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A Review On Recent Approach In Synthetic Methods, Chemical Characteristics And Biological Potential Of Triazine And Quinazolinone Derivatives

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Abstract

Triazine and Quinazolinone is an attractive class of heterocyclic compounds. Numerous synthetic analogs of triazineand Quinazoninone have been prepared and evaluated for many pharmacological activities in different models. Some analogs have shown potent pharmacological activity and may be considered as lead molecule for the development of future drugs. Triazine and Quinazolonione ware first synthesized over a century ago, but still attracts the attention of scientists, chemists, biologists, and other specialists. In recent years, antiviral, anti-inflammatory, antifertility, anti-tubercular activity, anticancer activity, antimicrobial activity, antimalarial activity, protein kinase inhibitor activity, anti-angiogenic activity, anti-trypanosomal activity, the antioxidant activity of triazine have been published. This review is an attempt to organize the chemical and pharmacological aspects of triazines and Quinazolinoeanalogs reported to date systematically since 1970.

Keywords: Anticancer activity, antimicrobial activity, antiprotozoal, *in vivo*, triazine, Quinazolinoe and Quinazoline

1. INTRODUCTION

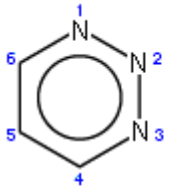
Triazinehas been frequently used in medicine because of its wide spectrum of biological activities. Different-s- triazine derivatives have been reported for their antibacterial [1], antiviral[2,3], antimicrobial[4] and herbicidal activities[5]. These are also used for treatment of HIV infection. 2,4,6-Trisubstituted-s-Triazine derivatives have been demonstrated to possess anticancer[6], anticonvulsant[7], antimalarial, hypotensive and antiamoebic properties[8].1,3,5-Triazine derivatives are known to be effective plant protection agents but their application strongly depends upon their environmental behavior. At present the polymer formulation of pesticides is a rather advantageous approach to obtain ecologically more tolerable product of lower toxicity and of prolonged effect[9].

The most common derivative of 1,3,5-triazine is 2,4,6-triamino-1,3,5-triazine, commonly known as melamine or cyanuramide.Trichloro-1,3,5-triazine is the starting point for the manufacture of many herbicides such as simazin. Another important derivative is 2,4,6-trihydroxy-1,4,5-triazine better known as cyanuric acid[10].

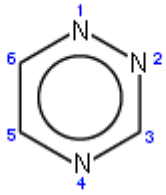
Quinazolines and quinazolinones are classes of fused heterocycles that are of considerable interest because of the diverse range of their biological properties[11]. Many substituted quinazoline and quinazolinone derivatives possess a wide range of bioactivities such as antimalarial, anticancer,

antimicrobial, antifungal, antiviral, antiprotozoan, anti-inflammatory, diuretic, muscle relaxant, antitubercular, antidepressant, anticonvulsant, acaricidal, weedicide, and many other biological activities. Quinazoline and quinazolinone compounds are also used in preparation of various functional materials for synthetic chemistry and also present in various drugs molecules. This review is an attempt to expand the huge potentiality and focused on the various biological activities of quinazolines and quinazolinones[12]. Quinazolinones will be classified into the following five categories, based on the substitution patterns of the ring system[13]. These are 2-substituted-4(3H)-quinazolinones, 3-substituted-4(3H)-quinazolinones, 4-substituted-quinazolines, 2,3-disubstituted-4(3H)-quinazolinones, and 2,4- disubstituted-4(3H)-quinazolinones. Depending upon the position of the keto or oxo group, these compounds may be classified into three types[14]. Out of the three (2(1H)quinazolinones, 4(3H)quinazolinones and 2,4(1H,3H) quinazolinedione) 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 (anthranilic acid or various esters, isatoic anhydride, anthranilamide, and anthranilonitrile) while the 2(1H)-quinazolinone is predominantly a product of anthranilonitrile or benzamides with nitriles [14].

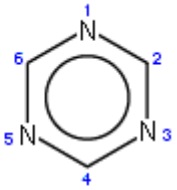
Isomers The 1, 3, 5-triazine is one of three triazines, the two other isomers being 1,2,3-triazine and 1,2,4-triazine.



1,2,3-triazine

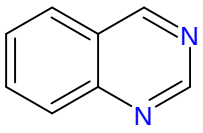


1,2,4-triazine

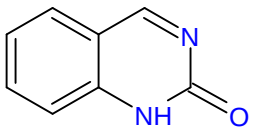


1,3,5-triazine
or
s-triazine

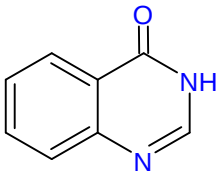
Some marketed available drugs contain quinazoline and quinazolinone moiety



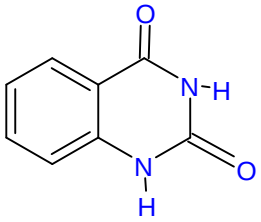
Quinazoline



2(1H quinazoline)



4(3H)quinazolinone

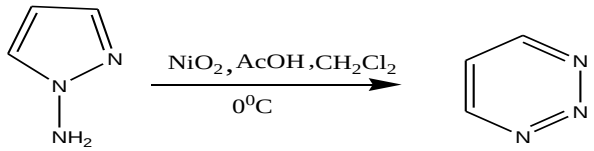


4(1H,3H)quinazolinedione

2. METHOD OF PREPARATION, TRIAZINE DERIVATIVES

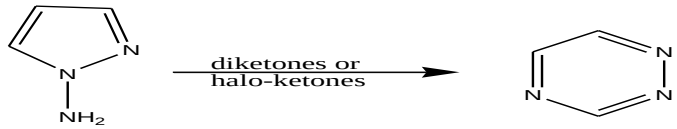
1, 2, 3-Triazines

1, 2, 3-Triazines has been prepared by the oxidation of 1-aminopyrazole[15].



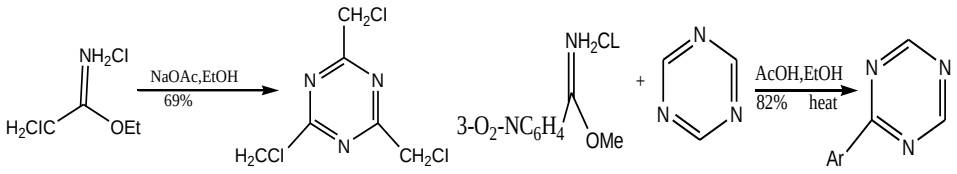
1, 2, 4- Triazines

1, 2, 4-Triazines has been prepared by the condensation of 1-aminopyrazoles with diketones, or halo-ketones[16].

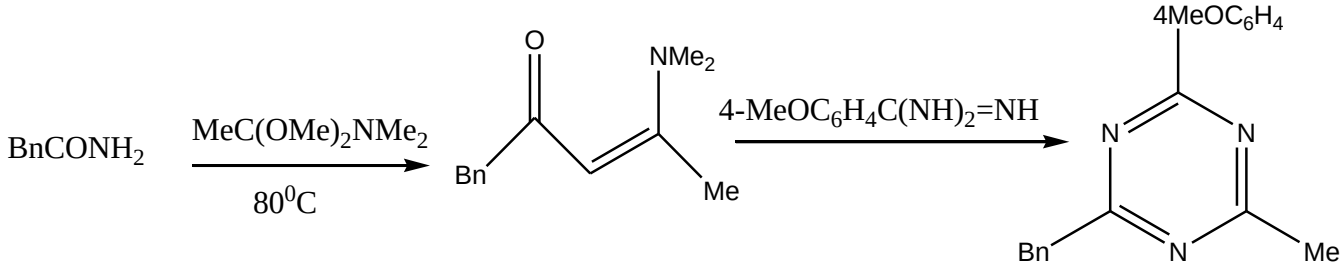


1,3,5-Triaznes

1,3,5-Triazines are usually most easily obtained by substitution reaction on 2,4,6-triachloro-1,3,5-triazine, but the ring system can also be synthesized by cyclocondensation reactions.Trimerization of nitriles are imidates gives symmetrically substituted compounds; mono-substituted 1,3,5-triazine can be obtained via reaction of imidates with 1,3,5-triazine itself[17].



A route which allows the synthesis of 1,3,5-triazines with different substituents at each carbon is exemplified below –an N'-acyl-N,N-dimethylamidine with an amidine or guanidine to form a 1,3,5-triazine[18-21].



1,2,4,5-Triazines

1,2,4,5-triazines can be produced by condensation of hydrazine with carbonyl compound at acid oxidation level, followed by oxidation of the dihydro product; this generally produces 3,6-identically – substituted derivatives, crossed condensation reaction being inefficient[22].

1,3,5-Triazine

The chemical compound1,3,5-triaine, also called s-triazine, is an organic chemical compound whose chemical structure has a six membered heterocyclic aromatic ring consisting of three carbon atoms and three nitrogen atoms. It is a common reagent, and readily forms derivatives, which are used as pharmaceutica lproducts and herbicides[23].

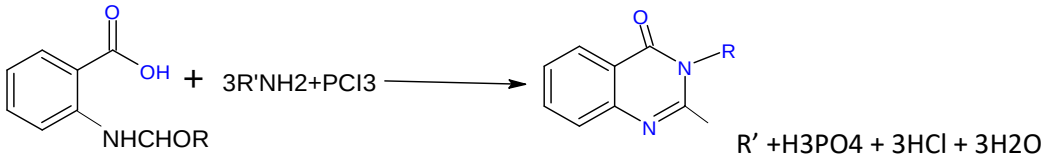
2,4,6-Tris (trinitromethyl)-1,3,5-triazine2,4,6-Tris(trinitromethyl)-1,3,5-triazine is a chemical compound that is a derivative of triazine first prepared in 1995. It is synthesized by destructive nitration of 2,4,6-tricarboxyl-1,3,5-triazine. It is noteworthy for having more nitro groups than it does carbon atoms, so could be used as an oxygen source, or added to oxygen-poor explosives to increase their power[24-25].

3. **Method of Preparation Quinazoline and Quinazoline Compounds**

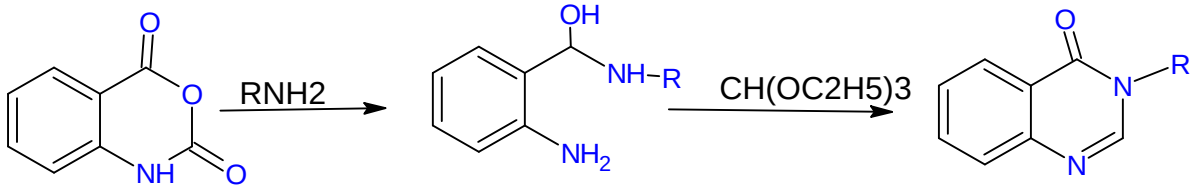
Various methods were reported for the synthesis of oxoquinazolines. [25-29]

3.1. Niementowski's Synthesis. Compound 3 or 4-substituted anthranilic acid when reacted with formamide at 125–130◦ C gave 3,4-dihydro-4-oxoquinazoline .

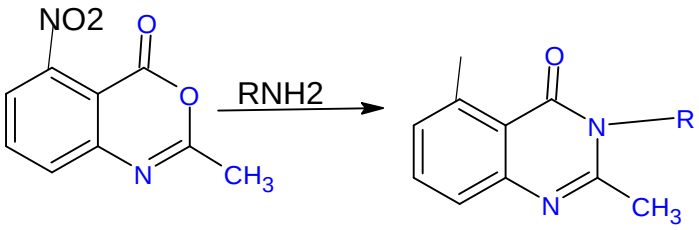
3.2. Grimmel, Guinther, and Morgan's Synthesis. The o-amino benzoic acids, when heated with an amine together with phosphorous trichloride in toluene for two hours, gave 2,3- disubstituted 3,4-dihydro-4-oxoquinazolines



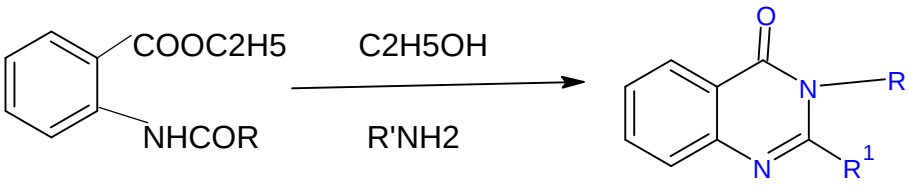
3.3. From Isatoic Anhydride. Isatoic anhydride was readily reacted with amines to dihydro-4-oxoquinazolines by refluxing ethyl orthoformate for 1–6 hrs without isolating the intermediate amides .



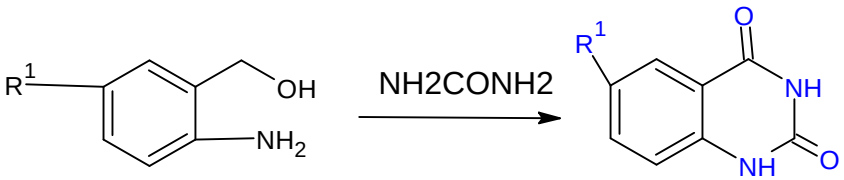
3.4. From 3,1,4-Benoxazones (Acylanthranils) and Amines. 3,1,4-Benoxazones react with amines to give 3,4-dihydro-4- oxoquinazolines. Primary aliphatic amines and anilines react with 2-methyl-5-nitro-4-oxoquinazolines.



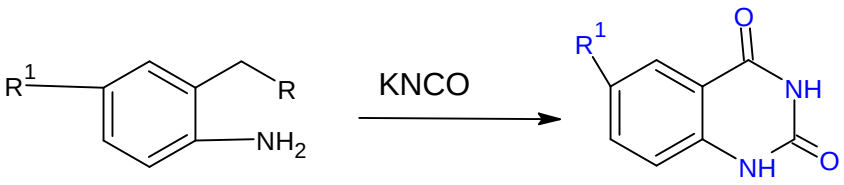
3.5. From Ethyl 2-Acetamido-5-nitrobenzoate. Ethyl 2- acetamido-5-nitrobenzene and alcoholic ammonia when heated gave 3,4-dihydro-methyl-6-nitro-4-oxoquinazoline.



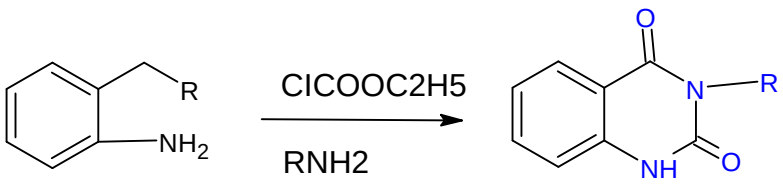
3.6 The fusion of anthranilic acid with urea gave 1,2,3,4-tetrahydro-2,4-dioxoquinazoline .



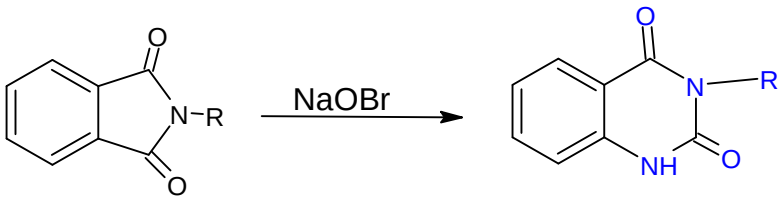
3.7 From O-Ureidobenzoic Acid. The o-ureidobenzoic acids are prepared from the corresponding anthranilic acid and potassium cyanate. The ureido acids are then easily cyclized to the respective 1,2,3,4-tetrahydro-2,4-dioxoquinazolines by heating with acid or alkali.



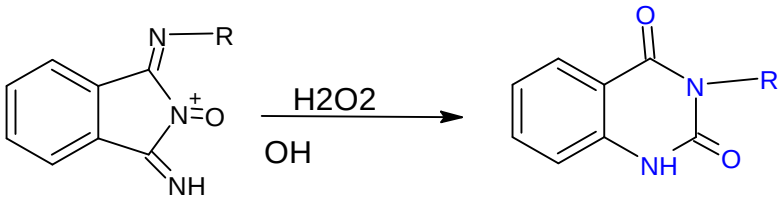
3.8 From O-Ethoxy Carbonylaminobenzoic Esters or Amides. When o-ethoxycarbonylaminobenzamide and its 4-methyl derivatives are heated over their melting points, then they lose water and form 1,2,3,4-tetrahydro-2,4-dioxoquinazoline .



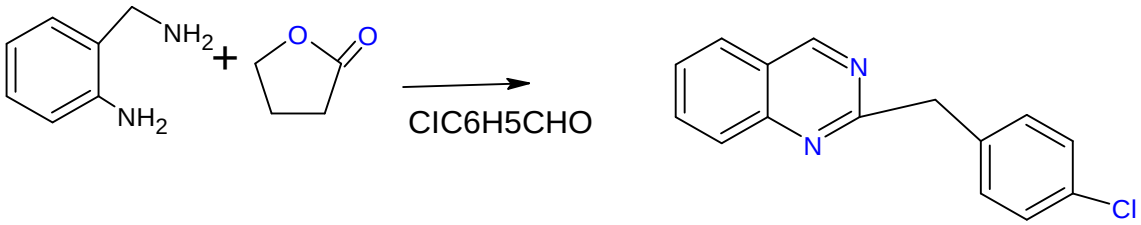
3.9 From Phthalic Acid Derivatives. The derivatives of phthalic acid used for the preparation of dioxoquinazoline necessitate rearrangement of the Hoffmann Curties or Lossan type. Reaction of phthalamide or phthalimide, N-methyl, and N-ethyl phthalimide with alkali hypobromite gives the 1,2,3,4-tetrehydro 2,4-dioxoquinazoline .



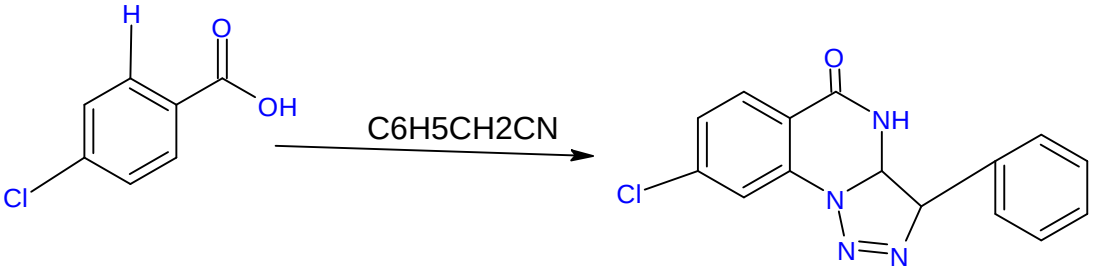
3.10 From Isatins. α-Isatinoxime rearranges to 1,2,3,4- tetrahydro-2,4-dioxoquinazoline on heating with dilute sodium hydroxide; β-imino derivatives of isatin, on the other hand, require oxidation with hydrogen peroxide in alkaline solution in order to form the dioxoquinazoline.



3.11 From 2-Aminobenzylamine. The 2-aminobenzylamine reacts with butyrolactone which involves forming intermediate compound and further condensed with benzaldehyde to give 3-(2-chlorobenzylidene)-1,2,3,9-tetrahydropyrrolo-2- quinazoline.



3.12 From 2-Azido-4-chlorobenzoic Acid. The 2-azido-4- chlorobenzoic acid reacts with benzyl nitrile and formed 7-chloro-3-phenyl-[1, 2, 3]triazolo[1,5-a]quinazoline-5-one [30].

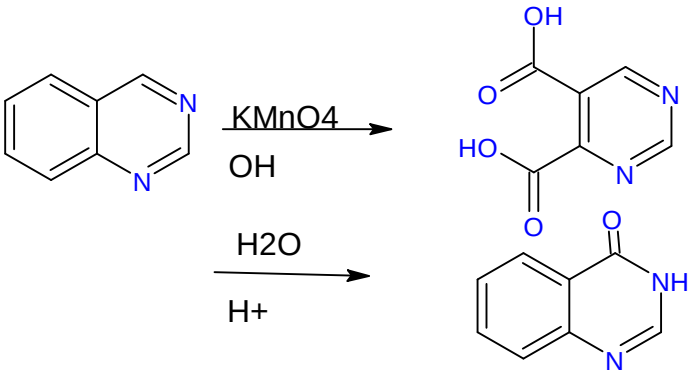


4. **Chemical Properties**

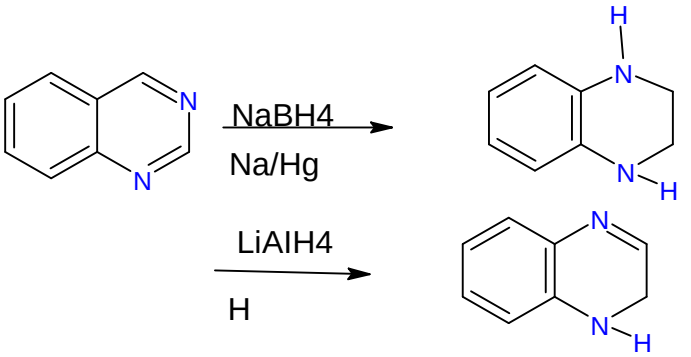
The chemistry of quinazoline was reviewed by Williamson in 1957 and then by Lindquist in 1959 and brought up to date by Armarego in 1963. Quinazolines is stable in cold dilute acid and alkaline solutions, but it is destroyed when these solutions are boiled. O-Aminobenzaldehyde, ammonia, and formic acid are formed when quinazoline is boiled with hydrochloric acid.

4.1. Hydrolysis, Oxidation, and Reduction. Oxidation of quinazoline in dilute aqueous acid with two equivalents of hydrogen peroxide at room temperature gave 3,4-dihydro4-oxo quinazoline. In alkaline medium, the anhydrous neutral species of quinazoline were predominantly undergo oxidation with KMnO4 and yielded 3,4-dihydro-6 4-oxo quinazoline.

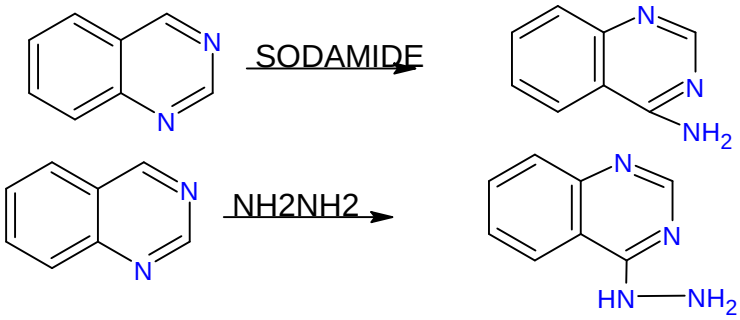
4.1.1. Oxidation. Catalytic hydrogenation of quinazoline stopped after the absorption of one molecule of hydrogen and gave 3,4-dihydro quinazoline.



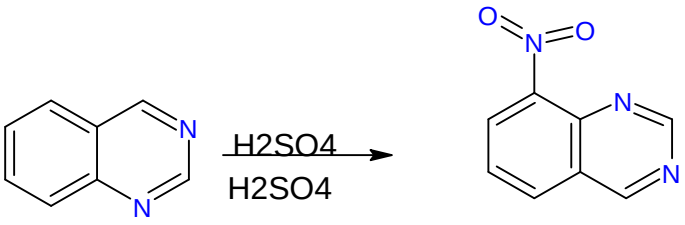
4.1.2. Reduction. Reduction with sodium amalgam gave 1,2,3,4-tetrahydroquinazoline. Lithium aluminum hydride and sodium borohydride gave 3,4-dihydro and 1,2,3,4- tetra hydroquinazoline .



4.2. Nucleophilic and Electrophilic Substitution Reactions. The two known nucleophilic substitution reactions of quinazoline are sodamide and hydrazine most probably proceed via the intermediate addition products, and gave 4-amino and 4- hydrazine quinazoline.

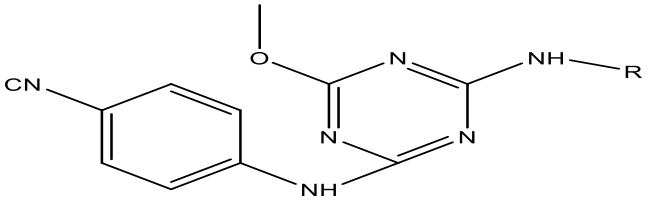


4.2.1. Electrophilic Substitution Reaction of Quinazoline. Nitration is the only known electrophilic substitution reaction of quinazoline. The expected order of reactivity is at positions 8 > 6 > 5 > 7 > 4 > 2. Quinazoline gives 6- nitroquinazoline with fuming nitric acid in concentrated H2SO4. No oxidation of the heterocyclic ring can occur under these conditions because the hydrated cation is not present .



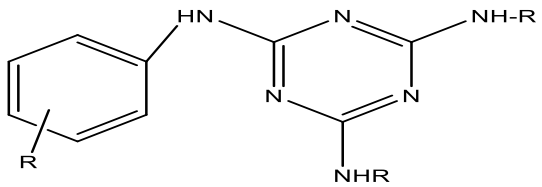
5. REVIEW AND PHARMACOLOGICAL ACTIVITIES

Aymanet al. was reported synthesis of di and tri-substituted –s- triazine derivatives(I).The s-triazine undergoes sequential nucleophile substitution reaction and order of nucleophile is very crucial. The molecules exhibiting excellent antimicrobial activity[31].



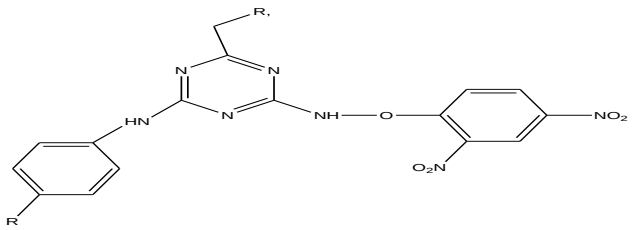
(I)

Barmase et al. was reported 1,3,5, triazine derivative(II) are synthesized by replacement of chlorine ions of cyanuric chloride and 1,3,5-triazine derivatives are showing promising biologically activity such as anti bacterial, antifungal, antimalarial, antivirus and anticancer. The present study reported the synthesis of 2,4,6- trisubstituted 1,3,5-triazine derivatives by microwave mediated method[32].



(II)

Jain et al. synthesized of some compound (III) derivatives on subsequent treatment of these compound with N-hydroxyphthalimide or N-hydroxysuccinimide in the presence of triethlamine gave final compounds, IR, ^{1}H NMR and mass spectra were used to confirm their structure. Compounds were screened for antibacterial and antifungal activities[33].

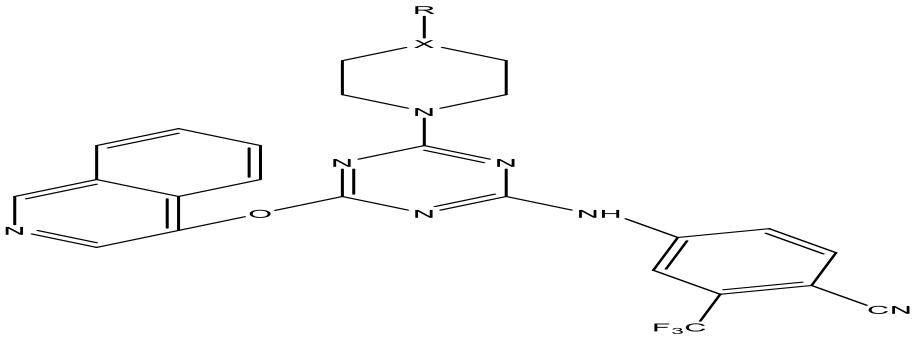


(X) R= Cl, CH_3, Br, NO_2

R, = phthalimidoxy/succinimidoxy

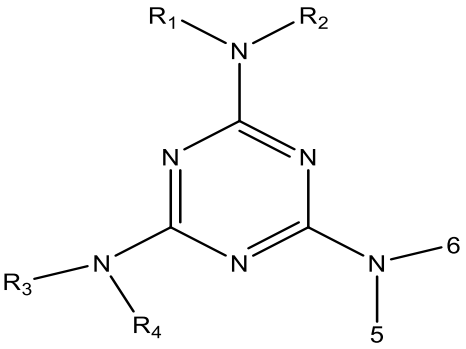
(III)

Mewada et al.reported new biological entities (IV) to fight back with recent drug resistant microbial flora. Reported a library of s-triazine derivatives. The intermediate 4(4-chlro-6-methoxy-1,3,5-trizine-2-yl)amino) bezonitrile 3 was substituted with various thio phenol, phenol, aniline and piperazinepiperidine morphine moieties to furnish the 35 target compound[34].



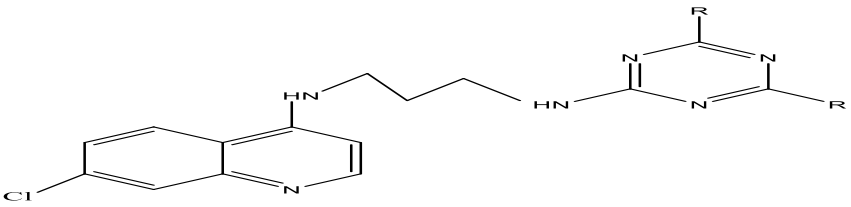
(IV)

Wang et al. reported the Structure-activity relationship studies focused on(V) improving the solubility and mouse pharmacokinetic profile of JSF-2019 and culminated in JSF-2513, relying on the key introduction of a morpholine. Mechanistic studies with JSF-2019, JSF2513, and other triazines stressed the significance of achieving potent in vitro efficacy via release of intra bacterial NO, along with inhibition of InhA and, more generally, the FAS-II pathway. This study highlights the importance of probing IBDM and its potential to clarify mechanism of action, which in this case is a combination of NO, release and InhA inhibition[35].



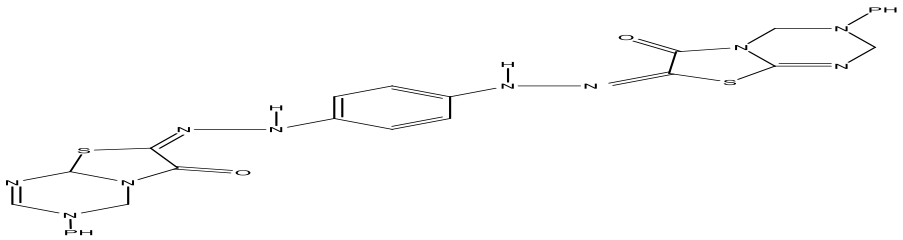
(V)

Bhat et al. reported a novel series of hybrid 4- aminoquinolies-1,3,5-triazine (VI)were synthesized by aromatic nucleophilic displacement of chlorine atoms 2,4,6-trichloro-1,3,5-trizine[36].



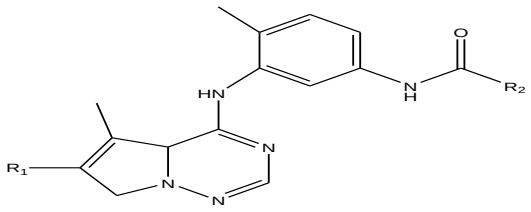
(VI)

Mohamed et al. reported 2-iminothiazolidine-4-one(VII)was utilized for the synthesis of several new thiazolo {3,2-a} [1,3,5]triazine derivatives. 3-phenyl1-3,4-dihydo 2H-thiazolo[3,3,-2][1,3,5]tiazine-6 (7H)one was prepared according to Mannich procedure[37].



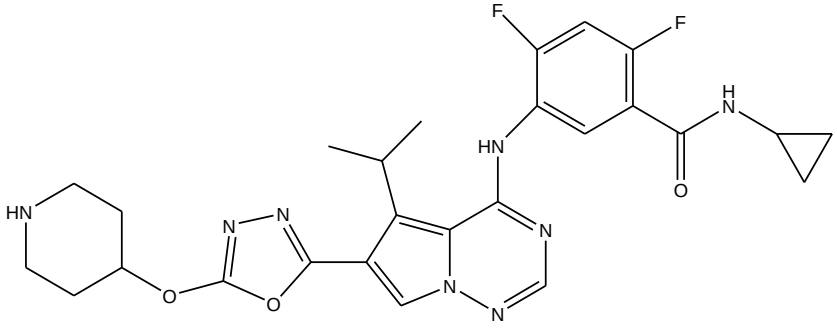
(VII)

Stephen T et al. synthesized and reported of novel series of substituted (VIII) have resulted in the identification of subnanomolar inhibitors of the p38* MAP kinase. Subsequent X-ray co-crystallographic studies with compound have revealed the binding mode of this class of inhibitors within the p38* active site[38].



(VIII)

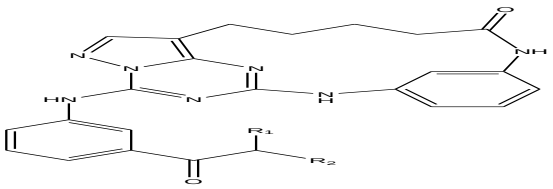
Zhen- wei et al. reported (IX) group at the C-4 position of the pyrrolo[2,1-f][1,2,4]triazine scaffold led to the discovery of a novel sub-series of inhibitors of VEGFR-2 kinase activity. Antitumor efficacy was observed with this compound against L2987 human lung carcinoma xenografts in athymic mice[39].



(IX)

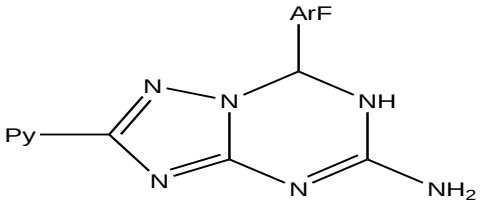
Zhe et al. have prepared a series of macrocyclic derivatives have been designed and synthesized based on the X-ray co-crystal structures of (X) with corn CK2 protein. Bioassays demonstrated that this

macrocyclicpyrazolo [1,5-a][1,3,5] triazine compounds are potent CK2 inhibitor, and they strongly inhibit cancer cell growth[40].



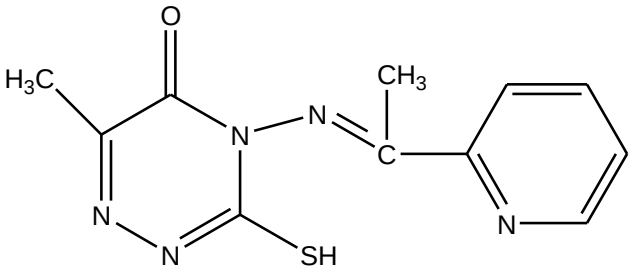
(X)

Anton et al. reported a simple procedure for the synthesis of (XI) was developed and their structure and anticancer properties were investigated[41].



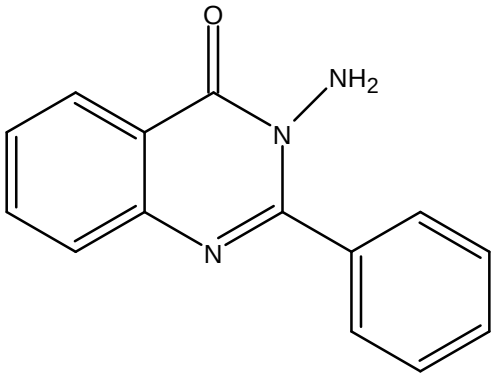
(XI)

Singh et al. Have reported a few (1:1) and (1:2) metal complexes of cobalt(II), nickel(II), copper(II) and zinc(II) have been isolated with ligand derived from the condensation of (XII) with 2-acetylpyridine (L^1) and some of the chemically synthesized compounds have been screened in-vitro against the three Gram-positive (Staphylococcus aureus, Staphylococcus epidermidis and Bacillus subtilis) and two Gram-negative (Salmonella typhi and Escherichia coli) organisms[42].



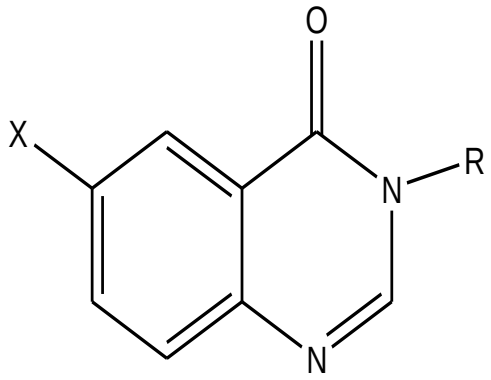
(XII)

Kumar Ashish et al. Synthesized of compounds (XIII) was reported. All the compounds contained a common phenyl group at the 2-position, while the substituents on the arylidineamino group were varied. The compounds were investigated for their antimicrobial activity.[43]



(XIII)

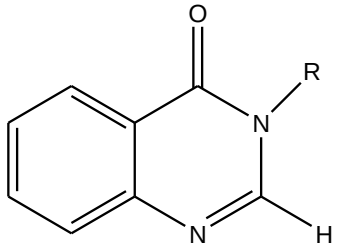
Ouyang Guiping et al. A simple, efficient, and general method has been developed for the synthesis of various (XIV) derivatives from quinazolin-4-one treated with alkyl bromide under phase transfer catalysis condition. The title compound 6-bromo-3-propylquinazolin-4-one was found to posse's good antifungal activity.[44]



(XIV)

Where X=H, F, Cl, Br. R=Et, n-Pr, Allyl

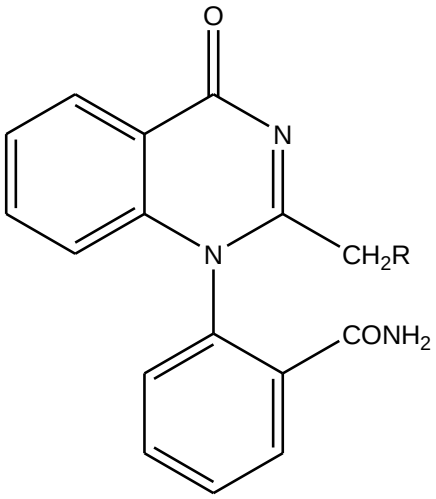
M. Schleiss, et al. Have done on the method for the synthesis of 3-substituted quinazoline-4(3H)-ones (XV)using the convergent reactions of formic acid, a primary amine, and isatoic anhydride under solvent-free conditions and with brief microwave irradiation is described.[45]



(XV)

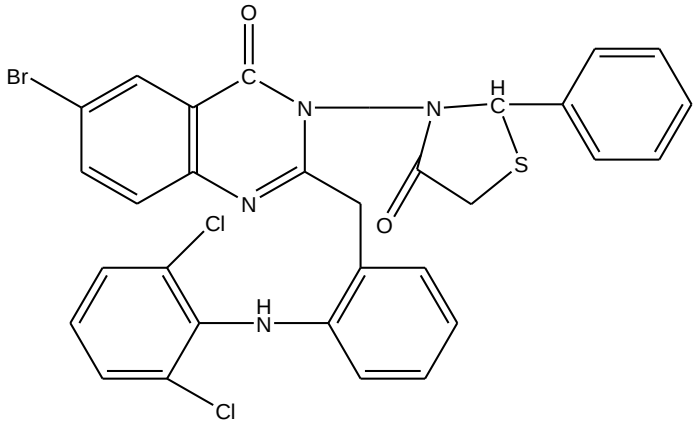
Where R=Aryl or Alkyl

A. Kumar, **et al.** Synthesized of some 1-phenyl-2-(substituted)-4-(1H) quinazolinones (XVI) have been synthesized, purified and characterized on the basis of spectra data such as IR,^{1}H NMR and mass spectral studies. Test compounds were screened for in-vivo analgesic and antiinflamatory activity by acetic acid induced writhing method and carrageen an induced rat hind paw method respectively.[46]



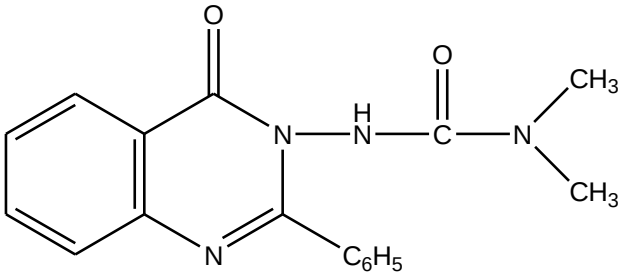
(XVI)

Patel N.B. et al. Synthesized of compound (XVII) via Schiff's bases is being described. The synthesized compound have been characterized by analytical and spectral studies and screened for their antimicrobial activity.[47]



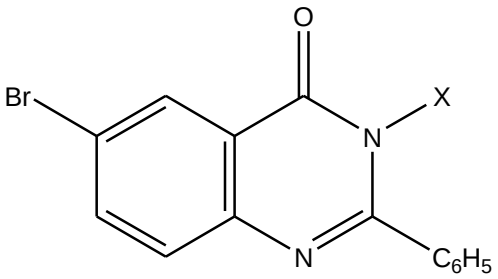
(XVII)

Alagarsamy V. et al. Synthesized 2-phenyl3-substituted quinazolin-4(3H)-ones (XVIII) by treating methyl-N-(2-phenyl quinazolin-3-yl-4(3H)-one) dithiocarbamate with different amines, the starting material dithiocarbamate was synthesized from anthranilic acid. The title compounds were investigated for analgesic, anti-inflammatory and antibacterial activities. All the test compounds exhibited significant activity, the compounds A1, A2 and A3 shown more potent analgesic activity and the compound A3 shown more potent anti-inflammatory activity than the reference standard diclofenac sodium.[48]



(XVIII)

Rghavendra N. M. et al. Synthesized 2,3,6-trisubstituted quinazolin-4-1 ones.(XIX) The nine compounds contained a bromine atom at position 6. A phenyl group at position 2 while at position 3, one compound has free amino group and the remaining 8 compounds have substituted benzalamine group. The synthesized compounds screened for the anti-cancer activity. [49]



(XIX)

6. CONCULSION

Triazine nuclei have occupied a propitious place in pharmaceutical chemistry due to their diverse biological behaviour. The marketed drugs such as Azacitidine, Melarsoprol, Altretamine and Almitrine display broad pharmacological activities like anti-cancer, anti-parasitic, anti-inflammatory, Respiratory stimulant and many more. Literature studies reveal that the 2, 4, and 6 substitution on s-triazine is important for varied biological activities. This diversity in pharmacological activities of triazine scaffold has fascinated the various researchers to further investigate its applications in the treatment of several diseases.

Triazine has been frequently used in medicine because of their wide spectrum of biological activities. Different-s- triazine derivatives have been reported for their antibacterial, antiviral, antimicrobial and herbicidal activities. These are also used for treatment of HIV infection.

2,4,6-Trisubstituted-s-Triazine derivatives have been demonstrated to possess anticancer, anticonvulsant, antimalarial, hypotensive and antiamoebic properties.

1,3,5-Triazine derivatives are known to be effective plant protection agents but their application strongly depends upon their environmental behavior. At present the polymer formulation of pesticides is a rather advantageous approach to obtain ecologically more tolerable product of lower toxicity and of prolonged effect.

The various structural modifications around the fused ring of quinazoline and quinazolinone subsequently evaluate are for their usefulness in treating various disease conditions. Quinazoline and

quinazolinone, being the central body of the pharmacophore, hold different types of substituent. Based on their various physicochemical properties, they exerted a diversified range of therapeutic efficacy. Thus we can conclude that this review will definitely provide the researchers with a thorough understanding of the structure activity relationship study, which further helps in designing good large number of quinazoline and quinazolinone compounds with a strong impact in curing many fatal disorders.

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