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Microwave-promoted syntheses of fluoren-9-ones and benzisoxazoles

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Abstract Synthesis of some new fluoren-9-ones and benzisoxazoles under both thermal and microwave conditions is reported. The prepared products under microwave conditions are obtained with high yields and within shorter reaction times. Reaction of lithiated bromobenzene with aromatic aldehydes **2a**,**b** delivered diarylmethanols **3a**,**b** that were oxidized to **4a,b**. Compound **4a** was cyclized to give methoxyfluoren-9-one **5,** which was demethylated affording hydroxyfluoren-9-one **6**. Compound **4b** was reacted with triethyl phosphite to produce benzisoxazole **10**. On the other hand, reaction of triethyl phosphite with **13a,b** afforded a mixture of phosphoramidates **14a,b** and benzisoxazoles **15a,b**. The structures of the synthesized compounds have been elucidated unambiguously by NMR-spectroscopic methods including HH COSY, HSQC, and HMBC experiments.

Keywords Microwave · Benzisoxazoles · Fluorenes · Benzophenones and C–H activation

Introduction

Fluorenes and related compounds have broad-spectrum biological activities. The biologically active fluoren-9-ones such as dendroflorin, denchrysan A, and 1,4,5-trihydroxy-7-methoxyfluoren-9-one, which have been isolated from plants, are used as health foods [1]. In the last decade, hipposudoric and norhipposudoric acids, two natural dyes with a fluorene framework, have been isolated from the red sweat of *Hippopotamus amphibius* by Hashimoto, see Nakata et al. [2–4]. It has been reported that hipposudoric acid exhibits antibiotic activity while the two natural dyes may act as sunscreens. Various methods have been developed to synthesize

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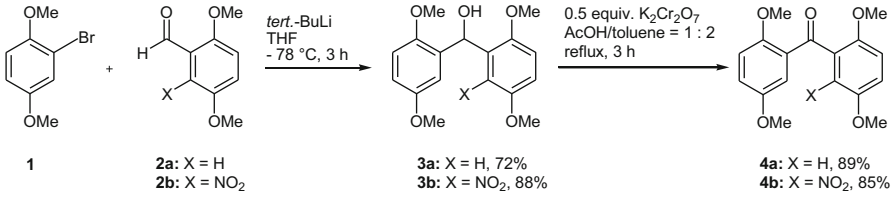
fluorenes and their related compounds. For example, one approach involves the intramolecular Friedel–Crafts acylation of biaryls [5]. Using an alternative directed metallation methodologies, Snieckus and coworkers have prepared a range of substituted fluoren-9-ones [6]. Langer et al. have recently reported the synthesis of fluoren-9-one using a [3 + 3] cyclization/Suzuki cross-coupling/Friedel–Crafts acylation route starting from a 1,3-bis-silyl enol ether and a silyloxypentenone [7]. Over the past years, notable progress has been achieved in the field of Cu(I)-catalyzed C-, N-, O-, and S-arylations [8, 9]. Depending on the substrate ratio and the reaction conditions, 4*H*-chromenes or naphthalenes were synthesized via Cu(I)-catalyzed domino reactions [10]. Haggam reported a novel and simple intramolecular Cu(I)-catalyzed cyclization of substituted 2-iodobenzophenones under both thermal and microwave conditions to build methoxy-substituted fluoren-9-ones [11].

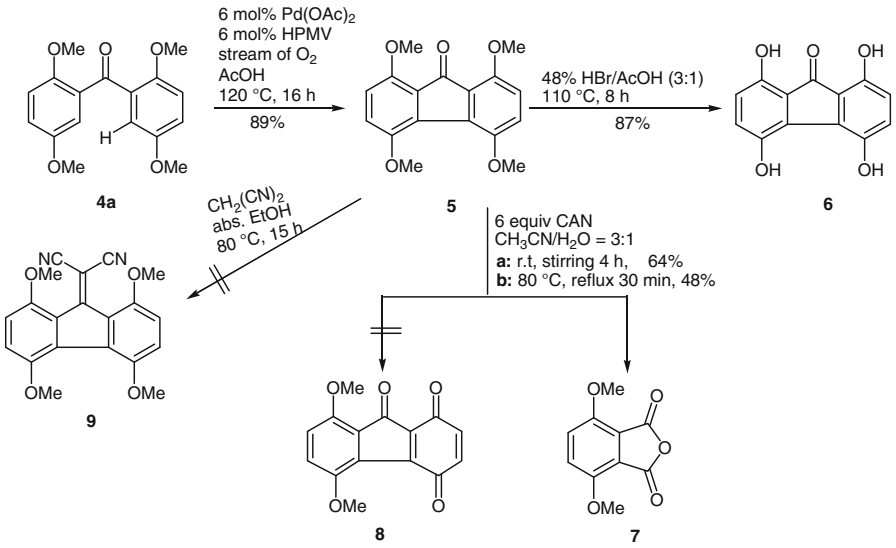
Results and discussion

We report on the synthesis of some novel fluoren-9-one, benzisoxazole and phosphoramidate derivatives utilizing aryl bromides and aromatic aldehydes as commercial starting materials. The ether cleavage of methoxy-substituted fluoren-9-ones was carried out via a demethylating agent 48 % HBr/AcOH. The substituted diarylmethanols **3a**,**b** were prepared by reaction of the lithiated bromobenzene with the methoxy-substituted aromatic aldehydes **2a**,**b** according to the method described by Qabaja and Jones [12]. The reactions among the methoxy-substituted 2-bromobenzene **1**, *t*-butyllithium, and the aldehydes **2a**,**b** were performed at −78 °C. After quenching with ammonium chloride solution, the crude products were purified by column chromatography to produce **3a** in 72 % and **3b** in 88 % yields [4, 13]. Oxidation of the secondary alcohols **3a**,**b** to the corresponding ketones **4a** in 89 % and **4b** [4, 13] in 85 % yields was performed using potassium dichromate depending on the procedure of Fieser and Williamson [14, 15] (Scheme 1).

Several attempts were made to cyclize bis-(2,5-dimethoxyphenyl)methanone (**4a**) using different reagents such as $Pd(OAC)_2$ or/and $Cu(OAC)_2$ under different reaction conditions. Unfortunately, all of these trials failed to achieve our goal. We found that heating of **4a** with a mixture of $Pd(OAc)_2$ and heteropolymolybdovanadic acid (HPMV) [16] in acetic acid within a stream of oxygen at 120 °C for 16 h resulted in the formation of the methoxyfluoren-9-one **5** in 89 % yield (Scheme 2).



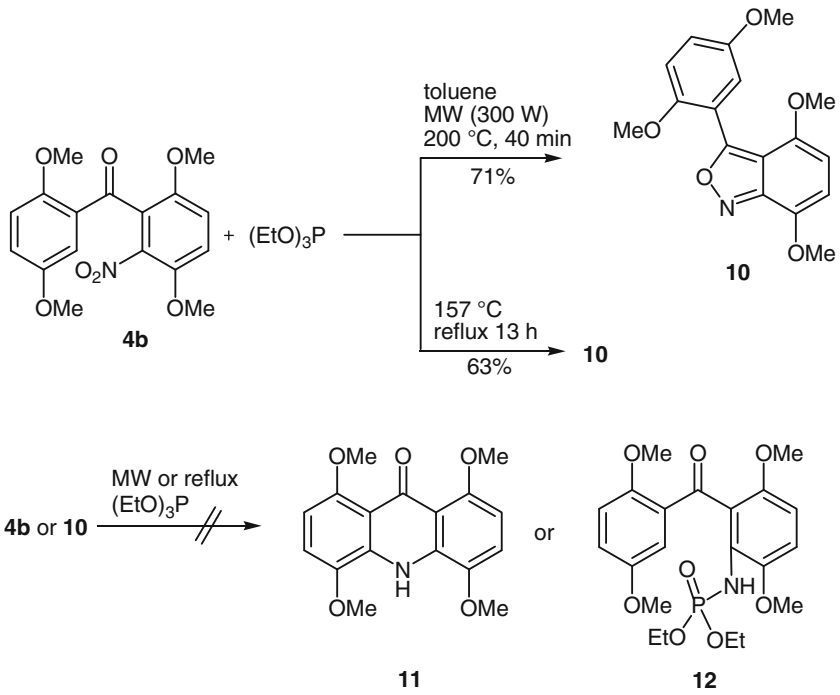
Scheme 1 Synthesis of the starting materials **4a,b**



Scheme 2 Reaction of fluoren-9-one **5** with different reagents under various reaction conditions

After the successful cyclization of **4a**, the methoxy substituents in the cyclization product **5** had to be transformed into the free hydroxyl groups. For this purpose, a mixture of compound **5**, acetic acid, and 48 % HBr was refluxed for 8 h according to the method of Ciske and Jones [17]. After work-up and purification of the resulting crude product by column chromatography, the hydroxy-substituted fluoren-9-one **6** was obtained in 87 % yield. Other trials were undertaken to realize the oxidation of methoxyfluoren-9-one **5** to the corresponding tricyclic quinone **8** [18, 19]. Compound **5** was treated with cerium ammonium nitrate (CAN) in acetonitrile as a solvent under reflux at 80 °C for 30 min. However, the formation of compound **8** could not be achieved (Scheme 2). Instead, the unexpected anhydride **7** (48 %) was obtained. The reaction was repeated by adding a solution of CAN in water to a stirred solution of tetramethoxyfluoren-9-one **5** in acetonitrile for 4 h. The crude product was purified to give the anhydride **7** in (64 %) yield but no appearance for the quinone **8**. In accordance with the condensation reactions of fluoren-9-one **5**, the chalkone **9** could not be observed via TLC when compound **5** was refluxed with malononitrile under various reaction conditions (Scheme 2).

The substituted 2-nitrobenzophenone **4b** was treated with triethyl phosphite under reflux at 157 °C for 13 h to produce the 3-aryl 2,1-benzisoxazole **10** in 63 % yield [20]. On the other hand, performing the reaction under microwave conditions (300 W, 20 bar) at 200 °C in toluene for 40 min the 3-aryl 2,1-benzisoxazole **10** was also obtained but with higher yield (71 %). However, the synthesis of acridin-9-one **11** or diethyl *N*-arylphosphoramidate **12** could not be realized on treatment compounds **4b** or **10** with triethyl phosphite under thermal or microwave conditions at all (Scheme 3).



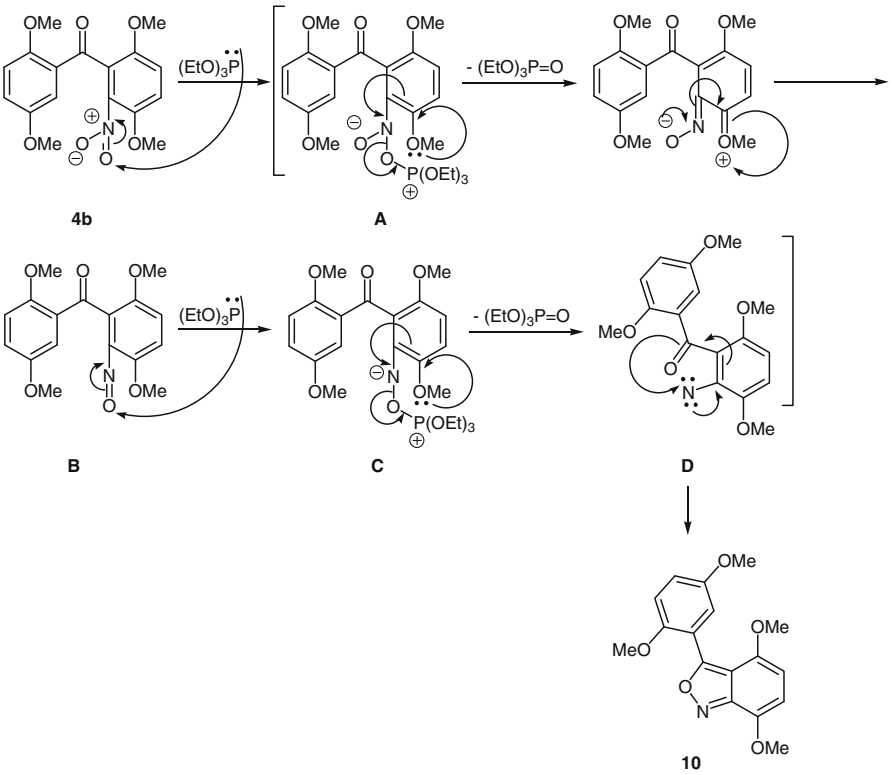
Scheme 3 Synthesis of 3-aryl 2,1-benzisoxazole **10** with yield (71 %) under microwave conditions

Regarding the proposal for the reaction mechanism of the cyclization of nitroaromatic **4b** to give benzisoxazole **10**, it is assumed that the reduction of **4b** takes place via the following steps [21–23]. The first step is the reduction of the nitro group to a nitroso compound **B** and triethyl phosphate through electrophilic attack of the phosphorous atom at the nucleophilic oxygen atom of **4b** via the intermediate **A**. The second step is the deoxygenation of **B** to give the arylnitrene **D** through the intermediate **C**. Lastly, compound **D** underwent intramolecular nucleophilic cyclization to deliver 3-aryl 2,1-benzisoxazole **10** (Scheme 4).

The chemical structure of compound **10** was elucidated by the analysis of its ^{1}H NMR and the ^{1}H,^{1}H-COSY spectra (Fig. 1), which displayed the presence of two doublets at $\delta = 6.05$ and 6.42 ppm with coupling constant $^{3}J = 7.9$ Hz for 5-H and 6-H protons. We deduce that both 5-H and 6-H protons are *ortho* to each other. In the same manner, both 3′-H and 4′-H protons are adjacent to each other.

The HSQC spectrum of **10** (Fig. 2) could be used to identify the carbon atoms that are directly attached to hydrogen atoms. The HSQC spectrum revealed the carbons C-5, C-6, C-3′, C-6′, and C-4′ at $\delta = 99.1$, 106.3, 113.1, 117.2, and 117.9 ppm, respectively.

The HMBC spectrum of compound **10** is used to determine the correlation between the carbons and the hydrogen atoms. From the ^{13}C NMR and HMBC (Fig. 3) spectra the proton 5-H showed strong $^{3}J_{CH}$-correlations with C-3a at



Scheme 4 Proposal for the reaction mechanism of the cyclization of nitroaromatic **4b** with triethyl phosphite

$\delta = 112.3$ ppm and C-7 at $\delta = 147.4$ ppm. On the other hand, the proton 6-H exhibited strong $^{3}J_{CH}$-correlation with C-4 at $\delta = 142.3$ ppm. This means that both 5-H and 6-H protons are attached with the same benzene ring. In addition, there are strong $^{3}J_{CH}$-correlations with 6′-H and both C-4′ at $\delta = 117.9$ ppm and C-3 at $\delta = 164.1$ ppm, respectively. The proton 3′-H displayed strong $^{3}J_{CH}$-correlation with C-3 at $\delta = 164.1$ ppm (Fig. 3).

By repeating the reaction using the 2-nitrobenzophenone **13a** as a monomethoxy substituent with triethyl phosphite at (300 W, 20 bar), 200 °C for 35 min the reaction gave two products, methoxyphosphoramidate **14a** and 3-methoxyphenyl 2,1-benzisoxazole **15a** in 55 and 34 % yields (Table 1, entry 1), respectively. Further experiments were carried out utilizing trimethoxy substituents **13b** for 25 min. In this case, the reaction also resulted in a mixture of trimethoxyphosphoramidate **14b** and 3-aryl 2,1-benzisoxazole **15b** with 58 and 35 % yields (Table 1, entry 2), respectively.

As another example, the discussion of the spectral data of 3-methoxyphenyl 2,1-benzisoxazole **15a** is given. The ^{1}H NMR and ^{1}H,^{1}H-COSY spectra of **15a** (Fig. 4) showed that two doublets of doublets at δ = 6.97 and 7.30 ppm with two coupling

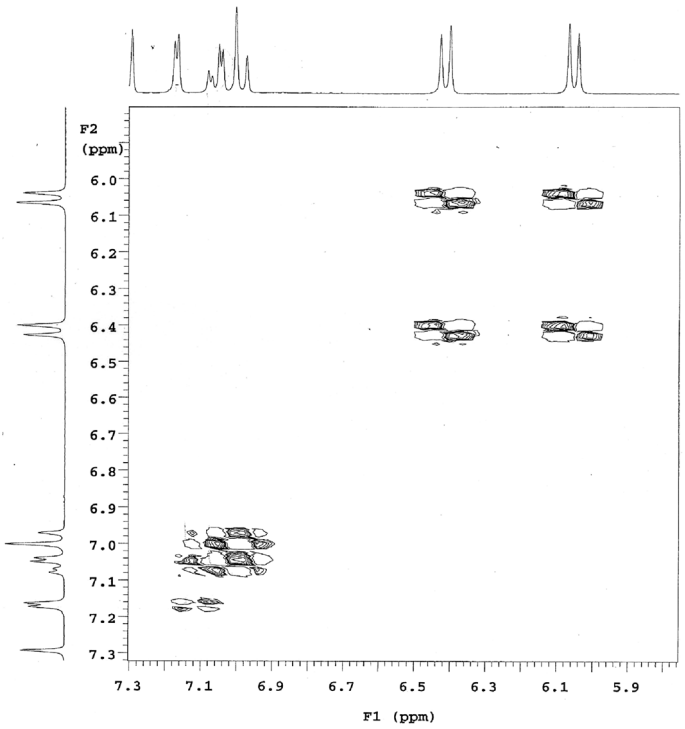


Fig. 1 Section of the $^{1}H,^{1}H$-COSY spectrum of **10**

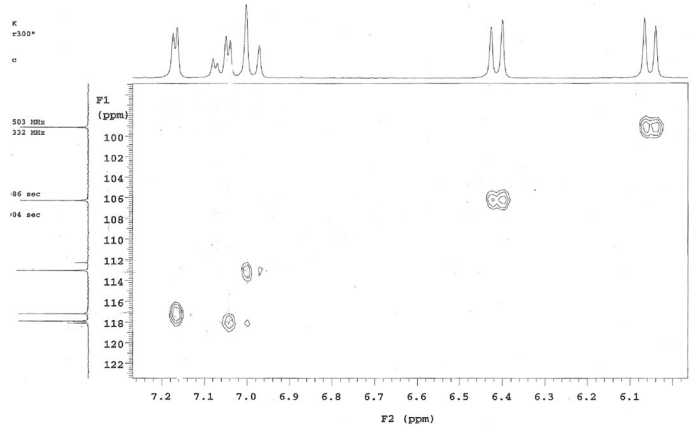


Fig. 2 Section of the HSQC spectrum of **10**

constants $^{3}J = 6.4$ Hz and $^{3}J = 8.8$ Hz for 5′-H and 4′-H protons, respectively. Also, there is a doublet at $\delta = 7.74$ ppm with $^{3}J = 8.8$ Hz for 6′-H. This indicates that 5′-H proton is *ortho* to both 4′-H and 6′-H protons. On the other hand 4-H and 5-H as well as 5-H and 6-H protons are adjacent to each other.

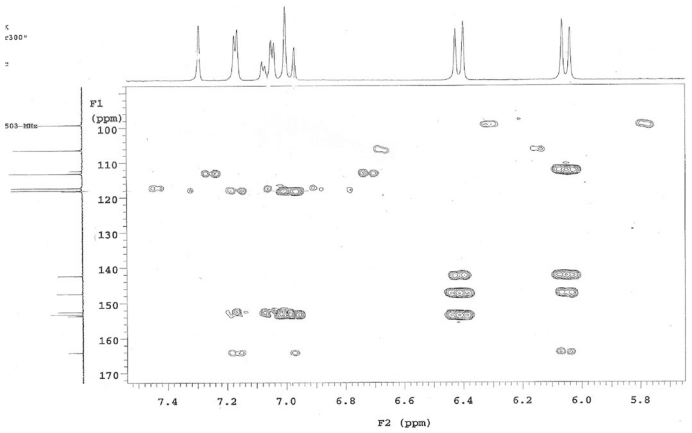
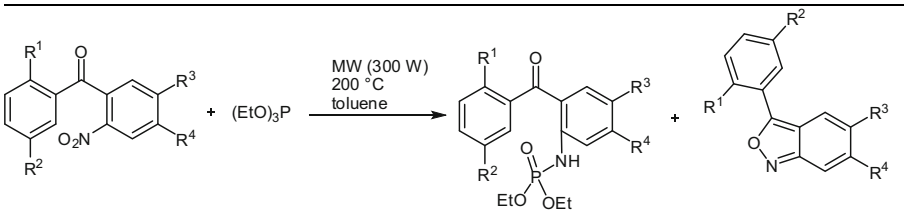


Fig. 3 Section of the HMBC spectrum of **10**

Table 1 Reaction of 2-nitrobenzophenone **13** with triethyl phosphite under microwave conditions



13 **14** **15**

Entry	13	R^1	R^2	R^3	R^4	Time (min)	[%] **14**	[%] **15**
1	**a**	OMe	H	H	H	35	55	34
2	**b**	OMe	H	OMe	OMe	25	58	35

The HSQC spectrum of **15a** showed the carbons C-7, C-5, C-4, C-6 appear at $\delta = 111.9$, 121.4, 130.7, and 132.1 ppm, respectively. In addition, the HSQC spectrum revealed the carbons C-3′, C-6′, C-5′, and C-5′ at $\delta = 115.3$, 122.8, 123.5 and 130.8 ppm, respectively (Fig. 5).

The ^{13}C NMR and HMBC spectra of compound **15a** showed that the proton 6′-H exhibited strong $^3J_{CH}$-correlations with C-4′ at $\delta = 130.8$ ppm, C-2′ at $\delta = 158.0$ ppm and C-3 at $\delta = 163.6$ ppm, respectively. The proton 4-H showed strong $^3J_{CH}$-correlations with both C-6 at $\delta = 132.1$ ppm and C-3 at $\delta = 163.6$ ppm as shown in (Fig. 6).

Experimental

Melting points were measured on a Büchi melting point apparatus B-545 with open capillary tubes and are uncorrected. IR spectra were recorded on a Perkin–Elmer

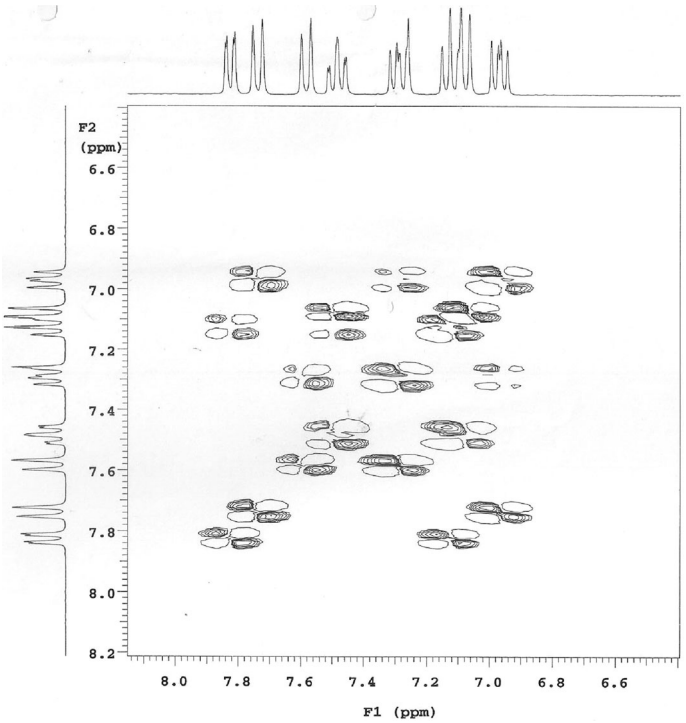


Fig. 4 Section of the $^{1}H,^{1}H$-COSY spectrum of **15a**

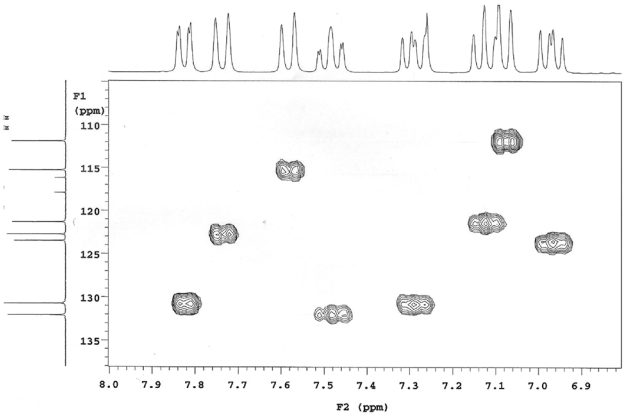


Fig. 5 Section of the HSQC spectrum of **15a**

Spectrum One (FT-IR- Spectrometer). UV–VIS spectra were measured with a Varian Cary 50. ^{1}H and ^{13}C NMR spectra were recorded at 300 (75) MHz on a Varian^{Inova} Spectrometer with $CDCl_3$ or DMSO as solvent and TMS as internal

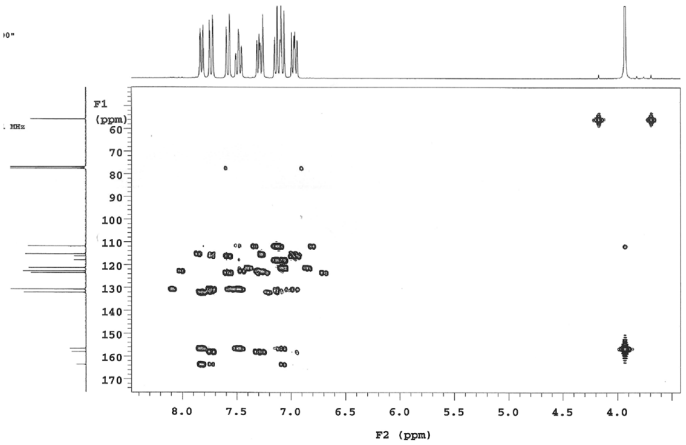


Fig. 6 The HMBC spectrum of **15a**

standard. The ^{1}H and ^{13}C chemical shifts were referenced to residual solvent signals at δH/C 7.26/77.00 ($CDCl_3$) and at δH/C 2.49/39.50 (DMSO). HSQC-, HMBC-, and COSY spectra were recorded on a Varian^{Inova} at 300 MHz. Coupling constants *J* [Hz] were directly taken from the spectra and are averaged. Low-resolution electron impact mass spectra (MS) and exact mass electron impact mass spectra (HRMS) were recorded on a Finnigan MAT 90 spectrometer operating at an ionization potential of 70 eV. Elemental analyses were carried out at the Institute of Organic and Biomolecular Chemistry, Göttingen University, Germany. Temperatures are reported as inner temperatures. Solvents used in extraction and purification were distilled prior to use. Thin-layer chromatography (TLC) was performed on Alugram SIL G/UV 254 (Macherey and Nagel). Compounds were visualized with UV light ($\lambda = 254$ nm) and/or by immersion in an ethanolic vanillin solution followed by heating. Products were purified by flash chromatography on silica gel 60 M, 230–400 mesh (Macherey and Nagel).

Bis-(2,5-dimethoxyphenyl)methanol (**3a**)

A mixture of *tert*-butyllithium 1.5 M in pentane (30.0 mmol) in dry THF (25 ml) was added dropwise over 30 min to a magnetically stirred solution of a 2-bromo-1,4-dimethoxybenzene (**1**) (20.0 mmol) in dry THF (25 ml) at −78 °C and under argon. After stirring for 30 min a solution of 1,4-dimethoxybenzaldehyde (**2a**) (16.0 mmol) in dry THF (25 ml) was added dropwise and the reaction mixture was stirred for 20 min at −78 °C and then allowed to warm up to room temperature with stirring for 3 h. After quenching with ammonium chloride solution (80 ml), the reaction mixture was extracted with *tert*-butylmethyl ether (4 × 80 ml). The combined organic layers were washed with brine (1 × 50 ml), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude products were purified by column chromatography (SiO_2; cyclohexane/EtOAc = 2:1) to give compound **3a** in 72 %

yield as pale yellow crystals. R_f (cyclohexane/EtOAc = 1:1) 0.62. Mp. 89–90 °C, IR (ATR): 3,528 cm^{-1} (OH), 1,228 cm^{-1} (C–O). λ_{max} (MeCN) (log ε) 208 (4.22), 293 (3.70) nm. ^{1}H NMR (300 MHz, $CDC1_3$): δ = 3.61 (br, 1H, OH), 3.76 (s, 6H, 5-OCH_3, 5′-OCH_3), 3.82 (s, 6H, 2-OCH_3, 2′-OCH_3), 6.27 (d, 1H, $^3J_{HH}$ = 1.9 Hz, CH-OH), 6.77 (dd, 2H, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 2.8 Hz, 4-H, 4′-H), 6.81 (d, 2H, $^3J_{HH}$ = 8.8 Hz, 3-H, 3′-H), 6.84 (d, 2H, $^4J_{HH}$ = 2.8 Hz, 6-H, 6′-H). ^{13}C NMR (300 MHz, $CDC1_3$): δ = 55.9 (5-OCH_3, 5′-OCH_3), 56.3 (2-OCH_3, 2′-OCH_3), 67.7 (CH-OH), 111.8 (C-3, C-3′), 113.1 (C-4, C-4′), 114.4 (C-6, C-6′), 132.3 (C-1, C-1′), 151.4 (C-2, C-2′), 153.9 (C-5, C-5′). *m/z* (EI, 70 eV) 304 (100, M^+), 165 (85), 139 (35), 138 (25 %). Anal. Calcd for $C_{17}H_{20}O_5$ (304.1305): C, 66.79; H, 6.52. Found: C, 66.89; H, 6.41.

Bis-(2,5-dimethoxyphenyl)methanone (**4a**)

Potassium dichromate (4.13 mmol) was dissolved in glacial acetic acid (20 ml). A solution of bis-(2,5-dimethoxyphenyl)methanol (**3a**) (8.22 mmol) in toluene (40 ml) was added dropwise at room temperature. The reaction mixture was heated for 3 h at 85 °C. After cooling to room temperature, the reaction mixture was filtered off and extracted with water (3 × 100 ml) to remove the acetic acid and the chromium salts. Then the mixture was extracted with ethyl acetate (3 × 60 ml). The combined organic layers were washed with 10 % NaOH solution (1 × 50 ml), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude products were purified by column chromatography (SiO_2; cyclohexane/EtOAc = 3:1) to give compound **4a** in 89 % yield as yellow crystals. R_f (cyclohexane/EtOAc = 2:1) 0.46. Mp. 86–87 °C, IR (ATR): 1,640 cm^{-1} (C = O), 1,290 cm^{-1} (C–O). λ_{max} (MeCN) (log ε) 225 (3.73), 341 (2.94) nm. ^{1}H NMR (300 MHz, $CDC1_3$): δ = 3.64 (s, 6H, 5-OCH_3, 5′-OCH_3), 3.84 (s, 6H, 2-OCH_3, 2′-OCH_3), 6.85 (d, 2H, $^3J_{HH}$ = 8.9 Hz, 3-H, 3′-H), 6.99 (dd, 2H, $^3J_{HH}$ = 8.9 Hz, $^4J_{HH}$ = 3.2 Hz, 4-H, 4′-H), 7.08 (d, 2H, $^4J_{HH}$ = 3.2 Hz, 6-H, 6′-H). ^{13}C NMR (300 MHz, $CDC1_3$): δ = 56.1 (2-OCH_3, 2′-OCH_3), 56.8 (5-OCH_3, 5′-OCH_3), 113.5 (C-3, C-3′), 114.8 (C-6, C-6′), 118.8 (C-4, C-4′), 131.1 (C-1, C-1′), 152.9 (C-5, C-5′), 153.7 (C-2, C-2′), 195.1 (C = O). *m/z* (EI, 70 eV) 302 (100, M^+), 165 (85), 151 (65 %). Anal. Calcd for $C_{17}H_{18}O_5$ (302.1149): C, 67.54; H, 6.00. Found: C, 67.35; H, 5.86.

1,4,5,8-Tetramethoxyfluoren-9-one (**5**)

Bis-(2,5-dimethoxyphenyl)methanone (**4a**) (0.60 mmol), $Pd(OAc)_2$ (0.06 mmol), and HPMV [16] (0.06 mmol) were added to a two-necked flask that contained acetic acid (6 ml). The reaction mixture was purged with a stream of oxygen for approximately 5 min. Subsequently, the reaction was then stirred at 120 °C in an oil bath for 16 h. The reaction mixture was diluted with water (50 ml) and extracted with *tert*-butyl methyl ether (4 × 40 ml). The combined organic layers were washed with water (2 × 50 ml) and potassium carbonate (1 × 50 ml), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2; cyclohexane/EtOAc = 1:1) to give compound **5** in 89 % yield as orange crystals. R_f (CH_2Cl_2/EtOAc = 1:1) 0.29. Mp. 133–134 °C, IR

(ATR): 1,692 cm^{-1} (C = O), 1,265 cm^{-1} (C–O). λ_{max} (MeCN) (log ε) 443 (3.83), 360 (3.53), 245 (3.82), 214 (3.80) nm. ^{1}H NMR (300 MHz, $CDC1_3$): δ = 3.91 (s, 6H, 1-OCH_3, 8-OCH_3), 3.96 (s, 6H, 4-OCH_3, 5-OCH_3), 6.86 (d, 2H, $^3J_{HH}$ = 8.9 Hz, 2-H, 7-H), 7.10 (d, 2H, $^3J_{HH}$ = 8.9 Hz, 3-H, 6-H). ^{13}C NMR (300 MHz, $CDC1_3$): δ = 56.8 (1-OCH_3, 8-OCH_3), 58.8 (4-OCH_3, 5-OCH_3), 115.3 (C-2, C-7), 122.0 (C-8a, C-9a), 124.0 (C-3, C-6′), 131.8 (C-4a, C-4b), 149.3 (C-1, C-8), 153.7 (C-4, C-5), 189.9 (C = O). *m/z* (EI, 70 eV) 300 (60, M^+), 285 (M^+-CH_3, 100), 242 (16 %). HRMS (EI, 70 eV): (M^+) $C_{17}H_{16}O_5$ found 300.0996 requires 300.0998.

1,4,5,8-Tetrahydroxyfluoren-9-one (**6**) [13]

A mixture of 1,4,5,8-tetramethoxyfluoren-9-one (**5**) (0.90 mmol), acetic acid (3 ml) and 48 % HBr (9 ml) was heated under reflux for 8 h. After cooling, the dark reaction mixture was poured into water (100 ml) and filtered off. The filtrate was extracted with *tert*-butyl methyl ether (4 × 30 ml), The ethereal extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2; cyclohexane/EtOAc = 1:3) to give compound **6** in 87 % yield as red crystals. R_f (cyclohexane/EtOAc = 2:3) 0.62. Mp. 238–239 °C, IR (ATR): 3,300–2,980 cm^{-1} (OH), 1,696 cm^{-1} (C = O), 1,259 cm^{-1} (C–O). λ_{max} (MeCN) (log ε) 474 (3.22), 364 (2.95), 243 (3.98), 217 (3.72) nm. ^{1}H NMR (300 MHz, $CDC1_3$): δ = 6.68 (d, 2H, $^3J_{HH}$ = 8.9 Hz, 2-H and 7-H), 6.89 (d, 2H, $^3J_{HH}$ = 8.9 Hz, 3-H and 6-H), 9.62 (s, 2H, 4-OH and 5-OH), 10.69 (s, 2H, 1-OH and 8-OH). ^{13}C NMR (300 MHz, $CDC1_3$): δ = 118.2 (C-8a and C-9a), 120.6 (C-2 and C-7), 126.0 (C-4a and C-4b), 126.3 (C-3 and C-6), 143.8 (C-4 and C-5), 151.3 (C-1 and C-8), 191.2 (C = O). *m/z* (EI, 70 eV) 244 (100, M^+), 222 (75), 177 (18), 150 (15), 28 (M^+-$C_{12}H_8O_4$, 100 %). HRMS (EI, 70 eV): (M^+) $C_{13}H_8O_5$ found 244.0331 requires 244.0339.

3,6-Dimethoxyphthalic anhydride (**7**)

Method A A mixture of 1,4,5,8-tetramethoxyfluoren-9-one (**5**) (0.44 mmol) in acetonitrile (30 ml) was heated at 80 °C. CAN [18] (5.33 mmol) dissolved in water (4 ml) was added. The reaction mixture was kept under reflux for 30 min. After cooling, the dark-blood mixture was poured over ethylacetate/water (80:150). The combined organic layers were washed with water (5 × 50 ml), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2; cyclohexane/EtOAc = 1:2) to give compound **7** in 48 % yield as yellow crystals.

Method B A solution of CAN [19] (11.8 mmol) in water (7 ml) was added to a stirred solution of 1,4,5,8-tetramethoxyfluoren-9-one (**5**) (0.99 mmol) in acetonitrile (15 ml). After 4 h, the thin-layer chromatography showed complete consumption of the starting materials. Water (100 ml) was added to the red solution and extracted with dichloromethane (3 × 50 ml). The combined organic layers were washed with water (5 × 50 ml), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2; cyclohexane/

EtOAc = 1:2) to give compound **7** in 64 % yield as yellow crystals. R_f (cyclohexane/EtOAc = 1:3) 0.41. Mp. 252–253 °C, IR (ATR): 1,769, 1,729 cm^{-1} (2 C = O), 1,276 cm^{-1} (C–O). λ_{max} (MeCN) (log ε) 317 (3.17) nm. ^1H NMR (300 MHz, $CDC1_3$): δ = 3.96 (s, 6H, 3-OCH_3, 5-OCH_3), 7.63 (s, 2H, 4-H, 5-H). ^{13}C NMR (300 MHz, $CDC1_3$): δ = 57.4 (3-OCH_3, 6-OCH_3), 117.5 (C-2a, C-6a), 123.3 (C-4, C-5), 151.9 (C-3, C-6), 161.2 (C-2, C-7). *m/z* (EI, 70 eV) 208 (100, M^+), 179 (24), 163 (M^+-COOH, 62), 162 (64), 134 (49 %). HRMS (EI, 70 eV): (M^+) $C_{10}H_8O_5$ found 208.0359 requires 208.0369.

General synthetic procedure under microwave conditions of compounds (10, 14a,b and 15a,b)

A mixture of (3,6-dimethoxy-2-nitrophenyl)(2′,5′-dimethoxyphenyl)methanone (**4b**) (1 mmol) or (2,5-dimethoxyphenyl)(2′-nitrophenyl)methanone (**13a,b**) (1 mmol), triethyl phosphite (6 mmol) and/or without toluene (3 ml) was sealed in a 10-ml septum vial and irradiated with microwaves (Discover by CEM, 2,450 MHz, 300 W, 20 bar, 200 °C). After removal of triethyl phosphite and triethyl phosphate at reduced pressure (10^{-1} mbar) and temperatures between 65 and 80 °C, the residue was diluted with EtOAc (45 ml), washed with water (2 × 50 ml) and brine (3 × 20 ml), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The remaining residue was purified by column chromatography over silica gel.

3-(2′,5′-Dimethoxyphenyl)-4,7-dimethoxybenzo[*c*]-2,1-isoxazole (**10**)

The crude product was purified by column chromatography (SiO_2; petroleum ether/EtOAc = 2:1) to give compound **10** in 71 % yield as yellow crystals. R_f (petroleum ether/EtOAc = 1:1) 0.35. Mp. 150–151 °C, IR (ATR): 1,640, 1,556, 1,503 cm^{-1} (C = C arom.), 1,266 cm^{-1} (C–O). λ_{max} (MeCN) (log ε) 367 (3.49), 334 (3.46), 247 (3.74), 222 (3.77) nm. ^1H NMR (300 MHz, $CDC1_3$): δ = 3.78 (s, 3H, 7-OCH_3), 3.82 (s, 3H, 5′-OCH_3), 3.84 (s, 3H, 2′-OCH_3), 3.99 (s, 3H, 4-OCH_3), 6.05 (d, 1H, $^3J_{HH}$ = 7.9 Hz, 5-H), 6.42 (d, 1H, $^3J_{HH}$ = 7.9 Hz, 6-H), 6.99 (1H, d, $^3J_{HH}$ = 9.1 Hz, 3′-H), 7.06 (dd, 1H, $^3J_{HH}$ = 9.1 Hz, $^4J_{HH}$ = 2.9 Hz, 4′-H), 7.14 (d, 1H, $^4J_{HH}$ = 2.9 Hz, 6′-H). ^{13}C NMR (300 MHz, $CDC1_3$): δ = 55.7 (7-OCH_3), 56.2 (4-OCH_3 and 5′-OCH_3), 56.7 (2′-OCH_3), 99.1 (C-5), 106.3 (C-6), 112.3 (C-3a), 113.1 (C-3′), 117.2 (C-6′), 117.9 (C-4′), 118.1 (C-1′), 142.3 (C-4), 147.4 (C-7), 152.5 (C-5′), 153.2 (C-2′), 153.6 (C-7a), 164.1 (C-3). *m/z* (EI, 70 eV) 315 (100, M^+), 284 (M^+-OCH_3, 20), 165 (15 %). HRMS (EI, 70 eV): (M^+) $C_{17}H_{17}NO_5$ found 315.1128 requires 315.1100. Anal. Calcd for $C_{17}H_{17}NO_5$ (315.1100): 64.74; H, 5.44; N, 4.44. Found: C, 64.65; H, 5.15; N, 4.73.

Diethyl *N*-2-(2′-methoxybenzoyl)phenylphosphoramidate (**14a**)

The crude product of **14a** was purified by column chromatography (SiO_2; cyclohexane/EtOAc = 1:1) to give compound **14a** in 55 % yield as pale yellow crystals. R_f (cyclohexane/EtOAc = 1:1) 0.27. Mp. 105–106 °C, IR (ATR): 1,633,

1,618, 1,577 cm^{-1} (C = C arom.), 1,252 cm^{-1} (C–O). λ_{max} (MeCN) (log ε) 336 (3.31), 262 (3.53), 223 (3.99) nm. ^1H NMR (300 MHz, $CDC1_3$): $\delta = 1.36$ (t, 6H, $^3J_{HH} = 7.1$ Hz, 2 × CH_3), 3.74 (s, 3H, 2′-OCH_3), 4.17–4.23 (m, 4H, 2 × OCH_2), 6.84 (t, 1H, $^3J_{HH} = 7.4$ Hz, 5-H), 6.98 (d, 1H, $^3J_{HH} = 8.5$ Hz, 4′-H), 7.04 (d, 1H, $^3J_{HH} = 8.5$ Hz, 5′-H), 7.23 (d, 1H, $^4J_{HH} = 1.5$ Hz, 6′-H), 7.39 (d, 1H, $^3J_{HH} = 8.5$ Hz, 3′-H), 7.42–7.48 (m, 1H, 3-H, 4-H), 7.52 (d, 1H, $^3J_{HH} = 7.4$ Hz, 6-H), 10.0 (d, 1H, $^2J_{PH} = 10.9$ Hz, NH). ^{13}C NMR (300 MHz, $CDC1_3$): $\delta = 16.4$ (d, $^3J_{PC} = 6.9$ Hz, 2 × CH_3), 55.9 (2′-OCH_3), 63.5 ($^2J_{PC} = 5.4$ Hz, 2 × OCH_2), 111.6 (C-4′), 118.4 (d, $^3J_{PC} = 2.4$ Hz, C-6), 119.9 (C-5), 120.7 (C-5′), 121.8 (d, $^3J_{PC} = 2.4$ Hz, C-1), 129.0 (C-6′), 129.6 (C-1′), 131.8 (C-3′), 135.2 (C-2), 135.3 (C-4), 144.4 (d, $^3J_{PC} = 2.4$ Hz, C-2), 156.8 (C-2′), 200.4 (C = O). Anal. Calcd for $C_{18}H_{22}NO_5P$ (363.3400): C, 59.50; H, 6.10; N, 3.85. Found: C, 59.36; H, 6.02; N, 3.68.

Diethyl *N*-2-(2′-methoxybenzoyl)-4,5-dimethoxyphenylphosphoramidate (**14b**)

The crude product of **14b** was purified by column chromatography (SiO_2; cyclohexane/EtOAc = 1:2) to give compound **14b** in 58 % yield as yellow oil. R_f (cyclohexane/EtOAc = 1:2) 0.24. IR (ATR): 1,627, 1,578 1,507 cm^{-1} (C = C arom.), 1,276 cm^{-1} (C–O). λ_{max} (MeCN) (log ε) 339 (3.52), 262 (3.53) nm. ^1H NMR (300 MHz, $CDC1_3$): $\delta = 1.42$ (t, 6H, $^3J_{HH} = 7.2$ Hz, 2 × CH_3), 3.76 (s, 3H, 2′-OCH_3), 3.83 (s, 3H, 5-OCH_3), 3.95 (s, 3H, 4-OCH_3), 4.16–4.22 (m, 4H, 2 × OCH_2), 6.80 (s, 1H, 3-H), 6.83 (d, 1H, $^3J_{HH} = 8.9$ Hz, 3′-H), 6.91 (d, 1H, $^3J_{HH} = 8.9$ Hz, 6′-H), 6.94 (s, 1H, 6-H), 7.00 (m, 1H, 5′-H), 7.20 (dd, 1H, $^3J_{HH} = 8.9$ Hz, $^4J_{HH} = 1.8$ Hz, 4′-H), 10.24 (d, 1H, $^2J_{PH} = 10.5$ Hz, NH). ^{13}C NMR (300 MHz, $CDC1_3$): $\delta = 16.5$ (d, $^3J_{PC} = 6.9$ Hz, 2 × CH_3), 56.3 (2′-OCH_3), 56.4 (4-OCH_3), 56.5 (5-OCH_3), 63.5 (d, $^2J_{PC} = 5.6$ Hz, 2 × OCH_2), 101.3 (d, $^3J_{PC} = 2.1$ Hz, C-6), 113.4 (C-3′), 114.1 (d, $^2J_{PC} = 2.3$ Hz, C-2), 114.6 (C-6′), 117.1 (C-3), 117.2 (C-4′), 123.2 (C-5′), 131.3 (C-1′), 141.6 (d, $^3J_{PC} = 2.1$ Hz, C-1), 143.0 (C-5), 155.2 (C-2′), 156.7 (C-4), 197.3 (C = O). *m/z* (EI, 70 eV) 423 (100, M^+), 392 (55 %). HRMS (EI, 70 eV): (M^+) $C_{20}H_{26}NO_7P$ found 423.1439 requires 423.1447.

3-(2′-Methoxyphenyl)benzo[*c*]-2,1-isoxazole (**15a**)

The crude product of **15a** was purified by column chromatography (SiO_2; cyclohexane/EtOAc = 8:1) to give compound **15a** in 34 % yield as yellow oil. R_f (cyclohexane/EtOAc = 4:1) 0.44. IR (ATR): 1,632, 1,600, 1,581 cm^{-1} (C = C arom.), 1,250 cm^{-1} (C–O). λ_{max} (MeCN) (log ε) 344 (3.06), 252 (3.93) nm. ^1H NMR (300 MHz, $CDC1_3$): $\delta = 3.94$ (s, 3H, 2′-OCH_3), 6.97 (dd, 1H, $^3J_{HH} = 6.4$ Hz, $^3J_{HH} = 8.8$ Hz, 2′-H), 7.08 (dd, 1H, $^3J_{HH} = 8.4$ Hz, $^4J_{HH} = 1.6$ Hz, 7-H), 7.13 (t, 1H, $^3J_{HH} = 7.7$ Hz, 5-H), 7.30 (dd, 1H, $^3J_{HH} = 6.3$ Hz, $^3J_{HH} = 8.8$ Hz, 5′-H), 7.49 (dt, 1H, $^3J_{HH} = 7.8$ Hz, $^4J_{HH} = 1.6$ Hz, 6-H), 7.58 (d, 1H, $^3J_{HH} = 9.1$ Hz, 3′-H), 7.74 (d, 1H, $^3J_{HH} = 8.9$ Hz, 6′-H), 7.83 (dd, 1H, $^3J_{HH} = 7.8$ Hz, $^4J_{HH} = 1.6$ Hz, 4-H). 10.30 (d, 1H, $^2J_{PH} = 10.6$ Hz, NH). ^{13}C NMR (300 MHz, $CDC1_3$): $\delta = 55.8$ (2′-OCH_3), 111.9 (C-7), 115.3 (C-3′), 116.2 (C-1′), 117.9 (C-3a), 121.4 (C-5), 122.8

(C-6′), 123.5 (C-5′), 130.75 (C-4), 130.77 (C-4′), 132.1 (C-6), 156.6 (C-7a), 158.0 (C-2′), 163.6 (C-3). *m/z* (EI, 70 eV) 255 (100, M^+), 196 (23 %). HRMS (EI, 70 eV): (M^+) $C_{14}H_{11}NO_2$ found 225.0776 requires 225.0787.

3-(2′-Methoxyphenyl)-5,6-dimethoxybenzo[*c*]-2,1-isoxazole (**15b)**

The crude product of **15b** was purified by column chromatography (SiO_2; cyclohexane/EtOAc = 2:1) to give compound **15b** in 35 % yield as yellow oil. R_f (cyclohexane/EtOAc = 4:1) 0.25. IR (ATR): 1,635, 1,616, 152 cm^{-1} (C = C arom.), 1,272 cm^{-1} (C–O). λ_{max} (MeCN) (log ε) 364 (3.48), 253 (3.75) nm. ^1H NMR (300 MHz, $CDC1_3$): δ = 3.87 (s, 3H, 2′-OCH_3), 3.93 (s, 3H, 5-OCH_3), 3.98 (s, 3H, 6-OCH_3), 6.88 (s, 1H, 7-H), 6.91 (dd, 1H, $^3J_{HH}$ = 9.0 Hz, $^3J_{HH}$ = 6.5 Hz, 5′-H), 7.03 (s, 1H, 4-H), 7.52 (d, 1H, $^3J_{HH}$ = 9.0 Hz, 3′-H), 7.61 (dd, 1H, $^3J_{HH}$ = 9.0 Hz, $^3J_{HH}$ = 6.5 Hz, 4′-H). ^{13}C NMR (300 MHz, $CDC1_3$): δ = 55.4 (6-OCH_3), 55.6 (5-OCH_3), 65.2 (2′-OCH_3), 113.7 (C-7), 111.4 (C-4), 115.3 (C-1′), 116.2 (C-3′), 118.2 (C-3a), 123.1 (C-6′), 124.2 (C-5′),144.1 (C-6), 148.3 (C-5), 157.0 (C-7a), 158.4 (C-2′). *m/z* (EI, 70 eV) 285 (100, M^+), 254 (M^+-OCH_3, 65 %). HRMS (EI, 70 eV): (M^+) $C_{16}H_{15}NO_4$ found 285.1011 requires 285.1001.

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