N-Bromosulfonamides catalyzed synthesis of new spiro [indoline-3,4'-pyrano[2,3-*c*]pyrazole] derivatives

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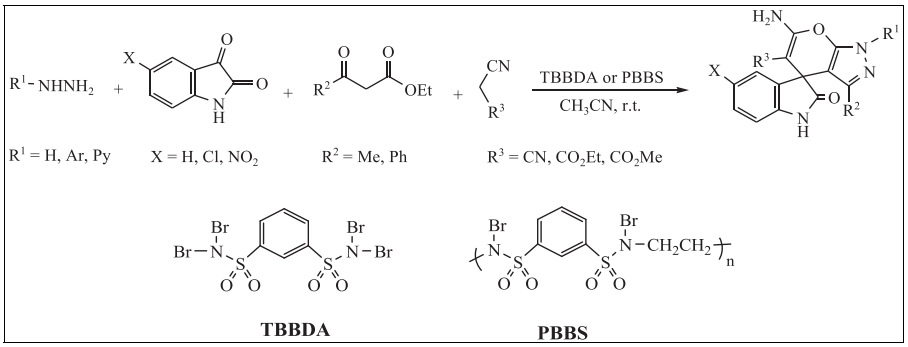

An efficient approach for the synthesis of pharmacologically important spiro[indoline-3,4'-pyrano[2,3-c] pyrazole] derivatives from tandem, four component reaction of various hydrazines, isatins, β-ketoesters, and malononitrile or methyl(ethyl)cyanoester in the presence of N,N,N',N'-tetrabromobenzene-1,3-disulfonamide [TBBDA] and poly(N,N'-dibromo-N-ethyl-benzene-1,3-disulfonamide) [PBBS] as efficient organocatalysts was reported.

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INTRODUCTION

Heterocyclic structures with a broad spectrum of biological properties exist in many natural products and applied in the agricultural and pharmaceutical sectors. Spiro heterocycles, especially spirocyclic oxindole nucleus, are a substantial category of natural alkaloids that possess various biological and pharmacological activities, such as spirotryptostatin A, B, which are isolated from the fermentation broth of *Aspergillus fumigates*, inhibits of cell cycle at G2/M phase [1] and *Koumine*, which is one of the alkaloids isolated from the *Gelsemium sempervirens* plant that has antitumor and analgesic activities [2]. Chitosenine as a *Gardneria multiflora* oxindole alkaloid has ganglioblocking action (Fig. 1) [3]. Subsequently, various approaches for the construction of spiroheterocyclic compounds have been reported [4–8]. Pyranopyrazoles are one of the most pharmacologically important fragments that condensed to 2-oxindole nucleus, which have been exhibited anti-inflammatory, [9] hypotensive, [10], and analgesic activities [11]. Because of unprecedented structural array and extremely biological activities of these compounds, during the last years, the synthesis of various spirooxindole systems has been receiving much attention [12–19].

RESULTS AND DISCUSSION

As a part of our studies on the role and application of *N*-halosulfonamides in organic synthesis [20–29], we report an efficient procedure for the synthesis of medicinally important spiropyrano[2,3-*c*]pyrazole derivatives, which contain various heterocyclic moieties, using *N,N,N',N'*-tetrabromobenzene-1,3-disulfonamide (TBBDA) and poly(*N,N'*-dibromo-*N*-ethyl-benzene-1,3-disulfonamide) (PBBS) [30] as efficient catalysts *via* four component cyclocondensation reaction under mild conditions (Scheme 1).

N,N,N',N'-Tetrabromobenzene-1,3-disulfonamide (TBBDA) and PBBS are inexpensive and non-hazardous catalysts, provided the TBBDA and PBBS are easy and stable under atmospheric conditions for two months. Also, after completion of the reaction, the catalyst is recovered and can be reused several times without significantly decreasing the yield (Scheme 2).

In order to optimize the reaction conditions, we first examined the effect of TBBDA, PBBS, *N,N,N',N'*-tetrachlorobenzene-1,3-disulfonamid (TCBDA) [31], trichloroisocyanuric acid (TCCA), and N-Chlorosuccinimide (NCS) as well as a variety of solvents for the synthesis of **5a** from four component reaction between phenyl hydrazine, malononitrile, ethylacetoacetate, and isatin as a model reaction. We found that in the absence of a catalyst, no product was formed even after prolonged reaction time. We found that the optimized reaction conditions for this reaction were TBBDA (0.035 g, 0.06 mmol) and/or PBBS (0.02 g) and CH_3CN as solvent system (Table 1, entries 8, 11). The results are listed in Table 1. These results encouraged us to investigate the scope and generality of this procedure for synthesis

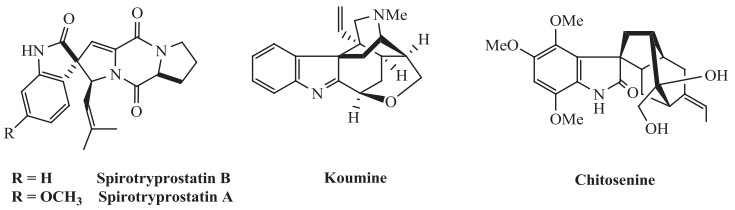


Figure 1. Structure of some biologically active spirocyclic oxindole alkaloids.

of spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole] derivatives under optimized reaction conditions. The cyclocondensation reaction of various hydrazines with either electron-withdrawing or electron-donating groups and isatin substituted with β-ketoester and malononitrile or ethyl (methyl)cyanoester with 1:1:1:1 molar ratios proceeded smoothly at ambient temperature, and corresponding products were prepared in good to high yields.

It is noteworthy that steric and electronic variation in the β-ketoester, isatin, and hydrazine derivatives have effected on speed of reaction and yield of products. The results are summarized in Table 2.

As demonstrated in Table 2, when ethyl(methyl) cyanoacetate was applied for this synthesis, ester substituent in products (**5d**, **5k**) was hydrolyzed to the corresponding acid.

Also, our experiments determined that TBBDA is a reusable catalyst; therefore, it is applied for the synthesis of **5a** that after three runs reused of the catalyst its catalytic activity is almost the same as that of a fresh catalyst (Table 2, entry 1). The average chemical yield for three consecutive runs of reused of the catalyst was (77%). The results are shown in Table 2.

Probable reaction mechanism in this way that initially these catalysts releases Br^+ *in situ*, which act as an electrophilic species and accelerated the formation of products. Therefore, the following mechanism can be suggested for the synthesis of spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole] derivatives (Scheme 3) [15,27]. Also, using a catalytic amount of aqueous 48% HBr instead of TBBDA to afford no desired product, this result indicates that the generation of the protic acid HBr may not be the only factor responsible for the catalytic activity of TBBDA. It is possible that the positive brominum moiety also has some role in facilitating the process.

CONCLUSION

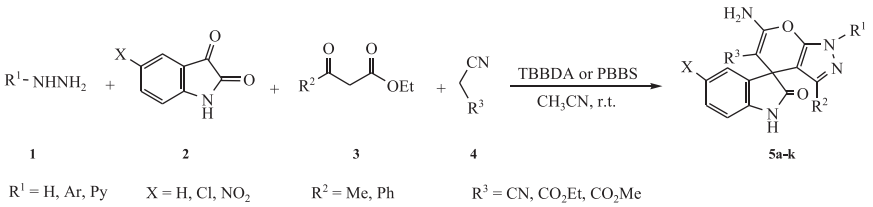
In summary, we have described regioselective, convenient synthesis of new spiro[indoline-3,4'-pyrano [2,3-*c*] pyrazole] derivatives from hydrazine derivatives, β-ketoester, substituted isatins, and malononitrile or ethyl (methyl)cyanoester in the presence of TBBDA or PBBS as efficient organocatalysts at ambient temperature under mild conditions. Good yields, simple procedure, easy of purification, and reusability of the catalyst are advantages of this process.

EXPERIMENTAL

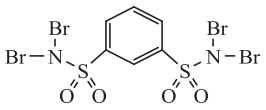
All commercially available chemicals were purchased from Merck and Fluka companies and used without further purification unless otherwise stated. ^{1}H and ^{13}C-NMR spectra were recorded on Bruker Avance 400MHz FT and Varian 90MHz NMR instrument. Chemical shifts were expressed in parts per million (ppm), *J* in hertz (Hz). Infrared (IR) spectroscopy was performed on a Perkin Elmer GX FT-IR spectrometer. Mass spectra were recorded on a Shimadzu QP 1100 BX Mass Spectrometer. Elemental analyses (C,H,N) were performed with CHNS-932, Leco, USA.

Typical Procedure for the Synthesis of 6′-Amino-3′-methyl-2-oxo-1′-(phenyl)-1′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile Using *N,N,N',N'*-tetrabromoben

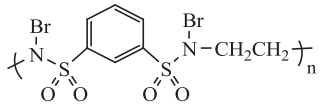
Scheme 1. Synthesis of new spiro pyranopyrazole derivatives using *N,N,N',N'*-tetrabromobenzene-1,3-disulfonamide (TBBDA) or poly(*N,N'*-dibromo-*N*-ethyl-benzene-1,3-disulfonamide) (PBBS).



Scheme 2. Structure of *N,N,N',N'*-tetrabromobenzene-1,3-disulfonamide (TBBDA) and poly(*N,N'*-dibromo-*N*-ethyl-benzene-1,3-disulfonamide) (PBBS).



TBBDA



PBBS

zene-1,3-disulfonamide or poly(*N,N'*-dibromo-*N*-ethyl-ben zene-1,3-disulfonamide) (Table 2, entry 1). A mixture of phenylhydrazine (0.108 g, 1 mmol), ethyl acetoacetate (0.130 g, 1 mmol), isatin (0.147 g, 1 mmol), malononitrile (0.066 g, 1 mmol), TBBDA (0.035 g, 0.06 mmol), or PBBS (0.02 g) in CH_3CN (2 mL) was stirred at room temperature for appropriate time (Table 2, entry 1). The progress of the reaction was monitored by TLC (9:3, *n*-hexane/acetone). After completion of the reaction, CH_3CN (10 mL) was added. The solid product was collected by filtration, washed with acetonitrile, and dried and purified by recrystallization from ethanol. After evaporation of the solvent under reduced pressure, CH_2Cl_2 was added and the catalyst was removed by filtration.

Physical and Spectroscopic Data. ***6′-Amino-3′-methyl-2-oxo-1′-(p-tolyl)-1′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (5b)***. Yield 0.28 g (75%); Yellow powder; m.p.: 213–214°C; IR (KBr, ν_{max}/cm^{-1}): 3448, 3328, 3186, 3030, 2191, 1712, 1649, 1619, 1530, 1396, 1223, 752 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d$_6$) δ_H (ppm) 1.53 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 6.93-6.95 (d, J = 7.6 Hz, 1H, ArH), 7.00–7.04 (m, 1H, ArH), 7.16–7.18 (d, J = 8.0 Hz, 1H, ArH), 7.26–7.32 (m, 3H, ArH), 7.54 (s, 2H, NH_2), 7.64–7.66 (m, 2H, ArH), 10.72 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d$_6$) δ_C (ppm) 12.11 (CH_3), 20.96 (CH_3), 48.24 (C), 56.60, 96.56, 110.2, 118.4, 120.6, 123.0, 125.3 (C Ar), 129.7, 130.2, 132.6 (C Ar), 135.3, 136.4 (C Ar), 142.0, 144.0, 145.2, 161.5 (C=O), 177.9. MS m/z = 383 [M$^+$] (8), 355 (70), 317 (64), 208 (55), 188 (82), 90 (100); Anal. calcd. for $C_{22}H_{17}N_5O_2$: C, 68.92; H, 4.47; N, 18.27%; Found: C, 68.01; H, 4.31; N, 17.95%.

6′-Amino-3′-methyl-2-oxo-1′-(p-chlorophenyl)-1′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (5c). Yield 0.28 g (71%); Yellow powder; m.p.: 234–236°C; IR (KBr, ν_{max}/cm^{-1}): 3366, 3307, 3169, 3087, 2202, 1693, 1644, 1521, 1487, 1394, 1216, 1090, 753; ^{1}H-NMR (90 MHz, DMSO-d$_6$) δ_H (ppm) 1.51 (s, 3H, CH_3), 7.02–7.19 (m, 4H, ArH), 7.55–7.57 (d, J = 1.8 Hz, 2H, ArH), 7.85–7.87 (d, J = 1.8 Hz, 2H, ArH), 8.84 (d, 2H, NH_2), 10.77 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d$_6$) δ_C (ppm) 11.67 (CH_3), 47.76 (C), 56.14, 96.33, 109.8, 117.9, 120.1, 122.6 (C Ar), 124.8, 126.5, 129.2 (C Ar), 129.4 (C Ar), 132.1, 137.2 (C Ar), 141.5, 143.9, 144.9, 161.0 (C=O), 177.4. MS m/z = 403 [M$^+$] (3), 384 (30), 309 (17), 208 (91), 195 (55), 168 (38), 79 (100). Anal. calcd. for $C_{21}H_{14}ClN_5O_2$: C, 62.46; H, 3.49; N, 17.34%; Found: C,61.71; H, 3.48; N, 16.70%.

6′-Amino-5-chloro-3′-phenyl-2-oxo-1′-(pyridyl)-1′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carboxylic acid (5d). Yield 0.36 g (70%); Yellow powder; m.p.: 325–326°C; IR (KBr, ν_{max}/cm^{-1}): 3261, 3153, 3013, 2806, 1729, 1688,

Table 1

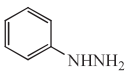
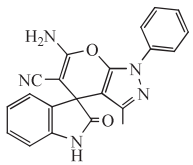
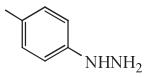
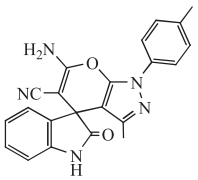
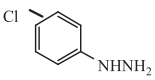
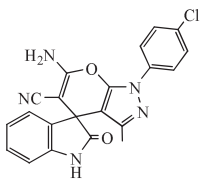
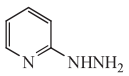
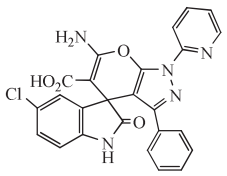
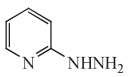
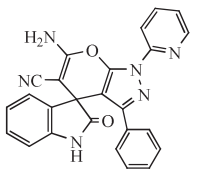
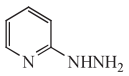
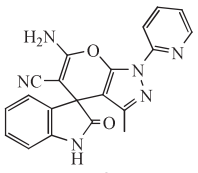
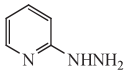
Optimization of reaction conditions for the synthesis of 6′-amino-3'-methyl-2-oxo-1′-(phenyl)-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*] pyrazole]-5′-carbonitrile.

Entry	Conditions	Time (hours)	Yield (%)
1	TCBDA (0.05 g), CH_3CN, rt	5	60
2	TCBDA (0.03 g), Acetone, rt	3	—
3	TCBDA (0.055 g), Solvent-free, rt	3	—
4	TCBDA (0.04 g), EtOH/H_2O (8:2), rt	3	—
5	BNBTS (0.02 g), Pryidine, rt	4	50
6	TCCA (0.03 g), EtOAc, rt	4	35
7	NCS (0.07 g), THF, rt	4	—
8	TBBDA (0.035 g), CH_3CN, rt	4	80
9	TBBDA (0.05 g), CH_3CN, rt	4	65
10	PBBS (0.04 g), EtOH, ref.	4	30
11	PBBS (0.02 g), CH_3CN, rt	4	70
12	No Catalyst, EtOH, rt	4	—

[a]Experimental conditions: phenyl hydrazine (1 mmol), ethyl acetoacetate (1 mmol), isatin (1 mmol), and malononitrile (1 mmol).
TCBDA, *N,N,N',N'*-tetrachlorobenzene-1,3-disulfonamid; TBBDA, *N,N,N',N'*-tetrabromobenzene-1,3-disulfonamide; PBBS, poly(*N,N'*-dibromo-*N*-ethyl-benzene-1,3-disulfonamide); BNBTS, N,N'-Dibromo-N,N'-1,2-ethanediylbis(p-toluenesulphonamide).

Table 2

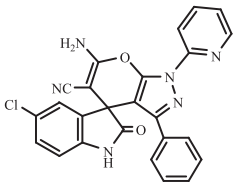
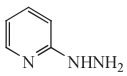
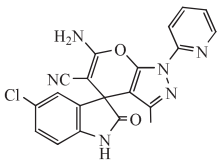
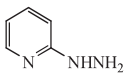
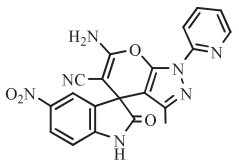
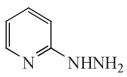
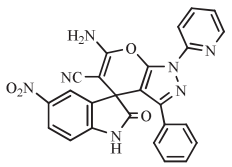
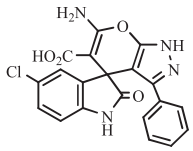
Substrate scope of spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole derivatives.

Entry	Hydrazine	R^2	X	R^3	Product	Time (hours) TBBDA	Time (hours) PBBS	Yield (%) TBBDA	Yield (%) PBBS	Ref.
1		Me	H	CN	 **5a**	4	4	[b]80	70	15
2		Me	H	CN	 **5b**	3	4	75	80	—
3		Me	H	CN	 **5c**	4.5	5	71	68	—
4		Ph	5-Cl	CO_2Et	 **5d**	4.5	4	70	80	—
5		Ph	H	CN	 **5e**	3	4	70	65	—
6		Me	H	CN	 **5f**	2.5	2	80	80	—
7		Ph	5-Cl	CN		2	3.5	60	50	—

(*Continues*)

Table 2

(Continued)

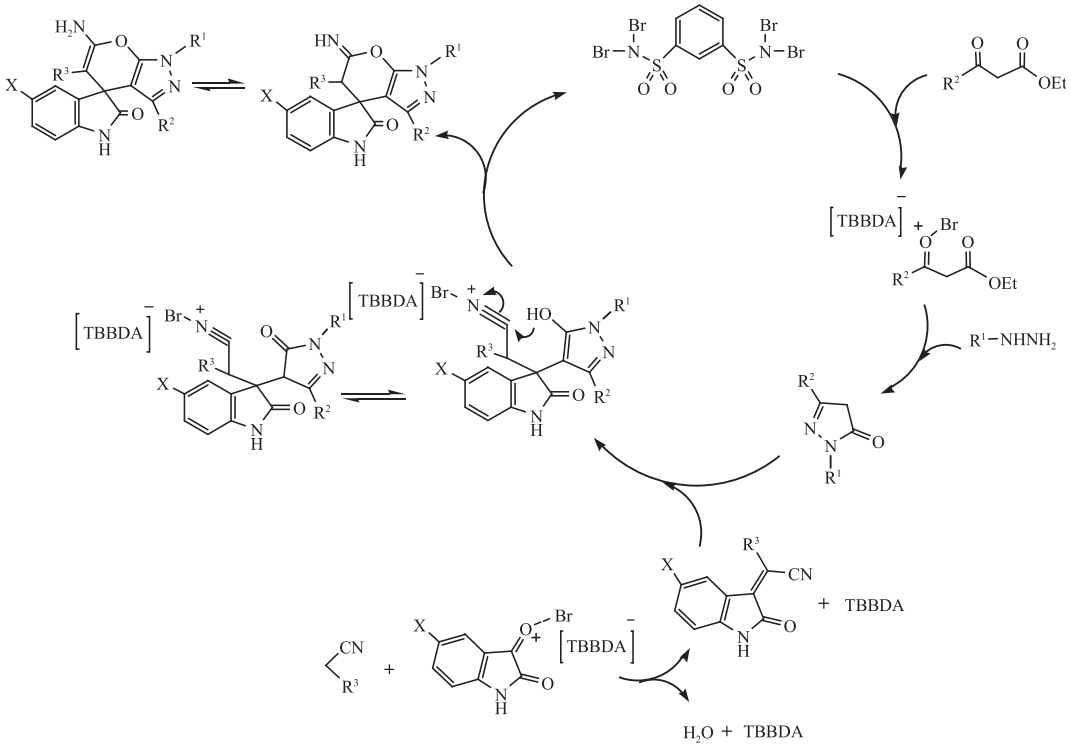
Entry	Hydrazine	R^2	X	R^3	Product	Time (hours) TBBDA	Time (hours) PBBS	Yield (%) TBBDA	Yield (%) PBBS	Ref.
					 **5g**					
8		Me	5-Cl	CN	 **5h**	1.5	4	80	71	—
9		Me	5-NO_2	CN	 **5i**	2	3	86	80	—
10		Ph	5-NO_2	CN	 **5j**	4	4.5	70	60	—
11	NH_2NH_2	Ph	5-Cl	CO_2Me	 **5k**	1	1	86	80	—

[a]Products were characterized from their physical properties, by comparison with authentic samples, and by spectroscopic methods.
[b]Isolated yield after three consecutive runs: 80, 77, 75.
TBBDA, *N,N,N',N'*-tetrabromobenzene-1,3-disulfonamide; PBBS, poly(*N,N'*-dibromo-*N*-ethyl-benzene-1,3-disulfonamide).

1572, 1438, 1305, 1200, 769 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm) 6.85–6.87 (d, J = 8 Hz, 1H, ArH), 6.94–6.96 (d, J = 8.4 Hz, 1H, ArH), 6.99 (s, 1H, ArH), 7.07–7.10 (t, J = 6.8 Hz, 1H, ArH), 7.29–7.33 (m, 2H, ArH), 7.45–7.47 (d, J = 8.4 Hz, 1H, ArH), 7.61–7.64 (m, 1H, ArH), 7.79–7.88 (m, 1H, ArH), 8.22 (s, 1H, ArH), 8.28–8.29 (d, J = 4.0 Hz, 1H, ArH), 8.37 (s, 1H, ArH), 10.67 (s, 1H, NH), 11.24 (br, 2H. NH_2), 12.75 (s, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm) 107.9, 112.6, 119.3, 119.4, 122.8 (C Ar), 126.7(C Ar), 129.0, 129.2 (C Ar), 139.3 (C Ar), 139.6, 148.7, 152.5, 155.0, 159.3 (C=O), 163.4 (C=O). MS m/z = 515 [M^+] (17), 413 (25), 384 (67), 368 (58), 320 (67), 272 (100).

6'-Amino-3'-phenyl-2-oxo-1'-(pyridyl)-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-5'-carbonitrile (5e). Yield 0.30 g (70%); Pale yellow powder; m.p.: 211–214°C; IR (KBr, ν_{max}/cm^{-1}): 3373, 3295, 3075, 2960, 2940, 1722, 1693, 1608, 1485, 1377, 1219, 1181, 1073 cm^{-1}; ^{1}H-NMR spectrum (400 MHz, DMSO-d_6) δ_H (ppm) 6.91–6.97 (m, 2H, ArH), 7.04–7.24 (m, 4H, ArH),

Scheme 3. Postulated mechanism for the synthesis of spiropyranopyrazole derivatives.



7.27–7.31 (t, J = 7.6 Hz, 1H, ArH), 7.45–7.50 (m, 2H, ArH), 7.55–7.59 (t, J = 7.2 Hz, 2H, ArH), 7.82–7.86 (t, J = 8.4 Hz, 2H, ArH), 8.05–8.08 (t, J = 6.8 Hz, 1H, ArH), 8.26–8.27 (d, 2H, NH_2), 11.11 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm) 107.1, 110.7, 116.3, 118.5, 119.2, 122.1 (C Ar), 122.5 (C Ar), 127.3 (C Ar), 127.9, 129.5 (C Ar), 131.9 (C Ar), 133.3 (C Ar), 138.8, 148.2, 148.5. MS m/z = 432 [M^+] (80), 325 (28), 234 (84), 206 (74), 160 (12), 115 (16), 91 (18); Anal. calcd. for $C_{25}H_{16}N_6O_2$: C, 69.44; H, 3.73; N, 19.43%; Found: C, 69.04; N, 19.27%.

6′-Amino-3′-methyl-2-oxo-1′-(pyridyl)-1′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (5f). Yield 0.29 g (80%); White powder; m.p.: 258–259°C; IR (KBr, ν_{max}/cm^{-1}): 3341, 3310, 3182, 3022, 2203, 1711, 1662, 1591, 1472, 1393, 1220, 1129, 1084, 785 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm) 1.55 (s, 3H, CH3), 6.94–6.96 (d, J = 8.0 Hz, 1H, ArH), 7.01–7.05 (m, 1H, ArH), 7.15–7.17 (d, J = 7.2 Hz, 1H, ArH), 7.27–7.31 (m, 1H, ArH), 7.39–7.43 (m, 1H, ArH), 7.47 (s, 2H, NH_2), 7.71–7.73 (d, J = 8.0 Hz, 2H, ArH), 7.98–8.02 (m, 1H, ArH), 8.53–8.54 (d, J = 5.6 Hz, 1H, ArH), 10.75 (s, 1H. NH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm) 12.17 (CH_3), 48.11 (C), 56.5, 97.5, 110.3, 115.8, 118.4, 122.9 (C Ar), 123.1, 125.3 (C Ar), 129.7, 132.5 (C Ar), 139.7, 142.0 (C Ar), 145.2 (C Ar), 146.1 (C Ar), 148.8, 150.6, 161.6 (C=O), 177.9. MS m/z = 370 [M^+] (7), 342 (52), 304 (80), 276 (100), 195 (80), 175 (82), 115 (57), 78 (63); Anal. Calc. for $C_{20}H_{14}N_6O_2$: C, 64.86; H, 3.81; N, 22.69%; Found: C, 64.78; H, 3.74; N, 21.88%.

6′-Amino-5-chloro-3′-phenyl-2-oxo-1′-(pyridyl)-1′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (5g). Yield 0.27 g (60%); Pale yellow powder; m.p.: 228–230°C; IR (KBr, ν_{max}/cm^{-1}): 3309, 3166, 2853, 2183, 1723, 1633, 1595, 1561, 1451, 1201, 769 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm) 6.83–6.85 (d, J = 8.4 Hz, 1H, ArH), 6.95–6.97 (m, 1H, ArH), 7.25–7.27 (d, J = 8.4 Hz, 1H, ArH), 7.32–7.34 (m, 3H, ArH), 7.44–7.54 (m, 7H, ArH, NH_2), 10.64 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm) 81.69, 95.96, 107.9, 112.7, 119.3, 119.4, 122.8 (C Ar), 126.7 (C Ar), 129.0 (C Ar), 129.2, 134.8 (C Ar), 139.3 (C Ar), 139.6, 148.7, 155.0 (C Ar), 157.8, 163.5 (C=O), 176.3. MS m/z = 466 [M^+] (2), 402 (48), 384 (60), 310 (100), 237 (46), 204 (40), 78 (72); Anal. Calc. for $C_{25}H_{15}ClN_6O_2$: C, 64.31; H, 3.24, N, 18.00%; Found: C, 64.87; H, 4.06; N, 18.66%.

6′-Amino-5-chloro-3′-methyl-2-oxo-1′-(pyridyl)-1′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (5h). Yield 0.32 g (80%); Yellow powder; m.p.: 214–215°C; IR (KBr, ν_{max}/cm^{-1}): 3353, 3311, 3186, 3083, 2984, 2208, 1713, 1660, 1592, 1472, 1393, 1086, 787 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm) 1.59 (s, 3H, CH_3), 6.95–6.98 (d, J = 6.8 Hz, 1H, ArH), 7.34–7.36 (m, 1H, ArH), 7.40–7.43 (m, 1H, ArH), 7.55 (s, 2H, NH_2), 7.71–7.73 (d, J = 8.4 Hz, ArH), 7.99–8.03 (m, 1H, ArH), 8.53–8.54

(d, J = 4.0 Hz, 1H, ArH), 10.90 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm) 12.2 (CH_3), 48.3(C), 55.8, 96.8, 111.8, 115.9, 118.3, 122.9 (C Ar), 125.5, 127.1 (C Ar), 129.7 (C Ar), 134.6 (C Ar), 139.7, 140.9 (C Ar), 145.0, 146.2 (C Ar), 148.8 (C Ar), 150.6, 161.6 (C=O), 177.7. MS m/z = 404 [M^+] (14), 376 (67), 339 (35), 229 (64), 175 (75), 134 (48), 78 (100); Anal. Calc. for $C_{20}H_{13}ClN_6O_2$: C, 59.34; H, 3.24; N, 20.76%; Found: C, 58.05; H, 3.01; N, 20.62%.

6′-Amino-3′-methyl-5-nitro-2-oxo-1′-(pyridyl)-1′H-spiro [indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (5i). Yield 0.35 g (86%); Pale yellow powder; m.p.: 268–269°C; IR (KBr, ν_{max}/cm^{-1}): 3402, 3307, 3192, 3090, 2205, 1721, 1670, 1626, 1594, 1462, 1340, 1079, 840, 633 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm) 1.59 (s, 3H, CH_3), 7.17–7.19 (d, J = 8.8 Hz, 1H, ArH), 7.41–7.44 (m, 1H, ArH), 7.64 (s, 2H, NH_2), 7.73–7.75 (d, J = 8.0 Hz, 1H, ArH), 7.99–8.04 (m, 1H, ArH), 8.17–8.18 (d, J = 2.4 Hz, 1H, ArH), 8.26–8.29 (m, 1H, ArH), 8.54–8.56 (m, 1H, ArH), 11.48 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm) 12.3 (CH_3), 48.2 (C), 55.2, 96.1, 110.7, 116.0, 118.2, 121.3, 123.0 (C Ar), 127.0 (C Ar), 133.7, 139.7 (C Ar), 143.6, 144.9 (C Ar), 146.4, 148.2 (C Ar), 148.8, 150.5, 161.8 (C=O), 178.4. MS m/z = 415 [M^+] (2), 382 (4), 240 (68), 210 (63), 154 (21), 79 (388).

6′-Amino-5-nitro-3′-phenyl-2-oxo-1′-(pyridyl)-1′H-spiro [indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (5j). Yield 0.33 g (70%); Opalescent powder; m.p.: 193–195°C; IR (KBr, ν_{max}/cm^{-1}): 3341, 3315, 3187, 2959, 2203, 1721, 1659, 1627, 1587, 1528, 1467, 1338, 1289, 1074, 745 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm) 6.92–6.94 (d, J = 8.4 Hz, 3H, ArH), 7.15–7.19 (m, 3H, ArH), 7.25–7.29 (m, 1H, ArH), 7.48–7.51 (q, J = 5.6 Hz, 1H, ArH), 7.65 (s, 1H, ArH), 7.86–7.88 (d, 2H, NH_2), 8.06–8.17 (m, 3H, ArH), 8.61–8.62 (d, J = 3.2 Hz, 1H, ArH), 11.31 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm) 110.5, 113.4, 116.8, 117.9, 121.2, 123.5, 125.3 (C Ar), 126.8, 127.8 (C Ar), 128.5, 129.1 (C Ar), 132.0, 133.0 (C Ar), 134.6 (C Ar), 138.6, 139.8 (C Ar), 143.3, 146.9 (C Ar), 148.4, 149.0 (C Ar), 155.5, 156.9, 161.3, 167.1, 178.5 (C=O), 183.0. MS m/z = 477 [M^+] (3), 267 (3), 239 (3), 169 (10), 113 (13), 102 (74), 79 (100); Anal. Calc. for $C_{25}H_{15}N_7O_4$: C, 62.89; H, 3.17; N, 20.54%; Found: C, 62.86; H, 3.10; N, 20.10%.

6′-Amino-5-chloro-3′-phenyl-2-oxo-1′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carboxylic acid (5k). Yield 0.35 g (86%); Yellow powder. m.p.: 204–206°C; IR (KBr, ν_{max}/cm^{-1}): 3404, 3270, 3187, 3095, 1742, 1715, 1633, 1614, 1579, 1465, 1203, 1146, 820 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm) 5.88 (s, 1H, NH), 6.82–6.88 (m, 1H, ArH), 7.22–7.24 (m, 1H, ArH), 7.25–7.32 (m, 1H, ArH), 7.38–7.41 (m, 2H, ArH), 7.65–7.67 (t, J = 7.2 Hz, 2H, ArH), 8.05 (d, J = 2.0 Hz, 1H, ArH), 9.04 (s, 2H, NH_2), 10.48 (s, 1H, NH), 12.03 (br, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm) 111.2, 111.8, 117.3, 118.4, 122.6, 124.5 (C Ar), 125.1 (C Ar), 125.4, 125.6 (C Ar), 126.0 (C Ar), 126.8, 127.3 (C Ar), 128.1 (C Ar), 128.3, 129.2 (C Ar), 137.5, 139.5, 166.1 (C=O). MS m/z = 408 [M^+] (4), 384 (10), 195 (84), 160 (100), 138 (84), 103 (94), 77 (55); Anal. Calc. for $C_{20}H_{13}ClN_4O_4$: C, 58.76; H, 3.21; N, 13.71%; Found: C, 58.54; H, 3.06; N, 12.22%.

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