19-MODIFIED STEROIDAL D-HOMOANDROST-4-EN-3-ONES: SYNTHESIS, *IN SILICO* ADME AND *IN VITRO* ANTITUMOR POTENTIAL

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INTRODUCTION:

Breast cancer is the most commonly occurring form of cancer in women and the second most common cancer overall. The growth of around 80% of breast cancers is stimulated by estrogens that bind to receptors in tumor cells. For the treatment of these cancers, antiestrogens and inhibitors of the enzyme aromatase are used. Some of these pharmaceuticals have steroid structures and were used in this work for the design of novel steroid derivatives as potential antitumor compounds.

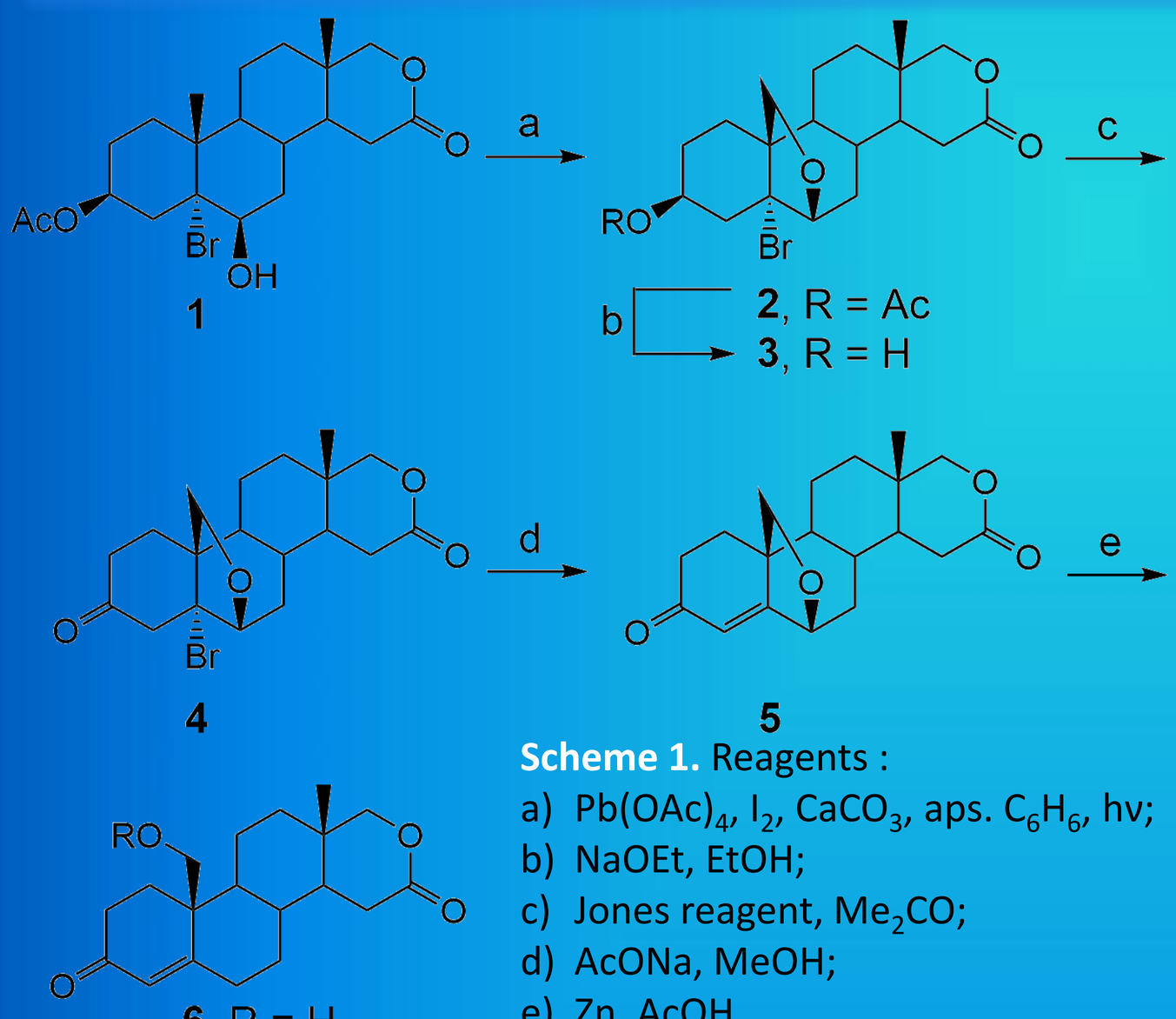
OBJECTIVES:

In this paper, we report the synthesis of two new 19-modified steroidal derivatives **6** and **7** (Scheme 1). In silico ADME properties of these compounds were tested using SwissADME online tool (Figure 1 and 2). Novel steroid derivates were tested for relative affinity to the ligand-binding domains of estrogen receptors (ERα and ERβ) and androgen receptor (AR) (Figure 3). In addition, these compounds were tested for their cytotoxic activity against six human tumor cell lines and one healthy human cell line (Table 1).

METHOD / DESIGN:

- Five-step synthesis from 3β-acetoxy-5α-bromo-6β-hydroxy-17-oxa-17a-homoandrostan-16-one (Scheme 1);
- In silico ADME - Analysis of Bioavailability Radars (Figure 2) and the BOILED-Egg model (Figure 1);
- Receptor binding - a fluorescence assay in yeast (Figure 3);
- Cytotoxicity - MTT assay, cell lines: MCF-7 (human breast adenocarcinoma ER+), MDA-MB-231 (human breast adenocarcinoma ER-), PC-3 (prostate cancer AR-), HeLa (cervical cancer), HT-29 (colon cancer), A549 (lung adenocarcinoma), MRC-5 (healthy fetal lung fibroblasts).

RESULTS:



Scheme 1. Reagents :

a) $Pb(OAc)_4$, I_2, $CaCO_3$, aps. C_6H_6, hv;
b) NaOEt, EtOH;
c) Jones reagent, Me_2CO;
d) AcONa, MeOH;
e) Zn, AcOH.

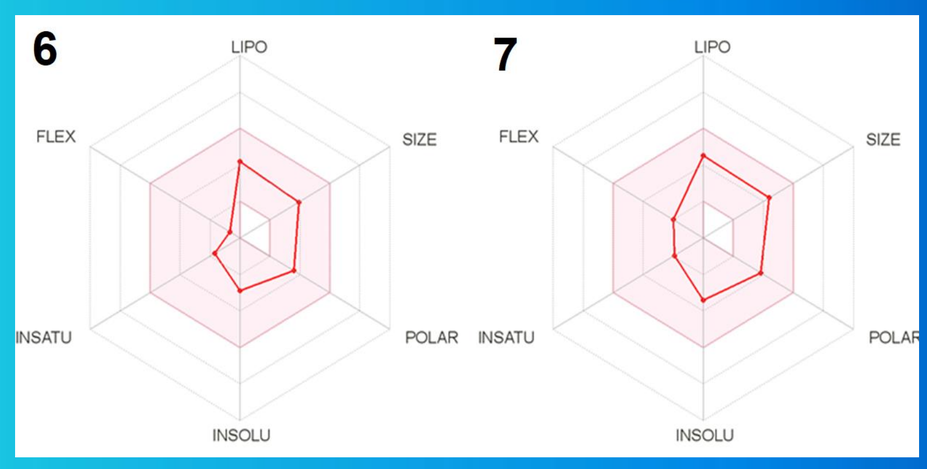


Figure 1. Bioavailability Radars of compounds **6** and **7**

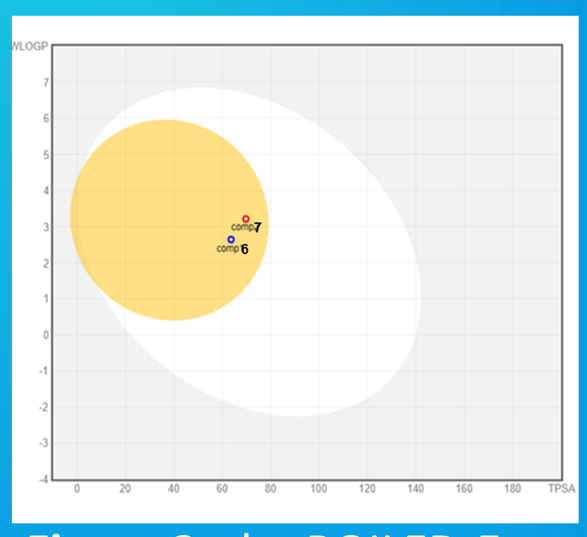


Figure 2. the BOILED-Egg model of compounds **6** and **7**

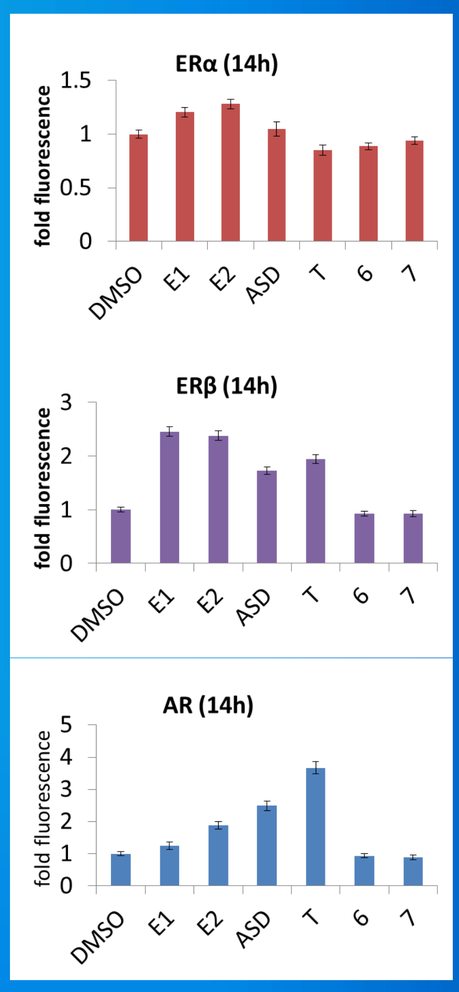


Figure 3. Results from the ligand binding assay for **6** and **7**

Table 1. Cytotoxic activity of compounds **6** and **7**

Comp.	IC_{50} (μM)						
	MCF-7	MDA-MB-231	PC-3	HeLa	HT-29	A549	MRC-5
6	20.27	55.90	>50	>50	>50	15.62	>50
7	1.71	>50	>50	>50	>50	>50	>50
cisplatin	1.60	2.64	4.56	2.10	4.10	3.20	0.24
formestane	>50	19.61	26.37	3.36	>50	38.59	>50

CONCLUSIONS:

Compounds **6** and **7** have shown good results in *in silico* ADME testing, meaning that they possess drug-like properties. Compound **7** showed high cytotoxicity and selectivity for MCF-7 cell line.

ACKNOWLEDGEMENT

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