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Synthesis of 5-substituted 2-ylidene-1,3-thiazolidin-4-one derivatives and evaluation of their anticancer and antioxidant activities

Khaled F. Saied[1]*, Kamal A. Kandeel[2], Salwa S. Abdelwahab[3], Osama M. Ahmed[4]

[1] *Department of Basic Science, Faculty of Oral and Dental Medicine, Nahda University, Beni-Suef 62511, Egypt; e-mail: fathykhaled905_7@yahoo.com*

[2] *Department of Chemistry, Faculty of Science, Ain Shams University, Abbassia, Cairo 11566, Egypt; e-mail: kamalkandeel@hotmail.com*

[3] *Faculty of Pharmaceutical Sciences and Pharmaceutical Industries, Future University in Egypt, New Cairo 11835, Egypt; e-mail: salwa_elsayed@yamil.com*

[4] *Department of Zoology, Faculty of Science, Beni-Suef University, Beni-Suef 62511, Egypt; e-mail: osamamoha@yahoo.com*

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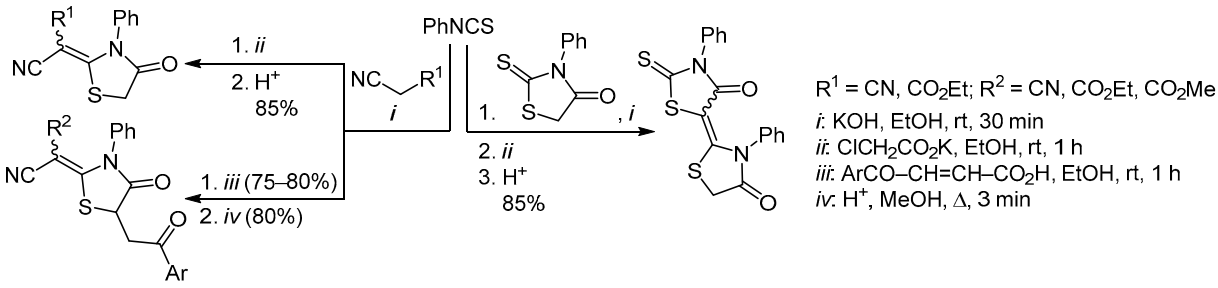


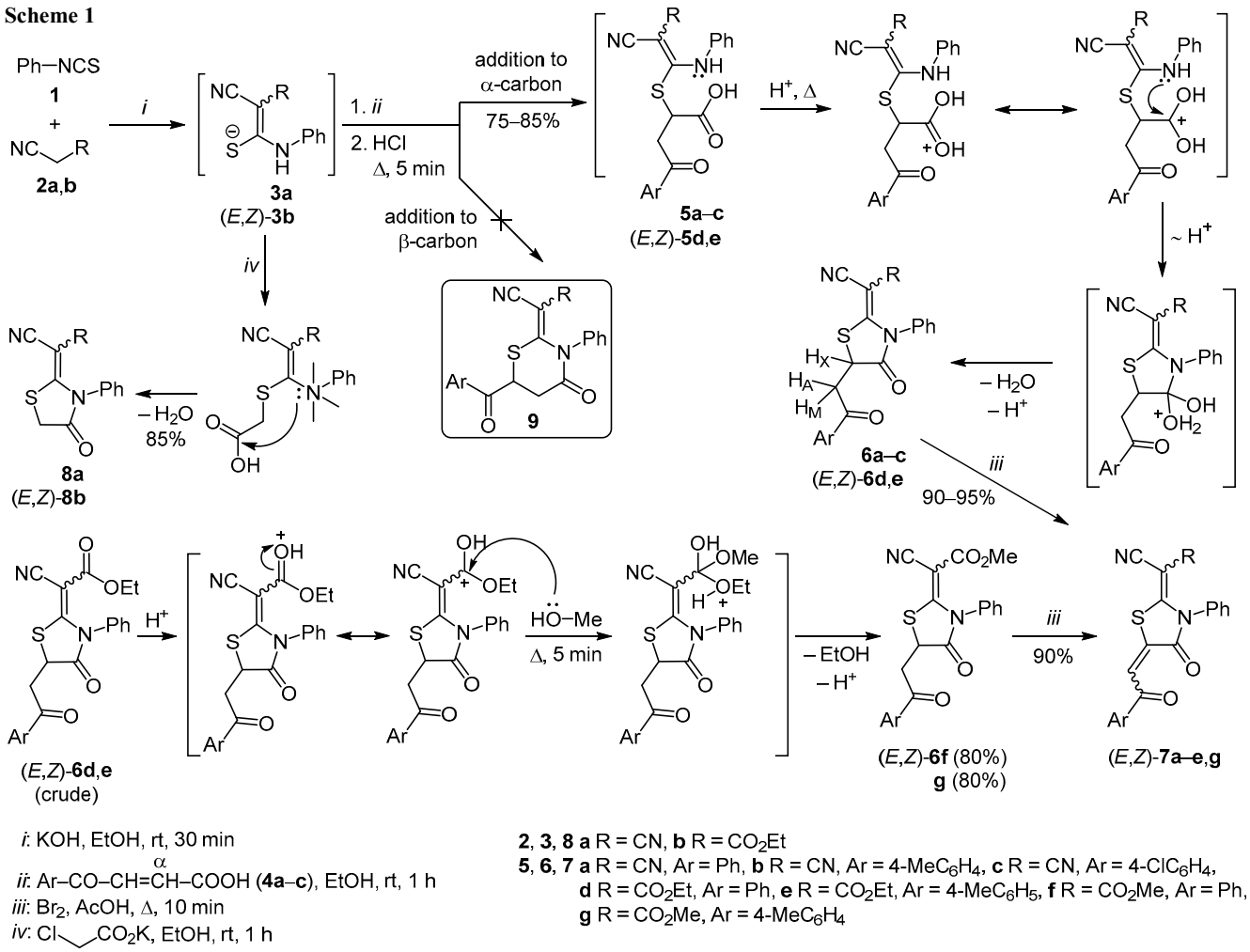
Novel 5-(aroyl)methyl- and 5-(aroyl)methylen-2-ylidene-1,3-thiazolidin-4-ones have been prepared in high yields using ketene *N*,*S*-acetal salts, obtained from phenyl isothiocyanate and propanedinitrile or ethyl cyanoacetate. Several of the newly synthesized 1,3-thiazolidin-4-one derivatives demonstrate high antioxidant and anticancer activities.

Keywords: ketene *N*,*S*-acetal, malononitrile, phenyl isothiocyanate, 1,3-thiazolidin-4-one, anticancer activity, antioxidant activity, cyclocondensation, transesterification.

Derivatives of 1,3-thiazolidin-4-one bearing thioxo, oxo, or imino group at C-2 atom are important compounds that exhibit antimicrobial,[1] antischistosomal,[2] and antitumor[3] properties and act as inhibitors of HIV-1 integrase.[4] In addition, 2- or 5-ylidene-1,3-thiazolidin-4-ones have also attracted increased interest due to their enhanced biological activity.[2,3,5] In this regard, ketene *N*,*S*-acetals, obtained by reaction of alkyl or aryl isothiocyanates and active methylene compounds, are valuable precursors of various heterocyclic compounds, including 2-ylidene-1,3-thiazolidin-4-ones.[6] Herein, we report the synthesis of novel 5-substituted 2-ylidene-1,3-thiazolidin-4-ones from ketene *N*,*S*-acetals. Anticancer and antioxidant activities of the obtained 1,3-thiazolidin-4-one derivatives have been demonstrated.

The synthesis of 5-substituted 2-ylidene-1,3-thiazolidin-4-ones commenced with KOH-promoted reaction of phenyl isothiocyanate (**1**) and propanedinitrile (**2a**) or ethyl cyanoacetate (**2b**) in EtOH. As expected,[1,6,7] nucleophilic addition of the *in situ* formed ketene *N*,*S*-acetal salts **3a**,**b** to the α-carbon of 4-phenyl-, 4-(4-methylphenyl)-, and 4-(4-chlorophenyl)-4-oxobut-2-enoic acids **4a**–**c**[8] led to formation of intermediates **5a**–**e**. Further acid-catalyzed cyclocondensation of adducts **5a**–**e** afforded 5-substituted 2-ylidene-1,3-thiazolidin-4-ones **6a**–**e**. In case of ketene *N*,*S*-acetal salt **3a**, obtained from propanedinitrile (**2a**), reaction in refluxing concd HCl provided [5-(2-aryl-2-oxoethyl)-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene]propanedinitriles **6a**–**c** as white solids, whereas similar reaction of ketene *N*,*S*-acetal salt **3b**, derived from ethyl cyanoacetate (**2b**), led to formation of ethyl (2*E*,2*Z*)-[5-(2-aryl-2-oxoethyl)-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene](cyano)-ethanoates **6d**,**e** that were isolated by extraction with PhMe as viscous oils. However, purification by refluxing products (*E*,*Z*)-**6d**,**e** in MeOH afforded the respective methyl esters (*E*,*Z*)-**6f**,**g** as white waxy solids. Most likely, suitable

Scheme 1



i: KOH, EtOH, rt, 30 min

α

ii: Ar–CO–CH=CH–COOH (**4a**–**c**), EtOH, rt, 1 h

iii: Br_2, AcOH, Δ, 10 min

iv: Cl–CH_2CO_2K, EtOH, rt, 1 h

2, **3**, **8** **a** R = CN, **b** R = CO_2Et

5, **6**, **7** **a** R = CN, Ar = Ph, **b** R = CN, Ar = 4-MeC_6H_4, **c** R = CN, Ar = 4-ClC_6H_4, **d** R = CO_2Et, Ar = Ph, **e** R = CO_2Et, Ar = 4-MeC_6H_5, **f** R = CO_2Me, Ar = Ph, **g** R = CO_2Me, Ar = 4-MeC_6H_4

conditions for this transesterification[9] were ensured by the acid contamination of crude ethyl esters (*E*,*Z*)-**6d**,**e** (Scheme 1).

IR spectra of compounds **6a**–**g** revealed characteristic absorption bands of C≡N group at 2210–2215 cm^{-1} and two (compounds **6a**–**c**) or three (compounds **6d**–**g**) C=O groups at 1663–1747 cm^{-1}. ^1H NMR spectra of 5-substituted 2-ylidene-1,3-thiazolidin-4-ones **6a**–**g** contained the expected signals of protons of $CHCH_2C(O)Ar$ group with AMX splitting pattern.[1a,2] For products (*E*,*Z*)-**6d**,**e**, signals of protons of OCH_2CH_3 group were observed as triplets at 1.18 and 1.17 ppm and multiplets at 4.13–4.20 and 3.93–4.19 ppm, respectively. Similarly, formation of methyl esters (*E*,*Z*)-**6f**,**g** was confirmed by a singlet at 3.70 ppm corresponding to the protons of CO_2CH_3 group. In addition, ^{13}C NMR spectrum of product **6g** contained two signals of C≡N group and two signals of OCH_3 group. This may be explained by the formation of a mixture of *E*- and *Z*-isomers of compound **6e** that was further converted into the respective methyl ester (*E*,*Z*)-**6g** and deshielding of the carbon atom of methyl group in compound (*E*)-**6g** by the phenyl substituent at nitrogen atom. For the same reason, ^{13}C NMR chemical shift of the signal of one C≡N group in propanedinitriles **6a**–**c** was observed in lower field than chemical shift corresponding to the signal of other C≡N group. Finally, mass spectra of 2-ylidene-1,3-thiazolidin-4-ones **6a**–**g**, containing signals with *m*/*z* values of the respective molecular ions, were in agreement with the proposed structures of products.

The synthesized novel 5-substituted 2-ylidene-1,3-thiazolidin-4-ones **6a**–**e**,**g** were further treated with Br_2 in refluxing AcOH[7,10] and converted into the respective (*E*,*Z*)-2,5-diylidene-1,3-thiazolidin-4-ones **7a**–**e**,**g** (Scheme 1). Structures of compounds **7a**–**e**,**g** were confirmed by IR and ^1H and ^{13}C NMR spectroscopy. Due to the conjugation with the newly formed C=C bond, IR absorption bands of 1,3-thiazolidin-4-one and aroyl C=O groups of products **6a**–**e**,**g** were shifted to longer wavelengths, for example, from 1739 and 1671 (compound **6a**) to 1731 and 1640 cm^{-1} (compound **7a**). According to ^1H NMR spectra, olefinic proton was observed as a singlet equivalent to one proton and C=C bond at C-5 atom of products **7a**–**e**,**g**, most likely, possessed *Z*-configuration. Such assignment was proposed by comparing chemical shift of this signal (8.20–8.46 ppm) with the corresponding chemical shifts of *E*- and Z-isomers (7.82–7.85 and 7.93–8.03 ppm, respectively) of 1,3-thiazolidin-4-ones.[7]

Furthermore, (4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene)-propanedinitrile (**8a**) and ethyl (2*E*,2*Z*)-cyano(4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene)ethanoate (**8b**) were

prepared by reaction of ketene *N*,*S*-acetal salts **3a**,**b** and potassium 2-chloroacetate[11] (Scheme 1). Structures of products **8a**,**b** were substantiated by comparing their melting points and R_f values with samples synthesized according to previously reported procedure.[6b] In addition, structure of compound **8a** was also confirmed by ^{1}H NMR spectroscopy and mass spectrometry.

In continuation of this study, condensation of (oxo)-phenylacetaldehyde and propanedinitrile **8a** or ethyl acetate (*E*,*Z*)-**8b** was carried out according to previously reported procedure.[12] Synthesis of compounds (*E*,*Z*)-**7a**,**d** allowed to compare their structure to the same products, obtained *via* addition of ketene *N*,*S*-acetal salts **3a**,**b** to 4-oxo-4-phenylbut-2-enoic acid (**4a**). Moreover, structures of compounds **6a**,**d** and (*E*,*Z*)-**7a**,**d** were thoroughly evidenced when (*E*,*Z*)-2,5-diylidene-1,3-thiazolidin-4-ones **7a**,**d** were converted into the respective 5-substituted 2-ylidene-1,3-thiazolidin-4-ones **6a**,**d** by regioselective hydrogenation of C=C bond at the C-5 atom using Zn in AcOH[13] (Scheme 2). Such chemical transformations allowed to rule out the possible addition of ketene *N*,*S*-acetal salts **3a**,**b** at β-carbon of 4-oxobut-2-enoic acids **4a**–**c** and formation of 1,3-thiazinan-2-ylidene derivatives **9** (Scheme 1). Compounds **6a**,**d** and (*E*,*Z*)-**7a**,**d**, synthesized from starting materials **8a**,**b**, were characterized by ^{1}H NMR spectroscopic data that were in agreement with the respective data for products **6a**,**d** and (*E*,*Z*)-**7a**,**d**, obtained from ketene *N*,*S*-acetal salts **3a**,**b** and 4-phenyl-4-oxobut-2-enoic acid (**4a**). The structure of slightly soluble in DMSO-d_6 (*E*,*Z*)-2,5-diylidene-1,3-thiazolidin-4-one **7a** was also confirmed by ^{13}C NMR spectroscopy.

Furthermore, bromination of propanedinitrile **8a** and ethyl acetate (*E*,*Z*)-**8b** in refluxing AcOH according to previously reported method,[10b] afforded the respective 5-bromo-1,3-thiazolidin-4-ones **10a**,**b**. Refluxing of compounds **10a**,**b** and KSCN in EtOH or AcOH promoted dimerization of starting materials **10a**,**b** leading to 5,5'-bithiazolylidenes (*E*,*Z*)-**11a**,**b**. Products (*E*,*Z*)-**11a**,**b** were also obtained from 5-bromo-1,3-thiazolidin-4-ones **10a**,**b** when KSCN was replaced with NaOCN or NaOAc. However, 5-(benzylamino)-1,3-thiazolidin-4-one **12** was successfully synthesized by treatment of benzylamine solution in Et_2O with a solution of compound **10a** in EtOAc (Scheme 2).

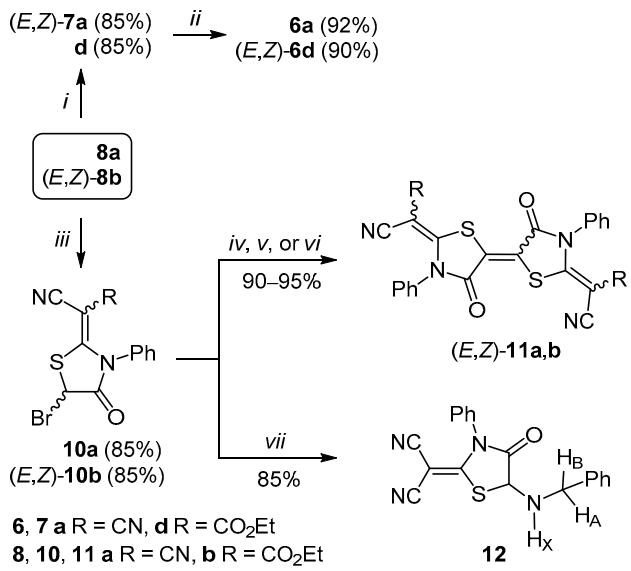
Structures of compounds **10a**,**b**, (*E*,*Z*)-**11a**,**b**, and **12** were established by IR and ^{1}H NMR spectroscopy and mass spectrometry. In addition, structures of 1,3-thiazolidin-4-ones (*E*,*Z*)-**10b** and **12** were also confirmed by ^{13}C NMR spectroscopy. The ^{13}C NMR spectrum of compound (*E*,*Z*)-**10b** revealed the expected number of carbon atoms for each of *E*- and *Z*-isomer.

Conversion of 5-bromo-1,3-thiazolidin-4-ones **10a**,**b** into the respective dimers (*E*,*Z*)-**11a**,**b**, most likely, occurs in a similar way as the dimerization of 5-bromo-1,3-thiazolidin-4-ones under treatment with Et_3N. The mechanism of this transformation has been suggested to proceed *via* formation of 1,3-thiazolidin-4-one-based carbanion or carbene.[14] However, there is still lack of evidence to confirm the most plausible reaction pathway.

The ^{1}H NMR spectrum of compound **12** showed ABq splitting pattern of the signals of NCH_2 protons at 4.23 and 4.33 ppm. The magnetic inequivalence of these protons was interpreted based on the chirality of the nitrogen atom.[15] Further splitting of the signals of NCH_2 protons was ensured by additional coupling with NH proton, which, on the other hand, was observed as a triplet. This rationalization was supported by the COSY spectrum of 5-(benzylamino)-1,3-thiazolidin-4-one **12** (Fig. 1).

In addition to (*E*,*Z*)-2,5-diylidene-1,3-thiazolidin-4-ones **7a**–**e**,**g**, synthesis of compound (*E*,*Z*)-**7h** from (4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene)propanedinitrile (**8a**) was also demonstrated. In this case, starting material **8a** was prepared by reaction of phenyl isothiocyanate (**1**), obtained *in situ* by decomposition of ammonium phenylcarbamodithioate (**13**), and propanedinitrile (**2a**). Subsequent condensation of compound **8a** and 4-methoxybenzaldehyde afforded (*E*,*Z*)-2,5-diylidene-1,3-thiazolidin-4-one **7h** in 90% yield (Scheme 3). The structure of product (*E*,*Z*)-**7h** was established by comparing its melting point and ^{1}H NMR spectroscopic data with previously reported

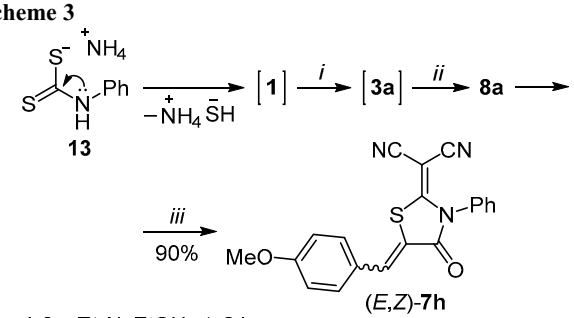
Scheme 2



6, **7 a** R = CN, **d** R = CO_2Et
8, **10**, **11 a** R = CN, **b** R = CO_2Et

i: PhCOCHO, NaOAc, AcOH, Δ, 20 min
ii: Zn, AcOH, Δ, 3 min; *iii*: Br_2, AcOH, Δ, 10 min
iv: KSCN, AcOH or EtOH, Δ, 10 min
v: NaOCN, AcOH or EtOH, Δ, 10 min
vi: NaOAc, AcOH or EtOH, Δ, 10 min
vii: $PhCH_2NH_2$, EtOAc–Et_2O, rt, 12 h

Scheme 3



i: **2a**, Et_3N, EtOH, rt, 2 h
ii: $ClCH_2CO_2H$, AcOH, 80°C, 30 min
iii: 4-$MeOC_6H_4CHO$, NaOAc, AcOH, Δ, 30 min

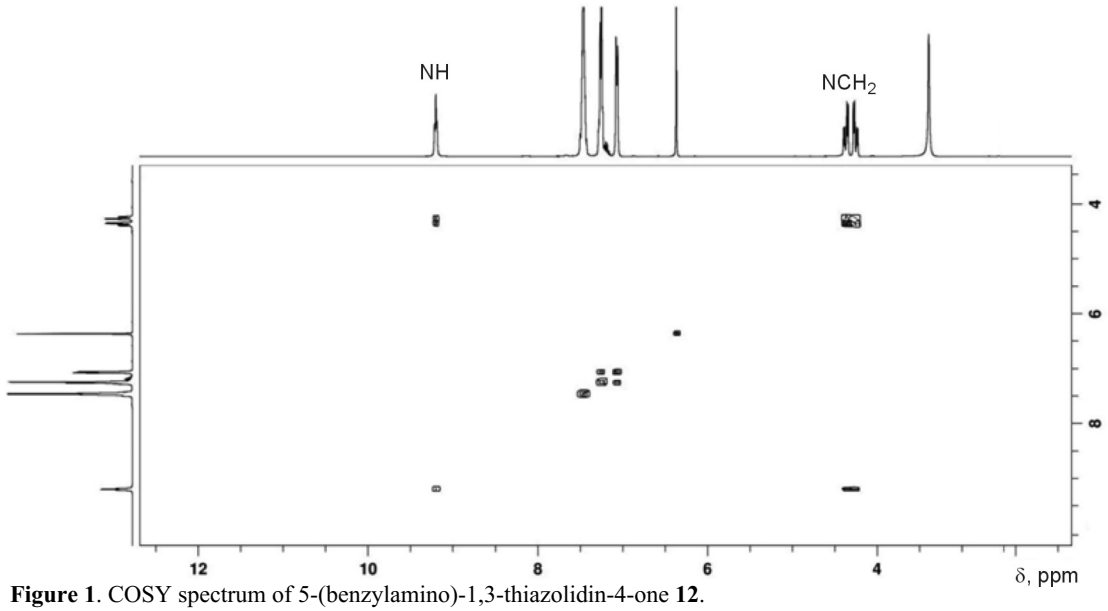


Figure 1. COSY spectrum of 5-(benzylamino)-1,3-thiazolidin-4-one **12**.

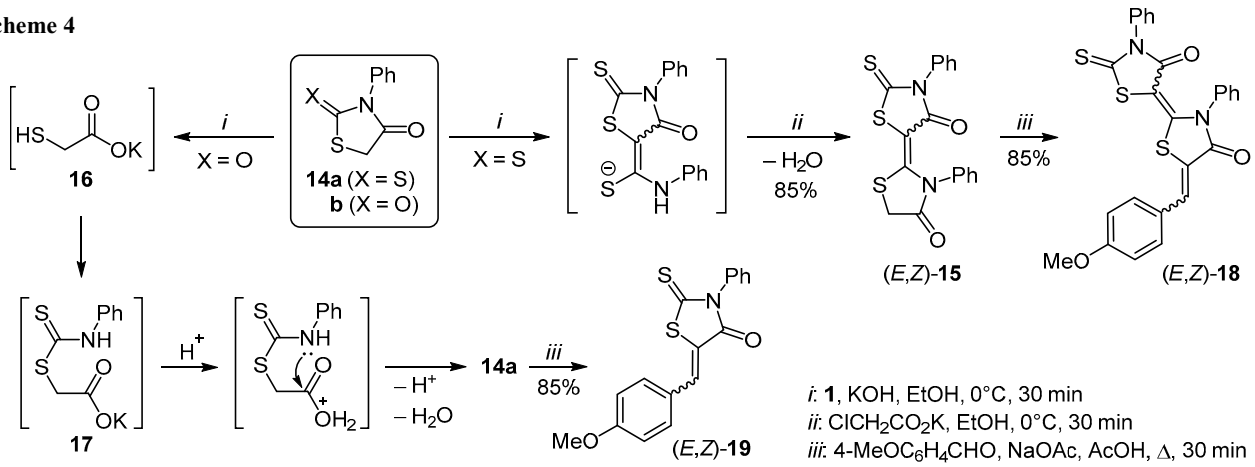
data.[6b] The ^{1}H NMR spectrum of compound (*E*,*Z*)-**7h** contained two singlets at 7.49 and 8.01 ppm in a ratio of 5:95 related to olefinic proton. Most likely, formation of (*Z*)-2,5-diylidene-1,3-thiazolidin-4-one **7h** is more preferred, since the olefinic proton is more deshielded by 4-oxo group than in the case of *E*-isomer.[7]

As described for propanedinitrile (**2a**), 3-phenyl-2-thioxo-1,3-thiazolidin-4-one (**14a**)[10b,16] and 3-phenyl-1,3-thiazolidine-2,4-dione (**14b**)[17] were also separately used in reactions with phenyl isothiocyanate (**1**), followed by treatment with potassium chloroacetate. Application of starting material **14a** provided (*E*,*Z*)-5-(4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene)-3-phenyl-2-thioxo-1,3-thiazolidin-4-one (**15**), while similar reaction of compound **14b** produced 2-thioxo-1,3-thiazolidin-4-one **14a**. Most likely, KOH-promoted cleavage of dione **14b** produced potassium sulfanylacetate (**16**),[14b] which reacted with phenyl isothiocyanate (**1**) to form intermediate **17**. Further cyclocondensation[18] of intermediate **17** under acidic conditions afforded 3-phenyl-2-thioxo-1,3-thiazolidin-4-one (**14a**) (Scheme 4). The IR spectrum of compound (*E*,*Z*)-**15** exhibited two absorption bands of C=O groups at 1671 and 1731 cm^{-1}, and the respective ^{1}H NMR spectrum contained signals of aliphatic and aromatic protons in a ratio of 1:5. Moreover, the mass spectrum of product (*E*,*Z*)-**15** displayed a molecular ion peak with *m*/*z* 384 and a base peak at *m*/*z* 80 corresponding to 3-isocyanatocycloprop-1-enyl cation.

Finally, condensation of 4-methoxybenzaldehyde and compound (*E*,*Z*)-**15** or **14a** (obtained from starting material **14b**) under previously reported conditions[7,12] afforded (*E*,*Z*)-2,5-diylidene-1,3-thiazolidin-4-one **18** and (*E*,*Z*)-5-(4-methoxybenzylidene)-3-phenyl-2-thioxo-1,3-thiazolidin-4-one (**19**),[19] respectively (Scheme 4). In addition to the multiplet representing ten protons of phenyl substituents, ^{1}H NMR spectrum of product (*E*,*Z*)-**18** exhibited two doublets at 7.16 and 7.29 ppm relating to protons of 4-methoxyphenyl substituent. Moreover, signal of protons of OCH_3 group was observed as a singlet at 3.85 ppm.

Products **6b**–**d**,**g**, (*E*,*Z*)-**7c**,**g**, and (*E*,*Z*)-**10b** were selected as test compounds for evaluation of antitumor and antioxidant activities of the synthesized 5-substituted 2-ylidene-1,3-thiazolidin-4-ones following previously reported procedures.[20] Glutathione was applied as a standard, and antioxidant activity was determined using

Scheme 4



solutions of the test compounds in EtOH with concentrations 0.25, 0.5, and 1.0 mg/ml (Table 1). The 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity (RSA) was calculated according to equation:

$$RSA = [(A_{control} - A_{sample})/A_{control}] \times 100\%,$$

where $A_{control}$ – absorbance of DPPH radical in EtOH, A_{sample} – absorbance of DPPH radical and test compound in EtOH.

All tested 1,3-thiazolidin-4-one derivatives exhibited antioxidant activity. 5-Substituted 2-ylidene-1,3-thiazolidin-4-one **6b** showed the highest antioxidant activity at concentration 1.0 mg/ml, whereas compound **6c** – at concentrations 0.25 and 0.5 mg/ml. At all applied concentrations, {5-[2-(4-methylphenyl)-2-oxoethyl]-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene}propanedinitrile (**6b**) was more effective in scavenging free radicals than glutathione. Compound **6c** demonstrated higher activity than glutathione at concentrations 0.25 and 0.5 mg/ml. Furthermore, 5-substituted 2-ylidene-1,3-thiazolidin-4-ones **6d**,**g** also possessed high RSA at all tested concentrations. Compound **6g** exhibited lower antioxidant activity than glutathione. However, RSA of 1,3-thiazolidin-4-one derivative **6d** at concentration 0.25 mg/ml was higher than the RSA of glutathione. Compounds (*E*,*Z*)-**7c**,**g** and (*E*,*Z*)-**10b** demonstrated moderate antioxidant activity, and the least active was 5-substituted 2-ylidene-1,3-thiazolidin-4-one (*E*,*Z*)-**7g**.

Antitumor activity of 5-substituted 2-ylidene-1,3-thiazolidin-4-ones **6b**–**d**,**g**, (*E*,*Z*)-**7c**,**g**, and (*E*,*Z*)-**10b** was compared with the activity of reference drug doxorubicin. The test compounds demonstrated antiproliferative effect on breast carcinoma cell line MDA-MB-231 and ensured gradual decrease in the survival percentage of cells MDA-MB-231, as the concentration of 1,3-thiazolidin-4-one derivatives increased from 0 to 100 μg/ml. Antitumor activity of all tested compounds increased according to the following order: compounds **6c**, (*E*,*Z*)-**7c**, **6b**, (*E*,*Z*)-**7g**, **6g**, (*E*,*Z*)-**10b**, **6d**, doxorubicin with the respective half maximal inhibitory concentration (IC_{50}) values 90, 83, 74, 54.4, 53.7, 45, 44, and 10 μg/ml (Fig. 2).

Table 1. DPPH radical scavenging activity (%) of glutathione and compounds **6b**–**d**,**g**, (*E*,*Z*)-**7c**,**g**, and (*E*,*Z*)-**10b**

Compound	Concentration*, mg/ml		
	0.25	0.5	1.0
6b	83.7 ± 0.1	88.2 ± 0.1	90.76 ± 0.07
6c	88.73 ± 0.04	86.7 ± 0.2	82.6 ± 0.2
6d	71.3 ± 0.2	74.4 ± 0.1	80.4 ± 0.1
6g	67.4 ± 0.2	72.0 ± 1.0	74.7 ± 0.6
(*E*,*Z*)-**7c**	41.5 ± 0.5	38.8 ± 0.1	41.9 ± 0.1
(*E*,*Z*)-**7g**	26.0 ± 0.2	22.9 ± 0.2	40.3 ± 0.3
(*E*,*Z*)-**10b**	35.1 ± 0.3	44.8 ± 1.0	58.2 ± 0.1
Glutathione	67.4 ± 0.9	85.6 ± 0.7	88.1 ± 0.7

* Solutions of glutathione and test compounds in EtOH.

Thus, the highest antitumor activity against cell line MDA-MB-231 exhibited by 5-substituted 2-ylidene-1,3-thiazolidin-4-ones **6d** and (*E*,*Z*)-**10b**, whereas the lowest activity by compound **6c**.

In conclusion, synthesis of novel 5-(aroyl)methyl- and 5-(aroyl)methylen-2-ylidene-1,3-thiazolidin-4-ones has been demonstrated. All tested compounds exhibited antioxidant and anticancer activities. The highest antioxidant activity was exhibited by {5-[2-(4-methylphenyl)-2-oxoethyl]-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene}- and {5-[2-(4-chlorophenyl)-2-oxoethyl]-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene}-propanedinitriles, the first one being more active than the applied standard antioxidant glutathione. Among the evaluated 1,3-thiazolidin-4-one derivatives, ethyl (2*E*,2*Z*)-cyano[4-oxo-5-(2-oxo-2-phenylethyl)-3-phenyl-1,3-thiazolidin-2-ylidene]ethanoate and ethyl (2*E*,2*Z*)-(5-bromo-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene)(cyano)ethanoate have the most potent antitumor properties. However, their antitumor activity is lower than that of doxorubicin. To propose a possible mechanism of action, further *in vitro* and *in vivo* studies of 5-substituted 1,3-thiazolidin-4-ones with the highest antioxidant and antitumor activities will be conducted.

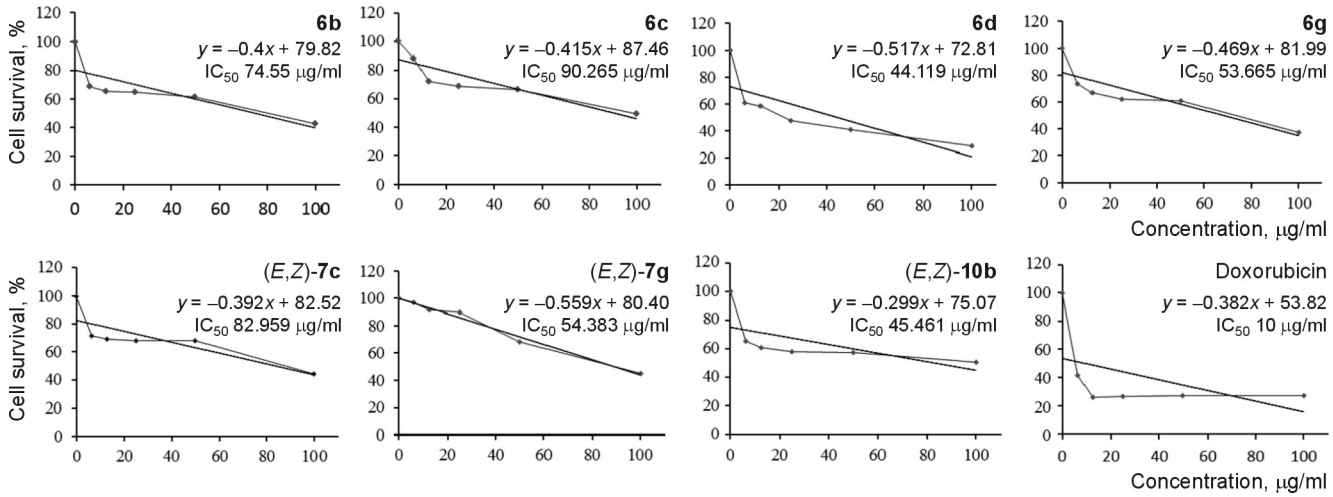


Figure 2. Antiproliferative effect of 5-substituted 2-ylidene-1,3-thiazolidin-4-ones **6b**–**d**,**g**, (*E*,*Z*)-**7c**,**g**, and (*E*,*Z*)-**10b** and reference drug doxorubicin on breast carcinoma cell line MDA-MB-231.

Experimental

IR spectra were recorded on a PerkinElmer 1600 FT-IR spectrometer using KBr pellets. ^{1}H and ^{13}C NMR spectra were acquired on Varian Mercury 300 (300 MHz (compounds **6b**–**g**, (*E*,*Z*)-**7b**–**e**,**g**,**h**, **8a**, **10a**,**b**, (*E*,*Z*)-**11a**,**b**, **12**, **14a**, (*E*,*Z*)-**15**, (*E*,*Z*)-**18**, (*E*,*Z*)-**19**) and 75 MHz (compounds **6a**,**g**), respectively) and Bruker Avance FT-NMR 400 (400 MHz (compounds **6a**, (*E*,*Z*)-**7a**) and 100 MHz (compounds **6b**–**e**, (*E*,*Z*)-**7a**, (*E*,*Z*)-**10b**, **12**, **15**), respectively) spectrometers in DMSO-d_6 or $CDCl_3$ (^{1}H NMR spectra of compounds **10a**,**b**) using TMS as internal standard. COSY spectrum of compound **12** was recorded on a Bruker Avance FT-NMR 400 (400 MHz) spectrometer. ^{13}C NMR spectra of compounds (*E*,*Z*)-**7c**, (*E*,*Z*)-**11a**,**b**, and (*E*,*Z*)-**18** were not obtained due to their negligible solubility in DMSO-d_6. Mass spectra were recorded on a Shimadzu GCMS-QP2010 Plus spectrometer (EI, 70 eV). Elemental analyses were performed on a Vario EL III elemental analyzer. Melting points were determined on a GallenKamp melting point apparatus and are uncorrected.

4-Aryl-4-oxobut-2-enoic acids **4a**–**c**,[8] 3-phenyl-2-thioxo-1,3-thiazolidin-4-one (**14a**),[10b,16] and 3-phenyl-1,3-thiazolidine-2,4-dione (**14b**)[17] were synthesized according to previously reported procedures. Antioxidant and antitumor activity assays were carried out according to previously reported methods.[20]

Synthesis of [5-(2-aryl-2-oxoethyl)-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene]propanedinitriles and -ethanoates 6a–g (General method). Propanedinitrile (**2a**) (0.66 g, 10 mmol) or ethyl cyanoacetate (**2b**) (1.1 ml, 10 mmol) was added to a solution of KOH (0.57 g, 10 mmol) and phenyl isothiocyanate (**1**) (1.2 ml, 10 mmol) in 95% EtOH (40 ml). The reaction mixture was stirred at room temperature for 30 min. 4-Aryl-4-oxobut-2-enoic acid **4a**–**c** (10 mmol) was then added, and stirring at room temperature was continued for 1 h. The mixture was poured into concd HCl (30 ml) and refluxed for 5 min. Solid products **6a**–**c** were filtered off, washed with H_2O (3×20 ml), air-dried, and crystallized from 1,4-dioxane–PhMe, 2:3. Purification method I. Oily residue, containing product **6d**,**e**, was extracted with PhMe (2×50 ml). The combined organic layers were dried over anhydrous $CaCl_2$, concentrated under reduced pressure to 15 ml, triturated with petroleum ether (5 ml), and kept at room temperature for 12 h. The obtained crystals were filtered off, air-dried, and crystallized from PhMe – petroleum ether, 3:2.

Purification method II. Oily residue, containing product **6d**,**e**, was decanted, dissolved in MeOH (20 ml), and refluxed for 3 min. The obtained solid product **6f**,**g** was filtered off, washed with H_2O (3×20 ml), air-dried, and crystallized from PhMe – petroleum ether, 3:2.

[4-Oxo-5-(2-oxo-2-phenylethyl)-3-phenyl-1,3-thiazolidin-2-ylidene]propanedinitrile (6a). Yield 2.90 g (80%), white crystals, mp 226–238°C. IR spectrum, ν, cm^{-1}: 3064 (=C–H), 2930 (C–H), 2215 (C≡N), 1739 (C=O), 1671 (C=O), 727 and 689 (C–H Ph). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.03 (2H, d, *J* = 7.2, H-2,6); 7.72 (1H, t, *J* = 8.0, H-4); 7.61–7.51 (7H, m, NPh, H-3,5); 4.97 (1H, dd, J_{AX} = 8.4, J_{MX} = 3.6, 5-CH$_X$); 4.28 (1H, dd, J_{AM} = 18.9, J_{MX} = 3.6, 1-CH$_M$); 4.02 (1H, dd, J_{AM} = 18.9, J_{AX} = 8.4, 1-CH$_A$). ^{13}C NMR spectrum, δ, ppm: 40.8; 43.6; 53.6 (=<u>C</u>(CN)$_2$); 109.8 (C≡N); 114.1 (C≡N); 128.2 (2C); 128.8; 128.9 (2C); 129.1; 129.6 (2C); 131.1; 133.4; 134.1; 135.1; 174.0; 174.6; 197.0 (C=O ketone). Mass spectrum, *m*/*z* (I_{rel}, %): 359 [M]$^+$ (30), 254 [M−PhCO]$^+$ (19), 226 [M−PhCO−CO]$^+$ (29), 105 [PhC≡O]$^+$ (100), 77 [Ph]$^+$ (93). Found, %: C 66.79; H 3.67; N 11.72. $C_{20}H_{13}N_3O_2S$. Calculated, %: C 66.84; H 3.65; N 11.69.

{5-[2-(4-Methylphenyl)-2-oxoethyl]-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene}propanedinitrile (6b). Yield 3.20 g (85%), white crystals, mp 255–257°C. IR spectrum, ν, cm^{-1}: 3061 (=C–H), 2922 (C–H), 2215 (C≡N), 1737 (C=O), 1669 (C=O), 813 (C–H Ar), 743 and 691 (C–H Ph). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.92 (2H, d, *J*= 8.1, H-2,6); 7.60–7.46 (5H, m, H Ph); 7.38 (2H, d, *J* = 8.1, H-3,5); 4.95 (1H, dd, J_{AX} = 8.4, J_{MX} = 3.6, 5-CH$_X$); 4.23 (1H, dd, J_{AM} = 18.9, J_{MX} = 3.6, 1-CH$_M$); 3.97 (1H, dd, J_{AM} = 18.9, J_{AX} = 8.4, 1-CH$_A$); 2.41 (3H, s, CH$_3$). ^{13}C NMR spectrum, δ, ppm: 21.7 (CH$_3$); 41.2; 44.2; 54.1 (=<u>C</u>(CN)$_2$); 110.4 (C≡N); 114.6 (C≡N); 128.8 (2C); 129.3; 129.6; 130.0 (3C); 130.1; 131.7; 133.2; 133.9; 145.3; 174.7; 175.2; 197.0 (C=O ketone). Mass spectrum, *m*/*z* (I_{rel}, %): 373 [M]$^+$ (13), 119 [4-MeC$_6$H$_4$C≡O]$^+$ (100), 91 [4-MeC$_6$H$_4$]$^+$ (40), 77 [Ph]$^+$ (13). Found, %: C 67.50; H 4.10; N 11.23. $C_{21}H_{15}N_3O_2S$. Calculated, %: C 67.54; H 4.05; N 11.25.

{5-[2-(4-Chlorophenyl)-2-oxoethyl]-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene}propanedinitrile (6c). Yield 3.35 g (85%), white crystals, mp 245–247°C. IR spectrum, ν, cm^{-1}: 3066 (=C–H), 2919 (C–H), 2213 (C≡N), 1736 (C=O), 1673 (C=O), 821 (C–H Ar), 733 and 690 (C–H Ph). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.03 (2H, dd, *J* = 8.4, *J* = 1.5, H-2,6); 7.67–7.49 (7H, m, H Ph, H-3,5); 4.96 (1H, dd, J_{AX} = 8.4, J_{MX} = 3.0, 5-CH$_X$); 4.27 (1H, dd, J_{AM} = 18.9, J_{MX} = 3.0, 1-CH$_M$); 3.99 (1H, dd, J_{AM} = 18.9, J_{AX} = 8.4, 1-CH$_A$). ^{13}C NMR spectrum, δ, ppm: 41.3; 44.1; 54.2 (=<u>C</u>(CN)$_2$); 110.4 (C≡N); 114.6 (C≡N); 129.3; 129.6 (3C); 130.1; 130.2; 130.6 (2C); 131.7; 133.9; 134.3; 139.6; 174.6; 175.1; 196.7 (C=O ketone). Mass spectrum, *m*/*z* (I_{rel}, %): 393 [M]$^+$ (44), 254 [M−4-ClC$_6$H$_4$CO]$^+$ (50), 139 [4-ClC$_6$H$_4$C≡O]$^+$ (100), 111 [4-ClC$_6$H$_4$]$^+$ (79), 77 [Ph]$^+$ (75), 64 [cycloC$_3$H$_2$CN]$^+$ (16). Found, %: C 61.02; H 3.19; N 10.87. $C_{20}H_{12}ClN_3O_2S$. Calculated, %: C 60.99; H 3.07; N 10.67.

Ethyl (2*E*,2*Z*)-cyano[4-oxo-5-(2-oxo-2-phenylethyl)-3-phenyl-1,3-thiazolidin-2-ylidene]ethanoate (6d). Yield 3.05 g (75%), white waxy flakes, mp 176–178°C. IR spectrum, ν, cm^{-1}: 3063 (=C–H), 2981 (C–H), 2210 (C≡N), 1747 (br, C=O), 1684 (br, C=O), 754 and 688 (C–H Ph). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.01 (2H d, *J* = 8.1, H-2,6); 7.72 (1H, t, *J* = 7.2, H-4); 7.59–7.44 (7H, m, H Ph, H-3,5); 4.62 (1H, dd, J_{AX} = 8.4, J_{MX} = 3.0, 5-CH$_X$); 4.20–4.13 (3H, m, OC<u>H</u>$_2$CH$_3$, 1-CH$_M$); 3.92 (1H, dd, J_{AM} = 18.9, J_{AX} = 8.4, 1-CH$_A$); ***E*-isomer** (50%): 1.178 (3H, t, *J* = 6.9, OCH$_2$C<u>H</u>$_3$); ***Z*-isomer** (50%): 1.175 (3H, t, *J* = 6.9, OCH$_2$C<u>H</u>$_3$). ^{13}C NMR spectrum, δ, ppm: 14.2 (OCH$_2$<u>C</u>H$_3$); 40.2; 41.5; 61.6 (O<u>C</u>H$_2$CH$_3$); 75.7 (=<u>C</u>CN);

112.6 (C≡N); 128.6 (2C); 129.4 (2C); 129.5; 129.8 (2C); 129.9; 131.0; 134.5; 135.5; 135.9; 165.4 (C=O ester); 172.3; 175.2; 197.5 (C=O ketone). Mass spectrum, *m/z* (I_{rel}, %): 406 $[M]^+$ (75), 273 $[M-PhCO-CO]^+$ (36), 255 $[M-PhCO-EtOH]^+$ (79), 105 $[PhC\equiv O]^+$ (66), 77 $[Ph]^+$ (100). Found, %: C 65.41; H 4.66; N 6.83. $C_{22}H_{18}N_2O_4S$. Calculated, %: C 65.01; H 4.46; N 6.89.

Ethyl (2*E*,2*Z*)-cyano{5-[2-(4-methylphenyl)-2-oxoethyl]-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene}ethanoate (6e). Yield 3.15 g (75%), white waxy flakes, mp 198–200°C. IR spectrum, ν, cm^{-1}: 3065 (=C–H), 2983 (C–H), 2930 (C–H), 2210 (C≡N), 1742 (C=O), 1689 (C=O), 1665 (C=O), 815 (C–H Ar), 760 and 701 (C–H Ph). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.90 (2H, d, *J* = 8.1, H-2,6); 7.55–7.43 (5H, m, H Ph); 7.37 (2H, d, *J* = 8.1, H-3,5); 4.59 (1H, dd, J_{AX} = 8.1, J_{MX} = 3.6, 5-CH_X); 4.19–3.93 (3H, m, OCH_2CH_3, 1-CH_M); 3.90 (1H, dd, J_{AM} = 18.9, J_{AX} = 8.4, 1-CH_A); 2.39 (3H, s, CH_3); ***E*-isomer** (50%): 1.174 (3H, t, *J* = 6.9, OCH_2CH_3); ***Z*-isomer** (50%): 1.171 (3H, t, *J* = 6.9, OCH_2CH_3). ^{13}C NMR spectrum, δ, ppm: 14.6 (OCH_2CH_3); 21.7 (CH_3); 41.3; 41.5; 61.6 (OCH_2CH_3); 76.6 (=CCN); 112.6 (C≡N); 128.8 (3C); 129.5; 129.8; 129.9 (3C); 131.0; 133.4; 135.5; 145.0; 165.5 (C=O ester); 172.3; 176.2; 197.0 (C=O ketone). Mass spectrum, *m/z* (I_{rel}, %): 420 $[M]^+$ (37), 301 $[M-4\text{-}MeC_6H_4CO]^+$ (67), 273 $[M-4\text{-}MeC_6H_4CO-CO]^+$ (69), 254 $[M-4\text{-}MeC_6H_4CO-S-CH_3]^+$ (100), 119 $[4\text{-}MeC_6H_4C\equiv O]^+$ (34), 91 $[4\text{-}MeC_6H_4]^+$ (97). Found, %: C 65.64; H 4.67; N 6.29. $C_{23}H_{20}N_2O_4S$. Calculated, %: C 65.70; H 4.79; N 6.66.

Methyl (2*E*,2*Z*)-cyano[4-oxo-5-(2-oxo-2-phenylethyl)-3-phenyl-1,3-thiazolidin-2-ylidene]ethanoate (6f). Yield 3.15 g (80%), white waxy flakes, mp 222–224°C. IR spectrum, ν, cm^{-1}: 3065 (=C–H), 2948 (C–H), 2214 (C≡N), 1741 (C=O), 1693 (C=O), 1672 (C=O), 755 and 688 (C–H Ar). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.01 (2H, d, *J* = 8.1, H-2,6); 7.72–7.45 (8H, m, H Ph, H-3,4,5); 4.63 (1H, dd, J_{AX} = 8.1, J_{MX} = 3.3, 5-CH_X); 4.18 (1H, dd, J_{AM} = 19.2, J_{MX} = 3.3, 1-CH_M); 3.92 (1H, dd, J_{AM} = 19.2, J_{AX} = 8.1, 1-CH_A); 3.70 (3H, s, CO_2CH_3). Mass spectrum, *m/z* (I_{rel}, %): 392 $[M]^+$ (30), 287 $[M-PhCO]^+$ (23), 255 $[M-PhCO-S]^+$ (55), 105 $[PhC\equiv O]^+$ (70), 80 $[cycloC_3H_2NCO]^+$ (94), 77 $[Ph]^+$ (100), 64 $[cycloC_3H_2CN]^+$ (53). Found, %: C 63.77; H 4.00; N 6.98. $C_{21}H_{16}N_2O_4S$. Calculated, %: C 64.27; H 4.11; N 7.14.

Methyl (2*E*,2*Z*)-cyano{5-[2-(4-methylphenyl)-2-oxoethyl]-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene}ethanoate (6g). Yield 3.25 g (80%), white waxy flakes, mp 202–204°C. IR spectrum, ν, cm^{-1}: 3069 (=C–H), 2986 (C–H), 2926 (C–H), 2211 (C≡N), 1742 (C=O), 1693 (C=O), 1663 (C=O), 815 (C–H Ar), 767 and 703 (C–H Ph). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.89 (2H, d, *J* = 7.5, H-2,6); 7.55–7.36 (7H, m, H Ph, H-3,5); 4.60 (1H, dd, J_{AX} = 8.1, J_{MX} = 3.0, 5-CH_X); 4.12 (1H, dd, J_{AM} = 19.2, J_{MX} = 3.0, 1-CH_M); 3.88 (1H, dd, J_{AM} = 19.2, J_{AX} = 8.1, 1-CH_A); 3.70 (3H, s, CO_2CH_3); 2.39 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 21.1 (CH_3); 40.1; 40.4; 52.3 (CO_2CH_3 *Z*-isomer); 61.1 (CO_2CH_3 *E*-isomer); 75.9 (=CCN); 112.1 (C≡N *E*-isomer); 120.7 (C≡N *Z*-isomer); 128.2 (3C); 128.9; 129.2 (2C); 129.4; 130.5; 133.0; 135.0 (2C); 144.5; 165.3 (C=O ester); 172.0; 175.6; 196.4 (C=O ketone). Mass spectrum, *m/z* (I_{rel}, %): 406 $[M]^+$ (7), 404 $[M-H_2]^+$ (14), 119 $[4\text{-}MeC_6H_4C\equiv O]^+$ (100), 91 $[4\text{-}MeC_6H_4]^+$ (42), 80 $[cycloC_3H_2NCO]^+$ (68), 64 $[cycloC_3H_2CN]^+$ (37). Found, %: C 65.29; H 4.76; N 6.73. $C_{22}H_{18}N_2O_4S$. Calculated, %: C 65.01; H 4.46; N 6.89.

Synthesis of [5-(2-aryl-2-oxoethylidene)-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene]propanedinitriles and -ethanoates (*E*,*Z*)-7a–e,g (General method).[7,10] A solution of Br_2 (0.3 ml, 6 mmol) in glacial AcOH (5 ml) was added portionwise to a stirred hot (100°C) solution of compound **6a**–**e**,**g** (5 mmol) in glacial AcOH (30 ml). The reaction mixture was refluxed for 10 min, then cooled to room temperature. The obtained solid was filtered off, washed with H_2O (3 × 30 ml), air-dried, and crystallized from 1,4-dioxane.

[(5*E*,5*Z*)-4-Oxo-5-(2-oxo-2-phenylethylidene)-3-phenyl-1,3-thiazolidin-2-ylidene]propanedinitrile (7a). Yield 1.60 g (90%), yellow crystals, mp 261–263°C. IR spectrum, ν, cm^{-1}: 3065 (=C–H), 2214 (C≡N), 1731 (C=O), 1640 (C=O), 733 and 693 (C–H Ph). Mass spectrum, *m/z* (I_{rel}, %): 357 $[M]^+$ (21), 190 $[M-PhNC=C(CN)_2]^+$ (23), 105 $[PhC\equiv O]^+$ (84), 80 $[cycloC_3H_2NCO]^+$ (94), 77 $[Ph]^+$ (100), 64 $[cycloC_3H_2CN]^+$ (34). Found, %: C 66.99; H 3.24; N 12.26. $C_{20}H_{11}N_3O_2S$. Calculated, %: C 67.22; H 3.10; N 11.76.

{(5*E*,5*Z*)-5-[2-(4-Methylphenyl)-2-oxo-ethylidene]-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene}propanedinitrile (7b). Yield 1.73 g (93%), yellow crystals, mp 252–254°C. IR spectrum, ν, cm^{-1}: 3064 (=C–H), 2215 (C≡N), 1730 (C=O), 1639 (C=O), 818 (C–H Ar), 740 and 688 (C–H Ph). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 8.43 (1H, s, =CH); 8.19 (2H, d, *J* = 8.1, H-2,6); 7.59 (5H, br. s, H Ph); 7.44 (2H, d, *J* = 8.1, H-3,5); 2.43 (3H, s, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 371 $[M]^+$ (25), 204 $[M-PhNC=C(CN)_2]^+$ (17), 119 $[4\text{-}MeC_6H_4C\equiv O]^+$ (100), 91 $[4\text{-}MeC_6H_4]^+$ (57), 80 $[cycloC_3H_2NCO]^+$ (59), 77 $[Ph]^+$ (32). Found, %: C 68.11; H 3.47; N 11.45. $C_{21}H_{13}N_3O_2S$. Calculated, %: C 67.91; H 3.53; N 11.31.

{(5*E*,5*Z*)-5-[2-(4-Chlorophenyl)-2-oxoethylidene]-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene}propanedinitrile (7c). Yield 1.86 g (95%), yellow crystals, mp 266–268°C. IR spectrum, ν, cm^{-1}: 3064 (=C–H), 2219 (C≡N), 1731 (C=O), 1639 (C=O), 833 (C–H Ar), 746 and 693 (C–H Ph). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.42 (1H, s, =CH); 8.29 (2H, d, *J* = 8.1, H-2,6); 8.13 (2H, d, *J* = 8.1, H-3,5); 7.60 (5H, br. s, H Ph). Mass spectrum, *m/z* (I_{rel}, %): 391 $[M]^+$ (12), 139 $[4\text{-}ClC_6H_4C\equiv O]^+$ (83), 111 $[4\text{-}ClC_6H_4]^+$ (74), 80 $[cycloC_3H_2NCO]^+$ (14), 77 $[Ph]^+$ (100), 64 $[cycloC_3H_2CN]^+$ (23). Found, %: C 61.33; H 2.59; N 10.82. $C_{20}H_{10}ClN_3O_2S$. Calculated, %: C 61.31; H 2.57; N 10.72.

Ethyl (2*E*,2*Z*)-cyano[(5*E*,5*Z*)-4-oxo-5-(2-oxo-2-phenylethylidene)-3-phenyl-1,3-thiazolidin-2-ylidene]ethanoate (7d). Yield 1.80 g (90%), pale-yellow crystals, mp 247–249°C. IR spectrum, ν, cm^{-1}: 3063 (=C–H), 2985 (C–H), 2214 (C≡N), 1732 (C=O), 1696 (C=O), 1642 (C=O), 726 and 695 (C–H Ph). ^{1}H NMR spectrum, δ, ppm: 8.23–8.21 (3H, m, H-2,6, =CH); 7.92–7.44 (8H, m, H Ph, H-3,4,5); 4.28–4.22 (2H, m, OCH_2CH_3); 1.26–1.19 (3H, m,

$OCH_2\underline{C}H_3$). ^{13}C NMR spectrum, δ, ppm: 14.5 ($OCH_2\underline{C}H_3$); 62.5 ($O\underline{C}H_2CH_3$); 80.3 (=$\underline{C}$CN); 112.0 (C≡N); 120.7 ($\underline{C}$H=C); 129.3 (2C); 129.7 (2C); 129.9 (4C); 131.4; 134.7; 135.0; 136.5; 140.5 (C-5); 164.5 (C=O ester); 166.1; 167.1; 189.4 (C=O ketone). Mass spectrum, *m*/*z* (I_{rel}, %): 404 $[M]^+$ (30), 331 $[M-CO_2Et]^+$ (67), 214 (26), 190 $[M-PhN=C=C(CN)CO_2Et]^+$ (26), 105 $[PhC\equiv O]^+$ (97), 77 $[Ph]^+$ (100). Found, %: C 65.01; H 3.89; N 7.11. $C_{22}H_{16}N_2O_4S$. Calculated, %: C 65.34; H 3.99; N 6.93.

Ethyl (2*E*,2*Z*)-cyano{(5*E*,5*Z*)-5-[2-(4-methylphenyl)-2-oxoethylidene]-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene}ethanoate (7e). Yield 2.00 g (95%), pale-yellow crystals, mp 260–262°C. IR spectrum, ν, cm^{-1}: 3063 (=C–H), 2985 (C–H), 2214 (C≡N), 1726 (C=O), 1697 (C=O), 1634 (C=O), 822 (C–H Ar), 748 and 691 (C–H Ph). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.20 (1H, s, =CH); 8.13 (2H, d, *J* = 8.1, H-2,6); 7.57–7.54 (5H, m, H Ph); 7.42 (2H, d, *J* = 8.1, H-3,5); 4.28–4.22 (2H, m, $OC\underline{H}_2CH_3$); 2.49 (3H, s, CH_3); 1.26–1.20 (3H, m, $OCH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 14.5 ($OCH_2\underline{C}H_3$); 21.8 (CH_3); 62.4 ($O\underline{C}H_2CH_3$); 80.2 (=$\underline{C}$CN); 112.0 (C≡N); 120.9 ($\underline{C}$H=C); 129.5 (2C); 129.8 (4C); 130.3 (2C); 131.3; 134.1; 134.7; 140.1; 145.8 (C-5); 163.9 (C=O ester); 165.5; 166.5; 188.3 (C=O ketone). Mass spectrum, *m*/*z* (I_{rel}, %): 418 $[M]^+$ (3), 403 $[M-CH_3]^+$ (10), 204 $[M-PhN=C=C(CN)CO_2Et]^+$ (30), 119 $[4\text{-}MeC_6H_4C\equiv O]^+$ (100), 91 $[4\text{-}MeC_6H_4]^+$ (40), 77 $[Ph]^+$ (19). Found, %: C 66.21; H 4.54; N 6.99. $C_{23}H_{18}N_2O_4S$. Calculated, %: C 66.02; H 4.34; N 6.69.

Methyl (2*E*,2*Z*)-cyano{(5*E*,5*Z*)-5-[2-(4-methylphenyl)-2-oxoethylidene]-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene}-ethanoate (7g). Yield 1.80 g (90%), pale-yellow crystals, mp 254–256°C. IR spectrum, ν, cm^{-1}: 3061 (=C–H), 2985 (C–H), 2214 (C≡N), 1726 (C=O), 1697 (C=O), 1634 (C=O), 822 (C–H Ar), 748 and 691 (C–H Ph). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.20 (1H, s, =CH); 8.14 (2H, d, *J* = 8.1, H-2,6); 7.55 (5H, br. s, H Ph); 7.42 (2H, d, *J* = 8.1, H-3,5); 3.80 (3H, s, CO_2CH_3); 2.42 (3H, s, CH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 404 $[M]^+$ (11), 204 $[M-PhN=C=C(CN)CO_2Me]^+$ (22), 119 $[4\text{-}MeC_6H_4C\equiv O]^+$ (100), 91 $[4\text{-}MeC_6H_4]^+$ (48), 77 $[Ph]^+$ (24), 65 $[cycloC_3H_3CN]^+$ (20). Found, %: C 65.40; H 3.87; N 6.73. $C_{22}H_{16}N_2O_4S$. Calculated, %: C 65.34; H 3.99; N 6.93.

Synthesis of 5-unsubstituted 1,3-thiazolidin-4-ones 8a,b (General procedure). Method I.[6b] Propanedinitrile (**2a**) (0.66 g, 10 mmol) or ethyl cyanoacetate (**2b**) (1.1 ml, 10 mmol) and phenyl isothiocyanate (**1**) (1.2 ml, 10 mmol) were added to a solution of KOH (0.57 g, 10 mmol) in 95% EtOH (30 ml). After stirring at room temperature for 30 min, a solution of potassium chloroacetate (1.31 g, 10 mmol) in H_2O (20 ml) was added. The reaction mixture was stirred at room temperature for 1 h, then poured into AcOH (50 ml) and refluxed for 15 min. After cooling to room temperature, the mixture was poured into cold H_2O (50 ml). The obtained solid was filtered off, washed with H_2O (50 ml), air-dried, and crystallized from 1,4-dioxane.

Method II (compound **8a**). A solution of ammonium phenylcarbamodithioate (**13**) (1.86 g, 10 mmol), propanedinitrile (**2a**) (0.66 g, 10 mmol), and few drops of Et_3N in EtOH (40 ml) was stirred at room temperature for 2 h. A solution of chloroacetic acid (10 mmol, 0.94 g) in AcOH (5 ml) was then added, and the reaction mixture was heated at 80°C for 30 min. After cooling to room temperature, concd HCl (2 ml) was added. The reaction mixture was vigorously shaken and poured into cold H_2O (50 ml). The obtained solid was filtered off, washed with H_2O (50 ml), air-dried, and crystallized from 1,4-dioxane–PhMe, 2:3.

(4-Oxo-3-phenyl-1,3-thiazolidin-2-ylidene)propanedinitrile (8a). Yield 2.04 g (85%, method I), 0.85 g (35%, method II), white crystals, mp 269–271°C (mp 273–275°C (EtOH)[6b]). IR spectrum, ν, cm^{-1}: 3058 (=CH), 2993 (C–H), 2942 (C–H), 2211 (C≡N), 1744 (C=O), 753 and 694 (C–H Ph). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.60–7.44 (5H, m, H Ph); 4.35 (2H, s, SCH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 241 $[M]^+$ (41), 167 $[M-SCH_2CO]^+$ (33), 77 $[Ph]^+$ (100).

Ethyl (2*E*,2*Z*)-cyano(4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene)ethanoate (8b). Yield 2.43 g (85%), white waxy flakes, mp 206–208°C (mp 208–210°C (EtOH)[6b]).

Synthesis of compounds (*E*,*Z*)-7a,d from 5-unsubstituted 1,3-thiazolidin-4-ones 8a,b. (Oxo)phenylacetaldehyde (1.07 g, 8 mmol) was added to a solution of 1,3-thiazolidin-4-one **8a** (1.20 g, 5 mmol) or (*E*,*Z*)-**8b** (1.15 g, 4 mmol) and dried NaOAc (1.23 g, 15 mmol) in refluxing glacial AcOH (30 ml). The reaction mixture was refluxed for 20 min, cooled to room temperature, and poured into cold H_2O (50 ml). The obtained solid was filtered off, washed with H_2O (50 ml), air-dried, and crystallized from glacial AcOH.

[(5*E*,5*Z*)-4-Oxo-5-(2-oxo-2-phenylethylidene)-3-phenyl-1,3-thiazolidin-2-ylidene]propanedinitrile (7a). Yield 1.50 g (85%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.46 (1H, s, =CH); 8.30 (2H, d, *J* = 8.0, H-2,6); 7.78 (1H, t, *J* = 8.0, H-4); 7.66–7.61 (7H, m, C_6H_5, H-3,5). ^{13}C NMR spectrum, δ, ppm: 58.5 (=$\underline{C}(CN)_2$); 109.9 (C≡N); 113.6 (C≡N); 121.3 ($\underline{C}$H=C); 129.6 (4C); 129.8 (2C); 130.16 (2C); 131.9; 133.2; 135.9; 139.2 (C-5); 165.5; 170.3; 189.4 (C=O ketone).

Ethyl (2*E*,2*Z*)-cyano[(5*E*,5*Z*)-4-oxo-5-(2-oxo-2-phenylethylidene)-3-phenyl-1,3-thiazolidin-2-ylidene]ethanoate (7d). Yield 1.38 g (85%).

Synthesis of compounds 6a,d from 1,3-thiazolidin-4-ones (*E*,*Z*)-7a,d (General method). Zn dust (0.50 g, 8 mmol) was added to a suspension of 1,3-thiazolidin-4-one (*E*,*Z*)-**7a**,**d** (1 mmol), obtained from 5-unsubstituted 1,3-thiazolidin-4-one **8a**,**b**, in refluxing glacial AcOH (50 ml). The reaction mixture was refluxed for 3 min, then filtered while hot. The filtrate was cooled to room temperature and poured into cold H_2O (50 ml). The obtained solid was filtered off, washed with H_2O (50 ml), air-dried, and crystallized from glacial AcOH.

[4-Oxo-5-(2-oxo-2-phenylethyl)-3-phenyl-1,3-thiazolidin-2-ylidene]propanedinitrile (6a). Yield 0.36 g (92%).

Ethyl (2*E*,2*Z*)-cyano[4-oxo-5-(2-oxo-2-phenylethyl)-3-phenyl-1,3-thiazolidin-2-ylidene]ethanoate (6d). Yield 0.35 g (90%).

[(5*E*,5*Z*)-5-(4-Methoxybenzylidene)-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene]propanedinitrile (7h). A suspension of powdered 5-unsubstituted 1,3-thiazolidin-4-one **8a** (1.20 g, 5.0 mmol), 4-methoxybenzaldehyde (0.7 ml,

5.0 mmol), and dried NaOAc (1.23 g, 15 mmol) in glacial AcOH (10 ml) was refluxed for 30 min. After cooling to room temperature, the reaction mixture was poured into cold H_2O (50 ml). The precipitate was filtered off, washed with H_2O (50 ml), air-dried, and crystallized from AcOH. Yield 0.43 g (90%), yellow crystals, mp 278–280°C (mp 275–278°C[6b]). IR spectrum, ν, cm^{-1}: 3061 (=C–H), 3024 (=C–H), 2964 (C–H), 2217 (C≡N), 1718 (C=O), 838 (C–H Ar), 719 and 693 (C–H Ph). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): ***Z*-isomer** (95%): 8.01 (1H, s, =CH); 7.71 (2H, d, *J* = 7.2, H-2,6); 7.58 (5H, br. s, NPh); 7.20 (2H, d, *J* = 7.2, H-3,5); 3.90 (3H, s, OCH_3); ***E*-isomer** (5%): 7.49 (1H, s, =CH); 7.20 (2H, d, *J* = 7.2, H-2,6); 7.58 (5H, br. s, NPh); 7.20 (2H, d, *J* = 7.2, H-3,5); 3.9 (3H, s, OCH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 359 $[M]^+$ (59), 164 $[M-C=(CN)_2-PhNCO]^+$ (100), 149 $[M-C=(CN)_2-PhNCO-CH_3]^+$ (49), 77 $[Ph]^+$ (45).

Synthesis of 5-bromo-1,3-thiazolidin-4-ones 10a,b (General method). A solution of Br_2 (0.5 ml, 10 mmol) in glacial AcOH (5 ml) was added portionwise to a suspension of powdered 5-unsubstituted 1,3-thiazolidin-4-one **8a**,**b** (5 mmol) in refluxing glacial AcOH (50 ml). The mixture was refluxed for 10 min till the color of solution had changed to pale-yellow. After cooling to room temperature, the reaction mixture was poured into cold H_2O (50 ml) and kept at room temperature for 1 h. The obtained solid was filtered off, washed with H_2O (50 ml), air-dried, and crystallized from $CHCl_3$ – petroleum ether, 3:2.

(5-Bromo-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene)-propanedinitrile (10a). Yield 1.35 g (85%), cream-colored granules, mp 212–214°C. IR spectrum, ν, cm^{-1}: 3066 (=C–H), 2218 (C≡N), 1764 (C=O), 737 and 695 (C–H Ph). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.70–7.59 (3H, m, H-3,4,5); 7.36 (2H, d, *J* = 7.5, H-2,6); 5.96 (1H, s, CHBr). Mass spectrum, *m*/*z* (I_{rel}, %): 321 $[M]^+$ (62), 320 $[M]^+$ (48), 291 (37), 263 (62), 123 $[M-PhNCO-CN-C\equiv CCN]^+$ (50), 69 $[M-PhNCO-CN-CN-Br]^+$ (100). Found, %: C 44.82; H 2.09; N 13.34. $C_{12}H_6BrN_3OS$. Calculated, %: C 45.02; H 1.89; N 13.12.

Ethyl (2*E*,2*Z*)-(5-bromo-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene)(cyano)ethanoate (10b). Yield 1.55 g (85%), cream-colored granules, mp 180–182°C. IR spectrum, ν, cm^{-1}: 3063 (=C–H), 2210 (C≡N), 1753 (C=O), 1689 (C=O), 762 and 695 (C–H Ph). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.65–7.60 (3H, m, H-3,4,5); 7.37 (2H, d, *J* = 8.1, H-2,6); 4.29 (2H, q, *J* = 6.9, $OC\underline{H}_2CH_3$); 3.85 (1H, s, CHBr); 1.31 (3H, t, *J* = 9.6, $OCH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: ***Z*-isomer**: 14.2 ($OCH_2\underline{C}H_3$); 38.9 ($O\underline{C}H_2CH_3$); 62.6 (C-5); 81.5; 110.9 (C≡N); 128.9; 130.0 (2C); 131.6 (2C); 133.8; 162.6 (C=O ester); 164.9; 167.8 (C=O ketone); ***E*-isomer**: 14.1 ($OCH_2\underline{C}H_3$); 40.4 ($O\underline{C}H_2CH_3$); 63.0 (C-5); 80.9; 110.4 (C≡N); 128.2; 130.1 (2C); 131.9 (2C); 133.7; 164.8 (C=O ester); 165.3; 170.2 (C=O ketone). Mass spectrum, *m*/*z* (I_{rel}, %): 368 $[M]^+$ (14), 366 $[M]^+$ (13), 367 $[M]^+$ (71), 365 $[M-H]^+$ (67), 185 $[M-Br-CO_2Et-H-CO]^+$ (20), 169 $[M-OEt-S-CHBrCO]^+$ 125 (57), 123 $[M-PhNCO-CN-C\equiv CCO_2Et]^+$ (56), 77 $[Ph]^+$ (100). Found, %: C 45.37; H 3.32; N 7.72. $C_{14}H_{11}BrN_2O_3S$. Calculated, %: C 45.79; H 3.02; N 7.63.

Synthesis of dimers (*E*,*Z*)-11a,b. 5-Bromo-1,3-thiazolidin-4-one **10a**,**b** (3 mmol) was dissolved in EtOH (10 ml) (methods I and II) or glacial AcOH (10 ml) (method III).

Method I. KSCN (0.31 g, 3.2 mmol) was added to the solution. The reaction mixture was refluxed for 10 min.

Method II. NaOCN (0.26 g, 3.2 mmol) was added to the solution. The reaction mixture was refluxed for 10 min.

Method III. NaOAc (0.26 g, 3.2 mmol) was added to the solution. The reaction mixture was refluxed for 10 min.

For methods I–III, the obtained solid was filtered off, washed with H_2O (50 ml), air-dried, and crystallized from 1,4-dioxane.

{(5*E*,5*Z*)-5-[2-(Dicyanomethylidene)-4-oxo-3-phenyl-1,3-thiazolidin-5-ylidene]-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene}propanedinitrile (11a). Yield 0.65 g (90%, method I), 0.65 g (90%, method II), 0.70 g (95%, method III), dark-orange flakes, mp >300°C. IR spectrum, ν, cm^{-1}: 3063 (=C–H), 2210 (C≡N), 1711 (C=O), 739 and 693 (C–H Ph). ^{1}H NMR spectrum, δ, ppm: 7.64 (10H, s, H Ph). Mass spectrum, *m*/*z* (I_{rel}, %): 478 $[M]^+$ (53), 283 $[M-PhN=C=C(CN)_2-CO]^+$ (100), 88 $[M-2(PhN=C=C(CN)_2)-2CO)]^+$ (67), 77 $[Ph]^+$ (51), 64 $[cycloC_3H_2CN]^+$ (40). Found, %: C 60.45; H 2.17; N 17.23. $C_{24}H_{10}N_6O_2S_2$. Calculated, %: C 60.24; H 2.11; N 17.56.

Ethyl (2*E*,2*Z*)-cyano[(5*E*,5*Z*)-5-{(2*E*,2*Z*)-2-[(cyano)-ethoxycarbonylmethylidene]-4-oxo-3-phenyl-1,3-thiazolidin-5-ylidene}-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene]-ethanoate (11b). Yield 0.70 g (90%, method I), 0.70 g (90%, method II), 0.75 g (95%, method III), dark-orange flakes, mp >300°C. IR spectrum, ν, cm^{-1}: 3063 (=C–H), 2215 (C≡N), 1698 (C=O), 1632 (C=O), 756 and 688 (C–H Ph). ^{1}H NMR spectrum, δ, ppm: 7.52–7.47 (10H, m, H 2Ph); 4.22–4.15 (4H, m, $2OC\underline{H}_2CH_3$); 1.20–1.13 (6H, m, $2OCH_2C\underline{H}_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 572 $[M]^+$ (28), 367 (13), 365 (67), 330 $[M-PhNCO-CN-C\equiv CCO_2Et]^+$ (31), 185 (20), 169 (22), 77 $[Ph]^+$ (100). Found, %: C 58.93; H 3.58; N 10.11. $C_{28}H_{20}N_4O_6S_2$. Calculated, %: C 58.73; H 3.52; N 9.78.

[5-(Benzylamino)-4-oxo-3-phenyl-1,3-thiazolidin-2-yl-idene]propanedinitrile (12). A solution of 5-bromo-1,3-thiazolidin-4-one **10a** (0.50 g, 1.5 mmol) in EtOAc (30 ml) was added dropwise at room temperature over period of 20 min to a solution of benzylamine (0.17 g, 1.5 mmol) in Et_2O (30 ml). The reaction mixture was kept at room temperature for 24 h allowing to slowly evaporate. The obtained solid was filtered off and crystallized from EtOH–PhMe, 2:3. Yield 0.46 g (85%), pale-gray flakes, mp 174–176°C. IR spectrum, ν, cm^{-1}: 3272 and 3062 (=C–H), 2972 (C–H), 2931 (C–H), 2215 (C≡N), 1664 (C=O), 748 and 694 (C–H Ph). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.15 (1H, t, *J* = 6.3, NH_X); 7.47–7.44 (3H, m, H-3,4,5); 7.43–7.18 (5H, m, $CH_2\underline{Ph}$); 7.07–7.04 (2H, m, H-2,6); 6.74 (1H, s, 5-CH); 4.33 (1H, dd, J_{AB} = 15.0, J_{BX} = 6.3, CH_B); 4.23 (1H, dd, J_{AB} = 15.0, J_{AX} = 5.0, CH_A). ^{13}C NMR spectrum, δ, ppm: 43.1 ($Ph\underline{C}H_2$); 47.5 (C-5); 66.5 ($=\underline{C}(CN)_2$); 112.4 (C≡N); 114.8 (C≡N); 125.4 (2C); 127.5; 127.6 (2C); 128.8 (2C); 129.5 (2C); 129.6; 136.7; 138.4; 163.3 (C-2); 174.4 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 346 $[M]^+$ (4), 106 $[M-CHSC=(CN)_2-PhNCO]^+$ (78), 104 $[M-CHSC=(CN)_2-PhNCO-H_2]^+$ (100), 91

$[PhCH_2]^+$ (49), 77 $[Ph]^+$ (82). Found, %: C 66.18; H 4.27; N 16.23. $C_{19}H_{14}N_4OS$. Calculated, %: C 65.88; H 4.07; N 16.17.

3-Phenyl-2-thioxo-1,3-thiazolidin-4-one (14a). A solution of phenyl isothiocyanate (**1**) (0.6 ml, 5 mmol), KOH (0.28 g, 5 mmol), and 1,3-thiazolidine-2,4-dione **14b** (0.96 g, 5 mmol) in EtOH (15 ml) was stirred at 0°C for 30 min. A solution of potassium chloroacetate (0.66 g, 5 mmol) in EtOH (30 ml) was added to the reaction mixture, and stirring at 0°C was continued for 30 min. The reaction mixture was poured into glacial AcOH (25 ml) and refluxed for 5 min. After cooling to room temperature, the obtained solid was filtered off, washed with H_2O (50 ml), air-dried, and crystallized from glacial AcOH. Yield 0.91 g (85%), pale-yellow crystals, mp 188–188°C (mp 192°C (AcOH)[10b]). IR spectrum, ν, cm^{-1}: 3046 (=C–H), 1736 (br, C=O), 751 and 693 (C–H Ph). ^1H NMR spectrum, δ, ppm: 7.35–7.13 (5H, m, H Ph); 4.39 (2H, s, 5-CH_2).

(5*E*,5*Z*)-5-(4-Oxo-3-phenyl-1,3-thiazolidin-2-ylidene)-3-phenyl-2-thioxo-1,3-thiazolidin-4-one (15). A solution of phenyl isothiocyanate (**1**) (0.6 ml, 5 mmol), KOH (0.28 g, 5 mmol), and 2-thioxo-1,3-thiazolidin-4-one **14a** (1.05 g, 5 mmol) in EtOH (15 ml) was stirred at 0°C for 30 min. A solution of potassium chloroacetate (0.66 g, 5 mmol) in EtOH (30 ml) was added to the reaction mixture and stirring at 0°C was continued for 30 min. The reaction mixture was poured into glacial AcOH (25 ml) and refluxed for 5 min. After cooling to room temperature, the obtained solid was filtered off, washed with H_2O (50 ml), air-dried, and crystallized from glacial AcOH. Yield 1.60 g (85%), pale-yellow crystals, mp 256–258°C. IR spectrum, ν, cm^{-1}: 3046 (=C–H), 1731 (C=O), 1671 (C=O), 750 and 693 (C–H Ph). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.68–7.49 (8H, m, H Ph); 7.24 (2H, dd, *J* = 7.5, *J* = 1.8, H Ph); 4.16 (2H, s, SCH_2). ^{13}C NMR spectrum, δ, ppm: 32.5 (C-5'); 93.9 (C-5); 129.1 (2C); 129.7 (2C); 130.4 (2C); 130.8 (2C); 131.9; 134.0; 135.7; 153.4; 166.9 (C-2'); 172.5 (C=O); 173.8 (C=O); 192.1 (C=S). Mass spectrum, *m*/*z* (I_{rel}, %): 384 $[M]^+$ (7), 80 $[cycloC_3H_2NCO]^+$ (100), 64 $[cycloC_3H_2CN]^+$ (50). Found, %: C 56.22; H 3.07; N 7.34. $C_{18}H_{12}N_2O_2S_3$. Calculated, %: C 56.23; H 3.15; N 7.29.

Synthesis of 1,3-thiazolidin-4-ones (*E*,*Z*)-18 and (*E*,*Z*)-19. A mixture of 4-methoxybenzaldehyde (0.2 ml, 1.3 mmol), dried NaOAc (0.41 g, 5.0 mmol), and compound (*E*,*Z*)-**15** (0.50 g, 1.3 mmol) or **14a** (0.35 g, 1.7 mmol) in glacial AcOH (10 ml) was refluxed for 30 min. After cooling to room temperature, the reaction mixture was poured into cold H_2O (50 ml). The obtained solid was filtered off, washed with H_2O (50 ml), air-dried, and crystallized from appropriate solvent.

(2*E*,2*Z*,5*E*,5*Z*)-5-(4-Methoxybenzylidene)-2-(4-oxo-3-phenyl-2-thioxo-1,3-thiazolidin-5-ylidene)-3-phenyl-1,3-thiazolidin-4-one (18). Yield 0.56 g (85%), brown crystals, mp >300°C (1,4-dioxane–DMF, 2:3). IR spectrum, ν, cm^{-1}: 3062 (=C–H), 1715 (C=O), 1636 (C=O), 828 (C–H Ar), 753 and 688 (C–H Ph). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.83 (1H, s, =CH); 7.71–7.50 (10H, m, H Ar); 7.29 (2H, d, *J* = 8.1, H Ar); 7.16 (2H, d, *J* = 9.0, H Ar); 3.85 (3H, s, OCH_3). Found, %: C 61.97; H 3.62; N 5.77. $C_{26}H_{18}N_2O_3S_3$. Calculated, %: C 62.13; H 3.61; N 5.57.

(5*E*,5*Z*)-5-(4-Methoxybenzylidene)-3-phenyl-2-thioxo-1,3-thiazolidin-4-one (19). Yield 0.36 g (85%), yellow crystals, mp 221–223°C (AcOH) (mp 223–225°C[19]). IR spectrum, ν, cm^{-1}: 3062 (=C–H), 1715 (C=O), 828 (C–H Ar), 753 and 686 (C–H Ph). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.81 (1H, s, =CH); 7.67 (2H, d, *J* = 8.7, H-2,6); 7.56–7.39 (5H, m, H Ph); 7.15 (2H, d, *J* = 8.7, H-3,5); 3.86 (3H, s, OCH_3). Found, %: C 62.44; H 3.98; N 4.30. $C_{17}H_{13}NO_2S_2$. Calculated, %: C 62.36; H 4.00; N 4.28.

Supplementary information file containing IR, ^1H and ^{13}C NMR, and mass spectra of compounds **6a**–**e**,**g**, (*E*,*Z*)-**7a**–**e**,**g**,**h**, **8a**, **10a**,**b**, (*E*,*Z*)-**11a**,**b**, **12**, (*E*,*Z*)-**15**, (*E*,*Z*)-**18**, and (*E*,*Z*)-**19** and COSY spectrum of compound **12** is available at the journal website at http://link.springer.com/journal/10593.

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