Steroids xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Steroids

journal homepage: www.elsevier.com/locate/steroids

Synthesis and biological evaluation of 11′ imidazolyl antiprogestins and mesoprogestins

Klaus Nickisch [a,*], Walter Elger [a], Bindu Santhamma [a], Robert Garfield [b], Zachary Killeen [b], Olga Amelkina [c], Birgitt Schneider [a], Reinhard Meister [d]

[a] Evestra, Inc., San Antonio, TX, USA
[b] St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA
[c] Leibnitz Institute for Zoological- and Wildlife Research, IZW, Berlin, Germany
[d] Beuth University of Applied Science, Berlin, Germany

ARTICLE INFO

Article history:
Received 23 March 2014
Received in revised form 25 July 2014
Accepted 17 August 2014
Available online xxxx

Keywords:
Antiprogestins
Postcoital fertility control
Cervix widening

ABSTRACT

Antiprogestins with a 4′ para imidazolylphenyl moiety were synthesized and their biochemical interactions with the progesterone and glucocorticoid receptor were investigated. Depending on the substitution pattern at the 17 position partial progesterone receptor (PR)-agonistic derivatives like compounds EC339 and EC336 or pure antagonists like compound EC317 were obtained. EC317 was investigated *in vivo* and found to be significantly more potent than RU 486 in cycling and pregnant guinea pigs. For testing the biological action progesterone receptor modulators (PRM), guinea pigs appears as a specific model when compare to pregnant human uterus. This model correlates to human conditions such as softening and widening of the cervix, the elevation of the uterine responsiveness to prostaglandins and oxytocin, and finally to induction of labor. The use of non-pregnant guinea pigs permitted the simultaneous assessment of PR-agonistic and PR-antagonistic properties and their physiological interactions with uterine and vaginal environment. These can histologically be presumed from the presence of estrogen or progesterone dominance in the genital tract tissues. The ovarian histology indicated the effects on ovulation. Corpora lutea in guinea pigs further reflects inhibitory effects of the progesterone-dependent uterine prostaglandin secretion. PRMs are initially synthesized as analogues of RU 486. They represent a heterogeneous group of compounds with different ratios of PR-agonistic and-antagonistic properties. PR-agonistic properties may be essential for uterine anti-proliferative effects. In various clinical studies these were also attributed to RU 486 or Ulipristal [1,2]. Adjusted PR-agonistic PRMs (EC312, EC313) [3] may be more effective in achieving a mitotically resting endometrium and superior uterine tumor inhibition. For the use in termination of pregnancy, progesterone-inhibitory effects are essentially needed. Even minor PR-agonistic properties compromise the therapeutic goals. Pure PR-antagonists, as EC317, clearly exceeded the gold standard RU 486 with respect to labor inducing effects. Mechanistically it is surprising that both types of compound may be potent inhibitors of ovulation.

1. Introduction

The first progesterone receptor antagonist, RU 486 [4] more than 30 years ago, has initiated an intense research effort and prospective new treatments in areas like fertility control, gynecological diseases such as endometriosis, myomas and hormone dependent cancers. Some of these studies did not provide expected results. Two antiprogestins have been approved till date were, RU 486 for the first widely used non-surgical induction of abortion and Ulipristal for postcoital fertility control and for preoperative treatment for uterine fibroids. Regarding the pharmacodynamic heterogeneity of PRMs [5–8], the key reason for the lack of additional marketed products in the gynecological therapy might be the lack of appropriate animal models applicable for the different needs of given indications. These may require different, better adapted pharmacodynamic profiles. Compounds that act as pure progesterone antagonists appear ideal for cervical ripening and labor induction, whereas compounds with a strong partial PR-agonist activity may lack labor inducing properties. They may help to safely achieve improved anti-proliferative effects in patients with endometriosis and uterine tumors (fibroid/myoma). It is hypothesized that for the existing and

* Corresponding author.
E-mail address: knickisch@evestra.com (K. Nickisch).

http://dx.doi.org/10.1016/j.steroids.2014.08.017
0039-128X/

potential new indications, optimized substances could be developed, that address the shortcomings of the first generation of PRM-products.

The development of Asoprisnil for indications like uterine fibroids and endometriosis proved the predictive value of the guinea pig model. This applies to the successful selection of this molecule and mechanistic aspects. The simultaneous manifestation of agonistic and antagonistic activity at the same dose level in target tissues in animals and in the human [5,6] represents an analogy of SPRMs to SERMs (Specific Estrogen Receptor Modulator). Due to this, the term SPRM (Specific Progestin Receptor Modulator) has been coined [5] and reserved to this type of mixed agonist-/antagonist activity at the receptor level of PR. Asoprisnil permitted for a chronic use, arresting menstrual bleeding and leading to a dramatic reduction of the size of uterine fibroids and the associated dysfunctional bleeding. This was achieved without unopposed estrogenic effects in the endometrium [5,9] (Table 1).

Over the years, knowledge about the structure activity relationship (SAR) of antiprogestins has increased considerably [4,10,11]. Two substitution patterns at the 17 position which attracted considerable interest in recent years are the 17,17spiroether group [12] and the pentafluoro ethyl group [13]. Both lead to compounds that bind strongly and selectively to the progesterone receptor, nothing is however reported about potential determinants of partial PR-agonistic activities.

There are only very few reports about antiprogestins with proven partial PR-agonistic activity *in vitro* [14]. Other methods showed apparent discrepancies of data from *in vitro* and *in vivo* studies showing *false negative* results *in vitro* for compounds with clear cut PR-agonistic effects *in vivo* (unpublished negative *in vitro* data from collaborating laboratories, including Asoprisnil).

The first SPRM was Asoprisnil (Fig. 1) for which a strong partial agonistic activity was proven in the classical animal models for progestational activity [7,15]. A mixed profile progesterone agonists/antagonists have been described for 11 pyridylphenyl derivatives [3,16] and 11furanylphenyl derivatives [3].

There is however no systematic investigation on substitution patterns in the molecules that lead to a full PR-antagonistic or a partial agonistic profile. The available biological and X-ray data suggest that substitution pattern at the 11 position determines the degree of agonistic and antagonistic activity. Small substitutes like methyl or vinyl lead to potent PR-agonistic properties [4] whereas substituted phenyl derivatives show different degrees of antagonistic activity. The most widely used moiety is the 4′ dimethyl amino function, present in RU 486 and Ulipristal impart an antagonistic activity whereas the 3 pyridylphenyl derivative leads to a partial agonistic profile.

For this study the 11 imidazolyl phenyl moiety was selected, because it is special arrangement of atoms and the pk_a's are somewhat in between the dimethyl amino and pyridyl group and combined with moieties at the 17 position that were reported to lead to potent antiprogestins. All molecules were investigated for antagonistic and partial agonistic activities.

2. Experimental

2.1. General

Nuclear magnetic resonance spectra were recorded on a Bruker ARX (300 MHz) spectrometer as deuterochloroform ($CDCl_3$) solutions using tetramethylsilane (TMS) as an internal standard ($\delta = 0$) unless noted otherwise. 'Flash column' chromatography was performed on 32–64 μM silica gel obtained from EM Science, Gibbstown, New Jersey. Thin-layer chromatography (TLC) analyses were carried out on silica gel GF (Analtech) glass plates (2.5 cm × 10 cm with 250 μM layer and pre-scored). Most chemicals and solvents were analytical grade and used without further purification. Commercial reagents were purchased from Aldrich Chemical Company (Milwaukee, WI).

2.2. Chemical synthesis

Compounds **2** and **10** were synthesized following literature procedures described by Rao et al. in Steroids; 1998; 63: 523–530 and by Jiang et al. in Bioorg Med Chem 2006; 14:6726–6732.

2.2.1. 3,3-Ethylenedioxy-5α-hydroxy-11β-[4′-iodophenyl]-estr-9-ene-17-one (**3**)

A solution of 1,4-diiodobenzene (13.2 g, 40 mmol) in anhydrous THF (80 mL) was cooled to −10 °C as a 2 M solution of isopropyl magnesium chloride (20 mL, 40 mmol) was added dropwise over a period of 15 min. After stirring for 20 min, cuprous chloride (898 mg, 9.07 mmol) was added as a solid and the reaction mixture was stirred for 30 min. A solution of the epoxide **2** (6 g, 18 mmol) in 60 mL of THF was added drop wise and stirred for 2 h slowly warming to 10 °C. The reaction was quenched with saturated aqueous ammonium chloride solution (50 mL) and was extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed further with water and brine, dried over sodium sulfate and evaporated *in vacuo* to afford the crude product. The crude product was triturated with di-isopropyl ether (120 mL) to precipitate the pure product which was filtered, washed with ice cold di-isopropyl ether (30 mL) and dried under vacuum to afford 6.9 g (72%) of **3** as an off white solid.

^{1}H NMR (δ, $CDCl_3$, 300 MHz): 0.49 (s, 3H), 3.88–4.04 (m, 4H), 4.26 (d, J = 7.1 Hz), 4.39 (s, 1H), 6.98 (d, J = 8.1 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H).

^{13}C NMR (δ, $CDCl_3$, 75 MHz): 14.36, 22.10, 23.36, 35.05, 35.51, 37.74, 37.78, 37.97, 39.02, 47.33, 47.43, 50.45, 64.08, 64.71, 69.88, 90.87, 108.43, 121.30, 128.62, 132.86, 135.95, 145.97, 219.48.

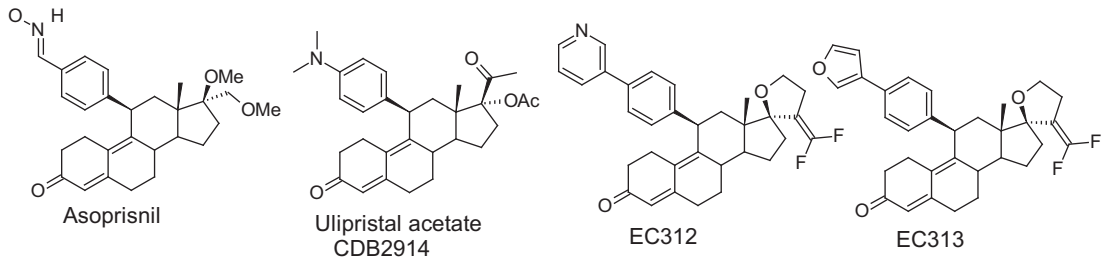
2.2.2. 3,3-Ethylenedioxy-5α-hydroxy-11β-[4′-(1-imidazolyl)phenyl]-estr-9-ene-17-one (**4**)

A mixture of compound **3** (9.7 g, 18 mmol), imidazole (1.4 g, 20 mmol), cuprous iodide (346 mg, 1.8 mmol), *N*,*N*-dimethyl glycine (374 mg, 3.6 mmol) and potassium carbonate (5 g, 36 mmol) in anhydrous DMSO (10 mL) was degassed three times applying

Table 1
Current uses of PRMs and hypothesis for future developments.

Target indication	Approved products	Optimized clinical Goal	Pharmacodynamic profile
Induction of labor and cervical softening	RU 486	Higher efficacy, faster onset of action	Pure antagonist
Postcoital fertility control	Ulipristal	Efficacy comparable or superior to classical OCs	Pure PR-antagonist with anti-ovulatory activity
Fibroids/endometriosis	Ulipristal	Resting endometrium. No time restriction for treatment	Strong partial agonistic activity at PR(SPRMs/mesoprogestins)
Breast cancer	None	High PR-mediated specific cytotoxicity	Pure PR-antagonist with high cytotoxicity

Please cite this article in press as: Nickisch K et al. Synthesis and biological evaluation of 11′ imidazolyl antiprogestins and mesoprogestins. Steroids (2014), http://dx.doi.org/10.1016/j.steroids.2014.08.017



Q7 **Fig. 1.**

vacuum and nitrogen and was immersed into a preheated oil bath at 110 °C. The reaction mixture was heated for 60 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (150 mL) and filtered through a Celite pad. The filtrate was transferred to a separatory funnel and was washed with water, brine and dried over anhydrous sodium sulfate. The solvent was removed under vacuum to afford the crude product, which on purification by chromatography on SiO_2 column eluting with 30% acetone in dichloromethane gave 7.6 g (91%) of required product **4** as a pale yellow solid.

^{1}H NMR (δ, $CDCl_3$, 300 MHz): 0.51 (s, 3H), 3.92–4.04 (m, 4H), 4.37–4.39 (m, 2H), 7.19 (s, 1H), 7.27–7.35 (m, 5H), 7.84 (s, 1H).

^{13}C NMR (δ, $CDCl_3$, 75 MHz): 14.4, 22.1, 23.4, 35.1, 35.5, 37.7, 37.9, 38, 39.2, 47.4, 47.4, 50.5, 64.1, 64.7, 69.9, 108.4, 121.3, 128.6, 132.9, 136, 146, 219.5.

*2.2.3. 3,3-Ethylenedioxy-5α,17β-dihydroxy-17-(1,1,2,2,2-pentafluoroethyl)-11β-(4′-(1-imidazolyl) phenyl)-estr-9-ene (**5**)*

Pentafluoroiodoethane (3.9 g, 16 mmol) was condensed into a solution of compound **4** (1.3 g, 2.7 mmol) in toluene (45 mL) kept at −78 °C. A 1.5 M solution of methyl lithium–lithium bromide complex (8.9 mL, 13.5 mmol) was added dropwise over a period of 15 min. The resulting reaction mixture was stirred at −78 °C for 1 h and allowed to stir at 0 °C for another hour. The reaction was quenched by the addition of saturated sodium bicarbonate solution (30 mL). Extracted with ethyl acetate (2 × 50 mL) and the combined organic layer were washed once with water, brine and dried over sodium sulfate. The solvent was removed under vacuum to obtain the crude product, which on purification by chromatography on SiO_2 column eluting with 10% acetone in dichloromethane gave 1.28 g (80%) of required product **5** as a pale yellow solid.

^{1}H NMR (δ, $CDCl_3$, 300 MHz): 0.60 (s, 3H), 3.89–4.04 (m, 4H), 4.37 (s, 2H), 7.18 (s, 1H), 7.27–7.32 (m, 5H), 7.67 (s, 1H).

^{13}C NMR (δ, $CDCl_3$, 75 MHz): 16.73, 23.31, 24.35, 25.45, 33.38, 35.09, 38.30, 39.37, 39.73, 47.42, 50.37, 51.45, 51.51, 53.39, 64.07, 64.70, 77.20, 108.46, 118.44, 121.37, 128.63, 129.19, 132.27, 134.47, 135.14, 135.49, 147.46.

*2.2.4. 11β-(4′-(1-Imidazolyl)phenyl)-17β-hydroxy-17-(1,1,2,2,2-pentafluoroethyl)-estra-4,9-diene-3-one (**EC317**)*

A solution of compound **5** (1 g, 1.68 mmol) in methanol (10 mL) was cooled to 0 °C as 5 N hydrochloric acid (1.6 mL, 8.4 mmol) was added drop wise. The reaction mixture was stirred for 1 h warming to room temperature. Quenched by the careful addition of saturated sodium bicarbonate solution and extracted with ethyl acetate (2 × 25 mL). Combined organic layers were washed with water, brine and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to obtain the crude product, which on purification by chromatography on SiO_2 column eluting with 10% acetone in dichloromethane gave 0.8 g (90%) of required compound **EC317** as an off white solid.

^{1}H NMR (δ, $CDCl_3$, 300 MHz): 0.68 (s, 3H), 4.48 (d, J = 6.6 Hz, 1H), 5.79 (s, 1H), 7.18 (s, 1H), 7.23–7.30 (m, 5H), 7.62 (s, 1H).

^{13}C NMR (δ, $CDCl_3$, 75 MHz): 16.84, 25.13, 25.75, 27.78, 31.11, 33.06, 36.57, 39.33 (d, J = 7.9 Hz), 39.58, 40.59, 50.44, 51.57 (d, J = 3.6 Hz), 83.94 (t, J = 23 Hz), 118.41, 121.68, 123.31, 128.39, 129.67, 130.15, 134.77, 135.17, 143.64, 145.18, 155.99, 199.17.

*2.2.5. 3,3-Ethylenedioxy-5α,17β-dihydroxy-17-(3,3,3-trifluoro-1-propynyl)-11β-{4′-[1′ imidazolyl) phenyl}-estr-9-ene (**6**)*

Freshly prepared lithium diisopropylamide solution made by the addition of *n*-BuLi (6.4 mL, 2.5 M, 16 mmol) to diisopropylamine (1.6 g, 16 mmol) in THF (20 mL) at −78 °C was added to a solution of 2-bromo-3,3,3-trifluoropropene (2.4 g, 14 mmol) in THF (15 mL) at −78 °C. The resulting purple solution was stirred at this temperature for 20 min. A solution of compound **4** (1.09 g, 2.3 mmol) in THF (10 mL) was introduced into the reaction mixture over a period of 20 min and was stirred for 1 h at −78 °C and allowed to warm to r.t. over a period of 16 h. Reaction mixture was quenched with aqueous ammonium chloride (50 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layer was washed further with water and brine, dried over anhydrous sodium sulfate and evaporated in vacuo to afford the crude product. Purification was performed on a silica gel column using 10% acetone in methylene chloride to afford compound **6** (1.55 g, 88%) as a brown amorphous solid.

^{1}H NMR (δ, $CDCl_3$, 300 MHz): 0.52 (s, 3H), 3.75–4.10 (m, 4H), 4.35–4.50 (m, 2H), 7.16 (s, 1H), 7.27–7.36 (m, 5H), 7.84 (s, 1H).

*2.2.6. 11β-(4′-(1-Imidazolyl)phenyl)-17β-hydroxy-17-(3,3,3-trifluoro-1-propynyl)-estra-4,9-diene-3-one (**EC335**)*

To a solution of compound **6** (800 mg, 1.4 mmol) in methanol (10 mL) at 0 °C was added 50% sulfuric acid (0.5 mL). After stirring for 90 min, the reaction mixture was carefully quenched by the addition of saturated sodium bicarbonate solution. Extracted with ethyl acetate (2 × 50 mL) and the combined organic layers were washed with water, brine and dried over an. sodium sulfate. The solvent was removed under vacuum to obtain the crude product which was purified on a silica column eluting with 20% acetone in methylene chloride to give compound **EC335** (600 mg, 84%) as a light brown amorphous solid.

^{1}H NMR (δ, $CDCl_3$, 300 MHz): 0.58 (s, 3H), 4.51 (d, J = 6.5 Hz, 1H), 5.82 (s, 1H), 7.20 (s, 1H), 7.27–7.34 (m, 5H), 7.83 (s, 1H).

^{13}C NMR (δ, $CDCl_3$, 75 MHz): 13.76, 23.43, 25.84, 27.31, 30.97, 36.57, 38.31, 39.09, 39.20, 39.82, 47.41, 49.99, 73.72 (d, J = 57 Hz), 90.62 (q, J = 6.6 Hz), 113.63 (d, J = 251 Hz), 118.17, 121.54, 123.52, 128.36, 130.01, 130.38, 135.06, 135.32, 143.46, 144.09, 155.72, 199.11.

*2.2.7. 3,3-Ethylenedioxy-5α,17β-dihydroxy-17-(3,3,3-trifluoroprop-1(E)-enyl)-11β-{4′-[1′ imidazolyl) phenyl}-estr-9-ene (**7**)*

A solution of compound **6** (1.8 g, 3.1 mmol) in anhydrous toluene (30 mL) was cooled to −78 °C as a 65% solution of Red-Al

(2.14 mL, 11 mmol) was added drop wise and the reaction mixture was stirred for 4 h at −78 °C. Reaction was quenched by the addition of saturated ammonium chloride. The separated organic layer was washed with water, brine and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to afford the crude product, which on purification by chromatography on silica column eluting with 20% acetone in methylene chloride gave compound **7** (1.5 g, 85%) as a brown foam.

^{1}H NMR (δ, $CDCl_3$, 300 MHz): 0.57 (s, 3H), 3.92–4.03 (m, 4H), 4.30 (d, J = 6.2 Hz, 1H), 4.42 (s, 1H), 5.90–5.98 (m, 1H), 6.52 (dd, J_1 = 15.4 Hz, J_2 = 1.8 Hz 1H) 7.16–7.34 (m, 6H), 7.83 (s, 1H).

2.2.8. 11β-(4′-(1-imidazolyl)phenyl)-17β-hydroxy-17-(3,3,3-trifluoroprop-1(E)-enyl)-estra-4,9-diene-3-one (*EC339*)

A solution of compound **7** (1 g, 1.5 mmol) in methanol (15 mL) was cooled to 0 °C as 5 N hydrochloric acid (1.2 mL, 6.22 mmol) was added drop wise. The reaction mixture was stirred for an hour warming to room temperature. Quenched by the careful addition of saturated sodium bicarbonate solution and extracted with ethyl acetate (2 × 25 mL). Combined organic layers were washed with water, brine and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to obtain the crude product, which on purification by chromatography on SiO_2 column eluting with 10% acetone in dichloromethane gave 1.06 g (67%) of required compound **EC339** as a pale brown solid.

^{1}H NMR (δ, $CDCl_3$, 300 MHz): 0.64 (s, 3H), 4.42 (d, J = 6.8 Hz, 1H), 5.80 (s, 1H), 5.98–6.05 (m, 1H), 6.59 (dd, J_1 = 15.5 Hz, J_2 = 1.8 Hz 1H) 7.17–7.30 (m, 6H), 7.77 (s, 1H).

^{13}C NMR (δ, $CDCl_3$, 75 MHz): 15.40, 23.81, 25.79, 27.49, 30.95, 36.56, 36.90, 38.83, 39.26, 39.89, 47.30, 50.10, 83.12, 116.12 (q, J = 33 Hz), 118.13, 121.43, 123.57 (d, J = 294 Hz), 128.31, 129.99, 130.28, 134.98, 135.27, 143.84, 144.20, 155.75, 199.01.

2.2.9. 11β-(4′-(1-Imidazolyl)phenyl)-17β-hydroxy-17-(1,1-difluoroprop-2-enyl)-estra-4,9-diene-3-one (*EC340*)

To a solution of compound **4** (1.9 g, 4 mmol) in pyridine (15 mL) was added DMAP (98 mg, 0.8 mmol) followed by acetic anhydride (2.86 g, 28 mmol) and the resulting mixture was heated at 60 °C for 30 h. The solvents were removed under vacuum and the crude was quickly passed through a short pad of silica and concentrated to obtain compound **8** (1.82 g, 3.9 mmol), which was dissolved in THF–ether–pentane (4:1:1, 80 mL) mixture and was cooled to −100 °C. 3-Bromo 3,3-difluoro-1-propene (3.12 g, 20 mmol) was added followed by the dropwise addition of *n*-BuLi (8 mL, 2.5 M, 20 mmol). The reaction mixture was allowed to stir for 90 min at −95 °C and allowed to warm to room temperature over 3 h. Quenched with ammonium chloride solution (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layer was concentrated under vacuum and the crude obtained was dissolved in methanol (20 mL) and treated with 5 N hydrochloric acid (1.7 mL) at 0 °C. Reaction was allowed to stir at room temperature for 2 h and was carefully quenched with saturated sodium bicarbonate solution (25 mL). Organic materials were extracted with ethyl acetate (3 × 30 mL) and the combined organic layers were dried over sodium sulfate, concentrated under vacuum. Purification was effected on a silica gel column using 10% acetone in methylene chloride to afford **EC340** (400 mg, 20%) as a pale yellow amorphous solid.

^{1}H NMR (δ, $CDCl_3$, 300 MHz): 0.62 (s, 3H), 4.44–4.46 (m, 1H), 5.56 (5.80 (s, 1H), 5.98–6.05 (m, 1H), 6.59 (dd, J_1 = 15.5 Hz, J_2 = 1.8 Hz 1H) 7.17–7.30 (m, 6H), 7.77 (s, 1H).

^{13}C NMR (δ, $CDCl_3$, 75 MHz): 17.09, 24.60, 25.85, 27.70, 31.11, 33.70, 36.74, 39.38, 40.41, 48.20, 51.03, 60.36, 85.1 (t, J = 27 Hz), 118.15, 120.4, 121.52, 123.35, 128.33, 130.02, 130.32, 135.09, 135.47, 144.19, 144.43, 156, 199.12.

2.2.10. 3,3-Ethylenedioxy-5α-hydroxy-11β-(4′-[iodophenyl)-17,23-epoxy-19,24-dinor-17α-chola-9,20-diene (*11*)

A solution of 1,4-diiodobenzene (5.14 g, 15.6 mmol) in anhydrous THF (50 mL) was cooled to −10 °C as a 2 M solution of isopropyl magnesium chloride (7.8 mL, 15.6 mmol) was added dropwise over a period of 15 min. After stirring for 20 min, cuprous chloride (257 mg, 2.6 mmol) was added as a solid and the reaction mixture was stirred for 30 min. A solution of the epoxide **10** (2 g, 5.2 mmol) in 20 mL of THF was added drop wise and stirred for 2 h slowly warming to 10 °C. Quenched with aqueous ammonium chloride solution (50 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layer was washed further with water and brine, dried over sodium sulfate and evaporated *in vacuo* to afford crude product. The crude product was purified on a silica column eluting with 30% ethyl acetate in hexane to afford 2.81 g (92%) of **11** as an off white solid.

^{1}H NMR (δ, $CDCl_3$, 300 MHz): 0.58 (s, 3H), 3.74 (s, 4H), 3.81–3.94 (m, 4H), 4.13 (d, J = 6.2 Hz, 1H), 4.85 (s, 1H), 5.13 (s, 1H), 5.77 (s, 1H), 6.91 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H).

^{13}C NMR (δ, $CDCl_3$, 75 MHz): 14.99, 23.14, 23.98, 24.08, 31.27, 34.1334.96, 35.01, 38.26, 38.91, 39.35, 39.91, 46.45, 47.38, 48.60, 63.98, 64.63, 69.95, 90.30, 94.70, 107.29, 108.55, 129.38, 133.61, 134.47, 137.11, 137.51, 147.19, 153.77.

2.2.11. 3,3-Ethylenedioxy-5α-hydroxy-11β-(4′-[1-imidazolyl)phenyl)-17,23-epoxy-19,24-dinor-17α-chola-9,20-diene (*12*)

A mixture of compound **11** (2.7 g, 4.6 mmol), imidazole (531 mg, 4.6 mmol), cuprous iodide (87 mg, 0.5 mmol), *N,N*-dimethyl glycine (94 mg, 0.9 mmol) and potassium carbonate (1.3 g, 9.2 mmol) in anhydrous DMSO (5 mL) was degassed three times applying vacuum and nitrogen and was immersed into pre-heated oil bath at 110 °C. The reaction mixture was heated for 60 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (100 mL) and filtered through a Celite pad. The filtrate was transferred to a separatory funnel and was washed with water, brine and dried over anhydrous sodium sulfate. The solvent was removed under vacuum to afford the crude product, which on purification by chromatography on SiO_2 column eluting with 10% acetone in ethyl acetate gave 2.4 g (98%) of required product **12** as a pale yellow amorphous solid.

^{1}H NMR (δ, $CDCl_3$, 300 MHz) 0.54 (s, 3H), 3.74–4.04 (m, 8H), 4.24 (d, J = 6.8 Hz, 1H), 4.83 (s, 1H), 5.10 (s, 1H), 7.19 (s, 1H), 7.27–7.36 (m, 5H), 7.84 (s, 1H).

^{13}C NMR (δ, $CDCl_3$, 75 MHz): 15.13, 23.22, 24.01, 24.11, 34.22, 35.08, 38.30, 38.9639.36, 40.03, 46.49, 47.42, 48.65, 64.04, 64.69, 64.73, 69.97, 94.73, 107.45, 108.54, 121.21, 128.68, 129.35, 133.62, 134.48, 134.72, 153.75.

2.2.12. 11β-(4′-[1-Imidazolyl]phenyl)-17,23-epoxy-19,24-dinor-17α-chola-4,9,20-triene-3-one (*EC336*)

A solution of compound **12** (2.29 g, 4.33 mmol) in methanol (20 mL) was cooled to 0 °C as 5 N hydrochloric acid (1.7 mL, 8.7 mmol) was added drop wise. The reaction mixture was stirred for 3 h warming to room temperature. Quenched by the careful addition of saturated sodium bicarbonate solution (30 mL) and extracted with ethyl acetate (2 × 50 mL). Combined organic layers were washed with water, brine and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to obtain the crude product, which on purification by chromatography on SiO_2 column eluting with 10% acetone in dichloromethane gave 1.63 g (81%) of required compound **EC336** as a white solid.

^{1}H NMR (δ, $CDCl_3$, 300 MHz) 0.60 (s, 3H), 4.35 (d, J = 7 Hz, 1H), 4.86 (s, 1H), 5.15 (s, 1H), 5.78 (s, 1H), 7.19 (s, 1H), 7.22–7.36 (m, 5H), 7.84 (s, 1H).

^{13}C NMR (δ, $CDCl_3$, 75 MHz): 15.19, 23.61, 25.22, 25.66, 32.28, 34.13, 34.87, 36.63, 38.82, 39.70, 40.06, 48.87, 64.71, 94.44,

Please cite this article in press as: Nickisch K et al. Synthesis and biological evaluation of 11′ imidazolyl antiprogestins and mesoprogestins. Steroids (2014), http://dx.doi.org/10.1016/j.steroids.2014.08.017

107.29, 118.04, 121.43, 123.52, 128.28, 129.24, 130.28, 134.53, 135.41,143.31, 144.82,153.62, 157.24, 199.23.

2.3. Biological assays

2.3.1. In vitro studies

Antiprogestational and antiglucocorticoid activity were determined as previously described using select screen assay system (Invitrogen-Life Technologies) [3,17,18]. Briefly, PR-UAS-bla HEK 293T and GR-UAS-bla HEK 293T cells were used for the PR antagonist screen and the GR antagonistic screen, respectively. Cells were activated by R5020 (PR agonist) and dexamethasone (GR agonist) for anti-PR and anti-GR screening. 0.032 mL of cell suspension was added to the wells and pre-incubated at 37 °C/5% CO_2 in a humidified incubator with compounds and control antagonists for 30 min. 4 μL of 10× control agonist R 5020 at the pre-determined EC80 concentration was added to wells containing the control antagonist or compounds. The plate was incubated for 16–24 h at 37 °C/5% CO2 in a humidified incubator. 8 μL of 1 μL substrate solution was added to each well and the plate was incubated for 2 h at room temperature. The plate was read on a fluorescence plate reader.

2.4. In vivo studies

2.4.1. The guinea pig model for the assessment of PR-agonistic and antagonistic properties of PRMs in non-pregnant animals (Luteolysis inhibition test)

Dunkin–Hartley Guinea Pigs (400–500 g body weight) were purchased from Charles River Laboratory. Animals were kept in an automatically climatized (21 °C) and illuminated (12:12 light/dark cycle) facilities. Tap water was available *ad libitum* from sipper tubes; the provided pelleted food fortified with Vitamin C and supplemented with fruits (oranges).

The studies were performed in cycling guinea pigs for the specific assessment of both PR-agonistic and PR-antagonistic activity and the interaction of corresponding properties. The studies were performed in the second half of the guinea pig cycle which is about 16 days long. The treatment was from cycle day 10–17by daily s.c. injection of test compounds in 0.2 mL vehicle (benzylbenzoate/castor oil, ratio 1:4 v/v). Control animals were treated with 0.2 mL vehicle. The time of autopsy (day 18) is 24–48 h after the expected ovulation of the next cycle. This timing permits the study of the effects of the tested compounds on the ovulation and also on the functional state of the old corpora lutea. Fresh corpora lutea confirm a recent ovulation. Persisting large functional old corpora lutea indicate a pure PR-antagonist [6,8] (Fig. 2). Progesterone secretion of these corpora lutea leads to high progesterone values in the circulation. The basis of this is the inhibitory effects on the luteolytic uterine PGF2α-secretion which is progesterone-driven [8,15]. Typically, beyond uterine growth "pure" PR-antagonists also lead a proliferation and cornification of the vaginal epithelium (Table 2/Fig. 3). An advanced stage of shedding of the cornified layers of the vaginal epithelium prevailed in ovulating controls at this stage of cycle (metestrus). On rare occasion controls were found in the process of ovulation on day 18 of the treatment cycle, in this case showing vaginal proliferation and cornification of the vagina (Figs. 3 and 4).

Assessment of unopposed estrogenic effects of pure PR-antagonists: As uterine growth, vaginal proliferation and cornification reflect the unopposed effects of the basal ovarian estrogen secretion of the ovary-intact animals. These indicators of estrogen dominance may occur despite the presence of very high levels of progesterone in the circulation, which is brought about by the maintenance of corpora lutea ("antiluteolytic effect"). Estrogen dominance in the presence of high progesterone shows that the PR-activation is blocked [8,15].

Assessment of PR-agonistic properties: In the vaginal epithelium these lead to various degrees of inhibition of the ER-stimulated proliferation and cornification. Stronger PR-dominance is indicated by a fundamental morphological change, the mucification of the vaginal epithelium. Ovary: Corpora lutea regress in a non-fertile cycle. If degeneration of corpora lutea is seen under an otherwise active PRM, this indicates the presence of PR-agonistic properties as a very sensitive indicator (Fig. 2).

Effects on ovulation: Antiovulatory effects are indicated by the absence of fresh corpora lutea on cycle day 18, these effects may result from both PR-agonistic and PR-antagonistic properties.

2.4.2. Pregnant guinea pig model for the assessment of PR antagonistic properties

Experiments were done as described earlier [6,8,19]. Female guinea pigs weighing around 500 g were tested for their cycle stage by checking the vaginal opening every day. Female animals were co-caged with a fertile male on day 15 after the vaginal opening. Day 16 of this cycle was counted as first day of pregnancy if mating occurred and later on a pregnancy was confirmed by palpation of

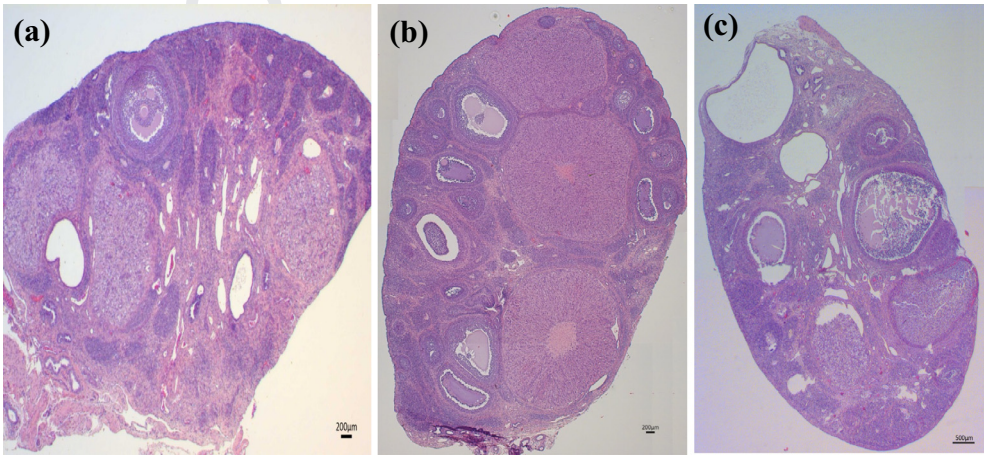


Fig. 2. Ovarian histology on day 18 of treatment cycle, (a) 10.0 mg EC339/day s.c.: 3 degenerated corpora lutea (CL), no formation of new ones, (b) 10.0 mg EC317/day s.c.: 3 large functional old CL, no formation of new ones, (c) vehicle control: one degenerated old CL, fresh bulging CL and bursting follicle with ocyte (right).

Please cite this article in press as: Nickisch K et al. Synthesis and biological evaluation of 11′ imidazolyl antiprogestins and mesoprogestins. Steroids (2014), http://dx.doi.org/10.1016/j.steroids.2014.08.017

Table 2
Summary of molecular properties of new PRM as orientating study concerning the ratio of PR-agonistic and antagonistic and antiovulatory properties in cycling guinea pigs (treatment from day 10–17 of the cycle, sacrifice day 18, s.c. injection of dose in 0.2 mL vehicle).

Code	PR-ant. **	GR-ant. **	Ovulation inhibition	Uterine weight	ER-/PR balance vagina	Ovary (CL)	Classification
				At max. dose (10 mg/day s.c.)			
RU 486	100	100	⩾3.0 mg	1.26	ER-domin (⩾1.0 mg)	deg. and funct. CL	PR-antagonist
CDB 4124	186	n.t.	⩽10.0	1.41	ER-domin	deg. and funct. CL	PR-antagonist
CDB 2914	349	n.t.	⩾10.0 mg	1.01	ER-domin	deg. CL	Blunted PR-antagonist
EC317	267	9	⩾0.1 mg	2.28	ER-domin (⩾0.1 mg)	Large funct. CL (!)	Pure PR-antagonist
EC312	244	27	⩾0.1 mg	1.03	PR-domin ⩾0.1 mg	deg. CL	Mesoprogestin
EC313	79	6	⩾0.1 mg	1.13	PR-domin (⩾0.1 mg)	deg. CL	Mesoprogestin
EC335	34	83	n.t.	n.t.	n.t.	n.t.	n.t.
EC336	163	5	10.0 mg inhibitory	0.90	PR-domin	deg. CL	Mesoprogestin
EC339	54	31	⩽10.0 mg	0.82	PR-domin	deg. CL	Mesoprogestin
EC340	90	13	n.t.	n.t.	n.t.	n.t.	n.t.
Controls			10/11 ovulation	1.05	Metestrus (9/11) estrus (2/11)	Fresh CL	n.a.

Abbreviations: CL, corpora lutea; deg., degenerating; n.t., not tested; n.a., not applicable.
Signs of ER-dominance: High uterine weight, vaginal epithelium proliferation of basal layers and cornification of upper layers; Signs of PR-dominance: absence of ER-dominance, mucification of vaginal epithelium.

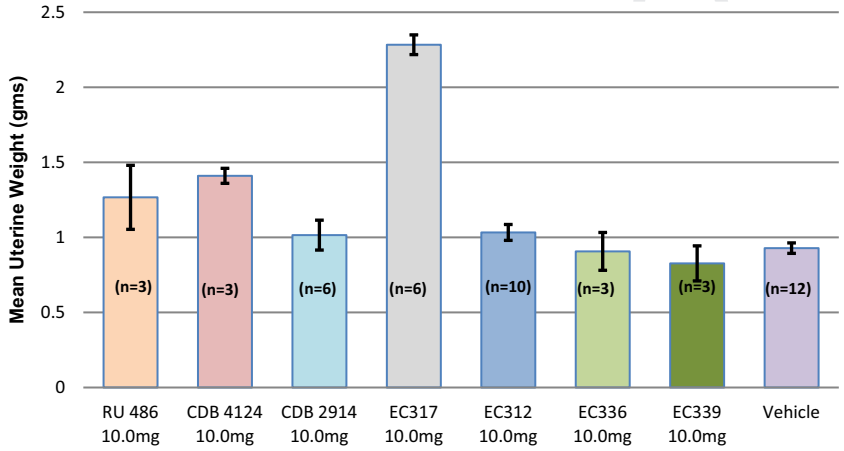


Fig. 3. Uterine weights on day 18 of treatment cycle. The effects of EC317 are statistically significant stronger vs controls and all shown compounds. Effects of RU 486 and CDB 4124 are statistically significant vs controls. Abbreviations: () = n animals/dose.

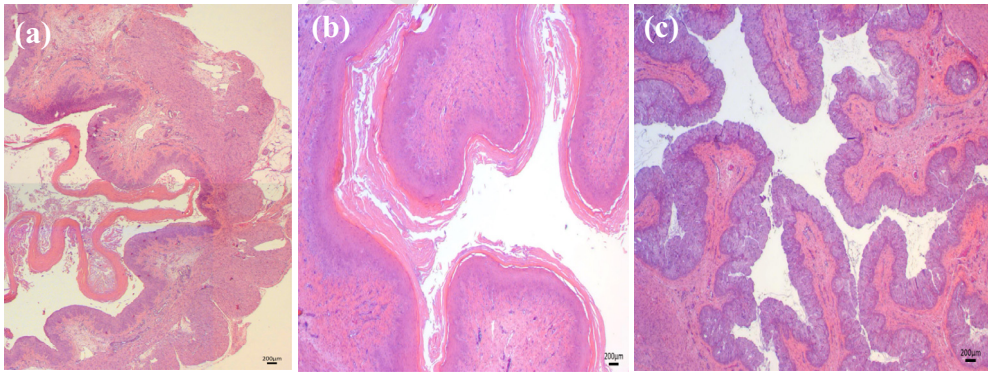


Fig. 4. Vaginal mucosa on day 18 of treatment cycle: (a) vehicle treated control. Proliferation of squamous epithelium, cornification of upper layers (in desquamation, animal at ovulation); (b) EC317 10.0 mg/day s.c. unopposed ER-dominance: proliferation and cornification of epithelium, (c) EC339 PR-dominance: non-proliferating and mucified epithelium.

the abdomen. The pregnant animals were allocated to the different treatment groups by randomization and were treated on day 43 and 44 of the pregnancy. The test substances were dissolved in vehicle (benzyl benzoate/castor oil (1:4 v/v)) and subcutaneously injected (0.2 mL). Animals were checked for vaginal bleeding and the expulsion of fetuses and placentae until day 50 of pregnancy. The animals were sacrificed at this time point. Both uterine horns were inspected with respect to the presence of fetuses, placentae, and former nidation sites.

2.5. Statistical evaluation

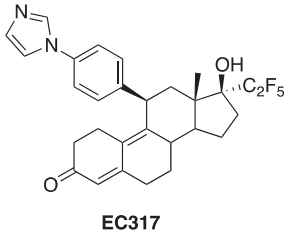
As described in [3], Uterine weights: *t*-test analysis (unpaired, 2 value, 2 tail, unequal variances).

Please cite this article in press as: Nickisch K et al. Synthesis and biological evaluation of 11′ imidazolyl antiprogestins and mesoprogestins. Steroids (2014), http://dx.doi.org/10.1016/j.steroids.2014.08.017

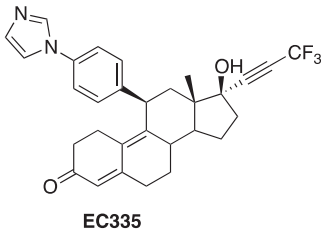
3. Results and discussion

3.1. Chemistry

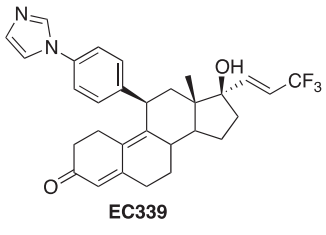
The following compounds have been synthesized:



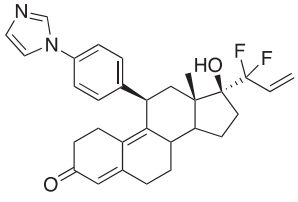
EC317



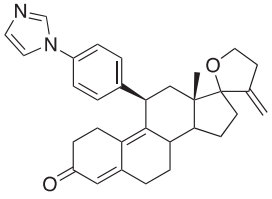
EC335



EC339



EC340



EC336

Q6 **EC317** was prepared by following the scheme outlined below (Scheme 1).

Intermediate **2** was synthesized following a literature procedure [20]. Addition of the aryl cuprate reagent generated by the reaction of 1,4-diiodo benzene, isopropyl magnesium chloride and catalytic amounts of cuprous chloride on intermediate **2** afforded compound **3**. The aryl iodo derivative **3** obtained was coupled with imidazole following Ullman reaction conditions employing cuprous iodide as the copper catalyst and *N*,*N*-dimethyl glycine as the ligand to give compound **4**. Pentafluorolithium addition on the 17-keto group of compound **4** followed by hydrolysis afforded **EC317**.

EC335 and **EC339** were synthesized according to the Scheme 2.

3,3,3-Trifluoropropynyl lithium, generated by treating 2-bromo-3,3,3-trifluoropropene with LDA at −78 °C was added to the 17-ketone of intermediate **4** to form compound **6** which on acid hydrolysis afforded the compound **EC335**. Red-Al reduction of intermediate **6** gave compound **7**, which on hydrolysis using 4 N hydrochloric acid furnished **EC339**.

EC340 was prepared following the Scheme 3.

Intermediate **4** was dehydrated at 5 position using excess acetic anhydride and pyridine to afford intermediate **8**. Due to its instability, crude 8 was used as such for the 17-difluoroallyl-lithium addition at −100 °C to generate compound **9**, which was quickly hydrolyzed under acidic conditions to afford **EC340**.

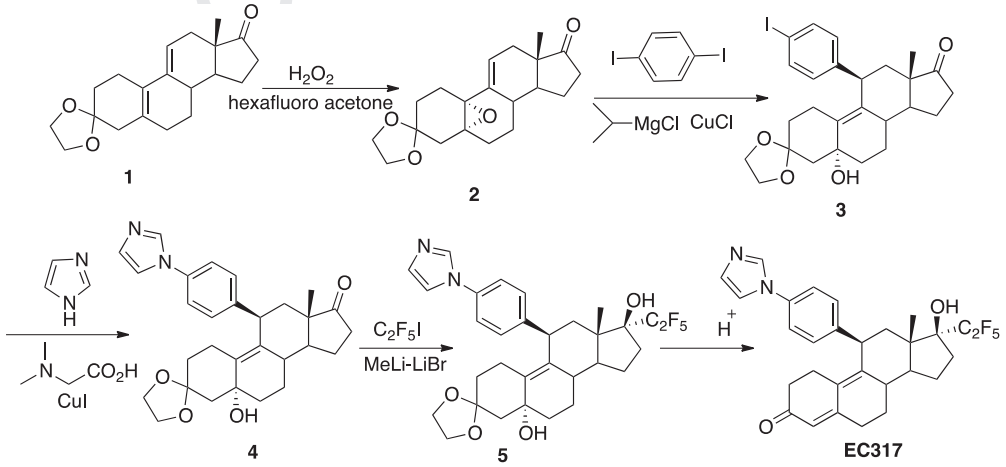
Synthesis of **EC336** was accomplished following the procedure outlined in Scheme 4.

Intermediate **10** was prepared following the procedure reported by [21]. An aryl cuprate addition on epoxide **10** using 1,4-diiodo benzene, isopropyl magnesium chloride and cuprous chloride afforded compound **11**. Ullman coupling of intermediate **11** with imidazole using cuprous iodide as the catalyst, *N*,*N*-dimethyl glycine as the ligand and potassium carbonate as the base furnished intermediate **12** which on acid hydrolysis afforded **EC336**.

3.2. Biological results

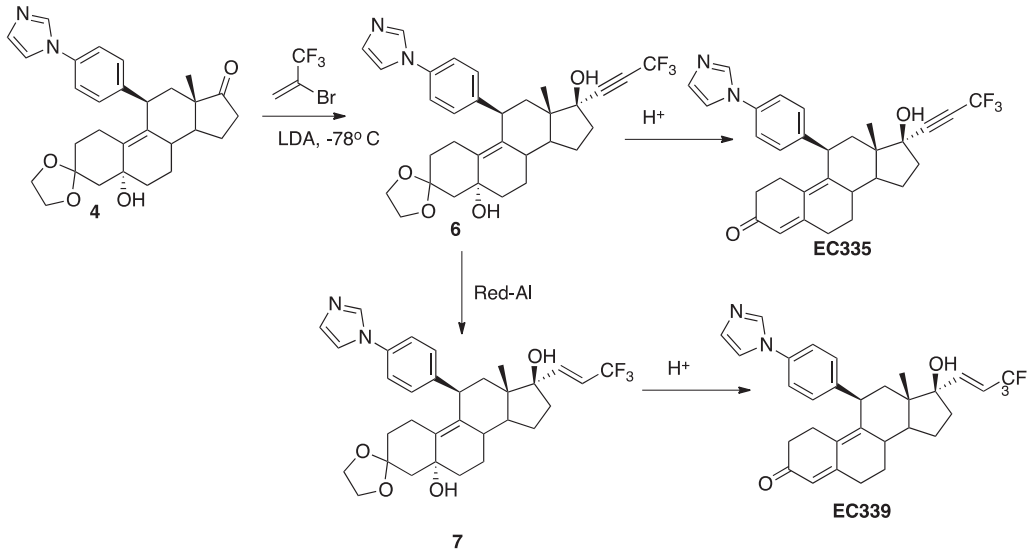
3.2.1. In vitro studies: antiglucocorticoid and antiprogestational activity

For the determination of the dissociation between antiglucocorticoid and antiprogestational activity transactivation studies were performed. RU 486 served as standard substance for antiglucocor-

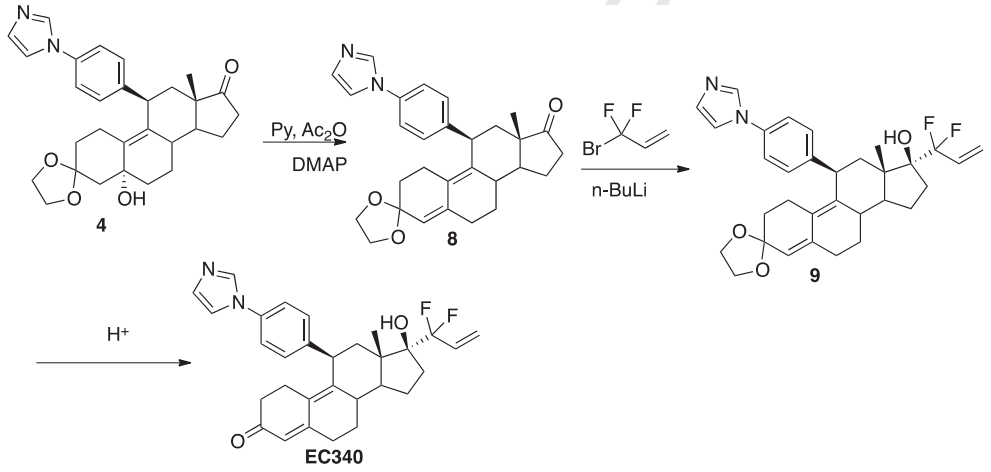


Scheme 1.

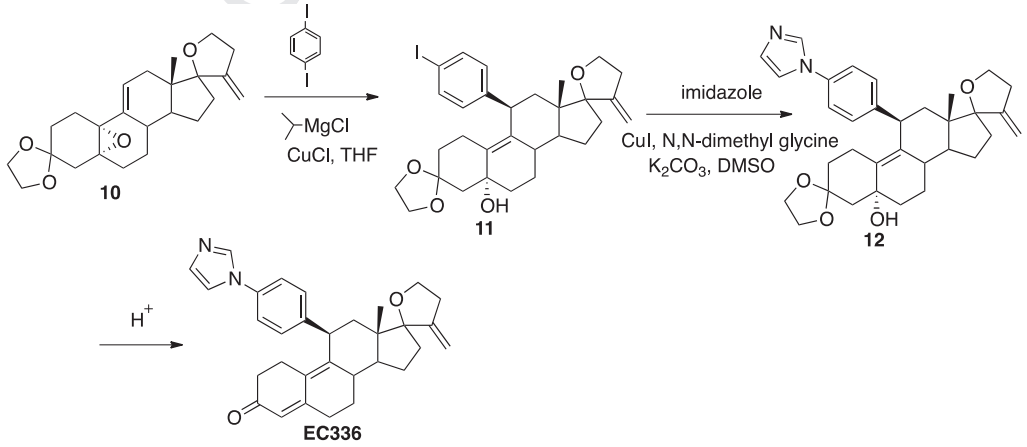
Please cite this article in press as: Nickisch K et al. Synthesis and biological evaluation of 11′ imidazolyl antiprogestins and mesoprogestins. Steroids (2014), http://dx.doi.org/10.1016/j.steroids.2014.08.017



Scheme 2.



Scheme 3.



Scheme 4.

Please cite this article in press as: Nickisch K et al. Synthesis and biological evaluation of 11′ imidazolyl antiprogestins and mesoprogestins. Steroids (2014), http://dx.doi.org/10.1016/j.steroids.2014.08.017

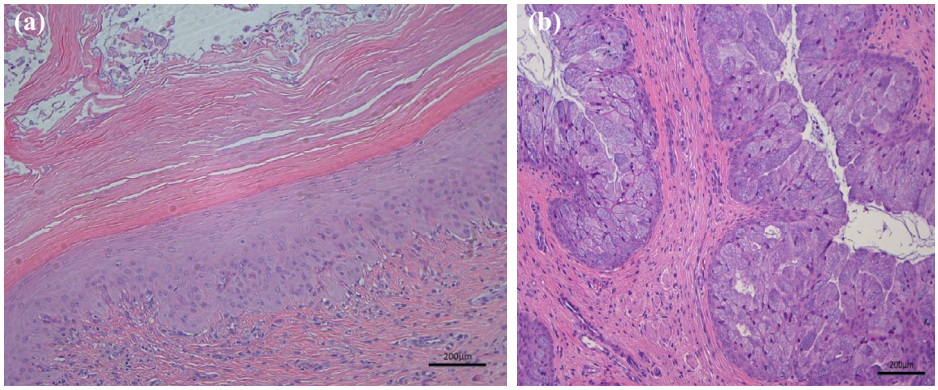


Fig. 5. Effect of pure vs PR-agonistic PRMs on the vaginal epithelium of guinea pigs on day 18 of the treatment cycle-, (a) EC317, 10.0 mg/day s.c., proliferation of squamous epithelium and cornification of upper layers, (b) **EC339**, 10.0 mg/day s.c., no basal proliferation, mucification of upper cell layer.

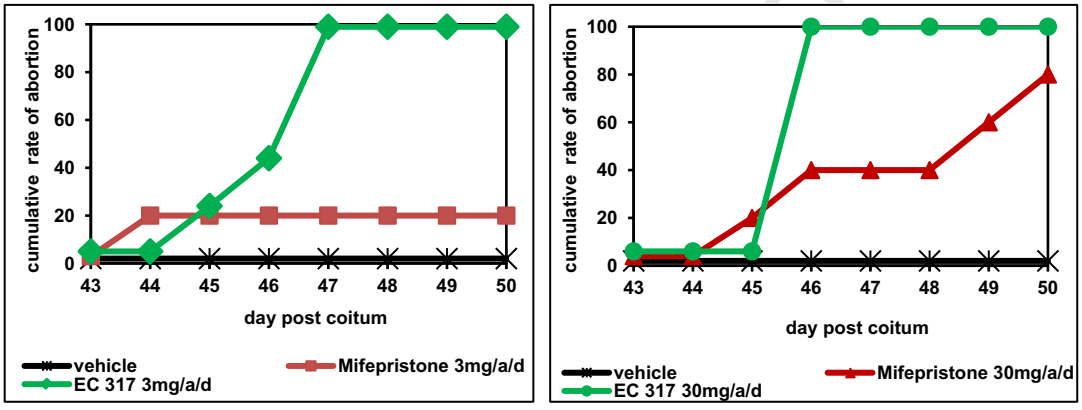


Fig. 6. Termination of pregnancy by induction of labor. Treatment of guinea pigs on day 43–44 of pregnancy by s.c. injection of dose in 0.2 mL vehicle (benzylbenzoate + castor oil 1+4 v/v), controls are vehicle treated. Observation of expulsion of fetuses and placentae until day 50 (autopsy), $N = 5$/dose).

ticoid and antiprogestational activity. Inhibitory activities were estimated (% of standard compound) (Table 2).

Clearly, compounds **EC317** and **EC336** stick out not only because of a superior inhibition of the progesterone receptor but also because of the rather low antiglucocorticoid activity indicating a more than 10-fold dissociation between PR-mediated and GR mediated activity *in vitro*.

3.2.2. In vivo characterization

3.2.2.1. PRM-Classification and antiovulatory effects. The plateau of a dose response curve in case of mixed agonists-/antagonists is lower compared to an agonist at the respective receptor. This difference reflects the dynamic balance of opposing agonistic and antagonistic properties. By the use of a single very high ("plateau") screening dose (10.0 mg/animal s.c.) in cycling guinea pigs this interference was tested and used for a first classification of compounds. Lower doses were only tested for the more interesting compounds, and also in order to determine the threshold of antiovulatory activity (see Table 2).

The evaluation of this high dose of the test compounds led in all cases to distinct and compound-specific results, reflecting the dynamic balance of PR-agonistic and PR-antagonistic properties. Both, compounds classified as pure PR-antagonist (see EC317) and PR-agonistic PRMs (mesoprogestins, e.g. EC312, EC313) [3] may exert very potent antiovulatory effects. As a rule, the compound-specific effects on genital tract and on ovulation are lost in the same range of the tested lower doses. All compounds described were assessed with different dose dependent concentrations of 0.1, 3.0 and 10 mg/animal.

Uterine weight: EC317 elevated the uterine weight more than two-fold whereas EC336, EC339, EC312, EC313, and CDB 2914 had no or minor effects on uterine weight (Table 2 and Fig. 3). The weight increase under RU 486 and CDB 4124 was statistically significant versus controls (Fig. 3).

3.2.2.2. Histology of ovaries/corpora lutea, and vaginal epithelium. Out of the 11 vehicle-treated control animals, 10 had fresh corpora lutea in their ovaries on day 18. This confirms reliable control of the cycle in the laboratory. According to the postovulatory stage on day 18, most controls showed a completed shedding of the cornified layers of the vaginal epithelium (metestrus) at this time point. Only two control animals showed a natural estrus (see Figs. 3 and 4). Ovulation: All tested compounds led to the absence of fresh corpora lutea in the ovaries at 10.0 mg/day which indicates the inhibition of ovulation at this dose. Some compounds inhibited the ovulation also at much lower doses (Table 2).

Old CL showed a substance-specific histological appearance. Large functional CL were seen at 10.0 mg/day EC317 and a wider range of lower doses (data of latter not shown). Some persisting CL were also seen after 10.0 mg/day in case of RU 486 and CDB 4124 (Fig. 2, Table 2). The other PRMs including all mesoprogestins did not interfere with the degeneration of the corpora lutea.

Under the different compounds, different states of the vaginal mucosa from ER- to PR-dominance, were seen. Pure PR-antagonists showed strong proliferation of the basal squamous cell layer and a thick cornified upper layer without any signs of mucification were seen after treatment with EC317 (Figs. 4 and 5).

Please cite this article in press as: Nickisch K et al. Synthesis and biological evaluation of 11′ imidazolyl antiprogestins and mesoprogestins. Steroids (2014), http://dx.doi.org/10.1016/j.steroids.2014.08.017

RU 486 induces strong proliferation and cornification of the vaginal epithelium; however, the mucification of the upper layers of the vaginal epithelium indicates a disturbance of the cornification process by PR-agonistic activity. RU 486 may thus not be classified as "pure" antagonist in this animal model.

Diminished ER-dominance: Compared to EC317 CDB 2914 led to a reduced and/or atypical cornification of the vaginal epithelium. After treatment with EC336 and EC339 there was no cornification of the upper layers of the epithelium. Mucification of the epithelium indicates that these compounds are mesoprogestins (Fig. 5). This also applies to EC312 and EC313.

4. Clinical significance

EC317 shows all attributes of a complete progesterone receptor antagonist lacking partial agonistic activity. Such a pharmacological profile might offer advantages in indications like postcoital fertility control [2] and induction of labor [22]. Ulipristal has been approved for the indication of postcoital fertility control. It is currently believed that Ulipristal's activity in this indication is based on the inhibition of ovulation [23]. The antiovulatory potency of EC317 and Ulipristal was therefore assessed in the guinea pig model (Table 2). EC317 clearly shows superior antiovulatory activity being 3–10 times as potent as Ulipristal. It is superior PR-antagonistic properties may further contribute to the efficacy of postcoital treatment.

RU 486 has been approved for the induction of abortion up to pregnancy of week 20. Data concerning human pregnancy are available for this compound when given alone and in combination with prostaglandins. A major issue of both approaches is a certain rate of failures to terminate the pregnancy. Incomplete abortions and strong bleedings were particularly seen after the use of RU 486 without a prostaglandin [1,2,24].

The inferior efficacy of RU 486 concerning the induction of labor may partly be explained by a counter-productive PR-agonistic action in the myometrium. Therefore, studies with RU 486 and EC317 were performed with respect to their ability to induce labor. This might be the key mechanism of PRMs action in the termination of pregnancy in the human and the guinea pig. If this assumption is correct compounds lacking partial PR-agonistic activity should exhibit a higher labor inducing activity than RU 486 or Ulipristal. Data of the performed comparative studies at different dose levels support this view. Fig. 6 shows that EC317 indeed induces labor much faster and in a higher rate of animals than RU 486.

5. Conclusions

Synthesis and biological characterization of new 11 imidazolylphenyl PRMs revealed two interesting findings. The degree of partial agonistic activity of PRMs can be influenced to a wide degree by the 17 moiety. Only the pentafluoroethyl moiety leads to full antagonists whereas all other 17 substituents lead to partial agonistic molecules. This unexpected observation offers new insight into the conformational changes of the receptor substrate complex. More detailed modeling studies will be described elsewhere.

Pure PR-antagonists: EC317 was found to be a potent progesterone receptor antagonist lacking detectable PR-agonistic activity. With respect to induction of labor EC317 was far superior to RU 486.

With respect to emergency contraception EC317 may be superior to CDB 2914 (Ulipristal) in both antiovulatory activity and potential desynchronizing effects in the genital tract.

Mesoprogestins: The discovered mesoprogestins, in particular EC339, EC312, and EC313, represent an alternative approach to improve Ulipristal in the opposite direction by superior antiproliferative and antiovulatory effects but lacking labor inducing properties. These mesoprogestins may open new avenue for therapies for chronic gynecologic disorders such as endometriosis and fibroid disease [3].The avoidance of unopposed estrogenic effects in the human endometrium is the key safety issue of this kind of chronic treatment. The lack of labor inducing properties (data not shown) will be important with respect to the careful elimination of a misuse potential. The absence of abortifacient properties may also open new options for the treatment of infertility which is an apparent issue in case of endometriosis.

Acknowledgements

We thank Dr. Katarina Jewgenow (IZW) for valuable advice and help performing the morphological evaluation, Mario Moreno for performing the animal studies and Monika Blankenburg for skillful help during the preparation of the manuscript. Dr. Harald Schubert and Dr. Sabine Bischoff from the Institute of Animal Science and Animal Welfare, Friedrich-Schiller-University Jena, were helpful supporting the animal studies in the ethical committee and providing the facilities for their performance, which is gratefully acknowledged.

References

[1] Spitz IM. Test article sample title placed here. Curr Opin Obstet Gynecol 2009;21:318–24.
[2] Chabbert-Buffet N, Pintiaux A, Bouchard P. The imminent dawn of SPRMS in obstetrics and gynecology. Mol Cell Endocrinol 2012;358:232–43.
[3] Nickisch K, Elger W, Cessac J, Kesavaran N, Das B, Garfield R, Shao-Qing Shi, Amelkina O, Meister R. Synthesis and biological evaluation of partially fluorinated antiprogestins and mesoprogestins. Steroids 2013;78:255–67.
[4] Teutsch G, Philibert D. History and perspectives of antiprogestins from the chemist's point of view. Hum Reprod 1994;9(Suppl. 1):12–31.
[5] Chwalisz K, Perez MC, Demanno D, Winkel C, Schubert G, Elger W. Selective progesterone receptor modulator development and use in the treatment of leiomyomata and endometriosis. Endocr Rev 2005;26:423–38.
[6] Elger W, Bartley J, Schneider B, Kaufmann G, Schubert G, Chwalisz K. Endocrine pharmacological characterization of progesterone antagonists and progesterone receptor modulators with respect to PR-agonistic and antagonistic activity. Steroids 2000;65:713–23.
[7] Schubert G, Elger W, Kaufmann G, Schneider B, Reddersen G, Chwalisz K. Discovery chemistry and reproductive pharmacology of Asoprisnil and related 11-benzaldoxime substituted selective progesterone receptor modulators (SPRMs). Semin Reprod Med 2005;23:58–73.
[8] Elger W, Neef G, Beier S, Fähnrich M, Gründel M, Heermann J, Malmendier A, Laurent D, Puri CP, Singh MM, Hasan SH, Becker H. Evaluation of antifertility activities of antigestagens in animal models. In: Van Look PFA, editor. Puri CP. Current Concepts in Fertility Regulation and Reproduction. New Delhi: Wiley Eastern limited, New Age international limited; 1992. p. 303–28.
[9] Chwalisz K, Elger W, McCrary K, Beckman P, Larsen L. Reversible suppression of menstruation in normal women irrespective of the effect on ovulation with the novel selective progesterone receptor modulator (SPRM) J867. J Soc Gynecol Invest 2002;9(Suppl. 1) (abstract 49).
[10] Schoonen WGEJ, Vermeulen GJ, Deckers GH, Verbost PM, Kloosterboer HJ. Antiprogestins: Their mechanism of action and the consequences for compound selection by in vitro and in vivo studies. Curr Top Steroid Res 1999;2:15–54.
[11] Neef G, Bayer S, Elger W, Henderson D, Wiechert R. New steroids with antiprogestional and antiglucocorticoid activities. Steroids 1984;44:349–72.
[12] Kloosterboer HJ, Deckers GH, Schoonen WGEJ, Hanssen RGJM, Rose UM, Verbost PM, et al. Preclinical experience with two selective progesterone receptor modulators on breast and endometrium. Steroids 2000;65:733–40.
[13] Cleve A, Klar U, Schwede W. Beneficial effects of fluorine in the anti-progestin ZK 230211. J Fluorine Chem 2005;126:217–20.
[14] Klein-Hitpass L, Cato AC, Henderson D, Ryffel GU. Two types of antiprogestins identified by their differential action in transcriptionally active extracts from T47D cells. Nucleic Acids Res 1991;19:1227–34.
[15] Elger W, Fähnrich M, Beier S, Qing SS, Chwalisz K. Endometrial and myometrial effects of progesterone antagonists in pregnant guinea pigs. Am J Obstet Gynecol 1987;157:1065–74.
[16] Rewinkel J, Enthoven M, Golstein I, van der Rijst M, Scholten A, van Tilborg M, de Weys D, Wisse J, Hamersma H. 11-(Pyridinylphenyl) steroids – A new class of mixed-profile progesterone agonists/antagonists. Bioorg Med Chem 2008;16:2753–63.
[17] Lieberman BA, Bona BJ, Edwards DP, Nordeen SK. The constitution of a progesterone response element. Mol Endocrinol 1993;7:515–27.

Please cite this article in press as: Nickisch K et al. Synthesis and biological evaluation of 11′ imidazolyl antiprogestins and mesoprogestins. Steroids (2014), http://dx.doi.org/10.1016/j.steroids.2014.08.017

[18] Boonyaratanakornkit V, McGowan E, Sherman L, Mancini MA, Cheskis BJ, Edwards DP. The role of extranuclear signaling actions of progesterone receptor in mediating progesterone regulation of gene expression and the cell cycle. Mol Endocrinol 2007;21:359–75.
[19] Elger W, Beier S, Fähnrich M, Hassan SH, Henderson D, Neef G, Rohde R. Studies on the mechanism of action of progesterone antagonists. J Steroid Biochem 1986;25:835–45.
[20] Rao PN, Wang Z, Cessac JW, Rosenberg RS, Jenkins DJA, Diamandis EP. New 11β-aryl-substituted steroids exhibit both progestational and antiprogestational activity. Steroids 1998;63:523–30.
[21] Jiang W, Allan G, Fiordeliso JJ, Linton O, Tannenbaum P, Xu J, Zhu P, Gunnet J, Demarest K, Lundeen S, Sui Z. New progesterone receptor antagonists: phosphorus-containing 11β-aryl-substituted steroids. Bioorg Med Chem 2006;14:6726–32.
[22] Chwalisz K. The use of progesterone antagonists for cervical ripening and as an adjunct to labour and delivery. Hum Reprod 1994;9(Suppl. 1): 131–61.
[23] Nallasamy S, Kim J, Sitruk-Ware R, Bagchi M, Bagchi I. Ulipristal blocks ovulation by inhibiting progesterone receptor-dependent pathways intrinsic to the ovary. Reprod Sci 2013;20(4):371–81.
[24] Kovacs L, Sas M, Resch BA, Ugocsai G, Swahn ML, Bygdeman M, Rowe PJ. Termination of very early pregnancy by RU 486-an antiprogestational compound. Contraception 1984;29(5):399–410.

Please cite this article in press as: Nickisch K et al. Synthesis and biological evaluation of 11′ imidazolyl antiprogestins and mesoprogestins. Steroids (2014), http://dx.doi.org/10.1016/j.steroids.2014.08.017