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Synthesis and Antiphospholipase Activity of 3,5-Disubstituted Thiotetronic Acid Derivatives

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Abstract—The condensation of 3-acetyltetrahydrothiophene-2,4-dione with aromatic aldehydes in the presence of piperidine as a catalyst gave a series of 5-arylmethylidene-3-acetyltetrahydrothiophene-2,4-diones. The reaction with excess aldehyde (2.5 equiv) led to the formation of bis-condensation products, 5-arylmethylidene-3-(3-aryl-1-oxoprop-2-enyl)tetrahydrothiophene-2,4-diones. Analogous 3,5-disubstituted tetrahydrothiophene-2,4-dione derivatives with different aryl groups in the ring and the side chain were synthesized by two-step condensation with the use of differently substituted aromatic aldehydes. Catalytic hydrogenation of both mono- and bis-adducts resulted in the reduction of the side-chain double C=C bond, while ionic hydrogenation with triethylsilane in trifluoroacetic acid in the presence of lithium perchlorate involved both the double C=C bond and carbonyl group in the side chain. The isolated products showed an appreciable effect on the activity of two secretory phospholipases A_2 from various sources.

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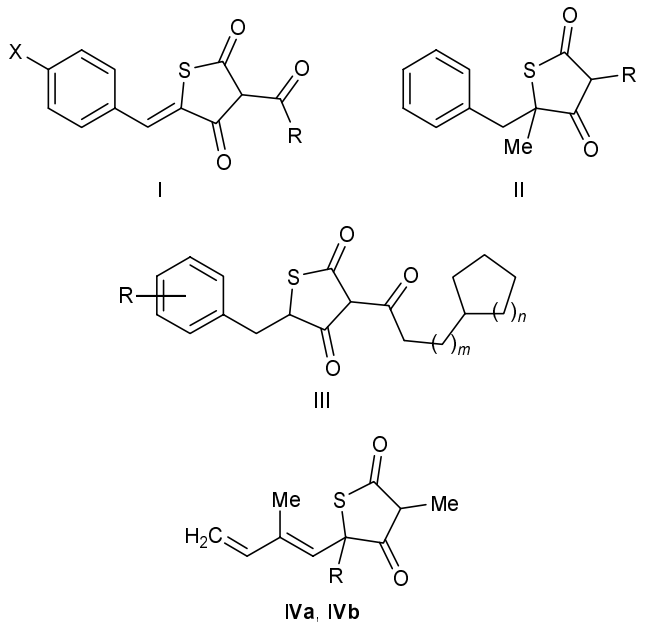
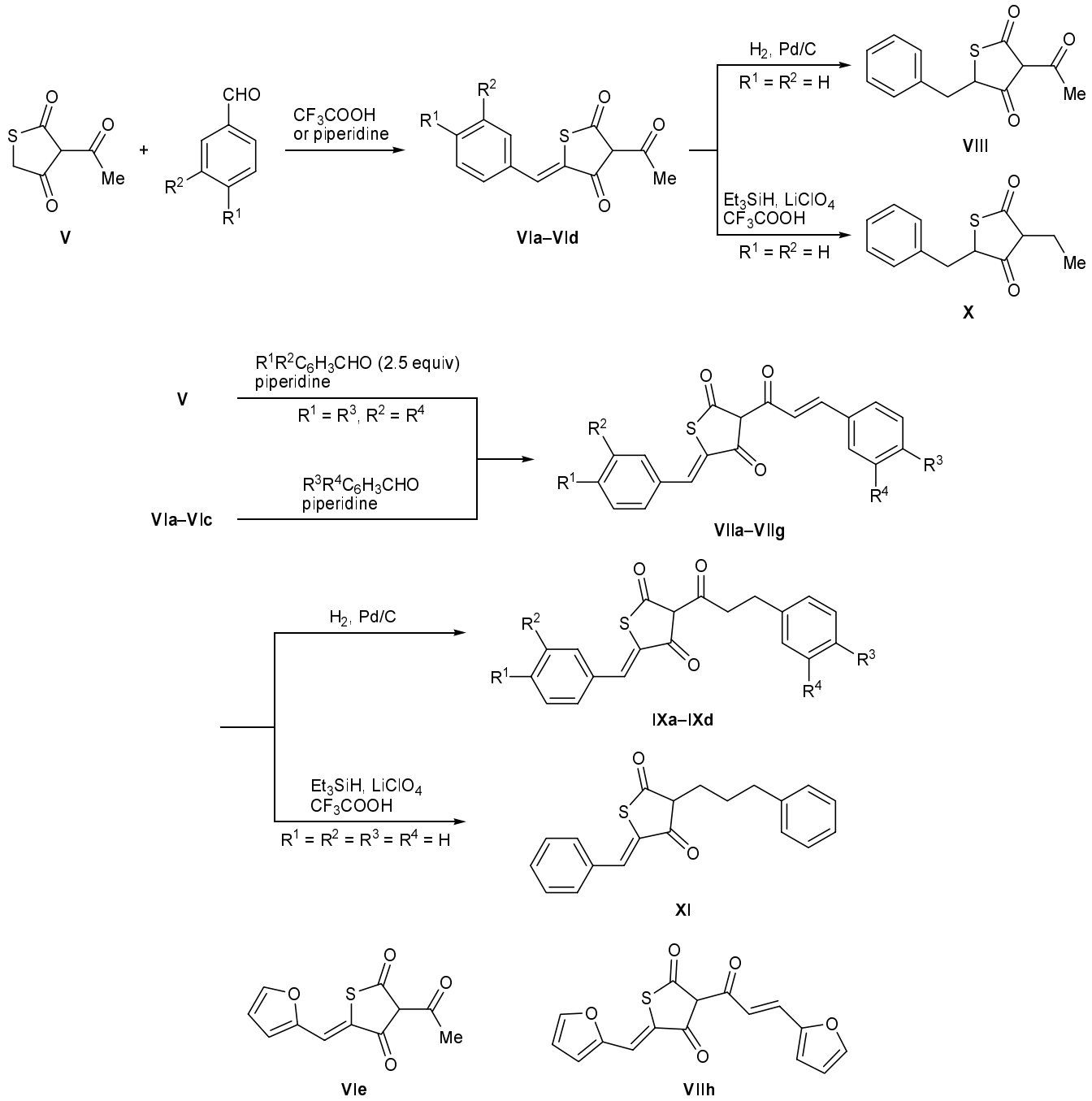
One method of acetyl group functionalization in 2-acylcycloalkane-1,3-diones is based on their condensation with aromatic aldehydes, followed by transformation of the ketovinylaryl moiety thus formed. This approach was explored in detail with β-triketones of the cyclohexane and cyclopentane series [1] and was applied to the synthesis of naturally occurring cyclic triacylmethanes [2] and prostaglandin analogs [3]. While studying sulfur-containing heterocyclic β-triketones [4–6], we focused on a number of biologically active 3-acyltetrahydrothiophene-2,4-diones **I**–**III** which were found to exhibit antiarthritic [7], immunosupressing [8], and antibacterial properties [9]. These compounds are structurally related to the natural antibiotics Thiolactomycin (**IVa**) and Thiotetromycin (**IVb**) isolated from *Nocardia* soil bacteria [10]. Compounds like **III** having a sufficiently bulky hydrophobic side chain were reported to inhibit phospholipase A_2 (PLA_2) [9].

Taking the above stated into account, with the goal of studying lipolytic reactions involving PLA_2 with different specificities in the present work we made an attempt to synthesize a series of new derivatives of thiotetronic acid (tetrahydrothiophene-2,4-dione) structurally related to compounds **I**–**III**. For this purpose, 3-acetyltetrahydrothiophene-2,4-dione (**V**) [11] was brought into reaction with aromatic aldehydes, fol-



X = Hlg; **I**, R = Alk, AlkO; **II**, R = Hlg, Alk, AlkO; **III**, R = H, Et, Ph, COMe; *m* = 1–15, *n* = 0–20; **IV**, R = Me (**a**), Et (**b**).

Scheme 1.



VI, $R^1 = R^2 = H$ (**a**), $R^1 = H$, $R^2 = Cl$ (**b**), $R^1 = R^2 = MeO$ (**c**), $R^1 = Br$, $R^2 = H$ (**d**); **VII**, $R^1 = R^2 = R^3 = R^4 = H$ (**a**), $R^1 = R^3 = H$, $R^2 = R^4 = Cl$ (**b**), $R^1 = R^3 = Br$, $R^2 = R^4 = H$ (**c**), $R^1 = R^2 = R^3 = R^4 = MeO$ (**d**), $R^1 = R^2 = R^3 = H$, $R^4 = Cl$ (**e**), $R^1 = R^2 = MeO$, $R^3 = R^4 = H$ (**f**), $R^1 = R^2 = H$, $R^3 = R^4 = MeO$ (**g**); **IX**, $R^1 = R^2 = R^3 = R^4 = H$ (**a**), $R^1 = R^2 = R^3 = H$, $R^4 = Cl$ (**b**), $R^1 = R^2 = MeO$, $R^3 = R^4 = H$ (**c**), $R^1 = R^2 = R^3 = R^4 = MeO$ (**d**).

lowed by reduction of the condensation products. Unlike 3-acyltetronic acids and 2-acylcycloalkane-1,3-diones [3, 12], the condensation of 3-acetylthiotetronic acid **V** with aromatic aldehydes occurred under conditions of both acid and base catalysis and involved the endocyclic methylene group rather than methyl group in the side-chain acetyl group, and the products were 5-arylmethylidene-3-acetyltetrahydrothiophene-2,4-diones **VI** [7, 13]. Using piperidine as catalyst, we obtained a series of β-triketones **VIa**–**VIe** (Scheme 1).

Effect of thiotetronic acid derivatives **VIIb**, **VIIc**, **VIIe**, and **IXa** on the activity of phospholipases (PLA_2) from pig pancreas (A) and *Naja naja oxiana* venom (B)[a]

PLA_2	Control		**VIIb**			**VIIc**			**VIIe**			**IXa**		
	hydrolysis, %	V_0	hydrolysis, %	V_i	V_i/V_0	hydrolysis, %	V_i	V_i/V_0	hydrolysis, %	V_i	V_i/V_0	hydrolysis, %	V_i	V_i/V_0
PC–Triton X-100														
A	14.6±0.7	4.1±0.2	4.0±1.2	1.1±0.3	0.3	11.8±0.4	3.3±0.1	0.8	13.8±2.0	3.9±0.6	0.9	13.7±0.3	3.8±0.1	0.9
B	35.4±0.3	1.77	24.5±0.8	1.3	0.7	29.5±3.8	1.5	0.9	37.2±4.0	1.8	1	31.1±0.6	1.5	0.9
PC–DC-Na														
A	23.4±0.4	6.6±0.1	11.0±0.6	3.1±0.2	0.5	14.2±2.2	4.0±0.6	0.6	15.8±3.5	4.4±0.1	0.7	11.9±0.4	3.3±0.01	0.5
B	19.0±0.2	0.95	16.6±0.1	0.8	0.9	22.4±1.7	1.1	0.1	7.1±0.1	0.4	0.4	8.2±0.1	0.3	0.3
PC–CTAB														
A	7.6±2.0	2.1±0.5	0.2±0.05	0.04±0	0	22.5±3.7	6.3±1.0	3.0	11.9±0.3	3.3±0.3	1.6	9.2±2.0	2.6±0.6	1.2
B	27.8±0.5	1.36	21.5±0.4	1.1	0.8	26.8±0.2	1.3	1.0	18.8±0.2	0.9	0.7	23.0±2.0	1.2	0.8

[a] Each run was repeated for 2–3 times, two samples being withdrawn in parallel; reaction time 2 min; the substrate was phosphatidylcholine (PC) from eggs; V_0 is the initial reaction rate, and V_i is the reaction rate after preliminary incubation of PLA_2 with thiotetronic acid derivatives; the reaction rates were expressed as the amount of hydrolysis product (μmol) formed in 1 min in the presence of 1 mg of the enzyme (μmol min^{-1} mg^{-1}).

Monitoring of the reaction course by thin-layer chromatography revealed formation of small amounts of compounds **VII** as a result of condensation of thiophenedione **V** with two aromatic aldehyde molecules. When the reaction of **V** was performed with 2.5 equiv of aromatic aldehyde and the reaction time was increased, bis-adducts **VIIa**–**VIId** and **VIIh** were isolated as the major products. However, compounds **VII** were not formed in trifluoroacetic acid, regardless of the reactant ratio and reaction time. By condensation of compounds **VIa**–**VIc** with aromatic aldehydes we succeeded in obtaining β-triketones **VIIe**–**VIIg** having differently substituted aryl groups on the ring and in the side chain; the reaction was not accompanied by exchange of the aryl groups.

We examined various ways of reduction of the condensation products using compound **VIa** as an example. Catalytic hydrogenation of **VIa** in methanol over palladium catalyst (10% Pd/C) resulted in almost quantitative formation of 5-benzyl derivative **VIII** via reduction of the exocyclic double C=C bond. Ionic hydrogenation of the same substrate with triethylsilane in trifluoroacetic acid in the presence of lithium perchlorate involved both exocyclic double bond and acetyl carbonyl group to give 60% of diketone **X**. Saturated β-triketones **IXa**–**IXd** were obtained in 75–80% yield by catalytic hydrogenation of both double bonds in compounds **VIIa**, **VIId**, and **VIIf**. No partial hydrogenation products were detected in the reaction mixtures by TLC. Ionic hydrogenation of bis-adduct **VIIa** gave 3,5-disubstituted tetrahydrothiophene-2,4-dione **XI** in a moderate yield (45–57%). The structure of the products was confirmed by their elemental analyses and ^{1}H NMR, IR, and mass spectra. In the ^{1}H NMR spectra of **VIa**–**VIe** and **VIIa**–**VIIh** we observed only one olefinic proton signal (a singlet at δ 7.6–7.9 ppm, C^5=CH), and compounds **VIIa**–**VIIh** displayed only one set of signals from the CH=CH olefinic protons; these data indicate that only one isomer among those possible is formed.

We previously showed that enhancement of hydrophobic properties of molecules in the series of 9-, 10-, and 11-methyl-substituted prostaglandins due to extension of the aliphatic ω-chain, as well as increase of the overall molecular rigidity via introduction of double and triple bonds or additional bulky heterocyclic substituents, makes the resulting compounds more potent inhibitors of secretory phospholipases A_2 [11, 12]. Therefore, we anticipated that 3,5-disubstituted tetrahydrothiophene-2,4-diones **VII** and **IX** would be potentially enhanced analogs of PLA_2 effectors [8]. Some of the synthesized thiotetronic acid derivatives were preliminarily tested for their activity in the hemolysis of erythrocytes on blood agar by the action of PLA_2 isolated from *Naja naja oxiana* venom [13–16]. Preincubation of PLA_2 with compounds **VIIb**, **VIIc**, **VIIe**, and **IXa** led to a visually distinct variation of the lysis zone area, indicating an appreciable effect of the tested

compounds on the hemolytic activity of PLA_2; the effect of these compounds on the hemolytic activity of PLA_2 isolated from *Naja naja oxiana* venom depended on their chemical structure. Essential differences were observed in the effects on PLA_2 from pig pancreas and *Naja naja oxiana* venom which are characterized by different substrate specificities for "acid" and "neutral" phospholipids [17].

Compounds **VII** and **IX** were also tested in the hydrolysis of a natural phospholipid, phosphatidylcholine, in the presence of PLA_2 in micellar phases formed by neutral (Triton X-100), anionic (sodium deoxycholate DC-Na), and cationic detergents (cetyltrimethylammonium bromide CTAB) (see table). Measurement of the rate of hydrolysis of phosphatidylcholine ($\mu mol\ min^{-1}\ mg^{-1}$) in the micellar phase containing *Naja naja oxiana* venom PLA_2 in the presence (V_i) and in the absence (V_0) of thiotetronic acid derivatives showed the following series of these compounds according their effect on the lipolysis: **VIIb** > **IXa** > **VIIc** > **VIIe**. Within the time interval corresponding to enzyme saturation with the substrate (5 to 10 min), an analogous pattern was observed in the hydrolysis of phosphatidylcholine with PLA_2 isolated from pig pancreas: **VIIb** = **IXa** > **VIIc** > **VIIe**. Thus, the most potent PLA_2 inhibitors were bis(chlorobenzylidene) derivative **VIIb** and triketone **IXa** having no olefinic bonds. The effect on pancreas PLA_2 was stronger: the rate of hydrolysis of phosphatidylcholine in the presence of the enzyme preincubated with **VIIb** and **IXa** was twice as low as that in control experiments during the whole time interval.

Thus lipolytic reactions with phospholipases in the presence of various compounds, including thiotetronic acid derivatives, may be used as a specific indicator of their biological activity against pathological disorders induced by increased PLA_2 activity (inflammatory, hypoxic, allergic, and other disorders).

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from samples prepared as KBr pellets (solid products) or thin films (liquids). The ^1H NMR spectra were measured on a Bruker AT-200 spectrometer from solutions in DMSO-d_6 (compounds **VIIa**–**VIIh**) or chloroform-*d* (the others) using TMS as internal reference. The mass spectra were obtained on an MKh-1320 instrument. The melting points were determined on a Boetius melting point apparatus. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 or Alufol UV-254 plates; spots were visualized by UV irradiation, followed by spraying with a solution of iron(III) chloride.

Condensation of 3-acetyltetrahydrothiophene-2,4-dione (V) with aromatic aldehydes (*general procedure***).** A solution of 1.58 g (10 mmol) of 3-acetyltetrahydrothiophene-2,4-dione (**V**), 11 mmol of the corresponding aromatic aldehyde, and 0.2 ml of piperidine in 50 ml of toluene was heated under reflux until water no longer separated as azeotrope (8–12 h, TLC). The mixture was cooled to room temperature, and the precipitate (5-arylmethylidene derivative **VIa**–**VIe**) was filtered off and recrystallized from methanol–ethyl acetate. In the synthesis of compounds **VIIa**–**VIId** and **VIIh**, 25 mmol of the corresponding aldehyde was used. Compounds **VIIe**–**VIIg** were synthesized by the above procedure in two steps without isolation of intermediate condensation product. In the first step, an equimolar amount of aldehyde was used, and in the second, 1.5 equiv.

3-Acetyl-5-[(*Z*)-phenylmethylidene]tetrahydrothiophene-2,4-dione (VIa). Yield 2.02 g (82%), mp 147–150°C; published data [7]: mp 151–152°C. IR spectrum, ν, cm^{-1}: 1660, 1640, 1620, 1580, 1565. ^1H NMR spectrum, δ, ppm: 2.62 s (3H, CH_3), 7.40–7.50 m (3H, H_{arom}), 7.55–7.60 m (2H, H_{arom}), 7.86 s (1H, SC=CH), 15.80 br.s (1H, OH, enol). Found, %: C 63.38; H 4.11; S 12.98. $[M]^+$ 246. $C_{13}H_{10}O_3S$. Calculated, %: C 63.40; H 4.09; S 13.02.

3-Acetyl-5-[(*E*)-3-chlorophenylmethylidene]-tetrahydrothiophene-2,4-dione (VIb). Yield 2.13 g (76%), mp 128–130°C. IR spectrum, ν, cm^{-1}: 1700, 1625, 1570, 1535. ^1H NMR spectrum, δ, ppm: 2.64 s (3H, CH_3), 7.36–7.60 m (4H, H_{arom}), 7.76 s (1H, SC=CH), 15.90 br.s (1H, OH, enol). Found, %: C 55.68; H 3.30; Cl 12.72; S 11.46. $[M]^+$ 280, $[M+2]^+$ 282. $C_{13}H_9ClO_3S$. Calculated, %: C 55.62; H 3.23; Cl 12.63; S 11.42.

3-Acetyl-5-[(*Z*)-3,4-dimethoxyphenylmethylidene]tetrahydrothiophene-2,4-dione (VIc). Yield 2.40 g (78%), mp 150–152°C. IR spectrum, ν, cm^{-1}: 1705, 1630, 1600, 1530. ^1H NMR spectrum, δ, ppm: 2.62 s (3H, CH_3), 3.96 s (3H, CH_3O), 3.98 s (3H, CH_3O), 6.96 d (1H, 5'-H, J = 8.0 Hz), 7.16 d (1H, 2'-H, J = 2.0 Hz), 7.24 d.d (1H, 6'-H, J_1 = 8.0, J_2 = 2.0 Hz), 7.86 s (1H, CC=CH), 16.80 br.s (1H, OH, enol). Found, %: C 58.92; H 4.78; S 10.36. $[M]^+$ 306. $C_{15}H_{14}O_5S$. Calculated, %: C 58.81; H 4.61; S 10.47.

3-Acetyl-5-[(*Z*)-4-bromophenylmethylidene]-tetrahydrothiophene-2,4-dione (VId). Yield 2.50 g

(77%), mp 179–182°C; published data [7]: mp 180–182°C. IR spectrum, ν, cm^{-1}: 1680, 1630, 1570, 1545. ^1H NMR spectrum, δ, ppm: 2.68 s (3H, CH_3), 7.46–7.55 m (2H, H_{arom}), 7.57–7.67 m (2H, H_{arom}), 7.68 s (1H, SC=CH), 15.60 br.s (1H, OH, enol). Found, %: C 48.18; H 2.73; Br 25.02; S 9.95. $[M - 1]^+$ 324, $[M + 1]^+$ 326. $C_{13}H_9BrO_3S$. Calculated, %: C 48.02; H 2.79; Br 24.57; S 9.86.

3-Acetyl-5-[(*Z*)-2-furylmethylidene]tetrahydrothiophene-2,4-dione (VIe). Yield 1.70 g (72%), mp 128–130°C. IR spectrum, ν, cm^{-1}: 1700, 1670 sh, 1620, 1580, 1540. ^1H NMR spectrum, δ, ppm: 2.62 s (3H, CH_3), 6.62 m (1H, OCH=C**H**), 6.88 d (1H, OC=CH, J = 4.0 Hz), 7.62 s (1H, SC=CH), 7.70 d (1H, OCH, J = 2.0 Hz), 15.60 br.s (1H, enol). Found, %: C 56.06; H 3.53; S 13.64. $[M]^+$ 236. $C_{11}H_8O_4S$. Calculated, %: C 55.92; H 3.41; S 13.57.

5-[(*Z*)-Phenylmethylidene]-3-[(*E*)-3-phenylprop-2-enoyl]tetrahydrothiophene-2,4-dione (VIIa). Yield 2.17 g (65%), mp 197–198°C. IR spectrum, ν, cm^{-1}: 1705, 1630, 1580, 1530. ^1H NMR spectrum, δ, ppm: 7.40–7.56 m (6H), 7.62 m (2H), and 7.70 m (2H) (H_{arom}); 7.89 s (1H, SC=CH); 8.02 d and 8.12 d [2H, C(O)CH=CH, J = 16.0 Hz]; 16.40 br.s (1H, enol). Found, %: C 71.80; H 4.31; S 9.64. $[M]^+$ 334. $C_{20}H_{14}O_3S$. Calculated, %: C 71.84; H 4.22; S 9.59.

5-[(*Z*)-3-Chlorophenylmethylidene]-3-[(*E*)-(3-chlorophenyl)prop-2-enoyl]tetrahydrothiophene-2,4-dione (VIIb). Yield 2.86 g (71%), mp 218–219°C. IR spectrum, ν, cm^{-1}: 1705, 1630, 1580, 1555. ^1H NMR spectrum, δ, ppm: 7.37–7.45 m (4H, H_{arom}), 7.45–7.55 m (2H, H_{arom}), 7.59 s (1H, H_{arom}), 7.69 s (1H, H_{arom}), 7.80 s (1H, SC=CH), 8.00 s [2H, C(O)CH=CH], 16.10 br.s (1H, OH, enol). Found, %: C 59.71; H 3.08; Cl 17.63; S 8.11. $[M]^+$ 402, $[M + 2]^+$ 404. $C_{20}H_{12}Cl_2O_3S$. Calculated, %: C 59.57; H 3.00; Cl 17.58; S 7.95.

5-[(*Z*)-4-Bromophenylmethylidene]-3-[(*E*)-3-(4-bromophenyl)prop-2-enoyl]tetrahydrothiophene-2,4-dione (VIIc). Yield 3.30 g (67%), mp 275–280°C. IR spectrum, ν, cm^{-1}: 1700, 1630, 1590, 1580, 1550, 1500. ^1H NMR spectrum, δ, ppm: 7.45–7.70 m (8H, H_{arom}), 7.78 s (1H, SC=CH), 8.05 s [2H, C(O)CH=CH], 16.30 br.s (1H, OH, enol). Found, %: C 48.93; H 2.60; Br 32.31; S 6.62. $[M - 2]^+$ 490, $[M]^+$ 492, $[M + 2]^+$ 494. $C_{20}H_{12}Br_2O_3S$. Calculated, %: C 48.81; H 2.46; Br 32.47; S 6.51.

5-[(*Z*)-3,4-Dimethoxyphenylmethylidene]-3-[(*E*)-3-(3,4-dimethoxyphenyl)prop-2-enoyl]tetrahydrothiophene-2,4-dione (VIId). Yield 3.12 g (69%), mp 200–202°C (decomp.). IR spectrum, ν, cm^{-1}: 1670, 1635, 1610, 1590, 1570, 1520. ^1H NMR spectrum, δ, ppm: 3.98 s (12H, $4CH_3O$), 6.75 d and 7.40 d [2H, C(O)CH=CH, J = 16.0 Hz], 6.88 d and 6.93 d (2H, 5'-H, 5"-H, J = 8.0 Hz), 7.07 d (1H, 2'-H, J = 8.0 Hz), 7.15–7.25 m (3H, 2"-H, 6'-H, 6"-H), 7.60 s (1H, SC=CH), 16.45 br.s (1H, OH, enol). Found, %: C 63.51; H 4.80; S 7.12. $[M]^+$ 454. $C_{24}H_{22}O_7S$. Calculated, %: C 63.42; H 4.88; S 7.05.

3-[(*Z*)-3-(3-Chlorophenyl)prop-2-enoyl]-5-[(*E*)-phenylmethylidene]tetrahydrothiophene-2,4-dione (VIIe). Yield 2.25 g (61%), mp 174–175°C. IR spectrum, ν, cm^{-1}: 1690, 1640, 1580, 1540. ^1H NMR spectrum, δ, ppm: 7.40–7.70 m (8H, H_{arom}), 7.86 s (1H, SC=CH), 8.00 s [2H, C(O)CH=CH], 16.00 br.s (1H, enol). Found, %: C 65.18; H 3.48; Cl 9.49; S 8.61. $[M]^+$ 368, $[M + 2]^+$ 370. $C_{20}H_{13}ClO_3S$. Calculated, %: C 65.13; H 3.55; Cl 9.61; S 8.69.

5-[(*E*)-3,4-Dimethoxyphenylmethylidene]-3-[(*E*)-3-phenylprop-2-enoyl]tetrahydrothiophene-2,4-dione (VIIf). Yield 2.55 g (65%), mp 198–199°C. IR spectrum, ν, cm^{-1}: 1690, 1660, 1620, 1590, 1530. ^1H NMR spectrum, δ, ppm: 3.96 s (6H, CH_3O), 6.96 d (1H, 6'-H, J = 8.0 Hz), 7.15 d (1H, 5'-H, J = 2.0 Hz), 7.24 d.d (1H, 2'-H, J_1 = 8.0, J_2 = 2.0 Hz), 7.46 m (3H) and 7.70 m (2H) (H_{arom}), 7.82 s (1H, SC=CH), 8.06 s [2H, C(O)CH=CH], 16.36 br.s (1H, enol). Found, %: C 67.08; H 4.71; S 8.22. $[M]^+$ 394. $C_{22}H_{18}O_5S$. Calculated, %: C 66.99; H 4.60; S 8.13.

3-[(*E*)-3-(3,4-Dimethoxyphenyl)prop-2-enoyl]-5-[(*E*)-phenylmethylidene]tetrahydrothiophene-2,4-dione (VIIg). Yield 2.20 g (56%), mp 178–180°C (decomp.). IR spectrum, ν, cm^{-1}: 1695, 1630, 1600, 1535. ^1H NMR spectrum, δ, ppm: 3.97 s and 3.99 s (6H, CH_3O), 6.94 d (1H, 5'-H, J = 8.0 Hz), 7.22 d (1H, 2'-H, J = 2.0 Hz), 7.32 d.d (1H, 6'-H, J_1 = 8.0, J_2 = 2.0 Hz), 7.40–7.52 m (3H) and 7.60–7.68 m (2H) (H_{arom}), 7.84 s (1H, SC=CH), 7.90 d and 8.07 d [2H, C(O)CH=CH, J = 16.0 Hz], 16.30 br.s (1H, enol). Found, %: C 66.92; H 4.58; S 8.16. $[M]^+$ 394. $C_{22}H_{18}O_5S$. Calculated, %: C 66.99; H 4.60; S 8.13.

5-[(*Z*)-2-Furylmethylidene]-3-[(*E*)-3-(2-furyl)-prop-2-enoyl]tetrahydrothiophene-2,4-dione (VIIh). Yield 2.00 g (64%), mp 199–203°C (decomp.). IR spectrum, ν, cm^{-1}: 1700, 1620, 1580, 1530. ^1H NMR spectrum, δ, ppm: 6.60 m (2H, 4'-H, 4"-H), 6.82 d and 6.89 d (2H, 3'-H, 3"-H, J = 4.0 Hz), 7.64 d and 7.70 d (2H, 5'-H, 5"-H, J = 2.0 Hz), 7.63 s (1H, SC=CH), 7.84 s [2H, C(O)CH=CH], 16.40 br.s (1H, enol).

Found, %: C 61.31; H 3.29; S 10.27. $[M]^+$ 314. $C_{16}H_{10}O_5S$. Calculated, %: C 61.14; H 3.21; S 10.20.

Catalytic hydrogenation of compounds VIa, VIIa, and VIId–VIIf (*general procedure***).** A solution of 5 mmol of compound **VIa**, **VIIa**, or **VIId–VIIf** in 50 ml of methanol was hydrogenated at room temperature under atmospheric pressure in the presence of 100 mg of 10% Pd/C until complete saturation with hydrogen (TLC). The catalyst was filtered off, the solvent was removed under reduced pressure, the residue was dissolved in chloroform, the solution was passed through a thin layer of silica gel (2 mm), and the solvent was removed under reduced pressure.

3-Acetyl-5-benzyltetrahydrothiophene-2,4-dione (VIII). Yield 1.21 g (98%), oily substance. IR spectrum, ν, cm^{-1}: 1705, 1685, 1630, 1590. ^1H NMR spectrum, δ, ppm: 2.54 s (3H, CH_3), 3.00 d.d (1H, SCHC$\mathbf{H}_A$H$_B$, J_1 = 14.0, J_2 = 10.0 Hz), 3.60 d.d (1H, SCHCH$_A\mathbf{H}_B$, J_1 = 14.0, J_2 = 4.0 Hz), 4.50 d.d (1H, SCH, J_1 = 10.0, J_2 = 4.0 Hz), 7.25–7.40 m (5H, H_{arom}), 15.80 br.s (1H, enol). Found, %: C 63.14; H 4.80; S 13.08. $[M]^+$ 248. $C_{13}H_{12}O_3S$. Calculated, %: C 62.88; H 4.87; S 12.91.

5-Benzyl-3-(3-phenylpropanoyl)tetrahydrothiophene-2,4-dione (IXa). Yield 1.60 g (95%), mp 98–100°C (from ethyl acetate–hexane). IR spectrum, ν, cm^{-1}: 1700, 1640, 1580, 1560. ^1H NMR spectrum, δ, ppm: 2.95 t (2H, $COCH_2$, J = 7.5 Hz), 3.00 d.d (1H, PhC$\mathbf{H}_A$H$_B$, J_1 = 14.0, J_2 = 10.0 Hz), 3.25 t (2H, $COCH_2C\mathbf{H}_2$, J = 7.5 Hz), 3.58 d.d (1H, PhCH$_A\mathbf{H}_B$, J_1 = 14.0, J_2 = 3.5 Hz), 4.50 d.d (1H, SCH, J_1 = 10.0, J_2 = 3.5 Hz), 7.20–7.40 m (10H, H_{arom}), 16.04 br.s (1H, enol). Found, %: C 70.81; H 5.28; S 9.60. $[M]^+$ 338. $C_{20}H_{18}O_3S$. Calculated, %: C 70.98; H 5.36; S 9.47.

5-Benzyl-3-[3-(3-chlorophenyl)propanoyl]tetrahydrothiophene-2,4-dione (IXb). Yield 1.80 g (97%), mp 65–66°C (from ethyl acetate–hexane). IR spectrum, ν, cm^{-1}: 1700, 1635, 1610, 1585, 1560. ^1H NMR spectrum, δ, ppm: 2.90 t (2H, $COCH_2$, J = 7.5 Hz), 2.94 d.d (1H, PhC$\mathbf{H}_A$H$_B$, J_1 = 14.0, J_2 = 10.0 Hz), 3.16 t (2H, $COCH_2C\mathbf{H}_2$, J = 7.5 Hz), 3.58 d.d (1H, PhCH$_A\mathbf{H}_B$, J_1 = 14.0, J_2 = 3.5 Hz), 4.50 d.d (1H, SCH, J_1 = 10.0, J_2 = 3.5 Hz), 7.20–7.40 m (9H, H_{arom}), 13.80 br.s (1H, enol). Found, %: C 64.37; H 4.76; Cl 9.62; S 8.46. $[M]^+$ 372, $[M + 2]^+$ 374. $C_{20}H_{17}ClO_3S$. Calculated, %: C 64.42; H 4.60; Cl 9.51; S 8.60.

5-(3,4-Dimethoxybenzyl)-3-(3-phenylpropanoyl)tetrahydrothiophene-2,4-dione (IXc). Yield 1.90 g (95%), oily substance. IR spectrum, ν, cm^{-1}: 1700, 1635, 1610, 1585, 1560. ^1H NMR spectrum, δ, ppm: 2.82 d.d (1H, SCHC$\mathbf{H}_A$H$_B$, J_1 = 14.0, J_2 = 10.0 Hz), 2.90 t (2H, $COCH_2$, J = 7.5 Hz), 3.18 m (2H, $COCH_2C\mathbf{H}_2$), 3.54 d.d (1H, SCHCH$_A\mathbf{H}_B$, J_1 = 14.0, J_2 = 4.0 Hz), 3.96 s and 3.98 s (6H, OCH_3), 4.24 d.d (1H, SCH, J_1 = 10.0, J_2 = 4.0 Hz), 6.85–7.30 m (8H, H_{arom}), 16.20 br.s (1H, enol). Found, %: C 66.48; H 5.68; S 8.16. $[M]^+$ 398. $C_{22}H_{22}O_5S$. Calculated, %: C 66.31; H 5.56; S 8.05.

5-(3,4-Dimethoxybenzyl)-3-[3-(3,4-dimethoxyphenyl)propanoyl]tetrahydrothiophene-2,4-dione (IXd). Yield 2.25 g (98%), mp 116–117°C (from hexane). IR spectrum, ν, cm^{-1}: 1700, 1635, 1610, 1585, 1560. ^1H NMR spectrum, δ, ppm: 2.95 t (2H, $COCH_2$, J = 7.5 Hz); 3.22 t (2H, $COCH_2C\mathbf{H}_2$, J = 7.5 Hz); 3.35 m (1H, PhC$\mathbf{H}_A$H$_B$); 3.82–3.92 m (2H, PhCH$_A\mathbf{H}_B$, SCH); 3.86 s, 3.89 s, 3.95 s, and 3.98 s (3H each, OCH_3); 6.80–7.22 m (6H, H_{arom}); 12.80 br.s (1H, enol). Found, %: C 63.00; H 5.81; S 7.07. $[M]^+$ 458. $C_{24}H_{26}O_7S$. Calculated, %: C 62.87; H 5.72; S 6.99.

Ionic hydrogenation of compounds VIa and VIIa. Triketone **VIa** or **VIIa**, 1 mmol, was dissolved in 5 ml of trifluoroacetic acid, and 2 ml of a 1% solution of lithium perchlorate in trifluoroacetic acid and 2.0 ml (12.5 mmol) of triethylsilane were added. The mixture was stirred for 8–12 h at room temperature (TLC), the solvent and excess reactant were removed under reduced pressure, the residue was dissolved in 50 ml of chloroform, the solution was washed with one portion of water and dried over magnesium sulfate, and the solvent was distilled off under reduced pressure.

5-Benzyl-3-ethyltetrahydrothiophene-2,4-dione (X). Yield 0.19 g (81%), oily substance. IR spectrum, ν, cm^{-1}: 1750, 1705, 1610. ^1H NMR spectrum, δ, ppm: 1.00 t (3H, CH_3, J = 7.5 Hz), 2.24 q (2H, $CH_3C\mathbf{H}_2$, J = 7.5 Hz), 2.93 d.d (1H, PhC$\mathbf{H}_A$, J_1 = 14.0, J_2 = 10.0 Hz), 3.55 d.d (1H, PhC$\mathbf{H}_B$, J_1 = 14.0, J_2 = 4.0 Hz), 4.40 d.d (1H, SCH, J_1 = 10.0, J_2 = 4.0 Hz), 7.20–7.34 m (5H, H_{arom}), 11.00 br.s (1H, enol). Found, %: C 66.48; H 6.12; S 13.44. $[M]^+$ 234. $C_{13}H_{14}O_2S$. Calculated, %: C 66.64; H 6.02; S 13.68.

5-Benzyl-3-(3-phenylpropyl)tetrahydrothiophene-2,4-dione (XI). Yield 0.22 g (68%), oily substance. IR spectrum, ν, cm^{-1}: 1760, 1710, 1610. ^1H NMR spectrum, δ, ppm: 1.74 m (2H, $CH_2C\mathbf{H}_2CH_2$), 2.25 t (2H, PhC$\mathbf{H}_2$, J = 7.5 Hz), 2.55 t (2H, $COC\mathbf{H}_2$-CH_2, J = 7.5 Hz), 2.88 d.d (1H, SCHC$\mathbf{H}_A$H$_B$, J_1 = 14.0, J_2 = 10.0 Hz), 3.53 d.d (1H, SCHCH$_A\mathbf{H}_B$, J_1 = 14.0, J_2 = 4.0 Hz), 4.37 d.d (1H, SCH, J_1 = 10.0, J_2 = 4.0 Hz), 7.20–7.40 m (10H, H_{arom}), 10.00 br.s (1H,

enol). Found, %: C 73.98; H 6.11; S 9.94. $[M]^+$ 324. $C_{20}H_{20}O_2S$. Calculated, %: C 74.04; H 6.21; S 9.88.

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