A Facile and General Synthesis of 2β-Aminosteroids

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Abstract: A facile and general synthesis of 2β-aminosteroids in high yields from 2,3α-epoxy-5α-androstan-17-one by regioselective aminolysis is developed using a zinc chloride/water catalytic system. The reaction is successful with both aliphatic and aromatic amines as well as with azoles.

Key words: amino alcohols, steroids, amines, epoxides, regioselectivity

Aminosteroids are pharmaceutically important compounds that display a broad spectrum of biological activity. A series of 2β-morpholinyl steroids has been shown to possess anesthetic activity and several examples have been selected for development as potential water-soluble steroidal intravenous anesthetics.[1] A steroid possessing a 2β-methylpiperazine moiety was reported to inhibit the proliferation of HL-60 or WEHI-3B cell lines and is a promising potential new drug for treatment of leukemia.[2] The rigid steroid skeleton, substituted with amino groups at different positions, provides an excellent means of studying structure–activity relationships within a series of neuromuscular blocking (NMB) agents.[3] These studies, carried out over the last forty years, have been very successful in producing highly active and selective drugs such as pancuronium, pipecuronium, vecuronium and rocuronium which are widely used in clinical practice. Another example, SZ-1677, which is related to rocuronium, is in the preclinical phase. These NMB agents have two acetylcholine-like (ACh-like) structural units located at the C-2 position of the A-ring and the C-16 position of the D-ring of the steroid. From many examples, it is clear that the D-ring ACh mimic is the NMB pharmacophore whereas the A-ring ACh moiety has muscarinic effects.[3c] The muscarinic action generally results in undesirable side-effects. Bronchospasm side-effects forced the withdrawal of rapacuronium shortly after its clinical introduction in the United States despite its rapid onset and short duration of action.[4] As demonstrated with rapacuronium, the important biological effects of the 2β-amino moiety on the steroid A-ring have encouraged medicinal chemists to synthesize and test a large number of novel molecules. Considering that the inclusion of different amino groups at the 2β-position of the steroid skeleton is an important synthetic strategy in drug discovery, we have prepared a number of 2β-aminosteroid derivatives.

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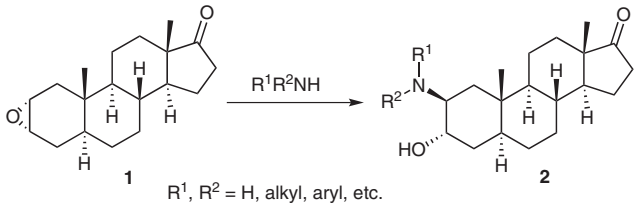
An attractive route for the synthesis of 2β-aminosteroids involves direct aminolysis of an epoxide. Ring-opening of epoxides is a practical and widely used method for the synthesis of β-amino alcohols.[5] The synthesis of optically pure epoxides from the corresponding alkenes is easy to accomplish.[6] We were therefore interested in the ring-opening of steroidal epoxide **1** with various amines in order to prepare axial 2β-aminosteroids of type **2** (Scheme 1). The most common method for the synthesis of compounds **2** involves treatment of steroidal epoxides with amines while heating in the presence of a catalytic amount of water.[2c,3a,7] 1,2-Ethanediol has been used as the solvent for the synthesis of 2-alkylamino-3-ol derivatives.[1d,8] Ionic liquids have been used both as solvents and catalysts for the ring-opening of 2,3-epoxy steroids with aromatic amines.[9] The aminolysis of 5,6α- and 5,10α-epoxy steroids in the presence of boron trifluoride diethyl etherate has been reported.[10] The ring-opening of hindered 2,3α-epoxy steroids with amines has been performed with a catalytic amount of gadolinium triflate [$Gd(OTf)_3$] in toluene, in a sealed tube, at high temperature under anhydrous conditions.[11] 4β-Aminocholestan-3-ol is obtained from the corresponding 3,4α-epoxide by reaction with ethanolic ammonia at 180 °C.[12] However, these methods do not overcome shortcomings such as poor yields, long reaction times, operational intricacy, toxic reagents, high pressure and expensive moisture/air-sensitive catalysts. Hence, the development of a more efficient and simple method for the regioselective aminolysis of steroidal epoxides would be of significant value. We report herein the use of the zinc chloride/water catalytic system to achieve this goal.

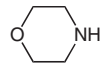
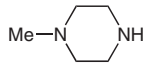
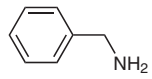
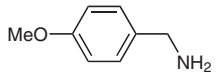
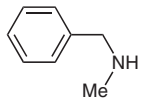
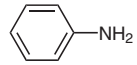
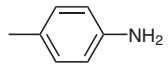
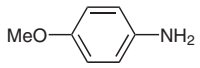
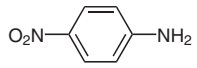
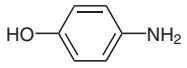
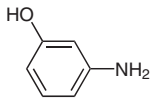
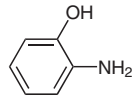
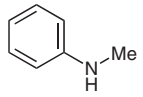


Scheme 1 Synthesis of 2β-aminosteroids

We have developed methods using Lewis acid catalysts to enhance the reactivity of epoxides towards nucleophilic cleavage with amines.[13] Extended heating in the presence of zinc chloride/water resulted in good reactivity and high regioselectivity in the ring-opening of epoxides with amines. Using these fairly mild conditions, we reacted 2,3α-epoxy-5α-androstan-17-one **1** with various aliphatic

and aromatic amines and azoles and obtained the corresponding 2β-amino-3α-ols **2** in high yields (Table 1). The structures and absolute configurations of **2** can be confirmed or conferred by consulting analyzing data of known compounds such as **2c**[14] and **2h**.[9] As anticipated, regioselective *trans*-diaxial epoxide opening led to the formation of 2β-amino-3α-ols **2** and no regioisomeric 3β-amino-2α-ols were detected.

Table 1 Synthesis of 2β-Aminosteroids **2** via Reaction of Epoxide **1** with Various Amines[a]

Entry	Amine	Time (h)	Product	Yield (%)[b]
1		24	**2a**	86
2		24	**2b**	89
3		24	**2c**	94
4		24	**2d**	91
5		24	**2e**	90
6		24	**2f**	84
7		24	**2g**	92
8		6	**2h**	87
9		6	**2i**	88
10		6	**2j**	81
11		6	**2k**	79
12		6	**2l**	83
13		6	**2m**	84
14		6	**2n**	80
15		12	**2o**	85
16		8	**2p**	93
17		8	**2q**	96

[a] Reaction conditions: **1** (10 mmol), amine (30 mmol), $ZnCl_2$ (10 mmol), H_2O (10 mL), 100 °C.
[b] Yield of pure isolated product characterized by ^1H NMR, ^{13}C NMR and MS spectroscopy.

Using water as the solvent, zinc-based catalysts proved to be more effective than other water-soluble Lewis acids such as tin tetrachloride (Table 2, entry 1) with respect to yield and reaction time. We observed that zinc perchlorate [$Zn(ClO_4)_2$] (Table 2, entry 2) was as potent as zinc chloride, however, the former is not recommended due to the potential risk of explosion. We attempted to prepare imidazolyl-substituted steroids under solvent-free conditions according to a previous report,[15] however, a very low yield (7%) of the product was observed (Table 2, entry 3). The same reaction was successful using the zinc chloride/water system affording an excellent 96% yield of the expected product (Table 1, entry 17). When zinc chloride or water were omitted, or the water was replaced with nonpolar or highly dipolar solvents (e.g. toluene or *N*,*N*-dimethylformamide), or the zinc chloride was replaced with hydrochloric acid or ammonium chloride, very low yields of the product resulted (Table 2, entries 4–9). Therefore, the zinc chloride/water system appears to be the best combination for the regioselective aminolysis of steroidal epoxides. In most cases, the products were extracted from the aqueous phase using dichloromethane.

Table 2 Aminolysis of Epoxide **1** under Various Conditions[a]

Entry	Amine	Catalyst	Solvent	Temp (°C)	Yield (%)[b]
1	morpholine	$SnCl_4$	H_2O	100	84
2	morpholine	$Zn(ClO_4)_2$	H_2O	100	93
3	imidazole	–	–	80	7
4	morpholine	–	H_2O	100	14
5	morpholine	$ZnCl_2$	–	110	6
6	morpholine	$ZnCl_2$	toluene	110	4
7	morpholine	$ZnCl_2$	DMF	110	9
8	morpholine	HCl	H_2O	100	17
9	morpholine	NH_4Cl	H_2O	100	15

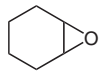
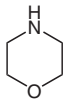
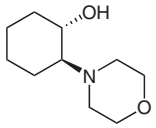
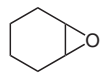
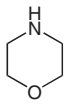
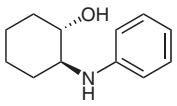
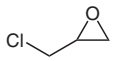
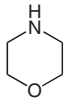
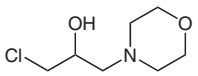
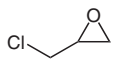
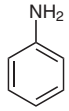
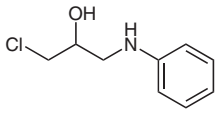
[a] Reaction conditions: **1** (5 mmol), amine (15 mmol), catalyst (5 mmol), solvent (5 mL), 24 h.
[b] Yield of isolated product.

The regioselectivity of the aminolysis of epoxide **1** and formation of the 2β-configured product should principally be influenced by the electronic and steric factors associated with the epoxide. In the area of Lewis acid catalyzed ring-opening of epoxides in water, Fringuelli et al.[16] have reported significant results and have pointed out that the regioselectivity and the reaction rate are influenced markedly by the pH of the reaction medium and by the presence of Lewis acids. Based on these results, we believe that the

Lewis acidity of zinc chloride plays a crucial role. The pH of our reactions was not regulated and they were performed at the pH obtained simply on mixing the reagents. On the other hand, we believe that in water the Lewis acids generate high concentrations of aqua ions which coordinate the oxygen atom of the epoxide ring and/or the nitrogen atom of the amine leading to significant acceleration of nucleophilic attack. While one or more of the reactants appeared to dissolve poorly in water, emulsions were formed upon addition of zinc chloride with stirring and heating. It is likely these heterogeneous conditions facilitated the reaction progress leading to short reaction times. Interestingly, the reaction times with aromatic amines (Table 1, entries 8–17) were shorter than those with aliphatic amines (Table 1, entries 1–7).

The applicability of the zinc chloride/water catalytic system was evaluated for the aminolysis of several simple epoxides with various amines (Table 3). The excellent yields obtained of the corresponding amino alcohols demonstrates the efficiency of this catalytic system. It is reasonable to assume that this mild Lewis acid catalyzed aminolysis in water might represent an economical and practical method for the synthesis of a wide range of β-amino alcohols in addition to sterically hindered β-aminosteroids.

Table 3 Aminolysis of Simple Epoxides under Zinc Chloride/Water Catalysis[a]

Entry	Epoxide	Amine	Product[b]	Yield (%)[c]
1				94
2				93
3				96
4				91

[a] Reaction conditions: epoxide (5 mmol), amine (15 mmol), $ZnCl_2$ (10 mmol), H_2O (5 mL), 8 h, 60 °C.
[b] Structure determined by GCMS and NMR spectroscopy.
[c] Isolated yield.

In summary, we have reported a general and efficient method for the regioselective preparation of 2β-aminosteroids. The method offers advantages of operational simplicity and high yields of products. Further studies on the application of the present methodology to the synthesis of biologically active compounds are in progress.

2,3α-Epoxy-5α-androstan-17-one **1** was prepared according to the literature.[17] The amines and azoles were obtained from commercial suppliers and used without further purification. Melting points were measured with an XT-4 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were obtained using a Bruker DPX400 apparatus and $CDCl_3$ or DMSO-d_6 as solvent with TMS as the internal standard. The ^1H NMR data presented are for key protons in the steroid structures. Mass spectra were recorded on a Finnigan-LC Qadvantage spectrometer (ESI). Elemental analysis (C, H, and N) data was obtained using a VarioEL III elemental analyzer. Column chromatography was performed using EM silica gel 60 (230–400 mesh). TLC was performed on glass plates precoated with silica gel (5–40 μm). Visualization was accomplished by spraying the TLC plates with a solution of H_2SO_4–EtOH (1:10, v/v) and heating in an oven at 105 °C for 3 minutes (until the color had developed). Petroleum ether (PE) refers to the fraction boiling in the 60–90 °C range.

3α-Hydroxy-2β-aminosteroids; General Procedure

To a mixture of epoxide **1** (10 mmol) and amine (30 mmol), a solution of $ZnCl_2$ (10 mmol) in H_2O (10 mL) was added. The mixture was heated at 100 °C with vigorous magnetic stirring and the extent of reaction was monitored by TLC. After completion of the reaction, the mixture was concentrated under reduced pressure to give a solid residue. Next, H_2O (15 mL) was added and the organic materials were extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried over anhyd Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (PE–EtOAc–Et_3N, or CH_2Cl_2–MeOH–Et_3N).

3α-Hydroxy-2β-(1-pyrrolidinyl)-5α-androstan-17-one (2a)

Solid; mp 146–147 °C (Lit.[7a] 145–148 °C); R_f = 0.33 (PE–EtOAc, 1:2).

^1H NMR (400 MHz, $CDCl_3$): δ = 0.85 (s, 3 H, H-18), 1.08 (s, 3 H, H-19), 2.35 (m, 1 H, H-2), 2.53 (m, 4 H, NCH_2), 4.05 (m, 1 H, H-3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.0, 12.9, 19.3, 20.8, 22.5, 26.7, 29.9, 30.6, 31.4, 33.6, 34.0, 34.9, 35.5, 38.3, 46.9, 50.6, 50.8, 54.3, 65.2, 66.9, 220.7.

MS (ESI): *m/z* (%) = 360 (100) [M + H^+].

Anal. Calcd for $C_{23}H_{37}NO_2$: C, 76.83; H, 10.37; N, 3.90. Found: C, 77.11; H, 10.25; N, 3.87.

3α-Hydroxy-2β-(1-piperidinyl)-5α-androstan-17-one (2b)

Solid; mp 256–257 °C (Lit.[7a] 255–257 °C); R_f = 0.20 (PE–EtOAc, 1:2).

^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (s, 3 H, H-18), 0.89 (s, 3 H, H-19), 2.34–2.59 (m, 5 H, NCH_2, H-2), 3.79 (m, 1 H, H-3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1, 16.8, 19.9, 21.0, 24.2, 26.1, 27.5, 29.7, 30.9, 31.8, 34.2, 34.4, 35.05, 35.12, 37.6, 47.2, 48.7, 50.6, 55.5, 62.6, 64.3, 220.6.

MS (ESI): *m/z* (%) = 374 (100) [M + H^+].

Anal. Calcd for $C_{24}H_{39}NO_2$: C, 77.16; H, 10.52; N, 3.75. Found: C, 77.52; H, 10.33; N, 3.71.

3α-Hydroxy-2β-(4-morpholinyl)-5α-androstan-17-one (2c)

Solid; mp 171–173 °C (Lit.[7a] 170–172 °C); R_f = 0.32 (PE–EtOAc, 2:1).

^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (s, 3 H, H-18), 0.91 (s, 3 H, H-19), 2.42–2.65 (m, 4 H, NCH_2), 2.56 (dd, *J* = 16.3, 8.6 Hz, 1 H, H-2), 3.69 (m, 4 H, OCH_2), 3.90 (m, 1 H, H-3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 16.3, 20.5, 21.7, 27.9, 30.5, 31.6, 32.5, 34.1, 34.9, 35.8, 35.9, 38.6, 47.8, 49.2, 51.3, 55.8, 63.8, 65.0, 67.3, 221.1.

MS (ESI): *m/z* (%) = 376 (100) [M + H$^+$].

Anal. Calcd for $C_{23}H_{37}NO_3$: C, 73.56; H, 9.93; N, 3.73. Found: C, 73.68; H, 9.86; N, 3.67.

3α-Hydroxy-2β-(4-methyl-1-piperazinyl)-5α-androstan-17-one (2d)

Solid; mp 180–181 °C (Lit.[7b] 180–181 °C); R_f = 0.41 (CH_2Cl_2–MeOH, 8:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (s, 3 H, H-18), 0.84 (s, 3 H, H-19), 2.26 (s, 3 H, NCH_3), 2.40–2.67 (m, 9 H, NCH_2, H-2), 3.85 (m, 1 H, H-3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 15.2, 18.8, 20.0, 26.3, 28.8, 29.9, 30.9, 32.7, 33.3, 34.1, 34.2, 36.8, 44.3, 46.2, 49.6, 53.9, 54.3, 62.0, 62.7, 219.5.

MS (ESI): *m/z* (%) = 389 (100) [M + H$^+$].

Anal. Calcd for $C_{24}H_{40}N_2O_2$: C, 74.18; H, 10.38; N, 7.21. Found: C, 74.34; H, 10.31; N, 7.17.

3α-Hydroxy-2β-[(phenylmethyl)amino]-5α-androstan-17-one (2e)

Solid; mp 139–140 °C; R_f = 0.50 (PE–EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (s, 3 H, H-18), 1.03 (s, 3 H, H-19), 2.83 (br s, 1 H, H-2), 3.71–3.85 (m, 2 H, NCH_2), 3.82 (br s, 1 H, H-3), 7.23–7.31 (m, 5 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1, 14.1, 18.6, 20.0, 26.2, 29.1, 29.9, 30.8, 33.0, 34.1, 34.5, 37.3, 37.6, 46.2, 49.7, 50.7, 53.8, 57.6, 67.6, 125.2, 126.3, 126.7, 139.0, 219.8.

MS (ESI): *m/z* (%) = 396 (100) [M + H$^+$].

Anal. Calcd for $C_{26}H_{37}NO_2$: C, 78.94; H, 9.43; N, 3.54. Found: C, 78.81; H, 9.52; N, 3.57.

3α-Hydroxy-2β-{[(4-methoxyphenyl)methyl]amino}-5α-androstan-17-one (2f)

Solid; mp 154–158 °C; R_f = 0.45 (PE–EtOAc–Et_3N, 66:33:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (s, 3 H, H-18), 1.02 (s, 3 H, H-19), 2.81 (m, 1 H, H-2), 3.65–3.81 (m, 6 H, NCH_2, OCH_3, H-3), 6.48 (d, *J* = 8.4 Hz, 2 H, H-3′,5′), 7.22 (d, *J* = 8.4 Hz, 2 H, H-2′,6′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 14.6, 20.2, 21.7, 27.9, 30.7, 31.6, 32.5, 34.6, 35.8, 36.2, 38.8, 39.2, 47.9, 51.4, 51.7, 55.2, 55.4, 59.1, 69.1, 113.8, 129.2, 132.6, 158.6, 221.6.

MS (ESI): *m/z* (%) = 426 (100) [M + H$^+$].

Anal. Calcd for $C_{27}H_{39}NO_3$: C, 76.20; H, 9.24; N, 3.29. Found: C, 75.98; H, 9.37; N, 3.31.

3α-Hydroxy-2β-[methyl(phenylmethyl)amino]-5α-androstan-17-one (2g)

Solid; mp 153–154 °C; R_f = 0.54 (PE–EtOAc, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (s, 3 H, H-18), 0.90 (s, 3 H, H-19), 2.13 (s, 3 H, NCH_3), 2.82 (m, 1 H, H-2), 3.49–3.65 (m, 2 H, NCH_2), 3.91 (m, 1 H, H-3), 7.30 (m, 5 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 17.4, 20.6, 21.7, 28.2, 30.4, 31.7, 32.3, 34.8, 35.1, 35.81, 35.84, 38.5, 47.9, 51.3, 56.2, 58.3, 63.7, 64.2, 127.1, 128.4, 128.7, 139.3, 221.3.

MS (ESI): *m/z* (%) = 410 (100) [M + H$^+$].

Anal. Calcd for $C_{27}H_{39}NO_2$: C, 79.17; H, 9.60; N, 3.42. Found: C, 78.93; H, 9.67; N, 3.56.

3α-Hydroxy-2β-(phenylamino)-5α-androstan-17-one (2h)

Solid; mp 220–221 °C; R_f = 0.42 (PE–EtOAc, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (s, 3 H, H-18), 1.02 (s, 3 H, H-19), 3.57 (br s, 1 H, H-2), 4.00 (br s, 1 H, H-3), 6.58 (d, *J* = 8.3 Hz, 2 H, H-2′,6′), 6.68 (t, *J* = 8.3 Hz, 1 H, H-4′), 7.16 (t, *J* = 8.3 Hz, 2 H, H-3′,5′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 15.1, 20.2, 21.7, 27.8, 30.7, 31.5, 32.1, 34.6, 35.8, 36.1, 38.3, 38.8, 47.9, 51.3, 54.4, 55.4, 68.3, 112.8, 117.4, 129.4, 147.1, 221.3.

MS (ESI): *m/z* (%) = 382 (100) [M + H$^+$].

Anal. Calcd for $C_{25}H_{35}NO_2$: C, 78.70; H, 9.25; N, 3.67. Found: C, 78.58; H, 9.29; N, 3.71.

3α-Hydroxy-2β-[(4-methylphenyl)amino]-5α-androstan-17-one (2i)

Solid; mp 238–240 °C; R_f = 0.20 (PE–EtOAc, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (s, 3 H, H-18), 1.01 (s, 3 H, H-19), 2.23 (s, 3 H, CH_3-4′), 3.53 (br s, 1 H, H-2), 3.98 (br s, 1 H, H-3), 6.50 (d, *J* = 8.3 Hz, 2 H, H-2′, 6′), 6.97 (d, *J* = 8.3 Hz, 2 H, H-3′, 5′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 15.1, 20.2, 20.3, 21.7, 27.8, 30.7, 31.5, 32.1, 34.6, 35.8, 36.1, 38.4, 38.9, 47.9, 51.3, 54.7, 55.4, 68.4, 113.0, 126.6, 129.9, 144.9, 221.3.

MS (ESI): *m/z* (%) = 396 (100) [M + H$^+$].

Anal. Calcd for $C_{26}H_{37}NO_2$: C, 78.94; H, 9.43; N, 3.54. Found: C, 79.13; H, 9.35; N, 3.48.

3α-Hydroxy-2β-[(4-methoxyphenyl)amino]-5α-androstan-17-one (2j)

Solid; mp 197–198 °C; R_f = 0.11 (PE–EtOAc, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (s, 3 H, H-18), 1.01 (s, 3 H, H-19), 3.49 (br s, 1 H, H-2), 3.74 (s, 3 H, OCH_3), 3.97 (m, 1 H, H-3), 6.55 (d, *J* = 8.8 Hz, 2 H, H-2′, 6′), 6.77 (d, *J* = 8.8 Hz, 2 H, H-3′, 5′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 14.7, 19.7, 21.3, 27.4, 30.2, 31.1, 31.7, 34.2, 35.4, 35.7, 38.1, 38.4, 47.4, 50.9, 54.9, 55.0, 55.4, 68.0, 113.8, 114.6, 141.0, 151.7, 220.8.

MS (ESI): *m/z* (%) = 412 (100) [M + H$^+$].

Anal. Calcd for $C_{26}H_{37}NO_3$: C, 75.87; H, 9.06; N, 3.40. Found: C, 75.68; H, 9.09; N, 3.43.

3α-Hydroxy-2β-[(4-nitrophenyl)amino]-5α-androstan-17-one (2k)

Solid; mp 246–247 °C; R_f = 0.35 (PE–EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (s, 3 H, H-18), 1.01 (s, 3 H, H-19), 3.70 (br s, 1 H, H-2), 4.00 (m, 1 H, H-3), 6.52 (d, *J* = 9.2 Hz, 2 H, H-2′, 6′), 8.07 (d, *J* = 9.2 Hz, 2 H, H-3′, 5′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 15.1, 20.2, 21.8, 27.8, 30.6, 31.6, 32.2, 34.6, 35.9, 36.1, 37.5, 38.6, 47.9, 51.3, 54.0, 55.3, 67.7, 111.3, 126.6, 138.1, 152.2, 221.3.

MS (ESI): *m/z* (%) = 427 (100) [M + H$^+$].

Anal. Calcd for $C_{25}H_{34}N_2O_4$: C, 70.39; H, 8.03; N, 6.57. Found: C, 70.18; H, 7.92; N, 6.51.

3α-Hydroxy-2β-[(4-hydroxyphenyl)amino]-5α-androstan-17-one (2l)

Solid; mp 241–243 °C; R_f = 0.42 (PE–EtOAc, 1:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.74 (s, 3 H, H-18), 0.90 (s, 3 H, H-19), 3.70 (br s, 1 H, H-2), 4.63 (m, 1 H, H-3), 6.41–6.54 (m, 4 H, ArH), 8.36 (s, 1 H, OH-4′).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.4, 13.9, 19.7, 21.3, 27.6, 30.5, 31.3, 31.6, 33.9, 35.2, 35.5, 36.0, 38.4, 47.1, 50.5, 54.4, 55.0, 67.2, 113.6, 115.6, 140.7, 148.0, 219.8.

MS (ESI): *m/z* (%) = 398 (100) [M + H$^+$].

Anal. Calcd for $C_{25}H_{35}NO_3$: C, 75.53; H, 8.87; N, 3.52. Found: C, 75.81; H, 8.64; N, 3.47.

3α-Hydroxy-2β-[(3-hydroxyphenyl)amino]-5α-androstan-17-one (2m)

Solid; mp 238–239 °C; R_f = 0.33 (PE–EtOAc, 1:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.73 (s, 3 H, H-18), 0.87 (s, 3 H, H-19), 3.72 (br s, 1 H, H-2), 4.69 (m, 1 H, H-3), 5.93 (d, *J* = 7.9 Hz, 2 H, H-6′), 5.99 (s, 1 H, H-2′), 6.02 (d, *J* = 7.9 Hz, 1 H, H-4′), 6.81 (t, *J* = 7.9 Hz, 1 H, H-5′), 8.85 (s, 1 H, OH-3′).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.4, 13.9, 19.8, 21.3, 27.7, 30.5, 31.3, 31.6, 33.9, 35.2, 35.5, 38.4, 47.1, 50.5, 53.4, 54.9, 67.4, 99.0, 102.8, 103.9, 129.3, 149.0, 158.1, 219.8.

MS (ESI): *m/z* (%) = 398 (100) [M + H$^+$].

Anal. Calcd for $C_{25}H_{35}NO_3$: C, 75.53; H, 8.87; N, 3.52. Found: C, 75.74; H, 8.80; N, 3.51.

3α-Hydroxy-2β-[(2-hydroxyphenyl)amino]-5α-androstan-17-one (2n)

Solid; mp 172–173 °C; R_f = 0.34 (PE–EtOAc, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (s, 3 H, H-18), 1.05 (s, 3 H, H-19), 3.55 (br s, 1 H, H-2), 4.02 (br s, 1 H, H-3), 6.57–6.84 (m, 4 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 14.9, 20.2, 21.7, 27.8, 30.7, 31.5, 32.1, 34.6, 35.9, 36.0, 38.6, 38.9, 48.0, 51.3, 54.5, 55.4, 68.4, 111.5, 114.2, 117.3, 121.7, 136.5, 143.8, 222.1.

MS (ESI): *m/z* (%) = 398 (100) [M + H$^+$].

Anal. Calcd for $C_{25}H_{35}NO_3$: C, 75.53; H, 8.87; N, 3.52. Found: C, 75.41; H, 8.95; N, 3.56.

3α-Hydroxy-2β-[methyl(phenyl)amino]-5α-androstan-17-one (2o)

Solid; mp 157–158 °C; R_f = 0.60 (PE–EtOAc, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (s, 3 H, H-18), 0.91 (s, 3 H, H-19), 2.74 (s, 3 H, NCH_3), 3.91 (dd, *J* = 19.0, 10.2 Hz, 1 H, H-2), 4.10 (m, 1 H, H-3), 6.80 (t, *J* = 8.2 Hz, 1 H, H-4′), 6.91 (d, *J* = 8.2 Hz, 2 H, H-2′,6′), 7.24 (t, *J* = 8.2 Hz, 2 H, H-3′,5′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.5, 16.2, 19.2, 20.4, 26.8, 29.0, 29.4, 30.2, 33.7, 33.8, 34.4, 34.6, 34.9, 37.5, 46.5, 49.9, 54.6, 59.8, 63.8, 113.7, 117.0, 127.8, 149.9, 219.7.

MS (ESI): *m/z* (%) = 396 (100) [M + H$^+$].

Anal. Calcd for $C_{26}H_{37}NO_2$: C, 78.94; H, 9.43; N, 3.54. Found: C, 78.61; H, 9.57; N, 3.49.

3α-Hydroxy-2β-(1*H*-pyrazol-1-yl)-5α-androstan-17-one (2p)

Solid; mp 212–213 °C; R_f = 0.19 (PE–EtOAc–Et_3N, 66:33:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.69 (s, 3 H, H-18), 0.84 (s, 3 H, H-19), 4.32 (m, 1 H, H-2), 4.62 (m, 1 H, H-3), 6.26 (m, 1 H, H-4′), 7.45 (d, *J* = 2.1 Hz, 1 H, H-5′), 7.52 (d, *J* = 1.4 Hz, 1 H, H-3′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 14.8, 20.6, 21.8, 27.8, 30.6, 31.6, 34.2, 34.8, 35.88, 35.94, 39.3, 41.6, 47.9, 51.4, 55.5, 62.2, 67.4, 105.4, 128.9, 139.0, 221.3.

MS (ESI): *m/z* (%) = 357 (100) [M + H$^+$].

Anal. Calcd for $C_{22}H_{32}N_2O_2$: C, 74.12; H, 9.05; N, 7.86. Found: C, 74.36; H, 8.98; N, 7.75.

3α-Hydroxy-2β-(1*H*-imidazol-1-yl)-5α-androstan-17-one (2q)

Solid; mp 224–226 °C; R_f = 0.44 (EtOAc–MeOH–Et_3N, 93:6:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.70 (s, 3 H, H-18), 0.84 (s, 3 H, H-19), 4.17 (m, 1 H, H-2), 4.31 (m, 1 H, H-3), 6.96 (s, 2 H, H-4′, 5′), 7.44 (s, 1 H, H-2′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 14.9, 20.5, 21.7, 27.7, 30.4, 31.5, 34.4, 34.7, 35.8, 36.0, 39.1, 41.9, 47.8, 51.2, 55.3, 58.7, 67.2, 117.4, 128.9, 136.1, 221.1.

MS (ESI): *m/z* (%) = 357 (100) [M + H$^+$].

Anal. Calcd for $C_{22}H_{32}N_2O_2$: C, 74.12; H, 9.05; N, 7.86. Found: C, 73.91; H, 9.11; N, 7.82.

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