BILE ACID DERIVATIVES AS PROMISING GLUCOCORTICOID RECEPTOR LIGANDS

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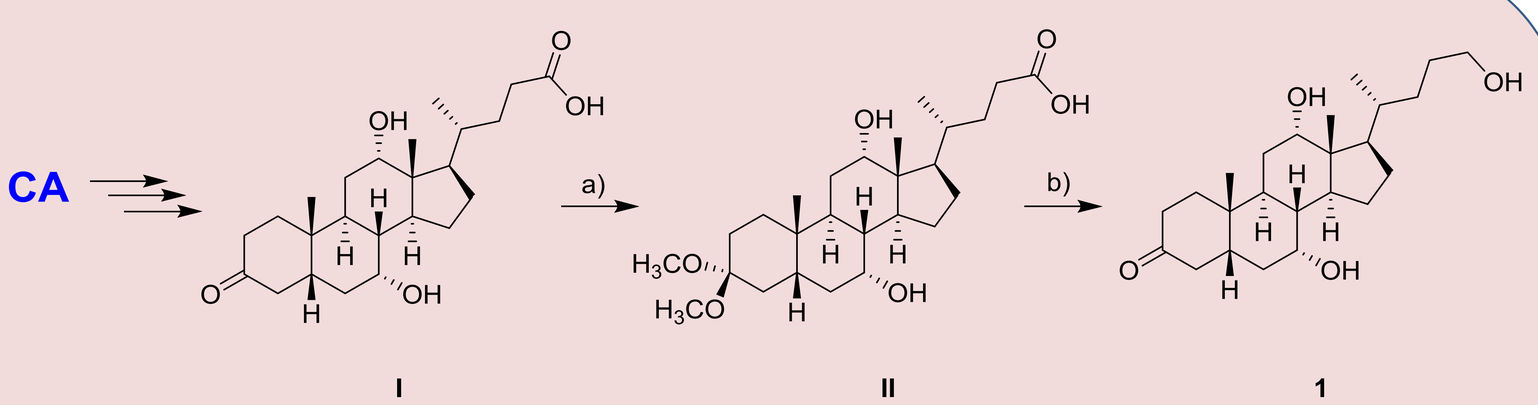
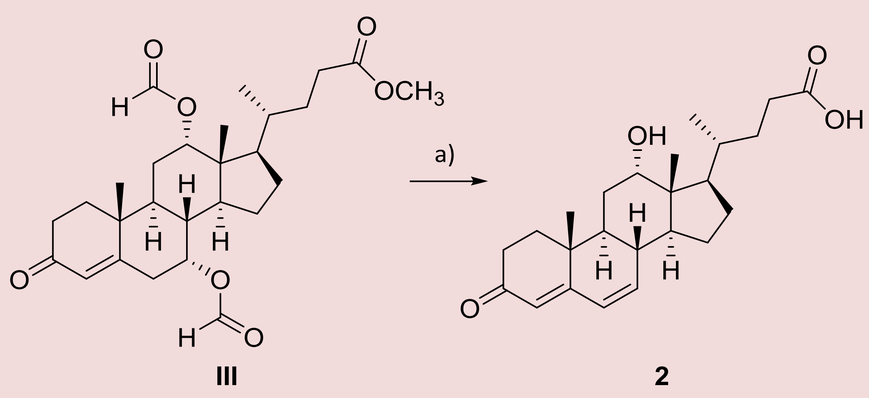
Glucocorticoids (GC) are among the most powerful medications for treatment of inflammation and autoimmune diseases. The first used for successful treatment of severe cases of COVID-19 in 2020. was semi-synthetic glucocorticoid dexamethasone. However, serious side effects, e.g., osteoporosis, Cushing's syndrome, high blood pressure, etc., limit the long-term and systematic use of these drugs. Glucocorticoids are necessary drugs in pharmacological arsenal and the search for GCs with better pharmacological properties is an urgent need. Our objective is synthesis of new GC compounds with good activity and less side effects. Glucocorticoids exert their physiological role by interacting with glucocorticoid receptor (GR). The first part toward reaching our objective was synthesis of potential GCs and testing their affinity for GR.

Results

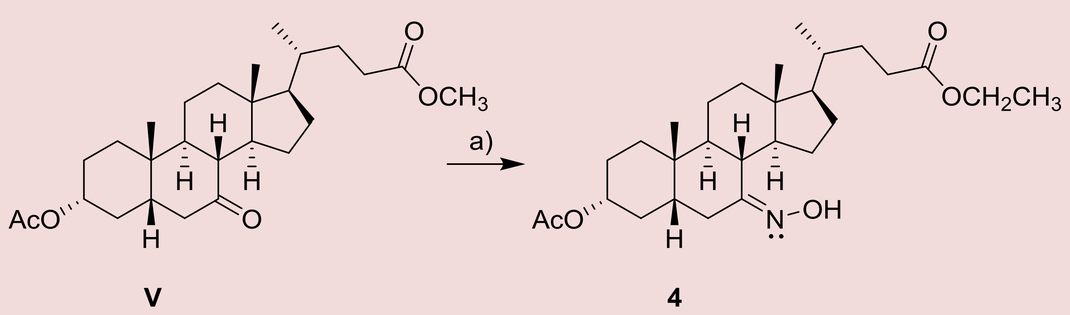
Starting from the cholic acid (CA), oxo-acid **I** was obtained by known procedure (scheme 1), consisting of protection, oxidation, deprotection reactions. Carbonyl group of oxo-acid **I** was protected in the form of acetal using methanol and 2,2-dimethoxypropane in acidic conditions to obtain **II**. Compound **II** was reduced to **1** in 15 min by using $LiAlH_4$ reagent.



Scheme 1. Reagents and conditions: a)MeOH, 2,2-dimethoxypropane, p-TsOH, reflux, 3 h, 88%; b) i) $LiAlH_4$, THF, RT, 15min; ii) 2M HCl, 79%.

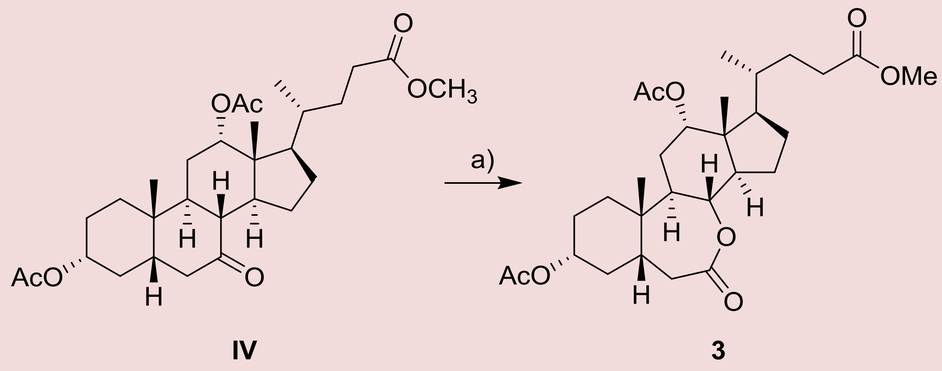


Scheme 2. Reagents and conditions: a) KOH, MeOH, reflux, 0.5 h; ii) 2M HCl, H_2O.



Scheme 4. Reagents and conditions: a) $NH_2OH{\cdot}HCl$, AcONa, EtOH, reflux, 3h, 84%.

Enone **III** was synthesized from CA by the known procedure. Triester **III** was subjected to saponification reaction (scheme 2) using KOH in methanol. After acidic workup, compound **2** was obtained. Dienone **2** is the result of the elimination and hydrolysis reaction. Compound **3** was obtained in Baeyer-Villiger reaction (scheme 3) from easily obtainable derivative **IV**.



Scheme 3. Reagents and conditions: a) m-CPBA, p-TSA, CH_2Cl_2, RT 67 h + reflux 5 h, 70%.

Oxime **4** was synthesized from 7-oxo compound **V** in reaction with hydroxylamine hydrochloride in refluxing ethanol (scheme 4).

New bile acid derivatives **1** and **2** showed moderate affinity for the ligand binding domain of glucocorticoid receptor (figure 1), while binding of compounds **3** and **4** was weak. The obtained results gave us important guidelines towards the design of new GR ligands, potentially new GCs.

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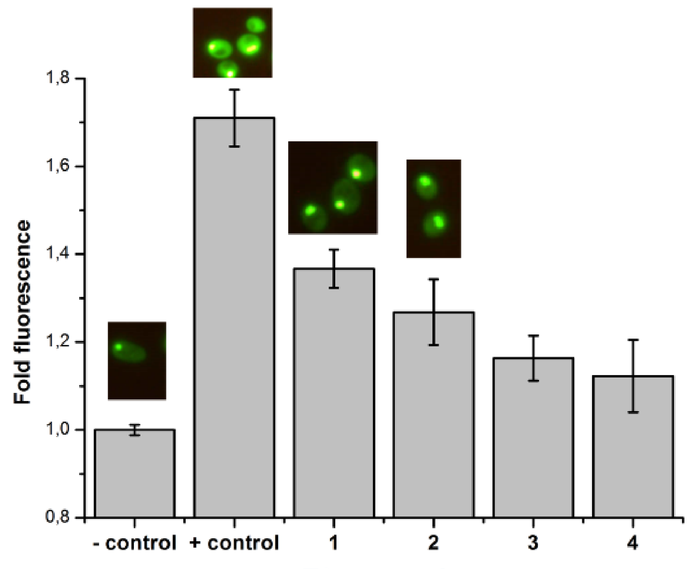

Figure 1