

INSIGHTS INTO BIOLOGICAL ACTIVITY AND MECHANISM OF ACTION OF NOVEL STYRYLQUINAZOLINE DERIVATIVES AS TYROSINE KINASE INHIBITORS

1. Objectives

Currently, many research in the field of medicinal chemistry focuses on the mechanisms of carcinogenesis, indicating the important role of specific protein - tyrosine kinases in cell cycle progression, differentiation, metabolism and intracellular signal transduction. Therefore, the oncogenic tyrosine kinases may be an attractive target for the design of novel groups of potential drugs, that may be used in targeted therapies. This is reflected in a significant number of programs in progress (30%) in the pharmaceutical industry, whose are focused on developing novel TKIs. Moreover, there is still strong need for exploration of novel TKIs, in search for a strong anti-tumor activity and also high selectivity, which in turn minimize side effects of the therapy.

The current project is focused on the search of a novel tyrosine kinase inhibitors, that are based on thioether derivatives of styrylquinazoline. The project involves a comprehensive studies consisting of three parts. The design, synthesis of novel derivatives and extensive biological tests. The preliminary studies revealed that styrylquinazoline derivatives containing sulfur atom may be attractive leading structures for TKI design. Therefore, this group of derivatives is particularly interesting for extensive investigation about mechanism of action in cancer cells. Characteristics of newly synthesized styryloquinazoline derivatives will be based on several steps in biological analysis.

In summary, the project takes into account the extensive approach to design drugs, synthesis novel compounds and the exact characteristics of novel TKI in cancer cells. For the lack of reports on similar structures we believe these results will be useful for our knowledge on cancer biology and new possibilities in drug design. In addition, a thorough understanding of the mechanisms regulating signaling pathways and mutual dependence interactions between proteins after treatment with styrylquinazoline derivatives allow to increase understanding of the development of multi-targeted therapies for the treatment of cancer.

2. Research methodology

In the framework of this project it is expected to create a virtual library of sulfur styryloquinazoline derivatives, then in silico studies will be performed as a docking to available structure of enzymes. In this way, we plan to select fifty compounds for synthesis and biological evaluations. In biological part, cytotoxicity assays on panel of cancer cell lines of different origin are main part of research. Especially interesting are those cell lines, in which mutations and overexpression of proto-oncogene Src and EGFR kinase plays crucial role in the progression of cancer. These are also the most frequently occurring cancers. Therefore, we plan to use colorectal carcinoma, breast cancer, pancreatic cancer, lung cancer and myeloid leukemia. In the next step, we plan to assess the impact of those synthesized compounds on activity of receptor and non-receptor tyrosine kinases. Then for a group of 8-10 active derivative conduct studies to determine the possible mechanism of action in cancer cells. Therefore, to determine the effect of potential TKIs the regulation of molecules involved in cell cycle progression and proteins involved in cell death by apoptosis or autophagy.

3. Reasons for choosing the research topic

Cancer is a major health problem worldwide. According to the World Health Organization reports, cancer accounts for over 13% of all deaths worldwide, which puts them in second place, immediately after cardiovascular diseases. Despite the knowledge, experience and a considerable amount of produced pharmaceuticals, as well as the huge investment in research, some types of cancer are still considered incurable. On the other hand, use of conventional therapies, such as cytotoxic chemotherapy or radiation are often inefficient by destroying rapidly dividing cells (even normal cells - bone marrow and gastrointestinal tract), which causes many adverse side effects. In addition, important problem in treatment is rapid development and transformation of cancers. Therefore, it is necessary to search and develop new effective drugs and treatment methods in the fight against cancer. In addition, important factor is better understanding the mechanisms of action of potential drug and their continuous improvement. These problems are ones of the most important challenges for modern science.