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# Arylidene pyruvic acids motif in the synthesis of new thiopyrano[2,3-*d*]thiazoles as potential biologically active compounds

**Abstract:** Novel *rel-(5R,6S,7S)-2-oxo-5,7-*diaryl-3,5,6,7tetrahydro-2*H*-thiopyrano[2,3-*d*]thiazol-6-yl-oxo-acetic acids were synthesized in 52–70% yields *via* regioselective and diastereoselective *hetero*-Diels-Alder reaction of 5-arylidene-4-thioxo-2-thiazolidinones with a series of arylidene pyruvic acids. The synthesized compounds were evaluated for anticancer activity in NCI60 cancer cell lines and for antiexudative activity on the carrageenan edema model in rats. Biological screening data led to identification of **3e** as having moderate antitumor activity on the colon cancer HT-29 cell line and of **3b** as having promising antiexudative effect.

**Keywords:** 5-arylideneisorhodanines; anticancer activity; antiexudative activity; arylidene pyruvic acids; *hetero*-Diels-Alder reaction; thiopyrano[2,3-*d*]thiazoles.

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## Introduction

Arylidene pyruvic acids (APAs) of a versatile structure have been used as starting materials for the synthesis of a large diversity of organic compounds [1]. In addition, this functionality is associated with biological properties and is present in a series of bioactive natural products [2–4]. Meanwhile, in our previous research, we obtained a number of arguments in favor of the hypothesis of the pharmacological potential of thiopyrano[2,3-*d*]thiazoles, synthetic precursors to biologically active 5-aryl(heteryl)idene-4-thiazolidinones.

Andrii Lozynskyi, Borys Zimenkovsky and Ihor Nektegayev: Department of Pharmaceutical, Organic and Bioorganic Chemistry, Danylo Halytsky Lviv National Medical University, Pekarska 69, 79010 Lviv, Ukraine Such derivatives may be considered as structures with 'fixed' thiazolidinone biophore in condensed heterosystems that allows to predict compounds' pharmacological profile saving and to extend the 'structure-activity' database. In support of this view, thiopyrano[2,3-*d*]thiazoles with anticancer, antimycobacterial, and antitrypanosomal properties have been identified [5–15]. In continuation of our research, the thiazolidinone moiety and a fragment of APAs were combined in a single heterocyclic system (Scheme 1). Herein, we report the synthesis and characterization of new thiopyrano[2,3-*d*]thiazoles using APAs as dienophiles in *hetero*-Diels-Alder reactions.

### **Results and discussion**

#### Chemistry

The synthesis of starting 5-arylidene-4-thioxo-2-thiazolidinones (5-arylideneisorhodanines) **1a–d** was accomplished by the reaction of 4-thioxo-2-thiazolidinone with appropriate aldehydes in glacial acetic acid in the presence of a catalytic amount of fused sodium acetate [8, 10]. Same results were obtained for the reaction conducted in ethanol in the presence of ethylenediaminediacetate (EDDA). The APAs were synthesized by the reaction of a corresponding aromatic aldehyde with a pyruvic acid in an aqueous methanol solution of KOH [16]. The *hetero*-Diels-Alder reaction of **2a–f** with 5-arylidene-4-thioxo-2-thiazolidinones **1a–d** regioselectively and diastereoselectively yielded a series of novel *rel-*(5*R*,6*S*,7*S*)-2-oxo-5,7-diaryl-3,5,6,7-tetrahydro-2*H*-thiopyrano[2,3-*d*]thiazol-6-yl-oxoacetic acids (Scheme 2).

The structure of the newly synthesized compounds was confirmed by elemental analysis and spectroscopic data (<sup>1</sup>H NMR and <sup>13</sup>C NMR). The stereochemical features of the above *hetero*-Diels-Alder reaction can be predicted. In particular, we have observed that the use of APAs in the [4+2]-cyclocondensation with 5-arylideneisorhodanines leads to a pair of *rel*-(*5R*,*6S*,*7S*)-diastereomers. This claim is based on the coupling constant values within the range

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Scheme 2 Synthesis of 2-oxo-5,7-diaryl-3,5,6,7-tetrahydro-2H-thiopyrano[2,3-d]thiazol-6-yl-oxo-acetic acids.

of 10.4–10.8 Hz and the observed spectral patterns of the thiopyran fragment (triplet and two doublets at 4.18–4.85 ppm), which show an axial-axial interaction of the 5-H, 6-H and the 6-H, 7-H proton pairs. Importantly, a similar pattern was observed earlier for cinnamic acids and their amides as dienophiles in the *hetero*-Diels-Alder reactions [9–11].

#### Evaluation of anticancer activity in vitro

Synthesized *rel*-(5*R*,6*S*,7*S*)-2-0x0-5,7-diaryl-3,5,6,7-tetrahydro-2*H*-thiopyrano[2,3-*d*]thiazol-6-yl-oxo-acetic acids **3e** and **3c** were selected by the National Cancer Institute (NCI) Developmental Therapeutic Program (www.dtp.nci. nih.gov) and evaluated for antitumor activity at  $10-\mu$ M concentration toward a panel of approximately 60 cancer cell lines. The human tumor cell lines were representing leukemia, melanoma, lung, colon, central nervous system, ovarian, renal, prostate, and breast cancers. Anticancer assays were performed according to the NCI protocol, which is described elsewhere [17–19]. The compounds were added at a single concentration, and the cell cultures were incubated for 48 h. The results for each compound are reported as the percentage of growth (GP%) of treated cells when compared with untreated control cells. The screening results are shown in Table 1.

The tested compounds **3e** and **3c** did not show significant activity in almost cancer cell lines. Nevertheless,

Test compounds	Average growth (%)	Range of growth (%)	Most sensitive cell line growth (%) (cancer line/ type)	
3e	95.52	53.15- 106.33	53.15 (HT-29/colon cancer) 82.81 (SK-MEL-2/melanoma) 77.37 (UO-31/renal cancer)	
3c	100.58	86.02- 114.04	89.62 (SK-MEL-2/melanoma) 86.02 (TK-10/renal cancer) 87.00 (UO-31/renal cancer) 89.06 (T-47-D/breast cancer)	

Table 1Cytotoxic activity of the tested compounds at concentration10-5 M against 60 cancer cell lines.

slight *in vitro* cytostatic effect was observed in the growth of SK-MEL-2 (melanoma), TK-10 and UO-31 (renal cancer), and T-47-D (breast cancer). Moreover, **3e** possessed moderate effect on the colon cancer HT-29 cell line (GP% = 53.15%).

#### Antiexudative activity

For antiexudative tests, adult male and female rats weighing 140-150 g were used. The carrageenan-induced hind paw edema in rats was produced using the method of Winter et al. [20]. Diclofenac sodium (10 mg/kg) and ketorolac tromethamine (10 mg/kg) were used as reference compounds. Carrageenan solution (1.0% in sterile 0.9% NaCl solution) was injected subcutaneously into the subplanar region of the hind paw (in volume of 0.1 mL to each paw) 1 h after administration of the test compound. The synthesized compounds were intraperitoneally injected (1 h before carrageenan) in a dose 100 mg/kg. Control rats only received a solution of 0.5% carboxymethylcellulose with one drop of Tween-80. The hind paw volume was measured with an electronic onkograph immediately before and 4 h after carrageenan injection. The effect of the test compounds on decreasing paw edema was compared with control rats. The antiexudative activity was expressed as a decrease in rat paw edema and is given in percentage (Table 2).

Among tested compounds, **3b** was found to be the most active. It decreased carrageenan-induced edema on 42.1%. This value is comparable with the effect of reference compounds. For other derivatives, **3a**, **3d**, and **3g**, moderate antiexudative activity was observed.

### Conclusions

5-Arylideneisorhodanines and APAs undergo regioselective and diastereoselective *hetero*-Diels-Alder reaction,  
 Table 2
 Antiexudative activity of the tested compounds on the carrageenan foot edema model in rats.

Test compound	Dose (mg/kg)	Cross section of rat paw (relative units)	Inhibition of rat paw edema (%) over control
Control	-	95.2	-
Diclofenac sodium	10	58.6	44.6
Ketorolac tromethamine	10	71.6	42.1
3a	100	89.4	27.6
3b	100	71.5	42.1
3d	100	87.0	29.6
3g	100	80.0	34.8

providing novel *rel*-(5*R*,6*S*,7*S*)-2-oxo-5,7-diaryl-3,5,6,7tetrahydro-2*H*-thiopyrano[2,3-*d*]thiazol-6-yl-oxo-acetic acids. Two tested compounds display slight antitumor activity against melanoma, renal, and breast cancers cell lines. The preliminary results of antiexudative activity on the carrageenan foot edema model in rats allowed identifying the active compound **3b** with effect level comparable to that of diclofenac sodium or ketorolac tromethamine.

## Experimental

#### Chemistry

All materials were purchased from commercial sources and used without purification. Melting points were measured in open capillary tubes and are uncorrected. Elemental analyses were performed using Perkin-Elmer 2400 CHN analyzer. The <sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) spectra were recorded on Varian Gemini 400 or Bruker 125 in DMSO- $d_6$  using tetramethylsilane as internal standard. The purity of all obtained compounds was checked by thin-layer chromatography.

The starting compounds, 2,4-thiazolidinedione [21] and 4-thioxo-2-thiazolidinone [22], were obtained as described previously. 5-Arylidene-4-thioxo-2-thiazolidinones **1a–d** were prepared by Knoevenagel condensation using method A or B.

**Method A:** A mixture of 4-thioxo-2-thiazolidinone (10 mmol), appropriate substituted benzaldehyde (10 mmol), and sodium acetate (10 mmol) in glacial acetic acid (10 mL) was heated under reflux for 20 min in water bath (100°C). The solid product was collected by filtration and used without further purification.

**Method B:** A mixture of 4-thioxo-2-thiazolidinone (10 mmol) and appropriate substituted benzaldehyde (10 mmol) in ethanol in the presence of catalytic amount of EDDA was heated under reflux for 10 min. The solid product was collected by filtration and used without further purification.

#### General procedure for *hetero*-Diels-Alder reaction affording 3a-g

A mixture of appropriate 5-arylidene-4-thioxo-2-thiazolidinone (5 mmol), APA (5.5 mmol), and a catalytic amount of hydroquinone (2–3 mg) in 15 mL of glacial acetic acid was heated under reflux for 4–7 h and then left overnight at room temperature. The resultant solid product was collected by filtration, washed with water, methanol (5–10 mL), diethyl ether, and crystallized from acetic acid or ethanol.

*rel*-(5*R*,6*S*,7*S*)-[7-(3,4-Dimetoxyphenyl)-5-phenyl-2-oxo-3,5,6,7tetrahydro-2*H*-thiopyrano[2,3-*d*]thiazol-6-yl]oxo-acetic acid (3a): Yield 60%; mp 192–194°C (AcOH); <sup>1</sup>H NMR: δ 3.71 (s, 3H, OCH<sub>3</sub>), 3.72 (s, 3H, OCH<sub>3</sub>), 4.21 (d, 1H, *J* = 10.8 Hz, 7-H), 4.64 (t, 1H, *J* = 10.8 Hz, 6-H), 5.00 (d, 1H, *J* = 10.8 Hz, 7-H), 6.69 (d, 1H, *J* = 8.1 Hz, arom.), 6.82 (t, 1H, *J* = 7.5 Hz, arom.), 6.86 (s, 1H, arom.), 7.27–7.36 (m, 3H, arom.), 7.44 (d, 2H, *J* = 7.5 Hz, arom.), 11.47 (s, 1H, NH); <sup>13</sup>C NMR: δ 192.6, 172.6, 170.8, 165.6, 145.2, 141.9, 137, 131.6, 130.4, 128.9, 128.5, 121.4, 119.2, 115.4, 109.2, 6.11, 6.23, 55.5, 48.6, 42.1. Anal. Calcd for C<sub>22</sub>H<sub>19</sub>NO<sub>6</sub>S<sub>2</sub>: C, 57.76; H, 4.19; N, 3.06. Found: C, 57.77; H, 4.20; N, 3.07.

*rel*-(5*R*,6*S*,7*S*)-[5-(3,4-Dimetoxyphenyl)-7-(4-methoxyphenyl)-2oxo-3,5,6,7-tetrahydro-2*H*-thiopyrano[2,3-*d*]thiazol-6-yl]oxo-acetic acid (3b): Yield 52%; mp 184–186°C (EtOH); <sup>1</sup>H NMR: δ 3.74 (s, 3H, OCH<sub>3</sub>), 3.75 (s, 3H, OCH<sub>3</sub>), 3.86 (s, 3H, OCH<sub>3</sub>), 4.17 (d, 1H, *J* = 10.4 Hz, 7-H), 4.48 (t, 1H, *J* = 10.4 Hz, 6-H), 4.77 (d, 1H, *J* = 10.4 Hz, 5-H), 6.85 (d, 1H, *J* = 8.4 Hz, arom.), 6.96 (s,1H, arom.), 7.04 (d, 1H, *J* = 8.4 Hz, arom.), 7.09 (d, 2H, *J* = 8.0 Hz, arom.), 7.58 (d, 2H, *J* = 8.0 Hz, arom.), 11.25 (s, 1H, NH); <sup>13</sup>C NMR: δ 196.5, 170.8, 170.5, 161.3, 160.6, 158.6, 148.8, 135.9, 132.7, 129.5, 127.3, 121.1, 115.0, 111.5, 108.2, 55.6, 55.4, 54.9, 47.8, 45.1. Anal. Calcd for  $C_{23}H_{21}NO_7S_2$ : C, 56.66; H, 4.34; N, 2.87. Found: C, 56.65; H, 4.33; N, 2.88.

*rel*-(5*R*,6*S*,7*S*)-[7-(4-Methoxyphenyl)-5-phenyl-2-oxo-3,5,6,7tetrahydro-2*H*-thiopyrano[2,3-*d*]thiazol-6-yl]oxo-acetic acid (3c): Yield 69%; mp 186–188°C (EtOH); <sup>1</sup>H NMR: δ 3.75 (s, 3H, OCH<sub>3</sub>), 4.18 (d, 1H, *J* = 10.4 Hz, 7-H), 4.49 (t, 1H, *J* = 10.4 Hz, 6-H), 4.85 (d, 1H, *J* = 10.4 Hz, 5-H), 6.80 (d, 2H, *J* = 8.4 Hz, arom.), 7.09 (d, 2H, *J* = 8.4 Hz, arom.), 7.29–7.37 (m, 3H, arom.), 7.39 (d, 2H, *J* = 7.2 Hz, arom.), 11.29 (s, 1H, NH); <sup>13</sup>C NMR: δ 193.51, 171.43, 171.65, 167.32, 145.19, 142.88, 139.22, 133.54, 131.54, 129.74, 121.18, 117.76, 111.56, 56.44, 55.73, 49.65, 41.22. Anal. Calcd for C<sub>21</sub>H<sub>17</sub>NO<sub>5</sub>S<sub>2</sub>: C, 59.00; H, 4.01; N, 3.28. Found: C, 59.02; H, 4.02; N, 3.27.

*rel*-(5*R*,6*S*,7*S*)-[7-(4-Chlorophenyl)-5-(4-methoxyphenyl)-2-oxo-3,5,6,7-tetrahydro-2*H*-thiopyrano[2,3-*d*]thiazol-6-yl]oxo-acetic acid (3d): Yield 65%; mp 192–194°C (EtOH); <sup>1</sup>H NMR:  $\delta$  3.73 (s, 3H, OCH<sub>3</sub>), 4.17 (t, 1H, *J* = 10.4 Hz, 6-H), 4.38 (d, 1H, *J* = 10.4 Hz, 7-H), 4.94 (d, 1H, *J* = 10.4 Hz, 5-H), 6.79 (d, 2H, *J* = 8.0 Hz, arom.), 7.19 (d, 2H, *J* = 8.4 Hz, arom.), 7.25 (d, 2H, *J* = 8.0 Hz, arom.), 7.29 (d, 2H, *J* = 8.4 Hz, arom.), 11.29 (s, 1H, NH); <sup>13</sup>C NMR:  $\delta$  192.4, 172.6, 170.6, 164.1, 141.5, 139.8, 131.5, 130.6, 129.4, 128.6, 118.2, 114.2, 107.8, 55.8, 5.2, 46.7, 43.8. Anal. Calcd for C<sub>21</sub>H<sub>16</sub>ClNO<sub>5</sub>S<sub>2</sub>: C, 54.60; H, 3.49; N, 3.03. Found: C, 54.61; H, 3.48; N, 3.02.

*rel-*(5*R*,6*S*,7*S*)-[5-(4-Methoxyphenyl)-7-(4-methylphenyl)-2-oxo-3,5,6,7-tetrahydro-2*H*-thiopyrano[2,3-*d*]thiazol-6-yl]oxo-acetic acid (3e): Yield 55%; mp 172–174°C (EtOH); 'H NMR:  $\delta$  2.26 (s, 3H, CH<sub>3</sub>), 3.72(s, 3H, OCH<sub>3</sub>), 4.19 (d, 1H, *J* = 10.4 Hz, 7-H), 4.49 (t, 1H, *J* = 10.4 Hz, 6-H), 4.86 (d, 1H, *J* = 10.4 Hz, 5-H), 6.88 (d, 2H, *J* = 8.7 Hz, arom.), 7.12 (d, 2H, J = 8.1 Hz, arom.), 7.35 (d, 2H, J = 8.7 Hz, arom.), 7.59 (d, 2H, J = 8.1 Hz, arom.), 11.45 (s, 1H, NH); <sup>13</sup>C NMR:  $\delta$  192.8, 171.6, 171.0, 165.8, 143.5, 141.3, 133.4, 132.8, 132.0, 131.4, 121.2, 116.9, 109.5, 55.8, 51.2, 45.3, 41.5, 23.3. Anal. Calcd for C<sub>22</sub>H<sub>19</sub>NO<sub>5</sub>S<sub>2</sub>: C, 59.85; H, 4.34; N, 3.17. Found: C, 59.83; H, 4.33; N, 3.18.

*rel*-(*5R*, *6S*, *7S*)-[7-(4-Methylphenyl)-5-phenyl-2-oxo-3, *5*, *6*, 7tetrahydro-2*H*-thiopyrano[2, 3-*d*]thiazol-6-yl)]oxo-acetic acid (3f): Yield 56%; mp 182–184°C (EtOH); <sup>1</sup>H NMR:  $\delta$  2.25 (s, 3H, CH<sub>3</sub>), 4.24 (d, 1H, *J* = 10.6 Hz, 7-H), 4.56 (t, 1H, *J* = 10.6 Hz, 6-H), 4.98 (d, 1H, *J* = 10.6 Hz, 5-H), 7.11 (d, 2H, *J*=8.7 Hz, arom.), 7.13 (d, 2H, *J*=8.7 Hz, arom.), 7.29–7.35 (m, 3H, arom.), 7.42 (d, 2H, *J* = 7.2 Hz, arom.), 11.48 (s, 1H, NH); <sup>13</sup>C NMR:  $\delta$  196.6, 170.4, 160.4, 137.2, 135.8, 135.3, 129.2, 128.8, 128.5, 128.2, 126.6, 120.0, 108.1, 54.5, 47.9, 45.5, 20.7. Anal. Calcd for C<sub>21</sub>H<sub>µ</sub>, NO<sub>4</sub>S<sub>2</sub>: C, 61.30; H, 4.16; N, 3.40. Found: C, 61.31; H, 4.15; N, 3.41.

*rel*-(5*R*,6*S*,7*S*)-[7-(4-Chlorophenyl)-5-phenyl-2-oxo-3,5,6,7-tetrahydro-2*H*-thiopyrano[2,3-*d*]thiazol-6-yl)oxo-acetic acid (3g): Yield 70%; mp 178–180°C (EtOH); <sup>1</sup>H NMR:  $\delta$  4.27 (d, 1H, *J* = 10.8 Hz, 7-H), 4.47 (t, 1H, *J* = 10.8 Hz, 6-H), 4.86 (d, 1H, *J* = 10.8 Hz, 5-H), 7.21 (d, 2H, *J* = 8.4 Hz, arom.), 7.29–7.31 (m, 5H, arom.), 7.38 (d, 2H, *J* = 7.2 Hz, arom.), 11.40 (s, 1H, NH); <sup>13</sup>C NMR:  $\delta$  193.2, 171.3, 171.4, 162.6, 140.1, 139.8, 133.3, 129.5, 120.2, 115.6, 109.8, 55.7, 50.2, 45.1, 41.2. Anal. Calcd for C<sub>20</sub>H<sub>14</sub>ClNO<sub>4</sub>S<sub>2</sub>: C, 55.62; H, 3.27; N, 3.24. Found: C, 55.61; H, 3.28; N, 3.25.

#### Cytotoxic activity against malignant human tumor cells

Anticancer *in vitro* assay was performed on the human tumor cell lines panel derived from nine neoplastic diseases, in accordance with the protocol of the Drug Evaluation Branch, National Cancer Institute, Bethesda, MD, USA [17–19]. Tested compounds were added to the culture at a single concentration (10<sup>-5</sup> M), and the cultures were incubated for 48 h. End point determinations were made with a protein binding dye, sulforhodamine B. Results for each tested compound were reported as the GP% of the treated cells when compared with the untreated control cells. GP% was evaluated spectrophotometrically vs. controls not treated with test agents.

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