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Original article

Regioselective synthesis and antimicrobial screening of novel ketocarbazolodispiropyrrolidine derivatives

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ABSTRACT

A series of novel dispiropyrrolidine derivatives have been synthesized through 1,3-dipolar cycloaddition reaction of azomethine ylide generated from sarcosin and di/tri ketone with the dipolarophile (*E*)-2-arylidine-1-keto-carbazoles.
The cycloadducts ketocarbazalo spiro *N*-methyl pyrrolidines showed the most interesting antimicrobial activity at lower concentration.

1. Introduction

Highly substituted pyrrolidines have gained much prominence since they form the central skeleton of many natural products [1]. Generally, pyrrolidine derivatives adopt conformation of the incipient oxocarbenium cation postulated as the transition state of enzymatic glycoside hydrolysis and moreover, substituted polyhydroxylated pyrrolidine and piperidine alkaloids are one of the most widespread secondary metabolite sugar mimics [2]. Plants in the Hyacinthaceae are rich source of glycosidase inhibitors with structural diversity, such as pyrrolidine, pyrrolizidine, piperidine and their glycosides, which are receiving considerable attention as potential therapeutic agents [3–5]. Furthermore, oral treatment of lysosomal storage diseases with specific glycosidase and glycosyl transfer inhibitors is attracting great interest [6,7]. Spiro compounds represent an important class of naturally occurring substances characterized by highly pronounced biological properties [8]. Natural product isopteropodine **1** (Fig. 1) has been shown to modulate the function of muscarinic and serotonin receptors while some of the synthetic compounds containing spirooxindole as the core structure have potent non-peptide inhibitor of p53-MDM2 interaction [9]. Gelsemine, pseudotabersonime, formosanine, isoformosanine and mitraphylline are some of the alkaloids containing spiro ring systems [10]. Of particular interest, spiropyrrolidinyloxindole ring systems are also found in a number of alkaloids like elacomine, spirotryprostatins A and B, etc. Hence, there has been renewed interest in the synthesis of such interesting compounds.

Carbazole derivatives are known for their pharmacological activities [11]. Carbomycines A and B have been found to be useful as antibacterial and antifungal agents [12,13]. It has been reported that pyridocarbazoles show marked anticancer and anti-HIV activities [14–16]. One of the most important naturally occurring alkaloid ellipticine and its isomer olivacine which are derived from carbazole show antineoplastic activity [17]. Moreover, the derivatives of carbazoles were able to intercalate with DNA [18] and it was found to possess antileukemic activity [19]. In this context of general interest, we describe here the synthesis of ketocarbazolodispiropyrrolidine derivatives by 1,3-dipolar cycloaddition of azomethine ylides with substituted 2-arylbenzylidine-1,2,3,4-tetrahydro-1-keto-carbazoles as dipolarophile. We have screened these compounds for antibacterial activity.

2. Results and discussion

2.1. Chemistry

The required dipolarophiles (*E*)-2-arylidene-1-keto-carbazoles were prepared by the reaction of 1-keto-carbazole [20] (Scheme 1)

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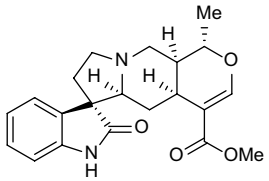


1

Isopeteropodine

Fig. 1. Representation of spiro compound.

with various substituted benzaldehydes and the geometry of dipoloraphiles was assigned by using spectroscopic analysis. The reaction of non-stabilized azomethine ylide (generated *in situ* from decarboxylative condensation of triketone, ninhydrin **7** and sarcosine **6**) with the dipolarophiles **5a–f** in refluxing dioxane and methanol (1:1) furnished dispiropyrrolidines **8a–f** in moderate yields (46–58% Method A, Scheme 2).

The structures of the products were confirmed on the basis of their spectral and elemental analyses. In particular, the regiochemistry proposed for the product **8c** was decided on the basis of its ^{1}H NMR spectrum exhibiting a triplet at δ 4.87 for the benzylic proton. If other isomer **9c** was formed, one would expect a singlet instead of a triplet. The methylene protons of pyrrolidine ring showed a doublet at δ 2.48 ($J = 14.5$ Hz). The ^{13}C NMR spectrum of **8c** showed two peaks at δ 60.9 and 80.9 ppm reflecting the presence of two spiro carbons, the keto-carbazole and indanedione carbonyl carbons exhibited peaks at δ 187.7, 199.6 and 200.9 ppm, respectively. The mass spectrum of the compound showed a molecular ion peak at m/z 490.5 (M^+), which further confirmed the formation of cycloadduct. Identical results were furnished by other compounds with identical stereochemistry. The structure of **8d** was established by X-ray (Fig. 2) single crystal analysis [21], which also proved the regiochemistry of cycloadduct.

To enhance the scope of the above methodology, we reacted the same dipolarophiles with azomethine ylide generated from the diketone, acenathenequinone **10** and sarcosine **6**. The reaction yielded novel dispiropyrrolidine derivatives **11a–f** in moderate yield (43–60%) (Method A) *via* one pot three component reactions (Scheme 3). The ^{1}H NMR spectrum of **11a** showed a triplet at δ 5.18 for benzylic proton, which confirmed the regiochemistry of the cycloadduct. The methylene protons of pyrrolidine ring showed as a doublet at δ 2.34 ($J = 14.6$ Hz). These results again confirm the regiochemistry of compound **11a**. The ^{13}C NMR spectrum showed two peaks at δ 192.1 and 207.4 ppm for carbonyl carbons of keto-carbazole and acenapthenenone ring systems. The mass spectrum of the product **11a** showed a molecular ion peak at m/z 482 (M^+) and elemental analysis was also found to be satisfactory. The structure of the adduct **11a** was established by X-ray (Fig. 3) single crystal analysis [22].

In the next series of experiments, we have examined the reactions of the same dipolarophile with nonstablized azomethine ylide generated from sarcosine **6** with diketone, isatin **13** which afforded moderate yield of dispiro adducts **14a–f**. (43–57%, Method A) (Scheme 4).

As observed in the earlier case, the regio- and stereochemistry of the cycloadducts were confirmed primarily by ^{1}H NMR spectrum. The compound **14b** showed a triplet for the benzylic proton at δ 5.01 and the methylene proton of pyrrolidine ring showed a doublet at δ 2.52 ($J = 14.0$ Hz). The ^{13}C NMR spectrum of **14b** exhibited two peaks at δ 183.5 and 190.3 ppm for carbonyl carbons for oxindole and keto-carbazole ring systems. Finally, the molecular weight of compound **14b** was also confirmed by a peak at m/z 461.5 (M^+) in mass spectrum and the elemental analysis also showed satisfactory results. The coupling constant (J value) of the benzylic proton will remain the same irrespective of the stereochemistry of the phenyl group as the proton is positioned adjacent to two methylene protons.

We have carried out the above reactions under three different conditions. (1) Refluxing in methanol (Method A). (2) Reacting in microwave irradiation (600 W) with K-10 Montimorillonite clay (Method B). (3) Reacting under microwave irradiation under neat condition (Method C). Methods B and C were found to give better yield of the products compared to Method A as shown in Tables 1, 2 and 3.

2.1.1. Pharmacological studies

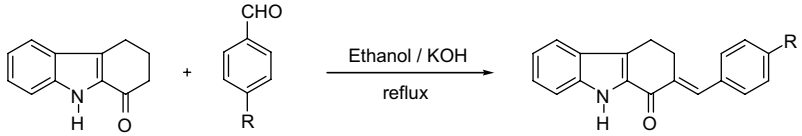
We have subjected all the synthesized compounds for bioactivity studies against microorganisms and the results are shown below.

The bioactivity studies were carried out against bacteria, *Proteus vulgaris*; *Proteus mirabilis*; *Staphylococcus aureus*; and *Salmonella typhi*, which were obtained from Microbial Metabolite Lab Culture collection, University of Madras, Chennai.

2.1.2. Antimicrobial activity of dispiropyrrolidines (agar diffusion assay)

The agar diffusion method [23] was used for the determination of antibacterial activity of novel dispiropyrrolidines against microorganism listed above. About 9 ml of nutrient agar media were poured into petri plates (9 cm in diameter) and inoculated with respective test organism. Wells are made with cork borer on the solid agar and loaded with 25–100 μg/ml of the test compound with tetracycline as control. Petri dishes were incubated at 37 °C for 24 h and the average diameter of the inhibition zone surrounding the wells was measured after specified incubation period.

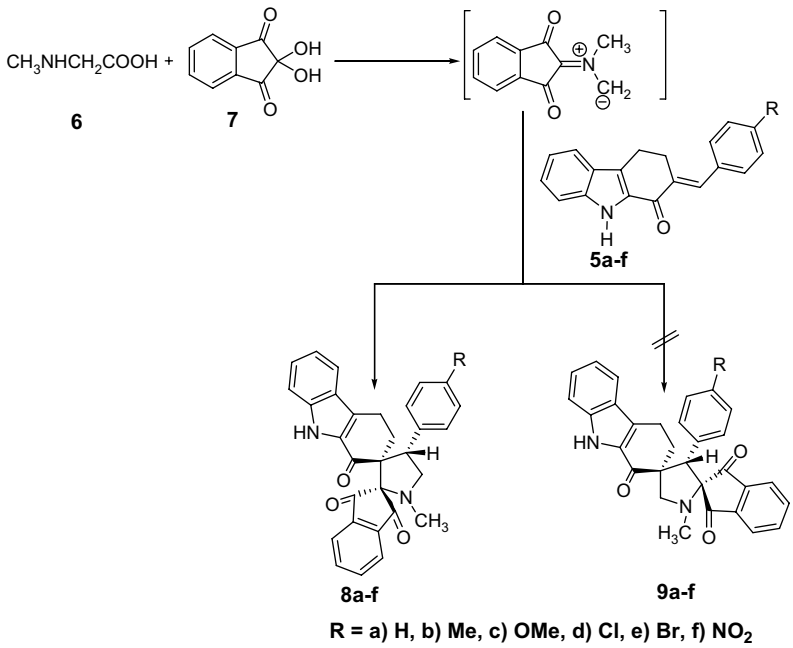
The antibacterial activity of the carbazole derived compound against human bacterial pathogens as determined by agar diffusion method with tetracycline as reference control is presented in the table. The maximum antimicrobial activity and inhibition zone were observed for compounds derived from acenapthenequinone (**11d** and **f**) followed by oxindole derivative (**14d**). The ninhydrin derived compounds showed less activity (**8c**). All the compounds showed good inhibitory activity in higher concentrations against nearly all the test pathogens except **8d** and **b**, which are void of antimicrobial activity against *S. aureus* even in higher concentration. The acenapthenequinone derived compounds and isatin derived compounds showed excellent activity against all the



3 **4a-f** **5a-f**

R = a) H, b) Me, c) OMe, d) Cl, e) Br, f) NO_2

Scheme 1.



Scheme 2.

pathogens in low concentration, which is comparable to the reference control. It was observed that all the antimicrobial activities of the present studied compounds are dose dependent. The acenapthenequinone derived compounds **11d**, **f**, **a** and **b** were found to be effective in controlling all the test pathogens and very effective in controlling *P. vulgaris* and *P. mirabilis* than the rest of the compounds tested in the present study. The activity is very much comparable to the reference control. Next to acenapthenequinone-derived compounds, the isatin derived compounds **14d** and **c** exhibited good antimicrobial activity against *P. vulgaris*, *P. mirabilis* and *S. typhi* which showed strong antimicrobial activity in higher concentration. The ninihydrin derived compounds show less antimicrobial activity, exhibits moderate antimicrobial activity against *P. vulgaris* and *P. mirabilis*, and ineffective in controlling *S. aureus* and *S. typhi* even in higher concentration. Further clinical studies are required to validate the effective compounds of the present study as an antimicrobial agent. The results are summarised in Tables 4–7.

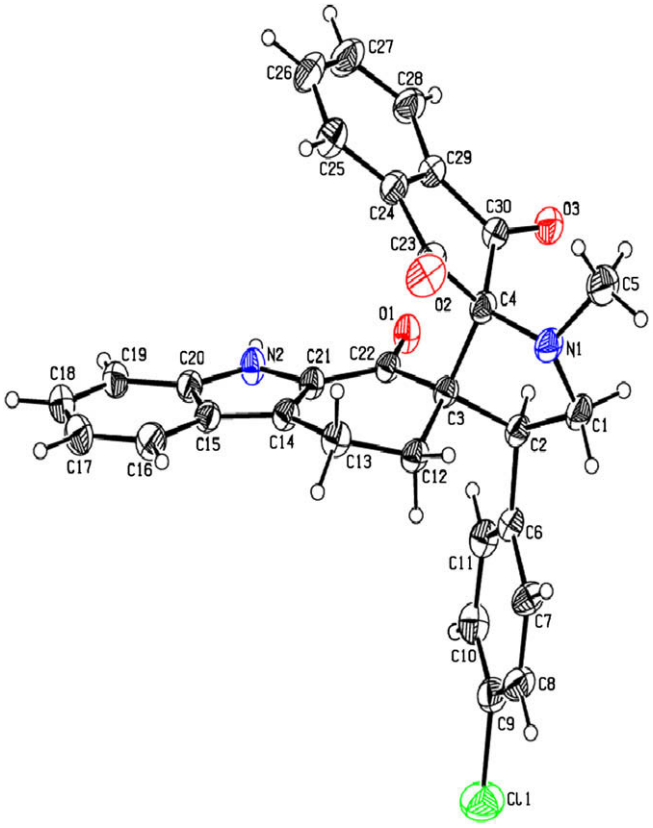


Fig. 2. ORTEP diagram of **8d**.

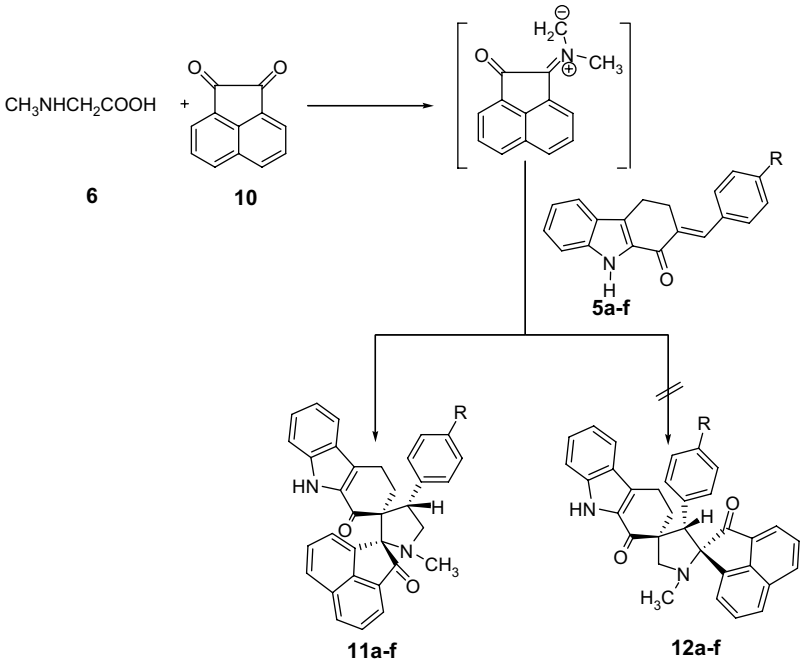
3. Conclusions

In conclusion, we have successfully synthesized a series of novel dispiropyrrolidines and evaluated their structure–antimicrobial activity relationship. The synthetic route involves 1,3-dipolar cycloaddition reaction of azomethine ylide generated from di- and tri ketones and sarcosine with (*E*)-2-aryledene-1-keto-carbazoles as dipolarophiles. Among the various conditions employed, the microwave irradiation method was found to be synthetically useful in achieving high yields of the products with reduced reaction time compared to conventional heating. Generally it was found that all the synthetic spiropyrrolidines showed antimicrobial activity.

4. Experimental

4.1. General considerations

All melting points are uncorrected. IR spectra were recorded on a SHIMADZU FT-IR 8300 instrument. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on JEOL 400 MHz, Mass spectra were recorded by JEOL-DX303 HF mass spectrometer. Elemental analyses were carried out on a Perkin–Elmer 2400B instrument.



Scheme 3.

4.2. General procedure for the synthesis of dispiro heterocylces

Method A. A mixture of sarcosine **1** (1 mmol), ninhydrin **2**/acenapthenequionone **6**/isatin **9** (1 mmol), and (*E*)-2-aryledene-1-keto-carbazole was refluxed in dioxan:methanol (1:1). Completion of the reaction was evidenced by TLC analysis. The solvent was removed *in vacuo* and the crude product was subjected to column chromatography using petroleum ether, ethyl acetate mixture (8:2) as eluent.

Method B. A mixture of sarcosine **1** (1 mmol), ninhydrin **2**/acenapthenequionone **6**/isatin **9** (1 mmol), and (*E*)-2-aryledene-1-keto-carbazole (1 mmol) was ground with K-10 Montmorillonite clay and irradiated under microwave conditions (600 W). After completion of the reaction, the product was extracted with dichloromethane and the organic layer was dried over $MgSO_4$. The solvent was then removed *in vacuo* and the crude product was subjected to column chromatography using petroleum ether, ethyl acetate mixture (8:2) as eluent.

Method C. A mixture of sarcosine **1** (1 mmol), ninhydrin **2**/acenapthenequionone **6**/isatin **9** (1 mmol), and (*E*)-2-aryledene-1-keto-carbazole (1 mmol) was ground and irradiated under microwave conditions (600 W). After completion of the reaction, the product was allowed to stand at room temperature until it gets solidified and the crude product was subjected to column chromatography using petroleum ether, ethyl acetate mixture (8:2) as eluent.

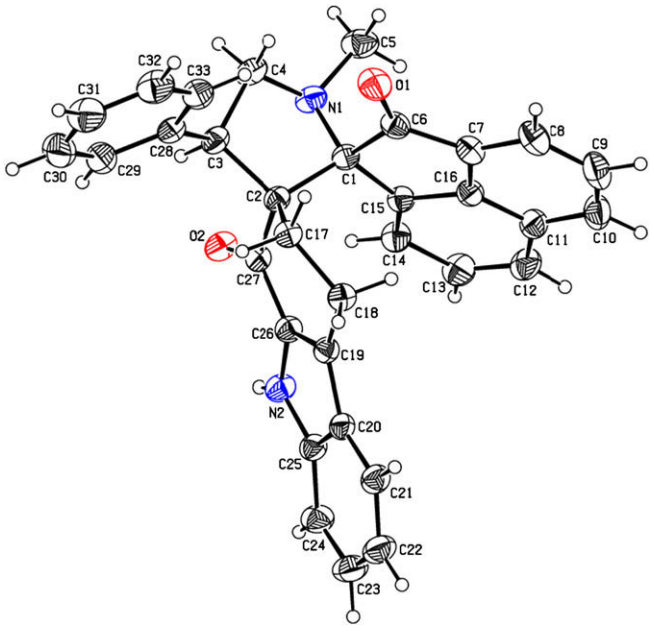


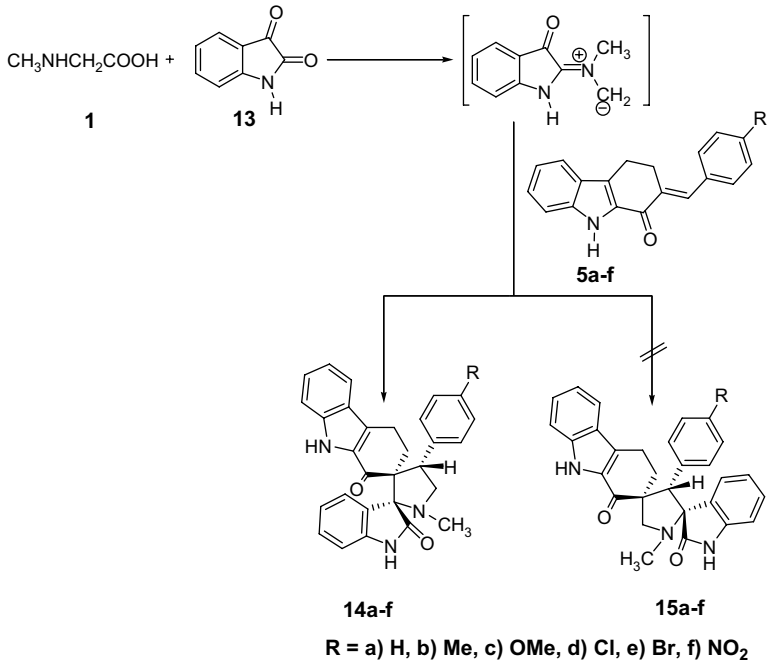
Fig. 3. ORTEP diagram of **11a**.

4.2.1. 4′-Phenyl-1′-methyl-4,9-dihydrodispiro[carbazole-2,3′-pyrrolidine-2′,2″-indene]-1,1″,3″(3H)-trione (**8a**)

Pale yellow solid, mp 195–197 °C; ν_{max} (KBr) 1705, 1739, 3289 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.73 (m, 2H, C(3)H_2); 2.23 (s, 3H, NCH_3); 2.49 (d, 2H, *J* 19.5 Hz); 3.62 (t, 1H, C(4)*H*, *J* 9.32, 9.32 Hz); 3.84 (t, 1H, C(4)*H*, *J* 9.27, 9.28 Hz); 5.00 (t, 1H, benzylic *H*); 6.99–7.71 (m, 13H, Ar*H*); 8.90 (s, 1H, N*H*). δ_C (100 MHz, $CDCl_3$) 18.1, 27.9, 35.7, 46.4, 57.6, 61.1, 81.1, 112.4, 120.3, 121.2, 122.0, 122.7, 125.1, 127.0, 128.0, 128.4, 131.1, 131.4, 132.8, 135.6, 136.3, 140.9, .141.0, 188.0, 199.3, 200.7; EI-MS *m*/*z* 460.52 (M^+); Anal. Calcd for $C_{30}H_{24}N_2O_3$: C, 78.24; H, 5.25; N, 6.08%. Found: C, 78.59; H, 5.51; N, 5.83%.

4.2.2. 4′-(4-Methylphenyl)-1′-methyl-4,9-dihydrodispiro[carbazole-2,3′-pyrrolidine-2′,2″-indene]-1,1″,3″(3H)-trione (**8b**)

Pale yellow solid, mp 208–210 °C; ν_{max} (KBr) 1704, 1740, 3285 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.53 (m, 2H, C(3)H_2); 2.16 (s, 3H, NCH_3); 2.30 (s, 3H, Ph-CH_3); 2.51 (d, 2H, *J* 14.6 Hz); 3.56 (t, 1H, C(4)*H*, *J* 9.19, 9.23 Hz); 3.79 (t, 1H, C(4)*H*, *J* 9.21, 9.23 Hz); 4.96 (t, 1H, benzylic *H*); 7.01–7.86 (m, 12H, Ar*H*); 8.92 (s, 1H, N*H*). δ_C (100 MHz, $CDCl_3$) 17.6, 26.9, 32.6, 34.7, 45.9, 58.2, 60.9, 80.9, 112.4, 120.3, 121.2,



Scheme 4.

122.0, 122.7, 125.2, 128.1, 129.0, 132.1, 132.8, 135.6, 136.5, 140.9, 141.1, 187.7, 199.1, 201.2; EI-MS *m*/*z* 474.1 (M^+); Anal. Calcd for $C_{31}H_{26}N_2O_3$: C, 78.46; H, 5.52; N, 5.90%. Found: C, 78.61; H, 5.72; N, 5.73%.

*4.2.3. 4′-(4-Methoxyphenyl)-1′-methyl-4,9-dihydrodispiro[carbazole-2,3′-pyrrolidine-2′,2″-indene]-1,1″,3″(3*H*)-trione (**8c**)*

Pale yellow solid, mp 212 °C; ν_{max} (KBr) 1705, 1739, 3283 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.51 (m, 2H, C(3)H_2); 2.09 (s, 3H, NCH_3); 2.48 (d, 2H, *J* 14.5 Hz); 3.49 (t, 1H, C(4)*H*, *J* 9.21, 9.23 Hz); 3.72 (t, 1H, C(4)*H*, *J* 9.23, 9.25 Hz); 3.82 (s, 3H, OCH_3) 4.87 (t, 1H, benzylic *H*); 6.92–7.761 (m, 12H, Ar*H*); 8.61 (s, 1H, N*H*). δ_C (100 MHz, $CDCl_3$) 17.6, 26.9, 32.6, 34.7, 45.9, 58.2, 60.9, 80.9, 112.4, 120.3, 121.2, 122.0, 122.7, 125.2, 128.1, 129.0, 132.2, 132.7, 135.6, 136.5, 140.9, 141.1, 187.7, 199.6, 200.9; EI-MS *m*/*z* 490.5 (M^+); Anal. Calcd for $C_{31}H_{26}N_2O_4$: C, 75.90; H, 5.34; N, 5.71%. Found: C, 75.69; H, 5.42; N, 5.81%.

*4.2.4. 4′-(4-Chlorophenyl)-1′-methyl-4,9-dihydrodispiro[carbazole-2,3′-pyrrolidine-2′,2″-indene]-1,1″,3″(3*H*)-trione (**8d**)*

Yellow solid, mp 204 °C. ν_{max} (KBr) 1704, 1740, 3285 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.78 (m, 2H, C(3)H_2); 2.35 (s, 3H, NCH_3); 2.52 (d, 2H, *J* 16.64 Hz); 3.62 (t, 1H, C(4)*H*, *J* 9.32, 9.33 Hz); 3.89 (t, 1H, C(4)*H*, *J* 9.28, 9.21 Hz); 5.09 (t, 1H, benzylic *H*); 6.97–7.70 (m, 12H, Ar*H*); 8.90 (s, 1H, N*H*). δ_C (100 MHz, $CDCl_3$) 18.6, 28.7, 35.7, 46.6, 57.6, 63.8, 81.1, 112.4, 120.4, 121.2, 122.1, 122.7, 125.1, 127.0, 128.4, 131.1, 131.4, 132.8, 135.6, 136.0, 136.4, 140.9, 141.2, 187.9, 199.4, 200.7; EI-MS *m*/*z* 494.97 (M^+); Anal. Calcd for $C_{30}H_{23}ClN_2O_3$: C, 72.80; H, 4.68; N, 5.66%. Found: C, 72.69; H, 4.59; N, 5.79%.

*4.2.5. 4′-(4-Bromophenyl)-1′-methyl-4,9-dihydrodispiro[carbazole-2,3′-pyrrolidine-2′,2″-indene]-1,1″,3″(3*H*)-trione (**8e**)*

Yellow solid, mp 198 °C; ν_{max} (KBr) 1702, 1740, 3282 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.77 (m, 2H, C(3)H_2); 2.21 (s, 3H, NCH_3); 2.49 (d, 2H, *J* 16.01 Hz); 3.60 (t, 1H, C(4)*H*, *J* 9.32, 9.32 Hz); 3.85 (t, 1H, C(4)*H*, *J* 9.26, 9.28 Hz); 4.98 (t, 1H, benzylic *H*); 6.88–7.71 (m, 12H, Ar*H*); 8.90 (s, 1H, N*H*). δ_C (100 MHz, $CDCl_3$) 18.4, 28.6, 35.7, 46.6, 57.6, 61.6, 80.1, 112.0, 120.4, 121.2, 122.1, 122.7, 125.1, 126.9, 127.2, 130.0, 131.5, 132.7, 135.7, 136.1, 141.0, 141.2, 187.9, 199.3, 200.6; EI-MS *m*/*z* 539.42 (M^+); Anal. Calcd for $C_{30}H_{23}BrN_2O_3$: C, 66.80; H, 4.30; N, 5.19%. Found: C, 67.01; H, 4.46; N, 5.35%.

*4.2.6. 4′-(4-Nitrophenyl)-1′-methyl-4,9-dihydrodispiro[carbazole-2,3′-pyrrolidine-2′,2″-indene]-1,1″,3″(3*H*)-trione (**8f**)*

Yellow solid, mp 210–212 °C; ν_{max} (KBr) 1704, 1738, 3289 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.65 (m, 2H, C(3)H_2); 2.19 (s, 3H, NCH_3); 2.42 (d, 2H, *J* 16.01 Hz); 3.58 (t, 1H, C(4)*H*, *J* 9.28, 9.27 Hz); 3.75 (t, 1H, C(4)*H*, *J* 9.25, 9.28 Hz); 5.06 (t, 1H, benzylic *H*); 6.79–7.68 (m, 12H,

Table 1
Influence of conventional heating and microwave irradiation on 1,3-dipolar cycloaddition reaction of **5a–f** with **6** and **7**

Cycloadduct 8	Method A	Method B	Method C
	Yield in 6 h (%)	Yield in 15 min (%)	Yield in 15 min (%)
a	48	78	85
b	53	71	82
c	50	84	88
d	58	95	95
e	54	86	89
f	46	75	86

Method A: conventional reflux; Method B: K-10 Montmorillonite clay/MW; Method C: neat/MW.

Table 2
Influence of conventional heating and microwave irradiation on 1,3-dipolar cycloaddition reaction of **5a–f** with **6** and **10**

Cycloadduct 11	Method A	Method B	Method C
	Yield in 6 h (%)	Yield in 15 min (%)	Yield in 15 min (%)
a	51	82	89
b	43	79	83
c	52	85	91
d	60	96	93
e	55	94	96
f	43	81	85

Method A: Conventional reflux; Method B: K-10 Montmorillonite clay/MW; Method C: neat/MW.

Table 3
Influence of conventional heating and microwave irradiation on 1,3-dipolar cycloaddition reaction of **5a–f** with **6** and **13**

Cycloadduct 10	Method A	Method B	Method C
	Yield in 6 h (%)	Yield in 15 min (%)	Yield in 15 min (%)
a	50	78	84
b	48	80	89
c	57	88	83
d	43	90	96
e	45	93	94
f	52	86	81

Method A: Conventional reflux; Method B: K-10 Montmorillonite clay/MW; Method C: neat/MW.

Ar*H*); 8.92 (s, 1H, N*H*). δ_C (100 MHz, $CDCl_3$) 18.2, 27.9, 35.6, 45.3, 58.8, 60.6, 81.0, 112.0, 120.6, 121.3, 122.1, 122.6, 124.4, 125.6, 126.9, 128.8, 130.6, 132.2, 135.1, 135.4, 141.7, 141.8, 188.2, 199.1, 201.2; EI-MS *m*/*z* 502.52 (M^+); Anal. Calcd for $C_{30}H_{23}N_3O_5$: C, 71.28; H, 4.59; N, 8.31%. Found: C, 71.45; H, 4.36; N, 8.51%.

*4.2.7. 1′-Methyl-4′-phenyl-4″,9″-dihydro-2*H*-dispiro[acenapthylene-1,2′-pyrrolidine-3′,2″-carbazole]-1″,2(3″*H*)-dione (**11a**)*

Yellow crystalline solid, mp 222 °C; ν_{max} (KBr) 1638, 1702, 3351 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.46 (m, 1H, C(3)*H*); 1.86 (m, 1H, C(3)*H*); 2.07 (s, 3H, NCH_3); 2.34 (d, 2H, *J* 14.64 Hz); 3.63 (t, 1H, C(4)*H*, *J* 8.80, 8.28 Hz); 4.17 (t, 1H, C(4)*H*, *J* 10.30, 9.3 Hz); 5.19 (t, 1H, benzylic *H*); 6.81–7.89 (m, 15H, Ar*H*); 9.15 (s, 1H, N*H*). δ_C (100 MHz, $CDCl_3$) 19.2, 32.4, 34.7, 47.0, 58.4, 62.6, 80.1, 112.2, 119.8, 120.3, 120.9, 122.5, 124.9, 125.1, 126.6, 126.8, 127.6, 127.8, 128.2, 128.3, 130.1, 130.4, 131.6, 131.7, 137.0, 138.0, 139.1, 142.1, 192.1, 207.4; EI-MS *m*/*z* 482.58 (M^+); Anal. Calcd for $C_{33}H_{26}N_2O_2$: C, 82.13; H, 5.43; N, 5.81%. Found: C, 82.31; H, 5.58; N, 5.71%.

*4.2.8. 1′-Methyl-4′-(4-methylphenyl)-4″,9″-dihydro-2*H*-dispiro[acenapthylene-1,2′-pyrrolidine-3′,2″-carbazole]-1″,2(3″*H*)-dione (**11b**)*

Pale yellow solid, mp 210 °C; ν_{max} (KBr) 1644, 1705, 3349 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.44 (m, 1H, C(3)*H*); 1.84 (m, 1H, C(3)*H*); 2.05 (s, 3H, NCH_3); 2.28 (d, 2H, *J* 14.31 Hz); 2.30 (s, 3H, PhCH_3); 3.60 (t, 1H, C(4)*H*, *J* 8.70, 8.68 Hz); 4.10 (t, 1H, C(4)*H*, *J* 9.28, 9.31 Hz); 5.16 (t, 1H, benzylic *H*); 6.79–7.80 (m, 14H, Ar*H*); 9.15 (s, 1H, N*H*). δ_C (100 MHz, $CDCl_3$) 19.2, 32.4, 34.7, 47.0, 58.4, 62.6, 80.1, 112.2, 119.7, 120.3, 120.9, 122.3, 124.8, 125.0, 126.6, 126.7, 127.5, 127.8, 128.2, 128.6, 130.0, 130.4, 131.6, 131.7, 137.0, 138.0, 138.8, 142.5, 192.2, 206.5; EI-MS *m*/*z* 496.6 (M^+); Anal. Calcd for $C_{34}H_{28}N_2O_2$: C, 82.23; H, 5.68; N, 5.64%. Found: C, 82.42; H, 5.75; N, 5.48%.

*4.2.9. 1′-Methyl-4′-(4-methoxyphenyl)-4″,9″-dihydro-2*H*-dispiro[acenapthylene-1,2′-pyrrolidine-3′,2″-carbazole]-1″,2(3″*H*)-dione (**11c**)*

Yellow solid, mp 190 °C; ν_{max} (KBr) 1642, 1705, 3351 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.42 (m, 1H, C(3)*H*); 1.80 (m, 1H, C(3)*H*); 2.03 (s, 3H, NCH_3); 2.23 (d, 2H, *J* 14.02 Hz); 3.56 (t, 1H, C(4)*H*, *J* 8.68, 8.65 Hz); 3.62 (s, 3H, OCH_3); 4.09 (t, 1H, C(4)*H*, *J* 9.28, 9.30 Hz); 5.14 (t, 1H, benzylic *H*); 6.71–7.68 (m, 14H, Ar*H*); 9.13 (s, 1H, N*H*). δ_C (100 MHz, $CDCl_3$) 19.2, 32.4, 34.6, 46.9, 58.3, 62.6, 80.1, 112.2, 119.7,

Table 4
Effect of dispiropyrrolidines on the growth of human pathogen *Proteus vulgaris*

Organism	Compound	Concentration of the compound (μg/ml)			
		25	50	75	100
		Zone of inhibition (mm)			
Proteus vulgaris	**8a**	11	15	18	21
	8b	–	–	9	12
	8c	13	15	16	21
	8d	–	14	18	24
	8e	9	13	16	18
	8f	12	17	18	18
	11a	–	14	18	21
	11b	11	14	16	20
	11c	9	12	13	17
	11d	19	18	24	>40
	11e	12	16	20	22
	11f	13	22	27	>40
	14a	12	16	20	26
	14b	12	16	18	21
	14c	11	13	18	20
	14d	9	18	24	26
	14e	11	14	18	21
	14f	9	13	18	22
	Tetracycline	18	24	28	>40

Table 5
Effect of dispiropyrrolidines on the growth of human pathogen *Proteus mirabilis*

Organism	Compound	Concentration of the compound (μg/ml)			
		25	50	75	100
		Zone of inhibition (mm)			
Proteus mirabilis	**8a**	–	9	13	15
	8b	9	11	14	18
	8c	13	15	17	20
	8d	–	9	14	23
	8e	9	11	14	16
	8f	9	13	18	21
	11a	11	13	22	32
	11b	11	14	18	21
	11c	14	16	20	22
	11d	12	16	24	36
	11e	13	15	18	22
	11f	9	13	17	21
	14a	9	12	14	16
	14b	11	14	16	18
	14c	9	13	16	21
	14d	13	15	18	22
	14e	11	14	16	18
	14f	12	13	16	20
	Tetracycline	18	24	28	>40

Table 6
Effect of dispiropyrrolidines on the growth of human pathogen *Staphylococcus aureus*

Organism	Compound	Concentration of the compound (μg/ml)			
		25	50	75	100
		Zone of inhibition (mm)			
Staphylococcus aureus	**8a**	–	14	16	20
	8b	9	14	18	21
	8c	9	13	15	20
	8d	9	11	16	19
	8e	–	12	19	21
	8f	11	14	18	18
	11a	14	19	21	26
	11b	14	18	23	27
	11c	9	16	21	30
	11d	14	18	22	34
	11e	11	14	18	22
	11f	9	16	21	31
	14a	11	13	16	18
	14b	9	13	16	20
	14c	12	14	17	20
	14d	9	14	18	21
	14e	11	15	18	22
	14f	–	11	14	20
	Tetracycline	22	24	28	>40

Table 7
Effect of dispiropyrrolidines on the growth of human pathogen *Salmonella typhi*

Organism	Compound	Concentration of the compound (μg/ml)			
		25	50	75	100
		Zone of inhibition (mm)			
Salmonella typhi	**8a**	9	13	14	18
	8b	–	9	14	16
	8c	–	11	16	21
	8d	9	13	16	19
	8e	–	9	18	19
	8f	9	11	13	18
	11a	11	14	20	28
	11b	12	15	21	29
	11c	13	15	18	26
	11d	13	16	21	31
	11e	9	14	21	30
	11f	11	14	18	25
	14a	9	11	13	18
	14b	9	12	14	16
	14c	12	14	18	21
	14d	11	15	17	18
	14e	–	9	13	16
	14f	9	16	18	22
	Tetracycline	18	22	28	>40

120.1, 120.8, 122.3, 124.8, 125.0, 126.6, 126.7, 127.4, 127.8, 128.1, 128.2, 130.1, 130.2, 131.3, 131.6, 137.1, 138.0, 138.6, 142.3, 191.9, 206.5; EI-MS *m*/*z* 512.6 (M^+); Anal. Calcd for $C_{34}H_{28}N_2O_3$: C, 79.67; H, 5.51; N, 5.46%. Found: C, 79.80; H, 5.40; N, 5.54%.

*4.2.10. 1′-Methyl-4′-(4-chlorophenyl)-4″,9″-dihydro-2*H*-dispiro[acenapthylene-1,2′-pyrrolidine-3′,2″-carbazole]-1″,2(3″*H*)-dione (**11d**)*

Pale yellow solid, mp 198 °C; ν_{max} (KBr) 1639, 1705, 3348 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.42 (m, 1H, C(3)*H*); 1.85 (m, 1H, C(3)*H*); 2.15 (s, 3H, NC*H*$_3$); 2.30 (d, 2H, *J* 17.2 Hz); 3.61 (t, 1H, C(4)*H*, *J* 8.79, 8.18 Hz); 4.07 (t, 1H, C(4)*H*, *J* 10.28, 9.96 Hz); 5.12 (t, 1H, benzylic *H*); 6.81–7.89 (m, 14H, Ar*H*); 9.21 (s, 1H, N*H*). δ_C (100 MHz, $CDCl_3$) 19.2, 29.7, 32.5, 34.6, 46.4, 58.5, 62.5, 80.0, 112.2, 119.9, 120.9, 122.0, 125.0, 125.1, 126.7, 127.7, 127.9, 128.2, 128.4, 130.1, 130.6, 131.8, 131.9, 132.6, 135.3, 136.8, 137.8, 138.1, 142.1, 191.9, 207.4; EI-MS *m*/*z* 517.02 (M^+); Anal. Calcd for $C_{33}H_{25}ClN_2O_2$: C, 76.66; H, 4.87; N, 5.42%. Found: C, 76.48; H, 5.01; N, 5.55%.

*4.2.11. 1′-Methyl-4′-(4-bromophenyl)-4″,9″-dihydro-2*H*-dispiro[acenapthylene-1,2′-pyrrolidine-3′,2″-carbazole]-1″,2(3″*H*)-dione (**11e**)*

Pale yellow solid, mp 194 °C; ν_{max} (KBr) 1644, 1704, 3343 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.40 (m, 1H, C(3)*H*); 1.83 (m, 1H, C(3)*H*); 2.03 (s, 3H, NC*H*$_3$); 2.30 (d, 2H, *J* 16.91 Hz); 3.62 (t, 1H, C(4)*H*, *J* 8.78, 8.92 Hz); 4.05 (t, 1H, C(4)*H*, *J* 10.29, 9.98 Hz); 5.09 (t, 1H, benzylic *H*); 6.82–7.89 (m, 14H, Ar*H*); 9.22 (s, 1H, N*H*). δ_C (100 MHz, $CDCl_3$) 19.2, 29.7, 32.6, 34.7, 46.4, 58.5, 62.5, 80.0, 112.3, 119.9, 120.7, 122.0, 124.9, 125.0, 126.6, 127.7, 127.9, 128.1, 128.4, 130.3, 130.6, 131.8, 131.9, 132.6, 135.3, 136.7, 137.7, 138.0, 142.1, 190.9, 207.4; EI-MS *m*/*z* 561.47 (M^+); Anal. Calcd for $C_{33}H_{25}BrN_2O_2$: C, 70.59; H, 4.49; N, 4.99%. Found: C, 70.81; H, 4.56; N, 5.12%.

*4.2.12. 1′-Methyl-4′-(4-nitrophenyl)-4″,9″-dihydro-2*H*-dispiro[acenapthylene-1,2′-pyrrolidine-3′,2″-carbazole]-1″,2(3″*H*)-dione (**11f**)*

Yellow solid, mp 202–204 °C; ν_{max} (KBr) 1648, 1706, 3346 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.38 (m, 1H, C(3)*H*); 1.79 (m, 1H, C(3)*H*); 2.11 (s, 3H, NC*H*$_3$); 2.28 (d, 2H, *J* 16.53 Hz); 3.48 (t, 1H, C(4)*H*, *J* 8.52, 8.68 Hz); 4.28 (t, 1H, C(4)*H*, *J* 10.11, 9.97 Hz); 5.18 (t, 1H, benzylic *H*); 6.99–7.98 (m, 14H, Ar*H*); 9.54 (s, 1H, N*H*). δ_C (100 MHz, $CDCl_3$) 18.6, 28.6, 32.9, 33.5, 45.9, 59.2, 61.6, 80.8, 112.3, 119.9, 120.5, 121.8, 124.6, 125.4, 126.2, 126.9, 127.8, 128.6, 129.6, 130.4, 130.6, 131.8, 131.9, 132.3, 134.8, 136.1, 136.4, 138.8, 142.6, 192.0, 206.5; EI-MS *m*/*z* 527.58 (M^+); Anal. Calcd for $C_{33}H_{25}BrN_2O_2$: C, 75.13; H, 4.78; N, 7.96%. Found: C, 75.32; H, 4.63; N, 8.12%.

*4.2.13. 4′-Phenyl-1′-methyl-4,9-dihydrodispiro[carbazole-2,3′-pyrrolidine-2′,3″-indole]-1,2″(3*H*)-dione (**14a**)*

Yellow solid, mp 120–122 °C; ν_{max} (KBr) 3281, 1704, 1656 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.63 (m, 1H, C(3)*H*); 1.91 (m, 1H, C(3)*H*); 2.21(s, 3H, NC*H*$_3$); 2.58 (d, 2H, *J* 14.21 Hz); 3.58 (t, 1H, C(4)*H*, *J* 8.71, 8.69 Hz); 4.12 (t, 1H, C(4)*H*, *J* 10.18, 9.83 Hz); 5.19 (t, 1H, benzylic *H*); 6.81–7.58 (m, 13H, Ar*H*); 8.17 (s, 1H, N*H*); 9.18 (s, 1H, N*H*). δ_C (100 MHz, $CDCl_3$) 19.1, 21.1, 32.6, 34.8, 46.5, 57.7, 61.3, 81.8, 109.4, 112.3, 121.2, 122.4, 126.5, 126.8, 128.6, 128.9, 129.1, 130.4, 133.8, 136.4, 138.2, 140.7, 183.6, 190.3; EI-MS *m*/*z* 447.5 (M^+); Anal. Calcd for $C_{29}H_{25}N_3O_2$: C, 77.83; H, 5.63; N, 9.39%. Found: C, 77.71; H, 5.75; N, 9.20%.

*4.2.14. 4′-(4-Methylphenyl)-1′-methyl-4,9-dihydrodispiro[carbazole-2,3′-pyrrolidine-2′,3″-indole]-1,2″(3*H*)-dione (**14b**)*

Yellow solid, mp 132 °C; ν_{max} (KBr) 3281, 1702, 1643 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.55 (m, 1H, C(3)*H*); 1.85 (m, 1H, C(3)*H*); 2.17 (s, 3H, NC*H*$_3$); 2.3 (s, 3H); 2.52 (d, 2H, *J* 14.00 Hz); 3.53 (t, 1H, C(4)*H*, *J* 8.72, 8.69 Hz); 4.04 (t, 1H, C(4)*H*, *J* 9.91, 9.73 Hz); 5.01 (t, 1H, benzylic *H*); 6.65–7.71 (m, 12H, Ar*H*); 8.17 (s, 1H, N*H*); 9.03 (s, 1H, N*H*). δ_C (100 MHz, $CDCl_3$) 18.8, 21.0, 32.4, 34.7, 46.5, 57.7, 61.3, 81.8, 109.3, 112.2, 121.2, 122.4, 126.5, 126.8, 128.6, 128.9, 129.2, 130.4, 135.8, 136.5, 138.2, 140.7, 183.5, 190.3; EI-MS *m*/*z* 461.5 (M^+); Anal. Calcd for $C_{30}H_{27}N_3O_2$: C, 78.07; H, 5.90; N, 9.10%. Found: C, 77.89; H, 5.73; N, 9.22%.

*4.2.15. 4′-(4-Methoxyphenyl)-1′-methyl-4,9-dihydrodispiro[carbazole-2,3′-pyrrolidine-2′,3″-indole]-1,2″(3*H*)-dione (**14c**)*

Pale yellow solid, mp 132 °C; ν_{max} (KBr) 3284, 1703, 1643 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.53 (m, 1H, C(3)*H*); 1.87 (m, 1H, C(3)*H*); 2.06 (s, 3H, NC*H*$_3$); 2.48 (d, 2H, *J* 14.10 Hz); 3.21 (t, 1H, C(4)*H*, *J* 8.68, 8.70 Hz); 3.68 (s, 3H, OC*H*$_3$); 3.96 (t, 1H, C(4)*H*, *J* 9.80, 9.91 Hz); 4.95 (t, 1H, benzylic *H*); 6.64–7.70 (m, 12H, Ar*H*); 8.11 (s, 1H, N*H*); 9.03 (s, 1H, N*H*). δ_C (100 MHz, $CDCl_3$) 18.7, 20.9, 32.4, 34.7, 36.2, 57.6, 61.3, 81.8, 109.4, 112.2, 121.1, 122.4, 126.4, 126.8, 128.6, 128.9, 129.0, 131.0, 135.1, 136.3, 137.9, 140.3, 183.5, 190.3; EI-MS *m*/*z* 477.56 (M^+); Anal. Calcd for $C_{30}H_{27}N_3O_3$: C, 75.45; H, 5.70; N, 8.80%. Found: C, 75.63; H, 5.52; N, 9.02%.

*4.2.16. 4′-(4-Chlorophenyl)-1′-methyl-4,9-dihydrodispiro[carbazole-2,3′-pyrrolidine-2′,3″-indole]-1,2″(3*H*)-dione (**14d**)*

Pale yellow solid, mp 162 °C; ν_{max} (KBr) 3284, 1706, 1656 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.51 (m, 1H, C(3)*H*); 1.83 (m, 1H, C(3)*H*); 2.10 (s, 3H, NC*H*$_3$); 2.50 (d, 2H, *J* 14.21 Hz); 3.20 (t, 1H, C(4)*H*, *J* 8.67, 8.69 Hz); 3.98 (t, 1H, C(4)*H*, *J* 9.80, 9.76 Hz); 5.24 (t, 1H, benzylic *H*); 6.88–7.88 (m, 12H, Ar*H*); 8.23 (s, 1H, N*H*); 9.10 (s, 1H, N*H*). δ_C (100 MHz, $CDCl_3$) 18.2, 20.3, 32.4, 33.1, 45.9, 56.8, 61.1, 81.2, 109.1, 112.0, 120.9, 122.1, 125.7, 125.9, 128.3, 128.5, 129.3, 130.6, 135.2, 136.1, 137.0, 140.2, 182.9, 190.0; EI-MS *m*/*z* 481.98 (M^+); Anal. Calcd for $C_{29}H_{24}ClN_3O_2$: C, 71.27; H, 5.02; N, 8.72%. Found: C, 71.16; H, 5.19; N, 9.01%.

*4.2.17. 4′-(4-Bromophenyl)-1′-methyl-4,9-dihydrodispiro[carbazole-2,3′-pyrrolidine-2′,3″-indole]-1,2″(3*H*)-dione (**14e**)*

Pale yellow solid, mp 186–188 °C; ν_{max} (KBr) 3281, 1703, 1654 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.48 (m, 1H, C(3)*H*); 1.68 (m, 1H, C(3)*H*); 2.00 (s, 3H, NC*H*$_3$); 2.11 (d, 2H, *J* 14.21 Hz); 3.08 (t, 1H, C(4)*H*, *J* 8.59, 8.60 Hz); 3.42 (t, 1H, C(4)*H*, *J* 9.80, 9.78 Hz); 4.87 (t, 1H, benzylic *H*); 6.61–7.68 (m, 12H, Ar*H*); 8.06 (s, 1H, N*H*); 9.01 (s, 1H,

N*H*). δ_C (100 MHz, $CDCl_3$) 17.4, 18.6, 28.2, 31.7, 32.9, 42.3, 56.1, 60.9, 80.0, 109.1, 112.0, 120.8, 121.4, 124.2, 125.6, 126.8, 127.8, 128.1, 130.8, 134.2, 135.2, 136.8, 140.2, 182.9, 190.1; EI-MS *m*/*z* 526.43 (M^+) Anal. Calcd for $C_{29}H_{24}BrN_3O_2$: C, 66.17; H, 4.60; N, 7.98%. Found: C, 66.38; H, 4.72; N, 8.12%.

*4.2.18. 4′-(4-Nitrophenyl)-1′-methyl-4,9-dihydrodispiro[carbazole-2,3′-pyrrolidine-2′,3″-indole]-1,2″(3*H*)-dione (**14f**)*

Yellow solid, mp 198–200 °C; ν_{max} (KBr) 3282, 1705, 1652 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.39 (m, 1H, C(3)*H*); 1.60 (m, 1H, C(3)*H*); 2.13 (s, 3H, NCH_3); 2.20 (d, 2H, *J* 14.10 Hz); 2.98 (t, 1H, C(4)*H*, *J* 8.62, 8.61 Hz); 3.38 (t, 1H, C(4)*H*, *J* 9.79, 9.78 Hz); 5.14 (t, 1H, benzylic *H*); 6.92–7.86 (m, 12H, Ar*H*); 8.15 (s, 1H, N*H*); 9.23 (s, 1H, N*H*). δ_C (100 MHz, $CDCl_3$) 17.3, 18.2, 26.2, 30.5, 32.2, 42.6, 56.8, 61.2, 80.4, 109.2, 112.2, 120.8, 122.3, 124.6, 124.9, 125.2, 126.6, 128.0, 128.1, 130.6, 135.4, 135.8, 136.2, 140.3, 182.2, 190.6; 492.54; EI-MS *m*/*z* 492.54 (M^+); Anal. Calcd for $C_{29}H_{24}N_4O_4$: C, 70.72; H, 4.91; N, 11.38%. Found: C, 70.49; H, 4.75; N, 11.51%.

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