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Synthesis of some new testosterone derivatives fused with substituted pyrazoline ring as promising 5α-reductase inhibitors

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Condensation of 3β-hydroxy-16-[(4-chlorophenyl)methylene]androst-5-en-17-one (**1**) with hydrazine hydrate in acetic acid afforded *N*-acetyl pyrazoline derivative **2,** while condensation of **1** with semicarbazide afforded compound **3**. Also, compound **1** was treated with hydrazine hydrate in absolute methanol or ethanol to afford the corresponding α-methoxy (**4**) and α-ethoxy (**5**) derivatives, which were cyclized with etherated boron trifluoride to the pyrazoline derivative **6**. The latter could be prepared directly by refluxing **1** with hydrazine hydrate in dioxane. Oxidation of compound **6** with Oppenour or Moffat oxidizing agents yielded 3-oxo-derivatives **7** and **8**, respectively. On the other hand, condensation of compound **1** with substituted hydrazines, gave the corresponding 3β-hydroxy-androstenopyrazolines **9a,b**, which were oxidized using the Moffat method to give 3-oxo-androstenopyrazolines **10a,b**, which were condensed with ethylene triphenyl-phosphorane in DMSO to yield 3-ethylene androstenopyrazolines **11a,b**. Dehydrogenation of **9a,b** with Wettestein oxidation afforded $\Delta^{4,6}$-diene-3-one analogues **12a,b**, which were treated with chloranil to yield $\Delta^{4,6,8(14)}$-tri- ene-3-one analogues **13a,b**. Oppenour oxidation of **9a,b** afforded Δ^{4}-ene-3-one analogues **14a,b**, which were treated with dichlorodicyanoquinone (DDQ) in dioxane to give $\Delta^{1,4,6}$-triene-3-one analogues **15a,b**. Pharmacological screening showed that many of these compounds inhibit 5α-reductase activity.

*Keywords***:** testosterone, pyrazolines, Moffat oxidation, 5α-reductase inhibitor

In a previous work we found that certain substituted steroidal derivatives showed androgenic, anabolic and anti-inflammatory activities (1). Pyrazolines are an interesting group of compounds, many of which possess wide-spread pharmacological properties

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such as analgesic, antipyretic, antidepressant and antirheumatic activities (2, 3) and are also well known for their pronounced anti-inflammatory activity (4) and are used as potent antidiabetic agents (5, 6). Recently, pyrazolines were reported as a DP-IV inhibitors and antitumor agents (7–9). Some nitrogen heterocyclic compounds were reported to be antiparkinsonian (10), anticancer (11–13), antimicrobial (14–16) and anti-inflammatory agents (17, 18). In recent years, heterocyclic nitrogen derivatives exhibited a general ionophoric potency for divalent cations (19) and are used as novel thiocyanate-selective membrane sensors (20). In view of these reports and in continuation of our previous work in heterocyclic chemistry, we have herein synthesized some new compounds containing pyrazoline ring fused with a steroidal structure to be evaluated as 5α-reductase inhibitors compared to anastrozole as a standard drug.

EXPERIMENTAL

Melting points were uncorrected and were recorded on a Digital Melting Point Apparatus (Electrothermal IA 9100 MK2, LABEQUIP^{TM}, UK). Microanalytical data were obtained from the Microanalytical Unit, Cairo University, Egypt, and their results were found to be in agreement with the proposed structures. IR spectra (KBr) were recorded on a FT IR-8201 PC Spectrophotometer (Shimadzu, Japan). ^{1}H NMR spectra were measured with Jeol (Japan) 270 MHz in DMSO-d_6 or $CDCl_3$ and the chemical shifts were recorded in δ ppm relative to TMS. Mass spectra were run at 70 eV with a Finnigan SSQ 7000 (Thermo-instrument System Incorporation, USA) spectrometer using EI. The reactions were followed by TLC (silica gel, aluminum sheets 60 F_{254}, Merck, Germany).

Physicochemical and spectral data for the synthesized compounds are given in Tables I and II.

*Synthesis of 1′-acetyl-1′H-5′-(4-chlorophenyl]androst-5-ene[17,16-c]-pyrazoline-3β-ol (**2**)*

A mixture of 3β-hydroxy-16-[(4-chlorophenyl)methylene]androst-5-en-17-one (**1**) (1) (1.64 g, 4 mmol) and hydrazine hydrate (0.8 mL, 16 mmol) in glacial acetic 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 methanol-ethyl acetate to give the corresponding pyrazoline derivative **2** (Scheme 1).

*Synthesis of 1′-carbamoyl-1′H-(2′H)-5′-(4-chlorophenyl)androst-5-ene[17,16-c]-pyrazoline-3β-ol (**3**)*

A solution of **1** (4.11 g, 10 mmol) and semicarbazide hydrochloride (1.34 g, 12 mmol) in sodium ethoxide [sodium metal (460 mg, 20 mmol) in 25 mL absolute ethanol] was refluxed for 8 h. The solvent was concentrated under reduced pressure and the reaction mixture was acidified with 10% hydrochloric acid. The obtained solid was filtered off, washed with water, dried and crystallized from methanol to give **3** (Scheme 1).

Table I. Physical and analytical data of new by synthesized compounds

Compd. No.	Yield (%)	M. p. (°C)	$[\alpha]_D$ (*c* 1, MeOH)	Mol. formula (M_r)	Calcd./found (%) C	H	N
2	65	167	+96	$C_{28}H_{35}ClN_2O_2$ (467.05)	72.00 71.89	7.55 7.48	6.00 5.90
3	65	158	+51	$C_{27}H_{34}ClN_3O_2$ (468.03)	69.28 69.19	7.32 7.26	8.98 8.92
4	65	217	+61	$C_{27}H_{37}ClN_2O_2$ (457.05)	70.95 70.88	8.16 8.08	6.13 6.05
5	72	203	+91	$C_{28}H_{39}ClN_2O_2$ (471.08)	71.38 71.31	8.34 8.27	5.95 5.88
6	A 55 B 64	194	+88	$C_{26}H_{33}ClN_2O$ (425.01)	73.47 73.40	7.83 7.76	6.59 5.52
7	60	316	+16	$C_{26}H_{31}ClN_2O$ (422.99)	73.82 73.74	7.39 7.32	6.62 6.57
8	55	219	+93	$C_{26}H_{31}ClN_2O$ (422.99)	73.82 73.77	7.39 7.31	6.62 6.56
9a	62	211	+64	$C_{27}H_{35}ClN_2O$ (439.04)	73.86 73.75	8.04 7.98	6.38 6.33
9b	66	201	+37	$C_{32}H_{37}ClN_2O$ (501.11)	76.69 76.60	7.44 7.38	5.59 5.52
10a	68	192	+128	$C_{27}H_{33}ClN_2O$ (437.02)	74.20 73.98	7.61 7.55	6.41 6.36
10b	65	166	+89	$C_{32}H_{35}ClN_2O$ (499.09)	77.00 76.88	7.07 6.96	5.61 5.55
11a	58	171	+19	$C_{29}H_{37}ClN_2$ (449.07)	77.56 77.48	6.51 6.43	6.24 6.18
11b	72	197	+170	$C_{34}H_{39}ClN_2$ (511.15)	79.89 79.81	7.69 7.62	5.48 5.43
12a	55	109	+36	$C_{27}H_{31}ClN_2O$ (435.00)	74.54 74.48	7.18 7.05	6.44 6.36
12b	50	273	+38	$C_{32}H_{33}ClN_2O$ (497.07)	77.32 77.24	6.69 6.61	5.64 5.58
13a	62	213	+19	$C_{27}H_{29}ClN_2O$ (432.99)	74.89 74.81	6.75 6.67	6.47 6.39
13b	72	266	+17	$C_{32}H_{31}ClN_2O$ (495.06)	77.63 77.52	6.31 6.22	5.66 5.55
14a	75	198	+26	$C_{27}H_{33}ClN_2O$ (437.02)	74.20 74.12	7.61 7.56	6.41 6.34
14b	68	210	+34	$C_{32}H_{35}ClN_2O$ (499.09)	77.00 76.85	7.07 6.96	5.61 5.55
15a	55	156	+38	$C_{27}H_{29}ClN_2O$ (432.99)	74.89 74.77	6.75 6.66	6.47 6.38
15b	62	226	+21	$C_{32}H_{31}ClN_2O$ (495.06)	77.63 77.54	6.31 6.24	5.66 5.58

Table II. Spectral data of the newly synthesized compounds

Compd. No.	Mass m/z (%)	IR (ν, cm^{-1})	^1H NMR (δ, ppm)
2	467 [M^+] (10), 469 [M^++2] (3)	1737 (C=O), 1640 (C=N), 1600 (C=C)	0.79 (s, 3H, CH_3), 0.91 (s, 3H, CH_3), 0.95–1.00 (m, 1H, CH), 1.25–1.30 (m, 4H, 2CH_2), 1.40–1.55 (m, 4H, 2CH_2), 1.60–1.85 (m, 4H, 2CH_2), 1.95 (m, 1H, CH), 2.15–2.30 (m, 2H, CH_2), 2.40 (s, 3H, $NCOCH_3$), 2.45 (m, 1H, CH), 2.48 (m, 1H, pyrazoline-H), 3.28 (d, 1H, pyrazoline-H), 3.60 (m, 1H, 3α-CH), 5.21 (m, 1H, H-6), 7.32–7.45 (m, 4H, Ar-H), 10.25 (s, 1H, OH, exchangeable with D_2O)
3	468 [M^+] (35), 470 [M^++2] (100)	3498 (OH), 3418–3390 (NH_2), 1663–1631 (C=O, amide)	0.75 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.90–0.95 (m, 1H, CH), 1.25–1.32 (m, 4H, 2CH_2), 1.38–1.60 (m, 4H, 2CH_2), 1.65–1.85 (m, 4H, 2CH_2), 2.05 (m, 1H, CH), 2.34 (m, 1H, pyrazoline-H), 2.38–2.42 (m, 2H, CH_2), 2.48 (m, 1H, CH), 3.26 (d, 1H, pyrazoline-H), 3.54 (m, 1H, 3α-CH), 5.18 (m, 1H, H-6), 6.20 (br.s, 2H, NH_2 exchangeable with D_2O), 7.10–7.60 (m, 4H, Ar-H), 10.35 (s, 1H, OH, exchangeable with D_2O)
4	457 [M^+] (14), 459 [M^++2] (4)	3483 (OH), 3420–3395 (NH, NH_2), 1605 (C=C)	0.75 (s, 3H, CH_3), 0.85 (s, 3H, CH_3), 0.88–0.96 (m, 1H, CH), 1.22–1.35 (m, 4H, 2CH_2), 1.40–1.58 (m, 4H, 2CH_2), 1.65–1.84 (m, 4H, 2CH_2), 2.00 (m, 1H, CH), 2.36–2.40 (m, 2H, CH_2), 2.48 (m, 1H, CH), 3.45 (m, 1H, 3α-CH), 3.87 (s, 3H, OCH_3), 4.09 (m, 2H, NH_2, exchangeable with D_2O), 5.25 (m, 1H, H-6), 5.65 (s, 1H, CH), 6.25 (br.s, 1H, NH, exchangeable with D_2O), 7.25–7.65 (m, 4H, Ar-H), 10.05 (s, 1H, OH, exchangeable with D_2O)
5	471 [M^+] (22), 473 [M^++2] (7)	3479 (OH), 3421–3380 (NH, NH_2), 1600 (C=C)	0.73 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.90–0.95 (m, 1H, CH), 1.24–1.30 (m, 4H, 2CH_2), 1.32 (t, 3H, CH_3), 1.44–1.55 (m, 4H, 2CH_2), 1.62–1.80 (m, 4H, 2CH_2), 1.98 (m, 1H, CH), 2.35–2.42 (m, 2H, CH_2), 2.50 (m, 1H, CH), 3.55 (m, 1H, 3α-CH), 3.90 (q, 2H, CH_2), 4.22 (m, 2H, NH_2, exchangeable with D_2O), 5.23 (m, 1H, H-6), 5.68 (s, 1H, CH), 6.38 (br.s, 1H, NH, exchangeable with D_2O), 7.19–7.32 (m, 4H, Ar-H), 10.15 (s, 1H, OH, exchangeable with D_2O)
6	425 [M^+] (17), 427[M^++2] (5)	3510 (OH), 3418 (NH), 1635 (C=N), 1610 (C=C)	0.72 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 0.95–1.05 (m, 1H, CH), 1.20–1.26 (m, 4H, 2CH_2), 1.35–1.58 (m, 4H, 2CH_2), 1.65–1.92 (m, 4H, 2CH_2), 2.10 (m, 1H, CH), 2.28 (m, 1H, pyrazoline-H), 2.35–2.42 (m, 2H, CH_2), 2.45 (m, 1H, CH), 3.30 (d, 1H, pyrazoline-H), 3.55 (m, 1H, 3α-CH), 5.20 (m, 1H, H-6), 7.23–7.42 (m, 4H, Ar-H), 9.45 (s, 1H, NH, exchangeable with D_2O), 10.00 (s, 1H, OH, exchangeable with D_2O)
7	423 [M^+] (27), 425 [M^++2] (8)	3435 (NH), 1670 (C=O), 1640 (C=N), 1600 (C=C)	0.69 (s, 3H, CH_3), 0.81 (s, 3H, CH_3), 0.88–0.95 (m, 1H, CH), 1.24–1.30 (m, 4H, 2CH_2), 1.36–1.60 (m, 4H, 2CH_2), 1.70–1.95 (m, 6H, 3CH_2), 2.00 (m, 1H, CH), 2.32 (m, 1H, pyrazoline-H), 2.46 (m, 1H, CH), 3.45 (d, 1H, pyrazoline-H), 5.72 (s, 1H, H-4), 7.23–7.45 (m, 4H, Ar-H), 9.86 (s, 1H, NH, exchangeable with D_2O)

Table II. contind.

Compd. No.	Mass m/z (%)	IR (ν, cm^{-1})	^{1}H NMR (δ, ppm)
8	423 [M$^+$] (18), 425 [M$^+$+2] (5)	3422 (NH), 1728 (C=O), 1638 (C=N), 1620 (C=C)	0.73 (s, 3H, CH_3), 0.83 (s, 3H, CH_3), 0.90–1.00 (m, 1H, CH), 1.22–1.30 (m, 4H, 2CH_2), 1.36–1.60 (m, 4H, 2CH_2), 1.68–1.95 (m, 4H, 2CH_2), 2.00 (m, 1H, CH), 2.26 (m, 1H, pyrazoline-H), 2.30–2.40 (m, 2H, CH_2), 2.50 (m, 1H, CH), 3.38 (d, 1H, pyrazoline-H), 5.22 (m, 1H, H-6), 7.28–7.39 (m, 4H, Ar-H), 9.65 (s, 1H, NH, exchangeable with D_2O)
9a	439 [M$^+$] (26), 441 [M$^+$+2] (8)	3491 (OH), 1638 (C=N), 1605 (C=C)	0.74 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.90–0.95 (m, 1H, CH), 1.20–1.32 (m, 4H, 2CH_2), 1.38–1.62 (m, 4H, 2CH_2), 1.70–1.95 (m, 4H, 2CH_2), 1.98 (m, 1H, CH), 2.15 (s, 3H, N-CH_3), 2.35 (m, 1H, pyrazoline-H), 2.38–2.42 (m, 2H, CH_2), 2.48 (m, 1H, CH), 3.40 (d, 1H, pyrazoline-H), 3.60 (m, 1H, 3α-CH), 5.16 (m, 1H, H-6), 7.31–7.42 (m, 4H, Ar-H), 10.25 (s, 1H, OH, exchangeable with D_2O)
9b	501 [M$^+$] (10), 503 [M$^+$+2] (3)	3488 (OH), 1645 (C=N), 1615 (C=C)	0.75 (s, 3H, CH_3), 0.84 (s, 3H, CH_3), 0.88–0.95 (m, 1H, CH), 1.24–1.30 (m, 4H, 2CH_2), 1.40–1.60 (m, 4H, 2CH_2), 1.68–1.90 (m, 4H, 2CH_2), 2.05 (m, 1H, CH), 2.24 (m, 1H, pyrazoline-H), 2.35–2.40 (m, 2H, CH_2), 2.50 (m, 1H, CH), 3.36 (d, 1H, pyrazoline-H), 3.57 (m, 1H, 3α-CH), 5.18 (m, 1H, H-6), 7.24–7.65 (m, 9H, Ar-H), 10.18 (s, 1H, OH, exchangeable with D_2O)
10a	437 [M$^+$] (13), 439 [M$^+$+2] (4)	1738 (C=O), 1635 (C=N), 1610 (C=C)	0.76 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 0.95–1.05 (m, 1H, CH), 1.22–1.32 (m, 4H, 2CH_2), 1.34–1.62 (m, 4H, 2CH_2), 1.65–1.90 (m, 4H, 2CH_2), 1.96 (m, 1H, CH), 2.22 (s, 3H, N-CH_3), 2.28 (m, 1H, pyrazoline-H), 2.35–2.45 (m, 2H, CH_2), 2.55 (m, 1H, CH), 3.35 (d, 1H, pyrazoline-H), 5.24 (m, 1H, H-6), 7.35–7.45 (m, 4H, Ar-H)
10b	499 [M$^+$] (18), 501 [M$^+$+2] (6)	1740 (C=O), 1638 (C=N), 1615 (C=C)	0.75 (s, 3H, CH_3), 0.91 (s, 3H, CH_3), 0.94–1.00 (m, 1H, CH), 1.25–1.35 (m, 4H, 2CH_2), 1.38–1.60 (m, 4H, 2CH_2), 1.66–1.98 (m, 4H, 2CH_2), 2.00 (m, 1H, CH), 2.26 (m, 1H, pyrazoline-H), 2.35–2.48 (m, 2H, CH_2), 2.57 (m, 1H, CH), 3.28 (d, 1H, pyrazoline-H), 5.21 (m, 1H, H-6), 7.30–7.65 (m, 9H, Ar-H)
11a	449 [M$^+$] (35), 451 [M$^+$+2] (12)	1645 (C=N), 1615 (C=C)	0.77 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), 0.92–0.98 (m, 1H, CH), 1.25–1.35 (m, 4H, 2CH_2), 1.40–1.60 (m, 4H, 2CH_2), 1.64 (d, 3H, CH_3-CH=C), 1.68–1.98 (m, 4H, 2CH_2), 2.05 (m, 1H, CH), 2.18 (s, 3H, N-CH_3), 2.30 (m, 1H, pyrazoline-H), 2.36–2.40 (m, 2H, CH_2), 2.60 (m, 1H, CH), 3.32 (d, 1H, pyrazoline-H), 5.17 (m, 1H, H-6), 5.65 (q, 1H, methine protone), 7.31–7.43 (m, 4H, Ar-H)
11b	511 [M$^+$] (6), 513 [M$^+$+2] (2)	1641 (C=N), 1610 (C=C)	0.78 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.96–1.05 (m, 1H, CH), 1.24–1.36 (m, 4H, 2CH_2), 1.42–1.60 (m, 4H, 2CH_2), 1.65 (d, 3H, CH_3-CH=C), 1.70–1.90 (m, 4H, 2CH_2), 1.98 (m, 1H, CH), 2.26 (m, 1H, pyrazoline-H), 2.36–2.40 (m, 2H, CH_2), 2.56 (m, 1H, CH), 3.36 (d, 1H, pyrazoline-H), 5.13 (m, 1H, H-6), 5.62 (q, 1H, methine proton), 7.29–7.66 (m, 9H, Ar-H)

Table II. contind.

Compd. No.	Mass m/z (%)	IR (ν, cm^{-1})	^{1}H NMR (δ, ppm)
12a	435 [M$^+$](32), 437 [M$^+$+2], (10)	1671 (C=O), 1640 (C=N), 1615 (C=C)	0.76 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 0.92–1.00 (m, 1H, CH), 1.25–1.35 (m, 4H, 2CH_2), 1.40–1.60 (m, 2H, CH_2), 1.68–1.96 (m, 2H, CH_2), 2.00 (m, 1H, CH), 2.18 (s, 3H, N-CH_3), 2.26 (m, 1H, pyrazoline-H), 2.35–2.45 (m, 2H, CH_2), 2.57 (m, 1H, CH), 3.32 (d, 1H, pyrazoline-H), 5.59 (m, 1H, H-7), 5.75 (d, 1H, H-6), 5.84 (s, 1H, H-4), 7.30–7.46 (m, 4H, Ar-H)
12b	497 [M$^+$] (32), 499 [M$^+$+2] (10)	1668 (C=O), 1638 (C=N), 1610 (C=C)	0.77 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 0.95–1.10 (m, 1H, CH), 1.24–1.38 (m, 4H, 2CH_2), 1.42–1.64 (m, 2H, CH_2), 1.70–1.95 (m, 2H, CH_2), 2.05 (m, 1H, CH), 2.30 (m, 1H, pyrazoline-H), 2.36–2.44 (m, 2H, CH_2), 2.55 (m, 1H, CH), 3.36 (d, 1H, pyrazoline-H), 5.61 (m, 1H, H-7), 5.78 (d, 1H, H-6), 5.91 (s, 1H, H-4), 7.32–7.56 (m, 9H, Ar-H)
13a	433 [M$^+$](42), 435 [M$^+$+2] (13)	1669 (C=O), 1642 (C=N), 1610 (C=C)	0.78 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 2.24 (s, 3H, N-CH_3), 1.23–1.35 (m, 4H, 2CH_2), 1.40–1.65 (m, 2H, CH_2), 1.68–1.95 (m, 2H, CH_2), 1.99 (m, 1H, CH), 2.35 (m, 1H, pyrazoline--H), 2.40–2.46 (m, 2H, CH_2), 2.60 (m, 1H, CH), 3.38 (d, 1H, pyrazoline-H), 5.58 (d, 1H, H-7), 5.87 (d, 1H, H-6), 6.10 (s, 1H, H-4), 7.32–7.54 (m, 4H, Ar-H)
13b	495 [M$^+$] (16), 497 [M$^+$+2] (5)	1665 (C=O), 1636 (C=N), 1605 (C=C)	0.81 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.25–1.38 (m, 4H, 2CH_2), 1.45–1.58 (m, 2H, CH_2), 1.65–1.95 (m, 2H, CH_2), 2.00 (m, 1H, CH), 2.34 (m, 1H, pyrazoline-H), 2.39–2.45 (m, 2H, CH_2), 2.55 (m, 1H, CH), 3.40 (d, 1H, pyrazoline-H), 5.56 (d, 1H, H-7), 5.86 (d, 1H, H-6), 6.00 (s, 1H, H-4), 7.30–7.58 (m, 9H, Ar-H)
14a	437 [M$^+$] (8), 439 [M$^+$+2] (3)	1669 (C=O), 1640 (C=N), 1615 (C=C)	0.74 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.90–0.95 (m, 1H, CH), 1.20–1.32 (m, 4H, 2CH_2), 1.38–1.62 (m, 4H, 2CH_2), 1.70–1.95 (m, 4H, 2CH_2), 1.98 (m, 1H, CH), 2.26 (s, 3H, N-CH_3), 2.32 (m, 1H, pyrazoline-H), 2.38–2.42 (m, 2H, CH_2), 2.48 (m, 1H, CH), 3.38 (d, 1H, pyrazoline-H), 5.78 (s, 1H, H-4), 7.24–7.38 (m, 4H, Ar-H)
14b	499 [M$^+$] (14), 501 [M$^+$+2] (5)	1668 (C=O), 1638 (C=N), 1616 (C=C)	0.76 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 0.95–1,00 (m, 1H, CH), 1.25–1.35 (m, 4H, 2CH_2), 1.42–1.65 (m, 4H, 2CH_2), 1.68–1.96 (m, 4H, 2CH_2), 2.00 (m, 1H, CH), 2.30 (m, 1H, pyrazoline-H), 2.40–2.46 (m, 2H, CH_2), 2.52 (m, 1H, CH), 3.40 (d, 1H, pyrazoline-H), 5.74 (s, 1H, H-4), 7.30–7.60 (m, 9H, Ar-H)
15a	433 [M$^+$] (36), 435 [M$^+$+2] (12)	1669 (C=O), 1636 (C=N), 1605 (C=C)	0.81 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.15–1.20 (m, 1H, CH), 1.40–1.55 (m, 2H, CH_2), 1.68–1.97 (m, 2H, CH_2), 1.98 (m, 1H, CH), 2.25 (s, 3H, N-CH_3), 2.34 (m, 1H, pyrazoline-H), 2.40–2.50 (m, 2H, CH_2), 2.60 (m, 1H, CH), 3.33 (d, 1H, pyrazoline-H), 5.61 (m, 1H, H-7), 5.82 (d, 1H, H-6), 6.12 (s, 1H, H-4), 6.41 (d, 1H, H-1), 7.20 (d, 1H, H-2), 7.38–7.60 (m, 4H, Ar-H)
15b	495 [M$^+$] (16), 497 [M$^+$+2] (5)	1670 (C=O), 1638 (C=N), 1615 (C=C)	0.78 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 0.95–1.00 (m, 1H, CH), 1.38–1.65 (m, 2H, CH_2), 1.70–1.95 (m, 2H, CH_2), 2.00 (m, 1H, CH), 2.25 (m, 1H, pyrazoline-H), 2.42–2.47 (m, 2H, CH_2), 2.58 (m, 1H, CH), 3.28 (d, 1H, pyrazoline-H), 5.65 (m, 1H, H-7), 5.85 (d, 1H, H-6), 6.05 (s, 1H, H-4), 6.38 (d, 1H, H-1), 7.22 (d, 1H, H-2), 7.34–7.70 (m, 9H, Ar-H)

*Synthesis of 16-(α-methoxy-4′-chlorophenyl)-17-hydrazinoandrost-5,16-diene-3β-ol (**4**) and 16-(α-ethoxy-4′-chlorophenyl)-17-hydrazinoandrost-5,16-diene-3β-ol (**5**)*

General procedure. – A mixture of **1** (1.64 g, 4 mmol) and hydrazine hydrate (0.4 mL, 8 mmol) in absolute methanol or ethanol (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 to give the corresponding 16-(α-substituted-4'-chlorophenyl)-17-hydrazinoandrost-5,16-diene-3β-ols, **4** and **5**, respectively (Scheme 1).

*Synthesis of 1′H-5′-(4-chlorophenyl)androst-5-ene[17,16-c]pyrazoline-3β-ol (**6**)*

Method A. – A mixture of **1** (1.64 g, 4 mmol) and hydrazine hydrate (0.8 mL, 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 **6** (Scheme 1).

Method B. – A mixture of **4** or **5** (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 **6** (Scheme 1).

*Synthesis of 1′H-5′-(4-chlorophenyl)androst-4-ene[17,16-c]pyrazoline-3-one (**7**)*

Oppenour method. – To a solution of **6** (6.9 mmol) in cyclohexanone (50 mL, 0.48 mol) and dry benzene (45 mL), freshly distilled aluminium *i*-propoxide (2 g, 9.7 mmol) in dry benzene (5 mL) was added. The reaction mixture was refluxed for 10 h, after cooling, the mixture was treated with water (4 mL) dropwise. The precipitated aluminum salt was collected by filtration, the filtrate was evaporated under reduced pressure, and the residue was crystallized from petroleum ether to give compound **7** (Scheme 1).

Synthesis of 1′H-5′-(4-chlorophenyl)androst-5-ene[17,16-c]pyrazoline-3-one (8)

Moffat method. – The pyrazoline derivative **6** (0.85 g, 2 mmol) was dissolved in a mixture of benzene (3 mL), dimethylsulfoxide (3 mL), pyridine (0.16 mL) and trifluoroacetic acid (TFA) (0.01 mL) and then dicyclohexylcarbodiimide (1.24 g, 6 mmol) was added. The reaction mixture was kept overnight at room temperature, diethyl ether (50 mL) was added and then oxalic acid (0.54 g, 6 mmol) in methanol (5 mL); after 30 minutes, water (50 mL) was added. The obtained dicyclohexylurea was removed by filtration. The product was extracted from the filtrate with ether, washed with 5% sodium bicarbonate, and then with water. The ethereal solution was dried over anhydrous sodium sulfate and evaporated under reduced pressure; the formed residue was crystallized from ethanol to give the corresponding 3-oxo-derivative **8** (Scheme 1).

*Synthesis of 1′-methyl-1′H-5′(4-chlorophenyl)androst-5-ene[17,16-c]-pyrazoline-3β-ol (**9a**) and 1′-phenyl-1′H-5′-(4-chlorophenyl)androst-5-ene-[17,16-c]pyrazoline-3β-ol (**9b**)*

A mixture of **1** (1.64 g, 4 mmol) and hydrazine derivatives (5 mmol), namely, methyl- or phenyl hydrazine in glacial acetic acid (15 mL), was refluxed for 6 hours. After cooling, the obtained solid was filtered off, washed with water, dried and crystallized from the proper solvent to give *N*-substituted pyrazoline derivatives **9a,b** (Scheme 2).

*Synthesis of 1′-methyl-1′H-5′-(4-chlorophenyl)androst-5-ene[17,16-c]-pyrazoline-3-one (**10a**) and 1′-phenyl-1′H-5′-(4-chlorophenyl)androst-5-ene[17,16-c]pyrazoline-3-one (**10b**)*

Compounds **10a,b** were prepared from **9a,b** according to the procedure described for **8** (Scheme 2).

*Synthesis of 1′-methyl-1′H-5′-(4-chlorophenyl)androst-5-ene[17,16-c]pyrazoline-3-ethylidene (**11a**) and 1′-phenyl-1′H-5′-(4-chlorophenyl)androst-5-ene[17,16-c]pyrazoline--3-ethylidene (**11b**)*

To a stirred solution of ethylidene triphenylphosphorane (1.2 mmol) in dimethyl--sulfoxide (100 mL), cycloketone derivatives **10a,b** (1 mmol) in dry benzene (60 mL) were added dropwise, and then heated at 60 °C for 10–12 hour. The reaction mixture was cooled, poured into ice-water, the solid formed was filtered off, washed with water, dried, then crystallized from the proper solvent to give compounds **11a,b** (Scheme 2).

*Synthesis of 1′-methyl-1′H-5′-(4-chlorophenyl)androst-4,6-diene[17,16-c]-pyrazoline -3-one (**12a**) and 1′-phenyl-1′H-5′-(4-chlorophenyl)androst-4,6-diene[17,16-c]pyrazoline-3-one (**12b**)*

These compounds were prepared according the reported methods (21, 22) (Scheme 2).

*Synthesis of 1′-methyl-1′H-5′-(4-chlorophenyl)androst-4,6,8(14)-triene[17,16-c]-pyrazoline-3-one (**13a**) and 1′-phenyl-1′H-5′-(4-chlorophenyl)androst-4,6,8(14)-triene--[17,16-c]pyrazoline-3-one (**13b**)*

A solution of **12a,b** (6 mmol) and chloranil (1.6 g) in dioxan (40 mL) was refluxed for 7 h in the presence of *p*-toluene sulphonic acid (PTSA) (0.1 g). The reaction mixture was evaporated under reduced pressure, the residue was dissolved in diethyl ether, then washed with sodium bicarbonate (1%). The ethereal part was dried over anhydrous sodium sulphate and eluted through a short sintered glass funnel containing 3 g of alumina (activity I), evaporated and crystallized from hexane/benzene to give the corresponding triene-derivatives **13a,b** (Scheme 2).

*Synthesis of 1′-methyl-1′H-5′-(4-chlorophenyl)androst-4-ene[17,16-c]pyrazoline-3-one (**14a**) and 1′-phenyl-1′H-5′-(4-chlorophenyl)androst-4-ene[17,16-c]pyrazoline-3-one (**14b**)*

Compounds **14a,b** were prepared from **9a,b** according to the procedure described for **7** (Scheme 2).

*Synthesis of 1′-methyl-1′H-5′-(4-chlorophenyl)androst-1,4,6-triene[17,16-c]pyrazoline--3-one (**15a**) and 1′-phenyl-1′H-5′- (4-chlorophenyl)androst-1,4,6-triene [17,16-c]-pyrazoline-3-one (**15b**)*

Anhydrous hydrogen chloride was bubbled for a few seconds into a mixture of compounds **14a,b** (6 mmol) and dichlorodicyanoquinone (DDQ) (1.8 g) in dioxane (40 mL). The mixture was kept for 30 min at room temperature under stirring, the hydroquinone precipitate was filtered off and the filtrate was diluted with water, then extracted with ether, the ethereal solution was washed with 1% sodium hydroxide, water, and dried over anhydrous sodium sulphate. The ether part was evaporated under reduced pressure to dryness, then crystallized from the proper solvent to give corresponding 3--oxo-triene derivatives **15a,b** (Scheme 2).

Biological assay

Treatment of animals. – Animals were obtained from the animal house colony of the National Research Center, Cairo, Egypt. All animals were allowed free access to water and were kept on a constant standard diet. Twenty three groups, each of 12 male Sprague-Dawley rats in the postnatal third days, were treated subcutaneously with the 5α--reductase inhibitor (tested compound or reference standard). The tested compounds were dissolved in 5%. Tween 80 in water. The solvent was used for both standard and negative control group, beginning on the postnatal third day until the age of seven weeks. Twenty-one groups were used to test the activities, of which one was used as the positive control for anastrozole and another served as the negative control group. After sacrifying blood was withdrawn for testosterone and dihydrotestosterone (DHT) determination (23). Moreover, intraprostatic concentrations of testosterone and DHT were determined (24). The biological experiments were performed according to the official standards.

Radioimmuno assay for testosterone and dihydrotestosterone. – Serum testosterone and dihydrotestosterone were measured by radioimmuno assay in serum extracts using specific antisera without prior chromatography. Serum samples of 0.5 mL were extracted with 2 mL of freshly purified peroxide-free diethyl ether by shaking for 60 sec on a Vortex mixer. The aqueous phase was frozen at –70 °C, the ether phase containing steroids was transferred to a conical test tube and evaporated in BSA/phosphate buffer (pH = 7.4) containing (1,2,6,7-^{3}H)-testosterone or (1,2,6,7-^{3}H)-dihydrotestosterone and then specific antisera were added and incubated over a period of 24 h at 4 °C under non-equilibrium conditions. Bound hormone and free hormone were separated by adsorption on dextran--coated charcoal. The activity of each sample was determined in a Beckman-β-counter (USA) using a commercially available scintillation cocktail (Mini-RIA, Zinsser, Spain).

As for other steroid hormones, commercially available KIA-kits, *e.g.*, Biermann GmbH, Germany, can be used.

The hormone level in the sample was calculated from a standard curve by means of a computer program (KIA-Calc, LKB, Canada), using appropriate control sera. Steroid levels of rats treated with different doses of 5α-reductase inhibitors were compared with vehicle-treated controls (Table III).

The relative potency was calculated by dividing the ED_{50} (dose that causes 50% of pharmacological response in the test) of anastrozole by that of a tested compound.

Determination of acute toxicity. – LD_{50} and LD_{90} were determined by using 108 adult male albino rats and injecting them with different increasing doses of agents. Doses that killed 50% and 90% of the tested animals, respectively, were calculated according to Austen *et al.* (25) (Table III).

Table III. Evaluation of ED_{50}, LD_{50}, LD_{90} *and 5α-reductase inhibitor activities relative to anastrozole*

Compd. No.	ED_{50}[a] (mg kg^{-1})	LD_{50}[b] (mg kg^{-1})	LD_{90}[c] (mg kg^{-1})	Potency relative to anastrozole
2	2.31	413	790	0.47
3	1.71	314	810	0.64
4	2.51	460	930	0.43
5	1.75	473	1011	0.62
6	1.89	514	1112	0.58
7	3.40	640	1310	0.32
8	2.56	318	730	0.43
9a	2.33	645	1016	0.47
9b	6.51	463	953	0.17
10a	3.14	468	699	0.35
10b	2.44	567	1314	0.45
11a	2.21	478	991	0.49
11b	2.55	491	980	0.43
12a	1.73	513	1213	0.63
12b	4.41	416	738	0.25
13a	5.43	317	813	0.20
13b	2.31	388	751	0.47
14a	2.17	356	813	0.50
14b	2.15	393	820	0.51
15a	2.36	394	920	0.46
15b	2.45	378	914	0.44
anastrozole	1.09	2.415	3.69	1.00

[a] ED_{50}: Dose caused 50% of pharmacological response in the test.
[b] LD_{50}: Dose killed 50% of the tested animals.
[c] LD_{90}: Dose killed 90% of the tested animals.

RESULTS AND DISCUSSION

Arylmethylene of 3β-hydroxyandrosten-17-one derivative **1** was synthesized according to the reported procedure (1). It was condensed with hydrazine hydrate in refluxing glacial acetic acid to afford the 3β-hydroxyandrosteno-*N*-acetylpyrazoline derivative **2**. Also, reaction of compound **1** with semicarbazide hydrochloride gave the corresponding 3β-hydroxyandrosteno-*N*-aminocarbonylpyrazoline derivative **3** (Scheme 1). The IR spectra of **2** and **3** showed the absence of bands corresponding to α,β-unsaturated system for compound **1** and the presence of band at 1737 cm^{-1} for compound **2**, and a broad band at 3418–3390 cm^{-1} corresponding to ν (NH_2) for compound **3**.

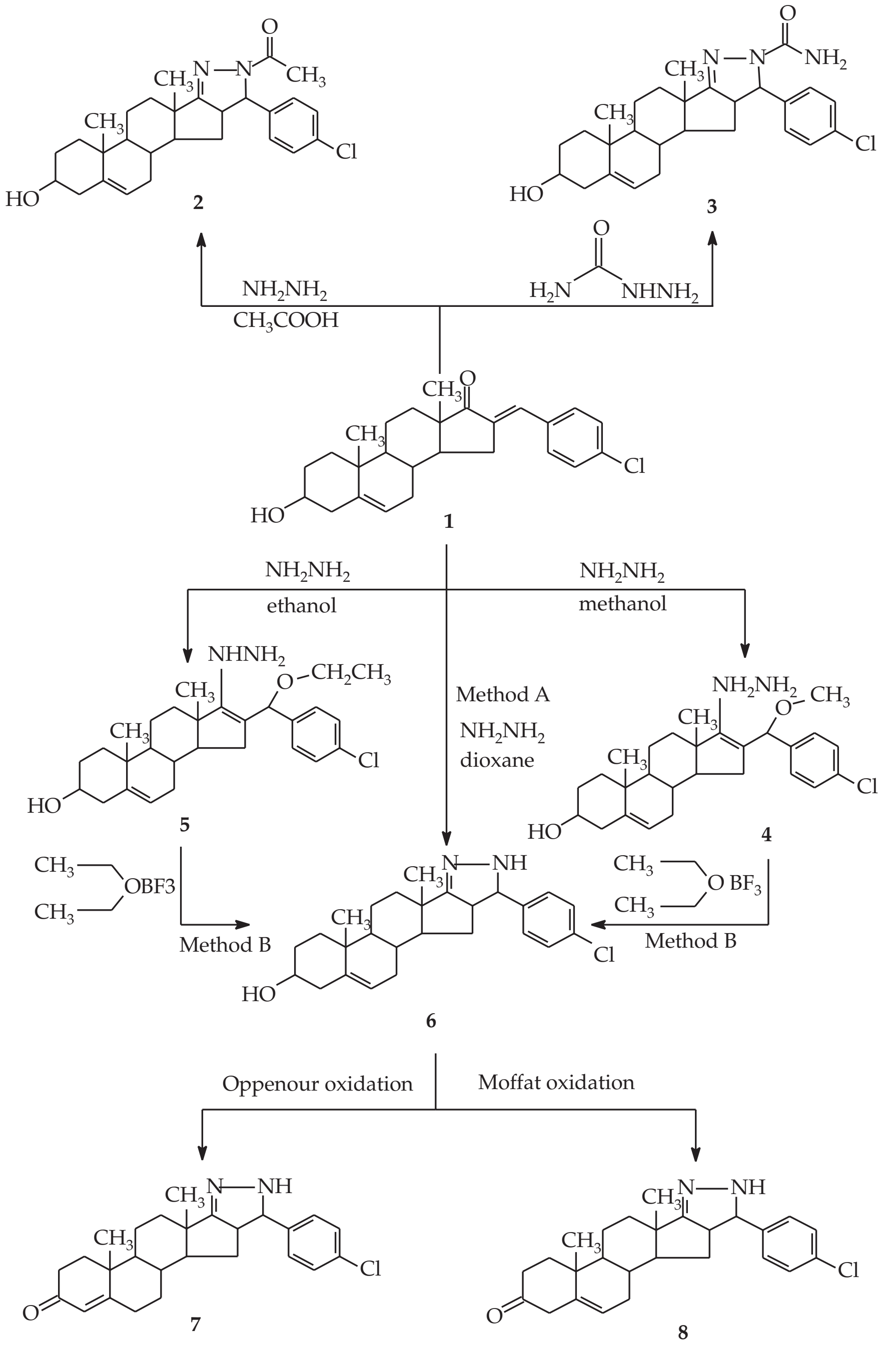
Compound **1** was condensed with hydrazine hydrate in refluxing absolute methanol or ethanol to give the corresponding *α*-methoxy- (**4**) and *α*-ethoxyhydrazino (**5**) derivatives. Cyclization of compounds **4** and **5** using etherated boron trifluoride gave the pyrazoline derivative **6**, which can be obtained directly by condensation of arylmethylene **1** with hydrazine hydrate in refluxing dioxane (Scheme 1). The IR spectra of **5** and **6** showed the absence of ν(C=O) for compound **1** and the presence of broad bands at 3420––3395 cm^{-1} corresponding to ν($NHNH_2$). Oxidation of **6** using the Oppenour oxidizing agent afforded the corresponding 3-oxo-androstenopyrazoline derivative **7** with migration of the Δ^5-ene into the corresponding Δ^4-ene. Oxidation of **6** with the Moffat oxidizing agent in the presence of dicyclohexylcarbodiimide under stirring at room temperature gave the corresponding 3-oxo-androstenopyrazoline derivative **8** without affecting the Δ^5-ene. The IR spectra of **7** and **8** showed the absence of band ν(OH) at 3510 cm^{-1} for **6** and the presence of bands at 1670 cm^{-1} for **7** and at 1728 cm^{-1} for **8** corresponding to ν(C=O). Syntheses of compounds **2–8** are outlined in Scheme 1.

On the other hand, condensation of compound **1** with substituted hydrazines, namely, methylhydrazine or phenylhydrazine in refluxing glacial acetic acid, gave the corresponding 3β-hydroxyandrosteno-*N*-substituted pyrazolines **9a,b**, which were oxidized using the Moffat method to give 3-oxo-androsteno-*N*-substituted pyrazolines **10a,b**. They were condensed with ethylene triphenylphosphorane by heating at 60 °C in dimethylsulphoxide to yield 3-ethylene androsteno-*N*-substituted pyrazolines **11a,b**. Dehydrogenation of compounds **9a,b** with *p*-benzoquinone as hydrogen acceptor in the Wettstein oxidation afforded $\Delta^{4,6}$-diene-3-one analogues **12a,b**, which were treated with chloranil, affording $\Delta^{4,6,8(14)}$-triene-3-one analogues **13a,b**. Oxidation of **9a,b** using the Oppenour oxidizing agent afforded the corresponding Δ^4-ene-3-one analogues **14a,b**, which were treated with dichlorodicyanoquinolinone (DDQ) in dioxane to afford $\Delta^{1,4,6}$-triene-3-one analogues **15a,b.** Syntheses of compounds **9–15** are outlined in Scheme 2.

Pharmacological screening

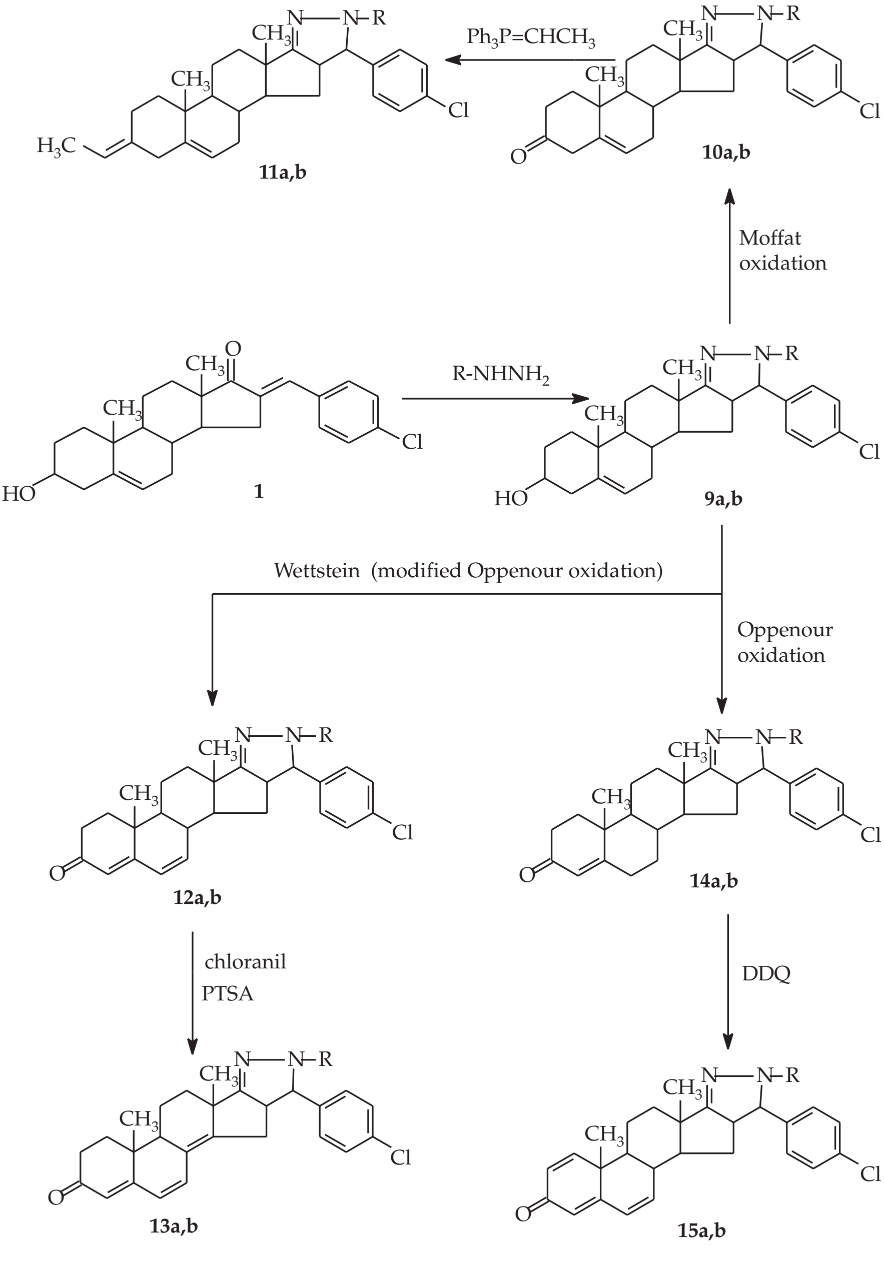
Circulating testosterone and dihydrotestosterone hormone levels or tissue concentrations were measured after administration of 5α-reductase inhibitor radioimmuno assays.

All synthesized compounds were tested for their 5α-reductase inhibitor activity *in vivo;* the ED_{50}, LD_{50} and LD_{90} data were determined and are given in Table III. All the tested compounds showed 5α-reductase inhibitor activities with good ED_{50} in the range



2
3
NH_2NH_2
CH_3COOH
H_2N
$NHNH_2$
1
NH_2NH_2
ethanol
NH_2NH_2
methanol
5
4
Method A
NH_2NH_2
dioxane
$OBF3$
Method B
$O\ BF_3$
Method B
6
Oppenour oxidation
Moffat oxidation
7
8

Scheme 1



a R = CH_3; **b** R = Ph

DDQ – dichlorodicyanoquinone
PTS – *p*-toluene sulphonic acid

Scheme 2

of 1.7–6.5 mg kg^{-1}. Both LD_{50} and LD_{90} for all compounds were high enough to provide good therapeutic windows and a soft profile margin.

The biological investigations indicated that six compounds (**3**, **5**, **6**, **12a**, **14a** and **14b**) revealed 50–60% activity of the reference drug anastrozole. It appeared that Wettstein modified Oppenour) or Oppenour oxidation of compounds **9** (Scheme 2) affording 1′-methyl(or phenyl)-1′H-5′-(4-chlorophenyl)androst-4,6-diene[17,16-c]-pyrazoline-3-one (**12**) and 1′-methyl(or phenyl)-1′H-5′-(4-chlorophenyl)androst-4-ene[17,16-c]pyrazoline-3-one (**14**), was associated with enhancement of the biological activity.

CONCLUSIONS

Twenty-one pyrazoline testosterone steroid derivatives were synthesized and tested as 5α-reductase inhibitors. The pyrazoline moiety fused with steroidal structure containing conjugated double bonds was found to be essential for 5α-reductase inhibitor activities. Future work will involve the design of steroidal molecules of such features.

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S A Ž E T A K

Sinteza novih derivata testosterona sa supstituiranim pirazolinskim prstenom kao inhibitora 5α-reduktaze

ABD EL-GALIL EL-SAYED AMR, NEHAD AHMED ABDEL-LATIF i MOHAMED MOSTAFA ABDALLA

Kondenzacijom 3β-hidroksi-16-[(4-klorofenil)metilen]androst-5-en-17-ona (**1**) s hidrazin hidratom u octenoj kiselini dobiven je derivat *N*-acetil pirazolina **2,** a kondenzacijom **1** sa semikarbazidom priređen je spoj **3**. Reakcijom spoja **1** s hidrazin hidratom u apsolutnom metanolu ili etanolu nastali su odgovarajući α-metoksi (**4**) i α-etoksi (**5**) derivati, koji su ciklizirani s borovim trifluoridom u derivat pirazolina **6**. Isti spoj je pripravljen izravno refluksiranjem spoja **1** s hidrazin hidratom u dioksanu. Oksidacijom spoja **6** s Oppenourovim ili Moffatovim oksidansom dobiveni su 3-okso derivati **7**, odnosno **8**. S druge strane, kondenzacija spoja **1** sa supstituiranim hidrazinima dala je odgovarajuće 3β-hidroksiandrostenopirazoline **9a,b**, koji su oksidirani Moffatovom metodom u 3-okso-androstenopirazoline **10a,b**. Ovi produkti su dalje kondenzirani s etilen trifenil-fosforanom u DMSO u 3-etilen androstenpirazoline **11a,b**. Wettesteinovom dehidrogenacijom **9a,b** dobiveni su $\Delta^{4,6}$-dien-3-on analozi **12a,b**, koji su s kloranilom dali $\Delta^{4,6,8(14)}$-trien-3-on analoge **13a,b**. Oppenourovom oksidacijom **9a,b** dobiveni su Δ^{4}-en-3-on analozi **14a,b**, koji su s diklorodicianokinonom (DDQ) u dioksanu dali $\Delta^{1,4,6}$-trien-3-on analoge **15a,b**. Farmakološka ispitivanja pokazuju da mnogi od sintetizirnih spojeva inhibiraju 5α-reduktazu.

Ključne riječi: testosteron, pirazolini, Moffatova oksidacija, inhibitor 5α-reduktaze

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