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*Short Note*

# *rel*-2-[4-Chloro-2-[(5*R*,6*R*,7*S*)-6-[5-(4-methoxyphenyl)-3-(2-naphthyl)-3,4-dihydropyrazole-2-carbonyl]-5-methyl-2-oxo-3,5,6,7-tetrahydrothiopyrano[2,3-*d*]thiazol-7-yl]phenoxy]acetic Acid

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**Abstract:** The hetero-Diels–Alder reaction is the main synthetic tool for obtaining pharmacological agents with a thiopyrano[2,3-*d*]thiazole motif. In the present work, an efficient method for the synthesis of pyrazoline-containing thiopyrano[2,3-*d*]thiazole is described. The pyrazoline-bearing dienophile was proposed and used as effective building block for the synthesis of the title compound. The structure of the synthesized *rel*-2-[4-chloro-2-[(5*R*,6*R*,7*S*)-6-[5-(4-methoxyphenyl)-3-(2-naphthyl)-3,4-dihydropyrazole-2-carbonyl]-5-methyl-2-oxo-3,5,6,7-tetrahydrothiopyrano[2,3-*d*]thiazol-7-yl]phenoxy]acetic acid (**3**) was confirmed by $^{1}$H, $^{13}$C, 2D NMR, and LC-MS spectra. Anticancer activity in "60 lines screening" (NCI DTP protocol) was studied in vitro for the title compound.

**Keywords:** thiopyrano[2,3-*d*]thiazoles; pyrazoline; acylation; hetero-Diels–Alder reaction



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## 1. Introduction

Thiopyrano[2,3-*d*]thiazole derivatives are attractive objects in modern medicinal chemistry and possess a wide range of valuable biological activities, such as anticancer [1], antimicrobial [2], antiviral [3], and antifungal [4]. A retrosynthetic approach to thiopyrano[2,3-*d*]thiazoles leads to 5-ene-4-thiazolidinones, which contain enone fragments in their structures and in this regard are characterized as PAINs with low selectivity and high reactivity toward the nucleophilic centers of biological molecules [5,6] (Figure 1). Application of the hetero-Diels–Alder reaction is a useful synthetic tool for the transformation of the 5-ene-4-thiazolidinones to the respective thiopyrano[2,3-*d*]thiazoles, which enables retaining or improving the pharmacological properties and removing the PAIN features from the molecules.

Numerous protocols have reported the use of varieties of 5-aryl/heterylideneiso(thio)rhodanines as dienes and 1,4-naphthoquinone, arylidene pyruvic, acrylic, maleic, crotonic acids or their derivatives as dienophiles in thiopyrano[2,3-*d*]thiazoles synthesis via the hetero-Diels-Alder reaction [1–4,7]. Moreover, it was observed and reported that the structural features of dienophiles have a significant impact on the biological properties of the target Diels–Alder adducts as well as the ability to change the biological profile [1,8]. So, as reported in [1], the thiopyrano[2,3-*d*]thiazoles with a 1,4-naphthoquinone moiety in the molecule inhibited SK-MEL-5 melanoma and OVCAR-3 colon cancer lines, whereas the structural change of 1,4-naphthoquinone on 3,4-dimethylbenzoyl moiety had an impact on the RPMI-8226 leukemia line (Figure 1).

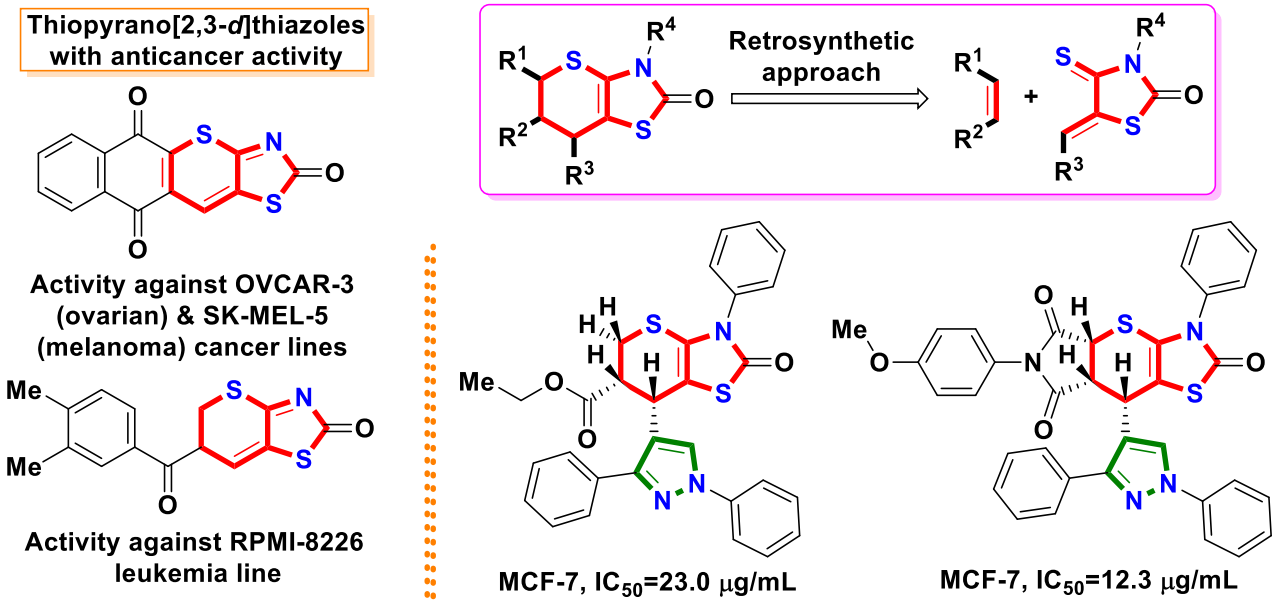



**Figure 1.** The scheme of the retrosynthetic approach to thiopyrano[2,3-*d*]thiazoles and some examples of bioactive representatives from this class of heterocycles as background for the present research [1,8].

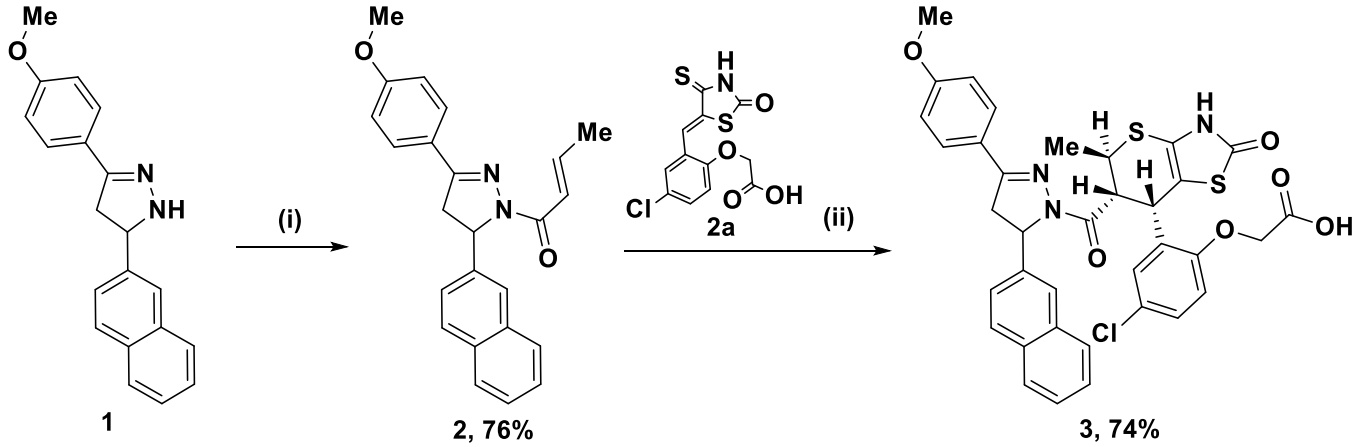
Despite the wide range of studies and examples of application of the different dienophile types for the abovementioned transformation, data on the application of diene or dienophile with pharmacologically attractive pyrazoline-bearing moieties are limited [9–11]. The work of Metwally's team [8] reported the application of pyrazoline-containing heterodiene for the design of potential anticancer agents, and their strategy was successful for targeting liver (HEPG2) and breast (MCF7) cancer cell lines (Figure 1).

Taking into account the abovementioned data, and due to our ongoing interest in pyrazoline-bearing molecules [7,12,13], we report the application of pyrazoline-containing dienophile to the construction of novel thiopyrano[2,3-*d*]thiazole via the hetero-Diels–Alder reaction. The structure characterization of the synthesized molecule, using NMR and LC-MS spectra and an in vitro anticancer activity evaluation, according to the "60 lines screening" algorithm (DTP NCI, USA), are also presented.

## 2. Results and Discussion

### *2.1. Synthesis of the Title Compound* **3**

The 3-(4-methoxyphenyl)-5-(2-naphthyl)-4,5-dihydro-1*H*-pyrazole (**1**) was synthesized following the protocol described in [14] and used as a starting compound (Scheme 1). Crotonic anhydride was used for the acylation of **1**, and a reaction was performed by reflux for 3 h in dry toluene with a yield of 76%. In addition, dry dioxane was tested as a reaction medium, and the yield was 62%. The obtained pyrazoline-containing dienophile **2** was purified by recrystallization from ethanol and used in the next step. This approach may be successfully used for obtaining other pyrazoline-containing dienophiles from respective NH-unsubstituted pyrazolines. At the next stage, the hetero-Diels–Alder reaction was applied to construct the target title compound **3**. The appropriate heterodiene—(*Z*)-2-{4-chloro-2-[(2-oxo-4-thioxothiazolidin-5-ylidene)methyl]phenoxy}acetic acid (**2a**) was obtained from 4-thioxothiazolidin-2-one and 2-(4-chloro-2-formylphenoxy)acetic acid following the protocol described in [15]. The interaction of **2** with the synthesized heterodiene **2a** under reflux conditions for 2 h in the glacial acetic acid with the presence of hydroquinone (0.1 mmol%) obtained **3** with a yield of 74% (Scheme 1). The crude product **3** was obtained as a precipitate directly from the reaction mixture, isolated by filtration, and purified by recrystallization from the mixture DMF: ethanol (1:2).




**Scheme 1.** Synthesis of the title compound **3**. Reagents and conditions: (**i**)—**1** (10 mmol), crotonic anhydride (10 mmol), toluene (15 mL), reflux 3 h; (**ii**)—**2** (5 mmol), **2a** (5 mmol), hydroquinone (0.1 mmol%), acetic acid (10 mL), reflux 2 h.

The structures of the synthesized compounds **2** and **3** were confirmed by $^{1}$H, $^{13}$C NMR, and LC-MS spectra (copies of the spectra are presented in the Supplementary Materials). In the NMR spectra, the signals of all hydrogen and carbon atoms were presented.

In the $^{1}$H NMR spectrum of compound **2**, the protons of the propene residue resonated as a triplet at 1.92 ppm, a sextet at 6.79 ppm, and a doublet at 7.06 ppm with $J$ = 15.4 Hz, which indicated the *trans*-orientation of the protons at the double bond. The protons of the pyrazoline ring had the characteristic pattern of three doublets of doublets at 3.27, 3.93, and 5.61 ppm with the appropriate coupling constants. All presented in the molecule aromatic protons appeared in the relevant area. In the $^{13}$C NMR spectrum of compound **2**, the signals of the carbons of the $CH_3$ groups were observed at 17.8 ppm (C-5) and 55.1 ppm (methoxy). The carbons of the pyrazoline ring resonated at 41.6, 59.2, and 154.4 ppm. The signal of carbon in the carbonyl group (C=O) appeared at 162.1 ppm.

In the $^{1}$H NMR spectrum of compound **3,** the thiopyrano ring protons resonated as a multiplet at 3.55–3.63 ppm (5-H), doublet of doublets at 4.14 ppm with $J$ = 10.6, 4.8 Hz, (6-H), and a doublet at 4.87 ppm with $J$ = 4.7 Hz (7-H). The value $J$ = 4.7 Hz for 7-H indicated a *cis*-position for 7-H and 6-H in the thiopyrano ring. Additionally, we performed the ROESY experiment for **3**, which allowed the observation of the interaction between protons of the methyl group at C-5 and H-6 and between 5-H and the *ortho*-proton in the phenyl ring at C-7 (Figure 2). Such a spectral pattern suggested the stereochemistry of the thiopyrano ring protons, as presented in Scheme 1, and was reported previously [16]. The signals of the methylene group protons in the acetic acid residue appeared as two doublets at 4.56 and 4.70 ppm. Other protons signals were located in the corresponding aliphatic and aromatic regions as expected and described above. The $^{13}$C NMR spectra of compound **3** showed 30 carbon signals, and some signals were overlapping. The carbon atoms in the thiopyrano ring produced a set of signals at 33.8, 48.2, 114.3, and 130.9 ppm, and one signal overlapped with the signal of the methoxy group carbon at 55.0 ppm. The signal of the methylene group carbon in the acetic acid residue appeared at 65.9 ppm. The carbon signal of the three carbonyl groups (C=O) appeared at 166.5, 169.8, and 170.8 ppm. The molecular ion peak observed at the m/z value of 700.2 $[M + H]^{+}$ in the positive ionization mode in the mass spectrum confirmed the formation of the title compound **3**.

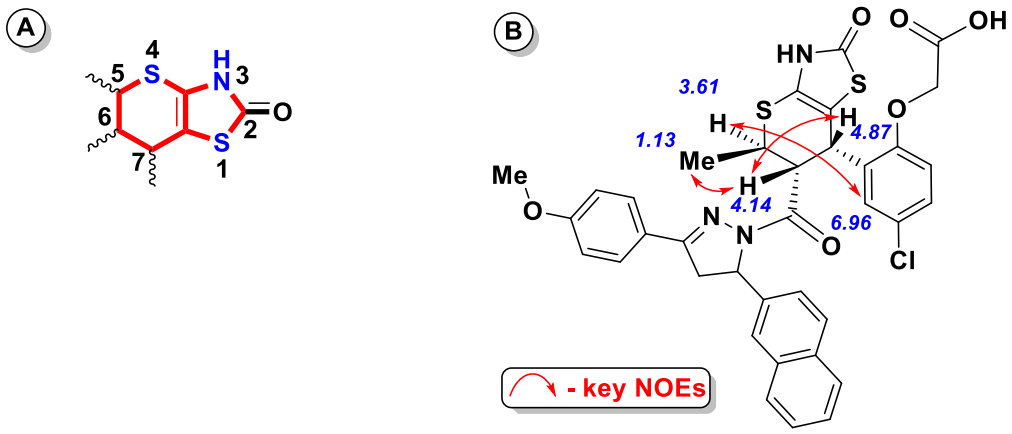



**Figure 2.** The scheme of atom numbering in the thiopyrano[2,3-*d*]thiazole core (**A**) and key interactions in the relevant ROESY spectrum of compound **3** (**B**).

### *2.2. In Vitro Evaluation of the Anticancer Activity of Compound* **3**

Antitumor activity screening was performed for title compound **3**, according to the standard protocols of the National Cancer Institute (NCI, Bethesda, MD, USA) Developmental Therapeutic Program (DTP) [17–20]. The screening process included evaluation of antitumor activity at the concentration of 10 μM against a panel of approximately sixty cancer cell lines representing different types of cancer, including leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate, and breast cancers. The results of the screening assay are summarized in Table 1, and the complete data are presented in the Supplementary Materials.

**Table 1.** Anticancer activity data of compound **3** at a concentration of 10 μM.

| Compound | 60 Cell Lines Assay in One Dose, 10 μM | |
|---|---|---|
| | Mean Growth, % | Most Sensitive Cell Line(s) Growth Inhibition Percent/Line/Panel |
| **3** | 104.68 | 92.48/RPMI-8226/Leukemia<br>92.77/CCRF-CEM/Leukemia<br>92.90/K-562/Leukemia<br>92.74/SF-539/CNS |

The screening results revealed that the synthesized compound **3** possessed a low level of anticancer activity, and the tumors lines' growth ranged from 92.48 to 126.61%, with an average growth value of 104.68%. Compound **3** had a weak impact on leukemia cancer lines RPMI-8226 (growth percent 92.48%), CCRF-CEM (growth percent 92.77%), K-562 (growth percent 92.90%), and central nervous system cancer line SF-539 (growth percent 92.74%).

## 3. Materials and Methods

The melting points were measured in open capillary tubes on a BÜCHI B-545 melting point apparatus (BÜCHI Labortechnik AG, Flawil, Switzerland) and were uncorrected. The elemental analyses (C, H, N) were performed using the Perkin-Elmer 2400 CHN analyzer (PerkinElmer, Waltham, MA, USA) and were within ±0.4% of the theoretical values. The 500 MHz $^{1}$H and 100 MHz $^{13}$C NMR spectra were recorded on a Varian Unity Plus 500 (500 MHz) spectrometer (Varian Inc., Paulo Alto, CA, USA). All spectra were recorded at room temperature, except where indicated otherwise, and were referenced internally to solvent reference frequencies. Chemical shifts (δ) are quoted in ppm and coupling constants (*J*) are reported in Hz. LC-MS spectra were obtained on a Finnigan MAT INCOS-50 (Thermo Finnigan LLC, San Jose, CA, USA). The reaction mixture was monitored by thin layer chromatography (TLC) using commercial glass-backed TLC plates (Merck Kieselgel 60 F254, Merck, Darmstadt, Germany). Solvents and reagents that are

commercially available were used without further purification. The 3-(4-methoxyphenyl)-5-(2-naphthyl)-4,5-dihydro-1*H*-pyrazole **1** was prepared according to the method described in [14].

*1-[3-(4-Methoxyphenyl)-5-naphthalen-2-yl-4,5-dihydropyrazol-1-yl]-but-2-en-1-one (**2**)*

A mixture of 3-(4-methoxyphenyl)-5-(2-naphthyl)-4,5-dihydro-1*H*-pyrazole **1** (3.45 g, 10 mmol) and crotonic anhydride (1.75 g, 10 mmol) in toluene (15 mL) was heated under a reflux condition for 3 h (monitored by TLC). After completion of the reaction, the mixture was cooled to room temperature, and the solvent was evaporated to obtain a pure yellow liquid of **2** that was poured into ice water. The formed yellow solid of **2** was collected by filtration and recrystallized from ethanol.

Yield 76%, yellow crystal powder, mp 142–144 °C (EtOH).

$^1$H NMR (500 MHz, DMSO-$d_6$, δ): 1.92 (t, *J* = 6.0 Hz, 3H, $CH_3$), 3.27 (dd, *J* = 17.8, 3.9 Hz, 1H, $CH_2$), 3.71 (s, 3H, $OCH_3$), 3.93 (dd, *J* = 17.8, 11.8 Hz, 1H, $CH_2$), 5.61 (dd, *J* = 11.8, 3.9 Hz, 1H, $CH_2$), 6,79 (sext, *J* = 6.9 Hz, 1H, =CH), 6.88 (d, *J* = 8.5 Hz, 2H, arom.), 7.06 (d, *J* = 15.4 Hz, 1H, =CH), 7.13 (d, *J* = 8.5 Hz, 2H, arom.), 7.58 (dq, *J* = 6.3, 3.6, 2.3 Hz, 2H, arom.), 7.93–8.01 (m, 3H, arom.), 8.10 (d, *J* = 7.8 Hz, 1H, arom.), 8.20 (s, 1H, arom.).

$^{13}$C NMR (100 MHz, DMSO-$d_6$, δ): 17.8, 41.6, 55.1, 59.2, 113.9, 122.6, 123.1, 126.8, 127.3, 127.5, 127.7, 128.3, 128.4, 128.7, 132.7, 133.6, 134.4, 141.2, 154.4, 158.4, 162.1 (C=O).

LCMS (Electrospray ionization ESI+): *m*/*z* 371.1 (100%, $[M + H]^+$).

Anal. calc. for $C_{24}H_{22}N_2O_2$: C, 77.81%; H, 5.99%; N, 7.56%; Found: C, 77.92%; H, 6.11%; N, 7.68%.

*rel-2-[4-Chloro-2-[(5R,6R,7S)-6-[5-(4-methoxyphenyl)-3-(2-naphthyl)-3,4-dihydropyrazole-2-carbonyl]-5-methyl-2-oxo-3,5,6,7-tetrahydrothiopyrano[2,3-d]thiazol-7-yl]phenoxy]acetic acid (**3**)*

A mixture of compound **2** (1.85 g, 5 mmol) and [4-chloro-2-(2-oxo-4-thioxothiazolidin-5-ylidenemethyl)-phenoxy]-acetic acid (1.65 g, 5 mmol) with hydroquinone (0.1 mmol%) in the glacial acetic acid (10 mL) was heated under reflux for 2 h (monitored by TLC). After completion, the reaction mixture was cooled to room temperature. The resultant yellow solid of compound **3** was collected by filtration, washed with water and ethanol (5–10 mL), and recrystallized from the mixture DMF:ethanol (1:2).

Yield 74%, yellow crystal powder, mp 228–230 °C (DMF:EtOH 1:2).

$^1$H NMR (600 MHz, DMSO-$d_6$, δ): 1.13 (d, *J* = 6.5 Hz, 3H, $CH_3$), 1.89 (s, 1H), 3.24 (dd, *J* = 17.9, 5.0 Hz, 1H, pyrazoline), 3.55–3.63 (m, 1H, 5-H), 3.67 (s, 3H, $OCH_3$), 3.96 (dd, *J* = 17.9, 11.8 Hz, 1H, $CH_2$, pyrazoline), 4.14 (dd, *J* = 10.6, 4.8 Hz, 1H, 6-H), 4.55 (d, *J* = 16.3 Hz, 1H, $CH_2$), 4.68 (d, *J* = 16.3 Hz, 1H, $CH_2$), 4.87 (d, *J* = 4.7 Hz, 1H, 7-H), 5.35 (dd, *J* = 11.7, 5.1 Hz, 1H, pyrazoline), 6.82 (d, *J* = 8.5 Hz, 2H, arom.), 6.90 (d, *J* = 8.9 Hz, 1H, arom.), 6.96 (d, *J* = 2.7 Hz, 1H, arom.), 7.10 (d, *J* = 8.4 Hz, 2H, arom.), 7.23–7.28 (m, 2H, arom.), 7.56–7.60 (m, 2H, arom.), 7.94–8.02 (m, 2H, arom.), 8.07 (d, *J* = 8.6 Hz, 1H, arom.), 8.21 (s, 1H, arom.), 11.54 (s, 1H, NH), 13.02 (brs, 1H, COOH).

$^{13}$C NMR (100 MHz, DMSO-$d_6$, δ): 18.5, 33.8, 42.2, 48.2, 55.0, 59.2, 65.9, 104.1, 113.8, 114.3, 120.9, 123.3, 124.6, 126.6, 126.8, 127.3, 127.7, 128.0, 128.3, 128.4, 128.7, 128.9, 130.9, 132.7, 133.6, 134.2, 154.6, 154.7, 158.3, 166.5 (C=O), 169.8 (C=O), 170.8 (C=O).

LCMS (Electrospray ionization ESI+): *m*/*z* 700.2 (100%, $[M + H]^+$).

Anal. calc. for $C_{36}H_{30}ClN_3O_6S_2$: C, 61.75%; H, 4.32; N, 6.00; Found: C, 61.89%; H, 4.43; N, 6.11.

## 4. Conclusions

In the present work, we reported an efficient synthetic protocol for constructing a new pyrazoline-bearing thiopyrano[2,3-*d*]thiazole derivative via the hetero-Diels–Alder reaction with satisfactory yield and high purity. The structure of the compound was characterized and elucidated using NMR spectroscopy and LC-MS spectrometry analysis. The in vitro anticancer activity of the title compound was studied.

**Supplementary Materials:** Figures S1–S9: $^1$H NMR, $^{13}$C NMR, and LC–MS spectra of compounds **2** and **3**, data of anticancer activity of compound **3**.

**Author Contributions:** Conceptualization, I.Y., S.H., O.I. and R.L.; methodology, I.Y., S.H., O.I. and R.L.; software, I.Y., S.H. and O.I.; validation, I.Y., S.H. and O.I.; investigation, I.Y., S.H. and O.I.; writing—original draft preparation, I.Y., S.H., O.I. and R.L.; writing—review and editing, I.Y., S.H., O.I. and R.L.; supervision, R.L.; project administration, R.L. All authors have read and agreed to the published version of the manuscript.

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