ABSTRACT
Quinazoline derivatives occupy a distinct and unique place in the medicinal chemistry as they possess diverse biological activities. As on date, about 25 clinically used drugs are quinazoline derivatives. This review has presented a comprehensive detail of quinazoline derivatives which are under clinical trial.

Keywords: Quinazoline, Clinical Trial, Balaglietzone, Ispinesib, Tandutinib

INTRODUCTION
Appreciable number of heterocyclic compounds containing nitrogen atom, obtained by laboratory synthesis have turned out to be potential chemotherapeutic and pharmacotherapeutic agents. Various useful synthetic analogs with improved therapeutic properties can be obtained from a single lead compound by structural modification. The same principle is applicable to quinazolines. Quinazoline (1) is a compound made up of two fused benzene and pyrimidine rings.

Quinazoline nucleus has attracted the attention of medicinal chemists due to its diverse biological activities. The biological activities of quinazoline derivatives have been reviewed [1-2]. A review on the marketed drugs containing quinazoline moiety has also been published [3]. The present review highlights quinazoline derivatives which are under clinical trial.

Quinazoline derivatives under clinical trial
There are many quinazoline derivatives which are under different phases of trial i.e. Pre-clinical trial, Phase I trial, Phase II trial, Phase III trial or Phase IV trial. The authors believe that previous reviews [1-3] do not provide any insight about quinazoline derivatives which are under Phase I trial, Phase II trial or Phase III trial. The authors have also located some quinazoline derivatives that were under clinical trial, but have been discontinued for further development. Therefore, in this review present authors emphasize on quinazoline derivative which are currently under Phase I trial, Phase II trial or Phase III trial and are being investigated for further development. Quinazoline derivative which are under Phase I trial, Phase II trial and Phase III trial are discussed below.

Balaglietzone
Balaglietzone (DRF 2593), a quinazolone analogue of thiazolidinedione, is chemically 5-[(4-[(3,4-dihydro-3-methyl-4-oxo-2-quinazolinyl)methoxy]phenyl)methyl]-2,4-thiazolidinedione of following formula.

Balaglietzone is a selective partial PPAR-γ agonist. Common side effects associated with PPAR-γ receptor agonists are weight gain, oedema and adipogenesis. Balaglietzone is a selective partial PPAR-γ agonist and it has been speculated that such compounds have a more favourable safety margin than full agonists [4]. Balaglietzone has excellent antidiabetic and hypolipidemic properties but shows less adipogenic activity [5,6]. Balaglietzone is being developed by Dr. Reddy’s Laboratories. Dr. Reddy’s entered into a 10-year agreement with Rheoscience A/S of Denmark for the joint development and commercialization of Balaglietzone. Rheoscience holds this product’s marketing rights for the European Union and...
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China, while the rights for the US and the rest of the world will be held by Dr. Reddy’s. In January 2010, Dr. Reddy’s Laboratories announced that its first later-stage trial of the experimental diabetes drug Balaglitazone hit its primary endpoint for the reduction of blood glucose levels[7, 8]. Dr Reddy’s claims the data "leaves the program on track to an eventual regulatory approval".

Afatinib
Afatinib, an anilino-quinazoline derivative, chemically is N-[4-[(3-Chloro-4-fluorophenyl) amino]-7-[(3S)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-(dimethy lamino)-2-butenamide of following formula.

Unlike first-generation reversible EGFR TKIs such as erlotinib and gefitinib, afatinib covalently binds and irreversibly inhibits the tyrosine kinase activity of all ErbB family members and is therefore expected to block both partners in the ErbB receptor dimer. This results in a more effective signaling blockade and greater anti-tumour efficacy when compared with agents targeting EGFR alone[9]. Boehringer Ingelheim is developing afatinib, an orally bioavailable irreversible inhibitor of epidermal growth factor receptor (EGFR) and HER2 receptor tyrosine kinases, as a potential therapeutic for solid tumors including nonsmall cell lung cancer (NSCLC), breast cancer, head and neck cancer and glioma. Afatinib is currently in Phase III clinical development in NSCLC, the most common type of lung cancer and breast cancer. At this stage of development, results have indicated that afatinib may have potential benefits compared to other signal transduction inhibitors[10, 11].

Dacomitinib
Dacomitinib (PF 299804), chemically is (2E)-N-[4-[(3-chloro-4-fluorophenyl) amino]-7-methoxyquinazolin-6-yl]-4-(piperidin-1-yl)but-2-enamide having following formula[12].

Pfizer is developing dacomitinib, an orally available selective and irreversible inhibitor of the HER family of kinases, for the treatment of cancer. Dacomitinib is being evaluated in Phase III[13].

GS 1101
GS 1101 (CAL 101) is chemically, 5-fluoro-3-phenyl-2-[(1S)-1-(9H-purin-6-ylamino)propyl]-4(3H)-quinazolinone having CAS No. 870281-82-6 and following formula.

Gilead Sciences (formerly Calistoga) is developing GS 1101 (CAL 101), an oral small molecule inhibitor of the delta isoform of PI3-kinase (p110delta), for the treatment of hematological cancer[14, 15].

Nolatrexed
Nolatrexed chemically is, 2-Amino-6-methyl-5-(4-pyridylthio)-1H-quinazolin-4-one having following formula.

Nolatrexed is a thymidylate synthase inhibitor, for use in the treatment of solid tumors. Nolatrexed was created using protein structure-based drug design technology to identify inhibitors of thymidylate synthase[16].

Albaconazole
Albaconazole, chemically is 7-chloro-3-[(2R,3R)-3-(2,4-difluorophenyl)-3-hydroxy-4-(1,2,4-triazol-1-yl)butan-2-yl]quinazolin-4-one having following formula[17].

Palau Pharma is developing the broad-spectrum antifungal, albaconazole (UR 9825), for the oral treatment of superficial fungal infections. Albaconazole is a new potent quinazoline derivative available as an oral preparation. The drug has excellent bioavailability and is widely distributed throughout body fluids. It has activity against Candida spp., Cryptococcus spp., Malassezia spp., dermatophytes, Aspergillus spp., and Paecilomyces spp. Phase II studies have been
conducted in adults with vulvovaginitis and onchomyosis\cite{18,19}.

**Barasertib**

Barasertib, chemically is 5-[[7-[[3-[[ethyl[2-(phosphonoxy)ethyl]amino]propoxy]-4-quinazolinyl]amino]-N-(3-fluorophenyl)-1H-pyrazole-3-acetamide of following formula\cite{20}.

AstraZeneca is developing barasertib (AZD1152), an aurora kinase inhibitor, for the treatment of acute myeloid leukemia (AML). Barasertib entered Phase II clinical trials for colorectal carcinoma and melanoma (both discontinued), as well as for acute myelogenous leukaemia (still ongoing). Although no conclusion about the clinical efficacy of these drugs can be made, as no information have been reported so far in the literature concerning the results of these trials, evidence that targeting Aurora kinases may be a promising approach for the treatment of human solid tumours has been derived from preclinical and clinical Phase I studies\cite{21}.

**Cediranib**

Cediranib, chemically is 4-[(4-fluoro-2-methyl-1H-indol-5-yl)oxy]-6-methoxy-7-[3-(pyrrolidin-1-yl)propoxy]quinazoline having following formula.

AstraZeneca is developing cediranib (RECENTIN), an orally active vascular endothelial growth factor receptor 2 (VEGFR2) tyrosine kinase inhibitor, for the treatment of solid tumors, hematological malignancies and liver metastases.

Cediranib (AZD2171, Recentin) is an oral pan-VEGFR tyrosine kinase inhibitor with additional activity against platelet-derived growth factor β and c-Kit. It has a half-life of 22 hours thus allowing once-daily dosing. Currently cediranib is under investigation in paediatric patients with recurrent CNS tumors and in several adult studies. There is an ongoing phase I trial of the combination with gamma-secretase/Notch signalling pathway inhibitor RO4929097 in solid tumors. The addition of gefitinib versus placebo to cediranib is explored in a randomized phase II study in recurrent glioma, while another phase II is evaluating the addition of cediranib versus placebo to chemoradiotherapy in newly diagnosed glioblastoma. Cediranib plus the triple angiokinase inhibitor BIBF1120 in recurrent glioblastoma is tested in a phase II safety and efficacy study and finally cediranib and cilengitide, which targets the αvβ3 and αvβ5 integrin receptors are combined in a phase Ib study in a recurrent glioblastoma patient population\cite{22}.

**Elinogrel**

Elinogrel, chemically is N-[(5-chlorothiophen-2-yl)sulfonyl]-N'-{4-[(6-fluoro-7-(methylamino)-2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl]phenyl}urea of following formula\cite{23}.

Novartis is developing elinogrel (PRT 128), a P2Y12 ADP receptor antagonist, for the prevention and treatment of thrombosis in patients with acute coronary syndrome (ACS) or undergoing percutaneous coronary intervention (PCI), and for the secondary prevention of myocardial infarction and stroke. Similarly to ticagrelor and in contrast to clopidogrel, elinogrel is a reversible inhibitor that acts fast and short (about 12 hours), and it is not a prodrug but pharmacologically active itself. The substance can be used intravenously for acute treatment and orally for long-term treatment. It is used in form of its potassium salt\cite{24}.

**Ispinesib**

Ispinesib chemically is N-(3-aminopropyl)-N-[(1R)-1-[7-chloro-3,4-dihydro-4-oxo-3-(phenylmethyl)-2-quinazolinyl]-2-methylpropyl]-4-methyl-benzamide of following formula\cite{25}.

Ispinesib is being developed as Ispinesib mesilate. It is a KSP inhibitor that was found to be more selective for KSP over other members of the
kinesin family. It effectively induced tumor regression in several preclinical models. Ispinesib was chosen for further development as an antimitotic agent and has shown efficacy in phase I and II trials in patients with solid tumors. Cytokinetics is developing ispinesib (SB 715992; CK 0238273) as a potential treatment of solid tumors.[26]

**Letermovir**

Letermovir, chemically is (4S)-8-fluoro-3,4-dihydro-2-[4-(3-methoxyphenyl)-1-piperazinyl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-4-quinazolineacetic acid of following formula.[27]

![Letermovir](image1)

Letermovir (AIC246) belongs to a novel class of anti-CMV agents that exhibits outstanding antiviral activity and acts via a mechanism of action that is distinct from all currently approved drugs. In all clinical trials performed so far, AIC246 has been generally well tolerated in healthy subjects as well as in CMV-infected transplant patients. Efficacy was shown in a proof-of-concept trial in pre-emptively treated solid-organ transplant patients and a patient with multidrug-resistant CMV disease involving several organs. Results from a Phase IIb dose-finding trial for prophylactic use in human blood precursor cell transplanted patients are expected in early 2012. AiCuris is developing leternovir (AIC 246), a non-nucleoside human cytomegalovirus (HCMV) inhibitor, for the treatment of HCMV infection in transplant recipients and other immunocompromised individuals.[28, 29].

**Milciclib**

Milciclib (PHA-848125) chemically is 4,5-dihydro-N,1,4,4-tetramethyl-8-[4-(4-methyl-1-piperazinyl)phenyl]amino]-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide of following formula.[30]

![Milciclib](image2)

Nerviano Medical Sciences is developing milciclib, an oral CDK2, CDK1, CDK4 and tyrosine kinase A (TrkA) oral inhibitor, for the treatment of cancer. This agent is one of the small molecules discovered through the CDK2 inhibitors program conducted by Nerviano Medical Sciences. It is under phase II clinical trial[31].

**Sotrastaurin**

Sotrastaurin chemically is 3-[(1H-indol-3-yl)-4-[2-(4-methyl-1-piperazinyl)-4-quinazolinyl]-1H-pyrrole-2,5-dione of following formula.[32]

![Sotrastaurin](image3)

Novartis is developing sotrastaurin, an orally active T-cell activation inhibitor that targets protein kinase C (PKC), for the prevention of transplant rejection and psoriasis. Sotrastaurin (AEB-071, NVP-AEB-071) is an orally bioavailable compound that exerts its effects through the selective inhibition of the classic and novel forms of protein kinase C (PKC), thereby inhibiting early T-cell activation and IL-2 production. In preclinical studies, sotrastaurin reduced the rejection of allogeneic solid organ and islet transplants and interacted in a synergistic manner with the immunosuppressive agent ciclosporin. Sotrastaurin is being investigated in a number of clinical trials aimed at exploring its efficacy and safety in T-cell-mediated conditions such as transplant rejection, psoriasis, uveitis and ulcerative colitis. The compound has shown acceptable toxicity profiles in healthy individuals and transplant recipients. Provided sotrastaurin shows continued promise in the ongoing clinical studies, it may be a safe and effective alternative or adjunct to calcineurin inhibitors.[33, 34].

**Tandutinib**

Tandutinib chemically is 4-[6-methoxy-7-[3-(1-piperidinyl)propoxy]-4-quinazolinyl]-N-[4-(1-methyllethoxy)phenyl]-1-piperazinecarboxamide of following formula.[35]

![Tandutinib](image4)
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Millennium, a Takeda subsidiary, is developing tandutinib (MLN 518), an inhibitor of the FLT3, PDGF and c-KIT receptor tyrosine kinases (RTK), as an orally delivered therapy with potential in the treatment of glioblastoma. Tandutinib (MLN518), which was initially developed as a FLT-3 inhibitor, also shows activity against wild-type and juxtamembrane mutated and active site mutated (D816V) c-KIT. It is being evaluated in phase studies for relapsed or refractory AML.

Varlitinib
Varlitinib chemically is N4-[3-chloro-4-(2-thiazolylmethoxy)phenyl]-N6-[(4R)-4,5-dihydro-4-methyl-2-oxazolyl]-4,6-quinazolinediamine of following formula.

Array BioPharma and ASLAN are developing varlitinib (ARRY 543), an orally active small molecule tyrosine kinase inhibitor, for the treatment of cancer. Varlitinib acts by disrupting the receptor tyrosine kinases ErbB-2, ErbB-4 and EGFR. It is being developed as tosylate salt.

Verubulin
Verubulin chemically is N-(4-methoxyphenyl)-N,2-dimethyl-4-quinazolinamine of following formula.

Myrexis (formerly Myriad Pharmaceuticals) is developing verubulin (MPC 6827; MX 128495; AZIXA) as an injectable anticancer agent. The agent acts as a cytotoxin, a vascular disrupting agent and as a microtubule destabilizer. It is being developed as Verubulin hydrochloride. Verubulin hydrochloride (MPC-6827) is a 4-aryl-aminoquinazoline with two distinct mechanisms of action. First, it causes apoptosis through the inhibition of tubulin polymerization, resulting in cell cycle arrest and cell death in a manner similar to other microtubule-interfering, proapoptotic chemotherapeutic agents, including the taxanes and the vinca alkaloids. Second, verubulin also has a vascular disrupting action through disrupting the microtubule cytoarchitecture in newly forming vessels. In preclinical testing, the agent was found to have excellent blood-brain barrier penetration, efficacy in multidrug-resistant cell lines and low CNS toxicity, making it a particularly attractive candidate as a brain tumor chemotherapeutic.

There are many quinazoline derivatives that have been discontinued after clinical / preclinical trial namely Belaperidone, Doqualast, Olcegepant, Prinoxodan, Saracatinib, Tiacrilast and Zenarestat.

CONCLUSION
The literature is self explanatory about the clinical therapeutic potential of quinazoline and its derivatives. As on date, about 25 clinically used drugs are quinazoline derivatives. This review has presented a comprehensive detail of quinazoline and its derivatives which are under clinical trial. It would be interesting to see the outcome of these clinical trials.

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