REVIEW ON THE SIGNIFICANCE OF QUINAZOLINE DERIVATIVES AS BROAD SPECTRUM ANTI-CANCER AGENTS.

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ABSTRACT

Cancer is one of the major causes of human mortality worldwide. A number of approved antineoplastic medications and treatment regimens are already working in the field, and several new compounds are in different phases of clinical trials. An extensive series of anticancer drugs exist in the market, and studies explained that these molecules are associated with different types of adverse side effects. The reduction of the cytotoxicity of drugs to normal cells is a major problem in anticancer therapy. Therefore, researchers around the globe are involved in the development of more efficient and safer anticancer drugs. An interesting output of extensive research is that the quinazoline scaffold and its various derivatives can be explored further as a significant class of cancer chemotherapeutic agents that has already shown promising activities against different tumors. In general, quinazoline derivatives have already occupied a crucial place in modern medicinal chemistry. Quinazoline is one of the most studied moieties in medicinal chemistry due to the wide range of biological properties such as the anticancer, antibacterial, anti-inflammatory, antimalarial and antihypertensive activities. The anticancer activity of this scaffold has been well established.

Keywords: Quinazoline, cancer, Immunomodulators, thymidylate enzyme, DNA inhibition, tubulin polymerization
Objectives

The aim of this review is to compile and highlight the developments concerning the anticancer activity of quinazoline derivatives as well as to suggest some new aspects of the expansion of anticancer activity of novel quinazoline derivatives as anticancer agents in the near future.

Results

Exhaustive literature survey indicated that quinazoline derivatives are associated with properties of inhibiting EGFR, VEGFR, and thymidylate enzymes. It was also found to be involved in disturbing tubulin assembly. Furthermore, quinazoline derivatives have been found to inhibit critical targets such as DNA repair enzymes. These derivatives have shown significant activity against cancer.

Introduction

Cancer is one of the major causes of worldwide human mortality. A wide range of cytotoxic drugs is available on the market, and several compounds are in different phases of clinical trials. Many studies suggest that these cytotoxic molecules are also associated with different types of adverse side effects; therefore, researchers around the globe are involved in the development of more efficient and safer anticancer drugs. In recent years, quinazoline and its derivatives have been considered an important class of cancer chemotherapeutic agents that show promising activity against different tumors (Ahmad 2017). Quinazolines and their derivatives can exhibit an antitumor effect via: inhibition of receptor tyrosine kinases (for example, epidermal growth factor receptor — EGFR) (Alqasoumi, Al-Taweel et al. 2010), inhibition of tubulins (Chinigo, Paige et al. 2008), induction of apoptosis (Sirisoma, Pervin et al. 2010), inhibition of phosphatidylinositol-3-kinases (PI3K) (Peng, Tu et al. 2016) and inhibition of ABC transporters to overcome the multidrug resistance of tumors (Krapf, Gallus et al. 2017).

Of all the above-mentioned spectrum of targets for the antitumor action of quinazolines and their derivatives, inhibitors of receptor tyrosine kinases (RTK), mostly EGFR inhibitors have received the greatest development. This specificity reflects, firstly, the current trend in oncology towards the creation of targeted anticancer drugs, and, secondly, the important role of RTK in vital activity of cells, including cancer cells (Marzaro, Guiotto et al. 2012), (Ravez, Castillo-Aguilera et al. 2015).

In this work, quinazoline derivatives of anti-cancer activity are classified according to the chemical structure as follows:

4-Amino-quinazoline approved by FDA as EGFR inhibitors.

Gefitinib (1), Erlotinib (2), and Afatinib (3), epidermal growth factor receptor (EGFR) inhibitors, had been approved for the treatment of non-small cell lung cancer (NSCLC) (Chen, Du et al. 2014).
Another 4-amino-quinazoline derivative as anti-cancer

A series of 1-(4-(bis(2-chloroethyl)amino)phenyl)urea derivatives (4a–c) was evaluated for their antitumor activity. They showed anticancer activities against human solid tumor breast carcinoma (MX-1) and colon carcinoma (HCT-116) more potent than the positive control (Cisplatin). Moreover, compounds (4a–c) displayed significant anti-proliferative activity against lung carcinoma (H1299) and prostate carcinoma cell growth (PC3) at low micromolar concentrations (Marvania, Lee et al. 2011).

Marzaro and co-workers designed 4-biarylaminoquinazoline analogues. Compounds (5-7) acted as dual inhibitors. The synthesized 4-biarylaminoquinazoline analogues are promising examples of dual tyrosine kinase inhibitors and tubulin polymerase inhibitor (Marzaro, Coluccia et al. 2014).
In 2013, 2-chloro-4-anilino-quinazolines were designed as EGFR and VEGFR-2 as dual inhibitors. EGFR inhibition was shown by compounds 8a-d at (IC$_{50}$ range of 0.90 μM - 4.30 μM), while VEGFR-2 inhibition was reported to the same derivatives (8a-d) at (IC$_{50}$ range of 0.85 μM - 2.10 μM) (Hamed, Abou El Ella et al. 2013).

In 2020, a series of 4-anilinoquinazoline derivatives having disulfide moiety were designed, synthesized and evaluated as potent EGFR inhibitors. The results demonstrated that the most active compound (9) with GI$_{50}$ 0.78 μM. against NSCLC cell line H3255 bearing EGFR mutant (Zheng, Zhang et al. 2020).

| COMP | R       |
|------|---------|
| A    | SO$_2$NH$_2$  |
| B    | SO$_2$NHCH$_3$ |
| C    | OH      |
| D    | CONH$_2$ |
4-Aminoquinazoline containing semicarbazide and thiosemicarbazide

In 2012, a series of novel derivatives of quinazoline containing thiosemicarbazide moiety have been synthesized and tested for their antitumor activities \textit{in vitro} against a panel of five human cancer cell lines. Compounds 10a-c showed the more potent inhibitory activity with \textit{IC}_{50} 2.33 \pm 0.62 \mu M, 2.51 \pm 0.81 \mu M and 1.87 \pm 0.40 \mu M respectively against CNE2 (nasopharyngeal carcinoma cell) (He, Wang et al. 2012).

![Chemical Structure of 10a-c](image)

Wufu Zhu synthesized a new quinazoline analogues bearing aryl semicarb-azone scaffolds as potent EGFR inhibitors and found the most promising compound 11 showed the best activity against A549, HepG2, MCF-7 and PC-3 cancer cell lines and EGFR kinase, with the \textit{IC}_{50} values of 1.32 \pm 0.38 \mu M, 0.07 \pm 0.01 \mu M, 0.91 \pm 0.29 \mu M and 4.89 \pm 0.69 \mu M, which were equal to more active than afatinib (1.40 \pm 0.83 \mu M, 1.33 \pm 1.28 \mu M, 2.63 \pm 1.06 \mu M and 3.96 \pm 0.59 \mu M), respectively (Tu, Wang et al. 2017).
A series of novel quinazoline derivatives containing thiosemicarbazide moiety were evaluated for their antitumor activity. It was reported that compounds (12a-c) showed significant in vitro cytotoxic activities against (KB) human oral carcinoma, (CNE2) human nasopharyngeal carcinoma, (MGC803) human gastric carcinoma, (MCF-7) human breast adenocarcinoma and (GLC-82) human lung cancer (He, Wang et al. 2012).

![Chemical structure of 11 and 12a-c]

Quinazoline compounds containing piperazine moiety

Tandutinib (CT53518) (13) is a quinazoline analogue containing piperazine moiety has been entered phase II clinical trials for the treatment of myeloid leukemia and advanced myelodysplasia (Knesl, Röseling et al. 2006).
Wu et al. synthesized piperazine containing quinazolinone derivatives. Upon evaluation of the antitumor activities, compounds 14 and 15 showed promising activities with IC\(_{50}\) values of 0.11 and 2.01 µM, respectively. Moreover, compounds 14 and 15 were found to have significant potency against the HOP-92 cancer cell line with IC\(_{50}\) values of 0.11 and 1.70 µM, respectively. Accordingly, the introduction of piperazinyl acetamide at position 7 of quinazoline revealed an effective anticancer scaffold (Wu, Xie et al. 2010).

In 2016, Sheng-Li Cao and Xingzhi Xu have synthesized a series of quinazoline derivatives bearing piperazine-1-carbodithioate moiety at the C4-position. They reported that fourteen of twenty-six final compounds inhibited the proliferation of human lung cancer A549, breast adenocarcinoma MCF-7, and colorectal cancer HCT-116 cancer cell lines with IC\(_{50}\) values less than 10 µM. In particular, compound 16 which also found to HCT-116 cells at G0/G1 phase of the cell cycle (Zhang, Yang et al. 2016).
A series of novel quinazoline derivatives containing piperazine analogs were synthesized and evaluated for their anti-proliferative activities against A549, HepG2, K562, and PC-3 cell lines. Compound 17 showed biological activity almost equal to that of the control, Gefitinib with IC\textsubscript{50} values less than 10 µM (Li, Chen et al. 2020).

Quinozolines containing sulphonamide moiety:

In 2015, Compound 18 was identified as a potent compound exhibiting an IC\textsubscript{50} value of 2.51 µM on the NCI cell line. Whereas The reference drug (methotrexate) exhibited an IC\textsubscript{50} value of 2.4 µM (Zayed, Ahmed et al. 2015).

In 2016, novel quinazoline-sulfonamide hybrids were synthesized and their in vitro anticancer activity was evaluated on four human cancer cell lines namely, lung cancer cell line (A549), cervical (HeLa) cancer cell line, colorectal cell line (LoVo) and breast cancer cell line (MDA-MB-231) using doxorubicin as reference drug. It was found that two candidates (compounds 19 and 20) showed effectiveness on the four cell lines, the
active compounds could be considered as useful templates for further development to obtain more potent anticancer agent (Ghorab, Alsaid et al. 2016).

Al-Obaid, A.M., et al have synthesized some of new 2-thieno-4(3H)-quinazolinone derivatives. They reported their biological evaluation as antitumor agents. Compound (21) 2-(2-thieno)-4-[4-sulfonam-iodobenzyl-amino]-6-iodo–quinazoline was the most active member for inhibition of EGFR and was evaluated against pancreatic (Miapaca2) and prostate (DU145) cancer cell lines for in vitro antitumor activity compared with parent Gefitinib (Al-Obaid, Abdel-Hamide et al. 2009).

Quinazoline containing triazolo moiety

New series of triazolo [4,3-c]quinazolines were designed, synthesized as EGFR inhibitors. The synthesized derivatives were evaluated for their in vitro antitumor activity against HepG2, MCF7, PC-3, HCT-116 and HeLa cancer cell lines. ELISA-based EGFR-TK assay was performed for the most promising hybrids using Gefitinib as a reference drug. The results revealed that compounds 22, 23 and 24 exhibited strong EGFR inhibitory activity (Ewes, Elmorsy et al. 2020).
Banerji, B., et al synthesized A series of triazole-substituted quinazoline hybrid molecules as anticancer agents. The results showed that compound (25) has moderate to good antiproliferative effects against four different cell lines HCT116, HepG2, PC-3, and MCF-7 (Banerji, Chandrasekhar et al. 2018).

New series of triazolo[4,3-c]quinazolines were designed, synthesized and evaluated for their in vitro antitumor activity against HepG2, MCF7, PC-3, HCT-116 and HeLa cancer cell lines using MTT assay. It was found that all compounds showed variable in vitro cytotoxicity. Distinct derivatives exhibited higher inhibitory activity against the tested cell lines with IC_{50} values ranging from 8.27 to 10.68 µM using DOX standard (IC_{50} = 4.17–8.87 µM). In vitro epidermal growth factor receptor (EGFR) inhibition assay was performed. Results revealed that compounds 26 and 27 exhibited worthy EGFR inhibitory activity with IC_{50} values ranging from 0.69 to 1.8 µM in comparison to the reference drug Gefitinib (IC_{50} = 1.74 µM). Further investigation showed that active candidates 26 and 27 caused cell cycle arrest at the G2/M phase, and interestingly, induced cell death by apoptosis of MCF-7 cells cumulatively with 7.14 and 17.52 µM respectively, compared with DOX as a positive reference (29.09%) (Ewes, Elmorsy et al. 2020).
Quinazoline containing morpholine moiety

Gefitinib (Iressa®) (1) is one of quinazoline analogue containing morpholine moiety approved by FDA on May, 2003 as monotherapy for the treatment of patients having locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of both platinum-based and docetaxel chemotherapies. Iressa was found to cause significant shrinkage in tumors in about 10% of patients (Ismail, Ismail et al. 2016).

Peng, W., et al have synthesized a series of novel 7 or 8-substituted 4-morpholine-quinazoline derivatives. Their PI3Ka inhibitory activities, antiproliferative activities against seven cancer cell lines, namely, PC-3, DU145, MCF-7, BT474, SK-BR-3, U937 and A431, were evaluated in vitro, and reported that Compound 28 proved to be a potent compound candidate with high PI3Ka inhibition activity (IC$_{50}$ = 4.2 nM) and good antiproliferative activity. Compound 28 was also tested for its inhibitory activities against other kinases, such as PI3Kb, PI3Kg, PI3Kd and mTOR, its effects on p-Akt (S473) and cell cycle (Peng, Tu et al. 2016).

In 2016 a series of novel morpholin-3-one fused quinazoline derivatives were designed, synthesized and their biological activities were evaluated. Most compounds showed good inhibitory activities against EGFR$^{wt}$ kinase (IC$_{50}$ < 1 μM). Among them, compound 29 demonstrated the most potent inhibitory activity (IC$_{50}$ = 53.1 nM against EGFR$^{wt}$kinase) (Qin, Lv et al. 2016).
Yin, S., *et al.* synthesized a novel quinozoline derivatives as anti-proliferative activity and demonstrated compound 30 and 31 also had well exhibition to excellent anti-proliferation activity against human lung adenocarcinoma cell line (A549) and human breast cancer cell line (SK-BR3), and 31 also exhibited the lowest toxicity against Human Embryonic Lung Fibroblast cell line (HEL) cell. Finally, compound 31 presented remarkably higher inhibition efficacy towards tumor growth than Lapatinib in a mouse Lewis Lung Cancer (LLC) xenograft model (Yin, Tang *et al.* 2016).

Smaill, J.B., *et al.* synthesized novel quinozoline derivatives as Tyrosine Kinase Inhibitors. Irreversible Inhibitors of the Epidermal Growth Factor Receptor and one derivative compound 32 (CI 1033) has been selected for clinical evaluation (Smaill, Rewcastle *et al.* 2000).

**Quinazoline containing triazine moiety**

In 2020 hybrid quinazoline-1,3,5-triazine derivative as EGFR inhibitors, which were synthesized and tested by using a variety of in vitro, in silico, and in vivo techniques. The derivatives were found to be active against different cancer cell lines and nontoxic against normal ones, and compound 33, showed a marginal potency against MCF-7
(IC$_{50}$=17.2μM), HeLa (IC$_{50}$=17.3μM), HepG2 (IC$_{50}$=15.1μM), and HL-60 (IC$_{50}$=14.3μM) respectively (Pathak, Rimac et al. 2021).

![Chemical Structure](image1)

**Quinazoline containing piperdine moiety**

Vandetanib (Caprelsa®) (34) quinazoline analog containing piperidine moiety it is used for treatment of metastatic medullary thyroid cancer. Vandetanib was approved by FDA on April, 2011 (Kalyan, Vijay et al. 2014).

![Chemical Structure](image2)

2-{3-[4-(4-Fluorophenyl)-3,6-dihydro-1(2H)-pyridinyl]propyl}-8-methyl-4-(3H)-quinazolin-one (35) was identified by Kinoshita and co-workers as potent PARP1 inhibitor with an IC$_{50}$ value of 14 nM Poly (ADP-ribose) polymerase-1 (PARP-1) is involved in many fundamental processes, including DNA repair and transcriptional regulation (Kinoshita 2004).

![Chemical Structure](image3)

Out of all the synthesized derivatives, the most active compound was N-(1-benzylpiperidin-4-yl)-2-(4-phenylpiperazin-1-yl) quinazolin-4-amine (36) when tested on human lymphoma U-937 and RAJI cells. It induced the highest proliferation arrest and cell death induction starting from 10μM, in agreement with its DNMT3A inhibitory potency (Garofalo, Goossens et al. 2010).
A series of novel C-5 substituted aniline quinazoline derivatives containing piperdine moiety displayed superior EGFR inhibitory activity at nanomolar concentration, compounds (37) and (38) results at (IC\textsubscript{50} values 21 nM and 10 nM, respectively) (Ballard, Bradbury et al. 2006).

**Quinazoline containing oxazole moiety**

Jian-Ping Yong synthesized 14 novel structures of isoxazole moiety containing quinazoline derivatives for the first time and in vitro anticancer activity was preliminarily evaluated. Compounds 39a, 39b, 39c and 39d exhibited the more potent and a broad spectrum of anticancer activity against A549, HCT116 and MCF-7 cell lines, which can be regarded as the promising drug-candidates for development of anticancer drugs (Yong, Lu et al. 2015).
2014 a series of quinazoline derivatives possessing oxazole scaffold have been designed and synthesized, and their biological activities were also evaluated as potent EGFR inhibitory firstly and then anticancer activity. Compound 40 demonstrated the most potent inhibitory activity (IC₅₀ = 0.95 μmol/L for EGFR and 2.53 μmol/L for A431 cells proliferation), which could be optimized as a potential EGFR inhibitor and anticancer drug in the further study (Hou, Zhang et al. 2014).

2018 Six series of quinazoline derivatives bearing an oxazole or imidazole moiety were designed, synthesized and evaluated for IC₅₀ values against three cancer cell lines (A549, MCF-7 and PC-3). Most of the thirty-five target compounds showed excellent anti proliferative activity three selected compounds bearing oxazole moiety (40, 41 and 42) were further evaluated for the inhibitory activity against EGFR kinases and all of them exhibited excellent activity with the IC₅₀ values at the nanomole level compared with afatinib (OuYang, Wang et al. 2018).
Conclusion

Quinazolinone is an important pharmacophore, which is considered to be a privileged structure in medicinal chemistry. These structures represent molecules, which are capable of binding at multiple sites with high affinity and facilitate more rapid discovery of useful medicinally active compounds. Alfuzosine hydrochloride, prazosin hydrochloride, doxazosine mesylate and terazosine hydrochloride are approved drugs with quinazolinone structure in the market. Cytotoxic activity of the quinazolinone derivatives on various cell lines, for example, HeLa, L1210, and HT29, has also been reported. Gefitinib (Iressa®) and erlotinib are derivatives of quinazolinones introduced to the market as anticancer agents. For cancer treatments, Quinazoline derivatives seem to be quite promising and act through various mechanisms that are well established. A lot of potentials are still hidden, which demands to be discovered for upgrading quinazoline derivatives efficacy. We can summarize that the properties of substituted quinazolines depend largely on (a) the nature of the substituents, (b) whether they are in the pyrimidine ring or in the benzene ring, and (c) whether or not complete conjugation is present in the pyrimidine ring. This review has shown that quinazoline derivatives can further be explored for the betterment of chemotherapy. Future investigation of quinazolinone structure could give some more hopeful results in the field of medicinal chemistry

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المقدمة:

معناً خاصية المشتقات الكينازولين كمضادات للسرطان واسعة المجال، و(has been) واحد من أهم اسباب الوفاة على مستوى العالم مما دفع الى تطوير العديد من العقاقير والانظمة الدوائية المتخصصة في علاج السرطان وسائر الكثير منها تحت التجارب السريرية لذلك وبالبحث والرجوع الى المراجع العلمية المتعددة التي تتناول تعدد مركبات جديدة ذات فاعلية عالية لمرض السرطان وجد لبعض المشتقات الجديدة لنواد الكينازولين فاعلية عالية في تثبيط الخلايا السرطانية وقد تناولنا في هذا البحث بعض المشتقات لنواد الكينازولين ذات فاعلية في علاج السرطان وتم تصنيفها على أساس الشكل الكيميائي.

الكلمات المفتاحية: الكينازولين, السرطان, المعالجات المناعية, انزيم التثبيت النموي, بلمرة التوبولين