New steroid sulfatase inhibitors based on 1,2,4-oxadiazole sulfamate derivatives

The forceful medicine development and constantly expanding knowledge about structure and the human body functioning, significantly revolutionized medical science allowing for effective diagnostic and to fight many diseases. For that reason, people suffering from incurable, formerly fatal diseases today have a chance to undertake effective, modern therapy and overcome illness. Regrettably, despite many breakthrough discoveries that have led to the development of a number of innovative medical therapies, the extremely complicated and multistage process of carcinogenesis of various tissues prevents the development of one unique cancer treatment method.

Studies reveal, that breast cancer is the most common type of cancer among women in high-developed countries and in 90% of cases it has hormone-dependent nature[1]. According to the *International Agency for Research on Cancer* data in 2018 about 18 million new cancer cases were diagnosed, of which breast and prostate cancers were make up 18.6% of all cases resulting in the death of about 990 000 people. It is estimated that by 2040 the number of breast and prostate cancer cases will increase by 50%[2]. For that reason, development of innovatory, effective treatment methods that will enable more effective fight against cancer, including hormone-dependent breast cancer (HDBC) takes on a special significance.

One of the treatment method of HDBC is hormone therapy. It involves using of synthetic, biologically active substances that inhibit enzymes responsible for steroid biosynthesis (estrogens and androgens) stimulating the development of hormone-dependent cancer tissue. Until now, three enzyme pathways responsible for the formation of estrogens active form have been identified: pathway of the enzyme aromatase complex, 17β-hydroxysteroid dehydrogenase (17β-HSD) and steroid sulfatase (STS). It is proved that STS activity in cancerous breast tissue is few order of magnitude higher than the aromatase enzyme complex. This implies that steroid sulfatase plays essential role in the development of breast cancer, making it attractive new molecular target that may contribute to development of much more effective HDBC treatment. Over the past few years intensive research has been ongoing to develop new, effective STS inhibitors. Unfortunately, most of substances exhibiting high level of enzyme inhibition showed undesirable estrogenic properties, which in the light of recent studies are the main cause of hormone-dependent cancer tissues progressing and they are the reason of negative clinical trial results. In order to overcome these properties the development of compounds that effectively mimic the steroid structure of natural STS substrates and do not show estrogenic properties has begun.

Substances containing a 1,2,4-oxadiazole heterocyclic ring in constitution are distinguished by their enormous application potential. Literaturely known compounds based on 1,2,4-oxadiazole framework exhibit anticancer, anti-inflammatory, anticonvulsant, antiviral, antibacterial, antifungal and antidepressant activities[3]. They also exhibit promising physicochemical and pharmacodynamic properties, being the ideal core in the development for new, potential drugs. Moreover, the chemical structure of 4-(5-phenyl-1,2,4-oxadiazol-3-yl)phenyl sulfamate derivatives effectively mimics the ABC system of steroid rings of natural STS substrates without being steroid. Therefore, there is a high probability that designed new STS inhibitors will exhibit lack of undesirable estrogenic properties.

This project assumes design, synthesis and examination of biological activity of the new STS inhibitors based on 1,2,4-oxadiazole sulfamate derivatives. The use of molecular modeling techniques will allow for initial verification of the application potential of the designed compounds and selection of the most promising derivatives, which will reduce the time as well as costs of research. Obtained new STS inhibitors will be tested for their biological activity using *in vitro* assays. This research will contribute to the acquirer of a wide range of new substances that can be potentially used in the treatment of hormone-dependent carcinomas.

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[1] Pasqualini, J.R.: Biochim. Biophys. Acta, 2004, 123-143.

[2] International Agency for Research on Cancer, https://gco.iarc.fr/ (retrieved 07.06.2020)

[3] Biernacki K., Daśko M., Ciupak O., Kubiński K., Rachon J., Demkowicz S.; *Pharmaceuticals*, 2020, 13, E111