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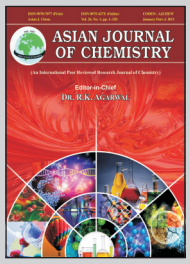

Design and Synthesis of Prednisone Derivatives

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In this study, some prednisone derivatives were synthesized. The first stage involves the synthesis of 3,11-*bis*-(2-amino-ethylimino)-17-[1-(2-amino-ethylimino)-2-hydroxyethyl]-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[a]phenanthren-17-ol (**3**) by the reaction of prednisone with ethylenediamine using boric acid as catalyst. The second stage was achieved by reaction of 1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**4**) with the compound **3** using boric acid as catalyst resulting in imino bond formation involved in the compound 2-[3,11-*bis*-{2-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylideneamino)}-10,13,17-trimethyl-6,7,8,9,10,11,12,12,14,15,16,17-dodecahydro-3*H*-cyclopenta[a]phenanthren-17-yl]-2-[2-(1,7,7-trimethyl-bycyclo[2.2.1]hept-2-ylideneamino)ethylimino]ethanol (**5**). In addition, the third stage was achieved by reaction of compound **3**, benzaldehyde and compound **4** using proline as catalyst to form the compound 3-({2-[2-hydroxy-3-(17-hydroxy-3,11-*bis*[2-(1,7,7-trimethyl-byciclo[2.2.1]heptan-2-one-3-ylenamino)phenyl-methyl]-10,13-dimethyl-6,7,8- 9,10,11,12,13,14,15-16,17,-dodecahydro-3*H*-cyclopenta[a]phenanthren-17-yl)-propilidene amino]ethyl-amino}phenyl-methyl)-1,7,7-trimethyl-byciclo[2.2.1]heptan-2-one (**7**). Finally, the four stage was achieved by reaction of 7,7-dimethyl-2-oxobicyclo-[2.2.1]hept-1-yl) methanesulfonic acid, compound **3** and benzaldehyde using proline as catalyst to form the compound 3-({2-[2-hydroxy-3-(17-hydroxy-3,11-*bis*[2-{7,7-dimethyl-3-(ylenamino-phenyl-methyl)-2-oxo-bicyclo[2.2.1]hept-1-yl}methansulfonic acid]-100,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[a]phenanthren-17-yl)propiliden-amino]ethylamino)-7,7-dimethyl-3-(ylenamino-phenyl-methyl)-2-oxo-bicyclo[2.2.1]hept-1-yl-methansulfonic acid] (**9**).The structure of compounds obtained was confirmed by spectroscopy and spectrometry data.

Keywords: Prednisone, Ethylenediamine, Proline.

INTRODUCTION

There are been increasing interest in the development of corticosteroid derivatives[1-3]. For example, the synthesis of 3,20-dioxopregn-4-en-21-al by oxidation of 21-hydroxypregn-4-ene-3,20-dione with cupric acetate[4]. Other studies[5] showed the preparation of methyl (17-hydroxy-3,11,20-trioxopregn-4-en-21-yl-2,3,4-tri-O-acetyl-β-D-glucoside)uronate by the reaction of cortisone with 2,3,4-tri-O-acetyl-1-bromo-l-deoxy-α-D-glucuronate. In addition, there are some reports on the preparation of 9α,11β-dichloro-17α,21-dihydroxy-l6α-methyl-l,4-pregnadiene-3,20-dione 17-(2´-furoate) 21-acetate by the reaction of 9α,11β-dichloro-17α,21-dihydroxy-l6α-methyl-l,4-pregnadiene-3,20-dione 21-acetate with 2-furoyl chloride using 4-DMAP as catalyst[6]. Other data indicate the synthesis of *bis*(μ-chloro)-*bis*[(4-6-η-17α,20,20,21-*bis*(methylenedioxy)-11β-hydroxy-3-oxopregnenyl)palladium^{II}] by the reaction of cortisol-*bis*(methy1enedioxy)ether with palladium(II) chloride[7]. Additionally, other studies shown that 3α-acetoxy-16-methy1-16-pregnene-11,20-diene was catalytically reduced using palladium on charcoal in acetic acid[8]. Also, other corticosteroid derivative (1,4-pregnadiene-l7α,20β,21-triol-3,11-dione-20-mesylate-21-acetate) was synthetized by the reaction of 1,4-pregnadiene-17α,20β,21-trio1-3,11-dione-21-acetate with methane sulfonyl chloride in presence of pyridine[9]. Other data, showed the synthesis of glucocorticoid-C_{60} hybrids by the reaction of prednisone with methanofullerene carboxylic acid using N,N'-dicyclohexyl-carbodiimide/4-dimethylamino-pyridine[9]. All these data showed several procedures for synthesis of corticosteroide derivatives; for this, expensive

reagents and special conditions are required. Therefore, in this study some prednisone derivatives were synthetized using some strategies.

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 were recorded using KBr pellets on a Perkin Elmer Lambda 40 spectrometer. ^{1}H 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 elemental analyzer.

Synthesis of 3,11-*bis*-(2-amino-ethylimino)-17-[1-(2-aminoethylimino)-2-hydroxy-ethyl]-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[a]phenanthren-17-ol (3): A solution of prednisone (100 mg, 0.28 mmol), ethylenediamine (100 µL, 1.50 mmol) and boric acid (100 mg, 1.61 mmol) in 10 mL of ethanol was stirring for 72 h to room temperature. The reaction mixture was evaporated to a smaller volume (Fig. 1). After the mixture was diluted with water and the precipitate was separated and washed with excess of water yielding 80 % of product, m.p. 158 °C; IR (ν_{max}, cm^{-1}): 3380 (OH), 3330, 1620; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.85 (m, 1H), 1.19 (s, 3H), 1.21(s, 3H), 1.31-2.86 (m, 11H), 2.96 (t, 2H, *J* = 6.44 Hz), 2.98 (t, 2H, *J* = 6.44 Hz), 3.34 (t, 2H, *J* = 6.44 Hz), 3.36 (m, 1H), 3.68 (t, 2H, *J* = 8.79 Hz), 3.72 (t, 2H, *J* = 8.79 Hz), 3.75 (t, 2H, *J* = 8.79 Hz), 3.96 (broad, 8H), 4.26 (t, 2H, *J* = 6.44 Hz), 6.09 -6.90 (d, 3H, 9.93 Hz) ppm. ^{13}C NMR (75.4 Hz, $CDCl_3$) δ_C : 16.54 (C-18), 21.30 (C-23), 23.90 (C-17), 26.50 (C-14), 29.70 (C-4), 31.44 (C-5), 31.80 (C-16), 35.24 (C-11) 36.9 0 (C-3), 40.50 (C-21), 41.18 (C-26), 41.20 (C-32), 46.68 (C-20), 48.62 (C-34), 51.00 (C-2), 53.10 (C-1), 53.38 (C-31), 53.60 (C-25), 63.38 (C-12), 91.44 (C-15), 95.76 (C-7), 113.42 (C-9), 130.65 (C-29), 144.70 (C-10), 154.22 (C-6), 165.12 (C-13), 171.80 (C-8) ppm. EI-MS *m/z*: 484.30 (M^+, 12), Anal. Calcd (%) for $C_{27}H_{44}N_6O_2$: C, 66.91; H, 9.15; N, 17.34; Found (%): C, 66.88; H, 9.12.

Synthesis of 2-[3,11-*bis*-{2-(1,7,7-trimethyl-bicyclo-[2.2.1]hept-2-ylideneamino)}-10,13,17-trimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[a]-phenanthren-17-yl]-2-[2-(1,7,7-trimethyl-bicyclo[2.2.1]-hept-2-ylideneamino)ethylimino]ethanol (5): A solution of compound **3** (100 mg, 0.20 mmol), 1,7,7-trimethylbicyclo-[2.2.1]heptan-2-one (100 mg, 0.66 mmol) and boric acid (100 mg, 1.61 mmol) in 10 mL of methanol was stirring for 72 h to room temperature. The reaction mixture was evaporated to a smaller volume (Fig. 2). After the mixture was diluted with

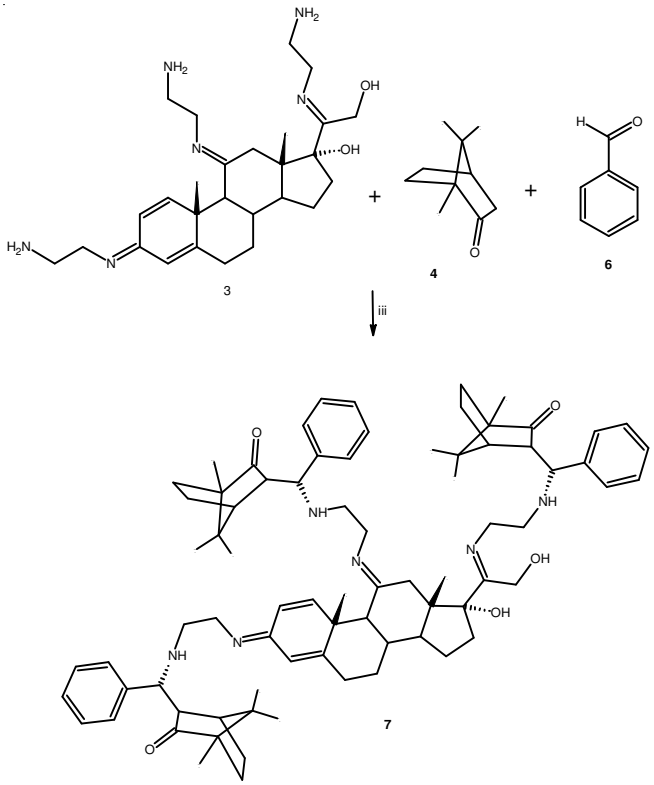

Fig. 2. Synthesis of 2-[3,11-*bis*-{2-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylideneamino)}-10,13,17-trimethyl-6,7,8,9,10,11,12,12,14,15,16,17-dodecahydro-3*H*-cyclopenta[a]phenanthren-17-yl]2-[2-(1,7,7-trimethyl-bycyclo[2.2.1]hept-2-ylideneamino)ethylimino]-ethanol (**5**). Reaction of a prednisone derivative (**3**) with 1,7,7-trimethyl- bicyclo[2.2.1]heptan-2-one and boric acid (**4**) using boric acid as catalyst to form **5**. ii = methanol/room temperature (rt)

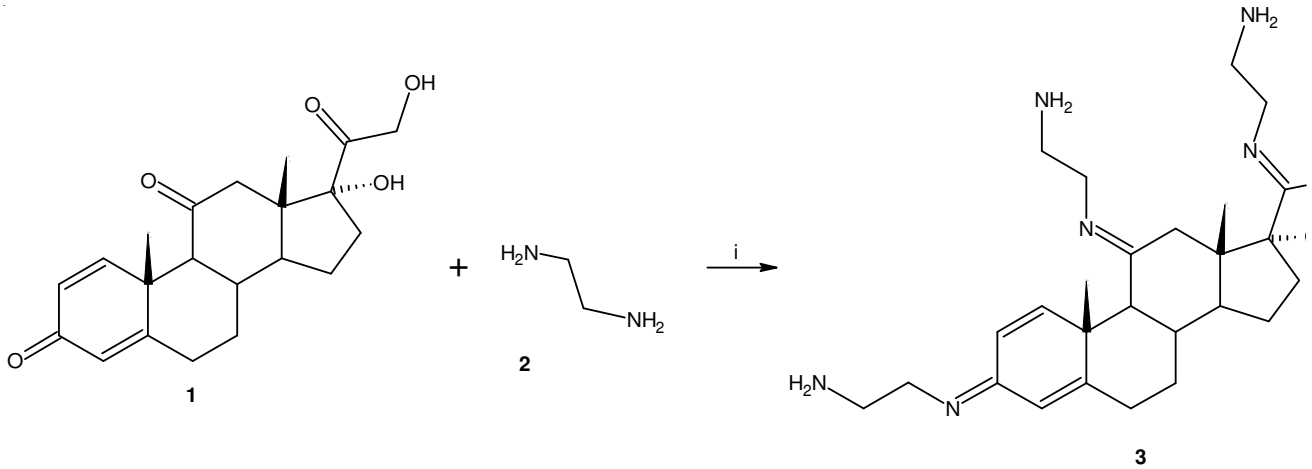

Fig. 1. Synthesis of 3,11-*bis*-(2-aminoethylimino)-17-[1-(2-aminoethylimino)-2-hydroxy-ethyl]-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[a]phenanthren-17-ol (**3**). Reaction of prednisone with ethylenediamine using boric acid as catalyst to form **3**. i = Methanol/rt

water and the precipitate was separated and washed with excess of water yielding 75 % of product, m.p. 140-142 °C; IR (ν_{max}, cm^{-1}): 3330 (OH), 3320, 1604;^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.65 (s, 3H), 0.70 (s, 3H), 0.75 (s, 3H), 0.8 (m, 1H), 0.85 (s, 3H), 0.90 (s, 6H), 0.95 (s, 6H), 1.12 (s, 3H), 1.17 (s, 3H), 1.19-1,21 (m, 6H), 1.26 (s, 3H), 1.28 (m, 1H), 1.50 (m, 3H), 1.55 (m, 1H), 1.77 (m, 7H), 1.78-2.06 (m, 4H), 2.10 (m, 1H), 2.19-2.24 (m, 2H), 2.32 (broad, 2H), 2.42 (m, 1H), 2.48 (m, 1H), 2.51 (m, 1H), 2.53-2.71 (m, 3H), 2.94-3.14 (m, 2H), 3.21 (t, 2H), 3.48 t, 2H), 3.70 (t, 4H), 3.74 (t, 4H), 4.24 (d, 2H), 6.10-7.22 (d, 3H) ppm. ^{13}C NMR (75.4 Hz, $CDCl_3$) δ_C: 11.20 (C-10, C-60, C-63), 16.48 (C-36), 19.08 (C-9, C-62, C-65), 19.10 (C-8, C-61, C-64), 21.18 (C-48), 23.90 (C-32), 26.34 (C-30), 27.28 (C-3), 27.50 C-46, C-57), 29.66 (C-20), 31.18 (C-21), 31.20 (C-4, C-46, C-58), 32.01 (C-31), 35.60 C-27), 36.10 (C-47, C-59), 37.68 (C-19), 38.44 (C-7), 43.70 (C-2), 43.75 (C-44, C-56), 45.22 (C-38), 47.40 (C-1, C-43, C-55), 48.46 (C-33), 49.90 (C-5), 50.98 (C-18), 51. 76 (C-13), 52.10 (C-50), 52.21 (C-39), 52.50 (C-51), 52.56 (C-12), 53.46 (C-17), 56.29 (C-42, C-54), 63.56 (C-28), 90.88 (C-16), 95.35 (C-23), 113.10 (C-25), 130.92 (C-15), 144.12 (C-26), 154.88 (C-22), 165.08 (C-29), 172.10 (C-6), 172.08 (C-6), 172.22 (C-24), 180.78 (C-41, C-53) ppm. EI-MS *m/z*: 886.60 (M^+, 12), Anal. Calcd for $C_{57}H_{86}N_6O_2$: C, 77.15; H, 9.77; N, 9.47; Found (%): C, 77.12; H, 9.72.

Synthesis of 3-({2-[2-hydroxy-3-(17-hydroxy-3,11-*bis*-[2-(1,7,7-trimethyl-byciclo[2.2.1]heptan-2-one-3-ylenamino)phenyl-methyl]-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15-16,17-dodecahydro-3*H*-cyclopenta[a]phenanthren-17-yl)-propilidenamino]ethylamino}phenyl-methyl)-1,7,7-trimethyl-byciclo[2.2.1]heptan-2-one (7): A solution of compound **3** (100 mg, 0.20 mmol), 1,7,7-trimethyl-bicyclo-[2.2.1]heptan-2-one (100 mg, 0.66 mmol), benzaldehyde (100 µL, 0.98 mmol) and proline (150 mg, 1.3 mmol) in 10 mL of methanol was stirring for 72 h to room temperature. The reaction mixture was evaporated to a smaller volume (Fig. 3). After the mixture was diluted with water and the precipitate was separated and washed with excess of water yielding 75 % of product, m.p. 140-142 °C; IR (ν_{max}, cm^{-1}): 3330 (OH), 3318, 1602; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.85 (s, 18H), 0.86 (m, 1H), 0.94(s, 6H), 1.26 (s, 3H), 1.28 (m, 1H), 1.30 (s, 3H), 1.32 (m, 1H), 1.37 (m, 3H), 1.39-1.47 (m, 6H), 1.55 (m, 1H), 1.57-1.64 (m, 6H), 1.78 (m, 2H), 1.83 (m, 1H), 1.83-1.91 (m, 3H), 1.94-2.52 (m, 6H), 2.54-2.70 (m, 3H), 2.92 (t, 2H), 2.94 (m, 1H), 3.00 (t, 1H), 3.19 (m, 1H), 3.20 (broad, 7H), 3.49 (t, 2H, J = 6.44 Hz), 3.56 (t, 2H, J = 9.75 Hz), 3.74 (t, 2H, J = 9.75 Hz), 4.16 (m, 1H), 4.18 (m, 1H), 4.20 (m, 1H), 4.22 (t, 2H, 13.47), 4.90 (m, 1H), 5.95-6.87 (d, 3H, J = 2.52 Hz), 7.03-7.26 (m, 15H) ppm. ^{13}C NMR (75.4 Hz, $CDCl_3$) δ_C: 9.38 (C-10, C-85, C-89), 16.18 (C-42), 19.22 (C-9, C-84, C-88), 19.68 (C-8, C-83, C-87), 20.90 (C-3, C-74, C-81), 21.30 (C-74), 23.76 (C-34), 26.86 (C-40), 29.60 (C-4, C-73, C-80), 29.90 (C-38), 31. 36 (C-33), 31.70 (C-33), 35.60 (C-27), 37.09 (C-29), 44.80 (C-69, C-76), 45.10 (C-1, C-71, C-78), 45.30 (C-7), 48.58 (C-67), 49.88 (C-58), 49.90 (C-47), 50.89 (C-2, C-70, C-77), 51.10 (C-30), 52.36 (C-46), 52.72 (C-57), 53.04 (C-31), 53.19 (C-22), 57.69 (C-5, C-72, C-79), 60.02 (C-14), 60.70 (C-12), 62.98 (C-49,C-60), 63.30 (C-28), 91.30 (C- 32), 93.10 (C-25), 113.70 (C-35), 125.78 (C-17, C-21), 126.34 (C-51, C-55), 126.50 (C-62, C-66), 127.90 (C-19,C-53,C-64),129.10 (C-18, C- 20), 129.14 (C-52,C-54, C-63,C-65), 130.42 (C-44), 144.22 (C-50, C-61), 144.46 (C-16), 144.60 (C-36), 155.60 (C-26), 158.12 (C-39), 174.02 (C-24), 220.04 (C-6, C-75, C-82) ppm. EI-MS *m/z*:1219.80 (M^+, 12), Anal. calcd. (%) for $C_{78}H_{105}N_7O_5$: C, 76.74; H, 8.67; N, 8.03; Found (%): C, 76.70; H, 8.64.

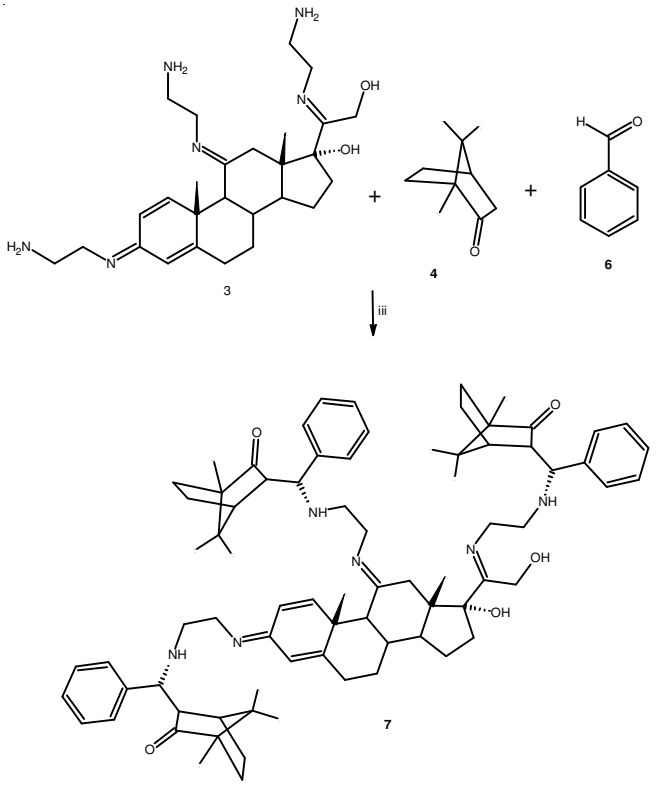

Fig. 3. Synthesis of 3-({2-[2-hydroxy-3-(17-hydroxy-3,11-*bis*[2-(1,7,7-trimethyl-byciclo[2.2.1]heptan-2-one-3-ylenamino)phenyl-methyl]-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[a]phenanthren-17-yl)propilidenamino]ethylamino}-phenyl-methyl)-1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-one (**7**). Reaction of prednisone derivative (**3**) with 1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-one (**4**) and benzaldehyde using proline as catalyst to form **7**. iii = Methanol/rt

Synthesis of 3-({2-[2-hydroxy-3-(17-hydroxy-3,11-*bis*[2-{7,7-dimethyl-3-(ylenamino-phenyl-methyl)-2-oxo-bicyclo[2.2.1]hept-1-yl}methansulfonic acid]-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[a]phenanthren-17-yl)propilidenamino]-ethylamino)-7,7-dimethyl-3-(ylenamino-phenyl-methyl)-2-oxo-bicyclo[2.2.1]hept-1-yl-methansulfonic acid] (9): A solution of compound **3** (100 mg, 0.20 mmol), (7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonic acid (150 mg, 0.64 mmol), benzaldehyde (100 µL, 0.98 mmol) and proline (150 mg, 1.3 mmol) in 10 mL of methanol was stirring for 72 h to room temperature. The reaction mixture was evaporated to a smaller volume (Fig. 4). After the mixture was diluted with water and the precipitate was separated and washed with excess of water yielding 64 % of product, m.p. 126 °C; IR (ν_{max}, cm^{-1}): 3332 (OH), 3320, 1602, 1345; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H:0.85 (m, 1H), 0.88 (s, 9H), 1.07 (s, 9H), 115 (s, 3H), 1.20 (s, 3H), 1.31 (m, 1H), 1.48 (m, 6H), 1.51 (m, 1H), 160-1.76 (m, 6H), 1.81 (m, 1H), 1.84 (m, 3H), 1.88 (m, 1H), 2.00-2.46

(m, 6H), 2.54-2.68 (m, 3H), 2.86 (t, 2H), 2.89 (m, 1H), 3.02 (t, 2H), 3.18 (m, 3H), 3.24 (m, 1H), 3.31-3.43 (t, 2H), 3.51 (t, 2H), 3.57 (t, 2H), 3.65 (m, 3H), 3.80-3.97 (d, 3H), 4.27 (d, 2H), 4.87 (broad, 10H), 4.98 (d, 1H), 6.11-7.00 (d, 3H), 7.07-7.29 (d, 15H) ppm. ^{13}C NMR (75.4 Hz, $CDCl_3$) δ_C:16.2 (C-48), 16.69 (C-9, C-88, C-94), 19.33(C-8, C-87, C-93), 21.93 (C-53), 22.82 (C-3,C-78, C-85), 23.76 (C-36), 26.40 (C-34), 27.21 (C-4, C-77, C-84), 29.92 (C-24), 31.10 (C-25), 31.47 (C-35), 35.63 (C-31), 37.09 (C-23), 45.22 (C-1, C-75, C-82), 46.24 (C-7, C-73), 46.81 (C-80), 47.91 (C-10, C-89, C-95), 48.62 (C-45), 49.92 (C-16, C-56), 50.88 (C-22), 51.11 (C-5, C-76, C-83), 52.31 (C-2, C-74, C-81), 52.48 (C-17), 52.70 (C-55), 53.08 (C-21), 53.19 (C-50), 55.94 (C-66), 60.01 (C-51), 61.53 (C-14, C-58), 63.23 (C-32), 91.30 (C-20, C-27), 113.76 (C-29), 126.43 (C-72, C-68), 126.87 (C-40, C-44, C-60), 127.90 (C-42, C-62, C-70), 129.04 (C-69, C-71), 129.06 (C-41, C-43, C-61, C-63), 130.58(C-19), 144.50 (C-30), 144.84 (C-39, C-59), 145.25 (C-67), 155.60 (C-26), 165.00 (C-33), 173.59 (C-28), 213.12 (C-6, C-79, C-86) ppm. EI-MS *m/z*: 1458.60 (M^+, 12), Anal. Calcd (%) for $C_{79}H_{106}N_6O_{14}S_3$: C, 64.99; H, 7.32; N, 5.76; S, 6.59. Found (%): C, 64.96; H, 7.30.

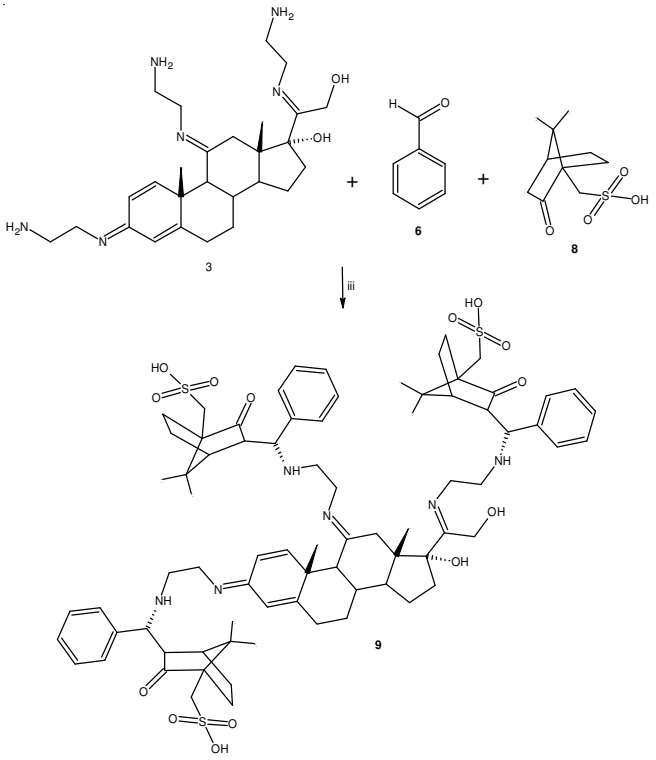

Fig. 4. Synthesis of 3-({2-[2-hydroxy-3-(17-hydroxy-3,11-*bis*[2-{7,7-dimethyl-3-(ylenamino-phenyl-methyl)-2-oxo-bicyclo[2.2.1]hept-1-yl}-methansulfonic acid]-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[a]phenanthren-17-yl)-propilidenamino]-ethylamino)-7,7-dimethyl-3-(ylenamino-phenyl-methyl)-2-oxo-bicyclo[2.2.1]hept-1-yl-methansulfonic acid] (**9**). Reaction of prednisone derivative (**3**) with 7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)methanesulfonic acid (**8**) and benzaldehyde (**6**) using proline as catalyst to form **9**. iii = methanol/room temp.

RESULTS AND DISCUSSION

In this study, several straight forward routes are reported for the synthesis of some prednisone derivatives. The first stage was achieved by reaction of aprednisone with ethylenediamine resulting in imino bond formation (C_3, C_{11} and C_{17}) involved in the compound **3**. It is important to mention that many procedures for the synthesis of imino groups are described in the literature[10-13]. In this study boric acid was used as a catalyst, because it is not an expensive reagent and no special conditions for its use are required[14]. ^{1}H NMR spectra of compound **3** shows signals at 1.19 and 1.21 ppm for methyl groups; at 0.85, 1.31-2.86, 3.36 and 6.09-6.90 ppm for protons involved in the steroid nucleus; at 2.96 and 3.75 ppm for hydrogen atoms of arm bound to both iminoethanol and amino groups; at 2.98 and 3.68 ppm for methylene groups of arm bound ring-C of steroid nucleus; at 3.34 and 3.72 ppm for methylene groups of arm bound ring-A of steroid nucleus. Finally, other signals at 3.96 ppm for both amino and hydroxyl groups were found[15-17].

On the other hand, ^{13}C NMR spectrum contains peaks at 16.54 and 21.30 ppm for methyl groups; at 23.90-36.90, 51.00-53.10, 63.38-113.42 and 144.70-171.80 ppm for steroid nucleus; at 40.50 and 46.68 ppm for carbonsinvolved in the arm bound to ring-A; 41.18 and 53.60 ppm for carbons of arm bound ring C of steroid nuleus; at 41.20 and 53.38 ppm for methylene groups of arm bound to iminoethanol group. Finally, other signals at 48.62 ppm for methylene group bound to hydroxyl group; at 130.65 for carbon bound to both imino group and ring-D of steroid nucleus were found. In addition, the presence of **3** was further confirmed from mass spectrum which showed a molecular ion at *m/z* 484.30.

In the second stage, compound **5** was achieved by reaction of 1,7,7-trimethylbicyclo[2.2.1]heptan-2-one with the compound **3** using boric acid as catalyst resulting in imino bond formation involved in the compound **5**. The results indicate that ^{1}HNMR spectrum of **5** showed several signals at 0.65, 0.70, 0.75 and 0.85 ppm for methyl groups involved in bicyclic rings; at 1.28, 1.55, 1.78-2.06, 2.19-2.24, 2.42, 2.51, 2.94-3.44 and 6.10-7.22 ppm for steroid nucleus; at 1.17 and 1.26 ppm for methyl groups of steroid moiety; at 1.19-1.21, 1.50, 1.77, 2.10, 2.48 and 2.53-2.71 ppm for bicyclic rings. Finally, other signals at 2.32 ppmfor hydroxylgroups; at 3.21-3.48 ppm for protons involved in the arm bound to both imino and iminoethanol groups; 3.70 ppm for methylene groups of arm bound Ring-C of steroid nucleus; at 3.74 ppm for methylene groupsinvolved in the arm bound to ring-A; at 4.24 ppm for methylene group bound to hydroxyl group were found.

Other data indicate that ^{13}C NMR spectrum contains peaks at 16.54 and 21.30 ppm for methyl groups; at 11.20-16.48, 19.08-19.10 ppm for methyl groups of bicyclic groups; at 16.48 and 21.18 for methyl groups of steroid nucleus; at 23.90-26.34, 29.66-31.18, 32.01-35.60, 37.68, 50.98, 53.46, 63.56-113.10, 144.12-165.08 and 172.22 ppm for steroid nucleus; at 26.34-27.50, 31.20, 36.10, 38.44-43.75, 47.40, 49.90, 56.29, 172.08 and 180.78 ppm for bicyclic groups; at 45.22 and 52.21 for methylene groups involved in the arm bound ring-A of steroid nucleus; at 51.76 and 52.56 ppm for carbons involved in the arm bound to ring-D of steroid nucleus; at 52.10 and 52.50 ppm for methylene groups of arm bound to ring-C of steroid nucleus; at 46.46 ppm for methylene group bound to hydroxyl group. Finally, the presence of **5** was further confirmed from mass spectrum which showed a molecular ion at *m/z* 886.60.

In the third stage, compound **7** was synthesized the using the three-component system (1,7,7-trimethylbicyclo[2.2.1]-

heptan-2-one, compound **3** and benzaldehyde). It is important to mention that there are studies which show the use of proline as catalyst in three-component system reactions (ketone, aldehyde and amine groups). Therefore, in this study the proline was used as catalyst to form **7**. ^{1}H NMR spectrums of **7** shows signals at 0.85 and 0.94 ppm for methyl groups of bicyclic rings; at 1.26 and 1.30 ppm for methyl groups bound in steroid nucleus; at 0.86, 1.28, 1.32, 1.55, 1.78, 1.94-2.52, 2.94, 3.19 and 5.95-6.87 ppm for steroid nucleus; at 1.37-1.47, 1.83-1.91 and 2.54-2.70 ppm for bicyclic rings; at 2.92, 3.00 and 3.56 ppm for methylene groups involved in the arm bound to ring-C of steroid nucleus; at 3.49 and 4.90 ppm for methylene groups involved in the arm bound to ring-A of steroid nucleus; at 2.92, 3.00 and 3.74 ppm for methylene groups involved in the arm bound to ring-D of steroid nucleus; at 3.20 ppm for both hydroxyl and amino groups; at 4.16-4.20 for both phenyl and amino groups; at 7.03-7.26 ppm for phenyl groups.

On the other hand, ^{13}C NMR spectrum contains peaks at 16.54 and 21.30 ppm for methyl groups; at 9.38, 19.22 and 19.68 ppm for methyl groups bound to bicyclic rings; at 16.18 and 21.30 for methyl groups bound to steroid nucleus; at 20.99, 29.60, 44.80-45.30, 50.89, 57.69 for bicyclic rings; at 23.76-26.86, 35.60-37.09, 51.10, 53.04, 63.60-113.70 and 144.60-174.02 ppm for steroid nucleus; at 53.19 and 60.02 ppm for methylene groups involved in the arm bound to ring-A of steroid nucleus; at 49.88 and 52.72 ppm for methylene groups involved in the arm bound to ring-C of steroid nucleus; at 49.90 and 52.46 ppm for methylene groups involved in the arm bound to ring-D of steroid nucleus; at 30.92 ppm for carbons bound to both imino group and the ring-D of steroid nucleus; at 60.70 for carbons bound to both amino and phenyl groups; at 125.28, 126.34-127.90, 129.10, 144.16 and 144.22 ppm for carbons involved in the phenyl groups. Finally, the presence of **7** was further confirmed from mass spectrum which showed a molecular ion at *m/z* 1219.80.

The four stage was achieved by reaction of 7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonic acid, compound **3** and benzaldehyde using proline as catalyst to form **9**. ^{1}H NMR spectra of **7** show signals at 0.86 and 1.04 ppm for methyl groups bound to bicyclic rings; at 1.15 and 1.20 ppm for methyl groups of steroid nucleus; at 0.85, 1.31, 1.51, 1.81, 1.98-2.46, 2.89, 3.24 and 6.11-7.00 ppm for steroid nucleus; at 1.48, 1.60-1.76, 1.84, 2.54-2.68 ppm for methylene groups involved in the bicyclic rings; at 2.86, 3.00 and 357 ppm for methylene groups involved in the arm bound to ring-D of steroid nucleus; at 2.86, 3.00 and 3.50 ppm for methylene groups involved in the arm bound to ring-C of steroid nucleus; at 3.31, 3.43 and 4.98 ppm for methylene groups involved in the arm bound to ring-A of steroid nucleus; at 3.18 and 3.65 ppm for methylene groups bound to both bicyclic rings and sulfonic acid group; at 3.80 and 3.97 ppm for methylene group bound to both phenyl and amino groups; at 4.87 ppm for both amino and hydroxyl groups; at 7.07-7.29 ppm for phenyl groups.

On the other hand, ^{13}C NMR spectrum contains peaks at 16.20 and 21.43 ppm for methyl groups bound to steroid nucleus; at 16.69 and 19.30 for methyl groups bound to bicyclic rings, at 23.76-26.40, 29.92-37.09, 50.88, 53.08, 63.23-113.76, 144.50, 155.60-173.59 ppm for steroid nucleus; at 22.82, 27.21, 45.22-46.81, 51.11-52.31 ppm for bicyclic rings; at 47.91 ppm for carbon bound to sulfonic acid group; at 48.62 ppm for methylene group bound to hydroxyl group; at 49.92 and 52.70 ppm for methylene groups involved in the arm bound to ring-C of steroid nucleus; at 49.92 and 52.48 ppm for methylene groups involved in the arm bound to ring-D of steroid nucleus; at 53.19 and 60.01 ppm for methylene groups involved in the arm bound to ring-A of steroid nucleus; at 55.94 and 61.53 ppm for carbons bound to both phenyl and amino groups; at 126.40-129.06 and 144.84-145.20 ppm for phenyl groups; at 130.58 ppm for methylene group bound to both imino and ring-D; at 213.12 for ketone groups.

Conclusion

In conclusion, this study reported the several strategies for the synthesis of some prednisone derivatives. It is important to mention that the methods used are highly versatile and the yield is good.

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