Practical One-Pot Two-Step Protocol for the Microwave-Assisted Synthesis of Highly Functionalized Rhodanine Derivatives

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A fast and efficient protocol for the generation of substituted 5-arylidene rhodanines in a sequential one-pot two-step process combining the "Holmberg method" and the Knoevenagel condensation under microwave-assisted conditions has been developed. The final compounds **11a**−**k** have been obtained in high yield and purity after a simple precipitation from methanol, making this procedure facile, practical, and rapid to execute.

In 1986, Evans and co-workers introduced the concept of "Privileged structure" as a single molecular framework able to provide ligands for diverse receptors.[1] Such preferred molecular scaffolds have an inherent tendency for biological activity which can be directed toward different targets through appropriate modifications. As nicely summarized by Tomašiæ and Mašiè in a recently published review,[2] rhodanine (2-thiazolidin-4-ones) represent a very interesting privileged scaffold whose functionalization has led to compounds endowed with antibacterial, antifungal, antiviral, antimalarial, insecticidal, herbicidal, antitumor, anti-inflammatory, and cardiotonic activities. In particular, 5-alkylidene- and 5-arylidene rhodanine derivatives constitute a recurring scaffold of many active compounds, and its importance is further underlined by the presence on the market of the aldose reductase inhibitor Epalrestat for the treatment of diabetic complications.[3]

Among these 5-arylidene rhodanine derivatives, our research group has recently identified the first small molecule able to inhibit HIV replication by targeting a cellular enzyme: the RNA helicases DDX3.[4] The precise combination of functional groups on the rhodanine scaffold was shown to be responsible for the DDX3 inhibitory activity and selectivity of the hit compound FE15 (Figure 1).

In times where a premium is put on speed, diversity, and efficiency in the drug discovery process, it is important to rely on combinatorial approaches for the discovery and optimization of new drugs. Rhodanine derivatives have been synthesized so far assembling the functionalized heterocycles by reaction of α-halogencarboxylic acid and maleic acid derivatives with carbon disulfide and amines or by reaction of isothiocyanates with thioglicolates.[5] A few multicomponent approaches, based on the construction of the functionalized rhodanine scaffold, have been recently developed: (*i*) Gabillet et al. reported the phosphine catalyzed reaction of dithiocarbamates, preparated in situ, and arylpropiolates;[6] (*ii*) Alizadeh et al. reported the three-component reaction between CS_2, primary amines and acetylenic esters or fumaryl chloride;[7] (*iii*) Attanasi et al. reported the three-component reaction between CS_2, primary amines, and 1,2-diaza-1,3-dienes.[8] These multicomponent protocols present, however, a few drawbacks for combinatorial application, such as the use of toxic carbon disulfide and the low chemical diversity that can be created as a consequence of the limited flexibility (and/or commercial availability) of one of the substrates (e.g., arylpropiolates, acetylenic esters, fumaryl chloride, 1,2-diaza-1,3-dienes) to be used in the multicomponent procedures.

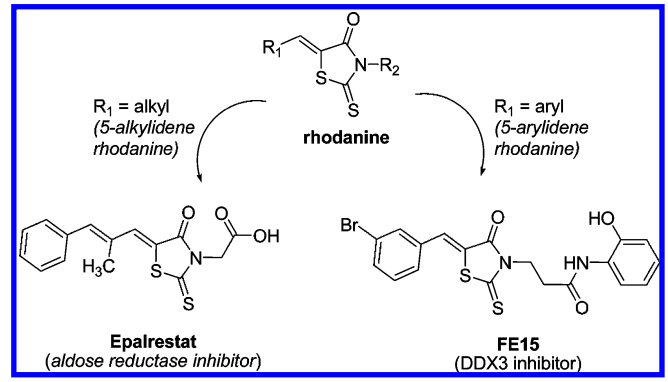

Figure 1. 5-Alkylidene- and 5-arylidene rhodanine derivatives.

With the aim to develop a more efficient synthetic process for the synthesis of highly functionalized rhodanine derivatives and in continuation of our recent interest in the development of combinatorial approaches to the synthesis of new heterocycles,[9] herein we describe a practical, inexpensive, and rapid microwave-assisted method for the synthesis of highly functionalized 5-arylidene rhodanines.

An interesting multicomponent approach for the generation of several 3,5-disubstituted 1,3-thiazolidine-2,4-diones via direct functionalization of the heterocyclic scaffold has been

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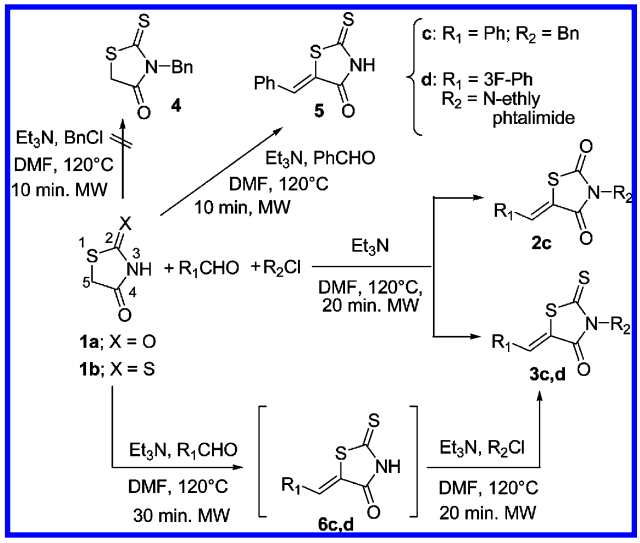
Scheme 1. Multicomponent Approaches to 3-Substituted-5-arylidene Rhodanine Derivatives



recently reported by Yang et al.:[10] reacting the 1,3-thiazolidine-2,4-dione (**1a**) in an ionic liquid with the opportune aldehyde and alkylating agent gave the desired 3,5-disubstituted compounds in good yields. Unfortunately, the authors observed that rhodanine (**1b**) did not react under the same reaction conditions. On the basis of these results, we envisioned to develop a modified microwave-assisted protocol for the direct functionalization of the rhodanine scaffold. The latter protocol was initially validated on the 1,3-thiazolidine-2,4-diones **1a** (synthesized following a reported procedure):[11] reacting this compound in *N*,*N*-dimethylformamide (DMF) with benzaldehyde (2 equiv) and benzyl chloride (1 equiv) under microwave irradiation (120 °C, sealed tube), it was possible to obtain the desired product **2c** in 70%. This procedure gave results comparable to that reported by Yang (in terms of yield) and allowed to access the desired compound in only 20 min (Scheme 1).

However, when the same protocol was applied to the rhodanine (**1b**), a complex mixture was obtained: the desired compound **3c** was isolated, after a difficult chromathographic purification, in 18% yield together with other uncharacterized byproducts.[12] The unsatisfactory results obtained by application of the above multicomponent protocol to the rhodanine (**1b**) were explained considering the difficulty connected with the N-alkylation of rhodanines which are commonly converted into the corresponding sodium or potassium salts to allow the formation of N-alkylated products.[5,13] In fact, when we tried the simple microwave-assisted benzylation of **1b**, only traces of the product **4** were obtained while, under the same experimental conditions, the Knoevenagel reaction gave the desired compound **5** in 60% yield (Scheme 1). We tried therefore to react the rhodanine **1b** in a one-pot two-step procedure consisting in a preliminary Knoevenagel condensation with the opportune aldehydes to give the intermediates **6c,d** which were directly treated with the opportune alkylating agents thus allowing us to obtain the desired products **3c,d** (Scheme 1). The latter compounds were, however, obtained in low to moderate yields (10% and 27%, respectively) after a time-consuming chromatographic purification. For this reason we decided to drop this synthetic strategy

Scheme 2. Model Reaction

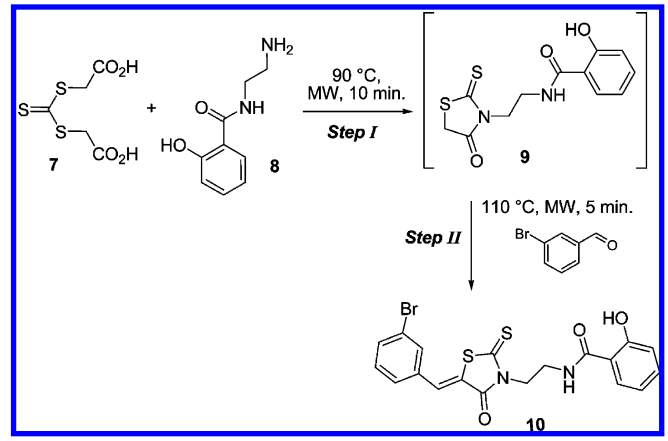


Table 1. Model Reaction, Conditions, and Yield

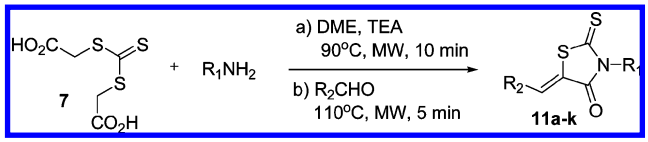
entry	solvent	step I (Et_3N eq.)	step II (Et_3N eq.)	yield[a](%)
1	iPrOH		1	20
2	iPrOH	1		53
3	iPrOH	1	1	61
4	DME		1	42
5	DME	1		69
6	DME	1	1	59
7	DMF		1	46
8	DMF	1		53
9	DMF	1	1	26

[a] Isolated yield.

and to focus on the poorly exploited "Holmberg method" which is based on the reaction between bis(carboxymethyl)-trithiocarbonate (**7**) and primary amines, usually in ethanol or water, to give the corresponding N-functionalized rhodanine.[14] A one-pot two-step protocol combining the Holmberg method and the Knoevenagel condensation was thus attempted to produce directly the 3-substituted 5-arylidene rhodanines (Scheme 2). To validate this protocol, the reaction conditions were optimized for the synthesis of compound **10**, a closely related analogue of our DDX3 inhibitor FE15. After a preliminary screening of the microwave irradiation conditions (temperature and time), a few parameters were changed to optimize the two-step sequence: the equivalents of base (Et_3N) added and the solvent used for the reaction (Table 1). As shown in Table 1, the best results were obtained using dimethoxyethane (DME) as solvent and adding 1 equiv of triethylamine only in the first step of the reaction (see entry 5). Following the optimized protocol, bis(carboxymethyl)trithiocarbonate **7** (1 equiv) and the amine **8** (1equiv) (synthesized following a reported procedure)[15] were dissolved in DME, and the resulting mixture heated at 90 °C under microwave irradiation for 10 min. After this time, 3-bromobenzaldehyde (1 equiv) was added, and the mixture was heated at 110 °C under microwave irradiation for 5 min. The desired product (**10**) was finally obtained in high yield and purity after a simple precipitation from methanol (Table 1, entry 5).

To verify the versatility and efficiency of the optimized one-pot two-step protocol, different commercially available amines (R_1NH_2) and aldehydes (R_2CHO) were used as building blocks to generate a collection of 3,5-disubstituted rhodanine derivatives **11a**−**k** (Scheme 3, Table 2): in all cases, the products were isolated in high purity and in

Scheme 3. One-Pot Two-Step Synthesis of 3-Substituted-5-arylidene Rhodanines



moderate to good yields after a simple precipitation from MeOH. In most of the cases, the thermodynamically more stable *Z*-isomers predominated (*Z*/*E* ratio ≥ 98/2), and the configuration was assigned as previously reported in the literature (Table 2).[16] Only in two cases (Table 2, entries 1 and 4), the supposed *E*-isomers were observed in higher amount from HPL-MS analysis but never isolated.

This protocol can be applied to heterocyclic- or aryl aldehydes in combination with phenylethyl-, benzyl-, and aliphatic amines (Entries 1−7). A few amines bearing functional groups suitable for further scaffold elaboration have also been used (Entries 8−11): propargylamine (Entry 8) gave a product (**11h**) that could be further elaborated via click-chemistry approaches; aminoacetaldehyde diethyl acetal (Entry 9) gave a product (**11i**) with a masked aldehyde that could be easily decorated; N-Boc-ethylenediamine (Entry 10) gave a product (**11j**) whose exocyclic amine moiety could be further reacted to give potential DDX3 inhibitors (such as compounds **10** and **11k**).

In conclusion, we developed a fast and efficient protocol for the generation of substituted rhodanine derivatives in a sequential one-pot two-step process combining the "Holmberg method" and the Knoevenagel condensation under microwave-assisted conditions. The present method can be exploited for the generation of 5-arylidene rhodanines endowed with a high level of structural diversity starting from commercially available amines and aldehydes. It is also worth noting that the final compounds have been obtained in high yield and purity after a simple precipitation from methanol, making this procedure facile, practical, and rapid to execute.

Experimental Section

General Information. All commercially available chemicals were used as purchased. Anhydrous reactions were run under a positive pressure of dry N_2. Thin-layer chromatography (TLC) was carried out using Merck TLC plates silica gel 60 F254. Chromatographic purifications were performed on columns packed with Merck 60 silica gel, 23−400 mesh, for flash technique. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz on a Bruker Avance DPX400 spectrometer. Chemical shifts are reported relative to CDCl3 at δ 7.24 ppm and tetramethylsilane at δ 0.00 ppm. Melting points were taken using a Gallenkamp melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer PE 2004 elemental analyzer, and the data for C, H, and N are within 0.4% of the theoretical values.

HPLC and MS Analysis. The purity of compounds was assessed by reversed-phase liquid chromatography and a mass spectrometer (Agilent series 1100 LC/MSD) with a UV detector at $\lambda = 254$ nm and an electrospray ionization source (ESI). The LC elution method (using a Zorbax Eclipse XDB, 4.6 × 150 mm, 5-μm C8 column) was the following: Temp = 25 °C, mobile phase composed of (A) 85% methanol and (B) 15% water at a flow rate of 1.0 mL/min (all solvents were HPLC grade, Sigma Aldrich).

Mass spectral (MS) data were obtained using an Agilent 1100 LC/MSD VL system (G1946C) with a 0.4 mL/min flow rate using a binary solvent system of 95:5 methyl alcohol/water. UV detection was monitored at 254 nm. Mass spectra were acquired in positive mode scanning over the mass range of 50−1500. The following ion source parameters were used: drying gas flow, 9 mL/min; nebulizer pressure, 40 psig; drying gas temperature, 350 °C.

Microwave Irradiation Experiments. Microwave reactions were conducted using a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC). The machine consists of a continuous focused microwave power delivery system with operator-selectable power output from 0 to 300 W. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature control mounted under the reaction vessel. All experiments were performed using a stirring option whereby the contents of the vessel are stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel.

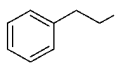
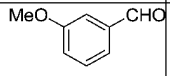
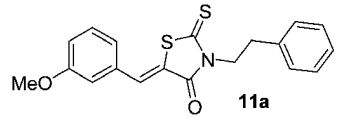
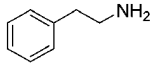
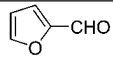
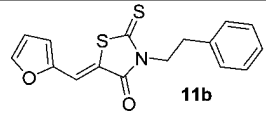
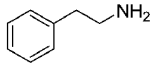
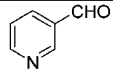
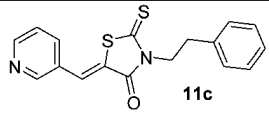
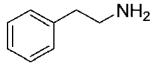
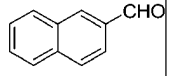
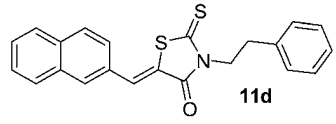
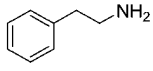
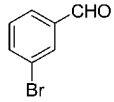
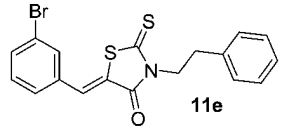
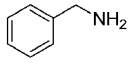
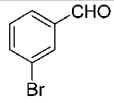
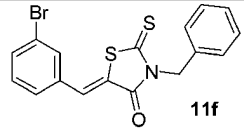
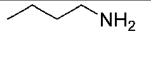
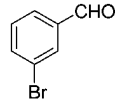
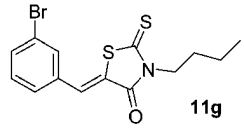
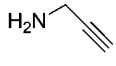
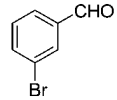
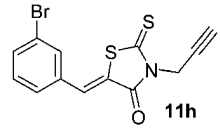
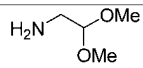
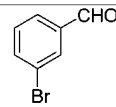
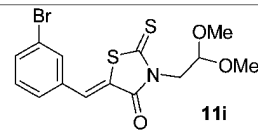
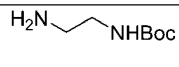
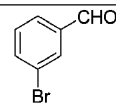
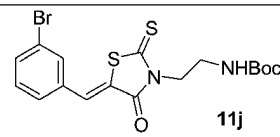
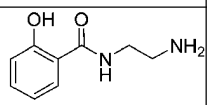
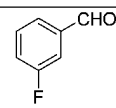
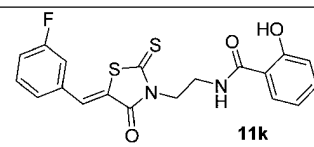
Multicomponent Synthesis of (Z)-3-benzyl-5-benzylidenethiazolidine-2,4-dione (2c) and (Z)-3-benzyl-5-benzylidene-2-thioxothiazolidin-4-one (3c). General Procedure. To a solution of 1,3-thiazolidine-2,4-diones (**1a**) or 2-Thioxo-4-thiazolidinone (**1b**) (0.171 mmol) in DMF (0.5 mL), TEA (0.342 mmol), benzyl chloride (0.205 mmol) and benzaldehyde (0.342 mmol) were added. The resulting mixture was heated at 120 °C under microwave irradiation for 20 min and then it was cooled down to room temperature. Water was added and the mixture was extracted with ethyl acetate; organic phases were collected, washed with brine, dried over Na_2SO_4. After removal of the solvent, the crude mixture was purified by flash chromatography (EtOAc/hexane, 1:5) to give the pure products.

(Z)-3-benzyl-5-benzylidenethiazolidine-2,4-dione (2c). (Yield: 70%) Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) 7.84 (1H, s), 7.47−7.21 (10H, m), 4.84 (2H, s) ppm. MS (ESI): *m*/*z* 296 $[M+H]^+$; Anal. ($C_{17}H_{13}NO_2S$) C, H, N.

(Z)-3-benzyl-5-benzylidene-2-thioxothiazolidin-4-one (3c). (Yield 18%) Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) 7.79 (1H,s), 7.55−7.26 (10H, m), 5.31 (2H, s) ppm. ^{13}C NMR (CDCl3, 100 MHz) 47.5, 122.9, 128.1, 128.5, 128.9, 129.3, 130.6, 130.7, 133.2, 133.3, 134.8, 167.8, 193.1. MS (ESI): *m*/*z* 312 $[M+H]^+$; Anal. ($C_{17}H_{13}NOS_2$) C, H, N.

One-Pot Two-Steps Microwave-Assisted Synthesis of (Z)-5-benzylidene-3-phenethyl-2-thioxothiazolidin-4-one (3c) and 2-(2-((Z)-5-(3-fluorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)ethyl)isoindoline-1,3-dione (3d). General Procedure. To a solution of 2-thioxo-4-thiazolidinone **1b** (1 equiv) in DMF (1.0 mL) were added TEA (1.2 equiv) and the opportune aldehyde (R_1CHO, 1 equiv). The reaction mixture was heated at 110 °C for 30 min under microwave irradiation. After this time, TEA (1.2 equiv) and the opportune alkyl chloride (2.4 equiv) were added, and the mixture was heated at 110 °C for 20 min under microwave irradiation. Water was added, and the mixture was

Table 2. Collection of 3-Substituted-5-arylidene Rhodanines (**11a**−**k**), Purity and Yield

Entry	R_1NH_2	R_2CHO	Product	Purity[a] (%)	Z/E[a]	Yield[b] (%)
1			 **11a**	>99	89/11	63
2			 **11b**	98	100/0	64
3			 **11c**	>99	98/2	47
4			 **11d**	96	81/19	58
5			 **11e**	89	98/2	56
6			 **11f**	>99	100/0	59
7			 **11g**	>99	100/0	44
8			 **11h**	>99	100/0	37
9			 **11i**	>99	100/0	58
10			 **11j**	>99	99/1	31
11			 **11k**	98	100/0	62

[a] Determined by HPLC-MS using a Zorbax Eclipse XDB, 4.6 × 150 mm, 5-μm C8 column (methanol/water 85:15, flow rate 1.0 mL/min, UV-254 nm). [b] Isolated yield.

extracted with ethyl acetate; organic phases were collected, washed with NH_4Cl, dried over Na_2SO_4. After removal of the solvent, the crude mixture was purified by flash chromatography (EtOAc/hexane, 1:4) to give the pure products.

(Z)-3-benzyl-5-benzylidene-2-thioxothiazolidin-4-one (3c). (Yield 10%) Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) 7.79 (1H,s), 7.55−7.26 (10H, m), 5.31 (2H, s) ppm. ^{13}C NMR (CDCl3, 100 MHz) 47.5, 122.8, 128.0, 128.3, 128.9, 129.3, 130.6, 131.0, 133.1, 133.2, 135.0, 167.8, 192.8 ppm. MS (ESI): *m/z* 312 $[M+H]^+$, Anal. ($C_{17}H_{13}NOS_2$) C, H, N.

2-(2-((Z)-5-(3-fluorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)ethyl)isoindoline-1,3-dione (3d). (Yield 27%) Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) 7.74−7.72 (2H, m), 7.62−7.61 (2H, m), 7.52 (1H, s), 7.39−7.32 (1H, q), 7.20−7.16 (1H, d), 7.09−7.06 (2H, m), 4.40−4.38 (2H, t), 4.07−4.00 (2H, t) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 193.3, 168.1, 167.7, 164.2, 161.7, 135.4, 131.9, 131.6, 130.9, 126.4, 124.2, 117.8, 117.6, 117.1, 116.9, 43.1, 35.3 ppm. MS (ESI): *m/z* 413 $[M+H]^+$; Anal. ($C_{20}H_{13}FN_2O_3S_2$) C, H, N.

(Z)-5-benzylidene-2-thioxothiazolidin-4-one (5). To a solution of rhodanine **1b** (0.15 mmol) in DMF (0.5 mL) were added TEA (0.18 mmol) and benzaldehyde (0.15 mmol). The mixture was heated at 110 °C under microwave irradiation for 20 min, and then it was cooled down to room temperature. Water was added, and the mixture was extracted with diethyl ether; organic phases were collected, washed with NH_4Cl, dried over Na_2SO_4, and concentrated in vacuo. After removal of the solvent, the crude mixture was purified by flash chromatography (EtOAc/hexane; 1:6) to give the pure product **5** in 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 7.4−7.3 (m, 5H); 4.9 (s, 2H). ^{13}C NMR (CDCl3): 49.3; 133.9; 128.8; 128.6; 128.5; 167.1. MS (ESI): *m/z* 222 $[M+H]^+$; Anal. ($C_{10}H_7NOS_2$) C, H, N.

One-Pot Two-Steps Microwave-Assisted Synthesis of N-substituted 5-Arylidene-thiazol-4-ones. General Procedure. To a solution of bis(carboxymethyl)trithiocarbonate **7** (1 equiv) in DME (1.0 mL) were added TEA (1 equiv) and the opportune amine (R_1NH_2, 1 equiv). The reaction mixture was heated at 90 °C for 10 min under microwave irradiation. After this time, the opportune aldehyde (R_2CHO, 1 equiv) was added, and the mixture was heated at 110 °C for 5 min under microwave irradiation. The reaction mixture was evaporated to dryness, and the residue was additioned with MeOH; the final rhodanine derivative was obtained as a pure precipitate upon standing, isolated by filtration, washed with hexane, and finally dried under high vacuum.

(Z)-5-(3-methoxybenzylidene)-3-phenethyl-2-thioxothiazolidin-4-one (11a). HPLC t_R 5.92 min. Yellow solid. Mp 122−125. ^{1}H NMR (400 MHz, $CDCl_3$) 7.60 (1H, s), 7.34−7.18 (6H, m), 7.03−7.01 (1H, d), 6.92 (2H, s), 4.29−4.25 (2H, t, J = 7.9 Hz), 3.79 (3H, s), 2.96−2.92 (2H, t, J = 7.9 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 193.1, 167.5, 160.1, 137.5, 134.6, 133.1, 130.4, 129.0, 128.9, 128.7, 128.6, 126.8, 123.2, 116.9, 115.2, 55.4, 45.7, 32.9 ppm. MS (ESI): *m/z* 356 $[M+H]^+$, 378 $[M+Na]^+$; Anal. ($C_{19}H_{17}NO_2S_2$) C, H, N.

(Z)-5-((furan-2-yl)methylene)-3-phenethyl-2-thioxothiazolidin-4-one (11b). HPLC t_R 4.10 min. Orange solid. Mp 150−152 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 7.63 (1H, s), 7.38 (1H, s), 7.3−7.1 (5H, m), 6.76 (1H, m), 6.52 (1H, m), 4.27−4.23 (2H, t, J = 7.9 Hz), 2.95−2.91 (2H, t, J = 7.9 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 194.3, 167.3, 150.2, 147.0, 137.6, 129.0, 128.6, 126.8, 120.9, 118.6, 118.3, 113.5, 45.6, 33.0 ppm. MS (ESI): *m/z* 316 $[M+H]^+$, 338 $[M+Na]^+$; Anal. ($C_{16}H_{13}NO_2S_2$) C, H, N.

(Z)-3-phenethyl-5-((pyridin-3-yl)methylene)-2-thioxothiazolidin-4-one (11c). HPLC t_R 3.42 min. Yellow solid. Mp 138−140 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 8.69 (1H, s), 8−57−8.56 (1H, d, J = 4.4 Hz), 7.70−7.68 (1H, d, J = 7.9 Hz), 7.59 (1H, s), 7.36−7.33 (1H, dd, J = 4.7 Hz, J = 7.9 Hz), 7.26−7.16 (5H, m), 4.28−4.24 (2H, t, J = 7.9), 2.95−2.91 (2H, t, J = 7.9 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 192.0, 167.1, 151.9, 150.8, 137.3, 136.3, 129.4, 128.9, 128.8, 128.7, 126.9, 125.5, 124.0, 45.8, 32.9 ppm. MS (ESI): *m/z* 327 $[M+H]^+$, 449 $[M+Na]^+$; Anal. ($C_{17}H_{14}N_2OS_2$) C, H, N.

(Z)-5-((naphthalen-3-yl)methylene)-3-phenethyl-2-thioxothiazolidin-4-one (11d). HPLC t_R 8.23 min. Yellow solid. Mp 174−176 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 7.90−7.79 (5H, m), 7.53−7.46 (3H, m), 7.29−7.19 (5H, m), 4.30−4.26 (2H, t, J = 7.9 Hz), 2.98−2.94 (2H, t, J = 7.9 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 193.1, 167.5, 137.6, 133.9, 133.2, 132.1, 130.8, 129.2, 129.0, 128.9, 128.7, 128.3, 127.8, 127.2, 126.8, 126.2, 45.7, 33.0 ppm. MS (ESI): *m/z* 376 $[M+H]^+$; Anal. ($C_{22}H_{17}NOS_2$) C, H, N.

(Z)-5-(3-bromobenzylidene)-3-phenethyl-2-thioxothiazolidin-4-one (11e). HPLC t_R 7.83 min. Yellow solid. Mp 102−104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 7.56−7.49 (3H, m), δ 7.36−7.13 (7H, m), δ 4.30−4.26 (2H, t, J = 7.8 Hz), δ 2.96−2.92 (2H, t, J = 7.8 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 192.5, 167.3, 137.3, 137.1, 135.3, 133.4, 133.1, 130.9, 130.7, 128.9, 126.9, 124.06, 123.0, 45.75, 32.93 ppm. MS (ESI): *m/z* 405 $[M+H]^+$, 427 $[M+Na]^+$; Anal. ($C_{18}H_{14}BrNOS_2$) C, H, N.

(Z)-5-(3-bromobenzylidene)-3-benzyl-2-thioxothiazolidin-4-one (11f). HPLC t_R 6.90 min. Yellow solid. Mp 112−113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.47 (3H, m), δ 7.41−7.24 (7H, m), δ 5.25 (2H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 192.5, 167.6, 135.3, 134.7, 133.5, 133.2, 131.2, 130.8, 129.0, 128.8, 128.6, 128.3, 124.7, 123.5, 47.6 ppm. MS (ESI): *m/z* 414 $[M+Na]^+$; Anal. ($C_{17}H_{12}BrNOS_2$) C, H, N.

(Z)-5-(3-bromobenzylidene)-3-butyl-2-thioxothiazolidin-4-one (11g). HPLC t_R 7.95 min. Yellow solid. Mp 113−115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 7.51−7.45 (3H, m), 7.33−7.24 (2H, m), 4.05−4.02 (2H, t, J = 7.5 Hz), 1.61−1−59 (2H, m, J = 7.5 Hz), 1.32−1.29 (2H, m, J = 7.5 Hz), 0.90−0.87 (3H, t, J = 7.2 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 192.7, 167.5, 135.4, 133.3, 133.2, 130.7, 128.7, 124.9, 123.4, 44.6, 29.0, 20.1, 13.7 ppm. MS (ESI): *m/z* 356 $[M+H]^+$; Anal. ($C_{14}H_{14}BrNOS_2$) C, H, N.

(Z)-5-(3-bromobenzylidene)-3-(prop-2-ynyl)-2-thioxothiazolidin-4-one (11h). HPLC t_R 3.44 min. Orange solid. Mp 159−161 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (1H, s), δ 7.55 (1H,s), δ 7.51−7.49 (1H, d, J = 7.7 Hz), δ 7.35−7.34 (1H, d, J = 7.7 Hz), δ 7.29−7.19 (1H, t, J = 7.7 Hz), δ 4.81−4.80 (2H, d, J = 2.1 Hz), δ 2.19−2.18 (1H, t, J = 2.1 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 191.2, 166.4, 135.2,

133.7, 133.6, 133.3, 133.2, 131.8, 131.6, 130.9, 130.7, 128.9, 128.7, 124.4, 123.5, 75.7, 72.3, 33.6 ppm. MS (ESI): *m/z* 346 $[M+Na]^+$; Anal. ($C_{13}H_8BrNOS_2$) C, H, N.

(Z)-5-(3-bromobenzylidene)-3-(2,2-dimethoxyethyl)-2-thioxothiazolidin-4-one (11i). HPLC t_R 4.23 min. Yellow solid. Mp 124−126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−7.52 (2H, m), δ 7.48−7.46 (1H, d, J = 7.8 Hz), δ 7.33−7.31 (1H, d, J = 7.8 Hz), δ 7.28−7.24 (1H, t, J = 7.8 Hz), δ 4.85−4.82 (1H, t, J = 5.6 Hz), 4.19−4.18 (2H, d, J = 5.6 Hz), 3.31 (6H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 193.0, 167.4, 135.3, 133.5, 133.2, 131.2, 130.7, 128.8, 124.5, 123.5, 99.3, 53.9, 45.0 ppm. MS (ESI): *m/z* 412 $[M+Na]^+$; Anal. ($C_{14}H_{14}BrNO_3S_2$) C, H, N.

(Z)-5-(3-bromobenzylidene)-3-(2-(tert-butylamino)ethyl)-2-thioxothiazolidin-4-one (11j). HPLC t_R 3.78 min. Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (2H, s), δ 7.48−7.52 (1H, d, J = 7.85 Hz), δ 7.33−7.38 (1H,d, J = 7.85 Hz), δ 7.26−7.32 (1H, t, J = 7.85 Hz), δ 4.20−4.27 (2H, t, J = 5.37 Hz), δ 3.41−3.47 (2H, t, J = 5.37 Hz), δ 1.45−1.52 (1H, bs, NH), δ 1.28−1.37 (9H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 193.2, 167.8, 155.9, 135.4, 133.4, 133.2, 130.8, 128.7, 124.6, 123.5, 79.6, 44.4, 38.3, 28.3 ppm. MS (ESI): *m/z* 467 $[M+Na]^+$; Anal. ($C_{16}H_{19}BrN_2OS_2$) C, H, N, S.

N-(2-((Z)-5-(3-fluorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)ethyl)-2-hydroxybenzamide (11k). HPLC 3.34 min. Yellow solid. ^{1}H NMR (400 MHz, DMSO) 12.31 (1H, s), 8.86−8.85 (1H, t, J = 4.6 Hz), 7.72 (1H, s), 7.58−7.50 (2H, m), 7.45−7.37 (2H, m), 7.31−7.29 (2H, m), 6.80−6.76 (2H, m), 4.23−4.17 (2H, t, J = 4.5 Hz), 3.61−3.53 (2H, q, J = 4.6 Hz); ^{13}C NMR (100 MHz, DMSO) 193.8, 169.8, 167.2, 164.8, 160.2, 135.4, 133.7, 131.7, 131.6, 130.8, 127.6, 126.0, 125.9, 124.3, 118.6, 117.4, 114.9, 43.9, 36.2 ppm. MS (ESI): *m/z* 403 $[M+H]^+$, 425 $[M+Na]^+$; Anal. ($C_{19}H_{15}FN_2O_3S_2$) C, H, N.

N-(2-((Z)-5-(3-bromobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)ethyl)-2-hydroxybenzamide (10). Yellow solid. ^{1}H NMR (400 MHz, DMSO) 12.32 (1H, s), 8.86 (1H, t, J = 5.2 Hz), 7.80 (1H, s), 7.71 (1H, s), 7.64−7.62 (1H, d, J = 7.9 Hz), 7.57−7.54 (2H, m), 7.46−7.42 (1H, t, J = 7.9 Hz), 7.32−7.28 (1H, t, J = 7.7 Hz), 6.80−6.75 (2H, t, J = 8.6 Hz), 4.21−4.18 (1H, t, J = 5.2 Hz), 3.58−3.57 (1H, q, J = 5.2 Hz) ppm. ^{13}C NMR (100 MHz, DMSO) 194.2, 170.2, 167.6, 160.7, 135.9, 133.9, 131.1, 129.0, 128.1, 124.8, 123.1, 115.4, 44.4, 36.7 ppm. MS (ESI) *m/z*: 460.9 $[M-H]^-$. Anal. ($C_{19}H_{15}BrN_2O_3S_2$) C, H, N.

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Supporting Information Available. LC/MS, ^{1}H and ^{13}C NMR spectra for the collection of 3-substituted-5-arylidene rhodanines (**11a**−**k**). This material is available free of charge via the Internet at http://pubs.acs.org.

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