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ORIGINAL PAPER

Synthesis, characterization, and evaluation of antioxidant and antibacterial activities of novel indole-hydrazono thiazolidinones

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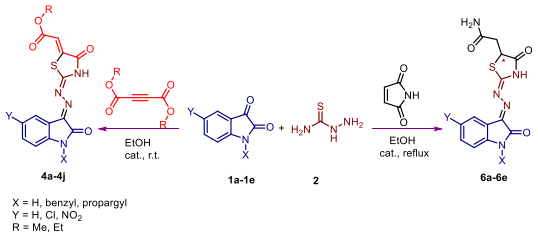
Abstract

Three-component reactions of oxindole derivatives, thiosemicarbazide with dialkyl acetylenedicarboxylate (or maleimide) led to novel indole-hydrazono thiazolidinones in high-to-excellent yields. The antioxidant activities of the synthesized compounds were studied by 1,1-diphenyl-2-picrylhydrazyl radical scavenging assay. Among the products, those with amide moiety exhibited better antioxidant activities than other ester derivatives of indole-hydrazono thiazolidinones. Minimum bactericidal concentration (MBC) was evaluated against Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) at different concentrations. However, the MBC values for compounds with amide group in their skeleton exhibited higher antibacterial activity than compounds with ester group. Therefore, it is assumed that these compounds could be used as effective antioxidant and antibacterial agents.

Graphical abstract



Keywords Three-component reactions · Dialkyl acetylenedicarboxylate · Maleimide · Indole-hydrazono thiazolidinones · Antioxidant activities · Antibacterial activities

Introduction

The heterocyclic compounds are widely used in pharmaceutical industries. Therefore, the synthesis of new heterocycles has always been an interesting subject for researchers [1–3]. N- and S-heterocycles are the main compounds of many important medicines. For example, 4-thiazolidinone nucleus with sulfur and nitrogen atoms in a five membered ring has been used in clinical drugs [4]. They are one of the most promising nucleus because of their multifarious biological and pharmaceutical properties including anti-inflammatory [5], analgesic [6], anti-proliferative [7], anticonvulsant [8], anti-diabetic [9], antihyperlipidemic [10], antitubercular [11],

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anticancer [12, 13], and anti-HIV [14]. In addition, thiazolidinone derivatives have given a huge blow to the fungal and bacterial resistance by many of the antibiotics and drugs [15–18]. On the other hand, oxindoles exhibit significant medicinal and biological activities such as antitumor [19], therapeutic [20], antimicrobial [21], antifungal [22], and antiviral [23, 24]. For example, isatin-β-thiosemicarbazone (**I**) [23], and *N*-methylisatin-β-thiosemicarbazone or methisazone (**II**) [24] are known as antiviral agent against poxviruses (Fig. 1). These results have initiated organic chemists and pharmacologists to synthesize novel thiazolidinone derivatives.

Many approaches for the synthesis of thiazolidinones were reported in the literature. Thiazolidinones were synthesized using cyclization reaction of thiourea derivatives with bromoacetic acid [25, 26]. Ocal et al. synthesized thiazolidinones from the reaction of a carbonyl compound, amine, and a mercaptoacid [27]. Nagarajan et al. reported cyclization reactions of acetylenedicarboxylic esters with *N*,*N*′-dialkylthiourea for synthesis of 4-thiazolidinones [28]. Ansari et al. have obtained 4-thiazolidinones from the reactions of chalcone with mercaptoacetic acid and ammonium carbonate [29]. Moghaddam et al. produced iminothiazolidinones from the reactions of aryl or alkyl isothiocyanate with α-chloroamides [30]. In addition, these compounds have been prepared by reacting various carbonyl compounds with thiosemicarbazide and subsequently with α-halocarbonyl compounds [31–36]. Based on the above facts and considering the significant biological properties of thiazolidinones and oxindole, synthesis of novel derivatives containing both heterocyclic moieties could be an interesting subject to be investigated. Herein, we report three-component reactions of oxindole derivatives **1a**–**1e**, thiosemicarbazide (**2**) with dialkyl acetylenedicarboxylate **3a**, **3b** that led to the novel indole-hydrazono thiazolidinone acetates **4a**–**4j** in high-to-excellent yields (Scheme 1). In addition, the reactions of oxindoles **1a**–**1e** and thiosemicarbazide with maleimide **5** performed which afforded the corresponding novel indole-hydrazono thiazolidin acetamides **6a**–**6e** in high yields (Scheme 1).

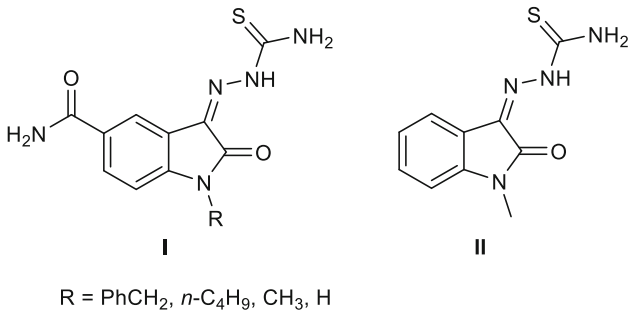


Fig. 1 Oxindole thiosemicarbazones with previously reported antiviral protease inhibitors

Results and discussion

Initially, the reaction of oxindole (**1a**), thiosemicarbazide (**2**), and dimethyl acetylenedicarboxylate (**3a**) was carried out in the presence of chloroacetic acid as a catalyst that leads to **4a** in high yield (87%), as shown in Table 1. To determine the scope and limitation of the reactions, we extended our work with the other oxindole derivatives **1b**–**1e**. The obtained results indicated that oxindole derivatives including electron-withdrawing substituents (Cl, NO_2) afforded the corresponding products in higher yields (for example, entries 3 and 5 compared to entry 1). Whereas, electron-donating substituents such as benzyl or propargyl group decreased the reaction yields (entries of 7 and 9 compared to 1). It seems that the electrophilicity of carbonyl group of oxindoles plays an important role in the reaction. When the reactions of oxindole **1a**–**1e** with thiosemicarbazide were performed in the presence of maleimide (**5**) instead of acetylenic diester, the yields of the reactions decreased (for example, entry 11 compared to entry 1). It can be due to less electrophilicity of maleimide related to acetylenic diesters.

The structures of newly synthesized compounds **4a**–**4j** were confirmed from IR, ^{1}H, ^{13}C NMR, and mass spectra. The IR spectrum of **4a** displayed two signals at 3438 and 3139 cm^{-1} for the two NH groups, two strong absorption bands at 1701 and 1640 cm^{-1} for the carbonyl groups, and a signal at 1613 cm^{-1} for the C=N group. The ^{1}H NMR spectrum of **4a** in DMSO-d_6 exhibited a singlet at 3.79 ppm for the OCH_3 group and another singlet at 6.72 ppm for the vinyl proton (=CH). The aromatic protons were observed as a triplet at 7.04 ppm ($^3J_{HH}$ = 7.6 Hz), a triplet of doublet at 7.39 ($^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.2 Hz), and two doublets at 6.86 and 7.56 ppm ($^3J_{HH}$ = 7.6 Hz). In addition, two broad signals appeared at 10.76 ppm and 13.40 ppm for the two NH groups. The proton-decoupled ^{13}C NMR spectrum of **4a** showed 14 signals with appropriate chemical shifts. The mass spectrum of **4a** exhibited the molecular ion peak ($M^{+\cdot}$) at *m/z* = 330 and the base peak at *m/z* = 118 due to loss of thiazolidinone ring, which are in agreement with the proposed structure. The ^{1}H and ^{13}C NMR spectra of **4b**–**4j** are similar to those of **4a**, except for the oxindole and ester moieties, which exhibited characteristic signals.

The structures of compounds **6a**–**6e** were also deduced from their IR, ^{1}H, ^{13}C NMR, and mass spectral data. The IR spectrum of **6a** showed absorption bands at about 3198 and 3422 cm^{-1} for the NH groups. The ^{1}H NMR spectrum of **6a** displayed an AB quartet of doublet at 2.74 ($^2J_{HH}$ = 16.0 Hz, $^3J_{HH}$ = 9.2 Hz, CH_2) and 2.97 ppm ($^2J_{HH}$ = 16.0 Hz, $^3J_{HH}$ = 4.0 Hz) for CH_2 group, a doublet of doublet at 4.40 ppm ($^3J_{HH}$ = 9.2 Hz, $^3J_{HH}$ = 4.0 Hz) for

Scheme 1

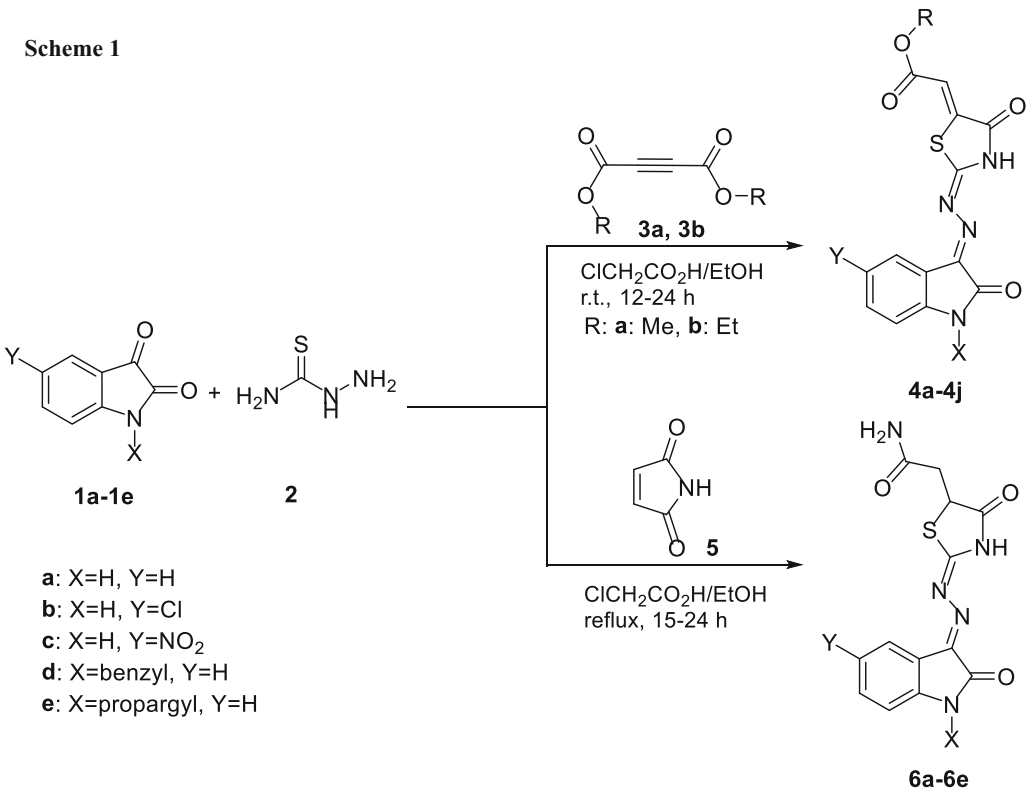


Table 1 Preparation of indole-hydrazono thiazolidinone derivatives

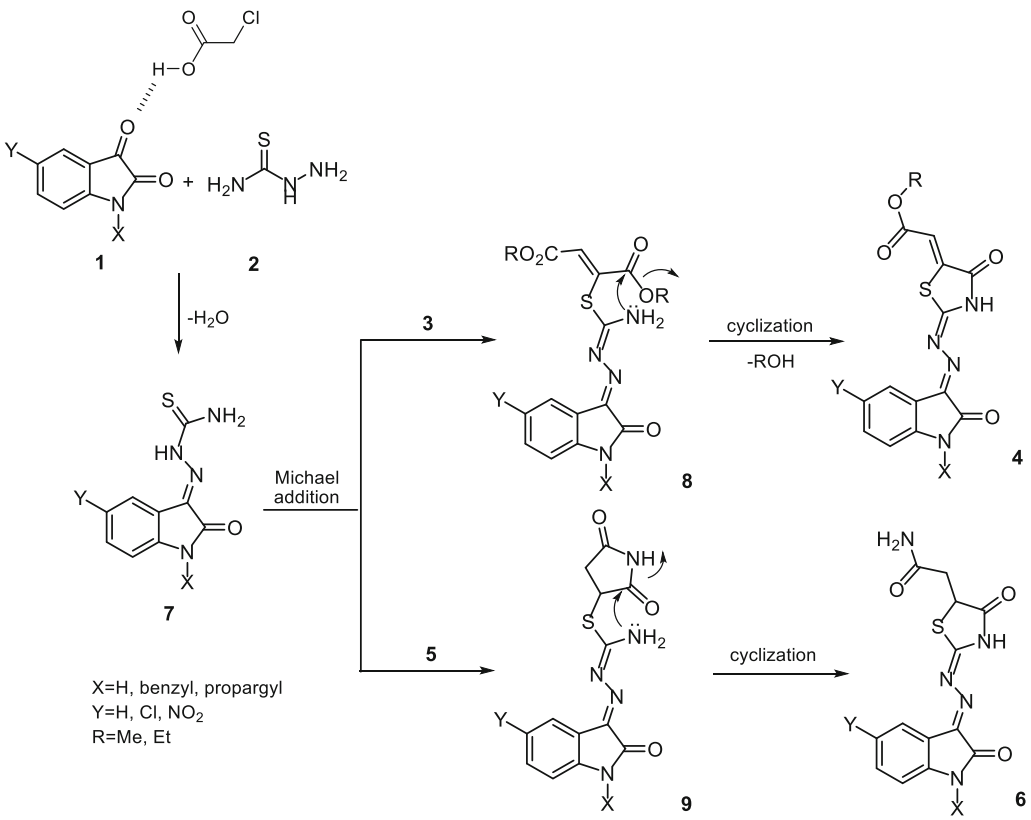
Entry	Oxindole	**3**	**5**	**4** and **6**	Time/h	M.p./°C	Yield/%
1	X = H, Y = H	R = Me	–	**4a**	13	264–266	87
2	X = H, Y = H	R = Et	–	**4b**	15	260–262	88
3	X = H, Y = Cl	R = Me	–	**4c**	12	331–333	92
4	X = H, Y = Cl	R = Et	–	**4d**	14	322–325	89
5	X = H, Y = NO_2	R = Me	–	**4e**	12	315–318	95
6	X = H, Y = NO_2	R = Et	–	**4f**	13	321–323	94
7	X = benzyl, Y = H	R = Me	–	**4g**	17	217–220	81
8	X = benzyl, Y = H	R = Et	–	**4h**	18	214–217	78
9	X = propargyl, Y = H	R = Me	–	**4i**	20	229–231	79
10	X = propargyl, Y = H	R = Et	–	**4j**	24	238–240	75
11	X = H, Y = H	–	Maleimide	**6a**	17	283–285	80
12	X = H, Y = Cl	–	Maleimide	**6b**	15	315–318	87
13	X = H, Y = NO_2	–	Maleimide	**6c**	15	310–312	90
14	X = benzyl, Y = H	–	Maleimide	**6d**	20	288–290	77
15	X = propargyl, Y = H	–	Maleimide	**6e**	24	282–284	71

Reaction conditions: oxindole derivatives (1 mmol), thiosemicarbazide (1 mmol), DMAD/DEAD (1 mmol) or maleimide (1 mmol), and 0.01 g chloroacetic acid as a catalyst

the methine proton, two broad singlets in the region 7.11 and 7.55 ppm for the amide protons (NH_2), and two broad signals at 10.71 ppm and 12.38 ppm for the two NH groups. In addition, the oxindole ring protons appeared in appropriate region (6.86–8.22 ppm). The proton-decoupled ^{13}C NMR spectrum of **6a** showed 13 signals in agreement with the suggested structure. The mass spectrum of **6a** exhibited the molecular ion peak at m/z = 317 (M^+).

The proposed mechanism based on the results for the synthesis of hydrazono thiazolidin-4-ones is shown in

Scheme 2



Scheme 2. Initially, reaction between oxindole **1** and thiosemicarbazide (**2**) led to thiosemicarbazone **7**. Then, the sulfur atom of compound **7** performs Michael addition on acetylenic diester **3** or maleimide (**5**) to afford intermediate **8** or **9**, respectively. Intermediate **8** undergoes a cyclization reaction and loss of ROH to produce compound **4**. Intermediate **9** carries out cyclization reaction and then ring opening maleimide ring to afford the desired compound **6**. Chloroacetic acid was used as an acidic catalyst for increasing of electrophilicity of carbonyl groups in this reaction.

Antioxidant activity

1,1-Diphenyl-2-picrylhydrazyl (DPPH) is a stable free radical of purple color that changes to light yellow color in the presence of antioxidants. The absorbance of DPPH radicals decreases in the presence of antioxidants which could be due to hydrogen transfer or electron donation from the antioxidants. The antioxidant activity of the synthesized indole-hydrazono thiazolidinones **4a**–**4j** and **6a**–**6e** was evaluated. As depicted in Fig. 2, these compounds exhibited good-to-high $DPPH^{\bullet}$ scavenging ability (61.8–85.9%). Interestingly, compound **6b** showed to possess more potent antioxidant activity (85.9%) comparing with other synthesized compounds and ascorbic acid as a standard antioxidant (82.3%) [37]. This might be attributed to presence of sulfur atom as an easily oxidisable element [38] in thiazolidine ring or hydrogen donors [39] such as NH_2 and NH groups in the structure of **6b**. To prove this hypothesis, compound **4j** was synthesized. This compound showed the lowest antioxidant activity which is due to replacement of NH_2 and NH groups with OEt and NR groups, respectively. This result confirm that NH_2 and NH groups are better radical scavengers than OEt and NR groups. It is assumed that the exchangeable hydrogens in the NH_2 and NH groups are responsible for the high antioxidant activity of compound **6b**.

Antibacterial activity

Minimum bactericidal concentration (MBC) of compounds **4a**, **4c**, **4g**, **6a**, **6b**, and **6d** was evaluated against Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) at different concentrations. As

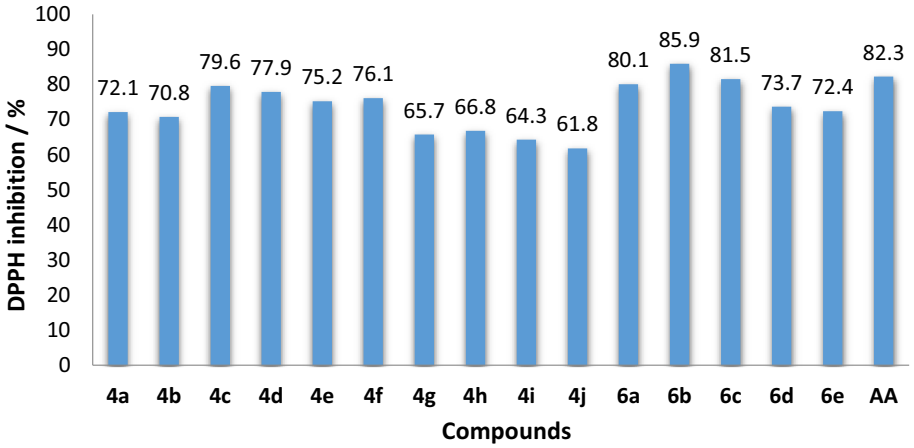


Fig. 2 Antioxidant activity of indole-hydrazono thiazolidinone (**4a**–**4j** and **6a**–**6e**; 1.0 mg/cm^{-3}). Each value represents mean ± SD (n = 3)

shown in Table 2, compounds **6a**, **6b**, and **6d** with amide moiety indicated higher antibacterial activity (0.1–0.15 mg cm^{-3}) than compounds **4a**, **4c**, and **4g** (0.5–2.0 mg cm^{-3}). When alkyl groups were substituted on nitrogen atom in indole ring, the antibacterial activities decreased (for example, **6d** compared to **6a** in Table 2). It seem that the exchangeable hydrogens in compounds **6a**, **6b**, and **6d** (NH_2 and NH groups) play important role in their antibacterial activity.

Conclusions

In summary, we have reported novel indole-hydrazono thiazolidinone acetates **4a**–**4j** and indole-hydrazono thiazolidin acetamides **6a**–**6e** of potential synthetic and pharmaceutical interest. We envisioned that from many synthetic methods for the construction of these skeletons, multicomponent reaction would be highly appealing because of the simplicity of procedure, the mild reaction conditions, and high yields. Antioxidant activity of the synthesized compounds was evaluated by 1,1-diphenyl-2-picrylhydrazyl radical scavenging assay. The results showed that compound **6b** possesses more potent antioxidant activity comparing with other synthesized compounds and ascorbic acid as a standard antioxidant. This might be attributed to the presence of sulfur atom as an easily oxidisable element in thiazolidine ring or hydrogen donors such as NH_2 and NH groups in the structure of **6b**. The antibacterial activities of compounds **4a**, **4c**, **4g**, **6a**, **6b**, and **6d** were investigated. In general, compounds **6a**, **6b**, and **6d** showed better antibacterial activities than compounds **4a**, **4c**, and **4g** against both Gram-positive and Gram-negative bacteria. Therefore, it is assumed that these compounds with amide group in their structure could be used as effective antioxidant and antibacterial agents.

Experimental

All of the reagents and solvents were purchased from Merck Company (Germany) and Sigma-Aldrich (Germany) in high purity and were used without further purification. Melting points of products were measured with Electrothermal 9100 apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker DRX-400 AVANCE instrument (400.1 MHz for ^{1}H, 100.6 MHz for ^{13}C). NMR spectra were obtained in DMSO-d_6 solution and reported as parts per million (ppm) downfield from tetramethylsilane as internal standard. IR spectra were recorded on an FT-IR Bruker vector 22 spectrometer. EI-MS (70 eV) was performed by Finnigan-MAT-8430 mass spectrometer. Elemental analyses were performed using a Costech ECS 4010 CHNS/O Elemental Analyzer.

Table 2 Minimum bactericidal concentration (MBC) of the compounds

Test strain	Minimum bactericidal concentration (MBC) of the compounds/mg cm^{-3}						
	4a	**4c**	**4g**	**6a**	**6b**	**6d**	Tetracycline
E. coli	0.75	0.5	2.0	0.15	0.1	0.2	0.02
P. aeruginosa	0.75	0.75	1.5	0.15	0.15	0.2	0.05
S. aureus	1.0	0.5	2.0	0.15	0.1	0.15	0.05
B. subtilis	1.0	0.5	2.0	0.1	0.15	0.15	0.02

General procedure for the synthesis of compounds 4a–4j

A mixture of oxindole derivatives **1a**–**1e** (1.0 mmol), thiosemicarbazide (**2**, 1.0 mmol), and dialkyl acetylenedicarboxylate **3a**, **3b** (1.0 mmol) in the presence of 0.01 g chloroacetic acid as a catalyst in 5 cm^3 of absolute EtOH was magnetically stirred at room temperature for 12–24 h. After the completion of the reaction (followed by TLC), the solvent was removed and the residue recrystallized in EtOH and the product **4a**–**4j** was obtained as an orange powder.

Methyl (2*E*)-[(2*Z*)-4-oxo-2-[(2*Z*)-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazono]-1,3-thiazolidin-5-ylidene]acetate (4a, $C_{14}H_{10}N_4O_4S$) Yield: 0.29 g (87%); m.p.: 264–266 °C; R_f = 0.52 (*n*-hexane/ethyl acetate 3:2); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ = 3.79 (s, 3H, OMe), 6.72 (s, 1H, C=CH), 6.86 (d, 1H, $^3J_{HH}$ = 7.6 Hz, $CH_{Oxindole}$), 7.04 (t, 1H, $^3J_{HH}$ = 7.6 Hz, $CH_{Oxindole}$), 7.39 (td, 1H, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.2 Hz, $CH_{Oxindole}$), 7.56 (d, 1H, $^3J_{HH}$ = 7.6 Hz, $CH_{Oxindole}$), 10.76 (s, 1H, NH), 13.40 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 53.0 (OMe), 110.9 ($CH_{Oxindole}$), 111.0 ($CH_{Oxindole}$), 115.8 (CH_{Vinyl}), 120.8 (C_q), 122.3 ($CH_{Oxindole}$), 122.6 ($CH_{Oxindole}$), 133.6 (C_q), 142.5 (C_q), 144.1 ($C{=}N_{Oxindole}$), 144.3 ($C{=}O_{Oxindole}$), 147.7 ($C{=}N_{Thiazole}$), 159.1 (C=O), 166.3 ($C{=}O_{Thiazole}$) ppm; IR (KBr): $\bar{\nu}$ = 3438 and 3139 (NH), 3069 (C_{sp2}-H), 2890 (C_{sp3}-H), 1701, 1685 and 1640 (C=O), 1613 (C=N), 1551 and 1465 (C=C) cm^{-1}; MS (70 eV): *m*/*z* = 330 (95, $M^{+\cdot}$), 302 (69), 270 (10), 243 (78), 145 (29), 131 (76), 118 (100), 103 (60), 85 (47), 59 (22).

Ethyl (2*E*)-[(2*Z*)-4-oxo-2-[(2*Z*)-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazono]-1,3-thiazolidin-5-ylidene]acetate (4b, $C_{15}H_{12}N_4O_4S$) Yield: 0.30 g (88%); m.p.: 260–262 °C; R_f = 0.52 (*n*-hexane/ethyl acetate 3:2); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ = 1.27 (t, 3H, $^3J_{HH}$ = 6.8 Hz, CH_3), 4.25 (q, 2H, $^3J_{HH}$ = 6.8 Hz, OCH_2), 6.69 (s, 1H, C=CH), 6.86 (d, 1H, $^3J_{HH}$ = 8.0 Hz, $CH_{Oxindole}$), 7.04 (t, 1H, $^3J_{HH}$ = 7.6 Hz, $CH_{Oxindole}$), 7.39 (td, 1H, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.2 Hz, $CH_{Oxindole}$), 7.55 (d, 1H, $^3J_{HH}$ = 7.6 Hz, $CH_{Oxindole}$), 10.76 (s, 1H, NH), 13.37 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.5 (CH_3), 61.9 (OCH_2), 111.0 ($CH_{Oxindole}$), 116.1 (CH_{Vinyl}), 120.8 (C_q), 120.9 ($CH_{Oxindole}$), 122.2 ($CH_{Oxindole}$), 122.6 ($CH_{Oxindole}$), 133.6 (C_q), 142.9 (C_q), 144.1 ($C{=}N_{Oxindole}$), 144.2 ($C{=}O_{Oxindole}$), 147.7 ($C{=}N_{Thiazole}$), 159.1 (C=O), 166.3 ($C{=}O_{Thiazole}$) ppm; IR (KBr): $\bar{\nu}$ = 3460 and 3203 (NH), 3071 (C_{sp2}-H), 2986 (C_{sp3}-H), 1723, 1688 and 1642 (C=O), 1613 (C=N), 1550 and 1466 (C=C) cm^{-1}; MS (70 eV): *m*/*z* = 344 (82, $M^{+\cdot}$), 316 (55), 329 (2), 299 (9), 270 (5), 243 (90), 158 (20), 145 (27), 131 (87), 118 (100), 103 (65), 85 (45).

Methyl (2*E*)-[(2*Z*)-2-[(2*Z*)-(5-chloro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazono]-4-oxo-1,3-thiazolidin-5-ylidene]-acetate (4c, $C_{14}H_9ClN_4O_4S$) Yield: 0.33 g (92%); m.p.: 331–333 °C; R_f = 0.4 (*n*-hexane/ethyl acetate 3:2); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ = 3.80 (s, 3H, OMe), 6.73 (s, 1H, C = CH), 6.87 (d, 1H, $^3J_{HH}$ = 8.4 Hz, $CH_{Oxindole}$), 7.42 (dd, 1H, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 2.0 Hz, $CH_{Oxindole}$), 7.47 (d, 1H, $^4J_{HH}$ = 2.0 Hz, $CH_{Oxindole}$), 10.88 (s, 1H, NH), 13.50 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 63.0 (OMe), 112.6 ($CH_{Oxindole}$), 116.1 (CH_{Vinyl}), 121.5 (C_q), 122.5 ($CH_{Oxindole}$), 126.6 (C–Cl), 132.8 ($CH_{Oxindole}$), 142.3 (C_q), 142.9 (C_q), 146.7 ($C{=}N_{Oxindole}$), 158.8 ($C{=}O_{Oxindole}$), 166.2 ($C{=}N_{Thiazole}$), 166.5 (C=O), 168.2 ($C{=}O_{Thiazole}$) ppm; IR (KBr): $\bar{\nu}$ = 3450 and 3217 (NH), 3065 (C_{sp2}-H), 2905 (C_{sp3}-H), 1724, 1684 and 1643 (C=O), 1614 (C=N), 1544 and 1444 (C=C) cm^{-1}; MS (70 eV): *m*/*z* = 366 (33, $M^{+\cdot}$+2), 364 (100, $M^{+\cdot}$), 338 (92), 336 (31), 304 (9), 279 (25), 277 (76), 167 (21), 165 (64), 152 (93), 124 (42), 85 (44), 59 (13).

Ethyl (2*E*)-[(2*Z*)-2-[(2*Z*)-(5-chloro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazono]-4-oxo-1,3-thiazolidin-5-ylidene]-acetate (4d, $C_{15}H_{11}ClN_4O_4S$) Yield: 0.34 g (89%); m.p.: 322–325 °C; R_f = 0.42 (*n*-hexane/ethyl acetate 3:2); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ = 1.28 (t, 3H, $^3J_{HH}$ = 6.8 Hz, CH_3), 3.80 (q, 3H, $^3J_{HH}$ = 6.8 Hz, OCH_2), 6.68 (s, 1H, C=CH), 6.85 (d, 1H, $^3J_{HH}$ = 8.4 Hz, $CH_{Oxindole}$), 7.40 (dd, 1H, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 2.4 Hz, $CH_{Oxindole}$), 7.45 (d, 1H, $^4J_{HH}$ = 2.4 Hz, $CH_{Oxindole}$), 10.86 (s, 1H, NH), 13.44 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.5 (CH_3), 62.0 (OCH_2), 112.6 ($CH_{Oxindole}$), 116.3 (CH_{Vinyl}), 121.4 (C_q), 122.5 ($CH_{Oxindole}$), 126.6 (C–Cl), 132.8 ($CH_{Oxindole}$), 142.3 (C_q), 142.9 (C_q), 146.6 ($C{=}N_{Oxindole}$), 158.7 ($C{=}O_{Oxindole}$), 165.8 ($C{=}N_{Thiazole}$), 166.6 (C=O), 168.5 ($C{=}O_{Thiazole}$) ppm; IR (KBr): $\bar{\nu}$ = 3446 and 3193 (NH), 3042 (C_{sp2}-H), 2918 (C_{sp3}-H), 1729, 1696 and 1643 (C=O), 1615 (C=N), 1537 and 1463 (C=C) cm^{-1}; MS (70 eV): *m*/*z* = 380 (32, $M^{+\cdot}$+2), 378 (96, $M^{+\cdot}$), 352 (33), 350 (100), 324 (7), 322 (22), 279 (16), 277 (47), 165 (56), 152 (62), 85 (40).

Methyl (2*E*)-[(2*Z*)-2-[(2*Z*)-(5-nitro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazono]-4-oxo-1,3-thiazolidin-5-ylidene]-acetate (4e, $C_{14}H_9N_5O_6S$) Yield: 0.36 g (95%); m.p.: 315–318 °C; R_f = 0.34 (*n*-hexane/ethyl acetate 3:2); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ = 3.81 (s, 3H, OMe), 6.76 (s, 1H, C=CH), 6.89 (d, 1H, $^3J_{HH}$ = 8.4 Hz, $CH_{Oxindole}$), 7.43 (dd, 1H, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 2.4 Hz, $CH_{Oxindole}$), 8.25 (d, 1H, $^4J_{HH}$ = 2.4 Hz, $CH_{Oxindole}$), 10.44 (s, 1H, NH), 13.45 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 53.2 (OMe), 112.6 ($CH_{Oxindole}$), 116.5 (CH_{Vinyl}), 118.5

($CH_{Oxindole}$), 126.4 ($CH_{Oxindole}$), 128.6 (C_q), 133.2 (C-NO_2), 142.2 (C_q), 143.8 (C_q), 149.3 (C=$N_{Oxindole}$), 164.7 (C=$O_{Oxindole}$), 166.1 (C=$N_{Thiazole}$), 166.2 (C=O), 168.9 (C=$O_{Thiazole}$) ppm; IR (KBr): $\bar{\nu}$ = 3450 and 3305 (NH), 3016 (C_{sp2}-H), 2944 (C_{sp3}-H), 1728, 1674 and 1656 (C=O), 1615 (C=N), 1544 and 1448 (C=C) cm^{-1}; MS (70 eV): *m/z* = 375 (10, $M^{+\cdot}$), 347 (7), 275 (27), 261 (52), 233 (23), 206 (33), 187 (30), 116 (25), 88 (22), 64 (100).

Ethyl (2*E*)-[(2*Z*)-2-[(2*Z*)-(5-nitro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazono]-4-oxo-1,3-thiazolidin-5-ylidene]-acetate (4f, $C_{15}H_{11}N_5O_6S$) Yield: 0.35 g (94%); m.p.: 321–323 °C; R_f = 0.34 (*n*-hexane/ethyl acetate 3:2); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ = 1.26 (t, 3H, $^3J_{HH}$ = 7.2 Hz, CH_3), 4.24 (q, 3H, $^3J_{HH}$ = 7.2 Hz, OCH_2), 6.64 (s, 1H, C=CH), 6.86 (d, 1H, $^3J_{HH}$ = 8.4 Hz, $CH_{Oxindole}$), 7.40 (dd, 1H, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 2.4 Hz, $CH_{Oxindole}$), 8.20 (d, 1H, $^4J_{HH}$ = 2.4 Hz, $CH_{Oxindole}$), 10.92 (s, 1H, NH), 13.40 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.5 (CH_3), 62.0 (OCH_2), 112.5 ($CH_{Oxindole}$), 116.6 (CH_{Vinyl}), 118.4 ($CH_{Oxindole}$), 126.4 ($CH_{Oxindole}$), 128.6 (C_q), 133.1 (C–NO_2), 142.0 (C_q), 143.8 (C_q), 149.2 (C=$N_{Oxindole}$), 164.7 (C=$O_{Oxindole}$), 165.6 (C=$N_{Thiazole}$), 166.0 (C=O), 169.0 (C=$O_{Thiazole}$) ppm; IR (KBr): $\bar{\nu}$ = 3455 and 3265 (NH), 3041 (C_{sp2}-H), 2998 (C_{sp3}-H), 1721, 1674 and 1658 (C=O), 1617 (C=N), 1548 and 1452 (C=C) cm^{-1}; MS (70 eV): *m/z* = 389 (93, $M^{+\cdot}$), 361 (28), 316 (7), 288 (65), 248 (100), 237 (84), 206 (35), 190 (67), 144 (77), 115 (37).

Methyl (2*E*)-[(2*Z*)-2-[(2*Z*)-(1-benzyl-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazono]-4-oxo-1,3-thiazolidin-5-ylidene]-acetate (4g, $C_{21}H_{16}N_4O_4S$) Yield: 0.34 g (81%); m.p.: 217–220 °C; R_f = 0.6 (*n*-hexane/ethyl acetate 3:2); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ = 3.80 (s, 3H, OMe), 4.92 (s, 2H, CH_2), 6.75 (s, 1H, C=CH), 6.95 (d, 1H, $^3J_{HH}$ = 7.6 Hz, $CH_{Oxindole}$), 7.09 (t, 1H, $^3J_{HH}$ = 7.2 Hz, $CH_{Oxindole}$), 7.24–7.29 (m, 1H, CH_{Ar}), 7.30–7.36 (m, 4H, CH_{Ar}), 7.39 (td, 1H, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.2 Hz, $CH_{Oxindole}$), 7.61 (d, 1H, $^3J_{HH}$ = 7.2 Hz, $CH_{Oxindole}$), 13.50 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 43.0 (CH_2), 53.0 (OMe), 110.3 ($CH_{Oxindole}$), 116.0 (CH_{Vinyl}), 120.2 (C_q), 122.0 ($CH_{Oxindole}$), 123.3 ($CH_{Oxindole}$), 127.7 (CH_{Ar}), 128.0 (CH_{Ar}), 129.2 (CH_{Ar}), 133.4 ($CH_{Oxindole}$), 136.5 (C_q), 142.4 (C_q), 144.3 (C_q), 144.3 (C=$N_{Oxindole}$), 157.5 (C=$O_{Oxindole}$), 166.3 (C=$N_{Thiazole}$), 166.5 (C=O), 167.6 (C=$O_{Thiazole}$) ppm; IR (KBr): $\bar{\nu}$ = 3436 (NH), 3063 (C_{sp2}-H), 2946 (C_{sp3}-H), 1725, 1696 and 1645 (C=O), 1608 (C=N), 1531 and 1465 (C=C) cm^{-1}; MS (70 eV): *m/z* = 420 (100, $M^{+\cdot}$), 392 (31), 360 (5), 329 (67), 301 (11), 235 (22), 207 (98), 193 (45), 144 (31), 91 (98).

Ethyl (2*E*)-[(2*Z*)-2-[(2*Z*)-(1-benzyl-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazono]-4-oxo-1,3-thiazolidin-5-ylidene]-acetate (4h, $C_{22}H_{18}N_4O_4S$) Yield: 0.34 g (78%); m.p.: 214–217 °C; R_f = 0.6 (*n*-hexane/ethyl acetate 3:2); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ = 1.28 (t, 3H, $^3J_{HH}$ = 7.2 Hz, CH_3), 4.26 (q, 3H, $^3J_{HH}$ = 7.2 Hz, OCH_2), 4.92 (s, 2H, CH_2), 6.72 (s, 1H, C=CH), 6.95 (d, 1H, $^3J_{HH}$ = 8.0 Hz, $CH_{Oxindole}$), 7.09 (t, 1H, $^3J_{HH}$ = 7.6 Hz, $CH_{Oxindole}$), 7.25–7.29 (m, 1H, CH_{Ar}), 7.30–7.36 (m, 4H, CH_{Ar}), 7.39 (td, 1H, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 0.8 Hz, $CH_{Oxindole}$), 7.61 (d, 1H, $^3J_{HH}$ = 7.6 Hz, $CH_{Oxindole}$), 13.48 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.5 (CH_3), 43.0 (CH_2), 62.0 (OCH_2), 110.3 ($CH_{Oxindole}$), 116.2 (CH_{Vinyl}), 120.3 (C_q), 122.0 ($CH_{Oxindole}$), 123.3 ($CH_{Oxindole}$), 127.7 (CH_{Ar}), 128.0 (CH_{Ar}), 129.2 (CH_{Ar}), 133.4 ($CH_{Oxindole}$), 136.5 (C_q), 142.3 (C_q), 144.3 (C_q), 146.6 (C=$N_{Oxindole}$), 157.5 (C=$O_{Oxindole}$), 165.8 (C=$N_{Thiazole}$), 166.5 (C=O), 167.7 (C=$O_{Thiazole}$) ppm; IR (KBr): $\bar{\nu}$ = 3436 (NH), 3062 (C_{sp2}-H), 2933 (C_{sp3}-H), 1708, 1684 and 1641 (C=O), 1612 (C=N), 1553 and 1468 (C=C) cm^{-1}; MS (70 eV): *m/z* = 434 (98, $M^{+\cdot}$), 406 (42), 389 (13), 360 (4), 343 (55), 235 (18), 207 (100), 193 (45), 144 (20), 91 (98).

Methyl (2*E*)-[(2*Z*)-2-[(2*Z*)-(2-oxo-1-prop-2-yn-1-yl-1,2-dihydro-3*H*-indol-3-ylidene)hydrazono]-4-oxo-1,3-thiazolidin-5-ylidene]acetate (4i, $C_{17}H_{12}N_4O_4S$) Yield: 0.29 g (79%); m.p.: 229–231 °C; R_f = 0.5 (*n*-hexane/ethyl acetate 3:2); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ = 3.29 (t, 1H, $^4J_{HH}$ = 2.4 Hz, ≡CH), 3.79 (s, 3H, OMe), 4.54 (d, 2H, $^4J_{HH}$ = 2.4 Hz, N-CH_2), 6.72 (s, 1H, C=CH), 7.14 (m, 2H, $CH_{Oxindole}$), 7.50 (t, 1H, $^3J_{HH}$ = 7.2 Hz, $CH_{Oxindole}$), 7.24–7.29 (m, 1H, CH_{Ar}), 7.30–7.36 (m, 4H, CH_{Ar}), 7.39 (t, 1H, $^3J_{HH}$ = 7.2 Hz, $CH_{Oxindole}$), 7.61 (d, 1H, $^3J_{HH}$ = 7.2 Hz, $CH_{Oxindole}$), 13.46 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 29.1 (N–CH_2), 53.0 (OMe), 75.0 (≡CH), 78.2 (C_q), 110.4 ($CH_{Oxindole}$), 116.0 (CH_{Vinyl}), 120.2 (C_q), 122.0 ($CH_{Oxindole}$), 123.6 ($CH_{Oxindole}$), 133.4 ($CH_{Oxindole}$), 142.4 (C_q), 143.3 (C_q), 146.1 (C_q), 156.5 (C=$N_{Oxindole}$), 166.3 (C=$O_{Oxindole}$), 166.5 (C=O), 168.2 (C=$O_{Thiazole}$) ppm; IR (KBr): $\bar{\nu}$ = 3439 (NH), 3176 (C_{sp}-H), 3063 (C_{sp2}-H), 2924 (C_{sp3}-H), 1716, 1684 and 1641 (C=O), 1614 (C=N), 1547 and 1470 (C=C) cm^{-1}; MS (70 eV): *m/z* = 368 (100, $M^{+\cdot}$), 355 (37), 340 (56), 329 (26), 315 (21), 285 (58), 270 (30), 245 (63), 230 (28), 183 (12).

Ethyl (2*E*)-[(2*Z*)-4-oxo-2-[(2*Z*)-(2-oxo-1-prop-2-yn-1-yl-1,2-dihydro-3*H*-indol-3-ylidene)hydrazono]-1,3-thiazolidin-5-ylidene]acetate (4j, $C_{18}H_{14}N_4O_4S$) Yield: 0.28 g (75%); m.p.: 238–240 °C; R_f = 0.5 (*n*-hexane/ethyl acetate 3:2); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ = 1.28 (t, 3H, $^3J_{HH}$ = 6.8 Hz, CH_3), 3.30 (t, 1H, $^4J_{HH}$ = 2.4 Hz, ≡CH), 4.25 (q, 3H, $^3J_{HH}$ = 6.8 Hz, OCH_2), 4.55 (d, 2H, $^4J_{HH}$ =

2.4 Hz, N–CH_2), 6.71 (s, 1H, C=CH), 7.16 (m, 2H, $CH_{Oxindole}$), 7.51 (td, 1H, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.2 Hz, $CH_{Oxindole}$), 7.63 (dd, 1H, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.2 Hz, $CH_{Oxindole}$), 13.53 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.5 (CH_3), 29.1 (N–CH_2), 62.0 (OCH_2), 75.0 (≡CH), 78.2 (C_q), 110.4 ($CH_{Oxindole}$), 116.3 (CH_{Vinyl}), 120.2 (C_q), 122.0 ($CH_{Oxindole}$), 123.6 ($CH_{Oxindole}$), 133.4 ($CH_{Oxindole}$), 142.22 (C_q), 144.3 (C_q), 146.2 (C=$N_{Oxindole}$), 156.5 (C=$O_{Oxindole}$), 165.8 (C=$N_{Thiazole}$), 166.4 (C=O), 168.0 (C=$O_{Thiazole}$) ppm; IR (KBr): $\bar{\nu}$ = 3439 (NH), 3177 (C_{sp}-H), 3062 (C_{sp2}-H), 2933 (C_{sp3}-H), 1722, 1685 and 1648 (C=O), 1615 (C=N), 1546 and 1467 (C=C) cm^{-1}; MS (70 eV): *m*/*z* = 382 (100, $M^{+\cdot}$), 354 (60), 343 (35), 337 (5), 315 (9), 281 (10), 253 (5), 224 (6), 196 (9), 169 (10).

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

To a stirred solution of oxindole **1a**–**1e** (1.0 mmol) in 5 cm^3 of absolute EtOH were added thiosemicarbazide (**2**, 1.0 mmol), maleimide (**5**, 1.0 mmol) in the presence of 0.01 g chloroacetic acid as a catalyst. The reaction mixture was refluxed for 12–24 h. After the completion of the reaction (monitored by TLC), the mixture was filtered and residue powder recrystallized in EtOH that afford to the desired indole-hydrazono thiazolidin acetamides **6a**–**6e** as an orange powder.

2-[(2*Z*)-4-Oxo-2-[(2*Z*)-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazono]-1,3-thiazolidin-5-yl]acetamide (6a, $C_{13}H_{11}N_5O_3S$) Yield: 0.25 g (80%); m.p.: 283–285 °C; R_f = 0.3 (*n*-hexane/ethyl acetate 3:2); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ = 2.74 (AB quartet, 1H, $^2J_{HH}$ = 16.0 Hz, $^3J_{HH}$ = 9.2 Hz, CH_2) and 2.97 (AB quartet, 1H, $^2J_{HH}$ = 16.0 Hz, $^3J_{HH}$ = 4.0 Hz, CH_2), 4.40 (dd, 1H, $^3J_{HH}$ = 9.2 Hz, $^3J_{HH}$ = 4.0 Hz, CH), 6.86 (d, 1H, $^3J_{HH}$ = 8.0 Hz, $CH_{Oxindole}$), 7.00 (td, 1H, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 0.8 Hz, $CH_{Oxindole}$), 7.11 (s, 1H, NH), 7.35 (td, 1H, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.2 Hz, $CH_{Oxindole}$), 7.55 (s, 1H, NH), 8.22 (d, 1H, $^3J_{HH}$ = 8.0 Hz, $CH_{Oxindole}$), 10.71 (s, 1H, NH), 12.38 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 37.6 (CH_2), 44.8 (CH), 110.9 ($CH_{Oxindole}$), 117.6 ($CH_{Oxindole}$), 117.6 (C_q), 122.3 ($CH_{Oxindole}$), 128.9 ($CH_{Oxindole}$), 133.1 ($CH_{Oxindole}$), 144.5 (C_q), 148.2 (C=$N_{Oxindole}$), 165.3 (C=$O_{Oxindole}$), 171.3 (C = $N_{Thiazole}$), 172.9 (C=O), 176.2 (C=$O_{Thiazole}$) ppm; IR (KBr): $\bar{\nu}$ = 3422 and 3198 (NH), 3085 (C_{sp2}-H), 2962 (C_{sp3}-H), 1715, 1668 and 1642 (C=O), 1625 (C=N), 1554 and 1457 (C=C) cm^{-1}; MS (70 eV): *m*/*z* = 317 (35, $M^{+\cdot}$), 300 (2), 289 (12), 273 (47), 245 (7), 203 (23), 192 (100), 146 (42), 129 (28), 118 (44), 76 (55), 59 (42).

2-[(2*Z*)-2-[(2*Z*)-(5-Chloro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazono]-4-oxo-1,3-thiazolidin-5-yl]acetamide (6b, $C_{13}H_{10}ClN_5O_3S$) Yield: 0.31 g (87%); m.p.: 315–318 °C; R_f = 0.24 (*n*-hexane/ethyl acetate 3:2); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ = 2.76 (AB quartet, 1H, $^2J_{HH}$ = 16.0 Hz, $^3J_{HH}$ = 9.2 Hz, CH_2) and 2.98 (AB quartet, 1H, $^2J_{HH}$ = 16.0 Hz, $^3J_{HH}$ = 3.6 Hz, CH_2), 4.42 (dd, 1H, $^3J_{HH}$ = 9.2 Hz, $^3J_{HH}$ = 3.6 Hz, CH), 6.87 (d, 1H, $^3J_{HH}$ = 8.0 Hz, $CH_{Oxindole}$), 7.12 (s, 1H, NH), 7.39 (dd, 1H, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 2.4 Hz, $CH_{Oxindole}$), 7.56 (s, 1H, NH), 8.27 (d, 1H, $^4J_{HH}$ = 2.4 Hz, $CH_{Oxindole}$), 10.84 (s, 1H, NH), 12.51 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 37.5 (CH_2), 45.0 (CH), 112.3 ($CH_{Oxindole}$), 118.8 (C_q), 126.2 ($CH_{Oxindole}$), 128.3 (C–Cl), 132.4 ($CH_{Oxindole}$), 143.1 (C_q), 147.1 (C=$N_{Oxindole}$), 165.0 (C=$O_{Oxindole}$), 171.3 (C=$N_{Thiazole}$), 174.2 (C=O), 176.4 (C=$O_{Thiazole}$) ppm; IR (KBr): $\bar{\nu}$ = 3425 and 3291 (NH), 3004 (C_{sp2}-H), 2917 (C_{sp3}-H), 1726, 1663 and 1641 (C=O), 1626 (C=N), 1540 and 1450 (C=C) cm^{-1}; MS (70 eV): *m*/*z* = 353 (3, $M^{+\cdot}$ + 2), 351 (9, $M^{+\cdot}$), 335 (31), 333 (93), 305 (37), 280 (2), 195 (47), 179 (65), 166 (9), 152 (79), 129 (44), 59 (100).

2-[(2*Z*)-2-[(2*Z*)-(5-Nitro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazono]-4-oxo-1,3-thiazolidin-5-yl]acetamide (6c, $C_{13}H_{10}N_6O_5S$) Yield: 0.33 g (90%); m.p.: 310–312 °C; R_f = 0.24 (*n*-hexane/ethyl acetate 3:2); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ = 2.75 (AB quartet, 1H, $^2J_{HH}$ = 16.2 Hz, $^3J_{HH}$ = 9.2 Hz, CH_2) and 2.99 (AB quartet, 1H, $^2J_{HH}$ = 16.2 Hz, $^3J_{HH}$ = 4.2 Hz, CH_2), 4.44 (dd, 1H, $^3J_{HH}$ = 9.2 Hz, $^3J_{HH}$ = 4.2 Hz, CH), 6.88 (d, 1H, $^3J_{HH}$ = 8.0 Hz, $CH_{Oxindole}$), 7.12 (s, 1H, NH), 7.37 (dd, 1H, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 2.0 Hz, $CH_{Oxindole}$), 7.56 (s, 1H, NH), 8.27 (d, 1H, $^4J_{HH}$ = 2.0 Hz, $CH_{Oxindole}$), 10.83 (s, 1H, NH), 12.50 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 37.4 (CH_2), 44.9 (CH), 112.2 ($CH_{Oxindole}$), 118.7 ($CH_{Oxindole}$), 126.2 ($CH_{Oxindole}$), 128.2 (C_q), 132.3 (C-NO_2), 143.1 (C_q), 147.1 (C=$N_{Oxindole}$), 164.9 (C=$O_{Oxindole}$), 171.2 (C=$N_{Thiazole}$), 174.2 (C=O), 176.3 (C=$O_{Thiazole}$) ppm; IR (KBr): $\bar{\nu}$ = 3374, 3277 and 3193 (NH), 3070 (C_{sp2}-H), 2924 (C_{sp3}-H), 1700 (C=O), 1616 (C=N), 1518 and 1470 (C=C) cm^{-1}; MS (70 eV): *m*/*z* = 362 (2, $M^{+\cdot}$), 265 (60), 248 (56), 237 (100), 204 (35), 190 (42), 176 (14), 144 (43), 115 (30).

2-[(2*Z*)-2-[(2*Z*)-(1-Benzyl-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazono]-4-oxo-1,3-thiazolidin-5-yl]acetamide (6d, $C_{20}H_{17}N_5O_3S$) Yield: 0.31 g (77%); m.p.: 288–290 °C; R_f = 0.4 (*n*-hexane/ethyl acetate 3:2); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ = 2.76 (AB quartet, 1H, $^2J_{HH}$ = 16.2 Hz, $^3J_{HH}$ = 9.2 Hz, CH_2) and 2.98 (AB quartet, 1H, $^2J_{HH}$ = 16.2 Hz, $^3J_{HH}$ = 4.0 Hz, CH_2), 4.43 (dd, 1H, $^3J_{HH}$ = 9.2 Hz, $^3J_{HH}$ = 4.0 Hz, CH), 4.96 (s, 2H, N-CH_2), 6.98 (d, 1H, $^3J_{HH}$ = 7.6 Hz, $CH_{Oxindole}$), 7.07 (td,

1H, $^{3}J_{HH}$ = 7.4 Hz, $^{4}J_{HH}$ = 1.2 Hz, $CH_{Oxindole}$), 7.13 (s, 1H, NH), 7.25–7.29 (m, 1H, CH_{Ar}), 7.31–7.38 (m, 5H, CH_{Ar}), 7.57 (s, 1H, NH), 8.28 (dd, 1H, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 1.2 Hz, $CH_{Oxindole}$), 12.46 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 37.5 (CH_2), 43.1 (CH), 44.9 (CH_2), 110.1 ($CH_{Oxindole}$), 117.1 (C_q), 123.0 (CH_{Ar}), 127.7 ($CH_{Oxindole}$), 127.9 (CH_{Ar}), 128.8 ($CH_{Oxindole}$), 129.2 (CH_{Ar}), 133.0 ($CH_{Oxindole}$), 136.7 (C_q), 144.5 (C_q), 147.1 ($C{=}N_{Oxindole}$), 164.1 ($C{=}O_{Oxindole}$), 171.3 ($C{=}N_{Thiazole}$), 173.8 (C=O), 176.4 ($C{=}O_{Thiazole}$) ppm; IR (KBr): $\bar{\nu}$ = 3462 and 3363 (NH), 3031 (C_{sp2}-H), 2925 (C_{sp3}-H), 1721, 1661 and 1648 (C=O), 1609 (C=N), 1555 and 1469 (C=C) cm^{-1}; MS (70 eV): *m*/*z* = 407 (9, $M^{+\cdot}$), 363 (9), 300 (42), 257 (35), 235 (100), 207 (47), 129 (26), 91 (28), 59 (12).

2-[(2*Z*)-4-Oxo-2-[(2*Z*)-(2-oxo-1-prop-2-yn-1-yl-1,2-dihydro-3*H*-indol-3-ylidene)hydrazono]-1,3-thiazolidin-5-yl]acetamide (6e, $C_{16}H_{13}N_5O_3S$) Yield: 0.25 g (71%); m.p.: 282–284 °C; R_f = 0.3 (*n*-hexane/ethyl acetate 3:2); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ = 2.76 (AB quartet, 1H, $^{2}J_{HH}$ = 16.4 Hz, $^{3}J_{HH}$ = 9.2 Hz, CH_2) and 2.98 (AB quartet, 1H, $^{2}J_{HH}$ = 16.4 Hz, $^{3}J_{HH}$ = 4.0 Hz, CH_2), 3.30 (t, 1H, $^{4}J_{HH}$ = 2.4 Hz, ≡ CH), 4.42 (dd, 1H, $^{3}J_{HH}$ = 9.2 Hz, $^{3}J_{HH}$ = 4.0 Hz, CH), 4.59 (d, 2H, $^{4}J_{HH}$ = 2.4 Hz, N-CH_2), 7.11–7.16 (m, 2H, $CH_{Oxindole}$), 7.18 (s, 1H, NH), 7.49 (td, 1H, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 1.2 Hz, $CH_{Oxindole}$), 7.56 (s, 1H, NH), 8.29 (d, 1H, $^{3}J_{HH}$ = 7.2 Hz, $CH_{Oxindole}$), 12.48 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 29.2 (N-CH_2), 37.5 (CH_2), 44.9 (CH), 74.9 (≡CH), 78.4 (C_q), 110.2 ($CH_{Oxindole}$), 117.1 (C_q), 123.3 ($CH_{Oxindole}$), 128.7 ($CH_{Oxindole}$), 133.0 ($CH_{Oxindole}$), 143.6 (C_q), 146.8 ($C{=}N_{Oxindole}$), 163.1 ($C{=}O_{Oxindole}$), 171.4 ($C{=}N_{Thiazole}$), 174.0 (C=O), 176.4 ($C{=}O_{Thiazole}$) ppm; IR (KBr): $\bar{\nu}$ = 3421 and 3339 (NH), 3126 (C_{sp}-H), 3060 (C_{sp2}-H), 2957 (C_{sp3}-H), 1730, 1707 and 1658 (C=O), 1617 (C=N), 1529 and 1470 (C=C) cm^{-1}; MS (70 eV): *m*/*z* = 355 (21, $M^{+\cdot}$), 338 (5), 311 (37), 258 (100), 230 (47), 184 (65), 170 (17), 129 (47), 97 (93), 59 (42).

Evaluation of antioxidant activity

Radical scavenging activities of the hydrazono thiazolidin-4-ones (**4a**–**4j** and **6a**–**6e**) were determined against stable DPPH radical spectrophotometrically [40]. A stock solution (1.0 mg cm^{-3}) of compounds was prepared in DMSO. Then, 1.0 cm^3 of each compound solution was added to 1.0 cm^3 of a 0.004% methanol solution of the DPPH radical and shaken vigorously. After 60 min of incubation in the dark at room temperature, the absorbance was observed against a blank at 517 nm. The assay was carried out in triplicate and the percentage of inhibition was calculated using the following formula:

$$\% \text{ Inhibition } = (A_C - A_s)/A_C \times 100,$$

where A_C is the absorbance value of the control sample, A_s is the absorbance value of the tested sample, and the results were reported as mean ± SD after three repeats.

Evaluation of antibacterial activity

The in vitro biocidal screening, antibacterial activities of the synthesized compounds were assayed onto LB plates contained: bacto^{TM} tryptone, 10.0 g dm^{-3}; yeast extract, 5.0 g dm^{-3}; NaCl, 5.0 g dm^{-3}; glucose, 1.0 g dm^{-3}; and agar 12.0 g dm^{-3} [41]. The synthesized hydrazono thiazolidin-4-ones was well dissolved into DMSO and added into LB medium to give a final concentration of 1–300 μg cm^{-3} as required, then sterilised at 121 °C for 15 min. The antibacterial activities of the hydrazono thiazolidin-4-one compounds were also compared with known antibiotic tetracycline at the same concentration. Minimum bactericidal concentration (MBC) of these compounds was assayed using a standard method against some bacteria including *E. coli* PTCC 1330, *P. aeruginosa* PTCC 1074, *S. aureus* ATCC 35923, and *B. subtilis* PTCC 1023. Late exponential phase of the bacteria was prepared by inoculating 1% (v/v) of the cultures into the fresh LB medium and incubating on an orbital shaker at 37 °C and 100 rpm overnight. The fresh culture was inoculated onto LB plates containing different concentrations of the synthesized compounds then incubated at 37 °C. The compounds sensitivity of the strains was assayed for positive or negative growth after 24–48 h.

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