Chemical and Process Engineering Research
ISSN 2224-7467 (Paper) ISSN 2225-0913 (Online)
Vol.9, 2013

Progesterone utility in the synthesis of steroidal heterocyclic compounds with antitumor activity

Nahid Y. Khaireldin[1*], Maher A. El-Hashash[3], Mervat M. Abdelhalim[2], Dina A. Rayan[1], Nadia R.Mohamed[1,4]

[1] National Research Centre, Photochemistry Department, Dokki, Giza, Egypt.

[2] National Research Centre, Hormones Department, Dokki, Giza, Egypt.

[3] Ain Shams University, Faculty of science, Chemistry Department, Cairo, Egypt.

[4] Chemistry Department, El-Aflaj Science and Humanity College, Salman Bin Abdul-Aziz University, Kingdom of Saudi Arabia.

Corresponding Author: Nahid Y. Khaireldin E-mail address: nahid_khaireldin@hotmail.com

Abstract

One–pot and efficient method for the synthesis of progesteronpyridine **5a-c**, **6a-c** and **7a,b** and/or progesteronpyran derivatives **9a-c** and **10a,b** by condensation reaction of progesterone **1** with different aldehydes and active methylene compounds in the presence of ammonium acetate or piperidine. New progesteronopyrimidine derivatives **12a-d** and **13a, b** were synthesized *via* interaction of progesterone **1** with urea or thiourea and/or guanidine reagents and aldehyde. Progesterone **1** was examined to synthesize heterocyclic compound **16** containing γ-Lactone chiral carbon via the reaction of hydrazone derivative **14** with phenyl isothiocyanate followed by boiling with chloroacetic acid in benzene. The biological activity of compounds **5a, 5b, 6b, 7a, 9b, 9c, 12a, 12c,** and **13a** were evaluated as growth inhibitors of the liver and the breast carcinoma human cell line (**HEPG2 & MCF7**). Compounds **13a, 12a** and **7a** showed a higher potency than the standard.

Key Words: Progesterone, MCR's (multicomponents reaction), (pyridine, pyran, pyrimidine, γ-Lactone) derivatives, HEPG2 & MCF7.

1. Introduction:

Progesterone is a female sex hormone that plays an important physiological role to regularize and rebuild the changes caused to the body by estrogen in the luteal phase of the menstrual cycle.[1] Progestrone is a steroid hormone consists chemically of four fused hydrocarbons containing the functional groups of ketone, acetyl and two methyl groups. It is a precursor of all steroid hormones and an intermediate in the biosynthesis of androgens, estrogens and the corticoid.[2] Synthetic compounds with progesterone are used in the prevention of miscarriage, treatment of menstrual disorders and development in the cosistuent of some contraceptives.[3] Progesterone like pregnenlone and dehydroepi androsterone, belongs to the group of neurosteroids that are found in high concentrations in certain areas in the brain and are synthesized there. Neurosteroids affect synaptic functioning is neuroprotective and also affect myelinisation. They are being investigated for their potential to improve memory and cognitive ability.[4, 5] Progesterone plays an important role in other systems. For example it raises epidermal growth factor-1 levels [6] reduces spasm and increases core temperature during ovulation.[7] In addition, it relaxes smooth muscles, acts as an anti-inflammatory agent[8] and regulates the immune response, normalizes blood clotting and vascular tone. [9] Moreover it assists the thyroid function in bone building and prevents endometrial cancer by regulating the effects of estrogen.[10] On the other hand; pyridine and pyrimidine nucleuses are prevalent in numerous natural products and are extremely important in chemistry of biologically systems. [11, 12] They play a key role catalyzing both biological and chemical systems. In many enzymes of living organisms, it is the prosthetic pyridine nucleotide that is involved in various oxidation-reduction processes. The pyridine ring exists also in the important vitamins niacin and pyridoxine (vitamin B_6) and in the highly toxic alkaloids such as nicotine.[13-15] Moreover, substituted pyridines are reported as leukotriene B-4 antagonists. [16, 17] The literature survey have also revealed the important of pyran nucleus as a

privileged structure because many of its derivative possess useful pharmacological [18, 19] and anticancer activities. [20,21] Poly functionalized pyrans and their derivatives have been the subject of significant interest from the synthetic community and have been widely recognized as versatile scaffolds with diverse biological activity. [22,23] Upon all the previous information and in continuation of our previous work for synthesis of different bioactive fused heterocyclic derivatives using MCR's as useful tool for synthesis. [24, 25] This report explains the building of poly functionally heterocyclic rings over progesterone skeleton to improve its physiological activity. Examination the activity of some newly synthesized products as antitumor agents have been carried out.

Experimental:

Progesterone was purchased from Sigma Company, USA. The appropriate precautions in handling moisture sensitive compounds were under taken. Melting points were determined on an electro thermal apparatus (Buchi 535, Switzerland) in an open capillary tube and are uncorrected. IR spectra expressed in cm^{-1} were recorded in KBr pellets on a PA-9721 IR spectrophotometer. ^{1}H and ^{13}C-NMR spectra were recorded in [D_6] DMSO as solvent on a Jeol 270&/or 500 MHz spectrometer and the chemical shifts were recorded in δ values (ppm) relative to TMS as internal reference. Mass spectra were recorded on Kratos (75 eV) Ms equipment. Elemental analysis was carried out by the micro-analytical unit at the National Research Centre, Giza, Egypt. All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel 60 F-254 (Merck) plates using UV light (245 and 365 nm) for detection.

General Procedure:

Synthesis of **5a-c, 6a-c** and **7a,b**

To a solution of progesterone **1** (0.134 g, 0.001 mol), added aldehyde (0.001 mol), and malononitrile (0.066 g, 0.001 mol) or ω-cyano-acetophenone (0.113g, 0.001 mol) and/or ethyl cyanoacetate (0.130g, 0.001 mol) in (30 ml) ethanol containing ammonium acetate (0.980g, 2% excess). The reaction mixture was heated under reflux for 3-5 h., until all starting materials had disappeared indicated by TLC. The solvent was evaporated under reduced pressure and the remaining solids were crystallized from the proper solvent.

2-Amino-6-(3-oxo-androst-4-ene-17-yl)-4-phenyl-nicotinonitrile **5a**

Yellow crystals from benzene. Yield (86%), mp. 90 ºC. Ms (EI) m/z, (%): 465 [M^+, 80.2%],; IR (KBr, cm^{-1}): 3329 (NH_2); 3126 (C-H, aromatic); 2862 (CH_3); 2217 (CN); 1696 (C=O); 1640 (C=C); 1603 (C=N). ^{1}H-NMR (500 MHz, DMSO-d_6, TMS): δ 0.81 (s, 3H, CH_3-19); 1.13 (s, 3H, -CH_3-18); 5.63 (s, 1H, CH-4 of progesterone); 6.61 (s, 2H, NH_2, D_2O exchangeable); 7.17-7.94 (m, 6H, 5 aromatic protons+1H pyridine ring). ^{13}C-NMR (125 MHz, DMSO-d_6, TMS): δ 19.6 (C-18), 20.0 (C-19), 20.8 (C-15), 20.9 (C-11), 25.8 (C-16), 28.7 (C-8), 30.4 (C-1), 30.8 (C-6), 30.9 (C-7), 31.1 (C-12), 38.5 (C-2), 38.5 (C-10), 40.0 (C-13), 43.2 (C-9), 46.7 (C-14), 47.2 (C-17), 118.0 (CN), 119.3 (C-4), 126.7, 129.1, 138.1 (C-phenyl), 91.7, 110.5, 155.2, 164.3 ,166.1(C-pyridine ring), 162.6 (C-5) ,197.6 (C-3). Anal. Calcd. For $C_{31}H_{35}N_3O$: C, 79.71%; H, 7.58%; N, 9.02%; Found: C, 79.40%; H, 7.50%; N, 9.00%.

2-Amino-4-(4-chloro-phenyl)-6-(3-oxo-androstene-4-ene-17-yl)-nicotinonitrile **5b**

Pale yellow crystals from EtOH. Yield (82%), mp. 120 ºC. Ms (EI) m/z, (%): 501[M^{+2}, 5.6%]; 499[M^+,16.3%]; 362[M^+-(Ar+CN),65.4%] ; IR (KBr, cm^{-1}): 3305 (NH_2); 3126 (C-H, aromatic); 2962 (CH_3); 2216 (CN); 1700 (C=O); 1645 (C=C); 1602 (C=N). ^{1}H-NMR (270 MHz, DMSO-d_6, TMS): δ 0.88 (s, 3H, CH_3-19); 1.14(s, 3H, -CH_3-18); 5.58 (s, 1H, CH-4, of progesterone); 6.81(s, 2H, NH_2 ,D_2O exchangeable); 7.15(s,1H,pyridine proton); 7.30 (dd,2H, aromatic protons J_{HH} =8Hz);7.44 (dd,2H, aromatic protons J_{HH} =8Hz). ^{13}C-NMR (125 MHz, DMSO-d_6, TMS): δ 19.3 (C-18), 20.1 (C-19), 20.8 (C-15), 20.9 (C-11), 25.6 (C-16), 28.3 (C-8), 30.2 (C-1), 29.9 (C-7), 30.8 (C-6), 31.1 (C-12), 38.0 (C-2), 38.1 (C-10), 39.1 (C-13), 42.5 (C-9), 47.7 (C-17), 47.4 (C-14), 118.0 (CN), 119.8 (C-4), 128.1, 129.3, 134.5, 136.4 (C- aromatic), 91.7, 111.2, 155.8, 164.3, 166.4 (C-pyridine ring), 160.6 (C-5) ,198.4 (C-3). Anal. Calcd. For $C_{31}H_{34}ClN_3O$: C, 74.50%; H, 6.85%; N, 8.40%; Cl, 7.09%. Found: C, 74.20%; H, 6.71%; N, 8.35%, Cl, 7.00%.

2-Amino-4-(2, 5-dimethoxy-phenyl)-6-(3-oxo-androst-4-ene-17-yl)-nicotinonitrile **5c**

Yellow crystals from EtOH. Yield (73%), mp. 110 ºC. Ms (EI) m/z,(%): 525 [M^+, 30.2%]; IR (KBr, cm^{-1}): 3315 (NH_2); 3126 (C-H, aromatic); 2845 (CH_3); 2212 (CN); 1700 (C=O); 1644 (C=C); 1604 (C=N). ^{1}H-NMR (270 MHz, DMSO-d_6, TMS): δ 0.78 (s, 3H, CH_3-19); 1.13 (s, 3H, CH_3-18); 3.64 (s, 3H, OCH_3); 3.71 (s, 3H, OCH_3), 5.65 (s, 1H, CH-4 of progesterone); 6.52 (s, 2H, NH_2, D_2O exchangeable); 6.63(d,1H,aromatic proton); 6.71(d, 1H, aromatic proton); 6.73(s, 1H, aromatic proton); 7.41(s,1H, pyridine proton). Anal. Calcd. For $C_{33}H_{39}N_3O_3$: C, 75.40%; H, 7.51%; N, 8.00%; Found: C, 75.20%; H, 7.32%; N, 7.95%.

6-(3-oxo-androst-4-ene-17-yl)-2, 4-diphenyl-nicotinonitrile **6a**

Yellow crystals from EtOH. Yield (71%), mp. 145 ºC. Ms (EI) m/z, (%): 526 [M^+, 89.7%]; IR (cm^{-1}): 3126 (C-H, aromatic); 2862 (CH_3); 2220 (CN); 1699 (C=O); 1640 (C=C); 1606 (C=N). ^{1}H-NMR (270 MHz, DMSO-d_6, TMS): δ 0.97 (s, 3H, CH_3-19); 1.14 (s, 3H, CH_3-18); 5.63 (s, 1H, CH-4 of progesterone); 7.26-7.97 (m, 11H, 5H phenyl+5H phenyl+1H pyridine proton). ^{13}C-NMR (125 MHz, DMSO-d_6, TMS): δ 19.7 (C-18), 20.5 (C-19), 20.8 (C-15), 20.9 (C-11), 25.1 (C-16), 29.7 (C-8), 30.4 (C-1), 30.9 (C-7), 32.6(C-6), 34.5 (C-12), 37.9 (C-2), 39.1 (C-10), 42.5 (C-13), 42.9 (C-9), 45.7 (C-14), 47.1 (C-17), 118.9 (CN), 119.1 (C-4), 127.1,127.6, 129.1,129.5, 136.0, 137.4 (C-phenyl), 105.8, 106.4, 154.8, 163.3, 167.7 (C-pyridine ring), 162.6 (C-5), 197.6 (C-3) . Anal. Calcd. For $C_{37}H_{38}N_2O$: C, 84.4%; H, 7.30%; N, 5.30%; Found: C, 84.30 %; H, 7.22%; N, 5.12%.

4-(4-Chloro-phenyl)-6-(3-oxo-androst-4-ene-17-yl)-2-phenyl-nicotinonitrile **6b**

Orange crystals from EtOH. Yield (83%), mp. 105 ºC. Ms (EI) m/z, (%): 562[M^{+2}, 8.2%]; 560[M^+,24.6%]; 424[M^+-(Ar+CN), 54.5%]; IR (cm^{-1}): 3126 (C-H, aromatic); 2862 (CH_3); 2210 (CN); 1695 (C=O); 1640 (C=C); 1614 (C=N). ^{1}H-NMR (270 MHz, DMSO-d_6, TMS): δ 0.97 (s, 3H, CH_3-19); 1.14 (s, 3H, CH_3-18); 5.63 (s, 1H, CH-4 of progesterone); 7.32-8.06 (m, 10H, 5Hphenyl+4H aromatic +1H pyridine proton). ^{13}C-NMR (125 MHz, DMSO-d_6, TMS): δ 19.3 (C-18), 20.0 (C-19), 20.8 (C-15), 20.9 (C-11), 25.8 (C-16), 29.7 (C-8), 30.4 (C-1), 30.9 (C-7), 32.8 (C-6), 34.2 (C-12), 38.5 (C-2), 39.0 (C-10), 42.8 (C-13), 42.9 (C-9), 45.7 (C-14), 47.3 (C-17), 118.0 (CN), 119.8 (C-4), 127.4, 127.6, 129.4, 136.2 (C-aromatic),128.8, 129.3, 134.8, 136.1 (C- phenyl), 105.9, 106.2, 154.5, 163.6, 167.4 (C-pyridine ring) , 162.6 (C-5), 197.6 (C-3). Anal. Calcd. For $C_{37}H_{37}ClN_2O$: C, 79.20%; H, 6.65%; N, 4.99%; Cl, 6.32. Found: C, 79.12%; H, 6.62%; N, 4.85%; Cl, 6.28%.

4-(2, 5-Dimethoxyphenyl)-6-(3-oxo-androst-4-ene-17-yl)-2-phenyl-nicotinonitrile **6c**

Orange crystals from EtOH . Yield (68%), mp. 95 ºC. Ms (EI) m/z,(%): 586 [M^+, 40.0%]; IR (cm^{-1}): 3126 (C-H, aromatic); 2862 (CH_3); 2210 (CN); 1699 (C=O); 1641 (C=C); 1610 (C=N). ^{1}H-NMR (270 MHz, DMSO-d_6, TMS): δ 0.71 (s, 3H, CH_3-19); 1.09 (s, 3H, CH_3-18); 3.62(s, 3H, OCH_3); 3.69 (s, 3H, OCH_3), 5.31 (s, 1H, CH-4 of progesterone); 6.42(d,1H, aromatic proton); 6.60(d,1H, aromatic proton); 6.81 (s,1H, aromatic proton); 7.25-7.99 (m, 6H, 5H phenyl+1H pyridine proton). Anal. Calcd. For $C_{39}H_{42}N_2O_3$: C, 79.80%; H, 7.21%; N, 4.77%; Found: C, 79.72%; H, 7.12%; N, 4.65%.

4- phenyl-6-(3-Oxo-androst-4-ene-17-yl)-2-oxo-1,2-dihydro-pyridine-3-carbonitrile **7a**

Yellow crystals from EtOH. Yield (81%), mp. 132 ºC. Ms (EI)m/z, (%): 466 [M^+, 37.1%]; IR (KBr, cm^{-1}): 3150 (NH), 3026 (C-H, aromatic); 2860 (CH_3); 2219 (CN); 1700 (C=O); 1689 (C=O), 1646 (C=C). ^{1}H-NMR (500 MHz, DMSO-d_6, TMS): δ 0.88 (s, 3H, CH_3-19); 1.18 (s, 3H, CH_3-18); 5.21 (s, 1H, CH-4 of progesterone) 5.70(s,1H, pyridine proton); 7.10-7.43 (m, 5H, 5 aromatic protons); 8.10 (s,1H,NH , D_2O exchangeable). ^{13}C-NMR (125 MHz, DMSO-d_6, TMS): δ 18.4 (C-16); 20.0(C-18); 20.5(C-19); 20.9(C-11); 21.0 (C-15); 28.8 (C-1); 29.1(C-8); 30.6 (C-7); 31.4 (C-12); 32.5 (C-6); 37.5 (C-13); 38.2 (C-2); 39.0 (C-10); 42.2 (C-9); 46.0 (C-14); 50.2 (C-17); 95.5, 102.2, 141.4, 162.7,169.2 (C- pyridine); 117.2 (CN); 119.8 (C-4); 126.5, 127.1, 128.9, 134.7 (C-phenyl); 162.3 (C-5); 197.5 (C-3). Anal. Calcd. For $C_{31}H_{34}N_2O_2$: C, 79.80%; H, 7.34%; N, 6.00%; Found: C, 79.73%; H, 7.22%; N, 5.93%.

4-(2,5-Dimethoxyphenyl)-6-(3-oxo-androst-4-ene-17-yl)-2-oxo-1,2-dihydro-pyridine-3-carbonitrile **7b**

Yellow crystals from EtOH. Yield (77%), mp. 160 ºC. Ms (EI)m/z,(%): 526 [M^+, 62.4%]; IR (KBr, cm^{-1}): 3152 (NH), 3026 (C-H, aromatic); 2862 (CH_3); 2219 (CN); 1699 (C=O); 1680 (C=O), 1641 (C=C). ^{1}H-NMR (500 MHz, DMSO-d_6, TMS): δ 0.88 (s, 3H, CH_3-19); 1.16(s, 3H, CH_3-18); 3.73 (s, 3H, OCH_3); 3.96 (s, 3H, OCH_3), 5.21 (s, 1H, CH-4 of progesterone); 5.91(s, 1H, pyridine proton); 6.83-7.10 (m, 3H, 3 aromatic protons); 8.16(s, 1H, NH ,D_2O exchangeable). Anal. Calcd. For $C_{33}H_{38}N_2O_4$: C, 75.26%; H, 7.27%; N, 5.32%; Found: C, 75.17%; H, 7.12%; N, 5.17%.

General procedure: for synthesis **9a-c** and **10a, b**

To a solution of progesterone **1** (0.314 g, 0.001 mol), in 30ml ethanol added aldehyde (0.001 mol) and malononitrile (0.066 g, 0.001 mol) or ω-cyanoacetophenone (0.113 g, 0.001 mol) with a few drops of piperidine. The mixture was refluxed for 3-7 h., until all starting materials had disappeared as indicated by TLC. The solvent was evaporated and the obtained solids crystallized from the proper solvent.

2-Amino-6-(3-oxo-androst-4-ene-17-yl)-4-phenyl-*4H*-pyran-3-carbonitrile **9a**

Buff crystals from EtOH . Yield (81%), mp. 106 ºC. Ms (EI) m/z,(%): 468 [M^+, 83.2%]; IR (KBr, cm^{-1}): 3342 (NH_2), 3026 (C-H, aromatic); 2962 (CH_3); 2219 (CN); 1698 (C=O); 1640 (C=C), 1222 (O-C). ^{1}H-NMR (270 MHz, DMSO-d_6, TMS): δ 0.87 (s, 3H, CH_3-19); 1.18 (s, 3H, CH_3-18); 3.91(s,1H,CH-4 of pyran proton); 4.42 (s,1H, CH-5 of pyran proton); 5.72 (s, 1H, CH-4 of progesterone); 6.82 (s, 2H, NH_2, ,D_2O exchangeable), 7.14-7.55 (m, 5H, 5 aromatic protons). ^{13}C-NMR (125 MHz, DMSO-d_6, TMS): δ 17.9 (C-16), 20.4 (C-18), 20.5 (C-19), 21.4 (C-15), 21.1 (C-11), 28.4 (C-1), 29.8 (C-8), 30.7 (C-7), 32.9 (C-6), 31.6 (C-12), 38.9 (C-2), 37.0 (C-13), 39.2 (C-10), 42.9 (C-9), 46.5 (C-14), 49.8 (C-17), 117.6 (CN), 119.7 (C-4), 125.6, 127.9, 128.4, 142.4 (C-phenyl), 29.4, 58.1, 119.9, 158.4, 159.9 (C- pyran ring), 161.2 (C-5), 196.6 (C-3). Anal. Calcd. For $C_{31}H_{36}N_2O_2$: C, 79.50%; H, 7.70%; N, 5.90%; Found: C, 79.42%; H, 7.62%; N, 5.81%.

2-Amino-4-(4-chloro-phenyl)-6-(3-oxo-androst-4-ene-17-yl)-*4H*-pyran-3-carbonitrile **9b**

Orange crystals from EtOH . Yield (73%), mp. 110 ºC. Ms (EI) m/z, (%): 504[M^{+2}, 12.3%]; 502[M^+,37.1%]; IR (KBr, cm^{-1}): 3347 (NH_2), 3026 (C-H, aromatic); 2872 (CH_3); 2212 (CN); 1699 (C=O); 1640 (C=C), 1232 (O-C). ^{1}H-NMR (270 MHz, DMSO-d_6, TMS): δ 0.88 (s, 3H, CH_3-19); 1.11 (s, 3H, -CH_3-18); 4.01(s, 1H, CH-4 of pyran proton); 4.49 (s,1H,CH-5 of pyran proton); 5.70 (s, 1H, CH-4 of progesterone); 6.61 (s, 2H, NH_2 ,D_2O exchangeable); 6.90 (dd, 2H, aromatic protons); 7.03 (dd, 2H, aromatic protons). ^{13}C-NMR (125 MHz, DMSO-d_6, TMS): δ16.1 (C-16), 20.2 (C-18), 20.6 (C-19), 21.9 (C-15), 22.1 (C-11), 28.4 (C-1), 29.8 (C-8), 30.4 (C-7), 32.2 (C-6), 31.9 (C-12), 38.9 (C-2), 37.1 (C-13), 39.7 (C-10), 42.9 (C-9), 46.5 (C-14), 49.6 (C-17), 117.0 (CN), 119.8 (C-4), 128.6, 130.4, 131.9, 140.7 (C-aromatic), 29.4, 58.0, 119.9, 158.7, 159.2 (C- pyran ring), 160.9 (C-5), 197.2 (C-3), Anal. Calcd. For $C_{31}H_{35}ClN_2O_2$: C, 74.00%; H, 7.00%; N, 5.60%; Cl, 7.05%. Found: C, 73.95%; H, 6.92%; N, 5.49%; Cl, 7.01 %.

2-Amino-4-(2,5-dimethoxyphenyl)-6-(3-oxo-androst-4-ene-17-yl)-4*H*-pyran-3-carbonitrile **9c**

Yellow crystals from Benzene . Yield (68%), mp. 78 ºC. Ms (EI) m/z, (%): 528 [M^+, 65.0%]; IR (cm^{-1}): 3340 (NH_2), 3016 (C-H, aromatic); 2870 (CH_3); 2210 (CN); 1698 (C=O); 1645 (C=C), 1225 (O-C). ^{1}H-NMR (270 MHz, DMSO-d_6, TMS): δ 0.78 (s, 3H, CH_3-19); 1.14 (s, 3H, CH_3-18); 3.76 (s, 6H, 2OCH_3); 3.89 (s,1H, CH4-pyran proton); 4.41 (s,1H, CH5-pyran proton); 5.65 (s, 1H, CH-4 of progesterone); 6.62 (s, 2H, NH_2 ,D_2O exchangeable); 6.77-7.05 (m, 3H, 3 aromatic protons). Anal. Calcd. For $C_{33}H_{40}N_2O_4$: C, 74.91%; H, 7.60%; N, 5.30%; Found: C, 74.82%; H, 7.52%; N, 5.22%.

4-(4-chloro-phenyl)-6-(3-oxo-androst-4-ene-17-yl)-2-phenyl-4*H*-pyran-3-carbonitrile **10a**

Yellow crystals from EtOH. Yield (69%), mp. 144 ºC. Ms (EI) m/z, (%):565[M^{+2}, 3.6%]; 563[M^+,10.5%]; IR (KBr, cm^{-1}): 3016 (C-H, aromatic); 2950 (CH_3); 2221 (CN); 1700 (C=O); 1641 (C=C), 1214 (O-C). ^{1}H-NMR (270 MHz, DMSO-d_6, TMS): δ 0.84 (s, 3H, Me-19); 1.08 (s, 3H, -CH_3-18); 3.87(s,1H,CH-4 of pyran proton); 4.34(s, 1H, CH-5

of pyran proton); 5.60 (s, 1H, CH-4 of progesterone); 7.12-7.21 (m, 4H, 4 aromatic protons); 7.38-7.49(m, 5H, phenyl protons). Anal. Calcd. For $C_{37}H_{38}ClNO_2$: C, 78.80%; H, 6.80%; N, 2.50%; Cl, 6.28%. Found: C, 78.72%; H, 6.75%; N, 2.43%; Cl, 6.12%.

4-(2, 5-Dimethoxyphenyl)-6-(3-oxo-androst-4-ene-17-yl)-2-phenyl-4*H*-pyran-3-carbonitrile **10b**

Brown crystals from Benzene. Yield (62%), mp. 70 ºC. Ms (EI) m/z, (%): 589 [M^+, 88.2%]; IR (KBr, cm^{-1}): 3080 (C-H, aromatic); 2850 (CH_3); 2223 (CN); 1700 (C=O); 1651 (C=C), 1222 (O-C). ^{1}H-NMR (270 MHz, DMSO-d_6, TMS): δ 0.80 (s, 3H, CH_3-19); 1.08 (s, 3H, -CH_3-18); 3.77(s, 6H, OCH_3); 3.89 (s, 1H, CH4-pyran proton); 4.21 (s,1H, CH5-pyran proton); 5.62 (s, 1H, CH-4 of progesterone); 6.82-6.91 (m, 3H, 3 aromatic protons); 7.14-7.40(m,5H, 5phenyl protons). Anal. Calcd. For $C_{39}H_{43}NO_4$: C, 79.40%; H, 7.40%; N, 2.40%; Found: C, 79.32%; H, 7.35%; N, 2.33%.

General procedure: Synthesis of progesterone pyrimidine derivatives of **12a-d** and **13a,b**

To a suspension of progesterone **1** (0.314g, 0.001mmol) in freshly prepared Sodium ethoxide, in absolute ethanol the aldehyde (0.001mmol), urea, thiourea and guanidine (0.001mmol) were added. The reaction mixture was heated under reflux for 3-5 h., until the starting materials had disappeared as indicated by TLC, and then poured into ice-water. The solid product so formed dried and crystallized from the appropriate solvent.

6-(4-Chloro-phenyl)-4-(3-oxo-androst-4-ene-17yl)-1*H*-pyrimidin-2-one **12a**

Yellow crystals from Benzene. Yield (82%), m.p. 80 ºC. Ms (m/z, %): 478[M^{+2}, 8.4%]; 476[M^+,25.0%]; 365[M^+-*P*-ClC_6H_4, 45.3%]; IR (KBr, cm^{-1}): 3158 (NH), 3090 (C-H, aromatic); 2933 (CH_3); 1700 (C=O); 1659 (C=O); 1609 (C=N). ^{1}H-NMR (500 MHz, DMSO-d_6, TMS): δ 0.90 (s, 3H, CH_3-19); 1.12 (s, 3H, -CH_3-18); 5.61 (s, 1H, CH-4 of progesterone), 6.97(s, 1H, pyrimidine ring); 7.25 (d, 2H, aromatic protons); 7.36 (d, 2H, aromatic protons); 7.91(s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (125 MHz, DMSO-d_6, TMS): δ 17.3 (C-16), 20.1 (C-11), 20.9 (C-18), 21.1 (C-19), 21.4 (C-15), 29.7 (C-8), 28.4 (C-1), 30.2 (C-7), 31.4 (C-12), 32.5 (C-6), 38.9 (C-2), 39.1(C-10), 35.9 (C-13), 42.3 (C-9), 43.4 (C-17), 46.4 (C-14), 120.1 (C-4), 127.6, 128.8, 130.1, 133.0 (C-aromatic), 87.9, 144.2, 159.8 ,164.5 (C-pyrimidine ring), 161.9 (C-5), 197.1 (C-3). Anal. Calcd. For $C_{29}H_{33}ClN_2O_2$: C, 73.02%; H, 6.97%; N, 5.87%; Cl, 7.43%. Found: C, 72.81%; H, 6.12%; N, 5.31%; Cl, 7.23%.

4-(3-oxo-androst-4-ene-17yl)-6-furan-2-yl-1*H*-pyrimidin-2-one **12b**

Yellow crystals from MeOH. Yield (77%), m.p. 170 ºC. Ms (m/z, %): 432 [M^+, 40.0%]; IR (KBr, cm^{-1}): 3150 (NH), 3054 (C-H, aromatic); 2925 (CH_3); 1700 (C=O); 1673 (C=O); 1609(C=N). ^{1}H-NMR (500 MHz, DMSO-d_6, TMS): δ 0.89 (s, 3H, CH_3-19); 1.08 (s, 3H, -CH_3-18); 5.59 (s, 1H, CH-4 of progesterone), 6.53 (s, 1H, pyrimidine proton); 6.62 (d, 1H, furan proton), 6.94 (t, 1H, furan proton), 7.82 (d, 1H, furan proton), 8.12 (s, 1H, NH, D_2O exchangeable). Anal. Calcd. For $C_{27}H_{32}N_2O_3$: C, 74.97 %; H, 7.46 %; N, 6.48%; Found: C, 74.75 %; H, 7.12%; N, 6.32 %.

17-[6-(4-Chlorophenyl)-2-thioxo-1, 2 -dihydro-pyrimidin-4-yl]-3-oxo-androst-4-ene **12c**

Yellow crystals from MeOH. Yield (76%), m.p. 148 ºC. Ms (m/z, %): 494[M^{+2}, 12.1%]; 492[M^+,36.1%]; 381[M^+- *P*-ClC_6H_4, 50.1%]; IR (KBr, cm^{-1}): 3128 (NH), 3080 (C-H, aromatic); 2924 (CH_3); 1699 (C=O); 1654 (C=C); 1609 (C=N); 1190 (C=S). ^{1}H-NMR (500 MHz, DMSO-d_6, TMS): δ 0.71 (s, 3H, CH_3-19); 1.09 (s, 3H, CH_3-18); 5.63 (s, 1H, CH-4, of progesterone), 6.87 (s, 1H, pyrimidine proton); 7.24 (d, 2H, aromatic protons); 7.35 (d, 2H, aromatic protons); 9.93 (s, 1H,NH, D_2O exchangeable). Anal. Calcd. For $C_{29}H_{33}ClN_2OS$: C, 70.60%; H, 6.75%; N, 5.68%; Cl, 7.19. Found: C, 70.30%; H, 6.61%; N, 5.60%; Cl, 7.00%.

17-(6-Furan-2-yl-2-thioxo-1, 2-dihydro-pyrimidin-4-yl)-3-oxo-androst-4-ene **12d**

Pale yellow crystals from MeOH. Yield (63%), m.p. 160 ºC. Ms (m/z, %): 448 [M^+, 23.7%], 372 [M^+- furan, 46%]. IR (KBr, cm^{-1}): 3130 (NH), 3090 (C-H, aromatic); 2924 (CH_3); 1698 (C=O); 1645 (C=C); 1603 (C=N); 1195 (C=S). ^{1}H-NMR (500 MHz, DMSO-d_6, TMS): δ 0.78 (s, 3H, CH_3-19); 1.18 (s, 3H, CH_3-18); 5.62 (s, 1H, CH-4, of progesterone), 6.62 (s, 1H, pyrimidine ring); 6.95 (d, 1H, furan proton), 7.35 (t, 1H, furan proton), 7.83 (d, 1H, furan proton), 10.01 (s, 1H, NH, D_2O exchangeable). Anal. Calcd. For $C_{27}H_{32}N_2O_2S$: C, 72.29 %; H, 7.19 %; N, 6.24 %; Found: C, 72.01 %; H, 7.01%; N, 6.22 %.

17-[2-Amino-6(4-chlorophenyl)-pyrimidin-4-yl] - 3-oxo-androst-4-ene **13a**

White crystals from MeOH. Yield (70%), m.p. 118 ºC. Ms (m/z, %): 477[M^{+2}, 6.3%]; 475[M^+, 18.2%]; 364[M^+- *P*-ClC_6H_4, 47.1%]; IR (KBr, cm^{-1}): 3363 (NH_2), 3085 (C-H, aromatic); 2954 (CH_3); 1700 (C=O); 1645 (C=C); 1609 (C=N). ^{1}H-NMR (500 MHz, DMSO-d_6, TMS): δ 0.87 (s, 3H, CH_3-19); 1.05 (s, 3H, CH_3-18); 5.59 (s, 1H, CH-4, of progesterone), 6.52 (s, 1H, NH_2, D_2O exchangeable), 6.54 (s, 1H, pyrimidine ring), 7.46 (d, 2H, aromatic protons); 7.71 (d, 2H, aromatic protons). ^{13}C-NMR (125 MHz, DMSO-d_6, TMS): δ 20.0 (C-18); 22.5 (C-11); 22.8 (C-19); 25.0(C-16); 26.6 (C-15); 31.3 (C-7); 32.3 (C-6); 34.0 (C-2); 35.0 (C-1); 35.5 (C-8); 36.2 (C-12); 37.2 (C-10); 42.1 (C-13); 50.1 (C-9); 51.2 (C-17); 55.5 (C-14); 123.8 (C-4); 128.8, 129.0 131.4, 134.7 (C-aromatic); 98.6, 159.9, 162.4, 165.0 (C-pyrimidine); 170.0 (C-5), 198.7 (C-3). Anal. Calcd. For $C_{29}H_{34}ClN_3O$: C, 73.17%; H, 7.20%; N, 8.83%; Cl, 7.45%. Found: C, 73.05%; H, 7.02%; N, 8.71%; Cl, 7.30%.

17-(2-Amino-6-furan-2-yl-pyrimidin-4-yl)-3-oxo-androst-4-ene **13b**

Yellow crystals from Benzene. Yield (77%), m.p. 190 ºC. Ms (m/z, %): 431 [M^+, 39.0%]; IR (KBr, cm^{-1}): 3351 (NH_2), 3092 (C-H, aromatic); 2924 (CH_3); 1699 (C=O); 1645 (C=C); 1611 (C=N). ^{1}H-NMR (500 MHz, DMSO-d_6, TMS): δ 0.89 (s, 3H, Me-19); 1.14 (s, 3H, -CH_3-18); 5.62 (s, 1H, CH-4, of progesterone), 6.30 (s, 2H, NH_2, D_2O exchangeable), 6.62 (s, 1H, pyrimidine ring); 6.92 (t, 1H, furan ring), 7.31 (d, 1H, furan ring), 7.83 (d, 1H, furan ring). Anal. Calcd . For $C_{27}H_{33}N_3O_2$: C, 75.14%; H, 7.71 %; N, 9.74%; Found: C, 75.01 %; H, 7.15 %; N, 9.22%.

17-(1-Hydrazonoethyl)-10-(androst-4-ene-3-ylidene) hydrazone **14**

To a solution of progesterone **1** (0.314 g, 0.001 mol) added hydrazine hydrate 98% (0.05 g, 0.001 mol) in ethanol and refluxed for 1 h., the solvent was evaporated under reduced pressure and the residue was purified with the proper solvent.

White crystals from EtOH. Yield (90%), mp. 180 ºC. Ms (m/z, %): 342 [M^+, 34.5%]; IR (KBr, cm^{-1}): 3343 (NH_2), 2872 (CH_3), 1647 (C=C), 1043(C=N);. ^{1}H-NMR (270 MHz, DMSO-d_6, TMS): δ 0.81 (s, 3H, Me-19); 0.90 (s,3H, $\underline{H_3}CC=NNH_2$); 1.09 (s, 3H, -CH_3-18); 5.86 (s, 2H, NH_2, D_2O exchangeable); 5.61 (s, 1H, CH-4, of progesterone). Anal. Calcd. For $C_{21}H_{34}N_4$: C, 73.60%; H, 10.10%; N, 16.40%; Found: C, 73.55%; H, 10.02%; N, 16.36%.

17-(1-2-(phenylcarbamothioyl)hydrazono)ethyl)androst-4-ene-3-ylidine–N-phenylhydrazine-carbothioamide **15**

To a solution of **14** (0.150 g, 0.001 mol) in ethanol (20 ml) phenyl isocyanate (0.135 g, 0.001 mol) was added. The reaction mixture was heated under reflux for about 4h., then cooling it to the room temperature and filters the product which crystallized from (EtOH).

Yellow crystals from EtOH. Yield, 71%, mp. 139 ºC. Ms (m/z, %): 612 [M^+, 25.0%]; IR (KBr, cm^{-1}): 3279 (br,NH), 3016 (C-H, Aromatic), 2922 (CH_3); 1595 (C=N), 1177 (C=S). ^{1}H-NMR (270 MHz, DMSO-d_6, TMS): δ 0.86 (s, 3H, Me-19); 0.91(s, 3H, $C\underline{H_3}C=NNH$); 1.11 (s, 3H, -CH_3-18); 5.40 (s, 1H, CH-4, of progesterone); 6.64-7.11 (m, 10H, phenyl protons); 9.31 (s,1H, NN$\underline{H}$, D_2O exchangeable), 9.36 (s, 1H, NN$\underline{H}$, D_2O Exchangeable), 9.76(s, 1H, NHPh, D_2O Exchangeable), 10.01 (s, 1H, NHPh, D_2O Exchangeable). Anal. Calcd. For $C_{35}H_{44}N_6S_2$: C, 68.60%; H, 7.20%; N, 13.70%; Found: C, 68.52%; H, 7.03%; N, 13.61 %.

Cyclopenta[α]phenanthren-3-hydrazinyl-2-(phenylamino)-1, 3-oxathiolan-5-one **16**

To a solution of **15** (0.600 g, 0.001 mol) in benzene (20 ml), chloroacetic acid (0.094 g, 0.001 mol) was added. The reaction mixture was heated under reflux for about 3h. Then cooled to the room temperature and filtered the product was crystallized from (benzene).

Yellow crystal from benzene. Yield 67%, mp. 162 ºC. Ms (m/z, %):728 [M^+, 45.0%]; IR (KBr, cm^{-1}): 3426(br,NH); 3016 (C-H, Aromatic), 2922 (CH_3); 2849 (CH_2), 1726 (C=O, lactone), 1645 (C=C); 1600 (C=N); 1459 (CH_2 bending). ^{1}H-NMR (270 MHz, DMSO-d_6, TMS): δ 0.88 (s, 3H, Me-19); 0.91 (s. 3H, C$\underline{H}_3$-CH=N); 1.09 (s, 3H, -CH_3-18); 4.04 (d, 4H, 2C$\underline{H}_2$-C=O); 4.28 (s, 2H, 2N$\underline{H}$-Ph, D_2O exchangeable); 5.83 (s, 1H, CH-4, progesterone); 7.31-7.64 (m, 12H, 10 aromatic protons +2 N$\underline{H}$ lactone). ^{13}C-NMR (125 MHz, DMSO-d_6, TMS): δ 20.5 (C-18), 22.2 (C-11), 22.7 (C-19), 23.4 (C-16), 26.6 (C-2), 27.1 (C-15), 28.4 (C$\underline{H}_2$-lactone), 31.4 (C-7), 33.0 (C-6), 35.1 (C-8), 37.1 (C-12), 37.5 (C-17), 38.5 (C-10), 39.1(C-1), 42.0 (C-13),50.1 (C-9), 56.0 (C-14), 111.5 (C-4), 113.2, 117.2, 129.0, 147.6 (C-phenyl), 128.3 (C-lactone), 155.3 (C-3), 164.6 (C$\underline{H}_3$-CH=N), 166.4 (C-5), 172.3 (C=O- lactone). Anal. Calcd. For $C_{39}H_{48}N_6O_4S_2$: C, 64.70%; H, 6.64%; N, 11.53%; Found: C, 64.10%; H, 6.22%; N, 11.01%.

Bioassay

Cytotoxic effect on human cell lines (HEPG2 & MCF7)

Cell viability was assessed by the mitochondrial dependent reduction of yellow MTT [3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazoliumbromide] to purple formazan[26].

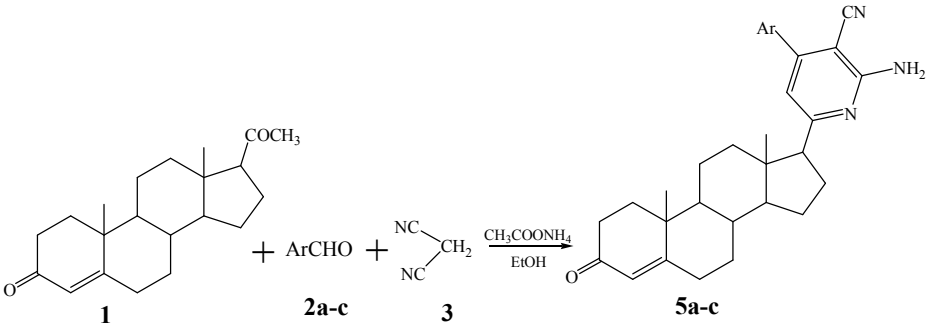
Procedure:

All the following procedures were done in a sterile area using a Laminar flow cabinet biosafety class II level (**Baker, SG403INT, and Sanford, ME, USA**). Cells were batch cultured for 10 days, then seeded at concentration of 10x103 cells/well in fresh complete growth medium in 96-well microtiter plastic plates at 37 ºC for 24 h under 5% CO_2 using a water jacketed Carbon dioxide incubator (**Sheldon, TC2323, Cornelius, OR, USA**). Media was aspirated, fresh medium (without serum) was added and cells were incubated either alone (negative control) or with different concentrations of sample to give a final concentration of (100.00 - 50.00 - 25.00 - 12.50 - 6.25 - 3.13 - 0.78 and 1.56 µg/ml). Cells were suspended in RPMI 1640 medium (for **HePG2** and **MCF7**), 1% antibiotic-antimycotic mixture (10,000 µg /ml Potassium Penicillin, 10,000 µg/ml Streptomycin Sulphate and 25 µg/ml Amphotericin B) and 1% L-glutamine in 96-well flat bottom micro plate at 37 ºC under 5% CO_2. After 48 h of incubation, medium was aspirated, 40 µl MTT salt (2.5 µg/ml) were added to each well and incubated for further four hours at 37ºC under 5% CO_2. To stop the reaction and dissolving the formed crystals, 200 µL of 10% Sodium dodecyl sulphate (SDS) in deionized water was added to each well and incubated overnight at 37ºC. A positive control composed of 100 µg/ml was used as a known cytotoxic natural agent gives 100% lethality under the same conditions.[27]

The absorbance was then measured using a microplate multi-well reader (**Bio-Rad Laboratories Inc., model 3350, Hercules, California, USA**) at 595nm and a reference wavelength of 620 nm. A statistical significance was tested between samples and negative control (cells with vehicle) using independent t-test by SPSS 11 program. DMSO is the vehicle used for dissolution of plant extracts and its final concentration on the cells was less than 0.2%. The percentage of change in viability was calculated according to the formula:
((Reading of extract / Reading of negative control) -1) x 10. A probit analysis was carried for LC_{50} and LC_{90} determination using SPSS 11 program.

2. Results and discussion:

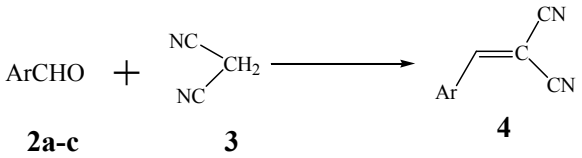
A simple one pot multicomponent reaction technique was utilized[24], for the synthesis of novel biologically active heterocyclic steroids. A mixture of progesterone **1**, aromatic aldehyde **2** and malononitrile **3** were heated in absolute ethanol containing ammonium acetate under reflux to afford the corresponding aminoprogestanopyridine derivatives **5a-c** (Scheme 1).

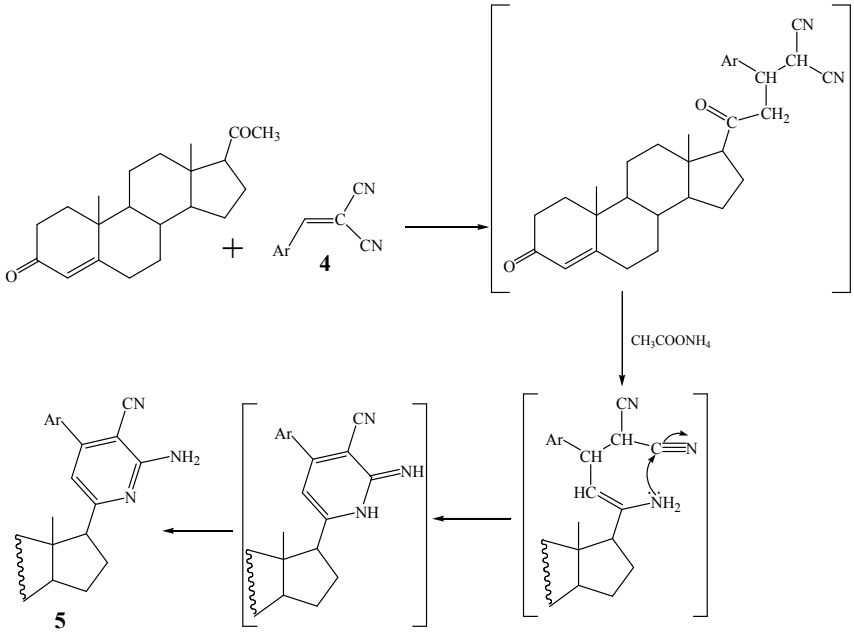


Ar = a: Ph
b:4-ClC_6H_4
c: 2,5-$(OCH_3)_2C_6H_3$

(Scheme 1)

The formation of adducts **5a-c** can be rationalized by initial formation of arylidene malononitrile **4** as fleeting intermediate *via* standard *Knoevenagael* condensation. This is followed by Michael type addition of progesterone **1** to the activated double bond of the arylidene that furnished the adduct product to cyclisize *via* intramolecular rearrangement yielding the desired product **5** (Scheme 2).



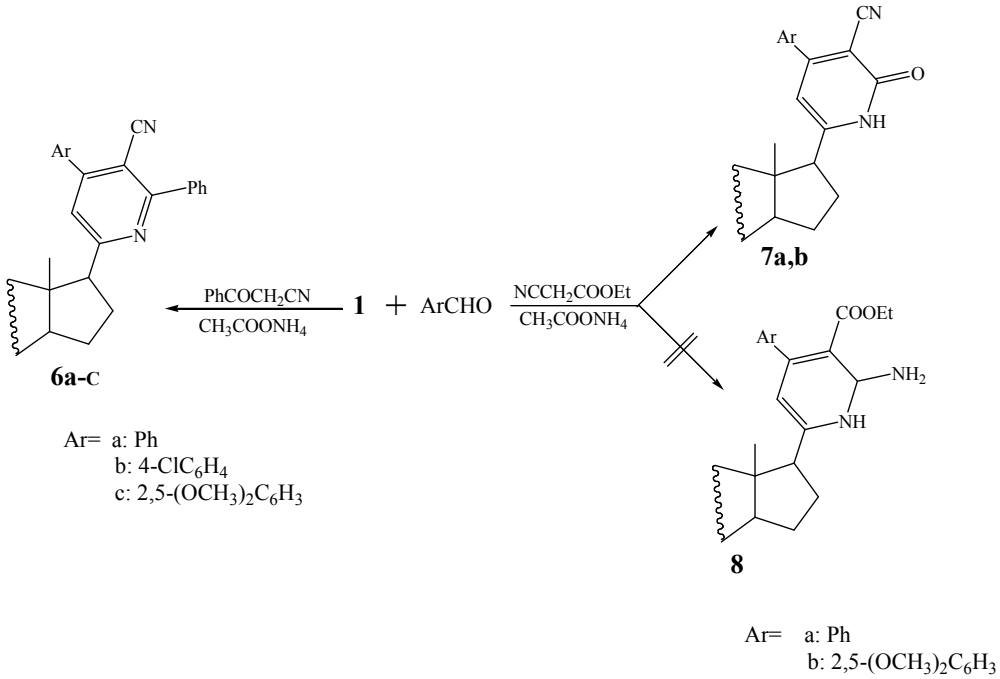


(Scheme 2)

The most important feature to confirm the aromatic structure of compound **5a** was the absence of hydrogen proton in ^{1}H-NMR spectrum of C-4 and NH of pyridine ring. It showed D_2O exchangeable of NH_2 at δ 6.61 ppm. All the other analytical and spectroscopic data were in accordance with the suggested structure **5** (cf. exp. section)

To generalize such methodology and synthesize other different pyridine derivatives, the previous reactions were conducted using other methylene reagents like ω-cyano-acetophenone and ethylcyanoacetate to form the corresponding pyridine derivatives **6a-c** and **7a, b** respectively (Scheme 3).

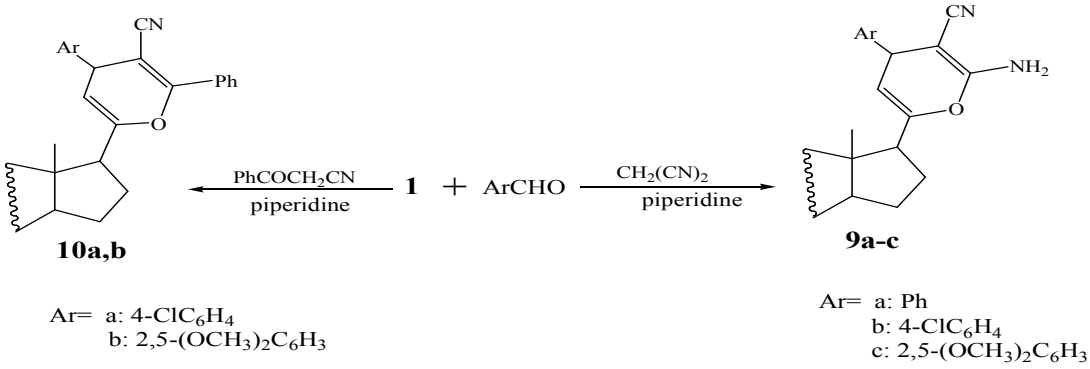
The structures of these products were assigned based on the elemental analysis and other spectroscopic data. The IR spectra showed the presence of the nitrile group at 2219 cm^{-1} and the pyridinone carbonyl group *v* 1689 cm^{-1}, respectively in **7a**, as an example. On the other hand the ^{1}H-NMR revealed the absence of the characteristic signals of the ester ethyl and the amino groups (c.f.exp. section).



(Scheme 3)

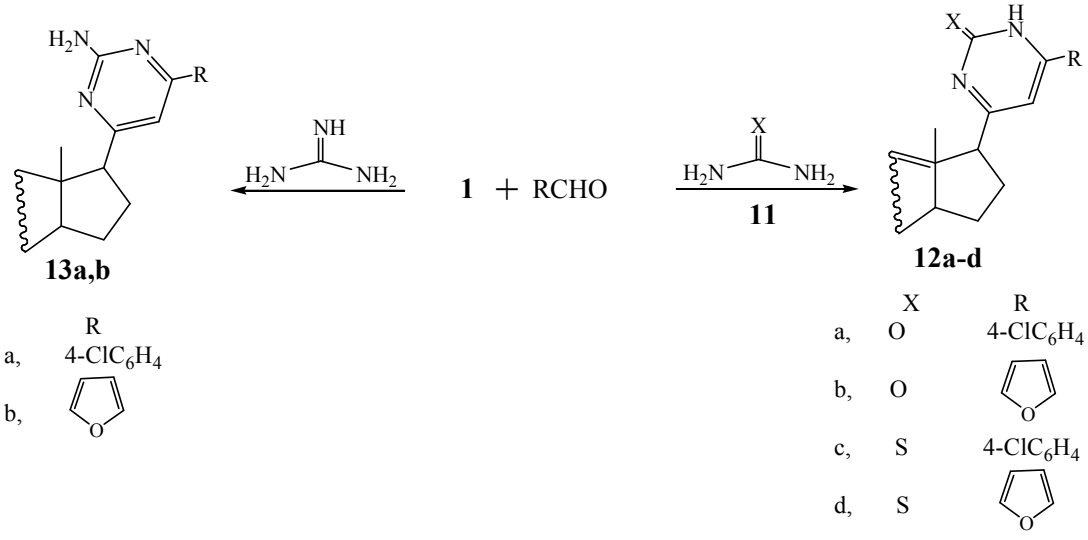
It is believed that compound **8** was not formed due to steric effect because ester group is more bulky than cyano group, so the formation of **7** is more stable.

Carrying out the previous reaction in the presence of piperidine instead of ammonium acetate led to the formation of the aminoprogesteno pyran derivatives **9** and **10** respectively (Scheme 4). All the micro-analysis and spectroscopic data were in accordance with the suggested structures **9a-c** and **10a, b** (c.f. exp. section).



(Scheme 4)

For more utility of the previous phenomena to synthesize different active heterocyclic steroids; urea, thiourea and guanidine were used. A mixture of progesterone **1**, aldehydes and nitrogen reagents **11** and guanidine were allowed to react in freshly prepared sodium methoxide to form the corresponding pyrimidine derivatives **12a-d** and **13a, b** respectively (Scheme 5).

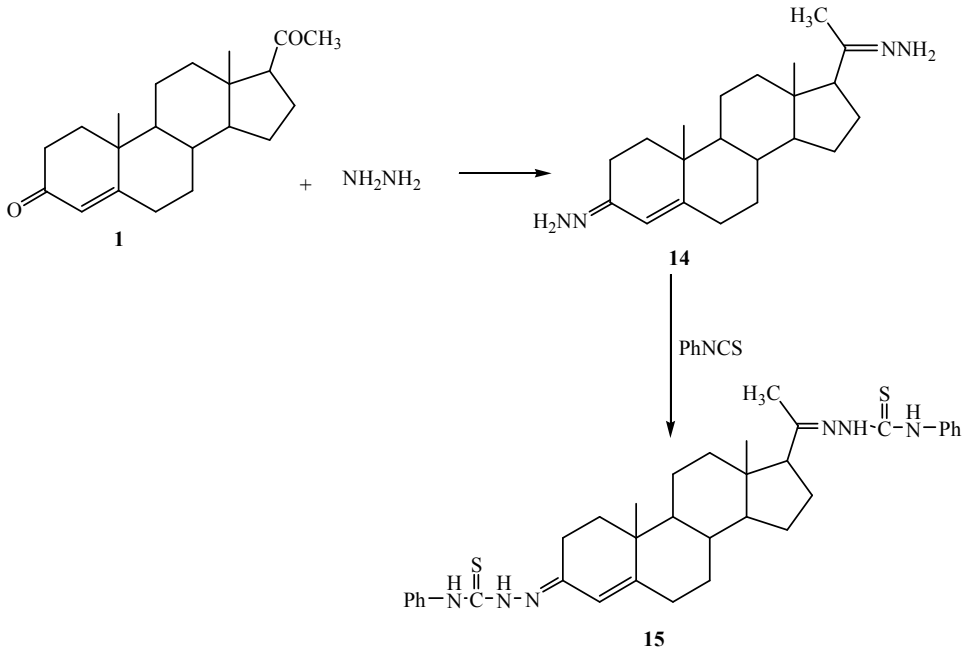


(Scheme 5)

Structure elucidation of **12a** was derived from its spectral data; IR spectrum reflected characteristic bands to the pyrimidine carbonyl group at ν 1659 cm^{-1} and NH band at ν 3158 cm^{-1}. The ^{1}H-NMR showed a singlet at δ 6.97 ppm of pyrimidine proton and D_2O exchangeable signals at δ 7.91 ppm for the NH group.

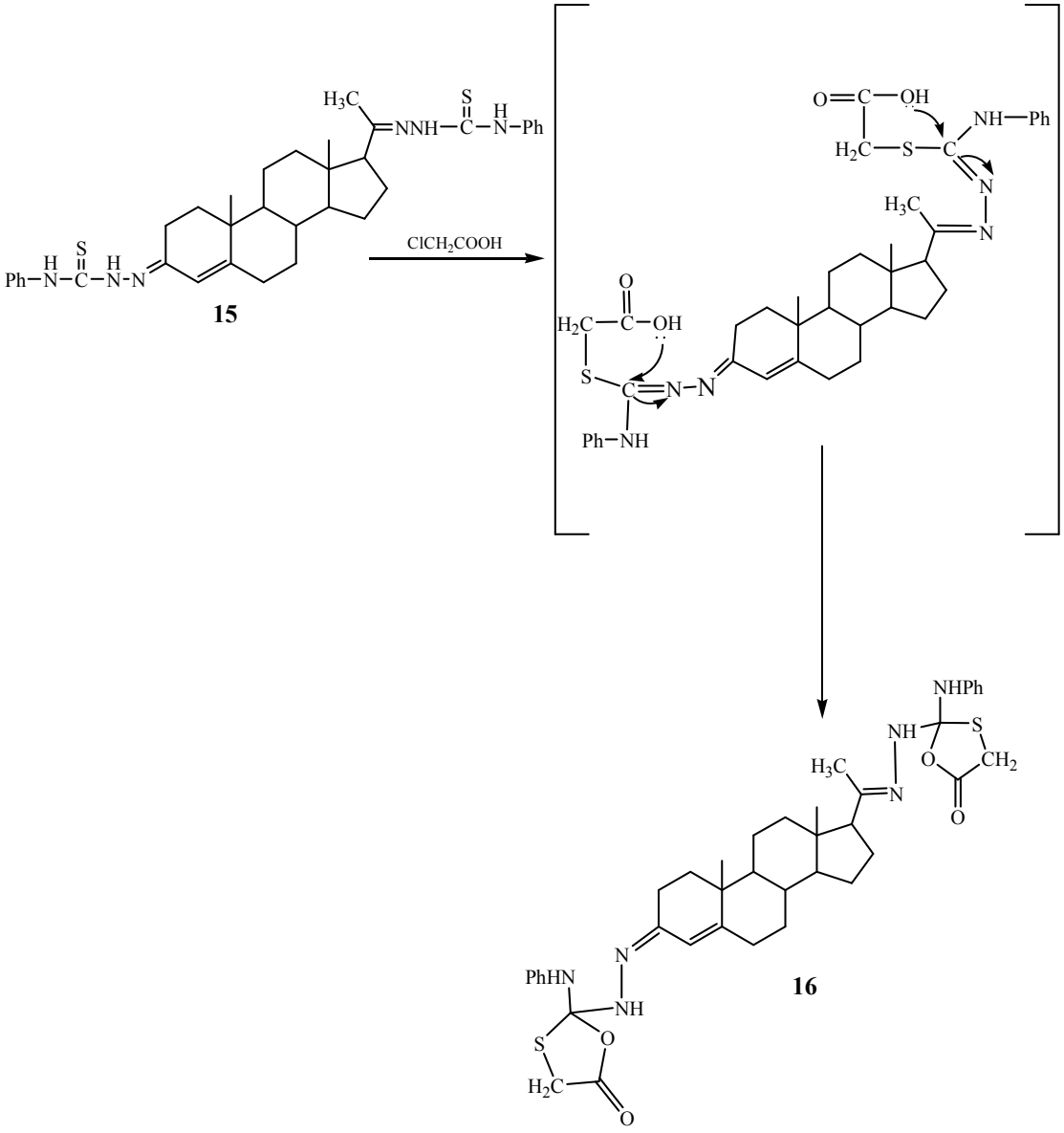
Furthermore, this study was extended to include the behaviour of progesterone **1** towards hydrazine hydrate to produce the hydrazone derivative **14** which was confirmed with analytical and spectroscopic data. Compound **14** was allowed to react with phenyl isothiocyanate to produce the corresponding acyclic structure **15**. (Scheme 6)

The ^{1}H-NMR of adduct **15** reflect the existence of the aromatic protons beside 4NH D_2O exchangeable signals at δ 9.31, 9.36, 9.76, 10.01, respectively (c.f., exp. Section).



(Scheme 6)

The thiobenzoyl adduct **15** was allowed to react with chloroacetic acid in boiling benzene afforded the lactone **16** adduct *via* SN2 mechanism on alkyl moiety rather than carboxyl group (chlorine atom is good leaving group) followed by cyclization on the activated C=N yielded the desired product **16** (Scheme 7).



(Scheme 7)

The IR spectrum of compound **16** exhibits strong absorption bands at ν 1600, 1726 cm^{-1} due to C=N and C=O of γ-lactone[28] (the lower frequency of carbonyl of lactone is due to transannular effect of sulphur atom through the ring). The ^{1}H-NMR spectrum of compound **16** when run in DMSO (d_6) showed the two singlets appearing at 4.04& 4.28 ppm respectively attributed to CH_2 lactone and NHPh. The ^{13}C-NMR explains the chiral carbon at δ128.3ppm (c.f., exp. Section).

Bioactivity
Antitumor activity

Cytotoxicity of Pyridine, Pyran, and Pyrimidine derivatives **5a**, **5b**, **6b, 7a**, **9b, 9c, 12a**, **12c**, and **13a** were bioassayed against two human tumour cell lines namely hepatocellular carcinoma cell line (HEPG2) and Caucasian

breast adenocarcinoma (MCF7) at Bioassay-Cell Culture Laboratory, National Research Centre, Egypt. LC_{50} of promising compounds were calculated after 48 h of continuous drug exposure as shown in Table (1).

Table (1): Cytotoxic activity of some new pyridine, pyran, and pyrimidine derivatives against HEPG2 and MCF7

Code sample	LC_{50} (µg/mL)	
	HEPG2	MCF7
Standard (Doxorubicin)	22.6	42.5
5a	55.2	49.8
5b	58.7	51.4
6b	-----	78.8
7a	19.6	22.3
9b	71.8	-----
9c	-----	84.5
12a	12.7	22.6
12c	-----	------
13a	12.2	8.5

The results displayed in Table (1), the values of LC50 of the compounds **13a**, **12a** and **7a** have high cytotoxic effect more than doxorubicin the chosen anticancer drug in both cell lines. Regarding HEPG2 cell line, LC_{50} values are nearly half that of the standard and their LC_{50} are 12.2 and 12.7 µg/ml for **13a**, **12a** respectively and 19.6 µg/ml for **7a**. While compounds **9b**, **5a** and **5b** have moderate exhibit activity against same cell line with LC_{50} are 71.8, 55.2 µg/ml and 58.7 µg/ml, respectively. Also, the results indicate that compounds **6b, 9c** and **12c** have no activity against liver anticancer cells (Fig. 1). Bio- assayed antitumor activity of the tested compounds against breast cancer cell lines **MCF7.** The results indicated that compounds **13a, 7a, 12a** have highest anticancer activity in comparison with that of the standard drug since its LC_{50} is 8.5, 22.3, and 22.6 µg/ml, respectively, while that of the standard equal to 42.5 µg/ml. On the other hand, compounds **5a**, **6b**, and **9c** showed very low breast anticancer activity, while the **12c** and **9b** compounds are of no cytotoxicity (Fig. 2). Therefore, it could be concluded that compounds **13a**, **12a**, and **7a** have high cytotoxic activity against both types of liver and breast cancer cells subjected in this study. The above mentioned results revealed that the materials under investigation have killing potency to the cancer cells with low concentrations and can be arranged in the following order: progesterone pyrimidine > pyridine > pyran. This may be attributable to the presence of nitrogen moiety in the ring.

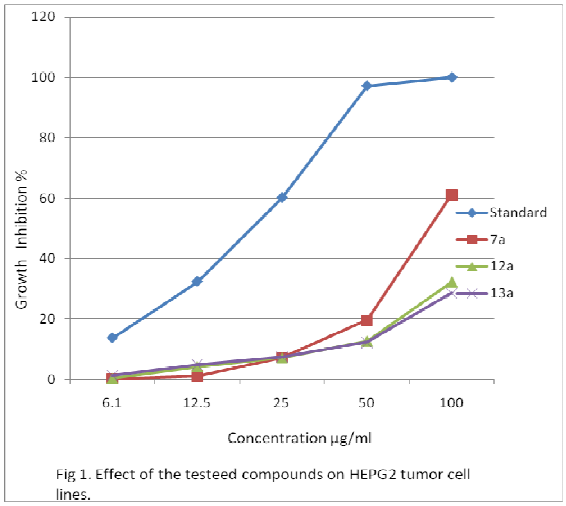


Fig 1. Effect of the testeed compounds on HEPG2 tumor cell lines.

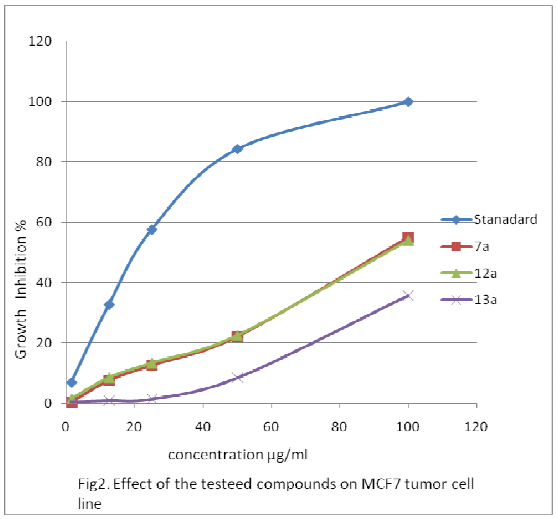


Fig2. Effect of the testeed compounds on MCF7 tumor cell line

References:

1- Blakemore, C. and Jennet, S., (2002).The Oxford Companion to the Body. New York: Oxford University press.,ISBN 019852403x Publchem compound, 458-9.
2- a/www.pubchem.ncbi.n/m.nih.gov/Citations.html.(2011) b/www.chemical book .com/ProductNameList-25-78200-EN.html.
3- Subhash, C., Bhatia, M. D., Shashi, K., Bhatia M. D.(2002) .Diagnosis and Treatment of Premenstrual Dysphoric Disorder. *Am. Fam. Physician*, 66 (77), 1239-1249.
4- Schumacher M., Guennoun R., Robert, F.(2004) .Local Synthesis and dual actions of progesterone in the nervous system: neuroprotection and myelination. *Growth Horm* , IGF 14 (Supp. A), S18-33.
5- Harburger L. L., Bennett J. C., Frick K. M., (2007). Effect of estrogen and progesterone on Spatial memory consolidation inaged females. *Neurobiology of Aging*, 28,602- 610.
6- Murphy L. J., Robert L., Stead B., Leigh C., Lazarus L.,(1986) Progestin Regulation of Epidermal Growth Factor Receptor in Human Mammary Carcinoma Cells. *J. Of Cancer Research*, 86, 728.
7- Hould F. S., Firied G. M.,Fazekas. A. G., Tremblay S., Mersereau W. A., (1988). Progesterone receptors regulate gallbladder motility. *J. Surg. Res*, 45(6), 505-12.
8- Fukuyama A., Tanaka K., Kakizaki I., Kasai K., Chiba M., Nakamura T., Mizunuma H., (2012). Anti-inflammatory effect of proleoglycen and progesterone on human uterine cervical fibroblasts. *Life Sciences*, 13-14, 484-488.
9- Dzugan S., Scipione A., (April 2006), Progesterone Misconceptions, *Life Extension Magazine*.
10- Kenneth A., Burry M. D., Phillip E., Patton M. D., Kent H. (1999). Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen. *Am. J. Jobstet Gynecol*, 180 (6) part 1, 1504-1511.
11- Bringmann G., Reichert Y., Kane V., (2004).The total synthesis of streptonigrin and related antitumor antibiotic natural products, *Tetrahedron*, 60, 3539.
12- Galvilan M. D., Gomez-Vidal J. A., Serrano F. R.,(2008). Anticancer activity of (1,2,3,5-tetrahydro-4, 1-benzoxazepine-3-yl)-pyrimidines and -purines against the MCF-7 cell line: Preliminary c-DNA microarray studies, *Bio. Med. Chem. Lett.,* 18, 1457-1460.
13- Zhou Y., Kijima T., Kuwahara S., Watanabe M., Izumi T.,(2008). Synthesis of ethyl 5-cyano-6-hydroxy-2-methyl-4-(1-naphthyl)-nicotinate, *Teterahedron lett.*, 49, 3757.
14- Franco L. H., Joffe E. B. K., Puricelly L., Tatian M., Selde A. M., Palermo J. A.,(1998) . Indole alkaloids from the tunicate Aplidium meridianum, *J. Nat. Prod.*, 61, 1130.
15- Farhanullah F, Agarwal N., Goel A., Ram V. J., (2003)Synthesis of Aminonicotinonitriles and Diaminopyridines through Base-Catalyzed Ring Transformation of 2H-Pyran-2-ones, *J. Org. Chem.*, 68, 2983.
16- Cooke M. W., Hanan G. S.,(2007) Luminescent polynuclear assemblies, *Chem. Soc. Rev.* 36, 1466.
17- Constable E. C., (2007) 2, 2′:6′, 2″-Terpyridines: From chemical obscurity to common supramolecular motifs, *Chem. Soc. Rev.*, 36, 246-253.

18- Werner W, Letsch G, Ihn W, Sohr R, Preiss R (1991). Synthesis of a potential metabolite of the carcinostatic bendamustin (Cytostasen), *Pharmazie*, 46,610.
19- Wang J. L., Liu D., Zhang Z. J., Shan S., Han X., (2000).Structure-based discovery of an organic compound that binds Bcl-2 protein and induces apoptosis of tumor cells, *Proc. Natl., Acad Sci*., 97, 7124-7129.
20- David R., Ana C. G., Jackson A. L., Wilson C., Evellyne A., Clandia P., Manoel O., Leticia V., Costa L., Raquel C., Vitor F.,(2011) .Synthesis of new 9-hydroxy-α- and 7- hydroxy-β-pyrannaphthoquinones and cytotoxicity against cancer cell lines , *Org. Biomol. Chem.*, 9 , 4315-4322.
21- Stephen J., Judith G., Micheal A.,(1978). Derepression of Nuclear Template Restrictions for DNA Synthesis by the Immunostimulator Pyran Copolymer, *J. of Cancer Res*., 38, 1610-1616.
22- Hata Keyama S., Ochi N., Numata H., Takano S., (1988).3-methoxycarbonyldihydropyrans; enatioselective synthesis of (−)-methyl elenolate, *J. Chem. Commun.*, 17, 1202- 1204.
23- Gonzalez R., Martin N., Seoan C., Marco J. L., Albert A., Cano F. H.,(1992;) The first asymmetric synthesis of polyfunctionalized 4H-pyrans via Michael addition of malononitrile to 2-acyl acrylates, *Tetrahedron Lett.*, 33, 3809-3812.
24- Mohamed N. R., Khaireldin N. Y., Fahmy A. F.,, El-Sayed A.A., , (2010).Facile synthesis of fused nitrogen containing heterocycles as anticancer agents, *Der Pharma Chemica*, 2(1), 400-417.
25- Abdel Halim M.M., Kamel E. M., Rabie S. T., Mohamed N. R.; (2011). Synthesis and biological evaluation of some nitrogen containing steroidal heterocycles; 76, 78-84.
26- Mosmann T., (1983) Rapid colorimetric assay for cellular growth and survival: Application to proliferation and cytotoxicity assays, *J. Immunol. Methods*. 65, 55-63.
27- Thabrew, M. I. ,Hughes, R. D., McFarlane, I. G., (1997). Screening of hepatoprotective plant components using a HepG2 cell cytotoxicity assay, *J. Pharm. Pharmacol.,* 49, 1132-5.
28- Silvrstein R. M., Bassler G. C., Morrill C. T., (1991). *Spectrometric Identification of organic compounds*. (5th ed.). John Wiley & Sons, New York.

This academic article was published by The International Institute for Science, Technology and Education (IISTE). The IISTE is a pioneer in the Open Access Publishing service based in the U.S. and Europe. The aim of the institute is Accelerating Global Knowledge Sharing.

More information about the publisher can be found in the IISTE's homepage: http://www.iiste.org

CALL FOR PAPERS

The IISTE is currently hosting more than 30 peer-reviewed academic journals and collaborating with academic institutions around the world. There's no deadline for submission. **Prospective authors of IISTE journals can find the submission instruction on the following page:** http://www.iiste.org/Journals/

The IISTE editorial team promises to the review and publish all the qualified submissions in a **fast** manner. All the journals articles are available online to the readers all over the world without financial, legal, or technical barriers other than those inseparable from gaining access to the internet itself. Printed version of the journals is also available upon request of readers and authors.

IISTE Knowledge Sharing Partners

EBSCO, Index Copernicus, Ulrich's Periodicals Directory, JournalTOCS, PKP Open Archives Harvester, Bielefeld Academic Search Engine, Elektronische Zeitschriftenbibliothek EZB, Open J-Gate, OCLC WorldCat, Universe Digtial Library , NewJour, Google Scholar