NEW POTENT STEROID SULFATASE (STS) INHIBITORS BASED ON FLUORINATED 4-(1-PHENYL-1*H*-[1,2,3]TRIAZOL-4-YL)-PHENYL SULFAMATES. SYNTHESIS AND BIOLOGICAL EVALUATION

Mateusz Daśko,[a] Sebastian Demkowicz,[b] Janusz Rachoń,[b] Karol Biernacki,[b] Maciej Masłyk, [c] and Konrad Kubiński [c]

[a]Department of Inorganic Chemistry, Faculty of Chemistry, Gdansk University of Technology, Narutowicza 11/12, 80-233 Gdansk, Poland
[b]Department of Organic Chemistry, Faculty of Chemistry, Gdansk University of Technology, Narutowicza 11/12, 80-233 Gdansk, Poland
[c]Department of Molecular Biology, Faculty of Biotechnology and Environment Sciences, The John Paul II Catholic University of Lublin, Konstantynów 1i, 20-708 Lublin, Poland

Hormone-dependent breast cancer (HDBC) is a major cause of mortality, and there is pressing need to develop novel treatment methods. According to International Agency of Research on Cancer (IARC), 2.1 million cases of breast cancer will be diagnosed in 2018. Over the past decades, numerous reports have suggested the importance of biologically active hormone precursors in regulating the supply of estrogens to HDBC. One approach for treatment of HDBC involves inhibitors of enzymes responsible for the biosynthesis of estrogens in peripheral tissues[1], especially STS which is detected in 90% of breast tumor[2]. A series of fluorinated analogs based on the framework of 4-(1-phenyl-1*H*-[1,2,3]triazol-4-yl)-phenyl sulfamates have been synthesized as steroid sulfatase inhibitors. The design of chemical structures of new potential STS inhibitors was supported by molecular docking techniques to determine the binding modes of the synthesized inhibitors and to identify potential interactions between inhibitors and amino acid residues located in the active site of the enzyme. The inhibitory potency of the synthesized compounds was evaluated on STS isolated from human placenta. In the course of our investigation, we found that compounds substituted with fluorine atom at the *meta* position demonstrated the highest inhibitory effects in enzymatic STS assay. The most active analog – 4-[1-(3,5-difluoro-phenyl)-1*H*-1,2,3-triazol-4-yl]-phenyl sulfamate – inhibited STS enzyme with the IC50 value of 36 nM.

[1] R. Shah, J. Singh, D. Singh, A. Singh Jaggi, N. Singh, *Eur. J. Med. Chem.* **2016**, *114*, 170-190

[2] P. A. Foster, M. J. Reed, A. Purohit, *Anti-Cancer Agents Med. Chem.* **2008**, *8*, 732-738.