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Original article

Chemotherapy of leishmaniasis part II: synthesis and bioevaluation of substituted arylketene dithioacetals as antileishmanial agents

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Abstract

Some novel aryl substituted ketene dithioacetals **6** (**a**–**d**), **9** (**a**–**c**) and **10** (**a**–**c**) have been synthesized using novel synthetic methods. The compounds were screened against *Leishmania donovani* in hamsters for their activity profile. Some of the compounds inhibited 50–65% parasite growth at 50 mg $kg^{-1} \times 5$ days.

Keywords: Ketene thioacetals; Leishmaniasis; In vivo studies

1. Introduction

Leishmaniasis is an infection caused by protozoa of the genus *Leishmania* presenting several forms of the disease such as cutaneous (CL), mucocutaneous (MCL) and visceral leishmaniasis (VL). The later form can be fatal if untreated. The disease is endemic in some tropical areas of the world and in underdeveloped countries, directly affecting about two million people per annum, with approximately 350 million people under the risk of contracting the disease worldwide [1,2]. The incidence for new cases of leishmaniasis is increasing everyday and the disease is currently emerging as a common and serious opportunistic infection in humans carrying immunodeficiency virus (HIV) [3]. The current treatment for the leishmaniasis is based on the pentavalent antimonials, such as sodium stibogluconate (pentostam) and meglumine antimoniate (glucantime). The long course of treatment with antimonials leads to the accumulation of the drug in the liver and spleen. The lengthy treatment, therefore, often causes side effects such as myalgia, pancreatitis, cardiac arrythmia and hepatitis leading to the reduction or cessation of treatment. Pentamidine is a second line of drug for the treatment of VL in patients who failed to respond to antimony therapy [4]. Although pentamidine is less toxic than antimonials but still it is not free from side effects such as hypoglycemia, diabetes, nephrotoxicity and pain at site of injection. Antibiotic amphoterecin-B is the second line of drug for the treatment of VL. It shows better response even in cases resistant to the antimonials and diamidines [5], but it is quite toxic and produces nephrotoxicity and cardiotoxicity [6]. The development of new antileishmanial agents is extremely important, considering the high toxicity of the existing clinical drugs.

In view of the high toxicity associated with the existing antileishmanial drugs, efforts are being made to search for new molecules from natural sources, which can act as a new lead in the chemotherapy of *Leishmania*. In this endeavour, diarylheptanoids [7], oxygenated abietanes [8], diterpene quinones [9,10], and chalcones [11] are showing promise in the in vitro antileishmanial studies. Curcumin **1** isolated from *Curcuma longa* Linn is not only showing promise as anticancer agent [7a] but it is showing antileishmanial activity profile in the in vitro studies [7b,12]. Exhaustive analoging of curcumin has generated some interesting results [13]. Lichochalcone **2** isolated from *Glycerrhiza* spp. was first reported for its antibacterial activity [14] is also showing promising antileishmanial activity [15]. Chemical library generated on the basis of Lichochalcone as a lead molecule is showing promise in the in vitro antileishmanial studies [11a].

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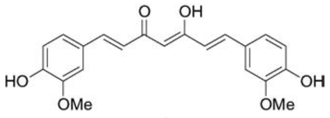
Phenolic diketone **3** isolated from *Zingiber officinale* [16] is a structural mimic of **1** and **2** and shows radical scavenging activities quite comparable to Curcumin **1**. In continuation of our efforts to generate natural product based novel antileishmanial agents [17] coupled with encouraging results on **1**, **2**, and **3**, we synthesized some novel arylketene dithioacetals and evaluated for their in vivo antileishmanial activity profile and the results are reported in this paper.



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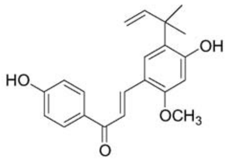

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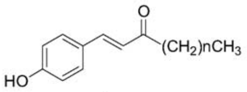

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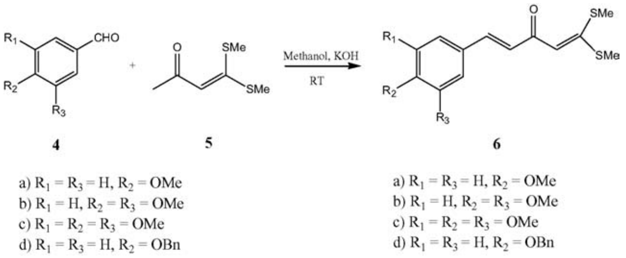
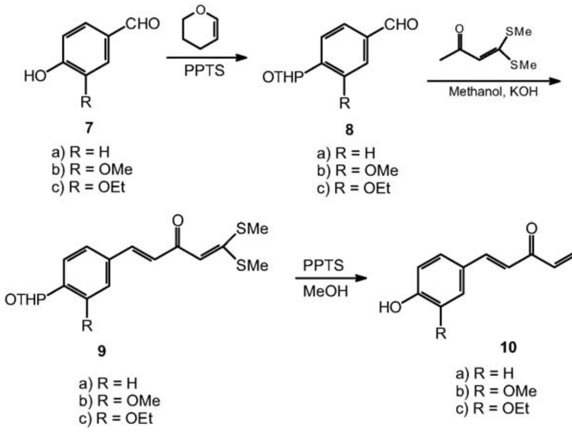
2. Chemistry

α-Oxoketene dithioacetals of aromatic substrates are very useful synthons in the synthesis of variety of heterocyclic and carbocyclic compounds [18]. However, they have been not fully exploited for their biological activity profile.

α-Oxoketene dithioacetals **6** (**a–d**) were prepared as shown in Scheme 1. The reaction of *p*-methoxybenzaldehyde **4a** with acetone based ketene dithioacetal **5** furnished **6a** as a yellow crystalline solid, melting at 110–11 °C. The structure of **6a** was assigned on the basis of ^{1}H and ^{13}C NMR data. Similarly, the reaction of substituted benzaldehydes **4** (**b–d**) with ketene dithioacetal **5** in the presence of methanolic potassium hydroxide furnished ketene dithioacetals **6** (**b–d**) in good yields as yellow crystalline solids. However, these conditions did not suit for the phenolic aldehydes **7** (**a–c**). The problem was circumvented by protecting them as tetahydropyranyl ethers as shown in Scheme 2. The reactions of phenolic aldehydes **7** (**a–c**) with dihydropyran in the presence of catalytic pyridinium *p*-toluenesulfonate (PPTS) furnished tetrahydropyranyl ethers **8** (**a–c**) in near quantitative yield. The reaction of tetrahydropyranyl ethers with dithiomethylketene acetal **5** in the presence of ethanolic potassium hydroxide furnished dithiomethylketene acetals **9** (**a–c**) in good yields. The reaction of tetrahydropyranyl ethers **9** (**a–c**) with pyridinium-*p*-toluenesulfonate (ppts) in methanol furnished dithiomethylketene acetals **10** (**a–c**) in quantitative yield. The compounds were fully analyzed using analytical techniques.



Scheme 1.



Scheme 2.

3. Biological activities

The in vivo leishmanicidal activity was determined in golden hamsters (*Mesocricotus aurctus*) infected with HOM/IN/80/DD8 strain of *Leishmania donovani* obtained through the courtesy of P.C.C. Garnham, Imperial College, London (UK).

For in vivo evaluation of compounds, the method of Beveridge [19] as modified by Bhatnagar et al. [20]; Gupta et al. [21] was employed. Male hamsters weighing 35–40 gm were infected with 1×10^7 amastigotes and the intensity of infection after 20 days was assessed by spleen biopsy. Animals with 2^+ infections (5–15 amastigote/100 cell nuclei) were selected for screening the compounds. The infected animals were randomized in to several groups on the basis of their parasitic burdens. Usually four to six animals were used for each compound and the same numbers were kept as untreated controls. The drug treatment was given intraperitoneally for five consecutive days at 50 mg kg^{-1} dose level. To assess the effect of test compounds spleen biopsies were performed on each animal after 7 and 28 days of last drug administration and amastigote counts were assessed by Giemsa staining. The percentage inhibition in amastigote multiplication was calculated using the following formula.

$$\text{P.I.} = 100 - \frac{\text{ANAT} \times 100}{\text{INAT} \times \text{TIUC}}$$

P.I. = Percent inhibition of amastigote multiplication.
ANAT = Actual no. of amastigotes in treated animal.
INAT = Initial no. of amastigotes in treated animals, and

TIUC = Times increase of parasites in untreated control animals.

4. Results and discussion

The leishmanicidal activity of various compounds **6** (**a–d**), **9** (**a–c**) and **10** (**a–c**) at 50 mg kg^{-1} × 5 days dose has been presented in Table 1. The nature of substitution at the *para* position of the aromatic ring has been found to have a profound role in the biological profile [22]. For instance, *p*-methoxy substitution as in **6a** resulted in complete loss of activity on day 28. To the contrary, 3,4-dimethoxy substitution as in **6b** and 3,4,5-trimethoxy substitution as in **6c** made the compounds less active as the compounds on day 7 were inactive but on day 28 they were potentially active. However, 3,4-dimethoxy substitution as in **6b** and 3,4,5-trimethoxy substitution as in **6c** are inactive at day 7 but are active at day 28 indicating that they might be acting through immunostimulation. Surprisingly *p*-benzyloxy substitution as in **6d** showed 65% inhibition on day 7. The activity of **6d** is in line with the reports of Gilbert et al. [11b] that *p*-benzyloxy and *p*-*n*-hexyloxy substitution has a substantial role to play in comparison to free phenols.

We anticipated better profile in the disubstituted phenolic compounds as **9** (**a–c**) and **10** (**a–c**) because they are the mimics of bioactive natural product, curcumin **1**. However, these compounds showed only marginal leishmanicidal activity.

5. Experimental protocol

The reported melting points (m.p., °C) are the uncorrected ones. The infrared spectra were recorded in KBr on a Perkin Elmer model 881. NMR spectra were obtained in $CDCl_3$ (with Me_4Si internal standard, Aldrich) and are reported in ppm downfield from Me_4Si. Proton, carbon NMR spectra were recorded on Bruker Advance DRx 2000 instrument. Electron impact (EI) mass spectra were recorded on a Jeol JMS-D-300 spectrometer with the ionization potential of 70 eV. Elemental analysis was carried out on a Carlo–Erba EA 1108 instrument.

Table 1
Antileishmanial activity of compounds against *L. donovani* in hamsters

Serial number	Compound number	Dose (mg kg^{-1})	In vivo % Inhibition	
			Day 7 PT	Day 28 PT
1	6a	50	27	–
2	6b	50	13	56
3	6c	50	18	66
4	6d	50	65	–
5	9a	50	–	–
6	9b	50	–	–
7	9c	50	30	–
8	10a	50	28	–
9	10b	50	21	–
10	10c	50	50	–
11	SSG	50	100	–

PT = post treatment.
SSG = Reference drug (sodium stibogluconate).

5.1. *5-(4-Methoxyphenyl)-1,1-bis(methylthio)-penta-1,4-dien-3-one (**6a**)*

To a solution of 1,1-bis(methylthio)-pent-1-en-3-one (**5**) (1.62 gm, 10 mmol) in methanol (40 ml) was added aqueous KOH solution (1.12 gm, 20 mmol in 10 ml water) and stirred it for 15 min at room temperature. To the above reaction mixture was added *p*-methoxybenzaldehyde (1.36 gm, 10 mmol) and stirred the reaction mixture for 12 h at room temperature. Solvent was removed in vacuo poured into water and extracted it with dichloromethane (50 ml × 3). The combined extract was washed with water (2 × 100 ml), brine (2 × 50 ml) dried (Na_2SO_4) and solvent was removed in vacuo. The crude product was purified by column chromatography (SiO_2, 60–120 mesh) to get yellow crystalline solid (1.6 gm, 57%); m.p. 110–111 °C; IR (KBr, cm^{-1}) 1640, 1592, 1474; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.45 (s, 6H), 3.75 (s, 3H), 6.20 (s, 1H), 6.60 (d, J = 16.00 Hz, 1H), 6.90 (d, J = 8.00 Hz, 1H), 7.55 (d, J = 8.00 Hz, 1H), 7.60 (d, J = 16.00 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 15.48 (q), 17.66 (q), 55.76 (q), 113.987 (d), 2 × 114.68 (d), 125.596 (d), 128.38 (s), 2 × 130.14 (d), 141.34 (d), 161.53 (s), 164.89 (s), 184.45 (s); MS (*m/e*) 280 (M^+), 265 (M^+-CH_3). Anal. Calcd. for $C_{14}H_{16}O_2S_2$: C, 59.96; H, 5.75; S, 22.86. Found: C, 59.16; H, 5.12; S, 23.06%.

5.2. *5-(3,4-Dimethoxyphenyl)-1,1-bis(methylthio)-penta-1,4-dien-3-one (**6b**)*

To a solution of **5** (1.62 gm, 10 mmol) in methanol (40 ml) was added 3,4-dimethoxybenzaldehyde (1.66 gm, 10 mmol) followed by aqueous KOH solution (1.12 gm, 20 mmol in 10 ml water) and the resulting reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated in vacuo poured into water and extracted it with dichloromethane (50 ml × 3). The combined extract was washed with water (2 × 100 ml), brine (2 × 50 ml) dried (Na_2SO_4) and solvent was removed in vacuo. The crude product was column chromatographed (SiO_2, 60–120 mesh) elution with 20% ethyl acetate in hexane furnished **6b** as a yellow crystalline solid (1.77 gm, 57.09%); m.p. 112–113 °C; IR (KBr, cm^{-1}) 1640, 1580, 1466; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.50 (s, 6H), 3.90 (s, 6H), 6.26 (s, 1H), 6.65 (d, J = 16.00 Hz, 1H), 6.85 (d, 1H), 7.10 (s, 1H), 7.15 (d, 1H), 7.55 (d, J = 16.00 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 15.46 (q), 17.65 (q), 56.29 (q), 56.34 (q), 110.19 (d), 111.53 (d), 113.88 (d), 123.06 (d), 125.82 (d), 128.65 (s), 141.57 (d), 149.57 (s), 151.28 (s), 165.02 (s), 184.34 (s); MS (*m/e*) 311 (M^+ + 1), 295 (M^+-CH_3). Anal. Calcd. for $C_{15}H_{18}O_3S_2$: C, 58.03; H, 5.04; S, 20.65. Found: C, 57.44; H, 5.23; S, 20.47%.

5.3. *5-(3,4,5-Trimethoxyphenyl)-1,1-bis(methylthio)-penta-1,4-dien-3-one (**6c**)*

To a solution of **5** (1.62 gm, 10 mmol) in methanol (40 ml) was added 3,4,5-trimethoxybenzaldehyde (1.96 gm, 10 mmol) followed by aqueous KOH solution (1.12 gm, 20 mmol in 10 ml water) and the resulting reaction mixture was stirred at room temperature for 12 h. It was concentrated in vacuo, poured into water (100 ml) and extracted with dichloromethane (50 ml × 3). The combined extract was washed with water (100 ml × 2), brine (2 × 50 ml), dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was column chromatographed (SiO_2, 60–120 mesh). Elution with 25% ethyl acetate in hexane furnished **6c** as a pale yellow crystalline solid (1.92 gm, 56.47%); m.p. 130–131 °C; IR (KBr, cm^{-1}) 1704, 1600, 1488; ^1H NMR (200 MHz, $CDCl_3$) δ 2.50 (s, 6H), 3.75 (s, 3H), 3.80 (s, 6H), 6.20 (s, 1H), 6.65 (d, J = 16.00 Hz, 1H), 6.70 (s, 2H), 7.55 (d, J = 16.00 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 15.49 (q), 17.65 (q), 2 × 56.53 (q), 61.19 (q), 105.17 (d), 105.67 (d), 113.65 (d), 127.13 (d), 131.17 (s), 140.22 (s), 141.50 (d), 2 × 153.75 (s), 165.77 (s), 184.06 (s); MS (*m/e*) 340 (M^+), 324 (M^+-CH_3). Anal. Calcd. for $C_{16}H_{20}O_4S_2$: C, 56.45; H, 5.92; S, 18.83. Found: C, 57.1; H, 6.21; S, 19.36%.

5.4. 5-(4-Benzyloxyphenyl)-1,1-bis(methylthio)-penta-1,4-dien-3-one (*6d*)

To a solution of **5** (1.62 gm, 10 mmol) in methanol (40 ml) was added aqueous KOH solution (1.12 gm, 20 mmol in 10 ml water) and stirred it for 15 min. To the above reaction mixture was added *p*-benzyloxybenzaldehyde (2.12 gm, 10 mmol) and stirred the reaction mixture for 12 h at room temperature. Solvent was removed in vacuo poured into water (100 ml) and extracted it with dichloromethane (50 ml × 3). The combined extract was washed with water (2 × 100 ml) brine solution (2 × 50 ml) dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product thus obtained was chromatographed (SiO_2, 60–120 mesh). Elution with 20% ethyl acetate in hexane furnished **6d** as a yellow crystalline solid (0.8 gm, 45%); m.p. 115–117 °C; IR (KBr, cm^{-1}) 1643, 1592, 1485, 1250, 1172, 1128; ^1H NMR (200 MHz, $CDCl_3$) δ 2.48 (s, 6H), 5.10 (s, 2H), 6.20 (s, 1H), 6.70 (d, J = 16.00 Hz, 1H), 7.00 (d, 1H), 7.60 (m, 9H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 15.50 (q), 17.67 (q), 70.51 (t), 114.05 (d), 2 × 115.62 (d), 125.76 (d), 2 × 127.86 (d), 128.51 (d), 2 × 128.68 (d), 129.04 (s), 2 × 130.17 (d), 136.98 (s), 141.33 (d), 160.73 (s), 164.91 (s), 184.45 (s); MS (*m/e*) 357 (M^+ + 1), 266 (M^+-benzyl). Anal. Calcd. for $C_{20}H_{20}O_2S_2$: C, 67.38; H, 5.84; S, 17.98. Found: C, 67.35; H, 5.31; S, 16.98%.

5.5. 5-[(4-Tetrahydropyran-2-yloxy)-phenyl]-1,1-bis(methylthio)-penta-1,4-dien-3-one (*9a*)

To a solution of *p*-hydroxybenzaldehyde (5.49 gm, 45 mmol) in dry dichloromethane (80 ml) was added ppts (0.36 gm) and dihydropyran (6.12 gm, 72 mmol) and stirred at room temperature for 5 h. The reaction mixture was taken up in separating funnel and washed with aqueous sodium carbonate solution (5 × 100 ml). Solvent was removed in vacuo to get **8a** in 90% yield. It was used for the next step without further purification.

To a solution of 1,1-bis(methylthio)-pent-1-en-3-one (2.43 gm, 15 mmol) in methanol (50 ml) was added **8a** (2.09 gm, 15 mmol) followed by aqueous KOH solution (1.65 gm, 30 mmol in 15 ml water) and the resulting reaction mixture was stirred at room temperature for 12 h. It was concentrated in vacuo, poured into water and extracted with dichloromethane (50 ml × 3). The combined extract was washed with water (3 × 75 ml), brine solution (2 × 50 ml), dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was purified by column chromatography (SiO_2, 60–120 mesh). Elution with 20% ethyl acetate in hexane furnished **9a** as a yellow crystalline solid (2.7 gm, 51%); m.p. 148–150 °C; IR (KBr, cm^{-1}) 2938, 1640, 1587, 1438, 1239, 1119; ^1H NMR (200 MHz, $CDCl_3$) δ 1.90 (m, 6H), 2.50 (s, 6H), 3.70 (m, 1H), 3.90 (m, 1H), 5.45 (m, 1H), 6.20 (s, 1H), 6.70 (d, J = 16.00 Hz, 1H), 7.05 (d, J = 8.00 Hz, 2H), 7.50 (d, J = 8.00 Hz, 2H), 7.60 (d, J = 16.00 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 15.49 (q), 17.65 (q), 19.01 (t), 25.52 (t), 30.61 (t), 62.42 (t), 96.61 (d), 114.03 (d), 2 × 130.00 (d), 141.39 (d), 159.01 (s), 164.83 (s) 184.48 (s); MS (*m/e*) 351 (M^+ + 1), 267 (M^+-THP). Anal. Calcd. for $C_{18}H_{22}O_3S_2$: C, 61.60; H, 6.32; S, 18.3. Found: C, 60.61; H, 6.06; S, 18.01%.

5.6. 5-(4-Hydroxyphenyl)-1,1-bis(methylthio)-penta-1,4-dien-3-one (*10a*)

To a solution of **9a** (0.35 gm, 1 mmol) in methanol (25 ml) was added ppts (0.02 gm, 0.1 mmol) and stirred it for 3 h at room temperature. Water (3–4 drops) was added to the above reaction mixture and further stirred for 3 h. Solvent was removed in vacuo, poured into water and extracted with dichloromethane (50 ml × 3). The combined extract was washed with aqueous sodium bicarbonate solution (5 × 50 ml). It was dried (Na_2SO_4), solvent was removed in vacuo. The crude product was chromatographed (SiO_2, 60–120 mesh). Elution with 20% ethylacetate in hexane furnished **10a** as a yellow crystalline solid (0.2 gm, 96%); m.p. 169–170 °C; IR (KBr cm^{-1}) 3447, 1600, 1559, 1465, 1237, 1140; ^1H NMR (200 MHz, $CDCl_3$): δ 2.51 (s, 6H), 5.80 (s, 1H), 6.20 (s, 1H), 6.70 (d, J = 16.00 Hz, 1H), 6.90 (d, J = 8.00 Hz, 2H), 7.50 (d, J = 8.00 Hz, 2H), 7.60 (d, J = 16.00 Hz, 1H); ^{13}C NMR (200 MHz, DMSO) δ 14.67 (q), 17.10 (q), 114.12 (d), 2 × 116.18 (d), 125.12 (d), 126.39 (s), 2 × 130.40 (d), 140.82 (d), 159.83 (s), 163.07 (s), 183.76 (s); MS (*m/e*) 267 (M^+ + 1); Anal. Calcd. for $C_{13}H_{14}O_2S_2$: C, 58.61; H, 5.29; S, 24.07. Found: C, 58.08; H, 4.70; S, 24.05%.

5.7. 5-(3-Methoxy-4-hydroxyphenyl)-1,1-bis(methylthio)-penta-1,4-dien-3-one (*10b*)

To a solution of vanillin (1.52 gm, 10 mmol) in dry dichloromethane (40 ml) was added dihydropyran (1.36 gm, 16 mmol) and ppts (0.08 gm, 1 mmol) and stirred it for 5 h at room temperature. The reaction mixture was taken up in separating funnel and washed with aqueous sodium carbonate solution (5 × 50 ml). It was dried (Na_2SO_4). Solvent was removed in vacuo to get **8b** as a thick liquid (1.89 gm).

To a solution of **5** (1.62 gm, 10 mmol) in methanol (40 ml) was added KOH solution (1.12 gm in 10 ml water) and stirred it for 15 min at room temperature followed by addition of **8b** (2.36 gm, 10 mmol) and the resulting reaction mixture was stirred for 12 h at room temperature. The solvent was removed in vacuo, poured into water and extracted with dichloromethane (3 × 50 ml). The combined extract was washed with water (2 × 100 ml), brine solution (2 × 50 ml) dried (Na_2SO_4). Solvent was removed in vacuo to get **9b** as a yellow thick liquid (1.82 gm).

The crude **9b** (0.95 gm) in methanol (25 ml) was treated with ppts (0.08 gm) and few drops of water and stirred the reaction mixture for 5 h at room temperature. The solvent was removed in vacuo, poured into water and extracted with dichloromethane (3 × 50 ml). The combined extract was washed with aqueous sodium carbonate (5 × 50 ml) dried (Na_2SO_4) and solvent was removed in vacuo. The crude product was chromatographed (SiO_2, 60–120 mesh). Elution with 20% ethyl acetate in hexane furnished **10b** as a yellow crystalline solid (0.612 gm, 83%); m.p. 153–154 °C; IR (KBr, cm^{-1}) 3432, 1638, 1572, 1480, 1273, 1127; ^1H NMR (200 MHz, $CDCl_3$) δ 2.51 (s, 3H), 2.52 (s, 3H), 3.94 (s, 3H), 5.85 (s, 1H), 6.25 (s, 1H), 6.70 (d, $J = 16.00$ Hz, 1H), 6.90 (d, $J = 8.00$ Hz, 1H), 7.10 (s, 1H), 7.10 (d, $J = 8.00$ Hz, 1H), 7.55 (d, $J = 16.00$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 15.49 (q), 17.68 (q), 56.37 (q), 110.10 (d), 113.84 (d), 115.19 (d), 123.31 (d), 125.51 (d), 128.19 (s), 141.86 (d), 147.23 (s), 148.20 (s), 165.14 (s), 184.48 (s); MS (*m*/*e*) 297 ($M^+ + 1$). Anal. Calcd. for $C_{14}H_{16}O_3S_2$: C, 56.73; H, 5.44; S, 21.63. Found: C, 56.46; H, 5.23; S, 22.89%.

5.8. 5-[3-Ethoxy-4-(tetrahydropyran-2-yloxy)-phenyl]-1,1-bis(methylthio)-penta-1,4-dien-3-one (*9c*)

To a solution of 3-ethoxy-4-hydroxybenzaldehyde (3.32 gm, 20 mmol) in dry dichloromethane (60 ml) was added dihydropyran (2.72 gm, 32 mmol), ppts (0.16 gm) and stirred it for 5 h at room temperature. The reaction mixture was taken up in separating funnel and washed with aqueous sodium carbonate solution (5 × 100 ml), dried (Na_2SO_4) and solvent was removed in vacuo. The crude product **8c** (4.32 gm) thus obtained was used for the next reaction.

To a solution of **5** (2.43 gm, 15 mmol) in methanol (60 ml) was added aqueous KOH solution (1.68 gm, 30 mmol in 15 ml water) and stirred it for 15 min at room temperature. To this reaction mixture was added **8c** from the above reaction and stirred at room temperature for 12 h. Solvent was removed in vacuo, poured into water and extracted with dichloromethane (3 × 100 ml). The combined extract was washed with water (3 × 100 ml), brine solution (2 × 50 ml) dried (Na_2SO_4) and solvent was removed in vacuo. The crude product was chromatographed (SiO_2, 60–120 mesh). Elution with 20% ethylacetate in hexane furnished **9c** as a crystalline solid (3.00 gm, 51%); m.p. 115–116 °C; IR (KBr cm^{-1}) 2958, 1644, 1582, 1490, 1431, 1253, 1127, 962; ^1H NMR (200 MHz, $CDCl_3$) δ 1.45 (t, $J = 7.00$ Hz, 3H), 1.65–1.90 (m, 6H), 2.51 (s, 3H), 2.52 (s, 3H), 3.65 (m, 1H), 3.95 (m, 1H), 4.10 (q, 2H), 5.50 (m, 1H), 6.25 (s, 1H), 6.70 (d, $J = 16.00$ Hz, 1H), 7.10 (s, 2H), 7.30 (s, 1H), 7.50 (d, $J = 16.00$ Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 15.33 (q), 15.46 (q), 17.66 (q), 18.99 (t), 25.62 (t), 30.61 (t), 62.42 (t), 65.34 (t), 97.76 (d), 2 × 113.86 (d), 118.24 (d), 122.74 (d), 126.19 (d), 130.12 (s), 141.56 (d), 149.02 (s), 150.16 (s), 165.02 (s), 184.36 (s); MS (*m*/*e*) 395 ($M^+ + 1$), 311 (M^+-THP). Anal. Calcd. for $C_{20}H_{26}O_4S_2$: C, 60.88; H, 6.64; S, 16.25. Found: C, 60.06; H, 6.75; S, 15.63%.

5.9. 5-(3-Ethoxy-4-hydroxyphenyl)-1,1-bis(methylthio)-penta-1,4-dien-3-one (*10c*)

To a solution of **9c** (0.98 gm, 2.5 mmol) in methanol (25 ml) was added ppts (0.08 gm) and 3–4 drops of water and stirred at room temperature for 5 h. The reaction mixture was concentrated in vacuo, poured into water and extracted with dichloromethane (50 ml × 3). The combined extract was washed with aqueous sodium carbonate (5 × 50 ml). It was dried (Na_2SO_4), and solvent was removed in vacuo to get **10c** as a crystalline solid which on recrystallization from dichloromethane and hexane furnished **10c** as a crystalline solid (0.50 gm, 81%); m.p. 144–145 °C; IR (KBr cm^{-1}) 3414, 1636, 1585, 1513, 1465, 1388, 1289, 1245, 1125; ^1H NMR (200 MHz, $CDCl_3$) δ 1.47 (t, $J = 7.00$ Hz, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 4.10 (q, $J = 14.00$ Hz, 7.00 Hz, 2H), 5.95 (s, 1H), 6.20 (s, 1H), 6.70 (d, $J = 16.00$ Hz, 1H), 6.95 (d, 1H), 7.10 (s, 1H), 7.15 (d, 1H), 7.55 (d, $J = 16.00$ Hz, 1H); ^{13}C NMR (200 MHz, DMSO) δ 14.67 (q), 15.07 (q), 17.12 (q), 64.33 (t), 112.73 (d), 114.16 (d), 116.09 (d), 123.18 (d), 125.33 (d), 126.93 (s), 141.19 (d), 147.45 (s), 149.63 (s), 162.98 (s), 183.76 (s); MS (*m*/*e*) 311 ($M^+ + 1$). Anal. Calcd. for $C_{15}H_{18}O_3S_2$: C, 58.03, H, 5.84, S, 20.65. Found: C, 58.71; H, 5.28; S, 20.31%.

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