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ScienceDirect
Tetrahedron 63 (2007) 8010–8016
Tetrahedron

TiO_2–silica mediated one pot three component 1,3-dipolar cycloaddition reaction: a facile and rapid synthesis of dispiro acenaphthenone/oxindole [indanedione/oxindole] pyrroloisoquinoline ring systems

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Received 14 December 2006; revised 2 May 2007; accepted 17 May 2007
Available online 24 May 2007

Abstract—TiO_2–silica is used as an efficient solid-supported catalyst for the synthesis of a series of novel dispiroheterocyclic systems by the cycloaddition of an azomethine ylide generated by the decarboxylative route from tetrahydroisoquinoline-3-carboxylic acid and acenaphthenequinone/isatin with various unusual dipolarophiles such as 2-arylidene-1,3-indanediones and (*E*)-2-oxoindolino-3-ylidene acetophenones in a one pot three component tandem reaction, in moderate to good yields. The regiochemistry and stereochemistry of the title compound were established by spectroscopic techniques.
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1. Introduction

Multicomponent 1,3-dipolar cycloaddition reactions are considered to be one of the most useful processes for the construction of five-membered heterocyclic ring systems.[1–3] These strategies offer significant advantages over more traditional approaches, allowing the construction of complex molecular architectures from easily available starting materials in a single synthetic operation without the need for isolation of intermediates. Particularly, the chemistry of the azomethine ylide has gained significance in recent years for the construction of nitrogen containing five-membered heterocycles, which are often the central ring systems of numerous natural products.[4] Among the various nitrogen containing heterocycles, functionalized pyrrolidine and pyrrolizidine alkaloids constitute classes of compounds with significant biological activity.[5,6] Spiro compounds represent an important class of naturally occurring substances characterized by highly pronounced biological properties.[7–12] 1,3-Indanediones have also captured much attention due to their important pharmocological properties[13] such as anti-inflammatory and anti-blood coagulation. Oxindole derivatives are found to be potent aldose reductase inhibitors (ARIs), which help to treat and prevent diabetic complications arising from elevated levels of sorbitol.[14] Spirooxindoles have been reported to behave as poliovirus and rhinovirus 3C-proteinase inhibitors.[15] In recent years there has also been increasing interest in solid-supported reagents coupled with microwave irradiation,[16] due to the benefits of enhanced reaction rates, improved yields, cleaner reaction profiles, greater selectivity and operational simplicity. In continuation of our interest[17–21] in surface solid state cycloaddition reactions coupled with microwave irradiation and with a view to synthesize a rare class of novel dispiroheterocyclic derivatives, we herein report for the first time TiO_2 impregnated silica gel as an efficient catalyst under solvent-free microwave irradiation condition for the synthesis of dispiropyrroloisoquinoline ring systems in a one pot, three component reaction.

2. Results and discussion

Azomethine ylides can be generated by a number of methods of which the decarboxylation route offers a convenient method for the synthesis of nitrogen containing heterocyclic compounds.[22] In this method an aldehyde and a primary/secondary amino acid are condensed to generate the reactive intermediate, which is then trapped by dipolarophiles. In some cases, these reactions were reported to be unsuccessful.[23] The required dipolarophile 2-arylidene-1,3-indanedione was prepared by the base catalyzed condensation of 1,3-indanedione with various benzaldehydes according to the literature procedure.[24]

The reaction of tetrahydroisoquinoline-3-carboxylic acid **1** with acenaphthenequinone **2**/isatin **5** under various

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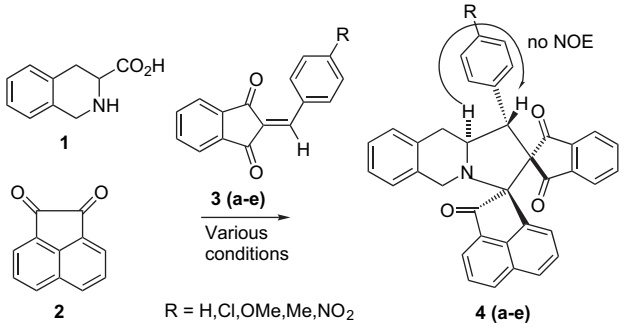
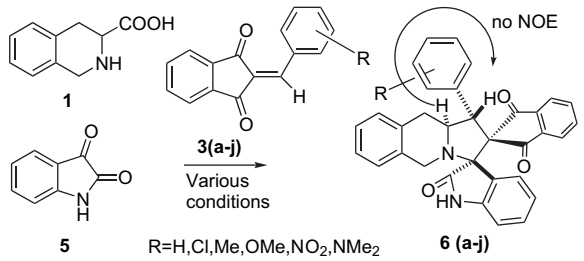
0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.05.063

conditions leads to the formation of an azomethine ylide, which readily undergoes 1,3-dipolar cycloaddition with 2-arylidene-1,3-indanediones to give a single cycloadduct, in a one pot three component process, as evidenced by thin layer chromatography and mass spectral studies (Schemes 1 and 2, Tables 1 and 2).



Scheme 1.



Scheme 2.

The reaction afforded a series of novel dispiroheterocycles **4** and **6** containing the acenaphthenone and oxindole ring systems by a regio- and stereocontrolled cycloaddition of the azomethine ylide to the exocyclic double bond of 2-arylidene-1,3-indanediones in all cases.

Control of the relative stereochemistry at the spiro centre is observed. Presumably, *anti*-ylides **7** and **8**[25–27] (Schemes 3 and 4) are involved in the transition state which adds to 2-arylidene-1,3-indanediones to give the observed cycloadducts. Formation of *syn*-ylide is not observed due to the unfavourable steric repulsion between the carbonyl group of acenaphthenone/oxindole and the isoquinoline ring.

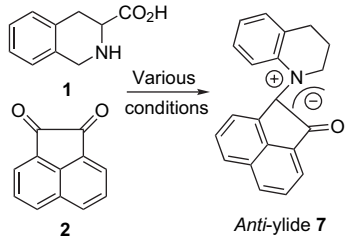
Table 1. 1,3-Dipolar cycloaddition of 1,3-dipole **7** with 2-arylidene-1,3-indanediones **3** (**a**–**e**) and (*E*)-2-oxoindolino-3-ylidene acetophenones **9** (**a**–**d**) under various conditions

	R	Method A		Method B		Method C	
		T (min)	*Y* (%)	*T* (min)	*Y* (%)	*T* (min)	*Y* (%)
4a	H	6.0	42	5.8	68	3.2	82
4b	Cl	5.5	48	5.0	72	3.0	88
4c	OMe	8.0	58	6.9	69	3.6	86
4d	Me	7.0	56	6.0	73	3.2	84
4e	NO_2	4.5	60	5.0	77	2.5	95
10a	H	7.0	50	6.0	74	3.0	85
10b	Cl	6.0	59	6.1	73	3.0	92
10c	OMe	7.5	56	6.5	72	3.2	86
10d	Me	5.7	5.8	6.3	69	3.3	84

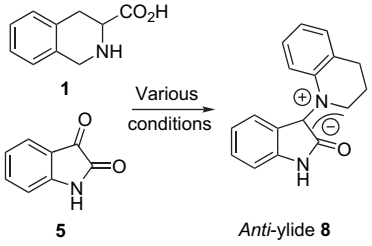
Table 2. 1,3-Dipolar cycloaddition of 1,3-dipole **8** with 2-arylidene-1,3-indanediones **3** (**a**–**j**) and (*E*)-2-oxoindolino-3-ylidene acetophenones **9** (**a**–**e**) under various conditions

	R	Method A		Method B		Method C	
		T (min)	*Y* (%)	*T* (min)	*Y* (%)	*T* (min)	*Y* (%)
6a	H	5.5	56	4.8	74	2.4	84
6b	*p*-Cl	4.8	54	4.6	72	2.8	86
6c	*p*-OMe	5.6	50	4.9	67	3.6	83
6d	*p*-Me	6.2	53	4.2	68	3.3	80
6e	*p*-NO_2	4.0	57	4.5	78	2.3	95
6f	*p*-NMe_2	6.4	52	6.0	70	3.4	84
6g	*m*-Cl	5.6	60	4.9	74	3.6	88
6h	*m*-NO_2	4.2	60	5.0	78	3.0	93
6i	*o*-Cl	5.0	57	5.5	66	3.0	81
6j	*o*-NO_2	5.1	61	4.2	72	2.7	88
11a	H	4.6	59	5.0	70	2.9	85
11b	Cl	4.8	55	6.1	69	3.0	88
11c	OMe	5.8	53	4.5	66	4.2	82
11d	Me	5.0	58	4.0	70	3.6	84
11e	Br	4.9	60	4.2	73	3.1	87

T (min)=time in minutes; *Y* (%)=yield in percentage. Method A: silica/MW; Method B: $BiCl_3$–silica/MW; Method C: TiO_2–silica/MW.



Scheme 3.



Scheme 4.

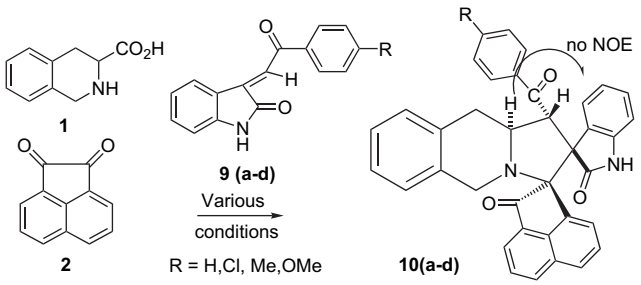
The cycloaddition proceeds via an *endo*-transition state[24] and the possibility of other isomer forming via an *exo*-transition state was ruled out by NOE studies. For example, in the case of **4a**, irradiation of the C_1 benzylic proton at δ 5.15 (J=9.45 Hz) did not cause any enhancement of the signal for the –NCH– proton of the pyrroloisoquinoline ring, which appeared as a multiplet in the region δ 4.96–4.98. The structure and regiochemistry of the cycloadducts **4** (**a**–**f**) were confirmed by spectroscopic data. For example, the IR spectrum of **4a** showed two carbonyl peaks at 1716 and 1747 cm^{-1} corresponding to acenaphthenone and indanedione ring carbonyls, respectively. In the ^1H NMR spectrum of **4a**, the benzylic proton exhibited a doublet at δ 5.15 (J=9.45 Hz), which clearly showed the regiochemistry of the cycloaddition reaction. The –NCH– proton of the pyrroloisoquinoline ring exhibited a multiplet in the region δ 4.96–4.98. The signals in the ^{13}C NMR spectrum of **4a** at δ 68.86 and 77.40 ppm corresponding to two spiro carbons were observed. The signals in the ^{13}C NMR spectrum at

δ 200.12 and 197.23, 197.74 ppm indicated the presence of acenaphthenone and indanedione ring carbonyls. Moreover, the presence of a molecular ion peak at *m/z* 531.6 (M^+) in the mass spectrum of **4a** confirmed the formation of the cycloadduct. Identical results were obtained with other derivatives of 2-arylidene-1,3-indanediones. In the case of **6a**, irradiation of the C_1 benzylic proton at δ 5.02 did not cause any enhancement of the signal for the –NCH– proton of the pyrroloisoquinoline ring, which appeared as multiplet in the region δ 4.46–4.48. The structure and regiochemistry of the cycloadduct **6** (**a**–**j**) were confirmed by spectroscopic data. The IR spectrum of **6a** exhibited peaks at 1706 and 1730 cm^{-1} corresponding to the oxindole and indanedione ring carbonyls, respectively. The ^1H NMR spectrum of **6a** exhibited a doublet at δ 5.02, which clearly showed the regiochemistry of the cycloaddition reaction. The –NCH– proton of the pyrroloisoquinoline ring exhibited a multiplet in the region δ 4.46–4.48. The ^{13}C NMR spectrum of **6a** exhibited peaks at δ 68.88 and 76.82 ppm corresponding to two spiro carbons. The signals at δ 177.68 and 196.95, 197.54 ppm indicated the presence of oxindole and indanedione ring carbonyls. Moreover, the presence of a molecular ion peak at *m/z* 496.5 (M^+) in the mass spectrum of **6a** confirmed the formation of the cycloadduct. Identical results were obtained with other derivatives of 2-arylidene-1,3-indanediones.

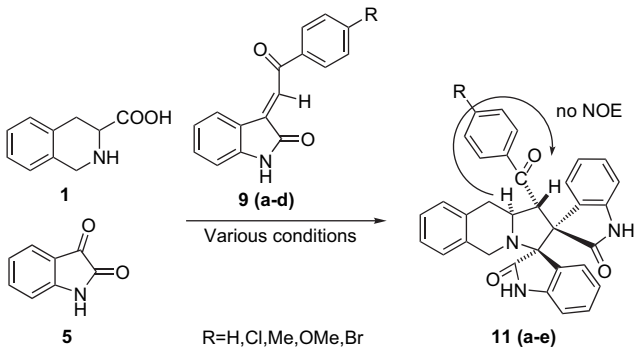
Evaluation of various solid supports and solvent systems was carried out for the synthesis of various novel dispiroheterocycles. After systematic screening, TiO_2 impregnated with silica gel in the rato 1:1 was found to be the best and superior to the conventional one as the reaction was clean, fast and high yielding. With silica gel alone as the solid support the reaction was very slow with poor yields (Tables 1 and 2).

In order to establish the generality of this cycloaddition reaction, we extended the methodology to other dipolarophiles containing exocyclic double bond such as (*E*)-2-oxoindoline-3-ylidene acetophenones **9** (**a**–**d**) (Schemes 5 and 6). These dipolarophiles reacted with acenaphthenequinone/isatin and tetrahydroisoquinoline-3-carboxylic acid under various conditions to give a series of cycloadducts in moderate to good yields (Table 2). The structure and regiochemistry of the cycloadducts were similar to those obtained from 2-arylidene-1,3-indanedione and this was confirmed by spectroscopic data.

Thus, for the first time, TiO_2–silica is used as an efficient catalyst for the synthesis of hitherto unknown novel dispiroheterocycles, namely, dispiropyrroloisoquinoline



Scheme 5.



Scheme 6.

ring containing the 1,3-indanedione/oxindole moiety, which has been accomplished in a one pot three component 1,3-dipolar cycloaddition reaction. The compounds synthesized carry diverse substitution patterns by choice, and are expected to have bioactivity.

3. Experimental

3.1. General

All melting points are uncorrected. IR spectra were recorded on a SHIMADZU-FT-IR 8300 instrument. Mass spectra were recorded on a JEOL DX 303 HF spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as an internal standard on a JEOL spectrometer at 400 and 100 MHz, respectively. Elemental analyses were carried out on a PERKIN–ELMER 240 B instrument. Microwave irradiated reactions were carried out in a Kenstar oven model 5250 at 2450 MHz (600 W). The starting materials (*E*)-2-oxoindolin-3-ylidene acetophenones were prepared according to literature procedure.[28]

3.1.1. General procedure for the cycloaddition reaction of the azomethine ylide generated from tetrahydroisoquinoline-3-carboxylic acid and acenaphthenequinone with various dipolarophiles under various conditions. *Method A*. A mixture of dipolarophile (1.0 mmol), acenaphthenequinone **2** (1.0 mmol)/isatin **5** (1.0 mmol) and tetrahydroisoquinoline-3-carboxylic acid **1** (1.0 mmol) were ground with 1 g of silica gel (60–120 mesh) followed by irradiation under microwave conditions (600 W). After the completion of the reaction as evidenced by TLC, the residue was chromatographed on silica gel using hexane–ethyl acetate as eluent to afford the cycloadducts.

Method B. A mixture of dipolarophile (1.0 mmol), acenaphthenequinone **2** (1.0 mmol)/isatin **5** (1.0 mmol), tetrahydroisoquinoline-3-carboxylic acid **1** (1.0 mmol) were ground with $BiCl_3$–silica (200 mg) in the ratio 1:1 and irradiated under microwave conditions (600 W). After completion of the reaction as evidenced by TLC, the mixture was extracted with dichloromethane, the organic layer dried over $MgSO_4$, the residue was chromatographed on silica gel using hexane–ethyl acetate as eluent to afford the cycloadducts.

Method C. A mixture of dipolarophile (1.0 mmol), acenaphthenequinone **2** (1.0 mmol)/isatin **5** (1.0 mmol), tetrahydroisoquinoline-3-carboxylic acid **1** (1.0 mmol) were ground

with TiO_2–silica (200 mg) in the ratio 1:1 and irradiated under microwave conditions (600 W). After completion of the reaction as evidenced by TLC, the mixture was extracted with dichloromethane, the organic layer dried over $MgSO_4$, the residue was chromatographed on silica gel using hexane–ethyl acetate as eluent to afford the cycloadducts.

3.1.1.1. 1,2,3,5,10,10a-Hexahydro-1-phenyl-spiro[2.2′]-indane-1′,3′-dione-spiro[3.2″]acenaphthen-1″-one-pyrrolo[1,2-*a*]isoquinoline (4a). Yield 0.32 g (68%), yellow solid, mp 182–183 °C; IR (KBr): 1716, 1747 cm^{-1}; ^1H NMR: δ 2.87 (d, J=6.35 Hz, 2H), 3.49 (d, J=14.2 Hz, 1H), 3.83 (d, J=14.2 Hz, 1H), 4.96–4.98 (m, 1H), 5.15 (d, J=9.45 Hz, 1H), 6.88–7.66 (m, 19H); ^{13}C NMR: δ 37.47, 47.31, 52.38, 57.19, 68.86, 77.40, 122.47, 122.89, 122.87, 125.76, 128.17, 128.24, 128.43, 129.11, 129.31, 130.60, 131.57, 131.8, 134.47, 135.35, 138.75, 141.82, 142.93, 197.13, 197.74, 200.12; MS m/z: 531.6 (M^+). Anal. Calcd for $C_{37}H_{25}NO_3$: C, 83.83; H, 4.95; N, 2.30. Found: C, 83.70; H, 4.83; N, 2.23.

3.1.1.2. 1,2,3,5,10,10a-Hexahydro-1-(*p*-chlorophenyl)-spiro[2.2′]indane-1′,3′-dione-spiro[3.2″]acenaphthen-1″-one-pyrrolo[1,2-*a*]isoquinoline (4b). Yield 0.31 g (65%), yellow solid, mp 190–191 °C; IR (KBr): 1716, 1747 cm^{-1}; ^1H NMR: δ 2.87 (d, J=6.35 Hz, 2H), 3.48 (d, J=14.0 Hz, 1H), 3.83 (d, J=14.0 Hz, 1H), 4.96–4.98 (m, 1H), 5.11 (d, J=9.4 Hz, 1H), 6.87–7.67 (m, 18H); ^{13}C NMR: δ 37.44, 47.39, 52.39, 57.21, 68.83, 77.37, 122.36, 122.81, 123.76, 127.81, 128.61, 129.06, 129.37, 130.48, 131.51, 131.78, 134.51, 135.30, 138.71, 141.73, 143.06, 197.41, 198.71, 200.49; MS m/z: 566 (M^+). Anal. Calcd for $C_{37}H_{24}ClNO_3$: C, 78.66; H, 4.40; N, 2.16. Found: C, 78.50; H, 4.30; N, 2.10.

3.1.1.3. 1,2,3,5,10,10a-Hexahydro-1-(*p*-methoxyphenyl)-spiro[2.2′]indane-1′,3′-dione-spiro[3.2″]acenaphthen-1″-one-pyrrolo[1,2-*a*]isoquinoline (4c). Yield 0.29 g (60%), yellow solid, mp 177–178 °C; IR (KBr): 1716, 1747 cm^{-1}; ^1H NMR: δ 2.88 (d, J=6.35 Hz, 2H), 3.48 (d, J=14.2 Hz, 1H), 3.76 (s, 3H), 3.85 (d, J=14.2 Hz, 1H), 4.95–4.97 (m, 1H), 5.10 (d, J=9.45 Hz, 1H), 6.87–7.66 (m, 18H); ^{13}C NMR: δ 37.42, 47.37, 52.35, 55.19, 57.23, 68.81, 77.39, 122.43, 127.76, 123.81, 127.91, 128.21, 128.61, 129.04, 129.27, 130.57, 131.51, 131.79, 134.38, 135.59, 141.91, 142.87, 197.38, 198.11, 200.52; MS m/z: 561.6 (M^+). Anal. Calcd for $C_{38}H_{27}NO_4$: C, 81.51; H, 4.59; N, 2.35. Found: C, 81.46; H, 4.50; N, 2.26.

3.1.1.4. 1,2,3,5,10,10a-Hexahydro-1-(*p*-methylphenyl)-spiro[2.2′]indane-1′,3′-dione-spiro[3.2″]acenaphthen-1″-one-pyrrolo[1,2-*a*]isoquinoline (4d). Yield 0.27 g (63%), yellow solid, mp 198–199 °C; IR (KBr): 1716, 1747 cm^{-1}; ^1H NMR: δ 2.32 (s, 3H), 2.89 (d, J=6.35 Hz, 2H), 3.47 (d, J=14.2 Hz, 1H), 3.85 (d, J=14.2 Hz, 1H), 4.94–4.96 (m, 1H), 5.11 (d, J=9.4 Hz, 1H), 6.88–7.67 (m, 18H); ^{13}C NMR: δ 24.33, 37.49, 47.35, 52.33, 57.28, 68.87, 77.42, 122.36, 122.81, 123.76, 125.80, 127.81, 128.61, 128.86, 129.06, 129.37, 130.48, 131.51, 131.78, 134.51, 135.30, 138.71, 141.73, 143.06, 191.41, 198.77, 200.57; MS m/z: 545.6 (M^+). Anal. Calcd for $C_{38}H_{27}NO_3$: C, 83.41; H, 6.12; N, 2.70. Found: C, 83.64; H, 5.96; N, 2.59.

3.1.1.5. 1,2,3,5,10,10a-Hexahydro-1-(*p*-nitrophenyl)-spiro[2.2′]indane-1′,3′-dione-spiro[3.2″]acenaphthen-1″-one-pyrrolo[1,2-*a*]isoquinoline (4e). Yield 0.34 g (70%), yellow solid, mp 202–203 °C; IR (KBr): 1345.3, 1520.5, 1716, 1747 cm^{-1}; ^1H NMR: δ 2.87 (d, J=6.35 Hz, 2H), 3.47 (d, J=14.0 Hz, 1H), 3.84 (d, J=14.0 Hz, 1H), 4.96–4.98 (m, 1H), 5.22 (d, J=9.5 Hz, 1H), 6.86–7.72 (m, 18H); ^{13}C NMR: δ 37.46, 47.39, 52.41, 57.27, 68.87, 77.46, 121.65, 122.31, 122.69, 123.77, 124.28, 127.84, 128.19, 128.54, 128.97, 129.16, 130.49, 131.47, 131.76, 134.30, 135.43, 141.86, 142.89, 197.17, 197.64, 200.62; MS m/z: 576.6 (M^+). Anal. Calcd for $C_{37}H_{24}N_2O_5$: C, 77.31; H, 3.85; N, 4.68. Found: C, 77.17; H, 3.98; N, 4.75.

3.1.1.6. 1,2,3,5,10a-Hexahydro-1-phenyl-spiro[2.2′]-indane-1′,3′-dione-spirooxindole[3.3″]pyrrolo[1,2-*a*]isoquinoline (6a). Pale yellow solid; mp: 200–201 °C; IR (KBr): 1706, 1730, 3351 cm^{-1}; ^1H NMR: δ 2.89 (d, J=6.6 Hz, 2H), 3.46 (d, J=14.2 Hz, 1H, NCH_2), 3.80 (d, J=14.2 Hz, 1H, NCH_2), 4.46–4.48 (m, 1H), 5.02 (d, J=9.8 Hz, 1H), 6.54–7.66 (m, 17H), 8.0 (s, 1H, NH); ^{13}C NMR: δ 37.48, 47.54, 52.45, 59.83, 66.88, 76.82, 109.86, 109.98, 122.81, 122.90, 123.44, 126.04, 128.35, 129.32, 130.34, 133.07, 135.49, 135.96, 140.46, 141.59, 142.46, 177.68, 196.95, 197.54; MS m/z: 496.5 (M^+). Anal. Calcd for $C_{33}H_{24}N_2O_3$: C, 79.82; H, 4.87; N, 5.64. Found: C, 79.73; H, 4.80; N, 5.73.

3.1.1.7. 1,2,3,5,10a-Hexahydro-1-(*p*-chlorophenyl)-spiro[2.2′]indane-1′,3′-dione-spiro[3.3″]oxindole-pyrrolo-[1,2-*a*]isoquinoline (6b). Pale yellow solid; mp: 211–212 °C; IR (KBr): 1706, 1730, 3351 cm^{-1}; ^1H NMR: δ 2.89 (d, J=6.6 Hz, 2H), 3.45 (d, J=14.2 Hz, 1H, NCH_2), 3.80 (d, J=14.2 Hz, 1H, NCH_2), 4.46–4.48 (m, 1H), 4.87 (d, J=9.75 Hz, 1H), 6.52–7.64 (m, 16H), 8.58 (s, 1H, NH); ^{13}C NMR: δ 37.42, 47.46, 52.39, 59.76, 68.78, 76.74, 122.83, 123.38, 125.98, 127.27, 129.24, 130.16, 133.20, 135.11, 139.41, 140.35, 142.29, 170.60, 196.89, 197.46; MS m/z: 531 (M^+). Anal. Calcd for $C_{33}H_{23}ClN_2O_3$: C, 74.64; H, 4.36; N, 5.72. Found: C, 74.46; H, 4.50; N, 5.59.

3.1.1.8. 1,2,3,5,10a-Hexahydro-1-(*p*-methylphenyl)-spiro[2.2′]indane-1′,3′-dione-spiro[3.3″]oxindole-pyrrolo-[1,2-*a*]isoquinoline (6c). Pale yellow solid; mp: 193–194 °C; IR (KBr): 1706, 1730, 3351 cm^{-1}; ^1H NMR: δ 2.27 (s, 3H), 2.91 (d, J=6.6 Hz, 2H), 3.44 (d, J=14.0 Hz, 1H, NCH_2), 3.83 (d, J=14.0 Hz, 1H, NCH_2), 4.46–4.48 (m, 1H), 5.03 (d, J=9.8 Hz, 1H), 6.53–7.63 (m, 16H), 8.56 (s, 1H, NH); ^{13}C NMR: δ 20.96, 36.98, 47.14, 52.20, 57.39, 68.66, 76.58, 109.87, 122.64, 123.22, 124.68, 126.32, 128.29, 129.24, 133.12, 135.38, 139.37, 140.28, 142.04, 177.48, 196.68, 197.23; MS m/z: 510.5 (M^+). Anal. Calcd for $C_{34}H_{26}N_2O_3$: C, 79.98; H, 5.13; N, 5.48. Found: C, 80.20; H, 5.05; N, 5.39.

3.1.1.9. 1,2,3,5,10a-Hexahydro-1-(*p*-methoxyphenyl)-spiro[2.2′]indane-1′,3′-dione-spiro[3.3″]oxindole-pyrrolo-[1,2-*a*]isoquinoline (6d). Pale yellow solid; mp: 178–179 °C; IR (KBr): 1706, 1730, 3350 cm^{-1}; ^1H NMR: δ 2.90 (d, J=6.6 Hz, 2H), 3.45 (d, J=14.2 Hz, 1H, NCH_2), 3.78 (s, 3H), 3.83 (d, J=14.2 Hz, 1H, NCH_2), 4.47–4.49

(m, 1H), 5.05 (d, J=9.8 Hz, 1H), 6.52–7.66 (m, 16H), 8.58 (s, 1H, NH); ^{13}C NMR: δ 37.10, 47.26, 52.16, 53.48, 57.52, 68.60, 76.51, 110.21, 121.36, 122.51, 123.40, 124.53, 126.24, 128.11, 129.27, 133.20, 135.29, 139.41, 140.32, 142.12, 177.48, 196.75, 197.31; MS *m*/*z*: 526.5 (M^+). Anal. Calcd for $C_{34}H_{26}N_2O_4$: C, 77.55; H, 4.97; N, 5.31. Found: C, 77.41; H, 4.95; N, 5.22.

3.1.1.10. 1,2,3,5,10a-Hexahydro-1-(*p*-nitrophenyl)-spiro[2.2′]indane-1′,3′-dione-spiro[3.3″]oxindole-pyrrolo-[1,2-*a*]isoquinoline (6e). Pale yellow solid; mp: 186–187 °C; IR (KBr): 1706, 1730, 3351 cm^{-1}; ^{1}H NMR: δ 2.89 (d, J=6.6 Hz, 2H), 3.44 (d, J=14.0 Hz, 1H, NCH_2), 3.81 (d, J=14.0 Hz, 1H, NCH_2), 4.44–4.46 (m, 1H), 5.07 (d, J=9.85 Hz, 1H), 6.56–7.68 (m, 16H), 8.60 (s, 1H, NH); ^{13}C NMR: δ 37.36, 47.42, 52.27, 59.71, 68.72, 76.68, 121.36, 122.77, 123.3 0, 124.97, 125.86, 127.19, 129.27, 133.20, 130.21, 132.87, 134.84, 138.63, 139.38, 140.30, 142.23, 177.53, 196.81, 197.39; MS *m*/*z*: 541.5 (M^+). Anal. Calcd for $C_{33}H_{23}N_3O_5$: C, 73.18; H, 4.28; N, 7.75. Found: C, 73.13; H, 4.24; N, 7.78.

3.1.1.11. 1,2,3,5,10a-Hexahydro-1-(*p*-*N*,*N*-dimethyl-aminophenyl)-spiro[2.2′]indane-1′,3′-dione-spiro[3.3″]-oxindole-pyrrolo[1,2-*a*]isoquinoline (6f). Yellow solid; mp: 183–184 °C; IR (KBr): 1706.3, 1730.2, 3351.6 cm^{-1}; ^{1}H NMR: δ 2.88 (d, J=6.6 Hz, 2H), 2.90 (s, 6H), 3.43 (d, J=14.0 Hz, 1H, NCH_2), 3.83 (d, J=14.0 Hz, 1H, NCH_2), 4.44–4.46 (m, 1H), 4.89 (d, J=9.75 Hz, 1H), 6.62–7.63 (m, 16H), 8.34 (s, 1H, NH); ^{13}C NMR: δ 37.42, 40.52, 47.38, 52.31, 59.69, 68.68, 76.71, 121.23, 122.68, 123.27, 124.87, 126.88, 129.32, 130.19, 132.74, 134.80, 139.1 8, 140.25, 142.31, 177.49, 196.77, 197.34; MS *m*/*z*: 539.6 (M^+). Anal. Calcd for $C_{35}H_{29}N_3O_3$: C, 77.90; H, 5.41; N, 7.78. Found: C, 78.02; H, 5.37; N, 7.90.

3.1.1.12. 1,2,3,5,10a-Hexahydro-1-(*m*-chlorophenyl)-spiro[2.2′]indane-1′,3′-dione-spiro[3.3″]oxindole-pyrrolo-[1,2-*a*]isoquinoline (6g). Yellow solid; mp: 197–198 °C; IR (KBr): 1706.2, 1731.5, 3351.2 cm^{-1}; ^{1}H NMR: δ 2.90 (d, J=6.8 Hz, 2H), 3.47 (d, J=14.4 Hz, 1H, NCH_2), 3.83 (d, J=14.4 Hz, 1H, NCH_2), 4.51–4.53 (m, 1H), 5.02 (d, J=9.75 Hz, 1H), 6.54–7.68 (m, 16H), 9.06 (s, 1H, NH); ^{13}C NMR: δ 37.19, 47.26, 52.18, 59.64, 68.72, 76.70, 110.09, 121.32, 122.68, 123.46, 125.61, 128.57, 133.20, 135.76, 138.83, 140.19, 141.38, 142.07, 177.45, 196.63, 197.14; MS *m*/*z*: 531 (M^+). Anal. Calcd for $C_{33}H_{23}ClN_2O_3$: C, 74.64; H, 4.36; N, 5.27. Found: C, 74.69; H, 4.44; N, 5.18.

3.1.1.13. 1,2,3,5,10a-Hexahydro-1-(*m*-nitrophenyl)-spiro[2.2′]indane-1′,3′-dione-spiro[3.3″]oxindole-pyrrolo-[1,2-*a*]isoquinoline (6h). Yellow solid; mp: 204–205 °C; IR (KBr): 1706, 1731, 3351 cm^{-1}; ^{1}H NMR: δ 2.89 (d, J=6.6 Hz, 2H), 3.44 (d, J=14.0 Hz, 1H, NCH_2), 3.79 (d, J=14.0 Hz, 1H, NCH_2), 4.46–4.48 (m, 1H), 5.09 (d, J=9.85 Hz, 1H), 6.58–7.69 (m, 16H), 8.62 (s, 1H, NH); ^{13}C NMR: δ 37.25, 47.38, 52.32, 59.74, 68.78, 76.51, 110.32, 121.91, 122.84, 124.79, 125.81, 127.20, 129.28, 130.14, 132.81, 134.77, 138.58, 139.47, 140.24, 142.23, 177.42, 196.68, 197.37; MS *m*/*z*: 541.5 (M^+). Anal. Calcd for $C_{33}H_{23}N_3O_5$: C, 73.18; H, 4.28; N, 7.75. Found: C, 73.11; H, 4.36; N, 7.78.

3.1.1.14. 1,2,3,5,10a-Hexahydro-1-(*o*-chlorophenyl)-spiro[2.2′]indane-1′,3′-dione-spiro[3.3″]oxindole-pyrrolo-[1,2-*a*]isoquinoline (6i). Yellow solid; mp: 207–208 °C; IR (KBr): 1706, 1731, 3350 cm^{-1}; ^{1}H NMR: δ 2.92 (d, J=6.8 Hz, 2H), 3.47 (d, J=14.4 Hz, 1H, NCH_2), 3.82 (d, J=14.4 Hz, 1H, NCH_2), 4.49–4.51 (m, 1H), 5.04 (d, J=9.8 Hz, 1H), 6.56–7.70 (m, 16H), 8.81 (s, 1H, NH); ^{13}C NMR: δ 37.26, 47.33, 52.21, 59.68, 68.77, 76.69, 110.16, 122.24, 122.73, 129.09, 130.03, 133.11, 135.29, 135.82, 139.37, 140.28, 141.57, 142.22, 177.58, 177.58, 196.76, 197.31; MS *m*/*z*: 531 (M^+). Anal. Calcd for $C_{33}H_{23}ClN_2O_3$: C, 74.64; H, 4.36; N, 5.27. Found: C, 74.70; H, 4.45; N, 5.40.

3.1.1.15. 1,2,3,5,10a-Hexahydro-1-(*o*-nitrophenyl)-spiro[2.2′]indane-1′,3′-dione-spiro[3.3″]oxindole-pyrrolo-[1,2-*a*]isoquinoline (6j). Yellow solid; mp: 213–214 °C; IR (KBr): 1706.4, 1730.5, 3351.7 cm^{-1}; ^{1}H NMR: δ 2.93 (d, J=6.6 Hz, 2H), 3.46 (d, J=14.0 Hz, 1H, NCH_2), 3.83 (d, J=14.0 Hz, 1H, NCH_2), 4.49–4.51 (m, 1H), 5.13 (d, J=9.9 Hz, 1H), 6.60–7.74 (m, 16H), 9.10 (s, 1H, NH); ^{13}C NMR: δ 37.18, 47.37, 52.34, 59.78, 68.81, 76.57, 110.24, 121.96, 123.28, 124.88, 125.78, 127.24, 129.32, 130.16, 132.76, 134.80, 138.66, 139.43, 140.28, 142.19, 177.48, 196.77, 197.42; MS *m*/*z*: 541.5 (M^+). Anal. Calcd for-$C_{33}H_{23}ClN_3O_5$: C, 73.18; H, 4.28; N, 7.75. Found: C, 72.94; H, 4.43; N, 7.93.

3.1.1.16. 1,2,3,5,10,10a-Hexahydro-1-benzoyl-spiro-[2.3′]oxindole-spiro[3.2″]acenaphthen-1″-one-pyrrolo-[1,2-*a*]isoquinoline (10a). Yield 0.32 g (73%), yellow solid, mp 191–192 °C; IR (KBr): 1687, 1780, 1716 cm^{-1}; ^{1}H NMR: δ 2.93 (d, J=6.4 Hz, 2H), 3.45 (d, J=14.4 Hz, 1H, NCH_2), 3.81 (d, J=14.4 Hz, 1H, NCH_2), 4.65 (d, J=9.5 Hz, 1H), 5.01–5.03 (m, 1H), 6.55–7.40 (m, 19H), 9.75 (s, 1H, NH); ^{13}C NMR: δ 38.11, 48.23, 52.96, 53.27, 61.80, 77.23, 119.18, 120.46, 121.11, 124.54, 124.90, 126.22, 126.86, 127.35, 127.50, 127.91, 128.56, 129.11, 130.80, 131.82, 131.90, 134.61, 135.72, 136.90, 137.20, 141.65, 142.86, 179.11, 196.84, 204.52; MS *m*/*z*: 546.6 (M^+). Anal. Calcd for $C_{37}H_{26}N_2O_3$: C, 81.54; H, 4.63; N, 5.25. Found: C, 81.30; H, 4.79; N, 5.12.

3.1.1.17. 1,2,3,5,10,10a-Hexahydro-l-(*p*-chlorobenzo-yl)-spiro[2.3′]oxindole-spiro[3.2″]acenaphthen-1″-one-pyrrolo[1,2-*a*]isoquinoline (10b). Yield 0.30 g (70%), yellow solid, mp 204–205 °C; IR (KBr): 1680, 1687, 1716 cm^{-1}; ^{1}H NMR: δ 2.49 (d, J=6.4 Hz, 2H), 3.44 (d, J=14.4 Hz, 1H, NCH_2), 3.82 (d, J=14.4 Hz, 1H, NCH_2), 4.66 (d, J=9.5 Hz, 1H), 5.02–5.04 (m, 1H), 6.56–7.40 (m, 18H), 9.80 (s, 1H, NH); ^{13}C NMR: δ 38.06, 48.16, 52.87, 53.19, 61.96, 77.18, 120.41, 121.32, 124.62, 124.87, 126.22, 126.91, 127.33, 127.61, 127.82, 127.93, 128.61, 128.79, 129.22, 130.76, 131.66, 131.84, 133.57, 134.76, 135.53, 135.84, 136.96, 137.21, 141.57, 142.81, 179.14, 196.76, 204.31; MS *m*/*z*: 518 (M^+). Anal. Calcd for $C_{37}H_{25}ClN_2O_3$: C, 76.71; H, 4.19; N, 5.03. Found: C, 76.48; H, 4.30; N, 4.85.

3.1.1.18. 1,2,3,5,10,10a-Hexahydro-1-(*p*-methoxybenzo-yl)-spiro[2,3′]oxindole-spiro[3,2″]acenaphthen-1″-one-pyrrolo[1,2-*a*]isoquinoline (10c). Yield 0.29 g (68%), yellow solid, mp 223–224 °C; IR (KBr): 1680, 1687.2, 1716.1 cm^{-1}; ^{1}H NMR: δ 2.92 (d, J=6.45 Hz, 2H), 3.45

(d, J=14.4 Hz, 1H), 3.78 (s, 3H), 3.81 (d, J=14.4 Hz, 1H), 4.65 (d, J=9.5 Hz, 1H), 5.01–5.03 (m, 1H), 6.50–7.38 (m, 18H), 9.82 (s, 1H, NH); ^{13}C NMR: δ 38.30, 48.34, 52.89, 53.32, 55.17, 61.78, 77.27, 120.59, 121.46, 124.77, 124.86, 126.27, 127.19, 127.63, 127.71, 127.89, 128.55, 128.61, 128.96, 129.40, 130.62, 131.66, 131.81, 133.48, 133.92, 134.77, 135.58, 136.64, 136.83, 137.41, 141.31, 142.66, 179.27, 196.74, 204.33; MS *m*/*z*: 576.6 (M^+). Anal. Calcd for $C_{38}H_{28}N_2O_4$: C, 79.42; H, 5.11; N, 4.55. Found: C, 79.25; H, 4.99; N, 4.75.

3.1.1.19. 1,2,3,5,10,10a-Hexahydro-1-(*p*-methylbenzoyl)-spiro[2.3′]oxindole-spiro[3.2″]acenaphthen-1″-one-pyrrolo[1,2-*a*]isoquinoline (10d). Yield 0.27 g (65%), yellow solid, mp 216–217 °C; IR (KBr): 1681, 1687, 1716.2 cm^{-1}; ^{1}H NMR: δ 2.34 (s, 3H), 2.93 (d, J=6.4 Hz, 2H), 3.47 (d, J=14.2 Hz, 1H), 3.81 (d, J=14.2 Hz, 1H), 4.64 (d, J=9.45 Hz, 1H), 5.00–5.02, (m, 1H), 6.57–7.41 (m, 18H), 9.80 (s, 1H, NH); ^{13}C NMR: δ 22.38, 38.23, 48.26, 52.91, 53.22, 61.84, 77.31, 120.63, 121.41, 124.71, 124.82, 126.31, 127.19, 127.46, 127.63, 128.66, 128.91, 129.31, 130.71, 130.93, 131.72, 131.86, 133.60, 134.81, 135.59, 135.81, 136.88, 137.32, 141.36, 142.29, 179.27, 196.89, 204.41; MS *m*/*z*: 560.6 (M^+). Anal. Calcd for $C_{38}H_{28}N_2O_3$: C, 81.70; H, 5.28; N, 4.73. Found: C, 81.50; H, 5.13; N, 4.89.

3.1.1.20. 1,2,3,5,10a-Hexahydro-1-benzoyl-spiro[2.3′]-oxindole-spiro[3.3″]oxindole-pyrrolo[1,2-*a*]isoquinoline (11a). Yellow solid; mp: 213–214 °C; IR (KBr): 1672, 1708.1, 1712 cm^{-1}; ^{1}H NMR: δ 2.96 (d, J=6.65 Hz, 2H), 3.46 (d, J=14.2 Hz, 1H, NCH_2), 3.81 (d, J=14.2 Hz, 1H, NCH_2), 4.57 (d, J=9.4 Hz, 1H), 5.42–5.44 (m, 1H), 6.46–7.78 (m, 17H), 8.34 (s, 1H, NH), 9.82 (s, NH); ^{13}C NMR: δ 36.14, 49.16, 51.32, 53.52, 61.95, 79.67, 109.10, 109.58, 121.27, 121.98, 128.18, 128.71, 129.05, 129.52, 130.10, 131.84, 136.90, 137.72, 141.65, 142.86, 175.92, 176.16, 196.81; MS *m*/*z*: 511.5 (M^+). Anal. Calcd for $C_{33}H_{25}N_3O_3$: C, 77.46; H, 4.92; N, 8.21. Found: C, 77.53; H, 4.86; N, 8.19.

3.1.1.21. 1,2,3,5,10a-Hexahydro-1-(*p*-chlorobenzoyl)-spiro[2.3′]oxindole-spiro[3.3″]oxindole-pyrrolo[1,2-*a*]isoquinoline (11b). Yellow solid; mp: 170–171 °C; IR (KBr): 1672, 1708, 1712 cm^{-1}; ^{1}H NMR: δ 2.95 (d, J=6.65 Hz, 2H), 3.45 (d, J=14.4 Hz, 1H, NCH_2), 3.80 (d, J=14.2 Hz, 1H, NCH_2), 4.57 (d, J=9.4 Hz, 1H), 5.42–5.44 (m, 1H), 6.48–7.76 (m, 16H), 8.56 (s, NH), 9.74 (s, 1H, NH); ^{13}C NMR: δ 36.19, 46.21, 51.27, 53.49, 61.97, 79.65, 109.07, 109.52, 121.32, 121.93, 128.21, 129.10, 130.13, 131.87, 136.92, 137.68, 141.61, 142.80, 175.89, 179.11, 196.77; MS *m*/*z*: 546 (M^+). Anal. Calcd for $C_{33}H_{24}ClN_3O_3$: C, 72.59; H, 4.43; N, 7.69. Found: C, 72.42; H, 4.58; N, 7.58.

3.1.1.22. 1,2,3,5,10a-Hexahydro-1-(*p*-methylbenzoyl)-spiro[2.3′]oxindole-spiro[3.3″]oxindole-pyrrolo[1,2-*a*]isoquinoline (11c). Yellow solid; mp: 152–153 °C; IR (KBr): 1672, 1708, 1712 cm^{-1}; ^{1}H NMR: δ 2.26 (s, 3H), 2.95 (d, J=6.6 Hz, 2H), 3.47 (d, J=14.2 Hz, 1H, NCH_2), 3.83 (d, J=14.2 Hz, 1H, NCH_2), 4.55 (d, J=9.45 Hz, 1H), 5.43–5.45 (m, 1H), 6.47–7.78 (m, 16H), 8.36 (s, 1H, NH), 9.86 (s, NH); ^{13}C NMR: δ 21.23, 36.21, 49.19, 51.37, 53.48, 61.93, 79.62, 109.13, 109.46, 121.32, 121.88, 128.21, 128.74, 129.16, 129.40, 130.02, 131.75, 136.86, 137.68, 140.96, 142.78, 175.84, 179.09, 196.76; MS *m*/*z*: 525.6 (M^+). Anal. Calcd for $C_{34}H_{27}N_3O_3$: C, 77.69; H, 5.17; N, 7.99. Found: C, 77.75; H, 5.30; N, 7.88.

3.1.1.23. 1,2,3,5,10a-Hexahydro-1-(*p*-methoxybenzoyl)-spiro[2.3′]oxindole-spiro[3.3″]oxindole-pyrrolo[1,2-*a*]isoquinoline (11d). Yellow solid; mp: 189–190 °C; IR (KBr): 1672.3, 1708.1, 1712.3 cm^{-1}; ^{1}H NMR: δ 2.96 (d, J=6.6 Hz, 2H), 3.46 (d, J=14.4 Hz, 1H, NCH_2), 3.76 (s, 3H), 3.80 (d, J=14.4 Hz, 1H, NCH_2), 4.57 (d, J=9.4 Hz, 1H), 5.42–5.44 (m, 1H), 6.48–7.79 (m, 16H), 8.30 (s, NH), 9.88 (s, 1H, NH); ^{13}C NMR: δ 36.27, 49.21, 51.42, 53.46, 55.41, 62.03, 79.70, 109.25, 109.56, 120.98, 121.81, 128.18, 128.68, 129.32, 129.64, 130.18, 131.69, 136.60, 136.81, 140.89, 140.94, 142.74, 175.78, 179.11, 196.80; MS *m*/*z*: 541.6 (M^+). Anal. Calcd for $C_{34}H_{27}N_3O_4$: C, 75.40; H, 5.02; N, 7.75. Found: C, 75.60; H, 5.13; N, 7.63.

3.1.1.24. 1,2,3,5,10a-Hexahydro-1-(*p*-bromobenzoyl)-spiro[2.3′]oxindole-spiro[3.3″]oxindole-pyrrolo[1,2-*a*]isoquinoline (11e). Yellow solid; mp: 172–173 °C; IR (KBr): 1672, 1708, 1712.3 cm^{-1}; ^{1}H NMR: δ 2.94 (d, J=6.6 Hz, 2H), 3.46 (d, J=14.4 Hz, 1H, NCH_2), 3.82 (d, J=14.4 Hz, 1H, NCH_2), 4.56 (d, J=9.4 Hz, 1H), 5.44–5.46 (m, 1H), 6.48–7.77 (m, 16H), 8.45 (s, NH), 9.84 (s, 1H, NH); ^{13}C NMR: δ 36.15, 46.18, 51.29, 53.50, 61.96, 79.67, 109.10, 109.58, 121.33, 121.96, 129.13, 129.47, 131.93, 136.94, 137.66, 141.68, 142.87, 175.91, 179.20, 196.82; MS *m*/*z*: 590.4 (M^+). Anal. Calcd for $C_{33}H_{24}BrN_3O_3$: C, 67.12; H, 4.09; N, 7.11. Found: C, 67.24; H, 4.20; N, 7.02.

Acknowledgements

A.R.S.B. thanks Council of Scientific and Industrial Research (CSIR), New Delhi for the award of Senior Research Fellowship. R.R. thanks DST and DST-FIST, New Delhi for financial assistance.

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