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Design and Synthesis of Naphthalene-Pregnen Derivative Using Some Strategies

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In this study, a naphthalene-pregnen derivative was synthesized using several strategies. The first step was achieved by the synthesis of 3,5-*bis*(2-naphthyloxy)benzoic acid (**2**) *via* displacement of nitro group from 3,5-dinitrobenzoic acid. In the second stage, N-(2-aminoethyl)-3,5-*bis*-(naphthalen-2-yloxy)benzamide (**4**) was synthesized by the reaction of **2** with ethylenediamine using boric acid as catalyst. Also **4** was developed by the reaction of *N*-(2-aminoethyl)-3,5-dinitrobenzamide with β-naphthol in presence of dimethyl sulfoxide. Third stage, was achieved by preparation of 3,20-*bis*-{2-[3,5-*bis*-(naphthalen-2-yloxy)benzoylamino]ethylimino}pregnene (**5**) by the reaction of **4** with progesterone using boric acid as catalyst. Additionally **5** was prepared by the reaction of N-[2-(1-{3-[2-(2,4-dinitrobenzenecarbonylamino)ethylimino]-10,13-dimethyl-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl}-ethylideneamino)ethyl]-2,4-di-nitro-benzamidewith β-naphthol in presence of dimethyl sulfoxide. Finally, other experiment involves the synthesis of 4-chloro-1-{(2-[3,5-*bis*-(naphthalen-2-yloxy)benzoylamino])ethyl}-1H,2H-spiro[azetidine-3,3´-17-(4-chloro-1-methyl-3-oxo-2-{(2-[3,5-*bis*-(naphthalene-2-yloxy)benzoylamino])ethyl}-2-aza-cyclobutyl)-10,13-dimethyl-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren]-2-one by the reaction of **5** with chloroacetyl chloride in the presence of triethylamine. The structure of all compounds obtained was confirmed by spectroscopic and spectrometric methods.

Keywords: Naphthalene, Progesterone, Benzoic acid, Ethylenediamine.

INTRODUCTION

In previous years, a series of aromatic-condensed derivatives have been developed *e.g.*, the synthesis of naphthyl-ketone derivatives by the reaction of *o*-alkynylbenzaldehydes with alkynes using $AuCl_3$ as catalyst [1]. Other studies shown the synthesis of 1,3-disubstituted naphthalenes from the Baylis-Hillman acetates with the aid of manganese(III) acetate [2]. Additionally, other study indicates the tandem pummerer-Diels-Alder sequence for the preparation of α-thio substituted naphthalene derivatives [3]. Other data [4] showed the synthesis of 1,8-diphenylnaphthalene and 1-iodo-8-phenyl-naphthalene by the reaction of lithium diphenylcuprate and aryl halides. Viswanathan *et al.* [5] shown the synthesis of polysubstituted naphthalene derivatives through gallium trichloride catalyzed by alkyne-aldehyde coupling. In addition, some carbamato-alkyl-naphthol derivatives [6] have been synthesized by condensation of β-naphthol, aromatic aldehyde and methyl carbamate in ionic liquid media. Other study indicates the enantioselective synthesis of binaphtholderivatives by oxidative coupling of naphthol derivatives catalyzed by chiral diamine-copper complexes [7]. Additionally, other report showed the chiral hypervalent iodine-catalyzed enantioselective oxidative Kita spirolactonization of 1-naphthol derivatives [8]. All these experimental results show several procedures that are available for synthesis of naphthalene derivatives. Nevertheless, expensive reagents and special conditions are required. Therefore, in this study a naphthalene-pregnene derivative (4-chloro-1-{(2-[3,5-*bis*-(naphthalen-2-yloxy)benzoylamino])ethyl}-1H,2H-spiro[azetidine-3,3´-17-(4-chloro-1-methyl-3-oxo-2-{(2-[3,5-*bis*-(naphthalene-2-yloxy)-benzoylamino])ethyl}-2-aza-cyclobutyl)-10,13-dimethyl-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren]-2-one) was synthetized using several strategies.

EXPERIMENTAL

The compounds *N*-(2-aminoethyl)-3,5-dinitrobenzamide (**3**) and N-[2-(1-{3-[2-(2,4-dinitro-benzenecarbonylamino)-ethylimino]-10,13-dimethyl-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl}-ethylideneamino)ethyl]-2,4-di-nitro-benzamide (**6**) were prepared according to previously reported methods [9,10]. Other 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. ^{1}H NMR 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/0 2400 elemental analyzer.

3,5-*Bis*(2-naphthyloxy)benzoic acid (2): A solution of 3,5-dinitro benzoic acid (100 mg, 0.47 mmol), β-naphthol (78 mg, 0.48 mmol) and potassium carbonate (40 mg, 0.30 mmol) in 10 mL of dimethyl sulfoxide was stirring for 72 h to 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, the residue was purified by crystallization from methanol:water (2:1) yielding 44 % of product, m.p. 74-76 °C; IR (KBr, ν_{max}, cm^{-1}): 1720, 1250; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 5.66 (broad, 1H), 6.90-7.40 (m, 3H), 7.50-7.60 (m, 6H), 7.70 (m, 2H), 7.80-7.90 (m, 6H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$) δ_C: 106.02 (**C**-4, **C**-11), 107.28 (**C**-9, **C**-24), 113.98 (**C**-2), 116.00 (**C**-16, **C**-20), 120.68 (**C**-13, **C**-26), 123.00 (**C**-14, **C**-27), 124.06 (**C**-12, **C**-25), 125.98 (**C**-11, **C**-22), 127.44 (**C**-15, **C**-28), 130.12 (**C**-17, (**C**-21), 131.00 (**C**-10, **C**-23), 137.08 (**C**-5), 153.08 (**C**-8, **C**-19), 168.00 (**C**-29), 168.32 (**C**-1, **C**-3) ppm. EI-MS *m/z:* 406.10 (M^+12). Anal. calcd. (%) for $C_{27}H_{18}O_4$: C, 79.79; H, 4.46; O, 15.75. Found (%): C, 79.74; H, 4.42.

N-(2-Amino-ethyl)-3,5-*bis*-(naphthalen-2-yloxy)benzamide (4)

Method A: A solution of **2** (100 mg, 0.25 mmol), ethylenediamine (40 mg, 0.27 mmol) and boric acid (30 mg, 0.48 mmol) in 10 mL of methanol was stirring for 72 h to room temperature. The reaction mixture was evaporated to a smaller volume. After the mixture was diluted with water and extracted with chloroform (Fig. 1). The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol:water (2:1) yielding 66 % of product, m.p. 98-100 °C; IR (KBr, ν_{max}, cm^{-1}): 3382, 3310, 1248; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.08 (t, 2H, *J* = 6.44 Hz), 3.40 (t, 2H, *J* = 6.44 Hz), 4.98 (broad, 3H), 6.50-6.82 (m, 3H), 7.10-7.90 (m, 14H) ppm. ^{13}C NMR (75.4 Hz, $CDCl_3$) δ_C: 43.66 (**C**-33), 46.40 (**C**-32), 105.46 ((**C**-9, **C**-24), 114.10 (**C**-16, **C**-20), 116.18 (**C**-2), 118.00 (**C**-4, **C**-6), 120.44 (**C**-26), 120.46 (**C**-13), 123.00 (**C**-14, **C**-27), 124.10 (**C**-12, **C**-25), 125.88 (**C**-11, **C**-22), 127.52 (**C**-15, **C**-28), 130.28 (**C**-17, **C**-21), 131.00 (**C**-10, **C**-23), 138.28 (**C**-5), 153.50 (**C**-8, **C**-19),

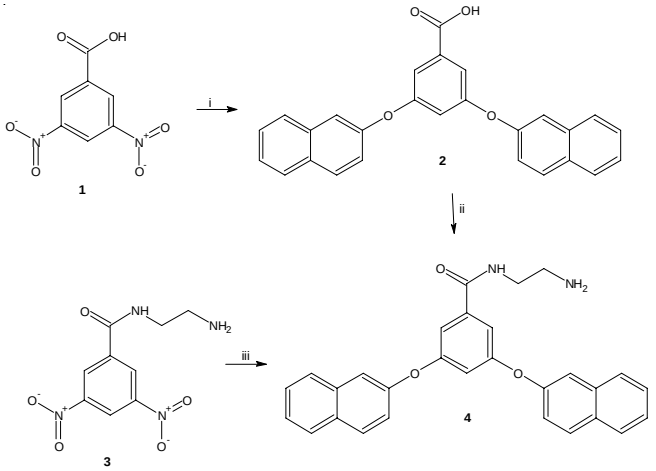

Fig. 1. Synthesis of N-(2-amino-ethyl)-3,5-*bis*-(naphthalen-2-yloxy)benzamide (**4**). First stage; reaction of 3,5-dinitrobenzoic acid (**1**) with β-naphthol in presence of dimethylsulfoxide (i) to form 3,5-*bis*(2-naphthyloxy)benzoic acid (**2**); Second stage, reaction of **2** with ethylenediamine (ii) to synthesis of **4**. Finally, **4** was developed by the reaction of *N*-(2-aminoethyl)-3,5-dinitro-benzamide (**3**) with β-naphthol in presence of dimethylsulfoxide (iii)

159.74 (**C**-1, **C**-3), 161.86 (**C**-29) ppm. EI-MS *m/z:* 448.10 (M^+12). Anal. calcd. (%) for $C_{29}H_{24}N_2O_3$: C, 77.66; H, 5.39; N, 6.25, O, 10.70. Found (%): C, 77.64; H, 5.38.

Method B: A solution of **3** (100 mg, 0.39 mmol), β-naphthol (58 mg, 0.40 mmol) and potassium carbonate (20 mg, 0.15 mmol) in 10 mL of dimethyl sulfoxide was stirring for 72 h to 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, the residue was purified by crystallization from methanol:water (4:1) yielding 38 % of product (Fig. 1). The ^{1}H NMR and ^{13}C NMR spectrums were similar in comparison with the product obtained by method A.

3,20-*Bis*-{2-[3,5-*bis*-(naphthalen-2-yloxy)-benzoylamino]-ethylimino}-pregnene (5)

Method A: A solution of **4** (100 mg, 0.13 mmol), progesterone (40 mg, 0.13 mmol) and boric acid (90 mg, 1.45 mmol) in 10 mL of methanol was stirring for 72 h to room temperature. The reaction mixture was evaporated to a smaller volume. After the mixture was diluted with water and extracted with chloroform (Fig. 2). The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol:water (2:1) yielding 62 % of product, m.p. 140-142 °C; IR (KBr, ν_{max}, cm^{-1}): 3320, 1676, 12340; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.84 (s, 3H), 0.98-1.02 (m, 2H), 1.06 (s, 3H), 1.28-1.64- (m, 6H), 1.68 (s, 3H), 1.70-1.96 (m, 5H), 2.10-2.40 (m, 7H), 3.06 (m, 2H), 3.46 (t, 2H, *J* = 6.44 Hz), 3.66 (t, 2H, *J* = 6.54 Hz), 3.70 (t, 2H, *J* = 6.44 Hz), 3.76 (t, 2H, *J* = 6.54 Hz), 3.82 (m, 2H), 5.80 (m, 1H), 5.88 (d, 1H), 5.92 (m, 1H) 6.50-6.88 (m, 7H), 7.00-7.60 (m, 14H), 7.74 (broad, 2H), 7.80-7.90 (m, 9H) ppm. ^{13}C NMR (75.4 Hz, $CDCl_3$) δ_C: 13.20 (**C**-18), 17.72 (**C**-32), 21.28 (**C**-5), 22.56 (**C**-33), 23.38 (**C**-71), 26.42 (**C**-8), 26.60 (**C**-9), 29.10 (**C**-74), 30.36 (**C**-15), 31.10 (**C**-16), 31.26 (**C**-11), 31.66 (**C**-10), 34.88 (**C**-3), 35.22 (**C**-17), 35.78 (**C**-28), 36.14 (**C**-22), 37.95 (**C**-6),

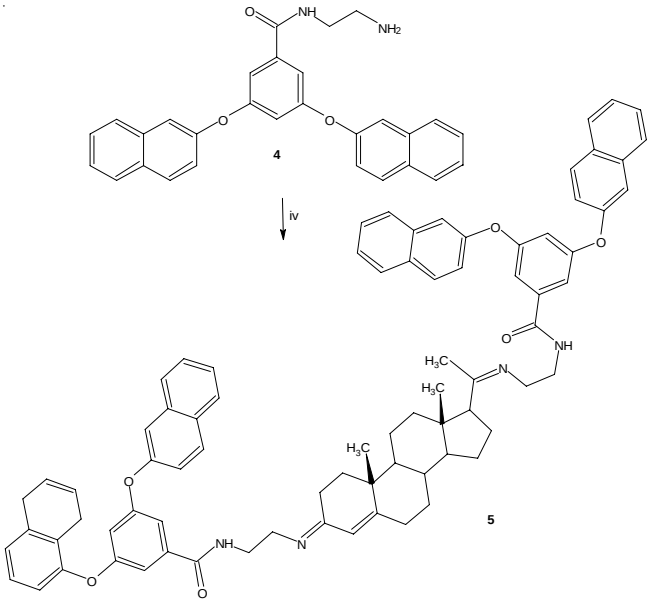

Fig. 2. Synthesis of 3,20-*bis*-{2-[3,5-*bis*-(naphthalen-2-yloxy)benzoyl-amino]ethylimino}pregnene (**5**). Reaction of N-(2-amino-ethyl)-3,5-*bis*-(naphthalen-2-yloxy)benzamide (**4**) with progesterone to form **5** using boric acid as catalyst (iv)

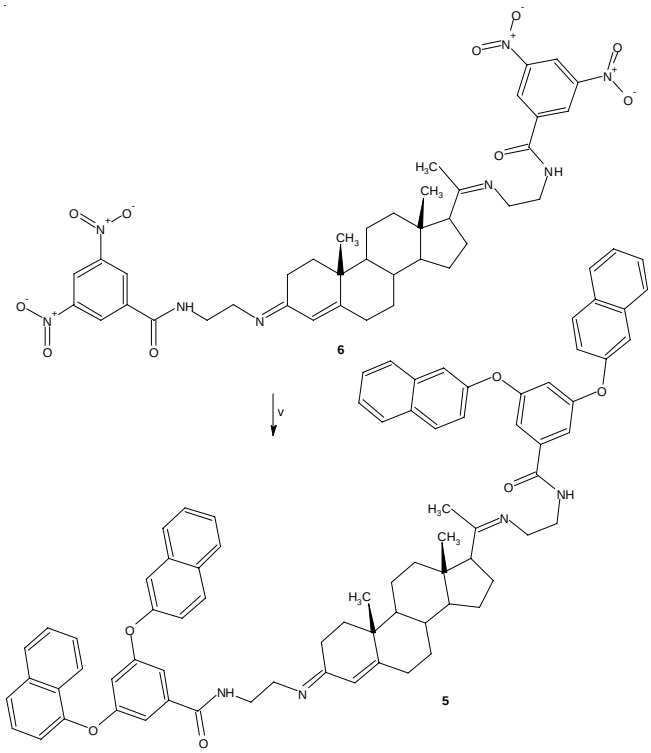

Fig. 3. Synthesis of 3,20-*bis*-{2-[3,5-*bis*-(naphthalen-2-yloxy)benzoyl-amino]ethylimino}pregnene (**5**). Reaction of N-[2-(1-{3-[2-(2,4-dinitro-benzenecarbonylamino)ethylimino]-10,13-dimethyl-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl}-ethylideneamino)ethyl]-2,4-dinitro-benzamide (**6**) with β-naphthol in presence of dimethyl sulfoxide (v)

42.76 (**C**-1), 51.94 (**C**-4), 52.73 (**C**-2), 54.38 (**C**-21), 54.40 (**C**-27), 56.58 (**C**-7), 105.50 (**C**-52, **C**-59, **C**-81), 108. 90 (**C**-78), 113.60 (**C**-43), 114.18 (**C**-48, **C**-63, **C**-88), 115.38 (**C**-41), 115.50 (**C**-13), 116.20 (**C**-37), 116.30 (**C**-41), 118.00 (**C**-35, **C**-39, **C**-45), 120.79 (**C**-54, **C**-66, **C**-85), 123.04 (**C**-55, **C**-65, **C**-86), 123.50 (**C**-76), 124.10 (**C**-53, **C**-67, **C**-84), 125.90 (**C**-50, **C**-61, **C**-83), 126.20 (**C**-77), 127.64 (**C**-56, **C**-64, **C**-87), 128.78 (**C**-73), 129.50 (**C**-72), 130. 30 (**C**-49, **C**-62, **C**-89), 131.00 (**C**-51, **C**-60, **C**-82), 137.66 (**C**-75), 146.10 (**C**-34, **C**-40), 149.34 **C**-69), 153.48 (**C**-47, **C**-58, **C**-80), 158.00 (**C**-12), 159.76 (**C**-36, **C**-38), 159.67 (**C**-38, **C**-44), 161.30 (**C**-42), 162.22 (**C**-24, **C**-30), 162.60 (**C**-19), 165.88 (**C**-14) ppm.EI-MS *m/z:* 1176.50 (M^+12). Anal. calcd. (%) for $C_{79}H_{76}N_4O_6$: C, 80.58; H, 6.51; N, 4.76, O, 8.15. Found (%): C, 80.54; H, 6.50.

Method B: A solution of **6** (100 mg, 0.13 mmol), β-naphthol (80 mg, 0.55 mmol) and potassium carbonate (20 mg, 0.15 mmol) in 10 mL of dimethyl sulfoxide was stirring for 72 h to room temperature. The reaction mixture was evaporated to a smaller volume. After the mixture was diluted with water and extracted with chloroform (Fig. 3). The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol:water (3:1) yielding 45 % of product. The ^{1}H NMR and ^{13}C NMR spectrums were similar in comparison with the product obtained by method A.

4-Chloro-1-{(2-[3,5-*bis*-(naphthalen-2-yloxy)benzoyl-amino])ethyl}-1H,2H-spiro[azetidi ne-3,3´-17-(4-chloro-1-methyl-3-oxo-2-{(2-[3,5-*bis*-(naphthalene-2-yloxy)-benzoyl-amino])ethyl}-2-aza-cyclobutyl)-10,13-dimethyl-2,3,6,7,8,9,10,11, 12,13, 14,15, 16,17-tetradecahydro-1H-cyclopenta[a]phenanthren]-2-one (7): A solution of **5** (100 mg, 0.13 mmol), triethylamine (100 µL, 1.50 mmol) and chloroacetyl chloride (128 µL, 1.60 mmol) in 10 mL of methanol was stirring for 72 h to room temperature. The reaction mixture was evaporated to a smaller volume. After the mixture was diluted with water and extracted with chloroform (Fig. 4). The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol:water (2:1) yielding 62 % of product, m.p. 118-120 °C; IR (KBr, ν_{max}, cm^{-1}): 1712, 1638, 1208; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.78 (s, 3H), 0.82-0.90 (m, 2H), 1.04 (s, 3H), 1.10-1.20 (m, 4H), 1.34 (s, 3H), 1.40-1.92 (m, 9H), 2.04-2.40 (m, 5H), 2.84-2.95 (m, 3H), 3.90 (t, 2H, *J* = 6.0), 3.96 (t, 2H, *J* = 6.0), 4.86-5.06 (m, 2H), 5.10 (m, 1H), 6.50-6.90 (m, 4H), 7.10-7.20 (m, 6H), 7.46-7.70 (m, 10H), 7.86-8.30 (m, 11H) ppm. ^{13}C NMR (75.4 Hz, $CDCl_3$) δ_C: 15.22 (**C**-39), 18.80 (**C**-30), 19.30 (**C**-47), 21.20 (**C**-15), 25.34 (**C**-17), 26..26 (**C**-18), 28.40 (**C**-29), 31.36 (**C**-19), 32.46 (**C**-20), 32.71 (**C**-28), 35.80 (**C**-41), 36.00 (**C**-13), 36.10 (**C**-6), 36.60 (**C**-27), 40.20 (**C**-16), 44.70 (**C**-11), 49.15 (**C**-5), 49.20 (**C**-40), 53.74 (**C**-14), 58.50 (**C**-10), 59.50 (**C**-12), 61.12 (**C**-23), 66.48 (**C**-2), 68.00 (**C**-26), 70.81 (**C**-3), 103.32 (**C**-82), 105.48 (**C**-54, **C**-61, **C**-89), 114.10 (**C**-50, **C**-65, **C**-96), 116.22 (**C**-36), 116.30 (**C**-71) 118.00 (**C**-34, **C**-38, **C**-75), 119.66 (**C**-22), 120.63 (**C**-56, **C**-68, **C**-93), 122.00 (**C**-80), 122.76 (**C**-85), 123.04 (**C**-57, **C**-67, **C**-94), 123.66 (**C**-83), 124.13 (**C**-55, **C**-69, **C**-92), 124.80 (**C**-78), 125.95 (**C**-52, **C**-63, **C**-91), 126.20 (**C**-84), 127.00 (**C**-81), 127.50 (**C**-86), 127.64 (**C**-58, **C**-66, **C**-95), 129.37 (**C**-79), 130.36 (**C**-51, **C**-64, **C**-97), 131.00 (**C**-53, **C**-62, **C**-90), 142.10 (**C**-21), 143.56 (**C**-33), 145.58 (**C**-70), 152.44 (**C**-77), 153.50 ((**C**-49, **C**-60, **C**-88), 159.73 (**C**-35, **C**-37), 161.78 (**C**-74), 162.12 (**C**-8, **C**-43), 163.28 (**C**-72), 165.66 (**C**-25), 166.39 (**C**-4) ppm. EI-MS *m/z:* 1326.50

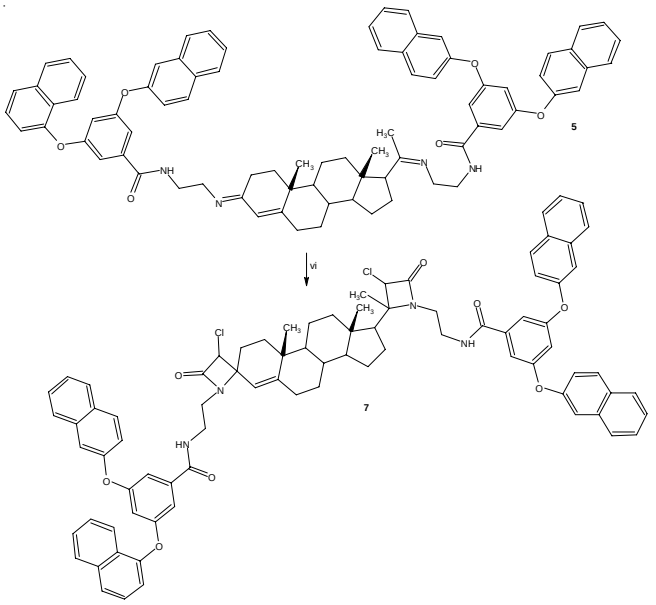

Fig. 4. Synthesis of 4-chloro-1-{(2-[3,5-*bis*-(naphthalen-2-yloxy)benzoylamino])ethyl}-1H,2H-spiro[azetidine-3,3´-17-(4-chloro-1-methyl-3-oxo-2-{(2-[3,5-*bis*-(naphthalene-2-yloxy)-benzoylamino])ethyl}-2-aza-cyclobutyl)-10,13-dimethyl-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren]-2-one(**7**). Reaction of 3,20-*bis*-{2-[3,5-*bis*-(naphthalen-2-yloxy)-benzoylamino]-ethylimino}-pregnene with chloroacetyl chloride in presence of triethylamine (vi)

(M^+12). Anal. calcd. (%) for $C_{83}H_{76}Cl_2N_4O_8$: C, 75.04; H, 5.27; Cl, 5.34; N, 4.22; O, 9.64. Found (%): C, 75.00; H, 5.24.

RESULTS AND DISCUSSION

In this study, a naphthalen-pregnen derivative was synthesized using some strategies; the first step was achieved by the synthesis of 3,5-*bis*(2-naphthyloxy)benzoic acid (**2**) *via* displacement of nitro group from 3,5-dinitrobenzoic acid. 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 whit methoxide using a dipolar aprotic solvent. In general, dipolar solvents are used to attain high yield of ether groups [11]. In this study, the compound **2** was synthetized by the reaction of 3,5-dinitro benzoic acid with β-naphthol in presence of dimetyhyl sulfoxide at mild conditions. The ^{1}H NMR spectrum of **2** shows signals at 5.60 ppm for carboxyl group; at 6.90-7.40 ppm for phenyl group bound to both ether groups; at 7.50-7.90 ppm for both naphthalene groups. The ^{13}C NMR spectrum of **2** contains peaks at 106.02, 113.98, 137.08 and 168.32 ppm for methylene groups of phenyl bound to both ether groups; at 107.28, 116.00-131.00 and 153.08 ppm for both naphthalene groups; at 168.00 ppm for carboxyl group. Finally, the presence of compound **2**was further confirmed from mass spectrum which showed a molecular ion at *m/z* 406.10.

The second stage, was achieved by the synthesis of N-(2-amino-ethyl)-3,5-*bis*-(naphthalen-2-yloxy)benzamide (**4**) using two methods. In the first step (method A), **4** was synthesized by the reaction of **2** with ethylenediamine to formation of amide group. It is important to mention that many procedures for the formation of amide groups are known in the literature [12-14], the most widely practiced method employs carboxylic acid chlorides as the electrophiles which react with the amino group in the presence of an acid scavenger [15]. Despite its wide scope, the former protocol suffers from several drawbacks; most notable are the limited stability of many acid chlorides and the need for hazardous reagents for their preparation (thionyl chloride) [16]. Other data indicate that boric acid catalyzed amidation of carboxylic acids and amines [17]; therefore, in this study the compound **4** was synthetized by the reaction of **2** with ethylenediamine using boric acid as catalyst. The ^{1}H NMR spectrum of **4** shows signals at 3.08 and 3.40 ppm for methylene groups bound to both amino and amide groups, at 4.98 ppm both amino groups; at 6.50-7.90 ppm for phenyl groups. The ^{13}C NMR spectrum of **4** contains peaks at 43.66 and 46.40 ppm for methylene groups bound to both amino and amide groups; at 105.46-159.74 for phenyl groups; at 161.86 ppm for amide group. Finally, the presence of compound **4** was further confirmed from mass spectrum which showed a molecular ion at *m/z* 448.10. In the second step (method B), was achieved by the reaction of **3** with β-naphthol for the synthesis of **4** using dimethyl sulfoxide at mild conditions. With this procedure it was found that the use of method A to development the compound **4** resulted in higher yields compared with method B.

On the other hand, the second stage was achieved by the synthesis of 3,20-*bis*-{2-[3,5-*bis*-(naphthalen-2-yloxy)-benzoylamino]ethylimino}pregnene (**5**). This compound was synthetized with two methods; in the method A, the compound **5** was developed by the reaction of **4** with progesterone to form **5** using boric acid as catalyst. The ^{1}H NMR spectrum of **5** shows signals at 0.84 and 1.06 ppm for methyl groups bound to steroid nucleus; at 1.68 ppm for methyl group bound to imino group; at 0.98-1.02, 1.28-1.64-2.40, 5.88 ppm for steroid moiety; at 3.46 and 3.76 ppm for methylene groups bound to both imino and amide groups (ring A); at 3.66 and 3.70 ppm for methylene groups bound to both imino and amide groups (ring D); at 3.06, 3.84-5.80, 5.98-7.90 ppm for phenyl groups; at 7.74 ppm for both amide groups. The ^{13}C NMR spectrum of **5** contains peaks at 13.20 and 17.72 ppm for methyl groups; at 22.56 ppm for methyl group bound to imino group; at 21.28, 26.42-26.60, 30.36-35.22, 37.95-52.73, 56.58, 115.50 and 158.00 ppm for steroid moiety; at 23.40, 29.12, 29.12, 105.50-115.40, 116.20-153.48 and 159.76-161.30 ppm for phenyl groups; at 35.78 and 54.40 ppm for methylene groups bound to both imino and amide groups (ring A); at 36.14 and 54.38 ppm for methylene groups bound to both imino and amide groups (ring D); at 162.22 ppm for both amide groups; at 162.60 and 165.88 ppm for both imino groups. Finally, the presence of compound **5** was further confirmed from mass spectrum which showed a molecular ion at *m/z* 1174.50.The method B was achieved by the reaction of **6** with β-naphthol in presence of dimethyl sulfoxide at mild conditions to form the compound **5**. The yielding of **5** was less in comparison with the method A, possibly this phenomenon is due to reaction time.

Finally, last stage was achieved by the synthesis of 4-chloro-1-{(2-[3,5-*bis*-(naphthalen-2-yloxy)benzoyl-amino])ethyl}-1H,2H-spiro[azetidine-3,3´-17-(4-chloro-1-

methyl-3-oxo-2-{(2-[3,5-*bis*-(naphthalene-2-yloxy)benzoyl-amino])ethyl}-2-aza-cyclobutyl)-10,13-dimethyl-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren]-2-one (**7**) by the reaction of **5** with chloroacetyl chloride in the presence of triethylamine. This method has been previously reported for other type of compound with imino groups involved in its structure chemical, which react with chloroacetyl chloride to form chloroazetidinone groups [16]. The ^{1}H NMR spectrum of **7** shows signals at 0.78 and 1.04 ppm for methyl groups bound to steroid nucleus; at 1.34 ppm for methyl bound to chloroazetidinone group; at 1.10-1.20, 2.04-2.40 and 5.10 ppm for steroid moiety; at 4.86-5.06 ppm for chloroazetidinone groups; at 2.84-2.95 and 3.90-3.96 ppm methylene groups bound to both chloroazetidinone and amide groups; at 6.50-7.46 ppm for phenyl groups. The ^{13}C NMR spectrum of **7** contains peaks at 15.22 and 19.30 ppm for methyl groups bound to steroid nucleus; at 18.80 ppm for methyl bound to chloroazetidinone group; at 15.18 and 19.00 ppm for methyl groups bound to steroid nucleus; at 21.20-32.71, 36.00, 36.60-44.70, 53.74-61.12, 119.66 and 142.10 ppm for steroid moiety; at 64.48-70.81, 165.66 and 166.39 for both chloroazetidinone groups; at 103.32-118.00, 120.63-131.00, 143.56-161.78 and 163.28 ppm for phenyl groups; at 162.12 ppm for both amide groups. Finally, the presence of compound **7** was further confirmed from mass spectrum which showed a molecular ion at *m/z* 1326.50.

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