SYNTHESIS AND *IN SILICO* TESTING OF NOVEL ANDROSTANE 1,3,4-THIADIAZOLINES

Tijana Šestić, Jovana Ajduković, Ivana Kuzminac, Andrea Nikolić, Marina Savić
Department of Chemistry, Biochemistry and Environmental Protection, Faculty of Sciences, University of Novi Sad, Trg Dositeja Obradovića 3, 21000 Novi Sad, Serbia

INTRODUCTION:

It is widely known that *N*-, *O*- and *S*-heterocycles are important structural units present in many drugs, natural and synthetic products with broad spectrum of pharmacological activities. Among them, the 1,3,4-thiadiazoline nucleus is one of the most studied, and its potency is demonstrated by drugs that are currently in clinical use, such as cefazolin, megazol or acetazolamide [1].

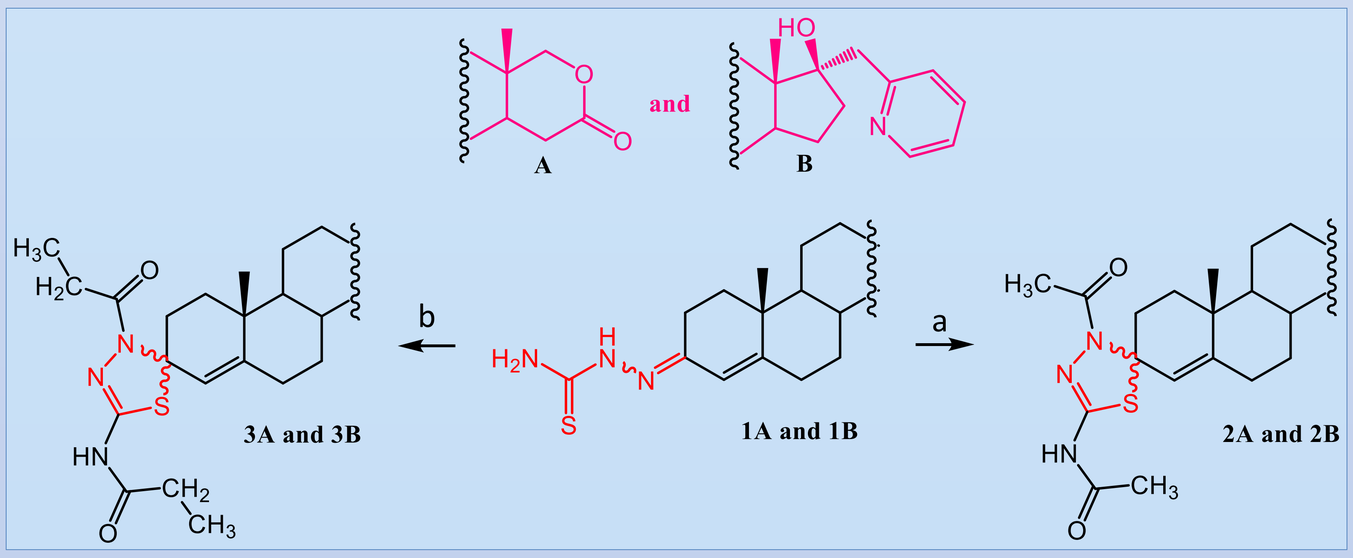
OBJECTIVES:

Bearing this in mind, we have synthesized androstane 3-thiosemicarbazone derivatives in 17a-homo lactone and 17α-picolyl (**1A** and **1B**, Figure 1) series, which were further subjected to ring closure reactions, affording 1,3,4-thiadiazolines (**2A, 2B** and **3A, 3B**, Scheme 1) in good yields. In addition, the physicochemical properties of the obtained compounds were predicted using the web tool SwissADME (Table 1) and compared with Lipinski, Veber, Egan, Ghose and Muegge criteria [2].

METHOD / DESIGN:

All new compounds were obtained according to established synthetic procedures and characterized by IR and NMR spectroscopic data. *In silico* ADME profile was determined as well, where the BOILED-Egg model provided information about gastrointestinal absorption and brain penetration (Figure 1), while bioavailability radars allowed a first insight into a drug-likeness of the compounds (Figure 2).

RESULTS:



Scheme 1. a) Acetic anhydride, Py, $CHCl_3$, reflux, 7 h (for **A**) or 80-85 °C, 3.5 h (for **B**); b) Propionic anhydride, Py, $CHCl_3$, reflux, 7 h (for **A**) or 80-85 °C, 3 h (for **B**).

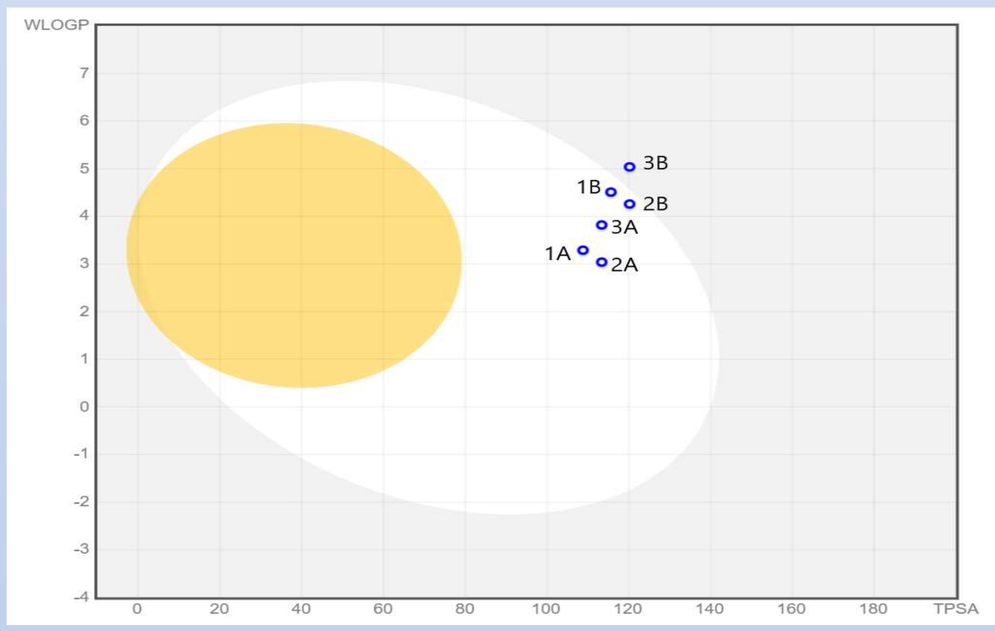


Figure 1. Graphical distribution of compounds **1A/B-3A/B** using the BOILED-Egg predictive model for intestine and brain permeation.

Table 1. *In silico* physicochemical properties of compounds **1A/B**, **2A/B** and **3A/B**.

Compound	Formula	MW	HBD	HBA	LogP	nrotb	TPSA	MR	No.rings
1A	$C_{20}H_{29}N_3O_2S$	375.53	2	3	3.09	2	108.80	107.07	4
1B	$C_{26}H_{36}N_4OS$	452.66	3	3	4.09	4	115.62	134.08	5
2A	$C_{25}H_{33}N_3O_4S$	459.60	1	5	3.23	3	113.37	131.86	5
2B	$C_{30}H_{40}N_4O_3S$	536.73	2	5	4.11	5	120.19	158.86	6
3A	$C_{26}H_{37}N_3O_4S$	487.65	1	5	3.91	5	113.37	141.47	5
3B	$C_{32}H_{44}N_4O_3S$	564.78	2	5	4.82	7	120.19	168.47	6

MW: molecular weight expressed in Daltons; HBD: number of hydrogen bond donors; HBA: number of hydrogen bond acceptors; LogP: partition coefficient, average of five predictions (iLOGP, XLOGP3, WLOGP, MLOGP and Silicos-IT LogP); nrotb: number of rotatable bonds; TPSA: topological polar surface area in $Å^2$; MR: molar refractivity.

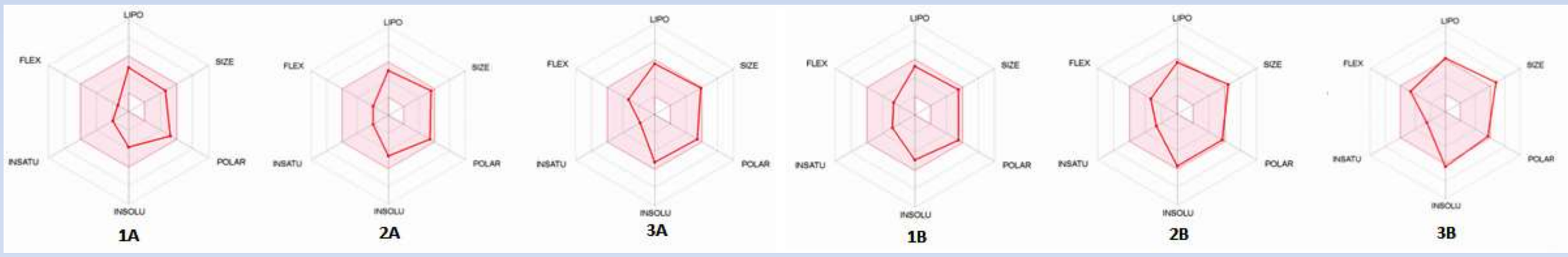


Figure 2. The Bioavailability Radars of synthesized compounds **1-3**. The pink area represents the optimal range for lipophilicity, polarity, solubility, saturation and flexibility.

CONCLUSIONS:

A suitable synthesis of new thiosemicarbazone and thiadiazoline derivatives was performed, starting from the corresponding 4-en-3-one androstanes. According to *in silico* ADME physicochemical properties, all compounds possess drug-like qualities which are required for Lipinski, Veber, Egan, Ghose and Muegge criteria. The bioavailability radars indicated that all compounds are in the optimal range for lipophilicity, polarity, solubility, saturation and flexibility, with a slight deviation in compounds **2B** and **3B** due to higher molecular weight. The BOILED-Egg model indicated that these compounds could be absorbable by the intestines (with the exception of **3B**), but couldn't penetrate the brain. From the obtained results it can be concluded that all compounds are good candidates for further *in vitro* studies.

REFERENCES:

[1] G. Serban, *et al.* , *Drug Design, Development and Therapy* **12** (2018) 1545.
[2] A. Daina, *et al.*, *Scientific Reports* **7** (2017) 42717.

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