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Bmim(OH)/chitosan/C_2H_5OH synergy: grinding induced, a new route for the synthesis of spiro-oxindole and its derivatives

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Here we report a synthetic strategy based on the synergistic effect of a catalyst system incorporating Bmim(OH), chitosan and C_2H_5OH. This powerful catalyst system is very effective and has several advantages such as being cost effective, involving shorter reaction times, being high yielding, involving the formation of no by-products and most importantly its easy recyclability (at least three times) with negligible reduction in its catalytic properties.

Introduction

A major challenge in the field of synthetic chemistry is to avoid a multistep synthetic method and the use of hazardous solvents and toxic chemicals.[1] Multi component reactions are a precise synthetic tool which can offer easy access to the synthesis of a multi functionalised compound in an easy way with atom and time economy.[2] In addition, a neat synthesis is the only way to save the environment from the harmful effects of the solvent.[3] An alternative route to escape the solvent is a grinding induced reaction in which mechanical action is used for the reaction.[4] First of all the reactants are broken down into fine particles which facilitate the reaction amongst them.[5] Without a query, catalysis gives an alternative path with a better yield, greater energy efficiency and improved economy.[6] According to literature a mono-catalyst system was famous and very successful but since last 37 years multi catalyst system made a place in the form of synergistic catalysis.[7] In this type of catalysis all components give the additive effect in the catalytic process.[7] Many research groups have focused on this type of catalysis. Eder. J. Lenardão synthesised vinyl sulphides and tellurides in the recyclable catalyst system – glycerol/CuI/Zn,[8] Jing and his co-worker reported our work, Henery-micheal by synergically catalysed by grafted chiral bases and inherent achiral hydroxyl on mesoporous surface.[9a] Our recent work[5b] involved the synthesis of functionalised pyrazoles with time economy by the use of a catalyst system which was prepared from ionic liquid and water. In extension to our recent work we have now used a catalyst which is prepared by 10 mol% Bim(OH), 10 mol% chitosan[9b] and 1 mL ethanol (Scheme 1). This catalyst system shows additive effect and serves as a superb catalyst.

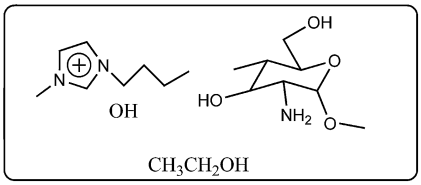
The reason behind the incorporation of 1-Bmim(OH) in the catalyst system is that a basic ionic liquid can dissolve many polar and non polar organic and inorganic molecules and also has good catalytic activity in base catalyzed reactions.[10]

In addition, 2-chitosan has amino and hydroxyl group, both of which are basic.[11] We have made continuous efforts to synthesise biologically active spiro compounds example spiro-oxindole compounds[12] which have been known to exhibit countless useful properties in the field of agriculture and pharmaceutical industry for example antioxidant,[13a] anti-fungal,[13b] anti-malarial,[13c] anti-tumor,[13d] anti-mycobacterial,[13e] anti-microbial[13f] properties, *etc.* Melanoderma is a form of skin cancer which is very dangerous. SOID-8, a derivative of spiro [pyrrolidin-3,3′-oxindole], inhibits growth and induces apoptosis of melanoma cells (Scheme 2).

Result and discussion

Spiro-oxindole serves as an intermediate for alkaloid potential drugs and has varying pharmacological activities. The desired compound is prepared by the starting material isatin, malononitrile and dimedone.[14] Initially we took staring materials in stoichiometric amounts in mortar and grinded with the help of pestle.

The product was formed in 45 minutes with the formation of some by products. In order to reduce the overall time of the



Scheme 1 Catalyst system.

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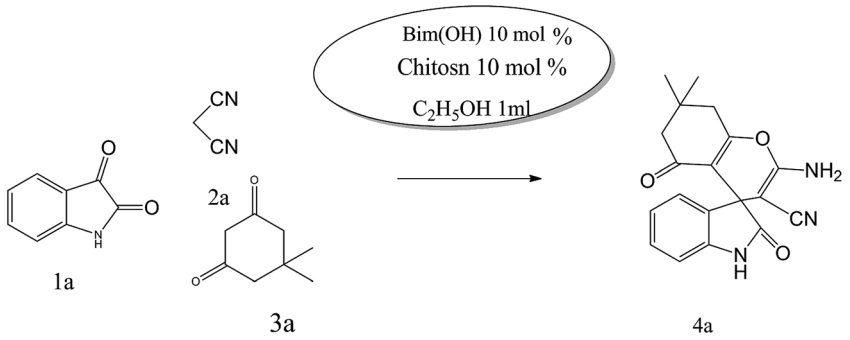
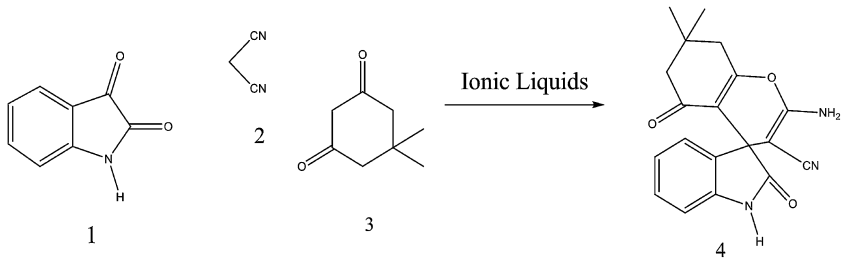


Scheme 2 Synthesis of target compound.

Table 1 Optimization of ionic liquid as a catalyst for the synthesis of spiro-oxindole



Entry	Ionic liquid	Time (min)	Yield[a]
1	(Bmim)OH	30	86
2	(Bmim)BF_4	35	58
3	(Hmim)HSO_4	40	56
4	(Bmim)Cl	35	50
5	(Bmim)PF_6	36	60
6	(Hmim)H_2SO_4	35	65

[a] Is isolated yield in %, amount of ionic liquid is 20 mol%.

Table 2 Effect of different amounts of chitosan with ethanol on the model reaction

Entry	Chitosan[b]	Time	Yield[a]
1	5	40	70
2	10	35	73
3	15	28	77
4	20	20	82
5	30	20	82
6	40	20	82
7	50	20	82

[a] Is isolated yield in %. [b] Is amount of chitosan in mol%.

reaction and to inhibit the formation of by-products, we grinded the starting materials in a sequential manner and introduced the ionic liquid to the reaction mixture as a catalyst. This alternative pathway proved to be beneficial only in the reduction of overall time but the reaction still took 30 minutes to complete. Among the different types of ionic liquids used as catalyst, the performance of basic ionic liquid Bmim(OH) (Table 1, entry 1) is best. We carried out further experiments in order to improve the efficiency of the reaction.

We grinded the staring material with varying amounts of chitosan ranging from 5 mol% to 50 mol% with 1 mL ethanol(Table 2). It was observed that there occurred a reduction in overall reaction time and an increase in yield by increasing the amount of chitosan up to 20 mol% (Table 2 entry 4). Further increase in the amount of chitosan affected neither the reaction time nor the yield of the product. Thus we concluded that the best result was obtained with 20 mol% of chitosan.

Next we performed the experiment with varying quantities of both the catalysts in one mL ethanol and discovered that the best yield of 92% was obtained with 10 mol% Bmim(OH) and 10 mol% chitosan (Table 3 entry 2). The adopted route was atom, time and reagent economical. A further increase in the amount of catalysts showed no beneficial results. In this synthesis use of ethanol as a solvent is to provides a homogeneous mixture of the reactants thus enhancing the reaction rate.

Table 3 Effect of catalyst system of reaction rate and yield of the product

Entry	Catalyst system[b]	Time (min)	Yield[a]
1	5, 5	10	84
2	10, 10	5	92
3	20, 20	5	92
4	30, 30	5	92
5	40, 40	5	92

[a] Is the isolated yield of the product. [b] Is the amount of Bmim(OH) and chitosan in mol%.

Chitosan and ionic liquid provide a basic medium which increases the reactivity of each step of the reaction (Scheme 3). Basicity of the reaction medium encourages it to run at a good speed with a reduction in the formation of by-products.

To standardize the optimization condition we performed a series of reactions and showed the electronic effect of the substituent on reactant. We found then when an electron withdrawing group is present on the isatin the reaction becomes fast because it facilitates the Knoevenagel reaction. On the other hand, when electron donating group is present on the isatin then the reaction becomes slower. All starting materials are activated by this catalyst system and moreover each step of the reaction is catalysed by this system.

Isatin and malononitrile are added through Knoevenagel reaction. Proton is abstracted by the base from active methylene group and is attached on the Knoevenagel adduct. After that tautomerisation occurs and enol form of active methylene attaches on nitrile.

At the end of the reaction, catalyst system is recovered and reused (Table 4). The recovered catalyst system was further used with the same substrate as a catalyst to check the yield obtained and catalytic activity of the recovered catalyst system. As shown in Table 4, the yield of spiro-oxindoles after three cycles was almost the same.

Conclusion

In summary, we have disclosed a new catalyst system which proves to be very effective not only in reducing the reaction time, but also in increasing the yield of the product. It involves simple procedure, is environment friendly and also incorporates special features like reagent economy, easy workup and easy handling.

Experimental

General information

Reagents were obtained from commercial suppliers, and used without further purification unless otherwise specified by a reference. All reactions were performed using oven-dried glassware. Organic solutions were concentrated using a Buchi rotary evaporator. TLC was performed using silica gel GF254 (Merck) plates. Melting points were determined by open glass capillary method and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 993 IR spectrophotometer, ^{1}HNMR spectra were recorded on a Bruker AVII 400 spectrometer in $CDCl_3$ using TMS as internal reference with chemical shift value being reported in ppm. All coupling constants (J) are reported in Hertz (Hz). ^{13}C NMR spectra were recorded on the same instrument at 100 MHz in CDCl3 and TMS was used as internal reference. Elemental analyses were carried out in a Coleman automatic carbon, hydrogen and nitrogen analyze.

General method

Isatin (1 mmol), malononitrile (1 mmol), and catalyst system, were thoroughly grinded with pestle and mortar. After the formation of Knoevenagel adduct, 1,3 diketone was added (1 mmol) and again thoroughly grinded for an appropriate time (Table 5). When the reaction was complete (checked by TLC using authentic samples) 5 mL water was added and the mixture was extracted with DCM (3 × 5 mL). The combined organic phase was dried over MgSO4.

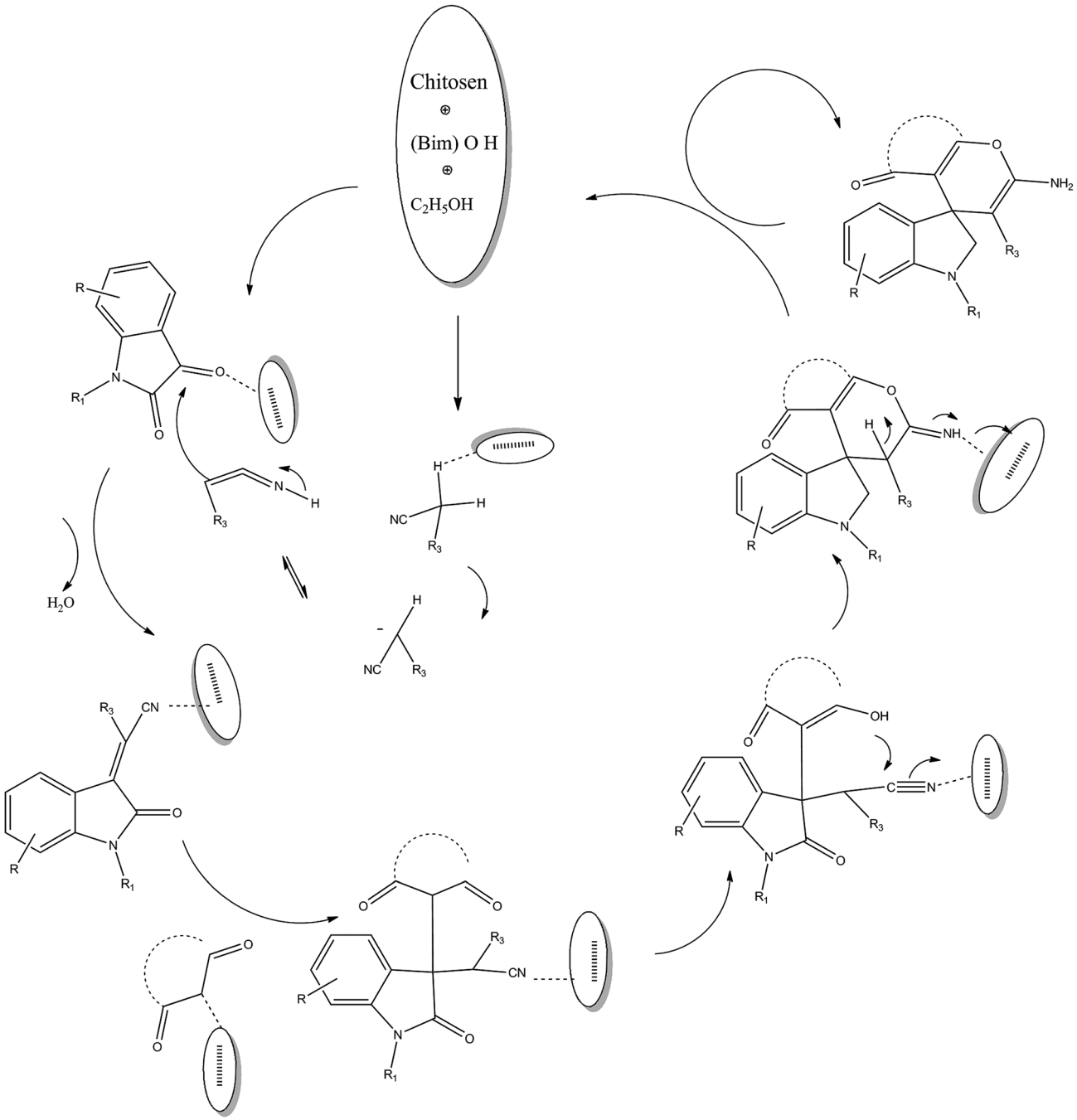
Recovery of catalyst system

After isolation of the product, the remaining mother liquid containing the ionic liquid and chitosan was poured in ethyl-acetate (to remove any organic impurity.) in separating funnel. Chitosan and ionic liquid separate from organic layer. Chitosan was recovered after centrifugation of water layer and further used in reaction. The recovery of the ionic liquid was also examined. Water layer dried under vacuum at 90 °C afforded (Bmim)OH, which was used in subsequent runs without purification.

4a 2-Amino-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile. White solid, mp 289–290 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.00 (s, 3H), 1.02 (s, 3H), 2.10 (d, J = 16.0 Hz, 1H), 2.14 (d, J = 16.0 Hz, 1H), 2.57 (s, 2H), 6.77 (d, J = 7.6 Hz, 1H), 6.86 (t, J = 7.4 Hz, 1H), 6.99 (d, J = 6.8 Hz, 1H), 7.15 (t, J = 8.2 Hz, 1H), 7.13 (s, 2H), 10.40 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.59, 28.17, 32.43, 47.21, 50.39, 57.89, 109.74, 111.19, 117.82, 122.13, 123.52, 128.59, 134.56, 142.48, 159.25, 164.56, 178.48, 195.30. Anal. calcd for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 67.06; H, 4.98; N, 12.49%.

4b 2-Amino-5′-chloro-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile. White solid, mp 293–295 °C ^{1}H NMR (400, MHz, DMSO-d_6) δ 1.01 (s, 3H), 1.02 (s, 3H), 2.16 (s, 2H), 2.48–2.57 (m, 2H), 6.79 (d, J = 8.0 Hz, 1H), 7.09 (s, 1H), 7.19 (d, J = 5.6 Hz, 1H), 7.28 (s, 2H), 10.52 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.76, 27.98, 32.45, 47.52, 50.43, 57.15, 110.68, 111.14, 117.77, 123.79, 126.15, 128.57, 136.93, 141.57, 159.34, 165.12, 178.30, 195.64. Anal. calcd for $C_{19}H_{16}ClN_3O_3$: C, 61.71; H, 4.36; N, 11.36. Found: C, 61.68; H, 4.30; N, 11.26%.

4c 2-Amino-5′-bromo-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile. Mp > 300 °C ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.04 (s, 6H), 2.14 (d, J = 16.8 Hz, 1H), 2.21 (d, J = 16.8 Hz, 1H), 2.50 (d, J = 17.6 Hz, 1H), 2.60 (d, J = 17.6 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 7.21 (s, 1H), 7.32 (d, J = 7.2 Hz, 1H), 7.33 (s, 2H), 10.56 (s, 1H).



Scheme 3 Plausible mechanism for the synthesis of spiro-oxindole.

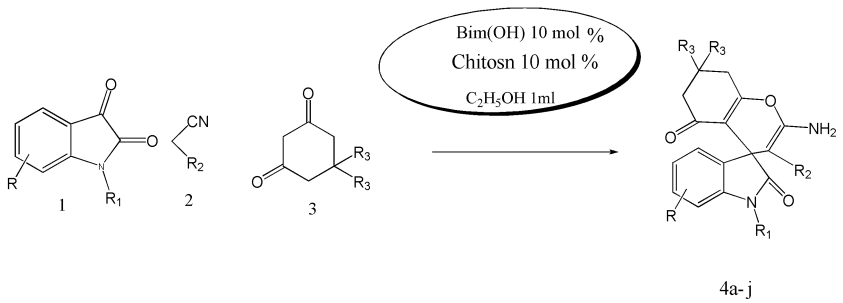
Table 4 Recovery and performance of catalyst system

Cycles[a]	Yield[b] (%)	Recovered[c] (%)
Native	94	90
1	92	87
2	91	85
2	90	84

[a] All reactions were carried out using isatin (1.0 mmol), malononitrile (1.0 mmol), 1,3 diketone (1.0 mmol) and catalyst system. [b] Is isolated yield of the product. [c] Is isolated yield of the catalyst system.

4d Ethyl 2-amino-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carboxylate. White solid, mp 278–280 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.78 (t, J = 6.8 Hz, 3H), 0.95 (s, 3H), 1.02 (s, 3H), 2.01 (d, J = 16.0 Hz, 1H), 2.15 (d, J = 16.0 Hz, 1H), 2.54 (m, 2H), 3.68 (q, J = 6.8 Hz, 2H), 6.67 (d, J = 7.6 Hz, 1H), 6.76 (t, J = 7.2 Hz, 1H), 6.83 (d, J = 7.2 Hz, 1H), 7.04 (t, J = 7.2 Hz, 1H), 7.85 (s, 2H), 10.11 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.64, 27.17, 28.22, 32.08, 47.12, 51.14, 59.39, 76.85, 108.60, 113.63, 121.06, 122.79, 127.66, 136.47, 144.53, 159.68, 162.83, 168.16, 180.28, 195.19. Anal. calcd for

Table 5 Reaction of isatin, malononitrile and enol form of 1,3 cyclic diketones. All reactions were carried out using isatin (1.0 mmol), malononitrile (1.0 mmol), 1,3 diketone (1.0 mmol) and catalyst system



R = H, Cl, Br, CH_3 R_1 = H, CH_3 R_2 = CN, $COOCH_3$, $COOCH_3$, $COOCH(CH3)_2$ R_3 = H, CH_3

Entry	R	R_1	R_2	R_3	Time[b]	Yield[a]
1	H	H	CN	CH_3	10	94
2	Cl	H	CN	CH_3	8	96
3	Br	H	CN	CH_3	8	96
4	H	H	$COOC_2H_5$	CH_3	20	93
5	CH_3	H	CN	CH_3	22	91
6	CH_3	H	$COOC_2H_5$	CH_3	25	89
7	H	CH_3	CN	CH_3	22	92
8	H	H	CN	H	8	93
9	Cl	H	CN	H	7	95
10	Br	H	CN	H	7	95

[a] Is isolated yield of the product. [b] Is time in minutes.

$C_{21}H_{22}N_2O_5$: C, 65.96; H, 5.80; N, 7.33. Found: C, 65.80; H, 5.72, N, 7.36%.

4e 2-Amino-7,7,7′-trimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile. White solid, mp 296–297 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.98 (s, 3H), 1.02 (s, 3H), 2.06 (d, J = 16.0 Hz, 1H), 2.17 (d, J = 16.0 Hz, 1H), 2.22 (s, 3H), 2.51–2.59 (m, 2H), 6.78 (t, J = 6.8 Hz, 1H), 6.83 (s, 1H), 6.96 (d, J = 6.8 Hz, 1H), 7.23 (s, 2H), 10.45 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 16.83, 27.44, 28.13, 32.41, 47.56, 50.52, 58.37, 111.43, 117.85, 118.77, 120.83, 122.05, 130.02, 134.50, 141.43, 159.22, 164.45, 178.96, 195.22. 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%.

4f Ethyl 2-amino-7,7,7′-trimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carboxylate. White solid, mp 289–291 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.78 (t, J = 7.24 Hz, 3H), 0.95 (s, 3H), 1.03 (s, 3H), 2.01 (d, J = 15.6 Hz, 1H), 2.14 (d, J = 16 Hz, 1H), 2.16 (s, 3H), 2.44–2.62 (m, 2H), 3.61–3.73 (m, 2H), 6.66 (d, J = 6.4 Hz, 1H), 6.67 (t, J = 7.2 Hz, 1H), 6.87 (d, J = 6.8 Hz, 1H), 7.84 (s, 2H), 10.18 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.32, 16.81, 27.04, 28.32, 32.05, 47.31, 51.12, 59.32, 77.02, 113.72, 117.51, 120.21, 121.02, 128.95, 136.01, 142.92, 159.51, 162.71, 168.21, 180.72, 195.04. Anal. calcd for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 65.29; H, 6.15; N, 7.08%.

4h 2-Amino-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile. White solid, mp 251–253 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.93 (t, J = 6.0 Hz, 2H), 2.17–2.28 (m, 2H), 2.51–2.66 (m, 2H), 6.78 (d, J = 7.6 Hz, 1H), 6.89 (t, J = 7.6 Hz, 1H), 7.01 (d, J = 7.2 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.19 (s, 2H), 10.38 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.25, 27.22, 36.88, 47.35, 58.09, 109.63, 112.30, 117.85, 122.16, 123.68, 128.64, 135.02, 142.47, 159.14, 166.59, 178.64, 195.53. Anal. calcd for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.67. Found: C, 66.49; H, 4.30; N, 13.69%.

4i 2-Amino-7′-chloro-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile. White solid, mp > 300 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.94 (t, J = 6.0 Hz, 2H), 2.18–2.27 (m, 2H), 2.65–2.69 (m, 2H), 6.94 (t, J = 8.0 Hz, 1H), 7.02 (d, J = 7.2 Hz, 1H), 7.22 (d, J = 8.1 Hz, 1H), 7.33 (s, 2H), 10.84 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.22, 27.28, 36.72, 48.25, 57.49, 112.01, 113.92, 117.05, 122.48, 1239, 128.76, 136.73, 140.27, 159.24, 166.82, 178.64, 195.65. Anal. calcd for $C_{17}H_{12}ClN_3O_3$: C, 59.75; H, 3.54; N, 12.30. Found: C, 59.75; H, 3.60; N, 12.35%.

4j 2-Amino-5′-bromo-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile. Mp: 291–292 °C ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.92–1.97 (m, 2H), 2.23–2.25 (m, 2H), 2.74 (t, J = 6.6 Hz, 2H), 6.75 (d, J = 8.0 Hz, 1H), 7.23–7.28 (m, 1H), 7.33 (s, 3H), 10.57 (s, 1H).

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