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THE OSTEOPROTECTIVE ACTION OF 6-OXA-8α-ANALOGUES OF STEROID ESTROGENS

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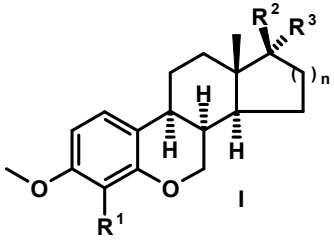
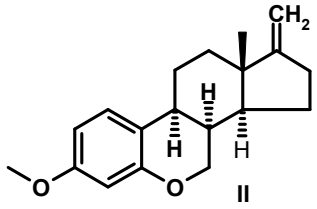
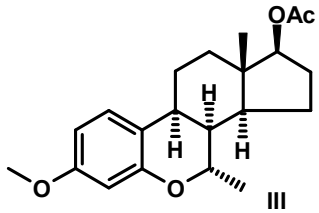


I

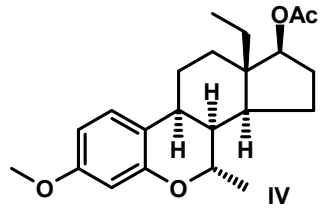
I	R^1	R^2	R^3	n
a	H	OAc	H	1
b	H	O		1
c	H	OEt	H	1
d	CH_3	OAc	H	1
e	CH_3	O		2
f	H	CH_2OAc	H	1



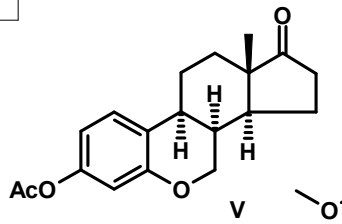
II



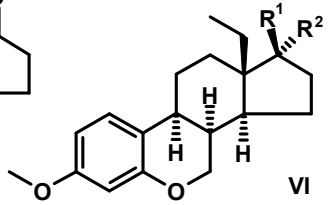
III



IV

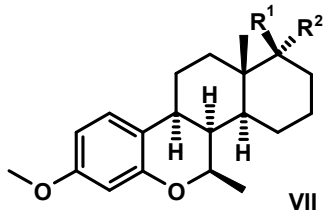


V



VI

a) R^1= OAc, R^2 = H
b) R^1 , R^2 = O



VII

a) R^1= OAc, R^2 = H
b) R^1 , R^2 = O

8α-Analogues of estradiol have a relatively high affinity for estrogen receptors [1–4] and are of potential interest for the production on their basis of medications with the improved biological properties. These steroids possess a cholesterol-lowering [5–9] and osteoprotective [10, 11] action and can serve as a basis for the design of compounds promising for the hormone replacement therapy.

In view of this, it was interesting to develop the methods for the synthesis of 6-oxa-8α-analogues of steroid estrogens and study some biological properties of this group. It was difficult to choose the most appropriate model compounds for the synthesis, because estrogens regulate the activity of no less than 12 genes in osteoblasts and osteoclasts [12]. The potentialities of steroids of the new group could be assessed only experimentally. The biological properties of some compounds are presented in the table.

Group of experimental rats (number of animals in the group)	Change of body weight,	Uterine weight, mg/100 g of body weight	Ash femur weight/ wet femur weight	Serum cholesterol, mg/dl
Sham-operated (15)	29.5 ± 3.2 *	154 ± 4*	0.432 ± 0.007*	57.2 ± 1.9*
Ovariectomized (20)	62.0 ± 5.2	32.4 ± 0.6	0.403 ±0.005	68.4 ± 2.4
Ovariectomized, treated with EE (20)	11.0 ±2.9*	157± 8*	0.422 ± 0.005*	30.0 ± 1.7*
Ovariectomized, treated with **Ib**	45.5 ± 3.8*	72± 3*	0.425 ±0.006*	51.9 ± 1.7*
Ovariectomized, treated with **If**	59.0 ± 4.7	30.9 ± 1.6	0.410 ±0.007	64.8 ± 2.4
Ovariectomized, treated with **VIIb**	60.7 ± 3.5	31.2 ± 1.2	0.404 ±0.005	62.5 ± 2.5

We have demonstrated the correlation between these activities: every modification in the structure of 6-oxa-8-analogues of steroid estrogens leading to the strong (>30%) reduction of uterotropic action induces the slump of osteoprotective activity. This data allows to make a conclusion that the main biotarget, responsible for the appearance of osteoprotective action is the α-estrogen receptor.

We have found the steroid estrogen analogues with cholesterol-lowering properties without uterotropic activity. Such steroids are of great interest for the hormonal replacement therapy.

[1]. US Patent 4 522 758 (**1985**). [2]. Li, J.J., Li, S.A., Oberley, T.D., and Parsons, J.A., *Cancer Res.,* **1995**, *55*, 4347. [3]. Gonzalez, F.B., Neef, G., et al. *Steroids*, **1982**, *40*, 171. [4]. Kaspar, P. and Witsel, H., *J. Steroid Biochem.*, **1985**, *25*, 259. [5]. Korkhov, V.V., Makusheva, V.P., Lupanova, G.E., Eliseev, I.I., Zhukovskii, E.A., Boronoeva, T.R., Martynov, V.F., and Shavva, A.G., *Khim.-Farm. Zh.*, **1986**, *20*, 574. [6]. Chernyaev, G.A., Barkova, T.I., Ananchenko, S.N., et al. *Bioorg. Khim.*, 1979, *5*, 869. [7]. Bull, J.R. and de Koning, P.D., *J. Chem. Soc., Perkin Trans. I*, **2000**, 1003. [8]. UK Patent 1 069 845, **1967**. [9]. UK Patent 1 108 664, **1968**. [10]. US Patent 3 407 217, **1968**. [11]. US Patent 5 395 831, **1995**. [12]. Lindberg, M.K., Moverare, S., Eriksson, A.-L., et al. *J. Bone Miner. Res.*, **2002**, *17*, 2183.