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Versatile Mechanisms of Substituted Quinazolines in Targeted Cancer Therapy

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ABSTRACT

Background: The aim of this review is to provide a minireview on diverse anticancer activities of substituted quinazoline derivatives.

Main Body: This minireview provides a correlation between the various mechanisms of action of quinazolines as anticancer and the substitution pattern around the nucleus.

Conclusion: The linker group and substitution at N-1, C-2, C-5, and C-6 positions have been found to be the most contributory factors for anticancer activity. This will help in the further design to afford more selective, potent, and multi-target anticancer of 2-substituted benzimidazole-based compounds.

Keywords: Heterocyclic; Qinazolines Anticancer; Cytotoxic Effect

Introduction

Cancer has become one of the leading causes that lead to a great increase in human mortality. Cancer is a group of cells that initiated from a single cell with no control on its growth and rapid proliferation properties. The main three options for cancer treatment are chemotherapy, radiotherapy, and surgery [1]. A wide range of cytotoxic drugs are used alone or in combination with other drugs to treat cancer. These cytotoxic drugs are accompanied by several disadvantages which is mainly about their inability to differentiate between cancerous and normal cell types which leads to causing serious side effects. Therefore, continuous efforts are being made to develop effective anti-cancer drugs with minimal side effects and targeting only cancerous cells [2] to save the lives of millions of people worldwide. Heterocyclic compounds are widely found in natural products as well as synthetic compounds, and most of them have been reported to have numerous biological activities such as anticancer, antiviral, antimalarial, antimicrobial, anti-inflammatory, anticonvulsant, antioxidant, and antihypertensive [3]. As a promising nitrogen-containing heterocycle nucleus, quinazoline is formed by the fusion of pyrimidine and benzene [3]. The properties of quinazoline derivatives depend on three factors which are [4]:

1. The substituents nature.
2. The presence of substituent depending on their presence in the pyrimidine ring or in the benzene ring.
3. The existence of conjugation in the pyrimidine ring

Synthesis of Quinazoline Ring

Griess prepared the first quinazoline derivative, 2-cyano-3,4-dihydro-4-oxoquinazoline in 1869, by reacting cyanogen with anthranilic acid. The bicyclic compound produced was called bicyanoamido benzoyl and this name was used until 1885. Bischler and Lang obtained the quinazoline moiety by decarboxylation of the 2-carboxy derivative many years later [5]. Several methods are reported for synthesis of quinazoline ring (Figure 1).

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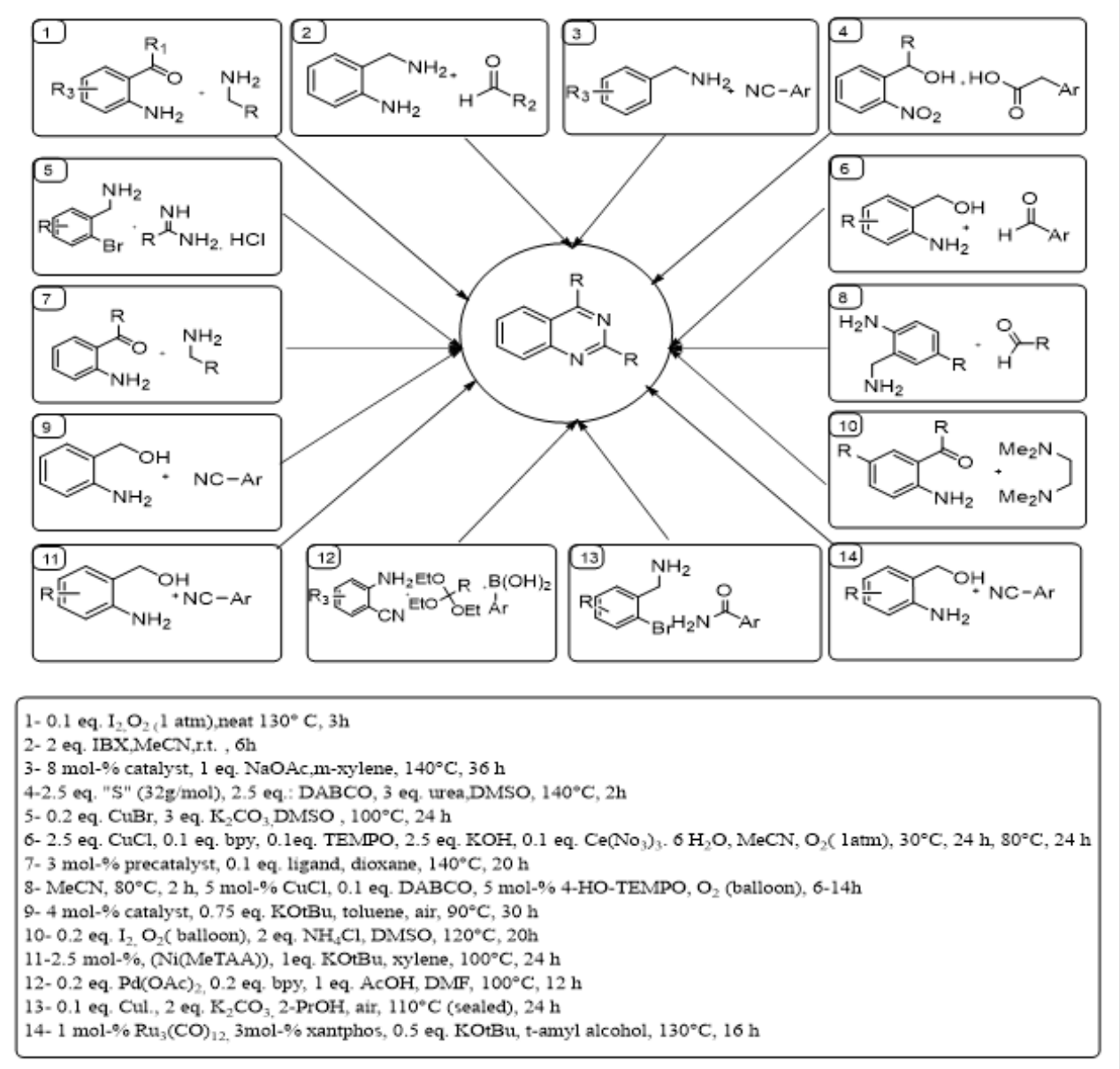

Figure 1

Anti-Cancer Activity of Quinazoline Ring

Quinazoline Derivatives as Protein Kinase Inhibitors

Protein kinases is a constituent of the most important human enzyme class that controls important events such as cell cycle development, cell division, and cell proliferation. When protein kinases are expressed in mutated, without a regulated form or when produced in high levels in an abnormal way, this can transform normal cells into cancerous cells. The development of non-toxic and selective protein kinases inhibitors is a promising target for the treatment of cancer. The discovery of erlotinib and gefitinib as anticancer drugs in early 2000s encouraged researchers to study 4-anilinoquinazoline compounds, which led to the development of promising and novel compounds such as lapatinib, vandetanib, and afatinib. Many patents and articles have been published that focus on the discussion of the feasibility of the anilinoquinazoline scaffold for the development of tyrosine kinase inhibitors (TKIs). The epidermal growth factor receptor (EGFR) remains the main biomolecular target of this class of compounds. Some compounds such as lapatinib, do not show high selectivity for EGFR, while vandetanib inhibits the kinase activities of both EGFR and VEGFR-2 [6]. EGFR is a very promising molecular target for cancer treatment; it has been noticed, that most of the patients developed resistance to the EGFR inhibitors. Due to this resistance, several new compounds were synthesized

by adding substituents on the benzene ring of the EGFR inhibitor gefitinib. As a result, in 2010, X. Wu et al. synthesized two series of 4-benzothienyl amino quinazoline derivatives as new analogues of gefitinib. Ethyl or methyl groups added on the side chains at position 7 of the compounds showed good pan-RTK inhibitor activity with improved apoptosis-inducing capabilities. X. Qin et al. designed and synthesized morpholin-3-one fused quinazoline derivatives, a novel series by intramolecular cyclization and assessed their biological activities with regard to EGFR inhibition (Figure 2). The most active compound of the series was 1. Furthermore, compound 1 showed antiproliferative activity against H358 and A549 cell lines and good inhibitory activity against mutant EGFRT790M/L858R compared to gefitinib and erlotinib [6].

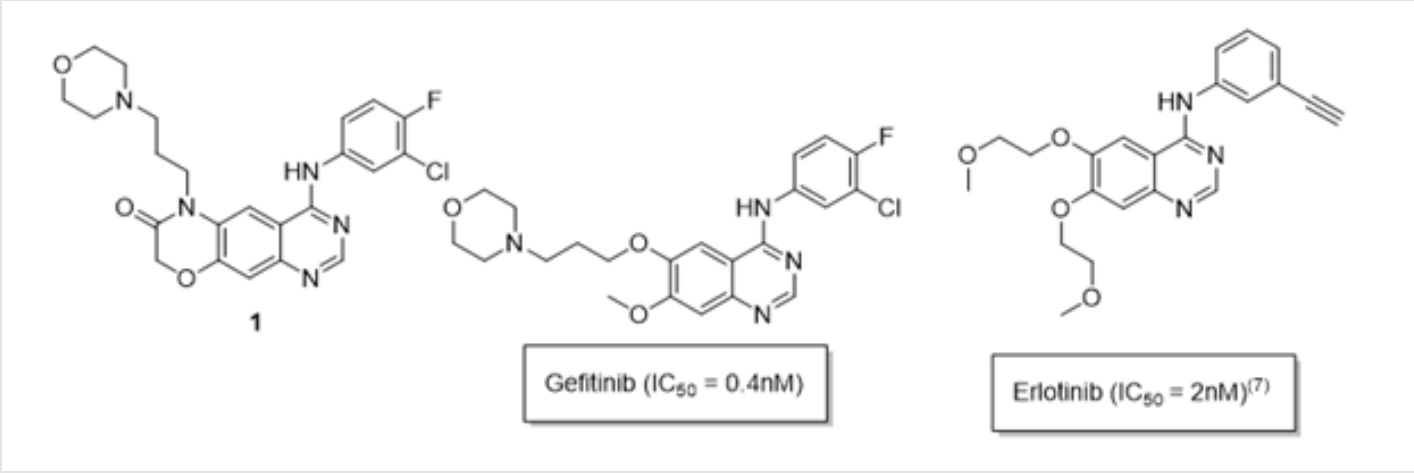

Figure 2

Quinazoline Derivatives Acting as Tubulin Polymerization Inhibitors

Tubulin has several drug binding sites and is an important target for anticancer drugs. A. Chilin and his colleagues reported biphenyl aminoquinazoline (2) as an inhibitor of EGFR, FGFR-1, PDGFRβ, Abl1, and Src kinase activities at submicromolar concentrations in 2013. Also, Compound (2) exhibited EC50s in the nanomolar range against numerous cancer cell lines. After studies of the mechanism of action of the biphenyl aminoquinazolines', it was noticed that these molecules showed anti-TK activity and also inhibited tubulin polymerization [6].

Quinazoline Derivatives Acting as Protein Lysine Methyltransferase Inhibitors

Protein lysine methyltransferase G9a is over-produced in cancer cells and acts as a catalyst in the process of methylation of lysine 9 of lysine 373 (K373) of p53 & histone H3 (H3K9). Genetic damage of G9a inhibits growth of the cancer cell through the di-methylation of p53 K373 which leads to the inactivation of p53. With the intention of studying the structure–activity relationship and improving the potency and selectivity, many regions of the quinazoline template were investigated. (Figure 3) As a result, compound (3) (UNC0224) was discovered as a potent G9a inhibitor with exceptional selectivity [6].

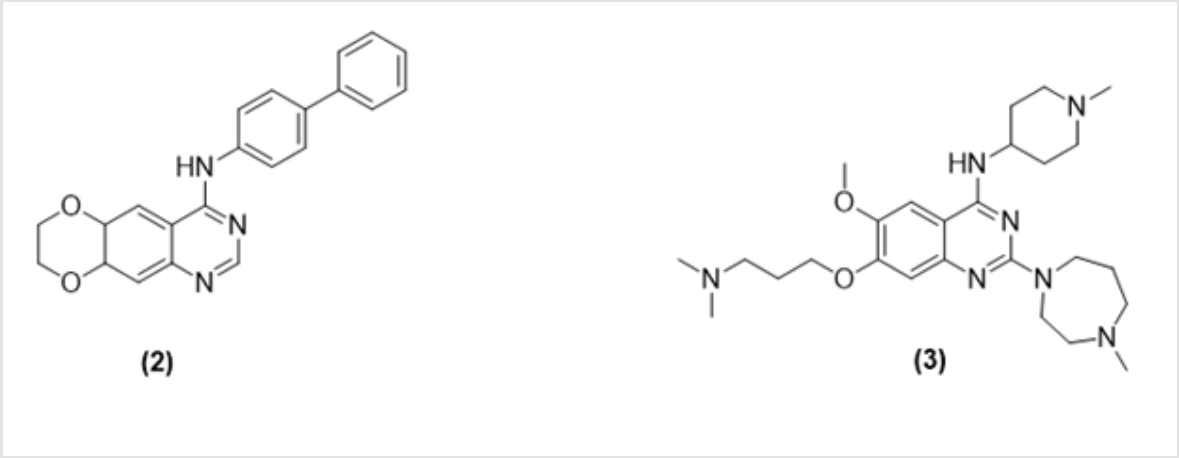

Figure 3.

Quinazoline Derivatives Acting as Topoisomerase I Inhibitors

DNA topoisomerases (Top) are a group of very important enzymes involved in the modification of the DNA during cellular processes: replication, transcription, and repair. They are divided into two major families according to whether they cleave only one or both DNA strands: 1.) Top: Type I (Top1) and 2.) Type II (Top2). A novel group of anticancer agents; Top1 enzyme inhibitors are considered to have a wide range of activity in solid tumors and hematological tumors. It was noticed that Top1 inhibitory activity depends on the nature of the chain at position 5, such as whether it is a type –O– or –NH– only, the linker length, and the terminal nitrogen containing group. The compounds which showed the most activity are the compounds that contained: dimethylaminoethylamino (4), dimethylaminopropylamino (5), and diethylaminoethylamino (6) chains [6] (Figure 4).

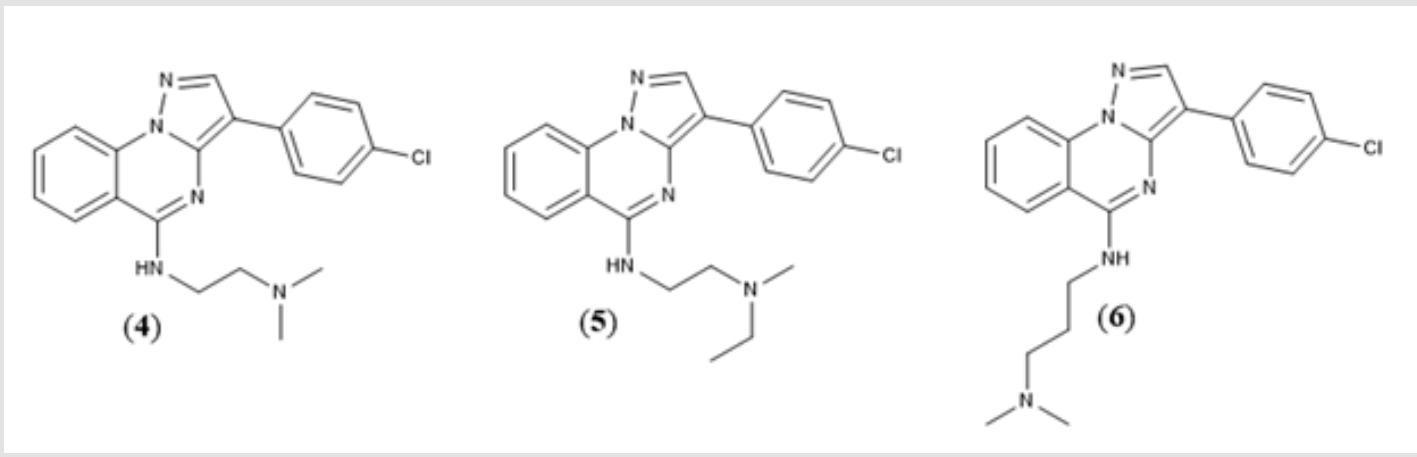

Figure 4.

Quinazoline Derivatives Acting as PI3K/Akt/mTOR Inhibitors

The PI3K/Akt/mTOR pathway has very important regulatory roles in different cellular functions, which include: cell proliferation, differentiation, migration, survival, and angiogenesis. The dysregulation of PI3K leads to uncontrolled cell growth which leads to malignant transformation. Quinolines and 1,3-dihydro-2H-imidazoij4,5-c] quinolin-2-ones are the two major classes of promising scaffolds with the PI3K inhibition effect [6]. A new series of 4,6-disubstituted quinazoline derivatives were designed by Y.-Y. Hei et al. as PI3K inhibitors. This was synthesized by replacing the 1,3-dihydro-2H-imidazoij4,5-c] quinolin-2-one skeleton of PF-04979064 with a quinazoline moiety and also by the opening the piperidine ring. All the compounds exhibited substantial anti-proliferative activity. Compound 7 displayed the most potent anti-proliferative and PI3K inhibitory activity [6]. The presence of a hydrogen-bond receptor group (for example: a cyano or a nitro group) at position 5 of the pyridine ring attached at position 6 of quinazoline is very essential for enhancing the anti-proliferative activity, this was suggested by the study of the structure–activity relationship. In 2016, W. Peng et al. anticipated that the replacement of a hydrogen atom on the quinazoline scaffold with other substituents such as 6-amino-4- (trifluoromethyl) pyridin-3-yl, 2-amino-pyrimdin-5-yl, and 3-hydroxyphenyl would result in good kinase inhibitory activity. As a result, a novel series of 7- or 8-substituted-4- morpholine-quinazoline derivatives were designed, synthesized, and tested for in vitro anti-cancer activities and kinase inhibitory. The results showed that compound 8 acts as a potent anticancer agent and PI3K inhibitor, which significantly inhibited the PI3K/Akt/mTOR pathway [6].

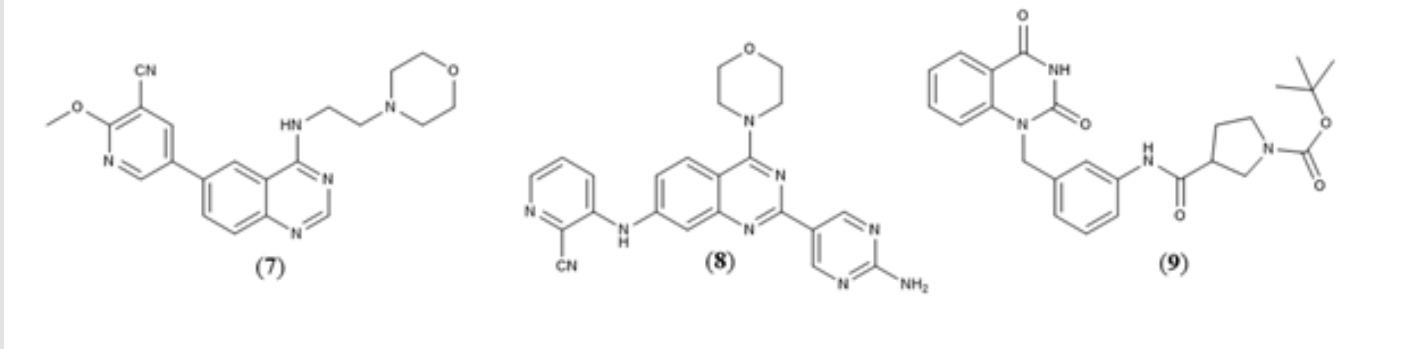

Figure 5.

Quinazoline Derivatives Acting as Poly(ADP-ribose) Polymerase-1 (PARP-1) Inhibitors

Poly(ADP-ribose)polymerase-1 (PARP-1) plays a vital role in the DNA repair process, therefore it is considered a promising anticancer drug target. The structure–activity relationship studies suggested that compounds having β-proline and piperidine-4-carboxylic acid groups are good PARP-1 inhibitors. Compound 29 having an (S)-N-Boc-pyrrolidin-3-yl substituent showed maximum activity as a PARP-1 inhibitor; as a result, it was chosen for further evaluation for growth inhibition, PARP-2 inhibitory activities, and temozolomide (TMZ) potentiation effects in cancer cells. The results were very pleasing, and compound (9) displayed high inhibitory activity at both enzymatic and cellular levels [6,7] (Figure 5).

Conclusion

From the above discussion, it is proven that quinazoline and its derivatives have a great potential as anticancer agents. In the light of discovering anti-cancer drugs, many research laboratories globally are focused on the synthesis of different quinazoline derivatives in order to produce novel and more potent anticancer drugs, therefore it is considered as an important pharmacophore. This minireview concentrated on the anticancer activities of quinazoline derivatives against different types of cancer cells. Hopefully, the information presented in this article will inform researchers about the reported quinazoline pharmacophore-based potent anticancer agents discovered recently and will provide support in the area of developing novel anticancer drugs.

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