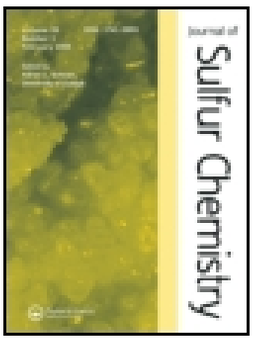

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One-pot, solvent-free facile stereoselective synthesis of rhodanine–furan hybrids from renewable resources

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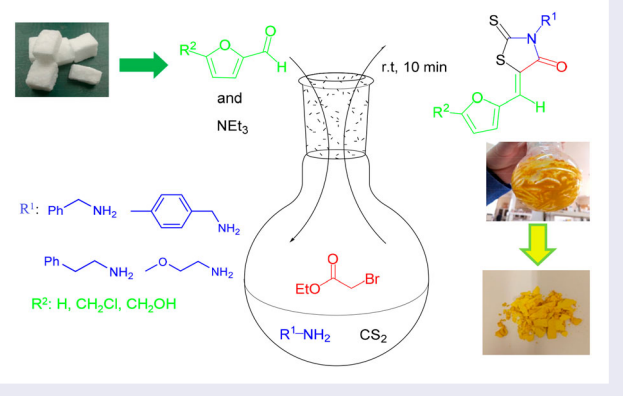
ABSTRACT

In this study, a one-pot, solvent-free stereoselective reaction was started between primary amines, carbon disulfide, ethyl bromoacetate, and furan derivatives derived from sugars at room temperature, which was completed within 10 min to produce rhodanine–furan hybrid molecules in good to high yields. The presence of the chloromethyl group in products derived from chloromethylfurfural (CMF) made it possible for the substitution of other functional groups such as amine group.



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5-arylidene rhodanines; furans; solvent-free reaction; multicomponent reactions (MCRs); biomass

Introduction

To optimize the biological activity of synthetic molecules, it is essential to have a different design of the molecules. The synthesis of hybrid molecules is a way to achieve this goal, which has been further considered in recent decades to improve the biological activity of synthetic compounds [1]. Sugars represent a renewable source for the production of furan derivatives. The furan scaffold consists of several bioactive natural products such as furanolactones, furano-flavonoids, and furanocoumarins. The furan

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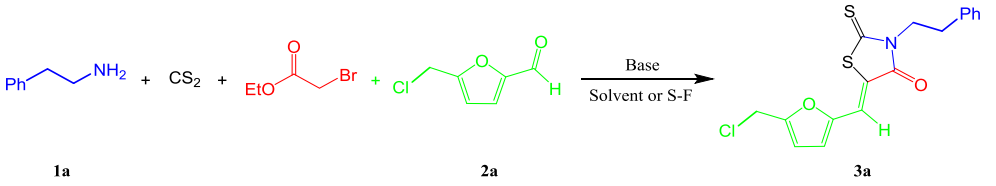
derivatives have been reported to show more than 18 various pharmacologically activities [2]. High remedial properties of furan-containing drugs have motivated organic chemists to synthesize various furan derivatives. On the other hand, the arylidene rhodanine-based compounds are considerable heterocyclic molecules with diverse pharmacological activities such as anticancer [3], anti-bacterial [4], anti-diabetic [5], antifungal [6], and anti-HIV [7]. These molecules also inhibit numerous targets such as aldose reductase [8], hepatitis C virus (HCV) NS3 protease [9], PRL-3 [10], and UDPN-acetylmuramate/L-alanine ligase [11]. Recently, rhodanine-based molecule supported on nanomagnetic particles has also been used to remove heavy metal contamination [12] or used as a catalyst for organic transformations [13,14].

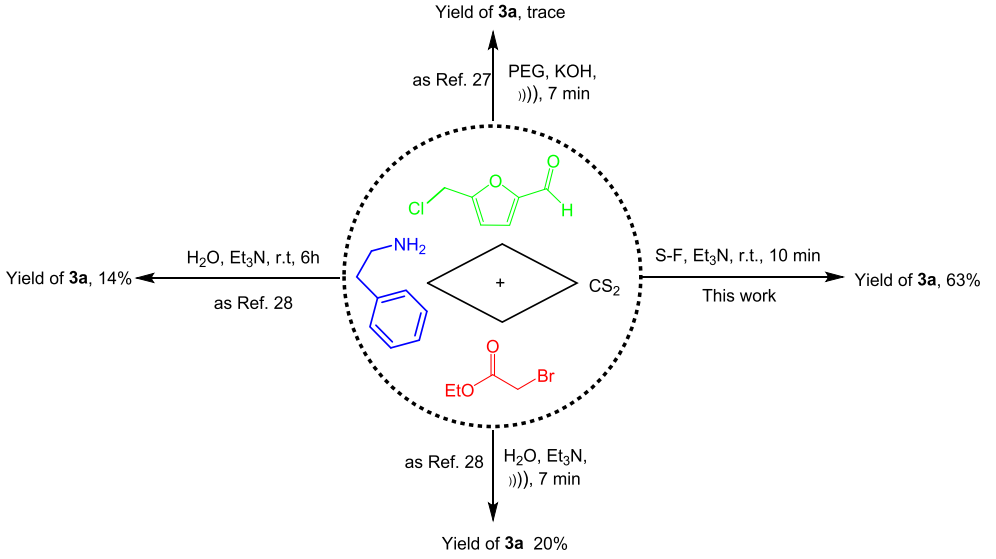
Due to the above observations, we were interested in the synthesis of hybrid molecules containing furan and rhodanine moieties (5-arylidene rhodanines) by the reaction of furanaldehydes (furfural and other furanaldehyde derivatives obtained from sugar), carbon disulfide, ethylbromoacetate, and primary amines. Among most of the reported synthesis methods used to generate arylidene rhodanines, the Knoevenagel condensation between rhodanine units and aldehydes has been done frequently through a separate step in the presence of an appropriate base [15–26]. Recently, a few reports have been published regarding the four-component synthesis of arylidene rhodanines. In these reports, ultrasonic or microwave conditions have been used to facilitate the reaction [27,28] or the reaction has been performed in ionic liquid [29] and to the best of our knowledge, there is no report about the one-pot solvent-free synthesis of arylidene rhodanines. To develop easy and green synthesis of arylidene rhodanines without isolation of reaction intermediates or purification step, and in continuation of our research on one-pot solvent-free synthesis of heterocyclic compounds [30–33], this study was conducted to report a one-pot solvent-free reaction between primary amines **1**, carbon disulfide, ethyl bromoacetate, and renewable furan derivatives **2** in the presence of a catalytic amount of triethylamine to produce rhodamine-furan hybrids **3** in good to high yields within 10 minutes.

Results and discussion

The one-pot reaction between phenethyl amine **1a**, carbon disulfide, ethyl bromoacetate, and chloromethylfurfural (CMF) **2a** was selected as a model reaction to produce rhodanine–furan hybrid **3a** (Scheme 1). At first, to achieve an efficient procedure, the one-pot methods reported in the literature were used for the synthesis of the compound **3a**. As illustrated in Scheme 2, when the reaction was carried out by the Azizi's method [27] in PEG and the presence of 300 mol% of KOH and ultrasonic condition, the reaction yield was negligible. Also, when the reaction was performed according to the Mermer's method [28] in water and the presence of 300 mol% of triethylamine and ultrasonic condition, the reaction yield was only 20%. The deletion of ultrasonic condition in the recent reaction [28] reduced reaction yield to 14%. When the reaction was carried out in solvent-free condition with an equimolar ratio of reactant and in presence of 20 mol% of triethylamine, **3a** created with a yield of 33% within 10 min (Table 1, entry 1). The increase in the amount of triethylamine did not influence on yield of **3a** (Table 1, entries 1, 2). In this reaction, bromoethylacetate was added to the mixture of phenethylamine and CS_2, and the reaction mixture was stirred by a glass rod for 2 minutes. Then, CMF and triethylamine were added respectively to the mixture and mixing was continued, and progress of the reaction



Scheme 1. One-pot reaction between phenetyl amine, CS_2, CMF, and ethyl bromoacetate.



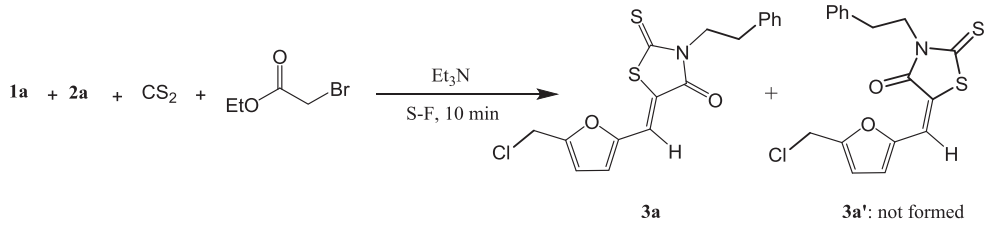
Scheme 2. Synthesis of **3a** through a number of methods reported in the literature.

Table 1. Optimization of the reaction conditions for the synthesis of compound **3a**.

	Molar ratio of reactants to CMF					
Entry	Phenethylamine	CS_2	Ethylbromoacetate	Et_3N	Time	Yield% of **3a**
1	1	1	1	0.2	10 min	33
2	1	1	1	0.4	10 min	33
3	1	1	1	0.2[a]	1 day	Trace
4[b]	1	1	1	0.2	10 min	–[c]
5	2	2	2	0.4	10 min	40
6	2.5	2.5	2.5	0.5	10 min	63
7	3	3	3	0.6	10 min	62

[a]When triethylamine was added to the reaction mixture before adding CMF.
[b]The reaction was carried out at 60°C.
[c]The reaction afforded a complex oily mixture.

was monitored by the TLC. After 8 min, the reaction was completed. The product was easily separated by adding ethanol to the reaction mixture. In this reaction, the progress of the reaction was significantly influenced by the order of the reactant addition. When triethylamine was added to the reaction mixture before adding CMF, the reaction yield was negligible after 24 hours (Table 1, entry 3). Also, this reaction was sensitive to temperature, and when the reaction was carried out at 60°C, the reaction afford a complex mixture



Scheme 3. One-pot, solvent-free stereoselective reaction between phenetyl amine, CS_2, CMF, and ethyl bromoacetate.

(Table 1, entry 4). To obtain the optimum reaction conditions in terms of reactant amount, the model reaction was checked in the presence of different ratios of reactant relative to CMF. As shown in Table 1, reasonable reaction yield was gained when the reaction was carried out using 2.5 times of reactant and 50 mol% of trimethylamine relative to CMF at room temperature (Table 1, entries 5–7).

As shown in Scheme 3, two possible stereoisomers (**3a** and **3a′**) can be formed in this reaction. These isomers can be detected from each other based on the chemical shift of olefinic hydrogen in the ^{1}H NMR. In the *Z*-form (**3a**), methine proton is located in the deshielding region of adjacent carbonyl group. This proton appears at about 7.0–8.0 ppm, while in the *E*-form (**3a′**), this proton should appear at about less than 6.5 ppm [15]. The^{1}H NMR chemical shift of methine proton in products of this reaction appears in a range of 7.4–7.6 ppm, showing that only *Z* isomer has been produced. The reason for the formation of **3** in Z-form is due to the high degree of thermodynamic stability of *Z*-form in this compound [3]. Structures of the produced 5-arylidene rhodanines derivatives were determined based on their IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopic data. For example, the ^{1}H NMR spectrum of **3c** showed three singlets (δ = 2.32, 4.63, and 5.28 ppm) related to the methyl, CH_2N, and CH_2Cl protons, respectively. Protons of the furan ring showed two doublets (δ = 6.55 and 6.78 ppm, $^3J_{HH}$ = 3.5 Hz). The methine proton of **3c** appeared as a singlet at δ = 7.44 ppm, revealing that the compound **3c** is produced as only *Z*-form [15]. Also, aromatic protons of **3c** produced two doublets at δ = 7.13 and δ = 7.36 ppm ($^3J_{HH}$ = 7.7 Hz). Also, the ^{13}C NMR spectrum of **3c** showed 15 distinct signals confirming the proposed structure. Mass spectrum of **3c** illustrated a molecular ion peak at the expected *m/z* value, *i.e.* 363 (Table 2).

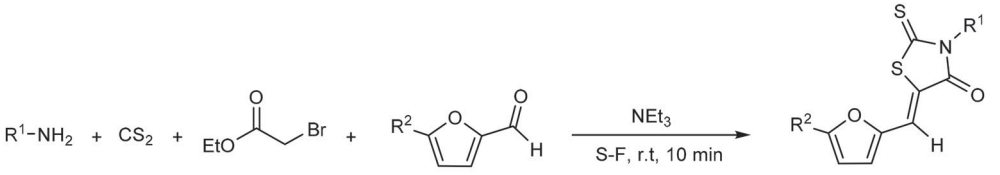
To generalize the reported method to other aldehydes, we examined this procedure for benzaldehyde. The yield of desired product was about 60%, indicating that this method can be extended to other aldehydes as well.

A proposed mechanism for this reaction is shown in Scheme 4. The reaction proceeds through an initial addition of the amine **1** to carbon disulfide to afford zwitterionic intermediate **I** [34] which then reacts with ethyl bromoacetate with the loss of one HBr molecule to convert it into the intermediate **II**. Intermediate **II** undergoes an intramolecular cyclization to produce rhodanine **III** with diverse R^1 groups with loss of the ethanol molecule. Condensation of rhodanine **III** with furan derivatives **2** in the presence of NEt_3 gave the rhodanine–furan hybrids 3.

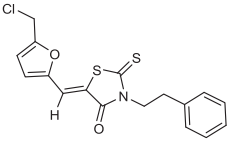
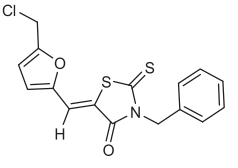
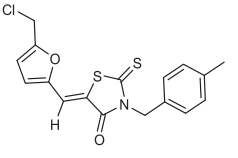
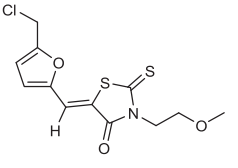
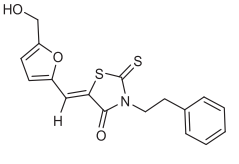
Chlorine atom in the compounds **3a**–**3d** has potential for substitution with various functional groups. The amino group is one of the most important functional group in

bioactive compounds, which by converting to ammonium salts, makes it possible to solubilize organic compounds in an aqueous medium. Compound **3a** easily reacted with hexamethylenetetramine to produce intermediate **4** (Scheme 5) which was converted to its

Table 2. One-pot, solvent-free stereoselective synthesis of rhodanine–furan hybrids **3a–3j**.

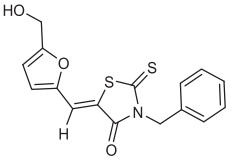
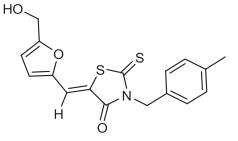
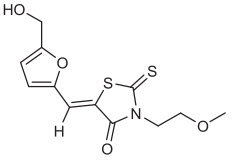
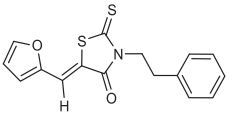
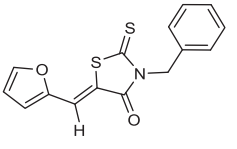


1 **2** **3a-3j**

Entry	R^1	R^2	Product	Yield (%)[a]
1	$PhCH_2CH_2$	CH_2Cl	 **3a**	63
2	$PhCH_2$	CH_2Cl	 **3b**	65
3	4-Me-$PhCH_2$	CH_2Cl	 **3c**	59
4	$CH_3OCH_2CH_2$	CH_2Cl	 **3d**	63
5	$PhCH_2CH_2$	CH_2OH	 **3e**	75

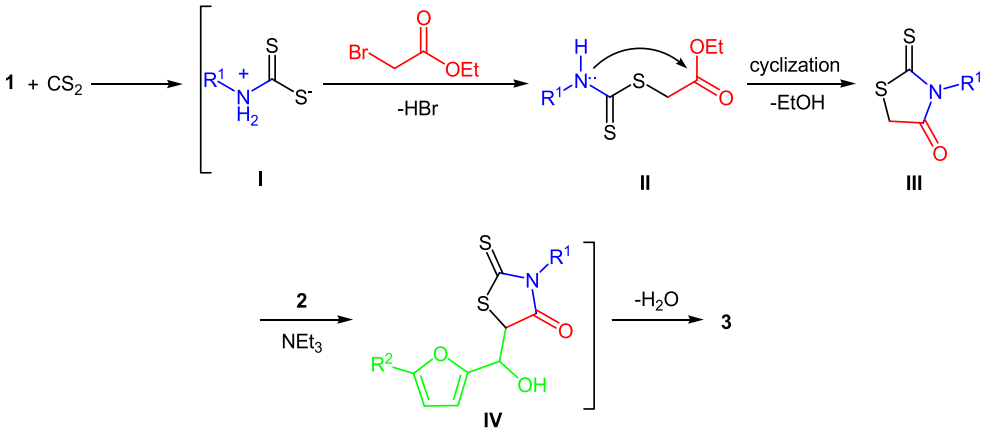
(*continued*).

Table 2. Continued.

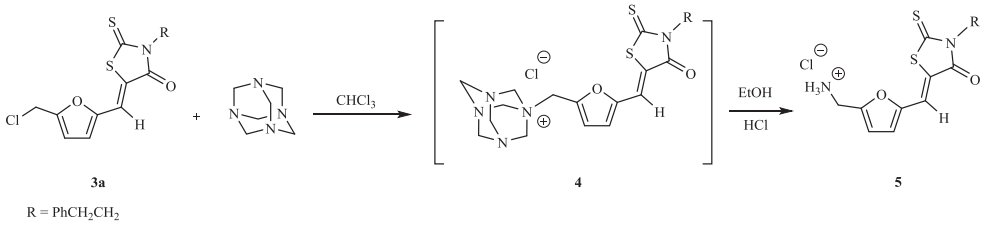
Entry	R^1	R^2	Product	Yield (%)[a]
6	$PhCH_2$	CH_2OH	 **3f**	45
7	4-Me-$PhCH_2$	CH_2OH	 **3g**	60
8	$CH_3OCH_2CH_2$	CH_2OH	 **3h**	48
9	$PhCH_2CH_2$	H	 **3i**	64
10	$PhCH_2$	H	 **3j**	57

[a]Isolated yields.

ammonium salt of rhodanine–furan hybrid **5** by treating with acidic ethanol at reflux condition [35]. The ^{1}H NMR spectrum of **5** showed a triplet ($\delta = 2.95$ ppm, $^3J_{HH} = 9.0$ Hz) related to CH_2-Ar protons, and the two methylene protons of CH_2-N moieties overlapped with each other at $\delta = 4.20$–4.24 ppm. One of the two protons of the furan ring showed a doublet at δ 6.86 ppm with $^3J_{HH} = 3.5$ Hz, and other proton of the furan ring overlapped with aromatic proton signals at $\delta = 7.19$–7.30 ppm. The methine proton appeared as a singlet at $\delta = 7.59$ ppm. The NH_3^+ protons of **5** resulted as a broad singlet at δ 8.87 ppm. This resonance disappeared after the addition of D_2O to the DMSO solution of **5**. In addition, the ^{13}C NMR spectrum of **5** showed 15 distinct signals confirming the proposed



Scheme 4. A proposed mechanism for the formation of rhodanine–furan hybrids through the reaction between primary amines, CS_2, furan derivatives, and ethyl bromoacetate.



Scheme 5. Synthesis of ammonium salt of rhodanine–furan hybrid **5**.

structure. Mass spectrum of **5** displayed a (M^+-HCl) peak at *m*/*z* 344, corresponding with the proposed structure.

Conclusion

The present one-pot solvent-free and stereoselective reaction between primary amines, carbon disulfide, ethylbromoacetate, and furfural derivatives derived from sugars provided a novel series of furan–rhodanine hybrids in good to high yields within 10 minutes. The presence of the chloromethyl group in products derived from CMF made it possible for the substitution of other functional groups such as amine group. Also, the simplicity of the present procedure and facility of the product isolation made it an interesting alternative to more complex methods.

Experimental section

General information

Thin layer chromatography was carried out using commercially available Merck F254 aluminum backed silica plates and Silica gel (60 meshes) was used for column chromatography. Melting points (un-corrected) were measured with a Stuart SMP-3 apparatus. IR spectra of products were measured with an FTIR Perkin Elmer RXI. NMR spectra were

recorded with a Bruker DRX-250 AVANCE instrument (250.1 MHz for ^{1}H and 62.5 MHz for^{13}C) or INOVA-500 (500 MHz for ^{1}H and 125 MHz for ^{13}C) with $CDCl_3$ or DMSO as the solvent. Chemical shifts are given in ppm (δ) relative to internal TMS, and coupling constants (J) are reported in Hertz (Hz). 5-(Chloromethyl)furfural was prepared from powdered sugar according to the published procedure [36]. 5-(Hydroxymethyl)furfural was prepared from fructose according to the published procedure [37]. Other starting materials and solvents were obtained from Merck (Germany) and were used without further purification.

General procedure for the preparation of 3-alkyl-5-((5-(hydroxymethyl)furan-2-yl) methylene)-2-thioxothiazolidin-4-one (3a–j)

To a mixture of amine (2.5 mmol) and CS_2 (2.5 mmol) was added ethyl bromoacetate (2.5 mmol). The contents were admixed by glass rod at room temperature for 2 minutes. Then furanaldehyde derivative (1 mmol) and NEt_3 (0.5 mmol) were added to the mixture and mixing was continued for 8 min. After the reaction completed, ethanol (when the aldehyde reactant was CMF) or water (when the aldehyde reactant was HMF or furfural) was added to the reaction mixture and the product was collected by filtration.

(Z)-5-((5-(Chloromethyl)furan-2-yl)methylene)-3-phenethyl-2-thioxothiazolidin-4-one (3a)

Yellow powder; mp: 144–147°C; 0.229 g, yield: 63%. IR (KBr) (υ_{max}/cm^{-1}): 3036, 1699, 1613, 1352, 1329, 1261, 1165. Ms: *m/z* (%) = 363 ($M^{+\cdot}$, 32), 328 (18), 259 (39), 172 (61), 137 (100), 83 (32). ^{1}H NMR (250 MHz, $CDCl_3$): δ ppm 3.00 (t, 2H, $^{3}J_{HH}$ = 8.0 Hz, CH_2Ar), 4.32 (t, 2H, $^{3}J_{HH}$ = 8.0 Hz, NCH_2), 4.63 (s, 2H, CH_2Cl), 6.55 (d, 1H, $^{3}J_{HH}$ = 3.5 Hz, CH_{Furan}), 6.78 (d, 1H, $^{3}J_{HH}$ = 3.5 Hz, CH_{Furan}), 7.29–7.40 (m, 5H, Ar), 7.43 (s, 1H, =C*H*); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ ppm 33.0 (CH_2Ph), 36.9 (CH_2Cl), 45.6 (CH_2N), 112.9 and 117.6 (2CH_{Furan}), 119.1 (CH=$C_{Rhodanin}$), 121 (CH=$C_{Rhodanin}$), 126.8 (*C*H), 128.6 (2*C*H), 128.9 (2*C*H), 137.5 (C_{Ar}), 150.6 and 154.7 (2C_{Furan}), 167.2 (C=O) and 194.1 (C=S).

(Z)-3-Benzyl-5-((5-(chloromethyl)furan-2-yl)methylene)-2-thioxothiazolidin-4 -one (3b)

Yellow powder; mp: 139–143°C; 0.226 g, yield: 65%. IR (KBr) (υ_{max}/cm^{-1}): 3035, 1702, 1610, 1301, 1187, 695, 529. MS (*m/z*, %): 349 (M^{+}, 53), 314 (25), 172 (58), 137 (100), 91 (56), 65 (25). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ ppm 4.63 (s, 2H, CH_2N), 5.31 (s, 2H, CH_2Cl), 6.55 (d, 1H, $^{3}J_{HH}$ = 3.5 Hz, CH_{Furan}), 6.78 (d, 1H, $^{3}J_{HH}$ = 3.5 Hz, CH_{Furan}), 7.28–7.34 (m, 3H, Ar), 7. 44 (s, 1H, =C*H*), 7.45–7.48 (m, 2H, Ar); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ ppm 37.0 (CH_2Cl), 47.6 (CH_2N), 113.1 (CH_{Furan}), 117.9 (CH_{Furan}), 119.3 (CH=$C_{Rhodanin}$), 122.1 (CH=$C_{Rhodanin}$), 128.2 (*C*H), 128.7 (2*C*H), 129.0 (2*C*H), 135.0 (C_{Ar}), 150.7 (C_{Furan}), 154.9 (C_{Furan}), 167.6 (*C*=O) and 194.3 (*C*=S).

(Z)-3-(4-Methyl-benzyl)-5-((5-(chloromethyl)furan-2-yl)methylene)-2-thioxothiaz olidin-4-one (3c)

Yellow powder; mp: 158–160°C; 0.214 g, yield: 59%. IR (KBr) (υ_{max}/cm^{-1}): 1702, 1609, 1341, 1306, 1184, 1044. MS (*m/z*, %): 363 (M^{+}, 53), 329 (21), 172 (31), 137 (53), 105 (100), 63 (61). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ ppm 2.32 (s, 3H, CH_3), 4.63 (s, 2H, NCH_2), 5.28 (s, 2H, CH_2Cl), 6.55 (d, 1H, $^{3}J_{HH}$ = 3.5 Hz, CH_{Furan}), 6.78 (d, 1H, $^{3}J_{HH}$ = 3.5 Hz,

CH_{Furan}), 7.13 (d, 2H, $^3J_{HH}$ = 7.7 Hz, Ar), 7.36 (d, 2H, $^3J_{HH}$ = 7.7 Hz, Ar), 7.43 (s, 1H, =C*H*); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ ppm 21.3 (CH_3), 37.0 (CH_2Cl), 47.4 (CH_2N), 113.1 (CH_{Furan}), 117.8 (CH_{Furan}), 119.3 ($CH=C_{Rhodanin}$), 122.2 ($CH=C_{Rhodanin}$), 129.0 (2CH), 129.4 (2CH), 132.0 (*C*), 138.0 (*C*), 150.7 (C_{Furan}), 154.9 (C_{Furan}), 167.6 (C=O) and 194.3 (C=S).

(Z)-5-((5-(Chloromethyl)furan-2-yl)methylene)-3-(2-methoxyethyl)-2-thioxothiazolidin-4-one (3d)

Yellow powder; mp: 134–140°C; 0.200 g, yield: 63%. IR (KBr) (υ_{max}/cm^{-1}): 1710, 1608, 1327, 1221, 1126, 1105. MS (*m/z*, %): 317 (M^+, 15), 282 (16), 258.9 (24), 172 (39), 137 (100), 63 (25). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ ppm 3.36 (s, 3H, CH_3O), 3.70 (t, 2H, $^3J_{HH}$ = 5.8 Hz, NCH_2), 4.35 (t, 2H, $^3J_{HH}$ = 5.8 Hz, OCH_2), 4.63 (s, 2H, CH_2Cl), 6.56 (d, 1H, $^3J_{HH}$ = 3.6 Hz, CH_{Furan}), 6.78 (d, 1H, $^3J_{HH}$ = 3.6 Hz, CH_{Furan}), 7. 44 (s, 1H, =C*H*); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ ppm 37.0 (CH_2Cl), 43.6 (CH_2N), 59.0 (CH_3O), 68.4 (CH_2O), 113.1(CH_{Furan}), 117.7 (CH_{Furan}), 119.2 ($CH=C_{Rhodanin}$), 121.9 ($CH=C_{Rhodanin}$), 150.6 (C_{Furan}), 154.7 (C_{Furan}), 167.5 (C=O) and 194.5 (C=S).

(Z)-5-((5-(Hydroxymethyl)furan-2-yl)methylene)-3-phenethyl-2-thioxothiazolidin-4-one (3e)

Yellow powder; mp: 108–109°C; 0.259 g, yield: 75%. IR (KBr) (υ_{max}/cm^{-1}): 3422, 1700, 1607, 1328, 1256, 1166, 1023, 805, 697. MS (*m/z*, %): 345 (M^+, 34), 241 (37), 154 (100). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ ppm 1.76 (s, 1H, OH), 3.01 (t, 2H, $^3J_{HH}$ = 10.0 Hz, CH_2-Ar), 4.33 (t, 2H, $^3J_{HH}$ = 10.0 Hz, N–CH_2), 4.73 (s, 2H, CH_2-OH), 6.51 (d, 1H, $^3J_{HH}$ = 3.5 Hz, CH_{Furan}), 6. 81 (d, 1H, $^3J_{HH}$ = 3.5 Hz, CH_{Furan}), 7.23–7.35 (m, 5H, Ar), 7. 42 (s, 1H, =C*H*);^{13}C NMR (125.7 MHz, $CDCl_3$): δ ppm 32.9 (CH_2Ph), 45.5 (CH_2-N), 57.6 (CH_2-OH), 111.1 (CH_{Furan}), 118.0 (CH_{Furan}), 119.5 ($CH=C_{Rhodanin}$), 120.6 ($CH=C_{Rhodanin}$), 126.6 (CH), 128.5 (2CH), 128.8 (2CH), 137.4 (C_{Ar}), 149.7 (C_{Furan}), 159.0 (C_{Furan}), 167.1 (C=O) and 194.0 (C=S).

(Z)-3-Benzyl-5-((5-(hydroxymethyl)furan-2-yl)methylene)-2-thioxothiazolidin-4-one(3f)

Yellow powder; mp: 150–152°C; 0.148 g, yield: 45%. IR (KBr) (υ_{max}/cm^{-1}): 3422, 1702, 1607, 1302, 1190, 1007. MS (*m/z*, %): 329 (M^+-2, 4), 311 (11), 134 (24), 91 (45), 63 (100).^{1}H NMR (500.1 MHz, $CDCl_3$): δ ppm 2.25 (s, 1H, O*H*), 4.69 (s, 2H, CH_2N), 5.30 (s, 2H, CH_2OH), 6.45 (d, 1H, $^3J_{HH}$ = 3.5 Hz, CH_{Furan}), 6.78 (d, 1H, $^3J_{HH}$ = 3.5 Hz, CH_{Furan}), 7.28–7.34 (m, 3H, Ar) 7. 44 (s, 1H, =C*H*), 7.45–7.47 (m, 2H, Ar);^{13}C NMR (125.7 MHz, $CDCl_3$): δ ppm 47.4 (CH_2N), 57.6 (CH_2OH), 111.2 (CH_{Furan}), 118.3 (CH_{Furan}), 119.8 ($CH=C_{Rhodanin}$), 120.6 ($CH=C_{Rhodan1in}$), 128.1 (CH), 128.6 (2CH), 128.9 (2CH), 134.9 (C_{Ar}), 149.8 (C_{Furan}), 159.4 (C_{Furan}), 167.6 (C=O) and 194.2 (C=S).

(Z)-3-(4-Methyl-benzyl)-5-((5-(hydroxymethyl)furan-2-yl)methylene)-2-thioxothiazolidin-4-one (3g)

Yellow powder; mp: 177–180°C; 0.207 g, yield: 60%. IR (KBr) (υ_{max}/cm^{-1}): 3424, 1699, 1608, 1342, 1305, 1188, 1022. MS (*m/z*, %): 345 (M^+, 29), 154 (44), 105 (43), 63 (100). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ ppm 2.31 (s, 3H, CH_3), 3.96 (s, 1H, O*H*), 4.70 (s, 2H, NCH_2), 5.26 (s, 2H, CH_2OH), 6.47 (d, 1H, $^3J_{HH}$ = 3.5 Hz, CH_{Furan}), 6.77 (d, 1H, $^3J_{HH}$ = 3.5 Hz, CH_{Furan}), 7.12 (d, 2H, J_{HH} = 7.8, Ar), 7.36 (d, 2H, J_{HH} = 8.0, Ar), 7. 41 (s, 1H, =C*H*); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ ppm 21.2 (CH_3), 47.2 (CH_2N), 57.7 (CH_2OH),

111.2(CH_{Furan}), 118.2 (CH_{Furan}), 119.6 ($CH=C_{Rhodanin}$), 120.8 ($CH=C_{Rhodanin}$), 129.0 (2CH), 129.2 (2CH), 131.9. (C), 137.9 (C), 149.8 (C_{Furan}), 159.2 (C_{Furan}), 167.6 ($C=O$), 194.2 ($C=S$).

(Z)-5-((5-(Hydroxymethyl)furan-2-yl) methylene)-3-(2-methoxyethyl)-2-thioxothi azolidin-4-one (3h)
Yellow powder; mp: 94–95°C; 0.144 g, yield: 48%. IR (KBr) (υ_{max}/cm^{-1}): 3423, 1705, 1606, 1340, 1328, 1219, 1187, 1163, 1020. MS (*m/z*, %): 299 (M^+, 20), 241 (25), 154 (54), 137 (21), 78 (91), 63 (100). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ ppm 2.42 (s, 1H, O*H*), 3.35 (s, 3H, CH_3O), 3.69 (t, 2H, $^3J_{HH}$ = 5.8 Hz, NCH_2), 4.32 (t, 2H, $^3J_{HH}$ = 5.8 Hz, OCH_2), 4.69 (s, 2H, CH_2OH), 6.48 (d, 1H, $^3J_{HH}$ = 3.5 Hz, CH_{Furan}), 6.77 (d, 1H, $^3J_{HH}$ = 3.5 Hz, CH_{Furan}), 7. 38 (s, 1H, $=CH$);^{13}C NMR (125.7 MHz, $CDCl_3$): δ ppm 43.4 (CH_2-N), 57.6 (CH_2-OH), 58.9 (CH_3-O), 68.3 (CH_2-O), 111.2(CH_{Furan}), 118.3 (CH_{Furan}), 119.7 ($CH=C_{Rhodanin}$), 120.5 ($CH=C_{Rhodanin}$), 149.8 (C_{Furan}), 159.5 (C_{Furan}), 167.6 ($C=O$) and 194.6 ($C=S$).

(Z)-5-((Furan-2-yl)methylene)-3-phenethyl-2-thioxothiazolidin-4-one (3i)
Yellow powder; 0.202 g, yield: 64%, mp: 151–152°C [27].

(Z)-3-Benzyl-5-((furan-2-yl)methylene)-2-thioxothiazolidin-4-one (3j)
Yellow powder; 0.172 g, yield: 57%, mp: 140–142°C [29].

Procedure for the preparation of hydrochloride salt of (Z)-5-((5-(aminomethyl)furan-2-yl)methylene)-3-phenethyl-2-thioxothiazolidin-4-one (5)

To a boiling solution of **3a** (364 mg, 1 mmol) in chloroform (6 mL) was added hexamethylenetetramine (196 mg, 1.4 mmol), and the reaction mixture was heated for 4 h under reflux condition. The obtained hexamethylenetetraammonium salt was filtered and dissolved in 4 mL ethanol. Then concentrated HCl (10.0 equiv.) was added to the reaction mixture and the mixture was heated at reflux condition. After 2 hours, compound **5** participate as a yellow powder. Mp: 209–210°C (decomposition); 0.141 g, yield: 37%. IR (KBr) (υ_{max}/cm^{-1}): 2864 (br), 1682, 1599, 1329, 1179. MS (*m/z*, %): 344 (M^+-36, 81), 240 (48), 153 (100), 96 (52).^{1}H NMR (500.1 MHz, DMSO): δ ppm 2.95 (t, 2H, $^3J_{HH}$ = 9.0 Hz, CH_2Ar), 4.20–4.24 (m, 4H, NCH_2), 6.86 (d, 1H, $^3J_{HH}$ = 3.5 Hz, CH_{Furan}), 7.19–7.22 (m, 4H, CH_{Furan} and Ar), 7.27–7.30 (m, 2H, Ar), 7.59 (s, 1H, $=CH$), 8.87 (bs, 3H, NH_3 exchange with D_2O). ^{13}C NMR (125.7 MHz, DMSO): δ ppm 32.2 (CH_2Ph), 35.2 (CH_2N), 45.3 (CH_2NH_3), 114.2 (CH_{Furan}), 118.4 (CH_{Furan}), 119.8 ($CH=C_{Rhodanin}$), 121.4 ($CH=C_{Rhodanin}$), 126.7 (CH), 128.6 (2CH), 128.7 (2CH), 137.6 (C_{Ar}), 149.7 (C_{Furan}), 153.4 (C_{Furan}), 166.5 ($C=O$) and 194.4 ($C=S$).

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Supporting information

^{1}H NMR,^{13}C NMR, and Mass spectra of all new compounds associated with this article can be found in the online version.

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