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REVIEW ARTICLE

A review: Recent investigations on Quinazoline Scaffold

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Abstract

The aim of this review is to endow with an outline of assorted pharmacological activities of quinazoline moiety. Quinazoline have drawn an enormous consideration owing to their extended applications in the area of medicinal chemistry. It has become a fashionable subject up of two fused six-membered aromatic ring system, a benzene ring and a pyrimidine ring due to its assorted uses. It is showed for its different Pharmacological activities and compounds with diverse substitutions convey together to acquaintance of a target with considerate of the molecule types that might interact with the target receptor. Quinazolines are a huge type of pharmacologically active compounds that showed a broad spectrum of pharmacological activities such as anticancer, anticonvulsant, anti-inflammatory, anti-microbial, antimalarial, anti-HIV, antioxidant, antifungal, antibacterial, anti-mutagenic, anti-depressant, anti-leishmanial, anti-leukemic activities. The aim of this review is to assemble literature work showed by researchers on Quinazoline for their diverse pharmacological activities and also reported current efforts made on this molecule.

INTRODUCTION

Quinazolines are classes of fused heterocycles that are of considerable interest because of their diverse pharmacological profile.[1] Quinazoline attract the scientists since 1888, with the discovery of the first natural representative of them - (+)-peganine (vasicine).[2] Quinazoline has become a well-liked topic up of two fused six-membered simple aromatic system, a pyrimidine ring and a benzene ring due to its manifold uses.

Numerous quinazoline moieties have been found to possess a broad spectrum of pharmacological activities, which encouraged the research activity in this area. Many substituted quinazoline derivatives possess an extensive range of biological activity such as anticancer, antimalarial, anticonvulsant, antiviral, antifungal, anti-protozoan, antimicrobial, anti-inflammatory, diuretic, muscle relaxant, antidepressant, anti-tubercular, acaricidal, weedicide, and many other pharmacological activities.[3-5] Quinazoline compounds are also used in preparation of a variety of functional materials for synthetic medicinal chemistry and also present in many drugs molecules. This review is a challenge to make bigger the huge potentiality and determined on the various pharmacological activities of quinazolines.[6] One of derivative of quinazoline is quinazolinone which is active like quinazoline. Quinazolinones will be classified into the subsequent five categories, based on the substitution patterns of the ring system.[7] (a) 2-Substituted-4(3H)-quinazolinones (b) 3-Substituted-4(3H)-quinazolinones (c) 4-Substituted-quinazolines (d) 2, 3-

disubstituted-4(3H)-quinazolinones (e) 2,4-disubstituted -4(3H)-quinazolinones. Depending upon the arrangement of the oxo or keto group, these lead compounds may be categories into three forms of which (**2**) 4(3H)-quinazolinones are most prevalent, either as intermediates or as natural products in many proposed biosynthetic pathways.[8]

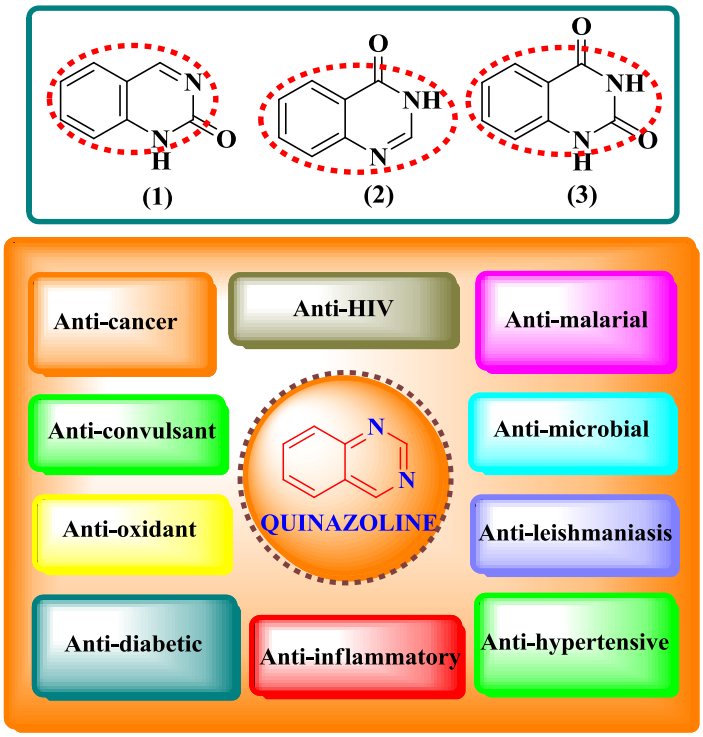


Fig.1: Biological profile of quinazoline scaffold.

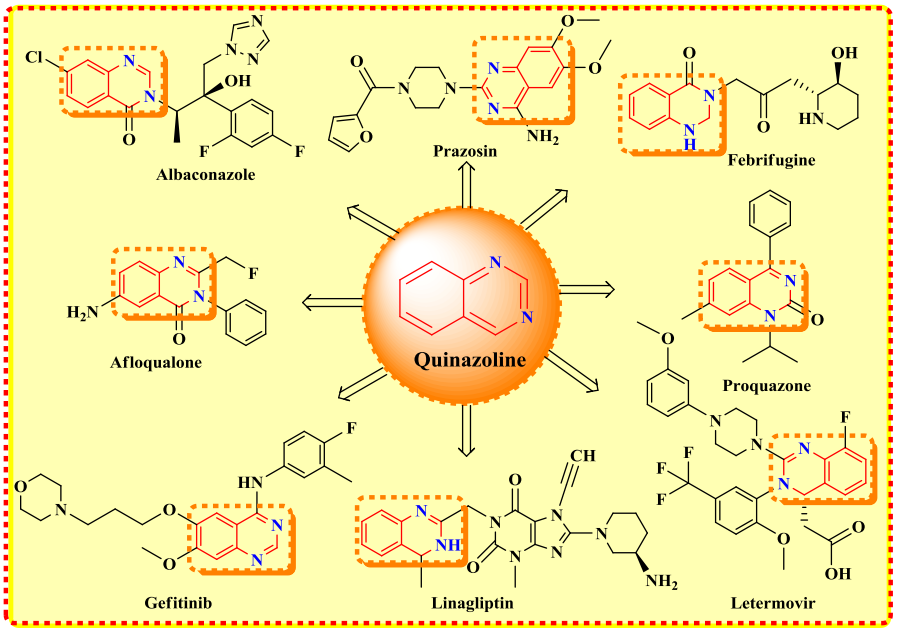


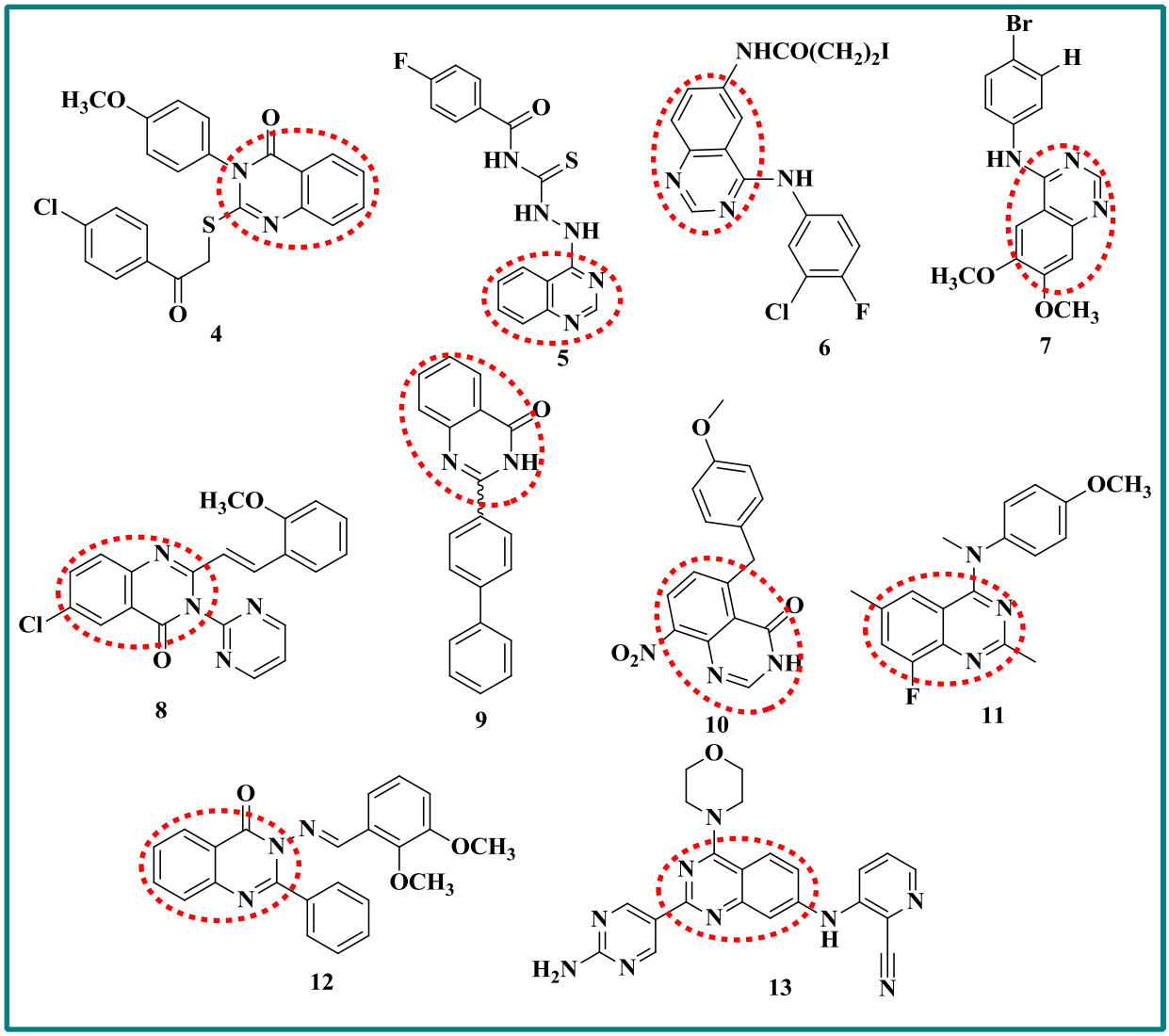
Fig.2: Marketed drugs containing quinazoline nucleus.

Biological Importance of Quinazoline Scaffold:

Quinazoline as Anticancer

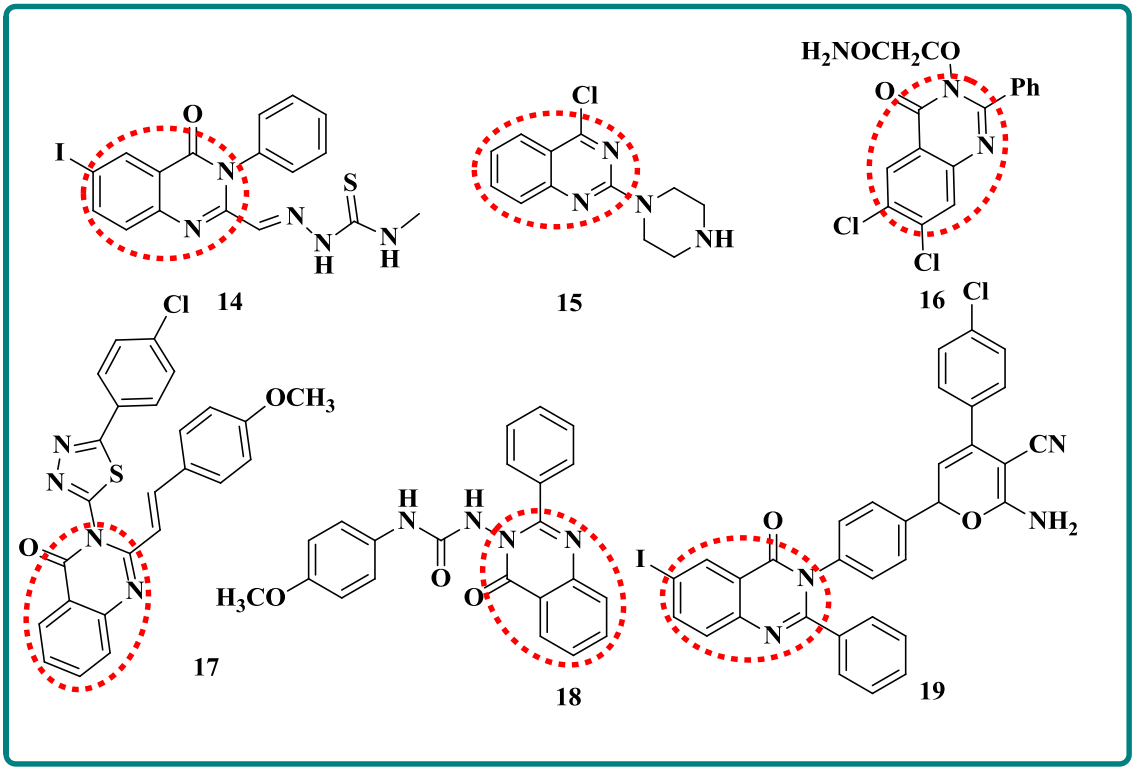
A major healthiness difficulty which concerns the medical society is cancer disease in all over the world. The extensive progress in diverse aspects of cancer research occurs in researcher, cancer chemotherapy is highly insufficient.[9] Abdel Gawad *et al.*(2010), synthesized the quinazolin-4(3H)-one containing derivatives comprise an

consider able class along with heterocyclic compounds industrial interest, technological and medical. various new 3-substituted quinazolin-4(3H)-ones and 3,4-dihydro-quinazolin-2(1H)-one derivatives are showed that compounds 2-[2-(4-chlorophenyl)-2-oxo-ethylthio]-3-(4-methoxyphenyl) quinazolin-4(3H) one and 3-(4-chlorophenyl)-2-[2(4-methoxyphenyl)-2-oxo-ethylthio] quinazolin-4(3H)-one**(4)** as broad-spectrum anti-tumor show effectiveness toward numerous cell lines that belong to different tumor subpanels.[10]A series of novel quinazoline derivatives**(5)** containing thiosemicarbazide moiety and evaluate their biological activity as antitumor agents by He *et al.* (2012).[11] The therapeutically important candidates are shown in structure. Fernandes *et al.* (2007) a series of quinazoline derivatives **(6)** were evaluated for their function as EGFR inhibitors by applying radio iodination. All these compounds were further evaluated for potential SPECT activity for molecular imaging of breast cancer.[12] Noolvi *et al.* (2013) synthesized a series of quinazoline derivatives **(7)** were evaluated for their biological activity against tyrosine kinase (EGFR).[13] The 3-(3-methylisoxazol-5-yl) and 3-(pyrimidin2-yl)-2 styrylquinazolin-4(3H)-ones **(8)** were prepared by refluxing in acetic acid the corresponding 2-methylquinazolinones with the benzoic aldehyde and tested for their in vitro anti-leukemic activity against L-1210 (murine leukaemia), K-562 (human chronic myelogenous leukemia), and HL-60 (human leukemia) cell lines showing in some cases good activity by Raffa *et al.* (2004).[14] In 2008, Chinigo and co-workers synthesized 2,3-dihydro-2-arylquinazolin-4-ones **(9)** and found to possess potent fluorescent tubulin inhibition with anticancer activity. In 2010, Tian and co-workers synthesized a series of 5, 8 disubstituted quinazolines **(10)** and they were found to possess antitumor activity. In 2010, Sirisoma and co-workers synthesized N-methyl-4-(4-methoxy anilino) quinazolines **(11)** and reported that these compounds induced apoptosis. Krishnan *et al.*(2011) synthesized a series of 3-(benzylideneamino)-2-phenyl quinazoline-4(3H)-ones **(12)** by reaction of 3-amino-2-phenyl-3H-quinazoline-4-one with various carbonyls compounds and investigated cytotoxic activity.[15] In this study, a series of novel 7 or 8-substituted 4-morpholine-quinazoline derivatives **(13)** was designed and synthesized. Their PI3Kα inhibitory activities, anti-proliferative activities against seven cancer cell lines, namely, PC-3, DU145, MCF-7, BT474, SK-BR-3, U937 and A431, were evaluated in vitro by Tu *et al*.(2015). Most active compound proved to be a potential drug candidate with high PI3Kα inhibition activity (IC = 4.2 μM) and good anti-proliferative activity. Active compound was also tested for its inhibitory activities against other kinases, such as PI3Kβ, PI3Kγ, PI3Kδ and mTOR, its effects on p-Akt (S473) and cell cycle. These results suggested that compound could significantly inhibit the PI3K/Akt/mTOR pathway as a potent PI3K inhibitor and anticancer agent.[16]



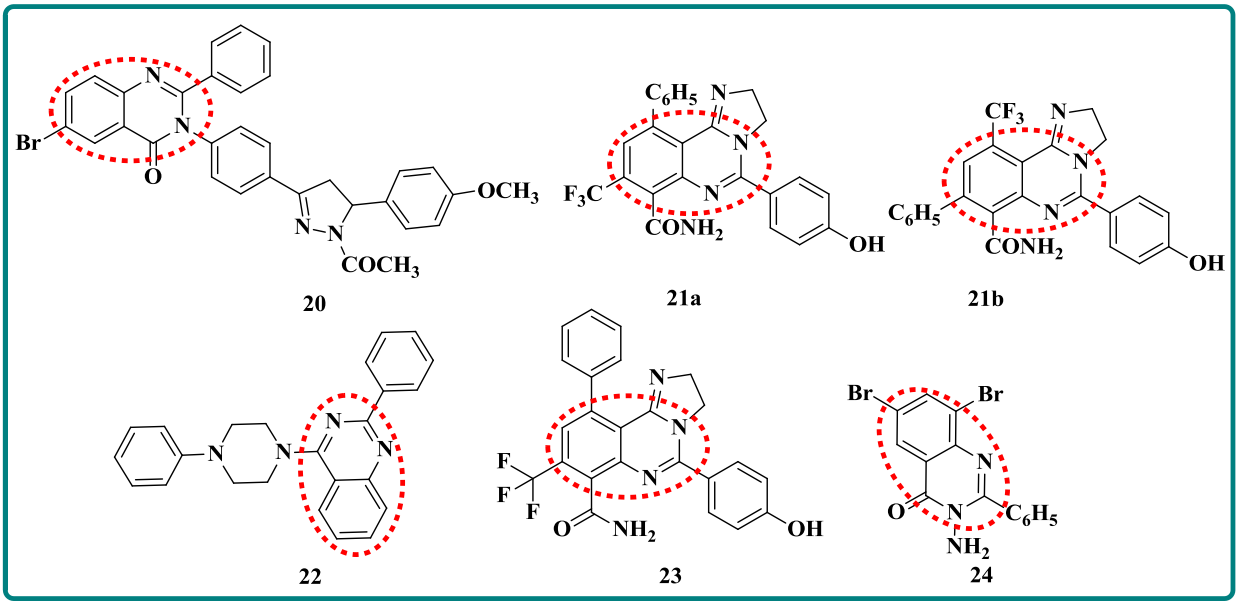
Quinazoline as Anticonvulsant

Epilepsy is a universal neurological condition, upsetting 0.5-1% of the people globally (45-100 million population). Epilepsy is a relations of neurologic disorders, if not treated, is connected with gradually function and impaired cognition brain damage and other neurologic deficits. In several cases, patients with epilepsy can preserve a normal and uninterrupted life because of antiepileptic drugs (AEDs), the most important continue for epilepsy management, can provide agreeable control or total relief of seizures.[17] Aly *et al.* (2010) synthesized a novel compound 3-aryl-4(3H)-quinazolinone-2 carboxaldehydes **(14)** their corresponding Schiff's base and thio-semicarbazone derivatives and reported compounds as anticonvulsants.[18] Mukhergee *et al.* (2014).[19] synthesized 2, 4-dichloroquinazoline **(15)** and the compound was reacted with different N-substituted piperazines to obtain a series of title compounds [6(A-G)]. All the new title compounds were characterized by spectral data and were screened for Anticonvulsant activity. Ibrahim *et al.*(1998) synthesized a series of 3-substituted-6,8-dichloro-2-phenyl-4(3H)-quinazolines **(16)** andstudied their anticonvulsant activity. These compounds were found to possess good anticonvulsant activity.[20] Jatav *et al.*(2008) prepared a series of novel 3-[5-substituted 1, 3, 4-thiadiazole-2-yl]-2styryl quinazoline-4(3H)-ones derivatives **(17)** were evaluated for their activity as antidepressant agents.[21] Several 1-(4-substitutedphenyl)-3-(4-oxo-2-phenyl/ethyl4H-quinazolin-3-yl)-urea derivatives **(18)** were screened for their anticonvulsant activity by MES and scPTZ-induced seizure models in mice and found that these compounds **(19)** were active in the MES screen whereas some compounds were found to be active in the scPTZ screen by Kashaw *et al.*(2009).[22]



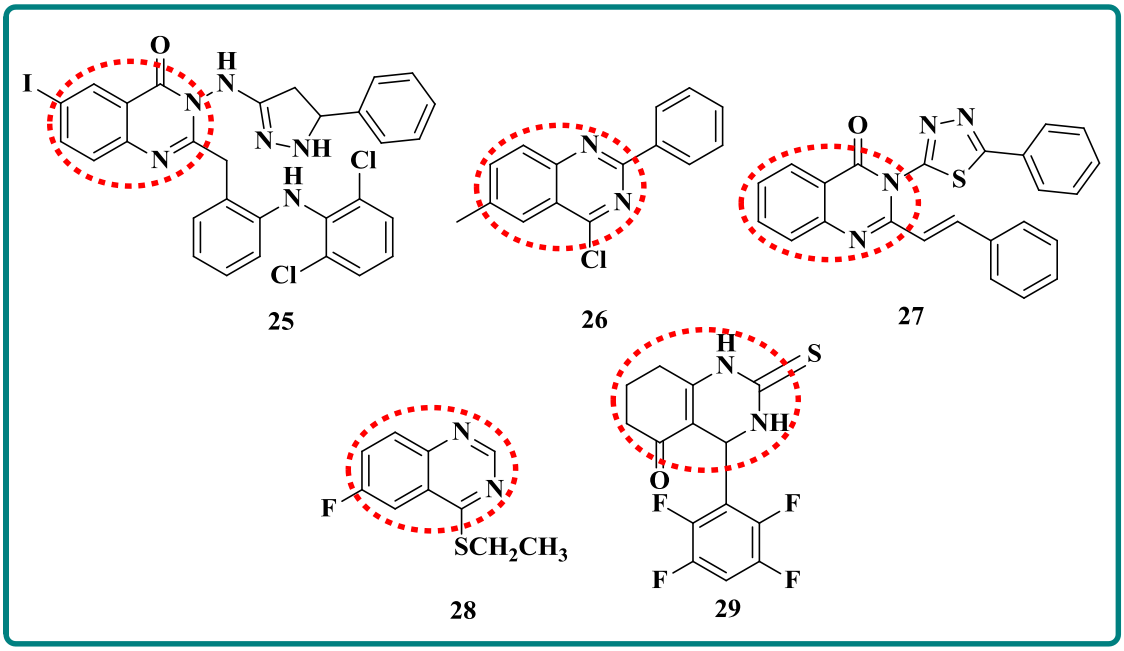
Quinazoline as Anti-inflammatory and Analgesic

Non-steroidal anti-inflammatory drugs (NSAIDs) such as acetylsalicylic acid (ASA) became healthy recognized in the management of inflammation and pain. Cycloxygenase (COX) is the essential enzyme in prostaglandin biosynthesis. It exists in 2 forms, constitutive COX-1 (responsible for physiological functions) and inducible COX-2 (involved in inflammation). Inhibition COX described both the beneficial effects (inhibition of COX-2) and adverse effects (inhibition of COX-1) of non-steroidal anti-inflammatory drugs (NSAIDs).[23] Two series of 2-phenyl-4(3H) quinazolinone derivatives **(20)** have been synthesized by Mohamed *et al*. Most of the tested quinazolinone derivatives showed considerable potent anti-inflammatory and analgesic activity of superior GIT safety profile in experimental rats in comparing to indomethacin as reference drug. Some compounds were the most potent anti-inflammatory in experimental rats in comparing to indomethacin as reference drug.[24] Baja kumar *et al.* (2010) synthesized a series of novel 8/10 trifluoromethyl-substituted-imidazo [1, 2-c] quinazolines **(21)** and evaluated *in vivo* (rat paw edema) for their anti-inflammatory activity and *in silico* (docking studies) to recognize the hypothetical binding motif with the Cycloxygenase enzymes (COX-1 and COX-2) employing GOLD (CCDC, 4.0.1 version) software and found that compounds shows good anti-inflammatory activity against standard: indomethacin.[25] Alafeefy *et al*.(2010) synthesized quinazoline derivatives **(22)** showed potent analgesic and anti-inflammatory activity. All these compounds demonstrated potent activity as anti-inflammatory analgesic more than the reference compound indomethacin.[26] Hemlatha *et al*.(2011) synthesized a series of some novel 2, 3-disubstituted quinazolinone derivatives **(23)** by condensing 2-methyl/ 2-phenyl/6-bromo-2-methyl/6-bromo-2-phenyl/6, 8-dibromo-2-methyl/ 6, 8-dibromo-2-phenyl benzoxazines with compounds containing amino group were confirmed by IR, C-NMR and Mass spectral data and evaluated for their analgesic activity and they reported that compound **(24)** show promising analgesic activity compared to standard drug diclofenac sodium.[27]



Quinazoline as Antimicrobial

The quantity of life-threatening infectious diseases caused by multidrug-resistant bacteria has reached and shocking level in many countries more or less the world. Currently, the Severe Acute Respiratory Syndrome (SARS) caused by the novel corona virus SARS-CoV and bird flu caused by avian influenza (H5N1) virus, have emerged as two important contagious diseases with epidemic prospective. Both infections crossed the species hurdle to transmit a disease to humans.[28] Patel *et al* (2011) synthesized a new series of new 2-[2-(2,6-dichlorophenyl) amino] phenyl methyl-3-[(5-substitutedphenyl)1,5-dihydro H-pyrazol-3-yl-amino]-6-iodoquinazolin-4(3H) ones **(25)** by adding of 2-[2-(2,6-dichlorophenyl)amino] phenyl methyl-3-1substituted phenyl acryl amido-6-iodoquinazolin-4(3H)-ones with hydrazine hydrate in the presence of glacial acetic acid. The synthesized compounds were tested for their antibacterial activity in vitro by measuring zone of inhibition in mm by cup-plate method against different strains like two Gram positive bacteria viz. Staphylcoccus aureus, Bacillus subtilis and two Gram negative bacteria viz. Escherichia coli, Certium at two different concentration 100 µg/mL and 50 µg /mL.[29] Gautam *et al*.(2012) synthesized some novel 4, 6-disubstituted derivatives **(26)** and evaluated their antimicrobial activity starting from anthracitic acid derivatives through conventional methods. Initially acylation followed by cyclisation to obtain benz-oxazinones which on further treatment with ammonia yielded the crucial intermediate, 2-substited, benzamide then product were subsequently cyclised to obtain quinazoline, chlorinated then hook to have various 4,6-disubstituted quinazoline derivatives.[30] Jatav *et al.(*2008) prepare 3-[5-(4-substituted phenyl)-1,3,4-thiadiazole-2yl]-2-styryl quinazoline-4(3H)-ones **(27)** reported their antibacterial and antifungal activity.[31] All of these compounds exhibited good antifungal activity, especially compound, having a wide spectrum of values ranging from 8.3 to 64.2 μg/mL. bioactivity; it shows potent inhibitory activity on the growth of most of the fungi with EC_{50} values ranging from 8.3 to 46.2 µg/ml. Octahydroquinazoline **(28)** was obtained by a modification of the Biginelli reaction with phenacyl bromide and bromomalononitrile to furnish thiazolo [2,3-b] quinazoline and they found the interaction of compound with formamide, formic acid, and phenyl isothiocyanate yielded the corresponding pyrimidine thiazolo [2,3-b] quinazolines**(29)** and exhibited antifungal activity against Candida albicans by Ghorab *et al*.(2000).[32]



Quinazoline as Anti-malarial

Malaria is the most excellent known protozoal disease. Malaria infects 300-600 million individuals and kills about three million in a year. While the most potent general weapon against malaria would be a lifelong vaccine, the failure of various vaccine developments indicates that extremely active vaccine is extended way from certainty. The rising incidence of multiple drug resistant strains in generally malaria prevalent field has extensively cheap the efficacy of recent anti-malarial drugs for prophylaxis and management of this ailment. Therefore, therapeutic agents based on new mode of action are mandatory to overcome the coming out of resistance and to manage an ever-increasing figure of epidemics caused by the malaria parasite.[33] Mohammed *et al.*(2015) worked six 3-aryl-2-(substituted styryl)-4(3H)-quinazolinones derivatives **(30)** were synthesized by the reaction of 3-aryl-2-methyl-4(3H)-quinazolinone(intermediate products) with different substituted aromatic aldehydes. Their structures were confirmed using IR, HNMR, CNMR spectroscopic methods and elemental microanalyses. The synthesized compounds were evaluated for their *in vivo* anti-malarial activity against P. berghei. Four of the synthesized compounds exhibited activity against the parasite. Among these one compound was found to be the most active compound. Results of acute toxicity study showed that oral administration of the synthesized compounds in single doses (100, 250 and 500 mg/kg) had no adverse effects, indicating that the compounds have high safety margin and their LD50 is higher than 500 mg/kg. In general this study indicates that 4(3H)-quinazolinones derivatives are potential sources of lead compounds for anti-malarial drugs.[34] Sen *et al.*[35] (2010) synthesized a series of 2-substituted and 2,3-substituted quinazolin-4(3H)-one derivatives **(31)** based on the structure of febrifugine. The *in vivo* biological activity test results indicated that those compounds exhibited antimalarial activities by Werbel *et al.* (1987) against Plasmodium berghei in mice, at a dose of 5 mg/kg. Compared to Chloroquine and Artemisinin, these compounds have the advantages of shorter synthetic routes and consequently are highly cost effective in nature. Werbel *et al.* (1987) synthesized a variety of analogues of 2, 4-diamino-6-[(aryl) thio] quinazolines **(32)** with known anti-malarial properties wherein the 4-amino group was replaced by hydrazino and hydroxyamino moieties and they found that such changes reduce markedly the anti-malarial properties of this series. The compound was tested against a normal drug-sensitive strain of Plasmodium berghei in mice by the parenteral route.[36]

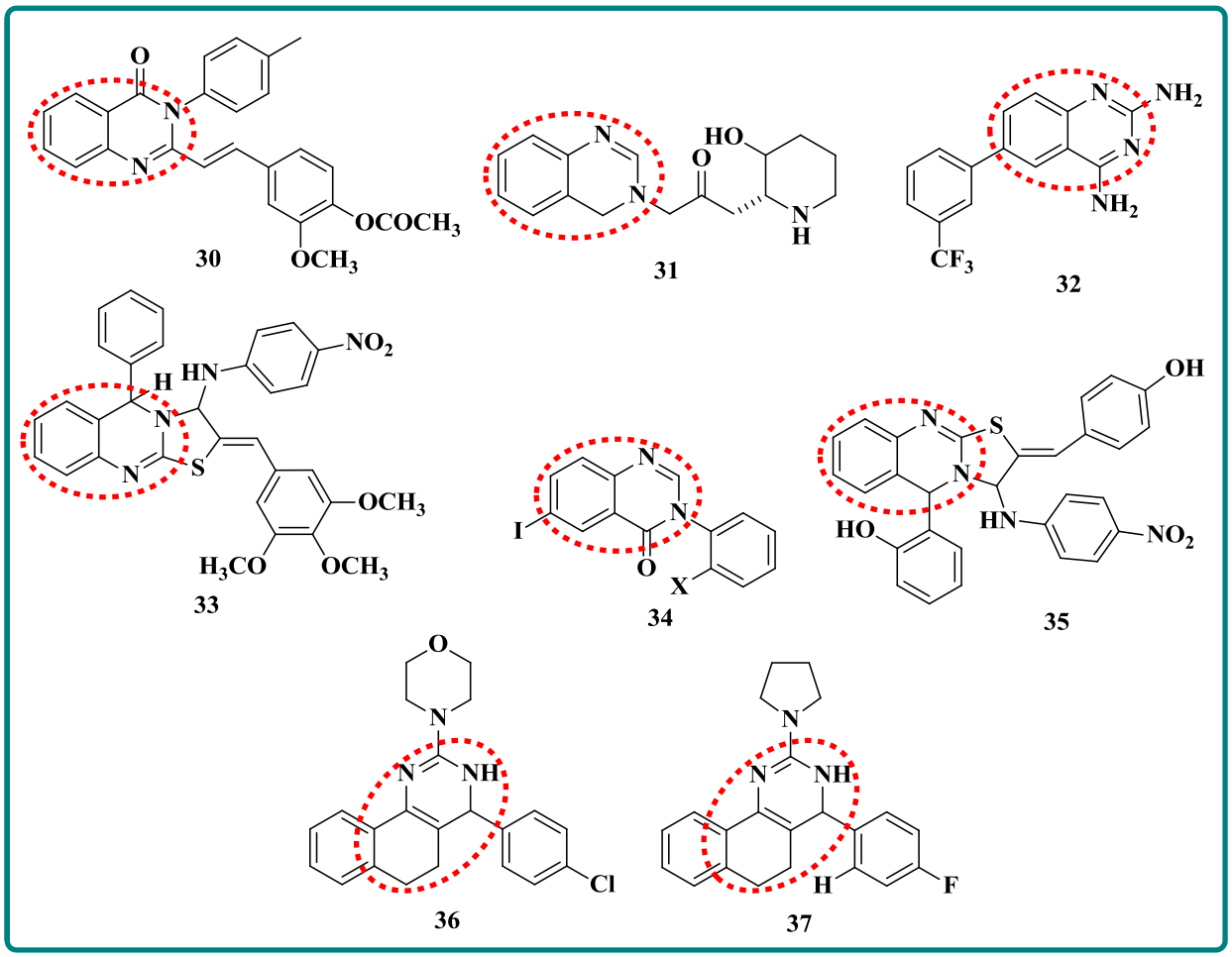
Quinazoline as Anti-oxidant

Selvam *et al.* (2010), synthesized a series of novel thiazolo quinazoline derivatives**(33)** by condensation of different aromatic aldehydes with 4-nitro aniline and chemical structures of the synthesized compounds were confirmed by means of IR, H-NMR, mass spectroscopy and elemental analyses and screened for antioxidant activity by DPPH radical assay, nitric oxide scavenging activity and Hydrogen Peroxide scavenging activity and reported that synthesized compound was found to be the most potent anti-oxidant activity.[37] Al-Omar *et al.* 2006[38] synthesized a new series of 6-iodo-2-propyl-4(3H)-quinazolinone **(34)** and its fused heterocyclic and screened for their

antioxidant activity. Selvam *et al.*(2010) synthesized by some compounds inhibited aldehyde oxidase exclusively by more than 98%. A series of novel thiazolo quinazoline derivatives **(35)** by condensation of different aromatic aldehydes with 4-nitro aniline are screened for antioxidant activity by DPPH radical assay, nitric oxide scavenging activity, and hydrogen peroxide scavenging activity and reported that synthesized compounds were found to be the most potent antioxidant activity.[39]

Quinazoline as Anti-leishmanial

Sinha *et al.* (2013) synthesized a novel series of compounds 4-(substituted benzyl dine)-2-substituted-3,4,5,6-tetrahydrobenzo[h]quinazolinefrom2-(substituted-benzyl dine)tetralone-1 **(36)** and several substituted guanidine sulphates are evaluated for their *in vitro* anti-leishmanial activity and they reported that compounds show promising anti-leishmanial activity against Leishmania donovani.[40] Agarwal *et al.* (2009) synthesized 4-(Substituted-benzylidine)-2-substituted-5, 6 dihydrobenzo[h]quinazoline and 4-(substituted benzylidine)-2-substituted-3, 4, 5, 6 tetrahydrobenzo[h]quinazoline **(37)** from 2-(substituted-benzylidine) tetralone-1 and several substituted guanidine sulfates and evaluated for their *in vitro* anti-leishmanial activity and they reported that compounds show promising anti-leishmanial activity against Leishmania donovani.[41]

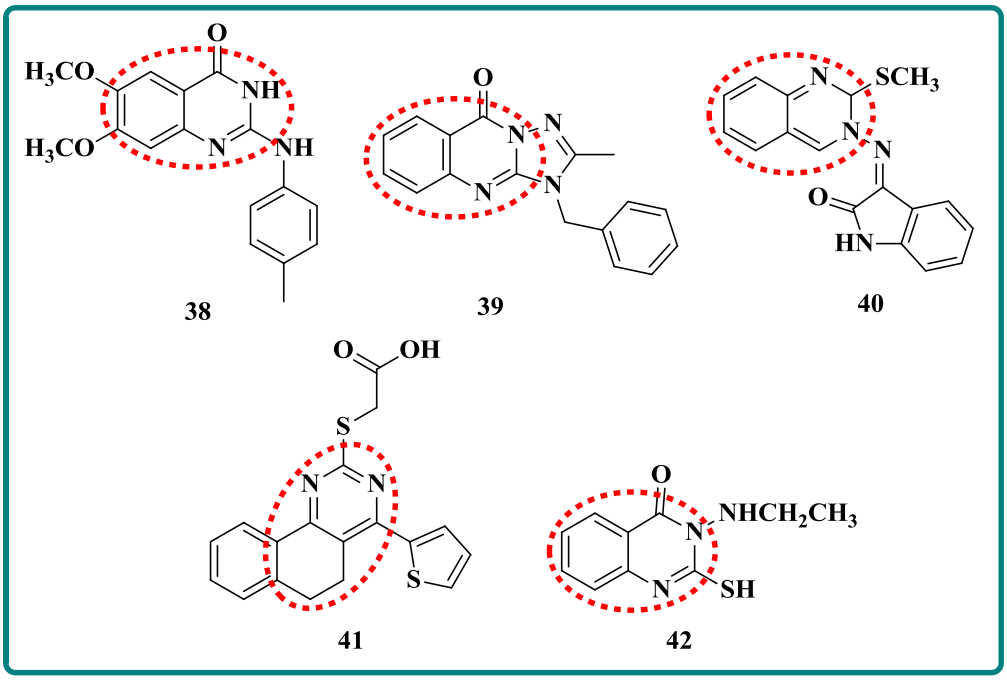


Quinazoline as Antihypertensive

Patel *et al.*(2013)[42] synthesized a new Quinazoline derivatives **(38)** by three steps and screened for α1-adrenergic receptor blocking activity. Alagarsamy *et al.(*2007) prepapred a new series of 3-benzyl-2 substituted-3H-[1,2 ,4]triazolo[5,1-b]quinazolin-9-ones **(39)** by the cyclocondensation of 3-amino-2-benzylamino-3H-quinazolin-4-one. The compounds were evaluated for their *in vivo* antihypertensive activity. All the test compounds exhibited significant antihypertensive activity.The compound 3-benzyl-2-methyl-3H-[1, 2,4]triazolo[5,1-b] quinazolin-9-one exhibited antihypertensive activity more than the reference drug prazocine.[43]

Quinazoline as Anti HIV

Pandeya *et al*. (1999) synthesize a new quinazolinones which shows that Anti-HIV activity where compounds 3-amino-2-methyl mercaptoquinazolin-4(3H)-one **(40)** was synthesized by condensing the acidic amino group of isatin with formaldehyde and secondary amines and evaluated for anti-HIV activity against HIV-1 III B in MT-4 cells.[44] Yahia *et al.*(2012)[45] synthesized a series of dihydrobenzo[h]quinazoline derivatives (**41)** using aryl ethylenethiopyrimidine and 2-(4-(thiophen-2-yl)-5,6-dihydrobenzo[h]quinazolin-2-ylthio) acetic acid as a starting materials. The biological screening showed that many of these compounds have good anticancer and antiviral activities. In the year (2004), anti-HIV activities of some novel 2,3- substituted quinazolin-4(3 H)-ones were reported by Agarsamy *et al.*, synthesized the compound 2-mercapto-3-[(benzimidazol-1--methylamine]-quinazolin-4-(3H)-one **(42)** exhibited maximum 31% and 25% protection respectively against HIV-1. Here, 2-mercapto-3-[(pyridine-2-yl)-methylamino]-inazolin-4-(3H)-one showed 27% protection against HIV-2.



Conclusion:

Quinazoline rings have been most frequently studied; the diverse structural modifications around the fused ring system of quinazoline subsequently estimate it for their effectiveness in treating different pathophysiological conditions. Quinazoline, being the vital body of the pharmacophore, hold various types of substituents. On the basis of diverse literature survey quinazoline moiety show various biological activities. Thus, we can conclude that this work will absolutely endow with diverse, current novel drugs discovery and developments for improved efficacy and less toxicity.

Conflict of interest

The authors confirm that this article content has no conflicts of interest.

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