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Electrocatalytic multicomponent transformation of cyclic 1,3-diketones, isatins, and malononitrile: facile and convenient way to functionalized spirocyclic (5,6,7,8-tetrahydro-4*H*-chromene)-4,3′-oxindole system

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Abstract—An electrochemically induced catalytic multicomponent transformation of cyclic 1,3-diketones, isatins, and malononitrile in alcohols in an undivided cell in the presence of sodium bromide as an electrolyte results in the formation of spirooxindoles with fused functionalized 5,6,7,8-tetrahydro-4*H*-chromene system in 83–98% yields. The application of this efficient electrocatalytic method to the formation of medicinally relevant spirocyclic (4*H*-chromene)-4,3′-oxindoles is beneficial from the viewpoint of diversity-oriented large-scale processes and represents novel, facile, and environmentally benign synthetic concept for multicomponent reaction strategy.

1. Introduction

The development of multicomponent reactions (MCRs) designed to produce elaborate biologically active compounds has become an important area of research in organic, combinatorial, and medicinal chemistry.[1] The MCR strategy offers significant advantages over conventional linear-type synthesis due to its flexible, convergent, and atom efficient nature.[2] In recent years, the synthesis of combinatorial small-molecule heterocyclic libraries has emerged as a valuable tool in the search for novel lead structures.[3] Thus, the success of combinatorial chemistry in the drug discovery process is considerably dependent on further advances in heterocyclic MCR methodology and, according to current synthetic requirements, environmentally benign multicomponent procedures are particularly welcome.

The heterocyclic spirooxindole ring system is a widely distributed structural framework present in a number of pharmaceuticals and natural products,[4] including such cytostatic alkaloids as spirotryprostatins A, B, and strychnophylline.[5] The unique structural array and the highly pronounced pharmacological activity displayed by the class of spirooxindole compounds have made them attractive synthetic targets.[6] Azaspiro derivatives are well-known,[6,7] but the preparation of the corresponding oxa analogues has evolved at a relatively slow pace.[8] Among the oxygen-containing heterocycles fused with spirooxindole ring system, 4*H*-chromenes are of particular utility as they belong to 'privileged medicinal scaffolds'—certain molecular frameworks serving for the generation of ligands for functionally and structurally discreet biological receptors.[9] Functionally substituted 4*H*-chromenes have received considerable attention due to their wide range of useful biological properties, which include spasmolitic-, diuretic-, anticoagulant-, anticancer-, and antianaphylactic activities.[10] The current interest in 5,6,7,8-tetrahydro-4*H*-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.[11]

To the best of our knowledge, there are only two reports on multicomponent entries to the synthesis of spirooxindoles with fused 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile systems. Both MCRs employ a three-component condensation of cyclic 1,3-diketones, isatins, and malononitile realized under two types of catalytic conditions. The catalysis of dimedone, isatin, and malononitrile with piperidine in ethanol affords spiro[(2-amino-3-cyano-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene)-4,3′-oxindole] in 83%

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yield at ambient temperature, but the reaction has been performed only on a single example with a lack of characterization data.[12] Recently Shanthi et al. reported a three-component condensation of cyclic 1,3-diketones, isatin, and malononitrile catalyzed by 20 mol % of indium(III) chloride.[13] Although this catalytic MCR leads to corresponding spiro[(4*H*-chromene)-4,3′-oxindoles] in 70–90% yields, it necessitates either reflux in acetonitrile for 1.5 h or microwave irradiation. Furthermore, column chromatography is required for purification of desired products. Thus, each of the known MCR procedures for the synthesis of corresponding spiro[(4*H*-chromene)-4,3′-oxindole] system has its merits, but the essence of facile and convenient multicomponent methodology has yet to be developed.

2. Results and discussion

The advances in electrosynthesis in the last few decades have provided organic chemists with a new versatile synthetic device of great promise.[14] Despite the significant synthetic potential and ecological advantages of electrochemical methods, the practical usage of electrochemical procedure is often limited on account of its technical complexity and generally long processing times. In the course of our study on the electrochemical transformation of organic compounds, we have found a new type of electrochemical transformation, namely the electrocatalytic chain transformation of organic compounds induced by a catalytic amount of an electrogenerated base in an undivided cell.[15] Recently, we have successfully applied this electrocatalytic procedure, developed by us, to the synthesis of a number of medicinally relevant 4*H*-chromene derivatives bearing nitrile functionality.[16] These unique electrochemical procedures utilize a simple undivided cell and are valuable for large-scale processes because of their catalytic nature and the use of a cheap and environmentally responsible chemical reagent—electricity. The use of the described electrocatalytic methodology in base-activated MCRs is highly promising as it allows for the combination of the synthetic virtues of the conventional MCR strategy with the ecological benefits and convenience of the facile electrocatalytic procedure.

In the present study we report our results on electrocatalytic multicomponent chain transformation of cyclic 1,3-diketones, isatins, and malononitrile into spiro[(2-amino-3-cyano-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene)-4,3′-oxindoles] under neutral and mild conditions by electrolysis in an undivided cell. The reaction is performed in alcoholic solvents in the presence of sodium bromide as an electrolyte (Scheme 1).

First, to evaluate the synthetic potential of the procedure proposed and to optimize the electrolysis conditions, the electrocatalytic multicomponent transformation of 5,5-dimethylcyclohexane-1,3-dione **1a**, isatin **2a**, and malononitrile into spirocyclic (4*H*-chromene)-4,3′-oxindole **3a** was studied (Table 1).

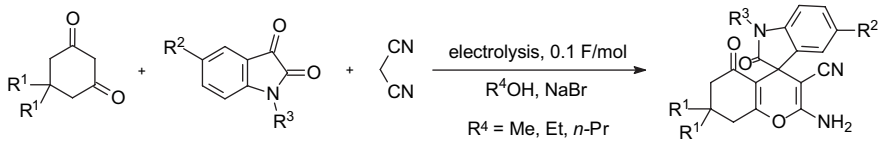
Excellent conversions of the starting compounds were obtained under 10 mA/cm^2 and 15 mA/cm^2 current densities after 0.1 F/mol of electricity had been passed. The current density of 10 mA/cm^2 (I=50 mA, electrodes surface 5 cm^2) was found to be optimal for the electrochemically induced chain process and allowed for the highest yield of spiro[(4*H*-chromene)-4,3′-oxindole] **3a**. An increase in the current density up to 15 mA/cm^2 (I=75 mA) resulted in a slight decrease in the reaction yield, and may be a result of the activation of the undesired direct electrochemical processes that lead to oligomerization of the starting material.

After electrolysis, spiro[(4*H*-chromene)-4,3′-oxindole] **3a** was directly crystallized from the reaction mixture. As for the alcoholic solvent, the usage of either EtOH or *n*-PrOH is preferred since the products can be filtered directly after electrolysis.[17] Under the optimal conditions (current density 10 mA/cm^2, 0.1 F/mol passed, EtOH as solvent) the electrolysis of cyclic 1,3-diketones **1a** and **1b**, isatins **2a–e**, and malononitrile in an undivided cell affords spiro[(4*H*-chromene)-4,3′-oxindoles] **3a–i** in yields of 83–98% at ambient temperature over a 32 min reaction period (Table 2).

Table 1. Electrocatalytic transformation of 5,5-dimethylcyclohexane-1,3-dione **1a**, isatin **2a**, and malononitrile into spiro[(4*H*-chromene)-4,3′-oxindole] **3a**[a]

I (mA)	Current density (mA/cm^2)	Time (min)	Alcohol	Electricity passed (F/mol)	Yield of **3a**[b] (%)
5	1	320	EtOH	0.1	71
10	2	160	EtOH	0.1	75
20	4	80	EtOH	0.1	82
50	10	32	EtOH	0.1	96
75	15	22	EtOH	0.1	87
50	10	32	MeOH	0.1	84
50	10	32	*n*-PrOH	0.1	92

[a] Reagents and conditions: **1a** (10 mmol), **2a** (10 mmol), malononitrile (10 mmol), NaBr (1 mmol), alcohol (20 mL), iron cathode (5 cm^2), graphite anode (5 cm^2), 20 °C.
[b] Yield of isolated product obtained by filtration of the reaction mixture.



1a,b

a R^1 = Me
b R^1 = H

2a-e

a R^2 = H, R^3 = H;
b R^2 = Br, R^3 = H;
c R^2 = H, R^3 = Me;
d R^2 = H, R^3 = Ac;
e R^2 = H, R^3 = Bn;

3a-i

a R^1 = Me, R^2 = H, R^3 = H; **b** R^1 = Me, R^2 = Br, R^3 = H;
c R^1 = Me, R^2 = H, R^3 = Me; **d** R^1 = Me, R^2 = H, R^3 = Ac;
e R^1 = Me, R^2 = H, R^3 = Bn; **f** R^1 = H, R^2 = H, R^3 = H;
g R^1 = H, R^2 = Br, R^3 = H; **h** R^1 = H, R^2 = H, R^3 = Me;
i R^1 = H, R^2 = H, R^3 = Ac;

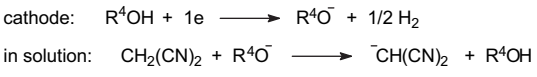
Scheme 1.

Table 2. Electrocatalytic transformation of cyclic 1,3-diketones **1**, isatins **2**, and malononitrile into spiro[(4*H*-chromene)-4,3′-oxindoles] **3**[a]

Cyclic 1,3-diketone	Isatin	Current density (mA/cm^2)	Time (min)	Electricity passed (F/mol)	Product	Yield of **3a–i**[b] (%)
1a	**2a**	10	32	0.1	**3a**	96
1a	**2b**	10	32	0.1	**3b**	87
1a	**2c**	10	32	0.1	**3c**	97
1a	**2d**	10	32	0.1	**3d**	90
1a	**2e**	10	32	0.1	**3e**	91
1b	**2a**	10	32	0.1	**3f**	89
1b	**2b**	10	32	0.1	**3g**	83
1b	**2c**	10	32	0.1	**3h**	98
1b	**2d**	10	32	0.1	**3i**	87

[a] Reagents and conditions: **1** (10 mmol), **2** (10 mmol), malononitrile (10 mmol), NaBr (1 mmol), EtOH (20 mL), iron cathode (5 cm^2), graphite anode (5 cm^2), 20 °C.
[b] Yield of isolated product obtained by filtration of the reaction mixture.

With the above results taken into consideration and the mechanistic data on the electrocatalytic chain cyclizations previously performed by us,[15,16] the following mechanism for the electrocatalytic chain transformation of cyclic 1,3-diketones **1**, isatins **2**, and malononitrile into substituted spiro[(4*H*-chromene)-4,3′-oxindoles] **3** is proposed. The initiation step of the catalytic cycle begins with the deprotonation of a molecule of alcohol at the cathode, which leads to the formation of an alkoxide anion. The subsequent reaction between the alkoxide anion and malononitrile gives rise to the malononitrile anion (Scheme 2).



Scheme 2.

The following process in the solution represents a typical cascade reaction. Knoevenagel condensation of the malononitrile anion with isatin **2** takes place with the elimination of a hydroxide anion and formation of isatylidenemalononitrile **4**.[18] The subsequent hydroxide-promoted Michael addition of cyclic 1,3-diketone **1** to electron deficient Knoevenagel adduct **4** followed by intramolecular cyclization leads to corresponding spiro[(4*H*-chromene)-4,3′-oxindoles] **3** with the regeneration of the alkoxide anion as the last step. The catalytic chain process then continues by the interaction of the alkoxide with the next molecule of malononitrile (Scheme 3). Thus, under the conditions of developed electrocatalytic process, the generation of even a single alkoxide anion at the cathode is theoretically sufficient for the total conversion of equimolar quantities of cyclic 1,3-diketone, isatin, and malononitrile into the corresponding spiro[(4*H*-chromene)-4,3′-oxindole].

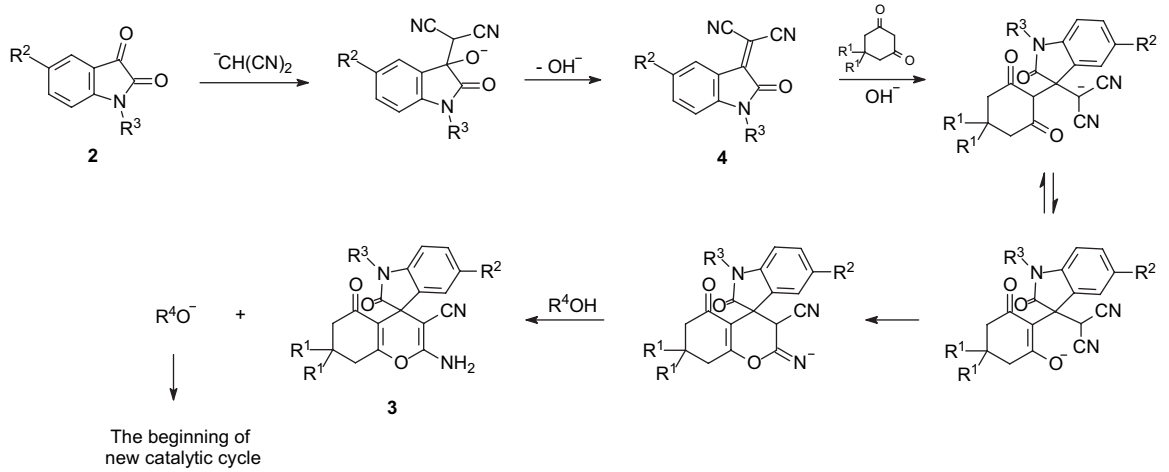
3. Conclusions

In conclusion, the simple electrocatalytic system can produce, under neutral and mild conditions, a fast and selective multicomponent transformaton of cyclic 1,3-diketones, isatins, and malononitrile into spiro[(2-amino-3-cyano-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene)-4,3′-oxindoles] in excellent yields. This novel electrocatalytic chain process offers an efficient and convenient way to create spirocyclic oxindole systems with fused cyano-functionalized 4*H*-chromene fragment—the hybridized ‘privileged drug scaffold’ for human neurodegenerative disorders therapy and different biomedical applications. The electrocatalytic procedure utilizes simple equipment and an undivided cell, and is easily carried out. This efficient electrocatalytic approach to spirocyclic (5,6,7,8-tetrahydro-4*H*-chromene)-4,3′-oxindole ring system represents a novel synthetic concept for multicomponent reactions, and allows for the combination of the synthetic virtues of conventional MCRs with ecological benefits and convenience of facile electrocatalytic procedure. Therefore, this novel MCR strategy brings us a step closer to the notion of ‘ideal synthesis’.[19]

4. Experimental section

4.1. General remarks

All melting points were measured with a Gallenkamp melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with Bruker AC-200, Bruker WM-250, and Bruker AC-300 spectrometers at ambient temperature. Chemical shifts values are relative to Me_4Si. IR spectra



Scheme 3.

were registered with a SPECORD M82 spectrometer in KBr pellets. Mass spectra (EI=70 eV) were obtained directly with a Finningan MAT INCOS 50 spectrometer.

4.2. Typical electrolysis procedure

A solution of cyclic 1,3-diketone (10 mmol), isatin (10 mmol), malononitrile (0.66 g, 10 mmol), and sodium bromide (0.1 g, 1 mmol) in the appropriate alcoholic solvent (20 mL) was electrolyzed in an undivided cell equipped with a magnetic stirrer, a graphite anode, and an iron cathode at 20 °C under a constant current density of 10 mA/cm^2 (I=50 mA, electrodes square 5 cm^2) until the catalytic quantity of 0.1 F/mol of electricity was passed (time: 32 min). After the electrolysis was finished, the solution was filtered to isolate the solid product, which was then twice rinsed with an ice-cold ethanol/water solution (9:1, 5 mL), and dried under reduced pressure.

4.2.1. 2-Amino-7,7-dimethyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (3a). White solid, yield 3.22 g (96%), mp 305–307 °C (from EtOH; lit. mp[12] 285–287 °C, from DMF/EtOH). δ_H (300 MHz, DMSO-d_6) 1.00 (3H, s, CH_3), 1.03 (3H, s, CH_3), 2.08–2.19 (2H, m, CH_2), 2.56 (2H, s, CH_2), 6.78 (1H, d, J 7.3 Hz, Ar), 6.89 (1H, t, J 7.3 Hz, Ar), 6.97 (1H, d, J 7.3 Hz, Ar), 7.14 (1H, t, J 7.3 Hz, Ar), 7.23 (2H, s, NH_2), 10.40 (1H, s, NH) ppm; δ_C (63 MHz, DMSO-d_6) 27.1 (CH_3), 27.7 (CH_3), 32.0 (CH_2), 40.0 (C), 46.9 (C), 50.1 (CH_2), 57.5 (C), 109.3 (CH), 110.9 (C), 117.4 (C), 121.8 (CH), 123.1 (CH), 128.2 (CH), 134.5 (C), 142.1 (C), 158.9 (C), 164.2 (C), 178.1 (C), 194.9 (C) ppm. MS (70 eV) m/z (relative intensity %): 335 ([M]$^+$, 30), 309 (9), 290 (9), 251 (100), 209 (26), 140 (11), 83 (25), 55 (31), 44 (45), 39 (41). IR (KBr): ν_{max} 3376, 3312, 3144, 2928, 2196, 1724, 1656, 1348, 1224, 1056 cm^{-1}. $C_{19}H_{17}N_3O_3$ calcd: C 68.05, H 5.11, N 12.53; found: C 67.94, H 5.17, N 12.42.

4.2.2. 2-Amino-5′-bromo-7,7-dimethyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (3b). White solid, yield 3.60 g (87%), mp 305–307 °C (from EtOH). δ_H (200 MHz, DMSO-d_6) 1.02 (6H, s, 2 CH_3), 2.16 (2H, s, CH_2), 2.45–2.65 (2H, m, CH_2), 6.76 (1H, d, J 8.1 Hz, Ar), 7.19 (1H, s, Ar), 7.24–7.36 (3H, m, Ar, NH_2), 10.52 (1H, s, NH) ppm; δ_C (63 MHz, DMSO-d_6) 27.3 (CH_3), 27.6 (CH_3), 32.1 (CH_2), 39.9 (C), 47.1 (C), 50.0 (CH_2), 56.8 (C), 110.3 (C), 111.3 (CH), 113.4 (C), 117.3 (C), 126.0 (CH), 131.0 (CH), 136.9 (C), 141.5 (C), 158.9 (C), 164.7 (C), 177.7 (C), 195.2 (C) ppm. MS (70 eV) m/z (relative intensity %): 415 ([M]$^+$, 35), 413 ([M]$^+$, 38), 387 (20), 371 (19), 329 (100), 289 (27), 251 (30), 152 (19), 83 (31), 55 (42), 44 (49). IR (KBr): ν_{max} 3360, 3288, 3160, 2956, 2200, 1728, 1656, 1352, 1224, 1056 cm^{-1}. $C_{19}H_{16}BrN_3O_3$ calcd: C 55.09, H 3.89, N 10.14; found: C 54.93, H 3.97, N 10.02.

4.2.3. 2-Amino-1′,7,7-trimethyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (3c). White solid, yield 3.39 g (97%), mp 248–250 °C (from EtOH; lit. mp[20] 225 °C, from CH_3CN). δ_H (300 MHz, DMSO-d_6) 1.03 (6H, s, 2 CH_3), 2.12 (2H, s, CH_2), 2.57 (2H, s, CH_2), 3.14 (3H, s, NCH_3), 6.93–7.04 (3H, m, Ar), 7.15–7.30 (3H, m, Ar, NH_2) ppm; δ_C (63 MHz, DMSO-d_6) 26.4 (CH_3), 27.1 (CH_3), 27.6 (CH_3), 32.0 (CH_2), 39.9 (C), 46.5 (C), 50.0 (CH_2), 57.1 (C), 108.2 (CH), 110.8 (C), 117.2 (C), 122.5 (CH), 122.8 (CH), 128.5 (CH), 133.6 (C), 143.6 (C), 158.9 (C), 164.3 (C), 176.6 (C), 194.9 (C) ppm. MS (70 eV) m/z (relative intensity %): 349 ([M]$^+$, 42), 334 (8), 323 (22), 295 (12), 265 (100), 223 (17), 140 (11), 89 (12), 55 (13), 44 (16). IR (KBr): ν_{max} 3368, 3324, 3176, 2960, 2200, 1712, 1672, 1356, 1224, 1052 cm^{-1}. $C_{20}H_{19}N_3O_3$ calcd: C 68.75, H 5.48, N 12.03; found: C 68.69, H 5.52, N 11.97.

4.2.4. 1′-Acetyl-2-amino-7,7-dimethyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (3d). White solid, yield 3.40 g (97%), mp 233–234 °C (from EtOH). δ_H (300 MHz, DMSO-d_6) 1.01 (3H, s, CH_3), 1.05 (3H, s, CH_3), 2.12–2.21 (2H, m, CH_2), 2.58 (2H, s, CH_2), 2.63 (3H, s, CH_3CO), 7.18–7.25 (2H, m, Ar), 7.28–7.38 (1H, m, Ar), 7.55 (2H, s, NH_2), 8.08 (1H, d, J 7.8 Hz, Ar) ppm; δ_C (63 MHz, DMSO-d_6) 26.0 (CH_3), 27.1 (CH_3), 27.6 (CH_3), 32.2 (CH_2), 39.8 (C), 47.5 (C), 49.5 (CH_2), 57.1 (C), 110.9 (C), 115.4 (CH), 117.1 (C), 123.4 (CH), 125.6 (CH), 128.8 (CH), 132.8 (C), 139.3 (C), 158.7 (C), 164.9 (C), 170.4 (C), 177.9 (C), 195.5 (C) ppm. MS (70 eV) m/z (relative intensity %): 377 ([M]$^+$, 35), 362 (8), 348 (9), 334 (100), 251 (25), 223 (10), 140 (11), 89 (8), 55 (9), 43 (75). IR (KBr): ν_{max} 3332, 3192, 2960, 2204, 1756, 1724, 1672, 1352, 1272, 1052 cm^{-1}. $C_{21}H_{19}N_3O_4$ calcd: C 66.83, H 5.07, N 11.13; found: C 66.78, H 5.14, N 11.04.

4.2.5. 2-Amino-1′-benzyl-7,7-dimethyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (3e). White solid, yield 3.87 g (91%), mp 280–281 °C (from EtOH). δ_H (250 MHz, DMSO-d_6) 1.03 (6H, s, 2 CH_3), 2.14–2.21 (2H, m, CH_2), 2.61 (2H, m, CH_2), 4.92 (2H, s, CH_2Ph), 6.65–6.73 (1H, m, Ar), 6.87–7.70 (10H, m, Ar, NH_2) ppm; δ_C (63 MHz, DMSO-d_6) 27.1 (CH_3), 27.7 (CH_3), 32.0 (CH_2), 40.0 (C), 43.4 (CH_2), 46.7 (C), 49.9 (CH_2), 57.3 (C), 108.9 (CH), 110.7 (C), 117.5 (C), 122.6 (CH), 123.0 (CH), 127.2 (3 CH), 128.3 (CH), 128.4 (2 CH), 133.7 (C), 136.2 (C), 142.7 (C), 159.0 (C), 164.6 (C), 176.8 (C), 195.1 (C) ppm. MS (70 eV) m/z (relative intensity %): 425 ([M]$^+$, 26), 397 (12), 341 (12), 334 (84), 234 (17), 222 (10), 140 (10), 91 (100), 83 (13), 65 (22). IR (KBr): ν_{max} 3380, 3300, 3208, 2964, 2200, 1716, 1660, 1352, 1220, 1052 cm^{-1}. $C_{26}H_{23}N_3O_3$ calcd: C 73.39, H 5.45, N 9.88; found: C 73.28, H 5.48, N 9.82.

4.2.6. 2-Amino-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro-[chromene-4,3′-indole]-3-carbonitrile (3f). White solid, yield 2.73 g (89%), mp 312–313 °C (from EtOH; lit. mp[21] 304–305 °C, from AcOH). δ_H (300 MHz, DMSO-d_6) 1.91–2.00 (2H, m, CH_2), 2.10–2.30 (2H, m, CH_2), 2.62–2.73 (2H, m, CH_2), 6.78 (1H, d, J 7.4 Hz, Ar), 6.88 (1H, t, J 7.4 Hz, Ar), 7.00 (1H, d, J 7.4 Hz, Ar), 7.14 (1H, t, J 7.4 Hz, Ar), 7.23 (2H, s, NH_2), 10.40 (1H, s, NH) ppm; δ_C (63 MHz, DMSO-d_6) 19.8 (CH_2), 26.8 (CH_2), 36.4 (CH_2), 46.9 (C), 57.6 (C), 109.2 (CH), 111.9 (C), 117.4 (C), 121.8 (CH), 123.3 (CH), 128.2 (CH), 134.6 (C), 142.0 (C), 158.7 (C), 166.1 (C), 178.2 (C), 195.1 (C) ppm. MS (70 eV) m/z (relative intensity %): 307 ([M]$^+$, 38), 281 (9), 262 (28), 251 (100), 209 (26), 140 (8), 89 (6), 55 (9), 44 (15), 39 (9). IR (KBr): ν_{max} 3352, 3296, 3176, 2952, 2204, 1712, 1656, 1352,

1216, 1076 cm^{-1}. $C_{17}H_{13}N_3O_3$ calcd: C 66.44, H 4.26, N 13.67; found: C 66.38, H 4.31, N 13.60.

4.2.7. 2-Amino-5′-bromo-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (3g). White solid, yield 3.20 g (83%), mp 273–275 °C (from EtOH). δ_H (250 MHz, DMSO-d_6) 1.78–2.08 (2H, m, CH_2), 2.10–2.35 (2H, m, CH_2), 2.56–2.79 (2H, m, CH_2), 6.75 (1H, d, *J* 7.3 Hz, Ar), 7.14–7.61 (4H, m, Ar, NH_2), 10.55 (1H, s, NH) ppm; δ_C (63 MHz, DMSO-d_6) 19.8 (CH_2), 26.8 (CH_2), 36.4 (CH_2), 47.2 (C), 56.9 (C), 111.2 (CH, C), 113.4 (C), 117.3 (C), 126.2 (CH), 130.9 (CH), 137.0 (C), 141.4 (C), 158.8 (C), 166.7 (C), 177.9 (C), 195.3 (C) ppm. MS (70 eV) *m/z* (relative intensity %): 387 ($[M]^+$, 24), 385 ($[M]^+$, 23), 342 (14), 329 (66), 289 (37), 273 (100), 248 (75), 151 (39), 89 (27), 55 (67), 44 (50). IR (KBr): ν_{max} 3424, 3304, 3180, 2956, 2204, 1708, 1672, 1352, 1176, 1080 cm^{-1}. $C_{17}H_{12}BrN_3O_3$ calcd: C 52.87, H 3.13, N 10.88; found: C 52.85, H 3.08, N 10.84.

4.2.8. 2-Amino-1′-methyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (3h). White solid, yield 3.15 g (98%), mp 247–248 °C (from EtOH). δ_H (300 MHz, DMSO-d_6) 1.78–2.05 (2H, m, CH_2), 2.08–2.34 (2H, m, CH_2), 2.56–2.89 (2H, m, CH_2), 3.14 (3H, s, NCH_3), 6.85–7.10 (3H, m, Ar), 7.18–7.36 (3H, m, Ar, NH_2) ppm; δ_C (63 MHz, DMSO-d_6) 19.8 (CH_2), 26.4 (CH_3), 26.8 (CH_2), 36.4 (CH_2), 46.6 (C), 57.2 (C), 108.1 (CH), 111.9 (C), 117.3 (C), 122.5 (CH), 123.0 (CH), 128.4 (CH), 133.7 (C), 143.6 (C), 158.8 (C), 166.2 (C), 176.7 (C), 195.1 (C) ppm. MS (70 eV) *m/z* (relative intensity %): 321 ($[M]^+$, 63), 295 (15), 265 (100), 236 (11), 223 (23), 193 (7), 140 (11), 89 (8), 55 (13), 44 (19). IR (KBr): ν_{max} 3564, 3464, 3365, 3148, 2964, 2200, 1704, 1676, 1352, 1216 cm^{-1}. $C_{18}H_{15}N_3O_3$ calcd: C 67.28, H 4.71, N 13.08; found: C 67.22, H 4.80, N 12.97.

4.2.9. 1′-Acetyl-2-amino-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (3i). White solid, yield 3.04 g (87%), mp 252–254 °C (from EtOH). δ_H (300 MHz, DMSO-d_6) 1.80–2.09 (2H, m, CH_2), 2.13–2-42 (2H, m, CH_2), 2.57 (3H, s, CH_3CO), 2.59–2.85 (2H, m, CH_2), 7.15–7.28 (2H, m, Ar), 7.28–7.41 (1H, m, Ar), 7.54 (2H, m, NH_2), 8.07 (1H, d, *J* 7.5 Hz, Ar) ppm; δ_C (50 MHz, DMSO-d_6) 19.7 (CH_2), 25.9 (CH_3), 26.6 (CH_2), 35.9 (CH_2), 47.5 (C), 57.1 (C), 111.9 (C), 115.3 (CH), 117.0 (C), 123.6 (CH), 125.5 (CH), 128.6 (CH), 132.9 (C), 139.2 (C), 158.6 (C), 166.8 (C), 170.4 (C), 178.0 (C), 195.6 (C) ppm. MS (70 eV) *m/z* (relative intensity %): 349 ($[M]^+$, 28), 334 (4), 321 (3), 306 (100), 251 (19), 222 (6), 140 (5), 88 (3), 55 (5), 43 (29). IR (KBr): ν_{max} 3412, 3324, 3184, 2204, 1748, 1716, 1668, 1352, 1272, 1204 cm^{-1}. $C_{19}H_{15}N_3O_4$ calcd: C 65.32, H 4.33, N 12.03; found: C 65.28, H 4.41, N 11.94.

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