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An Efficient Method for Multicomponent Synthesis of Spiro[4*H*-pyran-oxindole] Derivatives Catalyzed by Magnesium Perchlorate

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A simple and efficient method for the synthesis of spiro[4*H*-pyran-oxindole] derivatives by means of three-component reactions between isatins, malononitrile or ethyl cyano-acetate, and 1,3-dicarbonyl compounds in the presence of catalytic amount of magnesium perchlorate in 50% aqueous ethanol medium has been described.

Key Words : Multicomponent synthesis, Isatin, Spiro[4*H*-pyran-oxindole], Magnesium perchlorate

Introduction

The spirooxindole unit is a privileged heterocyclic motif that forms the core of a large family of natural products with strong bioactivity profiles and interesting structural properties.[1-3] For example, cytostatic alkaloids as spirotryprostatins A, and pteropodine, and isopteropodine have been shown to modulate the function of muscarinic serotonin receptors.[4] Owing to their medicinal utility, some reports on the multicomponent entry to chromene based spirooxindoles have appeared employing NaCl (sonication),[5] $HAuCl_4 \cdot 3H_2O$,[6] sodium stearate,[7] $InCl_3$,[8] NH_4Cl,[9] triethylbenzyl ammonium,[10] L-proline[11] as the catalysts. 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) offer significant advantages over conventional linear-type synthesis, as more often are recognized cost-effective and comparatively fast routes though generating less chemical waste.[12] Consequently, they are regarded as viable synthetic routes toward both economical and environmental benefits of chemical transformations.[13] In addition to the intrinsic atom economy and selectivity underlying such reactions, simpler procedures, equipment, time, and energy savings, as well as environmental friendliness have all led to a sizable effort to design and implement MCRS in both academia and industry.[14]

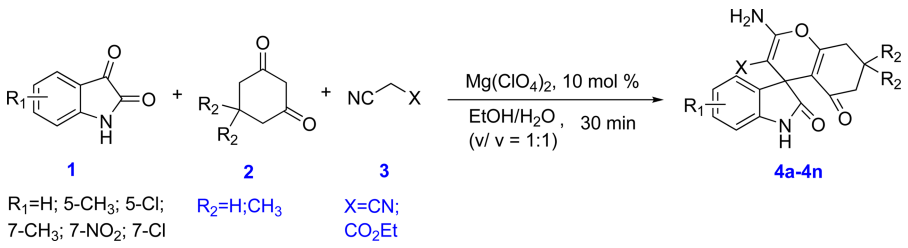
In recent years, magnesium perchlorate has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various transformations under mild and convenient conditions, affording the corresponding products in excellent yields with high selectivity.[15-19]

On the basis of biological studies that show the existence of two or more different heterocyclic moieties in a single molecule often remarkably enhances the biocidal profile we intended the synthesis of a series of spiro-fused pyran-oxindole derivatives through a three-component reaction of isatin, active methylene reagent, and 1,3-cyclohexanedione in the presence of green catalyst magnesium perchlorate in aqueous ethanol medium. To the best of our knowledge, there is no report available in the literature describing the use of magnesium perchlorate as the catalyst in aqueous ethanol media for the synthesis of spiro[4*H*-pyran-oxindole] derivatives.

Results and Discussion

In our initial study, evaluation of various solvent systems and different catalysts were carried out for the synthesis of spiro[4*H*-pyran-oxindole] **4a** by reacting isatin, dimedone, and malononitrile (Scheme 1). After screening, we have found that magnesium perchlorate has a unique capability to enhance the reaction rate in aqueous ethanol solution (50%, v/v). The results are summarized in Table 1 and Table 2.

It was found that the reaction with isatin, 5,5-dimethyl-1,3-cyclohexanedione, and malononitrile can be carried out using by 10 % mol of $Mg(ClO_4)_2$ in ethanol at 50 °C to get



Scheme 1. Synthesis of spiro[4*H*-pyran-oxindole] derivatives.

Table 1. Solvent effects on the reaction of isatin, dimedone and malononitrile, in the presence of 10 mol % magnesium perchlorate[a]

Entry	Solvent	Time (min)	Yield[c] (%)
1	DMF	120	Trace
2	CH_2Cl_2	120	Trace
3	CH_3OH	30	61
4	C_2H_5OH	30	83
5	C_2H_5OH/H_2O[b]	30	91
6	H_2O	30	78
7	CH_3CN	30	81
8	THF	30	85

[a]Reaction conditions: Isatin (2 mmol), malononitrile (2 mmol), dimedone (2 mmol); solvent (5 mL); temperature: 50 °C. [b]50% (v/v). [c]Isolated yield.

Table 2. Synthesis of spiro[4*H*-pyran-oxindole] using various catalysts

Entry	Catalyst	Mol %	Time (min)	Yield[a] %
1	-	-	180	Trace
2	$FeCl_3·6H_2O$	10	120	47
3	$ZnCl_2$	10	120	53
4	$MgBr_2$	10	120	51
5	$Zn(ClO_4)_2$	10	30	78
6	$Cu(ClO_4)_2$	10	30	85
7	$LiClO_4$	10	30	81
8	$Mg(ClO_4)_2$	5	30	83
9	$Mg(ClO_4)_2$	10	30	91
10	$Mg(ClO_4)_2$	15	30	90

[a]Isolated yield.

4a by filtration without column chromatography. When 1,3-cyclohexanedione was used as the material instead of 5,5-dimethyl-1,3-cyclohexanedione in the same reaction, but the product **4n** can't be crystallized from ethanol. Then aqueous ethanol solution (50%, v/v) was employed as the reaction solvent, and the result is satisfactory (Table 1, entry 5). Furthermore, water used as the solvent was also investigated, but the yield was only 78%, which may be owing to the poor solubility of the materials in water.

Then we examined this reaction in the absence and presence of acid catalysts. It was found that the reaction which was carried out without any additives resulted in poor yield even after longer reaction time (Table 2, entry 1). We also evaluated the amount of catalyst required for this transformation. It was found that using 10 mol % $Mg(ClO_4)_2$ in aqueous ethanol solution is sufficient to push the reaction forward (Table 2, entry 7). Increasing catalytic amount of $Mg(ClO_4)_2$ did not give any satisfactory yield. In order to evaluate the efficiency of this methodology, isatin, dimedone and malononitrile were further subjected to reaction using 10 mol % of a diverse type of Lewis acids such as $FeCl_3·6H_2O$, $ZnCl_2$, $MgBr_2$, $Zn(ClO_4)_2$, $Cu(ClO_4)_2$ and $LiClO_4$ under the investigated conditions. As seen from Table 2, rate enhancement of the reaction was observed when 10 mol % of $Mg(ClO_4)_2$ was used. However, use of amount 10 mol % of other acids led to lower yields (47-85%) even after longer reaction time.

Table 3. Synthesis of spiro[4*H*-pyran-oxindole] derivatives

Product	R_1	R_2	X	Time (min)	Yield[a] (%)	mp (lit) (°C)
4a	H	CH_3	CN	30	91	290-291(290-292)[5]
4b	H	CH_3	CO_2Et	60	90	279-281(278-280)[5]
4c	5-CH_3	CH_3	CN	30	93	279-281(278-280)[5]
4d	5-CH_3	CH_3	CO_2Et	60	89	284-285(282-284)[5]
4e	5-Cl	CH_3	CN	30	95	293-295(294-296)[5]
4f	5-Cl	CH_3	CO_2Et	60	92	292-293(292-294)[5]
4g	7-Cl	CH_3	CN	30	93	291-293(291-293)[7]
4h	7-Cl	CH_3	CO_2Et	60	94	278-280
4i	7-NO_2	CH_3	CN	30	88	279-281
4j	7-CH_3	CH_3	CN	30	91	296-297
4k	7-CH_3	CH_3	CO_2Et	60	92	289-290
4l	5-CH_3	H	CN	30	95	292-294(291-294)[20]
4m	7-Cl	H	CN	30	92	> 300
4n	H	H	CN	30	89	251-253(251-254)[9]

[a]Isolated yield.

As shown in Table 3 it was found that this procedure works with a wide variety of substrates. Six types of substituted isatins, and 1,3-cyclohexanediones were used in this reaction (Scheme 1). But the reaction with malononitrile was finished faster than with ethylcyanoacetate which may be owing to the difference of the activity between the two active methylene reagents. The most probable mechanism of this reaction includes a fast Knoevenagel condensation between isatin and CH-acidic cyanoacetic ester derivatives in the presence of $Mg(ClO_4)_2$ in aqueous ethanol solution in the first step and a Michael addition of diketones to the unsaturated nitrile, the product of Knoevenagel condensation, in the second stage and then the cycloaddition of the hydroxyl group to the cyano moiety to form the desired product. After the reaction was over (TLC), the resulting solid was filtered and washed with aqueous ethanol solution to yield pure substituted spiro[4*H*-pyran-oxindole] **4a-4n**. All the products were crystalline and characterized based on their melting points, elemental analysis, and spectral data (^{1}H NMR, ^{13}C NMR).

Conclusion

The present report describes $Mg(ClO_4)_2$ catalyzed multicomponent synthesis of spirooxindoles in excellent yields. This protocol is efficient, simple, mild, eco friendly, and also advantageous in terms of short reaction time and easy workup procedure.

Experimental

All Chemicals used were obtained from commercial suppliers and used without further purifications. ^{1}H NMR spectra were determined on a Bruker AVANCE DMX III 400M

spectrometer and ^{13}C NMR spectra were obtained on the same instrument, respectively. Samples were dissolved in deuterated DMSO, which provided the deuterium lock for the spectrometers. Elemental microanalysis was carried out on a Euro vector EA 3000 CHN analyzer. Melting points were measured using a BUCHI M-560 melting point apparatus. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates visualized with UV light.

General Procedure for the Synthesis of Spiro[4*H*-pyranoxindole] 4. $Mg(ClO_4)_2$ (10 mol %) was added to a mixture of isatin (2 mmol), malononitrile or ethyl cyanoacetate (2 mmol), and dimedone (2 mmol) in aqueous ethanol solution (50%, v/v, 5 mL), and the resulting mixture was stirred at 50 °C for 30-60 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 × 30 mL) and cold aqueous ethanol (2 × 1 mL) to afford pure product **4**.

2-Amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro [chromene-4,3'-indoline]-3-carbonitrile (4a): White solid (yield: 91%); mp 290-291 °C, ^1H NMR (400 MHz, DMSO-d_6) δ 1.00 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.09 (d, J = 16.0 Hz, 1H, CH_AH_B), 2.13 (d, J = 16.0 Hz, 1H, CH_AH_B), 2.56 (s, 2H, CH_2), 6.78 (d, J = 7.6 Hz, 1H, ArH), 6.88 (t, J = 7.4 Hz, 1H, ArH), 6.98 (d, J = 6.8 Hz, 1H, ArH), 7.14 (t, J = 8.2 Hz, 1H, ArH), 7.12 (s, 2H, NH_2), 10.39 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.5, 28.1, 32.4, 47.3, 50.4, 57.9, 109.7, 111.2, 117.8, 122.1, 123.5, 128.6, 134.9, 142.5, 159.2, 164.6, 178.5, 195.3. Anal. calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 68.04; H, 5.11, N, 12.54.

Ethyl-2-amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carboxlate (4b): White solid (yield: 90%); mp 279-281 °C, ^1H NMR (400 MHz, DMSO-d_6) δ 0.79 (t, J = 6.8 Hz, 3H, CH_3), 0.94 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 2.00 (d, J = 16.0 Hz, 1H, CH_AH_B), 2.14 (d, J = 16.0 Hz, 1H, CH_AH_B), 2.52 (m, 2H, CH_2), 3.69 (q, J = 6.8 Hz, 2H, CH_2), 6.66 (d, J = 7.6 Hz, 1H, ArH), 6.75 (t, J = 7.2 Hz, 1H, ArH), 6.82 (d, J = 7.2 Hz, 1H, ArH), 7.03 (t, J = 7.2 Hz, 1H, ArH), 7.84 (s, 2H, NH_2), 10.12 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.6, 27.1, 28.2, 32.0, 47.1, 51.1, 59.3, 76.8, 108.6, 113.6, 121.0, 122.7, 127.6, 136.4, 144.5, 159.6, 162.8, 168.1, 180.2, 195.1. Anal. calcd. for $C_{21}H_{22}N_2O_5$: C, 65.96; H, 5.80; N, 7.33. Found: C, 65.97; H, 5.81, N, 7.33.

2-Amino-5',7,7-trimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4c): White solid (yield: 93%); mp 279-281 °C, ^1H NMR (400 MHz, DMSO-d_6) δ 1.00 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.12 (m, 2H, CH_2), 2.19 (s, 3H, Ar-CH_3), 2.55 (m, 2H, CH_2), 6.67 (d, J = 7.2 Hz, 1H, ArH), 6.78 (s, 1H, ArH), 6.93 (d, J = 8.4 Hz, 1H, ArH), 7.19 (s, 2H, NH_2), 10.27 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.1, 27.7, 27.9, 32.4, 47.3, 50.5, 58.2, 109.4, 111.3, 117.8, 124.1, 128.9, 130.9, 135.0, 140.1, 159.2, 164.5, 178.4, 195.3. Anal. calcd. for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.73; H, 5.47, N, 12.04.

Ethyl-2-amino-5',7,7-trimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline-3-carboxlate (4d): White solid (yield: 89%); mp 284-285 °C, ^1H NMR (400 MHz, DMSO-d_6) δ 0.82 (t, J = 7.2 Hz, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 2.03 (d, J = 15.6 Hz, 1H, CH_AH_B), 2.13 (d, J = 15.6 Hz, 1H, CH_AH_B), 2.15 (s, 3H, CH_3), 2.48-2.54 (m, 2H, CH_2), 3.70 (q, J = 7.2 Hz, 2H, CH_2), 6.55 (d, J = 8.0 Hz, 1H, ArH), 6.64 (s, 1H, ArH), 6.84 (d, J = 7.6 Hz, 1H, ArH), 7.84 (s, 2H, NH_2), 10.02 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.5, 21.1, 27.3, 28.1, 32.0, 47.1, 51.1, 59.3, 76.9, 108.3, 113.6, 123.4, 127.9, 129.5, 136.5, 142.1, 159.5, 162.7, 168.2, 180.2, 195.1. Anal. calcd. for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.65; H, 6.11, N, 7.06.

2-Amino-5-chloro-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4e): White solid (yield: 95%); mp 293-295 °C, ^1H NMR (400 MHz, DMSO-d_6) δ 1.00 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 2.14 (s, 2H, CH_2), 2.49-2.56 (m, 2H, CH_2), 6.78 (d, J = 8.0 Hz, 1H, ArH), 7.08 (s, 1H, ArH), 7.17 (d, J = 5.6 Hz, 1H, ArH), 7.29 (s, 2H, NH_2), 10.51 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.7, 27.9, 32.4, 47.5, 50.4, 57.1, 110.6, 111.1, 117.7, 123.7, 126.1, 128.5, 136.9, 141.5, 159.3, 165.1, 178.3, 195.6. Anal. calcd. for $C_{19}H_{16}ClN_3O_3$: C, 61.71; H, 4.36; N, 11.36. Found: C, 61.72; H, 4.37, N, 11.37.

Ethyl-2-amino-5-chloro-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carboxlate (4f): White solid (yield: 92%); mp 292-293 °C, ^1H NMR (400 MHz, DMSO-d_6) δ 0.82 (t, J = 6.2 Hz, 3H, CH_3), 0.95 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 2.07-2.13 (m, 2H, CH_2), 2.48-2.55 (m, 2H, CH_2), 3.70 (q, J = 6.0 Hz, 2H, CH_2), 6.66 (d, J = 8.8 Hz, 1H, ArH), 6.88 (s, 1H, ArH), 7.10 (d, J = 8.0 Hz, 1H, ArH), 7.91 (s, 2H, NH_2), 10.29 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.6, 27.5, 27.9, 32.0, 47.4, 51.0, 59.4, 76.1, 109.8, 112.9, 122.9, 124.8, 127.5, 138.6, 143.6, 159.7, 163.4, 167.9, 180.0, 195.3. Anal. calcd. for $C_{21}H_{21}ClN_2O_5$: C, 60.51; H, 5.08; N, 6.72. Found: C, 60.50; H, 5.07, N, 6.71.

2-Amino-7-chloro-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4g): White solid (yield: 93%); mp 291-293 °C, ^1H NMR (400 MHz, DMSO-d_6) δ 0.99 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.10 (d, J = 16.0 Hz, 1H, CH_AH_B), 2.18 (d, J = 16.0 Hz, 1H, CH_AH_B), 2.49-2.62 (m, 2H, CH_2), 6.92 (t, J = 8.0 Hz, 1H, ArH), 6.98 (d, J = 6.8 Hz, 1H, ArH), 7.21 (m, 1H, ArH), 7.32 (s, 2H, NH_2), 10.84 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.5, 28.0, 32.4, 48.1, 50.3, 57.3, 110.9, 114.0, 117.6, 122.2, 123.5, 128.7, 136.6, 140.3, 159.3, 164.9, 178.4, 195.5. Anal. calcd. for $C_{19}H_{16}ClN_3O_3$: C, 61.71; H, 4.36; N, 11.36. Found: C, 61.70; H, 4.37, N, 11.35.

Ethyl-2-amino-7-chloro-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carboxlate (4h): White solid (yield: 94%); mp 278-280 °C, ^1H NMR (400 MHz, DMSO-d_6) δ 0.83 (t, J = 7.2 Hz, 3H, CH_3), 0.95 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.03 (d, J = 15.6 Hz, 1H,

CH_AH_B), 2.18 (d, J = 15.0 Hz, 1H, CH_AH_B), 2.47-2.62 (m, 2H, CH_2), 3.64-3.78 (m, 2H, CH_2), 6.79 (t, J = 7.6 Hz, 1H, ArH), 6.83 (d, J = 6.4 Hz, 1H, ArH), 7.10 (m, 1H, ArH), 7.92 (s, 2H, NH_2), 10.55 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.4, 27.2, 28.2, 32.0, 47.9, 51.0, 59.4, 76.3, 113.1, 121.3, 122.3, 127.6, 138.3, 142.2, 159.6, 163.2, 167.9, 180.2, 195.3. Anal. calcd. for $C_{21}H_{21}ClN_2O_5$: C, 60.51; H, 5.08; N, 6.72. Found: C, 60.49; H, 5.08, N, 6.71.

2-Amino-7-nitro-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4i): Yellow solid (yield: 88%); mp 279-281 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.01 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.13 (d, J = 16.0 Hz, 1H, CH_AH_B), 2.19 (d, J = 16.0 Hz, 1H, CH_AH_B), 2.50-2.60 (m, 2H, CH_2), 7.13 (d, J = 7.2 Hz, 1H, ArH), 7.52 (d, J = 7.2 Hz, 1H, ArH), 7.99 (d, J = 8.4 Hz, 1H, ArH), 7.47 (s, 2H, NH_2), 11.27 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.7, 27.8, 32.5, 46.5, 50.2, 56.4, 110.4, 117.4, 122.6, 123.7, 130.0, 130.9, 138.4, 139.1, 159.5, 165.6, 179.0, 195.7. Anal. calcd. for $C_{19}H_{16}N_4O_5$: C, 60.00; H, 4.24; N, 14.73. Found: C, 59.98; H, 4.23, N, 6.70.

2-Amino-7',7,7-trimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4j): White solid (yield: 91%); mp 296-297 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.99 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.07 (d, J = 16.0 Hz, 1H, CH_AH_B), 2.18 (d, J = 16.0 Hz, 1H, CH_AH_B), 2.21 (s, 3H, CH_3), 2.50-2.61 (m, 2H, CH_2), 6.79 (t, J = 6.8 Hz, 1H, ArH), 6.82 (s, 1H, ArH), 6.95 (d, J = 6.8 Hz, 1H, ArH), 7.21 (s, 2H, NH_2), 10.44 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 16.8, 27.4, 28.1, 32.4, 47.5, 50.5, 58.3, 111.4, 117.8, 118.7, 120.8, 122.0, 130.0, 134.6, 141.1, 159.2, 164.4, 178.9, 195.2. Anal. calcd. for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.74; H, 5.47, N, 12.02.

Ethyl-2-amino-7',7,7-trimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carboxlate (4k): White solid (yield: 92%); mp 289-290 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.79 (t, J = 7.2 Hz, 3H, CH_3), 0.94 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.00 (d, J = 15.6 Hz, 1H, CH_AH_B), 2.15 (d, J = 15.0 Hz, 1H, CH_AH_B), 2.17 (s, 3H, CH_3), 2.45-2.61 (m, 2H, CH_2), 3.63-3.74 (m, 2H, CH_2), 6.65 (d, J = 6.4 Hz, 1H, ArH), 6.68 (t, J = 7.2 Hz, 1H, ArH), 6.86 (d, J = 6.8 Hz, 1H, ArH), 7.84 (s, 2H, NH_2), 10.17 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.3, 16.8, 27.0, 28.3, 32.0, 47.3, 51.1, 59.3, 77.0, 113.7, 117.5, 120.2, 121.0, 128.9, 136.0, 142.9, 159.5, 162.7, 168.2, 180.7, 195.0. Anal. calcd. for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 60.64; H, 6.10, N, 6.70.

2-Amino-5-methyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4l): White solid (yield: 95%); mp 291-294 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.92 (t, J = 6.4 Hz, 2H, CH_2), 2.21-2.25 (m, 2H, CH_2), 2.23 (s, 3H, CH_3), 2.65 (t, J = 6.0 Hz, 2H, CH_2), 6.66 (d, J = 8.0 Hz, 1H, ArH), 6.81 (s, 1H, ArH), 6.93 (d, J = 7.6 Hz, 1H, ArH), 7.17 (s, 2H, NH_2), 10.26 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.2, 21.1, 27.2, 36.9, 47.4, 58.2, 109.3, 112.4, 117.9, 124.2, 128.9, 130.9, 135.1, 140.0, 159.0, 166.4, 178.5, 195.4. Anal. calcd. for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.29; H, 4.70, N, 13.07.

2-Amino-7-chloro-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4m): White solid (yield: 92%); mp > 300 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.93 (t, J = 6.0 Hz, 2H, CH_2), 2.17-2.29 (m, 2H, CH_2), 2.62-2.68 (m, 2H, CH_2), 6.92 (t, J = 8.0 Hz, 1H, ArH), 7.01 (d, J = 7.2 Hz, 1H, ArH), 7.21 (d, J = 8.0 Hz, 1H, ArH), 7.31 (s, 2H, NH_2), 10.83 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.2, 27.2, 36.7, 48.2, 57.4, 112.0, 113.9, 117.0, 122.4, 123.4, 128.7, 136.7, 140.2, 159.2, 166.8, 178.6, 195.6. Anal. calcd. for $C_{17}H_{12}ClN_3O_3$: C, 59.75; H, 3.54; N, 12.30. Found: C, 59.73; H, 3.54, N, 12.31.

2-Amino-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4n): White solid (yield: 89%); mp 251-253 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.92 (t, J = 6.0 Hz, 2H, CH_2), 2.16-2.29 (m, 2H, CH_2), 2.50-2.67 (m, 2H, CH_2), 6.77 (d, J = 7.6 Hz, 1H, ArH), 6.88 (t, J = 7.6 Hz, 1H, ArH), 7.00 (d, J = 7.2 Hz, 1H, ArH), 7.13 (t, J = 7.6 Hz, 1H, ArH), 7.18 (s, 2H, NH_2), 10.37 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.2, 27.2, 36.8, 47.3, 58.0, 109.6, 112.3, 117.8, 122.1, 123.6, 128.6, 135.0, 142.4, 159.1, 166.5, 178.6, 195.5. Anal. calcd. for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.67. Found: C, 66.45; H, 4.27, N, 13.67.

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