

"Dosis facit venenum."
(The dose makes the poison.)
Paracelsus, 1493–1541

Problem and hypothesis

According to the Central Statistical Office of Poland (GUS) data, cardiovascular disease accounts for 46% of all causes of death in Poland and this percentage still grows since '60. Thromboembolic events, leading to complications such as heart attack or stroke are associated with platelet activation. In the case of cardiovascular diseases, stimulated platelets cause arterial occlusion and obstruction of blood flow, resulting in deficiency of blood supply to the organs. In the light of literature data, it is rather safe to say that modulation of platelet activation can provide a reduction of thrombotic events. This would result in a reduction of a deadly toll associated with the above mentioned civilization disease.

Aim

The primary objective of this project is to study the antithrombotic (antiplatelet, anticoagulant, fibrinolytic and endothelial) and haemodynamic properties of the new group of substances: HNO donors, that we have synthesised. According to our initial studies, they have great potential to be used as an safe and effective antithrombotic therapy. We are convinced that we will be able to create modern, innovative and, above all, effective and safe drugs against the most dangerous civilization disease complications like myocardial infarction, brain stroke or pulmonary embolism.

The most important chemical constituent of these innovative substances is the endogenously generated (in biological systems) gas signal molecule (HNO). HNO donors, known as "nitroso" compounds, are represented by an innovative group of substances, which we started to synthesise for this project. They are distinguished by slow, stabilized release of the active substance, which makes them suitable for use as medicaments.

On the other hand, it is known that many beneficial effects of the gas signal molecule relays not only on their complex chemical interactions, but also on the regulation of their common extracellular and intracellular signaling pathways. While for other gasotransmitters, such as nitric oxide or carbon monoxide, these pathways are well known, the detailed mechanism of action of HNO (and its derivatives) on cellular signaling pathways remains a mystery. Therefore, this project will also focus on the discovery and detailed examination of the metabolic and biochemical pathways through which HNOs can affect living organisms.

Summary

The result of this project will be the developing and selection of candidates for innovative drugs for use in the prophylaxis and treatment of cardiovascular diseases and its complications, as well as tremendous progress in basic knowledge that will be made by learning the mechanism of HNO action.