Synthesis of cholestan-3-one derivatives possessing a C-2 spiro-oxindole substituent

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A series of C-2 cholestan-3-one spiro-oxindole derivatives were prepared by the 1:3 dipolar cycloaddition reaction between the cholestan-3-one substituted by a C-2 arylidene and the azomethine ylid derived from isatin and sarcosine. The dipolarophiles were efficiently obtained by a Claisen-Schmidt reaction of cholestan-3-one and aromatic aldehydes. The structures of the products were established by a combination of NMR, high-resolution mass spectrometry (HRMS) and X-ray data analysis.

Keywords: 1:3 dipolar cycloaddition, azomethine ylid, cholestan-3-one, steroidal spiro-oxindole

Chemical modification of the steroidal nucleus and side chain often gives products with increased structural diversity and biological activity.[1] In particular, the introduction of a heterocycle onto the steroid skeleton has been a focus for pharmaceutical chemists.[2]

Among the nitrogen heterocycles, spiro-oxindoles have attracted wide attention because of their unique structure and significant bioactivity.[3] The introduction of a spiro-oxindole moiety onto the steroid core has been attempted previously and has led to novel structures with potential activities (Fig. 1).[4–6] Yu Bin *et al*. obtained two groups of anti-proliferative steroidal derivatives by creating a spiro-oxindole structure on ring D and the C-17 side chain (II and III in Fig. 1).

All of these achievements stimulate our interest in constructing more novel steroidal heterocyclic structures, and in this paper we report the synthesis of steroidal spiro-oxindole derivatives obtained by modifying the A-ring of cholestan-3-one (Scheme 1).

Results and discussion

The arylidene-substituted cholestan-3-one (**1**) was efficiently obtained by a Claisen–Schmidt reaction of cholestan-3-one and an aromatic aldehyde.[7] The 1:3 dipolar cycloaddition reaction of the dipolarophile **1** to the azomethine ylid generated *in situ* from isatin and sarcosine yielded steroidal spiro-oxindole derivative **2**.

The structures of **1a–g** were established by examination of their NMR and HRMS data. The positive ESI-HRMS of **1a** gave a quasi-molecular ion peak at *m/z* 505.4039 ([M+H]$^+$), which indicated the addition of 4-methoxyphenyl methylene to cholestan-3-one. The characteristic arylidene proton was found as a singlet at δ 7.54 in the ^{1}H NMR. The protons of the aromatic ring and the 4-methoxyl group were clearly identified as two doublets at δ 7.38, 6.92 and a singlet at δ 3.84, respectively.

The related structures of **2a–g** were established by a combination of HRMS and 1D and 2D NMR data. The positive ESI-HRMS of **2a** exhibited a quasi-molecular ion peak at *m/z* 679.4836 ([M+H]$^+$), implying a molecular formula of $C_{45}H_{62}N_2O_3$. The ^{1}H NMR spectrum of **2a** showed seven methyl proton signals at δ 3.83 (–OCH_3), 2.13 (–NCH_3), 0.86 (CH_3-21), 0.85 × 2 (CH_3-26 and CH_3-27), 0.49 (CH_3-18) and –0.06 (CH_3-19). The upfield shift of CH_3-19 protons probably arose because of the anisotropic effect of the aromatic ring in the spiro-heterocycle moiety. The –NH proton of the oxindole

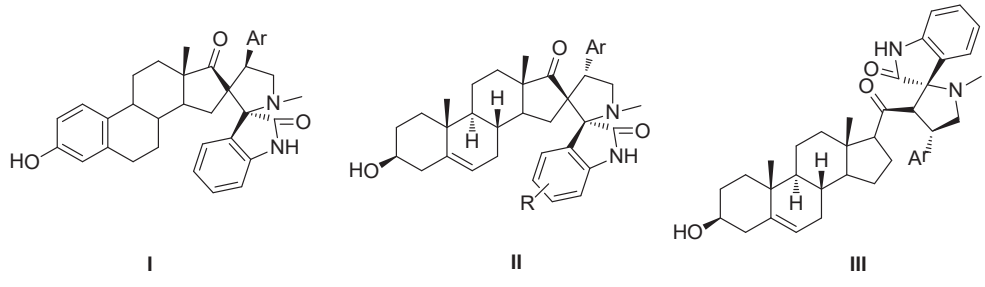
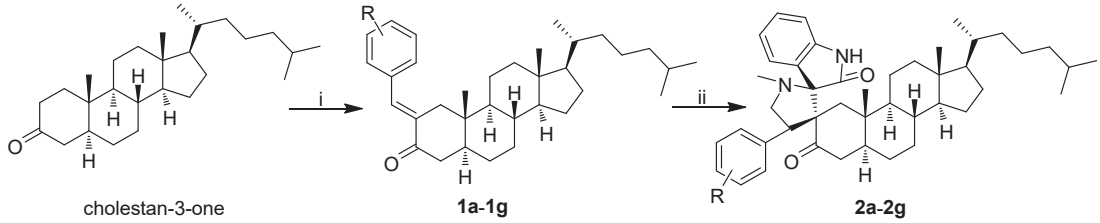


Fig. 1 Steroidal spiro-oxindole derivatives.



Reaction conditions: i; R–C$_6$H$_4$–CHO, NaOH-H_2O methanol, r.t., 24h. ii; isatin, sarcosine, methanol, reflux, 6 h.

R: a, 4-OCH_3; b, 4-SCH_3; c, 4-CH_3; d, 4-H; e, 4-F; f, 4-Cl; g, 4-Br

Scheme 1 Synthesis of cholestan-3-one spiro-oxindole derivatives.

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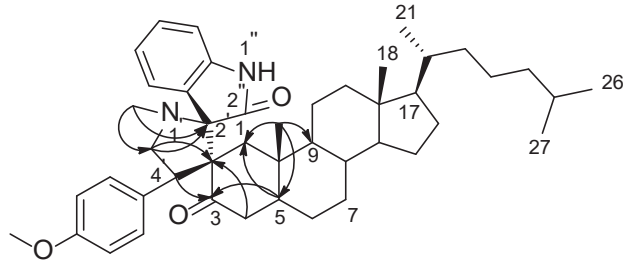

Fig. 2 Partial HMBC correlations of **2a**.

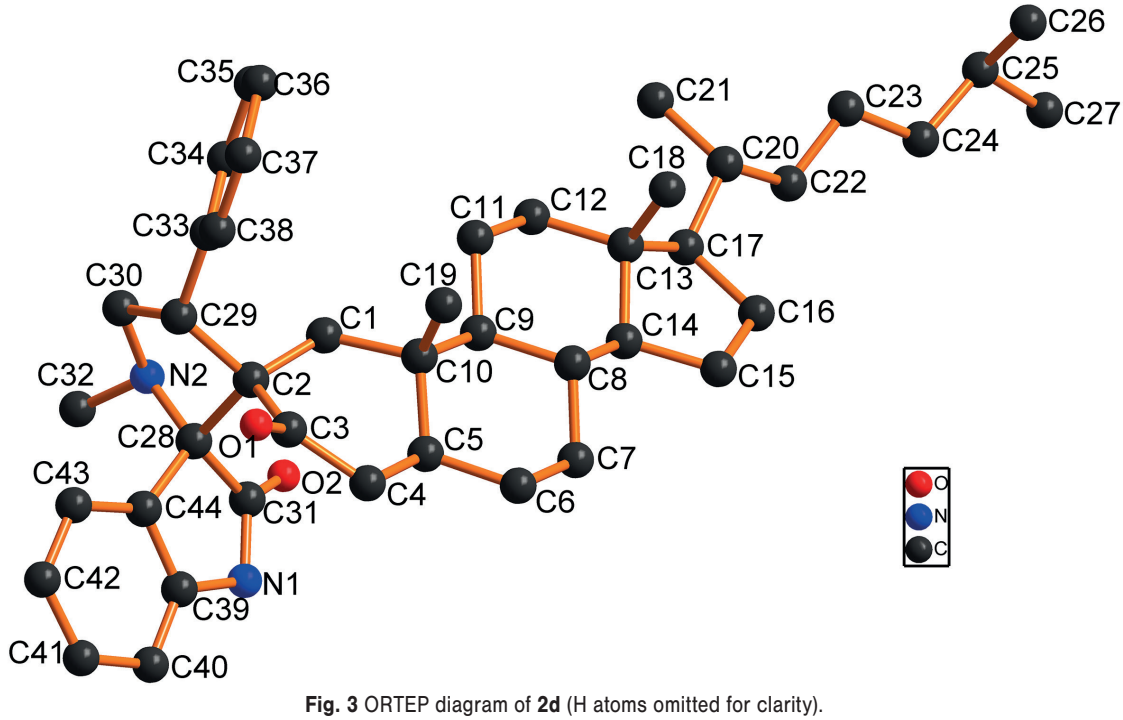

Fig. 3 ORTEP diagram of **2d** (H atoms omitted for clarity).

moiety appeared as a singlet at δ 8.38. The benzylic proton H4' occurred as a triplet at δ 4.71 (J = 8.6 Hz), which confirmed the regiochemistry of the cycloaddition reaction. Otherwise, it would have appeared as a singlet in the ^{1}H NMR spectrum. The H5' protons of the pyrrolidine moiety were identified as two triplets at δ 3.44 (J = 8.6 Hz) and δ 3.78 (J = 8.5 Hz). The carbonyl vicinal protons were identified as a doublet at δ 2.34 (J = 14.6 Hz, H4a) and an overlapping signal at δ 1.83 (m, H4b), and the H5 proton was located at δ 2.00 (m).

The ^{13}C NMR spectrum showed two spiro carbons at δ 64.33 (C2) and δ 80.14 (C2'), and the amide and cyclohexanone carbonyl carbons at δ 179.95 (C2") and δ 212.93 (C3), respectively. The signals at δ 35.19, 41.60 and 53.67 correspond to the carbons of C1, C5 and C9, respectively, in the cyclohexanone ring. The signal at δ 59.95 was assigned to the carbon of CH_2 (C5') in the pyrrolidine ring based on the heteronuclear multiple quantum coherence (HMQC) spectrum. In the heteronuclear multiple bond coherence (HMBC) spectrum, the correlations between the protons of CH_3-19 (δ −0.06) to C1, C5 and C9 were readily observed. The HMBC spectrum showed correlations between the characteristic –NCH_3 proton (δ 2.13) and C2' and C5' in the pyrrolidine ring. The protons of CH_2 (C5') correlated with the spiro carbons C2 and C2'. The H4a proton (δ 2.34) exhibited a correlation with the spiro carbon C2. The H4' (δ 4.71) and H5 (δ 2.00) protons correlated with the cyclohexanone carbonyl carbon C3. All of the HMBC correlations confirm the spiro pyrrolidine heterocycle structure of **2a** (Fig. 2). In addition, a suitable crystal of **2d** was obtained, and the relative structure of the product **2** was supported by X-ray data analysis. No reaction in this paper involved C-10 and C-13 in the starting steroidal skeleton. Since the angular methyl groups, CH_3-18 and CH_3-19, in cholestan-3-one were both initially β-oriented, the absolute configuration of **2** was further established as 2*R*, 5*S*, 8*R*, 9*S*, 10*S*, 13*R*, 14*S*, 17*R*, 20*R*, 2'*R* and 4'*R*, which is shown in Scheme 1 and Figs. 2 and 3.

Conclusion

An efficient synthesis of ring A steroidal spiro-oxindoles from the starting material cholestan-3-one was established by a 1:3 dipolar cycloaddition reaction in a catalyst-free, one-pot procedure. The dipolarophile, cholestan-3-one containing substituent arylidenes, was obtained by an efficient Claisen-Schmidt reaction of cholestan-3-one and an aromatic aldehyde. The dipole, azomethine ylid, was generated *in situ* from isatin and sarcosine. The regioselectivity of this reaction was established by single-crystal X-ray diffraction. This work provides a facile strategy for transforming 3-ketosteroids and allows for further modifications to other steroidal skeleta.

Experimental

All chemical reagents were obtained from commercial suppliers and were used without further purification. All solvents were dried and redistilled before use. TLC analysis was performed with silica gel GF254 plates. Column chromatography was carried out using silica gel (200–300 mesh). All NMR spectra were recorded on a Bruker AV-II 500 MHz NMR spectrometer, operating at 500 MHz for ^{1}H

Table 1 Crystallographic data for **2d**

Empirical formula	$C_{44}H_{60}N_2O_2$
M_r	648.46
Temperature	293(2) K
Crystal system	Monoclinic
Space group	*C2*
Unit cell dimensions	a = 23.1003(18) Å, α = 90° b = 9.8731(16) Å, β = 103.2250(10)° c = 17.7064(2) Å, γ = 90°
Volume	3931.2(5) Å^3
Z	4
Calculated density	1.096 g m^{-3}
Absorption coefficient μ	0.066 mm^{-1}
F(000)	1416
Reflections collected	6016 reflections, 5351 with $I > 2\sigma(I)$ for 439 parameters
Goodness-of-fit on F^2	1.057
Final R indices [I > 2sigma(I)]	R_1 = 0. 0422, wR_2 = 0.1110
R indices (all data)	R_1 = 0.0487, wR_2 = 0.1156

and 125 MHz for ^{13}C. Tetramethylsilane (TMS) was used as internal reference for ^{1}H and ^{13}C chemical shifts and $CDCl_3$ was used as the solvent. All mass spectra were obtained using a Waters ACQUITY UPLC XEVO Q-TOF mass spectrometer. Melting points were measured with a Yanaco MP500 melting point apparatus and are uncorrected. X-ray analysis was performed on a Bruker Apex-II CCD diffractometer.

The crystallographic data for compound **2d** are summarised in Table 1.

*Synthesis of arylidene substituted cholestan-3-one dipolarophiles (***1a–g***); general procedure*

A mixture of cholestan-3-one (200 mg, 0.52 mmol) and *p*-methoxybenzaldehyde (77.5 mg, 0.57 mmol) was dissolved in EtOH (10 mL) and aqueous KOH solution (KOH, 290 mg, 5.2 mmol, 2 mL) was added. The mixture was stirred at room temperature for 24 h. The reaction mixture was then filtered and washed with 50% aqueous EtOH solution. The residue was dried and identified as pure **1a** (234 mg, 92%) by TLC analysis eluted with petroleum ether–ethyl acetate (4:1, v/v). The other arylidene-substituted cholestan-3-one dipolarophiles (**1b–g**) were similarly prepared from the corresponding aromatic aldehydes with yields of 90–95%.

2-(4-Methoxybenzylidene)cholestan-3-one (**1a**)*:* White solid; yield 92%; m.p. 157–159 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (s, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 3.84 (s, 3H), 3.08 (d, *J* = 15.7 Hz, 1H), 2.43 (dd, *J* = 18.7, 5.1 Hz, 1H), 2.21 (dd, *J* = 18.1, 13.9 Hz, 2H), 2.03 (d, *J* = 12.4 Hz, 1H), 1.79 (m, 3H), 1.60–1.44 (m, 5H), 1.36 (m, 5H), 1.28–1.20 (m, 2H), 1.10 (m, 4H), 1.05–0.95 (m, 3H), 0.91 (d, *J* = 6.3 Hz, 3H), 0.86 (d, *J* = 5.6 Hz, 6H), 0.78 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.44, 159.92, 137.22, 133.29, 132.30 × 2, 128.36, 113.91 × 2, 56.38, 56.34, 55.31, 53.72, 42.68, 42.50, 42.15, 42.11, 39.98, 39.51, 36.16, 35.79, 35.78, 35.44, 31.53, 28.70, 28.24, 28.02, 24.25, 23.85, 22.83, 22.57, 21.47, 18.69, 11.98, 11.92; ESI-HRMS: Calcd for $[C_{35}H_{53}O_2]^+$ ([M+H]$^+$): 505.4040; found: 505.4039.

2-[4-Methylthiobenzylidene]cholestan-3-one (**1b**): Light-yellow solid; yield 93%; m.p. 159–161 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.25 (t, *J* = 6.7 Hz, 2H), 3.07 (d, *J* = 15.8 Hz, 1H), 2.50 (s, 3H), 2.44 (dd, *J* = 18.7, 5.0 Hz, 1H), 2.27–2.15 (m, 2H), 2.02 (d, *J* = 12.5 Hz, 1H), 1.88–1.68 (m, 3H), 1.53 (m, 5H), 1.40–1.31 (m, 5H), 1.29–1.18 (m, 3H), 1.10 (m, 4H), 1.04–0.95 (m, 3H), 0.91 (d, *J* = 6.3 Hz, 3H), 0.87 (d, *J* = 5.4 Hz, 6H), 0.78 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.41, 139.85, 136.74, 134.76, 132.24, 130.89 × 2, 125.70 × 2, 56.37, 56.33, 53.67, 42.74, 42.49, 42.26, 42.09, 39.95, 39.51, 36.16, 35.88, 35.78, 35.43, 31.51, 28.69, 28.24, 28.02, 24.24, 23.85, 22.83, 22.57, 21.47, 18.68, 15.23, 11.98, 11.91; ESI-HRMS: Calcd for $[C_{35}H_{52}SONa]^+$ ([M+Na]$^+$): 543.3631; found: 543.3631.

2-(4-Methylbenzylidene)cholestan-3-one (**1c**): White solid; yield 90%; m.p. 165–167 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (s, 1H), 7.30 (d, *J* = 7.5 Hz, 2H), 7.20 (d, *J* = 7.5 Hz, 2H), 3.10 (d, *J* = 15.8 Hz, 1H), 2.44 (dd, *J* = 18.5, 4.6 Hz, 1H), 2.37 (s, 3H), 2.27–2.15 (m, 2H), 2.01 (d, *J* = 12.2 Hz, 1H), 1.88–1.68 (m, 3H), 1.62–1.43 (m, 5H), 1.38–1.29 (m, 5H), 1.28–1.19 (m, 3H), 1.10 (m, 4H), 1.06–0.96 (m, 3H), 0.91 (d, *J* = 6.1 Hz, 3H), 0.87 (d, *J* = 5.4 Hz, 6H), 0.78 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.62, 138.75, 137.30, 134.61, 132.89, 130.47 × 2, 129.13 × 2, 56.38, 56.33, 53.66, 42.80, 42.49, 42.32, 41.99, 39.95, 39.51, 36.16, 35.88, 35.78, 35.43, 31.53, 28.70, 28.24, 28.02, 24.25, 23.85, 22.83, 22.57, 21.45, 21.40, 18.68, 11.98, 11.87; ESI-HRMS: Calcd for $[C_{35}H_{52}ONa]^+$ ([M+Na]$^+$): 511.3910; found: 511.3906.

2-Benzylidenecholestan-3-one (**1d**): White solid; yield 94%; m.p. 125–126 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (s, 1H), 7.39 (d, *J* = 3.3 Hz, 4H), 7.33 (d, *J* = 3.9 Hz, 1H), 3.11 (d, *J* = 15.7 Hz, 1H), 2.45 (dd, *J* = 18.6, 4.7 Hz, 1H), 2.21 (m, 2H), 2.01 (d, *J* = 12.3 Hz, 1H), 1.91–1.70 (m, 4H), 1.61–1.44 (m, 5H), 1.32 (m, 5H), 1.27–1.20 (m, 3H), 1.12 (m, 4H), 0.99 (m, 3H), 0.90 (d, *J* = 6.1 Hz, 3H), 0.87 (d, *J* = 5.3 Hz, 6H), 0.79 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.71, 137.12, 135.73, 135.46, 130.33 × 2, 128.36× 2, 128.12, 56.37, 56.33, 53.63, 42.87, 42.49, 42.41, 41.86, 39.93, 39.51, 36.16, 35.94, 35.78, 35.44, 31.52, 28.69, 28.24, 28.02, 24.24, 23.85, 22.82, 22.57, 21.43, 18.68, 11.97, 11.86; ESI-HRMS: Calcd for $[C_{34}H_{50}ONa]^+$ ([M+Na]$^+$): 497.3754; found: 497.3752.

2-(4-Fluorobenzylidene)cholestan-3-one (**1e**): White solid; yield 92%; m.p. 123–125 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.40–7.34 (m, 2H), 7.08 (t, *J* = 8.5 Hz, 2H), 3.04 (d, *J* = 15.7 Hz, 1H), 2.45 (dd, *J* = 18.6, 5.0 Hz, 1H), 2.23 (m, 1H), 2.16 (m, 1H), 2.02 (d, *J* = 12.6 Hz, 1H), 1.79 (m, 3H), 1.63–1.44 (m, 5H), 1.39–1.29 (m, 5H), 1.28–1.22 (m, 2H), 1.18–1.06 (m, 5H), 0.99 (m, 3H), 0.91 (d, *J* = 6.3 Hz, 3H), 0.87 (d, *J* = 5.1 Hz, 6H), 0.79 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.47, 162.58, 135.96, 135.23, 132.17 × 2, 131.84, 115.49 × 2, 56.35, 56.32, 53.62, 42.80, 42.48, 42.35, 41.83, 39.91, 39.51, 36.15, 35.93, 35.77, 35.43, 31.50, 28.67, 28.23, 28.01, 24.23, 23.84, 22.82, 22.56, 21.45, 18.67, 11.97, 11.88; ESI-HRMS: Calcd for $[C_{34}H_{49}FONa]^+$ ([M+Na]$^+$): 515.3660; found: 515.3658.

2-(4-Chlorobenzylidene)cholestan-3-one (**1f**): White solid; yield 95%; m.p. 146–148 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (s, 1H), 7.36 (d, *J* = 7.9 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 3.03 (d, *J* = 15.6 Hz, 1H), 2.45 (dd, *J* = 18.6, 4.3 Hz, 1H), 2.28–2.19 (m, 2H), 2.15 (d, *J* = 15.5 Hz, 1H), 2.02 (d, *J* = 12.3 Hz, 1H), 1.87–1.68 (m, 4H), 1.51 (m, 5H), 1.34 (m, 5H), 1.25 (m, 2H), 1.15–1.07 (m, 4H), 0.99 (m, 3H), 0.91 (d, *J* = 5.9 Hz, 3H), 0.87 (d, *J* = 5.1 Hz, 6H), 0.78 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.42, 136.04, 135.68, 134.44, 134.16, 131.48 × 2, 128.64 × 2, 56.34, 56.32, 53.59, 42.83, 42.48, 42.40, 41.84, 39.89, 39.51, 36.15, 35.98, 35.77, 35.42, 31.49, 28.67, 28.23, 28.01, 24.23, 23.84, 22.82, 22.57, 21.45, 18.67, 11.97, 11.87; ESI-HRMS: Calcd for $[C_{34}H_{49}ClONa]^+$ ([M+Na]$^+$): 531.3364; found: 531.3359.

2-(4-Bromobenzylidene)cholestan-3-one (**1g**): Light-yellow solid; yield 90%; m.p. 113–115 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.1 Hz, 2H), 7.45 (s, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 3.02 (d, *J* = 15.7 Hz, 1H), 2.45 (dd, *J* = 18.6, 4.8 Hz, 1H), 2.23 (dd, *J* = 18.4, 13.4 Hz, 1H), 2.14 (d, *J* = 15.5 Hz, 1H), 2.02 (d, *J* = 12.5 Hz, 1H), 1.88–1.68 (m, 3H), 1.62–1.44 (m, 5H), 1.33 (m, 5H), 1.29–1.21 (m, 3H), 1.13 (m, 5H), 1.05–0.94 (m, 3H), 0.90 (d, *J* = 6.2 Hz, 3H), 0.86 (d, *J* = 5.5 Hz, 6H), 0.78 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.43, 136.17, 135.69, 134.60, 131.71, 131.60, 122.75, 56.34, 56.31, 53.58, 42.84, 42.48, 42.42, 41.84, 39.89, 39.51, 36.16, 35.99, 35.77, 35.42, 31.49, 28.67, 28.23, 28.01, 24.23, 23.84, 22.83, 22.57, 21.45, 18.67, 11.97, 11.87; ESI-HRMS: Calcd for $[C_{34}H_{49}BrONa]^+$ ([M+Na]$^+$): 575.2859; found: 575.2863.

Synthesis of cholestan-3-one spiro-oxindole derivatives (**2a–g**)*; general procedure*

A solution of **1a** (100 mg, 0.2 mmol) in methanol (4 mL) was treated with isatin (44 mg, 0.3 mmol) and sarcosine (27 mg, 0.3 mmol). The

solution was refluxed (approx. 6 h) to afford the cycloadduct. After completion of the reaction, as monitored by TLC analysis eluted with petroleum ether–ethyl acetate (3:1, v/v), the solvent was evaporated under reduced pressure. The residue was sub*J*ected to silica gel (50 g) column chromatography and eluted with petroleum ether–ethyl acetate (3:1, v/v) to afford the product **2a** (103 mg) in 77 % yield. Using a similar procedure, the other steroidal spiro-oxindoles derivatives (**2b**–**g**) were prepared from the corresponding steroidal dipolarophiles (**1b**–**g**) with yields in the range 67–82%.

[2′.2]-1′-Methyl-2′-(indolin-2-one)-4′-(4″-methoxyphenyl)-tetrahydro-1H-pyrrolo-cholestan-3-one (**2a**): White solid; yield 77%; m.p. 189–191 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (s, 1H), 7.47 (d, *J* = 7.8 Hz, 2H), 7.28 (t, *J* = 8.8 Hz, 1H), 7.19 (d, *J* = 6.8 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 7.0 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 2H), 4.71 (t, *J* = 8.6 Hz, 1H), 3.83 (s, 3H), 3.78 (t, *J* = 8.5 Hz, 1H), 3.44 (t, *J* = 8.6 Hz, 1H), 2.34 (d, *J* = 14.6 Hz, 1H), 2.13 (s, 3H), 2.00 (m, 1H), 1.83 (m, 3H), 1.50 (m, 1H), 1.44 (m, 2H), 1.29 (m, 3H), 1.24–1.04 (m, 7H), 1.02–0.90 (m, 4H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.4 Hz, 6H), 0.79–0.69 (m, 1H), 0.68–0.59 (m, 1H), 0.54 (m, 1H), 0.50 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.93, 179.95, 158.66, 141.15, 132.77 × 2, 129.75, 127.84, 125.77, 125.14, 122.97, 113.48 × 2, 110.02, 80.14, 64.33, 59.69, 56.46, 56.40, 55.48, 53.67, 49.68, 44.33, 42.53, 41.60, 40.05, 39.99, 39.63, 36.28, 35.89, 35.59, 35.25, 35.19, 31.15, 28.55, 28.29, 28.13, 24.19, 24.00, 22.95, 22.69, 20.95, 18.75, 12.09, 11.81; ESI-HRMS: Calcd for $[C_{45}H_{63}N_2O_3]^+$ ([M+H]$^+$): 679.4833; found: 679.4836.

[2′.2]-1′-Methyl-2′-(indolin-2-one)-4′-(4″-methylthiophenyl)-tetrahydro-1H-pyrrolo-cholestan-3-one (**2b**): Light-yellow solid; yield 72%; m.p. 195–197 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 1H),7.23 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 6.4 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 7.2 Hz, 1H), 4.71 (t, *J* = 8.8 Hz, 1H), 3.78 (t, *J* = 8.6 Hz, 1H), 3.43 (t, *J* = 8.4 Hz, 1H), 2.48 (s, 3H), 2.27 (d, *J* = 14.7 Hz, 1H), 2.12 (s, 3H), 1.98 (m, 1H), 1.91–1.75 (m, 3H), 1.77–1.69 (m, 1H), 1.63 (s, 1H), 1.53–1.36 (m, 4H), 1.35–1.23 (m, 3H), 1.23–1.04 (m, 7H), 1.02–0.90 (m, 5H), 0.86 (d, *J* = 6.4 Hz, 6H), 0.85 (d, *J* = 6.4 Hz, 3H), 0.80 – 0.72 (m, 1H), 0.65 (m, 1H), 0.54 (m, 1H), 0.51 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.61, 178.09, 157.04, 140.99, 136.81, 132.09 × 2, 131.08, 129.67, 127.70, 126.54 × 2, 122.87, 109.90, 79.91, 64.30, 59.39, 56.33, 56.25, 53.48, 49.76, 44.16, 42.41, 41.41, 39.96, 39.83, 39.50, 36.15, 35.76, 35.45, 35.13, 35.06, 31.02, 28.41, 28.17, 28.00, 24.07, 23.87, 22.82, 22.57, 20.83, 18.63, 16.28, 11.97, 11.81; ESI-HRMS: Calcd for $[C_{45}H_{63}N_2SO_2]^+$ ([M+H]$^+$): 695.4605; found: 695.4608.

[2′.2]-1′-Methyl-2′-(indolin-2-one)-4′-(4″-methylphenyl)-tetrahydro-1H-pyrrolo-cholestan-3-one (**2c**): White solid; yield 67%; m.p. 204–205 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.39 (d, *J* = 7.3 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 5.1 Hz, 1H), 7.12 (d, *J* = 7.3 Hz, 2H), 7.05 (t, *J* = 7.1 Hz, 1H), 6.86 (d, *J* = 6.6 Hz, 1H), 4.73 (t, *J* = 8.2 Hz, 1H), 4.73 (t, *J* = 8.2 Hz, 1H), 3.81 (t, *J* = 8.4 Hz, 1H), 3.81 (t, *J* = 8.4 Hz, 1H), 3.42 (t, *J* = 8.6 Hz, 1H), 3.42 (t, *J* = 8.6 Hz, 1H), 2.35 (s, 3H), 2.30 (d, *J* = 15.1 Hz, 1H), 2.12 (s, 3H), 1.96 (m, 1H), 1.90–1.78 (m, 3H), 1.73 (s, 1H), 1.61 (s, 1H), 1.55–1.37 (m, 4H), 1.29 (m, 3H), 1.15 (m, 5H), 0.98 (m, 5H), 0.86 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 6.4 Hz, 6H), 0.78–0.70 (m, 1H), 0.66 (m, 1H), 0.56 (m, 1H), 0.49 (s, 3H), −0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.57, 178.30, 156.93, 140.91, 136.48, 131.45 × 2, 130.48, 129.58, 128.66 × 2, 127.76, 122.81, 109.82, 79.92, 64.40, 59.33, 56.31, 56.24, 53.52, 49.71, 44.15, 42.41, 41.36, 39.87, 39.81, 39.51, 36.15, 35.78, 35.50, 35.15, 35.01, 31.04, 28.43, 28.17, 28.00, 24.07, 23.88, 22.82, 22.57, 21.14, 20.77, 18.64, 11.96, 11.70; ESI-HRMS: Calcd for $[C_{45}H_{63}N_2O_2]^+$ ([M+H]$^+$): 663.4884; found: 663.4887.

[2′.2]-1′-Methyl-2′-(indolin-2-one)-4′-(4″-phenyl)-tetrahydro-1H-pyrrolo-cholestan-3-one (**2d**): White solid; yield 75%; m.p. 215–217 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.52 (t, *J* = 7.0 Hz, 2H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 7.0 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 7.5 Hz, 1H), 4.70 (t, *J* = 9.0 Hz, 1H), 3.77 (t, *J* = 9.1 Hz, 1H), 3.48 (t, *J* = 8.9 Hz, 1H), 2.27 (d, *J* = 14.8 Hz, 1H), 2.13 (s, 3H), 2.00 (m, 1H), 1.84 (m, 2H), 1.75 (m, 2H), 1.55–1.38 (m, 4H), 1.36–1.25 (m, 4H), 1.20–1.07 (m, 7H), 1.03–0.89 (m, 6H), 0.86 (d, *J* = 6.3 Hz, 9H), 0.78–0.70 (m, 1H), 0.69–0.60 (m, 1H), 0.52 (m, 1H), 0.49 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.83, 178.21, 141.11, 135.27, 133.24 × 2, 129.76, 127.66, 125.35, 122.94, 114.76 × 2, 109.89, 79.97, 63.99, 59.87, 56.33, 56.27, 56.22, 53.44, 49.76, 44.23, 42.39, 41.61, 40.27, 39.81, 39.50, 36.16, 35.76, 35.33, 35.10, 35.05, 30.99, 28.35, 28.16, 28.00, 24.06, 23.87, 22.81, 22.56, 20.78, 18.60, 11.92, 11.70; ESI-HRMS: Calcd for $[C_{44}H_{61}N_2O_2]^+$ ([M+H]$^+$): 649.4728; found: 649.4730.

[2′.2]-1′-Methyl-2′-(indolin-2-one)-4′-(4″-fluorophenyl)-tetrahydro-1H-pyrrolo-cholestan-3-one (**2e**): White solid; yield 70%; m.p. 194–197 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (brs, 1H), 7.52 (dd, *J* = 7.2, 6.0 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 6.8 Hz, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 7.02 (t, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 7.5 Hz, 1H), 4.70 (t, *J* = 9.0 Hz, 1H), 3.77 (t, *J* = 9.1 Hz, 1H), 3.48 (t, *J* = 8.8 Hz, 1H), 2.27 (d, *J* = 14.8 Hz, 1H), 2.12 (s, 3H), 2.00 (m, 1H), 1.84 (m, 2H), 1.74 (m, 2H), 1.63 (m, 1H), 1.55–1.47 (m, 1H), 1.43 (m, 2H), 1.29 (m, 3H), 1.20–1.05 (m, 7H), 1.02–0.89 (m, 6H), 0.85 (d, *J* = 6.5 Hz, 9H), 0.76–0.59 (m, 2H), 0.53 (m, 1H), 0.49 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.86, 178.58, 162.05, 141.28, 135.38, 133.34 × 2, 129.88, 127.76, 125.51, 123.05, 114.87 × 2, 110.12, 80.13, 64.16, 59.89, 56.47, 56.38, 53.60, 49.78, 44.33, 42.51, 41.69, 40.27, 39.96, 39.63, 36.29, 35.88, 35.48, 35.21, 35.17, 31.23, 28.49, 28.28, 28.13, 24.16, 23.99, 22.94, 22.69, 20.92, 18.74, 12.04, 11.84; ESI-HRMS: Calcd for $[C_{44}H_{60}FN_2O_2]^+$ ([M+H]$^+$): 667.4633; found: 667.4634.

[2′.2]-1′-Methyl-2′-(indolin-2-one)-4′-(4″-chlorophenyl)-tetrahydro-1H-pyrrolo-cholestan-3-one (**2f**): White solid; yield 82%; m.p. 172–174 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.50 (d, *J* = 7.6 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.28 (t, *J* = 6.8 Hz, 1H), 7.16 (d, *J* = 6.4 Hz, 1H), 7.07 (t, *J* = 6.8 Hz, 1H), 6.89 (d, *J* = 6.7 Hz, 1H), 4.70 (t, *J* = 8.3 Hz, 1H), 3.77 (t, *J* = 8.2 Hz, 1H), 3.46 (t, *J* = 9.0 Hz, 1H), 2.25 (d, *J* = 14.7 Hz, 1H), 2.12 (s, 3H), 2.01 (m, 1H), 1.89–1.78 (m, 3H), 1.73 (s, 1H), 1.59–1.37 (m, 4H), 1.33–1.25 (m, 4H), 1.23–1.07 (m, 8H), 1.03–0.92 (m, 5H), 0.86 (d, *J* = 5.3 Hz, 9H), 0.74 (m, 1H), 0.63 (m, 1H), 0.54 (m, 1H), 0.50 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.89, 178.41, 141.18, 138.17, 133.16 × 2, 132.90, 129.94, 128.21 × 2, 127.73, 125.33, 123.08, 110.09, 80.05, 64.02, 59.76, 56.39, 56.38, 53.54, 49.93, 44.28, 42.46, 41.62, 40.25, 39.89, 39.59, 36.23, 35.85, 35.47, 35.15, 35.14, 31.07, 28.46, 28.26, 28.12, 24.14, 23.95, 22.95, 22.69, 20.88, 18.71, 12.05, 11.90; ESI-HRMS: Calcd for $[C_{44}H_{60}ClN_2O_2]^+$ ([M+H]$^+$): 683.4338; found: 683.4340.

[2′.2]-1′-Methyl-2′-(indolin-2-one)-4′-(4″-bromophenyl)-tetrahydro-1H-pyrrolo-cholestan-3-one (**2g**): Light-yellow solid; yield 78%; m.p. 153–155 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ7.94 (s, 1H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.16 (d, *J* = 6.5 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 7.3 Hz, 1H), 4.69 (t, *J* = 8.8 Hz, 1H), 3.75 (t, *J* = 8.9 Hz, 1H), 3.46 (d, *J* = 8.5 Hz, 1H), 2.22 (d, *J* = 14.8 Hz, 1H), 2.12 (s, 3H), 1.99 (m, 1H), 1.83 (m, 3H), 1.78–1.69 (m, 1H), 1.57–1.38 (m, 4H), 1.37–1.24 (m, 4H), 1.23–1.08 (m, 8H), 1.03–0.92 (m, 5H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 6H), 0.81–0.71 (m, 1H), 0.65 (m, 1H), 0.54 (m, 1H), 0.51 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 212.70, 178.20, 141.17, 138.74, 133.54 × 2, 131.21 × 2, 129.94, 127.81, 125.48, 123.09, 121.18, 110.03, 80.01, 64.17, 59.69, 56.47, 56.42 , 53.62, 49.96, 44.29, 42.54, 41.60, 40.35, 39.95, 39.64, 36.29, 35.89, 35.49, 35.25, 35.19, 31.15, 28.52, 28.29, 28.13, 24.20, 24.00, 22.95, 22.70, 20.94, 18.76, 12.10, 11.98; ESI-HRMS: Calcd for $[C_{44}H_{60}BrN_2O_2]^+$ ([M+H]$^+$): 727.3833; found: 727.3837.

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Electronic Supplementary Information

CCDC 1524376 contains the supplementary crystallographic data for this paper, which can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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