Ultrasound-Accelerated Synthesis of Some Bis-Compounds and Their Biological Evaluation

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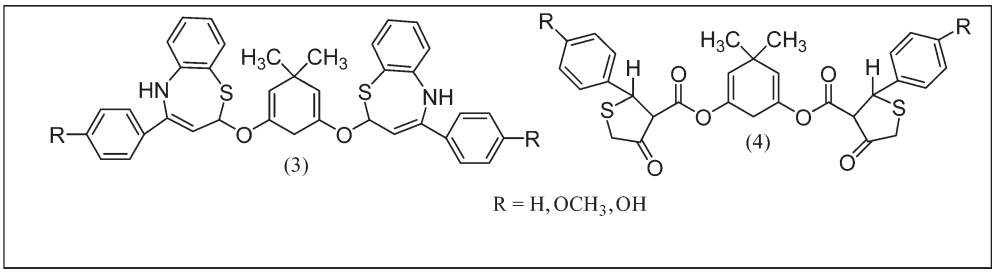

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A new series of bis-1,5-[2′*H*,3′*H*-dihydro-4′(substituted phenyl)-1′,5′-benzothiazipin-2′-oxy]-3,3-dimethyl-1,4-cyclohexadiene 3 and bis-1,5-[-2′,3′,4′,5′-teterahydro-2′-(substitutedphenyl)-4′-oxothiophen-3′-carboxylate]-3,3-dimethyl-1,4-cyclohexadiene 4 have been synthesized by reacting 1,3-bis-[substituted cinnamate]-3,3-dimethyl-1,4-cyclohexadiene 2 with 2-aminothiophenol and thiogylcolic acid, respectively, through an environmentally benign procedure. The title compounds have been evaluated for their antimicrobial activities. Reaction under ultrasound irradiation resulted in enhancement of yields and reaction rates. Structures of the synthesized compounds have been elucidated on the basis of the elemental analysis and spectral data.

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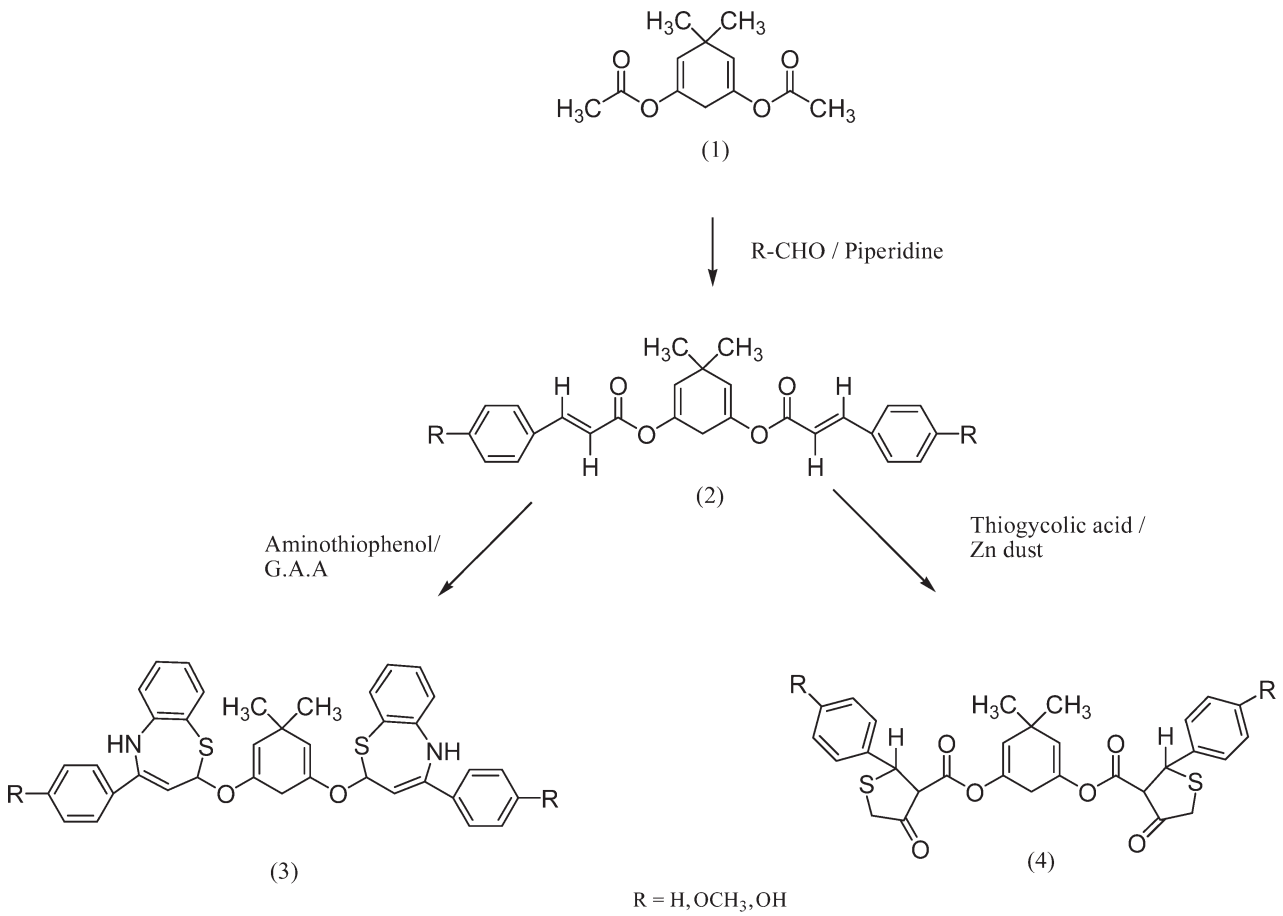
INTRODUCTION

The use of ultrasound irradiation for activating various reactions is well documented in the literature such as synthesis of azoles and diazenes [1], Reformatsky reaction [2], oxidation of substrates like hydroquinones [3], conversion of nitro compounds to carbamates [4], pinacol coupling [5], Ullmann condensation [6] *etc*.

The advantages of ultrasound-assisted chemical reactions include higher yields, shorter reaction times, and milder reaction conditions when compared with classical methods [7–11]. The effect of ultrasound has mostly been shown by increasing the yields of reactions and in some cases, changing the ratio of products formed. The most important effects of ultrasound arise from acoustic cavitation; formation, growth, and implosive collapse of bubbles in the liquid by passing ultrasonic waves through this medium [12,13]. The implosive collapse of the bubble generates localized hot spots through adiabatic compression or shock wave formation within the gas phase of the collapsing bubble. These bubbles create pressures of hundreds of atmospheres and temperature of thousands of degrees within the cavities during their collapse [14,15]. In all of these reactions, it was found that ultrasound accelerates the reactions [16–22].

Benzothiazepine derivatives possess potential anti-ulcer [23], analgesic [24], vaso-depressant [25], anti hypertensive [26], antidementia [27], antibacterial, and anti-fungal activities [28–30]. The biodynamic nature of benzothiazepines derivatives led to the current synthesis of 1,5-benzothiazepines having various substituents, which may prove to be of medical significance. Similarly, thiophenes derivatives are also well known for diverse biological activities and play a key role as anti-inflammatory [31,32], anti-protozoa [33], antitumor agents [34], and alternate substrate inhibitors of cholesterol eastrase [35]. In recent years, attention has been increasingly paid to the synthesis of bis-heterocyclic compounds, which exhibit various biological activities [36–45]. The wide range of therapeutic value of the above ring system prompted us to synthesize several new bis-1,5-[substituted cinnamate]-3,3-dimethyl-1,4-cyclohexadiene **2** and its utility as a building block in the synthesis of several new bis-1,5-[2′H,3′H-dihydro-4′(substituted phenyl)-1′,5′-benzothiazepin-2′-oxy]-3,3-dimethyl-1,4-cyclohexadiene **3** and bis-1,5-[-2′,3′,4′,5′-teterahydro-2′-(substitutedphenyl)-4′-oxothiophen-3′-carboxylate]-3,3-dimethyl-1,4-cyclohexadiene **4** compounds (Scheme 1). The structures of the products were confirmed by elemental analysis, IR, ^{1}H, ^{13}C NMR, and MS spectral analysis. The antimicrobial activities of the newly synthesized compounds were also investigated.

Scheme 1



RESULTS AND DISCUSSION

The reaction sequences leading to the different bis-heterocyclic ring is outlined in Scheme 1. The reaction of 3,3-dimethyl-1,5-dihydroxy-1,4-cyclohexadiene with acetic anhydride yielded bis-1,5-[acetoxy]-3,3-dimethyl-1,4-cyclohexadiene which was converted into bis-1,5-[substituted cinnamate]-3,3-dimethyl-1,4-cyclohexadiene **2**, on treatment with substituted aromatic aldehydes. Formation of compound **2** was evidenced by the appearance of a signal at 7.8 ppm (α,β unsaturated carbonyl) in the ^{1}H NMR spectra and in IR spectra band because of carbonyl at 1634 cm^{-1}. In the ^{13}C NMR spectra, the signal 188.24 ppm was observed due to O=C< in compound **2**. The reaction of 2-aminothiophenol with compounds having α,β unsaturated in conjugation with carbonyl system in acidic media afforded bis-1,5-[2′*H*,3′*H*-dihydro-4′(substitutedphenyl)-1′,5′-benzothiazipin-2′-oxy]-3,3-dimethyl-1,4-cyclohexadiene **3**. In ^{1}H NMR spectra of compound **3**, the signal at 3.74 was observed due to —NH—, 6.0 due to C—H and at 7.35 due to C—H and in the IR spectra of bis-benzothiazepine **3**, the band at 3070 (—N—H—) and 1432 cm^{-1} (—C—S—) also confirmed. In ^{13}C NMR spectra, the signal at 65 ppm was observed because of >CH—S— and 70 (>C—S—benzothiazepine ring).

Similarly, the bis-1,5-[substituted cinnamate]-3,3-dimethyl-1,4-cyclohexadiene **2** on treatment with thioglycolic acid underwent cyclization to the bis-1,5-[2′,3′,4′,5′-teterahydro-2′-(substitutedphenyl)-4′-oxothiophen-3′-carboxylate]-3,3-dimethyl-1,4-cyclohexadiene **4** (Scheme 1). The spectral data are in agreement with the proposed structures. The IR spectrum of **4** showed C—S stretching bands at 1340–1350 cm^{-1} and its ^{1}H NMR spectrum the chemical shifts due to CH_2 of ring was observed at 3.42 ppm. Appearance of two C=O at 196.66 and 199.23 ppm in ^{13}C NMR confirmed the formation of **4**. Keeping in view the advantages of ultrasound irradiation technique, the reaction was also carried out under sonication condition. The formation of compounds **2, 3,** and **4** was completed in 15 to 25 min under sonication condition when compared with conventional method, which took 4 to 5 h. The compounds obtained by both the routes were found identical as they showed same melting point and similar spectral data.

Table 1

Physical and analytical data of compounds **2**, **3**, and **4**.

Compound	*R*	m.p (°C)	Yield (%)	Yield (%) Conv	Molecular formula	Analysis % Calcd./Found C	H	N	S
2a	H	200–202	82	58	$C_{26}H_{24}O_4$	78.21	6.01	–	–
						77.87	5.91	–	–
2b	OCH_3	215–217	87	59	$C_{28}H_{28}O_6$	73.04	6.08	–	–
						72.84	5.85	–	–
2c	OH	198–199	81	59	$C_{26}H_{24}O_6$	72.22	5.55	–	–
						72.14	5.24	–	–
3a	H	70–72	72	58	$C_{38}H_{34}N_2O_2S_2$	73.22	5.76	4.74	10.84
						73.08	5.47	4.59	10.68
3b	OCH_3	73–76	79	67	$C_{40}H_{38}N_2O_4S_2$	70.15	5.84	4.30	9.84
						69.41	5.68	4.12	9.73
3c	OH	95–97	75	65	$C_{38}H_{34}N_2O_4S_2$	69.45	5.46	4.50	10.28
						69.32	5.34	4.38	10.11
4a	H	165–167	77	60	$C_{30}H_{28}O_6S_2$	69.49	5.40	–	12.35
						69.21	5.23	–	12.21
4b	OCH_3	148–149	70	58	$C_{32}H_{32}O_8S_2$	63.15	5.26	–	10.58
						62.94	5.11	–	10.32
4c	OH	158–160	76	55	$C_{30}H_{28}O_8S_2$	65.45	5.09	–	11.63
						65.23	4.96	–	11.32

The comparative data of the compounds have been listed in Table 1.

Antibacterial activity. All the newly synthesized compounds were initially screened for their *in vitro* antibacterial activities against the gram-positive *S aureus, C diphtheriae*, and *S cerevisiae,* the gram-negative *E coli* and *P aeruginosa* by disc diffusion method [46].The compounds were tested at a concentration of 100 μg/mL. The zone of inhibition was measured in mm and was compared with the reference standard antibiotics namely ampicillin trihydrates drugs 50 μg/mL. Compounds displayed good activity toward the gram-positive bacteria S *aureus, C diphtheriae*, and *S cerevisiae*, but the compounds showed less activity toward gram-negative bacteria *E coli* and *P aeruginosa*. The results of antibacterial screening studies are reported in Table 2.

CONCLUSIONS

In conclusion, the ultrasound irradiation for synthesis of the title compound offers significant reduction in the reaction time, operation simplicity, cleaner reaction, easy work-up, and improved yields. The procedure clearly highlights the advantages of ultrasound. The synthesized compounds also displayed noteworthy convincing antibacterial activity against gram-positive bacteria *S aureus, C diphtheriae*, *and S cerevisiae*.

Table 2

Antibacterial activity of compounds **2**, **3**, and **4**.

Compound	Concentration (μg/mL)	Zone of inhibition (mm)[a] Gram positive *S. aureus*	*S. cervesiae*	*C.diphtheria*	Gram negative *E. coli*	*P. aerugnosa*
2a	100	16	18	17	08	09
2b	100	17	19	18	09	08
2c	100	18	19	17	09	10
3a	100	19	18	18	08	09
3b	100	21	21	19	09	11
3c	100	22	20	17	09	10
4a	100	21	19	18	11	10
4b	100	20	17	21	09	11
4c	100	19	19	22	11	10
Ampicilin trihydrate	50	26	23	28	24	21
DMSO	–	00	00	00	00	00

[a] Diameter of the hole was 6 mm.

EXPERIMENTAL

Melting points of all synthesized compounds were determined in open capillary tubes on an electrothermal apparatus and are uncorrected. The purity of the compounds was monitored by TLC on silica gel coated aluminium plates (Merck) as adsorbent and UV light as visualizing agent; IR spectra (potassium bromide in cm^{-1}) were recorded on a Perkin-Elmer spectrophotometer in the range of 4000–400 cm^{-1}. ^1H NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using deuteriochloroform as solvent and trimethylsilane as an internal standard (chemical shifts in δ ppm) and MS spectra were taken on a Jeol sx-102/PA-6000 (EI) spectrometer. C, H, N estimation was recorded on Carlo Erba 1108 (CHN) Elemental Analyzer. Experiment under ultrasound irradiation is carried out in probe sonicator manufactured by Dakshin.

General preparation of bis-1,5-[substituted cinnamate]-3,3-dimethyl-1,4-cyclohexadiene (2a-c)

Method A (ultrasound method). A mixture of (0.02 mol) substituted aromatic aldehyde, (0.01 mol) 1, 2 mL (0.02 mol) of piperidine in 15 mL of ethanol were exposed to ultrasound irradiation for 15 min. On completion of the reaction (monitoring on TLC), the mixture was poured on crushed ice. The product that precipitated out was collected by filtration, washed with water, and recrystallized from ethanol.

Method B (conventional method). A solution of (0.02 mol) substitute aromatic aldehydes, (0.01 mol) 1, 2 mL (0.02 mol) piperidine in 15 mL of ethanol were refluxed on water bath for 4 h. The reaction was monitored by TLC, and after completion of the reaction, the contents were poured on crushed ice. The solid obtained was collected by filtration, washed with water, and recrystallized from ethanol to obtain compound 2(a-c).

Bis-1,5-[cinnamate]-3,3-dimethyl-1,4-cyclohexadiene (2a). This compound was obtained as white crystal, mp 200–202°C; IR (potassium bromide): CO 1645, C=C 1625 cm^{-1}; ^1H NMR (deuteriochloroform): δ 0.96 (s, 6-H, 2xCH_3), 2.44 (s, 2-H, CH_2), 4.69 (s, 2-H, CH), 7.82 (s, 4H, α, β unsaturated carbonyl), 6.98–8.02 (m, 10-H, aromatic protons). ^{13}C NMR: 27.28 $(CH_3)_2$, 37.33 (CH_2), 73.08 (tetrahedral carbon) and 108.21–115.32 (4xC=C), 125.69–131.56 (Ar—C), 188.42 (C=O), MS: *m/z* 402 (m^{+2}). *Anal*. Calcd. for $C_{26}H_{24}O_4$: C, 78.21; H, 6.01. Found: C, 77.87; H, 5.91.

Bis-1,5-[4″-methoxycinnamate]-3,3-dimethyl-1,4-cyclohexadiene (2b). This compound was obtained as light green crystal, mp 215–217°C; IR (potassium bromide): CO 1652, C=C 1620 cm^{-1}; ^1H NMR (deuteriochloroform): δ 1.07 (s, 6-H, 2xCH_3), 2.25 (s, 2-H, CH_2), 3.73 (s, 6-H, OCH_3), 4.75 (s, 2-H, CH), 7.89 (s, 4-H, α, β unsaturated carbonyl), 6.88–7.89 (m, 8-H, aromatic proton). ^{13}C NMR: 26.32 $(CH_3)_2$, 37.89 (CH_2), 41.21 (OCH_3), 73.87 (tetrahedral carbon) and 111.32–114.45 (4xC=C), 126.34–132.43 (Ar—C), 189.09 (C=O), MS: *m/z* 462 (m^{+2}). *Anal*. Calcd. for $C_{28}H_{28}O_6$: C, 73.04; H, 6.08. Found: C, 72.84; H, 5.85.

Bis-1,5-[4″-hydroxycinnamate]-3,3-dimethyl-1,4-cyclohexadiene (2c). This compound was obtained as yellow crystal, mp 198–199°C; IR (potassium bromide): OH 3421, CO 1631, C=C 1610 cm^{-1}, ^1H NMR (deuteriochloroform): δ 0.98 (s, 6-H, 2xCH_3), 2.34 (s, 2-H, CH_2), 4.56 (s, H, OH), 4.67 (s, 2-H, CH), 7.76 (s, 4-H, α, β unsaturated carbonyl), 6.95–7.79 (m, 8-H, aromatic proton). ^{13}C NMR: 26.86 $(CH_3)_2$, 37.64 (CH_2), 40.76 (OCH_3), 72.89 (tetrahedral carbon) and 113–115.35 (4xC=C), 125.89–131.83 (Ar—C), 189.98 (C=O), MS: *m/z* 432 (m^{+2}). *Anal*. Calcd. for $C_{26}H_{24}O_6$: C, 72.22; H, 5.67. Found: C, 72.14; H, 5.63.

General preparation of bis-1,5-[2′H,3′H-dihydro-4′(substitutedphenyl)-1′,5′-benzothiazipin-2′-oxy]-3,3-dimethyl-1,4-cyclohexadiene (3a-c)

Method A (ultrasound method). A mixture of (0.01 mol) 2, 2.14 mL (0.02 mol) 2-aminothiophenol and 1 mL acetic acid in 10 mL of ethanol was subjected to ultrasound irradiation for 24 min. The reaction mixture was poured on crushed ice. The solid separated, filtered, washed with water, and recrystallized from ethanol.

Method B (conventional method). A solution of (0.01 mol) 2, 2.14 mL (0.02 mol) 2-aminothiophenol and 1 mL acetic acid in 10 mL of ethanol was reflux on water bath for 3 h then poured on to ice, the product was isolated in a similar manner as described in the above method.

Bis-1,5-[2′H,3′H-dihydro-4′phenyl-1′,5′-benzothiazipin-2′-oxy]-3,3-dimethyl-1,4-cyclohexadiene (3a). This compound was obtained as light yellow crystal, mp 70–72°C; IR (potassium bromide): C=C 1632, C—S—C 1456 cm^{-1}, ^1H NMR (deuterio-chloroform): δ 0.96 (s, 6-H, 2xCH_3), 2.44 (s, 2-H, CH_2), 3.62 (s, 2-H, NH), 4.25 (s, 2-H, CH), 6.56 (d, 2-H, C_2—H), 7.24 (d, 2-H, C_3—H), 6.56–8.06 (m, 18-H, Aromatic protons). ^{13}C NMR: 27.24 (2xCH_3), 32.45 (CH_2), 65.45 (C_2—H), 72.21 (C_3—H), 73.54 (tetrahedral carbon) and 108.15–136.748 (C=C and Ar—C), MS: *m/z* 616 (m^{+2}). *Anal*. Calcd. for $C_{38}H_{34}N_2O_2S_2$: C, 73.22; H, 5.76; N,4.74; S, 10.84 Found: C, 73.08;H, 5.47; N, 4.59; S, 10.68.

Bis-1,5-[2′H,3′H-dihydro-4′(4″-methoxyphenyl)-1′,5′-benzothiazipin-2′-oxy]-3,3-dimethyl-1,4-cyclohexadiene (3b). This compound was obtained as greenish yellow crystal, mp 73–76°C; IR (potassium bromide): C=C 1625, C—S—C 1443 cm^{-1}, ^1H NMR (deuteriochloroform): δ 0.99 (s, 6-H, 2xCH_3), 2.44 (s, 2-H, CH_2), 3.55 (s, 2-H, NH), 3.85 (s, 6-H, OCH_3), 4.32 (s, 2-H, CH), 6.43 (d, 2-H, C_2—H), 7.37 (d, 2-H, C_3—H), 6.96–8.03 (m, 16-H, Aromatic protrons). ^{13}C NMR: 26.31 (2xCH_3), 32.89 (CH_2), 39.32 (OCH_3), 65.52 (C_2—H), 72.63 (C_3—H), 73.76 (tetrahedral carbon), 108–136.31 (C=C and Ar—C), MS: *m/z* 676 (m^{+2}). *Anal*. Calcd. for $C_{40}H_{38}N_2O_4S_2$: C, 70.15; H, 5.84; N,4.30; S, 9.84. Found: C, 69.41; H, 5.68; N, 4.12; S, 9.73.

Bis-1,5-[2′H,3′H-dihydro-4′(4″-hydroxyphenyl)-1′,5′-benzothiazipin-2′-oxy]-3,3-dimethyl-1,4-cyclohexadiene (3c). This compound was obtained as colorless crystal, mp 95–97°C; IR (potassium bromide): OH 3448, C=C 1636, C—S—C 1421 cm^{-1}, ^1H NMR (deuteriochloroform): δ 1.02 (s, 6-H, 2xCH_3), 2.34 (s, 2-H, CH_2), 3.57 (s, 2-H, NH), 4.32 (s, 2-H, CH), 4.73 (s, 1-H, OH), 6.38 (d, 2-H, C_2—H), 7.63 (d, 2-H, C_3—H), 6.73–7.83 (m, 16-H, Aromatic proton). ^{13}C NMR: 27.45 (2xCH_3), 31.67 (CH_2), 65.68 (C_2—H), 73.54 (C_3—H), 73.76 (tetrahedral carbon), 105.45–137.76 (C=C and Ar—C), MS: m/z 648 (m^{+2}). *Anal*. Calcd. for $C_{38}H_{34}N_2O_4S_2$: C, 69.45; H, 5.49; N,4.50; S, 10.28. Found: C, 69.32; H, 5.34; N, 4.38; S, 10.11.

General preparation of bis-1,5-[-2′,3′,4′,5′-teterahydro-2′-(substitutedphenyl)-4′-oxo-thiophen-3′-carboxylate]-3,3-dimethyl-1,4-cyclohexadiene (4a-c).

Method A (ultrasound method). A mixture of (0.01 mol) 2, 1.38 mL (0.02 mol) thiogylcolic acid, 1 g zinc dust in 10 mL of dioxane were subjected to ultrasound irradiation for 20 min.

After completion of the reaction, as monitored by TLC, the mixture was poured into ice-cold water. The solid obtained was collected by filtration and recrystallized from alcohol. The characteristic data of the compound are given in Table 2.

Method B (conventional method). A mixture of (0.01 mol) 2, 1.38 mL (0.02 mol) thiogylcolic acid and 1 g zinc dust in 10 mL of ethanol were heated under mild condition for 4.5 h. The product was isolated in a similar manner as described above.

Bis-1,5-[-2′,3′,4′,5′-teterahydro-2′-(phenyl)-4′-oxo-thiophen-3′-carboxylate]-3,3-dimethyl-1,4-cyclohexadiene (4a). This compound was obtained as light cream crystal, mp 165–167°C; IR (potassium bromide): CO 1628, C—S—C 1408 cm^{-1}. ^1H NMR (deuteriochloroform): δ 0.97 (s, 6-H, 2xCH_3), 2.44 (s, 2-H, CH_2), 3.21 (s, 2-H, C′$_2$—H), 3.46 (s, 4-H,2XCH_2), 3.90 (s, 2-H, C′$_3$—H), 4.69 (s, 2-H, CH), 7.19–8.02 (m, 10-H, Aromatic proton). ^{13}C NMR: 27.29 (2xCH_3), 29.28 (C′$_2$), 32.18 (CH_2), 42.21 (C′$_3$), 50.71(CH_2—C′$_5$), 73.21 (tetrahedral carbon), 109.10–115.5 (2xC=C), 128.21–131.56 (Ar—C), 196.44 (C=O), 210.21 (C=O). MS: *m/z* 520 (m^{+2}). *Anal*. Calcd. for $C_{30}H_{28}O_6S_2$: C, 69.49; H, 5.40; S, 12.35. Found: C, 69.21; H, 5.23; S, 12.21.

Bis-1,5-[-2′,3′,4′,5′-teterahydro-2′-(4″-methoxyphenyl)-4′-oxothiophen-3′-carboxylate]-3,3-dimethyl-1,4-cyclohexadiene (4b). This compound was obtained as dark green crystal, mp 148–149°C; IR (potassium bromide): CO 1610, C—S—C 1443 cm^{-1}. ^1H NMR (deuteriochloroform): δ 0.96 (s, 6-H, 2xCH_3), 2.36 (s, 2-H, CH_2), 3.21 (s, 2-H, C′$_2$—H), 3.46 (s, 4-H, 2xCH_2), 3.83 (s, 2-H, C′$_3$—H), 3.94 (s, 6-H, OCH_3), 4.43 (s, 2-H, CH), 6.81–7.83 (m, 8-H, Aromatic proton). ^{13}C NMR: 27.32 (2xCH_3), 29.43 (C′$_2$), 31.67 (CH_2), 39.34 (OCH_3), 41.54 (C′$_3$), 52.56 (CH_2—C′$_5$), 73.02 (tetrahedral carbon), 110.98–116.12 (2xC=C), 116.32–133.34 (Ar—C), 198.07 (C=O), 209.87 (C=O). MS: *m/z* 610 (m^{+2}). *Anal*. Calcd. for $C_{32}H_{32}O_6S_2$: C, 63.15; H, 5.26; S, 10.58. Found: C, 62.94; H, 5.11; S, 10.32.

Bis-1,5-[-2′,3′,4′,5′-teterahydro-2′-(4″-hydroxyphenyl)-4′-oxothiophen-3′-carboxylate]-3,3-dimethyl-1,4-cyclohexadiene (4c). This compound was obtained as colorless crystal, mp 158–160°C; IR (potassium bromide): CO 1615, C—S—C 1448 cm^{-1}. ^1H NMR (deuteriochloroform): δ 9.86 (s, 6-H, 2xCH_3), 2.21 (s, 2-H, CH_2), 3.28 (s, 2-H, C′$_2$—H), 3.38 (s, 4-H, 2xCH_2), 3.97 (s, 2-H, C′$_3$—H), 4.51 (s, 2-H, CH), 4.75 (s, 2-H, OH), 7.08–8.16 (m, 8-H, Aromatic proton). ^{13}C NMR: 27.12 (2xCH_3), 29.87 (C′$_2$), 32.54 (CH_2), 41.84 (C′$_3$), 52.93 (CH_2—C′$_5$), 73.12 (tetrahedral carbon), 109.12–116.23 (2xC=C), 116.34–136.65 (Ar—C), 196.78 (C=O), 204.45 (C=O). MS: *m/z* 552 (m^{+2}). *Anal*. Calcd. for $C_{30}H_{28}O_8S_2$: C, 65.45; H, 5.09; S, 11.63. Found: C, 65.23; H, 4.96; S, 11.32.

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