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Synthesis of 4,4-Disubstituted-4*H*-benzo[*d*][1,3]oxathiin-2-ones, a New Class of Compounds

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Abstract: 4,4-Dialkyl and 4,4-diaryl-4*H*-benzo[*d*][1,3]oxathiin-2-ones were synthesized by the reaction of 2-(mercapto-phenyl)-dialkyl- (or diaryl)-methanol with CDI in excellent yield. The 2-(mercaptophenyl)-dialkyl- (or diaryl)-methanols were prepared by the reaction of commercially available methylthiosalicylate with an appropriate alkyl or aryl Grignard reagent.

Keywords: CDI, cyclization, Grignard reagent, oxathiin-2-one, PR antagonist

Progesterone receptor- (PR), a group of ligand-activated nuclear transcription factors,[1] are members of the steroid receptor subfamily of the nuclear receptor superfamily. Current steroidal PR agonists are usually administered with steroidal estrogen for oral contraception and postmenopausal hormone therapy. However, various side effects such as nausea, headache, bloating, weight gain, breast tenderness, and moodiness are associated with these steroids. More important, coupling PR agonists with estrogen can lead to potential stroke, myocardial infarction, and venous thromboembolism. Theoretically, identifying novel, nonsteroidal PR drugs that target key tissues would

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prove to be less harmful than the current methods of steroidal chemotherapy. A number of nonsteroidal PR antagonists have been reported in the literature.[2–7] Among them Mifepristone (**1**), 6-arylbezimidazolones (**2**), 6-aryl benzoxazines (**3**),[8,9] and 6-aryl-1,4-dihydrobenzoxazin-2-ones (**4**)[10] (Figure 1) proved that this class of drug is not only potent but selective as well. To further study of the effects of variants of this class of PR modulators, a number of analogs were prepared in which the N-H group was replaced by sulfur because novel PR antagonists that are structurally distinct from the steroid class may have greater potential for selectivity against other steroid receptors.[11–13] We hope that this new class of drugs will also act as selective, highly potent PR antagonists. A detailed synthesis of these types of compounds is discussed herein.

4,4-Disubstituted-4*H*-benzo[*d*][1,3]oxathiin-2-one (**8a–8g**) were synthesized from methylthiosalicylate (**5**) according to the procedure shown in Scheme 1.

Methyl thiosalicylate **5** was prepared from thiosalicylic acid in refluxing anhydrous MeOH in the presence of a catalytic amount (1 drop) of concentrated sulfuric acid. Ester **5** was then treated with various Grignard reagents (**6a–g**),[14] affording the corresponding 2-(mercapto-phenyl)-dialkyl **7a–c** and diaryl)-methanol **7d–g** in excellent yields (>90%). Compounds **7a–c** and **7d–g** were then treated with excess *N,N′*-carbonyldiimidazole (CDI) in boiling THF solution to give the target molecules **8a–c** and **8d–g**, respectively. The yields of **8a–g** listed in Table 1 are very good.

The products were fully characterized by ^{1}H NMR, ^{13}C NMR, elemental analysis, and in the case of **8c**, X-ray crystallography. An ORTEP drawing **8c** is shown in Figure 3.

A possible mechanism, shown in Figure 2, involves a nucleophilic attack by the –OH group of the dialkyl (or aryl) methanol to the carbonyl carbon of the CDI and subsequent elimination of imidazole. In the next step, a second

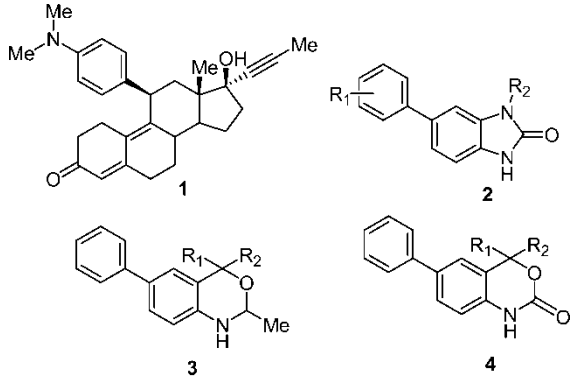
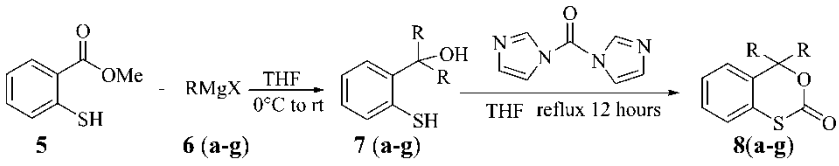


Figure 1. Typical examples of nonsteroidal PR antagonists.



Scheme 1. Synthesis of oxathiin-2-ones.

nucleophilic attack involving the $-S^-$ group onto the carbonyl carbon gives adduct **9**, which eliminates a second imidazole moiety, affording the target molecule **8**.

In summary, we have developed a new synthetic route for the synthesis of novel 4,4-dialkyl (or diaryl)-4*H*-benzo[*d*][1,3]oxathiin-2-ones. To our knowledge, there are no reports on the synthesis of this class of compounds. Work is in progress for detailed biological testing of these compounds.

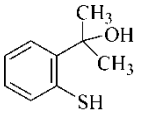
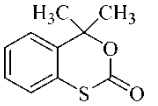
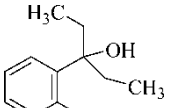
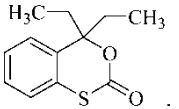
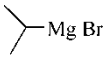
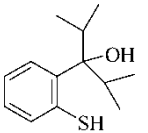
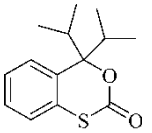
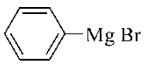
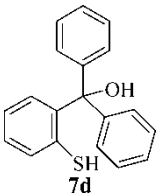
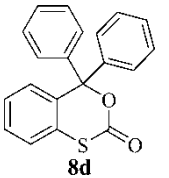
EXPERIMENTAL

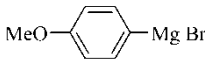
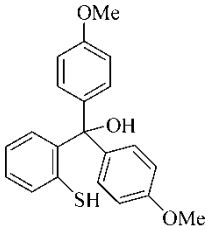
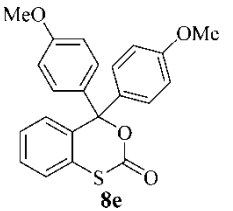
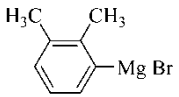
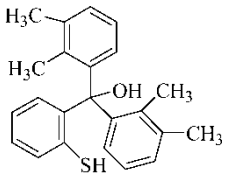
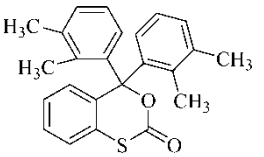
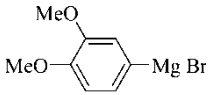
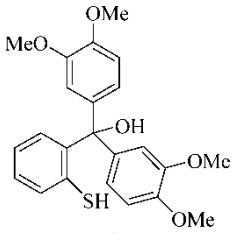
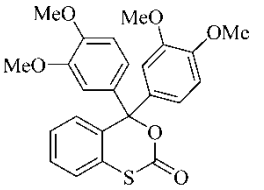
Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected with respect to stem correction. ^{1}H and ^{13}C NMR spectra were recorded on a 400-MHz Bruker Advance DRX-400 Multinuclear NMR spectrometer. Chemical shifts are reported in reference to TMS as internal standard. IR spectra were taken in Nicolet Magna-IR-560-Spectrometer (E.S.P). Elemental analysis were obtained from Southern Methodist University (SMU) Analytical Service Laboratories. All chemicals were purchased from Fisher Scientific or Aldrich chemicals.

General Procedure for the Preparation of 2-(Mercaptophenyl)-dialkyl (or Diaryl) Alcohols

Magnesium (0.72 g, 2.5 equiv, 29.7 mmol) dried over P_2O_5 in vacuo was placed in a 50-mL reaction flask. A THF (10 mL) solution of alkyl or aryl halide (2.5 equiv, 29.7 mmol) was added over a period of 30 min, and the reaction was completed by stirring the resulting mixture for 1 hr at rt. The Grignard reagent **6** was then added dropwise to a cold (0°C) solution of methyl thiosalicylate **5** (2.0 g, 11.9 mol) in THF over a period of 30 min. After stirring overnight at rt, the mixture was poured into 100 mL of a solution of saturated aqueous solution of ammonium chloride. The product was extracted with ethyl acetate (3 × 200 mL), and the combined extracts were dried (Na_2SO_4). The solvent was then evaporated under reduced pressure, and the crude products were chromatographed on a silica-gel column using hexane–ethyl acetate (9 : 1, v/v) as eluent.

Table 1. Synthesis of 4,4-disubstituted-4*H*-benzo[*d*][1,3]oxathiin-2-ones

Entry	Grignard reagent	Dialkyl/Diaryl methanol	Yield	Oxathiindole-2-one	Yield
1	CH_3MgBr **6a**	 **7a**	98%	 **8a**	99%
2	CH_3CH_2MgBr **6b**	 **7b**	92%	 **8b**	98%
3	 **6c**	 **7c**	98%	 **8c**	99%
4	 **6d**	 **7d**	92%	 **8d**	96%

5	 **6e**	 **7e**	86%	 **8e**	97%
6	 **6f**	 **7f**	90%	 **8f**	92%
7	 **6g**	 **7g**	96%	 **8g**	96%

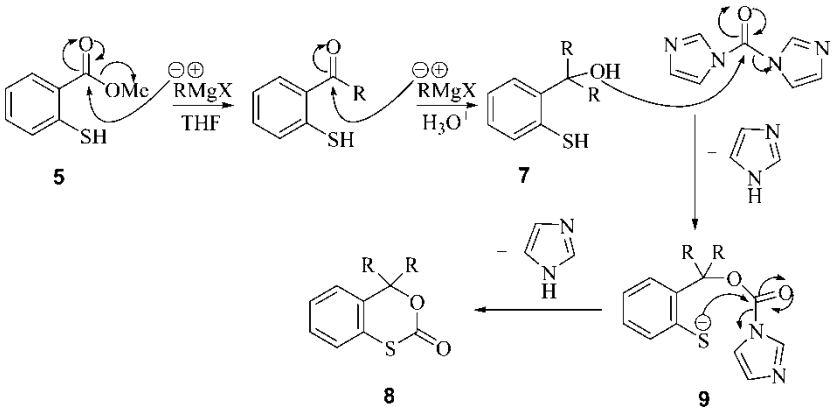
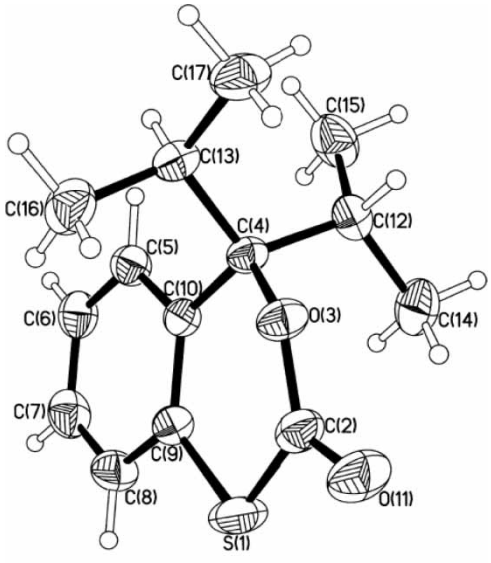


Figure 2. Possible mechanism for formation of titled compounds.

Physical Properties of Compounds (7a–h)

(7a): 2-(2-Mercaptophenyl)-propan-2-ol. Separated as a colorless oil. IR (KBr, $CHCl_3$) ν_{max}: 3585 cm^{-1} (–OH). ^1H NMR ($CDCl_3$): δ 1.71 (s, 6H, $CH_3 \times 2$), 2.64 (s, 1H, –SH), 4.14 (s, 1H, OH), 7.10 (dd, $J = 7.8$, 8.0 Hz, 2H, aromatic), 7.26 (d, $J = 7.8$ Hz, 1H, aromatic), 7.37 (d, $J = 8.0$ Hz, 1H,



ORTEP structure of compound **8c**

Figure 3.

aromatic). ^{13}C NMR ($CDCl_3$): δ 30.1, 74.2, 125.9, 126.6, 127.9, 130.4, 133.3, 145.2. Anal. calcd. for $C_9H_{12}OS$: C, 64.25; H, 7.19. Found: C, 64.40; H, 7.25.

(7b): 3-(2-Mercaptophenyl)-pentan-3-ol. Separated as a colorless oil. IR (KBr, $CHCl_3$) ν_{max}: 3485 cm^{-1}(−OH). ^{1}H NMR ($CDCl_3$): δ 0.80 (t, $J = 8.0$ Hz, 6H, $-CH_3 \times 2$), 1.95–2.16 (m, 4H, $-CH_2 \times 2$), 2.19 (s, 1H, SH), 3.84 (s, 1H, −OH), 7.11 (dd, $J = 7.6$, 7.8 Hz, 2H, aromatic), 7.23 (d, $J = 7.8$ Hz, 1H, aromatic), 7.34 (d, $J = 7.8$ Hz, 1H, aromatic). ^{13}C NMR ($CDCl_3$): δ 8.4 ($-CH_3 \times 2$), 32.5 ($-CH_2 \times 2$), 79.4, 125.5, 127.5, 128.6, 130.3, 133.2, 142.3. Anal. calcd. for $C_{11}H_{16}OS$: C, 67.30; H, 8.15. Found: C, 67.45; H, 8.20.

(7c): 3-(2-Mercaptophenyl)-2,4-dimethyl-pentan-3-ol. Separated as a reddish oil. IR (KBr, $CHCl_3$) ν_{max}: 3587 cm^{-1}(−OH). ^{1}H NMR ($CDCl_3$): δ 0.84 (d, $J = 4$ Hz, 6H, $-CH_3 \times 2$), 0.99 (d, $J = 4$ Hz, 6H, $-CH_3 \times 2$), 2.03 (s, 1 H, -SH), 2.31–2.33 (m, 2H, −CH−), 3.61 (s, 1H, −OH), 7.07 (d, $J = 7.8$ Hz, 1H, aromatic), 7.19 (d, $J = 7.8$ Hz, 1H, aromatic), 7.26 (dd, $J = 7.8$, 8.0 Hz, 2H, aromatic), ^{13}C NMR ($CDCl_3$): δ 17.0 ($-CH_3 \times 2$), 18.1 ($-CH_3 \times 2$), 36.0 ($-CH \times 2$), 84.7, 124.6, 127.1, 130.6, 132.2, 133.1, 140.1. Anal. calcd. for $C_{13}H_{20}OS$: C, 69.59; H, 8.98. Found: C, 69.65; H, 9.03.

(7d): (2-Mercaptophenyl)-diphenyl-methanol. Separated as a reddish brown oil. IR (KBr, $CHCl_3$) ν_{max}: 3680 cm^{-1} (−OH). ^{1}H NMR ($CDCl_3$): δ 3.47 (s, 1H, −SH), 5.13 (s, 1H, −OH), 6.67–7.09 (m, 2H, aromatic), 7.20–7.32 (m, 2H, aromatic), 7.33–7.41 (m, 10H, aromatic). ^{13}C NMR ($CDCl_3$): δ 83.2, 125.5, 126.6, 127.8, 127.9, 128.3, 128.5, 129.5, 129.7, 130.2, 131.1, 133.4, 135.0, 146.1, 146.5. Anal. calcd. for $C_{19}H_{16}OS$: C, 78.05; H, 5.52. Found: C, 78.24; H, 5.62.

(7e): (2-Mercaptophenyl)-bis-(4-methoxyphenyl)-methanol. Separated as a reddish oil. IR (KBr, $CHCl_3$) ν_{max}: 3287 cm^{-1}(−OH). ^{1}H NMR ($CDCl_3$): δ 2.08 (s, 1H, −SH), 3.76 (s, 3H, −OMe), 3.79 (s, 3H, −OMe), 4.16 (s, 1H, −OH), 6.86 (d, $J = 8$ Hz, 4H, aromatic), 7.03 (dd, $J = 7.8$, 8.0 Hz, 1H, aromatic), 7.17 (d, $J = 8.0$ Hz, 4H, aromatic), 7.57 (dd, $J = 7.8$, 8.0 Hz, 2H, aromatic), 7.76 (d, $J = 7.8$ Hz, 1H, aromatic). ^{13}C NMR ($CDCl_3$): δ 55.6, 55.8, 82.7, 112.2, 114.4, 127.0, 127.4, 128.6, 129.2, 129.8, 130.1, 130.7, 131.0, 133.2, 133.8, 134.1, 135.7, 144.1, 155.1, 155.8. Anal. calcd. for $C_{21}H_{20}O_3S$: C, 71.56; H, 5.72. Found: C, 71.73; H, 5.78.

(7f): Bis-(2,3-dimethylphenyl)-(2-mercaptophenyl)-methanol. Separated as a reddish brown oil. IR (KBr, $CHCl_3$) ν_{max}: 3679 cm^{-1}(−OH). ^{1}H NMR ($CDCl_3$): δ 2.18 (s, 3H, $-CH_3$), 2.21 (s, 6H, $-CH_3 \times 2$), 2.36 (s, 3H, $-CH_3$), 3.50 (s, 1H, −SH), 5.06 (s, 1H, −OH), 6.54 (d, $J = 8.0$ Hz, 1H, aromatic), 6.68 (d, $J = 8.0$ Hz, 1H, aromatic), 6.79 (d, $J = 8.0$ Hz, 1H, aromatic), 6.96 (dd, $J = 7.8$, 8.0 Hz, 2H, aromatic), 7.10 (dd, $J = 7.8$, 8.0 Hz, 2H, aromatic), 7.19 (dd, $J = 7.8$, 8.0 Hz, 1H, aromatic), 7.21–7.33 (m, 2H, aromatic). ^{13}C NMR ($CDCl_3$): δ 17.1, 19.1, 19.4, 19.5, 86.9, 124.8,

125.0, 126.7, 127.4, 127.9, 128.1, 129.5, 129.9, 130.0, 132.1, 132.9, 135.5, 137.9, 139.1, 139.6, 143.6, 143.7. Anal. calcd. for $C_{23}H_{24}OS$: C, 79.27; H, 6.94. Found: C, 79.32; H, 6.99.

(7g): Bis-(3,4-dimethylphenyl)-(2-mercaptophenyl)-methanol. Separated as a reddish oil. IR (KBr, $CHCl_3$) ν_{max}: 3585 cm^{-1}(−OH). ^1H NMR ($CDCl_3$): δ 3.5 (s, 1H, −SH), 3.83 (s, 6H, −OMe × 2), 3.87 (s, 6H, −OMe × 2), 5.1 (s, 1H, −OH), 6.56 (s, 2H, aromatic), 6.65 (d, $J = 7.8$ Hz, 2H, aromatic), 6.68 (d, $J = 7.8$ Hz, 2H, aromatic), 6.96 (dd, $J = 7.8$, 8.0 Hz, 1H, aromatic), 7.03 (dd, $J = 7.8$, 8.0 Hz, 2H, aromatic), 7.10 (d, $J = 8.0$ Hz, 1H, aromatic). ^{13}C NMR ($CDCl_3$): δ 55.9, 56.1, 56.2, 56.3, 83.1, 115.1, 115.3, 115.6, 121.3, 121.7, 125.7, 126.7, 128.7, 129.7, 132.5, 136.3, 136.7, 143.7, 155.1, 155.2, 159.1, 159.2. Anal. calcd. for $C_{23}H_{24}O_5S$: C, 66.97; H, 5.86. Found: C, 67.03; H, 5.90.

General Procedure for the Preparation of 4,4-Dialkyl- (or Diaryl)-4*H*-benzo[*d*][1,3]oxathiin-2-ones

N,N′-Carbonyldiimidazole (CDI) (1.31 g, 8 mmol) was added to a solution of the propan-2-ol **7a**–**g** (4.0 mmol) in dry THF (10 mL) under argon atmosphere, and the resulting reaction solution was heated overnight at 50°C. The solvent was removed in vacuo, and the residue was dissolved in ethyl acetate (100 mL). The solution was then washed with 1 N aqueous hydrochloride solution (2 × 50 mL) and brine (20 mL) and then dried over Na_2SO_4. The solvent was removed in vacuo, affording the crude product, which was purified by column chromatography using silica-gel packing and ethylacetate–hexane mixture (9 : 1, v/v) as eluent.

Products 8a–g

(8a): 4,4-Dimethyl-4*H*-benzo[*d*][1,3]oxathiin-2-one. Separated as a colorless gummy liquid. IR (KBr, $CHCl_3$) $\nu_{c=o}$: 1693 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.81 (s, 6H, $-CH_3$ × 2), 7.18 (d, $J = 7.8$ Hz, 1H, aromatic), 7.30 (dd, $J = 7.8$ Hz, 8.0 Hz, 2H, aromatic), 7.37 (d, $J = 7.8$ Hz, 1H, aromatic). ^{13}C NMR ($CDCl_3$): δ 27.2, 87.0, 124.8, 126.6, 128.1, 128.7, 129.3, 135.5, 165.3. Anal. calcd. for $C_{10}H_{10}O_2S$: C, 61.83; H, 5.19. Found: C, 61.86; H, 5.22.

(8b): 4,4-Diethyl-4*H*-benzo[*d*][1,3]oxathiin-2-one. Separated as yellowish solid, mp 58–60°C. IR (KBr) $\nu_{c=o}$: 1692 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.93 (t, $J = 8.0$ Hz, 6H, $-CH_3$ × 2), 2.15 (q, $J = 8.0$ Hz, 4H, $-CH_2$ × 2), 7.20 (dd, $J = 7.8$, 8.0 Hz, 2H, aromatic), 7.25 (d, $J = 7.8$ Hz, 1H, aromatic), 7.29 (d, $J = 8.0$ Hz, 1H, aromatic). ^{13}C NMR ($CDCl_3$): δ 8.4 ($-CH_3$ × 2), 30.4

($-CH_2-$ × 2), 93.5, 126.6, 126.7, 127.4, 129.0, 129.6, 132.0, 165.3. Anal. calcd. for $C_{12}H_{14}O_2S$: C, 64.83; H, 6.35. Found: C, 64.89; H, 6.44.

(8c): 4,4-Diisopropyl-4*H*-benzo[*d*][1,3]oxathiin-2-one. Separated as a white crystaline solid, mp 93–95°C. IR (KBr) $\nu_{c=o}$:1677 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.90 (d, $J = 8.0$ Hz, 6H, $-CH_3$ × 2), 1.03 (d, $J = 8.0$ Hz, 6H, $-CH_3$ × 2), 2.53–2.59 (m, 2H, $-CH-$ × 2), 7.07 (d, $J = 7.8$ Hz, 1H, aromatic), 7.19 (d, $J = 8.0$ Hz, 1H, aromatic), 7.26 (dd, $J = 7.8$ Hz, 8.0 Hz, 2H, aromatic). ^{13}C NMR ($CDCl_3$): δ 16.8, 18.3, 36.5, 100.2, 125.8, 126.8, 126.9, 128.5, 128.6, 129.8, 164.3. Anal. calcd. for $C_{14}H_{18}O_2S$: C, 64.25; H, 7.19. Found: C, 74.33; H, 64.31.

(8d): 4,4-Diphenyl-4*H*-benzo[*d*][1,3]oxathiin-2-one. Separated as a brownish solid, mp 85–87°C. IR (KBr) $\nu_{c=o}$: 1689 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.07–7.09 (m, 2H, aromatic), 7.21–7.29 (m, 10 H, aromatic), 7.30–7.32 (m, 2H, aromatic). ^{13}C NMR ($CDCl_3$): δ 82.7, 125.1, 126.2, 126.9, 127.0, 127.3, 127.6, 128.3, 128.6, 128.7, 129.8, 130.0, 131.6, 133.6, 137.8, 141.3, 164.5. Anal. calcd. for $C_{20}H_{14}O_2S$: C, 75.45; H, 4.43. Found: C, 75.44; H, 4.57.

(8e): 4,4-Bis-(4-methoxyphenyl)-4*H*-benzo[*d*][1,3]oxathiin-2-one. Separated as a reddish solid, mp 98–99°C. IR (KBr) $\nu_{c=o}$: 1678 cm^{-1} ^1H NMR ($CDCl_3$): δ 3.81 (s, 3H, $-OMe$), 3.82 (s, 3H, $-OMe$), 6.67 (d, $J = 8.0$ Hz, 4H, aromatic), 6.86 (d, $J = 8.0$ Hz, 4H, aromatic), 7.04 (dd, $J = 7.8$, 8.0 Hz, 1H, aromatic), 7.17 (d, $J = 8.0$ Hz, 2H, aromatic), 7.51 (dd, $J = 7.8$, 8.0 Hz, 1H, aromatic). ^{13}C NMR ($CDCl_3$): δ 55.6, 55.7, 88.1, 113.7, 114.0, 114.1, 124.4, 125.8, 126.3, 128.8, 129.4, 129.5, 129.7, 130.0, 130.2, 132.5, 135.3, 144.1, 159.1, 159.8, 163.9. Anal. calcd. for $C_{22}H_{18}O_4S$: C, 69.82; H, 4.79. Found: C, 69.88; H, 4.89.

(8f): 4,4-Bis-(2,3-dimethylphenyl)-4*H*-benzo[*d*][1,3]oxathiin-2-one. Separated as a colorless gummy liquid. IR ($CHCl_3$) $\nu_{c=o}$: 1678 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.19 (s, 6H, $-CH_3$ × 2), 2.26 (s, 6H, $-CH_3$ × 2), 6.63 (d, $J = 7.8$ Hz, 2H, aromatic), 6.95 (d, $J = 7.8$ Hz, 2H, aromatic), 6.97 (dd, $J = 7.8$, 8.0 Hz, 2H, aromatic), 7.09 (dd, $J = 7.8$, 8.0 Hz, 1H, aromatic), 7.18–7.20 (m, 3H, aromatic). ^{13}C NMR ($CDCl_3$): δ 17.2, 18.9, 19.1, 19.3, 82.3, 123.7, 125.7, 126.3, 127.9, 128.0, 128.1, 129.3, 129.5, 130.0, 132.1, 132.8, 135.5, 136.3, 137.2, 139.6, 143.6, 143.9, 164.5. Anal. calcd. for $C_{24}H_{22}O_2S$: C, 76.97; H, 5.92. Found: C, 76.91; H, 5.99.

(8g): 4,4-Bis-(3,4-dimethoxyphenyl)-4*H*-benzo[*d*][1,3]oxathiin-2-one. Separated as a yellowish oil. IR ($CHCl_3$) $\nu_{c=o}$: 1679 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.81 (s, 6H, $-OMe$ × 2), 3.86 (s, 6H, $-OMe$ × 2), 6.55 (s, 2H, aromatic), 6.69 (d, $J = 7.8$ Hz, 4H, aromatic), 6.71 (d, $J = 7.8$ Hz, 2H, aromatic), 6.98 (dd, $J = 7.8$, 8.0 Hz, 2H, aromatic). ^{13}C NMR ($CDCl_3$): δ 55.6, 55.9, 56.1, 56.2, 87.8, 114.9, 115.1, 115.6, 121.3, 121.5, 125.6, 126.5, 128.8, 130.1, 132.1, 136.5, 136.9, 144.1, 155.0, 155.5, 159.1, 159.3, 164.3. Anal. calcd. for $C_{24}H_{22}O_6S$: C, 65.74; H, 5.06. Found: C, 65.77; H, 5.11.

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