Existing limitations of cancer therapy initiated the search for new active compounds for more selective and efficient treatment. Unlimited potential of cancer cells to proliferate (contrary to physiologically normal cells), points to disturbance of mitotic division process as a main goal of cancer therapy. Mitotic spindle is a cellular structure that plays the key role in cell division. Therefore, several classes of anticancer drugs are targeted at protein fibrils known as microtubules, that build up mitotic spindle, determine its bipolarity and are necessary for correct chromosome segregation in dividing cells. However, microtubules play a crucial role in many other cellular processes besides the cell division, include motility, membrane and cellular scaffolding, intracellular transport, and secretion. Interference with those processes contributes to toxic drug side effects. Due to the limitations, a search for novel, more specific targets for anticancer therapy was commenced. Monastrol, discovered in 1999 by Mayer et al., was the first compound that specifically perturbed mitotic spindle formation without effects on microtubules. That compound was called monastrol due to generation of non-functional monoastral spindles surrounded by ring of chromosomes (Fig.). Monastrol turned out to be a specific inhibitor of single kinesin (Eg5), involved in formation of bipolar spindle and necessary for correct segregation of chromosomes. Therefore, inhibition of that kinesin leads to cell cycle arrest in mitosis (with monoastral spindle) and cell death. The important role of kinesins in cell cycle progression makes them an ideal candidate for drug discovery. Furthermore, increased expression of kinesins in extensively dividing cancer cells may contribute to improved selectivity of treatment.

The current project is aimed to synthesize and biologically characterize novel derivatives of a compound with promising antimitotic activity and monastrol-like mechanism of action, that has been previously investigated by our team (Fig.). Obtained results will allow for selection of the most potent from the investigated kinesin-specific agents. Moreover, study on different chemical derivatives will allow to determine structure-activity relationship and estimate the role of lipophilicity in compound's biological activity. Moreover, it should be pointed that identification of molecules that selectively perturb function of specific proteins involved in mitosis could provide an useful tool for studying cell cycle mechanisms.

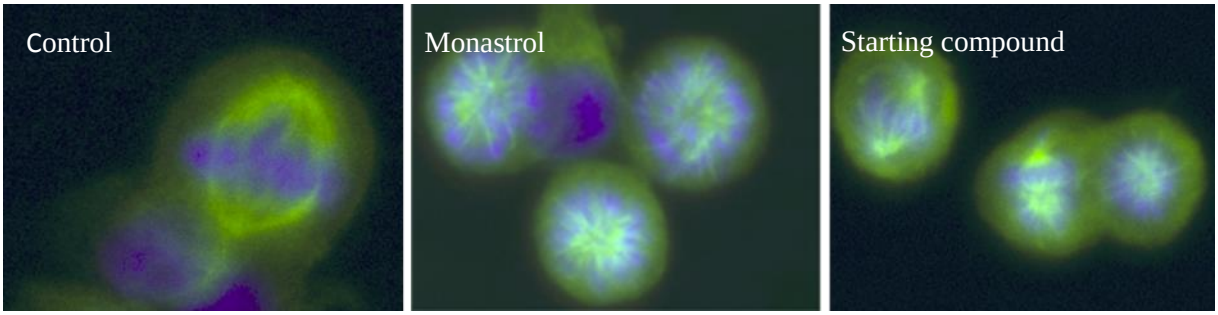

Fig. Confocal microscopy imaging of mitotic spindle in breast cancer cell line (MCF7): control and treated with monastrol and starting compound to further studies.