NEW ANDROSTANE 1,3,4-THIADIAZOLINES: SYNTHESIS AND PHYSICOCHEMICAL ANALYSIS

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INTRODUCTION:

Steroids are an essential class of natural compounds which regulate variety of metabolic processes and they are proven as good therapeutics for many diseases. In order to find new steroid derivatives with desirable biological activity, natural steroids are often modified by incorporation of heteroatoms or heterocyclic rings. 1,3,4-Thiadiazoline derivatives are the most studied among the different isomers, while they exhibit various biological activities due to the presence of =N-C-S- moiety [1]. On the other hand, incorporation of a nitrogen atom in the steroid A-ring can modify biological activity of parental molecules [2]. Aza-steroids are formed by replacement of one carbon atom in the steroid molecule by nitrogen, while aza-homosteroids are formed by incorporation of lactam moiety (-NH-CO-) into the steroid ring.

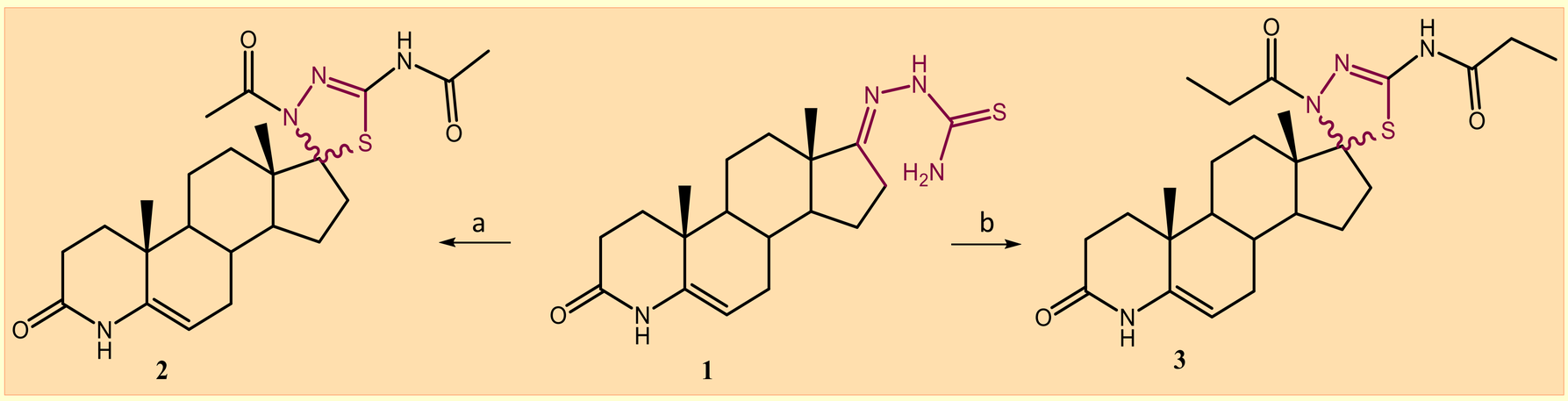
OBJECTIVES:

Considering the biological potential of steroid lactams and thiadiazolines, here we present the synthesis of novel aza-steroids with 1,3,4-thiadiazoline ring (**2** and **3**) obtained by the cyclization reaction of 17-thiosemicarbazone derivative **1** in the presence of acetic anhydride (a) or propionic anhydride (b) (Scheme 1). Furthemore, the physicochemical properties of the synthesized compounds were calculated using the web tool SwissADME (Table 1), and compared with Lipinski, Veber, Egan, Ghose and Muegge criteria [3].

METHOD / DESIGN:

All new compounds were characterized by IR and NMR spectroscopic techniques and *in silico* ADME profile was determined. The bioavailability radars allowed a first insight at the drug-likeness of the compounds (Figure 1), while the BOILED-Egg model provided information about gastrointestinal absorption and brain penetration (Figure 2).

RESULTS:



Scheme 1. a) Acetic anhydride, Py, $CHCl_3$, 80-85 °C, 9 h; b) Propionic anhydride, Py, $CHCl_3$, reflux, 5.5 h.

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

Compound	Formula	MW	HBD	HBA	LogP	nrotb	TPSA	MR	No.rings
1	$C_{19}H_{28}N_4OS$	360.52	3	2	2.52	2	111.60	107.90	4
2	$C_{23}H_{32}N_4O_3S$	444.59	2	4	2.71	3	116.17	132.68	5
3	$C_{25}H_{36}N_4O_3S$	472.65	2	4	3.39	5	116.17	142.29	5

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.

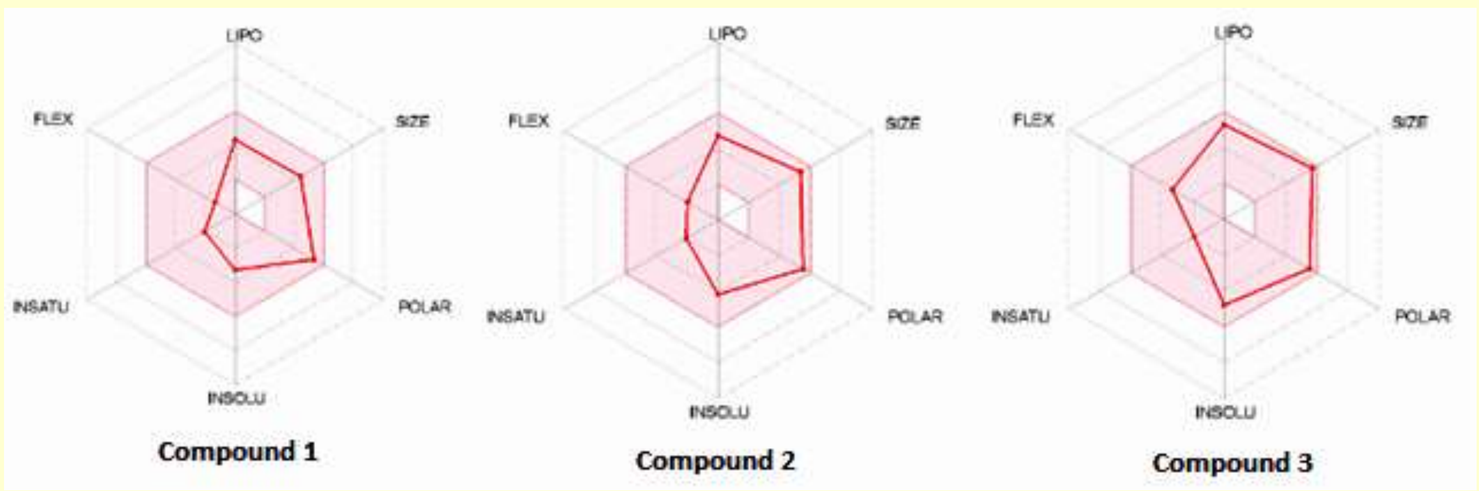


Figure 1. The Bioavailability Radars of synthesized compounds **1-3**. The pink area represents the optimal range for lipophilicity, polarity, solubility, saturation and flexibility.

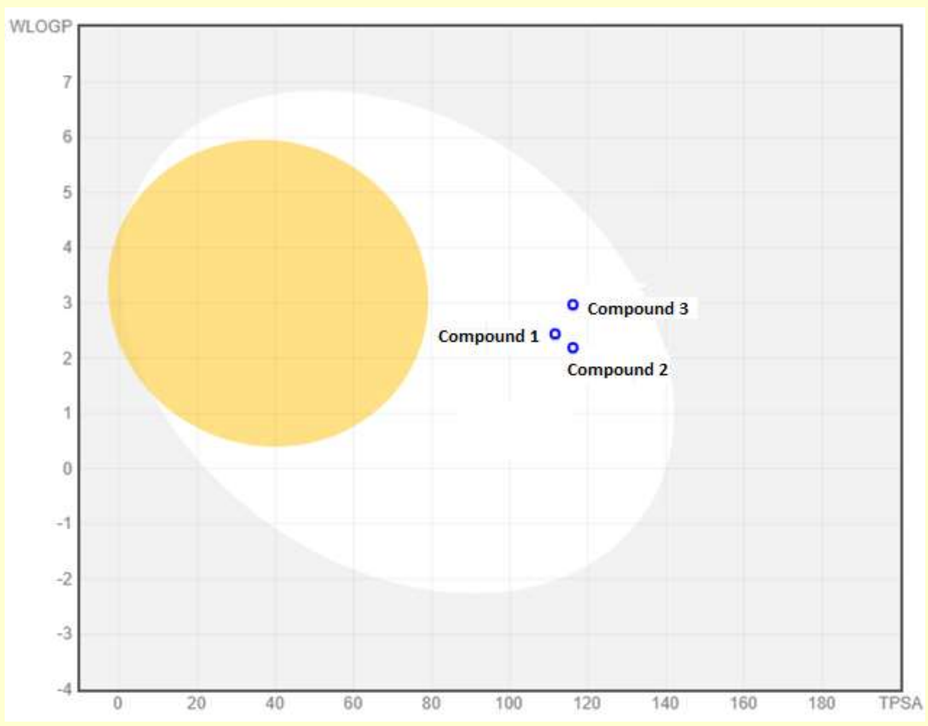


Figure 2. Graphical distribution of compounds **1-3** using the BOILED-Egg predictive model for intestine and brain permeation.

CONCLUSIONS:

In this work, the synthesis of new thiosemicarbazone and thiadiazoline aza-steroid derivatives was described. Analysis of *in silico* ADME physicochemical properties showed that all newly synthesized compounds possess drug-like properties according to Lipinski, Veber, Egan, Ghose and Muegge criteria. The bioavailability radars showed that all compounds are in the optimal range for lipophilicity, polarity, solubility, saturation and flexibility. The BOILED-Egg model indicated that these compounds are absorbable by the intestines but couldn't penetrate the brain. Obtained results indicate that all compounds are good candidates for further *in vitro* investigations.

REFERENCES:

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[3] A. Daina, *et al.*, *Sci. Rep. UK* **7** (2017) 42717.

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