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Stereoselective synthesis of (2,4-dinitrophenyl)hydrazono-
and (2-tosylhydrazono)-4-oxo-thiazolidine derivatives and
screening of their anticancer activity

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Abstract: Stereoselective synthesis of (Z)-methyl 2-[(Z)-3-substituted-2-(2-(2,4-dinitrophenyl)hydrazono)-4-oxothiazolidine-5-ylidene)]acetates and (Z)-methyl 2-[(Z)-3-substituted-2-(2-(tosylhydrazono)-4-oxothiazolidine-5-ylidene)]acetates *via* the cyclization of *N*-substituted-2-arylhydrazino-carbothioamides with dialkyl acetylenedicarboxylates in absolute ethanol is reported. The structures were confirmed by spectroscopic data as well as single crystal X-ray analyses. The mechanism of nucleophilic addition and the role of electronic factors were discussed. The anticancer activity of the newly synthesized compounds was evaluated against a panel of 60 cell lines derived from nine different types of cancers including, leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate, and breast cancers and the results revealed that the cyclohexyl derivative has a significant broad anticancer activity especially against different leukemia and colon cancer cell lines .

Keywords: Anticancer activity • Heterocycles • NMR spectroscopy •
Nucleophilic additions • Solvent effect • Spectroscopy • Crystal structure.

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1 Introduction

2 Thiazolidinone is one of the most frequent heterocyclic nucleuses as
3 it exhibits many types of biological activities [1]. It has been reported that
4 thiazolidin-4-ones are explored as anti-inflammatory [2-5], antiviral [6,7],
5 anticonvulsant [8-10], antidiabetic [11], anticancer [12] and anti-HIV [13-
6 15] activities. Also, the thiazolidin-4-one ring occurs in nature, for
7 example, actithiazic acid [(-)-2-(5-carboxyphenyl)thiazolidin-4-one)] was
8 isolated from Streptomyces [16].

9 Different methods for the synthesis of 1,3-thiazolidin-4-ones were
10 reported from thiosemicarbazides [16-20], thiocarbohydrazides [21,22],
11 hydrazinocarbothioamides [23,24], and thioureas [25-27]. Several efforts
12 from chemists have been oriented towards reactions of thione group and
13 dialkyl acetylenedicarboxylate for the synthesis of thiazolidinones
14 [18,19,28].

15 The regioselective synthesis of 3-substituted-2-(anthracenylimino)-
16 thiazolidinone together with 2-substituted-imino-3-(anthracenyl)-
17 thiazolidinones has been observed [29]. Also, Sathishkumar has been
18 reported the regioselective synthesis of (Z)-3-alkyl/aryl-2-(2-
19 phenylcyclohexenyl-imino)thiazolidin-4-one [30].

20 Regioisomeric products, 2-(3-ethyl-4-(3*H*)-quinazolinone-2-yl)-
21 mercaptoacetylhydrazono)-3-alkyl/aryl-5-methyl-4-thiazolidinones and 2-

1 arylimino-3-(3-ethyl-4(3*H*)-quinazolinone-2-yl-mercaptoacetylamino)-5-
2 methyl-4-thiazolidin-ones were synthesized from quinazolinone derivatives
3 [31].

4 Symmetrical and unsymmetrical-1,3-diarylthioureas with dialkyl
5 acetylenedicarboxylate in ethanol at room temperature was considered an
6 efficient method for the regioselective synthesis of iminothiazolidinone
7 products[32, 33].

8 Recently, the isolation of (Z)-methyl-2-[(Z)-4-oxo-3-(phenylamino)-
9 2-(substituted imino)thiazolidin-5-ylidene]acetates **3a-c** from the reaction
10 of *N*,2-disubstituted hydrazinecarbothioamides **1a-c** and dimethyl
11 acetylenedicarboxylate (**2a**) in absolute ethanol under heating for 8-10 hrs
12 has been reported (Scheme 1) [34].

13 Thiazolidin-4-one is a versatile scaffold for designing potential
14 bioactive agents. Mechanisms of thiazolidin-4-one and related
15 heterocycles for anticancer activity may be associated with their affinity to
16 anticancer biotargets, such as non-membrane protein tyrosine phosphatase
17 (SHP-2), JNK-stimulating phosphatase-1 (JSP-1), tumor necrosis factor
18 TNF- α , antiapoptotic biocomplex Bcl-XL-BH3 and integrin $\alpha\text{v}\beta 3$ (19), etc
19 [35].

20 Liu et al, strongly suggest the potential of 3-(2-aminoethyl)-5-(3-
21 cyclohexylpropylidene) thiazolidine-2,4-dione (**I**, Figure 1) as a new lead

1 compound with multi-target properties and encourage further optimization
2 of this compound to develop more potent and effective analogs as
3 anticancer agents. This cyclohexyl derivative may execute its anti-
4 proliferative activity through apoptotic effects in U937, M12 and DU145
5 cancer cells. Furthermore, it arrested U937 cells at the S-phase. In addition,
6 it was stated that it inhibits both MEK and PI3K, the critical kinases
7 involved in the signal transduction of the Raf/MEK/ERK and PI3K/Akt
8 cascades. Growth inhibition of the cyclohexyl derivative $< 3 \mu\text{M}$ indicates;
9 that signaling blockage and growth inhibition in U937 cells. This may
10 suggest an important role of the steric effects due to the presence of
11 cyclohexane ring at this specific domain [36].

13 **Figure 1.** 3-(2-Aminoethyl)-5-(3-cyclohexylpropylidene)thiazolidine-2,4-
14 dione **I**

15 Results and Discussion

16 Herein, we decided to report the highly efficient, straight forward
17 stereoselective synthesis of (Z)-methyl 2-[(Z)-3-substituted-2-(2-(2,4-
18 dinitrophenyl)hydrazono)-4-oxothiazolidine-5-ylidene)]acetates **4a-j** and
19 (Z)-methyl 2-[(Z)-3-substituted-2-(2-(tosylhydrazono)-4-oxothiazolidine-5-

ylidine)]acetates **4k-r** from various *N*,2-disubstituted hydrazinecarbo-
thioamides **1d-l** and **2a,b** and investigate the factors governing the
stereoselectivity in this reaction. The synthesis of compounds **4a-r** was
carried out as depicted in scheme 1. 1,4-Disubstituted hydrazinecarbo-
thioamides **1d-l** were obtained by the procedure described in literature
[37,38]. An equimolar amounts of **1d-l** and dialkyl acetylene dicarboxylate
2a,b were allowed to reflux 30 min for **1d-h** and 4-8 hrs for **1i-l** in
absolute ethanol. With respect to the starting materials consumed (100%
conversion, indicated by TLC), the reaction proceeded efficiently. The
reaction was optimized by using different solvents. The reaction gave the
products **4a-r** in high yields (89–96%) by using EtOH or MeOH as the
solvent of reaction. Upon using other solvents such as CH₃CN, CH₂Cl₂,
THF and DMF, the products yield was very low. Further heating the
reaction mixture in EtOH for long time, did not improve the yield of the
product. When using Et₃N as the base catalyst, mixtures of products were
obtained. In all cases the thiazolidinone derivatives **4a-r** were isolated in
varied of good to high yields (Table 1). Table 1 shows some of the
analytical data (yields and melting points of compounds **4a-r**).

Scheme 1

Reaction of hydrazinecarbothioamides 1d-l with dialkyl acetylenedicarboxylates

Table 1. Analytical data (yield %) and melting points (M.p) of compounds

4a-r

Compound	Ar	R	R'	Yield %	M.p
4a	2,4-dinitro-ph	PhCH ₂	Me	93	251-253
4b	2,4-dinitro-ph	Ph	Me	96	240-242
4c	2,4-dinitro-ph	Cyclohexyl	Me	90	225-227
4d	2,4-dinitro-ph	Et	Me	91	212-214
4e	2,4-dinitro-ph	Allyl	Me	93	236-238
4f	2,4-dinitro-ph	PhCH ₂	Et	92	259-261
4g	2,4-dinitro-ph	Ph	Et	94	249-251
4h	2,4-dinitro-ph	Cyclohexyl	Et	93	230-232
4i	2,4-dinitro-ph	Et	Et	94	218-220
4j	2,4-dinitro-ph	Allyl	Et	90	243-245
4k	<i>p</i> -tosyl	PhCH ₂	Me	93	236-238
4l	<i>p</i> -tosyl	Ph	Me	95	215-217
4m	<i>p</i> -tosyl	Et	Me	91	185-186
4n	<i>p</i> -tosyl	Allyl	Me	92	200-202
4o	<i>p</i> -tosyl	PhCH ₂	Et	92	228-230

4p	<i>p</i> -tosyl	Ph	Et	91	221-223
4q	<i>p</i> -tosyl	Et	Et	89	190-191
4r	<i>p</i> -tosyl	Allyl	Et	90	208-210

1

2 **IR spectra for compounds 4a-r**

3 The obtained compounds were characterized by absorption bands at 3202-
4 3252 due to NH-group. Strong absorption bands appeared at 1707-1719
5 and 1700-1692 cm⁻¹ region were diagnostic for thiazolidinone ring system-
6 CO [39] and ester-CO. Two absorption bands were observed at 1425-1443
7 and 1326-1335 cm⁻¹ due to NO₂ groups.

8 **¹H NMR and ¹³C NMR spectra for compounds 4a-r.**

9 From the ¹H NMR and ¹³C NMR spectra of products **4a-r**, it could be
10 concluded that the products were isomerically pure and the absence of the
11 isomers in the final products.

12 The ¹H NMR study of (Z)-methyl 2-[(Z)-3-benzyl-2-(2-(2,4-dinitrophenyl)-
13 hydrazono)-4-oxothiazolidine-5-ylidene)]acetates **4a**, clearly showed the
14 appearance of vinylic protons at $\delta = 6.95$ ppm. The presence of vinylic
15 proton above $\delta = 6.90$ ppm supported the Z-configuration of exocyclic
16 double bond, due to high degree of thermodynamic stability of these
17 isomers [40]. A broad signal was observed at $\delta = 10.84$ ppm due to NH-
18 proton (Figure 2).

Figure 2. ^1H NMR of compound **4a**

The ^{13}C NMR of **4a** confirmed the presence of cyclic amidic-CO at $\delta = 162.1$ ppm and CO-ester at $\delta = 165.8$, thiazolidine-C2, C5 at $\delta = 156.5$ and 133.0 , respectively and vinyl-CH at 139.0 ppm. The benzyl-CH₂ observed at $\delta = 48.0$ ppm (Figure 3).

Figure 3. ¹³C NMR of compound **4a**

Mass Spectrometry of compounds **4a-r**

The results obtained from elemental analyses as well as mass spectrometry of compounds **4a-r** clarified that the obtained thiazolidinones **4a-r** were formed from the addition of equimolar quantities of **1d-l** and **2a,b** via elimination of a molecule of appropriate alcohol (R'OH). The mass spectrum of compound **4a** as an example shows molecular ion peak at $m/z = 457$ (100%) which confirm the formation of **4a** from combination of one molecule of 4-benzyl 1-(2,4-dinitrophenyl)thiosemicarbazide **1d** with one molecule of dimethyl acetylenedicarboxylate **2a** with elimination of MeOH.

X-ray structure determination of **4a**, **4m** and **4o**.

The X-ray crystal of **4a** confirmed the stereoselective formation of (Z)-methyl 2-((Z)-3-benzyl-2-(2-(2,4-dinitrophenyl)hydrazono)-4-oxo-thiazolidin-5-ylidene)acetate instead of other structure, the crystal structure of **4a** (Figure 4) was characterized with S1-C5 single bond = 1.7408 (13) Å, C2-N6 with double bond = 1.2793 (17) Å. The thiazolidine moiety is planar (mean deviation from the l.s.-plane S1, C2, N3 C4 C5 0.009 Å).

Figure 4: Molecular structure of compound **4a** (displacement parameters are shown at 50% probability level)

The molecular structures of (Z)-methyl 2-((Z)-3-ethyl-4-oxo-2-(2-tosylhydrazono)thiazolidin-5-ylidene)acetate **4m** (Figure 5) is confirmed by a crystal structure.

Figure 5: Molecular structure of compound **4m** (one of the two crystallographic independent molecules is shown, displacement parameters are shown at 50% probability level).

Figure 6 shows the molecular structure of **4o**, which confirmed the formation of (Z)-methyl 2-((Z)-3-benzyl-4-oxo-2-(2-tosylhydrazono)-thiazolidin-5-ylidene)acetate as a monoclinic space group, with colorless plates.

Figure 6: Molecular structure of compound **4o** (displacement parameters are shown at 50% probability level).

1 **A plausible mechanism for the synthesis of 4a-r**

2 As shown in scheme 2, the decrease of the nucleophilicity of NH-attached
3 to phenyl group in **1d-l** by the presence of electron-withdrawing groups
4 such as (NO₂ or SO₂) **dramatically**, led to the formation of intermediates **7**
5 and **8** *via* the formation of intermediates **5** and **6**. Removal a molecule of
6 methanol/ethanol from **7** gave thiazolidinone derivatives **4a-r** (Scheme 2).
7 The reaction was optimized by using different solvents. The reaction gave
8 the products **4a-r** in high yields (89 – 96 %) by using EtOH or MeOH as
9 the solvent of reaction. Upon using other solvents such as CH₃CN, CH₂Cl₂,
10 THF and DMF, the products yield was very low. Further heating the
11 reaction mixture in EtOH for long time, did not improve the yield of the
12 product. When using Et₃N as the base catalyst, mixtures of products were
13 obtained. The regiocontrol of the intermediates **7** and **8** was influenced by
14 electronic factors. Electron-withdrawing substituents such as NO₂ and SO₂
15 groups make conjugative stabilization nitrogen. **Better yields and short time**
16 **of reactions were observed in presence of electron-withdrawing groups**
17 **attached to ¹NH in compounds 1d-l compared with phenyl group in**
18 **compounds 1a-c** (Scheme 1) [34].

19 *Scheme 2*

1 **Biology**

2 The anticancer activity of the thiazolidine derivatives **4a-f,I,k-m** was
3 evaluated (Tables 2 and 3) according to the protocol of the drug evaluation
4 branch of the national cancer institute (NCI), Bethesda, USA, for in vitro
5 anticancer activity. Tables 2 and 3 show the results for each tested
6 compound were reported as the percentage of growth of the treated cells
7 when compared to the untreated control cells.

8 Thiazolidinone **4c** exhibited potential anticancer activity against leukemia
9 (RPMI-8226 (complete cell death), K-562, HL-60, CCRF-CEM, G% =
10 17.83, 8.63 and 17.93 respectively). Moreover, **4c** showed strong activity
11 against NSC lung cancer (HOP-92, G% = 8.36), colon cancer (HCT-15,
12 HT29 and SW-620 G% = 10.98, 26.73 and 22.73 respectively). In addition,
13 **4c** revealed remarkable anticancer activity against renal cancer (SN12C,
14 UO-31, G% = 21.57 and 19.18, respectively), prostate cancer (PC-3, G% =
15 18.40), breast cancer (MCF7 and T-47D, G% = 23.10 and 12.95) and
16 ovarian cancer (OVCAR-3, G% = 25.19). On the other hand, Thiazolidinone
17 **4f** revealed significant activity against RPMI-8226 leukemia with G% 7.78.
18 The rest of compounds exhibited weak anticancer activity, and this may
19 confirm the importance of the introduction cyclohexyl moiety to thiazolidine
20 ring as an essential moiety for anticancer activity [36].

1 **Table 2.** Sixty cell line in vitro anticancer screening data of compounds

2 **4a-e.**

<i>Subpanel tumor cell lines</i>	<i>Growth % (G%)</i>				
	4a	4b	4c	4d	4e
	NSC 822636	NSC 822637	NSC 822638	NSC 822639	NSC 822640
<i>Leukemia</i>					
<i>CCRF-CEM</i>	85.15	94.47	17.93	97.52	90.72
<i>HL-60(TB)</i>	103.20	98.79	8.63	119.42	108.14
<i>K-562</i>	81.04	82.31	17.83	82.81	86.99
<i>MOLT-4</i>	93.04	87.43	42.72	97.15	97.60
<i>RPMI-8226</i>	87.61	97.10	-21.82	96.03	76.61
<i>Non-Small Cell Lung Cancer</i>					
<i>A549/ATCC</i>	96.57	101.21	87.65	98.20	101.65
<i>EKVX</i>	101.89	100.93	78.49	99.51	105.34
<i>HOP-62</i>	101.19	102.80	86.80	108.98	98.34
<i>HOP-92</i>	99.78	91.71	8.36	83.21	95.01
<i>NCI-H226</i>	107.82	104.55	80.66	112.99	103.11
<i>NCI-H23</i>	96.57	97.58	60.00	96.62	99.34
<i>NCI-H322M</i>	97.96	103.39	99.32	98.34	100.46
<i>NCI-H460</i>	108.38	104.30	35.11	105.70	104.43
<i>NCI-H522</i>	95.11	87.38	43.63	83.36	72.28
<i>Colon Cancer</i>					
<i>COLO 205</i>	113.27	111.27	42.46	114.77	107.15

<i>HCC-2998</i>	105.17	110.65	63.08	110.03	110.45
<i>HCT-116</i>	94.69	102.84	29.79	94.41	86.89
<i>HCT-15</i>	100.35	96.41	10.98	94.96	87.50
<i>HT29</i>	108.89	103.62	26.73	106.20	100.11
<i>KM12</i>	99.50	102.11	45.88	103.53	101.88
<i>SW-620</i>	102.03	96.63	22.73	103.73	95.60
<i>CNS Cancer</i>					
<i>SF-268</i>	100.77	96.37	71.02	103.66	103.00
<i>SF-295</i>	99.66	105.52	77.14	97.62	106.17
<i>SF-539</i>	101.96	102.74	69.19	101.32	107.06
<i>SNB-19</i>	96.39	92.92	51.29	94.67	95.64
<i>SNB-75</i>	80.73	91.94	51.39	86.72	74.11
<i>U251</i>	96.56	98.09	25.82	96.24	98.69
<i>Melanoma</i>					
<i>LOX IMVI</i>	96.97	103.01	72.41	99.54	95.73
<i>MALME-3M</i>	103.56	105.14	87.52	95.35	99.45
<i>M14</i>	102.87	105.07	78.10	103.59	100.43
<i>MDA-MB-435</i>	100.39	100.38	78.96	100.59	101.05
<i>SK-MEL-2</i>	116.42	112.40	90.51	105.54	104.74
<i>SK-MEL-28</i>	106.88	104.83	86.52	105.32	108.83
<i>SK-MEL-5</i>	98.40	99.17	82.35	98.62	90.52
<i>UACC-257</i>	98.81	98.32	80.07	99.32	109.30
<i>UACC-62</i>	95.25	94.92	38.69	78.25	82.49
<i>Ovarian Cancer</i>					
<i>IGROV1</i>	101.45	105.00	58.38	105.28	101.08

<i>OVCAR-3</i>	104.15	105.99	25.19	104.97	104.07
<i>OVCAR-4</i>	97.73	95.93	47.14	82.49	89.11
<i>OVCAR-5</i>	103.62	102.73	84.30	115.36	103.39
<i>OVCAR-8</i>	100.83	104.24	35.42	102.49	98.50
<i>NCI/ADR-RES</i>	103.81	112.12	29.73	110.44	111.05
<i>SK-OV-3</i>	108.28	111.02	96.84	105.67	99.62
<i>Renal Cancer</i>					
<i>786-0</i>	100.99	107.48	61.09	98.79	103.99
<i>A498</i>	93.26	107.51	63.06	100.37	53.22
<i>ACHN</i>	103.43	104.39	42.30	100.70	92.69
<i>CAKI-1</i>	93.44	84.91	57.11	86.29	87.08
<i>RXF 393</i>	111.79	109.55	61.98	118.08	114.17
<i>SN12C</i>	95.72	97.33	21.57	94.93	90.69
<i>TK-10</i>	109.38	121.82	60.25	106.19	122.18
<i>UO-31</i>	77.86	87.43	19.18	89.44	80.39
<i>Prostate Cancer</i>					
<i>PC-3</i>	93.45	92.50	18.40	96.15	95.32
<i>DU-145</i>	105.72	101.05	44.17	98.77	102.43
<i>Breast Cancer</i>					
<i>MCF7</i>	97.70	91.63	23.10	88.29	88.72
<i>MDA-MB-231/ATCC</i>	97.54	104.53	59.77	91.18	89.95
<i>HS 578T</i>	100.05	102.57	65.23	111.14	95.62
<i>BT-549</i>	--	125.31	85.98	--	--
<i>T-47D</i>	85.15	83.93	12.95	77.61	69.67
<i>MDA-MB-468</i>	114.68	100.93	45.12	102.84	94.03

1

2 **Table 3.** Sixty cell line in vitro anticancer screening data of compounds3 **4f,i,k-m**

Subpanel tumor cell lines	Growth % (G%)				
	4f NSC 822641	4i NSC 822642	4k NSC 822643	4l NSC 822645	4m NSC 822644
Leukemia					
<i>CCRF-CEM</i>	39.61	86.93	72.52	100.75	98.18
<i>HL-60(TB)</i>	76.33	102.05	102.88	104.84	106.08
<i>K-562</i>	54.73	84.30	81.76	84.53	89.09
<i>MOLT-4</i>	67.46	96.13	91.18	93.95	94.22
<i>RPMI-8226</i>	7.78	91.57	97.92	105.84	100.49
Non-Small Cell Lung Cancer					
<i>A549/ATCC</i>	93.21	93.10	99.59	98.60	98.05
<i>EKVX</i>	86.44	95.02	104.24	100.15	102.48
<i>HOP-62</i>	103.48	105.02	105.03	99.36	97.35
<i>HOP-92</i>	71.51	79.11	87.99	91.41	92.69
<i>NCI-H226</i>	93.06	94.43	101.68	97.76	108.05
<i>NCI-H23</i>	76.84	91.75	91.32	102.46	97.03
<i>NCI-H322M</i>	97.88	100.72	99.15	99.60	93.29
<i>NCI-H460</i>	93.06	100.80	104.66	103.98	110.72
<i>NCI-H522</i>	68.63	87.74	87.67	91.90	97.31
Colon Cancer					
<i>COLO 205</i>	99.06	113.50	116.25	121.50	120.60
<i>HCC-2998</i>	93.05	103.29	100.99	121.39	115.34
<i>HCT-116</i>	75.30	94.45	96.98	102.85	97.84
<i>HCT-15</i>	35.77	90.36	90.14	98.67	104.89
<i>HT29</i>	85.87	108.02	115.83	117.33	118.15
<i>KM12</i>	97.47	99.50	98.22	101.42	100.22
<i>SW-620</i>	70.92	97.64	106.75	106.37	108.61
CNS Cancer					
<i>SF-268</i>	89.66	98.48	101.45	97.99	99.12
<i>SF-295</i>	95.11	95.86	99.06	104.69	100.43
<i>SF-539</i>	99.58	97.40	102.44	100.04	99.86
<i>SNB-19</i>	82.93	95.89	98.42	97.03	98.96
<i>SNB-75</i>	55.70	72.63	73.20	83.81	75.48
<i>U251</i>	71.70	95.05	94.41	102.31	100.59
Melanoma					

<i>LOX IMVI</i>	85.96	97.49	95.33	98.68	97.62
<i>MALME-3M</i>	93.13	101.30	104.74	110.29	107.07
<i>M14</i>	100.49	101.42	99.09	107.07	102.31
<i>MDA-MB-435</i>	98.23	99.25	100.19	101.76	100.43
<i>SK-MEL-2</i>	101.76	108.39	108.12	107.05	112.30
<i>SK-MEL-28</i>	98.58	100.60	103.56	104.41	104.67
<i>SK-MEL-5</i>	96.77	97.97	98.14	100.17	98.95
<i>UACC-257</i>	90.11	95.45	94.66	99.47	96.81
<i>UACC-62</i>	74.15	83.18	98.03	95.24	98.64
Ovarian Cancer					
<i>IGROV1</i>	88.48	107.46	110.01	102.96	101.32
<i>OVCAR-3</i>	83.55	101.14	105.45	105.01	108.77
<i>OVCAR-4</i>	69.21	86.46	97.49	91.03	99.50
<i>OVCAR-5</i>	94.96	103.62	109.99	108.64	104.78
<i>OVCAR-8</i>	73.35	97.31	96.51	99.81	99.32
<i>NCI/ADR-RES</i>	75.16	97.84	98.75	107.60	102.08
<i>SK-OV-3</i>	103.72	104.80	114.35	111.48	107.98
Renal Cancer					
<i>786-0</i>	91.25	101.02	105.31	107.81	103.98
<i>A498</i>	70.44	73.14	82.78	80.57	88.74
<i>ACHN</i>	84.33	103.83	94.72	103.76	105.35
<i>CAKI-1</i>	81.07	85.02	93.37	96.55	94.77
<i>RXF 393</i>	78.01	102.25	104.32	111.43	111.86
<i>SN12C</i>	57.30	97.06	94.13	98.62	95.88
<i>TK-10</i>	115.28	116.42	124.81	109.18	100.32
<i>UO-31</i>	66.44	95.08	92.24	90.80	85.46
Prostate Cancer					
<i>PC-3</i>	64.47	88.64	94.84	96.38	101.42
<i>DU-145</i>	81.36	99.65	101.88	105.32	107.03
Breast Cancer					
<i>MCF7</i>	72.83	87.51	86.59	94.54	97.22
<i>MDA-MB-231/ATCC</i>	84.92	93.05	109.05	109.37	98.28
<i>HS 578T</i>	84.30	97.41	104.84	98.92	99.20
<i>BT-549</i>	109.41	90.98	--	115.39	--
<i>T-47D</i>	56.03	91.42	96.24	99.20	101.02
<i>MDA-MB-468</i>	84.20	102.27	108.68	101.73	116.51

1

2 Conclusion

3 In conclusion, an efficient and facile stereoselective synthesis of (2,4-
4 dinitrophenyl)hydrazono- and (2-tosylhydrazono)-4-oxo-thiazolidine
5 derivatives are reported. The stereoselective reactions showed that the

presence of electron-withdrawing groups at phenyl ring facilitate the attack of NH-Ph proton on C/C triple bond of **2**, followed by nucleophilic attack of thione group and formation the thiazolidinones. The structure was unambiguously confirmed by X-ray analyses. Ten of the newly synthesized compounds were selected for screening by NCI, and the results showed that thiazolidine **4c** showed broad anticancer activity against different cancer cell lines where, thiazolidine **4f** showed a significant activity against RPMI-8226 leukemia.

Experimental

Instrumentation

The melting points of the products were recorded on Gallenkamp melting point apparatus and are uncorrected. The infrared spectra were determined on Alpha, Bruker FT-IR instruments using KBr discs. NMR spectra were recorded in (DMSO-*d*₆ and CDCl₃), with tetramethylsilane as the internal standard for ¹H NMR (400 MHz) and ¹³C NMR (100 MHz), and using a Bruker AM400 spectrometry. The mass spectra observed on a varian mat FAB (70 eV, EI). Elemental analyses were performed on Elmyer 306. All reactions were monitored by TLC (silica gel coated alumina sheets).

Chemicals

Starting materials

The starting materials have been prepared according to published literature (**1d-h** [37] and **1i-l** [38]). Dialkyl acetylenedicarboxylates were purchased from Aldrich.

General procedure for the synthesis of thiazolidinone derivatives 4a-r

An equimolar amount of *N*,2-disubstituted hydrazinecarbothioamides **1d-l** (0.001 mol) and dialkyl acetylenedicarboxylates **2a,b** (0.001 mol) were mixed and allowed to reflux 30 min for **1d-h** and 4-8 hrs for **1i-l** in (15 ml) absolute ethanol. The formed precipitate was filtered, washed several times with ethanol and recrystallized from appropriate solvent affording thiazolidinone derivatives **4a-r**.

(Z)-Methyl 2-(((*Z*)-3-benzyl-2-(2-(2,4-dinitrophenyl)hydrazono)-4-oxo-thiazolidin-5-ylidene)acetate (C₁₉H₁₅N₅O₇S, **4a**).

Red crystals (methanol); ¹H NMR (400 MHz, DMSO-d₆): δ = 3.82 (s, 3H, OCH₃), 5.12 (s, 2H, benzyl-CH₂), 6.95 (s, 1H, vinyl-H), 7.33-7.51 (m, 6H, Ar-H), 8.32-8.34 (m, 1H, Ar-H), 8.82-8.84 (m, 1H, Ar-H), 10.84 (br, s, 1H, NH) ppm; ¹³C NMR (100 MHz, DMSO-d₆): δ = 48.0 (benzyl-CH₂), 49.6 (OCH₃), 116.8, 123.1, 125.4, 127.9, 128.6, 130.1 (Ar-CH), 129.7, 135.4, 137.3, 144.3 (Ar-C), 133.0 (C5), 139.0 (vinyl-CH), 156.5 (C2), 162.1 (C4), 165.8 (ester-CO) ppm; IR (KBr): $\bar{\nu}$ = 3230 (NH), 3068 (Ar-CH), 2959 (ali-CH), 1708 and 1699 (C=O), 1606 (C=N), 1581 (Ar-C=C), 1425 and 1332 (NO₂) cm⁻¹; MS (70 eV): *m/z* (%) = 457 (M⁺, 100), 442 (25), 426

(50), 347 (61), 289 (38), 273 (26), 183 (44), 91 (53); Anal. Calcd for $C_{19}H_{15}N_5O_7S$ (457.42): C 49.89, H 3.31, N 15.31, S, 7.01; Found: C 49.97, H 3.36, N 15.17, S 6.90.

(Z)-Methyl 2-((*Z*)-2-(2-(2,4-dinitrophenyl)hydrazono)-4-oxo-3-phenylthiazolidin-5-ylidene)acetate ($C_{18}H_{13}N_5O_7S$, **4b**).

Red crystals (methanol); 1H NMR (400 MHz, DMSO- d_6): δ = 3.84 (s, 3H, OCH₃), 6.96 (s, 1H, vinyl-H), 7.13-7.18 (m, 1H, Ar-H), 7.53-7.62 (m, 5H, Ar-H), 8.32-8.34 (m, 1H, Ar-H), 8.81-8.83 (m, 1H, Ar-H), 10.81 (br, s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO- d_6): δ = 48.6 (OCH₃), 117.8, 124.1, 125.6, 128.1, 129.3, 130.7 (Ar-CH), 131.7, 132.7, 138.0, 145.3 (Ar-C), 134.4 (C5), 138.3 (vinyl-CH), 156.5 (C2), 161.2 (C4), 165.4 (ester-CO) ppm; IR (KBr): $\bar{\nu}$ = 3202 (NH), 3058 (Ar-CH), 2953 (ali-CH), 1707 and 1696 (C=O), 1609 (C=N), 1584 (Ar-C=C), 1434 and 1326 (NO₂) cm^{-1} ; MS (70 eV): m/z (%) = 443 (M^+ , 100), 428 (31), 373 (27), 333 (43), 278 (38), 259 (25), 183 (42), 168 (63); Anal. Calcd for $C_{18}H_{13}N_5O_7S$ (443.39): C 48.76, H 2.96, N 15.80, S 7.23; Found: C 48.86, H 2.89, N 15.89, S 7.30.

(Z)-Methyl 2-((*Z*)-3-cyclohexyl-2-(2-(2,4-dinitrophenyl)hydrazono)-4-oxothiazolidin-5-ylidene)acetate ($C_{18}H_{19}N_5O_7S$, **4c**).

Reddish orange crystals (methanol); 1H NMR (400 MHz, DMSO- d_6): δ = 1.18-1.40 (m, 3H, cyclohexyl-CH₂), 1.65-1.87 (m, 5H, cyclohexyl-CH₂), 2.24-2.49 (m, 2H, cyclohexyl-CH₂), 3.80 (s, 3H, OCH₃), 4.41-4.50 (m, 1H,

1 cyclohexyl-CH), 6.85 (s, 1H, vinyl-H), 7.48-7.55 (m, 1H, Ar-H), 8.41-8.45
2 (m, 1H, Ar-H), 8.86-8.87 (m, 1H, Ar-H), 10.80 (br, s, 1H, NH) ppm; ^{13}C
3 NMR (100 MHz, DMSO- d_6): δ = 25.4, 27.1, 33.4 (cyclohexyl- CH_2), 48.2
4 (OCH_3), 52.9 (cyclohexyl-CH), 116.8, 126.1, 130.0 (Ar-CH), 131.7, 137.7,
5 144.6 (Ar-C), 133.4 (C5), 139.6 (vinyl-CH), 156.6 (C2), 162.8 (C4), 165.8
6 (ester-CO) ppm; IR (KBr): $\bar{\nu}$ = 3210 (NH), 3073 (Ar-CH), 2932 (ali-CH),
7 1707 and 1698 (C=O), 1607 (C=N), 1580 (Ar-C=C), 1429 and 1327 (NO_2)
8 cm^{-1} ; MS (70 eV): m/z (%) = 449 (M^+ , 100), 434 (38), 339 (13), 281 (25),
9 266 (42), 183 (73), 168 (59); Anal. Calcd for $\text{C}_{18}\text{H}_{19}\text{N}_5\text{O}_7\text{S}$ (449.44): C
10 48.10, H 4.26, N 15.58, S 7.13; Found: C 48.19, H 4.35, N 15.47, S 7.21.

11 (*Z*)-Methyl 2-((*Z*)-2-(2-(2,4-dinitrophenyl)hydrazono)-3-ethyl-4-
12 oxothiazolidin-5-ylidene)acetate ($\text{C}_{14}\text{H}_{13}\text{N}_5\text{O}_7\text{S}$, **4d**).

13 Reddish orange crystals (methanol); ^1H NMR (400 MHz, DMSO- d_6): δ =
14 1.26-1.31 (t, 3H, J = 7.77, CH_3), 3.92-3.96 (q, 2H, J = 7.77, CH_2), 3.81 (s,
15 3H, OCH_3), 6.89 (s, 1H, vinyl-H), 7.61-7.64 (m, 1H, Ar-H), 8.37-8.40 (m,
16 1H, Ar-H), 8.89-8.90 (m, 1H, Ar-H), 10.81 (br, s, 1H, NH) ppm; ^{13}C NMR
17 (100 MHz, DMSO- d_6): δ = 21.4 (CH_3), 45.2 (CH_2N), 48.9 (OCH_3), 116.8,
18 123.5, 130.4 (Ar-CH), 131.7, 137.7, 145.0 (Ar-C), 133.0 (C5), 139.3
19 (vinyl-CH), 156.9 (C2), 163.1 (C4), 166.4 (ester-CO) ppm; IR (KBr): $\bar{\nu}$ =
20 3220 (NH), 3067 (Ar-CH), 2973 (ali-CH), 1711 and 1695 (C=O), 1606
21 (C=N), 1586 (Ar-C=C), 1435 and 1329 (NO_2) cm^{-1} ; MS (70 eV): m/z (%) =

395 (M^+ , 100), 380 (33), 363 (25), 227 (72), 212 (56), 183 (81), 168 (53);
Anal. Calcd for $C_{14}H_{13}N_5O_7S$ (395.35): C 42.53, H 3.31, N 17.71, S 8.11;
Found: C 42.46, H 3.20, N 17.64, S 8.22.

(*Z*)-Methyl 2-((*Z*)-3-allyl-2-(2-(2,4-dinitrophenyl)hydrazono)-4-oxo-
thiazolidin-5-ylidene)acetate ($C_{15}H_{13}N_5O_7S$, **4e**).

Reddish orange crystals (methanol); 1H NMR (400 MHz, DMSO- d_6): δ =
3.82 (s, 3H, OCH₃), 4.52-4.54 (m, 2H, allyl-CH₂N), 5.23-5.32 (m, 2H,
allyl-CH₂=), 5.85-5.95 (m, 1H, allyl-CH=), 6.91 (s, 1H, vinyl-H), 7.58-7.62
(m, 1H, Ar-H), 8.37-8.40 (m, 1H, Ar-H), 8.89-8.90 (m, 1H, Ar-H), 10.84
(br, s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO- d_6): δ = 45.6 (allyl-
CH₂N), 48.9 (OCH₃), 118.6 (allyl-CH₂=), 116.1, 124.4, 130.4 (Ar-CH),
135.0 (allyl-CH=), 131.2, 137.5, 144.9 (Ar-C), 134.0 (C5), 138.7 (vinyl-
CH), 156.8 (C2), 162.8 (C4), 165.5 (ester-CO) ppm; IR (KBr): $\bar{\nu}$ = 3245
(NH), 3075 (Ar-CH), 2970 (ali-CH), 1710 and 1698 (C=O), 1610 (C=N),
1583 (Ar-C=C), 1440 and 1335 (NO₂) cm^{-1} ; MS (70 eV): m/z (%) = 407
(M^+ , 100), 392 (32), 376 (23), 224 (46), 339 (25), 183 (37), 168 (55); Anal.
Calcd for $C_{15}H_{13}N_5O_7S$ (407.36): C 44.23, H 3.22, N 17.19, S 7.87; Found:
C 44.12, H 3.33, N 17.08, S 7.94.

(*Z*)-Ethyl 2-((*Z*)-3-benzyl-2-(2-(2,4-dinitrophenyl)hydrazono)-4-oxo-
thiazolidin-5-ylidene)acetate ($C_{20}H_{17}N_5O_7S$, **4f**).

1 Red crystals (methanol); ^1H NMR (400 MHz, DMSO- d_6): δ = 1.26-1.32 (t,
2 3H, J = 7.66, CH₃), 4.21-4.30 (q, 2H, J = 7.66, OCH₂), 5.10 (s, 2H, benzyl-
3 CH₂), 6.87 (s, 1H, vinyl-H), 7.35-7.55 (m, 6H, Ar-H), 8.37-8.39 (m, 1H,
4 Ar-H), 8.87-8.88 (m, 1H, Ar-H), 10.86 (br, s, 1H, NH) ppm; ^{13}C NMR (100
5 MHz, DMSO- d_6): δ = 14.4 (CH₃), 49.3 (benzyl-CH₂N), 59.8 (CH₂O),
6 117.0, 124.4, 125.4, 127.4, 128.1, 130.0 (Ar-CH), 131.4, 135.0, 137.7,
7 144.1 (Ar-C), 133.3 (C5), 138.8 (vinyl-CH), 156.4 (C2), 162.5 (C4), 166.8
8 (ester-CO) ppm; IR (KBr): $\bar{\nu}$ = 3236 (NH), 3076 (Ar-CH), 2972 (ali-CH),
9 1715 and 1692 (C=O), 1602 (C=N), 1583 (Ar-C=C), 1425 and 1333 (NO₂)
10 cm⁻¹; MS (70 eV): m/z (%) = 471 (M⁺, 100), 456 (30), 441 (21), 303 (20),
11 288 (44), 183 (32), 168 (60), 91 (72); Anal. Calcd for C₂₀H₁₇N₅O₇S
12 (471.44): C 50.95, H 3.63, N 14.86, S 6.80; Found: C 51.05, H 3.55, N
13 14.97, S 6.87.

14 *(Z)*-Ethyl 2-((*Z*)-2-(2-(2,4-dinitrophenyl)hydrazono)-4-oxo-3-
15 phenylthiazolidin-5-ylidene)acetate (C₁₉H₁₅N₅O₇S, **4g**).

16 Red crystals (methanol); ^1H NMR (400 MHz, CDCl₃): δ = 1.24-1.30 (t, 3H,
17 J = 7.77, CH₃), 4.25-4.35 (q, 2H, J = 7.77, OCH₂), 6.90 (s, 1H, vinyl-H),
18 7.22-7.58 (m, 6H, Ar-H), 8.23-8.29 (m, 1H, Ar-H), 9.10 (s, 1H, Ar-H),
19 10.80 (br, s, 1H, NH) ppm; ^{13}C NMR (100 MHz, CDCl₃): δ = 14.3 (CH₃),
20 62.2 (OCH₂), 115.7, 123.3, 124.8, 125.7, 127.4, 128.3 (Ar-CH), 129.8,
21 130.3, 132.7, 144.7 (Ar-C), 134.2 (C5), 138.3 (vinyl-CH), 158.5 (C2), 163.3

(C4), 165.7 (ester-CO) ppm; IR (KBr): $\bar{\nu}$ = 3227 (NH), 3072 (Ar-CH), 2961 (ali-CH), 1709 and 1693 (C=O), 1610 (C=N), 1590 (Ar-C=C), 1431 and 1325 (NO₂) cm⁻¹; MS (70 eV): m/z (%) = 457 (M⁺, 100), 428 (21), 364 (12), 333 (35), 276 (17), 228 (43), 183 (82), 168 (57), 91 (53); Anal. Calcd for C₁₉H₁₅N₅O₇S (457.42): C 49.89, H 3.31, N 15.31, S 7.01; Found: C 49.77, H 3.19, N 15.20, S 6.89.

(Z)-Ethyl 2-((Z)-3-cyclohexyl-2-(2-(2,4-dinitrophenyl)hydrazono)-4-oxothiazolidin-5-ylidene)acetate (C₁₉H₂₁N₅O₇S, **4h**).

Reddish orange crystals (methanol); ¹H NMR (400 MHz, CDCl₃): δ = 1.15-1.41 (m, 5H, CH₃ and cyclohexyl-CH₂), 1.65-1.78 (m, 4H, cyclohexyl-CH₂), 1.84-1.92 (m, 2H, cyclohexyl-CH₂), 2.25-2.35 (m, 2H, cyclohexyl-CH₂), 4.20-4.30 (q, 2H, J = 7.76, OCH₂), 4.50-4.55 (m, 1H, cyclohexyl-CH), 6.90 (s, 1H, vinyl-H), 7.45-7.50 (m, 1H, Ar-H), 8.25-8.30 (m, 1H, Ar-H), 9.10 (s, 1H, Ar-H), 10.72 (br, s, 1H, NH) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 14.2 (CH₃), 25.2, 26.3, 27.4, 28.8 (cyclohexyl-CH₂), 56.9 (cyclohexyl-CH), 62.2 (OCH₂), 115.8, 123.4, 128.7 (Ar-CH), 129.8, 130.3, 144.8 (Ar-C), 133.4 (C5), 138.3 (vinyl-CH), 157.7 (C2), 163.3 (C4), 165.7 (ester-CO) ppm; IR (KBr): $\bar{\nu}$ = 3223 (NH), 3086 (Ar-CH), 2944 (ali-CH), 1702 and 1695 (C=O), 1611 (C=N), 1586 (Ar-C=C), 1425 and 1330 (NO₂) cm⁻¹; MS (70 eV): m/z (%) = 463 (M⁺, 100), 434 (25), 418 (20), 337 (37), 281 (43),

1 183 (37), 168 (53), 91 (76); Anal. Calcd for C₁₉H₂₁N₅O₇S (463.46): C
2 49.24, H 4.57, N 15.11, S 6.92; Found: C 49.30, H 4.50, N 14.99, S 7.00.

3 (*Z*)-Ethyl 2-((*Z*)-2-(2-(2,4-dinitrophenyl)hydrazono)-3-ethyl-4-oxothi-
4 azolidin-5-ylidene)acetate (C₁₅H₁₅N₅O₇S, **4i**).

5 Red crystals (methanol); ¹H NMR (400 MHz, DMSO-d₆): δ = 1.25-1.31
6 (m, 6H, 2CH₃), 3.92-3.96 (q, 2H, *J* = 7.77, CH₂N), 4.23-4.31 (q, 2H, *J* =
7 7.66, OCH₂), 6.89 (s, 1H, vinyl-H), 7.61-7.64 (m, 6H, Ar-H), 8.37-8.41 (m,
8 1H, Ar-H), 8.86-8.87 (m, 1H, Ar-H), 10.84 (br, s, 1H, NH) ppm; ¹³C NMR
9 (100 MHz, DMSO-d₆): δ = 13.2 (CH₃), 14.5 (CH₃), 45.2 (CH₂N), 60.5
10 (CH₂O), 116.4, 124.1, 130.7 (Ar-CH), 132.0, 137.8, 145.0 (Ar-C), 134.0
11 (C5), 139.3 (vinyl-CH), 156.9 (C2), 162.5 (C4), 166.8 (ester-CO) ppm; IR
12 (KBr): $\bar{\nu}$ = 3252 (NH), 3071 (Ar-CH), 2951 (ali-CH), 1713 and 1695
13 (C=O), 1605 (C=N), 1588 (Ar-C=C), 1443 and 1328 (NO₂) cm⁻¹; MS (70
14 eV): *m/z* (%) = 409 (M⁺, 100), 394 (40), 341 (26), 324 (55), 183 (77), 168
15 (51); Anal. Calcd for C₁₅H₁₅N₅O₇S (409.37): C 44.01, H 3.69, N 17.11, S
16 7.83; Found: C 43.89, H 3.58, N 16.98, S 7.72.

17 (*Z*)-Ethyl 2-((*Z*)-3-allyl-2-(2-(2,4-dinitrophenyl)hydrazono)-4-
18 oxothiazolidin-5-ylidene)acetate (C₁₆H₁₅N₅O₇S, **4j**).

19 Reddish orange crystals (methanol); ¹H NMR (400 MHz, CDCl₃): δ = 1.24-
20 1.30 (t, 3H, *J* = 7.66, CH₃), 4.20-4.30 (q, 2H, *J* = 7.66, OCH₂), 4.40-4.50
21 (m, 2H, allyl-CH₂N), 5.20-5.32 (m, 2H, allyl-CH₂=), 5.76-5.90 (m, 1H,

1 allyl-CH=), 6.92 (s, 1H, vinyl-H), 7.48-7.55 (m, 1H, Ar-H), 8.25-8.32 (m,
2 1H, Ar-H), 9.05-9.08 (m, 1H, Ar-H), 10.73 (br, s, 1H, NH) ppm; ^{13}C NMR
3 (100 MHz, DMSO- d_6): δ = 14.2 (CH_3) 45.4 (allyl- CH_2N), 62.3 (OCH_2),
4 118.4 (allyl- $\text{CH}_2=$), 115.9, 123.3, 129.3 (Ar-CH), 134.2 (allyl-CH=), 123.6,
5 130.5, 144.7 (Ar-C), 133.1 (C5), 138.3 (vinyl-CH), 157.7 (C2), 162.8 (C4),
6 165.6 (ester-CO) ppm; IR (KBr): $\bar{\nu}$ = 3243 (NH), 3072 (Ar-CH), 2973
7 (ali-CH), 1709 and 1695 ($\text{C}=\text{O}$), 1612 ($\text{C}=\text{N}$), 1585 (Ar- $\text{C}=\text{C}$), 1439 and
8 1333 (NO_2) cm^{-1} ; MS (70 eV): m/z (%) = 421 (M^+ , 100), 392 (22), 376
9 (33), 339 (57), 183 (35), 168 (67), 91 (66); Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{N}_5\text{O}_7\text{S}$
10 (421.38): C 45.60, H 3.59, N 16.62, S 7.61; Found: C 45.67, H 3.50, N
11 16.49, S 7.54.

12 (*Z*)-Methyl 2-((*Z*)-3-benzyl-4-oxo-2-(2-tosylhydrazono)thiazolidin-5-
13 ylidene)-acetate ($\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_5\text{S}_2$, **4k**).

14 Yellow crystals (methanol); ^1H NMR (400 MHz, DMSO- d_6): δ = 2.31 (s,
15 3H, CH_3), 4.10 (s, 3H, OCH_3), 4.43 (s, 2H, benzyl- CH_2), 6.10 (s, 1H, vinyl-
16 H), 6.37-6.44 (m, 5H, Ar-H), 6.54-6.56 (m, 3H, Ar-H), 6.89-6.92 (m, 2H,
17 Ar-H and NH) ppm; ^{13}C NMR (100 MHz, DMSO- d_6): δ = 23.4 (CH_3), 46.7
18 (CH_3O), 49.1 (benzyl- CH_2N), 123.7, 124.4, 126.4, 126.7, 127.4 (Ar-CH),
19 134.6, 136.9, 142.3 (Ar-C), 133.6 (C5), 139.5 (vinyl-CH), 159.6 (C2), 162.9
20 (C4), 167.2 (ester-CO) ppm; IR (KBr): $\bar{\nu}$ = 3202 (NH), 3073 (Ar-CH),
21 2982 (ali-CH), 1707 and 1700 ($\text{C}=\text{O}$), 1614 ($\text{C}=\text{N}$), 1584 (Ar- $\text{C}=\text{C}$) cm^{-1} ;

MS (70 eV): m/z (%) = 445 (M^+ , 36), 430 (24), 415 (55), 335 (35), 290 (14), 261 (33), 154 (100), 91 (65); Anal. Calcd for $C_{20}H_{19}N_3O_5S_2$ (445.51): C 53.92, H 4.30, N 9.43, S 14.39; Found: C 53.81, H 4.38, N 9.34, S 14.50.

(Z)-Methyl 2-((Z)-4-oxo-3-phenyl-2-(2-tosylhydrazono)thiazolidin-5-ylidene)-acetate ($C_{19}H_{17}N_3O_5S_2$, **4l**).

Yellow crystals (methanol); 1H NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 6.55 (s, 1H, vinyl-H), 7.10-7.23 (m, 5H, Ar-H), 7.40-7.48 (m, 3H, Ar-H and NH), 7.55-7.57 (m, 2H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3 (CH_3), 46.7 (CH_3O), 123.8, 124.3, 127.6, 128.7, 129.3 (Ar-CH), 131.8, 134.9, 142.4 (Ar-C), 133.8 (C5), 139.5 (vinyl-CH), 159.3 (C2), 162.7 (C4), 167.3 (ester-CO) ppm; IR (KBr): $\bar{\nu}$ = 3225 (NH), 3078 (Ar-CH), 2986 (ali-CH), 1720 and 1698 (C=O), 1618 (C=N), 1594 (Ar-C=C) cm^{-1} ; MS (70 eV): m/z (%) = 431 (M^+ , 100), 416 (12), 400 (31), 355 (20), 325 (37), 276 (31), 155 (65), 91 (82); Anal. Calcd for $C_{19}H_{17}N_3O_5S_2$ (431.49): C 52.89, H 3.97, N 9.74, S 14.86; Found: C 52.99, H 3.88, N 9.81, S 14.94.

(Z)-Methyl 2-((Z)-3-ethyl-4-oxo-2-(2-tosylhydrazono)thiazolidin-5-ylidene)-acetate ($C_{15}H_{17}N_3O_5S_2$, **4m**).

Yellow crystals (methanol); 1H NMR (400 MHz, $CDCl_3$): δ = 1.08-1.12 (t, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.75-3.82 (m, 5H, CH_2N and CH_3O), 6.65 (s, 1H, vinyl-H), 6.82 (s, 1H, NH), 7.35-7.40 (m, 2H, Ar-H), 7.75-7.80 (m,

1 2H, Ar-H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ = 12.5 (CH_3), 21.7 (CH_3),
2 38.5 (CH_2N), 52.8 (CH_3O), 128.4, 129.7 (Ar-CH), 135.4, 144.8 (Ar-
3 C), 134.3 (C5), 140.2 (vinyl-CH), 160.4 (C2), 164.3 (C4), 166.0 (ester-CO)
4 ppm; IR (KBr): $\bar{\nu}$ = 3220 (NH), 3088 (Ar-CH), 2977 (ali-CH), 1711 and
5 1698 (C=O), 1610 (C=N), 1590 and 1488 (Ar-C=C) cm^{-1} ; MS (70 eV): m/z
6 (%) = 383 (M^+ , 25), 367 (28), 352 (8), 273 (64), 228 (13), 154 (100), 91
7 (44); Anal. Calcd for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_5\text{S}_2$ (383.44): C 46.99, H 4.47, N 10.96, S
8 16.72; Found: C 47.09, H 4.54, N 10.88, S 16.83.

9 (*Z*)-Methyl 2-((*Z*)-3-allyl-4-oxo-2-(2-tosylhydrazono)thiazolidin-5-
10 ylidene)acetate ($\text{C}_{16}\text{H}_{17}\text{N}_3\text{O}_5\text{S}_2$, **4n**).

11 Yellow crystals (methanol); ^1H NMR (400 MHz, DMSO-d_6): δ = 2.35 (s,
12 3H, CH_3), 3.82 (s, 3H, OCH_3), 4.10-4.18 (m, 2H, allyl- CH_2N), 4.32-4.48
13 (m, 2H, allyl- $\text{CH}_2=$), 4.98-5.15 (m, 1H, allyl- $\text{CH}=\text{}$), 6.46 (s, 1H, vinyl-H),
14 6.62-6.70 (m, 2H, Ar-H), 7.00-7.12 (m, 3H, Ar-H and NH) ppm; ^{13}C NMR
15 (100 MHz, DMSO-d_6): δ = 23.3 (CH_3), 46.7 (CH_3O), 47.1 (allyl- CH_2N),
16 118.5 (allyl- $\text{CH}_2=$), 123.8, 124.4 (Ar-CH), 133.7 (allyl $\text{CH}=\text{}$), 134.8, 142.4
17 (Ar-C), 133.6 (C5), 139.6 (vinyl-CH), 159.3 (C2), 162.5 (C4), 167.1 (ester-
18 CO) ppm; IR (KBr): $\bar{\nu}$ = 3159 (NH), 3073 (Ar-CH), 2988 (ali-CH), 1708
19 and 1687 (C=O), 1620 (C=N), 1588 (Ar-C=C) cm^{-1} ; MS (70 eV): m/z (%)
20 = 395 (M^+ , 100), 380 (17), 364 (3), 289 (6), 240 (45), 154 (36), 131 (31),

91 (76); Anal. Calcd for C₁₆H₁₇N₃O₅S₂ (395.45): C 48.60, H 4.33, N 10.63, S 16.22; Found: C 48.69, H 4.24, N 10.72, S 16.33.

(*Z*)-Ethyl 2-((*Z*)-3-benzyl-4-oxo-2-(2-tosylhydrazono)thiazolidin-5-ylidene)acetate (C₂₁H₂₁N₃O₅S₂, **4o**).

Yellow crystals (methanol); ¹H NMR (400 MHz, CDCl₃): δ = 1.21-1.27 (t, 3H, *J* = 7.77, CH₃), 2.31 (s, 3H, CH₃), 4.16-4.22 (q, 2H, OCH₂), 4.82 (s, 2H, benzyl-CH₂), 6.71 (s, 1H, NH), 6.85 (s, 1H, vinyl-H), 7.10-7.22 (m, 7H, Ar-H), 7.60-7.68 (m, 2H, Ar-H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 14.2 (CH₃), 21.7 (CH₃), 46.5 (benzyl-CH₂N), 62.2 (CH₂O), 124.3, 128.1, 128.6, 129.1, 129.7 (Ar-CH), 134.6, 136.5, 144.7 (Ar-C), 133.0 (C5), 139.5 (vinyl-CH), 159.9 (C2), 164.5 (C4), 165.5 (ester-CO) ppm; IR (KBr): $\bar{\nu}$ = 3223 (NH), 3085 (Ar-CH), 2990 (ali-CH), 1707 and 1685 (C=O), 1610 (C=N), 1588 (Ar-C=C) cm⁻¹; MS (70 eV): *m/z* (%) = 459 (M⁺, 100), 430 (23), 335 (51), 290 (26), 155 (76), 91 (81); Anal. Calcd for C₂₁H₂₁N₃O₅S₂ (459.54): C 54.89, H 4.61, N 9.14, S 13.96; Found: C 55.01, H 4.50, N 9.26, S 13.84.

(*Z*)-Ethyl 2-((*Z*)-4-oxo-3-phenyl-2-(2-tosylhydrazono)thiazolidin-5-ylidene)-acetate (C₂₀H₁₉N₃O₅S₂, **4p**).

Yellow crystals (methanol); ¹H NMR (400 MHz, CDCl₃): δ = 1.24-1.30 (t, 3H, *J* = 7.77, CH₃), 2.32 (s, 3H, CH₃), 4.20-4.30 (q, 2H, *J* = 7.77, OCH₂), 6.62 (s, 1H, vinyl-H), 7.08-7.20 (m, 5H, Ar-H), 7.30-7.41 (m, 3H, Ar-H

1 and NH), 7.50-7.54 (m, 2H, Ar-H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ =
2 14.2 (CH_3), 21.7 (CH_3), 62.1 (CH_2O), 127.5, 128.4, 128.5, 129.2, 129.3
3 (Ar-CH), 129.4, 133.3, 144.6 (Ar-C), 134.1 (C5), 139.4 (vinyl-CH), 161.4
4 (C2), 164.1 (C4), 165.6 (ester-CO) ppm; IR (KBr): $\bar{\nu}$ = 3227 (NH), 3075
5 (Ar-CH), 2988 (ali-CH), 1718 and 1695 ($\text{C}=\text{O}$), 1612 ($\text{C}=\text{N}$), 1592 (Ar-
6 $\text{C}=\text{C}$) cm^{-1} ; MS (70 eV): m/z (%) = 445 (M^+ , 100), 416 (18), 321 (57), 275
7 (41), 171 (65), 155 (71), 91 (82); Anal. Calcd. for $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_5\text{S}_2$ (445.51):
8 C 53.92, H 4.30, N 9.43, S 14.39; Found: C 54.02, H 4.43, N 9.52, S 14.51.
9 (*Z*)-Ethyl 2-((*Z*)-3-ethyl-4-oxo-2-(2-tosylhydrazono)thiazolidin-5-
10 ylidene)acetate ($\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}_5\text{S}_2$, **4q**).
11 Yellow crystals (methanol); ^1H NMR (400 MHz, DMSO-d_6): δ = 1.02-1.08
12 (t, 3H, J = 7.77, CH_3), 1.23-1.29 (t, 3H, J = 7.66, CH_3), 2.33 (s, 3H, CH_3),
13 3.60-3.66 (q, 2H, J = 7.66, CH_2N), 4.20-4.28 (q, 2H, J = 7.77, CH_2O), 6.66
14 (s, 1H, vinyl-H), 7.06 (s, 1H, NH), 7.32-7.38 (m, 2H, Ar-H), 7.68-7.74 (m,
15 2H, Ar-H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 12.1 (CH_3), 13.7
16 (CH_3), 21.1 (CH_3), 40.3 (CH_2N), 61.6 (CH_2O), 128.5, 129.6 (Ar-CH),
17 130.3, 143.8 (Ar-C), 135.0 (C5), 140.6 (vinyl-CH), 156.7 (C2), 163.5 (C4),
18 165.3 (ester-CO) ppm; IR (KBr): $\bar{\nu}$ = 3220 (NH), 3095 (Ar-CH), 2981
19 (ali-CH), 1709 and 1689 ($\text{C}=\text{O}$), 1610 ($\text{C}=\text{N}$), 1593 (Ar- $\text{C}=\text{C}$) cm^{-1} ; MS (70
20 eV): m/z (%) = 397 (M^+ , 100), 368 (28), 352 (33), 325 (64), 271 (22), 242
21 (15), 227 (39), 155 (75), 91 (57); Anal. Calcd for $\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}_5\text{S}_2$ (397.47):

1 C 48.35, H 4.82, N 10.57, S 16.13; Found: C 48.47, H 4.90, N 10.47, S
2 16.25.

3 (*Z*)-Ethyl 2-((*Z*)-3-allyl-4-oxo-2-(2-tosylhydrazono)thiazolidin-5-
4 ylidene)acetate (C₁₇H₁₉N₃O₅S₂, **4r**).

5 Yellow crystals (methanol); ¹H NMR (400 MHz, CDCl₃): δ = 1.22-1.28 (t,
6 3H, *J* = 7.66, CH₃), 2.32 (s, 3H, CH₃), 4.20-4.35 (m, 4H, CH₂O and allyl-
7 CH₂N), 5.05-5.13 (m, 2H, allyl-CH₂=), 5.61-5.76 (m, 1H, allyl-CH=), 6.68
8 (s, 1H, vinyl-H), 6.86 (s, 1H, NH), 7.20-7.28 (m, 2H, Ar-H), 7.70-7.78 (m,
9 2H, Ar-H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 14.2 (CH₃), 21.6 (CH₃),
10 45.2 (allyl-CH₂N), 62.0 (CH₂O), 118.0 (allyl-CH₂=), 128.4, 128.6 (Ar-CH),
11 132.7 (allylCH=), 129.5, 144.7 (Ar-C), 134.3 (C5), 139.6 (vinyl-CH), 160.4
12 (C2), 164.2 (C4), 165.5 (ester-CO) ppm; IR (KBr): $\bar{\nu}$ = 3222 (NH), 3098
13 (Ar-CH), 2985 (ali-CH), 1710 and 1691 (C=O), 1613 (C=N), 1595 (Ar-
14 C=C) cm⁻¹; MS (70 eV): *m/z* (%) = 409 (M⁺, 100), 380 (23), 285 (45), 239
15 (14), 155 (45), 91 (73); Anal. Calcd for C₁₇H₁₉N₃O₅S₂ (409.48): C 49.86, H
16 4.68, N 10.26, S 15.66; Found: C 49.75, H 4.80, N 10.37, S 15.76.

17 **Single crystal X-ray structure determination of 4a, 4m and 4o:**

18 The single crystal X-ray diffraction studies for **4a**, **4m** and **4o** were carried
19 out on Bruker D8 Venture diffractometer with Photon100 detector or
20 PhotonII detector at 123 k using CuKα radiation (λ = 1.54178 Å) for **4a**,
21 **4m** and **4o**. Dual space methods (SHELXT) [41] were used for structure

solution and refinement was carried out using SHEXL-2013/2014 [42] (full-matrix least-squares refinement on F^2). Hydrogen atoms were localized by difference fourier synthesis map and refined using a riding model [H (N) free]. Semi-empirical absorption corrections were applied. The absolute structure of **4m** and **4o** are determined by refinement of Parsons Flack parameter [43].

Compound 4a: $C_{19}H_{15}N_5O_7S$, $M_r = 457.42 \text{ g mol}^{-1}$, red plates, crystal size = $0.18 \times 0.10 \times 0.04 \text{ mm}$, monoclinic, space group $P2_1/c$ (no. 14), $a = 11.6368 (4) \text{ \AA}$, $b = 8.6707 (3) \text{ \AA}$, $c = 19.5077 (6) \text{ \AA}$, $\beta = 91.611 (2)^\circ$, $V = 1967.53 (11) \text{ \AA}^3$, $Z = 4$, $D_{\text{calcd}} = 1.544 \text{ Mg m}^{-3}$, $F(000) = 944$, $\mu (\text{CuK}\alpha) = 1.97 \text{ mm}^{-1}$, $T = 123 \text{ K}$, 19539 measured reflections ($2\theta_{\text{max}} = 144.2^\circ$), 3855 independent reflections [$R_{\text{int}} = 0.030$], 293 parameters, 1 restraint, $R_1[\text{for } 3397 \text{ with } I > 2\sigma(I)] = 0.030$, $wR_2 (\text{for all data}) = 0.077$, $S = 1.04$, largest diff. peak and hole = $0.23 \text{ e \AA}^{-3} / -0.23 \text{ e \AA}^{-3}$.

Compound 4m: $C_{15}H_{17}N_3O_5S_2$, $M_r = 383.43 \text{ g mol}^{-1}$, colorless blocks, crystal size = $0.36 \times 0.20 \times 0.10 \text{ mm}$, orthorhombic, $Pca2_1$ (no.29), $a = 26.3398 (11) \text{ \AA}$, $b = 9.0039 (4) \text{ \AA}$, $c = 14.9566 (6) \text{ \AA}$, $V = 3547.1 (3) \text{ \AA}^3$, $Z = 8$, $D_{\text{calcd}} = 1.436 \text{ Mg m}^{-3}$, $F(000) = 1600$, $\mu (\text{CuK}\alpha) = 3.01 \text{ mm}^{-1}$, $T = 123 \text{ K}$, 27416 measured reflections ($2\theta_{\text{max}} = 144.8^\circ$), 6956 independent reflections [$R_{\text{int}} = 0.042$], 461 parameters, 393 restraints, $R_1[\text{for } 6931 \text{ with } I > 2\sigma(I)] = 0.030$, $wR_2 (\text{for all data}) = 0.077$, $S = 1.04$, largest diff. peak and hole = $0.23 \text{ e \AA}^{-3} / -0.23 \text{ e \AA}^{-3}$.

$I > 2\sigma(I)] = 0.075$, wR_2 (for all data) = 0.191, $S = 1.18$, largest diff. peak and hole = $1.58 \text{ e } \text{\AA}^{-3} / -0.60 \text{ e } \text{\AA}^{-3}$, $x = 0.053(7)$.

Compound 4o: $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_5\text{S}_2$, $M_r = 445.50 \text{ g mol}^{-1}$, colorless plates, crystal size = $0.16 \times 0.14 \times 0.03 \text{ mm}$, monoclinic space group Cc (no. 9), $a = 8.0103(3) \text{ \AA}$, $b = 20.3622(7) \text{ \AA}$, $c = 12.5617(4) \text{ \AA}$, $\beta = 99.390(1)^\circ$, $V = 2021.45(12) \text{ \AA}^3$, $Z = 4$, $D_{\text{calcd}} = 1.464 \text{ Mg m}^{-3}$, $F(000) = 928$, $\mu(\text{CuK}\alpha) = 2.73 \text{ mm}^{-1}$, $T = 123 \text{ K}$, 17263 measured reflections ($2\theta_{\text{max}} = 144.4^\circ$), 3790 independent reflections [$R_{\text{int}} = 0.029$], 276 parameters, 2 restraints, $R_1[\text{for } 3758 \text{ with } I > 2\sigma(I)] = 0.025$, wR_2 (for all data) = 0.064, $S = 1.02$, largest diff. peak and hole = $0.21 \text{ e } \text{\AA}^{-3} / -0.21 \text{ e } \text{\AA}^{-3}$, $x = 0.000(2)$.

CCDC 1959132 (**4a**), 1959133 (**4m**) and 1959134 (**4o**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

The NCI-60 anticancer drug screen

The methodology of the NCI for primary anticancer assay was performed at 60 human tumor cell lines panel derived from nine neoplastic diseases, according to the protocol of the Drug Evaluation Branch, National Cancer Institute, Bethesda.

(<http://www.dtp.nci.nih.gov>).

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5 408 IR instrument

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Figure Captions

Figure 1: 3-(2-Aminoethyl)-5-(3-cyclohexyl-propylidene)thiazolidine-2,4-dione

Figure 2. ^1H NMR of compound **4a**

Figure 3. ^{13}C NMR of compound **4a**

Figure 4. Molecular structure of compound (Z)-methyl 2-((Z)-3-benzyl-2-(2-(2,4-dinitrophenyl)hydrazono)-4-oxo-thiazolidin-5-ylidene)acetate **4a** in the crystal.

Figure 5: Molecular structure of compound (Z)-methyl 2-((Z)-3-ethyl-4-oxo-2-(2-tosylhydrazono)thiazolidin-5-ylidene)acetate (**4m**) in the crystal.

Figure 6: Molecular structure of compound (Z)-methyl 2-((Z)-3-benzyl-4-oxo-2-(2-tosylhydrazono)thiazolidin-5-ylidene)acetate (**4o**) in the crystal.

Scheme captions

Scheme 1: Previous work, of hydrazinecarbothioamides **1a-c** with dimethyl acetylenedicarboxylate **2a** [33], and Reaction of hydrazinecarbothioamides **1d-l** with dialkyl acetylenedicarboxylates **2a,b**.

Scheme 2: Plausible mechanism for the stereoselective formation of thiazolidinones **4a-r**

Table 4 Elemental analyses of compounds **4a-r**.

Compound	C	H	N	S
4a	49.89	3.31	15.31	7.01
	49.97	3.36	15.17	6.90
4b	48.76	2.96	15.80	7.23
	48.86	2.89	15.89	7.30
4c	48.10	4.26	15.58	7.13
	48.19	4.35	15.47	7.21
4d	42.53	3.31	17.71	8.11
	42.46	3.20	17.64	8.22
4e	44.23	3.22	17.19	7.87
	44.12	3.33	17.08	7.94
4f	50.95	3.63	14.86	6.80
	51.05	3.55	14.97	6.87
4g	49.89	3.31	15.31	7.01
	49.77	3.19	15.20	6.89
4h	49.24	4.57	15.11	6.92
	49.30	4.50	14.99	7.00

4i	44.01	3.69	17.11	7.83
	43.89	3.58	16.98	7.72
4j	45.60	3.59	16.62	7.61
	45.67	3.50	16.49	7.54
4k	53.92	4.30	9.43	14.39
	53.81	4.38	9.34	14.50
4l	52.89	3.97	9.74	14.86
	52.99	3.88	9.81	14.94
4m	46.99	4.47	10.96	16.72
	47.09	4.54	10.88	16.83
4n	48.60	4.33	10.63	16.22
	48.69	4.24	10.72	16.33
4o	54.89	4.61	9.14	13.96
	55.01	4.50	9.26	13.84
4p	53.92	4.30	9.43	14.39
	54.02	4.43	9.52	14.51
4q	48.35	4.82	10.57	16.13
	48.47	4.90	10.47	16.25
4r	49.86	4.68	10.26	15.66
	49.75	4.80	10.37	15.76

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2 *Figure 1*

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4 *Figure 2*

2 *Figure 3* 4 *Figure 4*

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3 *Figure 5*

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6 *Figure 6*

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2 *Scheme 1* **1,3:** Ar = Ph.**a**, R = C₆H₅; **b**, R = C₂H₅; **c**, R = CH₂=CH-CH₂ [33]

Previous work, of hydrazinecarbothioamides 1a-c with dimethyl acetylenedicarboxylate 2a [33].

1d-l: Ar = 2,4-di-NO₂-C₆H₃, (**d**, R = PhCH₂; **e**, R = Ph; **f**, R = Cyclohexyl;**g**, R = Ethyl; **h**, R = Allyl).Ar = *p*-CH₃-C₆H₄SO₂, (**i**, R = CH₂Ph; **j**, R = Ethyl; **k**, R = Allyl; **l**, R = Ph)

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Reaction of hydrazinecarbothioamides 1d-l with dialkyl acetylenedicarboxylates

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5 *Scheme 2*

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1 Graphical abstract

18 examples

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