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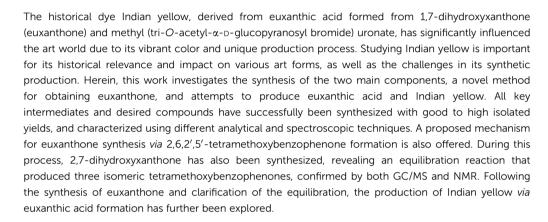
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# Investigation and development of novel synthetic approaches for synthesis of euxanthone and derived dyes†

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#### Introduction

Natural products and organic dyes play significant roles in cultural heritage and human health, from historical paints to medicinal applications for various diseases. 1-14 They have been used to relieve ailments, produce medicines from plant parts, 4,15-26 dye wool, and color historical paints for restoration. $^{1-15,17-19,27-37}$  Naturally occurring xanthones (Fig. 1) are notable organic dyes utilized in both pharmaceuticals and art.1-38 Xanthones, or 9H-xanthen-9-one (Fig. 1A), possess a dibenzo-y-pyrone structure and are not found in their unsubstituted form in nature. They are typically colored due to hydroxyl groups and are structurally similar to γ-pyrone derivatives, such as flavonoids and chromones (Fig. 1A-D).39-41 While unsubstituted xanthone is absent in nature, various oxygenated derivatives have been isolated from plant and animal sources, including euxanthone and mangostin from higher plants and lichexanthone from fungi.39,40 Natural xanthone derivatives have been classified by Denisova-Dyatlova et al.40 and studied for their chemotaxonomy and biogenesis pathways.42 In recent years, interest in natural xanthones has surged due to their promising pharmacological properties, including antidepresantimicrobial, antiviral, antifungal, antibacterial,

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antioxidant, antimalarial, anti-inflammatory, antithrombotic, and anticancer effects, largely attributed to their hydroxyl group positioning.<sup>39,40</sup> Thus, the study of both natural and synthetic xanthones suggests their potential as medicinal compounds.<sup>40</sup>

Indian yellow (Fig. 1D) and euxanthone (Fig. 1B), both part of the xanthone family, have intrigued artists, historians, and scientists for centuries, offering potential applications in pharmaceuticals, dyes, and materials science. 38,39,44,46-51 Indian yellow is noted for its intense orange-yellow color and its historical significance in art and medicine. 38,39 euxanthone and its derivatives are used as colorants in textiles and in fluorescence applications, including microscopy and organic photovoltaics (OPVs), due to their properties as organic semiconductors. They can also function as photocatalysts for various photochemical reactions, making further research into their potential essential. However, producing Indian yellow from euxanthone and glucuronic acid presents challenges, including ethical concerns with traditional methods, 1,52-54 limited raw material availability, labor-intensive processes, color and quality variability due to factors like animal diet and production methods,55,56 chemical instability, and a lack of modern production techniques. These issues pose difficulties for the preservation of artworks using Indian yellow, requiring careful handling to prevent degradation.<sup>57</sup> Addressing these challenges requires balancing historical preservation with the development of sustainable, ethical production methods. Continued research and innovation are crucial for ensuring the

Fig. 1 Chemical structures: (A) dibenzo- $\gamma$ -pyrone (xanthone) with numbering; (B) 1,7-dihydroxyxanthone (euxanthone), pale yellow needles from the heartwood of platonia insignis; (C) euxanthic acid, pale yellow needles with a  $\beta$ -type glycoside linkage to euxanthone, <sup>39,43</sup> and (D) Indian yellow, an O-glycoside of euxanthone and glucuronic acid, which increases water solubility, making it widely used as a yellow pigment in oil and watercolor painting on walls, doors, and frameworks. <sup>39,44,45</sup>

availability and longevity of Indian yellow pigment through euxanthone and glucuronic acid.

Given the existing literature on xanthones, 1-57 particularly Indian yellow from euxanthone and glucuronic acid, synthesizing these natural compounds has become a crucial research focus. Various synthetic techniques for euxanthone and its derivatives have been documented.58,59 Synthetic protocols can be categorized into six types: Michael-Kostanecki (e.g., 1,3dihydroxyxanthone),19 Ullmann (e.g., euxanthone),60 Robinson-Nishikawa (e.g., 1,3-dihydroxyxanthone),61-64 Asahina-Tanase (e.g., 3-methoxyxanthone),39 Tanase (e.g., 3,8-dihydroxy-1methoxyxanthone),39 and Friedel-Crafts (e.g., gentisin).64 Common analytical methods for separation and purification include solvent extraction (e.g., Soxhlet), chromatography (e.g., paper, thin-layer, and column), and recrystallization. 48,65 Key techniques for structural determination of xanthones are Fourier Transform Infrared (FTIR),65-68 UV/Vis absorption,69 Nuclear Magnetic Resonance (NMR),70 photo-induced luminescence (PL) imaging, 38,47,50,65,70-83 X-ray crystallography (XRD), mass spectrometry (MS), and high-performance liquid chromatography (HPLC).30,84

Taking into account the synthetic protocols, analytical and structural determination methods as well as separation and purification information provided by the abovementioned literature, this study aims to synthesize euxanthone and explore methods to produce it and euxanthic acid in sufficient quantities for Indian yellow synthesis, suitable for art conservation studies. The synthesis, characterization, and purification of euxanthone, along with the attempted synthesis of Indian yellow, have been reported.

#### Results and discussion

The primary goal of this work is to investigate existing synthetic protocols for xanthones to obtain euxanthone (1,7-dihydroxyxanthone), develop a novel synthetic approach, and attempt to synthesize its derived dye, Indian yellow, particularly for its significance in medicinal chemistry and art studies. Various

methods are documented for synthesizing naturally occurring xanthones, including Michael–Kostanecki,<sup>19</sup> Ullmann,<sup>60</sup> Robinson–Nishikawa,<sup>61-64</sup> Asahina–Tanase,<sup>39</sup> Tanase,<sup>39</sup> and Friedel–Crafts.<sup>64</sup> This study focuses on producing euxanthone and euxanthic acid in sufficient quantities for Indian yellow synthesis. Initially, the focus was on synthesizing euxanthone and then methyl(tri-*O*-acetyl-α-p-glucopyranosyl bromide) uronate, both essential for producing Indian yellow. The preparation of intermediates and desired compounds has been reported (Scheme 1), along with challenges encountered during synthesis and explanations for some anomalous findings.

As noted in several literature protocols where the synthesis of euxanthone was claimed, 19,39,60-64,85 the synthesis of euxanthone begins with 2,6-dihydroxybenzoic acid methyl ester (Scheme S1†). This ester precursor was obtained with a 76% isolated yield by reacting 2,6-dihydroxybenzoic acid with methanol in the presence of concentrated sulfuric acid. This compound was then used in various existing protocols 19,39,60-64,85 to synthesize euxanthone. In the first attempted protocol (Scheme S2†),85 the methyl ester and hydroquinone were refluxed; however, only 1,3-dimethoxybenzene, m-methoxyphenol, and CO<sub>2</sub> were identified as decomposition products in the <sup>1</sup>H-NMR and GC/MS results. Following this, the protocol was modified, heating the methyl ester and hydroquinone mixture to 225 °C (Scheme S3†). Although euxanthone was obtained in trace amounts (0.45%) after chromatographic purification, this protocol could not be reproduced despite multiple revisions. A similar approach was attempted using a microwave reactor (Scheme S4†) for 30 minutes (300 W, 250 °C, 293 psi, high stirring), but the desired euxanthone was not obtained, even after altering the conditions (Table S1†).

After the unsuccessful outcomes and decomposition of the methyl ester in the first protocol, another method was adopted<sup>18</sup> using 2-hydroxy-5-methoxybenzoic acid, resorcinol, and freshly fused zinc chloride (Scheme S5†). Euxanthone was expected to crystallize as yellow needles after purification; however, while the GC/MS results indicated the correct molecular weight, the <sup>1</sup>H-NMR spectrum (Fig. S8 and S9†) revealed signals for 2,7-

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Scheme 1 The new synthetic protocol for the synthesis of euxanthone and Indian yellow dye.

dihydroxyxanthone, likely due to an equilibration reaction of the benzophenone intermediate (Schemes S14 and S15 $\dagger$ ). Thus, euxanthone was not obtained *via* this protocol either. Substituting zinc chloride with polyphosphoric acid (PPA) or phosphorus oxychloride (POCl<sub>3</sub>) was also explored. In the case of POCl<sub>3</sub>, the GC/MS showed two peaks at 12.06 and 12.42 min with an *m/z* value of 302; however, euxanthone was not detected, and a new set of products was observed instead (*vide infra*).

Based on the previous synthetic protocols, it was concluded that these methods were not viable for producing euxanthone in sufficient quantities. Subsequently, other protocols3,86 were employed (Schemes S6 and S7†). The first step involved synthesizing 2-hydroxy-6-methoxy-2',5'-dimethoxybenzophenone and 2,6-dimethoxy-2'-hydroxy-5'-methoxybenzophenone by reacting 2,6-dimethoxybenzoic acid with oxalyl chloride in anhydrous benzene at room temperature (Scheme S7†). However, the resulting yellow oil was primarily ethyl 2,6-dimethoxybenzoate, not the expected benzophenone derivatives. Repeating the reaction yielded similar results, suggesting that the ether solvent and AlCl<sub>3</sub> might form a Lewis acid-base adduct or that AlCl<sub>3</sub> decomposed 2,6-dimethoxybenzoyl chloride, or both. Additionally, temperature and solvent effects likely contributed to the formation of unexpected products, as indicated by GC/MS and <sup>1</sup>H-NMR analyses, which showed rings and ethyl groups instead of methoxy and hydroxy groups. To address these issues, ether was replaced with dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>), and the reaction was performed at approximately 10 °C with AlCl<sub>3</sub> added in small portions (Scheme S8†). Following proper workup and purification, colorless crystals of 2,6,2',5'-tetramethoxybenzophenone a key intermediate for euxanthone synthesis-were obtained (Fig. S13, S14 and S16†) with a 73% isolated yield.

Alternatively (Scheme S9†),<sup>87-90</sup> a solution of 1,4-dimethoxybenzene in glacial acetic acid (AcOH) was treated dropwise with a bromine solution in AcOH at room temperature, yielding 2-bromo-1,4-dimethoxybenzene (73%). Next, 2.5 M *n*-butyl lithium in hexane was added to this intermediate in dry THF at

−78 °C. After stirring for 20 minutes, 2,6-dimethoxybenzaldehyde was introduced, and the mixture was allowed to warm to room temperature. Following proper workup and purification, 2,6,2′,5′-tetramethoxybenzophenone was obtained as a waxy solid (92%) after oxidizing the reaction mixture with pyridinium chlorochromate (PCC) in CH<sub>2</sub>Cl<sub>2</sub>, improving the isolated yield.

This key intermediate was then used to produce euxanthone (Scheme S10†) via a revised protocol, involving the dissolution of 2,6,2',5'-tetramethoxybenzophenone in phenol and the addition of hydroiodic acid, followed by heating for 8 hours. After the required coupling and removal of methoxy groups, the desired product crystallized as yellow needles with an isolated yield of 49%, confirmed by instrumental spectra (Fig. S1-S4 and S15†). The new protocol was repeated, first increasing the yield by 10% with the same conditions, then by another 10% after lowering the temperature to 125-130 °C, leading to high purity. A reaction mechanism for euxanthone formation was proposed (Scheme 2), illustrating a Friedel-Crafts acylation (an electrophilic aromatic substitution). The process involves replacing an aryl hydrogen atom with an acyl moiety from the acyl chloride, resulting in an alkyl aryl ketone. The acyl chloride first reacts with a Lewis acid catalyst (AlCl<sub>3</sub>) to form an acylium intermediate, which then releases a chloride ion to produce the acylium ion. This ion is electrophilic and undergoes nucleophilic attack by  $\pi$ -system of the aromatic ring. Deprotonation at the carbon bearing the acyl group restores aromaticity. In the next step, ring closure occurs in the presence of strong acid (HI), followed by demethylation with HI, yielding the desired euxanthone product.

A high-yielding synthetic protocol for euxanthone has been developed, but new findings reveal an equilibration reaction involving benzophenone intermediates. During attempts to synthesize euxanthone, multiple m/z=302 peaks were observed in the GC/MS spectra (Fig. S17–S19†) and NMR results (Fig. S10–S12†), indicating isomeric products. Notably, the derived

Scheme 2 A proposed mechanism for the synthesis of the desired compound euxanthone.

compound 2,7-dihydroxyxanthone emerged unexpectedly, suggesting an equilibration reaction (Schemes S14 and S15†) not previously discussed in literature. To investigate this, the synthesis of 2,6,2',5'-tetramethoxybenzophenone was repeated using 2,6-methoxybenzoic acid, 1,4-dimethoxybenzene, and polyphosphoric acid (PPA). Thin-Layer Chromatography (TLC) revealed three structural isomers (Scheme 3), confirmed by GC/MS and NMR: 2,5,2',5'-tetramethoxybenzophenone (isomer 1) leading to 2,7-dihydroxyxanthone, 2,4,2',5'-tetramethoxybenzophenone (isomer 2) leading to 2,6-dihydroxyxanthone, and 2,4,2',4'-tetramethoxybenzophenone (isomer 3) leading to 3,6-dihydroxyxanthone. GC/MS distinguished these isomers by

retention times of 14.12, 15.70, and 16.52 min for isomers 1, 2, and 3, respectively (Fig. S17–S19†), while the key intermediate had a retention time of 13.60 min. The <sup>1</sup>H NMR spectra of the isomers were distinct (Fig. S10–S12†), particularly isomer 2, which showed (Fig. S11†) characteristic singlets for methoxy groups and a signal at 6.40 ppm for the 3-position proton. Isomers 1 and 3 were similar, differing only in the singlet for isomer 3 at 6.40 ppm, indicating protons at the 3- and 3'-positions on the phenyl rings (Fig. S12†).

To determine if the key intermediate 2,6,2′,5′-tetramethoxybenzophenone was involved in the equilibration, a reaction was also conducted using this compound with PPA. Following Paper **RSC Advances** 

Scheme 3 A new discovery of an equilibrium reaction resulting with three isomers (1, 2, and 3) of 2,6,2',5'-tetramethoxybenzophenone leading to the euxanthone (left of dashed-line).

similar steps as before, three fractions were collected via TLC and analyzed by GC/MS and NMR. The analyses confirmed the same structural isomers, with retention times of 14.07, 15.31, and 16.07 min, all having an m/z value of 302.

These results indicate that the Friedel-Crafts reaction is reversible, and the desired benzophenone, 2,6,2',5'-tetramethoxybenzophenone, is not favored at equilibrium. Its synthesis is only feasible at lower temperatures, while other isomers are produced at room temperature or higher under acidic conditions. Initial attempts to synthesize euxanthone using high temperatures and acidic conditions resulted in low yields or undesirable products. This was confirmed when 2,6,2',5'-tetramethoxybenzophenone was obtained (Fig. S13 and S14†) at low temperatures without other isomers. Additionally, these equilibration results raise concerns about earlier protocols that claimed to synthesize euxanthone without adequate product characterization.

Once euxanthone was obtained and the equilibration reaction elucidated, the synthesis of the derived dye Indian yellow via euxanthic acid formation and deprotonation was investigated. The first step involved preparing methyl tetra-O-acetyl-β-D-glucopyranuronate (Scheme S11†) by reacting glucuronolactone with acetic anhydride in the presence of methanol, sodium hydroxide, and pyridine, following an existing protocol.91 After careful crystallization from 2-propanol, the desired β-anomer was obtained in high yield (91%), confirmed by <sup>1</sup>H-NMR (Fig. S5†) and GC/MS, which matched with the literature.91 After protecting the hydroxyl groups, the anomeric acetyl group ( $\beta$ ) was converted to a bromo group ( $\alpha$ )<sup>92</sup> to obtain methyl (tri-O-acetyl-α-D-glucopyranosyl bromide) uronate (Scheme S12†). This was achieved using a solution of HBr (27%) in acetic acid, successfully synthesizing the product, which was structurally confirmed by <sup>1</sup>H-NMR (Fig. S6†) and GC/MS. Although this intermediate decomposed after two days at room temperature, repeating the synthesis with commercial HBr (33%) yielded a high isolated yield (92%). Finally, Indian yellow synthesis was attempted using an adopted protocol91

with methyl (tri-O-acetyl-α-D-glucopyranosyl bromide) uronate and euxanthone in the presence of LiOH·H<sub>2</sub>O in methanol. However, TLC analysis showed only starting materials, and GC/ MS and <sup>1</sup>H-NMR confirmed the absence of the desired Indian yellow dye despite several modifications to the approach.

#### Conclusions

This work primarily focused on investigating synthetic protocols for 1,7-dihydroxyxanthone (euxanthone) and developing a novel approach to produce it, along with its derived dye, Indian yellow. Based on existing literature, key components and desired compounds were synthesized, purified, and characterized. Despite some unsuccessful attempts, the key precursor 2,6,2',5'-tetramethoxybenzophenone was obtained with a 92% yield. Using this intermediate, euxanthone was synthesized as yellow needles with a 49% yield, confirmed by 1D/2D NMR and GC/MS. The new and optimized protocol improved yield by 20-25% with high purity. A mechanistic proposal involving Friedel-Crafts acylation was presented. During the euxanthone synthesis attempts, 2,7-dihydroxyxanthone was coincidentally synthesized, leading to the discovery of an equilibration reaction producing three isomers with m/z = 302, identified as 2,5,2',5'-, 2,4,2',5'-, and 2,4,2',4'-tetramethoxybenzophenones. All isomers were confirmed by GC/MS and NMR. Initial hightemperature syntheses resulted in low yields and undesirable products due to isomerization. Analysis indicated that the Friedel-Crafts reaction is reversible and that 2,6,2',5'-tetramethoxybenzophenone forms only at lower temperatures, contrary to previous protocols. This equilibration detail was not addressed in earlier studies, which lacked thorough product characterization. Following the successful euxanthone synthesis and equilibration clarification, attempts to synthesize Indian yellow from euxanthic acid using euxanthone and methyl (tri-O-acetyl-α-D-glucopyranosyl bromide) uronate resulted only in the recovery of starting materials, despite various modifications. Further exploration of alternative methods to produce euxanthic acid and Indian yellow in sufficient quantities for art conservation studies is ongoing in our laboratories.

## **Experimental section**

#### **Experimental:** general methods

Material and instrumentation. All chemicals and reagents were purchased from commercial suppliers (Aldrich, Alfa Aesar, or Fisher) and used without further purification. All reactions were carried out in dried glassware under an argon and/or a nitrogen atmosphere. Dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>) and methanol (CH<sub>3</sub>OH) were either freshly distilled over CaH<sub>2</sub> under nitrogen or dried over molecular sieves. Thin-layer chromatography (TLC) was performed on silica gel 60 F254 (E. Merck). Reactions were monitored by TLC using UV light as visualizing agent. Column (Flash) chromatography was carried out on silica gel 60F (Merck 9385, 0.040-0.063 mm). Yield refers to chromatography and spectroscopically pure compounds, unless otherwise noted. All NMR spectra (1H and 13C) were recorded on a Bruker Avance 300 or 400 with a working frequency of 300/400 MHz, respectively. Chemical shifts were reported in ppm relative to the signals corresponding to the residual non-deuterated solvents (CDCl<sub>3</sub>: δ 7.26 ppm; DMSO-d<sub>6</sub> δ 2.50 ppm; acetone-d<sub>6</sub>  $\delta$  2.05 ppm for <sup>1</sup>H NMR, and CDCl<sub>3</sub>:  $\delta$  77.06 ppm; DMSO-d<sub>6</sub>  $\delta$  39.53 ppm; acetone-d<sub>6</sub>  $\delta$  29.82 and 206.03 ppm for <sup>13</sup>C NMR) or tetramethylsilane (TMS,  $\delta = 0.00$ ). Coupling constants, J, are reported in hertz (Hz). 1H-1H 2D-COSY NMR spectra were recorded on the Bruker Avance 300 spectrometer. UV-Vis absorbance spectra were collected (measured in highly diluted solutions (<10<sup>-5</sup> M)) at RT on a UV-3600 Shimadzu spectrophotometer. Mass spectra were measured with a Finnigan Trace DSQ GC-MS mass spectrometer (ESI). Melting points were determined by the open capillary tube method using a Mel-Temp melting point device. Some reactions were run with a microwave reactor (CEM Discover BenchMate). To remove solvents and other volatile impurities under reduced pressure, a Büchi Rotavapor R-114 and an Edwards oil pump were used.

#### Synthetic procedures and structural determination data

The detailed synthetic procedures and structural characterization data for the intermediates and desired compounds are presented in the ESI.† Some important details and structural determination data for the intermediates and desired product(s) are presented below.

**2,6,**2′,5′-**Tetramethoxybenzophenone**. Colorless crystals with m.p. of 98 °C (2.80 g, 92%); IR (KBr): v (cm $^{-1}$ ) 1675, 1600; UV/ Vis:  $\lambda_{\text{max}}$ : 302 nm;  $^{1}$ H NMR (400 MHz, CDCl $_{3}$ , 298 K)  $\delta$  7.33 (s, 1H), 7.25 (t, J = 8.4 Hz, 1H), 7.02 (dd, J = 9.2 Hz, J = 3.2 Hz, 1H), 6.87 (d, J = 8.8 Hz, 1H), 6.57 (d, J = 8.4 Hz, 1H), 3.78 (s, 3H), 3.70 (s, 6H), 3.60 (s, 3H);  $^{13}$ C NMR (100 MHz, CDCl $_{3}$ , 298 K)  $\delta$  193.5, 157.3, 154.4, 153.4, 130.1, 128.9, 121.7, 120.3, 115.6, 114.7, 104.2, 57.0, 56.0, 55.8 (Fig. S13 and S14†); MS(EI): m/z calcd for  $C_{17}H_{18}O_{5}$  [M] $^{+}$  302.12, found 302.25 with a retention time of 13.60 min (Fig. S16†).

**1,7-Dihydroxyxanthone** (euxanthone). Yellow needles with m.p. of 194–195 °C, (0.88 g, 49%); IR (KBr): v (cm<sup>-1</sup>) 3330, 1640;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>, 298 K)  $\delta$  12.9 (s, 1H, -OH exchangeable with D<sub>2</sub>O), 10.1 (s, 1H, -OH exchangeable with D<sub>2</sub>O), 7.71 (t, J = 8.4 Hz, 1H), 7.57 (d, J = 1.1 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.39 (dd, J = 1.1 and J = 8.4 Hz, 1H), 7.06 (dd, J = 1.1 and J = 8.4 Hz, 1H), 6.80 (dd, J = 1.1 and 8.4 Hz, 1H) (Fig. S1–S3†); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>, 298 K)  $\delta$  179.8, 161.9, 157.1, 153.9, 148.2, 136.7, 124.6, 121.3, 118.7, 110.3, 109.9, 109.8, 108.1 (Fig. S4†); MS(EI): m/z calcd for C<sub>13</sub>H<sub>8</sub>O<sub>4</sub> [M]<sup>+</sup> 228.04, found 227.97 with a retention time of 13.95 min (Fig. S15†).

Methyl tetra-*O*-acetyl-β-D-glucopyranuronate. Crystals with m.p. of 155–158 °C, (38.9 g, 91%); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 298 K) δ 5.30 (t, J = 9.0 Hz, 1H); 5.24 (d, J = 9.6 Hz, 1H); 5.15 (t, J = 8.4 Hz, 1H); 4.19 (d, J = 9.4 Hz, 1H); 3.75 (s, 3H), 2.12 (s, 3H); 2.03 (s, 6H); 1.56 (s, 3H) (Fig. S5†); MS(EI): m/z calcd for  $C_{15}H_{20}O_{11}$  [M]<sup>+</sup> 376.10, found 377.00.

Methyl(tri-*O*-acetyl-α-D-glucopyranosyl bromide). Yellow crystals with m.p. of 74–76 °C (2.92 g, 92%);  $^1$ H NMR (300 MHz, DMSO-d<sub>6</sub>, 298 K) δ 6.94 (d, J=4.0 Hz, 1H); 5.42 (t, J=9.4 Hz, 1H); 5.28 (t, J=9.4 Hz, 1H); 5.14 (dd, J=4.0 and J=9.2 Hz, 1H); 4.47 (d, J=9.4 Hz, 1H); 3.67 (s, 3H), 2.02 (s, 6H) (Fig. S6†); MS(EI): m/z calcd for  $C_{13}$ H<sub>17</sub>BrO<sub>9</sub> [M]<sup>+</sup> 396.01, found 396.38.

Tetramethoxybenzophenone isomers. The three structural isomers (Fig. S10-S12 and S17-S19†). Isomer 1 (2,5,2',5'-tetramethoxybenzophenone): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 298 K)  $\delta$  7.09 (d, J = 3.0 Hz, 2H), 6.99 (dd, J = 3.0 and J = 8.8 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 3.79 (s, 6H), 3.61 (s, 6H) (Fig. S10†); MS(EI): m/z calcd for  $C_{17}H_{18}O_5$  [M]<sup>+</sup> 302.12, found 302.11 with a retention time of 14.12 min (Fig. S17†); isomer 2 (2,4,2',5'tetramethoxybenzophenone): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 298 K)  $\delta$  7.54 (d, J = 8.6 Hz, 1H), 6.94 (d, J = 2.8 Hz, 1H), 6.89 (dd, J = 3.1 and J = 5.6 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 6.44 (dd, J = 2.3 and J = 6.3 Hz, 1H, 6.40 (s, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 3.65 (s, 3H)3H), 3.59 (s, 3H) (Fig. S11†); MS(EI): m/z calcd for  $C_{17}H_{18}O_5[M]^+$ 302.12, found 302.02 with a retention time of 15.70 min (Fig. S18†); isomer 3 (2,4,2',4'-tetramethoxybenzophenone): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 298 K)  $\delta$  7.49 (d, J = 8.7 Hz, 2H), 6.49 (dd, J = 2.3 and J = 8.6 Hz, 2H), 6.40 (s, 2H), 3.84 (s, 6H), 3.66 (s, 2H)6H) (Fig. S12†); MS(EI): m/z calcd for  $C_{17}H_{18}O_5$  [M]<sup>+</sup> 302.12, found 302.14 with a retention time of 16.52 min (Fig. S19†).

# Data availability

The data supporting this article have been included as part of the ESI.†

#### Author contributions

This manuscript and related documents regarding writing, reviewing, editing, data analysis, and other details have been prepared by M. Mustafa Cetin (MMC).

#### Conflicts of interest

There are no conflicts to declare. The author also declares no competing financial interest.

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