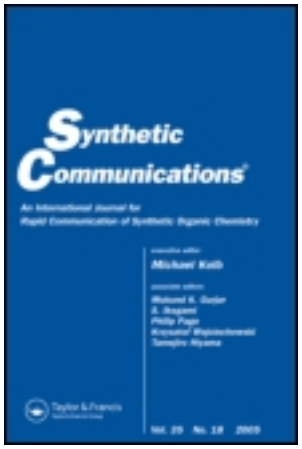

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Simple and Efficient Method for Three-Component Synthesis of Spirooxindoles in Aqueous and Solvent-Free Media

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SIMPLE AND EFFICIENT METHOD FOR THREE-COMPONENT SYNTHESIS OF SPIROOXINDOLES IN AQUEOUS AND SOLVENT-FREE MEDIA

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A clean, simple, one-pot, three-component synthesis of some important spirooxindole derivatives in the presence of tetrabutylammonium bromide (TBAB) was carried out under green and environmentally benign conditions.

Keywords: Aqueous; multicomponent; spirooxindole; TBAB

INTRODUCTION

Multicomponent reactions (MCRs) have attracted the attention of synthetic organic chemists for building highly functionalized organic molecules and pharmacologically important heterocyclic compounds.[1,2] The indole framework is common in a wide variety of pharmacologically and biologically active compounds.[3] Furthermore, it has been reported that sharing the indole 3-carbon atom in the formation of spiroindoline derivatives highly enhances the biological activity.[4,5] The spirooxindole system is the core structure of some pharmacological agents and natural alkaloids.[6–9]

Organic reactions in water without using harmful organic solvents being focused on today, especially in our environmentally conscious society.[10–13] To the best of our knowledge,[14–18] there have been a few reports about the synthesis of spirooxindole derivatives in an aqueous medium. As a consequence of our interest in the aqueous organic syntheses and our continued work on the synthesis of heterocyclic compounds,[19–21] guided by the observation that the presence of two or more different heterocyclic moieties in a single molecule often enhances the biological profile remarkably, we investigated a three-component reaction of isatin, molononitrile or ethyl cyanoacetate, and CH- acids (1,3-dicarbonyl compounds) to afford a series of spirooxindole derivatives in water or solvent-free conditions mediated by the TBAB (tetrabutyl ammonium bromide). In recent years, TBAB has been used as an extremely useful catalyst in various organic transformations.[22–25] TBAB is also

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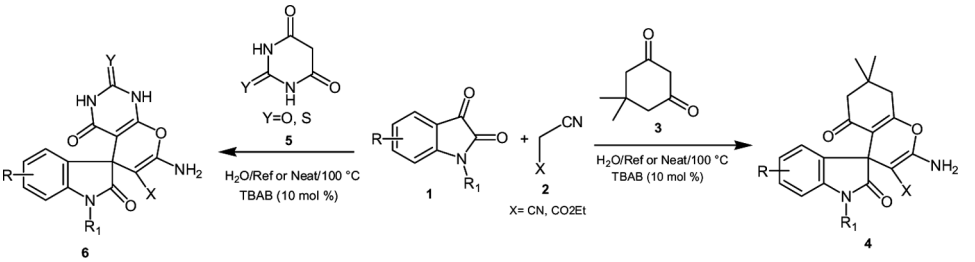
an inexpensive, available catalyst and has inherent properties such as environmental compatibility, greater selectivity, operational simplicity, noncorrosive nature, and ease of reusability.

RESULTS AND DISCUSSION

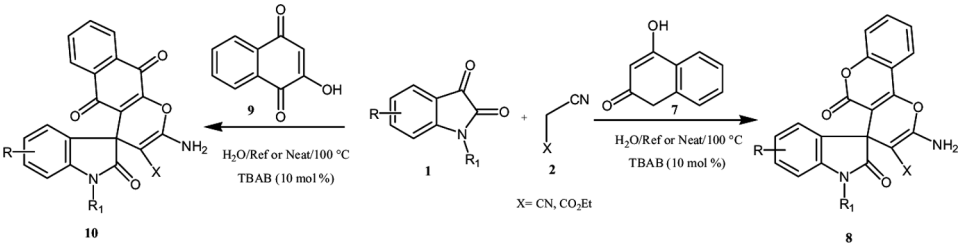
In our initial study, the evaluation of various conditions was studied for the synthesis of spirooxindole derivatives. After some preliminary experiments, it was found that a mixture of isatin, malononitrile, and dimedone in water in the presence of a catalytic amount of TBAB could afford 2-amino-5-oxo-7,7-dimethyl spiro[(4H)-5,6,7,8-tetrahydrochromene-4,3′-(3′H)-indol]-(1′H)-2′-one-carbonitrile in excellent yield (**4a**, Scheme 1). The procedure was simple and easy to operate. We have also investigated the synthesis of our target compounds under solvent-free neat conditions. Interestingly, the reaction was carried out for 40 min, and 90% of pure compound was obtained.

This method works with a wide variety of substrates. A series of substituted isatin and different CH- acids were used in this reaction (Schemes 1 and 2).

Additionally, the reaction with malononitrile or ethyl cyanoacetate also proceeded smoothly. Thereafter, different substituted spirooxindole derivatives were prepared successfully in water and under solvent-free neat conditions. Some of these derivatives are novel. The results are listed in Table 1. In this study, the products were characterized by melting point, infrared (IR), ^{1}H NMR, and ^{13}C NMR (some selected products) spectral data; as well as by elemental analyses.



Scheme 1. Synthesis of spirooxindoles from 1,3-dicarbonyl compounds promoted by TBAB.



Scheme 2. TBAB-catalyzed synthesis of spirooxindoles from CH- acids.

Table 1. Synthesis of spirooxindole derivatives in aqueous and solvent-free media

						Method A		Method B	
Entry	R	R_1	X	Y	Product	Time (min)	Yield (%)[a]	Time (min)	Yield (%)[a]
1	H	H	CN	—	**4a**	30	92	40	90
2	5-Br	H	CN	—	**4b**	40	89	45	83
3	H	CH_3	CN	—	**4c**	25	93	40	90
4	H	CH_2Ph	CN	—	**4d**	45	87	45	83
5	H	H	CO_2Et	—	**4e**	45	88	50	85
6	H	H	CN	O	**6a**	35	90	50	84
7	H	H	CO_2Et	O	**6b**	40	89	50	85
8	H	H	CN	S	**6c**	40	88	—	—[b]
9	H	H	CN	—	**8a**	40	90	60	88
10	5-Br	H	CN	—	**8b**	60	87	60	82
11	H	CH_3	CN	—	**8c**	50	91	60	83
12	H	CH_2Ph	CN	—	**8d**	75	88	75	79
13	H	H	CO_2Et	—	**8e**	60	86	75	80
14	H	CH_3	CO_2Et	—	**8f**	60	83	75	78
15	H	H	CN	—	**10a**	55	85	90	81
16	5-Br	H	CN	—	**10b**	75	82	90	80
17	H	CH_3	CN	—	**10c**	60	85	90	85
18	H	CH_2Ph	CN	—	**10d**	90	80	100	78
19	H	H	CO_2Et	—	**10e**	90	81	100	77
20	5-Br	H	CO_2Et	—	**10f**	90	80	100	78

[a]Isolated yields.
[b]A complex product was obtained.

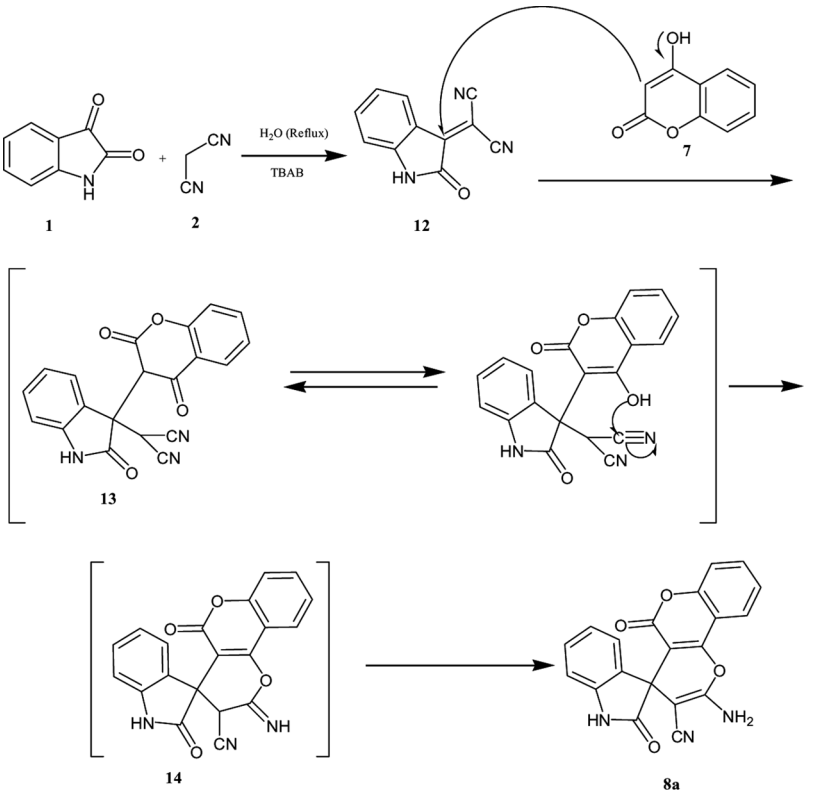
The proposed mechanism for the synthesis of spirooxindol derivative **8a** is described in Scheme 3. In this process, the isatin **1** first condenses with malononitrile **2** to afford isatylidene malononitrile derivative **12** in the presence of TBAB. This step is regarded as a fast Knoevenagel condensation. Then, **12** is attacked via Michael addition of CH- acids such as 4-hydroxy coumarine **7** to give the intermediate **13** followed by the cycloaddition of hydroxyl group to the cyano moiety to form the desired product **8a** (Scheme 3).

CONCLUSION

In conclusion, we have described a simple and efficient three-component reaction involving isatin, activated methylene reagent, and CH- acids (1,3-dicarbonyl compounds) for the synthesis of a series of spirooxindole derivatives, some of which are novel, in water and solvent-free conditions. Further merits of this method are its generality, short reaction times, good yields, simple operation, environmental compatibility, and easy workup.

EXPERIMENTAL

Melting points were obtained in open capillaries on an Electrothermal 5000 digital apparatus and are not corrected. IR spectra were recorded on a Galaxy series Fourier transform FT–IR 5000 spectrometer. NMR spectra were recorded on a



Scheme 3. The plausible mechanism for the synthesis of spirooxindoles.

Brucker-300-MHz spectrometer in dimethylsulfoxide (DMSO-d_6) with tetramethylsilane (TMS) as an internal standard. Microanalyses were performed on an elemental analyzer (Elemental, Vario EL III). Progress of the reactions was followed by thin-layer chromatography (TLC) using n-hexane/EtOAc (3:1 v/v) as an eluent.

Typical Procedure for the Synthesis of Spirooxindols

Method A (in water). In a typical reaction, a mixture of isatin (1 mmol), malononitrile, or ethyl cyanoacetate (1 mmol): dimedone or other CH- acids (1 mmol): and TBAB (10 mol%) in refluxing water (5 ml) was stirred for an appropriate time. After completion, monitored by TLC, the reaction mixture was allowed to cool to room temperature. The solid was filtered off, washed with water (2×10 ml), and recrystallized from EtOH/H_2O (3:1) to afford the product.

Method B (solvent-free). In this procedure, the components as mentioned previously were mixed thoroughly and heated in an oil bath maintained at 100 °C for the appropriate time. The reaction mixture was then cooled to room temperature. The mixture was washed with water (2×10 ml) and recrystallized from EtOH/H_2O (3:1) to afford the pure product.

Physical and Spectroscopic Data for Selected Compounds

2-Amino-5-oxo-7,7-dimethyl-spiro[(4H)-5,6,7,8-tetrahydrochromene-4,3′-(3′H)-indol]-(1′H)-2′-one-carbonitrile (4a). Mp 296–298 °C; IR (KBr) (ν_{max}): 3311, 3144, 2960, 2193, 1724, 1682, 1656, 1604, 1471, 1348, 1222, 1055, 764, 615 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δH: 10.43 (s, 1H, NH), 7.26 (br s, 2H, NH_2), 7.18 (t, 1H, $J = 7.6$ Hz, ArH), 7.01 (d, 1H, $J = 6.7$ Hz, ArH), 6.92 (t, 1H, $J = 6.8$ Hz, ArH), 6.82 (d, 1 Hz, $J = 7.6$ Hz, ArH), 2.52–2.65 (m, 2H, CH_2), 2.21 (d, 1H, $J = 16.0$ Hz, CH), 2.12 (d, 1H, $J = 16.0$ Hz, CH), 1.06 (s, 3H, CH_3), 1.02 (s, 3H, CH_3) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δC 195.4, 178.5, 164.3, 159.2, 142.4, 134.8, 128.6, 123.4, 122.1, 117.8, 111.2, 109.7, 57.9, 50.4, 47.2, 32.4, 28.0, 27.4, 26.7 ppm. Anal. calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53%. Found: C, 68.48; H, 5.27; N, 12.71%.

2-Amino-5-oxo-7,7-dimethyl-spiro[(4H)-5,6,7,8-tetrahydrochromene-4,3′-(3′H)-5′-bromo-indol]-(1′H)-2′-one-carbonitrile (4b). Mp >300 °C; IR (KBr) (ν_{max}): 3367, 3288, 3159, 2958, 2195, 1728, 1680, 1655, 1602, 1475, 1350, 1222, 1057, 810, 619 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δH 10.59 (s, 1H, NH), 7.37 (s, 2H, NH_2), 7.24–7.34 (m, 2H, ArH), 6.79 (d, 1H, $J = 8.1$ Hz, ArH), 2.53–2.66 (m, 2H, CH_2), 2.12–2.24 (m, 2H, CH_2), 1.05 (s, 3H, CH_3), 1.02 (s, 3H, CH_3) ppm; Anal. calcd. for $C_{19}H_{16}BrN_3O_3$: C, 55.09; H, 3.89; N, 10.14%. Found: C, 55.31; H, 3.98; N, 10.36%.

2-Amino-5-oxo-7,7-dimethyl-spiro[(4H)-5,6,7,8-tetrahydrochromene-4,3′-(3′H)-1′-methyl-indol]-(1′H)-2′-one-carbonitrile (4c). Mp 258–260 °C (254–256 °C);[18] IR (KBr) (ν_{max}): 3375, 3286, 3144, 2960, 2193, 1714, 1666, 1602, 1467, 1350, 1221, 740 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δH 7.34 (s, 2H, NH_2), 7.26–7.31 (m, 2H, ArH), 6.98–7.09 (m, 3H, ArH), 3.16 (s, 3H, CH_3), 2.53–2.65 (m, 2H, CH_2), 2.19 (d, 1H, $J = 16.0$ Hz, CH), 2.11 (d, 1H, $J = 16.0$ Hz, CH), 1.05 (s, 3H, CH_3), 1.02 (s, 3H, CH_3) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δC 195.3, 177.0, 164.7, 159.3, 144.01, 134.0, 128.8, 123.2, 122.9, 117.0, 111.1, 108.6, 57.4, 50.3, 46.9, 32.4, 28.0, 27.5, 26.8 ppm. Anal. calcd. for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03%. Found: C, 69.17; H, 5.47; N, 12.05%.

2-Amino-5-oxo-7,7-dimethyl-spiro[(4H)-5,6,7,8-tetrahydrochromene-4,3′-(3′H)-1′-benzyl-indol]-(1′H)-2′-one-carbonitrile (4d). Mp 271–273 °C (269–271 °C);[18] IR (KBr) (ν_{max}): 3385, 3321, 3205, 2962, 2197, 1716, 1660, 1601, 1467, 1352, 1219, 1051, 750 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δH 7.52 (d, 2H, $J = 7.1$ Hz, ArH), 7.38 (s, 2H, NH_2), 7.26–7.34 (m, 2H, ArH), 7.11–7.19 (m, 2H, ArH), 6.99 (t, 1H, $J = 7.4$ Hz, ArH), 6.72 (d, 1H, $J = 7.8$ Hz, ArH), 4.97 (d, 1H, $J = 16.2$ Hz, CH_2Ph), 4.90 (d, 1H, $J = 16.2$ Hz, CH_2Ph), 2.57–2.70 (m, 2H, CH_2), 2.25 (d, 1H, $J = 16.0$ Hz, CH), 2.16 (d, 1H, $J = 16.0$ Hz, CH), 1.08 (s, 3H, CH_3) 1.04 (s, 3H, CH_3) ppm. Anal. calcd. for $C_{26}H_{23}N_3O_3$: C, 73.39; H, 5.45; N, 9.88%. Found: C, 73.67; H, 5.58; N, 9.93%.

Ethyl 2-amino-5-oxo-7,7-dimethyl-spiro[(4H)-5,6,7,8-tetrahydrochromene-4,3′-(3′H)-indol]-(1′H)-2′-one-carboxylate (4e). Mp 232–235 °C; IR (KBr) (ν_{max}): 3371, 3180, 3113, 2960, 1714, 1689, 1650, 1601, 1741, 1348, 1226, 754 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δH 10.18 (s, 1H, NH), 7.90 (s, 2H, NH_2), 7.10

(t, 1H, $J = 7.5$ Hz, ArH), 6.97 (d, 1H, $J = 7.2$ Hz, ArH), 6.87 (t, 1H, $J = 7.2$ Hz, ArH), 6.72 (d, 1H, $J = 7.5$ Hz, ArH), 3.64 (q, 2H, $J = 7.8$ Hz, CH_2), 2.45–2.58 (m, 2H, CH_2), 2.06–2.36 (m, 2H, CH_2), 1.07 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 0.99 (t, 3H, $J = 7.8$ Hz, CH_3) ppm. Anal. calcd. for $C_{21}H_{22}N_2O_5$: C, 65.96; H, 5.80; N, 7.33%. Found: C, 66.19; H, 5.89; N, 7.47%.

2-Amino-5,7-dioxo-spiro[(3′H)-indol-3′,4,4(H)-5,6,7,8-tetrahydropyrano (2,3-d)pyrimidine]-(1′H)-2′-one-3-carbonitrile (6a). Mp 273–275 °C (lit. 275–276 °C);[18] IR (KBr) (ν_{max}): 3404, 3337, 3306, 3146, 2202, 1724,1672, 1620, 1531, 1392, 1330, 1111, 754 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δH 12.32 (br s, 1H, NH), 11.15 (s, 1H, NH), 10.51 (s, 1H, NH), 7.40 (s, 2H, NH_2), 7.15–7.22 (m, 2H, ArH), 6.94 (t, 1H, $J = 7.5$ Hz, ArH), 6.82 (d, 1H, $J = 7.5$ Hz, ArH) ppm. Anal. calcd. for $C_{15}H_9N_5O_4$: C, 55.73; H, 2.81; N, 21.66%. Found: C, 55.37; H, 2.85; N, 21.32%.

Ethyl 2-amino-5,7-dioxo-spiro[(3′H)-indol-3′,4,4(H)-5,6,7,8-tetrahydro-pyrano(2,3-d)pyrimidine]-(1′H)-2′-one-3-carboxylate (6b). Mp 207–209 °C. IR (KBr) (ν_{max}): 3618, 3495, 3321, 3202, 2980, 1720, 1695, 1682, 1616, 1471, 1327, 1253, 1118, 752 $c^{m^{-1}}$; ^{1}H NMR (300 MHz, DMSO-d_6): δH 12.20 (br s, 1H, NH), 11.00 (s, 1H, NH), 10.27 (s, 1H, NH), 7.98 (s, 2H, NH_2), 7.09 (t, 1H, $J = 7.5$ Hz, ArH), 6.97 (d, 1H, $J = 7.0$ Hz, ArH), 6.80 (t, 1H, $J = 7.0$ Hz, ArH), 6.70 (d, 1H, $J = 7.5$ Hz, ArH), 3.37 (q, 2H, $J = 7.0$ Hz, CH_2), 0.80 (t, 3H, $J = 7.0$ Hz, CH_3) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δC 179.7, 167.9, 161.6, 159.0, 152.6, 149.5, 144.4, 135.7, 127.8, 123.2, 121.1, 108.6, 89.6, 76.6, 59.5, 46.6, 13.4 ppm. Anal. calcd. for $C_{17}H_{14}N_4O_6$: C, 55.14; H, 3.81; N, 15.13%. Found: C, 55.02; H, 3.85; N, 15.25%.

2-Amino-5-oxo-7-thioxo-spiro[(3′H)-indol-3′,4,4(H)-5,6,7,8-tetrahydro-pyrano(2,3-d)pyrimidine]-(1′H)-2′-one-3-carbonitrile (6c). Mp 243–245 °C (lit. 238–242 °C);[18] IR (KBr) (ν_{max}): 3520, 3427, 3317, 3159, 2202, 1693, 1656, 1616, 1570, 1400, 1342, 1132, 767 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δH 13.7 (br s, 1H, NH), 12.55 (s, 1H, NH), 10.58 (s, 1H, NH), 7.46 (s, 2H, NH_2), 7.14–7.31 (m, 2H, ArH), 6.94 (t, 1H, $J = 7.5$ Hz, ArH), 6.82 (d, 1H, $J = 7.6$ Hz, ArH) ppm. Anal. calcd. for $C_{15}H_9N_5O_3S$: C, 53.09; H, 2.67; N, 20.64; S, 9.45%. Found: C, 53.22; H, 2.72; N, 20.51; S, 9.68%.

2-Amino-5-oxo-spiro[(3′H)-indol-3′,4,4(H)-pyrano(2,3-c)chromen]-(1′H)-2′-one-3-carbonitrile (8a). Mp 293–295 °C (lit. 292–294 °C);[18] IR (KBr) (ν_{max}): 3358, 3298, 3198, 3043, 2206, 1712, 1674, 1602, 1471, 1357, 1219, 1082, 976, 738 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δH: 10.72 (s, 1H, NH), 7.98 (d, 1H, $J = 6.8$ Hz, ArH), 7.87 (t, 1H, $J = 6.9$ Hz, ArH), 7.71 (s, 2H, NH_2), 7.5 (m, 2H, ArH), 7.24 (d, 2H, $J = 6.2$ Hz, ArH), 6.97 (t, 1H, $J = 7.5$, ArH), 6.89 (d, 1H, $J = 7.8$ Hz, ArH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δC 177.6, 158.9, 158.7, 155.5, 152.5, 142.6, 134.1, 133.5, 129.4, 125.5, 124.6, 123.1, 122.5, 117.4, 117.1, 112.9, 109.9, 101.8, 57.4, 48.1 ppm. Anal. calcd. for $C_{20}H_{11}N_3O_4$: C, 67.23; H, 3.10; N, 11.76%. Found: C, 67.05; H, 3.23; N, 11.90%.

2-Amino-5-oxo-spiro[(3′H)-5′-bromo-indol-3′,4,4(H)-pyrano(2,3-c)chromen]-(1′H)-2′-one-3-carbonitrile (8b). Mp > 300 °C. IR (KBr) (ν_{max}): 3323, 3246, 3205, 2200, 1739, 1710, 1670, 1606 1473, 1359, 1221, 1085, 763 cm^{-1}; ^{1}H NMR (300 MHz,

DMSO-d_6): δH: 10.88 (s, 1H, NH), 7.97 (d, 1H, $J = 7.8$ Hz, ArH), 7.78 (s, 2H, NH_2), 7.72–7.89 (m, 1H, ArH), 7.52–7.60 (m, 3H, ArH), 7.42 (d, 1H, $J = 7.3$ Hz, ArH), 6.86 (d, 1H, $J = 8.2$ Hz, ArH) ppm. Anal. calcd. for $C_{20}H_{10}BrN_3O_4$: C, 55.07; H, 2.31; N, 9.63%. Found: C, 55.39; H, 2.43; N, 9.65%.

2-Amino-5-oxo-spiro[(3′H)-1′-methyl-indol-3′,4,4(H)-pyrano(2,3-c)chromen]-(1′H)-2′-one-3-carbonitrile (8c). Mp 283–285 °C (lit. 287–288 °C);[18] IR (KBr) (ν_{max}): 3599, 3470, 3288, 3169, 2210, 1710, 1676, 1606, 1471, 1356, 1099, 966, 758 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δH 7.98 (d, 1H, $J = 7.9$ Hz, ArH), 7.80 (m, 3H, NH_2 and ArH), 7.52–7.61 (m, 2H, ArH), 7.31–7.39 (m, 2H, ArH), 7.03–7.12 (m, 2H, ArH), 3.24 (s, 3H, N-CH_3) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δC 176.1, 159.0, 158.7, 155.6, 152.5, 144.0, 134.2, 132.6, 129.5, 125.5, 124.3, 123.2, 123.1, 117.2, 117.1, 112.9, 108.9, 101.7, 57.0, 47.6, 27.0 ppm. Anal. calcd. for $C_{21}H_{13}N_3O_4$: C, 67.92; H, 3.53; N, 11.32%. Found: C, 68.12; H, 3.71; N, 11.38%.

2-Amino-5-oxo-spiro[(3′H)-1′-benzyl-indol-3′,4,4(H)-pyrano(2,3-c)chromen]-(1′H)-2′-one-3-carbonitrile (8d). Mp 282–283 °C (lit. 277–279 °C)[18]; IR (KBr) (ν_{max}): 3408, 3340, 3190, 3061, 2198, 1709, 1670, 1608, 1465, 1354, 1167, 964, 754 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δH 7.99 (d, 1H, $J = 7.9$ Hz, ArH), 7.82 (s, 2H, NH_2), 7.79–7.85 (m, 1H, ArH), 7.50–7.62 (m, 4H, ArH), 7.22–7.38 (m, 5H, ArH), 7.03 (t, 1H, $J = 7.4$ Hz, ArH), 6.84 (d, 1H, $J = 7.8$ Hz, ArH), 5.05 (d, 1H, $J = 16.0$ Hz, CH_2Ph), 4.97 (d, 1H, $J = 16.0$ Hz, CH_2Ph) ppm. Anal. calcd. for $C_{27}H_{17}N_3O_4$: C, 72.48; H, 3.83; N, 9.39%. Found: C, 72.77; H, 3.65; N, 9.42%.

Ethyl 2-amino-5-oxo-spiro[(3′H)-indol-3′,4,4(H)-pyrano(2,3-c)chromen]-(1′H)-2′-one-3-carboxylate (8e). Mp 214–215 °C (lit. 210 °C);[17] IR (KBr) (ν_{max}): 3477, 3385, 3277, 3144, 3082, 1720, 1687, 1650, 1614, 1489, 1354, 1276, 1107, 1022, 758 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δH 10.46 (s, 1H, NH), 8.18 (s, 2H, NH_2), 8.05 (d, 1H, $J = 7.9$ Hz, ArH), 7.77 (t, 1H, $J = 8.4$ Hz, ArH), 7.585 (t, 1H, $J = 7.6$, ArH), 7.48 (d, 1H, $J = 8.4$ Hz, ArH), 7.15 (t, 1H, $J = 7.6$ Hz, ArH), 7.05 (d, 1H, $J = 7.3$ Hz, ArH), 6.83 (t, 1H, $J = 7.6$ Hz, ArH), 6.77 (d, 1H, $J = 7.6$ Hz, ArH), 3.80 (q, 2H, $J = 7.1$ Hz, CH_2), 0.86 (t, 3H, $J = 7.1$ Hz, CH_3) ppm. Anal. calcd. for $C_{22}H_{16}N_2O_6$: C, 65.34; H, 3.99; N, 6.93%. Found: C, 65.73; H, 4.08; N, 6.85%.

Ethyl 2-amino-5-oxo-spiro[(3′H)-1′-methyl-indol-3′,4,4(H)-pyrano(2,3-c) chromen]-(1′H)-2′-one-3-carboxylate (8f). Mp 253–255 °C (lit. 244 °C);[17] IR (KBr) (ν_{max}): 3367, 3281, 3209, 2982, 1730, 1685, 1662, 1610, 1491, 1346, 1278, 1103, 1022, 754 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δH 8.22 (s, 2H, NH_2), 8.07 (d, 1H, $J = 7.8$ Hz, ArH), 7.46–7.63 (m, 3H, ArH), 7.26 (t, 1H, $J = 7.6$ Hz, ArH), 7.12 (d, 1H, $J = 7$ Hz, ArH), 6.90–6.98 (m, 2H, ArH), 3.75 (q, 2H, $J = 7.1$ Hz, Hz, CH_2), 3.20 (s, 2H, N-CH_3), 0.79 (t, 3H, $J = 7.1$ Hz, CH_3) ppm. Anal. calcd. for $C_{23}H_{18}N_2O_6$: C, 66.02; H, 4.34; N, 6.70%. Found: C, 66.48; H, 4.51; N, 6.77%.

2-Amino-5,10-dioxo-spiro[(3′H)-indol-3′,4,4(H)-benzo(g)chromen]-(1′H)-2′-one-3-carbonitrile (10a). Mp 250 °C (dec.). IR (KBr) (ν_{max}): 3447, 3346, 3067, 2206, 1732, 1668, 1593, 1469, 1411, 1342, 1201, 983, 754, 719 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δH 10.74 (s, 1H, NH), 8.11 (d, 1H, $J = 6.8$ Hz, ArH), 7.83–7.93 (m, 3H, ArH), 7.63 (br s, 2H, NH_2), 7.21–7.27 (m, 2H, ArH), 6.90–6.98

(m, 2H, ArH) ppm. Anal. calcd. for $C_{21}H_{11}N_3O_4$: C, 68.29; H, 3.00; N, 11.38%. Found: C, 68.87; H, 3.11; N, 11.57%.

2-Amino-5,10-dioxo-spiro[(3′H)-5′-bromo-indol-3′,4,4(H)-benzo(g)chromen]-(1′H)-2′-one-3-carbonitrile (10b). Mp > 300 °C. IR (KBr) (ν_{max}): 3456, 3379, 3171, 2218, 1741, 1674, 1595, 1473, 1336, 1205, 721 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δH 10.88 (s, 1H, NH), 8.12 (dd, 1H, $J = 5.7$, 2.6 Hz, ArH), 7.86–7.91 (m, 3H, ArH), 7.72 (s, 2H, NH_2), 7.56 (d, 1H, $J = 2.1$ Hz, ArH), 7.42 (dd, 1H, $J = 8.2$, 2.1 Hz, ArH), 6.88 (d, 1H, $J = 8.2$ Hz, ArH) ppm. Anal. calcd. for $C_{21}H_{10}BrN_3O_4$: C, 56.27; H, 2.25; N, 9.37%. Found: C, 56.43; H, 2.36; N, 9.29%.

2-Amino-5,10-dioxo-spiro[(3′H)-1′-methyl-indol-3′,4,4(H)-benzo(g)chromen]-(1′H)-2′-one-3-carbonitrile (10c). Mp 280–282 °C; IR (KBr) (ν_{max}): 3460, 3350, 3163, 2200, 1722, 1668, 1591, 1467, 1340, 1203, 763 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δH: 8.11 (d, 1H, $J = 7.5$ Hz, ArH), 7.81–7.90 (m, 3H, ArH), 7.68 (s, 2H, NH_2), 7.34 (d, 2H, $J = 8.3$ Hz, ArH), 7.14 (d, 1H, $J = 7.6$ Hz, ArH), 7.03 (t, 1H, $J = 7.5$ Hz, ArH), 3.28 (s, 3H, CH_3) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δC 182.2, 176.7, 176.5, 159.1, 150.9, 143.6, 135.2, 134.9, 134.0, 130.9, 130.7, 129.5, 126.7, 126.4, 124.4, 123.1, 119.6, 117.3, 109.0, 56.9, 48.0, 27.0 ppm. Anal. calcd. for $C_{22}H_{13}N_3O_4$: C, 68.93; H, 3.42; N, 10.96%. Found: C, 68.47; H, 3.59; N, 11.17%.

2-Amino-5,10-dioxo-spiro[(3′H)-1′-benzyl-indol-3′,4,4(H)-benzo(g)chromen]-(1′H)-2′-one-3-carbonitrile (10d). Mp 192–195 °C. IR (KBr) (ν_{max}): 3431, 3323, 3211, 2197, 1718, 1664, 1563, 1465, 1334, 1205, 752 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δH 10.76 (s, 1H, NH), 8.10 (d, 1H, $J = 7.2$ Hz, ArH), 7.73 (s, 2H, NH_2), 7.85–7.90 (m, 3H, ArH), 7.57 (d, 1H, $J = 7.5$ Hz, ArH), 7.24–7.40 (m, 5H, ArH), 7.01 (t, 1H, $J = 7.8$ Hz, ArH), 6.87 (d, 1H, $J = 7.8$ Hz, ArH), 5.11 (d, 1H, $J = 16.0$ Hz, CH_2Ph), 4.97 (d, 1H, $J = 16.0$ Hz, CH_2Ph) ppm. Anal. calcd. for $C_{28}H_{17}N_3O_4$: C, 73.20; H, 3.73; N, 9.15%. Found: C, 73.67.; H, 3.88; N, 9.23%.

Ethyl 2-amino-5,10-dioxo-spiro[(3′H)-indol-3′,4,4(H)-benzo(g)chromen]-(1′H)-2′-one-3-carboxylate (10e). Mp 270 °C (dec.); IR (KBr) (ν_{max}): 3445, 3404, 3306, 2984, 1734, 1680, 1654, 1614, 1508, 1352, 1271, 1211, 1072, 721 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δH 10.49 (s, 1H, NH), 8.20 (s, 2H, NH_2), 8.06 (d, 1H, $J = 8.4$ Hz, ArH), 7.82–7.90 (m, 3H, ArH), 7.16 (t, 1H, $J = 7.6$ Hz, ArH), 7.10 (d, 1H, $J = 7.2$ Hz, ArH), 6.79–6.83 (m, 2H, ArH), 3.79 (q, 2H, $J = 7.0$ Hz, CH_2), 0.88 (t, 3H, $J = 7.0$ Hz, CH_3) ppm. Anal. calcd. for $C_{23}H_{16}N_2O_6$: C, 66.34; H, 3.87; N, 6.73%. Found: C, 66.59; H, 4.01; N, 6.85%.

Ethyl 2-amino-5,10-dioxo-spiro[(3′H)-5′-bromo-indol-3′,4,4(H)-benzo(g) chromen]-(1′H)-2′-one-3-carboxylate (10f). Mp 200–202 °C. IR (KBr) (ν_{max}): 3396, 3144, 3068, 1714, 1682, 1645, 1614, 1469, 1303, 1271, 1213, 723, 530 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δH 10.60 (s, 1H, NH), 8.02 (d, 1H, $J = 7.8$ Hz, ArH), 7.78–7.90 (m, 3H, NH_2 and ArH), 7.41–7.48 (m, 2H, ArH), 6.86 (d, 1H, $J = 8.2$ Hz, ArH), 3.47 (q, 2H, $J = 7.0$ Hz, CH_2), 1.08 (t, 3H, $J = 7.0$ Hz, CH_3) ppm. Anal. calcd. for $C_{23}H_{15}BrN_2O_6$: C, 55.78; H, 3.05; N, 5.66%. Found: C, 55.47; H, 3.17; N, 5.59%.

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