The biologically active metabolite of vitamin D_3 - calcitriol – is a hormone involved in the regulation of calcium-phosphate homeostasis, immunological processes and cell differentation. It is also essential for the proper functioning of the human body. This suggests many applications of this steroid in the treatment of diseases such as rickets, psoriasis and some cancers. Unfortunately, using therapeutic doses of calcitriol is associated with high concentrations of this compound which causes hypercalcemia. For this reason, new analogues of vitamin D_3 are constantly sought, which while maintaining their beneficial properties, would be devoid of calcemic effects.

The activity of the vitamin hormone is determined mainly by the presence of hydroxyl groups in A ring and the side chain. However, these functional groups are responsible for key interactions of calcitriol with the nuclear vitamin D receptor (VDR), it does not explain the activity of analogues, which despite the removal of some elements of the molecule still show high affinity for the protein. This indicates the existence of other interactions that have an important influence on the activity of these compounds.

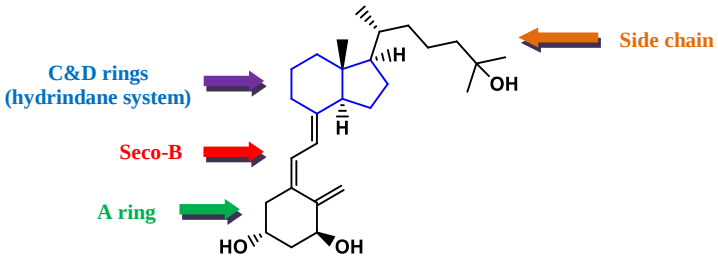

Fig. Structure of calcitriol

Most of the structural modifications introduced so far concerned the A ring and the side chain of calcitriol, and only a few compounds have been obtained with changes in the structure of the hydrindane system. It seems surprising due to the fact that this structure has a direct influence on the other elements of the molecule and can play a significant role during formation of interactions with the receptor.

The aim of this project is to obtain new calcitriol analogues with modified D-ring and using these compounds to determining the effect of such a modification on the biological activity of the vitamin hormone. Designed compounds will be obtained in a total synthesis followed by tests of VDR binding affinity, cell differentiation and calcemic properties. Structure analysis of analogues will allow to investigation of key interactions with the protein by comparison the experimental results with theoretical data obtained docking ligands into the receptor binding pocket. An important goal of the project is also a study of a new method for the synthesis of bicyclic systems.