

# Synthesis of biologically active conjugates on the modified estrone skeleton

The theses of Ph.D. dissertation

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## 1. Introduction and aims

Natural estrone and its synthetic derivatives belong to the family of steranes. Their pharmacological features are determined by their structure and by the nature and orientation of the functional groups at different positions. Therefore the conscious modifications of the estrane skeleton – for example epimerization, opening of ring D, substitution – may lead to antitumor effect with the loss of hormonal activity. Recently several heterocyclic steroid derivatives or conjugates with diverse structure proved to be antiproliferative, antimicrobial or enzyme inhibitory. Several synthetic strategies are available for the preparation of steroid conjugates, like transition metal catalyzed reactions. Furthermore the introduction of microwave methods enables synthetic chemists to perform reactions that are not feasible under conventional reaction conditions.

The aim of the present study was the synthesis of new, potentially antitumor estrone derivatives on 13-epimer and/or D-secoestrone skeleton:

- CuAAC reactions of new steroid alkynes
- Sonogashira reactions of estrone iodides with phenylacetylenes
- one-pot Sonogashira-CuAAC reactions on steroid model.

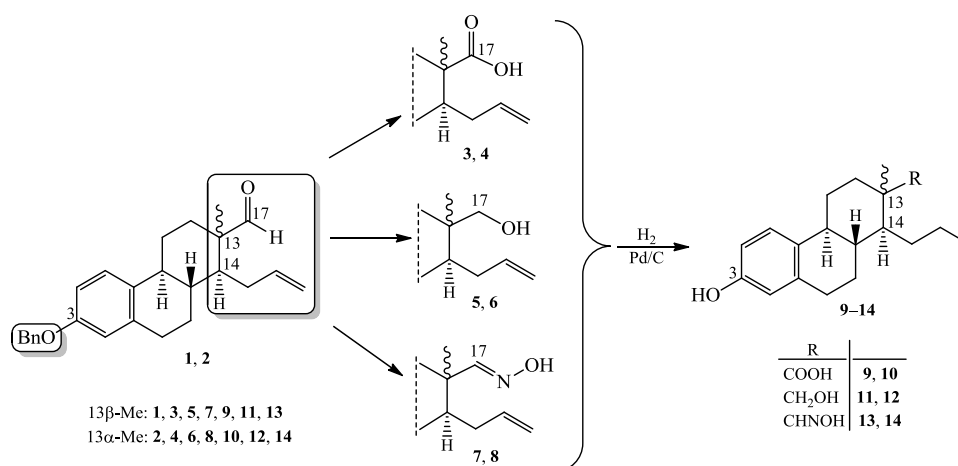
Our further aim was the *in vitro* investigation of antiproliferative and 17 $\beta$ -HSD1 enzyme inhibitory potential of the new compounds, in cooperation, and to determine SAR.

## 2. Experimental methods

Most reactions were carried out on a millimolar scale, and were monitored by thin-layer chromatography. The „click”-reactions were carried out by conventional heating, the palladium catalyzed cross couplings were performed in a CEM Discover SP microwave reactor. The purification of the reaction mixtures and the separation of the products were accomplished by flash chromatography. The structures of the new compounds were confirmed mainly by one- and two-dimensional NMR spectroscopic techniques.

### 3. Novel scientific results

3.1. The 3-benzyloxy-14 $\beta$ -(prop-2-en-yl)-*des*-D-estra-1,3,5(10)-trien-13 $\alpha$ -carbaldehyde (**1**) and its 13-epimer (**2**) were transformed into carboxylic acids (**3**, **4**) by Jones oxidation, into alcohols (**5**, **6**) with sodium borohydride and into oximes (**7**, **8**) by using hydroxylamine hydrochloride in the presence of sodium acetate (Scheme 1). The prepared basic compounds (**3–8**) were modified at three sites in the molecules: the alcoholic and the oxime hydroxyl functions were esterified by acetic anhydride, the 3-benzyl protecting group was removed, and the 14-(prop-2-en-yl) sidechain was saturated.



Scheme 1

3.2. The phenolic hydroxy groups of the 13 $\alpha$ -estrone (**15**) with intact ring D and the 13-epimeric D-secoalcohols and -oximes (**11–14**) were etherified by using 1 equiv. of propargyl bromide in the presence of potassium carbonate in acetone (Scheme 2). The reactions chemo- and regioselectively furnished different 3-propargyl ethers (**16–20**, „A-alkyne”) in excellent yields.

3.3. Starting from 3-protected D-seccarboxylic acids (**3**, **4**), we prepared carboxamide derivatives (**21**, **22**, „D-alkyne”) in excellent yields by using 1 equiv. of propargyl amine and peptide coupling agents: the 1:1 mixture of HBTU and HOBt, with the addition of DIPEA, in *N,N*-dimethylformamide (Scheme 2).

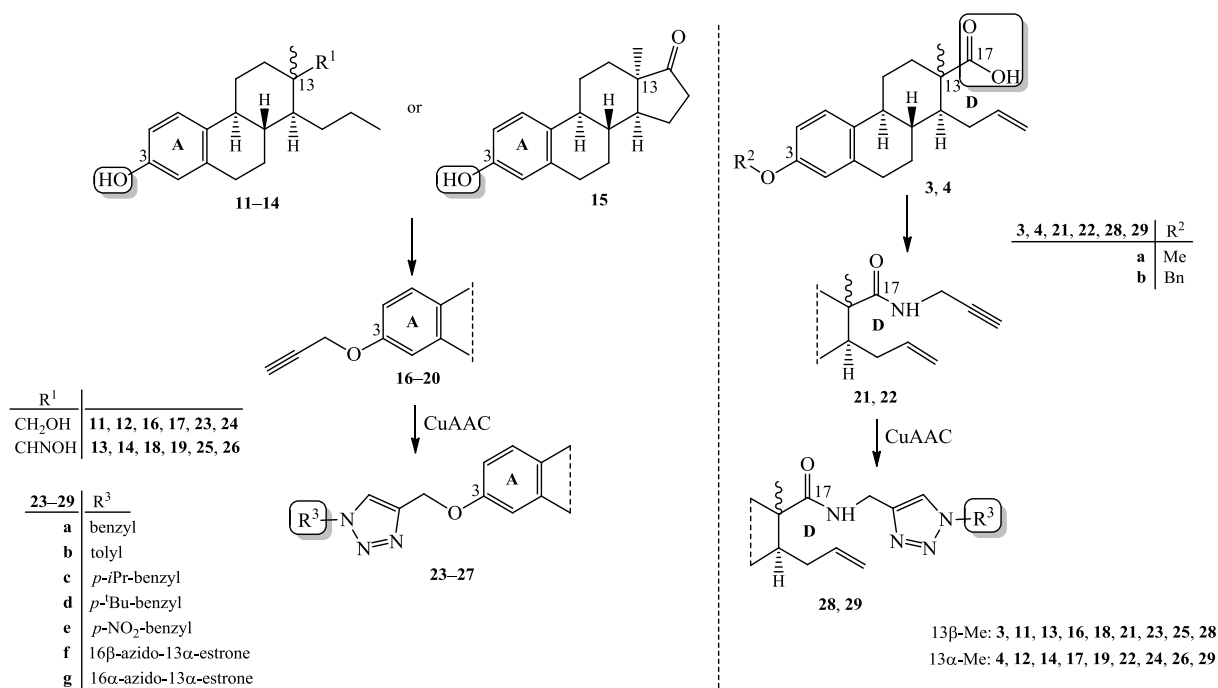
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\* The numbering of the molecules is independent from the numbering used in dissertation.

3.4. The different „A-alkynes” (**16–20**) were reacted with unsubstituted or *p*-substituted benzyl azides via Cu(I)-catalyzed azide-alkyne „click”-reactions using 10 mol% Cu(I)-iodide as a catalyst, 20 mol% triphenylphosphine as an accelerating ligand, and 3 equiv. of DIPEA as a base, in toluene (CuAAC, Scheme 2). Several new *N*-benzyltriazolylmethyl derivatives (**23–27**) were successfully synthesized.

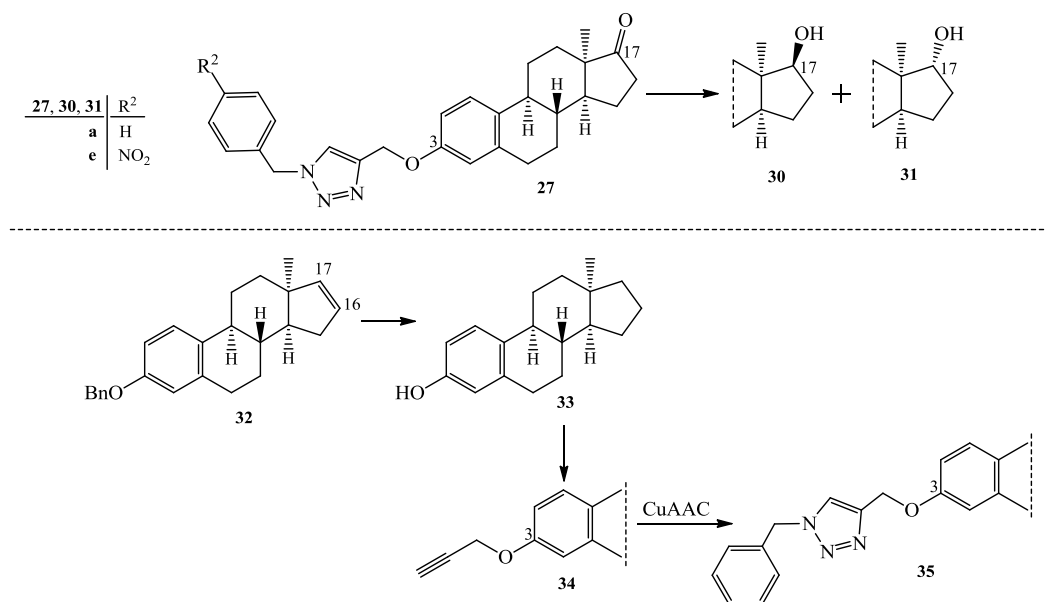
3.5. The „D-alkynes” (**21, 22**) were reacted with different benzyl azides via CuAAC reactions under the same reaction conditions as discussed in thesis 3.4. (Scheme 2). The cycloadditions resulted in conjugates (**27, 28**) bearing an *N*-benzyltriazolyl moiety attached to the opened ring D through an amide bond. All the reactions furnished the desired products regioselectively, in excellent yields, independently from the orientation of the angular methyl group, the position of the alkyne function and the nature of the *p*-substituent on benzyl azide.

3.6. The CuAAC reactions of the different steroid alkyne (**16–22**) were performed with steroid azides. Heterodimers (**23, 25, 27–29**: **f** and **g**) were formed, in which estrone units are connected through their D-A (**23, 25, 27**: **f** and **g**) or D-D (**28, 29**: **f** and **g**) rings (Scheme 2). The CuAAC reactions proceeded regioselectively, under short reaction times, in excellent yields (under the same conditions as described in thesis 3.4.), independently from the position of the alkyne function and the orientation of the 16-azide group.



Scheme 2

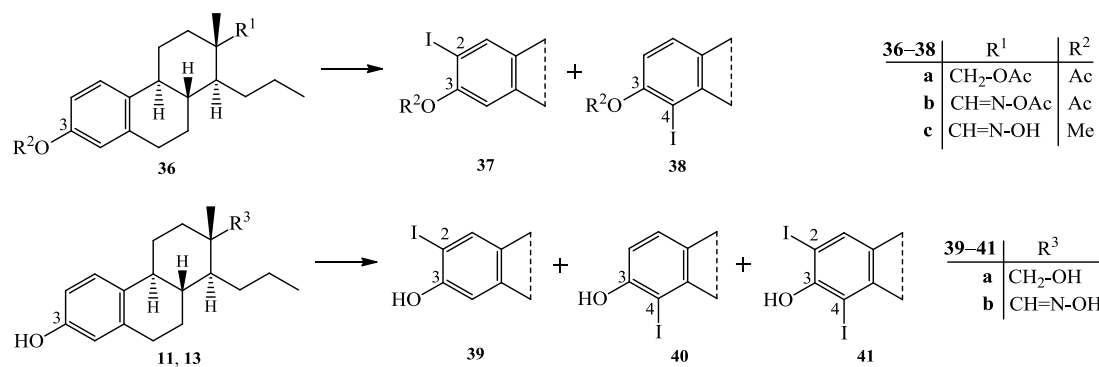
3.7. Triazolyl 13 $\alpha$ -estrone with intact ring D were further derivatized in order to investigate the impact of the oxygen function (at C-17) on the biological activity. Two „click”-products (**27a, e**) were chosen for reduction with sodium borohydride. The reactions resulted in a mixture of 17 $\alpha$ - (**30**) and 17 $\beta$ -hydroxy (**31**) compounds in a ratio of 1:1 (Scheme 3). Additionally, the 17-deoxy compound (**34**) was synthesized starting from the  $\Delta^{16,17}$ -derivative of 13 $\alpha$ -estrone (**32**) (under the same conditions as described in thesis 3.2.). The propargylated 17-deoxy derivative (**34**) was transformed into a triazole (**35**) via CuAAC reaction (under the same conditions as described in thesis 3.4.) (Scheme 3).



Scheme 3

3.8 We developed an efficient method for the iodination of the aromatic ring A of 13 $\beta$ -D-secoalcohols and -oximes (Scheme 4). The diacetate esters (**36a, b**), the 3-methyl ether (**36c**) and the 3-hydroxy derivatives (**11, 13**) were transformed with *N*-iodosuccinimide, in trifluoroacetic acid solvent, at room temperature. The reactions yielded the mixtures of regioisomeric iodo compounds (**37–41**).

3.9. We noticed that the ratio of the 2- and 4-iodo regioisomers depends on the nature of the functional group at C-3 (OAc, OMe, OH). The reactions proceeded chemoselectively and in case of the 3-protected derivatives (**36**) (OAc, OMe) regioselectively (**37:38**=3:1). The main product was the 2-iodo isomer (**37, 39**) in every case. The formation of the 2,4-*bis*iodo compound (**41**) was observed only in the presence of the phenolic OH group (**11, 13**) (**39:40:41**=2:1:1).

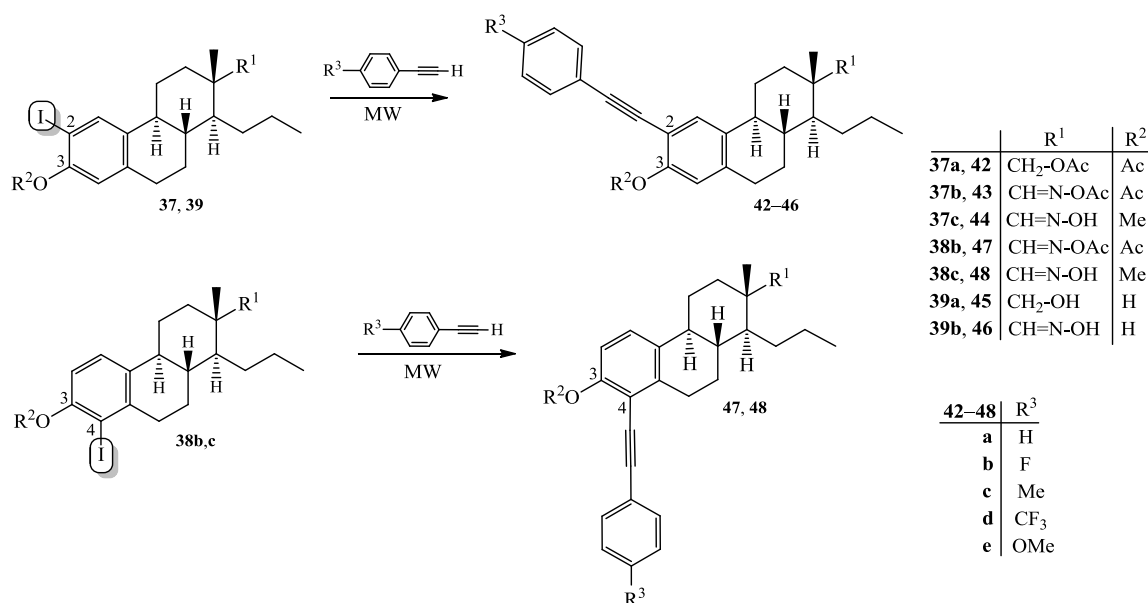


Scheme 4

3.10. We developed an efficient microwave-assisted method for the Sonogashira coupling of acetylated iodo compounds (**37a, b**; **38b**) and phenylacetylenes (Scheme 5). The 2- or 4-(phenethynyl)-products (**42, 43, 47**) were formed using 10 mol% Pd(OAc)<sub>2</sub> as catalyst and 5 mol% cataCXium A as ligand, in the presence of triethylamine base, under MW-irradiation (100 °C, 30 min) in good yields. The excess (3 equiv.) of the base and the high temperature led to the deacetylation and water elimination of the oxime function (**37b, 38b**), resulting in a D-seconitrile (**43, 47**) as an undesired product. Reactions of the 2-iodo derivative of D-secoalcohol diacetate (**37a**) with unsubstituted or *p*-substituted phenylacetylenes (under the same conditions as used for the coupling of oximes) furnished the desired 2-(phenethynyl) conjugates (**42**) in good yields without formation of any side-products (Scheme 5).

3.11. In the 3-methyl ether oxime series (**36c**) different Sonogashira conditions were established depending on the position of the iodine (Scheme 5). The sterically hindered 4-iodo isomer (**38c**) gave the desired 4-(phenethynyl) conjugates (**48**) in good yields, under the same conditions as described in thesis 3.10. The water elimination from the oxime function was avoided by decreasing the temperature from 100 °C to 60 °C and by shorter (20 min) MW-irradiation. The 2-iodo isomer (**37c**) was efficiently transformed under the same lowered temperature and shortened reaction time as it was established for the 4-iodo counterpart (**38c**). The Sonogashira couplings were achieved using 5 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> as catalyst, 2 mol% CuI co-catalyst and 3 equiv. of triethylamine, in tetrahydrofuran, in excellent yields (Scheme 5).

3.12. The 2-iodo compounds of 3-hydroxy-D-secooxime and -alcohol (**39a, b**) reacted with different phenylacetylenes under the same conditions as established for the appropriate 3-methyl ether (**37c**) (as described in thesis 3.11., Scheme 5). The best conversions were achieved using phenylacetylenes bearing an electron withdrawing group at *p*-position (**42–48 c and e**).



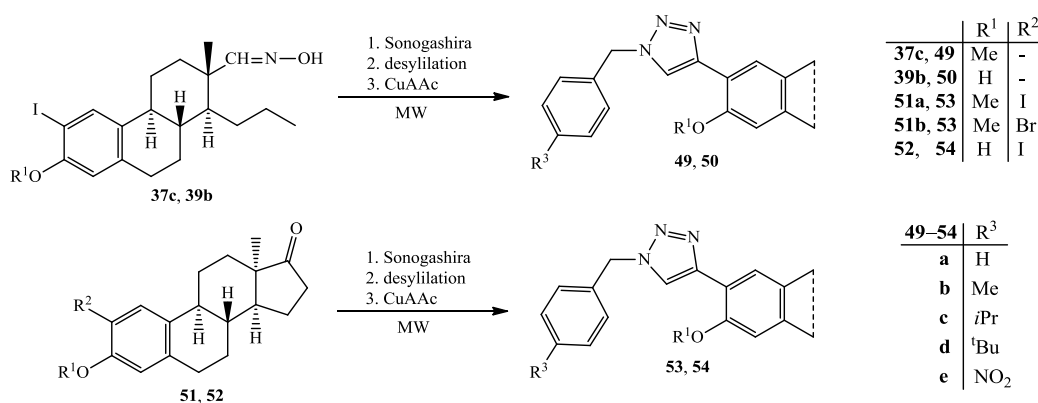
Scheme 5

3.13 Finally, we developed a microwave-assisted method for a step-by-step, one-pot Sonogashira-CuAAC reaction, on a steroid model. The TMS-ethynyl group was introduced into C-2 (**37c**, **39b**) by trimethylsilyl acetylene under the same conditions as described in thesis 3.11. (Scheme 6). The 2-(TMS-ethynyl) intermediate was further transformed without isolation. The silyl protecting group was removed via addition of 1 equiv. of tetrabutylammonium fluoride, then a CuAAC reaction was accomplished by the appropriate benzyl azide, under 20 min MW-irradiation at 60 °C. The reactions furnished the desired 2-triazolyl derivatives (**49**, **50**) stereoselectively, without steroidal side-product, under short reaction times and in good to excellent yields (Scheme 6).

3.14. The Sonogashira-CuAAC one-pot reaction of the 13 $\alpha$ -estrone 3-methyl ether was achieved from its 2-iodo and 2-bromo compound too (Scheme 6). Different Sonogashira conditions were established depending on the nature of the starting halogenated compound. The more reactive 2-iodo derivative (**51a**) was efficiently transformed into the desired Sonogashira product under copper and amine free conditions: using 5 mol% Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> as a catalyst, 6 equiv. of 1,4-diazabicyclo[2.2.2]octane as a base, in acetonitrile, under 100 °C, 10 min MW-irradiation. The less reactive 2-bromo steroid (**51b**) furnished the same 2-(TMS-ethynyl) intermediate using 5 mol% Pd(OAc)<sub>2</sub> as a catalyst and 2 mol% cataCXium A as a ligand, in the presence 3 equiv. of NEt<sub>3</sub>, in acetonitrile, by 20 min MW-irradiation. The next two steps were carried out under the same conditions as described in thesis 3.13. at 120°C.

The reactions led to the desired 2-triazolyl products (**53**) after 10 min, stereoselectively, in excellent yields.

3.15. The 3-hydroxy-2-iodo-13 $\alpha$ -estrone (**52**) furnished the appropriate 2-triazoles (**54**) under the same conditions as used for D-secooximes (**37c**, **39b**) (described in thesis 3.13.) stereoselectively, in excellent yields (Scheme 6).



Scheme 6

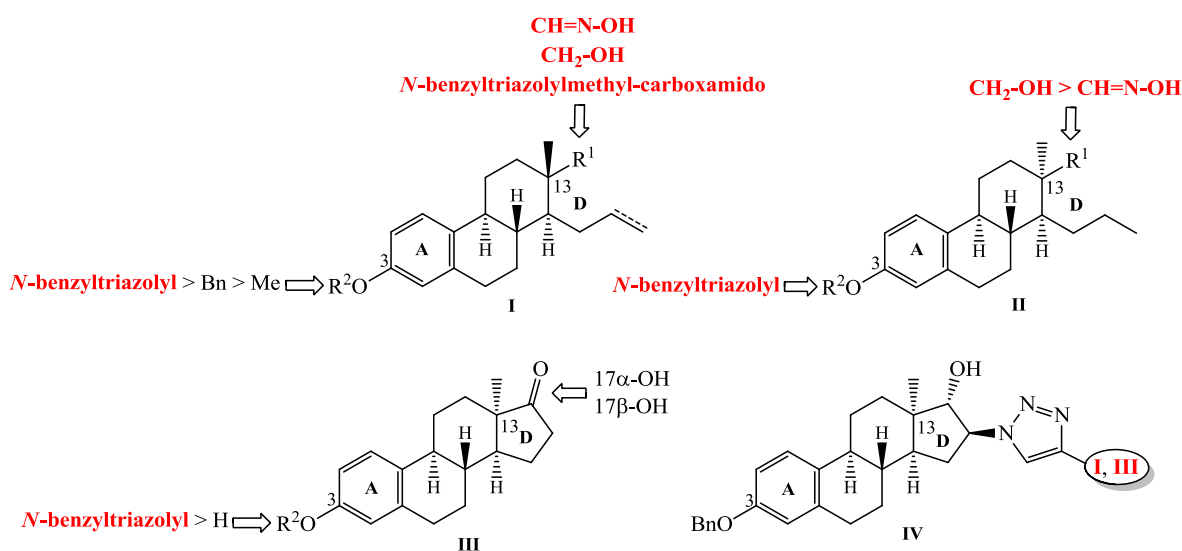
3.16. The antiproliferative effect of the compounds was investigated *in vitro* on human cancer cell lines: HeLa (cervix), A2780 (ovarian), MCF-7 (breast) and A431 (skin epidermoid) by means of MTT-assay at the Institute of Pharmacodynamics and Biopharmacy, University of Szeged. From the results we obtained the following structure-activity relationships. The 13 $\beta$ -epimers (**I**) are more potent than their 13 $\alpha$ -counterparts (**II**, Scheme 7). The etherification of the phenolic OH group improved the antiproliferative activity, which was further enhanced by the incorporation of a triazole moiety (**23–29: a–b**). The most potent conjugates were those bearing unsubstituted *N*-benzyl group (**23a–26a, 28ba**) or less bulky alkyl substituent on the benzyl ring (**23, 25, 28: b and c**). The significant activity of the better compounds makes them suitable for further investigations.

3.17. Concerning the antiproliferative behavior of the 13 $\alpha$ -estrone derivatives bearing intact ring D (**III**), the etherification of the phenolic OH group seemed to be disadvantageous (Scheme 7). The conjugation with benzyl azide (**27**) improved the antiproliferative effects, which were further enhanced by the reduction of the 17-oxo group in the case of the *p*-nitro-substituted “click” product (**30e, 31e**). The 17 $\alpha$ -hydroxy derivatives (**31**) were more potent than their 17 $\beta$ -isomers (**30**), however the 17-deoxy-triazole (**35**) proved to be inactive. It can



be stated that the presence of an oxygen-containing functionality at C-17 is essential for the antiproliferative activity.

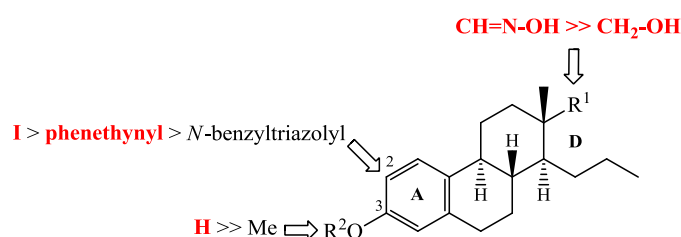
3.18. The antiproliferative activity of the heterodimers (**23**, **25**, **27–29**: **f** and **g**) was greatly influenced by the configuration of C-16 and C-17, namely the orientation of the triazolyl moiety and the hydroxyl group (Scheme 7). Only the 16 $\beta$ ,17 $\alpha$ -isomers (**23f**, **25f**, **27f–29f**) displayed significant antiproliferative effect in the diastereomer pair series. Furthermore the „D+A” type dimers (**23f**, **25f**, **27f**) were more potent than the „D+D” type conjugates (**28f**, **29f**).



Scheme 7

3.19. The 17 $\beta$ -HSD1 enzyme inhibitory potential of the compounds was investigated *in vitro* by radiosubstrate incubation method at the endocrine laboratory of the 1<sup>st</sup> Department of Medicine, University of Szeged. From the results – measured in HEPES buffer medium (pH=7.3), in the presence of an excess of NADPH cofactor – we established the following structure-activity relationships. Concerning the inhibitory data obtained for the basic D-secoestrone, it can be stated that the presence of the 13 $\beta$ -methyl group is more favorable than its 13 $\alpha$ -counterpart (Scheme 8). The presence of the 3-OH function is advantageous over the ether groups. The outstanding nanomolar inhibitory potential of the 13 $\beta$ -D-secooxime (**13**) decreased to micromolar in the 3-methyl ether of 13 $\beta$ -D-secooxime. The 13 $\beta$ -D-secooxime (**13**) proved to be as potent as the most effective 17 $\beta$ -HSD1 inhibitors described in the literature.

3.20. From the 17 $\beta$ -HSD1 enzyme inhibitory data of the derivatives prepared by the transformation of the aromatic ring of D-secoestrone (**11**, **13**, **36**), we established the following structure-activity relationships. The iodination of the aromatic ring (**37–41**) proved to be advantageous on the secoalcohol core (**11**), but disadvantageous on the secooxime (**13**) (Scheme 8). From the comparison of the results obtained for the 2- and the 4-phenethynyl derivatives (**42–48**) we established that only the 3-hydroxy oximes conjugated at C-2 (**46**) display good inhibitory properties. The exchange of the apolar 2-phenethynyl moiety to the more polar benzyltriazolyl one did not influence the inhibitory properties in the 3-hydroxy D-secooxime (**50**) series markedly. It can be stated that the outstanding inhibitory properties of the basic D-seco compounds could not be improved by the modifications at ring A.



Scheme 8

#### 4. Publications directly related to the dissertation

1. Mernyák E., **Szabó J.**, Bacsa I., Huber J., Schneider G., Minorics R., Bózsity N., Zupkó I., Varga M., Bikadi Zs., Hazai E., Wölfling J. Synthesis and antiproliferative effect of D-homo- and D-secoestrone, *Steroids*, **2014**, 87, 128–136. **IF: 2,639**
2. Mernyák E., Fiser G., **Szabó J.**, Bodnár B., Schneider G., Kovács I., Ocsovszki I., Zupkó I., Wölfling J., Synthesis and *in vitro* antiproliferative evaluation of D-secooxime derivatives of the 13 $\beta$ - and 13 $\alpha$ -estrone, *Steroids*, **2014**, 89, 47–55. **IF: 2,639**
3. **Szabó J.**, Bacsa I., Wölfling J., Schneider G., Zupkó I., Varga M., Herman B.E., Kalmár L., Szécsi M., Mernyák E., Synthesis and *in vitro* pharmacological evaluation of *N*-[(1-benzyl-1,2,3-triazol-4-yl)methyl]-carboxamides on D-secoestrone scaffolds, *J Enzyme Inhib Med Chem*, **2016**, 31, 574–579. **IF: 3,428**
4. **Szabó J.**, Jerkovics N., Schneider G., Wölfling J., Bózsity N., Minorics R., Zupkó I., Mernyák E., Synthesis and *in vitro* antiproliferative evaluation of C-13 epimers of

triazolyl-D-secoestrone alcohols: the first potent 13a-D-secoestrone derivative, *Molecules*, **2016**, *21*, 611–623. **IF: 2,465**

5. Szabó J., Pataki Z., Wölfling J., Schneider G., Minorics R., Zupkó I., Mernyák E., Synthesis and biological evaluation of 13a-estrone derivatives as potential antiproliferative agents, *Steroids*, **2016**, *113*, 14–21. **IF: 2,639**
6. Herman B.E., Szabó J., Bacsa I., Wölfling J., Schneider G., Bálint M., Hetényi Cs., Mernyák E., Szécsi M., Comparative investigation of the *in vitro* inhibitory potencies of 13-epimeric estrones and D-secoestrone toward 17 $\beta$ -hydroxysteroid dehydrogenase type 1 enzyme, *J Enzyme Inhib Med Chem*, **2016**, *31*, 574–579. **IF: 3,428**

**Total impact factor: 17,238**

## 5. Other publications

1. Mernyak E., Huber J., Szabó J., Schneider G., Hetényi A., Márk L., Maász G., Berényi Á., Kovács I., Minorics R., Zupkó I., Wölfling J., Cycloaddition of steroidal cyclic nitrones to C=N dipolarophiles: Stereoselective synthesis and antiproliferative effects of oxadiazolidinones in the estrone series, *Steroids*, **2013**, *78*, 1021–1028. **IF: 2,716**
2. Bózsity, N., Minorics, R., Szabó, J., Mernyák, E., Schneider, G., Wölfling, J., Wang, H-C., Wu, C-C., Ocsóvszki, I., Zupkó, I. Mechanism of antiproliferative action of a new D-secoestrone-triazole derivative in cervical cancer cells and its effect on cancer cell motility, *J Steroid Biochem Mol Biol*, **2017**, *165*, 247–257. **IF: 3,985 (2015)**
3. Bodnár, B., Mernyák, E., Szabó, J., Wölfling, J., Schneider, G., Zupkó, I., Kupihár, Z., Kovács, L. Synthesis and *in vitro* investigation of potential antiproliferative monosaccharide-D-secoestrone bioconjugates, *Bioorg Med Chem Lett*, **2017**, DOI: 10.1016/j.bmcl.2017.03.029. **IF: 2,486 (2015)**

**Total impact factor: 9,187**

## 6. Lectures and posters related to the dissertation

### Lectures

1. **Szabó J.** *Biológiailag aktív konjugátumok szintézise módosított ösztrán vázon*, MTA Szteroid és Terpenoidkémiái Munkabizottsági Ülés, **2016**, Szeged.
2. **Szabó J.**, Pancza T., Jerkovics N., Schneider G., Wölfling J., Herman B.E., Szécsi M., Bózsity N., Minorics R., Zupkó I., Mernyák E., *Szelektív antitumor hatású D-szekoöszttronok szintézise*, Innováció a Természettudományban – Doktorandusz Konferencia, **2015**, Szeged.
3. Herman B., **Szabó J.**, Wölfling J., Schneider G., Kalmár L., Valkusz Zs., Mernyák E., Szécsi M., *A 17 $\beta$ -HSD1 enzimaktivitás in vitro vizsgálata és gátlása D-szekoöszttron származékokkal*, Innováció a Természettudományban – Doktorandusz Konferencia, **2015**, Szeged.
4. **Szabó J.** *Heterociklusos, antitumor hatású öszttron-konjugátumok szintézise*, MTA Szteroid és Terpenoidkémiái Munkabizottsági Ülés, **2014**, Szeged.
5. **Szabó J.**, Pálházi B., Pataki Z., Wölfling J., Schneider G., Huber J., Zupkó I., Mernyák E., *The preparation of novel antitumor steroid conjugates*, 1<sup>st</sup>Innovationin Science 2014 – Doctoral Student Conference, **2014**, Szeged.
6. Bacsa I., **Szabó J.**, Wölfling J., Schneider G., Zupkó I., Mernyák E., *Synthesis and in vitro pharmacological evaluation of novel steroidal alkynes and their derivatives*, 1<sup>st</sup>Innovationin Science 2014 – Doctoral Student Conference, **2014**, Szeged.
7. Pálházi Balázs, **Szabó J.**, Wölfling J., Schneider G., Bózsity N., Minorics R., Zupkó I., Mernyák E., *Biológiailag aktív öszttron-dimerek szintézise*, XXXVII. Kémiai Előadói Napok, **2014**, Szeged.
8. Herman B.E., **Szabó J.**, Kalmár L., Wölfling J., Schneider Gy., Julesz J., Valkusz Zs., Mernyák E., Szécsi M., *In vitro investigation of 17 $\beta$ -HSD1 enzyme activity and its inhibition with 13 $\alpha$ -estrone derivatives (A 17 $\beta$ -HSD1 enzimaktivitás in vitro vizsgálata és gátlása 13 $\alpha$ -öszttron származékokkal)*, XX. Nemzetközi Vegyészkonferencia, **2014**, Kolozsvár.
9. Herman B., **Szabó J.**, Szabó N., Pataki Z., Wölfling J., Schneider G., Valkusz Zs., Mernyák E., Szécsi M., *13 $\alpha$ -Öszttron származékok 17 $\beta$ -HSD1 gátlásának vizsgálata in vitro radiosubsztrát inkubációs módszerrel*, MTA Szteroid és Terpenoidkémiái Munkabizottság előadójelentése, **2014**, Szeged.
10. **Szabó J.**, Mernyák E., Minorics R., Bózsity N., Zupkó I., *Új D-homo- és D-szekoöszttron-származékok szintézise és hatástani vizsgálata*, XXXVI. Kémiai Előadói Napok, Nívódíjas előadások, **2013**, Szeged.

## Posters

1. Herman B.E., **Szabó J.**, Bacsa I., Wölfling J., Schneider G., Gardi J., Valkusz Zs., Mernyák E., Szécsi M.: *A 17 $\beta$ -HSD1 enzimaktivitás in vitro gátlása ösztрон és 13 $\alpha$ -ösztрон származékokkal*, Magyar Endokrinológiai és Anyagcsere Társaság XXVI. Jubileumi Kongresszusa, **2016**, Szeged.
2. **Szabó J.**, Pancza T., Herman B.E., Schneider G., Wölfling J., Szécsi M., Mernyák E., *Pd-katalizált keresztkapcsolás ösztрон származékok A-gyűrűjében*, 2. Nemzeti Konferencia, **2015**, Hajdúszoboszló.
3. Herman B.E., **Szabó J.**, Pataki Z., Wölfling J., Schneider G., Szécsi M., Mernyák E., *13 $\alpha$ -ösztронtriazolok szintézise és 17 $\beta$ -HSD1 gátlásának in vitro vizsgálata*, 2. Nemzeti Konferencia, **2015**, Hajdúszoboszló.
4. **Szabó J.**, Herman B.E., Wölfling J., Schneider G., Szécsi M., Mernyák E., *Synthesis of D-secoalcohols and D-secooximes in the 13 $\alpha$ - and 13 $\beta$ -estrone series as potential 17 $\beta$ -HSD type 1 inhibitors*, V. Meeting of the Paul Ehrlich MedChem Euro-PhD Network, **2015**, Krakow, Poland.
5. **Szabó J.**, Jerkovics N., Herman B.E., Schneider G., Wölfling J., Minorics R., Bózsity N., Zupkó I., Szécsi M., Mernyák E., *Preparation and antiproliferative screening of heterocycle-fused D-secoalcohols in the 13 $\alpha$ - and 13 $\beta$ -estrone series*, IX<sup>th</sup> Joint Meeting in Medicinal Chemistry, **2015**, Athene, Greece.
6. Bózsity N., Minorics R., Mernyák E., **Szabó J.**, Schneider G., Wölfling J., Hui-Chun Wang, Chin-Chung Wu, Zupkó I., *D-secoestronetriazol: A new secoestrone derivative with antiproliferative and antimigration effects in cervical cancer cells*, The 20<sup>th</sup> World Congress on Advances in Oncology and 18<sup>th</sup> International Symposium on Molecular Medicine, **2015**, Athene, Greece.
7. **Szabó J.**, Pálházi B., Wölfling J., Schneider G., Minorics R., Zupkó I., Mernyák E., *Preparation and antiproliferative screening of new type of steroid dimers*, 22<sup>nd</sup> Conference on Isoprenoids, **2014**, Prague, Czech Republic.
8. **Szabó J.**, Pataki Z., Wölfling J., Schneider G., Zupkó I., Mernyák E., *Synthesis of novel anticancer 13 $\alpha$ -estrone conjugates*, 22<sup>nd</sup> Conference on Isoprenoids, **2014**, Prague, Czech Republic.
9. **Szabó J.**, Bacsa I., Wölfling J., Schneider G., Zupkó I., Mernyák E., *Synthesis of novel antiproliferative D-secoalkynes of 13 $\alpha$ - and 13 $\beta$ -estrone and their heterocyclic derivatives*, 20<sup>th</sup> International Conference on Organic Synthesis, **2014**, Budapest.
10. **Szabó J.**, Bodnár B., Wölfling J., Schneider G., Zupkó I., Mernyák E., *Preparation of novel cytostatic D-secoestrone conjugates*, 20<sup>th</sup> International Conference on Organic Synthesis, **2014**, Budapest.
11. **Szabó J.**, Mernyák E., Schneider G., Wölfling J., Minorics R., Bózsity N., Zupkó I., *Új D-homológok és D-szeko-származékok szintézise és hatástani vizsgálata az ösztрон sorban*, Vegyész Konferencia, **2013**, Hajdúszoboszló.

## 7. Lectures and posters not related to the dissertation

### Lecture

**Szabó J.**, Gyurcsik B., *Preparation and investigation of artificial zinc-finger fusion proteins*, Tsukuba Global Science Week, Leading Graduate Schools International Conference 2012, **2012**, Tsukuba, Japan.

### Poster

**Szabó J.**, Gyurcsik B., *Preparation and investigation of artificial zinc-finger fusion proteins*, Tsukuba Global Science Week, Leading Graduate Schools International Conference 2012, **2012**, Tsukuba, Japan.