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A simple and clean procedure for three-component synthesis of spirooxindoles in aqueous medium

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Abstract—A simple and efficient one-pot three-component synthesis of the biologically important spirooxindoles scaffold was carried out by the reaction of isatin, activated methylene reagent, and 1,3-dicarbonyl compounds in aqueous medium. This method is of great value because of its environmentally benign character, high yield processing, and easy handling.

1. Introduction

The indole nucleus is probably the most well-known heterocycle, a common and important feature of a variety of natural products and medicinal agents.[1] Compounds carrying the indole moiety exhibit antibacterial and antifungal activities.[2] Furthermore, it has been reported that sharing of the indole 3-carbon atom in the formation of spiroindoline derivatives highly enhances biological activity.[3–5] The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids.[6–9] For example, spirotryprostatin B, a natural alkaloid isolated from the fermentation broth of *Aspergillus fumigatus*, has been identified as a novel inhibitor of microtubule assembly,[7] and pteropodine and isopteropodine have been shown to modulate the function of muscarinic serotonin receptors (Fig. 1).[9]

Since Breslow demonstrated hydrophobic effects could strongly enhance the rate of some organic reactions and rediscovered the use of water as solvent in organic chemistry in 1980s,[10] there has been a growing recognition that water is an attractive medium for many organic reactions, such as Diels–Alder reactions,[11] Claisen rearrangement reactions,[12] Reformatsky reactions, [13] and pinacol-coupling reactions.[14] Organic reactions in water without using harmful organic solvents are one of the current focuses today especially in our environmentally conscious society.

However, to the best of our knowledge,[15–18] there have been few reports about the synthesis of spirooxindole derivatives in aqueous medium. As a consequence of our interest in the aqueous medium organic syntheses and our continual work on the synthesis of indole derivatives, [19] guided by the observation that the presence of two or more different heterocyclic moieties in a single molecule often enhances the biocidal profile remarkably, we investigated a three-component reaction of isatin (**1**), malononitrile or methyl cyanoacetate, and 1,3-dicarbonyl compounds to afford a series of spiro[indole-tetrahydrochromene], spiro[indole-pyrano(3,2-*c*)chromene], and spiro[indole-tetrahydropyrano(2,3-*d*)pyrimidine] derivatives in water mediated by the surfactant TEBA (triethylbenzylammonium chloride).

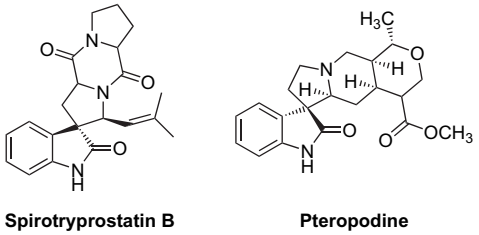

Figure 1. Representatives of spirooxindole-containing compounds.

2. Results and discussion

In recent years, many surfactants have been used as phase transfer catalysts in a number of organic reactions having unique capabilities to dissolve both organic and aqueous

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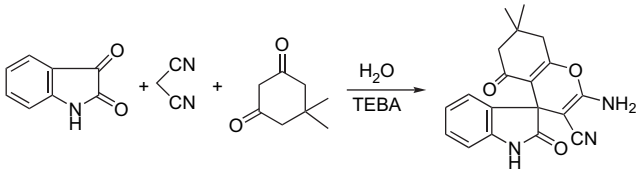
solutions to enhance the reaction rate.[20] In our initial study, evaluation of various additives was carried out for the synthesis of spirooxindole derivatives in aqueous medium. After some preliminary experiments, it was found that a mixture of isatin, malononitrile, and 5,5-dimethyl-1,3-cyclohexanedione in water in the presence of a catalytic amount of TEBA could afford 2-amino-5-oxo-7,7-dimethyl spiro[(4*H*)-5,6,7,8-tetrahydrochromene-4,3′-(3′*H*)-indol]-(1′*H*)-2′-one-carbonitrile (**4f**) in excellent yield (Scheme 1). The procedure was simple and easy to operate.



Scheme 1.

We examined this reaction in the absence and presence of several other additives. It was found that when the reaction was carried out without any additives resulted in poor yield (Table 1, entry 1). Some bases or acids such as $NaHCO_3$, K_2CO_3, and PTSA can push the reaction forward with moderate yields (Table 1, entries 2–4). When surfactants, for example, TBAB (tetrabutylammonium bromide), SDS (sodium dodecyl sulfate), and CTAC (cetyl trimethyl ammonium chloride) were used in this reaction system, the yields of products were improved (Table 1, entries 5–7). The best result was obtained when TEBA was used for which the yield was up to 94% (Table 1, entry 8).

Table 1. Optimization of reaction conditions[a]

Entry	Additive[b]	*T* (°C)	Time (h)	Yield[c]
1	—	60	6	23
2	$NaHCO_3$	60	5	62
3	K_2CO_3	60	5	67
4	PTSA	60	5	56
5	TBAB	60	3	85
6	SDS	60	3	78
7	CTAC	60	3	87
8	TEBA	60	2	94
9	TEBA	rt	6	64
10	TEBA	40	4	83
11	TEBA	70	2	93
12	TEBA	80	2	92
13	TEBA	90	2	88

[a] The reaction was carried out with isatin, malononitrile, and dimedone in water.
[b] The amount of each additive was 20 mol %.
[c] Isolated yields.

To optimize the reaction temperature, the reactions were carried out at different temperatures ranging from room temperature to 90 °C. We found that the yield of product **4f** was improved and the reaction time was shortened as the temperature was increased to 60 °C. The yield plateaued when temperature was further increased to 70, 80, and 90 °C (Table 1, entries 8–13). Therefore, the most suitable reaction temperature is 60 °C.

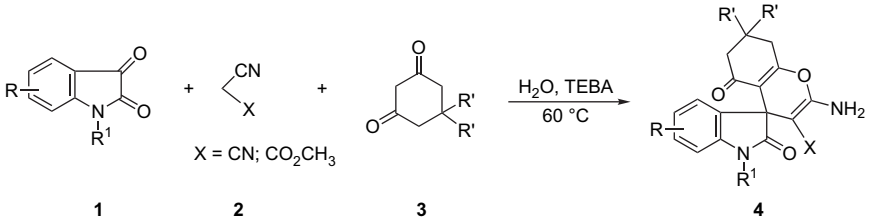
We also evaluated the amount of surfactant required for this transformation. It was found that when increasing the amount of the TEBA from 10 to 20 and 30 mol %, the yields increased from 85 to 94 and 93%, respectively. Using 20 mol % TEBA in water is sufficient to push the reaction forward. More amounts of the surfactant did not improve the yields.

Under the optimized reaction conditions, a series of spiro[tetrahydrochromene-4,3′-indole] derivatives **4** were synthesized (Scheme 2, Table 2).

As shown in Table 2, it was found that this method works with a wide variety of substrates. A series of different position substituted isatins including either electron-withdrawing or electron-donating groups and different substituted 1,3-cyclohexanedione were used in this reaction. Additionally, the reaction with methyl cyanoacetate or malononitrile also proceeded smoothly; however, the reaction time of methyl cyanoacetate with isatins and 1,3-dicarbonyl compounds was longer than those of malononitrile, which is probably due to the lower reactivities of the cyanoacetates.

Proposed mechanism for the synthesis of spiro derivative **4** was described in Scheme 3. The process represents a typical cascade reaction in which the isatin **1** first condenses with malononitrile **2** to afford isatylidene malononitrile derivative **5** in the presence of TEBA in water. This step was regarded as a fast Knoevenagel condensation. Then, **5** is attacked via Michael addition of dimedone **3** to give the intermediate **6** followed by the cycloaddition of hydroxyl group to the cyano moiety to form the desired product **4** (Scheme 3).

To further expand the scope of the present method, we investigated one-pot reactions involving 4-hydroxy coumarin and barbituric acid or 2-thiobarbituric acid. To our delight, under the above optimized conditions, the reactions proceeded smoothly and a variety of the desired spirooxindoles products **8** and **10** were obtained in good yields (Scheme 4 and Table 3).

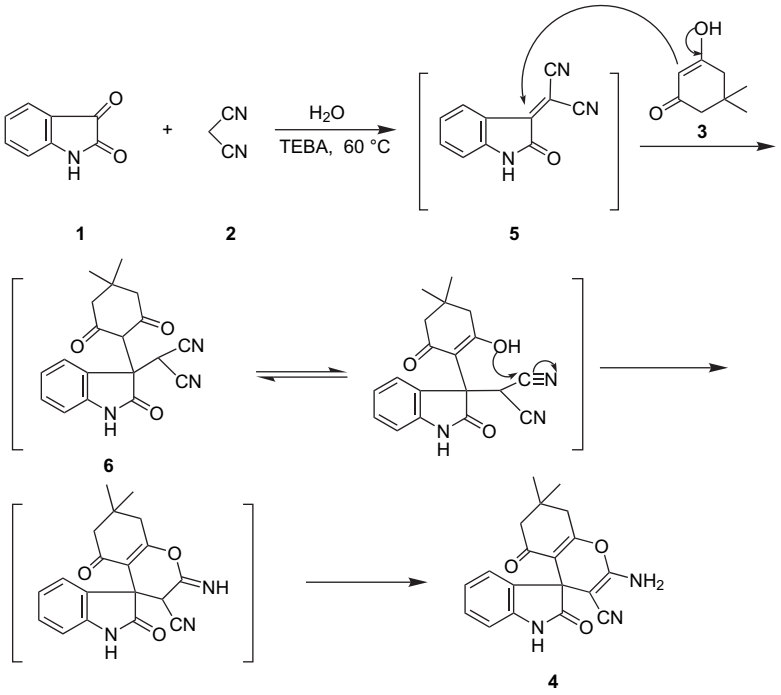


Scheme 2. Preparation of spirooxindoles from 1,3-cyclohexanedione or dimedone.

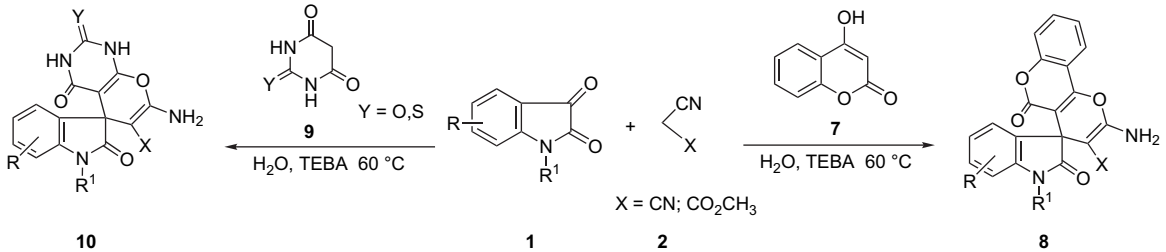
Table 2. Synthesis of compound **4** in aqueous medium

Entry	R	R^1	R′	X	Time (h)	Yield[a] (lit.) (%)	Mp (lit.) (°C)
4a	H	H	H	CN	3	90 (70)[15]	>300 (304–305)[15]
4b	4-Br	H	H	CN	4	82	>300
4c	6-Br	H	H	CN	3	88	>300
4d	H	H	H	CO_2CH_3	5	85	251–253
4e	6-Br	H	H	CO_2CH_3	6	77	276–277
4f	H	H	CH_3	CN	2	94 (83)[16]	289–290 (285–286)[16]
4g	4-Br	H	CH_3	CN	3	80	>300
4h	6-Br	H	CH_3	CN	3	84	>300
4i	5-CH_3	H	CH_3	CN	2	90	279–280
4j	7-Cl	H	CH_3	CN	2	92	>300
4k	H	CH_3	CH_3	CN	2	93	254–256
4l	H	CH_2Ph	CH_3	CN	2	91	269–271
4m	H	H	CH_3	CO_2CH_3	4	85	255–256
4n	6-Br	H	CH_3	CO_2CH_3	6	78	271–273
40	7-Cl	H	CH_3	CO_2CH_3	6	83	278–279

[a] Isolated yields.



Scheme 3. Plausible mechanism for the reaction of isatin and malononitrile with dimedone.



Scheme 4. Preparation of spirooxindoles from 4-hydroxy coumarin or barbituric acid/2-thiobarbituric acid.

Table 3. Synthesis of compounds **8** and **10** in aqueous medium

Entry	R	R^1	X	Y	Time (h)	Yield[a] (lit.) (%)	Mp (lit.) (°C)
8a	H	H	CN	—	3	88 (80)[15]	292–294 (291–292)[15]
8b	4-Br	H	CN	—	4	80	>300
8c	6-Br	H	CN	—	3	82	>300
8d	5-CH_3	H	CN	—	3	90	>300
8e	7-Cl	H	CN	—	4	91	>300
8f	H	CH_3	CN	—	3	86	287–288
8g	H	CH_2Ph	CN	—	3	89	277–279
8h	H	H	CO_2CH_3	—	5	82	275–277
8i	4-Br	H	CO_2CH_3	—	6	80	292–293
10a	H	H	CN	O	3	88	275–276
10b	4-Br	H	CN	O	4	80	256–258
10c	H	CH_3	CO_2CH_3	O	5	85	245–247
10d	H	H	CN	S	4	87	238–242
10e	6-Br	H	CN	S	4	84	232–234

[a] Isolated yields.

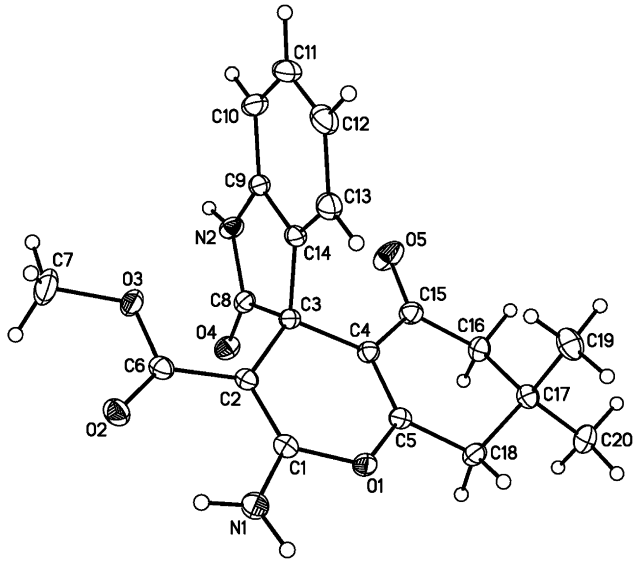


Figure 2. The crystal structure of **4m**.

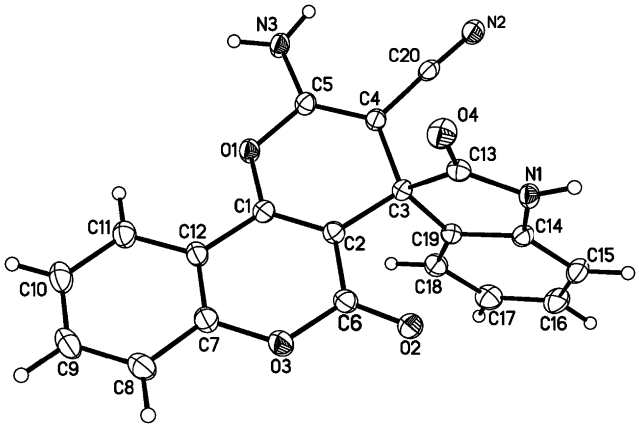


Figure 3. The crystal structure of **8a**.

In this study, all the products were characterized by melting point, IR, and ^1H NMR spectral data, as well as by elemental analyses. Furthermore, the structure of **4m**, **8a**, and **10d** was established by X-ray crystallographic analysis (Figs. 2–4).[21]

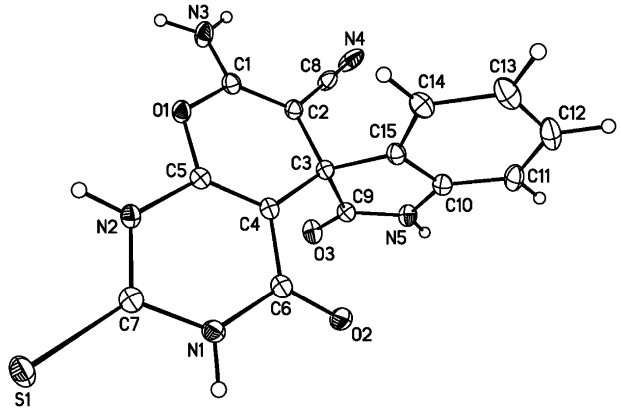


Figure 4. The crystal structure of **10d**.

3. Conclusion

In conclusion, we have described a simple one-pot three-component reaction involving isatin, activated methylene reagent, and 1,3-dicarbonyl compounds for the synthesis of a series of spirooxindoles derivatives in water. Particularly, valuable features of this method include the higher yields of the products, broader substrate scope, mild reaction conditions, reduced environmental impact, and the straightforwardness of the procedure, which make it a useful and attractive process for the synthesis of these important compounds.

4. Experimental

4.1. General

Melting points were recorded on an Electrothermal digital melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet FTIR500 spectrophotometer using KBr optics. ^1H NMR (400 MHz) spectra were recorded on a Varian Mercury MHz spectrometer using DMSO-d_6 or $CDCl_3$ as solvent and TMS as internal standard. CHN analyses were carried out on a Carlo–Erba EA1110 CNNO-S analyzer. X-ray diffraction data were recorded on a Rigaku Mercury CCD area detector with graphite monochromated Mo Kα radiation.

4.2. Typical experimental procedure

A mixture of isatin (1 mmol), malononitrile or methyl cyanoacetate (1 mmol), 5,5-bis-substituted-1,3-cyclohexanedione (1 mmol), and TEBA (20 mol %) in H_2O (3 mL) was stirred at 60 °C for several hours. Upon completion, monitored by TLC, the reaction mixture was allowed to cool to room temperature. The solid was filtered off and washed with water (2×20 mL) and cool ethanol (2×0.5 mL) to give shiny white powder of **4** (TLC pure) without further purification. Compounds for crystallographic analysis were recrystallized from appropriate solvent. This procedure was followed for the synthesis of all the spirooxindoles (**4a–4o**, **8a–8i**, and **10a–10e**).

4.2.1. 2-Amino-5-oxo-spiro[(4*H*)-5,6,7,8-tetrahydrochromene-4,3′-(3′*H*)-indol]-(1′*H*)-2′-one-3-carbonitrile (4a). White solid; mp >300 °C. IR: 3372, 3287, 3133, 2955, 2191, 1698, 1613, 1466, 1350, 1211, 1011, 933, 764, 679 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 10.39 (s, 1H, NH), 7.21 (br s, 2H, NH_2), 7.13 (t, 1H, J=7.6 Hz, ArH), 7.01 (d, 1H, J=7.6 Hz, ArH), 6.88 (t, 1H, J=7.6 Hz, ArH), 6.77 (d, 1H, J=8.0 Hz, ArH), 2.63–2.67 (m, 2H, CH_2), 2.30–2.37 (m, 2H, CH_2), 1.90–1.93 (m, 2H, CH_2). Anal. Calcd for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.67. Found: C, 66.23; H, 4.41; N, 13.89.

4.2.2. 2-Amino-5-oxo-spiro[(4*H*)-5,6,7,8-tetrahydrochromene-4,3′-(3′*H*)-4′-bromo-indol]-(1′*H*)-2′-one-3-carbonitrile (4b). White solid; mp >300 °C. IR: 3357, 3271, 3156, 2963, 2192, 1728, 1651, 1450, 1350, 1219, 1011, 910, 733, 656 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 10.66 (s, 1H, NH), 7.33 (br s, 2H, NH_2), 7.11 (t, 1H, J=7.2 Hz, ArH), 7.03 (d, 1H, J=8.0 Hz, ArH), 6.81 (d, 1H, J=7.6 Hz, ArH), 2.62–2.67 (m, 2H, CH_2), 2.25–2.32 (m, 2H, CH_2), 1.94–1.96 (m, 2H, CH_2). Anal. Calcd for $C_{17}H_{12}BrN_3O_3$: C, 52.87; H, 3.13; N, 10.88. Found: C, 52.77; H, 3.21; N, 10.92.

4.2.3. 2-Amino-5-oxo-spiro[(4*H*)-5,6,7,8-tetrahydrochromene-4,3′-(3′*H*)-6′-bromo-indol]-(1′*H*)-2′-one-3-carbonitrile (4c). White solid; mp >300 °C. IR: 3349, 3280, 3141, 2940, 2192, 1713, 1667, 1481, 1350, 1211, 1011, 910, 810, 656 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 10.59 (s, 1H, NH), 7.33 (br s, 2H, NH_2), 7.08 (d, 1H, J=8.0 Hz, ArH), 7.00 (d, 1H, J=7.6 Hz, ArH), 6.92 (s, 1H, ArH), 2.64–2.66 (m, 2H, CH_2), 2.22–2.24 (m, 2H, CH_2), 1.90–1.93 (m, 2H, CH_2). Anal. Calcd for $C_{17}H_{12}BrN_3O_3$: C, 52.87; H, 3.13; N, 10.88. Found: C, 52.91; H, 3.17; N, 10.94.

4.2.4. Methyl 2-amino-5-oxo-spiro[(4*H*)-5,6,7,8-tetrahydrochromene-4,3′-(3′*H*)-indol]-(1′*H*)-2′-one-3-carboxylate (4d). White solid; mp 251–253 °C. IR: 3349, 3241, 3187, 2956, 1697, 1613, 1520, 1474, 1350, 1296, 1227, 1142, 1080, 957, 756, 540 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 10.16 (s, 1H, NH), 7.81 (br s, 2H, NH_2), 7.02 (t, 1H, J=7.6 Hz, ArH), 6.84 (d, 1H, J=7.2 Hz, ArH), 6.75 (t, 1H, J=7.2 Hz, ArH), 6.67 (d, 1H, J=7.6 Hz, ArH), 3.24 (s, 3H, CH_3), 2.62–2.64 (m, 2H, CH_2), 2.16–2.22 (m, 2H, CH_2), 1.85–1.87 (m, 2H, CH_2). Anal. Calcd for $C_{18}H_{16}N_2O_5$: C, 63.52; H, 4.74; N, 8.23. Found: C, 63.45; H, 4.63; N, 8.16.

4.2.5. Methyl 2-amino-5-oxo-spiro[(4*H*)-5,6,7,8-tetrahydrochromene-4,3′-(3′*H*)-6′-bromo-indol]-(1′*H*)-2′-one-3-carboxylate (4e). White solid; mp 276–277 °C. IR: 3380, 3326, 3280, 2940, 1736, 1667, 1605, 1512, 1474, 1304, 1296, 1211, 1142, 1088, 926, 802, 625 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 10.20 (s, 1H, NH), 7.85 (br s, 2H, NH_2), 7.22 (d, 1H, J=7.6 Hz, ArH), 7.04 (d, 1H, J=7.2 Hz, ArH), 6.87 (s, 1H, ArH), 3.28 (s, 3H, CH_3), 2.63–2.66 (m, 2H, CH_2), 2.20–2.22 (m, 2H, CH_2), 1.88–1.90 (m, 2H, CH_2). Anal. Calcd for $C_{18}H_{15}BrN_2O_5$: C, 51.57; H, 3.61; N, 6.68. Found: C, 51.66; H, 3.69; N, 6.76.

4.2.6. 2-Amino-5-oxo-7,7-dimethyl-spiro[(4*H*)-5,6,7,8-tetrahydrochromene-4,3′-(3′*H*)-indol]-(1′*H*)-2′-one-3-carbonitrile (4f). White solid; mp 289–290 °C. IR: 3380, 3310, 3141, 2963, 2192, 1721, 1659, 1605, 1466, 1350, 1219, 1057, 903, 748, 679, 556 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 10.37 (s, 1H, NH), 7.20 (br s, 2H, NH_2), 7.14 (t, 1H, J=10.0 Hz, ArH), 6.97 (d, 1H, J=9.6 Hz, ArH), 6.88 (t, 1H, J=10.0 Hz, ArH), 6.78 (d, 1H, J=10.0 Hz, ArH), 2.56 (d, 2H, J=7.2 Hz, CH_2), 2.18 (d, 1H, J=21.2 Hz, CH), 2.08 (d, 1H, J=21.6 Hz, CH), 1.03 (s, 3H, CH_3), 1.00 (s, 3H, CH_3). Anal. Calcd for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 68.25; H, 5.21; N, 12.62.

4.2.7. 2-Amino-5-oxo-7,7-dimethyl-spiro[(4*H*)-5,6,7,8-tetrahydrochromene-4,3′-(3′*H*)-4′-bromo-indol]-(1′*H*)-2′-one-3-carbonitrile (4g). White solid; mp >300 °C. IR: 3365, 3311, 3152, 2963, 2199, 1726, 1659, 1605, 1497, 1350, 1219, 1049, 926, 748, 663 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 10.41 (s, 1H, NH), 7.28 (br s, 2H, NH_2), 7.14 (t, 1H, J=7.6 Hz, ArH), 6.98 (d, 1H, J=7.2 Hz, ArH), 6.78 (d, 1H, J=7.6 Hz, ArH), 2.56 (d, 2H, J=7.6 Hz, CH_2), 2.17 (d, 1H, J=15.6 Hz, CH), 2.08 (d, 1H, J=16.0 Hz, CH), 1.03 (s, 3H, CH_3), 1.00 (s, 3H, CH_3). Anal. Calcd for $C_{19}H_{16}BrN_3O_3$: C, 55.09; H, 3.89; N, 10.14. Found: C, 55.24; H, 3.93; N, 10.28.

4.2.8. 2-Amino-5-oxo-7,7-dimethyl-spiro[(4*H*)-5,6,7,8-tetrahydrochromene-4,3′-(3′*H*)-6′-bromo-indol]-(1′*H*)-2′-one-3-carbonitrile (4h). White solid; mp >300 °C. IR: 3357, 3310, 3172, 2963, 2199, 1728, 1667, 1605, 1481, 1358, 1219, 1049, 918, 802, 748, 663, 578 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 10.59 (s, 1H, NH), 7.35 (br s, 2H, NH_2), 7.09 (d, 1H, J=7.6 Hz, ArH), 6.93 (s, 1H, ArH), 6.78 (d, 1H, J=7.6 Hz, ArH), 2.53 (d, 2H, J=7.6 Hz, CH_2), 2.17 (d, 1H, J=16.0 Hz, CH), 2.10 (d, 1H, J=16.0 Hz, CH), 1.02 (s, 3H, CH_3), 1.00 (s, 3H, CH_3). Anal. Calcd for $C_{19}H_{16}BrN_3O_3$: C, 55.09; H, 3.89; N, 10.14. Found: C, 55.22; H, 3.96; N, 10.25.

4.2.9. 2-Amino-5-oxo-7,7-dimethyl-spiro[(4*H*)-5,6,7,8-tetrahydrochromene-4,3′-(3′*H*)-5′-methyl-indol]-(1′*H*)-2′-one-3-carbonitrile (4i). White solid; mp 279–280 °C. IR: 3364, 3311, 3141, 2964, 2192, 1721, 1659, 1605, 1497, 1350, 1219, 1165, 1049, 910, 810, 663 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 10.24 (s, 1H, NH), 7.16 (br s, 2H, NH_2), 6.92 (d, 1H, J=10.4 Hz, ArH), 6.76 (s, 1H, ArH), 6.67 (d, 1H, J=7.6 Hz, ArH), 2.51–2.55 (m, 2H, CH_2), 2.18 (s, 3H,

CH_3), 2.10–2.15 (m, 2H, CH_2), 1.02 (s, 3H, CH_3), 0.99 (s, 3H, CH_3). Anal. Calcd for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.92; H, 5.56; N, 12.12.

4.2.10. 2-Amino-5-oxo-7,7-dimethyl-spiro[(4*H*)-5,6,7,8-tetrahydrochromene-4,3′-(3′*H*)-7′-chloro-indol]-(1′*H*)-2′-one-3-carbonitrile (4j). White solid; mp 280–281 °C. IR: 3355, 3313, 3148, 2962, 2192, 1726, 1675, 1604, 1491, 1355, 1219, 1047, 911, 805, 748, 663,578 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 10.40 (s, 1H, NH), 7.45 (br s, 2H, NH_2), 7.10–7.21 (m, 1H, ArH), 6.81–6.89 (m, 2H, ArH), 2.51–2.54 (m, 2H, CH_2), 2.04–2.15 (m, 2H, CH_2), 1.02 (s, 3H, CH_3), 0.98 (s, 3H, CH_3). Anal. Calcd for $C_{19}H_{16}ClN_3O_3$: C, 61.71; H, 4.36; N, 11.36. Found C, 61.85; H, 4.52; N, 11.59.

4.2.11. 2-Amino-5-oxo-7,7-dimethyl-spiro[(4*H*)-5,6,7,8-tetrahydrochromene-4,3′-(3′*H*)-1′-methyl-indol]-(1′*H*)-2′-one-3-carbonitrile (4k). White solid; mp 254–256 °C. IR: 3377, 3316, 3172, 2958, 2194, 1705, 1670, 1608, 1493, 1352, 1220, 1165, 1052, 903, 751, 696 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 7.24 (br s, 2H, NH_2), 7.19–7.22 (m, 1H, ArH), 6.93–7.04 (m, 3H, ArH), 3.12 (s, 3H, CH_3), 2.50–2.55 (m, 2H, CH_2), 2.04–2.16 (m, 2H, CH_2), 1.02 (s, 3H, CH_3), 0.98 (s, 3H, CH_3). Anal. Calcd for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.72; H, 5.60; N, 12.21.

4.2.12. 2-Amino-5-oxo-7,7-dimethyl-spiro[(4*H*)-5,6,7,8-tetrahydrochromene-4,3′-(3′*H*)-1′-benzyl-indol]-(1′*H*)-2′-one-3-carbonitrile (4l). White solid; mp 269–271 °C. IR: 3386, 3322, 3206, 2962, 2198, 1711, 1660, 1610, 1487, 1352, 1220, 1168, 1051, 892, 749, 698, 552 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 7.47 (d, 2H, J=9.6 Hz, ArH), 7.21–7.35 (m, 5H, ArH, NH_2), 7.05–7.14 (m, 2H, ArH), 6.94 (t, 1H, J=10.0 Hz, ArH), 6.67 (d, 1H, J=10.0 Hz, ArH), 4.88 (d, 2H, J=7.6 Hz, CH_2), 2.53–2.59 (m, 2H, CH_2), 2.22 (d, 1H, J=21.2 Hz, CH), 2.10 (d, 1H, J=21.2 Hz, CH), 1.03 (s, 3H, CH_3), 1.00 (s, 3H, CH_3). Anal. Calcd for $C_{26}H_{23}N_3O_3$: C, 73.39; H, 5.45; N, 9.88. Found: C, 73.27; H, 5.40; N, 9.78.

4.2.13. Methyl 2-amino-5-oxo-7,7-dimethyl-spiro[(4*H*)-5,6,7,8-tetrahydrochromene-4,3′-(3′*H*)-indol]-(1′*H*)-2′-one-3-carboxylate (4m). White solid; mp 255–256 °C. IR: 3364, 3241, 3187, 2955, 1690, 1613, 1520, 1474, 1304, 1227, 1165, 1057, 926, 748, 609, 556 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.48 (s, 1H, NH), 7.14 (t, 1H, J=7.2 Hz, ArH), 6.88–6.94 (m, 2H, ArH), 6.80 (t, 1H, J=8.4 Hz, ArH), 6.49 (br s, 2H, NH_2), 3.40 (s, 3H, CH_3), 2.54 (d, 1H, J=17.2 Hz, CH), 2.41 (d, 1H, J=17.2 Hz, CH), 2.24 (d, 1H, J=16.0 Hz, CH), 2.11 (d, 1H, J=16.0 Hz, CH), 1.10 (s, 3H, CH_3), 1.01 (s, 3H, CH_3). Anal. Calcd for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 65.27; H, 5.40; N, 7.75.

4.2.14. Methyl 2-amino-5-oxo-7,7-dimethyl-spiro[(4*H*)-5,6,7,8-tetrahydrochromene-4,3′-(3′*H*)-6′-bromo-indol]-(1′*H*)-2′-one-3-carboxylate (4n). White solid; mp 271–273 °C. IR: 3357, 3282, 3126, 2943, 1725, 1689, 1617, 1534, 1414, 1304, 1217, 1142, 1051, 916, 744, 629, 554 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 10.30 (s, 1H, NH), 7.82 (br s, 2H, NH_2), 6.94 (d, 1H, J=10.4 Hz, ArH), 6.70–6.82 (m, 2H, ArH), 3.30 (s, 3H, CH_3), 2.59 (d, 1H, J=20.0 Hz, CH_2), 2.48 (d, 1H, J=20.0 Hz, CH_2), 2.16 (d, 1H, J=21.2 Hz, CH), 2.02 (d, 1H, J=21.6 Hz, CH), 1.02 (s, 3H, CH_3), 0.95 (s, 3H, CH_3). Anal. Calcd for $C_{20}H_{19}BrN_2O_5$: C, 53.71; H, 4.28; N, 6.26. Found: C, 53.57; H, 4.36; N, 6.35.

4.2.15. Methyl 2-amino-5-oxo-7,7-dimethyl-spiro[(4*H*)-5,6,7,8-tetrahydrochromene-4,3′-(3′*H*)-7′-chloro-indol]-(1′*H*)-2′-one-3-carboxylate (4o). White solid; mp 278–279 °C. IR: 3360, 3282, 3121, 2933, 1716, 1682, 1614, 1523, 1416, 1317, 1215, 1132, 1041, 898, 734, 645, 556 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 10.52 (s, 1H, NH), 7.86 (br s, 2H, NH_2), 7.07–7.11 (m, 1H, ArH), 6.75–6.81 (m, 2H, ArH), 3.27 (s, 3H, CH_3), 2.45–2.63 (m, 2H, CH_2), 2.16 (d, 1H, J=21.2 Hz, CH), 2.02 (d, 1H, J=21.2 Hz, CH), 1.02 (s, 3H, CH_3), 0.94 (s, 3H, CH_3). Anal. Calcd for $C_{20}H_{19}ClN_2O_5$: C, 59.63; H, 4.75; N, 6.95. Found: C, 56.73; H, 4.61; N, 6.79.

4.2.16. 2-Amino-5-oxo-spiro[(3′*H*)-indol-3′,4-4(*H*)-pyrano(3,2-*c*)chromen]-(1′*H*)-2′-one-3-carbonitrile (8a). White solid; mp 292–294 °C. IR: 3357, 3303, 3195, 2955, 2199, 1721, 1667, 1613, 1523, 1474, 1366, 1227, 1132, 1072, 972, 864, 748, 563 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 10.68 (s, 1H, NH), 7.95 (d, 1H, J=8.0 Hz, ArH), 7.77 (t, 1H, J=7.6 Hz, ArH), 7.67 (br s, 2H, NH_2), 7.57 (t, 1H, J=7.6 Hz, ArH), 7.50 (d, 1H, J=8.4 Hz, ArH), 7.22 (t, 2H, J=7.6 Hz, ArH), 6.93 (t, 1H, J=7.6 Hz, ArH), 6.85 (d, 1H, J=8.0 Hz, ArH). Anal. Calcd for $C_{20}H_{11}N_3O_4$: C, 67.23; H, 3.10; N, 11.76. Found: C, 67.33; H, 3.16; N, 11.69.

4.2.17. 2-Amino-5-oxo-spiro[(3′*H*)-4′-bromo-indol-3′,4-4(*H*)-pyrano(3,2-*c*)chromen]-(1′*H*)-2′-one-3-carbonitrile (8b). White solid; mp >300 °C. IR: 3372, 3310, 3179, 2192, 1728, 1674, 1605, 1450, 1358, 1234, 1111, 1080, 972, 910, 872, 764, 578 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 10.99 (s, 1H, NH), 7.96 (d, 1H, J=7.6 Hz, ArH), 7.84 (br s, 2H, NH_2), 7.79 (t, 1H, J=8.4 Hz, ArH), 7.53–7.59 (m, 2H, ArH), 7.21 (t, 1H, J=8.0 Hz, ArH), 7.12 (d, 1H, J=8.0 Hz, ArH), 6.91 (d, 1H, J=7.6 Hz, ArH). Anal. Calcd for $C_{20}H_{10}BrN_3O_4$: C, 55.07; H, 2.31; N, 9.63. Found: C, 55.21; H, 2.47; N, 9.51.

4.2.18. 2-Amino-5-oxo-spiro[(3′*H*)-6′-bromo-indol-3′,4,4(*H*)-pyrano(3,2-*c*)chromen]-(1′*H*)-2′-one-3-carbonitrile (8c). White solid; mp >300 °C. IR: 3364, 3313, 3172, 2201, 1713, 1605, 1481, 1353, 1228, 1112, 1085, 967, 905, 877, 769, 563 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 10.83 (s, 1H, NH), 7.93 (d, 1H, J=10.4 Hz, ArH), 7.75 (t, 1H, J=10.0 Hz, ArH), 7.70 (br s, 2H, NH_2), 7.46–7.54 (m, 2H, ArH), 7.19 (d, 1H, J=10.8 Hz, ArH), 7.11 (d, 1H, J=8.4, Hz, ArH), 7.00 (s, 1H, ArH). Anal. Calcd for $C_{20}H_{10}BrN_3O_4$: C, 55.07; H, 2.31; N, 9.63. Found: C, 55.28; H, 2.44; N, 9.57.

4.2.19. 2-Amino-5-oxo-spiro[(3′*H*)-5′-methyl-indol-3′,4,4(*H*)-pyrano(3,2-*c*)chromen]-(1′*H*)-2′-one-3-carbonitrile (8d). White solid; mp >300 °C. IR: 3362, 3309, 3154, 2198, 1711, 1612, 1474, 1335, 1210, 1097, 959, 883, 764, 567 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 10.58 (s, 1H, NH), 7.94 (d, 1H, J=7.6 Hz, ArH), 7.78 (t, 1H,

J=7.6 Hz, ArH), 7.66 (br s, 2H, NH_2), 7.49–7.57 (m, 2H, ArH), 7.00–7.04 (m, 2H, ArH), 6.79 (d, 1H, J=7.6 Hz, ArH), 2.19 (s, 1H, CH_3). Anal. Calcd for $C_{21}H_{13}N_3O_4$: C, 67.92; H, 3.53; N, 11.32. Found: C, 67.78; H, 3.41; N, 11.53.

4.2.20. 2-Amino-5-oxo-spiro[(3′*H*)-7′-chloro-indol-3′,4,4(*H*)-pyrano(3,2-*c*)chromen]-(1′*H*)-2′-one-3-carbonitrile (8e). White solid; mp >300 °C. IR: 3473, 3303, 3164, 2207, 1728, 1674, 1613, 1458, 1358, 1219, 1165, 1088, 972, 764, 617, 524 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 10.88 (s, 1H, NH), 7.94 (d, 1H, J=7.6 Hz, ArH), 7.81 (br s, 2H, NH_2), 7.75 (t, 1H, J=8.4 Hz, ArH), 7.54–7.60 (m, 2H, ArH), 7.22 (t, 1H, J=8.0 Hz, ArH), 7.11 (d, 1H, J=8.0 Hz, ArH), 6.90 (d, 1H, J=7.6 Hz, ArH). Anal. Calcd for $C_{20}H_{10}ClN_3O_4$: C, 61.32; H, 2.57; N, 10.73. Found: C, 61.21; H, 2.45; N, 10.57.

4.2.21. 2-Amino-5-oxo-spiro[(3′*H*)-1′-methyl-indol-3′,4,4(*H*)-pyrano(3,2-*c*)chromen]-(1′*H*)-2′-one-3-carbonitrile (8f). White solid; mp 287–288 °C. IR: 3409, 3300, 3191, 2195, 1718, 1670, 1608, 1468, 1358, 1237, 1116, 1059, 968, 754, 685, 540 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 7.93 (d, 1H, J=10.8 Hz, ArH), 7.76 (t, 1H, J=10.8 Hz, ArH), 7.71 (br s, 2H, NH_2), 7.55 (t, 1H, J=10.8 Hz, ArH), 7.49 (d, 1H, J=10.8 Hz, ArH), 7.26–7.34 (m, 2H, ArH), 6.98–7.08 (m, 2H, ArH), 3.19 (s, 3H, CH_3). Anal. Calcd for $C_{21}H_{13}N_3O_4$: C, 67.92; H, 3.53; N, 11.32. Found: C, 67.82; H, 3.42; N, 11.47.

4.2.22. 2-Amino-5-oxo-spiro[(3′*H*)-1′-benzyl-indol-3′,4,4(*H*)-pyrano(3,2-*c*)chromen]-(1′*H*)-2′-one-3-carbonitrile (8g). White solid; mp 277–279 °C. IR: 3408, 3341, 3215, 2199, 1710, 1670, 1609, 1464, 1355, 1167, 1109, 964, 755, 695, 537 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 7.99 (d, 2H, J=10.4 Hz, ArH), 7.80 (t, 1H, J=10.4 Hz, ArH), 7.74 (br s, 2H, NH_2), 7.47–7.59 (m, 4H, ArH), 7.28–7.34 (m, 3H, ArH), 7.22 (t, 1H, J=10.4 Hz, ArH), 7.00 (t, 1H, J=10.4 Hz, ArH) 6.80 (d, 1H, J=10.4 Hz, ArH), 4.97 (d, 2H, J=8.4 Hz, CH_2). Anal. Calcd for $C_{27}H_{17}N_3O_4$: C, 72.48; H, 3.83; N, 9.39. Found: C, 72.55; H, 3.74; N, 9.47.

4.2.23. Methyl 2-amino-5-oxo-spiro[(3′*H*)-indol-3′,4,4(*H*)-pyrano(3,2-*c*)chromen]-(1′*H*)-2′-one-3-carboxylate (8h). White solid; mp 275–277 °C. IR: 3380, 3314, 3094, 1713, 1667, 1613, 1528, 1443, 1358, 1288, 1111, 964, 910, 764, 663, 501 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 10.43 (s, 1H, NH), 8.08 (br s, 2H, NH_2), 8.04 (d, 1H, J=8.0 Hz, ArH), 7.74 (t, 1H, J=8.0 Hz, ArH), 7.53 (t, 1H, J=7.6 Hz, ArH), 7.45 (d, 1H, J=8.4 Hz, ArH), 7.11 (t, 1H, J=7.6 Hz, ArH), 7.01 (d, 1H, J=7.2 Hz, ArH), 6.79 (t, 1H, J=7.6 Hz, ArH), 6.75 (d, 1H, J=7.6 Hz, ArH), 3.22 (s, 3H, CH_3). Anal. Calcd for $C_{21}H_{14}N_2O_6$: C, 64.62; H, 3.62; N, 7.18. Found: C, 64.77; H, 3.54; N, 7.29.

4.2.24. Methyl 2-amino-5-oxo-spiro[(3′*H*)-4′-bromo-indol-3′,4,4(*H*)-pyrano(3,2-*c*)chromen]-(1′*H*)-2′-one-3-carboxylate (8i). White solid; mp 292–293 °C. IR: 3434, 3310, 3164, 1723, 1670, 1619, 1527, 1446, 1353, 1281, 1125, 957, 779, 668, 521 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 10.71 (s, 1H, NH), 8.17 (br s, 2H, NH_2), 8.05 (d, 1H, J=8.0 Hz, ArH), 7.77 (t, 1H, J=7.6 Hz, ArH), 7.54 (t, 1H, J=7.6 Hz, ArH), 7.48 (d, 1H, J=8.4 Hz, ArH), 7.10 (t, 1H, J=8.0 Hz, ArH), 6.96 (d, 1H, J=8.4 Hz, ArH), 6.80 (d, 1H, J=8.0 Hz, ArH), 3.34 (s, 3H, CH_3). Anal. Calcd for $C_{21}H_{13}BrN_2O_6$: C, 53.75; H, 2.79; N, 5.97. Found: C, 53.65; H, 2.64; N, 5.71.

4.2.25. 2-Amino-5,7-dioxo-spiro[(3′*H*)-indol-3′,4,4(*H*)-5,6,7,8-tetrahydropyrano(2,3-*d*)pyrimidine]-(1′*H*)-2′-one-3-carbonitrile (10a). White solid; mp 275–276 °C. IR: 3448, 3287, 3141, 3033, 2204, 1697, 1643, 1511, 1443, 1396, 1242, 1114, 1003, 910, 846, 663, 563 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 12.49 (br s, 1H, NH), 12.08 (br s, 1H, NH), 10.53 (br s, 1H, NH), 7.41 (br s, 2H, NH_2), 7.17 (t, 2H, J=8.0 Hz, ArH), 6.91 (t, 1H, J=7.6 Hz, ArH), 6.79 (d, 1H, J=7.6 Hz, ArH). Anal. Calcd for $C_{15}H_9N_5O_4$: C, 55.73; H, 2.81; N, 21.66. Found: C, 55.62; H, 2.73; N, 21.51.

4.2.26. 2-Amino-5,7-dioxo-spiro[4′-bromo-(3′*H*)-indol-3′,4,4(*H*)-5,6,7,8-tetrahydropyrano(2,3-*d*)pyrimidine]-(1′*H*)-2′-one-3-carbonitrile (10b). White solid; mp 256–258 °C. IR: 3501, 3422, 3327, 3172, 2199, 1690, 1659, 1582, 1474, 1389, 1342, 1250, 1188, 1065, 918, 776, 679, 578 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 12.62 (br s, 1H, NH), 12.25 (br s, 1H, NH), 10.36 (br s, 1H, NH), 7.02 (t, 1H, J=8.0 Hz, ArH), 6.95 (d, 1H, J=8.0 Hz, ArH), 6.89 (br s, 2H, NH_2), 6.71 (d, 1H, J=7.6 Hz, ArH). Anal. Calcd for $C_{15}H_8BrN_5O_4$: C, 44.80; H, 2.01; N, 17.41. Found: C, 44.67; H, 2.13; N, 17.57.

4.2.27. Methyl 2-amino-5,7-dioxo-spiro[1′-methyl-(3′*H*)-indol-3′,4,4(*H*)-5,6,7,8-tetrahydropyrano(2,3-*d*)pyramidine]-(1′*H*)-2′-one-3-carboxylate (10c). White solid; mp 245–247 °C. IR: 3503, 3426, 3318, 3162, 2201, 1692, 1656, 1578, 1468, 1390, 1342, 1188, 1134, 918, 826, 771, 578 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 12.53 (br s, 1H, NH), 12.04 (br s, 1H, NH), 10.92 (br s, 1H, NH), 7.89 (br s, 2H, NH_2), 7.14 (t, 1H, J=10.0 Hz, ArH), 6.98 (d, 1H, J=10.4 Hz, ArH), 6.81–6.86 (m, 2H, ArH), 3.21 (s, 3H, CH_3), 3.08 (s, 3H, CH_3). Anal. Calcd for $C_{17}H_{14}N_4O_6$: C, 55.14; H, 3.81; N, 15.13. Found: C, 55.28; H, 3.72; N, 15.29.

4.2.28. 2-Amino-5-oxo-7-thioxo-spiro[(3′*H*)-indol-3′,4,4(*H*)-5,6,7,8-tetrahydropyrano(2,3-*d*)pyrimidine]-(1′*H*)-2′-one-3-carbonitrile (10d). White solid; mp 238–242 °C. IR: 3503, 3426, 3318, 3162, 2201, 1692, 1656, 1578, 1468, 1390, 1342, 1188, 1134, 918, 826, 771, 578 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 12.65 (br s, 1H, NH), 12.22 (br s, 1H, NH), 10.57 (br s, 1H, NH), 7.47 (br s, 2H, NH_2), 7.20 (t, 2H, J=8.0 Hz, ArH), 7.01 (t, 1H, J=7.6 Hz, ArH), 6.83 (d, 1H, J=7.6 Hz, ArH). Anal. Calcd for $C_{15}H_9N_5O_3S$: C, 53.09; H, 2.67; N, 20.64. Found: C, 53.18; H, 2.77; N, 20.51.

4.2.29. 2-Amino-5-oxo-7-thioxo-spiro[6′-bromo-(3′*H*)-indol-3′,4,4(*H*)-5,6,7,8-tetrahydropyrano(2,3-*d*)pyramidine]-(1′*H*)-2′-one-3-carbonitrile (10e). White solid; mp 232–234 °C. IR: 3421, 3287, 3118, 2199, 1720, 1629, 1492, 1404, 1341, 1215, 1140, 902, 788, 663, 571 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 12.70 (br s, 1H, NH), 12.34 (br s, 1H, NH), 10.85 (br s, 1H, NH), 7.61 (br s, 2H, NH_2), 7.17 (t, 1H, J=8.0 Hz, ArH), 7.09 (d, 1H, J=8.0 Hz, ArH), 6.85 (d, 1H, J=7.6 Hz, ArH). Anal. Calcd for $C_{15}H_8BrN_5O_3S$: C, 43.08; H, 1.93; N, 16.75. Found: C, 43.17; H, 2.05; N, 16.88.

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21. Crystallographic data for the structures of **4m**, **8a**, and **10f** reported in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication with Nos. CCDC-602822, 299591, and 643534, respectively. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (E-mail: linstead@ccdc.cam.ac.uk or deposit@ccdc.cam.ac.uk; fax: +44 1223 336033). Structural parameters for **4m**: data collection: Rigaku Mercury CCD area detector; radiation: crystal size: $0.35\times0.32\times0.20$ mm^3; $C_{21}H_{23}N_2O_6$, M_r=399.41, monoclinic, space group $P21/n$, a=8.5465(13), b=11.8483(17), c=18.841(3) Å, α=90.00, β=98.952(3), γ=90.00, V=1884.6(5) Å^3, Z=4, D_{calcd}=0.408 g cm^{-3}, (Mo Kα)=0.104 mm^{-1}. Structural parameters for **8a**: data collection: Rigaku Mercury CCD area detector; radiation: crystal size: $0.31\times0.30\times0.20$ mm^3; $C_{20}H_{11}N_3O_4$, M_r=357.32, monoclinic, space group $C2/c$, a=25.265(4), b=11.0076(12), c=14.864(2) Å, α=90.00, β=125.820(3), γ=90.00, V=3351.9 (8)Å^3, Z=8, D_{calcd}=1.416 g cm^{-3}, (Mo Kα)=0.102 mm^{-1}. Structural parameters for **10e**: data collection: Rigaku Mercury CCD area detector; radiation: crystal size: $0.80\times0.70\times0.50$ mm^3; $C_{21}H_{27}N_7O_7S$, M_r=521.56, monoclinic, space group $P21/c$, a=8.6650(12), b=16.830(2), c=17.602(3) Å, α=90.00, β=94.640(3), γ=90.00, V=2558.5 (6) Å^3, Z=8, D_{calcd}=1.354 g cm^{-3}, (Mo Kα)=0.181 mm^{-1}.