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Mifepristone (RU-486), the recently developed antiprogesterone drug and its analogues†

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Abstract

Mifepristone (RU-486) is the first antiprogesterone drug used for the termination of early pregnancies (6 to 8 weeks pregnancies), a steroid synthesized in the laboratory. It has higher affinity for the progesterone receptor. It also has other potential applications as anticancer and glucocorticoid antagonist. It is desirable to increase its antiprogestational potency and eliminate the antiglucocorticoid property. Therefore, an intense effort is directed towards the synthesis of mifepristone analogues and study their biological activity. This review gives an account of the research carried out in this area.

Keywords: Mifepristone, RU-486, antiprogesterone, antiglucocorticoid, anticancer, abortifacient.

1. Introduction

Steroid hormone progesterone (**1**) plays an important role in human reproduction. It is essential for the initiation and maintenance of pregnancy. It enters the cell and binds to a specific protein known as the progesterone receptor, thereby exerting its biological effects. The compound which inhibits the binding of progesterone to its receptor–an antiprogesterone or progesterone antagonist–would have many therapeutic possibilities in female reproductive health. With this view in mind, scientists at the French pharmaceutical company, Roussel Uclaf, Daniel Philibert, Roger Deraedt and Georges Teutsch in 1981, discovered[1–3] RU-38486, a progesterone antagonist with anti-glucocorticoid activities. In fact, the scientists were looking for a glucocorticoid antagonist, an agent which inhibits the action of cortisol. Although the hormone cortisol is essential for life, under certain circumstances it is secreted in excess and produces undesirable effects. RU 38486 was subsequently abbreviated to RU 486, and is now known by its generic name Mifepristone. It was the first antiprogestin to be developed.

Chemically, mifepristone is 11β-(4-dimethylaminophenyl)-17β-hydroxy-17-(prop-1-ynyl)-estra-4,9-dien-3-one (**2**) (Fig.1). Mifepristone (RU 486) (**2**) is a 19-norsteroid that blocks the action of the female hormone progesterone (**1**), which is necessary for initiating pregnancy and for sustaining it. In the absence of progesterone (**1**), the uterine lining breaks down and bleeding occurs, resulting in the termination of pregnancy. Mifepristone (**2**) when used with a small amount of a synthetic prostaglandin (misoprostol) terminates early pregnancies (up to 6 to 8 weeks) effectively and safely. This drug is an alternative to surgical termination of pregnancy. Mifepristone is already in use as an abortifacient in France, UK, Sweden and China. In October 2000, the United States Food and Drug Administration approved the introduction of mifepristone, thus

† Dedicated to Prof. S. C. Bhattacharyya.
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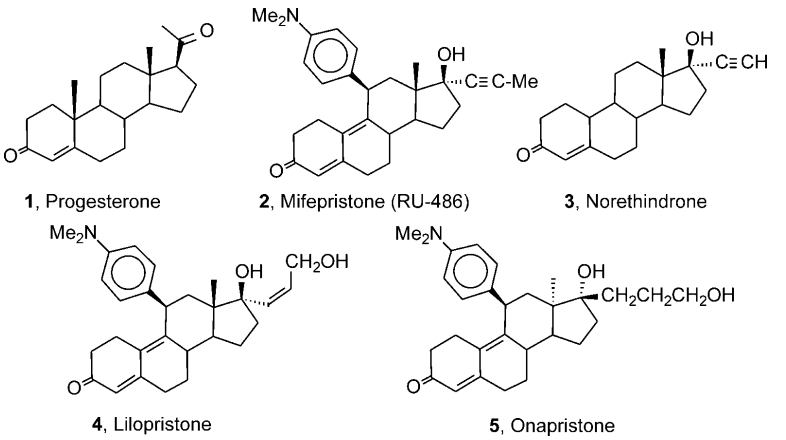


FIG. 1.

culminating a 14-year legal battle. In India, the Indian Council of Medical Research (ICMR) has approved its use under proper medical supervision. Mifepristone lacks the C-19 methyl group and the two-carbon side chain at C-17 of progesterone and the glucocorticoids. It is a derivative of the progestin norethindrone (**3**) and has an additional 4-(dimethylamino)phenyl side chain at 11β position and a 1-propynyl chain at 17α position. The 11β-(4-dimethylamino)phenyl group is perpendicular to the steroid skeleton. It also has a conjugated double bond at C-9–C-10.

After the discovery of mifepristone (**2**), over 400 additional antiprogestins have been synthesized and several of them have undergone preliminary clinical evaluation. Lilopristone (**4**) has *cis* (*Z*) configuration in 3-hydroxy-1-propenyl side chain at the 17α position and its structure is very similar to that of mifepristone (**2**). The two-dimensional structure of onapristone (**5**) is like those of mifepristone and lilopristone; however, it has a different molecular shape because of configurational inversion at C-13 and C-17 positions. Another antiprogestin which is well studied in animals is ORG 31710 (**6**) (Fig. 2), a 17-spirotetrahydrofuran analogue of mifepristone. This class of steroids displays extremely high binding affinities for the progesterone receptor. The most active compound in this series, ORG 33628 (**7**) is claimed to be 32 times as active as mifepristone (**2**) in inducing abortion in rats while being significantly less active as an antiglucocorticoid.[4] Although it has been suggested that these antiprogestins as well as lilopristone (**4**) and onapristone (**5**) have less antiglucocorticoid activity than mifepristone, none is a pure antiprogestin. Nevertheless, a number of compounds can be described as dissociated antiprogestins. One such example is RU 46556 (**8**) which is spirotetrahydrofuran derivative (Fig. 3). Another development by scientists at Roussel is the synthesis of water-soluble compounds such as RU 39973 (**9**) and the hemisuccinate RU 52562 (**10**).

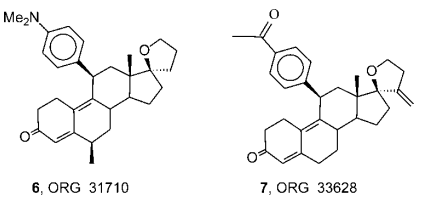
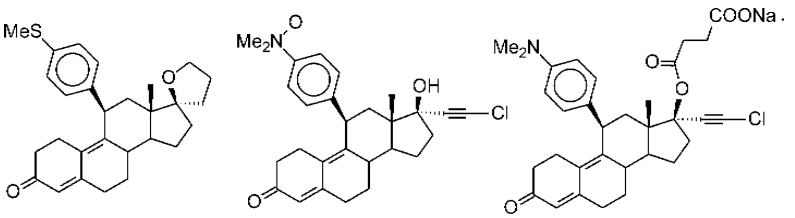


FIG. 2.



8, RU 46556 **9**, RU 39973 **10**, RU 52562

FIG. 3.

2. Mechanism of action

Progesterone (**1**) exerts its biological effect by entering into the cell and binding to specific proteins, progesterone receptors, which are situated in the nucleus of the cell. When this binding occurs, the receptor gets activated. These receptors also have domain for DNA binding. Progesterone (**1**) and other progestins cause a dramatic change in the conformation of the progesterone receptor, which transforms the receptor from non-DNA binding into one that will bind to DNA. This transformation is associated with a loss of heat shock proteins and dimerization of the receptor molecules. The activated receptor dimer then increases the gene transcription rates producing progesterone agonistic effects at cellular and tissue level which are essential for continuation of pregnancy (Fig. 4). When mifepristone (**2**) binds to the inactive receptor, it induces equally dramatic change in the receptor conformation, loss of heat shock protein and dimerization. However, in this case, the DNA-bound receptors are transcriptionally inactive, suppressing progestin effects, thus terminating the pregnancy.

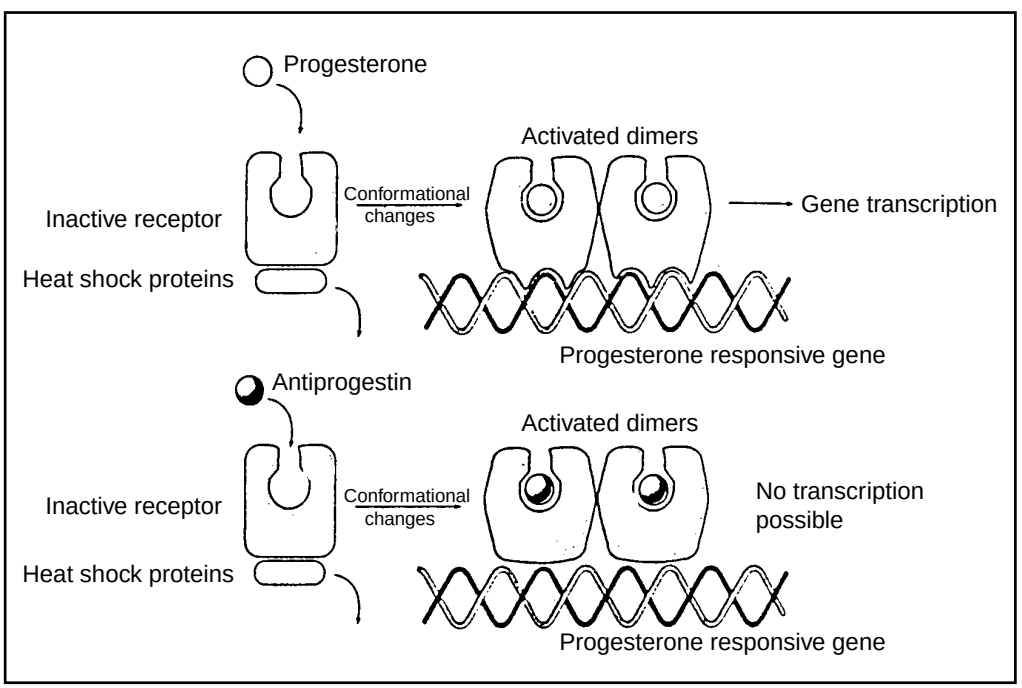


FIG. 4.

3. Other uses of mifepristone

In addition to termination of early pregnancy, mifepristone (**2**) is useful for preparing women for surgical abortion as it promotes dilation of the uterine cervix as effectively as the prostaglandins, but with fewer side effects. It has also been used to induce labour, after spontaneous death of the foetus in the uterus. Antiprogestins also have antiglucocorticoid activity. For this reason, mifepristone (**2**) could be used to treat the patients with over reactivity of the adrenal glands known as Cushing's syndrome which may arise from inoperable tumors.[5] Other applications may include eye drops containing mifepristone to lower pressure of the eyes of the patients of glaucoma and oral administration of the drug to prevent viral diseases. It is also a potent antiglucocorticoid and shows promising activity in treating estrogen-dependent gynaecological disorders and hormone-deficient tumors. A large number of applications of mifepristone (**2**) have been reported in the recent literature.[6,7]

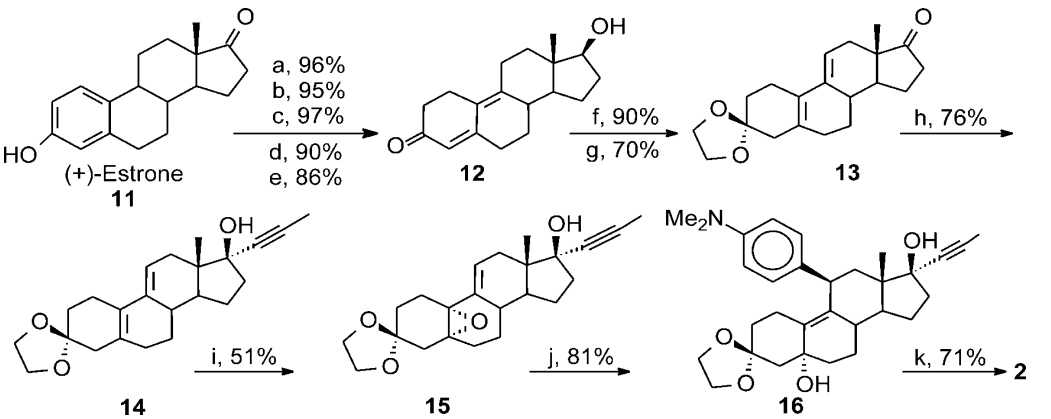
4. Side effects

Like most of the synthetic drugs, mifepristone also shows some unwanted side effects. A few women who receive single doses of mifepristone to interrupt pregnancy experienced side effects, which include heavy bleeding, nausea, vomiting, abdominal pain and fatigue. Other side effects are slight weight loss and skin rashes.

5. Synthesis of mifepristone and its analogues

Mifepristone (**2**) was first synthesized[8] by the scientists at Roussel Uclaf. Synthesis of racemic and also optically active mifepristone (**2**) has been reported[9] by Chinese scientists. We, at the National Chemical Laboratory, Pune, have synthesized[10] mifepristone (**2**) starting from (+)-estrone (**11**) (Scheme 1). Intermediate **12** was synthesized from (+)-estrone following the reported[11, 12] five steps in 68% overall yield. The protection of the 3-keto functionality of compound **12** as ketal, followed by Oppenauer oxidation of the 17β-hydroxy group furnished 17-keto compound (**13**) as a crystalline solid, in 63% overall yield in two steps. For the introduction of prop-1-ynyl side chain at 17α orientation, an efficient procedure for the *in situ* generation of propynyllithium in the reaction mixture has been found out. This was accomplished by the reaction of 1,1-dibromoprop-1-ene with 2 equivalents of *n*-BuLi. Alkynylation of **13** by this procedure proceeded smoothly to give 17α-alkynylated product (**14**) in 76% yield. Chemoselective epoxidation of the 5(10) double bond of **14** was achieved with H_2O_2 and a catalytic amount of hexafluoroacetone trihydrate to get a mixture of 5,10α-epoxide (**15**) and 5,10β-epoxide in good yield in a 4:1 ratio. The required 5,10α-epoxide (**15**) was isolated by column chromatography over silica gel in 51% yield. The 11β-(4-dimethylamino)phenyl sustituent was introduced by S_N2' opening of the oxirane ring of compound **15** with Grignard reagent prepared from 4-bromo-*N,N*-dimethylaniline in the presence of a catalytic amount of copper iodide. The 11β-substituted compound (**16**) was obtained as a solid in 81% yield. Deketalization and simultaneous dehydration of **16** with 70% acetic acid gave the target compound **2** in 71% yield as a pale yellow crystalline solid.

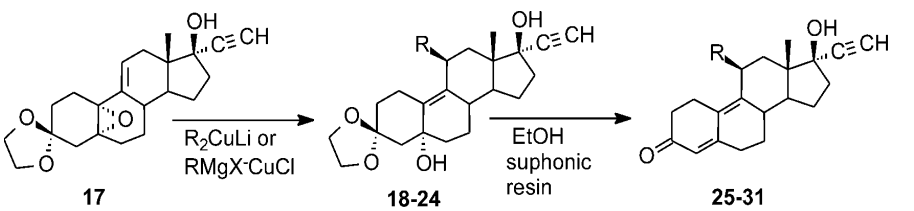
After the discovery of mifepristone, more effort has been devoted in recent years to the synthesis of more potent and more selective antiprogestins. A number of analogues of mifepristone have been synthesized and tested for their antiprogestin activity. Tetsch and coworkers[13] have synthesized a variety of 11β-substituted 19-norsteroids (**25–31**) using conjugate opening of the



Reagents and conditions: (a) $(CH_3)_2SO_4$, KOH, MeOH, 40ºC, 12 h; (b) $NaBH_4$, MeOH, 30ºC,12 h; (c) Li, NH_3 (liq.) –30ºC, 30 min/EtOH, 30ºC, 12 h; (d) Oxalic acid, acetone, 30ºC, 1.5 h; (e) Pyridinium bromide perbromide, Py, 5–50ºC, 1.5 h; (f) Ethylene glycol, PTSA, benzene, reflux, 3 h; (g) Aluminium isopropoxide, cyclohexane, benzene, 70–75ºC, 4 h; (h) 1,1-Dibromoprop-1-ene, *n*-BuLi, THF, –78 to –40ºC, 2 h and 25ºC, 8 h; (i) Hexafluoroacetone, H_2O_2, CH_2Cl_2 0–30ºC, 3.5 h; (j) 4-Bromo-*N,N*-dimethylaniline Mg, CuI, THF, 5–30ºC, 6 h and (k) 70% AcOH, 50–60ºC, 1 h.

Scheme 1.

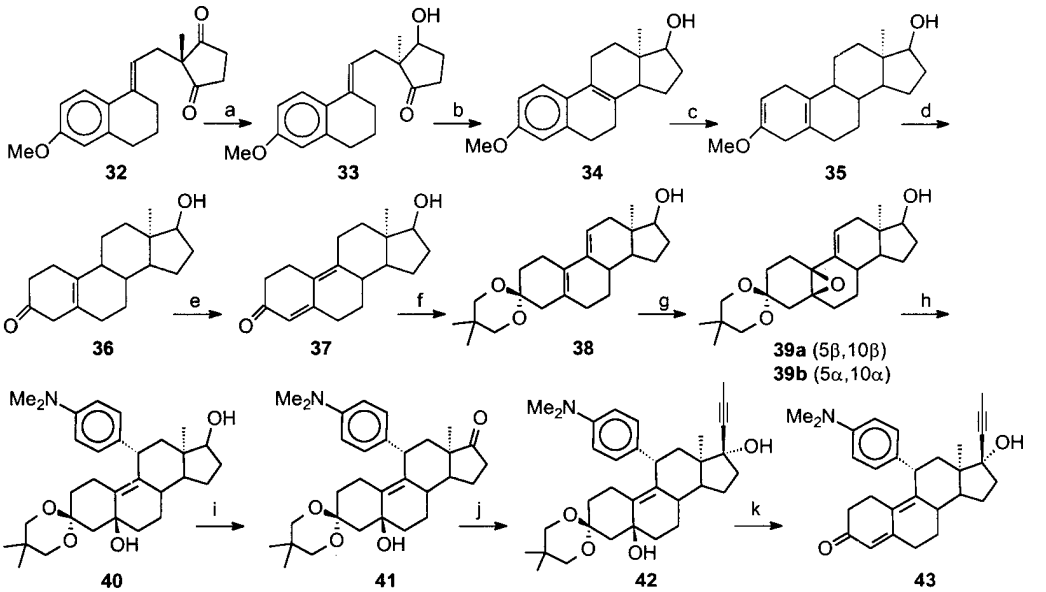
allylic epoxide (**17**) by organo-copper reagents or with organo-magnesium halides in the presence of catalytic amount of Cu(I) chloride (Scheme 2). Among these, 11β-vinyl (**28**) and 11β-phenyl (**29**) analogues showed high binding affinities to the cytoplasmic uterine progestin receptor, whereas 11β-allyl (**30**) and 11β-benzyl (**31**) derivatives showed very low binding affinities. Thus shifting the unsaturation by one carbon atom practically eliminated the receptor-binding affinity.



18, 25 R = Et; **19, 26** R = ^{i}Pr; **20, 27** R = ^{t}Bu; **21, 28** R = $CH{=}CH_2$; **22, 29** R = Ph; **23, 30** R = $CH_2CH{=}CH_2$; **24, 31** R = CH_2Ph

Scheme 2.

Synthesis of *ent*-11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(prop-1-ynyl)-4,9-estradien-3-one (**43**), an antipode of mifepristone (**2**) from easily synthesizable Torogov's intermediate was reported by Ottow *et al*.[14] (Scheme 3). Enantioselective microbial reduction of **32** by the microorganism *Bacillus thuringiensis* gave the hydroxy ketone **33**. Acid-catalyzed cyclization of **33** followed by catalytic reduction produced **34**. Birch reduction of **34** yielded the crude dienolether (**35**) which was cleaved by acid hydrolysis to the unconjugated enone (**36**). Bromination–dehydrobromination of **36** followed by ketalization of the dienone **37** gave compound **38**. Regioselective 5,10β epoxidation of **38**, copper (I)-catalyzed S_N2' opening of the allyl epoxide with 4-*N,N*-dimethylaminophenylmagnesium bromide in an *anti* fashion afforded compound **40**.

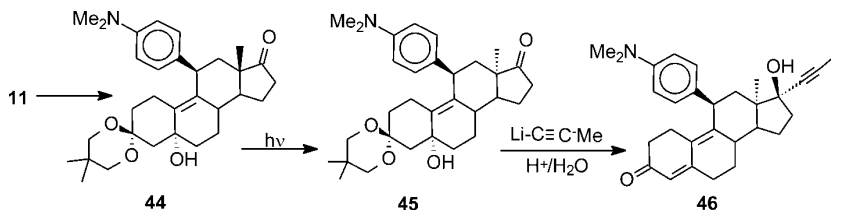


(a) [H], enzyme; (b) H^+; H_2/catalyst; (c) Li, NH_3; (d) H^+; (e) Br_2; -2HBr; (f) $Me_2C(CH_2OH)_2$, H^+; (g) H_2O_2, catalyst; (h) 4-$Me_2NC_6H_4MgBr$, Cu(I); (i) $Al(O^iPr)_3$, $(CH_2)_5C{=}O$; (j) Li-C≡CMe, THF; (k) H^+.

Scheme 3.

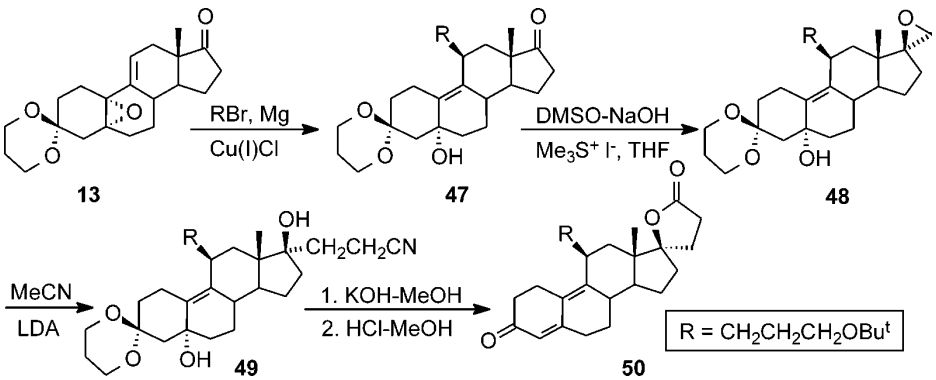
Oppenauer oxidation at C-17 of **40**, addition of propynyllithium to the resulting ketone (**41**) and concomitant dehydration–deketalization established the diene system and generated the *ent* mifepristone (**43**). The progesterone antagonistic activity of compound **43** was tested on female Wistar rats. Compound **43** showed no abortive effect at different doses.

Neef *et al.*[15] chose to invert the C-13 stereochemistry, which ultimately led to 13-epimeric mifepristone (**46**) (Scheme 4). This idea was inspired by a previous observation that the C-13 epimer of norethisterone showed comparable affinities for the progesterone receptor. Compound **44** was synthesized from (+)-estrone (**11**) following known synthetic sequence. Irradiation of **44** proceeded smoothly with the formation of its C-13 epimer (**45**) in 62% yield. Alkynylation at C-17 followed by acid hydrolysis produced the target compound **46**.



Scheme 4.

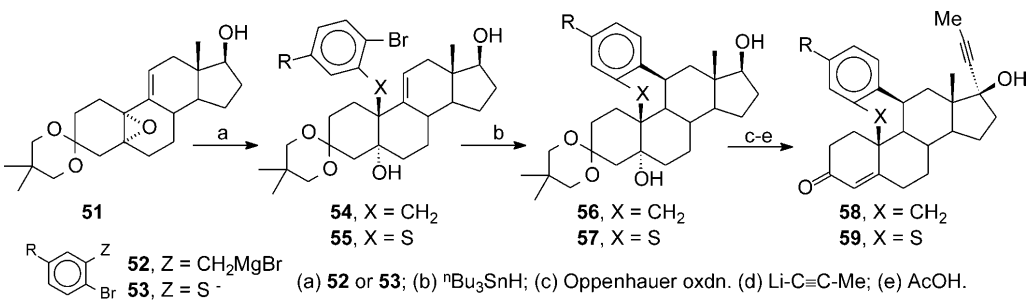
High binding affinity of the 11β-19-norsteroids led to the hypothesis that in the region corresponding to 11β-position of steroids, a pocket exists in the progesterone receptor where hydrophobic interactions are probably involved. On the other hand, it has also been observed that electronic interactions also could be involved in the same area since 11β-halogen or 11β-bulky



Scheme 5.

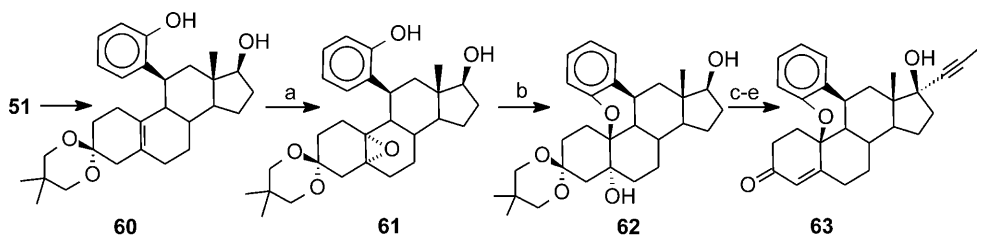
substituents bearing a hetero atom can also increase the receptor-binding affinity. This empirical structure activity relationship prompted Faraj *et al*.[16] to synthesize 11β-(3-*tert*-butyloxypropyl)-19-norsteroid (**50**) with a 17γ-lactone moiety. This compound is typical of the mineralocorticoid receptor antagonist. The key intermediate to these compounds is 5,10α-epoxyestra-9(11)-ene (**13**) (Scheme 5). The epoxide (**13**) on treatment with the corresponding organomagnesium halide in the presence of a catalytic amount of copper (I) chloride gave the required alkoxy alkylated product (**47**). The 17γ-lactone functionality was introduced by methylene transfer to the 17-keto function of compound **47** with dimethyl sulphonium methylide followed by the condensation of acetonitrile on the spiro oxirane (**48**) to furnish the compound **49**. The resulting cyanoethyl-17β-hydroxy steroid (**49**) after alkaline hydrolysis and subsequent acid treatment afforded the 17γ-lactone (**50**)

Ottow and coworkers [17,18] have synthesized two new analogues **58** and **59** of mifepristone **2** which contain a methylene bridge and a thia bridge between C-10 of the steroid skeleton and 11β-aryl residue (Scheme 6). The protocol leading to methylene or thia compounds (**58** and **59**) involved S_N2' opening of the α-epoxide (**51**) by benzyl Grignard reagent (**52**) or a thiophenolate (**53**) followed by regiospecific 6-*endo trig* intramolecular radical cyclization to furnish bridged intermediates **56** and **57**, respectively. These intermediates were converted to mifepristone analogues **58** and **59** by a reported procedure.



Scheme 6.

An analogous strategy to synthesize oxygen-bridged steroid (**63**) by Cleve *et al.*[19] remained unsuccessful as intermolecular epoxide opening by the weaker nucleophile phenolate/phenol was not expected to be a favored process. In order to overcome this difficulty and to accomplish the synthesis of the novel oxygen-bridged steroid **63**, a different synthetic strategy was adopted[19] (Scheme 7). The epoxide **51** on reaction with 2-methoxyphenylmagnesium bromide followed by deketalization, dehydration, Li/NH_3 reduction, reketalization of 3-keto group followed by deprotection of the methyl ether furnished the 11β-phenolic compound (**60**). Compound **60** was epoxidized to obtain the 5,10α-epoxide (**61**) as a major product. Cyclization of **61** in a *trans* diaxial manner took place to **62** upon treatment with dilute acetic acid. In accordance with these experiments, *m*-CPBA epoxidation of **60** without sodium bicarbonate directly led to compound **62** in good yield. Compound **62** was transformed to the targeted oxobridged steroid (**63**) by reported synthetic manipulations.



(a) *m*-CPBA; (b) dil. AcOH; (c) PCC; (d) Li-C≡C-Me; (e) AcOH.

Scheme 7.

Cleve *et al.*[20] have described an efficient approach to 14β-*H* antiprogestins in which they have prepared the 14β-*H* analogues of the 11β,19-bridged series (type A) as well as of the 10β-H, 11β-aryl series (type B). In both the series, the inversion of stereochemistry at C-14 did not lead to further improvement of dissociation between antiprogestational and antiglucocorticoid activities (Fig. 5).

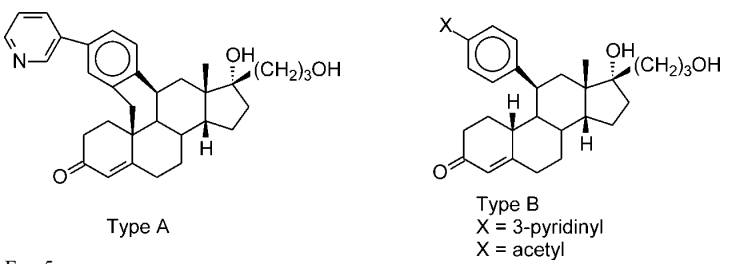


FIG. 5.

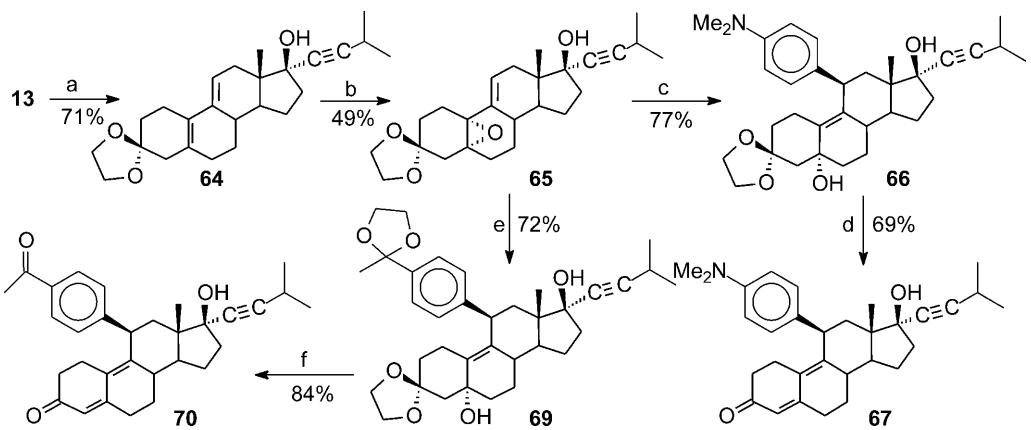
A recent study by Spitz and Agranat[2] revealed that 17α-substituent imparts higher binding affinity for the receptor and the substituent at 11β-position is responsible for its antagonistic activity. It has also been reported that replacement of 11β-(dimethylaminophenyl) substituent with 11β-(acetophenyl) moiety increases the relative binding affinity for glucocorticoid receptor.

In anticipation of changing the relative binding affinity for the receptor, we incorporated an isopropyl group in place of methyl (i.e. 3-methyl-1-butynyl side chain) at 17α-position and successfully achieved the synthesis of a new analogue **67** of mifepristone (**2**). Furthermore, with this

new 17α-alkynyl moiety, 4-acetophenyl group was introduced in the 11β-position to afford another new analogue (**70**) of mifepristone (**2**). Competitive binding assay for progesterone receptor was performed and relative binding affinities for progesterone receptor were determined for these two analogues (**67** and **70**). As compared to mifepristone (**2**), the analogue (**67**) was found to be much more active while compound **70** was found to be less active than mifepristone **2**.

We have synthesized[21] the two analogues (**67** and **70**) of mifepristone (**2**) starting from (+)-estrone **11**. Alteration of synthetic sequences furnished the target compounds **67** and **70** in higher overall yields. Moreover, the introduction of 3-methyl-1-butynyl moiety at 17α-position by a nonhazardous modified method and a highly chemoselective epoxidation of 5(10) olefin with a catalytic amount of hexafluoroacetone in H_2O_2 are the salient features of these syntheses. The structure of compound **67** was confirmed by single-crystal X-ray analysis.

Intermediate **13** was synthesized from estrone **11** following a reported[10–12] seven-step synthetic sequence in 43% overall yield (Scheme 8). Introduction of a 3-methyl-1-butynyl side chain at 17α orientation of compound **13** was tried with 3-methylbut-1-yne and *n*-butyllithium in THF at temperatures ranging from –78 to 25ºC. The reaction furnished a complex mixture of products from which we failed to isolate the desired product (**64**). We then turned our attention to an efficient procedure for the generation of 3-methyl-1-butynyllithium *in situ* in the reaction mixture. This was accomplished by the reaction of 3-methyl-1,1-dibromobut-1-en in THF with 2 equivalents of *n*-BuLi in hexane. 3-Methyl-1,1-dibromobut-1-ene was prepared by the reaction of CBr_4 with isobutyraldehyde in the presence of triphenylphosphine following a reported procedure.[22] Alkynylation of **13** with 3-methyl-1-butynyllithium proceeded smoothly to give the 17α-alkynylated compound **64** in 71% yield. Epoxidation of the 5(10)-double bond of **64** was attempted with *m*-CPBA in the presence of Na_2HPO_4 which afforded a mixture of 5,10α- and 5,10β-epoxides along with 5,10α,9,11α-diepoxide in poor yield. Lack of chemoselectivity and



Reagents and conditions: (a) 1,1-Dibromo-3-methyl-1-butene, *n*-BuLi, THF, –78ºC to -40ºC, 2 h and 25ºC, 8 h; (b) Hexafluoroacetone, H_2O_2, CH_2Cl_2, 0–30ºC, 3.5 h; (c) 4-Bromo-*N,N*-dimethylaniline, Mg, CuI, THF, 5–30ºC, 6 h; (d) 70% AcOH, 50–60ºC, 1 h; (e) 2-Methyl-2-(4-bromophenyl)-1,3-dioxalane (**11**), Mg, CuI, THF, 5–30ºC, 6 h; (f) 70% AcOH, 50–60ºC, 1 h.

Scheme 8.

also stereoselectivity of the 5(10), 9(11)-steroid diene with *m*-CPBA is known in the literature. Chemoselective epoxidation of the 5(10) double bond of **64** was achieved finally with H_2O_2 and a catalytic amount of hexafluoroacetone trihydrate to get a mixture of 5,10α-epoxide (**65**) and 5,10β-epoxide in good yield in a 4:1 ratio. The isomeric ratio was assigned from the integration of the 200 MHz ^{1}H NMR spectrum of the epoxides, which showed two signals at 6.1 and 5.9 ppm for the C-11 hydrogen of the α and the β isomers, respectively. The combination of hexafluoroacetone with H_2O_2 produces 2-hydroperoxyhexafluoro-2-propanol, a reactive oxidizing agent possessing considerable selectivity, particularly in the oxidation of sterically hindered olefins. Moreover, the byproduct of epoxidation, 2-hydroxyhexafluoro-2-propanol, readily disproportionates with H_2O_2 to regenerate 2-hydroperoxyhexafluoro-2-propanol, thereby implementing a simple catalytic cycle. The required 5,10α-epoxide (**65**) was isolated by column chromatography over silica gel in 49% yield as a solid. The 11β-(4-dimethylaminophenyl) substituent was introduced by S_N2' opening of the oxirane ring of compound **65** with the Grignard reagent prepared from 4-bromo-*N,N*-dimethylaniline in the presence of a catalytic amount of Cu(I) iodide. The 11β-substituted compound **66** was obtained as a solid in 77% yield. The Cu(I)-catalyzed reaction is highly stereo- and regiospecific with a rather low sensitivity to steric hindrance. 11β-Stereochemistry at C-11 is evident from the large shielding effect in the proton resonance of the C-18 methyl group. In the 11-unsubstituted compound (**65**), the 18-methyl signal comes at 0.82 ppm, whereas the introduction of 11β-aryl moiety shifts the 18-methyl signal to 0.59 ppm in compound **66**. Deketalization and simultaneous dehydration of **66** with 70% AcOH gave the target compound **67** in 69% yield as a crystalline solid. The structure of compound **67** was finally confirmed by single-crystal X-ray analysis. For the synthesis of 11β-(acetophenyl)-17β-hydroxy-17α-(3-methyl-1-butynyl)-estra-4,9-dien-3-one (**70**), the 5,10α-epoxide (**65**) was utilized. 2-Methyl-2-(4-bromophenyl)-1,3-dioxalane (**68**) was prepared from 4-bromoacetophenone by ketalization with ethylene glycol in the presence of a catalytic amount of PTSA. The Grignard reagent prepared from **68** reacted with the 5,10α-epoxide (**65**) in S_N2' mode, in the presence of a catalytic amount of CuI, to furnish as a solid after column chromatographic purification of the 11β-substituted steroid **69** in 72% yield. Deketalization of **69** and concomitant dehydration with 70% AcOH afforded the 11β-(4-acetophenyl) substituted steroid (**70**) as a foam in 84% yield.

6. Relative binding affinities of compounds 2, 67 and 70 for progesterone receptors

Competitive binding assay for progesterone receptors (PR) was performed using rabbit uterine cytosol and ^{3}H progesterone (radioligand) in the presence of unlabelled cortisol at 4°C. Competitor dilutions were prepared in DMF: Tris-HCl buffer pH 7.4 (1:1). Results calculated as per cent relative binding affinity for PR, revealed that compound **67** was the most active. Compound **2** showed RBA (103%) almost equivalent to that of progesterone (100%). Compound **67** showed an RBA of 175%. Compound **70** showed 35% RBA that is approximately 1/5 of that of compound **2**. As compared to compound **2**, i.e. mifepristone, compound **67** is more active whereas compound **70** is less active. The activity of progesterone **1** was taken as 100%.

7. Conclusion

The primary structures of the steroid receptors show strong similarity. Hence substituents often enhance or reduce more than one hormonal activity and it is very difficult to find more selective steroids. But it is obvious that the results obtained in one hormonal series could often be used as

leads for the synthesis in other hormonal series. Abortion is only one application for this new group of compounds. Antiprogestins are among the most interesting therapeutic compounds developed over the past two decades and are finding wider use in medical science. For long-term use at high doses, a more selective antiprogestin would be required and research in this direction should be continued.

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