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Synthesis of novel D-ring fused 7′-aryl-androstano[17,16-d][1,2,4]triazolo[1,5-a]pyrimidines

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ABSTRACT

The preparation of novel steroidal heterocycles containing the 7-aryl-substituted 1,2,4-triazolo[1,5-a]pyrimidine moiety fused to the 16,17-positions of the steroid nucleus is described. The Aldol reaction of 4-aza-androst-3,17-dione (**1a**) and dehydroepiandrosterone (DHEA, **1b**) with aromatic aldehydes was catalyzed by KF/Al_2O_3 to give the corresponding 3-oxo-4-aza-5α- and 3β-hydroxy-5-en-16-arylidene-17-ketosteroids (**2a**–**r**). Subsequently, the intermediates **2a**–**r** reacted with dinucleophilic 3-amino-1,2,4-triazole in presence of *t*-BuOK to afford the title compounds (**3a**–**r**). All the synthesized heterosteroids are new and are currently being evaluated for their biological activities.

1. Introduction

During the last decades, steroids bearing heterocycles fused to the A- or D-ring of the steroid skeleton continue to attract much pharmaceutical interest as many of these heterosteroids possess widespread biological activities (Fig. 1, **I**–**III**) [1–8]. For example, Cortivazol (**I**) and similar arylpyrazolo steroids exhibited powerful glucocorticoids and have been extensively investigated as anti-inflammatory agents [2]. Steroidal[17,16-d]thiopyridone derivative (**II**) also showed significant anti-inflammatory activity and was found to be more potent but less toxic than Prednisolone [7]. In addition, Potter et al. reported that N-substituted 1,3,5(10)-estratrien[17,16-c]pyrazole (**III**) was a potent inhibitors of 17β-hydroxysteroid dehydrogenases (17β-HSD) with an IC_{50} of 530 nM in T47-D human breast cancer cells [8]. Considering the remarkable importance from the pharmacological and synthetic viewpoints, great efforts are being made to annelate steroidal moiety with pyrazole, isoxazole, pyridine, pyran, pyrrole or pyrimidine rings using various synthetic strategies [9–13].

On the other hand, 1,2,4-triazolo[1,5-a]pyrimidines (TPs), which are analogues of purine bases widely investigated (Fig. 1 **IV** and **V**) [14], have been identified to possess multifaceted pharmacological properties, including antihypertensive, cardiac stimulant, antimalarial, antifungal, anti-HBV, antimicrobial, anticancer and herbicidal activities [15–22]. The most widely known derivative is the simple molecule of Trapidil (**IV**), a clinically used vasodilator, which acts as a platelet-derived growth factor (PDGF) antagonist and as a phosphodiesterase inhibitor [15b]. Recently, a new antibiotic substance named Essramycin (**V**), the first isolated 1,2,4-triazolo[1,5-a]pyrimidine natural product, was reported to exhibit broad-spectrum antibacterial properties [20b].

In view of the therapeutic importance of heterosteroids and in continuation of our previous work in developing new biologically active modified steroids [23], we are interested in the design, synthesis and biological evaluation of novel heterosteroids. According to the literatures [24], 16-arylidene-17-ketosteroids reacted with dinucleophilic urea or hydrazines to afford the corresponding steroidal pyrimidines or pyrazoles. Furthermore, the condensation of aromatic α,β-unsaturated ketones with dinucleophilic 3-amino-1,2,4-triazole (3-AT) was a facile approach to prepare TPs [19,21b,25]. Herein, we report the synthesis of a novel class of heterosteroids containing the 7-aryl-substituted 1,2,4-triazolo[1,5-a]pyrimidine moiety fused with

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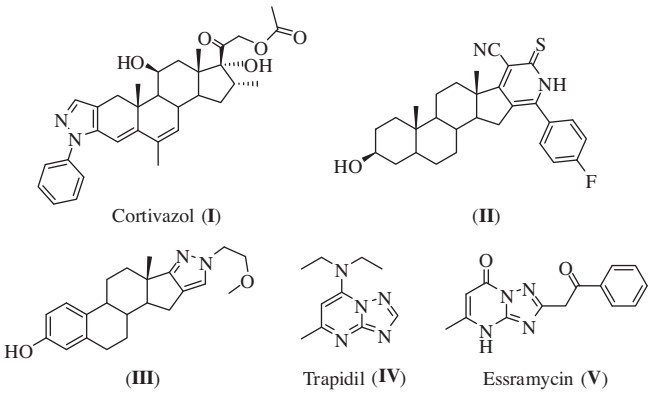

Fig. 1. Structures of heterosteroids **I–III** and 1,2,4-triazolo[1,5-a]pyrimidines **IV**, **V**.

D-ring via the condensation of 3-AT with readily available 16-arylidene-17-ketosteroids.

2. Experimental

2.1. General remarks

All reagents and solvents used were of analytical grade purchased from commercial sources. Thin-layer chromatography (TLC) was carried out on glass plates coated with silica gel (Qingdao Haiyang Chemical Co., G60F-254) and visualized by UV light (254 nm). The products were purified by column chromatography over silica gel (Qingdao Haiyang Chemical Co., 200–300 mesh). Melting points were determined on a Beijing Keyi XT4A apparatus and are uncorrected. All NMR spectra were recorded with a Bruker DPX 400 MHz spectrometer, with TMS as internal standard in $CDCl_3$. Chemical shifts are given as δ ppm values relative to TMS. Mass spectra (MS) were recorded on Esquire3000 mass spectrometer by electrospray ionization (ESI).

2.2. General procedure for the synthesis of 16-arylidene-17-ketosteroids ***2a–r***

A mixture of 4-aza-androst-3,17-dione (**1a**) [26] or dehydroepiandrosterone (DHEA, **1b**) (2.0 mmol), aromatic aldehydes (2.1 mmol) and KF/Al_2O_3 (1.6 mmol) [27] in EtOH (20 mL) was heated to reflux for about 1 h. After completion of the reaction as evident from TLC, the slurry was filtered and the residue was washed thoroughly with CH_2Cl_2. The filtrate was condensed under reduced pressure, and the solid obtained was crystallized from EtOH or MeOH to yield the corresponding 16-arylidene-17-ketosteroids **2a–r** (Table 1).

2.2.1. 4-Aza-5α-16-benzylidene-androst-3,17-dione (***2a***)

White solid, yield 92%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 6.8 Hz, 2H, ArH), 7.44–7.35 (m, 4H, ArH and Ar–CH═), 6.49 (s, 1H, 4-NH), 3.09 (dd, J_1 = 12.0 Hz, J_2 = 4.0 Hz, 1H, 5α-H), 0.97 (d, J = 3.2 Hz, 6H, 18-CH_3 and 19-CH_3). HRMS (ESI): m/z calcd for $C_{25}H_{32}NO_2$ $(M+H)^+$, 378.2433; found, 378.2334.

2.2.2. 4-Aza-5α-16-(4-chlorobenzylidene)-androst-3,17-dione (***2b***)

White solid, yield 92%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J = 8.8 Hz, 2H, ArH), 7.40–7.38 (m, 3H, ArH and Ar–CH═), 6.53 (brs, 1H, 4-NH), 3.09 (dd, J_1 = 12.4 Hz, J_2 = 4.0 Hz, 1H, 5α-H), 0.97 (s, 6H, 18-CH_3 and 19-CH_3). HRMS (ESI): m/z calcd for $C_{25}H_{31}ClNO_2$ $(M+H)^+$, 412.2043; found, 412.2044.

2.2.3. 4-Aza-5α-16-(3-nitrobenzylidene)-androst-3,17-dione (***2c***)

Yellow solid, yield 94%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, J = 1.6 Hz, 1H, ArH), 8.21 (d, J = 8.0 Hz, 1H, ArH), 7.82 (d, J = 7.6 Hz, 1H, ArH), 7.61 (t, J = 8.0 Hz, 1H, ArH), 7.46 (s, 1H, Ar–CH═), 6.31 (brs, 1H, 4-NH), 3.10 (dd, J_1 = 12.4 Hz, J_2 = 3.2 Hz, 1H, 5α-H), 0.99 (d, J = 9.2 Hz, 6H, 18-CH_3 and 19-CH_3). HRMS (ESI): m/z calcd for $C_{25}H_{31}N_2O_4$ $(M+H)^+$, 423.2284; found, 423.2286.

2.2.4. 4-Aza-5α-16-(3,4,5-trimethyoxybenzylidene)-androst-3,17-dione (***2d***)

White solid, yield 92%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (s, 1H, Ar–CH═), 6.77(s, 2H, ArH), 5.73 (brs, 1H, 4-NH), 3.89 (d, J = 0.8 Hz, 9H, Ar-$(OCH_3)_3$), 3.10 (dd, J_1 = 12.4 Hz, J_2 = 4.0 Hz, 1H, 5α-H), 0.98 (d, J = 5.6 Hz, 6H, 18-CH_3 and 19-CH_3). HRMS (ESI): m/z calcd for $C_{28}H_{38}NO_5$ $(M+H)^+$, 468.2750; found, 468.2751.

2.2.5. 4-Aza-5α-16-(4-bromobenzylidene)-androst-3,17-dione (***2e***)

White solid, yield 95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 8.4 Hz, 2H, ArH), 7.40–7.37 (m, 3H, ArH and Ar–CH═), 5.86 (brs, 1H, 4-NH), 3.10 (dd, J_1 = 12.4 Hz, J_2 = 4.0 Hz, 1H, 5α-H), 0.97 (s, 6H, 18-CH_3 and 19-CH_3). HRMS (ESI): m/z calcd for $C_{25}H_{31}BrNO_2$ $(M+H)^+$, 456.1538; found, 456.1540.

2.2.6. 4-Aza-5α-16-(4-fluorobenzylidene)-androst-3,17-dione (***2f***)

White solid, yield 93%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (m, 2H, ArH), 7.40 (d, J = 2.0 Hz, 1H, Ar–CH═), 7.14–7.08 (m, 2H, ArH), 5.93 (brs, 1H, 4-NH), 3.10 (dd, J_1 = 12.0 Hz, J_2 = 4.0 Hz, 1H, 5α-H), 0.97 (s, 6H, 18-CH_3 and 19-CH_3). HRMS (ESI): m/z calcd for $C_{25}H_{31}FNO_2$ $(M+H)^+$, 396.2339; found, 396.2340.

2.2.7. 4-Aza-5α-16-(4-methoxybenzylidene)-androst-3,17-dione (***2g***)

White solid, yield 90%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, J = 8.8 Hz, 2H, ArH), 7.41 (s, 1H, Ar–CH═), 6.96 (d, J = 8.7 Hz, 2H, ArH), 6.40 (s, 1H, 4-NH), 3.86 (s, 3H, Ar-OCH_3), 3.10 (dd, J = 12.2, 3.8 Hz, 1H, 5α-H), 0.97 (d, J = 1.8 Hz, 6H, 18-CH_3 and 19-CH_3). HRMS (ESI): m/z calcd for $C_{26}H_{34}NO_3$ $(M+H)^+$, 408.2539; found, 408.2536.

2.2.8. 4-Aza-5α-16-(4-dimethylaminobenzylidene)-androst-3,17-dione (***2h***)

Yellow solid, yield 92%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, J = 8.8 Hz, 2H, ArH), 7.40 (s, 1H, Ar–CH═), 6.73 (d, J = 8.9 Hz, 2H, ArH), 6.29 (s, 1H, 4-NH), 3.10 (dd, J = 12.2, 3.8 Hz, 1H, 5α-H), 3.04 (s, 6H, Ar-$N(CH_3)_2$), 0.97 (d, J = 4.8 Hz, 6H, 18-CH_3 and 19-CH_3). HRMS (ESI): m/z calcd for $C_{27}H_{37}N_3O_3$ $(M+H)^+$, 421.2855; found, 421.2854.

2.2.9. 4-Aza-5α-16-(4-isopropylbenzylidene)-androst-3,17-dione (***2i***)

White solid, yield 91%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, J = 8.1 Hz, 2H, ArH), 7.44 (s, 1H, Ar–CH═), 7.30 (d, J = 9.2 Hz, 2H, ArH), 6.37 (s, 1H, 4-NH), 3.10 (dd, J = 12.2, 3.7 Hz, 1H, 5α-H), 1.28 (d, J = 6.9 Hz, 6H, Ar$CH(CH_3)_2$), 0.97 (d, J = 8.6 Hz, 6H, 18-CH_3 and 19-CH_3). HRMS (ESI): m/z calcd for $C_{26}H_{38}NO_2$ $(M+H)^+$, 420.2903; found, 420.2903.

2.2.10. 4-Aza-5α-16-(4-morpholinylbenzylidene)-androst-3,17-dione (***2j***)

Yellow solid, yield 90%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, J = 8.7 Hz, 2H, ArH), 7.39 (s, 1H, Ar–CH═), 6.92 (d, J = 8.7 Hz, 2H, ArH), 6.25 (s, 1H, 4-NH), 3.93–3.81 (m, 4H, protons of morpholine), 3.33–3.20 (m, 4H, protons of morpholine), 3.10 (dd, J = 12.2, 3.6 Hz, 1H, 5α-H), 0.97 (d, J = 3.2 Hz, 6H, 18-CH_3 and 19-CH_3). HRMS (ESI): m/z calcd for $C_{29}H_{39}N_2O_3$ $(M+H)^+$, 463.2961; found, 463.2958.

Table 1
Synthesis of steroidal[17,16-d]triazolopyrimidines (**3a**–**r**).

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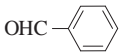
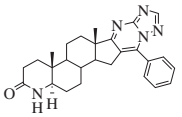
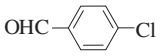
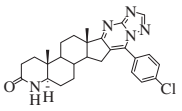
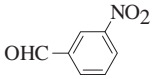
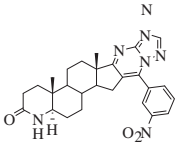
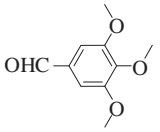
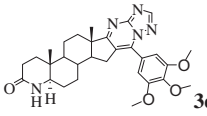
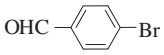
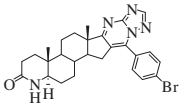
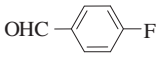
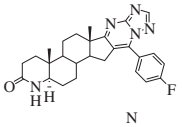
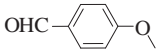
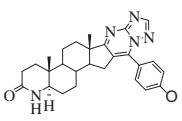
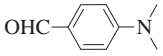
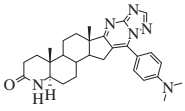
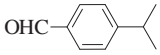
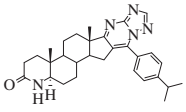
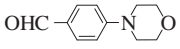
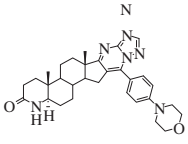
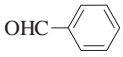
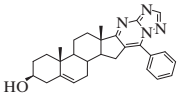
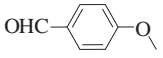
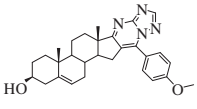
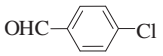
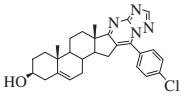
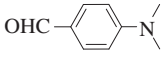
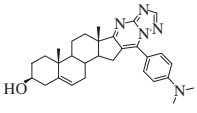
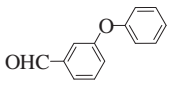
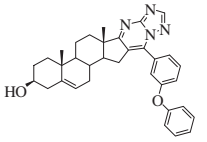
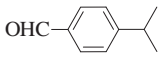
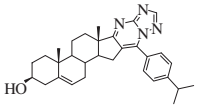
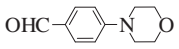
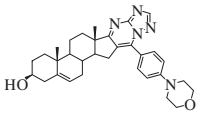
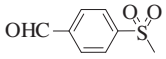
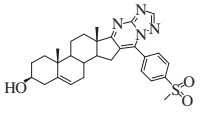
1	**1a**		**2a**/92	 **3a**	58
2	**1a**		**2b**/92	 **3b**	67
3	**1a**		**2c**/94	 **3c**	64
4	**1a**		**2d**/92	 **3d**	52
5	**1a**		**2e**/95	 **3e**	65
6	**1a**		**2f**/93	 **3f**	68
7	**1a**		**2g**/90	 **3g**	54
8	**1a**		**2h**/92	 **3h**	55
9	**1a**		**2i**/96	 **3i**	60
10	**1a**		**2j**/90	 **3j**	51
11	**1b**		**2k**/94	 **3k**	67
12	**1b**		**2l**/91	 **3l**	63
13	**1b**		**2m**/93	 **3m**	65
14	**1b**		**2n**/90	 **3n**	61

(*continued on next page*)

Table 1 (*continued*)

Entry	1	ArCHO	2/Yields[a] (%)	Product[b]	Yields[c] (%)
15	**1b**		**2o**/92	 **3o**	71
16	**1b**		**2p**/93	 **3p**	66
17	**1b**		**2q**/88	 **3q**	63
18	**1b**		**2r**/90	 **3r**	70

[a] Reaction conditions: **1a** or **1b** (2.0 mmol), aromatic aldehydes (2.1 mmol), KF/Al_2O_3 (1.6 mmol) EtOH (20 mL), reflux, 1 h.
[b] Reaction conditions: **2** (1.0 mmol), 3-AT (2.0 mmol), *t*-BuOK (2.0 mmol), *n*-BuOH (10 mL), reflux, 30 h.
[c] Isolated yields.

*2.2.11. 3β-Hydroxy-16-benzylidene-5-androsten-17-one (**2k**)*

White solid, yield 94%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 7.4 Hz, 2H, ArH), 7.49–7.34 (m, 4H, ArH and Ar–CH═), 5.45–5.37 (m, 1H, 6-H), 3.63–3.49 (m, 1H, 3α-H), 1.18–1.04 (m, 5H), 1.00 (s, 3H, 18-CH_3). HRMS (ESI): *m*/*z* calcd for $C_{26}H_{33}O_2$ $(M+H)^+$, 377.2481; found, 377.2479.

*2.2.12. 3β-Hydroxy-16-(4-methoxybenzylidene)-5-androsten-17-one (**2l**)*

White solid, yield 91%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 8.7 Hz, 2H, ArH), 7.42 (s, 1H, Ar–CH═), 6.96 (d, *J* = 8.7 Hz, 2H, ArH), 5.46–5.38 (m, 1H, 6-H), 3.85 (d, *J* = 8.8 Hz, 3H, Ar-OCH_3), 3.56 (m, 1H, 3α-H), 1.18–1.03 (m, 5H), 0.99 (s, 3H, 18-CH_3). HRMS (ESI): *m*/*z* calcd for $C_{27}H_{35}O_3$ $(M+H)^+$, 407.2586; found, 407.2584.

*2.2.13. 3β-Hydroxy-16-(4-chlorobenzylidene)-5-androsten-17-one (**2m**)*

White solid, yield 93%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.4 Hz, 2H, ArH), 7.40 (d, *J* = 8.1 Hz, 3H, ArH and Ar–CH═), 5.42 (d, *J* = 4.8 Hz, 1H, 6-H), 3.63–3.49 (m, 1H, 3α-H), 1.19–1.04 (m, 5H), 1.00 (s, 3H, 18-CH_3). HRMS (ESI): *m*/*z* calcd for $C_{26}H_{32}ClO_2$ $(M+H)^+$, 411.2091; found, 411.2092.

*2.2.14. 3β-Hydroxy-16-(4-dimethylaminobenzylidene)-5-androsten-17-one (**2n**)*

Yellow solid, yield 90%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.8 Hz, 2H, ArH), 7.41 (s, 1H, Ar–CH═), 6.73 (d, *J* = 8.8 Hz, 2H, ArH), 5.42 (d, *J* = 5.1 Hz, 1H, 6-H), 3.55 (d, *J* = 3.7 Hz, 1H, 3α-H), 3.04 (s, 6H, Ar-$N(CH_3)_2$), 1.18–1.02 (m, 5H), 0.98 (s, 3H, 18-CH_3). HRMS (ESI): *m*/*z* calcd for $C_{28}H_{38}NO_2$ $(M+H)^+$, 420.2903; found, 420.2900.

*2.2.15. 3β-Hydroxy-16-(3-phenoxybenzylidene)-5-androsten-17-one (**2o**)*

White solid, yield 92%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (dd, *J* = 11.9, 4.0 Hz, 4H, ArH), 7.27 (d, *J* = 7.8 Hz, 1H, Ar–CH═), 7.22–7.12 (m, 2H, ArH), 7.05 (ddd, *J* = 12.8, 8.4, 1.6 Hz, 3H, ArH), 5.42 (d, *J* = 5.0 Hz, 1H, 6-H), 3.63–3.49 (m, 1H, 3α-H), 1.20–1.02 (m, 5H), 0.97 (s, 3H, 18-CH_3). HRMS (ESI): *m*/*z* calcd for $C_{32}H_{37}O_3$ $(M+H)^+$, 469.2743; found, 469.2745.

*2.2.16. 3β-Hydroxy-16-(4-isopropylbenzylidene)-5-androsten-17-one (**2p**)*

White solid, yield 93%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56–7.40 (m, 3H, ArH and Ar–CH═), 7.36–7.23 (m, 2H, ArH), 5.41 (d, *J* = 6.6 Hz, 1H, 6-H), 3.55 (m, 1H, 3α-H), 1.92–1.68 (m, 6H, Ar-$CH(CH_3)_2$), 1.09 (m, 5H), 0.99 (d, *J* = 12.7 Hz, 3H, 18-CH_3). HRMS (ESI): *m*/*z* calcd for $C_{29}H_{39}O_2$ $(M+H)^+$, 419.2950; found, 419.2953.

*2.2.17. 3β-Hydroxy-16-(4-morpholinylbenzylidene)-5-androsten-17-one (**2q**)*

Yellow solid, yield 87%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 3.7 Hz, 2H, ArH), 7.40 (s, 1H, Ar–CH═), 6.93 (d, *J* = 3.7 Hz, 2H, ArH), 5.41 (s, 1H, 6-H), 3.88 (d, *J* = 4.2 Hz, 4H, protons of morpholine), 3.55 (d, *J* = 4.5 Hz, 1H, 3α-H), 3.26 (d, *J* = 4.2 Hz, 4H, protons of morpholine), 1.11 (m, 5H), 0.98 (d, *J* = 4.5 Hz, 3H, 18-CH_3). HRMS (ESI): *m*/*z* calcd for $C_{30}H_{40}NO_3$ $(M+H)^+$, 462.3008; found, 462.3004.

*2.2.18. 3β-Hydroxy-16-(4-methylsulfonylbenzylidene)-5-androsten-17-one (**2r**)*

White solid, yield 93%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.3 Hz, 2H, ArH), 7.71 (d, *J* = 8.4 Hz, 2H, ArH), 7.46 (s, 1H, Ar–CH═), 5.45–5.36 (m, 1H, 6-H), 3.60–3.50 (m, 1H, 3α-H), 3.09 (s, 3H, Ar-SO_2CH_3), 1.19–1.04 (m, 5H), 1.01 (s, 3H, 18-CH_3). HRMS (ESI): *m*/*z* calcd for $C_{27}H_{34}O_4SNa$ $(M+Na)^+$, 477.2075; found, 477.2075.

*2.3. General procedure for the synthesis of steroidal[17,16-d]triazolopyrimidines **3a–r***

The condensation products **2a–r** (1.0 mmol) was dissolved in *n*-BuOH (10 mL). To the solution was added 3-AT (2.0 mmol) and *t*-BuOK (2.0 mmol). The resulting mixture was refluxed for 30 h. The solvent was removed and CH_2Cl_2 was added. The insoluble *t*-BuOK was filtered and washed thoroughly with CH_2Cl_2. After removal of the solvent, the residue was purified by silica gel chromatography with ethyl acetate/petroleum ether/acetone

(4:2:1) and petroleum ether/ethyl acetate (3:2) to give the corresponding steroidal[17,16-d]triazolopyrimidines **3a–j** and **3k–r**, respectively (Table 1).

*2.3.1. 3-Oxo-4-aza-7′-phenyl-5α-androstano[17,16-d][1,2,4]triazolo-[1,5-a]pyrimidine (**3a**)*

White solid, yield 58%, mp > 300 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (s, 1H, 2′-H), 7.81 (dd, *J* = 6.7, 3.0 Hz, 2H, Ar–H), 7.64–7.56 (m, 3H, Ar–H), 6.40 (s, 1H, 4-NH), 3.10 (dd, *J* = 12.2, 3.8 Hz, 1H, 5α-H), 1.20 (s, 3H, 18-H), 1.00 (s, 3H, 19-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.4, 172.4, 155.8, 154.7, 143.0, 131.1, 129.6, 129.1, 128.7, 122.4, 60.6, 55.3, 51.4, 46.7, 36.0, 34.2, 33.2, 32.8, 29.0, 29.0, 28.5, 27.0, 20.7, 17.4, 11.4. HRMS (ESI): *m*/*z* calcd for $C_{27}H_{32}N_5O$ $(M+H)^+$, 442.2607; found, 442.2610.

*2.3.2. 3-Oxo-4-aza-7′-(4-chlorophenyl)-5α-androstano[17,16-d][1,2,4]triazolo[1,5-a] pyrimidine (**3b**)*

White solid, yield 67%, mp > 300 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H, 2′-H), 7.78 (d, *J* = 8.2 Hz, 2H, Ar–H), 7.57 (d, *J* = 8.2 Hz, 2H, Ar–H), 6.56 (s, 1H, 4-NH), 3.09 (d, *J* = 9.5 Hz, 1H, 5α-H), 1.19 (s, 3H, 18-H), 1.00 (s, 3H, 19-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.4, 172.3, 155.9, 154.8, 141.7, 137.3, 131.0, 129.1, 127.5, 122.4, 60.6, 55.3, 51.5, 46.8, 35.9, 34.3, 33.2, 32.8, 29.0, 29.0, 28.6, 27.0, 20.7, 17.4, 11.4. HRMS (ESI): *m*/*z* calcd for $C_{27}H_{31}ClN_5O$ $(M+H)^+$, 476.2217; found, 476.2223.

*2.3.3. 3-Oxo-4-aza-7′-(3-nitrophenyl)-5α-androstano[17,16-d][1,2,4]triazolo[1,5-a]pyrimidine (**3c**)*

White solid, yield 64%, mp > 300 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (t, *J* = 1.7 Hz, 1H, Ar-H), 8.44 (dd, *J* = 8.3, 1.3 Hz, 1H, Ar–H), 8.38 (s, 1H, 2′–H), 8.21 (d, *J* = 7.8 Hz, 1H, Ar–H), 7.82 (t, *J* = 8.0 Hz, 1H, Ar–H), 6.49 (s, 1H, 4-NH), 3.09 (dd, *J* = 12.2, 3.7 Hz, 1H, 5α-H), 1.21 (s, 3H, 18-H), 1.00 (s, 3H, 19-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.7, 172.3, 155.8, 155.0, 148.3, 140.1, 135.5, 130.7, 129.9, 125.7, 124.8, 123.0, 60.5, 55.3, 51.5, 46.9, 36.0, 34.3, 33.2, 32.8, 29.0, 28.8, 28.5, 26.9, 20.6, 17.5, 11.4. HRMS (ESI): *m*/*z* calcd for $C_{27}H_{31}N_6O_3$ $(M+H)^+$, 487.2458; found, 487.2459.

*2.3.4. 3-Oxo-4-aza-7′-(3,4,5-trimethoxyphenyl)-5α-androstano[17,16-d][1,2,4]triazolo[1,5-a] pyrimidine (**3d**)*

White solid, yield 52%, mp 197–199 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (s, 1H, 2′-H), 7.01 (s, 2H, Ar–H), 6.58 (s, 1H, 4-NH), 3.92 (d, *J* = 17.1 Hz, 9H, Ar-$(OCH_3)_3$), 3.08 (dd, *J* = 12.1, 3.3 Hz, 1H, 5α-H), 1.18 (s, 3H, 18-H), 0.98 (s, 3H, 19-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.3, 172.3, 156.0, 154.8, 153.3, 142.9, 140.4, 124.0, 122.2, 107.3, 61.0, 60.6, 56.4, 55.3, 51.5, 46.7, 35.9, 34.2, 33.2, 32.8, 29.2, 29.1, 28.5, 26.9, 20.7, 17.4, 11.4. HRMS (ESI): *m*/*z* calcd for $C_{30}H_{38}N_5O_4$ $(M+H)^+$, 532.2924; found, 532.2921.

*2.3.5. 3-Oxo-4-aza-7′-(4-bromophenyl)-5α-androstano[17,16-d][1,2,4]triazolo[1,5-a]pyrimidine (**3e**)*

White solid, yield 65%, mp > 300 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H, 2′-H), 7.73 (q, *J* = 8.6 Hz, 4H, Ar–H), 5.98 (s, 1H, 4-NH), 3.12 (dd, *J* = 11.9, 3.6 Hz, 1H, 5α-H), 1.20 (s, 3H, 18-H), 1.02 (s, 3H, 19-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.4, 172.2, 155.9, 154.8, 141.8, 132.0, 131.2, 127.9, 125.8, 122.3, 60.6, 55.3, 51.5, 46.8, 36.0, 34.3, 33.2, 32.8, 29.7, 29.0, 28.5, 27.1, 20.7, 17.4, 11.4. HRMS (ESI): *m*/*z* calcd for $C_{27}H_{31}BrN_5O$ $(M+H)^+$, 520.1712; found, 520.1710.

*2.3.6. 3-Oxo-4-aza-7′-(4-fluorophenyl)-5α-androstano[17,16-d][1,2,4]triazolo[1,5-a] pyrimidine (**3f**)*

White solid, yield 68%, mp > 300 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (s, 1H, 2′-H), 7.84 (dd, *J* = 8.5, 5.3 Hz, 2H, Ar–H), 7.29 (t, *J* = 8.5 Hz, 2H, Ar–H), 6.34 (s, 1H, 4-NH), 3.14–3.06 (m, 1H, 5α-H), 1.19 (s, 3H, 18-H), 1.00 (s, 3H, 19-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.4, 172.4, 155.9, 154.7, 143.0, 131.1, 129.6, 129.1, 128.7, 122.4, 60.6, 55.3, 51.5, 46.7, 36.0, 34.3, 33.2, 32.8, 29.0, 29.0, 28.5, 27.0, 20.7, 17.4, 11.4. HRMS (ESI): *m*/*z* calcd for $C_{27}H_{31}FN_5O$ $(M+H)^+$, 460.2513; found, 460.2518.

*2.3.7. 3-Oxo-4-aza-7′-(4-methoxyphenyl)-5α-androstano[17,16-d][1,2,4]triazolo[1,5-a] pyrimidine (**3g**)*

White solid, yield 54%, mp 268–270 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H, 2′-H), 7.81 (d, *J* = 8.8 Hz, 2H, Ar–H), 7.10 (d, *J* = 8.8 Hz, 2H, Ar–H), 6.36 (s, 1H, 4-NH), 3.92 (s, 3H, Ar-OCH_3), 3.10 (dd, *J* = 12.1, 3.7 Hz, 1H, 5α-H), 1.19 (s, 3H, 18-H), 1.00 (s, 3H, 19-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.2, 172.3, 161.6, 156.0, 154.6, 142.9, 131.4, 121.6, 121.2, 114.1, 60.6, 55.5, 55.4, 51.5, 46.7, 36.0, 34.3, 33.2, 32.8, 29.3, 29.0, 28.6, 27.0, 20.7, 17.4, 11.4. HRMS (ESI): *m*/*z* calcd for $C_{28}H_{34}N_5O$ $(M+H)^+$, 472.2713; found, 472.2702.

*2.3.8. 3-Oxo-4-aza-7′-(4-dimethylaminophenyl)-5α-androstano[17,16-d][1,2,4]triazolo[1,5-a] pyrimidine (**3h**)*

Yellow solid, yield 55%, mp 257–259 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H, 2′-H), 7.79 (d, *J* = 8.9 Hz, 2H, Ar–H), 6.83 (d, *J* = 8.9 Hz, 2H, Ar–H), 6.52 (s, 1H, 4-NH), 3.09 (s, 7H, 5α-H and Ar–$N(CH_3)_2$), 1.18 (s, 3H, 18-H), 1.00 (s, 3H, 19-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.9, 172.4, 156.1, 154.4, 151.8, 143.7, 131.2, 125.0, 120.6, 115.6, 111.1, 60.6, 55.5, 51.5, 46.6, 40.1, 35.9, 34.3, 33.2, 32.9, 29.7, 29.1, 28.6, 27.0, 20.7, 17.3, 11.4. HRMS (ESI): *m*/*z* calcd for $C_{29}H_{37}N_6O$ $(M+H)^+$, 485.3029; found, 485.3033.

*2.3.9. 3-Oxo-4-aza-7′-(4-isopropylphenyl)-5α-androstano[17,16-d][1,2,4]triazolo[1,5-a] pyrimidine (**3i**)*

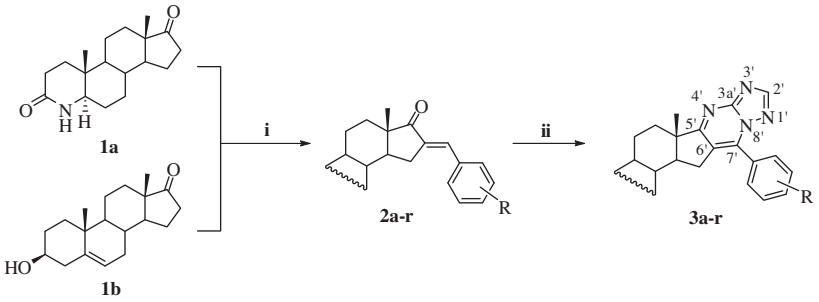
White solid, yield 60%, mp 234–236 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H, 2′-H), 7.75 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.45 (d, *J* = 8.0 Hz, 2H, Ar–H), 6.33 (s, 1H, 4-NH), 3.10 (dd, *J* = 12.0, 3.4 Hz, 1H, 5α-H), 3.08–2.97 (m, 1H, Ar-$CH(CH_3)_2$), 1.33 (d, *J* = 6.8 Hz, 6H, Ar-$CH(CH_3)_2$), 1.19 (s, 3H, 18-H), 1.00 (s, 3H, 19-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.3, 172.2, 156.0, 154.7, 152.3, 143.1, 129.6, 126.8, 126.5, 122.0, 60.6, 55.4, 51.5, 46.7, 36.0, 34.3, 34.2, 33.3, 32.9, 29.1, 29.1, 28.6, 27.0, 23.7, 23.7, 20.7, 17.4, 11.4. HRMS (ESI): *m*/*z* calcd for $C_{30}H_{37}N_5ONa$ $(M+Na)^+$, 506.2896; found, 506.2897.

*2.3.10. 3-Oxo-4-aza-7′-(4-morpholinylphenyl)-5α-androstano[17,16-d][1,2,4]triazolo[1,5-a] pyrimidine (**3j**)*

Yellow solid, yield 51%, mp 298–300 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H, 2′-H), 7.81 (d, *J* = 8.7 Hz, 2H, Ar–H), 7.04 (d, *J* = 8.7 Hz, 2H, Ar–H), 6.20 (s, 1H, 4-NH), 3.98–3.82 (m, 4H, protons of morpholine), 3.43–3.27 (m, 4H, protons of morpholine), 3.10 (dd, *J* = 12.0, 3.7 Hz, 1H, 5α-H), 1.19 (s, 3H, 18-H), 1.01 (s, 3H, 19-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.0, 172.2, 156.1, 154.6, 152.7, 143.1, 131.2, 121.1, 119.1, 114.0, 66.6, 60.6, 55.5, 51.5, 47.9, 46.6, 36.0, 34.3, 33.3, 32.9, 29.4, 29.1, 28.6, 27.1, 20.7, 17.3, 11.4. HRMS (ESI): *m*/*z* calcd for $C_{31}H_{38}N_6O_2Na$ $(M+Na)^+$, 549.2954; found, 549.2949.

*2.3.11. 3β-Hydroxy-5-en-7′-phenyl-androstano[17,16-d][1,2,4]triazolo[1,5-a]pyrimidine (**3k**)*

White solid, yield 67%, mp > 300 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (s, 1H, 2′-H), 7.82 (m, 2H, Ar–H), 7.64–7.57 (m, 3H, Ar–H), 5.37 (d, *J* = 5.0 Hz, 1H, 6-H), 3.63–3.46 (m, 1H, 3α-H), 1.21 (s, 3H, 18-H), 1.19–1.08 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.7, 156.0, 154.7, 142.8, 141.4, 131.0, 129.6, 129.2, 128.7, 122.6, 120.6, 71.5, 56.0, 50.3, 46.4, 42.2, 37.1, 36.8, 33.0, 31.6, 31.2, 31.1, 29.2, 20.5, 19.5, 17.1. HRMS (ESI): *m*/*z* calcd for $C_{28}H_{32}N_4ONa$ $(M+Na)^+$, 463.2474; found, 463.2478.



Scheme 1. Protocol for the synthesis of 7′-aryl-androstano[17,16-d][1,2,4]triazolo[1,5-a] pyrimidines (**3a**–**r**). Reagents and conditions: (i) ArCHO, KF/Al_2O_3, EtOH, reflux; (ii) 3-amino-1,2,4-triazole, *t*-BuOK, *n*-BuOH, reflux.

*2.3.12. 3β-Hydroxy-5-en-7′-(4-methoxyphenyl)-androstano[17,16-d][1,2,4]triazolo[1,5-a] pyrimidine (**3l**)*

White solid, yield 63%, mp 275–277 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H, 2′-H), 7.83 (d, *J* = 8.7 Hz, 2H, Ar–H), 7.10 (d, *J* = 8.6 Hz, 2H, Ar–H), 5.37 (d, *J* = 4.5 Hz, 1H, 6-H), 3.92 (s, 3H, Ar-OCH_3), 3.61–3.48 (m, 1H, 3α-H), 1.20 (s, 3H, 18-H), 1.18–1.08 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.6, 161.6, 156.0, 154.5, 142.8, 141.4, 131.5, 122.0, 121.3, 120.6, 114.8, 71.5, 56.1, 55.5, 50.3, 46.4, 42.2, 37.1, 36.8, 33.0, 31.6, 31.2, 31.1, 29.4, 20.5, 19.5, 17.1. HRMS (ESI): *m*/*z* calcd for $C_{29}H_{34}N_4O_2Na$ $(M+Na)^+$, 493.2579; found, 493.2581.

*2.3.13. 3β-Hydroxy-5-en-7′-(4-chlorophenyl)-androstano[17,16-d][1,2,4]triazolo[1,5-a]pyrimidine (**3m**)*

White solid, yield 65%, mp 291–293 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H, 2′-H), 7.79 (d, *J* = 8.4 Hz, 2H, Ar–H), 7.58 (d, *J* = 8.4 Hz, 2H, Ar–H), 5.38 (d, *J* = 4.8 Hz, 1H, 6-H), 3.61–3.48 (m, 1H, 3α-H), 1.21 (s, 3H, 18-H), 1.19–1.08 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.8, 155.9, 154.7, 141.6, 141.4, 137.3, 131.1, 129.0, 127.6, 122.7, 120.5, 71.5, 56.0, 50.3, 46.5, 42.2, 37.1, 36.8, 33.0, 31.6, 31.2, 31.1, 29.2, 20.5, 19.5, 17.1. HRMS (ESI): *m*/*z* calcd for $C_{28}H_{32}ClN_4O$ $(M+H)^+$, 475.2265; found, 475.2260.

*2.3.14. 3β-Hydroxy-5-en-7′-(4-dimethylaminophenyl)-androstano[17,16-d][1,2,4]triazolo [1,5-a]pyrimidine (**3n**)*

Yellow solid, yield 61%, mp > 300 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (s, 1H, 2′-H), 7.81 (d, *J* = 8.8 Hz, 2H, Ar–H), 6.84 (d, *J* = 8.8 Hz, 2H, Ar–H), 5.37 (d, *J* = 4.1 Hz, 1H, 6-H), 3.60–3.49 (m, 1H, 3α-H), 3.09 (s, 6H, Ar–$N(CH_3)_2$), 1.20 (s, 3H, 18-H), 1.14 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.3, 154.3, 151.8, 143.6, 141.4, 131.2, 125.0, 120.9, 120.7, 115.8, 111.1, 71.5, 56.2, 50.4, 46.3, 42.2, 40.1, 37.1, 36.8, 33.1, 31.6, 31.2, 31.1, 29.8, 20.5, 19.5, 17.1. HRMS (ESI): *m*/*z* calcd for $C_{30}H_{38}N_5O$ $(M+H)^+$, 484.3076; found, 484.3079.

*2.3.15. 3β-Hydroxy-5-en-7′-(3-phenoxyphenyl)-androstano[17,16-d]-[1,2,4]triazolo[1,5-a] pyrimidine (**3o**)*

White solid, yield 71%, mp 167–169 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H, 2′-H), 7.65–7.51 (m, 2H, Ar–H), 7.48–7.35 (m, 3H, Ar–H), 7.26–7.15 (m, 2H, Ar–H), 7.12 (d, *J* = 7.7 Hz, 2H, Ar–H), 5.39 (d, *J* = 4.9 Hz, 1H, 6-H), 3.60–3.52 (m, 1H, 3α-H), 1.18 (s, 3H, 18-H), 1.17–1.05 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.7, 157.7, 156.4, 155.9, 154.7, 142.1, 141.5, 130.7, 130.1, 130.0, 124.2, 124.1, 122.7, 120.8, 120.5, 119.7, 119.4, 71.5, 55.9, 50.3, 46.4, 42.2, 37.1, 36.8, 33.0, 31.6, 31.2, 31.1, 29.1, 20.5, 19.5, 17.1. HRMS (ESI): *m*/*z* calcd for $C_{34}H_{37}N_4O_2$ $(M+H)^+$, 533.2917; found, 533.2915.

*2.3.16. 3β-Hydroxy-5-en-7′-(4-isopropylphenylphenyl)-androstano[17,16-d][1,2,4]triazolo [1,5-a]pyrimidine (**3p**)*

White solid, yield 66%, mp 248–250 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (s, 1H, 2′-H), 7.77 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.46 (d, *J* = 8.1 Hz, 2H, Ar–H), 5.37 (d, *J* = 4.2 Hz, 1H, 6-H), 3.62–3.49 (m, 1H, 3α-H), 3.08–2.98 (m, 1H, Ar-$CH(CH_3)_2$), 1.34 (d, *J* = 6.8, 3H, Ar-$CH(CH_3)_2$), 1.33 (d, *J* = 6.8, 3H, Ar-$CH(CH_3)_2$), 1.21 (s, 3H, 18-H), 1.19–1.08 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.7, 156.0, 154.6, 152.2, 143.0, 141.4, 129.7, 126.8, 126.6, 122.4, 120.6, 71.5, 56.1, 50.3, 46.4, 42.2, 37.1, 36.8, 34.3, 33.0, 31.6, 31.2, 31.1, 29.3, 23.8, 23.7, 20.5, 19.5, 17.1. HRMS (ESI): *m*/*z* calcd for $C_{31}H_{39}N_4O$ $(M+H)^+$, 483.3124; found, 483.3122.

Table 2
Optimization of reaction conditions for preparation of **3a**.

Entry	Catalyst	Solvent	Yields[a] (%)
1	Lewis acids	EtOH	0[b]
2	NaOH	EtOH	15[b]
3	DBU	CH_3CN	24[b]
4	$NaOCH_3$	MeOH	28[b]
5	$NaOCH_3$	EtOH	31[b]
6	*t*-BuOK	EtOH	36[b] 41[c]
7	*t*-BuOK	*t*-BuOH	38[b] 44[c]
8	*t*-BuOK	*n*-BuOH	47[b] 58[c]

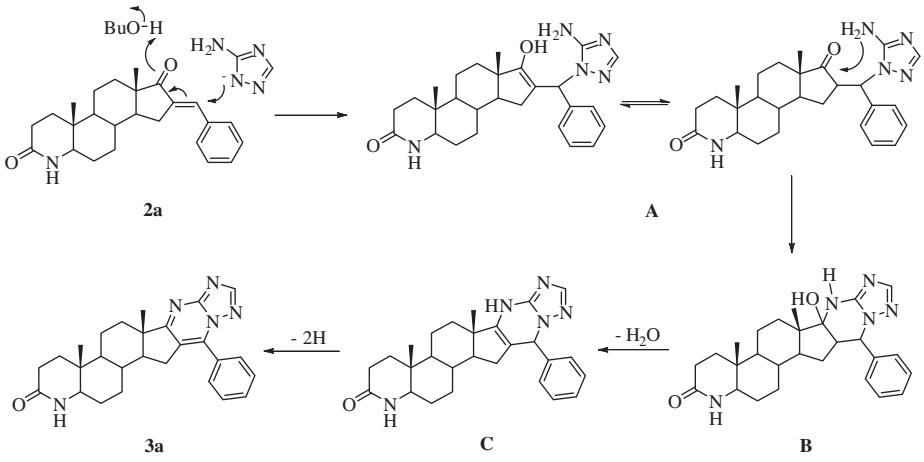
[a] Isolated yields.
[b] **2a** (1 mmol), 3-AT (2 mmol), catalyst (1 mmol), solvent (10 mL), reflux, 30 h.
[c] Under the same other conditions except that the amount of catalyst was increased to 2 mmol.

*2.3.17. 3β-Hydroxy-5-en-7′-(4-morpholinylphenyl)-androstano[17,16-d][1,2,4]triazolo[1,5-a] pyrimidine (**3q**)*

Yellow solid, yield 63%, mp > 300 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H, 2′-H), 7.82 (d, *J* = 8.9 Hz, 2H, Ar–H), 7.05 (d, *J* = 8.9 Hz, 2H, Ar–H), 5.38 (d, *J* = 4.9 Hz, 1H, 6-H), 3.97–3.83 (m, 4H, protons of morpholine), 3.61–3.49 (m, 1H, 3α-H), 3.42–3.26 (m, 4H, protons of morpholine), 1.21 (s, 3H, 18-H), 1.19–1.07 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.4, 156.1, 154.5, 152.6, 143.0, 141.4, 131.2, 121.5, 120.6, 119.2, 114.0, 76.7, 71.6, 66.7, 56.2, 50.3, 47.9, 46.3, 42.2, 37.1, 36.8, 33.0, 31.6, 31.2, 31.1, 29.6, 20.5, 19.5, 17.1. HRMS (ESI): *m*/*z* calcd for $C_{32}H_{40}N_5O_2$ $(M+H)^+$, 526.3182; found, 526.3185.

*2.3.18. 3β-Hydroxy-5-en-7′-(4-methylsulfonylphenyl)-androstano[17,16-d][1,2,4]triazolo [1,5-a]pyrimidine (**3r**)*

White solid, yield 70%, mp > 300 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H, 2′-H), 8.18 (d, *J* = 8.4 Hz, 2H, Ar–H), 8.04 (d, *J* = 8.4 Hz, 2H, Ar–H), 5.38 (d, *J* = 4.9 Hz, 1H, 6-H), 3.62–3.48 (m, 1H, 3α-H), 3.16 (s, 3H, Ar–SO_2CH_3), 1.22 (s, 3H, 18-H), 1.20–1.07 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.1, 155.8, 154.9, 142.6, 141.4, 140.5, 134.5, 130.7, 127.8, 123.5, 120.4, 71.5, 56.0, 50.3, 46.6, 44.4, 42.2, 37.1, 36.8, 33.0, 31.6, 31.2, 31.1, 29.0, 20.5, 19.5, 17.1. HRMS (ESI): *m*/*z* calcd for $C_{29}H_{35}N_4O_3S$ $(M+H)^+$, 519.2430; found, 519.2429.



Scheme 2. Proposed mechanism for the formation of steroidal triazolopyrimidine **3a**.

3. Results and discussion

The protocol for the synthesis of 7′-aryl-androstano[17,16-d][1,2,4]triazolo[1,5-a]pyrimidines (**3a**–**r**) is very simple and straightforward involving condensation reaction of 16-arylidene-17-ketosteroids (**2a**–**r**) with 3-AT (Scheme 1). The intermediates **2a**–**r** containing the aromatic α,β-unsaturated ketone moiety were prepared in excellent yields via Aldol condensation of 4-aza-androstane-3,17-dione (**1a**) or DHEA (**1b**) with aromatic aldehydes in ethanol catalyzed by KF/Al_2O_3 [28]. The results was shown in Table 1.

Initially, the reaction for the synthesis of target compounds was carried out using 16-arylidene-17-ketosteroid (**2a**) and 3-AT as model substrates with a molar ratio of 1:2 in presence of Lewis acids in ethanol. Unfortunately, the desired product was not observed. Presumably, the presence of a acid was not conducive to nucleophilic attack of aminotriazole, although it could activate the aromatic α,β-unsaturated ketone. Thus, we turned our attention to Lewis bases to promote the reaction. To our delight, the desired product 3-oxo-4-aza-7′-phenyl-5α-androstano[17,16-d][1,2,4]triazolo[1,5-a]pyrimidine (**3a**) could be isolated after refluxing a mixture of **2a** and 3-AT in ethanol in the presence of NaOH for 30 h, although the yield was low (15%, Table 2).

Structural elucidation of **3a** was determined from 1D and 2D NMR spectra. Compared to **2a**, the ^1H NMR spectra of **3a** exhibited the characteristic 2′-H signal (N–CH═N) as a sharp singlet at 8.38 ppm and absence of the olefinic proton (>C═CH–C_6H_5). In addition, the other five characteristic aromatic protons, 4-NH and 5α-H protons appeared at 7.56–7.81, 6.40 and 3.10 ppm, respectively. The ^{13}C, 2D NMR and mass spectra of **3a** were also in accordance with its proposed structure. Based on the DEPT-135 and 2D NMR spectra, the characteristic signal at 154.71 ppm was assigned to 2′-C. There were five quaternary carbon signals at 180.4, 172.3, 155.8, 142.9, and 122.3 ppm, respectively belonging to 3a′-C, 3-C, 7′-C, 5′-C and 6′-C. The ^{13}C NMR spectrum of **3a** also exhibited four signals at 131.1, 129.6 (2C), 129.1 and 128.7 (2C) ppm for six aromatic carbons and absence of the 17-C carbonyl carbon compared with **2a**.

After the structure of **3a** was identified, the determination of the optimum conditions regarding both the catalyst and solvent to perform the protocol was investigated. A variety of experimental conditions were examined using **2a** and 3-AT as model substrates (Table 2). As shown in Table 2, the optimized conditions for preparation of **3a** were **2a** (1.0 mmol), 3-AT (2.0 mmol) and *t*-BuOK (2.0 mmol) in *n*-BuOH (10 mL) at reflux for 30 h which resulted in the formation of **3a** in 58% yield. With the optimized reaction conditions in hand, we then applied the protocol to the condensation reaction of different 16-arylidene-17-ketosteroids (**2b**–**r**) with 3-AT, affording the desired steroidal[17,16-d][1,2,4]triazolo[1,5-a]pyrimidines (**3b**–**r**) in moderate to good yields (Table 1). All the new compounds were characterized by ^1H, ^{13}C NMR and mass spectra.

A proposed mechanism for the ring formation of these novel heterosteroids is shown in Scheme 2. Under basic conditions, aminotriazole exists as the anion and attacks the double bond of aromatic α,β-unsaturated ketone (**2a**) through aza-Michael addition reaction to afford the intermediate **A**. Subsequently, the amino group attacks the 17-ketone to form the heterocycle **B** via an intramolecular cyclisation reaction followed by elimination of H_2O to give the dihydrotriazolopyrimidine **C**. Finally, the 7′-phenyl-substituted steroidal[17,16-d][1,2,4]triazolo[1,5-a]pyrimidine (**3a**) is formed by automatic aromatization of intermediate C under the reaction conditions.

In conclusion, we have developed a facile approach for the synthesis of novel 7′-aryl-androstano[17,16-d][1,2,4]triazolo[1,5-a]pyrimidines (**3a**–**r**) starting from readily available 4-aza-androstane-3,17-dione (**1a**) or DHEA (**1b**). This provides a facile strategy to annelate steroid nucleus with widespread bioactive 1,2,4-triazolo[1,5-a]pyrimidine moiety, extending the categories of heterosteroids. The strategy can be applied to diverse 3- or 17-ketosteroids and the steroidal triazolopyrimidines may also allow further modifications on the steroid skeleton. Biological evaluation of these new compounds is in progress and will be reported elsewhere.

Acknowledgements

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