

REVIEW OF QUINAZOLINONE SCAFFOLD AS ANTICANCER AGENTS

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ABSTRACT

Although many types of chemotherapeutic agents are currently used to treat human cancers, either in combination or alone, they have limited effectiveness, the response rates remain largely unimproved in clinical trials. Quinazolinone a class of epidermal growth factor receptor (EGFR) inhibitors which plays a vital role in cell growth regulation and considered one of the most intensely studied targets of tyrosine kinases inhibitors. Despite, chemistry of quinazolinone being as an established area, day by day newer, more complex derivatives of quinazolinone compounds are still being discovered. Moreover, an assortment of literature, quinazolinone exhibits a strong lactam-lactim tautomeric interaction and furthermore, when the methyl group is

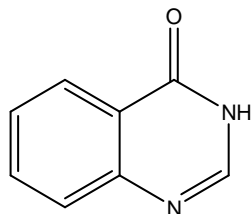
present in the position-2, the tautomeric effect is increased, including structure activity relationship studies of quinazolinone ring system states that the position -2,6 and 8, of the ring system, these positions are very much important for structure activity studies and also suggested that the inclusion of different heterocyclic moieties at position -3 of the quinazolinone ring system could be increased chemotherapeutic activity. Pharmacologically quinazolinone are the most important class of heterocyclic compounds among the quinazolinone nucleus. The stability of nucleus has inspired medicinal chemists to introduce many bioactive moieties to synthesize new potential therapeutic agents. This review was based on the quinazolinone and, its derivatives exhibiting various types of cancer activities with different substituent.

KEYWORDS: quinazolinone, EGFR, antitumor, cytotoxic activity, anti proliferative activity.

INTRODUCTION

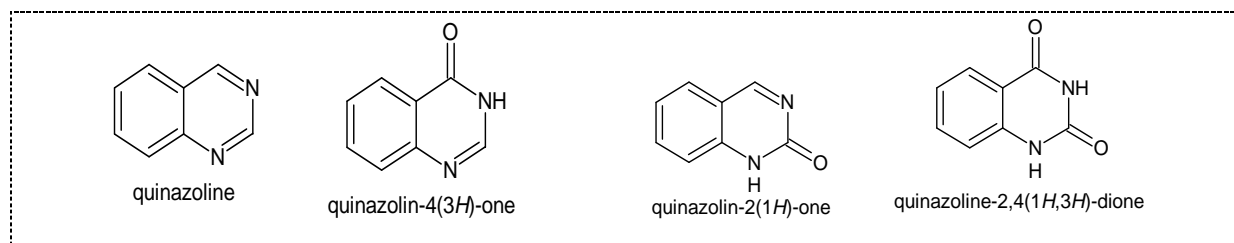
Cancer is one of the leading causes of death worldwide, still and the pursuit of novel clinically useful anti cancer agents is therefore, one of the top priorities for medicinal chemists^[1]. Despite major advances in management of chemotherapeutic agent and cancer biology, cancer still poses a serious threat to human health globally^[2]. Moreover, the great similarity between tumor and normal cells, diversity of tumor types are the main hurdles(risk) preventing the development of an ultimate anticancer therapy^[3]. Thus, persistent commitment to the arduous task of discovering, designing new anticancer agents remain critically essential. The epidermal growth factor receptor(EGFR) plays vital role in cell growth regulation and one of the most important consideration studied targets of tyrosine kinases (TK) inhibitors^[4]. Several TKs play a vital roles in cell proliferation,differentiation,metastasis and survival, unregulated activation through mechanisms such as point mutations could lead to large percentage of clinical cancers^[5]. EGFR is over expressed in numerous tumors, including brain, lung, bladder, ovarian, colon, breast, head, and prostate tumors^[6]. Moreover ,assortment of literature the quinazolinone based molecules were found to inhibit the epidermal growth factor receptor(EGFR)and tyrosine kinases^[7]. Quinazoline is one of the most widespread scaffolds among natural and synthetic bioactive compounds, although the first natural quinazoline –based alkaloid, peganine, was discovered in 1888, the literature about quinazoline chemistry effectively began only in 1940s^[8] quinazoline scaffolds resembles both the purine nucleus and pteridine one. As a consequence, some compounds able to inhibit the purinic^[9] or the folic acid^[10-13] metabolic pathway have been discovered. The discovery of quinazoline compound a change in number of structural modifications which enhanced their biological activities such as anticonvulsant, antibacterial, antitubercular, antihistaminic, analgesic, anti inflammatory activity which have arracted the medicinal chemists. The drug discovery which plays an important role in development of new, safer anticancer agents with broad spectrum of cytotoxicity to tumor cells. Therefore, new therapeutic target molecules have been reported that the antitumor efficacy of chemotherapeutic agents correlated with their growth inhibiting, differentiation inducing or apoptosis inducing abilities^[14].

QUINAZOLINONE



Common name: Quinazolinone and quinazolindione^[15, 16].

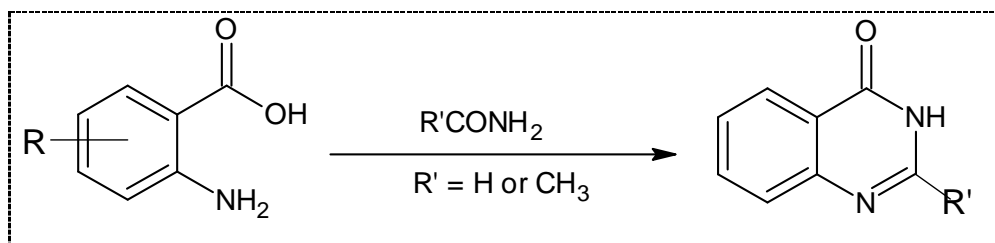
Chemical name: Quinazolin-4(3H)-one (chen,etal.,2006), 4(3H)-Quinazolinone,3,4-Dihydroquinazolin-4 one, (3H)-Quinazolone, 4-oxo-3,4 dihydroquinazoline, 4-Oxoquinazoline, 4-quinazolinol, .4-Quinazolinone chemical with two conjoined aromatic rings incorporating two nitrogen atoms and one of the carbon oxidised with keto oxygen. Quinazolinone is a heterocyclic compound. There are two structural isomers – 2-Quinazolinone and 4-Quinazolinone with the 4-isomer being the more common.

SYNTHESIS^[16,60]

The first reported synthesis of a quinazolinone occurred in 1869, which was prepared from anthranillic acid and cyanide in ethanol, creating 2-ethoxy-4(3H)-quinazolinone. Most of the methods used for the synthesis of 4-(3H)-quinazolinone make use of anthranillic acid or one of their functional derivatives as the preparatory materials. Quinazolin-4-one is synthesized when the keto group is introduced in the pyrimidine ring of quinazoline. The most common method for the synthetic of 4(3H) quinazolinone is by the condensation of anthranillic acid with amides or primary amines.

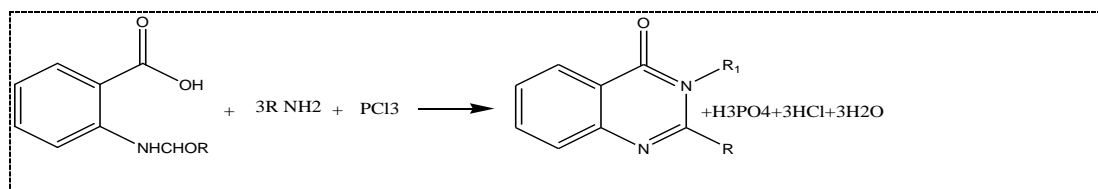
Niementowski synthesis

3 or 4-substituted anthranilic acid when reacted with formamide at 125-130°C gave 3,4-dihydro-4-oxoquinazoline.



Grimmel Guinther & Morgan's synthesis

The o-amino benzoic acid, when heated with an amine together with phosphorus trichloride in toluene for two hours gave 2,3-disubstituted 3,4-dihydro-4-oxoquinazolines.



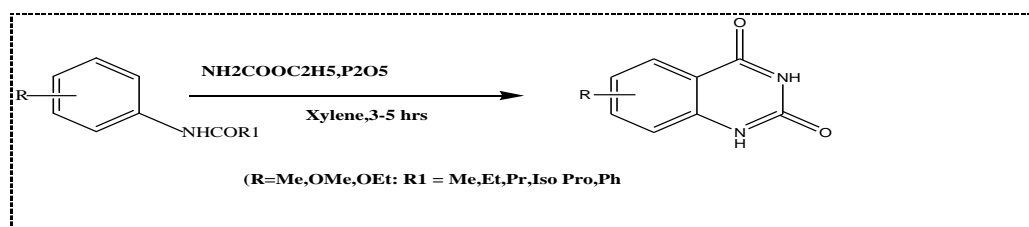
From Benoxazin-4(3H)-one

3,1,4-Benoxazones react with amines to give 3,4-dihydro-4-oxoquinazolines. Primary aliphatic amines and anilines react with 2-methyl-5-nitro-4-oxoquinazolines.



Sen. and Ray's Synthesis

Boiling a solution of normal or isobutyranilides with urethane and phosphorus pentoxide in xylene gave 2-isopropyl-3,4-dioxoquinazolines



EGFR BIOLOGY

Epidermal growth factor receptor (EGFR) is a cellular transmembrane glycoprotein which comprises one from four members of the erbB family of tyrosine kinases receptors. EGFR plays a very powerful role in commencing the signals which gives direction towards the

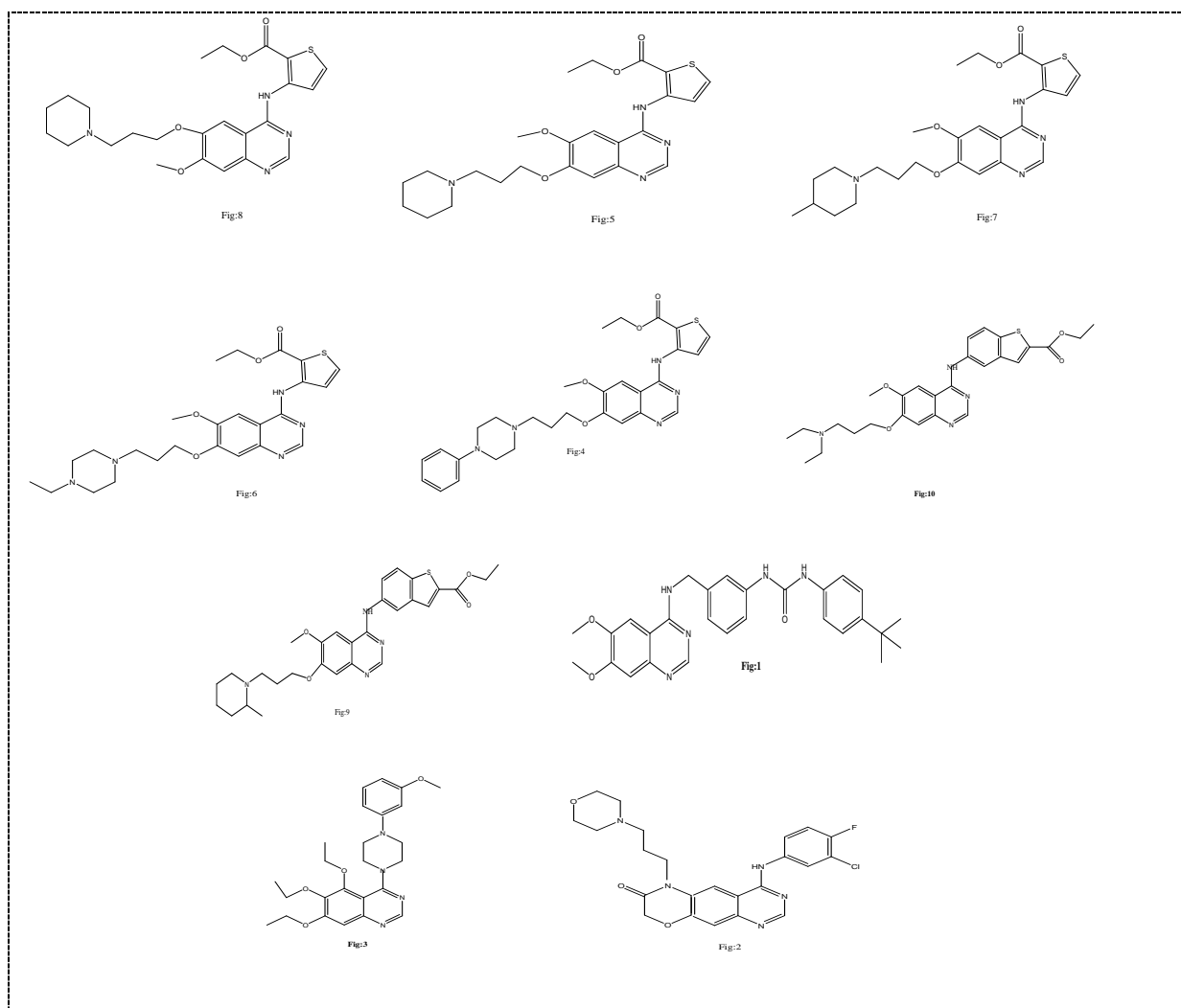
behavior of epithelial cells, tumors of epithelial cell origin. EGFR shows similar structure, functions of four transmembrane growth factor receptor proteins. EGFR also known as HER-1 or c-erbB. It's consisting of extracellular receptor domain, a Trans membrane region, intracellular domain with tyrosine kinases function. Remaining members of this groups like HER2(c-erbB-2), HER-3(c-erbB-3), HER-4(c-erbB-4)^[17]. Epidermal growth factor receptor present in ranges from 40,000 to 1, 00,000 receptors per normal cell^[18]. EGFR is expressed in number of solid tumors, including breast cancer, renal cancer, ovarian cancer, on small cell lung cancer (NSCLC), colon cancer, Head and neck cancer^[19]. Ligands are bind to EGFR in close TGF- α (transforming growth factor -alpha), epidermal growth factor(EGF), betaceluin, Amphiregulin and Heparin binding EGF. Whrever cognate Ligands binds with EGFR leads to autophosphorylation of tyrosine kinases receptor subsequently activation of signal transduction pathways which plays a important role in regulating cellular proliferation, differentiation, survival^[20]. There are two pharmacological avenues for, to inhibit the EGFR which is mainly first monoclonal antibodies, small molecule inhibitors. Monoclonal anti bodies play a vital role in blocking Ligands binding to the extracellular domain, whereas small molecule inhibitors exhibit their effects at intracellular portion of the receptor to prevent tyrosine kinases phosphorylation, lastly activation of signal transduction pathways. EGFR inhibitors having ability to show their anti cancer activity^[21].

QUINAZOLINE DERIVATIVES AS ANTICANCER AGENTS

PROTEIN KINASE INHIBITORS

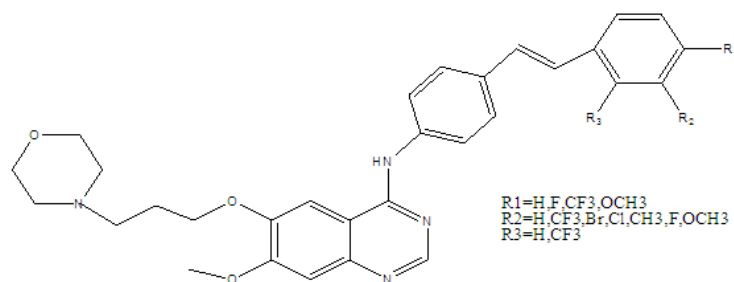
Protein kinases constitute the most important human enzyme class which controls the sequence of cell cycle progression, cell division, cell proliferation. The protein kinases, when expressed in mutated, unregulated forms or when produced in abnormally high levels, are capable of transforming normal cells into cancer cells, thus plays important roles in tumorigenesis. PKs also support the angiogenesis process, that is required for tumor growth, metastasis and control cell division. In tumor cells, therefore, the development of non-toxic, selective protein kinases inhibitors which is considered as promising target or cancer treatment. The most important protein kinases involved in a cancer state, over expressed in neoplastic cells, commonly targeted include several kinases such as receptor tyrosine kinases, including EGFRs, insulin-like GFRs, platelet-derived GFRs, fibroblast GFRs, vascular enthelial GFRs and others like serine/threonine kinases, including GC, CAMK, CK1, CMGC, STE and TKL kinases. Extracellular signal- regulated kinases (ERK 1 and 2) are related

protein serine /threonine kinases that participate in the Ras-Raf-MEK-ERK signal transduction cascade and histidine kinases^[22-27].



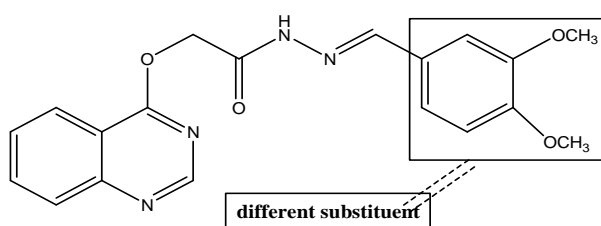
EGFR INHIBITORS

New classes of epidermal growth factor receptor (EGFR) inhibitors, novel 4-stilbenylamino quinazoline derivatives were synthesized through a dimorthrearrangement reaction by Liuchang Wang, Pengna Li *et al.*,^[28]. The newly synthesized compounds characterized by IR, ¹H-NMR, ¹³C-NMR and HRMS, compounds were evaluated for anti tumor activity in vitro against eight human tumor cells lines with an MTS assay, most synthesized compounds exhibited more potent activity ($IC_{50}=2.0\mu\text{m}$) than gefitinib ($IC_{50}\geq 10.0\mu\text{M}$) against A431, A549, BGC-823 cell lines. Docking methodology of compound 6c and 6i binding into the ATP site of EGFR was carried out. The results showed that fluorine and trifluoromethyl played an important role in efficient cell activity.



VEGFR INHIBITORS

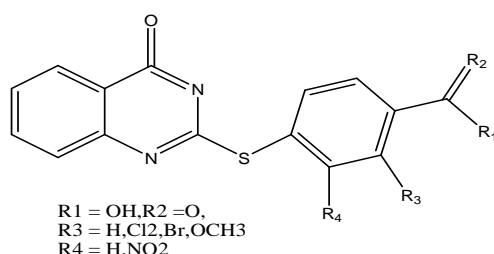
A series of novel quinazoline derivatives have been designed, synthesized by Liang Lu, a.hai-liang zhu, a Dong-dong li et al,^[29]. And their inhibitory activities were also tested against carcinoma human alveolar basal epithelial cell (A549), Breast cancer (MCF-7) and cervical cancer cell (Hela). the compound containing methoxy group showed the most potent inhibitory activity (IC₅₀=0.22μg/ml for HeLa, IC₅₀=0.15μg/ml for A549, IC₅₀=0.24μg/ml for MCF-7) which was compared with the positive control tivozanib. Docking simulation were performed to position compound methoxy group bearing molecule in the vascular endothelial growth factor receptor (VEGFR) active site to determine the probable binding model. Moreover methoxy group bearing compound with potent inhibitory activity in tumor growth inhibition as a potential anti cancer agent and also, that electron donating group substituent improved the VEGFR2 inhibitory Activity compared to electron withdrawing group substituent.



TYROSINE KINASE INHIBITORS

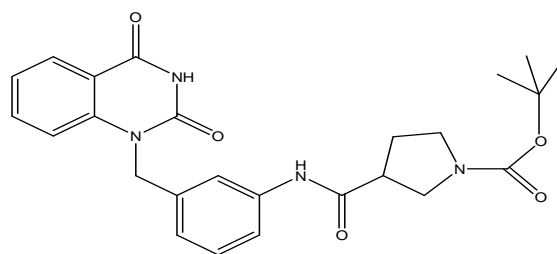
A series of benzoic acid substituted quinazolinone were synthesized from refluxing CS₂ and 2 amino benzoic acid in acetic acid by Maruthamuthu, Alex, Bharathi Dileepan, Shameela Rajan, and Christina Ruby Stella^[30]. All the synthesized compounds were tested their anticancer activity against breast cancer cell line (MCF-7) using MTT assay. Most of the compounds exhibited moderate to good anti-breast cancer activity. Cytotoxicity was checked at 24 hrs and 48hrs duration, it was found that the activity of compounds were increased after

48hrs as compared to 24 hrs. among the tested compounds Br, NO₂ Group containing compounds showed potent activity and percentage growth inhibition was 45.568, 42.236 at 100 μ M/ml and also showed IC₅₀=50 μ M/ml and 32.466 μ M/ml. all the synthesized Compounds were characterized by IR, ¹H NMR, ¹³CNMR. docking studies of synthesized compounds was done with the help of iGEMDOCKv2.1 software using GRIP batch docking method, to study their observed activity. Docking studies were carried out by taking tyrosine kinases domain as a target for anticancer activity.



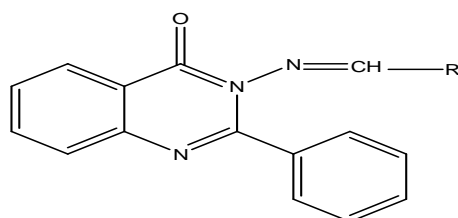
POLY (ADP-RIBOSE) POLYMERASE-1 (PARP-1) INHIBITORS

Quinazoline derivatives as poly (ADP- ribose) polymerase-1 (PARP-1) inhibitors which play an important role in the DNA repair process, therefore it is considered as promising anti cancer drug target. A Series of quinazoline 2,4(1H,3H)-dione derivatives, by .H.Ya building o et al^[31]. Via employing a range of amino acid building blocks as key pharmacophoric groups, evaluating their PARP inhibition activity and binding features at the PARP active site. Several compounds in this series exhibited promising PARP-1 inhibitor activity with IC₅₀ values at nano molar range. The SAR studies states that compounds having β -proline, piperidine-4-carboxylic acid groups were good PARP-1 inhibitors. Compound having an (S-N-Boc-pyrrolidin-3-yl) substituent exhibited maximum activity as a PARP-1 inhibitor, moreover, it was selected for further evaluation for PARP-2 inhibitory activities and growth inhibition, temozolomide(TMZ) potentiation effects in cancer cells. Also the results were very satisfactory, in both enzymatic, cellular levels, compound showed high inhibitory activity.

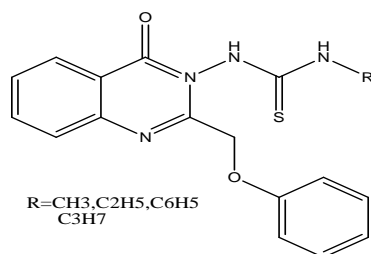


a poly (ADP-ribose) polymerase 1 (PARP-1) inhibitor

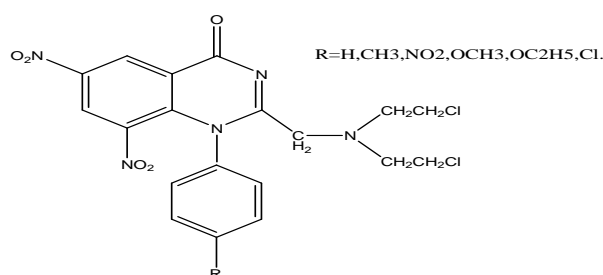
Based on molecular docking studies, a novel quinazolinone derivatives of eight molecules were synthesized and screened, anti oxidant activities, anticancer activity, toxicity study by Benu kumara, suvarna G Kini, Muhammad mubeen^[32]. The newly synthesized compounds have been characterized by spectral analysis. The evaluation of anti oxidant activity done by DPPH method and anti cancer activity done by MTT assay method. All these compounds were tested or their anti cancer activity using MCF-7,HCT-116 cell lines indicating that substitution of lipophilic group in position 3 showed good dock score and anti cancer activity. These results revealed that these compounds can be evaluated further (EGFR-TK) Epidermal growth factor receptor tyrosine kinases inhibitory activity.



The present work involves, synthesis of the target quinazolinone-4(3H)-one derivative of twenty two compounds, were tested for cytotoxic activity against human mammary carcinoma cell line (MCF7) using doxorubicin as a standard drug by Safinaz E. Abbas, Nagwa M. Abdel Gawad, Hanan H. Georgey, Jalal H. Abdullah^[33]. The newly synthesized sixteen derivatives are active as anti tumor, furthermore, the replacement of the 3-amino group by thio urea moiety enhance in the activity, also cyto toxic activity indicated that, the phenyl thio urea showed increased activity than ethyl one. Moreover, the incorporation of the benzylidene moiety at position 3 of quinazolinone compounds showed with varied anti tumor activity.

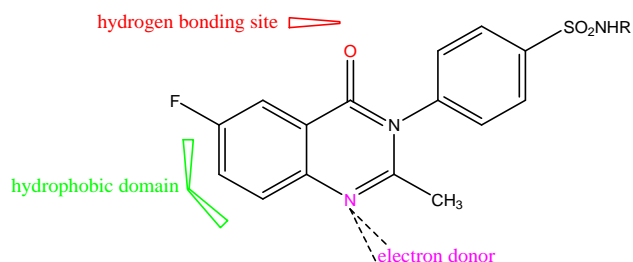


Synthesis of six 2-((Bis-(2-chloroethyl) amino) methyl)-6,8-dinitro-1-(4-substituted ethyl)1H-quinazolin-4-one derivatives by Yuvaraj Govindaraj et al^[34]. The newly synthesized compounds were screened for their anti-cancerous activity by short term in vitro anti tumor and in-vivo anti cancer activity via body weight analysis, mean survival time and percentage increase in life span at a dose of 100mg/kg body weight in Swiss albino mice inoculated with Daltons Lymphoma Ascites cells (DLA) (1×10^6). The newly synthesized compounds contain nitro group at position 6 and 8 of quinazolinone moiety, a phenyl group at position 1 and also the compounds were incorporated with nitrogen mustard moiety. Furthermore, 1,6,8 trisubstituted quinazolinone with a nitrogen mustard moiety connected through a methylene group at position 2 are effective in mice bearing DLA cells. So that the quinazolinone-2-methyl nitrogen mustard with either a nitro or chloro group at Para phenyl position is a most potent anticancer compound, which can be further developed.



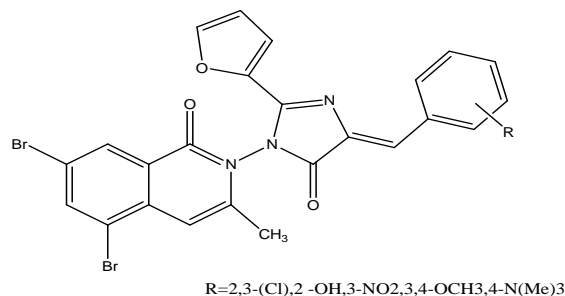
The present research was synthesized several novel fluorinated quinazoline-sulphonamide derivatives were evaluated invitro cytotoxic activity by Mohamed syed F et al^[35]. The newly synthesized eight compounds of anti cancer activities were determined through (3(4,5 dimethyl -2-thiazoly)-2,5 diphenyltetrazolium bromide) by MTT assay using three cell line. Among eight compounds one exhibited significant anticancer activity with low toxicity when compared with reference drug methotrexate, remaining showed moderate activity. Moreover the newly synthesized compounds having IC₅₀ value ranges from 2.51 μ m, 2.89-46.34 μ m

whereas reference drug IC₅₀ value is 2.4µm on the three cell lines and also the synthesized compounds had lower toxicity on the three cell lines than methotrexate. In addition increasing the lipophilicity of these compounds using lipophilic substituent increases the anticancer activity of the resulting compounds.

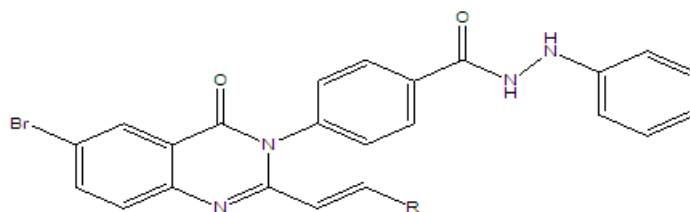


R = Hydrogen, pyridin-2-yl, 3,4-dimethylisoxazol-5-yl, thiazol-2-yl, 5-methylisoxazol-3-yl, 4,6-dimethylpyrimidin-2-yl, 4-methylpyrimidin-2-yl, diaminomethylene.

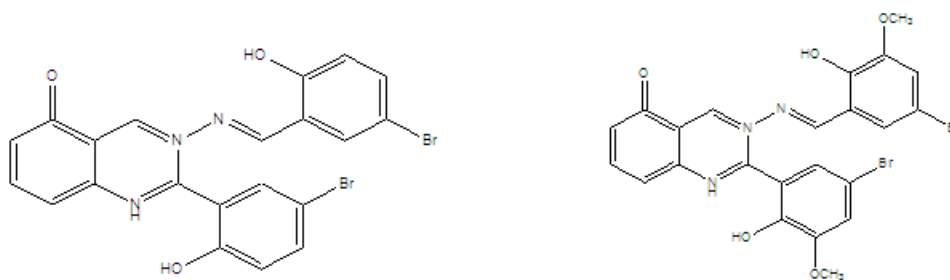
A series of novel imidazolone fused quinazolinone derivatives were synthesized by Deepak Kumar, G.kumar, Asif Husain, J. Monga^[36]. All the newly synthesized compounds were evaluated in vitro cytotoxic activity against cervical cancer (HeLa), breast cancer (MCF-7), Leukemia cells (HL-60), Hepato cellular carcinoma (HepG2) cell lines, compounds were characterized by IR, NMR, Mass spectra and elemental analysis. In synthesized compounds containing methoxy group at Para position in phenyl ring of imidazolone displayed three fold potent activity against breast cancer, two fold against liver cancer more than the standard drug cisplatin, whereas cervical cancer, blood cancer equivalent activity to that of standard drug. SAR states that the compounds of electron donating group enhances the activity while, electron withdrawing group decreases the activity.



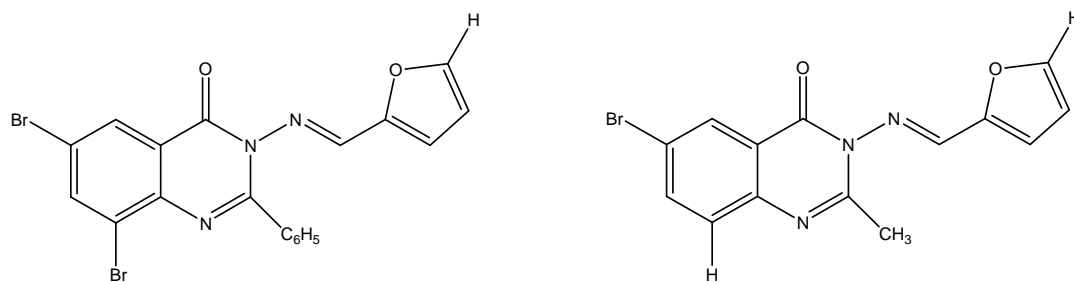
The anticancer potency of new 2-substituted-4-(3H)-Quinazolinone by Murugan V, et al^[37]. The synthesized compounds were screened, both in-vivo and in-vitro anti tumor activity. The invitro evaluation was performed on DLA cells by trypan blue dye exclusion test, in addition, in –vivo anti tumor evaluation was carried out on DLA cells in mice at a dose of 50 and 100mg/kg p.



The newly synthesized quinazoline Schiff bases were screened anticancer activity against MCF-7 human breast cancer cell line by Fadhil lafta faraj et al^[37]. These compounds shown anticancer potential against MCF-7 cells and also possess the capacity of inducing intrinsic and extrinsic apoptosis pathway, which was regulated by caspase enzymes. Mitochondrial active role in the cell death was confirmed by reducing MMP, cytochrome c, ROS elevation. The newly synthesized compounds exhibited promising anticancer activity.

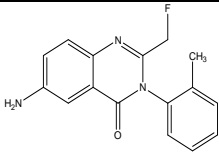
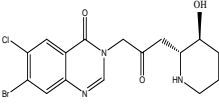
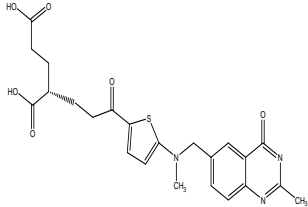
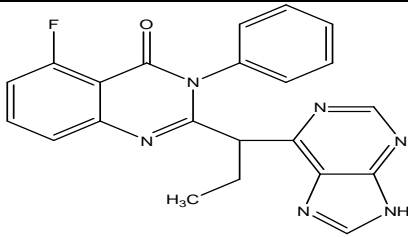
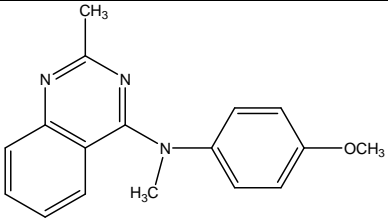
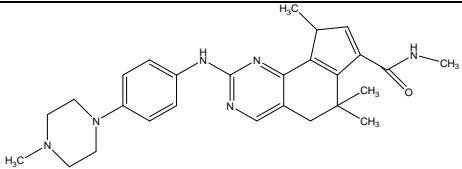
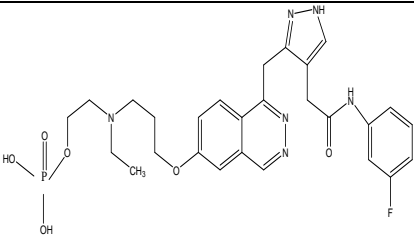


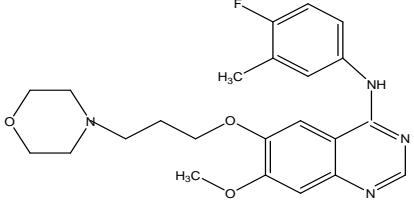
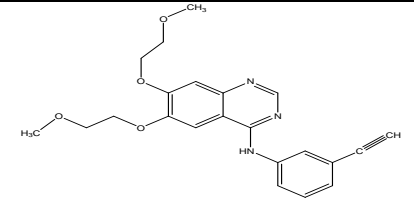
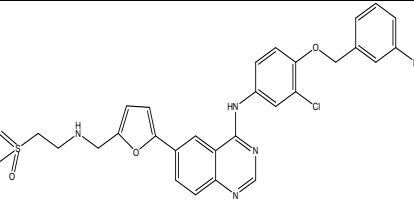
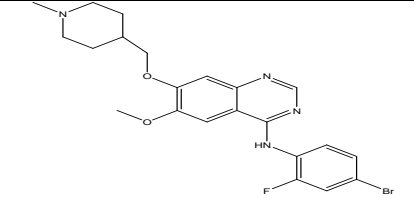
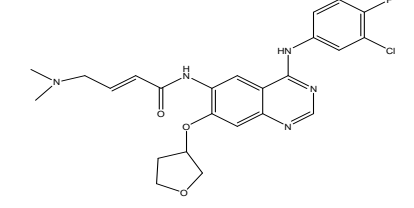
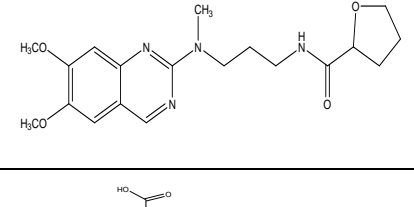
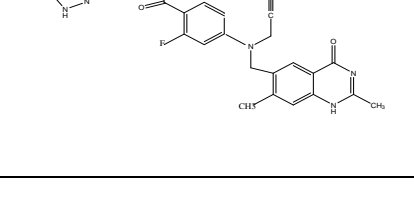
Synthesis of series of novel substituted-3-((1E)-(Substituted-2-furyl)-methylene)-amino) quinazoline-4(3H)-one by Raghavendra et al^[42]. The newly synthesized compounds were screened and tested anticancer activities. Among the synthesized compounds 5a & 6a exhibited potent anticancer agents.

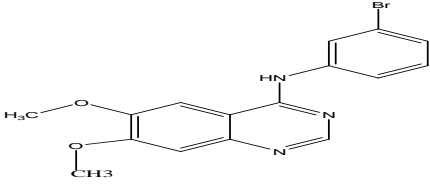
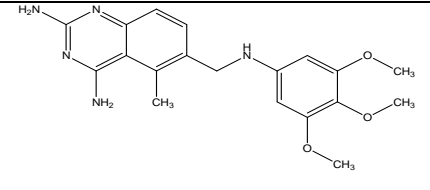


Some of marketed and clinically active quinazoline containing drugs

S.No	Quinazoline derivatives	Chemical structure	Medicinal use	Trade name & marketed.
1	Ispinesib ^[39,40]		To treat solid tumor. (KSP inhibitors)	Ispinesib mesylate (SB 715992; CK 0238273).
2	Dacomitinib ^[41]		Anti cancer (irreversible inhibitors of HER family of kinases)	PF-00299804. Pfizer XTANDI
3.	Varlitinib ^[43]		Anti cancer drug. (TKs inhibitor like EGFR, ErbB-2, ErbB-4)	Array 543, ASLAN & Array bio pharma.
4	Cediranib ^[44]		Heamatological cancer, liver metastases. (VEGFR2TKs inhibitors).	Recentin. Astrazeneca
5	Nolatrexed ^[45]		To treat solid tumor, (thymidylate synthase inhibitor)	US9174982

6	Afloqualone ^[46,47]		Anti cancer agents	Arofuto
7	Halofuginone ^[48]		Anti tumor	Halocur
8	Ralititrexed ^[49,50]		To treat colorectal cancer. (thymidylate synthase inhibitor)	Tomudex Astrazeneca.
9	GS1101 ^[50,51] (CAL01)		To treat haematological cancer	GS 110 . Gilead sciences(Calisto g a).
10	Verubulin ^[52]		Anti cancer (acts as a cytotoxin, a vascular disrupting agent).	AZIXA(MPC 6827:MX 128495) Myrexix (Myriad pharmaceuticals).
11	Miliciclib ^[53,54]		Anti cancer. (TKAs oral inhibitors).	PHA- 848125. Nerviano medical sciences.
12	Barasertib ^[55]		Acute myeloid leukemia (An aurora kinase inhibitors)	AZD 1152. Astrazeneca

13	Gefitinib ^[56]		To treat, metastatic non small- cell lung cancer(NSCLC). (EGFR inhibitors).	Iressa, AstraZeneca
14	Erlotinib ^[57]		To treat metastatic pancreatic cancer (EGFR TKs inhibitor)	Tarceva
15	Lapatinib ^[58]		To treat breast cancer. (EGFR-2,HER2/neu, EGFR pathway inhibitors)	Lapatinib (Tykreb®)
16	Vandetanib ^[59]		To treat metastatic medullary thyroid cancer.(VEGFR Antagonist & EGFR,)(TKs inhibitor)	Zactima, & (ZD6474) Caprelsa®)
17	Afatinib ^[58,59]		To treat ,metastatic non small -cell lung cancer(NSCLC). Irreversibly inhibits the TKs activity of all ErbB Families.)	Gilotrif
18	Alfuzocin ^[61]		Anti cancer (To treat BPH).	UroXatral, Urion, Xatral, Alfetim.
19	ZD 9331 ^[62]		To treat for solid tumor, colorectal cancer (a non polyglutamatabeathy midylate synthase inhibitor)	BGC 9331 AstraZeneca

20	EBE -A22 ^[63]		Antineoplastic agent & intercalating agent.(used in the study of DNA).	PD 153035
21	Trimetrexate ^[64]		To treat for leiomyosarcoma (Dihydrofolate reductase enzyme inhibitors)	Analog of methotrexate.

CONCLUSION

These reviews give, information about the research and development of derivatives of quinazoline molecule, and also conclude that the quinazoline & quinazoline-4(3H)-one derivative exhibited anticancer activities, which is a versatile nucleus in the field of medicinal chemistry and possess a variety of medicinal properties. Hence this unique moiety will be serving as future therapeutic lead molecule of developing anticancer agents. Moreover, this review has revealed necessary, important details of quinazoline-4-one analogues, potent compounds, method or technique involved in evaluation process for anti cancer activity. quinazoline derivatives which plays a vital in inhibitors of Protein kinases, the most important protein kinases involved in a cancer state, over expressed in neoplastic cells, commonly targeted include several kinases such as receptor tyrosine kinases, including EGFRs, insulin-like GFRs, platelet-derived GFRs, fibroblast GFRs, vascular endothelial GFRs and others like serine/threonine kinases, including GC, CAMK, CK1, CMGC, STE and TKL kinase. The biological profiles of currently presenting new generation of quinazoline & quinazoline 4 ones studies which will represent much valuable, scientific knowledge of information for future development of more potential therapeutic anticancer agents.

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