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Ligand free Synthesis of oxacyclic spirooxindole derivatives through Zn, I_2 catalyzed intramolecular Carbonylation of ring-closing oxindole enynes.

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Abstract: An efficient approach for a ligand free catalyst based synthesis of novel fused spirooxindole scaffolds from oxindole enynes has been developed. The reaction involves a metal-catalyzed C-3 allylation/vinylation of N-substituted isatins which gives rise to the corresponding alcohols that can be converted into the required enynes. Further transformation to diverse complex molecular scaffolds proceeds via a subsequent Zinc acetate and Iodine–catalyzed, Carbon monoxide induced intramolecular ring-closing cyclization enyne. This strategy provides a facile approach to various spirooxindole in good to excellent yields.

Keywords: diversity-oriented synthesis (DOS); C-3 allylation/vinylation; fused cyclopentenones; Zinc acetate and Iodine–catalyst; Carbon monoxide, intramolecular ring-closing cyclization; spirooxindoles; oxindoleenynes.

Introduction

Synthesis of novel fused spirooxindole scaffolds play a significant role in various natural and pharmaceutical products. Spirooxindoleemerged as a powerful tool to get the maximum structural variability from simple starting materials.Especially, oxygen- and nitrogen-containing heterocycles have attracted the attention of synthetic and medicinal chemists because of the widespread occurrence of such structural motifs in natural and unnatural products and their use as building blocks.[1-2] The spirooxindole framework has drawn tremendous interest of researchers in the area of synthetic organic chemistry and medicinal chemistry worldwide because it occurs in many natural products and it's become a privileged skeleton given their broad and promising activities in various therapeutic areas such as spirotryprostatins, horsfiline, gelsemine,[3]gelseverine, [3] **(Figure-1)**rhynchophylline, and elacomine, etc. and has been reported to have various types of bioactivity.[4] Some bioactive spirocyclic oxindole derivatives, for example **(Figure-1**),

XEN907,[5] luminescent,[6] CB2 receptor antagonist,[7] progesterone receptor modulators,[8] anti-HIV,[9] anticancer,[10]antitubercular,[11] antimalarial,[12,13] and MDM2 inhibitors,[14] were found in the literature. Therefore, the construction of spirooxindole skeletons has attracted great attention of synthetic chemists.[15]

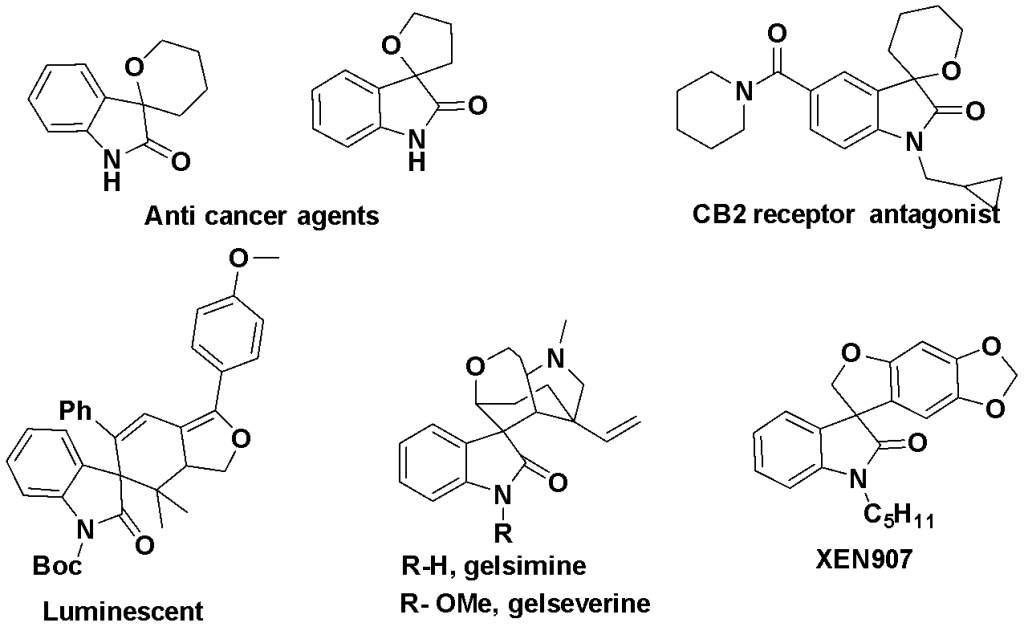


Figure-1: some natural and bioactive compounds containing spirocyclic oxindole scaffolds.

Additionally, interesting and biologically active natural products containing bicyclic fused cyclopentenones are also common.[16,17] These are demonstrated in **Figure-2**. Among these, bicyclo[4.3.0]nonane,[16]and bicyclo[3.3.0]octane[17] frameworks normally originate in bioactive natural products. For example, alisol-L,[16a] minwaninone,[16c]jiadifenin,[16c]hirsutanolA,[17a]incarnal,[17a]chondrosterinA[17a] are some of the representative natural products bearing 5,6-bicyclic, and 5,5-bicyclic cyclopentenone motifs in their structures.

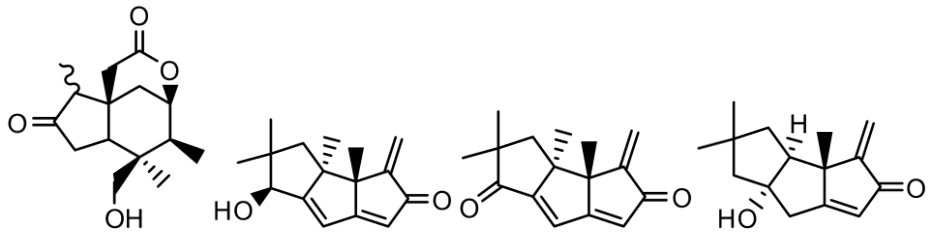
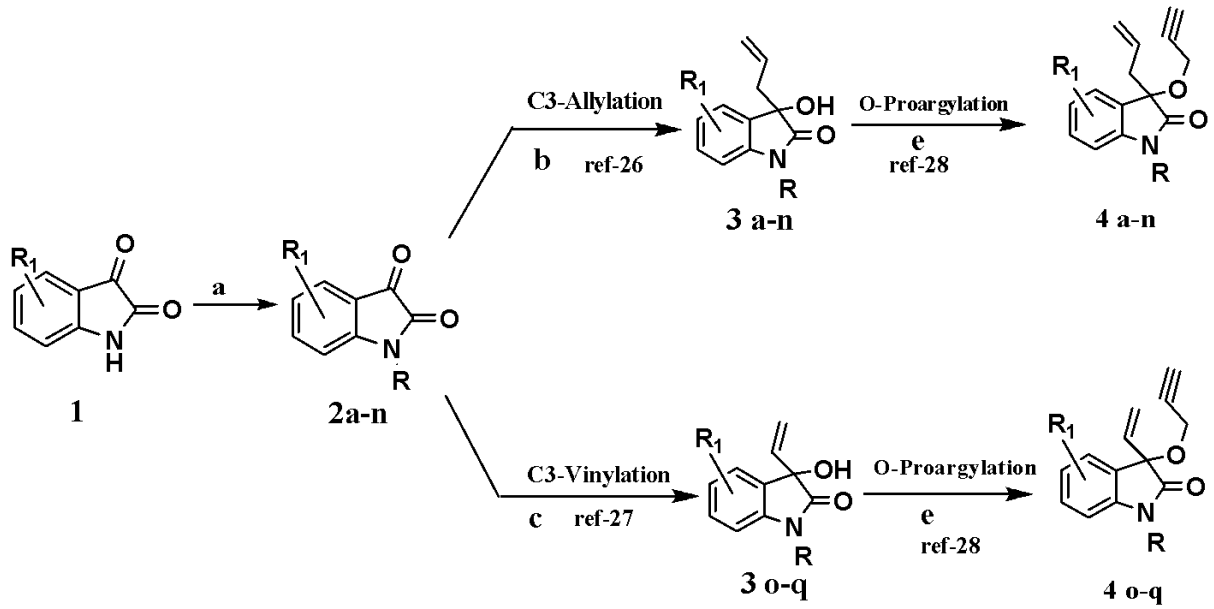


Figure-2: Natural products having a bicyclic fused cyclopentenone system

The intra molecular ring-closing enynemetathesis[18]has attracted attention due to its synthetic potential in the generation of ring structures with 1,3-diene moieties, which can subsequently be further functionalized. Meanwhile the Pauson–Khand reaction (PKR)[19] is widely used as a powerful method for the synthesis of cyclopentenone ring systems. In contrast, several metal catalyzed methods have been developed carbonylation[20] between aryl halides and amines using carbon monoxide was considered an appropriate and effective method. Accordingly, numerous Pd-based catalysts have been explored to serve the purpose.[21–25] The intramolecular version of the reaction has gained much popularity because it can afford cyclopentenone-

fused ring systems, which are difficult to construct. Due to their important roles, but we have utilized easily available catalyst and reagents for synthesis of spirocyclic oxindole-based compounds from oxindole enynes. We started our investigation with the preparation of the desired oxindole alcohols 3a–q from isatins**(Scheme-2).** For this, first we synthesized N-alkylated isatins 2a–n by treating various isatins (1) with K_2CO_3**(a)**and different alkyl halides. Then these were subjected to a metal-mediated nucleophilic addition to the ketone group at the C-3 position to realise a variety of transformations such as C-3 allylation[22] 3a–n, C-3 vinylation[23] 3o–q, with good yields as illustrated in **Scheme-1**.



Scheme -1: Diverse synthesis of oxindole enynes starting from isatins

R=Et, Me, iPr, Bn ; R_1= H, 5-F, 5-Cl, 6-Cl, 7-Cl, 4-Br, 5-Br, 5-Me, 5-OMe, 5-$OCF_3$4a-n =(1,7)-enynes ; 4o-q = (1,6)-enynes ;b ,c ,d –reagents and procedure taken from reference no 26 ,27 .

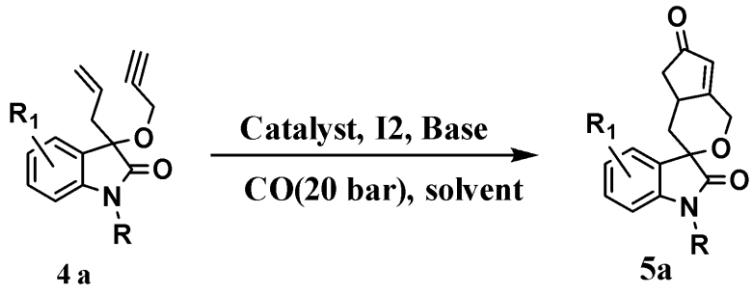
Reagents and conditions: *(a) K2CO3, R-X, CH3CN, rt-reflux, 12-24 h; (b) Allylbromide, In, NaI, DMF, 0 ^oC- rt, 2 h; (c) Vinylmagnesium bromide, THF, -78 ^oC-rt, (d) (i) 4-Bromo-1-butene, Mg, THF, reflux, 2 h, (ii)* ***2*** *in THF, -78 ^oC (2 h)-rt (2 h); (e) Propargyl bromide, NaH, TBAI (cat.), Dry THF, 0 ^oC-rt, 8-12 h.*

Results and Discussion

Now, the desired enyne intermediates, 3-allyl-1-substituted- 3-prop-2-ynyloxy)-indolin-2-ones (1,7-enynes, 4a–n) could be accessed in 90–98% yields by O-propargylation of the homoallylic alcohols 3a–n with propargyl bromide in the presence of NaH and a catalytic amount of TBAI in dry THF at 0 ^0C to room temperature. Under similar conditions, propargylation of 3o–q yielded 1-substituted-3-(prop-2-ynyloxy)- 3-vinylindolin-2-ones (1,6-enynes, 4o–q), respectively, as shown in **Scheme-1**.These enynes 4a–q would in turn become suitable substrates for selected transition metal-catalyzed transformations

Next, we turned our attention towards catalyst based intramolecular carbonylation[21]These reactiongenerates three new carbon bonds as it forms a cyclopentenone in one step. The intramolecular route is reliable for the synthesis of [3.3.0] and [3.4.0] bicyclic systems. We carried out an optimization of the reaction conditions, the results of which are summarized in **Table-1.**

Table-1: Optimization of the reaction conditions.



4 a 5a

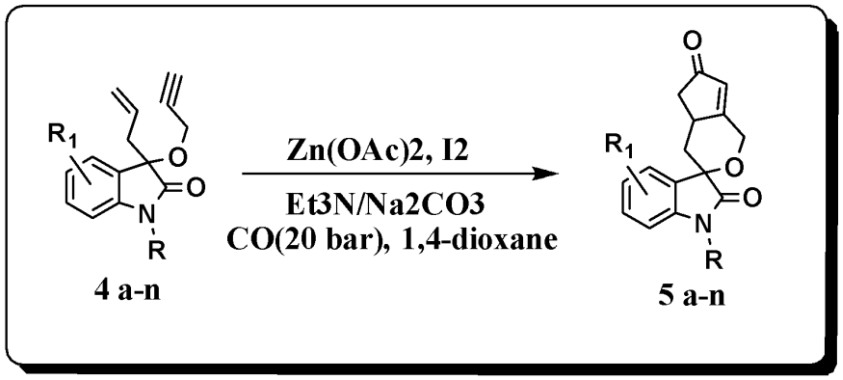
S.No	Catalyst (mol%)	Base	Solvent	Temp(^{0}C)/Time(h)	Yield(%)
1	$Zn(OAc)_2$(5)	Et_3N	1,4-dioxane	RT/16	-
2	$Zn(OAc)_2$(10)	Et_3N	1,4-dioxane	50/24	-
3	$Zn(OAc)_2$(10)	Et_3N	1,4-dioxane	100/24	-
4	$Zn(OAc)_2$(10)	DABCO	1,4-dioxane	100/24	-
5	$Zn(OAc)_2$(10)	Et_3N/Na_2CO_3	1,4-dioxane	50/6	40
6	$Zn(OAc)_2$(5)	$NaHCO_3$	1,4-dioxane	100/16	25
7	$Zn(OAc)_2$(5)	Cs_2CO_3	1,4-dioxane	100/16	traces
8	$Zn(OAc)_2$(5)	Et_3N/Na_2CO_3	1,4-dioxane	50/20	25
9	$Zn(OAc)_2$(10)	**Et_3N/Na_2CO_3**	**1,4-dioxane**	**100/16**	**87**
10	$Zn(OAc)_2$(10)	Et_3N/Na_2CO_3	Toluene	100/16	20
11	$Zn(OAc)_2$(10)	Et_3N/Na_2CO_3	Acetonitrile	100/20	traces
12	$Zn(OAc)_2$(10)	Et_3N/Na_2CO_3	THF	100/16	---
13	$Zn(OAc)_2$(10)	Et_3N/Na_2CO_3	DMF	100/16	65

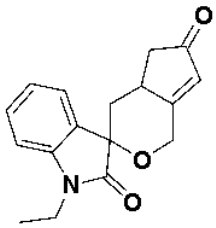
Reaction conditions: 4a (1.0 mmol.), I_2 (5 mmol.), catalyst (5 mol %), base (2 mmol.), solvent (10 mL), 100 °C, 16 h.Yields refer to pure products after column chromatography.

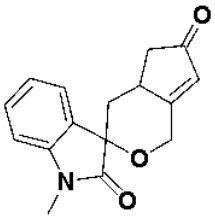
To establish the reaction conditions, 4a (enyne compound) and Iodine were chosen as a model system. The carbonylation reaction was explored at 20 bar of CO pressure by using $Zn(OAc)_2$ catalysts and bases. During the initial trails, all the reactions were performed at 100 ^{0}C (Table 1, entries 1–13). When the reaction was performed using different bases and in the presents of Zn(II) catalyst, no required product 5a was noticed even after 24 h (Table 1, Entry 1-4 and 12). Changing the catalyst to 10 mol% of $Zn(OAc)_2$ produced compound 5a in 87% yield (Table 1, entry 9). Further bringing down the concentration of the catalyst to 5 mol% dropped the yields accordingly (Table 1, entries 6–8). Having the best result in hand (Table 1, entry 4) the screening of the reaction conditions was further continued. Replaces the different bases such as Na2CO3, NaHCO3 and Cs2CO3 produced only moderate yields (40%, 25% and trace amountrespectively; Table 1, entries 5–7) but by using Et_3N, Na_2CO_3 in DMF solvent the yield of the compound 5a was improved to 65% (Table 1, entry 13) and could serve as an alternative to 1,4-dioxane solvent. Using the best reaction conditions (10 mol% Zn(OAc)2, DABCO and CO (20 bar) and carrying out the reaction at 50 ^{0}C temperature resulted product 5a was not formed after 24 h (Table 1, entry 4). Increasing the temperature to 100 ^{0}C in Toluene did not improve the result any better (20%) (Table 1, entry 10). The effects of different CO pressures and solvent studies suggest

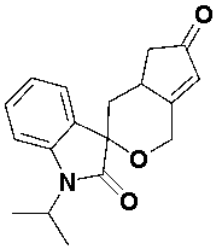
that theuse of 20 bar CO pressure and 1,4-dioxane as a solvent proved to be the best reaction conditions (Table S1, entry 9(Supporting Information).

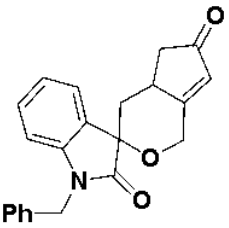
Table 2: Substrate scopeof the intramolecular cyclization of (1,7)-enynes



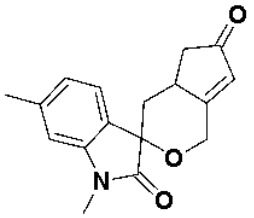

5a, 87%

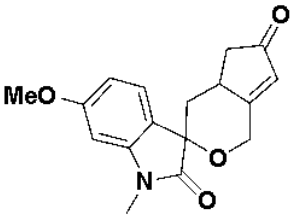

5b, 85%


5c, 86%

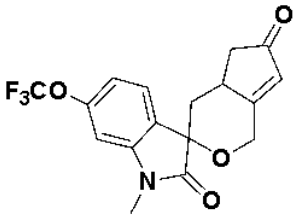


5d, 85%

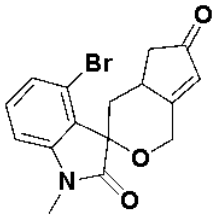

5e, 86%



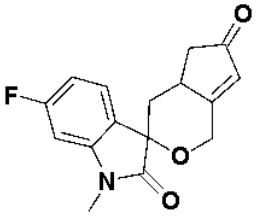
5f, 85%



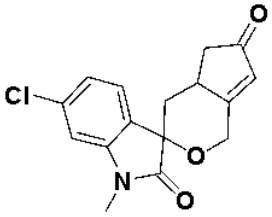
5g, 88%



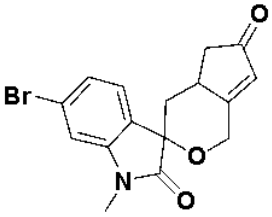
5h, 78%



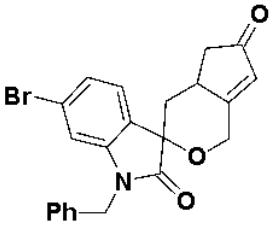
5i, 75%



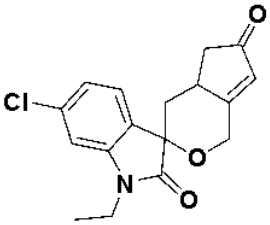
5j, 77%



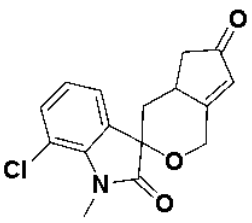
5k, 79%



5l, 80%



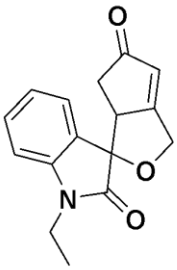
5m, 78%



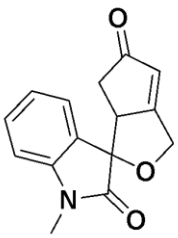
5n, 80 %

Table 3: Substrate scopeof the intramolecular cyclization of (1,6)-enynes

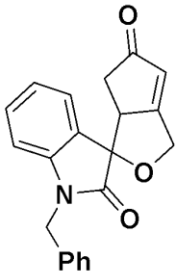




5o, 74%



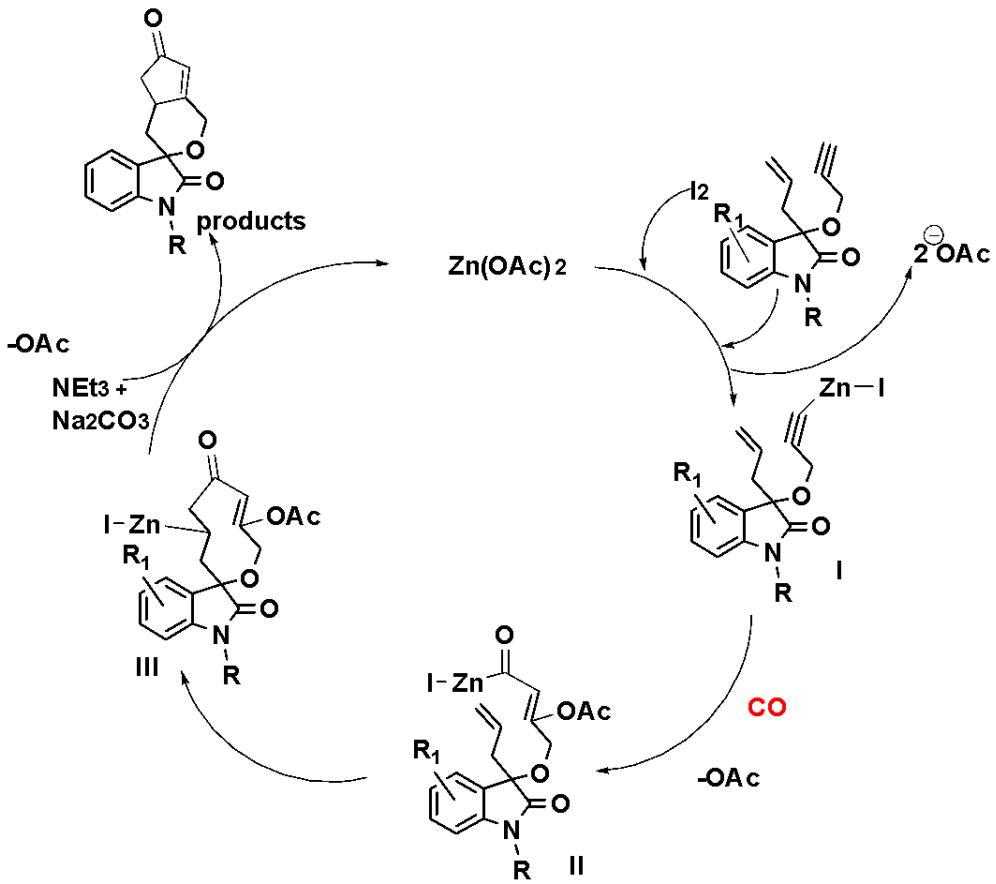
5p, 80%



5q, 77%

Based on the experimental results, the generality of this method was studied on a number of oxindole enynes for the synthesis of various oxacyclicspirooxindoles. After exploring the best reaction conditions, further the applicability of this methodology was extended to used on the corbonylation reaction was chosen with different (1,7)-enynes to obtain the corresponding spirooxindole-5,6-bicyclic fused cyclopentenone derivatives 5a–n with good to excellent yields. shown in Table 2,At the same time, in the case of (1,6)-enynes we successfully achieved 5,5-bicyclic fused cyclopentenones 6o–q with good yields (shown in Table 3) by catalyst based intra molecular cyclization with carbonylation using $Zn(OAc)_2$catalyst

Scheme-3: A plausible reaction mechanism.



Based on the experimental studies and from the available literature,[28, 29] a hypothetical mechanism could be proposed as shown in Scheme 2. Initially, Zn(II)-salt reacted with iodide to form alkyne zinc iodide Int-I. Then addition of CO molecule on to the intermediated I to generate intermediated II, subsequent cyclizationto CO molecule on to the intermediate II leads to intermediate III. the nucleophilic attack by the amine base on intermediate-III facilitate the formation of the desired products and regenerate the active Zn(II) salt catalyst to complete the catalytic cycle.

Notably, to the best of our knowledge, this is the first approach to synthesize diverse spirooxindole- 5,6-bicyclic/5,5-bicyclic cyclopentenone derivatives from oxindole enynes proving the practical application of the methodology.

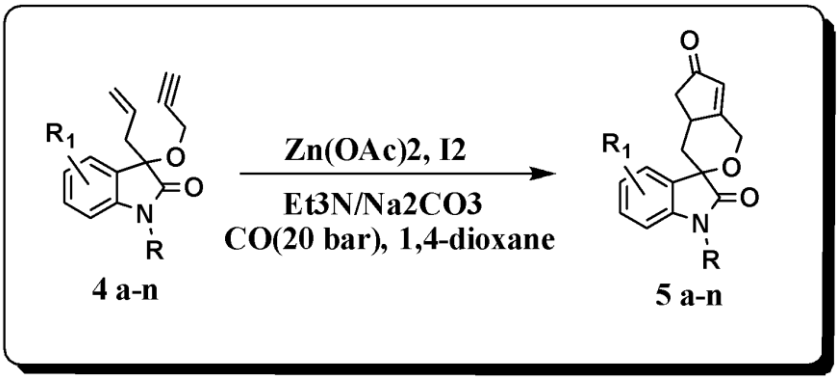
Conclusion

In summary, we have developed an efficient strategy for fused spirooxindole scaffolds from oxindole enynes via intramolecular carbonylation followed by cyclization reactions. Here, we disclose the synthesis of novel diversespirooxindole-5,6-bicyclic/5,5-bicyclic fused cyclopentenone derivatives from (1,6)/(1,7) with good to excellent yields. It provides spirocycles that are of increasing interest to the pharmaceutical industry. These kinds of low molecular weight small molecule libraries will be used in drugdiscovery, including those relying on fragment-based drug discovery (FBDD), high-throughput is screening (HTS). We believe that the developed reaction approach will find applications on relevant substrates for the synthesis of bioactive compounds.

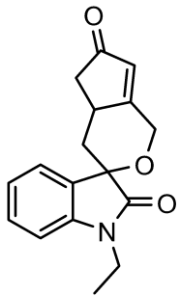
EXPERIMENTAL PROCEDURE

General Information. All the reactions were carried out in anhydrous solvents under inert atmosphere. ^{1}H NMR spectra were measured on 300 MHz, 400 MHz and 500 MHz spectrometers. Thin-layer chromatography (TLC) was performed using silica gelplates. The products were purifiedby short column chromatography on silica gel 60-120 or 100−200 mesh. Commercially available $Zn(OAc)_2$and I_2 were used without furtherpurification.

General Procedure for Intramolecular cyclization Reaction: Preparation of Spirocyclic Fused Cyclopentenones 6a–q (Table 2 and Table 3).

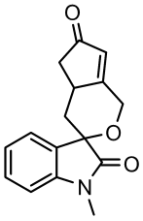


To a stirred solution of aryl iodide (1.0 mmol), secondary amine (1.5 mmol) in 1,4- dioxane (5 mL) in a dry steel bomb, Zn(OAc)2 (10 mol%) and DBU (3.0 mmol) were added. The resulting mixture was then sealed and stirred at 100 C for 16 h under 20 bar CO pressure. The progress of the reaction was monitored using TLC and LC-MS and after completion, reaction mixture was then cooled to rt. The excess solvent was



***1'-ethyl-4a,5-dihydro-1H-spiro[cyclopenta[c]pyran-3,3'-indoline]-2',6(4H)-dione (6a)*:** R*f* = 0.3 (petroleumether/ethylacetate,7:3);offwhitesolid(152mg,86%),mp142−144°C;IR(KBr)3065,2932, 2821, 1709, 1622, 1491, 1469, 1334, 1190, 1065, 1010, 741, 691 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3)δ1.29(t,*J*=7.2Hz,3H),1.91-2.08(m,2H),2.23(dd,*J*1=13.7Hz,*J*2=5.9Hz,1H),2.68 (dd,*J*1=18.7Hz,*J*2=6.6Hz,1H),3.74(q,*J*=7.2Hz,2H),

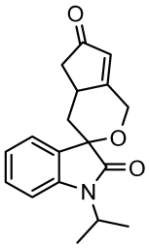
3.91-4.02(m,1H),4.64(d,*J*=13.6Hz, 1H),5.40(d,*J*=13.6Hz,1H),6.08(s,1H),6.85(d,*J*=7.8Hz,1H),7.09(td,*J*1=7.6Hz,*J*2=0.8 Hz,1H),7.24-7.38(m,2H);^{13}CNMR(100MHz,CDCl3)δ12.5,33.6,34.3,39.6,41.7,62.7,75.3, 108.6,123.1,123.7,127.7,129.1,130.1,141.9,174.7,175.2,207.5;HRMScalcdforC18H18NO3 284.1287 $[M + H]^{+}$, found 284.1289.



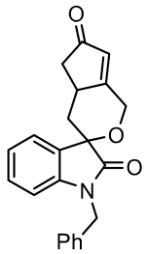
***1'-methyl-4a,5-dihydro-1H-spiro[cyclopenta[c]pyran-3,3'-indoline]-2',6(4H)-dione (6b)*:** R*f* = 0.3 (petroleumether/ethylacetate,7:3);offwhitesolid(110mg,84%),mp125−127°C;IR(KBr)3059,2927, 2823, 1710, 1618, 1487, 1470, 1342, 1181, 1052, 1012, 778, 686 cm^{-1}; ^{1}H NMR (500 MHz, CDCl3)δ1.88-2.10(m,2H),2.16-

2.29(m,1H),2.68(d,*J*=18.0Hz,1H),3.20(s,3H),3.97(brs,1H),4.64(d,*J*=12.9Hz,1H),5.40(d,*J*1=12.8Hz,1H),6.08 (s,1H),6.74-6.92(m,1H),7.03-7.17(m,1H),7.19-

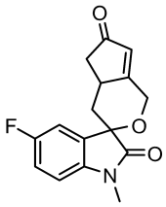
7.44(m,3H);^{13}CNMR(100MHz,CDCl3)δ25.8,33.6,39.6,41.8,62.8,75.5,108.5,123.3, 123.5, 127.8, 128.9, 130.2, 142.9, 175.0, 175.1, 207.1; HRMS calcd for C16H16NO3 270.1130 $[M + H]^{+}$, found 270.1133.



***1'-isopropyl-4a,5-dihydro-1H-spiro[cyclopenta[c]pyran-3,3'-indoline]-2',6(4H)-dione (6c)*:** R*f* = 0.3 (petroleumether/ethylacetate,7:3);offwhitesolid(101mg,86%),mp142−144°C;IR(KBr)3064, 2923, 2852, 1709, 1630, 1608, 1481, 1430, 1350, 1276, 1179, 1080, 698 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3) δ 1.50 (dd, *J*1 = 7.1 Hz, *J*2 = 0.9 Hz, 6H), 1.88-1.98 (m, 1H), 2.02 (dd, *J*1 = 18.7 Hz, *J*2 = 2.8 Hz,1H),2.21(dd,*J*1=18.7Hz,*J*2=5.8Hz,1H),2.68(dd,*J*1=18.7Hz,*J*2=6.6Hz,1H),3.91-4.03 (m, 1H), 4.52-4.68 (m, 2H), 5.41 (d, *J* = 13.6 Hz, 1H), 6.08 (s, 1H), 6.99 (d, *J* = 7.8 Hz, 1H), 7.07(td, *J*1=7.5Hz,*J*2=0.7Hz,1H),7.24-7.34(m,2H);^{13}CNMR(100MHz,CDCl3)δ19.2,19.4,33.6, 39.8, 41.8, 43.5, 62.8, 75.0, 110.2, 122.7, 123.8, 127.7, 129.5, 129.9, 141.6, 174.9, 175.3, 207.5; HRMS calcd for C18H19NO3Na 320.1263 $[M + Na]^{+}$, found 320.1282.

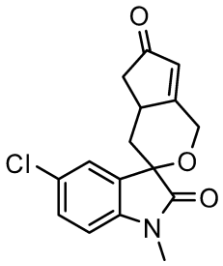


***1'-benzyl-4a,5-dihydro-1H-spiro[cyclopenta[c]pyran-3,3'-indoline]-2',6(4H)-dione (6d)*:** R*f* = 0.3 (petroleumether/ethylacetate,7:3);offwhitesolid(85mg,85%),mp125−127°C;IR(KBr)3060,2921, 2854, 1708, 1613, 1490, 1467, 1360, 1176, 1074, 1004, 750, 698 cm^{-1}; ^{1}H NMR (500 MHz, CDCl3) δ 1.96-2.09 (m, 2H), 2.29 (dd, *J*1 = 13.7 Hz, *J*2 = 5.8 Hz, 1H), 2.71 (dd, *J*1 = 18.6 Hz, *J*2 = 6.4 Hz, 1H), 3.96-4.06 (m, 1H), 4.69 (d, *J* = 13.6 Hz, 1H), 4.84 (d, *J* = 15.7 Hz, 1H), 4.94 (d, *J* = 15.7Hz,1H), 5.44 (d, *J* = 13.7 Hz, 1H), 6.10 (s, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 7.06 (td, *J*1 = 7.6 Hz, *J*2 = 0.8Hz, 1H), 7.18-7.38 (m, 7H); ^{13}C NMR (75 MHz, CDCl3) δ 33.5, 39.6, 41.7, 43.2, 62.7, 75.4, 109.4,123.2, 123.5, 126.9, 127.6, 128.6, 128.8, 128.9, 129.9, 135.2, 141.9, 174.9, 175.1, 207.3; HRMS calcdfor C22H20NO3 346.1443 $[M + H]^{+}$, found 346.1444.

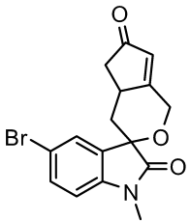


***5'-fluoro-1'-methyl-4a,5-dihydro-1H-spiro[cyclopenta[c]pyran-3,3'-indoline]-2',6(4H)-dione (6e)*:** R*f* = 0.3 (petroleum ether/ethyl acetate, 7:3); off white solid (60 mg, 75%), mp 150−152 °C; IR (KBr) 3069,2924,2857,1711,1625,1498,1465,1363,1276,1133,1099,1009,820,698cm^{-1};^{1}HNMR (400 MHz, CDCl3) δ 1.87-2.09 (m, 2H), 2.23 (dd, *J*1 = 13.6 Hz, *J*2 = 5.7 Hz, 1H), 2.68 (dd, *J*1 = 18.7 Hz,*J*2=6.6Hz,1H),3.19(s,3H),3.86-4.03(m,1H),4.65(d,*J*=13.6Hz,1H),5.39(d,*J*=13.7Hz, 1H),6.09(s,1H),6.72-

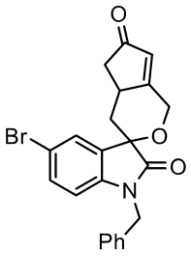
6.81(m,1H),7.00-7.09(m,2H);^{13}CNMR(125MHz,CDCl3)δ26.0,33.5, 39.6,41.7,62.9,75.5,109.1(d,*JC-F* =7.3Hz),111.9(d,*JC-F* =24.5Hz),116.4(d,*JC-F* =23.6Hz), 127.9, 130.5 (d, *JC-F* = 7.3 Hz), 138.8, 159.5 (d, *JC-F* = 242.5 Hz), 174.5, 174.9, 207.2; HRMS calcd for C16H14FNO3Na 310.0855 [M + Na]$^+$, found310.0831.



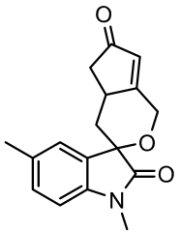
***5'-chloro-1'-methyl-4a,5-dihydro-1H-spiro[cyclopenta[c]pyran-3,3'-indoline]-2',6(4H)-dione (6f)*:** R*f* = 0.3 (petroleum ether/ethyl acetate, 7:3); off white solid (76 mg, 77%), mp 180−182 °C; IR (KBr) 3062,2923,2854,1709,1629,1611,1492,1461,1361,1252,1140,1103,1010,826cm^{-1};^{1}HNMR (400 MHz, CDCl3) δ 1.89-1.98 (m, 1H), 2.03 (dd, *J*1 = 18.7 Hz, *J*2 = 2.8 Hz, 1H), 2.23 (dd, *J*1 = 13.7 Hz, *J*2 = 5.7 Hz, 1H), 2.68 (dd, *J*1 = 18.7 Hz, *J*2 = 6.6 Hz, 1H), 3.19 (s, 3H), 3.89-4.00 (m, 1H), 4.65(d, *J* = 13.7 Hz, 1H), 5.37 (d, *J* = 13.6 Hz, 1H), 6.09 (s, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 7.25-7.28 (m, 1H), 7.32(dd,*J*1=8.3Hz,*J*2=2.0Hz,1H);^{13}CNMR(125MHz,CDCl3)δ25.9,33.4,39.5,41.7,62.9, 75.4, 109.5, 124.3, 127.9, 128.8, 130.0, 130.5, 141.5, 174.4, 174.7, 207.1;HRMS calcd for C16H15NO3Cl 304.0740 [M + H]$^+$, found 304.0742.



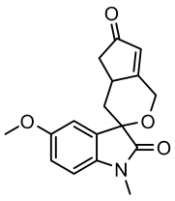
***5'-bromo-1'-methyl-4a,5-dihydro-1H-spiro[cyclopenta[c]pyran-3,3'-indoline]-2',6(4H)-dione (6g)*:** R*f* = 0.3 (petroleum ether/ethyl acetate, 7:3); off white solid (84 mg, 79%), mp 175−177 °C; IR (KBr) 3059,2924,2854,1714,1628,1609,1490,1462,1359,1274,1140,1102,1010,824cm^{-1};^{1}HNMR(400 MHz, CDCl3) δ 1.88-2.08 (m, 2H), 2.23 (dd, *J*1 = 13.7 Hz, *J*2 = 5.7 Hz, 1H), 2.68 (dd, *J*1 = 18.7 Hz,*J*2=6.5Hz,1H),3.18(s,3H),3.87-3.99(m,1H),4.64(d,*J*=13.7Hz,1H),5.37(d,*J*=13.6Hz, 1H), 6.08 (s, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 7.40 (d, *J* = 2.0 Hz, 1H), 7.47 (dd, *J1* = 8.2 Hz, *J2* = 2.0Hz, 1H);^{13}CNMR(125MHz,CDCl3)δ25.9,33.4,39.5,41.7,62.9,75.4,109.9,115.9,127.1,127.9, 130.8,132.9,141.9,174.4,174.6,207.1;HRMScalcdforC16H15NO3Br348.0235[M+H]$^+$,found 348.0240



***1'-benzyl-5'-bromo-4a,5-dihydro-1H-spiro[cyclopenta[c]pyran-3,3'-indoline]-2',6(4H)-dione (6h)*:** R*f* = 0.3 (petroleum ether/ethyl acetate, 7:3); off white solid (89 mg, 80%), mp 186−188 °C; IR (KBr) 3063,2923,2853,1712,1631,1607,1483,1429,1349,1275,1176,1074,1004,734,cm^{-1};^{1}HNMR(400 MHz, CDCl3) δ 1.92-2.12 (m, 2H), 2.29 (dd, *J*1 = 13.6 Hz, *J*2 = 5.5 Hz, 1H), 2.71 (dd, *J*1 = 18.6 Hz,*J*2=6.4Hz,1H),3.90-4.05(m,1H),4.68(d,*J*=13.6Hz,1H),4.78-4.97(m,2H),5.42(d,*J*= 13.5Hz,1H),6.10(s,1H),6.56(d,*J*=8.2Hz,1H),7.16-7.46(m,7H);^{13}CNMR(100MHz,CDCl3) δ33.5,39.7,41.7,43.4,62.9,75.4,111.0,116.0,127.0,127.1,127.9,128.0,128.9,130.9,132.9, 134.8, 141.0, 174.3, 174.7, 207.1; HRMS calcd for $C_{22}H_{18}BrNO_3Na$ 446.0368 $[M + Na]^+$,found:446.0360

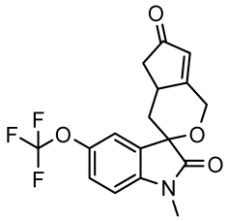


***1',5'-dimethyl-4a,5-dihydro-1H-spiro[cyclopenta[c]pyran-3,3'-indoline]-2',6(4H)-dione (6i)*:**R*f*=0.3(petroleum ether/ethyl acetate, 7:3); off white solid (78 mg, 86%), mp 147−149 °C; IR (KBr) 3055, 2921, 2849, 1718, 1627, 1611, 1495, 1461, 1362, 1264, 1139, 1108, 1019, 841 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3) δ 1.90-2.09 (m, 2H), 2.23 (dd, *J*1 = 13.6 Hz, *J*2 = 5.6 Hz, 1H), 2.33 (s, 3H), 2.68 (dd, *J*1 = 18.7 Hz, *J*2 = 6.5 Hz, 1H), 3.19 (s, 3H), 3.91-4.05 (m, 1H), 4.64 (d, *J* = 13.6 Hz, 1H), 5.40 (d,*J* = 13.6 Hz, 1H), 6.08 (s, 1H), 6.73 (d, *J* = 7.9 Hz, 1H), 7.06-7.20 (m, 2H); ^{13}C NMR (100 MHz,CDCl3) δ 20.9, 25.9, 33.7, 39.7, 41.8, 62.8, 75.5, 108.2, 124.3, 127.7, 128.9, 130.4, 133.0, 140.5, 175.1, 175.2, 207.5; HRMS calcd for C17H18NO3 284.1281 $[M + H]^+$, found284.1288.

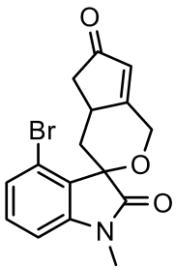


***5'-methoxy-1'-methyl-4a,5-dihydro-1H-spiro[cyclopenta[c]pyran-3,3'-indoline]-2',6(4H)-dione (6j)*:** R*f* = 0.3 (petroleum ether/ethyl acetate, 7:3); off white solid (70 mg, 85%), mp 165−167 °C; IR (KBr) 3058,2929,2848,1715,1631,1602,1489,1451,1342,1262,1137,1112,1009,832cm^{-1};^{1}HNMR(500 MHz, CDCl3) δ 1.89-2.06 (m, 2H), 2.23 (dd, *J*1 = 13.6 Hz, *J*2 = 5.6 Hz, 1H), 2.68 (dd, *J*1 = 18.8 Hz,*J*2=6.6Hz,1H),3.18(s,3H),3.79(s,3H),3.92-4.02(m,1H),4.65(d,*J*=13.6Hz,1H),5.41(d, *J*=13.6Hz,1H),6.08(s,1H),6.74(d,*J*=8.4Hz,1H),6.83-6.91(m,2H);^{13}CNMR(100MHz,

CDCl3)δ25.9,33.6,39.8,41.8,55.9,62.9,75.9,109.0,110.5,114.9,127.7,130.0,136.2,156.6,174.9, 175.0, 207.4; HRMS calcd for C17H18NO4 300.1230 $[M + H]^+$, found 300.1237

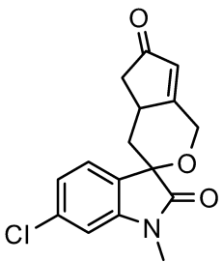


1'-methyl-5'-(trifluoromethoxy)-4a,5-dihydro-1H-spiro[cyclopenta[c]pyran-3,3'-indoline]-2',6(4H)-dione(6k) **:**R*f*=0.3(petroleumether/ethylacetate,7:3);offwhitesolid(74mg,88%),mp178−180 °C; IR (KBr) 3068, 2931, 2849, 1715, 1621, 1611, 1489, 1452, 1357, 1266, 1138, 1106, 1009, 829 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3) δ 1.86-2.08 (m, 2H), 2.23 (dd, *J*1 = 13.6 Hz, *J*2 = 5.6 Hz, 1H), 2.66 (dd, *J*1 = 18.7 Hz, *J*2 = 6.5 Hz, 1H), 3.19 (s, 3H), 3.86-4.00 (m, 1H), 4.64 (d, *J* = 13.6 Hz, 1H), 5.36(d, *J*=13.6Hz,1H),6.07(s,1H),6.81(d,*J*=8.4Hz,1H),7.13-7.24(m,2H);^{13}CNMR(100MHz, CDCl3)δ25.9,33.3,39.4,41.6,62.8,75.3,108.9,117.7,120.3(q,*JC-F*=256.8Hz),123.2,127.9, 130.4,141.5,145.1,174.2,174.9,207.0;HRMScalcdforC17H15F3NO4 354.0947$[M+H]^+$,found 354.**095**9.

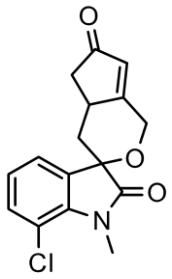


4'-bromo-1'-methyl-4a,5-dihydro-1H-spiro[cyclopenta[c]pyran-3,3'-indoline]-2',6(4H)-dione (6l)**:** R*f* = 0.3 (petroleum ether/ethyl acetate, 7:3); off white solid (66 mg, 78%), mp 169−171 °C; IR (KBr) 3058,2926,2849,1712,1629,1607,1489,1458,1354,1265,1136,1106,1019,836cm^{-1};^{1}HNMR (400 MHz, CDCl3) δ 2.01-2.14 (m, 2H), 2.63-2.76 (m, 2H),

3.18 (s, 3H), 3.92-4.03 (m, 1H), 4.73 (d,*J* =13.6Hz,1H),5.40(d,*J*=13.6Hz,1H),6.09(s,1H),6.77(dd,*J1*=6.6Hz,*J2*=2.1Hz,1H),7.15-7.23(m,2H);^{13}CNMR(125MHz,CDCl3)δ25.9,32.9,35.4,41.8,62.7,76.9,107.8,119.4,126.4, 127.7,127.8,131.3,144.9,174.7(2C),207.5;HRMScalcdforC16H15NO3Br348.0235$[M+H]^+$, found 348.0233.

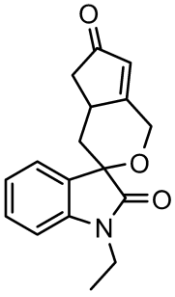


***6'-chloro-1'-methyl-4a,5-dihydro-1H-spiro[cyclopenta[c]pyran-3,3'-indoline]-2',6(4H)-dione (6m)*:** R*f* = 0.3 (petroleum ether/ethyl acetate, 7:3); off white solid (78 mg, 75%), mp 179−181 °C; IR (KBr) 3062,2931,2856,1711,1619,1612,1481,1428,1362,1282,1134,1112,1018,837cm^{-1};^{1}HNMR (500 MHz, CDCl3) δ 1.89-1.98 (m, 1H), 2.03 (dd, *J1* = 18.8 Hz, *J2* = 2.7 Hz, 1H), 2.21 (dd, *J1* = 13.7 Hz, *J2* = 5.8 Hz, 1H), 2.68 (dd, *J1* = 18.6 Hz, *J2* = 6.6 Hz, 1H), 3.18 (s, 3H), 3.89-3.99 (m, 1H), 4.64(d, *J*=13.7Hz,1H),5.36(d,*J*=13.6Hz,1H),6.08(s,1H),6.84(d,*J*=1.8Hz,1H),7.07(dd,*J1*=7.9 Hz,*J2*=1.8Hz,1H),7.19(d,*J*=7.8Hz,1H);^{13}CNMR(125MHz,CDCl3)δ25.9,33.5,39.5,41.7, 62.8, 75.1, 109.3, 123.1, 124.6, 127.3, 127.9, 136.1, 144.2, 174.5, 174.9, 207.2; HRMS calcd for C16H15NO3Cl 304.0740 [M + H]$^{+}$, found 304.0739



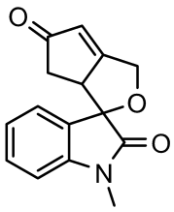
***7'-chloro-1'-methyl-4a,5-dihydro-1H-spiro[cyclopenta[c]pyran-3,3'-indoline]-2',6(4H)-dione (6n)*:** R*f* = 0.3 (petroleum ether/ethyl acetate, 7:3); off white solid (72 mg, 79%), mp 176−178 °C; IR (KBr) 3065,2926,2851,1709,1619,1601,1488,1456,1345,1268,1139,1101,1011,832cm^{-1};^{1}HNMR (500 MHz, CDCl3) δ 1.86-1.94 (m, 1H), 2.02 (dd, *J1* = 18.8 Hz, *J2* = 2.7 Hz, 1H), 2.21 (dd, *J1* = 13.6 Hz, *J2* = 5.6 Hz, 1H), 2.68 (dd, *J1* = 18.8 Hz, *J2* = 6.6 Hz, 1H), 3.56 (s, 3H), 3.89-3.98 (m, 1H), 4.64(d, *J* = 13.7 Hz, 1H), 5.36 (d, *J* = 13.7 Hz,

1H), 6.08 (s, 1H), 7.01 (dd, *J1* = 8.1 Hz, *J2* = 7.5 Hz, 1H), 7.16 (dd, *J1* = 7.5 Hz, *J2* = 1.2 Hz, 1H), 7.27 (dd, *J1* = 8.1 Hz, *J2* = 1.1 Hz, 1H); ^{13}C NMR (100 MHz, CDCl3)δ29.2,33.5,39.7,41.7,62.8,74.8,115.8,122.2,124.1,127.9,131.7,132.4,138.8,174.6, 175.3, 207.2; HRMS calcd for C16H15NO3Cl 304.0740 [M + H]$^{+}$, found 304.0739.

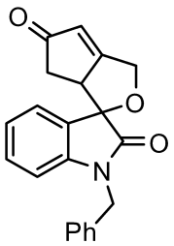


***1'-ethyl-6,6a-dihydrospiro[cyclopenta[c]furan-1,3'-indoline]-2',5(3H)-dione*:** R*f* = 0.3 (petroleumether/ethylacetate,7:3);offwhitesolid(20mg,74%),mp128−130°C;IR(KBr)3066, 2935, 2864, 1709, 1628, 1611, 1492, 1428, 1343, 1277, 1172, 1078, 1008, 733 cm^{-1}; ^{1}H NMR (500 MHz, CDCl3) δ 1.24 (t, *J* = 7.2 Hz, 3H), 2.05 (dd, *J*1 = 16.9 Hz, *J*2 = 4.0 Hz, 1H), 2.44 (dd, *J*1 = 17.4 Hz, *J*2 = 6.6 Hz, 1H), 3.57-3.78 (m, 3H), 5.03 (d, *J* = 15.6 Hz, 1H), 5.12 (d, *J* = 15.6 Hz, 1H), 6.23(s, 1H),6.86(d,*J*=7.8Hz,1H),7.13(t,*J*=7.5Hz,1H),7.37(t,*J*=7.8Hz,1H),7.42(d,*J*=7.0Hz,

1H);^{13}CNMR(100MHz,CDCl3)δ12.7,34.5,37.8,52.9,66.9,83.1,108.8,123.1,123.9,125.4, 126.2,130.6,143.2,173.5,181.2,207.6;HRMScalcdforC16H15NO3Na292.0950[M+Na]$^{+}$,found 292.0925.



***1'-methyl-6,6a-dihydrospiro[cyclopenta[c]furan-1,3'-indoline]-2',5(3H)-dione (6p)*:** R*f* = 0.3 (petroleumether/ethylacetate,7:3);offwhitesolid(17mg,80%),mp123−125°C;IR(KBr)3049, 2929, 2871, 1711, 1630, 1606, 1481, 1429, 1348, 1262, 1169, 1078, 1009, 728 cm^{-1}; ^{1}H NMR (500 MHz, CDCl3) δ 2.07 (dd, *J*1 = 17.5 Hz, *J*2 = 4.3 Hz, 1H), 2.44 (dd, *J*1 = 17.4 Hz, *J*2 = 6.6 Hz, 1H), 3.14 (s, 3H), 3.64-3.71 (m, 1H), 5.00-5.15 (m, 2H), 6.20-6.27 (m, 1H), 6.84 (d, *J* = 7.9 Hz, 1H), 7.14 (td,*J*1 =7.6Hz,*J*2=0.9Hz,1H),7.35-7.45(m,2H);^{13}CNMR(100MHz,CDCl3)δ25.9,37.8,52.7,66.9, 83.1, 108.7, 123.3, 123.8, 125.5, 125.9, 130.7, 144.2, 173.9, 181.1, 207.6; HRMS calcd for C15H13NO3Na 278.0793 [M + Na]$^{+}$, found 278.0783



***1'-benzyl-6,6a-dihydrospiro[cyclopenta[c]furan-1,3'-indoline]-2',5(3H)-dion(6q)*:**R*f*=0.3 (petroleum ether/ethyl acetate, 7:3); yellow thick liquid (23 mg, 77%); IR (neat) 3065, 2931,2862, 1707, 1632, 1608, 1489, 1430, 1350, 1278, 1179, 1080, 1001, 732 cm^{-1}; ^{1}H NMR (500 MHz, CDCl3) δ2.12(dd,*J*1=17.4Hz,*J*2=4.1Hz,1H),2.48(dd,*J*1=17.4Hz,*J*2=6.6Hz,1H),3.66-3.74(m,1H), 4.69(d,*J*=15.6Hz,1H),4.95(d,*J*=15.6Hz,1H),5.03-5.21(m,2H),6.23-6.28(m,1H),6.74(d,*J* = 7.9 Hz, 1H), 7.11 (td, *J*1 = 7.5 Hz, *J*2 = 0.8 Hz, 1H), 7.23-7.36 (m, 6H), 7.42 (dd, *J*1 = 7.3 Hz, *J*2 = 0.8 Hz,1H);^{13}CNMR(125MHz,CDCl3)δ37.9,43.6,52.9,67.0,83.1,109.7,123.3,123.9,125.5, 126.0,127.2,127.8,128.9,130.6,135.2,143.4,173.9,181.2,207.6;HRMScalcdforC21H17NO3Na 354.1106 [M + Na]$^{+}$, found 354.1087

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