An Efficient Protocol for Multicomponent Synthesis of Spirooxindoles Employing L-Proline as Catalyst at Room Temperature

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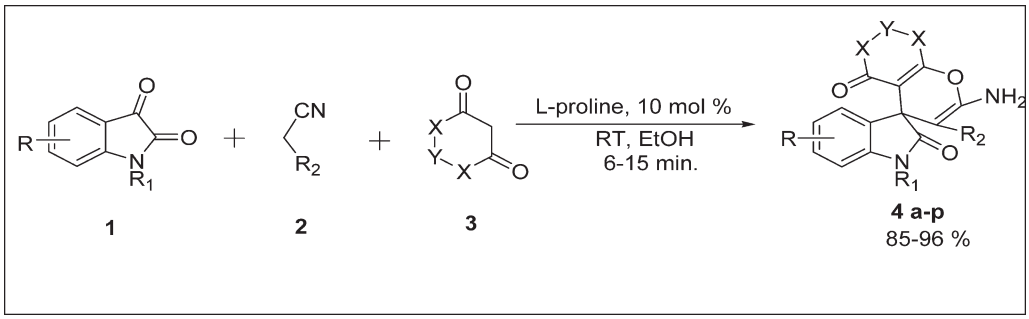

An efficient three-component one-pot synthesis of medicinally important spirooxindoles is described by the reaction of isatin, malononitrile/ethyl cyanoacetate, and dimedone/barbituric acid using L-proline as catalyst in ethanol at room temperature. This approach is convenient, mild, and affords the products in high yields without the use of chromatography.

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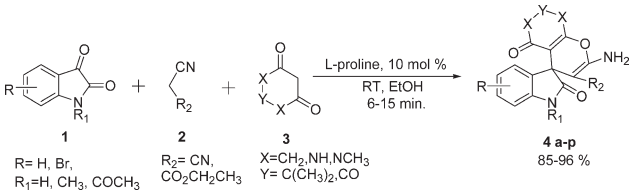
INTRODUCTION

Indole nucleus is the most common and important feature of a variety of natural products and pharmaceuticals [1,2]. Sharing of the indole 3-carbon atom in the formation of spirooxindole system has stimulated much interest in medicinal and biological chemistry [3–9]. The unique structural array and the pharmacological activity displayed by the class of functionalized spirooxindole compounds have made them attractive synthetic targets [10]. Azaspiro derivatives are well-known [10,11], but the preparation of the corresponding oxa analogues has evolved at a relatively slow pace [12]. Among the oxygen-containing heterocycles fused with indole ring system, chromene-based structures are found to manifest diverse activities such as antidepresssant, antihypertensive, anti-tubulin, antiviral, antioxidative, *etc*., [13–23]. The current interest in 5,6,7,8-tetrahydro-4H-chromene derivatives bearing nitrile functionality, especially 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles, arises from their potential application in the treatment of human neurodegenerative disorders [24]. Owing to their medicinal utility, some reports on the multicomponent entry to chromene based spirooxindoles have appeared employing TEBA-H_2O (2–6 h, 60°C) [25], electrocatalytic strategy (NaBr/ROH, 32–64 min) [26], and $InCl_3/SiO_2$ (1.5 h; MW, 3–3.5 min) [27]. Despite the availability of these methods, there remains enough scope for an efficient, high yielding, and mild approach to achieve such systems.

Multicomponent reactions (MCRs) have recently emerged as valuable tool in the preparation of structurally diverse drug-like heterocyclic compounds [28,29]. The MCR strategy offers significant advantages over conventional linear-type synthesis due to its flexible, convergent, and atom efficient nature [30]. Reactions using organocatalysts have attracted a great deal of attention in recent years to avoid the use of expensive transition metals [31]. Several amino acids have undoubtedly been the most successful catalysts in enamine- and iminium-type transformations. L-Proline has been regarded as the simplest 'enzyme' and has been elegantly used as a versatile organocatalyst in various synthetic routes for carbon—carbon and carbon—heteroatom bonds [32–34]. The rigid ring structure, easy availability, nontoxic nature, economical viability, and simple to use make this tiny molecule a remarkable organocatalyst in synthesizing molecules of biological interest.

Considering the biomedical applications of spirooxindole derivatives and in view of the limitations of the existing methods, we were prompted to exploit the catalytic potential of L-proline (10 mol %) for a facile and efficient multicomponent synthesis of functionalized spirooxindoles by the reaction of isatins, malononitrile or

Scheme 1



ethyl cyanoacetate, and barbituric acids or dimedone at room temperature (Scheme 1).

RESULTS AND DISCUSSION

To optimize the reaction conditions, a typical reaction of isatin **1a**, malononitrile **2**, and dimedone **3a** was carried out in the presence of various catalysts in ethanol and water at different temperatures. The outcome is given in Table 1. The optimum concentration of the catalyst L-proline was also determined for the model reaction at 5, 10, and 15 mol % in ethanol at room temperature, affording the product **4a** in 75, 92, and 92% yields respectively. After systematic screening, the best result is obtained when the reaction is carried out with 10 mol % of L-proline in ethanol at room temperature (*cf.* entry 9). Organocatalytic activity of L-proline is mainly due to its Lewis base character, capability for inducing enamine formation, and hydrogen bonding with electronegative atoms of other functionalized groups. It is worthwhile to mention that the reaction is also catalyzed significantly by an ionic liquid [bmim]BF_4 in water. The use of ionic liquid alone as solvent could improve the yield of the product further (entries 14 and 15), but not comparable to the yield obtained under L-proline catalyzed conditions in ethanol (entry 9). The other catalysts viz., $ZnCl_2$, K_2CO_3, and KF/Al_2O_3 did not work well under the investigated conditions.

Under the optimized set of reaction conditions (entry 9), isatin, 5-bromoisatin, N-methylisatin, and N-acetylisatin **1** were allowed to undergo L-proline (10 mol %) catalyzed multicomponent reaction with malononitrile or ethyl cyanoacetate **2** and barbituric acid or dimedone **3** in an equimolar ratio in ethanol at room temperature. The results are given in Table 2. After the reaction was over (TLC), the resulting solid was filtered and washed from ethanol/methanol to yield pure substituted spirooxindoles **4a–4p**. All the products were crystalline and fully characterized based on their melting points, elemental analyses, and spectral data (IR, ^{1}H NMR, ^{13}C NMR).

CONCLUSIONS

The present report describes L-proline catalyzed multicomponent synthesis of spirooxindoles in excellent yields. This protocol is efficient, simple, mild, ecofriendly, and also advantageous in terms of short reaction time and easy workup.

EXPERIMENTAL

IR spectra were recorded on a JASCO FT/IR-5300 spectrophotometer; whereas, NMR was run on a JEOL AL300 FT NMR spectrometer. The chemical shifts are given in δ ppm with respect to TMS as internal standard. Elemental analysis (C, H, N) for final compounds were performed on a Model

Table 1

Optimization of reaction conditions for the preparation of **4a**.

Entry	Catalyst	Temperature (°C)	Time (min)	Yield[a] (%) EtOH	Yield[a] (%) H_2O
1	Nil	RT	120	Trace	Nil
2	Nil	60	120	25	10
3	$ZnCl_2$	RT	120	17	12
4	$ZnCl_2$	60	90	34	20
5	K_2CO_3	RT	120	28	25
6	K_2CO_3	60	90	56	52
7	KF-Al_2O_3	RT	120	35	27
8	KF-Al_2O_3	60	90	62	65
9	L-Proline	RT	7	92	85
10	L-Proline	60	15	90	85
11	L-Proline	Reflux	15	90	84
12	[bmim]BF_4	RT	30	65	74
13	[bmim]BF_4	60	20	68	79
14	[bmim]BF_4	RT	120	(77)[b]	
15	[bmim]BF_4	60	90	(81)[b]	

[a] Yield based on isatin.
[b] Yield obtained by the use of ionic liquid as solvent without water or ethanol.

Table 2

L-Proline catalyzed multicomponent synthesis of spirooxiindole derivatives **4**.

Product	R	R_1	R_2	X	Y	Time (min)	Yield[a] (%)	Mp (°C)
4a	H	H	CN	CH_2	$C(CH_3)_2$	7	92	305–306
4b	Br	H	CN	CH_2	$C(CH_3)_2$	6	87	304–305
4c	H	CH_3	CN	CH_2	$C(CH_3)_2$	6	94	247–248
4d	H	$COCH_3$	CN	CH_2	$C(CH_3)_2$	7	92	232–233
4e	H	H	CN	CH_2	CH_2	6	90	310–311
4f	Br	H	CN	CH_2	CH_2	6	86	273–274
4g	H	CH_3	CN	CH_2	CH_2	7	96	245–246
4h	H	$COCH_3$	CN	CH_2	CH_2	6	93	251–252
4i	H	H	CN	NH	CO	7	85	277–278
4j	H	H	CN	NCH_3	CO	6	94	228–229
4k	H	CH_3	CN	NCH_3	CO	6	90	225–226
4l	H	$COCH_3$	CN	NCH_3	CO	7	91	228–229
4m	H	H	CO_2Et	CH_2	$C(CH_3)_2$	12	87	228–230
4n	Br	H	CO_2Et	CH_2	$C(CH_3)_2$	12	85	260–262
4o	H	H	CO_2Et	NH	CO	15	90	189–190
4p	Br	H	CO_2Et	NH	CO	15	86	264–265

[a] Yields based on isatins.

CE-440 CHN Analyzer. The TLC spots were detected using iodine chamber. All commercially available chemicals were purchased from Aldrich (USA) and E. Merck (Germany).

General experimental procedure for the synthesis of spirooxindoles 4. L-Proline (10 mol %) was added to a mixture of isatin (**1**, 1 mmol), malononitrile or ethyl cyanoacetate (1 mmol), and dimedone or barbituric acid (1 mmol) in ethanol (2 mL), and the resulting mixture was stirred at room temperature for 6–15 min. Upon completion of the reaction (TLC), the mixture was allowed to cool to room temperature. The resulting solid was filtered and washed successively with water (2 × 20 mL) and cold ethanol (2 × 0.5 mL) to afford pure product **4** (white shiny powder).

2-Amino-7,7-dimethyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (4a). IR (KBr): 3376, 3313, 3143, 2961, 2192, 1722, 1655, 1349, 1219, 1054 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.02 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.10–2.19 (m, 2H, CH_2), 2.58 (s, 2H, CH_2), 6.79 (d, *J* = 7.5 Hz, 1H, Ar), 6.89 (t, *J* = 7.5 Hz, 1H, Ar), 6.97 (d, *J* = 7.5 Hz, 1H, Ar), 7.14 (t, *J* = 7.5 Hz, 1H, Ar), 7.23 (s, 2H, NH_2), 10.41 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 27.1, 27.7, 32.0, 40.0, 46.9, 50.1, 57.5, 109.3, 110.9, 117.4, 121.8, 123.1, 128.2, 134.5, 142.1, 158.9, 164.2, 178.1, 194.9 ppm; Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 67.94; H, 5.17; N, 12.42.

2-Amino-5′-bromo-7,7-dimethyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (4b). IR (KBr): 3361, 3287, 3163, 2956, 2200, 1729, 1657, 1352, 1224, 1056 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.03 (s, 6H, $2CH_3$), 2.15 (s, 2H, CH_2), 2.45–2.65 (m, 2H, CH_2), 6.78 (d, *J* = 8.0 Hz, 1H, Ar), 7.19 (s, 1H, Ar), 7.24–7.36 (m, 3H, Ar, NH_2), 10.52 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 27.3, 27.8, 32.2, 39.9, 47.1, 50.0, 56.8, 110.3, 111.6, 113.4, 117.3, 126.5, 131.0, 136.9, 141.5, 158.9, 165.2, 177.7, 194.9 ppm; Anal. Calcd. for $C_{19}H_{16}BrN_3O_3$: C, 55.09; H, 3.89; N, 10.14. Found: C, 54.90; H, 3.96; N, 10.03.

2-Amino-1′,7,7-trimethyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (4c). IR (KBr): 3370, 3325, 3178, 2960, 2205, 1711, 1672, 1356, 1224, 1053 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.04 (s, 6H, 2 CH_3), 2.11 (s, 2H, CH_2), 2.56 (s, 2H, CH_2), 3.14 (s, 3H, NCH_3), 6.94–7.06 (m, 3H, Ar), 7.14–7.32 (m, 3H, Ar, NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 26.5, 27.3, 27.9, 32.0, 39.9, 46.5, 50.2, 57.1, 108.2, 110.8, 116.8, 122.2, 122.9, 128.5, 134.6, 144.0, 158.9, 164.3, 176.6, 194.7 ppm; Anal. Calcd. for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.67; H, 5.54; N, 11.95.

1′-Acetyl-2-amino-7,7-dimethyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (4d). IR (KBr): 3335, 3194, 2962, 2208, 1754, 1720, 1675, 1350, 1271, 1054 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.01 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.13–2.21 (m, 2H, CH_2), 2.57 (s, 2H, CH_2), 2.64 (s, 3H, CH_3CO), 7.17–7.26 (m, 2H, Ar), 7.29–7.38 (m, 1H, Ar), 7.55 (s, 2H, NH_2), 8.06 (d, *J* = 7.8 Hz, 1H, Ar) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 6.3, 27.1, 27.8, 32.4, 39.8, 47.6, 49.5, 57.1, 110.8, 115.5, 117.3, 123.4, 126.2, 128.8, 133.0, 139.5, 158.8, 164.9, 171.0, 177.9, 195.4 ppm; Anal. Calcd. for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.13. Found: C, 66.78; H, 5.14; N, 11.04.

2-Amino-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro-[chromene-4,3′-indole]-3-carbonitrile (4e). IR (KBr): 3356, 3295, 3178, 2956, 2214, 1708, 1656, 1353, 1212, 1071 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.92–2.05 (m, 2H, CH_2), 2.13–2.32 (m, 2H, CH_2), 2.65–2.71 (m, 2H, CH_2), 6.76 (d, *J* = 7.5 Hz, 1H, Ar), 6.89 (t, *J* = 7.5 Hz, 1H, Ar), 7.02 (d, *J* = 7.5 Hz, 1H, Ar), 7.14 (t, *J* = 7.5 Hz, 1H, Ar), 7.24 (s, 2H, NH_2), 10.42 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.10, 26.9, 36.14, 46.5, 57.3, 108.9, 112.2, 117.6, 121.5, 123.8, 128.5, 135.0, 142.3, 158.7, 166.7, 178.4, 195.2 ppm; Anal. Calcd. for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.67; found: C, 66.29; H, 4.33; N, 13.56.

2-Amino-5′-bromo-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (4f). IR (KBr): 3428, 3314, 3185, 2953, 2210, 1702, 1678, 1360, 1180, 1085 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.77–2.06 (m, 2H, CH_2), 2.12–2.37 (m, 2H, CH_2), 2.55–2.77 (m, 2H, CH_2), 6.77 (d, *J*

= 7.3 Hz, 1H, Ar), 7.16–7.63 (m, 4H, Ar, NH_2), 10.56 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.5, 27.0, 36.8, 47.4, 56.5, 111.5, 113.6, 117.0, 125.9, 130.8, 137.3, 141.2, 159.0, 166.9, 177.5, 195.4 ppm; Anal. Calcd. for $C_{17}H_{12}BrN_3O_3$: C, 52.87; H, 3.13; N, 10.88; found: C, 52.78; H, 3.05; N, 10.76.

2-Amino-1′-methyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (4g). IR (KBr): 3460, 3371, 3142, 2956, 2202, 1709, 1671, 1359, 1221 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.77–2.05 (m, 2H, CH_2), 2.10–2.35 (m, 2H, CH_2), 2.57–2.90 (m, 2H, CH_2), 3.15 (s, 3H, NCH_3), 6.86–7.11 (m, 3H, Ar), 7.18–7.37 (m, 3H, Ar, NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.6, 26.5, 26.9, 36.7, 46.4, 57.5, 108.3, 112.0, 117.6, 122.8, 124.0, 128.7, 133.4, 143.8, 158.6, 166.2, 176.7, 195.2 ppm; Anal. Calcd. for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08; found: C, 67.13; H, 4.82; N, 12.95.

1′-Acetyl-2-amino-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (4h). IR (KBr): 3441, 3329, 3187, 2200, 1750, 1712, 1669, 1358, 1275, 1202 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.81–2.09 (m, 2H, CH_2), 2.14–2.42 (m, 2H, CH_2), 2.56 (s, 3H, CH_3CO), 2.60–2.86 (m, 2H, CH_2), 7.13–7.25 (m, 2H, Ar), 7.27–7.43 (m, 1H, Ar), 7.56 (m, 2H, NH_2), 8.06 (d, *J* = 7.4 Hz, 1H, Ar) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.8, 25.8, 26.5, 36.0, 47.9, 57.2, 111.9, 115.5, 117.1, 123.4, 125.6, 128.8, 133.1, 139.0, 158.8, 166.9, 170.6, 178.2, 195.5 ppm; Anal. Calcd. for $C_{19}H_{15}N_3O_4$: C, 65.32; H, 4.33; N, 12.03; found: C, 65.25; H, 4.43; N, 11.91.

7-Amino-2,2′,4-trioxo-1,1′,2,2′,3,4-hexahydrospiro[indole-3′,5-pyrano[2,3-d]pyrimidine]-6-carbonitrile (4i). IR (KBr): 3446, 3285, 3142, 3035, 2208, 1700, 1645, 1512, 1441, 1398, 1245 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.76 (d, *J* = 7.9 Hz, 1H, Ar), 6.90 (t, *J* = 7.9 Hz, 1H, Ar), 7.10–7.15 (m, 2H, Ar), 7.34 (s, 2H, NH_2), 10.45 (s, 1H, NH), 11.04 (s, 1H, NH), 12.29 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 46.8, 57.7, 86.9, 109.4, 116.8, 121.6, 124.0, 128.5, 134.1, 142.3, 149.2, 153.3, 158.5, 161.7, 177.8 ppm; Anal. Calcd. for $C_{15}H_9N_5O_4$: C, 55.73; H, 2.81; N, 21.66. Found: C, 55.60; H, 2.72; N, 21.49.

7-Amino-1,3-dimethyl-2,2′,4-trioxo-1,1′,2,2′,3,4-hexahydrospiro[indole-3′,5-pyrano[2,3-d]pyrimidine]-6-carbonitrile (4j). IR (KBr): 3348, 3182, 3015, 2205, 1715, 1668, 1540, 1478, 1385, 1225 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.00 (s, 3H, CH_3), 3.35 (s, 3H, CH_3), 6.79 (d, *J* = 7.3 Hz, 1H, Ar), 6.87 (t, *J* = 7.3 Hz, 1H, Ar), 7.09–7.16 (m, 2H, Ar), 7.56 (s, 2H, NH_2), 10.42 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 27.3, 29.5, 47.8, 57.6, 87.2, 109.5, 116.7, 121.7, 123.8, 128.3, 133.4, 142.2, 149.5, 152.0, 158.0, 159.0, 177.4 ppm; Anal. Calcd. for $C_{17}H_{13}N_5O_4$: C, 58.12; H, 3.73; N, 19.93. Found: C, 57.95; H, 3.62; N, 19.81.

7-Amino-1,1′,3-trimethyl-2,2′,4-trioxo-1,1′,2,2′,3,4-hexahydrospiro[indole-3′,5-pyrano[2,3-d]pyrimidine]-6-carbonitrile (4k). IR (KBr): 3354, 3248, 3150, 2212, 1725, 1682, 1493, 1376, 1210 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.02 (s, 3H, CH_3), 3.14 (s, 3H, CH_3), 3.38 (s, 3H, CH_3), 6.92–7.10 (m, 2H, Ar), 7.20 (d, *J* = 7.3 Hz, 1H, Ar), 7.27 (t, *J* = 7.3 Hz, 1H, Ar), 7.64 (s, 2H, NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 26.7, 27.5, 29.3, 47.4, 57.8, 87.6, 108.5,116.6, 122.5, 123.5, 128.9, 132.9, 143.8, 149.7, 152.2, 158.0, 159.9, 176.4 ppm; Anal. Calcd. for $C_{18}H_{15}N_5O_4$: C, 59.18; H, 4.14; N, 19.17. Found: C, 58.97; H, 4.36; N, 19.03.

1′-Acetyl-7-amino-1,3-dimethyl-2,2′,4-trioxo-1,1′,2,2′,3,4-hexahydrospiro[indole-3′,5-pyrano[2,3-d]pyrimidine]-6-carbonitrile (4l). IR (KBr): 3385, 3310, 3208, 3186, 2218, 1725, 1695, 1660, 1500, 1387 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.61 (s, 3H, CH_3), 3.04 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 7.20 (t, *J* = 7.2 Hz, 1H, Ar), 7.25–7.40 (m, 2H, Ar), 7.86 (s, 2H, NH_2), 8.10 (d, *J* = 7.9 Hz, 1H, Ar) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 26.4, 27.6, 29.7, 48.6, 57.5, 87.2, 115.3, 116.6, 124.0, 126.0, 129.2, 132.4, 139.8, 149.5, 152.6, 158.2, 159.9, 170.8, 177.5 ppm; Anal. Calcd. for $C_{19}H_{15}N_5O_5$: C, 58.02; H, 3.84; N, 17.80. Found: C, 57.85; H, 3.92; N, 17.65.

Ethyl 2-amino-7,7-dimethyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carboxylate (4m). IR (KBr): 3368, 3237, 3113, 2959, 1684, 1614, 1525, 1474, 1349 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.79 (t, *J* = 6.9 Hz, 3H, CH_3), 0.95 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.98–2.18 (m, 2H, CH_2), 2.45–2.61 (m, 2H, CH_2), 3.67–3.71 (m, 2H, CH_2), 6.65 (d, *J* = 7.2 Hz, 1H, Ar), 6.73 (t, *J* = 7.2 Hz, 1H, Ar), 6.81 (d, *J* = 7.2 Hz, 1H, Ar), 7.01 (t, *J* = 7.2 Hz, 1H, Ar), 7.85 (s, 2H, NH_2), 10.13 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.0, 26.6, 27.7, 31.5, 46.6, 50.6, 58.8, 76.3, 108.1, 113.0, 120.5, 122.1, 127.2, 135.9, 144.0, 159.0, 162.3, 167.6, 179.76, 194.5 ppm; Anal. Calcd. for $C_{21}H_{22}N_2O_5$: C, 65.96; H, 5.80; N, 7.33. Found: C, 65.81; H, 5.72; N, 7.20.

Ethyl 2-amino-5′-bromo-7,7-dimethyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carboxylate (4n). IR (KBr): 3365, 3240, 3187, 2955, 1690, 1612, 1520, 1472, 1345 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.82 (t, *J* = 7.2 Hz, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.0 (s, 3H, CH_3), 2.0–2.1 (m, 2H, CH_2), 2.53 (s, 2H, CH_2), 3.72–3.74 (m, 2H, CH_2), 6.62 (d, *J* = 7.8 Hz, 1H, Ar), 6.99 (s, 1H, Ar), 7.20 (d, *J* = 7.8 Hz, 1H, Ar), 7.91 (s, 2H, NH_2), 10.29 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.2, 26.5, 27.9, 31.5, 46.8, 50.5, 58.9, 76.5, 108.3, 113.8, 120.7, 122.1, 127.3, 136.0, 144.3, 159.2, 162.1, 167.7, 179.75, 194.7 ppm; Anal. Calcd. for $C_{21}H_{21}BrN_2O_5$: C, 54.68; H, 4.59; N, 6.07. Found: C, 54.55; H, 4.61; N, 5.92.

Ethyl 7-amino-2,2′,4-trioxo-1,1′,2,2′,3,4-hexahydrospiro[indole-3′,5-pyrano[2,3-d]pyrimidine]-6-carboxylate (4o). IR (KBr): 3425, 3318, 3162, 2201, 1692, 1650, 1578, 1468, 1390, 1342 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.77 (t, *J* = 7.2 Hz, 3H, CH_3), 3.69–3.72 (m, 2H, CH_2), 6.65 (d, *J* = 7.5 Hz, 1H, Ar), 6.77 (t, *J* = 7.5 Hz, 1H, Ar), 6.92–7.08 (m, 2H, Ar), 7.92 (s, 2H, NH_2), 10.21 (s, 1H, NH), 10.94 (s, 1H, NH), 12.14 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.1, 46.2, 59.2, 76.3, 89.2, 108.3, 120.8, 122.7, 127.4, 135.3, 144.0, 149.1, 152.2, 158.6, 161.2, 167.4, 179.4 ppm; Anal. Calcd. for $C_{17}H_{14}N_4O_6$: C, 55.14; H, 3.81; N, 15.13. Found: C, 54.95; H, 3.74; N, 15.02.

Ethyl 7-amino-5′-bromo-2,2′,4-trioxo-1,1′,2,2′,3,4-hexahydrospiro[indole-3′,5-pyrano[2,3-d]pyrimidine]-6-carboxylate (4p). IR (KBr): 3420, 3315, 3160, 2201, 1692, 1655, 1579, 1463, 1395, 1348 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.79 (t, *J* = 7.5 Hz, 3H, CH_3), 3.70–3.73 (m, 2H, CH_2), 6.68 (d, *J* = 7.5 Hz, 1H, Ar), 6.94–7.11 (m, 2H, Ar), 7.93 (s, 2H, NH_2), 10.22 (s, 1H, NH), 10.94 (s, 1H, NH), 12.16 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.3, 46.1, 59.5, 76.4, 89.5, 108.1, 121.0, 122.9, 128.1, 135.5, 144.2,

149.3, 152.5, 158.4, 161.0, 167.2, 179.5 ppm; Anal. Calcd. for $C_{17}H_{13}BrN_4O_6$: C, 45.45; H, 2.92; N, 12.47. Found: C, 45.29; H, 2.83; N, 12.35.

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