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Ambient synthesis of spiro[4*H*-pyran-oxindole] derivatives under [BMIm]BF_4 catalysis

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ABSTRACT

A simple and efficient one-pot approach for assembling some fused spiro[4*H*-pyran-oxindole] heterocycles by means of three-component reactions between isatins, malononitrile or ethyl cyano-acetate, and 1,3-dicarbonyl compounds is reported. The combinatorial syntheses were achieved for the first time without applying extra activation energy at ambient temperature while making use of [BMIm]BF_4 as an ionic liquid catalyst. Good functional group tolerance and broad scope of usable substrates are other prominent features of the present methodology.

1. Introduction

Innovation of straight synthetic pathways and easy access to more complex products are of the main incentives existing behind the recent researches in organic synthesis. To meet these goals, chemists have been attempting specially to develop multi-component reactions (MCR).[1] Since these reactions offer significant advantages over conventional linear-type syntheses, as more often are recognized cost-effective and comparatively fast routes though generating less chemical waste.[2] Consequently, they are regarded as viable synthetic routes toward both economical and environmental benefits of chemical transformations. In this view, designing of MCRs without using toxic catalysts in solvent-free conditions as well as in recyclable solvents, such as ionic liquids is particularly worthwhile for complementing the significant characters of MCRs, so as to satisfy the green chemistry principles.[3] Recently, ionic liquids have received recognition as the new generation of solvents having unique chemical and physical properties of nonvolatility, nonflammability, and thermal stability. Their dual organic and ionic natures allows them to establish nearly all kinds of interactions with reacting species including transition states, and hence sometimes give rise to improved yields and rate enhancements.[4] Structural variation of ionic liquids gives more flexibility to their applications due to the possibility of fine tunning their miscibility to merit phase-separation from products. Moreover, functionalized ionic liquids offer specific types for catalysis applications and were served as solution phase supports in combinatorial syntheses.[5] In contrast to solid-phase combinatorial syntheses, the ionic liquid supports are taken into solution phase with the reactants where the reactions are expected to show distinct selectivity and pronounced efficiencies in terms of reaction times and yields. These interesting features would tend to popularize ionic liquids as solution phase supports and solvent catalysts for combinatorial synthesis of diverse molecules.[6] To make a contribution to these ongoing research fields connected with our interest in the synthesis of spiro-oxindole compounds,[7] and also in performing reactions with the aid of ionic liquids,[8] we report an ionic liquid-assisted multi-component synthesis of spiro-oxindole heterocycles containing fused 4H-pyran ring. The indole ring system is probably the most well-known heterocycle, a common and important feature of various natural products and medicinal agents.[9] It constitutes the core of spiro-oxindoles, a recurring subclass of indole alkaloids in nature, which exhibit highly pronounced biological activities so as deserve to occupy a unique place among pharmacological agents.[10] Gelsemine, pseudotabersonine, morroniside, formosanine, isoformosanine, and mitraphylline are representatives of the alkaloids, which incorporate spiro-oxindole ring systems.[11] Certain members of this class, possessing significant bioactivities, have prompted many attempts toward synthesis of structurally related mimetics in search for new drug-like lead molecules.[12] For example, spirotryprostatin A and B, two natural alkaloids isolated from the fermentation broth of *Aspergillus fumigatus*, have been identified as novel inhibitors of microtubule assembly, while pteropodine and isopteropodine have been shown to

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modulate the function of muscarinic serotonin receptors.[10a,13] On the other hand, pyran-containing heterocycles have been found to have various biological activities.[14] For examples, zanthosimuline **I** is active against multidrug resistant KB-VI cancer cells, while huajiaosimuline **II** exhibits a selective cytotoxicity profile showing the greatest activity with estrogen receptor-positive ZR-75-1 breast cancer cells (Fig. 1).[15]

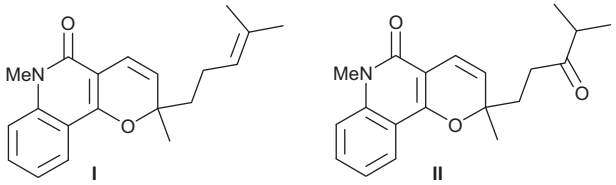


Fig. 1. Representative pyran-containing compounds.

In view of these important profiles enlightened by the recognition that molecules comprised of two or more heterocyclic nucleuses often possess heightened pharmacological activities,[16] remarkable attention has been aimed at synthesis of the spiro [4*H*-pyran-oxindole] ring system. Interest in the synthesis of these compounds was increased further by the fact that indoles spiro-fused at the 3-position generally show intensive biological properties.[17] The main synthetic avenue and direct method for assembling of spiro[4*H*-pyran-oxindole] compounds is based on the three-component condensations of two (usually different) 1,3-dicarbonyl compounds, or alternatively their synthetic equivalents, with isatin derivatives. These reactions are generally slow processes by themselves at room temperature, so several methods describing activation by heating and assistance in aqueous media by using various catalysts, such as ammonium chloride,[18] ethylenediamine diacetate,[19] surfactant metal carboxylates,[20] L-proline,[21] triethylbenzyl ammonium (TEBA) salt,[22] and β-cyclodextrin[23] were devised so far to facilitate the synthesis. Beside traditional heating methods, microwave dielectric heating employing $InCl_3$ under solvent-free conditions has been similarly used to shorten the reaction times significantly.[24] Alternatively, Et_3N-catalyzed three-component condensations[25] and piperidine assisted two-component reactions were invoked to give spiro-fused pyran-oxindole scaffold in refluxing ethanol solutions.[26] All the above mentioned methods despite using catalysts need thermal treatment to force the reactions to perform. Elinson and co-workers undertook an electrolytic procedure to provide electrochemical activation to the reactions whereby they were able to afford similar syntheses at ambient temperature.[27] Although each of the recent methods has merit, some methods are weakened by at least one limitation, such as low yields especially when bulky substituents on substrates lead to low solubility in water, complicated workup procedure, requiring large amounts of organic solvents for chromatographic separation, and technical intricacy.

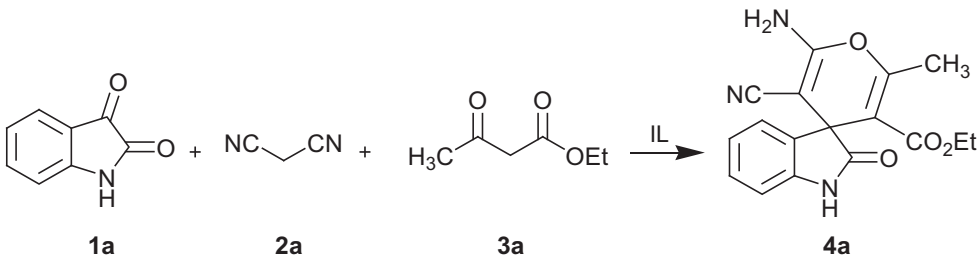
Therefore the development of a simple and efficient method, addressing the management of the above mentioned drawbacks, for synthesis of spiro-fused pyran-oxindole heterocycles would be an interesting challenge.

2. Results and discussion

At the onset of study, an equimolar mixture of the model substrates; isatin **1a**, malononitrile **2**a, and ethyl aceto-acetate **3**a was treated with the selected ionic liquids without any added catalyst or solvent (Scheme 1).

The results are shown in Table 1, implying the essential role of ionic liquids to carry on the reaction in reasonable time even at extended temperatures. This screening also covers a short range of pH conditions associated with the selected ionic liquids to investigate the effect of acidity or basicity of these media on the reaction performance. As can be seen from Table 1, excellent results in terms of reaction time and yield were obtained in the neutral ionic liquid, $[BMIm]BF_4$, still at ambient temperature (entry 7). The model reaction was similarly catalyzed in the neutral ionic liquid medium of [BMIm]Br, however to less extent comparing with $[BMIm]BF_4$ but superior to those of acidic (entry 8) and basic guanidinium ionic liquids (entries 3 and 5). These observations reasonably lend support to the acceptance of the pure ionic nature of the catalysis interactions and so would account for its dependence on the entity of the ion constituents. The interesting evidence in support of this hypothesis comes from the observation that substantial improvements in catalytic activity of TMGT and $TMGT_f$ were gained by addition of either NH_4Cl or NH_4AcO to these ionic liquids. In these improved ionic liquids, the model reaction takes place efficiently at room temperature in contrast with aqueous solutions of these ammonium salts in which the reaction becomes feasible only above 80 °C. Notably, Table 1 shows that in the less active ionic liquids the reaction stops at production of the two-component product derived from isatin and malononitrile.

After detecting $[BMIm]BF_4$ as the more efficient catalyst solvent, we examined the method with a range of substrates to determine the reaction specificity and scope. Consequently, various substituted isatins **1a**–**f** were used to react with malononitrile **2a** or ethyl cyano-acetate **2b** and six 1,3-dicarbonyl compounds **3a**–**f** under the optimized conditions (Table 2). From the results shown in Table 2, it is evident that both electron-deficient and electron-rich isatins afford fairly high yields of the desired spiro-condensates in reaction with malononitrile and a variety of 1,3-dicarbonyl compounds in a few minutes at ambient temperature. Moreover, employing ethyl cyano-acetate instead of malononitrile furnished similar connective assembly of spiro-annulated pyran-oxindole products. The general aspect of the present method partially lies on the fact that amidic N–H group of isatins do not affect the course of the reactions, as *N*-substituted and unsubstituted isatins take part similarly in the reaction to give the corresponding products. Although, Table 2 highlights a variety of structures accepted by the method to give fairly high yields of the desired products, the scope of the method is expected to be even wider due to its mild conditions without applying extra activation energy,



Scheme 1. The model reaction.

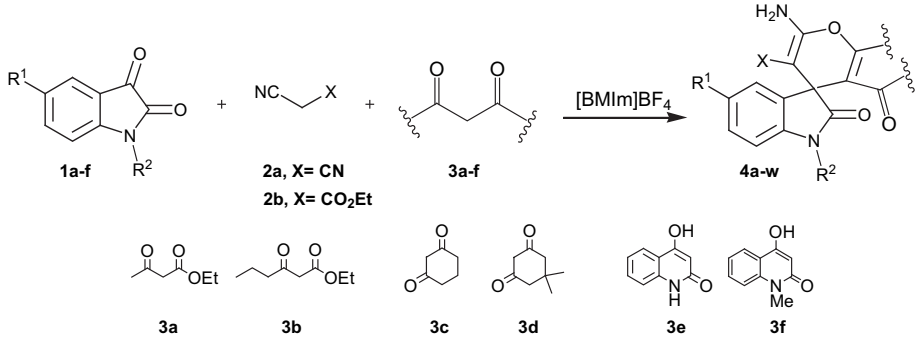
Table 1
Optimization of reaction condition

Entry	ILs	T(°C)	Time(min)	Yield[a] (%)
1	—	rt (25)	180	Trace
2	—	80	60	Trace
3	TMGT	rt (25)	60	Intermediate[b]
4	TMGT	100	90	79
5	$TMGT_f$	rt (25)	30	20
6	$TMGT_f$	100	30	83
7	$[BMIm]BF_4$	rt (25)	<1	95
8	[BMIm]Br	rt (25)	20	72
9	$[HMIm]/HSO_4$	rt (25)	100	Intermediate[b]
10	$[HMIm]/HSO_4$	100	100	Intermediate[b]

[a] Isolated yields.
[b] Just intermediate **5** was formed. TMGT stands for *N,N,N,N*-tetramethyl guanidinium trifluoroacetate. $TMGT_f$ stands for *N,N,N,N*-tetramethyl guanidinium triflate.

pathways, namely A and B (Scheme 2). Once the three components are mixed, isatin **1a** undergoes Knoevenagel condensation with malononitrile **2a** in the ionic liquid, $[BMIm]BF_4$, to afford isatylidene malononitrile **5**, which is subsequently attacked by **3a** to furnish the central intermediate **7** (path A) Alternatively, intermediate **7** is likely formed from initial condensation of isatin **1a** with **3a** to afford **6**, followed by nucleophilic addition of malononitrile **2** (path B). The two pathways go through polar transition states **TS1** wherefrom as a consequence of dipole–dipole coulombic-type interactions with the ionic medium require less activation energy to give **5** or **6**. The ionic liquid is also considered to facilitate the dehydration of the initially formed aldol-adducts. Catalysis effect of the ionic liquid can also be foreseen when considering the following step where the cyclization of **7** occurs also via a dipolar transition state **TS2** amenable to establish favored

Table 2
Synthesis of spiro-oxindole derivatives **4** in the presence of $[BMIm]BF_4$

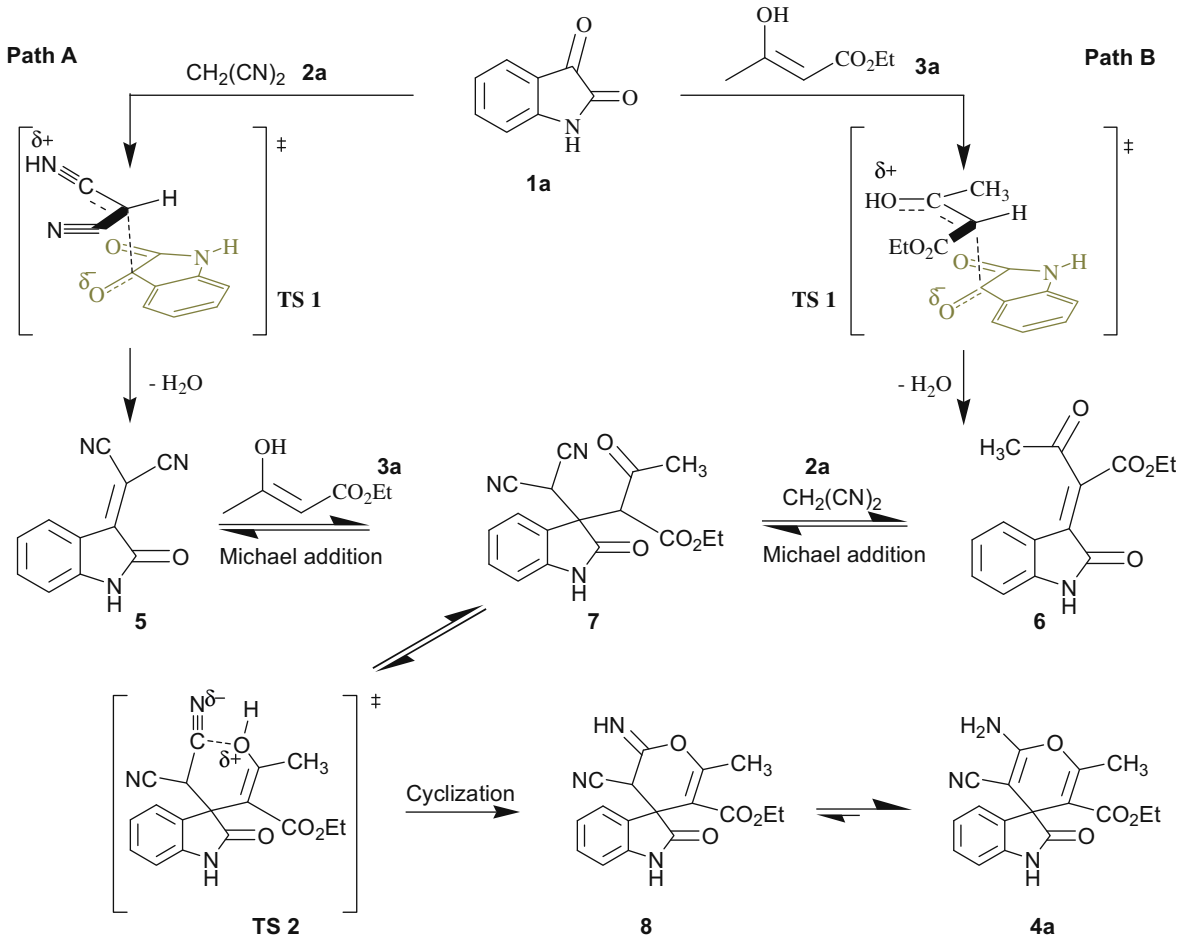


Entry	Product	R^1	R^2	X	1,3-Diketone	Time (min)	Yield (%)
1	**4a**	H	H	CN	**3a**	<1	95[a]
2	**4b**	H	H	CN	**3b**	2	93
3	**4c**	H	H	CN	**3c**	3	91[b]
4	**4d**	H	H	CN	**3d**	3	94[b]
5	**4e**	H	H	CN	**3e**	5	89[c]
6	**4f**	H	H	CN	**3f**	5	90
7	**4g**	Br	H	CN	**3a**	<1	93[d]
8	**4h**	Br	H	CN	**3b**	2	93
9	**4i**	Cl	H	CN	**3a**	<1	91[d]
10	**4j**	Cl	H	CN	**3b**	2	92
11	**4k**	NO_2	H	CN	**3a**	<1	93
12	**4l**	NO_2	H	CN	**3b**	2	92
13	**4m**	OCH_3	H	CN	**3a**	<1	94
14	**4n**	OCH_3	H	CN	**3b**	2	92
15	**4o**	H	H	CO_2Et	**3c**	5	93[e]
16	**4p**	H	H	CO_2Et	**3d**	5	91[e]
17	**4q**	H	H	CO_2Et	**3e**	5	88
18	**4r**	H	H	CO_2Et	**3f**	5	90[d]
19	**4s**	OCH_3	H	CN	**3e**	5	89
20	**4t**	OCH_3	H	CO_2Et	**3f**	5	90
21	**4u**	NO_2	H	CN	**3e**	5	88
22	**4v**	NO_2	H	CO_2Et	**3e**	5	86
23	**4w**	H	Bn	CN	**3d**	3	94[f]

[a] Ref. 20,21,27.
[b] Ref. 18,20,21.
[c] Ref. 28.
[d] Ref. 21.
[e] Ref. 18,21.
[f] Ref. 20.

base, or acid catalysts. The products were collected by simple filtration thus resulting in a very efficient and easy-going procedure.

All the reactions featured a strict selectivity toward synthesis of the spiro-annulated 2-amino-4*H*-pyran compounds **4**. A plausible mechanism explaining the aforementioned results and the selectivity is depicted in Scheme 2. The process represents a typical cascade of Knoevenagel condensation, Michael addition, and a Thorpe-Ziegler type cyclization,[29] which might initiate via two interactions with the ionic field. The intermediate **7** along with the two other conceivable 3,3-disubstituted oxindoles, i.e., those derived from addition of **2a** onto **5** and addition of **3a** onto **6**, apparently exist in a complex equilibrium, which reasonably is inclined toward substitution of the weaker carbon-acid, i.e., malononitrile. Presumably, among the 3,3-disubstituted oxindoles involved in the equilibrium only the mixed substituted component **7** could undergo cyclization to **8** and subsequently to the more stable



Scheme 2. Possible mechanism for the formation of products **4a**.

tautomer **4a**. The later transformations would bias the equilibrium toward formation of **7** and give rise to selective synthesis of the desired product **4a**.

In the next phase of study the viability of catalysis by the recycled ionic liquid was evaluated. In this regard preparation of **4a** was chosen as the model. After completion of the reaction the ionic liquid was washed using water, evaporated under reduced pressure and then subjected to the next run with the same substrates and the same reaction time. Table 3 displays similar high conversions obtained after consecutive recycling of the ionic liquid (Table 3).

Table 3
Recyclability of $[BMIm]BF_4$

Entry	Cycle	Yield (%)
1	Fresh	95
2	First recycle	94
3	Second recycle	92
4	Third recycle	90
5	Fourth recycle	90

3. Conclusion

In summary, an efficient method for the synthesis of the spiro-annulated pyran-oxindole ring system by using simple and readily available starting materials under catalysis of the ionic liquid, $[BMIm]BF_4$, was introduced here. The ionic liquid acts as a catalyst solvent and can be recovered for reuse several times. Another advantage of the present method may be no requirement for metal catalysts or additional solvent and proceeding with similar rate with respect to the methods that gave the similar structure. We expect this method will find extensive applications in the field of combinatorial chemistry, diversity-oriented synthesis, and drug discovery.

4. Experimental section

4.1. Typical procedure for preparation of ethyl 2′-amino-3′-cyano-6′-methyl-2-oxo-spiro[indoline-3,4′-pyran]-5′-carboxylate

A mixture of isatin **1a** (0.147 g, 1 mmol), malononitrile **2a** (0.066 g, 1 mmol), and ethyl aceto-acetate **3a** (0.13 mL, 1 mmol) was added to a vial containing a magnetic stirring bar and the ionic liquid ($[BMIm]BF_4$, 5 drops). The reaction mixture was sealed and stirred at room temperature until disappearance of the starting materials (under 1 min). At this stage, the product due to poor solubility in the ionic liquid appears as a precipitate. In order to extract the ionic liquid, after completion of the reaction, the residue was washed with 2×10 mL of either water or diethyl ether. Washing the solid residue with ethanol (10 mL, 95.5%) has given remarkably pure powders of product **4a**. The ionic liquid was recovered from the aqueous or ethereal extracts by evaporating under reduced pressure and reused in the next cycles.

*4.1.1. Ethyl 2′-amino-3′-cyano-6′-methyl-2-oxo-spiro[indoline-3,4′-pyran]-5′-carboxylate (**4a**).* White powder. Yield (0.31 g, 95%). Mp: 260–262 °C. IR (KBr), ν_{max}: 3397, 3300, 3185, 2926, 2200, 1720, 1694, 1675, 1619, 1592 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ:

0.78 (t, 3H, *J* 7.2 Hz, O–CH_2CH_3), 2.32 (s, 3H, 6′-CH_3), 3.70–3.84 (m, 2H, O–CH_2CH_3), 6.79 (d, 1H, *J* 7.6 Hz, 7-H), 6.93 (dt, 1H, *J* 7.2 and 0.8 Hz, 5-H), 7.06 (d, 1H, *J* 7.2 Hz, 4-H), 7.15 (s, 2H, NH_2), 7.18 (dt, 1H, *J* 7.6 and 1.2 Hz, 6-H), 10.41 (s, 1H, NH).

*4.1.2. Ethyl 2′-amino-3′-cyano-6′-propyl-2-oxo-spiro[indoline-3,4′-pyran]-5′-carboxylate (**4b**).* White powder. Yield (0.33 g, 93%). Mp: 198–200 °C. IR (KBr), ν_{max}: 3400, 3294, 3180, 2960, 2197, 1717, 1695, 1617, 1592 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ: 0.79 (t, 3H, *J* 7.2 Hz, $CH_2CH_2CH_3$), 0.95 (t, 3H, *J* 7.4 Hz, OCH_2CH_3), 1.63 (m, 2H, $CH_2CH_2CH_3$), 2.59–2.71 (m, 2H, $CH_2CH_2CH_3$), 3.70–3.83 (m, 2H, OCH_2CH_3), 6.79 (d, 1H, *J* 7.6 Hz, 7-H), 6.94 (t, 1H, *J* 7.4 Hz, 5-H), 7.02 (d, 1H, *J* 7.2 Hz, 4-H), 7.15 (s, 2H, NH_2), 7.18 (t, 1H, *J* 7.6 Hz, 6-H), 10.40 (s, NH). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 13.4 (CH_3), 13.7 (CH_3), 20.6 ($CH_2CH_2CH_3$), 33.3 ($CH_2CH_2CH_3$), 49.5 (C_{spiro}), 56.7 (*C*–C≡N), 60.7 (O–CH_2CH_3), 105.5 (*C*–CO_2Et), 109.8 (*C*≡N), 118.0 (C-3a), 122.3, 123.8, 129.0, 134.9, 142.6 (C-7a), 159.6, 161.5 (C-2′ and C-6′), 164.9 (C=O ester), 179.0 (C=O amide). MS (EI, 70 eV) *m*/*z* (%): 353 (M^+, 13), 327 (14), 280 (100), 251 (11), 210 (21). Anal. Calcd for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89%. Found: C, 64.52; H, 5.47; N, 12.03%.

*4.1.3. 2-Amino-2′,5-dioxo-5,6,7,8-tetrahydro-spiro[chromene-4,3′-indoline]-3-carbonitrile (**4c**).* White powder. Yield (0.28 g, 91%). Mp: 296–298 °C. IR (KBr), ν_{max}: 3354, 3295, 3153, 2198, 1717, 1674, 1653, 1615, 1596 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ: 1.91–1.95 (m, 2H, 7-H), 2.18–2.27 (m, 2H, 8-H), 2.66 (t, 2H, *J* 6.4 Hz, 6-H), 6.78 (d, 1H, *J* 7.6 Hz, 7′-H), 6.89 (dt, 1H, *J* 7.2 and 0.8 Hz, 5′-H), 7.00 (d, 1H, *J* 6.8 Hz, 4′-H), 7.14 (dt, 1H, *J* 7.6 and 1.2 Hz, 6′-H), 7.22 (s, 2H, NH_2), 10.40 (s, 1H, NH).

*4.1.4. 2-Amino-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydro-spiro[chromene-4,3′-indoline]-3-carbonitrile (**4d**).* White powder. Yield (0.30 g, 94%). Mp: 290–292 °C. IR (KBr), ν_{max}: 3364, 3300, 3145, 2198, 1718, 1700, 1648, 1559 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ: 1.00 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.10 (d, 1H, *J* 16.0 Hz, 8-H_B), 2.18 (d, 1H, *J* 16.0 Hz, 8-H_A), 2.53 (d, 1H, *J* 16.0 Hz, 6-H_B), 2.59 (d, 1H, *J* 16.0 Hz, 6-H_A) 6.79 (d, 1H, *J* 7.6 Hz, 7′-H), 6.89 (dt, 1H, *J* 7.6 and 0.8 Hz, 5′-H), 6.98 (d, 1H, *J* 6.8 Hz, 4′-H), 7.14 (dt, 1H, *J* 7.6 and 1.2 Hz, 6′-H), 7.23 (s, 2H, NH_2), 10.40 (s, 1H, NH).

*4.1.5. 2-Amino-2′,5-dioxo-5,6-dihydro-spiro[pyrano[3,2-c]quinoline-4,3′-indoline]-3-carbonitrile (**4e**).* White powder. Yield (0.32 g, 89%). Mp >300 °C. IR (KBr), ν_{max}: 3370, 3250, 3200, 2200, 1724, 1674, 1618, 1585 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ: 6.83 (d, 1H, *J* 7.6 Hz, 7′-H), 6.88 (dt, 1H, *J* 7.6 and 0.9 Hz, 5′-H), 7.03 (d, 1H, *J* 7.2 Hz, 4′-H), 7.18 (dt, 1H, *J* 7.6 and 1.2 Hz, 6′-H), 7.33 (t, 1H, *J* 8.0 Hz, 9-H), 7.35 (d, 1H, *J* 8.4 Hz, 7-H), 7.45 (s, 2H, NH_2), 7.62 (dt, 1H, *J* 7.8 and 1.2 Hz, 8-H), 7.95 (dd, 1H, *J* 8.2 and 1.2 Hz, 10-H), 10.52 (s, 1H, NH), 11.73 (s, 1H, NH).

*4.1.6. 2-Amino-6-methyl-2′,5-dioxo-5,6-dihydro-spiro[pyrano[3,2-c]quinoline-4,3′-indoline]-3-carbonitrile (**4f**).* Pale yellow powder. Yield (0.33 g, 90%). Mp >300 °C. IR (KBr), ν_{max}: 3420, 3220, 3230, 2199, 1721, 1675, 1620, 1589 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ: 3.47 (s, 3H, CH_3), 6.84 (d, 1H, *J* 7.6 Hz, 7′-H), 6.87 (t, 1H, *J* 7.6 and 0.8 Hz, 5′-H), 7.02 (d, 1H, *J* 7.2 Hz, 4′-H), 7.17 (dt, 1H, *J* 7.6 and 1.2 Hz, 6′-H), 7.43 (dt, 1H, *J* 7.2 and 0.8 Hz, 9-H), 7.49 (s, 2H, NH_2), 7.57 (d, 1H, *J* 8.4 Hz, 7-H), 7.74 (dt, 1H, *J* 8.0 and 1.6 Hz, 8-H), 8.06 (dd, 1H, *J* 8.0 and 1.6 Hz, 10-H), 10.56 (s, 1H, NH). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 29.7 (CH_3), 48.6 (C_{spiro}), 57.7 (*C*–C≡N), 106.9 (C-4a), 109.7 (*C*≡N), 112.7 (C-10a), 115.5, 118.0, 122.2, 122.8, 122.9, 123.9, 128.8, 132.7, 134.7, 139.1 (C-6a), 143.0 (C-7′a), 152.0 (C-10b), 159.2, 159.4 (C-2 and C=O), 178.3 (oxindole C=O). MS (EI) *m*/*z* (%): 370 (M^+, 71), 344 (58), 327 (33), 316 (60), 195 (94), 175 (100). Anal. Calcd for $C_{21}H_{14}N_4O_3$: C, 68.10; H, 3.81; N, 15.13%. Found: C, 68.17; H, 3.79; N, 15.09%.

*4.1.7. Ethyl 2′-amino-5-bromo-3′-cyano-6′-methyl-2-oxo-spiro[indoline-3,4′-pyran]-5′-carboxylate (**4g**).* White powder. Yield (0.37 g, 93%). Mp: 262–264 °C. IR (KBr), ν_{max}: 3397, 3300, 3200, 3185, 2200, 1708, 1665, 1612, 1584 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ: 0.83 (t, 3H, *J* 6.4 Hz, O–CH_2CH_3), 2.33 (s, 3H, 6′-CH_3), 3.81 (m, 2H, O–CH_2CH_3), 6.77 (d, 1H, *J* 7.8 Hz, 7-H), 7.24 (s, 2H, NH_2), 7.29 (s, 1H, 4-H), 7.36 (d, 1H, *J* 7.8 Hz, 6-H), 10.56 (s, 1H, NH).

*4.1.8. Ethyl 2′-amino-5-bromo-3′-cyano-6′-propyl-2-oxo-spiro[indoline-3,4′-pyran]-5′-carboxylate (**4h**).* White powder. Yield (0.40 g 93%). Mp: 240 °C decomp. IR (KBr), ν_{max}: 3455, 3260, 3125, 3000, 2200, 1723, 1671, 1617, 1586 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ: 0.84 (t, 3H, *J* 7.2 Hz, $CH_2CH_2CH_3$), 0.94 (t, 3H, *J* 7.4 Hz, O–CH_2CH_3), 1.63 (br sextet, 2H, $CH_2CH_2CH_3$), 2.67 (m, 2H, $CH_2CH_2CH_3$), 3.82 (m, 2H, O–CH_2CH_3), 6.77 (d, 1H, *J* 7.6 Hz, 7-H), 7.22 (s, 1H, 4-H), 7.24 (s, 2H, NH_2), 7.37 (d, 1H, *J* 7.6 Hz, 6-H), 10.57 (s, 1H, NH). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 13.5 (CH_3), 13.8 (CH_3), 20.6 ($CH_2CH_2CH_3$), 33.4 ($CH_2CH_2CH_3$), 49.8 (C_{spiro}), 56.2 (*C*–C≡N), 60.9 (O–CH_2CH_3), 104.6 (*C*–CO_2Et), 111.8 (*C*≡N), 113.9 (*C*–Br), 117.8 (C-3a), 126.5, 131.8, 137.5 (3CH), 142.0 (C-7a), 159.6, 162.5 (C-2′ and C-6′), 164.7 (C=O ester), 178.0 (C=O amide). MS (EI, 70 eV) *m*/*z* (%): 433 (M^+, ^{81}Br, 20), 431 (M^+, ^{79}Br, 21), 405 (17), 360 (100), 331 (16). Anal. Calcd for $C_{19}H_{18}BrN_3O_4$: C, 52.79; H, 4.20; N, 9.72%. Found: C, 52.73; H, 4.29; N, 9.70%.

*4.1.9. Ethyl 2′-amino-5-chloro-3′-cyano-6′-methyl-2-oxo-spiro[indoline-3,4′-pyran]-5′-carboxylate (**4i**).* White powder. Yield (0.33 g, 91%). Mp: 255–257 °C. IR (KBr), ν_{max}: 3396, 3292, 3185, 2200, 1715, 1700, 1618, 1588 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ: 0.84 (t, 3H, *J* 6.8 Hz, O–CH_2CH_3), 2.34 (s, 3H, CH_3), 3.77–3.87 (m, 2H, O–CH_2CH_3), 6.81 (d, 1H, *J* 8.4 Hz, 7-H), 7.19 (d, 1H, *J* 2.2 Hz, 4-H), 7.23 (dd, 1H, *J* 8.4 and 2.2 Hz, 6-H), 7.24 (s, 2H, NH_2), 10.55 (s, 1H, NH).

*4.1.10. Ethyl 2′-amino-5-chloro-3′-cyano-6′-propyl-2-oxo-spiro[indoline-3,4′-pyran]-5′-carboxylate (**4j**).* White powder. Yield (0.36 g, 92%). Mp: 218–220 °C. IR (KBr), ν_{max}: 3400, 3303, 3196, 2950, 2200, 1718, 1684, 1600 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ: 0.84 (t, 3H, *J* 7.2 Hz, CH_3), 0.95 (t, 3H, *J* 7.2 Hz, CH_3), 1.59–1.67 (m, 2H, $CH_2CH_2CH_3$), 2.63–2.72 (m, 2H, $CH_2CH_2CH_3$), 3.77–3.87 (m, 2H, O–CH_2CH_3), 6.82 (d, 1H, *J* 8.0 Hz, 7-H), 7.11 (d, 1H, *J* 2.0 Hz, 4-H), 7.25 (dd, 1H, *J* 8.0 and 2.0 Hz, 6-H), 7.24 (s, 2H, NH_2), 10.56 (s, 1H, NH). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 13.5 (CH_3), 13.8 (CH_3), 20.6 ($CH_2CH_2CH_3$), 33.4 ($CH_2CH_2CH_3$), 49.8 (C_{spiro}), 56.2 (*C*–C≡N), 60.9 (O–CH_2CH_3), 104.6 (*C*–CO_2Et), 111.3 (*C*≡N), 117.8 (C-3a), 123.9, 126.2, 128.9 (3CH), 137.1 (C-5), 141.5 (C-7a), 159.6, 162.5 (C-2′ and C-6′), 164.7 (C=O ester), 178.8 (C=O amide). MS (EI, 70 eV) *m*/*z* (%): 387 (M^+, 8), 361 (5), 314 (25), 252 (9), 43 (100). Anal. Calcd for $C_{19}H_{18}ClN_3O_4$: C, 58.84; H, 4.68; N, 10.84%. Found: C, 58.82; H, 4.71; N, 10.89%.

*4.1.11. Ethyl 2′-amino-5-nitro-3′-cyano-6′-methyl-2-oxo-spiro[indoline-3,4′-pyran]-5′-carboxylate (**4k**).* Pale yellow powder. Yield (0.34 g, 93%). Mp: 270–272 °C. IR (KBr), ν_{max}: 3400, 3300, 3182, 2200, 1719, 1704, 1622, 1584, 1520, 1337 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ: 0.85 (t, 3H, *J* 7.2 Hz, OCH_2CH_3), 2.38 (s, 3H, 6′-CH_3), 3.78–3.87 (m, 2H, OCH_2CH_3), 7.03 (d, 1H, *J* 8.6 Hz, 7-H), 7.36 (s, 2H, NH_2), 8.04 (d, 1H, *J* 2.4 Hz, 4-H), 8.19 (dd, 1H, *J* 8.6 and 2.4 Hz, 6-H), 11.18 (s, 1H, NH). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 13.5 (O–CH_2CH_3), 19.4 (6′-CH_3), 49.6 (C_{spiro}), 55.7 (*C*–C≡N), 61.1 (OCH_2CH_3), 103.5 (*C*–CO_2Et), 110.0 (*C*≡N), 117.6 (C-3a), 119.6, 126.5, 136.4 (3CH), 142.9 (C-7a), 149.0 (C-5), 159.5, 161.0 (C-2′ and C-6′), 164.7 (C=O ester), 179.6 (C=O amide). MS (EI, 70 eV) *m*/*z* (%): 325

(37), 295 (17), 71 (47), 43 (100). Anal. Calcd for $C_{17}H_{14}N_4O_6$: C, 55.14; H, 3.81; N, 15.13%. Found: C, 55.10; H, 3.86; N, 15.17%.

*4.1.12. Ethyl 2′-amino-5-nitro-3′-cyano-6′-propyl-2-oxo-spiro[indoline-3,4′-pyran]-5′-carboxylate (**4l**).* White powder. Yield (0.36 g, 92%). Mp: 238–240 °C. IR (KBr), ν_{max}: 3392, 3303, 3200, 2992, 2200, 1722, 1675, 1620, 1595, 1521, 1338 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ: 0.85 (t, 3H, *J* 7.2 Hz, CH_3), 0.96 (t, 3H, *J* 7.2 Hz, CH_3), 1.63 (br sextet, 2H, $CH_2CH_2CH_3$), 2.65–2.80 (m, 2H, $CH_2CH_2CH_3$), 3.79–3.87 (m, 2H, O–CH_2CH_3), 7.04 (d, 1H, *J* 8.6 Hz, 7-H), 7.38 (s, 2H, NH_2), 7.96 (d, 1H, *J* 2.4 Hz, 4-H), 8.20 (dd, 1H, *J* 8.6 and 2.4 Hz, 6-H), 11.20 (s, 1H, NH). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 13.5 (CH_3), 13.8 (CH_3), 20.6 ($CH_2CH_2CH_3$), 33.6 ($CH_2CH_2CH_3$), 49.7 (C_{spiro}), 55.4 (C–C≡N), 61.1 (O–CH_2CH_3), 103.9 (C–CO_2Et), 110.1 (C≡N), 117.6 (C-3a), 119.3, 126.6, 136.2 (3CH), 142.9 (C-7a), 149.1 (C-5), 159.7, 163.5, 164.5 (C=O ester), 179.5 (C=O amide). MS (EI, 70 eV) *m*/*z* (%): 400 (M^+, 80), 295 (37), 105 (100). Anal. Calcd for $C_{19}H_{18}N_4O_6$: C, 57.28; H, 4.55; N, 14.06%. Found: C, 57.25; H, 4.59; N, 14.17%.

*4.1.13. Ethyl 2′-amino-5-methoxy-3′-cyano-6′-methyl-2-oxo-spiro[indoline-3,4′-pyran]-5′-carboxylate (**4m**).* White powder. Yield (0.33 g, 94%). Mp: 214–216 °C. IR (KBr), ν_{max}: 3445, 3296, 3172, 2200, 1716, 1700, 1681, 1621, 1600, 1494 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ: 0.81 (t, 3H, *J* 7.0 Hz, OCH_2CH_3), 2.32 (s, 3H, 6′-CH_3), 3.68 (s, 3H, OCH_3), 3.74–3.84 (m, 2H, O–CH_2CH_3), 6.68 (d, 1H, *J* 2.4 Hz, 4-H), 6.71 (d, 1H, *J* 8.4 Hz, 7-H), 6.75 (dd, 1H, *J* 8.4 and 2.4 Hz, 6-H), 7.14 (s, 2H, NH_2), 10.22 (s, 1H, NH). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 13.5 (O–CH_2CH_3), 19.1 (6′-CH_3), 49.9 (C_{spiro}), 55.9 (OCH_3), 57.1 (C–C≡N), 60.7 (O–CH_2CH_3), 105.0 (C–CO_2Et), 110.2, 110.7, 113.6, 118.0 (C-3a), 135.9, 136.3, 155.5, 159.1, 159.4, 165.0 (C=O ester), 179.0 (C=O amide). MS (EI, 70 eV) *m*/*z* (%): 355 (M^+, 13), 282 (28), 225 (33), 210 (41), 177 (54), 149 (85), 106 (100). Anal. Calcd for $C_{18}H_{17}N_3O_5$: C, 60.84; H, 4.82; N, 11.83%. Found: C, 60.83; H, 4.89; N, 11.75%.

*4.1.14. Ethyl 2′-amino-5-methoxy-3′-cyano-6′-propyl-2-oxo-spiro[indoline-3,4′-pyran]-5′-carboxylate (**4n**).* White powder. Yield (0.35 g, 92%). Mp: 230–232 °C. IR (KBr), ν_{max}: 3400, 3300, 3200, 2960, 2200, 1722, 1668, 1600, 1485 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ: 0.82 (t, 3H, *J* 7.2 Hz, CH_3), 0.95 (t, 3H, *J* 7.2 Hz, CH_3), 1.63 (br sextet, 2H, $CH_2CH_2CH_3$), 2.61–2.71 (m, 2H, $CH_2CH_2CH_3$), 3.68 (s, 3H, OCH_3), 3.74–3.83 (m, 2H, OCH_2CH_3), 6.61 (d, 1H, *J* 2.4 Hz, 4-H), 6.71 (d, 1H, *J* 8.4 Hz, 7-H), 6.76 (dd, 1H, *J* 8.4 and 2.4 Hz, 6-H), 7.14 (s, 2H, NH_2), 10.22 (s, 1H, NH). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 13.5 (CH_3), 13.7 (CH_3), 20.6 ($CH_2CH_2CH_3$), 33.3 ($CH_2CH_2CH_3$), 49.9 (C_{spiro}), 55.9 (OCH_3), 56.9 (C–CN), 60.7 (O–CH_2CH_3), 105.5 (C–CO_2Et), 110.2, 110.7, 113.5, 118.0 (C-3a), 135.9, 136.2, 155.5 (C-5), 159.6, 161.6 (C-2′ and C-6′), 164.9 (C=O ester), 178.9 (C=O amide). MS (EI, 70 eV) *m*/*z* (%): 383 (M^+, 16), 328 (14), 310 (32), 57 (58), 43 (100). Anal. Calcd for $C_{20}H_{21}N_3O_5$: C, 62.65; H, 5.52; N, 10.96%. Found: C, 62.60; H, 5.58; N, 10.87%.

*4.1.15. Ethyl 2-amino-2′,5-dioxo-5,6,7,8-tetrahydro-spiro[chromene-4,3′-indoline]-3-carboxylate (**4o**).* White powder. Yield (0.31 g, 93%). Mp: 252–254 °C. IR (KBr), ν_{max}: 3374, 3230, 3180, 1718, 1708, 1685, 1650, 1618, 1590 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ: 0.79 (t, 3H, *J* 7.2 Hz, OCH_2CH_3), 1.80–1.92 (m, 2H, CH_2), 2.10–2.26 (m, 2H, CH_2), 2.64 (t, 2H, *J* 6.4 Hz, CH_2), 3.64–3.75 (m, 2H, OCH_2CH_3), 6.66 (d, 1H, *J* 7.6 Hz, 7′-H), 6.76 (dt, 1H, *J* 7.2 and 0.8 Hz, 5′-H), 6.85 (d, 1H, *J* 6.8 Hz, 4′-H), 7.04 (dt, 1H, *J* 7.6 and 1.2 Hz, 6′-H), 7.85 (s, 2H, NH_2), 10.14 (s, 1H, NH).

*4.1.16. Ethyl 2-amino-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydro-spiro[chromene-4,3′-indoline]-3-carboxylate (**4p**).* White powder. Yield (0.35 g, 91%). Mp: 255–257 °C. IR (KBr), ν_{max}: 3360, 3230, 3190, 1713, 1682, 1664, 1610, 1520 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ: 0.80 (t, 3H, *J* 7.2 Hz, OCH_2CH_3), 0.95 (s, 3H, 7-CH_3), 1.02 (s, 3H, 7-CH_3), 2.01 (d, 1H, *J* 16 Hz, 8-H_B), 2.15 (d, 1H, *J* 16 Hz, 8-H_A), 2.48 (d, 1H, *J* 17.6 Hz, 6-H_B), 2.58 (d, 1H, *J* 17.6 Hz, 6-H_A), 3.69–3.72 (m, 2H, OCH_2CH_3), 6.67 (d, 1H, *J* 7.6 Hz, 7′-H), 6.76 (t, 1H, *J* 7.2 Hz, 5′-H), 6.83 (d, 1H, *J* 7.2 Hz, 4′-H), 7.04 (t, 1H, *J* 7.2 Hz, 6′-H), 7.86 (s, 2H, NH_2), 10.14 (s, 1H, NH).

*4.1.17. Ethyl 2-amino-2′,5-dioxo-5,6-dihydro-spiro[pyrano[3,2-c]quinoline-4,3′-indoline]-3-carboxylate (**4q**).* Yellow powder. Yield (0.35 g, 88%). Mp >300 °C. IR (KBr), ν_{max}: 3300, 3200, 2950, 1720, 1690, 1670, 1620, 1365 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ: 0.84 (t, 3H, *J* 7.2 Hz, OCH_2CH_3), 3.70–3.82 (m, 2H, OCH_2CH_3), 6.71 (d, 1H, *J* 7.6 Hz, 7′-H), 6.75 (t, 1H, *J* 7.2 Hz, 5′-H), 6.87 (d, 1H, *J* 7.2 Hz, 4′-H), 7.07 (t, 1H, *J* 7.6 Hz, 6′-H), 7.30 (t, 1H, *J* 7.2 Hz, 9-H), 7.31 (d, 1H, *J* 8.0 Hz, 7-H), 7.59 (dt, 1H, *J* 7.8 and 1.4 Hz, 8-H), 8.02 (d, 1H, *J* 7.6 Hz, 10-H), 8.05 (s, 2H, NH_2), 10.27 (s, 1H, NH), 11.53 (s, 1H, NH). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 13.6 (CH_3), 48.2 (C_{spiro}), 59.4 (O–CH_2), 76.4 (C-4a), 108.6, 110.0, 112.0, 115.5, 121.0, 122.4, 122.6, 123.2, 127.8, 132.0, 136.1, 138.1, 145.0, 151.6, 159.7, 159.8, 168.1 (C=O), 180.1 (C=O). MS (EI) *m*/*z* (%): 403 (M^+, 3), 381 (100), 330 (M^+–CO_2Et, 14), 253 (45). Anal. Calcd for $C_{22}H_{17}N_3O_5$: C, 65.50; H, 4.25; N, 10.42%. Found: C, 65.51; H, 4.33; N, 10.37%.

*4.1.18. Ethyl 2-amino-6-methyl-2′,5-dioxo-5,6-dihydro-spiro[pyrano[3,2-c]quinoline-4,3′-indoline]-3-carboxylate (**4r**).* White powder. Yield (0.37 g, 90%). Mp >300 °C. IR (KBr), ν_{max}: 3305, 3197, 2996, 1715, 1685, 1623, 1524, 1465, 1360, 1287 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ: 0.87 (t, 3H, *J* 7.2 Hz, OCH_2CH_3), 3.45 (s, 3H, 6-CH_3), 3.71–3.83 (m, 2H, OCH_2CH_3), 6.72 (d, 1H, *J* 7.6 Hz, 7′-H), 6.74 (t, 1H, *J* 7.6 Hz, 5′-H), 3.86 (d, 1H, *J* 6.8 Hz, 4′-H), 7.07 (dt, 1H, *J* 7.6 and 1.2 Hz, 6′-H), 7.41 (t, 1H, *J* 7.4 Hz, 9-H), 7.53 (d, 1H, *J* 8.4 Hz, 7-H), 7.71 (dt, 1H, *J* 8.0 and 1.2 Hz, 8-H), 8.08 (s, 2H, NH_2), 8.15 (dd, 1H, *J* 8.0 and 1.2 Hz, 10-H), 10.29 (s, 1H, NH).

*4.1.19. 2-Amino-5′-methoxy-2′,5-dioxo-5,6-dihydro-spiro[pyrano[3,2-c]quinoline-4,3′-indoline]-3-carbonitrile (**4s**).* Yellow powder. Yield (0.34 g, 89%). Mp >300 °C. IR (KBr), ν_{max}: 3530, 3402, 3300, 3155, 2198, 1707, 1670, 1620, 1588, 1486, 1360 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ: 3.63 (s, 3H, OCH_3), 6.69 (br s, 1H, 4′-H), 6.74 (m, 2H, 6′-H and 7′-H), 7.33 (t, 1H, *J* 7.6 Hz, 9-H), 7.36 (d, 1H, *J* 7.6 Hz, 7-H), 7.45 (s, 2H, NH_2), 7.62 (dt, 1H, *J* 7.6 and 1.4 Hz), 7.95 (dd, 1H, *J* 8.0 and 1.2 Hz, 10-H), 10.35 (s, 1H, NH), 11.72 (s, 1H, NH). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 48.7 (C_{spiro}), 55.8 (OCH_3), 57.7 (C–C≡N), 107.4, 110.0, 110.7, 112.1, 113.6, 115.8, 118.0, 122.5, 122.6, 132.2, 136.0, 136.2, 138.3, 152.9 (C-5′), 155.5 (C-4b), 159.4, 159.9 (C-2 and C-5), 178.3 (C=O oxindoline). MS (EI) *m*/*z* (%): 381 (M^+–NH_2, 4), 370 (6), 368 (5), 342 (18), 305 (100), 277 (57), 250 (39). Anal. Calcd for $C_{21}H_{14}N_4O_4$: C, 65.28; H, 3.65; N, 14.50%. Found: C, 65.25; H, 3.65; 14.61%.

*4.1.20. Ethyl 2-amino-5′-methoxy-6-methyl-2′,5-dioxo-5,6-dihydro-spiro[pyrano[3,2-c]quinoline-4,3′-indoline]-3-carboxylate (**4t**).* Yellow powder. Yield (0.40 g, 90%). Mp >300 °C. IR (KBr), ν_{max}: 3350, 3280, 2965, 1705, 1685, 1645, 1593, 1484, 1358, 1282 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ: 0.88 (t, 3H, *J* 6.8 Hz, OCH_2CH_3), 3.46 (s, 3H, N–CH_3), 3.58 (s, 3H, O–CH_3), 3.78 (m, 2H, OCH_2CH_3), 6.50 (d, 1H, *J* 2.2 Hz, 4′-H), 6.62 (d, 1H, *J* 8.0 Hz, 7′-H), 6.65 (dd, 1H, *J* 8.4 and 2.2 Hz, 6′-H), 7.40 (t, 1H, *J* 8.0 Hz, 9-H), 7.53 (d, 1H, *J* 8.4 Hz, 7-H), 7.72 (dt, 1H, *J* 7.8 and 1.6 Hz, 8-H), 8.07 (s, 2H, NH_2), 8.15 (dd, 1H, *J* 8.0 and 1.2 Hz, 10-H), 10.12 (s, 1H, NH). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 13.6 (OCH_2CH_3), 29.6 (N–CH_3), 49.0 (C_{spiro}), 55.7 (OCH_3), 59.4 (OCH_2CH_3), 76.5 (C–C≡N), 108.6, 109.4, 110.5, 112.1, 112.7, 115.2, 122.6, 123.1, 132.4, 137.3, 138.8, 139.0, 150.8 (C-5′), 154.8 (C-4b), 159.1, 159.6 (C-2 and C-5), 168.1 (C=O ester), 179.9 (C=O oxindoline). MS (EI) *m*/*z* (%): 447 (M^+, 26), 374 (M^+–CO_2Et, 59), 317 (100), 249 (84). Anal. Calcd for $C_{24}H_{21}N_3O_6$: C, 64.42; H, 4.73; N, 9.39%. Found: C, 64.37; H, 4.77; N, 9.43%.

*4.1.21. 2-Amino-5′-nitro-2′,5-dioxo-5,6-dihydro-spiro[pyrano[3,2-c]quinoline-4,3′-indoline]-3-carbonitrile (**4u**).* Yellow powder. Yield

(0.35 g, 88%). Mp >300 °C. IR (KBr), ν_{max}: 3400, 3332, 3250, 3204, 2200, 1734, 1670, 1616, 1520, 1339 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ: 7.07 (d, 1H, *J* 8.8 Hz, 7′-H), 7.35 (t, 1H, *J* 7.6 Hz, 9-H), 7.37 (d, 1H, *J* 8.4 Hz, 7-H), 7.64 (t, 1H, *J* 8.0 Hz, 8-H), 7.66 (s, 2H, NH_2), 7.97 (d, 1H, *J* 7.6 Hz, 10-H), 8.13 (d, 1H, *J* 2.4 Hz, 4′-H), 8.19 (dd, 1H, *J* 8.8 and 2.4 Hz, 6′-H), 11.30 (s, 1H, NH), 11.83 (s, 1H, NH). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 48.4 (C_{spiro}), 56.1 (*C*–C≡N), 106.2, 109.8, 112.2, 116.0, 117.8, 120.0, 122.6, 122.8, 126.3, 132.4, 135.8, 138.4, 143.0 (C-5′), 149.4 (C-7′a), 153.5 (C-4b), 159.8 (C-2), 160.0 (C=O), 179.0 (C=O oxindoline). MS (EI) *m*/*z* (%): 400 (M^+−1, 3), 381 (37), 225 (70), 216 (100). Anal. Calcd for $C_{20}H_{11}N_5O_5$: C, 59.85; H, 2.76; N, 17.45%. Found: C, 59.79; H, 2.80; N, 17.51%.

*4.1.22. Ethyl 2-amino-5′-nitro-2′,5-dioxo-5,6-dihydro-spiro[pyrano [3,2-c]quinoline-4,3′-indoline]-3-carboxylate (**4v**).* Yellow powder. Yield (0.38 g, 86%). Mp >300 °C. IR (KBr), ν_{max}: 3480, 3360, 3300, 3150, 1720, 1686, 1675, 1507, 1480, 1362, 1337 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ: 0.86 (t, 3H, *J* 7.0 Hz, CH_3), 3.79 (q, 2H, OCH_2), 6.93 (d, 1H, *J* 8.8 Hz, 7-H), 7.32 (d, 1H, *J* 8.4 Hz, 7′-H), 7.33 (t, 1H, *J* 7.2 Hz, 9-H), 7.61 (t, 1H, *J* 7.6 Hz, 8-H), 7.87 (d, 1H, *J* 2.4 Hz, 4′-H), 8.05 (d, 1H, *J* 7.2 Hz, 10-H), 8.12 (dd, 1H, *J* 8.4 and 2.4 Hz, 6′-H), 8.20 (s, 2H, NH_2), 11.09 (s, 1H, NH), 11.64 (s, 1H, NH). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 13.7 (CH_3), 48.0 (C_{spiro}), 59.6 (OCH_2), 75.14 (*C*–C≡N), 108.50, 108.54, 112.0, 115.6, 118.9, 122.6, 122.8, 125.7, 132.3, 137.3, 138.2, 142.1 (C-7′a), 151.7 (C-4b), 152.3 (C-5), 160.0 (C-2), 167.6 (C=O ester), 180.8 (C=O oxindoline). MS (EI) *m*/*z* (%): 448 (M, 12), 431 (31), 375 (37), 313 (25), 57 (100). Anal. Calcd for $C_{22}H_{16}N_4O_7$: C, 58.93; H, 3.60; N, 12.50%. Found: C, 58.88; H, 3.66; N, 12.53%.

*4.1.23. 2-Amino-1′-benzyl-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydro-spiro[chromene-4,3′-indoline]-3-carbonitrile (**4w**).* White powder. Yield (0.39 g, 94%). Mp: 265–268 °C. IR (KBr), ν_{max}: 3396, 3304, 3200, 2200 (C≡N), 1717, 1678, 1655, 1596, 1347 cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ: 1.02 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.13 (d, 1H, *J* 16.0 Hz, 8-H_B), 2.22 (d, 1H, *J* 16.0 Hz, 8-H_A), 2.58 (d, 1H, *J* 17.6 Hz, 6-H_B), 2.64 (d, 1H, *J* 17.6 Hz, 6-H_A), 4.88 (d, 1H, *J* 16.4 Hz, Bn–H_B), 4.94 (d, 1H, *J* 16.4 Hz, Bn–H_A), 6.69 (d, 1H, *J* 8.0 Hz, 7′-H), 6.96 (t, 1H, *J* 7.4 Hz, 5′-H), 7.09 (d, 1H, *J* 7.2 Hz, 4′-H), 7.13 (t, 1H, *J* 7.6 Hz, 6′-H), 7.26 (t, 1H, *J* 7.2 Hz, Ph), 7.31 (t, 2H, *J* 7.6 Hz, Ph), 7.34 (s, 2H, NH_2), 7.49 (d, 2H, *J* 7.2 Hz, Ph).

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References and notes

1. (a) Mont, N.; Teixidó, J.; Borrell, J. I.; Kappe, C. O. *Tetrahedron Lett.* **2003**, *44*, 5385; (b) Bagley, M. C.; Dale, J. W.; Bower, J. *Chem. Commun.* **2002**, 1682; (c) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, *24*, 4957; (d) Huang, Y. J.; Yang, F. Y.; Zhu, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 16386.
2. (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168; (b) Dömling, A. *Chem. Rev.* **2006**, *17*, 106.
3. (a) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Zanatta, N.; Bonacorso, H. *Chem. Rev.* **2008**, *108*, 2015; (b) Holbrey, J. D.; Turner, M. B.; Reichert, W. M.; Rogers, R. D. *Green Chem.* **2003**, *5*, 731.
4. Fremantle, M. *Chem. Eng. News* **1998**, *76*, 32.
5. (a) Yadav, J. S.; Reddy, B. V. S.; Baishya, G.; Reddy, K. V.; Narsaiah, A. V. *Tetrahedron* **2005**, *61*, 9541; (b) Mi, X.; Luo, S.; He, J.; Cheng, J.-P. *Tetrahedron Lett.* **2004**, *45*, 4567; (c) Legeay, J. C.; Vanden Eynde, J. J.; Bazureau, J. P. *Tetrahedron* **2005**, *61*, 12386.
6. Wasserscheid, P.; Welton, T. *Ionic Liquids in Synthesis*; Wiley-VCH: Stuttgart, Germany, 2002.
7. Rad-Moghadam, K.; Youseftabar-Miri, L. *Synlett* **2010**, 1969.
8. (a) Rad-Moghadam, K.; Sharifi-Kiasaraie, M. *Tetrahedron* **2009**, *65*, 8816; (b) Rad-Moghadam, K.; Sharifi-Kiasaraie, M.; Taheri-Amlashi, H. *Tetrahedron* **2009**, *66*, 2316.
9. Hoalihan, W. J.; Remers, W. A.; Brown, R. K. *Indoles: Part 1*; Wiley: New York, NY, 1992.
10. (a) Ma, J.; Hecht, S. M. *Chem. Commun.* **2004**, 1190; (b) Edmondson, S.; Danishefsky, S. J.; Sepp-Lorenzinol, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147; (c) Smith, W. P.; Sollis, L. S.; Howes, D. P.; Cherry, C. P.; Starkay, D. I.; Cobley, N. K. *J. Med. Chem.* **1998**, *41*, 787.
11. (a) Early, W. G.; Oh, T.; Overman, L. E. *Tetrahedron Lett.* **1988**, *29*, 3785; (b) Ban, Y.; Seto, M.; Oishi, T. *Chem. Pharm. Bull.* **1975**, *23*, 2605; (c) Ban, Y.; Taga, N.; Oishi, T. *Tetrahedron Lett.* **1974**, *2*, 187.
12. (a) Dandia, A.; Singh, R.; Khaturia, S.; Merienne, C.; Morgant, G.; Loupy, A. *Bioorg. Med. Chem.* **2006**, *14*, 2409; (b) Sebahhar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666.
13. Kang, T. H.; Matsumoto, K.; Murakami, Y.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H. *Eur. J. Pharmacol.* **2002**, *444*, 39.
14. Kulkarni, S. K.; Kaul, P. N. *Indian J. Exp. Biol.* **1980**, *13*, 270.
15. Chen, T. S.; Wu, S. J.; Tsai, I. L.; Wu, T. S.; Pezzuto, J. M.; Lu, M. C.; Chai, H.; Suh, N.; Teng, C. M. *J. Nat. Prod.* **1994**, *57*, 1206.
16. (a) Hilton, S. T.; Ho, T. C. T.; Pljevaljcic, G.; Jones, K. *Org. Lett.* **2000**, *2*, 2639; (b) Fresneda, P. M.; Molina, P.; Bleda, J. A. *Tetrahedron* **2001**, *57*, 2355.
17. (a) Da-Silva, J. F. M.; Garden, S. J.; Pinto, A. C. *J. Braz. Chem. Soc.* **2001**, *12*, 273; (b) Joshi, K. C.; Jain, R.; Sharma, K. *J. Indian Chem. Soc.* **1988**, *115*, 202.
18. Dabiri, M.; Bahramnnejad, M.; Baghbanzadeh, M. *Tetrahedron* **2009**, *65*, 9443.
19. Lee, Y. R.; Hari, G. S. *Synthesis* **2010**, *3*, 453.
20. Wang, L. M.; Jiao, N.; Qiu, J.; Yu, J. J.; Liu, J. Q.; Guo, F. L.; Liu, Y. *Tetrahedron* **2010**, *66*, 339.
21. Yuling, L.; Hui, C.; Chunling, S.; Daqing, S.; Shunjun, J. *J. Comb. Chem.* **2010**, *12*, 231.
22. Zhu, S.-L.; Ji, S.-J.; Zhang, Y. *Tetrahedron* **2007**, *63*, 9365.
23. Sridhar, R.; Srinivas, B.; Madhav, B.; Reddy, V. P.; Nageswar, Y. V. D.; Rao, K. R. *Can. J. Chem.* **2009**, *87*, 1704.
24. Shanthi, G.; Subbulakshmi, G.; Perumal, P. T. *Tetrahedron* **2007**, *63*, 2057.
25. Litvinov, Y. M.; Mortikov, V. Y.; Shestopalov, A. M. *J. Comb. Chem.* **2008**, *10*, 741.
26. El-Ahl, A. A.; Afeefy, H.; Metwally, M. A. *J. Chem. Res.* **1994**, *14*.
27. Elinson, M. N.; Ilovaisky, A. I.; Dorofeev, A. S.; Merkulov, V. M.; Stepanov, N. O.; Miloserdov, F. M.; Ogibin, Y. N.; Nikishin, G. I. *Tetrahedron* **2007**, *63*, 10543.
28. Dandia, A.; Gautam, S.; Jain, K. A. *J. Fluorine Chem.* **2007**, *128*, 1454.
29. Granik, V. G.; Kadushkin, A. V.; Liebsche, J. *Adv. Heterocycl. Chem.* **1998**, *72*, 79.