SCAFFOLD DECORATED 1,2,3-TRIAZOLES AS POTENTIAL ANTI-CANCER AGENTS

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ABSTRACT

1,2,3-triazole skeleton is a privileged building block for the discovery of new promising anticancer agents. Introduction of privileged scaffolds to the molecular framework of 1,2,3-triazole is an indispensable route to the wise exploitation of molecules with inherent potential for anticancer activities.

INTRODUCTION

About 13% of all human deaths throughout the world are caused by cancers, which are diseases characterized by uncontrolled cell growth, metastasis, and invasion. Although the risk of cancer increases with age, people of all ages even fetuses can be affected by the disease. Breast carcinoma (BC) is the commonest cancer among women and the second highest cause of cancer death. Most cases occur during age 45–55. It also occurs in men but is more than 100-fold less frequent than in women.

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Chemotherapy is considered as the most effective method among many other methods prevalent to treat cancer. At present, the cancer treatment by chemotherapeutic agents, surgery and radiation have not been fully effective against the high incidence or low survival rate of most the cancers. Several nucleoside drugs have been developed as cancer treatment agents: cladribine, clofarabine, capecitabine, cytarabine, fludarabine, gemcitabine, decitabine, and floxuridine. The development of new therapeutic approach to breast cancer remains one of the most challenging areas in cancer research.

Cyclin-dependent kinases (CDK) are classic Ser/Thr kinases with molecular weights of 30–40 kDa. This family of enzymes plays an important and well-defined role in cell cycle regulation and proliferation. Abnormal activation of various CDKs can ultimately lead to deregulated cell cycle progression, a common feature in many cancers. Given the pivotal role that dysregulation of CDK activity plays in cancers, targeting the CDKs is a viable strategy for blocking and/or interfering with tumor cell proliferation. Thirteen CDK's and at least 29 cyclins have been discovered from the human genome and have been extensively characterized in regards to controlling cell cycle. Mutations in CDK proteins can result in the overexpression and altered function of CDK's and specific cyclins.

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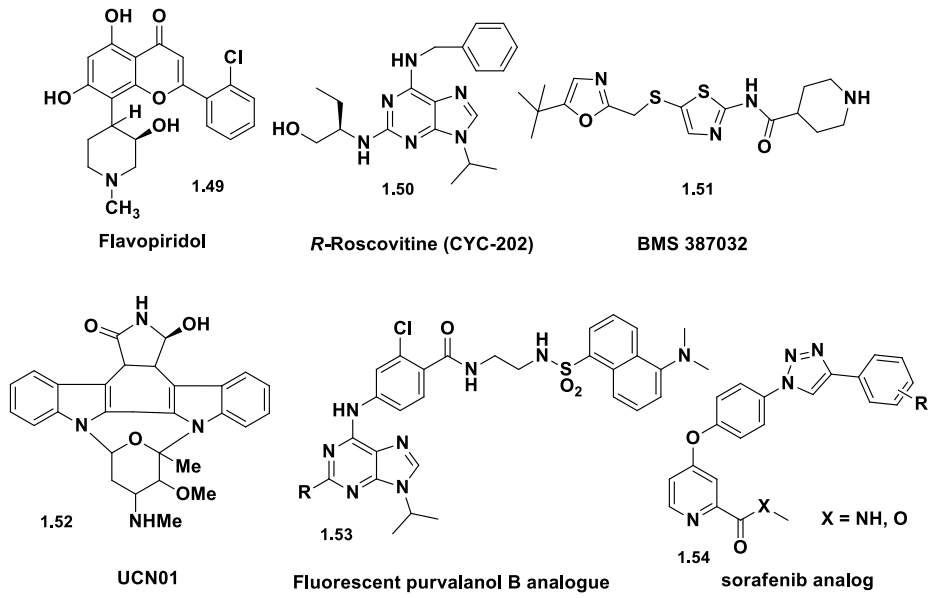

Figure 1. CDK inhibitors under clinical trials (**1.49**-**1.52**), an example for fluorescent CDK inhibitor (**1.53**) and a click derived CDK inhibitor (**1.54**)

Inhibitors of cyclin-dependent kinases (CDKs) are an emerging class of drugs for the treatment of breast cancers. Experimental evidence suggests that CDK inhibitors inhibit the cyclin D–dependent kinase activity and thus prevent tumor growth and/or at least partially revert the transformed phenotype. For example, reduction of cyclin D expression through antisense technology causes a concomitant decline in cyclin D–dependent kinase activity and results in inhibition of tumor growth, abolition of tumorigenicity, or, in some instances, tumor cell death. Several compounds are currently in clinical trials including flavopiridol (1.49), R-roscovitine (CYC202) (1.50), BMS-387032 (1.51), and UCN-01 (7-hydroxystaurosporine) (1.52). Most of these compounds, however, inhibit multiple CDKs, with CDK2 being a particularly common target in drug discovery programs because this enzyme is easily crystallized with inhibitors of varying molecular structure. CDK inhibitors are currently under evaluation in clinical trials as single agents and as

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sensitizers in combination with radiation therapy and chemotherapies. Fluorescent CDK inhibitors (1.53) offer potential as novel theranostic agents, combining therapeutic and diagnostic properties in the same molecule. Development of click derived CDK inhibitors is an emerging field of drug discovery processes since they exhibit higher potency than other non-triazole inhibitors and several of them have been reported (1.54) (Figure 1).

TAILORING MOLECULES FOR BIOLOGICAL APPLICATIONS

Structural complexity and diversity of molecules are important criteria in drug discovery as well as material sciences. This fact led to the scientists to use the Diversity Oriented Synthesis (DOS) for the development of diverse structures for various applications especially in drug discovery. This concept was introduced by Schreiber in 2000, which involves the deliberate simultaneous and efficient synthesis of more than one target compound in a diversity-driven approach to answer a complex problem. Structural diversity can be achieved through the variation in various aspects like building blocks, stereochemistry, functional groups and most importantly the molecular frame work. Methods like Multicomponent reactions (MCRs) and introduction of privileged scaffolds are usually used to generate the structural diversity and complexity in molecules.

MCRs are one of the most important processes for the preparation of highly functionalized complex organic compounds in modern synthetic chemistry. They are special types of chemical transformations in which three or more starting materials react to form a product where the essential parts of the reactants must be seen in the newly formed product. The majority of MCRs are based on classical condensations between carbonyl derivatives and various nucleophiles, the illustrative example being the first known MCR, the Strecker synthesis of amino acids from aldehydes, potassium cyanide, and ammonium chloride reported in 1850. Others, like the Mannich reaction, and a host

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of transformations designed for the synthesis of nitrogen-containing heterocycles including Biginelli, Hantzsch, or Asinger reactions, also rely on the classical condensation processes. The first example of MCR in natural product synthesis was reported in 1917 which is the Robinson synthesis of alkaloid tropinone.

Introduction of privileged scaffolds to the molecular frameworks is an indispensable route to the wise exploitation of molecules with inherent potential for biological as well as optical activities. The term 'privileged structures' was first described by Ben Evans of Merck research group during their work on benzodiazepines and has recently emerged as one of the guiding principles of modern drug discovery. Consequently, benzodiazepines were the first to be described as privileged. After this, many more privileged scaffolds were identified which include chalcone, benzopyrone, quinoline, isoquinoline, indole, pyrimidinone, oxazolones, *β*-lactams, tetracyclines, macrolides, coumarins, glycopeptidesetc and recently macrocycles are also identified as privileged scaffolds. These scaffolds tend to impart highly favorable characteristics, while alterations to the secondary structure lead to high levels of potency and specificity. Using these scaffolds as a starting point, Nature has generated thousands of distinct molecules serving various purposes. Chemists have taken advantage of the principle of privileged scaffolds via isolation and synthesis of natural products as well as subsequent alteration to these scaffolds to introduce new analogs that possess improved activities.

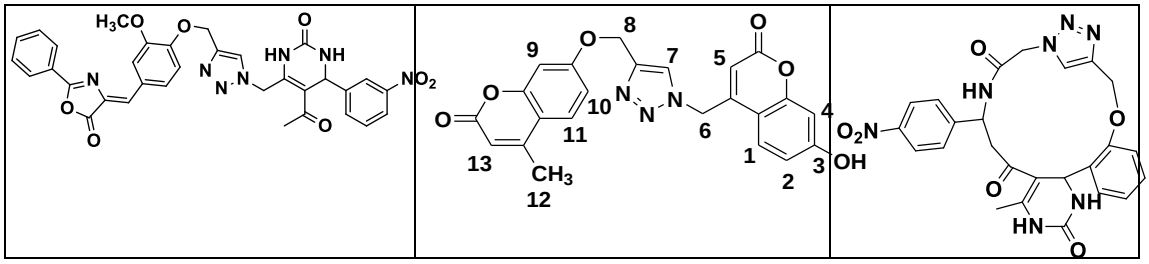

Figure 2. 1,2,3-triazole tailored with privileged scaffolds such as pyrimidinone, coumarin, oxazolones and macrocyclic variation of 1,2,3-triazole

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Figure 2 shows such 1,2,3-triazole tailored with privileged scaffolds such as pyrimidinone, coumarin and oxazolones. The cytotoxicity evaluation results are promising and point to possibilities of these molecules as potential inhibitors of human breast cancer cell line MCF-7.

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