SYNTHESIS, *IN SILICO* ADMET PROPERTIES AND VIRTUAL SCREENING OF NEWLY *O*-SUBSTITUTED DERIVATIVES OF DEHYDROEPIANDROSTERONE (16*E*)-OXIME

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INTRODUCTION:

The steroid scaffold is present in many FDA-approved drugs for the treatment of various diseases such as inflammation, allergic reaction, heart disease, cancer, and metabolic disease. The steroid skeleton is a favorable scaffold for the design and development of novel agents with pharmacological activities because even a small change in steroid moiety can lead to changes in the properties and biological activity of the compound. Introduction of a *H*-bond-donating oxime group into a hydrophobic steroid skeleton can increase their ability to interact with cell membranes which is important for the biological activity of such molecules. This approach proved as an excellent strategy for obtaining potent cytotoxic agents. *O*-Alkyl derivatives of oximes containing the *H*-bond-accepting group can change activity against cancer cells.

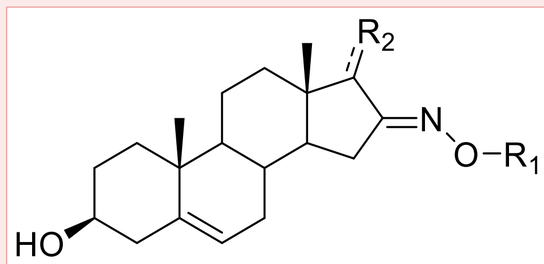
OBJECTIVES:

The aim of this work was the synthesis of new steroid *O*-substituted (16*E*)-oximes with and without *H*-bond-donating group as well as *in silico* assessment of their physicochemical properties and pharmacokinetics.

METHOD / DESIGN:

The structures of synthesized compounds were determined based on their spectral data. *In silico* ADMET properties were studied for all synthesized compounds using SwissADME and ProTox-II web tools.

New steroidal *O*-substituted (16*E*)-oximes were prepared from dehydroepiandrosterone (16*E*)-oxime.



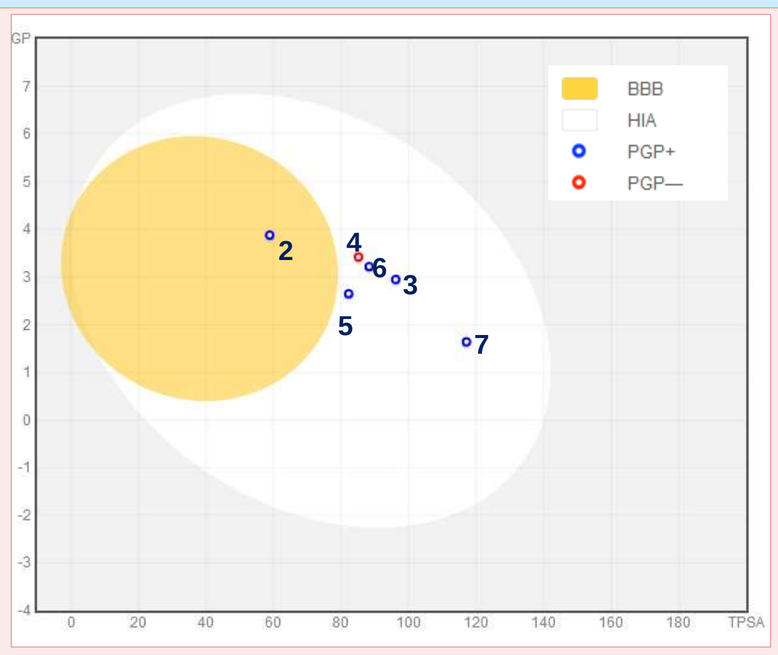
1 $R_1 = H$; $R_2 = O$
2 $R_1 = CH_2CH_3$; $R_2 = O$
3 $R_1 = CH_2COOH$; $R_2 = O$
4 $R_1 = CH_2COOCH_2CH_3$; $R_2 = O$
5 $R_1 = CH_2CH_2OH$; $R_2 = 17\beta$-OH
6 $R_1 = CH_2COOCH_2CH_3$; $R_2 = 17\beta$-OH
7 $R_1 = CH_2CONHNH_2$; $R_2 = 17\beta$-OH

a, **b**, **c**, **d**, **e**

a) CH_3CH_2Br, K_2CO_3, 18-crown-6, THF, reflux, 5 h ;
b) $ClCH_2COOH$, K_2CO_3, 18-crown-6, THF, reflux, 5 h (84%);
c) $ClCH_2COOEt$, K_2CO_3, 18-crown-6, THF, reflux, 2 h (83 %);
d) $NaBH_4$, EtOH, rt, 30 min. (27% for compound **5** , 40% for compound **6**);
e) $NH_2NH_2 \cdot H_2O$, EtOH, reflux, 3 h (32 %).

The Bioavailability Radar, which takes into account six physicochemical properties: lipophilicity, size, polarity, solubility, flexibility, and saturation, showed that all parameters of the synthesized compounds were in the optimal range.

Prediction of pharmacokinetic behavior showed that tested compounds could be absorbed by the human intestine but couldn't cross the blood-brain barrier (except **2**).



The drug-likeness evaluation revealed that synthesized compounds fulfill the requirements of the five different rule-based filters (Lipinski, Weber, Egan, Ghose, and Muegge).

Lipinski: MW ≤ 500; HBD ≤ 5; HBA ≤ 10; LogP ≤ 5
Veber: nrotb ≤ 10; TPSA ≤ 140 Å2
Egan: LogP ≤ 5,88; TPSA ≤ 131,6 Å2
Ghose: 160 ≤ MW ≤ 480; -0,4 ≤ LogP ≤ 5,6; 40 ≤ MR ≤ 130; 20 ≤ atoms≤ 70
Muegge: 200 ≤ MW ≤ 600; -2 ≤ LogP ≤ 5; TPSA ≤ 150 Å2; num.rings≤ 7; num. carbon> 4; num. heteroatoms > 1; nrotb ≤ 15; HBD ≤ 5; HBA ≤ 10

Compound	Formula	MW	HBD	HBA	LogP	nrotb	TPSA	MR	Num. rings
2	$C_{21}H_{31}NO_3$	345.48	1	4	3,45	2	58.89	99.74	4
3	$C_{21}H_{29}NO_5$	375.46	2	6	2,55	3	96.19	101.51	4
4	$C_{23}H_{33}NO_5$	403.51	1	6	3,27	5	85.19	110.64	4
5	$C_{21}H_{33}NO_4$	363.49	3	5	2,63	3	82.28	101.87	4
6	$C_{23}H_{35}NO_5$	405.53	2	6	3,23	5	88.35	111.60	4
7	$C_{20}H_{31}N_3O_4$	377.48	4	6	1,96	3	117.17	102.00	4

Androstane derivatives **2**, **3**, **5**, and **7** did not show inhibition effect on five major isoenzymes (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4) involved in the metabolic drug elimination.

Compounds **3**-**7** were found to bear a low risk of being mutagenic and carcinogenic, while carcinogenicity was predicted for compound **2**.

CONCLUSIONS:

In silico ADMET analysis showed that synthesized derivatives of dehydroepiandrosterone (16*E*)-oxime possess drug-like properties, and compounds **2-6** have better safety profile than **1**.

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