Review of Literature

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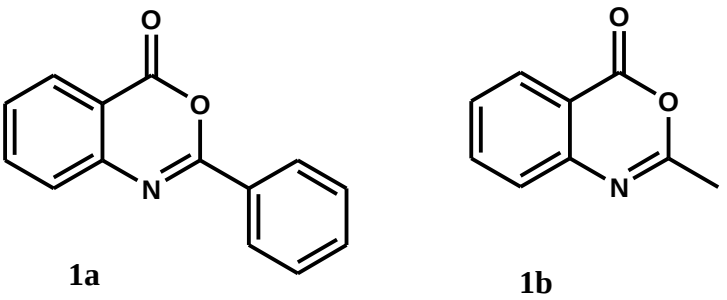
I. Brief introduction of Benzoxazine

4H-3,1-benzoxazinones are known for more than a century. They, being found in nature, are frequently utilized as suitable skeletons for the design of biologically active compounds (El-Mekabaty, 2013). They are also used in organic synthesis for building natural and designed synthetic compounds. Hence, they are considered as chemical synthons of various physiological significances and pharmaceutical utilities. Benzoxazine skeleton is known for their versatility, relative simplicity and accessibility, which put them up amongst the most promising sources of bioactive compounds (Macias *et al*., 2006). The general name given to members of this family is acylanthranils. Apparently, they are early synthesized from 2,1- benzisoxazole (anthranil) and an acylating agent (Coppola, 1999). The phenyl derivative 1a was first synthesized (Friedländer & Wleugel, 1883) and after seventeen years the methyl analog 1b was synthesized (Figure 1). Compounds possessing this ring system are also found in nature. e.g. Phytoalexins, Avenalumin, Dianthalexins and some hydroxylated derivatives (Hofman & Hofmanova, 1969).



1a **1b**

Figure 1: Structure of (1a) 2-phenyl-benzo[d][1,3]oxazine-4-one; (1b) 2-methyl-benzo[d][1,3]oxazine-4-one.

Table 1: Timeline representing Development of Quinazoline scaffold

Year	Discovery	Number of Quinazoline compounds known till date
1869	Griess prepared the first quinazoline derivative, 2-cyano-3,4-dihydro-4-oxoquinazoline	>300000 Quinazoline as a substructure compounds available in SciFinder. Interestingly, nearly 40000 compounds were found to be biologically active
1887	The name quinazoline (German: Chinazolin) was first proposed for this compound by Weddige	
1889	Paal and Bush suggested the numbering of quinazoline ring system	
1903	More satisfactory synthesis of quinazoline was subsequently devised	
1951	The first renowned quinazoline marketed drug – Methaqualone is used for its sedative–hypnotic effects	
1957	Chemistry of quinazoline was reviewed by Williamson	
1959	Chemistry of quinazoline was further reviewed by Lindquist	
1963	Brought up to date by Armarego in 1963	
1960-2010	More than hundred drugs containing Quinazoline moieties have made their way to the market	

II. Properties of Benzoxazine

(a) Physical properties

Benzoxazine has the ability to provide effective bleaching at as low as 40°C. It is cost effective as well as environment-friendly. Moreover, polybenzoxazines showed admirable strong thermal stability and near-zero shrinkage without showing any release of volatiles during polymerization. They exhibited low viscosity, no need of harsh catalysts, and rich molecular design flexibility (Ambujakshan *et al.*, 2008). The flexibility occurred in their molecular design, enable to develop several high performance benzoxazines, naphthazozines, phthalonitrile and phenylnitrile functional polybenzoxazines (Kim *et al*., 1999; Brunovska *et al.*, 2000).

(b) Chemical properties

4H-3,l-benzoxazin-4-one derivatives can be believed as semi-acid anhydrides because formed by cyclodehydration of acylanthranilic acids. They undergo many reactions of true acid anhydrides, but at slower rate (El-Hashash *et al.,* 2012). However, rarely electrophilic reactions on the benzene ring of the benzoxazinone nucleus occurred and are probably unnecessary due to the plethora of diversely available substituted anthranilic acids. It is considered that the synthesis of electronically unsaturated character of unstable benzoxazinones (4*H*)-3,1-benzoxazinones) which are bearing saturated substituents such as CH_3, CH_2COCH_3, CH_2CN and $CH_2CH_2CO_2H$ at position 2 renders their synthesis difficult. They are not considered as satisfactorily stable rings. But, they are indeed useful intermediates in organic synthesis affording through reaction with nitrogen nucleophiles 4(3*H*)quinazolinones **(**Essawy *et al.,* 1982; Mohamed *et al.,* 1981).

Reactions with hydrazine hydrate (Hydrazinolysis)

Heating 4H-3,1-benzoxazin-4-ones in neat hydrazine hydrate or in pyridine or xylene solutions produces the 3-amino-4-quinazolones (Patil *et al.,* 2009; Shweta *et al.,* 2009; El-Hashash *et al.,* 2012).

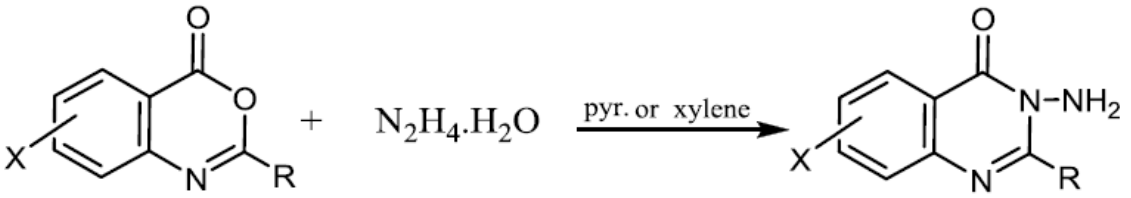


Figure 2: Heating of benzoxazinone derivatives with hydrazine hydrates

Similarly, heating benzoxazinone derivatives with hydrazine hydrate in n-butanol afford 3-aminoquinazolone derivatives (Madkour, 2014).

Reactions with Oxygen nucleophiles

The simplest and sometimes the most unwanted reaction of some 4H-3,1-benzoxazin-4-ones is hydrolysis. Where, the *4H*-3,1-benzoxazin-4-ones are

exceedingly labile to hydrolysis and the initial cleavage to N-acylanthranilic acids parallels that of benzoxazoles to acylarninophenol (Bolotin *et al.*, 1976).

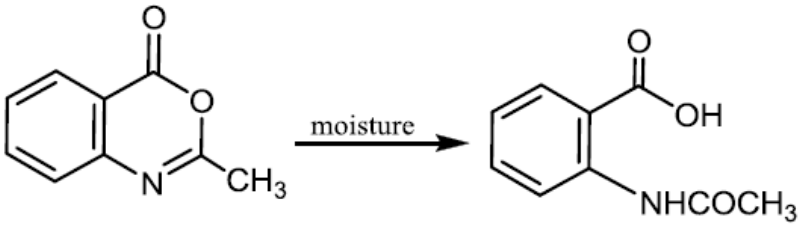


Figure 3: Hydrolysis of benzoxazine-4-one

III. Brief introduction of Quinazoline-4(3H)-one

Quinazoline-4(3H)-one and its derivatives constitute an important class of fused heterocycles that are found in more than 200 naturally occurring alkaloids. In 1950, medicinal chemists started to take interest after the elucidation of a quinazolinone alkaloid, 3-[β-keto-g-(3-hydroxy-2- piperidyl)- propyl]-4-quinazolone. This quinazolinone derivative was isolated from Traditional Chinese herbal *Dichroa febrifuga*, which is found to be effective against malaria (Koepfly *et al.,* 1947). Quinazolinones are the oxidized form of quinazoline. These structures are defined by the location of the oxygen and the oxygen and the hydrogen on the nitrogen (NH). Gabriela obtained quinazoline in good yield by oxidation of 3,4-dihydroquinazoline with alkaline pottsaium ferricyanide. This fused bicycle compound was earlier known as benzo-1,3-diazine. The name quinazoline (German: Chinazolin) was first proposed for this compound by Weddige, on observing that this was isomeric with the compounds cinnoline and quinoxaline (Asif, 2014). In 1889 the commonly accepted numbering for quinazolines and quinazolinone was first adopted by Paal and Buch, as suggested by Knorr and designated individual atoms of a ring with numbers. The most important class of compounds containing the quinazoline nucleus is composed of those compounds, which have hydroxyl group in the 2 or 4 positions in the quinazoline ring, adjacent to a heterocyclic nitrogen atom. Those quinazolines having a functional group, which is easily derived on conversion to hydroxyl group like alkoxy, aryloxy, chloro, amino, thioethers and seleno etc. are also included in important class**.** . Depending upon the position of the keto or oxo group, these compounds may be classified into two types: 2-(1H) quinazolinones and 4-(3H) quinazolines (Mhaske & Argade, 2006). Thus 4-hydroxyquinazoline, tautomeric with

4-keto-3,4-dihydroquinazoline, is commonly named 4(3H)-quinazolone, or simply 4-quinazoline (Mahato *et al*., 2011).

The major subclasses of quinazolinones based on the substituents present on different positions are as follows- .

- 2-Substituted-4(3H)-quinazolinones
- 3-Substituted-4(3H)-quinazolinones
- 4-Substituted-quinazolines
- 2,3-Disubstituted-4(3H)-quinazolinones

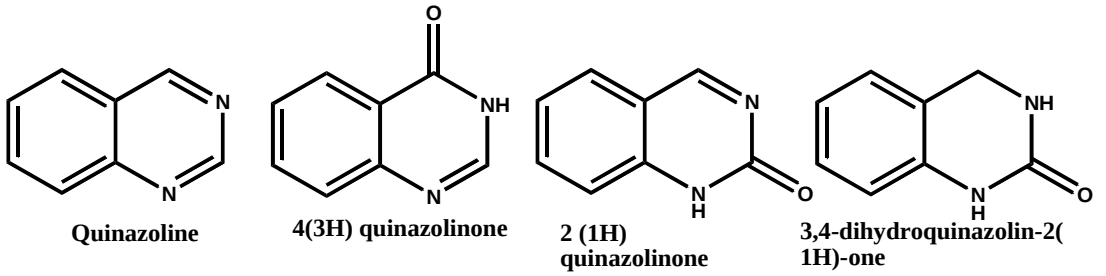


Figure 4: Different types of quinazoline

Among the four quinazolinone structures, 4(3H)-quinazolinones are most prevalent, either as intermediates or as natural products in many proposed biosynthetic pathways. This is partly due to the structure being derived from the anthranilates while the 2(1H)-quinazolinone is predominantly a product of anthrailonitrile, or benzamide with nitriles. Through the process of auto-oxidation quinazoline precursors can be converted to the corresponding 4(3H)-quinazolinone.

IV. Properties of Quinazolinone/Quinazoline-4(3H)-one

(a) Physical properties

Quinazolinones are known for high melting crystalline solids, extremely stable to light, heat, and air. It is insoluble in water and in most organic solvents but soluble in aqueous alkali, because of tautomerism. They are generally insoluble in dilute acids

but are sometimes soluble in concentrated acids. Although, simple 4-(3H)-quinazolinones are insoluble in dilute acids, but soluble in 6N hydrochloric acid. They form stable chloroplatinate, monohydrochlorides, chloroaurates and picrates . They also form stable metal salts of silver, mercury, zinc, copper, sodium and potassium. (Soderbaum & Widman, 1889; Korner, 1900).

(b) Chemical properties

Despite quinazolinone chemistry being considered to be an established area, day by day newer and more complex variants of the quinazolinone structures are still being discovered (Shobha & Raju, 2015). The first reported synthesis of a quinazolinone occurred in 1869, which was prepared from anthranilic acid and cyanide in ethanol, creating 2-ethoxy-4(3H)-quinazolinone. These findings were further confirmed by the synthesis of the derivatives 2-amino-4(3H)-quoinazolinone and 2,4(1H,3H)-quinazolinedione by reaction with ammonia and water respectively. A strong lactam-lactim tautomeric interaction is observed in quinazolinones as shown in Figure 5 (Weber *et al.,* 2003). This tautomeric interaction can also be observed when a 4(3H)-quinazolinone containing a methyl in the 3-position is subjected to chlorination with $POCl_3$, the methyl group is lost and chlorination proceeds (Bogert & Seil, 1907) and when the methyl group is present in the 2-position, the tautomeric effect is extended generating an exo methylene carbon. As result of these extended tautomeric effects, the reactivity of the substituted-4(3H)-quinazolinones is increased (Marr & Bogert, 1935). Hence, the quinazolinones are regarded to be a "privileged structure" for drug development and discovery (Cavalli *et al.,* 2009; Akbari *et al.,* 2013). Moreover, various literatures including Structure activity relationship studies of quinazolinone ring system revealed that position 2, 6 and 8 are very much important for structure activity studies. It is also suggested that chemotherapeutic activity could be increased by attachment of position 3 to different heterocyclic rings.

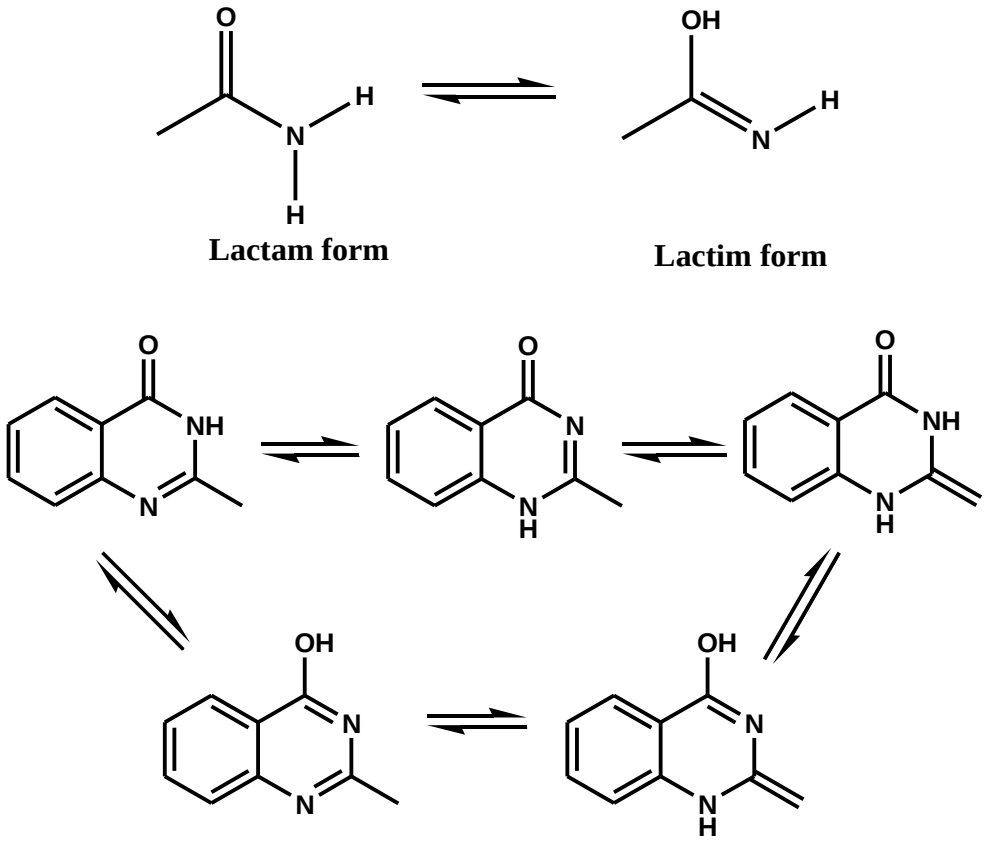


Figure 5: Representation of the different tautomeric forms of 2-methyl-4(3*H*)-quinazolinone

Aromatisation

When a simple and 2-substituted 4-(3H) quinazolinone is heated with an equivalent amount of phosphorous pentachloride in phosphorous oxychloride, the corresponding 4-chloroquinazoline is obtained. If a methyl group is present at 3-position, prohibiting the usual tautomerism, the methyl group is lost during the chlorination (Bogert & May, 1909).

Stability of the ring system

It was reported that the quinazolinone ring is quite stable towards oxidation, reduction and hydrolysis reactions. No reactions of ring degradation via simple chemical oxidation were cited till date (Armarego, 1963).

Chemical reactions

Oxidation

It is reported that after the absorption of one molecule of hydrogen catalytic hydrogenation of quinazoline ended and yields 3,4-dihydroquinazoline (Figure 6) (Armarego, 1963).

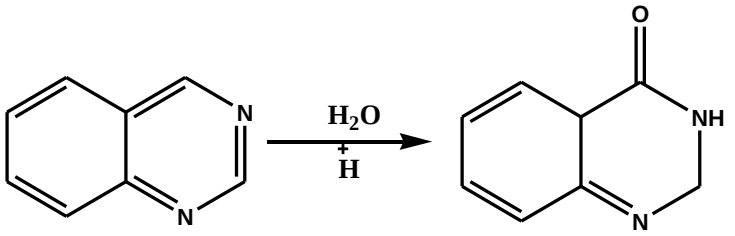


Figure 6: Oxidation of Quinazoline

Reduction

Reduction with sodium amalgam produce 1,2,3,4-tetrahydroquinazoline. However, Lithium aluminum hydride and sodium borohydride gave 3,4-dihydro and 1,2,3,4- tetrahydroquinazoline. The reduction of 3-methyl-4(3*H*)-quinazolinone with lithium aluminium hydride (LiAIH4) in benzene give 2-Hydro-3-methyl- 4(1*H*)-quinazolinone (Figure 7) (Akbari *et al.,* 2013).

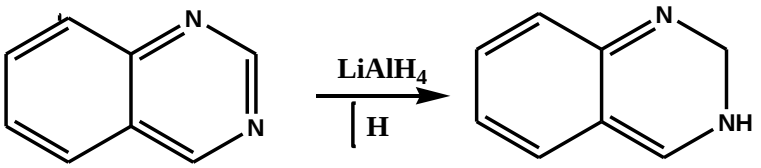


Figure 7: Reduction of Quinazoline

Nitration

It was observed that on boiling with nitric acid 4(3H)-Quinazolinone give 6-nitro-4 (3*H*)-quinazolinone (Figure 8) by substitution. It was also found that on further nitration, the second nitro group enters the 8-position to provide 6,8-dinitro derivatives. It is reported that under such conditions 2-substituted-4(3*H*)-quinazolinones were also behave similarly (Akbari *et al.,* 2013).

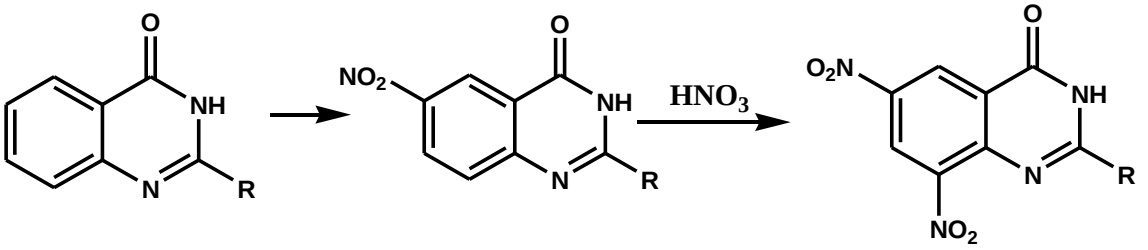


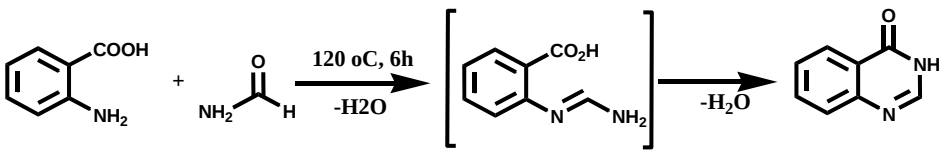
Figure 8: Nitration of Quinazolonone

IV. Methods of synthesis of 4-(3H) Quinazolinones

Most of the methods used for the synthesis of 4-(3H)-quinazolinones make use of anthranilic acid or one of their functional derivatives as the preparatory materials. Pharmacologically, quinazoline particularly quinazolin-4-one or quinazolinone are among the most important classes of heterocyclic compounds. Quinazolin-4-one is synthesized when the keto group is introduced in the pyrimidine ring of quinazoline. Based on this factor, the general methods of synthesis are listed as follows:

(a) Condensation of anthranilic acid with acid amides

A simple and easy conversion to 4-(3*H*) quinazolinones can be achieved when anthranilic acid is heated in an open container with excess of formamide at 120 °C. In this reaction, water is removed and proceeds via an o-amidobenzamide intermediate (Scheme 1) (Armarego, 1963). Commonly, this method is known as Niementowski synthesis. Howerever, Besson et al modified Niementowski synthesis to improve the yields and reaction time by using microwave irradiation techniques (He *et al.*, 2014).

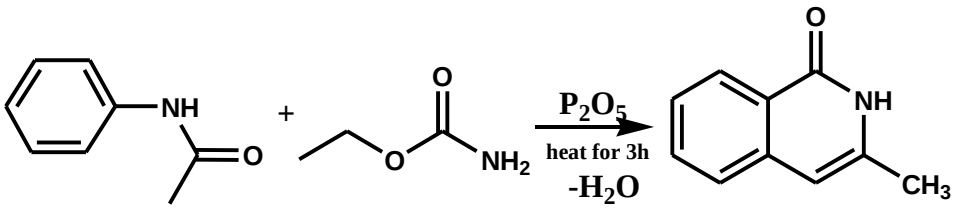


Scheme I: The Niementowski reaction

(b) Condensation of acetanilides with urethanes

Another effective conversion is to condense a urethane derivative with aniline to give 4-(3*H*) quinazolinone. 2-methyl-4-(3*H*) quinazolinone was synthesized by

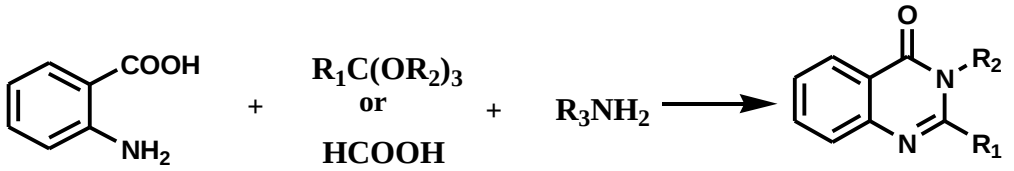
heating of urethane and acetanilide for 3 hours with phosphorus pentoxide in toluene (Scheme 2). Quinazolinones may also be synthesized directly from the corresponding N-acylanthranilic acid by heating with ammonia or substituted amines. 2-methyl-3-alkyl-6- nitro- 4-(3H) quinazolinones prepared from N-acyl-5-nitroanthranilic acid and a variety of primary amines (Armarego, 1963).



Scheme II: Synthesis of 2-methyl-4-(3H) quinazolinone

(c) Condensation of N-acylanthranilic acids with primary amines

A survey of the literature suggests that 4-(3*H*) Quinazolinones may also be synthesized directly from the corresponding N-acylanthranilic acid by heating with ammonia or substituted amines (Scheme 3). Therefore, a variety of primary amines and N-acyl-5-nitroanthranilic acid were condensed to synthesize 2-methyl-3-alkyl-6-nitro- 4-(3*H*) quinazolinones in good yields (Armarego, 1963).



Scheme III: Condensation of anthranilic acids with primary amines

V. Biological activities of Benzoxazine and Quinazolinone

. **(a) Biological activities of benzoxazine-4-one**

The phytochemists and researchers started to take interest in benzoxazine with the first isolation of 2, 4-dihydroxy-2H-1, 4-benzoxazin-3(4H)-one (DIBOA) and 2, 4- dihydroxy-7-methoxy-(2H)-1,4-benzoxazin-3(4H)-one (DIMBOA) benzoxazine derivatives (Macias et al, 2006). This has led to the discovery of a wide variety of

compounds that are of high interest from the point of view of antimicrobial, antimycobacterial, antidiabetic and antidepressant effects among others. They possess a variety of biological effects including antitubercular (Petrlíkova, 2010) antifungal (Shirodkar *et al.,* 2000; Grover & Kini, 2006), antimalarial, anticancer, anti-HIV (Grover & Kini, 2006; Habib *et al.,* 2013; Kandale *et al.,* 2014), antiviral and antibacterial activities (Grover & Kini , 2006; Habib *et al.,* 2013; Ozden *et al.,* 2000). They also act as DNA binding agents (Sugiyama *et al.,* 1986) and HSV-1 protease inhibitors (Jarves *et al.,* 1996). A literature survey identified several benzoxazine derivatives in the development phase as potential new drugs (Siddiquia *et al.,* 2010).

The 4H-3,1-benzoxazin-4-one core is a key structural fragment in a range of biologically active compounds and led to a number of drugs (Siddiquia *et al.,* 2010). They have attracted considerable attention as inhibitors of Serine proteases. Hays et al. have screened a series of 2- substituted 4H-3,1-benzoxazin-4-ones as inhibitors of Clr serine protease of the complement system (Hays *et al.,* 1998). 4H-3,1-benzoxazin-4-ones core linked to heterocycle or heteroaryl were disclosed as Serine hydrolase inhibitors. They were also found to be potent elastase inhibitor (Colson *et al.,* 2005; Oshida *et al.,* 1992).

5-Methyl-4H-3,1-benzoxazin-4-one derivatives are accomplished as specific inhibitors of Human Leukocyte Elastase (HLE), where they showed strong and highly specific inhibition of Human Sputum Elastase (HSE), which is equivalent to HLE (Hsieh, 2005). 4H-3,1-benzoxazin-4-one derivatives are accomplished as specific inhibitors of Human Leukocyte Elastase (Stein *et al.,* 1987; Krantz *et al.,* 1990; Uejima *et al.,* 1993; Arcadi *et al.,* 1999; Hsieh, 2005). Moreover, 2-substituted-4H-3,1-benzoxazin-4-one derivatives showed good cytotoxic activity (Pavlidis & Perrya, 1994). A series of 4H-3,1-benzoxazin-4-ones with different aromatic substitution pattern were evaluated as HIV-1 Reverse transcriptase inhibitors (Patel *et al.,* 1999). 2-Aryl-substituted 4H-3,1-benzoxazin-4-ones act as novel active substances for the cardiovscular system (Rose, 1991). The benzoxazine derivatives also showed anti-convulsant activity (Hays *et al.,* 1998).

Moreover, some 2-substituted 4H-3,1-benzoxazin-4-ones are also found to lower the levels of cholesterol and triglycerides in plasma, and to raise the proportion of total cholsterol carried by high-density lipoproteins (Fenton *et al.,* 1989).

The importance of these 4H-3,1-benzoxazin-4-one also resides in that, these compounds are useful precursors for the preparation of other pharmaceutically active heterocyclic compounds, mainly quinazoline derivatives (Baumann *et al.,* 2013). Extensive structure activity relationship studies suggest that the entire quinazolinon structure was required, but activity was further enhanced by halides or small hydrophobic substituents at position-6 (Jiang *et al.,* 1990). Particularly, hetero substituents and chemically active functional groups on C-2 position affect their reactivity and reaction rate. Thus, one of the most important features in (4H)-3,1-benzoxazinones chemistry is their use as key starting materials for further transformations in design and synthesis of biologically active compound (Nikpour *et al.,* 2014).

(b) Biological importance of Quinazolin-4(3H)-ones

The stability of the quinazolinone nucleus has inspired medicinal chemists to introduce many bioactive moieties to this nucleus to synthesize new potential medicinal agents. The quinazolinone skeleton is a frequently encountered heterocycle in medicinal chemistry literature with applications including antibacterial, analgesic, anti-inflammatory, antifungal, antimalarial, antihypertensive , CNS depressant, anticonvulsant, antihistaminic, antiparkinsonism, antiviral and anticancer activities (Cao *et al.,* 2005; Giri *et al.,* 2009; Helby *et al.,* 2003; Kadi *et al.,* 2006; Jatav *et al.,* 2008; Xia *et al.,* 2001; Jessy *et al.,* 2007; Alagarsamy *et al.,* 2006; Asif , 2014). However, few quinazolinones were reported for treatment of tuberculosis e.g 3-aryl-6,8-dichloro-2H-1,3-benzoxazine-2,4(3*H*)-diones and 3-arylquinazoline-2,4(1H,3H)-diones are reported as anti-mycobacterial agents (Mahto *et al.,* 2011). In the last few decades quinazoline heterocycles got much importance due to their wide range of biological properties.

Antileishmanial agents

Chauhan and co-workers reported four novel series of quinazolinone hybrids bearing interesting bioactive scaffolds (pyrimidine, triazine, tetrazole, and peptide). Most of the synthesized analogues exhibited potent leishmanicidal activity against intracellular amastigotes (Chauhan *et al.,* 2013). The SAR analysis revealed that among the synthesized quinazolinone hybrids, quinazolinone pyrimidine, triazine, and ferrocene containing quinazolinone peptide displayed potent antileishmanial activity (Sharma & Ravani, 2013).

Anticonvulsant agents

Gupta and co-workers (Gupta *et al.,* 2013) reported a new series of 2-phenyl-3- (3-(substituted-benzylideneamino))-quinazolin-4(3*H*)-one derivatives and screened for their anticonvulsant activity against standard models MES (maximal electroshock seizure test) for their ability to reduce seizure spread. Zheng and co-workers (Zheng *et al.,* 2013) described the syntheses and anticonvulsant activity of 5-phenyl[1,2,4]triazolo[4,3-c] quinazolin-3-amine derivatives. El-Azab and co-workers (El-Azab *et al.,* 2013) designed and synthesized a new series of quinazoline analogues and evaluated for their anticonvulsant activity. Khan and Malik (Malik & Khan, 2014) reported a new synthesis of quinazolin-4(3H)-one substituted 1H and 2H-tetrazole derivatives and evaluated for anticonvulsant screening based on the NIH anticonvulsant drug development (ADD) program protocol. Zayed and co-workers (Zayed & Hassan, 2014) synthesized some novel derivatives of 6,8-diiodo-2-methyl-3-substituted-quinazolin-4(3H)-ones and evaluated for their anticonvulsant activity by the maximal electroshock-induced seizure and subcutaneous pentylenetetrazole tests. The neurotoxicity was assessed using rotarod test. All the tested compounds showed considerable anticonvulsant activity in at least one of the anticonvulsant tests.

Antiinflammatory agents

Hussain (Hussain, 2013) reported the synthesis of 2,3-dihydro-2-(3,4-dihydroxyphenyl) pyrazolo [5,1-b] quinazolin-9(1*H*)-one and tested for their anti-inflammatory activity. Eweas and co-workers (Eweas *et al.,* 2013) designed and synthesized some novel 2-pyridyl (3H)-quinazolin-4-one derivatives and evaluated for

their anti-inflammatory activity. All the tested compounds showed good anti-inflammatory activity. Saravanan and co-workers (Alagarsamy & Saravanan, 2013) synthesized a new series of novel quinazolin-4(3H)-one derivatives and tested for their anti-inflammatory activity. A series of novel 2-(2,4-disubstituted-thiazole-5-yl)-3- aryl-3H-quinazoline-4-one derivatives which became good inhibitors of NFκB and AP-1 mediated transcription activation (Giri *et al.,* 2009). Zayed and Hassan synthesized some novel 6,8-diiodo-2-methyl-3-substituted-quinazolin-4(3H)-ones bearing sulfonamide derivatives and evaluated for their anti-inflammatory activity by carrageenan-induced hind paw edema test using ibuprofen as a standard drug. Among the screened compounds, aliphatic side chain bearing compounds were found to be more active than those with aromatic ones (Zayed *et al.,* 2014).

Antitumor Activity

Quinazoline scaffold resembles both the purine nucleus as well as the pteridine one. As a consequence, some compounds which are able to inhibit the purinic (Dempcy & Skibo, 1991) or the folic acid (Martin *et al.,* 1947; Davoll & Johnson, 1970; Oatis and Hynes, 1977; Scanlon *et al.,* 1979) metabolic pathways were discovered. Structure modification of folic acid has also led to the discovery of a number of antifolates as efficient anticancer agents (Nzila, 2006). In an effort to look for the possible non-classical antifolates acting as antitumor agents, Cao *et al*. (2005) incorporated the dithiocarbamate moiety with 4(3H)-quinazolinone. Thus, a series of 4(3H)-quinazolinone derivatives with dithiocarbamate side chains were synthesized and tested for their *in vitro* antitumor activity against human myelogenous leukemia K562 cells by MTT (3-(4,5-dimethylthiazol-2-yl) -2,5- diphenyl-tetrazolium bromide) assay. Among them, few exhibited significant inhibitory activity against K562cells with IC_{50} value of 0.5 μM (Cao *et al.,* 2005).

Antimicrobial Activity

It is well documented that 4-(3H)-Quinazolinones with 3-substitution are associated with antimicrobial properties (Nagarajan *et al.,* 2010). The 3-substitution which was reported, bridged phenyl rings, heterocyclic rings and aliphatic systems. It was also reported that hydrazine derived Schiff's bases have potential antibacterial activity. In our previous study, we have synthesized 3-(Arylideneamino)-2-

phenylquinazoline-4(3*H*)-ones by placinng two potential bio-active sites, a quinazolone moiety as well as a Schiff base in the system to increase biological activity. The compounds were found to inhibit the growth of both Gram-positive (*Staphylococcus aureus* 6571 and *Bacillus subtilis*) and Gram-negative bacteria (*Escherichia coli* K12 and *Shigella dysenteriae*). We have proposed the promising effect of such compounds against Multiple Antibiotic Resistant Gram-negative enteric bacteria could lead to the development of new drugs (Nanda *et al.,* 2007). Recently, Bouley *et al.,* (2015), have discovered E)-3-(3-carboxyphenyl)-2- (4-cyanostyryl)quinazolin-4(3*H*)-one as an antibiotic effective in vivo against methicillin-resistant *Staphylococcus aureus* (MRSA). They also found that this antibiotic damage cell-wall biosynthesis by binding penicillin-binding protein (PBP). They proposed this as a promise antibiotic in fighting MRSA infections.

A new series of novel 2-methyl-3-(1’3’4-thiadiazol-2-yl)-4-(3*H*) quinazoline was synthesised by reacting 2-amino-5-aryl/alkyl-1’3’4’-thiadiazoyl with 2-substituted benzoxazin-2-one (Jatav *et al.,* 2008). These compounds possessed antibacterial activity on *Staphylococcus aureus, Bacillus subtilis* and *Escherichia coli*. Antifungal activity was screened against *Candida albicans, Aspergillus niger* and *Curvularia lunata*. Moreover, synthesized compounds showed both antibacterial and antifungal activity.

VI. Quinazoline-4(3H)-ones drugs available in market

The limitation of the drug agents is not only the rapidly emergence of drug resistance but also the drug side effects. This fact creates a crisis in the usage of antimicrobial drugs. The unsatisfactory status of the present drugs has forced scientists to develop new antibacterial agents having broad antimicrobial spectrum. Moreover, in the present scenario, it has become imperative to resolve the setback of emergence of microbial resistance towards conventional antimicrobial agents and also to minimize the side effects of existing drugs.

It is well known that quinazolinone skeleton containing drugs have been considered as very important class of therapeutic agents; hence large number of quinazoline compounds were synthesized and evaluated for their different biological activities. This rapid development indicates that there will be more quinazoline

derivatives in clinical trials in the near future. These compounds are likely to surpass the available organic based pharmaceuticals in the very near future. The first renowned quinazoline marketed drug – Methaqualone is used for its sedative–hypnotic effects since 1951 (Mhaske & Argade ,2006). Presently, a large number of quinazoline derivates are patented and available in market as potential drug for various diseases. The following table lists out a few marketed quinazolinone drugs used for treatment of various diseases (Table 2).

Table 2- Some marketed available drugs contain quinazolinone moiety

S.no	Drug	IUPAC Name	Activity	References
1	Afloqualone	6-amino- 2(fluoomethyl)- 3-(2-methylphenyl) quinazolin- 4-one	Sedative, Hypnotic, Anticancer, Anti-Anxiety Agents	Ochiai and Ishida , 1982; Chen et al, 2006
2	Albaconazole	7-chloro-3-[(2R,3R)- 3-(2,4-difluorophenyl)-3-hydroxy-4-(1,2,4-triazol- 1-yl)butan-2-yl]quinazolin-4-one	Antifungal	Sorbera et al, 2003
3	Balaglitazone	5-[[4- [(3,4-dihydro-3-methyl-4-oxo-2-quinazolinyl) methoxy]phenyl]methyl]-2,4-thiazolidinedione	Peroxisome proliferator-activated receptor (PPAR) gamma agonist , Antidiabetic	Henriksen et al, 2009; Henriksen et al, 2011
4	Cloroqualone	3-(2,6-Dichlorophenyl)-2-ethyl-4-quinazolinone	Sedative	Ochiai and Ishida , 1982; Chen et al, 2006
5	Diproqualone	3-(2,3-dihydroxypropyl)-2-methyl-quinazolin-4-one	Analgesic, Antihistamine, Rheumatoid Arthritis	Audeval et al, 1988; Chen et al, 2006
6	Etaqualone	3-(2-ethylphenyl)-2-methyl-quinazolin-4-one	Sedative, Hypnotic	Parmar et al, 1969
7	Fluproquazone	4-(4-fluorophenyl)-7-methyl-1-propan-2-ylquinazolin- 2-one	Antipyretic activity, NSAID	Mohing et al, 1981; Wheatley, 1982

8	Halofuginone	7-Bromo-6 chloro-3-[3-[(2S,3R)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-4-quinazolinone	Antitumor, Autoimmune disorders	Sundrud et al, 2009
9	Isaindigotone	3-[(3,5-dimethoxy-4-oxocyclohexa-2,5-dien-1-ylidene)methyl]-2,4-dihydro-1H-pyrrolo[2,1-b]quinazolin-9-one	Acetylcholinesterase and butyrylcholinesterase	Tan et al, 2009
10	Ispinesib	N-(3-aminopropyl)-N-[(1R)-1-[7-chloro-3,4-dihydro-4-oxo-3-(phenylmethyl)-2-quinazolinyl]-2-methylpropyl]-4-methyl-benzamide	Anticancer	Blagden et al, 2008
11	Methaqualone	2-methyl-3-o-tolyl-4(3H)-quinazolinone	Hypnotic	Smith et al, 1973
12	Nolatrexed	2-Amino-6-methyl-5- (4-pyridylthio)-1H-quinazolin-4-one	Thymidylate synthase inhibitor, Anticancer	Andy et al, 2012
13	Piriqualone	3-(2-methylphenyl)-2-[(E)-2-pyridin-2-ylethenyl]quinazolin-4-one	Anticonvulsant	Koe et al, 1986
14	Quinethazone	7-chloro-2-ethyl-4-oxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide	Antihypertensive	Cohen et al, 1960
15	Raltitrexed	*N*-[(5-{methyl[(2-methyl-4-oxo-1,4-dihydroquinazolin-6-yl)methyl]amino}-2-thienyl)carbonyl]-L-glutamic acid	Anticancer	Wideman et al, 1999
16	Tempostatin	7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidyl]-2-oxo-propyl]quinazolin-4-one	inhibiting the deposition of collagen	Asif, 2014
17	Tiacrilast	(E)-3-[6-(Methylthio)-4-oxoquinazolin-3(4H)-yl]propenoic acid	Antiallergic	Welton et al, 1986
18	Rutaecarpine	8,13-Dihydroindolo[2',3':3,4]pyrido[2,1-b]quinazolin-5(7H)-one	Alzheimer's disease	Decker, 2005
19	Proquazone	1-Isopropyl-7-methyl-4-phenyl-2(1H)-quinazolinone	non-steroidal anti-inflammatory potential	Mohri, 2001

20	Fluproquazone	4-(4-Fluorophenyl)-1-isopropyl-7-methyl-2(1H)-quinazolinone	non-steroidal anti-inflammatory potential	Mohri, 2001
21	Diproqualone	3-(2,3-dihydroxypropyl)-2-methyl-quinazolin-4-one	analgesic effects	Mohri, 2001

In addition to all these, the other quinazoline marketed drugs are Gefitinib, Erlotinib, Trimetrexate, Vandetanib, Evodiamine, Dacomitinib, Barasertib, Cediranib, Elinogrel, Letermovir, Milciclib, Sotrastaurin, Tandutinib, Varlitinib etc (Selvan & Kumar, 2011).