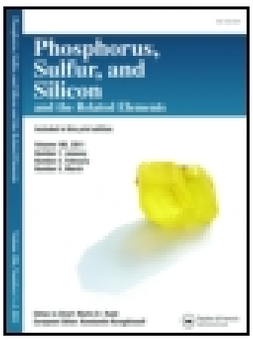


Taylor & Francis
Taylor & Francis Group

Phosphorus, Sulfur, and Silicon and the Related Elements

ISSN: 1042-6507 (Print) 1563-5325 (Online) Journal homepage: http://www.tandfonline.com/loi/gpss20

Synthesis, anticancer and antiviral activities of novel thiopyrano[2,3-d]thiazole-6-carbaldehydes

Andrii Lozynskyi, Sergii Golota, Borys Zimenkovsky, Dmytro Atamanyuk, Andrzej Gzella & Roman Lesyk

To cite this article: Andrii Lozynskyi, Sergii Golota, Borys Zimenkovsky, Dmytro Atamanyuk, Andrzej Gzella & Roman Lesyk (2016): Synthesis, anticancer and antiviral activities of novel thiopyrano[2,3-d]thiazole-6-carbaldehydes, Phosphorus, Sulfur, and Silicon and the Related Elements

To link to this article: http://dx.doi.org/10.1080/10426507.2016.1166108

Accepted author version posted online: 30 Mar 2016.

thiopyrano[2,3-*d*]thiazole-6-carbaldehydes

Synthesis, anticancer and antiviral activities of novel thiopyrano[2,3-*d*]thiazole-6-carbaldehydes

Andrii Lozynskyi[a], Sergii Golota[a], Borys Zimenkovsky[a], Dmytro Atamanyuk[a], Andrzej Gzella[b], Roman Lesyk[a,*]

[a]Department of Pharmaceutical, Organic and Bioorganic Chemistry, Danylo Halytsky Lviv National Medical University, 69 Pekarska, Lviv, 79010, Ukraine

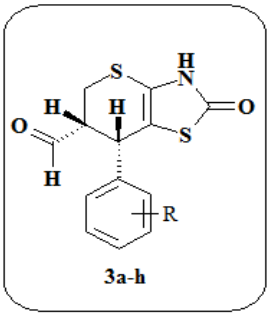
[b]Department of Organic Chemistry, Poznan University of Medical Sciences, Grunwaldzka 6, Poznan 60-780, Poland

[*]Corresponding author. E-mail: dr_r_lesyk@org.lviv.net (Roman Lesyk)

Abstract

Novel rel-(6R,7R)-2-oxo-7-phenyl-3,5,6,7-tetrahydro-2H-thiopyrano[2,3-d]thiazole-6-carbaldehydes were synthesized via regio- and diastereoselective hetero-Diels-Alder reaction of 5-arylidene-4-thioxo-2-thiazolidinones with acrolein. The synthesized compounds were evaluated for anticancer and antiviral activities by the National Institutes of Health (NIH) following US NCI and AACF protocols. Anticancer activity screening on NCI60 cell lines allowed identification of 7-phenyl-2-oxo-7-phenyl-3,5,6,7-tetrahydro-2H-thiopyrano[2,3-d]thiazole-6-carbaldehyde **3a** with the highest level of antimitotic activity against leukemia with mean GI_{50}/TGI values 1.26/25.22 μM. The screening of antiviral activity lead to identification of 7-(4-methoxyphenyl)-2-oxo-3,5,6,7-tetrahydro-2H-thiopyrano[2,3-d]thiazole-6-carbaldehyde **3b**

with a promising influence on EBV virus (EC_{50} = 0.07 μM, SI = 3279) and moderate effect on Herpes simplex virus type 1 and Varicella zoster virus and 7-[4-(benzyloxy)phenyl]-2-oxo-3,5,6,7-tetrahydro-2H-thiopyrano[2,3-d][1,3]thiazole-6-carbaldehyde **3e** with a promising influence on Hepatitis C virus (EC_{50} = 12.6 μM, SI = 43.1).



3a-h

Anticancer activity on the leukemia subpanel tumor cell lines
3a (R=H) GI_{50} = 0.89-3.24 μM

Antiviral activity
3b (R= 4-MeO) EC_{50} = 0.07 μM; SI = 3279 (EBV)
3e (R= 4-BzO-) EC_{50} = 12.6 μM; SI = 43.1 (HCMV)

Keywords

hetero-Diels-Alder reaction, thiopyrano[2,3-*d*]thiazoles, anticancer activity, antiviral activity.

INTRODUCTION

Thiazolidinone-based molecules are attaractive targets in the rational design of «drug-like» compounds which possess anti-inflammatory[1], antioxidant[2], antitumor, choleretic, diuretic[3] and other activities. In addition, 4-thiazolidinones are known as inhibitors of PRL-3 and JSP-1 phosphatases[4,5], HCV NS3 protease[6], antiapoptic proteins complex Bcl-X*L*-BH_3[7], TNFα-TNFRc-1 complex[8], Ras farnesyl transferase[9].

Among thiazolidinone derivatives, 5-arylidene-4-thiazolidinones are of wide interest due to their diverse biological activity and clinical applications[3]. However, these compounds often asigned as the frequent hitters or pan assay interference compounds (PAINS) due to their Michael acceptors properties[10-13]. Nevertheless, it was found that fixation of a highly active 5-arylidene-4-thiazolidinone moiety in a structure-related thiopyrano[2,3-*d*]thiazole core allows to store of this biophore fragment in a rigid fused system without Michael accepting functionalities. Thus, in our previous studies we reported about thiopyrano[2,3-*d*]thiazoles as potential antitripanosomal[14], antioxidant[15], anticancer[16-20] and anti-inflammatory[21] agents.

In the present work, we described our ongoing research effort in the synthesis of a series of novel thiopyrano[2,3-*d*]thiazole-6-carbaldehydes and characterization of these compounds for antitumor and antiviral activities. In view of these observations it was thought to synthesize these compounds by the [4+2]-cyclization with acrolein *via hetero*-Diels-Alder reaction.

RESULT AND DISCUSSION

Chemistry

The synthesis of target thiopyrano[2,3-*d*]thiazoles followed the general pathway outlined in Scheme 1. Firstly, the starting 5-arylidene-4-thioxo-2-thiazolidinones[21,22] **2a-h** were obtained by Knoevenagel condensation of 4-thioxo-2-thiazolidinone **1** with several aldehydes in the presence of EDDA as the base catalyst. The reactivity of the sulfur atom at the 4-position at 5-ylidene-4-thioxo-2-thiazolidinones allows it to be used as a highly active heterodiene component in *hetero*-Diels--Alder reactions[23,24]. In this work, we have synthesized several new *rel*-(6*R*,7*R*)-2-oxo-7-phenyl-3,5,6,7-tetrahydro-2*H*-thiopyrano[2,3-*d*]thiazole-6-carbaldehydes **3a-h** by coupling with acrolein as the dienophile. The heterodiene synthesis was accomplished in glacial acetic acid and a catalytic amount of hydroquinone, as a side polymerization inhibitor. The structures and stereochemical features of the synthesized compounds were elucidated by spectral data. Thus, CH_2-CH protons of the thiopyran fragment in the ^{1}H NMR spectra of synthesized compounds show characteristic patterns of an ABX system. The chemical shifts of these protons have been assigned a triplet at δ ~2.95-3.02, doublet at δ ~3.12-3.19 and multiplet at δ ~4.7-4.8, respectively, with corresponding coupling constans of $J_{5,6}$ = 13.0-13.8 Hz and $J_{6,7}$ = 4.4-4.7 Hz which indicated a equatorial-pseudoaxial interaction between the protons at C-6 and C-7. Signals of the aldehyde group appeared as single-proton singlet in weak magnetic field at δ ~ 9.60-9.75 ppm. In the ^{13}C NMR spectra of the synthesized compounds, the signals observed at δ 171.0--171.7 are assigned to the carbonyl group (C = O). The signals of carbon of the aldehyde group were observed at δ 200.5--202.6. Interestingly, similar spectral features were observed for acrylic acids and their esters as dienophiles in the *hetero*-Diels-Alder reaction[25].

The structure of the synthesized *rel*-(6*R*,7*R*)-7-(4-isopropylphenyl)-2-oxo-3,5,6,7-tetrahydro-2*H*-thiopyrano[2,3-*d*][1,3]thiazole-6-carbaldehyde (**3h**) was confirmed by X-ray

crystallographic analysis reaction (Supplemental Materials, Tables S 1-S 4)[26]. In the crystal structure of **3h** there are twelve symmetry-independent molecules in the asymmetric part of the unit cell. Displacement ellipsoids of the atoms of the *p*-isopropylphenyl residues in the molecules are increased. Simultaneously, some of the isopropyl moieties are disordered. The symmetry-independent molecules differ in terms of conformation. However, the differences mainly relate to the arrangement of isopropyl moiety.

In all the molecules the tetrahydrothiopyran ring is in a half-chair conformation. The hydrogen atoms at the stereogenic C7 and C8 centers have a *cis* axial-pseudoequatorial orientation. The torsion angles H7--C7--C8--H8 for the twelve symmetry-independent molecules are in the range of 43 – 48° and reveal a synclinal (+*sc*) conformation for atoms H(*C7*) and H(*C8*). The phenyl group is approximately perpendicular to the least squares plane of the dihydrothiopyran ring; the dihedral angles for symmetry-independent molecules A -- L are in the range of 87.4(3) – 89.3(3)°. The C4–C9 bond lengths that are in the range of 1.332(14) - 1.352(14) (molecules A -- L) confirm the presence of a double bond between these atoms. It is worth noting that the geometry of 2-oxo-7-phenyl-3,5,6,7-tetrahydro-2H-thiopyrano[2,3-d]thiazole molecule fragment in **3h** is close to those observed in two related structures (refcodes: LOBQEA and QEDBUY) found in Cambridge Structural Database, Version 5.37 [27].

Biological activity

In vitro evaluation of the anticancer activity

Anticancer assays of the compounds **3a-c, 3e, 3g** were performed according to the US NCI protocol, as described elsewhere [28-31]. Some synthesized compounds **3b**, **3e** were submitted and evaluated against the three human tumor cell lines panel, consisting of NCI-H460 (non-small cell lung cancer), MCF7 (breast cancer), and SF-268 (CNS cancer) cell lines. Thus, the substances which reduced the growth of the cell lines to 32% or less were passed on for evaluation in the full panel of 60 human tumor cells. As a result these compounds successfully passed the pre-screening phase. On the other hand, compounds **3a, 3g** were evaluated at the single concentration of 10^{-5}M against the full panel. The human tumor cell lines were derived from nine different cancer types: leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate, and breast cancers. The results for each compound are reported as the percent growth of treated cells and compared to untreated control cells. Range of growth (%) showed the lowest and highest growth that was found among different cancer cell line. The synthesized compounds **3a**, **3g** displayed significant activity in the *vitro* screen on tested cell lines. Thus, compound **3a** was highly active on renal cancer UO-31 cell line (GP = -1.20%) and compound **3g** was highly active on non-small cell lung cancer NCI-H522 cell line (GP = -2.71%). The results of the primary screening are shown in Table S 5 (Supplemental).

Finally, the previously selected compound **3a**, **3b**, **3e** as well as compound **3c** without the preliminary prescreening stage were tested in advanced assay against a full panel of about sixty tumor cell lines at 10-fold dilutions of five concentrations (100, 10, 1, 0.1 and 0.01 μM) [27-30]. All the tested compounds showed a broad spectrum of growth inhibition activity against human tumor cells with average GI_{50}/TGI_{50} values 33.64/65.27 (**3a**), 39.21/82.59 (**3b**), 46.71/89.79 (**3c**) and 17.65/46.41 (**3e**). Selectivity pattern analysis of cell lines by disease origin can definitely

affirm selective action of compounds **3a**, **3b**, **3c** and **3e** on leukemia cell lines. These compounds appeared to be most active against selected individual cell lines with the GI_{50} varying from 1.86 to 11.89. Compound **3a** was found to be a highly active inhibitor of the colon cancer line HT29, ovarian cancer line OVCAR-3, prostate cancer line DU-145, breast cancer line HS 578T. Compound **3b** showed selectivity on renal cancer cell line RXF 393, breast cancer cell line MCF7 and compound **3e** was highly active on melanoma cell line SK-MEL-5. The dose-dependent assay 60 cell line assay is summarized in Tables S 6 and S 7 (Supplemental Materials).

Empirical SAR study revealed that the presence of substituents in phenyl ring in position 7 of thiopyrano[2,3-d]thiazole core isn't favorable for anticancer potency. Interestingly, the introduction of bulky groups in *para*-position in phenyl ring in position 7 of thiopyrano[2,3-d]thiazole core is more tolerated than small lipophiles in position 3' and 4'.

Evaluation of antiviral activity

The synthesized compounds **3b**, **3d-h** were evaluated for antiviral activity according antimicrobial acquisition and coordinating facility (AACF) screening program [32-34]. The obtained results are summarized in Table S 8 (Supplemental materials). Among tested compounds **3b**, **3e** was found to be the most active. Regarding *Epstein--Barr virus* (EBV), it was found that compound **3b** showed excellent activity (EC_{50} = 0.07 μM, SI = 3279) by VCA Elisa test and possess moderate activity against *Herpes simplex virus 1* (SI = 31) and *Varicella zoster virus* (SI = 34) by viral CPE test. Importingly, compound **3e** with their EC_{50} values in the range of 12.66 μM and SI equal to 43.1 was more active than other derivatives against *Hepatitis C virus*. In addition, the moderate activity exhibited compound **3g** against *Varicella zoster virus* (VZV) in HFF cell culture with EC_{50} values in the range of 23.42 μM and selective index (SI) of 27.2.

EXPERIMENTAL

Chemistry

All materials were purchased from commercial sources and used without purification. Melting points were measured in open capillary tubes and were uncorrected. The elemental analyses (C, H, N) were performed using the Perkin--Elmer 2400 CHN analyzer and were within 0.4% of the theoretical values. The ^{1}H- and ^{13}C-NMR spectra were recorded on Varian Gemini 400 MHz or Bruker 125 MHz for frequencies 100 MHz in DMSO-*d*6 using tetramethylsilane as an internal standard. Chemical shifts are reported in ppm units with use of δ scale. The purity of all obtained compounds was checked by TLC.

The starting compounds: 2,4-thiazolidinedione[35], 4-thioxo-2-thiazolidinone[23] were obtained according to methods described previously. 5-Arylidene-4-thioxo-2-thiazolidinones (**2a-h**) were prepared under Knoevenagel condensation condition: A mixture of 4-thioxo-2-thiazolidinone (10 mmol), appropriate substituted benzaldehyde (10 mmol) in the ethanol medium in the presence of catalytic amount of EDDA was boiled for 10 min. Obtained solid product were collected by filtration and used without further purification. The Supplemental Materials contains sample ^{1}H and ^{13}C NMR spectra for products 3a-h (Figures S 1 -- S 16)

General procedure of hetero-Diels-Alder reaction affording 3a-3h

A mixture of appropriate 5-arylidene-4-thioxo-2-thiazolidinone (10 mmol) and acrolein (11 mmol) was refluxed for 1 h with a catalytic amount of hydroquinone (2--3 mg) in glacial acetic acid (10 mL), then left overnight at room temperature. The precipitated crystals were filtered off, washed with methanol (5--10 mL), and recrystallized from ethanol (10--15 mL).

***rel*-(6*R*,7*R*)-7-Phenyl-2-oxo-3,5,6,7-tetrahydro-2H-thiopyrano[2,3-d][1,3]thiazole-6-carbaldehyde (3a).** Yield 65%, mp 186-187°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.95 (t, J = 13.4 Hz, 1H, 5-H), 2.95 (dd, J = 2.4, 13.4 Hz, 1H, 5-H), 3.40 (m, 1H, 6-H), 4.71 (d, J = 4.5 Hz, 1H, 7-H), 7,15-7,35 (m, 5H, arom.), 9.74 (s, 1H, CHO), 11.48 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.9 (5-C), 44.1 (7-C), 55.6 (6-C), 109.9, 114.5, 121.3, 130.4, 145.4, 154.8, 171.3 (C = O), 201.7 (CHO). Calcd. for $C_{13}H_{11}NO_2S_2$: C, 56.30; H, 4.00; N, 5.05; Found: C, 56.32; H, 4.01; N, 5.04%.

***rel*-(6*R*,7*R*)-7-(4-Methoxyphenyl)-2-oxo-3,5,6,7-tetrahydro-2H-thiopyrano[2,3-d]thiazole-6-carbaldehyde (3b).** Yield 74%, mp 207-208°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.03 (t, J =

13.0 Hz, 1H, 5-H), 3.12 (d, *J* = 12.3 Hz, 1H, 5-H), 3.28 (m, 1H, 6-H), 3.86 (s, 3H, OCH_3), 4.60 (d, *J* = 4.5 Hz, 1H, 7-H), 6.82 (d, *J* = 8.8 Hz, 2H, arom.), 7.11 (d, *J* = 8.8 Hz, 2H, arom.), 9.72 (s, 1H, CHO), 11.22 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.2 (5-C), 38.3 (7-C), 51.6 (OCH_3), 55.6 (6-C), 105.5, 114.5, 121.3, 130.3, 130.4, 131.9, 159.2, 171.3 (C = O), 201.7 (CHO). Calcd. for $C_{14}H_{13}NO_3S_2$: C, 54.70; H, 4.26; N, 4.56; Found: C, 54.72; H, 4.24; N, 4.54%.

***rel*-(6*R*,7*R*)-7-(3,4-Dimethoxyphenyl)-2-oxo-3,5,6,7-tetrahydro-2H-thiopyrano[2,3-d]thiazole-6-carbaldehyde (3c)**. Yield 56%, mp 197-198°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.04 (t, *J* = 13.0 Hz, 1H, 5-H), 3.16 (d, *J* = 12.3 Hz, 1H, 5-H), 3.70 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 4,01 (m, 1H, 6-H), 4.52 (d, *J* = 4.5 Hz, 1H, 7-H), 6.69 (d, *J* = 8.2 Hz, 1H, arom.), 6.71 (s, 1H, arom.), 6.85 (d, *J* = 8.2 Hz, 1H, arom.), 9.45 (s, 1H, CHO), 11.44 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.7 (5-C), 38.3 (7-C), 49.4 (OCH_3), 52.4 (OCH_3), 55.6 (6-C), 109.9, 114.5, 124.5, 129.8, 131.9, 134.7, 141.6, 162.0, 171.7 (C = O), 202.1 (CHO). Calcd. for $C_{15}H_{15}NO_4S_2$: C, 53.40; H, 4.48; N, 4.15; Found: C, 53.42; H, 4.47; N, 4.14%.

***rel*-(6*R*,7*R*)-7-{2-[(2-Chlorobenzyl)oxy]-5-nitrophenyl}-2-oxo-3,5,6,7-tetrahydro-2H-thiopyrano[2,3-d][1,3]thiazole-6-carbaldehyde (3d)**. Yield 57%, mp 237-238°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.19 (dd, *J* = 2.4, 13.8 Hz, 1H, 5-H), 3.34 (m, 1H, 5-H), 3.44 (dd, *J* = 4.8, 13.8 Hz, 1H, 6-H), 4.75 (d, *J* = 4.4 Hz, 1H, 7-H), 5.33 (d, *J* = 12.1 Hz, 1H, CH_2),5.38 (d, *J* = 12.1 Hz, 1H, CH_2), 7.38-7.44 (m, 3H, arom.), 7.52 (d, *J* = 7,2 Hz, 1H, arom.), 7.61 (d, *J* = 7.2 Hz, 1H, arom.), 7.89 (s, 1H, arom.), 8.26 (d, *J* = 8.9 Hz, 2H, arom.), 9.63 (s, 1H, CHO), 11.53 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 32.4 (5-C), 32.7 (7-C), 49.2 (6-C), 68.8 (CH_2), 102.2, 113.4, 122.4, 125.4, 125.8, 128.0, 130.1, 130.5, 130.8, 131.6, 133.0, 133.8, 141.6, 160.7,

171.0 (C = O), 200.5 (CHO). Calcd. for $C_{20}H_{15}ClN_2O_5S_2$: C, 51.89; H, 3.27; N, 6.05; Found: C, 51.87; H,3.28; N, 6.04%.

***rel*-(6*R*,7*R*)-7-[4-(Benzyloxy)phenyl]-2-oxo-3,5,6,7-tetrahydro-2H-thiopyrano[2,3-d][1,3]thiazole-6-carbaldehyde (3e)**. Yield 75%, mp 218-219°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.02 (t, J = 13.0 Hz, 1H, 5-H), 3.13 (dd, J = 2.0, 13.0 Hz, 1H, 5-H), 3.32 (m, 1H, 6-H), 4.69 (d, *J* = 4.7 Hz, 1H, 7-H), 5.05 (d, *J* = 8.4 Hz, 2H, CH_2), 7.11 (d, *J* = 8.4 Hz, 2H, arom.), 7.39-7.43 (m, 5H, arom.), 9.75 (s, 1H, CHO), 11,48 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.8 (5-C), 32.4 (7-C), 49.2 (6-C), 69.9 (CH_2), 113.4, 123.2, 128.0, 130.5, 132.2, 133.0, 133.8, 141.6, 149.9, 163.4, 171.0 (C = O), 200.5 (CHO). Calcd. for $C_{20}H_{17}NO_3S_2$: C, 62.64; H, 4.47; N, 3.65; Found: C, 62.63; H, 4.48; N, 3.64%.

***rel*-(6*R*,7*R*)-7-[4-(Difluoromethoxy)-3-methoxyphenyl]-2-oxo-3,5,6,7-tetrahydro-2H-thiopyrano[2,3-d][1,3]thiazole-6-carbaldehyde (3f)**. Yield 55%, mp 196-197°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.02 (t, *J* = 13.4 Hz, 1H, 5-H), 3.13 (d, *J* = 13.4 Hz, 1H, 5-H), 3.32 (m, 1H, 6-H), 3.82 (s, 3H, OCH_3), 4.34 (d, *J* = 4.7 Hz, 1H, 7-H), 6.68 (s, 1H, $OCHF_2$), 6.76 (d, *J* = 8.7 Hz, 1H, arom.), 6.88 (s, 1H, $OCHF_2$), 7,11-7.11 (m, 2H, arom.), 9.60 (s, 1H, CHO), 11.33 (s,1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.5 (5-C), 37.9 (7-C), 51.9 (OCH_3), 56.5 (6-C), 104.2, 113.6, 117.3, 120.8, 121.2, 121.7, 141.3, 151.3, 171.1 (C = O), 200.7 (CHO). Calcd. for $C_{15}H_{13}F_2NO_4S_2$: C, 48.25; H, 3.51; N, 3.75; Found: C, 48.23; H, 3.52; N, 3.74%.

***rel*-(6*R*,7*R*)-7-(4-tert-Butylphenyl)-2-oxo-3,5,6,7-tetrahydro-2H-thiopyrano[2,3-d][1,3]thiazole-6-carbaldehyde (3g)**. Yield 72%, mp 226-227°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.25 (c, 9H, $3CH_3$), 2,96 (t, *J* = 13.4 Hz, 1H, 5-H), 3.19 (d, *J* = 13.4 Hz, 1H, 5-H), 3.40 (m,

1H, 6-H), 4.69 (d, *J* = 4.6 Hz, 1H, 7-H), 7.34 (d, *J* = 8.3 Hz, 2H, arom.), 7.38 (d, *J* = 8.3 Hz, 2H, arom.), 9.76 (s, 1H, CHO), 11.50 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 31.7 (CH_3), 31.8 (5-C), 34.8, 38.6, 105.2, 121.4, 126.0, 129.0, 137.1, 150.5, 171.3 (C = O), 201.7 (CHO). Calcd. for $C_{17}H_{19}NO_2S_2$: C, 61.23; H, 5.74; N, 4.20; Found: C, 61.22; H,5.72; N, 4.21%.

***rel*-(6*R*,7*R*)-7-(4-Isopropylphenyl)-2-oxo-3,5,6,7-tetrahydro-2H-thiopyrano[2,3-d][1,3]thiazole-6-carbaldehyde (3h)**. Yield 70%, mp 211-212°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.20 (d, *J* = 6.9 Hz, 6H, 2*CH_3), 2.86 (m, 1H, CH), 3.02 (t, *J* = 13.4 Hz, 1H, 5-H), 3.13 (d, *J* = 13.4 Hz, 1H, 5-H), 3.32 (m, 1H, 6-H), 4.65 (d, *J* = 4.7 Hz, 1H, 7-H), 7.09 (d, *J* = 8.8 Hz, 2H, arom.), 7.15 (d, *J* = 8.8 Hz, 2H, arom.), 9.73 (s, 1H, CHO), 11.33 (s,1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.2 (CH_3), 34.9 (5-C), 49.4, 51.6, 58.5, 114.5, 121.3, 130.8, 132.1, 160.2, 171.3 (C = O), 202.6 (CHO). Calcd. for $C_{16}H_{17}NO_2S_2$: C, 60.16; H, 5.36; N, 4.38; Found: C, 60.15; H,5.37; N, 4.37%.

Primary anticancer assay.

Primary anticancer assay was performed on a panel of approximately sixty human tumor cell lines derived from nine neoplastic diseases, in accordance with the protocol of the Drug Evaluation Branch, National Cancer Institute, Bethesda[27-30].

Methods for evaluation of antiviral activity.

Primary antiviral assay was performed at a biodefense virus's panel and a respiratory virus's panel [Flu A (H5N1), Flu B, SARS] with a protocol of the NIAID's antimicrobial acquisition and coordinating[31-33].

CONCLUSION

We have achieved a convenient protocol for the synthesis of thiopyrano[2,3-*d*]thiazole-6-carbaldehydes *via* regio- and diastereoselective *hetero*-Diels-Alder reaction of 5-arylidene-4-thioxo-2-thiazolidinone with acrolein. The synthesized compounds ware assessed for their antitumor and antiviral capacities. The preliminary results allowed to identify the most active compound **3a** with mean GI_{50}/TGI_{50} values 33.64/65.27 μM in the NCI 60 cell-line assay with certain sensitivity profile towards the leukemia SR cell line (GI_{50}/TGI values 0.89/6.88 μM). The 7-(4-methoxyphenyl)-2-oxo-7-phenyl-3,5,6,7-tetrahydro-2*H*-thiopyrano[2,3-*d*]thiazole-6-carbaldehyde **3b** (EC_{50} = 0.07 μM, SI = 3279) has shown the best antiviral activity against *Epstein--Barr virus* in Daudi cell cultures and compound **3e** (EC_{50} = 12.66 μM, SI = 43.1) was the most active against *Hepatitis C virus* than the other derivatives. Overall, the biological tests revealed the necessity for further investigations the antitumor and antiviral potential of tested compounds for the construction of novel chemical entities with better pharmacological profiles.

ACKNOWLEDGEMENTS

The authors are grateful to Dr. V. L. Narayanan from Drug Synthesis and Chemistry Branch, National Cancer Institute, Bethesda, MD, USA, for in vitro evaluation of anticancer activity and to Dr. Chris Tseng, from Division of Microbiology and Infectious Diseases NIAID/NIH, Bethesda, USA, for in vitro evaluation of antiviral activity.

REFERENCES

1. Geronikaki, A. A.; Lagunin, A. A.; Hadjipovlou-Litina, D. I.; Eleftheriou, P. T.; Filimonov, D. A.; Poroikov, V. V.; Alam, I.; Saxena A. K. *J. Med. Chem.* **2008**, 51, 1601-1609.

2. Shin, M. H.; Ke, F. Y. *Bioorg. Med. Chem. Lett*. **2004**, 12, 4633-4643.

3. Lesyk, R. B.; Zimenkovsky, B. S. *Curr. Org. Chem*. **2004**, 8, 1547–1577.

4. Cutshall, N. S.; O'Day, C.; Prezhdo, M. *Bioorg. Med. Chem. Lett*. **2005**, 15, 3374–3379.

5. Ahn, J. H.; Kim, S. J.; Park, W. S.; Cho, S. Y.; Ha, J. D.; Kim, S. S.; Kang, S. K.; Jeong, D. G.; Jung, S.-K.; Lee, S.-H.; Kim, H. M.; Park, S. K.; Lee, K. H.; Lee, C. W.; Ryu, S. E.; Choi, J.-K. *Bioorg. Med. Chem. Lett*. **2006**, 16, 2996–2999.

6. Sing, W. T.; Lee, C. L.; Yeo, S. L.; Lim, S. P.; Sim, M. M. *Bioorg. Med. Chem. Lett*. **2001**, 11, 91–94.

7. Liu, W.; Bulgaru, A.; Haigentz, M.; Stein, C.A.; Perez-Soler, R.; Mani. S. *Curr. Med. Chem.: Anti-Cancer Agents*. **2003**, 3, 217–223.

8. Carter, P. H.; Scherle, P. A.; Muckelbauer, J. A.; Voss, M. E.; Liu, R.-Q.; Thompson, L. A.; Tebben, A. J.; Solomon, K. A.; Lo, Y. C.; Li, Z.; Strzemienski, P.; Yang, G.; Falahatpisheh, N.; Xu, M.; Wu, Z.; Wu, Z.; Farrow, N. A.; Ramnarayan, K.; Wang, J.; Rideout, D.; Yalamoori, V.; Domaille, P.; Underwood, D. J.; Trzaskos, J. M.; Friedman, S. M.; Newton, R. C.; Decicco, C. P. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, 98, 11879-11884.

9. Lee, J.; Kim, J.; Koh, J. S.; Chung, H. H.; Kim, K. H. *Bioorg. Med. Chem. Lett*. **2006**, 16, 1954–1956.

10. Tomasic, T.; Masic, L. P. *Expert Opin. Drug Discov*. **2012**, 7, 549-560.

11. Baell, J. B. *Future Med. Chem*. **2010**, 2, 1529-1546.

12. Baell, J. B.; Holloway, G. A. *J. Med. Chem*. **2010**, 53, 2719-2740.

13. Mendgen, T.; Steuer, C.; Klein, C. D. *J. Med. Chem*. **2012**, 55, 743-753.

14. Zelisko, N.; Atamanyuk, D.; Vasylenko, O.; Grellier, P.; Lesyk, R. *Bioorg. Med. Chem. Lett*. **2012**, 22, 7071-7074.

15. Lozynskyi, A. V.; Kaminskyy, D. V.; Romanchyshyn, K. B.; Semenciv, N. G.; Ogurtsov, V.V.; Lesyk, R. B. *Biopolym. Cell*. **2015**, 31, 131-137.

16. Lesyk, R. B.; Zimenkovsky, B. S.; Kaminskyy, D. V.; Kryshchyshyn, A. P.; Havrylyuk, D. Ya.; Atamanyuk, D.V.; Subtel'na, I. Yu.; Khyluk, D. V. *Biopolym. Cell*. **2011**, 27, 107–117.

17. Lesyk R.; Zimenkovsky B.; Atamanyuk D.; Jensen F.; Kiec-Kononowicz K.; Gzella A. *Bioorg. Med. Chem*. **2006**, 14, 5230–5240.

18. Lozynskyi, A.; Zimenkovsky, B.; Lesyk, R. *Sci. Pharm*. **2014**, 82, 723-733.

19. Atamanyuk, D.; Zimenkovsky, B.; Lesyk R. *J. Sulfur Chem*. **2008**, 29, 151-162.

20. Kaminskyy, D.; Vasylenko, O.; Atamanyuk, D.; Gzella, A.; Lesyk R. *Synlett*. **2011**, 10, 1385–1388.

21. Lozynskyi, A.; Zimenkovsky, B.; Nektegayev, I.; Lesyk, R. *Heterocycl. Commun*. **2015**, 21, 55-59.

22. Lozynskyi, A.; Zimenkovsky, B.; Gzella, A.; Lesyk, R. *Synth. Commun*. **2015**, 45, 2266-2270.

23. Komaritsa, I. D.; Baranov, S. N.; Grishchuk, A. P. *Khimiya Geterotsiklicheskikh Soedinenii*. **1967**, 3, 533-534.

24. Metwally, N. H. *J. Sulfur Chem*. **2014**, 35, 528-537.

25. Zelisko, N.; Atamanyuk, D.; Vasylenko,O.; Bryhas,A.; Matiychuk,V.; Gzella, A.; Lesyk, R. *Tetrahedron*. **2013**, 70, 720-729.

26. The supplementary crystallographic data of **3h** have been deposited at the Cambridge Crystalographie Data Centre (CCDC) as supplementary publication CCDC1445170. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

27. Allen, F. H. *Acta Cryst.* **2002**, B58, 380–388.

28. http://dtp.nci.nih.gov

29. Boyd, M. R.; Paull, K. D. *Drug Dev Res*. **1995**, 34, 91-109.

30. Shoemaker,R. H. *Nat. Rev. Cancer*. **2006**, 6, 813–823.

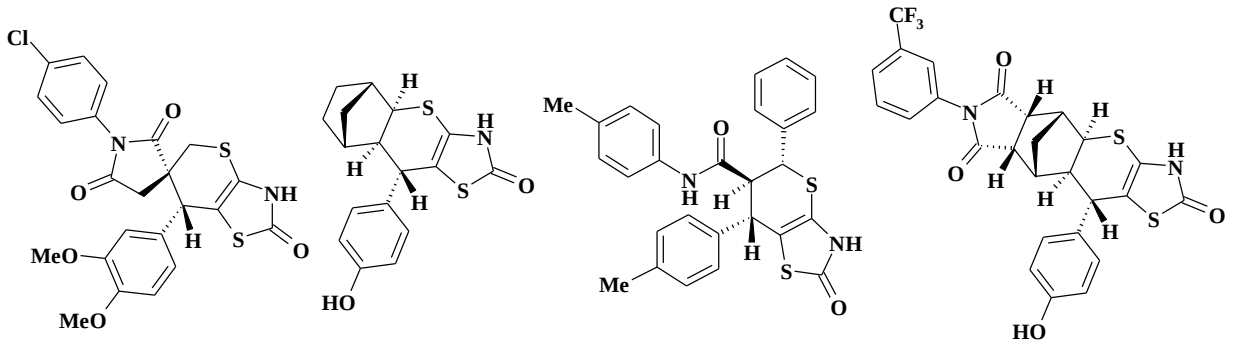
31. Monks, A.; Scudiero, D.; Skehan, P.; Shoemaker, R.; Paull, K.; Vistica, D.; Hose, C.; Langley, J.; Cronise, P.; Vaigro-Wolff A.; Gray-Goodrich, M.; Campbell, H.; Mayo, J.; Boyd, M. *J. Nat. Cancer Inst*. **1991**, 83, 757–766.

32. http://niaid-aacf.org

33. Huffman, J. H.; Sidwell, R. W.; Barnard, D. L.; Morrison, A.; Otto,M. J.; Hill, C.L.; Schinazi, R. F. *Antiv. Chem. Chemother*. **1997**, 8, 75-83.

34. Sidwell, R. W.; Smee, D. F. *Antiviral Res*. **2000**, 48, 1-16.

35. Turkevych, N. M.; Vvedenskij V. M.; Petlichnaya L. P. Method of obtaining pseudothiohydantoin and thiazolidinedione-2,4. *Ukr. Khim. Zh*. (*Russ. Ed*.) 1961, 27, 680-681.



***N. Zelisko et al.*, 2012 [13]** ***R. Lesyk et al.*, 2006 [16]** ***A. Lozynskyi et al.*, 2014 [17]** ***D. Atamanyuk et al.*, 2007 [18]**

Figure 1. Structures of biologically active thiopyrano[2,3-*d*]thiazoles.

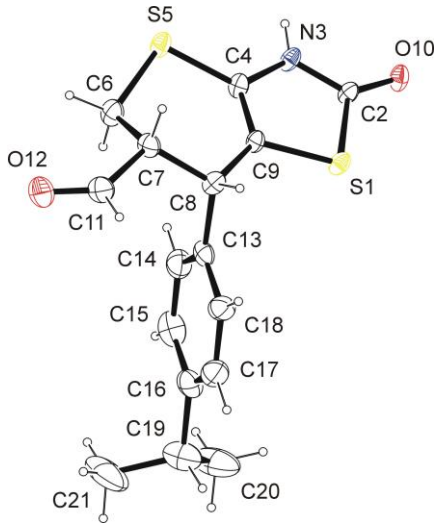
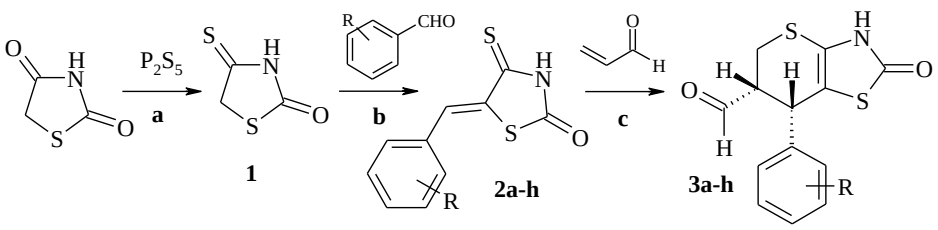


Figure 2. X-ray crystal structure (ORTEP plot) of one of twelve symmetry-independent molecules of 3h and the atom-labeling scheme.



Scheme 1. Synthesis of *rel*-(6*R*,7*R*)-2-oxo-7-phenyl-3,5,6,7-tetrahydro-2*H*-thiopyrano[2,3-*d*]thiazole-6-carbaldehydes. Reagents, conditions and yields: (a) dioxane, reflux 3h, 60%; (b) EDDA, EtOH, reflux 10 min; (c) AcOH, reflux 1h.