ejpmr, 2020,7(2), 225-234

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

CHEMICAL CHARECTERISTICS, SYNTHESIS AND BIOLOGICAL ACTIVITIES OF QUINAZOLINE DERIVATIVES

Dhanya S.*[1], Prasobh G. R.[1], S. M. Sandhya[1] and Sebha M. C.[1]

Sree Krishna College of Pharmacy and Research Centre, Parasala, Thiruvananthapuram, Kerala.

***Corresponding Author: Dhanya S.**

Sree Krishna College of Pharmacy and Research Centre, Parasala, Thiruvananthapuram, Kerala.

Article Received on 25/11/2019 **Article Revised on 15/12/2019** **Article Accepted on 05/01/2020**

ABSTRACT

Quinazoline is a fused aromatic ring system where a benzene ring is fused to 5th and 6th positions of pyrimidine ring. Quinazolines are medicinally important as anti-convulsant, anti-cancer, anti-microbial, and anti-tubercular properties etc. They target epidermal growth factor receptors on tumour cells. This work is aimed to review the quinazoline derivatives which could deliver drug specifically various receptors and can use as lead in future drug development processes.

KEYWORDS: anti-convulsant, anti-cancer, anti-microbial, and anti-tubercular.

INTRODUCTION

Heterocyclic Rings are organic compounds containing at least one atom of carbon and at least one element other than carbon such as sulfur, oxygen or nitrogen within a ring structure. These structures may comprise either simple aromatic rings or nonaromatic rings. Some examples are Aziridine, Pyrroline, Imidazole, Pyrazole, Pyridine, Triazine, furan, Quinoline, Qunazoline etc.

From about 1995 to 2006, the anticancer quinazolines panorama has been dominated by the 4-anilinoquinazolines as tyrosine kinase inhibitors. As extensive researches conducted in this period, there is a progressive reduction in the ability to file novel patents as shown in the 2007 - 2010 period. However, the growing knowledge of cancer-related pathways has recently highlighted some novel potential targets for therapy, with quinazolines receiving increasing attention. The structural heterogeneity in the patented compounds makes it difficult to derive general pharmacophores and make comparisons among claimed compounds. On the other hand, the identification of multi-target compounds seems a reliable goal. Thus, it is reasonable that quinazoline compounds will be studied and developed as anticancer agents.

In the course of identifying various chemical substances which may serve as leads for designing novel antitumor agents, we are particularly interested in present work with quinazoline derivatives which have been identified as a new class of cancer chemotherapeutic agents with significant therapeutic efficacy against solid tumors. The epidermal growth factor receptor (EGFR) protein belongs to the ErbB family of receptor tyrosine kinases (RTKS) which plays important role in the regulation of cell growth, differentiation, and survival. EGFR is over expressed in several human tumors (e.g., breast, ovarian, colon, and prostate) and correlates with a poor prognosis in many cancer patients. Thus EGFR is an attractive target for the design and development of compounds that can specifically bind to the receptor and inhibit its tyrosine kinase (TK) activity and its signal transduction pathway in cancer cells. In view of the previous rational and in continuation of ongoing program aiming at finding new structure leads with potential chemotherapeutic activities. The quinazoline nucleus was coupled with various chemical nucleuses leading to diverse pharmacological activities. The various therapeutically significant quinazoline derivatives and their biological activities are reviewed here.

QUINAZOLINES

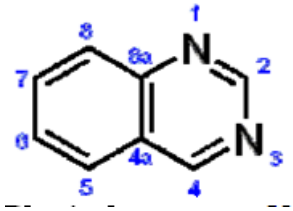
Quinazolin- 4(3H)-one: An overview

Quinazoline (‘phenmiazine’ or benzopyrimidine), a fused bicyclic compound earlier known as benzo-1 3-diazine ring system, was first prepared by Gabriel in 1903. The name quinazoline (German: Chinazoline) was first proposed for this compound by Weddige, on observing that, this was isomeric with the compounds cinnoline and quinoxaline. Paal and Bushsuggested the numbering of quinazoline ring system, which is currently used.

Quinazolines is considered as an important chemical synthesis of various physiological significance and pharmacological utility. The stability of the quinazolinones has inspired medicinal chemist to introduce many bioactive moieties to this nucleus to synthesis new potential medicinal agents.

Chemistry
General name: Benzopyrimidine, Phenmiazine.
IUPAC name: Quinazoline
Empirical formula: $C_8H_6N_2$

Chemical structure

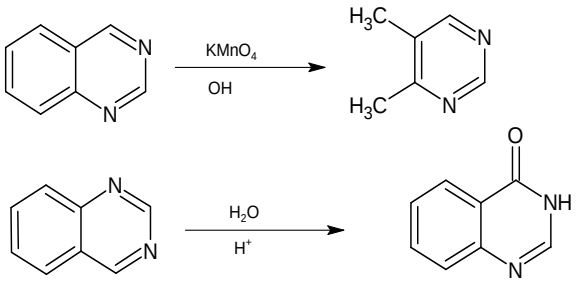


Physical property: Yellow and crystalline
Molecular weight: 130.15g/mol

Chemical Properties
Quinazolines are stable in cold dilute acid and alkaline solutions, but it is destroyed when these solutions are boiled. *O-aminobenzaldehyde*, ammonia and formic acid are formed when quinazoline is boiled with hydrochloric acid.

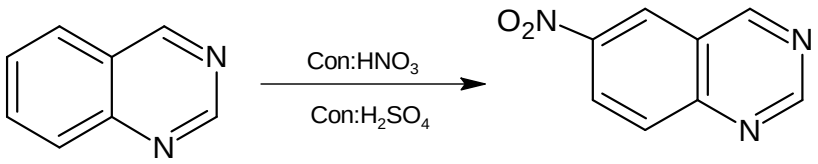
Hydrolysis, oxidation and reduction
Oxidation of quinazoline in dilute aqueous acid, with two equivalents of hydrogen peroxide at room temperature gave a high yield of 3, 4-dihydro-4-oxoquinazoline. In alkaline medium, the anhydrous neutral species of quinazoline predominantly undergo oxidation with potassium permanganate and furnished a high yield of 3, 4-dihydro-4-oxoquinazoline.

Catalytic hydrogenation of quinazoline stopped after the absorption of one molecule of hydrogen and gave 3, 4-dihydro quinazoline. Reduction with sodium amalgam gave 1, 2, 3, and 4- tetrahydroquinazoline. Lithium aluminum hydride and sodium borohydride gave 3, 4-dihydro and 1, 2, 3, 4- tetrahydroquinazoline.

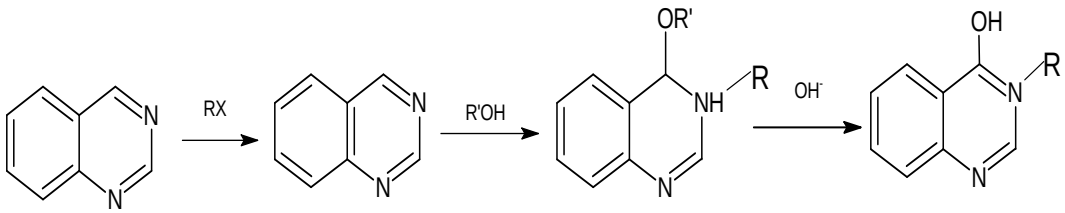


Nucleophilic and electrophilic substitution reactions
The two known nucleophilic substitution reactions of quinazoline with sodamide and hydrazine presumably proceed via the intermediate addition products and gave 4-amino and 4-hydrazine quinazoline.

Nitration is the only known electrophilic substitution reaction of quinazoline. Theoretical considerations show that the expected order of reactivity is at positions 8 > 6 > 5 > 7 > 4 > 2. Quinazoline gives 6-nitroquinazoline with fuming nitric acid in concentrated sulfuric acid. No oxidation of the heterocyclic ring can occur under these conditions because the hydrated cation is not present.

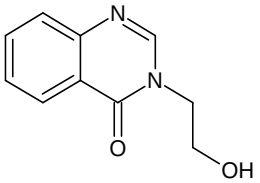
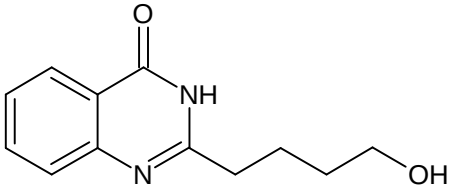
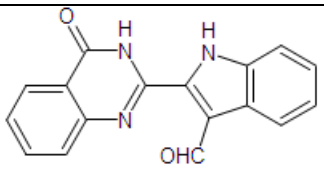


Alkylation reactions
Alkylation of quinazoline takes place on N, 3- methyl, 3-ethyl-3-alkyl and 3-benzyl quinazolinium salts which readily take up a molecule of alcohol to form the corresponding 4-alkoxy-3-alkyl-3, 4-dihydro quinazolinium salts. These salts yield the pseudo bases, 3- alkyl-3, 4-dihydro-4-hydroxy quinazolines on treatment with strong alkali.



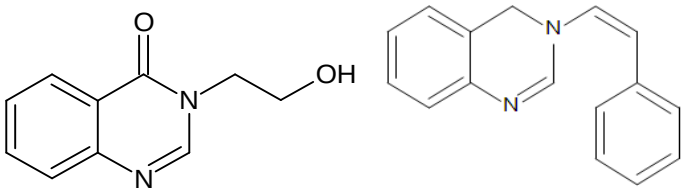
Addition reactions
Quinazoline is very reactive towards anionic reagents which attack at position 4. Sodium bisulphate, hydrogen cyanide, acetophenone, acetone, 2- butanone and cyclohexanone add across the 3, 4-double bond of quinazoline. Methyl, ethyl, isopropyl, benzyl, t-butyl, phenyl magnesium halides and phenyl lithium add across the 3, 4-double bond to give the corresponding 4-substituted 3, 4-dihydroquinazolines.

Table No. 1: ***Source and activity of 2-substituted quinazolinone alkaloid.***

Sl. No	Quinazolinone alkaloid	Source
1	 3-(2-hydroxyethyl)quinazolin-4(3*H*)-one	Casimiroa edulis
2	 2-(4-hydroxybutyl)quinazolin-4(3*H*)-one	Dichora febrifuge
3	 Bouchardatine	Bouchardatia neurococca

Simple 3-substituted quinazoline-4-ones

There are nine 3 substituted quinazoline-4-ones isolated from various species. A general route to this structural type can be exemplified by Niementoski synthesis of the 3H-quinazoline-4-one core using microwave irradiation and improved yields and reduced reaction time.



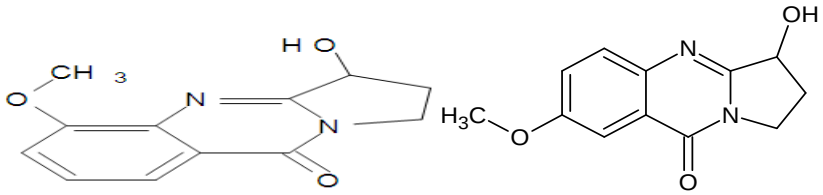
Echinozolinone Bogorin

2, 3-disubstituted quinazoline-4-ones

There are only two quinazolinone natural product isolated under the review period, substituted both at 2 and 3 positions and they are tryptoequivalence analogues, isolated from Aspergillus clavatus.

Quinazolinone fused with pyrrole ring system [1]

There are 5 naturally occurring quinazolinone alkaloids having quinazolinone ring fused with a pyrrole ring system. They all are analogs or derivatives of deoxyvasicinone or vasicinone isolated from various species.



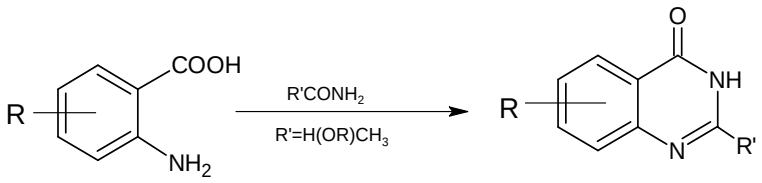
Adhavasinone 7-methoxy vasicinone

It is important to note that the quinazolinone alkaloids are a class of natural compounds with very diverse structures and hence at present approximately 50 quinazolinone derivatives with a wide variety of biological activities are available for clinical use.

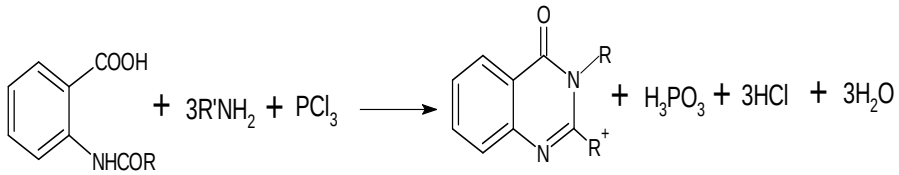
Synthesis of 4(3H)-Quinazolinones

Condensation of Anthranilic acid with Amides - Niementowski reaction [2]

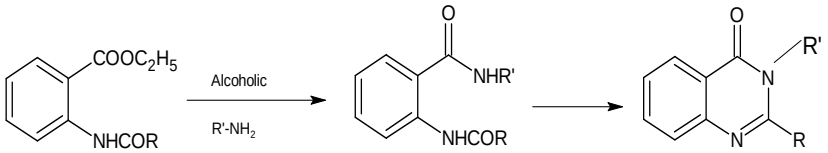
Using Niementoski Reaction, quinazolinone was prepared by heating anthranilic acid in an open container with excess of formamide at 120^0C, to yield 90% of 4(3H)-quinazolinone.



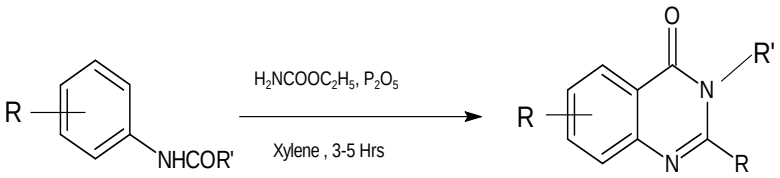
Grimmel, Guinther and Morgan's synthesis[3]
3 moles of *o*-amino benzoic acid, when heated with 3 moles of amine together with one mole of phosphorous trichloride in toluene for two hours, gave high yields of 2, 3-disubstituted 3, 4-dihydro-4- oxoquinazolines.



From ethyl 2-acetamido-5-nitrobenzoate[3]
Ethyl 2-acetamido-5-nitrobenzene and alcoholic ammonia when heated in a sealed tube at 170°C yields 3, 4-dihydro–methyl-6-nitro-4-oxoquinazoline.

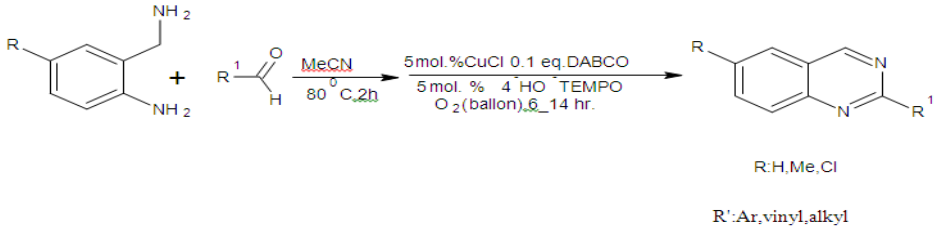


Sen and Ray's synthesis
Boiling a solution of isobutyrylanilides with urethane and phosphorous pentoxide in xylene gave 2-propyl and 2-isopropyl-3, 4- dihydro-4-oxoquinazolines.

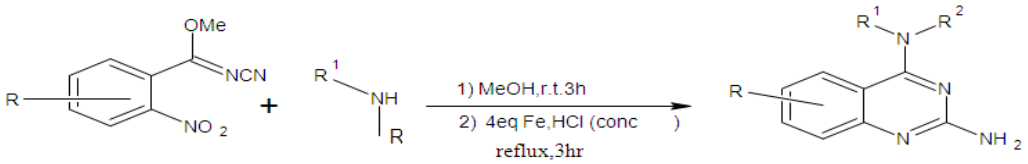


Condensation of Acetanilide with Urethanes
Urethane and acetanilide, heated for 3hours with phosphorous pentoxide in toluene, give 2-methyl-4(3H)-quinazolinones.

- *B. Han and coworkers* used CuCl/DABCO/4-HO-TEMPO as the catalysts and oxygen as the terminal oxidant, which enabled an efficient aerobic oxidative synthesis of 2-substituted quinazolines and 4*H*-3, 1-benzoxazines from the one pot reaction of aldehydes with 2-aminobenzylamines and 2-aminobenzyl alcohols, respectively.[4]



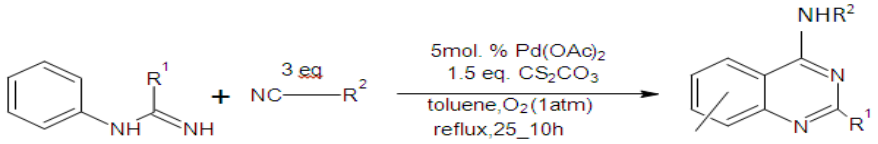
- *P. Yin et al*. described a tandem condensation of a cyanoimidate with an amine followed by reductive cyclization in an iron- HCl system enables an efficient route to N^4-substituted 2, 4-diaminoquinazolines.



1.R^1:alkyl

2.R^2:H,alkyl

- *Y. Wang et al* described an efficient method for the synthesis of 4-amino-2-aryl (alkyl) quinazolines from readily available *N*-arylamidines and isonitriles via palladium-catalysed intramolecular aryl C-H amidation by isonitrile insertion.[5]



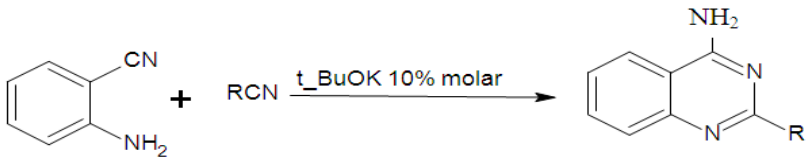
R :Ar,tBu,Cy2

R :alkyl,Ar

Microwave Method of Synthesis

- A mixture of 2-arylidenetetralin-1-one (0.02 mol) and thiourea (0.02 mol) in ethanolic KOH (1 g KOH in 25 mL ethanol) was irradiated under MW for 5.30 min. with a time interval of 10 seconds. The volume of the reaction mixture was reduced to half and kept overnight. The solid thus separated as shining needles, filtered and washed with aqueous ethanol to give -4-aryl 3, 4, 5, 6tetrahydrobenzo (h) quinazoline-2(1H) thiones.

- Cyano aromatic compounds react with anthranilonitrile in a domestic microwave oven affording good yields of the corresponding 4-aminoquinazolines in a very short irradiation time.

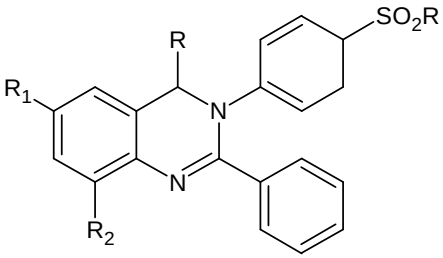


Some New Lead in Quinazolinone Discovery

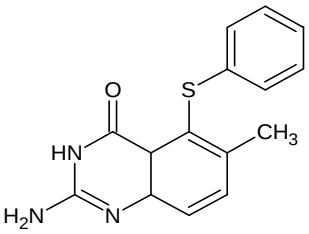
Quinazolines are a large class of active chemical compounds exhibiting a broad spectrum of biological activities in animals as well as in humans. Literature studies on quinazolinones have shown that these derivatives possess a wide variety of biological activities such as anti HIV, anticancer, antifungal, antibacterial, antimutagenic, anticoccidial, anticonvulsant, anti-inflammatory, CNS depressant, antimalarial, antioxidant, antileukemic activity, antileishmanial activity. Quinazolinone alkaloid luotonin A has attracted the attention of chemist and pharmacist worldwide, because it is strikingly reminiscent of the cytotoxic alkaloid camptothecin, whose derivatives are clinically useful anticancer agents.

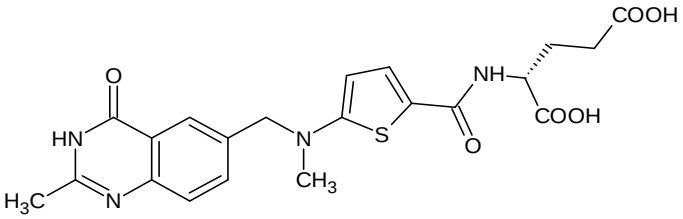
Quinazolinones as Anticancer Agent

- *Periyasamy Selvam et al.*, have designed and synthesized novel 2, 3-disubstituted quinazoline-4(3H)-ones by microwave technique and characterized them by spectral analysis. Synthesized compounds were screened for cytotoxicity and for anti-viral activity against influenza A.[6]



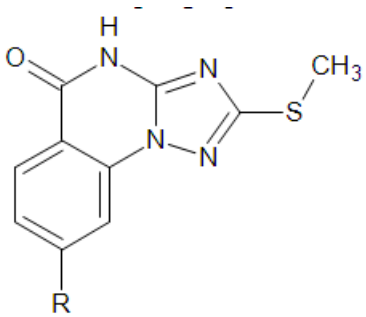
- *Ashraf A. Khalilet al.*, synthesized a new series of 2-substituted mercapto-3*H*-quinozolines bearing 6-iodo and 2-heteroarylthio functions and screened for their *in-vitro* anti-tumour activity.[7]



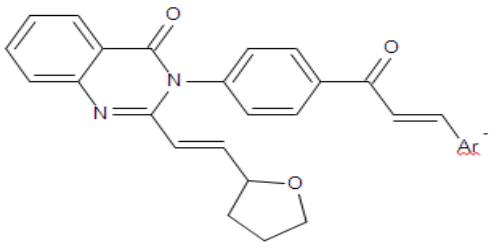


Quinazolinones as Anti-inflammatory Agents

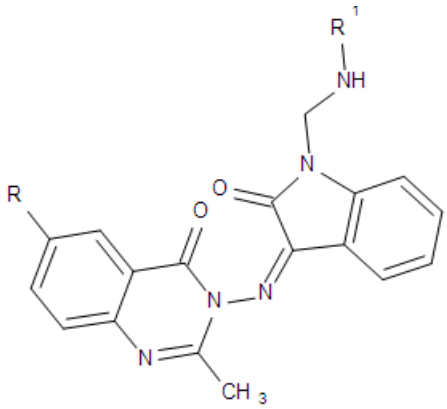
- *Rashad A et al.* synthesized a series of twenty five 2-methylsulfanyl[1,2,4]triazolo[1,5-*a*]quinazoline derivatives and investigated their cytotoxic effects against hepatocellular Hep-G2 and colon HCT-116 carcinoma cells and effect on the macrophage growth, in addition to their influence of the inflammatory mediators [nitric oxide (NO), tumor necrosis factor-α (TNF-α), prostaglandin E-2 (PGE-2) and in bacterial lipopolysachharide (LPS)-stimulated macrophages].[8]



- *K.M. Amin et al.* carried out the synthesis of three series of Spiro [(2H, 3H) quinazoline-2, 1′-cyclohexan]-4(1H)-one derivatives. These novel quinazolinone derivatives showed potent anti-inflammatory and analgesic activity of superior G.I.T. Safety profile in experimental rats in comparing to indomethacin and tramadol as reference drugs. Docking study into COX-2 has been made for derivatives of highest anti-inflammatory activity.
- *Ashok Kumar et al*. had done the substitution of different hetero cyclic moieties at 2, 3 position of quinazolinone nucleus to modulate the anti-inflammatory activity and they synthesized a new series of quinazolino derivatives by incorporation of azetidinones and thiazolidinones at 3rd position of quinazolinones. All these compounds were screened for their anti-inflammatory activity.
- *M. Fathalla et al.*, ***2008***, prepared (2-furan -2-yl – vinyl)-quinazoline -4(3H)-one derivatives, by condensing furyl acryloyl chloride with anthranilic acid in presence of pyridine followed by treatment with p-aminoacetophenone. This compounds were evaluated for their anti-inflammatory and antimicrobial effects.

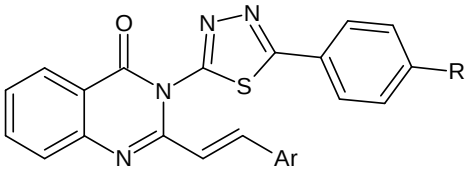


- A series of novel Schiff bases of 2-methyl quinazoline /6-bromo- 2-methyl quinazoline -4(3H)-ones containing 2, 3-indolinedione or Mannich bases of 2,3indolinediones residues was prepared. The synthesized derivatives were screened for their antimicrobial analgesic, anti-inflammatory and anthelmintic activities.

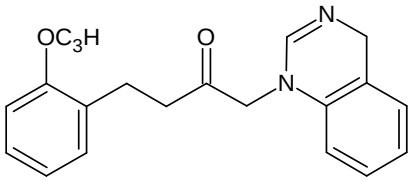


Quinazolinones as Anti-microbial Agents

- *Deepti Kohliet al.*, have been synthesized quinazolinone derivatives and evaluated for their antibacterial activity by cup plate method by measuring inhibition zone.
- *Varsha Jatavet al.*, have been synthesized 3- [5-(4-substituted phenyl)-1, 3, 4-thiadiazole-2-yl]-2-styryl quinazoline -4(3H)-ones and reported their anti-bacterial and anti-fungal activity.[9]



- *Yuliang Wanget al.*, have designed and synthesized series of 4-(2 methoxyphenyl)-2-oxobutylquinazoline derivatives and reported their antibacterial activity.



- *P.Praveen Kumar et al.*, have been synthesized 6, 7, 8, 9-tetrahydro-5(H)-5- nitrophenylthiazolo [2, 3-b]-quinazolin-3(2H)-one derivatives and the synthesized compounds have been screened for anti-microbial activity.

Quinazolinones as Anticonvulsant Agents

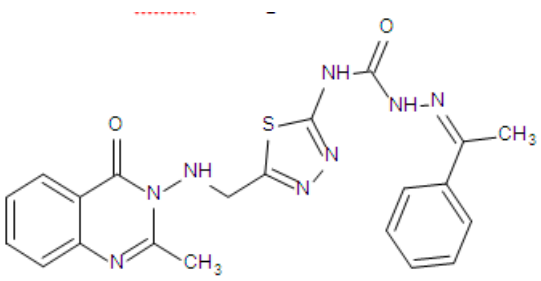
- *Rajak H et al*. synthesised three novel series of semicarbazones containing 1, 3, 4thiadiazole and quinazoline ring. The anticonvulsant activities of the compounds were investigated using maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (scPTZ) models. The rotarod test was conducted to evaluate neurotoxicity.[10]

Quinazolinones as Antihypertensive Agents

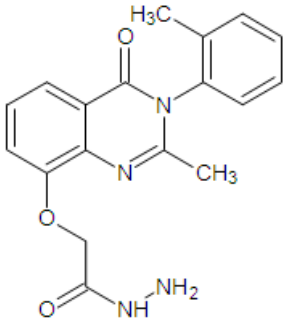
- *Veerachamyet al*., have been synthesized a series of 3-benzyl-2-substituted-3H-[1, 2, 4] triazolo [5, 1- b] quinazolin-9-ones by the cyclo condensation of 3-amino-2-benzylamino-3H-quinazolin-4- one with a variety of one-carbon donors. The compounds were evaluated for their in vivo antihypertensive activity using spontaneously hypertensive rats (SHR). While all the test compounds exhibited significant anti-hypertensive activity, 3-benzyl-2-methyl-3H-[1, 2, 4] triazolo [5, 1- b] quinazolin-9-one exhibited antihypertensive activity more than the reference standard prazocin.

Quinazolinones as Antimycobacterial Agents

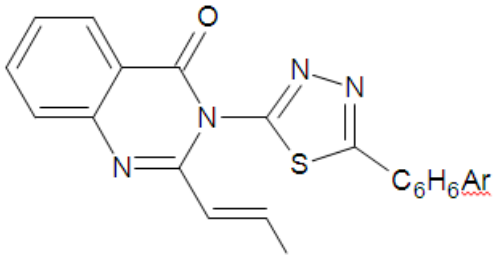
- *Omar Al-Deeb et al.*, have been synthesized a series of 21 new 2-alkylthio-6-iodo-3-substituted-quinazolin-4-one derivatives was prepared and screened for their in-vitro antitubercular activity against Mycobacterium tuberculosis strain HRv, using the radiometric BACTEC 460-TB methodology.



- *Adel S*. synthesized a new series of 8-substituted-4(3*H*)-quinazoline derivatives and these were evaluated for their anticonvulsant activity against chemically (PTZ, picrotoxin and strychnine) and electrically (MES) induced seizures and compared with the reference drugs valproate and methaqualone.



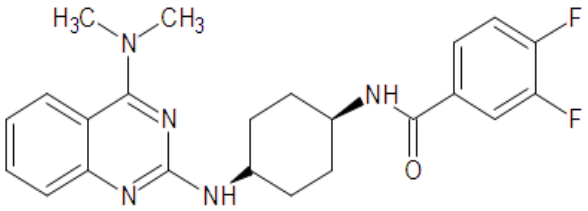
- Few novel 3-[5-(4-substituted) phenyl-1,3,4-oxadiazole-2-yl]-2-styryl quinazoline-4(3*H*)-ones were synthesized and evaluated for anticonvulsant, neurotoxicity, sedative-hypnotic, and phenobarbitone-induced hypnosis potentiation test
- *Sushil et al.* synthesized some novel 1-(4-substituted-phenyl)-3-(4-oxo-2-prpoyl 4H-quinazoline-3-yl)-urea and were screened for their CNS activity.
- *Shashikant and bhavana* carried out the synthesis of some novel 3-[5-substituted 1, 3, 4-thiadiazole –yl]-2-styryl quinazoline-4(3H)-one and these synthesized derivatives were tested *in-vivo* for their anticonvulsant activity.



C6H6Ar

Quinazolinones as Anxiolytic and antidepressant

- In order to produce new lead for anxiolytic and antidepressant drug, a new series of quinazoline analogues was designed to mimic ATC-0175 structural features and fitted with functional groups believed to enhance anxiolytic and antidepressant activity. The synthesized compounds were evaluated for anxiolytic and antidepressant activity by elevated plus-maze and tail-suspension method.

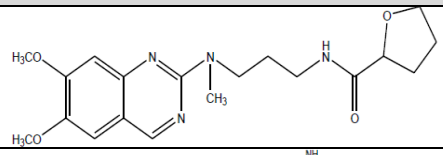
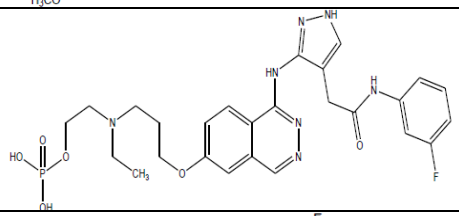
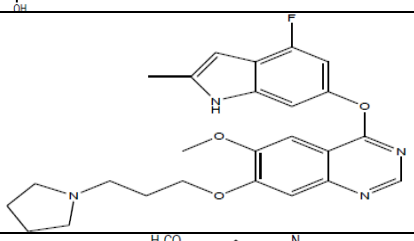
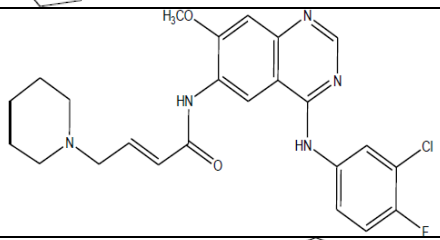
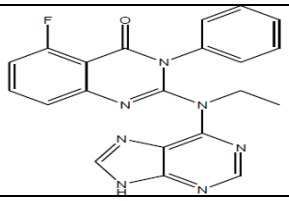


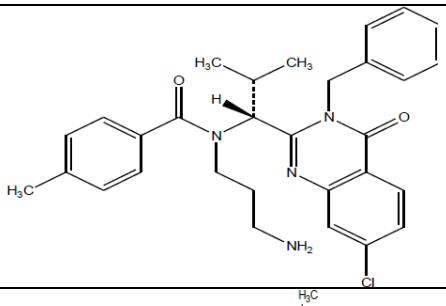
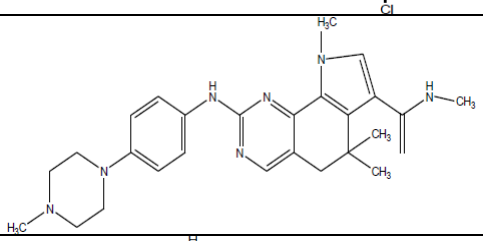
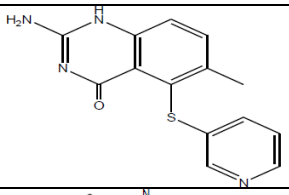
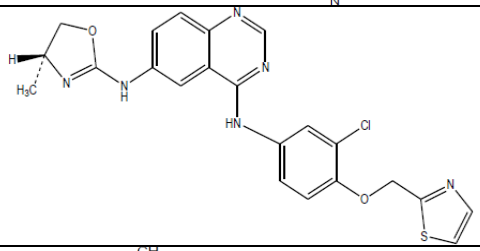
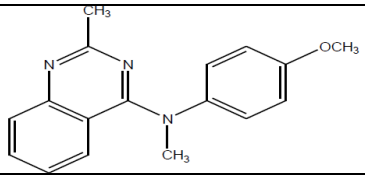
Docking Studies

- *Kamelia et al* prepared some new quinazoline and benzo[*d*]isothiazole-based antitumor agents and Docking study of the designed compounds into the ATP binding site of epidermal growth factor receptor (EGFR) tyrosine kinase was performed to compare the binding mode of these compounds to the known EGFR inhibitor, lapatinib.
- *Adel S et al.,* carried out docking studies of novel Quinazoline derivatives to probe their antitumor activity against three tumor cell lines in which EGFR is highly expressed. All tested compounds showed potent and selective activity against breast cancer (MCF-7) Virtual screening was carried out through docking, the designed compounds into the ATP binding site of epidermal growth factor receptor (EGFR) to predict if these compounds have analogous binding mode to the EGFR inhibitors.
- *Sisir Nandi et al*., carried out molecular docking analysis was to better understand of the interactions between EGFR target and aniline quinazoline derivatives. Hydrophobic and hydrogen-bond interactions lead to identification of active binding sites of EGFR protein in the docked complex.

Marketed Quinazoline Derivative Drugs

Table *2: Marketed Quinazoline Derivative Drugs.*

Sl No:	Quinazoline Derivative	Chemical Structure	Use
1	Alfuzocin		Anti-cancer activity
2	Barasertib		Acute myeloid leukemia
3	Cediranib		Heamatological cancer, Liver metastases
4	Dacomitinib		Anticancer
5	GS1101(CAL1 01)		To treat hematological cancer.

6	Ispinesib		To treat solid tumours.
7	Milciclib		Anticancer.
8	Nolatrexed		To treat solid tumors.
9	Varlitinib		Anticancer drug.
10	Verubulin		Anticancer drug.

CONCLUSION

Quinazoline skeleton is an important pharmacophore in new drug discovery. in addition to traditional synthetic methods some novel synthetic methods are also developed in recent years. the researches shows 2-, 4- and 6-position substituted quinazoline analogs are more receptor specific drugs. In future quinazolinone structure could give some more hopeful results in the field of medicinal chemistry.

REFERENCES

1. Demeunynck, M. and Baussanne, I. (2013). Survey of Recent Literature Related to the Biologically Active 4(3H)-Quinazolinones Containing Fused Heterocycles. *Current Medicinal Chemistry*, 20(6): 794-814.
2. Shemchuk, L., Chernykh, V. and Krys'kiv, O. (2006). Reaction of Anthranilic Acid Amides with Cyclic Anhydrides. *ChemInform*, 37(40).
3. Asif, M. (2014). Chemical Characteristics, Synthetic Methods, and Biological Potential of Quinazoline and Quinazolinone Derivatives. *International Journal of Medicinal Chemistry*, 2014; 1-27.
4. Han, B., Yang, X., Wang, C., Bai, Y., Pan, T., Chen, X. and Yu, W. (2011). CuCl/DABCO/4-HO-TEMPO-Catalyzed Aerobic Oxidative Synthesis of 2-Substituted Quinazolines and 4H-3,1-Benzoxazines. *The Journal of Organic Chemistry*, 77(2): 1136-1142.
5. Jatangi, N. and Palakodety, R. (2019). I2-Catalyzed oxidative synthesis of N,4-disubstituted quinazolines and quinazoline oxides. *Organic & Biomolecular Chemistry*, 17(15): 3714-3717.
6. Selvam, P., Breitenbach, J., Borysko, K. and Drach, J. (2009). Synthesis, Antiviral Activity, and Cytotoxicity of Some Novel 2-Phenyl-3-disubstituted Quinazolin-4(3H)-ones. *Antiviral Research*, 82(2): A55.
7. Khalil, A., Hamide, S., Al-Obaid, A. and El-Subbagh, H. (2003). Substituted Quinazolines, Part 2. Synthesis and In-Vitro Anticancer Evaluation of New 2-Substituted Mercapto-3H-quinazoline Analogs. *Archiv der Pharmazie*, 336(2): 95-103.
8. Al-Salahi, R. and Geffken, D. (2012). ChemInform Abstract: Synthesis of Novel 2-Methylsulfanyl-4H-

[1,2,4]triazolo[1,5-a]quinazolin-5-one (III) and Derivatives. *ChemInform*, 43(18).

9. Jatav, V., Kashaw, S. and Mishra, P. (2007). Synthesis, antibacterial and antifungal activity of some novel 3-[5-(4-substituted phenyl) 1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones. *Medicinal Chemistry Research*, 17(2-7): 169-181.
10. Pal, M. and et al., e. (2011). Chem Inform Abstract: A New Three-Component Reaction: Green Synthesis of Novel Isoindolo[2,1-a]quinazoline Derivatives as Potent Inhibitors of TNF-α. *Chem Inform*, 42(35).