

## A Review on Quinazolines as Anticancer Agents

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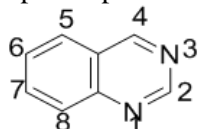
### ABSTRACT

Cancerous growth is the major causes of worldwide human mortality. A large number of antineoplastic drugs are existed in the market and most of the compounds are under clinical trials. Different studies revealed that these antineoplastic drugs have shown the various types of side effects, therefore researchers around the world are engaged in the designing of more efficient and novel antineoplastic drugs. In present years, Quinazoline and its derivatives have been considered as a novel class of neoplastic chemotherapeutic agents that shows of activity against different tumors. Due to the vast knowledge about cancer mechanisms there is a greater interest in discovering novel therapeutic agents. Quinazoline is one of the most interesting novel bioactive compounds amongst all the heterocyclic compounds. A number of research/ review papers present in the literature pertaining to the designing and development of Novel Quinazoline derivatives for cancer chemotherapy. Quinazoline derivatives have been found to possess antineoplastic activity which further encourages the research in this field.

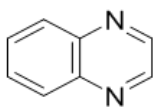
**KEY WORDS:** Quinazoline moiety, anticancer activity.

### 1. INTRODUCTION

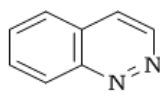
The practice of medicinal chemistry is dedicated to the development and discovery of novel agents for treating diseases (Usifoh and Scriba, 2000; Archana, 2002). Heterocyclic compounds occupy about 50% of the organic compounds. A variety of the medicinal compounds contains heterocyclic ring system. From the current medicinal chemistry investigation it was observed that quinazoline is one such important heterocyclic system has been gained importance due to the broad range of biological activities. Universally to mean the 1,3-benzodiazine ring system the name quinazoline (I) is used nowadays (Archana, 2002). Widdige was first proposed the name quinazoline (German chinazolin) in 1887 at the University of Leipzig. He found that his derivatives were isomeric with the known quinoxaline (II) and cinnoline (III) derivatives. In 1869 Peter Griess indicated his compound by the word bicyanoamidobenzoyl presently known as 2-cyano-4-quinazolinone (IV). Peter Griess was the first person who reported a compound possessing the quinazoline nucleus.



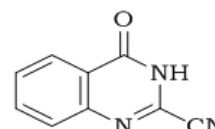
Quinazoline (I)



Quinoxaline (II)



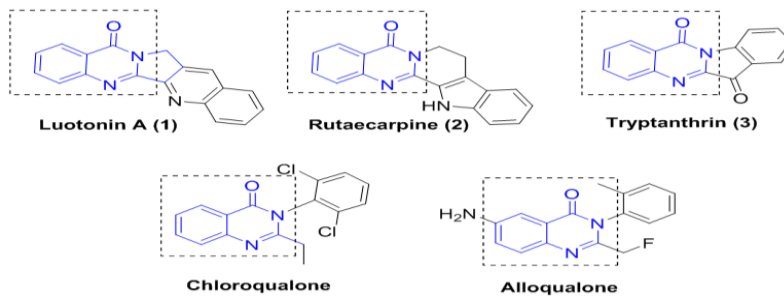
Cinnoline (III)



2-Cyano-4-quinazolinone (IV)

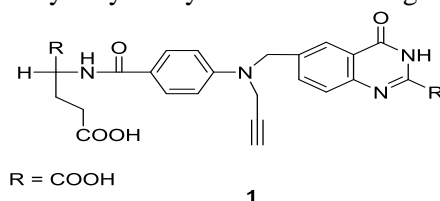
Following the discovery of quinazoline ring a number of structural modifications have been made sequentially to raise the biological activities such as anticonvulsant, antibacterial, antitubercular, antihistaminic, analgesic, antifungal, and anti-inflammatory activity which attracted the interest of medicinal chemists. The drug discovery has played an important role in development of newer and safer anticancer agents that have a broader spectrum of cytotoxicity to tumor cells. Therefore, new therapeutic targets have been reported such that the antitumor efficacy of chemotherapeutic agents correlated with their growth-inhibiting, differentiation-inducing or apoptosis-inducing abilities (Usifoh and Scriba, 2000). In recent years, interest in the development of new anticancer drugs increased mainly from emerging resistance against drugs. Several anticancer targets have been investigated for the development of structurally new drugs, which were found to have limitations, with issues related to their side effects and development of acquired drug resistance. However, the knowledge of tumor biology has exploded during the past decades and this may pave the way for more active, targeted anticancer drugs, some of which are in clinical trials and in the market (Archana, 2002). The development of potential drugs have efficiently improved therapeutic index and tumor growth inhibition. The aim of most cancer chemotherapeutic drugs currently in clinical use is to kill malignant tumor cells by inhibiting some of the mechanisms implied in cellular division. Early approaches to selectively inhibit tumor growth were generally disappointing in clinical studies. The investigation of tumor growth inhibitors is a major obstacle in the medical field (Archana, 2002). Alkaloids are one of the attractive natural products leading to medicinal drug development. Indeed, many alkaloids and their synthetic derivatives are widely used as clinical medicines. Among them, the natural products containing quinazolinone nucleus (luotonin, rutaecarpine, tryptanthrin, chloroqualone, alloqualone) represent the medicinally and pharmaceutically important class of compounds (Papoulis, 1999; Raffa, 1999), because of their diverse range of biological activities such as anti-cancer, diuretic, anti-inflammatory, anti-convulsant and anti-hypertensive (Spirkova, 1999; Hour, 2000; Lipunova, 2000; Sherbeny, 2000). In recent years, some quinazolinone embedded numerous natural products have been identified

(Wang, 2000; Lehner, 2000; El-Hiti, 2002; Forsch, 2002; Murgan, 2003). The cytotoxic alkaloid luotonin A and its derivatives infused with quinazolinone moiety are clinically proven anti-cancer agents (Usifoh and Scriba, 2000). Quinazolinone derivatives, the privileged structures in the field of medicinal chemistry not only act as good anticancer agents but also act as good DNA intercalates [1-2]. To estimate the possible intercalating ability of newly synthesized compounds molecular docking studies were performed. A thorough literature review is depicted herein for quinazolinone ring.

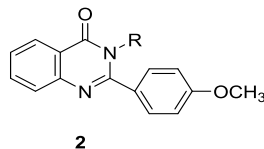


**Figure.1. Quinazolinone scaffold containing natural products**

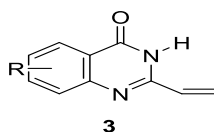
**Anticancer Activity:** In 1975 Robba, synthesized few novel 4-oxo quinazolyl-*L*-glutamic acid (1) & its analogs. These compounds were studied for their thymidylate synthetase inhibiting effects.



Hayashi, in 1978 reported the synthesis of *N*-heterocyclic compounds possessing the cyclic hydrazide structure (2) and evaluated its antitumor activity. Antitumor activity of synthesized compounds was done by total packed cell volume method in mouse.



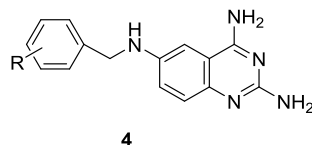
Design of 2-ethenyl and 2-(2'-haloethyl) substituted quinazolinones (3) as alkylating agents were reported by Dempcy, in 1992. The synthesized compounds were studied for mechanistic and purine nucleoside phosphorylase (PNPase) inhibition studies.



In 1993, Boyle, synthesized few novel 2-methyl-6-substituted quinazolines. These compounds were screened for their antitumor activity and found to possess antitumor activity with varying degree.

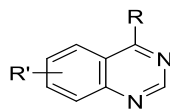
A series of benzimidazo-[1,2-*c*]quinazolines were prepared and its anticancer activity was examined in 1994 by Brana and co-workers. Results of the above study indicate that these compounds showed potent antitumor activity.

In the same year, Mang and co-workers (1994), reported the synthesis and anticancer activities of some new 2,4-diamino-6-substituted quinazolinone derivatives (4). Report clearly indicates the varying degree of anticancer activity exhibited by these compounds.



In 1997, synthesis and antitumor study of a number of substituted diphenylsulfoxide and sulfones were reported by Jones and co-workers (1997).

A series of novel 4,5,6,7-tetrasubstituted quinazolines (5) were prepared in 1995 by Arnold and co-workers. They screened the test compounds for their anticancer activity and found that this compound exhibits some anticancer activity.

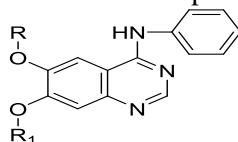


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5-Substituted quinazolinone derivatives were synthesized and their *in-vitro* inhibitory action was studied by Baek, in 1998. These compounds were tested as inhibitors of bacterial and human TS and as inhibitors of the growth of four tumor cell lines.

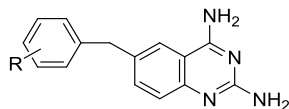
Preparation of several novel substituted quinazoline & quinazolinone derivatives were reported by Kazuo and co-workers in 1999. They screened the antitumor, anti-atherosclerotic, anti-arthritis, anti-diabetic and anti-psoriatic activities of these derivatives.

In 1999, Fathima and co-workers synthesized some novel 4-arylamino-6,7-disubstituted quinazoline derivatives (6). The antitumor activity of above mentioned compounds were studied by them.



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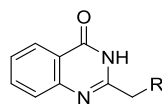
A series of novel 2,4,6-substituted-5,6,7,8-tetrahydro quinazolines (7) were synthesized and its antitumor activity was studied in the year 1999 by Papoulis and co-workers. These derivatives were reported to display antitumor activity. In addition these compounds were also tested for its anti-parasitic activity.



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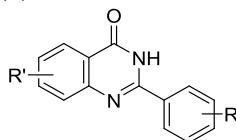
Raffa and co-workers synthesized various novel isoxazolyl quinazolines in 1999. Moreover they also studied the antineoplastic activity of above compounds.

Synthesis and biological activity of novel 2-substituted-4-(3*H*)-quinazolinones (8) was documented by Spirakova and co-workers in 1999. The cytotoxicity of prepared derivatives was studied on the transformed tumor cell line HeLa.



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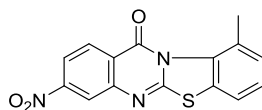
In the year 2000 Hour and co-workers reported the synthesis and anticancer activity of novel 2,6,7-trisubstituted-4(3*H*)-quinazolinone derivatives (9).



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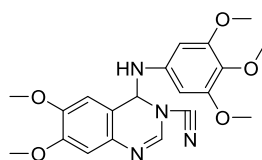
Synthesis and antitumor activity of some new fluorinated condensed quinazoline derivatives were reported by Lipunova and co-workers in 2000. Results clearly indicate that these analogues possess antitumor activity.

Sherbeny and co-workers in the year 2000, prepared a few novel benzothiazolo-[2,3-*b*]-quinazoline analogs (10). They tested these compounds for their antitumor activity and results indicates that compound (10) possess some antitumor activity. In addition these derivatives were also tested for their antiviral activity.



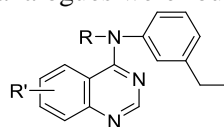
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The synthesis, antitumor activity, and SAR of some 4-substituted anilino-3-cyano-6,7-dimethoxy quinazolines (11) were reported in 2000 by Wang and co-workers.



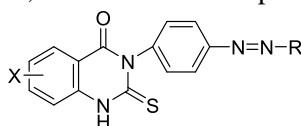
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Lehner and co-workers in 2000 synthesized and patented a sequence of 4-(3-ethyl phenyl amino)-6,7-substituted quinazolinone derivatives (12). These analogues were found to exhibit anticancer activity.



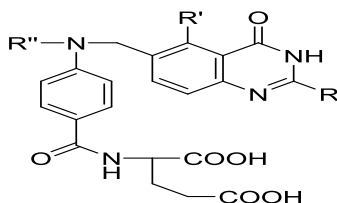
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In 2002 El-Hiti and co-workers documented the synthesis and reactions of novel 3-aryl-2-thioxo-4-(3*H*)-quinazolinones (13). The synthesized compounds have been evaluated in three cell lines, one dose primary anticancer assay. Three compounds are found to be active, out of six test compounds in primary anticancer assay.



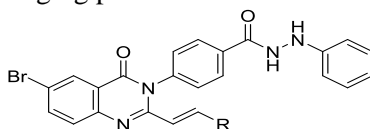
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Forsch and co-workers synthesized thiophene analogues of dideazafolic acid (14) in 2002 & screened its *in-vitro* anticancer potency.



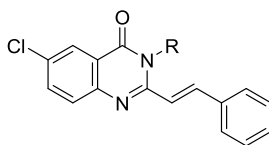
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Murgan, studied the anticancer potency of new 2-substituted-4-(3*H*)-quinazolinones (15) in 2003. The synthesized compounds were studied for both *in-vivo* and *in-vitro* antitumor activity. The *in-vitro* study was performed on DLA cells by trypan blue dye exclusion test. In addition, *in-vivo* antitumor study was carried out on DLA cells in mice at a dose of 50 and 100 mg/kg p.o.



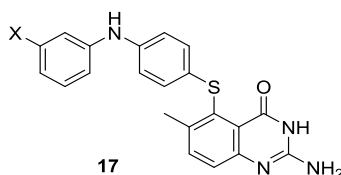
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Synthesis, cytotoxicity, and inhibitory effects on tubulin polymerization and cytotoxicity of some novel 3-heterocyclo substituted-2-styryl quinazolinone derivatives (16) were reported in 2004 by Raffa. These compounds were tested for inhibitory effects on the *in-vitro* growth of leukemia cells by evaluating cell viability following staining with trypan blue.



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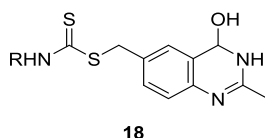
In 2004 Baek, synthesized and screened thymidylate synthase inhibitor activity of some non-classical quinazolin-4-(3*H*)-one antifolates (17). Against human and/or bacterial (*L. casei*) TS the entire test compounds were tested to study its antitumor potency.



Evaluation of cytotoxicity and detection of injury to DNA on human tumor cell line HeLa by triazolo quinazolinone was reported by Ovadekova and co-workers in 2005.

Girija, in 2005 reported the preparation & anticancer activity of some novel dibromo-4-(3*H*)-quinazolinones. Entire compounds were tested for their *in-vitro* cytostatic activity against MT4 and C type cells.

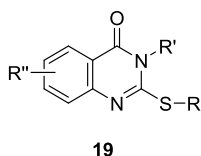
Some new quinazolinone analogues (18) having dithio carbamate side chain were synthesized and its *in-vitro* antitumor activity was studied by Cao, in 2005. By using MTT assay against human myelogenous leukemia K562 cells the title compounds were tested for their antitumor activity.



De Jonge and co-workers in 2006 documented the pharmacokinetic and phase I study of Halofuginone in advanced solid tumor patients.

In 2006 Jin and co-workers synthesized a series of 4,5,8-substitutedquinazolines and investigated its effect on tumor cells.

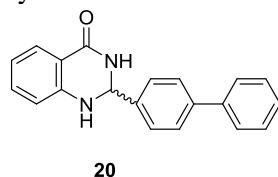
Al-Rashood and co-workers reported the synthesis, antitumor testing, DHF reductase inhibition, and molecular modeling study of a number of new quinazolin-4-(3*H*)-one derivatives (19) in 2006. The synthesized compounds were evaluated as DHFR inhibitors by DHFR inhibition assay method using Methotrexate as a positive control.



Jantova and co-workers in 2006 studied the result of 3,5,9-tri substituted triazolo quinazolines on stimulation of DNA fragmentation, action of caspase 3 in murine leukemia cell, cell cycle, and cell growth.

Synthesis of novel quinazolinone analogues having the pharmacologically active thione moiety was reported by Ghorab and co-workers in 2006. They tested these derivatives for their antitumor activity and found to possess antitumor activity.

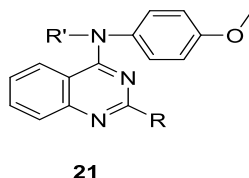
In 2008, 2,3-dihydro-2-aryl quinazolin-4-ones (20) were synthesized using asymmetric method by Chinigo and co-workers. The title compounds were tested for anticancer activity by fluorescent tubulin inhibition assay method. Reports indicate the anticancer potency of this derivative.



Jantova and co-workers reported the synthesis of a novel 6-bromo-2-(morpholin-1-yl)-4-anilino quinazolinone derivatives in 2008. Moreover they also examined the anti-proliferative potency of these compounds. In addition they also examined the apoptosis induced by the title compounds in cells of leukemia lines.

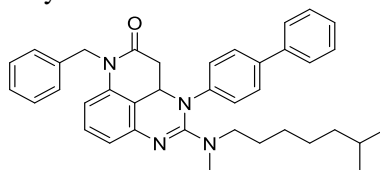
Syntheses of a series of novel triazolo quinazolinone were reported by Jantova in 2009. The title compounds activated P38 MAPK and encouraged ROS mitochondrial intervened death signaling in leukemia cell.

In the year 2009 Sirisoma and co-workers documented the synthesis and anticancer activity of 2,4-disubstituted quinazolin-4-amines (21). These compounds exhibited a great degree of anticancer activity with high BBB penetration.



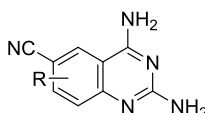
Synthesis and anticancer activity of new thia diazoyl quinazolinones was done by Joseph and co-workers in 2010.

Jung and co-workers in 2010 studied the synthesis and antitumor activity of 3,4-dihydro quinazoline dihydrochloride derivatives (22). Antitumor activity was studied in A549 xenograft nude mice. These compounds exhibited varying degree of antitumor activity.



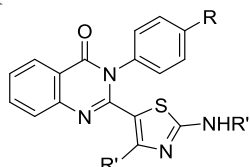
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Synthesis of a highly functionalized 2,4-diamino quinazoline derivatives (23) and its anticancer and anti HIV evaluations were studied in 2010 by Yan and co-workers. These derivatives demonstrated anticancer and anti HIV activities.



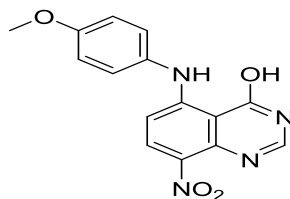
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Giri and co-workers synthesized new quinazolin-4-(3*H*)-one derivatives (24) in 2010. In addition they studied the anticancer activity of this title compounds.



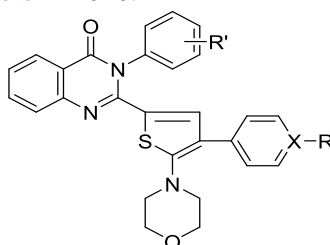
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In 2010, preparation & antitumor activity of new 5,8-disubstituted quinazolines (25) were reported by Tian and co-workers and the test compounds were found to possess antitumor activity by inhibiting microtubule polymerization.



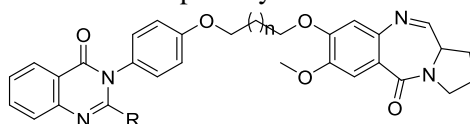
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Synthesis and transcriptional activation inhibitor activity of some new quinazolinone possessing thiophene ring (26) was reported by Giri and co-workers in 2010.



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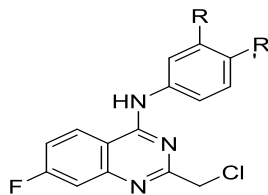
In the year 2010 Kamal and co-workers, synthesized several novel quinazolinone coupled pyrrolo benzo diazepine derivatives (27) and studied its anticancer potency.



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In the year 2010 Conconi and co-workers synthesized few novel fused tricyclic quinazolines. They showed some anti angiogenic activity.

Preparation & anticancer potency of new 2-chloromethyl-4(3H)-quinazolinone derivatives (28) was reported in 2010 by Li and co-workers.



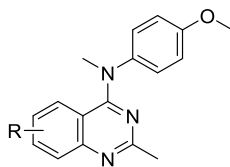
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New 4-substituted quinazoline derivatives were synthesized as DNA gyrase inhibitors by Boyapati and co-workers in 2010.

In the year 2010 synthesis of some novel 2-oxo/thioxooctahydro quinazolin-5-one analogs were reported by Kidwai and co-workers. The study revealed that many compounds of this series exhibits significant anticancer activity.

Synthesis and anticancer study of novel 4-amino-tetrahydro quinazolino[3,2-e] purine derivatives was reported in 2010 by Verones and co-workers in the year 2010. In addition they also reported the docking study of title compounds.

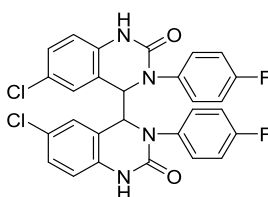
Sirisoma and co-workers synthesized a series of novel *N*-methyl-4-(4-methoxyanilino)-quinazoline derivatives (29) in 2010 and described that these derivatives induced apoptosis. SAR of quinazoline ring also reported.



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Ye Ding and co-workers in 2010 prepared some novel 8,9-dihydro-4,8-disubstituted-pyrazino quinazolin-7(6H)-ketones and reported that the title compounds possess antitumor activity.

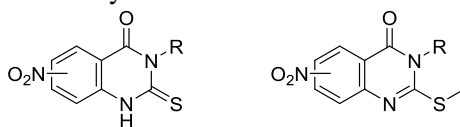
*In-vitro* anticancer activity and oriented synthesis of some novel biquinazoline-2,2'-diones (30) was studied by Dou and co-workers in 2010.



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Nandi and co-workers in 2010 studied the 3D QSAR and molecular docking of novel 4-anilino quinazoline derivatives on anticancer activity.

Preparation and anticancer activity of several new di substituted tetrahydro-2H-quinazolinone & disubstituted-4(3H)-quinazolinone (31-32) was reported in 2010 by Abdel Gawad and co-workers. Reports reveal that these compounds possess antitumor activity.

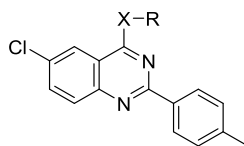


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In the year 2010, a series of *N*-alkyl (anilino)-quinazolines were prepared and its antitumor activity evaluation was done by Garofalo and co-workers.

Synthesis and screening of antitumor activity of some novel quinazoline derivatives (33) by molecular docking study was reported in 2010 by El-Azab and co-workers.



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Al-Omary and co-workers in 2010 synthesized a new antifolates (non-classical) as 2,6-disubstituted-4(3H)-quinazolinone & evaluated its antitumor activity. Results indicate that these derivatives possessed good antitumor activity. Molecular modelling study of title compounds were also studied by them.

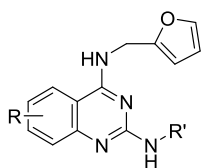
Antitumor activity of a series of novel di substituted dihydro pyrazino quinazolines was reported by Zhang in 2010. These analogues were found to possess antitumor activity.

A number of new spiro derivatives of benzo-[1H]-quinazoline were synthesized by Markosyan in 2010. From the study they found that these derivatives possess anti monoamino oxidase and antineoplastic activities.

Alafeefya and co-workers in 2011 reported anticancer activity of some novel quinazoline derivatives.

In the year 2011, Perchellet and co-workers prepared few 3-aryl-2-halo quinazolinium halide & screened their anticancer activity. They performed antitumor activity (*in-vitro*) in SKBR3 mammary tumor cell and L1210 leukemia cells. Results indicate the antitumor potency of this analogue.

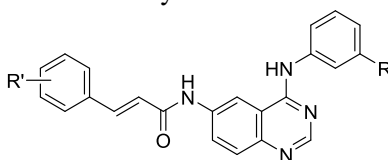
Thorat and co-workers reported the synthesis and protein inhibiting activities of 2,4-diaminoquinazoline derivatives (34) in 2011.



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Chen and co-workers synthesized and studied antitumor activity of novel 2,3-disubstituted-8-arylamino-3H-imidazo quinazolines in 2011. Title compounds were reported to exhibit superior antitumor activity in both *in-vivo* and *in-vitro* models.

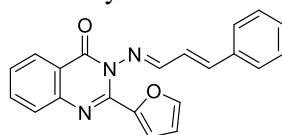
Synthesis of a number of novel 4-anilino quinazoline derivatives (35) were reported in 2011 by Li and co-workers. These compounds exhibited antitumor activity.



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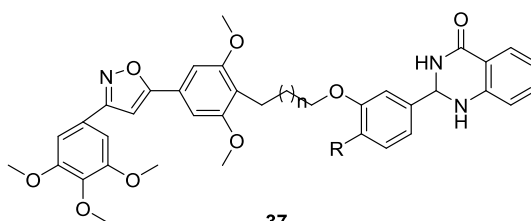
Anti-metastatic activity of some new 6-fluoro-(3-fluorophenyl)-4-(3-methoxy anilino)-quinazoline derivatives was reported by Chen and co-workers in 2011.

Noolvi and co-workers in 2011, synthesized a number of substituted quinazolin-4(3H)-ones and quinoxalines analog (36) and evaluated its *in-vitro* antitumor activity.



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Synthesis and anticancer activity of novel 3,5-diaryl isoxazole/isoxazoline bridged 2,3-dihydroquinazolin-4-ones (37) was reported by Kamal and co-workers in 2011.

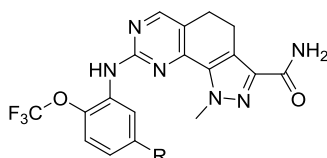


37

In the year 2011, Wu and co-workers synthesized a number of novel 4-pyrrylamino quinazoline analogues and screened their *in-vitro* antitumor activity.



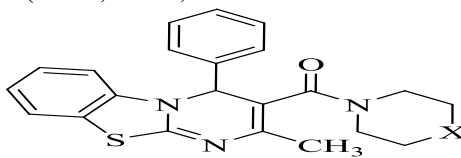
Synthesis and kinase inhibitor activity of novel 4,5-dihydro-1*H*-pyrazolo-[4,3-*H*]-quinazolines (38) was studied by Beria and co-workers in 2011. Results of the study indicate that these analogues possessed selective and potent kinase 1 inhibitor activity.



38

Patel, in 2011 synthesized a number of 3-substituted-2-furyl-2-yl-quinazoline derivatives and evaluated their *in-vitro* antitumor activity. Title compounds showed varying degree of activity.

In 2011 preparation of a number of phenyl-*N*-mustard quinazoline conjugates was reported by Marvania and co-workers. They screened the test compounds for their antitumor activity. In 2013 Lingaiah Nagarapu, reported novel series of building blocks (39) consisting of benzo[4,5]thiazolo[1,2-*a*]pyrimidine-3-carboxylate have been synthesized as potential anticancer compounds. These compounds were prepared from 2-aminobenzothiazole, benzaldehyde and ethyl acetoacetate in ethylene glycol by catalyzing with TBAHS followed by the formation of amide by reaction with several secondary amines in good yields. The cytotoxicity of these compounds was evaluated against human cancer cell lines *in vitro* (A549, HeLa, MDA-MB-231 and MCF-7).



39

X, **39a** = CH<sub>2</sub>;  
**39b** = N-CH<sub>3</sub>  
**39c** = O  
**39d** = N-Ph  
**39e** = N-Ph-NO<sub>2</sub>

## 2. CONCLUSION

This review give an outlook on the research developments regarding Quinazoline moiety. This heterocyclic moiety has great biological and medicinal significance. A large array of quiazoline derivatives possess a variety of medicinal properties. Quinazoline is considered as an important lead compound in drug discovery and drug development. Quinazoline occupy a distinct and unique place in the field of medicine. This article also provide a base for the future research work regarding possible modifications in quinazoline moiety and its implementation in drug discovery. Quinazoline moiety have been most frequently studied, many of its analogs are active against various pathological conditions, which are discussed in brief in this article. The possible improvements in the activity can be further achieved by slight modifications in the substituents on the basic quinazoline nucleus. Various recent new drug developments in quinazoline derivatives show better effect and less toxicity. This study gives valuable information for further development of more potent anticancer agents.

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