One-pot Regioselective Synthesis of Novel 1-*N*-Methyl-spiro[2,3′] oxindole-spiro[3,3″]-1″-*N*-arylpyrrolidine-2″,5″-dione-4-arylpyrrolidines through Multicomponent 1,3-Dipolar Cycloaddition Reaction of Azomethine Ylide

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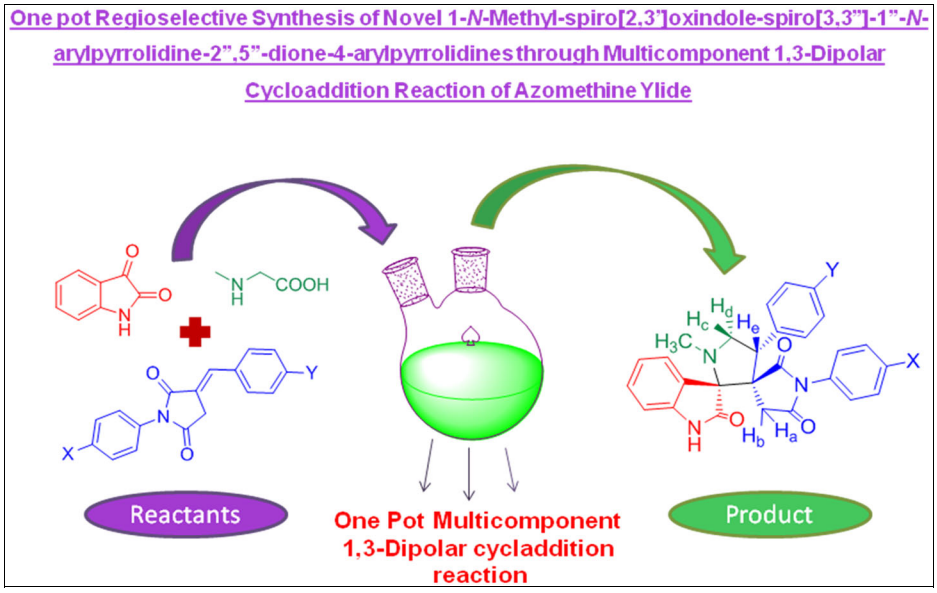
Received October 26, 2013
DOI 10.1002/jhet.2199
Published online 00 Month 2014 in Wiley Online Library (wileyonlinelibrary.com).



An atom economic and facile synthesis of novel dispiro–oxindole–pyrrolidines has been achieved *via* a three-component tandem cycloaddition of azomethine ylide generated *in situ* from isatin and sarcosine by decarboxylative condensation with *N*-aryl-3-benzylidene-pyrrolidine-2,5-dione derivatives as dipolarophiles. The salient features of synthetic procedure are characterized by the mild reaction conditions, high yields, high regioselectivity and stereoselectivity, one-pot procedure, and operational simplicity. This regioselectivity was assumed to be under the influence of π–π stacking interactions between the aromatic rings of azomethine ylide and *N*-aryl-3-benzylidene-pyrrolidine-2,5-diones that further control the exo–endo selectivity of the reaction 1,3-dipolar cycloaddition. The regiochemistry and structures of the cycloadducts were determined with spectroscopic data.

INTRODUCTION

Exploring novel pharmacological agents with minimum number of synthetic steps and less time is a major challenge for chemists [1,2]. In general, the conventional approach involves the use of multistep reaction sequences that are typically associated with low yields, high cost, and tedious isolation and purification of the resulting products. However, as a significant strategy superior to the conventional one, multicomponent reactions (MCRs) offer a valuable solution for such a situation [3–7]. The highly effective one-pot procedure of MCRs exhibits many advantages, including atom economy, facile synthesis, convergence, productivity, and easy execution [8]. MCRs have emerged as a powerful tool for delivering the molecular diversity needed in the combinatorial approaches for the syntheses of bioactive compounds [9]. MCRs leading to interesting heterocyclic scaffolds are particularly useful for the creation of diverse chemical libraries of "drug-like" molecules for biological screening [10,11]. Multicomponent 1,3-dipolar cycloaddition reactions are fundamental processes in organic chemistry [12], and their asymmetric version offers a powerful and reliable synthetic methodology to access five-membered heterocyclic rings in regiocontrolled and stereocontrolled fashion [13–15]. Indeed, the 1,3-dipolar cycloaddition reaction has been described as "the single most important method for the construction of heterocyclic five-membered rings in organic chemistry" [16]. The 1,3-dipolar cycloaddition of ylidic species such as azomethine ylides with dipolarophiles provides an efficient and convergent approach for constructing pyrrolidine rings that are classes of compounds with

significant biological activities [17–24]. While the cycloaddition of these dipoles to the exocyclic olefins results in the formation of spiro-pyrrolidines [25] that are endowed with a wide range of pharmacological activities [26–34]. The ease of generation of azomethine ylides coupled with the highly regioselective and stereoselective nature of their cycloaddition reactions has resulted in a number of syntheses that utilize such a reaction as the key step.

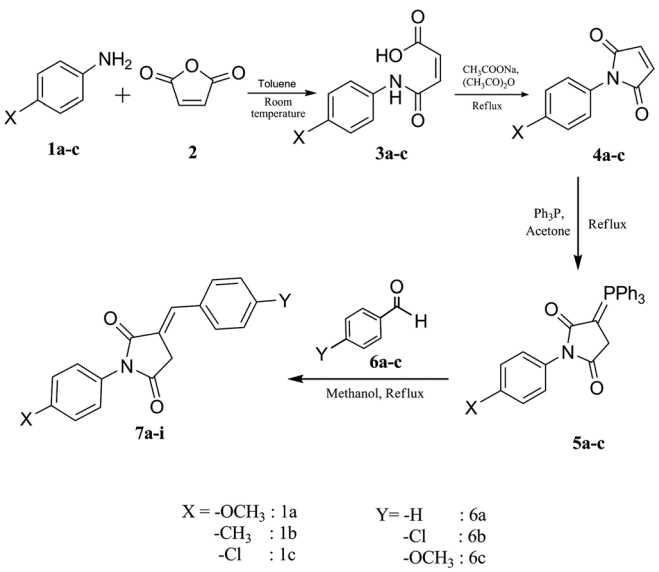
The ability to utilize azomethine ylide cycloaddition in organic synthesis depends heavily on understanding the factors that determine the stereochemistry of the reaction. As part of our ongoing research program directed toward the cycloaddition reactions [35], we report herein the regioselective and stereoselective synthesis of dispiro–oxindole–pyrrolidine derivatives through 1,3-dipolar cycloaddition reaction of an azomethine ylide generated by decarboxylative condensation reaction of isatin **8** and sarcosine **9**, with olefinic segment of *N*-aryl-3-benzylidene-pyrrolidine-2,5-diones, which makes possible the simultaneous formation of three stereocenters in the cycloadducts. In our work, we investigated the effect of approach of the dipolarophiles toward the azomethine ylide on the exo–endo selectivity of their cycloaddition reactions. This could ensure an entry to the control of the regiochemistry and stereochemistry of cycloaddition, where the π–π stacking interactions may play a significant role.

RESULT AND DISCUSSION

As a part of our endeavor to synthesize novel heterocycles *via* cycloaddition reactions and their screening for biological activities prompted us to investigate 1,3-dipolar cycloaddition reactions of azomethine ylides with variously substituted dipolarophiles [36]. With a view to synthesize novel dispiro heterocyclic derivatives, we herein report the 1,3-dipolar cycloaddition reaction of variously substituted *N*-aryl-3-benzylidene-pyrrolidine-2,5-dione derivatives as 2π components with the unstabilized azomethine ylides generated *in situ*. In this reaction, we prepared variously substituted *N*-aryl-3-benzylidene-pyrrolidine-2,5-dione (dipolarophile) **7a–i** employing Wittig reaction between a variety of substituted benzaldehydes **6ac** and *N*-aryl-3-(triphenylphosphinylidene)pyrrolidine-2,5-diones **5a–c**. The compound **5** itself was synthesized by refluxing triphenylphosphine and variously substituted maleimides **4a–c**. Subsequently, the Wittig reaction of **5** with variously substituted aromatic aldehydes proceeded smoothly under reflux conditions in methanol, giving **7a–i** in good yields (Scheme 1). The 1,3-dipolar cycloaddition of azomethine ylide **10** generated *in situ via* decarboxylative condensation of isatin **8** and sarcosine **9** with the exocyclic double bond of *N*-aryl-3-benzylidene-pyrrolidine-2,5-diones **7a–i** in methanol at reflux temperature yielded (Scheme 2) a series of dispiro–oxindole–pyrrolidines **11a–i** in good yields (Table 1). The reaction afforded only one diastereomer exclusively in all cases, as evidenced by TLC showing the regioselectivity of these 1,3-dipolar cycloadditions.

The preferred orientation of azomethine ylide **10** in the transition state seems to be the more thermodynamically stable "anti" one where nonbonding steric interactions are minimum as compared to the "syn-ylide" where the unfavorable steric repulsion between the carbonyl group of oxindole and methyl group of sarcosine raises the energy of this moiety (Fig. 1). As the dipole and dipolarophile approach each other, there occur secondary along with the primary interactions between the two substrates. The

Scheme 1. Schematic diagram describing the steps in the synthesis of *N*-aryl-3-benzylidene-pyrrolidine-2,5-diones from differently substituted aniline derivatives.



Scheme 2. Schematic diagram describing the synthesis of dispiro–oxindole–pyrrolidines from azomethine ylide and differently substituted *N*-aryl-3-benzylidene-pyrrolidine-2,5-diones.

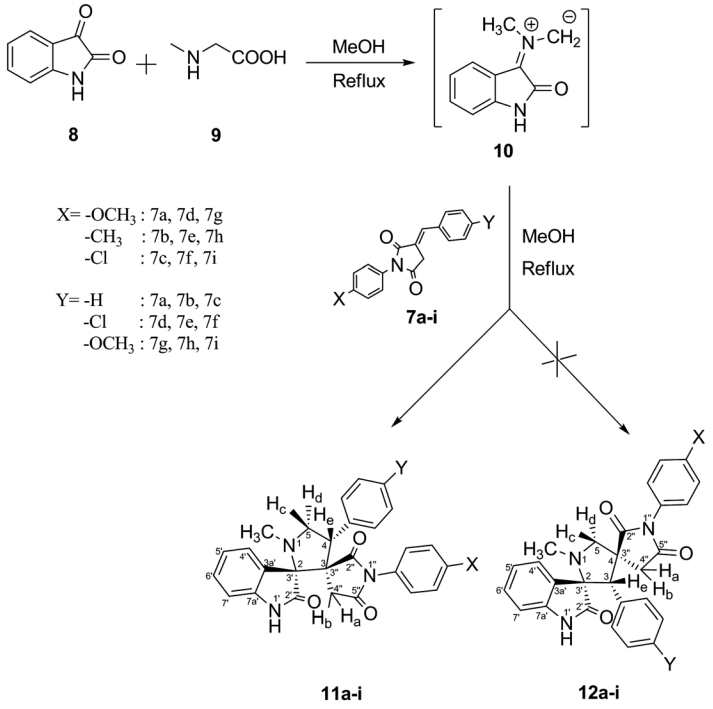
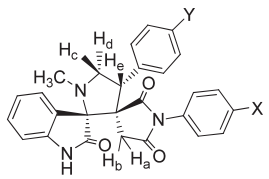


Table 1

Synthesis of 1-*N*-methyl-spiro[2,3′]oxindole-spiro[3,3″]-1″-*N*-arylpyrrolidine-2″,5″-dione-4-arylpyrrolidines (**11a–i**).



Entry	Products	*X*	*Y*	Melting point (°C)	Percentage yield
1	**11a**	OCH_3	H	214–216	69
2	**11b**	CH_3	H	228–230	75
3	**11c**	Cl	H	189–190	81
4	**11d**	OCH_3	Cl	208–210	72
5	**11e**	CH_3	Cl	216–218	80
6	**11f**	Cl	Cl	224–226	87
7	**11g**	OCH_3	OCH_3	212–214	65
8	**11h**	CH_3	OCH_3	224–226	72
9	**11i**	Cl	OCH_3	228–230	78

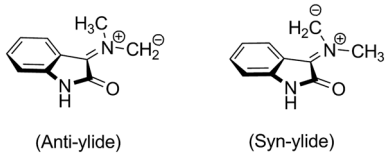


Figure 1. Configuration of azomethine ylide.

transition state seems to follow the "*endo* addition rule" where state there is a "maximum accumulation of double bonds" of the dipole and that of the dipolarophile. In this transition state, the benzene ring of oxindole nucleus of dipole and *N*-phenyl nucleus of the imide moiety of dipolarophile come parallel to each other that seems to stabilize the transition state. From a study of the Drieding models of the regioisomer **11** (Fig. 2), it has been found that this is the most favored conformation as nonbonded steric interaction are completely absent while secondary orbital interactions are present in this state, as compared with the other transition state, that is, the *exo* one where there are no such secondary interactions present (Fig. 3). This leads to the complete absence of the regioisomer **12**; hence, only one set of regioisomers **11a–i** was obtained.

Structural elucidation of the 1-*N*-Methyl-spiro[2,3′] oxindole-spiro[3,3″]-1″-*N*-arylpyrrolidine-2″,5″-dione-4-arylpyrrolidines was unambiguously accomplished by using one and two dimensional spectroscopic techniques (IR, ^{1}H-NMR, ^{13}C-NMR, ^{1}H-^{1}H COSY, NOESY, ESI-MS) and elemental analyses data as described for **11a**. The IR spectrum of 1-*N*-methyl- spiro[2,3′]oxindole-spiro [3,3′]-1″-*N*-(4-methoxyphenyl)pyrrolidine-2″,5″-dione-4-phenylpyrrolidines (**11a**) revealed the presence of carbonyl stretching intense vibration band (ν_{max}) at 1777 cm^{-1} due to mergence of carbonyl stretch bands of oxindole moiety and one carbonyl group of succinimide ring while a shoulder band at frequency 1708 cm^{-1} was assigned to the second carbonyl group of succinimide ring. Absorption band

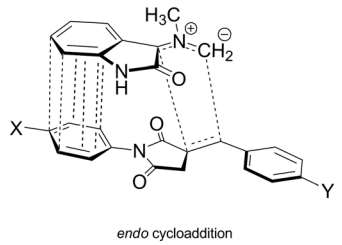


Figure 2. Drieding model of regioisomers **11a–i**.

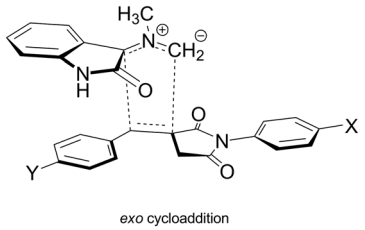


Figure 3. Drieding model of regioisomers **12a–i**.

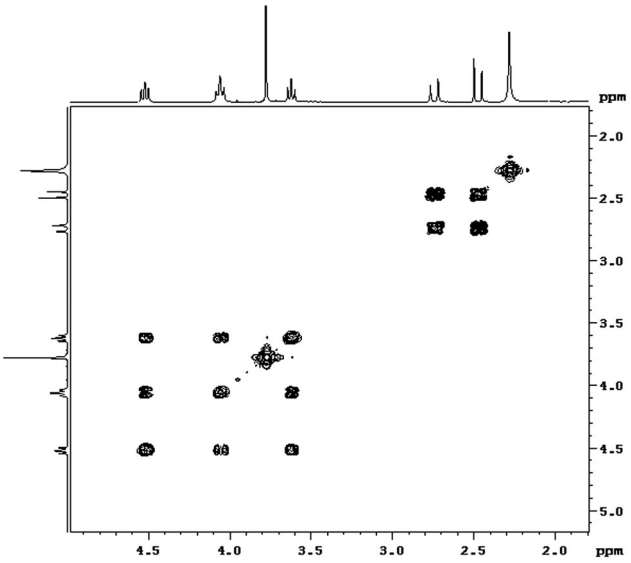


Figure 4. 400 MHz ^{1}H,^{1}H-COSY spectrum of **11a** $CDCl_3$.

at 3468 cm^{-1} was assigned to the —NH stretch of oxindole moiety. The ^{1}H-NMR spectrum of **11a** revealed one sharp singlet at δ 2.28 due to the *N*-methyl protons. The two geminal protons H_a and H_b at carbon C-4″ emerged as separate signals, that is, proton H_a appeared as doublet at δ 2.47 due to coupling with proton H_b ($J = 19.00$ Hz) where as the proton H_b appeared downfield as doublet at δ 2.74 ($J = 18.96$ Hz) due to coupling with H_a. Out of these two geminal protons, the proton H_b experienced a downfield shift as compared with proton H_a because of orientation of carbonyl group of oxindole moiety. As a result, proton H_b comes in deshielding zone of the π-bond electron cloud of the carbonyl group. Also, the two geminal protons at carbon C-5 exhibited separate signals. The proton H_c appeared as triplet at δ 3.62 on coupling with protons H_d and H_e ($J = 8.60$ Hz); another triplet at δ 4.06 was assigned to proton H_d on coupling with protons H_c and H_e ($J = 9.64$ Hz). The proton H_d shows downfield shift among these two geminal protons as H_d comes in the deshielding zone of the π-ring cloud of the phenyl ring present at carbon C-4 proving the syn-geometry of H_d with this phenyl ring. A fine singlet at δ 3.77 was assigned to methoxy protons present at the phenyl ring of succinimide moiety. The proton H_e exhibited a doublet of doublet at δ 4.52 on coupling with protons H_c and H_d ($J = 8.32$ and 9.80 Hz). The aromatic protons appeared as multiplet in the region of δ 6.64–7.50, and a broad singlet appeared at δ 7.70 due to —NH proton of oxindole moiety.

Further confirmation of the structure comes from their two-dimensional ^{1}H,^{1}H-COSY spectrum (Fig. 4). The geminal protons H_a and H_b at carbon C-4″ show the ^{1}H,^{1}H-COSY correlation as evident from the off diagonal cross-peaks at δ 2.47/2.74 having coupling constant $J \approx 19.00$ Hz proving their geminal nature. As evident from the ^{1}H-NMR spectrum, assigning the more downfield doublet of doublet in aliphatic region to benzylic proton H_e of pyrrolidine ring triggers the assignment of all the connected protons in the ring by its ^{1}H,^{1}H-COSY spectral analysis. From the ^{1}H,^{1}H-COSY correlations of H_e (off diagonal cross-peaks at δ 4.52/3.62 and δ 4.52/4.06), the triplets at δ 3.62 and 4.06 were assigned to the protons H_c and H_d, respectively. The δ 3.62 and 4.06 showed clean splitting pattern with J values large enough ($J_{Hc\text{-}He} = 8.60$ Hz and $J_{Hd\text{-}He} = 9.64$ Hz) to identify H_c and H_d as neighboring protons. The off diagonal cross-peaks at δ 3.62/4.06 proved the correlation of geminal protons H_c and H_d.

In the NOESY (Figs 5 and 6) spectrum of **11a**, there exist correlation cross-peaks from protons H_a/(H-2‴, H-6‴)

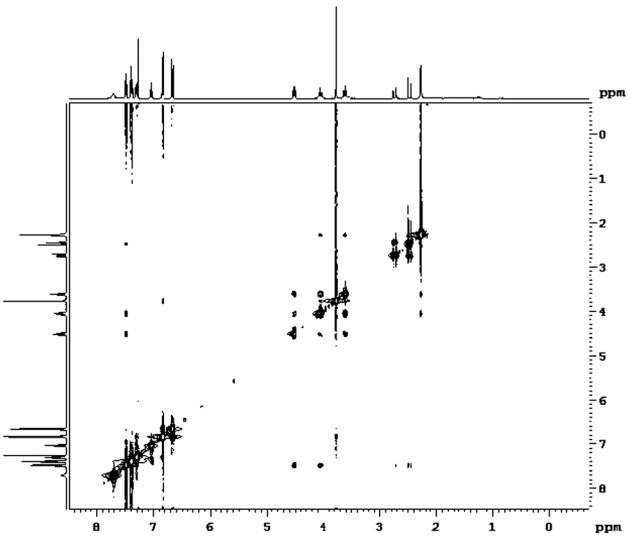
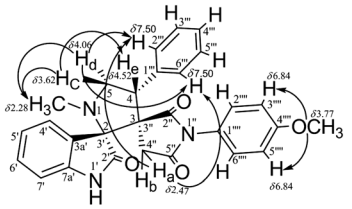


Figure 5. 400 MHz NOESY spectrum of **11a** in $CDCl_3$.



11a

Figure 6. Structure of compound **11a** and NOE correlation.

at δ 2.47/7.50 and H_d/(H-2‴, H-6‴) at δ 4.06/7.50 revealing the spatial proximity of protons H_a and H_d with the phenyl ring protons at carbon C-4, which signifies the same planarity of H_a, H_d, and C_4-phenyl ring. No NOESY correlation among H_c, H-2‴, and H-6‴ protons demonstrated the *trans*-stereochemistry of protons H_c and phenyl ring at C-4. Further, the stronger correlation cross-peaks for protons H_c/H_e at δ 3.62/4.52 than the protons H_d/H_e at δ 4.06/4.52 affirmed the syn-geometry of H_c and H_e protons and anti-geometry of H_d and H_e protons. Further, the NOESY experiment denoted the spatial interactions due to close proximity of protons H_c and H_d with *N*-methyl protons, as evident from the cross-peaks at δ 3.62/2.28 and δ 4.06/2.28. The —OCH_3 group present at C-4‴ carbon of *N*-phenyl ring of succinimide moiety also exhibited the correlation with the aromatic protons H-3‴ and H-5‴ through space as affirmed by the off diagonal cross-peaks at δ 3.77/6.84.

The off-resonance decoupled ^{13}C-NMR spectrum of **11a** exhibited a signal at δ 35.10 due to carbon C-4 while a signal at δ was assigned to carbon C-4″. The *N*-CH_3 and *N*-CH_2 carbons exhibited the signals at δ 49.77 and δ 59.03 because of presence of adjacent *N*-atom. The two peaks at δ 61.67 and 78.56 correspond to the two spiro carbons C-3 and C-2, respectively. Suitable signals due to aromatic carbons were assigned to the region of δ 110.15–159.54, and the imide carbonyl carbons C-2′, C-5″, and C-2″ resonated at δ 174.24, 177.80, and 178.82, respectively. Each of the succinimide carbonyl carbon exhibited a downfield shift as compared with carbonyl carbon of oxindole moiety because of the more deshielding effect of the two carbonyl groups present in the succinimide ring. The mass spectrum of **11a** revealed the molecular ion peak $[M^+ + 1]$ at *m*/*z* 468, and similar peak pattern was obtained with other derivatives of 1-*N*-Methyl-spiro[2,3′]oxindole-spiro[3,3″]-1″-*N*-arylpyrrolidine-2″,5″-dione-4-arylpyrrolidines.

CONCLUSION

In conclusion, we have successfully developed the regioselective version of bioactive pyrrolidines ring containing oxindole group in a one-pot, three-component cycloaddition reaction. It was observed that the unstabilized azomethine ylide generated, added stereoselectivity and regioselectively across the exocyclic double bonds of the dipolarophiles to give novel spiroheterocycles that indicates the high *endo*-diastereoselectivity due to stabilization by the secondary π-orbital interactions in the *endo*-approach of the transition state.

EXPERIMENTAL

General. Unless otherwise indicated, all common reagents were used as obtained from commercial suppliers (SIGMA-ALDRICH CORPORATION, Bangalore, India) without further purification, and the solvents were dried before use. All melting points were recorded on Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer RXIFT infrared spectrophotometer (manufactured at Buckinghamshire, England) using KBr pellets. ^{1}H-NMR, ^{1}H,^{1}H-COSY, and NOESY were recorded at 400 MHz on BRUKER spectrometer (manufactured at Fallanden, Switzerland) using tetramethylsilane as internal standard. The ^{13}C-NMR spectra were recorded at 100 MHz on BRUKER spectrometer using tetramethylsilane as internal standard. Mass spectra were recorded on Waters Micromass Q-T of Micro (ESI) spectrometer (manufactured at Vernon Hills, IL, USA). Elemental analysis was carried out using Elementar Vario MICRO cube CHN analyzer (Frankfurt, Germany). TLC analysis was carried out on glass plates coated with silica gel-G (Loba Chemie Pvt. Ltd, Mumbai, Maharashtra, India) suspended in methanol–chloroform. Column chromatography was performed using silica gel (100–200 mesh, Loba Chemie Pvt. Ltd).

General procedure for synthesis of maleimide (4a–c). Equimolar quantities of *p*-substituted aniline **1a–c** and maleic anhydride **2** were stirred in toluene at room temperature for 1 h to yield maleamic acid **3a–c**. The maleamic acid thus obtained was further cyclized to maleimide (Scheme 1) in acetic anhydride in the presence of anhydrous sodium acetate under reflux for one and half hour and then pouring the contents in ice cold water and keeping it overnight to afford the solid that was filtered and washed with water to give the maleimide **4a–c**.

General procedure for the synthesis of N-aryl-3-benzylidene-pyrrolidine-2,5-diones (7a–i). Stoichiometric amounts of maleimide **4a–c** and triphenylphosphine in anhydrous acetone were refluxed until the substrates were consumed as judged by TLC (Scheme 1). After cooling, the precipitates formed were filtered through a Buchner funnel, and the filter cake was washed with cold acetone (10 mL). Drying under reduced vacuum afforded *N*-aryl-3-(triphenylphosphanylidene) pyrrolidine-2,5-diones **5a–c** as a white solid. The solid was used for the next step without further purification.

A suspension of substituted benzaldehydes **6a–c** and *N*-aryl-3-(triphenylphosphanylidene)pyrrolidine-2,5-diones **5** in their equimolar amounts in MeOH were refluxed. Before the temperature reached the boiling point of methanol, the reaction mixture generally became a clear solution. During reflux, the precipitates were formed and filtered through a Buchner funnel after cooling. The filter cake was washed with methanol and proper solvents, depending on the property of the substituted benzaldehydes used for the reaction, to give the title product. The product precipitated out in this manner was characterized by melting point and TLC. The crude product obtained was recrystallized from toluene.

General procedure for the synthesis of dispiro–oxindole–pyrrolidine derivatives (11a–i). An oven-dried flask was

cooled under a stream of nitrogen and charged with mixture of isatin **8** (1 mmol), sarcosine **9** (1 mmol), and *N*-aryl-3-benzylidene-pyrrolidine-2,5-diones **7a–i** (1 mmol) methanol (25 mL). The flask was equipped with a reflux condenser, and the mixture was refluxed (Scheme 2) until the substrates were consumed as judged by TLC. On completion, the reaction mixture was concentrated, and the precipitated compound was filtered. The solvent was removed under vacuo, and the crude product was subjected to column chromatography using hexane:ethyl acetate (8 : 2) as an eluent to afford pure dispiro–oxindole–pyrrolidines **11a–i**.

1-N-Methyl-spiro[2,3′]oxindole-spiro[3,3″]-1″-N-(4-methoxyphenyl)pyrrolidine-2″,5″-dione-4-phenylpyrrolidine (11a). Compound obtained as white solid (0.32 g, 69 %), mp 214–216°C; IR (KBr pellets, ν_{max}/cm^{-1}): 1619 (C═C), 1708, 1777 (C═O), 3468 (N—H); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 2.28 (s, 3H, —NCH_3), 2.47 (d, 1H, J = 19.00 Hz, H_a), 2.74 (d, 1H, J = 18.96 Hz, H_b), 3.62 (t, 1H, J = 8.60 Hz, H_c), 3.77 (s, 3H, —OCH_3), 4.06 (t, 1H, J = 9.64 Hz, H_d), 4.52 (dd, 1H, J = 8.32, 9.80 Hz, H_e), 6.64–7.50 (m, 13H, ArH), 7.70 (brs, 1H, —NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 35.19 (C-4), 37.07 (C-4″), 49.77 (—NCH_3), 55.45 (4‴—OCH_3), 59.03 (C-5), 61.76 (C-3), 78.56 (C-2), 110.15 (C-3a′), 114.31 (C-3‴, 5‴), 123.38 (C-7′), 124.02 (C-2‴, 6‴), 125.12 (C-5′), 127.44 (C-2‴, 4‴, 6‴), 127.89 (C-3‴, 5‴), 129.15 (C-6′), 130.19 (C-4′), 130.22 (C-1‴), 137.76 (C-7a′), 141.58 (C-1′‴), 159.54 (C-4‴′), 174.24 (C-2′, C═O), 177.80 (C-5″, C═O), 178.82 (C-2″, C═O); MS: *m/z*: 468 [M^+ + 1], *Anal*. Calcd for $C_{28}H_{25}N_3O_4$: C, 71.94; H, 5.35; N, 8.99, found: C, 72.09; H, 5.33; N, 9.02.

1-N-Methyl-spiro[2,3′]oxindole-spiro[3,3″]-1″-N-(4-methylphenyl)pyrrolidine-2″,5″-dione-4-phenylpyrrolidine (11b). Compound obtained as white solid (0.33 g, 75 %), mp 228–230°C; IR (KBr pellets, ν_{max}/cm^{-1}): 1620 (C═C), 1708, 1719, 1781 (C═O), 3475 (N—H); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 2.27 (s, 3H, —CH_3), 2.32 (s, 3H, —NCH_3), 2.48 (d, 1H, J = 19.04 Hz, H_a), 2.73 (d, 1H, J = 19.04 Hz, H_b), 3.61 (t, 1H, J = 8.52 Hz, H_c), 4.05 (t, 1H, J = 9.56 Hz, H_d), 4.51 (dd, 1H, J = 8.12, 9.84 Hz, H_e), 6.62–7.51 (m, 13H, ArH), 7.73 (brs, 1H, —NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 21.22 (4‴—CH_3), 35.20 (C-4), 37.11 (C-4″), 49.78 (—NCH_3), 59.03 (C-5), 61.77 (C-3), 78.48 (C-2), 110.06 (C-3a′), 123.47 (C-7′), 125.04 (C-2‴, 6‴), 126.47 (C-5′), 127.49 (C-2‴, 4‴, 6‴), 127.91 (C-3‴, 5‴), 128.74 (C-6′), 129.16 (C-4′), 129.69 (C-3‴, 5‴), 130.20 (C-4‴), 137.72 (C-1‴), 138.81 (C-7a′), 141.41 (C-1‴), 174.09 (C-2′, C═O), 177.60 (C-5″, C═O), 178.68 (C-2″, C═O); MS: *m/z*: 452 [M^+ + 1], *Anal*. Calcd for $C_{28}H_{25}N_3O_3$: C, 74.50; H, 5.54; N, 9.31, found: C, 74.70; H, 5.52; N, 9.33.

1-N-Methyl-spiro[2,3′]oxindole-spiro[3,3″]-1″-N-(4-chlorophenyl)pyrrolidine-2″,5″-dione-4-phenylpyrrolidine (11c). Compound obtained as white solid (0.38 g, 81 %), mp 189–190°C; IR (KBr pellets, ν_{max}/cm^{-1}): 1615 (C═C), 1710, 1782 (C═O), 3470 (N—H); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 2.15 (s, 3H, —NCH_3), 2.36 (d, 1H, J = 18.44 Hz, H_a), 2.69 (d, 1H, J = 18.36 Hz, H_b), 3.49 (t, 1H, J = 8.52 Hz, H_c), 3.90 (t, 1H, J = 9.24 Hz, H_d), 4.39 (t, 1H, J = 9.40 Hz, H_e), 6.74–7.50 (m, 13H, ArH), 10.71 (s, 1H, —NH); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 34.52 (C-4), 36.74 (C-4″), 48.36 (—NCH_3), 58.62 (C-5), 61.16 (C-3), 77.61 (C-2), 109.89 (C-3a′), 121.84 (C-2‴, 6‴), 124.73 (C-7′), 126.08 (C-5′), 127.18 (C-2‴, 4‴, 6‴), 128.11 (C-3‴, 5‴), 128.42 (C-6′), 129.70 (C-4′), 129.87 (C-1‴), 130.03 (C-3‴, 5‴), 133.07 (C-4‴), 137.76 (C-7a′), 142.75 (C-1‴), 172.53 (C-2′, C═O), 177.05 (C-5″, C═O), 177.31 (C-2″, C═O); MS: *m/z*: 472 [M^+ + 1], 473 [M^+ + 2] *Anal*. Calcd for $C_{27}H_{22}ClN_3O_3$: C, 68.71; H, 4.66; N, 8.90, found: C, 68.89; H, 4.67; N, 8.87.

1-N-Methyl-spiro[2,3′]oxindole-spiro[3,3″]-1″-N-(4-methoxyphenyl)pyrrolidine-2″,5″-dione-4-(4-clorophenyl)pyrrolidine (11d). Compound obtained as white solid (0.36 g, 72 %), mp 208–210°C; IR (KBr pellets, ν_{max}/cm^{-1}): 1615 (C═C), 1707, 1780 (C═O), 3466 (N—H); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 2.25 (s, 3H, —NCH_3), 2.43 (d, 1H, J = 18.92 Hz, H_a), 2.72 (d, 1H, J = 18.88 Hz, H_b), 3.60 (dd, 1H, J = 8.24, 8.96 Hz, H_c), 3.77 (s, 3H, OCH_3), 3.97 (t, 1H, J = 9.40 Hz, H_d), 4.47 (dd, 1H, J = 8.16, 9.76 Hz, H_e), 6.65–7.47 (m, 12H, ArH), 7.86 (s, 1H, —NH); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 35.71 (4-CH_3), 37.04 (C-4″), 49.04 (—NCH_3), 55.45 (4‴—OCH_3), 59.25 (C-5), 61.60 (C-3), 78.50 (C-2), 110.15 (C-3a′), 114.32 (C-3‴, 5‴), 123.50 (C-7′), 123.91 (C-2‴, 6‴), 124.91 (C-5′), 127.37 (C-3‴, 5‴), 127.84 (C-6′), 129.30 (C-4′), 130.33 (C-2‴, 6‴), 131.62 (C-1‴), 133.82 (C-4‴), 136.38 (C-7a′), 141.46 (C-1‴), 159.58 (C-4‴), 173.90 (C-2′, C═O), 177.60 (C-5″, C═O), 178.64 (C-2″, C═O); MS: *m/z*: 502 [M^+ + 1], 503 [M^+ + 2], *Anal*. Calcd for $C_{28}H_{24}ClN_3O_4$: C, 67.00; H, 4.78; N, 8.37, found: C, 67.25; H, 4.76; N, 8.39.

1-N-Methyl-spiro[2,3′]oxindole-spiro[3,3″]-1″-N-(4-methylphenyl)pyrrolidine-2″,5″-dione-4-(4-chlorophenyl)pyrrolidine (11e). Compound obtained as white solid (0.39 g, 80 %), mp 216–218°C; IR (KBr pellets, ν_{max}/cm^{-1}): 1613 (C═C), 1715, 1783 (C═O), 3469 (N—H);^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 2.18 (s, 3H, —CH_3), 2.25 (s, 3H, —NCH_3), 2.36 (d, 1H, J = 18.96 Hz, H_a), 2.65 (d, 1H, J = 18.92 Hz, H_b), 3.53 (dd, 1H, J = 8.36, 8.88 Hz, H_c), 3.90 (t, 1H, J = 9.48 Hz, H_d), 4.40 (dd, 1H, J = 8.16, 9.80 Hz, H_e), 6.54–7.40 (m, 12H, ArH), 7.57 (s, 1H, —NH); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.19 (4‴—CH_3), 35.10 (C-4), 37.07 (C-4″), 49.06 (N—CH_3), 59.23 (C-5′), 61.62 (C-3), 78.46 (C-2), 110.09 (C-3a′), 123.53 (C-7′), 124.89 (C-2‴, 6‴), 126.41 (C-5′), 127.41 (C-2‴, 6‴), 128.68 (C-6′), 129.30 (C-4′), 129.67 (C-3‴, 5‴), 130.31 (C-3′′′′, 5′′′′), 131.62 (C-1‴), 133.82 (C-4‴), 136.37 (C-4′′′′), 138.84 (C-7a′), 141.38 (C-1′′′′), 173.74 (C-2′, C═O), 177.44 (C-5″, C═O), 178.50 (C-2″, C═O); MS: *m/z*: 486 [M^+ + 1], 487 [M^+ + 2] *Anal*. Calcd for $C_{28}H_{24}ClN_3O_3$: C, 69.20; H, 4.94; N, 8.65, found: C, 68.97; H, 4.93; N, 8.68.

1-N-Methyl-spiro[2,3′]oxindole-spiro[3,3″]-1″-N-(4-chlorophenyl)pyrrolidine-2″,5″-dione-4-(4-chlorophenyl)pyrrolidine (11f). Compound obtained as white solid (0.44 g, 87 %), mp 224–226°C; IR (KBr pellets, ν_{max}/cm^{-1}): 1620 (C═C), 1716, 1789 (C═O), 3471 (N—H); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 2.25 (s, 3H, —NCH_3), 2.43 (d, 1H, J = 18.92 Hz, H_a), 2.74 (d, 1H, J = 18.92 Hz, H_b), 3.60 (t, 1H, J = 8.48 Hz, H_c), 3.96 (t, 1H, J = 9.52 Hz, H_d), 4.46 (dd, 1H, J = 8.16, 9.72 Hz, H_e), 6.70–7.46 (m, 12H, ArH), 7.67 (s, 1H, —NH); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 35.08 (C-4), 37.10 (C-4″), 48.90 (—NCH_3), 59.26 (C-5), 61.79 (C-3), 78.45 (C-2), 110.20 (C-3a′), 123.53 (C-7′), 124.81 (C-2′′′′, 6′′′′), 127.19 (C-5′), 127.81 (C-2‴, 6‴), 129.19 (C-3‴, 5‴), 129.34 (C-3′′′′, 5′′′′), 129.73 (C-6′), 130.43 (C-4′), 131.59 (C-1‴), 133.91 (C-4′′′′), 134.57 (C-4‴), 136.21 (C-7a′), 141.37 (C-1′′′′), 173.20 (C-2′, C═O), 177.37 (C-5″, C═O), 178.12 (C-2″, C═O); MS: *m/z*: 507 [M^+ + 1], 508 [M^+ + 2], 510 [M^+ + 4] *Anal*. Calcd for $C_{27}H_{21}Cl_2N_3O_3$: C, 64.03; H, 4.15; N, 8.30, found: C, 64.12; H, 4.16; N, 8.32.

1-N-Methyl-spiro[2,3′]oxindole-spiro[3,3″]-1″-N-(4-methoxyphenyl)pyrrolidine-2″,5″-dione-4-(4-methoxyphenyl)pyrrolidine (11g). Compound obtained as white solid (0.32 g, 65 %), mp 212–214°C; IR (KBr pellets, ν_{max}/cm^{-1}): 1613 (C═C), 1707, 1727, 1780 (C═O), 3471 (N—H); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 2.26 (s, 3H, —NCH_3), 2.51 (d, 1H, J = 19.00 Hz, H_a), 2.72 (d, 1H, J = 18.96 Hz, H_b), 3.59 (t, 1H, J = 8.72 Hz, H_c), 3.77 (s, 3H, —OCH_3), 3.82 (s, 3H, —OCH_3), 3.99 (t, 1H, J = 9.52 Hz, H_d), 4.46 (dd, 1H, J = 8.24, 9.84 Hz, H_e), 6.66–7.43 (m, 12H, ArH), 7.93 (brs, 1H, —NH); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 35.21 (C-4), 36.99 (C-4″), 49.21 (—NCH_3), 55.34 (4‴—OCH_3), 55.46 (4′′′′—OCH_3), 59.17 (C-5), 61.71 (C-3), 78.47 (C-2), 110.10 (C-3a′), 114.31 (C-3‴, 5‴), 114.48 (C-3′′′′, 5′′′′), 123.40 (C-7′), 124.01 (C-2′′′′, 6′′′′), 125.09 (C-5′), 127.48 (C-2‴, 6‴), 127.89 (C-6′), 129.58 (C-4′), 130.22 (C-1‴), 131.27 (C-7a′), 141.49 (C-1′′′′), 159.15 (C-4′′′′), 159.51 (C-4‴), 174.33 (C-2′, C═O), 177.66 (C-5″, C═O), 178.94 (C-2″, C═O); MS: *m/z*: 498 [M^+ + 1], *Anal*. Calcd for $C_{28}H_{24}ClN_3O_4$: C, 70.02; H, 5.43; N, 8.45, found: C, 70.21; H, 5.44; N, 8.47.

1-N-Methyl-spiro[2,3′]oxindole-spiro[3,3″]-1″-N-(4-methylphenyl)pyrrolidine-2″,5″-dione-4-(4-methoxyphenyl)pyrrolidine (11h). Compound obtained as white solid (0.34 g, 72 %), mp 224–226°C; IR (KBr pellets, ν_{max}/cm^{-1}): 1619 (C═C), 1712, 1783 (C═O), 3472 (N—H); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 2.25 (s, 3H, —CH_3), 2.32 (s, 3H, —NCH_3), 2.51 (d, 1H, J = 18.96 Hz, H_a), 2.71 (d, 1H, J = 19.00 Hz, H_b), 3.58 (t, 1H, J = 8.24 Hz, H_c), 3.81 (s, 3H, —OCH_3), 3.99 (t, 1H, J = 9.48 Hz, H_d), 4.46 (dd, 1H, J = 8.16, 9.88 Hz, H_e), 6.63–7.43 (m, 12H, ArH), 7.95 (s, 1H, —NH); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.19 (4′′′′—CH_3), 35.16 (C-4), 37.02 (C-4″), 49.24 (—NCH_3), 55.32 (4‴—OCH_3), 59.14 (C-5), 61.75 (C-3), 78.48 (C-2), 110.05 (C-3a′), 114.49 (C-3‴, 5‴), 123.39 (C-7′), 125.13 (C-2′′′′, 6′′′′), 126.46 (C-5′), 127.50 (C-6′), 128.81 (C-4′), 129.61 (C-2‴, 6‴), 129.66 (C-3′′′′, 5′′′′), 130.16 (C-1‴), 131.26 (C-4′′′′), 138.15 (C-7a′), 141.51 (C-1′′′′), 159.17 (C-4‴), 174.16 (C-2′, C═O), 177.70 (C-5″, C═O), 178.81 (C-2″, C═O); MS: *m/z*: 482 [M^+ + 1], *Anal*. Calcd for $C_{29}H_{27}N_3O_4$: C, 72.34; H, 5.61; N, 8.73, found: C, 72.46; H, 5.62; N, 8.70.

1-N-Methyl-spiro[2,3′]oxindole-spiro[3,3″]-1″-N-(4-chlorophenyl)pyrrolidine-2″,5″-dione-4-(4-methoxyphenyl)pyrrolidine (11i). Compound obtained as white solid (0.39 g, 78 %), mp 228–230°C; IR (KBr pellets, ν_{max}/cm^{-1}): 1619 (C═C), 1710, 1776 (C═O), 3469 (N—H); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 2.25 (s, 3H, —NCH_3), 2.50 (d, 1H, J = 18.96 Hz, H_a), 2.73 (d, 1H, J = 18.96 Hz, H_b), 3.58 (t, 1H, J = 8.64 Hz, H_c), 3.81 (s, 3H, OCH_3), 3.98 (t, 1H, J = 9.48 Hz, H_d), 4.45 (dd, 1H, J = 8.16, 9.88 Hz, H_e), 6.71–7.41 (m, 12H, ArH), 7.73 (s, 1H, —NH); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 35.14 (C-4), 37.05 (C-4″), 49.09 (—NCH_3), 55.32 (4‴—OCH_3), 59.16 (C-5), 61.94 (C-3), 78.42 (C-2), 110.10 (C-3a′), 114.52 (C-3‴, 5‴), 123.17 (C-7′), 125.07(C-2′′′′, 6′′′′), 127.32 (C-5′), 127.85 (C-6′), 129.17 (C-4′), 129.43 (C-2‴, 6′′′), 129.88 (C-3′′′′, 5′′′′), 130.27 (C-1‴), 131.22 (C-4′′′′), 134.47 (C-3a′), 141.40 (C-1′′′′), 159.23 (C-4′′′), 173.60 (C-2′, C═O), 177.49 (C-5″, C═O), 178.40 (C-2″, C═O); MS: *m/z*: 502 [M^+ + 1], 503 [M^+ + 2]*Anal*. Calcd for $C_{28}H_{24}ClN_3O_4$: C, 67.00; H, 4.78; N, 8.37, found: C, 67.16; H, 4.79; N, 8.39.

Acknowledgments. The authors acknowledge the financial support from University Grant Commission (UGC) New Delhi and are grateful to the Department of Chemistry, Punjabi University, Patiala, and the Sophisticated Analytical Instrumentation Facility (SAIF) Panjab University, Chandigarh, for spectral analysis.

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