Research Article

Design and Synthesis of an Indole-Estrogen Derivative

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There are several methods reported for synthesis of aromatic-condensed derivatives; nevertheless, expensive reagents and special conditions are required. Therefore, in this study, an indole-estrogen derivative (3-[4-(2-butyl-3-cyclohexylimino-4-piperidin-1-yl-cyclobutylidencarbamoyl)]-phenoxy-NH-indolo[2',3':17,16]estra-1,3,5(10)triene) was synthesized using some strategies. The structure of all compounds obtained was confirmed by spectroscopic and spectrometric methods. In conclusion, a facile procedure for the formation of an indole-estrogen derivative was developed in this study.

1. Introduction

Indole derivatives are a very important heterocyclic compounds which induced several biological activities [1, 2]. It is important to mention that there are several methods reported for synthesis of aromatic-condensed derivatives, for example, the synthesis of indole derivatives via palladium-catalyzed heteroannulation of internal alkynes [3]. Other studies showed the synthesis of an indole derivative by reaction of *N*-aryl Amides with ethyl diazoacetate [4]. In addition, some indole derivatives were development using the palladium-catalyzed coupling of alkynes with iodoaniline derivatives [5]. Other data showed that ruthenium catalyzed synthesis of indole from *N*-substituted anilines and alkanolamines [6]. Also a study shows the synthesis of 2-substituted indole derivatives from 2-ethynylanilines with tetrabutylammonium fluoride [7].

On the other hand, a series of indole-steroid derivatives have been developed, for example, the synthesis of 1'-methylindolo(3',2':2,3)-2(5 α)-androst-17-one by the reaction of 5 α -androstan-3,17-dione with 1-methyl-1-phenylhydrazine [8, 9]. Other data indicate the preparation of (Z)-16-(7-aza-1H-indol-1-yl)methylen-17-oxoandrost-5-en-3 β -yl acetate by the reaction of 17-chloro-16-formylandrosta-5,16-dien-3-yl acetate with 7-azaindole under N₂ atmosphere [10]. In addition, the synthesis of 17-indazole androstene derivative was prepared by the reaction of 17-chloro-16-formylandrosta-5,16-dien-3 β -yl acetate with indazole [11]. Additionally, other studies show the synthesis of 1'*H*-5 α -cholest-2-eno[3,2-*b*]indole using the Fisher reaction [12]. Recently, an indole-dihydrotestosterone derivative was synthesized by the reaction of dihydrotestosterone with phenylhydrazine using hydrochloric acid as catalyst [13]. All these experimental results show several procedures which

FIGURE 1: Synthesis of 4-(13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6-H-cyclopenta[a]phenanthren-3-yloxy)-benzoyl azide (3). Reaction of *p*-nitrobenzoyl azide (1) with estrone (2) to form 3. (i) = potassium carbonate/dimethyl sulfoxide.

are available for synthesis of indole derivatives; nevertheless, expensive reagents and special conditions are required. Therefore, in this study, an indole-steroid derivative was synthesized using some strategies.

2. Experimental

The compounds evaluated in this study were purchased from Sigma-Aldrich Co., Ltd. The melting points for the different compounds were determined on an Electrothermal (900 model). Infrared spectra (IR) were recorded using KBr pellets on a Perkin Elmer Lambda 40 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian VXR-300/5 FT NMR spectrometer at 300 and 75.4 MHz in CDCl_3 using TMS as internal standard. EIMS spectra were obtained with a Finnigan Trace GC Polaris Q. spectrometer. Elementary analysis data were acquired from a Perkin Elmer Ser. II CHNS/O 2400 elemental analyzer. The parameter $[\text{M}^+]$ indicates ion molecular.

2.1. Synthesis of 4-(13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6-H-cyclopenta[a]phenanthren-3-yloxy)-benzoyl azide (3). A solution of 4-nitrobenzoyl azide (100 mg, 0.52 mmol), estrone (140 mg, 0.52 mmol), and potassium carbonate (40 mg, 0.30 mmol) in 10 mL of dimethyl sulfoxide was stirring for 72 h at room temperature (Figure 1). The reaction mixture was evaporated to a smaller volume. After the mixture was diluted with water and extracted with chloroform, the organic phase was evaporated to dryness under reduced pressure and the residue was purified by crystallization from methanol:water (3:1) yielding 66% of product, m.p. 268–270°C; IR (V_{max} , cm^{-1}): 1724, 2112, and 1250; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 0.94 (s, 3H), 1.18–1.50 (m, 5H), 1.76–1.90 (m, 2H), 2.00–2.20 (m, 4H), 2.40–3.00 (m, 4H), 6.60–6.70 (m, 2H), 6.90 (m, 2H, $J = 2.40$ Hz), 7.10 (m, 1H), 7.76 (m, 2H) ppm. ^{13}C NMR (75.4 MHz, CDCl_3) δ_{C} : 13.16, 21.66, 25.70, 26.34, 29.22, 30.90, 35.56, 37.55, 44.70, 48.00, 48.60, 114.20, 114.44, 115.30, 124.60, 125.00, 129.36,

FIGURE 2: Synthesis of 3-(tert-butyl-dimethyl-silanyloxy)-NH-indolo[2'3':17,16]estra-1,3,5(10)-triene (5). The first stage involves protection of hydroxyl group from estrone (2) with tert-butyldimethylsilyl chloride (ii) to form the compound 4 (3-(tert-butyl-dimethyl-silanyloxy)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-cyclopenta[a]phenanthren-17-one). In the following stage, 4 was made reacting with phenylhydrazine hydrochloride to the synthesis of 5. (iii) = and acetic acid/methanol.

132.46, 139.48, 154.76, 163.56, 170.32, 219.76 ppm. EI-MS m/z : 415.18 ($\text{M}^+ 12$). Anal. Calcd. for $\text{C}_{25}\text{H}_{25}\text{N}_3\text{O}_3$: C, 72.27; H, 6.06; N, 10.11; O, 11.55. Found: C, 72.26; H, 6.02.

2.2. Synthesis of 3-(Tert-butyl-dimethyl-silanyloxy)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-cyclopenta[a]phenanthren-17-one (4). A solution of estrone (100 mg, 0.37 mmol) and tert-Butyldimethylsilyl chloride (200 μL , 1.07 mmol) in 5 mL of methanol was stirring for 8 h at room temperature (Figure 2). The reaction mixture was evaporated to a smaller volume. After the mixture was diluted with water and extracted with chloroform, the organic phase was evaporated to dryness under reduced pressure and the residue was purified by crystallization from methanol:water (4:1) yielding 87% of product, m.p. 224–226°C; IR (V_{max} , cm^{-1}): 1728 and 1148; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 0.28 (s, 6H), 0.96 (s, 3H), 1.04 (s, 9H), 1.24–1.36 (m, 4H), 1.50–1.90 (m, 3H), 2.10–2.22 (m, 4H), 2.46–3.00 (m, 4H), 6.70 (m, 1H, $J = 1.00$ Hz), 6.78–7.36 (m, 2H) ppm. ^{13}C NMR (75.4 MHz, CDCl_3) δ_{C} : -4.40, 13.45, 18.06, 21.70, 25.66, 25.80, 26.44, 29.50, 31.20, 35.18, 37.00, 43.40, 48.12, 49.14, 117.02, 119.90, 125.88, 132.08, 137.50, 153.30, 219.64 ppm. EI-MS m/z : 384.22 ($\text{M}^+ 10$). Anal. Calcd. for $\text{C}_{24}\text{H}_{36}\text{O}_2\text{Si}$: C, 74.94; H, 9.43; O, 8.32; Si, 7.30. Found: C, 74.92; H, 9.42.

2.3. Synthesis of 3-(Tert-butyl-dimethyl-silanyloxy)-NH-indolo[2'3':17,16]estra-1,3,5(10)-triene (5). A solution of 4 (100 mg,

FIGURE 3: Synthesis of 3-(4-azidocarbonyl-phenoxy)-NH-indolo[2',3':17,16]estra-1,3,5(10)-triene (7). The first stage was achieved by the reaction of 5 with hydrofluoric acid (iv) to form compound 6 (NH-indolo[2',3':17,16]estra-1,3,5(10)trien-3-ol). In addition, 6 was made reacting with *p*-nitrobenzoyl azide for synthesis of 7. (v) = dimethyl sulfoxide.

0.25 mmol), phenylhydrazine hydrochloride (70 mg, 0.48 mmol), and acetic acid (1 mL) in 10 mL of methanol was stirring for 72 h at room temperature. The reaction mixture was evaporated to a smaller volume. After the mixture was diluted with water and extracted with chloroform, the organic phase was evaporated to dryness under reduced pressure and the residue was purified by crystallization from methanol:water:hexano (3:1:2) yielding 44% of product, m.p. 200–202°C; IR ($V_{\max}$, cm^{-1}): 3520 and 1150; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 0.26 (s, 6H), 1.06 (s, 9H), 1.28–1.50 (m, 2H), 1.60 (s, 3H), 1.68–1.98 (m, 3H), 2.00–2.86 (m, 7H), 3.10 (m, 1H), 6.70–6.82 (m, 2H), 7.10 (m, 1H, $J = 7.60$ Hz), 7.20–7.25 (m, 2H), 7.30 (m, 1H), 7.40 (m, 1H) and 8.30 (broad 1H) ppm. ^{13}C NMR (75.4 MHz, CDCl_3) δ_{C} : –4.40, 18.08, 19.20, 25.60, 26.70, 27.80, 29.44, 31.10, 35.22, 35.30, 36.70, 44.90, 48.90, 110.80, 114.66, 117.10, 118.06, 119.00, 119.92, 120.90, 125.48, 126.10, 133.88, 134.85, 137.66, 153.30, 153.34 ppm. EI-MS m/z : 457.26 (M^+ 12). Anal. Calcd. for $\text{C}_{30}\text{H}_{39}\text{NOSi}$: C, 78.72; H, 8.59; N, 3.06; O, 3.50; Si, 6.14. Found: C, 78.70; H, 8.56.

2.4. Synthesis of NH-indolo[2',3':17,16]estra-1,3,5(10)trien-3-ol (6). A solution of 5 (100 mg, 0.21 mmol) and hydrofluoric acid (2 mL) in 8 mL of methanol was stirring for 72 h at room temperature. The reaction mixture was evaporated to a smaller volume. After the mixture was diluted with water and extracted with chloroform, the organic phase was evaporated to dryness under reduced pressure and the residue was purified by crystallization from methanol:water (4:1) yielding 85% of product, m.p. 318–320°C; IR ($V_{\max}$, cm^{-1}): 3520 and 3408; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 1.28–1.50 (m, 2H), 1.54 (s, 3H), 1.62–2.10 (m, 6H), 2.62–2.80 (m, 4H), 3.10 (m, 1H), 6.54–6.62 (m, 2H), 7.00 (broad, 2H), 7.10 (m, 1H, $J = 7.60$ Hz), 7.20 (m, 1H) and 7.24–7.48 (m, 3H) ppm. ^{13}C NMR (75.4 MHz, CDCl_3) δ_{C} : 19.18, 26.88, 27.50, 29.80, 31.00, 35.22, 35.40, 36.70,

44.59, 48.86, 110.80, 113.20, 114.54, 115.44, 118.16, 119.00, 120.90, 125.56, 126.40, 134.26, 134.80, 137.42, 153.30, 155.00 ppm. EI-MS m/z : 343.18 (M^+ 8). Anal. Calcd. for $\text{C}_{24}\text{H}_{25}\text{NO}$: C, 83.93; H, 7.34; N, 4.08; O, 4.66. Found: C, 83.90; H, 7.32.

2.5. Synthesis of 3-(4-Azidocarbonyl-phenoxy)-NH-indolo[2',3':17,16]estra-1,3,5(10)-triene (7). A solution of 6 (100 mg, 0.29 mmol), *p*-nitrobenzoyl azide (60 mg, 0.31 mmol), and potassium carbonate (40 mg, 0.30 mmol) in 10 mL of dimethyl sulfoxide was stirring for 72 h at room temperature (Figure 3). The reaction mixture was evaporated to a smaller volume. After the mixture was diluted with water and extracted with chloroform, the organic phase was evaporated to dryness under reduced pressure and the residue was purified by crystallization from methanol:water:hexano (1:3:1) yielding 80% of product, m.p. 258–260°C; IR ($V_{\max}$, cm^{-1}): 3522, 2123, and 1152; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 1.30–1.50 (m, 2H), 1.60 (s, 3H), 1.68–2.08 (m, 6H), 2.66–2.80 (m, 4H), 3.10 (m, 1H), 6.62–6.70 (m, 2H), 6.90 (m, 2H), 7.00 (m, 1H), 7.12–7.40 (m, 4H), 7.78 (m, 2H, $J = 8.37$ Hz) and 8.30 (broad 1H) ppm. ^{13}C NMR (75.4 MHz, CDCl_3) δ_{C} : 19.20, 26.70, 27.50, 29.84, 31.08, 35.22, 35.42, 36.70, 44.44, 48.94, 110.80, 114.18, 114.50, 114.70, 115.22, 118.22, 119.00, 120.90, 123.45, 124.70, 125.60, 132.50, 134.10, 134.78, 139.72, 153.30, 154.78, 163.80, 171.52 ppm. EI-MS m/z : 488.20 (M^+ 8). Anal. Calcd. for $\text{C}_{31}\text{H}_{28}\text{N}_4\text{O}_2$: C, 76.21; H, 5.78; N, 11.47; O, 6.55. Found: C, 76.20; H, 5.76.

2.6. Synthesis of *N*-(3-Butyl-1-cyclohexyl-4-cyclohexylimino-azetidin-2-ylidene)-4-(13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[*a*]phenanthren-3-yloxy)-benzamide (II). A solution of 3 (300 mg, 0.72 mmol), 1-hexyne (90 μL , 0.78 mmol), *N,N'*-Dicyclohexylcarbodiimide (150 mg, 0.72 mmol), and cupric chloride anhydrous (100 mg, 0.72 mmol) in 8 mL of methanol/dimethyl sulfoxide (2:6)

FIGURE 4: Synthesis of *N*-(3-butyl-1-cyclohexyl-4-cyclohexylimino-azetidin-2-ylidene)-4-(13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yloxy)-benzamide (**11**). Reaction of **3** with 1-hexyne (**8**) and *N,N'*-Dicyclohexylcarbodiimide (**9**) to form **11**. (vi) = methanol/dimethyl sulfoxide.

was stirring for 72 h at room temperature (Figure 4). The reaction mixture was evaporated to a smaller volume. After the mixture was diluted with water and extracted with chloroform, the organic phase was evaporated to dryness under reduced pressure and the residue was purified by crystallization from methanol: water (3:1) yielding 66% of product, m.p. 262–264°C; IR ($V_{\max}$, cm^{-1}): 1720, 1650, and 1148; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 0.86 (s, 3H), 0.96 (s, 3H), 1.02–1.16 (m, 6H), 1.20 (m, 1H), 1.22 (m, 1H), 1.24–1.26 (m, 2H), 1.29 (m, 1H), 1.34 (m, 1H), 1.36–1.44 (m, 6H), 1.48 (m, 2H), 1.50–1.53 (m, 3H), 1.54 (m, 1H), 1.60 (t, 2H, $J = 1.09$ Hz), 1.62–1.66 (m, 3H), 1.76 (m, 1H), 1.78 (m, 1H), 1.90 (m, 1H), 1.92–3.00 (m, 9H), 3.10–3.20 (m, 2H), 4.70 (m, 1H), 6.60–6.72 (m, 2H), 6.90 (m, 2H), 7.10 (m, 1H) and 8.36 (m, 2H) ppm. ^{13}C NMR (75.4 MHz, CDCl_3) δ_{C} : 13.58, 14.12, 21.66, 23.00, 23.10, 24.36, 25.40, 25.70, 26.06, 26.34, 26.36, 29.18, 29.30, 29.70, 30.78, 32.27, 35.60, 37.55, 38.70, 44.65, 48.00, 48.65, 57.90, 59.74, 114.24, 114.55, 116.68, 124.60, 131.00, 132.48, 132.65, 134.38, 139.50, 154.80, 163.67, 164.16, 175.88, 219.76 ppm. EI-MS m/z : 675.42 (M^+ 12). Anal. Calcd. for $\text{C}_{44}\text{H}_{57}\text{N}_3\text{O}_3$: C, 78.18; H, 8.50; N, 6.22; O, 7.10. Found: C, 78.16; H, 8.47.

2.7. Synthesis of 3-[4-(2-Butyl-3-cyclohexylimino-4-piperidin-1-yl-cyclobutylidencarbamoyl)]-phenoxy-NH-indolo[2',3':17,16]estra-1,3,5(10)triene (**10**)

2.7.1. Method A. A solution of **7** (300 mg, 0.61 mmol), 1-hexyne (90 μL , 0.78 mmol), *N,N'*-dicyclohexylcarbodiimide (150 mg, 0.72 mmol), and cupric chloride anhydrous (100 mg, 0.72 mmol) in 8 mL of methanol/dimethyl sulfoxide (2:6)

was stirring for 72 h at room temperature. The reaction mixture was evaporated to a smaller volume. After the mixture was diluted with water and extracted with chloroform, the organic phase was evaporated to dryness under reduced pressure and the residue was purified by crystallization from methanol: water (3:1) yielding 66% of product, m.p. 238–240°C; IR ($V_{\max}$, cm^{-1}): 3520, 3320, 1166, and 1152; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 0.86 (s, 3H), 1.08–1.28 (m, 8H), 1.30 (m, 1H), 1.36–1.44 (m, 6H), 1.48 (m, 2H), 1.50–1.54 (m, 3H), 1.58 (t, 2H, $J = 1.10$ Hz), 1.60 (s, 3H), 1.60 (m, 1H), 1.62 (m, 1H), 1.63 (m, 1H), 1.66 (m, 2H), 1.76 (m, 1H), 1.84–1.86 (m, 2H), 1.92 (m, 1H), 1.96–3.10 (m, 8H), 3.18–3.22 (m, 2H), 4.70 (m, 1H), 6.60–7.00 (m, 5H), 7.10–7.40 (m, 4H), 8.34–9.20 (m, 3H) ppm. ^{13}C NMR (75.4 MHz, CDCl_3) δ_{C} : 14.18, 23.00, 23.10, 24.32, 24.38, 25.44, 26.00, 26.34, 26.70, 27.44, 29.18, 29.65, 29.70, 31.10, 32.27, 35.58, 36.44, 38.70, 38.92, 44.50, 48.67, 57.90, 59.74, 111.64, 114.24, 114.55, 116.75, 117.48, 118.56, 119.20, 119.64, 124.66, 125.10, 130.98, 132.60, 134.28, 134.34, 139.70, 140.66, 149.24, 154.80, 163.45, 164.10, 175.88 ppm. EI-MS m/z : 748.46 (M^+ 10). Anal. Calcd. for $\text{C}_{50}\text{H}_{60}\text{N}_4\text{O}_2$: C, 80.17; H, 8.07; N, 7.48; O, 4.27. Found: C, 80.14; H, 8.06.

2.7.2. Method B. A solution of **11** (100 mg, 0.25 mmol), phenylhydrazine hydrochloride (70 mg, 0.48 mmol), and acetic acid (1 mL) in 10 mL of methanol was stirring for 72 h at room temperature. The reaction mixture was evaporated to a smaller volume. After the mixture was diluted with water and extracted with chloroform, the organic phase was evaporated to dryness under reduced pressure and the residue was purified by crystallization from methanol: water (4:1) yielding 78% of product. The signals IR, ^1H NMR, and ^{13}C NMR were confirmed by spectroscopic analyses. Similar signals were obtained as in the first method mentioned above.

3. Results and Discussion

In this study, an indole-steroid derivative was developed using some strategies; the first step was achieved by the synthesis of 4-(13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yloxy)-benzoyl azide (**3**) via displacement of nitro group from 4-nitrobenzoyl azide. It is important to mention that there are several methods for displacement of nitro groups, for example, the synthesis of bis(2-bromo-4-methoxyphenyl)methanone by the reaction of 2,2'-dibromo-4,4'-dinitrobenzophenone with methoxide using a dipolar aprotic solvent. In general, dipolar solvents are used to attain high yield of ether groups [14, 15]. In this study, compound **3** was synthesized by the reaction of 4-nitrobenzoyl azide with estrone in presence of dimethyl sulfoxide at mild conditions. The ^1H NMR spectrum of **3** shows signals at 0.94 ppm for methyl group bound to steroid nucleus; at 1.18–6.70 and 7.10 ppm for steroid moiety; and at 6.90 and 7.76 ppm for protons of benzoyl azide group. The ^{13}C NMR spectrum of **3** contains peaks at 13.16 ppm for methyl group bound to steroid nucleus; at 21.66–114.44, 124.60, and 132.46–154.76 ppm for steroid moiety; at 115.30, 125.00–129.36, and 163.56 ppm for phenyl bound to amide group; at 170.32 ppm

for amide group; and at 219.76 ppm for ketone group. Finally, the presence of compound **3** was further confirmed from mass spectrum which showed a molecular ion at m/z 415.18.

The second reaction stage was accomplished by protecting the hydroxyl group of the estrone in order to avoid possible reaction of hydroxyl group with any substance involved in the following reaction. It is important to mention that several organosilyl groups have been employed for protection of hydroxyl groups such as tert-butyldimethylsilyl and tert-butyldiphenylsilyl [16]. In this study, the estrone was made reacting with tert-butyldimethylsilyl chloride to form 3-(tert-Butyl-dimethyl-silanyloxy)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-cyclopenta[a]phenanthren-17-one (**4**). The ^1H NMR spectrum of **4** shows signals at 0.28 and 1.04 ppm for methyl groups involved in the tert-butyldimethylsilane fragment; at 0.96 ppm for methyl group bound to steroid nucleus; and at 1.24–7.36 ppm for steroid moiety. The ^{13}C NMR spectrum of **4** contains peaks at –4.40 and 25.66 ppm for methyl groups involved in the tert-butyldimethylsilane fragment; at 13.45 ppm for methyl group bound to steroid nucleus; at 18.06 ppm for carbon bound to methyl groups involved in the tert-butyldimethylsilane fragment; at 21.70–153.30 ppm for steroid moiety; and at 219.64 ppm for ketone group. Finally, the presence of compound **4** was further confirmed from mass spectrum which showed a molecular ion at m/z 384.22.

The third stage was achieved by the synthesis of an indole-steroid derivative (**5**); it is important to mention that there are several procedures which are available for synthesis of indole derivatives; nevertheless, expensive reagents and special conditions are required [5–12]. Therefore, in this study, the Fischer indole method was used to form **5** by the reaction of **4** with phenylhydrazine in mild medium. The ^1H NMR spectrum of **5** shows signals at 0.26 and 1.06 ppm for methyl groups involved in the tert-butyldimethylsilane fragment; at 1.60 ppm for methyl group bound to steroid nucleus; at 1.28–1.50, 1.68–6.82, and 7.30 ppm for steroid moiety; at 7.10–7.40 ppm for protons involved in indole group; and at 8.30 ppm for amino group. The ^{13}C NMR spectrum of **5** contains peaks at –4.40 and 25.60 ppm for methyl groups involved in the tert-butyldimethylsilane fragment; at 18.08 ppm for carbon bound to methyl groups involved in the tert-butyldimethylsilane fragment; at 19.20 ppm for methyl group bound to steroid nucleus; at 26.70–48.90, 114.54–117.10, 119.92, 126.10–133.88, and 137.66–153.34 ppm for steroid moiety; and at 110.80, 118.06–119.00, 120.90–125.48, and 134.85 ppm for indole group. Finally, the presence of compound **5** was further confirmed from mass spectrum which showed a molecular ion at m/z 457.28.

The following stage was achieved with the synthesis of NH-indolo[2',3':17,16]estra-1,3,5(10)trien-3-ol (**6**) by the reaction of **5** with hydrofluoric acid which is an excellent reagent for the removal of the t-butyldimethylsilyl protecting group [17]. The ^1H NMR spectrum of **6** shows signals at 1.28–1.50, 1.62–6.62, and 7.20 ppm for steroid moiety; at 1.54 ppm for methyl group bound to steroid nucleus; at 7.00 ppm for

the protons of both amino and hydroxyl groups; and at 7.10 and 7.24–7.48 ppm for indole group. The ^{13}C NMR spectrum of **6** contains peaks at 19.18 ppm for methyl group; at 26.88–48.66, 113.20–115.44, 126.40–134.26, and 137.42–155.00 ppm for steroid moiety; at 110.80, 118.16–125.56, and 134.80 ppm for indole group. Finally, the presence of compound **6** was further confirmed from mass spectrum which showed a molecular ion at m/z 343.18.

On the other hand, the fifth stage was achieved by preparation of **7** by reaction of **6** with *p*-nitrobenzoyl azide. The ^1H NMR spectrum of **7** shows signals at 1.60 ppm for methyl group bound to steroid nucleus; at 1.30–1.50, 1.68–6.70, and 7.00 ppm for steroid moiety; at 6.90 and 7.78 ppm for benzoyl azide group; at 7.12–7.40 ppm for indole group; and at 8.30 ppm for amino group. The ^{13}C NMR spectrum of **7** contains peaks at 19.20 ppm for methyl group bound to steroid nucleus; at 26.70–48.94, 114.18–114.70, 124.70, 134.10, and 139.72–154.78 ppm for steroid moiety; at 110.80, 118.22–120.90, and 134.78 ppm for indole group; at 115.22, 123.45, 125.60–132.50, and 163.80 ppm for benzoyl azide group; and at 171.52 ppm for amide group. Finally, the presence of compound **7** was further confirmed from mass spectrum which showed a molecular ion at m/z 488.20.

In the following stage, the compound *N*-(3-butyl-1-cyclohexyl-4-cyclohexylimino-azetidin-2-ylidene)-4-(13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yloxy)-benzamide (**11**) was prepared with the three-component system (compound **3**, 1-hexyne, and *N,N'*-dicyclohexylcarbodiimide) using cupric chloride as catalyst. It is important to mention that the reaction mechanism involved may be through a [2 + 2] cycloaddition such as happening with the other type of compounds [18]. The ^1H NMR spectrum of **11** shows signals at 0.86 ppm for methyl group involved in the arm bound to azetidine ring; at 0.96 ppm for methyl group bound to steroid nucleus; at 1.02–1.16, 1.22, 1.29, 1.36–1.44, 1.50–1.53, 1.62–1.66, and 3.10–3.20 ppm for both cyclohexane rings; at 1.20, 1.24–1.26, 1.34, 1.54, 1.78, 1.92–3.00, 6.60–6.72, and 7.10 ppm for steroid moiety; at 1.48, 1.60, 1.76, and 1.90 ppm for methylene groups involved in the arm bound to azetidine ring; at 4.70 ppm for proton of azetidine ring; and at 6.90 and 8.36 ppm for phenyl group bound to both ether and amide groups. The ^{13}C NMR spectrum of **11** contains peaks at 13.58 ppm for methyl group; at 14.12 ppm for methyl group involved in the arm which is bound to azetidine ring; at 21.66, 25.70, 26.36, 29.30, 30.78, 35.60–37.55, 44.65–48.65, 114.24–114.55, 124.60, 132.48, and 139.50–154.80 ppm for steroid moiety; at 23.00, 24.36–25.40, 26.06–26.34, 32.27, and 57.90–59.74 ppm for both cyclohexane rings; at 23.10, 29.18, and 29.70 ppm for methylene groups involved in the arm bound to azetidine ring; at 38.70 ppm for carbon involved in the azetidine ring; at 116.68, 131.00, and 132.65 ppm for phenyl group bound to both ether and amide groups; at 163.67 ppm for ether group; at 164.16, 134.38 ppm for both imino groups; at 175.88 ppm for amide group; and at 219.76 ppm for ketone group. Finally, the presence of compound **11** was further confirmed from mass spectrum which showed a molecular ion at m/z 675.42.

FIGURE 5: Synthesis of 3-[4-(2-butyl-3-cyclohexylimino-4-piperidin-1-yl-cyclobutylidencarbamoyl)]-phenoxy-NH-indolo[2',3':17,16]estra-1,3,5(10)triene (**10**). Reaction of **7** with 1-hexyne (**8**) and *N,N'*-Dicyclohexylcarbodiimide (**9**) to form **10**. (vii) = cupric chloride/rt.

FIGURE 6: Synthesis of 3-[4-(2-butyl-3-cyclohexylimino-4-piperidin-1-yl-cyclobutylidencarbamoyl)]-phenoxy-NH-indolo[2',3':17,16]estra-1,3,5(10)triene (**10**). Reaction of **11** with phenylhydrazine hydrochloride (**12**) to form the compound **10**. (viii) = acetic acid/methanol.

In addition, the last stage was achieved with the synthesis of 3-[4-(2-butyl-3-cyclohexylimino-4-piperidin-1-yl-cyclobutylidencarbamoyl)]-phenoxy-indolo[2',3':17,16]estra-1,3,5(10)triene (**10**) with the three-component system (compound **7**, 1-hexyne and *N,N'*-Dicyclohexylcarbodiimide) using cupric chloride as catalyst (Method A) (Figure 5). The ^1H NMR spectrum of **10** shows signals at 0.86 ppm for methyl involved in the arm bound to azetidine ring; at 1.08–1.28, 1.36–1.44, 1.50–1.54, 1.62, 1.66, and 3.18–3.22 ppm for both cyclohexane rings; at 1.30, 1.60, 1.63 1.84–1.86, 1.96–3.10, and 6.60–7.00 ppm for steroid moiety; at 1.48, 1.58, 1.76, and 1.92 ppm or methylene groups involved in the arm bound to azetidine group; at 1.60 ppm for methyl group bound to steroid nucleus; at 4.70 ppm for azetidine ring; at 7.10–7.40 ppm for indole group; and at 8.34–9.20 ppm

for phenyl group bound to both ether and amide groups. The ^{13}C NMR spectrum of **10** contains peaks at 14.18 ppm for methyl involved in the arm bound to azetidine ring; at 23.00, 24.38–26.34, 32.27, and 57.90–59.74 ppm for both cyclohexane rings; at 23.10 and 29.18–29.65 for methylene involved in the arm bound to azetidine ring; at 24.32 ppm for methyl group bound steroid nucleus; at 26.70–27.44, 29.70–31.10, 35.58–36.44, 38.92–48.67, 114.24–114.55, 117.48, 124.66–125.10, 134.34–139.70, and 149.24 ppm for steroid moiety; at 38.70, 134.28, and 164.10 ppm for azetidine ring; at 111.64, 118.56–119.64, and 140.66 ppm for indole group; at 116.75 and 130.98–132.60 ppm for phenyl group; at 154.80–163.45 ppm for carbons of ether; and at 175.88 ppm for amide group. Finally, the presence of compound **10** was further confirmed from mass spectrum which showed a molecular

ion at m/z 748.46 (Figure 6). Also **10** was synthesized using Fisher reaction by the reaction of **11** with phenylhydrazine in acid medium (Method B). ^1H NMR and ^{13}C NMR data were similar with two methods. However, it is important to mention that, with method B, the yielding is higher in comparison with that of method A.

4. Conclusions

In conclusion, a facile procedure for the formation of an indole-estrogen derivative was developed in this study.

Conflict of Interests

The authors declare that they do not have any financial relations with any of the commercial entities mentioned in the paper that could lead to a conflict of interests.

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