Search for low molecular weight inhibitors of the osteoclastogenesis process.

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The process of bone resorption plays a crucial role in the bone remodeling. Together with bone formation, it is responsible for giving each bone its specific shape and plays an important role in calcium homeostasis. It is therefore important to sustain the balance between processes of resorption and creation of the new bone. The first stage of bone resorption is osteoclastogenesis, which leads to the formation of osteoclast cells which consume bone tissue. The increase of their amount and/or activity leads to many pathological conditions such as: osteoporosis, Paget's disease, bone tumors, rheumatoid arthritis etc.

It is known that cysteine proteinases such as cystatin C are involved in the bone resorption during the solubilization of bone matrix. The majority of the cysteine proteinases are produced by osteoclasts and among them cathepsin K is present in high concentration during different stages of osteoclast formation. It is known that it is responsible for fission of triple helix of collagen and involved in activation of TRAP enzyme, which plays role in creation of haematopoetic cells and acts as a phosphataze. This knowledge led to the assumption that the inhibition of cathepsin K would stop the process of osteoclast formation or decrease the resorption which was confirmed by further research.

The research carried out by dr B. Żołnowska concerning the development of effective and non-toxic inhibitors of osteoclastogenesis based structurally on cystatin C showed that these compounds have the capability to decrease the production of osteoclasts, but their mechanism of action is not connected to the ability of inhibition of cathepsin K or cysteine proteases. The research lead to the conclusion that there is probably another different path of action which is influenced by the inhibitors based on the cystatins' C structure.

The main objective of the project was to design, synthetize and perform preliminary biological assay of new low molecular weight inhibitors of osteoclastogenesis process. The structure of the compounds was designed basing on the cystatin's C active site and the conclusions from the structure-activity dependence research done previously.

Synthesis of new compounds that would have the ability of restraining of osteoclast formation or maturation will have a great influence on the existing therapies of bone diseases connected to loss of bone mass as there is a need to develop new, non-toxic and more efficient therapeutics.