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Therapeutic Potential of Quinazoline Derivatives

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ABSTRACT

Lately, molecular hybridization technology has been used to combine two or more pharmacophores of bioactive scaffolds to create hybrid analogs with increased potency. An essential class of biologically active substances is comprised of heterocyclic compounds. This review summarizes the progress of quinazoline hybrid lead compounds and their related heterocycles in medicinal chemistry. Molecular hybridization of various biologically active pharmacophores with quinazoline derivatives yielded lead compounds with diverse biological activities, including both specific and multiple targets. Due to their considerable biological activity, heterocyclic compounds with a quinazoline moiety have attracted a lot of research in recent years. It has been observed that a wide variety of compounds with a quinazoline moiety exhibit a broad spectrum of therapeutic activities, including antifungal, antiviral, antidiabetic, anticancer, anti-inflammatory, antibacterial, and antioxidant properties. This study speeds up the developing process to produce more physiologically active candidates.

INTRODUCTION

Nowadays, “one drug one target one disease approach” is not appropriate in complex diseases such as cancer and infectious diseases. This conventional approach of disease treatment cannot overcome the phenomenon of drug resistance1,2. By combining two or more active pharmacophores known to regulate multiple disease targets simultaneously, molecular hybrids were created. A covalently bonded mixture of two or more independently active pharmacophores is referred to as a molecular hybrid.

It can be achieved by the method of linking or framework integration to form one molecule, having increased the pharmacological activity4. The heterocycles are widely investigated bioactive molecules and are considered important synthetic targets for the development of novel therapeutic agents5-7. Among all heterocyclic moieties, quinazoline has been taken for this review, as quinazoline has a very broad spectrum of pharmacological activities with minimum side effects8. Due to its resemblance to both the purine and the pteridine nucleus, its derivatives are able to inhibit the Purinic, or the folic acid metabolic path-ways. Due to their broad range of pharmacological activities, which include antimicrobial9,10, antimalarial11, anti-inflammatory12-14, anticonvulsant15,16, antihypertensive17, antioxidant18, antiviral19, anti-HIV20and anticancer21-24, quinazoline and its derivatives have attracted the attention of biologists and medicinal chemists. Quinazoline and its derivatives have been identified as a new class of cancer chemotherapeutic agents with significant therapeutic efficacy against solid tumors25-37. Quinazoline having the chemical formula C8H6N2. Quinazoline is a light yellow crystalline solid and is also known as 1,3-diazanaphthalene, Quinazoline is a nitrogen-containing fused heterocycle, having four isomeric forms, i.e., quinazoline, quinoxaline, cinnoline, and phthalazine, depending upon the position of the nitrogen atom in the heterocyclic ring system. By decarboxylating a 2-carboxy derivative, August Bischler and Lang reported the first quinazoline synthesis in 1895. 38, By using the Niementowski synthesis, anthranilic acid was treated with amide to produce 4-oxo-3,4-dihydroquinazolies 39.

SYNTHESIS ROUTES OF QUINAZOLINE

There are several reported methods to synthesize quinazoline moiety.

1. Niementowski quinazoline synthesis: Anthranilic acid when treated with formamide at higher temperature resulted 3,4 dihydro-4-oxaquinazoline (Figure 2) 40.

2. Grimmel, Guinther and Morgan's synthesis: The 2-acetamidobenzoic acid reacts with an amine in the presence of phosphorous trichloride gave 2-methyl-3-phenylquinazolin4(3H)-one (Figure 3) 40.

3. Synthesis of quinazolin-4(3H)-one from Isotoic anhydride: The Isotoic acid anhydride reacts with amine followed by refluxing with ethyl orthoformate resulting in dihydro-4-oxaquinazolines (Figure 4) 8.

4. Synthesis of 2-methyl-5-nitroquinazolin-4(3H)-one from 2-methyl-5-nitro-4H-benzo[d] oxazin-4-one: Amines reacted with 2-methyl-5-nitro-4H-benzo[d][1,3]oxazin-4-one to give respective quinazoline (Figure 5) 41.

5. Grimmel, Guinther and Morgan's synthesis: The 2-acetamidobenzoic acid reacts with an amine in the presence of phosphorous trichloride gave 2-methyl-3-phenylquinazolin-4(3H)-one (Figure 6) 40.

6. Synthesis of 2-phenylquinazolin-4(3H)-one: 2-aminobenzamide reacted with styrene using di-tertiary-butyl peroxide (DTBP) and P-Toluene sulfonic acid (P-TsOH) to get 2-phenylquinazolin-4(3H)-one (Figure 7) 42.

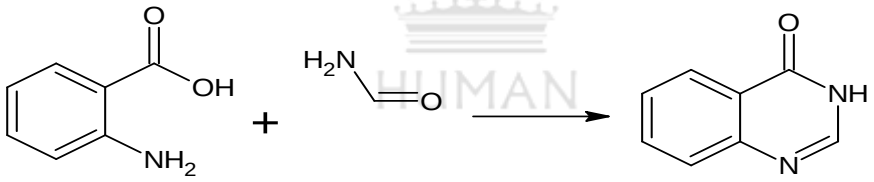
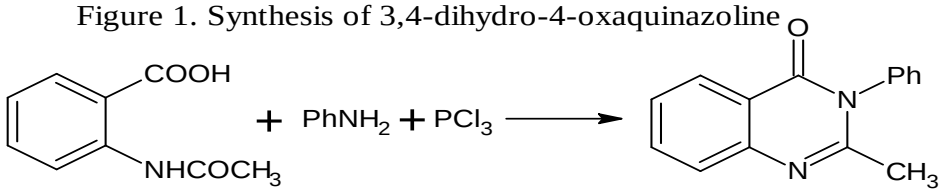


Figure 1. Synthesis of 3,4-dihydro-4-oxaquinazoline



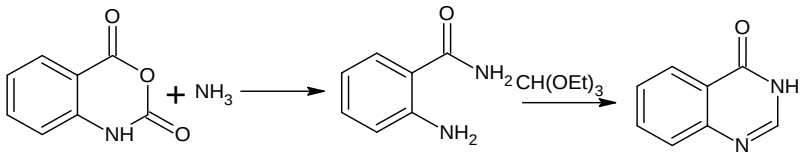


Figure 3. Synthesis of Quinazolin-4(3H)-one

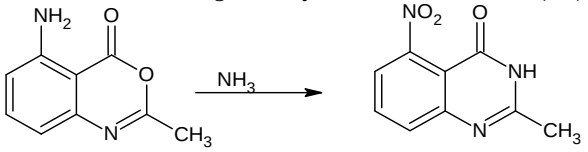


Figure 4. Synthesis of 2-Methyl-5-nitroquinazolin-4(3H)-one

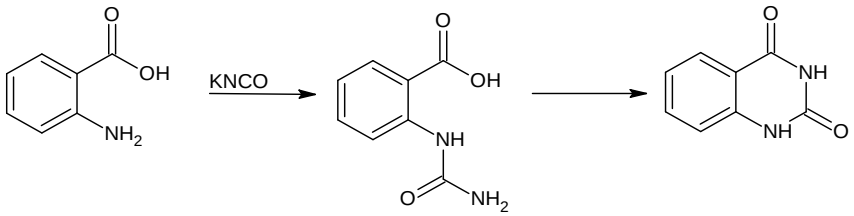
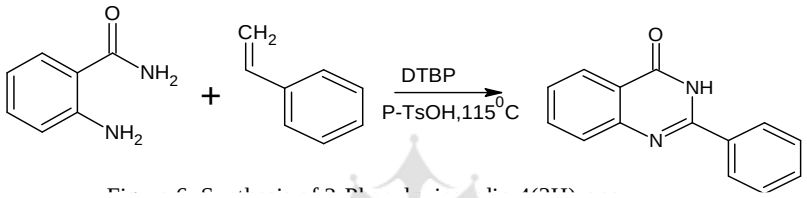
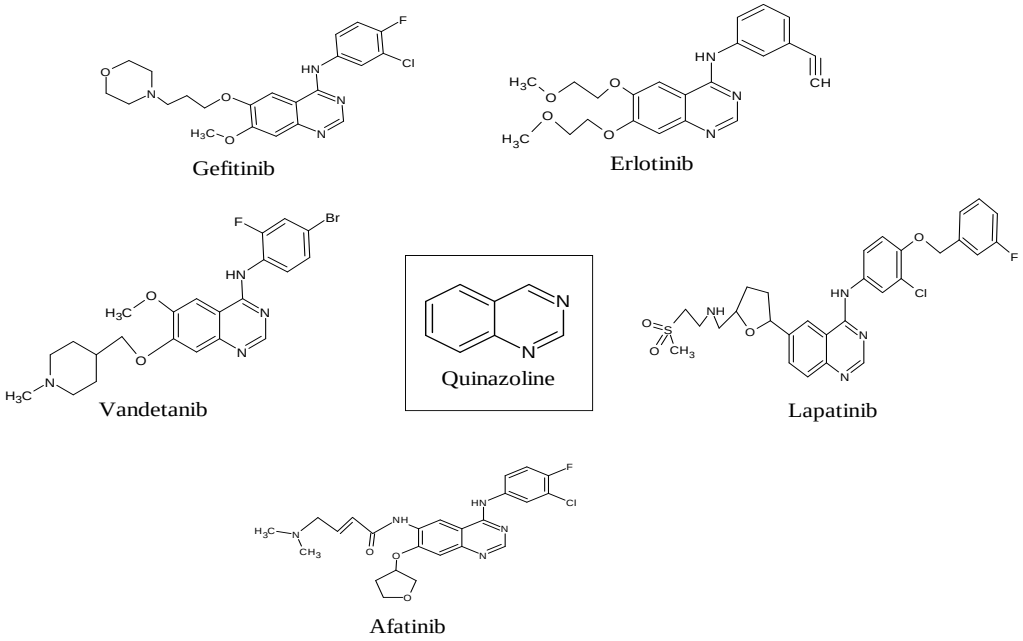


Figure 5. Synthesis of Quinazoline-2,4(1H,3H)-dione



The Food and Drug Administration (FDA) has approved several quinazoline derivatives for clinical use as anti-cancer drugs. These include gefitinib, erlotinib, lapatinib, afatinib and Vandetanib (Fig.7) 43. Gefitinib (Iressa®) was Approved by FDA in 2003 for the treatment of locally advanced or metastatic non-small-cell lung cancer (NSCLC) in patients after failure of both platinum-based and ordocetaxel chemotherapies. In 2004, erlotinib (Tarceva®) Approved by FDA for treating NSCLC. Furthermore, in 2005, the FDA approved erlotinib in combination with gemcitabine for treatment of locally advanced, unrespectable, or metastatic pancreatic cancer. Erlotinib acts as a reversible tyrosine kinase inhibitor. Lapatinib (Tykreb®) was Approved by FDA in 2012 for breast cancer treatment. It inhibits the activity of both human epidermal growth factor receptor-2 (HER2/neu) and epidermal growth factor receptor(EGFR) pathways. Vandetanib (Caprelsa®) Approved by FDA in 2011 for the treatment of metastatic medullary thyroid cancer. It acts as a kinase inhibitor of a number of cell receptors, mainly the vascular endo the lial growth factor receptor (VEGFR), EGFR, and rearranged during transfection (RET)-tyrosine kinase (TK). Afatinib (Gilotrif®) Approved by FDA in 2013for NSCLC treatment. It acts as an irreversible covalent inhibitor of the receptor tyrosine kinases (RTK) for EGFR and erbB-2 (HER2).



PHARMACOLOGICAL SIGNIFICANCE OF QUINAZOLINE DERIVATIVES

There are many anti-cancer drugs in the market but still the demand is evergreen due to drug resistance. Hybrid drugs with multiple mechanisms of action may be of great value for cancer treatment.

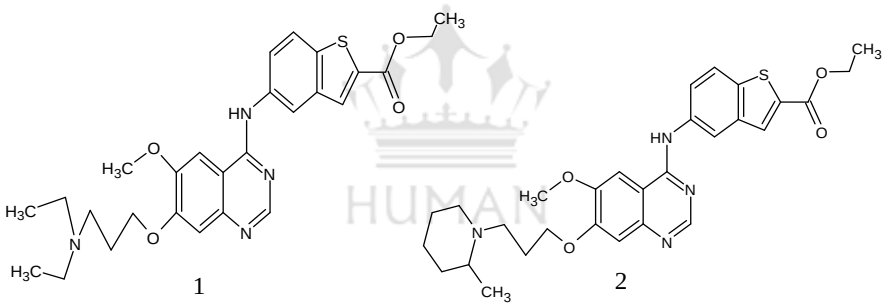
Quinazoline based molecules are significant in pharmaceutical chemistry because of their broad range of medicinal and therapeutic activities, such as anti-tumor, antifungal, anti-inflammatory, antibacterial, antioxidant and other activities.

The present review article was written as an effort to compile and discuss recently published studies concerning the therapeutic activity of quinazoline derivatives as anticancer agents.

In the early 2000s, discovery of the erlotinib and gefitinib as anticancer drugs encouraged researchers to investigate 4-anilinoquinazoline compounds, which led to the development of new and promising compounds such as lapatinib, Vandetanib, and afatinib. In previous studies, several patents and articles have been published that discuss the feasibility of the anilino quinazoline scaffold for the development of tyrosine kinase inhibitors (TKIs)44. The main biomolecular target of this class of compounds remains epidermal growth factor receptor (EGFR). Some compounds, however, do not show high selectivity for EGRF such as lapatinib, which is a dual EGFR/Her-2 inhibitor, whereas Vandetanib inhibits the kinase activities of both EGFR and VEGFR-2. Therefore, continuous and international efforts are being undertaken in order to develop more selective and efficient TKIs. EGFR is a very

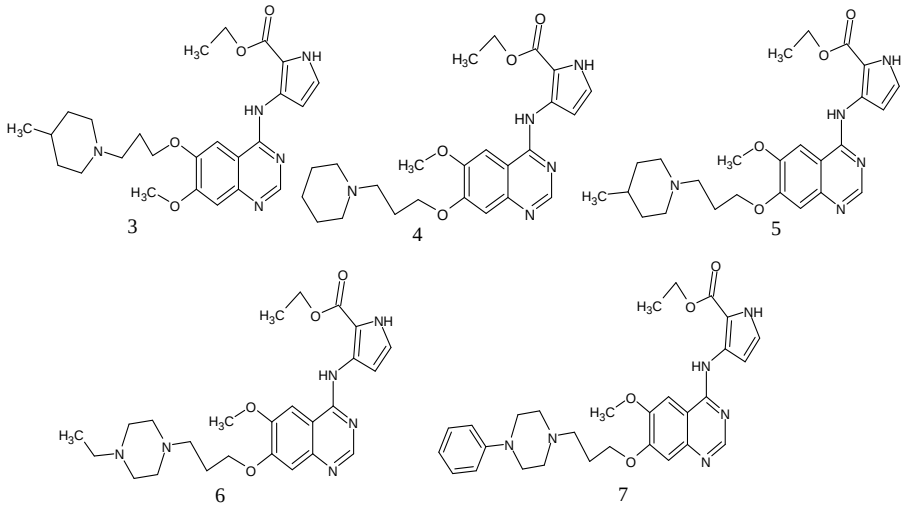
promising molecular target for cancer therapy; it has been observed, however, that most of the patients developed resistance to the EGFR inhibitors45-47. Therefore, continuous efforts are being undertaken to synthesize new and more potent EGFR inhibitors with improved anti-tumor activities. In this regard, several novel compounds were synthesized by introducing substitution on the benzene ring of the EGFR inhibitor, gefitinib.

X Wu et al. designed and synthesized two series of 4-benzothienyl amino quinazoline derivatives as new analogues of gefitinib48. 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 gefitinib, analogues (1) and (2) (Fig. 8) 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.

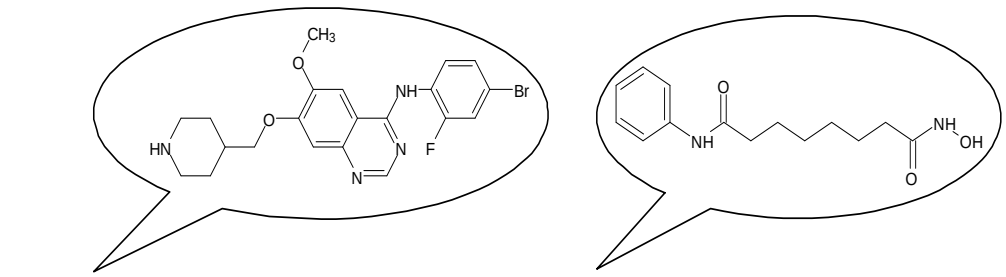


1 2

In order to develop novel RTK inhibitors with improved anticancer activity, X Wu et al. designed and synthesized two series of 4-pyrrylamino quinazolines49. 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) (Fig. 9). 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 a significant role in determining these compounds cytotoxicity.

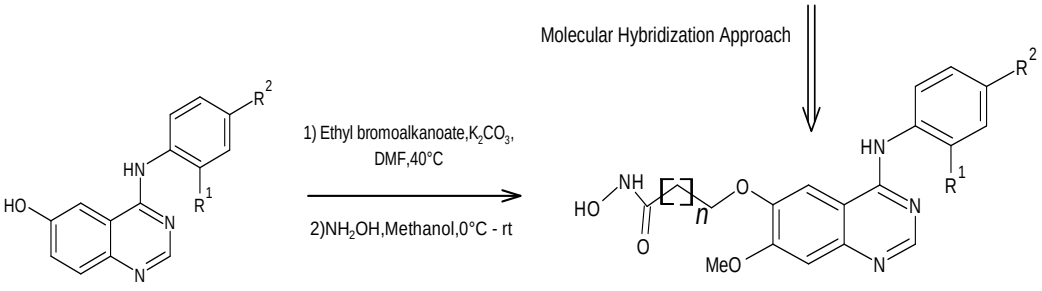


Peng et al. designed molecular hybrids having desired features for VEGFR-2 and HDAC inhibition.50 The hybrid molecules were synthesised by considering the structural characteristic of Vandetanib potent VEGFR-2 inhibitor and vorinostata potent HDAC inhibitor. As shown in (fig.10), 4-aminoquinazolinepharmacophore was linked with hydroxamic acid through a long alkyl chain. The obtained potent compounds show binding at the active site of VEGFR-2 kinase (PDB: 2QU5) and Histone Deacetylase Like Protein (HDLP) (PDB: 1C3S). thus, the potent compounds were tested for HDAC and VEGFR-2 inhibition, followed by anti-cancer screening against the MCF-7 cell line. Compound (8) was found to have potent inhibitory actionon both VEGFR-2 and HDAC, with IC_{50} values of 74 and 2.2 µM, respectively. Also, it was found to be cytotoxic against the MCF-7 cell line with an IC_{50} of 0.85 µM.



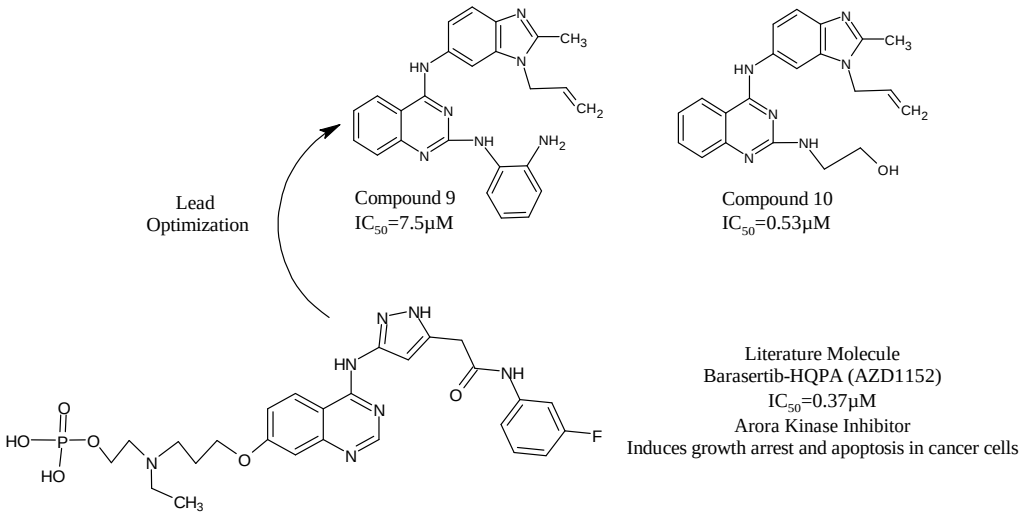
Vandetanib
VEGFR-2 inhibitors

Vorinostat
HDAC Inhibitor

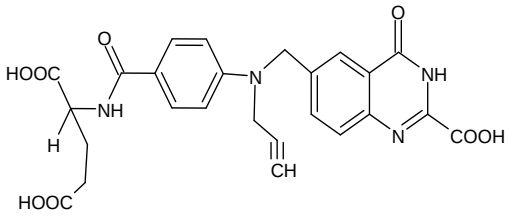


Compound 8 Dual VEGFR-2/HDAC Inhibitor
n=5, R^1=H, R^2=Br
IC_{50}=2.2nM, against HDAC
IC_{50}= 74nM, against VEGFR-2
Shows potent anti-cancer activity against MCF-7 cell line
(IC_{50}=0.85µM)

Luxami et al. has developed hybrid analogues having the structural characteristics of benzimidazole and 4-aminoquinazoline (important scaffold with anti-cancer potential)51. Amongst the synthesized analogues, compounds (9) and (10) have shown Arora kinase inhibition with IC_{50} values of 7.50 and 0.53 µM, respectively (Fig. 11). Along with aurora kinase inhibition, these potent compounds were also found to be useful as ratio metric chemo sensors for the estimation of lead and cyanide concentration in the given sample. Heavy metals are found to be toxic to the environment as well as human health; hence, chemo sensors will be effective for the detection of such ions. Pb^{2+} and CN^- binding property was investigated via UV-Vis spectroscopy, fluorescence spectroscopy, 1 H NMR titration experiment, and DFT calculations. Compound (9) was used to estimate CN^- (2– 500 mM) and compound (10) was used to estimate the Pb^{2+} ion (0.05–1500 mM) ratiometrically.



Robba et al. design and development a few novel 4-oxo quinazolyl-L-glutamic acid (11) (Fig. 12) & its analogs. These compounds were studied for their thymidylate synthetase inhibiting effects52. The synthesis of quinazolinone antifolates bearing functionalized alkyl substituents at C2 was the forms obtained from the modification of the potent Thymidylate Synthase (TS) inhibitor 1-[[N-[4- [N-[(3,4-dihydro-2-methyl-4-oxo-6-quinazolinyl)methyl]-N-prop-2-ynylamino]benzoyl]amino]methyl]-3-nitrobenzene (12). The compound was found to have good TS (IC_{50}<1µM) and growth inhibition (IC_{50} 0.1-1 µM)53.



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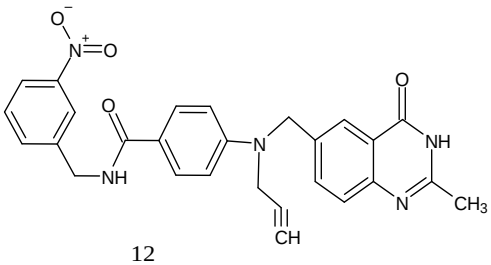
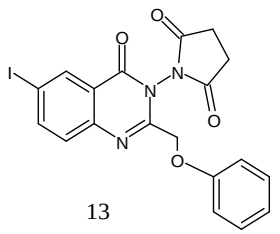


12

Abbas et al. have designed and synthesized a few novel 6-iodo-2-phenoxymethyl 3-substituted quina- zolin-4(3H)-ones (13-17) The synthesized compounds were tested against the MCF-7 breast cell line using doxorubicin (IC_{50}: 5.46lmol/ml) as a reference drug. Compound (13) exhibited a remarkable antitumor activity (IC50: 5.49lmol/ml) almost similar to that expressed by the reference drug, whereas compounds (14), (15), (16) and (17) (IC_{50}: 6.80, 6.23 and 6.55lmol/ml, respectively) showed a considerable activity 54.



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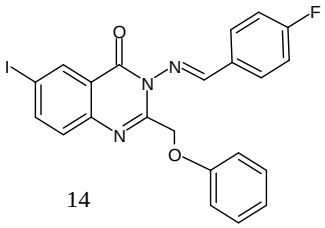

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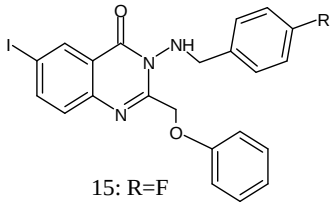
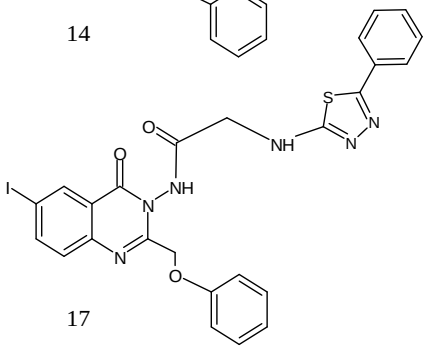


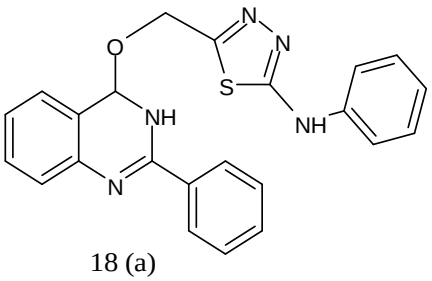
15: R=F
16: R=OCH_3



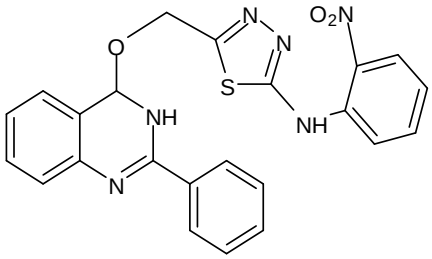
17

Srinivas et al.55 prepared a series of novel derivatives of quinazoline and tested their anticancer activity. Synthesized compounds 5-((3,4-dihydro-2-phenylquinazolin-4- yloxy)

methyl)-N-phenyl-1,3,4-thiadiazol-2-amine and 5-((3,4-dihydro-2-phenylquinazolin-4-yloxy) methyl)-N-(2-nitrophenyl)-1,3,4-thiadiazol-2-amine as Compound 18(a and b), are the most potent glycogen synthase kinase (GSK-3) inhibitors and showed high hypoglycaemic activity.

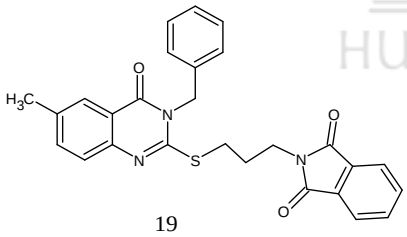


18 (a)



18 (b)

Hatem A. Abuelizz et al. have designed and synthesized a new series of quinazoline derivatives. The cytotoxicity of the compounds was evaluated in vitro against the HeLa and MDA-MB231 cancer cell lines, using MTT assay. The IC_{50} values of the target compounds were reported in µM, using gefitinib as a standard. Thus, compounds 19-21 exhibited potential anticancer agents, with IC_{50} values ranging from 1.85 to 2.81µM in relation to gefitinib (IC_{50} = 4.3 and 28.3 µM against HeLa and MDA-MB231 cells, respectively)56.



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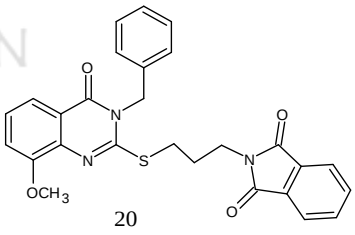

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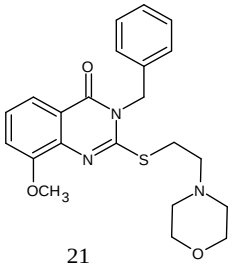

21

CONCLUSION

In the field of pharmaceutical chemistry, quinazoline is a structure of great interest since it contains a variety of medications, clinical prospects, and bioactive compounds. In the hunt for new anti-cancer medications, the pharmacophore quinazoline plays a significant role.

Many research facilities across the world are devoted to synthesizing various quinazoline derivatives. The anticancer effects of synthetic quinazoline derivatives on numerous cancer cell types were the main focus of this review article. This review has demonstrated that quinazoline derivatives can be further researched to improve chemotherapy. Further research into quinazolinone structure may produce more encouraging outcomes in the area of medicinal chemistry.

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