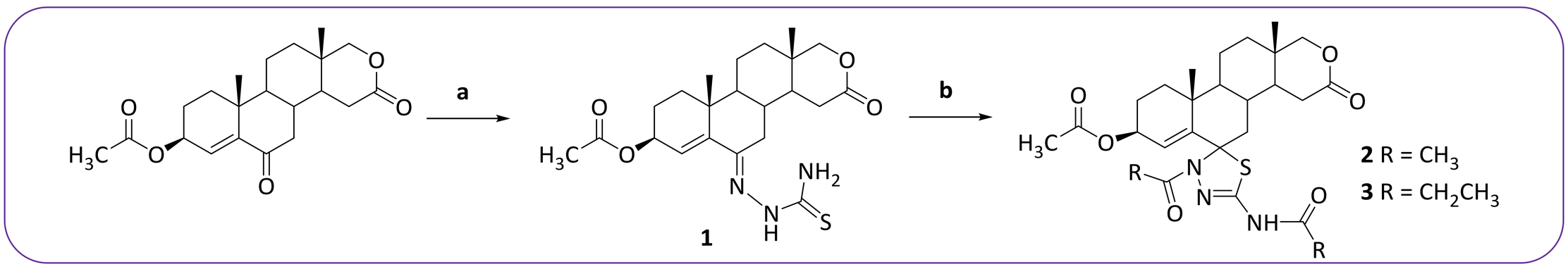
SYNTHESIS AND *IN SILICO* ADMET ANALYSIS OF NEW ANDROSTANE 6-THIOSEMICARBAZONE AND 1,3,4-THIADIAZOLINE DERIVATIVES

Marina P. Savić, Tijana Lj. Šestić, Jovana J. Ajduković
Department of Chemistry, Biochemistry and Environmental Protection, Faculty of Sciences, University of Novi Sad, Trg Dositeja Obradovića 3, 21000 Novi Sad, Serbia

INTRODUCTION Steroids are a major class of natural compounds with a broad spectrum of biological activities and the ability to penetrate the cell membranes and bind to the nuclear and membrane receptors. *N*-, *O*- and *S*-Heterocycles are important structural units present in many drugs, natural and synthetic products with diversity of pharmacological activities. Among them, the 1,3,4-thiadiazoline nucleus is one of the most studied.

RESULTS AND DISCUSSION With the aim to obtain the new thiadiazoline androstane derivatives with potential biological activity, 6-thiosemicarbazone derivative **1** was synthesized from the starting 17-oxa-17a-homoandrost-4-ene-6,16-dion-3β-yl acetate [1]. The reaction of 6-thiosemicarbazone derivative **1** with acetic anhydride or propionic anhydride in chloroform, upon addition of pyridine resulted in the new 1,3,4-thiadiazoline derivatives **2** or **3**, respectively (Scheme 1).



Scheme 1. Reagents: a) thiosemicarbazide, glac. CH_3COOH, CH_3CH_2OH, reflux, 90 min.; b) acetic anhydride or propionic anhydride, pyridine, $CHCl_3$, 80-85 °C, 14 h or reflux, 9h and 30 min.

New derivatives were characterized by spectroscopic methods and the SwissADME [2] online prediction tool was applied to determine the physicochemical properties of new compounds **1**-**3**. Using the Bioavailability Radars allowed a first insight at the drug-likeness of the compounds (Fig. 1). These data were compared with five sets of criteria: Lipinski, Veber, Egan, Ghose and Muegge.

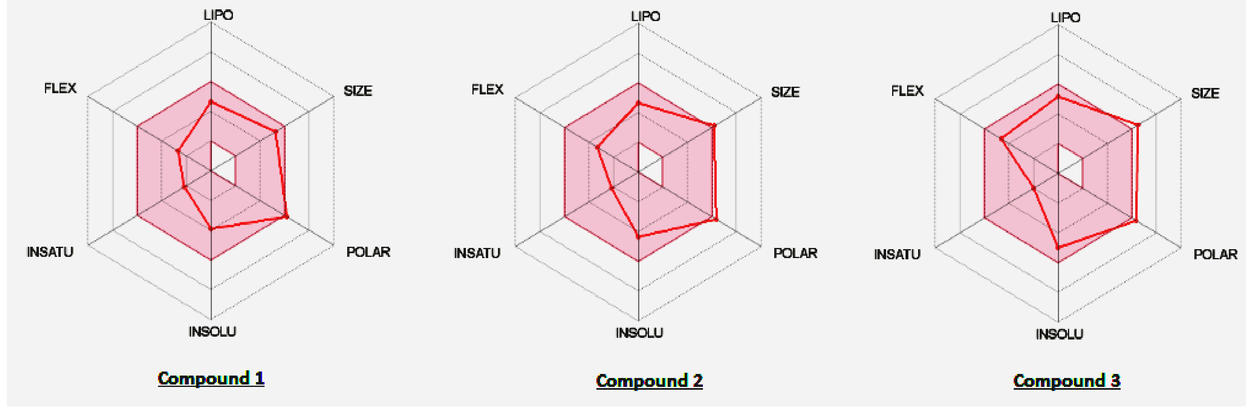


Figure 1. Bioavailability Radars of compounds **1**-**3**.

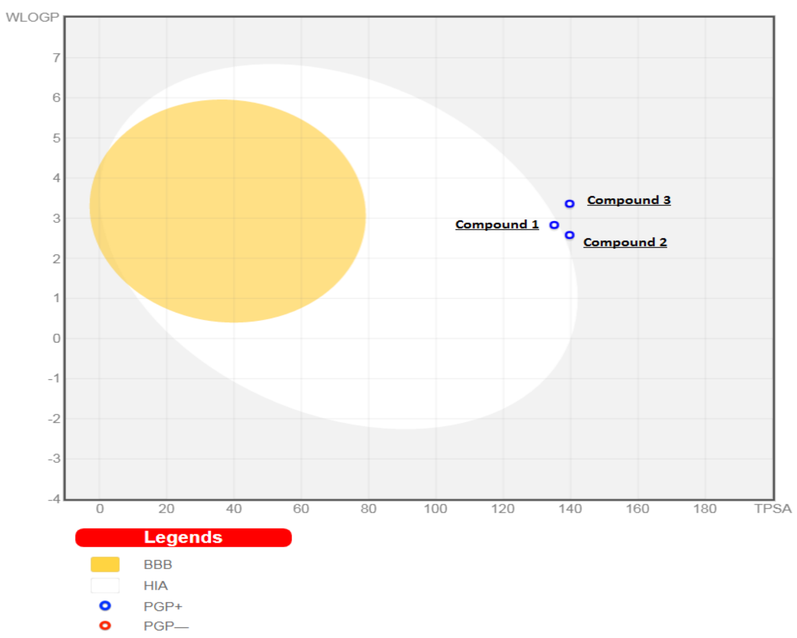


Figure 2. Graphical distribution of compounds **1-3** using the BOILED-Egg predictive model for intestine and brain permeation.

The bioavailability radars indicated that new compounds are in the optimal range for lipophilicity, solubility, saturation and flexibility, while the starting thiosemicarbazone derivative **1** also has a satisfactory size and polarity. The BOILED-Egg model [3] indicated that only thiosemicarbazone compound could possess high gastrointestinal absorption, but could not penetrate the brain (Fig. 2).

The ProTox-II web tool [4] was used for *in silico* tests, to predict the toxicity of the synthesized compounds. The results showed that the synthesized compounds do not belong to mutagenic and carcinogenic substances, but may be immunotoxic.

CONCLUSION In this work, the new 1,3,4-thiadiazoline derivatives **2** and **3** were obtained, from starting 6-thiosemicarbazone derivtaive **1**. Although all compounds possess drug-like qualities required for Lipinski, Veber, Egan, Ghose and Muegge criteria, thiosemicarbazone appears to be the best candidate. From the obtained results it can be concluded that all compounds are good candidates for further *in vitro* studies.

[1] M. P. Savić, E. A. Djurendić, E. T. Petri, A. Ćelić, O. R. Klisurić, M. N. Sakač, D. S. Jakimov, V. V. Kojić, K. M. Penov Gaši, *RSC Adv.* 2013, *3*, 10385.
[2] A. Daina, O. Michielin, V. Zoete, *Sci. Rep.-UK* 2017, *7*, 42717.
[3] A. Daina, V. Zoete, *ChemMedChem* 2016, *11*, 1117.
[4] https://tox-new.charite.de/protox_II/index.php?site=compound_input

This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Grant No. 451-03-9/2021-14/200125) and by the Provincial Secretariat for Higher Education and Scientific Research of the Autonomous Province of Vojvodina (Project: Development of steroid derivatives of potential biomedical importance, No. 142-451-2309/2021-01).