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ORIGINAL PAPER

"On water" synthesis of spiro-indoles via Schiff bases

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Abstract A fast, efficient, and clean "on water" synthesis of new Schiff bases and their conversion to spiro compounds under microwave irradiation, as well as in water, is reported. Indol-2,3-diones were reacted separately with various heterocyclic and aromatic amines in water at room temperature to obtain corresponding Schiff bases in high purity and yield. These were then converted into corresponding spiro compounds using mercaptoacetic acid under microwave irradiation in neat conditions as well as in water on refluxing. Hence, a green synthetic protocol is developed to synthesize new molecules with improved profile under ecofriendly conditions, in which no wastes or side-products are formed.

Keywords Schiff bases · Spiro compounds · Cycloadditions · Green chemistry · Water · Microwave

Introduction

Indoles are an important class of nitrogen heterocycles, being used as key building blocks for synthesis of many pharmaceuticals. Spiro-indoles and Schiff bases are known to exhibit diverse biological activities [1–7]. Of these, spiro[indole-thiazolidines] have attracted our attention because of their anti-inflammatory, fungistatic, bacteriostatic, and anticonvulsant activities [8, 9]. On the other hand, benzothiazoles have also found application as potential therapeutic agents for various diseases [10] and also as enzyme inhibitors [11], plant growth regulators [12], fluorescent material [13], and dyes [14].

Encouraged by the above-cited literature reports, an idea was developed to introduce separately benzothiazole as well as indazole moiety into the above-mentioned spiro[indole-thiazolidine] under ecofriendly conditions, in order to improve its biological properties and broaden the activity spectrum of the resulting new spiro compounds.

Typically, synthesis of Schiff bases and spiro-indoles employs various organic solvents and reagents under different conditions [15–21]. Some reactions involve high temperatures, use of catalyst, and hazardous organic solvents. Therefore, development of a simple and efficient protocol under mild conditions for construction of these heterocycles has been advocated. Tight legislation to maintain greenness requires us to prevent generation of waste, avoid use of auxiliary substances (e.g., organic solvents, additional reagents), and minimize energy requirements. In this context, use of water as the reaction medium offers several advantages [22–24] as: (1) it is cheap, nonflammable, nontoxic, and safe to use; (2) it eliminates the additional efforts required to make the substrates/reagents dry before use and thus reduces/eliminates consumption of drying agents, energy, and time; (3) the unique physical and chemical properties of water often increase reactivity or selectivity, unattainable in organic solvents; and (4) the product may be easily isolated by filtration. All these inspired us to continue our focus on the aspect of "on water" heterocycle synthesis.

Electronic supplementary material The online version of this article (doi:10.1007/s00706-011-0697-x) contains supplementary material, which is available to authorized users.

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Results and discussion

As a part of our continuing interest in synthesis of new spiro heterocycles of medicinal interest by molecular modification [25–29], we have now developed a protocol for synthesis of Schiff bases by stirring 1*H*-indol-2,3-dione with different aromatic and heterocyclic amines in water at room temperature to afford the corresponding Schiff bases as colored solids in excellent yield (Table 1). For **3a**, the infrared (IR) spectrum showed a characteristic absorption band at 1,613 cm^{-1} for C=N stretching, thus indicating the formation of a Schiff base. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) data provided the final evidence for the formation of a Schiff base.

The cyclocondensation of the Schiff base with mercaptoacetic acid was accelerated by microwave irradiation (70 W) at 100 °C for 5 min in a CEM Discover Focussed Microwave Synthesis System, and the desired product was obtained in 5 min in very good yield. The same reaction was also carried out in water under traditional refluxing condition to obtain the desired product in good yield (Table 2). For **5a**, two one-proton characteristic doublets at $\delta = 4.04$ and 4.20 ppm ($J = 15.6$ Hz) in ^{1}H and a peak at 32.8 ppm in ^{13}C NMR for the methylene group of the newly formed thiazolidinone ring supported the formation of spiro[indole-thiazolidine]-2,4′-diones.

Thus, we have introduced herein a highly selective and efficient method for constructing Schiff bases and spiro-indoles without using any catalyst. In general, after completion of the reactions, the Schiff bases were settled down on standing and were isolated in pure form after filtration and air drying, whereas spiro-indoles were precipitated out upon neutralization by sodium bicarbonate. The isolated products were obtained in pure form (by spectral data) and did not require any further additional efforts for purification. To generalize the methodology we have prepared a number of known and unknown Schiff bases and spiro-indoles by following the ecofriendly methodology.

To ensure that no metal ion is leaching out from the glass reaction vessel and is responsible for providing catalytic assistance, the reaction of 1*H*-indol-2,3-dione (3 mmol) with 4-methylaniline (3 mmol) was also carried out in a plastic vessel in water for 5 h, and the corresponding Schiff base was obtained in 94% yield. Further, the reaction of 5-fluoro-1*H*-indol-2,3-dione with 4-methylaniline was carried out separately in distilled water, tap water, and saturated brine solution. No significant difference was observed either in the reaction time or in the product yield. The Schiff base was obtained in 94%, 95%, and 94% yield, respectively, after 4 h at room temperature. Further, we carried out the reaction in deionized water to rule out the possibility of any metallic impurities from tap water catalyzing such reactions. The Schiff base was obtained in 92% yield, and no appreciable rate retardation was observed. All the reactions were carried out in tap water to avoid the effort and energy consumption needed to prepare distilled water.

To find out if water provides a kinetic advantage over other solvents, the progress of the reaction of 5-methyl-1*H*-indol-2,3-dione with 6-aminobenzothiazole was monitored in various solvents. Since 6-aminobenzothiazole and the corresponding Schiff base had close R_f values, the consumption of 5-methyl-1*H*-indol-2,3-dione was taken as a measure of reaction completion.

Complete consumption of 5-methyl-1*H*-indol-2,3-dione, as observed on high-performance thin-layer chromatography (HP-TLC), took place after 9, 8, 7, 5, 5, 4, and 3 h in methanol, tetrahydrofuran, ethanol, acetic acid, dimethyl sulfoxide, dimethyl formamide, and water, respectively. A graphical representation of the time required for complete consumption of 5-methyl-1*H*-indol-2,3-dione and the yield of each reaction is given in Figs. 1 and 2.

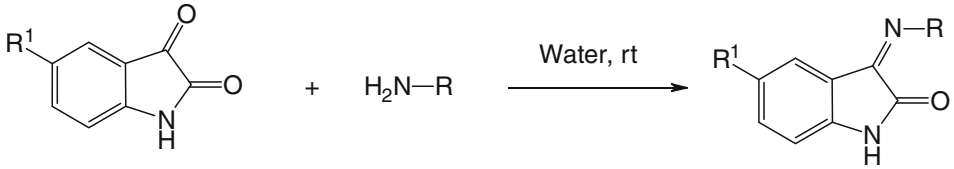
Spiro-indoles were synthesized by microwave irradiation of a homogeneous mixture of Schiff base and mercaptoacetic acid without using any solvent, catalyst, or supporting material. This reaction was completed in 5 min.

The above reaction was also carried out in presence of solvents such as methanol, dimethyl formamide, and toluene along with supporting materials such as silica or K-10 clay, but no significant difference was observed either in the yield or in the purity of the compound, as compared with one prepared under neat condition (Scheme 1).

We have also carried out the above reaction in water under traditional refluxing condition and under microwave irradiation under dry condition on large scale. It proceeds nearly to completion in water, while some amount of reactants are left when carried out under dry condition under microwave irradiation, indicating that “on water” synthesis is more efficient than under dry condition on small as well as large scale.

In conclusion, we describe herein a fast, efficient, cleaner, and greener methodology for “on water” synthesis of Schiff bases and spiro-indoles. The advantages such as (1) no requirement of additional reagent/catalyst, (2) nonflammable and nontoxic reaction medium, (3) high yield, (4) virtually no waste generation, and (5) ease of product isolation/purification fulfill the triple bottom-line philosophy of green chemistry and make the present methodology environmentally benign. This protocol is associated with readily available starting materials, mild conditions, easy operation, and a broad range of substrates.

Table 1 Synthesis of 3-(heteroaryl/arylimino)-5-substituted indoline-2-ones **3a**-**3u**



1a: $R^1 = H$
1b: $R^1 = F$
1c: $R^1 = CH_3$

2a-2g

3a-3u

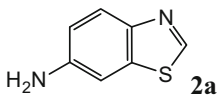
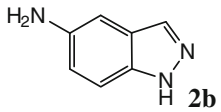
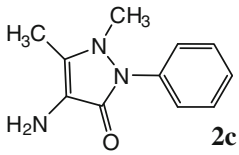
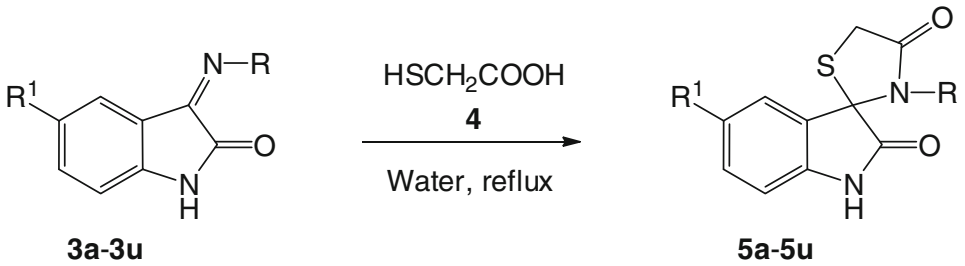
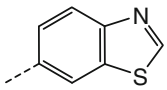
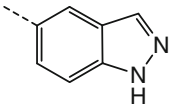
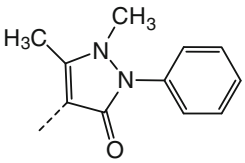
Prod.	1	2	Time/h	Yield/%	M.p./°C
3a	**1a**	 **2a**	3.0	98	248–250
3b	**1b**	**2a**	3.5	96	259–261
3c	**1c**	**2a**	3.0	98	146–147
3d	**1a**	 **2b**	3.5	91	>280 [29]
3e	**1b**	**2b**	4.0	95	>280 [29]
3f	**1c**	**2b**	4.5	92	266–267
3g	**1a**	 **2c**	0.5	98	129–131 [28]
3h	**1b**	**2c**	0.5	96	141–142 [30]
3i	**1c**	**2c**	0.5	94	153–155 [31]
3j	**1a**	Aniline (**2d**)	4.0	92	183–184 [32]
3k	**1b**	**2d**	5.0	91	154–155 [33]
3l	**1c**	**2d**	5.0	90	142–144
3m	**1a**	4-Fluoroaniline (**2e**)	4.0	90	210–211 [8]
3n	**1b**	**2e**	4.5	90	220–221 [33]
3o	**1c**	**2e**	4.5	90	275–276 [34]
3p	**1a**	4-Methylaniline (**2f**)	5.0	94	261–262 [35]
3q	**1b**	**2f**	4.0	95	249–250
3r	**1c**	**2f**	4.0	96	241–243 [35]
3s	**1a**	4-Methoxyaniline (**2g**)	4.5	92	251–253 [35]
3t	**1b**	**2g**	4.0	96	245–247
3u	**1c**	**2g**	4.0	98	221–222 [34]

Table 2 Synthesis of 3′-(heteroaryl/aryl)spiro[3*H*-indol-3,2′-thiazolidine]-2,4′(1*H*)-diones **5a**-**5u**



3a-3u **5a-5u**

Prod.	R	R^1	Time/h	Yield/%	M.p./°C
5a		H	4.0	90	294–296
5b		F	6.0	88	302–304
5c		CH_3	4.0	88	273–274
5d		H	4.0	85	>280 [29]
5e		F	6.0	89	>280 [29]
5f		CH_3	6.0	82	181–182
5g		H	5.0	89	305–307 [29]
5h		F	6.0	88	307–309 [31]
5i		CH_3	5.0	88	305–306 [30]
5j	C_6H_5-	H	6.0	82	230–231 [32]
5k		F	6.0	85	265–266 [15–19]
5l		CH_3	6.0	87	86–88
5m	4-F-C_6H_4-	H	4.5	82	244–246 [8]
5n		F	6.0	83	180–182 [15–19]
5o		CH_3	4.0	88	193–195
5p	4-CH_3-C_6H_4-	H	4.0	82	123–125
5q		F	5.0	80	102–104
5r		CH_3	4.0	82	>280 [36]
5s	4-CH_3O-C_6H_4-	H	5.0	85	210–211 [37]
5t		F	4.0	90	196–197
5u		CH_3	5.0	82	201–203

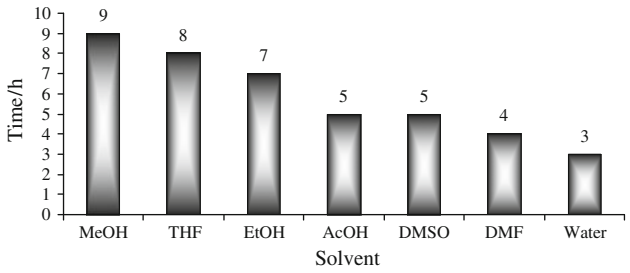


Fig. 1 Time required for complete consumption of 5-methyl-1*H*-indol-2,3-dione during its reaction with 6-aminobenzothiazole

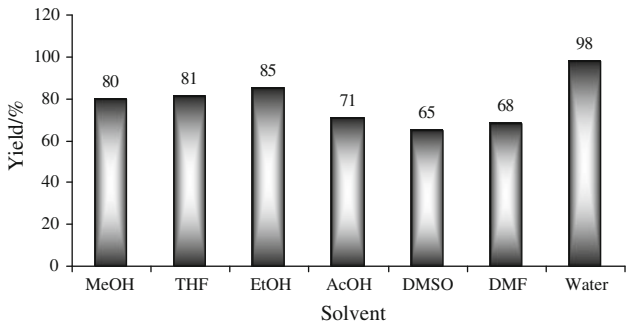
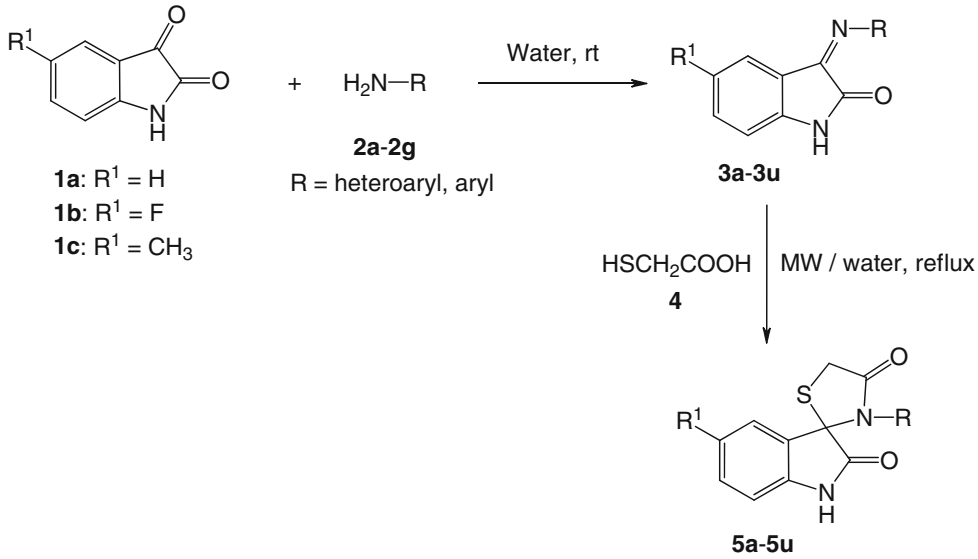


Fig. 2 Schiff base formation during reaction of 5-methyl-1*H*-indol-2,3-dione with 6-aminobenzothiazole using various solvents

Scheme 1



1a: $R^1 = H$
1b: $R^1 = F$
1c: $R^1 = CH_3$

Experimental

Melting points were determined in a capillary tube in sulfuric acid bath. IR spectra were recorded on a Shimadzu model IR-435 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-400 (400 MHz for ^1H, 100 MHz for ^{13}C) in DMSO-d_6. Elemental analyses were performed on a PerkinElmer series 11 CHNS/O analyzer 2400 and were within 0.4% of calculated values. Mass spectra were recorded on a Micromass Quattro Micro™ instrument. A CEM Discover Focussed Microwave Synthesis System was used for microwave irradiation. Substituted 1*H*-indol-2,3-diones **1b**-**1c** were prepared by literature procedures starting from the corresponding anilines [28].

Typical procedure for synthesis of 3-(heteroaryl/aryl)imino-5 substituted 1,3-dihydro-2H-indole-2-ones

Substituted isatin (1.0 mmol) and heterocyclic or aromatic amine (1.0 mmol) were taken in a 50-cm^3 round-bottom flask and stirred in 10 cm^3 tap water. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the solvent was removed by filtration and the Schiff base isolated. All the compounds were characterized by their spectral data [IR, NMR, and mass spectrometry (MS)], and for known compounds these were compared with literature values.

3-(Benzothiazol-6-ylimino)-1,3-dihydro-2H-indole-2-one (**3a**, $C_{15}H_9N_3OS$)
IR (KBr): $\bar{\nu}$ = 3,167, 2,918, 1,723, 1,613, 1,463, 1,341, 1,220, 854, 751, 639 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 6.30 (d, J = 7.6 Hz, 1H), 6.65 (d, J = 7.6 Hz, 1H), 6.88 (d, J = 7.2 Hz, 1H), 7.18 (d, J = 7.2 Hz, 1H), 7.30 (dd, J = 7.7, 7.6 Hz, 1H), 7.77 (s, 1H), 8.14 (d, J = 8.4 Hz, 1H), 9.32 (s, 1H), 11.00 (s, 1H, NH, D_2O exchangeable) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 110.9, 111.3, 119.6, 121.7, 124.8, 125.8, 135.1, 146.3, 148.4, 151.3, 158.9, 163.9 (C-2) ppm; MS: m/z = (ES+) 280.13 [M^+ + 1], (ES−) 278.13 [M^+ − 1].

3-(Benzothiazol-6-ylimino)-5-fluoro-1,3-dihydro-2H-indole-2-one (**3b**, $C_{15}H_9FN_3OS$)
IR (KBr): $\bar{\nu}$ = 3,183, 2,929, 1,721, 1,620, 1,474, 1,306, 1,263, 1,194, 852, 826, 635 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 6.88 (m, 2H), 7.22-719 (m, 2H), 7.80 (s, 1H), 8.16 (d, J = 8.4 Hz, 1H), 9.34 (s, 1H), 11.04 (s, 1H, NH, D_2O exchangeable) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 111.2, 113.3, 116.5, 123.0, 124.5, 135.5, 144.0, 147.7, 155.5, 159.0, and 163.9 (C-2) ppm; MS: m/z = (ES+) 298.18 [M^+ + 1], (ES−) 296.13 [M^+ − 1].

3-(Benzothiazol-6-ylimino)-1,3-dihydro-5-methyl-2H-indole-2-one (**3c**, $C_{16}H_{11}N_3OS$)
IR (KBr): $\bar{\nu}$ = 3,338, 2,923, 1,739, 1,623, 1,484, 1,304, 1,259, 1,205, 1,120, 854, 806, 652 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.22 (s, 3H, CH_3), 6.77 (m, 2H), 7.08 (d, J = 1.6 Hz, 1H), 7.29 (s, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 8.84 (s, 1H), 10.90 (s, 1H, NH, D_2O exchangeable) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.5 (CH_3), 104.2, 112.5, 115.4, 118.2, 123.5, 125.3, 132.5, 135.7, 139.2, 145.2, 147.8, 149.0, 149.6, 159.9, 185.0 (C-2) ppm; MS: m/z = (ES+) 294.14 [M^+ + 1], (ES−) 292.11 [M^+ − 1].

1,3-Dihydro-3-(1H-indazol-5-ylimino)-5-methyl-2H-indole-2-one (**3f**, $C_{16}H_{12}N_4O$)
IR (KBr): $\bar{\nu}$ = 3,189, 2,924, 1,738, 1,616, 1,485, 1,307, 1,209, 956, 831, 651 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 1.94 (s, 3H, CH_3), 6.46 (s, 1H), 6.80 (d,

$J = 7.9$ Hz, 1H), 7.09 (m, 2H), 7.34 (s, 1H), 7.63 (d, $J = 8.7$ Hz, 1H), 8.01 (s, 1H), 10.74 (s, 1H, NH, D_2O exchangeable), 13.00 (s, 1H, NH, D_2O exchangeable) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 21.3$ (CH_3), 109.0, 111.2, 116.7, 119.7, 123.6, 126.1, 131.1, 134.6, 144.0, 155.6, 164.6 (C-2) ppm; MS: m/z = (ES+) 277.12 [$M^+ + 1$], (ES−) 275.14 [$M^+ - 1$].

1,3-Dihydro-5-methyl-3-(phenylimino)-2H-indole-2-one (**3l**, $C_{15}H_{12}N_2O$)
IR (KBr): $\bar{\nu} = 3{,}288$, 2,926, 1,745, 1,628, 1,492, 1,307, 1,198, 1,129, 831, 692 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.23$ (s, 3H, CH_3), 6.19 (s, 1H), 6.75 (m, 2H), 6.89 (d, $J = 7.9$ Hz, 1H), 7.02 (d, $J = 8.1$ Hz, 1H), 7.28 (m, 2H), 7.36 (d, $J = 7.9$ Hz, 1H), 10.60 (s, 1H, NH, D_2O exchangeable) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 21.1$ (CH_3), 109.5, 111.5, 114.1, 112.7, 118.8, 122.9, 143.4, 159.1, 164.1 (C-2) ppm; MS: m/z = (ES+) 237.19 [$M^+ + 1$] (ES−) 235.19 [$M^+ - 1$].

5-Fluoro-1,3-dihydro-3-[(4-methylphenyl)imino]-2H-indole-2-one (**3q**, $C_{15}H_{11}FN_2O$)
IR (KBr): $\bar{\nu} = 3{,}432$, 2,926, 1,748, 1,621, 1,475, 1,300, 1,187, 834, 652 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.23$ (s, 3H, CH_3), 6.20 (d, $J = 8.0$ Hz, 1H), 6.96 (m, 2H), 7.16 (m, 2H), 7.30 (m, 2H), 10.95 (s, 1H, NH, D_2O exchangeable) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 22.5$ (CH_3), 109.5, 111.1, 112.9, 113.6, 116.1, 124.3, 142.8, 154.1, 158.8, 164.4 (C-2) ppm; MS: m/z = (ES+) 255.10 [$M^+ + 1$], (ES−) 253.16 [$M^+ - 1$].

5-Fluoro-1,3-dihydro-3-[(4-methoxyphenyl)imino]-2H-indole-2-one (**3t**, $C_{15}H_{11}FN_2O_2$)
IR (KBr): $\bar{\nu} = 3{,}434$, 2,928, 1,739, 1,605, 1,474, 1,251, 1,186, 1,032, 820, 773, 655 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.83$ (s, 3H, OCH_3), 6.92 (d, $J = 8.1$ Hz, 2H), 7.05 (m, 2H), 7.17 (m, 1H), 7.29 (d, $J = 8.1$ Hz, 1H), 6.42 (d, $J = 6.8$ Hz, 1H), 10.93 (s, 1H, NH, D_2O exchangeable) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 55.5$ (OCH_3), 109.5, 111.9, 112.7, 113.6, 116.4, 119.8, 123.7, 143.4, 154.3, 158.8, 164.1 (C-2) ppm; MS: m/z = (ES+) 271.26 [$M^+ + 1$], (ES−) 269.22 [$M^+ - 1$].

Typical procedure for synthesis of 3′-(heteroaryl/aryl)spiro[3H-indole-3,2′-thiazolidine]-2,4′(1H)-diones

A dried heavy-walled Pyrex tube containing a small stir bar was charged with 3-indolylimine (1.0 mmol) and mercaptoacetic acid (1.2 mmol) without any solvent. The contents were subjected to microwave irradiation (70 W) at 100 °C for 5 min in cooling mode. A sticky solid was formed, which was treated with saturated solution of sodium bicarbonate to remove excess acid. The solid left was filtered, washed with water, and dried to obtain the desired product.

Alternate method: A mixture of 3-indolylimine (1.0 mmol) and mercaptoacetic acid (1.2 mmol) was mixed with 10 cm^3 water in a round-bottom flask. The contents were refluxed for 4–5 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was neutralized by $NaHCO_3$. The precipitate was filtered, washed with water, and dried to obtain the desired product.

3′-(Benzothiazol-6-yl)spiro[3H-indole-3,2′-thiazolidine]-2,4′(1H)-dione (**5a**, $C_{17}H_{11}N_3O_2S_2$)
IR (KBr): $\bar{\nu} = 3{,}167$, 2,851, 1,727, 1,689, 1,470, 1,401, 1,339, 1,224, 1,185, 855, 764, 622 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 4.04$ (d, $J = 15.6$ Hz, 1H), 4.20 (d, $J = 15.6$ Hz, 1H), 6.71 (d, $J = 7.6$ Hz, 1H), 6.97 (dd, $J = 7.6$, 7.6 Hz, 1H), 7.14 (d, $J = 6.8$ Hz, 1H), 7.17 (d, $J = 7.6$ Hz, 1H), 7.57 (d, $J = 7.2$ Hz, 1H), 7.89 (s, 1H), 7.97 (d, $J = 8.8$ Hz, 1H), 9.37 (s, 1H), 10.77 (s, 1H, NH, D_2O exchangeable) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 32.8$ (S-CH_2), 70.1 (spiro carbon), 111.1, 123.3, 124.9, 126.7, 127.0, 131.7, 133.9, 134.5, 142.0, 152.9, 158.5, 172.5 (C-2), 176.6 (thiazolidine C=O) ppm; MS: m/z = (ES+) 354.15 [$M^+ + 1$], (ES−) 352.15 [$M^+ - 1$].

3′-(Benzothiazol-6-yl)-5-fluorospiro[3H-indole-3,2′-thiazolidine]-2,4′(1H)-dione (**5b**, $C_{17}H_{10}FN_3O_2S_2$)
IR (KBr): $\bar{\nu} = 3{,}449$, 2,926, 1,734, 1,691, 1,486, 1,357, 1,181, 887, 635 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 4.04$ (d, $J = 15.6$ Hz, 1H), 4.18 (d, $J = 15.2$ Hz, 1H), 6.71 (d, $J = 8.0$ Hz, 1H), 7.02 (d, $J = 7.8$ Hz, 1H), 7.19 (d, $J = 7.6$ Hz, 1H), 7.61 (d, $J = 7.8$ Hz, 1H), 7.84 (s, 1H), 8.01 (d, $J = 7.6$ Hz, 1H), 9.39 (s, 1H), 10.79 (s, 1H, NH, D_2O exchangeable) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 32.8$ (S-CH_2), 70.3 (spiro carbon), 112.3, 114.8, 118.5, 123.5, 124.0, 127.0, 133.7, 134.6, 138.1, 153.0, 157.5, 158.6, 159.9, 172.4 (C-2), 176.5 (thiazolidine C=O) ppm; MS: m/z = (ES+) 372.17 [$M^+ + 1$], (ES−) 370.12 [$M^+ - 1$].

3′-(Benzothiazol-6-yl)-5-methylspiro[3H-indole-3,2′-thiazolidine]-2,4′(1H)-dione (**5c**, $C_{18}H_{13}N_3O_2S_2$)
IR (KBr): $\bar{\nu} = 3{,}182$, 1,729, 1,689, 1,491, 1,467, 1,348, 1,203, 1,169, 860, 815, 694, 637 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.18$ (s, 3H, CH_3), 4.01 (d, $J = 15.6$ Hz, 1H), 4.17 (d, $J = 15.6$ Hz, 1H), 6.59 (d, $J = 8.0$ Hz, 1H), 6.96 (d, $J = 8.0$ Hz, 1H), 7.14 (d, $J = 8.8$ Hz, 1H), 7.39 (s, 1H), 7.89 (s, 1H), 7.98 (d, $J = 8.4$ Hz, 1H), 9.37 (s, 1H), 10.67 (s, 1H, NH, D_2O exchangeable) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 21.0$ (CH_3), 32.8 (S-CH_2), 70.2 (spiro carbon), 110.9, 123.3, 123.9, 125.0, 126.7, 127.4, 132.0, 132.4, 134.0,

134.6, 139.5, 152.8, 158.4, 172.6 (C-2), 176.5 (thiazolidine C=O) ppm; MS: *m/z* = (ES+) 368.19 [$M^+ + 1$], (ES−) 366.19 [$M^+ - 1$].

3′-(1H-Indazol-5-yl)-5-methylspiro[3H-indole-3,2′-thiazolidine]-2,4′(1H)-dione (**5f**, $C_{18}H_{14}N_4O_2S$)
IR (KBr): $\bar{\nu}$ = 3,424, 2,926, 1,720, 1,685, 1,494, 1,380, 1,209, 942, 812, 633 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.38 (s, 3H, CH_3), 3.88 (d, J = 15.3 Hz, 1H), 4.29 (d, J = 15.3 Hz, 1H), 6.60 (d, J = 8.9 Hz, 1H), 6.81 (s, 1H), 6.96 (d, J = 8.3 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 7.30 (s, 1H), 7.42 (d, J = 7.9 Hz, 1H), 7.76 (s, 1H), 10.33 (s, 1H, NH, D_2O exchangeable), 13.08 (s, 1H, NH, D_2O exchangeable) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.4 (CH_3), 33.1 (S-CH_2), 68.1 (spiro carbon), 111.4, 121.3, 126.9, 127.6, 131.7, 139.6, 143.2, 172.8 (C-2), 174.3 (thiazolidine C=O) ppm; MS: *m/z* = (ES+) 351.11 [$M^+ + 1$], (ES−) 349.14 [$M^+ - 1$].

5-Methyl-3′-phenylspiro[3H-indole-3,2′-thiazolidine]-2,4′(1H)-dione (**5l**, $C_{17}H_{14}N_2O_2S$)
IR (KBr): $\bar{\nu}$ = 3,447, 2,925, 1,734, 1,687, 1,493, 1,363, 1,207, 817, 757, 694 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.19 (s, 3H, CH_3), 3.91 (d, J = 15.5 Hz, 1H), 4.15 (d, J = 15.4 Hz, 1H), 6.65 (d, J = 7.9 Hz, 1H), 6.98 (m, 3H), 7.25 (m, 4H), 10.62 (s, 1H, NH, D_2O exchangeable) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.1 (CH_3), 32.6 (S-CH_2), 69.8 (spiro carbon), 109.7, 111.8, 124.8, 127.0, 127.9, 128.3, 129.4, 130.5, 132.2, 139.2, 172.2 (C-2), 176.5 (thiazolidine C=O); MS: *m/z* = (ES+) 311.22 [$M^+ + 1$], (ES−) 309.22 [$M^+ - 1$].

3′-(4-Fluorophenyl)-5-methylspiro[3H-indole-3,2′-thiazolidine]-2,4′(1H)-dione (**5o**, $C_{17}H_{13}FN_2O_2S$)
IR (KBr): $\bar{\nu}$ = 3,441, 2,928, 1,731, 1,689, 1,490, 1,354, 1,247, 1,198, 1,065, 810, 751, 694, 632 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.31 (s, 3H, CH_3), 3.96 (d, J = 15.0 Hz, 1H), 4.11 (d, J = 15.0 Hz, 1H), 6.84 (m, 2H), 6.92 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.0 Hz, 1H), 10.60 (s, 1H, NH, D_2O exchangeable) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.2 (CH_3), 32.2 (S-CH_2), 70.0 (spiro carbon), 112.1, 114.5, 116.6, 117.9, 118.0, 127.4, 130.2, 138.4, 152.0, 165.2, 171.9 (C-2), 176.5 (thiazolidine C=O) ppm; MS: *m/z* = (ES+) 329.23 [$M^+ + 1$], (ES−) 327.18 [$M^+ - 1$].

3′-(4-Methylphenyl)spiro[3H-indole-3,2′-thiazolidine]-2,4′(1H)-dione (**5p**, $C_{17}H_{14}N_2O_2S$)
IR (KBr): $\bar{\nu}$ = 3,440, 2,926, 1,739, 1,680, 1,495, 1,363, 1,237, 932, 827, 757, 691, 629 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.23 (s, 3H, CH_3), 3.90 (d, J = 15.1 Hz, 1H), 4.15 (d, J = 15.1 Hz, 1H), 6.80 (m, 2H), 6.89 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.31 (m, 2H), 10.58 (s, 1H, NH, D_2O exchangeable) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.2 (CH_3), 32.3 (S-CH_2), 70.4 (spiro carbon), 112.1, 114.3, 115.9, 117.9, 118.4, 127.3, 130.6, 138.8, 152.3, 154.4, 171.8 (C-2), 176.2 (thiazolidine C=O) ppm; MS: *m/z* = (ES+) 311.19 [$M^+ + 1$], (ES−) 309.21 [$M^+ - 1$].

5-Fluoro-3′-(4-methylphenyl)spiro[3H-indole-3,2′-thiazolidine]-2,4′(1H)-dione (**5q**, $C_{17}H_{13}FN_2O_2S$)
IR (KBr): $\bar{\nu}$ = 3,449, 2,928, 1,734, 1,682, 1,487, 1,365, 1,273, 1,234, 1,190, 816, 697, 624 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.19 (s, 3H, CH_3), 3.86 (d, J = 15.2 Hz, 1H), 4.16 (d, J = 15.2 Hz, 1H), 6.71 (m, 1H), 6.92 (m, 3H), 7.03 (m, 2H), 7.22 (d, J = 7.1 Hz, 1H), 10.61 (s, 1H, NH, D_2O exchangeable) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.3 (CH_3), 33.1 (S-CH_2), 69.8 (spiro carbon), 109.7, 111.8, 124.8, 127.2, 128.3, 129.0, 130.5, 131.9, 132.4, 139.2, 173.1 (C-2), 176.1 (thiazolidine C=O) ppm; MS: *m/z* = (ES+) 329.19 [$M^+ + 1$], (ES−) 327.17 [$M^+ - 1$].

5-Fluoro-3′-(4-methoxyphenyl)spiro[3H-indole-3,2′-thiazolidine]-2,4′(1H)-dione (**5t**, $C_{17}H_{13}FN_2O_3S$)
IR (KBr): $\bar{\nu}$ = 3,447, 2,922, 1,734, 1,688, 1,493, 1,363, 1,207, 817, 757, 694, 635 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 3.70 (s, 3H, OCH_3), 3.95 (d, J = 15.3 Hz, 1H), 4.17 (d, J = 15.3 Hz, 1H), 6.74 (m, 2H), 6.82 (d, J = 8.9 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 7.8 Hz, 1H), 10.66 (s, 1H, NH, D_2O exchangeable) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 32.5 (S-CH_2), 55.4 (OCH_3), 70.1 (spiro carbon), 111.8, 113.9, 114.6, 117.6, 118.0, 127.1, 129.9, 138.0, 157.0, 159.2, 171.9 (C-2), 176.5 (thiazolidine C=O) ppm; MS: *m/z* = (ES+) 350.11 [$M^+ + 1$], (ES−) 348.10 [$M^+ - 1$].

3′-(4-Methoxyphenyl)-5-methylspiro[3H-indole-3,2′-thiazolidine]-2,4′(1H)-dione (**5u**, $C_{18}H_{16}N_2O_3S$)
IR (KBr): $\bar{\nu}$ = 3,447, 2,923, 1,734, 1,687, 1,501, 1,373, 1,205, 811, 735, 678, 635 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.21 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 3.95 (d, J = 15.0 Hz, 1H), 4.15 (d, J = 15.0 Hz, 1H), 6.79 (m, 2H), 6.82 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 7.8 Hz, 2H), 7.28 (m, 1H), 10.66 (s, 1H, NH, D_2O exchangeable) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.5, 32.5 (S-CH_2), 55.6 (OCH_3), 70.2 (spiro carbon), 112.1, 113.7, 114.6, 117.5, 118.4, 128.0, 129.7, 139.3, 157.0, 164.2, 171.8 (C-2), 176.2 (thiazolidine C=O) ppm; MS: *m/z* = (ES+) 341.17 [$M^+ + 1$], (ES−) 339.11 [$M^+ - 1$].

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