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Eco-friendly polyethylene glycol (PEG-400): a green reaction medium for one-pot, four-component synthesis of novel asymmetrical bis-spirooxindole derivatives at room temperature†

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PEG-400 has been used as a green and biodegradable polymeric solvent for the one-pot, two-step, multi-component synthesis of novel asymmetrical bis-spirooxindole derivatives by the reaction of *N*-alkyl isatin, isatin derivatives, alkylmalonates and C–H activated carbonyl compounds in the presence of K_2CO_3 at room temperature. Using this procedure, all the products were obtained in good to excellent yields.

Introduction

In recent years, the development of a high efficiency, high selectivity, green, safe, atom- and step-economical synthesis strategy has become of paramount importance in the field of organic chemistry. One-pot, multi-component reactions are a powerful tool in organic and medicinal chemistry because they can shorten the reaction time, simplify the separation step, reduce costs, and give a relatively higher total chemical yield compared to multistep synthesis.[1,2]

Solvents are widely used in organic synthesis and have been a cause of major concern due to their associated environmental hazards. Therefore, replacement of harmful organic solvents with an eco-friendly medium is one of the major focal points of green chemistry.[3–10] Polyethylene glycol (PEG) and modified polyethylene glycol derivatives have become more popular alternate reaction media, due to their interesting properties like non-toxicity, bio-compatibility, and bio-degradability. Moreover, PEG is considered as a natural, inexpensive, safe, recyclable, degradable, non-flammable, facile, environmentally benign and abundantly available green solvent.[11]

Spirooxindoles are commonly occurring heterocyclic ring systems and are found in many natural products and pharmaceuticals.[12,13] These compounds are known to display anti-tubercular,[14] antifungal,[15] anti-mycobacterial,[16] anti-tumor,[17,18] anti-malarial[19] and anti-microbial[20] activities. Until recently, there have been few reports on the synthesis of symmetric bis-spirooxindole derivatives.[21–24] In continuation of our research interest in the synthesis of biologically important heterocyclic compounds,[25–33] herein we report a synthetic route for the preparation of novel asymmetrical bis-spirooxindoles **6** *via* a one-pot four-component condensation reaction of *N*-alkyl isatin **1** (1 eq.), isatin derivatives **2** (1 eq.), alkyl malonates **4** (2 eq.) and C–H activated carbonyl compounds **5** (2 eq.) in the presence of K_2CO_3 in polyethylene glycol medium at room temperature (Scheme 1).

Results and discussion

At first, the *N*-alkyl isatins **1** were prepared from the reaction of 5-methyl isatin (**7**, 1 eq.) with dihalidederivatives (**8**, excess) in the presence of K_2CO_3 in PEG-400 at room temperature (Scheme 2).

Then, to optimize the reaction conditions for the synthesis of asymmetrical bis spirooxindole derivatives, the reaction of 1-(4-(chloromethyl)benzyl)-5-methylindoline-2,3-dione (**1a**), isatin (**2a**), malononitrile (**4a**) and 1,3-cyclohexanedione (**5b**) its behavior was studied in the presence of different catalytic systems, and the results are summarized in Table 1. As it is shown in Table 1, higher yield and shorter reaction time were obtained when the reaction was carried out in the presence of 1 mmol of K_2CO_3 in PEG-400 at room temperature (Table 1, entry 9).

Subsequently, the scope and efficiency of the reagent were explored under the optimized reaction conditions for the condensation of different asymmetrical bis-isatins **3** with a broad range of structurally diverse carbonyl compounds and alkyl malonatesto furnish the related products. The structural diversity of reactants is summarized in Fig. 1 and the results are displayed in Table 2.

The synthetic pathway for the synthesis of titled compounds is consisting of two steps. At first, asymmetrical bis-isatin derivatives are obtained from the condensation reaction of *N*-alkyl isatin **1** and isatin derivatives **2**. Then, the resulting products are treated with alkyl malonates **4** and carbonyl compounds **5** to afford the related asymmetrical bis-spirooxindole derivatives as the desired products.

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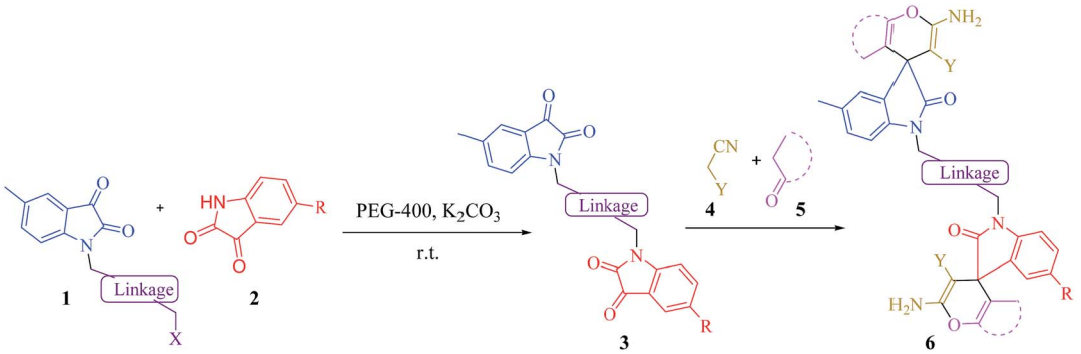
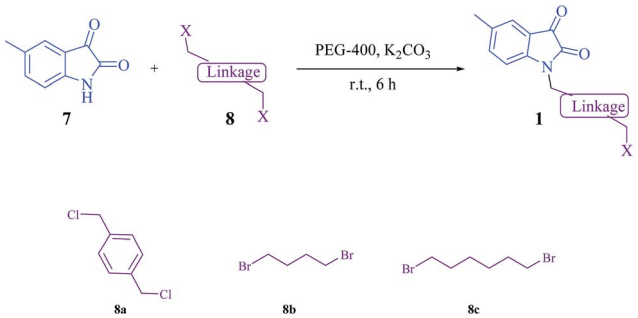


Scheme 1 The synthesis of novel asymmetrical bis-spirooxindoles **6** *via* the reaction between *N*-alkyl isatin **1**, isatin derivatives **2**, alkyl malonates **4** and carbonyl compounds **5** in the presence of K_2CO_3in PEG-400 at room temperature.



Scheme 2 Synthetic pathway for the synthesis of *N*-alkyl isatin derivatives.

As Table 2 indicates, a variety of isatin derivatives, alkyl malonates and carbonyl compounds were successfully applied in this process to afford the corresponding asymmetrical bis-spirooxindole derivatives as novel and potentially biologically important compounds in excellent yields.

Experimental

All chemicals were purchased from Merck or Fluka chemical companies. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were run on a BrukerAvance400. Melting points were recorded on a Stuart Scientific Apparatus SMP3 (UK) in open capillary tubes. Elemental C, H and N analyses were performed using a Costech CHNS–O elemental analyzer.

General procedure for the synthesis of asymmetrical bisspirooxindolederivatives 6

K_2CO_3 (1 mmol) was added to a stirred mixture of *N*-alkylisatin **1** (1 mmol), isatin derivative **2** (1 mmol) in PEG-400 (3 mL) and the

Table 1 Effects of reagent and solvent on the reaction of 1-(4-(chloromethyl)benzyl)-5-methylindoline-2,3-dione, isatin, malononitrile and 1,3-cyclohexanedion under different conditions[a]

Entry	Reagent	reagent (mmol)	Solvent	Temp. (°C)	Time (h)	Yield (%)
1	—	—	PEG-400	r.t.	48	—
2	L-Proline	1.0	PEG-400	r.t.	48	—
3	DABCO	1.0	PEG-400	r.t.	48	—
4	Et_3N	1.0	PEG-400	r.t.	48	—
5	Cs_2CO_3	1.0	PEG-400	r.t.	24	65
6	Na_2CO_3	1.0	PEG-400	r.t.	24	30
7	$NaHCO_3$	1.0	PEG-400	r.t.	24	—
8	$CaCO_3$	1.0	PEG-400	r.t.	24	25
9	K_2CO_3	1.0	PEG-400	r.t.	7	95
10	K_2CO_3	0.5	PEG-400	r.t.	15	70
11	K_2CO_3	0.8	PEG-400	r.t.	15	87
12	K_2CO_3	1.5	PEG-400	r.t.	7	94
13	K_2CO_3	1.0	MeCN	r.t.	48	Trace
14	K_2CO_3	1.0	H_2O	r.t.	48	—
15	K_2CO_3	1.0	EtOH	r.t.	48	—
16	K_2CO_3	1.0	MeOH	r.t.	24	—
17	K_2CO_3	1.0	*n*-Propanol	r.t.	24	—
18	K_2CO_3	1.0	*tert*-Butanol	r.t.	24	—
19	K_2CO_3	1.0	DMSO	r.t.	13	80
20	K_2CO_3	1.0	DMF	r.t.	15	80
21	K_2CO_3	1.0	—	80	48	—
22	K_2CO_3	1.0	—	100	48	—

[a] Isolated yields.

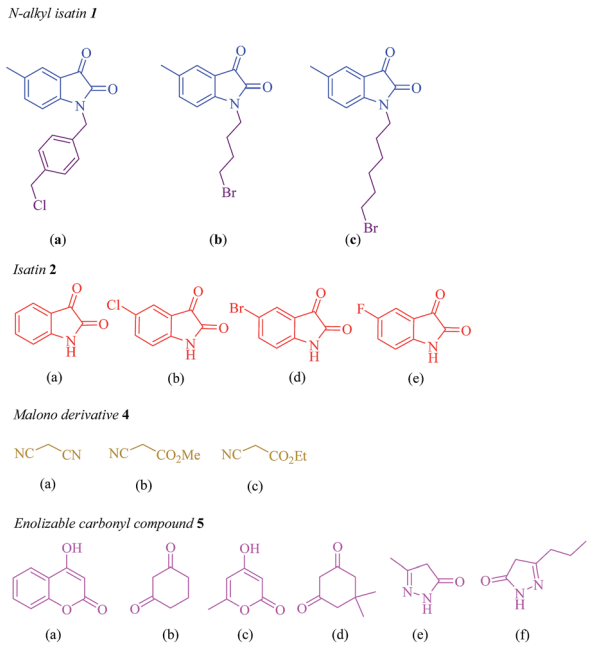


Fig. 1 Diversity elements employed for synthesis of asymmetrical bis-spirooxindoles.

reaction mixture was stirred at room temperature to complete the formation of related asymmetrical bis-isatin **3** (monitored by TLC). Subsequently, alkyl malonates **4** (2 mmol) and cyclic ketone **5** (2 mmol) were added to this reaction mixture and reacted at room temperature for the appropriate amount of time (see Table 2). After completion of the reaction, 3 ml of water was added to the reaction mixture; the precipitate was filtrated and recrystallized from hot ethanol to afford the pure products.

2-Amino-1′-(4-((2-amino-3-cyano-5′-methyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indolin]-1′-yl)methyl)benzyl)-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile 6a. White powder, mp > 270 °C, ^{1}H NMR (DMSO-d_6,400 MHz) δ (ppm): 1.96 (t, J = 6.0 Hz, 4H), 2.23 (s, 3H), 2.25–2.31 (m, 4H), 2.70–2.73 (m, 4H), 4.88 (d, J = 10.0 Hz, 4H), 6.56 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 7.6 Hz, 1H), 6.93–6.99 (m, 3H), 7.12–7.16 (m, 3H), 7.34 (d, J = 8.8 Hz, 3H), 7.45 (s, 4H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 20.2, 21.1, 27.3, 31.2, 36.8, 43.6, 47.1, 47.2, 57.7, 57.9, 70.3, 109.1, 109.3, 112.2, 112.2, 117.9, 117.9, 123.0, 123.6, 124.2, 127.6, 128.7, 128.9, 131.9, 134.2, 134.2, 135.5, 135.6, 140.7, 143.0, 159.1, 159.2, 159.2, 166.8, 166.9, 177.2, 177.3, 195.6. Anal. calcd for $C_{43}H_{34}N_6O_6$: C, 70.67; H, 4.69; N, 11.50%. Found: C, 70.65; H, 4.72; N, 11.48%.

6′-Amino-1-(4-((6′-amino-5′-cyano-3′,5-dimethyl-2-oxo-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazol]-1-yl)methyl)benzyl)-5-bromo-3′-methyl-2-oxo-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile 6b. Cream powder, mp > 270 °C, ^{1}H NMR (DMSO-d_6,400 MHz) δ (ppm): 0.98 (s, 3H), 1.05 (s, 3H), 2.35 (s, 3H), 4.71 (d, J = 15.6 Hz, 2H), 4.97 (d, J = 15.6 Hz, 2H), 6.65–6.69 (m, 2H), 6.85–7.06 (m, 6H), 7.42 (s, 1H), 7.59 (s, 4H), 7.97 (s, 1H), 12.43 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 21.1, 27.7, 28.0, 32.5, 43.6, 47.1, 50.4, 57.8, 109.2, 128.3, 130.3, 132.5, 133.3, 138.1, 139.0, 139.2, 140.1, 140.2, 142.0, 143.0, 146.3, 147.6, 148.3, 149.7, 149.9, 156.5, 157.1, 159.5, 171.2, 173.0, 173.8. Anal. calcd for $C_{39}H_{29}BrN_{10}O_4$: C, 59.93; H, 3.74; Br, 10.22; N, 17.92%. Found: C, 59.96; H, 3.72; N, 17.90%.

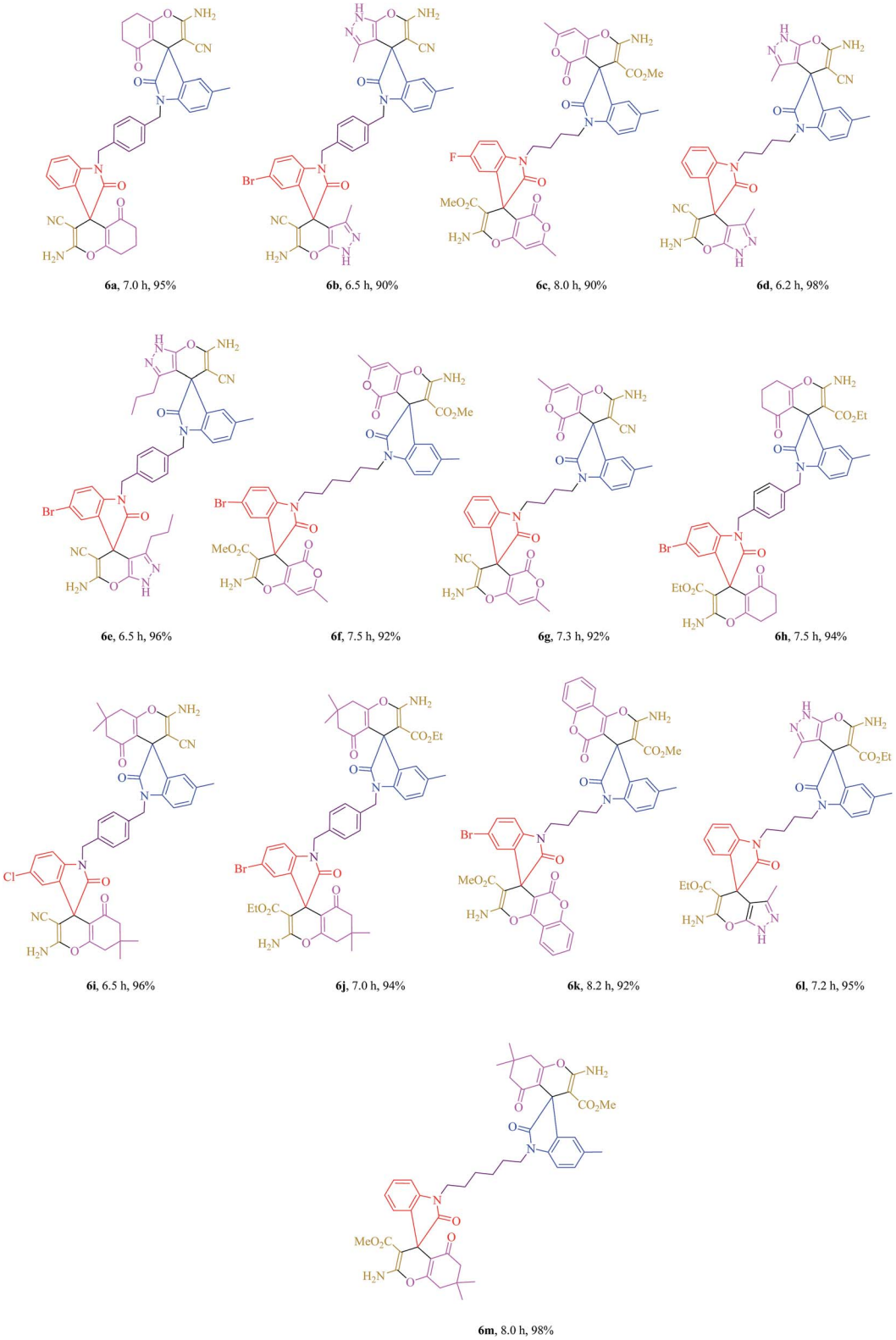
Methyl 2′-amino-1-(4-(2′-amino-3′-(methoxycarbonyl)-5,7′-dimethyl-2,5′-dioxo-5′*H*-spiro[indoline-3,4′-pyrano[4,3-*b*]pyran]-1-yl)butyl)-5-fluoro-7′-methyl-2,5′-dioxo-5′*H*-spiro[indoline-3,4′-pyrano[4,3-*b*]pyran]-3′-carboxylate 6c. Cream powder, mp > 270 °C, ^{1}H NMR (DMSO-d_6,400 MHz) δ (ppm): 1.49–1.51 (m, 2H), 1.64–1.72 (m, 2H), 2.21 (s, 3H), 2.98 (s, 3H), 3.02 (s, 3H), 3.23 (s, 3H), 3.37 (s, 3H), 3.55–3.64 (m, 2H), 3.71–3.74 (m, 2H), 6.32 (s, 2H), 6.80–6.93 (m, 2H), 6.99–7.00 (m, 1H), 7.11–7.19 (m, 2H), 8.03 (s, 2H), 8.08 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 27.5, 27.7, 28.0, 32.5, 43.5, 47.2, 50.3, 56.9, 110.0, 110.1, 117.7, 121.0, 121.5, 125.5, 127.7, 128.4, 129.3, 130.6, 137.9, 157.6, 159.6, 163.1, 163.9, 165.6, 167.9, 178.6, 195.7. Anal. calcd for $C_{41}H_{35}FN_4O_{12}$: C, 61.96; H, 4.44; F, 2.39; N, 7.05%. Found: C, 61.94; H, 4.42; N, 7.08%.

6′-Amino-1-(4-(6′-amino-5′-cyano-3′,5-dimethyl-2-oxo-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazol]-1-yl)butyl)-3′-methyl-2-oxo-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile 6d. Pink powder, mp > 270 °C, ^{1}H NMR (DMSO-d_6,400 MHz) δ (ppm): 1.31–1.42 (m, 2H), 1.57–1.65 (m, 2H), 2.05 (s, 3H), 3.08 (s, 6H), 3.60–3.68 (m, 4H), 6.90–6.94 (m, 1H), 6.99 (d, J = 8.4 Hz, 2H), 7.42 (dd, J = 8.4, 2.0 Hz, 4H), 7.49–7.52 (m, 2H), 8.06 (s, 4H), 12.03 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 14.1, 14.4, 25.0, 44.5, 47.3, 59.3, 62.4, 121.2, 123.4, 125.4, 125.7, 127.0, 127.7, 127.9, 128.3, 130.3, 134.5, 134.7, 135.6, 139.3, 147.4, 152.6, 155.4, 157.5, 158.5, 159.08, 159.3. Anal. calcd for $C_{35}H_{30}N_{10}O_4$: C, 64.21; H, 4.62; N, 21.39%. Found: C, 64.22; H, 4.60; N, 21.41%.

6′-Amino-1-(4-((6′-amino-5′-cyano-5-methyl-2-oxo-3′-propyl-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazol]-1-yl)methyl)benzyl)-5-bromo-2-oxo-3′-propyl-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile 6e. White powder, mp > 270 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 0.86–0.92 (m, 3H), 1.02–1.08 (m, 3H), 1.91–1.94 (m, 2H), 2.19–2.25 (m, 2H), 2.69 (s, 3H), 3.01–3.06 (m, 4H), 4.67–4.79 (m, 2H), 4.88–4.99 (m, 2H), 6.65–6.68 (m, 3H), 6.82–6.85 (m, 2H), 6.94 (d, J = 6.8 Hz, 1H), 7.02–7.06 (m, 4H), 7.59 (s, 2H), 7.91 (s, 2H), 12.21 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 14.1, 14.4, 25.0, 27.1, 28.3, 32.1, 45.0, 46.6, 51.1, 59.0, 62.4, 76.6, 113.9, 114.0, 119.6, 119.7, 124.9, 125.6, 126.1, 129.6, 130.7, 130.9, 133.9, 136.2, 136.2, 137.5, 137.6, 142.6, 144.9, 161.1, 161.2, 161.2, 168.8, 168.9, 179.2, 179.3. Anal. calcd for $C_{43}H_{37}BrN_{10}O_4$: C, 61.65; H, 4.45; Br, 9.54; N, 16.72%. Found: C, 61.67; H, 4.43; N, 16.71%.

Methyl 2′-amino-1-(6-(2′-amino-3′-(methoxycarbonyl)-5,7′-dimethyl-2,5′-dioxo-5′*H*-spiro[indoline-3,4′-pyrano[4,3-*b*]pyran]-1-yl)hexyl)-5-bromo-7′-methyl-2,5′-dioxo-5′*H*-spiro[indoline-3,4′-pyrano[4,3-*b*]pyran]-3′-carboxylate 6f. White powder, mp > 270 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 1.02–1.08 (m, 2H), 1.46–1.49 (m, 2H), 1.59–1.63 (m, 4H), 2.10 (s, 3H), 2.20 (s, 6H), 3.36 (s, 6H), 3.59–3.72 (m, 2H), 6.31 (s, 2H), 6.79 (d, J = 8.4 Hz, 3H), 6.97 (d, J = 7.2 Hz, 2H), 7.60 (d, J = 7.6 Hz, 1H), 8.02 (s, 4H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 14.0, 19.6, 21.0, 26.7, 27.4, 46.5, 50.9, 59.3, 76.0, 114.2, 125.0, 128.1, 129.3, 129.6, 130.4, 133.3, 135.4, 137.7, 137.8, 138.9, 139.9, 140.2, 142.5, 146.4, 146.7, 147.4, 149.1, 149.4, 159.5, 164.7, 167.4, 170.3,

Table 2 One-pot, four-component synthesis of asymmetrical bis-spirooxindole derivatives in the presence of K_2CO_3 in PEG-400 at room temperature[a]



[a] Isolated yields.

171.1, 171.1, 174.6. Anal. calcd for $C_{43}H_{39}BrN_4O_{12}$: C, 58.44; H, 4.45; Br, 9.04; N, 6.34%. Found: C, 58.42; H, 4.44; N, 6.36%.

2′-Amino-1-(4-(2′-amino-3′-cyano-5,7′-dimethyl-2,5′-dioxo-5′*H*-spiro[indoline-3,4′-pyrano[4,3-*b*]pyran]-1-yl)butyl)-7′-methyl-2,5′-dioxo-5′*H*-spiro[indoline-3,4′-pyrano[4,3-*b*]pyran]-3′-carbonitrile 6g. Cream powder, mp > 270 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 1.03–1.08 (m, 4H), 2.10 (s, 3H), 2.23 (s, 3H), 2.24 (s, 3H), 3.59–3.65 (m, 2H), 3.74–3.80 (m, 2H), 6.34 (s, 2H), 6.86–6.91 (m, 1H), 6.97–7.02 (m, 4H), 7.14–7.20 (m, 2H), 8.09 (s, 4H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 14.2, 27.2, 28.2, 32.1, 44.4, 46.7, 51.0, 59.1, 76.7, 113.3, 114.3, 114.5, 118.3, 120.2, 122.4, 122.7, 124.2, 124.8, 124.9, 125.3, 127.3, 131.1, 131.7, 132.6, 136.3, 144.3, 149.6, 152.4, 155.5, 155.5, 156.0, 156.3, 169.3. Anal. calcd for $C_{39}H_{30}N_6O_8$: C, 65.91; H, 4.25; N, 11.83%. Found: C, 65.89; H, 4.26; N, 11.85%.

Ethyl 2-amino-1′-(4-((2-amino-3-(ethoxycarbonyl)-5′-methyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indolin]-1′-yl)methyl)benzyl)-5′-bromo-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carboxylate 6h. Pink powder, mp > 270 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 0.38 (q, J = 7.2 Hz, 3H), 0.59 (q, J = 7.2 Hz, 3H), 1.92 (t, J = 6.0 Hz, 4H), 2.10 (s, 3H), 2.20–2.30 (m, 4H), 2.69 (t, J = 5.8 Hz, 4H), 3.41–3.49 (m, 2H), 3.76–3.83 (m, 2H), 4.69 (d, J = 16.0 Hz, 2H), 4.97 (dd, J = 15.8, 2.6 Hz, 2H), 6.64 (dd, J = 8.0, 2.4 Hz, 4H), 7.17 (d, J = 1.6 Hz, 1H), 7.25 (d, J = 8.4 Hz, 4H), 7.56 (s, 4H), 8.02 (s, 1H). Sample solubility was too low for ^{13}C-NMR even after heating. Anal. calcd for $C_{47}H_{43}BrN_4O_{10}$: C, 62.46; H, 4.80; Br, 8.84; N, 6.20%. Found: C, 62.47; H, 4.78; N, 6.22%.

2-Amino-1′-(4-((2-amino-3-cyano-5′,7,7-trimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indolin]-1′-yl)methyl)benzyl)-5′-chloro-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile 6i. Cream powder, mp > 270 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 0.57 (d, J = 2.4 Hz, 1H), 0.59 (d, J = 2.4 Hz, 1H), 0.99 (s, 3H), 1.04 (s, 3H), 1.23 (s, 3H), 1.25 (s, 3H), 2.90 (s, 2H), 4.66 (d, J = 16.0 Hz, 2H), 4.96 (d, J = 15.6 Hz, 2H), 6.52 (d, J = 7.6 Hz, 3H), 6.75 (s, 1H), 6.85 (d, J = 7.6 Hz, 4H), 7.57 (s, 4H), 7.95 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 10.4, 11.3, 20.2, 21.2, 27.3, 31.2, 36.7, 43.5, 47.1, 47.2, 57.7, 57.9, 70.3, 109.1, 109.3, 112.2, 112.3, 117.9, 117.9, 123.0, 123.6, 124.2, 127.5, 128.8, 128.9, 132.0, 134.2, 134.2, 135.4, 135.6, 140.6, 143.0, 159.2, 159.2, 159.2, 166.8, 166.9, 177.2, 177.3, 192.5, 192.6. Anal. calcd for $C_{47}H_{41}ClN_6O_6$: C, 68.73; H, 5.03; Cl, 4.32; N, 10.23%. Found: C, 68.74; H, 5.05; N, 10.21%.

Ethyl 2-amino-1′-(4-((2-amino-3-(ethoxycarbonyl)-5′,7,7-trimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indolin]-1′-yl)methyl)benzyl)-5′-bromo-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carboxylate 6j. White powder, mp > 270 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 0.55 (t, J = 6.4 Hz, 6H), 0.98 (s, 6H), 1.05 (s, 6H), 2.04–2.11 (m, 2H), 2.21 (d, J = 16.0 Hz, 2H), 2.62–2.69 (m, 2H), 2.91 (s, 3H), 3.05 (d, J = 9.6 Hz, 2H), 3.72–3.78 (m, 4H), 4.71 (d, J = 16.4 Hz, 1H), 4.76 (d, J = 16.0 Hz, 1H), 4.90 (d, J = 15.6 Hz, 1H), 4.97 (d, J = 15.6 Hz, 1H), 6.68 (d, J = 3.6 Hz, 2H), 6.86 (d, J = 7.2.0 Hz, 4H), 6.94 (d, J = 6.0 Hz, 2H), 7.05 (s, 1H), 7.59 (s, 4H), 7.95 (d, J = 4.4 Hz, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 13.9, 21.0, 26.2, 27.1, 31.2, 42.8, 46.8, 50.9, 51.1, 53.4, 62.4, 62.5, 76.9, 79.1, 122.9, 123.5, 124.1, 127.5, 128.7, 128.9, 132.0, 134.2, 134.2, 135.4, 135.6, 140.7, 143.0, 159.1, 159.2, 159.2, 166.8, 166.9, 177.2, 177.3, 195.7. Anal. calcd for $C_{51}H_{51}BrN_4O_{10}$: C, 63.82; H, 5.36; Br, 8.32; N, 5.84%. Found: C, 63.81; H, 5.38; N, 5.82%.

Methyl 2′-amino-1-(4-(2′-amino-3′-(methoxycarbonyl)-5-methyl-2,5′-dioxo-5′*H*-spiro[indoline-3,4′-pyrano[3,2-*c*]chromen]-1-yl)butyl)-5-bromo-2,5′-dioxo-5′*H*-spiro[indoline-3,4′-pyrano[3,2-*c*]chromene]-3′-carboxylate 6k. White powder, mp > 270 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 0.67–0.74 (m, 4H), 1.85 (s, 3H), 3.04 (s, 3H), 3.27 (s, 3H), 3.66–3.72 (m, 2H), 3.75–3.82 (m, 2H), 6.86–6.89 (m, 2H), 7.04–7.08 (m, 3H), 7.10 (d, J = 7.2 Hz, 2H), 7.19 (t, J = 7.0 Hz, 1H), 7.47 (d, J = 6.8 Hz, 1H), 7.55 (t, J = 7.6 Hz, 2H), 7.77 (t, J = 7.8 Hz, 2H), 8.07 (d, J = 8.0 Hz, 1H), 8.21 (s, 4H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 14.1, 20.1, 27.4, 44.3, 46.8, 50.9, 53.7, 76.7, 113.2, 125.7, 128.0, 129.3, 129.5, 130.6, 133.3, 135.4, 137.7, 137.7, 139.0, 140.9, 141.2, 143.7, 147.2, 147.8, 148.4, 149.1, 149.4, 159.4, 164.6, 167.4, 169.5, 170.1, 170.1, 173.4. Anal. calcd for $C_{47}H_{35}BrN_4O_{12}$: C, 60.85; H, 3.80; Br, 8.61; N, 6.04%. Found: C, 60.87; H, 3.82; N, 6.01%.

Ethyl 6′-amino-1-(4-(6′-amino-5′-(ethoxycarbonyl)-3′,5-dimethyl-2-oxo-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazol]-1-yl)butyl)-3′-methyl-2-oxo-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carboxylate 6l. Cream powder, mp > 270 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 0.64–0.70 (m, 6H), 0.96 (s, 6H), 1.83 (s, 3H), 2.02–2.06 (m, 2H), 2.59–2.61 (m, 2H), 3.34–3.48 (m, 4H), 3.58–3.64 (m, 2H), 3.72–3.78 (m, 2H), 6.85 (td, J = 7.4, 2.4 Hz, 2H), 6.91–6.95 (m, 3H), 7.11 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 7.94 (s, 4H), 12.43 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 14.2, 27.1, 27.2, 28.2, 28.3, 31.2, 32.1, 44.3, 45.2, 46.7, 50.9, 59.1, 76.7, 101.6, 121.3, 124.2, 126.2, 130.7, 131.9, 133.0, 133.0, 135.7, 140.0, 140.4, 141.0, 141.3, 142.8, 152.5, 161.4, 164.2, 167.5, 167.5. Anal. calcd for $C_{39}H_{40}N_8O_8$: C, 62.56; H, 5.38; N, 14.96%. Found: C, 62.57; H, 5.40; N, 14.94%.

Methyl 2-amino-1′-(6-(2-amino-3-(methoxycarbonyl)-5′,7,7-trimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indolin]-1′-yl)hexyl)-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carboxylate 6m. White powder, mp > 270 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 0.70 (s, 3H), 0.93 (s, 6H), 1.01 (s, 6H), 1.45–1.52 (m, 2H), 1.61–1.69 (m, 2H), 1.98 (d, J = 15.6 Hz, 2H), 2.11 (d, J = 15.6 Hz, 2H), 2.15 (d, J = 16.0 Hz, 4H), 2.91 (s, 6H), 3.10–3.21 (m, 4H), 3.62 (t, J = 7.0 Hz, 4H), 6.82–6.91 (m, 3H), 7.13 (t, J = 7.6 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.88 (s, 4H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 14.4, 24.8, 25.0, 27.1, 28.3, 32.1, 42.8, 44.6, 46.8, 50.9, 51.1, 53.4, 62.4, 123.0, 126.5, 128.6, 129.2, 134.3, 135.0, 135.4, 136.1, 136.3, 137.6, 138.9, 142.3, 143.3, 144.5, 145.6, 145.9, 152.5, 153.1, 155.5, 167.2, 169.2, 169.9, 202.5. Anal. calcd for $C_{47}H_{52}N_4O_{10}$: C, 67.77; H, 6.29; N, 6.73%. Found: C, 67.75; H, 6.31; N, 6.72%.

Conclusions

In conclusion, we have reported a highly efficient method for the synthesis of asymmetrical bis-spirooxindole derivatives *via* a one-pot, two-step, four-component condensation reaction using K_2CO_3 in PEG-400 as a green and biodegradable polymeric solvent at room temperature.

Conflicts of interest

There are no conflicts to declare.

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