Simple and Clean Procedure for Three-Component Syntheses of Spiro{pyrido[2,1-*b*]benzothiazole-3,3′-indolines} and Spiro{thiazolo[3,2-*a*]pyridine-7,3′-indolines} in Aqueous Medium

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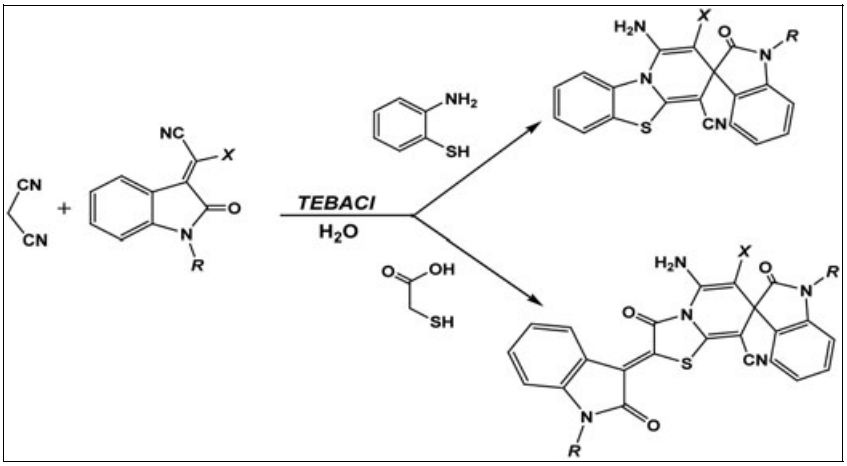

A simple and efficient one-pot three component synthesis of spiro{pyrido[2,1-*b*]benzothiazole-3,3′-indoline} and/or spiro{thiazolo[3,2-*a*]pyridine-7,3′-indoline} derivatives were carried out by the reaction of 2-mercaptoaniline and/or mercaptoacetic acid, malononitrile, and a series of 2-oxoindoline-3-ylidines in aqueous medium. This method is of great value because of its environmentally benign character, high yield processing, and easy handling.

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INTRODUCTION

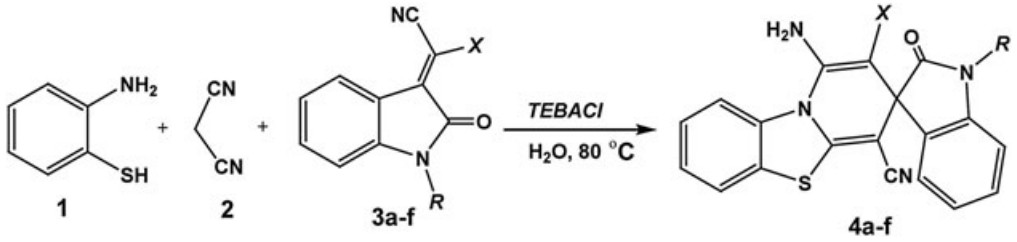
The need to reduce the amount of toxic waste and byproducts arising from chemical processes requires increasing emphasis on the use of less toxic and more environmentally compatible materials in the design of new synthetic methods [1]. One of the most promising approaches uses water as reaction medium [2]. In recent years, there has been increasing recognition that water is an attractive medium for many organic reactions [3,4]. The aqueous medium with respect to organic solvents is less expensive, less dangerous, and more environmentally friendly. The indole nucleus is probably the most well known heterocycle, a common and important feature of a variety of natural products and medicinal agents [5]. Compounds carrying the indole moiety exhibit antibacterial and antifungal activities [6]. Furthermore, it has been reported that sharing of the indole 3-carbon atom in the formation of spiroindoline derivatives highly enhances biological activity [7–11]. As a consequence of our interest in the aqueous medium organic synthesis of spiroheterocycles containing indoline moiety [12–16], we investigated a three-component reaction of 2-mercaptoaniline and/or mercaptoacetic acid, malononitrile, and 2-oxoindoline-3-ylidines to afford a series of some new spiro{pyrido [2,1-*b*]benzothiazole-3,3′-indoline} and/or spiro{thiazolo[3,2-*a*]pyridine-7,3′-indoline} derivatives in water mediated by the surfactant *TEBACl* (triethylbenzylammonium chloride).

RESULTS AND DISCUSSION

In recent years, many surfactants have been used as phase transfer catalysts in number of organic reactions having unique capabilities to dissolve both organic and aqueous solutions to enhance the reaction rate. After some preliminary experiments, it was found that an equimolar mixture of 2-mercaptoaniline **1**, malononitrile **2**, and 2-oxoindoline-3-ylidines **(3a-f)**, were stirred for 3–6 h at 80°C in aqueous medium in the presence of *TEBACl* (20 mol %) could afford spiro{pyrido[2,1-*b*] benzothiazole-3,3′-indoline} derivatives **(4a-f)** in excellent yields (93–98%) (Scheme 1).

To optimize the reaction temperature, the reactions were carried out at different temperatures ranging from room temperature to 100°C. We found that the yield of product **(4e)** was improved and the reaction time was shortened as the temperature was increased to 80°C. Surprising, the yield decreased when temperature was further increased

Scheme 1



to 90 and 100°C (Table 1). Therefore, the most suitable reaction temperature is 80°C. We also evaluated the amount of surfactant required for this transformation. It was found that when increasing the amount of *TEBACl* from 15 to 20 and 25 mol %, the yields increased from 90 to 98 and 94 % respectively. Using 20 mol % *TEBACl* in water is sufficient to push the reaction forward. More amounts of the surfactant did not improve the yields.

Table 2 shows the results using a series of 2-oxoindoline-3-ylidines **(3a-f)** that undergo the reaction to give high yield (93–98%) of the products. This procedure does not require the use of any organic solvent. In this reaction *TEBACl* is necessary. If *TEBACl* is not added the reaction takes a long time and the yield is very low.

Table 1

Optimization of the reaction conditions.[a]

Entry	Temp. °C	Time (h)	Yield (%)[b]
1	rt	24	trace
2	40	15	20
3	50	12	26
4	60	9	58
5	70	5	81
6	80	3	98
7	90	3	80
8	100	3	72

[a]The reaction was carried out with 2-mercaptoaniline **1**, malononitrile **2**, and **3e** in water in the presence of *TEBACl* (20 mol %).
[b]The isolated yield.

Table 2

Synthesis of spiro{pyrido[2,1-*b*]benzothiazole-3,3′-indolines}in aqueous medium at 80°C and *TEBACl* (20 mol %).

Entry	R	X	Time (h)	Yield (%)	m.p (°C)
4a	H	CN	4	96	236–237
4b	H	$CO_2C_2H_5$	5	94	223–224
4c	CH_3	CN	4	94	234–235
4d	CH_3	$CO_2C_2H_5$	6	93	212–213
4e	C_2H_5	CN	3	98	227–228
4f	C_2H_5	$CO_2C_2H_5$	5	95	209–210

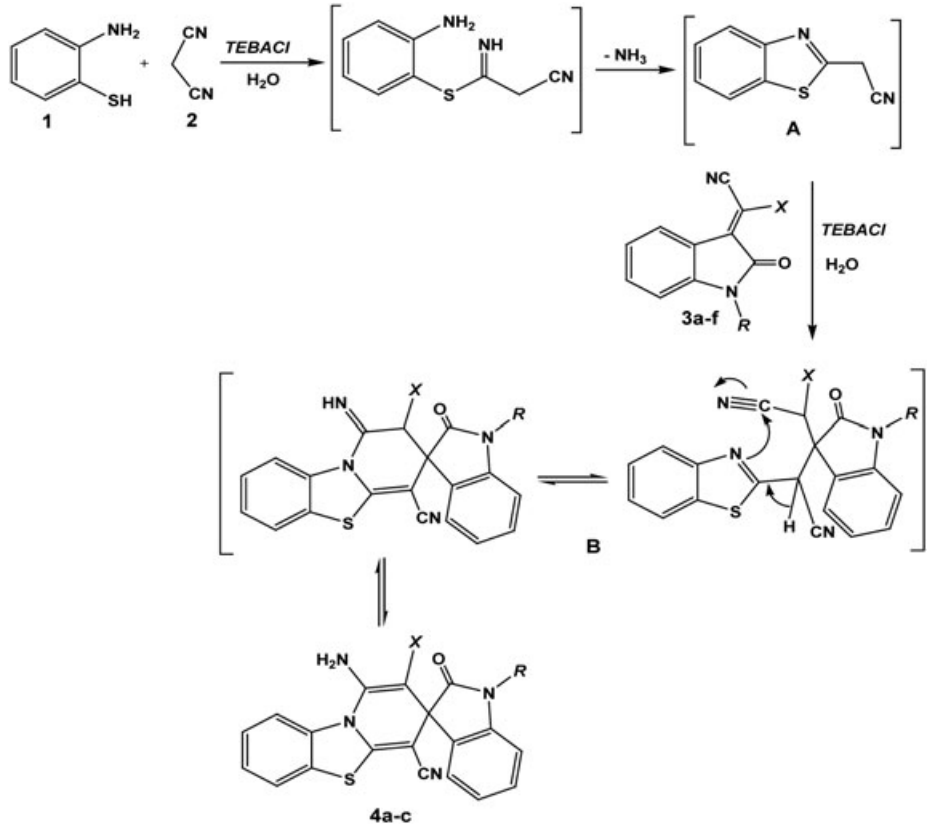
The structures of spiro{pyrido[2,1-*b*]benzothiazole-3,3′-indolines} **(4a-f)** were unambiguously characterized by elemental analysis, IR, ^{1}HNMR, ^{13}CNMR, and MS. For example, the IR spectrum of **(4e)** showed absorption bands at $\acute{\upsilon}$ = 3400, 3305 cm^{-1} for (NH_2), a strong absorption band at 2200 cm^{-1} corresponding to (CN) group, and an absorption band at 1695 cm^{-1} for (C═O) group. Its ^{1}HNMR spectrum in showed signals at δ 6.90 (s, 2H, deuterium oxide exchangeable) for NH_2 protons, 3.78 (q, 2H), 1.16 (t, 3H) for the ethyl protons. Also, ^{13}CNMR spectra confirmed the structure of **(4e)**, where the key signals were at δ 12.4, 34.6 for the ethyl carbons, 50.4 (spiro C), 130.1, 131.2 for the two cyano groups, and 174.6 (C═O).

The formation of **(4a-f)** can be explained by the possible mechanism presented in (Scheme 2). The reaction occurs via initial formation of benzothiazol-2-yl acetonitrile **A** by the reaction of 2-mercaptoaniline and malononitrile which suffers nucleophilic attack to 2-oxoindoline-3-ylidines **(3a-f)** via a type of Michael addition to give the intermediate **B** which cyclized to afford **(4a-f)**.

To further expand the scope of the present method, we investigated one-pot reaction involving mercaptoacetic acid **5**, malononitrile **2**, and 2-oxoindoline-3-ylidines **(3a-f)** with molar ratio of 1:1:1. To our delight, under the above conditions, the reactions proceeded smoothly and 2-(oxoindolin-3"-ylidene)-spiro{thiazolo[3,2-*a*]pyridine-7,3′-indoline} derivatives **(6a-f)** were obtained in poor to moderate yields (38–48%) rather than the expected spiro {thiazolo[3,2-*a*]pyridine-7,3′-indoline} **(7a-f)** (Scheme 3, Table 3).

The structure of products **(6a-f)** was confirmed chemically when the reaction carried out between **5**, **2**, and **(3a-f)** at the same reaction condition with molar ratio of 1: 1: 2 respectively, the yield of the products **(6a-f)** improved to 80–91% (Table 3). The structure of products **(6a-f)** was deduced from elemental analysis, IR, ^{1}HNMR, ^{13}CNMR, and MS. For example, the IR spectrum of **(6c)** showed absorption bands at ύ = 3400, 3300 cm^{-1} for (NH_2), a strong absorption band at 2200 cm^{-1} corresponding to (CN) group, and two absorption bands at 1705 and 1695 cm^{-1} for two (C═O) groups. Its ^{1}HNMR spectrum showed signals at δ 7.84 (s, 2H, deuterium oxide exchangeable) for NH_2 protons, 1.63, 1.21 for the two

Scheme 2



methyl protons. Also, the MS spectrum of **(6c)** showed the molecular ion peak at *m/z* = 492.

The formation of **(6a-f)** can be suggested by the possible mechanism illustrated in (Scheme 4). First, the nucleophilic addition of 2-mercaptoacetic acid **5** to malononitrile **2** yielded the intermediate **(C)**, which further gave thiazolinone derivatives **(D)** via intramolecular dehydration. Then, the intermediate **(D)** underwent

Scheme 3

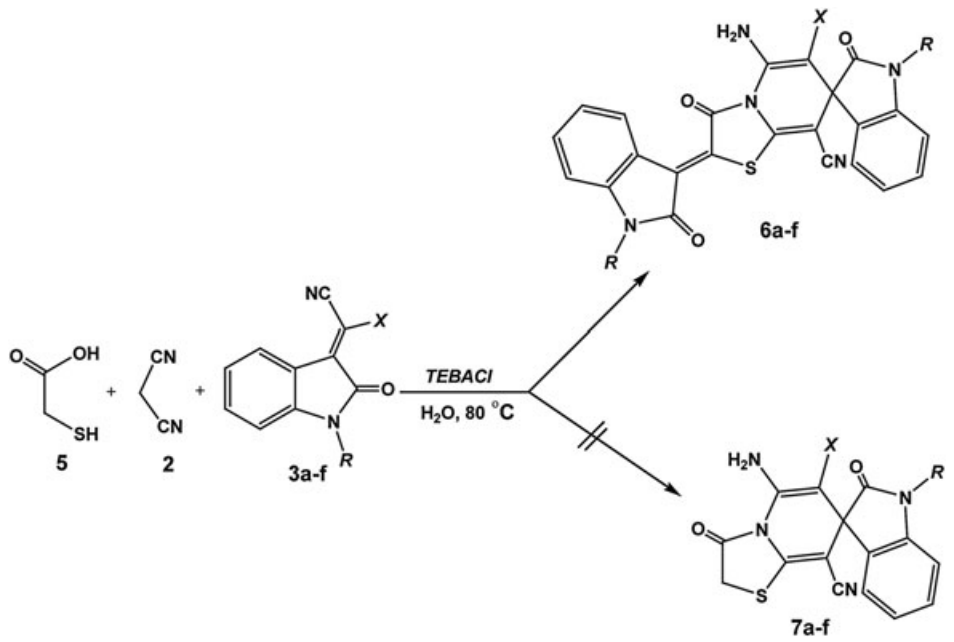


Table 3

Synthesis of 2-(oxoindolin-3"-ylidine)-spiro{thiazolo[3,2-*a*]pyridine-7,3′-indolines} in aqueous medium at 80°C and *TEBACl* (20 mol %).

Entry	R	X	Time (h)	Yield (%)[a]	Yield (%)[b]	m.p (°C)
6a	H	CN	3	41	82	255–256
6b	H	$CO_2C_2H_5$	4	38	80	241–243
6c	CH_3	CN	5	46	91	285–287
6d	CH_3	$CO_2C_2H_5$	4	43	84	234–235
6e	C_2H_5	CN	5	48	86	290–292
6f	C_2H_5	$CO_2C_2H_5$	5	39	83	271–273

[a]The isolated yield when the reaction of **5**, **2**, and **3a-f** with molar ratio of 1: 1: 1.
[b]The isolated yield when the reaction of **5**, **2**, and **3a-f** with molar ratio of 1: 1: 2.

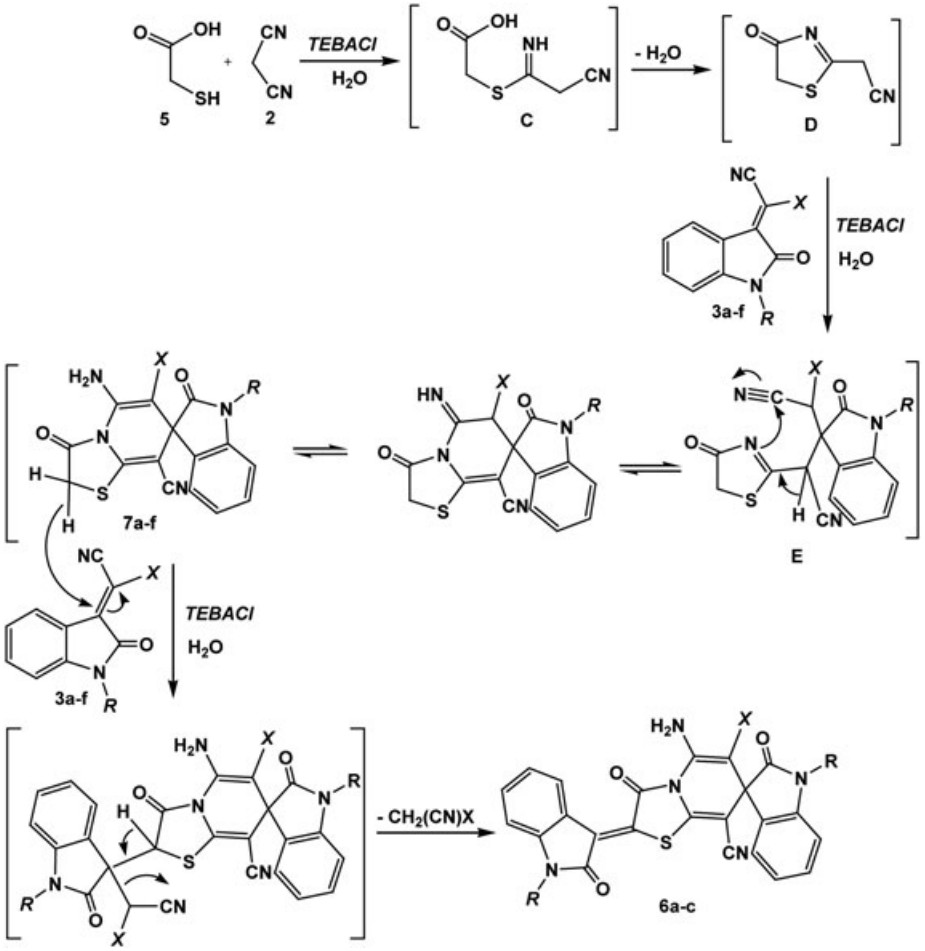
Michael addition with 2-oxoindoline-3-ylidines **3a-f** to give an open-chain intermediate **(E)**, which was subsequently intramolecular cyclized and isomerized to afford the expected product **(7a-f)** which underwent Michael addition with another molecule of **(3a-f)** to afford the desired product **(6a-f)** via elimination of $CH_2(CN)X$ molecule (X= CN, $CO_2C_2H_5$).

In summery, we developed an efficient three-component reaction of 2-mercaptoaniline and/or mercaptoacetic acid, malononitrile, and 2-oxoindoline-3-ylidines for the synthesis of some new spiro{pyrido[2,1-*b*]benzothiazole-3,3′-indoline} and/or spiro{thiazolo[3,2-*a*]pyridine-7,3′-indoline} derivatives respectively, using water as reaction medium. This new protocols have the advantages of simple operation, higher yields, low cost and is an environmentally benign procedure.

EXPERIMENTAL

The time required for completion of each reaction was monitored by TLC. All melting points are uncorrected and were measured on a

Scheme 4



Gallen Kamp apparatus. The IR spectra were recorded on a Shimadzu 470 IR spectrometer (potassium bromide) ύ cm^{-1}. The ^1H, ^{13}CNMR spectra were measured on Varian EM-200, 90 MHz spectrometer with TMS as internal standard and (dimethyl sulfoxide d_6) as solvent. Mass spectra were determined on a Jeol-600 spectrometer. Elemental analyses (C, H, N, and S) were performed on an elemental analysis system GmbH varioel $V_{2.3}$, the results were found to be in good agreement with the calculated values.

Spiro{pyrido[2,1-*b*]benzothiazole-3,3′-indolines} (4a-f). ***General procedure.*** A mixture of 2-mercaptoaniline 1 (1.25 g, 10 mmol), malononitrile 2 (0.66 g, 10 mmol), 2-oxoindoline-3-ylidines (3a-f) (10 mmol), and triethylbenzylammonium chloride (0.45 g, 20 mol %) in water (20 mL) was stirred at 80°C for 3–6 h (table 2). After completion of the reaction (TLC), the reaction mixture was cooled to room temperature. The solid product was filtered off and washed with water (3 −; 10 mL) and cold ethanol (2 −; 10 mL) to give (4a-f) (TLC pure) without further purification.

1-Amino-2,4-dicyanospiro{pyrido[2,1-b]benzothiazole-3,3′-indoline}-2′-one (4a). Shiny yellow crystals, yield 3.54 g (96 %); IR: ύ = 3320 (NH), 3280-3200 (NH_2), 2200 (CN), 1710 (C═O) cm^{-1}; ^{1}HNMR: δ = 10.90 (s, 1H, NH, deuterium oxide exchangeable), 7.90-6.91 (m, 8H, Ph-H), 6.81 (s, 2H, NH_2, deuterium oxide exchangeable) ppm; MS: *m/z* (%) = 369 (M^+, 2.4), 302 (100), 275 (17), 104 (20). *Anal*. Calcd. for $C_{20}H_{11}N_5OS$: C, 65.03; H, 3.00; N, 18.96; S, 8.68. Found: C, 64.99; H, 2.89; N, 18.91; S, 8.59.

Ethyl 1-amino-4-cyano-2′-oxospiro{pyrido[2,1-b]benzothiazole-3,3′-indoline}-2-carboxylate (4b). Pale brown crystals, yield 3.91 g (94 %); IR: ύ = 3390 (NH), 3250-3200 (NH_2), 2200 (CN), 1705 (C═O) cm^{-1}; ^{1}H-NMR: δ = 11.06 (s, 1H, NH, deuterium oxide exchangeable), 10.43 (s, 2H, NH_2, deuterium oxide exchangeable), 8.60-6.80 (m, 8H, Ph-H), 3.80 (q, 2H, CH_2, *J* = 8.2 Hz), 0.77 (t, 3H, CH_3, *J* = 8.2 Hz) ppm; ^{13}C-NMR: δ = 12.9 (CH_3), 59.3 (CH_2), 81.1 (spiro C), 109.1 (2C), 116.4 (CH), 116.6 (CH), 121.9 (CH), 123.2 (CH), 123.6 (CH), 124.7 (CH), 126.8 (CH), 128.4 (CH), 135.6 (CN), 136.9 (2C), 140.9 (2C), 151.9 (2C), 167.7 (C═O), 178.6 (C═O) ppm; MS: *m/z* (%) = 416 (M^+, 1), 343 (2), 302 (100), 174 (32). *Anal*. Calcd. for $C_{22}H_{16}N_4O_3S$: C, 63.45; H, 3.87; N, 13.45; S, 7.70. Found: C, 63.34; H, 3.82; N, 13.36; S, 7.66.

1-Amino-2,4-dicyano-1′-methylspiro{pyrido[2,1-b]benzothiazole-3,3′-indoline}-2′-one (4c). Pale brown crystals, yield 3.60 g (94 %); IR: ύ = 3400-3300 (NH_2), 2200 (CN), 1700 (C═O) cm^{-1}; ^{1}HNMR: δ = 7.95-7.15 (m, 8H, Ph-H), 6.81 (s, 2H, NH_2, deuterium oxide exchangeable), 3.40 (s, 3H, CH_3) ppm; MS: m/z (%) = 383 (M^+, 9), 315 (100), 288 (40), 174 (53)). *Anal*. Calcd. for $C_{21}H_{13}N_5OS$: C, 65.78; H, 3.42; N, 18.27; S, 8.36. Found: C, 65.72; H, 3.38; N, 18.23; S, 8.32.

Ethyl 1-amino-4-cyano-1′-methyl-2′-oxospiro{pyrido[2,1-b]benzothiazole-3,3′-indoline}-2-carboxylate (4d). Pale brown crystals, yield 3.99 g (93 %); IR: ύ = 3400-3300 (NH_2), 2200 (CN), 1705 (C═O) cm^{-1}; ^{1}HNMR: δ = 7.85-6.86 (m, 8H, Ph-H), 6.82 (s, 2H, NH_2, deuterium oxide exchangeable), 3.80 (q, 2H, CH_2, *J* = 8.8 Hz), 3.39 (s, 3H, CH_3), 0.85 (t, 3H, CH_3, *J* = 8.8 Hz) ppm; MS: m/z (%) = 430 (M^+, 3), 357 (19), 316 (100). *Anal*. Calcd. for $C_{23}H_{18}N_4O_3S$: C, 64.17; H, 4.21; N, 13.01; S, 7.45. Found: C, 64.00; H, 4.17; N, 12.94; S, 7.32.

1-Amino-2,4-dicyano-1′ethylspiro{pyrido[2,1-b]benzothiazole-3,3′-indoline}-2′-one (4e). Brown crystals, yield 3.89 g (98 %); IR: ύ = 3400-3305 (NH_2), 2200 (CN), 1695 (C═O) cm^{-1}; ^{1}HNMR: δ = 7.91-7.15 (m, 8H, Ph-H), 6.90 (s, 2H, NH_2, deuterium oxide exchangeable), 3.78 (q, 2H, CH_2, *J* = 6.2 Hz), 1.16 (t, 3H, CH_3, *J* = 6.2 Hz) ppm; ^{13}CNMR: δ = 12.4 (CH_3), 34.6 (CH_2), 50.4 (spiro C), 63.9 (C), 76.5 (C), 109.2 (2C), 116.2 (CH), 116.7 (CH), 117.1 (CH), 123.3 (CH), 123.4 (CH), 124.9 (CH), 125.4 (CH), 127.0 (CH), 130.1 (CN), 131.2 (CN), 137.0 (C), 141.3 (C), 151.1 (C), 154.2 (C), 174.6 (C═O) ppm; MS: *m/z* (%) = 397 (M^+, 7), 331 (75), 302 (37), 174 (100). *Anal*. Calcd. for $C_{22}H_{15}N_5OS$: C, 66.48; H, 3.80; N, 17.62; S, 8.07. Found: C, 66.36; H, 3.74; N, 17.50; S, 7.95.

Ethyl 1-amino-4-cyano-1′-ethyl-2′-oxospiro{pyrido[2,1-b]benzothiazole-3,3′-indoline}-2-carboxylate (4f). Pale brown crystals, yield 4.21 g (95%); IR: ύ = 3250-3125 (NH_2), 2200 (CN), 1700 (C═O) cm^{-1}; ^{1}HNMR: δ = 8.09 (s, 2H, NH_2, deuterium oxide exchangeable), 7.96-7.05 (m, 8H, Ph-H), 3.86 (q, 2H, O$\underline{CH_2}CH_3$, *J* = 8.4 Hz), 3.73 (q, 2H, N-$\underline{CH_2}CH_3$, *J* = 6.8 Hz), 1.35 (t, 3H, $\underline{CH_3}CH_2O$, *J* = 8.4 Hz), 0.81 (t, 3H, $\underline{CH_3}CH_2N$, *J* = 6.8 Hz) ppm; MS: *m/z* (%) = 444 (M^+, 7), 371 (53), 331 (100), 261 (25). *Anal*. Calcd. for $C_{24}H_{20}N_4O_3S$: C, 64.85; H, 4.54; N, 12.60; S, 7.21. Found: C, 64.80; H, 4.45; N, 12.46; S, 7.11.

2-(Oxoindolin-3''-ylidene)-spiro{thiazolo[3,2-a]pyridine-7,3′-indolines} (6a-f). ***General procedure***. A mixture of mercaptoacetic acid **5** (0.92 g, 10 mmol), malononitrile **2** (0.66 g, 10 mmol), 2-oxoindoline-3-ylidines **(3a-f)** (20 mmol), and triethylbenzylammonium chloride (0.45 g, 20 mol %) in water (20 mL) was stirred at 80°C for 3–5 h (table 2). After completion of the reaction (TLC), the reaction mixture was cooled to room temperature. The solid product was filtered off and washed with water (3 −; 10 mL) and cold ethanol (2 −; 10 mL) to give **(6a-f)** (TLC pure) without further purification.

5-Amino-6,8-dicyano-2-(oxoindolin-3''-ylidene)-spiro{thiazolo[3,2-a]pyridine-7,3′-indoline}-2′,3-dione (6a). Brown crystals, yield 3.80 g (82 %); IR: ύ = 3400 (NH), 3300-3200 (NH_2), 2200 (CN), 1710 (C═O), 1700 (C═O) cm^{-1}; ^{1}HNMR: δ = 11.66 (s, 1H, NH, deuterium oxide exchangeable), 10.85 (s, 1H, NH, deuterium oxide exchangeable), 8.20-6.96 (m, 8H, Ph-H), 6.55 (s, 2H, NH_2, deuterium oxide exchangeable) ppm; MS: m/z (%) = 464 (M^+, 5), 268 (100), 142 (21). *Anal*. Calcd. for $C_{24}H_{12}N_6O_3S$: C, 62.06; H, 2.60; N, 18.09; S, 6.90. Found: C, 61.93; H, 2.49; N, 18.00; S, 6.75.

Ethyl 5-amino-8-cyano-2′,3-dioxo-2-(oxoindolin-3''-ylidene)-spiro{thiazolo[3,2-a]pyridine-7,3′-indoline}-6-carboxylate (6b). Brown crystals, yield 4.08 g (80 %); IR: ύ = 3300-3200 (NH_2), 2200 (CN), 1710 (C═O), 1700 (C═O), 1640 (C═N) cm^{-1}; ^{1}HNMR: δ = 11.18 (s, 1H, NH, deuterium oxide exchangeable), 10.62 (s, 1H, NH, deuterium oxide exchangeable), 8.32-6.55 (m, 8H, Ph-H), 5.15 (s, 2H, NH_2, deuterium oxide exchangeable), 4.18 (q, 2H, CH_2, *J* = 10.6 Hz), 1.23 (t, 3H, CH_3, *J* = 10.6 Hz) ppm; ^{13}C-NMR: δ = 12.1 (CH_3), 52.1 (CH_2), 82.5 (spiro C), 99.3 (C), 109.9 (C), 121.5 (2CH), 122.8 (2CH), 125.1 (CH), 126.6 (CH), 127.2 (CH), 128.3 (CH), 129.8 (CN), 132.2 (C), 132.9 (C), 134.5 (C), 138.6 (C), 139.4 (C), 141.8 (C), 146.1 (C), 150.2 (C), 165.4 (C=O), 167.7 (C=O), 170.7 (C═O), 178.6 (C═O) ppm; MS: *m/z* (%) = 511 (M^+, 2), 466 (30), 268 (100). *Anal*. Calcd. for $C_{26}H_{17}N_5O_5S$: C, 61.05; H, 3.35; N, 13.69; S, 6.27. Found: C, 60.88; H, 3.21; N, 13.43; S, 6.39.

5-Amino-6,8-dicyano-1′-methyl-2-(1''-methyloxoindolin-3''-ylidene)-spiro{thiazolo[3,2-a]pyridine-7,3′-indoline}-2′,3-dione (6c). Reddish brown crystals, yield 4.47 g (91 %); IR: ύ = 3400-3300 (NH_2), 2200 (CN), 1705 (C═O), 1695 (C═O), 1640 (C═N) cm^{-1}; ^{1}HNMR: δ = 8.66 (d, 1H, CH arom.), 7.84 (s, 2H, NH_2, deuterium oxide exchangeable), 7.71-6.79 (m, 7H, Ph-H), 3.64 (s, 3H, CH_3), 1.63 (s, 3H, CH_3) ppm; ^{13}CNMR: δ = 12.9

(CH_3), 14.1 (CH_3), 77.6 (spiro C), 93.8 (C), 109.5 (C), 121.6 (2CH), 122.2 (2CH), 125.3 (CH), 126.6 (CH), 127.3 (CH), 128.7 (CH), 129.4 (CN), 130.6 (CN), 131.6 (C), 133.2 (C), 134.5 (C), 139.3 (C), 140.2 (C), 141.8 (C), 146.7 (C), 151.9 (C), 165.4 (C═O), 167.7 (C═O), 170.7 (C═O) ppm; MS: *m/z* (%) = 492 (M^+, 9), 395 (51), 249 (67), 211 (47), 189 (100). *Anal*. Calcd. for $C_{26}H_{16}N_6O_3S$: C, 63.41; H, 3.27; N, 17.06; S, 6.51. Found: C, 63.17; H, 3.02; N, 16.82; S, 6.26.

Ethyl 5-amino-8-cyano-1′-methyl-2′,3-dioxo-2-(1′′-methyloxoindolin-3′′-ylidene)-spiro{thiazolo[3,2-a]pyridine-7,3′-indoline}-6-carboxylate (6d). Brown crystals, yield 4.52 g (84 %); IR: υ = 3400-3300 (NH_2), 2200 (CN), 1705 (C═O), 1696 (C═O), 1640 (C═N) cm^{-1}; ^{1}HNMR: δ = 8.25-6.61 (m, 8H, Ph-H), 6.24 (s, 2H, NH_2, deuterium oxide exchangeable), 4.08 (q, 2H, CH_2, *J* = 10.2 Hz), 3.25 (s, 3H, CH_3, *J* = 10.2 Hz), 2.92 (s, 3H, CH_3), 0.97 (t, 3H, CH_3) ppm; MS: *m/z* (%) = 539 (M^+, 8), 494 (28), 466 (100). *Anal*. Calcd. for $C_{28}H_{21}N_5O_5S$: C, 62.33; H, 3.92; N, 12.98; S, 5.94. Found: C, 62.08; H, 3.85; N, 12.71; S, 5.82.

5-Amino-6,8-dicyano-1′-ethyl-2-(1′′-ethyloxoindolin-3′′-ylidene)-spiro{thiazolo[3,2-a]pyridine-7,3′-indoline}-2′,3-dione (6e). Dense brown crystals, yield 4.47 g (86 %); IR: υ = 3400-3300 (NH_2), 2200 (CN), 1710 (C═O), 1695 (C═O), 1645 (C═N) cm^{-1}; ^{1}HNMR: δ = 8.62-6.91 (m, 8H, Ph-H), 6.28 (s, 2H, NH_2, deuterium oxide exchangeable), 3.83 (q, 2H, CH_2, *J* = 8.0 Hz), 3.35 (q, 2H, CH_2, *J* = 7.6 Hz), 1.11 (t, 3H, CH_3, *J* = 8.0 Hz), 0.86 (t, 3H, CH_3, *J* = 7.6 Hz) ppm; MS: *m/z* (%) = 520 (M^+, 5), 494 (16), 423 (45), 217 (100). *Anal*. Calcd. for $C_{28}H_{20}N_6O_3S$: C, 64.60; H, 3.87; N, 16.14; S, 6.16. Found: C, 64.42; H, 3.69; N, 15.91; S, 6.11.

Ethyl 5-amino-8-cyano-1′-ethyl-2′,3-dioxo-2-(1′′-ethyloxoindolin-3′′-ylidene)-spiro{thiazolo[3,2-a]pyridine-7,3′-indoline}-6-carboxylate (6f). Brown crystals, yield 4.70 g (83%); IR: υ = 3400-3200 (NH_2), 2200 (CN), 1705 (C═O), 1698 (C═O), 1640 (C═N) cm^{-1}; ^{1}HNMR: δ = 8.64 (d, 1H, CH arom.), 8.25 (s, 2H, NH_2, deuterium oxide exchangeable), 7.98-6.88 (m, 7H, Ph-H), 4.12 (q, 2H, CH_2, *J* = 10.4 Hz), 3.93 (q, 2H, CH_2, *J* = 8.2 Hz), 3.65 (q, 2H, CH_2, *J* = 7.2 Hz), 1.39 (t, 3H, CH_3, *J* = 10.4 Hz), 1.02 (t, 3H, CH_3, *J* = 8.2 Hz), 0.88 (t, 3H, CH_3, *J* = 7.2 Hz) ppm; MS: *m/z* (%) = 567 (M^+, 3), 522 (45), 494 (58), 296 (100). *Anal*. Calcd. for $C_{30}H_{25}N_5O_5S$: C, 63.48; H, 4.44; N, 12.34; S, 5.65. Found: C, 63.19; H, 4.35; N, 12.22; S, 5.45.

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