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Review Article

Chemistry and activity of quinazoline moiety: A systematic review study

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ABSTRACT

Quinazoline is a compound with amalgamated heterocyclic system popular for their biological activities. Quinazoline is a compound made up six membered fused aromatic rings i,e a benzene ring with pyrimidine ring. Its chemical formula is $C_8H_6N_2O$. It is yellow colour and found in the crystalline form. Molecular optimization of potentially lead compounds through a chemist is an needy and upcomming approach for the discovery of new pharmaceuticals. More than two combinations of pharmacophore and making them one moiety is a noval and popular procedure of exploitation of synthesis now a days and this cause an additive increment of biological activities with taking away of surplus side effects. Present communication studies about the structure origin, diversity and chemical modification with change in pharmacological activities of Quinazoline.

1. Introduction

Quinazolin-4(3H)-one and its derivatives have structural importance of nearly two hundred naturally found alkaloids which are isolated and collectted from various of species of the plants, micro-organisms and animals. The name of quinazoline was first given by Weddige as he observed that it is isomeric with two compounds i.e cinnoline and quinoxaline.

Naturally, quinazolinone alkaloids forms a basic core of febrifugine and isofebrifugine, which was found to be immense antimalarial activity and are extracted from the traditional chisnese medicine.[1,2] Chemically, quinazolin constitutes an important class of fused heterocycles six membered (benzene and pyrimidine) rings (Figure 1).In which two conjoined aromatic rings incorporate with two nitrogen atoms and one of the carbon oxidized with keto oxygen. The structure is also called as quinazolindiones, chemically can be called as Quinazolin-4(3H)-one. 2-quinazolinone and 4-quinazolinone are the two structural isomers have been known, but studies shows that the 4-isomers is most common (Figure 2).

The first quinazolinones (1) found to be synthesized in 1860 from anthranilic acid and cyanogens, which results in 2-cyanoquinazolinone (2) and methaqualone (3)[3] (Figure 3). It was found to be most well known synthetic quinazolinone drug, prominent for its sedative-hypnotic activity.[4] Quinazolinone nucleus has attracted much interest because of a wide range of pharmacological activites like antitumor,[5–7] anticonvulsant,[8] antitubercular,[9,10] antiviral,[11] anti-inflammatory,[12] analgesics,[13] antimicrobial,[14] antihypertensive,[15] antioxidant[16] activities etc (Figure 4). Recently quinazolinone chemistry has got new direction due to some resemblance with folic acid. The synthesis of quinazolinones is mainly cyclisation from bifunctional intermediates

In light of the growing number of applications in recent years, there has been an enormous increase in the interest among biologists and chemists in their rapid synthesis and prominent therapeutic activity of quinazolinone derivatives. Manny marketed drugs are available which contain quinazolinone nucleus are tried to list in the study.[17,18] (Table 1).

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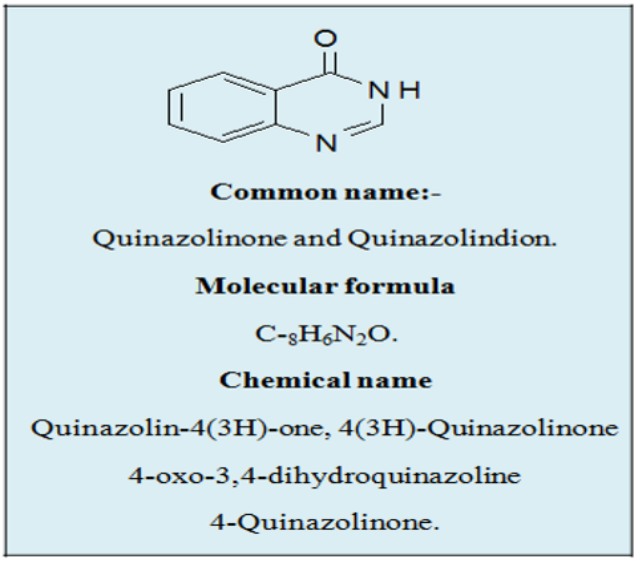


Fig. 1: Structure, molecular formula and IUPAC of quinazolin

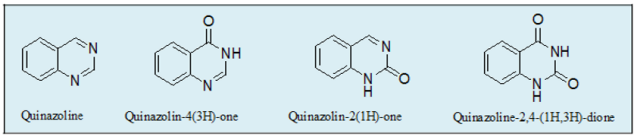


Fig. 2: Structural isomers of quinazolin

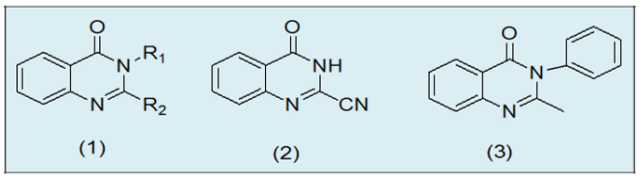


Fig. 3: Synthesis of first quinazolinones

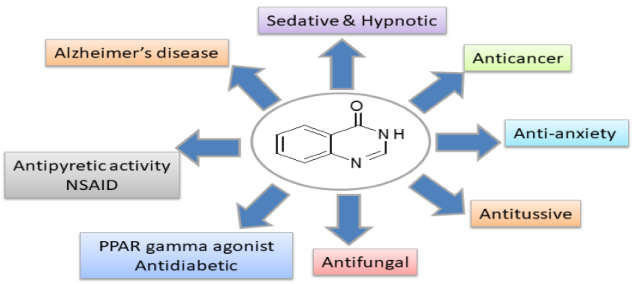


Fig. 4: Representing various pharmacological activity of quinazolinone moiety

1.1. Chemistry of quinazolinones

Chemistry of quinazolinone is regarded as well-known region in synthesis, although still many novel and multifaceted variants of quinazolinone structures are needed to be discovered. When its structure was studied it was found that there is a lactam-lactam tautomeric interaction. This interaction also seen when 4(3H)-quinazolinone is with a methyl moiety present in 3^{rd} position and projected for chlorination with $POCl_3$. It was observed that methyl group get lost and chlorination goes on. Further it was seen, when the methyl group is in 2^{nd} position, this tautomeric effect get exceeded resulting in an exo methylene carbon. It causes increase in the reactivity of the substituted 4-(3H)- quinazolinones. Therefore, quinazolinones are known to be a "fortunate structure" for drug discovery and development f newer pharmaceuticals (Figure 5). In continuation with SAR studies of the moiety, it shows that the 2^{nd}, 6^{th} and 8^{th} position of the ring are very much imperative for the pharmacological studies. It is also suggests, physicochemical properties could be augmented by the inclusion of diverse heterocyclic moieties to 3^{rd} position of the ring. [17]

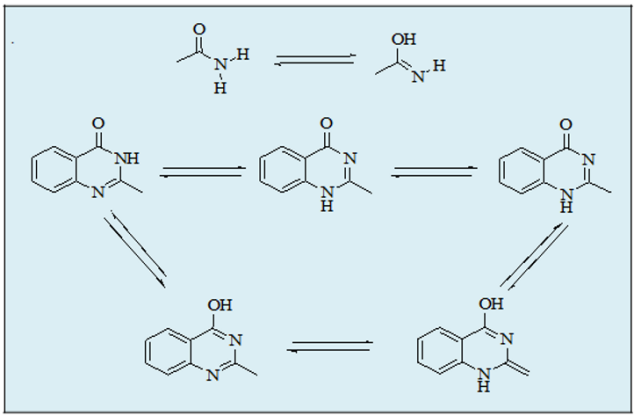


Fig. 5: Presentation of tautomeric forms of quinazolinone compound

Quinazolinone derivatives are elevated melting crystalline products, which are generally insoluble in water and organic solvents but found to be soluble in alkali (aq) and sometimes in concentrated acids like 6N hydrochloric acid. They used to form stable salts of mono-hydrochlorides, chloro-platinate, chloro-aurates and picrates also their metal salts like silver, mercury, zinc, copper, sodium and potassium. [19]

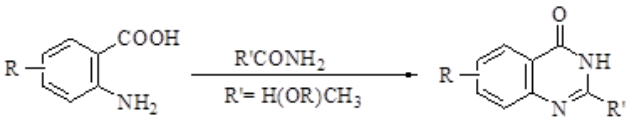
2. Methods for the synthesis of quinazolinone

Very common synthetic method for quinazolinone is through condensation of anthranillic acid with amides / primary amines.

2.1.

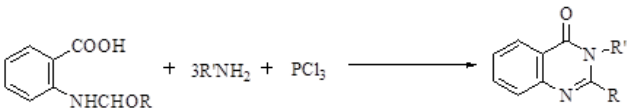
2.1.1. Niementowski's synthesis

It gives 3,4-dihydro-4-oxoquinazoline when substituted formamide reacts with anthranilic acid at 125-130 C.[20–24]



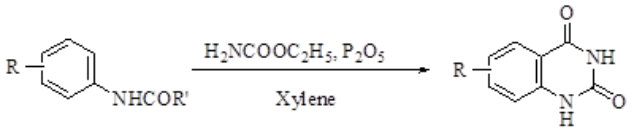
2.1.2. Grimmel, Guinther and Morgans's synthesis

It results in disubstitued 3,4-dihydro-4-oxoquinazolines when ortho-amino benzoic acids, heated with amine and phosphorous trichloride.[25]



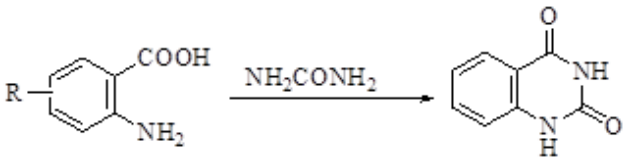
2.1.3. Sen and Ray's synthesis

It results in 2-propyl / 2-isopropyl-3,4-dihydro-4-oxoquinazolines when a solution isobutyrylanilides heated with urethane and phosphorous pentaoxide.[26]



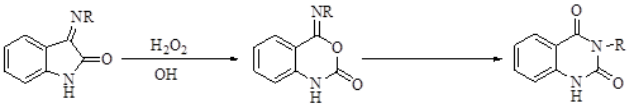
2.1.4. Synthesis from Anthranilic acid and urea

It results in 1,2,3,4-tetrahydro-2,4-dioxo-quinazoline when anthranilic acid fused with urea.[26]



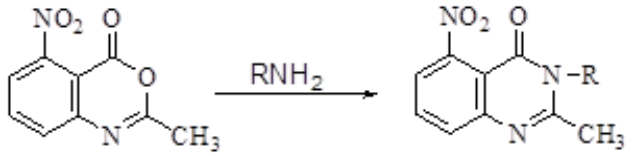
2.1.5. Synthesis from Isatins

It forms dioxoquinazoline and its derivatives when β-imino compounds heated with hydrogen peroxide in alkaline solution.[26]



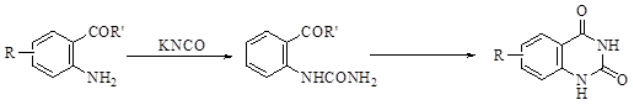
2.1.6. Synthesis from Benoxazones

Here benoxazones compounds reacts with primary amines and resuo form 3,4-dihydro-4-oxoquinazolines.[26,27]



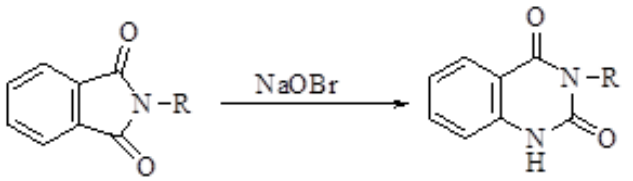
2.1.7. Synthesis from Ureido-benzoic Acid

Here ureido-benzoic acids are synthesised from anthranilic acid with potassium cyanate by heating with acid /alkali.[28]



2.1.8. From Phthalic Acid and its Derivatives

Phthalimide reacts with alkali hypobromite to form 1,2,3,4-tetrahydro-2,4-dioxoquinazoline.[28]



3. Conclusion

Quinazoline, a hetero cyclic nucleus plays a critical role in the field of synthesis which often shows diversify biological activities. As a hetero cyclic moiety many drugs get synthesized and screened for their biological activity. Substituted quinazoline compounds shows a significant Pharmacological activity which has been shown in Table 1. Literature review suggested that soon quinazoline based drugs will rapidly become an important class of pharmaceuticals. It also estimated that, Modern Pharmaceutical industries are showing deep interest in the moiety for development of the novel process and predicted that it will soon available in global market due to its versatile spectrum of activities.

Table 1: Tabular description of some quinazolinone nucleus containing marketed drugs with pharmacological activity

S. No	Drugs	Activity	REF
1	Afloqualone	Sedative & Hypnotic, Anticancer Activity, Anti-anxiety	50,51
2	Cloroqualone	Sedative Activity & Antitussive Activity	
3	Albaconazole	Antifungal Activity	29
4	Balaglitazone	PPAR- Gamma-agonist Activity, antidiabetic Activity	30
5	Diproqualone	Anxiolytic Activity, Analgesic, Antihistamine Activity & Used in Rheumatoid arthritis	31
6	Etaqualone	Anti-depressant Activity	32
7	Fluproquazone	Antipyretic activity, Used as NSAID	33,34
8	Halofuginone	Antitumor Activity, Used in Autoimmune disorders	35,36
9	Isaindigotone	Acetylcholinesterase Activity	37
10	Ispinesib	Anticancer Activity	38
11	Methaqualone	Hypnotic Activity	39
12	Nolatrexed	Anticancer Activity & Thymidylate synthase inhibitor Activity,	40
13	Piriqualone	Anticonvulsant Activity	41
14	Quinethazone	Antihypertensive Activity	42
15	Raltitrexed	Anticancer Activity	43
16	Tiacrilast	Antiallergic Activity	44
17	Rutaecarpine	Alzheimer Activity	45
18	Proquazone	NSAID Activity	46
19	Fabrifugine	Antimalarial Activity	47
20	Evodiamine	Anticancer	48
21	Fenquizone	Diuretic	49

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6. Conflict of Interst

None.

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