 2H, Ar) 7.24 (d, J = 8.5 Hz, 2H, Ar), 6.67 (s, 2H, Ar), 6.47 (s, 2H, Ar), 5.95 (s, 1H, $CH_{bridging}$); ^{13}C NMR (500 MHz, CD_3OD-d_4) δ 156.7, 154.8, 154.0, 147.8, 134.4, 131.1, 124.3, 123.9, 104.7, 99.9, 44.1; IR 3437 2921, 1735, 1606, 1512, 1428, 1346, 1201, 1120, 1054 cm^{-1}; Mpt 226–227 °C; MS (LRESI): 509.89 (M−H).
31. *General debromination method of Dibromoresorcinol dimers* **4**–**8**. A stirred mixture of the dibromoresorcinol dimers **4**–**8** (15–25 mg), and 10% Pd/Al_2O_3 (15 mg) in methanol (10 ml) was hydrogenated using H_2 balloon at room temperature for 4 h. The reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was partitioned between ethyl acetate and H_2O, and the organic layer was concentrated and purified by RP-18 HPLC with a mixture of water and methanol as an eluent to afford corresponding phenolic compounds **11**–**16**, respectively. Compound **9**: HPLC yield = 21%, ^{1}H NMR (500 MHz, CD3OD-d_4) δ 7.10 (s, 1H, Ar), 6.94 (d, J = 8.0 Hz. 1H, Ar), 6.38 (s, 1H, Ar), 6.27 (d, J = 8.0 Hz, 1H, Ar), 6.26 (s, 1H, Ar), 4.34 (t, J = 7.5 Hz, 1H, $CH_{bridging}$), 1.90 (m, 2H, $1CH_2$), 1.27 (m, 6H, $3CH_2$), 0.87 (t, J = 7.0 Hz, 3H, $1CH_3$); ^{13}C NMR (500 MHz, CD3OD-d_4) δ 157.3, 156.6, 156.2, 153.5, 132.4, 129.3, 127.2, 123.8, 107.9, 104.7, 103.7, 100.5, 36.3, 35.3, 33.1, 28.9, 23.8, 14.6; IR 3384, 2928, 1616, 1507, 1457, 1431, 1290, 1161 cm^{-1}; Mpt 105–107 °C; MS (LRESI) 381.17 (M−H). Compound **10**: HPLC yield = 38%, ^{1}H NMR (500 MHz, CD_3OD-d_4) δ 6.82 (d, J = 8.5 Hz, 2H, Ar), 6.67 (s, 1H, Ar) 6.66 (d, J = 7.5 Hz, 2H, Ar), 6.47 (d, J = 8.0 Hz, 1H, Ar), 6.41 (s, 1H, Ar), 6.28 (d, J = 2.0 Hz, 1H, Ar), 6.18 (d, J = 9.0 Hz, 1H, Ar), 5.78 (s, 1H, $CH_{bridging}$); ^{13}C NMR (500 MHz, CD_3OD-d_4) δ 157.7, 156.9, 156.4, 156.4, 153.8, 136.7, 134.6, 131.7, 131.3, 126.8, 123.7, 115.8, 107.0, 104.6, 103.6, 99.7, 42.8; IR 3351, 2919, 1734, 1613, 1511, 1427, 1240, 1011 cm^{-1}; Mpt 124–126 °C; MS (LRESI) 403.11 (M−H). Compound **11**: HPLC yield = 57% ^{1}H NMR (500 MHz, CD_3OD-d_4) δ 7.26 (d, J = 7.5 Hz, 1H, Ar), 7.25 (s, 1H, Ar) 7.11 (t, J = 8.0 Hz, 1H, Ar), 6.77 (s, 1H, Ar), 6.61 (d, J = 8.0 Hz, 1H, Ar), 6.38 (s, 1H, $CH_{bridging}$), 6.38 (d, J = 5.0 Hz, 1H, Ar), 6.30 (d, J = 2.5 Hz, 1H, Ar), 6.19 (dd, J = 2.5, 8.0 Hz, 1H, Ar); ^{13}C NMR (500 MHz, CD_3OD-d_4) δ 158.1, 157.3, 156.8, 154.1, 141.0, 137.7, 135.2, 131.9, 130.3, 128.7, 123.2, 119.4, 107.1, 104.1, 103.4, 99.7, 43.1; IR 3246, 2916, 1609, 1510, 1430, 1206 cm^{-1}; Mpt 127–129 °C; MS (LRESI) 455.01 (M−H). Compound **12**: HPLC yield = 50%, ^{1}H NMR (500 MHz, CD_3OD-d_4) δ 8.03 (d, J = 8.0 Hz, 1H, Ar), 7.84 (s, 1H, Ar), 7.47 (t, J = 7.5 Hz, 1H, Ar), 7.43 (d, J = 7.5 Hz, 1H, Ar), 6.70 (s, 1H, Ar), 6.47 (d, J = 8.5 Hz, 1H, Ar), 6.46 (s, 1H, Ar), 6.33 (d, J = 2.0 Hz, 1H, Ar), 6.23 (dd, J = 2.5, 8.5 Hz, 1H, Ar), 5.99 (s, 1H, $CH_{bridging}$); ^{13}C NMR (500 MHz, CD_3OD-d_4) δ 158.4, 157.1, 156.7, 154.6, 149.7, 149.1, 136.7, 134.6, 131.7, 130.1, 124.6, 121.8, 121.7, 107.4, 104.7, 104.7, 103.8, 99.9, 43.8; IR 3409, 2928, 1609, 1523, 1427, 1351, 1198, 1126, 1095 cm^{-1}; Mpt 123–125 °C; MS (LRESI) 430.01 (M−H). Compound **13**: HPLC yield = 23%, ^{1}H NMR (500 MHz, CD_3OD-d_4) δ 8.11 (d, J = 8.5 Hz, 2H, Ar), 7.24 (d, J = 8.0 Hz, 2H, Ar), 6.70 (s, 1H, Ar), 6.47 (d, J = 8.5 Hz, 1H, Ar), 6.45 (s, 1H, Ar), 6.33 (d, J = 2.5 Hz, 1H, Ar), 6.22 (dd, J = 2.5, 8.0 Hz, 1H, Ar), 5.99 (s, 1H, $CH_{bridging}$); ^{13}C NMR (500 MHz, CD_3OD-d_4) δ 158.4, 157.1, 156.7, 154.9, 154.6, 147.6, 134.6, 131.8, 131.1, 124.6,124.2, 121.7, 107.3, 104.6, 103.8, 99.9, 44.0; IR 3400, 2917, 1606, 1512, 1427, 1345, 1199, 1125, 1013 cm^{-1}; Mpt 127–129 °C; MS (LRESI) 430.04 (M−H). Compound **14**: HPLC yield = 46%, ^{1}H NMR (500 MHz, CD_3OD-d_4) δ 8.14 (d, J = 9.0 Hz, 2H, Ar) 7.24 (d, J = 8.5 Hz, 2H, Ar), 6.67 (s, 2H, Ar), 6.47 (s, 2H, Ar), 5.95 (s, 1H, $CH_{bridging}$); ^{13}C NMR (500 MHz, CD_3OD-d_4) δ 156.7, 154.8, 154.0, 147.8, 134.4, 131.1, 124.3, 123.9, 104.7, 99.9, 44.1; IR 3303, 2929, 1619, 1508, 1460, 1301, 1158 cm^{-1}; Mpt 169–171 °C, MS (LRESI) 301.17 (M−H).
32. Shin, D. S.; Kim, S.; Yang, H. C.; Oh, K.-B. *J. Microbiol. Biotecnol.* **2005**, *15*, 652.