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# Synthesis of 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(3-methyl-1-butynyl)-4, 9-estradien-3-one and 11β-(4-acetophenyl)-17β-hydroxy-17α-(3-methyl-1-butynyl)-4, 9-estradien-3-one: two new analogs of mifepristone (RU-486)☆,☆☆,☆☆☆

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**Abstract**

From the structure activity relationship, two new analogs, **2** and **3,** of the potent progesterone antagonist mifepristone **1** have been designed. The syntheses of these two analogs have been achieved in eleven steps through modified synthetic sequences and improved procedures starting from (+)-estrone. In comparison with mifepristone **1**, the relative binding affinities of compound **2** for the progesterone receptor was found to be more, whereas that of compound **3** was less. 

*Keywords:* Mifepristone analogs; Progesterone antagonist; Abortifacient; Antiglucocorticoid; Antiprogestin; 19-Norsteroids

## 1. Introduction

In 1980, the French pharmaceutical company Roussel–Uclaf announced the discovery [1,2] of RU-486, now known by the generic name mifepristone (**1**). This was the first antiprogestin to be developed. Mifepristone (**1**), when used in combination with a prostaglandin, effectively and safely terminates early pregnancies. It is already in use [1,2] as an abortifacient in France, UK, Sweden, and China, has passed the clinical trials in USA, and is under clinical trials in India. It is also a potent antiglucocorticoid and shows promising activity in treating estrogen-dependent gynecological disorders and hormone deficient tumors.

Over the years, a number of mifepristone analogs have been synthesized [3–6] and were tested for their antiprogestin activity. Teutsch et al. [7] have synthesized a variety of 11β-substituted 19-norsteroids. Among these compounds, 11β-vinyl and 11β-phenyl compounds showed a high degree of binding affinity for the cytoplasmic uterine progesterone receptor, whereas the 11β-allyl and 11β-benzyl-19-norsteroids showed very low binding affinity. Thus, shifting the unsaturation by one carbon atom practically eliminates the receptor binding affinity. High binding affinity of the 11β-19-norsteroid led to the hypothesis that in the region corresponding to the 11β-position of the steroids, a pocket exists in the progesterone receptor, where hydrophobic interactions are probably involved (Scheme 1).

A very recent study by Spitz and Agranat [8] revealed that the 17α-substituent imparts higher binding affinity for the receptor and the substituent at 11β-position is responsible for its antagonistic action. It has also been reported [9] that replacement of the 11β-(dimethylaminophenyl) substituent with the 11β-(acetophenyl) moiety increases the relative binding affinity for the progesterone receptor in rat and lowers the relative binding affinity for the glucocorticoid receptor than that of mifepristone (**1**). In fact, the most active compound in this series, ORG

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☆☆☆ Dedicated to Prof. D. Nasipuri on his 75th birthday.

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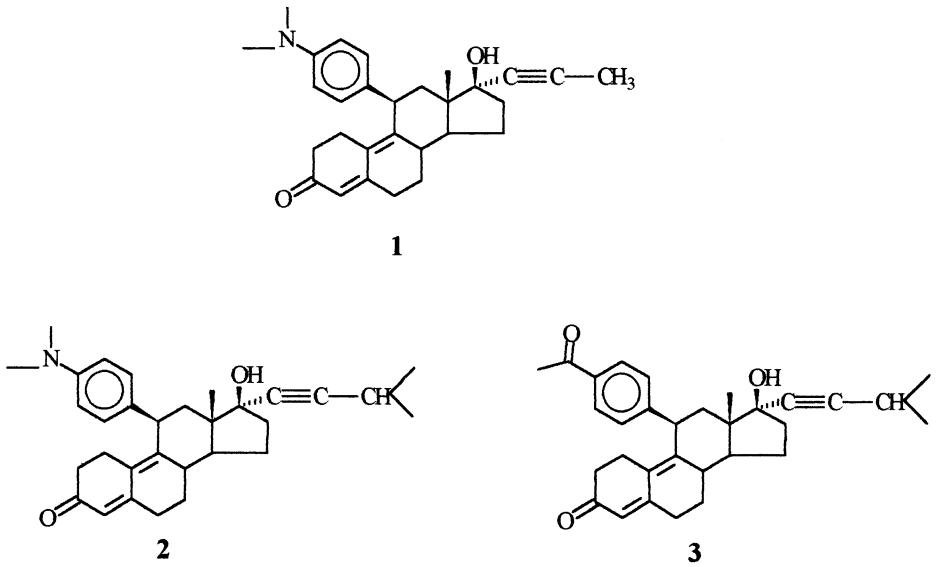


Scheme 1.

33628, has been claimed to be 32× as active as mifepristone in inducing abortions in rats, while being significantly less active as an antiglucocorticoid [8]. Compound ORG 33628, is a 17-spirofuran, 11$\beta$-(4-acetophenyl) analog of mifepristone.

In anticipation of changing the relative binding affinity for the receptor, we planned to incorporate an isopropyl group in place of methyl (e.g. 3-methyl-1-butynyl side chain), at 17$\alpha$-position and successfully achieved the synthesis of a new analog (**2**) of mifepristone (**1**). Furthermore, with this new 17$\alpha$-alkynyl moiety in compound (**2**), 4-acetophenyl group was introduced in the 11$\beta$-position to afford another new analog (**3**) of mifepristone (**1**). Modification of both the active sites (at 17$\alpha$ and 11$\beta$) are expected to bring about a cumulative effect on the receptor binding affinity as well as antiglucocorticoid activity of compound (**3**).

Herein, we wish to report, the syntheses of two new analogs, (**2**) and (**3**), of mifepristone (**1**), starting from (+)-estrone. Alteration of reported [6] synthetic sequences furnished the target compounds (**2**) and (**3**) in higher overall yields. Moreover, introduction of 3-methyl-1-butynyl moiety at 17$\alpha$-position by 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 (**2**) was confirmed by a single crystal X-ray.

## 2. Experimental

All solvents and reagents used were of commercial grade. Dry tetrahydrofuran (THF) was freshly obtained by taking the liquid to reflux under nitrogen, in a recirculation still over sodium. Pyridine was purified by distillation and stored over KOH pellets. Reactions were monitored by TLC using TLC aluminum sheets, silica gel $60F_{254}$ precoated, Merck, Germany, and locating the spots spraying with ethanolic solution of phosphomolybdic acid followed by heating. Usual work-up means the organic extract was thoroughly washed with water and brine and finally dried over anhydrous sodium sulfate. -IR: Perkin–Elmer 599B. -$^1$H NMR: Bruker AC 200 (200 MHz). For $^1$H NMR, $CDCl_3$ as solvent and TMS as an internal standard and *J* values are given in Hz. -MS: Finnigan 1020C (70eV). -$[\alpha]_D$: JASCO-181 (4893 $^0$A). $[\alpha]_D$ values are given in $10^{-1}$ deg cm$^2$/g, m.p. (uncorrected): Yanaco Micro m.p. apparatus.

### *2.1. Estra-5 (10), 9( 11)-dien-3-one, 17β-hydroxy-17α-(3-methyl-1-butynyl) cyclic 3-(1,2-ethanediyl acetal) (5)*

In a 25-ml two-necked flask equipped with a septum and a nitrogen assembly, 3-methyl-1, 1-dibromobut-1-en (0.454 g, 2 mmol) in dry THF (5 ml) was placed under nitrogen. The solution was cooled to −78°C and to it was added n-BuLi (2 ml, 2 M solution in hexane). The reaction mixture was then slowly brought to −40°C and stirred at that temperature for 2 h. After this period, it was again cooled to −78°C and the 17-keto compound **4** (0.314 g, 1 mmol) in THF (3 ml) was added dropwise to it and was stirred for a further 8 h at 25°C. It was then quenched with ice-cold saturated ammonium chloride solution and the mixture was extracted with ethyl acetate (4 × 50 ml). After usual work up solvent was removed under vacuo to afford gum (0.432 g). Column chromatographic purification over silica gel by using hexane/ethyl acetate (9:1) as eluent furnished compound **5** as colorless foam (0.271 g, 71%), m.p. 56–58°C; $[\alpha]^{30} = +128.35°$ (c 0.79 in $CHCl_3$); -IR (nujol) $\gamma$ 3410 cm$^{-1}$(OH); -$^1$H NMR ($CDCl_3$): $\delta$ = 0.85 (s, 3H, 18-$H_3$), 1.15 (d, 6H, *J* = 6, isopropyl $CH_3$), 2.46–2.75 (m, 2H,

4-$H_2$), 4.0 (s, 4H, ketal -$CH_2$), 5.65 (bd, 1H, 11-H); -MS (70 eV): *m/z* (%): 382 ($M^+$), 369, 332, 235, 159, 99 (100%); -$C_{25}H_{34}O_3$ (382.52): calculated C 78.5, H 8.96; Found C 78.7, H 8.8.

### *2.2. Estra-5α,10α-epoxy-9 (11)-en-3-one, 17β-hydroxy-17α-(3-methyl-1-butynyl) cyclic 3-(1,2-ethanediyl acetal) (**6**)*

Compound **5** (0.095 g, 0.25 mmol) was dissolved in $CH_2Cl_2$ (3 ml) and the solution was cooled to 0°C. Added to it was $Na_2HPO_4$ (0.090 g, 0.63 mmol), followed by hexafluoroacetone trihydrate (0.013 g, 0.059 mmol) and 44.6% $H_2O_2$ (0.0076 g, 0.225 mmol). The reaction mixture was then slowly brought to 25°C and was stirred at that temperature for 3 h. It was then diluted with $CH_2Cl_2$ and to it was added 10% sodium thiosulphate solution (1 ml), stirred for an additional 30 min. The reaction mixture was extracted with $CH_2Cl_2$ (4 × 25 ml), washed with water (3 × 25 ml) and brine (2 × 25 ml), and dried over anhydrous sodium sulfate. Removal of solvent under vacuo afforded a gum (0.102 g) that was chromatographed over silica gel by using hexane/ethyl acetate (9:1) as eluent furnished compound **6** (0.048 g, 49%) as colorless crystalline solid, m.p. 178°C (from hexane/ethyl acetate); $[\alpha]^{32} = -5.6$ (c 0.56 in $CHCl_3$); -IR (nujol) $\gamma$ 3410 $cm^{-1}$ (OH); -$^1$H NMR ($CDCl_3$): $\delta = 0.82$ (s, 3H, 18-$H_3$), 1.16 (d, 6H, $J = 6$, isopropyl $CH_3$), 2.41–2.65 (m, 2H, 4-$H_2$), 3.95 (m, 6H, ketal -$CH_2$), 6.1 (bd, 1H, 11-H); -MS (70 eV): *m/z* (%) 398 ($M^+$), 383 ($M^+$-$CH_3$), 337, 312, 297, 223, 141, 129, 59 (100%); -$C_{25}H_{34}O_4$ (398.55): calculated C 75.34, H 8.6; Found C 75.5, H 8.9.

### *2.3. 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(3-methyl-1-butynyl)-estra-9-en-5α,17β-diol-3-one, cyclic 1,2-ethandiyl acetal (**7**)*

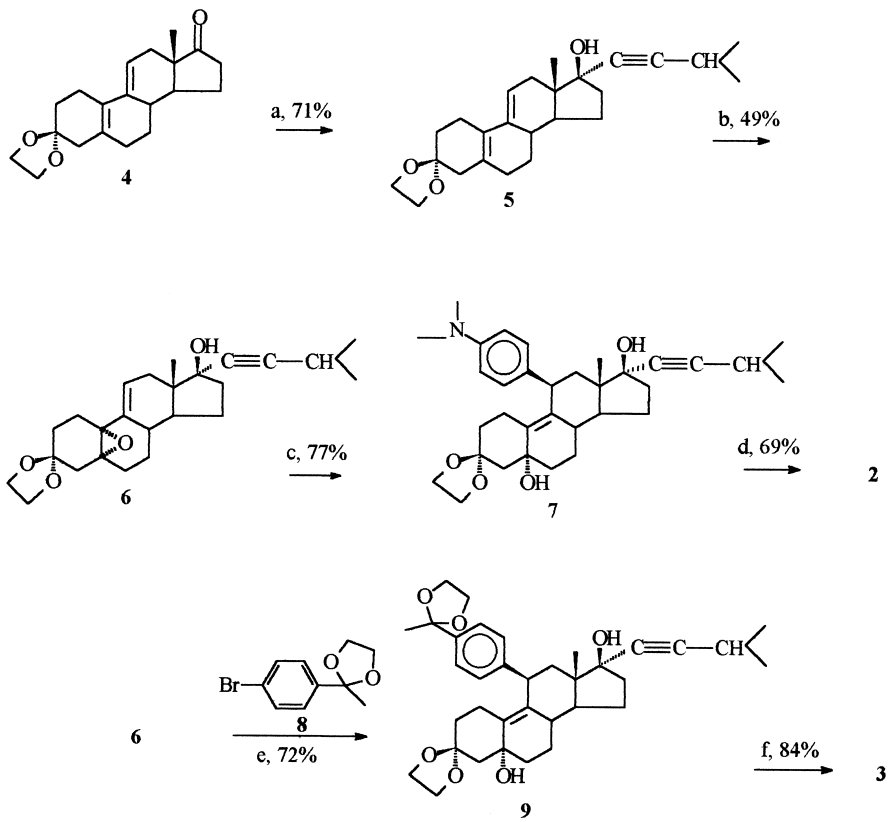
In a 25-ml two-necked flask equipped with a septum and nitrogen assembly, Mg (0.053 g, 2.2 mmol) was placed and to it 4-bromo-*N*,*N*-dimethylaniline (0.455 g, 2.27 mmol) in THF (1 ml) was introduced with a syringe. The mixture was heated at 45–50°C for 2 h, and during this period, all Mg disappeared, resulting a yellowish solution. In another two-necked flask, the α-epoxide **6** (0.074 g, 0.18 mmol) and CuI (0.0095 g, 0.05 mmol) in THF (3 ml) were placed under nitrogen and cooled to 0°C. To it the preformed Grignard reagent was added dropwise. The resulting reaction mixture was slowly brought to 25°C and was stirred at that temperature for a period of 6 h. It was then quenched with cold saturated $NH_4Cl$ solution and extracted with diethyl ether (4 × 25 ml). The ether extract was worked up in the usual way. Removal of solvent under reduced pressure furnished a gum (0.103 g) that was chromatographed over silica gel to afford **7** (0.074 g, 77%) as a solid, m.p. 103°C (from hexane/ethyl acetate); -IR (nujol) $\gamma$ 3460 $cm^{-1}$ (OH), 1510 (aromatic); -$^1$H NMR ($CDCl_3$): $\delta = 0.59$ (s, 3H, 18-$H_3$), 1.19 (d, 6H, $J = 7$, isopropyl $CH_3$), 1.25 (m, 1H, isopropyl -CH), 2.90 (s, 6H, N, N-$CH_3$), 3.96 (m, 4H, ketal -$CH_2$), 4.26 (d, 1H, $J = 5$, 11-H), 6.66 (d, 2H, $J = 10$, Ar-$H_2$), 7.05 (d, 2H, $J = 10$, Ar-$H_2$); -$C_{33}H_{45}NO_4$ (519.70): calculated C 76.26, H 8.73; Found C 76.43, H 8.6.

### *2.4. 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(3-methyl-1-butynyl)-estra-4, 9-dien-17β-ol-3-one (**2**)]*

The solution of the hydroxy ketal **7** (0.074 g, 0.142 mmol) in 70% AcOH (0.5 ml) was heated at 50°C for 2 h. It then was cooled and neutralized with cold aqueous $NaHCO_3$. Usual work up followed by removal of solvent under vacuo afforded a yellow gum (0.087 g) that was chromatographed over silica gel by using hexane/ethyl acetate (6:4) as an eluent to furnished **2** (0.045 g, 69%), as a solid, m.p. 178°C (from hexane/diethyl ether); $[\alpha]^{32} = +126.25°$ (c 0.48 in $CHCl_3$); -IR (nujol) $\gamma$ $cm^{-1}$ 3415 (-OH), 1652 (-C = O), 1517 (aromatic); $^1$H NMR ($CDCl_3$) $\delta = 0.56$ (s, 3H, 18-$H_3$), 1.22 (d, 6H, isopropyl -$CH_3$), 2.95 (s, 6H, N, N-$CH_3$) 4.37 (d, 1H, $J = 5$, 11-H) 5.78 (s, 1H, 4-H), 6.67 (d, 2H, $J = 8$, Ar-$H_2$), 7.04 (d, 2H, $J = 8$, Ar-$H_2$); -MS (70 eV): *m/z* (%) 457 ($M^+$), 439 ($M^+$-$H_2O$), 121 (100%); -$C_{31}H_{39}NO_2$ (457.63): calculated C 81.36, H 8.59; Found C 81.3, H 8.7.

### *2.5. 11β-[2-methyl-2-phenyl-1,3-dioxalan)-17α-(3-methyl-1-butynyl)-estra-9-en-5α,17β-diol-3-one, cyclic 1,2-ethandiyl acetal (**9**)*

In a two-necked flask equipped with a septum and a nitrogen assembly, Mg (0.036 g, 1.5 mmol) was placed and to it 2-methyl-2-(bromophenyl)-1, 3-dioxalan **8** (0.318 g, 1.5 mmol) in THF (1 ml) was introduced. The reaction mixture was heated at 45 to 50°C for 2 h, and during this time, all Mg disappeared, resulting in a dark-colored solution. In another flask, compound **6** (0.120 g, 0.3 mmol) and CuI (0.0057 g, 0.03 mmol) in THF (4 ml) were placed under nitrogen and cooled to 0°C. To it the dark-colored solution of the Grignard reagent was added dropwise. The resulting reaction mixture was slowly brought to 25°C and was stirred at that temperature for a period of 6 h. It then was quenched with cold saturated $NH_4Cl$ and extracted with diethyl ether (4 × 25 ml). Usual work up of the organic extract and removal of solvent under reduced pressure afforded a gum (0.318 g) that on column chromatographic purification over silica gel using ethyl acetate/hexane (2:8) as an eluent afforded compound **9** as solid (0.130 g, 77%); m.p. 173–174°C (from hexane/diethyl ether); $[\alpha]^{28} = -46.1°$ (c 0.36 in $CHCl_3$); -IR (nujol) $\gamma$ $cm^{-1}$ 3400 (-OH); $^1$H NMR ($CDCl_3$) $\delta = 0.52$ (s, 3H, 18-$H_3$), 1.2 (d, 6H, $J = 6$, isopropyl -$CH_3$), 1.65 (s, 3H, acetophenyl $CH_3$), 3.65–4.05 (m, 8H, ketal $CH_2$), 4.3 (bd, 1H, $J = 5$, 11H), 7.16 and 7.35 (AB pattern, $J = 10$, Ar-H); -MS (70eV): *m/z* (%) 562 ($M^+$), 544 (100%), 434, 366, 191, 178, 133, 105; -$C_{35}H_{46}O_6$ (562.72): calculated C 74.7, H 8.24; Found C 74.3, H 8.35.




Scheme 2.

*2.6. 11β-(4-acetophenyl)-17α-(3-methyl-1-butynyl)-estra-4, 9-dien-17β-ol-3-one (**3**)*

A solution of the hydroxy ketal **9** (0.038 g, 0.067 mmol) in 70% AcOH (0.5 ml) was heated at 50 to 60°C for 2 h. The solution was then cooled and neutralized with cold aqueous $NaHCO_3$ solution. The resultant gummy mass was extracted with $CH_2Cl_2$ (3 × 25 ml), washed thoroughly with water (3 × 25 ml) and brine (2 × 25 ml), and was dried over anhydrous sodium sulfate. Removal of solvent afforded a yellowish gum (0.062 g) that was chromatographed over silica gel to get pure compound **3** (0.026 g, 84%) as foam, m.p. 97–100°C; $[\alpha]^{30} = +86.25°$ (c 0.26 in $CHCl_3$); -IR (nujol) $\gamma$ $cm^{-1}$ 3459 (-OH), 1665 (-C = O); $^1H$ NMR ($CDCl_3$) $\delta = 0.49$ (s, 3H, 18-$H_3$), 1.2 (d, 6H, J 6, isopropyl -$CH_3$), 2.6 (s, 3H, acetophenyl $CH_3$), 4.49 (bd, 1H, $J = 5$, 11-H), 7.3 and 7.9 (AB pattern, 4H, $J = 10$, Ar-H); -MS (70 eV): *m/z* (%) 439 ($M^+$-OH), 413, 395, 346, 236, 147, 91, 67 (100%); -$C_{31}H_{36}O_3$ (456.60): calculated C 81.54, H 7.95; Found C 81.3, H 8.1.

## 3. Results and discussion

Syntheses of our two new analogs **2** and **3** of mifepristone **1** start from estra-5 (10), 9 (11)-dien-3,17-dione, cyclic-3-(1,2-ethanediyl acetal) **4** [10,11] (Scheme 2). Introduction of a 3-methyl-1-butynyl side chain at 17 $\alpha$ orientation of compound **4** was tried with 3-methylbut-1-yne [12] and n-butyl lithium in THF at temperatures ranging from −78° to 25°C. The reaction furnished a complex mixture of products from which we failed to isolate the desired product **5.** We then turned our attention at 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-en was prepared by the reaction of $CBr_4$ with isobutyraldehyde in the presence of triphenylphosphine by a reported [13] procedure. Alkynylation of **4** with 3-methyl-1-butynyl lithium proceeded smoothly to give the 17$\alpha$-alkynylated compound **5** in 71% yield as a foam. Chemoselective epoxidation of the 5 [10] double bond of **5** was achieved with $H_2O_2$ and a catalytic amount of hexafluoroacetone trihydrate to get a mixture of 5, 10$\alpha$-epoxide **6** and 5, 10$\beta$-epoxide in good yield and in the ratio of 4:1. The isomeric ratio was assigned from the integration of the 200 MHz $^1H$ NMR spectrum of the epoxides that showed two signals at 6.1 and 5.9 ppm for the C-11 hydrogen of the $\alpha$ and the $\beta$ isomer respectively. The combination of hexafluoroacetone with $H_2O_2$ produces 2-hydroperoxyhexafluoro-2-propanol, a reactive oxidizing agent [14] possessing con-

siderable selectivity, particularly in the oxidation of strerically 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, 10$\alpha$-epoxide **6** was isolated by column chromatography over silica gel in 49% yield as a solid. The 11$\beta$-(4-dimethenylaminophenyl) substituent was introduced by $S_N2$ opening of the oxirane ring of compound **6** with the Grignard reagent prepared from 4-bromo-*N*,*N*-dimethyl aniline in presence of a catalytic amount of Cu (I) iodide. The 11$\beta$-substituted compound **7** was obtained as solid in 77% yield. 4-Bromo-*N*,*N*-dimethyl aniline was prepared [15] by the regioselective monobromination of *N*,*N*-dimethylaniline with 2, 4, 4, 6-tetrabromo-2, 5-cyclohexadien [16]. 11$\beta$ 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 **6,** the 18-methyl signal comes at 0.82 ppm whereas, introduction of 11$\beta$-aryl moiety, shields the 18-methyl signal to 0.59 ppm in compound **7**. Deketalization and simultaneous dehydration of **7** with 70% AcOH gave the target compound **2** in 69% yield as a pale yellow crystalline solid. The structure of compound **2** was finally confirmed by single crystal X-ray analysis.

For the synthesis of 11$\beta$-(acetophenyl)-17$\beta$-hydroxy-17$\alpha$-(3-methyl-1-butynyl)-estra-4, 9-dien-3-one **3**, the 5, 10$\alpha$-epoxide **6** was utilized (Scheme 2). 2-Methyl-2-(4-bromophenyl)-1, 3-dioxalan **8** was prepared from 4-bromoacetophenone by ketalization with ethylene glycol in the presence of catalytic amount of PTSA, which in turn was prepared from bromobenzene by Fridel Craft acylation with acetic anhydride [17]. The Grignard reagent prepared from **8** reacted with the 5, 10$\alpha$-epoxide **6** in $S_N2$ mode, in presence of a catalytic amount of CuI, to furnish after column chromatographic purification the 11$\beta$-substituted steroid **9** in 72% yield as a solid. Deketalization of **9** and concomitant dehydration with 70% AcOH afforded the 11$\beta$-(4-acetophenyl) substituted steroid **3** as a foam in 84% yield. This new mifepristone analog **3** was fully characterized by IR, $^1$H NMR, and mass and elemental analysis.

### *3.1. Relative binding affinities of compounds **1**, **2**, and **3** 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 percent relative binding affinity for PR, revealed that compound **2** was the most active. Compound **1** showed RBA (103%) almost equivalent to that of progesterone (100%; Table 1). Compound **2** showed an RBA of 175%. Compound **3** showed 35% RBA that is approximately 1/5 of that of compound **2**. As compared to compound **1** i.e. mifepristone, compound **2** is more active whereas compound **3** is less active. The activity of progesterone is taken as 100%.

Table 1
Relative binding affinities of compounds **1**, **2,** and **3** for progesterone receptors

| S. No. | Compound no. | Relative binding affinity (%)[a] |
|---|---|---|
| 1. | 1 (Mifepristone) | 103 |
| 2. | 2 | 175 |
| 3. | 3 | 35 |
| 4. | Progesterone | 100 |

[a] Values are mean of two separate experiments.

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