A Highly Regioselective Synthesis of 1-*N*-Methyl-spiro-[2,3'"]-oxindole-spiro-[3,2"]indane-1", 3"-dione-4-arylpyrrolidines through 1,3-Dipolar Cycloaddition Protocol

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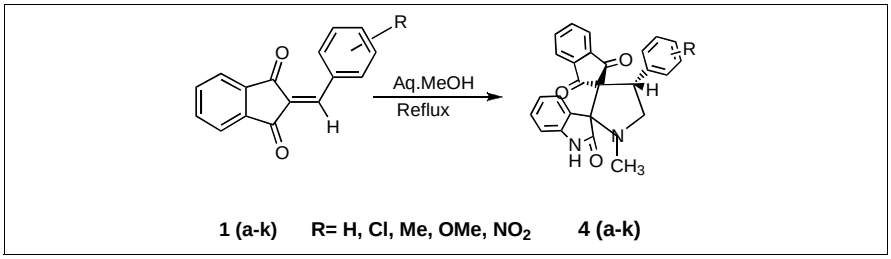
Received November 30, 2005



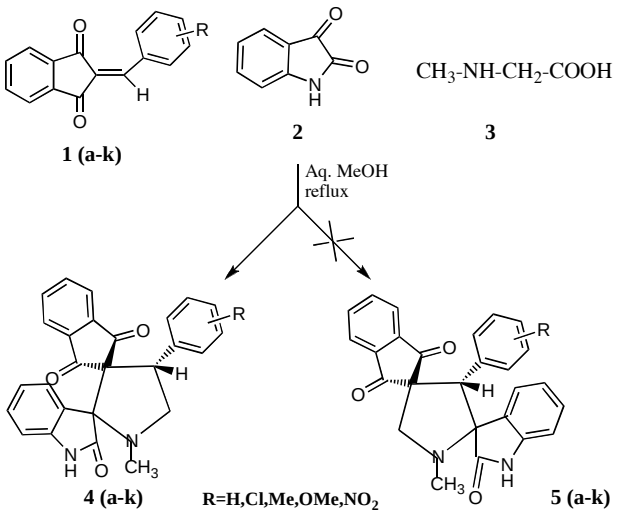
2-Arylidene-1,3-indanediones undergo a regioselective 1,3-dipolar cycloaddition reaction with the azomethine ylide derived from isatin and sarcosine by decarboxylative route affording a series of 1-N-methyl – spiro[2.3'"]oxindole-spiro[3.2"]indane-1",3"-diones-4-aryl pyrrolidines. The structures were established by spectroscopic techniques as well as single crystal X-ray analysis. Density functional theory at B3L YP/6-31G* and the semi empirical AM_1 calculations were employed to rationalize the observed results. The experimental regioselectivity of 1,3-dipolar cycloadditions could be corroborated nicely with the computed Fukui frontier orbital energies and reaction energies.

J. Heterocyclic Chem., **43**, 1467 (2006).

Introduction.

Great attention has been paid in recent years to the intermolecular 1,3-dipolar cycloaddition reaction of azomethine ylide with olefins since they represent an efficient and convergent method for the construction of the pyrrolidine structural unit [1,2]. This method is widely used in the synthesis of natural products such as alkaloids and pharmaceuticals [3]. Spiro-oxindole ring system represents an important class of naturally occurring substances characterised by highly pronounced biological properties [4-6]. Oxindole derivatives are found to be potent aldose reductase inhibitors (ARIs), which help to treat and prevent diabetic complications arising from elevated level of sorbitol [7]. Pyrrolidine and oxindole alkaloids [8] constitute another class of compounds with significant biological activity, which are normally found in rhyncophylline, corynoxeine, mitraphylline, vincatine, horsifiline etc. [9]. 1,3-Indanediones have also captured much attention due to their important pharmacological properties [10] such as anti-inflammatory and anti-blood coagulant properties. Recently we have reported the bioactivity of some of the spiro-pyrrolidine and spiro-oxindolepyrrolidines [11]. We anticipate that pyrrolidine containing both oxindole and indanedione moiety may have highly pronounced biological activity. As apart of our ongoing research programme in the area of cycloaddition reactions [12-14] for the construction of spiro-pyrrolidine ring system, we herein report the facile synthesis of dispiro-[oxindole/indanedione]pyrrolidine ring systems through regioselective cycloaddition of 2-arylidene-1,3-indanediones **1(a-k)** with the azomethine ylide generated from isatin **2** and sarcosine **3** by decarboxylative route.

Scheme 1



Computational studies were carried out to unravel the underlying reasons for the observed regioslectivity. Frontier orbital shapes and energetics, activation energies, reaction exothermicities and Fukui functions were

considered to explain the observed trends. The parent systems **4a** and **5a** are fully optimised at B3LYP/6-31G level and the geometries obtained at this level are similar to those at AM1 optimised geometries. Also, the single point calculations at B3LYP/6-31G* level on B3LYP/6-31G and AM1 are very comparable [19], and therefore for all the substituted systems (**4b**-**4k; 5b-5k**) geometry optimisations were carried out only at AM1 level. Semiempirical AM1 and B3LYP/6-31G*//AM1 calculations were also executed to calculate HOMO-LUMO energy gaps. Fukui functions, which are the local reactivity descriptors [20], for the nucleophilic and electrophilic attacks, were calculated using the equations 1 and 2.

$$f_k^+ = [q_k(N+1) - q_k(N)] \text{ for nucleophilic attack} \quad (1)$$
$$f_k^- = [q_k(N) - q_k(N-1)] \text{ for electrophilic attack} \quad (2)$$

Previous computational studies substantiate excellent performance of these qualitative measures in patterning and predicting the regioselectivity of cycloaddition reactions in general including the 1,3-dipolar reactions [26]. All the calculations were done using the GAUSSIAN 98W programme package [27].

Results and Discussion.

Refluxing a solution of 2-arylidene-1,3-indanediones **1(a-k)** in methanol with isatin **2** and sarcosine **3** afforded 1-*N*-methyl-spiro[2.3''']oxindole-spiro[3.2'']-indane-1'',3''-dione-4-aryl-pyrrolidines **4(a-k)** (Scheme 1 and Table 1). The reaction gave a single product in all the cases studied, as evidenced by thin layer chromatography, through regio-selective cycloaddition of azomethine ylide to the exocyclic double bonds of the 2-arylidene-1,3-indanediones. No trace of the other regioisomer **5(a-k)** was detected.

The cycloaddition proceeded to afford the *syn-endo* cycloadducts. The regio and stereochemical outcome of the cycloaddition was determined by spectroscopic data and X-ray *Anal*ysis of **4g** (Figure 1) and **4h** (Figure 2) respectively. The IR spectra of **4i** reveals the presence of a carbonyl peak at 1751.2 cm^{-1} showing an increase of 19.3 cm^{-1} from the normal value observed for 2-(*o*-nitro) phenyl-1,3-indanedioone indicating the loss of conjugation. It also exhibited peaks at 1523.7 cm^{-1} and 1361.7 cm^{-1} attributed for -NO_2 group. Peaks at 1708.8 cm^{-1} due to carbonyl group of oxindole and at 3344.3 cm^{-1} due to the -NH of the oxindole are observed. The ^{1}H NMR spectrum of **4f** exhibits peaks at δ values 2.10 (s, 3H, -NCH_3), 4.10 (m, 1H, H_b), 4.25 (m, 1H, H_c), 5.14 (dd, J = 9.75, 6.3 Hz, 1H, H_a), 6.40-7.70 (m, 12H, ArH), 10.28 (bs, 1H, -NH). ^{13}C NMR spectra of **4 (a-k)** add conclusive support of the proposed structures. ^{13}C NMR spectra of **4i** exhibits the presence benzylic carbon at δ 58.35, spirocarbons at 68.98 and 70.07, N-methyl carbon at δ 34.69, -NCH_2 at δ 49.13, oxindole carbonyl at 175.91 and indanedione carbonyls at δ 195.02 and δ196.55 respectively.

Table 1

1,3-Dipolar cycloaddition reactions of 2-arylidene-1,3-indanediones **1(a-k)** and azomethine ylide generated from isatin **2** and sarcosine **3**.

Entry	Product	R	Time (h)	Yield (%)
1	**4a**	H	3	90
2	**4b**	*p*-Cl	3	85
3	**4c**	*p*-Me	3	60
4	**4d**	*p*-OMe	4	67
5	**4e**	*p*-NO_2	2.5	95
6	**4f**	*m*-Cl	3	77
7	**4g**	*m*-NO_2	2.5	90
8	**4h**	*o*-Cl	3	86
9	**4i**	*o*-NO_2	2.5	87
10	**4j**	3',4'-OMe	4.5	67
11	**4k**	3',4',5'-OMe	5	59

These observed chemical shift values confirmed the proposed structure. The mass spectrum of **4i** showed a peak at *m/z* 453 (M^+). Identical results were obtained with other derivatives of 2-arylidene-1, 3-indanediones.

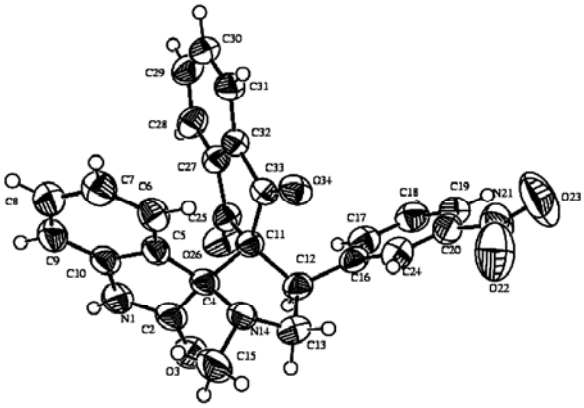


Figure 1. Ortep diagram of **4g**.

To the best of our knowledge to date there has been no report of the cycloaddition reaction of the 1,3-dipole azomethine ylide derived from isatin and sarcosine with 2-arylidene-1,3-indanediones as dipolarophiles.

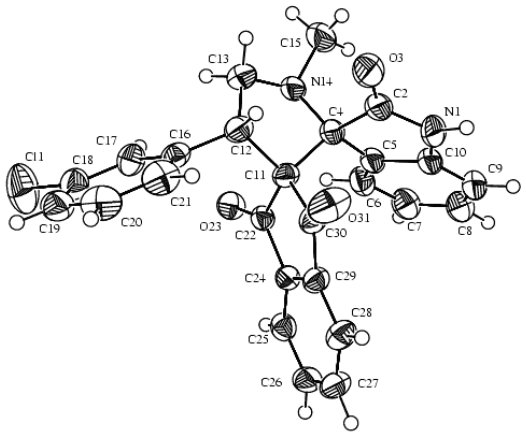


Figure 2. Ortep diagram of **4h**.

Conclusion.

A facile and efficient synthesis of a new class of dispiro[oxindole/indanedione]pyrrolidine ring systems from azomethine ylide generated from isatin and sarcosine with 2-arylidene-1,3-indanediones has been described. The cycloaddition studied is of interest since it paves the way for the synthesis of a variety of biologically significant spiro-oxindole derivatives using easily available starting materials. Computational studies explain that the observed regioselectivity is both kinetically and thermodynamically favoured.

EXPERIMENTAL

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 with MASPEC SYSTEM (msw/9629). ^{1}H and ^{13}C NMR were recorded in $CDCI_3$/DMSO-d_6 using TMS as internal standard on a JEOL spectrometer at 500 and 300 MHz, respectively. Elemental *Anal*yses were carried out on a PERKIN-ELMER 240 B instrument. The starting materials **1(a-k)** were prepared as per the literature procedure [15]. The X-ray structure of **4g**, **4h**, and **4k** were solved by direct methods using the program SHELXS97 [16]. The structures were refined by the full matrix least squares method using SHELXL97 [17].

General Procedure for the Cycloaddition Reaction of 2-Arylidene-1,3-indanedione **1(a-k)** and the Ylide Generated from Isatin and Sarcosine.

A mixture of 2-arylidene-1,3-indanediones **1 (a-k)** (1 mmol), isatin **2** (1 mmol) and sarcosine **3** (1 mmol) were refluxed in methanol (25 ml) until the disappearance of the starting materials as evidenced by the TLC. The reaction conditions are listed in Table 1. After the reaction was over the solvent was removed *in vacuo* and the residue was chromatographed on silica gel using hexane-ethylacetate (4:1) as eluent to give **4(a-k)**.

Crystallographic Data for Compound **4h** [18].

Molecular formula: $C_{26}H_{19}CIN_2O_3$. Molecular weight 442.99, triclinic, P1. a=7.8394(9)Å, b=11.676099)Å, c=11.8628(10)Å, Dx=1.367 mg/m^3, V=1076.22(15)Å^3, α=85.657(1)°, β=89.752(1)°, γ=83.726(2)°. MoKα radiation, absorption coefficient =0.21 mm^{-1}. The crystal is yellow and needle shaped. Number of atoms = 51. A crystal with dimensions of 0.18x0.16x0.16 mm is used for X-ray data collection at 293K on a Bruker SMART APEX CCD area detector using molybdenum radiation and a graphite monochromator, θ range for data collection was 2.4-26.9°. A total of 6811 reflections were measured. R indices on all data was R_1=0.015, wR_2=0.172. Goodness of fit on F^2 was 1.09.

Crystallographic Data for Compound **4g** [19].

Molecular formula: $C_{26}H_{19}N_3O_5$. Molecular weight: 453.44. Triclinic, P1, a= 7.7610(6) Å, b=11.6696(10) Å, c= 11.9952(9) Å, Dx= 1.392 Mg/m^3, V= 1081.98(15) Å^3, α=93.392(2)°, β= 91.092(1)°, γ=93.660(1)°. Mokα radiation. Absorption coefficient = 0.10 mm^{-1}. The crystal is yellow and needle shaped. Number of atoms =53. A crystal with dimension of 0.21x 0.16x 0.14 mm was used for X-ray data collection at 293 K on a Brucker SMART APEX CCD area detector diffractometer using molybdenum radiation and a graphite monochromator. θ Range for data collection was 2.4 –27.2°. A total of 6822 reflections were measured. R indices on all data was R_1= 0.052, wR_2=0.163. Goodness of fit on F2 was 1.01.

Theoretical Studies.

Computing the frontier orbital energy differences and considering the appropriate orbital sizes of the dipole and the dipolarophile were attempted first to rationalize the observed regioselectivity. Thus, the HOMO-LUMO and the LUMO-HOMO energy gaps were estimated, which reveal that all the [3+2] cycloaddition reactions considered in the present study follow normal electron demand (Table 2). Thus, the controlling interaction is that between the HOMO of the dipole and LUMO of the dipolarophile, and the trend is independent of the substituents (Table 2). Figure 3 indicates that the shapes and the orbital coefficient sizes of the dipole and the dipolarophile are also in agreement with the observed regioselectivity in the parent systems (**4a** and **5a**). The activation energy barriers were calculated for the systems **4a** and **5a** to further elucidate the observed regioselectivity. The barrier energies were calculated to be 8.7 kcal/mol and 17.7 kcal/mol respectively. Thus, the results indicate that **4a** is a kinetically more favoured product. The structures along with the energy barriers are given in Figure 5. The reaction exothermicity differences, $\Delta(\Delta E_r)$, support the experimental observation with an exemption of *p*-OMe and 3',4'-OMe where the $\Delta(\Delta E_r)$ values were calculated to be 0.09 and 0.75 kcal/mol respectively. The structures of the products **4a** and **5a** along with the reaction energies are depicted in Figure 5. In general the exothermicity differences indicate that major product is thermodynamically more stable (Table 2). The deviation in the case of *p*-OMe and 3',4'-OMe could be explained by means of Fukui function indices.

Table 2

HOMO-LUMO Energy gaps in (eVs) between dipole and dipolarophile at AM1 level and the reaction exothermicity differences (Δ(ΔE)) (in kcal/mol) at B3LYP/6-31G*//AM1 level.

R	HOMO-LUMO	LUMO-HOMO	$\triangle(\triangle E_\alpha)^b$
H	6.6 **(2.2)**[a]	9.0 **(5.1)**	-0.88[c] (-1.23)[d]
p-Cl	6.5 **(2.0)**	9.0 **(5.1)**	-0.22
p-Me	6.7 **(2.3)**	8.8 **(4.9)**	-0.06
p-OMe	6.7 **(2.4)**	8.5 **(4.5)**	-0.09
p-NO_2	5.9 **(1.5)**	9.8 **(5.6)**	-0.46
m-Cl	6.5 **(2.0)**	9.1 **(5.2)**	-0.67
m-NO_2	6.2 **(1.8)**	9.7 **(5.5)**	-0.82
o-Cl	6.6 **(2.0)**	9.1 **(5.2)**	-0.18
o-NO_2	6.2 **(1.9)**	9.7 **(5.3)**	-1.28
3',4'-OMe	6.6 **(2.4)**	8.2 **(4.2)**	0.75
3',4',5'-OMe	6.5 **(2.3)**	8.5 **(4.3)**	-0.68

a) Values in parenthesis are at B3LYP/6-31G* level, b) $\triangle(\triangle E_\alpha)$= $\triangle E_\alpha$(4a)-$\triangle E_\alpha$(5a), c) Values are at B3LYP/6-31G*//6-31G level d) Values in parenthesis are at B3LYP/6-31G level

Table 3

Fukui functions (au) values for diene and dienophile. The calculations were done at B3LYP/6-31G* level. Numbering is according to the Figure 3.

Reactant	**1**		**3**	
	f_k^+	f_k^-	f_k^+	f_k^-
Dipole	0.04	0.15	0.12	0.08
Dipolarophile	**4**		**5**	
	f_k^+	f_k^-	f_k^+	f_k^-
H	0.04	0.15	0.12	0.08
p-Cl	0.04	0.12	0.15	0.09
p-Me	0.04	0.12	0.15	0.09
p-OMe	0.03	0.11	0.15	0.11
p-NO_2	0.04	0.09	0.11	0.06
m-Cl	0.04	0.12	0.15	0.07
m-NO_2	0.03	0.11	0.13	0.04
o-Cl	0.05	0.10	0.14	0.07
o-NO_2	0.02	0.07	0.10	0.10
3',4'-OMe	0.03	0.10	0.15	0.13
3',4',5'-OMe	0.03	0.10	0.15	0.13

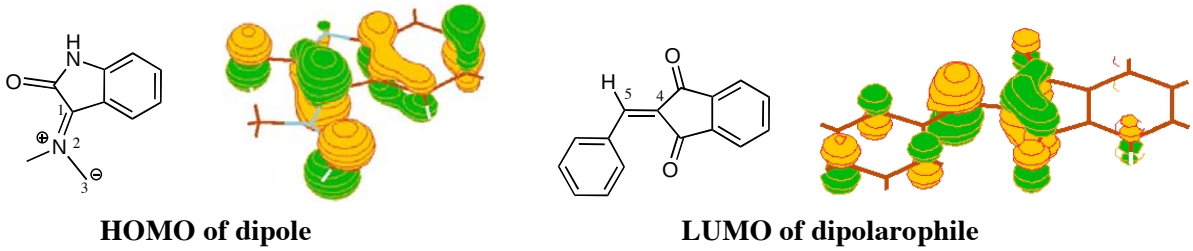
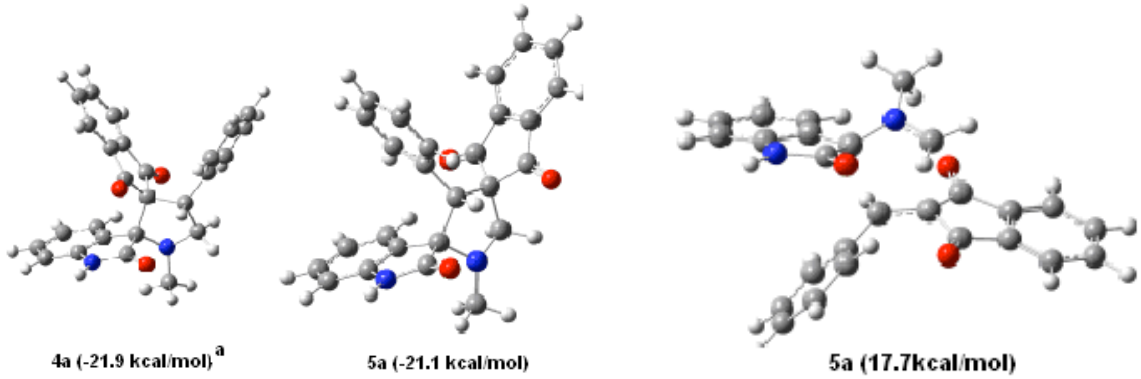


Figure 3. The frontier orbital shapes



Transition States of Products

Figure 4. Structures of the products and transition states, **4a** and **5a,** along with the reaction energies and the activation energy barriers (in parenthesis).

1-*N*-Methyl–spiro[2,3''']oxindole-spiro[3.2'']indane-1'',3''-dione-4-phenyl-pyrrolidine (**4a**).

Yellow solid; 0.21 g, 87%, mp: 216-218 °C; IR (KBr): 1708.8, 1743.5, 3143.8 cm-1, ^{1}H NMR: δ 2.14 (s, 3H), 3.58 (m, 1H), 4.04 (m, 1H), 5.04 (dd, J=9.75, 6.3 Hz, 1H), 6.58 –7.72 (m, 13H), 10.46 (bs, 1H); ^{13}C NMR: 34.58, 45.45, 55.51, 69.38, 77.20, 109.74, 121.26, 122.52, 123.36, 125.07. 126.15, 127.12, 128.22, 128.34, 129.87, 133.46, 136.14, 136.19, 136.69, 140.77, 142.01, 142.54, 175.40, 196.56, 197.56; MS *m/z:* 405.45 (M+).

Anal. Calcd for $C_{26}H_{20}N_2O_3$: C, 76.45; H, 4.93; N, 6.86. Found: C, 76.27; H, 4.90; N, 6.95.

1-*N*-Methyl–spiro[2,3''']oxindole-spiro[3,2''] indane-1'',3''-dione-4-(4'-chlorophenyl)-pyrrolidine (**4b**).

Yellow solid; 0.25 g, 85%, mp: 233-234 °C; IR (KBr): 1701.1, 1731.9, 3332.8 cm^{-1}, ^{1}H NMR: δ 2.16 (s, 3H), 3.59 (m, 1H), 3.99 (m, 1H), 5.09 (dd, J=9.75, 6.3 Hz, 1H), 6.56 –7.62 (m, 12H), 10.23 (bs, 1H); ^{13}C NMR: 34.11, 45.84, 55.62, 65.13, 69.92, 110.74, 120.23, 121.19, 122.17, 123.45. 125.17, 127.01, 127.92, 129.04, 135.92, 136.21, 136.63, 140.53, 142.20, 142.35, 172.40, 196.31, 197.42; MS *m/z:* 443 (M+).

Anal. Calcd for $C_{26}H_{19}ClN_2O_3$: C, 70.51; H, 4.32; N, 6.33. Found: C, 70.32; H, 4.43; N, 6.25.

1-*N*-Methyl–spiro[2,3''']oxindole-spiro[3,2''] indane-1'',3''-dione-4-(4'-methylphenyl)-pyrrolidine (**4c**).

Yellow solid; 0.12 g, 60%, mp: 231-232 °C; IR (KBr): 1702, 1736, 3334 cm^{-1}, ^{1}H NMR: δ 2.12 (s, 3H), 2.30 (m,3H), 2.81 (m, 1H), 3.83 (m, 1H), 5.03 (dd, J=9.75, 6.3 Hz, 1H), 6.55 –7.66 (m, 12H) , 9.15 (bs , 1H) ; ^{13}C NMR:33.34, 54.06, 58.41, 68.05, 75.60, 104.24, 108.29, 119.76, 120.81, 121.01. 123.87, 128.19, 130.16, 134.18, 134.64, 134.89, 139.74, 140.76, 141.23, 150.77, 173.98, 195.51, 196.02; MS *m/z:* 422.48 (M+).

Anal. Calcd for $C_{27}H_{22}N_2O_3$: C, 76.76; H, 5.25; N, 6.63. Found: C, 76.91; H, 5.20; N, 6.59.

1-*N*-Methyl–spiro[2.3'''']oxindole-spiro[3.2''] indane-1'',3''-dione-4-(4'-methoxyphenyl)-pyrrolidine (**4d**).

Yellow solid; 0.14g, 60%. mp: 198-200 °C; IR (KBr): 1704, 1739, 3325 cm^{-1}, ^1H NMR: δ 2.12 (s, 3H), 3.55 (m,1H), 3.73 (m, 3H), 4.07 (m, 1H), 5.06 (dd, J=9.75, 6.3 Hz, 1H), 6.41 – 7.73 (m, 12H) ,10.16 (bs ,1H) ; ^{13}C NMR:33.56, 47.32, 55.73, 65.24, 69.13, 112.21, 120.34, 122.19, 123.23, 123.56. 125.28, 126.71, 127.71, 129.15, 135.13, 136.74, 140.64, 142.31, 142.46, 172.51, 196.42, 197.33; MS *m/z:* 438.48 (M+).

Anal. Calcd for $C_{27}H_{22}N_2O_4$: C, 73.96; H, 5.06; N, 6.39. Found: C, 73.89; H, 5.14; N, 6.42.

1-*N*-Methyl–spiro[2,3'''']oxindole-spiro[3,2''] indane-1'',3''-dione-4-(4'-nitrophenyl)-pyrrolidine (**4e**).

Yellow solid; 0.20 g, 90%, mp: 246-248 °C; IR (KBr): 1346.2, 1515.9, 1701.1, 1728.1, 3340.5 cm^{-1}, ^1H NMR: δ 2.20 (s, 3H), 3.72 (m,1H), 4.09 (m, 1H), 5.03 (dd, J=9.75, 6.3 Hz, 1H), 6.53 –7.89 (m, 12H) ,10.26 (bs ,1H) ; ^{13}C NMR: 34.09, 44.26, 48.37, 54.91, 68.56, 109.15, 120.60, 121.72, 122.17, 122.17. 122.56, 124.33, 128.96, 134.81, 135.28, 140.15, 141.22, 141.58, 143.47, 145.64, 174.56, 195.65, 195.78; MS *m/z:* 453 (M+).

Anal. Calcd for $C_{26}H_{19}N_3O_5$: C, 68.87; H, 4.22; N, 9.26. Found: C, 68.91; H, 4.19; N, 9.29.

1-*N*-Methyl–spiro[2,3'''']oxindole-spiro[3,2'']indane-1'',3''-dione-4-(3'-chlorophenyl)-pyrrolidine (**4f**).

Yellow crystal; 0.15 g, 77%., mp: 233-234 °C; IR(KBr): 1703.5, 1734, 3350 cm^{-1}, ^1H NMR: δ 2.25 (s, 3H), 3.70 (m,1H), 4.08 (m, 1H), 5.12 (dd, J=9.75, 6.3 Hz, 1H), 6.6 –7.8 (m, 12H) ,10.60 (bs ,1H); ^{13}C NMR: 34.09, 43.34, 48.37, 54.94, 67.36, 68.47, 107.27, 120.48, 121.59, 121.92, 122.38. 122.50, 123.33, 127.94, 133.63, 140.28, 140.45, 141.44, 142.37, 143.53, 144.15, 174.7, 195.35, 196.21; MS *m/z:* 443 (M+).

Anal. Calcd for $C_{26}H_{19}CIN_2O_3$: C, 70.51; H, 4.32; N, 6.33. Found: C, 70.33; H, 4.66; N, 6.35.

1-*N*-Methyl–spiro[2,3'''']oxindole-spiro[3,2''] indane-1'',3''-dione-4-(3'-nitrophenyl)-pyrrolidine (**4g**).

Yellow solid; 0.18 g, 90%, mp: 241-242 °C; IR (KBr): 1352, 1517, 1706.2, 1749.3, 3344.1 cm^{-1}, ^1H NMR: δ 2.12 (s, 3H), 4.18 (m, 1H), 4.25 (m, 1H), 5.16 (dd, J=9.75, 6.3 Hz, 1H), 6.50 –7.70 (m, 12H), 10.39 (bs, 1H) ; ^{13}C NMR: 34.57, 48.69, 57.92, 68.83, 70.24, 110.10, 110.23, 121.72, 122.71, 122.93 123.31, 123.90, 130.61, 130.78, 131.20, 131.70, 132.48, 132.74, 132.87, 133.70, 136.06, 140.98, 142.67, 175.88, 195.11, 195.49; MS *m/z:* 453 (M+).

Anal. Calcd for $C_{26}H_{19}N_3O_5$: C, 68.87; H, 4.22; N, 9.26. Found: C, 68.92; H, 4.30; N, 9.12.

1-*N*-Methyl–spiro[2,3'''']oxindole-spiro[3,2''] indane-1'',3''-dione-4-(2'-chlorophenyl)-pyrrolidine (**4h**).

Yellow crystal; 0.20 g, 86%, mp: 241-242 °C; IR (KBr): 1703.2, 1735.5, 3315.6 cm^{-1}, ^1H NMR: δ 2.30 (s, 3H), 4.55 (m,1H), 4.75 (m, 1H), 5.65 (dd, J=9.75, 6.3 Hz, 1H), 6.69 – 7.60 (m, 12H) ,10.40 (bs ,1H) ; ^{13}C NMR:33.79, 42.23, 56.79, 68.28, 76.27, 109.02, 120.56, 121.27, 121.54, 121.79. 125.31, 125.44, 125.54, 127.39, 128.15, 128.89, 130.14, 133.61, 134.18, 134.76, 14o.53, 140.84, 142.31, 176.20, 196.63, 195.94; MS *m/z:* 443 (M+).

Anal. Calcd for $C_{26}H_{19}CIN_3O_5$: C, 70.51; H, 4.32; N, 6.33. Found: C, 70.79; H, 4.29; N, 6.36.

1-*N*-Methyl–spiro[2,3'''']oxindole-spiro[3,2''] indane-1'',3''-dione-4-(2'-nitrophenyl)-pyrrolidine (**4i**).

Yellow solid; 0.18 g, 87%, mp: 167-168 °C; IR (KBr): 1361.7, 1523.7, 1708.8, 1751.2, 3344.3 cm^{-1}, ^1H NMR: δ 2.10 (s, 3H), 4.10 (m,1H), 4.25 (m, 1H), 5.14 (dd, J=9.75, 6.3 Hz, 1H), 6.40 –7.70 (m, 12H) ,10.28 (bs ,1H) ; ^{13}C NMR:34.68, 49.13, 58.35, 68.98, 70.07, 110.05, 110.20, 121.79, 122.74, 123.31. 123.36, 123.98, 130.41, 130.55, 131.11, 131.95, 132.68, 133.78, 136.07, 141.92, 143.10, 175.91, 195.02, 196.55; MS *m/z:* 453 (M+).

Anal. Calcd for $C_{26}H_{19}N_3O_5$: C, 68.87; H, 4.22; N, 9.26. Found: C, 68.99; H, 4.18; N, 9.38.

1-*N*-Methyl–spiro[2,3'''']oxindole-spiro[3,2'']indane-1'',3''-dione-4-(3',4'-dimethoxyphenyl)-pyrrolidine (**4j**).

Yellow solid; 0.12 g, 67%, mp: 201-202 °C; IR (KBr): 1702.7, 1738.8, 3321.2 cm^{-1}, ^1H NMR: δ 2.24 (s, 3H), 3.60 (s,3H), 3.63 (s, 3H), 3.70 (m, 1H), 4.06 (m, 1H), 5.04 (dd, J=9.75, 6.3 Hz, 1H), 6.56 –7.63 (m, 11H) ,10.20 (bs ,1H) ; ^{13}C NMR:39.62, 40.27, 52.73, 53.94, 54.96, 56.49, 69.98, 110.19, 114.32, 121.61, 123.01. 123.48, 125.60, 128.31, 130.07, 130.40, 135.29, 136.59, 137.21, 143.09, 157.76, 175.84, 197.41, 198.19; MS *m/z:* 468.50 (M+).

Anal. Calcd for $C_{28}H_{24}N_2O_5$: C, 71.78; H, 5.16; N, 5.98. Found: C, 71.92; H, 5.32; N, 6.21

1-*N*-Methyl–spiro[2,3'''']oxindole-spiro[3,2''] indane-1'',3''-dione-4-(3',4',5'-trimethoxyphenyl)-pyrrolidine (**4k**).

Yellow solid; 0.10 g, 59%, mp: 203-204 °C; IR (KBr): 1701, 1736, 3320 cm^{-1}, ^1H NMR: δ 2.22 (s, 3H), 3.68 (m, 1H), 3.70 (s, 9H), 4.04 (m, 1H), 5.02 (dd, J=9.75, 6.3 Hz, 1H), 6.58 –7.66 (m, 11H) ,10.20 (bs ,1H) ; ^{13}C NMR:39.58, 41.20,51.60, 52.94, 56.30, 56.45, 69.94, 109.97, 112.20, 120.42, 121.38, 123.11. 123.21, 125.48, 128.10, 129.97, 130.20, 135.19, 136.48, 137.19, 142.68, 157.41, 175.79, 197.32, 197.54; MS *m/z:* 498.53 (M+).

Anal. Calcd for $C_{29}H_{26}N_2O_6$: C, 69.87; H, 5.26; N, 5.62. Found: C, 69.60; H, 5.43; N, 5.80.

Acknowledgements.

A.R.S. and ***G.G.*** thank Council of Scientific and Industrial Research (CSIR), New Delhi for the award of junior research fellowship. Financial support from CSIR and DST, New Delhi is gratefully acknowledged.

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