DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF THE NEW STEROID SULFATASE (STS) INHIBITORS BASED ON SULFAMATE ANALOGS CONTAINING C-F BONDS

Cancer is one of the most complex problems in modern society. Lifestyle, environment, genetic predisposition or diet, are just a few of the multifactorial causes of this disease. Thus, is it possible to thoroughly eliminate it? Unfortunately, the fight against cancer is extremely complicated. Taking into account the complexity of biological processes responsible for the tumor growth, it is impossible to apply one multipurpose and flexible therapy. Focusing our deliberations on breast cancer problem we come across some questions – is it possible to find a method for its complete elimination and whether the actual state of scientific knowledge is large enough to cure such diseases in an effective way?

Breast cancer is a major cause of mortality of postmenopausal women in developed countries, therefore it is of great priority to find a new and effective treatment method. Recent research clearly indicate the influence of endocrine precursors, such as estrogens, on stimulating of the cancer cell proliferation. One of the most promising anticancer strategy is obtaining of the biologically active compounds that precise inhibit enzymes responsible for the estrogen biosynthesis in tissues. Until now, scientists have identified three metabolic pathways which are the main sources of active estrogens in breast tissues: aromatase, 17β-hydroxysteroid dehydrogenase and steroid sulfatase. Considering the STS action mechanism that includes the estrogen sulfates hydrolysis in order to obtain their biologically active forms, it seems that STS may have a very important role in breast cancer cell proliferation[1]. In recent years intensified scientific research has been carried out in order to obtain effective and potent STS inhibitors. The most potent STS inhibitors are compounds where a sulfate function of the natural STS substrates was replaced by a sulfamate moiety. Unfortunately, a series of potential drugs, especially those with a steroidal scaffolds, despite possessing STS inhibitory properties, also stimulated a cancer cell proliferation. Efforts to eliminate the adverse effects of steroid based STS inhibitors, led to obtaining a series of sulfamate tricyclic coumarin derivatives. One of them, 667 COUMATE, has recently entered into the clinical trials[2].

Design of the sulfamate-based STS inhibitors that are able to mimic steroidal rings seems to be a very promising scientific direction. All the facts listed above, encouraged us to undertake the task of design, synthesis and biological evaluation of the new STS inhibitors based on sulfamate derivatives containing C-F bonds. As is widely known, introducing a fluorine atom into the structures of biologically active compounds, significantly affects for its physicochemical properties. The fluorine atom may also participate in numerous electrostatic interactions including hydrogen bonding[3]. The ability to establish hydrogen bonds in the enzyme active site may have a significant impact on the enzyme-inhibitor complex stability and leads to a higher biological activities of fluorinated inhibitors. Moreover, considering the influence of fluorine atom on the lipophilicity, we expect that compounds with a C-F bonds in their structures will be much better distributed in tissues, and will exhibit more potent biological activities.

Nowadays, rational designing of the new therapeutic compounds demands involvement of the modern calculating methods, needful for identifying the pharmacophore specific for a corresponding enzyme. This approach allows to significantly reduce research costs and required time[4]. Thus, our project assumes the use of molecular modeling tools in order to better understand and visualize the enzyme active site and explore the potential interactions between designed compounds and the active site of STS. These calculations will lead us to choose only these compounds that exhibit the best binding ability within the active site of STS.

In summary, the development of effective breast cancer therapies requires conducting intensive research on drugs that are able to inhibit the process of carcinogenesis. Scientific reports suggest that steroid sulfatase can play a key role in stimulating of the tumor growth and STS seems to be a very interesting molecular target for the discovery of potential new drugs. However, it is necessary to increase funding for the development of innovative cancer treatments, starting from basic research involving rational design, synthesis and biological evaluation of the new drug candidates, up to clinical trials.

References

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