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Short Note

Synthesis and Characterization of Novel Thiazolidinones and Thioxothiazolidinones Derived from Substituted Indole

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Abstract: Based on recent discoveries concerning the numerous biological properties of thiazolidinones and thiosemicarbazones, new *N*-substituted heterocyclic derivatives have been designed by combining the indole ring with thioxothiazolidinone, thiazolidinone or thiosemicarbazone. Thus, a series of new thioxothiazolidinone, thiazolidinone, or thiosemicarbazone derivatives bearing indole-based moiety have been designed, synthesized, and developed in good yields.

Keywords: indole; thiosemicarbazone derivatives; thiazolidinone derivatives; thioxothiazolidinone derivatives

Citation: Rekiba, N.; Benmohammed, A.; Khanoussi, S.; Djafri, A.; Thibonnet, J. Synthesis and Characterization of Novel Thiazolidinones and Thioxothiazolidinones Derived from Substituted Indole. *Molbank* **2021**, *2021*, M1284. https://doi.org/10.3390/M1284

Academic Editor: Ian R. Baxendale

Received: 24 August 2021
Accepted: 27 September 2021
Published: 30 September 2021

1. Introduction

The indolic nucleus is a heteroaromatic organic compound that is highly common in nature. This structural unit is present in many bioactive molecules, whether natural or synthetic. Indoles are an important class of heterocyclic compounds, and this kind of structure has been revealed to have antimicrobial [1,2], antifungal [3], anti-inflammatory and analgesic [4–6], anticonvulsant [7], anticancer [8,9], and anti-malarial properties [10]. The 4-thiazolidinone derivatives are one of the heterocyclic types which play an important role in therapeutical chemistry, due to their variety in biological activity, as antiviral [11], anti-inflammatory [12], anticancer [13], antimicrobial [14,15], antidiabetic [16], antioxidant [17], anti-HIV agents [18]. Moreover, the 5-arylidene-2-thioxothiazolidin-4-one or 5-arylidenerhodanine derivatives represent particularly privileged moieties in drug discovery because of their inherent tendency for biological activity [19–21]. For example, it was reported that the incorporation of indolyl moiety as in *N*′-[(1*H*-indol-3-yl)methylene]-isonicotinohydrazide derivative showed excellent to good anti-tubercular activity (compound **I**, Figure 1) [22]. Compound **II** displayed potent broad-spectrum antibacterial and antifungal activities [15]. Moreover, benzyl-1*H*-indole derivatives (indibulin **III**) also possess prominent antitumor activity, for example, acting as a novel synthetic microtubule inhibitor [23].

A new series of thiosemicarbazones **5a**–**e** was prepared by the reaction of substituted indole-3-carbaldehyde **3a**–**e** on 4-chlorophenylthiosemicarbazide in ethanol, with acetic acid as a catalyst. Substituted thiazolidinones compounds **7a**–**e** were prepared by a cycling reaction in ethanol with sodium acetate. The arylidenerhodanines **10a**–**e** were also prepared by condensation reactions of 2-thioxothiazolidin-4-one on several substituted indole-3-carbaldehyde compounds. In the previous work [24], we synthesized new indole

derivatives of potential biological interest. The biological activity of this kind of compound will be interesting for further work. The synthesis of the target compounds (**A**, **B**, or **C** series) was carried out as outlined in Scheme 1. The spectral data and elemental analysis results of the synthesized compounds were in agreement with the proposed structures.

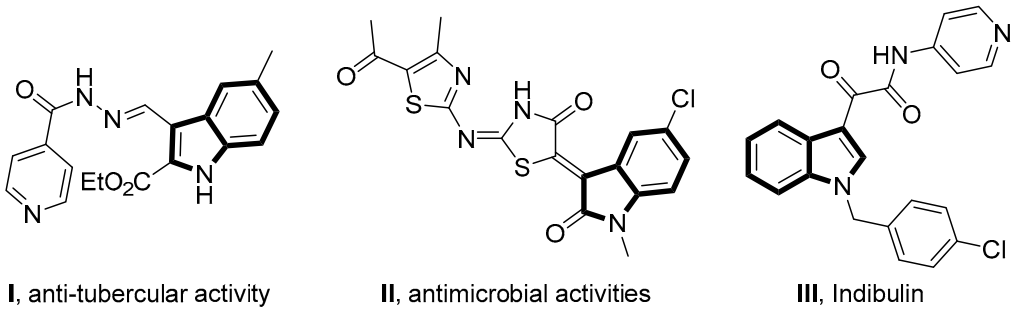
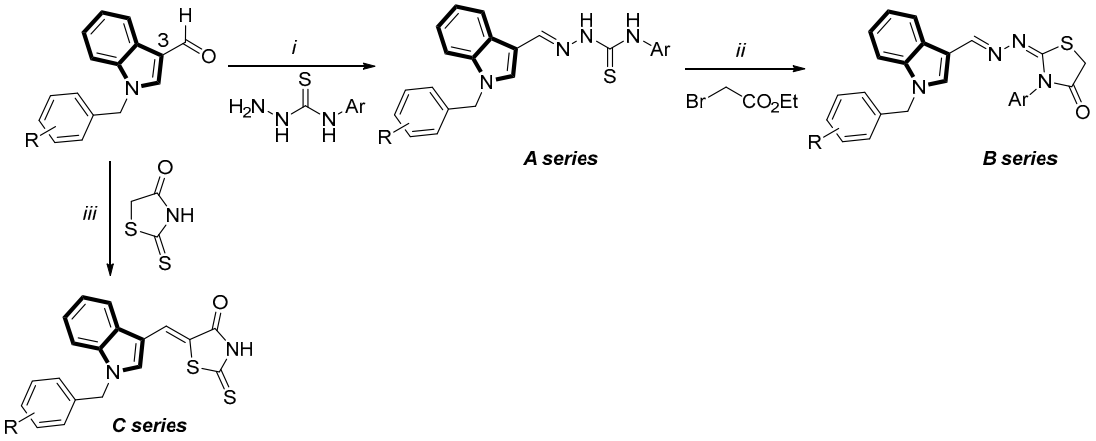


Figure 1. Selected biologically active compounds bearing indole-based moiety.

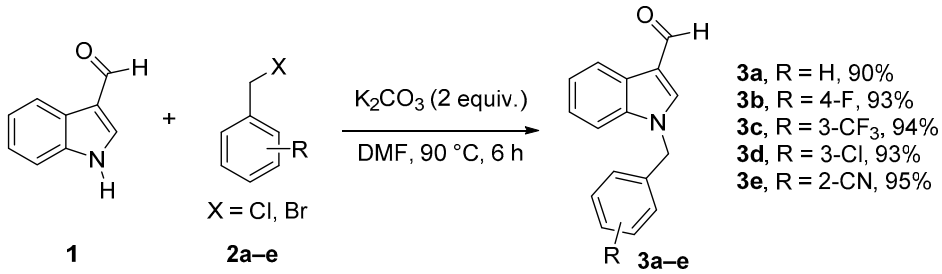


Scheme 1. Preparation of **A**, **B**, or **C** series.

2. Results and Discussion

2.1. Synthesis of N-Benzylindole-3-carboaldehyde Derivatives

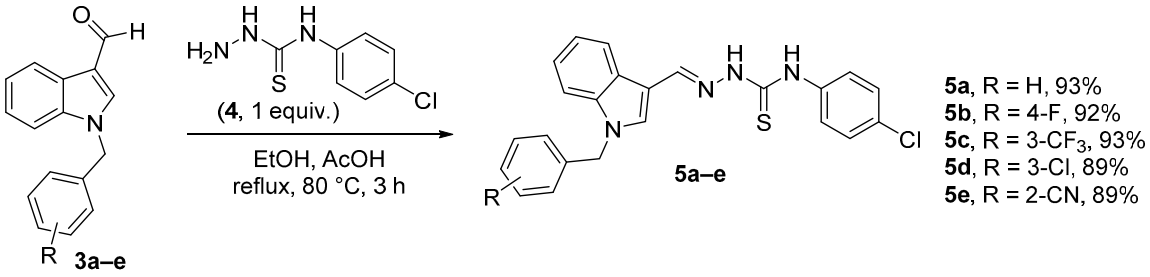
Substituted *N*-benzylindole-3-carboxaldehyde derivatives **3a**–**e** were prepared with 90–95% yield by the reaction of the indole-3-carboxaldehyde **1** with various substituted benzyl halides **2a**–**e** with K_2CO_3 as a base, in *N*,*N*-dimethylformamide (DMF) (Scheme 2) [25]. The structures of the synthesized compounds **3a**–**e** were confirmed by their ^{1}H-NMR and ^{13}C-NMR spectral data. The ^{1}H-NMR spectrum of compounds **3a**–**e** shows characteristic signals near δ 5.70 and 10.00 assignable to CH_2 and CHO. Further confirmation was achieved by the ^{13}C-NMR spectrum, which showed signals at δ 49.78 and 185.0 due to CH_2 and CHO, respectively (see Supporting Information).



Scheme 2. Preparation of *N*-benzylindole-3-carboaldehyde derivatives **3a**–**e**.

2.2. Synthesis of Thiosemicarbazones

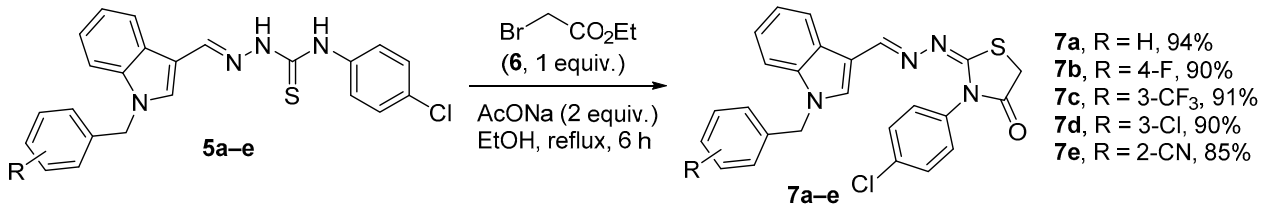
The reaction of 4-(4-chlorophenyl)-3-thiosemicarbazide **4** with indole-3-carbaldehyde derivatives **3a**–**e** with a few drops of acetic acid, stirred for 3 h at 80 °C, lead to the corresponding 4-(4-chlorophenyl)-3-thiosemicarbazone derivatives **5a**–**e** in good yields (Scheme 3). In the ^{1}H-RMN spectrum, the most characteristic signals of thiosemicarbazones **5a**–**e** correspond to the CH=N and the N–H protons. The ^{1}H-RMN studies show that the N–H protons of thiosemicarbazones **5a**–**e** are in the range of 9.62 to 11.68 ppm for the N–H adjacent to the mono-substituted phenyl ring and for the N–H adjacent to the CH=N fraction, while CH=N protons are in the range of 8.41 to 8.53 ppm. All synthesized compounds are in the *E* configuration, which was confirmed by the ^{1}H-RMN spectroscopy, because the NH group signal is in the range of 9 to 12 ppm, compared to the *Z* isomer, which has a characteristic signal between 14 and 15 ppm [26,27].



Scheme 3. Preparation of thiosemicarbazones **5a**–**e**.

2.3. Synthesis of Thiazolidin-4-One Derivatives

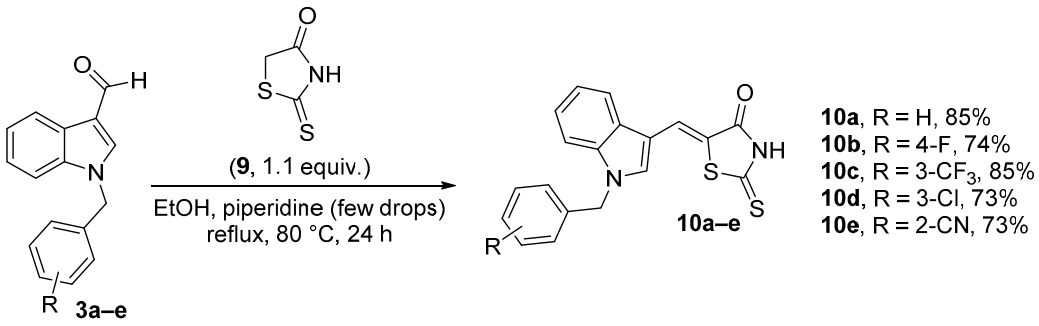
The resulting thiosemicarbazones **5a**–**e** were cyclized with ethyl bromoacetate in ethanol and sodium acetate under reflux for 3 h to give 1,3-thiazolidin-4-one derivatives **7a**–**e**, and final products were obtained in good yield (85–94%) (Scheme 4). The structures of new compounds **7a**–**e** were defined by their ^{1}H-NMR and ^{13}C-NMR data. The ^{1}H-NMR spectra present resonances assigned to the SCH_2 group of the thiazolidine ring, and this signal appears as a singlet at 4.08 ppm due to the methylene protons. The CH=N protons in these kinds of structures were observed at 8.45 and 8.46 ppm.



Scheme 4. Preparation of thiazolidin-4-one derivatives **7a**–**e**.

At the final step for the synthesis of products **10a**–**e**, the 2-thioxothiazolidin-4-one **9** has undergone a condensation with indole-3-carbaldehydes **3a**–**e**. The interaction was realized in boiling alcohol with piperidine as a base, and final products were obtained with moderate to good yields (85–73%) (Scheme 5).

In the ^{1}H-NMR spectrum, a large singlet at δ = 13.57 ppm was assigned to the –NH group, and the ^{13}C-NMR spectrum showed signals at δ = 169.1 and 194.6 ppm assigned to the (C=O) and (C=S) functionalities for the compound **10a**. The arylidenerhodanines synthesis **10a**–**e** leads to two isomers, *Z* and *E*. *Z*-isomers are predominant (Z > 75%) and thermodynamically more stable [26,27]. The exocyclic C=CH double bond configuration can be determined by NMR spectroscopy. The *Z*-configuration of the 5-arylidene **10a**–**e** derivatives was confirmed by the signal for the C=CH methine proton with a higher chemical shift between 7.90 and 7.95 ppm in a singlet form [28–33].



Scheme 5. Preparation of thioxothiazolinones **10a**–**e**.

3. Materials and Methods

3.1. General Information

The reagents were purchased from commercial suppliers and used without further purification. Melting points were determined on Büchi B-540 apparatus and are uncorrected. All solvents were dried following the procedure described by Armarego and Chai [34]. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance 300 MHz at 300 and 75 MHz, respectively. ^{1}H-NMR spectra were recorded in $CDCl_3$ referenced to the residual $CHCl_3$ at 7.26 ppm, and ^{13}C-NMR spectra were referenced to the central peak of $CDCl_3$ at 77.0 ppm. ^{19}F-NMR was recorded at 282 MHz on the same instrument, using the $CFCl_3$ as internal reference (δ 0.0). Chemical shifts were reported in parts per million (ppm, δ), and coupling constants (*J*) were given in Hertz (Hz). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; dd, doublet of doublets; dq, doublet of quartets; m, multiplet. High-resolution mass spectra (HRMS) were obtained by electrospray ionization time-of-flight (ESI) mass spectrometry. Thin-layer chromatography (TLC) was performed on TLC silica gel 60 F_{254}. Compounds were visualized with UV light (λ = 254 nm) and/or by immersion in a $KMnO_4$ solution followed by heating. Products were purified by flash column chromatography on silica gel (0.04–0.063 mm) using various mixtures of EtOAc and petroleum ether (35–60 °C fraction) as eluent. Heating was performed using a magnetic stirrer hotplate and an appropriately sized heating block. The compound names follow the IUPAC recommendations.

3.2. Experimental Section

3.2.1. General Procedure for the Synthesis of 1-Substituted-1*H*-indole-3-carbaldehydes (**3a**–**e**) (**35**)

1-Substituted-1*H*-indole-3-carbaldehyde was synthesized by reaction of 1*H*-indole-3-carbaldehyde **1** (1.45 g, 0.01 mol), the corresponding benzyl chloride **2a**–**e** (0.011 mol), and anhydrous K_2CO_3 (2.76 g, 0.02 mol) in *N*,*N*-dimethylformamide (30 mL). The reaction mixture was stirred at 90 °C for 6 h, and the reaction was monitored by thin-layer chromatography. The reaction was stopped and cooled at room temperature, and the mixture was poured into ice-cold water. The resulting precipitate was collected by filtration and washed with water. The crude product was purified by recrystallization from ethanol and dried under vacuum to give the desired compounds (**3a**–**e**).

1-Benzyl-1H-indole-3-carbaldehyde (**3a**): White solid, 90%, 2.21 g. mp 107–109 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.99 (s, 1H, C*H*O), 8.36–8.32 (m, 1H, indole C_7-*H*), 7.69 (s, 1H, indole C_2-*H*), 7.36–7.29 (m, 6H), 7.21–7.15 (m, 2H), 5.34 (s, 2H, CH_2) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 184.7 (*C*HO), 138.6 (indole C_2), 137.5 (C_{quat}), 135.4 (C_{quat}), 129.2 (2 *C*H), 128.5 (*C*H), 127.3 (2 *C*H), 125.6 (C_{quat}), 124.3 (*C*H), 123.1 (*C*H), 122.2 (*C*H), 118.6 (C_{quat}), 110.5 (indole C_7), 51.0 (CH_2) ppm.

1-(4-Fluorobenzyl)-1H-indole-3-carbaldehyde (**3b**): White solid, 93%, 2.35 g. mp 117–119 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.98 (s, 1H, C*H*O), 8.35–8.30 (m, 1H, indole C_7-*H*), 7.69 (s, 1H, indole C_2-*H*), 7.36–7.29 (m, 3H, indole C_4-*H*, C_5-*H* and C_6-*H*), 7.18–7.14 (m, 2H, 2H phenyl), 7.03 (t, *J* = 8.6 Hz, 2H, 2H phenyl), 5.32 (s, 2H, CH_2) ppm. ^{13}C-NMR (75 MHz,

$CDCl_3$): δ = 184.8 (*C*HO), 138.5 (indole C_2), 137.4 (C_{quat}), 136.6 (C_{quat}), 131.6 (q, *J* = 32.5 Hz, C_{quat}), 130.4 (q, *J* = 1.1 Hz, *C*H), 129.9 (*C*H), 125.6 (C_{quat}), 125.4 (q, *J* = 3.7 Hz, *C*H), 124.6 (CH), 123.9 (q, *J* = 3.8 Hz, *C*H), 123.8 (q, *J* = 272 Hz, C_{quat}), 123.4 (*C*H), 122.4 (*C*H), 118.9 (C_{quat}), 110.3 (indole C_7), 50.5 (CH_2) ppm.

1-(4-(Trifluoromethyl)benzyl)-1H-indole-3-carbaldehyde (**3c**): White solid, 94%, 2.85 g. mp 133–13509 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 10.02 (s, 1H, C*H*O), 8.37–8.32 (m, 1H, indole C_7-*H*), 7.74 (s, 1H, indole C_2-*H*), 7.60 (d, *J* = 7.8 Hz, 2H, 2H phenyl), 7.51 (bs, 1H, 1H phenyl), 7.46 (t, *J* = 7.8 Hz, 1H, 1H phenyl), 7.37–7.26 (m, 4H, C_4-*H*, C_5-*H*, C_6-*H* and 1H phenyl), 5.43 (s, 2H, CH_2) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 184.7 (*C*HO), 138.6 (indole C_2), 137.5 (C_{quat}), 135.4 (C_{quat}), 129.2 (2 *C*H), 128.5 (*C*H), 127.3 (2 *C*H), 125.6 (C_{quat}), 124.3 (*C*H), 123.1 (*C*H), 122.2 (*C*H), 118.6 (C_{quat}), 110.5 (indole C_7), 51.0 (CH_2) ppm.

1-(3-Chlorobenzyl)-1H-indole-3-carbaldehyde (**3d**): White solid, 93%, 2.50 g. mp 79–81 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.99 (s, 1H, C*H*O), 8.36–8.31 (m, 1H, indole C_7-*H*), 7.72 (s, 1H, indole C_2-*H*), 7.36–7.25 (m, 5H, indole C_4-*H*, C_5-*H*, C_6-*H*, 2H phenyl), 7.17 (bs, 1H, 1H phenyl), 7.04–7.00 (m, 1H, 1H phenyl), 5.32 (s, 2H, CH_2) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 184.8 (*C*HO), 138.6 (indole C_2), 137.5 (C_{quat}), 137.4 (C_{quat}), 135.1 (C_{quat}), 130.5 (*C*H), 128.7 (*C*H), 127.3 (*C*H), 125.5 (C_{quat}), 125.3 (*C*H), 124.5 (*C*H), 123.3 (*C*H), 122.3 (*C*H), 118.7 (C_{quat}), 110.4 (indole C_7), 50.4 (CH_2) ppm.

2-((3-Formyl-1H-indol-1-yl)methyl)benzonitrile (**3e**): White solid, 94%, 2.44 g. mp 133–135 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.99 (s, 1H, C*H*O), 8.45 (s, 1H, indole C_2-*H*), 8.18 (d, *J* = 8 Hz, 1H, indole C_4-*H*), 7.97 (d, 1H, *J* = 8 Hz, 1H, indole C_7-*H*), 7.67 (1H, td, *J* = 1.4 Hz, *J* = 7.7 Hz, Ar-H), 7.60–7.52 (m, 2H, Ar-H), 7.35–7.25 (m, 2H, Ar-H), 7.07 (1H, d, *J* = 7.58 Hz, Ar-H), 5.83 (s, 2H, CH_2) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.0 (*C*HO), 141.2 (indole C_2), 140.0 (C_{quat}), 137.1 (C_{quat}), 133.8 (*C*H), 133.5 (*C*H), 128.7 (*C*H), 127.8 (*C*H), 124.7 (*C*H), 123.9 (*C*H), 122.8 (*C*H), 121.2 (*C*H), 117.7 (C_{quat}), 117.2 (C_{quat}), 111.1 (C_{quat}), 110.4 (*C*H), 48.2 (CH_2) ppm.

3.2.2. General Procedure for the Synthesis of Thiosemicarbazones (**5a**–**e**) (**35**)

To a solution of 4-chlorophenylthiosemicarbazide **4** (0.605 g, 3 mmol, 1 equiv) in ethanol (33 mL) were added the 1-substituted-1*H*-indole-3-carbaldehyde (6.3 mmol, 1.05 equiv) and acetic acid (0.50 mL). The mixture was stirred and heated under reflux for 3 h. The reaction was stopped and cooled to room temperature. After, the solid was filtered and recrystallized from ethanol-DMF (3:1) to give compounds **5a**–**e**.

(E)-2-((1-Benzyl-1H-indol-3-yl)methylene)-N-(4-chlorophenyl)hydrazine-1-carbothioamide (**5a**): Beige solid, 93%, 0.97 g. mp 203–205 °C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.68 (bs, 1H, N*H*), 9.68 (bs, 1H, N*H*), 8.41 (s, 1H, indole C_2-*H*), 8.26 (d, 1H, *J* = 7.3 Hz, Ar-*H*), 8.10 (s, 1H, C*H*=N), 7.68 (d, 2H, *J* = 8.7 Hz, Ar-*H*), 7.52 (d, 1H, *J* = 7.6 Hz, Ar-*H*), 7.42 (d, 2H, *J* = 8.7 Hz, Ar-*H*), 7.36–7.14 (m, 7H, Ar-*H*), 5.47 (s, 2H, PhCH_2) ppm. ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 174.5 (*C*S), 141.0 (*C*H), 138.3 (C_{quat}), 137.4 (C_{quat}), 136.9 (C_{quat}), 134.3 (*C*H), 128.9 (C_{quat}), 128.6 (2*C*H), 127.9 (2*C*H), 127.6 (*C*H), 127.1 (2*C*H), 126.9 (2*C*H), 124.7 (C_{quat}), 122.9 (*C*H), 122.2 (*C*H), 121.1 (*C*H), 110.7 (*C*H), 110.6 (C_{quat}), 49.4 (CH_2) ppm. HRMS (ESI): calcd. for $C_{23}H_{20}ClN_4S$ $[M + H]^+$ 419.10972; found 419.10981.

(E)-N-(4-Chlorophenyl)-2-((1-(4-fluorobenzyl)-1H-indol-3-yl)methylene)hydrazine-1-carbothioamide (**5b**): Beige solid, 92%, 0.97 g. mp 211–213 °C. ^{1}H-NMR (300 MHz, Acetone-d_6): δ = 10.5 (bs, 1H, N*H*), 9.62 (bs, 1H, N*H*), 8.51 (s, 1H, indole C_2-*H*), 8.28 (dd, 1H, *J* = 7.1 Hz, *J* = 1.3 Hz, Ar-*H*), 7.96 (s, 1H, C*H*=N), 7.90–7.83 (m, 2H, Ar-*H*), 7.51 (d, 1H, *J* = 7.4 Hz, Ar-*H*), 7.40 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 7.37–7.31 (m, 2H, Ar-*H*), 7.29–7.18 (m, 2H, Ar-*H*), 7.11 (t, 2H, *J* = 8.8 Hz, Ar-*H*), 5.53 (s, 2H, PhCH_2) ppm. ^{19}F-NMR (282 MHz, DMSO-d_6): δ = −116.3 ppm. ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 174.5 (*C*S), 161.5 (d, *J* = 244 Hz, C_{quat}), 140.9 (*C*H), 138.3 (C_{quat}), 136.8 (C_{quat}), 134.2 (*C*H), 133.6 (d, *J* = 3.1 Hz, C_{quat}), 129.3 (d, *J* = 3.2 Hz, 2*C*H), 128.9 (C_{quat}), 127.9 (2*C*H), 126.8 (2*C*H), 124.8 (C_{quat}), 122.9 (*C*H), 122.3 (*C*H), 121.1 (*C*H), 115.4 (d, *J* = 21.6 Hz, 2*C*H), 110.7 (C_{quat}), 110.6 (*C*H), 48.6 (CH_2) ppm. HRMS (ESI): calcd. for $C_{23}H_{19}ClFN_4S$ $[M + H]^+$ 437.10030; found 437.10029.

(E)-N-(4-Chlorophenyl)-2-((1-(3-(trifluoromethyl)benzyl)-1H-indol-3-yl)methylene)hydrazine-1-carbothioamide (**5c**): White solid, 89%, 1.00 g. mp 224–226 °C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.68 (bs, 1H, N*H*), 9.69 (bs, 1H, N*H*), 8.42 (s, 1H, indole C_2-*H*), 8.28 (d, 1H, *J* = 7.1 Hz, Ar-*H*), 8.12 (s, 1H, C*H*=N), 7.67 (d, 2H, *J* = 8.7 Hz, Ar-*H*), 7.54 (d, 1H, *J* = 7.7 Hz, Ar-*H*), 7.42 (d, 2H, *J* = 8.7 Hz, Ar-*H*), 7.38–7.32 (m, 3H, Ar-*H*), 7.27–7.15 (m, 3H, Ar-*H*), 5.49 (s, 2H, PhCH_2) ppm. ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 174.6 (*C*S), 140.9 (*C*H), 138.9 (C_{quat}), 138.3 (C_{quat}), 136.8 (C_{quat}), 134.3 (*C*H), 131.2 (*C*H), 129.8 (*C*H), 129.3 (q, *J* = 31.7 Hz, C_{quat}), 128.9 (C_{quat}), 127.9 (2*C*H), 126.9 (2*C*H), 124.7 (C_{quat}), 124.4 (q, *J* = 3.6 Hz, *C*H), 124.0 (q, *J* = 272 Hz, C_{quat}), 123.7 (q, *J* = 3.8 Hz, *C*H), 123.1 (*C*H), 122.4 (*C*H), 121.2 (*C*H), 110.9 (C_{quat}), 110.5 (*C*H), 48.7 (*C*H_2) ppm. HRMS (ESI): calcd. for $C_{24}H_{19}ClF_3N_4S$ [M + H]$^+$ 487.09710; found 487.09720.

(E)-2-((1-(3-Chlorobenzyl)-1H-indol-3-yl)methylene)-N-(4-chlorophenyl)hydrazine-1-carbothioamide (**5d**): Beige solid, 93%, 0.97 g. mp 203–205 °C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.68 (bs, 1H, N*H*), 9.68 (bs, 1H, N*H*), 8.41 (s, 1H, indole C_2-*H*), 8.26 (d, 1H, *J* = 7.3 Hz, Ar-*H*), 8.10 (s, 1H, C*H*=N), 7.68 (d, 2H, *J* = 8.7 Hz, Ar-*H*), 7.52 (d, 1H, *J* = 7.6 Hz, Ar-*H*), 7.42 (d, 2H, *J* = 8.7 Hz, Ar-*H*), 7.36–7.14 (m, 7H, Ar-*H*), 5.47 (s, 2H, PhCH_2) ppm. ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 174.6 (*C*S), 140.9 (*C*H), 139.9 (C_{quat}), 138.3 (C_{quat}), 136.8 (C_{quat}), 134.3 (*C*H), 133.2 (C_{quat}), 130.6 (*C*H), 128.9 (C_{quat}), 127.9 (2*C*H), 127.6 (*C*H), 127.0 (*C*H), 126.9 (2*C*H), 125.8 (*C*H), 124.7 (C_{quat}), 123.1 (*C*H), 122.3 (*C*H), 121.2 (*C*H), 110.8 (C_{quat}), 110.6 (*C*H), 48.7 (*C*H_2) ppm. HRMS (ESI): calcd. for $C_{23}H_{19}Cl_2N_4S$ [M + H]$^+$ 453.07075; found 453.07083.

(E)-N-(4-Chlorophenyl)-2-((1-(2-cyanobenzyl)-1H-indol-3-yl)methylene)hydrazine-1-carbothioamide (**5e**): Beige solid, 89%, 1.00 g. mp 229–231 °C. ^{1}H-NMR (300 MHz, Acetone-d_6): δ = 10.56 (bs, 1H, N*H*), 9.64 (bs, 1H, N*H*), 8.53 (s, 1H, indole C_2-*H*), 8.31 (d, 1H, *J* = 7.2 Hz, Ar-*H*), 7.99 (s, 1H, C*H*=N), 7.90–7.82 (m, 3H, Ar-*H*), 7.63 (td, 1H, *J* = 7.6 Hz, *J* = 1.4 Hz, Ar-*H*), 7.58–7.50 (m, 2H, Ar-*H*), 7.40 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 7.32–7.22 (m, 2H, Ar-*H*), 7.09–7.04 (m, 1H, Ar-*H*), 5.78 (s, 2H, PhCH_2) ppm. ^{13}C-NMR (75 MHz, $CHCl_3$): δ = 174.7 (*C*S), 140.8 (*C*H), 140.7 (C_{quat}), 138.3 (C_{quat}), 137.0 (C_{quat}), 134.5 (*C*H), 133.8 (*C*H), 133.4 (*C*H), 128.9 (C_{quat}), 128.6 (*C*H), 127.9 (2*C*H), 127.6 (*C*H), 126.9 (2*C*H), 124.7 (C_{quat}), 123.3 (*C*H), 122.5 (*C*H), 121.4 (*C*H), 117.2 (C_{quat}), 111.2 (C_{quat}), 110.4 (*C*H), 110.3 (C_{quat}), 47.8 (*C*H_2) ppm. HRMS (ESI): calcd. for $C_{24}H_{19}ClN_4S$ [M + H]$^+$ 444.10497; found 444.10489.

3.2.3. General Procedure for the Synthesis of Thiazolidin-4-ones (**7a**–**e**)

A mixture of compound **5a**–**e** (1.5 mmol, 1 eq), ethyl 2-bromoacetate **6** (0.24 mL, 1.5 mmol), and anhydrous sodium acetate (0.37 g, 4.5 mmol, 3 eq) in ethanol (30 mL) was stirred at 80 °C for 6 h. The reaction mixture was cooled at room temperature, poured into ice cold water, and the solid was filtered, washed with water, and recrystallized from a mixture of ethanol-DMF (3:1).

2-(2-((1-Benzyl-1H-indol-3-yl)methylene)hydrazono)-3-(4-chlorophenyl)thiazolidin-4-one (**7a**): Yellow solid, 94%, 0.43 g. mp 250–252 °C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.45 (s, 1H, indole C_2-*H*), 8.43–8.40 (m, 1H, Ar-*H*), 7.85 (s, 1H, C*H*=N), 7.56 (d, 2H, *J* = 8.9 Hz, Ar-*H*), 7.52–7.46 (m, 3H, Ar-*H*), 7.36–7.22 (m, 7H, Ar-*H*), 5.52 (s, 2H, PhCH_2), 4.06 (s, 2H, CH_2) ppm. ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 172.2 (*C*O), 161.8, 153.9, 137.9, 137.7, 135.3, 134.6, 133.6, 130.6, 129.5, 129.1, 127.6, 125.8, 123.4, 122.7, 121.6, 111.3, 50.0 (*C*H_2), 32.7 (*C*H_2) ppm. HRMS (ESI): calcd. for $C_{25}H_{20}ClN_4OS$ [M + H]$^+$ 459.10463; found 459.10475.

2-(2-((1-(4-Fluorobenzyl)-1H-indol-3-yl)methylene)hydrazono)-3-(4-chlorophenyl)thiazolidin-4-one (**7b**): Brown solid, 94%, 0.42 g. mp 242–244 °C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.45 (s, 1H, indole C_2-*H*), 8.27–8.24 (m, 1H, Ar-*H*), 7.96 (s, 1H, C*H*=N), 7.61 (d, 2H, *J* = 8.9 Hz, Ar-*H*), 7.57–7.46 (m, 1H, Ar-*H*), 7.46 (d, 2H, *J* = 8.7 Hz, Ar-*H*), 7.33–7.28 (m, 2H, Ar-*H*), 7.25–7.21 (m, 2H, Ar-*H*), 7.15 (t, 2H, *J* = 8.9 Hz, Ar-*H*), 5.46 (s, 2H, PhCH_2), 4.08 (s, 2H, CH_2) ppm. ^{19}F-NMR (282 MHz, DMSO-d_6): δ = −114.9 ppm. ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 171.9 (*C*O), 161.7 (C_{quat}), 161.5 (d, *J* = 243 Hz, C_{quat}), 153.3, 136.9, 134.8, 134.0, 133.5 (d, *J* = 3.2 Hz, C_{quat}), 133.1, 130.2, 129.3 (d, *J* = 8.3 Hz), 129.1, 125.2, 123.0, 122.3, 121.3, 115.4 (d, *J* = 21.5 Hz), 111.6, 110.8, 48.6 (*C*H_2), 32.7 (*C*H_2) ppm. HRMS (ESI): calcd. for $C_{25}H_{19}ClFN_4OS$ [M + H]$^+$ 477.09521; found 477.09528.

2-(2-((1-(3-(Trifluoromethyl)benzyl)-1H-indol-3-yl)methylene)hydrazono)-3-(4-chlorophenyl) thiazolidin-4-one (**7c**): Beige solid, 91%, 0.48 g. mp 230–232 °C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.46 (s, 1H, indole C_2-*H*), 8.29–8.26 (m, 1H, Ar-*H*), 8.02 (s, 1H, C*H*=N), 7.66–7.58 (m, 4H, Ar-*H*), 7.56–7.53 (m, 3H, Ar-*H*), 7.47 (d, 2H, *J* = 8.7 Hz, Ar-*H*), 7.28–7.20 (m, 2H, Ar-*H*), 5.60 (s, 2H, PhCH_2). 4.09 (s, 2H, CH_2) ppm. ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 171.8 (*C*O), 161.8, 153.3, 138.9, 136.9, 134.9, 134.0, 133.1, 131.1, 130.2, 129.8, 129.7 (q, *J* = 31 Hz), 129,1, 125.2, 124.4 (q, *J* = 3.7 Hz), 124.0 (q, *J* = 272 Hz), 123.7 (q, *J* = 4 Hz), 123.1, 122.3, 121.4, 111.8, 110.7, 48.7 (*C*H_2), 32.3 (*C*H_2) ppm. HRMS (ESI): calcd. for $C_{26}H_{19}ClF_3N_4OS$ [M + H]$^+$ 527.09202; found 527.09212.

2-(2-((1-(3-Chlorobenzyl)-1H-indol-3-yl)methylene)hydrazono)-3-(4-chlorophenyl)thiazolidin-4-one (**7d**): Yellow solid, 90%, 0.44 g. mp 252–254 °C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.45 (s, 1H, indole C_2-*H*), 8.27–8.24 (m, 1H, Ar-*H*), 7.96 (s, 1H, C*H*=N), 7.60 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 7.56–7.51 (m, 1H, Ar-*H*), 7.47 (d, 2H, *J* = 8.7 Hz, Ar-*H*), 7.33–7.20 (m, 6H, Ar-*H*), 5.47 (s, 2H, PhCH_2), 4.09 (s, 2H, CH_2) ppm. ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 171.9 (*C*O), 161.7, 153.4, 137.4, 137.1, 135.0, 134.1, 133.1, 130.2, 129.1, 128.8 (2*C*H), 127.6, 127.1 (2*C*H), 125.2, 123.0, 122.3, 121.3, 111.5, 110.9, 49.4 (*C*H_2), 32.3 (*C*H_2) ppm. HRMS (ESI): calcd. for $C_{25}H_{19}Cl_2N_4OS$ [M + H]$^+$ 493.06566; found 493.06574.

2-(2-((1-(2-Cyanobenzyl)-1H-indol-3-yl)methylene)hydrazono)-3-(4-chlorophenyl)thiazolidin-4-one (**7e**): Beige solid, 85%, 0.41 g. mp 253–255 °C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.46 (s, 1H, indole C_2-*H*), 8.31–8.28 (s, 1H, Ar-*H*), 7.93 (s, 1H, C*H*=N), 7.91–7.90 (m, 1H, Ar-*H*), 7.62–7.58 (m, 3H, Ar-*H*), 7.52–7.45 (m, 4H, Ar-*H*), 7.25–7.22 (m, 1H, Ar-*H*), 5.72 (s, 2H, PhCH_2), 4.09 (s, 2H, CH_2) ppm. ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 171.8 (*C*O), 161.9 (C_{quat}), 153.3 (*C*H), 140.6 (C_{quat}), 137.2 (C_{quat}), 135.1 (*C*H), 134.0 (C_{quat}), 133.7 (*C*H), 133.4 (*C*H), 133.1 (C_{quat}), 130.2 (2*C*H), 129.1 (2*C*H), 128,5 (*C*H), 127.7 (*C*H), 125.1 (C_{quat}), 123.2 (*C*H), 122.4 (*C*H), 121.5 (*C*H), 117.2 (C_{quat}), 112.0 (C_{quat}), 110.6 (CH), 110.3 (C_{quat}), 47.8 (*C*H_2), 32.3 (*C*H_2) ppm. HRMS (ESI): calcd. for $C_{26}H_{19}ClN_5OS$ [M + H]$^+$ 484.09988; found 484.09994.

3.2.4. General Procedure for the Synthesis of Thioxothiazolinones (**10a**–**e**)

We mixed 2-thioxothiazolidin-4-one **9** (0.2 g, 1.5 mmol, 1 equiv) and indole-3-carbaldehyde (**3a**–**e**) (1.65 mmol, 1.1 equiv) in a two-neck round-bottom flask, with a sufficient quantity of ethanol for the dissolution of the starting reagents. The reaction mixture was heated at reflux at 80 °C, and 10 mol% of piperidine was added. The reaction was followed by TLC and at the end of the reaction, the reaction was stopped, and the mixture was cooled to room temperature. The final product was filtered and washed with distilled water to remove traces of piperidine.

(Z)-5-((1-Benzyl-1H-indol-3-yl)methylene)-2-thioxothiazolidin-4-one (**10a**): Yellow solid, 85%, 0.45 g. mp 243–245 °C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 13.58 (s, 1H, N*H*), 8.11 (s, 1H), 7.97 (dd, 1H, *J* = 7.0 Hz, *J* = 1.6 Hz, Ar-*H*), 7.91 (s, 1H), 7.57 (dd, 1H, *J* = 7.0 Hz, *J* = 1.5 Hz, Ar-*H*), 7.36–7.20 (m, 7H, Ar-*H*), 5.60 (s, 2H, PhCH_2) ppm. ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 194.6 (*C*S), 169.1 (*C*O), 136.9 (C_{quat}), 136.1 (C_{quat}), 132.7 (*C*H), 128.7 (2*C*H), 127.7 (*C*H), 127.5 (C_{quat}), 127.3 (2*C*H), 123.8 (*C*H), 123.4 (*C*H), 121.7 (*C*H), 118.8 (C_{quat}), 118.5 (*C*H), 111.4 (CH), 110.5 (C_{quat}), 49.8 (*C*H_2) ppm. HRMS (ESI): calcd. for $C_{19}H_{15}N_2OS_2$ [M + H]$^+$ 351.06258; found 351.06264.

(Z)-5-((1-(4-Fluorobenzyl)-1H-indol-3-yl)methylene)-2-thioxothiazolidin-4-one (**10b**): Yellow solid, 74%, 0.41 g. mp 219–221°C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 13.58 (s, 1H, N*H*), 8.12 (s, 1H), 7.96 (dd, 1H, *J* = 7.0 Hz, *J* = 1.4 Hz, Ar-*H*), 7.91 (s, 1H), 7.59 (dd, 1H, *J* = 7.3 Hz, *J* = 1.1 Hz, Ar-*H*), 7.43–7.36 (m, 2H, Ar-*H*), 7.29–7.14 (m, 4H, Ar-*H*) 5.58 (s, 2H, PhCH_2) ppm. ^{19}F-NMR (282 MHz, DMSO-d_6): δ = −114.8 ppm. ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 194.6 (*C*S), 169.1 (*C*O), 161.9 (d, *J* = 243 Hz, C_{quat}), 136.5 (C_{quat}), 133.1 (d, *J* = 3.1 Hz, C_{quat}), 132.6 (CH), 129.5 (d, *J* = 8.3 Hz, *C*H), 127.6 (C_{quat}), 123.8 (*C*H), 123.5 (*C*H), 121.8 (CH), 118.8 (CH), 118.6 (C_{quat}), 115.4 (d, *J* = 21.5 Hz, CH), 113.4 (CH), 110.6 (C_{quat}), 49.0 (CH_2) ppm. HRMS (ESI): calcd. for $C_{19}H_{14}FN_2OS_2$ [M + H]$^+$ 369.05316; found 369.05319.

(Z)-2-Thioxo-5-((1-(3-(trifluoromethyl)benzyl)-1H-indol-3-yl)methylene)thiazolidin-4-one (**10c**): Yellow solid, 85%, 0.50 g. mp 208–210 °C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.08 (s, 1H), 7.91–7.87

(m, 1H, Ar-*H*), 7.87 (s, 1H), 7.73 (bs, 1H, Ar-*H*), 7.64 (d, 1H, *J* = 7.8 Hz, Ar-*H*), 7.59–7.53 (m, 2H, Ar-*H*), 7.46 (d, 1H, *J* = 7.6 Hz, Ar-*H*), 7.28–7.17 (m, 2H, Ar-*H*), 5.69 (s, 2H, PhCH_2) ppm. ^{19}F-NMR (282 MHz, DMSO-d_6): δ = −61.1 ppm. ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 179.6 (*C*S), 172.4 (*C*O), 138.9 (C_{quat}), 136.1 (C_{quat}), 131.0 (*C*H), 130.3 (*C*H), 129.8 (*C*H), 129.2 (q, *J* = 31.7 Hz, C_{quat}), 127.5 (C_{quat}), 124.3 (q, *J* = 3.8 Hz, CH), 124.0 (q, *J* = 272 Hz, C_{quat}), 123.7 (q, *J* = 3.8 Hz, CH), 123.5 (Cquat), 123.1 (CH), 121.1 (CH), 120.7 (CH), 118.7 (CH), 111.0 (Cquat), 110.9 (CH), 48.9 (*C*H_2) ppm. HRMS (ESI): calcd. for $C_{20}H_{14}ClF_3N_2OS_2$ $[M + H]^+$ 419.04996; found 419.05003.

(Z)-5-((1-(3-Chlorobenzyl)-1H-indol-3-yl)methylene)-2-thioxothiazolidin-4-one (**10d**): Yellow solid, 73%, 0.42 g. mp 265–267 °C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 13.6 (bs, 1H, N*H*), 8.13 (s, 1H), 7.97 (d, *J* = 7.7 Hz, Ar-*H*), 7.90 (s, 1H), 7.58 (d, 1H, *J* = 7.8 Hz, Ar-*H*), 7.41–7.22 (m, 5H, Ar-*H*), 5.61 (s, 2H, PhCH_2) ppm. ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 179.6 (*C*S), 161.1 (*C*O), 140.0, 136.5, 133.7, 133.0, 131.2, 131.1, 128.3, 128.2, 127.6, 126.4, 124.0, 122.3, 119.4, 111.8, 111.3, 49.6 (*C*H_2) ppm. HRMS (ESI): calcd. for $C_{19}H_{14}ClN_2OS_2$ $[M + H]^+$ 385.02361; found 385.02372.

(Z)-2-((3-((4-Oxo-2-thioxothiazolidin-5-ylidene)methyl)-1H-indol-1-yl)methyl)benzonitrile e (**10e**): Yellow solid, 73%, 0.42 g. mp 244–246 °C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.04 (s, 1H), 7.95–7.91 (d, *J* = 7.7 Hz, Ar-*H*), 7.88 (s, 1H), 7.60 (td, 1H, *J* = 7.7 Hz, *J* = 1.4 Hz, Ar-*H*), 7.51–7.46 (m, 2H, Ar-*H*), 7.28–7.20 (m, 2H, Ar-*H*), 6.84 (d, *J* = 7.7 Hz, Ar-*H*), 5.83 (s, 2H, PhCH_2) ppm. ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 179.6 (*C*S), 172.3 (*C*O), 140.8 (C_{quat}), 136.3 (C_{quat}), 133.8 (*C*H), 133.4 (*C*H), 130.8 (*C*H), 128.4 (*C*H), 127.4 (C_{quat}), 127.2 (*C*H), 123.7 (C_{quat}), 123.3 (*C*H), 121.3 (*C*H), 120.6 (*C*H), 118.8 (*C*H), 117.3 (C_{quat}), 111.2 (C_{quat}), 110.8 (*C*H), 110.1 (C_{quat}), 48.7 (*C*H_2) ppm. HRMS (ESI): calcd. for $C_{20}H_{14}N_3OS_2$ $[M + H]^+$ 376.05783; found 376.05788.

4. Conclusions

In summary, we have developed an effective new protocol for the preparation of indole substituted at position 1 and 3 for the series **A**. Knoevenagel-type condensation affords a new series of thiosemicarbazones or thioxothiazolinones with excellent yields according to the procedures described in [35]. The cyclization of thiosemicarbazones with ethyl bromoacetate furnished a new series of thiazolidinones also with a good yield. In vitro studies of the antimicrobial activity of all these molecules on various pathogenic bacteria (*Staphylococcus aureus* and *Pseudomonas aeruginosa*) are in progress in our laboratory.

Supplementary Materials: The following are available online. ^{1}H- & ^{13}C-NMR for compounds **3a**–**e**, **4a**, **5a**–**e**, **7a**–**e**, and **10a**–**e**.

Author Contributions: Conceptualization, A.B. and A.D.; data curation, N.R. and A.B.; formal analysis, N.R., J.T. and A.B.; investigation, A.B.; methodology, N.R. and S.K.; project administration, A.B.; validation, A.D.; resources, J.T.; writing—original draft preparation, J.T. and A.B.; writing—review and editing, J.T. and A.B.; visualization, J.T. and A.B.; supervision, J.T. All authors discussed the results and commented on the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: We acknowledge Frédéric Montigny (Analysis Department, Tours University) for HRMS analysis. We acknowledge the Algeria Minister of Higher Education and Scientific Research for the financial support.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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