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Novel Chemical synthesis and medicinal aspects of some quinazoline and pyrimidine derivatives

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Abstract
Quinazoline and pyrimidine derivatives exhibit a wide range of therapeutic properties. This research paper is highlights the medicinal and synthetic aspects of pyrimidine and quinazoline derivatives.

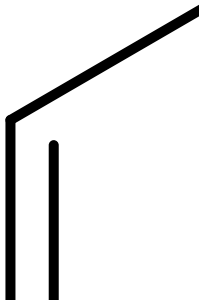
1. Introduction
Quinazoline derivatives **1 [Fig. 1]**, have drawn attention of chemists because of their widespread biopharmaceutical properties[1]. Quinazoline derivatives show various biological properties such as anti-microbial, anti-hypertension, anti-cancer, antimalarial, anti-inflammation, anti-obesity, analgesic, anti-virus, anti-cytotoxin, anti-tuberculosis, anti-spasm, anti-oxidation, anti-diabetes, anti-psychotic, etc. Medicinal chemists have developed various synthetic methods to produce a large number of quinazoline compounds[2] and their therapeutical applications in have also been explored.

Pyrimidine derivatives **2 [Fig. 2]** are known to exhibit wide range of therapeutic properties and this nucleus is present in several pharmaceuticals and natural products. The development of more efficient approach for the synthesis of pyrimidines is an important topic in chemical research. The first pyrimidine derivative, alloxan, was discovered by Brugnatelli in 1818, through the nitric acid oxidative degradation of uric acid. Pyrimidine was first isolated by Gabriel and Colman in 1899[3].

2. Biological aspects of quinazoline

The quinazoline and quinazolinone skeleton is often encountered in medicinal chemistry. In 1903, Gabriel, first synthesized and isolated this from the Chinese plant Aseru[4]. The biological activities of Quinazoline recognized after the synthesis of 2-methyl-1,3-aryl-4-quinazoline derivatives which acts as sleep inducing agent and sedative in nature.

As well known, Quinazolines play a versatile and important role in various biological activities[5]. It comprises many biological properties including antihypertensive[6], antimicrobial[7,8,9], antihyperlipidemic[10], anti-inflammatory[11], anticonvulsant[12,13,14], antiviral[15], antimalarial[16], anticancer[17], diuretic[18,19], analgesic and COX-2 inhibitory activities[20].
Similarly, the derivatives of quinazoline are also potential bioactive agents and have been reported to exhibit a wide spectrum of pharmalogical properties[21-24]. Proquazone[25] **3** and the recently developed derivatives of 2,3-diarylquinazolinone[26] **4** are quinazolinone derivatives with potent anti-inflammatory activity (**Fig. 3**).



Gefitinib is the first member from this family which is considered for the treatment of Non-Small Cell Lung Cancer[27, 28]. Further 4-anilinoquinazoline is reported to be potent and highly selective inhibitors of RTKs[29]. Some examples shown in **Fig. 4** includes which are currently approved drugs or in clinical trials[30].

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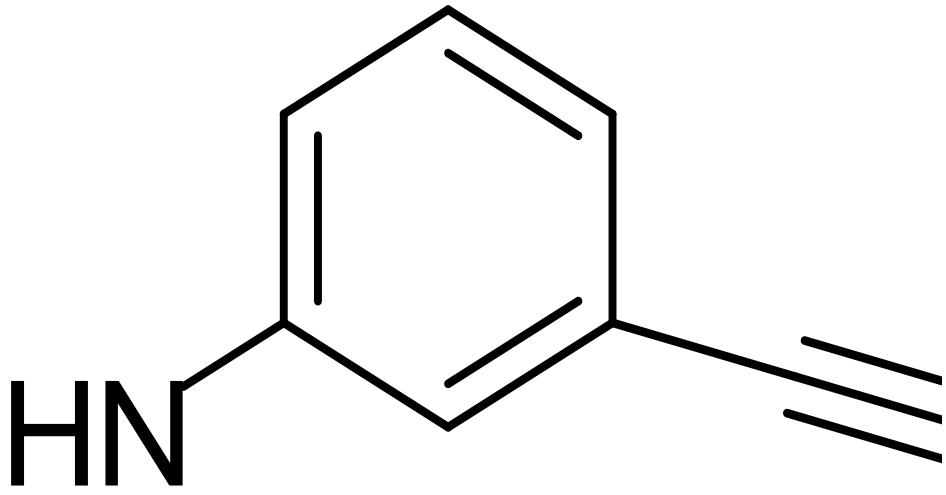
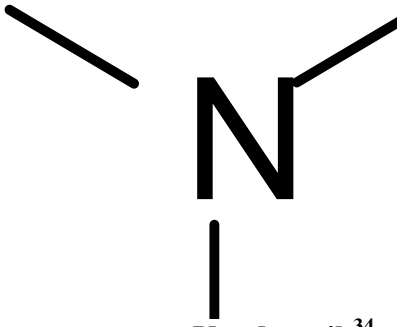


Fig. 4

Table-1 Marketed drugs[31] having quinazoline pharmacophore

S.No	Structure and name of the compound	Medicinal properties
1	**Erlotinib[32]** **11**	Used against lung cancer and pancreatic cancer
2	 **Trimetrexate[33]** **12**	Antiparasitic agent against pneumocystis pneumonia in AIDS patients, antineoplastic agent and as non classical folic acid inhibitor,

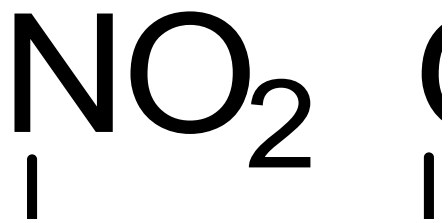
3	 **Vandetanib**[34] **13**	Tyrosine kinase inhibitor, an antagonist of the vascular endothelial growth factor receptor (VEGFR) and the epidermal growth factor receptor (EGFR), and treatment of thyroid cancer.
4	**Febrifugine**[35] **14**	Antimalarial
5	 **Quazinone**[36] **15**	A cardiotonic and vasodilator

3. Synthetic aspects of quinazoline

1. **Niementowski's Synthesis**: Anthranilic acids **16** react with formamide to give quinazoline **17 (Scheme 1)**[37a,b].

2. **Grimmel, Guinther, and Morgan's Synthesis**: The amino benzoic acids **18**, when heated with an amine together with phosphorous trichloride in toluene for two hours, give 2,3-disubstituted 3,4-dihydro-4-oxoquinazolines **19 (Scheme 2)**[38a].

3. **From benoxazones (acylanthranils) and amines**: Benoxazones **20** react with amines to give oxoquinazolines **21 (Scheme 3)**[38a]**.**



4. **From Ethyl 2-Acetamido-5-nitrobenzoate**: Ethyl 2-acetamido-5-nitrobenzene **22** and alcoholic ammonia when heated gave 3,4-dihydro-methyl-6-nitro 4-oxoquinazoline **24 (Scheme 4)**[38a].

5. **Sen and Ray's Synthesis**: Reaction of butyrylanilides **25** with urethane and phosphorous pentoxide gave quinazolines **26 (Scheme 5)**[38a].

6. **From Isatoic Anhydride:** Reaction of isatoic anhydride **27** and aryl aldehydes with primary aliphatic and aromatic amines using montmorillonite K-10 as a catalyst provided the disubstituted derivatives of quinazolinone **29 (Scheme 6)**[39].

7. **Ceric ammonium nitrate (CAN)- TBHP catalysed synthesis**: Reaction of 2-aminobenzophenone **30** and benzylamines **31** using ceric ammonium nitrate (CAN) as catalyst at 80 ºC for 7- 8.5 h gave 2-phenylquinazolines **32** in good yield **(Scheme 7)**[40]**.**

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8. **Copper-catalyzed synthesis of quinazoline:** Reaction of aldehydes **34** with (2-aminophenyl) methanols **33** using the combination of cerium nitrate hexahydrate along with NH_4Cl and KOH leads to 2-substituted quinazolines **35 (Scheme 8)**[41].

9. **CuCl/DABCO/4-HO-TEMPO catalysed synthesis:** The treatment of aldehydes **37** with 2-aminobenzylamines **36** and 2-aminobenzyl alcohols, in the presence of CuCl/DABCO/4-HO-TEMPO as the catalysts and oxygen as the terminal oxidant afforded the quinazoline **38 (Scheme 10)**[42]**.**

10. **Photochemically induced Fries rearrangement of anilides followed by microwave assisted cyclization of acylamides:** This rearrangement of anilides produced *ortho*-aminoacylbenzene derivatives that were acylated. These acylamides **39** in the presence of ammonium formate & microwave conditions gave quinazolines **40 (Scheme 11)**[43]**.**

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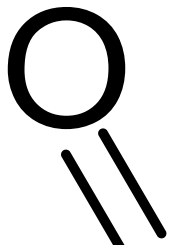

4. Biological aspects of pyrimidine derivatives

Pyrimidine pharmacophore is a chief and central part of RNA and DNA and play an essential role in various biological phenomenons. Alloxan **41** is considered as diabetogenic in animals. The three important constituents of nucleic acids Uracil **42**, Thymine **43**, Cytosine **44** contain pyrimidine ring[44].

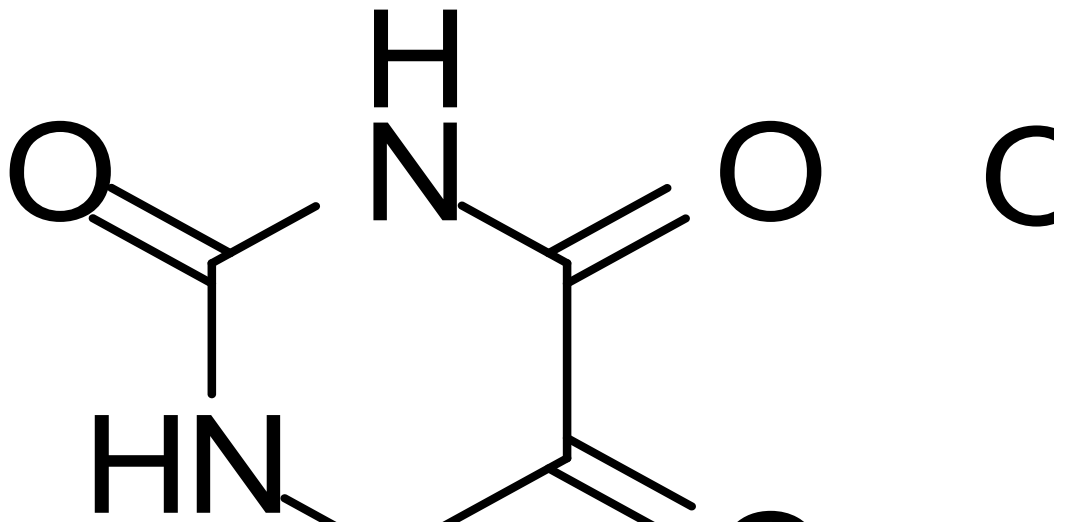

Fig. 5

Many vitamins also contain pyrimidine ring like thymine[45] **46**, riboflavin[46] **47** and folic acid[46] **48**. Barbitone[47] **45**, the first barbiturate hypnotic sedative and anticonvulsant is a pyrimidine derivative[48, 49] **[Fig. 5]**.

Pyrimidines also have important chemical and pharmacological utility as anticancer[50], antiviral[51], antimycobacterial[52], anti-inflammatory[53], analgesic[54], antiallergic[55], anti-HIV[56], antimicrobial, anti-avian influenza virus (H5N1)[57], against herpes simplex virus type-1 (HSV-1)[57] and hepatitis-A virus (HAV)[57], serotonin 5-HT6 receptor antagonist[57], anti-arrhythmic agents[57,58], etc.

Table 2: Marketed drugs having pyrimidine pharmacophore

S. No.	Structure and name of the drug	Medicinal properties
1	5-Fluorouracil[59] **(49)**	Anti cancer
2	Raltegravir[60] **(50)**	Anti HIV
3	Buspirone[61] **(51)**	Anti psycotic
4	Thonzylamine[62] **(52)**	Anti histaminic
5	Etravirine[63] **(53)**	Anti-HIV, Anti viral
6	Iclaprim[64] **(54)**	Antibiotic

5. Synthetic aspects of Pyrimidine

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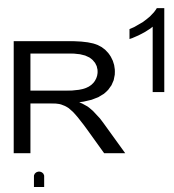
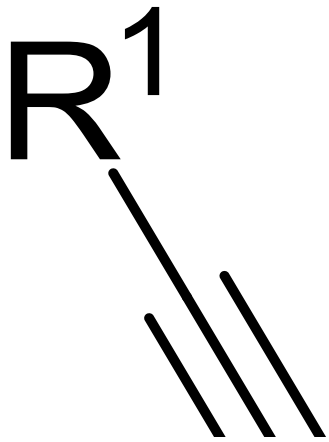
Due to the interesting medicinal properties of pyrimidine nucleus extensive research work has been done on their synthesis and pharmacological properties which has led to the discovery of new synthetic routes and has resulted in the accumulation of vast amount of patented literature for its synthesis in the last few decades.

Generally pyrimidines are synthesized from those compounds in which the ring is formed from two fragments which provide C-C-C and N-C-N atoms respectively.

1. **Pinner pyrimidine synthesis:** The condensation reaction of amidines **55** with 1,3-dicarbonyl compound **54** gives pyrimidine derivatives **56 (Scheme 12)**[65].



2. **From diacetylenic ketoesters and amidinium chlorides:** Adamo et al prepared the 2,4,6-trisubstituted pyrimidines **60** using diacetylenic ketoesters **58** and amidinium chlorides **59 (Scheme 13)**[65].



3. **One pot synthesis:** Molteni et al developed the one pot method for the preparation of 2,4,5-trisubstituted pyrimidines **64** from cyclic 1,3-diketones **61**, imidinium chlorides **62** and dimethylformamide dimethylacetal **63 (Scheme 14)**[65].

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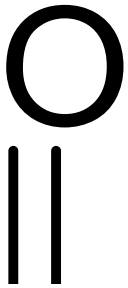

4. **Kiselyov synthesis:** Kislyov et al reported the synthesis of pyrimidine derivative **69** from α,β-unsaturated imines, which were generated *insitu* from alkylphosphonates and aryl nitriles. The condensation of amidinium or guanidinium chlorides with imine gives polysubstituted pyrimidines **(Scheme 15)**[65].

5. **Microwave assisted synthesis:** Good yields was obtained by microwave assisted synthesis of pyrimidines **(Scheme 16)**[65].

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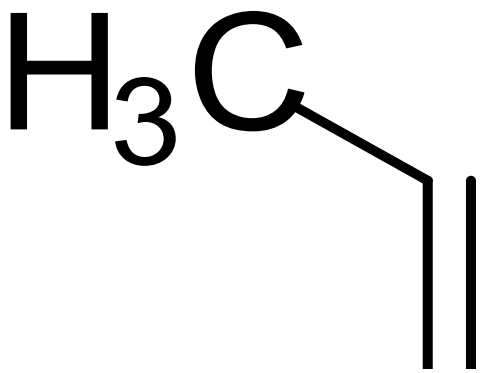
6. **Condensation of urea with ethyl crotonate:** A dihydropyrimidine **76** is formed by the condensation of urea **73** with ethyl crotonate **72** in presence of a base which on oxidation yields corresponding pyrimidine **75 (Scheme 17)**[66]**.**

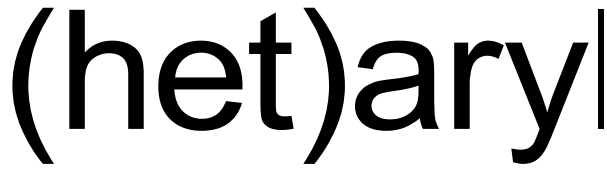


7. **Reaction of β-enaminoketones with formamide**: β-enaminoketones **80** were formed by the reaction of formamide **79** with active methyl group of acetophenone **77** which in presence of excess of formamide cyclises to 4-phenyl pyrimidine **81 (Scheme-18)**[67]**.**

8. **From amidinium salts:** Amidinium salts **82** on reaction with sodium salt of 3,3-dimethoxy-2-methoxycarbonylprope-1-ol **83** gives 2-substituted pyrimidine-5-carboxylic ester **84 (Scheme-19)**[68]**.**

9. **Samarium chloride catalysed microwave synthesis of pyrimidine**: An efficient and novel synthesis of pyrimidine **87** involves samarium chloride catalysed cyclisation of β-formyl enamide **85** with urea **86** as a source of ammonia under microwave irradiation **(Scheme 20)**[69].

10. **Sonogashira coupling:** The Sonogashira coupling of (het)aryl chlorides **88** and (TMS)-acetylene with triethylamine give TMS-ynones **89**, which on addition of amidinium or guanidinium salts together with 2.5-3 equiv of sodium carbonate decahydrate gives the pyrimidine **90 (Scheme 21)**[70].



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