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Laccase-catalyzed synthesis of catechol thioethers by reaction of catechols with thiols using air as an oxidant†

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The laccase-catalyzed reaction between catechols and thiols using aerial oxygen as the oxidant delivers the corresponding catechol thioethers with yields up to 96% under mild reaction conditions.

The development of selective, efficient, economic and sustainable oxidations presents a major challenge to synthetic organic chemistry.[1] Against this background, enzyme-catalyzed oxidations using aerial oxygen as the oxidant are receiving particular attention.[2] Laccases, which belong to the class of multicopper oxidases (benzenediol: O_2 oxidoreductase E.C. 1.10.3.2.), are among the most attractive enzymes in this respect[2,3] since they are characterized by a number of features and advantages: laccases are easily accessible; they are capable of catalyzing the oxidation of numerous substrates in aqueous solvent systems under mild reaction conditions (temperature, pH, pressure) with oxygen; the oxidation of the substrates is linked to the formation of water as the only byproduct; and the substrate scope of laccase-catalyzed reactions can be broadened by using laccase/mediator systems allowing for the oxidation of substrates with higher oxidation potentials.

So far, laccase-catalyzed oxidations have mostly been used for oxidizing several functional groups[4] and for oxidative couplings of electron rich phenolic substrates.[5] One particular promising aspect of the laccase-catalyzed transformations is the potential for combining the laccase-catalyzed generation of highly reactive molecules with subsequent non-oxidative chemical transformations to new domino processes. This approach has been used for the formation of quinoid systems and their subsequent reactions with *C*-nucleophiles.[6] The nucleophilic 1,4-addition of different *N*-nucleophiles to *o*- and *p*-quinones obtained by laccase-catalyzed oxidation of catechol and hydroquinone, respectively, has also been explored.[3b,7] However, little is known about the laccase-catalyzed reaction between hydroquinones or catechols and thiols.[8] So far, it has been reported that 3-substituted 1,2,4-triazolo[4,3-*b*]-(4,1,2)benzothiadiazine-8-ones can be synthesized by laccase-catalyzed *in situ* generation of *p*-benzoquinone followed by reaction with 5-substituted 4-amino-3-mercapto-1,2,4-triazoles.[8d] Wellington *et al.* have reported on the laccase-catalyzed reaction between 1,4-dihydroxynaphthalenes and thiols to form various naphthoquinone sulfides.[8b,c] Even less is known about enzyme-catalyzed reactions between catechols and thiols. The only exception is the laccase-initiated domino reaction between catechols and 6-substituted 1,2,3,4-tetrahydro-4-oxo-2-thioxo-5-pyrimidinecarbonitriles for the synthesis of pyrimidobenzothiazole derivatives.[8a] The 1,4-addition of simple thiols to *o*-benzoquinones generated by enzyme-catalyzed oxidation of catechols to deliver the corresponding catechol thioethers is still unexplored.

Catechol thioethers are known to exhibit various biological (*e.g.*, antibacterial and antioxidant) activities.[9] That is why their synthesis is of interest. Aromatic thioethers can be synthesized by a number of methods, including the Pd-, Cu- and Rh-catalyzed reaction of aryl halides with thiols under basic conditions.[10] Most catechol thioethers have been obtained by oxidation of catechols in the presence of the corresponding thiols. The oxidation of the catechols to *o*-benzoquinones has been achieved either by using $K_3[Fe(CN)_6]$ as the oxidant[11] or by anodic oxidation.[12] Clearly, both methods face some problems, such as the use of at least stoichiometric amounts of an inorganic oxidant or the use of special equipment not available in many laboratories.

Against this background, we considered the laccase-initiated domino reaction between catechols and thiols as a highly attractive alternative for the synthesis of catechol thioethers (Scheme 1).

The catechols and the heterocyclic thiols used for the synthesis of the catechol thioethers are depicted in Fig. 1. The reaction between catechol (**1a**) and 2-mercaptobenzoxazole (**2a**) on a 1 mmol scale was selected as a model reaction (Table 1). When equimolar amounts of **1a** and **2a** were reacted in the presence of 300 U laccase from *Agaricus bisporus* (6 U mg^{-1}) in

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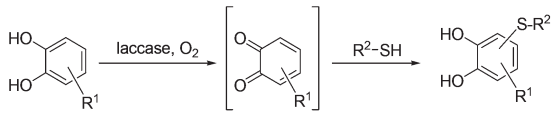
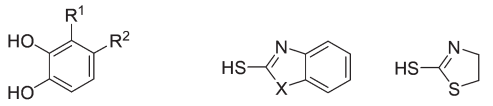
† Electronic supplementary information (ESI) available: Experimental data and copies of the ^{1}H NMR and ^{13}C NMR spectra. See DOI: 10.1039/c3gc41968a



Scheme 1 Synthesis of catechol thioethers by laccase-catalyzed reaction between catechols and thiols.

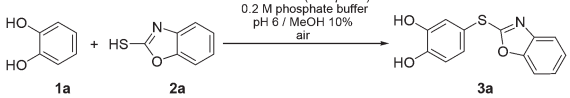


1a R^1 = H R^2 = H
1b R^1 = CH_3 R^2 = H
1c R^1 = OCH_3 R^2 = H
1d R^1 = F R^2 = H
1e R^1 = CN R^2 = H
1f R^1 = COOH R^2 = H
1g R^1 = $COOCH_3$ R^2 = H
1h R^1 = H R^2 = CH_3
1i R^1 = H R^2 = C_2H_5
1j R^1 = H R^2 = NO_2

2a X = O
2b X = S
2c

Fig. 1 Substrates for the laccase-catalyzed transformations.

Table 1 Optimization of the laccase-catalyzed reaction between catechol (**1a**) and 2-mercaptobenzoxazole (**2a**) under air



Entry	Laccase (U)	*T*	Time (h)	Yield of **3a** (%)
1[a]	300	rt	20	77
2[b]	300	rt	15	93
3[b]	150	rt	16	95
4[b]	120	rt	16	93
5[c]	60	rt	16	93
6[b]	120	50 °C	12	84
7[b]	100	rt	17	—[d]
8[b]	75	rt	24	—[d]
9[b]	—	rt	24	—[e]

[a] 1 mmol **1a** and 1 mmol **2a** were reacted. [b] 1.25 mmol **1a** and 1 mmol **2a** were reacted. [c] 0.63 mmol **1a** and 0.50 mmol **2a** were reacted. [d] Incomplete conversion. [e] No reaction.

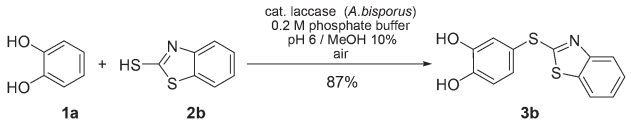
0.2 M phosphate buffer at pH 6.0/MeOH (9 : 1) for 20 h at rt, the corresponding catechol thioether **3a** was isolated in 77% (Table 1, entry 1). The yield of **3a** could be improved to 93% when the reaction was performed with a slight excess (1.25 equiv.) of **1a** (Table 1, entry 2). It should be emphasized that the thioether **3a** was formed exclusively; no disulfide formation was observed.[4a] This result confirms the observation that the laccase-catalyzed generation of *o*-benzoquinones from catechols does not require a mediator.[6a–d,f,g,i–k] It is also remarkable that only the monothioether was formed; not a trace of the corresponding bisthioether could be detected.

Further experiments devoted to the influence of the amount of the laccase from *A. bisporus* clearly demonstrated that the reaction of **1a** with **2a** tolerates a stepwise reduction of the catalyst load from 300 U to 120 U without any loss of yield (Table 1, entries 3 and 4). A further decrease did not pay off, since with 100 or 75 U laccase the transformations did not run to completion (Table 1, entries 7 and 8). The experiment with 120 U laccase was also performed at 50 °C; however, the yield dropped from 93 to 84% (Table 1, entry 6). Notably, the reaction could be run successfully on a 0.50 mmol scale with as little as 60 U laccase (Table 1, entry 5). Therefore, all further experiments were performed with 0.50 mmol thiol.‡ Finally, a control experiment was conducted to show that the formation of the thioether **3a** does not proceed in the absence of the laccase (Table 1, entry 9).

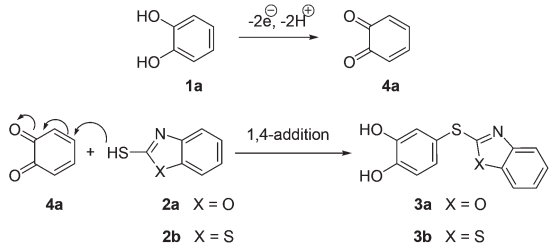
The reaction was not restricted to 2-mercaptobenzoxazole (**2a**) as a thiol, but could also be performed with 2-mercaptobenzothiazole (**2b**). When **2b** was reacted with unsubstituted catechol (**1a**) under the conditions developed for the transformation with **2a** (Table 1, entry 5), the catechol thioether **3b**§ was obtained exclusively in 87% yield (Scheme 2).

It is assumed that the process starts with the laccase-catalyzed oxidation of catechol (**1a**) to the corresponding *o*-benzoquinone (**4a**), followed by the intermolecular nucleophilic 1,4-addition of 2-mercaptobenzoxazole (**2a**) or 2-mercaptobenzothiazole (**2b**) to produce the corresponding catechol thioethers **3a**, **b** (Scheme 3).

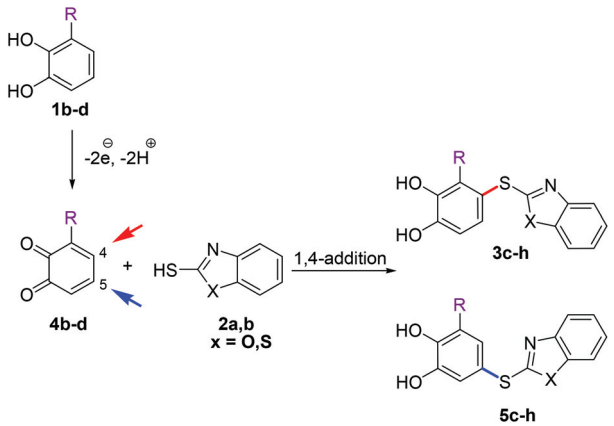
Then, we focused on the reactions between **2a**, **b** and monosubstituted catechols **1b–j**. In a first set of experiments, **2a**, **b** were reacted with 3-substituted catechols **1b–d** under the conditions described in Table 1, entry 5. Depending on whether the intermolecular nucleophilic attack of the heterocyclic thiols **2a**, **b** occurs at C-4 or C-5 of the corresponding *o*-benzoquinones **4b–d** (Scheme 4), either products of type **3** or type **5** were formed. The reaction between 3-methylcatechol (**1b**) and 2-mercaptobenzoxazole (**2a**) gave 90% of a 69 : 31 mixture of the regioisomers **3c** and **5c** (Table 2, entry 3). A similar result was observed with 2-mercaptobenzothiazole (**2b**) (Table 2, entry 4). The isomers arising from the C-4 attack also preferentially formed in the reactions of 3-fluorocatechol (**1d**): with **2a** as the nucleophile, a 63 : 37 mixture of **3g** and **5g** was obtained (Table 2, entry 7); with **2b** the isomers **3h** and **5h** were formed in a 69 : 31 ratio (Table 2, entry 8). The only exceptions were the transformations between 3-methoxycatechol (**1c**) and **2a**, **b**. With both nucleophiles, the 5-substituted catechol thioethers **5e** and **5f** were formed as the major isomers (Table 2, entries 5 and 6). It should be noted that the C-4 addition of **2a**, **b** to **4b** and **4d** (quinones) was unexpected, since laccase-catalyzed 1,4-additions of *C*-nucleophiles are known to proceed at C-5.[6a–d,f,g,i–k] However, the laccase-catalyzed 1,4-additions of thiols to the *o*-quinone resulting from 3-methylcatechol (**1b**) show a close



Scheme 2 Laccase-catalyzed reaction between catechol (**1a**) and 2-mercaptobenzothiazole (**2b**).



Scheme 3 Possible reaction mechanism for the laccase-catalyzed reaction between **1a** and **2a**, **b**.

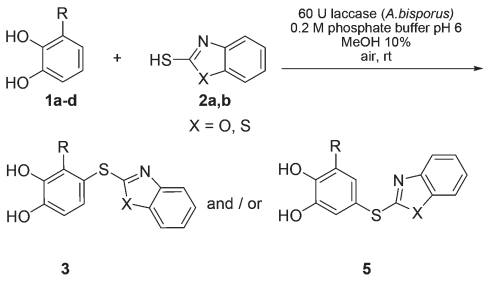


Scheme 4 Regioselectivity of the laccase-catalyzed reactions between 3-substituted catechols **1b–d** and thiols **2a**, **b**.

resemblance to some of the results from reactions run under electrochemical conditions.[12b,c] Thioethers were not formed when 3-substituted catechols having an electron withdrawing group at the 3-position, *i.e.* **1e** (R = CN), **1f** (R = COOH) and **1g** (R = COOMe), were used as substrates.

Next, the reactions between 2-mercaptobenozoxazole (**2a**) and 2-mercaptobenzothiazole (**2b**) with a number of 4-substituted catechols were performed under the reaction conditions given in Table 1, entry 5. It was interesting to see that the reactions with 4-methylcatechol (**1h**) and 4-ethylcatechol (**1i**) exclusively delivered the catechol thioethers **6a–d** resulting from the nucleophilic attack of **2a**, **b** at C-5 of the corresponding *o*-benzoquinone intermediates **4h,i** (Scheme 5) with yields ranging from 83 to 90% (Table 3, entries 1–4). However, with 4-nitrocatechol (**1j**) as the substrate, the 1,4-addition selectively took place at C-3 of the corresponding *o*-benzoquinone **4j** to deliver the thioether **7a** exclusively in 85% yield (Scheme 5, Table 3, entry 5).

Table 2 Laccase-catalyzed reaction between 3-substituted catechols **1a–d** and thiols **2a**, **b**[a]

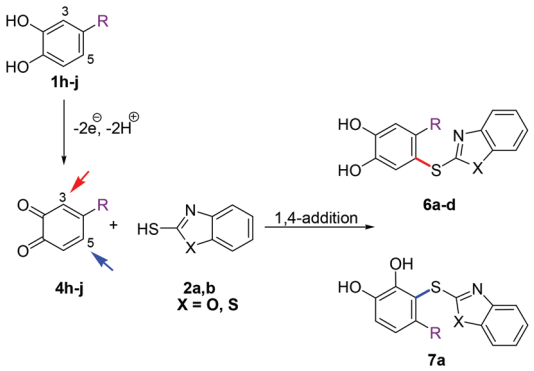


Entry	1	R	2	X	Time (h)	Product	3 : 5[b]	Yield (%)
1	**a**	H	**a**	O	16	**3a**	100 : 0	93
2	**a**	H	**b**	S	17	**3b**	100 : 0	87
3	**b**	CH_3	**a**	O	24	**3c**, **5c**	69 : 31	90
4	**b**	CH_3	**b**	S	17	**3d**, **5d**	62 : 38	95
5	**c**	OCH_3	**a**	O	17	**3e**, **5e**	22 : 78	96
6	**c**	OCH_3	**b**	S	17	**3f**, **5f**	17 : 83	95
7	**d**	F	**a**	O	17	**3g**, **5g**	63 : 37	90
8	**d**	F	**b**	S	17	**3h**, **5h**	69 : 31	86

[a] 0.63 mmol **1** and 0.5 mmol **2** were reacted. [b] Ratio determined from the ^{1}H NMR spectrum of the crude product.

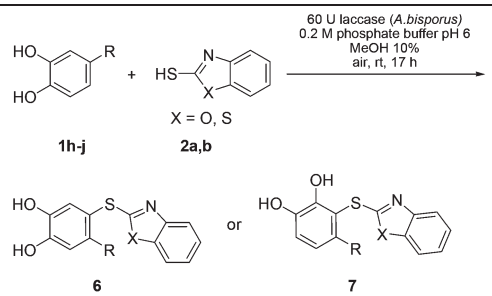
Finally, 2-mercaptothiazoline (**2c**) was reacted with unsubstituted catechol (**1a**) and the 4-substituted catechols **1h**, **i** under the conditions displayed in Table 1, entry 5. In accordance with the results of **2a** and **2b**, the corresponding catechol thioethers **8a–c** were formed exclusively with yields ranging from 74 to 83% (Table 4).

The newly developed laccase-catalyzed reaction between catechols **1** and thiols **2** complies with the principles of green chemistry[13] for a number of reasons: the reaction is a highly selective enzyme-catalyzed transformation that allows the selective preparation of catechol thioethers in a single step with yields up to 96%. No toxic byproducts were formed. The reactions were performed with atmospheric oxygen as the oxidant, avoiding any toxic reagents. Atmospheric oxygen is not only one of the cheapest oxidants, but it is also considered to be environmentally benign. During the course of the reaction, oxygen is reduced to completely safe and nontoxic water, which is the only byproduct of the entire process. Using the laccase-catalyzed reaction between catechol (**1a**) and 2-mercaptobenzoxazole (**2a**) as an example, the E-factor (kg waste per kg product)[1a,14] of the process is 7.88 kg kg^{-1}. This value compares well with the E-factors of other synthetic methods for the synthesis of catechol thioethers. The atom economy[15] of the presented method is high (94%). A mixture of phosphate buffer (pH 6.0) and 10 vol% methanol, which is a safe and environmentally preferred solvent,[1c,16] was used as the reaction medium. The laccase-catalyzed domino reaction can be carried out under mild reaction conditions (room temperature, atmospheric pressure, pH 6.0). The laccase-catalyzed formation of catechol thioethers is characterized by high turnover numbers (TON), *e.g.*, in the reaction between **1a** and **2a**, it amounts to 4512. This value underlines the high catalytic efficiency of the



Scheme 5 Regioselectivity of the laccase-catalyzed reactions between 4-substituted catechols **1h–j** and thiols **2a**, **b**.

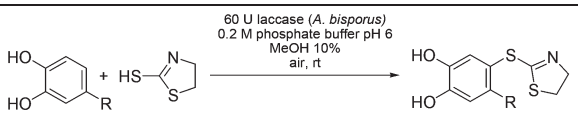
Table 3 Laccase-catalyzed domino reaction between 4-substituted catechols **1h–j** and thiols **2a**, **b**



Entry	1	R	2	X	Product	Yield (%)
1[a]	**h**	CH_3	**a**	O	**6a**	85
2[a]	**h**	CH_3	**b**	S	**6b**	90
3[a]	**i**	C_2H_5	**a**	O	**6c**	83
4[a]	**i**	C_2H_5	**b**	S	**6d**	83
5[b]	**j**	NO_2	**a**	O	**7a**	85

[a] 0.63 mmol **1** and 0.5 mmol **2** were reacted. [b] 0.50 mmol **1j** and 0.5 mmol **2a** were reacted.

Table 4 Laccase-catalyzed reaction between catechols **1a**, **h**, **i** and 2-mercapto-thiazoline (**2c**) under air[a]



Entry	1	R	Time (h)	8	Yield (%)
1	**a**	H	20	**a**	83
2	**h**	CH_3	17	**b**	74
3	**i**	C_2H_5	17	**c**	82

[a] 0.63 mmol **1** and 0.5 mmol **2c** were reacted.

enzyme-catalyzed reaction. The turnover frequencies of the process are good; in the example mentioned above the TOF amounts to 282 h^{-1}.

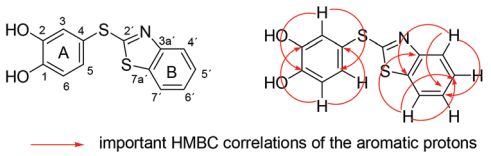


Fig. 2 Structure of **3b** and important HMBC correlations.

Structures of all compounds were unambiguously elucidated by mass spectrometry and NMR spectroscopy including 2D NMR for the full assignment of the ^1H and ^{13}C chemical shifts. For example, analysis of the gCOSY spectrum of compound **3b** (Fig. 2) revealed two scalar coupled ^1H spin systems, one consisting of protons 3-H, 5-H and 6-H (ring A) and the other of aromatic protons 4′-H, 5′-H, 6′-H and 7′-H (ring B). Their corresponding directly bonded carbons were identified by gHSQC. The quaternary carbons C-1, C-2 and C-4 (ring A) were assigned by gHMBC optimized for J_{CH} = 8 Hz. A strong ^3J-HMBC correlation between 3-H as well as 5-H and the phenolic carbon at δ 148.66 ppm established the C-1 position of the latter. The chemical shifts of the remaining A ring carbons (C-2/C-4) at δ 146.61 and 116.66 ppm respectively were deduced by the strong ^3J-HMBC correlations to 6-H. However, the unambiguous assignment of the C-2 or C-4 position to the observed values and thus the substitution pattern at C-2 and C-4 was not possible even with a gHMBC experiment optimized for J_{CH} = 1 Hz. Therefore, the ^{13}C NMR chemical shifts were computed by DFT quantum mechanical DFT calculations at the DFT GIAO mPW1PW91/6-311+G(2d,p)//mPW1PW91/6-31G(d) level of theory.[17] On the basis of computationally calculated ^{13}C chemical shifts, the quaternary carbons C-2 and C-4 were assigned to be at δ 146.61 (δ calcd 142.71 ppm) and 116.66 (δ calcd 119.25 ppm), respectively. Similarly, the quaternary carbons C-3a′ and C-7a′ of ring B were assigned at δ 153.71 (δ calcd 153.07 ppm) and δ 134.75 (δ calcd 139.77 ppm), respectively. The most downfield shifted carbon at δ 171.99 ppm was tentatively assigned to the C-2′ position.

Conclusion

To summarize, a simple-to-perform, efficient and sustainable method for the synthesis of substituted catechol thioethers has been developed. It relies on the laccase-catalyzed oxidation of a catechol to the corresponding *o*-benzoquinone which in turn undergoes an intermolecular 1,4-addition with a thiol as a nucleophile. The reactions can be performed under mild reaction conditions with air as the oxidant, and the products are formed with yields ranging between 74 and 96%. Depending on the substituent on the catechol moiety, different regioisomers are formed.

Acknowledgements

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Notes and references

‡General procedure for the laccase-catalyzed synthesis of catechol thioethers: a 100 mL round bottomed flask with a magnetic stir bar was charged with a solution or suspension of the catechol **1** (0.63 mmol) and the thiol **2** (0.5 mmol) in methanol (3 mL). Phosphate buffer (0.2 M, pH 6, 27 mL) and laccase from *A. bisporus* (10 mg, 6 U mg^{-1}) were added and the mixture was stirred under air at rt for the time given (see Tables 1–4). The reaction mixture was acidified with 2 M HCl to pH ~ 4 and saturated with solid NaCl. The precipitated product was filtered with suction using a Buchner funnel. The filter cake was washed with aq. NaCl (15%, 25 mL) and water. The crude products obtained after drying exhibit a purity of 90–95% (NMR). Analytically pure products were obtained by column filtration (CH_2Cl_2–EtOAc 5 : 1 to 1 : 1) of the crude products.

§Selected analytical data of 4-(benzo[*d*]thiazol-2′-ylthio)benzene-1,2-diol (**3b**): pale yellow solid; mp 198–200 °C; R_f = 0.53 (CH_2Cl_2–EtOAc = 5 : 1); λ_{max}(MeCN)/nm 284 (log ε, 4.60) and 206 (4.20); $\tilde{\nu}_{max}$ (atr)/cm^{-1} 3426 (br), 3054 (C–H), 1593, 1415, 1270 and 1030; δ_H (300 MHz; DMSO-d_6) 6.90 (1H, d, $^3J_{5\text{-H},6\text{-H}}$ 8.1 Hz, 6-H), 7.07 (1H, dd, $^3J_{5\text{-H},6\text{-H}}$ 8.4 Hz, $^4J_{3\text{-H},5\text{-H}}$ 2.1 Hz, 5-H), 7.13 (1H, d, $^4J_{3\text{-H},5\text{-H}}$ 2.1 Hz, 3-H), 7.29 (1H, ddd, $^3J_{5'\text{-H},6'\text{-H}}$ 7.2 or 7.9 Hz, $^3J_{6'\text{-H},7'\text{-H}}$ 7.2 or 7.9 Hz, $^4J_{4'\text{-H},6'\text{-H}}$ 1.1 Hz, 6′-H), 7.42 (1H, ddd, $^3J_{4'\text{-H},5'\text{-H}}$ 7.3 or 8.2 Hz, $^3J_{5'\text{-H},6'\text{-H}}$ 7.3 or 8.2 Hz, $^4J_{5'\text{-H},7'\text{-H}}$ 1.3 Hz, 5′-H), 7.79 (1H, ddd, $^3J_{4'\text{-H},5'\text{-H}}$ 8.1 Hz, $^4J_{4'\text{-H},6'\text{-H}}$ 1.2 or 0.6 Hz, $^5J_{4'\text{-H},7'\text{-H}}$ 1.2 or 0.6 Hz, 4′-H), 7.89 (1H, ddd, $^3J_{6'\text{-H},7'\text{-H}}$ 8.0 Hz, $^4J_{5'\text{-H},7'\text{-H}}$ 1.3 or 0.7 Hz, $^5J_{4'\text{-H},7'\text{-H}}$ 1.3 or 0.7 Hz, 7′-H) and 9.63 (2H, br, 1-OH and 2-OH); δ_C (75 MHz; DMSO-d_6) 116.66 (C-4), 117.01 (C-6), 121.12 (C-4′), 121.64 (C-7′), 122.45 (C-3), 124.13 (C-6′), 126.27 (C-5′), 127.66 (C-5), 134.75 (C-7a′), 146.61 (C-2), 148.66 (C-1), 153.71 (C-3a′) and 171.99 (C-2′); *m*/*z* (EI, 70 eV) 275 (M^+, 100%), 242 (M^+ − SH, 5), 167 ($C_7H_5S_2N^+$, 8) and 115 (15); HRMS (EI, M^+) found 275.0051 calcd for $C_{13}H_9S_2NO_2$: 275.0075.

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