medical sciences forum

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Abstract

Identification of Novel ERβ Ligands †

Sofija S. Bekić [1,*], Andrea R. Nikolić [1], Marija N. Sakač [1], Edward T. Petri [2] and Anđelka S. Ćelić [2]

[1] Department of Chemistry, Biochemistry and Environmental Protection, Faculty of Sciences, University of Novi Sad, Trg Dositeja Obradovića 3, 21000 Novi Sad, Serbia
[2] Department of Biology and Ecology, Faculty of Sciences, University of Novi Sad, Trg Dositeja Obradovića 2, 21000 Novi Sad, Serbia
* Correspondence: sofija.bekic@dh.uns.ac.rs
† Presented at the 8th International Electronic Conference on Medicinal Chemistry, 1–30 November 2022; Available online: https://ecmc2022.sciforum.net/.

Abstract: The estrogen receptor (ER) is a major therapeutic target in treating estrogen-related diseases, such as breast cancer. There is a need to develop potent ER ligands capable of selectively targeting cancer cells without affecting normal cells. Blocking ERα action by antagonists and inhibiting steroidogenic enzymes has been standard therapy in breast cancer treatment for many years. On the other hand, the ERβ isoform usually has antiproliferative and tumor-suppressive functions, so targeting ERβ with specific agonists represents a promising new approach not only in breast cancer but also in prostate cancer therapy. Besides the anticancer activity of ERβ agonists, their application is considered in treating depression, anxiety, and inflammation. To obtain potent antiproliferative agents, a triazole ring is often incorporated as a pharmacophore in the steroid skeleton. This study evaluates the binding affinity of novel *N*(2)-substituted D-condensed steroidal triazoles for ligand-binding domains (LBDs) of ERβ and androgen receptors using a yeast-based fluorescent assay. The LBD of the steroid receptor was expressed in-frame with a yellow fluorescent protein (YFP) in *Saccharomyces cerevisiae*. Upon ligand-binding induced dimerization, fluorescence resonance energy transfer (FRET) between YFP molecules was analyzed using fluorescence spectroscopy and microscopy. We identified new selective ERβ ligands without androgenic properties, but further experiments are required to determine whether their mechanism of action is agonistic or antagonistic. Considering the broad therapeutic potential of specific ERβ ligands, our findings indicate that steroid derivatives containing triazole are promising bioactive compounds in the field of anticancer agents.

Keywords: biosensor; cancer; estrogen receptor β; ligand; steroid receptor; triazole

Citation: Bekić, S.S.; Nikolić, A.R.; Sakač, M.N.; Petri, E.T.; Ćelić, A.S. Identification of Novel ERβ Ligands. *Med. Sci. Forum* **2022**, *14*, 40. https://doi.org/10.3390/ECMC2022-13154

Academic Editor: Alfredo Berzal-Herranz

Published: 1 November 2022

Supplementary Materials: The presentation material of this work is available online at https://www.mdpi.com/article/10.3390/ECMC2022-13154/s1.

Author Contributions: Conceptualization, A.S.Ć. and E.T.P.; methodology, S.S.B. and A.R.N.; software, S.S.B.; validation, A.S.Ć., E.T.P. and S.S.B.; formal analysis, S.S.B.; investigation, S.S.B., A.R.N. and M.N.S.; resources, A.S.Ć., E.T.P. and M.N.S.; data curation, S.S.B. and A.S.Ć.; writing—original draft preparation, S.S.B.; writing—review and editing, A.S.Ć., A.R.N. and E.T.P.; visualization, S.S.B.; supervision, A.S.Ć. and E.T.P.; project administration, M.N.S.; funding acquisition, M.N.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Ministry of Education, Science and Technological Development of the Republic of Serbia [Grant No. 451-03-68/2022-14/200125] and the Provincial Secretariat for Higher Education and Scientific Research of the Autonomous Province of Vojvodina [Project: New steroid derivatives - potential chemotherapeutics, No. 142-451-2667/2021].

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.