S N Morozkina et al., J Cancer Sci Ther 2014, 6:10
http://dx.doi.org/10.4172/1948-5956.S1.033

OMICS Group Conferences
Accelerating Scientific Discovery

4th World Congress on
Cancer Science & Therapy
October 20-22, 2014 DoubleTree by Hilton Hotel Chicago-North Shore Conference Center, USA

Antioxidant effect of new synthetic steroid estrogens: New compounds for hormonal replacement therapy

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Atherosclerosis, hardening of arteries, is the primary cause of cardiovascular disease. Oxidative damage plays an important role in atherogenesis, the key events of which are modification of low density lipoprotein (LDL) and its retention in arterial wall. In addition to atherosclerosis, oxidative stress and lipid peroxidation have been implicated in neurodegenerative diseases and aging. Estrogens are known antioxidants. The antioxidant effects of estrogens are mainly due to direct free-radical scavenging, independent of binding to estrogen receptors. Other possible mechanisms include reduction or chelation of redox-active metal ions. Based on previous studies on human endogenous estrogens, the structural determinants for the *in vitro* antioxidant activity include a phenolic A-ring, 1 or 2 adjacent methoxy groups to the phenolic OH, and incorporation of an aromatic B-ring. In the present study, we describe the synthesis of novel steroidal estrogen analogues with various substitutions in the steroidal skeleton. In addition to develop synthetic methodology, the aim was to study structural determinants of estrogen antioxidant effects.We set out to explore the *in vitro* antioxidant activity of the new estrogen analogues in aqueous LDL solution, in comparison with the principal endogenous estrogen, 17β-estradiol. We tested a wide series of steroidal estrogen analogues (n=45) with unnatural ring junction and having various substituents on the steroidal skeleton, most of these compounds (n=22) were new and thus, their antioxidant or other biological effects unknown. The synthetic strategy was based on the method of Torgov and Ananchenko, which enables to synthesize steroidal compounds of diverse structures. In summary, our results demonstrate the way of increasing of antioxidant capacity through structural changes. For example in the group of 6-oxa analogues, the extension of D-ring led to increment of activity up to level of 17β-E2. Analogues with fluorine atom at C-2 exhibited antioxidant effects similar or more potent to 17β-E2. Thus, in addition to their metabolic stability, these compounds are of interest as antioxidative agents. Antioxidant activity of estrogen analogues without a free phenolic hydroxyl group was observed for the first time and it is worth further investigations. More studies are also needed to determine the role of steric factors in the interaction between antioxidants and LDL particles, using synthetic estrogen analogues with substitutions in D-ring and different orientation of ring junction.

Biography

S N Morozkina is working in steroid research at the Department of Natural Chemistry Department at Saint-Petersburg State University start from 2004 after Post-doctoralship in Organic Chemistry. She has 15 patents and more than 45 articles.

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