Synthesis of novel spiro[cyclopropane-indazole] derivatives *via* magnesium-mediated conjugate addition of bromoform

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A novel series of 2,2-dibromo-3-aryl-1'-phenyl-6',7'-dihydrospiro[cyclopropane-1,5'-indazol]-4'(1'*H*)-ones derivatives were prepared in moderate to good yields by conjugate addition of bromoform to (*E*)-5-arylmethylene-1-phenyl-6,7-dihydro-1*H*-indazol-4(5*H*)-ones in the presence of magnesium under N_2. The structures of all the products were characterised by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, elemental analysis and mass spectrometry.

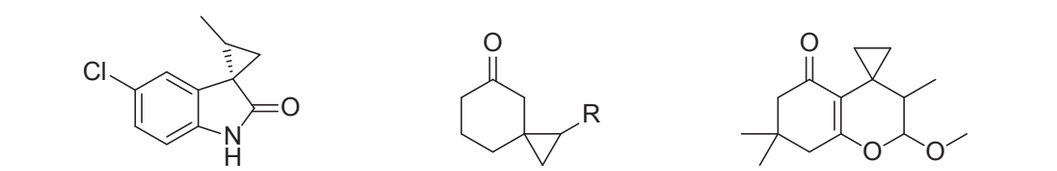
Keywords: cyclopropane, indazole, spiroheterocyclic

Cyclopropane rings are a significant feature in a wide variety of natural products and in drug molecules such as erispatene, indolizomycin, halicholactone and related compounds.[1–4] In the past years, many valuable compounds which contain a cyclopropane ring have been synthesised and isolated, such as the insecticide (+)-*trans*-chrysanthemic acid, the plant hormone precursor 1-aminocyclopropane-1-carboxylic acid (ACC), the renal dehydropeptidase inhibitor cilastatin and the anticancer agent (+)-ptaquiloside.[5,6] Spirocyclopropanes represent an important area of cyclopropane research and many useful products have been synthesised and investigated (Fig. 1).[7,8] During these studies many ways to synthesise cyclopropanes have been developed and the main methods include additions of dihalocarbenes, diazoalkanes, or sulfonium ylides to alkenes or activated alkenes.[9–11] However, all these methods are not well suited for the preparation of spirocyclopropanes from enones. In particular, the Mg-mediated addition of bromoform to enones is a convenient and efficient way to synthesise spirocyclopropanes.[12]

During research on small-molecule modulators, indazole and indazolone derivatives have attracted increasing interest because of their various biological properties such as anti-inflammatory, antibacterial, and anticancer activities.[13–15] Despite the proven importance of indazolone derivatives in biomedical research, a convenient and efficient synthesis of such compounds remains a challenge. We now describe efforts to design and synthesise novel indazolone derivatives with potential biological activity, and the introduction of cyclopropane rings into indazolone molecules. We herein report a convenient and efficient way to synthesise a series of new spiro-indazolone compounds containing a cyclopropane ring framework by Mg-mediated conjugate addition of bromoform (Scheme 1). In this procedure, the reaction actually proceeds *via* conjugate addition of Br_3CMgBr to the enone rather than by cycloaddition of dibromocarbene.[12]

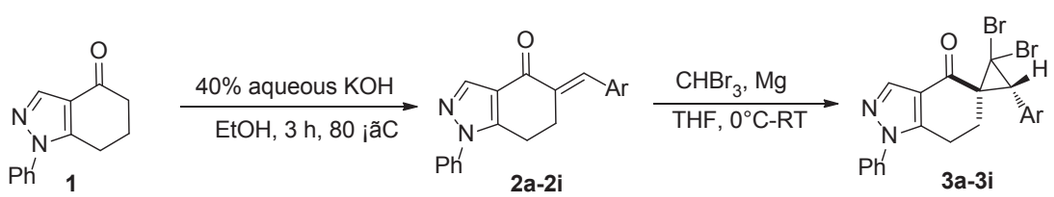
Results and discussion

The condensation reaction of 1-phenyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one **1** with the appropriate aromatic aldehyde gave (*E*)-5-arylmethylene-1-phenyl-6,7-dihydro-1*H*-indazol-4(5*H*)-ones **2** in moderate yields in a simple operation. Subsequent conjugate addition of bromoform (20 equiv.) in the presence of Mg (10 equiv.) to the indazolones **2** resulted in the formation of the dibromo-cyclopropanes **3** in moderate to high



spiro[cyclopropane-indolin]-one spirooctanone spiro[chromene-cyclopropan]-one

Fig. 1 Some important compounds bearing a spirocyclopropane moiety.



Ar: a, C_6H_5; **b,** 4-ClC_6H_4; **c,** 4-FC_6H_4; **d**, 4-$CH_3C_6H_4$; **e**, 4-$(CH_3)_3CC_6H_4$; **f**, 4-$CH_3SC_6H_4$; **g**, 4-$CH_3OC_6H_4$; **h**,3,5-$(CH_3O)_2C_6H_3$; **i**, 3,4,5-$(CH_3O)_3C_6H_2$;

Scheme 1

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Table 1 Synthesis of spiro[cyclopropane-indazol] derivatives

Entry	Ar	Product	Time/h	Yield/%
1	C_6H_5	**3a**	2.0	52
2	$4Cl–C_6H_4$	**3b**	2.5	86
3	$4\text{-}FC_6H_4$	**3c**	3.0	68
4	$4\text{-}CH_3C_6H_4$	**3d**	1.5	62
5	$4\text{-}(CH_3)_3CC_6H_4$	**3e**	2.0	71
6	$4\text{-}CH_3SC_6H_4$	**3f**	1.5	56
7	$4\text{-}CH_3OC_6H_4$	**3g**	2.5	75
8	$3,5\text{-}(OCH_3)_2C_6H_3$	**3h**	1.0	82
9	$3,4,5\text{-}(OCH_3)_3C_6H_2$	**3i**	1.5	88

yields (Table 1). The progress of this reaction was monitored by TLC and the target products were purified by flash column chromatography on silica gel. In order to expand the range of substrates for this reaction, different arylidene groups containing either electron donating or electron withdrawing substituents (in **2**) were tested in the reaction. As shown in Table 1, the conjugate addition-cyclopropanation reaction sequence was complete in less than 3 h, and the products were isolated in moderate to high yield (52–88%). The substituents on the benzylidene moiety in **2** have little effect on the yield or the reaction time.

The structures of all compounds **2a**–**i** and **3a**–**i** were established by a variety of spectroscopic techniques (NMR, IR, MS and elemental analysis). The elemental analysis and MS (ESI) of **3d** were consistent with the formula $C_{22}H_{18}Br_2N_2O$, which indicated addition of the bromoform to the (*E*)-5-(4-methylbenzylidene)-1-phenyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one **2d**. The IR spectrum of **3d** revealed the presence of a carbonyl stretching band at 1680 cm^{-1}. The ^1H NMR spectrum of **3d** revealed the presence of two double doublets of doublets at δ 2.01 (ddd, J_1 = 14.0 Hz, J_2 = 4.5 Hz, J_3 = 2.0 Hz, 1H) and at 2.58 (ddd, J_1 = 14.0 Hz, J_2 = 12.5 Hz, J_3 = 4.5 Hz, 1H) corresponding to the protons of the C-6′ methylene group. Another double doublet of doublets at δ 3.46 (ddd, J_1 = 17.0 Hz, J_2 = 12.5 Hz, J_3 = 4.5 Hz, 1H) together with a multiplet in the range 2.89–2.92 ppm corresponded to the C-7′ methylene protons. Three singlets at δ 2.33, 3.91 and 8.16 corresponded to the tolyl methyl protons, the CH (HC-3) in the cyclopropane ring and the pyrazole ring CH (HC-3′) proton, respectively.

The ^{13}C NMR spectrum of the product **3d** exhibited the presence of a carbonyl carbon at δ 185.2 (C-4′). The signals at δ 21.3 and 30.5 were assigned to the carbons from the CH_2 units of H_2C-7′ and H_2C-6′ respectively (based on HSQC). The signal at δ 37.8 is in agreement with the carbon of the CH (HC-3), from the cyclopropane ring (based on HSQC). The signal at δ 42.0 is in accord with the spiro carbon of C-1.

In the ^1H–^{13}C HMBC map of **3d** (Fig. 2), protons from the H_2C-6′ and H_2C-7′ units from the indazolone ring and HC-3 in the cyclopropane ring correlate with the spiro carbon C-1 (42.0 ppm), whilst the protons from H_2C-6′ correlate with the C-3 carbon (37.8 ppm). The correlation of H_2C-6′ and HC-3 with C-4′ indicates the carbonyl carbon (C-4′) at 185.2 ppm. The stereochemistry of the products was determined by NOESY. It is straightforward to differentiate **3** from its isomer (in which Ar and H have been interchanged) since the latter would, of course, be expected to show a NOESY correlation. There is no correlation between the HC-3 proton and the H_2C-6′ protons in the NOESY spectrum of **3d**, which indicates that the HC-3 proton and those from the H_2C-6′ moiety are on different sides of the cyclopropane ring. This stereochemistry of the products **3a**–**i** is similar to the result reported previously.[12]

A plausible mechanism for the conversion of **2** to **3** is outlined in Scheme 2. Firstly, magnesium reacts with excess bromoform to form initially tribromomethylmagnesium-bromide which undergoes conjugate addition to the enone moiety of the indazolone **2**. The resulting enolate intermediate cyclises to give the spiro-cyclopropane ketone, 2,2-dibromo-3-aryl-1′-phenyl-6′,7′-dihydrospiro[cyclopropane-1,5′-indazol]-4′(1′*H*)-one **3**. Evidence for the participation of a tribromomethyl enolate in related reactions has been reported recently.[12]

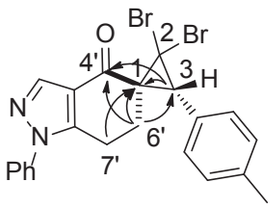


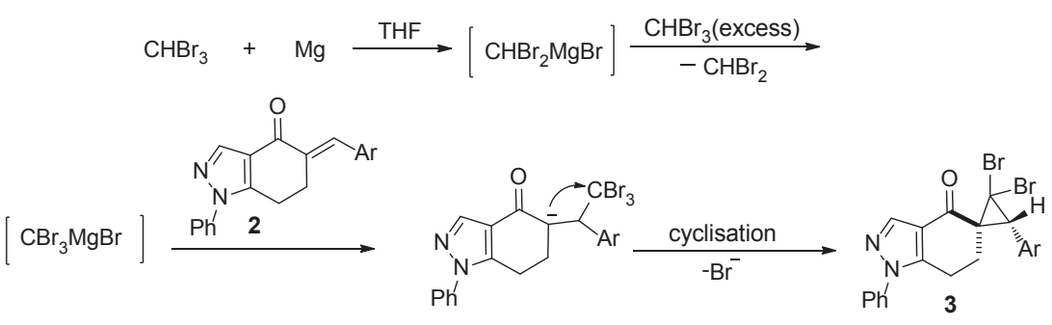
Fig. 2 Partial HMBC diagram of **3d**.

Conclusion

A facile and novel synthesis of 2,2-dibromo-3-aryl-1′-phenyl-6′,7′-dihydrospiro[cyclopropane-1,5′-indazol]-4′(1′*H*)-ones by the conjugate addition of bromoform to (*E*)-5-arylmethylene-1-phenyl-6,7-dihydro-1*H*-indazol-4(5*H*)-ones in the presence of Mg in THF has been developed. This work provides a simple method to synthesise spiro(dibromocyclopropanated) products incorporating the important indazolone and cyclopropane rings.

Experimental

Compound **2** was prepared according to the reported procedure.[16] All NMR spectra were recorded on a Bruker AV-II 500 MHz NMR spectrometer, operating at 500 MHz for ^1H, and 125 MHz for ^{13}C. TMS was used as an internal reference for both ^1H and ^{13}C chemical shifts and $CDCl_3$ was used as solvent. MS was obtained with a Finnigan LCQ Advantage MAX mass spectrometer. IR spectra were recorded



Scheme 2 A plausible mechanism for the conversion of **2** to **3**.

on a PE-2000 spectrometer in KBr pellets and are reported in cm^{-1}. Melting points were measured with a Yanaco MP500 melting point apparatus and are uncorrected. Elemental analysis was measured by Elementar analyser (vario EL II). Mg turnings were activated by washing with 1% dilute HCl, water, and acetone followed by drying in an oven overnight. The solvents were all distilled prior to use. THF was distilled from sodium. Other commercially available materials were purchased from Aladdin-Reagent, and were used without further purification.

*Synthesis of (E)-5-arylmethylene-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-one (***2a-i***); general procedure*

A solution of 1-phenyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one **1** (10 mmol) and the appropriate aromatic aldehyde (10 mmol) in EtOH (10 mL) was stirred at 80 °C for 3 h in the presence of 40% aqueous NaOH (2 mL). Then the crude product was isolated by filtration through a Buchner funnel. The residue thus obtained was washed with water and purified by crystallisation from ethanol to give pure product **2**.

*(*E*)-5-Benzylidene-1-phenyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one* (**2a**): White solid, yield 65%; m.p. 188–189 °C, (lit.[17] 162–163 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.05 (t, *J*=6.5 Hz, 2H), 3.16–3.19 (m, 2H), 7.36–7.38 (m, 1H), 7.40–7.46 (m, 5H), 7.51–7.54 (m, 4H), 7.82 (s, 1H), 8.21 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.8, 26.4, 121.2, 123.6, 128.3, 128.4, 128.5, 129.5, 129.6, 134.9, 135.9, 136.1, 138.6, 139.5, 147.9, 183.5; IR (KBr) ν_{max}/cm^{-1} 1655; MS (ESI) *m/z* 301 $[M+H]^+$. Anal. calcd for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33; found: C, 79.85; H, 5.46; N, 9.21%.

*(*E*)-5-(4-Chlorobenzylidene)-1-phenyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one* (**2b**): White solid, yield 58%; m.p. 208–209 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.05 (t, *J*=6.5 Hz, 2H), 3.12–3.14 (m, 2H), 7.33 (d, *J*=8.5 Hz, 2H), 7.40 (d, *J*=8.5 Hz, 2H), 7.43–7.46 (m, 1H), 7.51–7.55 (m, 4H), 7.75 (s, 1H), 8.21 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.7, 26.4, 121.1, 123.6, 128.4, 128.8, 129.5, 130.9, 134.3, 134.4, 134.8, 135.4, 138.5, 139.6, 147.8, 183.1; IR (KBr) ν_{max}/cm^{-1} 1655; MS (ESI) *m/z* 335 $[M+H]^+$. Anal. calcd for $C_{20}H_{15}ClN_2O$: C, 71.75; H, 4.52; N, 8.37; found: C, 71.57; H, 4.58; N, 8.42%**.**

*(*E*)-5-(4-Fluorobenzylidene)-1-phenyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one* (**2c**): White solid, yield 69%; m.p. 190–191 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.04 (t, *J*=6.5 Hz, 2H), 3.13 (t, *J*=6.5 Hz, 2H), 7.11 (d, *J*=8.5 Hz, 2H), 7.36–7.39 (m, 2H), 7.42–7.46 (m, 1H), 7.51–7.54 (m, 4H), 7.75 (s, 1H), 8.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.7, 26.3, 115.5, 115.7, 121.1, 123.5, 128.3, 129.5, 131.5, 131.6, 131.89, 131.91, 134.7, 135.0, 138.5, 139.6, 147.8, 161.5, 163.5, 183.3; IR (KBr) ν_{max}/cm^{-1} 1656; MS (ESI) *m/z* 319 $[M+H]^+$. Anal. calcd for $C_{20}H_{15}FN_2O$: C, 75.46; H, 4.75; N, 8.80; found: C, 75.31; H, 4.69; N, 8.71%.

*(*E*)-5-(4-Methylbenzylidene)-1-phenyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one* (**2d**): White solid, yield 59%; m.p. 211–212 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.02 (t, *J*=6.5 Hz, 2H), 3.16 (t, *J*=6.5 Hz, 2H), 7.22 (d, *J*=8.0 Hz, 2H), 7.30 (d, *J*=8.0 Hz, 2H), 7.41–7.44 (m, 1H), 7.49–7.51 (m, 4H), 7.78 (s, 1H), 8.19 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.4, 22.8, 26.4, 121.2, 123.6, 128.3, 129.2, 129.5, 129.7, 133.0, 134.1, 136.2, 138.58, 138.64, 139.5, 147.8, 183.5; IR (KBr) ν_{max}/cm^{-1} 1660; MS (ESI) *m/z* 315 $[M+H]^+$. Anal. calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91; found: C, 80.12; H, 5.83; N, 8.86%.

*(*E*)-5-[4-(*tert*-Butyl)benzylidene]-1-phenyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one* (**2e**):White solid, yield 72%; m.p. 184–185 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.35(s, 9H), 3.03 (t, *J*=6.5 Hz, 2H), 3.19 (d, *J*=6.5 Hz, 2H), 7.35 (d, *J*=8.0 Hz, 2H), 7.35 (d, *J*=8.5 Hz, 2H), 7.51–7.52 (m, 3H), 7.79 (s, 1H), 8.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.8, 26.4, 31.2, 34.8, 121.2, 123.6, 125.5, 128.2, 129.6, 133.0, 134.1, 138.6, 139.5, 147.8, 151.8, 183.5; IR (KBr) ν_{max}/cm^{-1} 1671; MS (ESI) *m/z* 357 $[M+H]^+$. Anal. calcd for $C_{24}H_{24}N_2O$: C, 80.87; H, 6.79; N, 7.86; found: C, 80.69; H, 6.65; N, 7.83%.

*(*E*)-5-[4-(Methylthio)benzylidene]-1-phenyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one* (**2f**): White solid, yield 46%; m.p. 195–196 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.52 (s, 3H), 3.04 (t, *J*=6.5 Hz, 2H), 3.16 (t, *J*=6.5 Hz, 2H), 7.26 (d, *J*=8.5 Hz, 2H), 7.33 (d, *J*=8.5 Hz, 2H), 7.41–7.45 (m, 1H), 7.49–7.54 (m, 4H), 7.75 (s, 1H), 8.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.3, 22.7, 26.5, 121.1, 123.6, 125.8, 128.3, 129.5, 130.2, 132.3, 134.2, 135.7, 138.5, 139.6, 139.7, 147.8, 183.4; IR (KBr) ν_{max}/cm^{-1} 1650; MS (ESI) *m/z* 347 $[M+H]^+$. Anal. calcd for $C_{21}H_{18}N_2OS$: C, 72.80; H, 5.24; N, 8.09; found: C, 72.68; H, 5.21; N, 8.13%.

*(*E*)-5-(4-Methoxybenzylidene)-1-phenyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one* (**2g**): White solid, yield 56%; m.p. 192–193 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.03 (t, *J*=6.5 Hz, 2H), 3.17 (t, *J*=6.5 Hz, 2H), 3.84 (s, 3H), 6.94 (d, *J*=8.5 Hz, 2H), 7.37 (d, *J*=8.5 Hz, 2H), 7.41–7.44 (m, 1H), 7.49–7.53 (m, 4H), 7.77 (s, 1H), 8.19 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.7, 26.4, 55.4, 114.0, 121.2, 123.6, 128.2, 128.4, 129.5, 131.5, 132.9, 136.0, 138.6, 139.5, 147.7, 159.8, 183.5; IR (KBr) ν_{max}/cm^{-1} 1655; MS (ESI) *m/z* 331 $[M+H]^+$. Anal. calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48; found: C, 76.45; H, 5.54; N, 8.42%.

*(*E*)-5-(3,5-Dimethoxybenzylidene)-1-phenyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one* (**2h**): White solid, yield 58%; m.p. 188–189 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.01 (t, *J*=6.5 Hz, 2H), 3.15 (t, *J*=6.5 Hz, 2H), 3.81 (s, 6H), 7.41–7.44 (m, 1H), 7.49–7.53 (m, 4H), 7.72 (s, 1H), 8.19 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.8, 26.5, 55.4, 100.3, 107.6, 121.2, 123.6, 128.3, 129.5, 135.3, 136.0, 137.8, 138.5, 139.5, 148.0, 160.7, 183.3; IR (KBr) ν_{max}/cm^{-1} 1663; MS (ESI) *m/z* 361 $[M+H]^+$. Anal. calcd for $C_{22}H_{20}N_2O_3$: C, 73.32; H, 5.59; N, 7.77; found: C, 73.28; H, 5.68, N7.71%.

*(*E*)-1-Phenyl-5-(3,4,5-trimethoxybenzylidene)-6,7-dihydro-1*H*-indazol-4(5*H*)-one* (**2i**): White solid, yield 52%; m.p. 191–192 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.05 (t, *J*=6.5 Hz, 2H), 3.19 (t, *J*=6.5 Hz, 2H), 3.88 (s, 6H), 3.89 (s, 3H), 6.62 (s, 2H), 7.42–7.45 (m, 1H), 7.50–7.54 (m, 4H), 7.74 (s, 1H), 8.19 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.7, 26.5, 56.2, 61.0, 107.0, 121.1, 123.6, 128.3, 129.5, 131.4, 134.3, 136.3, 138.4, 138.5, 139.5, 147.8, 153.1, 183.2; IR (KBr) ν_{max}/cm^{-1} 1654; MS (ESI) *m/z* 391 $[M+H]^+$. Anal. calcd for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68; N, 7.17; found: C, 70.61; H, 5.64; N, 7.22%.

Synthesis of 2,2-dibromo-3-aryl-1'-phenyl-6',7'-dihydrospiro-[cyclopropane-1,5'-indazol]-4'(1'H)-ones (**3a**–**i**)*; general procedure*

Bromoform (5.4 g, 2 mL, 22 mmol) was dropwise added into a stirred mixture of magnesium (192 mg, 8 mmol) and the appropriate (*E*)-5-arylmethylene-1-phenyl-6,7-dihydro-1*H*-indazol-4(5*H*)-one **2** (1 mmol) in dry THF (20 mL) over a period of 10 min at 0 °C under a protective N_2 atmosphere. After that, the reaction mixture was brought to room temperature. The reaction was conducted until TLC analysis showed that none of the reactant remained. Then the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL). The organic layer was separated and concentrated *in vacuo* to give the crude product. The latter was subjected to column chromatography using petroleum-ethyl acetate (6 : 1) as eluent to afford the corresponding spiro-cycle **3**.

*2,2-Dibromo-1',3-diphenyl-6',7'-dihydrospiro[cyclopropane-1,5'-indazol]-4'(1'*H*)-one* (**3a**): White solid, yield 52%; m.p. 199–201 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.01 (ddd, J_1=14.0 Hz, J_2=4.5 Hz, J_3=2.0 Hz, 1H), 2.59 (ddd, J_1=14.0 Hz, J_2=12.5 Hz, J_3=4.5 Hz, 1H), 2.91 (ddd, J_1=17.0 Hz, J_2=4.5 Hz, J_3=2.0 Hz, 1H), 3.46 (ddd, J_1=17.0 Hz, J_2=12.5 Hz, J_3=4.5 Hz, 1H), 3.97 (s, 1H, HC-3), 7.27 (d, *J*=8.0 Hz, 2H), 7.31–7.37 (m, 3H), 7.43 (d, *J*=7.5 Hz, 1H), 7.51 (d, *J*=8.5 Hz, 1H), 7.56 (t, *J*=8.5 Hz, 3H), 8.17 (s, 1H, HC-3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.3, 30.5, 35.2, 38.0, 42.1, 119.8, 123.6, 127.7, 128.48, 128.51, 129.5, 129.9, 133.1, 138.4, 139.3, 148.9, 185.1; IR (KBr) ν_{max}/cm^{-1} 1686; MS (ESI) *m/z* 391 $[M–Br]^+$. Anal. calcd for $C_{21}H_{16}Br_2N_2O$: C, 53.42; H, 3.42; N, 5.93; found: C, 53.35; H, 3.52; N, 5.86%.

*2,2-Dibromo-3-(4-chlorophenyl)-1'-phenyl-6',7'-dihydrospiro-[cyclopropane-1,5'-indazol]-4'(1'*H*)-one* (**3b**): White solid, yield 86%; m.p. 202–204 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.98 (ddd, J_1=14.0 Hz, J_2=4.5 Hz, J_3=2.0 Hz, 1H), 2.58 (ddd, J_1=14.0 Hz, J_2=12.5 Hz, J_3=4.5 Hz, 1H), 2.94 (ddd, J_1=17.0 Hz, J_2=4.5 Hz, J_3=2.0 Hz, 1H), 3.47 (ddd, J_1=17.0 Hz, J_2=12.5 Hz, J_3=4.5 Hz, 1H),

3.91 (s, 1H, HC-3), 7.21 (d, J=8.0 Hz, 2H), 7.34 (d, J=8.0 Hz, 2H), 7.45 (t, J=7.5 Hz, 1H), 7.51–7.58 (m, 4H), 8.17 (s, 1H, HC-3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.3, 30.4, 34.7, 37.3, 42.1, 119.7, 123.5, 128.5, 128.8, 129.6, 131.3, 131.5, 133.8, 139.3, 148.8, 184.7; IR (KBr) ν_{max}/cm^{-1} 1677; MS (ESI) *m/z* 425 [M–Br]$^+$. Anal. calcd for $C_{21}H_{15}Br_2ClN_2O$: C, 49.79; H, 2.98; N, 5.53; found: C, 49.83; H, 3.05; N, 5.51%.

*2,2-Dibromo-3-(4-fluorophenyl)-1′-phenyl-6′,7′-dihydrospiro-[cyclopropane-1,5′-indazol]-4′(1′*H*)-one* (**3c**): White solid, yield 68%; m.p. 190–192 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.00 (ddd, J_1=14.0 Hz, J_2=4.5 Hz, J_3=2.0 Hz, 1H), 2.58 (ddd, J_1=14.0 Hz, J_2=12.5 Hz, J_3=4.5 Hz, 1H), 2.94 (ddd, J_1=17.0 Hz, J_2=4.5 Hz, J_3=2.0 Hz, 1H), 3.48 (ddd, J_1=17.0 Hz, J_2=12.5 Hz, J_3=4.5 Hz, 1H), 3.92 (s, 1H, HC-3), 7.07 (d, J=8.5 Hz, 2H), 7.24–7.28 (m, 2H), 7.44–7.47 (m, 1H), 7.53–7.59 (m, 4H), 8.18 (s, 1H, HC-3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.3, 30.4, 35.0, 37.3, 42.1, 115.5, 115.7, 119.8, 123.6, 128.5, 128.78, 128.81, 129.5, 131.56, 131.62, 138.4, 139.3, 148.8, 161.2, 163.2, 184.9; IR (KBr) ν_{max}/cm^{-1} 1683; MS (ESI) *m/z* 409 [M–Br]$^+$. Anal. calcd for $C_{21}H_{15}Br_2FN_2O$: C, 51.46; H, 3.08; N, 5.72; found: C, 51.48; H, 3.18; N, 5.78%.

*2,2-Dibromo-1′-phenyl-3-(*p*-tolyl)-6′,7′-dihydrospiro-[cyclopropane-1,5′-indazol]-4′(1′*H*)-one* (**3d**): White solid, yield 62%; m.p. 196–198 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.01 (ddd, J_1=14.0 Hz, J_2=4.5 Hz, J_3=2.0 Hz, 1H), 2.33 (s, 3H, –CH_3), 2.58 (ddd, J_1=14.0 Hz, J_2=12.5 Hz, J_3=4.5 Hz, 1H), 2.92 (ddd, J_1=17.0 Hz, J_2=4.5 Hz, J_3=2.0 Hz, 1H), 3.46 (ddd, J_1=17.0 Hz, J_2=12.5 Hz, J_3=4.5 Hz, 1H), 3.91 (s, 1H, HC-3), 7.16–7.18 (m, 4H), 7.43 (t, J=7.5 Hz, 1H), 7.51 (d, J=8.5 Hz, 1H), 7.55 (t, J=8.0 Hz, 1H), 8.16 (s, 1H, HC-3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.2, 21.3, 30.5, 35.6, 37.6, 42.0, 119.9, 123.6, 128.5, 129.2, 129.5, 129.8, 130.0, 137.4, 138.4, 139.3, 148.9, 185.2; IR (KBr) ν_{max}/cm^{-1} 1680; MS (ESI) *m/z* 405 [M–Br]$^+$. Anal. calcd for $C_{22}H_{18}Br_2N_2O$: C, 54.35; H, 3.73; N, 5.76; found: C54.44; H, 3.62; N, 5.71%.

*2,2-Dibromo-3-[4-(*tert*-butyl)phenyl]-1′-phenyl-6′,7′-dihydrospiro-[cyclopropane-1,5′-indazol]-4′(1′*H*)-one* (**3e**): White solid, yield 71%; m.p. 175–177 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.32 (s, 9H, –$C(CH_3)_3$), 2.07 (ddd, J_1=14.0 Hz, J_2=4.5 Hz, J_3=2.0 Hz, 1H), 2.59 (ddd, J_1=14.0 Hz, J_2=12.5 Hz, J_3=4.5 Hz, 1H), 2.92 (ddd, J_1=17.0 Hz, J_2=4.5 Hz, J_3=2.0 Hz, 1H), 3.47 (ddd, J_1=17.0 Hz, J_2=12.5 Hz, J_3=4.5 Hz, 1H), 3.92 (s, 1H, HC-3), 7.20 (d, J=8.0 Hz, 2H), 7.37 (d, J=8.5 Hz, 2H), 7.43–7.46 (m, 1H), 7.52–7.58 (m, 4H), 8.18 (s, 1H, HC-3′); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.3, 30.5, 31.3, 34.6, 35.6, 37.8, 42.0, 119.9, 123.6, 125.4, 128.4, 129.51, 129.52, 130.0, 138.4, 139.3, 148.9, 150.6, 185.2; IR (KBr) ν_{max}/cm^{-1} 1676; MS (ESI) *m/z* 447 [M–Br]$^+$. Anal. calcd for $C_{25}H_{24}Br_2N_2O$: C, 56.84; H, 4.58; N, 5.30; found: C, 56.90; H, 4.39; N, 5.14%.

*2,2-Dibromo-3-[4-(methylthio)phenyl]-1′-phenyl-6′,7′-dihydrospiro-[cyclopropane-1,5′-indazol]-4′(1′*H*)-one* (**3f**): White solid, yield 56%; m.p. 167–169 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): 1.99 (ddd, J_1=14.0 Hz, J_2=4.5 Hz, J_3=2.0 Hz, 1H), 2.47 (s, 1H, –SCH_3), 2.56 (ddd, J_1=14.0 Hz, J_2=12.5 Hz, J_3=4.5 Hz, 1H), 2.90 (ddd, J_1=17.0 Hz, J_2=4.5 Hz, J_3=2.0 Hz, 1H), 3.45 (ddd, J_1=17.0 Hz, J_2=12.5 Hz, J_3=4.5 Hz, 1H), 3.89 (s, 1H, HC-3), 7.17 (d, J=8.5 Hz, 2H), 7.21–7.25 (m, 2H), 7.41–7.45 (m, 1H), 7.50–7.57 (m, 4H), 8.16 (s, 1H, HC-3′); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.5, 21.3, 30.5, 35.3, 37.5, 42.1, 119.8, 123.6, 128.5, 129.5, 129.6, 130.3, 138.2, 138.4, 139.3, 148.8, 185.0; IR (KBr) ν_{max}/cm^{-1} 1672; MS (ESI) *m/z* 437 [M–Br]$^+$. Anal. calcd for $C_{22}H_{18}Br_2N_2OS$: C, 50.98; H, 3.50; N, 5.41; found: C, 50.78; H, 3.63; N, 5.31%.

*2,2-Dibromo-3-(4-methoxyphenyl)-1′-phenyl-6′,7′-dihydrospiro-[cyclopropane-1,5′-indazol]-4′(1′*H*)-one* (**3g**): White solid, yield 75%; m.p. 158–160 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.00 (ddd, J_1=14.0 Hz, J_2=4.5 Hz, J_3=2.0 Hz, 1H), 2.56 (ddd, J_1=14.0 Hz, J_2=12.5 Hz, J_3=4.5 Hz, 1H), 2.90 (ddd, J_1=17.0 Hz, J_2=4.5 Hz, J_3=2.0 Hz, 1H), 3.45 (ddd, J_1=17.0 Hz, J_2=12.5 Hz, J_3=4.5 Hz, 1H), 3.79 (s, 3H, –OCH_3), 3.79 (s, 1H, HC-3), 6.88 (d, J=9.0 Hz, 2H), 7.18 (d, J=8.0 Hz, 2H), 7.43 (t, J=7.5 Hz, 1H), 7.50–7.57 (m, 4H), 8.16 (s, 1H, HC-3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.3, 30.5, 35.8, 37.4, 42.0, 55.3, 114.0, 120.0, 123.6, 125.0, 128.5, 129.5, 131.0, 138.4, 139.3, 148.9, 159.0, 185.2; IR (KBr) ν_{max}/cm^{-1} 1672; MS (ESI) *m/z* 421 [M–Br]$^+$. Anal. calcd for $C_{22}H_{18}Br_2N_2O_2$: C, 52.62; H, 3.61; N, 5.58; found: C, 52.51; H, 3.69; N, 5.54%.

*2,2-Dibromo-3-(3,5-dimethoxyphenyl)-1′-phenyl-6′,7′-dihydrospiro-[cyclopropane-1,5′-indazol]-4′(1′*H*)-one* (**3h**): White solid, yield 82%; m.p. 178–180 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.09 (ddd, J_1=14.0 Hz, J_2=4.5 Hz, J_3=2.0 Hz, 1H), 2.59 (ddd, J_1=14.0 Hz, J_2=12.5 Hz, J_3=4.5 Hz, 1H), 2.94 (ddd, J_1=17.0 Hz, J_2=4.5 Hz, J_3=2.0 Hz, 1H), 3.48 (ddd, J_1=17.0 Hz, J_2=12.5 Hz, J_3=4.5 Hz, 1H), 3.78 (s, 6H, –OCH_3), 3.93 (s, 1H, HC-3), 6.42 (s, 3H), 7.43–7.46 (m, 1H), 7.52–7.58 (m, 4H), 8.17 (s, 1H, HC-3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.4, 30.7, 35.0, 38.2, 42.1, 55.4, 99.6, 107.8, 119.8, 123.6, 128.5, 129.5, 135.0, 138.4, 139.3, 148.9, 160.8, 185.0; IR (KBr) ν_{max}/cm^{-1} 1678; MS (ESI) *m/z* 451 [M–Br]$^+$. Anal. calcd for $C_{23}H_{20}Br_2N_2O_3$: C, 51.90; H, 3.79; N, 5.26; found: C, 51.74; H, 3.68; N, 5.29%.

*2,2-Dibromo-1′-phenyl-3-(3,4,5-trimethoxyphenyl)-6′,7′-dihydrospiro[cyclopropane-1,5′-indazol]-4′(1′*H*)-one* (**3i**): White solid, yield 88%; m.p. 184–186 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.06 (ddd, J_1=14.0 Hz, J_2=4.5 Hz, J_3=2.0 Hz, 1H), 2.59 (ddd, J_1=14.0 Hz, J_2=12.5 Hz, J_3=4.5 Hz, 1H), 2.96 (ddd, J_1=17.0 Hz, J_2=4.5 Hz, J_3=2.0 Hz, 1H), 3.48 (ddd, J_1=17.0 Hz, J_2=12.5 Hz, J_3=4.5 Hz, 1H), 3.84 (s, 3H, –OCH_3), 3.84 (s, 6H, –OCH_3), 3.92 (s, 1H, HC-3), 6.47 (s, 2H), 7.43–7.46 (m, 1H), 7.51–7.58 (m, 4H), 8.17 (s, 1H, HC-3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.4, 30.8, 35.2, 38.2, 42.1, 56.2, 60.9, 106.9, 119.8, 123.6, 128.3, 128.5, 129.5, 137.5, 138.3, 139.2, 148.9, 153.2, 185.1; IR (KBr) ν_{max}/cm^{-1} 1677; MS (ESI) *m/z* 481 [M–Br]$^+$. Anal. calcd for $C_{24}H_{22}Br_2N_2O_4$: C, 51.27; H, 3.94; N, 4.98; found: C, 51.24; H, 3.78; N, 5.12%.

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