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11,21-Bisphenyl-19-norpregnane derivatives are selective antiglucocorticoids

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Abstract: An efficient eight-step synthesis of 11,21-bisphenyl-19-norpregnane derivatives (**10**) starting from 19-norandrosta-4,9-diene-3,17-dione (**5**) is described. It is shown that specific combinations of polar substitutions on the 11- and the 21-phenylring in compounds (**10**) lead to selective antiglucocorticoids with relative high binding to the glucocorticoid receptor and almost negligible binding to the progesterone receptor.

Glucocorticoid hormones, secreted by the adrenal glands, are crucially involved in the physiological regulation of carbohydrate metabolism (increased gluconeogenesis) in the liver and protein metabolism (increased catabolism) in muscles. In addition, glucocorticoids have strong anti-inflammatory and immunosuppressive properties[1]. The principal glucocorticoid in man is cortisol (**1**); in rats, rabbits and mice this is corticosterone (**2**). Many diseases, e.g. Cushing's syndrome, hypertension, diabetes, depression and glaucoma, are characterized by elevated levels of circulating cortisol. Therefore antagonists of cortisol may be expected to have therapeutic potential in the treatment of these diseases[2].

The glucocorticoid antagonist well-known to date with strong in vitro and in vivo activity is RU (38)486 (**3**, mifepristone)[3]. A serious drawback of RU (38)486 is its potent antiprogestagenic activity, which is the basis for its application as an abortifacient drug. The 19-benzyl androstane RU 43044 (**4**) has been reported to be a very selective glucocorticoid antagonist. However, this compound appears to be active in vitro but not in vivo[4]. This means that a highly selective *and* potent antiglucocorticoid for oral or subcutaneous treatment is currently not available.

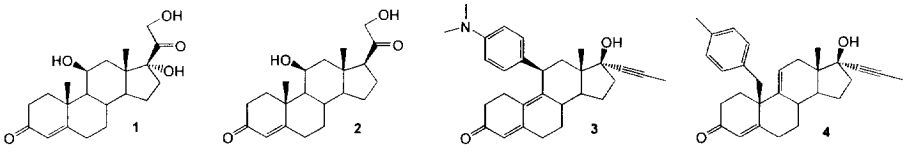

***Figure 1**: Structures of cortisol (1), corticosterone (2), RU (38)486 (3) and RU 43044 (4)*

As part of our investigations in this field, we now report that specific substitution of the 21-phenyl group in 19-nor-11,21-bisphenylpregnanes (**10**) significantly reduces binding to the progesterone receptor, whereas the high affinity for the glucocorticoid receptor is hardly affected. In vivo, the antiglucocorticoid activity of these compounds is confirmed.

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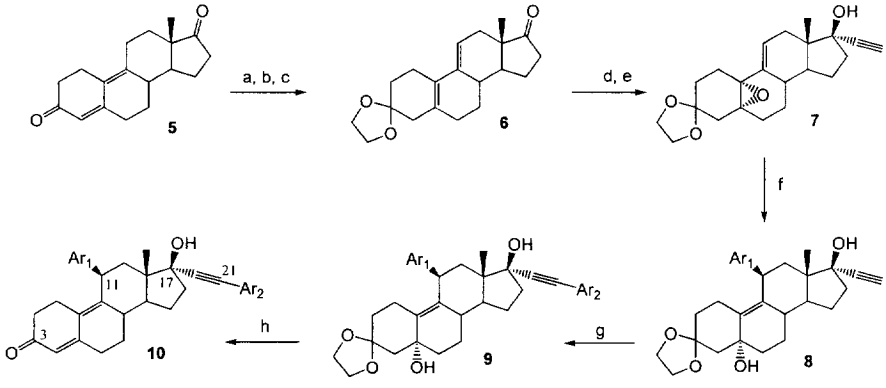
Chemistry: For the synthesis of a series of these 11,21-bisphenylpregnanes (**10**), ethynyl-epoxide (**7**) is the preferred intermediate; it allows maximum flexibility for the introduction of differently substituted phenyl-groups at C11 and C21. According to scheme 1, compound **7** is readily prepared from 19-nor-androsta-4,9-diene-3,17-dione (**5**) in five steps. Selective reduction of the 17-ketofunction with sodium borohydride in THF/methanol (1/1 v/v; -10 °C), followed by ketalisation of the 3-carbonylgroup (ethyleneglycol, triethyl-orthoformate, p-toluenesulfonate) and reoxidation of the 17-hydroxyfunction (pyridinium chlorochromate) gives the crystalline mono-ketal (**6**) in an overall yield of 50%. Subsequent ethynylation of the 17-carbonylgroup (acetylene, KOtBu, THF) followed by epoxidation (H_2O_2, trifluoroacetophenone, pyridine, CH_2Cl_2)[5] of the crude product gives, after purification, the desired 5α,10α-epoxide (**7**) as a crystalline solid. According to the procedure developed by Teutsch and coworkers[6], a copper-catalyzed Grignard reaction stereospecifically provides the desired 11β-phenylsteroid (**8**), generally in 80-100% yield.



Scheme 1: *a) $NaBH_4$, THF/MeOH; b) $(CH_2OH)_2$, $(EtO)_3CH$, pTsOH; c) pyridinium chlorochromate, CH_2Cl_2 d) acetylene, KOtBu; e) H_2O_2, trifluoroacetophenone, pyridine; f) Ar_1Br, Mg, CuCl; g) Ar_2Br, $Pd(OAc)_2$, CuI, PPh_3; h) H_2SO_4, acetone.*

The cross-coupling between terminal alkynes and arylhalides is well-documented[7]. In general this reaction is achieved by the joint catalytic action of a copper-salt and a bivalent or zerovalent palladium compound in the presence of a base. For a clean and high-yield conversion of 17α-ethynylsteroid (**8**) to the corresponding phenylethynyl compound (**9**), it was found that in particular the base/solvent used is of importance. For the conversion of (**8**) to (**9**) the following procedure was used: equimolar amounts of steroid (**8**) and the desired aryl bromide were dissolved in pyrrolidine[8] in N_2 atmosphere; CuI (2 mol%), $Pd(OAc)_2$ (2 mol%) and triphenylphosphine (6 mol%) were added and the mixture was refluxed for 30-90 min., depending on the phenylsubstituent. In addition to the desired coupled product (**9**) (80-90% yield) a small amount of a dimeric steroid was obtained. The formation of this product can be explained by an oxidative coupling of two ethynyl

groups, generating the zerovalent palladium compound, which is the actual catalyst[9]. In the last step compound (**9**) is treated with H_2SO_4 in acetone. Dehydration and concomittant deprotection gives mainly the desired 3-keto-$\Delta^{4,9}$-steroid (**10**) together with 10-15% of the corresponding $\Delta^{5(10),9(11)}$ isomer. The desired compound can easily be separated from its isomer by column chromatography. In this way, a large series of differently substituted 11,21-bisphenylpregnanes (**10**) has been prepared.

It appeared that compounds (**10**) with Ar_2 having an electron-donating substituent are unstable under the acid deprotection condition used for the conversion of (**9**) → (**10**). An acid-catalyzed allenic rearrangement, favoured by the electron-donating phenylsubstituent, results in a clean conversion of the phenylethynyl moiety into the corresponding α,β-unsaturated ketone (Meyer-Schuster rearrangement[10]; fig. 2). By carefully controlling the reaction time, this rearrangement can largely be suppressed.

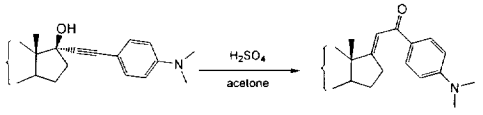
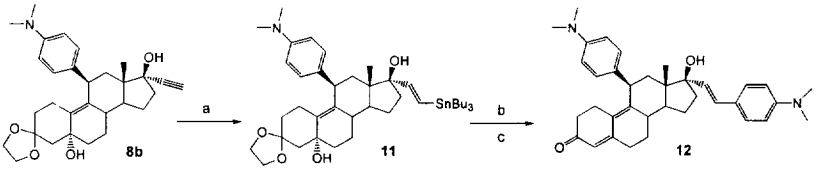


***Figure 2**: Meyer-Schuster rearrangement of 17-phenylethynyl steroids*

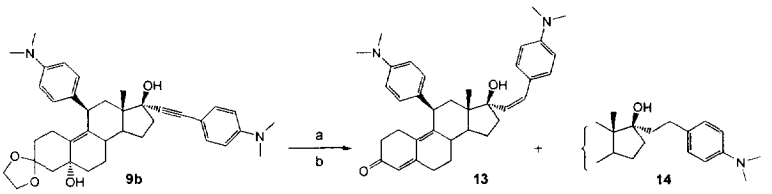
To investigate the effect of conformational flexibility of the large 17α-substituent in compounds (**10**) on the activity of these compounds, the E- and Z-phenylethenyl- and the saturated phenylethyl derivative of bis-N,N-dimethylaminophenylsteroid (**10b**) were required. For the preparation of the E-phenylethenyl derivative, compound (**8b**) was converted to stannane (**11**) (3 eq. Bu_3SnH, 0.8 eq. AIBN, toluene, 80 °C) in an E/Z isomer ratio of 5/1. The E-stannane was purified with column chromatography and subsequently coupled with 4-bromo-N,N-dimethylaniline (LiCl, $Pd(OAc)_2$, Ph_3P, DMF) to give the desired coupled product in 35% yield[11]. Acid hydrolysis eventually provided the desired E-ethenyl derivative (**12**) (scheme 2).



***Scheme 2**: a) tributyltin hydride, AIBN, toluene, 80 °C; b) 4-bromo-N,N-dimethylaniline, LiCl, $Pd(OAc)_2$, Ph_3P, DMF, 80 °C; c) H_2SO_4, acetone.*

The corresponding Z-phenylethenyl and the phenylethyl derivative of compound (**12**) were prepared via catalytic reduction of compound (**9b**) (scheme 3). Unexpectedly, most of the standard reduction catalysts (e.g. Lindlar) failed or gave a mixture of starting material and fully saturated product. With Pd/C (5%) in DMF, absorption of 1 eq. of hydrogen resulted in a mixture of ca. 15% of the partially reduced Z-phenylethenyl

steroid, 40% of the phenylethyl product and 25% of the starting material. The sterically hindered $\Delta^{9,10}$ was not affected during the reduction. Acidic hydrolysis followed by chromatographic separation, provided the desired Z-phenylethenyl steroid (**13**) and phenylethylsteroid (**14**).



***Scheme 3**: a) H_2, Pd/C, DMF; b) H_2SO_4, acetone.*

Results and discussion: The synthesized compounds were tested for their ability to bind to the human glucocorticoid receptor (GR; IM-9 cells, cytosol) and the human progesterone receptor (PR; MCF-7 cells, cytosol) using reported procedures[12]. A selection of the results is summarized in table 1. Of the approximately 80 different compounds (**10**) that have been prepared and tested, many showed a GR/PR-ratio comparable to the unsubstituted compound **10a** previously reported by Roussel-Uclaf[4]. It appears that only a limited number of compounds combine a high binding to the GR with a low binding to the PR (thus a high GR/PR). Although a solid structure-activity relationship has not yet been found, several general observations can be made. It appears that the GR-activity and selectivity are critically dependent on both the substituent at Ar_1 and Ar_2. The optimum substituent at Ar_1 seems to be the 4-N,N-dimethylamino- or the 3,4-(m)ethylenedioxogroup. The 3-(thio)methoxy- or 3-N,N-dimethylaminogroup which were reported to induce high selectivity for the GR[4], led to a significant decrease in affinity for the GR upon combination with a substituted 21-phenylgroup (data not shown). As shown in Table 1, substitution of Ar_2 by a 4-N,N-dimethylamino (**10b**), 4-sulfone (**10c,d**) or 4-pyrrolidone (**10e**) moiety leads to a dramatic increase of the GR/PR ratio as compared to the unsubstituted Ar_2 (**10a**). A 4-carboxamide or a 4-sulfonamide group in Ar_2 has a similar though slightly less pronounced effect (not shown). Reduction of the triple bond to the E-double bond (as in **12**), leads to a significant decrease in GR- and an increase in PR-binding. Similar results were obtained upon reduction of the triple bond to the Z-double (as in **13**) or the saturated bond (as in **14**; results not shown).

Apparently the GR can accommodate 11-phenyl substituted steroids with a rigid 17α-substituent as large as a phenylethynyl function[13]; moreover, specific polar substitution of this 17α-phenylethynyl group provides compounds which are highly selective for the GR. It has been reported that the GR is more hydrophilic than the PR[14] in the area which interacts with the steroidal D-ring. However, considering the distance between the polar phenylethynylsubstituent and the steroidal D-ring (ca. 8.5 Å) it seems unlikely that this hydrophilic area in the GR accounts for the high selectivity observed for e.g. compounds **10b,c,d** and **e**.

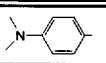
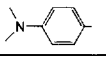
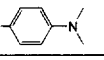
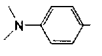
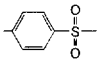
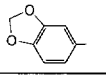
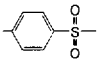
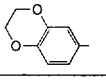
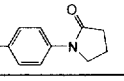
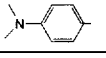
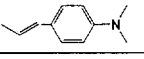
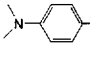
	Ar_1	Ar_2	GR (%)[a]	PR (%)[b]	GR/PR
10a			98	16	6
10b			84	1.7	49
10c			87	2	44
10d			195	0.4	488
10e			98	0.2	490
12			5.9	6.1	1
RU (38)486		CH_3	193	36	5.4

Table 1: a) IM-9 cells, cytosol; relative binding affinity; dexamethasone = 100%
b) MCF-7 cells; cytosol; relative binding affinity; Org 2058 = 100%

In vivo antiglucocorticoid activity of the novel compounds is assessed by measuring the effect on body weight gain and thymus weight of dexamethasone-treated immature male rats[12]. In this test compound **10b** clearly antagonized the dexamethasone effect with an ED_{50} of 10 mg/kg after oral administration[15]. The antiglucocorticoid activity of the other compounds is currently investigated. In addition, the antiprogestagenic activity of these compounds will be measured. These results will be reported separately.

Acknowledgements:

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8) Reaction in e.g. piperidine or triethylamine took considerably longer and gave more by-products.
9) a) Sonogashira, K.; Tohda, Y.; Hagihara N. *Tetrahedron Lett.* **1975**, *50*, 4467; b) upon using $Pd(Ph_3P)_4$ as a catalyst, the dimeric by-product was not formed.
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12) Kloosterboer, H.J.; Deckers, G.H.J.; Van der Heuvel, M.J.; Loozen, H.J.J. *J. Steroid Biochem.* **1988**, *31*, 567.
13) Analogues of **10** without 11-phenyl group hardly bind to the glucocorticoid receptor.
14) Zeelen, F.J. in *QSAR Strategies in Design of Bioactive Compounds*; Seydel, J.K. (Ed.), VCH, Weinheim, 1985, pp 135-141.
15) In this test, the reference compound RU (38)486 shows antiglucocorticoid activity with an ED_{50} of 6 mg/kg after oral administration.

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