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SYNTHESIS OF 17β-*N*-PHENYLPYRAZOLYL STEROIDAL DERIVATIVES AND THEIR INHIBITORY EFFECT ON CELL PROLIFERATION

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Abstract – The synthesis of several 17β-*N*-phenylpyrazolyl steroid derivatives derived from progesterone are described. The Claisen condensations of $\Delta^{1,4}$-pregnadien-3,20-dione (**1**) and 4-chloro-$\Delta^{1,4}$-pregnadiene-3,20-dione (**2**) with dimethyl oxalate afforded 21-methoxalylpregna-1,4-diene-3,20-dione (**3**) and 4-chloro-21-methoxalylpregna-1,4-diene-3,20-dione (**4**), respectively. Furthermore, the reactions of **3** and **4** with substituted phenylhydrazines yielded 5'-pyrazolyl derivatives as main products, and the 5'-pyrazolyl isomers **6a-k** (and **7a-k**) were isolated from the crude reaction mixture (3'-pyrazolyl regioisomers as minor products). The newly synthetized compounds were evaluated *in vitro* by means of SRB assays for antiproliferative activity against HepG-2 (hepatoma), HeLa (cervix adenocarcinoma) and MCF-7 (breast adenocarcinoma). The preliminary results showed that compounds **6d**, **6i** and **7d** possessed moderate antiproliferative activities.

INTRODUCTION

Steroidal derivatives which D-ring is modified with *exo*-heterocycles exhibit numerous forms of biological activity and are attractive for medicine.[1-4] Steroids as well as their derivatives have the potential to be developed as drugs for the treatment of a large number of diseases including cardiovascular,[5] autoimmune diseases,[6] prostate cancer,[7] etc. Inspired by Abiraterone (17-(3'-pyridyl)androsta-5,16-dien-3β-ol) which is successfully applied in the treatment of prostatic

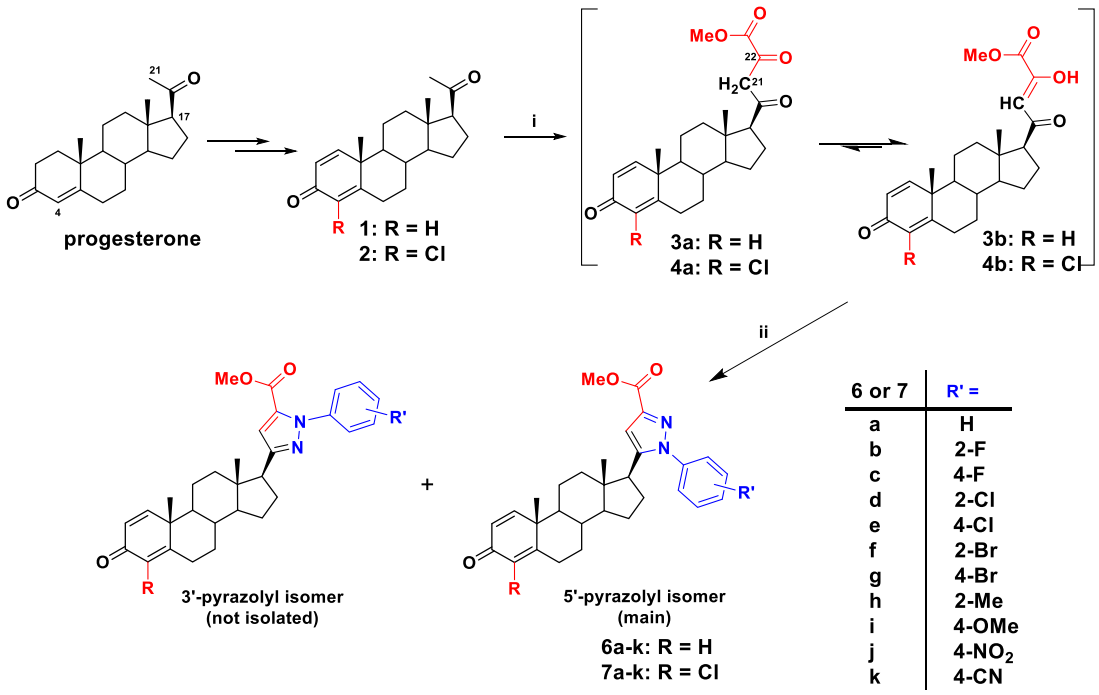
carcinoma,[8] a large number of steroid derivatives containing five- or six-membered 17β-*exo*-heterocycles, such as pyrazolinyl,[9,10] triazolyl[11,12] and pyrazolyl[13,14] have been found to exert potential anticancer activity.

As a relatively inexpensive pregnane and a traditional medicine, progesterone has been used to synthesize some new derivatives with biological activity.[15-18] We have recently described the synthesis of *5′*-phenyl (or substituted phenyl) epimeric C-17 pyrazolinyl derivatives of progesterone. The unseparated epimeric mixtures were tested for their antiproliferative properties on several human cancer cell lines (NCI-H460, HeLa, HepG2). Some of the compounds exerted significant cytotoxic activities, which varied substantially on change of the position and the nature of a substituent on the C-*5′* phenyl ring.[19] Taking inspiration from the number of reported biological activities associated with structurally related analogs, and as a part of our commitment to search for novel potential anticancer agents related to steroidal derivatives,[20,21] we report here the synthesis of a new kind of 17β-*exo*-heterocyclic derivatives of progesterone: a Δ^1-double bond or a chlorine atom at C-4 as well as a Δ^1-double bond, and a methoxycarbonyl group as well as a substituted phenyl attached to the pyrazole unit incorporating with C-17 of D-ring. The introduction of the methoxycarbonyl group was intended to significantly influence the afforded ratio of 3'- and 5'-pyrazolyl regioisomers in the cyclization process. We additionally investigated the antiproliferative effects of the new synthesized steroidal derivatives. This is the first report on antiproliferative activities of this group of steroidal derivatives bearing a phenylpyrazole scaffold.

RESULTS AND DISCUSSION

The synthetic procedure of D-ring substituted pyrazolyl steroidal derivatives **6a-k** and **7a-k** is shown in **Scheme 1**, which commenced with progesterone as starting material. The key intermediates, $\Delta^{1,4}$-pregnadiene-3, 20-dione **1** and 4-chloro-$\Delta^{1,4}$-pregnadiene-3,20-dione **2** were synthesized according to our procedure.[17] The Claisen condensation of **1** (or **2**) with dimethyl oxalate in dichloromethane afforded 21-methoxalyl derivatives **3** (or **4**) in high yields (85% for **3**, 82% for **4**). Theoretically, **3** (or **4**) could exist as any of the tautomeric forms **3a** (**4a**) or **3b** (**4b**) or as an equilibrium mixture of them. In the NMR spectrum of **3** (or **4**) in deuteriochloroform, there was no observed signal corresponding to the aldehydic proton[22] and the 21-H signal was located at 6.30 ppm, demonstrating that the α-ketocarboxylic acid esters **3b** and **4b** were the unique forms present in this solvent, respectively.

With **3** and **4** in hand, we carried out the pyrazole cyclization reaction between nonsymmetrical β-ketoaldehydes **3** (or **4**) and monosubstituted hydrazines, which lead to the formation of a mixture of pyrazole isomers, even when one of them is present in a very small amount and the process can be considered regioselective.[23] In this manner, the reaction of **3** (or **4**) with phenylhydrazine **5a** in buffered



Scheme 1. Synthesis of steroidal D-ring substituted pyrazolyl derivatives **6a-k** and **7a-k**. Reagents and conditions: (i) dimethyl oxalate, NaOMe, CH_2Cl_2; (ii) phenylhydrazine or substituted phenylhydrazine **5a-k**, acetic acid and KOAc, rt.

acetic acid afforded two regioisomers: one is 5'-pyrazolyl isomer and the other is 3'-pyrazolyl isomer, and the integrals of ^{1}H NMR show the isomer product ratio (5'-pyrazolyl: 3'-pyrazolyl) is nearly 9:1. According to the result of reaction, 5'-pyrazolyl isomer **6a** (or **7a)** was the main product in good yield. Furtherore, the similiar main products **6b-k** (or **7b-k)** were also observed in another reactions of **3** (or **4**) with various substituted phenylhydrazine (**5b-k**) in nearly 9:1 ratio. A possible explanation for the predominance of the 5'-pyrazolyl isomer in the product mixtures is the electronic effect of the methoxycarbonyl group on the side-chain of **3** (or **4**), as its electron-withdrawing properties improve the electrophilic character of the C-22 carbonyl group. Nucleophilic attack of the phenylhydrazine NH_2 group on C-22 is therefore more probable, mainly resulting in 5'-pyrazolyl isomers.

Due to the very low yields of the 3'-pyrazolyl isomers, we mainly isolated the 5'-pyrazolyl isomers from the crude reaction mixture. The structures of the 5'-pyrazolyl isomers (**6a-k** and **7a-k**) were proved by NMR techniques. The singlet of the methoxycarbonyl methyl group is at 3.92 ppm in the spectra and the signals of the phenyl group and 4'-H of pyrazole are present in the aromatic region. In the ^{13}C NMR spectra, the corresponding methoxycarbonyl carbonyl group is present at 163 ppm, the position of the heteroaromatic C-4' signal which appears between 106 to 108 ppm. These spectra were similar to the peaks in the case of the previously described *N*-phenyl 5-pyrazoles.[24]

The *in vitro* antiproliferative activity of this novel series of compounds against three human cancer cell

lines, HepG-2 (hepatoma), HeLa (cervix adenocarcinoma) and MCF-7 (breast adenocarcinoma) were evaluated and etoposide (VP-16) was used as a positive control. **Table 1** showed the inhibitory effects on cell proliferation. As a general finding, these compounds were proved to exert only weak or modest actions on cell growth: the inhibition values at 10 μM were practically always less than 20%, the two exceptions being the effect of **6g** and **6i** on HepG-2 cells. At the concentrations of 50 μM, most of the tested compounds showed some inhibition activity, which were inferior to the positive control etoposide. Compounds **6c**, **6h**, **6i** and **7h** displayed a moderate cytotoxic activity (all inhibition rate over 50%) to HepG-2 cells, compounds **6d**, **6h**, **6i**, **7a**, **7d** and **7h** exhibited the same activity to HeLa cells (highest inhibition rate is 68%), however, only **6c** and **6i** were found to have the similar inhibition activity (58% and 52%, respectively) to MCF-7 cells.

Table 1. *In vitro* inhibitory effects of all compounds against **HepG-2, HeLa** and **MCF-7** cells at 10 μM and 50 μM

Entry	Inhibitory effects (%)[a]					
	HepG-2		HeLa		MCF-7	
	10 μM	50 μM	10 μM	50 μM	10 μM	50 μM
6a	N.A.[b]	32	N.A.[b]	N.A.[b]	N.A.[b]	N.A.[b]
6b	N.A.[b]	40	N.A.[b]	49	N.A.[b]	36
6c	N.A.[b]	54	N.A.[b]	47	N.A.[b]	58
6d	N.A.[b]	40	N.A.[b]	68	N.A.[b]	48
6e	N.A.[b]	44	N.A.[b]	20	N.A.[b]	35
6f	N.A.[b]	51	N.A.[b]	35	N.A.[b]	31
6g	24	47	N.A.[b]	N.A.[b]	N.A.[b]	N.A.[b]
6h	N.A.[b]	59	N.A.[b]	55	N.A.[b]	33
6i	22	61	N.A.[b]	51	N.A.[b]	52
6j	N.A.[b]	N.A.[b]	N.A.[b]	N.A.[b]	N.A.[b]	N.A.[b]
6k	N.A.[b]	38	N.A.[b]	28	N.A.[b]	30
7a	N.A.[b]	46	N.A.[b]	55	N.A.[b]	40
7b	N.A.[b]	45	N.A.[b]	31	N.A.[b]	N.A.[b]
7c	N.A.[b]	49	N.A.[b]	40	N.A.[b]	39
7d	N.A.[b]	44	N.A.[b]	61	N.A.[b]	30
7e	N.A.[b]	34	N.A.[b]	N.A.[b]	N.A.[b]	23
7f	N.A.[b]	48	N.A.[b]	32	N.A.[b]	20
7g	N.A.[b]	45	N.A.[b]	N.A.[b]	N.A.[b]	21
7h	N.A.[b]	51	N.A.[b]	56	N.A.[b]	N.A.[b]
7i	N.A.[b]	41	N.A.[b]	46	N.A.[b]	27
7j	N.A.[b]	N.A.[b]	N.A.[b]	24	N.A.[b]	25
7k	N.A.[b]	22	N.A.[b]	42	N.A.[b]	21
etoposide	92	-	86	-	90	-

[a] All data are the average of four determinations, which were reproducible with deviation less than ± 10%. [b] N.A. means inhibition values <20%.

Although the cytotoxicity response was sensitive to a variety of functional groups and positions on the benzene ring, there is no obviously trend to match our previous results that some steroidal derivatives of progesterone which introduced the unsaturated double bond at C1-C2 and then introduced a chlorine atom into C-4 position could significantly improve cytotoxicity against certain cancer cell lines.[19,20] It was observed that compounds **6d**, **6i** and **7d** exhibit moderate activities (all inhibition rate over 60% to different cells) and were the most potent of all the screened compounds.

EXPERIMENTAL

General methods

The melting points of the products were determined on an X-4 apparatus (Beijing Tech Instrument Co., Beijing, P. R. China) and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance spectrometer (Unity plus 500 MHz) (Bruker Bios pin, Rheinstetten, Germany) with tetramethylsilane (TMS) as internal standard. Chemical shift values (δ) were given in parts per million (ppm). Thin-layer chromatography (TLC) was performed on silica gel GF_{254} (Qingdao Marine Chemical Ltd., P. R. China). Column chromatography (CC) was performed over silica gel (200-300 mesh, Qingdao Marine Chemical Ltd.), High resolution electrospray ionization mass spectrometry (HRESIMS) data were recorded on LCMS-IT-TOF (Shimadzu, Kyoto, Japan). Commercial solvents and reagents were of reagent grade.

Preparation of **3** and **4**

Compound **1** (or **2**) (5 mmol) was dissolved in 30 mL CH_2Cl_2, and 1.18 g (10 mmol) dimethyl oxalate and 1.35 g (25 mmol) NaOMe were then added. The mixture was stirred at room temperature for 4 h. The resulting suspension was added 15 mL MeOH and diluted with 30 mL hydrochloric acid solution (1 mol/L). The organic phase was washed with water, dried with Na_2SO_4 and evaporated in vacuum. The residue was crystallized from acetone to afford **3** (or **4**).

21-Methoxalylpregna-1,4-diene-3,20-dione (3): Yellow solid (1.69 g, 85%). Mp 143-145 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.71 (3H, s, 18-CH_3), 1.23 (3H, s, 19-CH_3), 3.89 (3H, s, $COOCH_3$), 6.07 (1H, s, 4-H), 6.24 (1H, dd, *J* = 1.5, 10.0 Hz, 2-H), 6.30 (1H, s, 21-H), 7.04 (1H, d, *J* = 10.0 Hz, 1-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 13.55, 18.73, 22.69, 24.59, 26.92, 32.76, 33.51, 35.63, 38.22, 43.48, 45.92, 52.19, 53.19, 55.66, 60.94, 102.51, 124.01, 127.65, 155.55, 162.78, 165.94, 168.75, 186.30, 203.26. HR-MS(ESI): *m/z* 399.2169 $[M+H]^+$ (calcd for $C_{24}H_{31}O_5$, 399.2166).

4-Chloro-21-methoxalylpregna-1,4-diene-3,20-dione (4): Yellow solid (1.77 g, 82%). Mp 128-130 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.71 (3H, s, 18-CH_3), 1.29 (3H, s, 19-CH_3), 3.89 (3H, s, $COOCH_3$), 6.30 (1H, s, 21-H), 6.36 (1H, d, *J* = 10.0 Hz, 2-H), 7.07 (1H, d, *J* = 10.0 Hz, 1-H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ ppm 13.54, 19.18, 22.43, 23.06, 24.54, 28.87, 32.40, 35.56, 38.18, 45.84, 46.18, 52.89, 53.18, 55.53, 60.82, 102.44, 126.37, 128.37, 155.15, 162.23, 162.76, 166.16, 178.26, 203.05. HR-MS (ESI): *m/z* 433.1777 $[M+H]^+$ (calcd. for $C_{24}H_{30}ClO_5$, 433.1776).

General procedure for the preparation of pyrazolyl derivatives (**6a-k** and **7a-k**)

Compound **3** (or **4**) (0.2 mmol, 80 or 86 mg) and KOAc (40 mg, 0.4 mmol) were dissolved in glacial acetic acid (1 mL), and phenylhydrazine hydrochloride (**5a**) or one of its *p*-substituted derivatives (**5b-k**) (1.2 equivalent) was added. The reaction mixture was stirred at room temperature for 4 h, and then ice-cold water (10 mL) was poured into it. The precipitate that formed was filtered off and washed with water. The residue obtained was dissolved in CH_2Cl_2 and chromatographed on silica gel with EtOAc/CH_2Cl_2 (3:1:1, v/v) as eluent to afford and **6a-k** (or **7a-k**).

17-(1-Phenyl-3-methoxycarbonyl-1*H*-pyrazol-5-yl)androsta-1,4-dien-3-one (6a): White solid (80 mg, 81%). Mp 263-265 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.72 (3H, s, 18-CH_3), 1.17 (3H, s, 19-CH_3), 3.92 (3H, s, $COOCH_3$), 6.01 (1H, s, 4-H), 6.14 (1H, dd, *J* = 1.5, 10.0 Hz, 2-H), 6.84 (1H, s, 4'-H), 6.94 (1H, d, *J* = 10.0 Hz, 1-H), 7.33 (2H, d, *J* = 8.0 Hz, Ar-H); 7.42-7.44 (3H, m, Ar-H); ^{13}C NMR (125MHz, $CDCl_3$): δ ppm 13.51, 18.64, 22.42, 24.38, 29.30, 32.70, 33.40, 35.84, 36.92, 43.42, 44.58, 46.76, 52.06, 52.06, 54.71, 108.30, 123.85, 127.02, 127.47, 129.06, 129.16, 139.31, 143.14, 146.11, 155.60, 163.11, 168.80, 186.19. HR-MS(ESI): *m/z* 493.2466 $[M+Na]^+$ (calcd for $C_{30}H_{34}N_2NaO_3$, 493.2462).

17-(1-(2'-Fluorophenyl)-3-methoxycarbonyl-1*H*-pyrazol-5-yl)androsta-1,4-dien-3-one (6b): White solid (74 mg, 76%). Mp 267-269 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.74 (3H, s, 18-CH_3), 1.17 (3H, s, 19-CH_3), 3.92 (3H, s, $COOCH_3$), 6.01 (1H, s, 4-H), 6.15 (1H, dd, *J* = 1.5, 10.0 Hz, 2-H), 6.84 (1H, s, 4'-H), 6.94 (1H, d, *J* = 10.0 Hz, 1-H), 7.17-7.24 (2H, m, Ar-H); 7.42-7.46 (2H, m, Ar-H); ^{13}C NMR (125MHz, $CDCl_3$): δ ppm 13.47, 18.63, 22.43, 24.35, 29.22, 29.67, 32.69, 33.40, 35.84, 43.41, 44.50, 47.20, 52.10, 52.14, 54.75, 107.92, 116.64, 123.84, 124.62, 127.17, 127.27, 127.48, 129.91, 131.35, 144.12, 147.44, 155.57, 162.90, 168.78, 186.16. HR-MS(ESI): *m/z* 489.2544 $[M+H]^+$ (calcd for $C_{30}H_{34}FN_2O_3$, 489.2548).

17-(1-(4'-Fluorophenyl)-3-methoxycarbonyl-1*H*-pyrazol-5-yl)androsta-1,4-dien-3-one (6c): White solid (73 mg, 77%). Mp 200-202 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.72 (3H, s, 18-CH_3), 1.17 (3H, s, 19-CH_3), 3.91 (3H, s, $COOCH_3$), 6.01 (1H, s, 4-H), 6.14 (1H, dd, *J* = 1.5, 10.0 Hz, 2-H), 6.83 (1H, s, 4'-H), 6.94 (1H, d, *J* = 10.0 Hz, 1-H), 7.10-7.14 (2H, m, Ar-H); 7.30-7.33 (2H, m, Ar-H); ^{13}C NMR (125MHz, $CDCl_3$): δ ppm 13.50, 18.65, 22.42, 24.36, 29.35, 32.68, 33.39, 35.88, 37.09, 43.38, 44.62, 46.87, 52.05, 52.08, 54.79, 108.33, 116.08, 123.90, 127.55, 128.92, 135.44, 143.33, 146.31, 155.43, 162.60 (d, *J* = 249 Hz, C-F), 162.96, 168.61, 186.11. HR-MS(ESI): *m/z* 489.2544 $[M+H]^+$ (calcd for $C_{30}H_{34}FN_2O_3$, 489.2548).

17-(1-(2'-Chlorophenyl)-3-methoxycarbonyl-1*H*-pyrazol-5-yl)androsta-1,4-dien-3-one (6d): White solid (88 mg, 69%). Mp 250-252 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.77 (3H, s, 18-CH_3), 1.19 (3H, s, 19-CH_3), 3.92 (3H, s, $COOCH_3$), 6.02 (1H, s, 4-H), 6.14 (1H, dd, *J* = 1.5, 10.0 Hz, 2-H), 6.84 (1H, s, 4'-H), 6.95 (1H, d, *J* = 10.0 Hz, 1-H), 7.35-7.48 (4H, m, Ar-H); ^{13}C NMR (125MHz, $CDCl_3$): δ ppm 13.61, 18.67, 22.46, 24.36, 29.47, 32.72, 33.43, 35.92, 37.28, 43.45, 44.47, 47.67, 52.07, 52.17, 54.73, 107.83, 123.88, 127.44, 127.53, 129.97, 130.69, 131.00, 132.47, 136.93, 144.03, 147.55, 155.54, 162.96, 168.78, 186.17. HR-MS(ESI): *m/z* 505.2251 $[M+H]^+$ (calcd for $C_{30}H_{34}ClN_2O_3$, 505.2252).

17-(1-(4'-Chlorophenyl)-3-methoxycarbonyl-1*H*-pyrazol-5-yl)androsta-1,4-dien-3-one (6e): White solid (78 mg, 80%). Mp 171-173 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.72 (3H, s, 18-CH_3), 1.17 (3H, s, 19-CH_3), 3.92 (3H, s, $COOCH_3$), 6.02 (1H, s, 4-H), 6.16 (1H, dd, *J* = 1.5, 10.0 Hz, 2-H), 6.84 (1H, s, 4'-H), 6.95 (1H, d, *J* = 10.0 Hz, 1-H), 7.28 (2H, d, *J* = 8.0 Hz, Ar-H), 7.41 (2H, d, J = 8.0 Hz, Ar-H); ^{13}C NMR (125MHz, $CDCl_3$): δ ppm 13.52, 18.67, 22.42, 24.37, 29.31, 32.69, 33.40, 35.89, 37.08, 43.39, 44.71, 46.86, 52.05, 52.09, 54.79, 108.50, 123.92, 127.56, 128.29, 129.34, 135.12, 137.89, 143.52, 146.23, 155.46, 162.92, 168.62, 186.13. HR-MS(ESI): *m/z* 505.2251 $[M+H]^+$ (calcd for $C_{30}H_{34}ClN_2O_3$, 505.2252).

17-(1-(2'-Bromophenyl)-3-methoxycarbonyl-1*H*-pyrazol-5-yl)androsta-1,4-dien-3-one (6f): White solid (78 mg, 71%). Mp 210-212 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.77 (3H, s, 18-CH_3), 1.18 (3H, s, 19-CH_3), 3.92 (3H, s, $COOCH_3$), 6.02 (1H, s, 4-H), 6.15 (1H, dd, *J* = 1.5, 10.0 Hz, 2-H), 6.83 (1H, s, 4'-H), 6.95 (1H, d, *J* = 10.0 Hz, 1-H), 7.33-7.35 (1H, m, Ar-H), 7.40-7.42 (2H, m, Ar-H), 7.64 (1H, d, *J* = 8.0 Hz, 1-H); ^{13}C NMR (125MHz, $CDCl_3$): δ ppm 13.65, 18.66, 22.46, 24.36, 29.59, 32.72, 33.42, 35.91, 37.31, 43.44, 44.44, 47.79, 52.06, 52.15, 54.70, 107.91, 122.59, 123.86, 127.52, 128.01, 130.84, 131.20, 133.10, 138.51, 143.90, 147.39, 155.55, 162.97, 168.80, 186.17. HR-MS(ESI): *m/z* 549.1745 $[M+H]^+$ (calcd for $C_{30}H_{34}BrN_2O_3$, 549.1747).

17-(1-(4'-Bromophenyl)-3-methoxycarbonyl-1*H*-pyrazol-5-yl)androsta-1,4-dien-3-one (6g): White solid (86 mg, 79%). Mp 167-169 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.72 (3H, s, 18-CH_3), 1.17 (3H, s, 19-CH_3), 3.92 (3H, s, $COOCH_3$), 6.02 (1H, s, 4-H), 6.16 (1H, dd, *J* = 1.5, 10.0 Hz, 2-H), 6.83 (1H, s, 4'-H), 6.95 (1H, d, *J* = 10.0 Hz, 1-H), 7.22 (2H, d, *J* = 8.0 Hz, Ar-H), 7.57 (2H, d, J = 8.0 Hz, Ar-H); ^{13}C NMR (125MHz, $CDCl_3$): δ ppm 13.51, 18.66, 22.41, 24.36, 29.31, 32.69, 33.40, 35.89, 37.06, 43.39, 44.71, 46.85, 52.03, 52.09, 54.78, 108.52, 123.13, 123.90, 127.55, 128.55, 132.32, 138.39, 143.55, 146.18, 155.46, 162.90, 168.53, 186.12. HR-MS(ESI): *m/z* 549.1745 $[M+H]^+$ (calcd for $C_{30}H_{34}BrN_2O_3$, 549.1747).

17-(1-(2'-Methylphenyl)-3-methoxycarbonyl-1*H*-pyrazol-5-yl)androsta-1,4-dien-3-one (6h): White solid (67 mg, 69%). Mp 263-265 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.80 (3H, s, 18-CH_3), 1.19 (3H, s, 19-CH_3), 1.89 (3H, s, Ar-CH_3), 3.91 (3H, s, $COOCH_3$), 6.02 (1H, s, 4-H), 6.15 (1H, dd, *J* = 1.5, 10.0

Hz, 2-H), 6.84 (1H, s, 4'-H), 6.95 (1H, d, *J* = 10.0 Hz, 1-H), 7.22-7.33 (4H, m, Ar-H); ^{13}C NMR (125MHz, $CDCl_3$): δ ppm 13.60, 16.82, 18.67, 22.45, 24.40, 29.92, 32.71, 33.41, 35.90, 37.29, 43.43, 44.41, 47.19, 51.97, 52.12, 54.69, 107.62, 123.88, 126.38, 127.51, 128.85, 129.82, 130.56, 135.94, 138.16, 143.37, 146.78, 155.53, 163.17, 168.71, 186.14. HR-MS(ESI): *m/z* 485.2797 $[M+H]^+$ (calcd for $C_{31}H_{37}N_2O_3$, 485.2799).

17-(1-(4'-Methoxyphenyl)-3-methoxycarbonyl-1*H*-pyrazol-5-yl)androsta-1,4-dien-3-one (6i): White solid (58 mg, 60%). Mp 231-232 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.72 (3H, s, 18-CH_3), 1.17 (3H, s, 19-CH_3), 3.81 (3H, s, Ar-OCH_3), 3.90 (3H, s, $COOCH_3$), 6.01 (1H, s, 4-H), 6.15 (1H, dd, *J* = 1.5, 10.0 Hz, 2-H), 6.80 (1H, s, 4'-H), 6.91 (2H, d, *J* = 8.0 Hz, Ar-H), 6.95 (1H, d, *J* = 10.0 Hz, 1-H), 7.22 (2H, d, J = 8.0 Hz, Ar-H); ^{13}C NMR (125MHz, $CDCl_3$): δ ppm 13.48, 18.63, 22.43, 24.36, 29.38, 32.69, 33.41, 35.85, 37.00, 43.43, 44.46, 46.80, 51.96, 52.10, 54.72, 55.49, 108.02, 114.04, 123.82, 127.46, 128.24, 132.19, 142.86, 146.26, 155.60, 159.88, 163.13, 168.81, 186.15. HR-MS(ESI): *m/z* 501.2746 $[M+H]^+$ (calcd for $C_{31}H_{37}N_2O_4$, 501.2748).

17-(1-(4'-Nitrophenyl)-3-methoxycarbonyl-1*H*-pyrazol-5-yl)androsta-1,4-dien-3-one (6j): White solid (60 mg, 59%). Mp 284-286 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.70 (3H, s, 18-CH_3), 1.17 (3H, s, 19-CH_3), 3.94 (3H, s, $COOCH_3$), 6.01 (1H, s, 4-H), 6.15 (1H, dd, *J* = 1.5, 10.0 Hz, 2-H), 6.90 (1H, s, 4'-H), 6.92 (1H, d, *J* = 10.0 Hz, 1-H), 7.59 (2H, d, *J* = 8.0 Hz, Ar-H), 8.34 (2H, d, *J* = 8.0 Hz, Ar-H); ^{13}C NMR (125MHz, $CDCl_3$): δ ppm 13.53, 18.65, 22.38, 24.35, 29.08, 32.65, 33.36, 35.87, 37.13, 43.34, 45.05, 46.94, 51.98, 52.29, 54.86, 109.28, 123.94, 124.65, 127.59, 127.65, 144.41, 144.50, 146.40, 147.57, 155.39, 162.64, 168.56, 186.15. HR-MS(ESI): *m/z* 516.2491 $[M+H]^+$ (calcd for $C_{30}H_{34}N_3O_5$, 516.2493).

17-(1-(4'-Cyanophenyl)-3-methoxycarbonyl-1*H*-pyrazol-5-yl)androsta-1,4-dien-3-one (6k): White solid (77 mg, 78%). Mp 283-285 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.69 (3H, s, 18-CH_3), 1.16 (3H, s, 19-CH_3), 3.92 (3H, s, $COOCH_3$), 6.01 (1H, s, 4-H), 6.15 (1H, dd, *J* = 1.5, 10.0 Hz, 2-H), 6.87 (1H, s, 4'-H), 6.93 (1H, d, *J* = 10.0 Hz, 1-H), 7.52 (2H, d, *J* = 8.0 Hz, Ar-H), 7.77 (2H, d, *J* = 8.0 Hz, Ar-H); ^{13}C NMR (125MHz, $CDCl_3$): δ ppm 13.48, 18.63, 22.35, 24.30, 29.06, 32.62, 33.32, 35.82, 37.04, 43.30, 44.94, 46.84, 51.92, 52.21, 54.78, 109.10, 112.97, 117.66, 123.90, 127.46, 127.57, 133.15, 142.95, 144.20, 146.24, 155.35, 162.63, 168.51, 186.09. HR-MS(ESI): *m/z* 496.2591 $[M+H]^+$ (calcd for $C_{31}H_{34}N_3O_3$, 496.2595).

17-(1-Phenyl-3-methoxycarbonyl-1*H*-pyrazol-5-yl)-4-chloroandrosta-1,4-dien-3-one (7a): White solid (87 mg, 83%). Mp 235-237 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.74 (3H, s, 18-CH_3), 1.24 (3H, s, 19-CH_3), 3.93 (3H, s, $COOCH_3$), 6.29 (1H, d, *J* = 10.0 Hz, 2-H), 6.86 (1H, s, 4'-H), 6.98 (1H, d, *J* = 10.0 Hz, 1-H), 7.33 (2H, d, *J* = 8.0 Hz, Ar-H); 7.44-7.46 (3H, m, Ar-H); ^{13}C NMR (125MHz, $CDCl_3$): δ ppm 13.56, 19.12, 22.84, 24.37, 28.85, 29.34, 32.33, 35.83, 36.93, 44.60, 46.16, 46.78, 52.09, 52.83, 54.65, 108.37, 126.25, 127.05, 128.27, 129.12, 129.22, 139.36, 143.23, 146.05, 155.23, 162.30, 163.15,

178.21. HR-MS(ESI): *m/z* 527.2079 $[M+Na]^+$ (calcd for $C_{30}H_{33}ClN_2NaO_3$, 527.2072).

17-(1-(2'-Fluorophenyl)-3-methoxycarbonyl-1*H*-pyrazol-5-yl)-4-chloroandrosta-1,4-dien-3-one (7b): White solid (76 mg, 73%). Mp 177-179 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.74 (3H, s, 18-CH_3), 1.23 (3H, s, 19-CH_3), 3.91 (3H, s, $COOCH_3$), 6.27 (1H, d, *J* = 10.0 Hz, 2-H), 6.84 (1H, s, 4'-H), 6.97 (1H, d, *J* = 10.0 Hz, 1-H), 7.17-7.24 (2H, m, Ar-H); 7.42-7.46 (2H, m, Ar-H); ^{13}C NMR (125MHz, $CDCl_3$): δ ppm 13.46, 19.06, 22.78, 24.28, 28.78, 29.21, 29.58, 32.27, 35.89, 44.46, 46.11, 47.13, 52.07, 52.78, 54.60, 107.92, 116.54, 124.56, 126.17, 127.13, 127.23, 128.17, 129.89, 131.36, 144.12, 147.34, 155.21, 162.29, 162.87, 178.13. HR-MS(ESI): *m/z* 523.2158 $[M+H]^+$ (calcd for $C_{30}H_{33}ClFN_2O_3$, 523.2158).

17-(1-(4'-Fluorophenyl)-3-methoxycarbonyl-1*H*-pyrazol-5-yl)-4-chloroandrosta-1,4-dien-3-one (7c): White solid (72 mg, 69%). Mp 146-148 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.73 (3H, s, 18-CH_3), 1.24 (3H, s, 19-CH_3), 3.92 (3H, s, $COOCH_3$), 6.28 (1H, d, *J* = 10.0 Hz, 2-H), 6.83 (1H, s, 4'-H), 6.97 (1H, d, *J* = 10.0 Hz, 1-H), 7.11-7.14 (2H, m, Ar-H); 7.30-7.33 (2H, m, Ar-H); ^{13}C NMR (125MHz, $CDCl_3$): δ ppm 13.52, 19.10, 22.79, 24.31, 28.79, 29.34, 32.28, 35.81, 37.04, 44.60, 46.09, 46.82, 52.07, 52.77, 54.67, 108.37, 116.11, 126.27, 128.27, 128.91, 135.42, 143.35, 146.21, 155.07, 162.13, 162.60 (d, *J* = 249 Hz, C-F), 162.95, 178.10. HR-MS(ESI): *m/z* 523.2158 $[M+H]^+$ (calcd for $C_{30}H_{33}ClFN_2O_3$, 523.2158).

17-(1-(2'-Chlorophenyl)-3-methoxycarbonyl-1*H*-pyrazol-5-yl)-4-chloroandrosta-1,4-dien-3-one (7d): White solid (75 mg, 70%). Mp 258-260 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.76 (3H, s, 18-CH_3), 1.24 (3H, s, 19-CH_3), 3.92 (3H, s, $COOCH_3$), 6.29 (1H, d, *J* = 10.0 Hz, 2-H), 6.84 (1H, s, 4'-H), 6.98 (1H, d, *J* = 10.0 Hz, 1-H), 7.35-7.48 (4H, m, Ar-H); ^{13}C NMR (125MHz, $CDCl_3$): δ ppm 13.59, 19.09, 22.78, 24.28, 28.81, 29.44, 32.27, 35.78, 37.16, 44.41, 46.13, 47.56, 52.10, 52.78, 54.53, 107.83, 126.20, 127.43, 128.19, 129.98, 130.61, 131.02, 132.42, 136.83, 143.98, 147.44, 155.22, 162.34, 162.94, 178.18. HR-MS(ESI): *m/z* 539.1862 $[M+H]^+$ (calcd for $C_{30}H_{33}Cl_2N_2O_3$, 539.1863).

17-(1-(4'-Chlorophenyl)-3-methoxycarbonyl-1H-pyrazol-5-yl)-4-chloro-androst-1,4-dien-3-one (7e): White solid (85 mg, 79%). Mp 140-142 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.73 (3H, s, 18-CH_3), 1.25 (3H, s, 19-CH_3), 3.94 (3H, s, $COOCH_3$), 6.31 (1H, d, *J* = 10.0 Hz, 2-H), 6.86 (1H, s, 4'-H), 6.99 (1H, d, *J* = 10.0 Hz, 1-H), 7.29 (2H, d, *J* = 8.0 Hz, Ar-H), 7.42 (2H, d, *J* = 8.0 Hz, Ar-H); ^{13}C NMR (125MHz, $CDCl_3$): δ ppm 13.57, 19.15, 22.81, 24.35, 28.85, 29.32, 32.32, 35.84, 37.03, 44.72, 46.13, 46.82, 52.20, 52.74, 54.69, 108.59, 126.33, 128.24, 128.30, 129.41, 135.19, 137.87, 143.55, 146.17, 155.17, 162.22, 162.97, 178.23. HR-MS(ESI): *m/z* 539.1862 $[M+H]^+$ (calcd for $C_{30}H_{33}Cl_2N_2O_3$, 539.1863).

17-(1-(2'-Bromophenyl)-3-methoxycarbonyl-1*H*-pyrazol-5-yl)-4-chloroandrosta-1,4-dien-3-one (7f): White solid (80 mg, 69%). Mp 259-261 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.77 (3H, s, 18-CH_3), 1.24 (3H, s, 19-CH_3), 3.92 (3H, s, $COOCH_3$), 6.28 (1H, d, *J* = 10.0 Hz, 2-H), 6.83 (1H, s, 4'-H), 6.98 (1H, d, *J* = 10.0 Hz, 1-H), 7.33-7.35 (1H, m, Ar-H), 7.40-7.42 (2H, m, Ar-H), 7.64 (1H, d, *J* = 8.0 Hz, 1-H);

^{13}C NMR (125MHz, $CDCl_3$): δ ppm 13.63, 19.08, 22.77, 24.27, 28.80, 29.55, 32.25, 35.76, 37.18, 44.37, 46.12, 47.66, 52.09, 52.75, 54.50, 107.90, 122.55, 126.19, 128.00, 128.16, 130.75, 131.22, 133.09, 138.39, 143.84, 147.27, 155.22, 162.33, 162.94, 178.17. HR-MS(ESI): *m/z* 583.1357 $[M+H]^+$ (calcd for $C_{30}H_{33}BrClN_2O_3$, 583.1358).

17-(1-(4'-Bromophenyl)-3-methoxycarbonyl-1*H*-pyrazol-5-yl)-4-chloroandrosta-1,4-dien-3-one (7g): White solid (85 mg, 73%). Mp 131-132 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.72 (3H, s, 18-CH_3), 1.24 (3H, s, 19-CH_3), 3.92 (3H, s, $COOCH_3$), 6.29 (1H, d, *J* = 10.0 Hz, 2-H), 6.84 (1H, s, 4'-H), 6.98 (1H, d, *J* = 10.0 Hz, 1-H), 7.22 (2H, d, *J* = 8.0 Hz, Ar-H), 7.57 (2H, d, *J* = 8.0 Hz, Ar-H); ^{13}C NMR (125MHz, $CDCl_3$): δ ppm 13.52, 19.10, 22.75, 24.30, 28.80, 29.26, 32.27, 35.77, 36.96, 44.68, 46.10, 46.76, 52.15, 52.66, 54.61, 108.56, 123.15, 126.26, 128.24, 128.52, 132.34, 138.32, 143.52, 146.09, 155.17, 162.22, 162.90, 178.17. HR-MS(ESI): *m/z* 583.1357 $[M+H]^+$ (calcd for $C_{30}H_{33}BrClN_2O_3$, 583.1358).

17-(1-(2'-Methylphenyl)-3-methoxycarbonyl-1*H*-pyrazol-5-yl)-4-chloroandrosta-1,4-dien-3-one (7h): White solid (65 mg, 63%). Mp 254-256 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.81 (3H, s, 18-CH_3), 1.26 (3H, s, 19-CH_3), 1.90 (3H, s, Ar-CH_3), 3.93 (3H, s, $COOCH_3$), 6.30 (1H, d, *J* = 10.0 Hz, 2-H), 6.85 (1H, s, 4'-H), 7.01 (1H, d, *J* = 10.0 Hz, 1-H), 7.24-7.35 (4H, m, Ar-H); ^{13}C NMR (125MHz, $CDCl_3$): δ ppm 13.62, 16.85, 19.13, 22.82, 24.36, 28.83, 29.92, 32.29, 35.81, 37.21, 44.39, 46.16, 47.12, 52.05, 52.78, 54.54, 107.67, 126.24, 126.40, 128.22, 128.81, 129.87, 130.61, 135.95, 138.10, 143.37, 146.71, 155.26, 162.33, 163.19, 178.21. HR-MS(ESI): *m/z* 519.2408 $[M+H]^+$ (calcd for $C_{31}H_{36}ClN_2O_3$, 519.2409).

17-(1-(4'-Methoxyphenyl)-3-methoxycarbonyl-1*H*-pyrazol-5-yl)-4-chloroandrosta-1,4-dien-3-one (7i): White solid (69 mg, 65%). Mp 167-169 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.73 (3H, s, 18-CH_3), 1.24 (3H, s, 19-CH_3), 3.82 (3H, s, Ar-OCH_3), 3.91 (3H, s, $COOCH_3$), 6.28 (1H, d, *J* = 10.0 Hz, 2-H), 6.81 (1H, s, 4'-H), 6.91 (2H, d, *J* = 8.0 Hz, Ar-H), 6.98 (1H, d, *J* = 10.0 Hz, 1-H), 7.22 (2H, d, *J* = 8.0 Hz, Ar-H); ^{13}C NMR (125MHz, $CDCl_3$): δ ppm 13.50, 19.08, 22.80, 24.31, 28.81, 29.38, 32.30, 35.78, 36.96, 44.44, 46.14, 46.75, 51.99, 52.80, 54.60, 55.52, 108.06, 114.07, 126.19, 128.19, 128.24, 132.18, 142.89, 146.17, 155.24, 159.90, 162.30, 163.13, 178.14. HR-MS(ESI): *m/z* 535.2358 $[M+H]^+$ (calcd for $C_{31}H_{36}ClN_2O_4$, 535.2358).

17-(1-(4'-Nitrophenyl)-3-methoxycarbonyl-1*H*-pyrazol-5-yl)-4-chloroandrosta-1,4-dien-3-one (7j): White solid (84 mg, 77%). Mp 283-285 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.70 (3H, s, 18-CH_3), 1.23 (3H, s, 19-CH_3), 3.94 (3H, s, $COOCH_3$), 6.27 (1H, d, *J* = 10.0 Hz, 2-H), 6.90 (1H, s, 4'-H), 6.95 (1H, d, *J* = 10.0 Hz, 1-H), 7.59 (2H, d, *J* = 8.0 Hz, Ar-H), 8.34 (2H, d, *J* = 8.0 Hz, Ar-H); ^{13}C NMR (125MHz, $CDCl_3$): δ ppm 13.53, 19.09, 22.73, 24.28, 28.76, 29.06, 32.23, 35.79, 37.06, 45.01, 46.03, 46.87, 52.29, 52.64, 54.71, 109.30, 124.66, 126.30, 127.63, 128.29, 144.41, 144.48, 146.30, 147.55, 154.99, 162.04, 162.61, 178.09. HR-MS(ESI): *m/z* 550.2101 $[M+H]^+$ (calcd for $C_{30}H_{33}ClN_3O_5$, 550.2103).

17-(1-(4'-Cyanophenyl)-3-methoxycarbonyl-1*H*-pyrazol-5-yl)-4-chloroandrosta-1,4-dien-3-one (7k): White solid (86 mg, 82%). Mp 295-297 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.69 (3H, s, 18-CH_3), 1.23 (3H, s, 19-CH_3), 3.93 (3H, s, $COOCH_3$), 6.28 (1H, d, *J* = 10.0 Hz, 2-H), 6.88 (1H, s, 4'-H), 6.96 (1H, d, *J* = 10.0 Hz, 1-H), 7.52 (2H, d, *J* = 8.0 Hz, Ar-H), 7.77 (2H, d, *J* = 8.0 Hz, Ar-H); ^{13}C NMR (125MHz, $CDCl_3$): δ ppm 13.50, 19.08, 22.71, 24.25, 28.74, 29.05, 32.21, 35.75, 36.99, 44.92, 46.01, 46.79, 52.23, 52.60, 54.65, 109.14, 112.98, 117.66, 126.29, 127.56, 128.26, 133.18, 142.93, 144.23, 146.15, 154.98, 162.03, 162.62, 178.07. HR-MS(ESI): *m/z* 530.2205 $[M+H]^+$ (calcd for $C_{31}H_{33}ClN_3O_3$, 530.2205).

Antiproliferative activity assay

The HepG-2, HeLa and MCF-7 cell lines were originally obtained from Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences. The two cells were grown in RPMI-1640 (Sigma) medium containing 10% (v/v) thermally inactivated fetal bovine serum (FBS), penicillin (100 KU/L) and streptomycin (100 KU/L) at 37 °C in a 5% CO_2 humidified incubator. Cells were always used at < 90% of confluence. Antiproliferative activity *in vitro* was assessed by the SRB colorimetric assay. Briefly, 100 μL exponentially growing cells containing 2.5 × 10^4 cells/mL were added to each well of a 96-well flat-microtiter plate and let cells attach for 24 h. Then the medium was replaced by fresh medium and cells were incubated with various amounts of the test compound for an additional periods. After incubation at 37 °C, culture medium was moved and cells were fixed *in situ* with trichloroacetic acid (TCA), and plates were washed and dried. Sulforhodamine B solution was added to each well. After the unbound dye is removed and plates were air dried. Bound sulforhodamine B was subsequently solubilized with Tris-base, and the absorbance was read at 540 nm using an Epoch (Bio-Tek) microplate reader. The percentage of cell viability was calculated relative to control wells designated as 100% viable cells.

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