An Efficient and Easy Method for the One-pot Synthesis of Spirooxindoles in the Presence of Na_2CO_3

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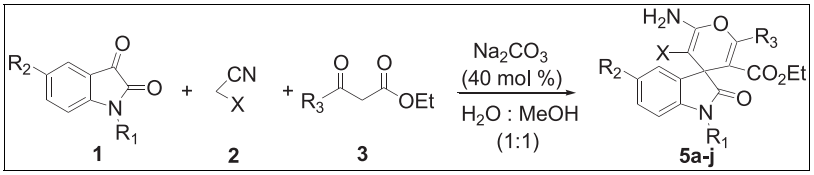

An efficient and easy procedure for the one-pot synthesis of spirooxindoles in the presence of Na_2CO_3 in water : methanol (1:1) is described. The salient features of this method are simple methodology, shorter reaction time, easy product isolation, and no chromatographic purification.

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INTRODUCTION

Spirooxindoles have become privileged skeletal framework with significant and promising pharmacological properties in various therapeutic areas [1]. They possess biological activities like anti-human immunodeficiency virus [2], antifungal [3], anticancer [4], antitubercular [5], antimalarial [6], progesterone receptor modulator [7], and MDM2 inhibitor [8]. A number of spirooxindole-based motifs are present in many natural products and biologically active molecules (Fig. 1) [9]. For example, spirotryprostatins A and B inhibits the G21M progression of cell division in mammalian tsFT210 cells [10]. MI-219 is a novel orally active MDM2 inhibitor that activates the p53 pathway and is selectively toxic to tumor cells [11]. NITD609 is used for the treatment of malaria [12]. The therapeutic activity of spirooxindoles is extraordinary and has been a key driving force in the development of new, easy, and convenient method for their synthesis.

Multicomponent reactions in aqueous media will serve as an attractive tool for rapid construction of heterocycles in terms of cost, safety, and environmental concern [13]. There are many methods available for the preparation of spirooxindoles. Among which, three-component reactions of isatin, malononitrile, and 1,3-dicarbonyl compound offer a convenient method for the synthesis of these elegant targets in the presence of NEt_3 [14], sodium stearate [15], tris(2-hydroxyethyl)amine [16], NH_4Cl [17], ethylenediamine diacetate [18], $InCl_3$ [19], tetrabutylammonium bromide [20], β-cyclodextrin [21], L-proline [22], and lipase [9h]. This reaction can also be performed by electrocatalytic method [23]. However, to the best of my knowledge, most of these methods suffer from tedious synthetic routes, long reaction times, drastic reaction conditions, toxicity, corrosiveness, cost, preparation of catalyst, and so forth. Thus, there is still ample room for design of a convenient, low cost, and clean method to assemble these compounds using mild catalyst.

In continuation of our ongoing research on the synthesis of spirooxindoles [19,24], we herein describe an improved, new, and convenient method for synthesis of spirooxindoles in H_2O/MeOH system using Na_2CO_3 as catalyst at room temperature within a shorter period of time. We believe that our method will serve as an easy and clean method for the synthesis of spirooxindoles under column chromatography-free condition. High yield, shorter reaction time under room temperature condition and water : methanol (1:1) medium, use of cheap and nontoxic catalyst, easy product isolation, and no column chromatographic purification make this procedure a sustainable one.

RESULTS AND DISCUSSION

Initially, we investigated the reaction of isatin, malononitrile, and ethyl acetoacetate with various carbonate catalysts such as Na_2CO_3, K_2CO_3, Li_2CO_3, and Cs_2CO_3. Among the four catalysts employed, Na_2CO_3 catalyst was found to be the best one in terms of yield and reaction time (Table 1). The product formation was observed within an hour and went to completion within few hours when the reaction was carried out with Na_2CO_3. In order to optimize the best condition, the reaction was conducted with 1 equiv of Na_2CO_3 catalyst at room temperature using various solvents (Table 2). Excellent results were obtained when the reaction was carried out in water : methanol (1:1). Similarly, the mole ratio of

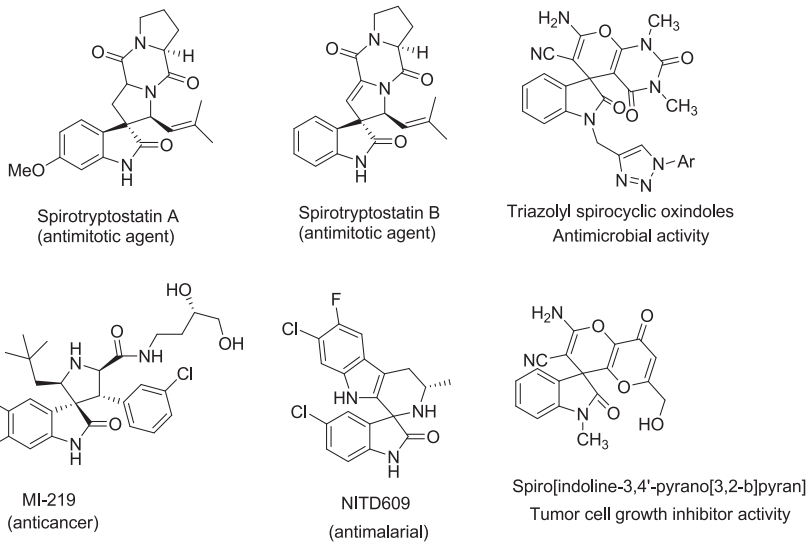


Figure 1. Examples of biologically active spirooxindole core structures.

Table 1

Screening of various carbonate catalysts[a].

Entry	Solvent	Time (h)	Yield (%)[a]
1	Na_2CO_3	6	55
2	K_2CO_3	11	40
3	Li_2CO_3	10	38
4	Cs_2CO_3	12	35

[a]Reaction carried out in methanol.

Table 2

Screening of various solvents.

Entry	Solvent	Time (h)	Yield (%)[a]
1	Ethanol	6	50
2	Methanol	6	55
3	Water	12	50
4	Water : Methanol (1:1)	4	90
5	Water : Ethanol (1:1)	4	80

[a]Isolated yields.

Na_2CO_3 was studied, and the results are listed in Table 3. The amount of Na_2CO_3 was found to be an important parameter for enhancement of yield of the reaction, with 40 mol % of Na_2CO_3 being optimum (Scheme 1).

In the beginning of the reaction, we observed reddish precipitate when malononitrile was added to isatin. After sequential addition of ethyl acetoacetate to the reaction mixture, the color of the reaction mixture changed from reddish to orange to pale yellow. Finally, after 4 h, we found the formation of a creamy white precipitate (Fig. 2). The obtained precipitate was filtered, washed

Table 3

Optimization of the reaction conditions.

Entry	Catalyst (equiv)	Time (h)	Yield (%)[a]
1	1	4	90
2	0.5	4	90
3	0.4	4	90
4	0.2	4	70
5	0.1	4	60

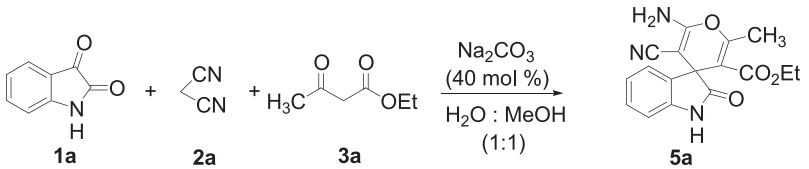
Reactions were carried out in 1-mmol scale.
[a]Isolated yields.

with ethanol, and dried to afford the product in pure form. The desired product was obtained in highly pure form just by filtration and does not require any column chromatographic purification. Another advantage of this method is that the progress of the reaction was easily followed from color changes.

With this established optimum condition, we intended to explore the generality of the developed protocol with several substituted isatins as well as ethyl cyanoacetate, and results are summarized in Scheme 2 and Table 4. We were delighted to find that array of isatin derivatives with diverse functional groups were well tolerated and afforded desired products in quantitative yield with very good purity under optimized condition without column chromatographic purification.

The structures of compounds **5a–j** were confirmed by IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopy, mass spectrometry, and elemental analysis. The IR spectrum of **5a** showed absorptions at 3479, 2189, 1678, and 1595 cm^{-1}, indicating the presence of $–NH_2$, cyano,

Scheme 1. One-pot three-component synthesis of spirooxindole 5a.



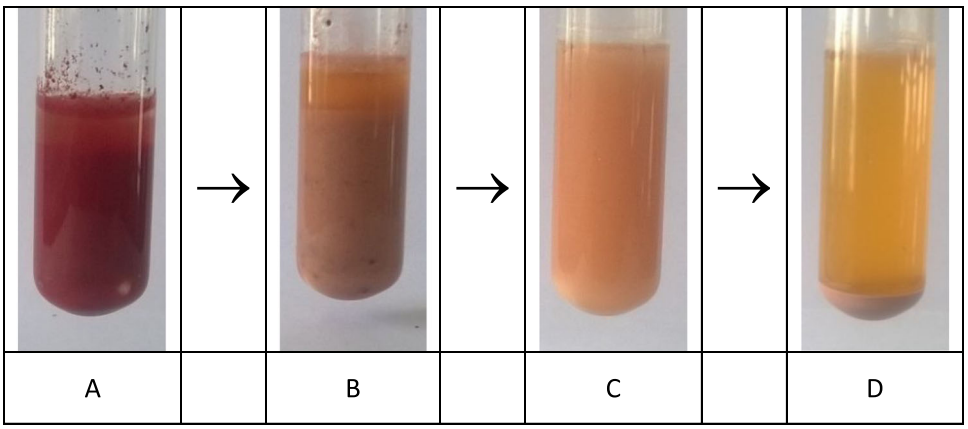


Figure 2. (A) Reaction mixture of isatin **1** (0.147 g, 1 mmol) and malononitrile **2** (0.066 g, 1 mmol) in 8-mL water : methanol (1:1) at room temperature. (B) Catalytic amount of Na_2CO_3 (0.042 g, 40 mol %) and ethyl acetoacetate **3** (0.130 g, 1 mmol) was added to the formed *in situ* isatylidenemalononitrile and stirring after 2 h, (C) stirring after 3.5 h, and (D) at the end of the reaction. [Color figure can be viewed at wileyonlinelibrary.com]

Scheme 2. One-pot three-component synthesis of spirooxindoles 5a–j.

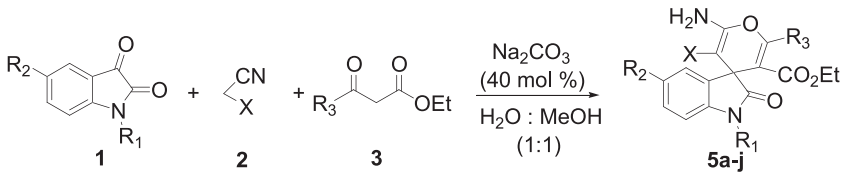
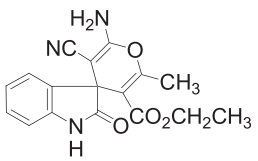


Table 4

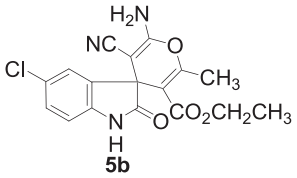
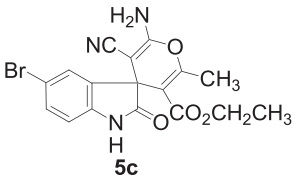
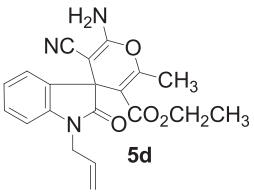
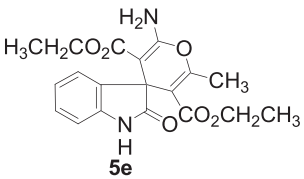
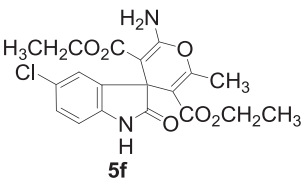
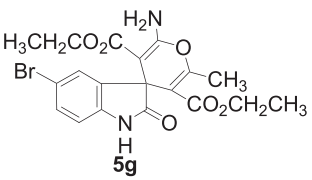
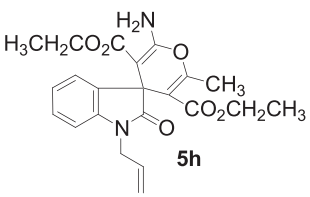
One-pot three-component synthesis of spirooxindoles.

Entry	Product	Time (h)	Yield (%)[a]
1	 **5a**	4	90

(*Continues*)

Table 4

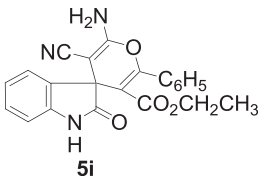
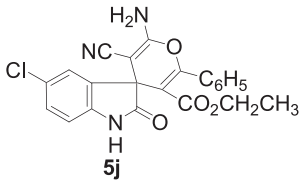
(*Continued*)

Entry	Product	Time (h)	Yield (%)[a]
2	 **5b**	3	82
3	 **5c**	2	86
4	 **5d**	2	92
5	 **5e**	2	87
6	 **5f**	3	85
7	 **5g**	2.5	92
8	 **5h**	1	94

(*Continues*)

Table 4

(*Continued*)

Entry	Product	Time (h)	Yield (%)[a]
9	 **5i**	7	78
10	 **5j**	5	82

[a]Isolated pure product.

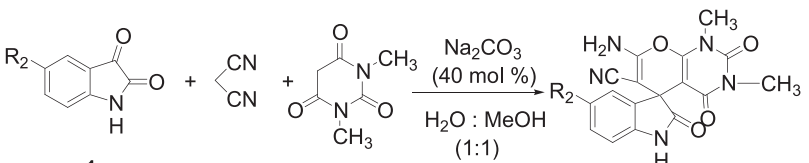
carbonyl, and double-bond functionalities, respectively. In the ^{1}H-NMR spectrum, aromatic signals were seen at δ 6.79–7.16, methyl at δ 2.32, and ethyl group of ester at δ 0.80 and 3.72, and $-NH_2$ and –NH groups were observed as a broad singlet at δ 7.14 and 10.39, respectively. The carbonyl resonated at δ 179.0 in the ^{13}C-NMR spectrum.

To further explore the potential of this protocol for heterocyclic synthesis, we investigated one-pot reaction of isatin and malononitrile with 1,3-dimethylbarbituric acid and obtained spirooxindoles**7a–c** in good yields (Scheme 3). The reaction proceeded smoothly at room temperature and yielded the products within 4–5 h.

We propose the possible mechanism to account for the formation of **5**. The process represents a typical cascade reaction in which the isatin **1** first condenses with malononitrile **2** to afford isatylidenemalononitrile derivative **4**. This step can be regarded as a fast Knoevenagel reaction. The second step involves Michael addition of ethyl acetoacetate **3** on the electrophilic C═C double bond followed by intramolecular nucleophilic attack of the enolic─OH group on the cyano group (Scheme 4) [25].

The efficiency of Na_2CO_3 has been compared with some of bases and catalysts reported previously in the literature for the synthesis of spirooxindoles (Table 5). From Table 5, it can be inferred that heating is not required and the reaction catalyzed by Na_2CO_3 proceeds smoothly at room temperature itself with higher yield of products. Moreover, Na_2CO_3 is a cheap, nontoxic, readily available, easy to handle, and a mild base.

Scheme 3. One-pot three-component synthesis of spirooxindoles 7a–c.



1 **2a** **6** **7a,b,c**

	R_2	Yield(%)
7a	H	80
7b	Cl	90
7c	Br	87

Scheme 4. Plausible mechanism for the formation of spirooxindoles 5a–j.

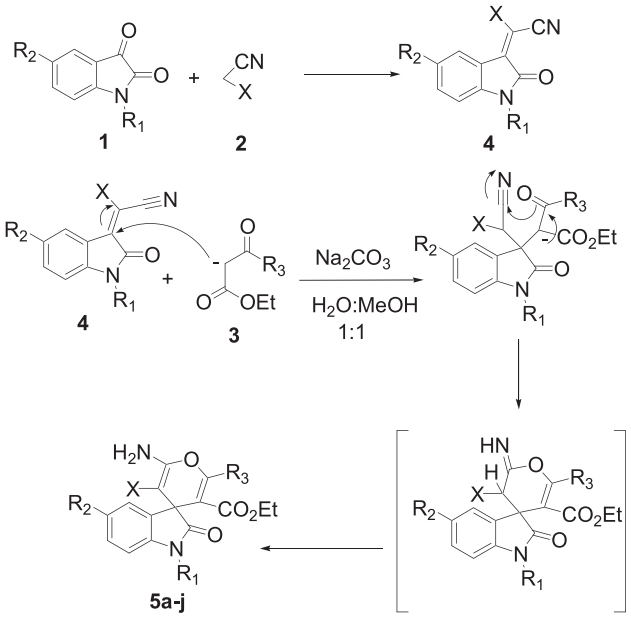


Table 5

Comparison of the efficiency of Na_2CO_3 with other catalysts for the synthesis of **5a**.

Entry	Catalyst	Solvent	*T* (°C)	Time	Yield (%)	Ref
1	Et_3N	EtOH	Reflux	30 min	80	[14]
2	Sodium stearate	H_2O	60°C	3 h	93	[15]
3	Tris(2-hydroxyethyl)amine	EtOH	Reflux	1–2 h	90	[16]
4	Ammonium chloride	H_2O	80°C	10 min	92	[17]
5	EDDA	H_2O	60°C	1 h	85	[18]
6	TBAB	H_2O	Reflux	1 h	90	[20]
7	β-Cyclodextrin	H_2O	60°C	5 h	90	[21]
8	L-Proline	H_2O	80°C	1 h	92	[22]
9	Na_2CO_3	H_2O : Methanol (1:1)	RT	4 h	90	This work

RT, room temperature.

CONCLUSIONS

In conclusion, we have developed a new, easy, and clean method for the synthesis of spirooxindoles catalyzed by Na_2CO_3 in water : methanol (1:1) at room temperature. The use of Na_2CO_3 as mild and easily available base catalyst and water : methanol (1:1) as the reaction medium makes this protocol a cheap and environmentally friendly approach. Further merits of this method are its shorter reaction times, high yields, wide substrate scope, easy product isolation, and no chromatographic purification. The protocol was also extended by replacing ethyl acetoacetate with 1,3-dimethylbarbituric acid.

EXPERIMENTAL

General. Isatin, 5-chloroisatin, 5-bromoisatin, malononitrile, ethyl cyanoacetate, ethyl acetoacetate, ethyl benzoacetate, and 1,3-dimethylbarbituric acid were purchased from Sigma-Aldrich. Na_2CO_3 was purchased from S.D. Fine-Chem. Limited, Chennai, India. Melting points were determined in capillary tubes and are uncorrected. IR measurements were performed as KBr pellets for solid using Fourier transform infrared (FTIR) (Thermo Electron Scientific Instruments, Madison, WI, USA) and Shimadzu Prestige 20 IR spectrometer (Shimadzu Corp., Kyoto, Japan). The ^{1}H-NMR and ^{13}C-NMR spectra

were recorded in DMSO-d_6 with Bruker 400- and 100-MHz high-resolution NMR spectrometer (Bruker Corp., Billerica, MA). DMSO-d_6 was used as the solvent for the NMR spectral measurements, and spectra were recorded in ppm with TMS as internal standard. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), multiplet (m), and broad (br). The mass spectra were analyzed by using an electrospray ionization method with Thermo Finnigan mass spectrometer (Thermo Fisher Scientific, Waltham, MA). Elemental analyses were recorded using a Thermo Finnigan FLASH EA 1112 CHN analyzer (Thermo Fisher Scientific). Analytical Thin layer chromatography was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2-mm thickness (Macherey–Nagel).

General procedure for the synthesis of spirooxindoles 5a–j and 7a–c. ***Representative procedure for spirooxindole 5a.*** To a stirred mixture of isatin (0.147 g, 1 mmol) and malononitrile (0.066 g, 1 mmol) in 8 mL water : methanol (1:1), a catalytic amount of Na_2CO_3 (0.042 g, 40 mol %) and ethyl acetoacetate (0.130 g, 1 mmol) was added (Table 4, entry 1). The reaction mixture was stirred at room temperature for about 4 h. After complete conversion as indicated from the color change and also from thin-layer chromatography, the precipitated solid was filtered and washed with ethanol to furnish analytically pure product.

Ethyl 2′-amino-3′-cyano-6′-methyl-2-oxospiro[indoline-3,4′-pyran]-5′-carboxylate (5a). Tan white solid; mp 257–259°C (reported 260–262°C) [26]; FTIR (cm^{-1}): 3479, 3155, 2978, 2189, 1678, 1595, 1467, 1381, 1286, 1211, 1070, 754, 678; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 0.80 (t, 3H, J = 1.6 Hz), 2.32 (s, 3H), 3.72 (m, 2H), 6.79 (d, 1H, J = 7.6 Hz), 6.9 (t, 1H, J = 7.2 Hz), 7.05 (d, 1H, J = 7.2 Hz), 7.14 (br s, 2H, NH_2), 7.16 (m, 1H), 10.39 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 13.4, 19.0, 49.4, 57.0, 60.7, 105.1, 109.8, 117.9, 122.3, 123.9, 129.0, 135.0, 142.6, 158.9, 159.4, 164.9, 179.0; *Anal*. Calcd. for $C_{17}H_{15}N_3O_4$ (325): C, 62.76; H, 4.65; N, 12.92%. Found: C, 62.70; H, 4.62; N, 12.90%.

Ethyl 2′-amino-5-chloro-3′-cyano-6′-methyl-2-oxospiro[indoline-3,4′-pyran]-5′-carboxylate (5b). Tan white solid; mp 258–260°C (reported 263–265°C) [26]; FTIR (cm^{-1}): 3360, 3230, 3149, 2790, 2201, 1715, 1680, 1630, 1590, 1450, 1375, 1340, 1280, 1220, 1075; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 0.83 (t, 3H, J = 7.2 Hz), 2.34 (s, 3H), 3.77 (m, 2H), 6.81 (d, 1H, J = 8.4 Hz), 7.19 (m, 4H), 10.54 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 13.5, 19.2, 49.8, 56.4, 60.9, 104.2, 111.2, 117.8, 124.1, 126.2, 128.9, 137.3, 141.5, 159.3, 159.9, 164.8, 178.8; *Anal*. Calcd. for $C_{17}H_{14}ClN_3O_4$ (359): C, 56.75; H, 3.92; N, 11.68%. Found: C, 56.70; H, 3.90; N, 11.65%.

Ethyl 2′-amino-5-bromo-3′-cyano-6′-methyl-2-oxospiro-[indoline-3,4′-pyran]-5′-carboxylate (5c). Tan white solid; mp 262–264°C; FTIR (cm^{-1}): 3392, 3300, 3204, 3182, 2204, 1704, 1662, 1608, 1585; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 0.84 (s, 3H), 2.34 (s, 3H), 3.82 (s, 2H), 6.77 (s, 1H), 7.23 (s, 4H), 10.55 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 13.5, 19.2, 49.7, 56.4, 60.9, 104.2, 111.8, 113.9, 117.8, 126.7, 131.3, 137.7, 141.9, 159.4, 160.0, 164.8, 178.7; *Anal*. Calcd. for $C_{17}H_{14}BrN_3O_4$ (404): C, 50.51; H, 3.49; N, 10.40%. Found: C, 50.47; H, 3.46; N, 10.36%.

Ethyl 1-allyl-2′-amino-3′-cyano-6′-methyl-2-oxospiro-[indoline-3,4′-pyran]-5′-carboxylate (5d). Tan white solid; mp 145–147°C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 0.71 (t, 3H, J = 7.2 Hz), 2.33 (s, 3H), 3.71 (m, 2H), 5.17 (m, 1H), 5.20 (m, 1H), 5.20 (m, 1H), 5.37 (m, 1H), 5.42 (m, 2H), 6.91 (m, 2H), 7.00 (m, 1H), 7.15 (m, 1H), 7.27 (m, 1H); *Anal*. Calcd. for $C_{20}H_{19}N_3O_4$ (365): C, 65.74; H, 5.24; N, 11.50%. Found: C, 65.70; H, 5.21; N, 11.46%.

Diethyl 2′-amino-6′-methyl-2-oxospiro-[indoline-3,4′-pyran]-3′,5′-dicarboxylate (5e). Tan white solid; mp 165–167°C (reported 169–170°C) [26]; FTIR (cm^{-1}): 3359, 3250, 2980, 2780, 2700, 1725, 1701, 1630, 1582, 1475, 1380, 1350, 1297, 1150, 1132, 1064; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 0.73 (t, 3H, J = 7.2 Hz), 0.86 (t, 3H, J = 6.8 Hz), 2.16 (s, 3H), 3.69 (m, 4H), 6.67 (d, 1H, J = 7.6 Hz), 6.79 (t, 1H, J = 7.2 Hz), 6.91 (d, 1H, J = 7.2 Hz), 7.07 (t, 1H, J = 6.4 Hz), 7.75 (br s, 2H, NH_2), 10.17 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 13.6, 18.8, 49.4, 59.2, 60.6, 75.7, 108.5, 108.8, 121.3, 123.5, 128.0, 136.4, 144.1, 154.1, 160.0, 165.5, 168.0, 180.2; *Anal*. Calcd. for $C_{19}H_{20}N_2O_6$ (372): C, 61.28; H, 5.41; N, 7.52%. Found: C, 61.24; H, 5.37; N, 7.48%.

Diethyl 2′-amino-5-chloro-6′-methyl-2-oxospiro-[indoline-3,4′-pyran]-3′,5′-dicarboxylate (5f). Tan white solid; mp 217–219°C (reported 213–219°C) [25]; FTIR (cm^{-1}): 3379, 3270, 3198, 1720, 1693, 1630, 1580, 1527, 1447, 1381, 1349, 1214, 1060; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 0.78 (t, 3H, J = 7.2 Hz), 0.90 (t, 3H, J = 7.2 Hz), 2.19 (s, 3H), 3.68 (m, 4H), 6.68 (m, 1H), 6.98 (m, 1H), 7.13 (m, 1H), 7.81 (br s, 2H, NH_2), 10.23 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 13.6, 13.7, 19.0, 49.7, 59.3, 60.8, 75.1, 107.6, 110.2, 123.6, 125.2, 127.9, 138.6, 143.1, 155.1, 160.0, 165.4, 167.7, 180.0; *Anal*. Calcd. for $C_{19}H_{19}ClN_2O_6$ (406): C, 56.09; H, 4.71; N, 6.89%. Found: C, 56.05; H, 4.67; N, 6.85%.

Diethyl 2′-amino-5-bromo-6′-methyl-2-oxospiro-[indoline-3,4′-pyran]-3′,5′-dicarboxylate (5g). Tan white solid; mp 280–282°C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 0.79 (m, 6H), 2.19 (s, 3H), 3.73 (m, 4H), 6.66 (s, 1H), 7.09 (m, 2H), 7.76 (br s, 2H, NH_2), 10.34 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 13.7, 19.0, 49.6, 59.3, 60.8, 75.1, 107.6, 110.8, 112.8, 126.3, 130.8, 139.0, 143.6, 155.1, 160.0, 165.4, 167.7, 179.9; *Anal*. Calcd. for $C_{19}H_{19}BrN_2O_6$ (451): C, 50.57; H, 4.24; N, 6.21%. Found: C, 50.53; H, 4.21; N, 6.18%.

Diethyl 1-allyl-2′-amino-6′-methyl-2-oxospiro[indoline-3,4′-pyran]-3′,5′-dicarboxylate (5h). Tan pink solid; mp 158–160°C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 0.60 (t, 3H,

J = 7.2 Hz), 0.78 (t, 3H, J = 7.2 Hz), 2.17 (s, 3H), 3.59 (m, 4H), 4.23 (m, 1H), 4.32 (m, 1H), 5.22 (d, 1H, J = 1.2 Hz), 5.47 (d, 1H, J = 1.6 Hz), 5.82 (m, 1H), 6.84 (d, 1H, J = 7.6 Hz), 6.90 (t, 1H, J = 7.2 Hz), 6.99 (d, 1H, J = 6.4 Hz), 7.15 (t, 1H, J = 6.8 Hz), 7.82 (br s, 2H, NH_2); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 13.8, 18.9, 43.1, 48.8, 58.9, 60.6, 75.4, 108.2, 118.4, 122.1, 123.3, 128.1, 132.9, 135.6, 144.4, 154.2, 160.2, 165.4, 167.7, 178.1; *Anal*. Calcd. for $C_{22}H_{24}N_2O_6$ (412): C, 64.07; H, 5.87; N, 6.79%. Found: C, 64.03; H, 5.81; N, 6.75%.

Ethyl 2′-amino-3′-cyano-2-oxo-6′-phenylspiro-[indoline-3,4′-pyran]-5′-carboxylate (5i). Tan white solid; mp: 200–202°C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 0.6 (t, 3H, J = 7.2 Hz), 3.62 (q, 2H, J = 3.6 Hz), 6.82 (d, 1H, J = 7.6 Hz), 6.96 (m, 1H), 7.18 (m, 2H), 7.28 (br s, 2H, NH_2), 7.42 (m, 5H), 10.50 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 13.3, 50.2, 56.6, 60.8, 107.1, 110.0, 118.0, 122.5, 124.5, 128.6, 128.7, 128.8, 129.4, 130.8, 133.0, 133.6, 142.7, 155.8, 160.4, 165.0, 178.5; *Anal*. Calcd. for $C_{22}H_{17}N_3O_4$ (387): C, 68.21; H, 4.42; N, 10.85%. Found: C, 68.19; H, 4.40; N, 10.80%.

Ethyl 2′-amino-5-chloro-3′-cyano-2-oxo-6′-phenylspiro-[indoline-3,4′-pyran]-5′-carboxylate (5j). Tan white solid; mp 180–182°C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 0.59 (t, 3H, J = 7.2 Hz), 3.64 (m, 2H), 6.84 (d, 1H, J = 8 Hz), 7.23 (m, 1H), 7.33 (m, 3H), 7.44 (m, 5H), 10.65 (s, 1H, NH); *Anal*. Calcd. for $C_{22}H_{16}ClN_3O_4$ (421): C, 62.64; H, 3.82; N, 9.96%. Found: C, 62.60; H, 3.80; N, 9.93%.

7′-Amino-1′,3′-dimethyl-2,2′,4′-trioxo-1′,2′,3′,4′-tetrahydrospiro[indoline-3,5′-pyrano[2,3-d]pyrimidine]-6′-carbonitrile (7a). Tan white solid; mp 230–231°C (reported 231–233°C) [27]; FTIR (cm^{-1}): 3315, 1637, 1267; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.09 (s, 3H), 3.16 (s, 3H), 6.83 (d, 1H, J = 7.6 Hz), 6.92 (t, 1H, J = .6 Hz), 7.08 (d, 1H, J = 7.6 Hz), 7.17 (m, 1H), 7.50 (br s, 2H, NH_2), 10.48 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 28.1, 29.8, 47.9, 58.1, 87.5, 110.0, 117.2, 122.6, 124.2, 129.1, 133.9, 142.3, 150.2, 152.6, 158.7, 160.0, 178.5; *Anal*. Calcd. for $C_{17}H_{13}N_5O_4$ (351): C, 58.12; H, 3.73; N, 19.93%. Found: C, 58.08; H, 3.67; N, 19.87%.

7′-Amino-5-chloro-1′,3′-dimethyl-2,2′,4′-trioxo-1′,2′,3′,4′-tetrahydrospiro[indoline-3,5′-pyrano[2,3-d]pyrimidine]-6′-carbonitrile (7b). White solid; mp 220–222°C; FTIR (cm^{-1}): 3356, 2921, 1651, 1264; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.04 (s, 3H), 3.36 (s, 3H), 6.81 (d, 1H, J = 8.0 Hz), 7.21 (d, 1H, J = 8.0 Hz), 7.23 (s, 1H), 7.65 (br s, 2H, NH_2), 10.64 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 28.1, 29.8, 48.1, 57.5, 86.9, 111.1, 117.2, 124.5, 126.2, 128.8, 136.2, 141.5, 150.1, 152.7, 158.6, 160.0, 177.8; *Anal*. Calcd. for $C_{17}H_{12}ClN_5O_4$ (385): C, 52.93; H, 3.14; N, 18.15%. Found: C, 52.89; H, 3.11; N, 18.11%.

7′-Amino-5-bromo-1′,3′-dimethyl-2,2′,4′-trioxo-1′,2′,3′,4′-tetrahydrospiro[indoline-3,5′-pyrano[2,3-d]pyrimidine]-6′-carbonitrile (7c). Tan white solid; mp 292–294°C (reported 295–297°C) [27]; FTIR (cm^{-1}): 3320, 2933, 1640, 1265; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.01(s, 3H), 3.35 (s, 3H), 6.80 (d, 1H, J = 8.4 Hz), 7.34 (s, 2H), 7.59 (br s, 2H, NH_2), 10.71 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 28.1, 29.8, 48.1, 57.4, 86.9, 111.9, 114.2, 117.1, 127.1, 131.8, 136.4, 141.7, 150.2, 152.8, 158.8, 160.1, 178.1; *Anal*. Calcd. for $C_{17}H_{12}BrN_5O_4$ (430): C, 47.46; H, 2.81; N, 16.28%. Found: C, 47.42; H, 2.79; N, 16.24%.

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