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CHEMISTRY AND PHARMACOLOGICAL EVALUATION OF QUINAZOLINE AND QUINAZOLINE DERIVATIVES – A REVIEW

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ABSTRACT

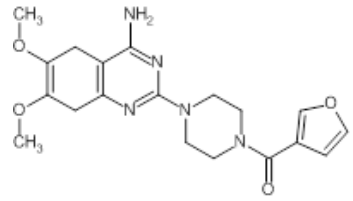
Quinazoline is the main six-membered heterocyclic ring system possesses a wide range of promising biological activities. The simple and versatile synthetic methodologies which gives advancement in research and development for years and continued interest in the quinazoline scaffold in medicinal chemistry. The stability of the quinazolinone nucleus has inspired researchers to introduce many bioactive moieties to this nucleus to create novel potent medicinal agents. This article outlined the chemistry and biological activities of quinazoline and its derivatives.

KEYWORDS: Quinazoline, Quinazolinone, Diuretic, Anti-hypertension, Anti-diabetic, Anti-convulsant, Anti-tubercular.

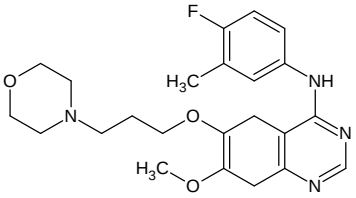
1. INTRODUCTION

Quinazoline which belongs to N- containing heterocycle compound is an important scaffold due to their widely and distinct biological activities. Heterocyclic chemistry involving heterocyclic compounds which has very much interest in our daily life. Heterocyclic compounds have one or more hetero atoms in their structure may be cyclic or non-cyclic in nature. The word “hetero” itself means “different from carbon and hydrogen”. Many heterocyclic compounds are extracted from plants and animals which shows various biological activity. Some are fundamentals of life like haeme derivatives in blood and in chlorophyll present in plants which is essential for the photosynthesis. Heterocycles are also seen in RNA and DNA. Therefore, heterocycles have wide range of application.

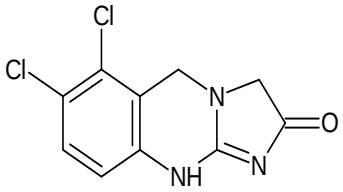
Quinazoline is a fused bicyclic compound made up of 2 fused 6-member aromatic rings – benzene and pyrimidine ring earlier known as benzo-1,3-diazine which has considerable interest because of its various biological activities. Also known as 1,2-diazanapthalene, benzo pyrimidine and phenamiazine. Substituted quinazoline derivatives have been synthesised for medicinal purpose and are reported for a wide range of biological activities such as anti-malarial, anti-convulsant, anti-depressants, anti-inflammatory, anti-cancer, anti-microbial, anti-fungal, anti-protozoan, diuretic, muscle relaxant, anti-tubercular, and many more biological activities. Quinazoline is an important basic nucleus so its derivatives are used for the preparation of synthetic compounds and are present in various drug molecules (fig1).



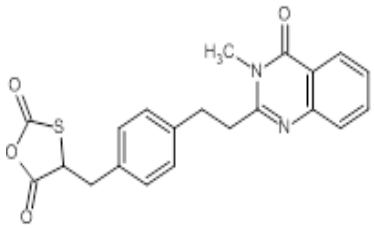
Prazosin antihypertension



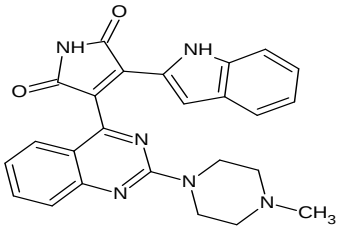
Gefitinib anticancer



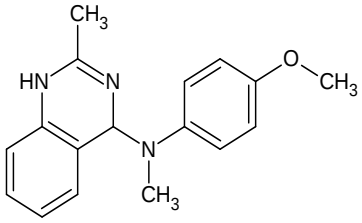
Anagrelid thrombocytosis



Balaglitazone Antidiabetic & hypolipidemic



Sotrastaurin Psoriasis, Ulcerative colitis

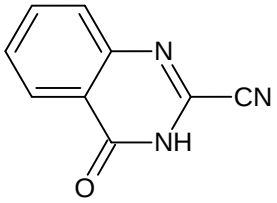


Verubulin Anticancer

Fig. 1: Some marketed available drugs containing quinazoline moiety.

2. HISTORY

First quinazoline derivative, 2-cyano-3,4-dihydro-4-oxoquinazoline [1] was prepared by Griess in1869, by the reaction of cyanogens and anthranilic acid.[1] The name quinazoline (German: chinazoline) was proposed by Widdege in 1887 because it is isomeric with compounds cinnoline, quinoxaline and phthalazine. The numbering of ring which currently used is suggested by Paal and Bush in 1889. After that in 1895 Bischler and Lang synthesised quinazoline by decarboxylation of 2-carboxy derivatives. but it was Siegmund Gabriel in 1903, who reported a satisfactory synthesis of quinazoline. In 1951 the first renowned quinazoline marketed drug – Methaqualone is used for its sedative and hypnotic effects. Chemistry of quinazoline was revised by Williamson (1957) which is further revised by Lindquist in1959 and brought up to the date by Armarego in 1963.[2]



2-cyano-3,4-dihydro-4-oxoquinazoline

3. SUBSTUTION IN QUINAZOLINE

Among most of the quinazoline derivatives ketoquinazolines also called as quinazolinones are most important which have hydroxyl group in the 2,4 positions of quinazoline ring received significant attention due to their widely and distinct biopharmaceutical activities.

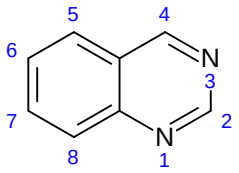
Depending upon substitution pattern of ring they are classified as[3]

- 2-substituted-4(3H)-quinazolinones
- 3-substituted-4(3H)-quinazolinones
- 4-substituted quinazolinones
- 2,3-disubstituted-4(3H)-quinazolinones
- 2,4-disubstituted-4(3H)-quinazolinones

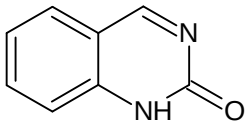
Depending upon position of keto or oxo group they are divided as[4]

- 2(1H) quinazolinones[2]
- 4(3H) quinazolinones[3]
- 2,4(1H,3H) quinazolinones[4]

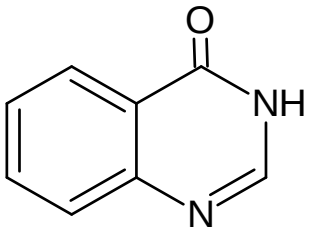
2(1H) quinazolinones is predominantly a product of anthranilonitrile or benzamides with nitriles. But among other quinazolinone structures 4(3H) quinazolinones are most prevalent being derived from anthranilates. The autooxidation of quinazoline precursors can be converted to the corresponding 4(3H) quinazolinones.



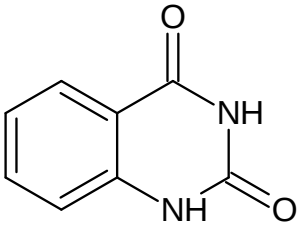
Quinazoline



2(1H)quinazolinone[2]



4(3H)quinazolinone



4(1H,3H)quinazolinone

4. PHYSICAL PROPERTISE[5]

Chemical formula: $C_8H_6N_2$

Molar mass: 130.150g/mol

Appearance: light yellow crystals

Density: 1.351g/cm^3, solid

Melting point: 48°c (118°F, 321K)

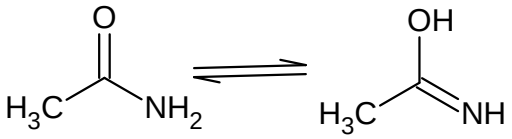
Boiling point: 243°c (469°F,516K)

Solubility: water soluble

pKa: 3.51

5. CHEMISTRY AND CHEMICAL PROPERTISE OF QUINAZOLINE

Day by day novel quinazoline derivatives of different pharmacological effect are still being discovered. Therefore, the chemistry of quinazoline being considered as established area. A strong lactam-lactim tautomeric interaction is found in the quinazolinones.[6]



Lactam form **Lactim form**

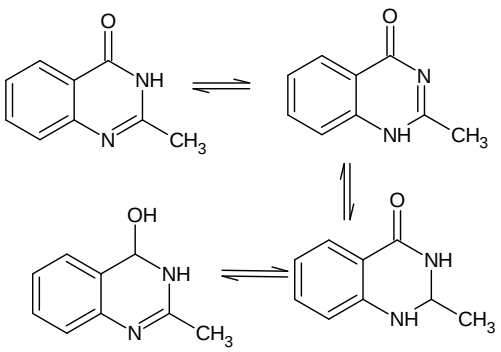


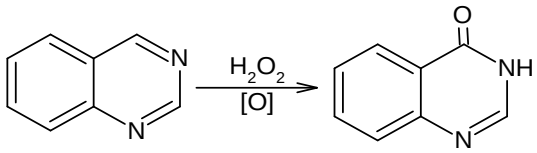
Fig: Representation of different tautomeric forms of 2-methyl-4(3H)-quinazolinone.

Hence, the quinazolinones are regarded as "privileged structure" for drug development and discovery. From structural activity relationship studies, it is found that the positions 2,6,8 are important for activity and also increases chemotherapeutic effect by the inclusion of different heterocyclic moieties to the 3rd position.

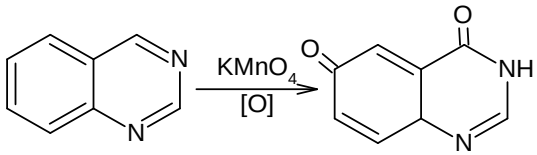
5.1. Oxidation

In acidic medium, quinazoline on oxidation produce 3,4-dihydro-4-oxo quinazoline in presence of H_2O_2 (scheme 1).

In alkaline medium, 3,4-dihydro-6,4-oxoquinazoline is produced on oxidation using $KMNO_4$ (scheme2).



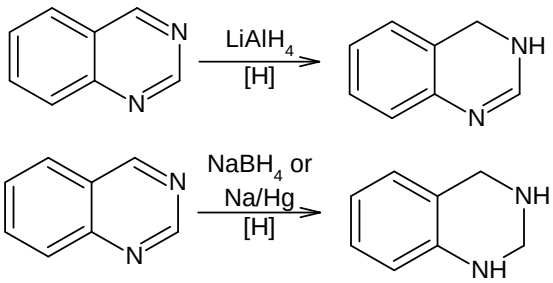
Scheme 1



Scheme 2

5.2. Reduction

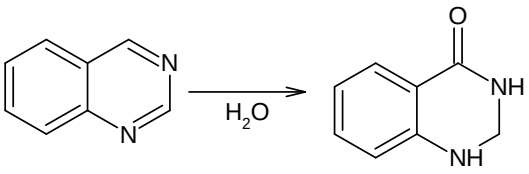
Quinazoline on catalytic hydrogenation using $LiAlH_4$ gives 3,4-dihydroquinazoline and using $NaBH_4$ or Na/Hg gives 1,2,3,4-tetrahydroquinazoline (scheme 3)



Scheme 3

5.3. Hydrolysis

Quinazoline undergo hydrolysis to produce 3,4-dihydro-4-oxoquinazoline (scheme 4).



Scheme 4

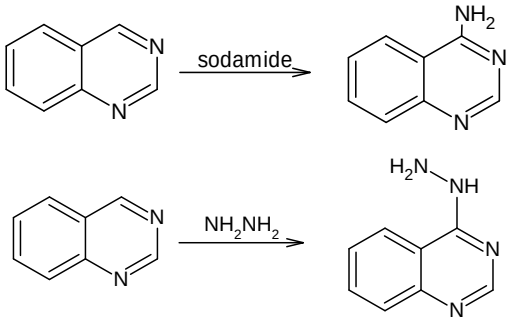
5.4. Addition reaction

Quinazoline favours addition reactions which is added across 3,4 double bonds. Quinazoline is highly reactive towards anionic reagent which attack on position 4 to give 4-substituted quinazoline derivative.

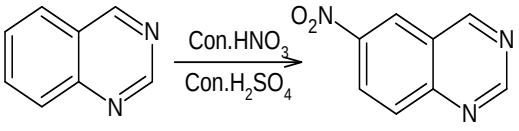
5.5. Substitution reaction

5.5.1. Nucleophilic substitution reaction: quinazoline undergoes nucleophilic substitution reactions with sodamide to give 4-amino quinazoline and with hydrazine gives 4-hydrazine quinazoline (scheme 5).

5.5.2.Electrophilic substitution reaction: it is found during nitration. The order of reactivity at positions are 8>6>5>7>4>2 (scheme 6)



Scheme 5



Scheme 6

It was found that the rings of quinazolines are stable towards oxidation, reduction, hydrolysis, addition and substitution reaction. No ring degradation occurs at moderate conditions.[7]

6. SYNTHESIS OF QUINAZOLINE AND QUINAZOLINE DERIVATIVES

1. Niementowski's synthesis

Anthranilic acid is heated with excess of formamide at 125-130^{o}c to give 4-(3H) quinazolinone (scheme 7).

2. From isatoic anhydride

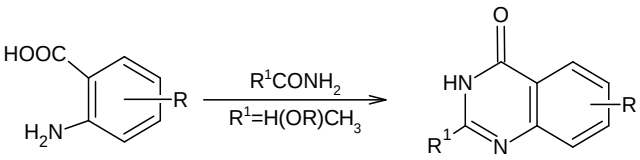
Dihydro-4-quinazolinones produced by the reaction of isatoic anhydride with amines refluxed for 1-6 hrs in ethyl orthoformate (scheme 8).

3. Aza-Diels Alder reaction

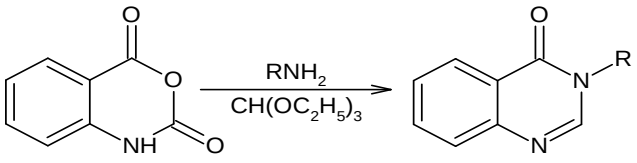
Chen *et al*. Synthesis quinazoline derivatives by using aniline and ethyl glycoxalate using $CuBr_2$ refluxed in toluene for 24 hrs. This reaction is an extent of Povarov imino- Diels Alder reaction (scheme 9).[8]

4. Aza witting reaction

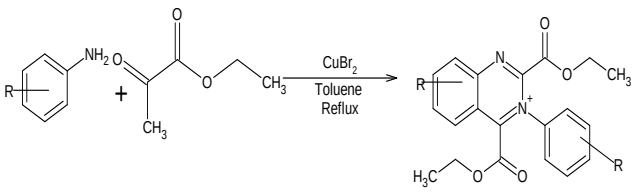
Ding *et al*. Synthesis 12 2-alkoxy-3H-quinazolin-4-ones from carbodiimide which was obtained from Aza Witting reaction of iminophosphorane with isocyanate (scheme 10).[9]



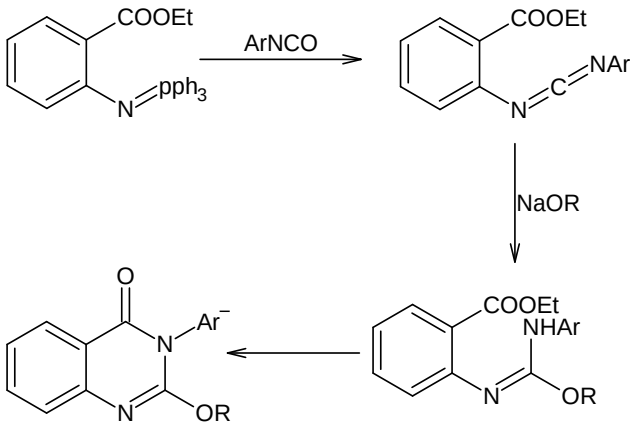
Scheme 7



Scheme 8



Scheme 9



Scheme 10

5. Microwave assisted synthesis

The long reaction time in traditional heating methods is overcome by the use of microwave.

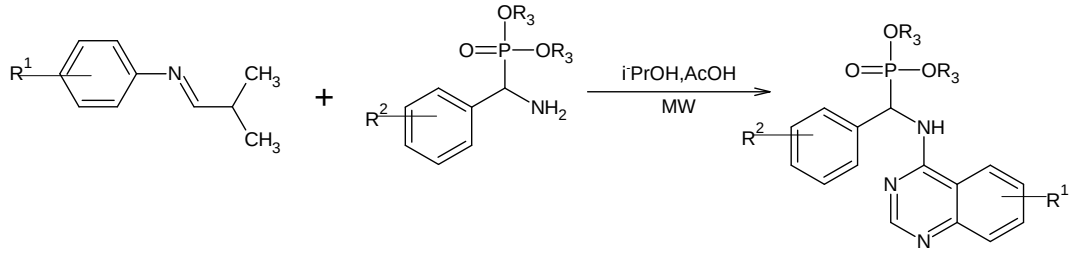
The 1st microwave assisted synthesis of 24 new quinazoline derivatives containing α-amino phosphate was reported by Luo *et al*. It is done by irradiated microwaves to the mixture of N-substituted (2-cyanophenyl)-N,N-dimethyl formamidine derivative and dialkyl amino phenyl in isopropanol acetic acid mixture for 20 mins. Among the synthesised derivatives 2 of them shows similar activity of Ningnanmycin (commercial reagent- antimicrobial) (Scheme 11).[10]

Kidwai *et al*. conduct studies, to synthesis quinazoline derivatives by solvent and catalyst free microwave assisted reaction using equimolar amount of aldehyde, 5,5-dimethyl-1,3-cyclohexanedione and urea/thiourea (scheme 12).[11]

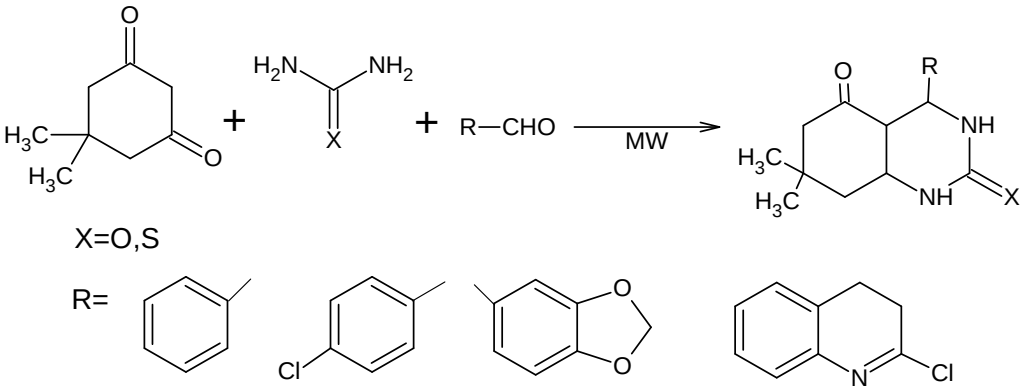
6. Metal mediated synthesis

Palladium catalysed synthesis

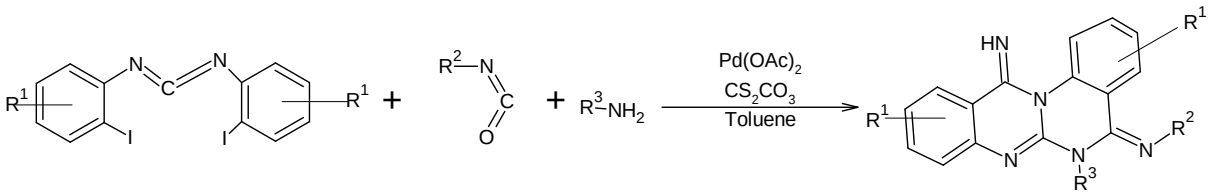
The optimum conditions for the palladium catalysed synthesis of quinazolino[3,2-a] quinazolines using 3 components was reported by Qiu *et al*. Using amine, isocyanide, carbodiimide in toluene (scheme 13).[12]



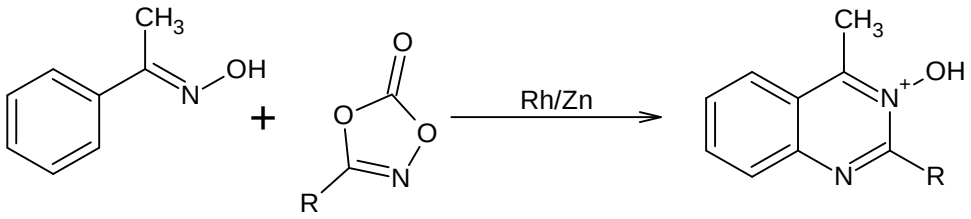
Scheme 11



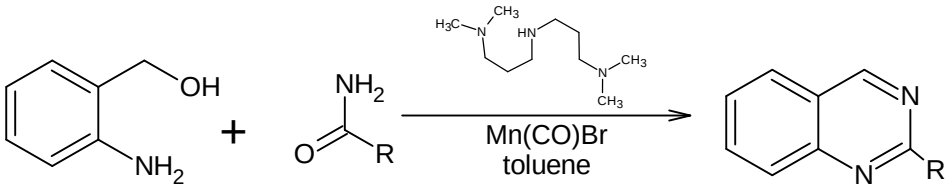
Scheme 12



Scheme 13



Scheme 14



12 examples (81% yield)

Scheme 15

Zinc and rhodium catalysed synthesis

Quinazoline-N-oxides prepared from simple ketoximes and 1,4-dioxazol-5-ones by Rh(I) catalysed C-H amidation and Zn(II) catalyzed cyclization (scheme 14).[13]

Manganese catalysed synthesis

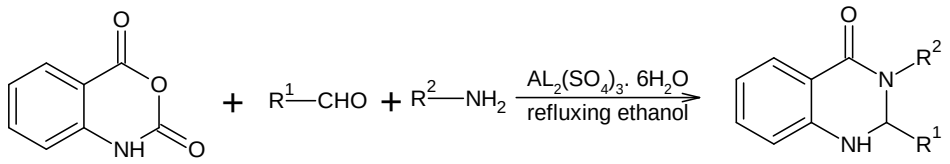
Akash *et al*. developed an efficient Mn(I) catalysed sustainable synthesis of quinazolines by the reaction of 2-aminobemmzyl alcohol with primary amides.[14]

7. One pot condensation

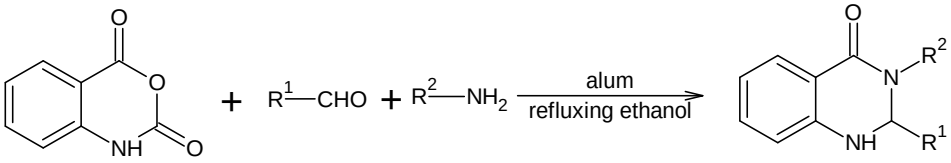
Alireza *et al*. report one pot 3 component condensation reaction to synthesised quinazoline derivatives by the reaction between aromatic aldehydes and isatoic anhydride with aniline derivatives refluxed in ethanol using aluminium sulfate as the catalyst (Scheme 15).[15]

Minoo *et al*. conducted one pot 3 component synthesis of 2,3-dihydroquinaolin-4(1H)-ones using alum as the catalyst (scheme 16).[16]

Anvar *et al.* synthesised quinazoline derivatives by one pot multi component reaction using nano-magnetic piperidinium benzene-1,3-disulfonate salt (PBDS-SCMNPS) and triethanol ammonium-2,2,2- trichloro acetate (TEATCA).[17]



Scheme 15

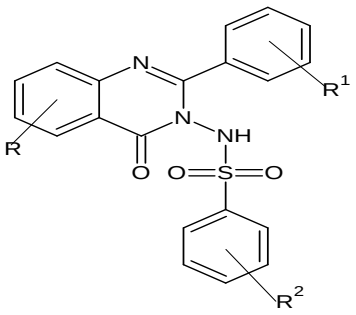


Scheme 16

8. BIOLOGICAL ACTIVITY

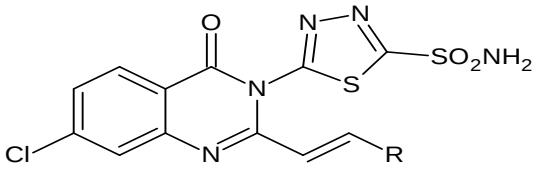
Diuretic

Mujeeb *et al*. synthesised 25 N-(substitured-4-oxo-2-substituted phenylquinaoline-3(4H) yl) substituted benzene sulfonamide derivatives and studied for diuretic activity[18]. Six compounds (7,9,14,15,19 and 20) shows better diuretic activity than standard drug metolazone.



Compound(R,R^1,R^2):1(H,H,H), 2(H,3-Br,H), 3(H,4-NO_2,H), 4(H,2-Cl,H), 5(H,4-CH_3,H), 6(4-F,H,H), 7(4-F,3-Br,H), 8(4-F,4-NO_3,H), 9(4-F,2-Cl,H), 10(4-F,4-CH_3,4-CH_3), 11(4-NO_2,H,4-CH_3), 12(4-NO_2,3-Br,4-CH_3), 13(4-NO_2,4-NO_2,4-CH_3), 14(4-NO_2,2-Cl,4-CH_3), 15(4-NO_2,4-OCH_3,4-CH_3), 16(4-Cl,H,4-CH_3), 17(4-Cl,3-Br,4-CH_3), 18(4-Cl,4-CH_3,4-CH_3), 19(4-Cl,2-Cl,4-NO_2), 20(4-Cl,4-OCH_3,NO_2), 21(4-Br,4-CH3,4-NO_2), 22(4-Br,2-Cl,4-NO_2), 23(4-Br,3-Br,4-NO_2), 24(4-Br,H,4-NO_2), 25(4-Br,4-NO_2,4-NO_2).

Azza *et al*. synthesised a new series of quinaolin-4(3H)-one derivatives (scheme 17) and studied their diuretic activity[19]. They found that synthesised 2-[2-(4-chloro-phenyl) vinyl]-7-chloro-3-(2-sufomoyl-1,3,4-thiadiaol-5-yl quinazolin-4(3H)-one (7c) exhibit significant diuretic activity.

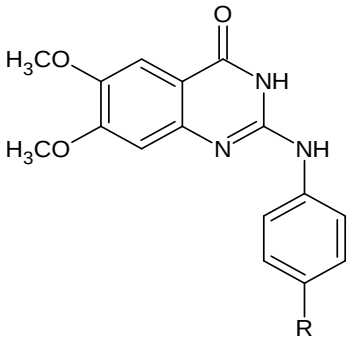


COMPOUND	R
7a	4-Br- C_6H_5
7b	4-Cl-C_6H_5
7c	3-pyridyl-2-thienyl

Scheme 17

Anti-hypertensive

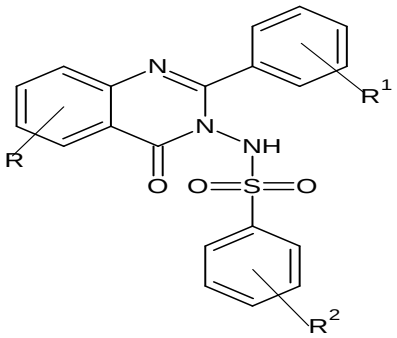
Harsha *et al*. synthesised 7 new quinazoline derivatives (scheme18) were screened for α-adrenergic receptor blocking activity[20]. 4b and 4e of them shows better activity



Scheme18

Mujeeb *et al*. studied antihypertensive activity of 25 synthesised N-(substituted-4-oxo-2-substituted phenyl quinaolin-3(4H) yl) substituted benzene sulfomaide derivatives and

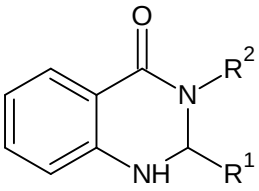
reported that 6 of them (7,9,14,15 and 19) shows significant antihypertensive activity against the standard drug prazosin and diazoxide whereas compound 20 showed significant antihypertensive activity by the non-invasive Tail Cuff method.[18]



Compound(R,R^1,R^2):1(H,H,H), 2(H,3-Br,H), 3(H,4-NO_2,H), 4(H,2-Cl,H), 5(H,4-CH_3,H), 6(4-F,H,H), 7(4-F,3-Br,H), 8(4-F,4-NO_3,H), 9(4-F,2-Cl,H), 10(4-F,4-CH_3,4-CH_3), 11(4-NO_2,H,4-CH_3), 12(4-NO_2,3-Br,4-CH_3), 13(4-NO_2,4-NO_2,4-CH_3), 14(4-NO_2,2-Cl,4-CH_3), 15(4-NO_2,4-OCH_3,4-CH_3), 16(4-Cl,H,4-CH_3), 17(4-Cl,3-Br,4-CH_3), 18(4-Cl,4-CH_3,4-CH_3), 19(4-Cl,2-Cl,4-NO_2), 20(4-Cl,4-OCH_3,NO_2), 21(4-Br,4-CH3,4-NO_2), 22(4-Br,2-Cl,4-NO_2), 23(4-Br,3-Br,4-NO_2), 24(4-Br,H,4-NO_2), 25(4-Br,4-NO_2,4-NO_2).

Anti-diabetic activity

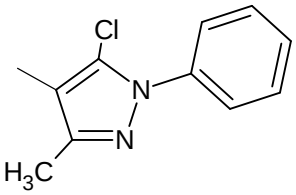
Alireza *et al.* synthesised 15 quinazoline derivatives (scheme 19) and all compounds showed potent anti-diabetic activity against standard acarbose.[15]



Compound	R^1	R^2
4a	C_6H_5-	C_6H_5-
4b	C_6H_5-	-$C_6H_4CH_3$
4c	C_6H_5-	-C_6H_4OH
4d	C_6H_5-	-C_6H_4Cl
4e	-C_6H_4OH	C_6H_5-
4f	-$C_6H_4NO_2$	C_6H_5-
4g	Car*	C_6H_5-
4h	Car*	-$C_6H_4CH_3$
4i	Car*	-C_6H_4OH
4j	Car*	-C_6H_4Cl

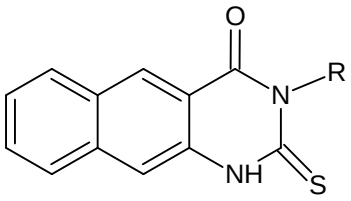
4k	Car*	$2CH_3 4CH_3 C_6H_3$
4l	Car*	$3CH_3 4CH_3 C_6H_3$

Car*

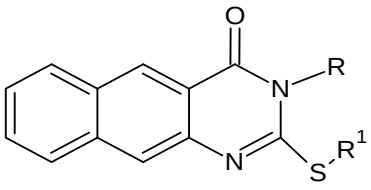


Scheme 19

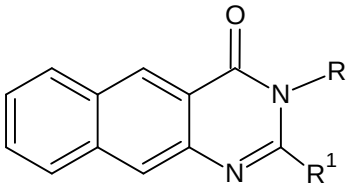
α-glucosidase inhibiting activity of 26 derivatives of 3-benzyl(phenethyl)-2-thioxobenzo[g]quinazolines by rashad *et al.*[28] Among 4 compounds exhibited highest activity when compared with standard acarbose.



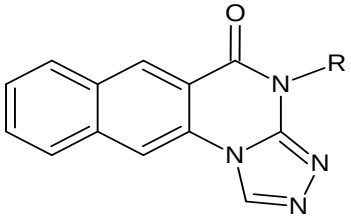
1&2



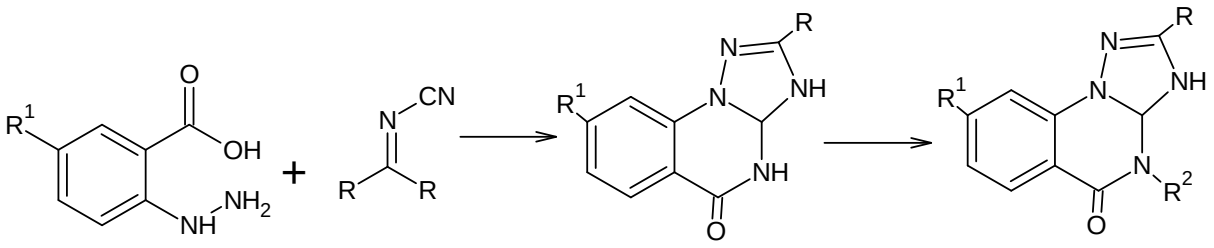
3-22



23&24



25&26



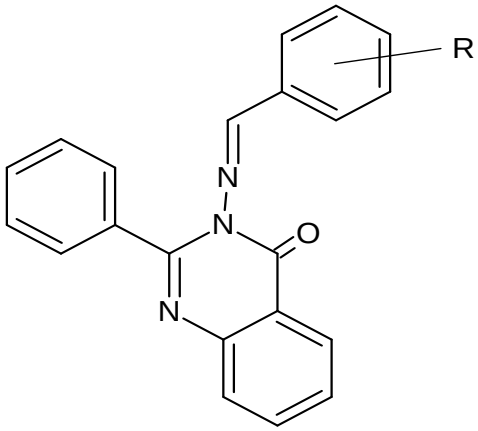
1-3 **4-14**

Scheme 20

Hatem *et al*. synthesised triazolo quinazoline derivatives[22] Out of 14, 4 derivatives (scheme 20) showed the highest inhibitory in relation to that of acarbose.

Anti-cancer activity

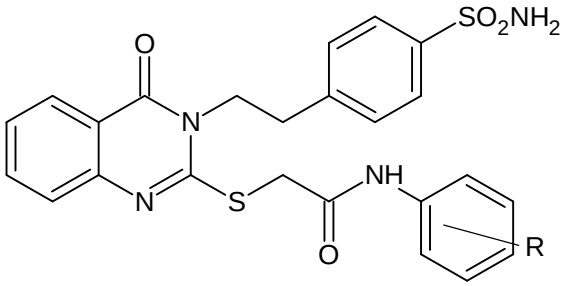
Subhadip *et al.*[23] prepared 3-(arylidene amino)-2-phenyl quinazolin-4(3H)-one derivatives. 2 of the showed higher cytotoxic activity on B16F10 cells (scheme 21).



Compound	R
Pa	3-NO_2
Pb	2-OH
Pc	4-OCH_3
Pd	3-OCH_3,4-OH

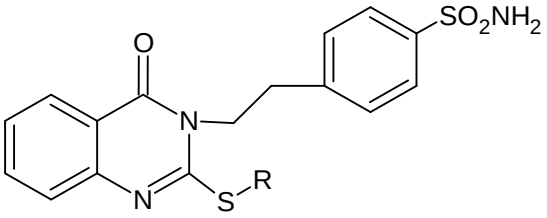
Scheme 21

Hamad *et al.*[24] synthesised 16 quinazolinone derivatives and evaluated for their cytotoxic activity. Reported that 5 compounds exhibit potent cytotoxic activity against standard drug sorafenib (scheme 22).



Scheme 22

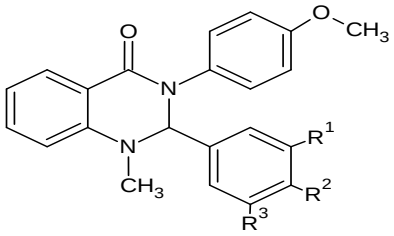
Adel *et al.*[25] evaluated invitro cytotoxicity of 15 substituted quinazolines, 5 of them showed potent anti-tumour activity using imatinib as standard (scheme23).



Scheme 23

Anti-tubercular

Pradeep *et al.*[26] screened a new series of 2,3-disubstituted quinazolin-4(1H)-ones (scheme 24) for invitro anti tubercular activity and they reported that 2 compounds exhibited potent anti-tubercular activity.

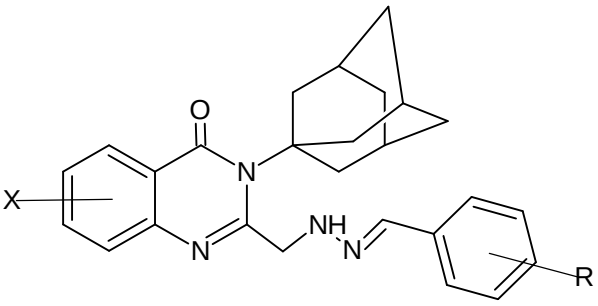


Compound	R^1	R^2	R^3
3a	H	H	H
3b	H	CH_3	H
3c	HH	OCH_3	H
3d	H	F	H
3e	H	Cl	H
3h	H	Br	H
3i	H	CF_3	H
3j	CF_3	H	CF_3
3k	H	OCF_3	H
3l	H	OH	H

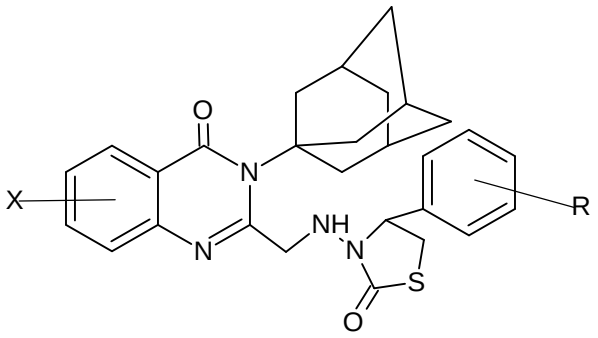
Scheme 24

Anti-parkinsonism

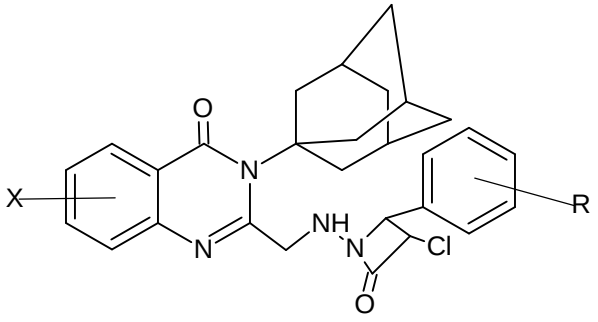
Sunil *et al.* prepared various azetidinonyl and thiazolidinonyl quinazoline derivatives and are screened for their parkinsonian activity. Thiazolidine derivative showed more potent anti-parkinsonian activity than azetidinone derivatives. They found that 3,4-dimethoxyphenyl group is beneficial for the anti-parkinsonian activity[27] (scheme 25).



5a-5l



6a-6l

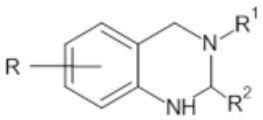


7a-7l

Scheme 25

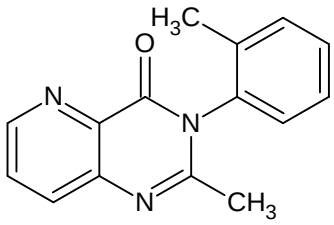
Anti-convulsant

Hatem *et al.*[28] evaluated a new series of quinazolin-4(3H)-ones(scheme 26) for anti-convulsant activity. And they reported that benzyl substitution at position 3 exhibit a strong activity but with less seizure prevention compared to butyl substitution.



Scheme 26

N. A. Vaidya *et al.*[28] synthesised 23 substituted 3,4-dihydro-4-oxoquinazolines and are evaluated for potential anti-convulsant activity. The azaquinazolone was found to possess the most significant activity (scheme 27).



Scheme 27

9. CONCLUSION

The heterocyclic fused nucleus quinazoline have drawn an immense attention to its wide application in the field of medicinal chemistry. Quinazoline is considered as privileged scaffold, in which structural modification is made around the quinazoline being the central body of the pharmacophore, hold different types of substituents. This review is an attempt to outline the chemistry and magnify the biological activities of quinazoline nucleus. This will also encourage the researchers with a thorough understanding of structural activity relationship to accelerate the designing process to generate more number of potent therapeutically valuable clinical candidates.

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Conflict of interest

The author does not have any conflict of interest regarding the publication of this paper.

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