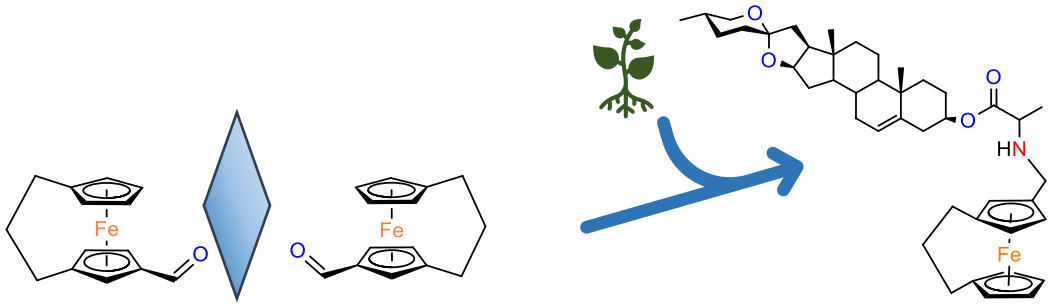
New bioactive planar chiral ansa-ferrocenes conjugates with natural compounds - synthesis, enantioseparation, in vitro biological and in silico molecular docking and ADME studies

Humans need at least 10 metallic elements for proper functioning and development. Until 1950s, little attention was paid to the presence of these elements in living organisms. Today it is assumed that sodium, potassium, magnesium, calcium, iron, manganese, cobalt, copper, zinc and molybdenum are elements necessary for life and our body must have the right amount of them. Iron is one of the micronutrients needed for the synthesis of basic proteins such as hemoglobin found in red blood cells and responsible for carrying oxygen to organs and tissues. The amount of elemental iron and in the body is estimated at 3-4 g, but this element may have other uses related to its presence in medicinal substances.

An interesting group of compounds with potential therapeutic effects are ferrocene derivatives. In these compounds, the iron atom is centered between two planar, parallel hydrocarbon (cyclopentadiene) rings. Such an arrangement of individual elements, resembling a sandwich made of two slices of bread, qualifies ferrocene to the group of sandwich complexes.

When the cyclopentadiene rings in the ferrocene are permanently connected by an additional chain consisting of atoms arranged in series, i.e. one after the other, we are talking about a compound called *ansa*-ferrocene or ferrocenophane. Recent studies show that ansa-ferrocenes combined with other active molecules have better biological activity than these active molecules themselves, as well as ferrocenes (without a bridge) of the same active compounds. So far, a small group of such compounds has been studied. Ferrocophanes with an additional substituent in the cyclopentadien ring, that changes its chemical properties, exibit planar chirality. Since stereoselectivity is a fundamental property of the molecular system and underlies many basic biomolecular processes, the synthesis of optically pure compounds plays an extremely important role in modern organic chemistry and medicine.



Scheme 1. Chiral planars ferrocene and an example of their use to obtain a hybrid with a compound of natural origin – diosgenin.

One of the modern approaches to the design of new, original active molecules is the modification of compounds known from biological sources (plants and animals) and commonly used in traditional medicine. This strategy is based on the safety of these compounds due to their long history of use and the assumption that chemical modification can lead to improved safety and efficacy.

As part of this project, various possible synthetic approaches to obtain ferrocenophanes containing in their structure a carbon chain of different lengths, connecting both cyclopentadiene rings, will be investigated.

Various functional groups will then be introduced into the obtained ferrocenophanes. It will cause the occurrence of planar chirality phenomenon. The resulting mixtures of two enantiomers, i.e. non-overlapping chemical molecules that are mirror images of each other (like the left and right hand) will be separated into individual compounds. They will be chemically connected to other compounds of natural origin with proven biological activity (e.g. diosgenin, ursolic acid derivatives). **In this way, a new group of completely new chemical compounds containing an iron atom in their structure will be obtained.** They will be tested in biological studies to determine their antitumor activity. Next, the mechanisms that cause cancer cell death (apoptosis and autophagy) will then be investigated. For selected compounds, computational studies will be carried out to determine the possibility of using compounds as drugs (ADME). In the next step, the interactions of compounds with protein structures of the human body (receptors) will be checked using computational methods in order to estimate the potential of compounds for further development as biologically active substances. **So far, the relationship between structure and biological activity has never been analyzed for pure enantiomers of ferrocenophanes. Studying the mechanism of their action will significantly contribute to the development of the field of biometalloorganic chemistry and will allow the selection of candidates for new potential drugs, mainly anti-cancer therapeutics.**