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An efficient synthesis of 4,6-dihydrospiro[azepino[4,3,2-*cd*]indole-3,3′-indoline]-2′,5(1*H*)-diones via multi-component reaction

Bin Zou *, Chun Chen, Seh Yong Leong, Mei Ding, Paul W. Smith

Novartis Institute for Tropical Diseases, 10 Biopolis Road, #05-01 Chromos, Singapore 138670, Singapore

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ABSTRACT

A facile and efficient one-pot three-component synthesis of spiroazepinoindolones has been developed. Using DMF as solvent without any additional acid or metal catalysts, the three-component reaction of readily available isatins, indolamines, and Meldrum's acid affords a new class of spiroheterocycles in moderate yield.

1. Introduction

Spirooxindole is a common feature in not only various natural alkaloids,[1–3] but also pharmaceutically interesting drugs (Fig. 1).[4–6] Due to the synthetic challenge of this unique structure and broad biological activities, spirooxindole-derivatives have received increasing attention from both academic and industrial chemists.[7–10]

Since developing spirooxindole NITD609 to clinical trials for the treatment of malaria,[6] we are continuously interested in exploring spirooxindole-derivatives as drug lead compounds. Recently, a number of groups have reported the synthesis of new spirooxindole-skeletons via multi-component reactions (MCRs).[11–14] Herein, we report an efficient synthesis of a novel spiroazepinoindolone template by three-component reaction of readily available isatins, indolamines, and Meldrum's acid (Scheme 1).

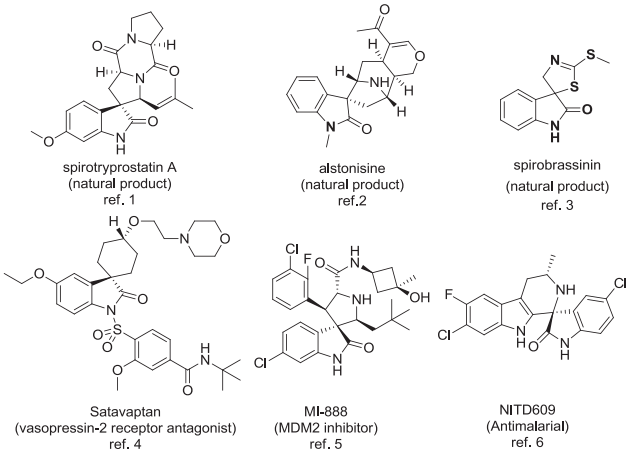
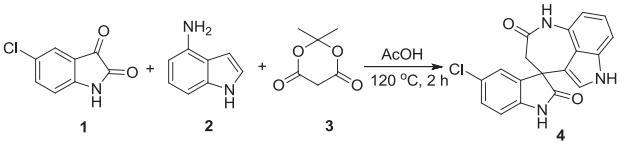


Fig. 1. Selected examples of natural products and pharmaceutical drugs/leads with spirooxindole moiety.

2. Results and discussion

Intrigued by acetic acid promoted condensation of 5-aminopyrazole, isatin, and Meldrum's acid reported by Krayushkin,[15] we considered 1*H*-indole-4-amine **2** as an alternative component to 5-aminopyrazole. With this idea in mind, we tested the reaction by heating the three starting materials 5-Cl-isatin **1**, 1*H*-indole-4-amine **2**, and Meldrum's acid **3** in acetic acid for 2 h



Scheme 1. Synthesis of 5′-chloro-4,6-dihydrospiro[azepino[4,3,2-*cd*]indole-3,3′-indoline]-2′,5(1*H*)-dione **4**.

* Corresponding author. Tel.: +65 67222921; fax: +65 67222918; e-mail address: bin.zou@novartis.com (B. Zou).

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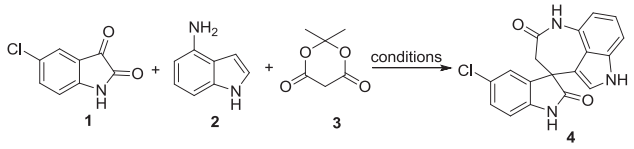
(Scheme 1). To our delight, the desired product **4** was isolated, although the yield was low (Table 1, entry 1). The structure of the compound **4** was further confirmed by ^{1}H NMR, ^{13}C NMR, COSY, NOESY, HMBC, and HSQC data analysis (see Supplementary data).

Our effort was next directed to optimize the reaction conditions and improve the yield. Some selected conditions attempted are summarized in Table 1. When the reaction was conducted under microwave conditions, the yield of desired compound **4** was marginally increased (entry 2). NaCl was reported as catalyst in aqueous conditions for MCRs by a few groups.[16,17] However, when similar reported conditions were applied to our reaction, the yield of compound **4** remained very low (entry 3). Then, we began to investigate the acid effect on this reaction. When Lewis acid $InCl_3$ (0.2–1.0 equiv) was used as catalyst,[18] the reaction was not clean and no desired product was isolated, despite lowering the temperature to 0 °C (entry 4). Similar results were found when stronger acid TfOH (2–20 equiv) in DCM and TFA/DCM (1:1) were used (entries 5 and 6). When weaker acid *p*-TsOH was employed, the reaction did not occur (entry 7). We noticed that starting materials were insoluble in toluene, which we assumed to be the reason why there was no reaction under these conditions. Therefore, we investigated solvent effects. Gratifyingly, without adding any acid or catalyst, polar solvents, such as MeOH and DMSO, gave much higher yield of **4** (entries 8 and 9). Further optimization led to the best solvent DMF, which provided product **4** in moderate yield (55%, entry 10).[19]

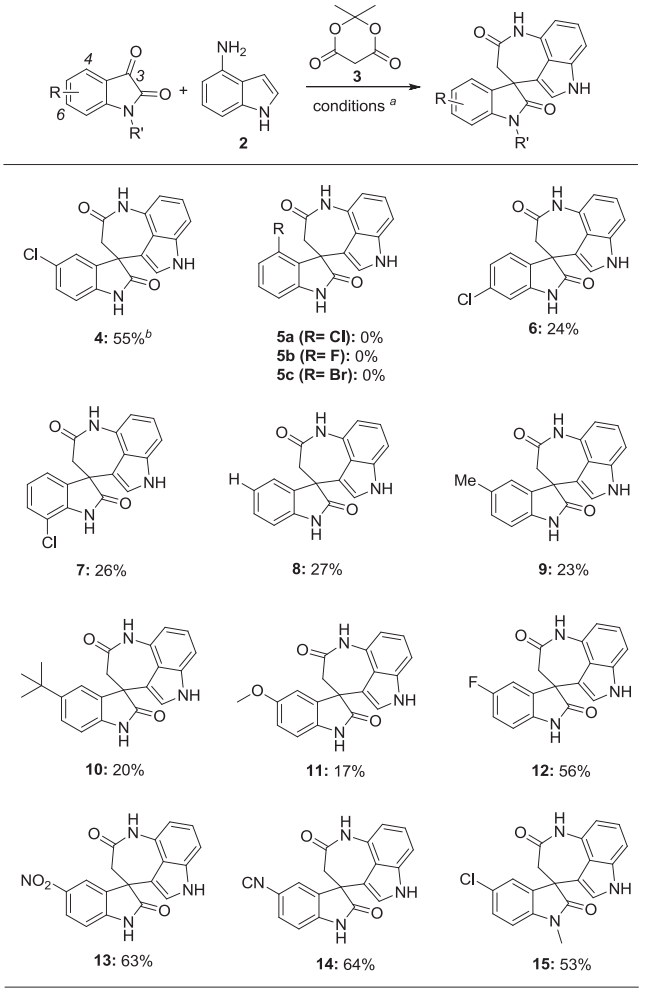
Table 1
Optimization of the reaction conditions



Entry	Conditions[a]	Yield[b] (%)
1	AcOH, 120 °C, 2 h	5
2	AcOH, 120 °C, microwave, 30 min	8
3	10 mol % NaCl/water, reflux, 12 h	8
4	$InCl_3$ (0.2–1.0 equiv), CH_2Cl_2, 0–40 °C, 4 h	0
5	TfOH (2–20 equiv), CH_2Cl_2, 0–40 °C, 4 h	0
6	TFA/CH_2Cl_2 (1:1), 40 °C, 1.5 h	0
7	*p*-TsOH (1–10 equiv), toluene, reflux, 2 h	NR[c]
8	MeOH, reflux, 1.5 h	38
9	DMSO, 120 °C, 1.5 h	28
10	DMF, 120 °C, 2 h	55

[a] The molar ratio of three starting materials is 1:1:1 (0.38 mmol).
[b] Isolated yield by preparative HPLC, product purity is >95%.
[c] No reaction.

With the optimized conditions in hand, we investigated the substrate scope of this reaction. As shown in Fig. 2, the methodology is apparently applicable to a range of substituted isatins. When 5-, 6- or 7-Cl substituted isatins were tested in the optimal reaction conditions, products **4**, **6**, and **7** were isolated in 55, 24, and 26% yields, respectively. Interestingly, when 4-Cl substituted isatin was used as substrate, starting materials remained intact and hence no desired product **5a** was isolated. Furthermore, there was no reaction when either 4-Br or 4-F isatin was used. We believe that the steric hindrance with larger substitutions at 4-position of the isatin prevents the 3-ketone accessibility for condensation (see proposed mechanism in Scheme 2). Then, electronic effects at the 5-position of the isatin were investigated. Compared to unsubstituted isatin (compound **8** with 27% yield), electron-donating groups (Me–, *t*-Bu–, and MeO–) afforded lower yields (compounds **9**, **10**, and **11** with 23, 20, and 17% isolated yields, respectively); In contrast, electron-withdrawing group (F–, NO_2–, and CN–) gave higher yields (compounds **12**, **13**, and **14** with 56, 63, and 64% yields, respectively). These results can be rationalized that electron-withdrawing groups increase the electrophilicity of isatin 3-ketone and hence the condensation step with the other nucleophilic components is easier to be triggered. Lastly, *N*-methyl isatin provided desired product **15** in moderate yield (53%) as well, which suggests that substitution on the isatin nitrogen is tolerated for this reaction.

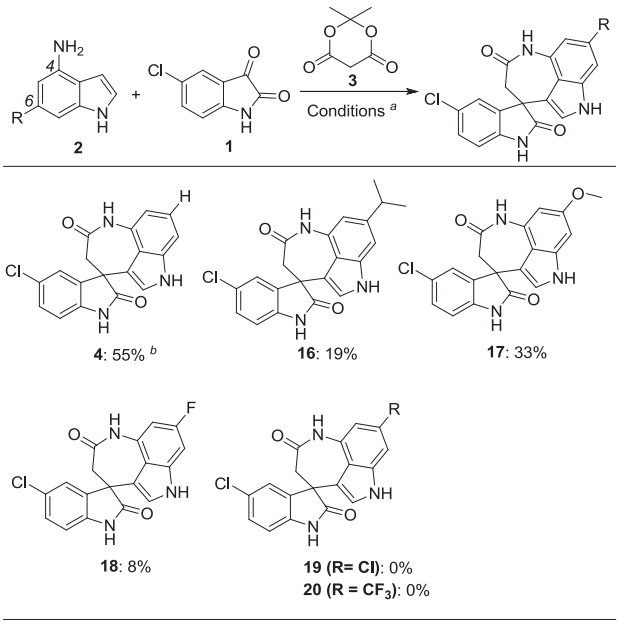


[a] Reaction conditions: DMF, 120 °C, 2 h. The molar ratio of three starting materials is 1:1:1 (0.38 mmol).
[b] Isolated yield by preparative HPLC, product purity is >95%.

Fig. 2. Spiroazepinoindolones formation using substituted isatins.

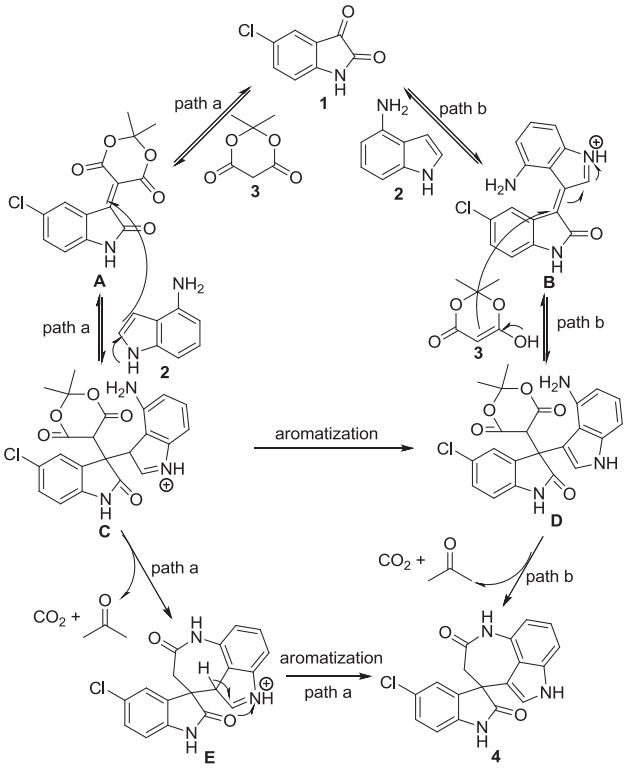
Next, substituted aminoindoles as substrates were investigated to form the spiroazepinoindolones. Due to limited commercially available substituted aminoindoles, a few 6-substituted aminoindoles were employed in the reaction conditions. As shown in Fig. 3, electron-donating groups (*i*-Pr– and MeO–) gave reasonable yields (compounds **16** and **17** with 19 and 33% yields, respectively). However, electron-withdrawing groups afforded significantly lower yields. For example, 6-fluoro-indolamine gave compound **18** in only 8% yield and 6-Cl/CF_3-indolamines prohibited the reaction completely (no compounds **19** and **20** formed). We suspect that the strong electron-withdrawing groups decrease the nucleophilicity of the indoleamine. As a result, the indoleamine is not nucleophilic enough to be involved in the condensation or addition with the other components (see proposed mechanism in Scheme 2).

A plausible mechanism for this transformation to form the spiroazepinoindolones is proposed as shown in Scheme 2. 5-Cl-isatin **1** can be either condensed with Meldrum's acid **3** to afford



[a] Reaction conditions: DMF, 120 °C, 2 h. The molar ratio of three starting materials is 1:1:1 (0.38 mmol).
[b] Isolated yield by preparative HPLC, product purity is >95%.

Fig. 3. Spiroazepinoindolones formation using substituted indoleamines.



Scheme 2. Proposed mechanism for formation of spiroazepinoindolone **4**.

oxoindolylidene **A** followed by addition of indoleamine **2** to give intermediate **C** (path a) or condensed first with indoleamine **2** to form oxoindolylidene **B**[20] followed by addition of Meldrum's acid **3** to give the intermediate **D** (path b).[15] Subsequently, intra-molecular condensation of intermediate **D** and elimination of CO_2 and acetone afford spiroazepinoindolone **4** (path b). Intermediate **C** can be either aromatized to form intermediate **D**, which is further converted to compound **4** via path b; or eliminated of CO_2 and acetone to give **E**, which is aromatized to afford spiroazepinoindolone **4** (path a).

3. Conclusion

A direct and efficient one-pot, three-component condensation reaction of readily available isatins, indolamines, and Meldrum's acid to give a novel spiroazepinoindolone template, has been developed. Without additional acid or catalyst, this reaction is environmentally benign and atom-economic. Using this established methodology, a new class of spiro-heterocyclic compounds is accessible for further biological evaluations.

4. Experimental section

4.1. General

All materials and reagents used were of the best commercially available grade and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were determined on a Bruker Ultrashield 400 MHz spectrometer. LC–MS analysis were performed using Waters Acquity UPLC using the following conditions: Acquity UPLC BEH C-18 column, 1.7 μm, 2.1×50 mm; mobile phase system of 0.1% formic acid/acetonitrile and a gradient of 5–95% acetonitrile; run time of 2.0 min; with wavelength detection of 254 and 214 nm and flow rate of 1.0 mL/min coupled with MS waters ZQ 2000; processing software: Masslynx V4.1; or Agilent UHPLC 1290 using the following conditions: Acquity UPLC BEH C-18 column, 1.7 μm, 2.1×50 mm; mobile phase system of 0.1% formic acid/acetonitrile and a gradient of 2–98% acetonitrile; run time of 2.0 min; with wavelength detection of 254 and 214 nm and flow rate of 1.0 mL/min coupled with mass spec: ABSciex API 3200; processing software: LP Analyst V1.6.1. Purifications were performed using Waters PrepLC Systems using the following conditions: Atlantis prep C-18 OBD 5 μm 19×150 mm column; mobile phase system of 0.1% formic acid/acetonitrile and a gradient of 5–95% acetonitrile; run time of 30–40 min; with wavelength detection of 254 and 214 nm and flow rate of 20 mL/min. Melting points were measured on BÜCHI B-540 apparatus. IR spectrums were obtained on a JASCO FT/IR-4100 spectrometer. In the ^{13}C NMR spectrums of compounds **7**, **9**, **10**, and **11**, one carbon peak is not observed due to overlap with the solvent peak.

4.2. General procedure for spiroazepinoindolones

The solution of isatin (380 μmol), 1*H*-indole-4-amine (380 μmol, 1.0 equiv), and Meldrum's acid (380 μmol, 1.0 equiv) in DMF (4.0 ml) was heated to 120 °C for 2 h. The reaction mixture was cooled down to room temperature and concentrated to remove the solvents. The crude residue was subjected to reverse phase preparative HPLC to provide pure products.

*4.2.1. 5′-Chloro-4,6-dihydrospiro[azepino[4,3,2-cd]indole-3,3′-indoline]-2′,5(1H)-dione (**4**).* General procedure was followed, light pink solid, mp: 287–289 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.15 (br s, 1H, NH), 10.66 (br s, 1H, NH), 10.42 (s, 1H, NH), 7.33–7.28 (m, 2H, ArH), 7.23 (d, J=2.0 Hz, 1H, ArH), 6.95 (d, J=8.5 Hz, 1H, ArH), 6.91 (d, J=8.5 Hz, 1H, ArH), 6.88 (br s, 1H, ArH), 6.23 (d, J=8.5 Hz, 1H, ArH), 3.04 (d, J=15.8 Hz, 1H, CH_2), 2.69 (d, J=15.8 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 178.9, 167.7, 140.5, 136.4, 135.5, 130.7, 128.4, 125.9, 125.0, 123.8, 118.7, 117.3, 111.3, 111.1, 106.0, 99.0, 51.1, 38.7; ESIMS m/z 338.0 $[M+H]^+$; IR (film) 3369, 3259, 1704,

1674, 1483, 1358 cm^{-1}; HRMS calcd for $C_{18}H_{13}ClN_3O_2$ $[M+H]^+$ 338.0691; found 338.0690.

*4.2.2. 6′-Chloro-4,6-dihydrospiro[azepino[4,3,2-cd]indole-3,3′-indoline]-2′,5(1H)-dione (**6**).* General procedure was followed, light brown solid, mp: 302–305 °C; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 11.14 (br s, 1H, NH), 10.69 (br s, 1H, NH), 10.42 (s, 1H, NH), 7.29 (br s, 1H, ArH), 7.18 (d, J=7.8 Hz, 1H, ArH), 7.08–7.00 (m, 1H, ArH), 6.95 (br s, 1H, ArH), 6.93–6.85 (m, 2H, ArH), 6.23 (d, J=8.3 Hz, 1H, ArH), 2.98 (d, J=15.8 Hz, 1H, CH_2), 2.69 (d, J=15.8 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 179.2, 167.7, 143.1, 136.4, 132.7, 132.4, 130.7, 125.2, 124.9, 121.8, 118.7, 117.3, 111.1, 109.8, 105.9, 99.0, 50.6, 38.8; ESIMS m/z 338.0 $[M+H]^+$; IR (film) 3316, 1674, 1491, 1354 cm^{-1}; HRMS calcd for $C_{18}H_{13}ClN_3O_2$ $[M+H]^+$ 338.0691; found 338.0691.

*4.2.3. 7′-Chloro-4,6-dihydrospiro[azepino[4,3,2-cd]indole-3,3′-indoline]-2′,5(1H)-dione (**7**).* General procedure was followed, brown solid, mp: 345–347 °C; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 11.14 (br s, 1H, NH), 10.96 (br s, 1H, NH), 10.43 (s, 1H, NH), 7.32 (d, J=7.8 Hz, 1H, ArH), 7.29 (t, J=2.5 Hz, 1H, ArH), 7.15 (d, J=7.3 Hz, 1H, ArH), 7.04–6.98 (m, 1H, ArH), 6.94–6.87 (m, 2H, ArH), 6.24 (d, J=8.5 Hz, 1H, ArH), 3.00 (d, J=15.8 Hz, 1H, CH_2), 2.74 (d, J=15.8 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 179.2, 167.7, 139.3, 136.4, 135.4, 130.7, 128.5, 125.0, 123.5, 122.4, 118.8, 117.3, 114.0, 111.1, 106.0, 99.0, 51.7; ESIMS m/z 338.2 $[M+H]^+$; IR (film) 3678, 2980, 1714, 1620, 1054 cm^{-1}; HRMS calcd for $C_{18}H_{13}ClN_3O_2$ $[M+H]^+$ 338.0691; found 338.0691.

*4.2.4. 4,6-Dihydrospiro[azepino[4,3,2-cd]indole-3,3′-indoline]-2′,5(1H)-dione (**8**).* General procedure was followed, brown solid, mp: 321–324 °C; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 11.12 (br s, 1H, NH), 10.54 (s, 1H, NH), 10.41 (s, 1H, NH), 7.29 (t, J=2.8 Hz, 1H, ArH), 7.25 (td, J=7.6, 1.2 Hz, 1H, ArH), 7.17 (d, J=7.0 Hz, 1H, ArH), 7.00–6.92 (m, 2H, ArH), 6.91–6.87 (m, 2H, ArH), 6.26 (d, J=8.5 Hz, 1H, ArH), 2.92 (d, J=15.8 Hz, 1H, CH_2), 2.70 (d, J=15.8 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 179.3, 167.9, 141.4, 136.3, 133.6, 130.7, 128.4, 124.8, 123.6, 122.0, 118.9, 117.3, 111.7, 109.7, 105.8, 98.9, 50.8, 39.2; ESIMS m/z 304.2 $[M+H]^+$; IR (film) 3346, 3274, 1670, 1469, 1358 cm^{-1}; HRMS calcd for $C_{18}H_{14}N_3O_2$ $[M+H]^+$ 304.1081; found 304.1080.

*4.2.5. 5′-Methyl-4,6-dihydrospiro[azepino[4,3,2-cd]indole-3,3′-indoline]-2′,5(1H)-dione (**9**).* General procedure was followed, brown solid, mp: 318–321 °C; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 11.12 (br s, 1H, NH), 10.46 (s, 1H, NH), 10.40 (s, 1H, NH), 7.29 (t, J=2.6 Hz, 1H, ArH), 7.04 (d, J=8.0 Hz, 1H, ArH), 6.97 (d, J=2.0 Hz, 1H, ArH), 6.93–6.87 (m, 2H, ArH), 6.83 (d, J=7.8 Hz, 1H, ArH), 6.28 (d, J=8.2 Hz, 1H, ArH), 2.84 (d, J=15.8 Hz, 1H, CH_2), 2.72 (d, J=15.8 Hz, 1H, CH_2), 2.20 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 179.3, 167.9, 138.8, 136.3, 133.8, 130.9, 130.6, 128.7, 124.9, 124.1, 119.0, 117.3, 111.9, 109.6, 105.9, 99.0, 50.9, 20.7; ESIMS m/z 318.1 $[M+H]^+$; IR (film) 3316, 1674, 1491, 1354 cm^{-1}; HRMS calcd for $C_{19}H_{16}N_3O_2$ $[M+H]^+$ 318.1237; found 318.1237.

*4.2.6. 5′-(tert-Butyl)-4,6-dihydrospiro[azepino[4,3,2-cd]indole-3,3′-indoline]-2′,5(1H)-dione (**10**).* General procedure was followed, yellow solid, mp: 347–348 °C; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 11.12 (s, 1H, NH), 10.42 (s, 1H, NH), 10.40 (s, 1H, NH), 7.30–7.24 (m, 2H, ArH), 7.23–7.21 (m, 1H, ArH), 6.90–6.83 (m, 3H, ArH), 6.23 (d, J=8.2 Hz, 1H, ArH), 2.97 (d, J=15.8 Hz, 1H, CH_2), 2.66 (d, J=15.8 Hz, 1H, CH_2), 1.20 (s, 9H, t-Bu); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 179.5, 168.1, 144.6, 139.0, 136.3, 133.2, 130.8, 124.9, 124.8, 120.5, 118.9, 117.3, 111.9, 109.1, 105.8, 98.9, 51.0, 34.1, 31.3, 30.9; ESIMS m/z 360.2 $[M+H]^+$; IR (film) 3407, 3339, 1685, 1594, 1492, 1356 cm^{-1}; HRMS calcd for $C_{22}H_{22}N_3O_2$ $[M+H]^+$ 360.1707; found 360.1706.

*4.2.7. 5′-Methoxy-4,6-dihydrospiro[azepino[4,3,2-cd]indole-3,3′-indoline]-2′,5(1H)-dione (**11**).* General procedure was followed, brown solid, mp: 248–250 °C; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 11.12 (s, 1H, NH), 10.37 (s, 1H, NH), 10.33 (s, 1H, NH), 7.28 (t, J=2.8 Hz, 1H, ArH), 6.93–6.79 (m, 5H, ArH), 6.24 (d, J=8.5 Hz, 1H, ArH), 3.65 (s, 3H, OCH_3), 2.99 (d, J=16.1 Hz, 1H, CH_2), 2.64 (d, J=16.1 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 179.2, 167.9, 155.1, 136.3, 134.8, 134.7, 130.7, 124.8, 119.0, 117.3, 112.9, 111.7, 110.8, 110.1, 105.8, 98.9, 55.4, 51.2; ESIMS m/z 334.1 $[M+H]^+$; IR (film) 3274, 1678, 1491, 1350, 1199 cm^{-1}; HRMS calcd for $C_{19}H_{16}N_4O_4$ 334.1186; found 334.1186.

*4.2.8. 5′-Fluoro-4,6-dihydrospiro[azepino[4,3,2-cd]indole-3,3′-indoline]-2′,5(1H)-dione (**12**).* General procedure was followed, brown solid, mp: 257–258 °C; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 11.14 (br s, 1H, NH), 10.53 (br s, 1H, NH), 10.40 (s, 1H, NH), 7.29 (t, J=2.8 Hz, 1H, ArH), 7.14–7.04 (m, 2H, ArH), 6.96–6.85 (m, 3H, ArH), 6.22 (d, J=8.5 Hz, 1H, ArH), 3.06 (d, J=15.8 Hz, 1H, CH_2), 2.65 (d, J=15.8 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 179.2, 167.7, 158.2 (d, J_{C-F}=236 Hz), 137.9, 136.5, 135.1 (d, J_{C-F}=8 Hz), 130.8, 125.0, 118.8, 117.3, 114.8 (d, J_{C-F}=23 Hz), 111.6 (d, J_{C-F}=24 Hz), 111.1, 110.6 (d, J_{C-F}=9 Hz), 105.9, 99.0, 51.3, 38.8; ESIMS m/z 322.1 $[M+H]^+$; IR (film) 3365, 3263, 1670, 1491, 1362 cm^{-1}; HRMS calcd for $C_{18}H_{13}FN_3O_4$ 322.0986; found 322.0986.

*4.2.9. 5′-Nitro-4,6-dihydrospiro[azepino[4,3,2-cd]indole-3,3′-indoline]-2′,5(1H)-dione (**13**).* General procedure was followed, yellow solid, mp: 361–363 °C; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 11.10 (br s, 2H, NH), 10.45 (s, 1H, NH), 8.17 (dd, J=8.6, 2.4 Hz, 1H, ArH), 8.01 (d, J=2.3 Hz, 1H, ArH), 7.25 (t, J=2.8 Hz, 1H, ArH), 7.08 (d, J=8.8 Hz, 1H, ArH), 6.89–6.81 (m, 2H, ArH), 6.19 (d, J=8.3 Hz, 1H, ArH), 3.11 (d, J=16.1 Hz, 1H, CH_2), 2.70 (d, J=16.1 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 179.6, 167.6, 148.2, 142.5, 136.6, 134.4, 130.9, 125.9, 125.2, 119.4, 118.6, 117.4, 110.5, 110.1, 106.1, 99.1, 50.9, 38.3; ESIMS m/z 349.2 $[M+H]^+$; IR (film) 3674, 3712, 2980, 1339, 1060, 1011 cm^{-1}; HRMS calcd for $C_{18}H_{13}N_4O_4$ 349.0931; found 349.0931.

*4.2.10. 2′,5-Dioxo-1,4,5,6-tetrahydrospiro[azepino[4,3,2-cd]indole-3,3′-indoline]-5′-carbonitrile (**14**).* General procedure was followed, light brown solid, mp: 354–356 °C; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 11.10 (br s, 1H, NH), 10.95 (br s, 1H, NH), 10.35 (s, 1H, NH), 7.69 (dd, J=8.0, 1.8 Hz, 1H, ArH), 7.57 (d, J=1.5 Hz, 1H, ArH), 7.23 (t, J=2.8 Hz, 1H, ArH), 7.03 (d, J=8.2 Hz, 1H, ArH), 6.86–6.80 (m, 2H, ArH), 6.11 (d, J=8.2 Hz, 1H, ArH), 3.07 (d, J=16.1 Hz, 1H, CH_2), 2.61 (d, J=16.1 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 179.2, 167.6, 146.3, 136.5, 134.5, 133.9, 130.9, 127.5, 125.1, 119.2, 118.6, 117.4, 110.7, 110.5, 106.0, 104.0, 99.0, 50.6, 38.4; ESIMS m/z 329.1 $[M+H]^+$; IR (film) 3369, 1715, 1666, 1613, 1483, 1377 cm^{-1}; HRMS calcd for $C_{19}H_{13}N_4O_2$ 329.1033; found 329.1033.

*4.2.11. 5′-Chloro-1′-methyl-4,6-dihydrospiro[azepino[4,3,2-cd]indole-3,3′-indoline]-2′,5(1H)-dione (**15**).* General procedure was followed, brown solid, mp: 296–298 °C; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 11.16 (br s, 1H, NH), 10.46 (s, 1H, NH), 7.43 (dd, J=8.4, 1.9 Hz, 1H, ArH), 7.35–7.25 (m, 2H, ArH), 7.16 (d, J=8.2 Hz, 1H, ArH), 6.94–6.86 (m, 2H, ArH), 6.19 (d, J=8.2 Hz, 1H, ArH), 3.17 (s, 3H, CH_3), 3.06 (d, J=15.8 Hz, 1H, CH_2), 2.71 (d, J=15.8 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 177.0, 167.7, 142.1, 136.5, 134.6, 130.8, 128.4, 126.6, 125.0, 123.5, 118.7, 117.3, 110.8, 110.4, 105.9, 99.0, 50.6, 38.6, 26.3; ESIMS m/z 352.4 $[M+H]^+$; IR (film) 3347, 1643, 1488, 1356 cm^{-1}; HRMS calcd for $C_{19}H_{15}ClN_3O_2$ 352.0847; found 352.0847.

*4.2.12. 5′-Chloro-8-isopropyl-4,6-dihydrospiro[azepino[4,3,2-cd]indole-3,3′-indoline]-2′,5(1H)-dione (**16**).* General procedure was followed, brown solid, mp: 226–230 °C; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 11.03 (d, J=2.01 Hz, 1H, NH), 10.67 (s, 1H, NH), 10.27 (s,

1H, NH), 7.30 (dd, J=8.4, 2.1 Hz, 1H, ArH), 7.11 (br s, 1H, ArH), 6.95 (d, J=8.3 Hz, 1H, ArH), 6.93 (br s, 1H, ArH), 6.67 (d, J=1.0 Hz, 1H, ArH), 6.56 (d, J=2.3 Hz, 1H, ArH), 3.15 (d, J=15.2 Hz, 1H, CH_2), 2.99–2.86 (m, 1H, CH), 2.72 (d, J=15.2 Hz, 1H, CH_2), 1.24 (d, J=7.0 Hz, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 177.9, 169.1, 143.1, 140.3, 137.8, 136.0, 130.3, 128.1, 125.8, 124.2, 120.0, 114.6, 113.1, 111.2, 106.5, 103.3, 48.1, 47.0, 33.7, 24.4, 24.3; ESIMS m/z 380.5 $[M+H]^+$; IR (film) 3713, 3674, 2972, 2871, 1058, 1012 cm^{-1}; HRMS calcd for $C_{21}H_{19}ClN_3O_2$ 380.1160; found 380.1159.

*4.2.13. 5′-Chloro-8-methoxy-4,6-dihydrospiro[azepino[4,3,2-cd]indole-3,3′-indoline]-2′,5(1H)-dione (**17**).* General procedure was followed, brown solid, mp: 236–238 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.08 (br s, 1H, NH), 10.87 (br s, 1H, NH), 10.35 (s, 1H, NH), 7.27–7.18 (m, 2H, ArH), 6.96 (d, J=8.5 Hz, 1H, ArH), 6.64 (br s, 1H, ArH), 6.44–6.41 (m, 1H, ArH), 6.40 (d, J=2.5 Hz, 1H, ArH), 3.67 (s, 3H, CH_3), 3.19 (d, J=16.3 Hz, 1H, CH_2), 2.49 (overlap with DMSO, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 179.4, 167.5, 151.9, 138.24, 138.15, 134.0, 128.1, 125.5, 124.8, 124.7, 124.0, 117.4, 108.0, 107.1, 98.2, 87.8, 55.3, 51.0, 36.0; ESIMS m/z 368.1 $[M+H]^+$; IR (film) 2925, 2852, 1719, 1678, 1491 cm^{-1}; HRMS calcd for $C_{19}H_{15}ClN_3O_3$ 368.0796; found 368.0795.

*4.2.14. 5′-Chloro-8-fluoro-4,6-dihydrospiro[azepino[4,3,2-cd]indole-3,3′-indoline]-2′,5(1H)-dione (**18**).* General procedure was followed, brown solid, mp: 277–280 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.33 (br s, 1H, NH), 11.17 (s, 1H, NH), 10.47 (s, 1H, NH), 7.38–7.34 (m, 1H, ArH), 7.30 (dd, J=8.6, 2.4 Hz, 1H, ArH), 7.00 (d, J=8.5 Hz, 1H, ArH), 6.85 (d, J=10.5 Hz, 1H, ArH), 6.51 (br s, 1H, ArH), 6.50 (d, J=2.3 Hz, 1H, ArH), 3.02 (d, J=16.3 Hz, 1H, CH_2), 2.70 (d, J=16.3 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 178.6, 166.9, 154.7 (d, J_{C-F}=235 Hz), 138.1, 137.3 (d, J_{C-F}=13 Hz), 134.4 (d, J_{C-F}=11 Hz), 128.7, 126.0, 125.8, 124.9, 124.0, 117.7, 110.2, 106.0 (d, J_{C-F}=22 Hz), 98.5, 91.4 (d, J_{C-F}=24 Hz), 50.7, 36.9; ESIMS m/z 356.5 $[M+H]^+$; IR (film) 3316, 2939, 1670, 1491, 1392, 1088 cm^{-1}; HRMS calcd for $C_{18}H_{12}ClFN_3O_2$ 356.0597; found 356.0597.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.12.010.

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