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QUINAZOLINE DERIVATIVES & PHARMACOLOGICAL ACTIVITIES: A REVIEW

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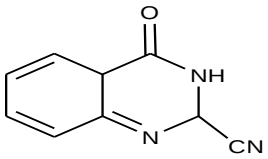
ABSTRACT

Quinazoline is the main fused heterocyclic ring system reported for their biological activities, compounds with varieties of pharmacophores, which bring together knowledge of a target with understanding of the molecule types that might interact with the target family. The molecular manipulation of promising lead compound is still a major line of approach for the discovery of new drugs. Combination of two or more moieties into one is a common procedure of manipulation and this can probably result in the increase of biological activity and removal of untoward side effects.

Keywords: Quinazoline, Pharmacophores, Discovery.

INTRODUCTION

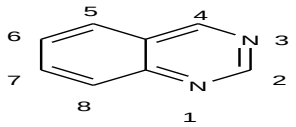
In 1869 Griess prepared the first quinazoline derivative, 2 – cyano 3, 4-dihydro-4-oxoquinazoline, by the reaction of cyanogens with anthranilic acid. Griess apparently recognized the bicylic nature of the product which, he called bicyanoamido benzoyl and used this name until 1885. When structure (1) was known with some certainly [1].



(1)

The preparation of the parent quinazoline came many years later when Bischler and Lang obtained it by decarboxylation of the 2-carboxy derivative.

A more satisfactory synthesis of quinazoline was subsequently devised by Gabriel in 1903 that studied properties and those of its derivatives in greater detail.



The name was proposed by Widdege. Other names such as phenmiazine, benzyleneamidine, benzo-1, 3-diazine, 5, 6-benzopyrimidine and 1, 3-diazanapthaline have occasionally been used. The numbering suggested by Paal and Busch is still in use.

The presence of a fused benzene ring alters the properties of the pyrimidine ring considerably. The two nitrogen atoms are not equivalent, and the marked polarization of the 3, 4- double bond is reflected in the reactions of quinazoline. The properties of substitute's quinazolines depend largely on

a. The nature of the substitutents.
b. Whether they are in the pyrimidine ring (or) in the benzene ring
c. Whether (or) not complete conjugation is present in the pyrimidine ring.

The chemistry of quinazoline was reviewed by Williamson in 1957, then by Lindquist in 1959 and brought up to date by Armarego in 1963.

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CHEMICAL PROPERTIES

Quinazolines is 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.

a). Hydrolysis, oxidation and reduction.

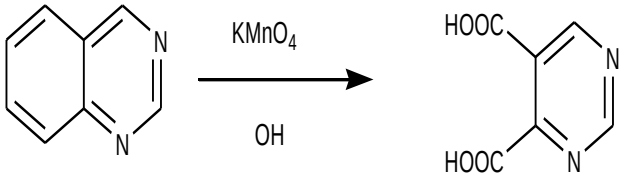
Oxidation of quinazoline in dilute aqueous acid, with two equivalents of hydrogen peroxide at room temperature gave a high yield of 3,4- dihydro-4-oxo quinazoline.

In alkaline medium, where the anhydrous neutral species of quinazoline were predominantly undergo oxidation with $KMnO_4$ furnished a high yield of 3,4-dihydro-4-oxo quinazoline was also formed.

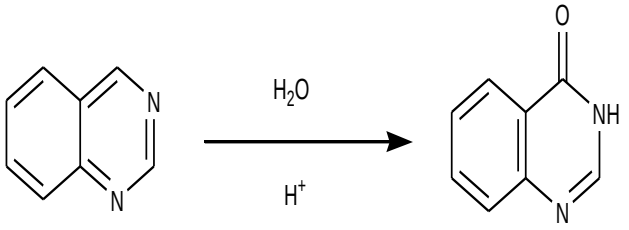
Oxidation

Catalytic hydrogenation of quinazoline stopped after the absorption of one molecules of hydrogen and gave 3, 4-dihydro quinazoline.

Reduction with sodium amalgam gave 1,2,3,4-tetrahydroquinazoline. Lithium aluminum hydride and sodium borohydride gave 3,4-dihydro and 1,2,3,4-tetrahydroquinazoline.



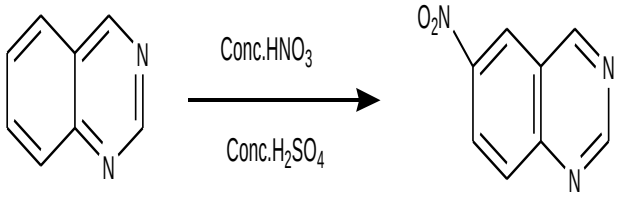
Reduction



b). Nucleophilic and electrophilic substitution reactions

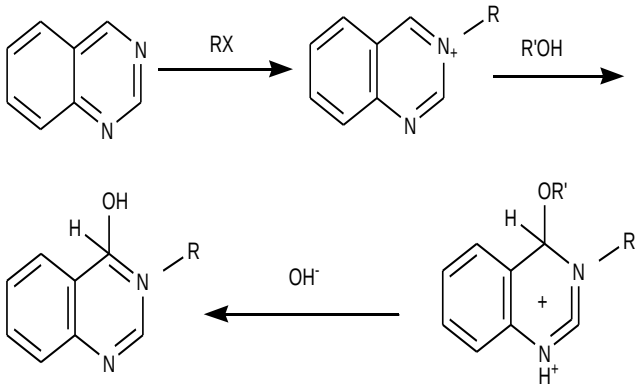
The two known nucleophilic substitution reactions of quinazoline namely with sodamide and hydrazine, presumably proceed via the intermediate addition products and gave 4-amino and 4-hydrazine quinazoline.

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 H_2SO_4. No oxidation of the heterocyclic ring can occur under these conditions because the hydrated cation is not present.



c). Alkylation reactions

Alkylation of quinazoline takes place on N, 3-methyl, 3-ethyl-3-alkyl and 3-benzyl quinazolinium salts 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.



d). Addition reactions

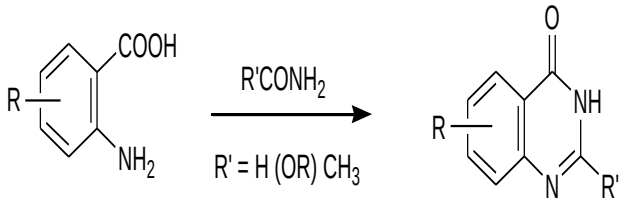
Quinazoline is very reactive towards anionid reagents which attack position 4. Sodium bisulphate, hydrogencyanide, acetophenone, acetone, 2- butanone and cyclohexanone add across the 3,4-double bond of quinazoline. Methyl, ethyl, isopropyl, benzyl, t-butyl and phenyl magnesium halides and phenyl lithium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

SYHTHESIS

Following methods were reported for the synthesis of oxoquinazolines.

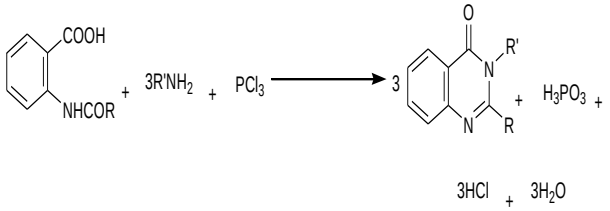
a). Niementowski's synthesis

Niementowski's found that 3 (or) 4 substituted anthranilic acid when reacted with formamide at 125 - 130ºC for 4 hours gave 86% yield of 3, 4-dihydro-4-oxoquinazoline.



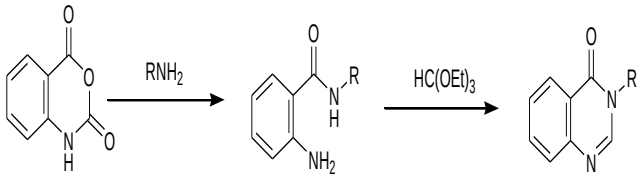
b). Grimmel, Guinther and Morgan's synthesis.

3 moles of O-amino benzoic acids, when heated with 3 moles of an 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.



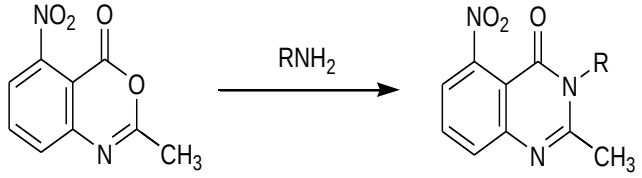
c). From isatoic anhydride

Isatoic anhydride readily reacts with equimolar quantity of amines to dihydro-4-oxoquinazolines by refluxing ethyl orthoformate for 1- 6hours without isolating the intermediate amides.



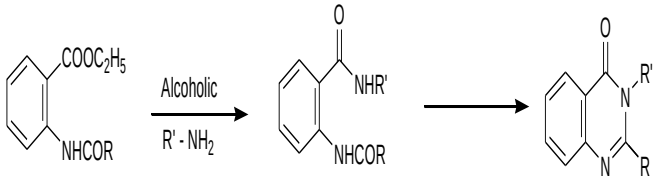
d). From 3,1,4-Benoxazones (Acylanthranils) and amines.

3,1,4-Benoxazones react with amines to give 3,4-dihydro-4-oxoquinazolines. Primary aliphatic amines and anilines react with 2-methyl-5-nitro-4-oxoquinazolines.



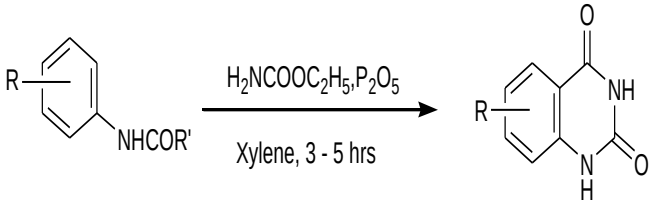
e). From ethyl 2-acetamido-5-nitrobenzoate.

Ethyl 2-acetamido-5-nitrobenzene and alcoholic ammonia when heated in a sealed tube at 170ºC, yields 3,4-dihydro –methyl-6-nitro-4-oxoquinazoline.



f). Sen and Ray's synthesis

Boiling a solution of normal (or) isobutyrylanilides with urethane and phosphorous pentoxide in xylene gave 2-propyl and 2-isopropyl-3,4-dihydro-4-oxoquinazolines.

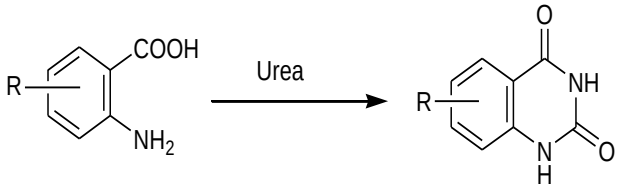


(R = Me, OMe, OEt; R' = Me, Et, Pr, Iso-Pro, Ph)

Following methods were reported for the synthesis of 2,4-dioxoquinazolines (benzoylene urea)

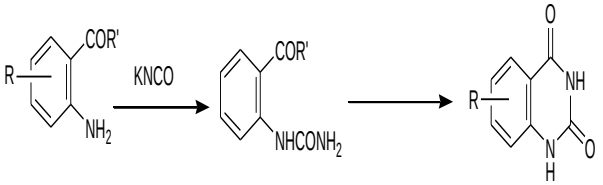
a) From anthranilic acid and ureas.

The fusion of anthranilic acid with urea to give 1,2,3,4-tetrahydro-2,4-dioxoquinazoline was first described by Griess.



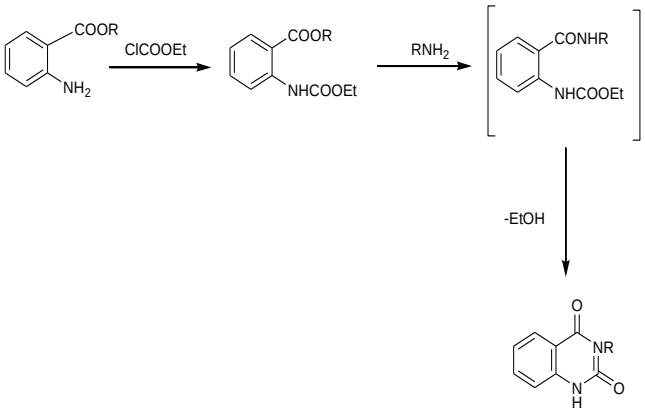
b). From O-ureidobenzoic acid.

O-ureidobenzoic acids are readily prepared from the corresponding anthranilic acid and potassium cyanate. The ureido acids are then easily cyclised to the respective 1,2,3,4-tetrahydro-2,4-dioxoquinazolines by heating with acid (or) alkali. Anthranilic esters and amides as well as undergo this reaction.



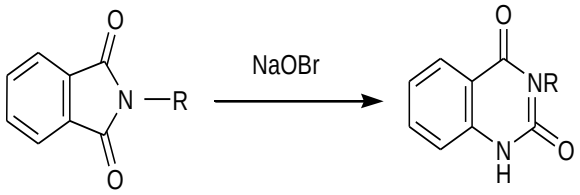
c) From O-ethoxy carbonylaminobenzoic esters (or) amides.

When O-ethoxycarbonylamino benzamide and its 4-methyl derivatives are heated above their melting points, they lose water and from 1,2,3,4-tetrahydro-2,4-dioxoquinazoline.



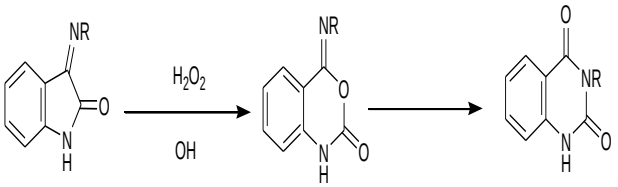
d). From phthalic acid derivatives.

The use of derivatives of phthalic acid for the preparation of dioxoquinazoline necessitates rearrangement of the Hoffmann curties (or) Lossan type. Reaction of phthalamide (or) phthalimide, N-methyl and N-ethyl phthalimide with alkali hypobromite gives the 1,2,3,4-tetrehydro 2,4-dioxoquinazoline.



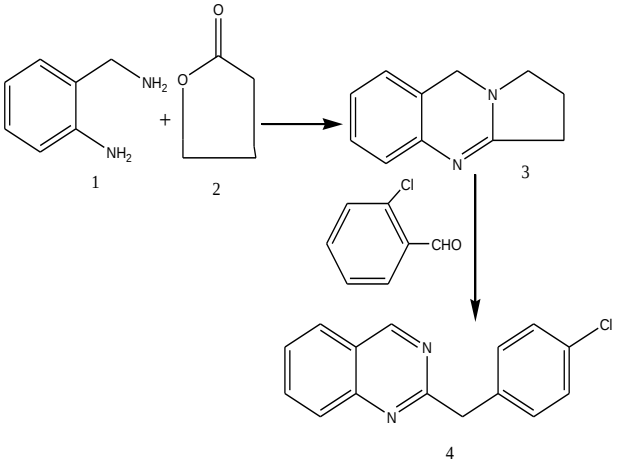
e). From Isatins

α-isatin oxime rearranges to 1,2,3,4-tetrahydro-2,4-dioxoquinazoline on heating with dilute sodium hydroxide, β-imino derivatives of isatin, on the other hand, require oxidation with hydrogen peroxide in alkaline solution in order to from the dioxoquinazoline.



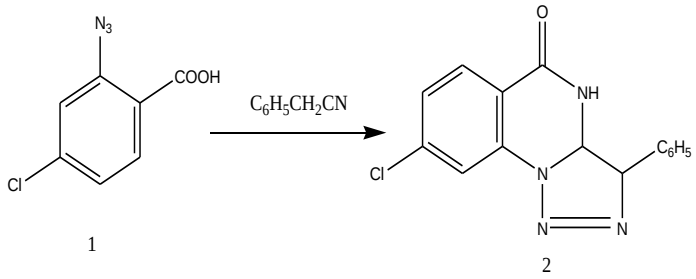
FROM 2-AMINOBENZYLAMINE

2-aminobenzylamine (1)reacts with butyrolactone which involoves to form int-ermediate compound (2)and further condensed with benzaldehyde to yeild product 3-(2-chlo- robenzylidene) -1,2,3,9-tetrahydropyrrolo-2-quinazoline.



FROM 2-AZIDO-4-CHLORO BENZOICACID

2-azido-4-chlorobezoic acid(1) readily reacts with benzyl nitrile and results in the formation of 7-chloro-3-phenyl-[1,2,3]triazolo[1,5-a]quinazoline-5-one(2). [2]



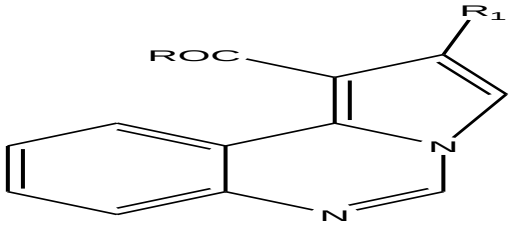
Won-Jea C et al., [4] In this study, virtual screening was employed for hit compound identification with chemical libraries using Surflex Dock. Subsequently, hit optimization for potent and selective candidate JAK2 inhibitors was performed through synthesis of diverse C-1 substituted quinazoline derivatives.(2011)

C.H.Rajveer *et al.,* [5] have been synthesized a number of substituted oxoquinazolines & reported their analgesic & anti-bacterial activity. (2010)

Vouy LT and Michelle M *et al.,* [6] Condensation of o-iodobenzaldehydes with amidine hydrochlorides under ligand-free coppercatalyzed Ullmann N-arylation conditions afforded the corresponding quinazolines in good to excellent yields.

J.P.Patil *et al.,* [7] 2-methyl-3(H)-Quinazolinone was synthesized by microwave irradiation method. (2009)

Florea Dumitrascu *et al..,* [8] have been synthesized pyrrol (1,2-c)quinazoline and investigated using X-ray diffraction and their NOE experiments in high resolution NMR.(2009)



Deepti Kohli *et al.,* [9] have been synthesized quinazolinone derivatives and evaluated for their antibacterial activity by cup plate method by measuring inhibition zone. (2009)

G.L.Talersa *et al.,* [10] Treatment of benzoxazine 1 with hydrazine hydrate in ethanol furnished 3 amino-2-phenylquinazolin-4-(3H)-one 2, which upon condensation with aldehydes yielded the corresponding 3-arylidenoamino derivatives. Cyclization of these derivatives using mercaptosuccinic acid afforded 1,3-thiazolidin-4-one ethanolic acids, which after esterfication with N-hydroxyphthalimide or N-hydroxysuccinamide via acid chlorides produced the respective ethanolic esters. (2009)

MD. Salahuddin *et al.,* [11] have been synthesized A series of novel 3-(6-substituted-1, 3-

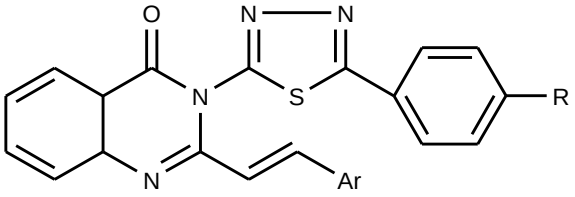
benzothiazole-2-yl)-2-[{(4-substituted phenyl) amino} methyl] quinazolines-4(3*H*)-ones and the Synthesized quinazolines-4-one derivative were investigated for their anti-inflammatory and antibacterial activity.(2009)

Olayinka O. Ajani *et al.,* [12] have been synthesized a series of novel quinoxalin-2(1*H*)-one-3-hydrazone derivatives, 2a - 8d were synthesized via condensation of 3-hydrazinoquinoxalin-2(1*H*)-one, with the corresponding ketones under microwave irradiation. The microwave assisted reaction was remarkably successful and gave hydrazones in higher yield at less reaction time compared to conventional heating method. (2009)

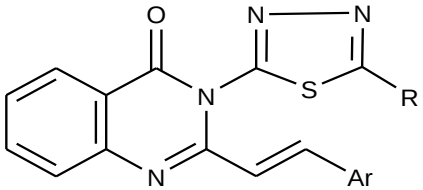
G.Chandrasekara Reddy *et al.,* [13] have been docking studies of a few newly synthesized 6,7-dialkoxy-4-anilinoquinazoline derivatives which showed EGFR-TK inhibitory Activity were conducted.(2009)

Gazi Irez *et al.,* [14] In this study, (hydroxyimino)(2-phenyl(1,2,3,4-tetrahydroquinazolin-2-yl)) methane and (hydroxyimino) (2-(2-thienyl)(1,2,3,4-tetrahydroquinazolin-2-yl)) methane were synthesized by the condensation of 2-(hydroxyimino)-1-phenylethan-1-one and 2-(hydroxyimino)-1-(2-thienyl) ethan-1-one with 2-aminobenzylamine (2-ABA). Complexes of these ligands with Co^{3+}were prepared with a metal: ligand ratio of 1:2. The ligands and their complexes were elucidated on the basis of elemental analyses, AAS, FT-IR, ^{1}H- and^{13}C-NMR spectra, mass spectra, magnetic susceptibility measurements, and molar conductivity. (2008)

Varsha Jatav *et al*., [15] have been synthesized 3-[5-(4- substituted phenyl)-1, 3, 4-thiadiazole-2-yl]-2-styryl quinazoline -4(3H)-ones and reported their antibacterial and antifungal activity. (2008)

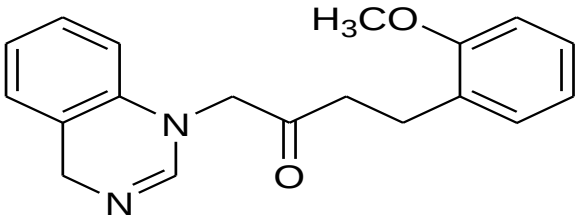


Varsa Jatav *et al.,* [16] have been synthesized 3-[5-substituted-1, 3, 4-thiadiazole-2-yl]-2- styryl quinazoline-4(3H)-ones and their CNS depressant activity was screened with the help of forced swim pool method. (2008)



Ar – C_6H_5, R – p OCH_3

Yuliang Wang *et al.,* [17] have designed and synthesized series of 4-(2-methoxyphenyl)-2-oxobutylquinazoline derivatives and reported their anticoccidial activity. (2008)

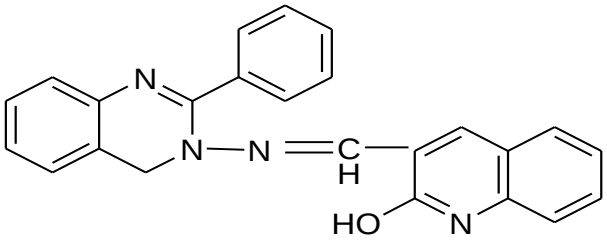


P.Praveen Kumar *et al.,* [18] have been synthesized 6,7,8,9-tetrahydro-5(H)-5-nitrophenylthiazolo[2,3-b]-quinazolin-3(2H)-one derivatives and the synthesized compounds have been screened for antimicrobial activity. (2008)

Omar Abd el-Fattah m. Fathalla *et al.,* [19] have been synthesize new series of some 2-[(E)-2-furan-2-yl-vinyl]-quina- zolin-4(3H)-ones incorporated into pyrazoline, isoxazoline, pyrimidine or pyrimidine-thione ring systems at position-3 of the quinazoline ring. The antimicrobial activity and anti-inflammatory effect of some of these compounds were studied. (2008)

Omar Al-Deeb *et al.,* [20] 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. 2008

K. Siddappa *et al.,* [21] have been synthesized 3-[(2-Hydroxy-quinolin-3-ylmethylene)-amino]-2-phenyl-3H-quinazolin-4-one and its Metal (II) Complexes and reported their Antimicrobial activity. (2008)



HQMAPQ Ligand

Cedric Loge *et al.,* [22] Continuous efforts in microwave-assisted synthesis and the structure activity relationships' (SARs) studies of novel modified 9-oxo-thia-zolo[5,4-f]quinazoline-2-carbonitriles, allowed identification of new amidine and imidate derivatives as potent and dual CDK1/GSK-3 inhibitors. Combination of lead optimization and molecular modeling studies allowed identification of a dual CDK1/GSK-3 inhibitor (compound 13d) with submicromolar values. (2008)

Gloria D Galarce *et al.,* [23] This study describes the effect of novel 6-Arylbenzimidazo [1,2-*c*]quinazoline derivatives as tumor necrosis factor alpha (TNF-α) production inhibitors. The newly synthesized compounds were tested for their *in* vitroability to inhibit the lipolysaccharide (LPS) induced TNF- α secretion in the

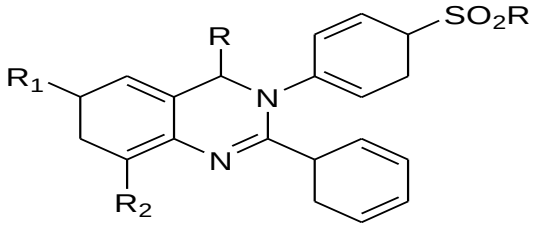
human promyelocytic cell line HL-60. The compound 6-Phenyl-benzimidazo [1,2-*c*]quinazoline, coded as G1, resulted as the most potent inhibitor and with no significant cytotoxic activity. Thus, 6-Arylbenzimidazo [1,2-*c*]quinazoline derivatives may have a potential as anti-inflammatory agents.(2008)

R.Suthakaran *et al.,* [24] have been synthesized by condensing 2-methyl / phenyl / Chloro methyl disubstituted benzooxazine-4-one and 1-(2- amino ethyl)–4- substituted benzylidene-2-phenyl-1H–Imidazoles–5(4H)-one, gave 30 imidazoloquinazoline-4- one derivatives. All the compounds have been screened for their antimicrobial activities. Most of the compounds have shown promising antibacterial, and antifungal activity. (2008)

Chan Seong Cheong *et al*., [25] have been Studied on the Selective Reduction of 1*H*-Quinazoline-2,4-diones.(2008)

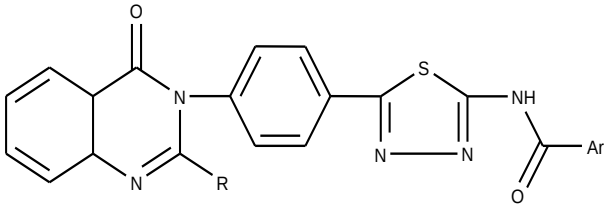
Ashraf A. Aly *et al.,* [26] have been Synthesis of a series of triazoloquinazolinones and benzimidazoquinazolinones has been achieved under microwave irradiation. The products were obtained in nearly quantitative yields within few minutes during the reaction of aromatic aldehydes with 5-amino-1(*H*)-1,2,4-triazole (or 2-aminobenzimidazole) and dimedone in DMF.(2007)

Periyasamy Selvam *et al.,* [27] have designed and synthesized novel 2,3-disubtituted quinazoline-4(3H)-ones by microwave technique and characterized them by spectral analysis. Synthesized compounds were screened for cytotoxicity and for antiviral activity against influenza A. (2007)



Veerachamy *et al*., [28] have been synthesized a series of 3-benzyl-2-substituted-3H-[1,2,4]triazolo[5,1-b]quinazolin-9-ones have been synthesized 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 antihypertensive 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.(2007).

Desai N C *et al*., [29] have been reported the synthesis and characterization of new quinazolines as potential antimicrobial agents.(2007)



R = 2- chlorophenyl, Ar = Different aryl groups

V. Alagarsamy *et al*., [30] A series of novel 1-substituted-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-ones were synthesized by the cyclization of 2-hydrazino-3-benzyl-3H-quinazolin-4-one with various one-carbon donors. When tested for their in vivo H_1-antihistaminic activity on guinea pigs, all the test compounds protected the animals from histamine induced bronchospasm significantly. (2007)

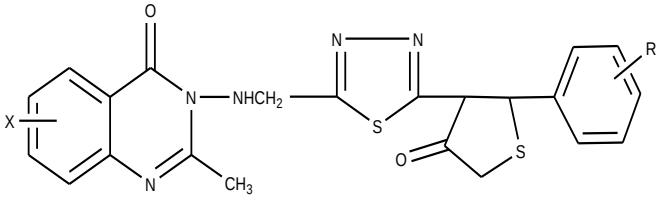
B.D. Mistry *et al.,* [31] have been synthesized 6–bromo–2–alkyl/aryl–3{[phenyl(phenyldiazenyl)methylene]amino}quinazolin–4(3*H*)–one reported their Antimicrobial activity..(2006)

Mosaad Sayed Mohamed *et al.,* [32] have been synthesized a series of new 5-(4-chlorophenyl)-9-iodo-3-substituted-l,2,4-triazolo[4,3-c]quinazoline and 2- (4-chlorophenyl)-6-iodo-4-substituted-quinazoline was prepared via several synthetic routes. The synthesized compounds were evaluated as anti-inflammatory agents through the carrageenin-induced paw edema test. The screening data revealed that nine of the tested compounds have activity comparable to indomethacin. (2005)

Terzio Glu *et al.,* [33] Two regioisomer series, 2-(3-ethyl-4(3H)-quinazolinone-2-ylmercaptoacetylhydrazono)-3-alkyl/3-aryl-5-methyl-4-thiazolidinones (12-21) and 2-arylimino-3-(3-ethyl-4(3H)-quinazolinone-2-ylmercaptoacetyla-mino)-5-methyl-4-thiazolidinones were synthesized and reported their anticonvulsant activity.(2005)

Sona Jantova *et al.,* [34] The antibacterial activity of ten series of substituted quinazolines (157 derivatives) against bacterial strains Escherichia coli CCM 3988,Pseudomonas aeruginosa CCM 3955, Bacillus subtilis ATCC 6663 and Staphylococcus aureus CCM 3953 by micro dilution assay was investigated. The sensitivity of the Gram positive bacteria to the tested quinazolines was higher than that of Gram negative bacteria. The most effective of ten quinazoline structure series were condensed [1,2,4]triazoloquinazolines and 10H-[1,2,4]triazino[5,4-b]quinazolin-10-ones.(2004)

Archana *et al*., [35] have been synthesized derivatives of substituted quinazolinonyl-2-Oxo/thiobarbituric acid and their anticonvulsant activity was screened against maximal electroshock (MES) and pentylenetetrazole (PTZ) models.(2004)

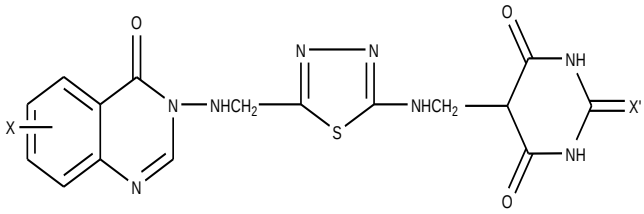


X – H, R – H or p- OCH_3

Abdel Ghany Aly El-helby *et al*., [36] A series of halogenated derivatives, 3-methyl, 3-ethyl and 3-phenyl-6-mono and 6,8-disubstituted-3*H*-quinazolin-4-one derivatives was also synthesized and evaluated for anticonvulsant activity. Reduced anticonvulsant activity was recorded. Phenobarbitone sodium was used as a reference. (2003)

R. Chioua *et al*., [37] The [4+2] cycloaddition between 2,4-diphenylpyrimidine ortho-quinodimethane and dimethyl acetylenedicarboxylate leads to 2,4-diphenylquinazoline-6,7-dicarboxylate .2,4-Diphenylfuro [3,4-g]quinazoline-6,8-dione is also obtained by basic hydrolysis of compound , followed by the closure of the resulting diacid in acetic anhydride.(2002)

Archana *et al*., [38] have been synthesized some thiadiazolyl and thiazolidinonyl quinazoline-4(3H)-ones screened them for anticonvulsant activity against maximal electroshock (MES) induced convulsions in animal models.(2002)

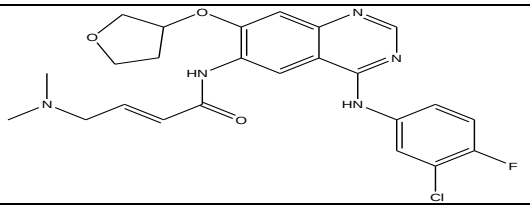
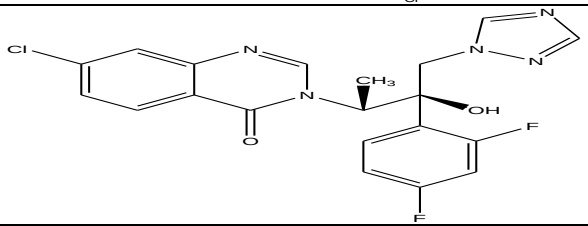
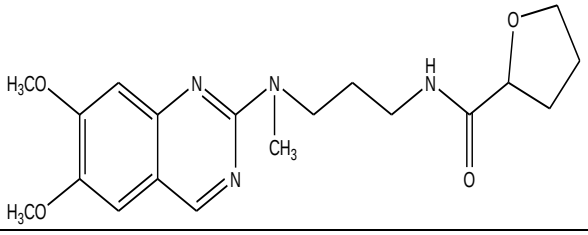


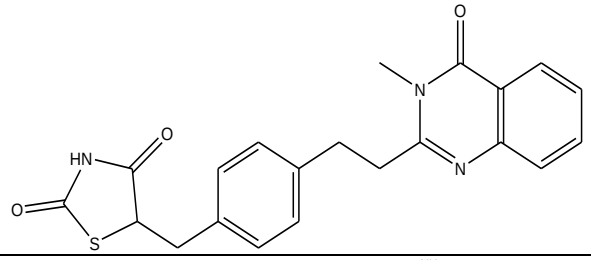
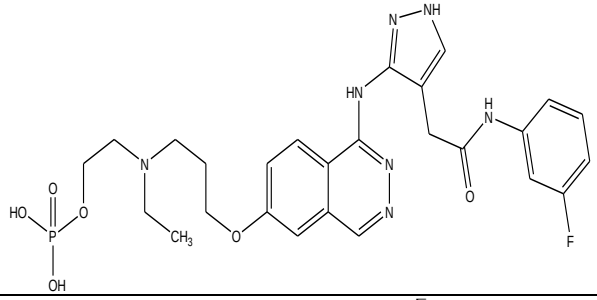
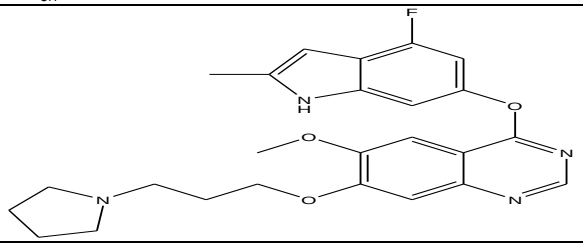
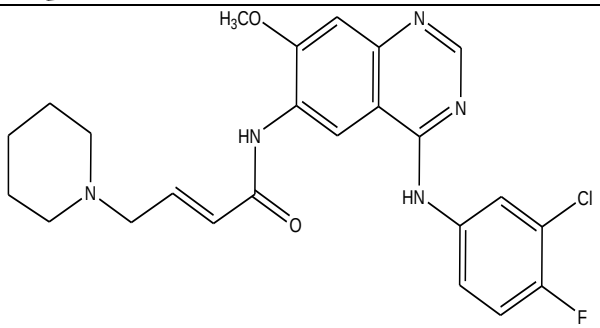
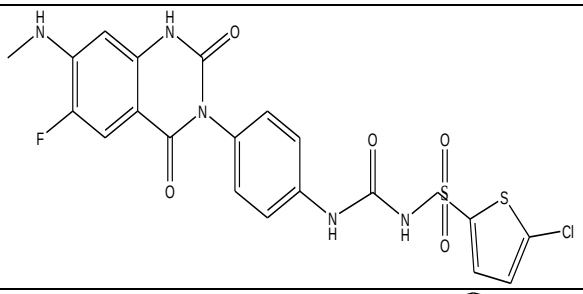
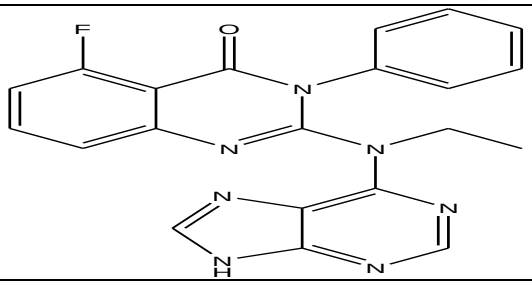
X – H or Cl, X' – O

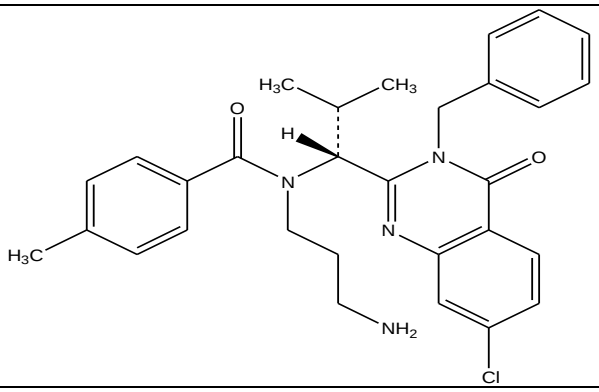
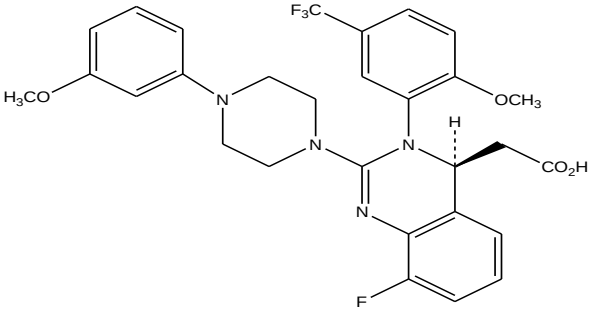
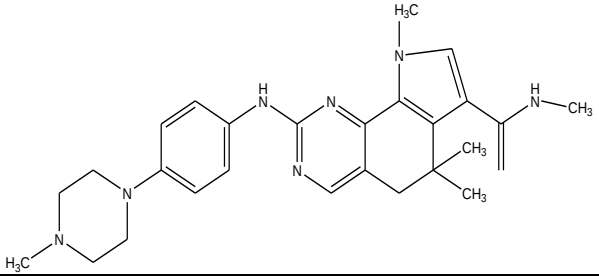
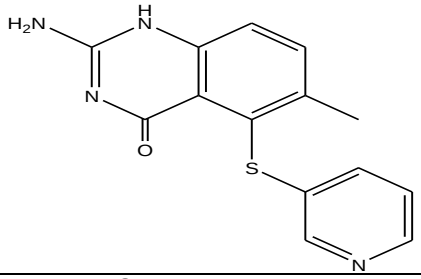
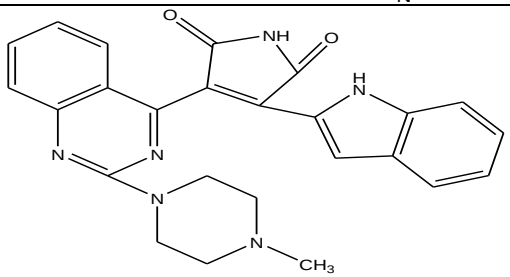
V.K.Pandey *et al.*, [39] have been synthesized 1,4-disubstituted 3-[3'-(2'-phenyl-4'-oxo-quinazolinyl)]-2-azetidinones and reported their Antiferitility activity. (1986)

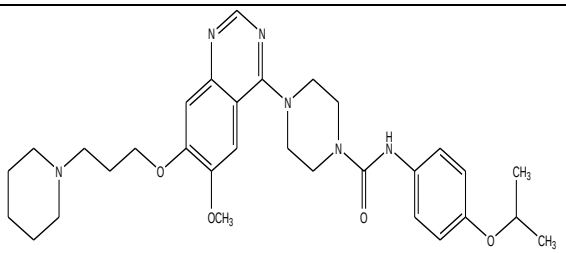
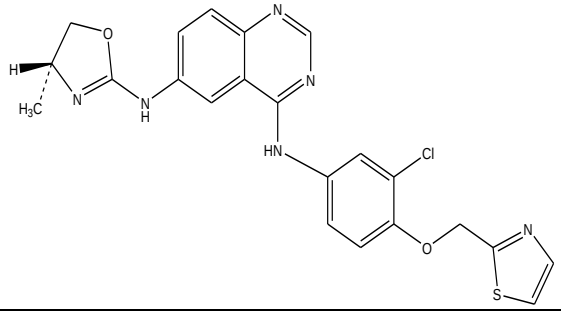
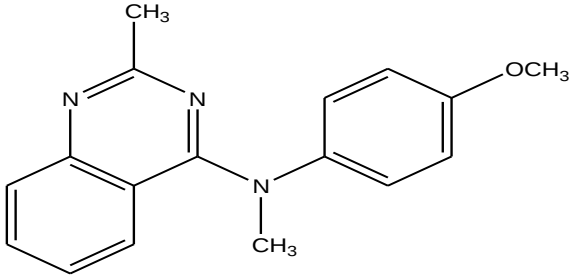
Piyush Kumar *et al*., [40] have been synthesized 6- substituted 6- substituted-2-phenyl-3-(5-substituted mercapto-1, 3, 4- thiadiazol-2-yl) quinazoline-4-(3H)-ones and reported their anti tubercular activity.(1983)

Table 1. Marketed Available Quinazoline Derivative Drugs [3]

S. No	Quinazoline Derivative	Chemical Structure	Use
1	Afatinib		Antifungal activity
2	Albaconazole		Antifungal activity
3	Alfuzocin		Anticancer activity

4	Balaglitazone		Antidiabetic and hypolipidimic property
5	Barasertib		Acute myeloid leukemia
6	Cediranib		Heamatological cancer,Liver metastases
7	Dacomitinib		Anticancer
8	Elinogrel		To treat thrombosis.
9	GS1101(CAL101)		To treat haematological cancer.

10	Ispinesib		To treat solid tumors.
11	Letermovir		Human cytomegalovirus.
12	Milciclib		Anticancer.
13	Nolatrexed		To treat solid tumours.
14	Sotrastaurin		Psoriasis,ulcerative colitis.

15	Tandutinib		Glioblstoma.
16	Varlitinib		Anticancer drug.
17	Verubulin		Anticancer drug.

CONCLUSION

Hetero cyclic compound containing quinazoline nucleus plays most important role in the the field of clinical therapeutics. It shows wide range of activities for medication purpose. Vast number of quinazoline containing compounds have been synthesized and evaluated for their biological activity. The various substituted quinazoline are having significant anti hypertensive activity, Significant antineoplastic, antidepressant, Antipsychotic. Whereas some of the derivatives of quinazoline are found to be effective as analgesic, antipsychotic, Antiarrhythmic, sedative hypnotics. Recently it was proven that, some of the important marketed quinazoline nucleus containing drug having different biological or pharmacological activity were discussed in table 1. The quinazoline based pharmaceutical are rapidly becoming very important class of therapeutic agents and are likely to replace many obtainable organic based pharmaceuticals in the very near future. The quinazoline based pharmaceuticals will be created on a large scale by modern drug Discovery Company by different research development processes and will become available commercially for therapeutic use. The biological profiles of this new generation of quinazoline represent much progress with regard to the older compounds.

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