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Synthesis of modified steroids as a novel class of non-ulcerogenic, anti-inflammatory and anti-nociceptive agents

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ABSTRACT

The identification of compounds able to treat both pain and inflammation with limited side effects is one of the prominent goals in biomedical research. This study aimed at the synthesis of new modified steroids with structures justifying non-ulcerogenic, anti-inflammatory and anti-nociceptive activities. The steroid derivatives were synthesized via straightforward and efficient methods and their structures were established based on the analytical and spectral data. The *in vivo* anti-inflammatory, anti-nociceptive and anti-ulcerogenic activities of some of these compounds were studied. The newly synthesized compounds **8b, 19b, 24** and **31a** showed anti-inflammatory, anti-nociceptive and anti-ulcerogenic activity with various intensities. Oedema was significantly reduced by either dose 25 or 50 mg/kg of all tested compounds at 3 and 4 h post-carrageenan. Compound **19b** was the most effective in alleviating thermal pain. The analgesic activity of either dose of the compounds **8b**, **24**, **31a** as well as the high dose **19b** was significantly higher than that for indomethacin (IND). Gastric mucosal lesions caused in the rats by the administration of 96% EtOH and IND were inhibited by all tested compounds administered at (50 mg/kg) dose in the study.

1. Introduction

Inflammatory diseases are widely prevalent throughout the world. Drugs used for the treatment of acute and chronic inflammatory disorders suppress biological processes that contribute to the onset and symptoms of inflammation [1,2]. Pain is widely accepted to be one of the most important determinations of quality of life. A study reported by the World Health Organization demonstrated that individuals who live with persistent pain suffer fourfold more from depression or anxiety compared to healthy subjects [3,4]. The identification of compounds able to treat both pain and inflammation with limited side effects is one of the prominent goals in biomedical research.

The chronic use of the anti-inflammatory drugs is limited for their severe side effects such as gastrointestinal injury, especially gastrointestinal perforation, peptic ulceration or significant bleeding [5,6]. Thus, developing new therapeutic agents that can overcome gastrointestinal injury and at the same time could lead to an enhanced anti-inflammatory effect become an urgent need for inflammation patients.

Although the beneficial effects of corticosteroids in the management of inflammatory and allergic conditions have been appreciated for over 50 years, complications arising from the steroid therapy have imposed limitations on the clinical use of this class of drugs [7]. A considerable research effort has been devoted to the structural modifications of glucocorticoids, with the hope of increasing their potencies while minimizing their propensity to elicit systemic adverse effects. The incorporation of phenylpyrazole ring at C-2 and C-3 or fused oxazole ring at C-16 and C-17 [8,9] increased lipophilicity of glucocorticoids and proved to be useful for topical application. There has been considerable interest in the synthesis and biological study of several heterocyclic steroids as high potent anti-inflammatory agents [10–12].

In recent years our research has focused on the design, synthesis and pharmacological evaluation of new molecules with analgesic, anti-inflammatory and antinociceptive activity as potential safe and effective drugs [12–14]. We report herein on the synthesis of new steroidal heterocyclic derivatives with structures justifying anti-inflammatory, anti-nociceptive and/or non-ulcerogenic activities. The *in vivo* anti-inflammatory, anti-nociceptive and anti-ulcerogenic activities of some of these compounds were studied.

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[1] Blessing and mercy to the soul of our dear fellow (late) Marian G. William.

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2. Experimental

2.1. Synthetic methods, analytical and spectral data

The starting steroid, progesterone, was purchased from Sigma Company, USA. All solvents were dried by distillation prior to using. All melting points were measured using an Electrothermal apparatus and are uncorrected. The IR spectra were recorded in (KBr discs) on a shimadzu FT-IR 8201 PC spectrometer and expressed in cm^{-1}. The ^1H NMR and ^{13}C NMR spectra were recorded with Jeol instrument (Japan), at 270 and 125 MHz, respectively, in DMSO-d_6 or $CDCl_3$ as solvent and chemical shifts were recorded in ppm relative to TMS. The spin multiplicities were abbreviated by the letters: s-singlet, d-doublet, t-triplet, q-quartet and m (multiplet, more than quartet). Mass spectra were recorded on a GCMS-QP 1000 Ex spectra mass spectrometer operating at 70 eV. Elemental analyses were carried by the Microanalytical Data Unit at the National Research Center, Giza, Egypt and the Microanalytical Data Unit at Cairo University, Giza, Egypt. The reactions were monitored by thin layer chromatography (TLC) which was carried out using Merck 60 F254 aluminum sheets and visualized by UV light (254 nm). The mixtures were separated by preparative TLC and gravity chromatography. For the nomenclature of steroid derivatives, we used the definitive rules for the nomenclature of steroids published by the Joint Commission on the Biochemical Nomenclature (JCBN) of IUPAC [15,16]. All described compounds showed the characteristic spectral data of cyclopentanoperhydrophenanthrene nuclei of pregnene series and were similar to those reported in the literatures [17,18].

2.1.1. Synthesis of 17-(oxiran-2′-yl)androst-4-ene-3-one derivatives (**3**, **15**, and **24**)

2.1.1.1. General procedure. To a solution of progesterone **1** (0.31 g, 1 mmol) in potassium *tert*-butoxide {prepared by the reaction of anhydrous *tert*-butanol (30 mL) with potassium metal (0.5 g) [19]}, equimolar amount of ethyl chloroacetate **2** (0.12 g, 1 mmol), chloroacetone **14** (0.09 g, 1 mmol), or α-bromoacetophenone **23** (0.20 g, 1 mmol) was added. The reaction mixture was stirred at room temperature for 24 h and then heated for 6 h in water bath at 70 °C. After cooling at room temperature, the reaction mixture poured over an ice/water mixture and the resulted semisolid was subjected to extraction with chloroform (2 × 30 mL). The organic layer was dried over magnesium sulfate and then filtered. The oil product that formed in each case on removal of the solvent in vacuum was solidified by boiling in petroleum ether (60–80 °C), collected and crystallized from the appropriate solvent.

*2.1.1.2. Ethyl 17-(2′-methyloxiran-2′-yl)-3-oxo-androst-4-en-3′-carboxylate (**3**).* Dark yellow crystals from absolute ethanol, yield 0.28 g (72%), mp 98–100 °C, IR (KBr, cm^{-1}): υ = 2956–2878 (CH-aliphatic), 1708 (C-3, C=O), 1742 (ester-C=O), 1643 (C=C), ^1H NMR (DMSO-d_6, ppm): δ = 0.87 (s, 3H, CH_3-19), 1.03 (s, 3H, CH_3-18), 1.28 (s, 3H, CH_3), 1.37 (t, J = 7 Hz, 3H, ester-CH_3), 3.45 (s, 1H, oxarine-CH), 4.25 (q, J = 7 Hz, 2H, ester-CH_2), 5.76 (s, 1H, C_4-H). M.S. (EI): m/z (%): 400 (M^+, 29), 327 (M^+-CO_2Et, 45), 271 ($C_{19}H_{27}O$, 100), 129 (40), 74 (67), 57 (38), Calc. for $C_{25}H_{36}O_4$ (400.551): C, 74.96; H, 9.06; found: C, 75.08; H, 9.29%.

*2.1.1.3. 17-(3′-Acetyl-2′-methyloxiran-2′-yl)androst-4-en-3-one (**15**).* Pale yellow crystals from dioxane, yield 0.29 g (78%), mp 192–194 °C, IR (KBr, cm^{-1}): υ = 2960–2875 (CH-aliphatic), 1708 (C-3, C=O), 1718 (*CO*CH_3), 1645 (C=C), ^1H NMR (DMSO-d_6, ppm): δ = 0.81 (s, 3H, CH_3-19), 1.05 (s, 3H, CH_3-18), 1.32 (s, 3H, CH_3), 2.07 (s, 3H, $COCH_3$), 3.37 (s, 1H, oxarine-CH), 5.87 (s, 1H, C_4-H). M.S. (EI): m/z (%): 370 (M^+, 43), 327 (M^+-COCH_3, 38), 271 ($C_{19}H_{27}O$, 100), 256 (24), Calc. for $C_{24}H_{34}O_3$ (370.525): C, 77.80; H, 9.25; found: C, 78.03; 9.42%.

*2.1.1.4. 17-(3′-Benzoyl-2′-methyloxiran-2′-yl)androst-4-ene-3-one (**24**).* Orange crystals from dioxane, yield 0.32 g (74%), mp 173–175 °C, IR (KBr, cm^{-1}): υ = 3030 (CH-aromatic), 2963–2870 (CH-aliphatic), 1710 (C-3, C=O), 1723 (*CO*Ph), 1649 (C=C). ^1H NMR (DMSO-d_6, ppm): δ = 0.93 (s, 3H, CH_3-19), 1.07 (s, 3H, CH_3-18), 1.30 (s, 3H, CH_3), 3.87 (s, 1H, oxarine-CH), 5.82 (s, 1H, C_4-H), 7.30–7.82 (m, 5H, C_6H_5), ^{13}C NMR (DMSO-d_6, ppm): δ = 35.7 (C-1), 34.0, (C-2), 197.2 (C-3), 125.3 (C-4), 170.9 (C-5), 32.7 (C-6), 31.2 (C-7), 35.4 (C-8), 50.7 (C-9), 37.8 (C-10), 22.0 (C-11), 36.5 (C-12), 39.2 (C-13), 56.3 (C-14), 27.1 (C-15), 22.5 (C-16), 55.8 (C-17), 22.1 (C-18), 20.7 (C-19), 195.6 (C=O), 19.4 (CH_3), 72.4, 63.0 (C-oxarine), 136.2, 128.7, 129.0, 133.4 (C-phenyl). M.S. (EI): m/z (%): 432 (M^+, 43), 327 (M^+-COPh, 76), 271 ($C_{19}H_{27}O$, 54), 161 (34), 105 (100). Calc. for $C_{29}H_{36}O_3$ (432.594): C, 80.52; H, 8.39; found: C, 80.29; H, 8.66%.

2.1.2. Synthesis of 17-(3′-arylaminobutanyl)androst-4-ene-3-one derivatives (**16a–c**), (**16a–c**), and (**25a–c**)

2.1.2.1. General procedure. To a solution of either compound **3** (0.80 g, 2 mmol), compound **15** (0.74 g, 2 mmol), or compound **24** (0.86 g, 2 mmol) in absolute ethanol (30 mL) containing a catalytic amount of triethylamine (1 mL), either aniline **4a** (0.18 g, 2 mmol), *p*-chloroaniline **4b** (0.25 g, 2 mmol), or *p*-methoxyaniline **4c** (0.24 g, 2 mmol) was added. The reaction mixture, in each case, was heated under reflux for 6–8 h until all the reactants had disappeared as indicated by TLC. The reaction mixture poured over an ice/water mixture and neutralized with dilute hydrochloric acid. The solid product that formed, in each case, was filtered off, dried and crystallized from the appropriate solvent.

*2.1.2.2. 17-[Ethyl 3′-hydroxy-2′-(phenylamino)butanoate]androst-4-ene-3-one (**5a**).* Reddish brown powder from methanol, yield 0.67 g (68%), mp 78–80 °C, IR (KBr, cm^{-1}): υ = 3546–3387 (OH, NH), 3035 (CH-aromatic), 2970–2878 (CH-aliphatic), 1708 (C-3, C=O), 1745 (CO-ester), 1640 (C=C). ^1H NMR ($CDCl_3$, ppm): δ = 0.96 (s, 3H, CH_3-19), 1.13 (s, 3H, CH_3-18), 1.30 (s, 3H, CH_3), 1.37 (t, J = 6 Hz, 3H, ester-CH_3), 3.52 (s, 1H, CH), 4.23 (q, J = 6 Hz, 2H, ester-CH_2), 4.59 (s, 1H, OH, D_2O-exchangable), 5.85 (s, 1H, C_4-H), 6.73–7.02 (m, 5H, C_6H_5), 8.03 (brs, 1H, NH, D_2O-exchangable). M.S. (EI): m/z (%): 492 (M^+-1, 59), 420 (M^+-CO_2Et, 40), 401 (34), 271 ($C_{19}H_{27}O$, 76), 92 (100), 77 (36). Calc. for $C_{31}H_{43}NO_4$ (493.677): C, 75.42; H, 8.78; N, 2.84; found: C, 75.18; H, 8.57; N, 2.57%.

*2.1.2.3. 17-[Ethyl 3′-hydroxy-2′-(p-chlorophenylamino)butanoate] androst-4-en-3-one (**5b**).* Yellow crystals from absolute ethanol, yield 0.76 g (72%), mp 65–67 °C, IR (KBr, cm^{-1}): υ = 3548–3380 (OH, NH), 3038 (CH-aromatic), 2978–2872 (CH-aliphatic), 1711 (C-3, C=O), 1740 (CO-ester), 1643 (C=C). ^1H NMR ($CDCl_3$, ppm): δ = 0.99 (s, 3H, CH_3-19), 1.07 (s, 3H, CH_3-18), 1.32 (s, 3H, CH_3), 1.38 (t, J = 6 Hz, 3H, ester-CH_3), 3.58 (s, 1H, CH), 4.25 (q, J = 6 Hz, 2H, ester-CH_2), 4.68 (s, 1H, OH, D_2O-exchangable), 5.85 (s, 1H, C_4-H), 6.42 (dd, 2H-aromatic, J_{HH} = 8 Hz), 7.05 (dd, 2H-aromatic, J_{HH} = 8 Hz), 8.12 (brs, 1H, NH, D_2O-exchangable). M.S. (EI): m/z (%): 528 (M^+, 39), 454 (M^+-CO_2Et, 56), 271 ($C_{19}H_{27}O$, 43), 126 (100), 111 (38). Calc. for $C_{31}H_{42}ClNO_4$ (528.122): C, 70.50; H, 8.02; N, 2.65; found: C, 70.74; H, 7.82; N, 2.91%.

*2.1.2.4. 17-[Ethyl 3′-hydroxy-2′-(p-methoxyphenylamino)butanoate] androst-4-en-3-one (**5c**).* Brown crystals from absolute ethanol, yield 0.80 g (77%), mp 175–177 °C, IR (KBr, cm^{-1}): υ = 3546–3380 (OH, NH), 3035 (CH-aromatic), 2978–2876 (CH-aliphatic), 1705 (C-3, C=O), 1745 (CO-ester), 1647 (C=C). ^1H NMR ($CDCl_3$, ppm): δ = 1.02 (s, 3H, CH_3-19), 1.12 (s, 3H, CH_3-18), 1.28 (s, 3H, CH_3), 1.35

(t, J = 5.3 Hz, 3H, ester-CH_3), 3.49 (s, 1H, CH), 3.78 (s, 3H, OCH_3), 4.25 (q, J = 5.3 Hz, 2H, ester-CH_2), 4.65 (s, 1H, OH, D_2O-exchangable), 5.80 (s, 1H, C_4-H), 6.38 (dd, 2H-aromatic, J_{HH} = 8 Hz), 7.02 (dd, 2H-aromatic, J_{HH} = 8 Hz), 8.20 (brs, 1H, NH, D_2O-exchangable). M.S. (EI): m/z (%): 521 (M^+-2, 25), 450 (M^+-CO_2Et, 64), 401 (37), 271 ($C_{19}H_{27}O$, 50), 122 (100), 107 (36). ^{13}C NMR ($CDCl_3$, ppm): δ = 35.2 (C-1), 34.3, (C-2), 198.6 (C-3), 124.0 (C-4), 171.5 (C-5), 32.7 (C-6), 31.0 (C-7), 36.3 (C-8), 50.0 (C-9), 37.2 (C-10), 23.1 (C-11), 37.5 (C-12), 38.7 (C-13), 56.2 (C-14), 27.3 (C-15), 21.5 (C-16), 56.3 (C-17), 23.0 (C-18), 21.7 (C-19), 71.9 (CH), 21.4 (CH_3), 171.0 ($\underline{C}O_2Et$), 62.3 ($CO_2\underline{C}H_2CH_3$), 14.5 ($CH_2\underline{C}H_3$), 139.2, 115.6, 114.0, 150.4 (C-phenyl). Calc. for $C_{32}H_{45}NO_5$ (523.703): C, 73.39; H, 8.66; N, 2.67; found: C, 73.63; H, 8.39; N, 2.83%.

*2.1.2.5. 17-[2′-Hydroxy-4′-oxo-4′-methyl-3′-(phenylamino)butan-2-yl]androst-4-en-3-one (**16a**).* Yellow crystals from methanol, yield 0.72 g (78%), mp 192–194 °C, IR (KBr, cm^{-1}): υ = 3548–3390 (OH, NH), 3030 (CH-aromatic), 2973–2878 (CH-aliphatic), 1710 (C-3, C=O), 1722 ($\underline{C}OCH_3$), 1640 (C=C). ^1H NMR ($CDCl_3$, ppm): δ = 0.96 (s, 3H, CH_3-19), 1.13 (s, 3H, CH_3-18), 1.30 (s, 3H, CH_3), 2.10 (s, 3H, $COCH_3$), 3.55 (s, 1H, CH), 4.52 (s, 1H, OH, D_2O-exchangable), 5.76 (s, 1H, C_4-H), 6.78–7.06 (m, 5H, C_6H_5), 8.53 (brs, 1H, NH, D_2O-exchangable). M.S. (EI): m/z (%): 463 (M^+, 39), 420 (M^+-COCH_3, 47), 371 (23), 315 (100), 271 ($C_{19}H_{27}O$, 64), 92 (62), 77 (45). Calc. for $C_{30}H_{41}NO_3$ (463.651): C, 77.71; H, 8.91; N, 3.02; found: C, 77.96; H, 8.76; N, 2.83%.

*2.1.2.6. 17-[2′-Hydroxy-4′-oxo-4′-methyl-3′-(p-chlorophenylamino)butan-2-yl]androst-4-en-3-one (**16b**).* Pale brown crystals from absolute ethanol, yield 0.74 g (75%), mp 110–112 °C, IR (KBr, cm^{-1}): υ = 3546–3378 (OH, NH), 3028 (CH-aromatic), 2978–2872 (CH-aliphatic), 1706 (C-3, C=O), 1726 ($\underline{C}OCH_3$), 1643 (C=C). ^1H NMR (DMSO-d_6, ppm): δ = 0.98 (s, 3H, CH_3-19), 1.09 (s, 3H, CH_3-18), 1.32 (s, 3H, CH_3), 2.10 (s, 3H, $COCH_3$), 3.57 (s, 1H, CH), 4.64 (s, 1H, OH, D_2O-exchangable), 5.75 (s, 1H, C_4-H), 6.49 (dd, 2H-aromatic, J_{HH} = 8 Hz), 7.15 (dd, 2H-aromatic, J_{HH} = 8 Hz), 8.35 (brs, 1H, NH, D_2O-exchangable). M.S. (EI): m/z (%): 497 (M^+-1, 35), 454 (M^+-COCH_3, 24), 371 (34), 271 ($C_{19}H_{27}O$, 76), 126 (100), 111 (22). Calc. for $C_{30}H_{40}ClNO_3$ (498.046): C, 72.34; H, 8.09; N, 2.81; found: C, 72.14; H, 7.87; N, 2.98%.

*2.1.2.7. 17-[2′-Hydroxy-4′-oxo-4′-methyl-3′-(p-methoxyphenylamino)butan-2-yl]androst-4-en-3-one (**16c**).* Reddish brown powder from ethanol (70%), yield 0.78 g (79%), mp 136–137 °C, IR (KBr, cm^{-1}): υ = 3538–3387 (OH, NH), 3033 (CH-aromatic), 2980–2876 (CH-aliphatic), 1703 (C-3, C=O), 1727 ($CO\underline{C}H_3$), 1645 (C=C). ^1H NMR (DMSO-d_6, ppm): δ = 1.02 (s, 3H, CH_3-19), 1.12 (s, 3H, CH_3-18), 1.37 (s, 3H, CH_3), 2.09 (s, 3H, $COCH_3$), 3.48 (s, 1H, CH), 3.73 (s, 3H, OCH_3), 4.78 (s, 1H, OH, D_2O-exchangable), 5.83 (s, 1H, C_4-H), 6.37 (dd, 2H-aromatic, J_{HH} = 8 Hz), 7.05 (dd, 2H-aromatic, J_{HH} = 8 Hz), 8.30 (brs, 1H, NH, D_2O-exchangable). M.S. (EI): m/z (%): 493 (M^+, 46), 450 (M^+-COCH_3, 32), 371 (100), 271 ($C_{19}H_{27}O$, 27), 122 (47), 107 (18). Calc. for $C_{31}H_{43}NO_4$ (493.677): C, 75.42; H, 8.78; N, 2.84; found: C, 75.20; H, 9.02; N, 2.63%.

*2.1.2.8. 17-[2′-Hydroxy-4′-oxo-4′-phenyl-3′-(phenylamino)butan-2-yl]androst-4-en-3-one (**25a**).* Yellow powder from dioxane, yield 0.86 g (82%), mp 178–180 °C, IR (KBr, cm^{-1}): υ = 3534–3397 (OH, NH), 3030 (CH-aromatic), 2965–2860 (CH-aliphatic), 1706 (C-3, C=O), 1728 ($\underline{C}O$Ph), 1643 (C=C). ^1H NMR ($CDCl_3$, ppm): δ = 1.06 (s, 3H, CH_3-19), 1.13 (s, 3H, CH_3-18), 1.28 (s, 3H, CH_3), 4.17 (s, 1H, CH), 4.58 (s, 1H, OH, D_2O-exchangable), 5.87 (s, 1H, C_4-H), 6.48–7.86 (m, 10H, $2C_6H_5$), 8.85 (brs, 1H, NH, D_2O-exchangable). M.S. (EI): m/z (%): 525 (M^+, 42), 420 (M^+-COPh, 14), 271 ($C_{19}H_{27}O$, 76), 254 (100), 105 (60), 92 (33). Calc. for $C_{35}H_{43}NO_3$ (525.721): C, 79.96; H, 8.24; N, 2.66; found: C, 80.23; H, 7.98; N, 2.46%.

*2.1.2.9. 17-[2′-Hydroxy-4′-oxo-4′-phenyl-3′-(p-chlorophenylamino)butan-2-yl]androst-4-en-3-one (**25b**).* Brown crystals from absolute ethanol, yield 0.85 g (76%), mp 189–190 °C, IR (KBr, cm^{-1}): υ = 3540–3378 (OH, NH), 3035 (CH-aromatic), 2978–2870 (CH-aliphatic), 1716 (C-3, C=O), 1726 ($\underline{C}O$Ph), 1648 (C=C). ^1H NMR (DMSO-d_6, ppm): δ = 0.98 (s, 3H, CH_3-19), 1.10 (s, 3H, CH_3-18), 1.32 (s, 3H, CH_3), 4.12 (s, 1H, CH), 4.68 (s, 1H, OH, D_2O-exchangable), 5.75 (s, 1H, C_4-H), 6.37–7.85 (m, 9H, aromatic-H), 8.35 (brs, 1H, NH, D_2O-exchangable). M.S. (EI): m/z (%): 559 (M^+, 34), 453 (M^+-COPh, 14), 288 (53), 271 ($C_{19}H_{27}O$, 76), 126 (100), 105 (60). Calc. for $C_{35}H_{42}ClNO_3$ (559.285): C, 75.04; H, 7.56; N, 2.50 found: C, 75.26; H, 7.80; N, 2.23%.

*2.1.2.10. 17-[2′-Hydroxy-4′-oxo-4′-phenyl-3′-(p-methoxyphenylamino)butan-2-yl]androst-4-en-3-one (**25c**).* Pale yellow powder from methanol, yield 0.82 g (74%), mp 123–125 °C, IR (KBr, cm^{-1}): υ = 3536–3382 (OH, NH), 3032 (CH-aromatic), 2982–2876 (CH-aliphatic), 1698 (C-3, C=O), 1724 ($\underline{C}O$Ph), 1652 (C=C). ^1H NMR (DMSO-d_6, ppm): δ = 1.03 (s, 3H, CH_3-19), 1.14 (s, 3H, CH_3-18), 1.33 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.15 (s, 1H, CH), 4.72 (s, 1H, OH, D_2O-exchangable), 5.80 (s, 1H, C_4-H), 6.40–7.86 (m, 9H, aromatic-H), 8.35 (brs, 1H, NH, D_2O-exchangable). M.S. (EI): m/z (%): 554 (M^+-1, 53), 450 (M^+-COPh, 64), 284 (30), 271 ($C_{19}H_{27}O$, 63), 122 (100), 105 (60). Calc. for $C_{36}H_{45}NO_4$ (555.747): C, 77.80; H, 8.16; N, 2.52; found: C, 78.02; H, 7.97; N, 2.30%.

*2.1.3. Synthesis of 17-(pyrazol-5′-yl)androst-4-ene-3-one derivatives (**8a**,**b**), (**9a**,**b**), (**10a**,**b**), (**18a**,**b**), (**19a**,**b**), (**20a**,**b**), (**27a**,**b**), (**28a**,**b**) and (**29a**,**b**)*

2.1.3.1. General procedure. To a solution of either compound **5a** (0.98 g, 2 mmol), **5b** (1.05 g, 2 mmol), **5c** (1.04 g, 2 mmol), **16a** (0.92 g, 2 mmol), **16b** (0.99 g, 2 mmol), **16c** (0.98 g, 2 mmol) **25a** (1.05 g, 2 mmol), **25b** (1.12 g, 2 mmol) or **25c** (1.11 g, 2 mmol) in absolute ethanol (20 mL) containing a catalytic amount of triethylamine (1 mL) either hydrazine hydrate **6a** (0.1 g, 2 mmol) or phenyl hydrazine **6b** (0.21 g, 2 mmol) was added. The reaction mixture, in each case, was heated under reflux for 8–12 h until all the reactants had disappeared as indicated by TLC. The reaction mixture poured over an ice/water mixture and neutralized with dilute hydrochloric acid. The resulted semisolid was subjected to extraction with chloroform (2–3 × 30 mL). The organic layer was dried over magnesium sulfate and then filtered. The solid product that formed in each case on removal of the solvent in vacuum was collected, dried and crystallized from the appropriate solvent.

*2.1.3.2. 17-(4′,5′-Dihydro-3′-hydroxy-5′-methyl-4′-phenylamino-1′H-pyrazol-5′-yl)androst-4-ene-3-one (**8a**).* Red crystals from absolute ethanol, yield 0.75 g (82%), mp 290–292 °C, IR (KBr, cm^{-1}): υ = 3542–3378 (OH, 2NH), 3030 (CH-aromatic), 2978–2869 (CH-aliphatic), 1703 (C-3, C=O), 1670 (C=N), 1646 (C=C). ^1H NMR (DMSO-d_6, ppm): δ = 1.07 (s, 3H, CH_3-19), 1.12 (s, 3H, CH_3-18), 1.27 (s, 3H, CH_3), 4.68 (s, 1H, OH, D_2O-exchangable), 5.83 (s, 1H, C_4-H), 6.83–7.06 (m, 5H, C_6H_5), 8.34, 9.05 (2brs, 2H, 2NH, D_2O-exchangable). M.S. (EI): m/z (%): 461 (M^+, 37), 271 ($C_{19}H_{27}O$, 100), 266 (23), 92 (60), 77 (84). Calc. for $C_{29}H_{39}N_3O_2$ (461.639): C, 75.45; H, 8.52; N, 9.10; found: C, 75.24; H, 8.30; N, 8.83%.

*2.1.3.3. 17-(4′,5′-Dihydro-3′-hydroxy-5′-methyl-4′-phenylamino-1′-phenylpyrazol-5′-yl)androst-4-ene-3-one (**8b**).* Yellowish brown powder from ethanol (70%), yield 0.83 g (78%), mp 145–147 °C, IR (KBr, cm^{-1}): υ = 3538–3385 (OH, NH), 3025 (CH-aromatic), 2978–2872 (CH-aliphatic), 1705 (C-3, C=O), 1664 (C=N), 1642 (C=C). ^1H NMR (DMSO-d_6, ppm): δ = 0.97 (s, 3H, CH_3-19), 1.12 (s,

3H, CH_3-18), 1.35 (s, 3H, CH_3), 4.87 (s, 1H, OH, D_2O-exchangable), 5.74 (s, 1H, C_4-H), 6.65–7.15 (m, 10H, aromatic-H), 8.25 (brs, 1H, NH, D_2O-exchangable). ^{13}C NMR (DMSO-d_6, ppm): δ = 35.3 (C-1), 34.0, (C-2), 198.5 (C-3), 124.3 (C-4), 170.0 (C-5), 32.7 (C-6), 31.6 (C-7), 35.4 (C-8), 50.6 (C-9), 37.3 (C-10), 22.6 (C-11), 37.5 (C-12), 38.4 (C-13), 56.0 (C-14), 27.6 (C-15), 23.0 (C-16), 46.8 (C-17), 22.7 (C-18), 20.3 (C-19), 19.2 (CH_3), 156.2, 73.4, 53.0 (C-pyrazole), 147.0, 143.6, 129.0, 117.2, 113.6, (C-phenyl). M.S. (EI): *m/z* (%): 537 (M^+, 64), 271 ($C_{19}H_{27}O$, 100), 266 (34), 92 (56), 77 (67). Calc. for $C_{35}H_{43}N_3O_2$ (537.735): C, 78.18; H, 8.06; N, 7.81; found: C, 77.93; H, 8.23; N, 8.02.

*2.1.3.4. 17-[4′,5′-Dihydro-3′-hydroxy-5′-methyl-4′-(p-chlorophenylamino)-1′H-pyrazol-5′-yl]androst-4-ene-3-one (**9a**).* Brown crystals from dioxane, yield 0.78 g (75%), mp 268–270 °C, IR (KBr, cm^{-1}): υ = 3487–3365 (OH, 2NH), 3028 (CH-aromatic), 2969–2875 (CH-aliphatic), 1713 (C-3, C=O), 1665 (C=N), 1645 (C=C). ^1H NMR (DMSO-d_6, ppm): δ = 1.12 (s, 3H, CH_3-19), 1.18 (s, 3H, CH_3-18), 1.26 (s, 3H, CH_3), 4.57 (s, 1H, OH, D_2O-exchangable), 5.80 (s, 1H, C_4-H), 6.37 (dd, 2H-aromatic, J_{HH} = 8 Hz), 7.12 (dd, 2H-aromatic, J_{HH} = 8 Hz), 8.42, 9.45 (2brs, 2H, 2NH, D_2O-exchangable). M.S. (EI): *m/z* (%): 496 (M^+, 37), 271 ($C_{19}H_{27}O$, 45), 126 (35) 111 (84), 99 (100). Calc. for $C_{29}H_{38}ClN_3O_2$ (496.084): C, 70.21; H, 7.72; N, 8.47; found: C, 70.45; H, 7.98; N, 8.73.

*2.1.3.5. 17-[4′,5′-Dihydro-3′-hydroxy-5′-methyl-4′-(p-chlorophenylamino)-1′-phenyl-pyrazol-5′-yl]androst-4-ene-3-one (**9b**).* Yellow crystals from absolute ethanol, yield 0.82 g (72%), mp 198–200 °C, IR (KBr, cm^{-1}): υ = 3532–3372 (OH, NH), 3025 (CH-aromatic), 2974–2860 (CH-aliphatic), 1715 (C-3, C=O), 1667 (C=N), 1642 (C=C). ^1H NMR (DMSO-d_6, ppm): δ = 1.03 (s, 3H, CH_3-19), 1.14 (s, 3H, CH_3-18), 1.30 (s, 3H, CH_3), 4.65 (s, 1H, OH, D_2O-exchangable), 5.74 (s, 1H, C_4-H), 6.34 (dd, 2H-aromatic, J_{HH} = 7 Hz), 6.45–7.04 (m, 5H, C_6H_5), 7.14 (dd, 2H-aromatic, J_{HH} = 7 Hz), 8.37 (brs, 1H, NH, D_2O-exchangable). M.S. (EI): *m/z* (%): 573 (M^++1, 37), 271 ($C_{19}H_{27}O$, 60), 126 (34), 111 (50), 77 (67). Calc. for $C_{35}H_{42}ClN_3O_2$ (572.180): C, 73.47; H, 7.40; N, 7.34; found: C, 73.62; H, 7.59; N, 7.64.

*2.1.3.6. 17-[4′,5′-Dihydro-3′-hydroxy-5′-methyl-4′-(p-methoxyphenylamino)-1′H-pyrazol-5′-yl]androst-4-ene-3-one (**10a**).* Brown crystals from methanol, yield 0.73 g (75%), mp 290–292 °C, IR (KBr, cm^{-1}): υ = 3495–3375 (OH, 2NH), 3028 (CH-aromatic), 2969–2875 (CH-aliphatic), 1713 (C-3, C=O), 1665 (C=N), 1645 (C=C). ^1H NMR (DMSO-d_6, ppm): δ = 1.02 (s, 3H, CH_3-19), 1.17 (s, 3H, CH_3-18), 1.25 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 4.62 (s, 1H, OH, D_2O-exchangable), 5.87 (s, 1H, C_4-H), 6.52 (dd, 2H-aromatic, J_{HH} = 8 Hz), 6.72 (dd, 2H-aromatic, J_{HH} = 8 Hz), 8.42, 9.38 (2brs, 2H, 2NH, D_2O-exchangable). M.S. (EI): *m/z* (%): 491 (M^+, 37), 271 ($C_{19}H_{27}O$, 100), 202 (65), 122 (39), 107 (28). Calc. for $C_{30}H_{41}N_3O_3$ (491.665): C, 73.29; H, 8.41; N, 8.55; found: C, 73.08; H, 8.59; N, 8.70.

*2.1.3.7. 17-[4′,5′-Dihydro-3′-hydroxy-5′-methyl-4′-(p-methoxyphenylamino)-1′-phenylpyrazol-5′-yl]androst-4-ene-3-one (**10b**).* Pale brown powder from absolute ethanol, yield 0.88 g (78%), mp 249–251 °C, IR (KBr, cm^{-1}): υ = 3520–3386 (OH, NH), 3032 (CH-aromatic), 2974–2860 (CH-aliphatic), 1710 (C-3, C=O), 1667 (C=N), 1640 (C=C). ^1H NMR (DMSO-d_6, ppm): δ = 1.05 (s, 3H, CH_3-19), 1.14 (s, 3H, CH_3-18), 1.30 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 4.35 (s, 1H, OH, D_2O-exchangable), 5.80 (s, 1H, C_4-H), 6.48 (dd, 2H-aromatic, J_{HH} = 8 Hz), 6.64 (dd, 2H-aromatic, J_{HH} = 8 Hz), 6.87–7.06 (m, 5H, C_6H_5), 8.37 (brs, 1H, NH, D_2O-exchangable). M.S. (EI): *m/z* (%): 567 (M^+, 43), 271 ($C_{19}H_{27}O$, 63), 122 (58), 107 (100). Calc. for $C_{36}H_{45}N_3O_3$ (567.761): C, 76.16; H, 7.99; N, 7.40; found: C, 76.37; H, 8.18; N, 7.18.

*2.1.3.8. 17-(4′,5′-Dihydro-3′,5′-dimethyl-4′-phenylamino-1′H-pyrazol-5′-yl)androst-4-ene-3-one (**18a**).* Pale red crystals from absolute ethanol, yield 0.75 g (82%), mp 229–230 °C, IR (KBr, cm^{-1}): υ = 3405–3378 (2NH), 3030 (CH-aromatic), 2978–2869 (CH-aliphatic), 1717 (C-3, C=O), 1672 (C=N), 1646 (C=C). ^1H NMR (DMSO-d_6, ppm): δ = 1.07 (s, 3H, CH_3-19), 1.16 (s, 3H, CH_3-18), 1.31 (s, 6H, $2CH_3$), 5.80 (s, 1H, C_4-H), 6.45–7.08 (m, 5H, C_6H_5), 8.45, 9.35 (2brs, 2H, 2NH, D_2O-exchangable). M.S. (EI): *m/z* (%): 459 (M^+, 26), 271 ($C_{19}H_{27}O$, 100), 92 (47), 77 (55). Calc. for $C_{30}H_{41}N_3O$ (459.666): C, 78.39; H, 8.99; N, 9.14; found: C, 78.60; H, 9.18; N, 8.93.

*2.1.3.9. 17-(4′,5′-Dihydro-3′,5′-dimethyl-4′-phenylamino-1′-phenylpyrazol-5′-yl)androst-4-ene-3-one (**18b**).* Yellow powder from dioxane, yield 0.72 g (68%), mp 135–137 °C, IR (KBr, cm^{-1}): υ = 3385 (NH), 3035 (CH-aromatic), 2967–2872 (CH-aliphatic), 1715 (C-3, C=O), 1668 (C=N), 1642 (C=C). ^1H NMR (DMSO-d_6, ppm): δ = 1.02 (s, 3H, CH_3-19), 1.15 (s, 3H, CH_3-18), 1.35 (s, 6H, $2CH_3$), 5.82 (s, 1H, C_4-H), 6.43–7.10 (m, 10H, aromatic-H), 8.46 (brs, 1H, NH, D_2O-exchangable). ^{13}C NMR (DMSO-d_6, ppm): δ = 36.3 (C-1), 33.7, (C-2), 198.7 (C-3), 127.3 (C-4), 171.3 (C-5), 34.7 (C-6), 31.6 (C-7), 35.7 (C-8), 52.6 (C-9), 37.3 (C-10), 22.4 (C-11), 37.5 (C-12), 38.7 (C-13), 56.4 (C-14), 27.6 (C-15), 23.0 (C-16), 46.8 (C-17), 23.2 (C-18), 21.3 (C-19), 19.2, 16.7 ($2CH_3$), 155.2, 70.4, 56.0 (C-pyrazole), 147.0, 143.1, 128.2, 117.2, 113.6, (C-phenyl). M.S. (EI): *m/z* (%): 535 (M^+, 64), 271 ($C_{19}H_{27}O$, 39), 264 (34), 92 (29), 77 (26). Calc. for $C_{36}H_{45}N_3O$ (535.762): C, 80.70; H, 8.47; N, 7.84; found: C, 80.93; H, 8.29; N, 8.05.

*2.1.3.10. 17-[4′,5′-Dihydro-3′,5′-dimethyl-4′-(p-chlorophenylamino)-1′H-pyrazol-5′-yl]androst-4-ene-3-one (**19a**).* Brown crystals from methanol, yield 0.73 g (74%), mp 163–165 °C, IR (KBr, cm^{-1}): υ = 3427–3365 (2NH), 3028 (CH-aromatic), 2969–2875 (CH-aliphatic), 1713 (C-3, C=O), 1665 (C=N), 1645 (C=C). ^1H NMR (DMSO-d_6, ppm): δ = 1.02 (s, 3H, CH_3-19), 1.17 (s, 3H, CH_3-18), 1.30 (s, 6H, $2CH_3$), 5.80 (s, 1H, C_4-H), 6.56 (dd, 2H-aromatic, J_{HH} = 8 Hz), 7.06 (dd, 2H-aromatic, J_{HH} = 8 Hz), 8.56, 9.47 (2brs, 2H, 2NH, D_2O-exchangable). M.S. (EI): *m/z* (%): 494 (M^+, 72), 271 ($C_{19}H_{27}O$, 53), 126 (100) 111 (24). Calc. for $C_{30}H_{40}ClN_3O$ (494.111): C, 72.92; H, 8.16; N, 8.50; found: C, 73.11; H, 7.96; N, 8.71.

*2.1.3.11. 17-[4′,5′-Dihydro-3′,5′-dimethyl-4′-(p-chlorophenylamino)-1′-phenylpyrazol-5′-yl]androst-4-ene-3-one (**19b**).* Yellow crystals from absolute ethanol, yield 0.94 g (83%), mp 141–143 °C, IR (KBr, cm^{-1}): υ = 3372 (NH), 3035 (CH-aromatic), 2970–2864 (CH-aliphatic), 1713 (C-3, C=O), 1668 (C=N), 1625 (C=C). ^1H NMR (DMSO-d_6, ppm): δ = 0.97 (s, 3H, CH_3-19), 1.12 (s, 3H, CH_3-18), 1.32 (s, 6H, $2CH_3$), 5.74 (s, 1H, C_4-H), 6.37 (dd, 2H-aromatic, J_{HH} = 7 Hz), 6.45–7.04 (m, 5H, C_6H_5), 7.08 (dd, 2H-aromatic, J_{HH} = 7 Hz), 8.47 (brs, 1H, NH, D_2O-exchangable). ^{13}C NMR ($CDCl_3$, ppm): δ = 35.3 (C-1), 34.2, (C-2), 198.0 (C-3), 124.5 (C-4), 171.2 (C-5), 32.7 (C-6), 31.0 (C-7), 35.4 (C-8), 50.6 (C-9), 37.8 (C-10), 22.7 (C-11), 37.2 (C-12), 38.4 (C-13), 56.6 (C-14), 27.6 (C-15), 22.4 (C-16), 47.4 (C-17), 22.7 (C-18), 20.3 (C-19), 16.7, 19.3 ($2CH_3$), 155.0, 73.8, 56.0 (C-pyrazole), 114.3, 129.7, 122,0, 143.3, 128.6, 117.2 (C-phenyl). M.S. (EI): *m/z* (%): 572 (M^++2, 52), 271 ($C_{19}H_{27}O$, 23), 126 (100), 77 (24). Calc. for $C_{36}H_{44}ClN_3O$ (570.207): C, 75.83; H, 7.78; N, 7.37; found: C, 76.03; H, 7.59; N, 7.60.

*2.1.3.12. 17-[4′,5′-Dihydro-3′,5′-dimethyl-4′-(p-methoxyphenylamino)-1′H-pyrazol-5′-yl]androst-4-ene-3-one (**20a**).* Yellow crystals from absolute ethanol, yield 0.76 g (78%),

mp 192–194 °C, IR (KBr, cm^{-1}): υ = 3395–3364 (2NH), 3030 (CH-aromatic), 2969–2875 (CH-aliphatic), 1715 (C-3, C=O), 1660 (C=N), 1595 (C=C). ^{1}H NMR (DMSO-d_6, ppm): δ = 1.02 (s, 3H, CH_3-19), 1.14 (s, 3H, CH_3-18), 1.28 (s, 6H, $2CH_3$), 3.78 (s, 3H, OCH_3), 5.87 (s, 1H, C_4-H), 6.52 (dd, 2H-aromatic, J_{HH} = 8 Hz), 6.72 (dd, 2H-aromatic, J_{HH} = 8 Hz), 8.52, 9.08 (2brs, 2H, 2NH, D_2O-exchangable). M.S. (EI): *m*/*z* (%): 450 (M^++1, 57), 271 ($C_{19}H_{27}O$, 100), 122 (39), 107 (58). Calc. for $C_{31}H_{43}N_3O_2$ (489.692): C, 76.03; H, 8.85; N, 8.58; found: C, 75.82; H, 9.02; N, 8.74.

2.1.3.13. 17-[4′,5′-Dihydro-3′,5′-dimethyl-4′-(p-methoxyphenylamino)-1′-phenylpyrazol-5′-yl]androst-4-ene-3-one (***20b***). Orange crystals from DMF, yield 0.90 g (80%), mp 203–205 °C, IR (KBr, cm^{-1}): υ = 3387 (NH), 3032 (CH-aromatic), 2973–2876 (CH-aliphatic), 1715 (C-3, C=O), 1658 (C=N), 1598 (C=C). ^{1}H NMR (DMSO-d_6, ppm): δ = 0.96 (s, 3H, CH_3-19), 1.12 (s, 3H, CH_3-18), 1.32 (s, 6H, $2CH_3$), 3.85 (s, 3H, OCH_3), 5.80 (s, 1H, C_4-H), 6.32 (dd, 2H-aromatic, J_{HH} = 8 Hz), 6.43–7.08 (m, 5H, C_6H_5), 7.12 (dd, 2H-aromatic, J_{HH} = 8 Hz), 9.28 (brs, 1H, NH, D_2O-exchangable). M.S. (EI): *m*/*z* (%): 566 (M^++1, 57), 271 ($C_{19}H_{27}O$, 100), 122 (39), 107 (58), 77 (27). Calc. for $C_{37}H_{47}N_3O_2$ (565.788): C, 78.54; H, 8.37; N, 7.43; found: C, 78.32; H, 8.59; N, 7.68.

2.1.3.14. 17-(4′,5′-Dihydro-5′-methyl-4′-phenylamino-3′-phenyl-1′H-pyrazol-5′-yl)androst-4-ene-3-one (***27a***). Yellow crystals from absolute ethanol, yield 0.75 g (72%), mp 200–202 °C, IR (KBr, cm^{-1}): υ = 3415–3378 (2NH), 3030 (CH-aromatic), 2978–2869 (CH-aliphatic), 1714 (C-3, C=O), 1667 (C=N), 1626 (C=C). ^{1}H NMR (DMSO-d_6, ppm): δ = 1.07 (s, 3H, CH_3-19), 1.16 (s, 3H, CH_3-18), 1.30 (s, 3H, CH_3), 5.80 (s, 1H, C_4-H), 6.65–7.28 (m, 10H, $2C_6H_5$), 8.35, 9.05 (2brs, 2H, 2NH, D_2O-exchangable). M.S. (EI): *m*/*z* (%): 522 (M^++1, 46), 271 ($C_{19}H_{27}O$, 73), 92 (47), 77 (55). Calc. for $C_{35}H_{43}N_3O$ (521.735): C, 80.57; H, 8.31; N, 8.05; found: C, 80.33; H, 8.49; N, 8.29.

2.1.3.15. 17-(4′,5′-Dihydro-1′,3′-diphenyl-5′-methyl-4′-phenylaminopyrazol-5′-yl)androst-4-ene-3-one (***27b***). Yellow powder from dioxane, yield 1.00 g (84%), mp 136–137 °C, IR (KBr, cm^{-1}): υ = 3385 (NH), 3030 (CH-aromatic), 2967–2872 (CH-aliphatic), 1713 (C-3, C=O), 1668 (C=N), 1622 (C=C). ^{1}H NMR (DMSO-d_6, ppm): δ = 1.02 (s, 3H, CH_3-19), 1.15 (s, 3H, CH_3-18), 1.37 (s, 3H, CH_3), 5.82 (s, 1H, C_4-H), 6.48–7.38 (m, 15H, aromatic-H), 8.76 (brs, 1H, NH, D_2O-exchangable). ^{13}C NMR (DMSO-d_6, ppm): δ = 36.3 (C-1), 33.7, (C-2), 198.7 (C-3), 127.3 (C-4), 171.3 (C-5), 34.7 (C-6), 32.5 (C-7), 35.7 (C-8), 52.8 (C-9), 38.0 (C-10), 22.6 (C-11), 37.5 (C-12), 38.9 (C-13), 56.7 (C-14), 27.6 (C-15), 23.3 (C-16), 46.8 (C-17), 23.2 (C-18), 21.8 (C-19), 19.2 (CH_3), 155.2, 72.4, 56.3 (C-pyrazole), 147.0, 143.1, 128.7, 117.2, 113.8 (C-phenyl). M.S. (EI): *m*/*z* (%): 597 (M^+, 44), 271 ($C_{19}H_{27}O$, 100), 92 (29), 77 (26). Calc. for $C_{41}H_{47}N_3O$ (597.831): C, 82.37; H, 7.92; N, 7.03; found: C, 82.18; H, 8.07; N, 6.85.

2.1.3.16. 17-[4′,5′-Dihydro-5′-methyl-4′-(p-chlorophenylamino)-3′-phenyl-1′H-pyrazol-5′-yl]androst-4-ene-3-one (***28a***). Brown crystals from methanol, yield 0.78 g (80%), mp 190–210 °C, IR (KBr, cm^{-1}): υ = 3427–3365 (2NH), 3028 (CH-aromatic), 2969–2875 (CH-aliphatic), 1713 (C-3, C=O), 1658 (C=N), 1625 (C=C). ^{1}H NMR (DMSO-d_6, ppm): δ = 1.02 (s, 3H, CH_3-19), 1.17 (s, 3H, CH_3-18), 1.30 (s, 3H, CH_3), 5.82 (s, 1H, C_4-H), 6.37 (dd, 2H-aromatic, J_{HH} = 8 Hz), 7.06 (dd, 2H-aromatic, J_{HH} = 8 Hz), 7.32–7.61 (m, 5H, C_6H_5), 8.36, 8.97 (2brs, 2H, 2NH, D_2O-exchangable). M.S. (EI): *m*/*z* (%): 556 (M^+, 70), 271 ($C_{19}H_{27}O$, 43), 126 (100), 111 (34). Calc. for $C_{35}H_{42}ClN_3O$ (556.181): C, 75.58; H, 7.61; N, 7.56; found: C, 75.34; H, 7.40; N, 7.75.

2.1.3.17. 17-[4′,5′-Dihydro-1,3′-diphenyl-5′-methyl-4′-(p-chlorophenylamino)pyrazol-5′-yl]androst-4-ene-3-one (***28b***). Yellow crystals from absolute ethanol, yield 0.85 g (68%), mp 241–243 °C, IR (KBr, cm^{-1}): υ = 3372 (NH), 3035 (CH-aromatic), 2970–2864 (CH-aliphatic), 1703 (C-3, C=O), 1660 (C=N), 1580 (C=C). ^{1}H NMR (DMSO-d_6, ppm): δ = 0.98 (s, 3H, CH_3-19), 1.12 (s, 3H, CH_3-18), 1.32 (s, 3H, CH_3), 5.82 (s, 1H, C_4-H), 6.35 (dd, 2H-aromatic, J_{HH} = 7 Hz), 7.05 (dd, 2H-aromatic, J_{HH} = 7 Hz), 7.30–7.64 (m, 10H, $2C_6H_5$), 8.87 (brs, 1H, NH, D_2O-exchangable). M.S. (EI): *m*/*z* (%): 632 (M^+, 46), 271 ($C_{19}H_{27}O$, 23), 126 (100), 77 (34). Calc. for $C_{41}H_{46}ClN_3O$ (632.276): C, 77.88; H, 7.33; N, 6.65; found: C, 78.12; H, 7.59; N, 6.83.

2.1.3.18. 17-[4′,5′-Dihydro-5′-methyl-4′-(p-methoxyphenylamino)-3′-phenyl-1′H-pyrazol-5′-yl]androst-4-ene-3-one (***29a***). Orange crystals from dioxane, yield 0.85 g (78%), mp 198–199 °C, IR (KBr, cm^{-1}): υ = 3435–3327 (2NH), 3033 (CH-aromatic), 2969–2875 (CH-aliphatic), 1710 (C-3, C=O), 1656 (C=N), 1578 (C=C). ^{1}H NMR (DMSO-d_6, ppm): δ = 1.02 (s, 3H, CH_3-19), 1.15 (s, 3H, CH_3-18), 1.30 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 5.87 (s, 1H, C_4-H), 6.47 (dd, 2H-aromatic, J_{HH} = 8 Hz), 6.87 (dd, 2H-aromatic, J_{HH} = 8 Hz), 7.23–7.48 (m, 5H, C_6H_5), 8.45, 9.18 (2brs, 2H, 2NH, D_2O-exchangable). M.S. (EI): *m*/*z* (%): 552 (M^++1, 53), 271 ($C_{19}H_{27}O$, 100), 122 (39), 107 (58). Calc. for $C_{36}H_{45}N_3O_2$ (551.761): C, 78.36; H, 8.22; N, 7.62; found: C, 78.13; H, 7.99; N, 7.85.

2.1.3.19. 17-[4′,5′-Dihydro-1′,3′-diphenyl-5′-methyl-4′-(p-methoxyphenylamino)pyrazol-5′-yl]androst-4-ene-3-one (***29b***). Yellowish brown powder from ethanol (70%), yield 1.04 g (83%), mp 123–125 °C, IR (KBr, cm^{-1}): υ = 3386 (NH), 3035 (CH-aromatic), 2973–2876 (CH-aliphatic), 1708 (C-3, C=O), 1662 (C=N), 1596 (C=C). ^{1}H NMR (DMSO-d_6, ppm): δ = 0.96 (s, 3H, CH_3-19), 1.12 (s, 3H, CH_3-18), 1.32 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 5.80 (s, 1H, C_4-H), 6.43 (dd, 2H-aromatic, J_{HH} = 8 Hz), 7.10 (dd, 2H-aromatic, J_{HH} = 8 Hz), 7.25–7.65 (m, 10H, $2C_6H_5$), 8.68 (brs, 1H, NH, D_2O-exchangable). M.S. (EI): *m*/*z* (%): 627 (M^+, 35), 271 ($C_{19}H_{27}O$, 67), 122 (100), 107 (58), 77 (27). Calc. for $C_{42}H_{49}N_3O_2$ (627.857) C, 80.34; H, 7.87; N, 6.69; found: C, 80.55; H, 7.69; N, 6.88.

*2.1.4. Synthesis of 20-(imidazole-3-yl)pregn-4-ene-3-one derivatives (**13a–c**), (**22a–c**), (**31a–c**)*

2.1.4.1. General procedure. To a solution of either compound **5a** (0.98 g, 2 mmol), **5b** (1.05 g, 2 mmol), **5c** (1.04 g, 2 mmol), **16a** (0.92 g, 2 mmol), **16b** (0.99 g, 2 mmol), **16c** (0.98 g, 2 mmol) **25a** (1.05 g, 2 mmol), **25b** (1.12 g, 2 mmol), or **25c** (1.11 g, 2 mmol) in absolute ethanol (20 mL) containing a catalytic amount of triethylamine (1 mL), phenyl isothiocyanate **11** (0.27 g, 2 mmol) was added. The reaction mixture, in each case, was heated under reflux for 8–10 h until all the reactants had disappeared as indicated by TLC. The reaction mixture poured over an ice/water mixture and neutralized with dilute hydrochloric acid. The solid product that formed, in each case, was filtered off, dried and crystallized from the appropriate solvent.

2.1.4.2. 20-Hydroxy-20-[1′,3′-diphenyl-4′-hydroxy-2′-thioxo-1′,3′-imidazol-5′-yl]pregn-4-ene-3-one (***13a***). Brown crystals from absolute ethanol, yield 0.95 g (82%), mp 175–176 °C, IR (KBr, cm^{-1}): υ = 3542 (2OH), 3028 (CH-aromatic), 2978–2870 (CH-aliphatic), 1708 (C-3, C=O), 1592 (C=C), 1197 (C=S). ^{1}H NMR ($CDCl_3$, ppm): δ = 0.98 (s, 3H, CH_3-19), 1.07 (s, 3H, CH_3-18), 1.37 (s, 3H, CH_3), 4.82, 5.03 (2s,2H, 2OH, D_2O-exchangable), 5.80 (s, 1H, C_4-H), 6.82–7.35 (m, 10H, $2C_6H_5$), M.S. (EI): *m*/*z* (%): 582 (M^+, 34), 557 (M^+-CH_3, 32), 271 ($C_{19}H_{27}O$, 60), 77 (100). Calc. for $C_{36}H_{42}N_2O_3S$ (582.795): C, 74.19; H, 7.26; N, 4.81; S, 5.50; found: C, 74.40; H, 7.45; N, 4.52; S, 5.22%.

2.1.4.3. 20-Hydroxy-20-[4′-hydroxy-3′-phenyl-1′-(p-chlorophenyl)-2′-thioxo-1′,3′-imidazol-5′-yl]pregn-4-ene-3-one (**13b**). Yellow crystals from absolute ethanol, yield 0.96 g (78%), mp 78–80 °C, IR (KBr, cm^{-1}): υ = 3537 (2OH), 3030 (CH-aromatic), 2982–2878 (CH-aliphatic), 1705 (C-3, C=O), 1608 (C=C), 1195 (C=S). ^{1}H NMR ($CDCl_3$, ppm): δ = 0.88 (s, 3H, CH_3-19), 1.12 (s, 3H, CH_3-18), 1.34 (s, 3H, CH_3), 4.97, 5.20 (2s, 2H, 2OH, D_2O-exchangable), 5.82 (s, 1H, C_4-H), 6.47 (dd, 2H, aromatic, J_{HH} = 7 Hz), 6.53–7.08 (m, 5H, C_6H_5), 7.12 (dd, 2H-aromatic, J_{HH} = 7 Hz). ^{13}C NMR ($CDCl_3$, ppm): δ = 36.7 (C-1), 32.9, (C-2), 197.6 (C-3), 126.8 (C-4), 171.0 (C-5), 35.6 (C-6), 32.5 (C-7), 37.7 (C-8), 52.6 (C-9), 38.0 (C-10), 22.4 (C-11), 36.8 (C-12), 38.9 (C-13), 56.7 (C-14), 27.6 (C-15), 23.5 (C-16), 55.8 (C-17), 23.2 (C-18), 21.8 (C-19), 68.2 (C-20), 23.5 (C-21), 91.2, 172.4, 53.3 (C-imidazole), 134.4, 129.3, 126.4, 124.3, 132.0, 130.1, 129.5, 127.2 (C-phenyl). M.S. (EI): *m*/*z* (%): 618 (M^++1, 47), 602 (M^+-CH_3, 37), 600 (M^+-H_2O, 100), 271 ($C_{19}H_{27}O$, 52), 77 (64). Calc. for $C_{36}H_{41}N_2O_3SCl$ (617.240): C, 70.05; H, 6.70; N, 4.54; S, 5.20; found: C, 70.30; H, 6.92; N, 4.70; S, 5.37%.

2.1.4.4. 20-Hydroxy-20-[4′-hydroxy-3′-phenyl-1′-(p-methoxyphenyl)-2′-thioxo-1′,3′-imidazol-5′-yl]pregn-4-ene-3-one (**13c**). Yellow crystals from dioxane, yield 0.84 g (69%), mp 121–122 °C, IR (KBr, cm^{-1}): υ = 3540 (2OH), 3025 (CH-aromatic), 2975–2868 (CH-aliphatic), 1710 (C-3, C=O), 1587 (C=C), 1192 (C=S). ^{1}H NMR (DMSO-d_6, ppm): δ = 1.03 (s, 3H, CH_3-19), 1.18 (s, 3H, CH_3-18), 1.33 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 4.92, 5.06 (2s, 2H, 2OH, D_2O-exchangable), 5.87 (s, 1H, C_4-H), 6.48 (dd, 2H-aromatic, J_{HH} = 8 Hz), 6.82–7.13 (m, 5H, C_6H_5), 7.22 (dd, 2H-aromatic, J_{HH} = 8 Hz). M.S. (EI): *m*/*z* (%): 612 (M^+, 39), 597 (M^+-CH_3, 60), 271 ($C_{19}H_{27}O$, 100), 77 (28). Calc. for $C_{37}H_{44}N_2O_4S$ (612.821): C, 72.52; H, 7.24; N, 4.57, S, 5.23; found: C, 72.30; H, 7.49; N, 4.75; S, 5.50%.

2.1.4.5. 20-Hydroxy-20-[1′,3′-diphenyl-4′-methyl-2′-thioxo-1′,3′-imidazol-5′-yl]pregn-4-ene-3-one (**22a**). Pale yellow crystals from absolute ethanol, yield 0.83 g (72%), mp 156–158 °C, IR (KBr, cm^{-1}): υ = 3413 (OH), 3044 (CH-aromatic), 2977–2862 (CH-aliphatic), 1696 (C-3, C=O), 1596 (C=C), 1198 (C=S). ^{1}H NMR (DMSO. d_6, ppm): δ = 0.92 (s, 3H, CH_3-19), 1.07 (s, 3H, CH_3-18), 1.37 (s, 6H, $2CH_3$), 4.87 (s, 1H, OH, D_2O-exchangable), 5.90 (s, 1H, C_4-H), 7.13–7.62 (m, 10H, $2C_6H_5$). M.S. (EI): *m*/*z* (%): 581 (M^++1, 45), 549 (M^+-CH_3, 32), 271 ($C_{19}H_{27}O$, 56), 77 (100). Calc. For $C_{37}H_{44}N_2O_2S$ (580.823): C, 76.51; H, 7.64; N, 4.82; S, 5.52; found: C, 76.72; H, 7.45; N, 4.65, S, 5.30%.

2.1.4.6. 20-Hydroxy-20-[4′-methyl-3′-phenyl-1′-(p-chlorophenyl)-2′-thioxo-1′,3′-imidazol-5′-yl]pregn-4-ene-3-one (**22b**). Pale brown powder from methanol, yield 1.01 g (82%), mp 180–183 °C, IR (KBr, cm^{-1}): υ = 3427 (OH), 3037 (CH-aromatic), 2982–2878 (CH-aliphatic), 1709 (C-3, C=O), 1606 (C=C), 1192 (C=S). ^{1}H NMR ($CDCl_3$, ppm): δ = 0.88 (s, 3H, CH_3-19), 1.15 (s, 3H, CH_3-18), 1.39 (s, 6H, $2CH_3$), 5.07, 5.27 (2s, 2H, 2OH, D_2O-exchangable), 5.76 (s, 1H, C_4-H), 6.57 (dd, 2H-aromatic, J_{HH} = 7 Hz), 6.89–7.14 (m, 5H, C_6H_5) 7.27 (dd, 2H-aromatic, J_{HH} = 7 Hz). M.S. (EI): *m*/*z* (%): 616 (M^++1, 28), 600 (M^+-CH_3, 37), 597 (M^+-H_2O, 100), 271 ($C_{19}H_{27}O$, 52), 77 (64). Calc. for $C_{37}H_{43}N_2O_2SCl$ (615.267): C, 72.23; H, 7.04; N, 4.55; S, 5.21; found: C, 72.45; H, 7.23; N, 4.39; S, 5.50%.

2.1.4.7. 20-Hydroxy-20-[4′-methyl-3′-phenyl-1′-(p-methoxyphenyl)-2′-thioxo-1′,3′-imidazol-5′-yl]pregn-4-ene-3-one (**22c**). Yellow crystals from absolute ethanol, yield 0.95 g (78%), mp 132–134 °C, IR (KBr, cm^{-1}): υ = 3480 (OH), 3028 (CH-aromatic), 2945–2882 (CH-aliphatic), 1699 (C-3, C=O), 1601 (C=C), 1186 (C=S). ^{1}H NMR (DMSO-d_6, ppm): δ = 1.03 (s, 3H, CH_3-19), 1.09 (s, 3H, CH_3-18), 1.35 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 4.97, (2s, 2H, 2OH, D_2O-exchangable), 5.90 (s, 1H, C_4-H), 6.48 (dd, 2H-aromatic, J_{HH} = 8 Hz), 6.99–7.06 (m, 5H, C_6H_5), 7.22 (dd, 2H-aromatic, J_{HH} = 8 Hz). M.S. (EI): *m*/*z* (%): 610 (M^+, 39), 595 (M^+-CH_3, 60), 271 ($C_{19}H_{27}O$, 100), 77 (28). Calc. for $C_{38}H_{46}N_2O_3S$ (610.848): C, 74.72; H, 7.59; N, 4.59, S, 5.25; found: C, 74.46; H, 7.30; N, 4.75; S, 5.50%.

2.1.4.8. 20-Hydroxy-20-[1′,3′, 4′-triphenyl-2′-thioxo-1′,3′-imidazol-5′-yl]pregn-4-ene-3-one (**31a**). Yellow crystals from absolute ethanol, yield 1.02 g (80%), mp 144–145 °C, IR (KBr, cm^{-1}): υ = 3385 (OH), 3042 (CH-aromatic), 2977–2875 (CH-aliphatic), 1697 (C-3, C=O), 1596 (C=C), 1197 (C=S). ^{1}H NMR (DMSO-d_6, ppm): δ = 0.92 (s, 3H, CH_3-19), 1.07 (s, 3H, CH_3-18), 1.35 (s, 3H, CH_3), 4.87 (s, 1H, OH, D_2O-exchangable), 5.90 (s, 1H, C_4-H), 7.05–7.87 (m, 15H, $3C_6H_5$). ^{13}C NMR (DMSO-d_6, ppm): δ = 36.2 (C-1), 33.0, (C-2), 198.1 (C-3), 126.6 (C-4), 172.2 (C-5), 35.6 (C-6), 32.4 (C-7), 37.2 (C-8), 53.1 (C-9), 37.8 (C-10), 22.7 (C-11), 36.4 (C-12), 38.9 (C-13), 57.0 (C-14), 27.6 (C-15), 23.2 (C-16), 55.2 (C-17), 23.9 (C-18), 22.0 (C-19), 68.2 (C-20), 21.8 (C-21), 116.4, 171.5, 113.6 (C-imidazole), 135.6, 134.4, 129.3, 128.5, 126.4, 124.8, 124.0, 132.0, 130.1, 131.2, 129.7, 127.2 (C-phenyl). M.S. (EI): *m*/*z* (%): 642 (M^+, 45), 627 (M^+-CH_3, 50), 271 ($C_{19}H_{27}O$, 65), 77 (100). Calc. for $C_{42}H_{46}N_2O_2S$ (642.908): C, 78.47; H, 7.21; N, 4.36; S, 4.99; found: C, 78.66; H, 7.40; N, 4.60, S, 4.73%.

2.1.4.9. 20-Hydroxy-20-[3′,4′-diphenyl-1′-(p-chlorophenyl)-2′-thioxo-1′,3′-imidazol-5′-yl]pregn-4-ene-3-one (**31b**). Orange powder from DMF, yield 1.12 g (83%), mp 178–180 °C, IR (KBr, cm^{-1}): υ = 3367 (OH), 3040 (CH-aromatic), 2980–2856 (CH-aliphatic), 1698 (C-3, C=O), 1596 (C=C), 1190 (C=S). ^{1}H NMR (DMSO-d_6, ppm): δ = 0.87 (s, 3H, CH_3-19), 1.12 (s, 3H, CH_3-18), 1.34 (s, 3H, CH_3), 4.97, 5.20 (2s, 2H, 2OH, D_2O-exchangable), 5.82 (s, 1H, C_4-H), 7.01–7.58 (m, 14H, aromatic-H). M.S. (EI): *m*/*z* (%): 679 (M^++2, 58), 662 (M^+-CH_3, 37), 659 (M^+-H_2O, 100), 271 ($C_{19}H_{27}O$, 42), 77 (60). Calc. for $C_{42}H_{47}N_2O_2SCl$ (677.353): C, 74.48; H, 6.70; N, 4.14; S, 4.73; found: C, 74.30; H, 6.89; N, 4.36; S, 5.98%.

2.1.4.10. 20-Hydroxy-20-[3′,4′-diphenyl-1′-(p-methoxyphenyl)-2′-thioxo-1′,3′-imidazol-5′-yl]pregn-4-ene-3-one (**31c**). Pale brown crystals from methanol, yield 1.14 g (85%), mp 225–227 °C, IR (KBr, cm^{-1}): υ = 3383 (OH), 3035 (CH-aromatic), 2960–2885 (CH-aliphatic), 1705 (C-3, C=O), 1581 (C=C), 1184 (C=S). ^{1}H NMR (DMSO-d_6, ppm): δ = 1.03 (s, 3H, CH_3-19), 1.18 (s, 3H, CH_3-18), 1.33 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 4.97, (2s, 2H, 2OH, D_2O-exchangable), 5.87 (s, 1H, C_4-H), 6.93–7.53 (m, 14H, aromatic-H). M.S. (EI): *m*/*z* (%): 672 (M^+, 32), 657 (M^+-CH_3, 40), 271 ($C_{19}H_{27}O$, 100), 77 (36). Calc. for $C_{43}H_{50}N_2O_3S$ (672.917): C, 76.75; H, 7.19; N, 4.16, S, 4.77; found: C, 76.96; H, 7.35; N, 4.32; S, 4.53.

2.2. Pharmacological assay

2.2.1. Animals

Sprague-Dawley strain rats weighing 120–130 g or Swiss albino mice 20–25 g body weight were used throughout the experiments, supplied by the Animal House Colony of the National Research Centre, Cairo, Egypt and acclimated for one week in a specific pathogen-free (SPF) barrier area where temperature is 25 ± 1 °C and humidity is 55%. Animals were controlled constantly with 12 h light/dark cycle at the National Research Centre animal facility breeding colony. Animals were individually housed with *ad libitum* access to standard laboratory diet and tap water. All animal procedures were performed after approval from the Ethics Committee of the National Research Centre and in accordance with the recommendations for the proper care and use of laboratory animals (NIH publication No. 85-23, revised 1985).

2.2.2. Tests of Inflammation: carrageenan-induced paw oedema assay

Paw oedema was induced by sub-plantar injection of 100 μL of 1% sterile carrageenan lambda in saline into the right hind paw of

rats [20]. Contralateral paw received an equal volume of saline. Paw volume was determined immediately before carrageenan injection and at selected times thereafter using a plethysmometer (Ugo Basile, Milan, Italy). The oedema component of inflammation was quantified by measuring the paw volume (mL) at zero time (before carrageenan injection) and at 1, 2, 3 and 4 h after carrageenan injection and comparing it with the pre-injection value for each animal. Oedema was expressed as a percentage of change from control (pre-drug, zero time) values. The effect of systemic administration of compounds **8b**, **19b**, **24**, and **31a** (25 or 50 mg/kg, s.c., 0.2 mL, $n = 6$/group) given 30 min before induction of inflammation by subplantar carrageenan was studied. All tested compounds administrated in saline (0.9% NaCl) with one drop of Tween 80 as a vehicle in all pharmacological studies. The control group of carrageenan-treated rats received an equal volume of saline 30 min before subplantar carrageenan injection ($n = 6$ each). Another group administered indomethacin (18 mg/kg, s.c.) served as control positive.

2.2.3. Tests of nociception

2.2.3.1. Hot plate assay. The hot-plate test was performed using an electronically controlled hot plate (Ugo Basile, Italy) heated to 53 °C (±0.1 °C). Each mouse was placed unrestrained on hot plate for the baseline measurement just prior to saline or drug administration. Different groups of mice ($n = 6$/group) were given one of compounds **8b**, **19b**, **24** or **31a** (25 or 50 mg/kg; 0.2 mL, orally), tramadol (20 mg/kg, 0.2 mL, orally) (control +ve) or saline (control −ve). Measurements were then taken 60 min after drug administration. The experimenter was blind to doses. Latency to lick a hind paw or jump out of the apparatus was recorded for the control and drug-treated groups. The cut-off time was 30 s.

2.2.3.2. Acetic acid induced writhing. Separate groups of 6 mice each were administered saline, compound **8b**, **19b**, **24** or **31a** (25 or 50 mg/kg; 0.5 mL, orally) or indomethacin (18 mg/kg, 0.5 mL, orally). After 60 min, mice received an i.p. injection of 0.6% acetic acid (0.2 mL) [21]. The number of writhes (constrictions of abdomen, twisting of trunk and extension of hind legs) during 30 min observation period following acetic acid injection was compared with the control group and drug-treated groups.

2.2.4. Gastric ulcerogenic study

Gastric mucosal damage was evoked in rats by the administration of indomethacin (20 mg/kg, 0.2 mL, s.c.). The effect of either compound **8b**, **19b**, **24** or **31a** (50 mg/kg; 0.5 mL, orally) administered at time of indomethacin injection was studied. Rats were killed 24 h after indomethacin administration. In other experiments, the effect of tested compounds (50 mg/kg; 0.5 mL, s.c.) on gastric damage caused by ethanol (96%) was evaluated. Rats were fasted for 18 h, but allowed water *ad libitum*. They were administered either saline (control) or tested compounds 30 min prior to ethanol (96%, 1 mL, p.o.). Rats were killed 1 h after ethanol administration, stomachs excised, opened along the greater curvature, rinsed with saline, extended on a plastic board and examined for mucosal lesions. The number and severity of mucosal lesions were noted and lesions were scaled as described by Mózsik et al. [22].

2.3. Statistical analysis

Data were expressed as mean ± SE. Data were analyzed by one-way analysis of variance, followed by a Tukey's multiple range tests for post hoc comparison of group means. When there were only two groups a two-tailed Student's *t*-test was used. For all tests, effects with a probability of $P < 0.05$ were considered to be significant and that with a probability of $P < 0.001$ were considered to be highly significant.

3. Results and discussion

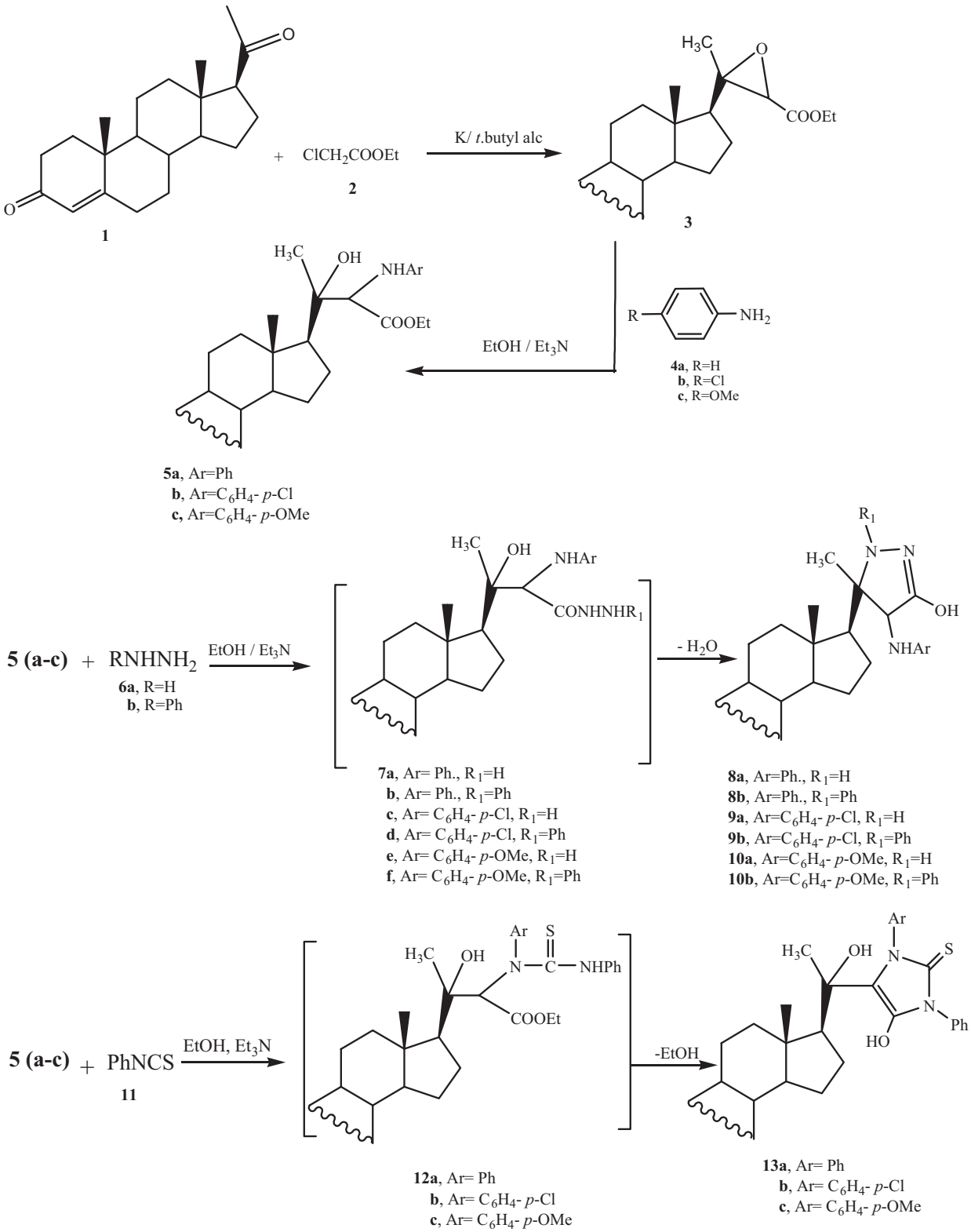
3.1. Chemistry

Oxiranes and azoles represent molecular frameworks those serve as platform for developing pharmaceutical agents for various applications. Many derivatives of these rings proved as anti-inflammatory and/or anti-nociceptive agents [23–26]. Introduction of the reactive oxirane in steroids results in dramatic changes in their biological activity [27]. We have attempted a straightforward synthesis of 17-(oxiran-2′-yl)androst-4-ene-3-one derivatives, progesterone (**1**) reacted with equimolar amount of ethyl chloroacetate **2** in potassium *tert*-butoxide via Darzens condensation to afford the ethyl 17-(oxiran-2′-yl)androst-4-ene-3′-carboxylate derivative **3** in 72% yield (Scheme 1). In this conversion, the selective epoxidation took place only at C-20 carbonyl moiety in progesterone. No product containing oxirane functionality at C-3 position was found. The mass spectrum (EIMS) of compound **3** revealed the presence of molecular ion peak at $m/z = 400$ (29%) and the IR spectrum showed two carbonyl groups stretching at $\upsilon = 1708\ cm^{-1}$ (C-3) and $\upsilon = 1742\ cm^{-1}$ (acetate, C=O). Also the ^1H NMR spectrum of compound **3** revealed, in addition to the expected signals of pregnene moiety, the presence of singlet signal at $\delta = 3.45$ ppm (1H) for the C-3 proton of oxirane ring and showed also triplet at $\delta = 1.37$ (3H) and quartet at $\delta = 4.25$ (2H) which are characteristic for the ethyl ester group. To generalize such a methodology, the previous reaction was carried out by using the α-haloketones, chloroacetone **14** or α-bromoacetophenone **23** under the same experimental conditions, to afford the corresponding 17-(oxiran-2′-yl)androst-4-ene-3-one derivative **15** in 78% yield (Scheme 2) and **24** in 74% yield, respectively (Scheme 3).

The reaction of compound **3** with either aniline **4a**, *p*-chloroaniline **4b** or *p*-methoxyaniline **4c** in refluxing absolute ethanol containing a catalytic amount of triethylamine afforded the corresponding ethyl androst-4-en-arylaminobutanoate derivatives **5a**, **5b**, and **5c**, respectively (Scheme 1). Similarly under the same experimental condition, compounds **15** and **24** reacted with either aniline **4a**, *p*-chloroaniline **4b**, or *p*-methoxyaniline **4c** to afford the corresponding 17-(3′-arylaminobutyl)androst-4-ene-3-one derivatives **16a**–**c** (Scheme 2) and **25a**–**c**, respectively (Scheme 3).

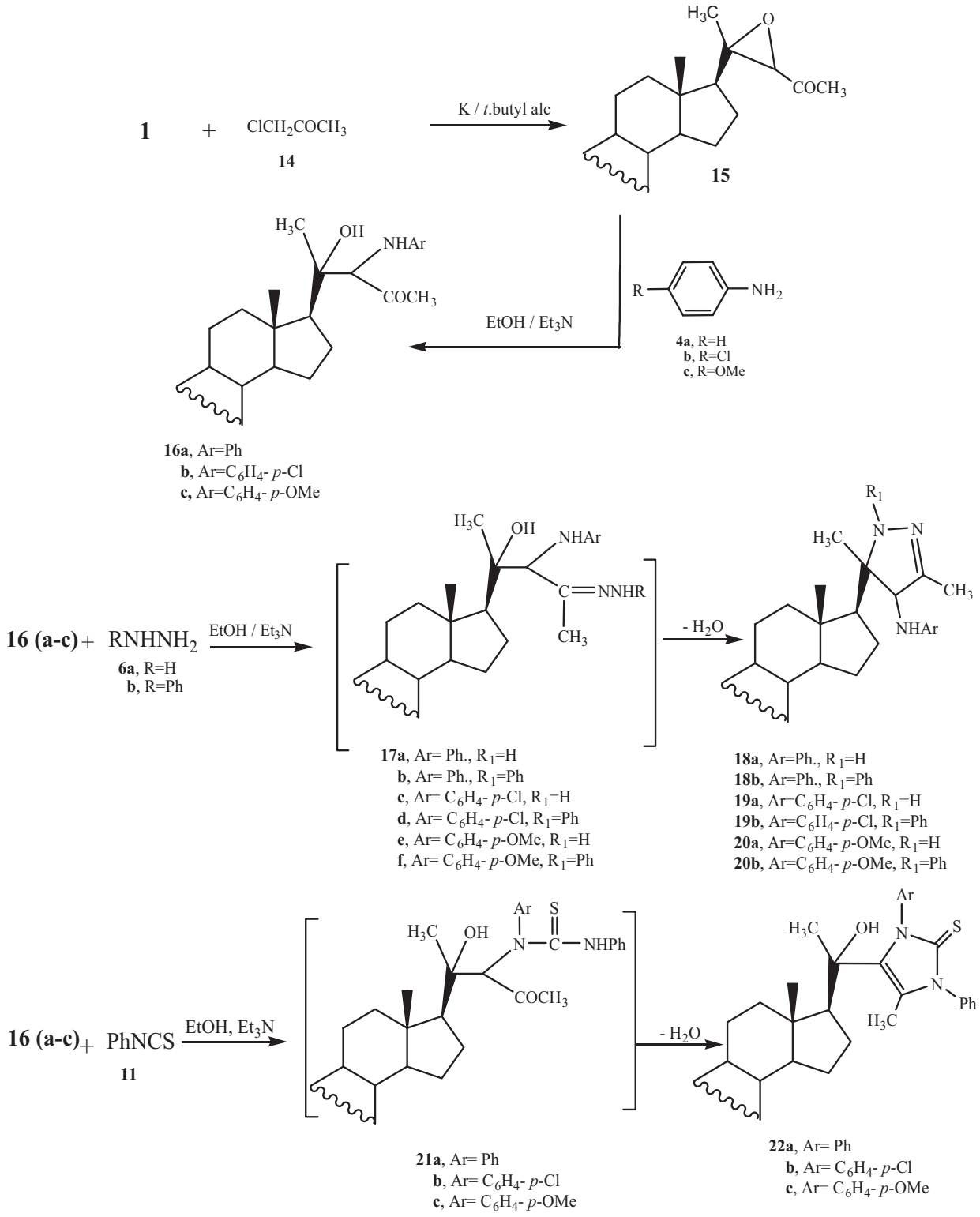
The azole moiety often shows some special biological activity when it is introduced to some biologically active compounds [28,29]. The basicity and hydrophilicity of an azole in theory might alter the biological function of a steroid [30]. The reactivity of compounds **5a**–**c** towards the reaction with some nucleophilic reagents was studied in the aim of forming new pyrazolyl steroids. Thus, compounds **5a**–**c** reacted with either hydrazine hydrate **6a** or phenyl hydrazine **6b** in ethanolic triethylamine to give the corresponding 17-(pyrazol-5′-yl)androst-4-ene-3-one derivatives **8a**,**b**, **9a**,**b** and **10a**,**b**, respectively. The reaction takes place via the non-isolable intermediates **7a**–**f** which undergo intermolecular cyclization to afford the isolable products **8a**,**b**, **9a**,**b** and **10a**,**b** (Scheme 1). Similarly, compounds **16a**–**c** and **25a**–**c** reacted with either hydrazine hydrate **6a** or phenyl hydrazine **6b** to give the corresponding 17-(pyrazol-5′-yl)androst-4-ene-3-one derivatives **18a**,**b**, **19a**,**b**, **20a**,**b** (Scheme 2) and **27a**,**b**, **28a**,**b**, **29a**,**b** (Scheme 3), respectively. Elucidation of proposed structures of the latter products was based on their correct elemental analysis and compatible IR, ^1H NMR, ^{13}C NMR and mass spectral data (cf. Section 2).

The reactivity of compounds **5a**–**c** towards the reaction with isothiocyanates was studied in the aim of forming new imidazolyl



Scheme 1.

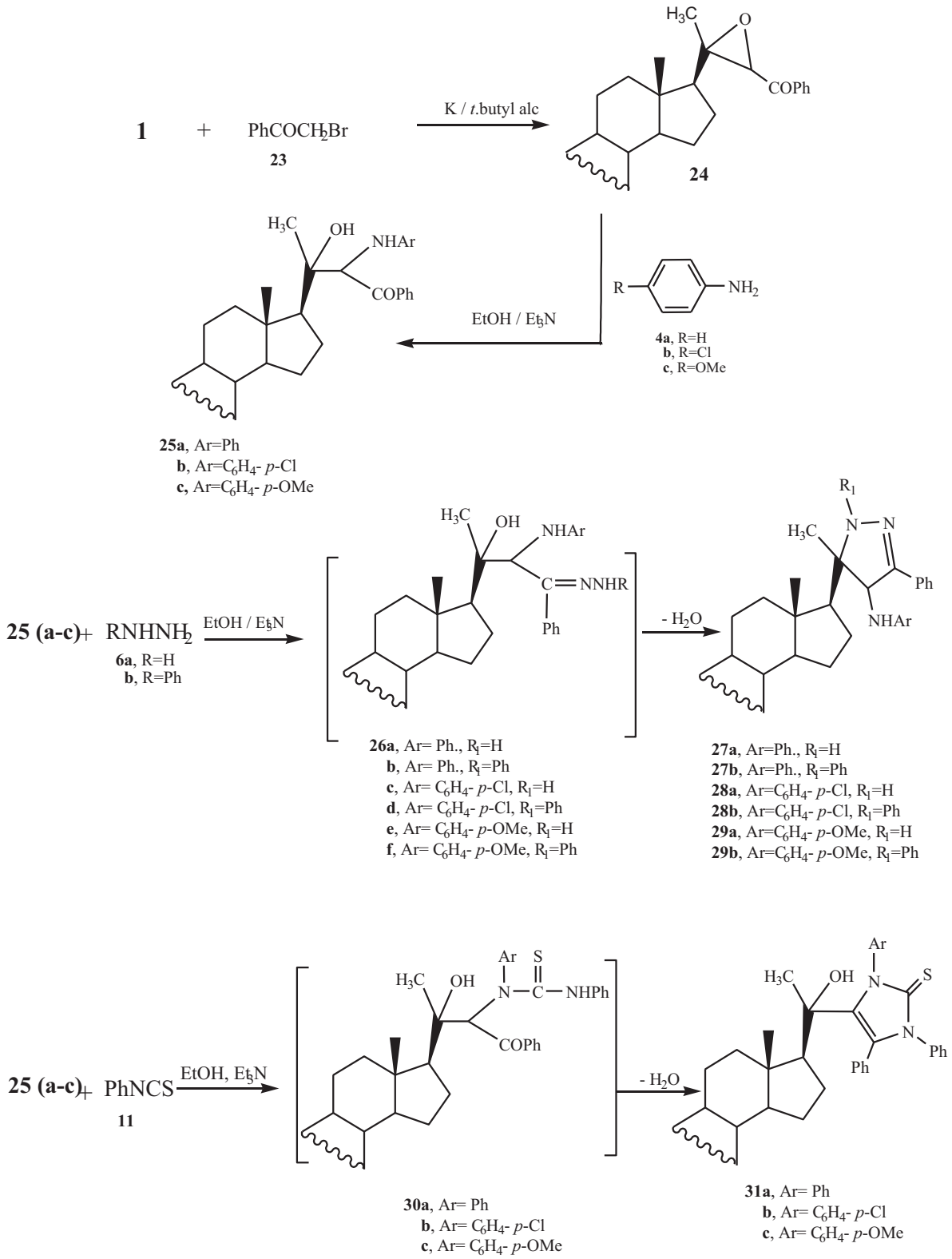
steroids. Thus, compounds **5a–c** reacted with phenylisothiocyanate **11** in refluxing absolute ethanol containing a catalytic amount of triethylamine to afford the corresponding 20-(imidazol-5′-yl)pregn-4-en-3-one derivatives **13a–c**. Formation of the latter products is explained in terms of the intermediate formation of **12a–c** (Scheme 1). The IR spectra of compounds **13a–c** revealed broad absorption peaks equivalent to the OH groups and showed also absorption peaks at $\upsilon = 1197$, 1195 and 1192 cm^{-1} for C=S groups, respectively. The mass spectra of compounds **13a–c** revealed the presence of molecular ion peaks at $m/z = 582$ (34%), 618 ($M^+ - 1$, 47%), and 612 (39%), respectively. Also, the ^{13}C NMR spectrum of compound **13b** showed the presence of the C=S carbon at $\delta = 172.4$. Similarly, the reaction of compounds **16a–c** and **25a–c** with phenylisothiocyanate **11** under the same



Scheme 2.

experimental conditions described before, afforded the corresponding 20-(imidazol-5′-yl)pregn-4-en-3-one derivatives **22a–c** (Scheme 2) and **31a–c** (Scheme 3), respectively. The structures of all new compounds were assigned by both correct elemental and spectral data (cf. Section 2).

It is interesting to note that most of the compounds synthesized in this work can exist in either *Z* or *E* structures. However, according to the concept of push–pull alkenes reviewed by Sandstrom [31], conjugated systems with unsaturated heterocyclic rings with conjugated alkyl chains, exemplify typical push–pull compounds, which can exist in *Z*/*E* equilibrium depending on the temperature and the nature of solvent. One may say that all the newly synthesized compounds in this work are typical push–pull compounds existing in *Z*/*E* equilibrium. Isolation and identification of these isomers is beyond the scope of this study.



Scheme 3.

3.2. Pharmacology

The most structurally promising of the novel steroidal heterocyclic derivatives, compounds **8b**, **19b**, **24** and **31a** were investigated individually as anti-inflammatory, anti-nociceptive and anti-ulcerogenic agents. During the study period, animals are observed carefully for all adverse symptoms. There were not any symptoms of toxicity during the study at all employed doses.

3.2.1. Anti-inflammatory assay

The effects of systemic injection of the tested compounds on oedema formation were studied using a carrageenan induced

Table 1
The anti-inflammatory effect of the tested compounds on carrageenan induced paw oedema.

Group	Basal	1 h	2 h	3 h	4 h
Control (Saline)	0.28 ± 0.006	0.53 ± 0.02 (88.3 ± 7.0)	0.6 ± 0.018 (107.8 ± 7.6)	0.59 ± 0.013 (112.2 ± 7.3)	0.60 ± 0.013 (113.3 ± 8.4)
8b (25 mg/kg)	0.305 ± 0.004	0.49 ± 0.02 (60.8 ± 6.1)	0.51 ± 0.02 (66.9 ± 6.3)*	0.475 ± 0.017(55.7 ± 5.1)*	0.475 ± 0.013(55.7 ± 4.4)*
8b (50 mg/kg)	0.298 ± 0.004	0.458 ± 0.02(53.7 ± 4.1)*	0.496 ± 0.01 (66.8 ± 5.6)*	0.456 ± 0.016(53.3 ± 4.8)*	0.415 ± 0.019(39.3 ± 2.3)*
19b (25 mg/kg)	0.325 ± 0.008	0.576 ± 0.03 (78.9 ± 5.2)	0.546 ± 0.012(68.9 ± 6.4)*	0.537 ± 0.012(65.8 ± 6.4)*	0.513 ± 0.009(58.5 ± 5.4)*
19b (50 mg/kg)	0.335 ± 0.014	0.51 ± 0.04 (54.3 ± 4.4)*	0.553 ± 0.026(65.1 ± 4.8)*	0.575 ± 0.019(73.2 ± 5.4)*	0.516 ± 0.004(55.6 ± 2.9)*
24 (25 mg/kg)	0.308 ± 0.004	0.55 ± 0.003 (80.1 ± 2.1)	0.535 ± 0.011(73.7 ± 4.5)*	0.498 ± 0.01 (62.0 ± 5.4)*	0.486 ± 0.012(58.2 ± 5.8)*
24 (50 mg/Kg)	0.301 ± 0.01	0.445 ± 0.02(48.8 ± 3.5)*	0.483 ± 0.02 (61.3 ± 5.9)*	0.457 ± 0.016(52.0 ± 4.9)*	0.43 ± 0.011 (43.9 ± 3.9)
31a (25 mg/kg)	0.3 ± 0.004	0.59 ± 0.009 (96.9 ± 4.5)	0.546 ± 0.011(82.5 ± 5.4)*	0.52 ± 0.011 (74.1 ± 5.0)*	0.49 ± 0.012 (63.4 ± 4.8)*
31a (50 mg/kg)	0.29 ± 0.003	0.53 ± 0.04 (78.4 ± 5.5)	0.453 ± 0.013(50.6 ± 3.5)*	0.45 ± 0.013 (53.4 ± 4.2)*	0.44 ± 0.013 (50.6 ± 4.7)*
Indomethacin (18 mg/kg)	0.288 ± 0.004	0.48 ± 0.02 (67.4 ± 5.6)*	0.47 ± 0.01 (64.6 ± 4.10)*	0.435 ± 0.019(51.4 ± 4.3)*	0.415 ± 0.015(44.4 ± 2.9)*

Results are expressed as percentage change for control (pre-drug) values. Data are expressed as mean ± S.E., $n = 6$ rats/group. Asterisks indicate significant change from control value. The s.c. administration of all tested compounds inhibited the carrageenan induced paw oedema (two-way ANOVA; treatment effect: $F_{13,280} = 30$; $P < 0.001$; time effect: $F_{3,280} = 23.8$; $P < 0.001$, time × drug effect: $F_{39,280} = 3$; $P < 0.001$). The values in parenthesis indicate the percentage (%) of increase in paw volume from basal (zero time) values.

paw inflammation. Each compound was injected sucutaneously (s.c.), in two doses (25 or 50 mg/kg), 30 min before sub-plantar carrageenan. All tested compounds decreased paw oedema in dose-dependent manner compared to the control group (pre-drug) (Table 1). Indomethacin was given at 18 mg/kg, s.c., 30 min before carrageenan as positive control. Data are expressed as mean ± S.E., $n = 6$ per group. The values in parenthesis in Table 1 indicate the percentage (%) of increase in paw volume (oedema) from basal (zero time) values.

*3.2.1.1. Effect of compounds **8b** and **24**.* The oedema response was significantly reduced by the administration of compounds **8b** or **24** at dose of 25 or 50 mg/kg. The two compounds at the dose of 25 mg/kg markedly and significantly inhibited the paw oedema response compared with the control group at 2, 3 and 4 h post-carrageenan where the percent of inhibition of oedema was (−37.9, −50.4, −50.8%) for compound **8b** and (−31.6, −44.7, −48.6%) for compound **24**. The higher dose (50 mg/kg) of compound **8b** or **24** significantly inhibited oedema, at 1, 2, 3 and 4 h time points, by (−38, −52.2, −65.3%) and (−43.1, −53.6, −61.3%), respectively (Fig. 1).

*3.2.1.2. Effect of compounds **19b** and **31a**.* Compounds **19b** and **31a** at the dose of 25 mg/kg significantly inhibited the paw oedema response compared with the control group at 2, 3 and 4 h post-carrageenan, the percent of oedema inhibition was (−36, −41.4, −48.4%) and (−23.5, −33.9, −44%), respectively. The higher dose (50 mg/kg) of compound **31a** significantly inhibited oedema by (−53.1, −52.4, −55.3) and that of compound **19b** significantly inhibited oedema by (−39.6, −34.8, −51%) at 2, 3 and 4 h time points, respectively (Fig. 2).

3.2.2. Tests of anti-nociceptive studies

3.2.2.1. Effect of tested compounds on thermal pain. The hot plate latency was significantly increased denoting analgesic effect after 1 h of the administration of either compound **8b** or **19b** at both administered doses (Table 2, Fig. 3). While, the administration of compound **24** or **31a** significantly increased the hot plate latency only at the dose of 50 mg/kg compared to the saline-treated group. The anti-nociceptive effect was most marked with compound **19b** with a maximal increase in hot-plate latency by 72.1% after drug administration at 50 mg/kg (Table 2, Fig. 3). Compound **19b**

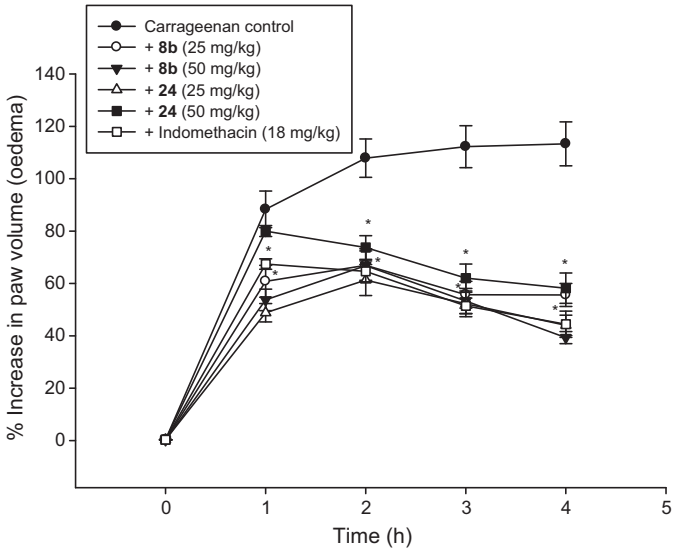


Fig. 1. Effect of tested compounds **8b** or **24** on the carrageenan paw oedema formation. Compound **8b** or **24** was given (25 or 50 mg/kg, i.p.) 30 min prior to carrageenan injection and rats were evaluated for paw oedema at 1, 2, 3 and 4 h post-carrageenan. The results are expressed as a percentage change from control (pre-drug) values, each point represents the mean ± S.E. of six rats per group. Asterisks indicate significant change from the control group at the corresponding time point.

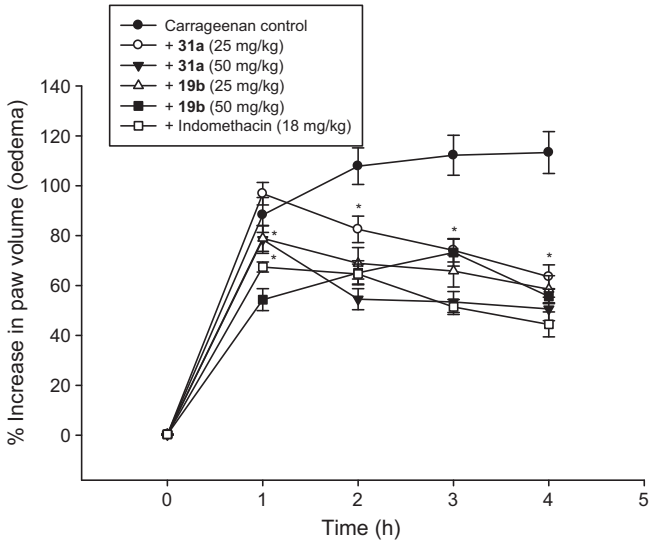


Fig. 2. Effect of tested compounds **31a** or **19b** on the carrageenan paw oedema formation. Compound **31a** or **19b** were given (25 or 50 mg/kg, i.p.) 30 min prior to carrageenan injection and rats were evaluated for paw oedema at 1, 2, 3 and 4 h post-carrageenan. The results are expressed as a percentage change from control (pre-drug) values, each point represents the mean ± S.E. of six rats per group. Asterisks indicate significant change from the control group at the corresponding time point.

Table 2
Percentage increase in hot plate latency in mice treated with tested compounds in comparison with tramadol.

Drug	0 time (basal)	1 h	% Change
Saline	13.2 ± 0.6	14.65 ± 1.1	
8b (25 mg/kg)	14.38 ± 1.3	18.4 ± 1.2	27.96*
8b (50 mg/kg)	15.0 ± 0.7	19.1 ± 1.0	27.33*
19b (25 mg/kg)	13.46 ± 1.2	18.62 ± 1.3	38.3**
19b (50 mg/kg)	13.76 ± 1.0	23.68 ± 1.6	72.1**
24 (25 mg/kg)	13.56 ± 1.1	15.98 ± 0.9	17.8
24 (50 mg/kg)	14.24 ± 0.66	17.29 ± 1.5	21.4*
31a (25 mg/kg)	14.64 ± 0.76	16.94 ± 1.3	15.7
31a (50 mg/kg)	14.28 ± 0.81	17.52 ± 1.2	22.7*
Tramadol (20 mg/kg)	12.86 ± 1.1	20.3 ± 1.6	57.9**

Data are expressed as mean ± S.E., $n = 6$ per group.
* $P < 0.05$ vs corresponding basal values.
** $P < 0.01$ vs corresponding basal values.

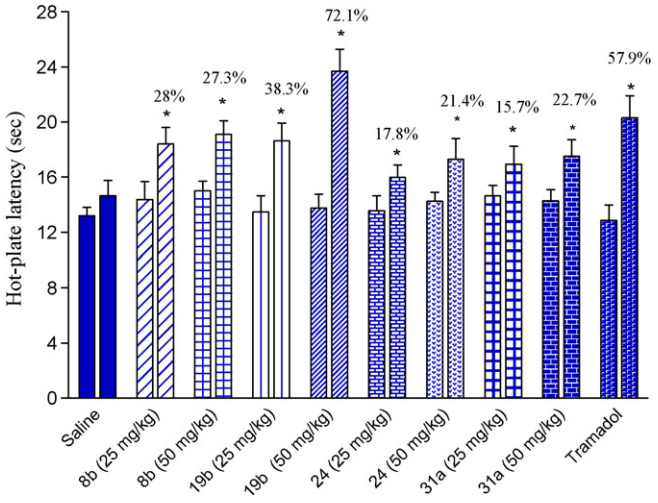


Fig. 3. Reaction time on the hot-plate in seconds after the administration of tested compounds at doses of 25 or 50 mg/kg. Shown are basal (pre-drug: first column) and 60 min (post-drug: second column) values. The percentage change from basal (pre-drug) values is shown ($n = 6$/group). Asterisks indicate significant change from the saline control group at the respective time point (ANOVA and Duncan's multiple comparison tests).

at 50 mg/kg was significantly more prolonged than tramadol at 20 mg/kg (57.9%).

3.2.2.2. Effect of tested compounds on acetic acid-induced writhing. All tested compounds significantly reduced the number of abdominal writhes induced by i.p. administration of dilute acetic acid in mice (Table 3, Fig. 4). The degree of inhibition of the writhing response by these compounds ranged from −55.0% to −99.5% as

Table 3
Effect of tested compounds on the number of writhes in the acetic acid test in mice.

Group	Number of abdominal constrictions/30 min	% Inhibition vs control
Saline	80.0 ± 5.3	
8b (25 mg/kg)	7.2 ± 0.5*	91.0%
8b (50 mg/kg)	7.0 ± 0.7*	91.3%
19b (25 mg/kg)	31.0 ± 2.3*	61.3%
19b (50 mg/kg)	17.5 ± 1.8*	78.2%
24 (25 mg/kg)	0.4 ± 0.24*	99.5%
24 (50 mg/kg)	1.0 ± 0.36*	98.8%
31a (25 mg/kg)	9.3 ± 0.8*	88.3%
31a (50 mg/kg)	1.83 ± 0.7*	97.8%
IND (18 mg/kg)	38 ± 2.8*	52.5%

Data are expressed as means and S.E.M. ($n = 6$/group). IND: indomethacin.
* $P < 0.05$ vs control values.

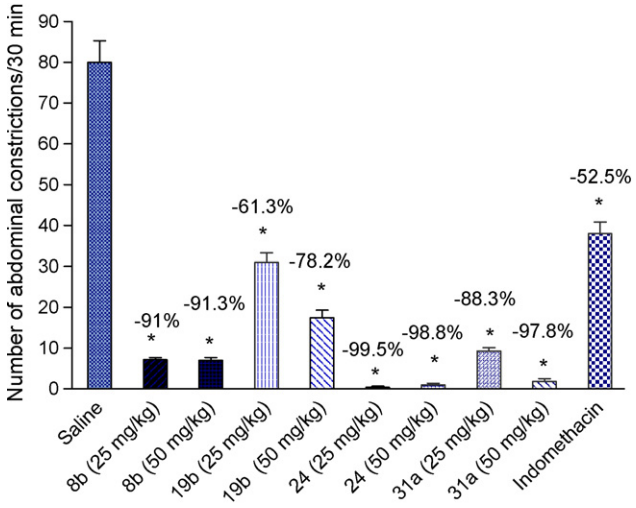


Fig. 4. Effect of tested compounds on acetic acid-induced writhing. Test compounds were administered at 25 or 50 mg/kg and the number of abdominal writhes induced by i.p. injection of acetic acid in mice was determined over 30 min period (mean ± S.E. of 6 mice/group). The percent decrease in the number of writhes from the saline control group is represented above the respective group bar. Asterisks indicate significant change from the saline control group (ANOVA and Duncun's multiple comparison tests).

compared to the saline-treated control group. The analgesic activity of either dose of compound **8b**, **24** or **31a** as well as the high dose of **19b** was significantly higher than that for indomethacin. In addition, the 50 mg/kg dose of compound **24** or **31a** was significantly more potent as analgesic vs that of compound **19b**.

3.2.3. Tests of gastric ulcerogenic studies

In order to evaluate the potential anti-ulcerogenic properties of the tested compounds, we examined the effect of the highest dose on the development of gastric mucosal lesions caused by ethanol or the non-steroidal anti-inflammatory drug indomethacin.

Gastric mucosal lesions caused in the rats by the administration of 96% ethanol were inhibited by all tested compounds administered at (50 mg/kg) dose in the study (Table 4, Fig. 5). Compounds **19b**, **24**, **31a** had significant effect vs the control and compound **8b**. Also, compounds **19b** and **31a** had significant effect vs compound **24**. Gastric mucosal lesions caused in the rats by the administration of indomethacin were inhibited by all tested compounds administered at 50 mg/kg in the study (Table 5, Fig. 6).

3.3. Conclusion

In this study we have described a straightforward and efficient synthesis of novel steroid derivatives containing fused oxiran or azole nucleus in addition to the pharmacophoric features of the steroid moiety. We investigated also the pharmaceutical importance of incorporating heterocyclic moiety to the steroid nucleus

Table 4
Effect of the tested compounds on gastric mucosal injury caused by 96% ethanol in rats.

Group	Number of lesions/rat	Severity of lesions/rat
Ethanol control	20.6 ± 2.1	63.8 ± 4.0
Ethanol + **8b**	16.4 ± 2.0^{NS}	58.6 ± 6.8^{NS}
Ethanol + **19b**	1.2 ± 1.2*	1.2 ± 1.2*
Ethanol + **24**	9.0 ± 1.6*	30.2 ± 2.9*
Ethanol + **31a**	1.4 ± 0.7*	2.8 ± 1.2*

Statistical comparison of the difference between the ethanol control group and other treated groups is indicated by asterisks; *$P < 0.05$, NS = not significant vs control values.

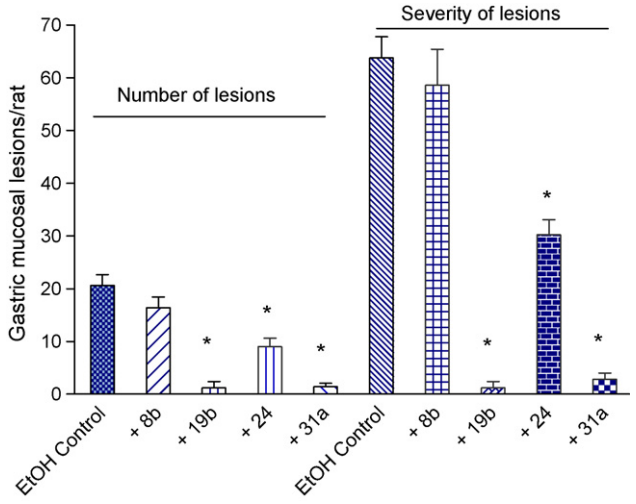


Fig. 5. Effect of test compounds administrated at 50 mg/kg, on the number and severity of gastric mucosal lesions caused by s.c. injection of EtOH (96%) in rats. The percentage decrease in the number or severity of gastric lesions from the EtOH (96%) control group is represented above the respective group bar. Asterisks indicate significant change from the corresponding EtOH (96%) control group (ANOVA and Duncan's multiple comparison tests).

Table 5
Effect of the tested compounds on gastric mucosal injury caused by indomethacin in rats.

Group	Number of lesions/rat	Severity of lesions/rat
IND (control)	3.6 ± 0.6	5.3 ± 0.8
IND + **8b**	0.4 ± 0.2*	0.4 ± 0.2*
IND + **19b**	0.0 ± 0.0*	0.0 ± 0.0*
IND + **24**	0.2 ± 0.2*	1.2 ± 0.5*
IND + **31a**	0.0 ± 0.0*	0.0 ± 0.0*

Statistical comparison of the difference between the indomethacin (IND) control group and other treated groups is indicated by asterisks; $^{*}P < 0.05$ vs control values.

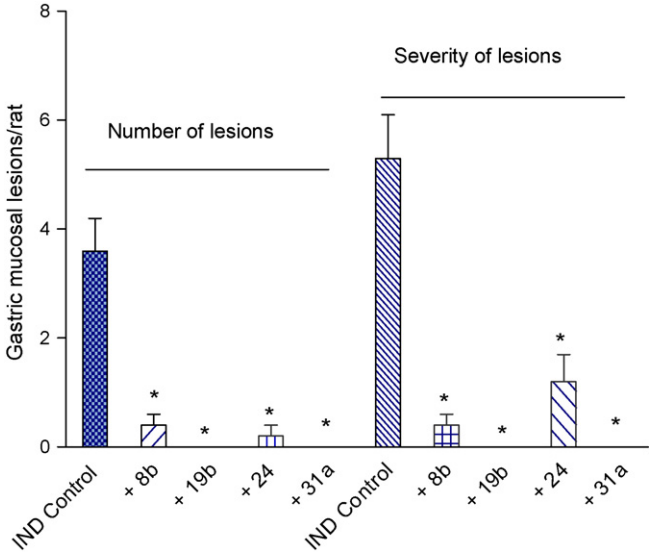


Fig. 6. Effect of tested compounds administrated at 50 mg/kg on the number and severity of gastric mucosal lesions caused by s.c. injection of indomethacin in rats. The percentage decrease in the number or severity of gastric lesions from the indomethacin (IND) control group is represented above the respective group bar. Asterisks indicate significant change from the corresponding IND control group (ANOVA and Duncan's multiple comparison tests).

to form new effective hybrid molecules. The novel synthesized derivatives **8b**, **19b**, **24**, and **31a** showed anti-inflammatory, anti-nociception and anti-ulcerogenic activities with various intensities. Oedema was significantly reduced by both doses (25 or 50 mg/kg) of tested compounds at 3 and 4 h post-carrageenan. Compound **19b** was most effective in alleviating thermal pain. The analgesic activity of either dose of compound **8b**, **24** or **31a** as well as the high dose of **19b** was significantly higher than that for indomethacin. Gastric mucosal lesions caused in the rats by the administration of 96% ethanol or indomethacin were inhibited by any of the tested compounds administered at 50 mg/kg. These results provide a unique opportunity to develop new anti-inflammatory drugs which lack the ulcerogenic liabilities associated with currently marketed drugs. Finally, the encouraging results displayed by these compounds are of interest to initiate further studies of the mechanism of action and toxicity profile of the promising tested compounds before application in phase 1 of clinical study in the hope of finding new potent prescriptions

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