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Design and Synthesis of Two Azetidin-haloperidol Derivatives using Some Strategies

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ABSTRACT

In this study is reported a straight forward route for synthesis of two azetidin-haloperidol derivatives using some strategies. The first stage was achieved by the synthesis of an azetidine derivative (3) by the reaction of a haloperidol derivative (1) with chloroacetyl chloride in presence oftriethylamine. The second stage was achieved by reaction of an estradiol derivative with 1 to forma haloperidol-estradiol derivative (5) using boric acid as catalyst. Finally, the third stage involves the synthesis of a second azetidine-derivative (6) by the reaction of 5 with chloroacetyl chloride usingtriethylamine as catalyst. The structure of the compounds obtained was confirmed by elemental analysis, spectroscopy and spectrometry data. The proposed method offers some advantages such as simple procedure, low cost, and ease of workup.

Key words: Azetidin-haloperidol derivatives, Elemental analysis, Spectroscopy.

INTRODUCTION

Since several years ago, have been prepared some azetidine derivatives using different methods. For example, the synthesis of 1,2,4-trisubstituted azetidines by reductive cyclization of aza-Michael adducts of chalcones[1]. Other study[2] showed the preparation of N-Benzyl-3-hydroxyazetidine by the reaction of N-Benzyl-3-chloro-2-hydroxypropylamine with $NaHCO_3$ in MeCN.

In addition, other data indicate the synthesis of azetidine-2,3-diones by mild hydrolysis of the product of the reaction between α-phenylthio-β-lactams and sulfuryl chloride[3]. Other report showed the synthesis of (2*R*,4*S*)-3-methyl-2,4-diphenylazetidine by the reaction of (2*S*,3*S*)-3-amino-2-methyl-1,3-diphenylpropan-1-ol with Et_3N and MsCl in basic medium[4].Additionaly, a study shown the synthesis of trans-l-(Diphenylmethyl)-2-methyl-3-azetidinol by the reaction of threo-3-bromo-1,2-epoxybutane with diphenylmethylamine[5]. Also other report indicate the preparation of 2-[22 -{42 2 -substituted aryl-32 2 -chloro-22 2 -oxo-azetidine}-acetyl amino]-4-phenyl-1,3-thiazole by the reaction of 2-(22 -Arylidene-hydrazino-acetyl)-amino-4-phenyl-1,3-thiazole with chloroacetyl chloride in presence of triethylamine[6]. Additionally, a study showed the synthesis of N-phenyl-3,3-dimethyl-azetidine-2,4-dione by reaction of phenylisocyanate with isobutyryl chloride using triethylamine as catalyst[7]. All these experimental results show several procedures which are available for synthesis of several azetidine derivatives; nevertheless, expensive reagents and special conditions are required. Therefore, in this study two azetidin-haloperidol derivatives were synthetized using some strategies.

EXPERIMENTAL

The compound 1-[4-(2-Amino-ethylimino)-4-(4-fluorocyclohexyl)-butyl]-4-(4-chloro-phenyl)-piperidin-4-ol (**1**) and 3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14, 15,16,17-decahydro-6H-cyclopenta [a]phenanthrene-2,4-dicarbaldehyde (4) were prepared according to previously reported method[8,9]. The 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. ^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 GCPolaris Q. spectrometer. Elementary analysis data were acquired from a Perkin Elmer Ser. II CHNS/0 2400 elementalanalyzer.

Chloro-aceticacid 1-(3-{3-chloro-1-[2-(2-chloro-acetylamino)-ethyl]-4-oxo-2-phenyl-azetidin-2-yl}-propyl)-4-(4-chloro-phenyl)-piperidin-4-yl ester (3).

A solution of 1 (100 mg, 0.24mmol), chloroacetyl chloride (50µl, 0.63mmol) and triethylamine (100µl, 0.71mmol) in 5 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. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol: water (3:1) yielding 69 % of product, m.p. 98-100°C; IR (V_{max}, cm^{-1}): 1724, 1712, 1648, 1210;^1H NMR (300 MHz, $CDCl_3$) δ_H: 1.64-1.79 (m, 4H), 1.80 (t, 2H, J = 7.47 Hz), 1.86-2.06 (m, 2H), 2.48 (t, 2H, J = 7.8 Hz), 2.80 (m, 1H), 2.84 (m, 2H), 2.88 (m, 1H), 3.06 (m, 2H), 3.84 (t, 2H, J = 6.03 Hz), 4.10 (t, 2H, J 13.62 Hz), 4.30 (t, 2H, J = 14.80 Hz), 5.32 (m, 1H), 6.60 (broad, 1H), 7.02-7.30 (m, 8H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$) δ_C: 23.00 (C-8), 32.80 (C-9), 33.98 (C-3, C-5), 35.39 (C-30), 42.00 (C-36), 42.40 (C-40), 46.90(C-2, C-6), 49.30 (C-29), 55.28 (C-7), 70.78 (C13), 74.00 (C-10), 79.66 (C-4), 115.08 (C-25, C-27), 122.38 (C-24, C-28), 128.30(C-19, C-21), 128.50 (C-18, C-22),134.22 (C-20), 136.40 (C-23), 141.00(C-17), 161.68 (C-26), 162.58(C-32), 166.30(C-12), 167.28(C-15) ppm. EI-MS *m/z:* 644.10 (M^+12). Anal. Calcd. for $C_{29}H_{32}Cl_4FN_3O_4$: C, 53.80; H, 4.98; Cl, 21.90; F, 2.93; N, 6.49; O, 9.89. Found: C, 53.78; H, 4.96.

2,4-Bis-({2-[4-[4-(4-chloro-phenyl)-4-hydroxy-piperridin-1-yl]-1-(4-fluoro-phenyl)-butylideneamino]-ethylimino}-methyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol (5)

A solution of 1 (100 mg, 0.24mmol), 4 (160 mg, 0.48 mmol) and boric acid (90 mg, 1.45mmol) in 5 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. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol:water (3:2) yielding 48 % of product, m.p. 112-114°C; IR (V_{max}, cm^{-1}): 3400, 3320, 1204, ^1H NMR (300 MHz, $CDCl_3$) δ_H: 0.68 (s, 3H), 0.80-1.40 (m, 7H), 1.58-1.66 (m, 8H), 1.70 (m, 4H), 1.78-2.16 (m, 5H), 2.46-2.52 (m, 8H), 2.80 (m, 4H), 2.96-2.98 (m, 2H), 3.02 (m, 4H), 3.03 (m, 1H), 3.50 (m, 4H), 3.68 (m, 1H), 3.76 (m, 4H), 6.90-7.20 (m, 12H), 7.40 (m, 1H), 7.84 (broad, 4H), 7.98-8.08 (m, 2H), 8.16 (m, 4H) ppm.^{13}C NMR (75.4 MHz, $CDCl_3$) δ_C:

13.20 (C-59), 23.76 (C-27), 25.50 (C-20), 25.67 (C-31), 26.80 (C-8, C-64), 27.92 (C-21), 31.10 (C-26), 35.12 (C-9, C-63), 35.60 (C-32), 38.25 (C-68), 38.30(C-3, C-5, C-70), 38.86 (C-22), 44.32 (C-24), 46.18 (C-30), 47.00(C-2, C-6, C-67, C-71), 48.94(C-23), 52.44(C-12, C-50), 54.25 (C-7, (C-65), 60.00(C-13, C- 49), 70.00 (C-4, C-70), 81.24 (C-25), 110.76(C-18), 115.00 (C-42, C-44, C-55, C-57), 119.66(C-16), 126.84 (C-41, C-45, C-54, C-58), 128.52(C-36, C-38, C-76, C-78), 128.8 (C-29), 129.10 (C-35, C-39, C-75, C-79), 134.98 (C-40, C-53), 135.60(C-28), 136.12(C-37, C-77), 145.14(C-34, C-74), 149.78 (C-19), 158.70(C-17), 162.50 (C-47), 162.88(C-15), 163.84(C-43, C-56), 165.08 (C-10, C-52) ppm.EI-MS *m/z:* 1126.50 (M^+10). Anal. Calcd. for $C_{66}H_{78}Cl_2F_2N_6O_4$: C, 70.26; H, 6.97; Cl, 6.28; F, 3.37; N, 7.45; O, 5.67. Found: C, 70.22; H, 6.96.

Chloro-aceticacid 2,4-bis-[3-chloro-1-(2-{3-chloro-2-[4-[4-(2-chloro-acetoxy)-4-(4-chlorophenyl)-piperidin-1-yl]-1-(4-fluoro-phenyl)-butyl]4-oxo-azetidin-1-yl}-ethyl)-4-oxo-azetidin-2-yl]-17-[(chlorocarbonyl)oxy]-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6-H-cyclopenta[a]phenanthren-3-yl ester (6)

A solution of **5** (200 mg, 0.18 mmol), chloroacetyl chloride (50 µl, 0.63mmol) and triethylamine (100 µl, 0.71 mmol) in 5 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. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol:water (3:1) yielding 86 % of product, m.p. 98-100°C; IR (V_{max}, cm^{-1}): 1722, 1710, 1206;^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.80 (s, 3H), 1.18-1.50 (m, 6H), 1.66 (m, 4H), 1.70 (m, 4H), 1.72-1.76 (m, 3H), 1.79 (m, 4H), 1.82 (m, 2H), 1.90 (m, 1H), 1.96 (m, 2H), 2.10-2.20 (m, 2H), 2.40 (m, 4H), 2.54-2.60 (m, 3H), 2.80-3.02 (m, 8H), 3.40 (m, 2H), 3.50-3.60(m, 8H),4.08 (m, 2H), 4.12-4.30 (m, 8H), 4.70-4.76 (m, 3H), 4.80 (m, 1H), 4.90-5.70 (m, 3H), 6.78-7.22 (m, 17H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$) d_C:11.78 (C-68), 23.83 (C-53), 25.97 (C-57), 27.25 (C-52), 27.71 (C-47), 27.80 (C-8, C-86),), 28.16 (C-46), 31.10(C-9, C-85), 34.00(C-3, C-5, C-90, C-92),37.28 (C-58), 38.80 (C-48), 40.56 (C-72), 40.78 (C-82), 42.00 (C-38, C-112), 43.10 (C-50), 44.68 (C-30, C-75), 45.04 (C-31, C-74), 46.10 (C-56), 46.50 (C-10, C-84), 47.00(C-2, C-6, C-89, C-93), 51.24 (C-49), 55.28(C-7, C-87), 60.40 (C-14, C-78), 61.32 (C-64),62.66 (C-64), 63.10 (C-67), 64.80(C-33), 71.44 (C-11, C-77), 79.22 (C-4, C-91),81.64 (C-51), 114.65 (C-26, C-28, C-100), 126.18 (C-54), 126.30 (C-42), 128.28(C-20, C-22, C-107, C-109), 128.50 (C-19, C-23, C-106, C-110),130.83 (C-25, 131.97 C-29, C-9), C-106), 131.10 (C-24, C-96),132.38 (C-44), 134.30(C-21, C-108), 135.53 (C-45), 140.61 (C-18, C-105), 141.66(C-43), 143.79 (C-55), 160.10 (C-27, C-99), 166.00(C-13, C-79),166.20 (C-35, C-66), 167.25(C-16, C-103), 168.00 (C-70), 168.16 (C-62) ppm. EI-MS *m/z:* 1762.30(M^+8). Anal. Calcd. for $C_{84}H_{90}Cl_{10}F_2N_6O_{12}$: C, 57.06; H, 5.13; Cl, 20.05; F, 2.15; N, 4.75; O, 10.86. Found: C, 57.04; H, 5.10.

RESULTS AND DISCUSSION

In this study is reporteda straight forward route for synthesis of two azetidin-haloperidol derivatives using some strategies. The first stage was achieved by the synthesis of 1-(3-{3-chloro-1-[2-(2-chloro-acetylamino)-ethyl]-4-oxo-2-phenyl-azetidin-2-yl}-propyl)-4-(4-chloro-phenyl)-piperidin-4-yl ester(**3**) by the reaction of **1** with chloroacetyl chloride using triethylamine as catalyst. It is important to mention that this method has been previously reported for other type of compound with animino group involved in its structure chemical, which react with chloroacetyl chloride to form an azetine group in presence of triethylamine[10]. However, it is noteworthy that amino group of compound **3**also reacting with chloroacetyl chloride to form a new chloroamide group; this method is different to several previously reported procedures for thechloroamides formation[11,12].The ^{1}H NMR spectrum of the 3 shows signals at1.64-1.79, 2.84 and 3.06 ppm for piperidine group; at 1.80-2.48 ppm for methylene groups bound to both piperidine and azetidinegroups; at 2.80, 3.84 for methylene groups bound to both azetidine and amide groups; at 4.10 ppm for methylene group bound to chloroacetamide group; at 4.30 ppm for methylene group bound to ester group; at 5.32 ppm for proton involved in the azetidinering; at 6.60 ppm for amide group; at 7.02-7.30 ppm for phenyl groups.The ^{13}C NMR spectra displays chemical shifts at23.00, 32.80 and 55.28 ppm for methylene groups bound to piperidine and azetidine groups, at 33.98, 46.90and 79.66 ppm for piperidine group; at 35.30

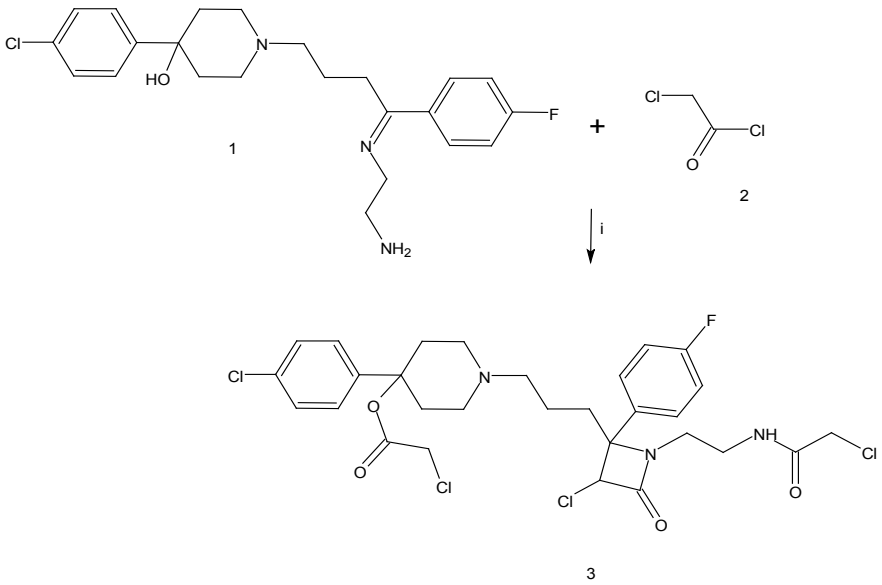

Fig. 1: Synthesis of Chloro-aceticacid 1-(3-{3-chloro-1-[2-(2-chloro-acetylamino)-ethyl]-4-oxo-2-phenyl-azetidin-2-yl}-propyl)-4-(4-chloro-phenyl)-piperidin-4-yl ester (3).Reactionof1-[4-(2-Amino-ethylimino)-4-(4-fluorocyclohexyl)-butyl]-4-(4-chloro-phenyl)-piperidin-4-ol (1) with chloroacetyl chloride (2) usingtriethylamine as catalyst (i)

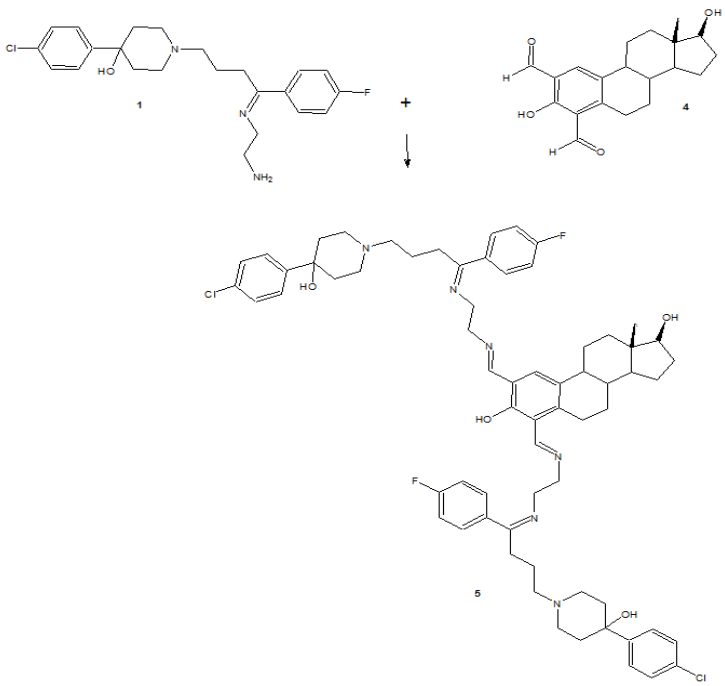

Figure 2. Synthesis of 2,4-Bis-({2-[4-[4-(4-chloro-phenyl)-4-hydroxy-piperridin-1-yl]-1-(4-fluoro-phenyl)-butylideneamino]-ethylimino}-methyl)-13-methyl-7,8,9,11,12,13,14,15,16, 17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol (5). Reactionof1with3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-2,4-dicarbaldehyde (4)tosynthesisof5 usingboricacid as catalyst (ii)

and 49.30 ppm for methylene bound to both azetidine and amide groups, at 42.00 ppm for methylene group bound to ester group; at 42.40 ppm for methylene group bound to chloroacetamide group; at 70.78 and 74.00 ppm for carbons involved in the azetidine group;at 115.08-161.68 ppm for phenyl groups; at 162.58 ppm for amide group; at 166.30 ppm for ketone group; at 167.28 ppm for ester group. Finally, the presence of **3** was further confirmed from mass spectrum which showed a molecular ion at m/z 644.

The second stage was achieved by reaction of 1 with an estradiol derivative to form the compound5. It is important to mention there are several reports which indicate the synthesis of imino groups; nevertheless, expensive reagents and special conditions are required[13]. In this study, boric acid was used as catalyst to formation of imino group involved in the chemical structure of 5. ^{1}H NMR spectrum of the 5 shows signals at0.68 ppm for methyl group; at 0.80-1.40, 1.78-2.16, 2.96-2.98, 3.03, 3.68 and 7.40 ppm for steroid moiety; at 1.58-1.66, 2.80 and 3.02 ppm for piperidine groups; at 1.70 and 2.46-2.52 ppm for methylene groups bound to both piperidine rings; at 3.50 and 3.76 ppm for methylene groups bound to imino groups; at 7.84 ppm for hydroxyl groups; at 6.90-7.20 and 8.16 ppm for phenyl groups; at 7.98-8.08 ppm for imino groups. The ^{13}C NMR spectra displays chemical shifts at13.20 ppm for methyl group bound to steroid nucleus; at 23.76-25.67, 27.92-31.10, 35.60, 38.86-46.18, 48.94, 81.24-110.76, 119.66, 128.80, 135.60 and 149.78-158.70 ppm for steroid moiety; at 26.80, 35.12 and 54.25 ppm for methylene groups bound to piperidine ring; at 52.44 and 60.00 ppm for methylene groups bound to both imine groups; at 38.25-38.30 and 47.00-70.00 ppm for piperidine ring; at 162.50-162.88 and 165.08 ppm for imino groups; at 115.00,

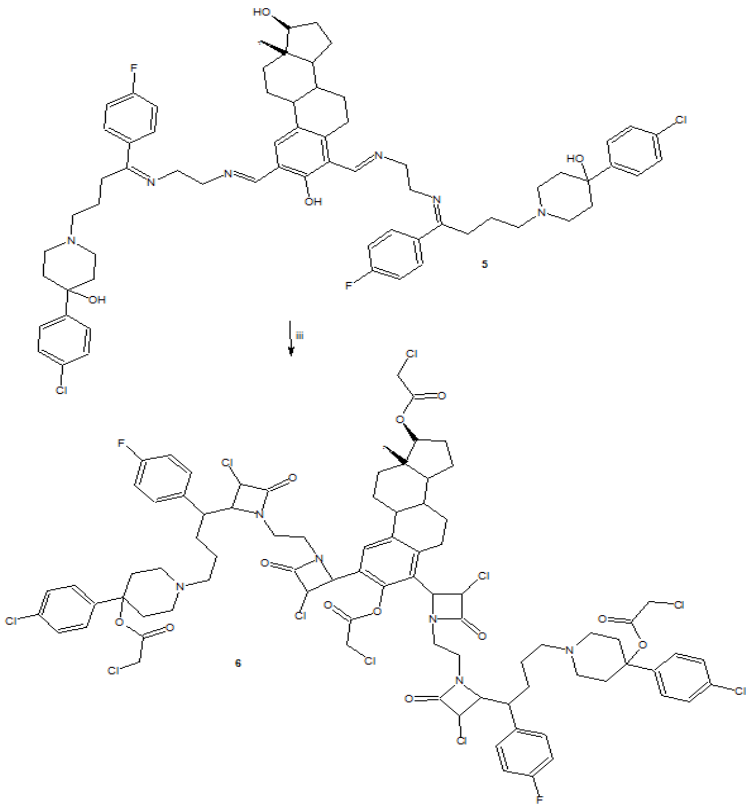

Fig. 3: Synthesis of Chloro-aceticacid 2,4-bis-[3-chloro-1-(2-{3-chloro-2-[4-[4-(2-chloro-acetoxy) -4-(4-chlorophenyl)-piperidin-1-yl]-1-(4-fluoro-phenyl)-butyl]4-oxo-azetidin-1-yl}-ethyl)-4-oxo-azetidin-2-yl]-17-[(chlorocarbonyl)oxy]-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6-H-cyclopenta[a]phenanthren-3-yl ester (6).Reactionof5withchloroacetyl chloride (2) usingtriethylamine as catalyst (iii)

126.84-128.52, 129.10-134.98, 136.12-145.14 and 163.84 ppm for phenyl groups. Finally, the presence of 5 was further confirmed from mass spectrum which showed a molecular ion at m/z1126.50.

The third stage was achieved by the preparation of an azetine-steroid derivative (6) by the reaction of 5with chloroacetylchloride to form an azetine groupinvolved in the compound 6 using triethylamine as catalyst. The ^{1}H NMR spectrum of the 6 shows signals at 0.80 ppm for methyl group; at 1.18-1.50, 1.72-1.76, 1.90, 2.10-2.20,, 2.54-2.60 and 4.80 ppm for steroid nucleus; at 1.66, 1.82, 1.96, and 2.40 ppm for methylene groups bound to both piperidine and phenyl groupsat 1.70, 1.79, 2.80-3.02 ppm from both piperidine rings; at 3.40 ppm for methylene groups bound to both phenyl and azetidine; at 3.50-3.60 ppm for methylene bound to azetidine groups; at 4.12-4.30 ppm for methylene bound to ester groups; at 4.08, 4.704.76, 4.90-5.70 ppm for protons involved in the azetidine rings; at 6.78-7.22 ppm for phenyl groups. The ^{13}C NMR spectra displays chemical shifts at11.78 ppm for methyl group; at 23.83-27.71. 28.16, 37.28-38.80, 43.10, 46.10, 51.24, 81.64, 126.18-126.30, 132.38, 135.53 and 141.36-143.79 ppm for steroid moiety; at 27.80, 31.10 and 55.28 ppm for methylene groups bound to both phenyl and piperidine groups; at 34.00, 47.00 and 79.22 ppm for piperidine ring; at 40.56-42.00 for methylene groups bound to ester groups; at 60.40-71.44, 166.00 for azetidine rings; at 44.68-45.04 ppm for methylene groups bound to azetidine rings; at 46.50 ppm for methylene bound to both phenyl and azetidine groups; at 114.65, 128.28-131.10, 134.30, 140.61 and 160.10 ppm for phenyl groups; at 167.25 and 168.16 ppm for ester groups; at 166.00-166.20 for ketone groups. Finally, the presence of 6 was further confirmed from mass spectrum which showed a molecular ion at m/z1762.30.

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