Synthesis and Reactions of Some New Substituted 3β-Hydroxyandrostan-17-Ones and Their Derivatives

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Abstract. A series of androstano[17,16-c] pyrazoline derivatives were synthesized using arylmethylene of 3β-hydroxyandrostan-17-one derivatives **1a-e**, which were protected by stirring with acetyl chloride to give acetate derivatives **2a-e**. Compounds **2a-d** was treated with hydrazine hydrate to afford the 17-hydrazino-androstane derivatives **3a-d** and **4a-d**, which were cyclized by trifluoroborane-etherate to yield androstanopyrazolines **5a-d**. Treatment of **2a-d** with refluxing hydrazine hydrate in propionic acid gave N-propionylpyrazoline derivatives **6a-d**. Similarly, compounds **1a,c,e** were protected by stirring with trifluoroacetic anhydride to give 3β-trifluoroacetate derivatives **7a-c**, which was treated with hydrazine hydrate in refluxing ethanol or methanol to afford 17-hydrazino-androstane derivatives **8a-c** and **9a-c**. Compounds **8a-c** and **9a-c** were cyclized in refluxing trifluoroborane-etherate to yield androstanopyrazoline derivatives **10a-c**. Finally, condensation of **7a-c** with refluxing hydrazine hydrate in propionic acid gave N-propionyl pyrazoline derivatives **11a-c**, respectively.

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1. Introduction

In a previous work, we found that certain substituted steroidal derivatives showed androgenic, anabolic, and anti-inflammatory activities [Amr and Abdulla; Amr et al., 2006]. Some new heterocyclic compounds containing nitrogen atom have been synthesized and used as antiparkinsonian [Amr et al., 2003a; Al-Harbi et al., 2013], antitumor [Amr and Abou-Ghalia 2004; Hernández-Vázquez et al., 2013; Stringer et al., 2013], antimicrobial [Amr et al., 2003b; Mandawad et al., 2013; Zampieri et al., 2008], and anti-inflammatory [de Oliveira Lopes et al., 2012; Peng et al., 2012] activities. Steroidal fused with different heterocyclic rings (pyrazole, pyridine, pyrimidine) present an interesting group of compounds, many of which possess widespread pharmacological properties such as 5α-reductase and aromatase inhibitors, anti-inflammatory, and analgesic agents [Hukki et al., 1968; Jung et al., 2005]. These derivatives are also well known for their pronounced anti-inflammatory properties [Bansal et al., (2001; Bhat et al., 1998] and are used as potent anti-diabetic agents [Ahn et al., 2004; Villhauer et al., 2002]. In addition, the pharmacological and antitumor activities of many compounds containing pyrazoline rings have been reviewed [Gökhan-Kelekçi et al., 2009; Congiu et al., 2010; Liu et al., 2012]. The heterocyclic nitrogen derivatives exhibited a general ionophoric potency for divalent cations [Hassan et al., 2003] and used a novel thiocyanate- selective membrane sensor [Hassan et al., 2008]. Heterocyclic compounds play an important role in designing a new class of structural entities of medicinal importance with new mechanisms of action. These heterocyclic compounds are well known to possess diverse pharmacological properties, viz. antimicrobial, analgesic, anti-inflammatory, anticancer, anticonvulsant and anti-malarial [Vijesh et al., 1962]. Recently, some new heterocyclic compounds containing steroid moieties have been synthesized and used as 5α-reductase inhibitors, antiviral and anti-tumor, aromatase and quinone reductase-2 inhibitors, anti-Alzheimer, anti-HIV-1, anti-HSV-1 and ant-arthritic, immunosuppressive agents [Al-Mohize et al., 2012; Abdalla et al., 2012; Bahashwan et al., 2012; Abdalla et al., 2012; Khalifa et al., 2013; Alanazi et al., 2013]. In view of these reports and in continuation of our previous work in heterocyclic chemistry, we have synthesized some new compounds containing pyrazoline ring fused with steroidal structure for the evaluation of androgenic-anabolic activities compared to testosterone as standard control.

2. Experimental

All melting points are uncorrected and were measured using an Electrothermal capillary melting point apparatus. The IR spectra were recorded on a Shimadzu FT-IR 8101 PC infrared spectrophotometer. The ^{1}H- and ^{13}C-NMR spectra were determined with

Bruker AM-200 MHz spectrometer. The chemical shifts are expressed on the δ (ppm) scale using TMS as the standard reference. Mass spectra were recorded on Finnigan SSQ operating at 70 ev.. Elemental analysis determined on a Perkin Elmer 240 (microanalysis), Microanalysis Center, Cairo University, Cairo, Egypt.

Synthesis of 16-[(substituted phenyl)methylene]-17-oxo-5α-androstan-3β-yl-acetate 2a-e

A mixture of the arylmethylene derivatives (**1a-e)** (1 mmol) and acetyl chloride (5 ml) was kept overnight at room temperature with stirring. The reaction mixture was evaporated under reduced pressure up to dryness and the obtained residue was washed with water. The solid formed was collected by filtration, washed with water, dried, and crystallized from methanol to give acetate derivatives (**2a-e**).

16-[(4-bromophenyl)methylene]-17-oxo-5α-androstan-3β-yl-acetate (2a).

Yield. 95%, mp. 213-215°C, $[\alpha]_D^{25}$ = + 121 (c 1, $CHCl_3$); IR (KBr): 1730 (C=O), 1620 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.83 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 0.98-1.10 (m, 1H, CH), 1.18-1.30 (m, 4H, $2CH_2$), 1.38-1.58 (m, 6H, $3CH_2$), 1.65-1.86 (m, 4H, $2CH_2$), 1.96 (m, 1H, CH), 2.06 (s, 3H, $COCH_3$), 2.25-2.35 (m, 2H, CH_2), 2.50 (m, 1H, CH), 2.60 (m, 1H, 3α-CH), 3.15 (m, 1H, 5α-CH), 7.20-7.60 (m, 4H, Ar-H), 7.85 (s, 1H, C=CH). MS (EI): m/z 499 (25%) [M^+]. Anal. $C_{28}H_{35}BrO_3$ (499): Calcd C, 76.21; H, 7.00; found C, 76.33; H, 7.01

16-[(4-chlorophenyl)methylene]-17-oxo-5α-androstan-3β-yl-acetate (2b).

Yield. 98%, mp. 187-189°C, $[\alpha]_D^{25}$ = + 98 (c 1, $CHCl_3$); IR (KBr): 1750 (C=O), 1650 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.86 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 1.01-1.12 (m, 1H, CH), 1.20-1.30 (m, 4H, $2CH_2$), 1.40-1.56 (m, 6H, $3CH_2$), 1.64-1.85 (m, 4H, $2CH_2$), 1.95 (m, 1H, CH), 2.04 (s, 3H, $COCH_3$), 2.26-2.34 (m, 2H, CH_2), 2.52 (m, 1H, CH), 2.62 (m, 1H, 3α-CH), 3.18 (m, 1H, 5α-CH), 7.22-7.58 (m, 4H, Ar-H), 7.82 (s, 1H, C=CH). MS (EI): m/z 454 (12%) [M^+]. Anal. $C_{28}H_{35}ClO_3$ (454.50): Calcd C, 74.01; H, 7.81; Cl, 7.85. Found: C, 73.92; H, 7.70; Cl, 7.81.

16-[(4-fluorophenyl)methylene]-17-oxo-5α-androstan-3β-yl-acetate (2c).

Yield. 92%, mp. 221-223°C, $[\alpha]_D^{25}$ = + 115 (c 1, $CHCl_3$); IR (KBr): 1754 (C=O), 1646 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.83 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 1.00-1.08 (m, 1H, CH), 1.19-1.28 (m, 4H, $2CH_2$), 1.38-1.55 (m, 6H, $3CH_2$), 1.60-1.80 (m, 4H, $2CH_2$), 1.94 (m, 1H, CH), 2.10 (s, 3H, $COCH_3$), 2.24-2.35 (m, 2H, CH_2), 2.50 (m, 1H, CH), 2.62 (m, 1H, 3α-CH), 3.23 (m, 1H, 5α-CH), 7.08-7.48 (m, 4H, Ar-H), 7.78 (s, 1H, C=CH). MS (EI): m/z 438 (12%) [M^+]. Anal. $C_{28}H_{35}FO_3$ (438.32): Calcd C, 77.00; H, 8.10. Found: C, 76.95; H, 7.99.

16-[(4-methoxyphenyl) methylene]-17-oxo-5α-androstan-3β-yl-acetate (2d).

Yield. 92%, mp. 216-218°C, $[\alpha]_D^{25}$ = + 94 (c 1, $CHCl_3$); IR (KBr): 1734 (C=O), 1618 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.86 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 1.01-1.12 (m, 1H, CH), 1.19-1.28 (m, 4H, $2CH_2$), 1.38-1.55 (m, 6H, $3CH_2$), 1.60-1.80 (m, 4H, $2CH_2$), 1.94 (m, 1H, CH), 2.06 (s, 3H, $COCH_3$), 2.26-2.37 (m, 2H, CH_2), 2.48 (m, 1H, CH), 2.60 (m, 1H, 3α-CH), 3.15 (m, 1H, 5α-CH), 3.62 (s, 3H, OCH_3), 7.20-7.60 (m, 4H, Ar-H), 7.85 (s, 1H, C=CH). MS (EI): m/z 450 (15%) [M^+]. Anal. $C_{29}H_{38}O_4$ (450): Calcd C, 77.41; H, 8.50; found C, 77.33; H, 8.44.

16-[(4-methylphenyl)methylene]-17-oxo-5α-androstan-3β-yl-acetate (2e).

Yield. 92%, mp. 206-208°C, $[\alpha]_D^{25}$ = + 179 (c 1, $CHCl_3$); IR (KBr): 1730 (C=O), 1620 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.83 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 0.98-1.10 (m, 1H, CH), 1.20-1.28 (m, 4H, $2CH_2$), 1.36-1.54 (m, 6H, $3CH_2$), 1.60-1.80 (m, 4H, $2CH_2$), 1.95 (m, 1H, CH), 2.04 (s, 3H, $COCH_3$), 2.24-2.30 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.50 (m, 1H, CH), 2.60 (m, 1H, 3α-CH), 3.18 (m, 1H, 5α-CH), 7.15-7.52 (m, 4H, Ar-H), 7.76 (s, 1H, C=CH). MS (EI): m/z 434 (8%) [M^+]. Anal. $C_{29}H_{38}O_3$ (434.28): Calcd C, 80.14; H, 8.81. found C, 80.18; H, 8.84.

Synthesis of 16[(α-ethoxy or methoxy)-substituted benzyl]-17-hydrazino-5α-androst-16-en-3β-yl-acetate derivatives 3a-d and 4a-d

A mixture of **2a-d** (4 mmol) and hydrazine hydrate (8 mmol) in absolute ethanol or methanol (30 mL) was refluxed for 5 h. The solvent was concentrated under reduced pressure, the formed precipitate was filtered off, washed with water, dried and crystallized from ethanol-ethyl acetate to give the corresponding **3a-d** and **4a-d**, respectively.

16[(α-ethoxy)-4-bromobenzyl]-17-hydrazino-5α-androst-16-en-3β-yl-acetate (3a).

Yield. 90%, mp. 189-191°C, $[\alpha]_D^{25}$ = + 156 (c 1, $CHCl_3$); IR (KBr): 3421–3380 (NH, NH_2), 1730 (C=O), 1620 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.83 (s, 3H, CH_3), 0.90-0.96 (m, 6H, $2CH_3$), 0.98-1.10 (m, 1H, CH), 1.18-1.30 (m, 4H, $2CH_2$), 1.38-1.58 (m, 6H, $3CH_2$), 1.65-1.86 (m, 4H, $2CH_2$), 1.96 (m, 1H, CH), 2.06 (s, 3H, $COCH_3$), 2.25-2.35 (m, 2H, CH_2), 2.50 (m, 1H, CH), 2.60 (m, 1H, 3α-CH), 3.15 (m, 1H, 5α-CH), 3.35 (q, 2H, CH_2), 4.65 (s, 2H, NH_2, exchangeable with D_2O), 4.80 (s, 1H, CH-O), 7.15-7.55 (m, 4H, Ar-H), 7.68 (br.s, 1H, NH, exchangeable with D_2O). MS (EI): m/z 560 (5%) [M^+]. Anal. $C_{30}H_{43}BrN_2O_3$ (559.58): Calcd C, 64.39; H, 7.75; Br,

14.28; N, 5.01; found C, 64.35; H, 7.70; Br, 14.22; N, 4.95.

16[(α-ethoxy)-4-chlororbenzyl]-17-hydrazino-5α-androst-16-en-3β-yl-acetate (3b).

Yield. 88%, mp. 216-218°C, $[\alpha]_D^{25}$ = + 116 (c 1, $CHCl_3$); IR (KBr): 3435–3376 (NH, NH_2), 1732 (C=O), 1624 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85-0.94 (m, 9H, $3CH_3$), 1.00-1.12 (m, 1H, CH), 1.18-1.32 (m, 4H, $2CH_2$), 1.38-1.56 (m, 6H, $3CH_2$), 1.65-1.85 (m, 4H, $2CH_2$), 1.95 (m, 1H, CH), 2.00 (s, 3H, $COCH_3$), 2.24-2.36 (m, 2H, CH_2), 2.50 (m, 1H, CH), 2.60 (m, 1H, 3α-CH), 3.15 (m, 1H, 5α-CH), 3.35 (q, 2H, CH_2), 4.60 (s, 2H, NH_2, exchangeable with D_2O), 4.78 (s, 1H, CH-O), 7.18-7.50 (m, 4H, Ar-H), 7.66 (br.s, 1H, NH, exchangeable with D_2O). MS (EI): m/z 515 (6%) [M^+]. Anal. $C_{30}H_{43}ClN_2O_3$ (515.13): Calcd C, 69.95; H, 8.41; Cl, 6.88; N, 5.44; found C, 69.90; H, 8.35; Cl, 6.82; N, 5.40.

16[(α-ethoxy)-4-fluorobenzyl]-17-hydrazino-5α-androst-16-en-3β-yl-acetate (3c).

Yield. 72%, mp. 316-318°C, $[\alpha]_D^{25}$ = + 136 (c 1, $CHCl_3$); IR (KBr): 3454–3383 (NH, NH_2), 1732 (C=O), 1616 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85 (s, 3H, CH_3), 0.92-0.98 (m, 6H, $2CH_3$), 1.05-1.12 (m, 1H, CH), 1.20-1.31 (m, 4H, $2CH_2$), 1.34-1.56 (m, 6H, $3CH_2$), 1.60-1.85 (m, 4H, $2CH_2$), 1.95 (m, 1H, CH), 2.02 (s, 3H, $COCH_3$), 2.22-2.36 (m, 2H, CH_2), 2.52 (m, 1H, CH), 2.64 (m, 1H, 3α-CH), 3.18 (m, 1H, 5α-CH), 3.36 (q, 2H, CH_2), 4.68 (s, 2H, NH_2, exchangeable with D_2O), 4.82 (s, 1H, CH-O), 7.14-7.58 (m, 4H, Ar-H), 7.72 (br.s, 1H, NH, exchangeable with D_2O). MS (EI): m/z 499 (16%) [M^+]. Anal. $C_{30}H_{43}FN_2O_3$ (498.67): Calcd C, 72.26; H, 8.69; N, 5.62; found C, 72.20; H, 8.63; N, 5.58.

16[(α-ethoxy)-4-methoxybenzyl]-17-hydrazino-5α-androst-16-en-3β-yl-acetate (3d).

Yield. 92%, mp. 287-289°C, $[\alpha]_D^{25}$ = + 126 (c 1, $CHCl_3$); IR (KBr): 3486-3378 (NH, NH_2), 1745 (C=O), 1615 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.84 (s, 3H, CH_3), 0.92-0.95 (m, 6H, $2CH_3$), 0.98-1.10 (m, 1H, CH), 1.16-1.30 (m, 4H, $2CH_2$), 1.38-1.58 (m, 6H, $3CH_2$), 1.65-1.86 (m, 4H, $2CH_2$), 1.96 (m, 1H, CH), 2.00 (s, 3H, $COCH_3$), 2.22-2.36 (m, 2H, CH_2), 2.50 (m, 1H, CH), 2.60 (m, 1H, 3α-CH), 3.15 (m, 1H, 5α-CH), 3.35 (q, 2H, CH_2), 3.56 (s, 3H, OCH_3), 4.62 (s, 2H, NH_2, exchangeable with D_2O), 4.78 (s, 1H, CH-O), 7.10-7.56 (m, 4H, Ar-H), 7.68 (br.s, 1H, NH, exchangeable with D_2O). MS (EI): m/z 511 (12%) [M^+]. Anal. $C_{31}H_{46}N_2O_4$ (510.71): Calcd C, 72.91; H, 9.08; N, 5.49; found C, 72.85; H, 9.00; N, 5.43.

16[(α-methoxy)-4-bromobenzyl]-17-hydrazino-5α-androst-16-en-3β-yl-acetate (4a).

Yield. 82%, mp. 219-221°C, $[\alpha]_D^{25}$ = + 146 (c 1, $CHCl_3$); IR (KBr): 3443-3376 (NH, NH_2), 1742 (C=O), 1616 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.97-1.10 (m, 1H, CH), 1.16-1.32 (m, 4H, $2CH_2$), 1.38-1.58 (m, 6H, $3CH_2$), 1.65-1.86 (m, 4H, $2CH_2$), 1.96 (m, 1H, CH), 2.06 (s, 3H, $COCH_3$), 2.23-2.37 (m, 2H, CH_2), 2.48 (m, 1H, CH), 2.60 (m, 1H, 3α-CH), 3.15 (m, 1H, 5α-CH), 3.24 (s, 3H, OCH_3), 4.65 (s, 2H, NH_2, exchangeable with D_2O), 4.80 (s, 1H, CH-O), 7.15-7.56 (m, 4H, Ar-H), 7.70 (br.s, 1H, NH, exchangeable with D_2O). MS (EI): m/z 501 (8%) [M^+]. Anal. C29H41BrN2O3 (545.55): Calcd C, 63.85; H, 7.58; N, 5.13; found C, 63.80; H, 7.52; N, 5.10.

16[(α-methoxy)-4-chlororbenzyl]-17-hydrazino-5α-androst-16-en-3β-yl-acetate (4b).

Yield. 83%, mp. 245-246°C, $[\alpha]_D^{25}$ = + 141 (c 1, $CHCl_3$); IR (KBr): 3434-3370 (NH, NH_2), 1738 (C=O), 1620 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.89 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.01-1.08 (m, 1H, CH), 1.19-1.32 (m, 4H, $2CH_2$), 1.38-1.56 (m, 6H, $3CH_2$), 1.63-1.84 (m, 4H, $2CH_2$), 1.96 (m, 1H, CH), 2.01 (s, 3H, $COCH_3$), 2.24-2.36 (m, 2H, CH_2), 2.50 (m, 1H, CH), 2.60 (m, 1H, 3α-CH), 3.15 (m, 1H, 5α-CH), 3.24 (s, 3H, OCH_3), 4.66 (s, 2H, NH_2, exchangeable with D_2O), 4.74 (s, 1H, CH-O), 7.12-7.54 (m, 4H, Ar-H), 7.68 (br.s, 1H, NH, exchangeable with D_2O). MS (EI): m/z 501 (5%) [M^+]. Anal. C29H41ClN2O3 (501.10): Calcd C, 69.51; H, 8.25; Cl, 7.08; N, 5.59; found C, 69.45; H, 8.20; Cl, 7.00; N, 5.53.

16[(α-methoxy)-4-fluorobenzyl]-17-hydrazino-5α-androst-16-en-3β-yl-acetate (4c).

Yield. 83%, mp. 234-236°C, $[\alpha]_D^{25}$ = + 89 (c 1, $CHCl_3$); IR (KBr): 3450-3378 (NH, NH_2), 1736 (C=O), 1612 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 1.05-1.12 (m, 1H, CH), 1.20-1.31 (m, 4H, $2CH_2$), 1.34-1.56 (m, 6H, $3CH_2$), 1.60-1.85 (m, 4H, $2CH_2$), 1.95 (m, 1H, CH), 2.02 (s, 3H, $COCH_3$), 2.22-2.36 (m, 2H, CH_2), 2.52 (m, 1H, CH), 2.64 (m, 1H, 3α-CH), 3.18 (m, 1H, 5α-CH), 3.24 (s, 3H, OCH_3), 4.68 (s, 2H, NH_2, exchangeable with D_2O), 4.82 (s, 1H, CH-O), 7.14-7.58 (m, 4H, Ar-H), 7.72 (br.s, 1H, NH, exchangeable with D_2O). MS (EI): m/z 485 (6%) [M^+]. Anal. $C_{29}H_{41}FN_2O_3$ (484.65): Calcd C, 71.87; H, 8.53; N, 5.78; found C, 71.82; H, 8.50; N, 5.72.

16[(α-methoxy)-4-methoxybenzyl]-17-hydrazino-5α-androst-16-en-3β-yl-acetate (4d).

Yield. 84%, mp. 317-319°C, $[\alpha]_D^{25}$ = + 134 (c 1, $CHCl_3$); IR (KBr): 3480-3377 (NH, NH_2), 1740 (C=O), 1610 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.84 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 0.98-1.10 (m, 1H, CH), 1.16-1.30 (m, 4H, $2CH_2$), 1.38-1.58 (m, 6H, $3CH_2$),

1.65-1.86 (m, 4H, $2CH_2$), 1.96 (m, 1H, CH), 2.00 (s, 3H, $COCH_3$), 2.22-2.36 (m, 2H, CH_2), 2.50 (m, 1H, CH), 2.60 (m, 1H, 3α-CH), 3.15 (m, 1H, 5α-CH), 3.24 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 4.62 (s, 2H, NH_2, exchangeable with D_2O), 4.78 (s, 1H, CH-O), 7.10-7.56 (m, 4H, Ar-H), 7.68 (br.s, 1H, NH, exchangeable with D_2O). MS (EI): m/z 497 (12%) [M^+]. Anal. $C_{30}H_{44}N_2O_4$ (496.68): Calcd C, 72.55; H, 8.93; N, 5.64; found C, 72.50; H, 8.90; N, 5.60.

Synthesis of 5α-androstan-[17,16-c]pyrazoline-3β-yl-acetate derivatives 5a-d

Method A. - A mixture of **2a-d** (4 mmol) and hydrazine hydrate (16 mmol) in dioxane (25 mL) was refluxed for 5 h. The solvent was evaporated under reduced pressure, the residue was solidified with water, filtered off, washed with water, dried and crystallized from methanol to give compound **5a-d**, respectively.

Method B.

A mixture of **3a-d** or **4a-d** (4 mmol) in etherated boron trifluoride (25 mL) was refluxed for 2 h. The reaction mixture was evaporated under reduced pressure, the residue was triturated with water, the obtained solid was filtered off, washed with water, dried and crystallized from methanol to give **5a-d**, respectively.

(1`H)-5``-(4-bromophenyl)-5α-androstan-[17,16-c]pyrazoline-3β-yl-acetate (5a).

Yield. 78%, mp. 248-250°C, $[\alpha]_D^{25}$ = + 136 (c 1, $CHCl_3$); IR (KBr): 3550 (NH), 1730 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.83 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 0.98-1.10 (m, 1H, CH), 1.18-1.30 (m, 4H, $2CH_2$), 1.38-1.58 (m, 6H, $3CH_2$), 1.65-1.86 (m, 4H, $2CH_2$), 1.96-1.98 (m, 2H, 2CH), 2.06 (s, 3H, $COCH_3$), 2.25-2.35 (m, 2H, CH_2), 2.50 (m, 1H, CH), 2.60 (m, 1H, 3α-CH), 3.15 (m, 1H, 5α-CH), 4.80 (s, 1H, CH), 7.15-7.55 (m, 4H, Ar-H), 9.85 (bs, 1H, NH, exchangeable with D_2O). MS (EI): m/z 513 (24%) [M^+]. Anal. $C_{28}H_{37}BrN_2O_2$ (513.51): Calcd C, 65.49; H, 7.26; N, 5.46; found C, 65.42; H, 7.20; N, 5.40.

1`H)-5``-(4-chlorophenyl)-5α-androstan-[17,16-c]pyrazoline-3β-yl-acetate (5b).

Yield. 90%, mp. 137-139°C, $[\alpha]_D^{25}$ = + 179 (c 1, $CHCl_3$); IR (KBr): 3542 (NH), 1736 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.87 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 0.99-1.12 (m, 1H, CH), 1.17-1.32 (m, 4H, $2CH_2$), 1.35-1.58 (m, 6H, $3CH_2$), 1.66-1.85 (m, 4H, $2CH_2$), 1.95-1.98 (m, 2H, 2CH), 2.02 (s, 3H, $COCH_3$), 2.26-2.36 (m, 2H, CH_2), 2.52 (m, 1H, CH), 2.64 (m, 1H, 3α-CH), 3.16 (m, 1H, 5α-CH), 4.78 (s, 1H, CH), 7.08-7.60 (m, 4H, Ar-H), 9.68 (bs, 1H, NH, exchangeable with D_2O). MS (EI): m/z 469 (24%) [M^+]. Anal. $C_{28}H_{37}ClN_2O_2$ (469.06): Calcd C, 71.70; H, 7.95; Cl, 7.56; N, 5.97; found C, 71.70; H, 7.95; Cl, 7.56; N, 5.97.

(1`H)-5``-(4-fluororphenyl)-5α-androstan-[17,16-c]pyrazoline-3β-yl-acetate (5c).

Yield. 94%, mp. 305-307°C, $[\alpha]_D^{25}$ = + 123 (c 1, $CHCl_3$); IR (KBr): 3538 (NH), 1736 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.88 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.05-1.12 (m, 1H, CH), 1.20-1.31 (m, 4H, $2CH_2$), 1.37-1.56 (m, 6H, $3CH_2$), 1.64-1.85 (m, 4H, $2CH_2$), 1.92-1.98 (m, 2H, 2CH), 2.00 (s, 3H, $COCH_3$), 2.23-2.34 (m, 2H, CH_2), 2.48 (m, 1H, CH), 2.58 (m, 1H, 3α-CH), 3.16 (m, 1H, 5α-CH), 4.79 (s, 1H, CH), 7.05-7.54 (m, 4H, Ar-H), 9.80 (bs, 1H, NH, exchangeable with D_2O). MS (EI): m/z 553 (24%) [M^+]. Anal. $C_{28}H_{37}FN_2O_2$ (452.60): Calcd C, 74.30; H, 8.24; F, 4.20; N, 6.19; found C, 74.24; H, 8.20; F, 4.15; N, 6.15.

(1`H)-5``-(4-methoxyphenyl)-5α-androstan-[17,16-c]pyrazoline-3β-yl-acetate (5d).

Yield. 84%, mp. 287-289°C, $[\alpha]_D^{25}$ = + 138 (c 1, $CHCl_3$); IR (KBr): 3548 (NH), 1734 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 0.98-1.14 (m, 1H, CH), 1.19-1.30 (m, 4H, $2CH_2$), 1.36-1.56 (m, 6H, $3CH_2$), 1.65-1.85 (m, 4H, $2CH_2$), 1.95-1.98 (m, 2H, 2CH), 2.05 (s, 3H, $COCH_3$), 2.25-2.35 (m, 2H, CH_2), 2.52 (m, 1H, CH), 2.64 (m, 1H, 3α-CH), 3.18 (m, 1H, 5α-CH), 3.48 (s, 3H, OCH_3), 4.79 (s, 1H, CH), 7.18-7.58 (m, 4H, Ar-H), 9.72 (bs, 1H, NH, exchangeable with D_2O). MS (EI): m/z 465 (24%) [M^+]. Anal. $C_{29}H_{40}N_2O_3$ (464.64): Calcd C, 74.96; H, 8.68; N, 6.03; found C, 74.90; H, 8.64; N, 6.00.

Synthesis of 1`-propionyl-1H-5-(substituted phenyl)-5α-androstan-[17,16-c]pyrazoline-3β-yl-acetate (6a-d)

A mixture of the arylmethylene derivatives **2a-d** (4 mmol) and hydrazine hydrate (16 mmol) in propionic acid (15 ml) was refluxed for 7 h. The reaction mixture was poured onto ice water and neutralized with sodium bicarbonate. The formed precipitate was collected by filtration, washed with water, dried, and crystallized from the proper solvent to give the corresponding N-substituted pyrazoline derivatives **6a-d,** respectively.

1`-propionyl-1H-5`-(4-bromophenyl)-5α-androstan-[17,16-c]pyrazoline-3β-yl-acetate (6a).

Yield. 58%, mp. 159-161°C, $[\alpha]_D^{25}$ = + 116 (c 1, $CHCl_3$); IR (KBr): 1740 (C=O), 1625 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.83-0.96 (m, 9H, $3CH_3$), 0.98-1.10 (m, 1H, CH), 1.18-1.30 (m, 4H, $2CH_2$), 1.38-1.58 (m, 6H, $3CH_2$), 1.65-1.88 (m, 4H, $2CH_2$), 1.94-1.98 (m, 2H, 2CH), 2.06 (s, 3H, $COCH_3$), 2.25-2.35 (m, 4H, $2CH_2$), 2.50 (m, 1H, CH), 2.56 (m, 1H, 3α-CH), 3.15 (m, 1H, 5α-CH), 4.80 (s, 1H, CH), 7.18-7.52 (m,

4H, Ar-H). MS (EI): m/z 570 (24%) [M^+]. Anal. $C_{31}H_{41}BrN_2O_3$ (569.57): Calcd C, 65.37; H, 7.26; N, 4.92; found C, 65.37; H, 7.26; N, 4.92.

1`-propionyl-1H-5`-(4-chlororophenyl)-5α-androstan-[17,16-c]pyrazoline-3β-yl-acetate (6b).

Yield. 60%, mp. 263-265°C, $[\alpha]_D^{25}$ = + 123 (c 1, $CHCl_3$); IR (KBr): 1734 (C=O), 1620 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.87-0.96 (m, 9H, $3CH_3$), 0.99-1.12 (m, 1H, CH), 1.17-1.32 (m, 4H, $2CH_2$), 1.35-1.58 (m, 6H, $3CH_2$), 1.66-1.85 (m, 4H, $2CH_2$), 1.95-1.98 (m, 2H, 2CH), 2.02 (s, 3H, $COCH_3$), 2.24-2.35 (m, 4H, $2CH_2$), 2.52 (m, 1H, CH), 2.64 (m, 1H, 3α-CH), 3.16 (m, 1H, 5α-CH), 4.78 (s, 1H, CH), 7.12-7.56 (m, 4H, Ar-H). MS (EI): m/z 525 (14%) [M^+]. Anal. C31H41ClN2O3 (525.12): Calcd C, 70.90; H, 7.87; Cl, 6.75; N, 5.33; N, 5.97; found C, 70.84; H, 7.82; Cl, 6.70; N, 5.30.

1`-propionyl-1H-5`-(4-fluorophenyl)-5α-androstan-[17,16-c]pyrazoline-3β-yl-acetate (6c).

Yield. 62%, mp. 254-256°C, $[\alpha]_D^{25}$ = + 146 (c 1, $CHCl_3$); IR (KBr): 1734 (C=O), 1614 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.87-0.96 (m, 9H, $3CH_3$), 1.05-1.12 (m, 1H, CH), 1.20-1.31 (m, 4H, $2CH_2$), 1.37-1.56 (m, 6H, $3CH_2$), 1.64-1.85 (m, 4H, $2CH_2$), 1.92-1.98 (m, 2H, 2CH), 2.00 (s, 3H, $COCH_3$), 2.18-2.35 (m, 4H, $2CH_2$), 2.48 (m, 1H, CH), 2.58 (m, 1H, 3α-CH), 3.16 (m, 1H, 5α-CH), 4.79 (s, 1H, CH), 7.12-7.50 (m, 4H, Ar-H). MS (EI): m/z 509 (16%) [M^+]. Anal. $C_{31}H_{41}FN_2O_3$ (508.67): Calcd C, 73.20; H, 8.12; N, 5.51; found C, 73.15; H, 8.06; N, 5.45.

1`-propionyl-1H-5`-(4-methoxyphenyl)-5α-androstan-[17,16-c]pyrazoline-3β-yl-acetate (6d).

Yield. 67%, mp. 228-229°C, $[\alpha]_D^{25}$ = + 177 (c 1, $CHCl_3$); IR (KBr): 1738 (C=O), 1615 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85-0.97 (m, 9H, $3CH_3$), 1.05-1.15 (m, 1H, CH), 1.20-1.31 (m, 4H, $2CH_2$), 1.36-1.56 (m, 6H, $3CH_2$), 1.65-1.85 (m, 4H, $2CH_2$), 1.95-1.98 (m, 2H, 2CH), 2.05 (s, 3H, $COCH_3$), 2.25-2.35 (m, 4H, $2CH_2$), 2.52 (m, 1H, CH), 2.64 (m, 1H, 3α-CH), 3.18 (m, 1H, 5α-CH), 3.50 (s, 3H, OCH_3), 4.76 (s, 1H, CH), 7.08-7.56 (m, 4H, Ar-H). MS (EI): m/z 521 (18%) [M^+]. Anal. $C_{32}H_{44}N_2O_4$ (520.70): Calcd C, 73.81; H, 8.52; N, 5.38; found C, 73.74; H, 8.45; N, 5.32.

7a-c:

A mixture of the arylmethylene derivatives **1a,c, CH_3** (1 mmol) and trifluoroacetic anhydride (5 ml) was kept overnight at room temperature. The reaction mixture was evaporated under reduced pressure up to dryness and the obtained residue was solidified with 1 N sodium bicarbonate (10 ml). The solid formed was collected by filtration, washed with water, dried, and crystallized from methanol to give 3-trifluoroacetate derivatives **7a-c**, respectively.

16-[(4-bromophenyl)methylene]-17-oxo-5α-androstan-3β-yl-acetate (7a).

Yield. 96%, mp. 257-259°C, $[\alpha]_D^{25}$ = + 147 (c 1, $CHCl_3$); IR (KBr): 1748 (C=O), 1624 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.84 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 0.98-1.12 (m, 1H, CH), 1.18-1.30 (m, 4H, $2CH_2$), 1.38-1.56 (m, 6H, $3CH_2$), 1.64-1.86 (m, 4H, $2CH_2$), 1.97 (m, 1H, CH), 2.22-2.35 (m, 2H, CH_2), 2.50 (m, 1H, CH), 2.58 (m, 1H, 3α-CH), 3.16 (m, 1H, 5α-CH), 7.16-7.64 (m, 4H, Ar-H), 7.78 (s, 1H, C=CH). MS (EI): m/z 553 (25%) [M^+]. Anal. $C_{28}H_{32}BrF_3O_3$ (553.45): Calcd C, 60.76; H, 5.83; found C, 60.70; H, 5.78.

16-[(4-fluorophenyl)methylene]-17-oxo-5α-androstan-3β-yl-acetate (7b).

Yield. 96%, mp. 226-228°C, $[\alpha]_D^{25}$ = + 174 (c 1, $CHCl_3$); IR (KBr): 1752 (C=O), 1632 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.84 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 1.02-1.12 (m, 1H, CH), 1.18-1.28 (m, 4H, $2CH_2$), 1.38-1.54 (m, 6H, $3CH_2$), 1.61-1.82 (m, 4H, $2CH_2$), 1.94 (m, 1H, CH), 2.24-2.35 (m, 2H, CH_2), 2.50 (m, 1H, CH), 2.62 (m, 1H, 3α-CH), 3.23 (m, 1H, 5α-CH), 7.12-7.54 (m, 4H, Ar-H), 7.76 (s, 1H, C=CH). MS (EI): m/z 492 (18%) [M^+]. Anal. $C_{28}H_{32}F_4O_3$ (492.55): Calcd C, 68.28; H, 6.55. Found: C, 68.20; H, 6.50.

16-[(4-methylphenyl)methylene]-17-oxo-5α-androstan-3β-yl-trifluoroacetate (7c).

Yield. 95%, mp. 256-258°C, $[\alpha]_D^{25}$ = + 174 (c 1, $CHCl_3$); IR (KBr): 1742 (C=O), 1628 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.88 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 1.05-1.14 (m, 1H, CH), 1.20-1.30 (m, 4H, $2CH_2$), 1.38-1.58 (m, 6H, $3CH_2$), 1.64-1.80 (m, 4H, $2CH_2$), 1.98 (m, 1H, CH), 2.24-2.36 (m, 5H, CH_2 + CH_3), 2.45 (m, 1H, CH), 2.58 (m, 1H, 3α-CH), 3.16 (m, 1H, 5α-CH), 7.15-7.60 (m, 4H, Ar-H), 7.85 (s, 1H, C=CH). MS (EI): m/z 488 (12%) [M^+]. Anal. $C_{29}H_{35}F_3O_3$ (488.58): Calcd C, 71.29; H, 7.22; found C, 71.22; H, 7.18.

Synthesis of 16-[(α-ethoxy- or methoxy) substituted 4-methylphenyl)methylene]-17-hydrazino-5α-androstan-16-en-3β-yl-trifluoroacetate derivatives 8a-c and 9a-c

A mixture of **7a-c** (4 mmol) and hydrazine hydrate (8 mmol) in absolute ethanol or methanol (30 mL) was refluxed for 5 h. The reaction mixture was evaporated under reduced pressure, the obtained residue was solidified with n-hexane. The formed precipitate was filtered off, washed with water, dried and crystallized from the proper solvents to give the corresponding **8a-c** and **9a-c**, respectively.

16[(α-ethoxy)-4-bromobenzyl]-17-hydrazino-5α-androst-16-en-3β-yl-trifluoroacetate (8a).

Yield. 86%, mp. 238-240°C, $[\alpha]_D^{25}$ = + 156 (c 1, $CHCl_3$); IR (KBr): 3432-3375 (NH, NH_2), 1732 (C=O), 1615 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85 (s, 3H, CH_3), 0.91-0.95 (m, 6H, $2CH_3$), 0.98-1.12 (m, 1H, CH), 1.17-1.31 (m, 4H, $2CH_2$), 1.38-1.58 (m, 6H, $3CH_2$), 1.65-1.86 (m, 4H, $2CH_2$), 1.96 (m, 1H, CH), 2.25-2.35 (m, 2H, CH_2), 2.50 (m, 1H, CH), 2.58 (m, 1H, 3α-CH), 3.16 (m, 1H, 5α-CH), 3.34 (q, 2H, CH_2), 4.65 (s, 2H, NH_2, exchangeable with D_2O), 4.78 (s, 1H, CH-O), 7.15-7.56 (m, 4H, Ar-H), 7.72 (br.s, 1H, NH, exchangeable with D_2O). MS (EI): m/z 514 (12%) [M^+]. Anal. $C_{30}H_{40}BrF_3N_2O_3$ (613.55): Calcd C, 58.73; H, 6.57; N, 4.57; found C, 58.67; H, 6.50; N, 4.50.

16[(α-ethoxy)-4-fluorobenzyl]-17-hydrazino-5α-androst-16-en-3β-yl-trifluoroacetate (8b).

Yield. 96%, mp. 276-278°C, $[\alpha]_D^{25}$ = + 136 (c 1, $CHCl_3$); IR (KBr): 3450-3380 (NH, NH_2), 1736 (C=O), 1618 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85 (s, 3H, CH_3), 0.92-0.98 (m, 6H, $2CH_3$), 1.05-1.12 (m, 1H, CH), 1.20-1.31 (m, 4H, $2CH_2$), 1.34-1.56 (m, 6H, $3CH_2$), 1.60-1.85 (m, 4H, $2CH_2$), 1.95 (m, 1H, CH), 2.20-2.35 (m, 2H, CH_2), 2.48 (m, 1H, CH), 2.62 (m, 1H, 3α-CH), 3.14 (m, 1H, 5α-CH), 3.37 (q, 2H, CH_2), 4.69 (s, 2H, NH_2, exchangeable with D_2O), 4.80 (s, 1H, CH-O), 7.14-7.52 (m, 4H, Ar-H), 7.70 (br.s, 1H, NH, exchangeable with D_2O). MS (EI): m/z 553 (26%) [M^+]. Anal. $C_{30}H_{40}F_4N_2O_3$ (552.64): Calcd C, 65.20; H, 7.30; N, 5.07; found C, 65.20; H, 7.30; N, 5.07.

16[(α-ethoxy)-4-methoxybenzyl]-17-hydrazino-5α-androst-16-en-3β-yl-trifluoroacetate (8c).

Yield. 76%, mp. 259-261°C, $[\alpha]_D^{25}$ = + 139 (c 1, $CHCl_3$); IR (KBr): 3484-3380 (NH, NH_2), 1742 (C=O), 1612 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85 (s, 3H, CH_3), 0.89-0.94 (m, 6H, $2CH_3$), 0.97-1.08 (m, 1H, CH), 1.16-1.30 (m, 4H, $2CH_2$), 1.38-1.58 (m, 6H, $3CH_2$), 1.65-1.86 (m, 4H, $2CH_2$), 1.96 (m, 1H, CH), 2.24-2.35 (m, 5H, CH_2 + CH_3), 2.50 (m, 1H, CH), 2.60 (m, 1H, 3α-CH), 3.15 (m, 1H, 5α-CH), 3.34 (q, 2H, CH_2), 4.60 (s, 2H, NH_2, exchangeable with D_2O), 4.78 (s, 1H, CH-O), 7.12-7.54 (m, 4H, Ar-H), 7.66 (br.s, 1H, NH, exchangeable with D_2O). MS (EI): m/z 549 (24%) [M^+]. Anal. C31H43F3N2O3 (548.68): Calcd C, 67.86; H, 7.90; N, 5.11; found C, 67.80; H, 7.86; N, 5.05.

16[(α-methoxy)-4-bromobenzyl]-17-hydrazino-5α-androst-16-en-3β-yl-trifluoroacetate (9a).

Yield. 68%, mp. 266-268°C, $[\alpha]_D^{25}$ = + 168 (c 1, $CHCl_3$); IR (KBr): 3436-3365 (NH, NH_2), 1738 (C=O), 1614 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.83 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.97-1.10 (m, 1H, CH), 1.16-1.32 (m, 4H, $2CH_2$), 1.38-1.58 (m, 6H, $3CH_2$), 1.65-1.86 (m, 4H, $2CH_2$), 1.96 (m, 1H, CH), 2.23-2.37 (m, 2H, CH_2), 2.48 (m, 1H, CH), 2.60 (m, 1H, 3α-CH), 3.15 (m, 1H, 5α-CH), 3.24 (s, 3H, OCH_3), 4.65 (s, 2H, NH_2, exchangeable with D_2O), 4.80 (s, 1H, CH-O), 7.15-7.56 (m, 4H, Ar-H), 7.72 (br.s, 1H, NH, exchangeable with D_2O). MS (EI): m/z 600 (8%) [M^+]. Anal. $C_{29}H_{38}BrF_3N_2O_3$ (599.52): Calcd C, 58.10; H, 6.39; N, 4.67; found C, 58.02; H, 6.35; N, 4.62.

16[(α-methoxy)-4-fluorobenzyl]-17-hydrazino-5α-androst-16-en-3β-yl-trifluoroacetate (9b).

Yield. 68%, mp. 258-260°C, $[\alpha]_D^{25}$ = + 116 (c 1, $CHCl_3$); IR (KBr): 3452-3366 (NH, NH_2), 1732 (C=O), 1610 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.84 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.05-1.14 (m, 1H, CH), 1.17-1.33 (m, 4H, $2CH_2$), 1.36-1.52 (m, 6H, $3CH_2$), 1.60-1.80 (m, 4H, $2CH_2$), 1.95 (m, 1H, CH), 2.22-2.36 (m, 2H, CH_2), 2.52 (m, 1H, CH), 2.64 (m, 1H, 3α-CH), 3.18 (m, 1H, 5α-CH), 3.24 (s, 3H, OCH_3), 4.68 (s, 2H, NH_2, exchangeable with D_2O), 4.82 (s, 1H, CH-O), 7.14-7.58 (m, 4H, Ar-H), 7.72 (br.s, 1H, NH, exchangeable with D_2O). MS (EI): m/z 539 (16%) [M^+]. Anal. $C_{29}H_{38}F_4N_2O_3$ (538.62): Calcd C, 64.67; H, 7.11; N, 5.20; found C, 64.60; H, 7.05; N, 5.14.

16[(α-methoxy)-4-methylbenzyl]-17-hydrazino-5α-androst-16-en-3β-yl-trifluoroacetate (9c).

Yield. 65%, mp. 215-217°C, $[\alpha]_D^{25}$ = + 154 (c 1, $CHCl_3$); IR (KBr): 3475-3373 (NH, NH_2), 1736 (C=O), 1614 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.05-1.10 (m, 1H, CH), 1.16-1.32 (m, 4H, $2CH_2$), 1.34-1.58 (m, 6H, $3CH_2$), 1.62-1.85 (m, 4H, $2CH_2$), 1.96 (m, 1H, CH), 2.22-2.36 (m, 5H, CH_2+CH_3), 2.50 (m, 1H, CH), 2.56 (m, 1H, 3α-CH), 3.15 (m, 1H, 5α-CH), 3.38 (s, 3H, OCH_3), 4.68 (s, 2H, NH_2, exchangeable with D_2O), 4.78 (s, 1H, CH-O), 7.10-7.56 (m, 4H, Ar-H), 7.68 (br.s, 1H, NH, exchangeable with D_2O). MS (EI): m/z 534 (12%) [M^+]. Anal. $C_{30}H_{41}F_3N_2O_3$ (534.65): Calcd C, 67.39; H, 7.73; F, 10.66; N, 5.24; found C, 67.33; H, 7.70; N, 5.20.

Synthesis of (1`H)-5`-(4-substituted phenyl)-5α-androstan-[17,16-c]pyrazoline-3β-yl-trifluoroacetate derivatives 10a-c

Method A.

A mixture of **7a-c** (4 mmol) and hydrazine hydrate (16 mmol) in dioxane (25 mL) was refluxed for 5 h. The solvent was concentrated under reduced pressure, the obtained solid, filtered off, washed with water, dried and crystallized from methanol to give compound **9a-c**, respectively.

Method B.

A mixture of **8a-c** or **9a-c** (4 mmol) in etherated boron trifluoride (25 mL) was refluxed for 2 h. The reaction mixture was evaporated under reduced

pressure, the obtained solid, filtered off, washed with water, dried and crystallized from methanol to give compound **10a-c,** respectively.

(1`H)-5`-(4-bromophenyl)-5α-androstan-[17,16-c]pyrazoline-3β-yl-trifluoroacetate (10a).

Yield. 90%, mp. 247-249°C, $[\alpha]_D^{25}$ = + 136 (c 1, $CHCl_3$); IR (KBr): 3544 (NH), 1736 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.86 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.00-1.11 (m, 1H, CH), 1.18-1.32 (m, 4H, $2CH_2$), 1.34-1.56 (m, 6H, $3CH_2$), 1.65-1.86 (m, 4H, $2CH_2$), 1.96-1.98 (m, 2H, 2CH), 2.25-2.35 (m, 2H, CH_2), 2.46 (m, 1H, CH), 2.55 (m, 1H, 3α-CH), 3.12 (m, 1H, 5α-CH), 4.76 (s, 1H, CH), 7.10-7.56 (m, 4H, Ar-H), 9.80 (bs, 1H, NH, exchangeable with D_2O). MS (EI): m/z 567 (8%) [M^+]. Anal. $C_{28}H_{34}BrF_3N_2O_2$ (567.48): Calcd C, 59.26; H, 6.04; N, 4.94; found C, 59.20; H, 5.96; N, 4.90.

(1`H)-5`-(4-fluororphenyl)-5α-androstan-[17,16-c]pyrazoline-3β-yl-trifluoroacetate (10b).

Yield. 85%, mp. 312-314°C, $[\alpha]_D^{25}$ = + 97 (c 1, $CHCl_3$); IR (KBr): 3538 (NH), 1736 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.87 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.05-1.12 (m, 1H, CH), 1.20-1.31 (m, 4H, $2CH_2$), 1.35-1.57 (m, 6H, $3CH_2$), 1.64-1.85 (m, 4H, $2CH_2$), 1.92-1.97 (m, 2H, 2CH), 2.20-2.30 (m, 2H, CH_2), 2.47 (m, 1H, CH), 2.57 (m, 1H, 3α-CH), 3.16 (m, 1H, 5α-CH), 4.78 (s, 1H, CH), 7.05-7.52 (m, 4H, Ar-H), 9.76 (bs, 1H, NH, exchangeable with D_2O). MS (EI): m/z 507 (21%) [M^+]. Anal. $C_{28}H_{34}F_4N_2O_2$ (506.58): Calcd C, 66.39; H, 6.77; N, 5.53; found C, 66.32; H, 6.73; N, 5.50.

(1`H)-5`-(4-methylphenyl)-5α-androstan-[17,16-c]pyrazoline-3β-yl-trifluoroacetate (10c).

Yield. 90%, mp. 289-291°C, $[\alpha]_D^{25}$ = + 110 (c 1, $CHCl_3$); IR (KBr): 3548 (NH), 1734 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 0.98-1.14 (m, 1H, CH), 1.19-1.30 (m, 4H, $2CH_2$), 1.36-1.56 (m, 6H, $3CH_2$), 1.65-1.85 (m, 4H, $2CH_2$), 1.95-1.98 (m, 2H, 2CH), 2.25-2.35 (m, 5H, CH_2+CH_3), 2.50 (m, 1H, CH), 2.64 (m, 1H, 3α-CH), 3.16 (m, 1H, 5α-CH), 4.79 (s, 1H, CH), 7.08-7.56 (m, 4H, Ar-H), 9.84 (bs, 1H, NH, exchangeable with D_2O). MS (EI): m/z 502 (24%) [M^+]. Anal. $C_{29}H_{37}F_3N_2O_2$ (502.61): Calcd C, 69.30; H, 7.42; N, 5.57; found C, 69.23; H, 7.36; N, 5.52.

Synthesis of 1`-propionyl-1H-5`-(4-substituted phenyl)-5α-androstan-[17,16-c]pyrazoline-3β-yl-trifluoroacetate derivatives 11a-c

A mixture of the arylmethylene derivatives **7a-c** (4 mmol) and hydrazine hydrate (0.8 ml, 16 mmol) in propionic acid (15 ml) was refluxed for ~7 h. The reaction mixture was poured onto cold water and neutralized with sodium bicarbonate. The formed precipitate was filtered off, washed with water, dried, and crystallized from the proper solvent to give the corresponding N-substituted pyrazoline derivatives **11a-c**, respectively.

1`-Propionyl-1H-5`-(4-bromophenyl)-5α-androstan-[17,16-c]pyrazoline-3β-yl-trifluoroacetate (11a).

Yield. 69%, mp. 316-318°C, $[\alpha]_D^{25}$ = + 136 (c 1, $CHCl_3$); IR (KBr): 1744 (C=O), 1620 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.86-0.96 (m, 9H, $3CH_3$), 0.99-1.13 (m, 1H, CH), 1.18-1.30 (m, 4H, $2CH_2$), 1.36-1.57 (m, 6H, $3CH_2$), 1.65-1.87 (m, 4H, $2CH_2$), 1.94-1.97 (m, 2H, 2CH), 2.25-2.35 (m, 4H, $2CH_2$), 2.46 (m, 1H, CH), 2.56 (m, 1H, 3α-CH), 3.16 (m, 1H, 5α-CH), 4.82 (s, 1H, CH), 7.18-7.50 (m, 4H, Ar-H). MS (EI): m/z 624 (24%) [M^+]. Anal. $C_{31}H_{38}BrF_3N_2O_3$ (623.54): Calcd C, 59.71; H, 6.14; N, 4.49; found C, 59.64; H, 6.10; N, 4.43.

1`-Propionyl-1H-5`-(4-fluorophenyl)-5α-androstan-[17,16-c]pyrazoline-3β-yl-trifluoroacetate (11b).

Yield. 59%, mp. >320°C, $[\alpha]_D^{25}$ = + 118 (c 1, $CHCl_3$); IR (KBr): 1745 (C=O), 1625 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.86-0.97 (m, 9H, $3CH_3$), 1.02-1.14 (m, 1H, CH), 1.22-1.31 (m, 4H, $2CH_2$), 1.37-1.58 (m, 6H, $3CH_2$), 1.65-1.82 (m, 4H, $2CH_2$), 1.90-1.98 (m, 2H, 2CH), 2.14-2.33 (m, 4H, $2CH_2$), 2.45 (m, 1H, CH), 2.55 (m, 1H, 3α-CH), 3.16 (m, 1H, 5α-CH), 4.79 (s, 1H, CH), 7.12-7.50 (m, 4H, Ar-H). MS (EI): m/z 563 (16%) [M^+]. Anal. $C_{31}H_{38}F_4N_2O_3$ (562.64): Calcd C, 66.18; H, 6.81; N, 4.98; found C, 66.12; H, 6.75; N, 4.92.

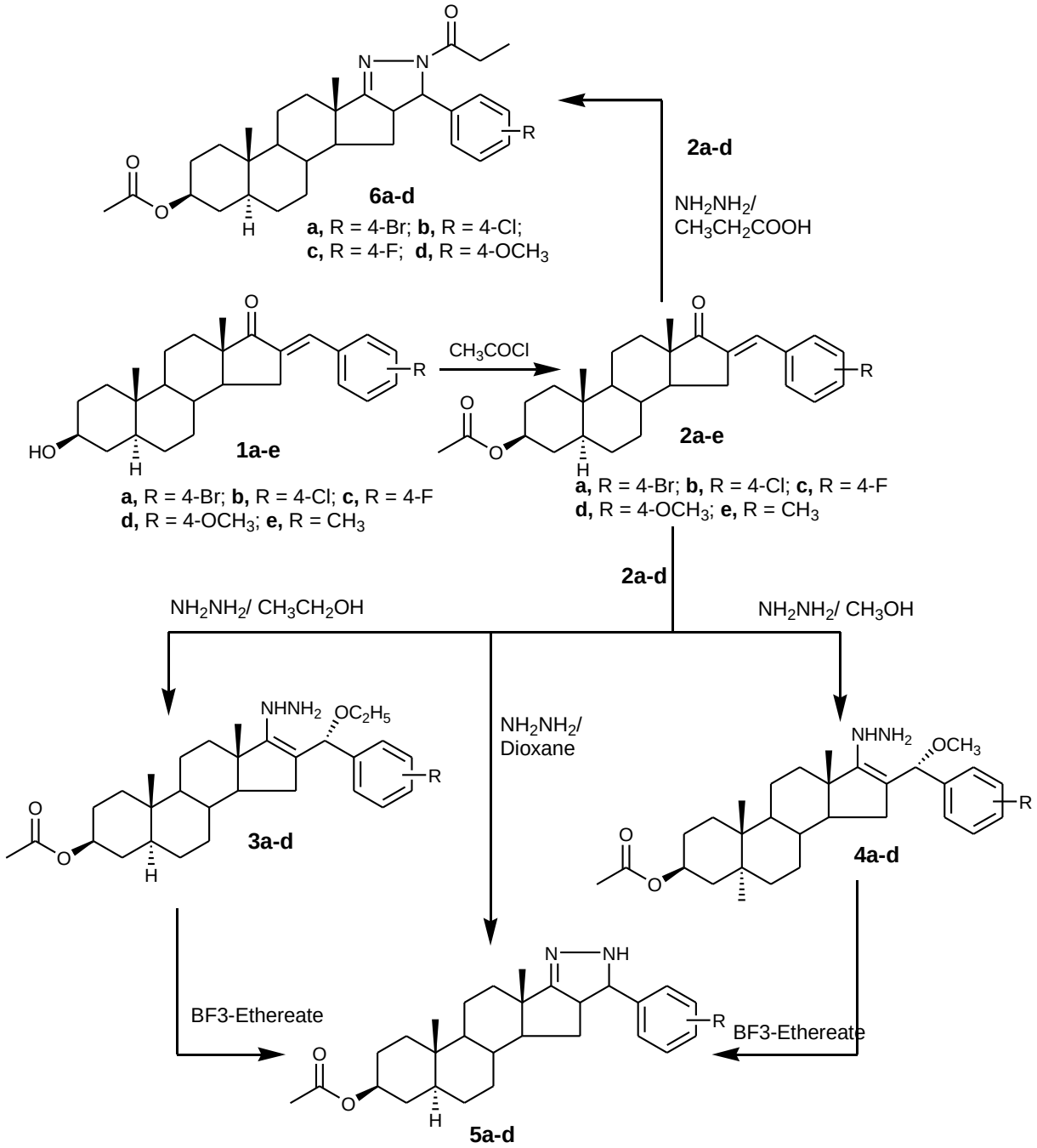
1`-Propionyl-1H-5`-(4-methylphenyl)-5α-androstan-[17,16-c]pyrazoline-3β-yl-trifluoroacetate (11c).

Yield. 62%, mp. 286-288°C, $[\alpha]_D^{25}$ = + 156 (c 1, $CHCl_3$); IR (KBr): 1748 (C=O), 1630 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85-0.98 (m, 9H, $3CH_3$), 1.05-1.15 (m, 1H, CH), 1.22-1.31 (m, 4H, $2CH_2$), 1.36-1.55 (m, 6H, $3CH_2$), 1.64-1.82 (m, 4H, $2CH_2$), 1.95-1.98 (m, 2H, 2CH), 2.25-2.35 (m, 7H, $2CH_2$ + CH_3), 2.52 (m, 1H, CH), 2.64 (m, 1H, 3α-CH), 3.15 (m, 1H, 5α-CH), 4.75 (s, 1H, CH), 7.14-7.57 (m, 4H, Ar-H). MS (EI): m/z 558 (18%) [M^+]. Anal. $C_{32}H_{41}F_3N_2O_3$ (558.67): Calcd C, 68.80; H, 7.40; N, 5.01; found C, 68.72; H, 7.34; N, 4.96.

3. Results and Discussion

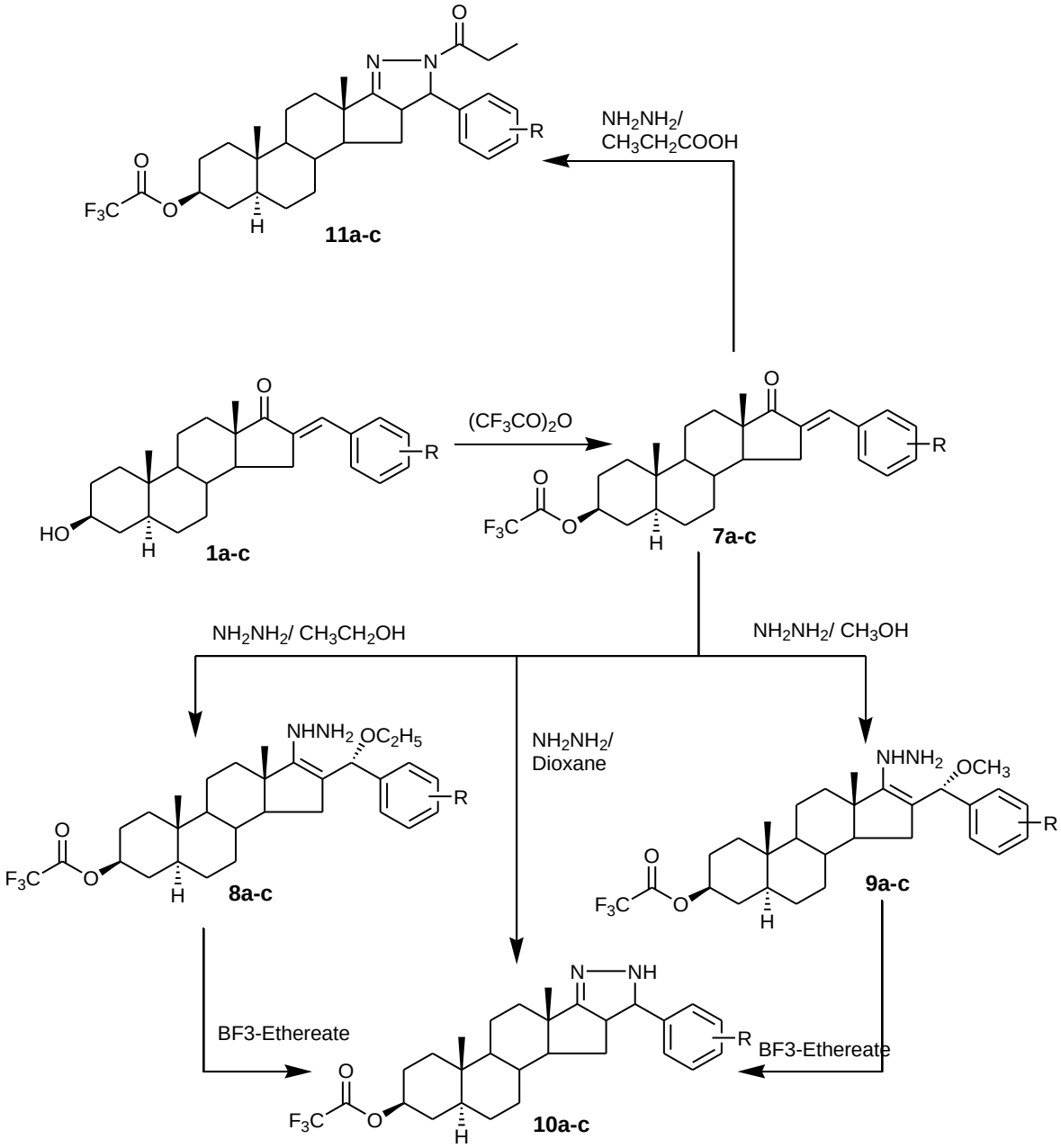
Arylmethylene of 3β-hydroxyandrostan-17-one derivatives **1a-e** were synthesized according to a reported procedures [1,2]. Compounds **1a-e** were protected by stirring at room temperature with acetyl chloride to give the corresponding 16-arylmethylene-17-oxo-5α-androstan-3β-yl-acetates **2a-e**, respectively. Compounds **1a-d** was treated with hydrazine hydrate in refluxing ethanol or methanol to afford the corresponding 17-hydrazino-androstane

derivatives **3a-d** and **4a-d**, which were cyclized in refluxing trifluoroborane-etherate to yield androstanopyrazoline derivatives **5a-d**, which can also be obtained directly by condensation of arylmethylene derivatives **2a-d** with hydrazine hydrate in refluxing dioxin. Also, condensation of **2a-d** with refluxing hydrazine hydrate in propionic acid gave the corresponding androstano-N-propionyl pyrazoline derivatives **6a-d**, respectively (Scheme 1).



Scheme 1

Additionally, compounds **1a,c,e** were protected by stirring at room temperature with trifluoroacetic anhydride to give the corresponding 3β-trifluoroacetate-16-arylmethylene-androstan-17-ones **(7a-c)**, which was treated with hydrazine hydrate in refluxing ethanol or methanol to afford the corresponding 3β-trifluoroacetate-17-hydrazino-androstane derivatives **8a-c** and **9a-c**, respectively. Compounds **8a-c** and **9a-c** were cyclized in refluxing trifluoroborane-etherate to yield 3β-trifluoroacetate androstanopyrazoline derivatives **10a-c**, which can also be obtained directly by condensation of 3β-trifluoroacetate arylmethylene derivatives **7a-c** with hydrazine hydrate in refluxing dioxin. Condensation of **7a-c** with refluxing hydrazine hydrate in propionic acid gave the corresponding 3β-trifluoroacetate androstano-N-propionyl pyrazoline derivatives **11a-c**, respectively (Scheme 2).



a, R = 4-Br; **b**, R = 4-F; **c** R = CH_3

Scheme 2

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