Acta Chimica and Pharmaceutica Indica

Mitochondrially targeted compounds and its clinical potential

Jan Stursa
IBT-Czech Academy of Sciences, Czech Republic

Abstract

Mitochondria have been recently recognized as an emerging target for new anti-cancer drugs. It is one of the main organelles in the cells participating in many important biochemical processes, including oxidative phosphorylation, which is crucial for the cell as a part of ATP synthesis. Mitochondria are also responsible for apoptosis by triggering the complex cell death process. A frequent approach to mitochondrial targeting is tagging the biologically active agents with lipophilic cation such as the alkyl triphenylphosponium moiety. Delocalized hydrophobic cations readily accumulate across the mitochondrial membrane due to the highly negative potential on the matrix side of the membrane.

Here we will present novel mitochondrially targeted compounds developed by our team. An example is mitochondrially targeted tamoxifen (MitoTam), an inhibitor of complex I of the respiratory chain, which has recently entered Phase I clinical trial. We will present the biological properties of MitoTam including its synthesis from milligram amounts scaled up to kilogram amounts. The strategy of preclinical evaluation and its design needed for approval by the regulator prior to launching the Phase I clinical trial will also be discussed.

Apart from the anti-cancer properties, MitoTam and its derivatives also selectively kill senescent cells. Cellular senescence is stress response activated in damaged cells. Inability of immune system to eliminate these senescence cells leads to development of age-related diseases, tissue damage, inflammation and enhanced carcinogenesis. Therefore, we can talk here about the repurposing of MitoTam to another clinically relevant scenario.

Another field of our interest are mitochondrially targeted compounds with the ability to affect iron metabolism. Exemplified by deferoxamine derivatives, these agents feature a migrastatic and tumour suppressive properties. Synthesis and biological results of such compounds will be presented.

The aim of this work was to determine the efficacy of L121 as solvent for carbon dioxide sorption. Successful method to capture CO2 are based on polyethylene and polypropylene glycols under high pressure as demonstrated by the spectral changes of the polymer in the liquid state before and after the gas exposure. L121 shows the CO2 typical bands in the NIR region of the spectra from 15 to 40 °C according to a linear correlation. The effect induced by temperature on the swelling degree of L121 was also investigated and compared to the data obtained by using other viscous media, as Triton X-100 and BMIM BF4 (Angelini et al. J. Mol. Liquids 2018, 258, 85-88).

Biography

Jan Stursa has expertise in organic chemistry and has been participating in numerous projects involving synthesis of fytoestrogens, juvenile hormons as well as the chemistry of calixarenes, carboranes and derivatization of nanodiamonds. For the last 10 years he has been mainly focusing on medicinal chemistry and especially on novel mitochondrially targeted substances with promising biological activity. He is one of the inventors of the substance MitoTam, which is undergoing Phase I clinical trial involving oncological patients. He works as a scientist in the Service technology laboratory (STL) at Institute of Biotechnology Czech Academy of Sciences. STL design and synthetize not only mitochondrially targeted substances but also offers a custom synthesis or academic collaborations. Jan is also involved in advanced technology transfer including design, documentation and management of preclinical and clinical trials.

Publications

1. Luminescence of Nanodiamond Driven by Atomic Functionalization: Towards Novel Detection Principles
2. High-power TR-24 cyclotron-based p-n convertor cooled by submerged orifice jet

Abstract Citation: Jan Stursa, *Mitochondrially targeted compounds and its clinical potential*, Chemistry 2020, 10th World Congress on Chemistry & Medicinal Chemistry, Rome, Italy, 28-29 February, 2020, 36