Synthesis of Trispiro[oxindole-pyrrolidine]-cyclopentanone-isoxazolines by 1,3-Dipolar Cycloaddition

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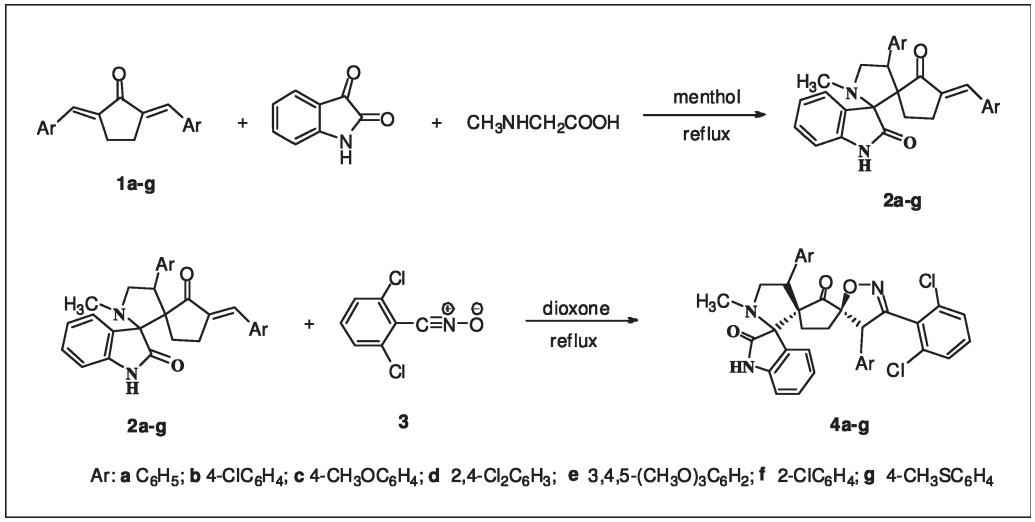

The 1,3-dipolar cycloaddition of an azomethine ylide generated by a decarboxylative route from sarcosine and isatin to 2,5-bis(arylmethylidene)-cyclopentanones afforded novel dispiro oxindole/pyrrolidines in moderate yields. Further cycloaddition of these dispiro oxindole/pyrrolidines with nitrile oxide afforded trispiro[oxindole-pyrrolidine]-cyclopentanone-isoxazolines in moderate yields with high regio- and stereoselectivity.

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INTRODUCTION

Spiro-compounds are an important class of organic compounds based on their biological activities [1], which are motifs in many pharmacologically important alkaloids, as typified by rhyncophylline, corynoxeine, mitraphylline, horsifiline, and spirotryprostatins [2]. Therefore, the synthesis of spiro-compounds has recently attracted the interest of organic chemists.

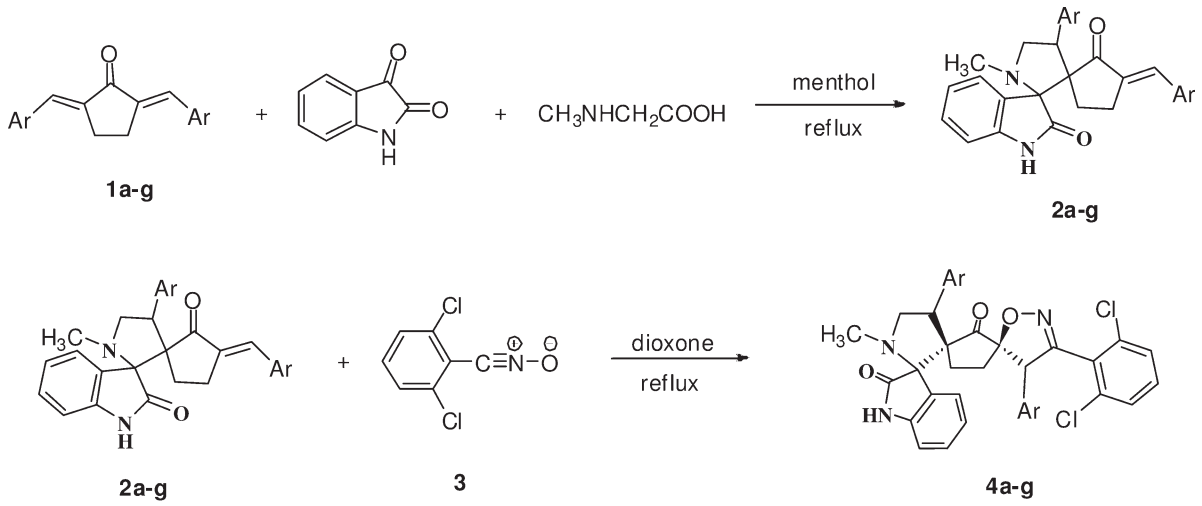
On the other hand, one of the most widely used methods for the synthesis of these compounds is via the intermolecular 1,3-dipolar cycloaddition reaction to exocyclic double bonds [3,4]. Therefore, the substrate with two exocyclic double bonds could be transformed to different spiro-groups by appropriate methods. Kumar and Perumal [5] used 1-methyl-3,5-bis[(E)-arylmethylidene]-tetrahydro-4(1H)-pyridinones through a tandem sequence comprising nitrile oxide cycloaddition to obtain cycloreversion mono-spiro-isoxazoline compounds other than the presumed tri-spiro product.

In the present work, we report the results of a tandem azomethine ylide/nitrile oxide cycloaddition of 2,5-bis(arylmethylidene)-cyclopentanone to obtain trispiro-[oxindole-pyrrolidine]-cyclopentanone-isoxazoline compound **4** (Scheme 1).

RESULTS AND DISCUSSION

The 1,3-dipolar cycloaddition of the azomethine ylide generated *in situ* from isatin and sarcosine to 2,5-bis(arylmethylidene)-cyclopentanone (**1a–g**) afforded novel dispiroheterocycles (**2a–g**) in moderate to good yields (80–85%) (Scheme 1). This cycloaddition reaction proceeded with high stereo- and regioselectivity to afford only one isomer, which was evidenced from TLC and ^{1}H-NMR of the crude reaction mixture. The ^{1}H-NMR spectrum of **2a** demonstrated the presence of four multiplet of cyclopentanone CH_2 at δ 1.23–1.30, 2.12–2.16, 2.17–2.21, 2.35–2.40: one doublet of doublets at δ 4.37

Scheme 1



Ar: **a** C_6H_5; **b** 4-ClC_6H_4; **c** 4-$CH_3OC_6H_4$; **d** 2,4-$Cl_2C_6H_3$; **e** 3,4,5-$(CH_3O)_3C_6H_2$; **f** 2-ClC_6H_4; **g** 4-$CH_3SC_6H_4$

and two triplets at δ 3.60, 3.99 assigned as pyrrolidine protons, and two singlets at δ 2.25 and 8.31 assignable to the —NCH_3 and —NH, respectively. The ^{13}C-NMR spectrum of **2a** demonstrated the presence of two spiro carbons at δ 65.61 and 77.73, two carbonyl carbons at δ 178.99 and 206.90.

The dispiroheterocycles **2** were reacted subsequently with nitrile oxide (Scheme 1) and tri-spiroheterocycles **3** were obtained in 70–85% yields. The stereo- and regioselectivity of this cycloaddition reaction was evidenced from TLC and ^{1}H-NMR of the crude reaction mixture. The structures of **4a–g** were confirmed by IR, NMR, elemental analyses together with X-ray. For example, the IR spectrum of **4a** exhibited two carbonyl peaks locating at 1746.7 and 1709.8 cm^{-1}, which was assigned to the carbonyl group in cyclopentanone ring and the carbonyl group of lactam, respectively. What is more, the mass spectrum of **4a** showed a molecular ion peak at *m/z* 623 (M+1), which confirmed the addition of **3** to the exocyclic double bonds of **2a**.

The ^{1}H-NMR spectrum of **4a** revealed a singlet at δ 2.15 resulting from N—CH3, four multiplets in the range of δ 0.99–1.02, 1.37–1.40, 1.53–1.55, and 1.66–1.70 resulting from the C**H**$_2$ in cyclopentanone ring, a triplet at δ 4.20 for C**H** and two triplets at δ 3.55 and 3.97 for C**H**$_2$ in pyrrole ring and a characterize singlet at δ 4.69 for PhC**H**. The ^{13}C-NMR spectrum of the product **4a** exhibited the presence of methyl carbon at δ 34.8; two **C**H_2 in cyclopentanone ring at δ 28.6 and 28.8; three spiro carbons at δ 92.4, 77.4, and 65.5; N—**C**H_2 at δ 59.4; benzylic carbons at δ 58.2 and 51.6, respectively; and carbonyl carbons at δ 177.7 and 213.4. Further, the structure of the product was confirmed by X-ray diffraction analysis of **4a** [6] (Fig. 1).

EXPERIMENTAL

1 [7] and **3** [8] were prepared according to the reported procedures. All NMR spectra were recorded on a Bruker AV-II 500 MHz NMR spectrometer, operating at 500 MHz for ^{1}H, and 125 MHz for ^{13}C. TMS was used as an internal reference for ^{1}H and ^{13}C chemical shifts. $CDCl_3$ was as solvent. Elemental analysis was measured by an Elementar analyzer (varioELII). MS was measured by a Finnigan LCQ Advantage MAX mass spectrometer; IR spectra were recorded on Perkin-Elmer spectrometer. Melting points were measured by a Yanaco MP500 melting points apparatus and uncorrected.

General procedure for the synthesis of spirooxindoles (2a–g). A solution of isatin (1mmol), sarcosine (1mmol), and 2,5-diarylidene-cyclopentanone **1** (1mmol) in methanol (30 mL) was refluxed overnight. Completion of the reaction was evidenced by TLC analysis. The solvent was removed *in vacuo*. The crude product was subjected to column chromatography using petroleum ether-ethyl acetate (v/v 5:1) as eluent to afford the corresponding **2**.

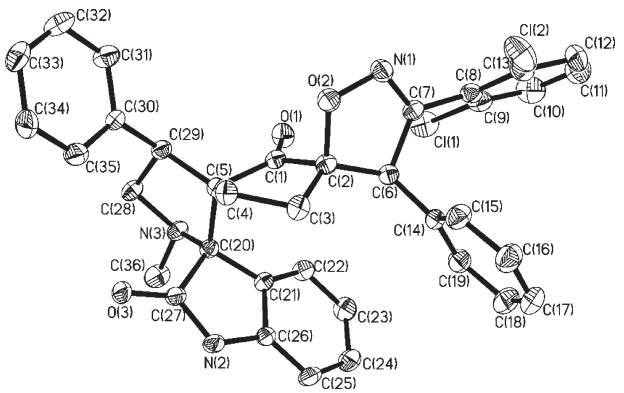


Figure 1. ORTEP diagram of **4a** (H atoms have been omitted for clarity).

1-N-Methyl-spiro[2.3′]oxindole-spiro[3.2″]5″-benzylidenecyclopentanone-4-phenyl-pyrrolidine (2a). White solid, yield 85%; mp: 206–208°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.23–1.30 (m, 1H), 2.12–2.16 (m, 1H), 2.17–2.21 (m, 1H), 2.25 (s, 3H), 2.35–2.40 (m, 1H), 3.60 (t, J = 8.0 Hz, 1H), 3.99 (t, J = 10.0 Hz, 1H), 4.37 (dd, J = 8.0, 10.0 Hz, 1H), 6.79–6.84 (m, 1H), 6.91 (t, J = 7.5 Hz, 1H), 7.10–7.13 (m, 1H), 7.18–7.20 (m, 3H), 7.22–7.27 (m, 5H), 7.31 (t, J = 8.0 Hz, 2H), 7.53 (d, J = 6.5 Hz, 2H), 8.31 (s, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 26.21, 30.70, 35.00, 49.15, 59.95, 65.61, 77.73, 109.21, 122.96, 125.99, 126.88, 127.78, 128.34, 128.48, 129.19, 129.38, 130.18, 130.38, 133.53, 135.37, 135.52, 139.59, 141.32, 178.99, 206.90; IR (KBr) v: 1721.4, 1704.3 cm^{-1}; MS(ESI) m/z: 435 $[M+H]^+$. Anal. Calcd. for $C_{29}H_{26}N_2O_2$: C 80.16, H 6.03, N 6.45; found C 80.06, H 6.17, N 6.49.

1-N-Methyl-spiro[2.3′]oxindole-spiro[3.2″]5″-(4-chloro)benzylidenecyclopentanone-4-(4-chloro)phenyl-pyrrolidine (2b). White solid, yield 85%; mp: 224–226°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.20–1.27 (m, 1H), 2.08–2.14 (m, 1H), 2.20 (s, 3H), 2.19–2.22 (m, 1H), 2.33–2.38 (m, 1H), 3.58 (t, J = 8.5 Hz, 1H), 3.92 (t, J = 9.5 Hz, 1H), 4.31 (dd, J = 8.5, 9.5 Hz, 1H), 6.77 (d, J = 7.5 Hz, 1H), 6.89 (t, J = 7.5 Hz, 1H), 7.11–7.14(m, 4H), 7.19–7.21 (m, 1H), 7.23–7.28 (m, 4H), 7.45 (d, J = 8.0 Hz, 2H), 8.14 (bs, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 26.11, 30.62, 34.92, 48.40, 59.99, 65.43, 77.52, 109.26, 122.99, 125.72, 127.70, 128.50, 128.82, 129.51, 131.29, 131.72, 132.33, 132.74, 133.71, 135.25, 135.72, 138.07, 141.24, 178.44, 206.48; IR (KBr) v: 1720.5, 1708.1 cm^{-1}; MS(ESI) m/z: 503 $[M+H]^+$. Anal. Calcd. for $C_{29}H_{24}Cl_2N_2O_2$: C 69.19, H 4.81, N 5.56; found C 69.37, H 4.92, N 5.48.

1-N-Methyl-spiro[2.3′]oxindole-spiro[3.2″]5″-(4-methoxy)-benzylidenecyclopentanone-4-(4-methoxy)phenyl-pyrrolidine (2c). White solid, yield 83%; mp: 188–190°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.24–1.35 (m, 1H), 2.06–2.17 (m, 2H), 2.20 (s, 3H), 2.31–2.36 (m, 1H), 3.56 (t, J = 8.5 Hz, 1H), 3.78 (s, 6H), 3.93 (t, J = 9.5 Hz, 1H), 4.29 (t, J = 9.0 Hz, 1H), 6.74 (d, J = 7.5 Hz, 1H), 6.79 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 6.89 (t, J = 7.5 Hz, 1H), 7.09 (t, J = 7.5 Hz, 2H), 7.17–7.22 (m, 3H), 7.43 (d, J = 7.5 Hz, 2H), 7.96 (bs, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 26.3, 30.6, 35.1, 48.5, 55.2, 55.3, 60.2, 65.5, 77.87, 109.3, 113.7, 114.1, 114.3, 122.9, 126.1, 127.8, 128.1, 129.3, 131.4, 131.7, 132.1, 132.6, 133.2, 133.5, 141.6, 158.5, 160.5, 179.2, 207.1; IR (KBr) v: 1718.6, 1704.7 cm^{-1}; MS(ESI) m/z: 495 $[M+H]^+$. Anal. Calcd. for $C_{31}H_{30}N_2O_4$: C 75.28, H 6.11, N 5.66; found C 75.34, H 6.21, N 5.45.

1-N-Methyl-spiro[2.3′]oxindole-spiro[3.2″]5″-(2,4-dichloro)-benzylidenecyclopentanone-4-(2,4-dichloro)phenyl-pyrrolidine (2d). White solid, yield 80%; mp: 239–241°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.16–1.18 (m, 1H), 1.99–2.05 (m, 2H), 2.20 (s, 3H), 2.23–2.26 (m, 1H), 3.59 (t, J = 8.5 Hz, 1H), 3.96 (t, J = 9.0 Hz, 1H), 4.87 (t, J = 9.0 Hz, 1H), 6.77–6.80 (m, 2H), 6.92 (t, J = 7.5 Hz, 1H), 7.06–7.09 (m, 1H), 7.14–7.18 (m, 2H), 7.27–7.30 (m, 1H), 7.33–7.36 (m, 2H), 7.52 (s, 1H), 7.83 (s, 1H), 8.03 (d, J = 9.0 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 25.93, 30.28, 34.96, 43.09, 58.70, 64.68, 77.49, 109.26, 123.26, 125.32, 126.79, 127.27, 127.93, 128.75, 128.84, 129.57, 129.74, 130.23, 132.29, 132.36, 133.01, 135.18, 135.96, 136.24, 136.36, 137.79, 141.28, 178.07, 204.96; IR (KBr) v: 1716.6, 1685.9 cm^{-1}; MS(ESI) m/z: 571 $[M+H]^+$. Anal. Calcd. for $C_{29}H_{22}Cl_4N_2O_2$: C 60.86, H 3.87, N 4.89; found C 60.97, H 3.81, N 4.99.

1-N-Methyl-spiro[2.3′]oxindole-spiro[3.2″]5″-(3,4,5-trimethoxy)benzylidenecyclopentanone-4-(3,4,5-trimethoxy)phenyl-pyrrolidine (2e). White solid, yield 82%; mp: 222–224°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.26–1.38 (m, 1H), 2.05–2.14 (m, 1H), 2.20 (s, 3H), 2.21–2.25 (m, 1H), 2.45–2.50 (m, 1H), 3.63 (t, J = 8.5 Hz, 1H), 3.78 (s, 6H), 3.84 (s, 6H), 3.87 (s, 6H), 3.96 (t, J = 9.0 Hz, 1H), 4.26 (dd, J = 8.5, 9.0 Hz, 1H), 6.46 (s, 2H), 6.77–6.92 (m, 4H), 7.11–7.18 (m, 2H), 7.23 (s, 1H), 8.44 (bs,1H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 26.16, 30.66, 34.98, 49.61, 56.06, 60.21, 60.45, 60.80, 60.90, 65.52, 77.69, 107.18, 107.61, 109.18, 122.84, 125.76, 127.64, 129.44, 130.84, 133.97, 134.64, 135.53, 163.50, 139.33, 141.55, 152.94, 152.99, 178.54, 207.10; IR (KBr) v: 1715.8, 1692.3 cm^{-1}; MS(ESI) m/z: 615 $[M+H]^+$. Anal. Calcd. for $C_{35}H_{38}N_2O_8$: C 68.39, H 6.23, N 4.56; found C 68.54, H 6.32, N 4.71.

1-N-Methyl-spiro[2.3′]oxindole-spiro[3.2″]5″-(2-chloro)benzylidenecyclopentanone-4-(2-chloro)phenyl-pyrrolidine (2f). White solid, yield 85%; mp: 234–236°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.16–1.23 (m, 1H), 1.99–2.06 (m, 2H), 2.22 (s, 3H), 2.24–2.29 (m, 1H), 3.60 (t, J = 8.5 Hz, 1H), 4.05 (t, J = 9.0 Hz, 1H), 4.94 (t, J = 9.0 Hz, 1H), 6.79–6.81 (m, 1H), 6.86–6.87 (m, 1H), 6.93–6.96 (m, 1H), 7.06–7.09 (m, 1H), 7.14–7.20 (m, 4H), 7.26–7.34 (m, 3H), 7.60 (s, 1H), 8.09 (d, J = 7.5 Hz, 1H), 8.19 (s, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 25.97, 30.32, 35.04, 43.61, 58.68, 64.81, 77.67, 109.24, 123.23, 125.55, 126.28, 126.87, 127.93, 128.00, 129.16, 129.45, 129.65, 129.77, 129.81, 129.87, 131.37, 133.85, 135.51, 135.86, 137.31, 137.64, 141.42, 178.48, 205.36; IR (KBr) v: 1715.7, 1702.5 cm^{-1}; MS(ESI) m/z: 503 $[M+H]^+$. Anal. Calcd. for $C_{29}H_{24}Cl_2N_2O_2$: C 69.19, H 4.81, N 5.56; found C 69.06, H 5.02, N 5.78.

1-N-Methyl-spiro[2.3′]oxindole-spiro[3.2″]5″-(4-methylsulfanyl)benzylidenecyclopentanone-4-(4-methylsulfanyl)phenyl-pyrrolidine (2g). White solid, yield 85%; mp: 203–204°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.26–1.33 (m, 1H), 2.08–2.14 (m, 1H), 2.20 (s, 3H), 2.18–2.22 (m, 1H), 2.32–2.37 (m, 1H), 2.43 (s, 3H), 2.45 (s, 3H), 3.57 (t, J = 8.5 Hz, 1H), 3.95 (t, J = 9.5, Hz, 1H), 4.31 (dd, J = 8.5, 9.5 Hz, 1H), 6.79 (d, J = 7.5 Hz, 1H), 6.88 (t, J = 7.5 Hz, 1H), 7.08–7.13 (m, 4H), 7.16–7.20 (m, 3H), 7.26–7.28 (m, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 8.5 Hz, 1H), 8.57 (bs, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 15.03, 15.87, 26.31, 30.64, 35.02, 48.71, 59.96, 65.54, 77.73, 109.30, 122.91, 125.59, 125.86, 125.95, 126.55, 127.75, 129.40, 130.62, 130.88, 131.14, 131.80, 132.35, 133.20, 133.40, 134.55, 136.54, 136.61, 136.78, 140.99, 141.16, 141.45, 178.82, 206.82; IR (KBr) v: 1719.4, 1702.3 cm^{-1}; MS(ESI) m/z: 527 $[M+H]^+$. Anal. Calcd. for $C_{31}H_{30}N_2O_2S_2$: C 70.69, H 5.74, N 5.32; found C 70.53, H 5.47, N 5.50.

General procedure for the synthesis of trispiro[oxindole-pyrrolidine]-cyclopentanone-isoxazoline (4a–g). A solution of **2** (1mmol), **3** (1mmol) in dioxane (30 mL) was refluxed overnight. Completion of the reaction was evidenced by TLC analysis. The solvent was removed *in vacuo*. The crude product was subjected to column chromatography using petroleum ether-ethyl acetate (v/v 5:1) as eluent to afford the corresponding **4**.

3‴-(2,6-Dichlorophenyl)-1′-methyl-4′,4‴-diphenyl-4‴,5‴-dihydroindole-3-spiro-2′-pyrrolidine-3′-spiro-1″-cyclopentane-3″-spiro-5‴-[1,2]oxazole-2(3H),2″-dione (4a). White solid, yield

83%; mp: 250–251°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 0.99–1.02 (m, 1H), 1.37–1.40 (m, 1H), 1.53–1.55 (m, 1H), 1.66–1.70 (m, 1H), 2.15 (s, 3H), 3.55 (t, J = 9.0 Hz, 1H), 3.97 (t, J = 9.0 Hz, 1H), 4.20 (t, J = 8.0 Hz, 1H), 4.69 (s, 1H), 6.54–6.55 (m, 2H), 6.77 (d, J = 8.0 Hz, 1H), 6.99–7.02 (m, 2H), 7.04–7.07 (m, 1H), 7.10–7.13 (m, 1H), 7.22–7.25 (m, 4H), 7.32–7.38 (m, 4H), 7.49 (d, J = 7.5Hz, 2H), 7.74 (br, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 28.59, 28.82, 34.80, 51.58, 58.17, 59.44, 65.46, 77.42, 92.37, 109.75, 123.43, 126.90, 127.06, 127.24, 128.01, 128.08, 128.35, 128.51, 128.74, 128.78, 129.46, 129.89, 130.29, 130.80, 132.73, 135.74, 138.18, 142.09, 155.16, 177.69, 213.37; IR (KBr) v: 1746.7, 1709.8 cm^{-1}; ESI MS m/z: 623 $[M+H]^+$. Anal. Calcd. for $C_{36}H_{29}Cl_2N_3O_3$: C 69.46, H 4.70, N 6.75; found C 69.32, H 4.59, N 6.91.

3‴-(2,6-Dichlorophenyl)-1′-methyl-4′,4‴-bis-(4-chlorophenyl)-4‴,5‴-dihydroindole-3-spiro-2′-pyrrolidine-3′-spiro-1″-cyclopentane-3″-spiro-5‴-[1,2]oxazole-2(3H),2″-dione (4b). White solid, yield 85%; mp: 203–206°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 0.97–0.99 (m, 1H), 1.46–1.54 (m, 2H), 1.77–1.84 (m, 1H), 2.12 (s, 3H), 3.54 (t, J = 8.5 Hz, 1H), 3.90 (t, J = 9.5 Hz, 1H), 4.18 (t, J = 9.0 Hz, 1H), 4.71 (s, 1H), 6.51–6.52 (m, 2H), 6.77–6.78 (m, 1H), 7.00–7.02 (m, 2H), 7.15–7.17 (m, 1H), 7.23–7.30 (m, 6H), 7.33–7.35 (m, 1H), 7.42–7.43 (m, 2H), 8.01 (br, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 28.75, 29.18, 34.67, 50.65, 57.33, 59.46, 65.48, 92.04, 109.97, 123.34, 126.67, 126.75, 128.31, 128.50, 128.67, 128.86, 129.96, 130.70, 131.04, 131.24, 131.56, 133.07, 134.14, 135.62, 136.81, 142.17, 155.00, 177.76, 212.72; IR (KBr) v: 1739.8, 1717.7 cm^{-1}; MS(ESI) m/z: 691 $[M+H]^+$. Anal. Calcd. for $C_{36}H_{27}Cl_4N_3O_3$: C 62.53, H 3.94, N 6.08; found C 62.47, H 3.98, N 6.16.

3‴-(2,6-Dichlorophenyl)-1′-methyl-4′,4‴-bis-(4-methoxyphenyl)-4‴,5‴-dihydroindole-3-spiro-2′-pyrrolidine-3′-spiro-1″-cyclopentane-3″-spiro-5‴-[1,2]oxazole-2(3H),2″-dione (4c). White solid, yield 80%; mp: 175–177°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.09–1.09 (m, 1H), 1.35–1.38 (m, 1H), 1.55–1.63 (m, 2H), 2.13 (s, 3H), 3.52 (t, J = 8.5 Hz, 1H), 3.65 (s, 3H), 3.79 (s, 3H), 3.90 (t, J = 9.5 Hz, 1H), 4.15 (t, J = 9.0 Hz, 1H), 4.63 (s, 1H), 6.46–6.54 (m, 4H), 6.80–6.82 (m, 1H), 6.86–6.87 (m, 2H), 7.11–7.12 (m, 1H), 7.21–7.26 (m, 3H), 7.34–7.37 (m, 2H), 7.41–7.43 (m, 2H), 8.30 (s, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 28.46, 28.52, 34.77, 51.00, 55.01, 55.22, 57.59, 59.56, 65.26, 77.51, 92.33, 109.85, 113.30, 113.80, 123.36, 124.55, 126.86, 127.12, 128.63, 128.73, 129.81, 130.13, 130.64, 130.74, 131.28, 135.67, 142.23, 155.22, 158.69, 159.18, 178.15, 213.82; IR (KBr) v: 1743.5, 1717.1 cm^{-1}; MS(ESI) m/z: 683 $[M+H]^+$. Anal. Calcd. for $C_{38}H_{33}Cl_2N_3O_5$: C 66.86, H 4.87, N 6.16; found C 67.01, H 4.78, N 6.27.

3‴-(2,6-Dichlorophenyl)-1′-methyl-4′,4‴-bis-(2,4-dichlorophenyl)-4‴,5‴-dihydroindole-3-spiro-2′-pyrrolidine-3′-spiro-1″-cyclopentane-3″-spiro-5‴-[1,2]oxazole-2(3H),2″-dione (4d). White solid, yield 76%; mp: 188–190°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.09–1.14 (m, 1H), 1.42–1.45 (m, 1H), 1.55–1.58 (m, 1H), 1.70–1.73 (m, 1H), 2.15 (s, 3H), 3.54 (t, J = 8.5 Hz, 1H), 3.84 (t, J = 8.5 Hz, 1H), 4.72 (t, J = 9.0 Hz, 1H), 5.26 (s, 1H), 6.76 (d, J = 7.5 Hz, 1H), 7.04–7.13 (m, 4H), 7.20–7.24 (m, 5H), 7.28–7.30 (m, 1H), 7.41–7.42 (m, 2H), 8.03 (br, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 27.33, 27.82, 34.82, 47.06, 52.66, 59.65, 62.72, 77.92, 92.84, 109.74, 124.12, 125.81, 126.38, 126.97, 127.15, 128.66, 128.75, 129.00, 129.13, 129.19, 129.22, 129.85, 131.19, 132.89, 132.96, 133.54, 134.36, 134.42, 143.82, 135.89, 136.80, 142.15, 154.93, 177.78, 211.60; IR (KBr) v: 1750.7, 1717.8 cm^{-1}; MS(ESI) m/z: 760 $[M+H]^+$. Anal. Calcd. for $C_{36}H_{25}Cl_6N_3O_3$: C 56.87, H 3.31, N 5.53; found C 56.84, H 3.17, N 5.40.

3‴-(2,6-Dichlorophenyl)-1′-methyl-4′,4‴-bis-(3,4,5-trimethoxyphenyl)-4‴,5‴-dihydroindole-3-spiro-2′-pyrrolidine-3′-spiro-1″-cyclopentane-3″-spiro-5‴-[1,2]oxazole-2(3H),2″-dione (4e). White solid, yield 70%; mp: 206–208°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.12–1.17 (m, 1H), 1.55–1.60 (m, 1H), 1.68–1.71 (m, 1H), 1.83–1.88 (m, 1H), 2.15 (s, 3H), 3.57 (t, J = 8.5 Hz, 1H), 3.70 (s, 6H), 3.72 (s, 3H), 3.83 (s, 3H), 3.87 (s, 6H), 3.94 (t, J = 9.5 Hz, 1H), 4.13 (t, J = 9.5 Hz, 1H), 4.61 (s, 1H), 6.78 (d, J = 7.5 Hz, 2H), 7.15–7.21 (m, 4H), 7.28–7.30 (m, 3H), 7.35 (d, J = 7.5 Hz, 2H), 8.19 (br, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 28.26, 28.98, 34.74, 52.06, 56.12, 56.22, 57.91, 59.52, 60.65, 60.80, 65.35, 92.50, 106.64, 109.86, 123.01, 126.88, 128.36, 128.54, 129.00, 129.71, 130.98, 134.08, 135.69, 136.78, 137.78, 142.46, 152.78, 153.05, 155.65, 177.65, 213.16; IR (KBr) v: 1742.0, 1713.1 cm^{-1}; MS(ESI) m/z: 803 $[M+H]^+$. Anal. Calcd. for $C_{42}H_{41}Cl_2N_3O_9$: C 62.84, H 5.15, N 5.23; found C 62.94, H 5.28, N 5.15.

3‴-(2,6-Dichlorophenyl)-1′-methyl-4′,4‴-bis-(2-chlorophenyl)-4‴,5‴-dihydroindole-3-spiro-2′-pyrrolidine-3′-spiro-1″-cyclopentane-3″-spiro-5‴-[1,2]oxazole-2(3H),2″-dione (4f). White solid, yield 70%; mp: 195–196°C; ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 1.03–1.07 (m, 1H), 1.27–1.32 (m, 1H), 1.36–1.39 (m, 1H), 1.62–1.64 (m, 1H), 2.01 (s, 3H), 3.39 (t, J = 9.0 Hz, 1H), 3.74 (t, J = 9.0 Hz, 1H), 4.50 (t, J = 9.0 Hz, 1H), 5.20 (s, 1H), 6.75 (d, J = 8.0 Hz, 1H), 7.02 (t, J = 8.0 Hz, 1H), 7.17–7.25 (m, 6H), 7.36–7.41 (m, 2H), 7.42–7.45 (m, 3H), 7.47–7.49 (m, 1H), 8.07–8.08 (m, 1H), 10.72 (s, 1H); ^{13}C-NMR (DMSO-d_6, 125 MHz) δ: 26.46, 27.13, 34.10, 47.13, 52.75, 59.07, 61.85, 77.08, 92.66, 109.64, 122.63, 125.42, 125.62, 126.95, 127.12, 128.00, 128.98, 129.02, 129.11, 129.38, 129.41, 129.65, 130.24, 131.95, 131.99, 132.42, 132.71, 134.74, 135.20, 143.81, 154.01, 176.97, 212.13; IR (KBr) v: 1746.3, 1701.1 cm^{-1}; MS(ESI) m/z: 691 $[M+H]^+$. Anal. Calcd. for $C_{36}H_{27}Cl_4N_3O_3$: C 62.53, H 3.94, N 6.08; found C 62.62, H 4.02, N 6.01.

3‴-(2,6-Dichlorophenyl)-1′-methyl-4′,4‴-bis-(4-methylsulfanylphenyl)-4‴,5‴-dihydroindole-3-spiro-2′-pyrrolidine-3′-spiro-1″-cyclopentane-3″-spiro-5‴-[1,2]oxazole-2(3H),2″-dione (4g). White solid, yield 74%; mp: 195–196°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.01–1.06 (m, 1H), 1.42–1.46 (m, 1H), 1.53–1.60 (m, 1H), 1.72–1.77 (m, 1H), 2.14 (s, 3H), 2.37 (s, 3H), 2.47 (s, 3H), 3.52 (t, J = 8.5 Hz, 1H), 3.92 (t, J = 9.5 Hz, 1H), 4.17 (t, J = 8.0 Hz, 1H), 4.66 (s, 1H), 6.46–6.48 (m, 2H), 6.75–6.76 (m, 1H), 6.87–6.88 (m, 2H), 7.11–7.14 (m, 1H), 7.21–7.24 (m, 5H), 7.33–7.35 (m, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.52 (br, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 15.07, 15.83, 28.61, 29.07, 34.76, 51.05, 57.64, 59.38, 65.44, 77.41, 92.26, 109.96, 123.38, 125.36, 126.65, 126.85, 126.96, 128.59, 128.83, 129.13, 129.83, 129.91, 130.71, 130.89, 135.08, 135.70, 137.22, 138.74, 142.25, 155.13, 178.06, 213.29; IR (KBr) v: 1732.6, 1713.1 cm^{-1}; MS(ESI) m/z: 715 $[M+H]^+$. Anal. Calcd. for $C_{38}H_{33}Cl_2N_3O_3S_2$: C 63.86, H 4.65, N 5.88; found C 63.65, H 4.56, N 6.04.

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REFERENCES AND NOTES

[1] (a) Hedin, P. A. J Agric Food Chem 1982, 30, 201; (b) Winfred, G. B.; Rutger, M.; Fieseler, F. J Org Chem 2000, 65, 8317; (c) Metwally, K. A.; Dukat, M. J Med Chem 1998, 41, 5084; (d) Suenaga, K.; Araki, K.; Sengoku, T. Org Lett 2001, 3, 527; (e) Barbara, C. M.; Potts, D.; John, F. J Am Chem Soc 1991, 113, 6321; (f) Nicholas, G. M.; Eckman, L. L.; Newton, G. L. Bioorg Med Chem 2003, 11, 601; (g) Patrizia, C.; Carmela, D.; Ernesto, F. J Nat Prod 1999, 62, 590.

[2] (a) Sebahar, P. R.; Williams, R. M. J Am Chem Soc 2000, 122, 5666; (b) Marti, C.; Carreira, E. M. Eur J Org Chem 2003, 2209; (c) Hiromitsu, T.; Yuhshin, T.; Mariko, K. J Org Chem 1994, 59, 4381.

[3] Caramella, P.; Grunanger, P. 1,3-Dipolar Cycloaddition Chemistry; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, p 291.

[4] Sridhar, G.; Gunasundari, T.; Raghunathan, R. Tetrahedron Lett 2007, 48, 319.

[5] Kumar, R. R.; Perumal, S. Tetrahedron 2007, 63, 12220.

[6] Li, X. F.; Feng, Y. Q.; Gao, B.; Li, N. Acta Crystallogr Sect E 2003, 59, 1659.

[7] Huitric, A. C.; Kumler, W. D. J Am Chem Soc 1956, 78, 614.

[8] Grundamann, C.; Dean, J. M. J Org Chem 1965, 30, 2810.