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New domino reaction. One pot synthesis of 4,7-dihydroxythioaurone derivatives from benzaldehydes and 4-acetyl-2-oxo-benz[1,3]oxathiole

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Abstract—A convenient synthesis of 4,7-dihydroxythioaurone derivatives by a one pot reaction of benzaldehydes with 4-acetyl-2-oxo-benz[1,3]oxathioles and piperidine acetate in DMSO is described. The structures of the compounds, including double bond geometry were proved unequivocally by NMR methods. The thioaurone ring system seems to be formed by three consecutive reactions: opening of the oxathiolone ring with piperidine, oxidation of the formed mercapto group with DMSO or/and air to disulfide, and condensation with aldehyde.

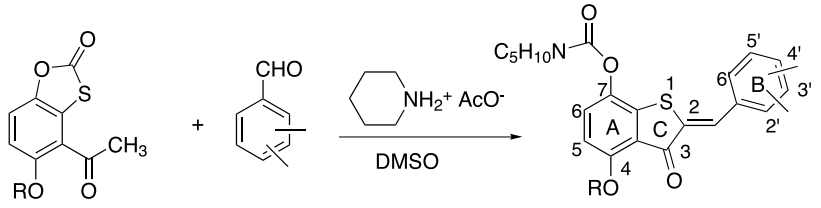
1. Introduction

Thioaurones constitute a relatively unexplored class of compounds. More than 50 years ago they were intensively studied as thioindigo-like dyes, and next as photochromic compounds.[1] Lately, they attracted some attention as photoswitchable molecules[2–4] and their chemistry was recently reviewed.[1] The most important method of preparation of the compounds is the condensation of 1-benzothiophene-3-ones with benzaldehydes,[5] although several other methods are also available.[1]

2. Results and discussion

Continuing our work on thio analogs of flavonoids of biological interest bearing *p*-hydroquinone functionality,[6,7] we now find that 4,7-dihydroxythioaurone derivatives can be prepared in one step from 4-acetyl-5-alkoxy-1,3-benzoxathiol-2-ones (**1**–**3**) and aromatic aldehydes (Scheme 1).

The reaction provided a convenient access to a broad range of 4,7-dihydroxythioaurone derivatives, as listed in Table 1.



1 R = CH_3
2 R = $CH_2CH_2N(C_2H_5)_2$
3 R = $CH_2CH{=}CH_2$

4 - 23

Scheme 1. Formation of thioaurones **4**–**23**.

Keywords: Thioaurones; Synthesis of; Structure of; Domino reaction.
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Table 1. Thioaurones prepared according to Scheme 1

Compound no.	Yield (%)	Substituents
4	62	3′,4,4′-triOCH$_3$
5	21	4-OCH$_3$; 3′,4′-diOH
6[a]	8	4-OCH$_3$; 3′,4′-diOH; 7-OH
7	29	4-OCH$_3$; 4′-Br
8	51	4-OCH$_3$;
9	19	4-OCH$_3$; pyridinyl-4 ring
10	57	2′,3′,4-triOCH$_3$
11	29	4,4′-diOCH$_3$
12	58	4-OCH$_3$; 4′-OH
13	27	4-OCH$_3$; 3′-OH
14	48	3′,4-diOCH$_3$; 4′-OH
15	36	4-OCH$_3$; 4′-Cl
16	42	4-OCH$_3$; 3′-Cl
17	30	4-OCH$_3$; 2′-Cl
18	52	4,5′-diOCH$_3$; 3′-Br; 4′-OH
19	55	4-OCH$_3$; 4′-N(CH$_3$)$_2$
20	10	4-OCH$_3$; 4′-NO$_2$
21	29	4,4′,5′-triOCH$_3$; 3′-Br
22	35	4-OCH$_2$CH$_2$N(C$_2$H$_5$)$_2$; 3′-Cl
23	42	4-OCH$_2$CH=CH$_2$; 3′-Cl

[a] Formed by hydrolysis of compound **5**. Traces of analogous 7-hydroxy derivatives were present in crude products of all reactions.

The structures of the compounds were proved by elemental analyses, IR and NMR spectra. The NMR gHMBC spectrum of compound **4** revealed long range couplings of the exocyclic hydrogen α with carbons 2′ and 6′, which confirmed the aurone structure. For the alternative flavone structure, such coupling seems to be improbable (Fig. 1).

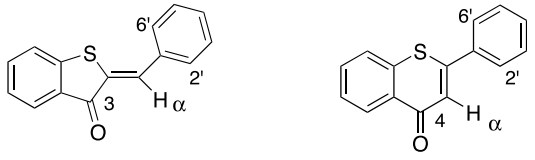


Figure 1. Comparison of thioaurone and thioflavone structures.

Measurement of coupling constants between the carbonyl carbon (carbon 3) and α-proton gave value $J=5$–6 Hz, which proved that the carbonyl group and the α-proton are located cis, as for the trans isomer the value of the coupling constant should be much larger ($J=12$–15 Hz).[8,9] The result is in agreement with previous observations that *Z* isomers of thioaurones are thermodynamically more stable than the *E* isomers, which can be prepared by irradiation of the *Z* form with UV–vis light.[1–4,10] The applied method of determination of double bond geometry seems to be more reliable than the earlier methods, based on chemical shift of the α-proton[2,10] or UV spectra.[2,3,11]

The described reaction seems to be general and takes place with a variety of benzaldehydes (Table 1). The piperidine acetate used as a catalyst and co-reactant could be replaced by the free amine or other amine acetates, including ammonium acetate. However, use of the piperidine acetate resulted in well crystallizing derivatives and for this reason all syntheses were performed with this particular salt, as ultimately we were interested in compounds with free hydroxy groups and the structure of the amine was not of primary importance for us. In most cases, the reactions were performed under argon but the inert atmosphere was not essential. However, the reaction should be run under anhydrous conditions to prevent hydrolysis of the carbamoyl group at the position 7 of the product. If present in larger amount, the product of hydrolysis (e.g., **6**) can only with difficulty be removed by crystallization and had to be separated by low temperature extraction with dilute sodium hydroxide or chromatography.

The mechanism of the reaction is still tentative but a few details are already clarified. Formation of thioaurone from compound **1** has to involve an oxidation step, and air or DMSO appeared as the two possible oxidants. In a related experiment, the reaction flask was flushed with a slow stream of argon and the gases were bubbled through a solution of methyl iodide in acetone, resulting in precipitation of a colorless solid, which was identified by IR as trimethylsulfonium iodide (yield 29 and 48% in relation to the isolated thioaurone; the experiment was not intended to be quantitatively valid, and probably more dimethyl sulfide was formed in the reaction). The result proved that DMSO indeed acted as the oxidant. However, reaction of the compound **1** with 3,4-dimethoxybenzaldehyde and piperidine run in methanol instead of DMSO also resulted in formation of thioaurone **4**, but the reaction time was longer, the yield of the product was lower (10% in comparison to 57% in DMSO), and the thioaurone **4** was accompanied by a complicated mixture of other compounds. One of them was isolated, and identified as 8-hydroxy-3′,4′,5-trimethoxythioflavanone (**24**) (yield 9%) (Fig. 2). The result suggests that oxidation with DMSO was advantageous but not necessary.

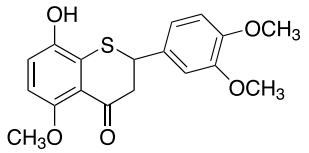
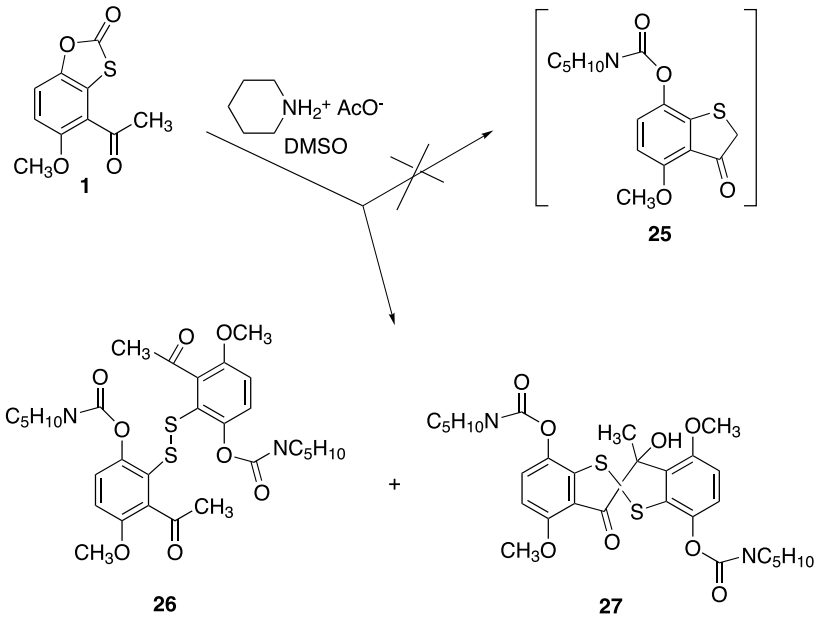


Figure 2. Compound **24**.

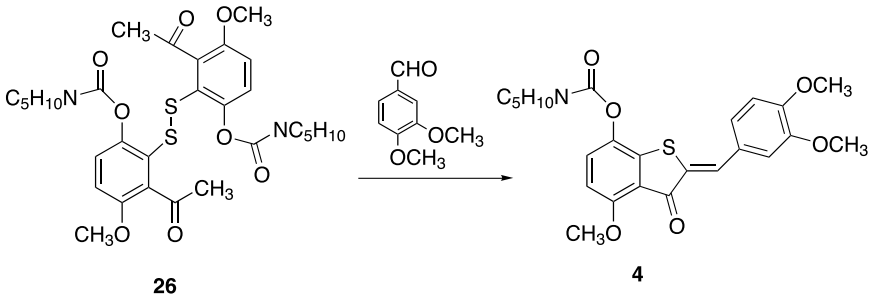
We speculated that formation of thioaurones goes via benzothiophen **25**. To check if compound **25** is indeed formed as an intermediate, reaction of benzoxathiol-2-one (**1**) with piperidine acetate in DMSO was run in the absence of benzaldehyde, but instead of the expected product **25**, disulfide **26** and spiro compound **27** were isolated in the ratio 1:4, respectively, (Scheme 2). Prolongation of the time of the reaction lead exclusively to **27**. The structure of the unusual spiro compound **27** was proved based on MS, IR and NMR ROESY, gHMBC, and gHSQC spectra. The NMR data demonstrated that the compound **27** existed as a mixture of two diastereoisomers.

Formation of the disulfide suggested, that this can be the sought after intermediate, as similar formation of thiaurones from disulfides was already reported by Samogyi.[12] Indeed, under the reaction conditions the disulfide **26** reacts cleanly with 3,4-dimethoxybenzaldehyde to give thioaurone **4** (Scheme 3).

The prepared compounds and their derivatives were tested as potential antitumor agents, the results will be published elsewhere.



Scheme 2. Formation of disulfide **26** and the spiro compound **27**.



Scheme 3. Transformation of disulfide **26** into thioaurone.

3. Conclusion

The described, one pot reaction provides a convenient access to 4,7-dihydroxy derivatives of thioaurones. It can be expected, that the reaction can be extended to other 4-acetyl-1,3-benzoxathiol-2-ones, and that preparatively useful synthesis of thioaurones, starting from 2-acetylthiophenoles or related disulfides and benzaldehydes in DMSO, should be possible. The presented, NMR methods of elucidation of structures of thioaurones seem to be superior to the previous ones, and applicable to aurones.

4. Experimental

4.1. General

Melting points are uncorrected. Infrared spectra were obtained from KBr pellets on Thermo Mattson Satellite instrument. The ^{1}H and ^{13}C NMR spectra were recorded on 200 MHz (Varian Gemini) or 500 MHz (Varian Unity Plus) spectrometers. Elemental analyses were performed on Carlo-Erba 1108 instrument. MALDI TOF mass spectra were obtained with a Bruker Biflex III instrument. Flash column chromatography was performed on silica gel (Merck, less than 230 mesh). TLC was carried out on Merck 0.2 mm silica gel 60 F254 aluminum plates. Commercially available chemicals were reagent grade, and DMSO was dried (Al_2O_3), distilled and stored over molecular sieves.

4.1.1. 4-Acetyl-5-methoxy-1,3-benzoxathiol-2-one (1). 4-Acetyl-5-hydroxy-1,3-benzoxathiol-2-one[13] (11.62 g, 0.055 mol), iodomethane (14 mL, 0.22 mol), dry potassium carbonate (20 g, 0.15 mol) in anhydrous acetone (150 mL) were refluxed, with stirring for 3 h. Water (300 mL) was added to the cooled mixture, and the precipitated solid was filtered off and washed with water. The wet product was dissolved in hot acetone, decolorized with charcoal, and precipitated by addition of water, to give 9.1 g (73%) of 4-acetyl-5-methoxy-1,3-benzoxathiol-2-one (**1**) as brightly yellow crystals, mp 140–142 °C. Anal. Calcd for $C_{10}H_8O_4S_1$: C, 53.57; H, 3.60; S, 14.27. Found: C, 53.40; H, 3.43; S, 14.17. IR (KBr, cm^{-1}): 1745, 1650, 1592, 1467, 1276, 1059. NMR (200 MHz, $CDCl_3$): δ 7.40 (d, 1H, $J=$ 9 Hz, H-7), 6.96 (d, 1H, $J=9$ Hz, H-6), 4.00 (s, 3H, OCH_3), 2.73 (s, 3H, $COCH_3$).

4.1.2. 4-Acetyl-5-[2′-(*N*,*N*-diethylamino)ethoxy]-1,3-benzoxathiol-2-one (2). 4-Acetyl-5-hydroxy-1,3-benzoxathiol-2-one (2.11 g, 0.01 mol), 2-chlorotriethylamine hydrochloride (3.44 g, 0.02 mol), dry potassium carbonate

(8.3 g, 0.06 mol) in anhydrous DMF (20 mL) were stirred at room temperature for 1.5 h. Water and ice were added to the cooled mixture, and the precipitated solid was filtered off and washed with water to give 2.4 g (79%) of crude product. Crystallization from methanol gave 1.93 g (62%) of 4-acetyl-5-[2′-(*N*,*N*-diethylamino)ethoxy]-1,3-benzoxathiol-2-one (**2**) as a gray solid, mp 98–99 °C. Anal. Calcd for $C_{15}H_{19}N_1O_4S_1$: C, 58.23; H, 6.19; N, 4.53; S, 10.34. Found: C, 58.18; H, 6.21; N, 4.52; S, 10.38. IR (KBr, cm^{-1}): 1744, 1662, 1594, 1460, 1274, 1051. NMR (500 MHz, DMSO): δ 7.72 (d, 1H, $J=9$ Hz, H-7), 7.31 (d, 1H, $J=9$ Hz, H-6), 4.23 (t, 2H, $J=6$ Hz, OCH_2), 2.85 (t, 2H, $J=6$ Hz, NCH_2), 2.72 (s, 3H, $COCH_3$), 2.54 (q, 4H, $J=7$ Hz, $2\times CH_2CH_3$), 0.95 (t, 6H, $J=7$ Hz, $2\times CH_2CH_3$).

4.1.3. 4-Acetyl-5-allyloxy-1,3-benzoxathiol-2-one (3). 4-Acetyl-5-hydroxy-1,3-benzoxathiol-2-one (2.11 g, 0.01 mol), allyl bromide (1.73 mL, 0.02 mol), dry potassium carbonate (4.15 g, 0.03 mol) in anhydrous DMF (20 mL) were stirred at room temperature for 1.5 h. Water and ice were added to the cooled mixture, and the precipitated solid was filtered off and washed with water to give 2.3 g (92%) of crude product. Crystallization from toluene–cyclohexane gave 1.8 g (73%) of 4-acetyl-5-allyloxy-1,3-benzoxathiol-2-one (**3**) as a gray solid, mp 120–123 °C. Anal. Calcd for $C_{12}H_{10}O_4S_1$: C, 57.59; H, 4.03; S, 12.79. Found: C, 57.38; H, 3.99; S, 12.85. IR (KBr, cm^{-1}): 1740, 1656, 1593, 1466, 1421, 1270, 1049. NMR (500 MHz, DMSO): δ 7.73 (d, 1H, $J=9$ Hz, H-7), 7.28 (d, 1H, $J=9$ Hz, H-6), 6.15 (m, 1H, =CH–), 5.49 (d, 1H, $J=17$ Hz, H_2C=), 5.34 (d, 1H, $J=11$ Hz, H_2C=), 4.80 (d, 2H, $J=5$ Hz, OCH_2), 2.69 (s, 3H, $COCH_3$).

4.2. General procedure for reaction of 4-acetyl-1,3-benzoxathiol-2-ones (1–3) with benzaldehydes

4-Acetyl-1,3-benzoxathiol-2-ones (**1**–**3**) (4 mmol), a benzaldehyde (6 mmol), piperidine acetate (870 mg, 6 mmol) in anhydrous DMSO (4 mL) were heated at 100–110 °C, with stirring for 1–2 h. The reaction mixture was cooled down and elaborated as described for particular benzaldehydes.

4.2.1. 2-(3′,4′-Dimethoxybenzylidene)-4-methoxy-7-piperidinocarbonyloxy-2,3-dihydro-benzo[*b*]thiophen-3-one (4). Reaction of **1** with 3,4-dimethoxybenzaldehyde. The product precipitated after cooling. The suspension was diluted with methanol and filtered. The yellow solid was washed with methanol, and crystallized from 2-methoxyethanol to give **4**, (62%) as yellow solid, mp 173–175 °C. Anal. Calcd for $C_{24}H_{25}O_6S_1N_1$: C, 63.28; H, 5.53; N, 3.07; S, 7.04. Found: C, 63.39; H, 5.38; N, 3.15; S, 6.87. IR (KBr, cm^{-1}): 1720, 1662, 1584, 1509, 1223, 1040. NMR (200 MHz, $CDCl_3$): δ 7.91 (s, 1H, H-α), 7.35–7.50 (m, 2H, H-6, H-6′), 7.3 (br s, 1H, H-2′), 7.05 (d, 1H, $J=8.4$ Hz, H-5′), 6.82 (d, 1H, $J=8.9$ Hz, H-5), 4.07 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 3.75 (br s, 2H, piperidine), 3.60 (br s, 2H, piperidine), 1.77 (br s, 6H, piperidine).

4.2.2. 2-(3′,4′-Dihydroxybenzylidene)-4-methoxy-7-piperidinocarbonyloxy-2,3-dihydro-benzo[*b*]thiophen-3-one (5) and 2-(3′,4′-dihydroxybenzylidene)-7-hydroxy-4-methoxy-2,3-dihydro-benzo[*b*]thiophen-3-one (6). Reaction of (**1**) with 3,4-dihydroxybenzaldehyde. The products were precipitated by addition of cold water, filtered, dried and separated on silica gel column in chloroform–methanol 20:1 solution to give **5**, (21%) as a yellow solid, mp 255–260 °C dec. Anal. Calcd for $C_{22}H_{21}O_6S_1N_1$: C, 61.81; H, 4.95; N, 3.28; S, 7.50. Found: C, 61.90; H, 5.14; N, 3.03; S, 7.61. IR (KBr, cm^{-1}): 1701, 1664, 1567, 1430, 1229, 1039. NMR (200 MHz, acetone): δ 8.5 (br s, 1H, OH), 8.4 (br s, 1H, OH), 7.70 (s, 1H, H-α), 7.43 (d, 1H, $J=8.9$ Hz, H-6), 7.29 (d, 1H, $J=2.1$ Hz, H-2′), 7.20 (dd, 1H, $J_1=8.7$ Hz, $J_2=2.1$ Hz, H-6′), 6.97 (m, 2H, H-5′, H-5), 3.96 (s, 3H, OCH_3), 3.70 (br s, 2H, piperidine), 3.51 (br s, 2H, piperidine), 1.71 (br s, 6H, piperidine), and **6**, (8%) as a brick-red solid, mp 174–178 °C. Anal. Calcd for $C_{16}H_{12}O_5S_1$: C, 60.75; H, 3.82; S, 10.14. Found: C, 60.57; H, 3.99; S, 10.02. IR (KBr, cm^{-1}): 3394, 1545, 1508, 1233, 1040. NMR (200 MHz, DMSO): δ 10.1 (br s, 1H, OH), 9.8 (br s, 1H, OH), 9.5 (br s, 1H, OH), 7.57 (s, 1H, H-α), 7.26 (d, 1H, $J=2.1$ Hz, H-2′), 7.12 (dd, 1H, $J_1=2.1$ Hz, $J_2=8.4$ Hz, H-6′), 7.05 (d, 1H, $J=8.7$ Hz, H-6), 6.87 (d, 1H, $J=8.1$ Hz, H-5′), 6.78 (d, 1H, $J=8.8$ Hz, H-5), 3.80 (s, 3H, OCH_3).

4.2.3. 2-(4′-Bromobenzylidene)-4-methoxy-7-piperidinocarbonyloxy-2,3-dihydro-benzo[*b*]thiophen-3-one (7). Reaction of (**1**) with 4-bromobenzaldehyde. The product precipitated after cooling. The suspension was diluted with methanol and filtered. The crude product was crystallized from 2-methoxyethanol to give **7**, (29%) as a yellow solid, mp 185–188 °C. Anal. Calcd for $C_{22}H_{20}O_4S_1N_1Br_1$: C, 55.70; H, 4.25; N, 2.95; S, 6.76. Found: C, 55.42; H, 4.20; N, 2.82; S, 6.50. IR (KBr, cm^{-1}): 1710, 1683, 1487, 1417, 1219, 1034. NMR (500 MHz, DMSO): δ 7.77 (s, 1H, H-α), 7.76 (d, 2H, Ar′), 7.69 (d, 2H, $J=8.3$ Hz, Ar′), 7.53 (d, 1H, $J=8.8$ Hz, H-6), 7.01 (d, 1H, $J=9.3$ Hz, H-5), 3.93 (s, 3H, OCH_3), 3.62 (br s, 2H, piperidine), 3.42 (br s, 2H, piperidine), 1.64 (br s, 4H, piperidine), 1.56 (br s, 2H, piperidine).

4.2.4. 2-Benzylidene-4-methoxy-7-piperidinocarbonyloxy-2,3-dihydro-benzo[*b*]thiophen-3-one (8). Reaction of (**1**) with benzaldehyde. The product precipitated after cooling. The suspension was diluted with methanol and filtered. The crude product was purified on silica gel column in chloroform to give **8**, (51%) as a yellow solid, mp 180–181 °C. Anal. Calcd for $C_{22}H_{21}O_4S_1N_1$: C, 66.82; H, 5.35; N, 3.54; S, 8.11. Found: C, 66.99; H, 5.51; N, 3.76; S, 8.34. IR (KBr, cm^{-1}): 1715, 1681, 1585, 1492, 1425, 1220, 1031, NMR (200 MHz, DMSO): δ 7.81 (s, 1H, H-α), 7.42–7.80 (m, 6H, Ar′, H-6), 7.00 (d, 1H, $J=9.0$ Hz, H-5), 3.93 (s, 3H, OCH_3), 3.62 (br s, 2H, piperidine), 3.44 (br s, 2H, piperidine), 1.64 (br s, 6H, piperidine).

4.2.5. 2-[(Pyridin-4yl)-methylene]-4-methoxy-7-piperidinocarbonyloxy-2,3-dihydro-benzo[*b*]thiophen-3-one (9). Reaction of (**1**) with 4-pyridinecarboxaldehyde. Water was added to the cooled reaction mixture, the precipitated oil was dissolved in methylene chloride, the solution was washed with water, dried and evaporated to dryness. The residue was purified on silica gel column in methylene chloride–ethyl acetate 3:1 solution to give 30%, and after crystallization from 2-methoxyethanol 19% of **9** as a yellow solid, mp 203–205 °C. Anal. Calcd for $C_{21}H_{20}N_2O_4S_1$: C, 63.62; H, 5.08; N, 7.07; S, 8.09. Found: C, 63.47; H, 5.20;

N, 7.28; S, 8.37. IR (KBr, cm^{-1}): 1720, 1978, 1583, 1427, 1226, 1034. NMR (200 MHz, $CDCl_3$): δ 8.73 (d, 2H, J= 4 Hz, H-2′,H-6′), 7.73 (s, 1H, H-α), 7.56 (d, 2H, J=6 Hz, H-3′, H-5′), 7.41 (d, 1H, J=8.9 Hz, H-6), 6.77 (d, 1H, J= 8.9 Hz, H-5), 4.01 (s, 3H, OCH_3), 3.69 (br s, 2H, piperidine), 3.55 (br s, 2H, piperidine), 1.71 (br s, 6H, piperidine).

4.2.6. 2-(2′,3′-Dimethoxybenzylidene)-4-methoxy-7-piperidinocarbonyloxy-2,3-dihydro-benzo[*b*]thiophen-3-one (10). Reaction of (**1**) with 2,3-dimethoxybenzaldehyde. The product precipitated after cooling. The suspension was diluted with methanol and filtered. The yellow solid was crystallized from 2-methoxyethanol to give **10** (57%) as a yellow solid, mp 166–167 °C. Anal. Calcd for $C_{24}H_{25}N_1O_6S_1$: C, 63.28; H, 5.53; N, 3.07; S, 7.04. Found: C, 63.10; H, 5.58; N, 3.00; S, 7.17. IR (KBr, cm^{-1}): 1724, 1681, 1582, 1488, 1425, 1224, 1084, 1034. NMR (200 MHz, DMSO): δ 8.00 (s, 1H, H-α), 7.51 (d, 1H, J= 8.9 Hz, H-6), 7.18–7.30 (m, 3H, Ar′), 7.00 (d, 1H, J= 8.9 Hz, H-5), 3.93 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.62 (br s, 2H, piperidine), 3.42 (br s, 2H, piperidine), 1.62 (br s, 6H, piperidine).

4.2.7. 2-(4′-Methoxybenzylidene)-4-methoxy-7-piperidinocarbonyloxy-2,3-dihydro-benzo[*b*]thiophen-3-one (11). Reaction of (**1**) with 4-methoxybenzaldehyde. Water was added to the cooled reaction mixture, the precipitated oil was washed with water, dissolved in chloroform, the solution was washed with water, dried and evaporated to dryness. The residue was purified on silica gel column in chloroform–toluene 3:1 solution and crystallized from 2-methoxyethanol to give 29% of **11** as a yellow solid, mp 156–157 °C. Anal. Calcd for $C_{23}H_{23}N_1O_5S_1$: C, 64.92; H, 5.45, N, 3.29; S, 7.54. Found: C, 64.67; H, 5.33; N, 3.11; S, 7.31. IR (KBr, cm^{-1}): 1727, 1673, 1571, 1509, 1426, 1225, 1176, 1029. NMR (200 MHz, DMSO): δ 7.77 (s, 1H, H-α), 7.72 (d, 2H, J=8.8 Hz, H-2′, H-6′), 7.49 (d, 1H, J= 8.9 Hz, H-6), 7.12 (d, 2H, J=8.7 Hz, H-3′, H-5′), 6.98 (d, 1H, J=9.0 Hz, H-5), 3.91 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.62 (br s, 2H, piperidine), 3.44 (br s, 2H, piperidine), 1.64 (br s, 6H, piperidine).

4.2.8. 2-(4′-Hydroxybenzylidene)-4-methoxy-7-piperidinocarbonyloxy-2,3-dihydro-benzo[*b*]thiophen-3-one (12). Reaction of (**1**) with 4-hydroxybenzaldehyde. The product precipitated after cooling. The suspension was diluted with methanol and filtered. The yellow solid was washed with methanol, crystallized from 2-methoxyethanol and washed with methanol to give **12**, (58%) as a yellow solid, mp 238–240 °C. Anal. Calcd for $C_{22}H_{21}N_1O_5S_1$: C, 64.22; H, 5.14; N, 3.40; S, 7.79. Found: C, 64.11; H, 5.00; N, 3.27; S, 7.53. IR (KBr, cm^{-1}): 3205, 1719, 1659, 1561, 1512, 1426, 1226, 1173, 1040. NMR (200 MHz, DMSO): δ 10.35 (br s, 1H, OH), 7.72 (s, 1H, H-α), 7.62 (d, 2H, J= 8.6 Hz, H-2′, H-6′), 7.47 (d, 1H, J=8.9 Hz, H-6), 6.96 (d, 1H, J=8.9 Hz, H-5), 6.94 (d, 2H, J=8.7 Hz, H-3′, H-5′), 3.91 (s, 3H, OCH_3), 3.62 (br s, 2H, piperidine), 3.54 (br s, 2H, piperidine), 1.63 (br s, 6H, piperidine).

4.2.9. 2-(3′-Hydroxybenzylidene)-4-methoxy-7-piperidinocarbonyloxy-2,3-dihydro-benzo[*b*]thiophen-3-one (13). Reaction of (**1**) with 3-hydroxybenzaldehyde. Water was added to the cooled reaction mixture, the precipitated oil was washed with water, dissolved in chloroform, the solution was washed with water, dried [$(Na)_2SO_4$] and evaporated to dryness. The residue was crystallized from 2-methoxyethanol and washed with methanol to give **13**, (27%) as a yellow solid, mp 255–258 °C. Anal. Calcd for $C_{22}H_{21}N_1O_5S_1$: C, 64.22; H, 5.14; N, 3.40; S, 7.79. Found: C, 64.47; H, 5.11; N, 3.23; S, 7.54. IR (KBr, cm^{-1}): 3322, 1711, 1670, 1578, 1489, 1227, 1042, NMR (200 MHz, DMSO): δ 9.86 (br s, 1H, OH), 7.70 (s, 1H, H-α), 7.50 (d, 1H, J=8.9 Hz, H-6), 7.32 (t, 1H, J=7.7 Hz, H-5′), 7.16 (m, 2H, H-2′, H-6′), 6.99 (d, 1H, J=9. 0 Hz, H-5), 6.88 (dd, 1H, J=7.8 Hz, H-4′), 3.92 (s, 3H, OCH_3), 3.53 (br s, 2H, piperidine), 3.43 (br s, 2H, piperidine), 1.63 (br s, 6H, piperidine).

4.2.10. 2-(4′-Hydroxy-3′-methoxybenzylidene)-4-methoxy-7-piperidinocarbonyloxy-2,3-dihydro-benzo[*b*]thiophen-3-one (14). Reaction of (**1**) with 4-hydroxy-3-methoxybenzaldehyde. The product precipitated after cooling and addition of methanol. The suspension was filtered, the yellow solid was washed with methanol, crystallized twice from 2-methoxyethanol and washed with methanol to give **14**, (48%) as an orange solid, mp 195–196 °C. Anal. Calcd for $C_{23}H_{23}N_1O_6S_1$: C, 62.57; H, 5.25; N, 3.17; S, 7.26. Found: C, 62.78; H, 5.39; N, 3.33; S, 7.02. IR (KBr, cm^{-1}): 3324, 1700, 1670, 1570, 1512, 1428, 1232, 1038. NMR (200 MHz, DMSO): δ 10.00 (br s, 1H, OH), 7.74 (s, 1H, H-α), 7.48 (d, 1H, J=8.8 Hz, H-6), 7.33 (d, 1H, J=2.0 Hz, H-2′), 7.26 (dd, 1H, J_1=8.2 Hz, J_2=2.0 Hz, H-6′), 6.97 (d, 1H, J=8.9 Hz, H-5), 6.94 (d, 1H, J=8.2 Hz, H-5′), 3.91 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.62 (br s, 2H, piperidine), 3.43 (br s, 2H, piperidine), 1.63 (br s, 6H, piperidine).

4.2.11. 2-(4′-Chlorobenzylidene)-4-methoxy-7-piperidinocarbonyloxy-2,3-dihydro-benzo[*b*]thiophen-3-one (15). Reaction of (**1**) with 4-chlorobenzaldehyde. The product precipitated after cooling. The suspension was diluted with methanol and filtered. The yellow solid was washed with methanol and dried to give 44% of crude product. The product was purified on silica gel column in chloroform to give **15**, (36%) as a yellow solid, mp 189–190 °C. Anal. Calcd for $C_{22}H_{20}N_1O_4S_1Cl_1$: C, 61.46; H, 4.69; N, 3.26; S, 7.46. Found: C, 61.27; H, 4.81; N, 3.13; S, 7.21. IR (KBr, cm^{-1}): 1714, 1681, 1582, 1492, 1425, 1221, 1027. NMR (500 MHz, DMSO): δ 7.79 (s, 1H, H-α), 7.76 (d, 2H, J= 8.3 Hz, H-2′, H-6′), 7.63 (d, 2H, J=8.3 Hz, H-3′, H-5′), 7.53 (d, 1H, J=8.9 Hz, H-6), 7.01 (d, 1H, J=8.9 Hz, H-5), 3.93 (s, 3H, OCH_3), 3.62 (br s, 2H, piperidine), 3.43 (br s, 2H, piperidine), 1.64 (br s, 4H, piperidine), 1.56 (br s, 2H, piperidine).

4.2.12. 2-(3′-Chlorobenzylidene)-4-methoxy-7-piperidinocarbonyloxy-2,3-dihydro-benzo[*b*]thiophen-3-one (16). Reaction of (**1**) with 3-chlorobenzaldehyde. The product precipitated after cooling. The suspension was diluted with methanol and filtered. The yellow solid was washed with methanol, crystallized from 2-methoxyethanol and washed with methanol to give **16**, (42%) as a yellow solid, mp 170–172 °C. Anal. Calcd for $C_{22}H_{20}N_1O_4S_1Cl_1$: C, 61.46; H, 4.69; N, 3.26; S, 7.46. Found: C, 61.25; H, 4.45; N, 3.08; S, 7.67. IR (KBr, cm^{-1}): 1714, 1683, 1582, 1490,

1425, 1222, 1026. NMR (500 MHz, DMSO): δ 7.81 (s, 1H, H-2′), 7.79 (s, 1H, H-α), 7.71 (d, 1H, J=7.8 Hz, H-2′), 7.59 (t, 1H, J=7.8 Hz, H-5′), 7. 55–7.57 (m, 2H, H-4′, H-6), 7.02 (d, 1H, J=8.9 Hz, H-5), 3.93 (s, 3H, OCH_3), 3.62 (br s, 2H, piperidine), 3.43 (br s, 2H, piperidine), 1.65 (br s, 4H, piperidine), 1.56 (br s, 2H, piperidine).

4.2.13. 2-(2′-Chlorobenzylidene)-4-methoxy-7-piperidinocarbonyloxy-2,3-dihydro-benzo[*b*]thiophen-3-one (17). Reaction of (**1**) with 2-chlorobenzaldehyde. Water was added to the cooled reaction mixture, the precipitated oil was washed with water, dissolved in chloroform, the solution was washed with water, dried ($MgSO_4$) and evaporated to dryness. The residue was purified on silica gel column in chloroform–toluene 3:1 solution to give 30% of **17** as a yellow solid, mp 170 171 °C. Anal. Calcd for $C_{22}H_{20}N_1O_4S_1Cl_1$: C, 61.46; H, 4.69; N, 3.26; S, 7.46. Found: C, 61.68; H, 4.62; N, 3.39; S, 7.24. IR (KBr, cm^{-1}): 1722, 1681, 1582, 1490, 1424, 1218, 1145, 1030. NMR (200 MHz, DMSO): δ 7.99 (s, 1H, H-α), 7.79 (dd, 1H, J_1=7.2 Hz, J_2= 1.9 Hz, H-6′), 7.44–7.70 (m, 4H, H-6, H-3′, H-4′, H-5′), 7.02 (d, 1H, J=9.1 Hz, H-5), 3.93 (s, 3H, OCH_3), 3.59 (br s, 2H, piperidine), 3.42 (br s, 2H, piperidine), 1.61 (br s, 6H, piperidine).

4.2.14. 2-(3′-Bromo-4′-hydroxy-5′-methoxybenzylidene)-4-methoxy-7-piperidinocarbonyloxy-2,3-dihydro-benzo[*b*]thiophen-3-one (18). Reaction of (**1**) with 3-bromo-4-hydroxy-5-methoxybenzaldehyde. The product precipitated after cooling. The suspension was diluted with methanol and filtered. The yellow solid was washed with methanol, crystallized from 2-methoxyethanol and washed with methanol to give **18**, (52%) as a yellow solid, mp 227–229 °C. Anal. Calcd for $C_{23}H_{22}N_1O_6S_1Br_1$: C, 53.08; H, 4.26; N, 2.69; S, 6.16. Found: C, 52.87; H, 4.45; N, 2.41; S, 6.00. IR (KBr, cm^{-1}): 3388, 1715, 1667, 1579, 1500, 1427, 1226, 1038. NMR (500 MHz, DMSO): δ 10.46 (br s, 1H, OH), 7.73 (s, 1H, H-α), 7.55 (d, 1H, J=1.9 Hz, H-2′), 7.51 (d, 1H, J=8.8 Hz, H-6), 7.39 (d, 1H, J=small, H-6′), 7.00 (d, 1H, J=9.3 Hz, H-5), 3.92 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.62 (br s, 2H, piperidine), 3.44 (br s, 2H, piperidine), 1.66 (br s, 4H, piperidine), 1.56 (br s, 2H, piperidine).

4.2.15. 2-(4′-Dimethylaminobenzylidene)-4-methoxy-7-piperidinocarbonyloxy-2,3-dihydro-benzo[*b*]thiophen-3-one (19). Reaction of (**1**) with 4-dimethylaminobenzaldehyde. Water was added to the cooled reaction mixture, the precipitated oil was washed with water, dissolved in chloroform, the solution was washed with water, dried ($MgSO_4$) and evaporated to dryness. The residue was washed with methanol, crystallized twice from 2-methoxyethanol and washed with methanol to give **19**, (55%) as a red solid, mp 218–222 °C. Anal. Calcd for $C_{24}H_{26}N_2O_4S_1$: C, 65.73; H, 5.98; N, 6.39; S, 7.31. Found: C, 65.82; H, 5.92; N, 6.30; S, 7.18. IR (KBr, cm^{-1}): 1723, 1665, 1561, 1522, 1369, 1228, 1033. NMR (200 MHz, DMSO): δ 7.70 (s, 1H, H-α), 7.60 (d, 2H, J=9.0 Hz, H-2′, H-6′), 7.45 (d, 1H, J=8.9 Hz, H-6), 6.94 (d, 1H, J=8.9 Hz, H-5), 6.85 (d, 2H, J=8.9 Hz, H-3′, H-5′), 3.90 (s, 3H, OCH_3), 3.62 (br s, 2H, piperidine), 3.43 (br s, 2H, piperidine), 3.03 (s, 6H, $N(CH_3)_2$), 1.64 (br s, 6H, piperidine).

4.2.16. 2-(4′-Nitrobenzylidene)-4-methoxy-7-piperidinocarbonyloxy-2,3-dihydro-benzo[*b*]thiophen-3-one (20). Reaction of (**1**) with 4-nitrobenzaldehyde. The product precipitated after cooling. The suspension was diluted with methanol and filtered. The yellow solid was washed with methanol, purified on silica gel column in chloroform, crystallized from 2-methoxyethanol and washed with methanol to give **20**, (10%) as a yellow solid, mp 242–244 °C. Anal. Calcd for $C_{22}H_{20}N_2O_6S_1$: C, 59.99; H, 4.58; N, 6.36; S, 7.28. Found: C, 60.23; H, 4.41; N, 6.53; S, 7.07. IR (KBr, cm^{-1}): 1715, 1688, 1582, 1512, 1490, 1427, 1339, 1226, 1031. NMR (200 MHz, DMSO): δ 8.37 (d, 2H, J= 8.7 Hz, H-2′, H-6′), 7.99 (d, 2H, J=8.7 Hz, H-3′, H-5′), 7.88 (s, 1H, H-α), 7.56 (d, 1H, J=8.9 Hz, H-6), 7.04 (d, 1H, J=8.9 Hz, H-5), 3.94 (s, 3H, OCH_3), 3.62 (br s, 2H, piperidine), 3.46 (br s, 2H, piperidine), 1.64 (br s, 6H, piperidine).

4.2.17. 2-(3′-Bromo-4′,5′-dimethoxybenzylidene)-4-methoxy-7-piperidinocarbonyloxy-2,3-dihydro-benzo[*b*]thiophen-3-one (21). Reaction of (**1**) with 3-bromo-4,5-dimethoxybenzaldehyde. The product precipitated after cooling. The suspension was diluted with methanol and filtered. The crude product was purified on silica gel column in chloroform–ethyl acetate 100:1 solution and crystallized from chloroform–methanol mixture to give **21**, (29%) a yellow solid, mp 194–196 °C. Anal. Calcd for $C_{24}H_{24}N_1O_6S_1Br_1$: C, 53.94; H, 4.53; N, 2.62; S, 6.00. Found: C, 53.90; H, 4.40; N, 2.54; S, 5.85. IR (KBr, cm^{-1}): 1716, 1675, 1582, 1489, 1428, 1229, 1039. NMR (200 MHz, DMSO): δ 7.73 (s, 1H, H-α), 7.55 (d, 1H, J=1.8 Hz, H-2′), 7.51 (d, 1H, J=9.0 Hz, H-6), 7.44 (d, 1H, J=1.9, H-6′), 6.99 (d, 1H, J=9.0 Hz, H-5), 3.92 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.61 (br s, 2H, piperidine), 3.45 (br s, 2H, piperidine), 1.64 (br s, 6H, piperidine).

4.2.18. 2-(3′-Chlorobenzylidene)-4-[2″-(*N*,*N*-diethylamino)ethoxy]-7-piperidinocarbonyloxy-2,3-dihydro-benzo[*b*]thiophen-3-one (22). Reaction of (**2**) with 3-chlorobenzaldehyde. The reaction mixture was poured into solution of potassium carbonate (2 g) in water (80 mL) to give a dark oil. Water was decanted and the oil was washed several time with water to remove DMSO. The residue was dissolved in ethyl acetate, washed with water, dried (sodium sulfate) and evaporated. The residue was purified on silica gel column in chloroform–methanol 10:1 solution and crystallized from methanol to give **22**, (35%) as a yellow solid, mp 122–123 °C. Anal. Calcd for $C_{27}H_{31}N_2O_4S_1Cl_1$: C, 62.96; H, 6.07; N, 5.44; S, 6.23. Found: C, 62.86; H, 5.91; N, 5.45; S, 6.16. IR (KBr, cm^{-1}): 1721, 1682, 1580, 1426, 1223, 1035. NMR (500 MHz, DMSO): δ 7.79 (br s, 2H, H-α, H-2′), 7.70 (d, 1H, J=7.8 Hz, H-6′), 7.59 (t, 1H, J=7.8 Hz, H-5′), 7.54 (d, 1H, J=7.8 Hz, H-4′), 7.50 (d, 1H, J=9.3 Hz, H-6), 7.02 (d, 1H, J=9.3 Hz, H-5), 4.19 (t, 2H, J=4.9 Hz, OCH_2), 3.62 (br s, 2H, piperidine), 3.43 (br s, 2H, piperidine), 2.84 (t, 2H, J=5.4 Hz, NCH_2), 2.60 (q, 4H, J=7.0 Hz, 2×CH_2), 1.65 (br s, 4H, piperidine), 1.56 (br s, 2H, piperidine), 0.99 (t, 6H, J= 7.3 Hz, 2×CH_3).

4.2.19. 2-(3′-Chlorobenzylidene)-4-allyloxy]-7-piperidinocarbonyloxy-2,3-dihydro-benzo[*b*]thiophen-3-one (23). Reaction of (**3**) with 3-chlorobenzaldehyde. The

product precipitated after cooling. The suspension was diluted with methanol and filtered. The crude product was crystallized from 2-methoxyethanol to give **23**, (42%) as a yellow solid, mp 144–146 °C. Anal. Calcd for $C_{24}H_{22}N_1O_4S_1Cl_1$: C, 63.22; H, 4.86; N, 3.07; S, 7.03. Found: C, 62.96; H, 4.73; N, 3.10; S, 7.13. IR (KBr, cm^{-1}): 1721, 1679, 1580, 1424, 1221, 1011. NMR (500 MHz, DMSO): δ 7.79 (s, 2H, H-α, H-2′), 7.70 (d, 1H, $J=7.3$ Hz, H-6′), 7.59 (t, 1H, $J=7.8$ Hz, H-5′), 7.54 (br d, 1H, $J=8.3$ Hz, H-4′), 7.50 (d, 1H, $J=9.3$ Hz, H-6), 7.00 (d, 1H, $J=8.8$ Hz, H-5), 6.07 (m, 1H, =CH–), 5.61 (d, 1H, $J=16.2$ Hz, H_2C=), 5.32 (d, 1H, $J=10.2$ Hz, H_2C=), 4.75 (d, 2H, $J=3.9$ Hz, OCH_2), 3.62 (br s, 2H, piperidine), 3.43 (br s, 2H, piperidine), 1.65 (br s, 4H, piperidine), 1.56 (br s, 2H, piperidine).

4.2.20. Reaction of 4-acetyl-5-methoxy-1,3-benzoxathiol-2-one (1) with 3,4-dimethoxybenzaldehyde in methanol. 4-Acetyl-5-methoxy-1,3-benzoxathiol-2-one (**1**) (224 mg, 1 mmol), 3,4-dimethoxybenzaldehyde (250 mg, 1.5 mmol) and piperidine (0.15 mL, 1.5 mmol) in methanol (2 mL) were stirred at 60 °C for 5 h, and the solution was left for cooling. The precipitated solid was filtered off, and washed with methanol, to give 2-(3′,4′-dimethoxybenzylidene)-4-methoxy-7-piperidinocarbonyloxy-2,3-dihydro-benzo[*b*]thiophen-3-one (**4**) (36 mg, 8%). The combined filtrates were evaporated and the residue was separated on silica gel column in chloroform, to give a second fraction of **4** (10 mg, 2%), and 8-hydroxy-3′,4′,5-trimethoxythioflavanone (**24**) (31 mg, 9%) as a yellow solid, mp 180–182 °C. Anal. Calcd for $C_{18}H_{18}O_5S_1$: C, 62.41; H, 5.24; S, 9.24. Found: C, 62.19; H, 5.30; S, 9.02. IR (KBr, cm^{-1}): 3285, 1646, 1570, 1518, 1466, 1246, 1037. NMR (500 MHz, DMSO): δ 9.76 (s, 1H, OH), 7.07 (d, 1H, $J=2$ Hz, H-2′), 6.99 (dd, 1H, $J_1=8.3$ Hz, $J_2=1.9$ Hz, H-6′), 6.94 (d, 1H, $J=8.8$ Hz, H-7), 6.93 (d, 1H, $J=8.3$ Hz, H-5′), 6.73 (d, $J=9.3$ Hz, H-6), 4.65 (dd, 1H, $J_1=13.1$ Hz, $J_2=3.0$ Hz, H-2), 3.76 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.32 (dd, 1H, $J_1=15.6$ Hz, $J_2=13.6$ Hz, H-3), 2.86 (dd, 1H, $J_1=15.2$ Hz, $J_2=3.0$ Hz, H-3).

4.2.21. Reaction of 4-acetyl-5-methoxy-1,3-benzoxathiol-2-one (1) with piperidine acetate in DMSO. Solution of 4-acetyl-5-methoxy-1,3-benzoxathiol-2-one (**1**) (224 mg, 1 mmol) and piperidine acetate (218 mg, 1.5 mmol) in dry DMSO (2 mL) was deoxygenated and stirred under argon at 60 °C for 5 h. The reaction mixture was cooled in ice, and products were precipitated by addition of water. The crude mixture (280 mg) was separated on silica gel column in chloroform–ethyl acetate 3:1 solution to give 2-acetyl-3-methoxy-6-piperidinocarbonyloxyphenyl disulfide (**26**) (20 mg, 6%) as a beige solid, mp 159–161 °C. Anal. Calcd for $C_{30}H_{36}O_8N_2S_2$: $M=616.726$; C-58.42; H-5.89; N-4.55; S-10.38. Found: C-58.75; H, 5.98; N, 4.44; S, 10.55. MS MALDI TOF: 639 (M^+ + Na), 655 (M^+ + K). IR (KBr, cm^{-1}): 1720, 1582, 1420, 1224, 1138, 1044, 1022. NMR (500 MHz, $CDCl_3$): δ 7.21 (d, 1H, $J=9.3$ Hz, H-4), 6.93 (d, 1H, $J=9.3$ Hz, H-5), 3.80 (s, 3H, OCH_3), 3.48 (br s, 4H, H-piperidine), 2.16 (s, 3H, $COCH_3$), 1.61 (br m, 6H, H-piperidine); As the second product was eluted 4,4′-dimethoxy-7,7′-di(piperidinocarbonyloxy)-3′-hydroxy-3′-methyl-3-keto-[3,3′-spirobi(2*H*,2′*H*,3*H*,3′*H*-benzo[*b*]thiophen)] (**27**), (150 mg, 50%) as a cream solid, mp 140–147 °C. Anal. Calcd for $C_{30}H_{34}O_8N_2S_2\times H_2O$: $M=632.75$; C, 56.95; H, 5.73; N, 4.43; S, 10.14. Found: C, 56.98; H, 5.63; N, 4.30; S, 10.13. MS MALDI TOF: 597 (M^+ − OH), 614 (M^+), 637 (M^+ + Na), 653 (M^+ + K). IR (KBr, cm^{-1}): 3442, 1722, 1580, 1488, 1425, 1225, 1141, 1048, 1020. NMR (500 MHz, DMSO) (the compound exists as a mixture of two diastereoisomers. Full NMR data, including ^{13}C, ROESY, gHSQC, and gHMBC spectra, are given in the Supplementary data, the following list presents only ^1H data for the main isomer): δ 7.48 (d, 1H, $J=8.8$ Hz, H-6), 7.09 (d, 1H, $J=9.3$ Hz, H-6′), 6.88 (d, 1H, $J=7.8$ Hz, H-5), 6.82 (d, 1H, $J=9.3$ Hz, H-5′), 6.46 (s, 1H, OH), 3.81 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3′), 3.34–3.60 (br m, 8H, piperidine), 1.42–1.65 (br m, 12H, piperidine), 1.64 (s, 3H, CH_3).

4.2.22. Reaction of 2-acetyl-3-methoxy-6-piperidinocarbonyloxyphenyl disulfide (26) with 3,4-dimethoxybenzaldehyde. 2-Acetyl-3-methoxy-6-piperidinocarbonyl-oxyphenyl disulfide (**26**) (11 mg, 0.028 mmol), 3,4-dimethoxybenzaldehyde (7 mg, 0.042 mmol) and piperidine acetate (6 mg, 0.04 mmol) in anhydrous DMSO (0.5 mL) were stirred at 90 °C for 1 h. The solution was cooled, the product was precipitated with water, filtered, washed with water and methanol, to give thioaurone **4** (4 mg).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.06.107

Table 1—NMR data of the spiro compound **27**; Figure 1—low field part of ^1H NMR spectrum of **27**; Figure 2—high field part of ^1H NMR spectrum of **27**; Figures 3 to 7—^{13}C NMR of **27**; Figure 8—ROESY spectrum of **27**; Figure 9—gHMBC spectrum of **27**; Figure 10—gHSQC spectrum of **27**.

References and notes

1. Konieczny, M. T.; Konieczny, W. *Heterocycles* **2005**, *2*, 451–464.
2. Eggers, K.; Fyles, T. M.; Montoya-Pelaez, P. J. *J. Org. Chem.* **2001**, *66*, 2966–2977.
3. Steinle, W.; Rück-Braun, K. *Org. Lett.* **2003**, *5*, 141–144.
4. Lougheed, T.; Borisenko, V.; Hennig, T.; Rück-Braun, K.; Woolley, G. A. *Org. Biomol. Chem.* **2004**, *2*, 2798–2801.
5. Auwers, K.; Arndt, F. *Chem. Ber.* **1909**, *42*, 537.
6. Konieczny, M. T.; Horowska, B.; Kunikowski, A.; Konopa, J.;

Wierzba, K.; Yamada, Y.; Asao, T. *J. Org. Chem.* **1999**, *64*, 359–364.
7. Konieczny, M. T.; Horowska, B.; Kunikowski, A.; Konopa, J.; Wierzba, K.; Yamada, Y.; Asao, T. *Synthesis* **2001**, 1363–1367.
8. Kalinowski, H. O.; Berger, S.; Braun, S. *Carbon 13 NMR Spectroscopy*; Wiley: NY, 1991; p 526.
9. Marshall, J. L. *Carbon–Carbon and Carbon–Hydrogen NMR Couplings*; Verlag Chemie Int.: Deerfield Beach, 1983; p 33.
10. Réamonn, L. S. S.; O'Sullivan, W. I. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1009–1012.
11. Mostoslavskii, M. A.; Izmail'skii, V. A. *J. Gen. Chem. USSR* **1961**, *17*, 21–31.
12. Somogyi, L. *Can. J. Chem.* **2001**, *79*, 1159–1165.
13. Lau, P. T. S.; Kestner, M. *J. Org. Chem.* **1968**, *33*, 4426–4431.