Electrostatic forces are one of the most important factors which influence the formation of new ligand-protein complexes. Electrostatic interactions could provide essential information in drug design. Experimental and theoretical charge density studies give information on intermolecular electrostatic interaction. Furthermore, charge densities enable determination of 3D structure of molecules and crystals and provide information about their properties. An excellent quality of crystals is required for studies of charge densities. Process of determining experimentally the charge density is not a trivial task and often X-ray diffraction data are not of good enough quality to get reliable charge density results. Commonly, in the case of routine X-ray data analysis, the Independent Atom Model (IAM) is used. In this model, atoms are located at the maxima of charge density function. IAM enables determination of approximate 3D structure (geometry) of compounds forming crystals. However, this model does not give quantitative details of electron density distribution as atom in this model are understood as spherical objects which cannot transfer electron density. A far better and more flexible model is so-called Hansen-Coppens pseudo-atom model of electron density. It has been noted that pseudoatom parameters for atoms in chemically identical environments are transferable. Therefore, an idea arose to create a pseudoatom database to aid the X-ray data refinement. Three different aspherical atom databases are well established: Experimental Library of Multipolar Atom Model (ELMAM), Invariom database and the University at Buffalo Databank (UBDB) was initiated by Prof. Philip Coppens who is the World leader in experimental charge density field. This last databank is now developed in our group and can be applied to reconstruct electron density in small and large molecules. Among others it may be used in drug design. New drugs are designed by using methods based on force field theory or by experimental "brutal force approach" based on synthesis of big libraries of numerous compounds to study their interaction properties. The first method is insufficiently specific (inaccurate and imprecise) whereas the second method is time-consuming and very expensive. The quantum methods are insufficiently developed for application in drug design area as they have to deal with immense size proteins. The approach in drug design based on Aspherical Pseudoatom Databanks, Hirshfeld surface analysis, Quantum Theory of Atoms In Molecules (QTAIM) seems to be attractive and feasible as it has an intermediary character between the above mentioned two limiting methods (in general theoretical ab-initio approach and methods based on molecular mechanics or dynamics). Furthermore, our approach enables studies on the properties of ligand-protein complexes and estimation of useful parameters such as energy of electrostatic interactions based on electron density distributions more advanced that the point charge model.

The aim of this project is experimental validation of a new method of drug design. By applying this new method some new agonists of VDR (Vitamin D Receptor) have been designed. The key point of my project is the synthesis of model vitamin D analogues predicted by pseudoatom approach and experimental verification of the predicted strength of their interactions with the vitamin D receptor (VDR). Verification of such new approach is planned by synthesis of the designed new calcitriol analogue, and three other compounds with similar structure but different modifications. We plan to study the obtained calcitriol analogues by crystallography and quantum methods and also study their physico- and biochemical properties. These experimental results will be compared with that obtained from pseudoatom modelling. Introduction of new modifications (19-norvitamin) into the calcitriol analogue is also planned for checking correlations between the properties of designed analogues.

A positive result of the project should validate a new method for drug design and for studying protein-ligand complexes. Therefore, it could begin new trends in drug design and protein-ligand research. Another result of this project is to make new calcitriol analogues with optimized biochemical properties. The A-ring building blocks and C/D-ring fragments obtained in this project could be used for synthesis of other more complicated calcitriol analogues which will be designed in a future.