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An efficient strategy for functionalized spirolactones and dispirodihydrofuranyl oxindoles using amines and activated alkynes

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ABSTRACT

A facile strategy for the synthesis of functionalized spirolactones from isatin, primary amines, and activated alkynes through Huisgen dipolar additions are discussed. A novel route for the formation of dispirodihydrofuranyl oxindoles from activated cyclic electrophiles, amines, and DMAD has also been developed. This method offers several advantages like high yield, readily available starting materials, and involves less hazardous chemical techniques.

Carbon–carbon and carbon–heteroatom bond-forming reactions play a vital role in organic synthesis. Polar reactions utilizing a variety of reactive intermediates in such bond-forming reactions are well known. Several methods are available for heterocyclic constructions of which trapping of zwitterionic species by suitable π-systems leading to five membered heterocycles occupies a prime position, chiefly attributable to the contributions of Huisgen.[1] A number of multi-component reactions involving nitrogen heterocycles, acetylenic esters, and electrophiles for the synthesis of spiro compounds have been reported.[2] In such multi-component reactions replacing nucleophiles derived from nitrogen heterocycles by several other nucleophiles like isocyanides, primary amines provide clean procedures for the synthesis of polysubstituted spirocycles.[3]

The development of efficient methods to construct spiro compounds has been a topic of great relevance in organic synthesis due to their pronounced biological activities. Spirooxindole cores form an important constituent in many natural and synthetic biologically active compounds, as well as in many drug molecules.[1c,4–6] Such diverse spirocyclic oxindoles are characterized by a spiro ring fusion at the C3 position of the oxindole core with varied heterocyclic motifs (Fig. 1).[7] Thus fusion of oxindole motifs with different heterocycles seeks the attention of many organic chemists in virtue of its biological response as they incorporate both oxindole and other heterocyclic moieties within a single framework.[8] Spiro compounds, especially spirolactone derivatives have been reported as anti-convulsants and antitumorals.[9] Dispiro oxindole compounds may provide promising candidates for

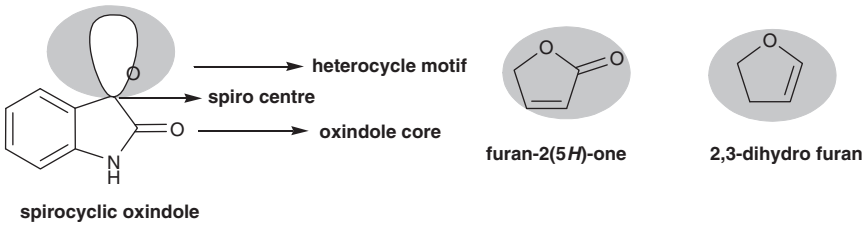

Figure 1. Illustrative representation of spiro oxindole incorporated with a heterocyclic motif at C3.

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Table 1
Screening of solvents and base catalysts for the synthesis of **4a**

Entry	Solvent	Base catalyst[a]	Time (hrs)	Yield[b] (%)
1	MeOH	-	24	35
2	MeOH	DBU	7	50
3	EtOH	DBU	24	58
4	MeOH	$NaHCO_3$	10	50
5	DMF	K_2CO_3	2.5	50
6	DCM	NEt_3	4	60
7	THF	NEt_3	8	66
8	**MeOH**	**NEt_3**	**4**	**85[c]**
9	DMF	DBU	10	20
10	MeOH	K_2CO_3	3	60

[a] All the reactions were performed using 20 mol% of base catalyst.
[b] Isolated yield after column chromatography
[c] Isolated yield after recrystallization.

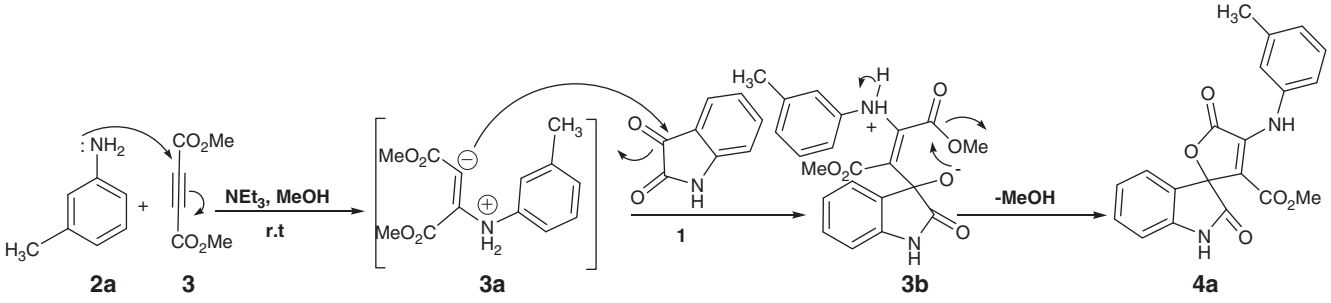
chemical biology and drug discovery, due to the fact that some spirocyclic bisindoles have recently been reported as potent scaffolds possessing anticancer activity.[10]

We recently reported the synthesis of spirooxindoles by Huisgen dipolar addition of zwitterions generated from primary amines and DMAD to isatylidene malononitrile adducts.[11] As a view to probe the generality of the course of the reaction, we were interested in the synthesis of spirooxindoles from such zwitterionic intermediates and isatin. Hence, our present investigation deals with the reactions of isatin, primary amines, and DMAD to synthesize functionalized spirolactones and dispirodihydrofuranyl oxindoles. It is also noteworthy to mention that this is the first report on the synthesis of dispirodihydrofuranyl oxindoles from cyclic electrophiles, primary amines, and DMAD.

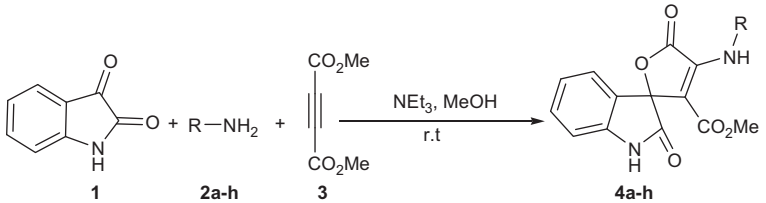
In an exploratory experiment isatin **1** (1 mmol), *m*-toluidine **2a** (1 mmol) and DMAD **3** (1 mmol) were stirred at room temperature till the completion of the reaction as evidenced by TLC to afford the product **4a**. The reaction was screened under the presence of various catalysts and solvent systems (Table 1). The study revealed that the reaction proceeded to completion and also provided the highest yield (85%) in the presence of 20 mol% of NEt_3 in methanol (Table 1, entry 8).

A plausible mechanism that could be accounted for the three-component reaction is given in Scheme 1. Initially *m*-toluidine **2a** adds on to DMAD **3** to provide the zwitterionic intermediate **3a** which adds on to isatin **1** to form **3b** and the latter undergoes intramolecular addition with concomitant MeOH elimination to give the spiro lactone **4a** (Scheme 1).

To expand the scope of our process, we examined the use of various other derivatives of amines to synthesize a series of spiro lactones **4a–h** under optimized conditions (Scheme 2).



Scheme 1. Plausible mechanism for the formation of **4a**.



Scheme 2. Synthesis of spirolactone derivatives **4a–h**.

Table 2
Synthesis of spirolactone derivatives **4a–h**

Entry	R	Product	Time[a]	Yield[b] (%)
1	3-$CH_3C_6H_4$	**4a**	4	85
2	C_6H_5	**4b**	4.5	83
3	4-$OCH_3C_6H_4$	**4c**	4	82
4	2,5-$(C(CH_3)_3)_2C_6H_3$	**4d**	5	80
5	4-NO_2-C_6H_4	**4e**	10	76
6	2,4-$(CH_3)_2C_6H_3$	**4f**	5	78
7	4-BrC_6H_4	**4g**	5	79
8	4-ClC_6H_4	**4h**	9	70

[a] Completion of the reaction in hrs.
[b] Isolated yield after recrystallization.

The reaction proceeded smoothly with aromatic primary amines possessing both electron withdrawing as well as electron releasing groups (Table 2) to produce spirolactone derivatives **4a–h** in good yields (70–85%). The results are summarized in Table 2.

The structures of compounds **4a–h** were consistent with IR, ^{1}H, ^{13}C NMR, mass spectroscopy, and elemental analysis data.[12,13] The IR spectrum of **4a** exhibited peaks at 1787, 1712, and 1631 cm^{-1} for the lactone ester, CO_2Me, and amide groups respectively. The ^{1}H NMR spectrum of **4a** showed two sharp singlets at δ 9.23 and 10.95 ppm for the –N*H* protons (D_2O exchangeable) of the amine and the oxindole rings respectively, clearly indicating the incorporation of both the moieties in the product. In ^{13}C NMR spectroscopy, the spiro carbon atom displayed a signal at δ 83.5 ppm and the lactone carbonyl carbon and ester carbonyl carbon atoms resonated at δ 162.1 and 167.7 ppm respectively.

To explore the synthetic utility of the spirolactones the latter was allowed to react with several other activated electrophiles like isatin. Spirolactone **4a** (1 mmol), and isatin **1** (1 mmol) were refluxed in methanol in the presence of NEt_3 as a base catalyst to the completion of the reaction. The reaction mixture was purified by column chromatography to afford the product as two distinct diastereomers (**5a** and **5′a**) in moderate yield[14] (Scheme 3).

The ^{1}H NMR spectrum of **5a** exhibited three singlets at δ 9.30, 10.23, and 10.39 ppm indicating the presence of three –N*H* protons (D_2O exchangeable) for the amine and the two oxindole rings, respectively. In ^{13}C NMR spectroscopy, signal for only one ester carbonyl carbon atom was observed which resonated at δ 165.3 ppm. The amide carbonyl carbon atoms resonated at δ 173.7 and 174.6 ppm. The absence of the lactone ring carbonyl carbon atom marked the cleavage of the lactone ring and the presence of two amide carbonyl carbon atoms suggested the formation of a bisoxindole product. The mass spectrum also exhibited a distinguishing peak at *m*/*z* 468.00. A similar spectrum was exhibited by **5′a**.[15,16] The structure and relative stereochemistry of the two diastereomers were further firmly established by single crystal

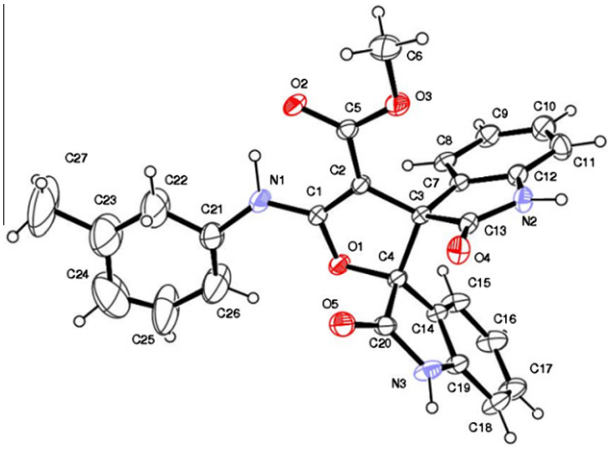


Figure 2. ORTEP diagram of dispirodihydrofuranyl bisoxindole **5a**.

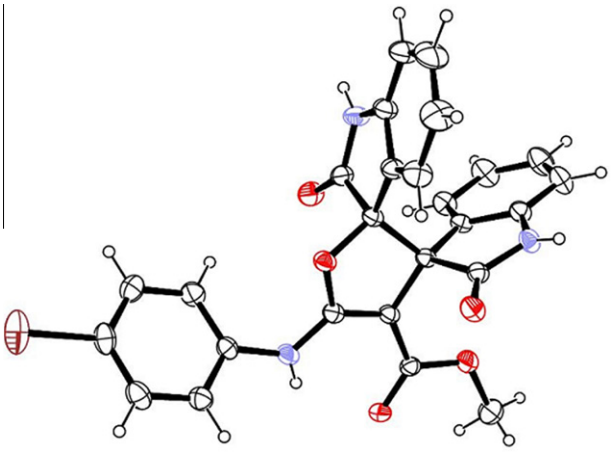
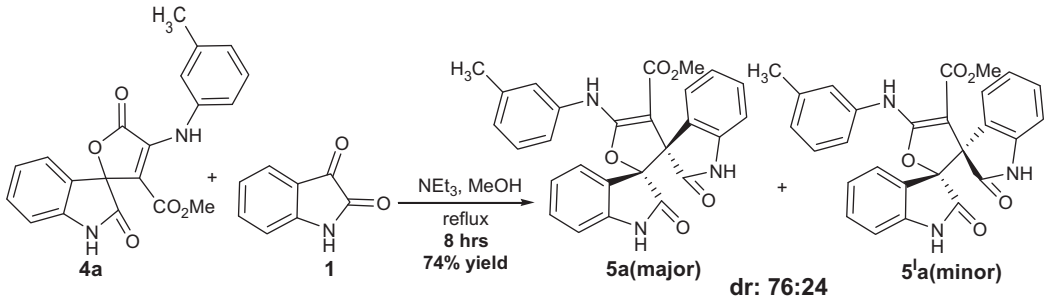


Figure 3. ORTEP diagram of dispirodihydrofuranyl bisoxindole **5′g**.

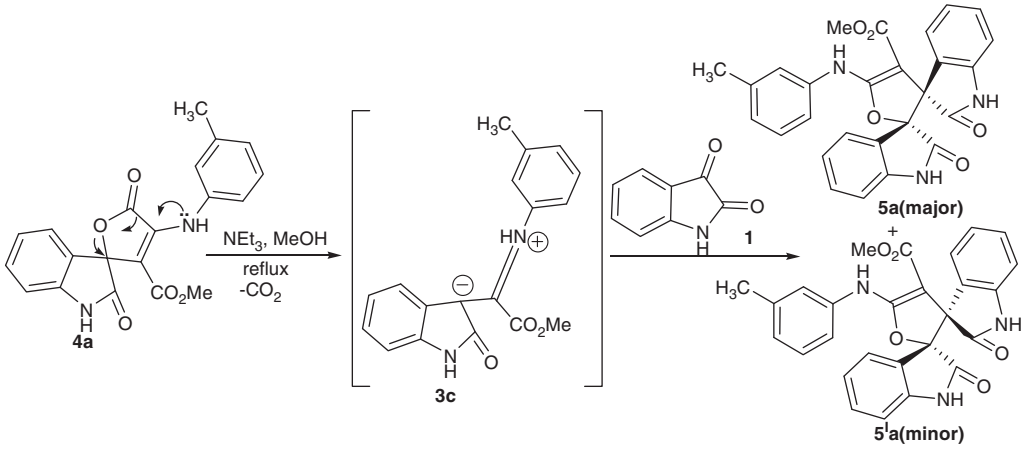
Table 3
Studies on spirolactone **4a** under various conditions

Entry	Substrates	Conditions[a]	Product
1	**1** + **2a** + **3** (1:1:1)	rt	**4a**
2	**4a**	Reflux	Untractable mixture
3	**1** + **2a** + **3** (1:1:1)	Reflux	Untractable mixture
4	**4a** + **1**	rt	No reaction
5	**4a** + **1**	Reflux	**5a** (major) + **5′a** (minor)
6	**1** + **2a** + **3** (2:1:1)	rt	**4a** + unreacted **1**
7	**1** + **2a** + **3** (2:1:1)	Reflux	**5a** (major) + **5′a** (minor)

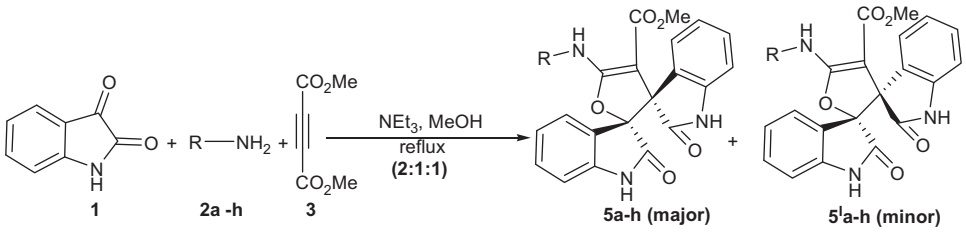
[a] All the reactions were carried out using NEt_3 (20 mol%) as base catalyst and methanol as solvent



Scheme 3. Synthesis of dispirodihydrofuranyl bisoxindole **5a** and **5′a**.



Scheme 4. Tentative mechanistic approach for the formation of dispirodihydrofurans **5a** and **5′a**.



Scheme 5. Synthesis of dispirodihydrofuranyl bisoxindole derivatives **5a–h** and **5′a–h**.

X-ray analysis performed for representative compounds **5a** and **5′g** (Figs. 2 and 3).[17,18]

In order to propose a suitable mechanism for the formation of diastereomeric dispirodihydrofuranyl bisoxindoles (**5a** and **5′a)** the reaction parameters such as temperature and stoichiometric quantities of the starting materials were varied. The observations are tabulated in Table 3.

Hence with the preceding results in hand a tentative mechanism could be proposed (Scheme 4). At reflux condition, the reaction proceeds further in the presence of isatin **1** (1 mmol) to provide a mixture of diastereomers. The lone pair of nitrogen may assist cleavage of the lactone **4a** followed by decarboxylation to give **3c**, and the latter undergoes addition to isatin **1** to give a mixture of two diastereomers **5a** and **5′a**.

Moreover the one pot reaction of isatin **1** (2 mmol), *m*-toluidine **2a** (1 mmol), and DMAD **3** (1 mmol) under reflux also afforded **5a** and **5′a** (Table 3, entry 7)[19] and this path was found to be more efficient in terms of yield, time, and diastereoselectivity compared to the reaction of spirolactone **4a** and isatin **1** (Table 3, entry 5). The reaction was extended to synthesize other derivatives of dispirodihydrofuranyl bisoxindoles (Scheme 5).

Interestingly, the reaction proceeds smoothly with other aromatic amines to provide dispirodihydrofuranyl bisoxindoles in good yields (75–85%). The results for the synthesis of dispirodihydrofuranyl bisoxindoles **5a–h** and **5′a–h** are summarized in Table 4.

With the optimized conditions in hand, the process was extended to other electrophiles like acenaphthenequinone **6**. The reaction proceeded in a similar manner and was purified by column chromatography to provide dispirodihydrofuranyl acenaphtho oxindoles (**7a–h** and **7′a–h)** as two distinct isomers (Scheme 6).[20,21] The results are elaborated in Table 5.

In summary, a promising Huisgen dipolar addition involving isatin, amines, and DMAD to afford spirolactones was discussed. This letter also brings forth a novel strategy for the synthesis of dispirodihydrofuranyl bisoxindoles and dispirodihydrofuranyl

Table 4
Synthesis of dispirodihydrofuranyl bisoxindole derivatives

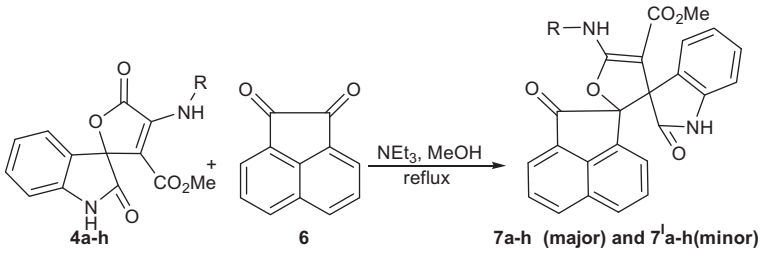
Entry	R	5	5′	Time[a]	Yield[b,c]	dr[d]
1	3-$CH_3C_6H_4$	**5a**	**5′a**	10	85	90:10
2	C_6H_5	**5b**	**5′b**	11	84	89:11
3	4-$OCH_3C_6H_4$	**5c**	**5′c**	11	80	85:15
4	2,5-$(C(CH_3)_3)_2C_6H_3$	**5d**	**5′d**	12	77	87:13
5	4-NO_2-C_6H_4	**5e**	**5′e**	24	75	81:19
6	2,4-$(CH_3)_2C_6H_3$	**5f**	**5′f**	15	79	92:8
7	4-BrC_6H_4	**5g**	**5′g**	13	80	86:14
8	4-ClC_6H_4	**5h**	**5′h**	13	81	82:18

[a] Completion of the reaction in hrs.
[b] Reaction carried out with isatin **1** (2 mmol), amines (**2a–h**) (1 mmol) and DMAD **3** (1 mmol) using 20 mol% of NEt_3 as base catalyst and methanol as solvent under reflux conditions.
[c] Isolated yield after column chromatography in %.
[d] Based on isolated yield.

Table 5
Synthesis of dispirodihydrofuranyl acenaphtho oxindole derivatives

Entry	4	7	7′	Time[a]	Yield[b]	dr[c]
1	**4a**	**7a**	**7′a**	12	82	80:20
2	**4b**	**7b**	**7′b**	13	84	81:19
3	**4c**	**7c**	**7′c**	12.5	75	85:15
4	**4d**	**7d**	**7′d**	14	77	87:13
5	**4e**	**7e**	**7′e**	24	75	79:21
6	**4f**	**7f**	**7′f**	12	79	84:16
7	**4g**	**7g**	**7′g**	20	80	83:17
8	**4h**	**7h**	**7′h**	17	78	82:18

[a] Completion of the reaction in hrs.
[b] Isolated yield after column chromatography in %.
[c] Based on isolated yield.



Scheme 6. Synthesis of dispiro dihydrofuranyl acenaphthyl oxindole derivatives **7a–h** and **7′a–h**.

acenaphtho oxindoles. The diastereomers could be separated easily by simple column chromatographic purification. The procedure features readily available starting materials and good yields. It is a very valuable new addition to the existing methods for the synthesis of functionalized spiro lactones and dispirodihydrofuranyl oxindoles.

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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.tetlet.2012.04.047.

References and notes

1. (a) Huisgen, R. *Proc. Chem. Soc.* **1961**, 357–369; (b) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley- Interscience: New York, 1984; Vol. 1, pp 1–176; c Huisgen, R. In *The Adventure Playground of Mechanisms and Novel Reactions*; American Chemical Society: Washington, DC, 1994; p 91; (d) Tzitzikas, T. Z.; Terzidis, M. A.; Stephanatou, J. S.; Tsoleridis, C. A.; Kostakis, G. E. *J. Org. Chem.* **2011**, *76*, 9008–9014.
2. (a) Nair, V.; Devipriya, S.; Suresh, E. *Tetrahedron* **2008**, *64*, 3567; (b) Nair, V.; Devipriya, S.; Suresh, E. *Tetrahedron Lett.* **2007**, *48*, 3667; (c) Yavari, I.; Mirzaei, A.; Moradi, L.; Khalili, G. *Tetrahedron Lett.* **2010**, *51*, 396; (d) Yavari, I.; Mokhtarporyani-Sanandaj, A.; Moradi, L.; Mirzaei, A. *Tetrahedron* **2008**, *64*, 5221; (e) Liu, W. B.; Jiang, H. F.; Zhang, M.; Qi, C. R. *J. Org. Chem.* **2010**, *75*, 966; (f) Cao, H.; Jiang, H. F.; Yao, W. J. *Org. Lett.* **1931**, *2009*, 11; (g) Liu, W. B.; Jiang, H. F.; Qiao, C. L. *Tetrahedron* **2009**, *65*, 2110; (h) Jing, S.; Er-Yan, X.; Qun, W.; Chao-Guo, Y. *Org Lett.* **2010**, *12*, 3678.
3. (a) Maghsoodlou, M. T.; Khorassani, S. M. H.; Moradi, A.; Hazeri, N.; Davodi, A.; Sajadikhah, S. *Tetrahedron* **2011**, *67*, 8492; (b) Azizian, J.; Karimi, A. R.; Arefrad, H.; Mohammadi, A. A.; Mohammadizadeh, M. R. *Monatsh. Chem.* **2004**, *135*, 729; (c) Esmaili, A. A.; Bodaghi, A. *Tetrahedron* **2003**, *59*, 1169.
4. (a) Nicholas, G. M.; Eckman, L. L.; Newton, G. L. *Bioorg. Med. Chem.* **2003**, *11*, 601; (b) Suenaga, K.; Araki, K.; Sengoku, T. *Org. Lett.* **2001**, *3*, 527; (c) Winfred, G. B.; Rutger, M.; Fieseler, F. *J. Org. Chem.* **2000**, *65*, 8317; (d) Patrizia, C.; Carmela, D.; Ernesto, F. *J. Nat. Prod.* **1999**, *62*, 590; (e) Metwally, K. A.; Dukat, M. *J. Med. Chem.* **1998**, *41*, 5084; (f) Barbara, C. M.; Potts, D.; John, F. *J. Am. Chem. Soc.* **1991**, *113*, 6321; (g) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003.
5. (a) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *Spirocyclic Systems in the Total Synthesis of Natural Products*; Simon, J., Ed.; John Wiley and Sons: New York, 1983; Vol. 5, p 264; (b) Sanchez-Larios, E.; Holmes, J. M.; Daschner, C. L.; Gravel, M. *Org. Lett*. **2010**, *12*, 5772–5775.
6. (a) Pandey, R. C.; Toussaint, M. W.; Stroshane, R. M.; Kalita, C. C.; Aszalos, A. A.; Garretson, A. L.; Wei, T. T.; Byrne, K. M.; Geoghegan, R. F.; White, R. J. *J. Antibiot.* **1981**, *34*, 1389–1401; (b) Goto, K.; Sudzuki, H. *Bull. Chem. Soc. Jpn.* **1929**, *4*, 220–224; (c) Tomita, M.; Okamoto, Y.; Kikuchi, T.; Osaki, K.; Nishikawa, M.; Kamiya, K.; Sasaki, Y.; Matoba, K.; Goto, K. *Tetrahedron Lett.* **1967**, *8*, 2421–2424; (d) Tomita, M.; Okamoto, Y.; Kikuchi, T.; Osaki, K.; Nishikawa, M.; Kamiya, K.; Sasaki, Y.; Matoba, K.; Goto, K. *Tetrahedron Lett.* **1967**, *8*, 2425–2430; (e) Tomita, M.; Okamoto, Y.; Kikuchi, T.; Osaki, K.; Nishikawa, M.; Kamiya, K.; Sasaki, Y.; Matoba, K.; Goto, K. *Chem. Pharm. Bull.* **1971**, *19*, 770–791.
7. Han, Y. Y.; Chen, W. B.; Han, W. Y.; Wu, Z. J.; Zhang, X. M.; Yuan, W. C. *Org. Lett.* **2012**, *14*, 490.
8. (a) Zhu, S.-L.; Ji, S.-J.; Yong, Z. *Tetrahedron* **2007**, *63*, 9365; (b) Abdel-Rahman, A. H.; Keshk, E. M.; Hanna, M. A.; El-Bady, S. M. *Bioorg. Med. Chem.* **2004**, *12*, 2483; (c) Da-Silva, J. F. M.; Garden, S. J.; Pinto, A. C. *J. Braz. Chem. Soc* **2001**, *12*, 273; (d) Joshi, K. C.; Chand, P. *Pharmazie* **1982**, *37*, 1; (e) Cao, Y.; Jiang, X.; Liu, L.; Shen, F.; Zhang, F.; Wang, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 9124.
9. (a) Peterson, E. M.; Xu, K.; Holland, K. D.; McKeon, A. C.; Rothman, S. M.; Ferrendelli, J. A.; Covey, D. F. *J. Med. Chem.* **1994**, *37*, 275; (b) Kupchan, S. M.; Dessertine, A. L.; Blaylock, B. T.; Bryan, R. F. *J. Org. Chem.* **1974**, *39*, 2477; (c) Trost, B. M.; Balkovec, J. M.; Mao, M. K.-T. *J. Am. Chem. Soc.* **1983**, *105*, 6755.
10. (a) Ji, X.; Liu, X.; Li, K.; Chen, R.; Wang, L. *Biomed. Environ. Sci.* **1991**, *4*, 332; (b) Liu, X. M.; Wang, L. G.; Li, H. Y.; Ji, X. *J. Biochem. Pharmacol.* **1996**, *51*, 545; (c) Wee, X. K.; Yeo, W. K.; Zhang, B.; Tan, V. B. C.; Lim, K. M.; Tay, T. E.; Go, M.-L. *Bioorg. Med. Chem.* **2009**, *17*, 7562.
11. Kiruthika, S. E.; Lakshmi, N. V.; Banu, B. R.; Perumal, P. T. *Tetrahedron Lett.* **2011**, *52*, 6508.
12. **Experimental procedure for the synthesis of spirolactone 4a** (Table 2, entry 1): Isatin **1** (1 mmol), *m*-toluidine **2a** (1 mmol), and DMAD **3** (1 mmol) were stirred at room temperature in MeOH in the presence of NEt3 (20 mol%) for 4 h to give the spirolactones which was filtered and recrystallized from methanol to afford the pure product **4a** as yellow solid. (85% yield).
13. **Spectral data for spirolactone 4a** (Table 2, entry 1): yellow solid. mp: 132–134 °C. υ_{max} (KBr): 3284, 3148, 3076, 3040, 2952, 2895, 2846, 2277, 1787, 1712, 1631, 1463, 1222, 1172, 1011, 955, 867, 759, 626, 496, 450 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): 2.25(s, 3H, -CH_3), 3.29(s, 3H, -CH_3), 6.91(m, 4H, -ArH), 6.98(t, 1H, *J* = 7.7 Hz, -ArH), 7.16(t, 1H, *J* = 7.7 Hz, -ArH), 7.34(m, 2H, -ArH), 9.23(s, 1H, -NH, D_2O exchangeable), 10.95(s, 1H, -NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 21.5, 51.9, 83.6, 111.0, 111.1, 120.1, 123.0, 123.5, 125.6, 125.6, 128.6, 131.2, 136.8, 138.1, 139.4, 143.4, 162.1, 167.7, 172.7. MS (ESI): *m*/*z* 364.80 $[M+H]^+$; Anal. Calcd For $C_{20}H_{16}N_2O_5$: C 65.93; H 4.43; N 7.69%. Found: C 65.90; H 4.46; N 7.70%.
14. **Experimental procedure for the synthesis of Dispirodihydrofuranyl oxindole 5a and 5′a** (Scheme 3): Spirolactone **4a** (1 mmol) and Isatin 1 (1 mmol) were stirred in MeOH in the presence of NEt_3 (20 mol%) at reflux for 8 h. The reaction mixture was distilled under reduced pressure and purified by column chromatography (35% EtOAc/Hexanes) and (50% EtOAc/Hexanes) to afford the dispirodihydrofuranyl bisoxindoles **5′a** and **5a** respectively as pure white solids (74% yield)..
15. **Spectral data for Dispirodihydrofuranyl oxindole 5a** (Table 4, entry 1): white solid. mp: 238–240 °C. υ_{max} (KBr): 3265, 3028, 2950, 1755, 1715, 1658, 1616, 1575, 1464, 1389, 762 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 2.21(s, 3H, -CH_3), 3.38(s, 3H, -CH_3), 6.54(t, 1H, *J* = 8.4 Hz, -ArH), 6.59(d, 1H, *J* = 8.4 Hz, -ArH), 6.70(t, 2H, *J* = 7.7 Hz, -ArH), 6.87(d, 1H, *J* = 7.7 Hz, -ArH), 6.94(t, 1H, *J* = 8.4 Hz, -ArH), 7.12(m, 5H, -ArH), 7.20(d, 1H, *J* = 8.4 Hz, -ArH), 9.30(s, 1H, -NH, D_2O exchangeable), 10.23(s, 1H, -NH, D_2O exchangeable), 10.39(s, 1H, -NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 21.5, 50.9, 60.2, 62.6, 81.2, 90.5, 109.9, 110.5, 119.3, 121.3, 121.6, 121.7, 122.7, 125.5, 125.7, 127.2, 129.4, 129.6, 129.7, 132.0, 137.7, 138.9, 141.7, 143.6, 165.3, 173.7, 174.6. MS (ESI): *m*/*z* 468.00 $[M+H]^+$; Anal. Calcd For $C_{27}H_{21}N_3O_5$: C 69.37; H 4.53; N 8.99%. Found: C 69.10; H 4.20; N 8.45%..
16. **Spectral data for Dispirodihydrofuranyl oxindole 5′a** (Table 4, entry 1): white solid. mp: 218–220 °C. υ_{max} (KBr): 3195, 1730, 1659, 1609, 1463, 1397, 1337, 1204, 1087, 1015, 941, 750, 691, 496 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 2.27(s, 3H, -CH_3), 3.37(s, 3H, -CH_3), 6.63(d, 1H, *J* = 7.5 Hz, -ArH), 6.67(d, 1H, *J* = 7.5 Hz, -ArH), 6.89–6.93(m, 2H, -Ar-H), 6.98(t, 1H, *J* = 7.5 Hz, -ArH), 7.11–7.14 (m, 3H, -Ar-H), 7.20(t, 1H, *J* = 7.5 Hz, -ArH), 7.26–7.28(m, 2H, -ArH), 7.51(d, 1H, *J* = 8.0 Hz, -ArH), 9.37(s, 1H, -NH, D_2O exchangeable), 10.29(s, 1H, -NH, D_2O exchangeable), 10.49(s, 1H, -NH, D_2O exchangeable). MS (ESI): *m*/*z* 468.30 $[M+H]^+$.
17. Crystallographic data for compound **5a** in this paper have been deposited with the Cambridge Crystallographic Data centre as supplemental publication no. CCDC- 837673. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 01223 336033 or email: deposit@ccdc.cam.ac.uk).
18. Crystallographic data for compound **5′g** in this paper have been deposited with the Cambridge Crystallographic Data centre as supplemental publication no. CCDC- 870395. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 01223 336033 or email: deposit@ccdc.cam.ac.uk).
19. **Experimental procedure for the synthesis of Dispirodihydrofuranyl oxindole 5a and 5′a** (Table 4, entry 1): Isatin **1** (2 mmol), *m*-toluidine **2a** (1 mmol) and DMAD **3** (1 mmol) were stirred in MeOH in the presence of NEt_3

(20 mol%) at reflux for 10 h. The reaction mixture was distilled under reduced pressure and purified by column chromatography (35% EtOAc/Hexanes) and (50% EtOAc/Hexanes) to afford the dispirodihydrofuranyl oxindoles **5′a** and **5a** respectively as pure white solids (85% yield).

20. **Experimental procedure for the synthesis of dispirodihydrofuranyl acenaphtho oxindole 7a and 7′a** (Table 5, entry 1): Spirolactone **4a** (1 mmol) and acenaphthenequinone **6** (1 mmol) were stirred in MeOH in the presence of NEt_3 (20 mol%) at reflux for 12 h. The reaction mixture was distilled under reduced pressure and purified by column chromatography (30% EtOAc/Hexanes) and (40% EtOAc/Hexanes) to afford the dispirodihydrofuranyl acenaphtho oxindoles **7′a** and **7a** as pure yellow solids (82% yield).
21. **Spectral data for dispirodihydrofuranyl acenaphtho oxindole 7a** (.Table 5, entry 1): white solid. mp: 242–244 °C. υ_{max} (KBr): 3355, 3058, 2949, 2372, 1739, 1671, 1460, 1336, 1269, 1197, 1092, 1006, 939, 831, 775, 686, 625, 540 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 2.24(s, 3H, -CH_3), 3.46(s, 3H, -CH_3), 6.50(d, 1H, J = 7.5 Hz, -ArH), 6.90(d, 1H, J = 7.5 Hz, -ArH), 7.06(t, 1H, J = 7.5 Hz, -ArH), 7.12–7.23(m, 5H, -ArH), 7.39(t, 1H, J = 7.8 Hz, -ArH), 7.45(d, 1H, J = 7.5 Hz, -ArH), 7.82(t, 1H, J = 7.5 Hz, -ArH), 7.95-7.98 (m, 2H, -ArH), 8.21(d, 1H, J = 8.0 Hz, -ArH), 9.43(s, 1H, -NH, D_2O exchangeable), 10.08(s, 1H, -NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 21.5, 50.6, 63.4, 93.8, 109.7, 118.0, 121.3, 121.6, 122.0, 123.8, 125.0, 125.3, 126.7, 127.8, 128.6, 129.1, 129.2, 129.9, 130.0, 130.1, 130.5, 131.3, 137.3, 138.9, 141.1, 141.2, 165.6, 174.7, 196.4. MS (ESI): m/z 503.07 $[M+H]^+$; Anal. Calcd For $C_{31}H_{22}N_2O_5$: C 74.09; H 4.41; N 5.57%. Found: C 74.13; H 4.43; N 5.50%.