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A new domino-Knoevenagel–hetero-Diels–Alder reaction

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ABSTRACT

Various novel 3,5a,6,11b-tetrahydro-2*H*,5*H*-chromeno[4′,3′:4,5]thiopyrano[2,3-*d*][1,3]thiazol-2-ones were synthesized in 60–80% yields via domino-Knoevenagel–hetero-Diels–Alder reactions of 4-thioxo-1,3-thiazolidin-2-one with 3,7-dimethyl-6-octenal, 2-allyloxybenzaldehydes and 2-formylphenyl (*E*)-3-aryl-2-propenoates with base catalysis. The possibility of stereo- and regioselective cycloaddition was investigated.

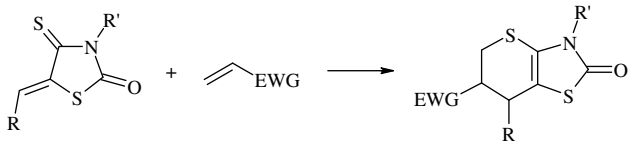
The creation of molecular complexity and diversity from simple substrates, while combining economic with environmental aspects constitutes a great challenge in modern organic chemistry. In this regard, the development of new domino reaction methodologies is very important.[1–3] This type of reaction minimizes waste, since the amount of solvents, reagents, adsorbents, and energy is dramatically decreased, compared to stepwise reactions. Often, these domino reactions are accompanied by dramatic increases in molecular complexity and impressive selectivity. Many of the reaction products have drug-like structures and might therefore exhibit interesting biological activities.

Tietze et al. reported the domino-Knoevenagel–hetero-Diels–Alder reaction of unsaturated aromatic and aliphatic aldehydes with different 1,3-dicarbonyl compounds[1–3] (Scheme 1).

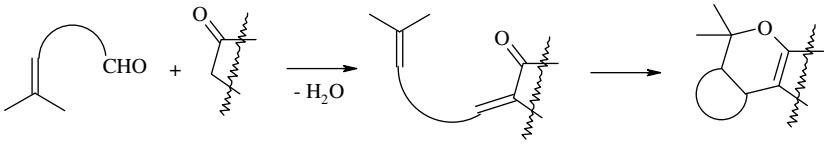
Acetylacetone, acetoacetate, 1,3-cyclohexanediones,[4] indanediones, Meldrum's acid,[5] and heterocyclic compounds such as barbituric acids, pyrazolones, isooxazolones, and 1,2,3,4-tetrahydro-2,4-pyridinedione,[6] 1,2,6-thiadiazinanedioxide-3,5-dione,[7] oxothiolane,[8] and 1-phenyl-3-indolinone[9] can be employed in this type of reaction. The reaction of heterocyclic and sugar-derived δ,ε-unsaturated aldehydes has also been demonstrated.[10]

In this Letter, we report a new domino-Knoevenagel–hetero-Diels–Alder reaction. As the methylene component we used 4-thioxo-1,3-thiazolidin-2-one **1**, which has been described previously as an excellent reagent for the synthesis of 3,5,6,7-tetrahydro-2*H*-thiopyrano[2,3-*d*][1,3]thiazol-2-ones via ylidene derivatives[11–13] (Scheme 2). Pharmaceutical interest in the abovementioned compounds appeared after approval of thiazolidinediones as a separate group of antihyperglycaemics. In addition, several compounds with antitumor and antioxidant activities among their fused analogs have been discovered.[14–16]

The reaction is controlled by the interaction of the HOMO of the diene and the LUMO of the dienophile (normal electron demand), and can be activated by lowering the energy of the dienophile-LUMO by the introduction of electron-withdrawing substituents. The cycloadditions are also highly regioselective and form products according to Frontier Orbital Theory.



Scheme 2.



Scheme 1.

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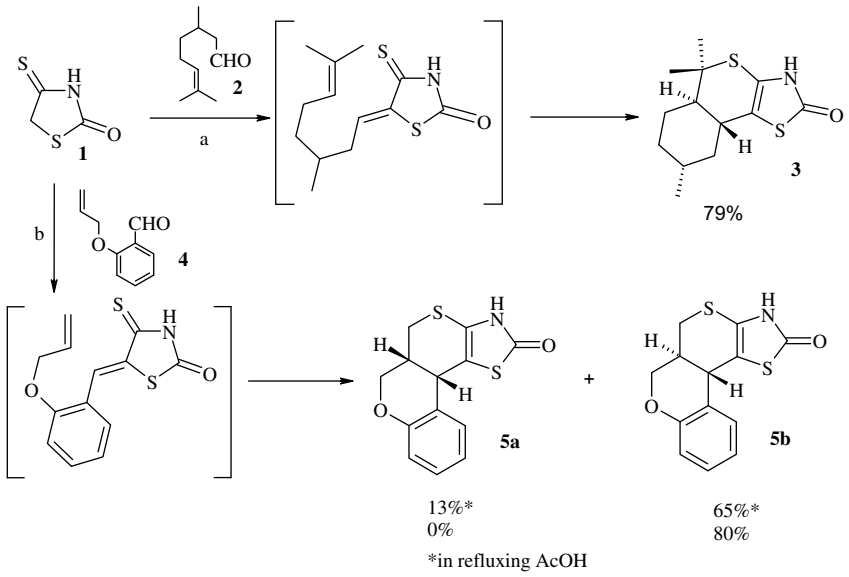


Scheme 3. Reactions of 4-thioxo-1,3-thiazolidine-2-one **1** with citronellal **2** and 2-allyloxybenzaldehyde **4**. Reagents and conditions: (a) **1** (1.0 equiv), EDDA (0.15 equiv), **2** (1.3 equiv), MeCN, rt, 24 h; (b) **5a** + **5b: 1** (1.0 equiv), **4** (1.0 equiv), NEt_3 (1.0 equiv), AcOH, reflux, 2 h, **5b:1** (1 equiv), **4** (1.0 equiv), NEt_3 (1.0 equiv), AcOH, room temperature, 12 h.[17,18]

The first substrate we examined was 3,7-dimethyloct-6-enal (citronellal) **2** (Scheme 3). Condensation of aldehyde **2** with 4-thioxo-1,3-thiazolidin-2-one **1** in the presence of a catalytic amount of ethylenediamine diacetate (EDDA) in acetonitrile or acetic acid at room temperature afforded the corresponding Knoevenagel adduct intermediate which cyclized via an intramolecular hetero-Diels–Alder reaction to give the tetracyclic product **3** with excellent selectivity.[17] The ene reaction was not observed.

Single crystal X-ray structure determination corroborated the structure of compound **3** (Fig. 1).[19] The hydrogen atoms at the stereogenic C7 and C12 centers have a trans axial–axial orientation. The torsion angle H7–C7–C12–H12 of −176° reveals an antiperiplanar conformation for atoms H7 and H12. In the solid state, the heterocyclic six-membered ring adopts a half-chair conformation {Cremer and Pople[20] puckering parameters: $Q = 0.565(2)$ Å, $\theta = 129.3(2)°$, $\phi = 94.9(2)°$}, whereas the carbocyclic ring adopts a chair conformation {Cremer and Pople puckering parameters: $Q = 0.578(2)$ Å, $\theta = 2.4(2)°$, $\phi = 319(5)°$}. The dihedral angles between the least-squares planes of the central ring of the tricyclic skeleton and the outer five- and six-membered rings were 6.79(7)° and 17.07(7)°. The angle between the outer rings was 21.88(7)°. The C4–C13 bond, 1.337(2) Å, being part of the five- and six-membered heterocyclic rings, is a double bond. In the five-membered thiazolone ring, the C2–N3 bond distance, 1.345(2) Å, is somewhat larger than a normal Csp^2–N bond [1.331(2) Å] for γ-lactams.[21]

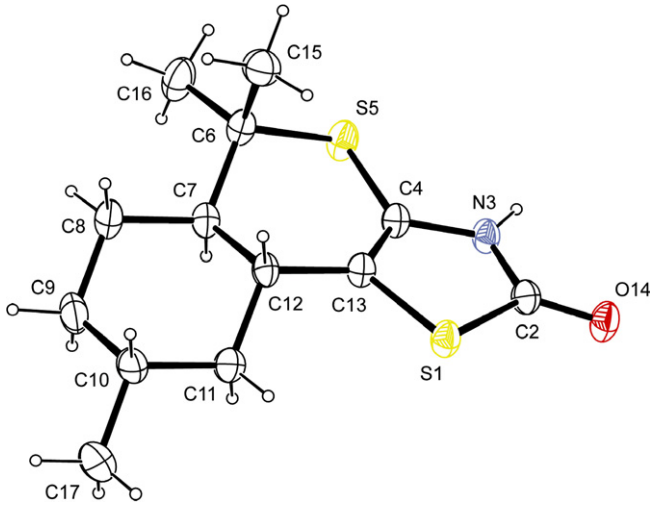


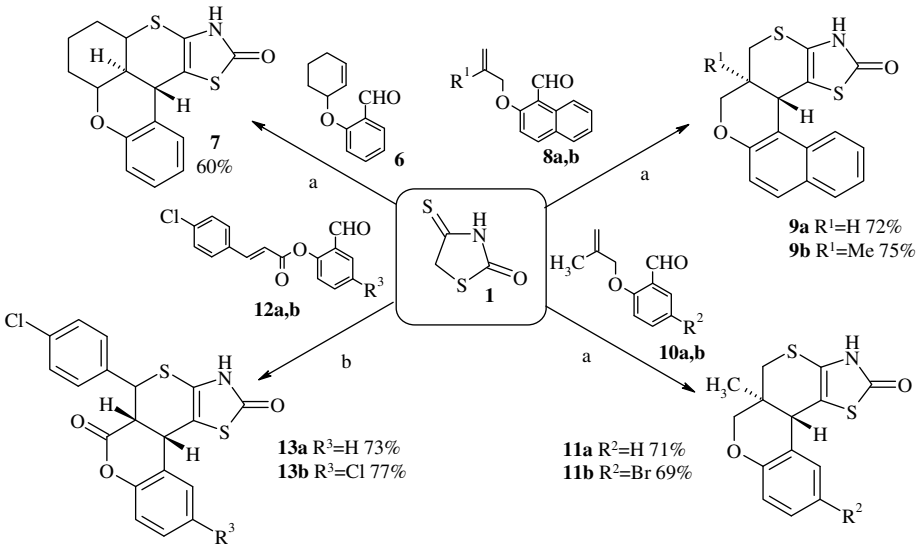
Figure 1. X-ray crystal structure (ORTEP plot) of **3**.

In the same way, thiazolidinone **1** was condensed with 2-allyloxybenzaldehyde **4** in acetic acid to give tetracyclic hetero-Diels–Alder cycloadduct **5**. In boiling acetic acid the cycloaddition was not diastereoselective. According to the ^1H NMR of the crude mixture, the ratio of trans/cis annulated cycloadducts was 5:1. At room temperature, we isolated pure (5a*RS*,11b*SR*)-3,5a,6,11b-tetrahydro-2*H*,5*H*-chromeno[4′,3′:4,5]thiopyrano[2,3-*d*][1,3]thiazol-2-one **5b** in 80% yield. The configuration of **5b** was deduced from the coupling constant between the 5a and 11b protons (Scheme 3).

Other examples of this reaction using aldehydes **6, 8a,b** and **10a,b** possessing an allyl moiety as the dienophile are shown in Scheme 4. Only one diastereoisomer was formed in these reactions.

To further the synthetic scope of this cycloaddition we studied the reaction of thiazolidinone **1** with 2-formyl-R^3-phenyl (*E*)-3-phenyl-2-propenoates **12a,b** at 80 °C in the presence of triethylamine. The reaction, after usual work-up, gave the corresponding (5a*RS*,11b*SR*)-5-aryl-3,5a,6,11b-tetrahydro-2*H*,5*H*-chromeno[4′,3′:4,5]thiopyrano[2,3-*d*]thiazole-2,6-diones **13a,b** in excellent yields.[23] The configuration of the protons at positions 5a and 11b of **7**, **9a**, **11a**, and **13** was deduced from the coupling constants, compounds **7**, **9a**, and **11a** were trans, whereas **13a**, **b** were cis. The stereochemistry of the final products of the Diels–Alder reaction depends on the *endo*- or *exo*-orientation of the dienophile in the transition state. In the case of compounds with an allyl moiety we observed *exo* transition states. In cinnamyl derivatives **13a,b**, due to secondary orbital interactions, *endo* transition states occurred.

The required starting unsaturated aldehydes (Scheme 4) were prepared through alkylation (**6**;**8a,b**;**10a,b**) of commercially available salicylaldehyde with 3-chlorocyclohexene, allyl or methallyl chloride and acylation (**12a,b**) of salicylaldehyde with 4-chlorocinnamoyl chloride.



Scheme 4. Reactions of 4-thioxo-1,3-thiazolidine-2-one **1** with unsaturated aldehydes. Reagents and conditions: (a) **1** (1.0 equiv), appropriate aldehyde (1.0 equiv), NEt_3 (1.0 equiv), AcOH, room temperature 12 h.[22,23] (b) **1** (1.0 equiv), appropriate aldehyde (1.0 equiv), NEt_3 (1.0 equiv), AcOH, 80 °C, 2 h.

Preliminary antitumor activity studies were performed[24] for compound **9a** according to the NCI (USA) standard protocol.[25–27]

In summary, we have successfully developed novel, efficient and stereoselective methods for the synthesis of 3,5a,6,11b-tetrahydro-2*H*,5*H*-chromeno[4′,3′:4,5]thiopyrano[2,3-*d*]thiazol-2-ones derivatives via a domino-Knoevenagel–hetero-Diels–Alder approach based on 4-thioxo-1,3-thiazolidine-2-one.

Acknowledgments

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17. Preparation of (5a*RS*,8*R*,9a*RS*)-5,5,8-trimethyl-3,5,5a,6,7,8,9,9a-octahydro-2*H*-[2]benzothiopyrano[3,4-*d*][1,3]thiazol-2-one (**3**). To a suspension of 10 mmol of 4-thioxo-2-thiazolidinone **1** in 10 ml of anhydrous acetonitrile, 13 mmol of citronellal **2** was added. Next, 5 mmol of EDDA in 10 ml of anhydrous acetonitrile was added under stirring. After 48 h, the reaction mixture was refluxed for 5 min and then cooled. The obtained precipitate was filtered off, washed with hexane and recrystallized from ethanol. Preparation of (5a*RS*,11b*RS*)-3,5a,6,11b-tetrahydro-2*H*,5*H*-chromeno[4′,3′:4,5]thiopyrano[2,3-*d*][1,3]thiazol-2-one (**5b**). A solution of 2-allyloxybenzaldehyde **4** (10 mmol) and thiazolidinone **1** (10 mmol) in acetic acid or acetonitrile (20 ml) was stirred at room temperature in the presence of a catalytic amount of triethyamine (10 mmol). The progress of the reaction was monitored by TLC. The solid product that formed was collected by filtration and recrystallized from dioxane.
18. Spectral and analytical data for new compounds **3** and **5b** are as follows. (5a*RS*,8*R*,9a*RS*)-5,5,8-trimethyl-3,5,5a,6,7,8,9,9a-octahydro-2*H*-[2]benzothiopyrano[3,4-*d*][1,3]thiazol-2-one **3**: Yield 79%, mp 189–190 °C (EtOH); ^{1}H NMR (400 MHz, DMSO-d_6): 0.87 (d, J = 6.8 Hz, 3H, CH_3CH), 0.90–1.05 (m, 3H), 1.25 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.42–1.51 (m, 1H), 1.55 (t, J = 12.0 Hz, 1H), 1.73 (d, J = 12.0 Hz, 1H), 1.83 (m, 2H), 2.24 (t, J = 8.0 Hz, 1H), 11.12 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 22.6, 23.8, 26.1, 27.9, 32.2, 35.0, 36.8, 42.8, 47.6, 50.6, 107.7, 119.1, 171.7; EI-MS (m/z): 269 (M^+). Anal. Calcd for $C_{13}H_{19}NOS_2$: C, 57.95; H, 7.11; N, 5.20. Found: C, 58.03; H, 7.27; N, 5.08. (5a*RS*,11b*RS*)-3,5a,6,11b-Tetrahydro-2*H*,5*H*-chromeno[4′,3′:4,5]thiopyrano[2,3-*d*][1,3]thiazol-2-one **5b:** Yield 80%, mp 230–231 °C (dioxane); ^{1}H NMR (400 MHz, DMSO-d_6): 2.22–2.36 (m, 1H, 5a-H), 3.00–3.08 (m, 1H, 5-H), 3.15 (dd, 1H, J = 3.6, 12.0 Hz, 5-H), 3.82–4.00 (m, 1H, 6-H), 3.97 (d, 1H, J = 10.5 Hz, 11b-H), 4.39 (dd, 1H, J = 3.6, 10.3 Hz, 6-H), 6.85 (d, 1H, J = 7.6 Hz, 8-H), 6.95 (t, 1H, J = 7.8 Hz, 10-H), 7.17 (t, 1H, J = 7.6 Hz, 9-H), 7.43 (d, 1H, J = 7.8 Hz, 11-H), 11.50 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 27.9, 30.2, 38.7, 69.2, 105.6, 117.4, 121.2,121.6, 123.4, 127.7, 129.2, 153.7, 170.9. EI-MS (m/z): 277 (100%, M^+). Anal. Calcd for $C_{13}H_{11}NO_2S_2$: C, 56.30; H, 4.00; N, 5.05. Found: C, 56.45; H, 4.15; N, 5.00.
19. Crystallographic data for **3**: Empirical formula: $C_{13}H_{19}NOS_2$, formula weight: 269.41, crystal color, habit: colorless, block, crystal system: monoclinic, space group: $P2_1/n$ (#14), a = 9.3084(4), b = 12.9824(4), c = 12.1118(4) Å, β = 104.462(4)°, V = 1417.28(9) Å^3, Z = 4, D_{calc} = 1.263 g/cm^3, $F(000)$ = 576, diffractometer: Kuma-KM-4-CCD, residuals: $R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$: 0.032, 0.096. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 655431. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1233 336033 or e-mail deposit@ccdc.cam.ac.uk).
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22. Typical procedure: A solution of appropriate unsaturated aldehyde (12 mmol), triethylamine (10 mmol) and 4-thioxo-2-thiazolidinone **1** (10 mmol) was stirred at room temperature in acetic acid (20 ml) for 12 h. The progress of the reaction was monitored by TLC. The solid product that formed was collected by filtration and recrystallized from ethanol.
23. Spectral and analytical data for new compounds: (7b*RS*,12b*RS*)-3,4a,5,6,7,7a,7b,12b-octahydro-2*H*-xantheno[9′,1′:4,5,6]thiopyrano[2,3-*d*][1,3]thiazol-2-one **7**: Yield 60%, mp 205–207 °C (EtOH); ^{1}H NMR (200 MHz, DMSO-d_6): 1.35–1.80 (m, 6H, CH_2), 2.31–2.41 (m, 1H, 7b-H), 3.50–3.65 (m, 1H, 4a-H), 4.09 (d, 1H, J = 11.2 Hz, 12b-H), 4.40–4.52 (m, 1H, 7a-H), 6.81 (d, 1H, J = 8.0 Hz, Ar), 6.90 (t, 1H, J = 7.4 Hz, Ar), 7.12–7.19 (m, 1H, Ar), 7.41 (d, 1H, J = 7.7 Hz, Ar), 11.46 (s, 1H, NH). ^{13}C NMR (95 MHz, DMSO-d_6): δ 22.5, 26.1, 28.5, 29.4, 39.7, 40.9, 74.7, 104.3, 117.2, 120.1, 122.2, 126.9, 128.3, 152.5, 170.4. EI-MS (m/z): 317 (M^+). Anal. Calcd for $C_{16}H_{15}NO_2S_2$: C, 60.54; H, 4.76; N, 4.41. Found: C, 60.29; H, 4.65; N, 4.30. (5a*RS*,13c*RS*)-3,5a,6,13c-Tetrahydro-2*H*,5*H*-naphtho[1″,2″:5′,6′]pyrano[4′,3′:4,5]thiopyrano[2,3-*d*]thiazol-2-one **9a**: Yield 72%, mp >260 °C (AcOH); ^{1}H NMR (200 MHz, DMSO-d_6): 2.77–2.87 (m, 1H, 5a-H), 3.25–3.33 (m, 1H, 5-H), 3.70 (dd, 1H, J = 2.6, 12.8 Hz, 5-H), 4.25 (t, 1H, J = 10.9 Hz, 6-H), 4.38 (dd, 1H, J = 2.9, 11.1 Hz, 6-H), 4.64 (d, 1H, J = 4.0 Hz, 13c-H), 7.05 (d, 1H J = 8.8 Hz, Ar), 7.34–7.41 (m, 1H, Ar), 7.49–7.57 (m, 1H, Ar),

7.74–7.87 (m, 2H, Ar), 7.97 (d, 1H, Ar), 11.29 (s, 1H, NH). ^{13}C NMR (95 MHz, DMSO-d_6): δ 27.3, 28.1, 29.5, 64.5, 105.8, 114.9, 117.5, 118.8, 122.3, 123.5, 126.5, 128.5, 128.6, 129.3, 132.1, 151.0, 170.3. EI-MS (m/z): 327 (M^+). Anal. Calcd for $C_{17}H_{13}NO_2S_2$: C, 62.36; H, 4.00; N, 4.28. Found: C, 62.50; H, 4.10; N, 4.40. (5a*RS*,13c*RS*)-3,5a,6,13c-Tetrahydro-5a-methyl-2*H*,5*H*-naphtho-[1″,2″:5′,6′]pyrano[4′,3′:4,5]thiopyrano[2,3-*d*]thiazol-2-one **9b**: Yield 75%, mp >250 °C (AcOH); ^{1}H NMR (400 MHz, DMSO-d_6): 1.21 (s, 3H, CH_3), 2.94 (d, 1H, J = 13.8 Hz, SCH_2), 3.51 (d, 1H, J = 13.8 Hz, SCH_2), 3.91 (d, 1H, J = 10.5 Hz, OCH_2), 4.56 (d, 1H, J = 10.5 Hz, OCH_2), 4.14 (s, 1H, 13c-H), 6.97–7.91 (6H, $C_{10}H_6$), 10.93 (s, 1H, NH). ^{13}C NMR (95 MHz, DMSO-d_6): δ 24.2, 29.5, 33.8, 36.1, 68.7, 107.8, 115.0, 117.9, 119.2, 122.8, 124.3, 127.1, 129.3, 129.6, 129.9, 133.1, 150.7, 171.2. EI-MS (m/z): 341 (M^+). Anal. Calcd for $C_{18}H_{15}NO_2S_2$: C, 63.32; H, 4.43; N, 4.10. Found: C, 63.07; H, 4.50; N, 4.14. (5a*RS*,11b*RS*)-3,5a,6,11b-Tetrahydro-5a-methyl-2*H*,5*H*-[1]benzopyrano[4′,3′:4,5]thiopyrano[2,3-*d*][1,3]thiazol-2-one **11a**: Yield 71%, mp 294–295 °C (dioxane); ^{1}H NMR (400 MHz, DMSO-d_6): 0.87 (s, 3H, CH_3), 2.85 (d, 1H, J = 11.7 Hz, 5-H), 3.08 (d, 1H, J = 11.7 Hz, 5-H), 3.89 (d, 1H, J = 9.8 Hz, 6-H), 4.09 (s, 1H, 11b), 4.12 (d, 1H, J = 9.8 Hz, 6-H), 6.86 (d, 1H J = 7.8 Hz, 8-H), 6.95 (t, 1H J = 7.8 Hz, 10-H), 7.18 (t, 1H J = 7.8 Hz, 9-H), 7.43 (d, 1H, J = 7.8 Hz, 11-H), 11.55 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 16.3, 33.1, 35.0, 41.4, 74.1, 104.6, 117.6, 121.4, 121.7, 121.8, 128.1, 129.0, 154.5, 170.9. EI-MS (m/z): 291 (M^+). Anal. Calcd for $C_{14}H_{13}NO_2S_2$: C, 57.71; H, 4.50; N, 4.81. Found: C, 57.47; H, 4.34; N, 4.92. (5a*RS*,11b*RS*)-10-Bromo-3,5a,6,11b-tetrahydro-5a-methyl-2*H*,5*H*-[1]benzopyrano[4′,3′:4,5]thiopyrano[2,3-*d*]thiazol-2-one **11b**: Yield 69%, mp 229–231 °C (AcOH); ^{1}H NMR (200 MHz, DMSO-d_6): 0.85 (s, 3H, CH_3), 2.85 (d, 1H, J = 11.9 Hz, 5-H), 3.08 (d, 1H, J = 11.9 Hz, 5-H), 3.90 (d, 1H, J = 10.4 Hz, 6-H), 4.12 (s, 1H, 11b-H), 4.14 (d, 1H, J = 10.4 Hz, 6-H), 6.84 (d, 1H, J = 8.6 Hz, Ar), 7.34 (d, 1H, J = 8.6 Hz, Ar), 7.55 (s, 1H, Ar), 11.61 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 15.9, 32.4, 34.2, 40.8, 73.8, 102.9, 111.7, 119.0, 121.5, 123.8, 129.7, 130.9, 153.1. 169.8. EI-MS (m/z): 369 (M^+, ^{79}Br), 371 (M^+, ^{81}Br). Anal. Calcd for $C_{14}H_{12}BrNO_2S_2$: C, 45.41; H, 3.27; N, 3.78. Found: C, 45.15; H, 3.20; N, 3.90. (5a*RS*,11b*SR*)-3,5a,6,11b-Tetrahydro-5-(4-chlorophenyl)-2*H*,6*H*-[1]benzopyrano[4′,3′:4,5]thiopyrano[2,3-*d*][1,3]thiazol-2,6-dione **13a**: Yield 73%, mp 240–242 °C (EtOH); ^{1}H NMR (400 MHz, DMSO-d_6): 3.75 (d, 1H, J = 4.9 Hz, 11b-H), 4.00–4.02 (m, 1H, 5a-H), 5.14 (d, 1H, J = 3.2Hz, 5-H), 7.13–7.18 (m, 2H, Ar), 7.30–7.44 (m, 6H, Ar) 11.66 (s, 1H, NH). ^{13}C NMR (95 MHz, DMSO-d_6): δ 31.2, 43.3, 43.6, 102.6, 117.4, 121.0, 124.2, 125.6, 128.5, 128.6, 129.2, 129.5, 130.4, 140.0, 150.5, 166.7, 170.9. MS (m/z): 401 (M^+). Anal. Calcd for $C_{19}H_{12}ClNO_3S_2$: C, 56.78; H, 3.01; N, 3.49. Found: C, 56.87; H, 3.12; N, 3.32. (5a*RS*,11b*SR*)-10-Chloro-5-(4-chlorophenyl)-3,5a,6,11b-tetrahydro-2*H*,6*H*-[1]benzopyrano[4′,3′:4,5]thiopyrano[2,3-*d*][1,3]-thiazol-2,6-dione **13b**: Yield 77%, mp 277–279 °C (EtOH); ^{1}H NMR (400 MHz, DMSO-d_6): 3.78 (d, 1H, J = 5.9 Hz, 11b-H), 3.83–3.86 (m, 1H, 5a-H), 5.08 (d, 1H, J = 3.9Hz, 5-H), 7.12 (d, 1H, J = 7.8 Hz Ar), 7.34–7.40 (m, 4H, Ar), 7.44 (d, 2H, J = 7.8 Hz Ar), 11.53 (s, 1H, NH). MS (m/z): 435 (M^+). Anal. Calcd for $C_{19}H_{11}Cl_2NO_3S_2$: C, 52.30; H, 2.54; N, 3.21. Found: C, 52.44; H, 2.65; N, 3.03.

24. Compound **9a** was evaluated toward a three human tumor cell line panel and showed the following growth percent values: at NCI-H460 cell line (Non-Small Cell Lung Cancer)—3%, MCF7 (Breast Cancer)—25%, and SF-268 (CNS Cancer)—31%. Therefore substance **9a** which reduced the growth of the cell lines to 32% or less was passed on for evaluation in the full panel of 60 human tumor cell lines. Compound **9a** showed the highest antitumor cytotoxicity against leukemia cell lines MOLT-4 ($\log GI_{50} = -4.08$) and RPMI-8226 ($\log GI_{50} = -4.70$), as well as the melanoma cell line SK-MEL-2 ($\log GI_{50} = -4.27$). These preliminary results are promising and need further investigation of the antitumor activity of reported and related compounds.
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