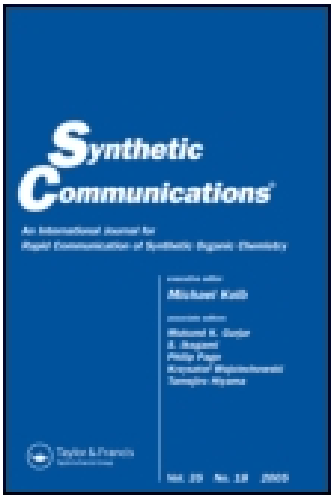

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Regioselective Synthesis of Dispirocycloalkanooxindolopyrrolidines and Dispirocyclalkanoindanopyrrolidines

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REGIOSELECTIVE SYNTHESIS OF DISPIROCYCLOALKANOOXINDOLOPYRROLIDINES AND DISPIROCYCLALKANOINDANOPYRROLIDINES

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Synthesis of a series of novel dispirocycloalkanone-oxindolopyrrolidines and dispirocycloalkanone-indanopyrrolidines is described. The nonstabilized azomethine ylides generated from a secondary amino acid, sarcosine, and carbonyl components (isatin and ninhydrin) have been effectively trapped by the dipolarophiles, arylidene cycloalkanones, to afford dispiropyrrolidines. The one-pot azomethine ylide cycloaddition reactions were highly regioselective.

Keywords: Azomethine ylide; dipolarophile; oxindole; regioselective; spiropyrrolidine

INTRODUCTION

1,3-Dipolar cycloaddition methodology is one effective tool for the construction of five-membered heterocycles.[1] Many stereochemically important natural products have been effectively synthesized by this strategy, because the generation of 1,3-dipoles is often associated with high regio- and stereoselectivities.[2–5] The pyrrolidine motif occurs in many families of biologically potent molecules, and because of the ease of substitution and modifications at several positions, a wide range of pyrrolidine derivatives have been synthesized with varying properties.[6] Pyrrolidine based molecules possess anti-influenza[7] and anticonvulsant activities.[8] The azomethine ylide represents one of the most reactive and versatile classes of 1,3-dipoles and is readily trapped by a range of dipolarophiles, forming substituted pyrrolidines.[9] The spiro ring system is frequently encountered in many pharmacologically important alkaloids. Synthetic spiropyrrolidine derivatives have activity against the aldose reductase enzyme, which controls influenza.[10] The synthesis of spirooxindole ring systems has gained considerable attention because they are the basic building units in many natural products such as gelsemine, pseudotabersonine, and morroniside.[11] In particular, spiroxindolopyrrolidine ring systems are found in a number of alkaloids such as horsfiline, spirotrypsostatine A and B, and elacomine.[12]

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It has been well established that cycloalkanone derivatives possess substantial antifertility activity in rodents[13] and have important pharmacological properties.[14] In continuation of our efforts in the synthesis of pyrrolidine-based heterocycles, and encouraged by the recent findings,[15] we present an efficient synthesis of some new spiropyrrolidines.

RESULTS AND DISCUSSION

We envisaged complex spiroheterocycles incorporating the aforesaid bioactive scaffolds with enhanced bioactivity. Two types of nonstabilized azomethine ylides were generated in situ and were trapped by the dipolarophiles. Among the methods for the generation of azomethine ylides, the decarboxylation route offers a general method in which an aldehyde or a ketone is reacted with α-amino acids.[16] In the first effort of our synthetic studies, we generated in situ a nonstabilized *anti*-dipole **3** by the decarboxylative condensation reaction of sarcosine with an 1,2-diketone, isatin (Scheme 1). Second, a triketone, indane-1,2,3-trione, was reacted with sarcosine to form the *anti*-ylide **8** (Scheme 2).

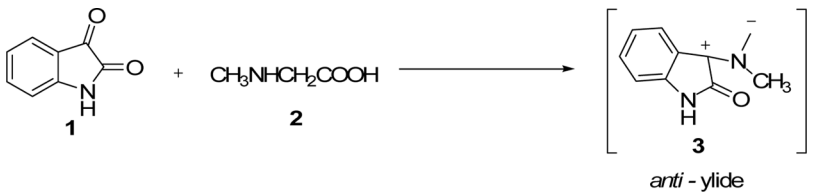
Arylidene cycloheptanones and arylidene cyclooctanones were used as dipolarophiles toward 1,3-dipolar cycloaddition reactions. Thus, arylidene cycloheptanones **4a–d** and arylidene cyclooctanones **4e–h** were prepared by condensation of cycloheptanone and cyclooctanone, respectively, with aromatic aldehydes in the presence of a base catalyst.[17,18] The geometry of the olefinic double bond was found to be *E* configuration in all cases, as evidenced by ^{1}H NMR spectra.

Synthesis of Dispirooxindolo Cycloalkanone Pyrrolidines

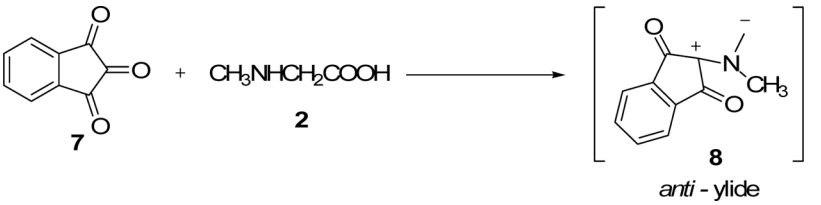
In a one-pot reaction, a solution of 2-arylidene-1-cycloheptan/octan-ones **4a–h** in methanol with isatin **1** and sarcosine **2** was refluxed for 3–4.5 h to afford a series of 1-*N*-methyl-spiro[2.3′]oxindole-spiro[3.2″]1″-cycloheptan/octan-one-4-aryl-pyrrolidines **5a–h** (Scheme 3; Table 1, entries 1–8). The reaction gave single products in all cases, as evidenced by thin-layer chromatography (TLC).

The cycloadducts have been formed through regioselective cycloaddition of azomethine ylide **3** to the exocyclic double bond of the 2-arylidene-1-cycloheptan/octanones, **4a–h**, in all cases (Scheme 4). No traces of other regioisomers (**6a–h)** were detected.

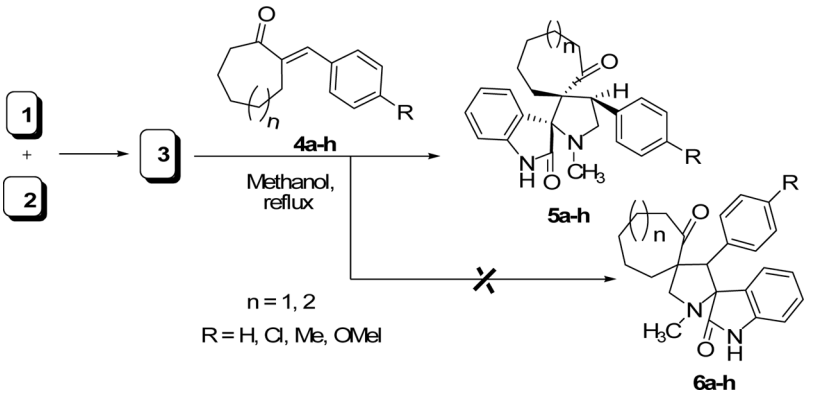
The regio- and stereochemical outcomes of the cycloaddition were determined by spectroscopic data. For instance, the infrared (IR) spectrum of the product **5e** exhibited a peak at 1693 cm^{-1} for cyclooctanone carbonyl, at 1716 cm^{-1} for the oxindole carbonyl, and at 3180 cm^{-1} for the NH absorption of the oxindole ring.



Scheme 1. Generation of azomethine ylide from isatin and sarcosine.



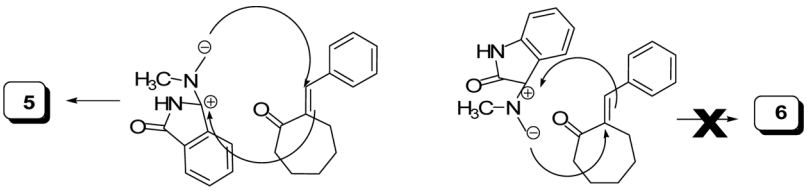
Scheme 2. Generation of azomethine ylide from ninhydrin and sarcosine.



Scheme 3. Reaction of azomethine ylide generated from isatin and cycloalkanones.

Table 1. Cycloaddition of azomethine ylide generated from isatin/sarcosine and ninhydrin/sarcosine toward arylidene cycloheptanones **4a–d** and arylidene cyclooctanones **4e–h**

Entry	Product	R	Yield (%)	*n*	Mp (°C)	Reaction time (h)
1	**5a**	H	69	1	210–212	4
2	**5b**	Cl	71	1	224–226	4.5
3	**5c**	Me	68	1	192–194	4
4	**5d**	OMe	67	1	207–209	3.5
5	**5e**	H	70	2	188–190	3
6	**5f**	Cl	71	2	160–162	5
7	**5g**	Me	65	2	199–201	4.5
8	**5h**	OMe	64	2	188–190	3
9	**9a**	H	71	1	128–130	5
10	**9b**	Cl	73	1	169–171	4.5
11	**9c**	Me	68	1	139–141	5
12	**9d**	OMe	67	1	151–153	6
13	**9e**	H	68	2	120–122	5.5
14	**9f**	Cl	67	2	162–164	5
15	**9g**	Me	66	2	142–144	6.5
16	**9h**	OMe	69	2	159–161	5.5



Scheme 4. Mode of attack of dipole **3** on the dipolarophile **4**.

In the ^{1}H NMR spectrum of **5e**, the cyclooctyl protons exhibited a cluster of multiplets in the range δ 0.63–2.47. The *N*-methyl protons appeared as a singlet at δ 2.12. The two NCH_2 protons appeared as two distorted triplets at (3.39 and 3.75. The benzylic proton appeared as a triplet at δ 4.83. The unusual triplet splitting patterns rather than doublet of doublets for these protons may be due to the geometrical disposition of the atoms and is analogous with our previous report.[19] The NH proton of the oxindole ring was observed as a singlet at δ 9.16. The ^{13}C NMR spectrum of **5e** exhibited a peak at 214.04 ppm for cyclooctanone carbonyl and at 179.26 ppm for oxindole carbonyl carbon. A peak at 59.85 ppm was due to C3-spiroquarternary carbon, and a peak at 70.85 ppm was due to C2 spirocarbon. Identical results were obtained for other derivatives of **5a–h**.

Furthermore, the structure of cycloadduct **5e** was unambiguously corroborated by single-crystal x-ray diffraction analysis (Fig. 1). The pyrrolidine ring in the oxindole system is not strictly planar with a slight deviation of C6 by 0.091 Å from the plane of the remaining atoms. The dihedral angle between the six- and five-membered rings in the oxindole system is 6.5 Å. Atom O1 deviates by 0.175 Å

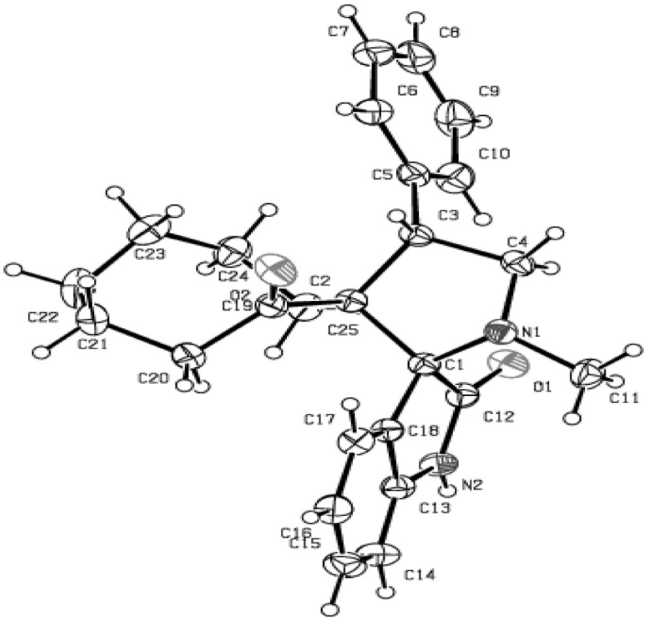


Figure 1. ORTEP diagram of **5e**.

from the plane of atoms C1, C6, N2, C7, and C12. The pyrrolidine ring adopts a twisted conformation with a pseudo-twofold axis passing through atom C2 and the midpoint of the C4-N1 bond. It was further observed that the molecule is stabilized by weak intramolecular C-H . . . O and C-H. . . π interactions.[20]

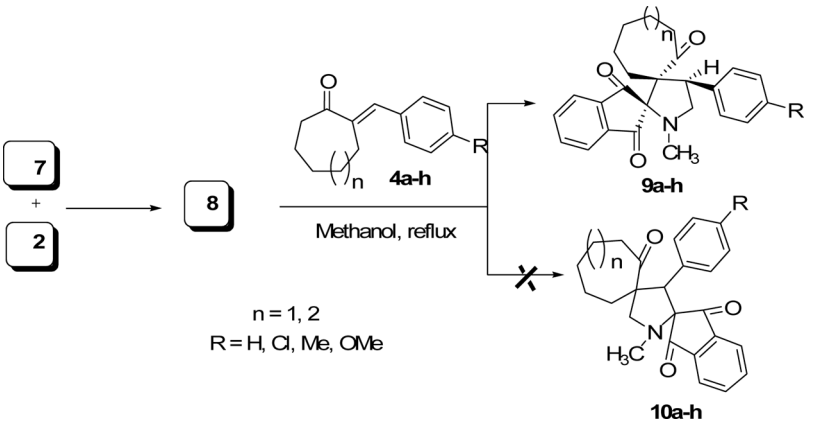
Synthesis of Dispiroindano Cycloalkanone Pyrrolidines

We performed a similar three-component reaction in which the azomethine ylide, **8**, generated from sarcosine, **2**, and ninhydrin, **7,** was reacted with dipolarophiles **4a–h** to yield a series of novel dispiroindano cycloheptan/octan-one pyrrolidines **9a–h** in good yields. The products were formed by the regioselective cycloaddition of the ylide, **8,** across the exocyclic double bond of the dipolarophiles **4a–h** (Schemes 5 and 6; Table 1, entries 9–16).

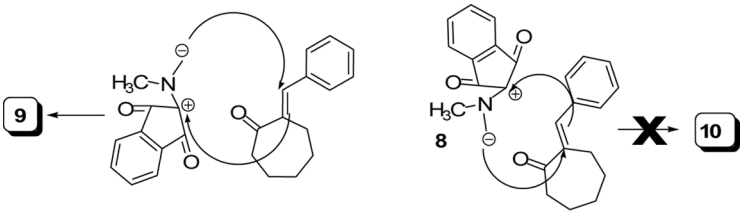
The structure and regiochemistry of the products **9a–h** were established by IR, ^{1}H and ^{13}C NMR spectroscopic, and mass spectrometric studies. For instance, the ^{1}H NMR spectrum of compound **9e** showed a sharp singlet at δ 2.20 due to *N*-methyl protons and multiplets in the range δ 0.72–2.51 due to cyclooctyl protons. One of the *N*-CH_2 protons exhibited a doublet of doublet at δ 3.48 ($J = 9$ and 6 Hz), whereas the other proton appeared as a triplet at δ 3.66 ($J = 9$ Hz). The benzylic proton appeared as a doublet of doublet at δ 4.48 ($J = 9$ and 6 Hz). If the other regiomer **10e** had formed, a singlet would be observed for the benzylic proton.

In the ^{13}C NMR spectrum of cycloadduct **9e**, the spiroquaternary carbons showed peaks at 74.68 ppm and 78.43 ppm. The two unsymmetrical ninhydrin carbonyl carbons resonated at 201.60 ppm and 203.29 ppm, whereas the ketone carbonyl of cyclooctanone ring exhibited a peak at 214.20 ppm. The mass spectrum of **9e** exhibited the molecular ion peak at m/z 401.98, and the compound gave satisfactory elemental analysis. The regiochemistry of the cycloaddition reaction was further confirmed by the single-crystal x-ray diffraction analysis of **9b** and **9e** (Figs. 2 and 3).[21,22]

In the molecular structure of **9e**, the indanedione group is planar, with a maximum deviation of 0.069 Å for atom C1. The keto atoms O1 and O2 deviate from the mean plane through the fused-ring system by 0.241 and 0.236 Å,



Scheme 5. Reaction of azomethine ylide generated ninhydrin with cycloalkanones.



Scheme 6. Mode of attack of dipole **8** on the dipolarophile **4**.

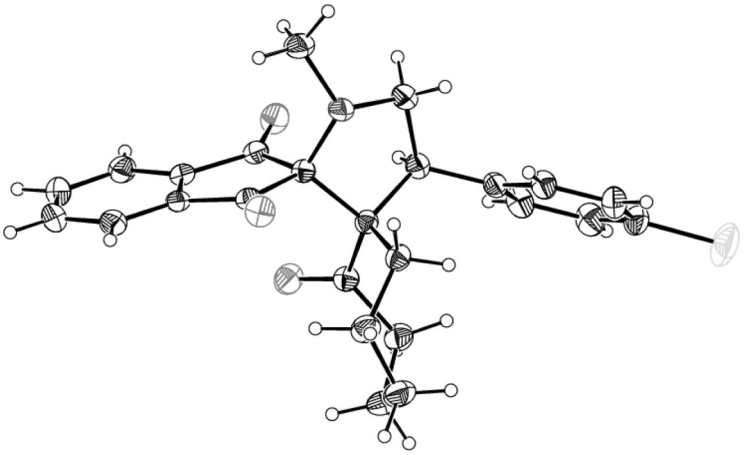


Figure 2. ORTEP diagram of **9b**.

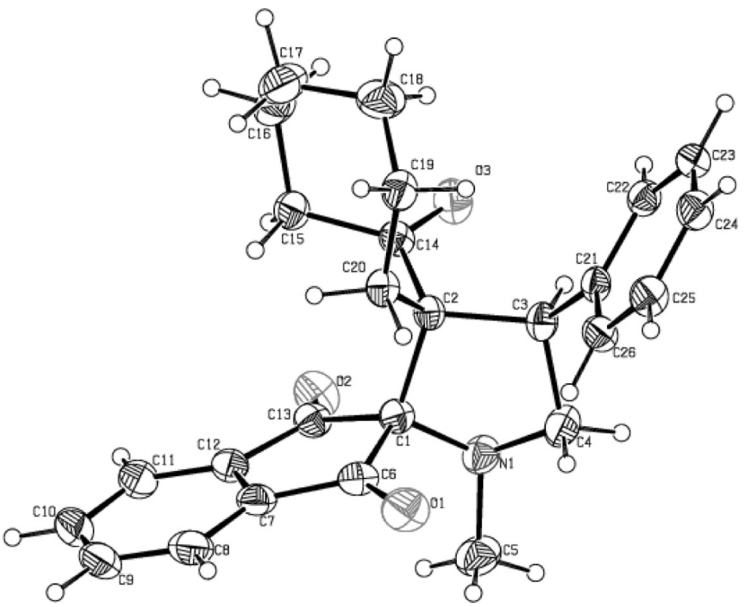


Figure 3. ORTEP diagram of **9e**.

respectively. The dihedral angle between the fused six-membered and five-membered rings is 1.2 Å. The cyclooctanone ring adopts a boat–chair conformation. The molecular structure is stabilized by weak C-H- - -O interactions and further influenced by a C-H- - -π interaction, such that atom H15*b* is 2.66 Å from the centoid of the C21–C26 benzene ring, with a C15-H15*B*- - -centroid angle of 154 and a C15 . . . . centroid distance of 3.557 Å.

CONCLUSION

In conclusion, a novel synthesis of some dispiropyrrolidines containing cycloalkanone, oxindole, and indanedione moieties has been accomplished in a one-pot, three-component 1,3-dipolar cycloaddition reaction. It was observed that the nonstabilized azomethine ylide generated by the reaction between diketone/triketone and secondary α-amino acids added regioselectively across the exocyclic double bonds of the dipolarophiles to give novel spiroheterocycles.

EXPERIMENTAL

General Considerations

IR spectra were recorded on a Shimadzu IR-8300 series Fourier transform (FT)–IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Jeol 400-MHz instrument in $CDCl_3$ solvent with tetramethylsilane (TMS) as a standard. Mass spectra were recorded on a Jeol-DX303 HF mass spectrometer. Elemental analyses were carried out on a Perkin-Elmer CHNS 2400 instrument. Single-crystal x-ray diffraction analysis was performed using a Endraf-Nonius CHD4 diffractometer and Bruker Smart Apex CCD area detector diffractometer. Column chromatography was performed on silica gel (Acme, 100–200 mesh). Routine monitoring of the reaction was made using thin-layer chromatography (TLC) developed on glass plates coated with silica gel G (Acme) 25 mm thick and visualized with iodine.

General Procedure for the Synthesis of Cycloadducts 5a–h

A mixture of isatin (0.147 g, 1 mmol), sarcosine (0.089 g, 1 mmol), and arylidene cycloheptan/octan-ones **4a–h** (1 mmol) in methanol (20 mL) was refluxed until the disappearance of the starting materials. The reaction mixture was then concentrated in vacuo, diluted with water (50 mL), and extracted with dichloromethane (50 mL). The organic layer was then washed with brine solution, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography with a hexane–ethyl acetate mixture (8:2) to get pure products **5a–h** in good yields.

Selected Data

1-*N*-Methyl-spiro[2.3′]oxindole-spiro[3.2″]1″-cycloheptanone-4-phenyl-pyrrolidine, 5a. Colorless solid, 69% (0.258 g); mp: 210–212°C; IR (KBr): 1714, 1696, 1476, 2913 and 3397 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88–2.10 (m,

10H, cycloheptyl), 2.15 (s, 3H, *N*-Me), 3.36 (t, 1H, NCH_2), 3.83 (t, 1H, NCH_2), 4.82 (t, 1H, benzyl), 6.72–7.47 (m, 9H, Ar-H), 8.34 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): 24.89, 27.55, 29.90, 30.67, 43.11, 45.00, 55.32, 59.65, 68.66, 109.29, 113.97, 122.03, 126.69, 126.23, 129.10, 131.10, 131.21, 141.55, 158.11, 178.60 and 212.65 ppm; mass spectrum (EI, 70 eV): m/z 374.20 (M^+). Anal. calcd. for $C_{24}H_{26}N_2O_2$: C, 76.98; H, 7.00; N, 7.48%. Found: C, 75.87; H, 7.12; N, 7.39%.

1-*N*-Methyl-spiro[2.3′]oxindole-spiro[3.2″]1″-cycloheptanone-4-(*p*-chloro) phenyl-pyrrolidine, 5b. Colorless solid; 71% (0.289 g); mp: 224–226°C; IR (KBr): 1714, 1693, 1477, 2911 and 3396 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.88–2.09 (m, 10H, cycloheptyl), 2.14 (s, 3H, *N*-Me), 3.37 (t, 1H, NCH_2), 3.84 (t, 1H, NCH_2), 4.81 (t, 1H, benzyl), 6.67–7.47 (m, 8H, Ar-H), 8.24 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): 24.87, 27.11, 29.90, 30.66, 43.31, 45.17, 55.66, 59.69, 68.11, 109.93, 113.77, 122.33, 126.66, 126.09, 129.18, 131.13, 131.29, 141.37, 158.30, 178.66 and 212.06 ppm; mass spectrum (EI, 70 eV): m/z 408.16 (M^+). Anal. calcd. for $C_{24}H_{25}ClN_2O_2$: C, 70.49; H, 6.16; N, 6.85%. Found: C, 70.38; H, 6.23; N, 6.73%.

1-*N*-Methyl-spiro[2.3′]oxindole-spiro[3.2″]1″-cycloheptanone-4-(*p*-methyl)-phenylpyrrolidine, 5c. Colorless solid, 68% (0.263 g); mp: 192–194°C; IR (KBr): 1717, 1690, 1474, 2913 and 3396 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.87–2.09 (m, 10H, cycloheptyl), 2.12 (s, 3H, Ar-Me), 2.14 (s, 3H, *N*-Me), 3.37 (t, 1H, NCH_2), 3.84 (t, 1H, NCH_2), 4.82 (t, 1H, benzyl), 6.77–7.40 (m, 8H, Ar-H), 8.34 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): 21.01, 24.23, 27.56, 29.67, 30.67, 35.44, 43.55, 45.34, 55.11, 59.34, 68.00, 109.12, 113.78, 122.46, 126.00, 126.16, 129.73, 131.34, 131.67, 141.30, 158.47, 178.13 and 212.49 ppm; mass spectrum (EI, 70 eV): m/z 388.22 (M^+). Anal. calcd. for $C_{25}H_{28}N_2O_2$: C, 77.29; H, 7.26; N, 7.21%. Found: C, 77.20; H, 7.38; N, 7.30%.

1-*N*-Methyl-spiro[2.3′]oxindole-spiro[3.2″]1″-cycloheptanone-4-(*p*-methoxy)phenylpyrrolidine, 5d. Colorless solid, 67% (0.268 g); mp: 207–209°C; IR (KBr): 1715, 1693, 1474, 2912.3 and 3398 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.90–2.09 (m, 10H, cycloheptyl), 2.15 (s, 3H, *N*-Me), 3.38 (t, 1H, NCH_2), 3.84 (t, 1H, NCH_2), 3.79 (s, 3H, OMe), 4.80 (t, 1H, benzyl), 6.83–7.47 (m, 8H, Ar-H), 8.11 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): 24.45, 27.82, 29.91, 30.25, 35.01, 43.30, 45.17, 55.19, 59.66, 68.13, 109.63, 113.47, 122.89, 126.59, 126.76, 129.38, 131.14, 131.89, 141.30, 158.33, 178.26 and 212.76 ppm; mass spectrum (EI, 70 eV): m/z 401.48 (M^+). Anal. calcd. for $C_{25}H_{28}N_2O_3$: C, 74.23; H, 6.98; N, 6.93%. Found: C, 74.38; H, 6.87; N, 6.99%.

1-*N*-Methyl-spiro[2.3′]oxindole-spiro[3.2″]1″-cyclooctanone-4-phenyl pyrrolidine, 5e. Colorless solid, 70% (0.271 g); mp: 188–190°C; IR (KBr): 1716, 1693, 1473, 2912 and 3398 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.64–2.48 (m, 12H, cyclooctyl), 2.12 (s, 3H, *N*-Me), 3.39 (t, 1H, NCH_2), 3.75 (t, 1H, NCH_2), 4.83 (t, 1H, benzyl), 6.92–7.67 (m, 9H, Ar-H), 9.16 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): 23.67, 25.06, 26.88, 27.12, 28.00, 35.21, 40.43, 45.06, 59.85, 70.85, 110.00, 122.70, 126.65, 127.27, 128.18, 128.41, 129.38, 130.05, 133.28, 140.89, 141.24, 179.26 and 214.04 ppm; mass spectrum (EI, 70 eV): m/z 388.37 (M^+). Anal. calcd. for $C_{25}H_{28}N_2O_2$: C, 77.29; H, 7.26; N, 7.21%. Found: C, 77.21; H, 7.35; N, 7.10%.

1-*N*-Methyl-spiro[2.3′]oxindole-spiro[3.2″]1″-cyclooctanone-4-(*p*-chloro)-phenylpyrrolidine, 5f. Colorless solid, 71% (0.299 g); mp: 160–162°C; IR (KBr): 1715, 1695, 1473, 2912 and 3397 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.64–2.38 (m, 12H, cyclooctyl), 2.14 (s, 3H, *N*-Me), 3.41 (t, 1H, NCH_2), 3.74 (t, 1H, NCH_2), 4.81 (t, 1H, benzyl), 6.89–7.66 (m, 8H, Ar-H), 8.67 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.70, 25.12, 26.43, 28.43, 35.99, 40.54, 45.24, 59.46, 70.90, 109.98, 122.70, 126.70, 127.31, 128.29, 130.30, 140.11, 141.29, 178.61 and 214.23; mass spectrum (EI, 70 eV): m/z 422.18 (M^+). Anal. calcd. for $C_{25}H_{27}ClN_2O_2$: C, 70.99; H, 6.43; N, 6.62%. Found: C, 70.84; H, 6.52; N, 6.50%.

1-*N*-Methyl-spiro[2.3′]oxindole-spiro[3.2″]1″-cyclooctanone-4-(*p*-methyl)-phenylpyrrolidine, 5g. Colorless solid, 65% (0.261 g); mp: 199–201°C; IR (KBr): 1715, 1696, 1473, 2912 and 3398 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.69–2.42 (m, 12H, cyclooctyl), 2.12 (s, 3H, Ar-CH_3), 2.15 (s, 3H, *N*-Me), 3.43 (t, 1H, NCH_2), 3.75 (t, 1H, NCH_2), 4.81 (t, 1H, benzyl), 6.77–7.56 (m, 8H, Ar-H), 8.37 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): 221.34, 23.34, 25.56, 26.77, 28.88, 35.34, 40.87, 45.89, 59.44, 70.80, 109.34, 122.86, 126.29, 127.83, 128.74, 130.55, 140.58, 141.09, 178.99 and 214.99 ppm; mass spectrum (EI, 70 eV): m/z 402.23 (M^+). Anal. calcd. for $C_{26}H_{30}N_2O_2$: C, 77.58; H, 7.51; N, 6.96%. Found: C, 77.47; H, 7.62; N, 6.82%.

1-*N*-Methyl-spiro[2.3′]oxindole-spiro[3.2″]1″-cyclooctanone-4-(*p*-methoxy)phenylpyrrolidine, 5h. Colorless solid, 64% (0.274 g); mp: 188–190°C; IR (KBr): 1716, 1695, 1474, 2912 and 3397 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.66–2.46 (m, 12H, cyclooctyl), 2.15 (s, 3H, *N*-Me), 3.43 (t, 1H, NCH_2), 3.75 (t, 1H, NCH_2), 3.78 (s, 3H, OMe), 4.82 (t, 1H, benzyl), 6.70–7.56 (m, 8H, Ar-H), 8.47 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.34, 25.16, 26.72, 28.23, 35.33, 40.56, 45.55, 59.41, 70.80, 109.67, 122.88, 126.11, 127.77, 128.22, 130.88, 140.13, 141.07, 178.23 and 214.67; mass spectrum (EI, 70 eV): m/z 428.23 (M^+). Anal. calcd. for $C_{26}H_{30}N_2O_3$: C, 74.61; H, 7.22; N, 6.69%. Found: C, 74.50; H, 7.34; N, 6.81%.

General Procedure for the Synthesis of Cycloadducts, 9a–h

A mixture of ninhydrin (0.178 g, 1 mmol), sarcosine (0.089 g, 1 mmol), and arylidenecycloheptanones **4a–d**/arylidenecyclooctanones **4e–h** (1 mmol) in methanol (20 mL) was refluxed until the disappearance of starting materials as shown by the TLC analysis. The reaction mixture was then concentrated in vacuo, diluted with water (50 mL), and extracted with dichloromethane (50 mL). The organic layer was washed with brine solution, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography with hexane–ethyl acetate mixture (8:2) to get compounds **9a–h** in good yields. The cycloadducts **9a** and **9e** were recrystallized from methanol by slow evaporation method for x-ray crystallographic analysis.

Selected Data

1-*N*-Methyl-spiro[2.1′]-indane,1′,*3*′-dione-spiro[3.2″]1″-cycloheptanone-4-phenylpyrrolidine, 9a. Orange/red solid, 71% (0.274 g); mp: 128–130°C; IR (KBr): 1742, 1716 and 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.73–2.51 (m,

10H, cycloheptyl), 2.22 (s, 3H, *N*-Me), 3.48 (dd, 1H, *N*-CH_2, $J = 6$, 9 Hz), 3.69 (t, 1H, *N*CH_2, $J = 9$ Hz), 4.47 (dd, 1H, benzyl, $J = 6$, 9 Hz), 7.28–7.99 (m, 9H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): 24.53, 26.66, 26.08, 29.07, 35.98, 39.64, 48.54, 61.75, 74.34, 78.43, 122.11, 122.54, 127.98, 128.03, 128.41, 129.27, 130.73, 135.45, 136.25, 139.38, 141.53, 142.10, 201.77, 203.09 and 214.83 ppm; mass spectrum (EI, 70 eV): m/z 387.18 (M^+). Anal. calcd. for $C_{25}H_{25}NO_3$: C, 77.49; H, 6.50; N, 3.61%. Found: C, 77.61; H, 6.41; N, 3.74%.

1-*N*-Methyl-spiro[2.1′]-indane,1′,3′-dione-spiro[3.2″]1″-cycloheptanone-4-(*p*-chloro)phenylpyrrolidine, 9b. Orange/red solid, 73% (0.307 g); mp: 169–171°C; IR (KBr): 1743, 1718 and 1704 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.76–2.32 (m, 10H, cycloheptyl), 2.20 (s, 3H, *N*-Me), 3.39 (dd, 1H, *N*-CH_2, $J = 6$, 9 Hz), 3.66 (t, 1H, *N*CH_2, $J = 9$ Hz), 4.44 (dd, 1H, benzyl, $J = 6$, 9 Hz), 7.29–7.99 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.79, 26.98, 28.90, 35.43, 40.33, 46.90, 61.12, 122.65, 122.76, 128.35, 128.96, 130.68, 131.52, 135.67, 136.04, 138.10, 141.25, 142.72, 201.87, 202.53 and 213.53; mass spectrum (EI, 70 eV): m/z 421.14 (M^+). Anal. calcd. for $C_{25}H_{24}ClNO_3$: C, 71.17; H, 5.73; N, 3.32%. Found: C, 71.28; H, 5.81; N, 3.20%.

1-*N*-Methyl-spiro[2.1′]-indane,1′,3′-dione-spiro[3.2″]1″-cycloheptanone-4-(*p*-methyl)phenylpyrrolidine, 9c. Orange/red solid, 68% (0.272 g); mp: 139–141°C; IR (KBr): 1742, 1714 and 1704 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.73–2.51 (m, 10H, cycloheptyl), 2.19 (s, 3H, Ar-Me), 2.24 (s, 3H, *N*-Me), 3.49 (dd, 1H, *N*-CH_2, $J = 6$, 9 Hz), 3.67 (t, 1H, *N*CH_2, $J = 9$ Hz), 4.48 (dd, 1H, benzyl, $J = 6$, 9 Hz), 7.09–7.96 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): 21.89, 24.53, 26.67, 26.88, 29.43, 35.56, 39.46, 48.85, 61.42, 74.12, 78.43, 122.86, 122.65, 127.23, 128.86, 128.98, 129.29, 130.79, 135.45, 136.54, 139.08, 141.99, 142.34, 201.09, 203.64 and 214.98 ppm; mass spectrum (EI, 70 eV): m/z 401.20 (M^+). Anal. calcd. for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49%. Found: C, 77.89; H, 6.87; N, 3.40%.

1-*N*-Methyl-spiro[2.1′]-indane,1′,3′-dione-spiro[3.2″]1″-cycloheptanone-4-(*p*-methoxy)phenylpyrrolidine, 9d. Orange/red solid, 67% (0.279 g); mp: 151–153°C; IR (KBr): 1742, 1714 and 1704 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.73–2.51 (m, 10H, cycloheptyl), 2.24 (s, 3H, *N*-Me), 3.49 (dd, 1H, *N*-CH_2, $J = 6$, 9 Hz), 3.67 (t, 1H, *N*CH_2, $J = 9$ Hz), 3.79 (s, 3H, Ar-OMe), 4.48 (dd, 1H, benzyl, $J = 6$, 9 Hz), 7.09–7.96 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): 24.53, 26.67, 26.88, 29.43, 34.56, 35.56, 39.46, 48.85, 61.42, 74.12, 78.43, 122.86, 122.65, 127.23, 128.86, 128.98, 129.29, 130.79, 135.45, 136.54, 139.08, 141.99, 142.34, 201.09, 203.64 and 214.98; mass spectrum (EI, 70 eV): m/z 417.19 (M^+). Anal. calcd. for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35%. Found: C, 74.90; H, 6.61; N, 3.23%.

1-*N*-Methyl-spiro[2.1′]-indane,1′,3′-dione-spiro[3.2″]1″-cyclooctanone-4-phenylpyrrolidine, 9e. Orange/red solid, 68% (0.273 g); mp: 120–122°C; IR (KBr): 1743, 1716 and 1704 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.72–2.51 (m, 12H, cyclooctyl), 2.20 (s, 3H, *N*-Me), 3.48 (dd, 1H, *N*-CH_2, $J = 6$, 9 Hz), 3.66 (t, 1H, *N*CH_2, $J = 9$ Hz), 4.48 (dd, 1H, benzyl, $J = 6$, 9 Hz), 7.28–7.99 (m, 9H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.72, 25.75, 26.24, 26.79, 29.03, 35.61, 39.92, 48.04, 61.52, 74.68, 78.43, 122.14, 122.90, 127.18, 128.23, 128.44, 129.65, 130.72, 135.45, 136.35, 139.78, 141.21, 142.22, 201.60, 203.29 and 214.20; mass spectrum

(EI, 70 eV): m/z 401.98 (M^+). Anal. calcd. for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49%. Found: C, 77.85; H, 6.85; N, 3.40%.

1-*N*-Methyl-spiro[2.1′]-indane,1′,3′-dione-spiro[3.2″]1″-cyclooctanone-4-(*p*-chloro)phenylpyrrolidine, 9f. Orange/red solid, 67% (0.291 g); mp: 162–164°C; IR (KBr): 1742, 1713 and 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.76–2.35 (m, 12H, cyclooctyl), 2.17 (s, 3H, *N*-Me), 3.37 (dd, 1H, *N*-CH_2, $J = 6$, 9 Hz), 3.66 (t, 1H, *N*CH_2, $J = 9$ Hz), 4.49 (dd, 1H, benzyl, $J = 6$, 9 Hz), 7.28–7.99 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.58, 25.81, 26.43, 28.93, 35.54, 40.02, 46.96, 61.41, 122.26, 122.96, 128.35, 128.66, 130.87, 131.85, 135.69, 136.44, 138.70, 141.22, 142.02, 201.33, 202.94 and 213.50; mass spectrum (EI, 70 eV): m/z 435.16 (M^+). Anal. calcd. for $C_{26}H_{26}ClNO_3$: C, 71.63; H, 6.01; N, 3.21%. Found: C, 71.54; H, 6.10; N, 3.30%.

1-*N*-Methyl-spiro[2.1′]-indane,1′,3′-dione-spiro[3.2″]1″-cyclooctanone-4-(*p*-methyl)phenylpyrrolidine, 9g. Orange solid, 66% (0.274 g); mp: 142–144°C; IR (KBr): 1742, 1712 and 1704 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.71–2.50 (m, 12H, cyclooctyl), 2.20 (s, 3H, Ar-Me), 2.23 (s, 3H, *N*-Me), 3.50 (dd, 1H, *N*-CH_2, $J = 6$, 9 Hz), 3.67 (t, 1H, *N*CH_2, $J = 9$ Hz), 4.49 (dd, 1H, benzyl, $J = 6$, 9 Hz), 7.00–7.90 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.08, 24.09, 26.97, 26.88, 29.43, 35.77, 39.47, 48.37, 61.13, 74.67, 78.89, 122.86, 122.67, 127.20, 128.82, 128.88, 129.20, 130.75, 135.44, 136.56, 139.02, 141.93, 142.39, 201.05, 203.66 and 214.48; mass spectrum (EI, 70 eV): m/z 415.21 (M^+). Anal. calcd. for $C_{27}H_{29}NO_3$: C, 78.04; H, 7.03; N, 3.37%. Found: C, 78.17; H, 6.92; N, 3.30%.

1-*N*-Methyl-spiro[2.1′]-indane,1′,3′-dione-spiro[3.2″]1″-cyclooctanone-4-(*p*-methoxy)phenylpyrrolidine, 9h. Orange/red solid, 69% (0.297 g); mp: 159–161°C; IR (KBr): 1743, 1713 and 1704 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.73–2.51 (m, 10H, cyclooctyl), 2.24 (s, 3H, *N*-Me), 3.47 (dd, 1H, *N*-CH_2, $J = 6$, 9 Hz), 3.67 (t, 1H, *N*CH_2, $J = 9$ Hz), 3.77 (s, 3H, Ar-OMe), 4.49 (dd, 1H, benzyl, $J = 6$, 9 Hz), 7.00–7.96 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.58, 26.07, 26.82, 29.87, 34.54, 35.76, 39.09, 48.34, 61.42, 74.10, 78.47, 122.85, 122.65, 127.33, 128.87, 128.90, 129.20, 130.77, 135.40, 136.64, 139.18, 141.98, 142.34, 201.49, 203.66 and 214.92; mass spectrum (EI, 70 eV): m/z 431.21 (M^+). Anal. calcd. for $C_{27}H_{29}NO_4$: C, 75.15; H, 6.77; N, 3.25%. Found: C, 75.25; H, 6.66; N, 3.37%.

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