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Quinazolines as Anticancer Agents Targeting Tyrosine Kinases

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Abstract

Cancer is a broad group of diseases that can affect any organ or tissue in the body due to abnormal cellular growth for unknown reasons. Many existing chemotherapeutic agents are highly toxic and have low selectivity. They also contribute to the development of therapeutic resistance. As a result, cancer treatment requires the development of targeted chemotherapeutic agents with low side effects and high selectivity. Quinazoline is a critical scaffold that has been linked to a variety of biological activities. One of the most notable biological activities of this scaffold is its anticancer activity. Several established anticancer quinazolines work on various molecular targets via different mechanisms. The goal of this review is to present various aspects of medicinal chemistry such as drug design, structure-activity relationship, and mode of action of some anticancer quinazoline derivatives. It focuses on the chemotherapeutic activity of quinazolines from the standpoint of drug discovery and development. This review provides medicinal chemists with a bird's-eye view to aid in their efforts to design and synthesise novel quinazolines as targeted chemotherapeutic agents.

Keywords: Quinazoline • Synthesis • Anticancer • Structure activity relationship

Introduction

Cancer is currently the most terrifying disease afflicting humanity. It is a group of diseases caused by abnormal cell growth that can spread to any part of the body. Cancer research accounts for 4% of all studies conducted worldwide. This research area continues to grow year after year, reflecting the global importance of this research area. Because cancer is a complex disorder, there are several challenges in the treatment process. Many anticancer drugs are used either alone or in combination with other drugs. Over the last 50 years, research into molecular targets and cellular proliferation has resulted in the development of over 100 FDA-approved anticancer drugs.

Literature Review

Anticancer medications such as alkylating agents, antifolates, and antimitotic agents were previously used to treat lymphoma and leukaemia. These classes of chemotherapeutic agents were toxic, had low selectivity, and developed resistance. The targeted therapy approach was used to create anticancer agents that are more selective, less toxic, and highly effective. Among this group, the quinazoline moiety is the most important in the field of medicinal chemistry for the treatment of diseases and infections. Quinazoline is a heterocyclic compound composed of two aromatic six-membered rings. The pyrimidine ring, which contains two nitrogen atoms, is fused to the second aromatic benzene ring. Quinazoline is thus a phenyl pyrimidine compound.

Quinazoline molecules are a popular class of multi-acting therapeutic agents in the pharmaceutical and biological fields. Because of its ease of preparation and wide range of pharmacological activities, this scaffold has become a popular therapeutic agent. The basic approach for the development of novel anticancer agents is to place different substituents at the 4, 6, and 7-positions of the quinazoline system. Many quinazoline derivatives are still in clinical trials for the treatment of various diseases. Among these agents are erlotinib, gefitinib, afatinib, dacomitinib, and many others. These agents are currently used to treat cancers such as colon, breast, prostate, and lung cancer.

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Discussion

Many researchers have made efforts to prepare a library of quinazoline derivatives due to their enormous synthetic importance and diverse therapeutic activities. The first derivative of 2-cyano-quinazolin-4-one. Bischler and Lang then decarboxylated quinazoline-2-carbocylic acid to produce quinazoline. Gabriel synthesised quinazoline in 1903 by reducing o nitrobenzylamine to o-aminobenzylamine, which condensed with formic acid to yield dihydroquinazoline, which was then oxidised to yield quinazolin-4-one. Quinazoline molecules have been prepared using a variety of synthetic methods. The following synthetic reactions demonstrate some of the most common traditional methods for preparing quinazolines.

Quinazolines are a promising class of anticancer agents with potent therapeutic activity against various types of tumours. The majority of quinazoline anticancer research has concentrated on the molecular mechanisms of their chemotherapeutic action. The majority of the quinazoline derivatives with anticancer activity were discovered to be protein kinase inhibitors. They prevent tumour growth by inhibiting DNA replication and transcription. Furthermore, by inhibiting breast cancer resistant proteins, some of these anticancer derivatives overcome breast cancer resistance. Anticancer quinazolines also inhibit other enzymes such as thymidylate synthase, poly ADP-ribose polymerase-1 (PARP), and topoisomerase. As a result, quinazolines exhibited chemotherapeutic activity via a variety of molecular interactions and mechanistic pathways.

X-ray crystallographic study of the modes of binding for two members of the quinazoline tyrosine kinase inhibitor family. Hydroxyaniline-6,7-dimethoxyquinazoline in complex with cyclin-dependent kinase 2 and methylsulfanylaniline-6,7-dimethoxyquinazoline in complex with p38 kinase were the two inhibitors. In both inhibitors, the 4-anilinoquinazoline moiety was attached in the ATP site, with the quinazoline ring system oriented along the peptide strand that connects the protein's two domains and the anilino substituent projecting into a hydrophobic pocket within the protein interior. In each case, the nitrogen at position-1 of the quinazoline accepted a hydrogen bond from a domain connector strand backbone NH, and aromatic hydrogen atoms at C2 and C8 interacted with peptide strand backbone carbonyl oxygen atoms.

Tyrosine kinases are essential components of oncoproteins associated with various types of cancer. As a result, they were chosen as a promising biological target for anticancer drugs. Protein tyrosine kinase is classified into two types: transmembrane receptor linked and non-receptor tyrosine kinase. Over 20 different types of receptor tyrosine kinases have been discovered.

Binding of the ligand to one of these tyrosine kinase extracellular receptors results in receptor dimerization. This causes the cytoplasmic tyrosine kinase to phosphorylate various types of tyrosine residues, resulting in the activation of various cell signalling pathways such as phosphoinositide 3-kinases, mitogen-activated protein kinase (MAPK), and signal transducer activator of transcription 3.Non-receptor tyrosine kinases, on the other hand, are enzymes that play an important role in the regulation of cell growth, differentiation, migration, adhesion, and apoptosis [1-6].

Conclusion

The development of novel anticancer agents has progressed from toxic non-selective agents to less toxic selective agents. Current chemotherapeutic drugs have significant drawbacks in terms of selectivity and toxicity. As a result, for the treatment of these life-threatening diseases, targeted therapy acting on a specific biological target is required. Continuous drug discovery research efforts have resulted in the investigation of quinazoline and its derivatives as a targeted anticancer agent. Quinazolines were used to treat cancer as tyrosine kinase inhibitors. A large body of scientific evidence demonstrated the efficacy of quinazolines as targeted anticancer agents. Several molecules of anticancer quinazolines have been approved by the FDA and are now available on the market for the treatment of various cancer diseases.

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Conflict of Interest

There are no conflicts of interest by author.

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