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QUINAZOLINE HETEROCYCLE AND ITS ANTI-CANCER ACTIVITY: AN OVERVIEW

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Keywords:

Quinazoline, Anti-cancer, DNA-interaction, Anti-Tumor

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ABSTRACT: The aim of this review is to provide an extensive overview of the diverse pharmacological activities of quinazoline moiety. Quinazolines are well-known and important nitrogen-containing heterocyclic compounds made chemical formula $C_8H_6N_2$. For the last few years, the heterocyclic fused nucleus quinazoline has drawn immense attention due to its diversified application in medicinal chemistry research. In the growing world of intense research, Quinazoline was considered as a privileged scaffold; the modification made with different substituents around the centroid paved the researchers away to deal with at ease. Being a fused ring, the heterocycle itself is capable of great pharmacological quality. Quinazoline is one of the heterocycles with diversifying scaffolds for various important biological activities for which considerable research has been done in order to examine its biomedical applications. In a number of biologically active compounds and drug molecules, the quinazoline nucleus is used as a basic framework. This paper is a sincere attempt to highlight the tremendous potential of this ring system because of its wide spectrum of pharmacological actions. This study can also speed up the design and synthesis process in order to create more therapeutically viable clinical candidates.

INTRODUCTION: Quinazoline heterocycle consists of two fused six-member aromatic rings, benzene & pyrimidine. Quinazoline derivatives, which belong to the N-containing heterocyclic compounds, have caused universal concerns due to their wide and distinct biopharmaceutical activities. The research on the biological activity of quinazoline compounds started when the compound 2-methyl-1,3-aryl-4-quinazoline derivative was synthesized [1].

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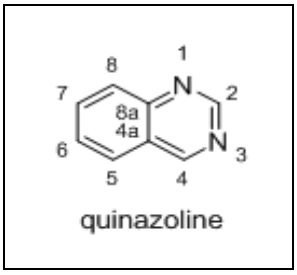
Some of the pharmacological responses attributed to these systems are analgesic, anti-inflammatory, anticonvulsant, sedative-hypnotic, anti-histaminic, anti-hypertensive, anti-cancer, anti-microbial, anti-tubercular and anti-viral activities. This multiplicity in the pharmacological response contours of quinazoline has attracted the notable consideration of medicinal chemists to explore this system to its multiple potentials against numerous activities [1]. Several of these synthetic and pharmacological investigations have been successively studied for structure-activity relationship (SAR) to correlate the particular structural features for their pharmacological target [1].

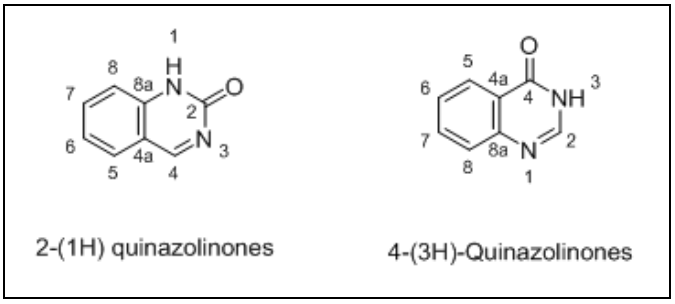
Quinazoline: Quinazoline consists of two fused six-membered aromatic rings *i.e.*, benzene and a pyrimidine ring are fused. Quinazoline is a fused

bicyclic compound, earlier known as benzo-1,3-diazine. It was first prepared in the laboratory by Gabriel [14]. In contrast, one of its derivatives was known much earlier. The name quinazoline (German: Chinazolin) was first proposed for this compound by Weddige on observing that this was isomeric with the compounds cinnoline and quinoxaline.

Paal and Bush suggested the numbering of quinazoline ring system, which is currently used. The other less commonly used names for this ring system are "phenmiazine" and 5,6-benzopyrimidine. However, the name quinazoline is now universally accepted. Many derivatives of the quinazoline system known so far, keto-quinazolines, also called as quinazolinones are the most important compounds.



Depending upon the position of the keto or oxo group, these compounds may be classified into two types:



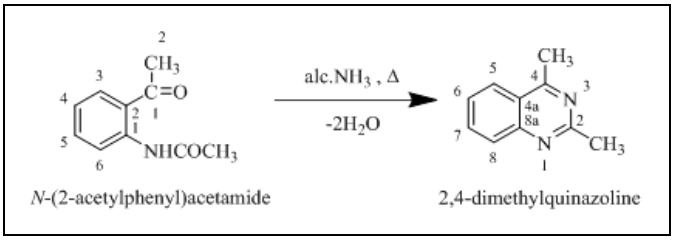
2-(1*H*) quinazolinones or 1,2-dihydro-2-oxo quinazolines and 4(*3H*)-quinazolines or 3,4-dihydrooxoquinazolines. These systems exhibit lactamlactim tautomerism and undergohydroxy group replacement reactions. 2-Cyano-4(3*H*)-quinazolinone was the first quinazolinone derivative to be synthesized.

Physical Properties: [2]

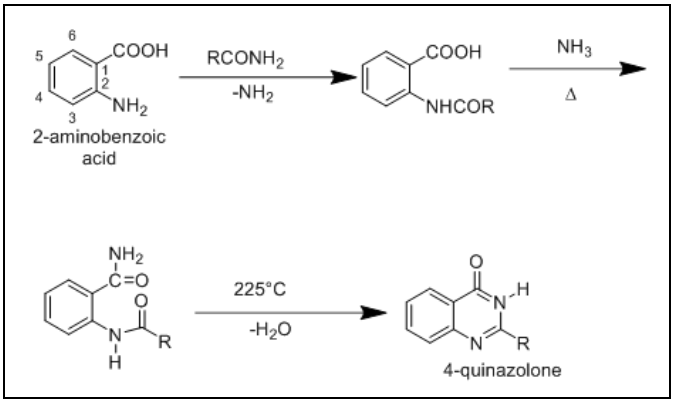
1. Quinazoline is a solid material.
2. Melting Point: 48°C.
3. It is soluble in water and most organic solvent.
4. It is basic in nature pKb:1.4

Synthesis:

1. Acyl derivatives of O-aminoacetophenone heating with ammonia gives substituted quinazoline derivatives [2].

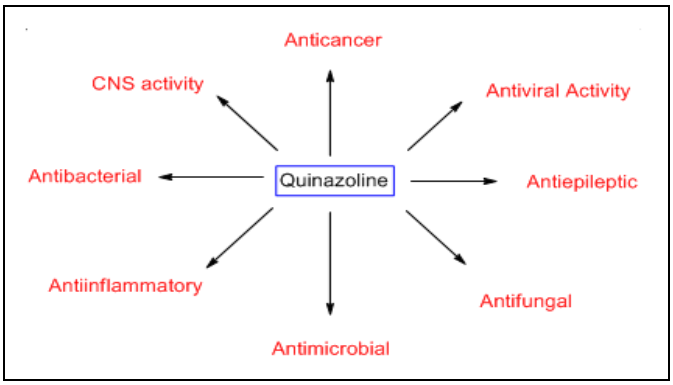


2. Niemantowski Reaction: In this reaction anthranilic acid on fusion with aliphatic amide yields 4-quinazoline derivatives [2].



Pharmacological Scaffold: Quinazoline due to its scaffold having a Great aspect of pharmacological effect.

Quinazoline has been studied for its different aspects of effect for the last decade to identify the capability to prepare and isolate a variety of pharmacological actions.

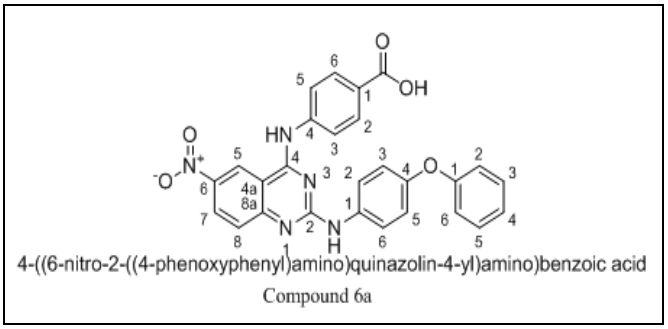


Anti-cancer Activity: Although substantial progress in early detection and treatment is made, cancer is one of the major health and social economic concerns.

By interfering with DNA replication, cytotoxic medicines work. Since the cancer cells are quickly split so that fresh DNA are synthesized quickly, the cell will die if damaged [3]. There are three main groups of molecules that can be used to interfere with DNA replication-Antimetabolites: they are molecules that appear to be as nucleotides. Alkylating agents: those are molecules that permanently attach to the DNA, distorting its shape 1. Unfortunately, these also attach to many other molecules in cells. DNA-binding agents: molecules that attach to the DNA chain break it, disengage from the chain, and then attach to another chain to repeat the process. These usually function in conjunction with an enzyme1. Presently, a wide range of cytotoxic drugs, either alone or in combination, are used to treat cancer, and several of these drugs are in different phases of clinical trials. These cytotoxic drugs are associated with several drawbacks and are not able to discriminate between cancerous and normal cell types; therefore, they can cause serious side effects that are often cumulative and dose-limiting. Many researchers have focused on developing novel and effective anti-cancer compounds due to the emergence and increase of multi-drug resistance to various conventional drugs and the continuing importance on healthcare expenditure. Quinazoline is one of the most widespread scaffolds amongst bioactive compounds.

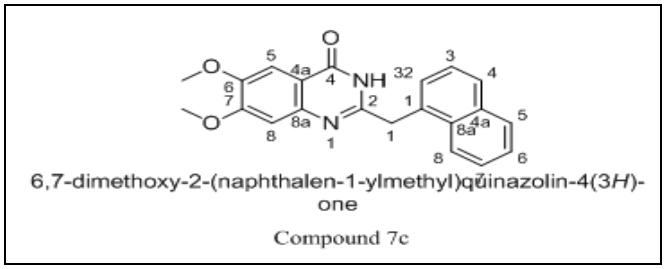
Several quinazoline derivatives have been authorized by the Food and Drug Administration (FDA) for clinical use as anti-cancer medicines. Gefitinib, erlotinib, lapatinib, afatinib, and vandetanib are some of them. A number of patents and publications relating to the discovery and development of novel potential quinazoline compounds for cancer chemotherapy can be found in the literature [4].

Literature Review: Lina Zhu *et al.*, reported A series of novel 2,4-disubstituted quinazoline derivatives and their inhibitory activities on hPin1, among them quinazoline compound 6a was identified as a potent compound with an IC_{50} of 4.87 μM by a random screening [8].


4-((6-nitro-2-((4-phenoxyphenyl)amino)quinazolin-4-yl)amino)benzoic acid

Compound 6a

Mange R. Yadav *et al.*, reported of a series of substituted 6,7-dimethoxyquinazoline derivatives. The cytotoxic activity of all synthesized compounds has been evaluated against HCT116 p53+/+ and HCT116p53-/- colon cancer cells and a HEY ovarian cancer cell line naturally resistant to cisplatin, among them derivative (7c) showed IC_{50} values of 0.7 and 1.7 μM in the two colon cancer cell lines [9].

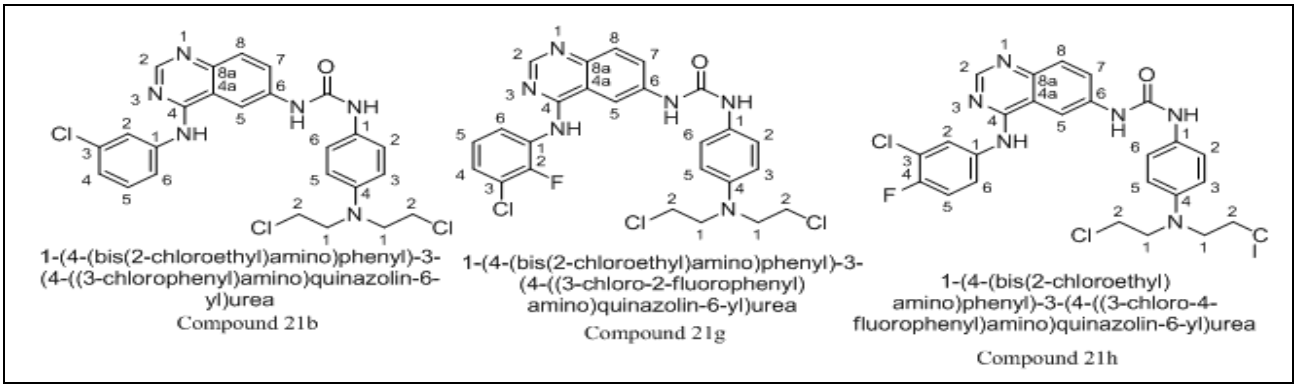

6,7-dimethoxy-2-(naphthalen-1-ylmethyl)quinazolin-4(3*H*)-one

Compound 7c

Bhavin Marvania *et al.*, reported A series of N-mustard-quinazoline conjugates, among the prepared derivatives. Compounds 21b, 21g, and 21h were selected for further antitumor activity evaluation against human breast carcinoma MX-1 and prostate PC-3 xenograft in an animal model. These agents showed 54–75% tumor suppression with low toxicity (5–7% body-weight changes) [10].

Jin C *et al.*, reported Three series of novel 4-benzothiazole amino quinazolines Dasatinib derivatives had been designed and synthesized. The entire target compounds were investigated for their in vitro cytotoxic activity by the MTT-based assay against 6 human cancer cell lines; among them, 1a, 1f and 3a-3f are more potential dual Src/Abl kinase inhibitors.

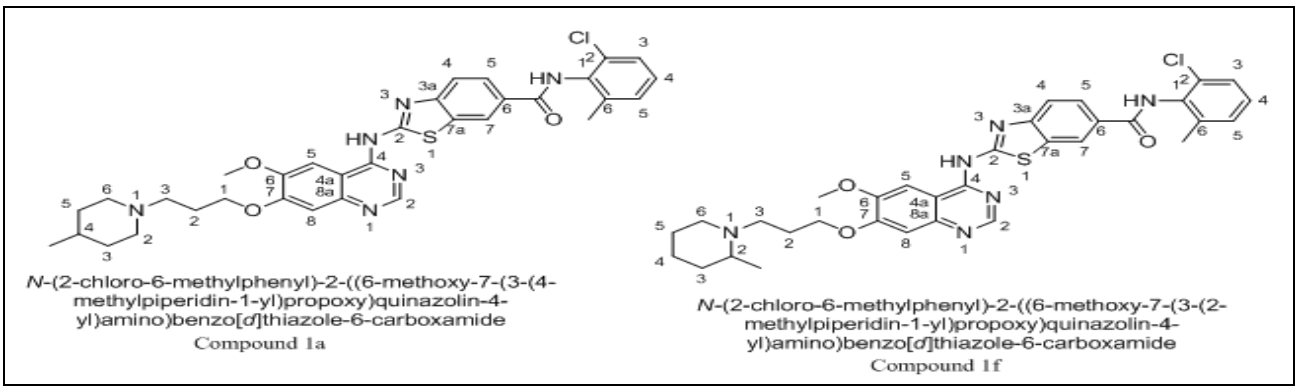
Thus, they may be promising lead compounds to be developed as an alternative for current Dasatinib therapy or Imatinib-resistant patients, potentially *via* simultaneously blocking multiple RTK signaling pathways [11].



1-(4-(bis(2-chloroethyl)amino)phenyl)-3-(4-((3-chlorophenyl)amino)quinazolin-6-yl)urea
Compound 21b

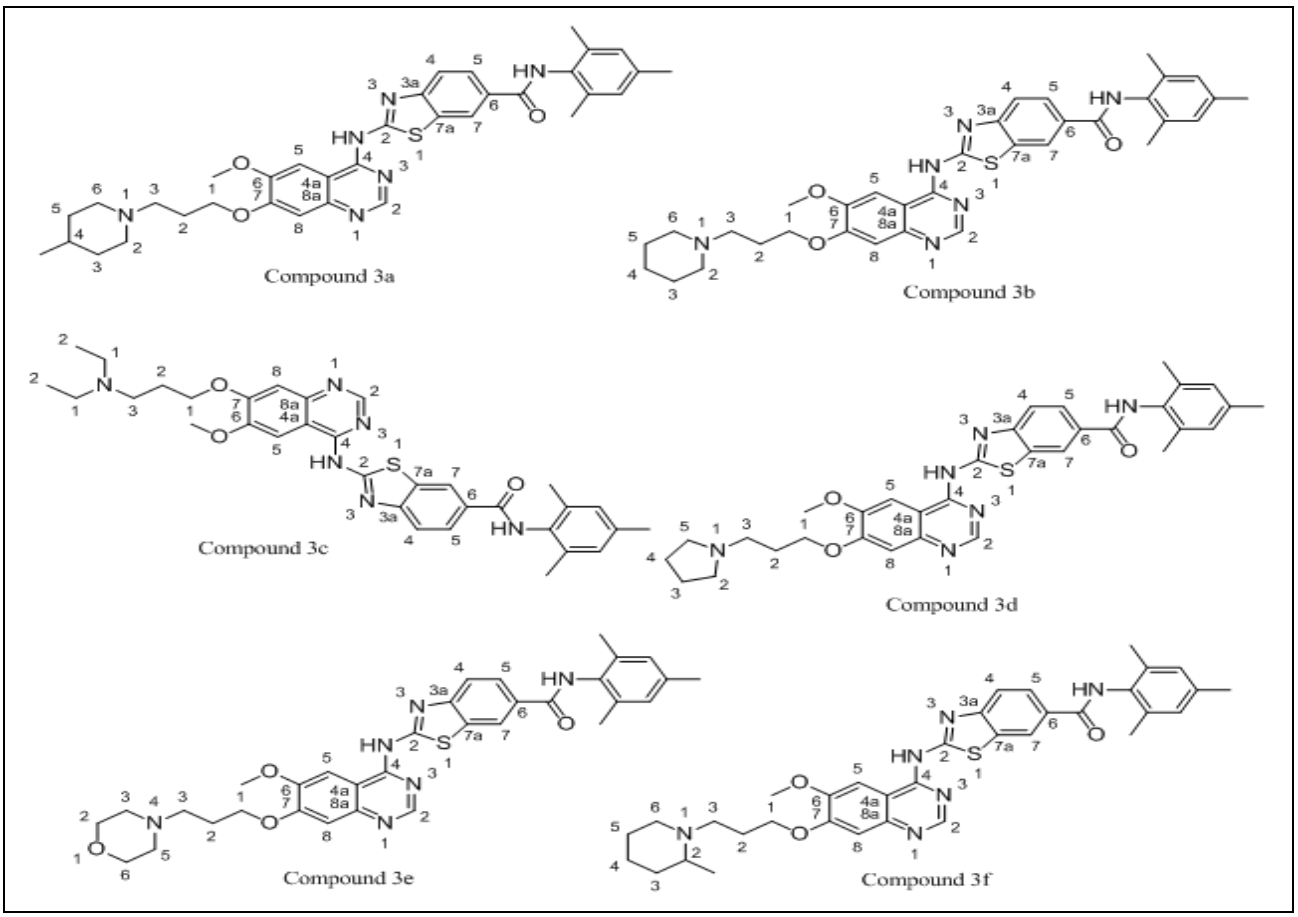
1-(4-(bis(2-chloroethyl)amino)phenyl)-3-(4-((3-chloro-2-fluorophenyl) amino)quinazolin-6-yl)urea
Compound 21g

1-(4-(bis(2-chloroethyl) amino)phenyl)-3-(4-((3-chloro-4-fluorophenyl)amino)quinazolin-6-yl)urea
Compound 21h



N-(2-chloro-6-methylphenyl)-2-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinazolin-4-yl)amino)benzo[*d*]thiazole-6-carboxamide
Compound 1a

N-(2-chloro-6-methylphenyl)-2-((6-methoxy-7-(3-(2-methylpiperidin-1-yl)propoxy)quinazolin-4-yl)amino)benzo[*d*]thiazole-6-carboxamide
Compound 1f



Compound 3a

Compound 3b

Compound 3c

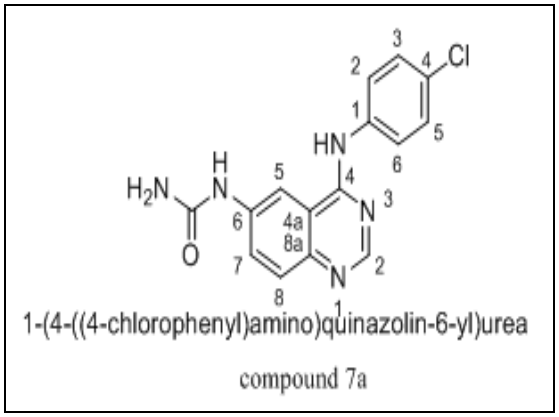
Compound 3d

Compound 3e

Compound 3f

Samar Mowafy *et al.*, reported 4-Anilino-6-substituted-quinazolines were designed, synthesized, and evaluated for EGFR-TK and tumor growth inhibitory activities, among them compound 7a was assayed full NCI 60 cell panel and exhibited remarkable growth inhibitory activity pattern

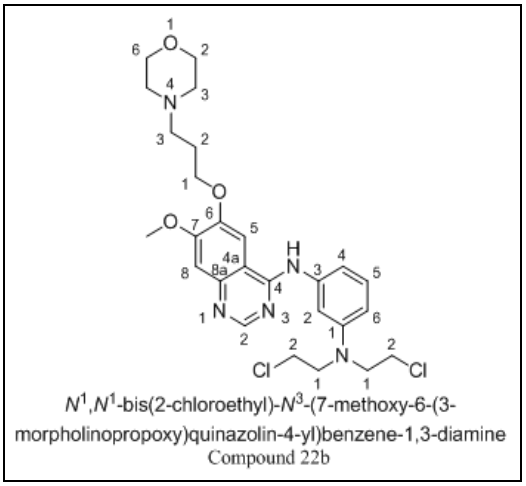
against Non-Small Cell Lung Cancer EKVX (GI_{50} = 0.37 µM), NCI-H322M (GI_{50} = 0.36 µM), Renal Cancer A498 (GI_{50} = 0.46 µM), TK-10(GI_{50} = 0.99 µM) and Breast Cancer MDA-MB-468 (GI_{50} =1.096 µM) which are of high EGFR expression.[12]



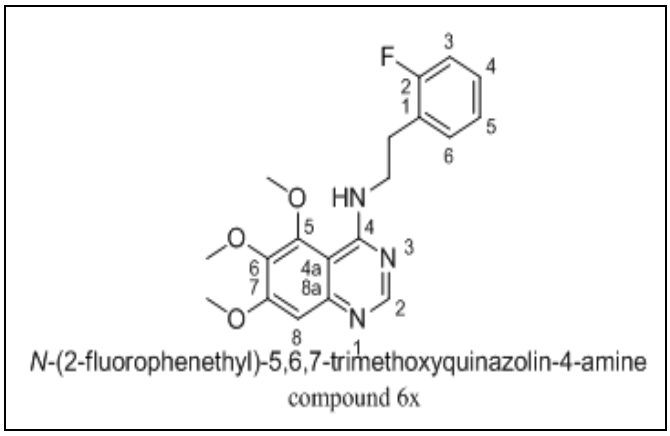
Shilei Li *et al.,* reported novel quinazoline nitrogen mustard derivatives were designed, synthesized, and evaluated for their anti-cancer activities *in vitro* and *in vivo*.

Cytotoxicity assays were carried out in five cancer cell lines (HepG2, SH-SY5Y, DU145, MCF-7, and A549) and one normal human cell line (GES-1), compound 22b showed very low IC_{50} to HepG2 (the IC_{50} value is 3.06 mM), which was lower than Sorafenib.

Compound 22b could inhibit the cell cycle at S and G2/M phase and induce cell apoptosis. In the HepG2 xenograft model, 22b exhibited significant cancer growth inhibition with low host toxicity *in-vivo* [13].

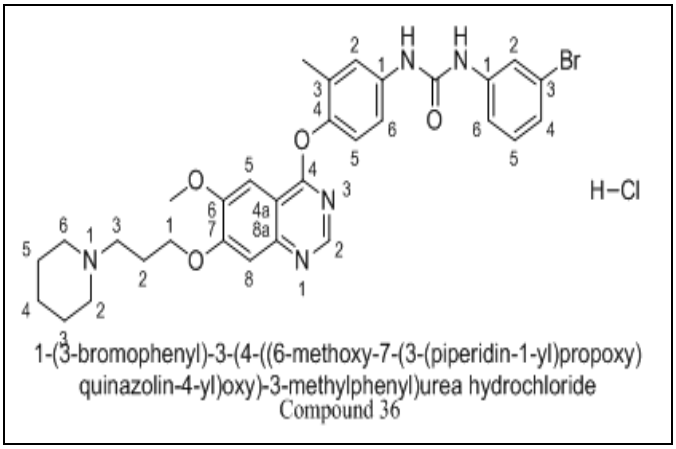


Ying Zhang *et al.,* reported A series of 5,6,7-trimethoxy-N-phenyl(ethyl)-4-aminoquinazoline among them Compounds 6p, 6q, and 6x strongly inhibited extracellular regulated kinase1/2 (ERK1/2) phosphorylation induced by epidermal growth factor (EGF) at 1.28 µM in PC3 cells [14].

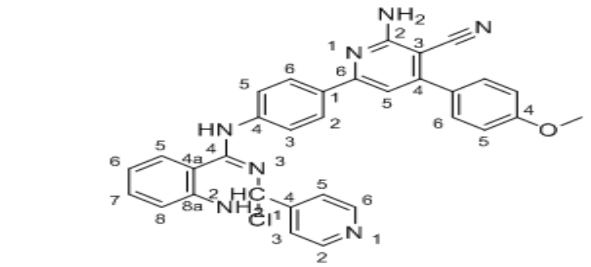


Séverine Ravez *et al.,* reported 7-Aminoalkoxy-4-aryloxy-quinazoline ureas as multiple tyrosine kinase inhibitor, among them that potent multi-kinase inhibitor 36 inhibited angiogenesis by preventing tube formation and suppressing endothelial cells invasion.

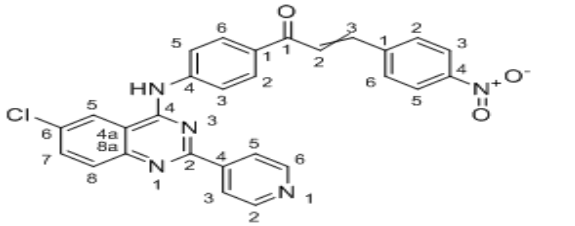
Lower proliferation inhibition against the normal cells MRC5, multi-kinase inhibitor 36 strongly represses the angiogenic process by inhibiting endothelial cell invasion and preventing tube formation with lower concentrations than those of the reference compound (cediranib) [15].



AAF. Wasfy *et al.,* reported novel quinazoline derivatives were synthesized screening system for evaluation of antitumor activity against Liver Cancer (HEPG2) tumor cell line, among the derivatives 6b, 8d show strong effects against human hepatocellular liver carcinoma (HepG2) [16].

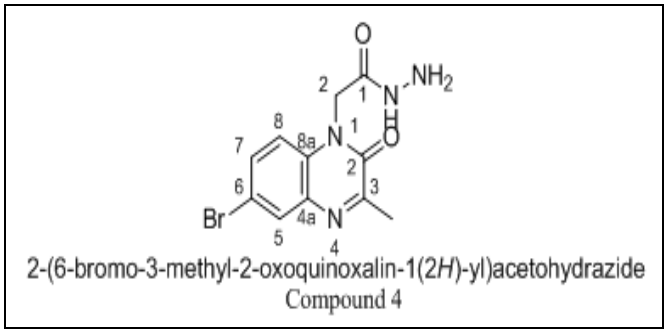


(*E*)-2-amino-*N*-(4-(6-amino-5-cyano-4-(4-methoxyphenyl)pyridin-2-yl)phenyl)-*N'*-(chloro(pyridin-4-yl)methyl)benzimidamide
Compound 6b



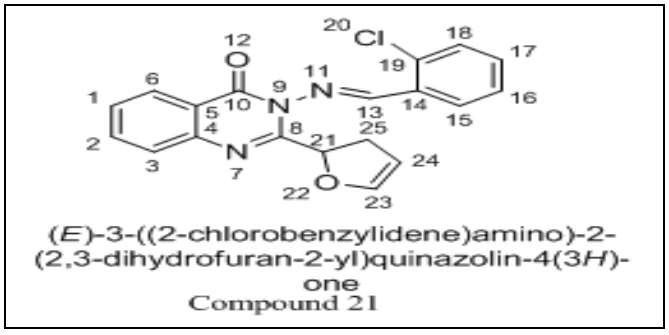
1-(4-((6-chloro-2-(pyridin-4-yl)quinazolin-4-yl) amino)phenyl)-3-(4-nitrophenyl)prop-2-en-1-one
Compound 8d

Hebat-Allah S. Abbas *et al.,* reported novel quinoxaline derivatives with potential anti-cancer activity as inhibitors of c-Met kinase (a receptor associated with high tumor grade and poor prognosis in a number of human cancers.) among them compounded 4 and showed a more potent inhibition activity than Doxorubicin [17].



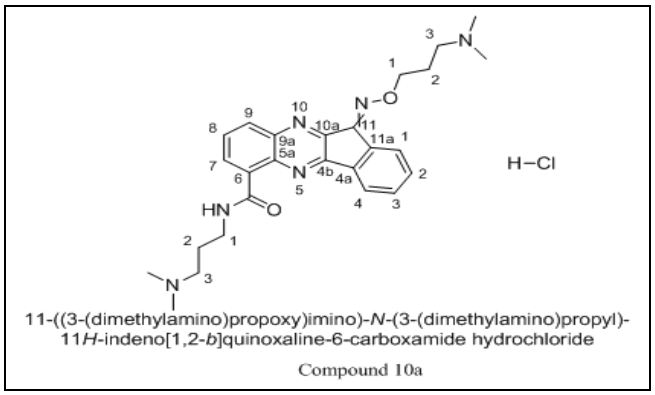
2-(6-bromo-3-methyl-2-oxoquinoxalin-1(2*H*)-yl)acetohydrazide
Compound 4

Malleshappa N. Noolvi *et al.,* reported some 2-furano-4(3H)-quinazolinones, diamides (open ring quinazolines), among them 3-(2-chloro benzylidene-amine)-2-(furan-2-yl) quinazoline-4(3h)-one 21 was found to be the most active candidate of the series at five dose level screening against Ovarian OVCAR-4 and Non-small cell lung cancer NCI-H522 with GI50 1.82 & 2.14 µM respectively [18].



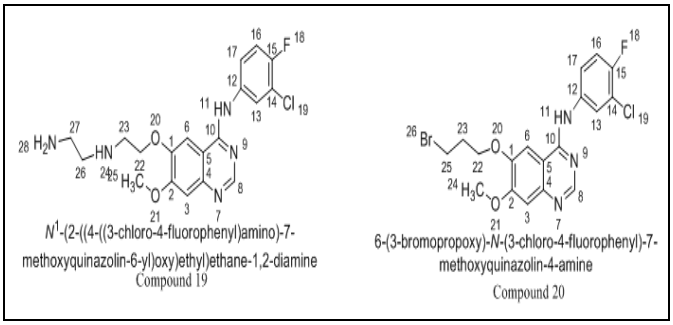
(*E*)-3-((2-chlorobenzylidene)amino)-2-(2,3-dihydrofuran-2-yl)quinazolin-4(3*H*)-one
Compound 21

Chih-Hua Tseng *et al.,* reported indeno[1,2-b] quinoxaline derivatives for antiproliferative evaluation. Among them, compound 10a induced cell cycle arrest at S phase *via* activation of caspase-3, -7 and an increase in the protein expression of Bad and Bax but a decrease in expression of Bcl-2 and PARP, which consequently cause cell death [19].



11-((3-(dimethylamino)propoxy)imino)-*N*-(3-(dimethylamino)propyl)-11*H*-indeno[1,2-*b*]quinoxaline-6-carboxamide hydrochloride
Compound 10a

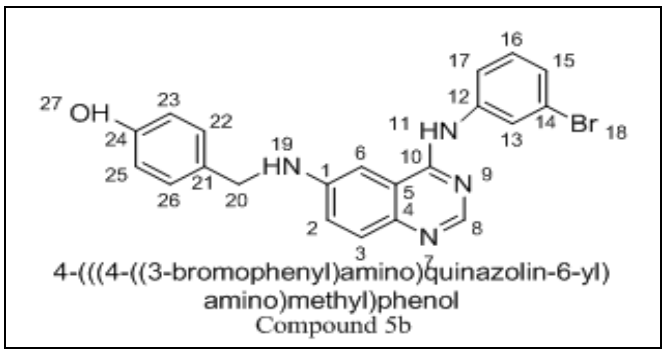
Shuang Lü *et al.,* reported a series of 4-anilinoquinazoline derivatives, as epidermal growth factor receptor (EGFR) inhibitors by modifications on the aniline ring or at the 6-alkoxy site of the 6,7-dimethoxy-4-anilinoquinazoline among them compounds 19 and 20 found the most potent EGFR inhibitors [20].



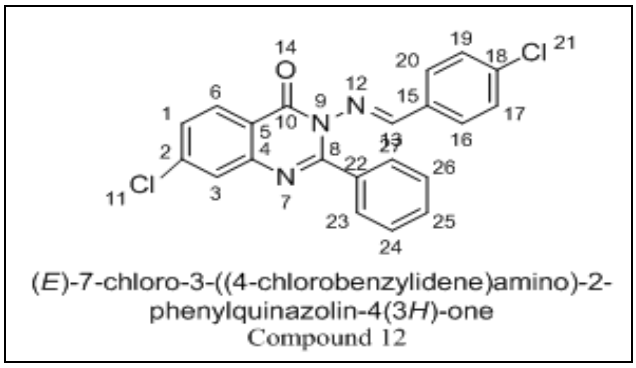
N^1-(2-((4-((3-chloro-4-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)ethyl)ethane-1,2-diamine
Compound 19

6-(3-bromopropoxy)-*N*-(3-chloro-4-fluorophenyl)-7-methoxyquinazolin-4-amine
Compound 20

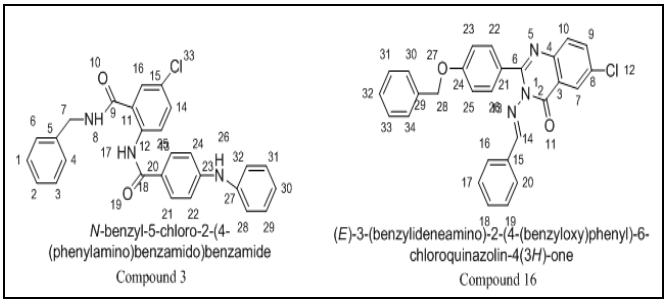
Huan-Qiu Li *et al.,* reported novel 4,6-substituted-(diphenylamino)quinazolines as potential EGFR inhibitors, among them Compound 5b showed the most potent inhibitory activity and effectively induces apoptosis in a dose-dependent manner in the Hep G2 cell line [21].


4-(((4-((3-bromophenyl)amino)quinazolin-6-yl) amino)methyl)phenol
Compound 5b

Malleshappa N. Noolvi *et al.*, reported A novel 3-(substituted benzylideneamino)-7-chloro-2-phenyl quinazoline-4(3H)-one derivatives among them compound 12 showed remarkable activity against CNS SNB-75 Cancer cell line [22].

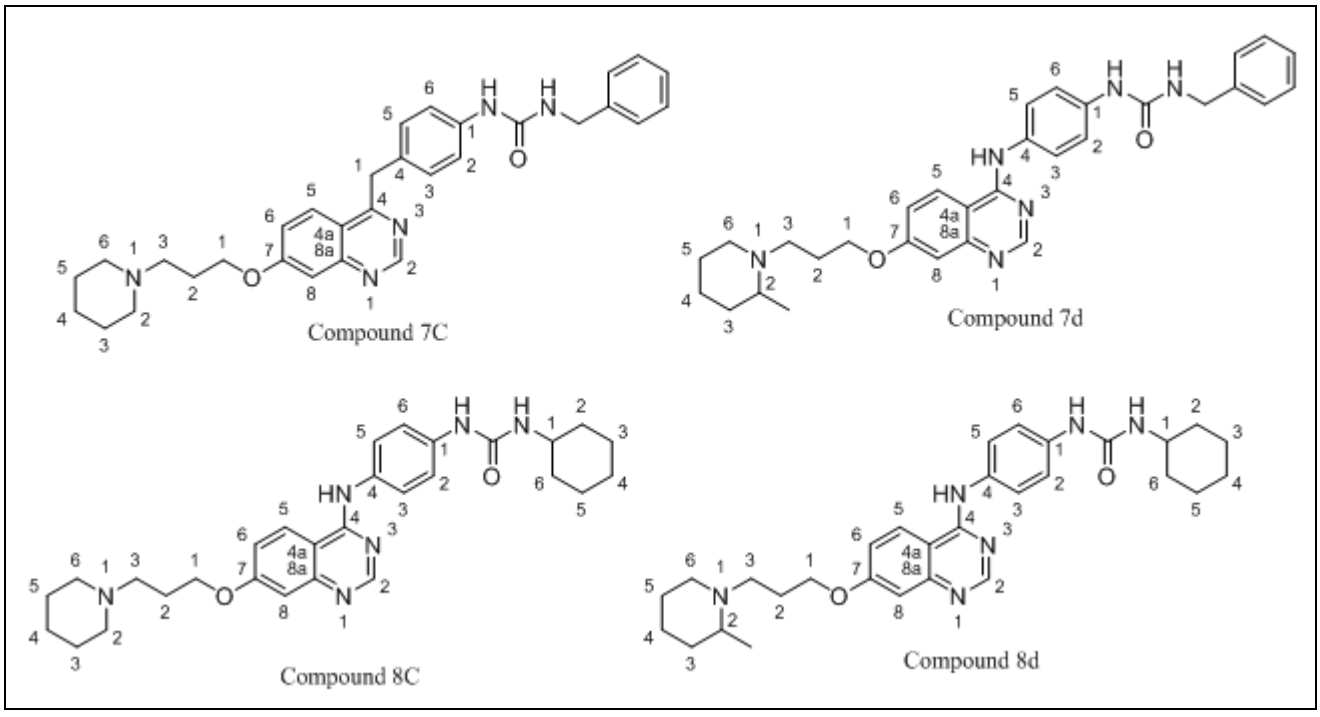

(*E*)-7-chloro-3-((4-chlorobenzylidene)amino)-2-phenylquinazolin-4(3*H*)-one
Compound 12

Amer M. Alanazi *et al.*, reported A novel series of 6-chloro-2-p-tolylquinazolinone and substituted-(4-methylbenzamido) benzamide for their *in-vitro* antitumor activity. Compounds 3 and 16 possessed remarkable broad-spectrum antitumor activity. Compound 16 was found to be a particularly active growth inhibitor of the renal cancer (GI_{50} = 4.07 µM), CNS cancer (GI_{50} = 7.41 mM) ovarian cancer (GI_{50} = 7.41 µM) and non-small cell lung cancer (GI_{50} = 7.94 µM) [23].


N-benzyl-5-chloro-2-(4-(phenylamino)benzamido)benzamide
Compound 3

(*E*)-3-(benzylideneamino)-2-(4-(benzyloxy)phenyl)-6-chloroquinazolin-4(3*H*)-one
Compound 16

Jin Cai *et al.*, reported 4-aminoquinazoline—urea derivatives for their *in-vitro* antiproliferative activity against six human cancer cell lines (K562, U937, A549, NCI-H661, HT29 and LoVo) using the MTT-based assay, Among them, 7c, 7d, 8c, and 8d are more potent against Aurora A kinase.[24].


Compound 7C

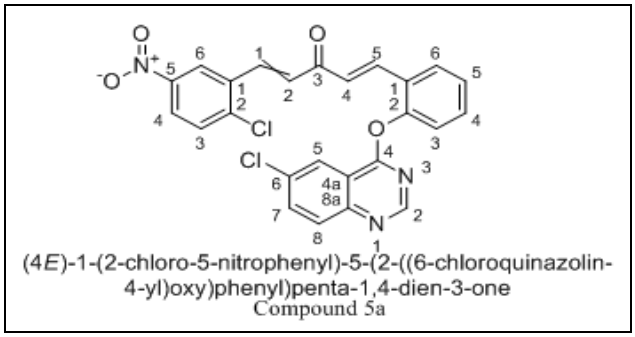
Compound 7d

Compound 8C

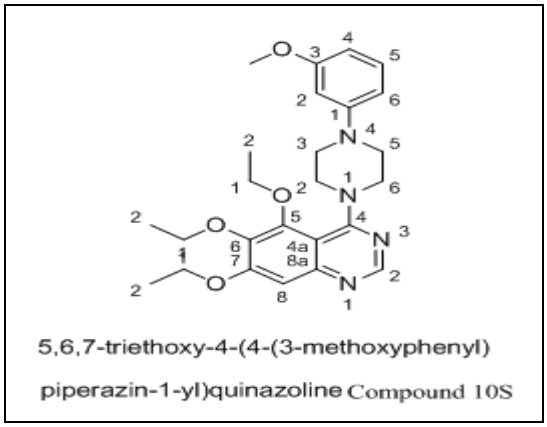
Compound 8d

Hui Luo *et al.*, reported Series of novel derivatives of 6-chloro-quinazolin, which this moiety was linked to a 1,5-diaryl-1,4-pentadien-3-one system, and tested for their antitumor activities *in vitro* against a panel of three human cancer cell lines (MGC-803, Bcap-37 and PC3 cells), among them 6-chloro-quinazolin derivatives 5a was the most active members in this study, and experimental

results of fluorescent staining and flow cytometry analysis revealed that they could induce apoptosis in MGC-803 and Bcap-37 cells, with apoptosis ratios of 31.7% and 21.9% at 24 h of treatment at10 µM in MGC-803 cells [25].

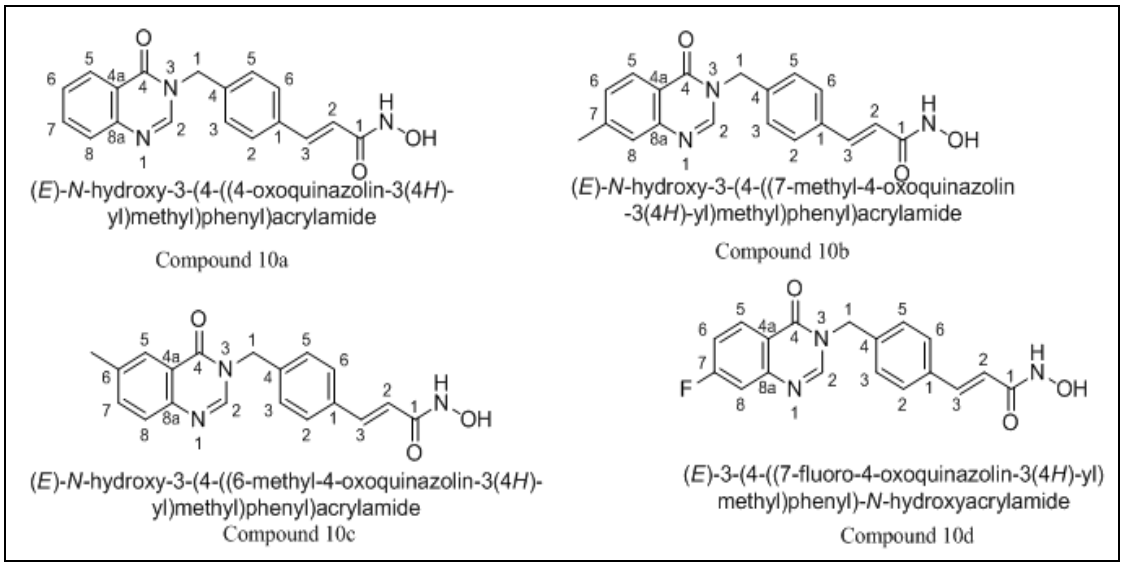

(4*E*)-1-(2-chloro-5-nitrophenyl)-5-(2-((6-chloroquinazolin-4-yl)oxy)phenyl)penta-1,4-dien-3-one
Compound 5a

Ying Zhang *et al.*, reported A series of 4-(4-substituted piperazin)-5,6,7-trialkoxy quinazoline, among them compound 10S found inhibitory activity against proliferation of A549 cells through the interruption of ERK1/2 and P38signaling pathways [26].


5,6,7-triethoxy-4-(4-(3-methoxyphenyl) piperazin-1-yl)quinazoline Compound 10S

Doan Thanh Hieu *et al.*, reported novel N-hydroxy benzamides/Nhydroxypropenamides incorporating quinazolin-4(3H)-ones as histone deacetylase inhibitors and antitumor agents, among them.

It was found that the N-hydroxypropenamides (10a-d) were the most potent, both in term of HDAC inhibition and cytotoxicity [27].


(*E*)-*N*-hydroxy-3-(4-((4-oxoquinazolin-3(4*H*)-yl)methyl)phenyl)acrylamide
Compound 10a

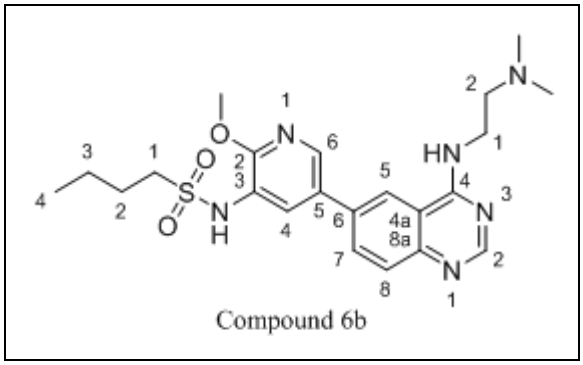
(*E*)-*N*-hydroxy-3-(4-((7-methyl-4-oxoquinazolin-3(4*H*)-yl)methyl)phenyl)acrylamide
Compound 10b

(*E*)-*N*-hydroxy-3-(4-((6-methyl-4-oxoquinazolin-3(4*H*)-yl)methyl)phenyl)acrylamide
Compound 10c

(*E*)-3-(4-((7-fluoro-4-oxoquinazolin-3(4*H*)-yl) methyl)phenyl)-*N*-hydroxyacrylamide
Compound 10d

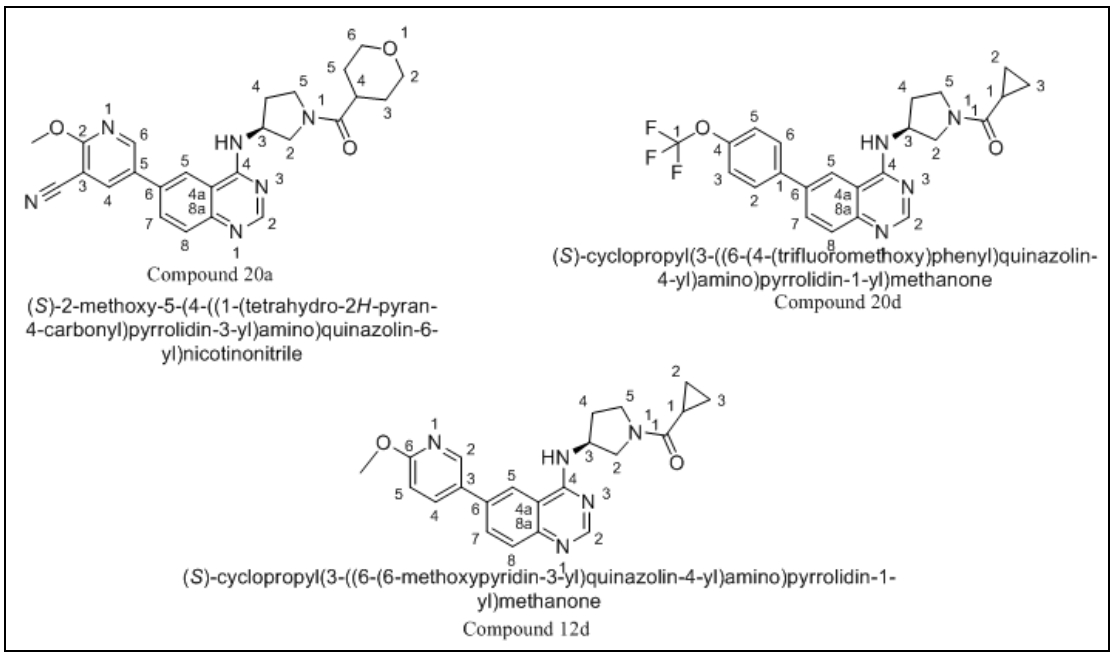
Yan-Hua Fan *et al.*, reported Novel 4-aminoquinazoline derivatives induce growth inhibition, cell cycle arrest and apoptosis *via* PI3Ka inhibition, among the prepared derivatives Compound 6b with the most potent anti-proliferative activity and without obvious cytoto-xicity to human normal cells was selected for further biological evaluation.

PI3K kinase assay showed that 6b has selectivity for PI3Ka distinguished from other isoforms and 6b has a therapeutic value as an anti-cancer agent *via* PI3Ka inhibition [28].

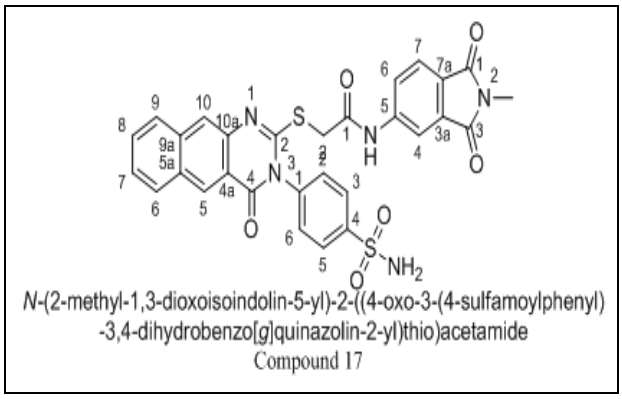

Compound 6b

Minhang Xin *et al.*, reported a novel series of 6-aryl substituted 4-pyrrolidineaminoquinazoline

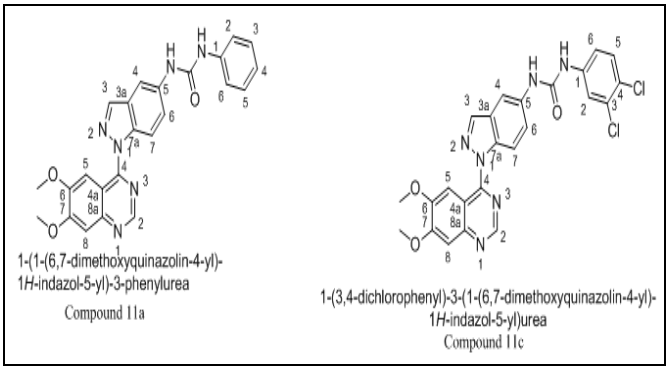
derivatives were designed and evaluated as potent PI3Kd inhibitors, among them compounds 12d, 20a and 20c displayed leading potent PI3Kd inhibition and showed distinct anti-proliferation profiles against four human B cell lines of Ramos, Raji, RPMI-8226 and SU-DHL-6 [29].



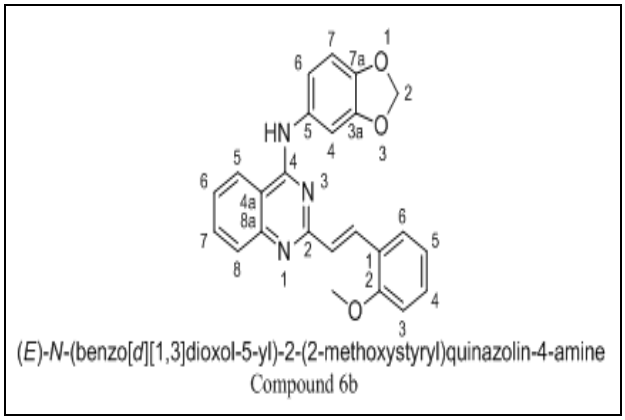
Mostafa M. Ghorab *et al.*, reported N-substituted-2-(4-oxo-3-(4-sulfamoylphenyl)-3,4-dihydrobenzo[g] quinazolin-2-ylthio) acetamide for their cytotoxic activity against MDA-MB-231 breast cancer cell line, among them Compound 17, the most potent towards EGFR in this series, undergoes cell cycle analysis and was found to arrest the cycle at the G2/M phase [30].



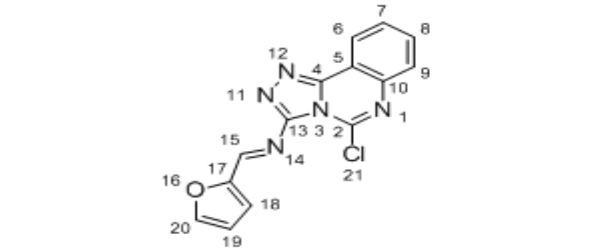
Elsayed MN *et al.*, reported of novel indazole-based derivatives, among them 11b and 11c showed strong inhibition of human umbilical vein endothelial cells (HUVEC) proliferation with 80% and 99.6% inhibition at 10 μM concentration, compound 11c represents a promising candidate for cancer treatment through antiangiogenic dependent and antiangiogenic independent modes of action [31].



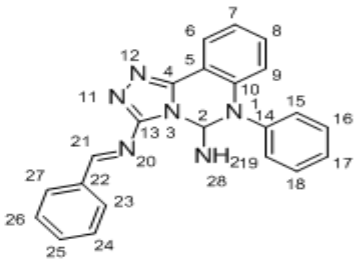
Jacek Mularski *et al.*, reported Quinazoline derivatives constitute a large family of small-molecule inhibitors of tyrosine kinases, among them compound 6b found more potent kinase inhibitory action [32].



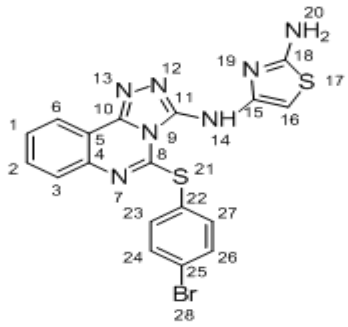
Ewesa WA *et al.*, reported triazolo[4,3-c]quinazolines derivatives EGFR-TK inhibitors, EGFR belongs to the ErbB family of receptor tyrosine kinase from which, HER2 (erbB2), a putative oncogene, has been associated with aggressive tumor progression. Many cancer types are exceedingly progressed and developed due to the altered protein expression and the activity of receptor tyrosine kinases (RTKs)as they regulate different cellular functions as proliferation, differentiation, migration, and angiogenesis, synthesized compounds They were evaluated for their *in-vitro* antitumor activity against HepG2, MCF-7, PC-3, HCT-116 and HeLa cancer cell lines using MTT assay, Compounds8, 19 and 21 caused cell cycle arrest at the G2/M phase, and interestingly, induced cell death by apoptosis of MCF-7 cells cumulatively with 7.14, 17.52 and 24.88%, respectively, compared with DOX as a positive reference (29.09%) [33].



5-Chloro-N[(furan-2-yl)methylene][1,2,4]triazolo[4,3-c] quinazolin-3-amine
Compound 8



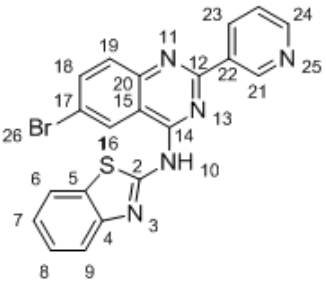
3-(Benzylidenamino)-N-phenyl-[1,2,4]triazolo[4,3-c]quinazolin-5-amine
Compound 9



N^4-(5-((4-bromophenyl)thio)-[1,2,4]triazolo[4,3-c]quinazolin-3-yl)thiazole-2,4-diamine
Compound 21

Allama HA *et al.*, reported some new 2,4,6-trisubstituted quinazoline derivative as an EGFR inhibitor Epidermal growth factor receptor (EGFR) signaling pathway has been extensively investigated for its significant role in the progression of different types of malignant tumors, where the development of small molecules targeting EGFR is a well-known strategy for the design of antitumor agents, compounds that showed potent inhibitory activity on wild-type EGFR were screened against mutant EGFR and assayed for their cytotoxicity against mutant EGFR expressing cell lines PC9 and HCC827.

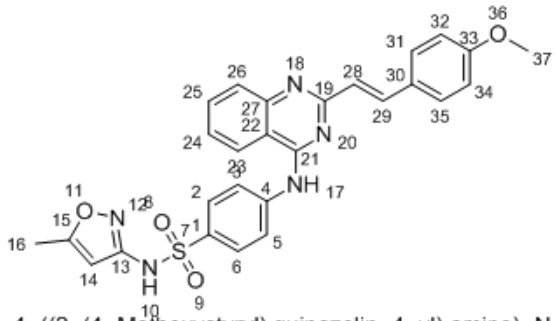
The unsubstituted benzothiazol-2-amine VIIa showing superior EGFR inhibition (IC_{50} = 0.096 μM) and anticancer activity against MCF-7 cell line (IC_{50} = 2.49 μM) [34].



N-(6-bromo-2-(pyridin-3-yl)quinazolin-4-yl)benzo[d]thiazol-2-amine
Compound VIIa

Amin NH *et al.*, synthesized and screened 2-styrylquinazoline derivatives as EGFR inhibitors and apoptosis inducers for the screening MTT cytotoxicity, *in-vitro* cell-free EGFR and anti-proliferative activity against EGFR/ A549 cell line

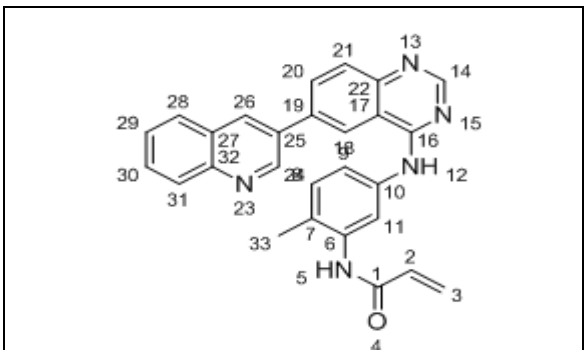
were used; among the synthesized compounds, Compound 8c is found to be a prominent candidate with (IC50 = 8.62 μM, 0.190 μM and = 79.25%), if compared tolapatanib (IC50 = 11.98 μM, 0.190 μM, and 79.25%) [35].



(E)- 4- ((2- (4- Methoxystyryl) quinazolin- 4- yl) amino)- N- (5-methylisoxazol- 3- yl) benzenesulfonamide

Compound 8c

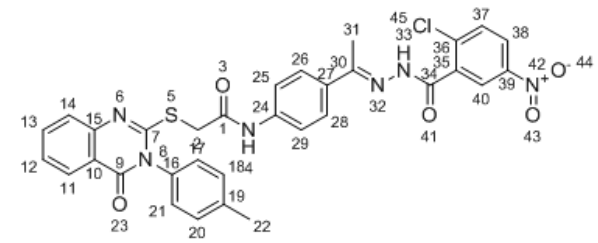
Teng U *et al.*, reported a series of quinazoline derivatives bearing acrylamide fragments were prepared using the skeleton-deconstruction strategy as potent PI3Kd inhibitors, Phosphoinositide-3-kinases (PI3Ks) are a family of lipid Kinases which can be divided into three main classes. Among four types of PI3Ks, PI3Kd is expressed dominantly in hematopoietic cells and plays a vital role in B-cell malignancies *via* PI3K/Akt signaling pathway. There area number of PI3K inhibitors have been approved by FDA for the treatment of B-cell malignancies. Among the synthesized compound 15c found to be a prominent candidate, Compound 15c exhibited excellent enzyme activity against PI3Kδ (IC_{50} = 27.5 nM) compared with BEZ235 as well as the significant anti-proliferation activities [36].



N-(2-methyl-5-((6-(quinolin-3-yl)quinazolin-4-yl)amino)phenyl)acrylamide

Compound 15c

El-Adl K *et al.*, reported and synthesized new quinazolin-4(3H)-ones derivatives, nineteen new quinazoline-4(3H)-one derivative were designed and synthesized. Preliminary cytotoxicity studies of the synthesized compounds were evaluated against three human cancer cell lines (HepG-2, MCF-7 and HCT-116) using MTT assay method. Doxorubicin and sorafenib were used as positive controls, Vascular endothelial growth factor (VEGF) is a potent angiogenic factor and was first described as an essential growth factor for vascular endothelial cells. VEGF is up-regulated in many tumors; overexpression of VEGF have been noticed in several types of cancer including colorectal cancer, breast cancer and hepatocellular carcinoma.13 Accordingly, inhibition of this signaling pathway should block angiogenesis and subsequent tumor growth; Compound 16f, containing a 2-chloro-5-nitrophenyl group, has emerged as the most active member. It was approximately 4.39-, 5.73- and 1.96-fold more active than doxorubicin and 3.88-, 5.59- and 1.84-fold more active than sorafenib against HepG2, HCT-116 and MCF-7cells, respectively.

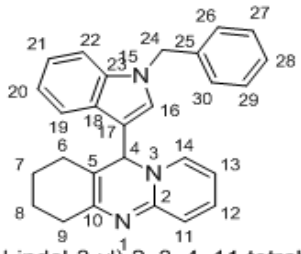


N-(4-(1-(2-(2-Chloro-5-nitrobenzoyl)hydrazono)ethyl)phenyl)-2-((4-oxo-3-(4-methylphenyl)-3,4-dihydroquinazolin-2-yl)thio)acetamide

Compound 16f

Bathula R *et al.*, reported and synthesized Substituted-1H-Pyrido[2,1-b] Quinazolines along with Molecular docking as an EGFR kinase (PDB code: 1M17) inhibitors, epidermal growth factor receptor (EGFR) is a member of a family of four closely related receptors: EGFR (or erbB1), HER2/neu (erbB2), HER3 (erbB3) and HER4 (erbB4). The EGFR mediates the actions of multiple ligands, including epidermal growth factor, transforming growth factor-α, amphiregulin and heparin-binding EGF, and may also be constitutively activated by mutation. Blocking EGFR may keep cancer cells from growing. Some epidermal growth factor receptor tyrosine kinase inhibitors are used to treat cancer. Also called EGFR inhibitor, EGFR tyrosine kinase inhibitor, and epidermal growth factor receptor inhibitor.

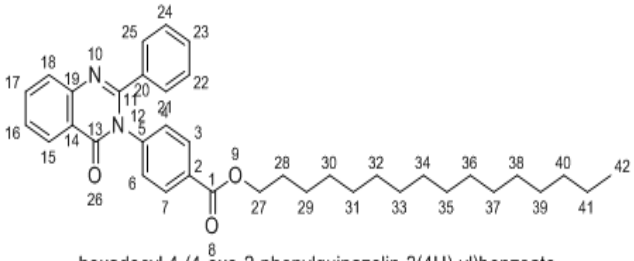
Among the compounds, (4i) showed most potent cytotoxicity against A549 and NCI-H460 lung cancer cell lines with IC_{50} values 4.57±0.25 and 5.53±0.49 μM, respectively. Moreover, compound 4i was found to be most potent considerable cell growth inhibition with GI_{50} values of 2.70±0.18 and 3.24±0.40 μM against A549 and NCI-H460 cell lines



11-(1-benzyl-1H-indol-3-yl)-2, 3, 4, 11-tetrahydro-1Hpyrido [2, 1-b] quinazoline

Compound 4i

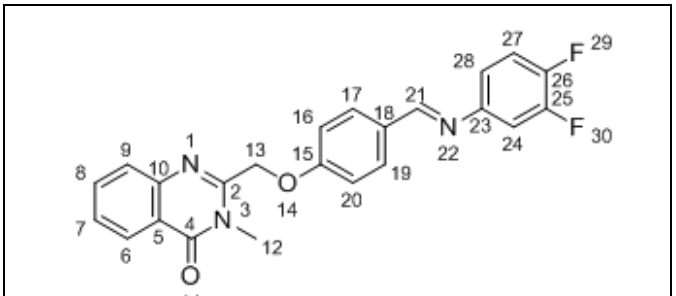
Noser AA *et al.,* reported and synthesized Some new New Quinazolinones as Anticancer Agents *via* Potential AKT Inhibition. The AKT pathway is one of human cancer's most often deregulated signals. AKT is also overexpressed inhuman cancers such as glioma, lung, breast, ovarian, gastric, and pancreas. Among the synthesized compounds, Compound 4 had more significant inhibitory effects on Caco-2, HepG2, and MCF-7 cancer cells with with IC_{50} values of 23.31 ± 0.09, 53.29 ± 0.25, and 72.22 ± 0.14μM, respectively



hexadecyl 4-(4-oxo-2-phenylquinazolin-3(4H)-yl)benzoate

Compound 4

Le Y *et al.,* reported and synthesized a series of novel 3-methyl-quinazolinone derivatives as EGFR inhibitors, Epidermal growth factor receptor (EGFR) tyrosine kinase (TK) plays an indispensable role in cancer cell proliferation, survival, adhesion, migration and differentiation. Overexpression and mutation of EGFR have been associated with a variety of cancers. Among the synthesized compounds, compound 5k displayed 10nM IC_{50} value against EGFRwt-TK activity. Apoptosis analysis in A549 cell line suggested that 5kdelayed cell cycle progression by arresting cells in the G2/M phase of the cell cycle, retarding cell growth.



(E)-2-((4-(((3,4-difluorophenyl)imino)methyl)phenoxy)-methyl)-3-methylquinazolin-4(3H)-one

Compound 5k

CONCLUSION: By looking at the innovative Quinazoline derivatives, it is evident that the heterocycle has a wide range of potential as a neoplastic agent. Quinazoline, with its effective activity and ability to interact with other heterocycles, may readily be utilized to make a variety of neoplastic derivatives. Quinazoline derivatives have also been shown to be effective anti-cancer medicines, as have hybrid derivatives of the heterocycle. Their ability to impact a variety of cell lines indicates that they might be effective and flexible anti-cancer treatments. It takes a lot less effort to create a scaffold that meets all of the criteria for a perfect anti-cancer drug.

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CONFLICTS OF INTEREST: We declare that we have no conflict of interest.

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