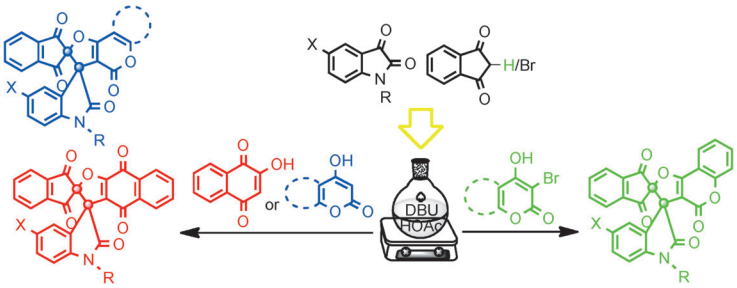

Crowded spaces! An organocatalytic modified Feist–Bénary reaction of cyclic dicarbonyl compounds, isatins, and cyclic α-bromo dicarbonyls was developed. This method affords bisspirooxindole-fused dihydrofurans containing two vicinal spiro centers (see scheme; DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene). Employing cyclic α-halo dicarbonyl compounds for the synthesis of bisspirooxindole-fused dihydrofurans has not been previously reported.

Spiro Compounds

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Highly Efficient Construction of Bisspirooxindoles Containing Vicinal Spirocenters through an Organocatalytic Modified Feist–Bénary Reaction

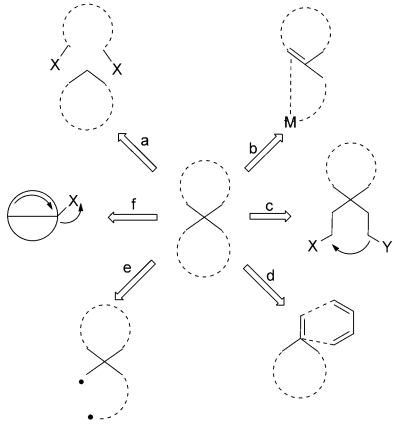
Somayeh Ahadi, Hamid Reza Khavasi, and Ayoob Bazgir*[a]

Abstract: We have developed an organocatalytic modified Feist–Bénary reaction of cyclic dicarbonyl compounds, isatins and cyclic α-bromo dicarbonyl compounds. This method affords bisspirooxindole-fused dihydrofurans containing two vicinal spiro centers. To the best of our knowledge, employing cyclic α-halo dicarbonyl compounds for the synthesis of bisspirooxindole-fused dihydrofurans has not been previously reported.

Keywords: Feist–Bénary reaction · fused-ring systems · organocatalysis · spiro compounds · synthetic methods

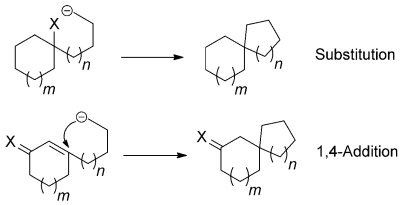
Introduction

Developing effective methods for the construction of spirocyclic frameworks has been a topic of great relevance in organic synthesis because of the outstanding biological activities of this class of compounds.[1] The spirocyclic compounds are synthesized by: a) alkylation methods, b) transition-metal-based processes, c) ring-closure methods, d) cycloaddition strategies, e) radical cyclizations, and f) rearrangement-based approaches involving cleavage of bridged ring systems[2] (Scheme 1).



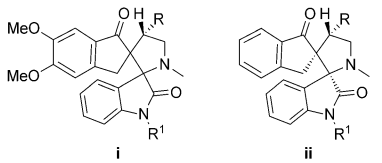
Scheme 1. The construction of spiro compounds.

Intramolecular alkylation on the quaternary carbon is one of the most conventional methods for the synthesis of spirocenters. The alkylation can be accomplished either through direct substitution or through 1,4-addition[3] (Scheme 2).



Scheme 2. Alkylation methods for the spirocenter formation.

Nucleophilic addition and annulation reactions with isatin electrophiles are major strategies that have been widely utilized for the synthesis of spirooxindoles.[4] Such compounds have drawn enormous interest from researchers in the area of synthetic and medicinal chemistry because they occur in many natural products and have a wide range of bioactivity;[5] they can act as progesterone receptor modulators,[6] anti-HIV,[7] anticancer,[8] antitubercular,[9] and antimalarial agents,[10,11] MDM2 inhibitors,[12] and antimicrobial and inhibitors of human NK-1 receptor.[13–15] For example, compounds **i** and **ii**, with the pyrrolidinyl spirooxindole framework, are known as an inhibitor of acetylcholinesterase and as an antitumor agent, respectively[16] (Scheme 3).



Scheme 3. Bioactive spirooxindoles.

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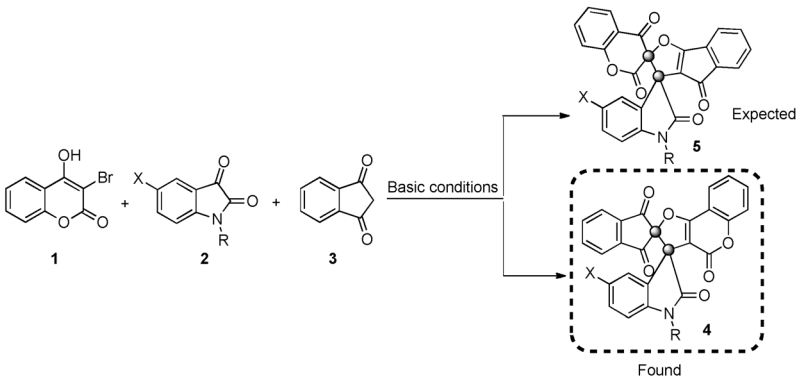
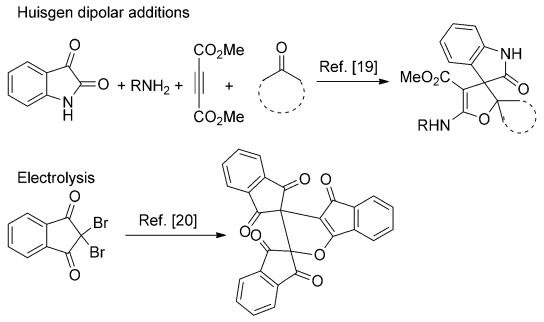
As a privileged scaffold, dihydrofuran is a ubiquitous subunit in many natural products with remarkable biological activities and its derivatives are widely applied in the pharmaceutical industry.[17] Therefore, the synthesis of new heterocycles containing both spirooxindole and dihydrofuran moieties may result in the development of new drug candidates. Whereas spirooxindoles fused to dihydrofuran have attracted attention,[18] bisspiro compounds incorporating both spirooxindole and dihydrofuran motifs or bisspiro compounds containing a dihydrofuran moiety have seldom been described. Very recently, the formation of dispirodihydrofuranyl oxindoles from activated cyclic electrophiles, amines, and dimethyl acetylenedicarboxylate (DMAD) through Huisgen dipolar additions has been reported.[19] In 2007, Barba and co-workers achieved the synthesis of 2,3-bis(spiro-2-indanyl-1,3-dione)indeno[1,2-*b*]through electrochemical reduction of 2,2-dibromo-1,3-indandione (Scheme 4).[20]

Interrupted Feist–Bénary dihydrofuran synthesis is a base-catalyzed reaction of α-halogen ketones and β-dicarbonyl compounds.[21] Recently, improved tandem reactions initiated by the reaction of stabilized carbanions on electrophiles followed by a cyclization step have been reported.[22–26] Very recently, we also described a modified Feist–Bénary reaction for the convenient synthesis of spiro-(indeno[1,2-*b*]furan)triones by using cyclic α-bromo diketone (Scheme 5).[27]

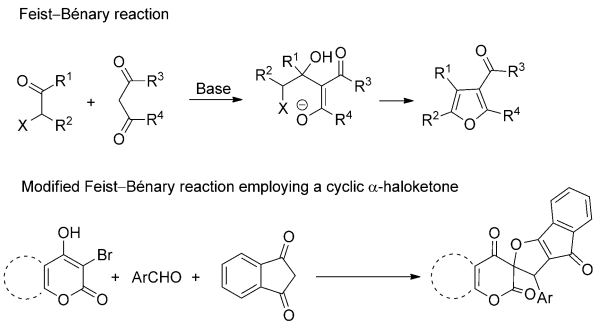


Scheme 6. Reaction of 3-bromo-4-hydroxycoumarin (**1**), isatins **2**, and 1,3-indandione (**3**).

According to the above reports and as a continuation of our previous work on the development of new methods for spirooxindole synthesis,[28–30] we herein report the first three-component organocatalytic modified Feist–Bénary reaction of 3-bromo-4-hydroxycoumarin (**1**), isatins **2**, and 1,3-indandione (**3**) for the construction of two vicinal spirocenters in a bisspirooxindole-containing furoindoline moiety. To our surprise, the expected product **5** was not obtained and only product **4** was isolated in a good yield (Scheme 6).



Scheme 4. Previous works for the synthesis of bisspiro compounds.



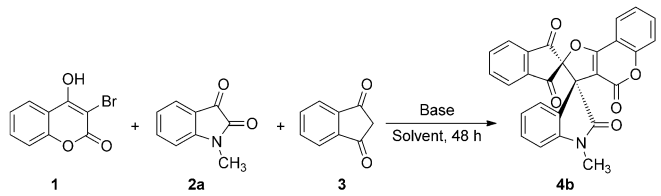
Scheme 5. Feist–Bénary reaction and our former work.

Results and Discussion

Our study commenced with a three-component reaction of **1**, *N*-methyl isatin (**2a**), and **3** as a model reaction in the presence of various bases and solvents (Table 1). Screening of the solvent revealed that acetic acid is the most suitable reaction media, providing 1″-methyl-4′*H*-dispiro(chromane-3,2′-indeno[1,2-*b*]furan-3′,3″-indoline)-2,2″,4,4′-tetraone (**4a**) in 91% isolated yield in presence of 30 mol% 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; entry 4). It was found that when the amount of DBU was increased from 10 to 20, and 30 mol%, the isolated yield increased from 70 to 74 and 91%, respectively; further increases in the amount of DBU did not improve the yield (entry 7). It should be mentioned that when the reaction was carried out in the absence of DBU the yield of the product was low (entry 9). When this reaction was carried out with other bases such as, NEt_3, Cs_2CO_3, K_2CO_3, NH_4OAc, or pyridine, the yield of the expected product was reduced. Furthermore, it was found that lower reaction temperature led to lower yield (entry 8).

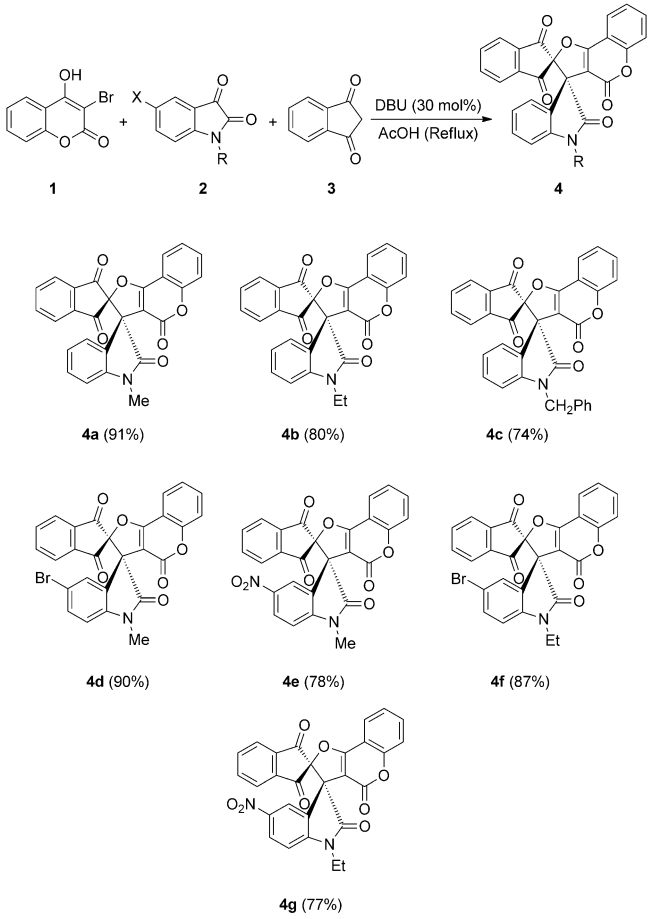
With optimal conditions in hand, we extended the reaction to various isatins **2** (Scheme 7). Reasonable yields were obtained by using N-alkyl isatins, however, when this reaction was carried out with N-H isatins, the expected products were obtained in only trace amounts.

Table 1. Optimization of the reaction.



Entry	Solvent	Temp. [°C]	Base ([mol %])	Yield [%][a]
1	CH_3CN	reflux	DBU (30)	65
2	EtOH	reflux	DBU (30)	45
3	H_2O	reflux	DBU (30)	50
4	HOAc	reflux	DBU (30)	91
5	HOAc	reflux	DBU (20)	84
6	HOAc	reflux	DBU (10)	70
7	HOAc	reflux	DBU (40)	91
8	HOAc	90	DBU (30)	81
9	HOAc	reflux	–	67
10	HOAc	reflux	Py (1equiv)	80
11	HOAc	reflux	K_2CO_3 (30)	76
12	HOAc	reflux	$CsCO_3$ (30)	80
13	HOAc	reflux	NEt_3 (30)	78
14	HOAc	reflux	NH_4OAc (30)	81

[A] Reaction time = 48 h.



Scheme 7. Synthesis of dispiro(indene-furochromene-indoline)tetraones **4**.

The structure of dispiro(indene-furochromene-indoline)tetraone **4a** was confirmed by single-crystal X-ray analysis (Figure 1).

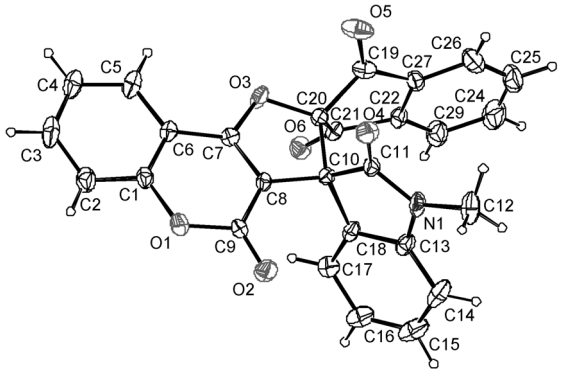
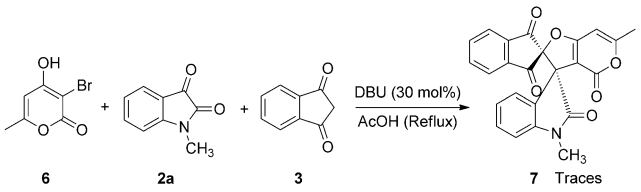


Figure 1. X-ray crystal structure of **4a**.

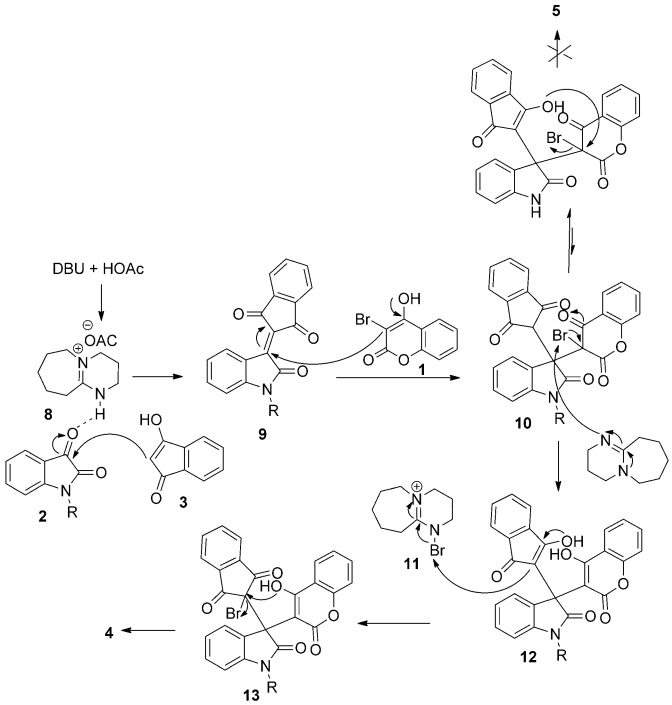
When the reaction was carried out with 3-bromo-4-hydroxy-6-methyl-2*H*-pyran-2-one (**6**) as a cyclic α-bromo diketone, TLC analysis and ^{1}H NMR spectra of the reaction mixture showed a combination of starting materials and numerous products; the desired product **7** was obtained in only trace amounts (Scheme 8).



Scheme 8. Use of 3-bromo-4-hydroxy-6-methyl-2*H*-pyran-2-one (**6**) in the reaction.

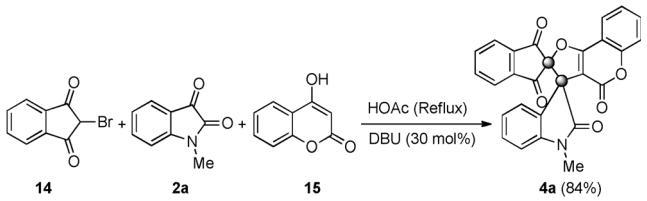
We have not established an exact mechanism for the formation of **4**, however, a reasonable possibility is shown in Scheme 9. Initially, salt **8** is formed in situ by acid–base reaction of DBU and HOAc. A hydrogen bond then forms between isatin **2** and **8**, thus activating the isatin, which then reacts with **3** by Knoevenagel condensation.[27] The Michael addition of 3-bromo-4-hydroxycoumarins **1** to intermediate **9** affords intermediate **10**. Subsequently, nucleophilic attack of DBU on **10** produces intermediate **12**[31] and bromo-pyrimidoazepinium **11** as the source of Br^+. Finally, the reaction of **11** and **12** affords intermediate **13**, which subsequently undergoes annulation to give the product **4** (Scheme 9).

Mechanistically, it is clear that Br^+ acts as a leaving group and the reaction proceeds via intermediate **13**. To clarify the proposed mechanism, 2-bromo-1*H*-indene-1,3(2*H*)-dione (**14**) was used as cyclic α-bromo diketone instead of **1**. In this way, we investigated the reaction of **14**, *N*-methyl isatin (**2a**), and 4-hydroxycoumarin (**15**) under the same reaction conditions and obtained the corresponding product **4a** in



Scheme 9. Proposed reaction mechanism.

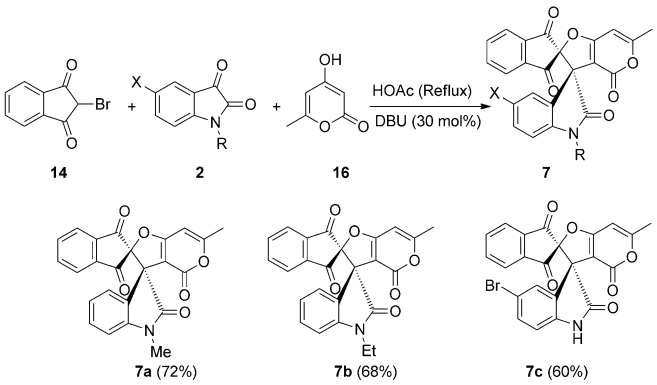
84% yield (Scheme 10). The structure of **4a** obtained in this way was confirmed by single-crystal X-ray analysis (see the Supporting Information).



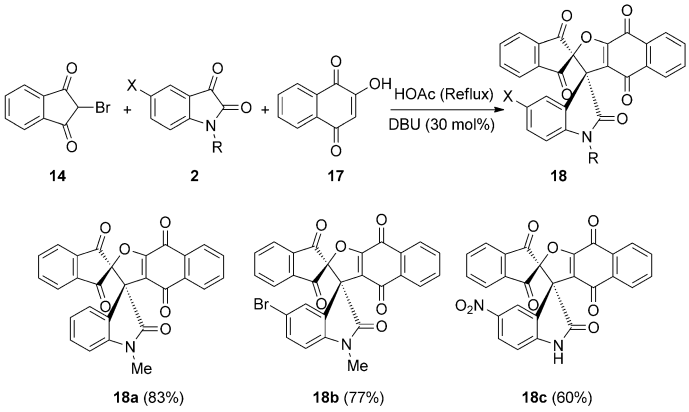
Scheme 10. Reaction of 2-bromoindandione (**14**), *N*-methylisatin (**2a**), and 4-hydroxycoumarin (**15**).

Encouraged by this success, we attempted to synthesize 6′-methyl-dispiro(indene-furo[3,2-*c*]pyranindoline)tetraones **7** by using **14**. Interestingly, dispiro(indene-furo[3,2-*c*]pyranindoline)tetraones **7a–c** were isolated in good yields by the reaction of **14**, **2**, and **16** (Scheme 11). Surprisingly, we found that the reaction also proceeds very efficiently with NH isatin, affording the desired product **7c** in good yield.

Naphthalene-1,4-dione derivatives are known to possess a wide spectrum of biological applications such as antibacterial, antifungal, antiinflammatory, anticancer, antidiabetic and antimalarial activities.[32] Considering the very important biologically activities of molecules containing the naphthalene-1,4-dione scaffold, we hypothesized that the integration of a naphthalene-1,4-dione moiety with a spirooxindole-fused dihydrofuran may result in the discovery of novel drug candidates with unknown biologically activities. Accordingly, we investigated the reaction of 2-hydroxynaphthalene-1,4-dione (**17**), **14**, and isatins **2** under the same reaction conditions and obtained the desired dispiro(indene-furo[3,2-*c*]pyranindoline)tetraones **18a–c** in good isolated yields (Scheme 12).



Scheme 11. Synthesis of dispiro(indene-furopyran-indoline)tetraones **7**.



Scheme 12. Synthesis of dispiro(indene-furo[3,2-*c*]pyranindoline)tetraones **18**.

Conclusion

We have developed an organocatalytic cascade Knoevenagel–Michael alkylation reaction of 1,3-dicarbonyl compounds, cyclic α-bromo diketones, and isatins for the synthesis of bisspirooxindoles containing two vicinal spirocenters. Prominent among the advantages of this method are novelty, simplicity, good yields, and the straightforward work-up procedures employed.

Experimental Section

General methods: Melting points were determined with a melting point Thermo Scientific 9100 apparatus and are uncorrected. IR spectra were taken with a Bomem FT-IR MB spectrometer. ^{1}H NMR spectra were recorded with a 300 MHz Bruker DRX Avance spectrometer. Chemical

shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Elemental C, H and N analyses were performed with a Heraeus CHN-O-Rapid analyzer. MS spectra were recorded with a Shimadzu QP 1100EX mass spectrometer operating at an ionization potential of 70 eV.

All chemicals were purchased from Merck or Aldrich and were used without further purification. 3-Bromo-4-hydroxycoumarin[33] and 2-bromo-1H-indene-1,3(2*H*)-dione[34] were prepared by reported procedures.

Due to very low solubility of the products **4**, **7** and **18**, no ^{13}C NMR data were obtained for these products.

X-ray crystallography: The X-ray diffraction measurements were made with a STOE IPDS-II diffractometer with graphite-monochromated $Mo_{K\alpha}$ radiation. Cell constants and an orientation matrix for data collection were obtained by least-squares refinement of diffraction data from 4998 unique reflections for **4a**. Data were collected at a temperature of 298(2) K to a maximum 2θ value of 51.98° and in a series of ω scans in 1° oscillations and integrated using the Stoe X-AREA[35] software package. The data were corrected for Lorentz and Polarizing effects. The structures were solved by direct methods and refined on F2 by full-matrix least-squares procedure. All hydrogen atoms were added at ideal positions and constrained to ride on their parent atoms, with Uiso(H)= 1.2Ueq. All refinements were performed by using the X-STEP32 crystallographic software package.[36] Complete crystallographic data for compound **4a** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-929571. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General procedure for the synthesis of 4: A mixture of isatins (1.0 mmol), 1,3-indandione (1.0 mmol), and 3-bromo-4-hydroxycoumarin (1 mmol) in HOAc (2 mL) in the presence of DBU (30 mol%) was heated to reflux for 48 h. Upon completion of the reaction (TLC), the mixture was evaporated under vacuum. Methanol (3 mL) was added and the precipitated product was filtered and washed with methanol (2 mL) to afford the pure product **4**.

1″-Methyl-4′H-dispiro(indene-2,2′-furo[3,2-c]chromene-3′,3″-indoline)-1,2″,3,4′-tetraone (4a): Yield: 95%; cream powder; m.p. 240°C (dec); ^1H NMR (300 MHz, [D$_6$]DMSO): δ=2.83 (s, 3H; CH3), 6.82 (d, ^3J(H,H)=7.8 Hz, 1H; H-Ar), 7.01–7.06 (m, 1H; H-Ar), 7.16 (d, 3J(H,H)= 7.3 Hz, 1H; H-Ar), 7.55–7.63 (m, 3H; H-Ar), 7.85–7.97 ppm (m, 6H; H-Ar); IR (KBr): $\tilde{\nu}$=1763, 1732, 1643 cm−1; MS (EI, 70 eV): *m*/*z* (%): 449 (29) $[M]^+$, 376 (58), 290 (29), 104 (100), 76 (56); elemental analysis calcd (%) for $C_{27}H_{15}NO_6$: C 72.16, H 3.36, N 3.12; found: C 72.10, H 3.41, N 3.07.

Crystal data for 4a: $C_{27}H_{15}NO_6$ (CCDC-929571); M=449.40 g mol^{-1}; monoclinic system; space group $P21/c$; a=9.8897(13) Å, b= 23.0963(19) Å, c=11.1997(14) Å, β=95.518(10)°; V=2546.3(5) Å^3; Z= 4; ρ_{cald}=1.172 g cm^{-3}; μ(Mo-Kα)=0.084 mm^{-1}; crystal dimension of 0.27×0.26×0.19 mm. The structure was solved by using SHELXS. The structure refinement and data reduction was carried out with SHELXL of the X-Step32 suite of programs. Non-hydrogen atoms were refined anisotropically by full matrix least-squares on F^2 values to final R_1= 0.0927, wR_2=0.2045 and S=0.938 with 308 parameters using 4998 independent reflection (θ range=2.54–25.99°). Hydrogen atoms were located from the expected geometry and were not refined.

1″-Ethyl-4′*H*-dispiro(indene-2,2′-furo[3,2-*c*]chromene-3′,3″-indoline)-1,2″,3,4′-tetraone (4b): Yield: 80%; brick-red powder; m.p. 257°C; ^1H NMR (300 MHz, [D$_6$]DMSO): δ=0.59 (t, ^3J(H,H)=6.50 Hz, 3H; CH$_3$), 3.30–3.39 (m, 1H; CH$_2$), 3.50–3.60 (m, 1H; H-Ar), 6.89 (d, ^3J-(H,H)=7.72 Hz, 1H; H-Ar), 7.02 (t, ^3J(H,H)=7.20 Hz, 1H; H-Ar), 7.14 (d, ^3J(H,H)=7.38, 1H; H-Ar), 7.27 (t, ^3J(H,H)=7.70 Hz, 1H; H-Ar), 7.54–7.67 (m, 3H; H-Ar), 7.85–7.90 (m, 2H; H-Ar), 7.94–7.97 ppm (m, 3H; H-Ar); IR (KBr): $\tilde{\nu}$=1761, 1729, 1646, 1602 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 466 (30) $[M]^+$, 390 (100), 290 (78), 104 (96), 76 (70); elemental analysis calcd (%) for $C_{28}H_{17}NO_6$: C 72.57, H 3.31, N 3.06; found: C 72.66, H 3.37, N 3.01.

1″-Benzyl-4′*H*-dispiro(indene-2,2′-furo[3,2-*c*]chromene-3′,3″-indoline)-1,2″,3,4′-tetraone (4c): Yield: 74%; cream powder; m.p. 245°C; ^1H NMR (300 MHz, [D$_6$]DMSO): δ=4.79 and 5.06 (AB system, ^3J(H,H)=15.8 Hz, 2H; CH$_2$), 6.92 (d, ^3J(H,H)=7.7 Hz, 1H; H-Ar), 6.99–7.02 (m, 2H; H-Ar), 7.23–7.28 (m, 1H; H-Ar), 7.40–7.47 (m, 5H; H-Ar), 7.79–7.93 (m, 3H; H-Ar), 8.09–8.23 ppm (m, 5H; H-Ar); IR (KBr): $\tilde{\nu}$=1745, 1723, 1643 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 528 (83) $[M]^+$, 434 (96), 390 (96), 286 (35), 104 (87), 91 (100); elemental analysis calcd (%) for $C_{33}H_{19}NO_6$: C 75.42, H 3.64, N 2.67; found: C 75.32, H 3.57, N 2.58.

5″-Bromo-1″-methyl-4′*H*-dispiro(indene-2,2′-furo[3,2-*c*]chromene-3′,3″-indoline)-1,2″,3,4′-tetraone (4d): Yield: 90%; white powder; m.p. 242°C (dec); ^1H NMR (300 MHz, [D$_6$]DMSO): δ=2.80 (s, 3H; CH$_3$), 6.84 (d, ^3J(H,H)=8.3 Hz, 1H; H-Ar), 7.45 (brs, 1H; H-Ar), 7.49–7.68 (m, 4H; H-Ar), 7.85–7.98 ppm (m, 5H; H-Ar); IR (KBr): $\tilde{\nu}$=1769, 1734, 1642, 1600 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 531 (56) $[M]^+$, 470 (87), 454 (100), 290 (22), 104 (96), 76 (52); elemental analysis calcd (%) for $C_{27}H_{14}BrNO_6$: C 61.38, H 2.67, N 2.65; found: C 61.30, H 2.63, N 2.71.

1″-Methyl-5″-nitro-4′*H*-dispiro(indene-2,2′-furo[3,2-*c*]chromene-3′,3″-indoline)-1,2″,3,4′-tetraone (4e): Yield: 78%; brick-red powder; m.p > 270°C; ^1H NMR (300 MHz, [D$_6$]DMSO): δ=2.92 (s, 3H; CH$_3$), 7.12 (d, ^3J(H,H)=8.7 Hz, 1H; H-Ar), 7.55–7.68 (m, 3H; H-Ar), 7.85–8.01 (m, 5H; H-Ar), 8.16 (brs, 1H; H-Ar), 8.26 ppm (d, ^3J(H,H)=8.7 Hz, 1H; H-Ar); IR (KBr): $\tilde{\nu}$=1728, 1651, 1604 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{14}N_2O_8$: C 65.59, H 2.85, N, 5.67; found: C 65.53, H 2.80, N 5.58.

5″-Bromo-1″-ethyl-4′*H*-dispiro(indene-2,2′-furo[3,2-*c*]chromene-3′,3″-indoline)-1,2″,3,4′-tetraone (4f): Yield: 87%; brick-red powder; m.p. > 270°C; ^1H NMR (300 MHz, [D$_6$]DMSO): δ=0.64 (t, ^3J(H,H)=6.7 Hz, 3H; CH$_3$), 3.31–3.38 (m, 1H; CH), 3.50–3.57 (m, 1H; CH), 6.87 (d, ^3J-(H,H)=8.1 Hz, 1H; H-Ar), 7.39 (brs, 1H; H-Ar), 7.45–7.58 (m, 3H; H-Ar), 7.68–7.70 (m, 1H; H-Ar), 7.82–7.66 ppm (m, 5H; H-Ar); IR (KBr): $\tilde{\nu}$=1762, 1736, 1642, 1598 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 545 (96) $[M]^+$, 468 (96), 390 (74), 293 (35), 104 (100), 76 (65); elemental analysis calcd (%) for $C_{28}H_{16}BrNO_6$: C 62.01, H 2.97, N 2.58; found: C 62.11, H 2.93, N 2.65.

1″-Ethyl-5″-nitro-4′*H*-dispiro(indene-2,2′-furo[3,2-*c*]chromene-3′,3″-indoline)-1,2″,3,4′-tetraone (4g): Yield: 77%; brick-red powder; m.p. > 270°C; ^1H NMR (300 MHz, [D$_6$]DMSO): δ=0.72 (t, ^3J(H,H)=6.9 Hz, 3H; CH$_3$), 3.42–3.52 (m, 1H; CH), 3.54–3.67 (m, 1H; CH), 7.16 (d, ^3J-(H,H)=8.7 Hz, 1H; H-Ar), 7.54–7.57 (m, 2H; H-Ar), 7.67–7.69 (m, 1H; H-Ar), 7.83–7.90 (m, 2H; H-Ar), 7.92–8.02 (m, 3H; H-Ar), 8.08–8.09 (m, 1H; H-Ar), 8.21–8.24 ppm (m, 1H; H-Ar); IR (KBr): $\tilde{\nu}$=1734, 1659, 1607 cm^{-1}; elemental analysis calcd (%) $C_{28}H_{16}N_2O_8$: C 66.14, H 3.17, N 5.51; found: C 66.09, H 3.24, N 5.58.

General procedure for the synthesis of 7 and 18: A mixture of isatins (1.0 mmol), C–H acid (1.0 mmol), and 2-bromo-1*H*-indene-1,3(2*H*)-dione (1 mmol) in HOAc (2 mL) in the presence of DBU (30 mol%) was heated to reflux for 48 h. Upon completion of the reaction (TLC), the mixture was evaporated under vacuum. Methanol (3 mL) was added and the precipitated product was filtered and washed with methanol (2 mL) to afford the pure product.

1″,6′-Dimethyl-4′*H*-dispiro(indene-2,2′-furo[3,2-*c*]pyran-3′,3″-indoline)-1,2″,3,4′-tetraone (7a): Yield: 72%; brick-red powder; m.p. > 270°C; ^1H NMR (300 MHz, [D$_6$]DMSO): δ=2.35 (s, 3H; CH$_3$), 2.79 (s, 3H; CH$_3$), 6.77 (d, ^3J(H,H)=7.7 Hz, 1H; H-Ar), 6.83 (s, 1H; =CH), 7.02–7.03 (m, 2H; H-Ar), 7.23–7.24 (m, 1H; H-Ar), 7.51–7.54 (m, 1H; H-Ar), 7.81–7.93 ppm (m, 3H; H-Ar); IR (KBr): $\tilde{\nu}$=1727, 1639 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 413 (38) $[M]^+$, 369 (52), 340 (71), 104 (100), 76 (59); elemental analysis calcd (%) $C_{24}H_{15}NO_6$: C 69.73, H 3.66, N 3.39; found: C 69.65, H 3.30, N 3.31.

1″-Ethyl-6′-methyl-4′*H*-dispiro(indene-2,2′-furo[3,2-*c*]pyran-3′,3″-indoline)-1,2″,3,4′-tetraone (7b): Yield: 68%; brown powder; m.p. > 270°C; ^1H NMR (300 MHz, [D$_6$]DMSO): δ=0.57 (t, ^3J(H,H)=6.8 Hz, 3H; CH$_3$), 2.35 (s, 3H; CH$_3$), 3.49–3.56 (m, 2H; H-Ar), 6.83–6.85 (m, 2H; H-Ar), 7.03 (brs, 2H; H-Ar), 7.24 (m, 1H; H-Ar), 7.55–7.57 (m, 2H; H-Ar), 7.81–7.83 (m, 1H; H-Ar), 7.94 ppm (brs, 2H, H-Ar); IR (KBr): $\tilde{\nu}$= 1733, 1698, 1678 cm^{-1}; elemental analysis calcd (%) $C_{25}H_{17}NO_6$: C 70.25, H 4.01, N 3.28; found: C 70.31, H 3.97, N 3.23.

5″-Bromo-6′-methyl-4′*H*-dispiro(indene-2,2′-furo[3,2-*c*]pyran-3′,3″-indoline)-1,2″,3,4′-tetraone (7c): Yield: 60%; cream powder; m.p. > 270°C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.89 (s, 3H; CH$_3$), 6.79–6.83 (m, 1H; H-Ar), 7.25–7.32 (m, 3H; H-Ar), 7.35–7.43 (m, 2H; H-Ar), 7.76–7.78 (m, 3H; H-Ar), 10.70 ppm (s, 1H; NH); IR (KBr): $\tilde{\nu}$ = 1740, 1712 cm^{-1}; elemental analysis calcd (%) for $C_{23}H_{12}BrNO_6$: C 57.76, H 2.53, N 2.93; found: C 57.85, H 2.60, N 2.85.

1″-Methyldispiro(indene-2,2′-naphtho[2,3-*b*]furan-3′,3″-indoline)-1,2″,3,4′,9′-pentaone (18a): Yield: 83%; cream powder; m.p. > 270°C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.81 (s, 3H; CH$_3$), 6.87 (d, ^3J(H,H) = 7.7 Hz, 1H; H-Ar), 7.01–7.06 (m, 1H; H-Ar), 7.27–7.32 (m, 2H; H-Ar), 7.38 (d, ^3J(H,H) = 7.4 Hz, 1H; H-Ar), 7.58 (d, ^3J(H,H) = 7.5 Hz, 1H; H-Ar), 7.80–7.89 (m, 4H; H-Ar), 7.96 (m, 2H; H-Ar), 8.12–8.14 ppm (m, 1H; H-Ar); IR (KBr): $\tilde{\nu}$ = 1778, 1732, 1689, 1645 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 461 (28), 433 (21), 388 (35), 290 (12), 104 (100), 76 (59); elemental analysis calcd (%) for $C_{28}H_{15}NO_6$: C 72.88, H 3.28, N 3.04; found: C 72.82, H 3.34, N 3.11.

5″-Bromo-1″-methyldispiro(indene-2,2′-naphtho[2,3-*b*]furan-3′,3″-indoline)-1,2″,3,4′,9′-pentaone (18b): Yield: 80%; yellow powder; m.p. > 270°C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.48 (s, 3H; CH$_3$), 6.88 (d, ^3J(H,H) = 5.78 Hz, 1H; H-Ar), 7.51 (d, ^3J(H,H) = 7.96 Hz, 1H; H-Ar), 7.69–7.67 (m, 1H; H-Ar), 7.75 (brs, 1H; H-Ar), 7.82–7.88 (m, 4H; H-Ar), 7.98 (brs, 2H; H-Ar), 8.12 ppm (brs, 1H; H-Ar); IR (KBr): $\tilde{\nu}$ = 1715, 1675, 1648, 1609 cm^{-1}; elemental analysis calcd (%) for $C_{28}H_{14}BrNO_6$: C 62.24, H 2.61, N 2.59; found: C 62.31, H 2.57, N 2.66.

5″-Nitrodispiro(indene-2,2′-naphtho[2,3-*b*]furan-3′,3″-indoline)-1,2″,3,4′,9′-pentaone (18c): Yield: 61%; brown powder; m.p. > 270°C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 6.90 (d, ^3J(H,H) = 8.282 Hz, 1H; H-Ar), 7.74 (d, ^3J(H,H) = 7.73 Hz, 1H; H-Ar), 7.84–7.90 (m, 4H; H-Ar), 8.01 (brs, 2H; H-Ar), 8.13–8.19 (m, 2H; H-Ar), 8.45 (s, 1H; H-Ar), 11.47 ppm (s, 1H; NH); IR (KBr): $\tilde{\nu}$ = 1728, 1685, 1631 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{12}N_2O_8$: C 65.86, H 2.46, N 5.69; found: C 65.77, H 2.40, N 5.60.

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