1st International Conference
on Chemo and BioInformatics
ICCBIKG 2021

# ICCBIKG

1st International Conference on
Chemo and BioInformatics

# BOOK OF PROCEEDINGS

October 26-27th, 2021,
Kragujevac, Serbia

www.iccbikg.kg.ac.rs

Ministry of Education, Science and Technological Development of the Republic of Serbia

SHIMADZU
Excellence in Science

KEFO
SINCE 1949

Alfamed

UNI-CHEM

SUPERLAB
Your Lab - Our Passion

ART WINE

ICCBIKG
1st International Conference on Chemo and BioInformatics

1st International Conference on Chemo and BioInformatics
**ICCBIKG 2021**

# BOOK OF PROCEEDINGS

October 26-27, 2021
Kragujevac, Serbia

Sponsored by

Ministry of Education, Science and Technological Development of the Republic of Serbia

SUPERLAB
Your Lab - Our Passion

SHIMADZU
Excellence in Science

KEFO
SINCE 1949

ART WINE

UNI-CHEM

Alfamed

1st International Conference on Chemo and BioInformatics, Kragujevac, October 26-27, 2021 Serbia

**Editors:**

Professor Zoran Marković

Professor Nenad Filipović

**Technical Editors:**

Vladimir Simić

Izudin Redžepović

Nikola Srećković

**Illustrations:**

Igor Stanković, „Vector Alchemist“ d.o.o.

**Publisher:**

Institute for Information Technologies, University of Kragujevac, Serbia, Jovana Cvijića bb, 2021

**Press:**

„Grafo Ink“, Kragujevac

**Impression:**

120 copies

CIP - Каталогизација у публикацији - Народна библиотека Србије, Београд

54:004(048)(0.034.2)
57+61]:004(082)(0.034.2)

INTERNATIONAL Conference on Chemo and BioInformatics (1 ; 2021 ; Kragujevac) Book of Proceedings [Elektronski izvor] / 1st International Conference on Chemo and BioInformatics, ICCBIKG 2021, October 26-27, 2021 Kragujevac, Serbia ; [editors Zoran Marković, Nenad Filipović]. - Kragujevac : University, Institute for Information Technologies, 2021 (Kragujevac : Grafo Ink). - 1 USB fleš memorija ; 3 x 2 x 1 cm

Sistemski zahtevi: Nisu navedeni. - Nasl. sa naslovne strane dokumenta. - Tiraž 120. - Bibliografija uz svaki rad.

ISBN 978-86-82172-01-7

a) Хемија - Информациона технологија - Зборници b) Биомедицина - Информациона технологија - Зборници

COBISS.SR-ID 48894473

# Organized by

- Institute for Information Technologies, Organizer


- Faculty of Science, University of Kragujevac, Suborganizer


- Faculty of Engineering, University of Kragujevac, Suborganizer


- University of Kragujevac, Supporting organization

- The Ministry of Education, Science and Technological Development of The Republic of Serbia, Supporting organization

# Committees

## International Organizing Committee:

| | |
|---|---|
| **Chairman:** | Prof. Zoran Marković (Serbia) |
| **Vice-chairmans:** | Prof. Zlatan Car (Croatia) |
| | Prof. Carlos Silva Lopez (Spain) |

### Members:

Dr Dejan Milenković (Serbia), Dr Dubravka Živković (Serbia), Dr Biljana Šmit (Serbia), Dr Miljan Milošević (Serbia), Dr Edina Avdović (Serbia), Dr Aleksandar Ostojić (Serbia), Dr Verica Jevtić (Serbia), Dr Milan Kovačević (Serbia), Dr Dragana Šeklić (Serbia), Dr Sanja Matić (Serbia), Dr Dušica Simijonović (Serbia), Dr Aleksandar Nikolić (Serbia), Dr Tatjana Miladinović (Serbia), Dr Saša Ćuković (Serbia), Dr Biljana Glišić (Serbia), Dr Vladimir Petrović (Serbia), Dr Andrija Ćirić (Serbia), Dr Nenad Janković (Serbia).

## International Scientific Committee:

| | |
|---|---|
| **Chairman:** | Prof. Nenad Filipović (Serbia) |
| **Vice-chairmans:** | Prof. Claudio Santi (Italy) |
| | Prof. Goran Kaluđerović (Germany) |

### Members:

Prof. Zoran Marković (Serbia), Prof. Ivan Gutman (Serbia), Prof. Miloš Kojić (USA), Prof. Velimir Popsavin (Serbia), Prof. Miloš Đuran (Serbia), Prof. Nenad Kostić (USA), Prof. Ljiljana Kolar-Anić (Serbia), Prof. Svetlana Marković (Serbia), Prof. Snežana Zarić (Serbia), Prof. Marija Stanić (Serbia), Prof. Biljana Petrović (Serbia), Prof. Dobrica Milovanović (Serbia), Prof. Miroslav Živković (Serbia), Prof. Nenad Grujović (Serbia), Prof. Dragoslav Nikezić (Serbia), Prof. Zlatan Car (Crotaia), Prof. Ivan Potočňák (Slovakia), Prof. Luciano Saso (Italy), Prof. Dražen Vikić-Topić (Croatia), Prof. Bakhtiyor Rasulev (USA), Prof. Erik Klein (Slovakia), Prof. Viktor Stefov (Macedonia), Prof. Svetlana Simova (Bulgaria), Prof. Enver Karahmet (Bosnia and Herzegovina), Prof. Themis Exarchos (Greece), Prof. Carlos Silva Lopez (Spain), dr. sc. Mario Vazdar (Czech Republic), Prof. Arturas Ziemys (USA), Prof. Jasmina Dimitrić-Marković (Serbia), Prof. Snežana Bogosavljević Bošković (Serbia), Prof. Jasmina Stevanović (Serbia).

# Local Executive Committee:

| | |
|---|---|
| **Chairman:** | Dr Dejan Milenković (Serbia) |
| **Vice-chairmans:** | Dr Jelena Đorović Jovanović (Serbia) |
| | Dr Jelena Katanić Stanković (Serbia) |

## Members:

Dr Darko Ašanin (Serbia), Dr Emina Mrkalić (Serbia), Žiko Milanović (Serbia), Vladimir Simić (Serbia), Bogdan Milićević (Serbia), Aleksandar Milovanović (Serbia), Nevena Veselinović (Serbia), Izudin Redžepović (Serbia), Nikola Srećković (Serbia).

doi: 10.46793/ICCBI21.403JS

# BINDING OF 17-SUBSTITUTED 16-NITRILE 16,17-SECOESTRANE COMPOUNDS TO ESTROGEN RECEPTORS - *IN VITRO* AND *IN SILICO* STUDY

**Suzana S. Jovanović-Šanta[1], Esma Isenović[2], Julijana A. Petrović[1], Yaraslau U. Dzichenka[3]**

[1] University of Novi Sad Faculty of Sciences, Department of Chemistry, Biochemistry and Environmental Protection, Trg Dositeja Obradovića 3, 21000 Novi Sad, Serbia
e-mail: suzana.jovanovic-santa@dh.uns.ac.rs
[2] Department of Radiobiology and Molecular Genetics, Institute for Nuclear Sciences "Vinča" 11000 Belgrade, Serbia
e-mail: isenovic@yahoo.com
[3] Institute of Bioorganic Chemistry, National Academy of Sciences, Kuprevich str. 5/2, 220141, Minsk, Belarus
e-mail: dichenko@iboch.by

## Abstract

About 75% of breast cancers express estrogen receptors (ERs), which is a good base for an efficient endocrine therapy. This gives the opportunity for the treatment of patients with antiestrogens, compounds that bind to the ERs and thus compete to estradiol (E2), preventing its action in progression of estrogen-depending cancers.

Here we present results of testing the effect of the modified steroids, namely 17-substituted 16-nitrile 16,17-secoestrane compounds on the E2-ER complex forming, its stability, nuclear translocation and binding to DNA. Almost all compounds in moderate to high rate induced lower forming of this complex, destabilizing it – they increased $K_d$ of this complex and decreased number of binding sites. Complex formed in the presence of some test secosteroids could pass to the nucleus, while other compounds inhibited translocation. In the presence of some compounds binding of the formed complex E2-ER to DNA was noticed.

Docking followed molecular dynamics simulation was performed to reveal binding mode of E2 to ER in the presence of test secosteroids. Amino acids important for binding process and complex stabilization were detected. Analysis of the simulation data allowed identifying key amino acids and type of binding of the secoestrane compounds, important for high affinity binding of the steroidal compounds.

**Keywords**: ER, secoestrane compounds, docking, molecular dynamics

## 1. Introduction

17β-Estradiol (E2), the main circulating estrogen hormone, regulates many physiological functions, where many of them are specific for female reproductive tissues. The effects of E2 on human cells are mediated by the estrogen receptors ERα and ERβ and complex transcription machinery. The ERs express similar, still different, regulatory potentials of cellular growth, differentiation and death. According to that, changes in E2 signaling *via* E2-ER could be important factors in the initiation and progression of malignancies, including cancers of reproductive tissues [1].

Many research studies are directed towards better understanding of the mechanisms which encompasses ERs, in order to get information necessary for discovery of novel and better drugs

for treatment of estrogen hormone dependent diseases, with substantial impacts on the systemic management of target tissue [2, 3].

There are two main strategies in the biology-driven medicinal chemistry of the drug development for the treatment of hormone-dependent diseases: A. development of compounds that inhibit enzymes that are essential for biosynthesis of active steroid hormones (e.g., aromatase for the treatment of estrogen-dependent breast cancer) and B. development of compounds that compete with the appropriate receptor proteins (e.g. estrogen receptor antagonists, such as 4-hydroxytamoxifen), as presented at Figure 1.

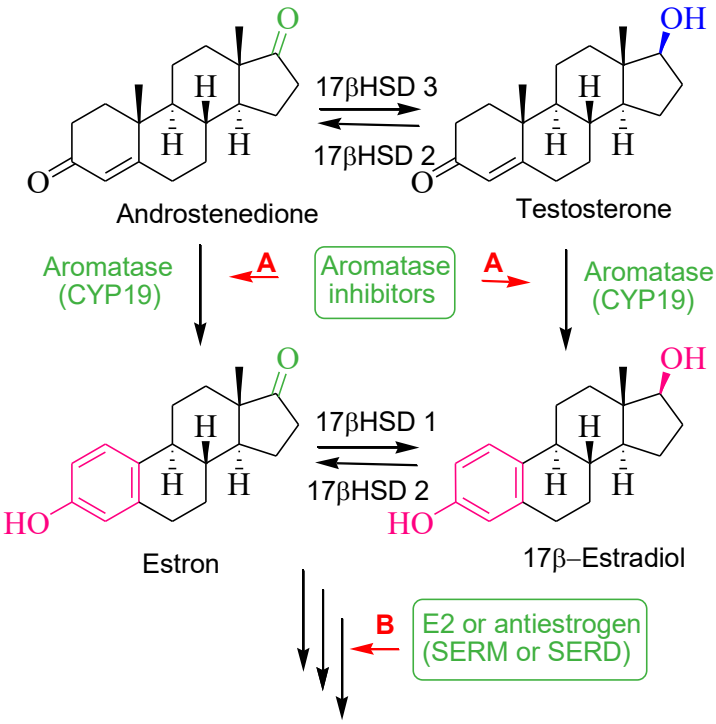


Fig. 1. Different strategies in the treatment of estrogen-dependent diseases: A. Lowering of biosynthesis of active estrogen hormones by inhibition of aromatase (CYP19) activity, and B. Lowering of the estradiol effect by blocking of E2-ER complex forming.

Binding of natural ligand or antagonist (steroidal or non-steroidal) causes different changes in the tertiary structure of the receptor, which allows ER signaling pathway continuation or suspension, as discovered in the studies of the complexes of ER with E2 and ER antagonist 4-hydroxytamoxifen [4, 5].

Modified estradiol-based steroids, including substituted, homo-, epi- and secoestranes, proved to be good partial or full antiestrogens (selective estrogen receptor modulators, SERMs, or down regulators, SERDs). Among them, D ring-secosteroids were of particular interest, since the modification of the rigid tetracyclic steroidal carbon skeleton by cleavage of the internal C-C bond provides more flexible compounds with new biological properties.

Based on known pharmacological effects of some secoestrane compounds [6, 7], binding of 16,17-secoestrane compounds was tested independently in *in vitro* and *in silico* experiments and results are compoared.

## 2. Results and discussion

The effect of secosteroids onto the estradiol binding to the estrogen receptors is measured *in vitro* by known procedure [7], by measuring binding parameters, namely dissociation constant of E2-ER complex and receptor number, as well as the forming, stability, nuclear translocation and binding to DNA of the complex formed. Almost all 17-substituted 16,17-secoestrane compounds inhibited E2-ER complex forming, which was obvious from increasing of $K_d$ of this complex and decreasing of binding sites number in the presence of secosteroids. Complex formed in the presence of some test secosteroids in some extent could pass to the nucleus, while other compounds inhibited translocation. In the presence of some compounds binding of the formed complex E2-ER to DNA was noticed.

Docking of ERα ligands was performed using of AutoDock Vina software (v.1.1.2) with next parameters: exhaustiveness: 256; energy range: 4 kcal/mol; number of binding modes: 20. Box dimensions and coordinates of the "docking box" for the tested compounds were picked according to their size. After docking all hits were ranked according to their RMSD towards similar known ligands, presented in corresponding structures from Protein Data Bank and according to values of AutoDock Vina scoring function. Spatial structures of steroidal derivatives were built from their 2D structures using MolView service. Structures were minimized in UCSF Chimera software before docking procedure. Molecular dynamics (MD) simulations were performed in explicit solvent (water, octahedron cell, TIP3P model). Experiment included next steps: minimization of the solvent (2000 steps), minimization of the whole system (2000 steps), heating of the system (NVT ensemble, 1 ns, temperature range: 0-298.15 K), equilibration (NPT ensemble, 1 ns), production (NPT ensemble, 50 ns).

*In silico* screening of binding affinity of the modified steroids toward ERα showed that interaction energy for the tested ligands is comparable with consequent value, calculated for the estradiol. Analysis of MD trajectories showed that tested compounds do not act dramatically on the receptor structure. It was found that radius of gyration (Rg) for all complexes quite similar and does not exceed 19,5 Å. Analysis of RMSF curves states that main differences between ligand-receptor complexes are located in coils, while amino acids forming binding pocket (residues 344-351, 386-394, 422-430, 518-525) are relatively stable during 50 ns MD simulation. RMSD for $C_a$ atoms of the receptor also does not exceed 4.5 Å during simulation.

Modified steroids interact with key points of the flexible hydrophobic ligand binding pocket (LBP) of estrogen receptor α (ERα), occupying the remaining large volume of the LBP equivalent to rings of the steroids

## 3. Conclusions

*In silico* studies (docking and molecular dynamics simulation) were performed to reveal binding mode of E2 to ER in the presence of test secosteroids and amino acids important for binding to ER, as well as E2-ER complex stabilization. Simulation data directed identification of the key amino acids and type of binding of the secoestrane compounds, which explain high affinity binding of steroidal compounds.

## Acknowledgment

The authors acknowledge financial support of the Ministry of Education, Science and Technological Development of the Republic of Serbia (Grant No. 451-03-9/2021-14/ 200125).

## References

[1] P. Yaşar, G. Ayaz, S. D. User, G. Güpür, M. Muyan, *Molecular mechanism of estrogen–estrogen receptor signaling*, Reproductive Medicine and Biology, 16 (2017) 4–20.
[2] C. Avendano, J.C. Menendez, *Medicinal Chemistry of Anticancer Drugs*, Elsevier, Oxford, 2008.

[3] J.R. Pasqualini, C. Sumida, N. Giambiagi, *Pharmacodynamic and biological effects of anti-estrogens in different models*. Journal of Steroidal Biochememistry, 31(4B) (1988) 613-643.

[4] A.M. Brzozowski, A.C.W. Pike, Z. Dauter, R.E. Hubbard, T. Bonn, O. Engstrëm, L. Öhman, G.L. Greene, J.A. Gustafsson, M. Carlquist, *Molecular basis of agonism and antagonism in the oestrogen receptor*. Nature, 389 (1997) 753–758.

[5] A.K. Shiau, D. Barstad, P.M. Loria, L. Cheng, P.J. Kushner, D.A. Agard, G.L. Greene, *The Structural Basis of Estrogen Receptor/Coactivator Recognition and the Antagonism of This Interaction by Tamoxifen*, Cell, 95 (1998) 927–937.

[6] J. Szabó , I. Bacsa , Jónos Wölfling , G. Schneider, I. Zupkó, M. Varga, B.E. Herman, László Kalmár , M. Szécsi, E. Mernyák, *Synthesis and in vitro pharmacological evaluation of N-[(1-benzyl-1,2,3- triazol-4-yl)methyl]-carboxamides on D-secoestrone scaffolds*, Journal of Enzyme Inhibition and Medicinal Chemistry, 31(4) (2016) 574–579.

[7] S. Jovanović-Šanta, J. Petrović, M. Sakač, Z. Žakula, E. Isenović, N. Ribarac-Stepić, *The influence of 17-oxo- and 17-hydroxy-16,17-seco-estratriene derivatives on estrogen receptor*, Collection of Czechoslovak Chemical Communications, 71 (2006) 532-542.