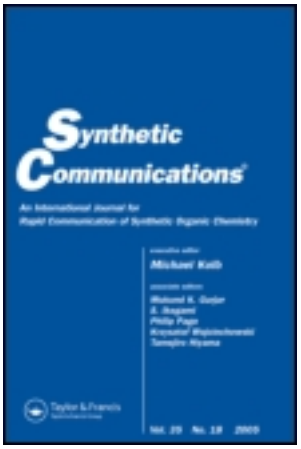

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5-Ethoxymethylidene-4-thioxo-2-thiazolidinone as Versatile Building Block for Novel Biorelevant Small Molecules with Thiopyrano[2,3-d][1,3]thiazole Core

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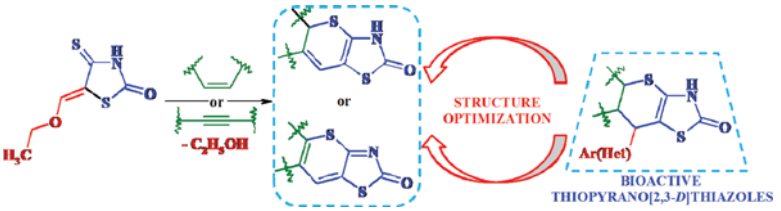
GRAPHICAL ABSTRACT



Abstract *5-Ethoxymethylidene-4-thioxo-2-thiazolidinone was studied as versatile core building block in the synthesis of new thiopyrano[2,3-*d*]thiazole derivatives relevant for medicinal chemistry purposes under* hetero-*Diels–Alder reaction conditions. Promising compounds (**6, 10**) were identified among synthesized series with high antitumor and moderate antiviral activity.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords Biological activity; 5-ethoxymethylidene-4-thioxo-2-thiazolidinone; *hetero*-Diels–Alder reaction; thiopyrano[2,3-*d*]thiazole

INTRODUCTION

At present 5-aryl/heteryl/idene-4-thiazolidinone derivatives constitute an important series of biologically active compounds and important intermediates in modern medicinal and synthetic organic chemistry by possessing synthetic multi-functionality[1–3] and bioactivity in diverse pharmacological areas.[4–10] Substituted ylidene fragment conjugation with the carbonyl group at position 4 of the

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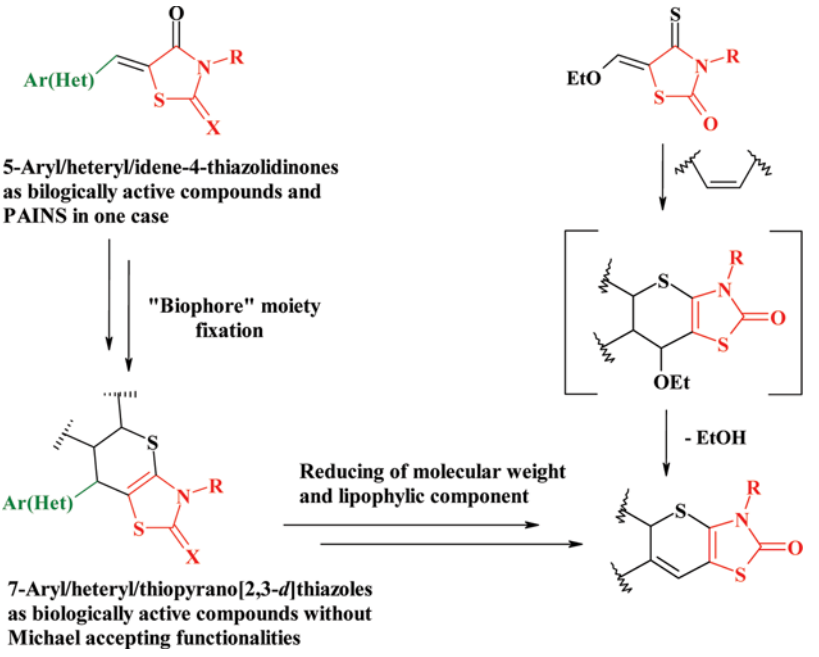
thiazolidine moiety rendered compounds potentially reactive because of possible Michael addition of the nucleophilic protein residues to the exocyclic double bond. This property characterizes 5-arylidene-4-thiazolidinones as frequent hitters or pan assay interference compounds (PAINS) that are useless in the modern drug discovery process because of their insufficient selectivity.[11–14] Following our previous findings we have proposed the possibility of avoiding the mentioned features. Thus, it was established that fixation of highly active 5-aryl/heteryl/idene-4-thiazolidinone moiety in structure-related 7-aryl/heteryl/thiopyrano[2,3-*d*][1,3]thiazole system usually allows conservation of the biological activity vector, and the latter systems could be considered as cyclic isosteric mimics of their synthetic precursors, 5-arylidene-4-thiazolidinones, without Michael accepting functionalities.[15–19] Experimental development of this concept gave us an opportunity to synthesize and select hit and lead compounds possessing antitumor,[15,17] antituberculosis,[19] and antitrypanosomal[20] activities. Modern approaches in drug discovery and development processes are oriented on low-molecular-weight compounds. Thus, we decided to pursue our efforts in simplification of thiopyrano[2,3-*d*][1,3]thiazoles while synthesizing new derivatives without aryl- or heteryl substituents in position 7 of the core heterocycle.[21]

Our synthetic strategy was based on 5-ethoxymethylidene-4-thioxo-2-thiazolidinone (5-ethoxymethylideneisorhodanine) as heterodiene in *hetero*-Diels–Alder reaction. The latter contains a C=C$_5$-C$_4$=S group and is an active heterodiene. According to literature data[22] *hetero*-Diels–Alder reaction of 5-ethoxymethylidene-4-thioxo-2-thiazolidinone and dienophiles leads to the formation of [4 + 2]-adducts that



Scheme 1. Background for applicability of simplified scaffolds in medicinal chemistry optimization studies. (Figure is provided in color online.)

undergo spontaneous ethanol elimination, forming endocyclic double bonds (Scheme 1).

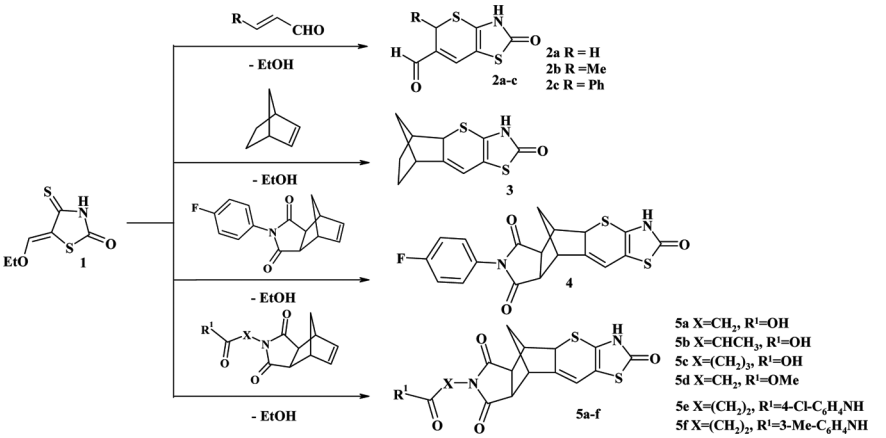
This approach allowed us to access low-molecular-weight thiopyrano[2,3-*d*][1,3]thiazoles as novel scaffolds for the drug discovery process. Nevertheless, this type of *hetero*-Diels–Alder reaction is rarely used. Only a limited number of dienophiles, such as acrylic and maleic acid derivatives and β-nitrostyrene, were studied in the reaction with 5-ethoxymethylideneisorhodanine.[22]

RESULTS AND DISCUSSION

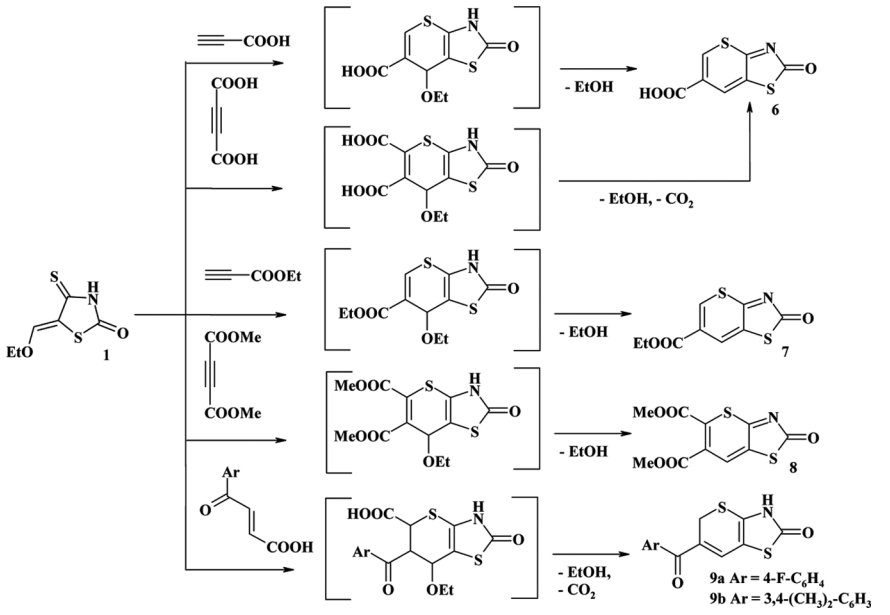
Hence, a series of new 3,5-dihydro-2*H*-thiopyrano[2,3-*d*][1,3]thiazoles were synthesized using *hetero*-Diels–Alder reaction based on 5-ethoxymethylidene-4-thioxo-2-thiazolidinone **1**.[22] We studied **1** in *hetero*-Diels–Alder reaction with several dienophiles, in particular, acrolein, crotonic aldehyde, 3-phenyl-2-propenal, acetylenedicarboxylic acid and its methyl ester, aroylacrylic acids, 2-norbonene, imides of 5-norbornene-2,3-dicarboxylic acid (endic acid), and naphthoquinone.

Thus, in the reactions of **1** with acrolein, crotonic aldehyde, and 3-phenyl-2-propenal, appropriate 5-R-2-oxo-3,5-dihydro-2*H*-thiopyrano[2,3-*d*][1,3]thiazole-6-carbaldehydes were synthesized (**2a–c**). Using as dienophiles 2-norbornene and several derivatives of endic acid imide (derivatives of 4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione) allowed us to obtain the expected tetra- (**3**) and pentacyclic structures (**4, 5**), containing 3,5-dihydrothiopyrano[2,3-*d*]thiazole-2-one fragment (Scheme 2).

We established that *hetero*-Diels–Alder reaction of acetylene derivatives as dienophiles in [4 + 2]-cyclocondensation with **1** passed with ethanol elimination and simultaneous conjugated double-bond rearrangement. Thus, reaction of **1** with propynoic acid and its ethyl ester as well as acetylenedicarboxylic acid dimethyl ester afforded corresponding 2-oxo-2*H*-thiopyrano[2,3-*d*][1,3]thiazole derivatives **6–8**. Acetylenedicarboxylic acid Diels–Alder adduct underwent unexpected decarboxylation, affording acid **6**. A similar decarboxylation was observed during



Scheme 2. Synthesis of new 5-R-2-oxo-3,5-dihydro-2*H*-thiopyrano[2,3-*d*][1,3]thiazole-6-carbaldehydes (**2a–c**) and polycyclic fused 3,5-dihydro-2*H*-thiopyrano[2,3-*d*][1,3]thiazoles containing norbornane moiety (**3–5**).

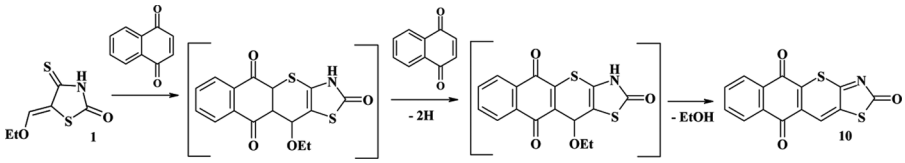


Scheme 3. Synthesis of new 2-oxo-2*H*-thiopyrano[2,3-*d*][1,3]thiazole derivatives **6–8** and 6-aryl-2-oxo-3,5-dihydro-2*H*-thiopyrano[2,3-*d*][1,3]thiazol-6-yl methanones **9a** and **b**.

[4 + 2]-cyclocondensation of **1** with aroylacrylic acids, yielding regioselectively 6-aryl-2-oxo-3,5-dihydro-2*H*-thiopyrano[2,3-*d*][1,3]thiazol-6-yl methanones **9a** and **b** (Scheme 3).

Elimination, double-bond rearrangement, and decarboxylation phenomena were confirmed by ^{1}H and ^{13}C NMR spectra and mass spectrometry (MS) (Supplementary Information). In the NMR spectra of **6–9** a shift of the proton in the 7 position in weak magnetic field ($\sigma \sim 5.90$–9.09) was observed, the latter being included into the conjugated double-bond system of 3,5-dihydrothiopyrano[2,3-*d*]thiazole. For **9a** and **b** singlets corresponding to two protons in position 5 and one in position 7 were characteristic as well.

Hetero-Diels–Alder reaction of **1** with 1,4-naphthoquinone (Scheme 4) afforded **10** and was followed by (i) the intermediate dehydrogenation because of hydroquinone excess, (ii) the formation of an additional endocyclic double bond, and (iii) EtOH elimination. Consequently, a rearrangement of conjugated double bonds took place, confirmed by the absence of a singlet NH group in ^{1}H NMR spectrum and MS of **10**.



Scheme 4. Synthesis of 5,10-dihydro-2*H*-benzo[6,7]thiochromeno[2,3-*d*][1,3]thiazole-2,5,10-trione **10**.

Table 1. Anticancer activity results (GI_{50}) of compound **10** for the most sensitive cancer cell lines (μM)

Type of cancer								
Leukemia		Non-small cell lung cancer		Melanoma			Prostate cancer	Breast cancer
HL-60(TB)	SR	HOP-62	NCI-H23	LOX IMVI	MALME-3M	SK-MEL-5	DU-145	MCF7
0.186	0.269	0.295	0.257	0.214	0.251	0.138	0.302	0.309

Synthesized compounds **6, 9a, 9b**, and **10** were tested by the National Cancer Institute Developmental Therapeutics Program (NCI DTP) (www.dtp.nci.nih.gov) for the *in vitro* anticancer activity[23–27] on 60 human tumor cell lines at concentration of 10 μM. Growth percent (GP) values were identified, and results are summarized in Table S1 (Supporting Information).

Derivatives **9a** and **9b**, besides low mean levels of tumor cells growth inhibition, have shown selectivity for leukemia cells (Table S1). The compound **10** was characterized by high levels of growth inhibition of cancer cell lines SK-MEL-5 (melanoma), OVCAR-3 (ovarian cancer), and MDA-MB-435 (breast cancer) and was tested at 5- to 10-fold dilutions, characterized with the following values of mean dose response parameters: $GI_{50} = 1.95\,\mu M$, $TGI = 20.42\,\mu M$, and $LC_{50} = 79.43\,\mu M$. The results of compound **10** activity at the most sensitive tumor cell lines are presented in Table 1.

Promising *in vitro* activity of compound **10** allowed its evaluation in the hollow fiber assay. This assay provides quantitative indications of the compound's drug efficacy on tumor cell death (http://dtp.nci.nih.gov/branches/btb/hfa.html).[28] However, **10** did not show significant activity in the hollow fiber assay but instead showed low cytotoxic activity.

Also compounds **6** and **10** were tested for antiviral activity according to the antimicrobial acquisition and coordinating facility (AACF) screening program.[29] Studied compounds did not show significant activity against viruses flu A (H1N1), flu A (H3N2), flu A (H5N1), flu B, measles, PIV (parainfluenza virus), RSV A (respiratory syncytial virus A) and SARS, but compound **10** did possess moderate activity against coronavirus SARS using both systems of results assesment: visual ($EC_{50vis} = 1.7$; $IC_{50vis} = 23$; $SI_{vis} = 14$) and with neutral red dye (EC_{50}-NR = 6; IC_{50}-NR = 14; SI-NR = 5.4).

EXPERIMENTAL

All starting materials were purchased from Merck, Sigma-Aldrich, or Lancaster and used without purification. Melting points are uncorrected and were measured in open capillary tubes on a Buchi B-545 melting-point apparatus. The ^1H NMR spectra were recorded on a Varian Gemini 400-MHz instrument and ^{13}C NMR spectra on Varian Mercury-400 100-MHz instrument in dimethylsulfoxide (DMSO-d_6) or CF_3COOD (compound **10**) with tetramethylsilane (TMS) as an internal standard [chemical shift values are reported in parts per million (ppm) units, coupling constants (J) are in hertz]. The elemental analyses

(C, H, N) performed on the Perkin-Elmer 2400 CHN analyzer were within ±0.4% of the theoretical values. Mass spectra were obtained on the Varian 1200 L instrument.

General Procedure of Thiopyrano[2,3-*d*][1,3]thiazol-2-one Derivative (2–10) Preparation

The starting 5-ethoxymethylidene-4-thioxo-2-thiazolidinone[22] and imides of 5-norbornene-2,3-dicarboxylic acid[17] were obtained according to the methods described previously. To a mixture of 5-ethoxymethylidene-4-thioxo-2-thiazolidinone (**1**) (10 mmol) and appropriative dienophile (10 mmol) for compound **10** [1,4-naphthoquinone (20 mmol)] were added glacial acetic acid (10 mL) and hydroquinone (2–3 mg), and the reaction mixture was heated with stirring at 100 °C for 1 h and then allowed to cool overnight to room temperature. The precipitated crystals were filtered off, washed with ethanol, and recrystallized from an appropriate solvent. Synthetic protocol of **10** involved 2 eq. of 1,4-naphthoquinone to ensure intermediate redox process.

Spectral and analytical data for compounds **2a, 6, 9a, 10** are as follows. Data on compounds **2b, 2c, 3–5, 7, 8**, and **9b** as well as data of primary antitumor activity assay of all synthesized substances are in the Supporting Information, available online.

2-Oxo-3,5-dihydro-2*H*-thiopyrano[2,3-*d*][1,3]thiazole-6-carbaldehyde (2a)

Yield 68%; mp 196–198 °C (EtOH). ^{1}H NMR (400 MHz, DMSO-d_6): 3.84 (s, 2H, CH_2-S), 7.24 (s, 1H, 7-H), 9.40 (s, 1H, CHO), 12.40 (br. s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 23.38, 106.88, 121.38, 137.23, 140.85, 172.03, 190.40. ESI-MS m/z 200 $(M+H)^+$.

2-Oxo-2*H*-thiopyrano[2,3-*d*][1,3]thiazole-6-carboxylic Acid (6)

Yield 78%, mp 228–230 °C (DMF). ^{1}H NMR (400 MHz, DMSO-d_6): 8.57 (d, 1H, $J = 1.5$ Hz, 5-H), 9.09 (d, 1H, $J = 1.5$ Hz, 7-H), 13.97 (br. s, 1H, COOH). ^{13}C NMR (100 MHz, DMSO-d_6): 126.10, 131.78, 138.74, 139.17, 164.34, 177.72, 178.87. ESI-MS m/z 214 $(M+H)^+$.

6-(4-Fluorobenzoyl)-3,5-dihydro-2*H*-thiopyrano[2,3-*d*][1,3]thiazol-2-one (9a)

Yield 76%, mp 220–222 °C (AcOH). ^{1}H NMR (400 MHz, DMSO-d_6): 4.66 (s, 2H, CH_2), 6.93 (s, 1H, 7-H), 7.37 (t, 2H, $J = 8.8$ Hz, arom.), 8.12 (dd, 2H, $J = 8.6$, 5.6 Hz, arom.), 12.10 (br. s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 114.28, 116.40, 116.62, 120.46, 129.27, 132.04, 132.13, 133.15, 165.89 (d, $J = 250.0$ Hz, C-F), 174.18, 195.62. ESI-MS m/z 293 $(M+H)^+$.

5,10-Dihydro-2*H*-benzo[6,7]thiochromeno[2,3-*d*] [1,3]thiazole-2,5,10-trione (10)

Yield 81%, mp > 250 °C (DMF). ^{1}H NMR (400 MHz, CF_3COOD): 7.80 (br. s, 2H, arom.), 7.92 (br. s, 2H, arom.), 9.11 (s, 1H, =CH). ESI-MS m/z 300 $(M+H)^+$.

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