

Article

Synthesis of Novel Highly Functionalized 4-Thiazolidinone Derivatives from 4-Phenyl-3-thiosemicarbazones

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Abstract: We present herein the synthesis in good yields of two series of highly functionalized thiazolidinone derivatives from the reactions of various 4-phenyl-3-thio-semicarbazones with ethyl 2-bromoacetate and diethyl acetylenedicarboxylate, respectively.

Keywords: 4-phenyl-3-thiosemicarbazones; thiazolidinones derivatives; ethyl 2-bromoacetate; diethyl acetylenedicarboxylate

1. Introduction

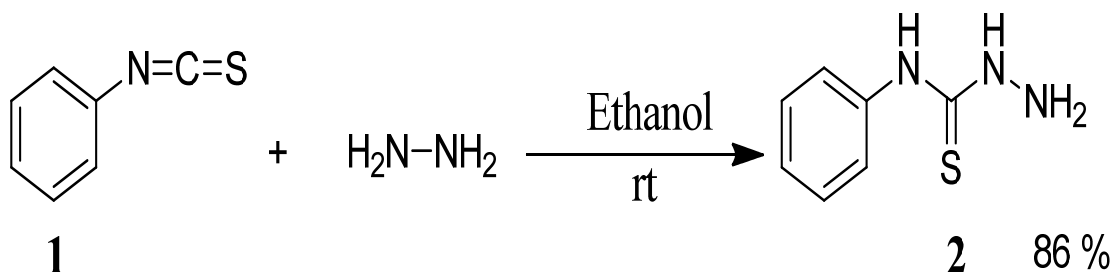
Thiosemicarbazones are a class of small molecules that have been evaluated over the last 50 years as antiviral [1] and as antitumoral agents [2–4], in addition to their antiparasitic and bacterial action against *Trypanosoma cruzi* [5–7] and *Toxoplasma gondii* and several bacterial strains [8]. Thiosemicarbazones have been used as intermediates for a great variety of heterocyclic products, such

as thiazolidinones, thiohydantoins, thioxopyrimidinediones. It is reported that thiazolidinones exhibit antibacterial [9], antifungal [10], anticonvulsant [11], antitubercular [12], anti-inflammatory [13], antihistaminic [14,15], cardiovascular [16] and anti-HIV [17] activities. As part of our research program on new bioactive compounds [18–22], we report herein an efficient synthesis of some new highly functionalized thiazolidinones derived from 4-phenyl-3-thiosemicarbazones.

2. Results and Discussion

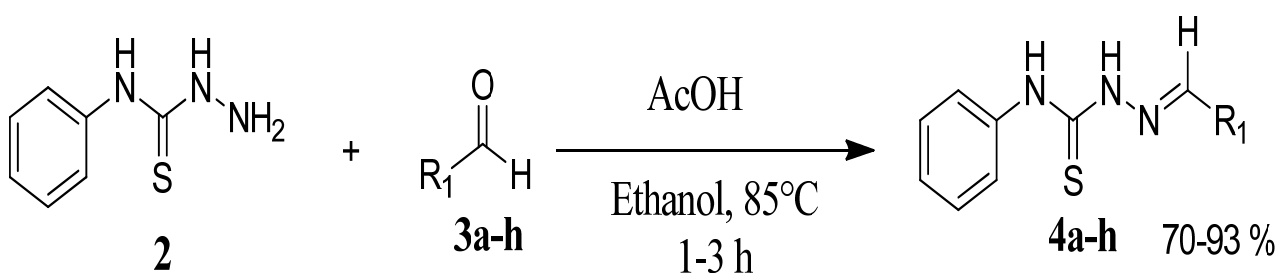
The starting materials, 4-phenyl-3-thiosemicarbazones **4a–h**, were synthesized in two steps. The first step was the preparation of 4-phenyl thiosemicarbazide (**2**) in 86% yield from phenyl isothiocyanate (**1**) and hydrazine hydrate in ethanol at room temperature [23] (Scheme 1).

Scheme 1. Preparation of 4-phenyl-3-thiosemicarbazide (**2**).



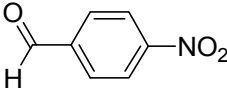
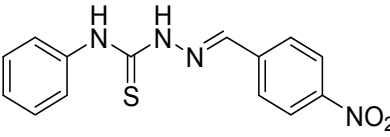
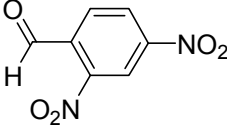
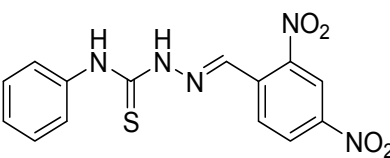
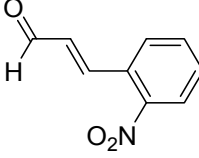
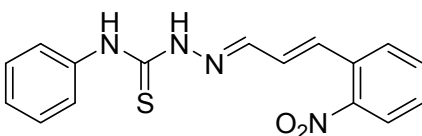
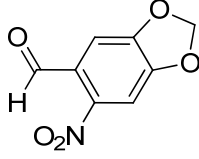
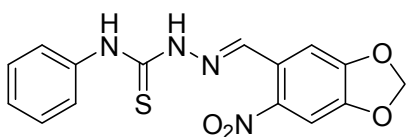
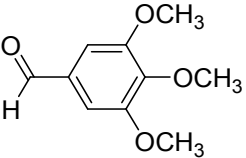
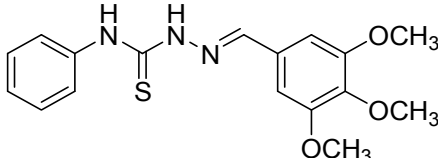
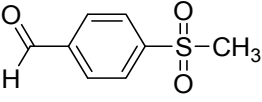
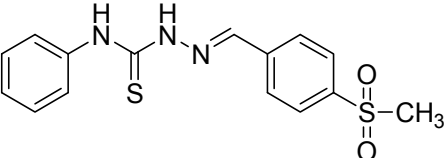
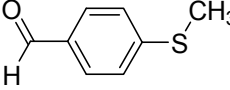
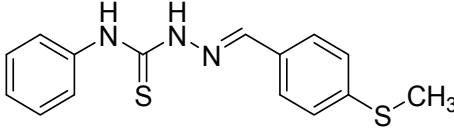
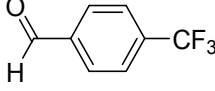
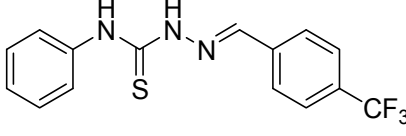
The reaction of 4-phenyl-3-thiosemicarbazide (**2**) with various aromatic aldehydes **3a–h** in the presence of few drops of acetic acid at 85 °C for 1–3 h, led to the corresponding 4-phenyl-3-thiosemicarbazone derivatives **4a–h** in good yields (70%–93%), as shown in Scheme 2 and Table 1.

Scheme 2. Preparation of 4-phenyl-3-thiosemicarbazones **4a–h**.



The most characteristic signals in the ^1H -NMR spectrum of this family of thiosemicarbazones were those corresponding to the $\text{CH}=\text{N}$ and $\text{N}-\text{H}$ protons. ^1H -NMR studies showed the $\text{CH}=\text{N}$ protons in the 7.86–8.62 ppm range, whereas thiourea $\text{N}-\text{H}$ protons are found in the 9.13–11.78 ppm interval for $\text{N}-\text{H}$ adjacent to the monosubstituted phenyl ring and for the $\text{N}-\text{H}$ adjacent to the $\text{CH}=\text{N}$ moiety, respectively. All of the synthesized compounds were in the *E*-configuration, which was confirmed using ^1H -NMR spectroscopy, as the signal of the NH group was in the 9–12 ppm range, in comparison to the *Z*-isomer, which possesses a characteristic NH signal in the 14–15 ppm range [24].

Table 1. Reaction of **2** with various aromatic aldehydes **3a–h**.

Carbonyl compound	Product	Product number	Reaction time (h)	Yield (%)
 3a		4a	1	70
 3b		4b	3	90
 3c		4c	2	93
 3d		4d	1	90
 3e		4e	1	91
 3f		4f	2	89
 3g		4g	2	91
 3h		4h	1	89

The reaction of various 4-phenyl thiosemicarbazones **4a–h** with ethyl 2-bromoacetate (**5**) as cyclizing reagent in boiling absolute ethanol containing three equivalents of anhydrous sodium acetate during 1–3 h, afforded to the thiazolidin-4-ones **6a–h** in good yields (68%–91%) as shown in Scheme 3 and Table 2.

Scheme 3. Preparation of thiazolidinones **6a–h**.

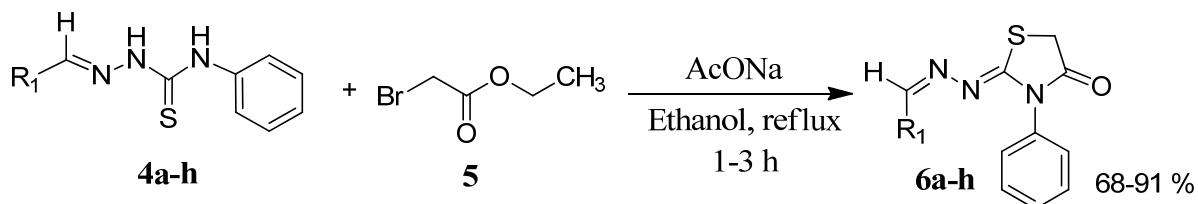
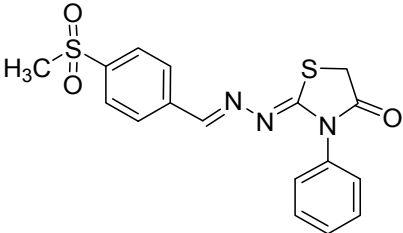
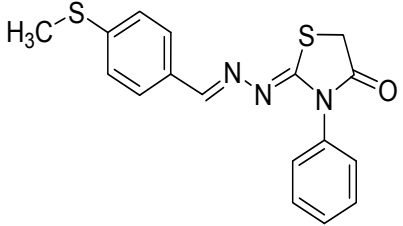
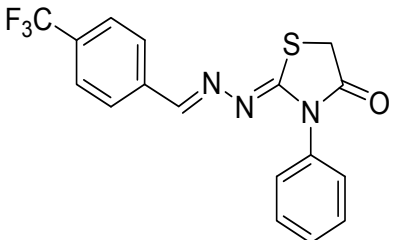


Table 2. Reactions of **4a–h** with ethyl 2-bromoacetate (**5**).

Compound	Product	Product number	Reaction time (h)	Yield (%)
4a		6a	1	91
4b		6b	3	68
4c		6c	3	82
4d		6d	2	86
4e		6e	2	80

Table 2. Cont.

Compound	Product	Product number	Reaction time (h)	Yield (%)
4f		6f	3	89
4g		6g	3	90
4h		6h	2	88

The structures of all new compounds **6a–h** were established by analysis of their IR, ^1H -NMR and ^{13}C -NMR data. The IR spectra of the thiazolidin-4-ones **6a–h** showed absorption bands at about $1,734\text{--}1,716\text{ cm}^{-1}$ characteristic of (amide group) C=O stretching vibrations. Further support was obtained from the ^1H -NMR spectra, where it did not display signs of the 4-phenyl-3-thiosemicarbazone (NH) protons. On the other hand, the ^1H -NMR spectra exhibited resonances assigned to the SCH_2 group of the thiazolidine ring appearing as a singlet at $3.97\text{--}4.10$ ppm due to the methylene protons. The $\text{CH}=\text{N}$ protons in these structures were observed in the $7.67\text{--}8.57$ ppm region. The formation of thiazolidinones **6a–h** occurred in two steps: the first step of this reaction is thought to be *S*-alkylation of thiosemicarbazide in its thiol form due to the sodium acetate used. Second step involved loss of ethanol to give the thiazolidin-4-one. The electronic and steric properties of the substituent at the 4-position of the thiosemicarbazones seems to be a determining factor for the formation of the thiazolidinone ring. Previous reports on these types of compounds reveal a small substituent such as phenyl or alkyl leads to a 4-thiazolidinone ring by loss of ethanol [25].

The next cyclization reaction of 4-phenyl-3-thiosemicarbazones derivatives **4a–h** was conducted using diethyl acetylenedicarboxylate in methanol for 1 h [26], as shown in Scheme 4 and Table 3. In this reaction both of the sulfur group and the amino group are capable of reacting with diethyl acetylenedicarboxylate. It was found that the 4-phenyl thiosemicarbazone derivatives **4a–h** reacted with diethyl acetylenedicarboxylate exclusively with the sulfur atom. In this reaction the intermediate **7** undergoes an intramolecular cyclization which leads to the compounds **8a–h**.

Scheme 4. Preparation of **8a–h** with 4-phenyl-3-thiosemicarbazones **4a–h** and diethyl acetylenedicarboxylate.

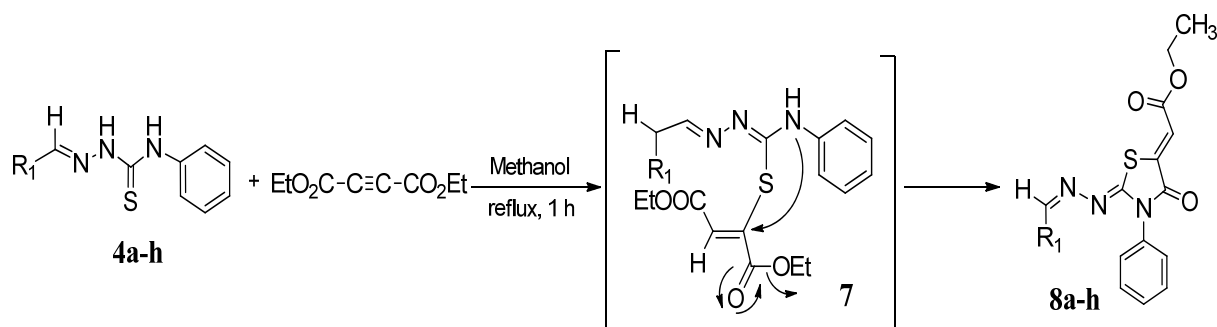
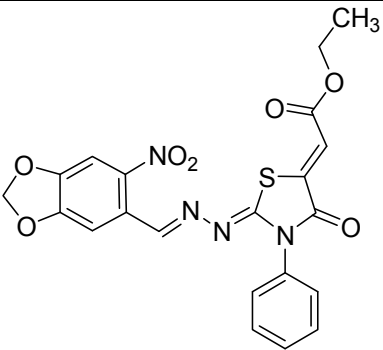
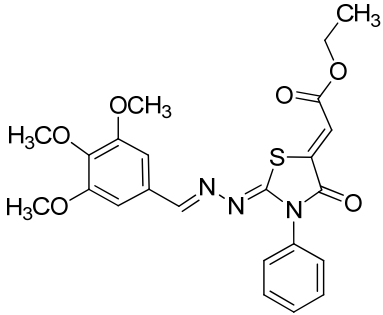
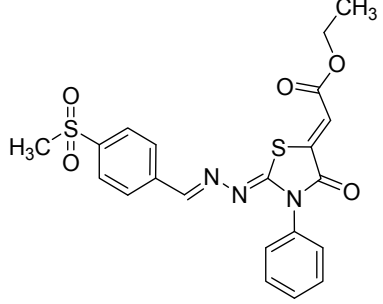
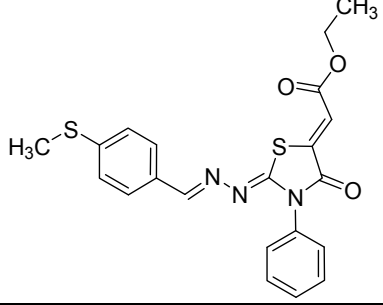
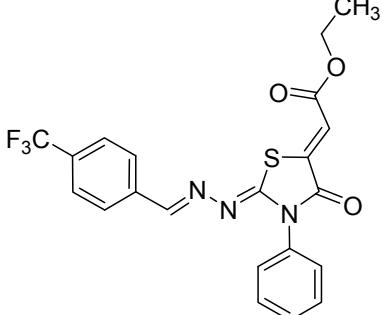


Table 3. Reactions of **4a–h** with diethyl acetylenedicarboxylate.

Compound	Product	Product number	Yield (%)
4a		8a	73
4b		8b	70
4c		8c	76

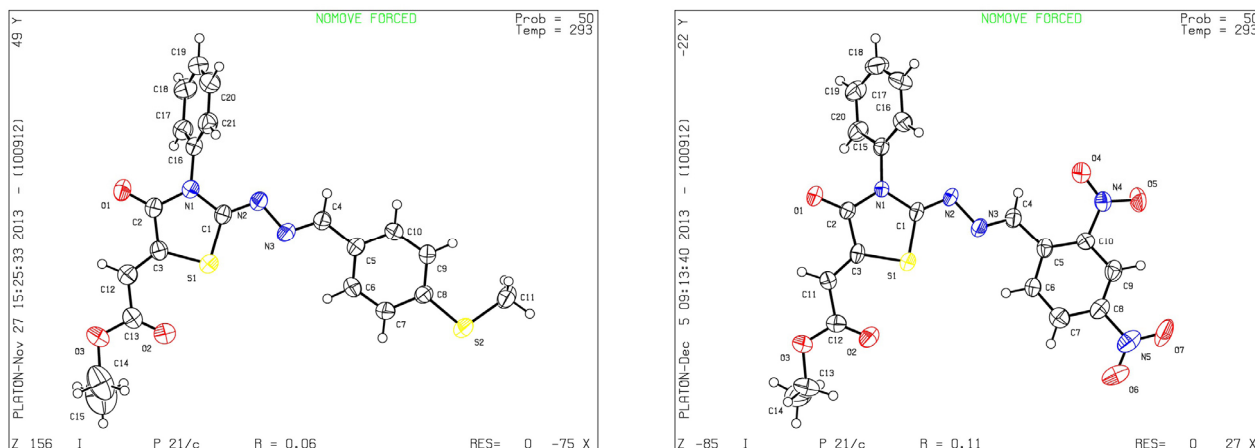
Table 3. Cont.

Compound	Product	Product number	Yield (%)
4d		8d	74
4e		8e	73
4f		8f	75
4g		8g	70
4h		8h	71

Although the two geometrical *E*- or *Z*- isomers of **8a–h** could be formed in almost equal amounts from the reaction of diethyl acetylenedicarboxylate with **4a–h**, $^1\text{H-NMR}$ revealed the presence of only

one singlet at 6.8 ppm (vinyl proton) indicating that only one *E*- or *Z*-isomer was formed. The structures of compound **8b** and **8g** obtained by X-ray structure analysis confirmed the *Z*-configuration for the double bond in the 5-position of the thiazolidin-4-ones (Figure 1) [27,28], probably due to the steric effect of the ester group.

Figure 1. ORTEP plots of **8b** and **8g**.



The chemical structures of the reaction products **8a–h** were confirmed by their IR, ^1H -NMR, ^{13}C -NMR spectra. The IR spectrum of compound **8a**, for example, showed absorptions at 1730, 1692 cm^{-1} due to the C=O functions of the ester and cyclic amide, respectively. Similarly, bands at 1595–1622 cm^{-1} are due to the C=N groups. The ^1H -NMR spectrum of **8a** showed a triplet at $\delta = 1.28$ ppm and a quartet at $\delta = 4.28$ ppm is due to the $\text{COOCH}_2\text{CH}_3$ protons. A singlet at $\delta = 6.80$ ppm is due to C=CH. Aromatic protons appeared as a multiplet at $\delta = 7.38$ – 7.60 ppm.

3. Experimental

3.1. General

Melting points were determined on Büchi B-540 apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a JASCO FT/IR4200 Fourier Transform infrared spectrometer and the reported wavenumbers are given in cm^{-1} . Elemental analyses were carried out at the Spectropole, Faculté des Sciences site Saint-Jérôme. ^1H -NMR (200 MHz) and ^{13}C -NMR (50 MHz) spectra were recorded on a Bruker ARX 200 spectrometer in CDCl_3 or D_2O at the Service Inter-Universitaire de RMN de la Faculté de Pharmacie de Marseille. The ^1H -NMR chemical shifts were reported as parts per million downfield from tetramethylsilane (Me_4Si), and the ^{13}C -NMR chemical shifts were referenced to the solvent peaks: CDCl_3 (76.9 ppm) or DMSO-d_6 (39.6 ppm). Silica gel 60 (Merck, 230–400 mesh) was used for column chromatography. Thin-layer chromatography was performed with silica gel Merck 60F-254 (0.25 mm layer thickness).

3.2. General Procedure for the Preparation of Compounds 4a–h

To a solution of 4-phenylthiosemicarbazide (**2**, 1 g, 6 mmol, 1 eq) in ethanol (33 mL) were added the benzaldehyde derivative (6.3 mmol, 1.05 eq) and acetic acid (0.50 mL). The mixture was stirred under reflux for 1–3 h and then cooled to room temperature. After, the solid separated was filtered and recrystallized from ethanol-DMF (3:1) to give compounds **4a–h**.

(*E*)-2-(4-Nitrobenzylidene)-*N*-phenylhydrazinecarbothioamide (**4a**): yellow solid; mp: 234 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3316 and 3138 (NH), 1543 (C=N), 1292 (C=S); $^1\text{H-NMR}$ (DMSO- d_6): δ 10.32 (s, 1H, NH), 8.24 (d, 2H, $J = 9.2$ Hz, Ar-H), 8.22 (s, 1H, CH=N), 8.17 (d, 2H, $J = 9.2$ Hz, Ar-H), 7.52 (d, 2H, $J = 7.9$ Hz, Ar-H), 7.38 (dd, 2H, $J = 7.9$ Hz, $J = 7.2$ Hz, Ar-H), 7.22 (t, 1H, $J = 7.2$ Hz, Ar-H); $^{13}\text{C-NMR}$ (DMSO- d_6): δ 177.0 (C), 148.1 (C), 141.0 (C), 140.6 (CH), 139.4 (C), 128.9 (2CH), 128.6 (2CH), 126.7 (2CH), 126.1 (CH), 124.4 (2CH); Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{N}_4\text{O}_2\text{S}$: C, 55.99; H, 4.03; N, 18.65; S, 10.68. Found: C, 55.98; H, 4.06; N, 18.49; S, 10.68.

(*E*)-2-(2,4-Dinitrobenzylidene)-*N*-phenylhydrazinecarbothioamide (**4b**): yellow solid; mp: 219 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3316 and 3138 (NH), 1543 (C=N), 1292 (C=S); $^1\text{H-NMR}$ (DMSO- d_6): δ 10.40 (s, 1H, NH), 8.87 (d, 1H, $J = 8.8$ Hz, Ar-H), 8.75 (d, 1H, $J = 2.2$ Hz, Ar-H), 8.62 (s, 1H, CH=N), 8.45 (dd, 1H, $J = 8.8$ Hz, $J = 2.2$ Hz, Ar-H), 7.52 (d, 2H, $J = 7.7$ Hz, Ar-H), 7.39 (dd, 2H, $J = 7.7$ Hz, $J = 7.3$ Hz, Ar-H), 7.24 (t, 1H, $J = 7.3$ Hz, Ar-H); $^{13}\text{C-NMR}$ (DMSO- d_6): δ 177.2 (C), 148.3 (C), 147.5 (C), 139.2 (C), 136.4 (CH), 134.6 (C), 130.3 (CH), 128.7 (2CH), 127.4 (CH), 126.6 (2CH), 126.3 (CH), 120.8 (CH); Anal. Calcd for $\text{C}_{14}\text{H}_{11}\text{N}_5\text{O}_4\text{S}$: C, 48.69; H, 3.21; N, 20.28; S, 9.29. Found: C, 48.83; H, 3.22; N, 20.08; S, 9.05.

(*E*)-2-((*E*)-3-(2-Nitrophenyl)allylidene)-*N*-phenylhydrazinecarbothioamide (**4c**): brown solid; mp: 185 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3226 and 3151 (NH), 1540 (C=N), 1247 (C=S); $^1\text{H-NMR}$ (CDCl_3): δ 9.67 (s, 1H, NH), 9.14 (s, 1H, NH), 8.02 (dd, 1H, $J = 8.2$ Hz, $J = 1.2$ Hz, Ar-H), 7.76–7.59 (m, 5H, Ar-H), 7.52–7.37 (m, 4H, Ar-H), 7.25–7.29 (m, 1H, Ar-H), 6.87 (dd, 1H, $J = 15.9$ Hz, $J = 9.2$ Hz, CH); $^{13}\text{C-NMR}$ (CDCl_3): δ 175.6 (C), 147.8 (C), 143.3 (CH), 137.7 (C), 134.8 (CH), 133.3 (CH), 131.3 (C), 129.4 (CH), 129.0 (CH), 128.8 (2CH), 128.2 (CH), 126.2 (CH), 125.0 (CH), 124.2 (2CH); Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{N}_4\text{O}_2\text{S}$: C, 58.88; H, 4.32; N, 17.17; S, 9.82. Found: C, 59.13; H, 4.40; N, 17.07; S, 9.78.

(*E*)-2-((6-Nitrobenzo[d][1,3]dioxol-5-yl)methylene)-*N*-phenylhydrazinecarbothioamide (**4d**): yellow solid; mp: 231 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3302 and 3283 (NH), 1547 (C=N), 1268 (C=S); $^1\text{H-NMR}$ (DMSO- d_6): δ 10.21 (s, 1H, NH), 8.58 (s, 1H, Ar-H), 8.17 (s, 1H, CH=N), 7.61 (s, 1H, Ar-H), 7.50 (dd, 2H, $J = 7.8$ Hz, $J = 1.2$ Hz, Ar-H), 7.37 (dd, 2H, $J = 7.8$ Hz, $J = 7.2$ Hz, Ar-H), 7.21 (td, 1H, $J = 7.2$ Hz, $J = 1.2$ Hz, Ar-H), 6.25 (s, 2H, CH_2); $^{13}\text{C-NMR}$ (DMSO- d_6): δ 176.9 (C), 152.2 (C), 149.2 (C), 143.9 (C), 139.4 (C), 138.5 (CH), 128.6 (2CH), 126.94 (2CH), 126.1 (CH), 125.9 (C), 106.6 (CH), 105.3 (CH), 104.1 (CH_2); Anal. Calcd for $\text{C}_{15}\text{H}_{12}\text{N}_4\text{O}_4\text{S}$: C, 52.32; H, 3.51; N, 16.27; S, 9.31. Found: C, 52.35; H, 3.46; N, 16.01; S, 9.20.

(*E*)-*N*-Phenyl-2-(3,4,5-trimethoxybenzylidene)hydrazinecarbothioamide (**4e**): white solid; mp: 161 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3291 and 3134 (NH), 1557 (C=N), 1262 (C=S); $^1\text{H-NMR}$ (CDCl_3):

δ 10.36 (s, 1H, NH), 9.14 (s, 1H, NH), 7.93 (s, 1H, CH=N), 7.63 (d, 2H, J = 7.8 Hz, Ar-H), 7.44 (dd, 2H, J = 7.8 Hz, J = 7.2 Hz, Ar-H), 7.30 (t, 1H, J = 7.2 Hz, Ar-H), 6.90 (s, 2H, Ar-H), 3.90 (s, 3H, OCH₃), 3.91 (s, 6H, OCH₃); ¹³C-NMR (CDCl₃): δ 175.6 (C), 153.6 (2C), 143.7 (CH), 140.5 (C), 137.7 (C), 129.0 (2CH), 128.4 (C), 126.6 (CH), 125.2 (2CH), 104.7 (2CH), 61.1 (CH₃), 56.3 (2CH₃); Anal. Calcd for C₁₇H₁₉N₃O₃S: C, 59.11; H, 5.54; N, 12.17; S, 9.28. Found: C, 59.25; H, 5.65; N, 12.06; S, 9.19.

(*E*)-2-(4-(Methylsulfonyl)benzylidene)-*N*-phenylhydrazinecarbothioamide (**4f**): yellow solid; mp: 225 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3325 and 3150 (NH), 1542 (C=N), 1267 (C=S); ¹H-NMR (DMSO-d₆): δ 10.30 (s, 1H, NH), 8.22 (s, 1H, CH=N), 8.19 (d, 2H, J = 8.4 Hz, Ar-H), 7.95 (d, 2H, J = 8.4 Hz, Ar-H), 7.55 (d, 2H, J = 7.60 Hz, Ar-H), 7.39 (dd, 2H, J = 7.2 Hz, J = 7.60 Hz, Ar-H), 7.23 (t, 1H, J = 7.2 Hz, Ar-H), 3.26 (s, 3H, CH₃); ¹³C-NMR (DMSO-d₆): δ 177.0 (C), 141.7 (C), 141.2 (CH), 139.44 (2C), 128.7 (2CH), 128.6 (2CH), 127.7 (2CH), 126.7 (2CH), 126.10 (CH), 43.9 (CH₃); Anal. Calcd for C₁₅H₁₅N₃O₂S₂: C, 54.03; H, 4.53; N, 12.60; S, 19.23. Found: C, 54.11; H, 4.55; N, 12.45; S, 19.21.

(*E*)-2-(4-(Methylthio)benzylidene)-*N*-phenylhydrazinecarbothioamide (**4g**): yellow solid; mp: 178 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3343 and 3152 (NH), 1541 (C=N), 1271 (C=S); ¹H-NMR (CDCl₃): δ 11.78 (s, 1H, NH), 10.08 (s, 1H, NH), 8.09 (s, 1H, CH=N), 7.82 (d, 2H, J = 8.4 Hz, Ar-H), 7.54 (d, 2H, J = 8.0 Hz, Ar-H), 7.35 (dd, 2H, J = 7.3 Hz, J = 8.0 Hz, Ar-H), 7.27 (d, J = 8.4 Hz, 2H, Ar-H), 7.18 (dd, 1H, J = 7.3 Hz, Ar-H), ¹³C-NMR (DMSO-d₆): δ 175.4 (C), 143.1 (CH), 142.5 (C), 137.8 (C), 129.6 (C), 128.9 (2CH), 127.8 (2CH), 126.3 (CH), 125.8 (2CH), 124.8 (2CH), 15.1 (CH₃); Anal. Calcd for C₁₅H₁₅N₃O₂S₂: C, 59.77; H, 5.02; N, 13.94; S, 21.28. Found: C, 59.68; H, 5.04; N, 13.78; S, 21.33.

(*E*)-*N*-Phenyl-2-(4-(trifluoromethyl)benzylidene)hydrazinecarbothioamide (**4h**): white solid; mp: 195 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3350 and 3138 (NH), 1542 (C=N), 1267 (C=S); ¹H-NMR (CDCl₃): δ 10.36 (s, 1H, NH), 9.18 (s, 1H, NH), 8.03 (s, 1H, CH=N), 7.85 (d, 2H, J = 8.1 Hz, Ar-H), 7.69–7.51 (m, 4H, Ar-H), 7.43 (d, 2H, J = 7.4 Hz, Ar-H), 7.29 (t, 1H, J = 7.3 Hz, Ar-H); ¹³C-NMR (CDCl₃): δ 176.0 (C), 141.4 (CH), 137.5 (C), 133.9 (C), 131.5 (q, J = 32.9 Hz, C), 129.5 (CH), 128.9 (3CH), 127.0 (q, J = 3.6 Hz, CH), 126.6 (CH), 124.9 (2CH), 123.9 (q, J = 3.6 Hz, CH), 123.7 (q, J = 272.6 Hz, C); Anal. Calcd for C₁₅H₁₂F₃N₃S: C, 55.72; H, 3.74; N, 13.00; S, 9.92. Found: C, 55.79; H, 3.66; N, 12.86; S, 9.81.

3.3. General Procedure for the Preparation of Compounds **6a–h**

A mixture of compound **4a–h** (1.5 mmol, 1 eq), ethyl 2-bromoacetate (0.24 mL, 1.5 mmol) and anhydrous sodium acetate (0.37 g, 4.5 mmol, 3 eq) in ethanol (30 mL) was stirred until reflux; the mixture was stirred under the same conditions till the completion of the reaction (1–3 h). The reaction mixture was left to cool, poured into ice cold water, and the separated solid was filtered, washed with water and recrystallized from a mixture of ethanol-DMF (3:1).

2-((4-Nitrobenzylidene)hydrazono)-3-phenylthiazolidin-4-one (**6a**): yellow solid; mp: 258 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 1716 (C=O), 1662 (C=N); ¹H-NMR (CDCl₃): δ 8.34 (s, 1H, CH=N), 8.25 (d, 2H,

$J = 8.8$ Hz, Ar-H), 7.88 (d, 2H, $J = 8.8$ Hz, Ar-H), 7.59–7.44 (m, 3H, Ar-H), 7.35 (dd, 2H, $J = 7.7$ Hz, $J = 1.9$ Hz, Ar-H), 4.00 (s, 2H, CH₂); ¹³C-NMR (CDCl₃): δ 171.6 (C), 166.9 (C), 156.2 (CH), 148.9 (C), 140.0 (C), 134.3 (C), 129.4 (2CH), 129.3 (CH), 128.6 (2CH), 127.7 (2CH), 124.0 (2CH), 32.55 (CH₂); Anal. Calcd for C₁₆H₁₂N₄O₃S: C, 56.46; H, 3.55; N, 16.46; S, 9.42. Found: C, 56.44; H, 3.5; N, 16.53; S, 9.53.

2-((2,4-Dinitrobenzylidene)hydrazono)-3-phenylthiazolidin-4-one (6b): yellow solid; mp: 275 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 1731 (C=O), 1592 (C=N); ¹H-NMR (DMSO-d₆): δ 8.74 (d, 1H, $J = 2.3$ Hz, Ar-H), 8.58 (dd, 1H, $J = 8.4$ Hz, $J = 2.3$ Hz, Ar-H), 8.57 (s, 1H, HC=N), 8.20 (d, 1H, $J = 8.4$ Hz, Ar-H), 7.54–7.45 (m, 3H, Ar-H), 7.41–7.36 (m, 2H, Ar-H), 4.14 (s, 2H, CH₂); ¹³C-NMR (DMSO-d₆): δ 172.6 (C), 170.1 (C), 152.8 (CH), 148.4 (C), 148.3 (C), 135.3 (C), 133.7 (C), 131.2 (CH), 129.4 (2CH), 129.3 (CH), 128.7 (2CH), 128.1 (CH), 120.6 (CH), 33.1 (CH₂); Anal. Calcd for C₁₆H₁₁N₅O₅S: C, 49.87; H, 2.88; N, 18.17; S, 8.32. Found: C, 49.99; H, 2.87; N, 17.93; S, 8.25.

2-(3-(2-Nitrophenyl)allylidene)hydrazono)-3-phenylthiazolidin-4-one (6c): orange solid; mp: 265 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 1732 (C=O), 1627 (C=N); ¹H-NMR (CDCl₃): δ 8.13 (d, 1H, $J = 9.5$ Hz, CH=N), 8.0 (dd, 1H, $J = 8.2$ Hz, $J = 1.0$ Hz, Ar-H), 7.75–7.57 (m, 3H, Ar-H), 7.53–7.43 (m, 4H, Ar-H), 7.39–7.32 (m, 2H, Ar-H), 7.01 (dd, 1H, $J = 15.8$ Hz, $J = 9.5$ Hz, CH), 3.98 (s, 2H, CH₂); ¹³C-NMR (CDCl₃): δ 171.6 (C), 164.5 (C), 160.2 (CH), 148.00 (C), 135.8 (CH), 134.4 (C), 133.3 (2CH), 131.4 (C), 130.1 (CH), 129.4 (2CH), 129.1 (CH), 128.3 (CH), 127.7 (2CH), 125.0 (CH), 32.5 (CH₂); Anal. Calcd for C₁₈H₁₄N₄O₃S: C, 59.01; H, 3.85; N, 15.29; S, 8.75. Found: C, 58.96; H, 3.92; N, 15.18; S, 8.50.

2-(3,4-(Methylenedioxy)-6-nitrobenzaldehyde)hydrazono)-3-phenylthiazolidin-4-one (6d): yellow solid; mp: 262 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 1717 (C=O), 1602 (C=N); ¹H-NMR (DMSO-d₆): δ 8.47 (s, 1H, Ar-H), 7.64 (s, 1H, HC=N), 7.56–7.44 (m, 3H, Ar-H), 7.35–7.40 (m, 1H, Ar-H), 7.36 (m, 2H, Ar-H), 6.27 (s, 2H, CH₂), 4.10 (s, 2H, CH₂); ¹³C-NMR (DMSO-d₆): δ 172.5 (C), 167.7 (C), 154.0 (CH), 152.0 (C), 149.8 (C), 144.0 (C), 135.4 (C), 129.6 (2CH), 129.3 (CH), 128.7 (2CH), 125.4 (C), 106.6 (CH), 105.6 (CH), 104.4 (CH₂), 32.9 (CH₂); Anal. Calcd for C₁₇H₁₂N₄O₅S: C, 53.12; H, 3.15; N, 14.58; S, 8.34. Found: C, 53.15; H, 3.10; N, 14.67; S, 8.26.

2-((3,4,5-Trimethoxybenzylidene)hydrazono)-3-phenylthiazolidin-4-one (6e): white solid; mp: 174 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 1720 (C=O), 1619 (C=N); ¹H-NMR (DMSO-d₆): δ 8.21 (s, 1H, HC=N), 7.55–7.44 (m, 3H, Ar-H), 7.39–7.35 (m, 2H, Ar-H), 7.06 (s, 2H, Ar-H), 4.08 (s, 2H, CH₂), 3.78 (s, 6H, OCH₃), 3.70 (s, 3H, OCH₃); ¹³C-NMR (DMSO-d₆): δ 172.6 (C), 165.4 (C), 158.0 (CH), 153.6 (2C), 140.3 (C), 135.5 (C), 130.0 (C), 129.5 (2CH), 129.1 (CH), 128.7 (2CH), 105.5 (2CH), 60.6 (CH₃), 56.3 (2CH₃), 32.7 (CH₂); Anal. Calcd for C₁₉H₁₉N₃O₄S: C, 59.21; H, 4.97; N, 10.90; S, 8.32. Found: C, 59.29; H, 5.08; N, 10.64; S, 8.21.

2-(4-(Methylsulfonyl)benzylidene)hydrazono)-3-phenylthiazolidin-4-one (6f): yellow solid; mp: 277 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 1734 (C=O), 1615 (C=N); ¹H-NMR (DMSO-d₆): δ 8.43 (s, 1H, HC=N), 8.00 (d, 2H, $J = 9.2$ Hz, Ar-H), 7.94 (d, 2H, $J = 9.2$ Hz, Ar-H), 7.54–7.44 (m, 3H, Ar-H), 7.41–7.36 (m, 2H, Ar-H), 4.12 (s, 2H, CH₂), 3.22 (s, 3H, CH₃); ¹³C-NMR (DMSO-d₆): δ 172.5 (C), 167.8 (C),

156.76 (CH), 142.5 (C), 139.2 (C), 135.4 (C), 129.6 (2CH), 129.2 (CH), 128.7 (4CH), 128.0 (2CH), 43.8 (CH₃), 32.9 (CH₂); Anal. Calcd for C₁₇H₁₅N₃O₃S₂: C, 54.67; H, 4.05; N, 11.25; S, 17.17. Found: C, 54.71; H, 4.05; N, 11.19; S, 17.14.

2-(4-(Methylthio)benzylidene)hydrazono)-3-phenylthiazolidin-4-one (6g): yellow solid; mp: 223 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 1732 (C=O), 1609 (C=N); ¹H-NMR (CDCl₃): δ 8.25 (s, 1H, HC=N), 7.64 (d, 2H, J = 8.5 Hz, Ar-H), 7.53–7.45 (m, 3H, Ar-H), 7.38–7.34 (m, 2H, Ar-H), 7.21 (d, 2H, J = 8.5 Hz, Ar-H), 3.97 (s, 2H, CH₂), 2.50 (s, 3H, CH₃); ¹³C-NMR (CDCl₃): δ 171.8 (C), 163.9 (C), 158.4 (CH), 142.6 (C), 134.5 (C), 130.7 (C), 129.4 (2CH), 129.1 (CH), 128.4 (2CH), 127.8 (2CH), 125.8 (2CH), 32.5 (CH₂), 15.2 (CH₃); Anal. Calcd for C₁₇H₁₅N₃OS₂: C, 59.80; H, 4.43; N, 12.31; S, 18.78. Found: C, 59.67; H, 4.43; N, 12.20; S, 18.88.

2-(4-(Trifluoromethyl)benzylidene)hydrazono)-3-phenylthiazolidin-4-one (6h): white solid; mp: 206 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 1732 (C=O), 1616 (C=N); ¹H-NMR (CDCl₃): δ 8.33 (s, 1H, HC=N), 7.84 (d, 2H, J = 8.2 Hz, Ar-H), 7.65 (d, 2H, J = 8.2 Hz, Ar-H), 7.59–7.43 (m, 3H, Ar-H), 7.39–7.32 (m, 2H, Ar-H), 3.99 (s, 2H, CH₂); ¹³C-NMR (CDCl₃): δ 171.7 (C), 165.8 (C), 157.3 (CH), 137.4 (C), 134.4 (C), 132 (q, J = 32.4 Hz, C), 129.4 (2CH), 129.2 (CH), 128.2 (2CH), 127.8 (3CH), 125.6 (q, J = 3.8 Hz, CH), 123.8 (q, J = 272.3 Hz, C), 32.5 (CH₂); Anal. Calcd for C₁₇H₁₂F₃N₃OS: C, 56.19; H, 3.33; N, 11.56; S, 8.82. Found: C, 56.17; H, 3.66; N, 12.82; S, 9.96.

3.4. General Procedure for the Preparation of Compounds 8a–h

An equimolar mixture of **4a–h** (1.5 mmol) and diethyl acetylenedicarboxylate (1.5 mmol) in methanol (20 mL) was refluxed for 1 h. After completion of the reaction, the reaction mixture was allowed to cool to the room temperature. The solid thus separated was collected by filtration and recrystallized using ethanol-DMF mixture.

(Z)-Ethyl-2-(2-((4-nitrobenzylidene)hydrazono)-4-oxo-3-phenylthiazolidin-5-ylidene) acetate (8a): yellow solid; mp: 206 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 1730 (C=O), 1692 (C=O), 1623 (C=N); ¹H-NMR (DMSO-d₆): δ 8.60 (s, 1H, CH=N), 8.32 (d, 2H, J = 8.8 Hz, Ar-H), 8.01 (d, 2H, J = 8.8 Hz, Ar-H), 7.58–7.48 (m, 5H, Ar-H), 6.80 (s, 1H, C=CH), 4.28 (q, 2H, J = 7.0 Hz, CH₂), 1.28 (t, 3H, J = 7.0 Hz, CH₃). ¹³C-NMR (DMSO-d₆): δ 166.0 (C), 164.6 (C), 163.6 (C), 158.5 (CH), 149.2 (C), 141.7 (C), 140.0 (C), 134.5 (C), 129.6 (3CH), 129.5 (2CH), 128.6 (2CH), 124.6 (2CH), 116.2 (CH), 62.0 (CH₂), 14.5 (CH₃); Anal. Calcd for C₂₀H₁₆N₄O₅S: C, 56.60; H, 3.80; N, 13.20; S, 7.55. Found: C, 55.68; H, 4.59; N, 10.67; S, 5.44.

(Z)-Ethyl-2-(2-((E)-2,4-dinitrobenzylideneamino)-4-oxo-3-phenylthiazolidin-5-ylidene) acetate (8b): yellow solid; mp: 193 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 1727 (C=O), 1698 (C=O), 1620 (C=N); ¹H-NMR (DMSO-d₆): δ 8.77 (d, 1H, J = 2.2 Hz, Ar-H), 8.7 (s, 1H, CH=N), 8.64 (dd, 1H, J = 8.6 Hz, J = 2.2 Hz, Ar-H), 8.25 (d, 1H, J = 8.6 Hz, Ar-H), 7.60–7.46 (m, 5H, Ar-H), 6.83 (s, 1H, C=CH), 4.29 (q, 2H, J = 7.1 Hz, CH₂), 1.28 (t, 3H, J = 7.1 Hz, CH₃); ¹³C-NMR (DMSO-d₆): δ 165.9 (C), 165.2 (C), 164.7 (C), 155.2 (CH), 148.6 (C), 141.5 (C), 134.5 (C), 133.3 (C), 131.4 (CH), 129.8 (CH), 129.7 (3CH),

128.7 (2CH), 128.3 (CH), 120.7 (CH), 116.6 (CH), 62.1 (CH₂), 14.5 (CH₃); Anal. Calcd for C₂₀H₁₅N₅O₇S: C, 51.17; H, 3.22; N, 14.92; S, 6.83. Found: C, 51.29; H, 3.15; N, 14.78; S, 6.77.

(*Z*)-Ethyl-2-(2-((*E*)-3-(2-nitrophenyl)allylidene)amino)-4-oxo-3-phenylthiazolidin-5-ylidene) acetate (**8c**): yellow solid; mp: 251 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 1727 (C=O), 1692 (C=O), 1618 (C=N); ¹H-NMR (DMSO-d₆): δ 8.27 (d, 1H, J = 9.4 Hz, CH), 8.01 (ddd, 2H, J = 7.1 Hz, J = 7.9 Hz, J = 1.1 Hz, Ar-H), 7.73 (dd, 1H, J = 7.9 Hz, J = 7.1 Hz, Ar-H), 7.63–7.42 (m, 7H, Ar-H), 7.20 (dd, 1H, J = 15.7 Hz, J = 9.4 Hz, Ar-H), 6.77 (s, 1H, C=CH), 4.27 (q, 2H, J = 7.1 Hz, CH₂), 1.27 (t, 3H, J = 7.1 Hz, CH₃); ¹³C-NMR (DMSO-d₆): δ 166.0 (C), 164.6 (C), 162.1 (CH), 161.5 (C), 148.6 (C), 141.9 (C), 137.3 (CH), 134.6 (C), 134.0 (CH), 130.7 (CH), 130.4 (C), 129.8 (CH), 129.6 (3CH), 129.0 (CH), 128.6 (2CH), 125.0 (CH), 115.9 (CH), 62.0 (CH₂), 14.5 (CH₃). Anal. Calcd for C₂₂H₁₈N₄O₅S: C, 58.66; H, 4.03; N, 12.44; S, 7.12. Found: C, 58.47; H, 3.92; N, 12.05; S, 6.64

(*Z*)-Ethyl-2-(2-((*E*)-(4-nitrobenzo[d][1,3]dioxol-5-yl)methyleneamino)-4-oxo-3-phenylthiazolidin-5-ylidene) acetate (**8d**): yellow solid; mp: 251 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 1721 (C=O) 1702 (C=O), 1597 (C=N); ¹H-NMR (DMSO-d₆): δ 8.59 (s, 1H, Ar-H), 7.70 (s, 1H, Ar-H), 7.54–7.47 (m, 5H, Ar-H), 7.38 (s, 1H, Ar-H), 6.80 (s, 1H, C=CH), 6.30 (s, 2H, CH₂), 4.27 (q, 2H, J = 7.1 Hz, CH₂), 1.27 (t, 3H, J = 7.1 Hz, CH₃); ¹³C-NMR (DMSO-d₆): δ 166.0 (C), 164.7 (C), 163.0 (C), 156.5 (CH), 152.1 (C), 150.3 (C), 144.3 (C), 141.8 (C), 137.2 (C), 134.6 (C), 129.7 (2CH), 128.7 (2CH), 124.9 (CH), 116.2 (CH), 106.8 (CH), 105.8 (CH), 104.6 (CH₂), 62.0 (CH₂), 14.5 (CH₃); Anal. Calcd for C₂₁H₁₆N₄O₇S: C, 53.84; H, 3.44; N, 11.96; S, 6.85. Found: C, 53.79; H, 3.42; N, 11.98; S, 6.75.

(*Z*)-Ethyl-2-(2-((*E*)-3,4,5-trimethoxybenzylideneamino)-4-oxo-3-phenylthiazolidin-5-ylidene) acetate (**8e**): yellow solid; mp: 145 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 1721 (C=O), 1689 (C=O), 1622 (C=N); ¹H-NMR (DMSO-d₆): δ 8.35 (s, 1H, CH=N), 7.58–7.47 (m, 5H, Ar-H), 7.11 (s, 2H, Ar-H), 6.77 (s, 1H, C=CH), 4.27 (q, 2H, J = 7.0 Hz, CH₂), 3.80 (s, 6H, OCH₃), 3.70 (s, 3H, OCH₃), 1.28 (t, 3H, J = 7.0 Hz, CH₃); ¹³C-NMR (DMSO-d₆): δ 165.9 (C), 164.6 (C), 160.6 (C), 160.4 (CH), 153.6 (2C), 142.0 (C), 140.9 (C), 134.7 (C), 129.6 (3CH), 129.4 (C), 128.6 (2CH), 115.7 (CH), 105.9 (2CH), 62.0 (CH₂), 60.6 (CH₃), 56.3 (2CH₃), 14.5 (CH₃); Anal. Calcd for C₂₃H₂₃N₃O₆S: C, 58.84; H, 4.94; N, 8.95; S, 6.83. Found: C, 58.47; H, 4.93; N, 8.77; S, 6.64.

(*Z*)-Ethyl-2-(2-((*E*)-4-(methylsulfonyl)benzylideneamino)-4-oxo-3-phenylthiazolidin-5-ylidene) acetate (**8f**): yellow solid; mp: 254 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 1722 (C=O), 1687 (C=O), 1611 (C=N); ¹H-NMR (DMSO-d₆): δ 8.58 (s, 1H, CH=N), 8.02 (s, 4H, Ar-H), 7.59–7.45 (m, 5H, Ar-H), 6.81 (s, 1H, C=CH), 4.29 (q, 2H, J = 7.1 Hz, CH₂), 3.24 (s, 3H, CH₃), 1.28 (t, 3H, J = 7.1 Hz, CH₃); ¹³C-NMR (DMSO-d₆): δ 166.0 (C), 164.7 (C), 163.2 (C), 159.0 (CH), 143.0 (C), 141.8 (C), 138.6 (C), 134.6 (C), 129.7 (3CH), 129.1 (2CH), 128.7 (2CH), 128.1 (2CH), 116.1 (CH), 62.1 (CH₂), 43.9 (CH₃), 14.5 (CH₃); Anal. Calcd for C₂₁H₁₉N₃O₅S₂: C, 55.13; H, 4.19; N 9.18; S, 14.02. Found: C, 55.18; H, 4.19; N, 8.96; S, 14.11.

(*Z*)-Ethyl-2-(2-((*E*)-4-(methylthio)benzylideneamino)-4-oxo-3-phenylthiazolidin-5-ylidene)acetate (**8g**): yellow solid; mp: 210 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 1720 (C=O), 1696 (C=O), 1604 (C=N); ¹H-NMR (DMSO-d₆): δ 8.40 (s, 1H, CH=N), 8.70 (d, 2H, J = 8.4 Hz, Ar-H), 7.58–7.44 (m, 5H, Ar-H), 7.33 (d,

2H, $J = 8.4$ Hz, Ar-H), 6.77 (s, 1H, C=CH), 4.28 (q, 2H, $J = 7.1$ Hz, CH₂), 3.31 (s, 3H, CH₃), 1.28 (t, 3H, $J = 7.1$ Hz, CH₃); ¹³C-NMR (DMSO-d₆): δ 166.0 (C), 164.6 (C), 160.9 (C), 160.0 (CH), 143.5 (C), 142.1 (C), 134.7 (C), 130.3 (C), 129.6 (3CH), 128.9 (2CH), 128.7 (2CH), 126.0 (2CH), 115.6 (CH), 62.0 (CH₂), 14.6 (CH₃), 14.5 (CH₃); Anal. Calcd for C₂₁H₁₉N₃O₃S₂: C, 59.27; H, 4.50; N 9.87; S, 15.07. Found: C, 59.10; H, 4.48; N, 9.74; S, 14.86.

(Z)-Ethyl-2-(2-((E)-4-(trifluoromethyl)benzylideneamino)-4-oxo-3-phenylthiazolidin-5-ylidene) acetate (**8h**): yellow solid; mp: 154 °C; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 1721 (C=O), 1690 (C=O), 1619 (C=N); ¹H-NMR (DMSO-d₆): δ 8.56 (s, 1H, CH=N), 8.00 (d, 2H, $J = 8.2$ Hz, Ar-H), 7.84 (d, 2H, $J = 8.2$ Hz, Ar-H), 7.58–7.45 (m, 5H, Ar-H), 6.80 (s, 1H, C=CH), 4.30 (q, 2H, $J = 7.1$ Hz, CH₂), 1.28 (t, 3H, $J = 7.1$ Hz, CH₃); ¹³C-NMR (DMSO-d₆): δ 166.0 (C), 164.6 (C), 162.9 (C), 159.1 (CH), 141.9 (C), 137.9 (C), 134.6 (C), 131.3 (q, $J = 32.2$ Hz, C), 129.6 (q, $J = 272.2$ Hz, C), 129.5 (3CH), 129.1 (2CH), 128.7 (2CH), 126.3 (q, $J = 3.2$ Hz, 2CH), 116.0 (CH), 62.0 (CH₂), 14.5 (CH₃); Anal. Calcd for C₂₁H₁₆F₃N₃O₃S: C, 56.37; H, 3.60; N, 9.39; S, 7.17. Found: C, 56.33; H, 3.51; N, 9.17; S, 7.10.

4. Conclusions

In conclusion, we have prepared a series of 4-phenyl-3-thiosemicarbazone derivatives from 4-phenyl-3-thiosemicarbazide and various aromatic aldehydes substituted with different electron-donor and -withdrawing groups. In a second step, these 4-phenyl-3-thiosemicarbazone derivatives were reacted with 2-ethyl bromoacetate and diethyl acetylenedicarboxylate, respectively, to afford an original series of highly functionalized thiazolidinone derivatives in good yields. The antiparasitic and antibacterial evaluations of all synthesized compound are under investigation.

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Author Contributions

A.D.; T.T. and P.V. conceived and designed the study. A.B. and O.K. designed the experiments and interpreted the results. A.B.; O.K.; A.D.; T.T. and P.V. wrote the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

References and Notes

1. Pirrung, M.C.; Pansare, S.V.; das Sarma, K.; Keith, K.A.; Kern, E.R. Combinatorial optimization of isatin- β -thiosemicarbazones as anti-poxvirus agents. *J. Med. Chem.* **2005**, *48*, 3045–3050.
2. Hu, W.-X.; Zhou, W.; Xia, C.-N.; Wen, X. Synthesis and anticancer activity of thiosemicarbazones. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2213–2218.

3. Kolocouris, A.; Dimas, K.; Pannecouque, C.; Witvrouw, M.; Foscolos, G.B.; Stamatiou, G.; Fytas, G.; Zoidis, G.; Kolocouris, N.; Andrei, G.; *et al.* New 2-(1-adamantylcarbonyl) pyridine and 1-acetyladamantane thiosemicarbazones-thiocarbonohydrazones: Cell growth inhibitory, antiviral and antimicrobial activity evaluation. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 723–727.
4. Tarasconi, P.; Capacchi, S.; Pelosi, G.; Cornia, M.; Albertini, R.; Bonati, A.; Dall’Aglia, P.P.; Lunghi, P.; Pinelli, S. Synthesis, spectroscopic characterization and biological properties of new natural aldehydes thiosemicarbazones. *Bioorg. Med. Chem.* **2000**, *88*, 157.
5. Pérez-Rebolledo, A.; Teixeira, L.R.; Batista, A.A.; Mangrich, A.S.; Aguirre, G.; Cerceretto, H.; González, M.; Hernández, P.; Ferreira, A.M.; Speziali, N.L.; *et al.* 4-Nitroacetophenone-derived thiosemicarbazones and their copper (II) complexes with significant *in vitro* anti-trypanosomal activity. *Eur. J. Med. Chem.* **2008**, *43*, 939–948.
6. Aguirre, G.; Boiani, L.; Cerceretto, H.; Fernández, M.; González, M.; Denicola, A.; Otero, L.; Gambino, D.; Rigol, C.; Olea-Azar, C.; *et al.* *In vitro* activity and mechanism of action against the protozoan parasite *Trypanosoma cruzi* of 5-nitrofuryl containing thiosemicarbazones. *Bioorg. Med. Chem.* **2004**, *12*, 4885–4893.
7. Du, X.; Guo, C.; Hansell, E.; Doyle, P.S.; Caffrey, C.R.; Holler, T.P.; McKerrow, J.H.; Cohen, E. Synthesis and structure-activity relationship study of potent trypanocidal thio- semicarbazone inhibitors of the trypanosomal cysteine protease cruzain. *J. Med. Chem.* **2002**, *45*, 2695–2707.
8. De Aquino, T.M.; Liesen, A.P.; da Silva, R.E.A.; Lima, V.T.; Carvalho, C.S.; de Faria, A.R.; de Araujo, J.M.; de Lima, J.G.; Alves, A.J.; de Melo, E.J.T.; *et al.* Synthesis, anti-*Toxoplasma-gondii* and antimicrobial activities of benzaldehyde 4-phenyl-3-thiosemicarbazones and 2-[(phenylmethylene) hydrazono]-4-oxo-3-phenyl-5-thiazolidine acetic acids. *Bioorg. Med. Chem.* **2008**, *16*, 446–456.
9. Mayekar, S.A.; Mulwad, V.V. Synthesis and antibacterial activity of 6-(5phenyl-{1,3,4} thiadiazol-2-ylimino)-benzopyran-2-ones. *Ind. J. Chem.* **2008**, *47*, 1438–1442.
10. Omar, K.; Geronikaki, A.; Zoumpoulakis, P.; Camoutsis, C.; Sokovic, M.; Ciric, A.; Glamoclija, J.; Novel 4- thiazolidinone derivatives as potential antifungal and antibacterial drugs. *Bioorg. Med. Chem.* **2010**, *18*, 426–432.
11. Bhat, M.A.; Siddiqui, N.; Khan, S.A. Synthesis, anticonvulsant and neurotoxicity screening of 2-(substituted phenyl)-3-[3-(2-oxo-2H-chromen-3-yl)-5-thioxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]-1,3-thiazolidin-4-ones. *Ind. J. Het. Chem.* **2008**, *17*, 287–288.
12. Babaoglu, K.; Page, M.A.; Jones, V.C.; McNeil, M.R.; Dong, C.; Naismith, J.H.; Lee, R.E. Novel inhibitors of an emerging target in mycobacterium tuberculosis; substituted thiazolidinones as inhibitors of dTDP-rhamnose synthesis. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3227–3230.
13. Vigorita, M.G.; Ottanà, R.; Monforte, F.; Maccari, R.; Monforte, M.T.; Trovato, A.; Taviano, M.F.; Miceli, N.; de Luca, G.; Alcaro, S.; *et al.* Chiral 3,3'-(1,2-ethanediyl)-bis[2-(3,4-dimethoxyphenyl)-4-thiazolidinones] with anti-inflammatory activity. Part 11: Evaluation of COX-2 selectivity and modeling. *Bioorg. Med. Chem.* **2003**, *11*, 999–1006.
14. Agrawal, V.K.; Sachan, S.; Khadikar, P.V. QSAR studies on antihistaminic activity of some thiazolidine-4-ones. *Acta Pharm.* **2000**, *50*, 281–290.
15. Diurno, M.V.; Mazzoni, O.; Correale, G.; Monterrey, I.G.; Calignano, A.; la Rana, G.; Bolognese, A. Synthesis and structure-activity relationships of 2-(substituted phenyl)-3-[3-(N,N-dimethylamino)-propyl]-1,3-thiazolidin-4-ones acting as H1-histamine antagonists. *Farmaco* **1999**, *54*, 579–583.

16. Suzuki, Y.; Akima, M.; Tamura, K. Effects of CP-060S, a novel cardioprotective drug, on cardiac function and myocardial oxygen consumption. *Gen. Pharmacol.* **1999**, *32*, 57–63.
17. Rawal, R.K.; Prabhakar, Y.S.; Katti, S.B.; de Clercq, E. 2-(Aryl)-3-furan-2-ylmethyl-thiazolidin-4-ones as selective HIV-RT inhibitors. *Bioorg. Med. Chem.* **2005**, *13*, 6771–6776.
18. Crozet, M.P.; Archaimbault, G.; Vanelle, P.; Nouguié, R. Reaction $S_{RN}1$ en série hétérocyclique: Réactivité des sels du diméthyl-2,2-nitro-5-dioxane-1,3. *Tetrahedron Lett.* **1985**, *26*, 5133–5134.
19. Amiri-Attou, O.; Terme, T.; Vanelle, P. Functionalization of 6-nitrobenzo[1,3]dioxole with carbonyl compounds via TDAE methodology. *Molecules* **2005**, *10*, 545–551.
20. Verhaeghe, P.; Azas, N.; Hutter, S.; Castera-Ducros, C.; Laget, M.; Dumètre, A.; Gasquet, M.; Reboul, J.P.; Rault, S.; Rathelot, P.; *et al.* Synthesis and *in vitro* antiparasmodial evaluation of 4-anilino-2-trichloromethylquinazolines. *Bioorg. Med. Chem.* **2009**, *17*, 4313–4322.
21. Crozet, M.D.; Botta, C.; Gasquet, M.; Curti, C.; Remusat, V.; Hutter, S.; Chapelle, O.; Azas, N.; de Méo, M.; Vanelle, P. Lowering of 5-nitroimidazole's mutagenicity: Towards optimal antiparasitic pharmacophore. *Eur. J. Med. Chem.* **2009**, *44*, 653–659.
22. Kabri, Y.; Azas, N.; Dumètre, A.; Hutter, S.; Laget, M.; Verhaeghe, P.; Gellis, A.; Vanelle, P. Original quinazoline derivatives displaying antiparasmodial properties. *Eur. J. Med. Chem.* **2010**, *45*, 616–622.
23. Huang, H.; Chen, Q.; Ku, X.; Meng, L.; Lin, L.; Wang, X.; Zhu, C.; Wang, Y.; Chen, Z.; Li, M.; *et al.* A series of α -heterocyclic carboxaldehyde thiosemicarbazones inhibit topoisomerase II α catalytic activity. *J. Med. Chem.* **2010**, *53*, 3048–3064.
24. Serda, M.; Malecki, J.G.; Mrozek-Wilczkiewicz, A.; Musiol, R.; Polanski, J. Microwave assisted synthesis, X-ray crystallography and DFT calculations of selected aromatic thiosemicarbazones. *J. Mol. Struct.* **2013**, *1037*, 63–72.
25. Küçüğüzel, G.; Kocayepé, A.; de Clercq, E.; Sahin, F.; Güllüce, M. Synthesis and biological activity of 4-thiazolidinones, thiosemicarbazides derived from diflunisal hydrazide. *Eur. J. Med. Chem.* **2006**, *41*, 353–359.
26. Vas'kevich, R.I.; Zborovskii, Y.L.; Staninets, V.I.; Chernega, A.N. Reaction of 4-Aryl-1-(4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)thiosemicarbazides with Dimethyl Acetylenedicarboxylate. *Russ. J. Org. Chem.* **2004**, *40*, 1047–1052.
27. CCDC contains the supplementary crystallographic data of compound **8b** for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.
28. CCDC contains the supplementary crystallographic data of compound **8g** for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

Sample Availability: Samples of the compounds **4a–h**, **6a–h** and **8a–h** are available from the authors.