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# Synthesis and Preliminary Pharmacological Evaluation of Aryl Dithiolethiones with Cyclooxygenase-2-Selective Inhibitory Activity and Hydrogen Sulfide-Releasing Properties

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A series of 5-aryl-1,2-dithiolethiones and 5-aryl-1,2-dithiole-3-ones were investigated as hydrogen sulfide-releasing anti-inflammatory drugs. Generally, phenolic acetophenones were best protected by methoxymethyl groups and the dithiolethione group installed by treatment with carbon disulfide, hexamethyldisilathiane, and hexachloroethane. However, ether-protected acetophenones could be elaborated to β-keto esters and converted to dithiolethiones by treatment with phosphorus pentasulfide and elemental sulfur. Dethionation of dithiolethiones to 1,2-dithiole-3-ones was accomplished by mercury(II)-promoted hydrolysis. A preliminary investigation of the dithiolethiones and dithiole-3-ones as inhibitors of cyclooxygenases COX-1 and COX-2 is discussed. Dithiolethiones bearing a 5-(2,6-di-*tert*-butyl-4-hydroxyphenyl) or 5-(2,6-di-*tert*-butyl-4-methoxyphenyl) substituent were the most effective inhibitors of COX-2 and displayed excellent selectivity against COX-1, comparable with rofecoxib, a representative coxib. It is shown that uncatalyzed hydrolysis of the thiocarbonyl group to release hydrogen sulfide leads to the corresponding carbonyl compound, and these carbonyl compounds are moderate COX-2 selective inhibitors.

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## Introduction

Cyclooxygenases (COX)-1 and 2 are isoenzymes that catalyze the oxidative cyclization of arachidonic acid to the prostaglandin endoperoxides $PGG_2$ and $PGH_2$, precursors of a wide range of prostaglandins.[1] Inhibition of COX-1 and/or COX-2 is an important therapeutic strategy for the treatment of inflammation and pain. Inflammation is a major cause of pain and contributes to tissue injury and dysfunction, in particular for arthritis and inflammatory bowel syndrome.[2] Inflammation has also been implicated in the pathogenesis of neurodegenerative conditions such as Alzheimer's and Parkinson's diseases.[3] COX-1 is constitutively expressed widely throughout the body and is a major target for aspirin, ibuprofen, and diclofenac, common non-steroidal anti-inflammatory drugs (NSAIDs). COX-2 is expressed in fewer tissue and cell types but is strongly upregulated by cytokines in response to injury and inflammation.[1] Most NSAIDs act on COX-1 and COX-2, with little selectivity for either enzyme. One major limitation associated with the clinical use of non-selective COX inhibitors is side effects that include gastrointestinal ulceration, bleeding, and impaired renal function.[1] Non-selective inhibition of COX enzymes has been highlighted as a potential cause of these adverse side effects, as inhibition of basal COX-1 expression prevents the synthesis of endogenous prostaglandins that are believed to be important for maintenance of gastric mucosa.[4] A series of COX-2 selective inhibitors, the coxibs (e.g. celecoxib and rofecoxib), were developed and introduced over the past decade (Fig. 1).[5] Coxibs have a reduced incidence of gastrointestinal ulceration and bleeding;[6] however, they still suffer from a side effect of inducing gastric damage by stimulating adherence of leukocytes to the vascular endothelium in the mesenteric circulation.[2]

Epidemiology studies have suggested that chronic use of non-selective COX inhibitors such as aspirin and diclofenac reduces rates of colorectal cancer.[7] Several large-scale clinical trials investigating the anticancer activity of rofecoxib and celecoxib were aborted owing to an increase in adverse cardiovascular effects.[8] These concerns have resulted in the addition of a black-box warning applying to all coxibs, with all but one coxib in the USA (celecoxib) and all but two coxibs in Europe (celecoxib and etoricoxib) being voluntarily withdrawn from the market,[1] although many remain in use in off-label applications. While some argue that COX-2 selective inhibition is a class effect causing adverse cardiac events,[1] it is clear that different coxibs possess different levels of cardiovascular toxicity, and thus that cardiovascular toxicity is compound-specific.[9] Reddy and Corey argued that the higher toxicity of rofecoxib may be a result of its facile auto-oxidation to a reactive intermediate.[10] Additionally, even in the context of the known cardiovascular risks, there remain specific indications and treatment groups for which coxibs possess a palatable risk–benefit profile; celecoxib is now used for regression treatment of familial polyopsis, an inherited disorder that leads to a very high rate of cancer.[1] For these


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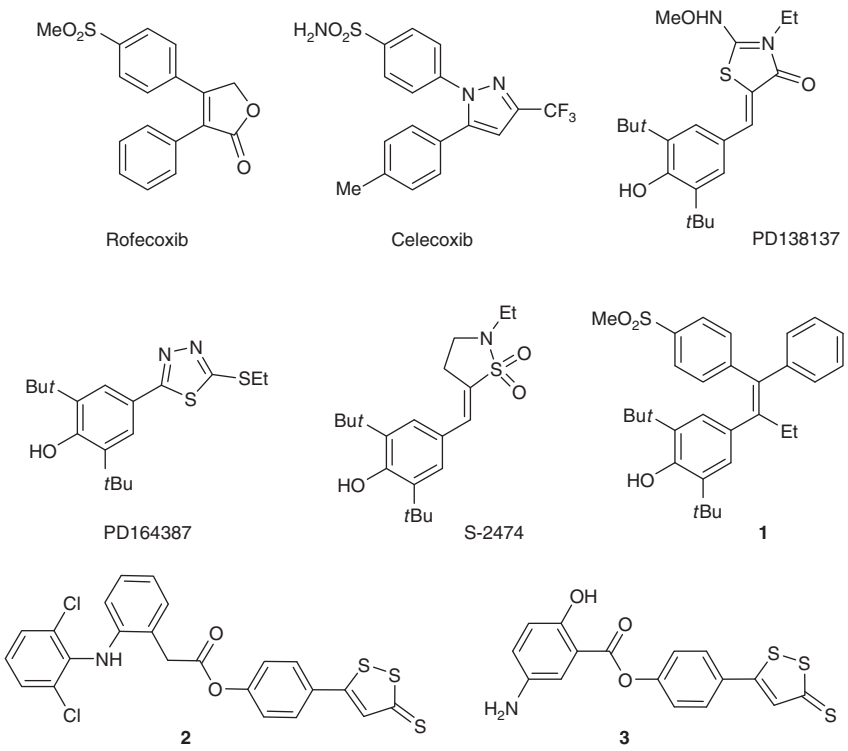



**Fig. 1.** Assorted anti-inflammatory compounds.

reasons, novel scaffolds with COX-2 selective inhibitory activity and the potential for reduced cardiovascular toxicity need to be found.

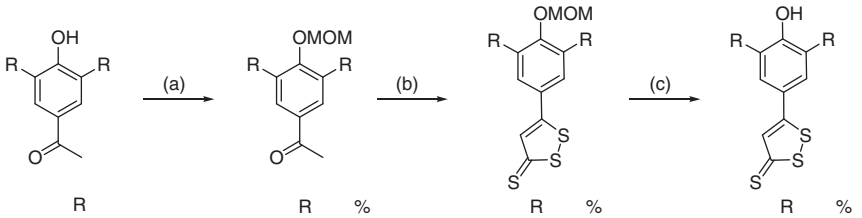
It has been demonstrated that the 3,5-di-*tert*-butyl-4-hydroxyphenyl-containing drugs PD138137,[11] PD164387,[12] S-2474,[13] and **1**[14] are potent anti-inflammatory agents, which act by dual inhibition of COX-2 and lipooxygenase-5 (Fig. 1). This is a different scaffold from approved coxibs, and thus these compounds might not suffer from metabolism-related side effects found in existing coxibs. Recently, interest has grown in the use of hydrogen sulfide-releasing drugs as anti-inflammatory treatments.[2] Hydrogen sulfide is an endogenous molecule produced through several pathways, such as the breakdown of L-cysteine by cysteine desulfhydrase, the post-translational modification of the active-site cysteine of sulfatases to formylglycine,[15] and through 'moonlighting' activities of the constitutive enzymes cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE).[16] The substrate for hydrogen sulfide production by CBS and CSE is L-cysteine, and the rates of production of hydrogen sulfide are in the range of 1–10 pmol $s^{-1}$ $mg^{-1}$ of protein.[17] It has been suggested that at physiological concentrations, hydrogen sulfide inhibits inflammation owing to its ability to suppress adherence of leukocytes to the vascular endothelium and their subsequent migration into underlying tissue.[2] These features make hydrogen sulfide an attractive molecule to exploit in the development of new and more effective anti-inflammatory drugs without gastrointestinal toxicity. Recently, reports on the synthesis and pharmacological properties of hybrid drugs formed by the esterification of several known NSAIDs such as diclofenac[18,19] and mesalamine[20] with a phenolic dithiolethione that functions as a hydrogen sulfide-releasing group have been published (compounds **2** and **3**) (Fig. 1). Preclinical studies suggest that **2**, **3**, and other derivatives are more potent than the parent NSAID as anti-inflammatory drugs and exhibit improved gastrointestinal safety.

Accordingly, we were prompted to ask whether a hybrid 3*H*-1,2-dithiole-3-thione bearing a 3,5-di-*tert*-butylhydroxyphenyl group might act as a novel COX inhibitor. We have recently published a preliminary report describing the synthesis, and biochemical and enzyme-docking studies of two new hybrid 3*H*-1,2-dithiole-3-thiones: one bearing a 3,5-di-*tert*-butylhydroxyphenyl group and the other the corresponding methyl ether.[21] Our studies revealed that both compounds are potent inhibitors of COX-2 (relative to rofecoxib), and exhibit good selectivity relative to COX-1. Here we report full experimental details for the preparation of a series of 5-aryl-3*H*-1,2-dithiole-3-thiones and their preliminary pharmacological evaluation. We also report on the mechanism of hydrogen sulfide release from these compounds.

## Results

Two general methods were used for the synthesis of 3*H*-1,2-dithiole-3-thiones. In Method A, acetophenones are treated with carbon disulfide and potassium hydride to produce dianions of 3-oxothioic acids. After sequential addition of hexamethyldisilathiane and the oxidizing agent hexachloroethane, the dithiolethione is formed.[22] In Method B, aryl β-ketoesters are directly converted to dithiolethiones by treatment with phosphorus pentasulfide and sulfur in the presence of hexamethyldisiloxane in refluxing xylene.[23,24] In order to study the effect of structural variation on COX inhibition, we prepared a series of compounds that varied through the nature of: the substituents *ortho* to the phenol; alkylation of the phenol; and methylation of C4. Additionally, we prepared compounds that possessed a carbonyl group in place of the thiocarbonyl group.

Acetophenone **4a** was commercially available whereas acetophenones **4b**–**d**[25] and **5a**[26] were prepared according to the literature. Protection of the phenols with methoxymethyl



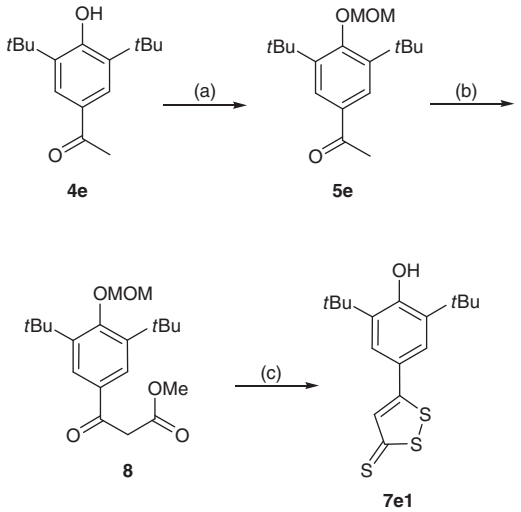
| | R |
|---|---|
| **4a** | H |
| **4b** | Me |
| **4c** | Et |
| **4d** | *i*Pr |

| | R | % |
|---|---|---|
| **5a** | H | 60 |
| **5b** | Me | 74 |
| **5c** | Et | 68 |
| **5d** | *i*Pr | 61 |

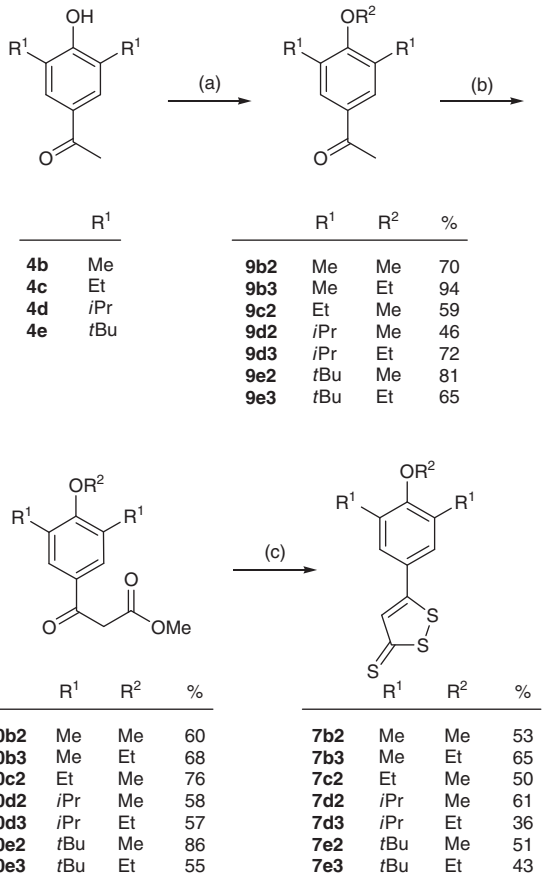
| | R | % |
|---|---|---|
| **6a** | H | 63 |
| **6b** | Me | 50 |
| **6c** | Et | 17 |
| **6d** | *i*Pr | 70 |

| | R | % |
|---|---|---|
| **7a1** | H | 60 |
| **7b1** | Me | 58 |
| **7c1** | Et | 33 |
| **7d1** | *i*Pr | 77 |

**Scheme 1.** Reagents and conditions: (a) (i) AcCl, $CH_2(OMe)_2$, $ZnCl_2$, toluene; (ii) phenol, $(i\text{Pr})_2\text{EtN}$; (b) (i) $CS_2$, HMDT; (ii) $C_2Cl_6$, DMPU, THF; (c) TFA, $CH_2Cl_2$.



**Scheme 2.** Reagents and conditions (a) (i) AcCl, $CH_2(OMe)_2$, $ZnCl_2$, toluene; (ii) phenol, $(i\text{Pr})_2\text{EtN}$, 60%; (b) $Me_2CO_3$, NaH, THF, 60%; (c) $P_4S_{10}$, $S_8$, HMDO, xylene, 43%.



| | $R^1$ |
|---|---|
| **4b** | Me |
| **4c** | Et |
| **4d** | *i*Pr |
| **4e** | *t*Bu |

| | $R^1$ | $R^2$ | % |
|---|---|---|---|
| **9b2** | Me | Me | 70 |
| **9b3** | Me | Et | 94 |
| **9c2** | Et | Me | 59 |
| **9d2** | *i*Pr | Me | 46 |
| **9d3** | *i*Pr | Et | 72 |
| **9e2** | *t*Bu | Me | 81 |
| **9e3** | *t*Bu | Et | 65 |

| | $R^1$ | $R^2$ | % |
|---|---|---|---|
| **10b2** | Me | Me | 60 |
| **10b3** | Me | Et | 68 |
| **10c2** | Et | Me | 76 |
| **10d2** | *i*Pr | Me | 58 |
| **10d3** | *i*Pr | Et | 57 |
| **10e2** | *t*Bu | Me | 86 |
| **10e3** | *t*Bu | Et | 55 |

| | $R^1$ | $R^2$ | % |
|---|---|---|---|
| **7b2** | Me | Me | 53 |
| **7b3** | Me | Et | 65 |
| **7c2** | Et | Me | 50 |
| **7d2** | *i*Pr | Me | 61 |
| **7d3** | *i*Pr | Et | 36 |
| **7e2** | *t*Bu | Me | 51 |
| **7e3** | *t*Bu | Et | 43 |

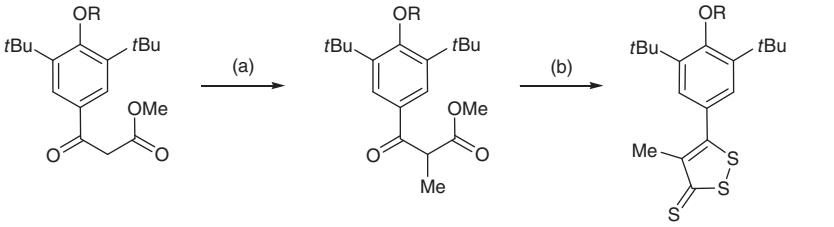
**Scheme 3.** Reagents and conditions: (a) RI, $K_2CO_3$, acetone; (b) $Me_2CO_3$, NaH, THF; (c) $P_4S_{10}$, $S_8$, HMDO, xylene.

(MOM) groups to afford **5b**–**d** was achieved using the procedure of Berliner,[27] using MOMCl prepared in situ from dimethoxymethane, acetyl chloride, and $ZnCl_2$. Treatment of acetals **5a**–**d** according to Method A smoothly afforded the dithiolethiones **6a**–**d**. Removal of the MOM groups was achieved by treatment with trifluoroacetic acid (TFA) in dichloromethane, affording phenolic dithiolethiones **7a1**, **7b1**, **7c1**, and **7d1** (Scheme 1).

For the preparation of the 5-(3′,5′-di-*tert*-butyl-4-hydroxyphenyl)-dithiolethione **7e1**, we investigated the use of Method B. Friedel–Crafts acetylation of 2,6-di-*tert*-butylphenol afforded acetophenone **4e**,[28] which was treated with MOMCl to afford the acetal **5e**. Methoxycarbonylation[29] of **5e** using dimethyl carbonate in the presence of sodium hydride afforded the β-ketoester **8**, which was treated according to Method B to afford the dithiolethione **7e1**,[21] with concomitant removal of the MOM group (Scheme 2). The removal of the MOM group was unexpected, but presumably occurs owing to the formation of acidic by-products during the thionation reaction. Attempts to apply this procedure to β-ketoesters derived from 2,6-disubstituted phenols with groups smaller than *tert*-butyl were unsuccessful; we conjecture that the more reactive nature of these phenols unveiled by removal of the MOM group leads to the formation of complex mixtures of (thio)phosphate adducts that are lost during product isolation.

Dithiolethiones **7b2**, **7b3**, **7c2**, **7d2**, **7d3**, **7e2**, and **7e3**, bearing alkyloxy substituents, were synthesized from the corresponding acetophenones **4b**–**e**. Alkylation of **4b**–**e** using methyl or ethyl iodide in the presence of potassium carbonate in refluxing acetone afforded ethers **9b2**, **9b3**, **9c2**, **9d2**, **9d3**, **9e2**, and **9e3**. Methoxycarbonylation with dimethyl carbonate and sodium hydride afforded the β-ketoesters **10b2**, **10b3**, **10c2**, **10d2**, **10d3**, **10e2**, and **10e3**. Finally, treatment of these β-ketoesters according to Method B afforded dithiolethiones **7b2**, **7b3**, **7c2**, **7d2**, **7d3**, **7e2**,[21] and **7e3** in good yields (Scheme 3).

2,6-Di-*tert*-butyl dithiolethiones with a C4 methyl substituent were prepared by α-methylation of β-ketoesters **8**, **10e2**, and **10e3** with methyl iodide and potassium carbonate in

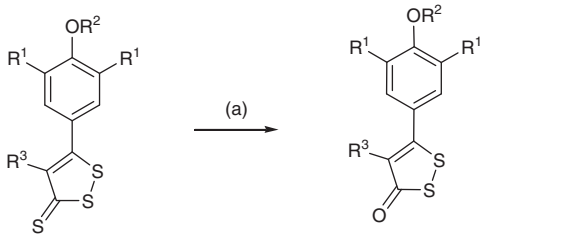



| | R |
|---|---|
| **8** | MOM |
| **10e2** | Me |
| **10e3** | Et |

| | R | % |
|---|---|---|
| **11** | MOM | 69 |
| **12e2** | Me | 65 |
| **12e3** | Et | 81 |

| | R | % |
|---|---|---|
| **13e1** | H | 98 |
| **13e2** | Me | 70 |
| **13e3** | Et | 99 |

**Scheme 4.** Reagents and conditions: (a) MeI, $K_2CO_3$, MeOH; (b) $P_4S_{10}$, $S_8$, HMDO, xylene.




| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **7b2** | Me | Me | H |
| **7e1** | *t*Bu | H | H |
| **7e2** | *t*Bu | Me | H |
| **13e1** | *t*Bu | H | Me |
| **13e2** | *t*Bu | Me | Me |
| **13e3** | *t*Bu | Et | Me |

| | $R^1$ | $R^2$ | $R^3$ | % |
|---|---|---|---|---|
| **14b2** | Me | Me | H | 48 |
| **14e1** | *t*Bu | H | H | 41 |
| **14e2** | *t*Bu | Me | H | 56 |
| **15e1** | *t*Bu | H | Me | 30 |
| **15e2** | *t*Bu | Me | Me | 79 |
| **15e3** | *t*Bu | Et | Me | 50 |

**Scheme 5.** Reagents and conditions: (a) $Hg(OAc)_2$, HOAc.

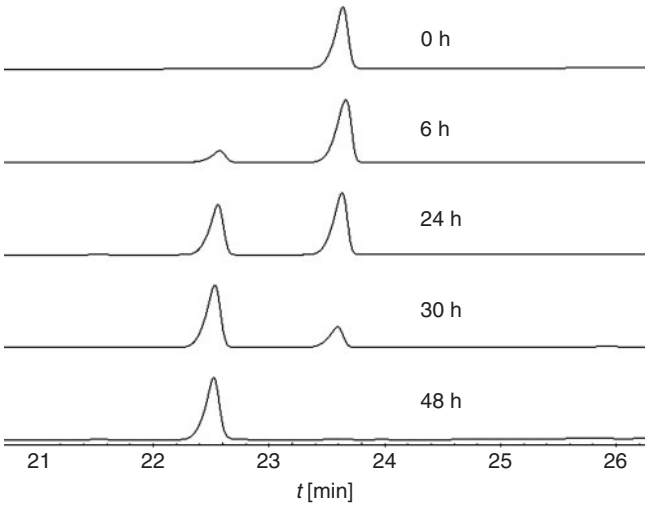



**Fig. 2.** HPLC traces showing time course for the hydrolysis of dithiolethione **7e2** (retention time 23.6 min) and the appearance of **14e2** (retention time 22.5 min). Hydrolysis conditions: 50% 100 mM phosphate buffer (pH 7.4) in DMSO, 120°C.

refluxing methanol.[30] Treatment of the α-methyl-β-ketoesters **11**, **12e2**, and **12e3** according to Method B afforded the target dithiolethiones **13e1**, **13e2**, and **13e3** in excellent yield (Scheme 4).

1,2-Dithiole-3-ones were prepared by dethionation of dithiolethiones **7b2**, **7e1**, **7e2**, **13e1**–**3** with mercuric acetate in boiling acetic acid, affording carbonyl derivatives **14b2**, **14e1**, **14e2**, **15e1**–**3** in moderate to good yields (Scheme 5).[31]

The ability of dithiolethiones to release hydrogen sulfide by hydrolysis was investigated. It is of interest to determine the overall propensity of dithiolethiones to hydrolyze as high rates of hydrolysis may lead to a burst in hydrogen sulfide release with unwanted consequences. For therapeutic applications, hydrogen sulfide release should be at a low but steady rate. Additionally, the identity of the hydrolysis product is of interest, as this will represent a possible metabolite, which may have its own inherent biological activity. Dithiolethione **7e2** was heated at 120°C in a mixture of DMSO and aqueous phosphate buffer (100 mM, pH 7.4). The gradual disappearance of **7e2** and the appearance of 1,2-dithiole-3-one **14e2** was monitored by HPLC, and required 48 h to run to completion (Fig. 2). The formation of **14e2** was confirmed by comparison of the retention time of authentic synthesized material and supported by high-resolution mass spectrometric analysis of the product.

## Cyclooxygenase Inhibition

A preliminary examination of the potencies of the synthesized dithiolethiones and dithioleketones as inhibitors of COX-1 and COX-2 enzymes was conducted using microsomal COX-1 isolated from human platelets and recombinant human COX-2 expressed in Sf21 insect cells (Table 1). For the sake of ranking inhibitor potencies, inhibition percentages were assessed at a single concentration (1 μM) (Table 1).

Considering COX-2 inhibitor potencies first, and starting with the simplest derivative, nor-anethiole **7a1**, variation of the substituents at the 3′ and 5′ positions (at $R^2$) shows that increasing the bulk of these groups increases the COX-2 inhibitory activity in the order H (**7a1**) ≈ Me (**7b1**) < Et (**7c1**) < *i*Pr (**7d1**) < *t*Bu (**7e1**). Methylation of the phenol of each of these derivatives (at $R^1$) to give **7b2**, **7c2**, **7d2**, and **7e2** results in some loss in activity, but the methyl ethers share the same general order of potency as the 3′,5′-substituents are varied. Ethylation of the phenol to give **7b3**, **7d3**, and **7e3** almost completely abolishes COX-2 inhibitory activity. Addition of steric bulk to the dithiolethione ring through a methyl group at $R^3$ leads to a reduction in inhibitory potency towards COX-2 (compare **7e1** and **13e1**, and **7e2** and **13e2**). Conversion of the thione of **7e1** and **7e2** to a carbonyl group (at $R^4$) in **14e1** and **14e2** leads to some loss in activity towards COX-2; similar transformation of **13e1** and **13e2** to give **15e1** and **15e2** results in similar changes. The inverse relationship holds for conversion of the thiocarbonyl group of **7b2** into a carbonyl group in **14b2** (Table 1).

**Table 1. COX-1 and COX-2 enzyme inhibition data for dithiolethiones and dithiole-3-ones**

| Compound | $R^1$ | $R^2$ | $R^3$ | $R^4$ | % Inhibition at 1 μM | |
|---|---|---|---|---|---|---|
| | | | | | COX-1[A] | COX-2[B] |
| **7e1** | H | *t*Bu | H | S | 44 | 98 |
| **7e2** | Me | *t*Bu | H | S | 7 | 69 |
| **7e3** | Et | *t*Bu | H | S | −1 | 8 |
| **14e1** | H | *t*Bu | H | O | 12 | 53 |
| **14e2** | Me | *t*Bu | H | O | 22 | 51 |
| **13e1** | H | *t*Bu | Me | S | 34 | 73 |
| **13e2** | Me | *t*Bu | Me | S | 31 | 29 |
| **13e3** | Et | *t*Bu | Me | S | 9 | 15 |
| **15e1** | H | *t*Bu | Me | O | −4 | 10 |
| **15e2** | Me | *t*Bu | Me | O | 11 | 43 |
| **15e3** | Et | *t*Bu | Me | O | – | – |
| **7d1** | H | *i*Pr | H | S | 10 | 64 |
| **7d2** | Me | *i*Pr | H | S | 0 | 35 |
| **7d3** | Et | *i*Pr | H | S | 4 | 18 |
| **7c1** | H | Et | H | S | 0 | 35 |
| **7c2** | Me | Et | H | S | 0 | 0 |
| **7b1** | H | Me | H | S | 16 | 13 |
| **7b2** | Me | Me | H | S | −7 | 5 |
| **7b3** | Et | Me | H | S | −4 | −4 |
| **14b2** | Me | Me | H | O | 0 | 41 |
| **7a1** | H | H | H | S | 0 | 17 |

[A]COX-1 from a microsomal preparation of human platelets.
[B]COX-2 from insect Sf21 cells expressing human COX-2.

**Table 2. COX-1 and COX-2 inhibition of 7e1, 7e2, rofecoxib, and indomethacin[21]**

| Compound | $IC_{50}$ [nM] | |
|---|---|---|
| | COX-1[A] | COX-2[B] |
| **7e1** | 3640 | 7.2 |
| **7e2** | >30 000 | 47.2 |
| Rofecoxib | – | 74.5 |
| Indomethacin | 28.2 | – |

[A]COX-1 from a microsomal preparation of human platelets.
[B]COX-2 from insect Sf21 cells expressing human COX-2.

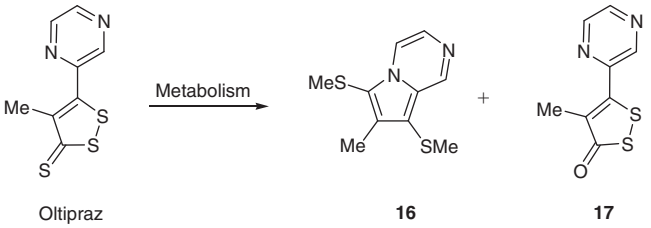
The series of dithiolethiones and 1,3-dithiole-3-ones are in most cases poorer inhibitors of COX-1 than COX-2; however, the selectivity between these enzymes varies considerably. Good selectivity for COX-2 was observed for dithiolethiones and dithiole-3-ones bearing *t*Bu groups at the 3′ and 5′ positions, as either phenols or methyl ethers (**7e1**, **7e2**, **14e1**, **14e2**). Methylation at C4 of the dithiolethione phenol **13e1** or dithiole-3-one **15e2** also gave COX-2 selective inhibitors. Some inhibitors with smaller 3′ and 5′ substituents, such as the diisopropylphenol dithiolethiones **7d1** and **7d3**, and the 3′,5′-dimethyl dithiole-3-one methyl ether **14b2**, showed good COX-2 selectivity, although the overall potency of these compounds as COX-2 inhibitors was poorer.

In order to better assess the inhibitory activity of the most active derivatives, compounds **7e1** and **7e2**, we determined their $IC_{50}$ values relative to the known COX-1 and COX-2 inhibitors indomethacin (a gold standard compound that combines both anti-inflammatory and analgesic activity)[32] and rofecoxib (a highly selective COX-2 inhibitor).[1] Both compounds are more potent inhibitors than rofecoxib, and it is noteworthy that each exhibits excellent selectivity for COX-2 over COX-1 (Table 2).

## Discussion

Curphey and coworkers have published a useful series of papers that report optimization of methods for the synthesis of dithiolethiones from either methyl ketones (Method A)[22] or β-ketoesters (Method B).[24] In our work, we have investigated these procedures for the preparation of dithiolethiones that possess additional functionality in the aryl substituent at C5. The choice of the appropriate method depends on its compatibility with the reactant. In general, phenols with 3′,5′-dimethyl, 3′,5′-diethyl, and 3′,5′-isopropyl substituents are incompatible with Method B, presumably owing to the formation of addition complexes of phosphorus pentasulfide and the phenol. MOM groups were investigated as a protecting group for the phenols as they are a sterically modest group that can be used to protect congested positions. Protection of the phenols with MOM groups before application of Method B provides no relief, as the MOM groups are unstable to the acidic conditions of Method B. Conversely, MOM groups are stable to the conditions of Method A, which therefore represents the method of choice for the preparation of dithiolethiones from phenols. The MOM groups can be removed from dithiolethiones using TFA in dichloromethane. As an interesting aside, 3′,5′-di-*tert*-butyl-4-hydroxyphenyl groups are compatible with the conditions of Method B, presumably owing to steric shielding of the phenol by the flanking *tert*-butyl groups.

Dithiolethiones have been investigated as a hydrogen sulfide-releasing pharmacophore for the development of anti-inflammatory drugs without gastric complications. Several studies have investigated the release of hydrogen sulfide as a function of time. Moore has suggested that hydrogen sulfide release is catalyzed by components of biological fluids, but it is not clear whether this corresponds to a hydrolysis reaction or alternative enzymatic processes, as suitable controls, such as heat inactivation of the enzyme, or identification of the resulting product, were not reported.[18] Fishbein reported




**Scheme 6.** Metabolism of oltipraz.

that reaction of thiols with dithiolethiones can lead to ring opening,[33] and in the case of oltipraz, the pyrazine ring engages in further reactions, leading to the major observed metabolite **16** (Scheme 6).[34] 1,2-Dithiole-3-one **17** is found as a minor metabolite of oltipraz.[34,35]

Hydrolysis of dithiolethione **7e2** occurs very slowly at room temperature and required heating to allow observation at acceptable rates. Hydrolysis occurs to form 1,2-dithiole-3-one **14e2** cleanly as the sole product, as demonstrated by the identical retention time with an authentic standard and further confirmation by high-resolution mass spectrometry. Interestingly, 1,2-dithiole-3-one **17** has been reported as a metabolite of oltipraz, and it is therefore likely that this metabolite arises from the non-enzymatic hydrolysis of the parent (Scheme 6). Time-course analysis of the rate of hydrolysis of dithiolethione **7e2** reveals it to be a slow process, which could only be conveniently monitored by raising the reaction temperature over 100°C. This is an interesting outcome, as applications of dithiolethiones as hydrogen sulfide-releasing drugs need to ensure that hydrogen sulfide is released at steady but low levels to ensure that toxic effects are avoided, and also that the drugs are stable for long-term storage. More detailed biological studies are required to assess whether other metabolic processes contribute to hydrogen sulfide release in vivo.

Our preliminary pharmacological analysis reveals that the *tert*-butyl-substituted dithiolethiones **7e1** and **7e2** are the most potent COX-2 inhibitors, with inhibition potencies exceeding that of rofecoxib. Moreover, **7e1** and **7e2** have excellent selectivities for COX-2 over COX-1. Our previously reported molecular modelling studies on **7e1** and **7e2** argued that such selectivity likely results from the smaller size of the COX-1 binding site, with a hydrogen bond from Ser530 to the oxygen of the phenol or methyl ether being observed in each case (Fig. 3).[21] The bulky *tert*-butyl groups are involved in hydrophobic interactions with Val349 and Ala527. Hydrolysis of the thione of **7e2** leads to the carbonyl derivative **14e2**, and pharmacological analysis of **14e2** reveals it to be a moderate inhibitor of COX-2 with good selectivity over COX-1. Thus, hydrolysis through non-enzymatic processes leads to a product that is unlikely to interfere with the pharmacological activity of the parent drug.

Dithiolethiones are under the spotlight as potential therapeutic agents in a range of conditions. In addition to the COX-2 selective inhibition and hydrogen sulfide-releasing activity studied here, dithiolethiones are known to be chemoprotective through induction of a battery of cytoprotective genes including those encoding for cytoprotective antioxidative and phase II enzymes such as haem oxidase-1, superoxide dismutase, γ-glutamylcysteine synthase, glutathione S-transferase, and NADPH quinone reductase.[36] Induction of phase II enzymes is mediated by interaction of the dithiolethione with the transcription factor Nrf2, allowing its binding to an antioxidant response element found upstream of many antioxidative and phase II

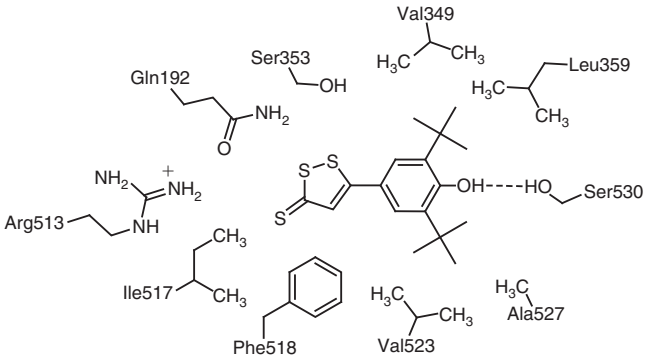



**Fig. 3.** Cartoon showing interactions of the dithiolethione **7e1** with the active site of COX-2, as determined by molecular modelling.[21]

genes.[37] In terms of their potential use an anti-inflammatory drugs, elevated levels of antioxidative enzymes would be of benefit in chemoprotection by quenching reactive oxygen species that are formed in high concentration by NADPH oxidase during an inflammatory response.[38] Interaction with Nrf2 is common to molecules with a dithiolethione pharmacophore,[37] and while not examined here, is to be expected for all compounds prepared herein.

## Conclusion

We have synthesized a range of 5-aryl dithiolethiones and report a detailed structure–activity analysis that supports the results of molecular modelling in the features required for effective COX-2 inhibition. Good COX-2 selectivity is observed only for the most bulky of derivatives, and is maximized for **7e1** and **7e2**. Hydrolysis studies reveal that release of hydrogen sulfide occurs through the conversion of the thione group to a carbonyl group, and in uncatalyzed systems occurs at a low and steady rate, suggesting that controlled therapeutic release of hydrogen sulfide should be possible. The carbonyl congeners remain moderate COX inhibitors but display different selectivities for COX-1 and COX-2. Given the need for improved pain-relieving drugs, these new hydrogen sulfide-releasing COX-2-selective dithiolethiones deserve additional examination in anti-inflammatory models to evaluate their capacity to act as non-steroidal anti-inflammatory drugs with the potential for favourable gastrointestinal and cardiovascular profiles.

## Experimental

### *General Methods*

Experimental details have been given previously.[39] Infrared spectra were obtained as thin films using a Perkin–Elmer Spectrum One Fourier-transform (FT)-IR spectrometer with a zinc selenide/diamond Universal ATR sampling accessory.

### *Representative Procedure for the Methoxycarbonylation of Acetophenones*

The acetophenone (1 mmol) in THF (4 mL) was added dropwise over 2 h to a refluxing solution of hexane-washed sodium hydride (5 mmol, 60% dispersion in mineral oil) and dimethyl carbonate (5 mmol) in THF (8 mL). The reaction was heated for a further 30 min, then cooled to rt. Water (50 mL) was then added, followed by ether. The organic extract was washed with water (×3), sat. $NaHCO_3$ (×1), brine (×1), dried ($Na_2SO_4$), and concentrated. The resulting β-ketoesters underwent

tautomerization to varying degrees, leading to complex NMR spectra.

### *3-(4-Methoxy-3,5-dimethylphenyl)-β-oxo-propanoic Acid Methyl Ester* ***10b2***

The title compound was prepared by the representative procedure starting from 1-(4-methoxy-3,5-dimethylphenyl)ethanone (**9b2**). After flash chromatography (10% EtOAc/petrol), **10b2** was obtained as a yellow oil (935 mg, 60%). $\delta_H$ (500 MHz, $CDCl_3$) 2.24 (s, 6H, ArC$H_3$ (enol) × 2), 2.25 (s, 6H, ArC$H_3$ (keto) × 2), 3.68 (s, 3H, $OCH_3$ (enol)), 3.69 (s, 3H, $OCH_3$ (keto)), 3.70 (s, 3H, $OCH_3$ (keto)), 3.72 (s, 3H, $OCH_3$ (enol)), 3.90 (s, 2H, $CH_2$ (keto)), 5.54 (s, 1H, CH (enol)), 7.38 (s, 2H, Ar (enol)), 7.56 (s, 2H, Ar (keto)), 12.46 (s, 1H, OH). $\delta_C$ (100 MHz, $CDCl_3$) 16.0 (Ar*C*$H_3$), 45.2 ($CH_2$), 52.1 ($OCH_3$), 59.4 ($OCH_3$), 85.9 (CH (enol)), 126.6, 129.4, 130.9, 131.2, 131.4, 161.6 (Ar), 167.9 (enol C), 171.4 ($CO_2$), 191.4 (ketone CO). $\nu_{max}/cm^{-1}$ 2952, 1744, 1680, 1597, 1137, 1004, 889. *m/z* (HRMS-ESI$^+$) $[M+Na]^+$ Anal. Calc. for $C_{13}H_{16}NaO_4$: 259.0941. Found 259.0938.

### *3-(4-Ethoxy-3,5-dimethylphenyl)-β-oxo-propanoic Acid Methyl Ester* ***10b3***

The title compound was prepared by the representative procedure starting from 1-(4-ethoxy-3,5-dimethylphenyl)ethanone (**9b3**). After flash chromatography (10% EtOAc/petrol), **10b3** was obtained as a yellow oil (971 mg, 68%). $\delta_H$ (400 MHz, $CDCl_3$) 1.40 (t, *J* 6.8, 3H, $CH_2CH_3$), 2.27 (s, 6H, ArC$H_3$ × 2 (enol)), 2.29 (s, 6H, ArC$H_3$ × 2 (keto)), 3.72 (s, 3H, $OCH_3$ (keto)), 3.76 (s, 3H, $OCH_3$ (enol)), 3.88 (q, *J* 6.8, 2H, $OCH_2$), 3.93 (s, 3H, $OCH_3$ (keto)), 5.57 (s, 1H, CH (enol)), 7.42 (s, 2H, Ar (enol)), 7.59 (s, 2H, Ar (keto)). $\delta_C$ (100 MHz, $CDCl_3$) 15.6, 16.3, 16.4 (ArC$H_3$,$CH_2CH_3$), 45.4 ($CH_2CH_3$), 51.2 (enol, $OCH_3$), 52.3 ($OCH_3$), 67.9, 68.0 ($OCH_2$), 86.0 (CH (enol)), 126.6, 128.3, 129.4, 131.2, 131.3, 131.5, 158.9, 161.0 (12C, Ar), 168.1 (enol C), 171.6, 173.5 ($CO_2$), 191.6 (ketone CO). $\nu_{max}/cm^{-1}$ 2980, 2956, 1746, 1680, 1483, 1140, 1108, 987, 662. *m/z* (HRMS-ESI$^+$) $[M+Na]^+$ Anal. Calc. for $C_{14}H_{18}NaO_4$: 273.1097. Found 273.1089.

### *3-(3,5-Diethyl-4-methoxyphenyl)-β-oxo-propanoic Acid Methyl Ester* ***10c3***

The title compound was prepared by the representative procedure starting from 1-(3,5-diethyl-4-methoxyphenyl)ethanone (**9c3**). After flash chromatography (10% EtOAc/petrol), **10c3** was obtained as a yellow oil (619 mg, 76%). $\delta_H$ (400 MHz, $CDCl_3$) 1.24 (t, *J* 7.6, 6H, $CH_2CH_3$), 2.69 (q, *J* 7.6, 4H, $CH_2CH_3$), 3.73 (s, 3H, $OCH_3$), 3.76 (s, 3H, $OCH_3$), 3.97 (s, 2H, $CH_2CO_2$), 7.66 (s, 2H, Ar). $\delta_C$ (100 MHz, $CDCl_3$) 14.6 ($CH_2CH_3$), 22.8 ($CH_2CH_3$), 45.6 ($CH_2CO_2$), 52.3, 61.0 ($OCH_3$), 125.0, 131.9, 137.6, 161.1 (6C, Ar), 168.1 ($CO_2$), 191.7 (CO). $\nu_{max}/cm^{-1}$ 2968, 1742, 1680, 1005, 880, 803. *m/z* (HRMS-ESI$^+$) $[M+H]^+$ Anal. Calc. for $C_{15}H_{20}NaO_4$: 287.1254. Found 287.1252.

### *3-(3,5-Diisopropyl-4-methoxyphenyl)-β-oxo-propanoic Acid Methyl Ester* ***10d2***

The title compound was prepared by the representative procedure starting from 1-(3,5-diisopropyl-4-methoxyphenyl)ethanone (**9d2**). After flash chromatography (10% EtOAc/petrol), **10d2** was obtained as a yellow oil (595 mg, 58%). $\delta_H$ (400 MHz, $CDCl_3$) 1.25 (d, *J* 7.0, 12H, $(CH_3)_2CH$ × 2), 3.36 (septet, *J* 7.0, 2H, $(CH_3)_2CH$ × 2), 3.75 (s, 3H, $OCH_3$ (keto)), 3.75 (s, 3H, $OCH_3$ (enol)), 3.77 (s, 3H, $OCH_3$ (keto)), 3.79 (s, 3H, $OCH_3$ (enol)), 3.99 (s, 2H, $CH_2CO_2$), 5.63 (s, 1H, CH (enol)), 7.52 (s, 2H, Ar (enol)), 7.65 (s, 2H, Ar (keto)), 12.53 (s, 1H, OH). $\delta_C$ (100 MHz, $CDCl_3$) 23.77, 23.83 ($(CH_3)_2CH$), 26.56, 26.59 ($CH(CH_3)_2$), 45.8 ($CH_2CO_2$), 51.3, 52.3, 62.2 ($OCH_3$), 86.1 (CH (enol)), 122.3, 125.1, 129.4, 132.3, 142.1, 142.5, 157.5, 159.6 (12C, Ar), 168.1 (enol C), 172.0, 173.5 ($CO_2$), 191.7 (ketone CO). $\nu_{max}/cm^{-1}$ 2963, 2872, 1743, 1682, 800. *m/z* (HRMS-ESI$^+$) $[M+H]^+$ Anal. Calc. for $C_{17}H_{25}O_4$: 293.1747. Found 293.1745.

### *3-(4-Ethoxy-3,5-diisopropylphenyl)-β-oxo-propanoic Acid Methyl Ester* ***10d3***

The title compound was prepared by the representative procedure starting from 1-(4-ethoxy-3,5-diisopropylphenyl)ethanone (**9d3**). After flash chromatography (10% EtOAc/petrol), **10d3** was obtained as a yellow oil (600 mg, 64%). $\delta_H$ (400 MHz, $CDCl_3$) 1.20 (d, *J* 6.8, 12H, $(CH_3)_2CH$), 1.42 (t, *J* 7.0, 3H, $CH_2CH_3$), 3.28 (septet, *J* 7.0, 2H, $(CH_3)_2CH$ × 2), 3.71 (s, 3H, $OCH_3$), 3.80 (q, *J* 7.0, $CH_2CH_3$), 3.95 (s, 2H, $CH_2CO_2$), 7.68 (s, 2H, Ar). $\delta_C$ (100 MHz, $CDCl_3$) 14.7 ($CH_2CH_3$), 23.8 ($CH(CH_3)_2$), 28.0 ($CH(CH_3)_3$), 47.9 ($CH_2CO_2$), 51.6 ($OCH_3$), 71.4 ($CH_3CH_2$), 123.5, 127.7, 136.1, 153.1 (6C, Ar), 168.1 ($CO_2$), 192.6 (CO). $\nu_{max}/cm^{-1}$ 2963, 1743, 1682, 1622, 1461, 1290, 1163, 800. *m/z* (HRMS-ESI$^+$) $[M+H]^+$ Anal. Calc. for $C_{18}H_{27}O_4$: 307.1904. Found 307.1906.

### *3-(3,5-Di-(*tert*-butyl)-4-methoxyphenyl)-β-oxo-propanoic Acid Methyl Ester* ***10e2***

The title compound was prepared by the representative procedure starting from 1-(3,5-di-(*tert*-butyl)-4-methoxyphenyl)ethanone (**9e2**). After flash chromatography (10% EtOAc/petrol), **10e2** was obtained as a brown oil (490 mg, 96%). $\delta_H$ (400 MHz, $CDCl_3$) 1.43 (s, 18H, $C(CH_3)_3$ × 2), 3.69 (s, 3H, $OCH_3$), 3.71 (s, 3H, $OCH_3$), 3.74 (s, 3H, $OCH_3$), 3.79 (s, 3H, $OCH_3$), 4.00 (s, 2H, $CH_2CO_2$), 5.59 (s, 1H, CH (enol)), 7.66 (s, 2H, Ar), 7.87 (s, 2H, Ar), 12.53 (OH). $\delta_C$ (100 MHz, $CDCl_3$) 31.7 ($C(CH_3)_3$), 35.8, 35.9 ($C(CH_3)_3$), 45.8 ($CH_2$), 51.2, 52.3, 64.4 ($OCH_3$), 85.9 (CH (enol)), 124.6, 127.4, 130.5, 144.0, 144.4, 164.6 (12C, Ar), 168.1 ($CO_2$), 191.8 (CO). $\nu_{max}/cm^{-1}$ 2956, 2876, 1744, 1680, 1619, 1203, 883. *m/z* (HRMS-ESI$^+$) $[M+Na]^+$ Anal. Calc. for $C_{19}H_{28}O_4Na$: 343.1885. Found 343.1877.

### *3-(3,5-Di-(*tert*-butyl)-4-ethoxyphenyl)-β-oxo-propanoic Acid Methyl Ester* ***10e3***

The title compound was prepared by the representative procedure starting from 1-(3,5-di-(*tert*-butyl)-4-ethoxyphenyl)ethanone (**9e3**). After flash chromatography (10% EtOAc/petrol), **10e3** was obtained as a brown oil (511 mg, 55%). $\delta_H$ (400 MHz, $CDCl_3$) 1.01 (t, *J* 7.2, 3H, $CH_2CH_3$), 1.02 (s, 18H, $C(CH_3)_3$ × 2), 3.32 (s, 3H, $CH_3$), 3.37 (q, *J* 7.2, 2H, $CH_2CH_3$), 3.56 (s, 2H, $CH_2CO_2$), 7.47 (s, 2H, Ar). $\delta_C$ (100 MHz, $CDCl_3$) 14.6 ($CH_2CH_3$), 31.6 ($C(CH_3)_3$), 35.7 ($C(CH_3)_3$), 45.6 ($CH_2CO_2$), 52.1 ($OCH_3$), 71.9 ($CH_2CH_3$), 127.4, 130.3, 144.2, 163.0 (6C, Ar), 168.0 ($CO_2$), 191.6 (CO). $\nu_{max}/cm^{-1}$ 2956, 1742, 1680, 1435, 1383, 1197, 733. *m/z* (HRMS-ESI$^+$) $[M+H]^+$ Anal. Calc. for $C_{20}H_{31}O_4$: 335.2217. Found 335.2217.

### *3-(3,5-Di-(*tert*-butyl)-4-(methoxymethoxy)phenyl)-β-oxo-propanoic Acid Methyl Ester* ***8***

The title compound was prepared by the representative procedure starting from 1-(3,5-di-(*tert*-butyl)-4-(methoxymethoxy)

phenyl)ethanone (**5e**). After flash chromatography (10% EtOAc/petrol) and recrystallization from EtOH/water, ester **8** was obtained as a yellow solid (1.15 g, 97%). mp 79–80°C. $\delta_H$ (400 MHz, $CDCl_3$) 1.43 (s, 18H, $C(CH_3)_3 \times 2$), 3.69 (s, 3H, $OCH_3$), 3.71 (s, 3H, $OCH_3$), 3.79 (s, 3H, $OCH_3$), 4.00 (s, 2H, $CH_2CO_2$), 4.89 (s, 2H, $OCH_2O$), 7.66 (s, 2H, Ar), 7.87 (s, 2H, Ar), 12.53 (OH). $\delta_C$ (100 MHz, $CDCl_3$) 32.0 ($C(CH_3)_3$), 36.2 ($C(CH_3)_3$), 46.1 ($CH_2CO_2$), 52.7 ($OCH_3$), 57.8 ($OCH_3$), 101.1 ($OCH_2O$), 127.6, 131.1, 145.4, 160.0 (6C, Ar), 168.4 ($CO_2$), 192.1 (CO). $\nu_{max}/cm^{-1}$ 2956, 2876, 1744, 1680, 1619, 1203, 883. *m/z* (HRMS-ESI$^+$) $[M + Na]^+$ Anal. Calc. for $C_{20}H_{30}O_5Na$: 373.1985. Found 373.1984. (Anal. Calc. for $C_{20}H_{30}O_5$: C 68.54, H 8.63. Found C 68.60, H 8.61%.)

### *Representative Procedure for the α-Methylation of β-Ketoesters*

Potassium carbonate (1 mmol) and methyl iodide (1 mmol) were added to a solution of the β-keto ester (1 mmol) in methanol (2.5 mL) and the mixture heated under reflux overnight. The reaction mixture was then cooled to rt and concentrated. Ether was added and the organic layer was washed with water (×3), brine (×1), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (5% EtOAc/petrol) to afford the methyl ester. The resulting α-methyl-β-ketoesters underwent tautomerization to varying degrees, leading to complex NMR spectra.

### *3-(3,5-Di-(*tert*-butyl)-4-methoxyphenyl)-α-methyl-β-oxo-propanoic Acid Methyl Ester* ***12e2***

The title compound was prepared by the representative procedure starting from 3,5-di-(*tert*-butyl)-4-methoxy-β-oxo-benzenepropanoic acid methyl ester (**10e2**). **12e2** was obtained as a colourless oil (1.92 g, 69%). $\delta_H$ (500 MHz, $CDCl_3$) 1.45 (s, 18H, $C(CH_3)_3 \times 2$), 1.50 (d, *J* 7.0, 3H, $CH_3$), 3.71 (s, 3H, $CH_3$), 3.73 (s, 3H, $CH_3$), 4.38 (q, *J* 7.0, 1H, CH), 7.94 (s, 2H, Ar). $\delta_C$ (100 MHz, $CDCl_3$) 14.2 ($CH_3$), 32.1 (C), 36.2 ($CH_3$), 48.4 (CH), 52.6 ($OCH_3$), 64.6 ($CH_3$), 127.8, 130.4, 144.6, 164.7 (6C, Ar), 171.8 (CO), 195.3 (CO). $\nu_{max}/cm^{-1}$ 2956, 2873, 1740, 1681, 1373, 1114, 873. *m/z* (HRMS-ESI$^+$) $[M + H]^+$ Anal. Calc. for $C_{20}H_{31}O_4$: 335.2217. Found 335.2217.

### *3-(3,5-Di-(*tert*-butyl)-4-ethoxyphenyl)-α-methyl-β-oxo-propanoic Acid Methyl Ester* ***12e3***

The title compound was prepared by the representative procedure starting from 3,5-di-(*tert*-butyl)-4-ethoxy-β-oxo-benzenepropanoic acid methyl ester (**10e3**). **12e3** was obtained as a colourless oil (632 mg, 65%). $\delta_H$ (400 MHz, $CDCl_3$) 1.41 (s, 18H, $C(CH_3)_3 \times 2$), 1.41 (t, *J* 6.8, 3H, $CH_3$), 1.47 (d, *J* 7.2, 3H, $CH(CH_3)$), 3.68 (s, 3H, $CH_3$), 3.76 (q, *J* 6.8, 2H, $CH_2$), 4.36 (q, *J* 7.2, 1H, $CH(CH_3)$), 7.91 (s, 2H, Ar). $\delta_C$ (100 MHz, $CDCl_3$) 13.9 ($CH_3$), 14.8 ($CH_3$), 31.7 (C), 35.9 ($CH_3$), 48.0 (CH), 52.3 ($CH_3$), 72.0 ($CH_2$), 127.6, 129.9, 144.2, 162.9 (6C, Ar), 171.5 (CO), 195.0 (CO). $\nu_{max}/cm^{-1}$ 2960, 2904, 2873, 1742, 1678, 1209, 1032, 887. *m/z* (HRMS-ESI$^+$) $[M + H]^+$ Anal. Calc. for $C_{21}H_{33}O_4$: 349.2373. Found 349.2373.

### *3-(3,5-Di-(*tert*-butyl)-4-(methoxymethoxy)phenyl)-α-methyl-β-oxo-propanoic Acid Methyl Ester* ***11***

The title compound was prepared by the representative procedure starting from 3-(3,5-di-(*tert*-butyl)-4-(methoxymethoxy) phenyl)-β-oxo-propanoic acid methyl ester (**8**). After flash chromatography (10% EtOAc/petrol), **11** was obtained as a yellow oil (604 mg, 72%). $\delta_H$ (400 MHz, $CDCl_3$) 1.45 (s, 18H, $C(CH_3)_3 \times 2$), 1.48 (d, *J* 6.8, 3H, $CH_3$), 3.64 (s, 3H, $CH_3$), 3.69 (s, 3H, $CH_3$), 4.36 (q, *J* 6.8, 1H, $CH(CH_3)$), 4.91 (s, 2H, $CH_2$), 7.93 (s, 2H, Ar). $\delta_C$ (100 MHz, $CDCl_3$) 13.8 ($CH_3$), 31.6 (C), 35.8 ($CH_3$), 48.0 (CH), 52.3 ($CH_3$), 57.3 ($CH_3$), 100.7 ($CH_2$), 127.4, 130.3, 144.9, 159.4 (6C, Ar), 171.4 (CO), 194.9 (CO). $\nu_{max}/cm^{-1}$ 2952, 1742, 1680, 1591, 1159, 1076, 856. *m/z* (HRMS-ESI$^+$) $[M + Na]^+$ Anal. Calc. for $C_{20}H_{33}NaO$: 387.2142. Found 387.2140.

### *Representative Procedure for the Thionation of β-Ketoesters*

$P_4S_{10}$ (0.6 mmol), sulfur (1.1 mmol) and HMDO (6.0 mmol) was added to the β-ketoester (1.0 mmol) in xylene (20.0 mL). The reaction was heated under reflux for 1.5 h, then cooled to rt. The reaction mixture was applied to silica gel and purified by flash chromatography (10% EtOAc/petrol). The residue was recrystallized from EtOAc/petrol to afford the 3*H*-1,2-dithiole-3-thione.

### *5-(4-Methoxy-3,5-dimethylphenyl)-3*H*-1,2-dithiole-3-thione* ***7b2***

The title compound was prepared by the representative procedure starting from 3-(4-methoxy-3,5-dimethylphenyl)-β-oxo-propanoic acid methyl ester (**10b2**). **7b2** was obtained as an orange solid (576 mg, 53%). mp 96–99°C. $\delta_H$ (500 MHz, $CDCl_3$) 2.33 (s, 6H, $CH_3 \times 2$), 3.77 (s, 3H, $CH_3$), 7.32 (s, 2H, Ar), 7.37 (s, 1H, CH). $\delta_C$ (125 MHz, $CDCl_3$) 16.2 ($CH_3$), 59.8 ($CH_3$), 127.1 (C4), 127.5, 132.5, 135.3, 160.6 (6C, Ar), 173.0 (C5), 215.3 (CS). $\nu_{max}/cm^{-1}$ 2937, 1599, 1470, 1181, 1064, 832. *m/z* (HRMS-ESI$^+$) $[M + H]^+$ Anal. Calc. for $C_{12}H_{13}OS_3$: 269.1023. Found 269.0125. (Anal. Calc. for $C_{12}H_{12}OS_3$: C 53.70, H 4.51. Found C 53.83, H 4.74%.)

### *5-(4-Ethoxy-3,5-dimethylphenyl)-3*H*-1,2-dithiole-3-thione* ***7b3***

The title compound was prepared by the representative procedure starting from 3-(4-ethoxy-3,5-dimethylphenyl)-β-oxo-propanoic acid methyl ester (**10b3**). **7b3** was obtained as an orange solid (709 mg, 65%). mp 110–112°C. $\delta_H$ (500 MHz, $CDCl_3$) 1.41 (t, 3H, $CH_3$), 2.29 (s, 6H, $CH_3 \times 2$), 3.86 (q, 2H, $CH_2$), 7.28 (s, 2H, Ar), 7.34 (s, 1H, CH). $\delta_C$ (125 MHz, $CDCl_3$) 15.7 ($CH_3$), 16.4 ($CH_3$), 68.2 ($CH_2$), 126.8 (C4), 127.5, 132.7, 135.1, 159.8 (Ar-4), 173.1 (C5), 215.2 (CS). $\nu_{max}/cm^{-1}$ 2972, 2920, 1596, 1471, 1165, 1062, 900. *m/z* (HRMS-ESI$^+$) $[M + H]^+$ Anal. Calc. for $C_{13}H_{15}OS_3$: 283.0280. Found 283.0280. (Anal. Calc. for $C_{13}H_{14}OS_3$: C 55.28, H 5.00. Found C 55.15, H 4.97%.)

### *5-(3,5-Diethylphenyl-4-methoxy)-3*H*-1,2-dithiole-3-thione* ***7c2***

The title compound was prepared by the representative procedure starting from 3-(3,5-diethyl-4-methoxyphenyl)-β-oxo-propanoic acid methyl ester (**10c2**). **7c2** was obtained as an orange solid (350 mg, 50%). mp 95–96°C. $\delta_H$ (500 MHz, $CDCl_3$) 1.24 (t, 6H, *J* 7.5, $CH_3$), 2.69 (q, 4H, *J* 7.5, $CH_2$), 3.79 (s, 3H, $CH_3$), 7.35 (s, 2H, Ar), 7.41 (s, 1H, CH). $\delta_C$ (125 MHz, $CDCl_3$) 14.6 ($CH_3$), 22.8 ($CH_2$), 61.2 ($CH_3$), 125.8, 127.5, 135.3, 138.7 (Ar-4), 159.9 (C4), 173.4 (C5), 215.3 (CS). *m/z* (HRMS-ESI$^+$) $[M + H]^+$ Anal. Calc. for $C_{14}H_{17}OS_3$: 297.0436. Found 297.0436.

*5-(3,5-Diisopropyl-4-methoxyphenyl)-3*H*-1,2-dithiole-3-thione* ***7d2***

The title compound was prepared by the representative procedure starting from 3-(3,5-diisopropyl-4-methoxyphenyl)-β-oxo-propanoic acid methyl ester (**10d2**). **7d2** was obtained as an orange solid (407 mg, 61%). mp 150–151°C. $\delta_H$ (500 MHz, $CDCl_3$) 1.26 (d, *J* 7, 12H, $CH(CH_3)_2 \times 2$), 3.35 (septet, *J* 7.0, 2H, $(CH_3)_2CH \times 2$), 3.78 (s, 3H, $CH_3$), 7.37 (s, 2H, Ar), 7.43 (s, 1H, CH). $\delta_C$ (125 MHz, $CDCl_3$) 23.8 ($CH_3$), 26.7 ($CH(CH_3)_2$), 62.3 ($CH_3$), 123.2 (C4), 127.9 (C5), 135.4, 143.6, 158.4, 173.8 (Ar-4), 215.3 (CS). $\nu_{max}/cm^{-1}$ 3045, 2958, 1595, 1500, 1383, 1163, 1001, 885, 670. *m/z* (HRMS-ESI$^+$) $[M+H]^+$ Anal. Calc. for $C_{16}H_{21}OS_3$: 325.0750. Found 325.0749. (Anal. Calc. for $C_{16}H_{20}OS_3$: C 59.22, H 6.21. Found C 59.26, H 6.26%.)

*5-(4-Ethoxy-3,5-diisopropylphenyl)-3*H*-1,2-dithiole-3-thione* ***7d3***

The title compound was prepared by the representative procedure starting from 3-(4-ethoxy-3,5-diisopropylphenyl)-β-oxo-propanoic acid methyl ester (**10d3**). **7d3** was obtained as an orange solid (250 mg, 37%). mp 96–97°C. $\delta_H$ (500 MHz, $CDCl_3$) 1.25 (d, *J* 7, 12H, $CH(CH_3)_2 \times 2$), 1.47 (t, *J* 7.0, $OCH_2CH_3$), 3.33 (septet, *J* 7.0, 2H, $(CH_3)_2CH \times 2$), 3.84 (q, *J* 7.0, $OCH_2CH_3$), 7.37 (s, 2H, Ar), 7.43 (s, 1H, CH). $\delta_C$ (125 MHz, $CDCl_3$) 15.7 ($CH_3$) 26.7 (CH), 70.7 ($CH_2$), 123.1 (C4), 127.8, 135.3, 143.7, 157.3 (6C, Ar), 173.9 (C5), 215.2 (CS). $\nu_{max}/cm^{-1}$ 3040, 2960, 2924, 2865, 1508, 1331, 1028, 1105, 777. *m/z* (HRMS-ESI$^+$) $[M+H]^+$ Anal. Calc. for $C_{17}H_{23}OS_3$: 339.0906. Found 339.0904. (Anal. Calc. for $C_{17}H_{22}OS_3$: C 60.31, H 6.55. Found C 60.39, H 6.64%.)

*5-(3,5-Di-(*tert*-butyl)-4-hydroxyphenyl)-3*H*-1,2-dithiole-3-thione* ***7e1****[21]*

The title compound was prepared by the representative procedure starting from 3-(3,5-di-(*tert*-butyl)-4-(methoxymethoxy) phenyl)-β-oxo-propanoic acid methyl ester (**8**). **7e1** was obtained as a brown solid (540 mg, 43%). mp 180–183°C. $\delta_H$ (500 MHz, $CDCl_3$) 1.47 (s, 18H, *t*Bu × 2), 5.72 (s, 1H, OH), 7.41 (s, 1H, CH), 7.48 (s, 2H, Ar). $\delta_C$ (125 MHz, $CDCl_3$) 30.3 (C), 34.8 ($CH_3$), 123.5 (C4), 124.5 134.7, 137.5, 158.1 (6C, Ar), 175.1 (C5), 215.2 (CS). $\nu_{max}/cm^{-1}$ 3429, 2960, 1593, 1514, 1419, 889, 715. *m/z* (HRMS-ESI$^+$) $[M+H]^+$ Anal. Calc. for $C_{17}H_{23}OS_3$: 339.0911. Found 339.0908. (Anal. Calc. for $C_{17}H_{22}OS_3$: C 60.31, H 6.55. Found C 60.37, H 6.55%.)

*5-(3,5-Di-(*tert*-butyl)-4-methoxyphenyl)-3*H*-1,2-dithiole-3-thione* ***7e2****[21]*

The title compound was prepared by the representative procedure starting from 3-(3,5-di-(*tert*-butyl)-4-methoxyphenyl)-β-oxo-propanoic acid methyl ester (**10e2**). **7e2** was obtained as an orange solid (117 mg, 28%). mp 106–107°C. $\delta_H$ (400 MHz, $CDCl_3$) 1.45 (s, 18H, $C(CH_3)_3 \times 2$), 3.74 (s, 3H, $CH_3$), 7.41 (s, 1H, CH), 7.53 (s, 2H, Ar). $\delta_C$ (100 MHz, $CDCl_3$) 31.8 (C), 36.2 ($CH_3$), 64.6 ($CH_3$), 125.5 (C4), 126.2, 135.2, 145.6, 163.5 (6C, Ar), 174.2 (C5), 215.2 (CS). $\nu_{max}/cm^{-1}$ 2948, 2865, 1744, 1587, 1498, 1304, 1110, 782. *m/z* (HRMS-ESI$^+$) $[M+H]^+$ Anal. Calc. for $C_{18}H_{25}OS_3$: 353.1062. Found 353.1063. (Anal. Calc. for $C_{18}H_{24}OS_3$: C 61.32, H 6.86, S 27.28. Found C 61.33, H 6.85, S 27.34%.)

*5-(3,5-Di-(*tert*-butyl)-4-ethoxyphenyl)-3*H*-1,2-dithiole-3-thione* ***7e3***

The title compound was prepared by the representative procedure starting from 3-(3,5-di-(*tert*-butyl)-4-ethoxyphenyl)-β-oxo-propanoic acid methyl ester (**10e3**). **7e3** was obtained as an orange solid (238 mg, 43%). mp 87–89°C. $\delta_H$ (400 MHz, $CDCl_3$) 1.44 (s, 18H, $C(CH_3)_3 \times 2$), 1.44 (t, *J* 7.2, 3H, $CH_3$), 3.80 (q, *J* 7.2, 2H, $CH_2$), 7.41 (s, 1H, CH), 7.52 (s, 2H, Ar). $\delta_C$ (100 MHz, $CDCl_3$) 14.9 ($CH_3$), 31.8 (C), 36.1 ($CH_3$), 72.3 ($CH_2$), 125.6 (C4), 126.0, 135.1, 145.6, 162.1 (6C, Ar), 174.3 (C5), 215.2 (CS). $\nu_{max}/cm^{-1}$ 2963, 1510, 1426, 1384, 1217, 1056, 888. *m/z* (HRMS-ESI$^+$) $[M+H]^+$ Anal. Calc. for $C_{19}H_{27}OS_3$: 367.1219. Found 367.1219.

*5-(3,5-Di-(*tert*-butyl)-4-hydroxyphenyl)-4-methyl-3*H*-1,2-dithiole-3-thione* ***13e1***

The title compound was prepared by the representative procedure starting from 3-(3,5-di-(*tert*-butyl)-4-(methoxymethoxy) phenyl)-α-methyl-β-oxo-propanoic acid methyl ester (**11**). **13e1** was obtained as an orange solid (600 mg, 81%). mp 174–175°C. $\delta_H$ (400 MHz, $CDCl_3$) 1.47 (s, 18H, *t*Bu × 2), 2.24 (s, 3H, $CH_3$), 5.61 (s, 1H, OH), 7.30 (s, 2H, Ar). $\delta_C$ (100 MHz, $CDCl_3$) 16.9 ($CH_3$), 30.1 (C), 34.5 ($CH_3$), 124.7 (C4), 125.7, 136.8, 140.8, 156.2 (6C, Ar), 170.2 (C5), 215.4 (CS). $\nu_{max}/cm^{-1}$ 3624, 2959, 2911, 1594, 1430, 1120, 885. (Anal. Calc. for $C_{18}H_{24}OS_3$: C 61.32, H 6.86, S 27.82. Found C 61.37, H 6.91, S 27.15%.)

*5-(3,5-Di-(*tert*-butyl)-4-methoxyphenyl)-4-methyl-3*H*-1,2-dithiole-3-thione* ***13e2***

The title compound was prepared by the representative procedure starting from 3-(3,5-di-(*tert*-butyl)-4-methoxyphenyl)-α-methyl-β-oxo-propanoic acid methyl ester (**12e2**). **13e2** was obtained as an orange solid (2.07 g, 98%). mp 83–84°C. $\delta_H$ (400 MHz, $CDCl_3$) 1.46 (s, 18H, *t*Bu × 2), 2.23 (s, 3H, C=C(Me)), 3.76 (s, 3H, OMe), 7.35 (s, 2H, Ar). $\delta_C$ (100 MHz, $CDCl_3$) 16.9 ($CH_3$), 31.9 (C), 36.0 ($CH_3$), 64.3 ($CH_3$), 127.1 (C4), 127.9, 141.2, 145.0, 161.8 (6C, Ar), 169.4 (C5), 215.5 (CS). $\nu_{max}/cm^{-1}$ 2961, 2869, 1525, 1307, 1223, 1007, 732. (Anal. Calc. for $C_{19}H_{23}OS_3$: C 62.25, H 7.15. Found C 62.34, H 7.25%.)

*5-(3,5-Di-(*tert*-butyl)-4-ethoxyphenyl)-4-methyl-3*H*-1,2-dithiole-3-thione* ***13e3***

The title compound was prepared by the representative procedure starting from 3-(3,5-di-(*tert*-butyl)-4-ethoxyphenyl)-α-methyl-β-oxo-propanoic acid methyl ester (**12e3**). **13e3** was obtained as an orange solid (480 mg, 70%). mp 83–84°C. $\delta_H$ (400 MHz, $CDCl_3$) 1.44 (bs, 21H, *t*Bu × 2, $CH_3CH_2O$), 2.23 (s, 3H, $CH_3$), 3.83 (q, 2H, $CH_3CH_2O$), 7.34 (s, 2H, Ar). $\delta_C$ (100 MHz, $CDCl_3$) 14.9 ($CH_3$), 16.8 ($CH_3$), 31.9 (C), 36.1 ($CH_3$), 72.1 ($CH_2$), 126.8 (C4), 127.6, 141.2, 145.0, 160.3 (6C, Ar), 169.5 (C5), 215.6 (CS). $\nu_{max}/cm^{-1}$ 2956, 1522, 1425, 1383, 1217, 1084, 886. *m/z* (HRMS-ESI$^+$) $[M+H]^+$ Anal. Calc. for $C_{20}H_{29}OS_3$: 381.1375. Found 381.1375. (Anal. Calc. for $C_{20}H_{28}OS_3$: C 63.11, H 7.41, S 25.47. Found C 63.15, H 7.50, S 25.11%.)

### *Representative Procedure for the Thionation of Acetophenones*

The acetophenone (1 mmol) in THF (0.5 mL) was added dropwise to a suspension of potassium hydride (2.1 mmol, 35% dispersion in mineral oil) in THF (2.0 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (1.00 mL).

The resulting suspension was then stirred for 15 min. A solution of carbon disulfide (1.10 mmol) in THF (1.0 mL) and DMPU (0.5 mL) was then added and the solution stirred for a further 10 min. Hexamethyldisilathiane (HMDT) (1.50 mmol) was then added and stirring was continued for 20 min. The reaction mixture was then cooled to 0°C and a solution of hexachloroethane (1 mmol) in THF (1.8 mL) was added and stirring was continued for 30 min. The solvent was removed and the residue purified by flash chromatography (5% EtOAc/petrol), and the residue recrystallized from EtOAc/petrol to afford 3*H*-1,2-dithiole-3-thione.

### *5-(4-(Methoxymethoxy))-3*H*-1,2-dithiole-3-thione* ***6a***

The title compound was prepared by the representative procedure starting from 1-(4-(methoxymethoxy)phenyl)ethanone (**5a**). **6a** was obtained as an orange solid (1.90 g, 63%). mp 92–95°C. $\delta_H$ (400 MHz, $CDCl_3$) 3.49 (s, 3H, OMe), 5.24 (s, 2H, $OCH_2$), 7.12 (d, 2H, *J* 6.8, 2H, Ph), 7.39 (s, 1H, CH), 7.61 (d, *J* 6.8, 2H, Ph). $\delta_C$ (100 MHz, $CDCl_3$) 56.3 ($CH_3$), 94.2 ($CH_2$), 117.0 (C4), 125.1, 128.5, 134.9, 160.5 (6C, Ar), 172.8 (C5), 215.2 (CS). $\nu_{max}/cm^{-1}$ 2962, 1512, 1456, 1262, 1159, 1097, 1034, 884, 666. *m/z* (HRMS-ESI$^+$) $[M+H]^+$ Anal. Calc. for $C_{11}H_{11}O_2S_3$: 270.9917. Found 270.9917.

### *5-(4-(Methoxymethoxy)-3,5-dimethylphenyl)-3*H*-1,2-dithiole-3-thione* ***6b***

The title compound was prepared by the representative procedure starting from 1-(4-(methoxymethoxy)-3,5-dimethylphenyl)ethanone (**5b**). **6b** was obtained as an orange solid (777 mg, 50%). mp 91–96°C. $\delta_H$ (500 MHz, $CDCl_3$) 2.34 (s, 6H, Me × 2), 3.62 (s, 3H, $CH_3$), 5.01 (s, 1H, $CH_2$), 7.32 (s, 2H, Ar), 7.37 (s, 1H, CH). $\delta_C$ (125 MHz, $CDCl_3$) 17.0 ($CH_3$), 57.5 ($CH_3$), 99.1 ($CH_2$), 127.4 (C4), 127.5, 132.8, 135.3, 158.6 (6C, Ar), 172.9 (C5), 215.3 (CS). $\nu_{max}/cm^{-1}$ 2951, 2923, 1509, 1473, 1272, 1061, 957, 665. *m/z* (HRMS-ESI$^+$) $[M+H]^+$ Anal. Calc. for $C_{13}H_{15}O_2S_3$: 299.0229. Found 299.0227.

### *5-(3,5-Diethylphenyl-4-(methoxymethoxy))-3*H*-1,2-dithiole-3-thione* ***6c***

The title compound was prepared by the representative procedure starting from 1-(4-(methoxymethoxy)-3,5-diethylphenyl)ethanone (**5c**). **6c** was obtained as an orange solid (160 mg, 17%). mp 65–67°C. $\delta_H$ (500 MHz, $CDCl_3$) 1.26 (t, *J* 7.5, 6H, $CH_3$ × 2), 2.75 (q, 4H, *J* 7.5, $CH_2$), 3.62 (s, 3H, $CH_3$), 4.99 (s, 2H, $CH_2$), 7.36 (s, 2H, Ar), 7.41 (s, 1H, CH). $\delta_C$ (125 MHz, $CDCl_3$) 14.5 ($CH_3$), 23.4 ($CH_2$), 57.5 ($CH_3$), 99.9 ($CH_2$), 125.8 (C4), 127.9, 135.4, 138.9, 157.8 (6C, Ar), 173.3 (C5), 215.3 (CS). $\nu_{max}/cm^{-1}$ 2966, 2876, 1511, 1458, 1269, 957. *m/z* (HRMS-ESI$^+$) $[M+H]^+$ Anal. Calc. for $C_{15}H_{19}O_2S_3$: 327.0542. Found 327.0545.

### *5-(3,5-Diisopropyl-4-(methoxymethoxy)phenyl)-3*H*-1,2-dithiole-3-thione* ***6d***

The title compound was prepared by the representative procedure starting from 1-(3,5-diisopropyl-4-(methoxymethoxy)phenyl) ethanone (**5d**). **6d** was obtained as an orange solid (1.30 g, 70%). mp 71–72°C. $\delta_H$ (400 MHz, $CDCl_3$) 1.25 (d, *J* 7, 12H, $CH(CH_3)_2$ × 2), 3.37 (septet, *J* 7.0, 2H, $(CH_3)_2CH$ × 2), 3.62 (s, 3H, $OCH_3$), 4.97 (s, 2H, $OCH_2$), 7.38 (s, 2H, Ar), 7.43 (s, 1H, CH). $\delta_C$ (100 MHz, $CDCl_3$) 23.7 ($CH_3$), 27.0 ($CH(CH_3)_2$), 57.5 ($OCH_3$), 100.5 ($CH_2$), 123.1 (C4), 128.2, 135.5, 143.7, 156.0 (6C, Ar), 173.6 (C5), 215.3 (CS). $\nu_{max}/cm^{-1}$ 2962, 1512, 1456, 1262, 1159, 1097, 1034, 884, 666. *m/z* (HRMS-ESI$^+$) $[M+H]^+$ Anal. Calc. for $C_{17}H_{23}O_2S_3$: 355.0855. Found 355.0853. (Anal. Calc. for $C_{17}H_{22}O_2S_3$: C 58.02, H 5.84, S 30.98. Found C 58.06, H 5.79, S 31.04%.)

### *Representative Procedure for the Deprotection of 3*H*-1,2-Dithiole-3-thione*

A mixture of the methoxymethyl 3*H*-1,2-dithiole-3-thione (1.00 mmol) and TFA (2.4 mL) in dichloromethane (12 mL) was stirred at rt for 2 h. The solvent was evaporated and the residue recrystallized from EtOAc/petrol to afford the hydroxyl 3*H*-1,2-dithiole-3-thione.

### *5-(4-Hydroxyphenyl)-3*H*-1,2-dithiole-3-thione* ***7a1***

The title compound was prepared by the representative procedure starting from 5-(4-(methoxymethoxy))-3*H*-1,2-dithiole-3-thione (**6a**). **7a1** was obtained as a brown solid (500 mg, 60%). mp 188–189°C (lit.[18] 192–193°C). $\delta_H$ (400 MHz, [$D_6$]DMSO) 6.84 (d, *J* 8.8, 2H, Ar), 7.65 (s, 1H, CH), 7.73 (d, *J* 8.8, 2H, Ar), 10.49 (bs, 1H, OH).

### *5-(4-Hydroxy-3,5-dimethylphenyl)-3*H*-1,2-dithiole-3-thione* ***7b1***

The title compound was prepared by the representative procedure starting from 5-(4-(methoxymethoxy)-3,5-dimethylphenyl)-3*H*-1,2-dithiole-3-thione (**6b**). **7b1** was obtained as a brown solid (250 mg, 58%). mp 222–223°C. $\delta_H$ (500 MHz, [$D_6$]DMSO) 2.20 (s, 6H, Me × 2), 7.53 (s, 2H, Ar) 7.66 (s, 1H, CH), 9.33 (s, 1H, OH). $\delta_C$ (100 MHz, [$D_6$]DMSO) 16.4 ($CH_3$), 122.1 (C4), 125.4, 127.5, 133.3, 157.9 (6C, Ar), 174.7 (C5), 214.1 (CS). $\nu_{max}/cm^{-1}$ 3438, 1569, 1500, 1295, 1165, 1077, 940, 696. *m/z* (HRMS-ESI$^-$) $[M-H]^-$ Anal. Calc. for $C_{11}H_9OS_3$: 252.9821. Found 252.9818.

### *5-(3,5-Diethylphenyl-4-hydroxy)-3*H*-1,2-dithiole-3-thione* ***7c1***

The title compound was prepared by the representative procedure starting from 5-(3,5-diethylphenyl-4-(methoxymethoxy))-3*H*-1,2-dithiole-3-thione (**6c**). **7c1** was obtained as a dark orange solid (45 mg, 33%). mp 110–113°C. $\delta_H$ (400 MHz, [$D_6$]DMSO) 1.14 (t, *J* 7.5, 6H, $CH_3$ × 2), 2.63 (q, *J* 7.5, 4H, $CH_2$ × 2), 7.50 (s, 2H, Ar), 7.72 (s, 1H, CH), 9.24 (s, 1H, OH). $\delta_C$ (100 MHz, [$D_6$]DMSO) 14.2 ($CH_3$), 22.8 ($CH_2$), 122.2 (C4), 126.0, 131.7, 133.5, 156.9 (6C, Ar), 174.9 (C5), 214.2 (CS). $\nu_{max}/cm^{-1}$ 3333, 1592, 1505, 1455, 1273, 1027, 979. *m/z* (HRMS-ESI$^-$) $[M-H]^-$ Anal. Calc. for $C_{13}H_{15}OS_3$: 283.0280. Found 283.0093.

### *5-(4-Hydroxy-3,5-diisopropylphenyl)-3*H*-1,2-dithiole-3-thione* ***7d1***

The title compound was prepared by the representative procedure starting from 5-(3,5-diisopropyl-4-(methoxymethoxy)phenyl)-3*H*-1,2-dithiole-3-thione (**6d**). **7d1** was obtained as a brown solid (606 mg, 77%). mp 154–155°C. $\delta_H$ (400 MHz, [$D_6$]DMSO) 1.29 (s, 12H, $CH(CH_3)_2$ × 2), 3.10 (septet, *J* 6.4, 2H, $CH(CH_3)_2$), 5.48 (bs, 1H, OH), 7.35 (s, 2H, Ar), 7.43 (s, 1H, CH). $\delta_C$ (100 MHz, [$D_6$]DMSO) 22.5 ($CH_3$), 27.2 (CH), 122.8 (C4), 124.1, 134.4, 135.1, 154.2 (6C, Ar), 174.5 (C5), 214.8 (CS). $\nu_{max}/cm^{-1}$ 3197, 2958, 1594, 1507, 1286, 1030, 771. *m/z* (HRMS-ESI$^+$) $[M+H]^+$ Anal. Calc. for $C_{15}H_{19}OS_3$: 311.0593. Found 311.0592. (Anal. Calc. for $C_{15}H_{18}OS_3$: C 58.02, H 5.84, S 30.98. Found C 58.06, H 5.84, S 31.04%.)

### *Representative Procedure for the Hydrolysis of 3*H*-1,2-Dithiole-3-thiones*

A hot solution of the 3*H*-1,2-dithiole (1 mmol) in acetic acid (5 mL) was added to a hot solution of $Hg(OAc)_2$ (2 mmol) in acetic acid (5 mL) and the reaction mixture was heated under reflux for 1.5 h. The reaction was cooled to rt and filtered. The filtrate was concentrated and the residue was purified by flash chromatography (10% EtOAc/petrol) and recrystallized from EtOAc/petrol, unless otherwise stated, to afford the 3*H*-1,2-dithiole-3-one.

### *5-(4-Methoxy-3,5-dimethylphenyl)-3*H*-1,2-dithiol-3-one* ***14b2***

The title compound was prepared by the representative procedure starting from 5-(4-methoxy-3,5-dimethylphenyl)-3*H*-1,2-dithiole-3-thione (**7b2**). **14b2** obtained as a colourless solid (108 mg, 48%). mp 95–96°C. $\delta_H$ (500 MHz, $CDCl_3$) 2.34 (s, 6H, $CH_3 \times 2$), 3.77 (s, 3H, $OCH_3$), 6.76 (s, 1H, C4–H), 7.29 (s, 2H, Ar). $\delta_C$ (125 MHz, $CDCl_3$) 16.2 (Ar*C*$H_3$), 59.8 ($OCH_3$), 117.0 (C4), 127.1, 128.1, 132.3, 160.2 (6C, Ar), 170.2 (C5), 194.1 (CO). $\nu_{max}/cm^{-1}$ 2924, 1659, 1546, 1237, 1001, 859. *m/z* (HRMS-ESI$^+$) $[M+H]^+$ Anal. Calc. for $C_{12}H_{13}O_2S_2$: 253.0351. Found 253.0351. (Anal. Calc. for $C_{12}H_{12}O_2S_2$: C 57.11, H 4.79. Found C 57.51, H 4.81%.)

### *5-(3,5-Di-(*tert*-butyl)-4-hydroxyphenyl)-3*H*-1,2-dithiol-3-one* ***14e1***

The title compound was prepared by the representative procedure starting from 5-(3,5-di-(*tert*-butyl)-4-hydroxyphenyl)-3*H*-1,2-dithiole-3-thione (**7e1**). The residue was recrystallized from ethyl acetate to give **14e1** as a light brown solid (450 mg, 47%). mp 223–226°C. $\delta_H$ (500 MHz, $CDCl_3$) 1.47 (s, 18H, $C(CH_3)_3 \times 2$), 5.68 (s, 1H, OH), 6.75 (s, 1H, C4–H), 7.44 (s, 2H, Ar). $\delta_C$ (125 MHz, $CDCl_3$) 30.0 (*C*$(CH_3)_3$), 34.5 (C(*C*$H_3)_3$), 116.0 (C4), 123.7, 124.2, 136.9, 157.2 (6C, Ar), 171.7 (C5), 194.3 (CO). $\nu_{max}/cm^{-1}$ 3514, 2954, 1632, 1549, 1116, 888, 734. *m/z* (HRMS-ESI$^+$) $[M+H]^+$ Anal. Calc. for $C_{17}H_{23}O_2S_2$: 323.1134. Found 323.1134. (Anal. Calc. for $C_{17}H_{22}O_2S_2$: C 63.32, H 7.17. Found C 63.83, H 7.17%.)

### *5-(3,5-Di-(*tert*-butyl)-4-methoxyphenyl)-3*H*-1,2-dithiol-3-one* ***14e2***

The title compound was prepared by the representative procedure starting from 5-(3,5-di-(*tert*-butyl)-4-methoxyphenyl)-3*H*-1,2-dithiole-3-thione (**7e2**). **14e2** was obtained as a light brown solid (650 mg, 59%). mp 109–112°C. $\delta_H$ (500 MHz, $CDCl_3$) 1.46 (s, 18H, $C(CH_3)_3 \times 2$), 3.74 (s, 3H, $OCH_3$), 6.77 (s, 1H, C4–H), 7.50 (s, 2H, Ar). $\delta_C$ (125 MHz, $CDCl_3$) 31.8 (*C*$(CH_3)_3$), 36.0 (C(*C*$H_3)_3$), 64.1 ($OCH_3$), 116.9 (C4), 124.9, 127.2, 145.3, 162.9 (6C, Ar), 171.2 (C5), 194.1 (CO). $\nu_{max}/cm^{-1}$ 2959, 1658, 1545, 1407, 1215, 1006, 887. *m/z* (HRMS-ESI$^+$) $[M+H]^+$ Anal. Calc. for $C_{18}H_{25}O_2S_2$: 337.1290. Found 337.1288.

### *5-(3,5-Di-(*tert*-butyl)-4-hydroxyphenyl)-4-methyl-3*H*-1,2-dithiol-3-one* ***15e1***

The title compound was prepared by the representative procedure starting from 5-(3,5-di-(*tert*-butyl)-4-hydroxyphenyl)-4-methyl-3*H*-1,2-dithiole-3-thione (**13e1**). **15e1** was obtained as a colourless solid (257 mg, 61%). mp 189–190°C. $\delta_H$ (400 MHz, $CDCl_3$) 1.47 (s, 18H, $(C(CH_3)_3 \times 2)$, 2.06 (s, 3H, C4–$CH_3$), 5.56 (s, 1H, OH), 7.26 (s, 2H, Ar). $\delta_C$ (100 MHz, $CDCl_3$) 14.1 (C4–*C*$H_3$), 30.1 (*C*$(CH_3)_3$), 34.5 (C(*C*$H_3)_3$), 125.2 (C4), 125.7, 136.6, 155.9 (6C, Ar), 164.3 (C5), 195.4 (CO). $\nu_{max}/cm^{-1}$ 3532, 2951, 1623, 1556, 1432, 1113, 950, 658. *m/z* (HRMS-ESI$^+$) $[M+H]^+$ Anal. Calc. for $C_{18}H_{25}O_2S_2$: 337.1290. Found 337.1292. (Anal. Calc. for $C_{18}H_{24}O_2S_2$: C 64.25, H 7.19. Found C 64.31, H 7.22%.)

### *5-(3,5-Di-(*tert*-butyl)-4-methoxyphenyl)-4-methyl-3*H*-1,2-dithiol-3-one* ***15e2***

The title compound was prepared by the representative procedure starting from 5-(3,5-di-(*tert*-butyl)-4-methoxyphenyl)-4-methyl-3*H*-1,2-dithiole-3-thione (**13e2**). **15e2** was obtained as a colourless solid (370 mg, 79%). mp 112–114°C. $\delta_H$ (400 MHz, $CDCl_3$) 1.45 (s, 18H, $C(CH_3)_3 \times 2$), 2.06 (s, 3H, C4–$CH_3$), 3.75 (s, 3H, $OCH_3$), 7.32 (s, 2H, Ar). $\delta_C$ (100 MHz, $CDCl_3$) 14.1 (C4–*C*$H_3$), 31.9 (*C*$(CH_3)_3$), 36.0 (C(*C*$H_3)_3$), 64.4 ($OCH_3$), 126.2 (C4), 126.6, 128.3, 144.8, 161.5 (6C, Ar), 163.8 (C5), 195.3 (CO). $\nu_{max}/cm^{-1}$ 2961, 2870, 1590, 1032. *m/z* (HRMS-ESI$^+$) $[M+H]^+$ Anal. Calc. for $C_{19}H_{27}O_2S_2$: 351.1447. Found 351.1447.

### *5-(3,5-Di-(*tert*-butyl)-4-ethoxyphenyl)-4-methyl-3*H*-1,2-dithiol-3-one* ***15e3***

The title compound was prepared by the representative procedure starting from 5-(3,5-di-(*tert*-butyl)-4-ethoxyphenyl)-4-methyl-3*H*-1,2-dithiole-3-thione (**13e3**). **15e3** was obtained as a colourless solid and was recrystallized from hot light petroleum (380 mg, 50%). mp 102°C. $\delta_H$ (500 MHz, $CDCl_3$) 1.43–1.45 (m, 21H, $C(CH_3)_3 \times 2$, $CH_2CH_3$), 2.06 (s, 3H, C4–$CH_3$), 3.82 (q, *J* 7.0, 2H, $CH_2$), 7.32 (s, 2H, Ar). $\delta_C$ (125 MHz, $CDCl_3$) 14.9, 16.8, 17.0 (3C, 4C–*C*$H_3$, $CH_2CH_3$, *C*$(CH_3)_3$), 72.1 ($OCH_2$), 126.1 (C4), 126.7, 128.2, 144.8, 160.0 (6C, Ar), 163.8 (C5), 195.3 (CO). $\nu_{max}/cm^{-1}$ 2956, 1522, 1425, 1216, 731. *m/z* (HRMS-ESI$^+$) $[M+H]^+$ Anal. Calc. for $C_{20}H_{29}O_2S_2$: 365.1603. Found 365.1606.

### *Hydrogen Sulfide Release*

A solution of dithiolethione **7e2** (5 mg) in DMSO (200 μL) and phosphate buffer (50 μL, 100 mM, pH 7.4) was heated at 120°C in a paraffin oil bath. The reaction was assayed at 6, 24, 30, and 48 h by taking an aliquot (20 μL) of the reaction mixture and diluting with methanol (20 μL) followed by a 25-μL injection into the HPLC. The disappearance of the dithiolethione **7e2** and formation of 1,2-dithiole-3-one **14e2** was monitored using an Agilent 1100 series HPLC fitted with a Supelco Discovery C18 15 cm × 4.6 mm column with particle size of 5 μM. Samples were eluted with a 0–100% gradient of buffer B in buffer A over 25 min with flow rate 1 mL $min^{-1}$ (buffer A 0.1% TFA/water; buffer B 0.1% TFA/acetonitrile). Compounds were monitored at 275 nm. The identity of the 1,2-dithiole-3-one **14e2** was confirmed by comparison with the retention time and mass spectrum of the authentic synthesized compound.

### *COX-1 and COX-2 Inhibition Assay*

Aliquots of a microsomal preparation of human platelets or of insect Sf21 cells expressing human COX-2 were pre-incubated with dilutions of the compounds in 1% DMSO for 15 min at 37°C. The enzyme reaction was started by the addition of arachidonic acid (100 μM for COX-1 or 0.3 μM for COX-2) and incubated for 15 min at 37°C. The reaction was then stopped with 15 μL of 0.2 M HCl and the amount of prostaglandin $E_2$ formed was quantitated using a validated, commercially available enzyme-linked immunoassay kit.

## Accessory Publication

Experimental details for the preparation of compounds **5b**–**e**, **9b2**, **9b3**, **9c2**, **9d2**, **9d3**, **9e2**, and **9e3**, and NMR spectra for compounds **5b**–**d**, **6b**, **7b1**, **7c1**, **7c2**, **7e3**, **9c2**, **9d2**, **9d3**, **10b2**, **10b3**, **10c3**, **10d2**, **10d3**, **10e3**, **11**, **12e2**, **12e3**, **14e2**, **15e2** are available on the Journal's website.

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