Review Article……!!!

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THERAPEUTIC POTENTIAL OF QUINAZOLINE AND ITS DERIVATIVES - A REVIEW

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ABSTRACT

Medicinal chemistry is concerned with discovery, development, synthesis in laboratory, thousands of new organic chemicals are prepared annually throughout world; many of them are entered to pharmacological screening for determining their biological activity. Heterocyclic chemistry is a chemistry involving the heterocyclic compounds, which has atoms of at least two different elements as member of ring. Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide. Quinazoline is a compound made up of two fused six member simple aromatic rings benzene and pyrimidine ring. It is a yellow coloured compound, found usually in crystalline form. Quinazoline is a building block for approximately 150 naturally occurring alkaloids, such as glycosminine, echinocerine, deoxyvasicinone, rutaecarpine and drugs like methaqualone isolated to date from a number of families of the plant kingdom, from animals and from microorganisms. According to recent data quinazoline nucleus has attracted the attention of medicinal chemists due to its well known anticancer activity and many substituted quinazoline derivatives have recently earned great interest in chemotherapy as antitumor drugs. It is also found in clinically useful molecules having diverse biological activities such as antiviral, antimalarial, anticonvulsant, antibacterial, diuretic, hypnotic, hypoglycaemic, antihypertensive, soporific, sedative, tranquilizing, analgesic, antitussive, myorelexant, antirheumatic, antiallergic, bronchodilating, cholangogue, cystatic, spermicidal, antifungal, anti-protozoan, antiinflammatory, antitubercular, CNS depressant, acaridical, weedicide, and many other functional materials.
INTRODUCTION

Quinazoline and Quinazolinones:

Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide. In particular, heterocyclic structures form the basis of many pharmaceutical, agrochemical and veterinary products. Quinazolin-2-ones, quinazoline-4-ones and related quinazolines are classes of fused heterocycles that are of considerable interest because of the diverse range of their biological properties\textsuperscript{1}. Methaqualone was synthesized for the first time in 1951 and it is the most well-known synthetic quinazoline drug, famous for its sedative–hypnotic effects\textsuperscript{2}. Quinazoline is a compound made up of two fused six-membered simple aromatic rings, a benzene ring and a pyrimidine ring. Its chemical formula is C\textsubscript{8}H\textsubscript{6}N\textsubscript{2}\textsuperscript{3}.

Moreover, the quinazoline skeleton is very common in several naturally occurring alkaloids displaying a wide range of biological activities useful in developing chemotherapeutic agents against many diseases and hence the exploration of this skeleton as privileged new chemical entities (NCE’s) in drug discovery research is of paramount importance\textsuperscript{4}. The quinazoline skeleton is of great importance to chemists as well as biologists as it is available in a large variety of naturally occurring compounds\textsuperscript{5}. Quinazolines, Quinazolin-2-one and quinazoline-4-one can possess hypnotic\textsuperscript{3} and diverse biological activities such as antiviral, antimalarial, anticonvulsant, antibacterial, diuretic, hypnotic, hypoglycaemic, antitumoral and antihypertensive\textsuperscript{2,5}. The derivatives of quinazolin-2-ones are potential drugs which can possess hypnotic, analgesic, antiallergic, anticonvulsant, antimalarial, and other effects\textsuperscript{4,6}. The sedative and hypnotic (neurotoxicity) properties of quinazolinone are well documented. The possibility that appropriate derivatives of quinazolinone as CNS-active compounds, which obviously cross the blood brain barrier, might find use as anticonvulsant or CNS depressant if the parent ring system could be appropriately functionalized. Among the few reports in the literature of tentative separation of anticonvulsant and sedative properties of quinazolinones\textsuperscript{5,6,7}.

QUINAZOLINE AS ANTI CANCER AGENTS

He et al synthesized a series of novel quinazoline derivatives\textsuperscript{8} containing thiosemicarbazide moiety (Fig 1-4) and evaluate their biological activity as antitumor agents. The therapeutically important compounds are as follows:
Marvania et al synthesized a series of phenyl N-mustard quinazoline derivatives\(^9\) (Fig 5) and subsequently evaluated their antitumor activity.
A series of few novel 4, 6- di substituted- (diaphenylamino)quinazolines derivatives (Fig 6) was synthesized by Li et al\textsuperscript{10}, which on evaluation for antitumor activity was considered as potent EGFR inhibitors.

![Fig 6](image)

Fernandes et al synthesized a series of quinazoline derivatives\textsuperscript{11} (Fig 7) and evaluated their function as EGFR inhibitors by applying radioiodination. All the research compounds were further evaluated for potential SPECT activity for molecular imaging of breast cancer.

![Fig 7](image)

Gellibert et al designed a series of novel quinazoline derivatives\textsuperscript{12} (Fig 8) that showed potent ALK5 inhibitory activity.

![Fig 8](image)

Wissner et al synthesized a quinazoline - based novel anti cancer molecule\textsuperscript{13} (Fig 9), that are dual irreversible kinase inhibitors.
A series of quinazoline derivatives (Fig 10) were synthesized by Noolvi et al\textsuperscript{14} and evaluated their biological activity against tyrosine kinase (EGFR).

Heath et al synthesized a series of 4-piperazin-1-yl quinazoline template based aryl and benzyl thiourea derivatives\textsuperscript{15} (Fig 11) that showed potent, selective and orally bioavailable antagonist of platelet-derived growth factor (PDGF) receptor.
Chen et al evaluate the biological activity of some novel 2, 3-disubstituted 8-arylamino-3H-imidazol[4,5-]quinazoline derivative\textsuperscript{16} (Fig 12) as a potent anti-tumour agent.

![Fig 12](image)

Above compound (fig 12) possessed the highest anti-NSCLC activity on the A549 cell line.

**QUINAZOLINE AS ANTI-TUBERCULAR AGENTS**

A series of quinazoline derivatives (Fig 13) was synthesized by Kunes et al\textsuperscript{17} and further evaluated for their pharmacological activity as antitubercular.

![Fig 13](image)

Most of the synthesized compounds exhibited antimycobacterial activity against the strains of Mycobacterium tuberculosis, Mycobacterium avium, Mycobacterium fortuitum, Mycobacterium kansasii and Mycobacterium intracellulare. The modification process with various hydrophobic chain clearly suggests the existence of hydrophobic pocket in the active site of the target of various strains of Mycobacterium species, which eventually raise the therapeutic efficacy.

**QUINAZOLINE AS ANTIFUNGAL AGENTS**

A series of few novel S-substituted-6-fluoro-4-alkyl (aryl) thioquinazoline derivatives (Fig 14) were synthesized by Xu et al\textsuperscript{18} and evaluated their pharmacological activity as antifungal. All of these compounds exhibited good antifungal activity, especially compound fig 14, having a wide spectrum of bioactivity it shows potent inhibitory activity on the growth of most of the fungi with EC50 values ranging from 8.3 to 64.2 μg/mL.
QUINAZOLINE AS ANTIMALARIAL AGENTS

Madapa et al synthesized a series of new 6-ureido-4-anilinoquinazolines\textsuperscript{19} (Fig 15-18) and evaluated their potent activity as antimalarial agents.

A series of 4-Thiophenoxy-2-trichloromethyquinazolines derivatives (Fig 19) were synthesized by Verhaeghe et al\textsuperscript{20} and their antiplasmodial activity against the human malarial parasite Plasmodium falciparum was determined. Compound 21a & 21b showed good activity against K1 Plasmodium falciparum (IC\textsubscript{50} = 1.9\textmu M and 0.9 \textmu M respectively), whereas IC\textsubscript{50} value of chloroquine is 0.5 \textmu M.
Verhaeghe et al Synthesized a new series of 4-aryl 2- trichloromethyl quinazolines\(^{21}\) (Fig 20) and subsequently evaluated their antiplasmodial activity.

**QUINAZOLINE AS ANTIVIRAL AGENTS.**

Schleiss et al evaluated protein kinase inhibitory activity and anti cytomegaloviral activity of the few quinazoline derivatives\(^{22}\) (Fig 21).

**QUINAZOLINE AS ANTI INFLAMMATORY ANALGESICS**

Alafeefy et al synthesized a series of quinazoline derivatives\(^{23}\) (Fig 22) which showed potent analgesic and anti-inflammatory activity.

All the synthesized compounds demonstrated potent activity as anti inflammatory analgesic than the reference compound indomethacin.
QUINAZOLINE AS NEUROPROTECTIVE AGENTS

Kim et al synthesized few quinazoline derivatives\textsuperscript{24} (Fig 23) and evaluated their activity as potent and highly selective PDE5 inhibitors to be employed for male erectile dysfunction.

\[
\begin{align*}
\text{Fig 23} \\
R & R_1 & R_2 \\
23a & C_3H_7 & OCH_3 & NHCOCF_3 \\
23b & CH_2CH_2OH & OCH_3 & NHCOCH_3 \\
23c & CH_2CH_2OH & OCH_3 & NHCOC_2H_5
\end{align*}
\]

QUINAZOLINE AS CNS DEPRESSANT AND ANTICONVULSANT

A series of novel 3-[5-substituted 1, 3, 4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones derivatives (Fig 24) was synthesized by Jatav et al\textsuperscript{25} and evaluated their activity as a CNS depressant agents.

\[
\begin{align*}
\text{Fig 24} \\
R & R_1 \\
24a & C_6H_5 & C_6H_5 \\
24b & 4-Cl-C_6H_4 & C_6H_5 \\
24c & 4-Cl- C_6H_4 & p-OCH_3C_6H_5
\end{align*}
\]

All the compounds showed anticonvulsant activity in MES screen, however, compound 26a showed potency similar to standard drug (phenytoin, carbamazepine) without any neurotoxicity.
A series of some novel 3-[5-substituted 1, 3, 4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-one derivatives (Fig 25) was synthesized by Jatav et al. and evaluated their activity as CNS depressant and anti-convulsant agents.

![Fig 25](image)

Compounds with the above substituents showed potent CNS depressant activity. Compound 25a showed anticonvulsant activity at 0.5 and 4 h in different test models, whereas 25c showed anticonvulsant activity at 4 h in MES screen and at 0.5 and 4 h in sub-cutaneous PTZ screen.

**QUINAZOLINE AS ANTIBACTERIAL AGENTS**

Bedi et al. synthesized a series of quinazolines derivatives (Fig 26) and evaluated their biological activity on various bacterial cultures.

![Fig 26](image)

Compounds (Fig 27) showed comparative activity against K. pneumoniae as compared to ciprofloxacin. Compound 28 exhibited greater activity against S. sonnei, E. faecalis and P. aeruginosa as compared to ciprofloxacin.
Alafeefy et al synthesized a series of some novel substituted iodoquinazoline derivatives (Fig 28) and evaluated their antimicrobial activity.

![Fig 28](image)

**QUINAZOLINE AS ANTI OBESITY AGENTS**

Sasmal et al synthesized a series of quinazoline derivatives (Fig 29) to be considered as an antagonist for melanin concentrating hormone receptor 1 (MCHR1).

![Fig 29](image)

**QUINAZOLINE MARKETED DRUGS**

**PRAZOSIN**

Prazosin is chemically 2-[4-(2-furoyl)piperazin-1-yl]-6,7-dimethoxyquinazolin-4-amine (Fig 30). It is a sympatholytic drug used to treat high blood pressure. It belongs to the class of alpha-adrenergic blockers, which lower blood pressure by relaxing blood vessels. Specifically, prazosin is selective for the alpha-1 receptors on vascular smooth muscle. These receptors are responsible for the vasoconstrictive action of norepinephrine, which would normally raise blood pressure. By blocking these receptors, prazosin reduces blood pressure. It is also known as Minipress, Vasoflex, Pressin and Hypovase.

![Fig 30](image)
GEFITINIB

Gefitinib (Fig 31) also known as Iressa marketed by Astra Zeneca and Teva. It is a drug used in the treatment of certain types of cancer. Gefitinib is an EGFR inhibitor (epidermal growth factor receptor) which interrupts signaling through the epidermal growth factor receptor in target cells. Gefitinib has yet to be proven to be effective in other cancers, there is potential for its use in the treatment of other cancers where EGFR over expression is involved. Applications to expand its label as a first line treatment in patients harbouring EGFR mutations is currently in process based on the latest scientific evidence. Chemically it is N-(3-chloro-4-fluoro-phenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy) quinazolin-4-amine\textsuperscript{31}.

ERLOTINIB

The trade name of Erlotinib (Fig 32) is Tarceva and its chemically known as N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine. It is a drug used to treat non-small cell lung cancer, pancreatic cancer and several other types of cancer. It is a tyrosine kinase inhibitor, which acts on the epidermal growth factor receptor (EGFR). Erlotinib is an EGFR inhibitor. The drug follows Iressa gefitinib, which was the first drug of this type.
Erlotinib specifically targets the epidermal growth factor receptor (EGFR) tyrosine kinase, which is highly expressed and occasionally mutated in various forms of cancer. It binds in a reversible fashion to the adenosine triphosphate (ATP) binding site of the receptor. It is an inhibitor of epidermal growth factor receptor tyrosine kinase.

\[
\begin{align*}
\text{Erlotinib} & \\
\text{Fig 32}
\end{align*}
\]

**ALFUZOSIN**

The trade name of alfuzosin (Fig 33) are UroXatral; Urion; Xatral; Alfetim, chemically known as N-[3-[(4-amino-6,7-dimethoxy-quinazolin-2-yl)-methyl-amino]propyl] tetrahydrofuran -2-carboxamide. It is a \( \alpha \)-1 receptor antagonist used to treat benign prostatic hyperplasia (BPH). It works by relaxing the muscles in the prostate and bladder neck, making it easier to urinate. Alfuzosin should be used with caution in patients with severe renal insufficiency, and should not be prescribed to patients with a known history of QT prolongation who are taking medications known to prolong the QT interval.

\[
\begin{align*}
\text{Alfuzosin} & \\
\text{Fig 33}
\end{align*}
\]

**TRIMETREXATE**

Trimetrexate (Fig 34) chemically known as 5-methyl-6-[(3,4,5-trimethoxyphenyl) aminomethyl] quinazoline-2,4-diamine, is a nonclassical folic acid inhibitor through its
inhibition of the enzyme dihydrofolate reductase. It is being tested for efficacy as an antineoplastic agent and as an antiparasitic agent against pneumocystis pneumonia in AIDS patients. Myelosuppression is its dose-limiting toxic effect. It has been used with leucovorin in treating pneumocystis pneumonia. It has been investigated for use in treating leiomyosarcoma. It is a methotrexate (MTX) analog that is active against transport-deficient MTX-resistant tumor cells that overcome the acquired and natural resistance to methotrexate. Other uses include skin lymphoma 34.

![Trimetrexate](image)

**Trimetrexate**

**BUNAZOSIN**

Bunazosin (Fig 35), trade name is andante, chemically known as 1-(4-(4-amino-6,7-dimethoxyquinazolin-2-yl)-1,4-diazepan-1-yl)butan-1-one, is an alpha-1 antagonist. Bunazosin was initially developed to treat benign prostatic hyperplasia (BPH). It has been approved in Japan in a topical form to treat glaucoma. The mechanism of action is a reduction of aqueous outflow through the uveoscleral pathway resulting in lowering the intraocular pressure. It also may act to improve blood flow to the ocular nerve. Systemic alpha-1 adrenergic receptor antagonists have been implicated in Intraoperative Floppy Iris Syndrome (IFIS). Bunazosin potentially could have the same effect but there has been no research to substantiate this as a risk for cataract surgery 35.

![Bunazosin](image)

**Bunazosin**

Fig 35
VANDETANIB
The trade name of Vandetanib is zactima, (Fig 36) also known as ZD6474, has chemical name N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-amine, it is an antagonist of the vascular endothelial growth factor receptor (VEGFR) and the epidermal growth factor receptor (EGFR). It is a tyrosine kinase inhibitor. Drug has a third target: inhibits RET-tyrosine kinase activity, an important growth driver in certain types of thyroid cancer\textsuperscript{35}. 

![Vandetanib](image)

ANAGRELIDE
Its trade name are Agrylin/Xagrid, Shire, anagrelide (Fig 37), and chemical name is 6,7-dichloro-1,5-dihydroimidazo(2,1-b)quinazolin-2(3H)-one, is a drug used for the treatment of essential thrombocytosis (ET), or overproduction of blood platelets. It also has been used in the treatment of chronic myeloid leukemia. Anagrelide works by inhibiting the maturation of platelets from megakaryocytes. The exact mechanism of action is unclear, although it is known to be a phosphodiesterase inhibitor. It is a potent (IC\textsubscript{50} = 36nM) inhibitor of phosphodiesterase-II. It inhibits PDE-3 and phospholipase A2. According to a 2005 Medical Research Council randomized trial, the combination of hydroxyurea with aspirin is superior to the combination of anagrelide and aspirin for the initial management of ET. The hydroxyurea arm had a lower likelihood of myelofibrosis, arterial thrombosis, and bleeding, but it had a slightly higher rate of venous thrombosis\textsuperscript{36}. 

![Anagrelide](image)
EVODIAMINE

Evodiamine (Fig 38) is chemically known as 21-methyl-3,13,21-triazapentacyclo [11.8.0.02,10.4, 9.015,20] henicosa-2(10),4,6,8,15,17,19-heptaen-14-one. It is extracted from the Evodia spp family of plants which has been shown to reduce fat uptake in mouse studies. Its method is believed to be similar to capsaicin, but retains none of the "hot" taste. This chemical has been known to appear in some bodybuilding over the counter supplements, while neither its fat-burning benefits, nor its potential risks and side effects, have ever been established scientifically or empirically. Evodiamine raises your body's temperature and can inhibit the growth of certain cancer cells. It also manipulates your metabolism when combined with certain drugs and influences the secretion of catecholamines from your adrenal glands.

![Evodiamine](image)

PROQUAZONE

Its trade name is Biarison (Fig 39) is chemically known as 1-isopropyl-7-methyl-4-phenylquinazolin-2(1H)-one. Proquazone is a non-steroidal anti-inflammatory drug.
NOLATREXED
Nolatrexed (Fig 40) has chemical name 2-Amino-6-methyl-5-(4-pyridylthio)-1H-quinazolin-4-one. Nolatrexed is a thymidylate synthase inhibitor\(^{38}\).

![Nolatrexed](Fig 40)

QUINETHAZONE
Its brand name is Hydromox (Fig 41) chemically known as 7-chloro-2-ethyl-4-oxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide. Quinethazone is a thiazide diuretic used to treat hypertension. Common side effects include dizziness, dry mouth, nausea, and low potassium levels\(^{39}\).

![Quinethazone](Fig 41)

ALBACONAZOLE
Albaconazole (UR-9825) (Fig 42) chemically known as 7-chloro-3-[(2R,3R)-3-(2,4-difluorophenyl)-3-hydroxy-4-(1,2,4-triazol-1-yl)butan-2-yl]quinazolin-4-one, is a triazole antifungal. It has potential broad-spectrum antibacterial activity\(^{35}\).

![Albaconazole](Fig 42)
FEBRIFUGINE
Febrifugine (Fig 43) chemically known as 3-{3-[2S,3R]-3-Hydroxypiperidin-2-yl]-2-oxo propyl} quinazolin-4(3H)-one is a quinazolinone alkaloid first isolated from Chinese herb Dichroa febrifuga, but also found in the garden plant Hydrangea. Febrifugine has antimalarial properties and the halogenated derivative halofuginone is used in veterinary medicine as a coccidiostat.\textsuperscript{40}

![Febrifugine](image)

AFLOQUALONE
Its brand name is Arofuto, (Fig 44) chemically known as 6-amino- 2-(fluoromethyl)- 3-(2-methyl phenyl) quinazolin- 4-one. It is an analogue of methaqualone developed in the 1980s in Japan. It has sedative and muscle relaxant effects, and has had some clinical use, although it causes photosensitization as a side effect which can cause skin problems such as dermatitis.\textsuperscript{41}

![Afloqualone](image)

FENQUIZONE
Its brand name is Idrolone, (Fig 45) chemically known as 7-chloro-4-oxo-2-phenyl-1,2,3,4-tetrahydro quinazoline-6-sulfonamide, is a diuretic, part of the class of low-ceiling sulphonamide diuretics. Fenquizone is used primarily in the treatment of treatment of oedema and hypertension.\textsuperscript{35}

![Fenquizone](image)
QUINAZOLINONE
It is also called as quinazolindiones, (Fig 46) chemically known as Quinazolin-4(3H)-one. Chemicals with two conjoined aromatic rings incorporating two nitrogen atoms and one of the carbons oxidized with keto oxygen. Quinazolinone is a heterocyclic chemical compound. There are two structural isomers, 2-quinazolinone and 4-quinazolinone, with the 4- isomer being the more common. Quinazolinones are also a class of drugs which function as hypnotic/sedatives that contain a 4-quinazolinone core. Their use has also been proposed in the treatment of cancer. Examples include afloqualone, cloroqualone, and diproqualone. Alkaloids containing the quinzolinone core include febrifugine and halofuginone42.

![Quinazolinone](image)

Fig 46

QUAZINONE
Its brand name are dozonone, posicor (Fig 47) chemically known as (3R)-6-chloro-3-methyl-5,10- dihydroimidazo[2,1-b]quinazolin-2(3H)-one, it is a cardiotonic and vasodilator drug which was developed and marketed in the 1980s for the treatment of heart disease. It acts as a selective PDE3 inhibitor43.

![Quazinone](image)

Fig 47

QUAZODINE
Its brand name are quazodinum, quazodina (Fig 48) chemically known as 4-ethyl-6,7-dimethoxyquinazoline. The effects of quazodine and theophylline have been studied on the rat hemidiaphragm and chick biventer cervicis preparations in vitro. Theophylline and quazodine enhanced maximal twitches and contractural responses to acetylcholine and carbachol. These actions on contractility were exerted directly upon the muscle fibres and were dependent upon the concentration of calcium ions in the bathing solution. In addition, quazodine enhanced the neuromuscular blocking activity of tubocurarine, probably by a prejunctval action44.
BENZOURACIL
Benzouracil (Fig 49) is chemically known as 2,4(1H,3H)-quinazolinedione. The substituted Benzouracil used in treating or preventing an infection due to a virus from the Flaviridae family by administering to a patient in need there of an effective amount of a quinazoline derivative according to the structural formula\(^3^5\).

TETRODOTOXIN
Tetrodotoxin (Fig 50) also known as "tetrodox" and frequently abbreviated as TTX, sometimes colloquially referred to as "zombie powder" by those who practice Vodou or are of Haitian descent) chemically known as (4R,4aR,5R,6S,7S,8S,8aR,10S,12S)-2-azoniumylidene-4,6,8,12-tetrahydroxy-6-(hydroximethyl)-2,3,4,4a,5,6,7,8-octahydro-1H-8a,10-methano-5,7-epoxymethanoxy) quinazolin-10-olate. It is a potent neurotoxin with no known antidote. There have been successful tests of a possible antidote in mice, but further tests must be carried out to determine efficacy in humans. Tetrodotoxin blocks action potentials in nerves by binding to the voltage-gated, fast sodium channels in nerve cell membranes, essentially preventing any affected nerve cells from firing by blocking the channels used in the process\(^3^5\).
NEWER QUINAZOLINE DERIVATIVES UNDER CLINICAL TRIAL BALAGLITAZONE

Balaglitazone (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. Balaglitazone is a selective partial PPAR-γ agonist. Common side effects associated with PPAR-γ receptor agonists are weight gain, oedema and adipogenesis. Balaglitazone is a selective partial PPAR-γ agonist and it has been speculated that such compounds have a more favourable safety margin than full agonists. Balaglitazone has excellent antidiabetic and hypolipidemic properties.45.

![Balaglitazone](image)

**Fig 51**

AFATINIB

Afatinib, an anilino-quinazoline derivative, chemically is N-[4-[(3-Chloro-4-fluorophenyl) amino]-7-[[(3S)-tetrahydro-3-furanyl]oxy]-6- quinazolinyl]-4-(dimethylamino)-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 antitumour efficacy when compared with agents targeting EGFR alone.46.

![Afatinib](image)

**Afatinib Fig 52**
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

\[
\begin{align*}
\text{N} & \quad \text{NH} \\
\text{F} & \quad \text{Cl} \\
\text{O} & \quad \text{CH}_3 \\
\end{align*}
\]

Pfizer is developing dacomitinib, an orally available selective and irreversible inhibitor of the HER family of kinases, for the treatment of cancer\(^{47}\).

BARASERTIB

Barasertib, chemically is 5-[[7-[3-ethyl[2- (phosphonoxy)ethyl]amino]propoxy]-4 quinazoliny]amino]-N-(3-fluorophenyl)-1Hpyrazole-3-acetamide of following formula

\[
\begin{align*}
\text{N} & \quad \text{NH} \\
\text{F} & \quad \text{O} \\
\text{CH}_3 & \quad \text{P} \\
\text{OH} & \quad \text{OH} \\
\end{align*}
\]

AstraZeneca is developing barasertib (AZD 1152), an aurora kinase inhibitor, for the treatment of acute myeloid leukemia (AML)\(^{48}\).

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\(^{49}\). 
ELINOGEREL

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. 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 stroke47.

SOTRASTURIN

Sotrastaurin chemically is 3-(1H-indol-3-yl)-4-[2- (4-methyl-1-piperazinyl)-4-quinazolinyl]-1Hpyrrole-2,5-dione of following formula. 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 immunosuppressive agent ciclosporin50.
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. 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 tumors47.

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. 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\(^5\).

![Letermovir](image)

**Letermovir**

Fig 59

**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. 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\(^4\).

![Milciclib](image)

**Milciclib**

Fig 60
TANDUTINIB
Tandutinib chemically is 4-[6-methoxy-7-[3-(1-piperidinyl)propoxy]-4-quinazolinyl] -N-[4-(1-methylethoxy)phenyl]-1-piperazinecarboxamide of following formula. 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 II studies for relapsed or refractory AML.

![Tandutinib](image)

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. 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, Prinnoxodan, Saracatinib, Tiacrilast and Zenarestat.

![Varlitinib](image)
VERUBULIN

Verubulin chemically is N-(4-methoxyphenyl)-N,N-dimethyl-4-quinazolinamine of following formula[41]. 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-arylamino quinazoline 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[50].

CONCLUSION

The above illustrations include various structural modifications around the fused ring, quinazoline and subsequently evaluate their usefulness in treating various disease conditions. Quinazoline, being the central body of the pharmacophore holds different types of substituent. Based on their various physicochemical properties, they exerted a diversified range of therapeutic efficacy.
This review has outlined the chemistry and biological activities of the quinazoline nucleus. The synthetic methodologies indicate the simplicity, maneuverability and versatility, which offer the medicinal chemist a complete range of novel derivatives. Given the advances in synthetic methodology and technology in recent years and the continued interest in the quinazoline skeleton in medicinal chemistry and drug development, the development of efficient and reliable methods for the construction of these molecules will ensure that this is an active and important area of research in heterocyclic chemistry. The high degree of protection against seizures can be positive signs for further investigation of quinazoline derivatives as anticonvulsants. The activity of quinazoline as antitubercular compounds in multi-drug resistant tuberculosis and their potent anthelmintic activity are promising. The broad spectrum antibacterial and antifungal activity of these compounds could lead to a new series of antimicrobials. The quinazoline derivatives have demonstrated significant antiviral and anticancer activities. The enzymes and receptor agonist or antagonist action of these derivatives furthers their biological importance.

Thus quinazoline is not only synthetically important but also possesses a wide range of promising biological activities. Future investigations of this study could give some more encouraging results. The review is self explanatory about the clinical therapeutic potential of quinazoline and its derivatives. As on date, about 26 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. Thus we can conclude that this review will definitely provide the researchers a thorough understanding of the structure activity relationship study, which further help in designing good many number of quinazoline compounds with a strong impact in curing many fatal disorders.

REFERENCES


