Original Article

ANTI-CANCER POTENTIAL OF QUINOXALINE DERIVATIVES: CURRENT SCENARIO AND FUTURE PERSPECTIVE

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Abstract

Despite significant advancements in diagnostic methods and medications, cancer remains a major health problem in the world. There are limitations to conventional therapies, however, as many of them are multidrug-resistant or have severe side effects. The genetic background and clinical features of bladder cancer make it a complex disorder. phytoconstituents such as certain alkaloids, saponins, tannins, polyphenols, and terpenoids exhibit anticancer effects. Sophoridine is a tetracyclic quinolizidine alkaloid isolated from the stem and leaves of medicinal plants Sophora alopecuroides L., Euchresta japonica Benth, and roots of Sophora alopecuroides Ait. Chinese Food and Drug Administration (CFDA) approved sophoridine as an antitumor agent in 2005. This review covers the antitumor activities of sophoridine and its derivatives. Analogs of sophoridine are evaluated according to their half-maximal inhibitory concentrations (IC50 values). Moreover, the current market of anticancer drugs and their expected growth are discussed. Prospects provide suggestions and clues for novel sophoridine-based anticancer agents with enhanced expected efficacy and minimum toxicity. The use of quinazoline and its derivatives in cancer chemotherapy has shown promising results in recent years. This article examines the recent developments concerning the anticancer properties of quinazoline derivatives and presents perspectives on the development of new quinazoline derivatives as anticancer agents.

Keywords: Alkaloid, Cancer, Phytochemical, kinase inhibition, quinazoline, antitumor, quinazoline derivatives, cytotoxic.

INTRODUCTION

Cancer is one of the diseases that claim the highest number of lives globally. According to WHO reports, cancerous diseases represent a severe burden for both men and women—over 244 million DALYs [1]. The next two frequent disorders are ischemic heart disease (203 million DALYs) and cerebrovascular accidents (137 million DALYs). The number of cases of cancer is slightly higher in men. The WHO Global Cancer Observatory (GLOBOCAN) registry from 2020 showed that the top three most frequent cancers are breast, prostate and lung cancer. Moreover, the highest mortality is observed in lung, breast and colorectal cancer. Scientists are still searching for new methods of early detection and effective treatment of cancer.

Evaluation of a case of cancer is carried out considering the type of cancer present, risk assessment, and many other factors that have an influence on the treatment process. Regarding tumor biology, it is known that it involves an abnormal growth of cells. This growth has no functional purpose besides the ability to spread to adjacent structures and other parts of the organism. Some factors encourage the development of cancer, e.g., viruses, metals, and radiation damage [2]. Genes that may underline tumor development and metastasis have also been extensively investigated.

Quinoxaline is formed by the fusion of two aromatic rings, benzene and pyrazine. For this reason is also called benzopyrazine, and is described as a bioisoster of quinoline, naphthalene and benzothiophene [3]. The atoms S and N play an important role in the ring since they stabilize ion radical species. Molecular weight of the quinoxaline is 130.15, with a molecular formula of C8H6N2, and it is a white crystalline powder, at standard conditions [1]. Chemically, quinoxaline is a low melting solid, purified by distillation, and a fraction of boiling point 108°-111°/12 mm has a melting point 29-30 °C [4]. Quinoxalines are soluble in water, and produces monoquaternary salts when treated with quaternizing agents, like dimethyl sulfate and methyl p-toluene sulphonate. The quaternary salts of 2-alkylquinoxalines are unstable and converted into complex colored products by oxidation [5]. It is acidic with a pKa of 0.60 inwater at 20 °C, and nitration occurs only under forcing conditions (Conc. HNO3, Oleum, 90 °C), resulting in the formation of two compounds: 5-nitroquinoxaline (1.5%) and 5,7-dinitro-quinoxaline (24%). Its second pKa is -5.52 indicating that quinoxaline is significantly diprotonated in a strongly acidic medium. One of the most active classes of nitrogen containing heterocyclic aromatic compounds, quinazolines (1,3-benzodiazine) are a group of substances that display a wide range of activities. They belong to the benzodiazines—diazonaphthalenes, which contain two atoms of nitrogen in the same ring. Together with other isomers: cinnolines (1,2-benzodiazine), phthalazines (2,3-benzodiazine) and quinoxalines (1,4-benzodiazine), they have broad biological features and have important applications in medicine, pharmacy and agriculture [6].

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FDA has approved several quinazoline derivatives as anticancer drugs from the past 15 years, such as gefitinib (4), erlotinib (5) and lapatinib (6). These 4-anilinoquinazolines inhibit kinase activity of EGFR as they interact with the ATP-binding site. In recent years, several studies have been carried out around 4-anilinoquinazoline scaffold as kinase inhibitors and they have led to a very high number of patents. This review summarizes new patent and articles published about quinazolines derivatives as anticancer drugs since 2011.

Quinazoline Derivatives in cancer treatment

Cancer is a disease that depends on changes in the cell cycle. This inevitably leads to uncontrolled cell division of abnormal cells. During the past few years, the Food and Drug Administration (FDA) has approved several innovative classes of anticancer chemotherapeutic factors from among the quinazoline derivatives. They have demonstrated significant therapeutic efficacy, especially against solid tumors. Many are approved for antitumor clinical use, e.g.,: erlotinib (*N*-(3-Ethynylphenyl)-6,7-bis(2- methoxyethoxy)quinazolin-4-amine), gefitinib (N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy)quinazolin-4-amine), afatinib ((E)-N-[4-(3-chloro-4-fluoroanilino)-7-[(3S)-oxolan-3-yl]oxyquinazolin-6-yl]-4-(dimethylamino)but-2-enamide), lapatinib (N-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[5-[(2methylsulfonylethylamino)methyl]furan-2-yl]quinazolin-4-amine), vandetanib (N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-amine) [8]. The antitumor effects of quinazolines can manifest through numerous pathways. EGFR is a very promising molecular target for cancer therapy; it has been observed, however, that most of the patients developed resistance to the EGFR inhibitors. Therefore, continuous efforts are being undertaken to design and develop new and more potent EGFR inhibitors with improved anti-tumor activities. In this regard, several novel compounds were synthesized by introducing substitution on the benzene ring of the EGFR inhibitor, gefitinib. However, replacement of benzene ring with another aromatic ring has rarely been reported in the

literature. Therefore, in 2010, X Wu et al. designed and synthesized two series of 4-benzothienyl amino quinazoline derivatives as new analogues of gefitinib. The anti-tumor activity of these novel gefitinib analogues in six human cancer cell lines was examined. Most of the compounds exhibited increased cytotoxicity to cancer cells when compared with the parental compound. The compounds containing ethyl or methyl groups as side chains at position 7 exhibited good pan-RTK inhibitor activity with enhanced apoptosis-inducing capabilities. In comparison to parental gefitinb, analogues 1 and 2 exhibited promising and selective apoptosis-inducing capabilities and enhanced anti-tumor activities in cancer cells with HER overexpression and were considered as promising lead compounds for further development. In order to develop novel RTK inhibitors with improved anticancer activity, X Wu et al. designed and synthesized two series of 4-pyrrylamino quinazolines [9]. Gefitinib was used as a parent compound in which the benzene ring was replaced by a pyrrole ring. All of the prepared compounds were evaluated against pancreatic (Miapaca2) and prostate (DU145) cancer cell lines for kinase inhibitory and antitumor activities. In vitro results suggested that most of the compounds exhibited increased antitumor activity in comparison to the parental gefitinib. The most promising compounds were 3–7. The structure-activity results suggested that the replacement of the benzene ring with a pyrrole ring increased the anticancer activity. In addition, the presence of a basic side chain at position 6 or 7 of the quinazoline nucleus plays significant role in determining these compounds' cytotoxicity.

Threonine kinases inhibitors

Serine/threonine protein kinases phosphorylate the hydroxyl group on the side chain of a serine or a threonine residue in a protein substrate. Serine/threonine kinases can regulate cell proliferation, programmed cell death (commonly called apoptosis), cell differentiation and embryonic development. Serine/threonine kinases include MAPKs, aurora kinases, the phosphoinositide-3-kinases (PI3Ks) among others. Activation of cell signaling by a selected panel of protein serine/threonine kinases is the hallmark of many cancers [10]. For example, expression of B-Raf, PI3K and aurora kinases are frequently altered in many types of cancer.

PI3K inhibitors Since the 1980s, the PI3K family has been found to play key regulatory roles in cell survival, proliferation and differentiation. PI3Ks transduce signals from various growth factors and cytokines into intracellular messages by generating phospholipids that in turn activate the serine/threonine kinase Akt. The tumor suppressor PTEN is the most important negative regulator of the PI3K signaling pathway [11]. Several studies have revealed that multiple components of the PI3K pathway are frequently mutated or altered in common human cancers, underscoring the importance of this pathway in cancer. LY294002 (11) was the first synthetic small-molecule inhibitor which targets the PI3K family members at concentrations in the micromolar range, but it shows considerable toxicity in animals. Since the discovery of LY294002, a number of PI3K inhibitors (Figure 3) containing quinazoline moieties have been synthesized [12].

Tubulin polymerization inhibitors

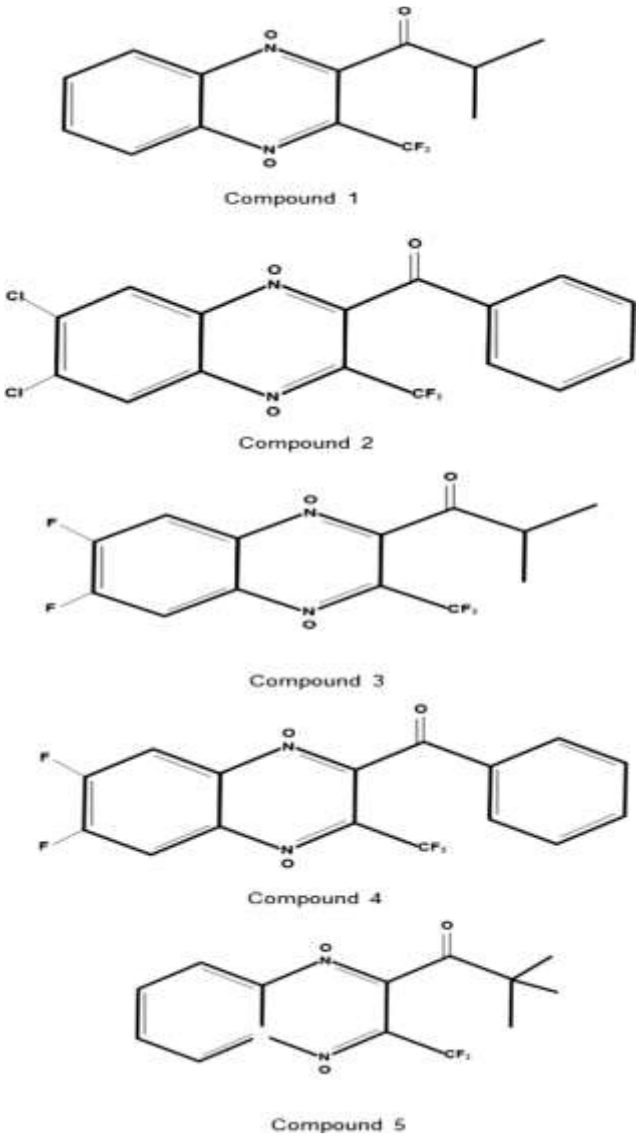
Tubulin has multiple drug binding sites and is considered as an important target for anticancer drugs. The most comprehensively examined binding sites were for taxoid, vinca, and colchicine. In previous studies, colchicine and its analogues have been shown to have promising activity by inhibiting tubulin polymerization in to microtubules. However, the clinical uses of these compounds are limited due to their high toxicity. Recently, several small molecules that act at the colchicine site on tubulin have been discovered. These molecules not only inhibit the growth of a wide variety of human cancer cell lines, but they also show vascular-disrupting effects on tumor endothelial cells required for cancer growth and are therefore considered vascular-disrupting agents (VDAs) [13]. In 2013, A Chilin and his coworkers reported biphenylaminoquinazoline (11) as an inhibitor of EGFR, FGFR-1, PDGFRβ, Abl1, and Src kinase activities at submicromolar concentrations; it also exhibited EC50’s in the nanomolar range against several cancer cell lines. After investigations of the biphenylaminoquinazolines' mechanism of action, it was observed that these molecules not only showed anti-TK activity but also inhibited tubulin polymerization. To identify the structural features required for dual TK/tubulin inhibition or to be selective anti-tubulin compounds, several heterobiaryl analogues of compound 11 were

designed, synthesized, and evaluated as TKIs and as tubulin polymerization inhibitors. The compounds were synthesized by replacing one of the two benzene rings of the biphenylamino moiety with a 5- or 6-atom heterocycle. The computational analysis and biological data of these compounds revealed some important structural features required for dual activity: 1) the dioxygenated function is required on the benzene of the quinazoline ring, however the carbon atom linker between the oxygen atom can be varied; 2) the aniline benzene is important for the dual activity, and its replacement with heteroaryl is not feasible; and 3) the terminal ring attached to the aniline benzene was considered as a switch between the two activities. Selective antitubulin activity was observed with the heterocyle whereas dual anti-tubulin/anti-TK activity was observed with phenyl rings. In 2013, X-F Wang et al. selected compounds 12 and 13 , which exhibited low nanomolar GI50 values against a human tumor cell line panel, inhibited tubulin assembly, and inhibited colchicine binding to tubulin [14]. For further modifications and structure activity studies, a series of 4-(N-cycloamino)phenylquinazolines were designed, synthesized, and evaluated in cellular and tubulin inhibition assays [66]. The compound showed significant activity and thus resulted in the discovery of new tubulin-polymerization inhibitors. The most promising compound of the series was 14 (7-Methoxy-4-(2-methylquinazolin-4-yl)-3,4- dihydroquinoxalin-2(1H)-one, which showed both low nanomolar antiproliferative activity in cellular assays and significant inhibition of tubulin assembly with an IC50 in micromolar range. The compound also showed exceptionally potent inhibition of colchicine binding to tubulin. The mechanistic study suggested that compound 14 arrested most cells in the G2/M phase of the cell cycle, disrupted cellular microtubules, and competed mostly at the colchicine site on tubulin [15].

B-Raf inhibitors

Raf kinases (A-Raf, B-Raf and C-Raf) participate in the MAPK cascade that plays a crucial role in the development of cancer. For this reason, Raf kinases are attractive cancer drug targets. For instance, the B-Raf kinase is inhibited by sorafenib (7) that has been approved by the FDA to treat unresectable hepatocellular carcinoma and advanced renal cell carcinoma (RCC) [16]. Since 2011, several patents regarding quinazoline derivatives as B-Raf inhibitors have been filed. Some representative compounds and their IC50 values are reported in Figure 1. Among the three patents that present quinazoline, two of them present a bis-aryl urea moiety like the sorafenib. The quinazolinone 8 has been patented and evaluated for B-Raf inhibition and shows an IC50 on isolated wild-type-BRaf of 0.0039 μM. This compound and its analogs are used for the treatment of leukemia, lymphoma, multiple myeloma and the like. The CN102311395 patent describes the preparation and the evaluation of some quinazoline-substituted di-phenyl urea inhibitors. This study shows that 4-aryloxyquinazoline 9 has an inhibition in wild-type B-Raf of 98.9% at a concentration of 10 μM. In 2002, Davies et al. identified a high frequency of B-Raf point mutations in melanoma and other human cancers [17]. This discovery has encouraged the development of small molecules as highly potent and selective ATP-competitive mutated B-Raf inhibitors by several groups. The most common mutation (90%) is the replacement of a valine residue by a glutamic acid residue at position 599 (V599E) that makes B-Raf V599E constitutively active. The compounds presented in the patent WO2011025938 differ from those presented in WO2011068187 and CN102311395 mainly for the absence of the bis-aryl urea group and for their activity on B-Raf mutations [18]. One of the most promising compounds (10) inhibits B-Raf V599E with an excellent IC50 value of 3.9 nM.

Figure1: New series of quinoxaline derivatives



A new series of 2-alkylcarbonyl and 2-benzoyl-3- triflurомethylquinoxaline-1,4-di-N-oxide derivatives was synthesized and evaluated for in vitro antitumor activity against a 3-cell line panel (MCF7 (breast), NCIH 460 (lung) and SF-268 (CNS)), and then evaluated in full panel of 60 human tumor cell lines, derived from nine cancer cell types [19]. It was showed that, in general, anticancer activity depends on the substituents in the carbonyl group, increasing the activity in the order: ethyl < isopropyl < tertbutyl < phenyl-ones. Among these the compounds 2- (3-methylbut-1-en-2-yl)-3-(trifluoromethyl)quinoxaline-1,4-di- N-oxide (Compound 1), 2-benzoyl-6,7-dichloro-3-trifluoromethylquinoxaline 1,4-di-N-oxide (Compound 2), their difluorinatedanalogs(6,7-difluoro-2-isobutyryl-3-trifluoromethylquinoxaline 1,4-di-N-oxide and 2-benzoyl-6,7-difluoro-3-trifluoromethylquinoxaline 1,4-di-N-oxide) (Compound 3 and 4), and 2-(2,2- dimethylpropanoyl)-3-trifluoromethyl-quinoxaline 1,4-di-N-oxide (Compound5) were the most active, with higher anticancer activity with mean GI50 (Growth Inhibition) values of 1.02, 0.42, 0.52, 0.15, and 0.49 mM, respectively (Table 1) [8,21]. The possible substituents of these compounds are presented in Table 1, represented by R and R0 [20].

Lysine methyltransferase inhibitors

Protein lysine methyltransferase G9a is over-expressed in cancer cells and acts as a catalyst during methylationlysine 9 of histone H3 (H3K9) and lysine 373 (K373) of p53. Genetic knockdown of G9a inhibits

cancer cell growth via the di-methylation of p53 K373 that leads to the inactivation of p53. Initially 2,4-diamino-6,7-dimethoxyquinazoline template represented by 17 (BIX01294) was discovered as a selective small molecule inhibitor of G9a and GLP [21]. In order to study the structure activity relationship and improve the potency and selectivity, multiple regions of the quinazoline template were investigated. This resulted in the discovery of compound 18 (UNC0224) as a potent G9a inhibitor with excellent selectivity. Additionally, high resolution X-ray crystal structural analysis of the G9a-18 complex was obtained and depending upon the structural insight discovered by G9a- 18co-crystal structure, F Liu et al. in 2010 optimized the 7-dimethylaminopropoxy side chain of the quinazoline scaffold. This led to the discovery of 19 (UNC0321), which was the most promising G9a inhibitor with picomolar potency. Investigation of the 2-and 4-amino and 7-aminoalkoxy regions of this quinazoline scaffold provided valued structure-activity relationship information. Compound 19 exhibited excellent in vitro potency; however, it had lower cellular potency. In addition, to improve the cellular potency of the quinazoline series, several novel analogs were designed and synthesized [22]. The focus was to improve cell membrane permeability while maintaining in vitro potency. The structure activity relationship studies were performed on these compounds with G9a biochemical (SAHH-coupled), cell-based functional (anti-H3K9me2 ICW), and cell toxicity (MTT) assays. The results led to the discovery of compounds 20 and 21, which exhibited high cellular potency and excellent separation of functional potency versus cell toxicity in a variety of cell lines.

OTHER ACTIVITY OF QUINAZOLINE DERIVATIVES

Antiviral activity

Viruses are small infectious agents that replicate only inside the living cells of an organism and can infect all types of organisms, from animals and plants to bacteria. Viruses such as Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) belong to the Herpesviridae family, are double-stranded DNA [23], and share high homology in genome structure and DNA sequence. These viruses can cause various illnesses states from asymptomatic infection to fulminant disseminated diseases, including labials herpes, keratitis (cornea inflammation), genital herpes, and encephalitis [25]. There are a wide number of drugs for treatment of HSV infections like acyclovir, ganciclovir, penciclovir, valaciclovir (converted to acyclovir) and famciclovir (converted to penciclovir), being acyclovir the most common drug used. However, there are drug-resistant strains of HSV emerging and increasing [25], leading to the search of new antiviral drugs.

Antifungal activity

Prevalence of fungal diseases has increased significantly in the past 50 years. Fungal diseases manifest themselves differently, including mycoses in the skin, hair, nails, but also as systemic mycoses, being the last one an issue of great medical concern due to the increase in the immunocompromised patient population [26]. One of the most common fungal infections is candidiasis, caused by Candida albicans, a diploid fungus that grows both as yeast and filamentous cells. This fungus can also develop resistance to antimycotic drugs that already exist in the market, being important a constant search for new drugs and treatments. Thieno[2,3-d]pyrimidines and pyrrolo[3,4-b]quinoxalines were synthesized and tested against C. albicans, and presented antifungal activity. Researchers also reported some 2-sulphonylquinoxalines and 3- [(alkylthio)methyl]quinoxaline-1-oxide derivatives as compounds with high antifungal activity [7], and also pyrazoloquinoxalines which were observed to be active against fungal infections [27].

Antiamoebic activity

Entamoeba histolytica is a protozoan responsible for the amoebiasis infection, causing amoebic colitis, brain and liver abscess, being an important leading cause of death worldwide. The traditional treatment used is based in antiamoebic compounds such as nitroimidazoles, but not always effective, raising the possibility of drug resistance, leading to the search of new compounds able to fight the infection successfully [28]. Some 1-

[thiazole[4,5-b]quinoxaline-2-yl]-3-phenyl-2-pyrazolines derivatives produced, were found to be a potent inhibitor of HM1:IMSS strain of E. histolytica, where the presence of 3-bromo or 3-chloro substituents on the phenyl ring and 4-methyl group on the pyrazoline ring affected antiamoebic activity to a great extent [29]. 2-Cyano-3-(4-phenylpiperazine-1-carboxamido)quinoxaline 1,4-dioxide derivatives have also presented activity against Leishmania, but were not effective against Plasmodium. In such study metronidazole was used as the reference drug and had a 50% inhibitory concentration of IC50 1.69-1.82 mM, and compound 5 with 3-bromo and 4-methyl substitution, and compound 6 with 3-chloro and 4-methyl substitution on pyrazoline ring, showed great effectiveness, being the most actives, presenting IC50 1.45 mM and IC50 0.72 mM, respectively [30].

Antiparasitic activity

Leishmaniasis is a parasitic disease cause by protozoan of the genus Leishmania in tropical and subtropical areas of the World, and despite all efforts to fight this disease about 1-2 million new cases are registered every year. Most of the drugs available against leishmaniasis are expensive and require a long treatment and are becoming more and more ineffective [9]. Malaria is also a tropical parasitic disease, cause by Plasmodium falciparum, leading to over a million deaths annually, and rising, probably due to a resistance increasing, requiring the development of cheaper and more effective drugs [31-33].

Diabetes

Diabetes Mellitus is a disease caused by the dysfunction of glucose homeostasis, in which glucose levels appear abnormal with tendency to hyperglycemia. Diabetes type 1 is insulin-dependent and requires a daily subcutaneous injection of insulin, while diabetes type 2 is non-insulin-dependent and can be treated with several drugs such as sulfonylureas, nateglinide, and biguanides, among others [34,35]. However these treatments have limited efficacy and tolerability, and could cause severe side effects [36]. In this regard, new transition metal complexes of quinoxaline thiosemicarbazone ligands L1H2 and L2H2 were prepared. The ligands were explored with copper and zinc complexes in diabetes induced Wister rats[37]. The compounds [ZnL1(H_2O)] and L2H2 have showed prominent reduction in blood glucose level [38].

CONCLUSION

As discussed above, quinazoline and its derivatives have immense potential as anticancer agents. Quinazoline is an important pharmacophore in the discovery of cancer drugs, and several laboratories around the world are developing novel and more potent anticancer drugs based on quinazoline derivatives. The biological properties of quinoxaline and its derivatives have led to its wide variety of applications in medicine, including antimicrobial, antidiabetic, antiproliferative, anti-inflammatory, anticancer, antiglaucoma, antidepressant, and AMPA-R antagonist effects. Synthetic quinazoline derivatives were studied for their anticancer properties against a variety of cancer cells in this review article. Research on quinazoline pharmacophore-based potent anticancer agents will be updated in this review article, and a new anticancer drug will be developed with the information presented.

REFERENCES

1. S. Salerno et al., “Recent advances in the development of dual topoisomerase I and II inhibitors as anticancer drugs,” Curr. Med. Chem., vol. 17, no. 35, pp. 4270–4290, 2010.
2. E. Durinikova et al., “Targeting the DNA damage response pathways and replication stress in colorectal cancer,” Clin. Cancer Res., vol. 28, no. 17, pp. 3874–3889, 2022.
3. P. D. W. Eckford and F. J. Sharom, “ABC efflux pump-based resistance to chemotherapy drugs,” Chem. Rev., vol. 109, no. 7, pp. 2989–3011, 2009.
4. M. F. Ullah, “Cancer multidrug resistance (MDR): a major impediment to effective chemotherapy,” Asian Pac. J. Cancer Prev., vol. 9, no. 1, pp. 1–6, 2008.

5. P. Perumal, R. Bilal Ahmad, R. S. R. Dontireddy, and R. K. Natesh, “Synthesis and anti-microbial screening of some Schiff bases of 3-amino-6,8-dibromo-2-phenylquinazolin-4(3H)-ones,” Eur. J. Med. Chem., vol. 44, no. 5, pp. 2328–2333, 2009.
6. M. A. H. Ismail, S. Barker, D. A. Abou el-Ella, K. A. M. Abouzid, R. A. Toubar, and M. H. Todd, “Design and synthesis of new tetrazolyl- and carboxy-biphenylylmethyl-quinazolin-4-one derivatives as angiotensin II AT1 receptor antagonists,” J. Med. Chem., vol. 49, no. 5, pp. 1526–1535, 2006.
7. K. Sak, “Chemotherapy and dietary phytochemical agents,” Chemother. Res. Pract., vol. 2012, p. 282570, 2012.
8. K. Manasa, R. V. Sidhaye, G. Radhika, and C. N. Nalini, “Synthesis, antioxidant and anticancer activity of quinazoline derivatives,” Journal of Current Pharma Research, vol. 1, no. 2, pp. 101–105, 2011.
9. “Synthesis and Biological Evaluation of a Novel Series of 6, 8- Dibromo-4 (3H) quinazolinone Derivatives as Anticancer Agents,” Synthesis and Biological Evaluation of a Novel Series, vol. 6.
10. Al-Snafi, S. Singh, P. Bhatt, and V. Kumar, “A review on prescription and non-prescription appetite suppressants and evidence-based method to treat overweight and obesity,” GSC biol. pharm. sci., vol. 19, no. 3, pp. 148–155, 2022.
11. A. S. El-Azab et al., “Design, synthesis and biological evaluation of novel quinazoline derivatives as potential antitumor agents: molecular docking study,” Eur. J. Med. Chem., vol. 45, no. 9, pp. 4188–4198, 2010.
12. A. M. Alafeefy, A. A. Kadi, A. S. El-Azab, S. G. Abdel-Hamide, and M.-H. Y. Daba, “Synthesis, analgesic and anti-inflammatory evaluation of some new 3H-quinazolin-4-one derivatives,” Arch. Pharm. (Weinheim), vol. 341, no. 6, pp. 377–385, 2008.
13. A. Kumar et al., “Some new 2,3,6-trisubstituted quinazolinones as potent anti-inflammatory, analgesic and COX-II inhibitors,” Bioorg. Med. Chem., vol. 11, no. 23, pp. 5293–5299, 2003.
14. I. A. Al-Suwaidan, A. M. Alanazi, A. A.-M. Abdel-Aziz, M. A. Mohamed, and A. S. El-Azab, “Design, synthesis and biological evaluation of 2-mercapto-3-phenethylquinazoline bearing anilide fragments as potential antitumor agents: molecular docking study,” Bioorg. Med. Chem. Lett., vol. 23, no. 13, pp. 3935–3941, 2013.
15. A. Gschwind, O. M. Fischer, and A. Ullrich, “The discovery of receptor tyrosine kinases: targets for cancer therapy,” Nat. Rev. Cancer, vol. 4, no. 5, pp. 361–370, 2004.
16. C. Dumontet and M. A. Jordan, “Microtubule-binding agents: a dynamic field of cancer therapeutics,” Nat. Rev. Drug Discov., vol. 9, no. 10, pp. 790–803, 2010.
17. M. T. Conconi et al., “Quinazoline-based multi-tyrosine kinase inhibitors: synthesis, modeling, antitumor and antiangiogenic properties,” Eur. J. Med. Chem., vol. 67, pp. 373–383, 2013.
18. S. Zhu, G. Chandrashekar, L. Meng, K. Robinson, and D. Chatterji, “Febrifugine analogue compounds: synthesis and antimalarial evaluation,” Bioorg. Med. Chem., vol. 20, no. 2, pp. 927–932, 2012.
19. P. Bhatt, S. Singh, S. Kumar Sharma, and S. Rabiu, “Development and characterization of fast dissolving buccal strip of frovatriptan succinate monoydrate for buccal delivery,” Int. J. Pharm. Investig., vol. 11, no. 1, pp. 69–75, 2021.
20. B. Goldenson and J. D. Crispino, “The aurora kinases in cell cycle and leukemia,” Oncogene, vol. 34, no. 5, pp. 537–545, 2015.
21. A. A. Mortlock et al., “Discovery, synthesis, and in vivo activity of a new class of pyrazoloquinazolines as selective inhibitors of aurora B kinase,” J. Med. Chem., vol. 50, no. 9, pp. 2213–2224, 2007.
22. S. Ahamed, P. Bhatt, S. J. Sultanuddin, R. Walia, M. A. Haque, and S. B. InayathAhamed, “An Intelligent IoT enabled Health Care Surveillance using Machine Learning,” in 2022 International Conference on Advances in Computing, Communication and Applied Informatics (ACCAI), 2022.
23. Bis-Quinazoline derivatives as inhibitors for epidermal growth factor receptor (EGFR) Tyrosine Kinase.
24. Pankaj, “Cyclodextrin modified block polymer for oral chemotherapy,” J. Pharm. Res. Int., pp. 21–29, 2021.
25. K. M. McGarvey, J. A. Fahrner, E. Greene, J. Martens, T. Jenuwein, and S. B. Baylin, “Silenced tumor suppressor genes reactivated by DNA demethylation do not return to a fully euchromatic chromatin state,” Cancer Res., vol. 66, no. 7, pp. 3541–3549, 2006.
26. M. Vieira, C. Pinheiro, R. Fernandes, J. P. Noronha, and C. Prudêncio, “Antimicrobial activity of quinoxaline 1,4-dioxide with 2- and 3-substituted derivatives,” Microbiol. Res., vol. 169, no. 4, pp. 287–293, 2014.
27. Pankaj, “Anti-cancer cyclodextrin nanocapsules based formulation development for lung chemotherapy,” J. Pharm. Res. Int., pp. 54–63, 2021.
28. C. Carmi, M. Mor, P. G. Petronini, and R. R. Alfieri, “Clinical perspectives for irreversible tyrosine kinase inhibitors in cancer,” Biochem. Pharmacol., vol. 84, no. 11, pp. 1388–1399, 2012.
29. S.-H. I. Ou, “Second-generation irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs): a better mousetrap? A review of the clinical evidence,” Crit. Rev. Oncol. Hematol., vol. 83, no. 3, pp. 407–421, 2012.
30. The isolation and structure of Campthotecin a novel alkaloidal leukemia and tumor inhibitor from Camptotheca acuminata.
31. X. Wang, M. Chen, J. Zhou, and X. Zhang, “HSP27, 70 and 90, anti-apoptotic proteins, in clinical cancer therapy (Review),” Int. J. Oncol., vol. 45, no. 1, pp. 18–30, 2014.
32. S. Singh, S. Kumar Sharma, P. Mehrotra, P. Bhatt, and M. Kaurav, “Blockchain technology for efficient data management in healthcare system: Opportunity, challenges and future perspectives,” Mater. Today, 2022.
33. S. P. Chand, S. Debnath, M. Rahimi, M. S. Ashraf, P. Bhatt, and S. A. Rahin, “Contextualization of trait nexus and gene action for quantitative and qualitative characteristics in Indian mustard,” J. Food Qual., vol. 2022, pp. 1–24, 2022.
34. Y.-Y. Hei, M. Xin, H. Zhang, X.-X. Xie, S. Mao, and S.-Q. Zhang, “Synthesis and antitumor activity evaluation of 4,6-disubstituted quinazoline derivatives as novel PI3K inhibitors,” Bioorg. Med. Chem. Lett., vol. 26, no. 18, pp. 4408–4413, 2016.
35. M. Zahedifard et al., “Synthesis, characterization and apoptotic activity of quinazolinone Schiff base derivatives toward MCF-7 cells via intrinsic and extrinsic apoptosis pathways,” Sci. Rep., vol. 5, no. 1, p. 11544, 2015.
36. S. I. Kovalenko et al., “Synthesis and anticancer activity of 2-(alkyl-, alkaryl-, aryl-, hetaryl-)-[1,2,4]triazolo[1,5-c]quinazolines,” Sci. Pharm., vol. 81, no. 2, pp. 359–391, 2013.
37. S. Rogosin and A. B. Sandler, “Beyond bevacizumab: antiangiogenic agents,” Clin. Lung Cancer, vol. 13, no. 5, pp. 326–333, 2012.
38. J. Tie and J. Desai, “Antiangiogenic therapies targeting the vascular endothelia growth factor signaling system,” Crit. Rev. Oncog., vol. 17, no. 1, pp. 51–67, 2012.