Eur J Med Chem (1995) 30, 423–427

Synthesis and biological evaluation of some novel 2-(pyrimidin-4-yl)estradiol derivatives

KA Ismail[1], AA El-Tombary[1], AMME Omar[1], OM Abouwafa[1]*, NI Madi[2]

[1]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Alexandria;*
[2]*Department of Pharmacology and Toxicology, Faculty of Medicine, University of Alexandria, Alexandria 21215, Egypt*

(Received 30 September 1994; accepted 15 January 1995)

Summary — The preparation and characterization of some novel 2-(pyrimidin-4-yl)estradiol derivatives are presented. The synthesis was achieved by the reaction of 2-benzoylacetylestradiol 17β-acetate with guanidines, urea, thiourea and a variety of thiourea derivatives according to the Traube synthesis. The synthesized compounds were evaluated for their uterotrophic and antifertility activities in mature female albino rats. All compounds showed relatively moderate uterotrophic activity (55–73%) based on dry uterine weight gain. The antifertility activity, as assessed by the post-coital antiimplantation activity test, was also of moderate potency for most compounds. However, 2-(1-*p*-bromophenyl-2(1*H*)-thioxo-6-phenylpyrimidin-4-yl)estradiol **8** displayed excellent antiimplantation activity (100%), and was equipotent to estradiol as an antifertility agent; **8** prevented implantation completely in rats at a dose of 0.035 mg/kg body weight.

2-acetylestradiol-17β-acetate / 2-benzoylacetylestradiol-17β-acetate / Traube synthesis / 2-(6-phenylpyrimidin-4-yl)estradiol derivative / uterotrophic activity / post-coital antiimplantation activity

Introduction

During the past decades, research on modified estrogens has been widespread embracing the functionalization of the steroid skeleton at various positions of the molecule. Such modification has been a target with a view toward obtaining derivatives that may possess better estrogenic properties or altogether a different pharmacological activity.

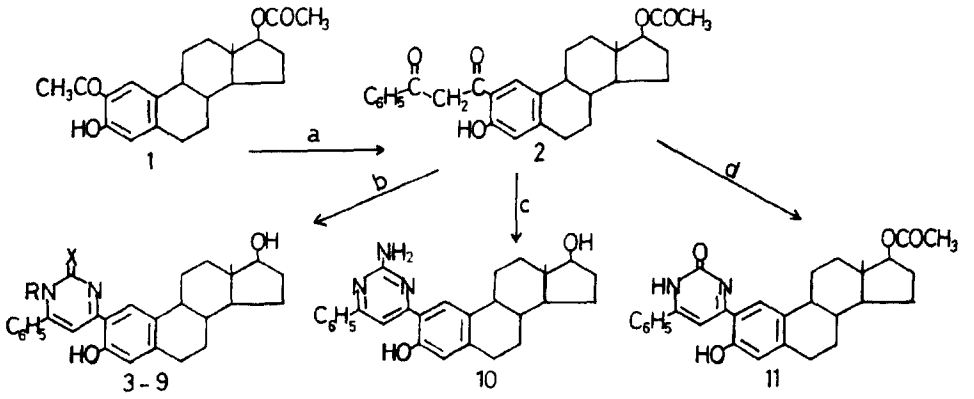
In our laboratory, we have prepared series of modified steroids [1–8] and have found some species with very good properties. The recent discovery of the excellent uterotrophic activity of 2-acetylestradiol [7] indicated that substitution at position 2 (C-2) of the estrogen skeleton might improve the metabolic profile of the estrogen and result in a useful alteration of its biological properties [9]. The synthesis of modified estrogens substituted at C-2 by a heterocyclic ring remains a challenge to us. Part of this challenge involves the selection of the appropriate ring and the size of the heterocyclic ring. We have previously had an interest in the design and synthesis of estrogens substituted with a 5-membered ring system such as pyrazole, isoxazole and thiazole at the 2-position [8]. Many interesting examples of these compounds have been found to possess good receptor-binding affinity, estrogenic and/or antifertility activity. The good biological activity elicited by these compounds convinced us to pursue the use of C-2 as a site of attachment of some 6-membered heterocyclic ring systems.

In this report, we described the synthesis of 2-(pyrimidin-4-yl)estradiols in order to study the effect of structural modulation around estradiol C-2 on its estrogenic and antifertility activities.

Chemistry

The new pyrimidinylestradiol derivatives were prepared from 2-acetylestradiol **1** [7, 10–12] according to scheme 1. The key-step in the synthesis was a Baker–Venkataraman rearrangement [13] of 2-acetylestradiol-3-benzoate 17β-acetate with potassium hydroxide in hot dry pyridine to afford the required diketone 2-benzoylacetylestradiol 17β-acetate **2** [8]. In the literature, the principal synthesis of pyrimidines is the reaction of a 1,3-dicarbonyl compound with amidines, urea and thiourea, the so-called Traube synthesis

*Correspondence and reprints



Scheme 1. Synthesis of compounds **3–9**: **3** (X = O; R = H), **4** (X = S; R = H); **5** (X = S; R = C_6H_5), **6** (X = S; R = *p*-C_6H_4Cl), **7** (X = S; R = *p*-C_6H_5Br), **8** (X = S; R = *p*-$C_6H_4CH_3$) and **9** (X = NH; X = NH_2). a) Benzoyl chloride/KOH/pyridine; b) $RNHCXNH_2$ or aminoguanidine carbonate/H_2SO_4/RT; c) guanidine carbonate/H_2SO_4/RT; and d) urea/glacial HOAc/TsOH.

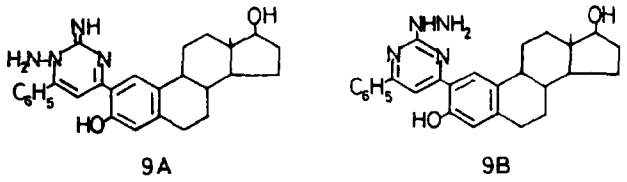
[14–23]. The most straightforward preparative method in this study appeared to be the condensation of the steroidal diketone **2** with urea, thiourea or substituted thiourea derivatives in ethanol at RT in the presence of a few drops of concentrated H_2SO_4 affording 2-(1-substituted 2(1*H*)oxo (or thioxo)-6-phenylpyrimidin-4-yl)estradiols **3–8** in relatively good yield after crystallization from ethanol or preparative TLC purification. Similarly, condensation of the dicarbonyl compound **2** with guanidine carbonate or aminoguanidine carbonate produced 2-(2-amino-6-phenylpyrimidin-4-yl)estradiol **10** and 2(1-amino-2(1*H*)imino-6-phenylpyrimidin-4-yl)estradiol **9**, respectively. The products were identified from spectroscopic data. In general, the IR spectra showed the C=N peak at 1630–1605 cm^{-1} and the NH stretching vibrations overlapped with that of the hydroxyl band in the case of compounds **3** and **4**. In all cases, the spectra lacked the carbonyl stretching vibration of the starting diketone **2** at 1680 and 1640 cm^{-1}. The ^{1}H-NMR spectra of compounds **3**, **4**, **6**, **9** and **10**, as representative examples of the series, showed the expected C-18, C-1 and C-4 protons and also a new singlet assigned to the pyrimidine C-5 proton resonating at 6.75–7.65 ppm. In addition, the spectra lacked the singlet at 4.60 ppm assigned to the methylenic protons of the diketone **2**. In every case, the pyrimidine synthesis was accompanied by deacetylation of the 17β-hydroxyl group as revealed by IR and ^{1}H NMR. The IR spectra indicated the absence of the carbonyl stretching vibration at ≈ 1730 cm^{-1} assigned to the 17β-acetyl moiety. ^{1}H-NMR spectra also lacked the signal characteristic for the 17β-acetyloxy protons of the starting diketone **2**.

The product obtained upon work-up of the reaction mixture of the diketone **2** with amino-guanidine carbonate was identified as 2-(1-amino-(1*H*)-imino-6-phenylpyrimidin-4-yl)estradiol (structure **9A**, fig 1). The possibility of formation of the isomeric hydrazino form (structure **9B**, fig 1) was ruled out on the basis of the IR study. Compound **9** had an NH stretching vibration of primary amines at 3475 cm^{-1}, which overlaps with the OH stretching vibration band, and a sharp band at a frequency of 3230 cm^{-1}. This was assigned to the NH group of *N*-heteroaromatic imine (νNH band of imino =NH [24, 25]); if the compound existed in the hydrazino form, such a peak would be absent. The IR spectrum of compound **9** also showed several medium bands characteristic for the immonium band C=NH at 2088–2000 cm^{-1} [25].

In another experiment, condensation of the steroidal diketone **2** with urea was attempted under different reaction conditions. The reaction was carried out in hot glacial acetic acid in the presence of toluene *p*-sulfonic acid. Work-up of the reaction mixture gave 2-(2(1*H*)-oxo-6-phenylpyrimidin-4yl)estradiol 17β-acetate **11**. Deacetylation of the 17β-OH group did not take place as indicated by IR and ^{1}H-NMR spectra. The IR spectrum showed the 17β-acetyloxy carbonyl band at 1720 cm^{-1} and the C-O-C symmetric and asymmetric stretching vibrations at 1250 and 1040 cm^{-1}, respectively. Similarly, the ^{1}H-NMR spectrum showed a singlet that integrated for 3 protons of the 17β-acetyloxy moiety resonating at 2.17 ppm.

Results and discussion

At a dose of 0.09 μmol/d/rat, the diketone **2** initiated an estrogenic response of only 50% that produced by estradiol [8]. All the synthesized 2-(pyrimidin-4-



9A 9B

Fig 1. Structures of compounds **9a** and **9b**.

yl)estradiol derivatives exhibited only moderate uterotrophic activity when administered subcutaneously (table I). The imino derivative **9** displayed the highest uterotrophic activity at 73% that of estradiol. A uterotrophic response of 69% was also observed for 2-(2(1*H*)-thioxo-6-phenylpyrimidin-4-yl)estradiol **4**. Evaluation of the post-coital contraceptive efficacy of these compounds showed that complete prevention of fertility (100%) in both horns of the uterus was observed with the *p*-bromophenyl derivative **7** at a dose of 0.0035 mg/kg. The uterotrophic activity of this compound was found to be only half that of estradiol (55%). On a molar ratio basis, none of the other tested compounds elicited any significant antiimplantation activity.

Conclusions

One of our strategies has been to search for the effect of substitution at the C-2 of the estrogenic steroid molecule on its estrogenic and antifertility activity. Of the synthesized 2-(pyrimidin-4-yl)estradiol derivatives **3–10**, the *p*-bromophenyl derivative **7** elevated the post-coital antiimplantation activity to 100%, while causing a substantial reduction in uterotrophic activity (50%) relative to estradiol. Such a finding indicated that C-2 substitution with a six-membered heterocyclic ring does not afford compounds with substantially improved uterotrophic characteristics. On the other hand, compound **7** may prove to be useful as an antiestrogen with low estrogenic activity. These new modified estrogens should be useful for seeking a novel chemical approach to the discovery of potent steroids and for providing the background for future additional studies on the role of C-2 substitution in the action of estrogenic and antiestrogenic steroids.

Experimental protocols

Chemistry

Melting points were determined in open capillary tubes on a Griffin melting point apparatus and are uncorrected. IR spectra were recorded for KBr pellets on a Perkin-Elmer 1430 ratio recording infrared spectrophotometer; ^{1}H-NMR spectra were determined at 60 MHz on a Varian EM-390 spectrometer or at 90 MHz on a Jeol 90Q FT spectrophotometer with tetramethylsilane as an internal standard. Values are given in ppm (δ) (s, singlet, d, doublet; t, triplet; m, multiplet; and dist, distorted). MS were performed on Shimadzu Gas Chromatograph-Mass Spectrometer GCMS-QP-1000. The homogeneity of the

Table I. Estrogenic potencies and post-coital antiimplantation efficacy of the synthesized compounds **3–10** in ovariectomized mature female rats.

Compound	*Wet uterine weight (mg)/100 g*	*Dry uterine weight (mg)/100 g*	*Dry weight/wet weight % (n)*[a]	*% Uterotrophic activity based on dry weight*	*Antiimplantation activity (number of implants) (n)*[a]	*% Antiimplantation activity*[b]
Control[c]	60.51 ± 2.87	15.108 ± 0.55	25.026 ± 0.54 (5)	–	4.50 ± 0.5 (5)	–
Estradiol	270.78 ± 17.85*	57.60 ± 2.05*	24.68 ± 3.45 (4)	100	0(5)	100
3	118.21 ± 13.36*	36.36 ± 3.14*	31.025 ± 0.95* (4)	63	3.50 ± 2.02 (5)	29
4	85.61 ± 11.03	33.09 ± 1.70*	39.98 ± 3.72* (4)	69	7.25 ± 2.46 (5)	14
5	103.91 ± 9.56*	32.24 ± 1.91*	31.508 ± 1.54* (5)	60	2.75 ± 1.03 (4)	36
6	102.13 ± 6.29*	32.52 ± 2.15*	31.81 ± 0.29* (5)	56	4.50 ± 1.848 (4)	22
7	84.83 ± 6.04*	31.57 ± 0.94*	37.71 ± 2.014* (5)	55	0(5)	100
8	83.22 ± 9.49	32.66 ± 3.11*	39.69 ± 2.18* (4)	57	3.50 ± 2.06 (5)	29
9	111.97 ± 12.01*	32.59 ± 2.67*	29.42 ± 1.07* (5)	57	3.00 ± 1.84 (4)	33
10	146.602 ± 11.92*	41.86 ± 2.29*	28.78 ± 0.88* (5)	73	4.75 ± 1.701 (4)	21

[a] n = number of animals. [b]Minimum effective dose for prevention of pregnancy (0.025 mg/kg body weight for estradiol). Doses of the tested compounds were calculated on a molar ratio basis. [c]Rats received vehicle (DMSO) and served as control. Results were expressed as means ± SEM. Data were analyzed by one-way variance. Student's t for unpaired observations was used. Differences between means were considered significant if $P < 0.05$. *$P < 0.01$.

products was determined by ascending TLC on a silica-gel-coated glass plates visualized by iodine vapor. Developing solvent systems were: benzene/ethyl acetate/chloroform (5:1:5 v/v/v) and benzene/ethyl acetate (7:3 v/v) and (3:7 v/v). Preparative TLC was performed on 20 x 20 cm^2 plates coated with 30 g silica gel 60 G F254 for TLC (Adwic Laboratory Chemicals, Egypt). A duo-UV lamp (Desega, Heidelberg, Germany) was used for location of the spots. Microanalyses were performed by the microanalytical unit, Faculty of Science, Cairo University, Egypt. Microanalytical data are indicated by the symbols of the elements and were within ±0.4% of theoretical values.

2-Benzoylacetylestradiol-17β-acetate 2
Compound **2** was prepared from 2-acetylestradiol according to the previously described method [7]; mp: 170–172°C, IR: ν 3450 (OH), 1730 (C=O, C-17-acetate), 1680 and 1640 (C=O), 1580, 1500 (C=C Ar), 1250 and 1080 cm^{-1} (C-O-C). ^{1}H-NMR ($CDCl_3$, 60 MHz): δ 0.85 (s, 3H, 18-CH_3), 2.08 (s, 3H, C-17-$OCOCH_3$), 4.60 (s, 2H, $COCH_2CO$), 4.70 (t, 1H, C-17 α-H), 6.80 (s, 1H, C-4-H), 7.50 (m, dist, 3H, Ar-H), 7.67 (s, 1H, C-1-H), 7.90, 8.00 (2d, dist, 2H, Ar-H *ortho* to C=O) and 11.88 (s, 1H, C-3-OH).

2-(Pyrimidin-4-yl)estradiol derivatives 3–10
An ice-cold (–10°C) and stirred solution of the diketone **2** (0.19, 0.217 mmol) in ethanol (10 ml) was treated with an equimolar amount of urea, thiourea, monosubstituted thioureas, guanidine carbonate or aminoguanidine carbonate and six drops of concentrated H_2SO_4. The mixture was well stirred at RT for 48 h. The product that separated was filtered, washed with ethanol and dried.

2-(2(1H)-Oxo-6-phenylpyrimidin-4-yl)estradiol 3. This was obtained in 78% yield after purification by preparative TLC using $CHCl_3$/EtOAc/benzene (5:1:5 v/v/v) as developing solvent, mp: 256–258°C. Anal $C_{28}H_{30}N_2O_3$ (C, H, N). IR ν 3475 (OH + NH), 1695 (C=O), 1605 (C=N + C=C Ar), 1485 cm^{-1} (C=C Ar). ^{1}H-NMR ($CDCl_3$, 90 MHz): δ 0.85 (s, 3H, 18-CH_3), 7.08 (s,1H, C-4-H), 7.60, (s, 1H, C-1-H), 7.62 (s, 1 H, pyrimidine-5-H), 7.77–8.00 (m, 3H, Ar-H), 8.20–8.37 (m, 2H, Ar-H) and 8.50 (s, 1H, NH).

2-(2(1H)-Thioxo-6-phenylpyrimidin-4-yl)estradiol 4. This was crystallized from ethanol in 46% yield; mp: 260–262°C. Anal $C_{28}H_{30}N_2O_2S$ (C, H, N). IR ν 3460 (OH + NH), 1630 (C=N), 1570 and 1490 (C=C Ar), 1550, 1300, 1055 and 915 cm^{-1} (NCS amide I, II, III and IV bands). ^{1}H-NMR ($CDCl_3$, 90 MHz): δ 0.84 (s, 3H, 18-CH_3), 7.157 (s, 1H, C-4-H), 7.55 (s, 1H, C-1-H), 7.57 (s, 1H, pyrimidine-5-H), 7.68–8.039 (m, 3H, Ar-H), 8.18–8.36 (m, 2H, Ar-H), and 8.43(s, 1H, NH).

2-(1-Phenyl-2(1H)-thioxo-6-phenylpyrimidin-4-yl)estradiol 5. This was crystallized from ethanol in 52% yield; mp: 221–223°C. Anal $C_{34}H_{34}N_2O_2S$ (C, H, N). IR ν 3460 (OH), 1620 (C=N), 1595, 1485 (C=C Ar), 1540, 1290, 1055 and 915 cm^{-1} (NCS amide I, II, III and IV bands).

2-(1-p-(Chlorophenyl)-2(1H)-thioxo-6-phenylpyrimidin-4-yl)-estradiol 6. This was crystallized from ethanol in 48% yield; mp: 255–257°C. Anal $C_{34}H_{33}ClN_2O_2S$ (C, H, N). IR ν 3480 (OH), 1630 (C=N), 1605, 1490 (C=C Ar), 1555, 1310, 1060 and 910 cm^{-1} (NCS amide I, II, III and IV bands). ^{1}H-NMR ($CDCl_3$, 90 MHz): δ 0.857 (s, 3H, 18-CH_3), 7.128 (s, 1H, C-4-H), 7.58 (s, 1H, C-1-H), 7.61 (s, 1H, pyrimidine-5-H), 7.818 (m, 5H, Ar-H), 8.20–8.38 (m, 4H, Ar-H) and 8.48 (s, 1H, NH). MS *m/z* (% relative abundance): M^+ 568, 570 absent, 400 (M^+ *p*-ClC_6H_4NCS, 100), 341 (56.3), 301 (22.4), 299 (11.8), 288 (61.5), 287 (36.1), 273 (32.5), 169 (5.3) and 171 (4.6).

2-(1-(p-Bromophenyl)-2-(1H)-thioxo-6-phenylpyrimidin-4-yl)-estradiol 7. This was crystallized from ethanol in 60% yield; mp: 263–265°C. Anal $C_{34}H_{33}BrN_2O_2S$ (C, H, N). IR ν 3480 (OH), 1620 (C=N), 1585, 1480 (C=C Ar), 1560, 1300, 1050 and 920 cm^{-1} (NCS amide I, II, III and IV bands).

2-(1-(p-Tolyl)-2(1H)-thioxo-6-phenylypyrimidin-4-yl)estradiol 8. This was crystallized from ethanol in 50% yield; mp: 260–261°C. Anal $C_{35}H_{36}N_2O_2S$ (C, H, N).

2-(1-Amino-2(1H)-imino-6-phenylpyrimidin-4-yl)estradiol 9. This was obtained in 75% yield after purification by preparative TLC using benzene/EOAc (3:7 v/v) as developing solvent, mp: 255–257°C. Anal $C_{28}H_{32}N_4O_2$ (C, H, N). IR ν 3475 (OH + NH_2), 3230 (tertiary NH), 2088–2000 (C=NH), 1620 (C=N), 1595 and 1490 cm^{-1} (C=C Ar). ^{1}H-NMR (DMSO-d_6, 60 MHz) δ 0.733 (s, 3H, 18-CH_3), 6.75 (s, 1H, pyrimidine-5-H), 7.233 (s, 1H, C-4-H), 7.30–7.566 (m, 4H, 3Ar-H + NH), 7.66 (s, 1H, C-1-H) and 7.78–8.00 (m, 4H, 2ArH + NH_2).

2-(2-Amino-6-phenylpyrimidin-4-yl)estradiol 10. This was crystallized from ethanol in 57% yield; mp: 268–270°C. Anal $C_{28}H_{31}N_3O_2$ (C, H, N). IR ν 3460 (OH + NH), 1630 (C=N), 1590 and 1480 cm^{-1} (C=C Ar). ^{1}H-NMR (DMSO-d_6, 60 MHz) δ 0.716 (s, 3H, 18-CH_3), 4.36 (t, J = 5 Hz, 1H, 17α-H), 6.783 (s, 1H, pyrimidine-5-H), 7.233 (s, 1H, C-4-H), 7.33–7.566 (m, 3H, Ar-H), 7.70 (s, 1H, C-1-H), 7.783–8.00 (m, 2H, Ar-H) and 8.20 (s, 2H, NH_2).

2-(2(1H)-Oxo-6-phenylpyrimidin-4-yl)estradiol-17-β-acetate 11. A mixture of the diketone **2** (0.1 g, 0.217 mmol), urea (0.02 g, 0.33 mmol) and toluene-*p*-sulfonic acid (0.028 g, 0.47 mmol) in glacial HOAc (5 ml) was heated under reflux for 36 h. The solution was left to cool to RT, treated with 50% aqueous EtOH and left overnight. The product **11** was filtered and crystallized from EtOH (63%); mp: 278–280°C. Anal $C_{30}H_{32}N_2O_4$ (C, H, N). IR ν 3410 (OH + NH), 1720 (C=O, 17β-acetyloxy), 1640 (C=O, pyrimidone), 1610 (C=N), 1595, 1490 (C=C Ar), 1250 and 1040 cm^{-1} (C-O-C). ^{1}H-NMR ($CDCl_3$, 90 MHz): δ 0.9 (s, 3H, 18-CH_3), 2.17 (s, 3H, 17β-$OCOCH_3$), 4.95 (t, J = 7.64 Hz, 1H, 17α-H), 7.12 (s, 1H, C-4-H), 7.63 (s, 1H, C-1-H), 7.65 (s, 1H, pyrimidine-5-H), 7.82–8.09 (m, 3H, Ar-H), 8.26–8.45 (m, 3H, Ar-H) and 8.52 (s, 1H, NH). MS *m/z* (% relative abundance): M^+ 484 absent, 443 (36.6), 442 (55.2), 400 (10.8), 399 (13.8), 341 (25.1), 290 (14.3), 288 (25.8), 287 (16.7), 274 (13.8), 273 (20), 262 (12.2), 261 (17.6), 115 (12.7) and 43 (100).

Biological activity

Uterotrophic activity
The uterotrophic activity [7, 26] of the synthesized compounds was evaluated by determining the uterine weight gain in mature ovariectomized female albino rats (100–170 g) (obtained from the animal house of the Faculty of Pharmacy, Alexandria). The compounds were administered subcutaneously once daily over a 4-d period in 0.1 ml DMSO (0.09 μmol/d/rat). The rats were weighed 24 h after the last dose and vaginal smears were taken and examined under the microscope. The animals were then sacrificed and the uteri were carefully dissected out, blotted, weighed, dried at 60°C for 24 h and weighed again. The gain in

uterine weight calculated as mg uterine weight/100 g body weight and the percentage of dry/wet weight are shown in table I.

Antiimplantation activity

Mature female cycling albino rats (150–200 g) were mated with active males during the night after the day of proestrus. Animals with evidence of positive mating (presence of sperm in the vaginal smears) received the test compound dissolved in 0.1 ml DMSO subcutaneously on day 1–7 post-coitus [7, 26–28]. The animals were examined by laparotomy on day 10 of pregnancy for the number of implantation sites. Results were compared with those obtained on administration of the standard estradiol (table I).

Acknowledgment

The authors thank Organon Pharmaceutical Co, Holland, for the generous donation of estradiol.

References

1 Ibrahim ESA, Omar AME, Habib NS, AboulWafa OM, Bourdais J (1982) *J Heterocycl Chem* 19, 761—768
2 Omar AME, AboulWafa OM (1982) *J Pharm Sci* 71, 983–986
3 Ibrahim ESA, Omar AME, Habib NS, AboulWafa OM, El-Sewedy SM, Bourdais J (1983) *J Pharm Sci* 72, 1205–1211
4 Omar AME, AboulWafa OM, Leclerq G (1984) *J Pharm Sci* 73, 1871–1873
5 Omar AME, AboulWafa OM (1984) *J Heterocycl Chem* 21, 1665–1667
6 Omar AME, AboulWafa OM (1984) *J Heterocycl Chem* 21, 1419–1423
7 AboulWafa OM, Omar AME, Mohy El-Din MM (1992) *Steroids* 57, 199–204
8 Omar AME, Ahmed IC, AboulWafa OM *et al* (1994) *Eur J Med Chem* 29, 25–32
9 MacLusky NJ, Clark CR, Paden CM, Naftolin F (1981) *In: Mechanisms of Steroid Action* (Lewis GP, Ginsburg M, eds), The MacMillan Press Ltd, London, UK, 115, 123–124
10 Nambara T, Honma S, Akiyama S (1970) *Chem Pharm Bull (Tokyo)* 18, 474–480
11 Crabbe P, Maldonado LA, Sanchez I (1971) *Tetrahedron* 27, 711–725
12 Xie R, Deng L, Gu H, Fan Y, Zhao H (1982) *Steroids* 40, 389–392
13 Corvaisier A (1962) *Bull Soc Chim Fr* 528–535
14 Hale WJ (1914) *J Am Chem Soc* 36, 104–115
15 Hale WJ, Williams AG (1915) *J Am Chem Soc* 37, 594–600
16 Donleavy JJ, Kise MA (1943) *Org Syntheses Coll* Vol II, 422–423
17 Roberts J C (1952) *J Chem Soc* 3065–3068
18 Snyder HR, Foster HM (1954) *J Am Chem Soc* 76, 118–123
19 Elderfield RC (ed) (1957) *Heterocyclic Compounds Vol 6*, John Wiley and Sons Inc, NY, USA, 234
20 Ramage GR, Landquist JK (1959) *In: Chemistry of Carbon Compounds Vol IV B* (Rodd EH, ed), Elsevier, Amsterdam, The Netherlands, 1257
21 Foster HM, Snyder HR (1963) *Org Syntheses Coll* 4, 638–640
22 Katritzky AR, Salgado HJ, Chermprapai A, Ponkshe NK (1982) *J Chem Soc Perkin Trans* 1, 153–158
23 Katritzky AR, Yousaf TI (1986) *Can J Chem* 64, 2087–2093
24 Brown DJ (1962) *In: The Chemistry of Heterocyclic Compounds: The Pyrimidines* (Weissberger A, ed) Interscience Publishers, NY, USA, 495
25 Nakanishi K (1962) *In: Infrared Absorption Spectroscopy, Practical* Holden-Day Inc, San Francisco, CA, USA, 39–41
26 Peters RH, Crowe DF, Avery MA, Chong WKM, Tanabe M (1989) *J Med Chem* 32, 1642–1652
27 Lal K, Sharma I, Agarwal AK, Agnihotri A, Ray S (1988) *J Med Chem* 31, 1261–1264
28 Dwivedy I, Singh AK, Singh MM, Ray S (1993) *Steroids* 58, 69–73