EXPEDITENT APPROACH FOR THE SYNTHESIS OF TRISPIROPYRROLIDINE BISOXINDOLES THROUGH 1,3-DIPOLAR CYCLOADDITION REACTIONS

Guo-Liang Feng, Yue Li, Li-Jun Geng, Hong-Li Zhang, Yan-Jing Shi, and Kai-Fang Wang

1 School of Science, Hebei University of Science and Technology, Shijiazhuang, China
2 Shijiazhuang Yonggangfangjing Co., Electronic Materials, Shijiazhuang, China

GRAPHICAL ABSTRACT

Abstract A series of trispiropyrrolidine bisoxindoles has been achieved via a three-component 1,3-dipolar cycloaddition reaction of 3-aryl-5-arylmethylenespiro[indole-3,0,2-[1,3]thiazolane]-2,4-dione, isatin, and sarcosine in refluxing toluene, which produced the corresponding cycloadducts in good yields (79–88%). Their structures were determined by infrared, 1H and 13C NMR, elementary analysis, and single-crystal x-ray diffraction analysis, and the cycloaddition reaction was found to be highly regio- and stereoselective.

Keywords Azomethine ylide; 1,3-dipolar cycloaddition reactions; isatin; trispiropyrrolidine bisoxindoles

INTRODUCTION

Multicomponent 1,3-dipolar cycloaddition, also known as the Huisgen [3 + 2] cycloaddition, is considered to be one of the most powerful tool for the construction
of a variety of five-membered heterocyclic compounds such as pyrrolidines, pyrroles, and pyrrolines.\cite{1,2} These strategies offer significant advantages over traditional approaches, allowing for the construction of complex molecular architectures from available starting materials in a single operation without the need for isolation of intermediates. The azomethine ylides, which are zwitterionic and composed of one positively charged nitrogen atom and two terminal sp\(^2\)-hybridized carbon atoms, are a class of powerful reagents used in 1,3-dipolar cycloaddition reactions and afford a range of important heterocyclic compounds, especially substituted pyrrolidine rings.\cite{3–5}

The heterocyclic spiro-oxindole framework is an important structural motif in relevant compounds as natural products. In addition, oxindole derivatives at C3 as spirocarbo- have served as potential synthetic intermediates for biological applications such as antifungal, antimycobacterial, antimicrobial, antimalarial, and others.\cite{6–9} The spiropyrrrolidine oxindoles have received considerable attention because of a myriad of biological activities such as antileukemic,\cite{10} anticonvulsant,\cite{11} local anaesthetic,\cite{12} and antiviral\cite{13} activities. To the best of our knowledge, there are only a few methods to synthesize dispiropyrrrolidine bisoxindoles using isatin derivatives as both dipoles and dipolarophiles in 1,3-dipolar cycloaddition reaction.\cite{14,15}

Recently, we described a new and efficient synthesis of spiropyrrrolidine oxindoles derivatives via a three-component 1,3-dipolar cycloaddition reaction.\cite{16–18} As a part of our own interest in multicomponent syntheses and cycloaddition reactions, we herein report the synthesis of trispiropyrrrolidine bisoxindoles via the three-component condensation of 3-aryl-5-arylmethylenespiro[indole-3',2-[1,3]thiazolane]-2'(1\(H\)),4-dione, isatin, and sarcosine in refluxing toluene (Scheme 1).

\section*{DISCUSSION}

To realize our plan, the starting compound 3-aryl-5-arylmethylenespiro[indole-3',2-[1,3]thiazolane]-2'(1\(H\)),4-dione 1 was prepared according to the procedure described by the literature.\cite{19,20} In our initial endeavor, we investigated the reaction in the different solvents under refluxing for the synthesis of compound 2a. The reactions in 1,4-dioxane, glycol monomethyl ether provided a small amount of the desired product. When the reactions were carried out in ethanol, methanol, ethylene glycol, acetonitrile, or benzene, compound 2a was obtained in moderate yields. It was exciting that the reaction proceeded well in toluene to give a good yield of 83%.
To extend the scope of this new procedure for the synthesis of tripiropyrrolidine bisoxindoles, a series of reactions was carried out in toluene. We were pleased to find that the reaction proceeded smoothly and that desired products were afforded in excellent yields. Notably, the electronic effects of the substituent on the aromatic ring have no significant influence on the reaction yields (Table 1).

The structures of the compounds 2a–2m were fully characterized and supported by spectroscopic studies and elementary analysis. Take compound 2j as an example: the peaks at 1732 cm$^{-1}$, 1712 cm$^{-1}$, and 1686 cm$^{-1}$ were rationally attributed to the vibration of the isatin and thiazolidinone ring carbonyls in the IR spectrum, respectively. In the $^1$H NMR spectrum of 2j, the –NH proton exhibited two singlets at $\delta$ 10.71 and $\delta$ 10.31 at the same time the methyl protons of –NCH$_3$ and ArCH$_3$ exhibited singlets at $\delta$ 2.30 and $\delta$ 2.12. In $^{13}$C NMR spectrum, the peaks at $\delta$ 177.0, 174.8, and 174.2 ppm confirmed the presence of three amide carbonyl atoms of oxindole and thiazolidinone rings, respectively. The stereochemical structure of spirocompounds is the key factors to determine the physiological activity. The stereochemical outcome of the cycloaddition was further confirmed by single-crystal x-ray structure of the cycloadduct 2j and 2m (Fig. 1).

Based on these results, a possible mechanism for the reaction was proposed (Scheme 2). The reaction proceeds through the generation of azomethine ylide via the decarboxylative condensation of isatin with sarcosine. 1,3-Dipolar cycloaddition of 3-aryl-5-arylmethylenespiro[indole-3,2-[1,3]thiazolane]-2(1H),4-dione 1 with azomethine ylides produced tripiropyrrolidine bisoxindoles derivatives 2. The regioselectivity in the product formation can be explained by considering the secondary orbital interaction of the carbonyl group orbital of dipolarophile with those of the ylide as shown in Scheme 2. Accordingly, the observed regioisomer 2 via path A is more favorable due to the secondary orbital interaction (SOI), which is not possible in path B.

| Entry | Ar     | Ar$^1$    | Product$^a$ | Time (h) | Yield (%)$^b$ |
|-------|--------|-----------|-------------|----------|---------------|
| 1     | 4-(CH$_3$)$_2$CH$_2$H$_4$ | 4-CH$_3$C$_6$H$_4$ | 2a         | 3        | 83            |
| 2     | 4-(CH$_3$)$_2$CH$_2$H$_4$ | 4-(CH$_3$)$_2$CH$_2$H$_4$ | 2b       | 3        | 79            |
| 3     | 4-(CH$_3$)$_2$CH$_2$H$_4$ | 4-(CH$_3$)$_2$CC$_6$H$_4$ | 2c       | 3        | 85            |
| 4     | 4-(CH$_3$)$_2$CH$_2$H$_4$ | 3,4-(CH$_3$)$_2$C$_6$H$_3$ | 2d       | 4        | 88            |
| 5     | 4-(CH$_3$)$_2$CH$_2$H$_4$ | 4-ClC$_6$H$_4$ | 2e       | 4        | 81            |
| 6     | 4-(CH$_3$)$_2$CH$_2$H$_4$ | 4-BrC$_6$H$_4$ | 2f       | 4        | 86            |
| 7     | 4-(CH$_3$)$_2$CH$_2$H$_4$ | 1-Naphthyl | 2g       | 4        | 82            |
| 8     | 4-(CH$_3$)$_2$CH$_2$H$_4$ | 2-thienyl | 2h       | 4        | 84            |
| 9     | C$_6$H$_5$ | C$_6$H$_5$ | 2i       | 4        | 86            |
| 10    | C$_6$H$_5$ | 4-CH$_3$C$_6$H$_4$ | 2j       | 4        | 83            |
| 11    | C$_6$H$_5$ | 4- (CH$_3$)$_2$CH$_2$H$_4$ | 2k       | 4        | 85            |
| 12    | C$_6$H$_5$ | 4-ClC$_6$H$_4$ | 2l       | 4        | 81            |
| 13    | C$_6$H$_5$ | 4-BrC$_6$H$_4$ | 2m       | 4        | 80            |

$^a$The products were characterized by NMR, IR, elemental analysis, and single-crystal x-ray diffraction.
$^b$Isolated yield.
All solvents and chemicals were obtained commercially and were used as received. Melting points were recorded on an electrothermal digital melting-point apparatus and uncorrected. $^1$H NMR and $^{13}$C NMR spectra were determined on a Varian VXP-500 s spectrometer using dimethyl sulfoxide (DMSO) as solvent and tetramethylsilane (TMS) as internal reference. Infrared (IR) spectra were obtained on a Nicolet 6700 spectrophotometer using KBr pellets. Elementary analyses were

Figure 1. Molecular structure of compounds 2j and 2m.

Scheme 2. Possible mechanism for synthesis of trispiropyrrolidine bisoxindole derivatives.

**EXPERIMENTAL**

All solvents and chemicals were obtained commercially and were used as received. Melting points were recorded on an electrothermal digital melting-point apparatus and uncorrected. $^1$H NMR and $^{13}$C NMR spectra were determined on a Varian VXP-500 s spectrometer using dimethyl sulfoxide (DMSO) as solvent and tetramethylsilane (TMS) as internal reference. Infrared (IR) spectra were obtained on a Nicolet 6700 spectrophotometer using KBr pellets. Elementary analyses were
Typical Experimental Procedure for 2a

A stirred mixture of 3-(4-isopropylphenyl)-5-(4-methylphenylmethylene)spiro[indole-3',2-[1,3]thiazolane]-2'(1H),4-dione 1 (1.0 mmol), isatin (1.2 mmol), and sarcosine (1.2 mmol) in toluene (20 mL) was heated under refluxing condition for the specified period of time. After completion of the reaction as indicated by thin-layer chromatographic (TLC) analysis, the mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The crude product was subjected to column chromatography using dichloromethane/petroleum ether (1:1) as eluent to afford the pure product 2a.

**3''-(4-Isopropylphenyl)-4'- (4-methylphenyl) -1'-methyltrispiro[indole-3,2'-pyrrolidine-3',5''-[1,3]thiazolane-2'',3'''-indole]-2,4'',2'''-trione (2a)**

White solid; mp 208.6–209.6 °C; 1H NMR (500 MHz, DMSO-d6): δ 10.69 (s, 1H), 10.29 (s, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 7.5 Hz, 1H), 7.14–7.03 (m, 7H), 6.72 (t, J = 8.0 Hz, 1H), 6.58 (d, J = 8.5 Hz, 2H), 6.54 (d, J = 7.5 Hz, 1H), 5.83 (d, J = 7.5 Hz, 1H), 4.47 (t, J = 8.5 Hz, 1H), 3.87 (t, J = 9.0 Hz, 1H), 3.46 (t, J = 8.5 Hz, 1H), 2.82–2.73 (m, 1H), 2.30 (s, 3H), 2.12 (s, 3H), 1.11–1.09 (m, 6H). 13C NMR (125 MHz, DMSO-d6): 176.5, 174.3, 173.7, 148.6, 144.5, 140.9, 135.9, 135.6, 133.4, 130.8, 130.5, 130.4, 129.1, 128.4, 127.2, 126.9, 126.2, 124.9, 124.5, 122.1, 122.0, 110.3, 109.6, 81.5, 70.0, 59.7, 58.2, 52.2, 51.1, 47.2, 46.2, 35.2, 32.8, 23.4, 20.7, 14.0. IR (KBr) ν 2959, 2870, 1732, 1717, 1663, 1616, 1510, 1471, 1392, 1325, 1249. Anal. calcd. for C37H34N4O3S: C, 72.29; H, 5.57; N, 9.11; Found: C, 72.41; H, 5.54; N, 9.03.

**4',3''-Di(4-isopropylphenyl) -1'-methyltrispiro[indole-3,2'-pyrrolidine-3',5''-[1,3]thiazolane-2'',3'''-indole]-2,4'',2'''-trione (2b)**

White solid; mp 219.5–220.8 °C; 1H NMR (500 MHz, DMSO-d6): δ 10.70 (s, 1H), 10.32 (s, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.47 (d, J = 7.5 Hz, 2H), 7.35 (d, J = 7.5 Hz, 3H), 7.19 (d, J = 8.0 Hz, 2H), 7.13–7.03 (m, 5H), 6.71 (t, J = 8.0 Hz, 1H), 6.58 (d, J = 8.5 Hz, 2H), 6.53 (d, J = 8.0 Hz, 1H), 5.82 (d, J = 7.5 Hz, 1H), 4.47 (t, J = 8.5 Hz, 1H), 3.88 (t, J = 9.0 Hz, 1H), 3.46 (t, J = 8.5 Hz, 1H), 2.93–2.85 (m, 1H), 2.82–2.73 (m, 1H), 2.12 (s, 3H), 1.23–1.21 (m, 6H), 1.12–1.09 (m, 6H). 13C NMR (125 MHz, DMSO-d6): 176.8, 174.6, 174.1, 148.9, 146.7, 144.8, 141.2, 136.5, 133.7, 131.1, 130.8, 130.7, 129.4, 127.5, 127.2, 126.5, 125.9, 125.3, 124.8, 122.5, 122.3, 110.6, 109.9, 81.8, 70.1, 67.7, 58.5, 52.4, 35.6, 33.2, 33.1, 24.2, 24.1, 23.8. IR (KBr) ν 3246, 2959, 2868, 1749, 1734, 1618, 1502, 1437, 1334, 1249. Anal. calcd. for C39H38N4O3S: C, 72.87; H, 5.96; N, 9.11; Found: C, 72.41; H, 5.54; N, 9.03.

**3''-(4-Isopropylphenyl)-4'- (4-tertbutylphenyl) -1'-methyltrispiro[indole-3,2'-pyrrolidine-3',5''-[1,3]thiazolane-2'',3'''-indole]-2,4'',2'''-trione (2c)**

White solid; mp 215–216.5 °C; 1H NMR (500 MHz, DMSO-d6): δ 10.71 (s, 1H), 10.34 (s, 1H), 7.53–7.47 (m, 3H), 7.34 (d, J = 8.0 Hz, 3H), 7.12–7.03 (m, 5H), 6.71 (t,
3′-(4-Isopropylphenyl)-4′-(2,4-dimethylphenyl)-1′-methyltrispiro[indole-3,2′-pyrroline-3′,5′-[1,3]thiazolane-2″,3″-indole]-2,4″,2″″-trione (2d)

White solid; mp 220–221.2 °C; 1H NMR (500 MHz, DMSO-d6): δ 10.67 (s, 1H), 10.31 (s, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.31 (s, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.13–7.03 (m, 6H), 6.71 (t, J = 7.5 Hz, 1H), 6.60 (d, J = 8.5 Hz, 2H), 6.54 (d, J = 7.5 Hz, 1H), 5.85 (d, J = 7.5 Hz, 1H), 4.45 (t, J = 8.5 Hz, 1H), 3.92–3.86 (m, 1H), 3.43 (t, J = 8.0 Hz, 1H), 2.81–2.73 (m, 1H), 2.24 (s, 3H), 2.21 (s, 3H), 2.12 (s, 3H), 1.11–1.09 (m, 6H). 13C NMR (125 MHz, DMSO-d6): 176.4, 174.3, 173.8, 170.2, 148.7, 148.6, 144.5, 140.9, 135.9, 133.4, 130.6, 130.5, 130.4, 129.1, 127.2, 126.9, 126.2, 125.0, 124.5, 124.4, 122.1, 122.0, 110.4, 109.6, 81.5, 69.7, 67.5, 59.7, 58.2, 52.0, 35.3, 34.1, 32.8, 31.2, 23.4, 20.7, 14.0. IR (KBr) ν 3215, 2963, 2870, 1736, 1724, 1697, 1616, 1510, 1471, 1359, 1323, 1219. Anal. calcd. for C40H40N4O3S: C, 73.14; H, 6.14; N, 8.53. Found: C, 73.18; H, 6.05; N, 8.42.

3′-(4-Isopropylphenyl)-4′-(4-chlorophenyl)-1′-methyltrispiro[indole-3,2′-pyrroline-3′,5′-[1,3]thiazolane-2″,3″-indole]-2,4″,2″″-trione (2e)

White solid; mp 234.3–235.1 °C; 1H NMR (500 MHz, DMSO-d6): δ 10.76 (s, 1H), 10.35 (s, 1H), 7.58 (d, J = 8.5 Hz, 2H), 7.53 (t, J = 7.5 Hz, 1H), 7.38 (d, J = 8.5 Hz, 3H), 7.15–7.03 (m, 5H), 6.73 (t, J = 7.5 Hz, 1H), 6.60 (d, J = 8.5 Hz, 2H), 6.55 (d, J = 7.5 Hz, 1H), 5.87 (d, J = 7.5 Hz, 1H), 4.53 (t, J = 9.0 Hz, 1H), 3.87 (t, J = 9.0 Hz, 1H), 3.52 (t, J = 8.5 Hz, 1H), 2.81–2.72 (m, 1H), 2.14 (s, 3H), 1.10–1.08 (m, 6H). 13C NMR (125 MHz, DMSO-d6): 176.8, 174.6, 173.8, 148.9, 144.8, 141.3, 138.2, 133.6, 133.1, 130.9, 129.3, 128.0, 127.6, 126.2, 125.2, 124.6, 122.5, 122.4, 110.7, 110.0, 81.7, 67.0, 58.4, 52.2, 35.5, 33.1, 23.7. IR (KBr) ν 3196, 2959, 2870, 1736, 1710, 1670, 1618, 1495, 1472, 1387, 1323, 1229. Anal. calcd. for C38H36N4O3S: C, 72.59; H, 5.77; N, 8.91. Found: C, 72.73; H, 5.71; N, 9.04.

3′-(4-Isopropylphenyl)-4′-(4-bromophenyl)-1′-methyltrispiro[indole-3,2′-pyrroline-3′,5′-[1,3]thiazolane-2″,3″-indole]-2,4″,2″″-trione (2f)

White solid; mp 214–215 °C; 1H NMR (500 MHz, DMSO-d6): δ 10.76 (s, 1H), 10.35 (s, 1H), 7.54–7.49 (m, 5H), 7.35 (d, J = 7.5 Hz, 1H), 7.14–7.10 (m, 3H), 7.07–7.04 (m, 2H), 6.72 (t, J = 7.5 Hz, 1H), 6.58–6.54 (m, 3H), 5.84 (d, J = 7.5 Hz, 1H), 4.48 (t, J = 9.0 Hz, 1H), 3.85 (t, J = 9.0 Hz, 1H), 3.51 (t, J = 8.5 Hz, 1H), 2.81–2.73
(m, 1H), 2.13 (s, 3H), 1.11–1.09 (m, 6H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): 177.0, 174.8, 174.0, 149.1, 144.9, 141.5, 138.8, 133.8, 133.7, 131.2, 131.1, 131.0, 129.5, 127.7, 127.4, 126.3, 125.4, 124.7, 122.7, 122.2, 120.7, 110.9, 110.0, 81.9, 70.2, 67.9, 58.5, 52.5, 35.7, 33.3, 23.9. IR (KBr) ν 3190, 2957, 2870, 1732, 1712, 1668, 1616, 1471, 1384, 1325, 1227. Anal. calcld. for C$_{36}$H$_{31}$BrN$_4$O$_3$S: C, 63.62; H, 4.60; N, 8.24. Found: C, 63.47; H, 4.73; N, 8.27.

$^{3''}$-(4-Isopropylphenyl)-4'-(naphth-1-yl)-1'-methyltrispiro[indole-3,2'-pyrrolidine-3',5''-[1,3]thiazole-2'',3''-indole]-2,4'',2'''-trione (2g)

White solid; mp 216–216.6 °C; $^1$H NMR (500 MHz, DMSO-$d_6$): δ 10.77 (s, 1H), 9.95 (s, 1H), 8.07 (d, $J = 9.0$ Hz, 1H), 7.99 (d, $J = 7.0$ Hz, 1H), 7.93 (d, $J = 8.0$ Hz, 1H), 7.84 (d, $J = 8.0$ Hz, 1H), 7.64 (t, $J = 7.5$ Hz, 1H), 7.57–7.53 (m, 3H), 7.46 (d, $J = 7.5$ Hz, 1H), 7.19–7.13 (m, 3H), 7.07 (d, $J = 8.0$ Hz, 1H), 7.01 (t, $J = 7.5$ Hz, 1H), 6.67 (t, $J = 7.5$ Hz, 1H), 6.55 (d, $J = 8.0$ Hz, 2H), 6.46 (d, $J = 8.0$ Hz, 1H), 5.69 (d, $J = 7.5$ Hz, 1H), 5.47 (t, $J = 9.0$ Hz, 1H), 4.13 (t, $J = 9.5$ Hz, 1H). 13C NMR (125 MHz, DMSO-$d_6$): 176.7, 174.1, 173.3, 149.0, 145.0, 141.1, 135.5, 133.8, 133.7, 130.9, 130.7, 129.3, 128.6, 127.7, 127.7, 127.6, 127.3, 127.0, 126.3, 125.7, 125.3, 125.0, 124.8, 124.2, 122.4, 122.3, 110.5, 110.0, 110.7, 122.6, 120.6, 110.9, 110.2, 82.0, 70.3, 67.5, 58.8, 46.5, 35.6, 33.1, 23.8. IR (KBr) ν 3265, 3055, 2959, 2874, 1738, 1711, 1682, 1618, 1508, 1470, 1369, 1321. Anal. calcld. for C$_{40}$H$_{34}$N$_4$O$_3$S: C, 73.82; H, 5.27; N, 8.61. Found: C, 73.68; H, 5.35; N, 8.79.

$^{3''}$-(4-Isopropylphenyl)-4'- (thien-2-yl)-1'-methyltrispiro[indole-3,2'-pyrrolidine-3',5''-[1,3]thiazole-2'',3''-indole]-2,4'',2'''-trione (2h)

White solid; mp 208–209.3 °C; $^1$H NMR (500 MHz, DMSO-$d_6$): δ 10.69 (s, 1H), 10.37 (s, 1H), 7.52 (t, $J = 8.0$ Hz, 1H), 7.41 (d, $J = 5.0$ Hz, 1H), 7.33 (d, $J = 7.0$ Hz, 1H), 7.21 (d, $J = 3.0$ Hz, 1H), 7.14–7.11 (m, 3H), 7.07–7.00 (m, 3H), 6.71 (t, $J = 7.5$ Hz, 1H), 6.66 (d, $J = 8.5$ Hz, 2H), 6.56 (d, $J = 8.0$ Hz, 1H), 5.76 (d, $J = 7.5$ Hz, 1H), 4.73 (t, $J = 7.5$ Hz, 1H), 3.87 (t, $J = 9.0$ Hz, 1H), 3.61 (t, $J = 8.5$ Hz, 1H), 2.82–2.74 (m, 1H), 2.12 (s, 3H), 1.10 (dd, $J = 5.0$ Hz and $J = 7.0$ Hz, 6H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): 176.6, 174.6, 173.6, 170.6, 149.0, 145.0, 142.1, 141.3, 133.6, 130.9, 129.4, 128.9, 127.3, 127.2, 126.9, 126.4, 125.6, 125.2, 124.4, 122.5, 122.3, 110.7, 110.0, 81.5, 70.2, 67.7, 60.0, 59.5, 47.6, 35.5, 33.1, 23.8, 21.0, 14.3. IR (KBr) ν 3266, 3055, 2957, 1747, 1719, 1682, 1616, 1508, 1471, 1362, 1319, 1217. Anal. calcld. for C$_{34}$H$_{30}$N$_4$O$_3$S$_2$: C, 67.30; H, 4.98; N, 9.23. Found: C, 67.21; H, 5.06; N, 9.28.

$^{4',3''}$-Diphenyl-1'-methyltrispiro[indole-3,2'-pyrrolidine-3',5''-[1,3]thiazole-2''-,3''-indole]-2,4'',2'''-trione (2i)

White solid; mp 213–214 °C; $^1$H NMR (500 MHz, DMSO-$d_6$): δ 10.73 (s, 1H), 10.31 (s, 1H), 7.56 (d, $J = 7.5$ Hz, 2H), 7.52 (t, $J = 7.5$ Hz, 1H), 7.37–7.32 (m, 3H), 7.25–7.23 (m, 4H), 7.11 (t, $J = 7.5$ Hz, 1H), 7.07–7.03 (m, 2H), 6.72 (t, $J = 7.5$ Hz, 1H), 6.66–6.64 (m, 2H), 6.53 (d, $J = 8.0$ Hz, 1H), 5.88 (d, $J = 8.0$ Hz, 1H), 4.53 (t, $J = 9.0$ Hz, 1H), 3.92 (t, $J = 9.0$ Hz, 1H), 3.50 (t, $J = 8.5$ Hz, 1H), 2.13 (s, 3H).
$^{13}$C NMR (125 MHz, DMSO-$d_6$): 176.8, 174.5, 173.9, 170.6, 144.8, 141.3, 139.1, 136.0, 131.3, 130.9, 130.8, 129.6, 129.3, 128.9, 128.0, 127.5, 127.1, 126.2, 125.3, 124.8, 122.5, 122.3, 110.7, 109.9, 81.8, 70.3, 67.8, 60.0, 58.5, 52.8, 35.5, 21.0, 14.3. IR (KBr) $\nu$ 3215, 3091, 2868, 1728, 1716, 1685, 1616, 1472, 1371, 1325, 1238. Anal. calcd. for C$_{33}$H$_{26}$N$_4$O$_3$S: C, 70.95; H, 4.69; N, 10.03. Found: C, 71.10; H, 4.62; N, 9.94.

$^{4'}$-(4-Methylphenyl)-3$''$-phenyl-1$'$-methyltrispiro[indole-3,2',-pyrrolidine-3',5'-[1,3]thiazolane-2'',3''-indole]-2,4',2'''-trione (2j)

White solid; mp 224.5 °C; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 10.71 (s, 1H), 10.31 (s, 1H), 7.52 (d, $J = 7.5$ Hz, 1H), 7.43 (d, $J = 8.0$ Hz, 2H), 7.34 (d, $J = 7.5$ Hz, 1H), 7.23 (t, $J = 3.5$ Hz, 3H), 7.14–7.04 (m, 5H), 6.72 (t, $J = 7.5$ Hz, 1H), 6.64–6.62 (m, 2H), 6.53 (d, $J = 8.0$ Hz, 1H), 5.85 (d, $J = 7.5$ Hz, 1H), 4.46 (t, $J = 9.0$ Hz, 1H), 3.87 (t, $J = 9.0$ Hz, 1H), 3.46 (t, $J = 8.0$ Hz, 1H), 2.30 (s, 3H), 2.12 (s, 3H).

$^{13}$C NMR (125 MHz, DMSO-$d_6$): 177.0, 174.8, 174.2, 170.7, 145.0, 141.6, 136.4, 136.2, 136.1, 131.3, 131.1, 130.9, 129.8, 129.5, 129.1, 128.9, 127.7, 126.4, 125.5, 125.0, 122.6, 122.5, 110.9, 110.1, 82.0, 70.5, 68.0, 65.4, 60.2, 58.8, 52.7, 35.7, 30.4, 21.2, 21.2, 14.5. IR (KBr) $\nu$ 3219, 3092, 2868, 1732, 1712, 1686, 1616, 1593, 1469, 1362, 1325, 1238. Anal. calcd. for C$_{34}$H$_{28}$N$_4$O$_3$S: C, 71.31; H, 4.93; N, 9.78. Found: C, 71.39; H, 4.80; N, 9.85.

$^{4'}$-(4-Isopropylphenyl)-3$''$-phenyl-1$'$-methyltrispiro[indole-3,2',-pyrrolidine-3',5'-[1,3]thiazolane-2'',3''-indole]-2,4',2'''-trione (2k)

White solid; mp 201–201.8 °C; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 10.71 (s, 1H), 10.33 (s, 1H), 7.52 (t, $J = 7.5$ Hz, 1H), 7.47 (d, $J = 8.0$ Hz, 2H), 7.33 (d, $J = 7.5$ Hz, 1H), 7.24 (t, $J = 3.0$ Hz, 3H), 7.19 (d, $J = 8.0$ Hz, 2H), 7.10 (t, $J = 7.5$ Hz, 1H), 7.06–7.03 (m, 2H), 6.72 (t, $J = 7.5$ Hz, 1H), 6.65–6.63 (m, 2H), 6.52 (d, $J = 8.0$ Hz, 1H), 5.85 (d, $J = 7.5$ Hz, 1H), 4.47 (t, $J = 8.5$ Hz, 1H), 3.87 (t, $J = 9.0$ Hz, 1H), 3.46 (t, $J = 8.5$ Hz, 1H), 2.91–2.86 (m, 1H), 2.12 (s, 3H), 1.23–1.21 (m, 6H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): 176.4, 174.2, 173.6, 170.3, 146.4, 144.5, 141.0, 136.2, 135.7, 130.8, 130.6, 130.5, 129.3, 129.0, 128.6, 127.2, 125.9, 125.6, 125.0, 124.5, 122.1, 122.0, 110.3, 109.6, 81.5, 69.8, 67.5, 59.7, 58.2, 52.0, 35.2, 32.9, 23.9, 23.7, 20.7, 14.0. IR (KBr) $\nu$ 2959, 2868, 1726, 1697, 1618, 1471, 1338, 1223. Anal. calcd. for C$_{36}$H$_{32}$N$_4$O$_3$S: C, 71.98; H, 5.37; N, 9.33. Found: C, 71.87; H, 5.46; N, 9.29.

$^{4'}$-(4-Chlorophenyl)-3$''$-phenyl-1$'$-methyltrispiro[indole-3,2',-pyrrolidine-3',5'-[1,3]thiazolane-2'',3''-indole]-2,4',2'''-trione (2l)

White solid; mp 219–220.3 °C; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 10.78 (s, 1H), 10.38 (s, 1H), 7.58 (d, $J = 8.5$ Hz, 2H), 7.53 (t, $J = 7.5$ Hz, 1H), 7.39 (d, $J = 9.5$ Hz, 2H), 7.35 (d, $J = 7.5$ Hz, 1H), 7.25–7.23 (m, 3H), 7.12 (t, $J = 7.5$ Hz, 1H), 7.07–7.04 (m, 2H), 6.73 (t, $J = 7.5$ Hz, 1H), 6.65–6.63 (m, 2H), 6.54 (d, $J = 8.0$ Hz, 1H), 5.87 (d, $J = 7.5$ Hz, 1H), 4.51 (t, $J = 8.5$ Hz, 1H), 3.86 (t, $J = 9.0$ Hz, 1H), 3.52 (t, $J = 8.5$ Hz, 1H), 2.13 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): 176.5, 174.3, 173.4, 170.3, 144.5, 141.1, 137.9, 135.9, 135.6, 132.8, 131.5, 130.7, 130.5, 129.2, 129.0, 128.6,
127.7, 127.2, 125.6, 125.0, 124.2, 122.2, 122.0, 110.3, 109.7, 81.4, 69.8, 67.5, 59.7, 58.1, 51.9, 35.2, 20.7, 14.0. IR (KBr) ν 3209, 3091, 2868, 1728, 1709, 1689, 1618, 1493, 1470, 1358, 1325, 1238. Anal. calcd. for C$_{33}$H$_{25}$ClN$_4$O$_3$S: C, 66.83; H, 4.25; N, 9.45. Found: C, 66.87; H, 4.19; N, 9.40.

4′-(4-Bromophenyl)-3′′-phenyl-1′-methyltrispiro[indole-3,2′-pyrrolidine-3′,5″-[1,3]thiazolane-2″,3″′-indole]-2,4″,2″″-trione (2 m)  
White solid; mp 214.8–216 °C; $^1$H NMR (500 MHz, DMSO-d$_6$): δ 10.78 (s, 1H), 10.38 (s, 1H), 7.55–7.50 (m, 5H), 7.35 (d, $J$ = 7.5 Hz, 1H), 7.26–7.23 (m, 3H), 7.12 (t, $J$ = 7.5 Hz, 1H), 7.07–7.04 (m, 2H), 6.73 (t, $J$ = 8.0 Hz, 1H), 6.64–6.62 (m, 2H), 6.54 (d, $J$ = 8.0 Hz, 1H), 5.87 (d, $J$ = 7.0 Hz, 1H), 4.50 (t, $J$ = 8.0 Hz, 1H), 3.85 (t, $J$ = 9.0 Hz, 1H), 3.52 (t, $J$ = 8.0 Hz, 1H), 2.13 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-d$_6$): 177.0, 174.8, 173.9, 170.7, 145.0, 141.6, 138.8, 136.1, 133.7, 131.2, 131.1, 131.0, 129.7, 129.5, 129.1, 127.7, 126.1, 125.5, 124.8, 122.7, 122.5, 120.7, 110.9, 110.2, 81.9, 70.2, 68.0, 60.2, 58.6, 52.4, 35.7, 21.2, 14.5. IR (KBr) ν 3215, 3091, 2868, 1730, 1709, 1689, 1618, 1472, 1325, 1240. Anal. calcd. for C$_{33}$H$_{25}$BrN$_4$O$_3$S: C, 62.17; H, 3.95; N, 8.79. Found: C, 62.28; H, 4.07; N, 8.62.

CONCLUSIONS

In summary, a number of interesting and novel trispiropyrrrolidine bisoxindoles derivatives were prepared and characterized through a one-pot, three-component reaction of azomethine ylides with 3-aryl-5-arylmethylenespiro[indole-3′,2′-thiazolane]-2′(1H),4-dione. The reaction itself proceeds in a highly regio- and stereo-selective manner, and the structures were determined by IR, NMR, and single-crystal x-ray.

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SUPPORTING INFORMATION

Full characterization data, $^1$H and $^{13}$C NMR spectra, and x-ray crystallographic materials for this article can be accessed on the publisher’s website.

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