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CHEMICAL AND PHOTOCHEMICAL BEHAVIOR OF PROGESTERONE HYBRIDS WITH ANTIVIRAL ACTIVITY

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ABSTRACT

The reaction of progesterone 1 with different aromatic aldehydes refluxed in absolute ethanol in the presence of sodium hydroxide afforded new progesterone chalcone hybrids (2a-e). Chalcone progesterone 2b reacted with (cyclohexyl amine, *o*-anisidine and *p*-toluidine) in boiling absolute ethanol to yield the corresponding adducts (3, 4 and 5). Treatment of 2b with (2-aminothiophenol) gave the adduct 6. Hetero-aryl chalcones (2d,e) were exposed to UV lamp (125w) in the presence of benzene yielded cyclobutane derivatives (7a,b). Compound 2d,e were irradiated in ethanol a pinacol dimeric products were obtained 8a,b. The antiviral of some newly products were examined.

Key words: Progesterone, chalcones, aza-micheal and thia-micheal reaction, UV irradiation.

INTRODUCTION

Chalcones (1,3-diaryl-2-progen-1-ones) are secondary metabolite precursors of flavonoids and isoflavonoids that are commonly found in edible plants. The good safety profile, the possibility of oral administration[1] and the ease of synthetic steps are the major factors contributing to the increasing interest in exploring the pharmacological activities of chalcones. Chalcones and their heterocyclic analogues exert various biological activities; such as anti-inflammatory[2,3], analgesic[3], antiulcerative[4], antiviral[5], antifungal[6], antimalarial[7], bactericidal[8], insecticidal [9], anti-fertility [10] and sedative[11]activities. Several research groups have focused on the antitumor activities of this class of compounds. There are a number of reports on the activity of chalcones against several cell lines including prostate[12] and breast cancer[13] in low nanomolar concentrations. In this work, a series of progesterone chalcone hybrids was synthesized. The cyclo pentanoperhydro phenanthrene moiety was fixed and diversity was created by introducing different substituent one carbon 3 of 2-propene-1-one moiety.

The intramolecular photocycloaddition of chalcones, heteroaryl chalcones and their derivatives yielded the cyclobutane ring adduct as the photochemical dimerization of α,β-unsaturated carbonyl compounds and particular of 1,3-diaryl-2-propen-1-one(chalcones)[14,15,16,17,18]. It has been proven to be fast and simple method to minimize the cyclopentane ring to the tricycles' system. The cycloaddition of trans-chalcones may give four possible stereoisomers, namely syn, anti, head-to-head and head-to-tail. The formation of stereoisomers depends on the state of the

substrate solution, solid or molten state; meanwhile, the regiospecific ring closure is certainly favored by the precursors' structures. In the literature various cyclobutane containing chalcones have been reported to be synthesized and isolated from various plants[16,19,20].

MATERIALS AND METHODS:

General Procedure: Synthesis of 2a-e: To a solution of progesterone **1** (0.134 g, 0.001 mol), aldehyde (30 ml) (0.001 mol) in ethanol was added in the presence of sodium hydroxide. The reaction mixture was heated under reflux for 3-5 hr., 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.

Androst-4-ene-17-(3-phenyl acryloyl)-3-one (2a): Yellow crystals from EtOH. Yield (82%), mp.109ºC. Ms (EI) m/z, (%): 402 [M^+,8.0%],; IR (KBr, cm^{-1}): 3028 (C-H, aromatic); 2938 (CH_3); 1676 (2C=O); 1606 (C=C). ^{1}H-NMR (500 MHz, DMSO-d_6, TMS): δ 0.88 (s, 3H, CH_3-19); 1.09 (s, 3H, -CH_3-18); 5.57 (s, 1H, CH-4 of progesterone); 6.91 (d, 1H, PhCH=C<u>H</u>); 7.18-7.26 (m, 3H, aromatic protons); 7.60-7.67 (m, 3H, 2 aromatic protons + 1H PhC<u>H</u>=CH). Anal. Calcd. For $C_{28}H_{34}O_2$: C, 83.51%; H, 8.58%; Found: C, 83.40%; H, 8.50%.

17-(3-(4-Chlorophenyl)acryloyl)-androst-4-ene-3-one (2b): Yellow crystals from MeOH. Yield (91%), mp.184ºC. Ms (EI) m/z, (%): 438 [M^{+2},8.3%], 436 [M^+,24.1] ; IR (KBr, cm^{-1}): 3045 (C-H, aromatic); 2948 (CH_3); 1701 (C=O); 1669 (C=O); 1608 (C=C). ^{1}H-NMR (500 MHz, DMSO-d_6, TMS): δ 0.89 (s, 3H, CH_3-19); 1.10 (s, 3H, CH_3-18); 5.59 (s, 1H, CH-4 of progesterone); 6.24 (d, 1H, ArCH=C<u>H</u>); 7.24-7.62 (m, 5H, 4H aromatic protons + 1H ArC<u>H</u>=CH). Anal. Calcd. For $C_{28}H_{33}ClO_2$: C, 76.91%; H, 7.62%; Found: C, 76.12%; H, 7.35%.

17-(3-(2,5- dimethoxy phenyl)acryloyl)-androst-4-ene-3-one (2c): Yellow crystals from EtOH. Yield (91%), mp.181ºC. Ms (EI) m/z, (%): 462 [M^+,13.7%]; IR (KBr, cm^{-1}): 3102 (C-H, aromatic); 2933 (CH_3); 1675 (2 C=O); 1603 (C=C). ^{1}H-NMR (500 MHz, DMSO-d_6, TMS): δ 0.88 (s, 3H, CH_3-19); 1.12 (s, 3H, CH_3-18); 3.72 (s, 6H, $2OCH_3$) 5.57 (s, 1H, CH-4 of progesterone); 6.50 (d, 1H, ArCH=C<u>H</u>); 7.70-7.89 (m, 3H, 3 aromatic protons); 7.81 (d, 1H, ArC<u>H</u>=CH). Anal. Calcd. For $C_{30}H_{38}O_4$: C, 77.91%; H, 8.32%; Found: C, 76.99%; H, 8.21%.

17-(3-(furan-2-yl)acryloyl)-androst-4-ene-3-one (2d): Yellow crystals from MeOH. Yield (68%), mp.115ºC. Ms (EI) m/z, (%): 392[M^+,16.1%]; IR (KBr, cm^{-1}): 3098 (C-H, aromatic); 2937 (CH_3); 1701(C=O); 1664 (C=O); 1604 (C=C). ^{1}H-NMR (500 MHz, DMSO-d_6, TMS): δ 0.89 (s, 3H, CH_3-19); 1.09 (s, 3H, CH_3-18); 5.60 (s, 1H, CH-4 of progesterone); 6.56 (t, 1H, furan ring); 6.62 (d, 1H, ArCH=C<u>H</u>); 6.94 (d, 1H, furan ring); 7.31 (d, 1H, ArC<u>H</u>=CH); 7.92 (d, 1H, furan ring). Anal. Calcd. For $C_{26}H_{32}O_3$: C, 79.61%; H, 8.22%; Found: C, 79.09%; H, 8.00%.

Androst-4-ene-17-(3-(thiophen-2-yl)acryloyl)-3-one (2e): Brown crystals from EtOH. Yield (85 %), mp.162ºC. Ms (EI) m/z, (%): 408 [M^+,6.9%]; IR (KBr, cm^{-1}): 2937 (CH_3); 1715 (C=O); 1673 (C=O); 1615 (C=C). ^{1}H-NMR (500 MHz, DMSO-d_6, TMS): δ 0.88 (s, 3H, CH_3-19); 1.06 (s, 3H, CH_3-18); 5.52 (s, 1H, CH-4 of progesterone); 6.67 (d, 1H, ArCH=C<u>H</u>); 7.03 (t, 1H, thiophene ring); 7.51-7.69 (m, 2H, thiophene ring + ArC<u>H</u>=CH). Anal.

Calcd. For $C_{26}H_{32}O_2S$: C, 76.42%; H, 7.92%; S, 7.85; Found: C, 76.10%; H, 7.60%; S, 7.55%.

General procedure: Synthesis of 3, 4, 5 and 6. To a solution of **2b** (0.001 mol) in ethanol (20 ml); cyclohexyl amine, o-anisidine, p-toludine and 2-amino thiophenol (0.001 mol) was added. The reaction mixture was heated under reflux for about 4hr., then cooling it to the room temperature; the product was filtered and crystallized from (EtOH).

17-(3-(4-Chlorophenyl)-3-(cyclohexylamine)propanoyl)-androst-4-ene-3-one (3). Orange crystals from EtOH. Yield (89%), mp.142ºC. Ms (EI) m/z, (%): 537 [M^{+2},7.1%], 535[M^{+},20.6]; IR (KBr, cm^{-1}): 3386 (NH); 3045 (C-H, aromatic); 2922 (CH_3); 1998 (C=O); 1656 (C=O); 1610 (C=C). ^{1}H-NMR (500 MHz, DMSO-d_6, TMS): δ 0.86 (s, 3H, CH_3-19); 1.09 (s, 3H, -CH_3-18); 2.06 (m, 1H, NH); 2.56-2.90 (m, 2H, CH_2); 4.25-4.27 (m, 1H, CH); 5.61 (s, 1H, CH-4 of progesterone); 7.26-7.46 (m, 4H, aromatic protons). Anal. Calcd. For $C_{34}H_{46}ClNO_2$: C, 76.22%; H, 8.77%; N, 2.66%; Cl, 6.61%; Found: C, 76.01%; H, 8.53%; N, 2.12%; Cl, 6.62%.

17-(3-(4-Chlorophenyl)-3-(2-methoxyphenylamino)propanoyl)-androst-4-ene-3-one (4): Yellow crystals from EtOH. Yield (65 %), mp.198ºC. Ms (EI) m/z, (%): 561 [M^{+2},12.5%],559 [M^{+},37.1] ; IR (KBr, cm^{-1}): 3445 (NH); 3045 (C-H, aromatic); 2938 (CH_3); 1705 (C=O); 1669 (C=O); 1608 (C=C). ^{1}H-NMR (500 MHz, DMSO-d_6, TMS): δ 0.91 (s, 3H, CH_3-19); 1.15 (s, 3H, -CH_3-18); 3.04-3.12 (m, 2H, CH_2); 3.83 (s, 3H, OCH_3); 4.21-4.25 (m, 1H, CH); 4.71(m, 1H, NH); 5.46 (s, 1H, CH-4 of progesterone); 6.32-6.88 (m, 4H, phenyl protons); 7.22-7.41 (m, 4H, p-Cl aromatic protons). Anal. Calcd. For $C_{35}H_{42}ClNO_3$: C, 75.12%; H, 7.62%; Cl, 6.33%; Found: C, 74.85%; H, 7.23%; Cl, 6.1%.

17-(3-(p-toluidino)-3-(4-Chlorophenyl)propanoyl)-androst-4-ene-3-one(5): Yellow crystals from EtOH. Yield (71%), mp.123ºC. Ms (EI) m/z, (%): 545 [M^{+2},8.1%],543 [M^{+}, 24.1]; IR (KBr, cm^{-1}): 3423 (NH); 3065 (C-H, aromatic); 2938 (CH_3); 1700 (C=O); 1657 (C=O); 1608 (C=C). ^{1}H-NMR (500 MHz, DMSO-d_6, TMS): δ 0.89 (s, 3H, CH_3-19); 1.09 (s, 3H, -CH_3-18); 3.06- 3.15 (m, 2H, CH_2); 4.15-4.20 (m, 1H, CH); 4.68 (m, 1H, NH); 5.46 (s, 1H, CH-4 of progesterone); 6.32- 6.84 (m, 4H, phenyl protons); 7.12-7.37 (m, 4H, p-Cl aromatic protons). Anal. Calcd. For $C_{35}H_{42}ClNO_3$: C, 77.32%; H, 7.80%; Cl, 6.52%; Found: C, 77.05%; H, 7.47%; Cl, 6.09%.

17-(3-(2-aminophenylthio)-3-(4-Chlorophenyl)propanoyl)-androst-4-ene-3-one (6): Brown crystals from EtOH. Yield (81%), mp.125ºC. Ms (EI) m/z, (%): 563 [M^{+2},9.1%], 561[M^{+},27.0]; IR (KBr, cm^{-1}): 3451 (NH_2); 3060 (C-H, aromatic); 2934 (CH_3); 1700 (C=O); 1662 (C=O); 1609 (C=C). ^{1}H-NMR (500 MHz, DMSO-d_6, TMS): δ 0.91 (s, 3H, CH_3-19); 1.13 (s, 3H, -CH_3-18); 3.01- 3.16 (m, 2H, CH_2); 4.28 (t, 1H, CH); 5.41 (s, 1H, NH_2); 5.61 (s, 1H, CH-4 of progesterone); 6.40-6.95 (m, 4H, phenyl protons); 7.27-7.49 (m, 4H, p-Cl aromatic protons). Anal. Calcd. For $C_{34}H_{40}ClNO_2S$: C, 72.68%; H, 7.25%; N, 2.51 %; Cl, 6.31; Found: C, 72.05%; H, 7.14%; N, 2.08 %; Cl, 6.11%.

General procedure of 7a,b: A solution of **2d,e** (0.001 mol) in benzene (300 ml) in a Pyrex vessel was irradiated with a high pressure Mercury lamp (HP, Philips, 125 W) for 6-8 hrs . The reaction was monitored by thin layer chromatography (TLC) using

aluminum sheets with silica gel 60 F254 (Merck). After evaporation of the solvent, the residue was chromatographed using (silica gel, 60 mesh) with eluent (ethyl acetate: petroleum ether 40-60, 8:2) to yield the photoproducts **7a,b**.

2,4-di(furan-2-yl)cyclobutane-1,3-diyl)bis(androst-4-ene-3-one-methanone) (7a): Yellow crystals. Yield (55%), mp.90 ºC. Ms (EI) m/z, (%): 392 [1/2 M^+,7 %]; IR (KBr, cm^{-1}): 2928 (CH_3); 1702(C=O); 1661 (C=O). ^{1}H-NMR (500 MHz, DMSO-d_6, TMS): δ 0.89 (s, 3H, CH_3-19); 1.12 (s, 3H, CH_3-18); 4.10 (m, 2H, methylene protons of cyclobutane); 5.59 (s, 1H, CH-4 of progesterone); 6.70 (t, 1H, furan ring); 7.33 (d, 1H, furan ring); 7.79 (d, 1H, furan ring); 9.30 (s, 1H, OH, the compound exhibit keto enol form). Anal. Calcd. For $C_{26}H_{32}O_3$: C, 79.61%; H, 8.22%; Found: C, 79.09%; H, 8.00%.

2,4-di(thiophen-2-yl)cyclobutane-1,3-diyl)bis(androst-4-ene-3-one-methanone) (7b): Yellow crystals. Yield (61%), mp.81 ºC. Ms (EI) m/z, (%): 816 [M^+, 5%]; IR (KBr, cm^{-1}): 2937 (CH_3); 1715(C=O); 1672 (C=O). ^{1}H-NMR (500 MHz, DMSO-d_6, TMS): δ 0.89 (s, 3H, CH_3-19); 1.12 (s, 3H, CH_3-18); 4.16 (m, 2H, methylene protons of cyclobutane); 5.56 (s, 1H, CH-4 of progesterone); 7.03 (t, 1H, thiophene ring); 7.51 (d, 1H, thiophene ring); 7.77 (d, 1H, thiophene ring); 9.95 (s, 1H, OH, the compound exhibit keto enol form). Anal. Calcd. For $C_{26}H_{32}O_3$: C, 79.61%; H, 8.22%; Found: C, 79.09%; H, 8.00%.

General procedure of 8a,b: A solution of **2d,e** (0.001 mol) in ethanol (300 ml) was irradiated for 7-9 hrs, until the starting material had disappeared indicated by TLC. The solvent was evaporated to furnish the photoproducts **8a, b.**

(1E,5E)-1,6-di(furan-2-yl)-3,4-di(androst-4-ene-3-one)hexa-1,5-diene-3,4-diol (8a): Yellow crystals. Yield (87%), mp. over 300 ºC. Ms (EI) m/z, (%): 784 [M^+-2H,6 %]; IR (KBr, cm^{-1}): 3450 (OH); 2940 (CH_3); 1701(C=O); 1663 (C=O);1603(C=C). ^{1}H-NMR (500 MHz, DMSO-d_6, TMS): δ 0.89 (s, 3H, CH_3-19); 1.09 (s, 3H, CH_3-18); 5.56 (s, 1H, CH-4 of progesterone); 6.52 (t, 1H, furan ring); 6.06 (d, 1H, -C<u>H</u>=CHAr); 6.71(d, 1H, -CH=C<u>H</u>Ar); 6.87 (d, 1H, furan ring); 7.56 (d, 1H, furan ring); 8.10 (s, 1H, OH). Anal. Calcd. For $C_{26}H_{32}O_3$: C, 79.61%; H, 8.22%; Found: C, 79.09%; H, 8.00%.

(1E,5E)-1,6-di(thiophen-2-yl)-3,4-di(androst-4-ene-3-one)hexa-1,5-diene-3,4-diol (8b): Yellow crystals. Yield (91%), mp.over 300 ºC. Ms (EI) m/z, (%): 818 [M^+, 2 %]; IR (KBr, cm^{-1}): 3425 (OH); 2925 (CH_3); 1670 (C=O); 1606 (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); 5.56 (s, 1H, CH-4 of progesterone); 5.82 (d,1H,-C<u>H</u>=CHAr); 6.68 (d, 1H, -CH=C<u>H</u>Ar), 7.13 (t, 1H, thiophene ring); 7.52 (d, 1H, thiophene ring); 7.72 (d, 1H, thiophene ring); 8.93 (s, 1H, OH). Anal. Calcd. For $C_{26}H_{32}O_3$: C, 79.61%; H, 8.22%; Found: C, 79.09%; H, 8.00%.

Bioassay: (Plaque reduction assay):
Assay was carried out according to the method[22] in a six well plate where MDCK cells (10^5cells/ml) were cultivated for 24 hrs at 37^{o}C. A/CHICKEN/ QALUBIA/ 1/2006 (H5N1) virus was diluted to give 10^4 PFU/well and mixed with the safe concentration of the tested compounds. 1 µg/ml of L-1-(tosyl-amido-2-phenyl) ethyl chloromethyl ketone (TCPK) was incubated for 1 hour at 37^{o}C before being added to the cells. Growth medium was removed from the cell culture plates and virus-cpd or virus-extract and Virus-Zanamivir mixtures were

inoculated (100 µl/well). After 1 hour contact time for virus adsorption, 3 ml of DMEM supplemented with 2% agarose was added onto the cell monolayer, plates were left to solidify and incubated at 37^{o}C till formation of viral plaques (3 to 4 days). Formalin (10%) was added for two hours then plates were stained with 0.1% crystal violet in distilled water. Control wells were included where untreated virus was incubated with MDCK cells and finally plaques were counted and percentage reduction in plaques formation in comparison to control wells was recorded as following

% inhibition=viral count (untreated) - viral count (treated)/viral count (untreated)x100

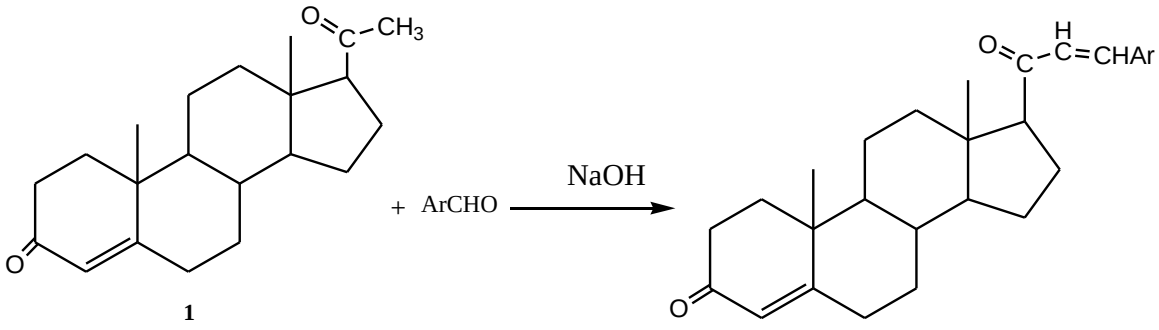
RESULTS AND DISCUSSION

A mixture of progesterone **1**, aldehydes (benzaldhyde, 4-Chloro-benzaldhyde, 2,5-dimethoxybenzaldehyde, furfuraldhyde, thiophenaldhyde) were heated in absolute ethanol in the presence of sodium hydroxide under reflux to afford the corresponding progesterone-chalcone hybrids **2a-e** (via Claisen Schmidt Condensation) between ketone and aldehydes catalyzed by alkali metal hydroxide[21]. The proposed structure for 2a-e was supported by IR spectra data showed strong absorption band at 1715-1664 cm^{-1} (C=O) and 1615-1603 cm^{-1} (C=C). The ^{1}H-NMR spectra (DMSO, δ ppm) showed bands at 6.24-6.91 corresponding to protons of (ArCH=C<u>H</u>) and at 7.24-7.81 due to protons of (ArC<u>H</u>=CH). When Chalcone Progesterone 2b reacted with different Aza-Micheal compounds namely (Cyclohexyl amine, *O*-anisidine and *P*-toluidine) were heated in absolute ethanol under reflux afford the corresponding adducts 3, 4 and 5.

The structures of compounds **3, 4, 5** were confirmed by IR spectra showed strong absorption band at 3489-3389 cm^{-1} (NH), 1705-1656 cm^{-1} (C=O). ^{1}H-NMR spectra (DMSO, δ ppm) showed bands at 2.56-3.15 (CH_2), 2.06-4.71 (NH), 4.15- 4.27(CH). Furthermore, chalcone progesterone **2b** reacted with Thia-Micheal compound namely (2-aminothiophenol) was heated in absolute ethanol under reflux to furnish the corresponding adduct **6.**

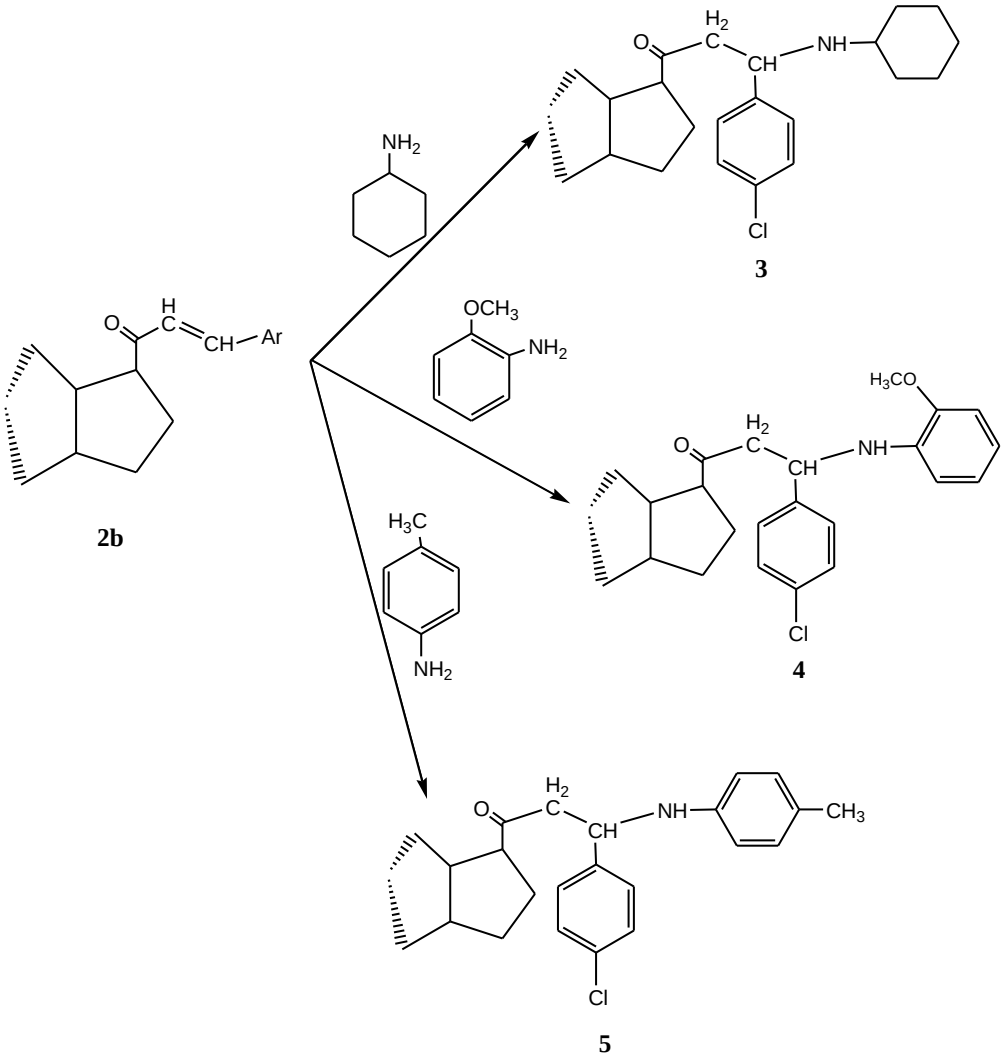
The reaction takes place via nucleophilic attack by lone pair of sulphur atom on the β-carbon and not by lone pair of nitrogen atom. This seems to be logical because sulphur is more nucleophilic than nitrogen. The structure of compounds **6** was confirmed by IR spectra which showed strong absorption band at 3451 cm^{-1} (NH_2), 1700 cm^{-1} (C=O) and 1662 cm^{-1} (C=O). ^{1}H-NMR spectra (DMSO, δ ppm) showed bands at 3.01-3.16 corresponding to (CH_2) proton, 4.28 (CH) and 5.41 (NH_2) proton. This study was extended to include the behavior of heteroaryl chalcones **2d,e** towards UV lamp (HP, Philips, 125W) for 6-8 hrs. in the presence of benzene to yield the cyclobutane derivatives **7a, b**.

The reaction takes place via intermolecular photocycloaddition (photochemical dimerization of α, β-unsaturated carbonyl compounds; (2+2) π electrons is photochemically allowed. The structures of compounds **7a,b** were confirmed by IR spectra which showed strong absorption band at 1661-1672 cm^{-1} (C=O). ^{1}H-NMR spectra (DMSO, δ ppm) showed bands at 4.10-4.16 for methylene protons of cyclobutane. On the other hand, when the solution of compounds **2d,e** were irradiated in ethanol for 7-9 hrs., (alcohols are excellent hydrogen donor), photo reduction of chalcone takes place and a pinacol dimeric products were obtained **8a,b**.



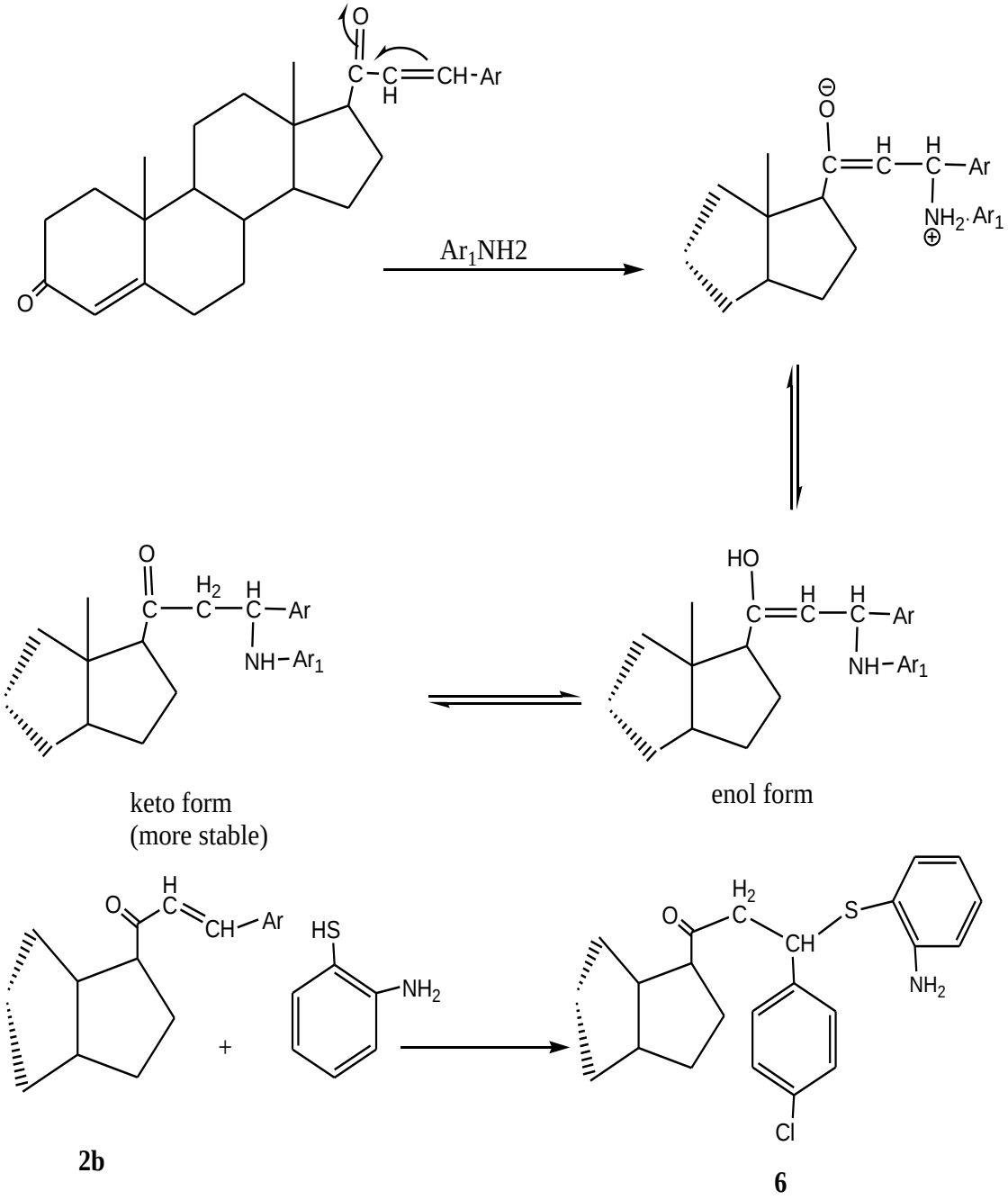
1 **2 a-e**

Ar a, C_6H_5
b, 4-C_6H_4Cl
c, 2,5-$(OCH_3)_2C_6H_3$
d, C_4H_3O
e, C_4H_3S

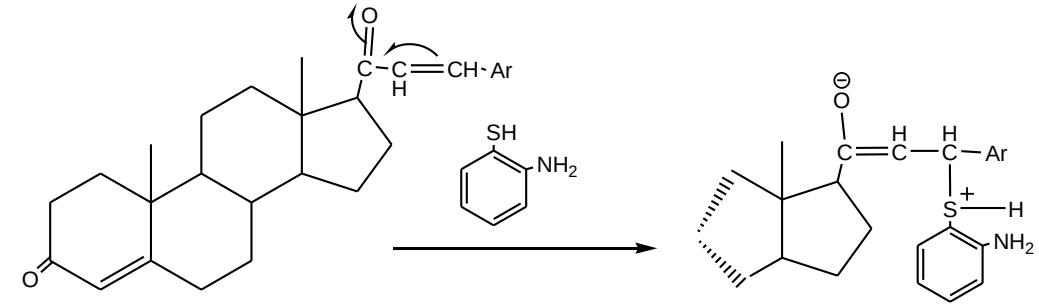


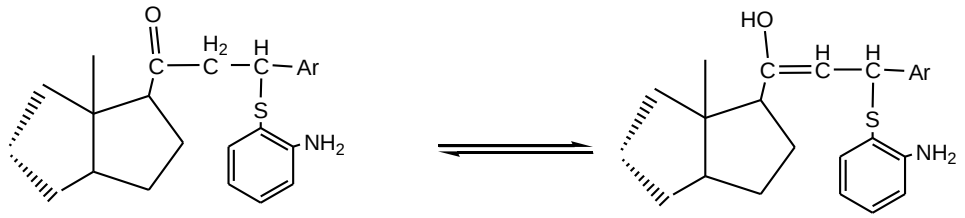
2b **3** **4** **5**

The reaction possibly takes place via the following mechanism:



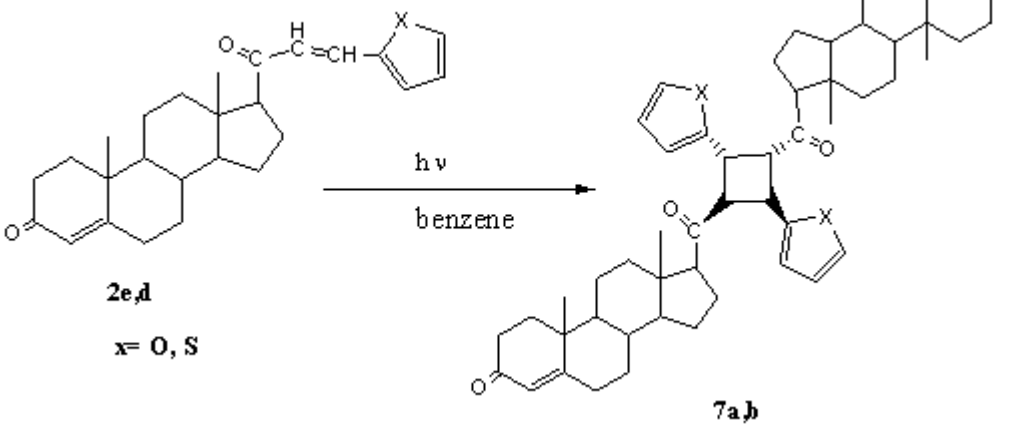
The reaction takes place via the following mechanism:





keto form
(more stable)

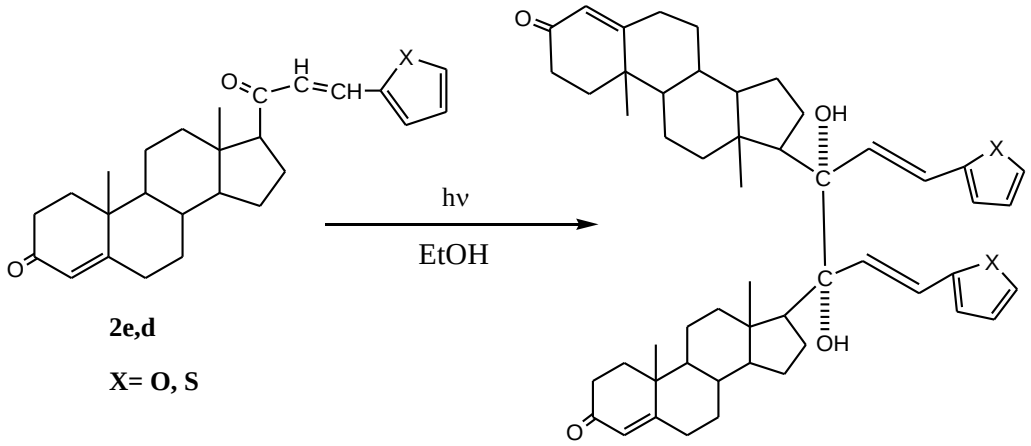
enol form



2e,d

x= O, S

7a,b

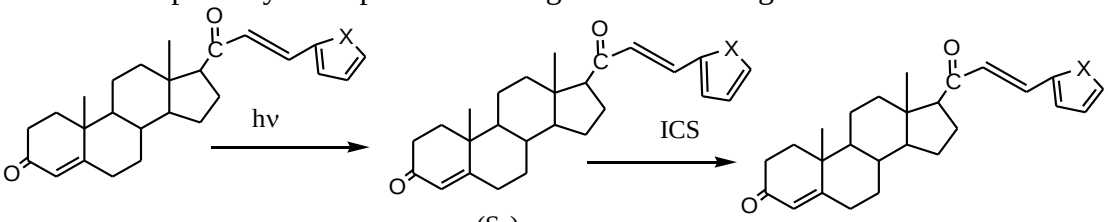


2e,d

X= O, S

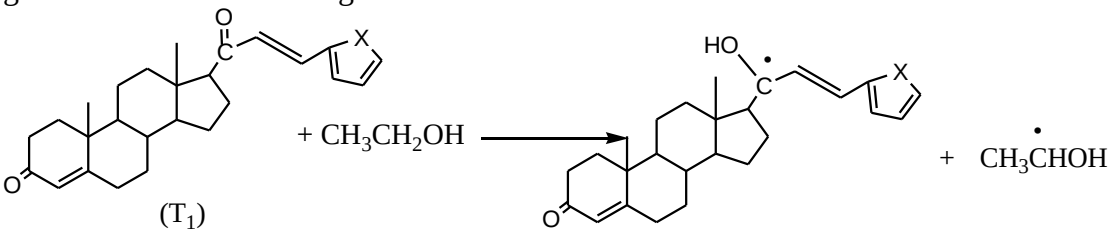
8a,b

The reaction possibly takes place according to the following scheme:



(S_1) (T_1)

Excited species change multiplicity (S_1- T_1); life time of the triplet state > 10^{-6} sec. which is greater than that of the singlet state =10^{-8} sec.

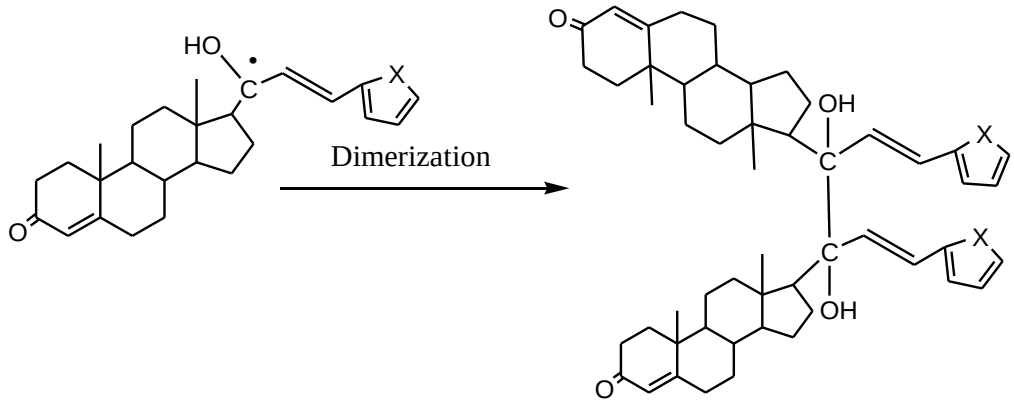


(T_1)

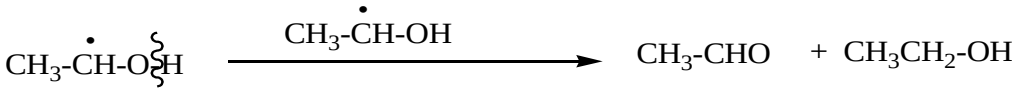
Fairly stable radical via Conjugation

stable via hyper conjugation

This step involves abstraction of ethyl alcohol hydrogen by the excited triplet state of chalcone. The hydrogen abstracted is the one that results in the more stable radical.



23a,b



The structure of compounds **8a,b** were established by IR spectra showed strong absorption band at 3325-3350 cm^{-1} (OH);1603-1606 cm^{-1} (C=O). ^{1}H-NMR spectra (DMSO, δ ppm) showed bands at 8.10-8.93 for (OH) proton.

Biological Activity (Antiviral Activity):

The seven samples showed low antiviral activity against an Egyptian avian influenza virus (H5N1) isolates in 2010.

Morphological characteristics:

Code	Lab Code	Microscopical (CPE score) after 24 hrs --- CPE : cytopathic effect									
		25 µg	25 µg	2.5 µg	2.5 µg	0.25 µg	0.25 µg	0.025 µg	0.025 µg	0.0025µg	0.0025 µg
2a	**13**	**+1**	**+1**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**
2b	**12**	**+4**	**+4**	**+3**	**+3**	**+1**	**+1**	**S**	**S**	**S**	**S**
2c	**14**	**+4**	**+4**	**+2**	**+2**	**+1**	**+1**	**S**	**S**	**S**	**S**
2e	**15**	**+4**	**+4**	**+3**	**+3**	**S**	**S**	**S**	**S**	**S**	**S**
3	**11**	**+4**	**+4**	**+3**	**+3**	**+1**	**+1**	**S**	**S**	**S**	**S**
6	**10**	**+4**	**+4**	**+3**	**+3**	**+1**	**+1**	**S**	**S**	**S**	**S**
7a	**9**	**+4**	**+4**	**+2**	**+2**	**+1**	**+1**	**S**	**S**	**S**	**S**

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