Synthesis, structural characterization, and *in silico* ADMET testing of novel 17β-acetoxy-17α-(pyridin-2-yl) estrane derivate

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Introduction: Steroidal compounds that contain a heterocyclic ring or heteroatom in their structure usually possess good anticancer activity. The main goal of modern medicinal chemistry is to find new potent agonists or antagonists of naturally occurring hormones for the treatment of hormone-dependent cancers such as the above-mentioned steroid derivatives. Here we reported a two-step synthesis of a new 17β-acetoxy-17α-(pyridin-2-yl) derivative of estra-1,3,5(10)-triene (**3**, Scheme 1). Configuration at the C17 position was determined using the 2D NMR spectra (Figure 1). Furthermore, *in silico* ADME properties were determined for the synthesized compound. The physicochemical properties were calculated by the SwissADME web tool and compared with five different sets of criteria: *Lipinski, Veber, Egan, Ghose,* and *Muegge* (Table 1). The toxicity of the synthesized compound was predicted and analyzed using a virtual lab ProTox II (Figure 4).

Scheme 1.

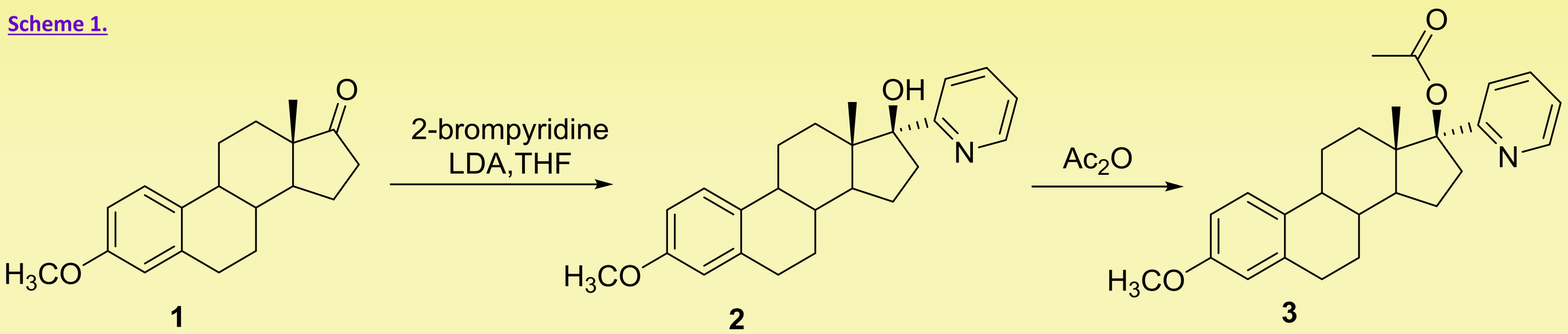
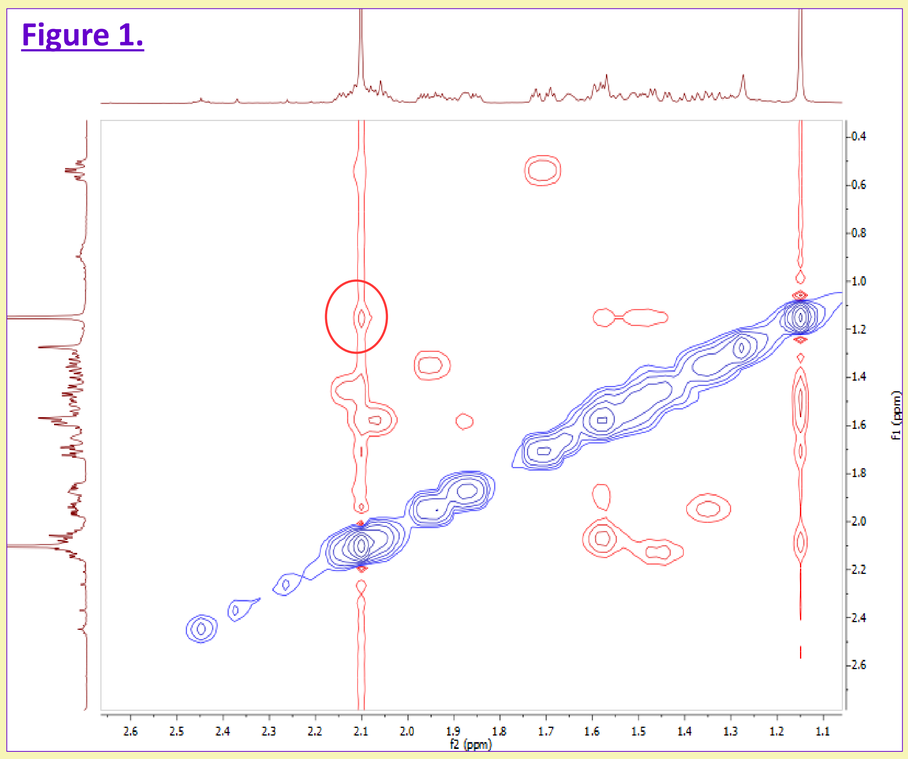


Table 1.

Comp.	MF	MW	HBA	HBD	logP	nrotb	TPSA	MR	No. rings
3	$C_{26}H_{31}NO_2$	405,53	4	0	4,68	4	48,42	117,40	5

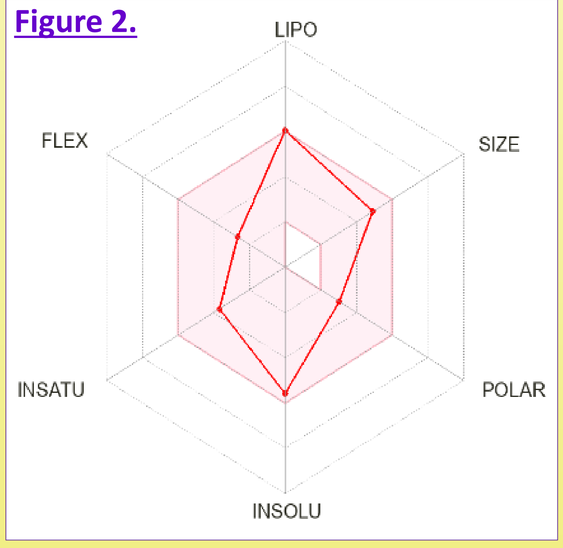
MW, molecular weight (gmol-1; <500); logP, logarithm of compound partition coefficient between n-octanol and water (<5); HBA, number of hydrogen bond acceptors (<10); HBD, number of hydrogen bond donors (<5); MR, molar refractivity; TPSA, topological polar surface area (Å2; <140); nrotb, number of rotatable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

Figure 1.



2D NOESY experiment was of particular use in determination of the stereochemistry of 17-acetoxy function. It can be seen that the signal at 2.1 ppm, which is assigned to H-3 proton from the acetoxy group, shows NOE interactions with angular methyl group protons H-18. This indicates the alpha orientation of the pyridin-2-yl group at C1.

Figure 2.



The Bioavailability Radar of synthesized compound enables faster insight into compounds drug-likeness. The pink area represents the optimal range for lipophilicity, size, polarity, solubility, saturation, and flexibility. Compound **3** falls entirely or partially in the pink area which represents the optimal range for each properties.

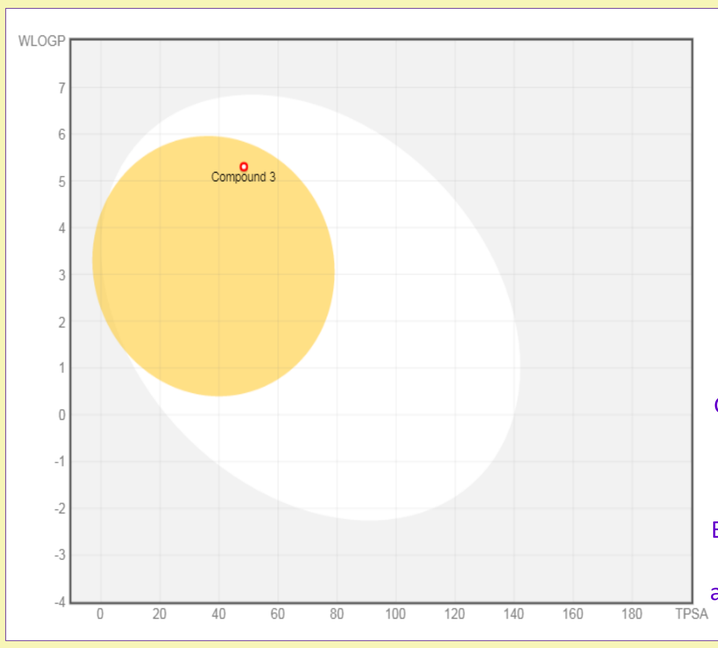
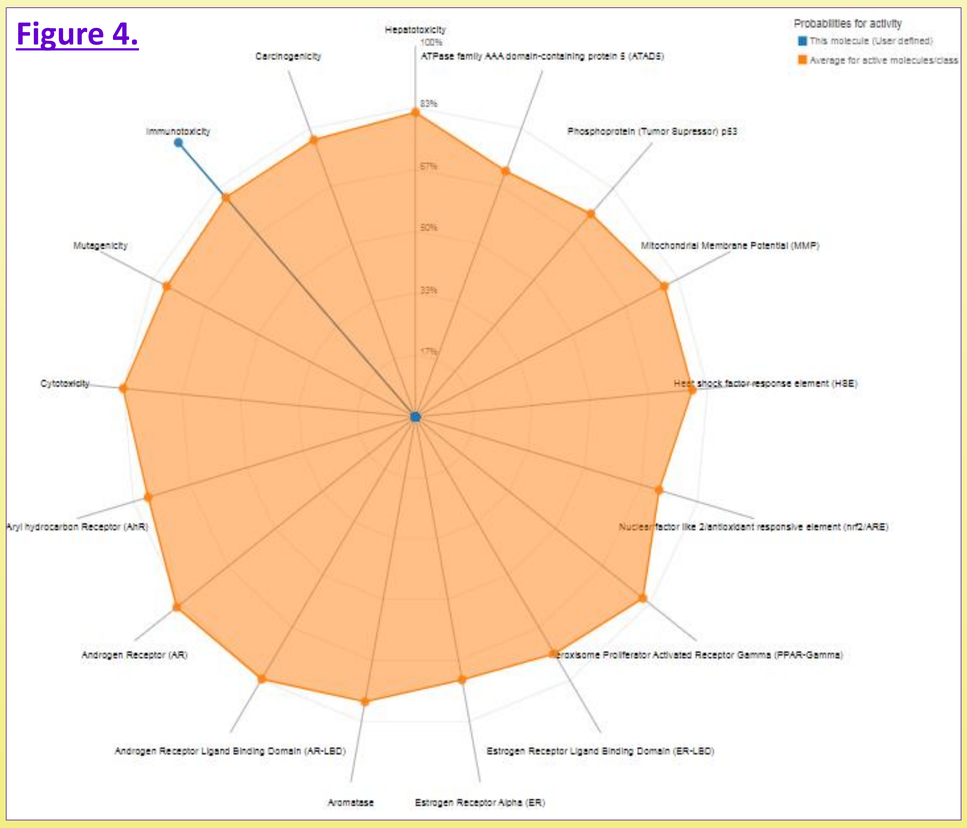


Figure 3.

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

The Radar Toxicity Table provides a quick illustration of the positive toxicity results compared to the average of its class.

Figure 4.



Conclusion:

In a two-step, we synthesized of a new 17β-acetoxy-17α-(pyridin-2-yl) derivative **3** of estra-1,3,5(10)-triene starting from the methyl ether of estrone (**1**, Scheme 1). Using 2D NOESY we determined a configuration of the pyridin-2-yl group at the C17 position of the steroidal core (Figure 1). For compound **3** *in silico* ADMET tests were performed (Table 1). Compound **3** doesn't show deviation from the pink area of the Bioavailability radar (Figure 2). Based on the BOILED-Egg model it can be concluded that compound **3** meets the parameters for both absorptions (Figure 3). The toxicity radar chart indicates possible immunotoxicity for the synthesized compound (Figure 4). However, this should not exclude compound **3** from further biological testing since this is a common side-effect of most cancer drugs.

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