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11-(Pyridinylphenyl)steroids—A new class of mixed-profile progesterone agonists/antagonists

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Abstract—Recently, a new class (often referred to as SPRMs: selective progesterone receptor modulators) of progesterone receptor ligands with mixed agonist/antagonist properties has been described. Such compounds are envisaged, for example, as treatment for endometriosis, uterine fibroids, and leiomyomas. Existing SPRMs include Asoprisnil **1** and Uliprisnil acetate **2**. In our hands, however, these compounds proved to have a predominantly or exclusively antagonistic in vitro profile, which may make this type of compound less attractive, for example, as contraceptives. We therefore aimed at a class of mixed-profile compounds that would show a more evenly balanced agonist/antagonist profile. A novel class of 11β-[4-(heteroaryl)phenyl]-substituted pregnanes was identified that displayed the desired balance. Contrary to known SPRMs, this novel class of MPP (mixed-profile progestagen) was found to have a truly mixed activity, including a sizeable agonist component.

1. Introduction

In recent years, interest has grown in progestagenic compounds that are neither full agonists nor full antagonists towards the progesterone receptor (PR), but show a mixed agonist/antagonist profile.[1] These compounds may be partial agonists/antagonists, or the agonist/antagonist balance may depend on tissue-specific factors that are not yet fully understood.[2] Thus, between full agonists such as R 5020 and Org 2058 on one hand, and full antagonists such as Onapristone on the other hand there should theoretically be a continuum of compounds of varying partial activities, where the agonistic/antagonistic efficacies range from, say, 90% agonistic/10% antagonistic to 10% agonistic/90% antagonistic. Indeed, qualitative indications of such profiles have been discussed, for example, based on the abortifacient activity.[3]

In recent years, compounds have been found for which partial and/or mixed agonist/antagonist progesterone activity has been described. Such compounds are often referred to as selective progesterone receptor modulators (SPRMs).[4,5]

To date, most compounds described as SPRMs are steroids (Fig. 1); notable examples are Asoprisnil **1** (J-867) and related estra-4,9-dienes.[6] SPRM activity has also been claimed for Uliprisnil acetate (CDB-2914) **2**[7] and related compounds,[8] as well as for derivatives of dexamethasone.[9] In addition, non-steroidal SPRMs have also been described.[10–12]

Various potential applications for SPRMs have been mentioned,[13] including treatment of leiomyomas[14] and of endometriosis.[15] Such uses are assumed to be linked to the antagonistic component of the SPRM profile.

We have, however, found that, in our hands, the in vitro agonist/antagonist balance of most of the available

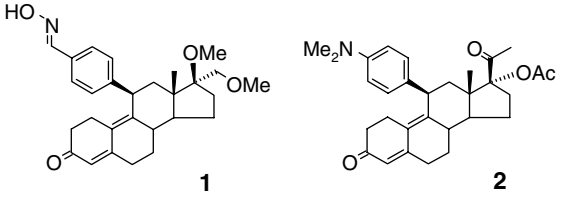

Figure 1. Steroidal SPRMs Asoprisnil (**1**) and Uliprisnil acetate (**2**).

Keywords: SPRM; Progestagens; Antiprogestagens; Progesterone receptor; Mixed profile.
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(steroidal) SPRMs is on the antagonist side; that is, in the PRA and PRB assays the antagonistic effect is very much larger than the agonistic one.[16] Similar findings have been reported in the literature[17]; these are also in line with the observation that Asoprisnil induces an antagonist conformation to PR.[18]

For our ongoing programme, we sought mixed-profile compounds for contraception. As mixed compounds, they should in effect combine in a single chemical entity the activities of a separate progesterone agonist and a progesterone antagonist, a combination which in itself has been demonstrated to be effective in principle. We had, however, reason to believe[19] that a considerable agonistic component should be present in our compounds. In addition, we sought to minimize the abortive potential of the compounds.

Thus, we set out to find truly mixed-profile progestagens (MPPs) where the agonistic and the antagonistic efficacies would be more comparable, that is where the agonistic efficacy, unlike in SPRMs, would be at least 20%, and preferably between 40% and 60%. Also, the agonistic and antagonistic activities should be comparable with respect to both EC_{50}s.

2. Chemistry

In our synthetic strategy we wanted to be able to introduce a variety of heteroaryl groups in the last step. Therefore, the synthetically versatile *p*-bromophenyl group was desired at the 11-position in our final building block **4** (Fig. 2). This bromide gave the opportunity to introduce a variety of pyridinyl groups in the last step via palladium-mediated cross-coupling reactions such as the Suzuki, Stille or Negishi reactions. The general access to (11β)-arylsteroids is the conjugate addition of aryl-Grignard reagent, catalysed by copper(I) ions, to 5α,10α-epoxy-9,11-unsaturated steroids, and this reaction was also applied to introduce the *p*-bromophenyl group at position 11 of the steroids. As a consequence of the chosen strategy the D-ring was modified at the beginning of the synthetic route before the conjugate addition at position 11 was applied.

The building block required for the preparation of the 17-spirocyclopentanone derivatives, 17,24-*cyclo*-19,21-dinorchol-5(10),9(11)-diene-3,20-dione cyclic 1,2-ethanediyl acetal (**6a**), has been described in the literature.[20] However, the 17-cyclopropylcarbonyl dienes **6b–f** were not described and a route to these dienes had to be explored and is depicted in Scheme 1. The readily available[21] estradienedione monoacetal **7** was transformed to enol triflate **8**, which via a palladium(0) catalyzed insertion gave amide **9**. Nucleophilic substitution at the amide by cyclopropyllithium yielded the versatile building block **10**. Using a conjugate addition at the α,β-unsaturated ketone system a variety of substituents could be introduced at position 16. When a copper-mediated conjugate addition of organomagnesium chlorides in the presence of chlorotrimethylsilane was applied,[22] this turned out to stereoselectively give the 16α isomer. When a proton was introduced at position 16 by reaction with lithium tri-*sec*-butylborohydride (L-selectride) as the nucleophile, methyl iodide could be used as the electrophile to yield the 17α-methyl substituent of **6d** stereoselectively.

With the D-ring substitution pattern complete, we turned our attention to the steps leading to introduction of the 11β-aryl. Selective oxidation of diene **6a** gave

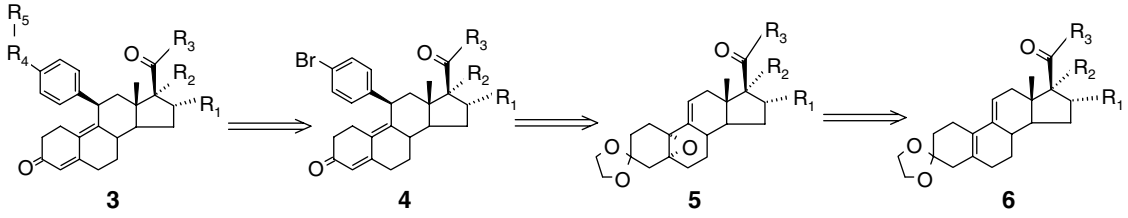
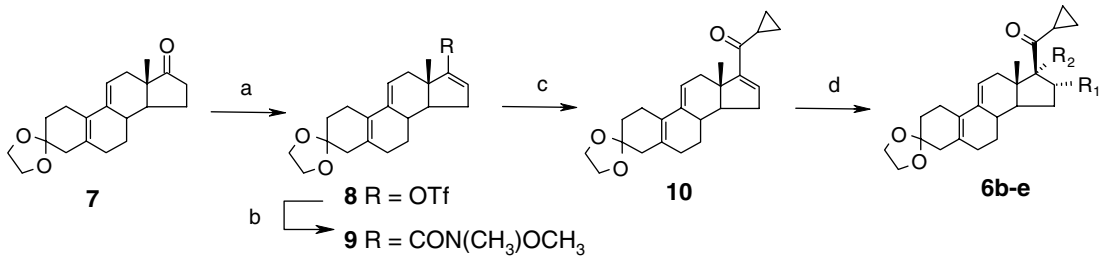
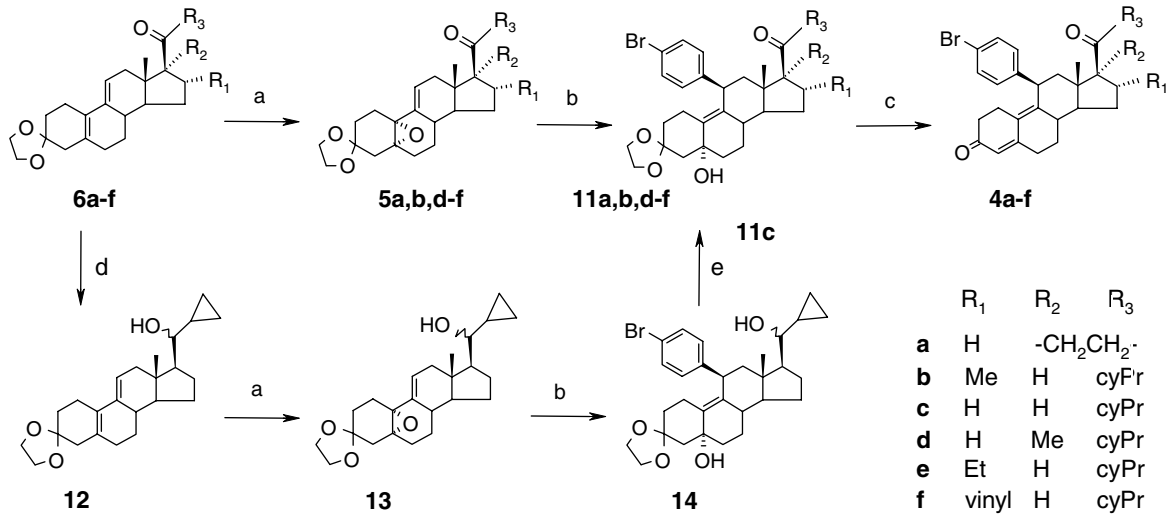


Figure 2. Synthetic strategy.



b R_1 = Me, R_2 = H; **c** R_1 = H, R_2 = H; **d** R_1 = H, R_2 = Me; **e** R_1 = Et, R_2 = H; **f** R_1 = CH=CH_2, R_2 = H

Scheme 1. Reagents and conditions: (a) i—LiHMDS, THF, −15 °C; ii—*N*-phenyl-bis(trifluoromethane-sulfonimide), 0 °C; (b) DMF, Et_3N, PPh_3, MeN(OMe)H·HCl, $Pd(OAc)_2$, CO, 60 °C; (c) c-PrLi, Et_2O, THF, 0 °C; (d) for **6b**, **e**, **f**: R_1MgCl, $Cu(OAc)_2$, Me_3SiCl, THF, 0 °C; for **6c**: K-Selectride, THF, −78 °C; for **6d**; i—L-Selectride, DMPU, THF, −78 °C; ii—MeI; −30 °C.



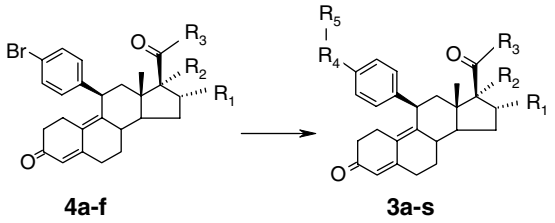
Scheme 2. Reagents and conditions: (a) CH_2Cl_2, pyridine, 30% aq H_2O_2, trifluoracetophenone; (b) *p*-BrPhMgBr, THF, Cu(I)Cl, −40 °C; (c) MeOH, aq H_2SO_4 or acetone, aq HCl; (d) Et_2O, $LiAlH_4$, 0 °C; (e) acetone, 4-methylmorpholine *N*-oxide.

epoxide **5a**, which was treated with *p*-bromophenylmagnesium bromide in the presence of copper(I) chloride to give addition at position 11 without a need to protect the ketone. Subsequent deketalisation and dehydration gave 3-keto-4,9-diene building block **4a**.

The same overall synthetic strategy was chosen to prepare 17-cyclopropylcarbonyl derivatives. The epoxidation and conjugate addition of aryl-Grignard reagent worked satisfyingly for the 17-spirocyclopentanone derivatives (considering the 46% and 65% yields, respectively, without using protection or a synthetic equivalent of the ketone). Nonetheless, with the cyclopropylketones both synthetic routes, that is without protection or using the hydroxyl function as synthetic equivalent of the ketone, were explored in parallel.

Without protection of the ketone, epoxidation of diene **6b** worked well as illustrated by an 81% yield of impure material containing 84% of the desired α-isomer **5b** and 16% of the undesired β-isomer (Scheme 2). In addition, the subsequent step, the copper(I) chloride catalysed conjugate addition of *p*-bromophenylmagnesium bromide to the mixture of epoxides, worked quite well with a 77% isolated yield of compound **11b**. Subsequent deketalisation and dehydration produced 3-keto-4,9-diene **4b** in 66% yield, which could be used as versatile building block in Suzuki reactions to introduce various pyridinyl analogues.

In parallel the second route was explored starting from diene **6c**. First, the ketone was reduced to the hydroxyl group in a quantitative yield; subsequent epoxidation afforded **13** in a moderate yield. The next steps, copper(I) chloride catalysed conjugate addition of *p*-bromophenylmagnesium bromide followed by restoring the ketone by oxidation of the hydroxyl of **14**, produced the desired **11c**, and after deketalisation and dehydration building block **4c** was obtained. The slightly diverse substituents at position 17 make a direct comparison difficult, but considering the 62% yield over the three steps from diene **6b** to compound **11b** compared to the 26% yield over the five steps from diene **6c** to compound **11c** it was clear that the shortest route without protection of the ketone was the preferred one and this route was applied to prepare building blocks **4d**–**f**.



Scheme 3. Reagents and conditions: R_5-R_4-boronic acid, K_2PO_4, Ph_3As, water, dioxane, $(PPh_3)_2PdCl_2$, 100 °C. See Table 1 for the legend for R1–R5.

Building blocks **4** were used in palladium-mediated cross-coupling reactions to obtain a variety of 11-(pyridinylphenyl)steroids (Scheme 3).

3. Results and discussion

For our compound design, we sought to combine in-house expertise with literature data. Unfortunately, much of the latter is conflicting with regard to the (combinations of) features that predispose a compound for a mixed progestagenic profile.

Our design started from the 17-spiromethylene-11β-[4-(3-pyridinyl)phenyl] compound **15**[23] (Fig. 3). This compound had been found (unpublished data) to combine in vitro progesterone agonist and antagonist activity. This result is in line with the observation[1] that the 11β-biphenylyl compound **16** also has a mixed profile (albeit predominantly antagonistic). Compounds with a mixed profile should be orally applicable to be useful in contraception. Since a biphenyl moiety is consider-

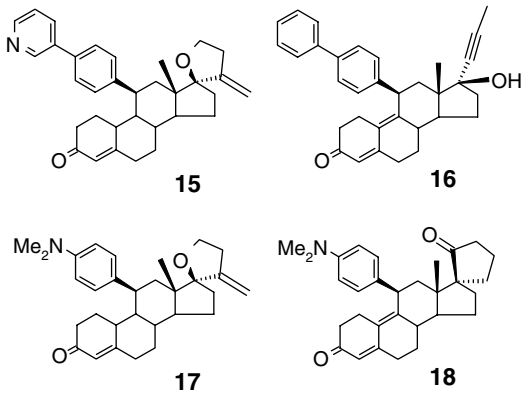


Figure 3. Starting points for the design of biphenyl-type compounds.

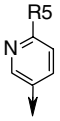
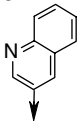
ably more lipophilic than a 4-(3-pyridinyl)phenyl moiety, the latter one is more appealing from a pharmacokinetic point of view. In addition, the basic pyridinyl could give an opportunity for making salts in formulation studies.

To investigate the influence of the pyridinylphenyl moiety, we decided to combine this substituent with a 17-spirocyclopentane moiety; earlier, it had been shown that, for other 11β substituents, no appreciable change in (anti)progestagenic activity was observed between analogues of these two series. Thus, the antiprogestagenic IC_{50} for both **17**[16] and **18**[24] is more or less equivalent at 0.2 nM. As 17-hydroxyestrane analogues with 11β-pyridinylphenyl substituents had previously been reported[25,26] to have only antagonistic activity, we decided to limit our further work to the pregnane series. Our first two target compounds thus became **3a** and **3b**; the latter was included because of indications in the literature that the basicity of nitrogen may influence the agonistic/antagonistic properties.[27] The methoxy substituent was placed in the 6-position, that is coaxially with the pyridinylphenyl moiety, to avoid steric effects of rotamers.

As we had hoped, both our initial target compounds **3a** and **3b** did show a mixed profile (see Table 1), but with the antagonistic component somewhat higher than we had aimed for (antagonistic efficacy:agonistic efficacy ~ 3:1). We then turned our attention from spiro compounds to the open-chain equivalents. Within this series, a number of 21-substituted compounds have been described which to some extent have a mixed (MPP-like) profile.[28] For stability considerations, as well as for easier handling during chemical manipulations elsewhere in the molecule, we preferred to have a carbon substituent in position 21. To avoid the possibility to duplicate known molecules, for which dominantly antiprogestagenic activity could be expected, we decided to introduce the cyclopropane moiety, which had received scant attention before.[29,30]

Both compounds with a tertiary (**3c**, **3d**) and with a quaternary (**3e**) C17-carbon atom were prepared. These three compounds also proved to have a sub-nanomolar

Table 1. Agonistic (EC_{50}) and antagonistic (IC_{50}) activity of substituted 11β-[4-(heteroaryl)phenyl]-19-norpregnanes **3** against PRB

Compound	EC_{50} (nM)	Eff	IC_{50} (nM)	Eff	R1	R2	R3	R4	R5
1	>100	—	0.2	97	—	—	—	—	—
2	>100	—	0.2	100	—	—	—	—	—
3a	0.29	17	0.33	71	H	$-CH_2CH_2-$	a	H	
3b	0.15	20	0.55	62	H	$-CH_2CH_2-$	a	OMe	
3c	0.82	36	0.75	66	H	H	cyPr	a	H
3d	0.51	28	0.43	57	H	H	cyPr	a	OMe
3e	0.49	38	0.13	58	H	Me	cyPr	a	H
3f	0.2	49	0.27	46	Me	H	cyPr	a	H
3g	0.23	34	0.6	53	Et	H	cyPr	a	H
3h	0.66	47	0.61	38	vinyl	H	cyPr	a	H
3i	0.12	42	0.63	59	Me	H	cyPr	a	OMe
3j	1.3	42	7.89	52	Et	H	cyPr	a	OMe
3k	0.74	41	0.98	45	vinyl	H	cyPr	a	OMe
3l	1.1	47	0.47	43	Me	H	cyPr	a	Cl
3m	0.49	51	8.48	50	Me	H	cyPr	a	F
3n	2.6	49	14.8	33	Me	H	cyPr	b	—
3o	4	56	2.5	27	Me	H	cyPr	c	—
3p	0.36	51	3.64	37	Me	H	cyPr	d	—
3q	2.54	52	3.25	>27	Me	H	cyPr	e	—
3r	1.13	54	1.3	35	Me	H	cyPr	f	—
3s	1	50	3.14	24	Me	H	cyPr	g	—
			a	b	c	d	e	f	g
Structure of the R4 substituent									

Values are the average of at least two independent determinations. cyPr = cyclopropyl.

activity for both agonistic and antagonistic activity towards PR; overall, they are slightly more agonistic than **3a** and **3b**, as the antagonistic/agonistic ratio was improved to ca 2:1.

Subsequently, we decided to investigate the influence of a 16α substituent. Previous findings by Cook suggested[31] that such a modification would turn the mixed 16α-unsubstituted compounds into full agonists. Three substituents were introduced: methyl, ethyl and vinyl. As can be observed from the results table, all these compounds **3f–k** have mixed profiles within the desired boundaries, as had the unsubstituted analogues **3c** and **3d**.

In most cases observed, the 6-methoxy-3-pyridinyl analogues have a similar progestagenic component in their mixed profile relative to the unsubstituted analogues. A case has been described before where the basicity of a nitrogen group directly attached to the 4-position of an 11β-phenyl group influences the agonistic or antagonistic activity of the compound; a lower basicity of the nitrogen (as with substitution by fluorine) results in predominantly or exclusively agonistic compounds.[27] However, in our series both the unsubstituted and the methoxy-substituted pyridines (with a lower basicity) clearly have an MPP profile. In addition, the two halopyridines **3l** and **3m** still have a perfectly mixed profile. Thus, in the pyridinylphenyl series basicity does not materially influence the agonistic/antagonistic character.

In the literature, we found contradictory indications for the influence of a 16α substituent on the progesterone agonist/antagonist profile. In the 11β-dimethylaminophenyl series, Cook reported[32] that, for 17α-unsubstituted compounds, introduction of a 16α-ethyl group switched the profile from mixed to agonistic. On the other hand, the same group found[33] that for 17α-acetoxy compounds, a 16α-ethyl group results in a mixed agonist/antagonist profile. Our findings, however, give no evidence of any influence of 16α-substitution in the 11β-pyridinylphenyl series.

Finally, a number of alternative nitrogen heterocycles were investigated. The resulting compounds all display a mixed agonist/antagonist profile. Although there does not appear to be a clear SAR, the most agonistic compounds appear to be those with a clear maximum in the negative electric potential in the region of the meta and para atoms in the distal aryl ring (methoxypyridine **3i**, fluoropyridine **3m** and pyridazine **3p**). The compound which clearly lacks a centre of electronegativity in this region, viz. the pyrimidine **3q**, is also the one with the highest antagonistic activity.

3.1. Docking

The results of the various heterocyclic substituents cannot be readily related to the properties of the progesterone receptor. Unfortunately, we have not been able to date to obtain a crystal structure of one of our compounds in PR. There have been claims[34] that manual docking of the antagonist RU 486 in the agonistic PR

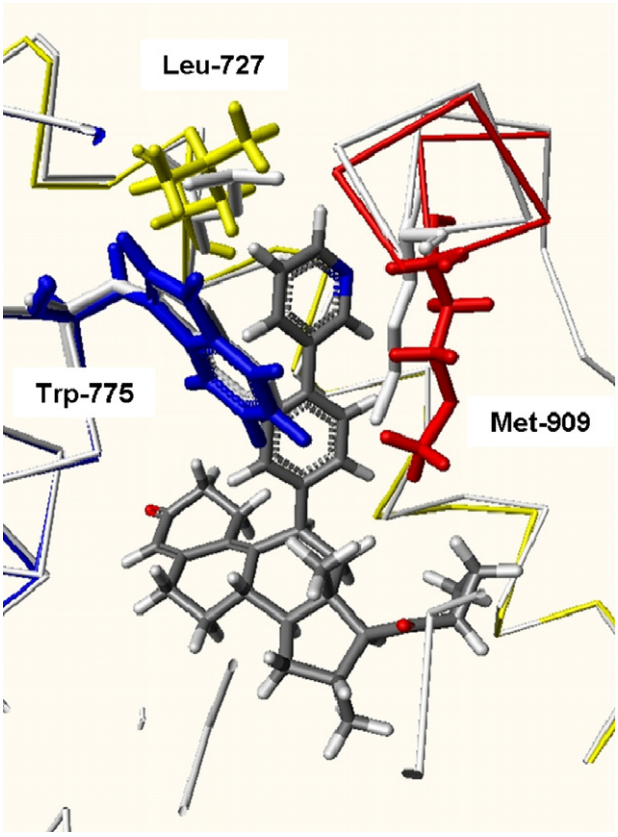


Figure 4. The pyridinylphenyl moiety of compound **3f** can be fitted between helices 3 (yellow), 4/5 (blue) and 12 (red) without requiring apparent dislocation. Superimposed (in white) are the corresponding helices of PR containing progesterone (itself not shown).

produces clashes of the ligand with helix 12. This seems to be confirmed by the recent findings[17] that Asoprisnil indeed causes a shift of the AF2 helix of PR. Our docking experiments, however, suggest that even an 11β-biphenyl-type substituent can be accommodated between helices 3, 4/5 and 12, without causing serious dislocation (see Fig. 4). Of the residues that are in closest contact with the pyridinylphenyl substituent, only Met-909 has been shifted over ca 1.5 Å. In addition, there are indications that, under certain circumstances, RU486 can indeed be accommodated in PR with helix 12 in the agonist position.[35] Taken together, these observations seem to suggest that a receptor structure where the AF2 helix has been shifted to an antagonistic conformation[17] is guided by 'pull' factors from corepressors rather than by 'push' factors caused by steric influence of and/or breaking helix–helix interactions by the ligand.

4. Conclusion

A series of 11β-[4-(heteroaryl)phenyl]pregnanes has been identified with an MPP (mixed progesterone agonist/antagonist) profile. Such compounds are promising candidates for a variety of (gynaecological) indications. However, additional vivo experiments are required to determine what agonist/antagonist balance, which in the series described ranges from 20% agonist/80% antag-

onist to 70% agonist/30% antagonist efficacy, produces the optimal effect.

5. Experimental

5.1. Chemical procedures

5.1.1. General. ^{1}H NMR spectra were recorded on a Bruker spectrometer (400 or 600 MHz) with deuterochloroform as the solvent. Chemical shifts are reported as δ values (parts per million) relative to tetramethylsilane as the internal standard, and coupling constants are expressed in Hertz. Melting points were obtained on a Büchi Melting point B-545 apparatus and are uncorrected. Thin layer chromatography was performed on pre-coated Merck Silica gel 60 F_{254} plates and visualized with UV light and/or with sulfuric acid in ethanol solution or the Usui reagent. Column chromatography was performed on Merck Silica gel 60 (230–400 mesh or 400–600 mesh). HPLC purifications were performed on Luna C18(2) column using water/acetonitrile as eluent. High resolution TOF mass spectra were acquired with an AB-Sciex QSTAR mass spectrometer equipped with an electron-spray ion source applying the positive ion mode (source voltage 4.5 kV). HRMS-a data were obtained after calibration using reserpine and testosterone with a resolution of approximately 10,000 at *m*/*z* 500. HRMS-b data were obtained after calibration using Agilent tuning mix prior to measurements with a resolution of approximately $R = 8000$ at *m*/*z* 500.

5.1.2. Abbreviations. DMF, *N*,*N*-dimethylformamide; EtOAc, ethyl acetate; Et_3N, triethylamine; HPLC, high performance liquid chromatography; LCMS, liquid chromatography/mass spectrometry; mp, melting point; SiO_2, silicon dioxide (silica gel); THF, tetrahydrofuran.

5.1.3. Synthesis of (11β)-11-[4-(3-pyridinyl)phenyl]-17,24-*cyclo*-19,21-dinorchola-4,9-diene-3,20-dione (3a)

5.1.3.1. (5α,10α)-17,24-*cyclo*-5,10-Epoxy-19,21-dinorchol-9-ene-3,20-dione cyclic 1,2-ethanediyl acetal (5a). To a stirred solution of 17,24-*cyclo*-19,21-dinorchol-5(10),9(11)-diene-3,20-dione cyclic 1,2-ethanediyl acetal[20] (35.1 g, 95 mmol) in a mixture of dichloromethane (615 mL), pyridine (3.3 mL, 42 mmol), trifluoroacetophenone (10.4 mL, 74 mmol) and hydrogen peroxide (30% in water, 147 mL) were added. The resulting two-phase system was vigorously stirred at ambient temperature for 42 h. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic layers were washed twice with a saturated aqueous $Na_2S_2O_3$ solution, washed with brine, dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by column chromatography (SiO_2, heptane/EtOAc, gradient 8/2 to 7/3) to give the title epoxide (16.7 g, 43 mmol, 46% yield). ^{1}H NMR: δ 0.74 (s, 3H), 1.13–2.50 (m, 24H), 3.85–3.98 (m, 4H), 6.00–6.04 (m, 1H).

5.1.3.2. (5α,11β)-11-(4-Bromophenyl)-17,24-*cyclo*-19,21-dinorchola-4,9-diene-5-hydroxy-3,20-dione cyclic 1,2-ethanediyl acetal (11a). A grain of iodine was added to magnesium (0.32 g, 13 mmol) and heated for 1 min. A solution of 1,4-dibromobenzene (3.2 g, 13 mmol) and a drop of 1,2-dibromoethane in THF (15 mL) were added dropwise under a nitrogen atmosphere while the temperature was kept at 45 °C. After 2 h stirring at 45 °C this Grignard suspension was added to a cooled (−30 °C) solution of (5α,10α)-17,24-*cyclo*-5,10-epoxy-19,21-dinorchol-9-ene- 3,20-dione cyclic 1,2-ethanediyl acetal **5a** (1.0 g, 2.6 mmol) and copper(I) chloride (0.13 g, 1.3 mmol) in THF (25 mL) under a nitrogen atmosphere while the temperature was kept at −40 °C. The reaction mixture was stirred for 2 h while the temperature rose to room temperature. A saturated aqueous NH_4Cl solution was added dropwise (exothermic). The organic layer was separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by column chromatography (SiO_2, heptane/EtOAc, 7/3 with a trace of Et_3N) to give compound **11a** (0.92 g, 1.7 mmol, 65% yield). ^{1}H NMR: δ 0.36 (s, 3H), 1.18–2.38 (m, 24H), 3.89–4.06 (m, 4H), 4.25 (d, $J = 7$ Hz, 1H), 4.39 (s, 1H), 7.02–7.06, (m, 2H), 7.32–7.36 (m, 2H).

5.1.3.3. (11β)-11-(4-Bromophenyl)-17,24-*cyclo*-19,21-dinorchola-4,9-diene-3,20-dione (4a). A solution of H_2SO_4 (75 μL) in water (0.55 mL) was added to a solution of acetal **11a** (0.92 g, 1.7 mmol) in methanol (18.4 mL). After stirring this solution for 30 min at room temperature, water (20 mL) was added. The solids were isolated to give dione **4a** (0.75 g, 1.6 mmol, 92% yield). ^{1}H NMR: δ 0.42 (s, 3H), 1.28–2.76 (m, 22H), 4.36 (d, $J = 7$ Hz, 1H), 5.79 (s, 1H), 6.98–7.02 (m, 2H), 7.35–7.40 (m, 2H).

5.1.3.4. (11β)-11-[4-(3-Pyridinyl)phenyl]-17,24-*cyclo*-19,21-dinorchola-4,9-diene-3,20-dione (3a). 0.15 g (0.31 mmol) of dione **4a**, 3-pyridinylboronic acid 1,3-propanediol cyclic ester (0.14 g, 0.85 mmol), potassium phosphate (78 mg, 0.46 mmol), bis(triphenylphosphine)palladium(II) chloride (7 mg, 0.012 mmol) and triphenylarsine (7 mg, 0.027 mmol) were dissolved in a mixture of dioxane (7 mL) and water (1.2 mL) under a nitrogen atmosphere. The reaction mixture was stirred for 3 h at 100 °C and then cooled to room temperature. Water was added and the mixture was extracted twice with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated to dryness. Purification by column chromatography (SiO2, heptane/EtOAc 1/1) gave title compound **3a** (100 mg, 0.21 mmol, 67% yield). ^{1}H NMR: δ 0.47 (s, 3H), 1.24–2.82 (m, 22H), 4.48 (d, $J = 7$ Hz, 1H), 5.80 (s, 1H), 7.23–7.27 (m, 2H), 7.35 (dd, $J = 8$ and 4 Hz, 1H), 7.46–7.51 (m, 2H), 7.84 (dt, $J = 8$ and 1 Hz, 1H), 8.58 (dd, $J = 4$ and 1 Hz, 1H), 8.82 (d, $J = 1$ Hz, 1H). HRMS-a *m*/*z* calcd 478.2746, obsd 478.2740.

5.1.4. Synthesis of (11β)-11-[4-(6-methoxypyridin-3-yl)phenyl]-17,24-*cyclo*-19,21-dinorchola-4,9-diene-3,20-dione (3b). Using the method described for compound **3a** treatment of dione **4a** (0.15 g, 0.31 mmol) with 6-methoxy-3-pyridinylboronic acid (82 mg, 0.53 mmol) followed by purification by column chromatography (SiO2, gradient heptane/EtOAc 7/3 to 1/1) gave the crude product. Addi-

tional purification by HPLC (Luna C18(2)) and lyophilisation yielded compound **3b** (99 mg, 0.19 mmol, 62% yield). ^{1}H NMR: δ 0.47 (s, 3H), 1.25–2.81 (m, 22H), 3.98 (s, 3H), 4.46 (d, J = 7 Hz, 1H), 5.80 (s, 1 H), 6.80 (d, J = 9 Hz, 1H), 7.18–7.22 (m, 2H), 7.40–7.44 (m, 2H), 7.75 (dd, J = 9 and 2 Hz, 1H), 8.36 (d, J = 2 Hz, 1H). HRMS-a m/z calcd 508.2851, obsd 508.2826.

5.1.5. Synthesis of (11β,17β)-17-cyclopropylcarbonyl-11-[4-(3-pyridinyl)phenyl]estra-4,9-dien-3-one (3c)

5.1.5.1. 17-[[(Trifluoromethyl)sulfonyl]oxy]estra-5(10),9(11),16-trien-3-one cyclic 1,2-ethanediyl acetal (8). Lithium hexamethyldisilazane (1M in THF, 478 mL, 478 mmol) was added to THF (1 L) and cooled to −40 °C under a nitrogen atmosphere. A solution of mono-acetal **7** (50 g, 159 mmol) in dry THF (500 mL) was added dropwise while the reaction temperature slowly rose to −15 °C. After stirring for 30 min at −15 °C, *N*-phenyl-bis(trifluoromethanesulfonimide) (62.5 g, 175 mmol) was added batchwise and the reaction mixture was stirred for 3 h at 0 °C. A saturated aqueous $NaHCO_3$ solution was added dropwise (exothermic) followed by water. The organic layer was separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by column chromatography (SiO_2, heptane/EtOAc, 4/1) to give compound **8** (90.1 g, 159 mmol, 100% yield, still containing some solvent). ^{1}H NMR: δ 0.91 (s, 3H), 1.20–2.55 (m, 16H), 3.98 (s, 4H), 5.52 (m, 1H), 5.59 (m, 1H).

5.1.5.2. *N*-Methoxy-*N*-methyl-3,3-[1,2-ethanediylbis-(oxy)]oxo-estra-5(10),9(11),16-triene-17-carboxamide (9). Triethylamine (221 mL, 1.59 mol), triphenylphosphine (6.67 g, 25 mmol) and *N*,*O*-dimethylhydroxylamine.HCl (82.2 g, 843 mmol) were added to a solution of compound **8** (70.9 g, 159 mmol) in DMF (1.5 L). Carbon monoxide was passed through the solution for 10 min, then palladium(II)acetate (2.86 g, 12.7 mmol) was added and the reaction mixture was stirred overnight at 60 °C under a CO atmosphere. The reaction mixture was poured into a saturated aqueous NH_4Cl solution and extracted three times with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by column chromatography (SiO_2, heptane/EtOAc, 2/1) to give compound **9** (59.7 g, 139 mmol, 87% yield, still containing some solvent). ^{1}H NMR: δ 0.97 (s, 3H), 1.25–2.58 (m, 16H), 3.25 (s, 3H), 3.62 (s, 3H), 3.99 (s, 4H), 5.58 (m, 1H), 6.41 (m, 1H).

5.1.5.3. 17-(Cyclopropylcarbonyl)estra-5(10),9(11),16-trien-3-one cyclic 1,2-ethanediyl acetal (10). A solution of cyclopropyl bromide (22.3 mL, 278 mmol) in diethyl ether (20 mL) was slowly added to a cooled suspension (0 °C) of crushed lithium (5.8 g, 834 mmol) in ether (380 mL) (exothermic) under a nitrogen atmosphere. The reaction mixture was stirred for 90 min while the temperature rose to room temperature. The solution of this lithiate was slowly added to a cooled solution (0 °C) of compound **9** (59.7 g, 139 mmol) in THF (260 mL). After stirring this mixture for 2 h at 0 °C, a saturated aqueous NH_4Cl solution was added dropwise (exothermic) followed by water. The organic layer was separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by column chromatography (SiO_2, heptane/EtOAc, 4/1) to give compound **10** (33.9 g, 93 mmol, 67% yield). ^{1}H NMR: δ 0.82–2.67 (m, 24H), 3.99 (s, 4H), 5.59 (m, 1H), 6.88 (m, 1H).

5.1.5.4. (17β)-17-(Cyclopropylcarbonyl)estra-5(10),9(11)-dien-3-one cyclic 1,2-ethanediyl acetal (6c). K-selectride (1 M in THF, 12.1 mL, 12.1 mmol) was added dropwise to a cooled solution (−78 °C) of compound **10** (3.7 g, 10.0 mmol) in THF (105 mL) under a nitrogen atmosphere while the reaction temperature was kept below −70 °C. After stirring this solution for 20 min, a saturated aqueous Na_2SO_4 solution was added dropwise followed by water. The organic layer was separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by column chromatography (SiO_2, heptane/EtOAc, 4/1) to give compound **6c** (2.1 g, 5.8 mmol, 57% yield). ^{1}H NMR: δ 0.59 (s, 3H), 0.80–2.59 (m, 23H), 2.86 (t, J = 9 Hz, 1H), 3.99 (s, 4H), 5.55–5.60 (m, 1H).

5.1.5.5. (17β)-17-(Cyclopropylhydroxymethyl)estra-5(10),9(11)-dien-3-one cyclic 1,2-ethanediyl acetal (12). A solution of compound **6c** (2.1 g, 5.8 mmol) in diethyl ether (54 mL) was added slowly to a cooled (0 °C) suspension of lithium aluminium hydride (262 mg, 6.9 mmol) in diethyl ether (36 mL) under a nitrogen atmosphere. After 1 h stirring at 0 °C a saturated aqueous Na_2SO_4 solution was added until the grey colour disappeared. Solid Na_2SO_4 was added and the mixture was filtered, washed with EtOAc and the filtrate evaporated to dryness to give cyclic compound **12** (2.2 g, 5.8 mmol, >100% yield, product still contained some EtOAc). ^{1}H NMR: δ 0.20–0.59 (m, 4H), 0.70 (s, 3H), 0.82–2.59 (m, 21H), 2.85 (dt, J = 9 and 4 Hz, 1H), 3.99 (s, 4H), 5.53–5.58 (m, 1H).

5.1.5.6. (5α,11β,17β)-11-(4-Bromophenyl)-17-(cyclopropylhydroxymethyl)-5-hydroxyestr-9-en-3-one cyclic 1,2-ethanediyl acetal (14). Following the procedures described to prepare compounds **5a** and **11a,** acetal **12** was transformed to the title compound **14** (26% yield). ^{1}H NMR: δ 0.12–0.57 (m, 7H), 0.79–0.89 (m, 1H), 1.10–2.12 (m, 17H), 2.27–2.40 (m, 2H), 2.65–2.76 (m, 2H), 3.88–4.03 (m, 4H), 4.14 (d, J = 7 Hz, 1H), 4.34 (s, 1H), 7.08–7.13 (m, 2H), 7.32–7.36 (m, 2H).

5.1.5.7. (5α,11β,17β)-11-(4-Bromophenyl)-17-(cyclopropylcarbonyl)-5-hydroxyestr-9-en-3-one cyclic 1,2-ethanediyl acetal (11c). To a solution of compound **14** (726 mg, 1.3 mmol) in acetone (25 mL), 4-methylmorpholine *N*-oxide (438 mg, 3.7 mmol) and tetra-*N*-propylammonium perruthenate (VII) (28 mg, 0.08 mmol) were added and the reaction mixture was stirred for 2 h at room temperature under a nitrogen atmosphere. Silica and heptane (14 mL) were added and the mixture was stirred for 1 h, then filtered through dicalite and washed

properly with EtOAc. The filtrate was evaporated to dryness to give compound **11c** (732 mg, 1.3 mmol, 100% yield). ^{1}NMR: δ 0.21 (s, 3H), 0.80–2.39 (m, 22H), 2.66–2.74 (m, 2H), 3.88–4.05 (m, 4H), 4.23 (d, J = 7 Hz, 1H), 4.37 (s, 1H), 7.06–7.10 (m, 2H), 7.34–7.38 (m, 2H).

5.1.5.8. (11β,17β)-11-(4-Bromophenyl)-17-cyclopropylcarbonylestra-4,9-dien-3-one (4c). 3 N Hydrochloric acid (2 mL, 6 mmol) was added to a solution of compound **11c** (0.73 g, 1.35 mmol) in acetone (25 mL). After stirring this solution for 15 min at room temperature, brine was added and the reaction mixture extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by column chromatography (SiO_2, heptane/EtOAc, 2/1) to give **4c** (0.45 g, 65% yield). ^{1}NMR: δ 0.27 (s, 3H), 0.83–2.83 (m, 22H), 4.34 (d, J = 7 Hz, 1H), 5.79 (s, 1H), 7.02–7.07 (m, 2H), 7.37–7.42 (m, 2H).

5.1.5.9. (11β,17β)-17-Cyclopropylcarbonyl-11-[4-(3-pyridinyl)phenyl]estra-4,9-dien-3-one (3c). Compound **4c** was transformed into crude title compound using the procedure described for the preparation of compound **3a**. Purification by preparative LCMS followed by lyophilisation gave **3c** (66% yield). ^{1}NMR (400 MHz, $CDCl_3$): δ 0.32 (s, 3H), 0.84–2.82 (m, 21H), 2.92 (d, J = 13 Hz, 1H), 4.46 (d, J = 7 Hz, 1H), 5.80 (s, 1H), 7.27–7.32 (m, 2H), 7.34 (dd, J = 8 and 5 Hz, 1H), 7.49–7.54 (m, 2H), 7.86 (dt, J = 8 and 1 Hz, 1H), 8.58 (d, J = 5 Hz, 1H), 8.84 (d, J = 1 Hz, 1H). HRMS-a m/z calcd 478.2746, obsd 478.2743.

5.1.6. Synthesis of (11β,17β)-17-cyclopropylcarbonyl-11-[4-(6-methoxypyridin-3-yl)phenyl]estra-4,9-dien-3-one (3d). Compound **4c** was transformed into crude title compound using the procedure described in experiment 5.1.3.4 for compound **3a** using 6-methoxy-3-pyridinylboronic acid as reagent. Purification by preparative LCMS followed by lyophilisation gave the title compound. (60% yield). ^{1}NMR: δ 0.32 (s, 3H), 0.83–2.81 (m, 21H), 2.91 (d, J = 13 Hz, 1H), 3.98 (s, 3H), 4.44 (d, J = 7 Hz, 1H), 5.80 (s, 1H), 6.80 (d, J = 8 Hz, 1H), 7.22–7.26 (m, 2H), 7.42–7.46 (m, 2H), 7.77 (dd, J = 8 and 2 Hz, 1H), 8.37 (d, J = 2 Hz, 1H). HRMS-a m/z calcd 508.2851, obsd 508.2822.

5.1.7. Synthesis of (11β,17β)-17-cyclopropylcarbonyl-17-methyl-11-[4-(3-pyridinyl)phenyl]estra-4,9-dien-3-one (3e)

5.1.7.1. (17β)-17-(Cyclopropylcarbonyl)-17-methylestra-5(10),9(11)-dien-3-one cyclic 1,2-ethanediyl acetal (6d). L-selectride (3.0 mL, 3.0 mmol, 1 M in THF) was slowly added to a cooled (−78 °C) and stirred solution of compound **10** (500 mg, 1.4 mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (0.33 mL, 2.7 mmol) in dry THF (20 mL) under a nitrogen atmosphere. After 1 h at −78 °C methyl iodide (1.7 mL, 27 mmol) was added. The reaction mixture was stirred for an additional 1.5 h while the temperature raised to −30 °C. The reaction mixture was poured into water and extracted with EtOAc. The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$) and the solvents were evaporated in vacuo. The crude product was purified by column chromatography (SiO_2, heptane/EtOAc = 9/1, v/v) to give compound **6d** (255 mg 0.67 mmol, 49% yield). ^{1}NMR: δ 0.67 (s, 3H), 0.78–2.72 (m, 27H), 1.23 (s, 3H), 3.96–4.02 (m, 4H), 5.57–5.61 (m, 1H).

5.1.7.2. (11β,17β)-17-Cyclopropylcarbonyl-17-methyl-11-[4-(3-pyridinyl)phenyl]estra-4,9-dien-3-one (3e). Compound **6d** was transformed to crude **3e** using the procedures described in experiments 5.1.3.1, 5.1.3.2, 5.1.5.8 and 5.1.3.4. Purification by HPLC (Luna C18(2)) followed by lyophilisation gave the title compound. (19 % yield over these four steps). ^{1}NMR: δ 0.42 (s, 3H), 0.80–2.82 (m, 24H), 2.28 (s, 3H), 4.48 (d, J = 8 Hz, 1H), 5.80 (s, 1H), 7.30 (d, J = 8 Hz, 1H), 7.34 (dd, J = 4 and 8 Hz, 1H), 7.50 (d, J = 8 Hz, 1H), 7.85 (dt, J = 2 and 8 Hz, 1H), 8.57 (dd, J = 2 and 4 Hz, 1H), 8.84 (d, J = 2 Hz, 1H). HRMS-b m/z calcd 492.2903, obsd 492.2842.

5.1.8. Synthesis of (11β,16α,17β)-17-cyclopropylcarbonyl-16-methyl-11-[4-(3-pyridinyl)phenyl]estra-4,9-dien-3-one (3f)

5.1.8.1. (16α,17β)-17-(Cyclopropylcarbonyl)-16-methylestra-5(10),9(11)-dien-3-one cyclic 1,2-ethanediyl acetal (6b). Methylmagnesium chloride (3 M in THF, 92.6 mL, 278 mmol) was added to a stirred and cooled solution (0 °C) of copper(II)acetate (1.7 g, 9.3 mmol) in THF (1 L) under a nitrogen atmosphere. A solution of compound **10** (33.9 g, 93 mmol) and trimethylsilyl chloride (58.5 mL, 463 mmol) in THF (500 mL) was added dropwise while the temperature was kept at 0 °C. After 1 h another equivalent of methylmagnesium chloride was added dropwise and stirring was continued for 30 min at 0 °C. A saturated aqueous NH_4Cl solution was added dropwise followed by water. The organic layer was separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated to dryness to give compound **6b** (32.9 g, 86 mmol, 93% yield). ^{1}H NMR: δ 0.61 (s, 3H), 0.80–2.79 (m, 26H), 3.99 (s, 4H), 5.55 (m, 1H).

5.1.8.2. (11β,16α,17β)-17-Cyclopropylcarbonyl-16-methyl-11-[4-(3-pyridinyl)phenyl]estra-4,9-dien-3-one (3f). Compound **6b** was transformed into crude title compound using the procedures described in experiments 5.1.3.1, 5.1.3.2, 5.1.5.8 and 5.1.3.4. Purification by column chromatography (SiO_2, heptane/EtOAc, gradient 2/1 to 1/2) and subsequently crystallisation from acetonitrile/water gave compound **3f** (22% yield over these four steps), mp 206 °C. ^{1}H NMR: δ 0.35 (s, 3H), 0.86–2.86 (m, 24H), 4.46 (d, J = 8 Hz, 1H), 5.80 (s, 1 H), 7.26–7.29 (m, 2H), 7.35 (dd, J = 10 and 6 Hz, 1H), 7.49–7.53 (m, 2H), 7.86 (dt, J = 10 and 4 Hz, 1H), 8.57 (dd, J = 6 and 4 Hz, 1H), 8.84 (d, J = 4 Hz, 1H). HRMS-a m/z calcd 492.2902, obsd 492.2928.

5.1.9. Synthesis of (11β,16α,17β)-17-cyclopropylcarbonyl-16-ethyl-11-[4-(3-pyridinyl)phenyl]-estra-4,9-dien-3-one (3g)

5.1.9.1. (16α,17β)-17-(Cyclopropylcarbonyl)-16-ethylestra-5(10),9(11)-dien-3-one cyclic 1,2-ethanediyl acetal (6e). Reaction of compound **10** and ethylmagnesium chloride according to the procedure described for compound **6b** in experiment 5.1.8.1 afforded the title com-

pound (87% yield). ^{1}H NMR: δ 0.60 (s, 3H), 0.80–2.64 (m, 28H), 3.99 (s, 4H), 5.54–5.58 (m, 1H).

5.1.9.2. (11β,16α,17β)-17-Cyclopropylcarbonyl-16-ethyl-11-[4-(3-pyridinyl)phenyl]-estra-4,9-dien-3-one (3g). Compound **6e** was transformed into crude title compound using the procedures described in experiments 5.1.3.1, 5.1.3.2, 5.1.5.8 and 5.1.3.4. Purification by preparative LCMS followed by lyophilisation gave the title compound. (22% yield over these four steps). ^{1}H NMR: δ 0.35 (s, 3H), 0.82 (t, J = 7 Hz, 3H), 0.87–0.98 (m, 3H), 1.07–1.14 (m, 1H), 1.25–1.34 (m, 2H), 1.41–1.64 (m, 5H), 1.91–1.99 (m, 1H), 2.03–2.11 (m, 1H), 2.24–2.85 (m, 10H), 4.46 (d, J = 7 Hz, 1H), 5.80 (s, 1H), 7.25–7.30 (m, 2H), 7.35 (dd, J = 7 and 5 Hz, 1H), 7.48–7.53 (m, 2H), 7.46 (dt, J = 8 and 1 Hz, 1H), 8.57 (dd, J = 5 and 1 Hz, 1H), 8.84 (d, J = 3 Hz, 1H). HRMS-a *m*/*z* calcd 506.3059, obsd 506.2685.

5.1.10. Synthesis of (11β,16α,17β)-17-cyclopropylcarbonyl-16-ethenyl-11-[4-(3-pyridinyl)phenyl]-estra-4,9-dien-3-one (3h)

5.1.10.1. (16α,17β)-17-(Cyclopropylcarbonyl)-16-ethenylestra-5(10),9(11)-dien-3-one cyclic 1,2-ethanediyl acetal (6f). Reaction of compound **10** and vinylmagnesium chloride according to the procedure described for compound **6b** in experiment 5.1.8.1 afforded the title compound (48% yield). ^{1}H NMR: δ 0.63 (s, 3H), 0.80–2.66 (m, 21H), 2.71 (d, J = 9 Hz, 1H), 3.30–3.39 (m, 1H), 3.99 (s, 4H), 4.84–4.97 (m, 2H), 5.54–5.58 (m, 1H), 5.71–5.81 (m, 1H).

5.1.10.2. (11β,16α,17β)-17-Cyclopropylcarbonyl-16-ethenyl-11-[4-(3-pyridinyl)phenyl]-estra-4,9-dien-3-one (3h). Compound **6f** was transformed into crude title compound using the procedures described in experiments 5.1.3.1, 5.1.3.2, 5.1.5.8 and 5.1.3.4. Purification by preparative LCMS followed by lyophilisation gave the title compound. (15% yield over these four steps). ^{1}H NMR: δ 0.38 (s, 3H), 0.84–0.99 (m, 3H), 1.08–1.15 (m, 1H), 1.46–2.88 (m, 16H), 3.26–3.35 (m, 1H), 4.47 (d, J = 7 Hz, 1H), 4.86–4.97 (m, 2 H), 5.70–5.79 (m, 1H), 5.81 (s, 1H), 7.26–7.30 (m, 2H), 7.35 (dd, J = 8 and 5 Hz, 1H), 7.49–7.53 (m, 2H), 7.86 (dt, J = 8 and 1 Hz, 1H), 8.58 (dd, J = 5 and 1 Hz, 1H), 8.84 (d, J = 1 Hz, 1H). HRMS-a *m*/*z* calcd 504.2902, obsd 504.2873.

5.1.11. Synthesis of (11β,16α,17β)-17-cyclopropylcarbonyl-11-[4-(6-methoxypyridin-3-yl)phenyl]-16-methylestra-4,9-dien-3-one (3i). Reaction of compound **4b** and 6-methoxy-3-pyridinylboronic acid using the procedure described in experiment 5.1.3.4 gave compound **3i** (54% yield). ^{1}H NMR: δ 0.35 (s, 3H), 0.84–0.99 (m, 6H), 1.08–1.15 (m, 1H), 1.33–1.39 (m, 1H), 1.45–1.54 (m, 1H), 1.62–1.70 (m, 2H), 1.91–1.97 (m, 1H), 2.01–2.08 (m, 1H), 2.24–2.53 (m, 6H), 2.58–2.64 (m, 2H), 2.68–2.85 (m, 3H), 3.98 (s, 3H), 4.44 (d, J = 8 Hz, 1H), 5.80 (s, 1H), 6.80 (d, J = 8 Hz, 1H), 7.23 (d, J = 7 Hz, 2H), 7.44 (d, J = 7 Hz, 2H), 7.75–7.79 (m, 1H), 8.36–8.38 (m, 1H).

5.1.12. Synthesis of (11β,16α,17β)-17-cyclopropylcarbonyl-16-ethyl-11-[4-(6-methoxypyridin-3-yl)phenyl]-estra-4,9-dien-3-one (3j). Compound **6e** was transformed into crude title compound using the procedures described in experiments 5.1.3.1, 5.1.3.2, 5.1.5.8 and 5.1.3.4. using 6-methoxy-3-pyridinylboronic acid in the last step. Purification by column chromatography gave compound **3j** (14% yield over four steps). δ 0.35 (s, 3H), 0.82 (t, J = 8 Hz, 3H), 0.85–0.99 (m, 4H), 1.07–1.13 (m, 1H), 1.25–1.34 (m, 2H), 1.41–2.84 (m, 16H), 3.98 (s, 3H), 4.44 (d, J = 7 Hz, 1H), 5.80 (s, 1H), 6.80 (d, J = 8 Hz, 1H), 7.21–7.25 (m, 2H), 7.42–7.46 (m, 2H), 7.77 (dd, J = 8 and 2 Hz, 1H), 8.37 (d, J = 2 Hz, 1H).

5.1.13. Synthesis of (11β,16α,17β)-17-(cyclopropylcarbonyl)-16-ethenyl-11-[4-(6-methoxypyridin-3-yl)phenyl]estra-4,9-dien-3-one (3k). Compound **6f** was transformed into crude title compound using the procedures described in experiments 5.1.3.1, 5.1.3.2, 5.1.5.8 and 5.1.3.4 (using 6-methoxy-3-pyridinylboronic acid in the last step). Purification by crystallisation from heptane gave compound **3k**. (24 % yield over these four steps), mp 197 °C. ^{1}H NMR: δ 0.39 (s, 3H), 0.84–2.87 (m, 20H), 3.26–3.34 (m, 1H), 3.98 (s, 3H), 4.45 (d, J = 7 Hz, 1H), 4.88 (d, J = 11 Hz, 1H), 4.95 (d, J = 16 Hz, 1H), 5.70–5.81 (m, 2 H), 6.81 (d, J = 8 Hz, 1 H), 7.23 (d, J = 8 Hz, 2H), 7.45 (d, J = 8 Hz, 2H), 7.77 (dd, J = 8 and 3 Hz, 1H), 8.37 (d, J = 3 Hz, 1H). HRMS-a *m*/*z* calcd 534.3008, obsd 534.3014.

5.1.14. Synthesis of (11β,16α,17β)-11-[4-(6-chloropyridin-3-yl)phenyl]-17-cyclopropylcarbonyl-16-methylestra-4,9-dien-3-one (3l). Compound **6d** was transformed into compound **4b** using the procedures described in experiments 5.1.3.1, 5.1.3.2 and 5.1.5.8. To prepare the title compound from compound **4b** and 6-chloro-3-pyridinylboronic acid the procedure described in experiment 5.1.3.4 was slightly modified. The reaction mixture was heated for 4 h and an additional two equivalents of 6-chloro-3-pyridinylboronic acid were added in four portions. Purification by LCMS followed by lyophilisation gave the product (4% yield over these four steps). ^{1}H NMR: δ 0.34 (s, 3H), 0.84–2.84 (m, 24H), 4.45 (d, J = 7 Hz, 1H), 5.80 (s, 1H), 7.25–7.30 (m, 2H), 7.38 (d, J = 8 Hz, 1H), 7.45–7.49 (m, 2H), 7.82 (dd, J = 8 and 3 Hz, 1H), 8.59 (d, J = 3 Hz, 1H). HRMS-b *m*/*z* calcd 526.2513, obsd 526.2510.

5.1.15. Synthesis of (11β,16α,17β)-17-cyclopropylcarbonyl-11-[4-(6-fluoropyridin-3-yl)phenyl]-16-methylestra-4,9-dien-3-one (3m). Compound **6b** was transformed into crude title compound using the procedures described in experiments 5.1.3.1, 5.1.3.2, 5.1.5.8 and 5.1.3.4 and using 6-fluoro-3-pyridinylboronic acid in the last step. Purification by LCMS followed by lyophilisation gave product **3m** (10% yield over these four steps). ^{1}H NMR: δ 0.34 (s, 3H), 0.80–2.85 (m, 24H), 4.45 (d, J = 7 Hz, 1H), 5.80 (s, 1H), 7.00 (dd, J = 8 and 3 Hz, 1H), 7.25–7.29 (m, 2H), 7.44–7.48 (m, 2H), 7.95 (dt, J = 8 and 3 Hz, 1H), 8.41 (d, J = 3 Hz, 1H). HRMS-b *m*/*z* calcd 510.2808, obsd 510.2811.

5.1.16. Synthesis of (11β,16α,17β)-17-cyclopropylcarbonyl-16-methyl-11-[4-(2-pyridinyl)phenyl]estra-4,9-dien-3-one (3n). Compound **6d** was transformed into compound **4b** using the procedures described in experiments 5.1.3.1, 5.1.3.2 and 5.1.5.8. To a solution of compound **4b** (200 mg, 0.41 mmol) in THF (4 mL) under a nitrogen atmosphere

were added $(PPh_3)_2PdCl_2$ (4 mg, 0.006 mmol), ferrocene palladium dichloride (6 mg, 0.009 mmol) and 2-pyridinylzinc bromide (2 mL, 1.0 mmol). The reaction mixture was stirred for 5 h at 60 °C and then cooled to room temperature. A saturated aqueous NH_4Cl solution was added and the mixture was extracted three times with dichloromethane. The combined organic layers were dried through a phase separation filter and evaporated to dryness. Purification by HPLC (Luna C18(2)) followed by lyophilisation gave compound **3n** (80 mg, 0.16 mmol, 40% yield from **4b**). ^{1}H NMR: δ 0.33 (s, 3H), 0.80–2.87 (m, 24H), 4.46 (d, J = 7 Hz, 1H), 5.80 (s, 1H), 7.20–7.23 (m, 1H), 7.25–7.29 (m, 2H), 7.68–7.77 (m, 2H), 7.89–7.92 (m, 2H), 8.67 (dt, J = 5 and 1 Hz, 1H). *m/z* calcd 492.2902, obsd 492.2897.

5.1.17. Synthesis of (11β,16α,17β)-17-cyclopropylcarbonyl-16-methyl-11-[4-(4-pyridinyl)phenyl]estra-4,9-dien-3-one (3o). Compound **6b** was transformed into crude title compound using the procedures described in experiments 5.1.3.1, 5.1.3.2, 5.1.5.8 and 5.1.3.4 using 4-pyridinylboronic acid in the last step. Purification by HPLC (Luna C18(2)) followed by crystallisation (acetonitrile/water) gave the product (18% yield). ^{1}H NMR: δ 0.33 (s, 3H), 0.84–2.85 (m, 24H), 4.46 (d, J = 7 Hz, 1H), 5.81 (s, 1H), 7.26–7.30 (m, 2H), 7.48–7.50 (m, 2H), 7.55–7.59 (m, 2H), 8.63–8.65 (m, 2H). HRMS-b *m/z* calcd 492.2903, obsd 492.2844.

5.1.18. Synthesis of (11β,16α,17β)-17-cyclopropylcarbonyl-16-methyl-11-[4-(4-pyridazinyl)phenyl]estra-4,9-dien-3-one (3p). *n*-Butyllithium (2.76 mL, 6.9 mmol, 2.5 M in hexane) was added dropwise to a cooled (0 °C) solution of diisopropylamine (0.97 mL, 6.9 mmol) in THF (2 mL) under a nitrogen atmosphere. After stirring for 30 min the reaction mixture was cooled to −78 °C and a solution of pyridazine (452 μL, 6.3 mmol) and tributyltin chloride (1.9 mL, 6.9 mmol) were added simultaneously while the temperature was kept below − 70 °C. The reaction mixture was stirred for 2 h at −78 °C; subsequently, a saturated aqueous NH_4Cl solution was added and the reaction mixture was extracted three times with EtOAc. The combined organic layers were dried ($MgSO_4$) and evaporated to dryness. The crude product was purified by LCMS to give tributylstannylpyridazine (197 mg, 0.53 mmol, 8% yield).[36]

This stannylpyridazine (183 mg, 0.49 mmol), compound **4b** (100 mg, 0.20 mmol, prepared according to the procedures described in experiments 5.1.3.1, 5.1.3.2 and 5.1.5.8) and bis(triphenylphosphine)palladium(II) chloride (3 mg, 0.004 mmol) were dissolved in dioxane (3 mL) under a nitrogen atmosphere. The reaction mixture was stirred overnight at 110 °C and then cooled to room temperature. Water was added and the mixture was extracted three times with dichloromethane. The combined organic layers were dried through a phase separate filter and evaporated to dryness. Purification by LCMS followed by lyophilisation gave compound **3p** (78 mg, 0.16 mmol, 79% yield from compound **4b**). ^{1}H NMR: δ 0.33 (s, 3H), 0.85–2.84 (m, 26H), 4.48 (d, J = 7 Hz, 1H), 5.81 (s, 1H), 7.33–7.37 (m, 2H), 7.60–7.64 (m, 3H), 9.21 (dd, J = 5 and 1 Hz, 1H), 9.46 (dd, J = 3 and 1 Hz, 1H). HRMS-b *m/z* calcd 493.2855, obsd 493.2766.

5.1.19. Synthesis of (11β,16α,17β)-17-cyclopropylcarbonyl-16-methyl-11-[4-(pyrimidin-2-yl)phenyl]estra-4,9-dien-3-one (3q). According to the procedure described for compound **3p** in experiment 5.1.18 compound **4b** and 2-tributylstannylpyrimidine were heated for 4 h at 110 °C to give the title compound (17% yield). ^{1}H NMR: δ 0.32 (s, 3H), 0.83–2.87 (m, 24H), 4.47 (d, J = 7.0 Hz, 1H), 5.80 (s, 1H), 7.18 (t, J = 4.7 Hz, 1H), 7.28–7.31 (m, 2H), 8.32–8.35 (m, 2H), 8.79 (d, J = 4.7 Hz, 2H).

5.1.20. Synthesis of (11β,16α,17β)-17-cyclopropylcarbonyl-16-methyl-11-[4-(pyrazin-2-yl)phenyl]estra-4,9-dien-3-one (3r). According to the procedure described for compound **3p** in experiment 5.1.18, compound **4b** and 2-tributylstannylpyrazine were heated in a microwave at 135 °C (150 W, 25 min) to give the title compound (35% yield). ^{1}H NMR: δ 0.33 (s, 3H), 0.84–2.86 (m, 24H), 4.47 (d, J = 7 Hz, 1H), 5.81 (s, 1H), 7.30–7.34 (m, 2H), 7.92–7.96 (m, 2H), 8.49 (d, J = 3 Hz, 1H), 8.61 (dd, J = 3 and 1 Hz, 1H), 9.01 (d, J = 1 Hz, 1H). HRMS-b *m/z* calcd 493.2855, obsd 493.2829.

5.1.21. Synthesis of (11β,16α,17β)-17-cyclopropylcarbonyl-16-methyl-11-[4-(3-quinolidinyl)phenyl]estra-4,9-dien-3-one (3s). Compound **6b** was transformed into crude title compound using the procedures described in experiments 5.1.3.1, 5.1.3.2, 5.1.5.8 and 5.1.3.4 and 6-using quinoline-3-boronic acid pinacolate and heating for 3 h in the last step. Purification by LCMS followed by lyophilisation gave the title compound (8% yield). ^{1}H NMR: δ 0.38 (s, 3H), 0.78–2.89 (m, 24H), 4.49 (d, J = 7 Hz, 1H), 5.81 (s, 1H), 7.30–7.34 (m, 2H), 7.58 (dt, J = 7 and 1 Hz, 1H), 7.63–7.67 (m, 2H), 7.72 (dt, J = 8 and 1 Hz, 1H), 7.87 (dd, J = 8 and 1 Hz, 1H), 8.13 (d, J = 8 Hz, 1H), 8.29 (d, J = 3 Hz, 1H), 9.17 (d, J = 3 Hz, 1H). HRMS-b *m/z* calcd 542.3059, obsd 542.3012.

5.2. Biological testing

The progestagenic activity of the compounds (EC_{50} and intrinsic agonistic activity) was determined in an in vitro bioassay of Chinese hamster ovary (CHO) cells as described before.[37] The efficacy is expressed as the percentage of the effect of the agonist (16α)-16-ethyl-21-hydroxy-19-norpregn-4-ene-3,20-dione (Org 2058) which was set to 100%.

The antiprogestagenic activity (IC_{50}) was determined in a setting comparable to the agonistic assay described above, by the inhibition of the transactivation via the progesterone receptor-B of the enzyme luciferase in the presence of 0.1 nM of the inducer Org 2058. The efficacy of the antagonistic effect was expressed relative to the effect, set to 100%, of the antagonist Org 31710 ((6β,11β,17β)-11-[4-(dimethylamino)phenyl]-4′,5′-dihydro-6-methylspiro[estra-4,9-diene-17,2′(3′H)-furan]-3-one).

Data are the average of at least two independent determinations.

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References and notes

1. Garcia, T.; Benhamou, B.; Gofflo, D.; Vergezac, A.; Philibert, D.; Chambon, P.; Gronemeyer, H. *Mol. Endocrinol.* **1992**, *6*, 2071.
2. Wardell, S. E.; Edwards, D. P. *Semin. Reprod. Med.* **2005**, *23*, 9.
3. Elger, W.; Bartley, J.; Schneider, B.; Kaufmann, G.; Schubert, G.; Chwalisz, K. *Steroids* **2000**, *65*, 713.
4. Chabbart-Buffet, N.; Meduri, G.; Bouchard, Ph.; Spitz, I. M. *Human Reprod. Update* **2005**, *11*, 293.
5. Spitz, I. M. *Curr. Opin. Invest. Drugs* **2006**, *7*, 882.
6. Schubert, G.; Elger, W.; Kaufmann, G.; Schneider, B.; Reddersen, G.; Chwalisz, K. *Semin. Reprod. Med.* **2005**, *23*, 58.
7. Blithe, D. L.; Nieman, L. K.; Blye, R. P.; Stratton, P.; Passaro, M. *Steroids* **2003**, *68*, 1013.
8. Allan, G. F.; Palmer, E.; Musto, A.; Lai, M.-T. *Steroids* **2006**, *71*, 578.
9. Giannoukos, G.; Szapary, D.; Smith, C. L.; Meerer, J. E. W.; Simons, S. S. *Mol. Endocrinol.* **2001**, *15*, 255.
10. Tabata, Y.; Iizuka, Y.; Kashikawa, J.; Takei Masuda, N.; Shinei, R.; Kurihara, K.; Okonogi, T.; Hoshiko, S.; Kurata, Y. *Eur. J. Pharmacol.* **2001**, *430*, 159.
11. Tabata, Y.; Iizuka, Y.; Shinei, R.; Kurihara, K.; Okonogi, T.; Hoshiko, S.; Kurata, Y. *Eur. J. Pharmacol.* **2003**, *461*, 73.
12. Winneker, R. C.; Fensome, A.; Wrobel, J. E.; Zhang, Z.; Zhang, P. *Semin. Reprod. Med.* **2005**, *23*, 46.
13. Spitz, I. M. *Endocrinologist* **2005**, *15*, 391.
14. Ohara, N. *Clin. Exp. Obstet. Gynecol.* **2005**, *32*, 9.
15. Chwalisz, K.; Garg, R.; Brenner, R. M.; Schubert, G.; Elger, W. *Ann. N. Y. Acad. Sci.* **2002**, *955*, 373.
16. Kloosterboer, H. J.; Deckers, G. J.; Schoonen, W. G. E. J.; Hanssen, R. G. J. M.; Rose, U. M.; Verbost, P. M.; Hsiu, J. G.; Williams, R. F.; Hodgen, G. D. *Steroids* **2000**, *65*, 733.
17. Madauss, K. P.; Grygielko, E. T.; Deng, S.-J.; Sulpizio, A. C.; Stanley, T. B.; Wu, C.; Short, S. A.; Thompson, S. K.; Stewart, E. L.; Laping, N. J.; Williams, S. P.; Bray, J. D. *Mol. Endocrinol.* **2007**, *21*, 1066.
18. Pullen, M. A.; Laping, N.; Edwards, R.; Bray, J. *Steroids* **2006**, *71*, 792.
19. Verbost, P. M.; Hanssen, R. G. J. M.; Korver, G. H. V.; Mulders, T. M. T. *Semin. Reprod. Med.* **2005**, *23*, 101.
20. Gaillard Kelly, M.; Nedelec, L.; Nique, F.; Philibert, D. Eur. Patent 443,957, 1991; *Chem. Abstr.* **1991**, *115*, 232605.
21. Gebhard, R.; van der Voort, H.; Schuts, W.; Schoonen, W. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2229.
22. Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015.
23. Hamersma, J. A. M.; Orlemans, E. O. M.; Rewinkel, J. B. M. Eur. Pat. Appl. 0,582,338, 1992; *Chem. Abstr.* **1994**, *121*, 231157.
24. Sathya, G.; Jansen, M. S.; Nagel, S. C.; Cook, C. E. *Endocrinology* **2002**, *143*, 3017.
25. Scholz, S.; Ottow, E.; Neef, G.; Elger, W.; Beier, S.; Chwaisz, K. Eur. Pat. Appl. 0,349,481, 1988; *Chem. Abstr.* **1990**, *112*, 235680.
26. Ottow, E.; Schwede, W.; Cleve, A.; Elger, W.; Chwalisz, K.; Schneider, M. US patent 5,843,931, 1991; *Chem. Abstr.* **1992**, *117*, 171819.
27. Cook, C. E.; Kepler, J. A.; Zhang, P. -S.; Lee, Y. -W.; Tallent, C. R. WO 99/45022, 1999; *Chem. Abstr.* **1999**, *131*, 199885.
28. Kloosterboer, H. J.; Deckers, G. H. J.; van der Heuvel, M. J.; Loozen, H. J. J. *J. Steroid Biochem.* **1988**, *31*, 567.
29. Lehmann, H.-G.; Müller, H.; Wiechert, R. *Chem. Ber.* **1965**, *98*, 1470.
30. Phillipps, G. H. *J. Steroid Biochem.* **1975**, *6*, 607.
31. Cook, C. E.; Wani, M. C.; Lee, Y.-W.; Fail, P. A.; Petrow, V. *Life Sci.* **1993**, *52*, 155.
32. Cook, C. E.; Lee, Y.-W.; Wani, M. C.; Fail, P. A.; Petrow, V. *Human Reprod.* **1994**, *9*, 32.
33. Wagner, B. L.; Pollio, G.; Leonhardt, S.; Wani, M. C.; Lee, D. Y.-W.; Imhof, M. O.; Edwards, D. P.; Cook, C. E.; McDonnell, D. P. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 8739.
34. Williams, S. P.; Sigler, P. B. *Nature* **1998**, *393*, 392.
35. Raaijmakers, H.; Uitdehaag, J.; Versteegh, J. Data presented at the meeting of the Netherlands Society for Crystallography, Lunteren, The Netherlands, 20–21 March 2006, in preparation.
36. Also see Sauer, J.; Heldmann, D. K.; Hetzenegger, Josef; Krauthan, J.; Sichert, H.; Schuster, J. *Eur. J. Org. Chem.* **1998**, *12*, 2885.
37. Schoonen, W. G. E. J.; de Ries, R. J. H.; Joosten, J. W. H.; Mathijssen-Mommers, G. J. W.; Kloosterboer, H. J. *Anal. Biochem.* **1998**, *261*, 222.