An Efficient, Three-Component Synthesis of Spiro[benzo[*g*]chromene-4,3′-indoline]-3-carbonitrile and Spiro[indoline-3,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile Derivatives

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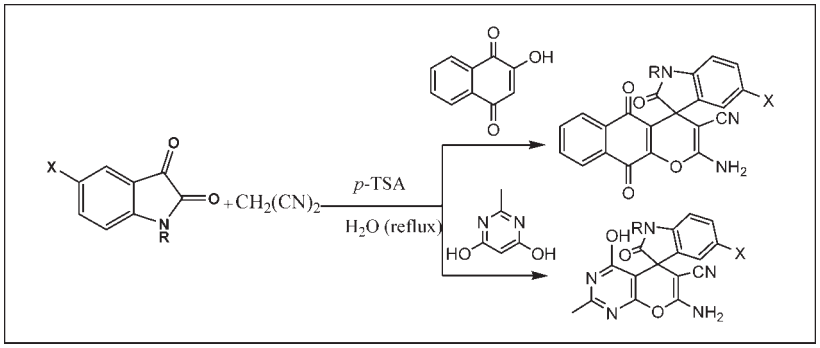

Spiro[benzo[g]chromene-4,3′-indoline]-3-carbonitriles and spiro[indoline-3,5′-pyrano[2,3-d]pyrimidine]-6′-carbonitriles were synthesized *via* a three-component reaction of isatins, 2-hydroxynaphthalene-1,4-dione or 2-methylpyrimidine-4,6-diol, and malononitrile in aqueous media.

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INTRODUCTION

With the emphasis on the search for atom-efficient transformations of easily available starting materials into complex organic molecules [1], reactions that provide maximum diversity are especially desirable. Here, expeditious domino [2] and multicomponent reactions [3] (MCRs) have emerged as powerful strategies. MCRs are economically and environmentally very advantageous, because multistep syntheses produce considerable amounts of waste mainly due to complex isolation procedures often involving expensive, toxic, and hazardous solvents after each step.

The indole moiety is probably the most well-known heterocycle, a common and important feature of a variety of natural products and medicinal agents [4]. Furthermore, it has been reported that sharing of the indole 3-carbon atom in the formation of spiroindoline derivatives highly enhance biological activity [5–7]. The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids [8–11].

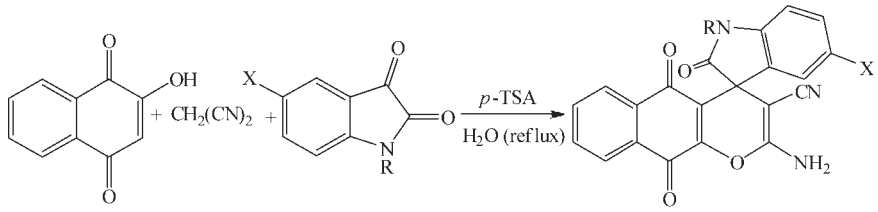
The quinone moiety is involved in a wide variety of biochemical processes including electron transport and oxidative phosphorylation [12]. Various biological properties, including enzyme inhibition, antibacterial, antifungal, and anticancer activities, have been reported for quinones and quinone derivatives [13–15]. Quinone-annulated heterocycles are found in nature, and most of them exhibit interesting biological activities. The chemistry of quinone annulated heterocycles is dependent largely on the substituent being either on the quinone or on adjacent rings [16,17]. These activities, combined with the diverse chemical behavior make quinones attractive targets in organic synthesis.

MCRs of isatins, malononitrile, and enol-neuclophilic compounds have recently attracted the interest of the synthetic community, because the formation of different condensation products can be expected depending on the specific conditions and structure of the building blocks [18–20]. 2-Hydroxynaphthalene-1,4-dione by containing enol group is a very interesting compound. As part of our program aimed at developing new selective and environmentally friendly methodologies for the preparation of heterocyclic compounds [21–28], we took advantage of enol group in 2-hydroxynaphthalene-1,4-dione for the preparation of spirooxindoles with fused chromene moiety. Fused chromenes have been found to have a wide spectrum of activities such as antimicrobial [29], antiviral [30], antiproliferative [31], sex pheromone [32], antitumor [33], and central nervous system activities [34].

RESULTS AND DISCUSSION

To achieve suitable conditions for the synthesis of spiro [benzo[*g*]chromene-4,3′-indoline]-3-carbonitriles, we first

Scheme 1



1 **2** **3a-j** **4a-j**

tested the reaction of 2-hydroxynaphthalene-1,4-dione 1, malononitrile 2 and isatin 3a, and as a simple model substrate in different solvents in the presence of *p*-toluenesulfonic acid (*p*-TSA) as an inexpensive and available catalyst at different conditions (Scheme 1). The results are shown in Table 1. It was found that water was a solvent of choice for the reaction, and the desired product was obtained in excellent yield in water (Entry 2).

Encouraged by this success, we extended the reaction of 2-hydroxynaphthalene-1,4-dione **1** and malononitrile **2** with a range of other isatin derivatives **3b-j** under similar conditions (Water/*p*-TSA) for 3–10 h, furnishing the respective 2-amino-2′,5,10-trioxo-5,10-dihydrospiro [benzo[*g*]chromene-4,3′-indoline]-3-carbonitrile derivatives **4b-j** in high yields. The optimized results are summarized in Table 2. The results were excellent in terms of yields and product purity using isatin derivatives in the presence of *p*-TSA, whereas without it for long period of time (24 h), the yields of products were low (< 30%). However, when this reaction was carried out with ethyl cyanoacetate, the thin layer chromatography (TLC) and ^{1}H NMR spectra of the reaction mixture showed a combination of starting materials and numerous products; the expected product was obtained in only trace amount.

A possible mechanism for the formation of **4** is proposed in Scheme 2. It is reasonable to assume that **4** results from initial formation of a intermediate **5** by standard Knoevenagel condensation of the malonitrile **2** and isatin **3**. Subsequently, Michael-type addition of the 2-hydroxynaphthalene-1,4-dione **1** to the intermediate **5**, followed by cyclization and tautomerization leads to the final products **4** (Scheme 2).

The nature of these compounds as 1:1:1 adducts was apparent from their mass spectra, which displayed, in each case, the molecular ion peak at appropriate *m*/*z* values. Compounds **4a–j** are stable solids whose structures are fully supported by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis.

As expected, when the 2-hydroxynaphthalene-1,4-dione **1** was replaced by 2-methylpyrimidine-4,6-diol **6**, another series of spiro[indoline-3,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitriles **7a–d** were obtained under the same reaction conditions (Scheme 3).

In conclusion, we have developed an efficient, clean, and three-component synthesis of new spiro[benzo[*g*]-chromene-4,3′-indoline] and spiro[indoline-3,5′-pyrano [2,3-*d*]pyrimidine]-6′-carbonitrile derivatives *via* cyclocondensation reaction of isatins, 2-malononitrile, and hydroxynaphthalene-1,4-dione or 2-methylpyrimidine-4, 6-diol in aqueous media.

Table 1

Conditions effect on the reaction.[a]

Entry	Conditions	Cat.	Yield (%)
1	Water/80°C	*p*-TSA	65
2	Water (reflux)	*p*-TSA	90
3	Water (reflux)	–	<30
4	CH_3CN (reflux)	*p*-TSA	45
5	EtOH (reflux)	*p*-TSA	63
6	DMF/100°C	*p*-TSA	50

[a] Malononitrile (**2**) (1 mmol), 2-hydroxynaphthalene-1,4-dione (**1**) (1 mmol), isatin (**3a**) (1 mmol) and *p*-TSA (0.1 g), time = 7 h.

EXPERIMENTAL

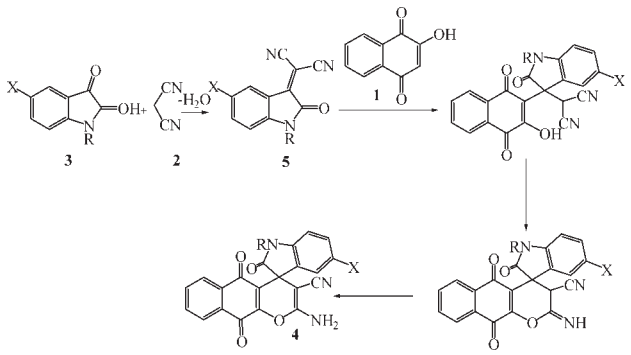
Melting points were measured on an Elecrtothermal 9100 apparatus and are uncorrected. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. IR spectra were recorded

Table 2

Synthesis of spiro[benzo[*g*]chromene 4,3′-indoline] derivatives **4**.

Products **4**	R	X	Time (h)	Yield (%)
a	H	H	7	90
b	Me	H	10	98
c	Et	H	10	85
d	H	NO_2	6	85
e	Me	NO_2	4.5	94
f	Et	NO_2	3	97
g	H	Br	6	86
h	Me	Br	3	93
i	Et	Br	3	80
j	H	Me	3	96

Scheme 2

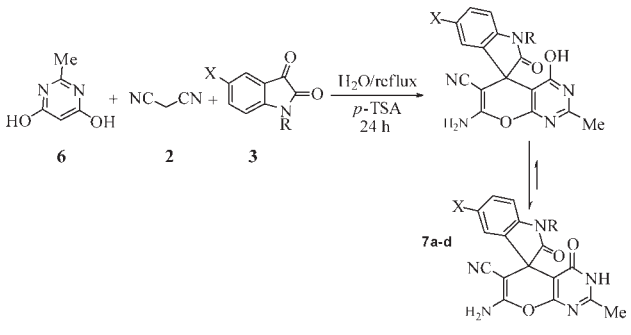


using an Shimadzu IR-470 apparatus. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

Typical procedure for the preparation of 2-amino-2′,5,10-trioxo-5,10-dihydrospiro[benzo[*g*]chromene-4,3′-indoline]-3-carbonitrile (4a). A mixture of malononitrile **2** (0.07 g, 1mmol), isatin **3** (0.15 g, 1mmol), 2-hydroxynaphthalene-1,4-dione **1** (0.17 g, 1 mmol), and *p*-TSA (0.1 g) was refluxed in water (5 mL) for 7 h (TLC). After cooling to room temperature, the resulting solid product was filtered, and the precipitate was washed with ethanol to afford the pure product **4a.** Light brown powder (90%); mp 295°C (dec.); ir (KBr) (ν_{max}/cm^{-1}): 3346 (NH_2), 3214 (NH), 2206 (CN), 1732, 1667, and 1633 (CO). MS(EI, 70 eV) *m*/*z* (%): 369 (M^+, 56), 325 (45), 105 (50), 76 (100). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 6.87–6.93 (m, 2H, H—Ar), 7.18–7.24 (m, 2H, H—Ar), 7.57 (s, 2H, NH_2), 7.82–7.88 (m, 3H, H—Ar), 8.05–8.07 (m, 1H, H—Ar), 10.68 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 48.49, 57.38, 110.04, 117.42, 119.93, 122.39, 124.69, 126.45, 126.68, 129.32, 130.75, 131.01, 134.94, 135.27, 124.17, 150.89, 159.08, 176.83, 178, 182.25. Anal. Calcd for $C_{21}H_{11}N_3O_4$: C, 68.29; H, 3.00; N, 11.38%. Found: C, 68.23; H, 2.95; N, 11.31%.

2-Amino-1′-methyl-2′,5,10-trioxo-5,10-dihydrospiro[benzo[*g*]chromene-4,3′-indoline]-3-carbonitrile (4b). Brown powder (98%); mp 265°C (dec.); ir (KBr) (ν_{max} /cm^{-1}): 3347 (NH_2), 2197 (CN), 1721, 1669, and 1627 (CO). MS (EI, 70 eV) *m*/*z* (%): 383 (M^+, 95), 338 (100), 105 (40), 76 (40). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.24 (s, 3H, CH_3), 6.99 (t, J = 5.7 Hz, 1H, H—Ar), 7.09 (d, J = 5.8 Hz, 1H, H—Ar), 7.31 (d, J = 6.1 Hz, 2H, H—Ar), 7.63 (s, 2H, NH_2), 7.76–7.88 (m, 3H, H—Ar), 8.05–8.07 (m, 1H, H—Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 27.0, 48.0, 56.9, 109.0, 117.3, 119.7, 123.1, 124.5, 126.5, 126.7, 129.5, 130.8, 131.0, 134.0, 134.9, 135.3, 142.6, 150.9, 159.1, 176.5, 176.7, 182.3. Anal. Calcd for $C_{21}H_{11}N_3O_4$: C, 68.29; H, 3.00; N, 11.38%. Found: C, 68.21; H, 3.06; N, 11.31%.

Scheme 3



Product **7**	R	X	Yield (%)
a	H	H	80
b	H	NO_2	82
c	Me	NO_2	65
d	Et	NO_2	63

2-Amino-1′-ethyl-2′,5,10-trioxo-5,10-dihydrospiro[benzo[*g*]chromene-4,3′-indoline]-3-carbonitrile (4c). Light brown powder (85%); mp 211°C (dec.); ir (KBr) (ν_{max} /cm^{-1}): 3349 (NH_2), 2196 (CN), 1717, 1668 and 1626 (CO). MS (EI, 70 eV) *m*/*z* (%): 397 (M^+, 100), 353 (100), 312 (58), 105 (40), 76 (45). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.25 (3H, t, J = 3.5 Hz, CH_3), 3.72–3.88 (2H, m, CH_2), 6.97 (t, J = 6.1 Hz, 1H, H—Ar), 7.12 (d, J = 6.0 Hz, 1H, H—Ar), 7.28–7.32 (m, 2H, H—Ar), 7.62 (s, 2H, NH_2), 7.78–7.88 (m, 3H, H—Ar), 8.06 (d, J = 6.2 Hz, 1H, H—Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.6, 47.9, 57.15, 109.1, 117.1, 119.7, 122.9, 124.6, 126.5, 126.7, 129.5, 130.7, 130.9, 134.2, 134.9, 135.2, 142.5, 150.9, 159.1, 175.9, 176.7, 182.2. Anal. Calcd for $C_{23}H_{15}N_3O_4$: C, 69.52; H, 3.80; N, 10.57%. Found: C, 69.47; H, 3.86; N, 10.51%.

2-Amino-5′-nitro-2′,5,10-trioxo-5,10-dihydrospiro[benzo[*g*]chromene-4,3′-indoline]-3-carbonitrile (4d). Light brown powder (85%); mp 290°C (dec.); ir (KBr) (ν_{max}/cm^{-1}): 3354 (NH_2), 3203 (NH), 2216 (CN), 1749, 1673, and 1629 (CO). MS (EI, 70 eV) *m*/*z* (%): 414 (M^+, 28), 371 (87), 324 (58), 297 (37), 174 (28), 105 (65), 43 (100). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 7.12 (d, J = 6.1 Hz, 1H, H—Ar), 7.80–7.89 (m, 5H, NH_2, 3H—Ar), 8.08 (d, J = 6.4 Hz, 1H, H—Ar), 8.19–8.22 (m, 1H, H—Ar), 8.33 (brs, 1H, H—Ar), 11.45 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 48.5, 56.0, 110.2, 117.1, 118.4, 120.8, 126.5, 126.7, 130.8, 135.0, 135.2, 135.6, 143.0, 148.6, 151.4, 159.3, 176.7, 178.5, 182.5. Anal. Calcd for $C_{21}H_{10}N_4O_6$: C, 60.88; H, 2.43; N, 13.52%. Found: C, 60.93; H, 2.47; N, 13.58%.

2-Amino-1′-methyl-5′-nitro-2′,5,10-trioxo-5,10-dihydrospiro[benzo[*g*]chromene-4,3′-indoline]-3-carbonitrile (4e). Light brown powder (94%); mp 320°C (dec.); ir (KBr) (ν_{max}/cm^{-1}): 3335 (NH_2), 2197 (CN), 1728, 1668, and 1632 (CO). MS (EI, 70 eV) *m*/*z* (%): 428 (M^+, 83), 384 (55), 364 (35), 254 (55), 224 (55), 174 (53), 76 (100). ^{1}H NMR (300 MH$_Z$, DMSO-d_6): δ_H 3.34 (s, 3H, CH_3), 7.38 (d, J = 8.8 Hz, 1H, H—Ar), 7.08–7.89 (m, 5H, NH_2, 3H—Ar), 8.07 (d, J = 8.9 Hz, 1H, H—Ar), 8.29–8.33 (m, 1H, H—Ar), 8.38–8.39 (m, 1H, H—Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 29.7, 111.6, 119.2, 122.7, 128.7, 128.9, 129.0, 133.0, 133.1, 136.9, 137.2, 137.4, 145.8, 151.7, 161.6, 178.8, 179.3, 184.7. Anal. Calcd for $C_{22}H_{12}N_4O_6$: C, 61.69; H, 2.82; N, 13.08%. Found: C, 61.75; H, 2.77; N, 13.00%.

2-Amino-1′-ethyl-5′-nitro-2′,5,10-trioxo-5,10-dihydrospiro[benzo[*g*]chromene-4,3′-indoline]-3-carbonitrile (4f). Light brown powder (97%); mp 287°C (dec.); ir (KBr) (ν_{max}/cm^{-1}): 3350 (NH_2), 2200 (CN), 1727, 1669, and 1630 (CO). MS (EI, 70 eV) *m*/*z* (%): 442 (M^+, 100), 398 (73), 367 (30), 297 (25), 105 (73), 76 (87). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.26 (t, 3H, J = 6.78 Hz, CH_3), 3.86–3.96 (m, 2H, CH_2), 7.43 (d, J =

8.7 Hz, 1H, H—Ar), 7.80–7.89 (m, 5H, NH_2, 3H—Ar), 8.08 (d, J = 8.8 Hz, 1H, H—Ar), 8.27–8.30 (m, 1H, H—Ar), 8.38 (brs, 1H, H—Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.6, 35.6, 47.8, 55.8, 109.3, 116.9, 118.2, 120.7, 126.5, 127.7, 130.8, 130.9, 135.1, 135.2, 143.4, 148.6, 151.6, 159.3, 176.6, 176.7, 182.5. Anal. Calcd for $C_{23}H_{14}N_4O_6$: C, 62.45; H, 3.19; N, 12.66%. Found: C, 62.39; H, 3.15; N, 12.61%.

2-Amino-5′-bromo-2′,5,10-trioxo-5,10-dihydrospiro[benzo[*g*]chromene-4,3′-indoline]-3-carbonitrile (4g). Light brown powder (86%); mp 275°C (dec.); ir (KBr) (ν_{max}/cm^{-1}): 3378 (NH_2), 3305 (NH), 2200 (CN), 1741, 1672, and 1651 (CO). MS (EI, 70 eV) m/z (%): 449 (M^++2, 40), 447 (M^+, 40), 405 (70), 76 (100). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 6.85 (d, J = 8.9 Hz, 1H, H—Ar), 7.37–8.05 (m, 6H, H—Ar), 7.83 (brs, 2H, NH_2), 10.83 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 48.6, 56.7, 111.9, 114.1, 117.3, 119.1, 126.5, 127.6, 130.8, 130.9, 132.0, 134.9, 135.2, 137.2, 141.5, 151.1, 159.1, 176.7, 177.6, 182.4. Anal. Calcd for $C_{21}H_{10}BrN_3O_4$: C, 56.27; H, 2.25; N, 9.37%. Found: C, 56.33; H, 2.20; N, 9.44%.

2-Amino-5′-bromo-1′-methyl-2′,5,10-trioxo-5,10-dihydrospiro[benzo[*g*]chromene-4,3′-indoline]-3-carbonitrile (4h). Light brown powder (93%); mp 282°C (dec.); ir (KBr) (ν_{max}/cm^{-1}): 3357 (NH_2), 2196 (CN), 1712, 1664, 1629 (CO). MS (EI, 70 eV) m/z (%): 464 (M^+ +2, 18), 462 (22), 419 (50), 391 (38), 105 (67), 76 (100). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.23 (s, 3H, CH_3), 7.09 (d, J = 6.3 Hz, 1H, H—Ar), 7.49–7.59 (m, 2H, H—Ar), 7.73 (s, 2H, NH_2), 7.82–7.87 (m, 3H, H—Ar), 8.06–8.09 (m, 1H, H—Ar).^{13}C NMR (75 MHz, DMSO-d_6): δ_C 27.1, 48.1, 56.4, 111.0, 114.9, 117.1, 118.9, 126.5, 126.7, 127.5, 130.8, 130.9, 132.1, 134.9, 135.2, 136.1, 142.9, 151.2, 159.2, 176.1, 176.7, 182.3. Anal. Calcd for $C_{22}H_{12}BrN_3O_4$: C, 57.16; H, 2.62; N, 9.09%. Found: C, 57.10; H, 2.67; N, 9.16%.

2-Amino-5′-bromo-1′-ethyl-2′,5,10-trioxo-5,10-dihydrospiro[benzo[*g*]chromene-4,3′-indoline]-3-carbonitrile (4i). Brown powder (80%); mp 288°C (dec.); ir (KBr) (ν_{max}/cm^{-1}): 3336 (NH_2), 2205 (CN), 1721, 1677, and 1632 (CO). MS (EI, 70 eV) m/z (%): 477 (M^++2, 55), 475 (M^+, 55), 433 (85), 105 (38), 76 (100). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.21 (t, 3H, J = 6.79 Hz, CH_3), 3.71–3.87 (m, 2H, CH_2), 7.12 (d, J = 9.1 Hz, 1H, H—Ar), 7.49 (d, J = 7.9 Hz, 1H, H—Ar), 7.59 (brs, 1H, H—Ar), 7.71 (s, 2H, NH_2), 7.81–8.08 (m, 4H, H—Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.5, 35.1, 47.9, 56.5, 111.1, 114.7, 117.0, 118.9, 126.5, 126.7, 127.6, 130.8, 130.9, 132.1, 134.9, 135.2, 136.4, 141.9, 151.2, 159.2, 175.6, 176.7, 182.3. Anal. Calcd for $C_{23}H_{14}BrN_3O_4$: C, 58.00; H, 2.96; N, 8.82%. Found: C, 57.93; H, 2.90; N, 8.89%.

2-Amino-5′-methyl-2′,5,10-trioxo-5,10-dihydrospiro[benzo[*g*]chromene-4,3′-indoline]-3-carbonitrile (4j). Light brown powder (98%); mp 310°C (dec.); ir (KBr) (ν_{max}/cm^{-1}): 3349 (NH_2), 3224 (NH), 2186 (CN), 1724, 1663, and 1631 (CO). MS (EI, 70 eV) m/z (%): 383 (M^+, 100), 339 (100), 311 (33), 282 (50), 104 (30), 76 (80). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.03 (3H, s, CH_3), 6.75–6.79 (m, 1H, H—Ar), 6.99–7.01 (m, 1H, H—Ar), 7.06 (brs, 1H, H—Ar), 7.57 (s, 2H, NH_2), 7.81–7.89 (m, 3H, H—Ar), 8.05–8.077 (m, 1H, H—Ar) 10.59 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.0, 48.5, 57.5, 109.7, 117.4, 120.0, 122.2, 126.4, 126.6, 129.5, 130.7, 131.0, 131.2, 134.8, 135.0, 135.2, 139.6, 150.8, 159.0, 176.8, 177.9, 182.2. Anal. Calcd for $C_{22}H_{13}N_3O_4$: C, 68.93; H, 3.42; N, 10.96%. Found: C, 68.99; H, 3.37; N, 11.04%.

Typical procedure for the preparation of 7′-amino-2′-methyl-2,4′-dioxo-3′,4′-dihydrospiro[indoline-3,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile (7a). A mixture of malononitrile **2** (0.07 g, 1mmol), isatin **3** (0.15 g, 1mmol), 2-methylpyrimidine-4,6-diol **6** (0.13 g, 1 mmol), *p*-TSA (0.1 g) was refluxed in water (5 mL) for 24 h (TLC). After cooling to room temperature, the resulting solid product was filtered, and the precipitate was washed with ethanol to afford the pure product **7a.** Cream powder (80%); mp 287°C (dec.); ir (KBr) (ν_{max}/cm^{-1}): 3378 (NH_2), 3306 (NH), 3142 (NH), 2207 (CN), 1716 and 1676 (CO). MS (EI, 70 eV) m/z (%): 321 (M^+). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 2.27 (s, 3H, CH_3), 6.78–7.18 (m, 4H, ArH), 7.31 (s, 2H, NH_2), 10.49 (s, 1H, NH), 12.61 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.4, 47.9, 57.1, 98.3, 109.7, 117.9, 122.2, 124.0, 128.8, 134.0, 142.6, 160.0, 160.3, 160.8, 161.0, 177.9. Anal. Calcd for $C_{16}H_{11}N_5O_3$: C, 59.81; H, 3.45; N, 21.80. Found: C, 59.76; H, 3.41; N, 21.86.

7′-Amino-2′-methyl-5-nitro2,4′-dioxo-3′,4′-dihydrospiro [indoline-3,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile (7b). Cream powder (82%); mp 270°C (dec.); ir (KBr) (ν_{max}/cm^{-1}): 3471 (NH_2), 3363 (NH), 2202 (CN), 1704, and 1658 (CO). MS (EI, 70 eV) m/z (%): 366 (M^+). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 2.28 (s, 3H, CH_3), 7.02 (d, J = 8.8 Hz, 1H, ArH), 7.50 (s, 2H, NH_2), 8.04 (s, 1H, ArH), 8.16 (d, J = 8.6 Hz, 1H, ArH), 11.24 (s, 1H, NH), 12.68 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.5, 48.1, 55.4, 97.2, 109.9, 117.7, 120.0, 126.4, 134.9, 142.9, 149.1, 160.4, 160.8, 161.1, 161.2, 178.7. Anal. Calcd for $C_{16}H_{10}N_6O_5$: C, 52.46; H, 2.75; N, 22.94. Found: C, 52.50; H, 2.80; N, 22.88.

7′-Amino-1,2′-dimethyl-5-nitro2,4′-dioxo-3′,4′-dihydrospiro [indoline-3,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile (7c). Cream powder (65%); mp 180°C (dec.); ir (KBr) (ν_{max}/cm^{-1}): 3429 (NH_2), 3322 (NH), 2202 (CN), 1730, and 1667 (CO). MS (EI, 70 eV) m/z(%): 380 (M^+). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 2.29 (s, 3H, CH_3), 3.25 (s, 3H, CH_3), 7.30 (d, J = 9.0 Hz, 1H, ArH), 7.57 (s, 2H, NH_2), 8.11 (s, 1H, ArH), 8.27 (d, J = 8.9 Hz, 1H, ArH), 12.66 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C. 21.5, 27.3, 47.7, 55.1, 97.1, 108.9, 117.6, 119.6, 126.4, 134.2, 143.4, 150.1, 160.6, 160.9, 161.0, 161.1, 177.3. Anal. Calcd for $C_{17}H_{12}N_6O_5$: C, 53.69; H, 3.18; N, 22.10. Found: C, 53.64; H, 3.22; N, 22.18.

7′-Amino-1-ethyl-2′-methyl-5-nitro2,4′-dioxo-3′,4′-dihydrospiro[indoline-3,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile (7d). Cream powder (63%); mp 233°C (dec.); ir (KBr) (ν_{max}/cm^{-1}): 3481 (NH_2), 3325 (NH), 2197 (CN), 1755, 1668, and 1647 (CO). MS (EI, 70 eV) m/z (%): 394 (M^+). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.17 (t, J = 8.4 Hz, 3H, CH_3), 2.22 (s, 3H, CH_3), 3.74 (m, 2H, CH_2), 7.10 (d, J = 8.9 Hz, 1H, ArH), 7.59 (s, 2H, NH_2), 8.14 (d, J = 8.9 Hz, 1H, ArH), 8.14 (s, 1H, ArH), 12.16 (brs, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 11.9, 18.0, 34.9, 39.07, 48.5, 95.3, 107.5, 118.4, 125.3, 135.3, 141.8, 150.6, 158.2, 161.4, 171.8, 178.6. Anal. Calcd for $C_{18}H_{14}N_6O_5$: C, 54.82; H, 3.58; N, 21.31. Found: C, 54.86; H, 3.63; N, 21.36.

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