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QUINAZOLINE DERIVATIVES AS ANTI CANCER AGENT-A REVIEW

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ABSTRACT

Cancerous growth is one of the major causes of worldwide human mortality. An outsized variety of antineoplastic medication are existed within the market and most of the compounds are below clinical trials. Different studies discovered that these antineoplastic medication have shown the various kinds of effects, thus researchers round the world are engaged within the coming up with of additional economical and novel antineoplastic medication. In gift years, Quinazoline and its derivatives are thought-about as a completely unique category of growth chemotherapeutical agents that shows of activity against totally different tumours. Quinazoline are a large class of active chemical compounds exhibiting a broad spectrum of biological activities in animals as well as in humans and it is one in all the foremost fascinating novel bioactive compounds amongst all the heterocyclic compounds. Various of research and review papers have shown the development of Novel Quinazoline derivatives for cancer therapy. This review was focussed on the Quinazoline derivatives with antineoplastic activity.

KEYWORDS

Quinazolinone and Anti-cancer.

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INTRODUCTON

Cancer is one in all the leading causes of death worldwide, still thus the pursuit of novel clinically helpful opposed cancer agents is therefore, one in all the highest priorities for medicative chemists[1]. Among that Quinazoline derivatives, that belong to the N-containing heterocyclic compounds, have caused universal considerations to their wide and distinct biopharmaceutical activities with the formula C8H6N2. It's aromatic heterocycle with a cyclic structure consisting of 2 amalgamate 6-membered aromatic rings, a benzol and a

pyrimidine ring. The quinazoline derivatives possessing a large spectrum of biological properties like anti-oxidant[2], anti-inflammatory[3], anticonvulsant[4], anti-HIV[5] antihypertensive[6], anticancerous[7] activities, that have attracted the medicative chemists. This review discusses a quinazolinone derivatives with anti-tumour activity activities.

AAF. Wasfy, *et al*[8] synthesized a Quinazoline and their fused-ring systems had shown the potential biological activity. In the recent study a replacement quinazoline derivatives were synthesized. The fresh synthesized compounds were characterised by IR, nuclear magnetic resonance analyses. All fresh synthesized compounds were screened malignant neoplasm studies. The results unconcealed that a number of the synthesized compounds have a major biological activity as malignant neoplasm agents.

Hatem A. Abuelizz, *et al*[9] synthesized new series of quinazoline derivatives (3–26) and characterised via chemistry and spectral suggests that Treatment of 2-amino-5-methylbenzoic acid with chemical group, chemical irritant resulted within the new 2-thioxoquinazolin-4-one (3). Alkylation and hydrazinolysis of the inherent thioxo cluster in (1-3) afforded the corresponding thio ethers (4–23) and reducer derivatives (24 and 25), then 24 was more remodelled into tricycle antidepressant by-product, 26 via cyclocondensation reaction. Compounds one and a couple of that were accidently synthesized, were found to exhibit antitumor activity. The toxicity of all compounds was evaluated in vitro against the HeLa and MDA-MB231 neoplastic cell lines, as well as one and a couple of for comparison, with MTT assay. The treatment of the cells was performed with the synthesized compounds and gefitinib at 0, 1, 5, 10, 25, and and 50μM and incubated for 24 h in 50% DMSO. The IC50 values of the target compounds were reported in μM gefitinib as a standard. Our results indicated that everyone compounds exhibited vital in vitro toxicity against each cell lines. Whereas compounds 1–3 showed sensible activity, compounds 21–23 were found to be strenuous than gefitinib. Thus, compounds 21–23 could also be potential antitumor agents, with IC50 values starting from 1.85 to 2.81μM in reference to gefitinib (IC_{50} = 4.3 and 28.3 against μM HeLa and MDA-MB231 cells, respectively.

Mostafa M. Ghorab, *et al*[10] synthesized a structural options of quinazoline and sulfonamides, novel hybrid compounds 2–21 were synthesized employing a straight forward and convenient technique. Analysis of those compounds against totally different cell lines known compounds 7 and 17 as most active antitumour agents as they showed effectiveness on the four tested cell lines. The antitumour screening results of the tested compounds provides associate in nursing encouraging framework that might cause the event of potent new antitumour agents.

Pallavi K J, *et al*[11] synthesized the 2, 3, 7-trisubstituted quinazoline derivatives (Compound HP1, HP2, HP3 and HP4) in 2 completely different concentrations were evaluated for antineoplastic activity against bacteriologist pathology cancer (EAC) and Dalton's malignant neoplastic disease pathology (DLA) bearing Swiss unusual person mice. Then the *in vivo* antineoplastic efficiency of quinazoline bases was measured in EAC model by assessing the rise in mean survival time of the treated drug over untreated management mice and treated normal (Gefitinib) mice. Their toxicity was assessed in vivo in traditional, normal and EAC bearing mice by measure the drug-induced changes in medicine parameters. The *in vivo* antineoplastic efficiency of quinazoline bases was assessed in DLA model by measure solid tumour volume, solid tumour weight and zippers inhibition of the tumour weight of the treated drug over untreated management mice and treated normal (Gefitinib) mice. Among the four quinazoline bases studied, HP1, HP3 and HP4 at a dose of 10mg/kg and 20 mg/kg, optimally restrained the expansion of EAC and DLA cells *in vivo*. Besides, the treatment with HP1 and HP3 (20 mg/kg) considerably rehabilitated the deviated medicine parameters in EAC challenged mice. *In vivo* result authenticates that compound HP3 at a dose of 20mg/kg was simplest. The apoptotic studies shows that, each HP1 and HP3, at 10 and 20 mg/kg weight showed induction of caspase-mediated cell death as

they considerably rehabilitated the deviated medicine parameters in EAC challenged mice.

Conclusion: Additional studies are needed to explore the mechanism of action of this novel molecule which could bring talented outcomes in cancer therapy.

Fadhil Lafta Faraj, *et al*[12] synthesized and characterised quinazoline Schiff bases one and a pair of were investigated for malignant tumor activity against MCF- 7 human carcinoma cell line. Compounds one and a pair of incontestable a stimulating antiproliferative result, with associate IC50 price of six. 246 × 10−6 mol/L and 5.910 × 10−6 mol/L, severally, when 72 hours of treatment. Most cell death morphological options in treated MCF-7 cells were discovered by AO/PI staining. The results of cell cycle analysis indicate that compounds didn't induce S and M part arrest in cell when twenty four hours of treatment. What is more, MCF-7 cells treated with one and a pair of subjected to cell death death, as exhibited by perturbation of mitochondrial membrane potential and cytochrome unharnessed similarly as increase in ROS formation. We have a tendency to conjointly found activation of caspases-3/7, -8, and -9 in compounds one and a pair of. Moreover, inhibition of NF-κB translocation in MCF-7 cells treated by compound 1 significantly exhibited the association of extrinsic apoptosis pathway. Acute toxicity results incontestable the nontoxic nature of the compounds in mice. Our results showed vital activity towards MCF-7 cells via either intrinsic or accidental mitochondrial pathway and are potential candidate for additional *in vivo* and clinical carcinoma studies.

V. Alapati, *et al*[13] synthesized a Quinazoline analogues (Compound 21, NSC: 95112/753439 and Compound 12, NSC: D-104834/ 758270) in 3 totally different completely different} concentrations were evaluated for anti-tumour activity against bacteriologist pathology cancer (EAC) and 2 different concentration were evaluated for antineoplastic activity against Dalton's pathology malignant neoplastic disease (DLA) bearing Swiss anomaly mice. The *in vivo* anti-tumor efficiency of Quinazoline bases was assessed in EAC model by activity the rise in mean survival time of the drug treated over untreated management mice and treated commonplace (Gefitinib) mice. Their toxicity was assessed *in vivo* in traditional, standard, and EAC bearing mice by activity the drug-induced changes in medical specialty parameters. The *in vivo* anti-tumor efficiency of Quinazoline bases was assessed in DLA model by activity solid neoplasm volume, solid neoplasm weight and zippers inhibition of the neoplasm weight of the drug treated over untreated management mice and treated commonplace (Gefitinib) mice. Among the 2 quinazoline bases studied, 3-(2-chloro benzylideneamine)-2-(furan-2-yl) quinazoline-4(3h) - one (Compound 21) at Associate in Nursing best dose of 20 mg/kg weight was found to reinforce the mean survival time of infected mice. medical specialty parameters and mean survival time in neoplasm bearing mice were found to be considerably improved towards traditional once treatment with Compound 21 at 20 mg/kg weight of mice in EAC model. neoplasm volume and neoplasm weight in neoplasm bearing mice were found to be considerably improved towards traditional once treatment with Compound 12 at 20 mg/kg weight of mice in DLA model. Compound 21 at a first-rate dose of 20 mg has shown promising antineoplastic activity *in vivo* against EAC and DLA models when put next to straight forward drug with minimum ototoxic effects.

Marwa F. Ahmed, *et al*[14] synthesized a completely unique series of 4-substituted 6, 8-dibromo-2-(4-chlorophenyl)-quinazoline derivatives are designed and synthesized. New derivatives were tested against MCF-7 (human breast cancer cell line) and screened for r inhibition activity against epidermic protein receptor amino acid enzyme (EGFR-TK). Most of the tested compounds show potent antiproliferative activity and EGFR-TK restrictive activity. Compounds VIIIc and VIIIb exerted powerful cytotoxic activity (IC50 3.1 and 6.3 μM) with potent inhibitory percent (91.1 and 88.4%) against EGFR-TK. Compounds IX, VIIa, X, VIIb, VIc, V, IV, VIa and VIb showed promising

cytotoxic effects with IC50 range (12-79 μM) with good activity against EGFR-TK with the inhibitory percent (85.4-60.8%). On the opposite hand, compounds VIIc, VIIIa exerted low cytotoxic effects as revealed from their IC50 value (124 and 144 μM) with low activity against EGFR-TK with inhibitory percent 30.6 and 29.1%severally.

Fadhil Lafta Faraj, *et al*[12] synthesized and characterised quinazoline Schiff bases one and a couple of were investigated for antitumor activity against MCF-7 human carcinoma cell line. Compounds one and a couple of incontestable a noteworthy antiproliferative result, with associate IC50 price of vi.246 × 10−6 mol/L and 5.910 × 10−6 mol/L, severally, when 72 hours of treatment. Most caspase-mediated cell death morphological options in treated MCF-7 cells were determined by AO/PI staining. The results of cell cycle analysis indicate that compounds failed to induce S and M section arrest in cell when 24 hours of treatment. Moreover, MCF-7 cells treated with one and a couple of subjected to caspase-mediated cell death death, as exhibited by perturbation of mitochondrial membrane potential and cytochrome unharnessed furthermore as increase in ROS formation. We tend to additionally found activation of caspases-3/7, -8, and -9 in compounds one and a couple of. Moreover, inhibition of NF-κB translocation in MCF-7 cells treated by compound 1 significantly exhibited the association of extrinsic apoptosis pathway. Acute toxicity results incontestable the nontoxic nature of the compounds in mice. Our results showed important activity towards MCF-7 cells via either intrinsic or outside mitochondrial pathway and area unit potential candidate for additional *in vivo* and clinical carcinoma studies.

Mani Chandrika, *et al*[15] synthesized a unique series of four, 6-disubstituted quinazoline derivatives are synthesized ranging from anthranilic acid derivatives one through typical strategies. Ab initio chemical action followed by cyclisation to get benz-oxazinones two that on additional treatment with ammonia yielded the crucial intermediate, 2-substituted benzamide (3). The product were later on cyclised to get quinazolones four, chlorinated five, then hooked to varied optically pure a-amino acids to own four,6-disubstituted quinazoline derivatives half dozen. All the derivatives half dozen square measure screened for medicinal drug and anti-cancer activity against U937 leucaemia cell lines. A number of the compounds exhibited promising anti-cancer activity with regard to normal drug Etoposide.

Arunachalam Sumathy, *et al*[16] synthesized some new semi carbazides containing quinazoline moieties are synthesized and their ability to inhibit growth of human neoplastic cell lines has been evaluated. The compound S1 and S3 has shown outstanding antitumour activity. The structures of FT-IR, NMR, and mass spectra analysis.

Zahra Haghighijoo, *et al*[17] synthesized a series of fifteen antecedently designed and synthesized 4-anilinoquinazoline analogs (4-18) were evaluated for cytotoxic activity on 2 carcinoma cell lines (MCF-7 and MDA-MB- 468). Matter potency and binding mode studies were additionally done and evaluated for doubtless EGFR repressing effects compared with imatinib and erlotinib as reference medication. Among the tested 4-anilinoquinazolines, compound eleven, that contains diethoxy at phenyl ring and morpholino pendants at positions 5 and 7 of the quinazoline ring, incontestible the foremost potent biological activity on each cell lines. Our new quinazoline derivatives with totally different substituents love cyclic or linear ethers and flour teams is also a promising cytotoxic lead compounds for any anti-breast cancer analysis.

Murat Bingul, *et al*[18] Identified the novel (E)-N1 -((2-chloro-7-methoxyquinolin-3-yl) methylene)-3-(phenylthio) propane hydrazide scaffold eighteen has semiconductor diode to the event of a replacement series of biologically active hydrazide compounds. The parent compound 18 and new quinoline derivatives 19–26 were ready from the corresponding quinoline hydrazones and substituted radical acids exploitation EDC-mediated amide coupling reactions. Additional modification of the parent compound 18 was achieved by replacement of the quinoline moiety with alternative aromatic systems. All the recently synthesized compounds

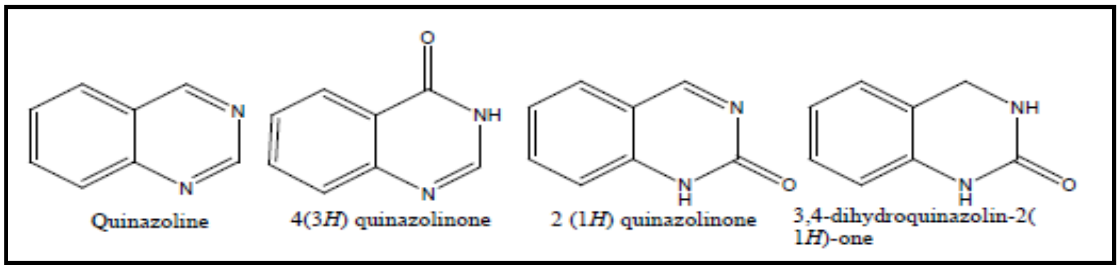
were evaluated for anti-cancer activity against the SH-SY5Y and Kelly malignant tumor cell lines, in addition because the MDA-MB-231 and MCF-7 breast glandular carcinoma cell lines. Analogues 19 and 22 considerably reduced the cell viability of malignant tumor cancer cells with micromolar efficiency and important property over traditional cells. The quinoline hydrazide 22 conjointly elicited G1 cell cycle arrest, in addition as upregulation of the p27kip1 cell cycle control supermolecule.

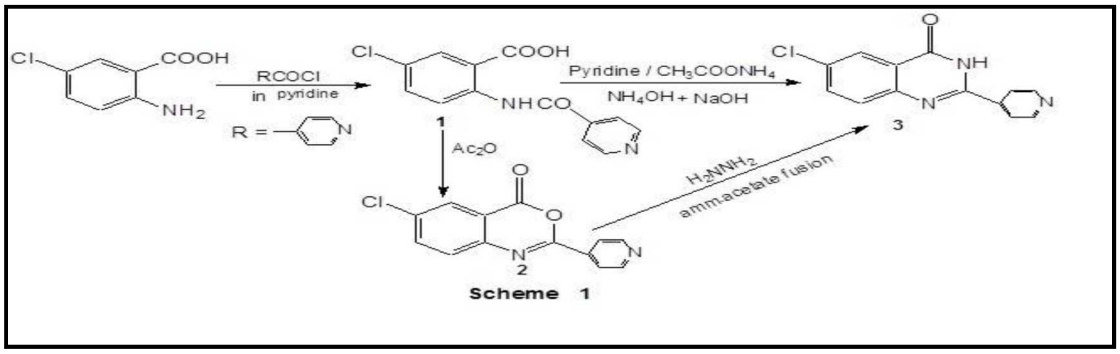
Ghorab M M, *et al*[19] synthesized sulfa bearing compounds possess many varieties of biological activities and have recently been according to indicate substantial growth activity *in vitro* and/or *in vivo*. There square measure a spread of mechanisms for the malignant tumor activity, and therefore the most outstanding mechanism is that the inhibition of chemical element anhydrase (CA) isozymes. This work reports the synthesis of twenty novel quinoline and pyrimido [4, 5-b] quinoline derivatives bearing a sulfa moiety. The new synthesized compounds were designed in compliance with the final pharmacophoric needs for CA inhibiting malignant tumor medication, as this might play a job in their malignant tumor activity. All the recently synthesized compounds were evaluated for his or her in vitro malignant tumor activity against human carcinoma cell line (MCF7). Compounds 6, 9 and 18 showed IC (50) values (72.9 microM, 72.1 microM and seventy one.9 microM, respectively) such as that of the reference drug antibiotic (IC (50) = seventy one.8 microM). On the opposite hand, compound 8 exhibited higher activity than antibiotic with Associate in Nursing IC (50) price of 64.5 micro M. In addition, the foremost potent compounds 8 and 18 were evaluated for ability to reinforce the cell killing result of gamma-radiation.

Yong J, *et al*[20] synthesized 21 new structures of quinazolines (3a~3u) and evaluated their *in vitro* antineoplastic activity against A549, HCT116 and MCF-7 cell lines exploitation the MTT technique. Most compounds showed smart to wonderful antineoplastic activity. Especially, 3o (regarded as erlotinib analogues) has marked antineoplastic activity against A549, HCT116 and MCF-7 cell lines (IC50s: 4.26, 3.92 and 0.14 μM, respectively) as compared with the quality antineoplastic drug gefitinib (IC50s: 17.9, 21.55 and 20.68 μM, respectively), and which may be considered the most effective candidate for development of antineoplastic medicine.

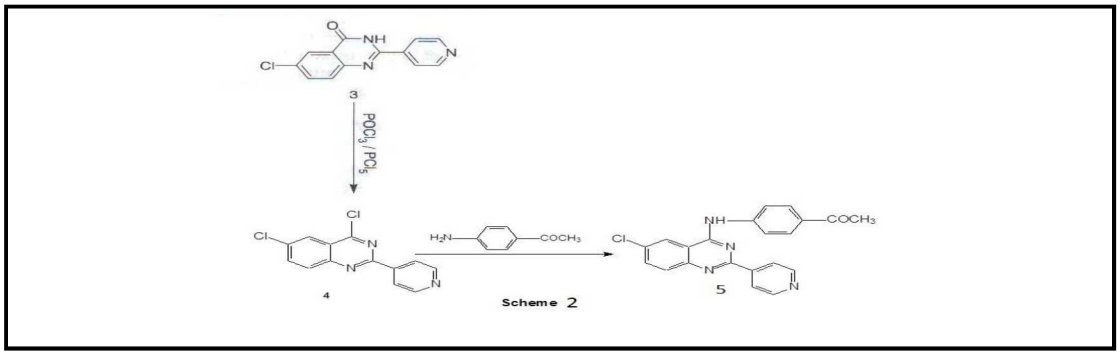
Hatem A. Abuelizz, *et al*[9] synthesized a new series of quinazoline derivatives (3–26) and characterised via chemistry and spectral suggests that. Treatment of 2-amino-5-methylbenzoic acid with chemical group chemical irritant resulted within the new 2-thioxoquinazolin-4-one (3). Alkylation and hydrazinolysis of the inherent thioxo cluster in (1–3) afforded the corresponding thioethers (4-23) and reducing agent derivatives (24 and 25), then 24 was additional reworked into antidepressant spin off 26 via cyclocondensation reaction. Compounds one and a couple of, that were antecedent synthesized, were found to exhibit metastatic tumor activity. The cytotoxicity of all compounds was evaluated *in vitro* against the Hel and MDA-MB231 neoplastic cell lines, as well as one and a couple of for comparison, exploitation MTT assay. The treatment of the cells was performed with the synthesized compounds and gefitinib at 0, 1, 5, 10, 25, and 50μM and incubated for 24 h in 50% DMSO. The IC50 values of the target compounds were reported in μM, exploitation gefitinib as a regular. Our results indicated that each one compounds exhibited important *in vitro* toxicity against each cell lines. Whereas compounds 1–3 showed sensible activity, compounds 21–23 were found to be harder than gefitinib. Thus, compounds 21–23 could also be potential metastatic tumor agents, with IC50 values starting from one.85 to 2.81 μM in relation to gefitinib (IC50 = 4.3 and 28.3μM against HeLa and MDA-MB231 cells, respectively).

Sapavat Madhavi, *et al*[21] synthesized a series of 10 novel chalcone incorporated quinazoline derivatives (11a–11j) were designed and synthesized. All the synthesized compounds were evaluated for metastatic tumor activities against four human neoplastic cell lines (A549, HT-29, MCF-7 and A375). Among them, four compounds, 11f, 11g, 11i and 11j showed harder metastatic tumor activity than the management drug, Combretastatin – A4.

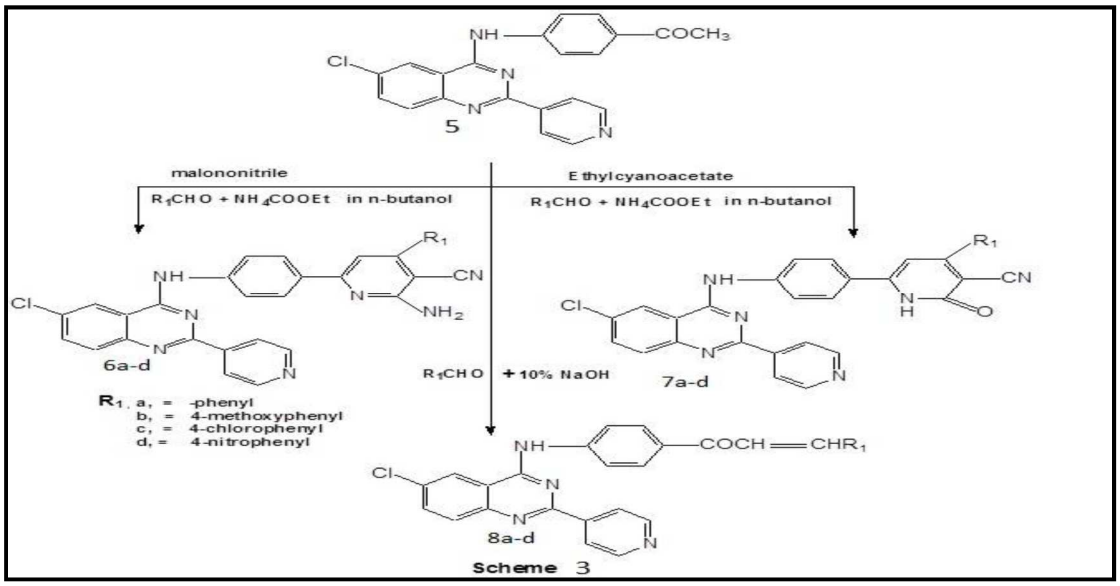




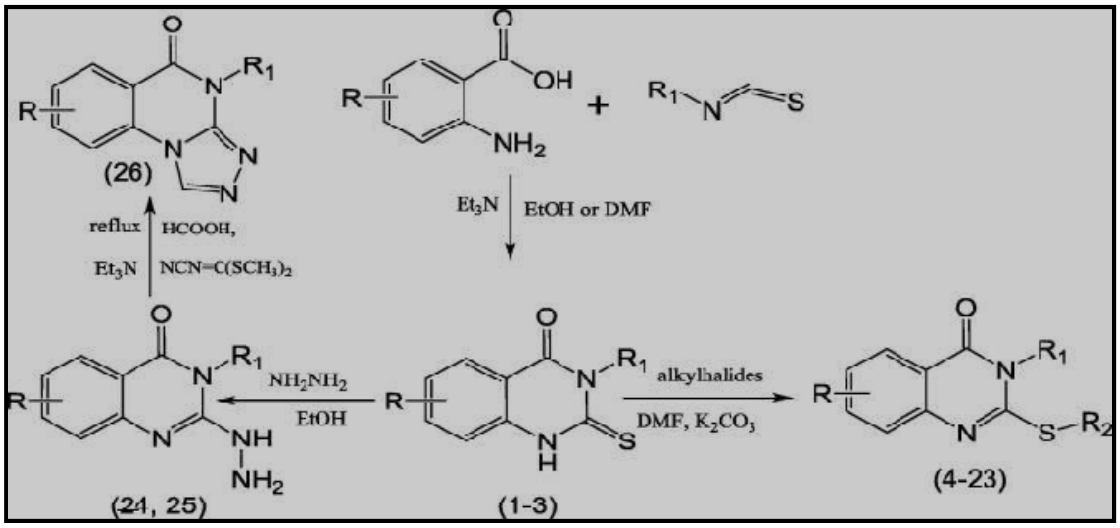
Scheme 1

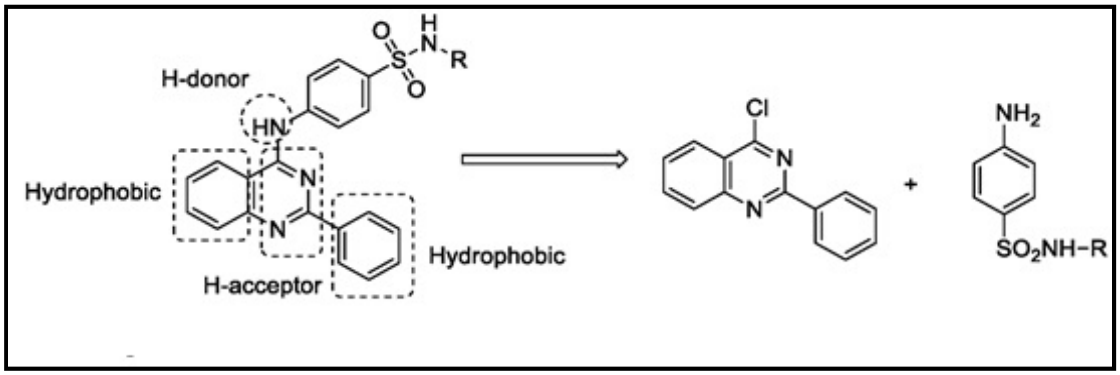


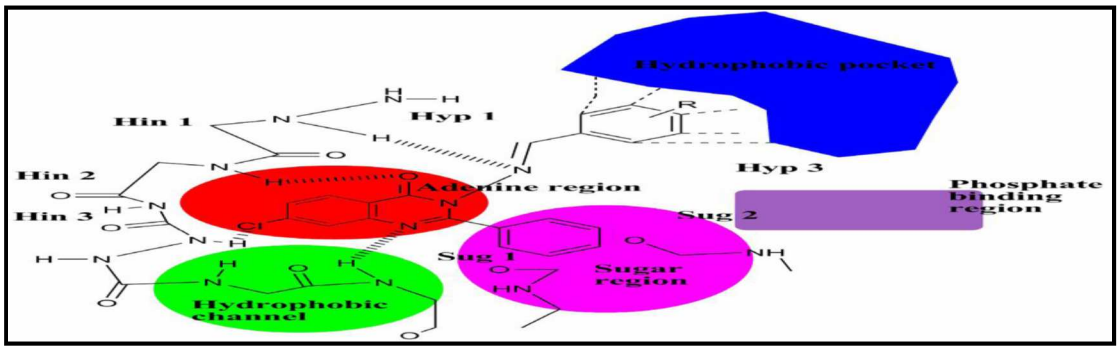
Scheme 2



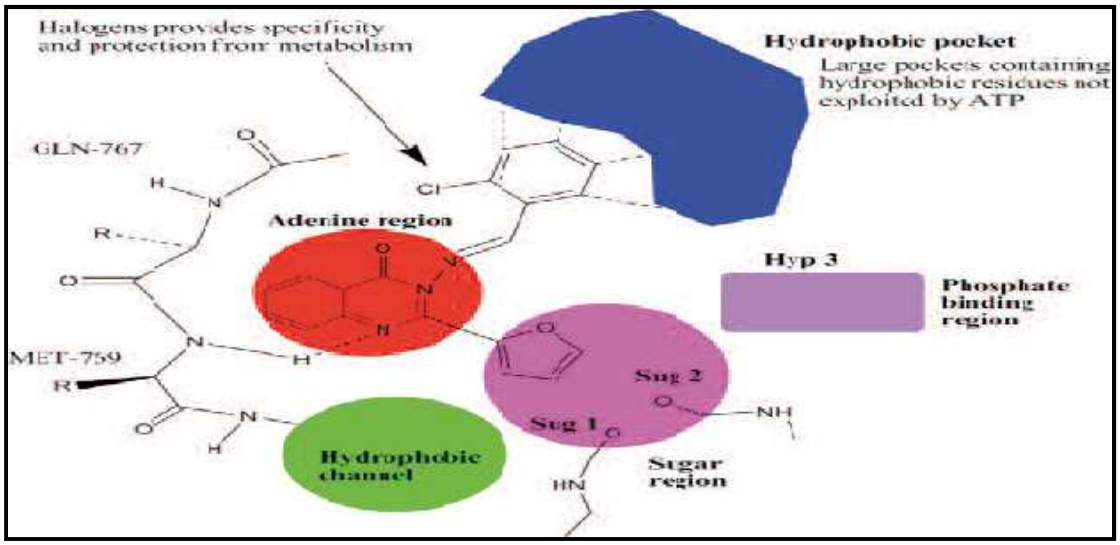
Scheme 3

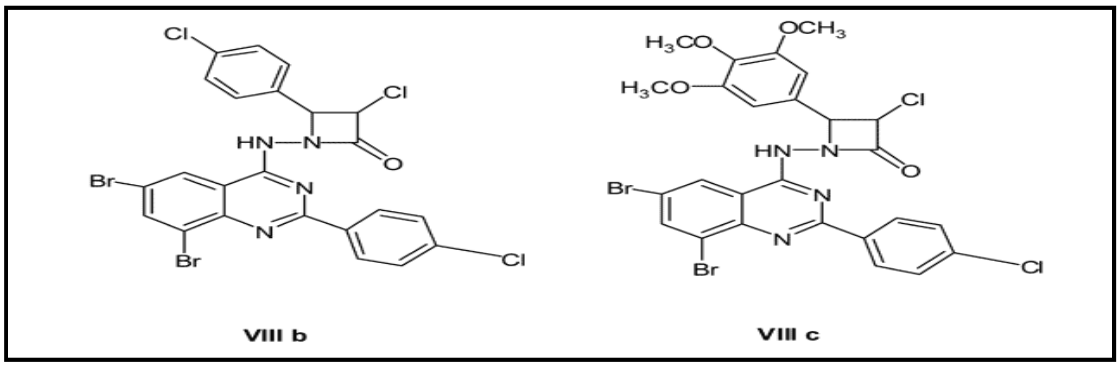


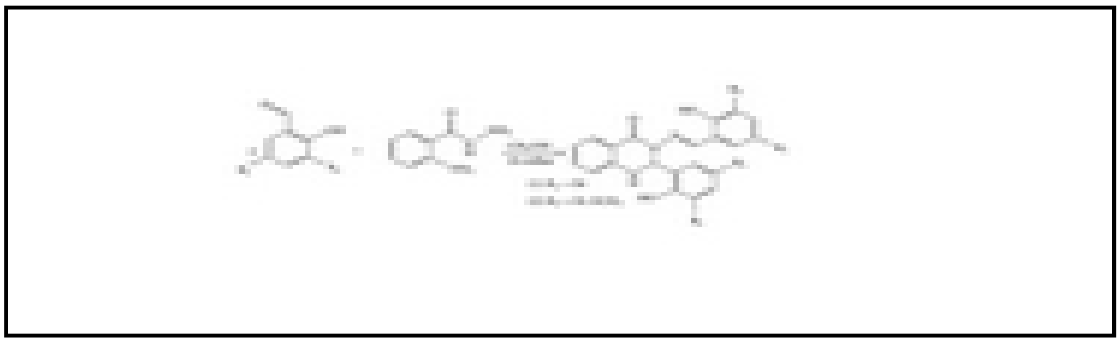


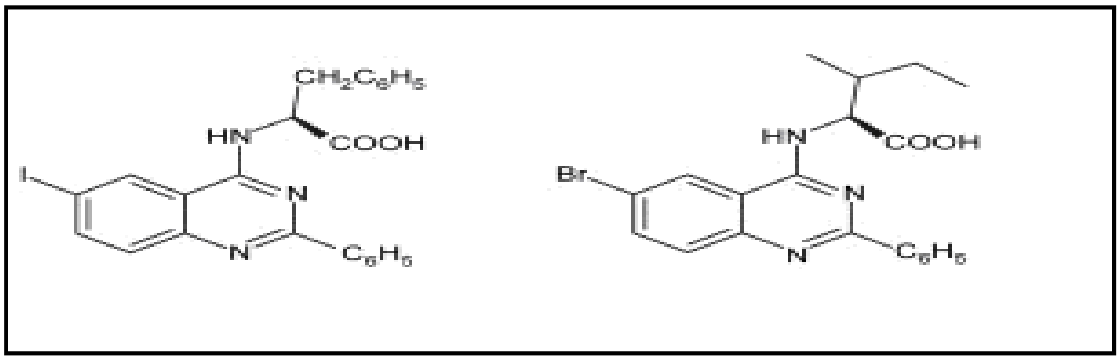


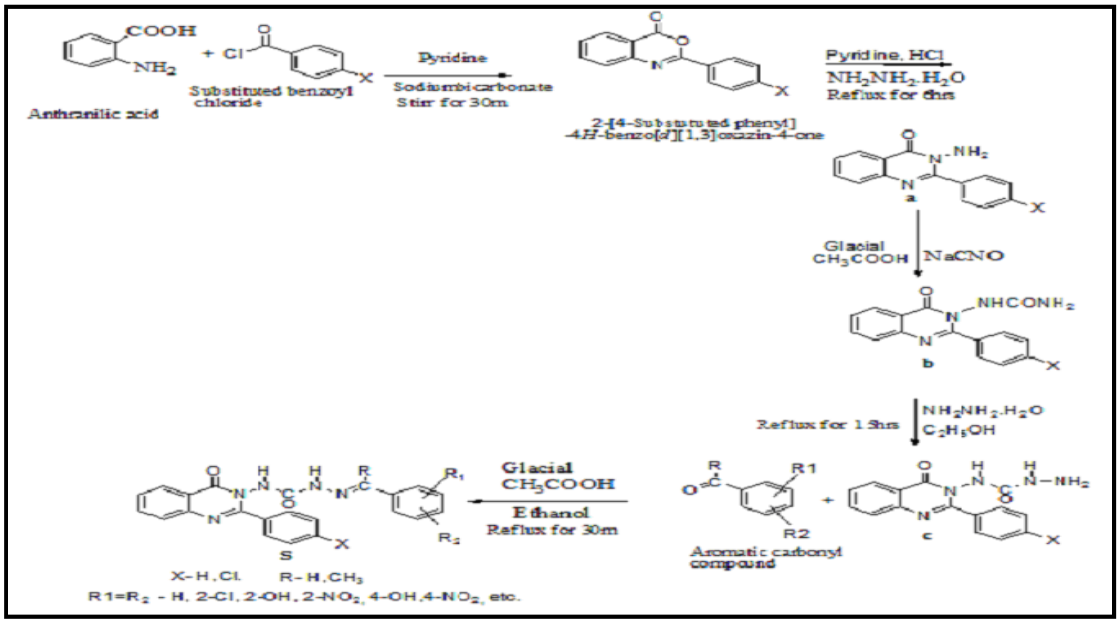
Proposed hypothetical model of the 2, 3, 7-trisubstituted quinazoline bound to ATP binding site of EGFR-protein tyrosine kinase

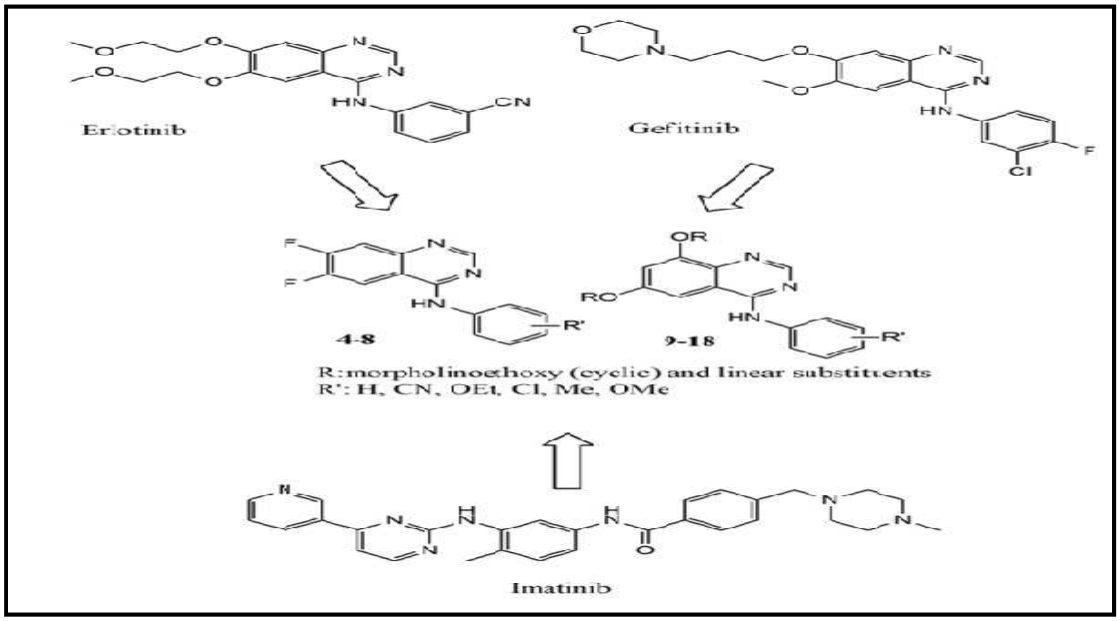

Halogens provides specificity and protection from metabolism
Hydrophobic pocket
Large pockets containing hydrophobic residues not exploited by ATP
GLN-767
Adenine region
Hyp 3
Phosphate binding region
MET-759
Sug 2
Sug 1
Hydrophobic channel
Sugar region

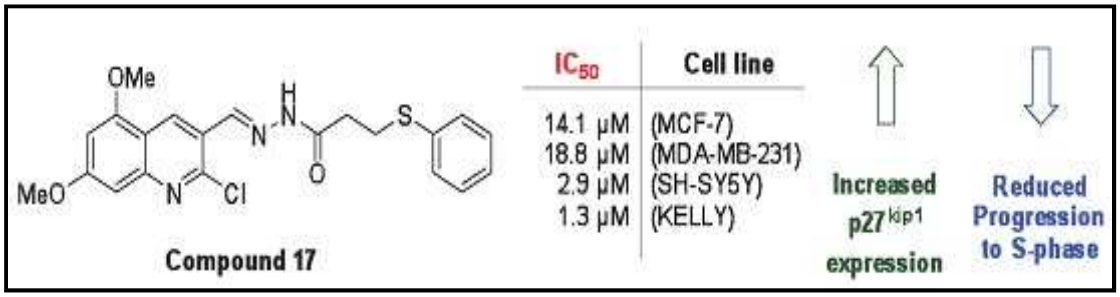

VIII b
VIII c

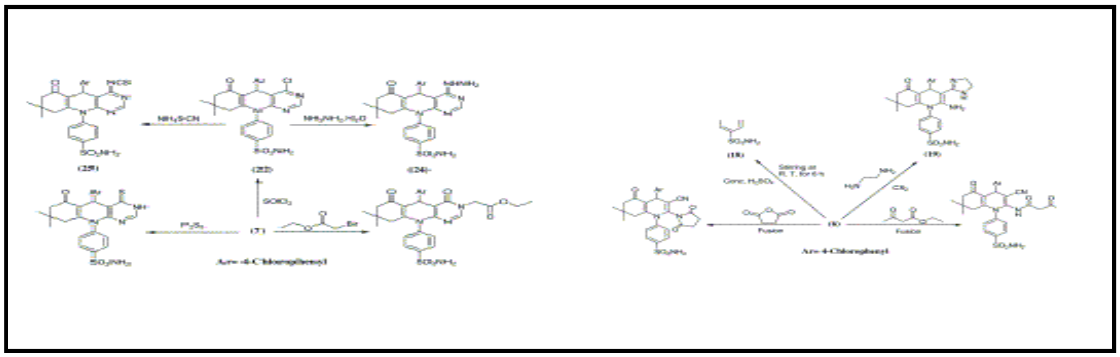


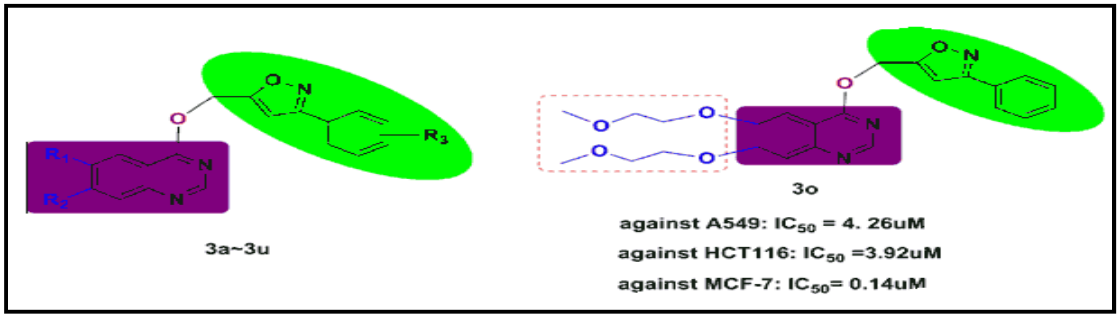


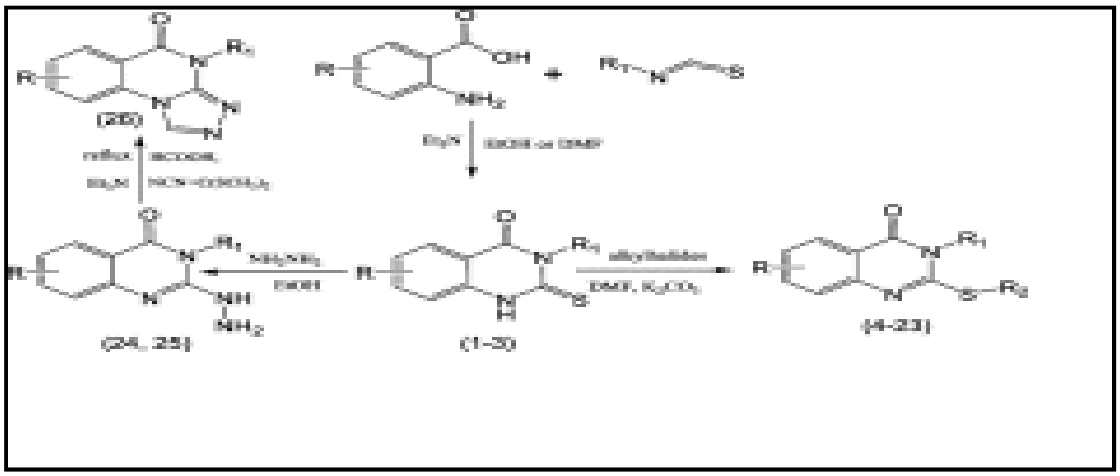

Anthranilic acid
Substituted benzoyl chloride
Pyridine
Sodiumbi-carbonate
Stir for 30m
Pyridine, HCl
$NH_2NH_2.H_2O$
Reflux for 6hrs
Glacial CH_3COOH
NaCNO
Reflux for 1.5hrs
$NH_2NH_2.H_2O$
C_2H_5OH
Glacial CH_3COOH
Ethanol
Reflux for 30m
Aromatic carbonyl compound
X-H,Cl R-H,CH_3
R1=R_2 - H, 2-Cl, 2-OH, 2-NO_2, 4-OH, 4-NO_2, etc.

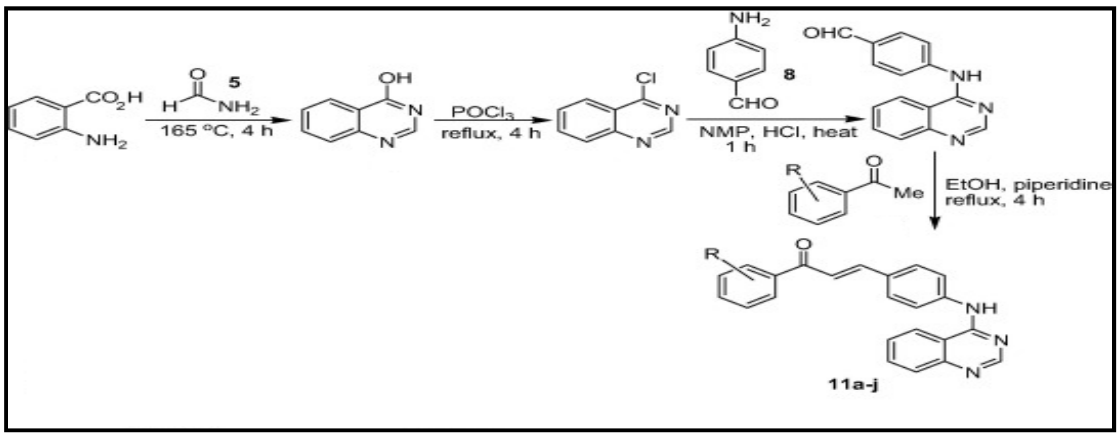

Erlotinib
Gefitinib
4-8
9-18
R:morpholinoethoxy (cyclic) and linear substitutents
R': H, CN, OEt, Cl, Me, OMe
Imatinib


Compound 17
IC_{50}
Cell line
14.1 µM (MCF-7)
18.8 µM (MDA-MB-231)
2.9 µM (SH-SY5Y)
1.3 µM (KELLY)
Increased $p27^{kip1}$ expression
Reduced Progression to S-phase




3a~3u
3o
against A549: IC_{50} = 4. 26uM
against HCT116: IC_{50} =3.92uM
against MCF-7: IC_{50}= 0.14uM




5
165 °C, 4 h
POCl3
reflux, 4 h
8
NMP, HCl, heat
1 h
EtOH, piperidine
reflux, 4 h
11a-j

CONCLUSION

This review provide associate outlook on the analysis developments concerning Quinazoline moiety. This heterocyclic moiety has nice biological and medicative significance. An oversized array of quniazoline derivatives possess a range of medicative properties. Quinazoline is taken into account as a vital lead compound in drug discovery and drug development. Quinazoline occupy a definite and distinctive place within the field of drugs. This next additionally offer a base for the long term analysis work concerning modifications in quinazoline moiety and its implementation in drug discovery. Quinazoline moiety are most often studied, several of its analogs are active against varied pathological conditions, that are mentioned briefly during this article. The enhancements within the activity will be more achieved by slight modifications within the substituents on the fundamental quinazoline nucleus. Varied recent new drug developments in quinazoline derivatives show higher impact and fewer toxicity. This review gives valuable information for further development for potent anti-cancer agents.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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