Synthesis and *in silico* ADMET prediction of 17α-(pyridin-2-yl)-estra-1,3,5(10)-triene derivatives

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The introduction of a heteroatom or heterocyclic ring into the steroid nucleus significantly affects its pharmacological and pharmacokinetic properties. Namely, the pyridine ring is an important structural characteristic of molecules used for therapeutic purposes. We report two new and one previously synthesized pyridine-containing steroid derivative. Starting from estrone (**1**) and its C3 analogs **2** and **3**, we have synthesized 17-(pyridin-2-yl) derivates of estra-1,3,5(10)-triene **4-6** (Scheme 1). *In silico* ADME properties were tested for all synthesized compounds (Table 1, Figures 1 and 2) by using two online tools SwissADME while *in silico* toxicology tests were performed with the ProTox-II virtual lab (Figure 3). Also, virtual screening was performed on the Swiss Target Prediction website in order to estimate the most probable macromolecular targets of obtained compounds and thus their biological activity (Figure 4).

Scheme 1.

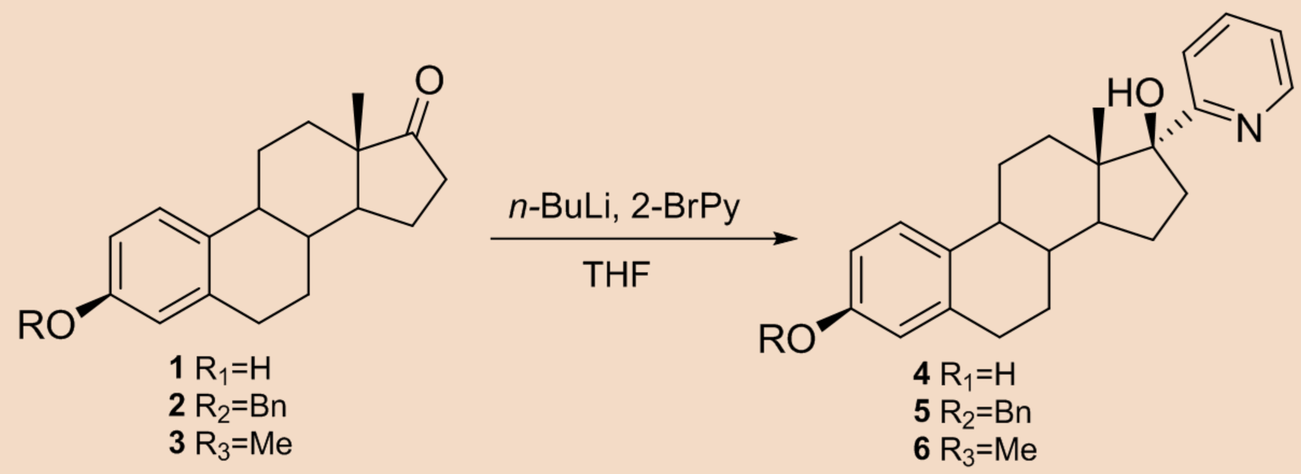

Table 1. Calculated molecular properties

Comp.	MF	MW	HBA	HBD	LogP	nrotb	TPSA	MR	No.ring
4	$C_{23}H_{27}NO_2$	349,47	3	2	3,78	1	53,35	103,19	5
5	$C_{30}H_{33}NO_2$	439,59	3	1	5,41	4	42,35	132,15	6
6	$C_{24}H_{29}NO_2$	363,49	3	1	4,23	2	42,35	107,66	5

MW, molecular weight (gmol-1; <500); logP, logarithm of compound partition coefficient between n-octanol and water (<5); HBA, number of hydrogen bond acceptors (<10); HBD, number of hydrogen bond donors (<5); MR, molar refractivity; TPSA, topological polar surface area (Å2; <140); nrotb, number of rotatable bonds (<12).

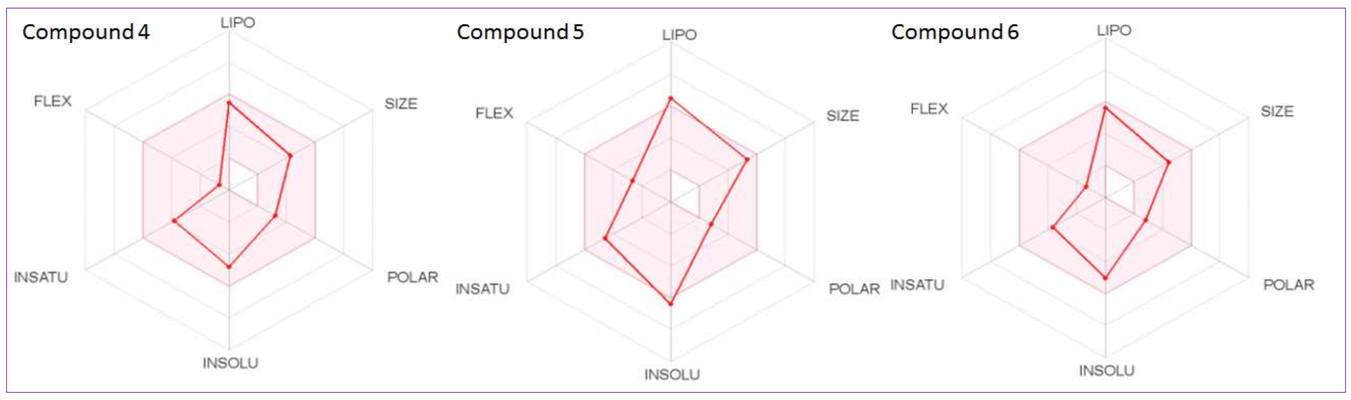

Figure 1. Swiss ADME The Bioavailability Radars of synthesized compounds enable faster insight at the drug likeness of compounds. The pink area represents the optimal range for each properties (lipophilicity: XLOGP3 between −0.7 and +5.0, size: MW between 150 and 500 g/mol, polarity: TPSA between 20 and 130 Å2, solubility: log S not higher than 6, saturation: fraction of carbons in the sp3 hybridization not less than 0.25, and flexibility: no more than 9 rotatable bonds)

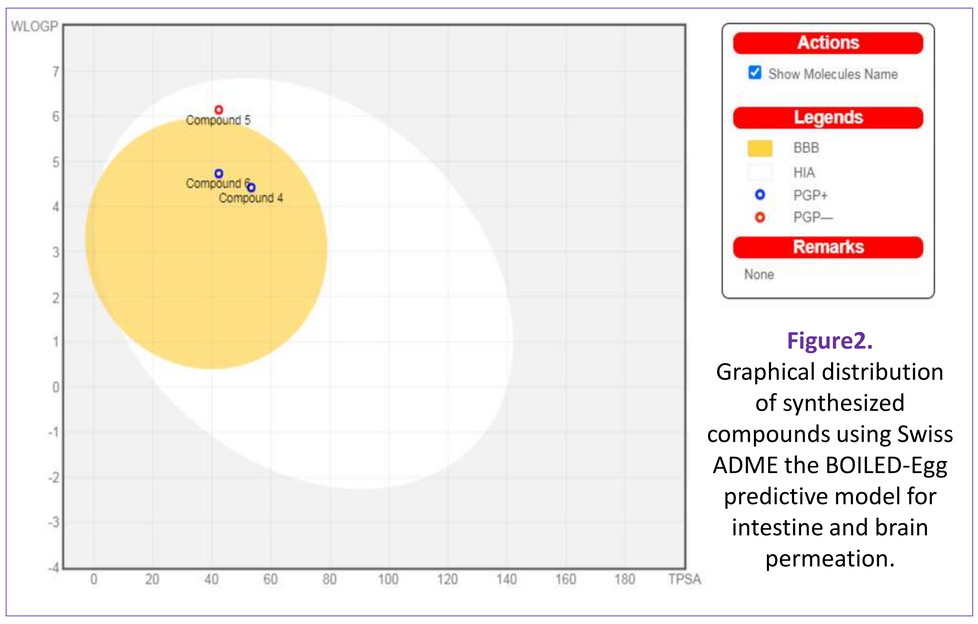

Figure2. Graphical distribution of synthesized compounds using Swiss ADME the BOILED-Egg predictive model for intestine and brain permeation.

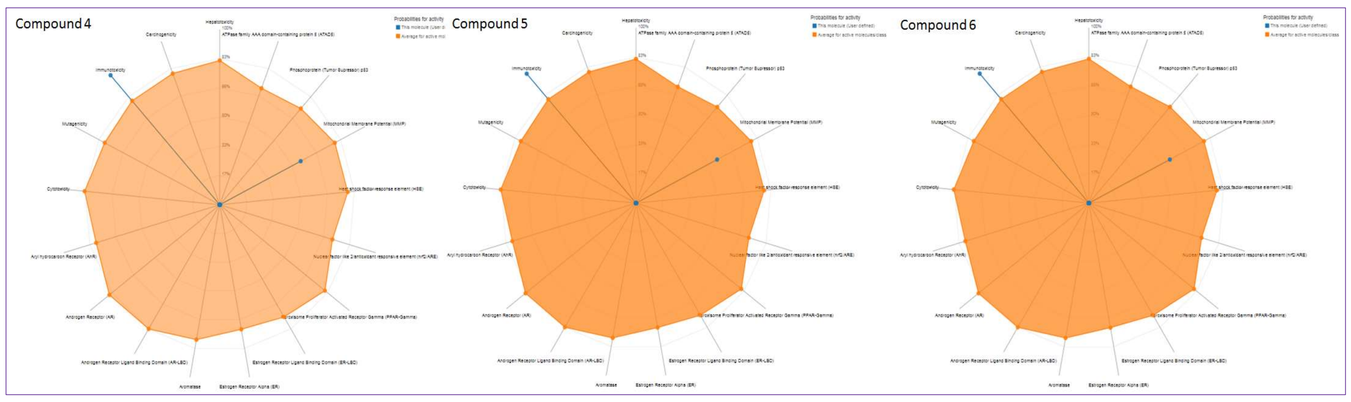

Figure 3. The toxicity radar chart provides a quick illustration of the positive toxicity results compared to the average of its class.

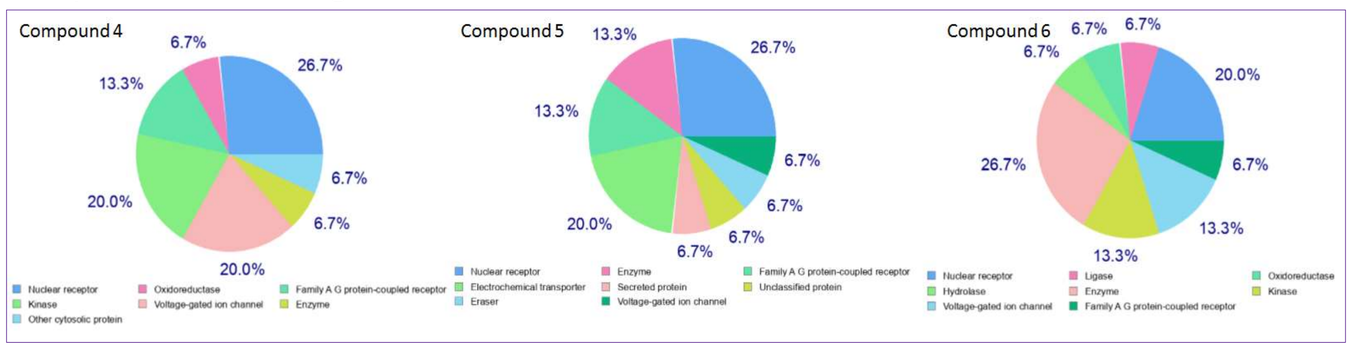

Figure 4. SwissTarget Prediction online tool is easily accessible from SwissADME server. Graphical distribution of molecular targets is shown on this figure.

Conclusion: Starting from estrone (**1**) and its C3 analogs **2** and **3**, we synthesized two new compounds and one previously known. For all synthesized compounds, *in silico* ADMET tests were performed. A small deviation from the pink area of the Bioavailability radar was observed of compound **5**. Based on the BOILED-Egg model it can be concluded that compound **5** is only absorbed in the gastrointestinal tract (HIA) (Figure 2), while compounds **4** and **6** meet the parameters for both absorptions. The toxicity radar charts indicate possible immunotoxicity for all three synthesized compounds. However, this should not exclude compounds from further biological testing since this is a common side-effect of most cancer drugs. Last, virtual screening has predicted nuclear receptors as molecular targets of these compounds. This indicates their possible broad spectrum of applications.

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