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Synthesis of novel 16-spiro steroids: 7-(Aryl)tetrahydro-1*H*-pyrrolo [1,2-*c*][1,3]thiazolo estrone hybrid heterocycles

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ABSTRACT

The 1,3-dipolar cycloaddition of azomethine ylides generated *in situ* from the reaction of isatins or acenaphthylene-1,2-dione and 1,3-thiazolane-4-carboxylic acid to various exocyclic dipolarophiles synthesized from estrone afforded a library of novel C-16 spiro oxindole or acenaphthylene-1-one – 7-(aryl)tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]thiazole – estrone hybrid heterocycles. These reactions occur regio- and stereo-selectively affording a single isomer of the spiro estrones in excellent yields with the formation of two C–C and one C–N bonds along with the generation of four new contiguous stereo-centers in a single step.

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1. Introduction

Steroids form a group of structurally related compounds widely distributed in nature and posses a broad spectrum of biological activities. Synthetic derivatives of steroids have also attracted a good deal of attention for the purpose of developing lead compounds to treat several diseases. In particular, the syntheses of steroids comprising heterocycles have received much attention of the chemists since many of such compounds have been shown to display important pharmacological properties [1].

Spiro steroids are ubiquitous in nature, for instance spirostanes, which include a spiro-acetal moiety in the structure have been shown to posses significant biological properties [2]. Further, it is noteworthy that investigations pertaining to the synthesis of steroids comprising a spiro heterocycle at C-17 [3] have gained much importance whereas the reports on the synthesis of C-16 spiro heterocyclic steroids are scarce [4]. The known C-16 spiro steroids are the cycloalkano derivatives [5], dioxaphosphorinanes [6], pyrazolines [7] and pyrrolidines [8]. In general, 1,3-dipolar cycloadditions offer a facile route towards the construction of spiro heterocycles and in particular, the cycloaddition of azomethine ylides to exocyclic olefins are among the best employed protocol for the construction of spiro-pyrrolidines, pyrrolizines, pyrrolothiazoles and octahydroindolizines [9]. Recently, we reported the synthesis of novel C-16 spiro steroids comprising *trans*-androsterone/dehydroandrosterone–tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]thiazole hybrid heterocycles [10] via 1,3-dipolar cycloaddition. In view of our continuous interest in synthesizing hybrid C-16 spiro steroids, we herein report for the first time the synthesis of novel C-16 spiro pyrrolo[1,2-*c*][1,3]thiazole containing estrone hybrid heterocycles.

Incidentally, estrone is a very vital steroid that has key role in many biological processes. Numerous methods for the synthesis of modified estrone derivatives have been reported in view of their wide range of biological applications. For instance, estrone derivatives are used as potent inhibitors of 17β-hydroxysteroid dehydrogenase type1 [11], steroid sulfatase inhibitors [12] and also exhibits antiproliferative [13], anticancer [14], antimicrobial and antifungal activities [15]. Many of the drugs for menopausal estrogen therapy contain estrone core [16].

2. Experimental

The melting points were measured in open capillary tubes and are uncorrected. The ^{1}H, ^{13}C and the 2D NMR spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as internal standard and $CDCl_3$ as solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in Hertz. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer. The single crystal X-ray data of **2b** were collected on Enraf–Nonius (CAD4) diffractometer with Mo Kα ($\lambda = 0.71073$ Å) radiation. Scan range was $2.02° \leqslant \theta \leqslant 24.97°$. SHELXTL software was used for structure solution and refinement. Silica gel-G plates (Merck) were used for tlc analysis with a mixture of petroleum ether (60–80 °C) and ethyl acetate as eluent.

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All the chemicals were purchased from Aldrich and used without any further purification.

2.1. General procedure for the synthesis of 16-(E)-arylidene-estrones **2**

A mixture of estrone **1** (1 mmol) and aromatic aldehyde (1 mmol) were dissolved in ethanol (5 mL) to which an alcoholic solution of potassium hydroxide (20%) was added. The mixture was refluxed on an oil bath with continuous stirring for 5 h and the progress of the reaction was monitored by TLC intermittently. After completion of the reaction, the mixture was allowed to cool. The precipitated solid was filtered, washed with water (100 mL) and dried under vacuum to afford the product **2** as yellow solid. The yields of the 16-(*E*)-arylidene-estrones **2** were almost quantitative except for the loss during work-up.

2.2. General procedure for the synthesis of spiro[5′.3″]oxindole/acenaphthylene-1″-one-spiro[6′.16]-7′-(aryl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrones **3**–**5**

A mixture of **2** (1 mmol), isatin/5-chloro-isatin/acenaphthylene-1,2-dione (1.1 mmol) and 1,3-thiazolane-4-carboxylic acid (1.2 mmol) were taken in isopropanol (10 mL) and boiled to reflux for 3 h. The progress of the reaction was monitored by TLC. After completion of the reaction as evident from TLC, the reaction mixture was poured into ice water (50 mL). The resultant precipitate was filtered, dried and purified by flash filtration column on silica gel employing petroleum ether/ethyl acetate (90:10) as eluting solvent to get the products **3**, **4** or **5**.

2.2.1. Spiro[5′.3″]oxindole-spiro[6′.16]-7′-(phenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**3a**)

Isolated as pure white solid; yield 82%; mp 185–186 °C; Anal. Calcd. for $C_{36}H_{36}N_2O_3S$: C, 74.97; H, 6.29; N, 4.86. Found: C, 74.89; H, 6.38; N, 4.80. ^{1}H NMR 0.32 (s, 3H), 0.50–0.60 (m, 1H), 0.95–0.97 (m, 1H), 1.04–1.18 (m, 2H), 1.23–1.33 (m, 1H), 1.60–1.61 (m, 2H), 1.62–1.68 (m, 2H), 1.80–1.84 (m, 1H), 2.01–2.05 (m, 1H), 2.50–2.51 (m, 1H), 2.54–2.69 (m, 2H), 2.82–2.95 (m, 2H), 3.63 (d, *J* = 6.6 Hz, 1H), 3.64 (d, *J* = 6.6 Hz, 1H), 3.73 (d, *J* = 9.6 Hz, 1H), 4.74–4.81 (m, 2H), 6.48 (d, *J* = 2.4 Hz, 1H), 6.54 (dd, *J* = 8.1, 2.4 Hz, 1H), 6.77 (d, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 7.04–7.34 (m, 7H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.60 (s, 1H). ^{13}C NMR 14.3, 25.2, 26.5, 29.0, 31.3, 31.4, 33.5, 36.9, 44.0, 47.2, 48.4, 55.1, 72.2, 72.7, 74.6, 109.7, 112.7, 115.3, 115.6, 122.3, 125.7, 126.0, 127.5, 128.5, 129.5, 129.8, 131.6, 137.1, 137.7, 140.6, 153.4, 179.1 and 219.5.

2.2.2. Spiro[5′.3″]oxindole-spiro[6′.16]-7′-(4-chlorophenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**3b**)

Isolated as white solid; yield 84%; mp 200–201 °C; Anal. Calcd. for $C_{36}H_{35}ClN_2O_3S$: C, 70.74; H, 5.77; N, 4.58. Found: C, 70.71; H, 5.73; N, 4.54. ^{1}H NMR 0.39 (s, 3H), 0.49–0.56 (m, 1H), 0.73–0.75 (m, 1H), 0.98–1.06 (m, 2H), 1.15–1.20 (m, 2H), 1.26–1.42 (m, 1H), 1.60–1.67 (m, 2H), 1.79–1.82 (m, 1H), 2.02–2.06 (m, 1H), 2.43 (d, *J* = 9.3 Hz, 1H), 2.71 (m, 2H), 2.79–2.91 (m, 2H), 3.59 (dd, *J* = 12.9, 6.0 Hz, 2H), 4.68–4.74 (m, 2H), 6.49 (d, *J* = 2.4 Hz, 1H), 6.55 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 9.6 Hz, 1H) 7.06 (t, *J* = 7.5 Hz, 1H), 7.21–7.39 (m, 6H), 7.57 (s, 1H). ^{13}C NMR 14.7, 25.3, 26.6, 29.1, 31.2, 33.1, 36.9, 44.1, 47.1, 47.2, 54.3, 72.2, 72.7, 74.3, 109.6, 112.8, 115.3, 122.6, 125.8, 126.1, 128.9, 129.4, 129.9, 131.3, 133.4, 136.1, 137.7, 140.7, 153.5, 178.5 and 219.7.

2.2.3. Spiro[5′.3″]oxindole-spiro[6′.16]-7′-(4-fluorophenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**3c**)

Isolated as white solid; yield 81%; mp 190–191 °C; Anal. Calcd. for $C_{36}H_{35}FN_2O_3S$: C, 72.70; H, 5.93; N, 4.71. Found: C, 72.67; H, 5.90; N, 4.68. ^{1}H NMR 0.33 (s, 3H), 0.49–0.59 (m, 1H), 0.95–1.05 (m, 1H), 1.10–1.20 (m, 2H), 1.23–1.28 (m, 1H), 1.60–1.61 (m, 2H), 1.62–1.66 (m, 2H), 1.80–1.82 (m, 1H), 2.00–2.04 (m, 1H), 2.48–2.51 (m, 1H), 2.64–2.67 (m, 2H), 2.80–2.93 (m, 2H), 3.61 (m, 2H), 3.70 (d, *J* = 9.6 Hz, 1H), 4.71 (dt, *J* = 7.6, 6.6 Hz, 1H), 5.06 (s, 1H), 6.47 (d, *J* = 2.4 Hz, 1H), 6.55 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 7.00–7.25 (m, 6H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.85 (s, 1H). ^{13}C NMR 14.6, 26.4, 28.8, 31.1, 31.3, 33.2, 34.4, 36.7, 40.3, 43.8, 47.2, 54.2, 72.1, 72.5, 74.3, 109.6, 112.6, 115.2, 115.5, 121.3, 122.3, 125.5, 125.8, 129.3, 129.7, 131.4, 132.8, 136.4, 137.5, 140.5, 153.3, 178.9 and 219.4.

2.2.4. Spiro[5′.3″]oxindole-spiro[6′.16]-7′-(4-bromophenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**3d**)

Isolated as white solid; yield 80%; mp 290–291 °C; Anal. Calcd. for $C_{36}H_{35}BrN_2O_3S$: C, 65.95; H, 5.38; N, 4.27. Found: C, 65.87; H, 5.49; N, 4.12. ^{1}H NMR 0.39 (s, 3H), 0.48–0.57 (m, 1H), 0.96–1.01 (m, 1H), 1.08–1.15 (m, 2H), 1.21–1.29 (m, 1H), 1.60–1.61 (m, 2H), 1.63–1.67 (m, 2H), 1.80–1.83 (m, 1H), 2.00–2.04 (m, 1H), 2.41–2.48 (m, 1H), 2.55–2.73 (m, 2H), 2.82–2.87 (m, 2H), 3.56 (d, *J* = 6.0 Hz, 1H), 3.61 (d, *J* = 6 Hz, 1H), 3.67 (m, 1H), 4.72 (dt, *J* = 7.6, 6.6, 1H), 4.96 (s, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 6.55 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 7.03–7.26 (m, 5H), 7.37 (d, *J* = 7.5 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.67 (s, 1H). ^{13}C NMR 14.7, 25.2, 26.5, 28.9, 31.1, 31.3, 33.0, 34.3, 36.8, 44.0, 47.1, 54.3, 72.1, 72.6, 74.5 109.5, 112.7, 115.2, 115.4, 121.5, 122.6, 125.8, 126.0, 129.3, 129.8, 131.5, 131.8, 136.6, 137.7, 140.7, 153.4, 178.3 and 219.7.

2.2.5. Spiro[5′.3″]oxindole-spiro[6′.16]-7′-(4-methylphenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**3e**)

Isolated as white solid; yield 85%; mp 199–200 °C; Anal. Calcd. for $C_{37}H_{38}N_2O_3S$: C, 75.22; H, 6.48; N, 4.74. Found: C, 75.34; H, 6.57; N, 4.79. ^{1}H NMR 0.33 (s, 3H), 0.52–0.59 (m, 1H), 0.95–0.97 (m, 1H), 1.00–1.18 (m, 2H), 1.23–1.33 (m, 1H), 1.59–1.74 (m, 4H), 1.81–1.84 (m, 1H), 1.99–2.04 (m, 1H), 2.33 (s, 3H), 2.51–2.56 (m, 1H), 2.64–2.67 (m, 2H), 2.80–2.95 (m, 2H), 3.61 (d, *J* = 6.6 Hz, 1H), 3.64 (d, *J* = 6.6 Hz, 1H), 3.70 (d, *J* = 9.6 Hz, 1H), 4.74 (dt, *J* = 6.6, 9.3 Hz, 1H), 5.03 (s, 1H), 6.55 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.77 (d, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 8.1, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.03–7.26 (m, 7H), 7.80 (s, 1H). ^{13}C NMR 14.3, 25.3, 26.5, 30.0, 31.3, 31.5, 33.7, 34.6, 44.0, 47.3, 47.4, 54.3, 55.0, 72.4, 72.8, 74.6, 109.8, 112.7, 113.4, 115.4, 122.3, 125.7, 126.0, 129.3, 129.5, 129.8, 131.6, 133.8, 137.2, 137.6, 140.6, 153.4, 179.5 and 220.0.

2.2.6. Spiro[5′.3″]oxindole-spiro[6′.16]-7′-(4-methoxyphenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**3f**)

Isolated as white solid; yield 86%; mp 214–215 °C; Anal. Calcd. for $C_{37}H_{38}N_2O_4S$: C, 73.24; H, 6.31; N, 4.62. Found: C, 73.12; H, 6.23; N, 4.69. ^{1}H NMR 0.29 (s, 3H), 0.52–0.60 (m, 1H), 0.95–1.00 (m, 1H), 1.03–1.18 (m, 2H), 1.23–1.30 (m, 1H), 1.60–1.61 (m, 2H), 1.62–1.70 (m, 2H), 1.80–1.83 (m, 1H), 1.99–2.04 (m, 1H), 2.52–2.57 (m, 1H), 2.63–2.65 (m, 2H), 2.80–2.96 (m, 2H), 3.61 (d, *J* = 6.9 Hz, 1H), 3.65 (d, *J* = 6.9, 1H), 3.69 (d, *J* = 9.6 Hz, 1H), 3.78 (s, 3H), 4.71 (dt, *J* = 6.0, 9.9 Hz, 1H), 5.34 (s, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 6.55 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 7.03–7.25 (m, 6H), 7.50 (d, *J* = 7.8 Hz, 1H), 8.03 (s, 1H). ^{13}C NMR 14.2, 25.0, 26.3, 28.8, 30.9, 31.2, 32.7, 36.6, 43.7, 46.5, 47.0, 54.7, 71.8, 72.5, 72.9, 73.7, 109.3, 112.5, 113.5, 115.0, 121.3, 125.4, 125.4, 128.4, 129.2, 130.0, 130.5, 134.0, 137.0, 141.8, 154.5, 158.4, 178.1 and 219.7.

*2.2.7. Spiro[5′.3″]oxindole-spiro[6′.16]-7′-(4-N,N-dimethylphenyl) tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**3g**)*

Isolated as white solid; yield 83%; mp 199–201 °C; Anal. Calcd. for $C_{38}H_{41}N_3O_3S$: C, 73.64; H, 6.67; N, 6.78. Found: C, 73.62; H, 6.78; N, 6.67. ^{1}H NMR 0.39 (s, 3H), 0.50–0.60 (m, 1H), 0.91–0.98 (m, 3H), 1.04–1, 13 (m, 2H), 1.13–1.30 (m, 1H), 1.55–1.72 (m, 2H), 1.60–1.62 (m, 2H), 1.79–1.82 (m, 1H), 2.05–2.10 (m, 1H), 2.49–2.53 (m, 1H), 2.63–2.67 (m, 2H), 2.81–2.95 (m, 2H), 3.03 (s, 6H), 3.60–3.69 (m, 3H), 4.68–4.73 (m, 1H), 5.09 (s, 1H), 6.54 (d, *J* = 8.4 Hz, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 6.72 (d, *J* = 9 Hz, 1H), 6.77 (d, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.20–7.23 (m, 4H), 7.43 (s, 1H), 7.49 (d, *J* = 9 Hz, 1H). ^{13}C NMR 14.7, 26.1, 26.8, 29.2, 29.5, 31.9, 32.6, 38.1, 40.1, 44.2, 46.2, 47.6, 49.0, 72.7, 73.3, 74.1, 111.1, 112.9, 115.3, 123.6, 124.2, 125.4, 126.4, 127.2, 128.3, 129.7, 131.0, 132.2, 132.4, 134.1, 138.0, 151.0, 153.6 and 210.0.

*2.2.8. Spiro[5′.3″]oxindole-spiro[6′.16]-7′-(2-chlorophenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**3h**)*

Isolated as white solid; yield 82%; mp 198–200 °C; Anal. Calcd. for $C_{36}H_{35}ClN_2O_3S$: C, 70.74; H, 5.77; N, 4.58. Found: C, 70.63; H, 5.70; N, 4.66. ^{1}H NMR 0.38 (s, 3H), 0.54–0.66 (m, 1H), 0.90–0.97 (m, 1H), 1.01–1.17 (m, 2H), 1.22–1.33 (m, 1H), 1.53–1.69 (m, 2H), 1.60–1.61 (m, 2H), 1.99–2.03 (m, 2H), 2.26–2.29 (m, 1H) 2.68–2.73 (m, 2H), 2.80–2.94 (m, 2H), 3.48 (d, *J* = 5.1 Hz, 1H), 3.62 (d, *J* = 5.1 Hz, 1H), 4.46 (d, *J* = 8.7 Hz, 1H), 4.70–4.74 (m, 2H), 6.48 (d, *J* = 2.7 Hz, 1H), 6.55 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.76 (d, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 7.03–7.07 (m, 1H), 7.17–7.23 (m, 2H), 7.33–7.37 (m, 3H), 7.53 (s, 1H), 7.91 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR 15.4, 25.0, 26.5, 28.9, 30.8, 32.3, 33.0, 36.7, 43.9, 46.5, 47.4, 49.0, 72.1, 72.5, 73.4, 109.5, 112.7, 115.1, 122.7, 125.9, 127.0, 128.1, 129.1, 129.3, 131.2, 131.5, 135.0, 135.9, 137.4, 141.1, 153.4, 178.4 and 219.5.

*2.2.9. Spiro[5′.3″]oxindole-spiro[6′.16]-7′-(2-methylphenyl) tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**3i**)*

Isolated as white solid; yield 83%; mp 199–200 °C; Anal. Calcd. for $C_{37}H_{38}N_2O_3S$: C, 75.22; H, 6.48; N, 4.74. Found: C, 73.34; H, 6.32; N, 4.63. ^{1}H NMR 0.43 (s, 3H), 0.55–0.62 (m, 1H), 0.95–0.99 (m, 1H), 1.03–1.19 (m, 2H), 1.23–1.32 (m, 1H), 1.60–1.61 (m, 2H), 1.62–1.67 (m, 2H), 1.80–1.81 (m, 1H), 1.90–2.04 (m, 2H), 2.24 (s, 3H), 2.63–2.69 (m, 2H), 2.80–2.86 (m, 2H), 3.53 (d, *J* = 5.7 Hz, 1H), 3,64 (d, *J* = 5.7 Hz, 1H), 4.15 (d, *J* = 9.3 Hz, 1H), 4.75–4.77 (m, 1H), 4.80 (s, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 6.55 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.76 (d, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 7.03–7.08 (m, 1H), 7.13–7.15 (m, 2H), 7.18–7.21 (m, 2H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.66 (s, 1H), 7.69 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR 14.7, 19.9, 25.2, 26.6, 29.0, 31.0, 32.7, 36.8, 44.0, 46.5, 46.8, 47.3, 49.2, 72.8, 73.5, 73.9, 109.5, 112.6, 115.2 122.6, 126.0, 126.2, 126.8, 129.3, 129.7, 130.4, 131.5, 135.9, 137.2, 137.6, 141.0, 153.4, 178.4 and 220.2.

*2.2.10. Spiro[5′.3″]oxindole-spiro[6′.16]-7′-(2-methoxyphenyl) tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**3j**)*

Isolated as white solid; yield 84%; mp 212–214 °C; Anal. Calcd. for $C_{37}H_{38}N_2O_4S$: C, 73.24; H, 6.31; N, 4.62. Found: C, 73.10; H, 6.39; N, 4.67. ^{1}H NMR 0.31–0.43 (m, 1H), 0.45 (s, 3H), 0.90–0.97 (m, 1H), 1.00–1.14 (m, 2H), 1.20–1.32 (m, 1H), 1.58–1.68 (m, 4H), 1.85–1.91 (m, 2H), 1.97–2.02 (m, 1H), 2.23–2.26 (m, 2H), 2.59–2.63 (m, 2H), 3.51 (d, *J* = 5.4 Hz, 1H), 3.62 (d, *J* = 6.0 Hz, 1H), 3.69 (s, 3H), 4.35 (d, *J* = 9.9 Hz, 1H), 4.77–4.85 (m, 1H), 5.10 (s, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 6.56 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 7.2 Hz, 1H), 7.17–7.24 (m, 2H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.85 (s, 1H). ^{13}C NMR 14.9, 25.2, 26.6, 28.9, 31.1, 32.4, 32.6, 36.9, 44.1, 44.7, 46.8, 47.2, 55.0, 72.0, 72.8, 74.6, 109.1, 110.1, 112.6, 115.1, 120.7, 122.5, 125.9, 126.5, 126.7, 127.9, 129.5, 130.4, 131.7, 137.7, 141.1, 153.3, 177.9 and 219.6.

*2.2.11. Spiro[5′.3″]oxindole-spiro[6′.16]-7′-(2-fluorophenyl) tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**3k**)*

Isolated as white solid; yield 81%; mp 192–194 °C; Anal. Calcd. for $C_{36}H_{35}FN_2O_3S$: C, 72.70; H, 5.93; N, 4.71. Found: C, 72.60; H, 5.98; N, 4.62. ^{1}H NMR 0.47 (s, 3H), 0.51–0.55 (m, 2H), 0.90–1.00 (m, 2H), 1.02–1.15 (m, 2H), 1.21–1.34 (m, 1H), 1.58–1.68 (m, 3H), 2.86–2.88 (m, 2H), 2.34–2.39 (m, 1H), 1.96–2.04 (m, 2H), 1.62–1.71 (m, 2H), 1.22–1.30 (m, 2H), 1.98–2.05 (m, 1H), 2.26–2.29 (m, 2H), 2.52–2.68 (m, 2H), 3.52 (d, *J* = 5.4 Hz, 1H), 3.62 (d, *J* = 5.4 Hz, 1H), 4.15–4.20 (m, 1H), 4.80 (s, 1H), 6.54 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H),7.03–7.07 (m, 2H), 7.20–7.26 (m, 5H), 7.47–7.48 (m, 1H), 7.84 (s, 1H). ^{13}C NMR 14.9, 25.2, 26.5, 26.9, 28.9, 30.4, 31.2, 31.5, 33.2, 36.8, 44.0, 46.6, 47.3, 72.4, 74.8, 109.5, 112.7, 115.2, 115.7, 122.7, 124.4, 126.0, 127.3, 128.6, 129.4, 129.8, 131.5, 137.0, 137.6, 140.7, 153.4, 179.0 and 219.8.

*2.2.12. Spiro[5′.3″]oxindole-spiro[6′.16]-7′-(3-fluorophenyl) tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**3l**)*

Isolated as white solid; yield 82%; mp 192–194 °C; Anal. Calcd. for $C_{36}H_{35}FN_2O_3S$: C, 72.70; H, 5.93; N, 4.71. Found: C, 72.65; H, 5.90; N, 4.75. ^{1}H NMR 0.40 (s, 3H), 0.53–0.56 (m, 1H), 0.95–0.97 (m, 1H), 1.02–1.15 (m, 2H), 1.17–1.30 (m, 1H), 1.57–1.69 (m, 4H), 1.82–1.84 (m, 1H), 2.01–2.05 (m, 1H), 2.49 (d, *J* = 9.3 Hz, 1H), 2.60–2.69 (m, 2H), 2.81–2.94 (m, 2H), 3.58–3.62 (m, 2H), 3.71 (d, *J* = 9.6 Hz, 1H), 4.69–4.75 (m, 1H), 4.88 (s, 1H), 6.48 (d, *J* = 2.7 Hz, 1H), 6.55 (dd, *J* = 11.1, 2.7 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.95 (d, *J* = 9.0 Hz, 1H), 7.00–7.02 (m, 1H), 7.03–7.09 (m, 1H), 7.21–7.24 (m, 2H), 7.29–7.35 (m, 2H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.74 (s, 1H). ^{13}C NMR 14.6, 25.3, 26.6, 29.0, 31.2, 31.4, 33.2, 36.9, 44.0, 47.2, 47.7, 54.6, 72.0, 72.6, 74.5, 109.7, 112.7, 114.4, 114.7, 115.3, 122.6, 125.7, 126.0, 129.4, 129.9, 131.6, 133.4, 137.7, 140.8, 141.3, 153.4, 178.8 and 219.8.

*2.2.13. Spiro[5′.3″]oxindole-spiro[6′.16]-7′-(2,4-dichlorophenyl) tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**3m**)*

Isolated as white solid; yield 83%; mp 195–197 °C; Anal. Calcd. for $C_{36}H_{34}Cl_2N_2O_3S$: C, 66.97; H, 5.31; N, 4.34. Found: C, 66.91; H, 5.39; N, 4.30. ^{1}H NMR 0.38–0.46 (m, 1H), 0.60 (s, 3H), 0.92–0.97 (m, 2H), 1.11–1.16 (m, 2H), 1.25–1.31 (m, 1H), 1.59–1.74 (m, 4H), 1.99–2.04 (m, 1H), 2.25 (d, *J* = 9.3 Hz, 1H), 2.67–2.70 (m, 2H), 2.79–2.93 (m, 2H), 3.46 (d, *J* = 5.1 Hz, 1H), 3.61 (d, *J* = 5.1 Hz, 1H), 4.40 (d, *J* = 8.4 Hz, 1H), 4.62–4.69 (m, 1H), 4.97 (s, 1H), 6.49–6.51 (m, 1H), 6.55–6.58 (m, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 1H), 7.02–7.08 (m, 1H), 7.21–7.23 (m, 2H), 7.30–7.38 (m, 1H), 7.74 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR 15.7, 25.2, 26.9, 29.1, 31.0, 32.4, 33.3, 36.8, 44.1, 45.5, 46.7, 48.7, 71.0, 72.5, 73.5, 109.6, 112.8, 115.3, 123.0, 126.0, 127.7, 129.1, 130.0, 131.5, 132.7, 133.4, 135.0, 135.7, 137.6, 141.2, 153.5, 178.3 and 219.0.

*2.2.14. Spiro[5′.3″]oxindole-spiro[6′.16]-7′-(3,4-dimethoxyphenyl) tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**3n**)*

Isolated as white solid; yield 85%; mp 213–215 °C; Anal. Calcd. for $C_{38}H_{40}N_2O_5S$: C, 71.67; H, 6.33; N, 4.40. Found: C, 71.61; H, 6.26; N, 4.45. ^{1}H NMR 0.35 (s, 3H), 0.54–0.57 (m, 1H), 0.90–1.00 (m, 2H), 1.15–1.26 (m, 2H), 1.57–1.65 (m, 4H), 1.74–1.77 (m, 2H), 1.99–2.04 (m, 2H), 2.46–2.49 (m, 1H), 2.62–2.64 (m, 2H), 2.84–2.93 (m, 2H), 3.62–3.67 (m, 2H), 3.87 (s, 6H), 4.71–4.75 (m, 1H), 6.47 (s, 1H), 6.54 (d, *J* = 8.1 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 7.03–7.08 (m, 3H), 7.21–7.26 (m, 3H), 7.39–7.42 (m, 1H), 8.14 (s, 1H). ^{13}C NMR 14.5, 25.3, 26.5, 26.8, 28.9, 31.3, 33.4, 34.6, 36.9, 44.0, 47.1, 47.3, 54.8, 55.7, 72.2, 72.7,

74.5, 109.6, 109.8, 111.1, 112.7, 115.3, 122.3, 125.9, 129.3, 129.9, 131.3, 137.6, 140.8, 148.2, 148.3, 148.9, 153.6, 179.0 and 220.2.

*2.2.15. Spiro[5′.3″]oxindole-spiro[6′.16]-7′-(naphthyl)-tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**3o**)*

Isolated as white solid; yield 81%; mp 192–194 °C; Anal. Calcd. for $C_{40}H_{38}N_2O_3S$: C, 76.65; H, 6.11; N, 4.47. Found: C, 76.71; H, 6.18; N, 4.42. ^{1}H NMR 0.18 (s, 3H), 0.37–0.41 (m, 1H), 0.90–0.99 (m, 1H), 1.01–1.19 (m, 2H), 1.20–1.25 (m, 1H), 1.60–1.61 (m, 2H), 1.62–1.70 (m, 2H), 1.94–1.98 (m, 2H), 2.36–2.41 (m, 1H), 2.56–2.62 (m, 2H), 2.81–2.84 (m, 2H), 3.57 (d, *J* = 5.4 Hz, 1H), 3.68 (d, *J* = 5.4 Hz, 1H), 4.70 (d, *J* = 4.7 Hz, 1H), 4.79 (s, 1H), 4.99–5.05 (m, 1H), 6.52 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.64 (m, 1H), 6.74 (m, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 7.71 (s, 1H), 7.07–7.12 (m, 1H), 7.37–7.60 (m, 4H), 7.77–7.96 (m, 4H). ^{13}C NMR 15.5, 25.2, 26.6, 26.9, 28.9, 31.0, 32.6, 36.8, 40.6, 44.1, 46.4, 47.4, 73.2, 73.5, 74.0, 109.8, 112.8, 115.3, 122.8, 123.5, 125.6, 126.0, 126.4, 127.3, 128.8, 129.3, 129.9, 131.5, 132.8, 133.8, 134.1, 137.6, 141.2, 153.4, 178.6 and 220.1.

*2.2.16. Spiro[5′.3″]-5″-chloro-oxindole-spiro[6′.16]-7′-(phenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**4a**)*

Isolated as white solid; yield 83%; mp 206–208 °C; Anal. Calcd. for $C_{36}H_{35}ClN_2O_3S$: C, 70.74; H, 5.77; N, 4.58. Found: C, 70.65; H, 5.72; N, 4.61. ^{1}H NMR 0.20 (s, 3H), 0.54–0.59 (m, 2H), 0.95–1.28 (m, 3H), 1.60–1.62 (m, 2H), 1.64–1.68 (m, 2H), 1.82 (s, 1H), 2.01–2.16 (m, 2H), 2.56–2.63 (m, 2H), 2.85 (dd, *J* = 10.2, 5.7 Hz, 1H), 2.96 (dd, *J* = 10.2, 5.7 Hz, 1H), 3.57 (d, *J* = 7.5 Hz, 1H), 3.65–3.75 (m, 2H), 4.70–474 (m, 1H), 5.76 (s, 1H), 6.45 (d, *J* = 2.7 Hz, 1H), 6.56 (dd, *J* = 8.4, 5.7 Hz, 1H), 7.23 (d, *J* = 2.4 Hz, 1H), 7.01–7.07 (m, 2H), 7.24–7.32 (m, 5H),7.63 (d, *J* = 2.1 Hz, 1H). ^{13}C NMR 14.0, 21.0, 25.2, 26.8, 31.3, 34.5, 36.9, 44.1, 47.0, 48.2, 55.2, 60.4, 72.6, 74.8, 76.5, 110.3, 110.4, 112.7, 115.2, 120.5, 125.9, 127.4, 127.9, 128.6, 129.5, 129.8, 131.4, 137.7, 139.3, 153.5, 155.6, 175.4 and 129.8.

*2.2.17. Spiro[5′.3″]-5″-chloro-oxindole-spiro[6′.16]-7′-(4-chlorophenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**4b**)*

Isolated as white solid; yield 86%; mp 118–220 °C; Anal. Calcd. for $C_{36}H_{34}Cl_2N_2O_3S$: C, 66.97; H, 5.31; N, 4.34. Found: C, 67.09; H, 5.37; N, 4.31. ^{1}H NMR 0.33 (s, 3H), 0.56–0.62 (m, 2H), 0.97–1.04 (m, 2H), 1.08–1.30 (m, 2H), 1.60–1.73 (m, 3H), 2.05–2.10 (m, 2H), 2.48–2.53 (m, 1H), 2.79–2.85 (m, 2H), 2.88–2.94 (m, 2H), 3.56–3.68 (m, 2H), 4.65–4.68 (m, 2H), 5.09 (s, 1H), 6.47–6.48 (m, 1H), 6.53–6.57 (m, 2H), 6.74 (d, *J* = 8.1 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 7.22–7.27 (m, 2H), 7.31–7.35 (m, 1H), 7.48–7.50 (m, 1H), 8.11 (s, 1H). ^{13}C NMR 19.4, 31.2, 33.7, 35.7, 36.0, 37.4, 41.6, 41.6, 48.8, 51,4, 51.7, 52.0, 58.7, 76.9, 77.6, 78.3, 110.8, 115.6, 117.6, 120.0, 130.4, 131.7, 132.2, 134.4, 134.6, 137.9, 138.9, 141.0, 141.9, 145.8, 159.6, 182.5 and 219.8.

*2.2.18. Spiro[5′.3″]-5″-chloro-oxindole-spiro[6′.16]-7′-(4-fluorophenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**4c**)*

Isolated as white solid; yield 83%; mp 213–215 °C; Anal. Calcd. for $C_{36}H_{34}ClFN_2O_3S$: C, 68.72; H, 5.45; N, 4.45. Found: C, 68.67; H, 5.51; N, 4.40. ^{1}H NMR 0.31 (s, 3H), 0.60–0.67 (m, 1H), 0.96–1.00 (m, 1H), 1.06–1.25 (m, 3H), 1.38–1.43 (m, 2H), 1.60–167 (m, 2H), 1.82–1.86 (m, 1H), 2.11–2.06 (m, 2H), 2.51–2.69 (m, 3H), 2.81–2.95 (m, 1H), 3.56 (d, *J* = 6.9 Hz, 1H), 3.64–3.70 (m, 2H), 4.63–4.70 (m, 1H), 4.89 (s, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 6.55 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.72 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 7.01–7.07 (m, 1H), 7.23–7.25 (m, 2H), 7.52 (d, *J* = 7.2 Hz, 1H), 7.59 (d, *J* = 6.2 Hz, 1H), 7.79 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR 14.4, 21.6, 25.3, 26.5, 26.8, 28.9, 33.2, 36.9, 44.1, 47.3, 47.6, 54.4, 63.4, 72.2, 72.7, 73.6, 110.2, 112.7, 115.3, 121.1, 125.9, 127.3, 128.0, 128.9, 129.7, 131.5, 137.7, 139.2, 153.4, 156.5, 164.2, 172.6 and 218.7.

*2.2.19. Spiro[5′.3″]-5″-chloro-oxindole-spiro[6′.16]-7′-(4-bromophenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**4d**)*

Isolated as white solid; yield 82%; mp 223–225 °C; Anal. Calcd. for $C_{36}H_{34}BrClN_2O_3S$: C, 62.66; H, 4.97; N, 4.06. Found: C, 62.61; H, 4.99; N, 4.03. ^{1}H NMR 0.33 (s, 3H), 0.53–0.64 (m, 2H), 0.98–1.05 (m, 2H), 1.05–1.26 (m, 3H), 1.60–1.74 (m, 3H), 2.06–2.10 (m, 2H), 2.52 (d, *J* = 11.1 Hz, 1H), 2.63–2.68 (m, 2H), 2.82–2.92 (m, 2H), 3.58–3.68 (m, 2H), 4.61–4.72 (m, 1H), 5.299 (s, 1H), 6.42–6.58 (m, 2H), 6.60 (d, *J* = 8.2 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 7.24–7.27 (m, 2H), 7.43–7.50 (m, 3H). ^{13}C NMR 14.6, 21.3, 25.3, 26.6, 28.9, 30.8, 31.2, 33.0, 36.9, 44.2, 47.3, 47.5, 54.4, 72.1, 72.7, 74.2, 110.3, 112.7, 115.3, 126.0, 128.2, 129.4, 129.7, 131.5, 131.8, 136.3, 137.6, 139.1, 153.4, 155.6, 164.4, 177.8 and 219.3.

*2.2.20. Spiro[5′.3″]-5″-chloro-oxindole-spiro[6′.16]-7′-(4-methylphenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**4e**)*

Isolated as white solid; yield 83%; mp 199–201 °C; Anal. Calcd. for $C_{37}H_{37}ClN_2O_3S$: C, 71.08; H, 5.96; N, 4.48. Found: C, 71.20; H, 5.91; N, 4.55. ^{1}H NMR 0.41 (s, 3H), 0.47–0.56 (m, 2H), 1.10–1.34 (m,6H), 1.61–1.82 (m,5H), 2.04–2.07 (d, *J* = 7.6 Hz, 1H), 2.46–2.52 (m, 2H), 2.77–2.89 (m, 3H), 3.61–3.66 (m, 2H), 4.14 (d, *J* = 9.6 Hz, 1H), 4.68–4.75 (m, 1H), 5.06 (s, 1H), 6.47 (d, *J* = 1.8 Hz, 1H), 6.55–6.58 (m 2H), 6.74 (d, *J* = 8.1 Hz, 1H) 6.96 (d, *J* = 8.7 Hz, 1H) 7.14–7.15 (m, 2H), 7.22–7.25 (m, 1H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR 14.2, 21.0, 25.3, 26.5, 28.9, 29.7, 31.4, 33.6, 36.9, 44.1, 47.3, 47.7, 55.0, 71.8, 72.4, 76.5, 110.3, 112.7, 115.2, 126.0, 127.6, 127.9, 129.3, 129.6, 129.9, 131.7, 133.6, 137.3, 137.7, 138.9, 153.4, 178.4 and 218.6.

*2.2.21. Spiro[5′.3″]-5″-chloro-oxindole-spiro[6′.16]-7′-(4-methyoxyphenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**4f**)*

Isolated as white solid; yield 83%; mp 226–228 °C; Anal. Calcd. for $C_{37}H_{37}ClN_2O_4S$: C, 69.30; H, 5.82; N, 4.37. Found: C, 69.36; H, 5.90; N, 4.40. ^{1}H NMR 0.52 (s, 3H), 0.85–0.89 (m, 1H), 0.90–1.09 (m, 1H), 1.05–1.17 (m, 2H), 1.25–1.27 (m, 2H), 1.39–1.46 (m, 1H), 1.62–1.68 (m, 2H), 1.69–1.73 (m,1H), 1.82–1.86 (m, 1H), 2.04–2.09 (m, 2H), 2.17–2.67 (m, 1H), 2.51–2.56 (m, 2H), 2.83–2.91 (m, 2H), 3.48 (d, *J* = 6.8 Hz, 1H), 3.58 (d, *J* = 6.8 Hz, 1H), 3.69 (s, 3H), 4.73–4.81 (m, 1H), 4.95 (s, 1H), 6.44 (d, *J* = 2.4 Hz, 1H), 6.55 (m, 2H), 6.71 (d, *J* = 6.9 Hz, 1H) 6.82 (d, *J* = 7.2 Hz, 1H), 6.91–7.05 (m, 2H), 7.15–7.26 (m, 2H), 7.52 (d, *J* = 6.9 Hz, 1H), 7.69 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR 7.86, 14.6, 22.3, 25.4, 26.8, 29.1, 29.3, 32.2, 33.6, 37.0, 44.4, 47.4, 53.4, 55.2, 71.2, 71.8, 72.7, 110.1, 111.0, 112.8, 115.4, 120.9, 125.2, 126.2, 126.5, 128.4, 129.6, 129.9, 130.1, 130.6, 131.8, 132.5, 156.2, 172.1, 218.9.

*2.2.22. Spiro[5′.3″]-5″-chloro-oxindole-spiro[6′.16]-7′-(2-chlorophenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**4h**)*

Isolated as white solid; yield 83%; mp 213–215 °C; Anal. Calcd. for $C_{36}H_{34}Cl_2N_2O_3S$: C, 66.97; H, 5.31; N, 4.34. Found: C, 66.90; H, 5.40; N, 4.38. ^{1}H NMR 0.60 (s, 3H), 0.94–0.99 (m, 2H), 1.09–1.19 (m, 2H), 1.25–1.46 (m, 3H), 1.59–1.80 (m, 3H), 2.05–2.16 (m, 2H), 2.27 (dd, *J* = 12.9, 3.6 Hz, 1H), 2.61–2.67 (m, 2H), 2.74–2.89 (m, 1H), 3.47 (d, *J* = 5.4 Hz, 1H), 3.59 (d, *J* = 5.1 Hz, 1H), 4.57 (d, *J* = 8.7 Hz, 1H), 4.68–4.70 (m, 1H), 4.85 (s, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 6.55–6.59 (m, 1H) 6.73 (d, *J* = 8.1 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 1H), 7.12–7.37 (m, 4H), 7.85–7.88 (m, 2H). ^{13}C NMR 15.5, 25.2, 26.7, 29.0, 32.3, 32.9, 36.8, 44.2, 45.4, 47.1, 47.6, 49.0, 72.8, 73.2,

73.5, 110.4, 112.8, 115.2, 126.1, 127.1, 128.0, 128.4, 128.6, 129.5, 129.8, 131.4, 131.6, 135.4, 137.5, 139.6, 153.4, 177.7 and 219.4.

*2.2.23. Spiro[5′.3″]-5″-chloro-oxindole-spiro[6′.16]-7′-(2-methylphenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**4i**)*

Isolated as white solid; yield 83%; mp 202–204 °C; Anal. Calcd. for $C_{37}H_{37}ClN_2O_3S$: C, 71.08; H, 5.96; N, 4.48. Found: C, 71.01; H, 6.08; N, 4.37. ^{1}H NMR 0.41 (s, 3H), 0.47–0.55 (m, 2H), 0.90–1.02 (m, 2H), 1.10–1.34 (m, 2H), 1.61–1.81 (m, 4H), 2.05–2.09 (m, 2H), 2.24 (s, 3H), 2.46–2,52 (m, 1H), 2.77–2.83 (m, 2H), 2.85–2.88 (m, 1H), 3.55 (d, *J* = 5.7 Hz, 1H), 3.60 (d, *J* = 5.7 Hz, 1H), 4.67–4.75 (m, 2H), 5.15 (s, 1H), 6.46–6.47 (m, 1H), 6.56 (d, *J* = 8.7 Hz, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 6.94–6.97 (m, 1H), 7.14–7.15 (m, 2H), 7.22–7.25 (m, 2H), 7.40 (s, 1H), 7.62 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR 14.5, 19.9, 25.2, 26.6, 28.9, 31.8, 32.8, 36.9, 44.1, 47.0, 47.4, 49.3, 72.7, 73.5, 74.3, 110.6, 112.8, 115.3, 126.1, 126.2, 127.0, 128.0, 128.2, 129.7, 129.9, 130.6, 131.5, 135.4, 137.4, 137.6, 139.4, 153.4, 178.4 and 219.2.

*2.2.24. Spiro[5′.3″]-5″-chloro-oxindole-spiro[6′.16]-7′-(2-fluorophenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**4k**)*

Isolated as white solid; yield 81%; mp 221–223 °C; Anal. Calcd. for $C_{36}H_{34}ClFN_2O_3S$: C, 68.72; H, 5.45; N, 4.45. Found: C, 68.58; H, 5.41; N, 4.43. ^{1}H NMR 0.54 (s, 3H), 0.60–0.67 (m, 1H), 0.95–1.12 (m, 2H), 1.25–1.30 (m, 2H), 1.38–1.43 (m, 2H), 1.6–1.62 (m, 1H), 1.71–1.98 (m, 2H), 2.01–2.16 (m, 2H), 2.23–2.31 (m, 1H), 2.62–2.66 (m, 2H), 2.84–2.90 (m, 1H), 3.56 (d, *J* = 6.9 Hz, 2H), 4.41–4.49 (m, 2H), 4.73 (s, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 6.41–6.58 (m, 2H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.95–7.00 (m, 2H), 7.03–7.15 (m, 2H), 7.22–7.33 (m, 1H). ^{13}C NMR 15.2, 25.2, 26.6, 26.8, 28.9, 31.8, 36.9, 44.2, 47.4, 52.1, 52.9, 58.3, 77.1, 77.6, 77.9, 110.2, 112.7, 115,7, 120.3, 124.5, 126.0, 128.1, 129.7, 131,5, 153.4, 153.4, 153.4, 177.3, 197.2 and 220.3.

*2.2.25. Spiro[5′.3″]-5″-chloro-oxindole-spiro[6′.16]-7′-(3-fluorophenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**4l**)*

Isolated as white solid; yield 81%; mp 209–212 °C; Anal. Calcd. for $C_{36}H_{34}ClFN_2O_3S$: C, 68.72; H, 5.45; N, 4.45. Found: C, 68.64; H, 5.52; N, 4.42. ^{1}H NMR 0.34 (s, 3H), 0.62–0.68 (m, 1H), 0.95–1.00 (m, 2H), 1.09–1.17 (m, 2H), 1.20–1.33 (m, 1H), 1.38–1.43 (m, 1H), 1.59–1.79 (m, 3H), 2.01–2.06 (m, 2H), 2.54–2.61 (m, 2H), 2.81–2.97 (m, 2H), 3.56 (d, *J* = 6.4 Hz, 1H), 3.63–3.72 (m, 2H), 4.66–4.69 (m, 1H), 4.94 (s, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 6.54 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.92–7.33 (m, 6H), 7.51 (d, *J* = 1.8 Hz, 1H). ^{13}C NMR 1 4.0, 24.6, 25.9, 28.4, 30.4, 30.6, 32.1, 36.3, 43.4, 46.3, 46.6, 53.7, 71.5, 72.2, 73.0, 110.3, 112.3, 114.6, 115.6, 125.1, 126.2, 126.9, 128.0, 128.9, 129.1, 136.5, 138.8, 139.2, 154.3, 177.1 and 219.4.

*2.2.26. Spiro[5′.3″]-5″-chloro-oxindole-spiro[6′.16]-7′-(2,4-dichlorophenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**4m**)*

Isolated as white solid; yield 84%; mp 228–230 °C; Anal. Calcd. for $C_{36}H_{33}Cl_3N_2O_3S$: C, 63.58; H, 4.89; N, 4.12. Found: C, 63.50; H, 4.83; N, 4.18. ^{1}H NMR 0.62 (s, 3H), 0.94–1.04 (m, 1H), 1.01–1.18 (m, 2H), 1.24–1.29 (m, 1H), 1.42–1.45 (m, 1H), 1.61–1.67 (m, 2H), 1.61–1.70 (m, 3H), 2.02–2.09 (m, 2H), 2.20–2.27 (m, 1H), 2.70–2.78 (m, 2H), 2.80–2.91 (m, 2H), 3.44 (d, *J* = 1.8 Hz, 1H), 3.57 (d, *J* = 5.1 Hz, 1H), 4.58–4.68 (m, 1H), 5.21 (s, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 6.56 (m, 1H), 6.77 (d, *J* = 7.8 Hz, 1H) 6.84 (d, *J* = 8.4 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 7.21–7.26 (m, 1H), 7.31–7.35 (m, 1H), 7.39 (d, *J* = 2.1 Hz, 1H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR 15.6, 22.5, 25.2, 26.7, 28.9, 29.6, 30.9, 32.1, 33.1, 36.8, 44.2, 47.5, 48.6, 72.8, 73.6, 110.4, 112.8, 115.2, 126.1, 127.6, 127.9, 128.6, 129.2, 129.5, 129.8, 131.4, 132.6, 133.5, 135.7, 137.5, 139.6, 153.5, 177.5 and 218.7.

*2.2.27. Spiro[5′.2″]acenaphthylene-1″-one-spiro[16.6′]-7′-(phenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**5a**)*

Isolated as white solid; yield 81%; mp 178–181 °C; Anal. Calcd. for $C_{40}H_{37}NO_3S$: C, 78.53; H, 6.10; N, 2.29. Found: C, 78.45; H, 6.17; N, 2.37. ^{1}H NMR 0.30 (s, 3H), 0.65–0.70 (m, 1H), 1.03–1.19 (m, 2H), 1.24–1.28 (m, 2H), 1.41–1.46 (m, 1H), 1.60–1.62 (m, 2H), 1.65–1.88 (m, 2H), 2.50–2.66 (m, 1H), 2.06–2.68 (m, 3H), 2.92–3.13 (m, 2H), 3.67 (d, *J* = 8.1 Hz, 1H), 3.83 (d, *J* = 8.1 Hz, 1H), 3.90 (d, *J* = 9.9 Hz, 1H), 4.76–4.82 (m, 2H), 6.46–6.53 (m, 2H), 6.86 (d, *J* = 8.4 Hz, 1H), 7.27–7.33 (m, 4H), 7.66–7.76 (m, 2H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.60 (m, 2H), 8.10 (d, *J* = 7.2 Hz, 1H), 7.907.47 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR 13.9, 25.0, 26.2, 28.8, 28.9, 31.4, 34.6, 36.8, 43.9, 47.2, 48.2, 50.1, 56.1, 71.9, 72.7, 80.0, 112.5, 115.2, 120.7, 125.4, 125.8, 126.1, 127.5, 127.7, 128.3, 128.5, 129.9, 130.5, 131.6, 131.7, 132.1, 132.7, 233.4, 134.7, 136.9, 137.8, 141.2, 153.4, 205.9 and 218.7.

*2.2.28. Spiro[5′.2″]acenaphthylene-1″-one-spiro[16.6′]-7′-(4-chlorophenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**5b**)*

Isolated as white solid; yield 82%; mp 199–200 °C; Anal. Calcd. for $C_{40}H_{36}ClNO_3S$: C, 74.34; H, 5.61; N, 2.17. Found: C, 74.44; H, 5.52; N, 2.25. ^{1}H NMR 0.16 (s, 3H), 0.51–0.60 (m, 1H), 0.95–1.37 (m, 3H), 1.60–1.62 (m, 2H), 1.64–1.68 (m, 2H), 1.84–1.89 (m, 1H), 2.45–2.52 (m, 1H), 2.63–2.66 (m, 2H), 2.88–3.08 (m, 2H), 3.76 (d, *J* = 7.5 Hz, 1H), 3.75 (d, *J* = 7.5 Hz, 1H), 3.84 (d, *J* = 9.9 Hz, 1H), 3.67 (m, 1H), 4.77–4.84 (m, 1H), 4.53 (s, 1H), 6.46–6.51 (m, 2H), 6.86 (d, *J* = 8.1 Hz, 1H), 7.27–7.33 (m, 6H), 7.68–7.74 (m, 4H), 8.10 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR 14.2, 24.9, 26.0, 28.8, 29.3, 31.2, 34.1, 36.6, 43.8, 47.0, 49.2, 50.4, 55.1, 72.1, 72.7, 79.2, 112.4, 115.1, 120.7, 125.4, 125.7, 125.9, 126.1, 127.7, 128.2, 128.7, 130.4, 131.1, 131.3, 131.6, 132.1, 133.3, 134.6, 135.7, 137.6, 141.3, 153.4, 206.0 and 219.3.

*2.2.29. Spiro[5′.2″]acenaphthylene-1″-one-spiro[16.6′]-7′-(4-bromophenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**5d**)*

Isolated as white solid; yield 79%; mp 176–178 °C; Anal. Calcd. for $C_{40}H_{36}BrNO_3S$: C, 69.56; H, 5.25; N, 2.03. Found: C, 69.50; H, 5.15; N, 2.09. ^{1}H NMR 0.37 (s, 3H), 0.48–0.59 (m, 1H), 0.96–1.18 (m, 2H), 1.21–1.88 (m, 3H), 1.60–167 (m, 4H), 2.04–2.66 (m, 4H), 2.88–3.07 (m, 2H), 3.65–3.84 (m, 4H), 4.57 (s, 1H), 6.45–6.52 (m, 2H), 6.86 (d, *J* = 8.4 Hz, 1H), 7.47–7.50 (m, 2H), 7.60–7.74 (m, 2H), 7.81–7.93 (m, 4H), 8.10 (d, *J* = 7.8 Hz, 1H), 8.32–8.35 (m, 1H), 8.63–8.66 (m, 1H). ^{13}C NMR 13.9, 22.5, 25.0, 26.1, 28.8, 31.5, 34.1, 36.7, 43.8, 47.1, 47.9, 49.2, 55.3, 72.2, 72.7, 79.1, 112.5, 115.1, 120.8, 121.5, 125.4, 125.8, 126.0, 127.4, 127.9, 128.3, 131.4, 131.7, 132.2, 133.3, 234.5, 135.1, 137.7, 141.3, 153.9, 158.5, 208.2 and 219.8.

*2.2.30. Spiro[5′.2″]acenaphthylene-1″-one-spiro[16.6′]-7′-(4-methylphenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**5e**)*

Isolated as white solid; yield 81%; mp 177–179 °C; Anal. Calcd. for $C_{41}H_{39}NO_3S$: C, 78.69; H, 6.28; N, 2.24. Found: C, 78.61; H, 6.20; N, 2.16. ^{1}H NMR 0.06 (s, 3H), 0.47–0.71 (m, 1H), 1.00–1.19 (m, 2H), 1.21–1.28 (m, 1H), 1.40–1.47 (m, 2H), 1.60–1.69 (m, 4H), 2.33–2.39 (m, 4H), 2.56–2.65 (m, 2H), 2.91–3.12 (m, 2H), 3.67 (d, *J* = 8.1 Hz, 1H), 3.77–3.88 (m, 1H), 4.73–4.86 (m, 2H), 6.46 (m, 2H), 6.87 (d, *J* = 8.4, 1H), 7.13–7.25 (m, 5H), 7.66–7.76 (m, 2H), 7.87–7.92 (m, 2H), 8.00–8.11 (m, 2H). ^{13}C NMR 13.9, 21.0, 25.1, 26.2, 28.5, 28.9, 31.4, 34.7, 36.8, 43.9, 47.1, 48.2, 50.6, 55.7, 71.9, 72.5, 80.3, 112.5, 115.2, 120.8, 125.4, 125.7, 125.2, 122.9, 126.1, 127.7, 128.3, 129.2, 130.4, 131.5, 131.9, 132.7, 132.2, 133.6, 134.6, 137.2, 137.8, 141.1, 153.5, 206.1 and 218.9.

*2.2.31. Spiro[5′.2″]acenaphthylene-1″-one-spiro[16.6′]-7′-(4-methoxyphenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**5f**)*

Isolated as white solid; yield 83%; mp 180–183 °C; Anal. Calcd. for $C_{41}H_{39}NO_4S$: C, 76.73; H, 6.12; N, 2.18. Found: C, 76.82; H, 6.19; N, 2.28. ^{1}H NMR 0.07 (s, 3H), 0.60–0.66 (m, 1H), 1.03–1.21 (m, 2H), 1.23–1.30 (m, 1H), 1.44–1.48 (m, 1H), 1.23–1.70 (m, 3H), 1.80–2.04 (m, 2H), 2.56–2.67 (m, 2H), 2.97–3.13 (m, 2H), 3.66 (d, *J* = 8.1, 1H), 3.79–3.86 (m, 2H), 3.79 (s, 3H), 4.70–4.73 (m, 1H), 5.21 (s, 1H), 6.47–6.53 (m, 2H), 6.86–6.89 (m, 2H), 7.02–7.10 (m, 1H), 7.66–7.76 (m, 3H), 7.88–7.92 (m, 3H), 8.04–8.12 (m, 3H). ^{13}C NMR 13.8, 26.2, 28.4, 28.9, 31.4, 34.7, 36.8, 43.9, 47.2, 48.3, 50.6, 55.2, 55.4, 71.9, 72.4, 80.3, 112.5, 113.9, 115.2, 120.8, 123.4, 125.4, 125.8, 126.1, 127.2, 127.8, 128.3, 128.7, 130.4, 131.0, 131.4, 132.2, 133.5, 134.5, 137.8, 141.1, 153.5, 158.9, 206.1 and 219.2.

*2.2.32. Spiro[5′.2″]acenaphthylene-1″-one-spiro[16.6′]-7′-(4-N,N dimethylaminophenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**5g**)*

Isolated as white solid; yield 82%; mp 178–180 °C; Anal. Calcd. for $C_{42}H_{42}N_2O_3S$: C, 77.03; H, 6.46; N, 4.28. Found: C, 77.11; H, 6.54; N, 4.20. ^{1}H NMR 0.06 (s, 3H), 0.46–0.63 (m, 1H), 0.93–1.13 (m, 4H), 1.14–1.82 (m, 5H), 2.04–2.54 (m, 2H), 2.68–2.84 (m, 4H), 2.96 (s, 6H), 3.64–3.88 (m, 3H), 4.76–4.79 (m, 2H), 6.48–6.52 (m, 2H), 6.67–6.71 (m, 2H), 6.88 (d, *J* = 8.4, 1H), 7.16–7.19 (m, 1H), 7.65–7.91 (m, 6H), 8.07–8.12 (m, 2H), 8.33 (d, *J* = 8.4, 1H), 8.65 (d, *J* = 8.4, 1H). ^{13}C NMR 13.8, 13.9, 22.5, 25.2, 26.2, 28.4, 31.4, 34.8, 36.9, 37.9, 40.3, 43.9, 47.2, 48.4, 50.6, 71.9, 72.6, 80.4, 112.3, 112.5, 118.8, 120.6, 124.2, 125.2, 127.7, 126.2, 127.3, 127.6, 128.2, 130.5, 131.6, 131.8, 132.0, 133.3, 134.8, 135.1, 137.8, 141.0, 149.8, 153.4, 205.9 and 218.8.

*2.2.33. Spiro[5′.2″]acenaphthylene-1″-one-spiro[16.6′]-7′-(2-chlorophenyl)tetrahydro-1H-pyrrolo[1′2′-c][1′,3′]thiazolo estrone (**5h**)*

Isolated as white solid; yield 85%; mp 192–194 °C; Anal. Calcd. for $C_{40}H_{36}ClNO_3S$: C, 74.34; H, 5.61; N, 2.17. Found: C, 74.30; H, 5.53; N, 2.14. ^{1}H NMR 0.17–0.38 (m, 1H), 0.51 (s, 3H), 1.07–1.60 (m, 3H), 1.56–1.67 (m, 4H), 1.81–1.81 (m, 2H), 2.01–2.17 (m, 2H) 2.41–2.51 (m, 3H), 2.90–3.04 (m, 2H), 3.54 (d, *J* = 6.0 Hz, 1H), 3.70 (d, *J* = 6.0 Hz, 1H), 4.57 (d, *J* = 8.4 Hz, 1H), 4.79–4.87 (m, 1H), 6.40–6.41 (m, 1H), 6.50 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.82 (d, *J* = 8.7 Hz, 1H), 7.20–7.25 (m, 2H), 7.36–7.48 (m, 2H), 7.62–7.73 (m, 4H), 7.86–8.01 (m, 3H), 8.10 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR 15.4, 24.9, 26.1, 28.7, 29.2, 29.5, 31.2, 32.4, 32.9, 36.5, 43.8, 46.5, 47.3, 47.4, 50.0, 73.2, 74.3, 77.3, 112.6, 115.1, 120.7, 125.4, 125.8, 126.2, 127.2, 127.9, 128.2, 128.5, 129.4, 130.4, 130.9, 131.3, 131.9, 132.3, 135.2, 135.5, 136.5, 137.5, 142.4, 153.5, 207.0 and 220.1.

*2.2.34. Spiro[5′.2″]acenaphthylene-1″-one-spiro[16.6′]-7′-(2-methylphenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**5i**)*

Isolated as white solid; yield 80%; mp 179–181 °C; Anal. Calcd. for $C_{41}H_{39}NO_3S$: C, 78.69; H, 6.28; N, 2.24. Found: C, 78.65; H, 6.23; N, 2.20. ^{1}H NMR 0.33 (s, 3H), 0.51–0.66 (m, 1H), 0.95–1.35 (m, 4H), 1.59–1.84 (m, 3H), 1.83–1.86 (m, 1H), 2.28 (s, 3H), 2.34–2.46 (m, 1H), 2.56–2.61 (m, 2H), 2.86–3.01 (m, 4H), 3.65 (d, *J* = 6.6 Hz, 1H), 3.72 (d, *J* = 6.6 Hz, 1H), 4.29 (d, *J* = 9.3 Hz, 1H), 4.69 (s, 1H), 6.42–6.51 (m, 2H), 6.83 (d, *J* = 8.4 Hz, 1H), 7.13–7.19 (m, 2H), 7.29–7.35 (m, 2H), 7.68–7.73 (m, 3H), 7.80–7.95 (m, 3H),8.10 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR 14.3, 19.9, 25.0, 26.1, 28.8, 31.1, 31.5, 33.6, 36.6, 43.8, 47.2, 47.5, 48.1, 50.2, 73.0, 74.0, 78.5, 112.5, 113.7, 115.1, 120.8, 125.4, 125.8, 126.0, 126.2, 127.9, 128.4, 130.1, 130.4, 130.5, 131.3, 131.8, 132.3, 135.4, 135.8, 137.5, 137.7, 141.8, 153.5, 206.6 and 220.0.

*2.2.35. Spiro[5′.2″]acenaphthylene-1″-one-spiro[16.6′]-7′-(2-methoxyphenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**5j**)*

Isolated as white solid; yield 82%; mp 191–193 °C; Anal. Calcd. for $C_{41}H_{39}NO_4S$: C, 76.73; H, 6.12; N, 2.18. Found: C, 76.79; H, 6.16; N, 2.23. ^{1}H NMR 0.61–0.71 (m, 1H), 0.80 (s, 3H), 0.96–0.99 (m, 1H), 1.10–1.16 (m, 2H), 1.29–1.71 (m, 3H), 1.88–1.97 (m, 2H), 1.99–2.69 (m, 2H), 2.91–3.16 (m, 3H), 3.64 (d, *J* = 8.1, 1H), 3.77–3.86 (m, 2H), 3.77 (s, 3H), 4.71–4.82 (m, 2H), 5.30 (s, 1H), 6.47–6.53 (m, 2H), 6.87 (d, *J* = 8.4, 3H), 7.26–7.33 (m, 1H), 7.66–7.76 (m, 3H), 7.9 (t, *J* = 6.3, 2H), 8.03–8.11 (m, 3H). ^{13}C NMR 13.9, 25.1, 26.2, 28.6, 28.9, 31.3, 34.6, 36.8, 43.9, 47.2, 48.3, 50.3, 55.1, 55.4, 72.1, 72.6, 80.1, 112.5, 113.9, 115.2, 120.7, 125.3, 125.8, 126.1, 126.1, 127.7, 128.2, 128.8, 130.5, 130.9, 131.5, 131.9, 132.1, 134.7, 135.4, 137.8, 141.6, 153.4, 158.9, 205.9 and 218.8.

*2.2.36. Spiro[5′.2″]acenaphthylene-1″-one-spiro[16.6′]-7′-(2-fluorophenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**5k**)*

Isolated as white solid; yield 79%; mp 178–180 °C; Anal. Calcd. for $C_{40}H_{36}FNO_3S$: C, 76.28; H, 5.76; N, 2.22. Found: C, 76.21; H, 5.70; N, 2.17. ^{1}H NMR 0.47 (s, 3H), 0.51–0.55 (m, 2H), 0.90–1.00 (m, 2H), 1.02–1.15 (m, 2H), 1.60–1.67 (m, 4H), 1.86–2.88 (m, 4H), 1.34–2.39 (m, 1H), 1.96–2.04 (m, 2H), 1.62–1.71 (m, 2H), 1.22–1.30 (m, 2H), 2.02–2.68 (m, 2H), 2.91–3.12 (m, 3H), 3.52 (d, *J* = 5.4 Hz, 1H), 3.62 (d, *J* = 5.4 Hz, 1H), 4.15–4.20 (m, 1H), 4.80 (s, 1H), 6.47–6.53 (m, 2H), 6.87 (d, *J* = 8.1, 1H), 7.27–7.34 (m, 1H), 7.66–7.75 (m, 3H), 7.81–7.93 (m, 3H), 8.06–8.12 (m, 2H), 8.33 (d, *J* = 7.2, 1H), 8.65 (d, *J* = 7.2, 1H). ^{13}C NMR 14.0, 14.7, 22.5, 25.1, 26.2, 28.9, 31.3, 34.5, 36.7, 43.9, 47.2, 48.1, 50.1, 51.1, 72.2, 79.8, 112.6, 114.4, 115.2, 115.7, 120.9, 125.5, 125.8, 126.1, 127.4, 127.9, 128.3, 130.5, 131.2, 131.6, 132.3, 133.4, 134.5, 135.3, 137.7, 141.2, 153.6, 160.5, 206.2 and 218.2.

*2.2.37. Spiro[5′.2″]acenaphthylene-1″-one-spiro[16.6′]-7′-(3-fluorophenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**5l**)*

Isolated as white solid; yield 80%; mp 176–178 °C; Anal. Calcd. for $C_{40}H_{36}FNO_3S$: C, 76.28; H, 5.76; N, 2.22. Found: C, 76.25; H, 5.72; N, 2.29. ^{1}H NMR 0.14 (s, 3H), 0.35–00.96 (m, 3H), 1.05–1.69 (m, 3H), 1.60–151 (m, 2H), 1.84–2.05 (m, 2H), 2.52–2.67 (m, 4H), 2.91–3.11 (m, 2H), 3.66 (d, *J* = 9.9 Hz, 1H), 3.79 (d, *J* = 7.8 Hz, 1H), 3.85 (d, *J* = 7.8 Hz, 1H), 4.77–4.87 (m, 2H), 6.47–6.54 (m, 2H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.96–7.02 (m, 1H), 7.10–7.12 (m, 1H), 7.30–7.35 (m, 1H), 7.67–7.75 (m, 2H), 7.81–7.98 (m, 3H), 8.10 (d, *J* = 8.1 Hz, 1H), 8.32–8.35 (m, 1H), 8.63–8.66 (m, 1H). ^{13}C NMR 14.2, 25.1, 28.9, 29.2, 31.4, 34.3, 36.8, 43.9, 47.2, 48.1, 49.6, 50.3, 55.6, 72.0, 72.7, 79.6, 112.6, 114.4, 114.6, 115.2, 116.6, 11 6.9, 120.8, 125.5, 125.7, 126.0, 127.4, 127.9, 128.3, 129.9, 130.1, 130.5, 131.3, 131.7, 132.3, 133.3, 134.6, 135.2, 137.7, 139.8, 141.3, 153.6, 161.2, 206.0 and 219.8.

*2.2.38. Spiro[5′.2″]acenaphthylene-1″-one-spiro[16.6′]-7′-(2,4-dichlorophenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**5m**)*

Isolated as white solid; yield 80%; mp 168–171 °C; Anal. Calcd. for $C_{40}H_{35}Cl_2NO_3S$: C, 70.58; H, 5.18; N, 2.06. Found: C, 70.53; H, 5.14; N, 2.02. ^{1}H NMR 0.26–0.32 (m, 1H), 0.54 (s, 3H), 0.92–0.97 (m, 1H), 1.11–1.32 (m, 3H), 1.60–1.68 (m, 4H), 1.83–1.86 (m, 1H), 2.06–2.11 (m, 2H), 2.51–2.56 (m, 2H), 2.89–3.03 (m, 2H), 3.52 (d, *J* = 5.7 Hz, 1H), 3.69 (d, *J* = 5.7 Hz, 1H), 4.50 (d, *J* = 8.1 Hz, 1H), 4.64 (s, 1H), 4.72–4.78 (m, 1H), 6.40–6.51 (m, 2H), 6.8 (d, *J* = 8.4 Hz, 1H), 7.39–7.42 (m, 2H), 7.59 (d, *J* = 6.9 Hz, 1H), 7.66–7.74 (m, 2H), 7.81–7.99 (m, 3H), 8.10 (d, *J* = 8.4 Hz, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 8.65 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR 14.0, 15.6, 24.9, 26.1, 26.8, 28.8, 31.1, 32.5, 32.8, 36.4, 43.7, 46.2, 47.1, 49.4, 73.1, 74.3, 112.6, 115.3, 120.1, 121.6, 125.9, 125.5, 126.5, 127.1, 127.7, 128.6, 131.3, 131.6, 132.4, 133.2, 234.7, 135.4, 137.5, 141.3, 153.9, 158.3, 208.4 and 219.7.

*2.2.39. Spiro[5′.2″]acenaphthylene-1″-one-spiro[16.6′]-7′-(3,4-dimethoxyphenyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**5n**)*

Isolated as white solid; yield 80%; mp 188–190 °C; Anal. Calcd. for $C_{42}H_{41}NO_5S$: C, 75.08; H, 6.15; N, 2.08. Found: C, 75.01; H, 6.10; N, 2.03. ^{1}H NMR 0.35 (s, 3H), 0.54–0.57 (m, 1H), 0.90–1.00 (m, 2H), 1.15–1.26 (m, 2H), 1.60–1.64 (m, 4H), 1.74–1.77 (m, 1H), 1.99–2.04 (m, 2H), 2.46–2.49 (m, 2H), 2.62–2.64 (m, 2H), 2.84–2.93 (m, 2H), 3.62–3.67 (m, 2H), 3.87 (s, 6H), 4.71–4.75 (m, 1H), 6.60–6.80 (m, 2H), 6.91 (d, J = 8.1, 1H), 7.15–7.21 (m, 3H), 7.40–7.43 (m, 1H), 7.80–7.86 (m, 3H), 8.31–8.35 (m, 2H), 8.62–8.65 (m, 2H). ^{13}C NMR 14.5, 25.9, 26.7, 28.9, 29.4, 31.6, 34.3, 37.9, 44.0, 47.6, 48.7, 50.1, 55.9, 72.1, 72.5, 80.6, 112.8, 113.3, 115.3, 118.8, 123.9, 126.3, 127.3, 127.4, 128.6, 130.2, 131.7, 131.9, 133.3, 133.4, 133.8, 135.1, 135.3, 137.7, 148.9, 150.3, 153.7, 160.4, 209.6 and 220.4.

*2.2.40. Spiro[5′.2″]acenaphthylene-1″-one-spiro[16.6′]-7′-(1-naphthyl)tetrahydro-1H-pyrrolo[1′,2′-c][1′,3′]thiazolo estrone (**5o**)*

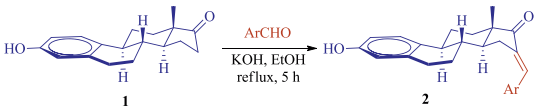
Isolated as white solid; yield 82%; mp 180–182 °C; Anal. Calcd. for $C_{44}H_{39}NO_3S$: C, 79.85; H, 5.94; N, 2.12. Found: C, 79.80; H, 5.89; N, 2.20. ^{1}H NMR 0.17 (s, 3H), 0.39–0.46 (m, 1H), 0.53–0.54 (m, 2H), 0.93–1.03 (m, 1H), 1.01–1.19 (m, 1H), 1.27–2.04 (m, 2H), 1.60–1.67 (m, 3H), 2.02–2.42 (m, 2H), 2.48–2.62 (m, 2H), 2.84–2.98 (m, 2H), 3.67 (d, J = 6.3 Hz, 1H), 3.77 (d, J = 6.3 Hz, 1H), 4.82–4.86 (m, 3H), 6.38–6.48 (m, 2H), 6.80 (d, J = 8.4 Hz, 1H), 7.43–8.17 (m, 11H), 8.33 (d, J = 8.4 Hz, 1H), 8.63–8.66 (m, 1H). ^{13}C NMR 18.7, 24.9, 25.2, 28.8, 29.3, 31.4, 33.5, 34.6, 36.4, 43.8, 47.4, 48.3, 48.7, 73.7, 78.1, 112.5, 115.1, 120.8, 123.6, 125.5, 125.7, 125.8, 126.0, 126.3, 127.4, 127.5, 127.6, 128.0, 128.5, 128.7, 130.4, 131.2, 132.3, 133.4, 134.1, 135.3, 135.6, 137.6, 142.0, 153.5, 160.5, 206.7 and 220.4.

3. Results and discussion

In the present work, the C-16 exocyclic dipolarophiles *viz.* (*E*)-16-arylidene estrones **2** were synthesized from the reaction of estrone **1** with various aromatic aldehydes (Scheme 1). An equivalent mixture of estrone and the appropriate aldehyde were dissolved in ethanol followed by the addition of alcoholic potassium hydroxide. The mixture was boiled to reflux for 5 h and the completion of the reaction was realized when the (*E*)-16-arylidene estrones **2** precipitated out of the reaction mixture as yellow solid, which was filtered and washed with water. A total of fifteen (*E*)-16-arylidene estrones **2a**–**o** were synthesized in almost quantitative yields (>91%, Scheme 1). However, the reaction failed to occur with aliphatic aldehydes.

The structure of these dipolarophiles **2** was elucidated with the help of NMR spectroscopy and is in complete agreement with the literature reports [8]. Moreover, the NMR spectra of (*E*)-16-arylidene estrones **2** and estrone **1** were similar except for the presence of new signals in the ^{1}H and ^{13}C NMR spectra of **2** due to the aromatic ring and benzylidene protons and carbons. Further, the DEPT-135 spectrum of **2** reveals the absence of one 'CH_2' carbon and appearance of new signals due to aromatic 'C' and 'CH' carbons. The structure of **2** assigned from NMR spectroscopy was further confirmed from single crystal X-ray studies. The ORTEP diagram of **2b** reveals (*E*)-configuration for the D-ring C-16 exocyclic alkene (Fig. 1) [17].

To begin with, the 1,3-dipolar cycloaddition of azomethine ylides generated *in situ* from the reaction of 1,3-thiazolane-4-carboxylic acid and isatin or 5-chloroisatin to (*E*)-16-arylidene estrones **2a**–**o** was investigated (Scheme 2). The reaction proceeded stereoselectively affording a single isomer of novel spiro[5′.3″]oxindole-spiro[6′.16]-7′-(aryl)-tetrahydro-1*H*-pyrrolo[1′,2′-*c*][1′,3′]



1 **2**

Entry	Comp	Ar	Yield[a] (%)
1	**2a**	C_6H_5	93
2	**2b**	4-ClC_6H_4	95
3	**2c**	4-FC_6H_4	92
4	**2d**	4-BrC_6H_4	97
5	**2e**	4-$CH_3C_6H_4$	95
6	**2f**	4-$CH_3OC_6H_4$	98
7	**2g**	4-$(CH_3)_2NC_6H_4$	94
8	**2h**	2-ClC_6H_4	96
9	**2i**	2-$CH_3C_6H_4$	97
10	**2j**	2-$CH_3OC_6H_4$	93
11	**2k**	2-FC_6H_4	94
12	**2l**	3-FC_6H_4	98
13	**2m**	2,4-$Cl_2C_6H_3$	94
14	**2n**	3,4-$(CH_3O)_2C_6H_3$	91
15	**2o**	Naphthyl	95

[a]Yields were quantitative except for the loss during workup

Scheme 1. Synthesis of (*E*)-16-arylmethylidene-estrones **2**.

thiazolo estrones **3a**–**o** and spiro[5′.3″]-5″-chloro-oxindole-spiro[6′.16]-7′-(aryl)tetrahydro-1*H*-pyrrolo[1′,2′-*c*][1′,3′]thiazolo estrones **4a**–**o**, respectively. The significances of this reaction include a facile one-pot three-component process, excellent yields (81–86%) with generation of four new contiguous stereo-centers and formation of two C–C and one C–N bonds in a single step. Further, this reaction assumes importance in the viewpoint of its high atom economy since the only by-products are water and carbon dioxide. A total of 26 new C-16 spiro estrone hybrid heterocycles **3** and **4** have been synthesized employing this cycloaddition. It is pertinent to note that the reaction proceeded smoothly with dipolarophiles **2** comprising electron-withdrawing or electron-donating group in the aryl ring affording the spiro estrones **3** and **4** in excellent yields. Further, the presence of sterically hindered groups and bulky 1-naphthyl in the aryl too had no adverse effects in the yield of the product **3**. However, the reaction failed to occur in the cases of **4g**, **4j**, **4n** and **4o**. Three cases *viz.* **4j**, **4n** and **4o** may presumably be attributed to the steric hindrance and/or other electronic effects but in the case of **4g** the reason is unclear.

The structure of all the C-16 spiro estrone hybrid heterocycles **3a**–**o** and **4a**–**o** were elucidated with the help of elemental analysis, ^{1}H, ^{13}C and 2D NMR spectroscopic techniques. As a representative case the selected H,H-COSY and HMBC correlations of **3b** are shown in Fig. 2 whereas the complete assignment of ^{1}H and ^{13}C chemical shifts of **3b** are shown in Fig. 3.

The spiro estrones **3** and **4** are formed by the addition of electron rich carbon of the 1,3-dipole to the β-carbon of the dipolarophiles **2**. This regioselectivity can be attributed to the polarization of the C=C bond of the α,β-unsaturated moiety with a more

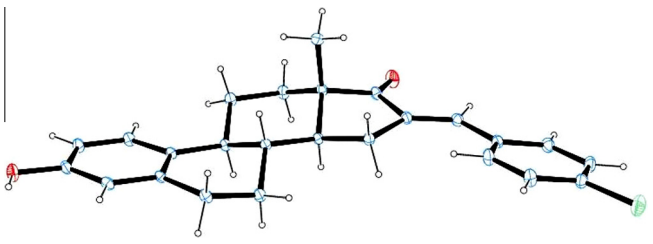
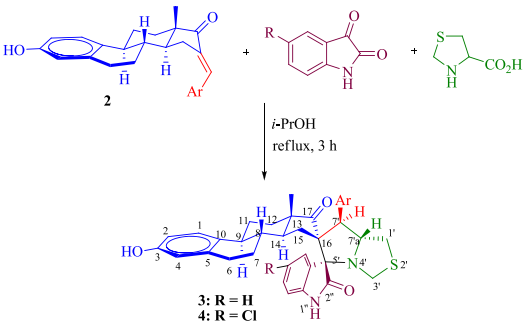


Fig. 1. ORTEP diagram of **2b** [17].



Entry	Comp		Ar	Yield[a] (%)		mp (°C)	
	3	4		3	4	3	4
1	3a	4a	C_6H_5	82	83	185–186	206–208
2	3b	4b	4-ClC_6H_4	84	86	200–201	218–220
3	3c	4c	4-FC_6H_4	81	83	190–191	213–215
4	3d	4d	4-BrC_6H_4	80	82	290–291	223–225
5	3e	4e	4-$CH_3C_6H_4$	85	83	199–200	199–201
6	3f	4f	4-$CH_3OC_6H_4$	86	83	214–215	226–228
7	3g	4g	4-$(CH_3)_2NC_6H_4$	83	–[b]	199–201	–
8	3h	4h	2-ClC_6H_4	82	83	198–200	213–215
9	3i	4i	2-$CH_3C_6H_4$	83	83	184–186	202–204
10	3j	4j	2-$CH_3OC_6H_4$	84	–[b]	212–214	–
11	3k	4k	2-FC_6H_4	81	81	192–194	221–223
12	3l	4l	3-FC_6H_4	82	81	192–194	209–212
13	3m	4m	2,4-$Cl_2C_6H_3$	83	84	195–197	228–230
14	3n	4n	3,4-$(CH_3O)_2C_6H_3$	85	–[b]	213–215	–
15	3o	4o	Naphthyl	81	–[b]	192–194	–

[a]Isolated yields after flash filtration column; [b]The reaction failed to occur

Scheme 2. Synthesis of C-16 spiro estrones **3** and **4**.

electron-deficient β-carbon which could preferentially react with the electron-rich site of the approaching 1,3-dipole.

The above reaction proceeds stereoselectively since a single isomer of the product was obtained in both the cases (**3** and **4**) even though four new chiral centers are generated during the cycloaddition (C-16, C-5′, C-7′ and C-7a′). As the crystallization of either **3** or **4** failed to afford suitable crystals for the single crystal X-ray studies, the determination of absolute configuration of the newly formed chiral centers of **3** and **4** were done on the basis of our earlier report [10] (ORTEP diagrams of androsterone analogs are provided in Supporting information) and were tentatively assigned as 16-*R*, 5′-*R*, 7′-*S* and 7a′-*S*.

Further, the facial selectivity involved in the cycloaddition leading to the formation of **3** and **4** is apparent from the fact that the azomethine ylides add to the dipolarophile **2** preferentially from the less hindered bottom side of the exocyclic C=C bond of **2**. The angular methyl group at 13th position of **2** presumably hinders the approach of the dipole from the top side (Fig. 4).

With a view to vary the 1,3-dipole, we further investigated the cycloaddition of azomethine ylide generated *in situ* from the reaction of acenaphthylene-1,2-dione and 1,3-thiazolane-4-carboxylic acid to the dipolarophiles **2**. The reaction afforded novel spiro[5′.2″]acenaphthylene-1″-one-spiro[16.6′]-(7′-aryl)-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]thiazolo estrone hybrid heterocycles **5** in

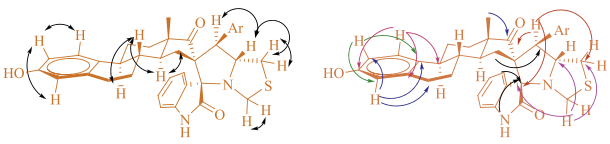


Fig. 2. Selected H,H-COSY and the HMBC correlations of **3b**.

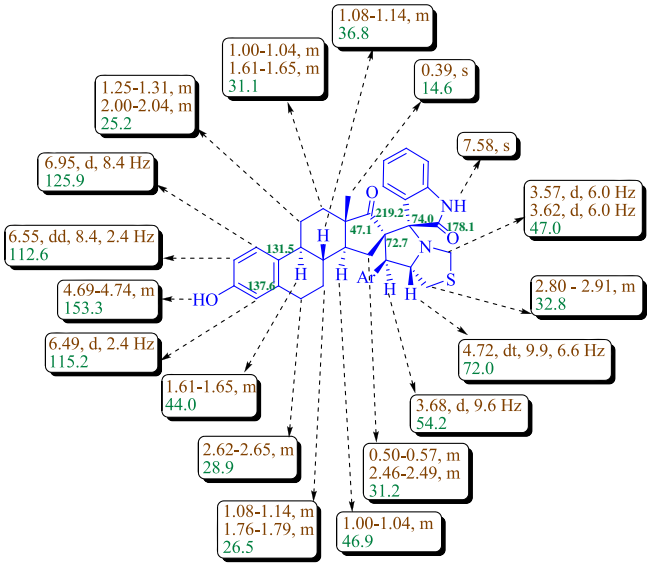
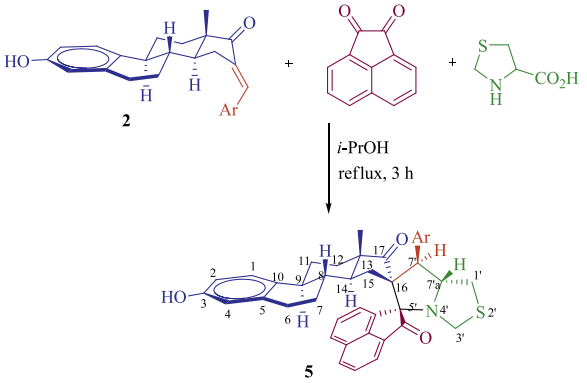


Fig. 3. ^{1}H and ^{13}C chemical shifts of **3b**.



Entry	Comp	Ar	Yield (%)[a]	mp (°C)
1	5a	C_6H_5	81	178–181
2	5b	4-ClC_6H_4	82	199–200
3	5d	4-BrC_6H_4	79	176–178
4	5e	4-$CH_3C_6H_4$	81	177–179
5	5f	4-$CH_3OC_6H_4$	83	180–183
6	5g	4-$(CH_3)_2NC_6H_4$	82	178–180
7	5h	2-ClC_6H_4	85	192–194
8	5i	2-$CH_3C_6H_4$	80	179–181
9	5j	2-$CH_3OC_6H_4$	82	191–193
10	5k	2-FC_6H_4	79	178–180
11	5l	3-FC_6H_4	80	176–178
12	5m	2,4-$Cl_2C_6H_3$	80	168–171
13	5n	3,4-$(CH_3O)_2C_6H_3$	80	188–190
14	5o	Naphthyl	82	180–182

[a]Isolated yields after flash filtration column

Scheme 3. Synthesis of C-16 spiro estrones **5**.

excellent yields (Scheme 3). A total of fourteen C-16 spiro estrone hybrid heterocycles **5a**–**o** were synthesized with varying substitutions in the aryl ring of **2**. It is pertinent to note that the reaction

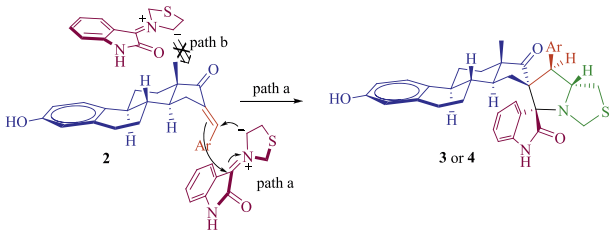


Fig. 4. Facial selectivity involved in the formation of **3** and **4**.

was found to be stereoselective as it was observed in the case of isatins. The structure of all the products **5** was elucidated with the help of elemental analysis, ^{1}H, ^{13}C and 2D NMR spectroscopic techniques.

In conclusion, a library of forty novel C-16 spiro estrone hybrid heterocycles **3**–**5** were synthesized in excellent yields stereoselectively through the 1,3-dipolar cycloaddition of azomethine ylides generated from the decarboxylative condensation of isatins or acenaphthylene-1,2-dione and 1,3-thiazolane-4-carboxylic acid to (*E*)-16-arylidene estrones **2**. The significances of these reactions include one-pot three-component atom economic process, excellent yields with generation of four new contiguous stereo-centers and formation of two C–C and one C–N bonds in a single step.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.steroids.2014.01.003.

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