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ORIGINAL PAPER

Synthesis and antimicrobial activities of new thiosemicarbazones and thiazolidinones in indole series

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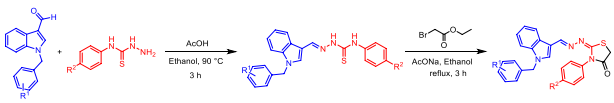
Abstract

New thiosemicarbazones were synthesized in excellent yield reaction of indole derivatives with thiosemicarbazides. These thiosemicarbazones were reacted with ethyl bromoacetate to produce original heterocyclic-substituted indole derivatives possessing a 4-oxo-thiazolidine group. Analytical IR and NMR spectra and elemental analysis were performed to reveal their structures. The antimicrobial activity of all synthesized compounds was evaluated for antibacterial activity in vitro against Gram-positive and Gram-negative bacteria. Antibacterial screening data showed that two compounds demonstrated activity against *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*. These preliminary results indicate that some of these newly synthesized compounds show a promising antibacterial potency.

Graphic abstract



Keywords Indoles · Thiosemicarbazones · Thiazolidinones · Nucleophilic addition · Heterocycles · Antibacterial activity

Introduction

Indoles and several *N*-substituted indoles are an important class of heterocycles. These compounds have been attracting attention for their wide range of biological activities and their potential in synthetic chemistry. Indole derivatives possess a broad spectrum of pharmacological activities such as antimicrobial [1], analgesic [2], anticonvulsant [3], antiviral [4], antihypertensive [5], anti-asthmatic [6], antidepressant [7], anti-Alzheimer [8], antimalaria [9], antidiabetic [10], and anti-HIV activities [11]. They offer particular promise in the search for new antitumor agents [12, 13]. Thiosemicarbazones represent a broad family of molecules with various pharmacological properties, including antiviral [14], antibacterial [15], and antitumor activities [16]. Moreover, thiazolidinone derivatives possess potential biological and medicinal activities [17], among them antimycobacterial [18], antioxidant [19], anticancer [20, 21], anticonvulsant [22], anti-inflammatory [23], analgesic [24], and antimicrobial [25–28]. In antibacterial activities, thiazolidinones

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are more active on Gram-negative bacteria than on Gram-positive bacteria. In an attempt to design and synthesize new antimicrobial molecules [29–32], we report here a synthesis of new thiosemicarbazone and thiazolidinone derivatives containing the indole moiety, with the aim of obtaining new biologically active compounds. The drug design process is based on the synthesis combining two potential pharmacophore systems in one molecule.

Results and discussion

The starting materials, N^4-substituted thiosemicarbazide derivatives **3a**, **3b**, were prepared through the nucleophilic addition reaction of 85% hydrazine hydrate with aryl isothiocyanate **1a**, **1b** in ethanol at room temperature [33] (Scheme 1). On the other hand, substituted *N*-benzylindole-3-carboxaldehyde derivatives **6a**–**6e** were obtained in 90–95% yield using procedures described in the literature [34]. The appropriate commercially available indole-3-carboxaldehyde (**4**) was treated with various substituted benzyl halides **5a**–**5e** in the presence of K_2CO_3 in *N*,*N*-dimethylformamide (DMF) (Scheme 1).

Thiosemicarbazone derivatives **7a**–**7j** were obtained in good yields (86–95%), via condensation of substituted *N*-benzylindole-3-carboxaldehyde derivatives **6a**–**6e** with N^4-substituted thiosemicarbazides **3a**, **3b** in the presence of a catalytic amount of AcOH in ethanol at 90 °C as solvent, as shown in Scheme 1 and Table 1.

After recrystallization of all thiosemicarbazones **7a**–**7j**, they were analyzed by ^{1}H and ^{13}C NMR, IR, as well as by elemental analysis. The IR spectra of compounds **7a**–**7j** showed characteristic absorptions in the range of 3343–3124 cm^{-1} (N–H bond), 1278–1189 cm^{-1} (C=S), and 1537–1550 cm^{-1} (CH=N bond). Thus, the presence and predominance of the thione form of synthesized thiosemicarbazones **7a**–**7j** were confirmed by the absence of absorption in the 2500–2600 cm^{-1} region [35, 36].

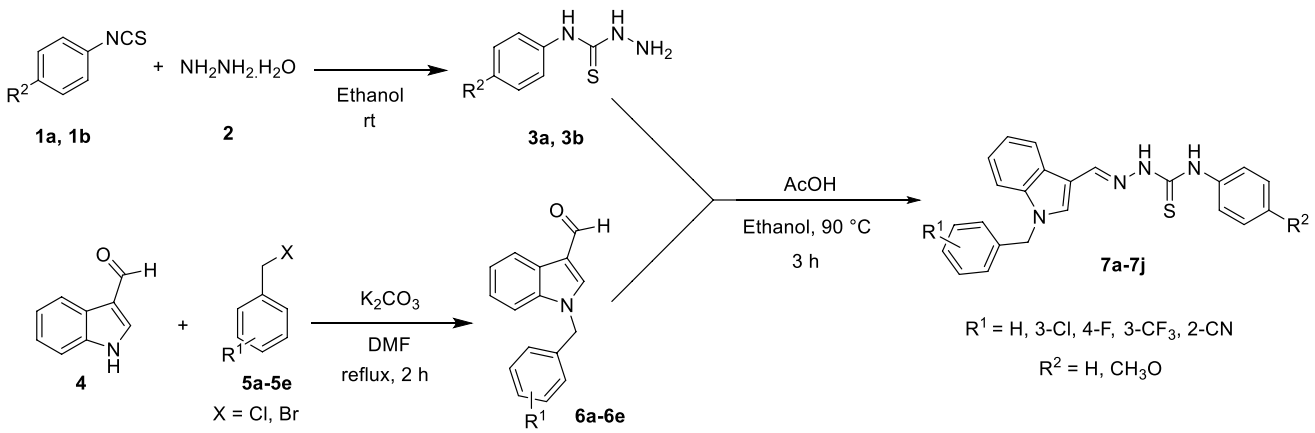
Table 1 Preparation of thiosemicarbazone derivatives **7a**–**7j** from reaction between **3a**, **3b** and **6a**–**6e**

Product	R^1	R^2	Yield/%[a]
7a	H	H	94
7b	3-Cl	H	87
7c	4-F	H	95
7d	3-CF_3	H	86
7e	2-CN	H	90
7f	H	4-OCH_3	95
7g	3-Cl	4-OCH_3	95
7h	4-F	4-OCH_3	91
7i	3-CF_3	4-OCH_3	92
7j	2-CN	4-OCH_3	95

[a]All yields refer to chromatographically isolated pure products and are relative to the respective N^4-substituted thiosemicarbazides **3a**, **3b**

The most characteristic signals in the ^{1}H NMR spectrum of this family of thiosemicarbazones were those corresponding to the –CH=N and N–H protons. ^{1}H NMR analysis showed the CH=N protons to be in the 8.02–8.15 ppm range, whereas the thiourea N–H protons were found to be in the 9.50–11.63 ppm interval for N–H adjacent to the mono-substituted phenyl ring and for the N–H adjacent to the CH=N moiety, respectively. In the ^{13}C NMR spectra, the chemical shift of the azomethine group (H–C=N) appeared at region 140.77–141.14 ppm, while for the C=S group, it occurred in the range 175–175.65 ppm, both comparable to the literature [37, 38]. All the thiosemicarbazone compounds synthesized were in configuration *E*, as confirmed by ^{1}H NMR spectroscopy, where a single peak was detected, indicating a chemical shift of 8.02–8.15 ppm for hydrogen azomethine (H–C=N–) simple [39]. In addition, a single thin-layer spot

Scheme 1



was observed under chromatography (TLC), indicating the presence of a single isomeric form. It has been noted by a number of authors that compounds possessing a *Z* isomer generally exhibit an NH-3 signal in the 14–15 ppm range, whereas those compounds possessing an *E* form display a signal in the 9–12 ppm range [40].

The reaction between ethyl bromoacetate **8** and thiosemicarbazone derivatives **7a**–**7j** in absolute ethanol containing anhydrous sodium acetate afforded the corresponding 4-thiazolidinone compounds **9a**–**9j** in good yields (82–95%), as shown in Scheme 2 and Table 2.

The chemical structures of thiazolidinones **9a**–**9j** were confirmed by their IR, ^{1}H NMR, and ^{13}C NMR spectra. The IR spectra of the thiazolidin-4-ones showed absorption bands due to the (NCS), (C=O) groups in the regions 1364–1328 and 1724–1711 cm^{-1}, respectively.

Further support was obtained from the ^{1}H NMR spectra, which showed no signs of the 4-phenyl-3-thiosemicarbazone (NH) protons. On the other hand, the ^{1}H NMR spectra exhibited resonances assigned to the SCH_2 group of the thiazolidine ring appearing as a singlet at 4.08–4.11 ppm due to the methylene protons. The CH=N protons in these structures were observed in the 8.45–8.84 ppm region. Similarly, in the ^{13}C NMR spectra, the chemical shift of the carbon of the carbonyl group of 4-thiazolidinone ring occurred between 172.30 and 172.52 ppm next to signals in the 48.32–50.01 ppm region attributed to methylene groups. The formation of thiazolidinones **9a**–**9j** occurred in two steps. The first step of this reaction is thought to be S-alkylation of thiosemicarbazide in its thiol form. The second step involved loss of ethanol to give the thiazolidin-4-ones as shown in Scheme 3.

Previous studies have shown that thiazolidinones with C-2- and N-3-substituted positions possess varying degrees of inhibition against many pathogens [17]. We are therefore considering a preliminary study of the antibacterial activity for thiosemicarbazone intermediates and thiazolidinone targets. The antibacterial activity in vitro of the synthesized thiosemicarbazone **7a**–**7j** and thiazolidinone **9a**–**9j** derivatives was evaluated against a Gram-positive bacterial strain, *Staphylococcus aureus* (ATCC-25923), and two Gram-negative bacterial strains, *Escherichia coli* (ATCC-25922) and *Pseudomonas aeruginosa* (ATCC-27853), using the conventional agar dilution method [41]. Minimum inhibitory concentrations (MIC) are defined as the concentration of a compound that inhibits the growth of the tested microorganisms.

Table 2 Preparation of thiazolidinone derivatives **9a**–**9j**

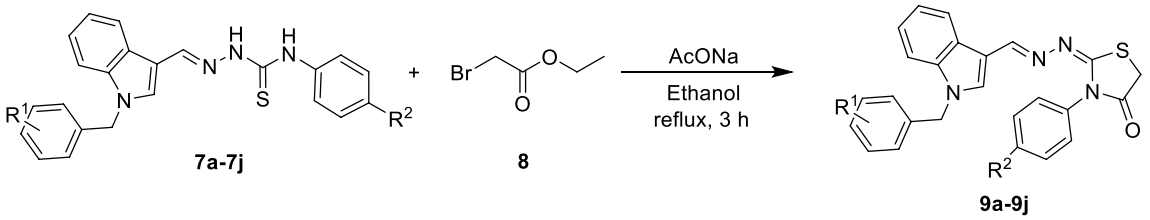
Product	R^1	R^2	Yield/%[a]
9a	H	H	94
9b	3-Cl	H	87
9c	4-F	H	91
9d	3-CF_3	H	86
9e	2-CN	H	82
9f	H	4-OCH_3	90
9g	3-Cl	4-OCH_3	91
9h	4-F	4-OCH_3	95
9i	3-CF_3	4-OCH_3	92
9j	2-CN	4-OCH_3	83

[a]All yields refer to chromatographically isolated pure products and are relative to the respective thiosemicarbazones **7a**–**7j**

The MIC varied from 0.25 to 128 μg/cm^3 according to the tested compound, compared with the standard ceftazidime (MIC = 0.5–4 μg/cm^3), imipenem (MIC = 0.5–1 μg/cm^3), and gentamicin (MIC = 0.06–2 μg/cm^3). It has been shown that each compound exhibited different action. According to Table 3, the product **7g** (R^1 = 3-Cl, R^2 = 4-OCH_3) and **9a** (R^1 = H, R^2 = H) presented the best antimicrobial activity for the three strains followed by **7h** (R^1 = 4-F, R^2 = 4-OCH_3) which exhibited a positive action against the Gram-negative bacteria (*E. coli* and *P. aeruginosa*). Among the other synthesized derivatives, for **7c** (R^1 = 4-F, R^2 = H), **7j** (R^1 = 2-CN, R^2 = 4-OCH_3), and **9i** (R^1 = 3-CF_3, R^2 = 4-OCH_3), the activity toward *P. aeruginosa* is to be underlined with an activity higher (at least four times) than that of the reference products.

In terms of structure–activity relationships, it can been seen that for the thiosemicarbazones active against *P. aeruginosa*, the most active derivatives (**7g**, **7h**, **7j**) are substituted in R^1 by an electron-withdrawing group (3-Cl, 4-F, 2-CN) and R^2 by an electron-donating group (4-OCH_3). Regarding the possible mechanism of thiosemicarbazones, we suggest membrane perturbing as well as intracellular mode of action

Scheme 2



Scheme 3

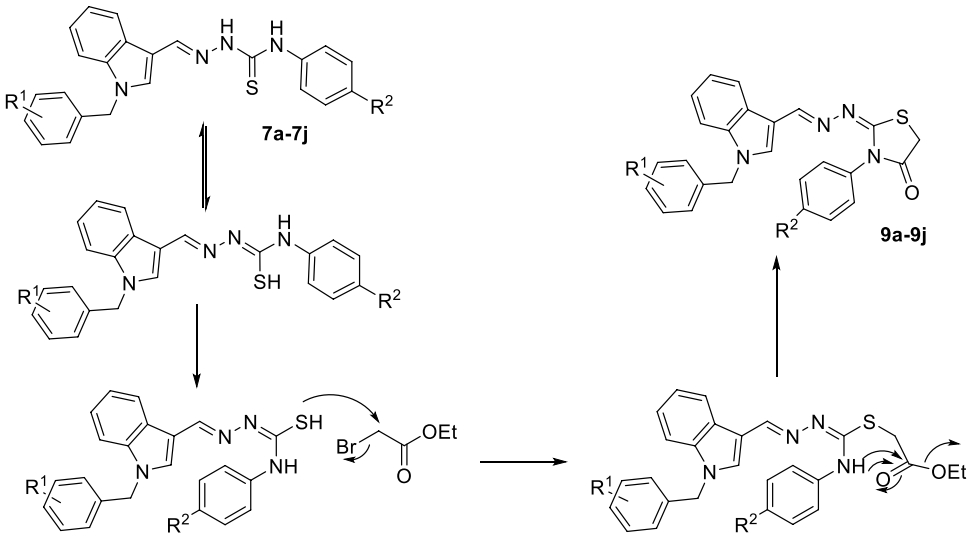


Table 3 Minimum inhibitory concentration (MIC/μg cm^{-3}) of the tested compounds against Gram-negative and Gram-positive microorganisms

Product	Gram−		Gram+
	Escherichia coli ATCC-25922	*Pseudomonas aeruginosa* ATCC-27853	*Staphylococcus aureus* ATCC29523
7a	0.25	1	> 128
7b	> 128	> 128	> 128
7c	> 128	0.25	> 128
7d	> 128	> 128	> 128
7e	> 128	> 128	> 128
7f	> 128	> 128	> 128
7g	0.25	0.25	0.25
7h	0.25	0.25	> 128
7i	64	64	> 128
7j	> 128	0.25	> 128
9a	0.25	0.25	0.25
9b	> 128	> 128	> 128
9c	32	> 128	> 128
9d	> 128	> 128	> 128
9e	> 128	> 128	0.25
9f	> 128	> 128	> 128
9g	0.25	> 128	0.25
9h	> 128	> 128	> 128
9i	> 128	0.25	> 128
9j	> 128	8	> 128
Ceftazidime	0.5	1	4
Imipenem	1	1	0.5
Gentamicine	0.25	2	0.06

of this class of compounds, as proposed recently [42]. For thiazolidinones, the substitution seems unfavorable, since the unsubstituted derivative **9a** ($R^1 = R^2 = H$) is the most active for the three strains.

Conclusion

In this study, a series of hybrid molecules indole-thiazolidinones easily was synthesized in very good yields (82–95%). The synthesized indole-thiazolidinones and their precursor thiosemicarbazones showed good activity in antibacterial assays. The products **7g** ($R^1 = 3$-Cl, $R^2 = 4$-OCH_3) and **9a** ($R^1 = H$, $R^2 = H$) showed the best antimicrobial activity for the three strains tested with an MIC value 0.25 μg/cm^3, followed by **7 h** ($R^1 = 4$-F, $R^2 = 4$-OCH_3) which exhibited a positive action against Gram-negative bacteria (*E. coli and P. aeruginosa*) with an MIC value 0.25 μg/cm^3. Among the other synthesized derivatives, for **7c** ($R^1 = 4$-F, $R^2 = H$), **7j** ($R^1 = 2$-CN, $R^2 = 4$-OCH_3), and **9i** ($R^1 = 3$-CF_3, $R^2 = 4$-OCH_3), the activity toward *P. aeruginosa* is to be underlined with an activity higher (at least four times) than that of the reference products. These results are comparable or more potent regarding their activity than the reference drugs. The first structure–activity relationship conclusions show that for thiosemicarbazones active against *P. aeruginosa*, the most active derivatives (**7g**, **7h**, **7j**) are substituted in R^1 by an electron-withdrawing group (3-Cl, 4-F, 2-CN) and R^2 by an electron-donating group (4-OCH_3). For thiazolidinones, the substitution seems unfavorable, since the unsubstituted derivative **9a** ($R^1 = R^2 = H$) is the most active. The pharmacomodulation of these series to confirm and

complete their structure–activity relationship is currently under investigation. In addition, the most active products **9a** and **7g** will be tested on resistant strains in the near future. The potential interactions of lead compounds will be studied by means of docking for example.

Experimental

Melting points were determined on a Büchi B-540 apparatus and are uncorrected. IR spectra were taken on Perkin-Elmer Spectrum two FT-IR spectrometer and the wave numbers reported in cm^{-1}. Elemental analyses were carried out at the Spectropole; Faculté des Sciences site Saint-Jérome. ^{1}H NMR spectra were recorded on a BRUKER AC 300P (300 MHz) spectrometer (Bruker, Bremen, Germany), ^{13}C NMR spectra on a BRUKER AC 300 P (75 MHz, Bruker) spectrometer in DMSO-d_6. The ^{1}H 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: 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).

General procedure for the preparation of compounds 6a–6e

1*H*-Indole-3-carbaldehyde (**4**, 1.45 g, 0.01 mol), the appropriate benzyl chloride **6a**–**6e** (0.011 mol), and 2.76 g anhydrous K_2CO_3 (0.02 mol) in 30 cm^3 N,*N*-dimethylformamide. The reaction mixture was refluxed for 2 h. Progress of the reaction was monitored by thin-layer chromatography. Upon cooling to room temperature, the mixture was poured into ice-cold water, and then, the precipitate was collected by filtration and dried. The crude product was purified by recrystallization from ethanol to give solids **6a**-**6e** in good yields.

1-Benzyl-1*H*-indole-3-carbaldehyde (6a, $C_{16}H_{13}NO$) Yield: 90%; white solid; m.p.: 107.9–108.2 °C; ^{1}H NMR (DMSO-d_6): $\delta = 9.98$ (s, 1H, CHO), 8.51 (s, 1H, indole H-2), 8.17–8.14 (m, 1H, Ar–H), 7.64–7.60 (m, 1H, Ar–H), 7.40–7.20 (m, 7H, Ar–H), 5.58 (s, 2H, CH_2) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 184.70$ (C=O), 141.00 (C), 137 (CH), 136.74 (C), 128.71 (2CH), 127.78 (CH), 127.23 (2CH), 124.78 (CH), 123.61 (CH), 122.5 (CH), 121.07 (C), 117.38 (C), 111.40 (CH), 49.78 (CH_2) ppm.

1-(3-Chlorobenzyl)-1*H*-indole-3-carbaldehyde (6b, $C_{16}H_{12}ClNO$) Yield: 93%; white solid; m.p.: 80.4–80.8 °C; ^{1}H NMR (DMSO-d_6): $\delta = 10$ (s, 1H, CHO), 8.54 (s, 1H, indole H-2), 8.19–8.12 (m, 1H, Ar–H), 7.68–7.61 (m, 1H, Ar–H), 7.45 (s, 1H, Ar–H), 7.44–7.35 (m, 2H, Ar–H), 7.33–7.25 (m, 3H, Ar–H), 5.58 (s, 2H, CH_2) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 184.79$ (C=O), 141.00 (C), 139.28 (CH), 136.44 (C), 133.30 (C), 130.66 (CH), 127.80 (CH), 127.23 (CH), 126.02 (CH), 124.75 (CH), 123.74 (CH), 122.66 (CH), 121.12 (C), 117.51 (C), 111.31 (CH), 49.06 (CH_2) ppm.

1-(4-Fluorobenzyl)-1*H*-indole-3-carbaldehyde (6c, $C_{16}H_{12}FNO$) Yield: 94%; white solid; m.p.: 117.1–117.7 °C; ^{1}H NMR (DMSO-d_6): $\delta = 10$ (s, 1H, CHO), 8.51 (s, 1H, indole H-2), 8.16–8.13 (m, 1H, Ar–H), 7.66–7.62 (m, 1H, Ar–H), 7.45–7.39 (m, 2H, Ar–H), 7.35–7.27 (m, 2H, Ar–H), 7.21 (t, 2H, $J = 8.85$ Hz, Ar–H), 5.56 (s, 2H, CH_2) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 184.70$ (C=O), 163.58 (d, $^1J_{CF} = 244.05$ Hz, C), 140.87 (CH), 136.83 (C), 133.0 (d, $^4J_{CF} = 3.22$ Hz, C), 129.65 (d, $^3J_{CF} = 8.27$ Hz, 2CH), 124.80 (CH), 123.64 (CH), 122.60 (CH), 121.08 (C), 117.43 (C), 115.71 (d, $^2J_{CF} = 21.60$ Hz, 2CH), 111.37 (CH), 49.0 (CH_2) ppm.

1-[3-(Trifluoromethyl)benzyl]-1*H*-indole-3-carbaldehyde (6d, $C_{17}H_{12}F_3NO$) Yield: 93%; white solid; m.p.: 134.8–135.6 °C; ^{1}H NMR (DMSO-d_6): $\delta = 10$ (s, 1H, CHO), 8.57 (s, 1H, indole H-2), 8.17–8.14 (m, 1H, Ar–H), 7.81 (s, 1H, Ar–H), 7.71–7.58 (m, 4H, Ar–H), 7.33–7.25 (m, 2H, Ar–H), 5.70 (s, 2H, CH_2) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 184.70$ (C=O), 138.41 (CH), 137.29 (C), 136.52 (C), 131.33 (q, $^2J_{CF} = 33$ Hz, C-CF_3), 130.3 (CH), 129.82 (CH), 125.51(C), 125.37 (q, $^4J_{CF} = 3.9$ Hz, CH), 124.50 (CH), 123.85 (q, $^3J_{CF} = 3.8$ Hz, CH), 123.34 (CH), 122.34 (CH), 122.0 (q, $^1J_{CF} = 272.35$ Hz, C-F), 118.82 (C), 111.20 (CH), 50.47 (CH_2) ppm.

1-(2-Cyanobenzyl)-1*H*-indole-3-carboxaldehyde (6e, $C_{17}H_{12}N_2O$) Yield: 95%; white solid; m.p.: 147.8–148.2 °C; ^{1}H NMR (DMSO-d_6): $\delta = 10$ (s, 1H, CHO), 8.45 (s, 1H, indole H-2), 8.20–8.17 (m, 1H, Ar–H), 7.97 (1H, dd, $J = 1.26$ Hz, 7.58 Hz, Ar–H), 7.67 (1H, td, $J = 1.42$ Hz, 7.74 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 (DMSO-d_6): $\delta = 185.00$ (C=O), 141.25 (C), 140.0 (C), 137.07 (CH), 133.84 (CH), 133.50 (CH), 128.71 (CH), 127.81 (CH), 124.67 (CH), 123.91 (CH), 122.79 (CH), 121.20 (C), 117.72 (C), 117.19 (C), 111.13 (C), 110.39 (CH), 48.19 (CH_2) ppm.

General procedure for the preparation of compounds 7a–7j

To a solution of N^4-substituted thiosemicarbazide **3a**, **3b** (6 mmol, 1 eq) in 33 cm^3 ethanol, 3-(4-substitutedphenyl)-1*H*-indole-3-carbaldehyde **6a**–**6e** (6.3 mmol, 1.05 eq) and 0.50 cm^3 acetic acid were added with stirring and the resulting reaction mixture was stirred at 90 °C for 3 h.

The reaction was monitored by thin-layer chromatography (TLC) for completion. The solid separated was then filtered and recrystallized from ethanol-DMF (3:1) to give compounds **7a**–**7j**.

(*E*)-1-[(1-Benzyl-1*H*-indol-3-yl)methylene]-4-phenylthiosemicarbazide (7a, $C_{23}H_{20}N_4S$) Yield: 94%; white solid; m.p.: 200–200.5 °C; IR (ATR): $\vec{\nu}$ = 3342 and 3124 (NH), 1538 (C=N), 1202 and 1272 (C=S) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 11.61 (s, 1H, NH), 9.63 (s, 1H, NH), 8.43 (s, 1H, indole H-2), 8.26 (dd, 1H, J = 6.60 Hz, 1.4 Hz, Ar–H), 8.10 (s, 1H, CH=N), 7.65 (d, 2H, J = 8.62 Hz, Ar–H), 7.53 (dd, 1H, J = 7.15 Hz, 1.1 Hz, Ar–H), 7.18–7.41 (m, 10H, Ar–H), 5.48 (s, 2H, $PhCH_2$) ppm; ^{13}C NMR (DMSO-d_6): δ = 175 (C=S), 141.14 (CH), 139.75 (C), 137.90 (C), 137.38 (C), 134.71 (CH), 129.12 (2CH), 128.61 (2CH), 128.07 (CH), 127.64 (2CH), 125.60 (2CH), 125.44 (CH), 125.23(C), 123.38 (CH), 122.63 (CH), 121.56 (CH), 111.20 (CH), 111.12 (C), 49.90 (CH_2) ppm.

(*E*)-1-[[1-(3-Chlorobenzyl)-1*H*-indol-3-yl]methylene]-4-phenylthiosemicarbazide (7b, $C_{23}H_{19}ClN_4S$) Yield: 87%; white solid; m.p.: 178.4–178.9 °C; IR (ATR): $\vec{\nu}$ = 3343 and 3143 (NH), 1541 (C=N), 1268 and 1204 (C=S) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 11.63 (s, 1H, NH), 9.64 (s, 1H, NH), 8.43 (s, 1H, indole H-2), 8.28 (dd, 1H, J = 6.7 Hz, 1.3 Hz, Ar–H), 8.12 (s, 1H, CH=N), 7.64 (dd, 2H, J = 8.25 Hz, 0.83 Hz, Ar–H), 7.55 (dd, 1H, J = 8.25 Hz, 1.28 Hz, Ar–H), 7.41–7.32 (m, 5H, Ar–H), 7.27–7.17 (m, 4H, Ar–H), 5.50 (s, 2H, $PhCH_2$) ppm; ^{13}C NMR (DMSO-d_6): δ = 175 (C=S), 141.09 (CH), 139.75 (C), 137.28 (C), 137.69 (C), 133.72 (CH), 131.1 (2CH), 128.61 (2CH), 128.07 (CH), 127.45 (CH), 126.32 (CH), 125.67 (2CH), 125.19 (C), 123.55 (CH), 122.76 (CH), 121.70 (CH), 111.36 (C), 111.11 (CH), 49.16 (CH_2) ppm.

(*E*)-1-[[1-(4-Fluororobenzyl)-1*H*-indol-3-yl]methylene]-4-phenylthiosemicarbazide (7c, $C_{23}H_{19}FN_4S$) Yield: 95%; white solid; m.p.: 193.5–193.9 °C; IR (ATR): $\vec{\nu}$ = 3292 and 3160 (NH), 1537 (C=N), 1268 and 1196 (C=S) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 11.61 (s, 1H, NH), 9.62 (s, 1H, NH), 8.42 (s, 1H, indole H-2), 8.28 (dd, 1H, J = 6.7 Hz, 1.3 Hz, Ar–H), 8.10 (s, 1H, CH=N), 7.64 (dd, 2H, J = 8.25 Hz, 0.83 Hz, Ar–H), 7.55 (dd, 1H, J = 8.25 Hz, 1.28 Hz, Ar–H), 7.41–7.32 (m, 5H, Ar–H), 7.27–7.17 (m, 4H, Ar–H), 5.46 (s, 2H, $PhCH_2$) ppm; ^{13}C NMR (DMSO-d_6): δ = 175.03 (C=S), 163.64 (d, $^1J_{CF}$ = 243.2 Hz, C), 141.12 (CH), 139.74 (C), 137.26 (C), 134.60 (CH), 134.13 (d, $^4J_{CF}$ = 3.30 Hz, C), 129.88 (d, $^3J_{CF}$ = 8.48 Hz, 2CH), 128.61 (3CH), 125.62 (2CH), 125.46 (CH), 125.23 (C), 123.43 (CH), 122.67 (CH), 121.62 (CH), 116.07 (d, $^2J_{CF}$ = 21.46 Hz, 2CH), 111.20 (CH), 49.12 (CH_2) ppm.

(*E*)-1-[[1-[3-(Trifluoromethyl)benzyl]-1*H*-indol-3-yl]methylene]-4-phenylthiosemicarbazide (7d, $C_{24}H_{19}F_3N_4S$) Yield: 86%; white solid; m.p.: 188.3–188.9 °C; IR (ATR): $\vec{\nu}$ = 3340 and 3141 (NH), 1538 (C=N), 1278 and 1195 (C=S) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 11.61 (s, 1H, NH), 9.63 (s, 1H, NH), 8.43 (s, 1H, Ar–H), 8.29 (dd, 1H, J = 6.8 Hz, 1.3 Hz, Ar–H), 8.15 (s, 1H, CH=N), 7.72–7.62 (m, 4H, Ar–H), 7.60–7.50 (m, 3H, Ar–H), 7.41–7.35 (m, 2H, Ar–H), 7.27–7.17 (m, 3H, Ar–H), 5.59 (s, 2H, $PhCH_2$) ppm; ^{13}C NMR (DMSO-d_6): δ = 175.6 (C=S), 156.30 (C), 140.85 (CH), 139.47 (C), 137.28 (C), 134.57 (CH), 132.70 (C), 131.7 (CH), 130.32 (CH), 129.54 (q, $^2J_{CF}$ = 32 Hz, C-CF_3), 127.77 (2CH), 125.17 (C), 124.90 (q, $^3J_{CF}$ = 4.0 Hz, CH), 124.26 (q, $^4J_{CF}$ = 3.8 Hz, CH), 123.55 (CH), 122.93 (CH), 122.75 (q, $^1J_{CF}$ = 272.35 Hz, C-F), 121.65 (CH), 113.77 (2CH), 111.5 (C), 111.0 (CH), 55.72 (OCH_3), 49.20 (CH_2) ppm.

(*E*)-1-[[1-(2-Cyanobenzyl)-1*H*-indol-3-yl]methylene]-4-phenylthiosemicarbazide (7e, $C_{24}H_{19}N_5S$) Yield: 90%; white solid; m.p.: 221.7–222.1 °C; IR (ATR): $\vec{\nu}$ = 3305 and 3147 (NH), 1536 (C=N), 1265 and 1198 (C=S) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 11.63 (s, 1H, NH), 9.65 (s, 1H, NH), 8.43 (s, 1H, Ar–H), 8.33–8.31 (m, 1H, Ar–H), 8.04 (s, 1H, CH=N), 7.92 (dd, 1H, J = 7.70 Hz, 1.10 Hz, Ar–H), 7.66–7.60 (m, 3H, Ar–H), 7.53–7.48 (m, 2H, Ar–H), 7.41–7.36 (m, 2H, Ar–H), 7.28–7.18 (m, 3H, Ar–H), 7.00 (d, 1H, J = 7.70 Hz, Ar–H), 5.72 (s, 2H, $PhCH_2$) ppm; ^{13}C NMR (DMSO-d_6): δ = 175 (C=S), 141.16 (C), 141 (CH), 139.75 (C), 137.52 (C), 134.87 (CH), 134.28 (CH), 133.89 (CH), 129.05 (CH), 128.61 (2CH), 128.14 (CH), 125.70 (2CH), 125.50 (CH), 125.14 (CH), 123.73 (CH), 122.88 (CH), 121.86 (CH), 117.75 (C), 111.68 (C), 111 (CH), 110.75 (C), 49.16 (CH_2) ppm.

(*E*)-1-[(1-Benzyl-1*H*-indol-3-yl)methylene]-4-(4-methoxyphenyl)thiosemicarbazide (7f, $C_{24}H_{22}N_4OS$) Yield: 95%; white solid; m.p.: 252.9–253.2 °C; IR (ATR): $\vec{\nu}$ = 3285 and 3160 (NH), 1538 (C=N), 1260 and 1191 (C=S) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 11.52 (s, 1H, NH), 9.50 (s, 1H, NH), 8.40 (s, 1H, indole H-2), 8.28 (dd, 1H, J = 7.00 Hz, 1.0 Hz, Ar–H), 8.10 (s, 1H, CH=N), 7.52 (d, 1H, J = 7.52 Hz, Ar–H), 7.46 (dt, 2H, J = 3.4 Hz, 2.1 Hz Ar–H), 7.36–7.31 (m, 2H, Ar–H), 7.29–7.24 (m, 3H, Ar–H), 7.23–7.19 (m, 1H, Ar–H), 7.15 (dd, 1H, J = 7.24 Hz, 1.1 Hz, Ar–H), 6.93 (dt, 2H, J = 3.48 Hz, 2.2 Hz Ar–H), 5.47 (s, 2H, $PhCH_2$), 3.77 (s, 3H, OCH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 175.52 (C=S), 157.3 (C), 141 (CH), 137.92 (C), 137.33 (C), 134.58 (CH), 132.67 (C), 129.12 (3CH), 128.07 (CH), 127.75 (CH), 127.64 (3CH), 125.19 (C), 123.36 (CH) 122.74 (CH), 121.50 (CH), 113.77 (2CH), 111.15 (C), 55.72 (OCH_3), 49.86 (CH_2) ppm.

(*E*)-1-[[1-(3-Chlorobenzyl)-1*H*-indol-3-yl]-methylene]-4-(4-methoxyphenyl)thiosemicarbazide (7g, $C_{24}H_{21}ClN_4OS$) Yield: 95%; white solid; m.p.: 237.7–238.5 °C; IR (ATR): $\vec{\nu}$ = 3310 and 3140 (NH), 1548 (C=N), 1273 and 1195 (C=S) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 11.53 (s, 1H, NH), 9.51 (s, 1H, NH), 8.41 (s, 1H, indole H-2), 8.29 (dd, 1H, J = 7.15 Hz, 0.73 Hz, Ar–H), 8.10 (s, 1H, CH=N), 7.53 (d, 1H, J = 7.70 Hz, Ar–H), 7.46 (dt, 2H, J = 3.4 Hz, 2.2 Hz, Ar–H), 7.27–7.18 (m, 2H, Ar–H), 7.15 (dd, 1H, J = 7.24 Hz, 1.0 Hz, Ar–H), 6.93 (dt, 2H, J = 3.4 Hz, 2.2 Hz, Ar–H), 5.5 (s, 2H, $PhCH_2$), 3.77 (s, 3H, OCH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 175.57 (C=S), 157.3 (C), 140.86 (CH), 140.38 (C), 137.25 (C), 134.55 (CH), 133.72 (C), 133.72 (C), 132.67 (C), 131.1 (CH), 128.07 (CH), 127.78 (2CH), 127.44 (CH), 126.33 (C), 125.17 (CH), 123.53 (CH), 122.85 (CH), 121.64 (CH), 113.8 (CH), 111.4 (C), 111.06 (CH), 55.72 (OCH_3), 49.16 (CH_2) ppm.

(*E*)-1-[[1-(4-Fluorobenzyl)-1*H*-indol-3-yl]-methylene]-4-(4-methoxyphenyl)thiosemicarbazide (7h, $C_{24}H_{21}FN_4OS$) Yield: 91%; white solid; m.p.: 239.6–240.4 °C; IR (ATR): $\vec{\nu}$ = 3313 and 3159 (NH), 1547 (C=N), 1274 and 1195 (C=S) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 11.53 (s, 1H, NH), 9.51 (s, 1H, NH), 8.41 (s, 1H, indole H-2), 8.29 (dd, 1H, J = 7.15 Hz, 0.83 Hz, Ar–H), 8.10 (s, 1H, CH = N), 7.53 (d, 1H, J = 7.70 Hz, Ar–H), 7.46 (dt, 2H, J = 3.4 Hz, 2.2 Hz, Ar–H), 7.39–7.32 (m, 3H, Ar–H), 7.27–7.15 (m, 3H, Ar–H), 6.93 (dt, 2H, J = 3.4 Hz, 2.2 Hz, Ar–H), 5.5 (s, 2H, $PhCH_2$), 3.77 (s, 3H, OCH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 175.6 (C=S), 163.64 (d, $^1J_{CF}$ = 243.75 Hz, C-F), 157.31 (C), 140.87 (C), 137.27 (C), 134.42 (CH), 134.14 (d, $^4J_{CF}$ = 2.75 Hz, C), 132.70 (C), 129.88 (d, $^3J_{CF}$ = 8.25 Hz, 2CH), 127.67 (2CH), 125.25 (CH), 123.40 (CH), 122.75 (CH), 121.54 (CH), 115.78 (d, $^2J_{CF}$ = 21.46 Hz, 2CH), 113.80 (2CH), 111.3 (C), 111.11 (CH), 55.74 (OCH_3), 49.12 (CH_2) ppm.

(*E*)-1-[[1-[3-(Trifluoromethyl)benzyl]-1*H*-indol-3-yl]-methylene]-4-(4-methoxyphenyl)thiosemicarbazide (7i, $C_{25}H_{21}F_3N_4OS$) Yield: 92%; white solid; m.p.: 232.3–232.8 °C; IR (ATR): $\vec{\nu}$ = 3316 and 3156 (NH), 1545 (C=N), 1273 and 1193 (C=S) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 11.54 (s, 1H, NH), 9.51 (s, 1H, NH), 8.41 (s, 1H, Ar–H), 8.31 (d, 1H, J = 7.34 Hz, Ar–H), 8.14 (s, 1H, CH=N), 7.70 (s, 1H, Ar–H), 7.65 (d, 1H, J = 7.70 Hz, Ar–H), 7.60–7.50 (m, 3H, Ar–H), 7.44 (d, 2H, J = 9.0 Hz, Ar–H), 7.27–7.15 (m, 2H, Ar–H), 6.94 (d, 2H, J = 9.0 Hz, Ar–H), 5.59 (s, 2H, CH_2), 3.77 (s, 3H, OCH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 175.6 (C=S), 156.30 (C), 140.85 (CH), 139.47 (C), 137.28 (C), 134.57 (CH), 132.70 (C), 131.7 (CH), 130.32 (CH), 129.54 (q, $^2J_{CF}$ = 32 Hz, C-CF_3), 127.77 (2CH), 125.17 (C), 124.90 (q, $^3J_{CF}$ = 4.0 Hz, CH), 124.26 (q, $^4J_{CF}$ = 3.8 Hz, CH), 123.55 (CH), 122.93 (CH), 122.75 (q, $^1J_{CF}$ = 272.35 Hz, C-F), 121.65 (CH), 113.77 (2CH), 111.5 (C), 111.0 (CH), 55.72 (OCH_3), 49.20 (CH_2) ppm.

(*E*)-1-[[1-(2-Cyanobenzyl)-1*H*-indol-3-yl]-methylene]-4-(4-methoxyphenyl)thiosemicarbazide (7j, $C_{25}H_{21}N_5OS$) Yield: 95%; white solid; m.p.: 271.9–272.3 °C; IR (ATR): $\vec{\nu}$ = 3312 and 3163 (NH), 1550 (C=N), 1274 and 1189 (C=S) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 11.54 (s, 1H, NH), 9.51 (s, 1H, NH), 8.41 (s, 1H, Ar–H), 8.31 (dd, 1H, J = 7.0 Hz, 1.4 Hz, Ar–H), 8.02 (s, 1H, CH=N), 7.93 (dd, 1H, J = 7.70 Hz, 1.10 Hz, Ar–H), 7.53–7.42 (m, 4H, Ar–H), 7.27–7.17 (m, 2H, Ar–H), 7.0–6.93 (m, 3H, Ar–H), 5.72 (s, 2H, $PhCH_2$), 3.77 (s, 3H, OCH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 175.65 (C=S), 157.32 (C), 141.21 (C), 140.77 (CH), 137.50 (C), 134.73 (CH), 134.28 (CH), 133.89 (CH), 132.68 (C), 129.04 (CH), 128.10 (CH), 127.80 (2CH), 125.11 (C), 123.7 (CH), 1230 (CH), 121.80 (CH), 117.76 (C), 113.78 (3CH), 111.73 (C), 110.72 (C), 55.72 (OCH_3), 49.16 (CH_2) ppm.

General procedure for the preparation of compounds 9a–9j

A mixture of compound **7a**–**7j** (3 mmol, 1 eq), 0.36 cm^3 ethyl 2-bromoacetate (1.1 eq) and 1 g anhydrous sodium acetate (6 mmol, 2 eq) in 30 cm^3 ethanol was stirred until reflux; the mixture was stirred under the same conditions until complete reaction (3–4 h). The reaction mixture was left to cool, and poured into ice-cold water, and the separated solid was filtered, washed with water, and recrystallized from a mixture of ethanol.

2-[2-[(1-Benzyl-1*H*-indol-3-yl)methylene]hydrazono]-3-phenylthiazolidin-4-one (9a, $C_{25}H_{20}N_4OS$) Yield: 94%; white solid; m.p.: 250.9–251.4 °C; IR (ATR): $\vec{\nu}$ = 1715 (C=O), 1573 and 1530 (C=N), 1337 (NCS) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 8.84 (s, 1H, CH=N), 8.26 (m, 1H, Ar–H), 7.95 (s, 1H, CH=C), 7.52–7.41 (m, 6H,Ar–H), 7.28–7.24 (m, 7H, Ar–H), 5.46 (s, 2H, $PhCH_2$), 4.10 (s, 2H, CH_2) ppm; ^{13}C NMR (DMSO-d_6): δ = 172.52 (C=O), 161.43(C), 153.72 (CH), 137.85 (C), 137.49 (C), 135.68 (C), 135.40 (CH), 129.55 (2CH), 129.12 (3CH), 128.74 (2CH), 128.07 (CH), 127.60 (2CH), 125.64 (C), 123.47 (CH), 122.76 (CH), 121.71 (CH), 112.00 (C), 111.36 (CH), 49.88 (CH_2), 32.68 (CH_2) ppm.

2-[2-[[1-(3-Chlorobenzyl)-1*H*-indol-3-yl]methylene]hydrazono]-3-phenylthiazolidin-4-one (9b, $C_{25}H_{19}ClN_4OS$) Yield: 87%; yellow solid; m.p.: 221.4–221.9 °C; IR (ATR): $\vec{\nu}$ = 1718 (C=O), 1573 and 1529 (C=N), 1339 (NCS) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 8.46 (s, 1H, CH=N), 8.30–8.27 (m, 1H, Ar–H), 7.98 (s, 1H, CH=C), 7.54 (t, 3H, J = 7.24 Hz, Ar–H), 7.48 (d, 1H,

$J = 7.00$ Hz, Ar–H), 7.41 (d, 2H, $J = 7.43$ Hz, Ar–H), 7.34 (t, 3H, $J = 4.68$ Hz, Ar–H), 7.25 (t, 2H, $J = 3.76$ Hz, Ar–H), 7.21–7.1 (m, 1H, Ar–H), 5.50 (s, 2H, $PhCH_2$), 4.11 (s, 2H, CH_2) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 172.52$ (C=O), 153.61 (CH), 140.4 (C), 137.57 (C), 135.81 (C), 135.13 (C), 135.34 (CH), 133.81 (C), 131.0 (CH), 129.55 (2CH), 129.03 (CH), 128.76 (2CH), 128.05 (CH), 127.43 (CH), 126.23 (CH), 125.81 (C), 123.56 (CH), 122.83 (CH), 121.78 (C), 112.38 (CH), 111.16 (C), 49.29 (CH_2), 32.66 (CH_2) ppm.

2-[2-[[1-(4-Fluorobenzyl)-1*H*-indol-3-yl]methylene]hydrazono]-3-phenylthiazolidin-4-one (9c, $C_{25}H_{19}FN_4OS$) Yield: 91%; white solid; m.p.: 263.8–264.2 °C; IR (ATR): $\vec{\nu} = 1711$ (C=O), 1562 and 1531 (C=N), 1337 (NCS) cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 8.45$ (s, 1H, CH=N), 8.30–8.25 (m, 1H, Ar–H), 7.95 (s, 1H, C=CH), 7.58–7.51 (m, 3H, Ar–H), 7.49–7.40 (m, 3H, Ar–H), 7.33–7.26 (m, 2H, Ar–H), 7.26–7.12 (m, 4H, Ar–H), 5.46 (s, 2H, N-CH_2), 4.10 (s, 2H, CH_2) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 172.50$ (C=O), 163.62 (d, $^1J_{CF} = 243.2$ Hz, C), 163.62 (C),153.68 (CH), 137.41 (CH), 135.71 (C), 135.24 (CH), 134.13 (d, $^4J_{CF} = 3.30$ Hz, C), 129.82 (d, $^3J_{CF} = 8.25$ Hz, 2CH), 129.53 (2CH), 129.03 (CH), 128.76 (2CH), 125.68 (C), 123.49 (CH), 122.80 (CH), 121.75 (CH), 116.07 (d, $^2J_{CF} = 21.46$ Hz, 2CH), 112.1 (CH), 111.3 (CH), 49.07 (CH_2), 32.70 (CH_2) ppm.

2-[2-[[1-[3-(Trifluoromethyl)benzyl]-1*H*-indol-3-yl]methylene]hydrazono]-3-phenylthiazolidin-4-one (9d, $C_{26}H_{19}F_3N_4OS$) Yield: 86%; green solid; m.p.: 208.7–209.6 °C; IR (ATR): $\vec{\nu} = 1718$ (C=O), 1561 and 1531 (C=N), 1364 (NCS) cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 8.47$ (s, 1H, CH=N), 8.32–8.29 (m, 1H, Ar–H), 8.00 (s, 1H, CH=C), 7.64 (d, 2H, $J = 10.82$ Hz, Ar–H), 7.57–7.52 (m, 4H,Ar–H), 7.74 (d, 2H, $J = 7.0$ Hz, Ar–H), 7.42 (d, 2H, $J = 7.24$ Hz, Ar–H), 7.29–7.14 (m, 2H, Ar–H), 5.60 (s, 2H, N-CH_2), 4.11 (s, 2H, CH_2) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 172.54$ (C=O), 162.62 (C), 153.7 (CH), 139.40 (C), 137.41 (C), 135.66 (C), 135.34 (CH), 131.64 (CH), 130.31 (CH), 129.66 (q, $^2J_{CF} = 31.7$ Hz, C-CF_3), 129.55 (2CH), 129.07 (CH), 128.74 (2CH), 125.62 (C), 125.0 (q, $^3J_{CF} = 3.7$ Hz, CH), 124.2 (q, $^4J_{CF} = 3.6$ Hz, CH), 123.66 (CH), 122.85 (CH), 122.70 (q, $^1J_{CF} = 272.35$ Hz, C-F), 121.88 (CH), 112.25 (CH), 111.23 (C), 49.17 (CH_2), 32.70 (CH_2) ppm.

2-[2-[[1-(2-Cyanobenzyl)-1*H*-indol-3-yl]methylene]hydrazono]-3-phenylthiazolidin-4-one (9e, $C_{26}H_{19}N_5OS$) Yield: 82%; white solid; m.p.: 264.9–265.6 °C; IR (ATR): $\vec{\nu} = 1718$ (C=O), 1572 and 1531 (C=N), 1346 (NCS) cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 8.46$ (s, 1H, CH=N), 8.35–8.29 (m, 1H, Ar–H), 8.00 (s, 1H, CH=C), 7.87 (d, 1H, $J = 1$ Hz, Ar–H),7.62 (td, 1H, $J = 7.8$ Hz, 1.4 Hz, Ar–H), 7.56–7.46 (m, 10H, Ar–H), 7.43 (d, 1H, $J = 1.47$ Hz, Ar–H), 7.41 (d, 1H, $J = 1$ Hz, Ar–H), 7.29–7.23 (m, 2H, Ar–H), 5.70 (s, 2H, N-CH_2), 4.11 (s, 2H, CH_2) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 172.30$ (C=O), 153.56 (CH), 141 (C), 137.73 (C), 135.80 (CH), 135.52 (CH), 135.27 (C), 134.13 (CH), 133.88 (CH), 129.42 (2CH), 129.05 (C), 128.91 (CH), 128.88 (2CH), 128.37 (CH), 128.08 (CH), 125.81 (C), 123.71 (CH), 122.90 (CH), 121.92 (C), 117.58 (C), 112.66 (C), 111.0 (CH), 48.40 (CH_2), 32.67 (CH_2) ppm.

2-[2-[(1-Benzyl-1*H*-indol-3-yl)methylene]-hydrazono]-3-(4-methoxyphenyl)thiazolidin-4-one (9f, $C_{26}H_{22}N_4O_2S$) Yield: 90%; white solid; m.p.: 271.6–272.0 °C; IR (ATR): $\vec{\nu} = 1716$ (C=O), 1561 and 1531 (C=N), 1343 (NCS) cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 8.46$ (s, 1H, CH=N), 8.30–8.26 (m, 1H, Ar–H), 7.91 (s, 1H, CH=C), 8.53–8.50 (m, 1H, Ar–H), 7.35–7.28 (m, 5H, Ar–H), 7.26–7.19 (m, 4H, Ar–H), 7.05 (dt, 2H, $J = 9.8$ Hz, 3.0 Hz, Ar–H), 5.46 (s, 2H, N-CH_2), 4.07 (s, 2H, CH_2), 3.8 (s, 3H, OCH_3) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 172.42$ (C=O), 169.54 (C), 162.30 (C), 153.50 (CH), 137.83 (C), 137.67 (C), 135.11 (CH), 129.77 (2CH), 129.07 (2CH), 128.39 (C), 128.02 (CH), 127.59 (2CH), 125.83 (C), 123.40 (CH), 122.78 (CH), 121.61 (CH), 114.80 (2CH), 112.20 (C), 111.22 (CH), 55.59 (CH_3), 50.01 (CH_2), 32.67 (CH_2) ppm.

2-[2-[[1-(3-Chlorobenzyl)-1*H*-indol-3-yl]methylene]-hydrazono]-3-(4-methoxyphenyl)thiazolidin4-one (9g, $C_{26}H_{21}ClN_4O_2S$) Yield: 91%; white solid; m.p.: 192.0–192.6 °C; IR (ATR): $\vec{\nu} = 1717$ (C=O), 1576 and 1531 (C=N), 1329 (NCS) cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 8.45$ (s, 1H, CH=N), 8.31–8.28 (m, 1H, Ar–H), 7.94 (s, 1H, CH=C), 7.54–7.51 (m, 1H, Ar–H), 7.38–7.27 (m, 5H, Ar–H), 7.27–7.17 (m, 3H, Ar–H), 7.06 (dd, 2H, $J = 9.8$ Hz, $J = 3.0$ Hz, Ar–H), 5.50 (s, 2H, N-CH_2), 4.08 (s, 2H, CH_2), 3.84 (s, 3H, OCH_3) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 172.52$ (C=O), 162.42 (C), 159.64 (C), 153.47 (CH), 140.41 (C), 137.58 (C), 135.07 (CH), 133.82 (C), 131.0 (CH), 129.77 (2CH), 128.38 (C), 128.05 (CH), 127.43 (CH), 126.23 (CH), 125.82 (C), 123.55 (CH), 122.84 (CH), 121.76 (CH), 114.80 (2CH), 112.42 (CH), 111.15 (C), 56.0 (CH_3), 49.3 (CH_2), 32.54 (CH_2) ppm.

2-[2-[[1-(4-Fluorobenzyl)-1*H*-indol-3-yl]methylene]-hydrazono]-3-(4-methoxyphenyl)thiazolidin4-one (9h, $C_{26}H_{21}FN_4O_2S$) Yield: 95%; white solid; m.p.: 242.4–242.9 °C; IR (ATR): $\vec{\nu} = 1716$ (C=O), 1573 and 1532 (C=N), 1352 (NCS) cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 8.44$ (s, 1H, CH=N), 8.28–8.25 (m, 1H, Ar–H), 7.96 (s, 1H, CH=C), 7.56–7.54 (m, 1H, Ar–H), 7.34–7.27 (m, 4H, Ar–H), 7.25–7.21 (m, 2H, Ar–H), 7.16 (d, 2H, $J = 8.9$ Hz, Ar–H), 7.06 (d, 2H, $J = 8.9$ Hz, Ar–H), 5.45 (s, 2H, N-CH_2), 4.07 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 172.66$ (C=O), 163.62 (d, $^1J_{CF} = 243.74$ Hz, C-F), 162.78

(C), 159.54 (C), 153.54 (CH), 137.38 (C), 135.23 (CH), 134.11 (d, $^{4}J_{CF}$ = 2.75 Hz, C), 129.84 (2CH), 129.72 (d, $^{3}J_{CF}$ = 8.25 Hz, 2CH), 128.19 (C), 125.67 (C), 123.50 (CH), 122.80 (CH), 121.75 (CH), 115.78 (d, $^{2}J_{CF}$ = 21.46 Hz, 2CH), 114.73 (2CH), 112.1 (C), 111.32 (CH), 55.85 (CH_3), 49.07 (CH_2), 32.60 (CH_2) ppm.

2-[2-[[1-[3-(Trifluoromethyl)benzyl]-1*H*-indol-3-yl]methylene]hydrazono]-3-(4-methoxyphenyl)thiazolidin-4-one (9i, $C_{27}H_{21}F_3N_4O_2S$) Yield: 92%; white solid; m.p.: 186.7–187.1 °C; IR (ATR): $\vec{\nu}$ = 1724 (C=O), 1563 and 1530 (C=N), 1328 (NCS) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 8.46 (s, 1H, CH=N), 8.32–8.28 (m, 1H, Ar–H), 7.93 (s, 2H, CH=C), 7.61 (t, 1H, J = 7.70 Hz, Ar–H), 7.49 (t, 2H, J = 6.70 Hz, Ar–H), 7.31 (d, 2H, J = 8.62 Hz, Ar–H), 7.27–7.24 (m, 2H, Ar–H), 7.06 (d, 2H, J = 8.62 Hz, Ar–H), 7.31 (d, 1H, J = 7.70 Hz, Ar–H), 5.72 (s, 2H, N-CH_2), 4.08 (s, 2H, CH_2), 3.84 (s, 3H, OCH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 172.42 (C=O), 162.47 (C), 159.64 (C), 153.47 (CH), 139.41 (C), 137.60 (C), 135.05 (CH), 131.60 (CH), 130.24 (CH), 129.96 (q, $^{2}J_{CF}$ = 31.36 Hz, C-CF_3), 129.77 (2CH), 128.37 (C), 125.82 (C), 124.83 (q, $^{3}J_{CF}$ = 3.7 Hz, CH), 124.15 (q, $^{3}J_{CF}$ = 3.7 Hz, CH), 123.58 (CH), 122.86 (CH), 122.72 (q, $^{1}J_{CF}$ = 272.35 Hz, C-F), 121.80 (CH), 114.8 (2CH), 112.50 (C), 111.10 (CH), 56.0 (CH_3), 49.34 (CH_2), 32.54 (CH_2) ppm.

2-[2-[[1-(2-Cyanobenzyl)-1*H*-indol-3-yl]methylene]-hydrazono]-3-(4-methoxyphenyl)thiazolidin-4-one (9j, $C_{27}H_{21}N_5O_2S$) Yield: 83%; white solid; m.p.: 191.4–192.1 °C; IR (ATR): $\vec{\nu}$ = 1720 (C=O), 1562 and 1530 (C=N), 1351 (NCS) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 8.46 (s, 1H, CH=N), 8.32–8.28 (m, 1H, Ar–H), 7.93 (s, 2H, CH=C), 7.61 (t, 1H, J = 7.70 Hz, Ar–H), 7.49 (t, 2H, J = 6.70 Hz, Ar–H), 7.31 (d, 2H, J = 8.62 Hz, Ar–H), 7.27–7.24 (m, 2H, Ar–H), 7.06 (d, 2H, J = 8.62 Hz, Ar–H), 7.31 (d, 1H, J = 7.70 Hz, Ar–H), 5.72 (s, 2H, N-CH_2), 4.08 (s, 2H, CH_2), 3.84 (s, 3H, OCH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 172.42 (C=O), 162.58 (C), 159.64 (C), 153.42 (CH), 140.00 (C), 137.73 (C), 135.21 (CH), 134.13 (CH), 133.82 (CH), 129.77 (2CH), 129.05 (CH), 128.37 (2CH), 125.81 (C), 123.71 (CH), 122.91 (CH), 121.91 (CH), 117.59 (C), 114.80 (2CH), 113.42 (C), 112.69 (C), 112.52 (C), 110.99 (CH), 55.95 (CH_3), 48.39 (CH_2), 32.55 (CH_2) ppm.

Minimum inhibitory concentration (MIC) evaluation

All compounds were screened in vitro for their antibacterial activities against three human pathogens' microorganisms: *Staphylococcus aureus* (ATCC-25923), *Escherichia coli* (ATCC-25922), and *Pseudomonas aeruginosa* (ATCC-27853). All strains were maintained on tryptic soy broth (TSB). Ceftazidime, imipenem (third-generation cephalosporin), and gentamicin (aminoglycosides) are used as standard antibacterial drugs. All the tested antibiotics were supplied from Oxoid.

The in vitro minimum inhibitory concentration (MIC) of the various compounds against bacterial strains was determined by the agar dilution method as recommended by NCCLS [41]. DMSO was used to prepare different concentrations ranging from 0.25 to 128 µg/cm^3 by serial dilutions. Petri dishes were spot-inoculated with 2 mm^3 of each bacterial suspension (1×10^4 CFU/spot) and incubated at 37 °C for 24 h. At the end of the incubation period, MIC was determined as the lowest concentration for the tested chemical that did not result in any visible growth on the plate. A control test was also conducted with DMSO media added to the same dilutions as used in the experiment, to ensure that the solvent had no influence on bacterial growth.

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