Isorhodanine and Thiorhodanine Motifs in the Synthesis of Fused Thiopyrano[2,3-*d*][1,3]thiazoles

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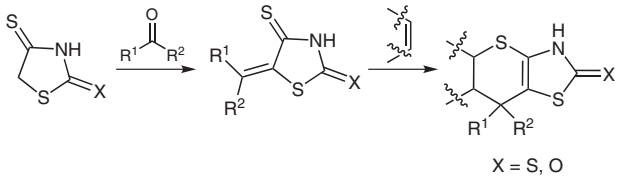
Abstract: Utilization of 4-thioxo-2-(thi)oxothiazolidines in the synthesis of new fused thiopyrano[2,3-*d*][1,3]thiazole derivatives under Knoevenagel and *hetero*-Diels–Alder reaction conditions has been studied.

Key words: iso(thio)rhodanine, condensation, Diels–Alder reaction, heterocycles, antitumor agents

Derivatives of thiazolidine (rhodanine, 2,4-thiazolidinedione) have gained significant popularity in drug design as privileged scaffolds possessing diverse biological activities. A wide range of lead compounds, drug candidates and patented compounds have been identified on their basis.[1] Fused heterocyclic systems based on 4-thioxo-2-thiazolidinone (isorhodanine) and 2,4-dithioxothiazolidine (thiorhodanine) are especially promising among such derivatives.[2,3] The hypothesis that fused heterocyclic systems can imitate the biological activity of their synthetic precursors, namely 5-ylidene-4-thiazolidinones, has been proposed as a basis for their design. The critical influence of the nature of C5-substituents on biological activity should also be taken into consideration.[1,4] This reasoning makes 5-aryl(heteryl)idene-4-thioxothiazolidines attractive building blocks for the synthesis of complex heterocyclic systems, especially as highly active heterodiene components. Although 5-alkylidene-4-thioxothiazolidines that include small lipophilic moieties are seldom used, they may be of interest because of their possible use in *hetero*-Diels–Alder type reactions.[5]

Hence, we have established the synthesis of a series of new thiopyrano[2,3-*d*][1,3]thiazoles using *hetero*-Diels–Alder reactions based on 5-alkylideneiso(thio)rhodanines (Scheme 1).

Synthesis of 5-alkylidene-4-thioxothiazolidines based on aliphatic aldehydes or ketones under commonly employed Knoevenagel reaction conditions (acetic acid medium in the presence of sodium acetate) gives low yields in comparison with aromatic aldehydes.[1,6] Therefore, we adapted a method[7] that involves use of an appropriate ketone as a solvent and ethanolamine as a catalyst. This allowed us to synthesize 5-alkylidene-4-thioxo-2-thiazolidinones **1a–c** with acceptable yields. The appropriate isosters based on thiorhodanine were not formed under the same conditions; instead, the series of 8,8-R^1,R^2-5,8-dihydro-2*H*-[1,3]thiazolo[5′,4′:5,6]thiopyrano-[2,3-*d*][1,3]thiazol-2,6(3*H*)-dithiones (**3a** and **3c**) was obtained (Scheme 2).[8,9]



Scheme 1 General scheme for thiopyrano[2,3-*d*][1,3]thiazole synthesis

Attempts to synthesize isosters **2** of compounds **3**, based on isorhodanine were undertaken to study the influence of heteroatom substitution on biological activity. For the synthesis of compounds **2a** and **2b**,[10,11] we modified the standard method: the reaction was performed in ethanol medium with heating of the reaction mixture. The mechanism of compounds **2** synthesis did not involve phase of 5-alkylidene-4-thioxo-2-thiazolidinones formation, probably because the reaction of compounds **1** with isorhodanine did not allow us to get the target compounds **2**. The obtained tricyclic heterocyclic systems were new thiazolodin(thi)one derivatives, and information on the synthesis of such systems is sparse. However, the use of Cu-nanoparticles as a recoverable catalyst for one-pot, three-component coupling of 2,4-thiazolidinedione, amines, and aldehyde derivatives yielding 8-R-5,8-dihydro-3*H*,4*H*-bisthiazolo[4,5-*b*; 5′,4′-*e*]pyridine-2,6-diones was described.[12]

Single crystal X-ray diffraction studies corroborated the structures of compounds **2a** and **2b**.[13] The molecular structures of these compounds, with labeling schemes, are shown in Figure 1 and Figure 2, respectively. Both compounds consisted of a fused 5,8-dihydro-2*H*-[1,3]thiazolo[5′,4′:5,6]thiopyrano[2,3-*d*][1,3]thiazol-2,6(3*H*)-dione system in which the five-membered rings were planar, while the six-membered ring had a flattened boat conformation.

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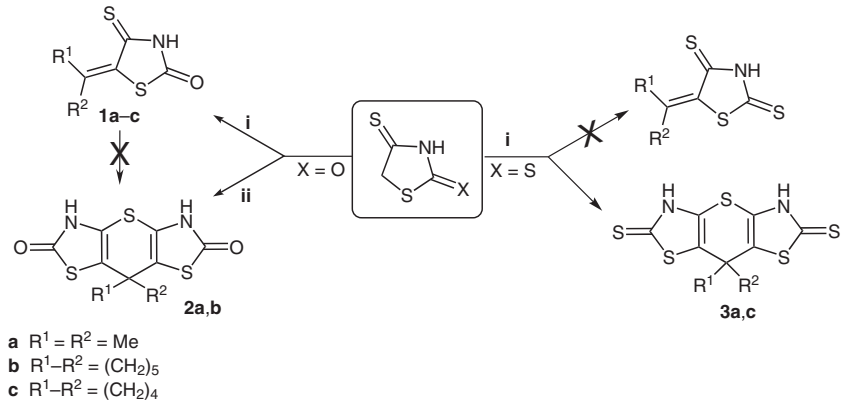


Scheme 2 Synthesis of 5-alkylidene-4-thioxo-2-thiazolidinones (**1**) and 8,8-R^1,R^2-5,8-dihydro-2*H*-[1,3]thiazolo[5′,4′:5,6]thiopyrano[2,3-*d*][1,3]thiazol-2,6(3*H*)-di(thi)ones (**2** and **3**). *Reagents and conditions*: (i) 4-thioxo-2-thiazolidinone or 2,4-dithioxothiazolidine (1.0 equiv), R^{1}COR^2 (15–20 equiv), ethanolamine (2–3 drops), r.t., 1 h; (ii) 4-thioxo-2-thiazolidinone (1 equiv), R^{1}COR^2 (1.2 equiv), ethanolamine (2–3 drops), EtOH, reflux, 15 min.

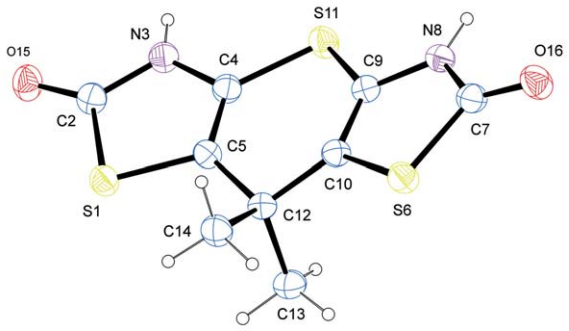


Figure 1 X-ray crystal structure (ORTEP plot) of **2a**

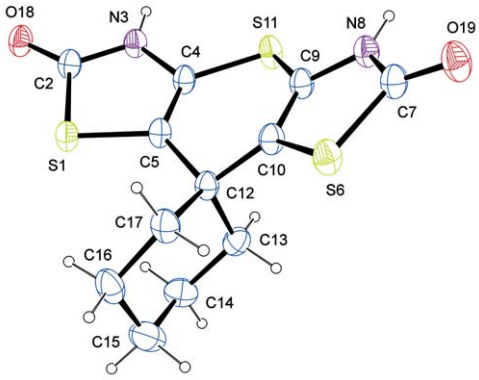
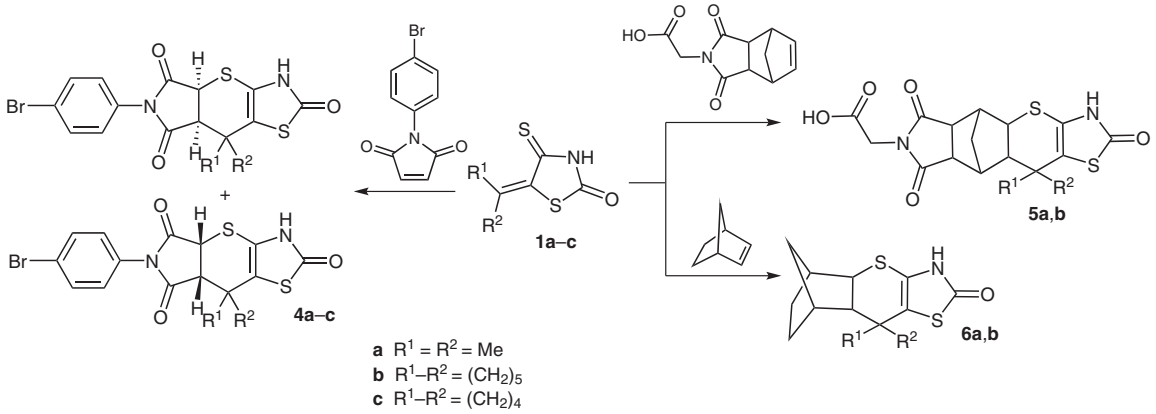


Figure 2 X-ray crystal structure (ORTEP plot) of **2b**

The two compounds, **2a** and **2b**, differ in the substituents at C12. In **2a**, the C12 atom is substituted by two methyl groups, whereas in **2b** this atom is shared between two rings, 4*H*-thiopyrane and cyclohexane. The least-squares planes through these rings are at an angle of 75.73(11)°. In the crystal lattice of **2a**, the molecules are connected by N3–H3···O16^{i} and N8–H8···O15^{ii} hydrogen bonds, forming chains parallel to the *c* axis, while in **2b** chains of molecules linked by N3–H3···O19^{i} and N8–H8···O18^{ii} hydrogen bonds, running parallel to the *a* axis, are observed. Using graph-set notation[14,15] first-order chains, C(8), C(8), and, more interesting, higher-order rings $R_2^2(8)$ were demonstrated in both crystals.

The possible use of compound from series **1** as effective heterodienes in hetero-Diels–Alder reactions has been shown with some dienophiles, namely 1-(4-bromophenyl)pyrrole-2,5-dione, (3,5-dioxo-4-azatricyclo[5.2.1.0^{2,6}]-dec-8-en-4-yl)acetic acid, and norbornene (Scheme 3). Reactions were performed in glacial acetic acid medium with a catalytic amount of hydroquinone (2–3 mg) to prevent polymerization processes.[16,17]



Scheme 3 Synthesis of new thiopyrano[2,3-*d*][1,3]thiazol-2-one derivatives (**4**–**6**). *Reagents and conditions*: **1** (1.0 equiv), dienophile (1.2 equiv), hydroquinone, AcOH, reflux, 1 h.

The NMR data of compounds **4**[17] revealed the presence of a mixture of stereoisomers with diastereomeric ratios from ~5:1 (**4a**) to ~12:1 (**4c**). However, spectral features consistent with only one stereoisomer for compounds **5** and **6** were present in the NMR spectra, indicating that the reaction is stereoselective, most probably due to steric hindrance.[2,17]

Newly synthesized compounds **2a**, **3a**, **4a**, **5a**, **6a**, and **2b** were selected by the National Cancer Institute 'Developmental Therapeutic Program' for *in vitro* cell line screening to investigate their anticancer activity. Anticancer assays were performed according to the US NCI protocol.[18–20] The tested compounds showed insignificant levels of anticancer activity; having weak average values, albeit with some specific influence on some cancer cell lines.[21] It was established that *IGROV-1* (ovarian cancer) and *UO-31* (renal cancer) cell lines were sensitive to compound **2b** action as well as *MOLT-4* (leukemia) cell line to **2a** and Leukemia cell lines to **4a**, correspondingly. Comparison of **2a** and **3a** activity levels showed that anticancer activity of thiorodanine derivative **3a** was lower than that of the oxo-analogue. Compound **6a** possessed the highest level of anticancer activity among the tested compounds, with $lgGI_{50} = -4.66$ (mean concentration of 50% growth inhibition 21.9 μM) and could be considered to be a prospective scaffold for further optimization.

Acknowledgment

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References and Notes

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(8) Preparation of 5-alkylidene-4-thioxo-2-thiazolidinone (**1**) and 8,8-R^1,R^2-5,8-dihydro-2*H*-[1,3]thiazolo[5′,4′:5,6]thiopyrano[2,3-*d*][1,3]thiazol-2,6 (3*H*)-dithione (**3**). To a solution of 4-thioxo-2-thiazolidinone or 2,4-dithioxothiazolidine (5 mmol) in the appropriate ketone (20 mL), 2–3 drops of ethanolamine were added. The reaction mixture was stirred at room temperature for 1 h, then diluted with H_2O and 2–3 drops of AcOH were added. The solid product was filtered off, washed with H_2O, EtOH, and Et_2O, and recrystallized with ethanol or toluene for **1** or with mixtures of DMF–EtOH or DMF–AcOH (1:2) for **3**
(9) Spectral and analytical data for compounds **1** and **3** are as follows. 5-Isopropylidene-4-thioxo-2-thiazolidinone (**1a**): Yield: 90%; mp 152–154 °C (EtOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.67 (s, 3 H, CH_3), 2.17 (s, 3 H, CH_3), 11.85 (s, 1 H, NH). 5-Cyclohexylidene-4-thioxo-2-thiazolidinone (**1b**): Yield: 76%; mp 120–122 °C (EtOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.65 (m, 8 H), 2.30 (m, 2 H, cyclohexylidene), 10.90 (s, 1 H, NH). 5-Cyclopentylidene-4-thioxo-2-thiazolidinone (**1c**): Yield: 74%; mp 174–176 °C (toluene). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.78 (quint., *J* = 6.8 Hz, 2 H), 1.89 (quint., *J* = 6.8 Hz, 2 H), 2.41 (t, *J* = 6.4 Hz, 2 H), 3.03 (t, *J* = 6.4 Hz, 2 H, cyclopentylidene), 13.24 (s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 192.83, 170.46, 166.64, 123.88, 39.71, 37.56, 27.69, 25.71. LC-MS: *m*/*z* (%) = 200.1 (100) [M$^+$ + 1]. 8,8-Dimethyl-5,8-dihydro-2*H*-[1,3]thiazolo[5′,4′:5,6]thiopyrano[2,3-*d*][1,3]thiazol-2,6 (3*H*)-dithione (**3a**): Yield: 52%; mp 190–192 °C (DMF–AcOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.54 (s, 6 H, 2 × CH_3), 13.53 (s, 2 H, NH). LC-MS: *m*/*z* (%) = 305.2 (100) [M$^+$ + 1]. Spiro[cyclopentane-1,8′-(5,8-dihydro-2*H*-[1,3]thiazolo[5′,4′:5,6]thiopyrano[2,3-*d*][1,3]thiazol)]-2,6 (3*H*)-dithione (**3c**): Yield: 24%; mp 155–157 °C (DMF–EtOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.55–2.03 (m), 2.10–2.45 (m, 8 H, cyclopentyl), 13.67 (s, 2 H, 2 × NH). LC-MS: *m*/*z* (%) = 331.1 (100)[M$^+$ + 1]
(10) Preparation of 8,8-R^1,R^2-5,8-dihydro-2*H*-[1,3]thiazolo-[5′,4′:5,6]thiopyrano[2,3-*d*][1,3]thiazol-2,6 (3*H*)-diones (**2**). To a solution of 4-thioxo-2-thiazolidinone (5 mmol) and the appropriate ketone (6 mmol) in EtOH (20 mL), a catalytic amount of ethanolamine was added. The reaction mixture was heated at reflux for 15 min. After cooling the reaction mixture to room temperature, the product was filtered off, washed with EtOH, and Et_2O, and recrystallized (DMF–EtOH, 1:2)
(11) Spectral and analytical data for compounds **2** are as follows. 8,8-Dimethyl-5,8-dihydro-2*H*-[1,3]thiazolo[5′,4′:5,6]-thiopyrano[2,3-*d*][1,3]thiazol-2,6 (3*H*)-dione (**2a**). Yield: 45%; mp 210–212 °C (DMF–EtOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.46 (s, 6 H, 2 × CH_3), 11.53 (s, 2 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.14, 112.40, 112.33, 36.24, 31.59. LC-MS: *m*/*z* (%) = 273.0(100) [M$^+$ + 1]. Spiro[cyclohexane-1,8′-(5,8-dihydro-2*H*-[1,3]thiazolo-[5′,4′:5,6]-thiopyrano[2,3-*d*][1,3]thiazol-2,6(3*H*)-dione (**2b**): Yield: 45%; mp 235–237 °C (DMF–EtOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.47 (br s, 2 H), 1.64 (br s, 4 H), 1.82 (t, *J* = 5.2 Hz, 4 H, cyclohexyl), 11.79 (s, 2 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.49, 114.67, 112.84, 39.66, 38.63, 24.84, 23.30. LC-MS: *m*/*z* (%) = 313.1 (100) [M$^+$ + 1]
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(13) Crystallographic data for **2a**: Empirical formula: $C_9H_8N_2O_2S_3$; formula weight: 272.35; yellow, block; crystal system: orthorhombic; space group: *Pbca* (#61); *a* = 10.0548 (17), *b* = 13.7198 (17), *c* = 16.3093 (18) Å; *V* = 2249.9 (5) Å^3; Z = 8; D_{calc} = 1.608 g/cm^3; *F*(000) = 1120; diffractometer: Kuma KM-4; residuals: *R*[$F^2 > 2\sigma(F^2)$], *wR*(F^2): 0.048, 0.1347.
Crystallographic data for **2b**: Empirical formula: $C_{12}H_{12}N_2O_2S_3$; formula weight: 312.42: colorless, lath; crystal system: orthorhombic; space group: *Pbca* (#61); *a* = 15.5909 (19), *b* = 10.2253 (9), *c* = 16.4741 (17) Å; *V* = 2626.3 (5) Å^3; Z = 8; D_{calc} = 1.580 g/cm^3; *F*(000) = 1296; diffractometer: Kuma KM-4; residuals: *R*[$F^2 > 2\sigma(F^2)$], *wR*(F^2): 0.040, 0.1329.

The supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre (CCDC), 12 Union ROAD, Cambridge CB2 1EZ (UK), Tel.: (+44) 1223/336–408, Fax: (+44) 1223/336–033, E-mail: deposit@ccdc.cam.ac.uk, World Wide Web: http://www.ccdc.cam.ac.uk (CCDC for **2a**: 780127, for **2b**: 780128)

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(16) General experimental procedure for the hetero-Diels–Alder reaction yielding fused derivatives of thiopyrano[2,3-*d*]-[1,3]thiazol-2-ones (**4**–**6**). A mixture of the appropriate 5-alkylidene-4-thioxo-2-thiazolidinone (10 mmol) and the appropriate dienophile {1-(4-bromophenyl)pyrrole-2,5-dione, (3,5-dioxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl)acetic acid or norbornene} (12 mmol) was heated at reflux for 1 h with a catalytic amount of hydroquinone (2–3 mg) in glacial AcOH (10 mL), then left overnight at r.t. The precipitated crystals were filtered off, washed with EtOH, and recrystallized from the appropriate solvent

(17) Spectral and analytical data for compounds (**4**–**6**) are as follows. 6-(4-Bromophenyl)-8,8-dimethyl-3,4a,7a,8-tetrahydropyrrolo[3′,4′:5,6]thiopyrano[2,3-*d*]thiazol-2,5,7-trione (**4a**): Yield 85%; mp >240 °C (DMF–EtOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.39 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3), 3.50 (d, *J* = 8.7 Hz, 1 , 7a-H), 4.93 (d, *J* = 8.7 Hz, 1 , 4a-H), 7.19 (d, *J* = 8.7 Hz, 2 H, ArH), 7.68 (d, *J* = 8.7 Hz, 2 H, ArH), 11.55 (s, 1 H, NH, major isomer). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.53, 172.92, 170.92, 132.91, 131.53, 122.52, 117.48, 116.12, 52.87, 43.57, 36.31, 26.93, 23.94 major isomer. LC-MS: *m*/*z* (%) = 426.0 (91.59) [M^+ + 1]. Spiro[cyclohexane-1,8′-(6-(4-bromophenyl)-3,4a,7a,8-tetrahydropyrrolo[3′,4′:5,6]thiopyrano[2,3-*d*]thiazol)]-2,5,7-trione (**4b**): Yield: 74%; mp 236–238 °C (EtOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.52–1.80 (m, 6 H), 2.03 (m, 3 H), 2.27 (m, 1 H, cyclohexyl), 4.14 (d, *J* = 8.4 Hz, 1 , 7a-H), 4.67 (d, *J* = 8.4 Hz, 1 , 4a-H), 7.13 (d, *J* = 8.8 Hz, 2 , ArH), 7.67 (d, *J* = 8.8 Hz, 2 , ArH), 11.50 (s, 1 H, NH, major isomer). Spiro[cyclopentane-1,8′-(6-(4-bromophenyl)-3,4a,7a,8-tetrahydropyrrolo[3′,4′:5,6]thiopyrano[2,3-*d*]thiazol)]-2,5,7-trione (**4c**): Yield: 70%; mp 227–229 °C (DMF–EtOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.48–1.62 (m, 1 H), 1.64–1.82 (m, 4 H), 1.87–1.96 (m, 1 H), 2.06–2.17 (m, 3 H, cyclopentyl fragment), 3.85 (d, *J* = 8.5 Hz, 1 , 7a-H), 4.78 (d, *J* = 8.5 Hz, 1 , 4a-H), 7.06 (d, *J* = 8.5 Hz, 2 H, ArH), 7.69 (d, *J* = 8.5 Hz, 2 H, ArH), 11.62 (s, 1 H, NH, major isomer). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.44, 174.37, 170.45, 132.61, 131.42, 129.07, 122.08, 118.44, 117.35, 53.68, 47.44, 44.65, 37.24, 36.84, 24.02, 23.42 major isomer. LC-MS: *m*/*z* (%) = 452.0 (90.64) [M^+ + 1]. 2-[9,9-Dimethyl-6,13,15-trioxo-3,7-dithia-5,14-diazapentacyclo[9.5.1.$0^{2,10}$.$0^{4,8}$.$0^{12,16}$]heptadec-4 (8)-en-14-yl]acetic acid (**5a**): Yield: 69%; mp >240 °C (EtOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.14 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 1.50 (d, *J* = 10.5 Hz, 1 H), 1.75 (d, *J* = 10.5 Hz, 1 H), 2.17 (d, *J* = 2.4 Hz, 1 H), 2.72 (dd, *J* = 4.7, 14.9 Hz, 2 H,), 3.23 (m, 1 H), 3.27–3.33 (m, 1 H), 3.38 (d, *J* = 8.2 Hz, 1 H, norbornane), 4.00 (d, *J* = 18.2 Hz, 1 H, NCH_2C), 4.08 (d, *J* = 18.2 Hz, 1 H, NCH_2C), 11.43 (s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.03, 176.76, 170.79, 169.20, 119.98, 116.91, 52.29, 49.48, 48.26, 47.98, 46.70, 41.87, 39.88, 36.01, 28.43, 25.99. LC-MS: *m*/*z* (%) = 395.21 (100) [M^+ + 1]. 2-{Spiro[cyclohexane-1,9′-(6,13,15-trioxo-3,7-dithia-5,14-diazapentacyclo[9.5.1.$0^{2,10}$.$0^{4,8}$.$0^{12,16}$]heptadec-4 (8)-en-14-yl)]}acetic acid (**5b**): Yield: 71%; mp >240 °C (EtOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.27–1.35 (m, 2 H), 1.38–1.67 (m, 8 H), 1.83–1.89 (m, 2 H), 2.77 (dd, *J* = 4.0, 14.6 Hz, 2 H), 3.19 (m, 3 H), 3.35 (d, *J* = 8.4 Hz, 1 H, norbornane and cyclohexyl), 3.99 (d, *J* = 17.3 Hz, 1 H, NC_2C), 4.11 (d, *J* = 17.3 Hz, 1H, NCH_2C), 11.31 (s, 1 H, NH), 13.21 (br. s, 1 H, COOH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.39, 177.04, 171.37, 169.51, 120.79, 51.03, 50.79, 49.74, 48.58, 46.27, 39.95, 39.50, 38.82, 26.01, 22.42, 22.27. LC-MS: *m*/*z* (%) = 435.2 (100) [M^+ + 1]. 9,9-Dimethyl-3,7-dithia-5-azatetracyclo[9.2.1.$0^{2,10}$.$0^{4,8}$]-tetradecen-4 (8)-one-6 (**6a**): Yield: 63%; mp 125–127 °C (MeCN). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.21 (s, 6 , 2 × CH_3), 1.03 (d, *J* = 9.9 Hz, 1 H), 1.38 (m, 2 H), 1.46–49 (m, 3 H), 1.87 (d, *J* = 8.2 Hz, 1 H), 2.22 (m, 2 H), 3.37 (d, *J* = 8.2 Hz, 1 H, norbornane fragment), 11.34 (s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.90, 120.65, 116.47, 58.06, 45.36, 38.94, 36.03, 35.02, 31.36, 28.75, 28.17, 24.70. LC-MS: *m*/*z* (%) = 268.0 (98.18) [M^+ + 1]. Spiro[cyclohexane-1,9′-(3,7-dithia-5-azatetracyclo-[9.2.1.$0^{2,10}$.$0^{4,8}$]tetradecen-4 (8)]one-6 (**6b**): Yield: 52%; mp 195–197 °C (EtOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.93 (d, *J* = 9.7 Hz, 1 H), 1.17 (m, 3 H), 1.32 (m, 3 H), 1.45–1.55 (m, 7 H), 1.79 (m, 1 H), 1.91 (m, 1 H), 2.17 (m, 2 H), 2.25 (d, *J* = 3.6 Hz, 1 H), 3.29 (d, *J* = 8.2 Hz, 1 H, norbornane and cyclohexyl), 11.35 (s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.23, 121.79, 50.48, 48.21, 37.17, 35.69, 34.57, 31.82, 27.95, 25.87, 22.53. LC-MS: *m*/*z* (%) = 308.1 (100) [M^+ + 1]

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(21) Compounds **2a**, **3a**, and **2b** were evaluated with a 60 human tumor cell lines panel at concentrations of 10^{-5} M and showed the following mean growth percent values: **2a** – 101.51%, **3a** – 108.41%, **2b** – 105.07%. However, decreases in the growth percent values were detected following treatment of selected cell lines with compounds: MOLT-4 (leukemia) – 62.73% (compound **2a**); IGROV1 (ovarian cancer) – 50.98% and UO-31 (renal cancer) – 49.34% (compound **2b**). Compounds **4a**, **5a**, and **6a** were passed on for evaluation in the full panel of 60 human tumor cell lines at 10-fold dilutions ranging from 10^{-4} to 10^{-8} M. Compounds were characterized by the following values of mean dose response parameters: $lgGI_{50}$ = –4.04, lgTGI = –4.01, $lgLC_{50}$ = –4.0 (compound **4a**); $lgGI_{50}$ = –4.00, lgTGI = –4.00, $lgLC_{50}$ = –4.00 (compound **5a**); $lgGI_{50}$ = –4.66, lgTGI = –4.25, $lgLC_{50}$ = –4.04 (compound **6a**). Compound **4a** showed the highest antitumor cytotoxicity against leukemia cell lines: HL-60 (TB), ($lgGI_{50}$ = –4.62), MOLT-4; ($lgGI_{50}$ = –4.48) and SR ($lgGI_{50}$ = –5.13). Compound **6a** sensitized melanoma UACC-62 cell line ($lgGI_{50}$ = –4.91) as well as breast cancer MDA-MB-435 cell line ($lgGI_{50}$ = –4.87) but did not show a selective influence on any whole cancer subtype cell line panel.