PHARMACOLOGICAL EVALUATION OF ORIGINALLY SYNTHESIZED ESTRONE AND ESTRADIOL STEREOISOMERS

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As the structure of the estrogen receptor (ER) ligand binding domain (LBD) determines a well defined cavity for binding each ligand, at the synthesis of new ligands it is necessary to investigate the influence of the functional groups position on the *in vitro* receptor binding ability and *in vivo* effectiveness.

Our present aim was to characterize the *in vitro* ER binding affinity and selectivity, and *in vivo* effectiveness of four estrone and twelve estradiol stereoisomers determined by radioligand binding assay and uterus weight gain measurement. Our molecules were modified estrone and estradiol analogs in the position of C3-, C13-, C16- and C17.

We proved that the ER recognized our molecules, although the differences among the inhibition constant (K_i) values reached the three orders of magnitude. The 16α-bromomethyl-estra-1,3,5(10)-triene-3,17β-diol exhibited the highest affinity to ER ($K_i = 2.55 \pm 0.64$ nM), so this compound bound to ER as strong as the endogenous estradiol does. The selectivity ratio (SR) of the compounds showed high divergence depending on the position of the different substituents. Moreover some isomers possessed higher affinity to progesterone or androgen receptor than to ER, although these K_i values (196.1 – 2963 nM) were not comparable to K_i values of the reference molecules (7.24 – 9.15 nM).

Only two compounds evoked significant *in vivo* uterotrophic effect. 16α-Bromomethylestra-1,3,5(10)-triene-3,17β-diol displayed strong, dose-dependent estrogenic effect on the uterine tissue. Surprisingly, the lowest dose (10 μg) of 16β-hydroxymethyl-estradiol induced significant increase in the uterus weight that could not be observed after the administration of the higher doses (30 or 50 μg).

Our results reflect that the stereoisomery possesses great influence on the ligand-receptor interaction, although a comparison can not made routinely between the *in vitro* and *in vivo* results. 16α-Bromomethylestra-1,3,5(10)-triene-3,17β-diol is considered a good ER-ligand with excellent specificity and its *in vivo* efficacy was also acceptable.