Synthesis of Novel Biaryl Derivatives of Sesamol (5-Benzodioxolol) and Evaluation of their Antioxidant Activity Against DPPH Radical

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A simple and direct arylation of sesamol with aryl halides by a photoinduced reaction is reported. Five 6-arylsesamol derivatives were synthesized in order to evaluate possible changes in their antioxidant properties as a function of the C_6 aryl substituent nature. Extension of the procedure to the reaction with *o*-dihalobenzenes leads to the synthesis of ring-closure products bearing a tetracyclic aromatic condensed ring system, although in lower overall yields ($\sim$45 %). The antioxidant activity of the synthetic derivatives towards 1,1-diphenyl-2-picrylhydrazyl radical was determined taking sesamol as the reference compound. In addition, the relationship between the antiradical activities of these molecules against this radical and the bond dissociation energies of their phenolic O–H group was calculated using computational chemistry methods.

Introduction

Sesamol (5-benzodioxolol) (**1**) is a potent antioxidative constituent of sesame products. It is well known that sesame, the seeds of *Sesamum indicum*, and its oil products have been used in foods since ancient times. Many beneficial properties of sesamol, including antioxidation,[1,2] cancer chemoprevention,[3] antimutagenicity,[4] and antihepatoxic activity[5] have also been reported. Thus, sesamol should be a promising constituent of functional foods.
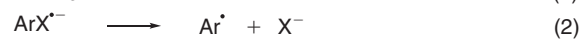
The antioxidant capacity of sesamol is derived from its phenolic group and a benzodioxole group in its molecular structure. Previous research has shown that 5-hydroxy-1,3-benzodioxole compounds exhibit greater antioxidant activity than α-tocopherol, 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT), and ascorbic acid[6,7] and comparable with the anti-oxidant potential of rosmarinic acid and carnosic acid against the 1,1-diphenyl-2-picrylhydrazyl radical (DPPH•).[8] These results clearly show the importance of studying the chemistry and properties of molecules containing this heterocyclic compound.

Radical nucleophilic substitution can be considered an alternative route for the formation of carbon–carbon bonds.[9] This type of reaction has found increasing applications in the synthesis of complex organic molecules,[10,11] particularly because such reactions are generally carried out under mild conditions and the substrates are compatible with many functional groups. It is well known that in an $S_{RN}1$ reaction,

a nucleophile is combined with an aryl radical to provide the corresponding coupling product (Scheme 1).[9] Traditionally, aryl halide substrates give the aryl radical in a photoinduced electron-transfer reaction from the nucleophile (Eqns 1, 2). The radicals thus formed are able to react with the nucleophile to give the radical anion of the substitution product (Scheme 1).

In previous work, we synthesized a family of biaryl derivatives of 4-hydroxycoumarin[12] using this synthetic pathway, and the effect of substituent groups with different electronic and steric natures on the antioxidant properties of this heterocycle was described.[13] 4-Hydroxycoumarin substitution in the *vicinal* position (C_3) to the OH group with aryl rings with electron-donor groups (4-methoxyphenyl and 2-methoxyphenyl groups) significantly improved the antioxidant activity.

Sesamol has higher antiradical activity than 4-hydroxycoumarin.[7,13] This behaviour can be ascribed to the presence of a phenolic OH group in the former compared with the vinyl OH group carried by 4-hydroxycoumarin. In addition,

$$ArX + Nu^- \xrightarrow{h\nu} ArX^{\bullet-} + Nu^{\bullet} \qquad (1)$$

$$ArX^{\bullet-} \longrightarrow Ar^{\bullet} + X^- \qquad (2)$$

$$Ar^{\bullet} + Nu^- \longrightarrow ArNu^{\bullet-} \qquad (3)$$

$$ArNu^{\bullet-} + ArX \longrightarrow ArNu + ArX^{\bullet-} \qquad (4)$$

Scheme 1.

to the best of our knowledge, there are only a few reports about the synthesis of sesamol biaryl derivatives.[14]

In order to evaluate the effect of different aryl substituents in the sesamol aromatic ring (*ortho* to OH) on the reactivity towards free radicals, as the main aim of this study, a series of 6-aryl derivatives of sesamol was synthesized, and the antioxidant activity of these synthetic compounds was compared with that of sesamol using the DPPH• assay.

Results and Discussion

Chemistry

The results of the photoinitiated reactions of the anion of sesamol (1^-) with different aryl halides (**2**) (Scheme 2) in DMSO are shown in Table 1. This anion 1^- was obtained by deprotonation of the phenolic group in C_5 of **1** using potassium *tert*-butoxide (KO^{t}Bu).

The photostimulated reaction of anion of **1** with **2a** in a 5 : 1 ratio, in excess base,[15] afforded a 16 % yield of the product corresponding to C_6 substitution of the sesamol ring, 6-(4-anisyl)-5-benzodioxolol (**3a**) (Table 1, experiment 1). The low reactivity of the anisyl radical in the coupling reaction with the nucleophile (Eqn 3, Scheme 1) favours secondary reactions of this intermediate.[9] Hydrogen-atom abstraction from the solvent by the radical intermediate or a reduction of this species followed by subsequent protonation are plausible routes to ArH (**4**) as the by-product observed in these reactions (see Scheme S1 in Supplementary Material).

When potassium *tert*-butoxide and the nucleophile were used in an equimolar ratio under light irradiation, a 90 % yield of iodide ions was obtained. This result shows the capacity of the anion of **1** as an excellent electron donor to initiate the reaction.[9]

The reactions carried out in absence of light stimulation did not take place (Table 1, experiment 2). This fact supports the assertion that these are photoinduced processes (Eqn 1, Scheme 1).

Different experimental conditions were assessed to improve the product yield. The photoinduced reaction of 1^- and **2a** in a 10 : 1 ratio was carried out (Table 1, experiment 3), affording an 18 % yield of **3a** and 74 % of anisole (**4a**). Unfortunately, the rise in the nucleophile/substrate ratio did not increase the amount of substitution product formed. The reaction of the base/**1**/**2a** in a 2 : 2 : 1 ratio, with a concentration of substrate four times higher than that used in previous experiments (Table 1, experiment 4) gave a low percentage of iodide ions (30 %), indicative of an inefficient initiation step, producing only 3 % (traces) of **3a**, and 25 % of **4a**.

In order to determine the effect of the solvent on the yield of products, the photoinduced reaction of 1^- with **2a** was carried out using ammonia as solvent (Table 1, experiment 5),[9] although no significant increase was observed in the substitution product yields under these conditions.

Continuing with the study, the reaction of the anion of **1** was evaluated with other aryl halides (**2b**–**d**). When the reaction was performed with 4-bromoanisole (**2b**), under conditions similar to experiment 3 but using a two-fold higher substrate concentration (Table 1, experiment 6), a 14 % yield of **3a** was obtained. Under both sets of experimental conditions (Table 1, experiments 3 and 6), similar substitution product yields were observed with bromine or iodine as leaving groups.

Moreover, the photoinduced reaction of **1** and 4-bromobenzonitrile (**2c**) using base and nucleophile in an equimolar ratio (Table 1, experiment 7), afforded a 17 % yield of C_6 substitution on the heterocycle, 6-(4-cyanophenyl)-5-benzodioxolol (**3c**). A similar yield was obtained when the reaction time was reduced to 90 min (Table 1, experiment 8).

In order to increase the yield of **3c**, the photoinduced reaction of base/**1**/**2c** in a 10 : 10 : 1 ratio (Table 1, experiment 9) was performed, affording a 43 % yield. A dependence of substitution product yield on the increase of the nucleophile : substrate ratio was observed for this radical.

The photoinduced reaction of KO^{t}Bu/**1**/**2c** in a 5 : 5 : 1 ratio was carried out using a concentration two-fold higher than that

Table 1. Photoinduced reactions of aryl halides with 1 in DMSO
Photoinitiated reactions (unless indicated) were carried out under nitrogen. Reaction time = 180 min. X^- (%) > 90 % determined potentiometrically on the basis of ArX concentration

Experiment	1 [mM]	Substrate [mM]	Base [mM]	Reaction time [min]	Substitution products, yield [%][A]
1	248	**2a**, 55	425	180	**3a**, 16
2[B]	520	**2a**, 52	520	180	**3a**, –
3	500	**2a**, 52	504	180	**3a**, 18
4[C]	490	**2a**, 228	491	90	**3a**, 3
5[D]	26	**2a**, 3	25	90	**3a**, 21
6	998	**2b**, 102	1002	180	**3a**, 14[E]
7	258	**2c**, 58	252	180	**3c**, 17
8[F]	255	**2c**, 50	250	90	**3c**, 15
9	502	**2c**, 55	496	90	**3c**, 43
10	517	**2c**, 102	500	120	**3c**, 33
11	503	**2c**, 100	508	180	**3c**, 30
12	998	**2c**, 200	997	180	**3c**, 28
13[F]	1040	**2c**, 104	1010	180	**3c**, 47
14[F]	1000	**2d**, 100	1008	180	**3d**, 38

[A]Determined by GLC using the internal standard method with respect to moles of ArX.
[B]Reaction carried out in the dark. X^- (%) < 5 %.
[C]X^- (%) = 30 %.
[D]Solvent = NH$_{3(l)}$.
[E]Isolated yield.
[F]X^- (%) = 85 %.

2a: Ar = 4-MeOC$_6$H$_4$, X = I
2b: Ar = 4-MeOC$_6$H$_4$, X = Br
2c: Ar = 4-CNC$_6$H$_4$, X = Br
2d: Ar = Ph, X = I

3a: Ar = 4-MeOC$_6$H$_4$
3c: Ar = 4-CNC$_6$H$_4$
3d: Ar = Ph
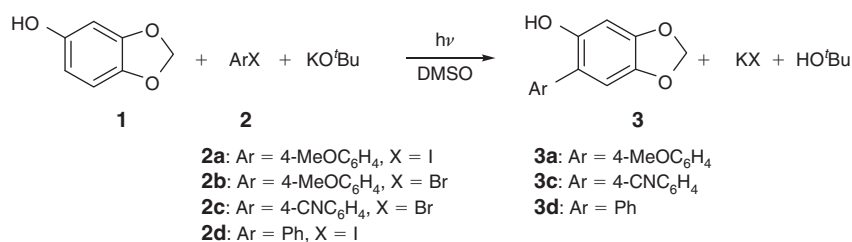
Scheme 2.

previously used for 120 min (Table 1, experiment 10) and this yielded 33 % of **3c**. A similar substitution product yield was obtained (30 %) when this reaction was irradiated for 180 min (Table 1, experiment 11). Under these experimental conditions, product yields higher than those of experiments 7 and 8 were obtained by increasing the concentration of substrate. However, in the reaction with a **2c** concentration four-fold higher than that in experiment 7, under similar conditions (Table 1, experiment 12), the yield of **3c** (28 %) was practically the same as in experiments 10 and 11.

The photoinduced reaction of base/**1**/**2c** in a 10 : 10 : 1 ratio, using a substrate concentration two-fold higher than that used in experiment 10 (Table 1, experiment 13) gave a 47 % yield of substitution product. This yield was similar to that found in experiment 9 but less solvent was necessary.

Clearly, the radical derived from **2c** coupled with the anion of **1** more efficiently than the radical formed from **2a**.

Under similar conditions, **1**$^-$ reacted with iodobenzene (**2d**) to give 6-phenyl-5-benzodioxolol (**3d**) in 38 % yield (Table 1, experiment 14). The radical resulting from this substrate has behaviour intermediate between that of anisyl and benzonitryl radicals.

It is important to mention that the *O*-arylated product of **1**[16] was neither formed in any of these reactions nor in the reaction with KO^{t}Bu.[9] The experimental proofs indicate an S$_{RN}$1 mechanism.[9] In the initiation step, a photoinduced electron transfer from **1**$^-$ to **2** takes place (Eqn 1, Scheme 1). After the fragmentation of the radical anion (Eqn 2), the radical formed can couple with the nucleophile to form the radical anion of the substitution product (Eqn 3).

By contrast, in the photoinduced reaction of **1**$^-$ with 1-chloro-4-nitrobenzene (**2e**), an *O*-substitution product[17] (**3e**, Fig. 1) was obtained in an excellent isolated yield (96 %, Table 2, experiment 1). This photoinduced reaction was not suppressed by the addition of a good electron-acceptor such as *p*-dinitrobenzene (*p*-DNB) (Table 2, experiment 2). Furthermore, a high yield of this ether was obtained from reaction in the dark, of 98 % (Table 2, experiment 3). These results are indicative that the mechanism of formation of product **3e** is a classical aromatic substitution, not light-dependent. This
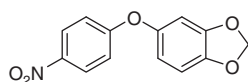
condition is an interesting alternative to obtaining the ether compound compared with other, harder methods.[16]

Based on the promising results obtained with the aryl halides tested, the photoinduced methodology was extended to the reaction of the anion of **1** with dihalobenzenes. The 1-chloro-4-iodobenzene **2f** gives the substitution product with the retention of chlorine (**3f**) in 20 % yield (Eqn 5); this product can then be modified by different chemical reactions, and 20 % yield of the substitution product with loss of the second halide, **3d** (Table 3, experiment 1).

(5)
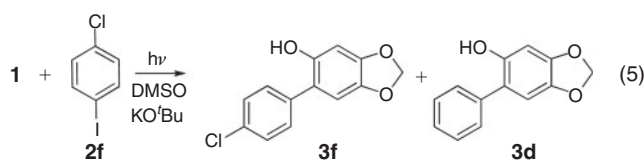
The reaction of **1** with 1-chloro-2-iodobenzene (**2g**) was studied as a procedure for the synthesis of the tetracyclic ring systems **5** (Fig. 2) by biaryl coupling followed by intramolecular heterocyclization (Eqn 6).[10]

(6)
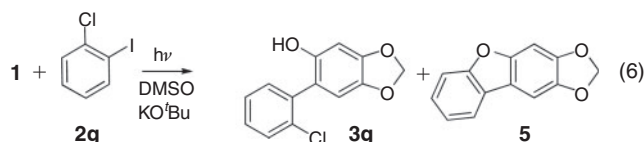
The experimental conditions for this reaction were similar to those used with the *p*-dihalobenzene, with a 12 : 10 : 1 ratio of base/**1**/substrate under irradiation for 240 min (Table 3, experiment 2), affording 42 % yield of cyclized product and only 7 % yield of **3g**. However, compound **3d** not was observed.

In summary, this is the report of the synthesis of novel 6-aryl-5-benzodioxolol derivatives from commercially available, easily handled and inexpensive reactants via photoinduced radical nucleophilic substitution under mild conditions with moderate yields. This procedure shows important advantages over the conventional cross-coupling procedures used to obtain biaryl systems.

Moreover, the reaction provides access to the tetracyclic system **5** in good yields (formation of two bonds, one C–C bond and one C–O bond). Further, the synthesis of an ether derivative of sesamol in an excellent yield by a classical mechanism is also reported.

Fig. 1. 5-(4-nitrophenoxy)-benzodioxolol (**3e**).

Table 2. Reactions of 2e with 1 in DMSO
Photoinitiated reactions were carried out under nitrogen. Reaction time = 240 min. Cl$^-$ (%) > 90 % determined potentiometrically on the basis of ArX concentration

Experiment	**1** [mM]	**2e** [mM]	Base [mM]	Yield of **3e** [%][A]
1	1008	101	1002	96[B]
2[C]	992	98	1012	97
3[D]	504	58	496	98

[A]Determined by GLC using the internal standard method with respect to moles of ArX.
[B]Isolated yield.
[C]*p*-Dinitrobenzene (62 mmol-% with respect to moles of ArX).
[D]Reaction carried out in the dark.

Table 3. Photoinduced reactions of anion of 1 with 2f and 2g in DMSO
Photoinitiated reactions were carried out under nitrogen. Reaction time = 240 min. X$^-$ (%) determined potentiometrically on the basis of ArX concentration

Experiment	**1** [mM]	Substrate [mM]	Base [mM]	Products and yield [%][A]			
				3d	**3f**	**3g**	**5**
1[B]	996	**2f**, 102	1200	20	20	–	–
2[C]	1010	**2g**, 98	1244	–	–	7	42

[A]Determined by GLC using the internal standard method with respect to moles of ArX.
[B]I$^-$ = 78 %; Cl$^-$ = 58 %.
[C]I$^-$ = 75 %; Cl$^-$ = 66 %.

Antioxidant Activity. DPPH• Scavenging Capacity Assay

Six synthetic sesamol derivatives were selected to analyze their antioxidant activity taking as reference the unsubstituted sesamol. Fig. 2 shows the chemical structures of the studied compounds.

Antiradical capacity against DPPH• was measured by monitoring radical consumption by action of the sesamol derivatives. This method is simple and highly sensitive. Further, DPPH• is one of the few stable and commercially available organic nitrogen radicals.[18] The kinetic profiles for DPPH• disappearance by addition of sesamol (**1**) are shown in Fig. 3.

The inset shows a linear variation of the antiradical activity (ARA) with the concentration of **1** in the system. Similar behaviour was observed for every compound of the family, indicating that the compounds studied behaved as dose-dependent antioxidants.

Table 4 shows the effective concentration of the studied compounds able to reduce 50 % of the radical concentration (EC_{50}). The increasing activity order observed in this system (inverse of the EC_{50} values) was **3e** $\approx$ **5** < **3d** < **3f** < **3a** < **3c** < **1**. Sesamol had the highest activity whereas the lowest corresponded to the non-phenolic compounds **3e** and **5**. These results show the importance of the free OH group of these molecules in presenting good antiradical activity. The EC_{50} value obtained for sesamol is in good agreement with previously reported data when the DPPH• assay was used under conditions similar to our experimental parameters.[7,19] Some reports show different results but it is necessary to take into consideration the differences in the methodologies employed in those articles compared with the methodology used in the present article.[3,8,20]

The substitution in C_6 of **1** with a series of substituted aryl groups did not increase radical scavenger activity. These groups do not modify the electronic nature of the heterocyclic centre. This is evidenced when comparing the geometry optimization of sesamol and derivative **3c** (Fig. 4).

In the series of biaryl derivatives of sesamol, **3c** shows the highest antiradical activity. The CN group behaves as an electron-withdrawing substituent of the aryl group located on C_6. The molecule with the lowest activity has a non-substituted phenyl group on C_6 of the base structure (**3d**). However, **3a** and **3f** showed intermediate behaviour between those compounds.

It has been proposed that the DPPH• radical reacts with phenols essentially via two different mechanisms: (i) a direct abstraction of the phenolic H atom by DPPH• (hydrogen atom transfer (HAT) reaction); and (ii) an electron-transfer process from the phenoxide anion to DPPH• (sequential proton loss electron transfer (SPLET) reaction), as shown in Scheme 3.[21]

The SPLET mechanism would be dramatically influenced by the pH of the reaction medium. At basic pH, the SPLET mechanism would be promoted because the phenol ionizes and exists predominantly as an anionic species, unlike the situation at acidic pH, where the neutral species would be predominant and, therefore, the main mechanism would be HAT (Scheme 3).

In order to evaluate the influence of the SPLET mechanism[22] in the global reactivity against DPPH• of the series of
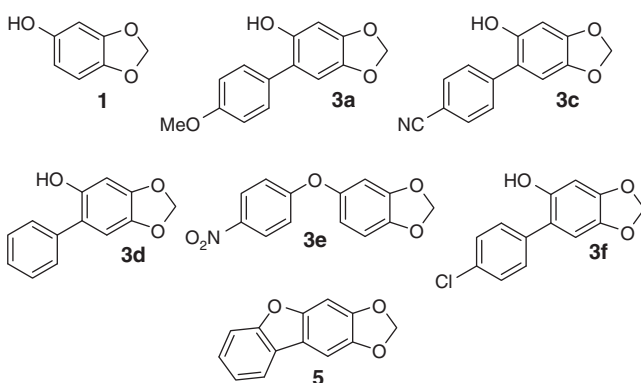

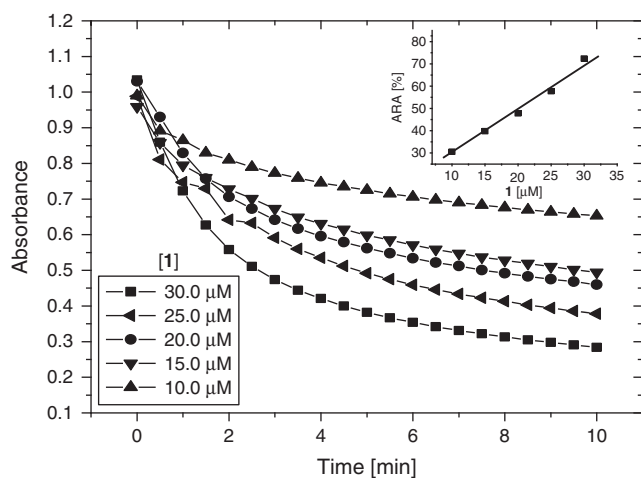**Fig. 2.** Chemical structures of **1** and their derivatives.

Fig. 3. Kinetic profiles at 515 nm corresponding to DPPH• (1,1-diphenyl-2-picrylhydrazyl radical) consumption by addition of **1**. Inset: antiradical activity of **1**.

Table 4.   Antioxidant activity

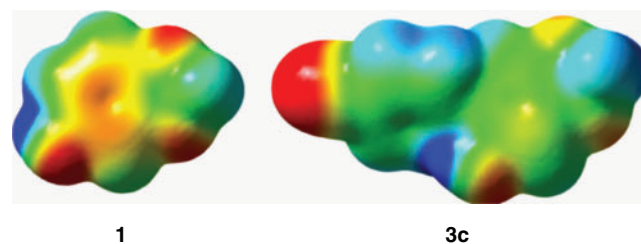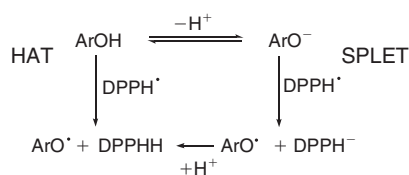| Compound	DPPH• EC_{50} [μM]
1	20.23 ± 0.01
3a	33.50 ± 0.02
3c	30.90 ± 0.01
3d	45.00 ± 0.03
3e	>1.3 mM
3f	37.71 ± 0.02
5	>1.3 mM

Fig. 4. Electrostatic potential maps (from red (negative) to blue (positive)) of molecules **1** and **3c**.

Scheme 3.

sesamol derivatives, the EC_{50} values for **1** were determined with the addition of acetic acid to final concentrations of 10 and 100 mM.[23] The EC_{50} value of compound **1** slightly increased in both cases, by 3 and 4 % respectively with respect to the standard experiment. The experiment makes it possible to determine the contribution of the SPLET mechanism to the global reaction, and to propose the HAT pathway as the primary mechanism of the sesamol reaction with DPPH• under the present experimental conditions.

The HAT mechanism corresponds to the homolytic dissociation of an O–H bond. This mechanism depends on two-bond dissociation enthalpies (BDE), the O–H BDE of the ArOH and the H–N BDE of the DPPH–H. The O–H BDE can be calculated from the following equation:[24,25]

$$BDE_{ArO-H} = \Delta H_f(ArO^\bullet) + \Delta H_f(H^\bullet) - \Delta H_f(ArOH) \quad (7)$$

A lower BDE value is usually attributed to a greater ability to donate a hydrogen atom from the hydroxyl group and results in a more efficient free-radical scavenging reaction.

In order to obtain the ΔH_f values for different species, the most stable conformer of the neutral and radical form of each compound was calculated using a density functional theory method.[26,27] For example, the structures of **3d** and its corresponding radical are shown in Fig. 5.

Table 5 shows the BDE of the studied compounds obtained using different approaches. The BDE_{E_0} were calculated from total electronic energies, E_0, without corrections. BDE were obtained on the basis of Eqn 7 with gas-phase values at 298.15 K. The solvent effect was taken into consideration with Tomasi's polarized continuum model (IEF-PCM).[28] In the presence of methanol, the solvent used in the experimental reactions, the BDE_s was determined in the same way as in the gas phase. For the enthalpy of the hydrogen atom, $\Delta H_{fs}(H^\bullet)$, we used reported enthalpy values.[29]

The gas phase BDE were lower than BDE_{E_0} values by 6–7 kcal mol^{-1} (25–29 kJ mol^{-1}). The difference in BDE of substituted compounds **3a–f** respect to **1** (ΔBDE) were of the same order in the three cases (BDE_{E_0}, BDE, and BDE_s).
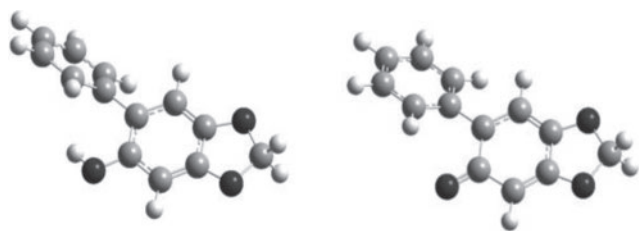

Fig. 5. The structures of ArOH and ArO• of **3d**.

In general, all 6-aryl substituted compounds had lower dissociation energies than sesamol although they are poorer antioxidants. This behaviour can be explained by the fact that sesamol is a small molecule in comparison with its derivatives and, therefore, has less steric hindrance in reacting with radical DPPH•.[30]

Fig. 6 shows the reactivity dependence of antiradical efficiency with BDE. The results obtained show that activity towards DPPH• correlated well with the BDE of the derivatives of sesamol. Unsubstituted sesamol is the only one that does not fit in the correlation because it is not a biaryl compound.

The calculation of thermodynamic parameters of a series of sesamols including compound **3d** has recently been reported but no experimental assays are available to compare these data, more expensive calculation procedures were used and the studied compounds were not synthesized.[31]

Conclusions

The photoinduced reaction of the sesamol anion with substituted aryl radicals gives C_6 substitution selectively. We have developed a simple versatile system for the first reported synthesis of 6-arylsesamols from commercially available, easily handled and inexpensive reactants. Moreover, the reaction provides access to the tetracyclic system **5** in moderate yields.

The antioxidant activity of the new 6-aryl-substituted sesamols was evaluated. The radical scavenging ability of the compounds was tested against the DPPH• radical. A very good correlation between computed BDE and experimental
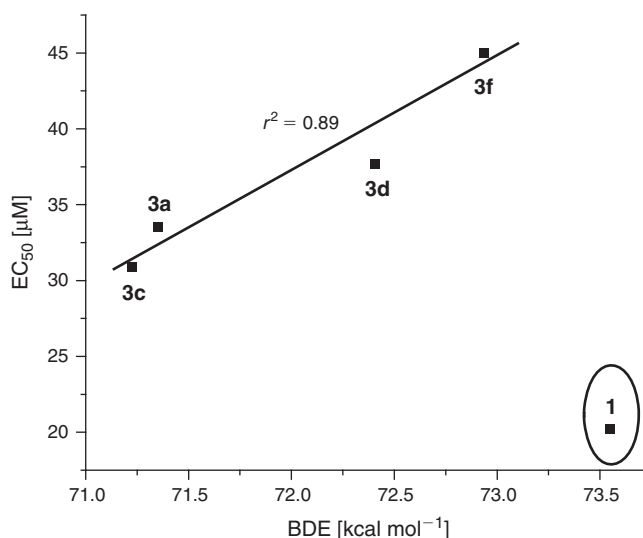

Fig. 6. EC_{50}(DPPH•) versus BDE of derivatives of sesamol. The oval highlights the outliers.

Table 5.   The bond dissociation enthalpies (BDE) of sesamol derivatives

Compound	BDE_{E_0} [kcal mol^{-1}]	ΔBDE_{E_0} [kcal mol^{-1}]	BDE [kcal mol^{-1}]	ΔBDE [kcal mol^{-1}]	BDE_s [kcal mol^{-1}]	ΔBDE_s [kcal mol^{-1}]
1	79.50	0	73.55	0	79.22	0
3a	77.87	−1.63	71.35	−2.20	77.04	−2.18
3c	77.15	−2.35	71.22	−2.33	76.95	−2.27
3d	78.89	−0.61	72.94	−0.61	77.86	−1.36
3f	78.34	−1.16	72.41	−1.14	77.54	−1.68

BDE = $\Delta H_f(ArO^\bullet)$ + (−0.49791 hartree) − $\Delta H_f(ArOH)$
BDE_{E_0} = $E_0(ArO^\bullet)$ + (−0.50027 hartree) − $E_0(ArOH)$
BDE_s = $E_{0s}(ArO^\bullet)$ + (−0.49837 hartree) − $E_{0s}(ArOH)$

EC$_{50}$(DPPH$^\bullet$) values of 6-arylsesamols was determined. This information could be valuable to predict the EC$_{50}$ values of differently substituted sesamols in order to select the most active compounds before chemical synthesis.

Experimental

Synthesis of Sesamol Derivatives

Materials and Methods

All starting materials were purchased from Sigma–Aldrich. They were used without further purification. DMSO was stored under molecular sieves (4 Å). ^{1}H and ^{13}C NMR spectra were recorded on a 400-MHz nuclear magnetic resonance spectrometer with CDCl$_3$ as solvent. Gas chromatographic analyses were performed on a chromatograph (Hewlett Packard 6890 series) with a flame-ionization detector and using an HP-5 capillary column (30 m × 0.32 mm × 0.25 μm film thickness). The GS-MS analyses were carried out on a Shimadzu GC-MS QP 5050 spectrometer, using a Vf-5 ms 30 m × 0.25 mm × 0.25 μm column. High-resolution mass spectra were recorded on a Bruker MicroTOF Q II, operated with an ESI or APPI source operated in positive or negative mode, using nitrogen as nebulizing and drying gas and 10 mM sodium formate as internal standard for calibration purposes. Irradiation was conducted in a reactor equipped with two 400-W lamps emitting at a maximum of 350 nm ((Philips Model HPT, air- and water-refrigerated). Potentiometric titration of halide ions was performed with a pH meter using an Ag/Ag+ electrode. Melting points are not corrected. Column chromatography was performed on silica gel (70–270 mesh).

General Synthesis Procedure of Sesamol Derivatives

The reactions were carried out in a 50-mL three-neck round-bottomed flask equipped with a nitrogen inlet and a magnetic stirrer. To 20 mL of dry and degassed DMSO under nitrogen were added potassium *tert*-butoxide (1.120 g, 10 mmol) and then sesamol (1.380 g, 10 mmol). After 5 min, 4-iodoanisole (234 mg, 1.0 mmol) was added and the reaction mixture was irradiated for 180 min. The reaction was quenched with an excess of ammonium nitrate and water (30 mL). The mixture was extracted three times with methylene chloride (20 mL); the organic extract was washed twice with water, dried with magnesium sulfate (MgSO$_4$), and quantified by GC. The iodide ions in the aqueous solution were determined potentiometrically. The reduction products (ArH) were compared by GLC with authentic commercial samples.

All products are unknown and were isolated by column or radial chromatography (hexane/acetone 9 : 1 or 4 : 1) and characterized by ^{1}H NMR and ^{13}C NMR, and mass spectrometry.

6-(4-Anisyl)-5-benzodioxolol 3a

Brown solid, 20 % yield (24.5 mg), mp 109–110°C. δ_H (400 MHz, CDCl$_3$) 3.84 (s, 3H), 5.92 (s, 2H), 6.54 (s, 1H), 6.67 (s, 1H), 6.98–7.00 (d, 2H), 7.30–7.32 (d, 2H). δ_C 55.37, 97.93, 101.13, 109.12, 114.81, 119.50, 129.20 (quarternary, q), 130.39, 141.51(q), 147.46(q), 147.56(q), 159.19(q). GCMS *m/z* 245 ([M+1], 16 %), 244 (100), 229 (26), 213 (6), 199 (17), 171 (7), 143 (7), 122 (9), 115 (25), 89 (7), 77 (5), 63 (7). HR-MS found 243.0673; C$_{14}$H$_{12}$O$_4$ [M − H] requires 243.0652.

6-(4-Cyanophenyl)-5-benzodioxolol 3c

Brown solid, 45 % yield (27.0 mg), mp 150.5–151.5°C. δ_H (400 MHz, CDCl$_3$) 5.97 (s, 2H), 6.52 (s, 1H), 6.72 (s, 1H), 7.58–7.00 (d, 2H), 7.71–7.73 (d, 2H). δ_C 98.72, 101.56, 108.91, 118.80(q), 129.88, 130.74(q), 132.61, 142.32(q), 142.58(q), 147,56(q), 148.70(q). GCMS *m/z* 240 ([M+1], 16 %), 239 (100), 238 (56), 180 (7), 153 (21), 152 (9), 127 (16), 126 (16), 103 (9), 77 (9), 69 (11), 63 (10), 53 (19). HR-MS found 262.0477; C$_{14}$H$_9$NO$_3$ [M + Na]$^+$ requires 262.0475.

6-Phenyl-5-benzodioxolol 3d

Oil, 39 % yield (20.9 mg). δ_H (400 MHz, CDCl$_3$) 5.96 (s, 2H), 6.58 (s, 1H), 6.73 (s, 1H), 7.37–7.54 (m, 5H). δ_C 98.08, 101.18, 109.05, 127.67, 129.18, 129.18, 130.56(q), 137.17(q), 141.65 (q), 147.45(q), 147.86(q). GCMS *m/z* 215 ([M+1], 12 %), 214 (100), 213 (35), 183 (9), 155 (7), 129 (11), 128 (32), 127 (18), 126 (11), 115 (10), 102 (19), 78 (21), 77 (18), 69 (8), 63 (9), 53 (16), 51 (14). HR-MS found 237.0508; C$_{13}$H$_{10}$O$_3$ [M + Na]$^+$ requires 237.0522.

5-(4-Nitrophenoxy)benzodioxolol 3e[16]

Yellow solid, 98 % yield (65 mg), mp 84.5–85.7°C. δ_H (400 MHz, CDCl$_3$) 6.02 (s, 2H), 6.54–6.57 (m, 1H), 6.60–6.61 (d, 1H), 6.81–6.84 (d, 1H), 6.97–6.99 (m, 2H), 8.17–8.19 (m, 2H). δ_C 101.91, 102.97, 113.3, 116.51, 125.92, 142.49(q), 145.25(q), 148.81(q), 148.89(q), 163.91(q). GCMS *m/z* 260 ([M+1], 21 %), 259 (100), 213 (25), 185 (13), 155 (29), 137 (12), 128 (10), 127 (28), 79 (23), 65 (14), 63 (23), 53 (13), 51 (18), 50 (14). HR-MS found 282.0368; C$_{13}$H$_9$NO$_5$ [M + Na]$^+$ requires 282.0373.

6-(4-Chlorophenyl)-5-benzodioxolol 3f

Oil, 19 % yield (24 mg). δ_H (400 MHz, CDCl$_3$) 5.96 (s, 2H), 6.58 (s, 1H), 6.73 (s, 1H), 7.36–7.56 (m, 4H). δ_C 98.32, 101.31, 108.95, 129.19, 129.42, 130.56, 131.08, 131.24, 133.62(q), 135.69(q), 138.34, 147.37(q), 148.09(q). GCMS *m/z* 250 ([M]+, 34 %), 249 (18), 248 (100), 247 (16), 213 (9), 183 (72), 155 (15), 127 (35), 126 (15), 105 (31), 101 (10), 77 (15), 75 (13), 69 (10), 63 (16), 53 (20). HR-MS found 247.0149; C$_{13}$H$_9$ClO$_3$ [M + Na]$^+$ requires 247.0156.

Benzo[b][1,3]dioxolo[4,5-f]benzofuran 5

White solid, 40 % yield (32 mg), mp 115.7–116.7°C. δ_H (400 MHz, CDCl$_3$) 6.05 (s, 2H), 7.06 (s, 1H), 7.29–7.31 (m, 2H), 7.34–7.38 (m, 1H), 7.50–7.52 (d, 1H), 7.79–7.82 (m, 1H). δ_C 94.03, 99.40, 101.64, 111.46, 119.59, 122.59, 124.76(q), 125.49, 127.24(q), 144.33(q), 147.88(q), 151.61(q), 156.55(q). GCMS *m/z* 213 ([M+1], 13 %), 212 (100), 211 (42), 156 (13), 128 (17), 127 (14), 126 (54), 106 (25), 76 (11), 75 (11), 74 (12), 63 (10).

Antioxidant Activity. DPPH$^\bullet$ Assay

Radical scavenging capacity due to sesamol action was determined according to Brand-Williams et al.[32] A typical procedure consisted in adding an aliquot of the sample to a cuvette containing 3 mL of ~85 μM DPPH$^\bullet$ solution. Reaction progress was followed by UV–vis spectrophotometry and measuring the absorbance at 515 nm in cycles for 15 min. Radical consumption was expressed as percentage of antiradical activity (ARA) (Fig. 3, inset) as proposed by Burda and Oleszek[33] and calculated according to the following equation (Eqn 8):

$$\%\text{ARA} = 100 \times [1 - A_{ss}/A_0] \tag{8}$$

where A_0 is the absorbance of the DPPH$^\bullet$ solution before adding the antioxidant and A_{SS} is the absorbance at the steady state

estimated by mathematical fitting of the kinetic curves (Fig. 3). Percentages of radical consumption for different antioxidant concentrations were measured. The EC_{50} value corresponds to the concentration that scavenges 50 % of the radical, expressed as the antioxidant/DPPH$^\bullet$ mole ratio.

Theoretical Calculations

The details of our methodology and those needed to obtain the BDE values are given here. All calculations reported in the present study were carried out applying the density functional theory as implemented in the *Gaussian 09* package.[34] The B3LYP[35] level of density functional theory was used. Geometry optimization of radicals and neutral species was performed with UB3LYP and the restricted B3LYP respectively using the 6–31G(d)basis set. In the computations, no constraints were imposed on the geometry. All possible conformers for ArOH and ArO$^\bullet$ were investigated. The conformer with the lowest electronic energy was used in this work. All structures were true minima on the calculated potential surface, verified by frequency calculations. Vibrational frequencies were computed at the same level of theory for all the optimized structures.

The enthalpy was obtained by thermal correction to the electronic energy by adding zero-point energy (ZPE), translational, rotational, and vibrational contributions.

Supplementary Material

The Supplementary Material contains ^{1}H NMR and ^{13}C NMR spectra and MS of compounds **3a**, **3c**, **3d**, **3f**, and **5**; the possible reaction mechanisms; and analysis of the differences between the calculations of BDE obtained in the present work and those reported in reference 31. These material are available on the Journal's website.

Acknowledgements

References

[1] R. Joshi, M. S. Kumar, K. Satyamoorthy, M. K. Unnikrisnan, T. Mukherjee, *J. Agric. Food Chem.* **2005**, *53*, 2696. doi:10.1021/JF0489769

[2] S. Ramachandran, N. Prasad, S. Karthikeyan, *Arch. Dermatol. Res.* **2010**, *302*, 733. doi:10.1007/S00403-010-1072-1

[3] G. J. Kapadia, M. A. Azuine, H. Tokuda, M. Takahashi, T. Mukainaka, T. Konoshima, H. Nishino, *Pharmacol. Res.* **2002**, *45*, 499. doi:10.1006/PHRS.2002.0992

[4] I. P. Kaur, A. Sani, *Mutat. Res.* **2000**, *470*, 71. doi:10.1016/S1383-5718(00)00096-6

[5] D. Z. Hsu, S. P. Chien, K. T. Chen, M. Y. Liu, *Shock* **2007**, *28*, 596.

[6] T. Geetha, B. Rohit, K. Pal, *Med. Chem.* **2009**, *5*, 367. doi:10.2174/157340609788681476

[7] J. E. Hayes, P. Allen, N. Brunton, M. N. O'Grady, J. P. Kerry, *Food Chem.* **2011**, *126*, 948. and references therein doi:10.1016/J.FOODCHEM.2010.11.092

[8] N. Erkan, G. Ayranci, E. Ayranci, *Food Chem.* **2008**, *110*, 76. doi:10.1016/J.FOODCHEM.2008.01.058

[9] (a) R. A. Rossi, A. B. Peñéñory, A. B. Pierini, *The Chemistry of Functional Groups, Supplement D2* (Eds S. Patai and Z. Rappoport) **1995**, Ch. 24. P. 1395 (John Wiley & Sons: Chichester).
(b) R. A. Rossi, A. B. Peñéñory, A. B. Pierini, *Chem. Rev.* **2003**, *103*, 71. doi:10.1021/CR960134O

[c] A. B. Pierini, A. B. Peñéñory, M. T. Baumgartner, *Electron Transfer Reactions in Organic Synthesis.* (Ed. P. Vanelle) **2002**, p. 63 (Research Signpost: Kerala).

[10] (a) T. C. Tempesti, A. B. Pierini, M. T. Baumgartner, *J. Org. Chem.* **2005**, *70*, 6508. doi:10.1021/JO050646F
(b) R. A. Rossi, M. T. Baumgartner, Targets in Heterocyclic Systems: Chemistry and Properties; (Eds O. A. Attanasi, D. Spinelli) **1999**, Vol. 3, Ch. 7, p. 215. (Societá Chimica Itliana: Rome).

[11] M.T. Baumgartner, T.C. Tempesti, A.B. Pierini, *Arkivoc* **2003**, *2003*, 420. doi:10.3998/ARK.5550190.0004.A40

[12] S. A. Rodríguez, M. T. Baumgartner, *Tetrahedron Lett.* **2010**, *51*, 5322. doi:10.1016/J.TETLET.2010.08.013

[13] S. A. Rodríguez, M. A. Nazareno, M. T. Baumgartner, *Bioorg. Med. Chem.* **2011**, *19*, 6233. doi:10.1016/J.BMC.2011.09.012

[14] (a) For examples, see: S. Jinno, T. Okita, K. Inouye, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1029. doi:10.1016/S0960-894X(99)00126-2
(b) Z. Novák, G. Timari, A. Kotschy, *Tetrahedron* **2003**, *59*, 7509. doi:10.1016/S0040-4020(03)01170-0
(c) S. Aslam, P. Stevenson, S. Phythian, D. Hall, *Tetrahedron* **2006**, *62*, 4214. doi:10.1016/J.TET.2006.02.015
(d) T. Masuda, A. Fujimoto, Y. Oyama, M. Tomomi, Y. Sone, *Tetrahedron Lett.* **2009**, *50*, 3905. doi:10.1016/J.TETLET.2009.04.063
(e) S. Chowdhury, M. Chafeev, S. Liu, J. Sun, V. Raina, R. Chui, W. Young, R. Kwan, J. Fu, J. Cadieux, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3676. doi:10.1016/J.BMCL.2011.04.088
(f) S. Waldvogel, B. Elsler, *Electrochim. Acta* **2012**, *82*, 434. doi:10.1016/J.ELECTACTA.2012.03.173

[15] The concentration of reactants, the relationship **1**:**2** base: ratios and the times of reaction are those generally used in reactions of hydroxyaryls with aryl halides. See refs [9], [11] and [12].

[16] For regioselectivity of the coupling between aryl radicals and arylhydroxy anions, see M. T. Baumgartner, G. A. Blanco, A. B. Pierini, *New J. Chem.* **2008**, *32*, 464. doi:10.1039/B710998A

[17] J. S. Yadav, B. V. Subba Reddy, *New J. Chem.* **2000**, *24*, 489. doi:10.1039/B001824O

[18] L. K. MacDonald-Wicks, L. G. Wood, M. L. Garg, *J. Sci. Food Agric.* **2006**, *86*, 2046. doi:10.1002/JSFA.2603

[19] P. Kanimozhi, N. R. Prasad, *Environ. Toxicol. Pharmacol.* **2009**, *28*, 192. doi:10.1016/J.ETAP.2009.04.003

[20] (a) K. Suja, A. Jayalekshmy, C. Arumughan, *J. Sci. Food Agric.* **2005**, *85*, 1779. doi:10.1002/JSFA.2170
(b) T. Geetha, B. Rohit, K. Pal, *Med. Chem.* **2009**, *5*, 367. doi:10.2174/157340609788681476
(c) K. Mishra, H. Ojha, N. Chaudhury, *Food Chem.* **2012**, *130*, 1036. doi:10.1016/J.FOODCHEM.2011.07.127

[21] G. Litwinienko, K. Ingold, *J. Org. Chem.* **2003**, *68*, 3433 and references therein. doi:10.1021/JO026917T

[22] (a) M. Foti, C. Daquino, C. Geraci, *J. Org. Chem.* **2004**, *69*, 2309. doi:10.1021/JO035758Q
(b) G. Litwinienko, K. Ingold, *J. Org. Chem.* **2004**, *69*, 5888. doi:10.1021/JO049254J

[23] Addition of small quantities of acetic acid did not cause any appreciable decay of DPPH within the reaction time.

[24] J. S. Wright, E. R. Johnson, G. A. DiLabio, *J. Am. Chem. Soc.* **2001**, *123*, 1173. doi:10.1021/JA002455U

[25] ΔH_f(ArO$^\bullet$) is the enthalpy of formation of the radical of sesamol generated after H abstraction, ΔH_f(H$^\bullet$) is the enthalpy of formation of the hydrogen atom, and ΔH_f(ArOH) is the enthalpy of formation of the antioxidant molecule.

[26] The BDE of phenol calculated by the above method is 87.57 kcal mol^{-1}, which is close to the 'best' experimental value of 87.30 kcal mol^{-1} in the gas phase.

[27] (a) E. Klein, V. Lukes, M. Ilčin, *Chem. Phys.* **2007**, *336*, 51. doi:10.1016/J.CHEMPHYS.2007.05.007
(b) E. Klein, V. Lukes, *J. Mol. Struct. THEOCHEM* **2006**, *767*, 43. doi:10.1016/J.THEOCHEM.2006.04.017

[28] The solvent effect was modelled with Tomasi's polarized continuum model (PCM) (S. Miertus, E. Scrocco, J. Tomasi, *Chem. Phys.* **1981**, *55*, 117; S. Miertus, J. Tomasi, *Chem. Phys.* **1982**, *65*, 239; M. Cossi,

B. Barone, R. Camini, J. Tomasi, *Chem. Phys. Lett.* **1996**, *255*, 327). The solvent effect was evaluated from single-point PCM calculations on the gas-phase optimized geometries at the B3LYP/6–31G* theory level, electrostatic and non-electrostatic contributions being considered. In the PCM model, the solvent is represented as a polarizable continuum (with dielectric constant ε) surrounding the molecular complex at an interface constructed by combining atomic van der Waal radii with the effective probe radius of the solvent. Charges are allowed to develop on this interface according to the electrostatic potential of the solute and ε, then the polarized reaction field of the solvent is taken into account in the quantum mechanical description of the solute. The wave function of the complex is relaxed self-consistently with the reaction field to solve the Poisson–Boltzmann (PB) equations. Solvent was represented with the following parameters: dielectric constant and probe radius.

[29] J. Rimarcik, V. Lukeš, E. Klein, M. Ilcin, *J. Mol. Struct. (THEOCHEM)* **2010**, *952*, 25. doi:10.1016/J.THEOCHEM.2010.04. 002

[30] D. Huang, B. Ou, R. Prior, *J. Agric. Food Chem.* **2005**, *53*, 1841. doi:10.1021/JF030723C

[31] M. Najaő, M. Najaő, H. Najaő, *Can. J. Chem.* **2012**, *90*, 915. In the suplementary material, we present the analysis of the differences between the calculations in this work and those reported.

[32] W. Brand-Williams, M. E. Cuvelier, C. Berset, *Lebensmittel– Wissenschaft und Technologie* **1995**, *28*, 25.

[33] S. Burda, W. Oleszek, *J. Agric. Food Chem.* **2001**, *49*, 2774. doi:10.1021/JF001413M

[34] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, *Gaussian 09, Revision A.01* **2009** (Gaussian, Inc.: Wallingford, CT).

[35] (a) C. Lee, W. Yang, R. G. Parr, *Phys. Rev.* **1988**, *B37*, 785. (b) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 1372. doi:10.1063/1.464304 (c) P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623. doi:10.1021/J100096A001