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A COMPREHENSIVE STUDY OF PYRIMIDINE AND ITS MEDICINAL APPLICATIONS

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Abstract – Pyrimidine is a heterocyclic aromatic organic compound which is versatile lead compound for designing potent therapeutic agents. Different pyrimidine derivatives have been synthesized by various conventional methods and also from green methods. The pyrimidine moiety widely occurs in biologically occurring compounds, such as nucleic acids components, folic acid and vitamin B_1 etc. This compound has various biological activities like anticancer, antitubercular, antimicrobial, antifungal, antibacterial, antioxidant, anticonvulsant, analgesic, CNS depressant, anti-inflammatory, anti-HIV, antihelmentic and herbicidal activity. Available data represents pyrimidine being heterocyclic six membered ring systems has various pharmacological actions and synthesis of pyrimidine and their derivatives are discussed.

CONTENTS

1. INTRODUCTION

The heterocyclic compounds have attracted numerous attentions due to their wide applications in medicinal chemistry research. Heterocycles are in abundance in nature and are very significant in our lives because of their existence in many naturally occurring molecules such as hormones, antibiotics, caffeine etc. Heterocyclic chemistry is the branch of organic chemistry dealing with the synthesis, properties, and applications of these heterocycles.[1]

Pyrimidine is the six membered heterocyclic organic colourless compound containing two nitrogen atoms at 1st and 3rd positions. Pyrimidine which is an integral part of DNA and RNA imparts diverse pharmacological properties. The pyrimidine has been isolated from the nucleic acid and are much weaker base than pyridine and soluble in water. In nucleic acids, three types of nucleobases are pyrimidine derivatives: cytosine (C), thymine (T), and uracil (U).

Electron lone pair availability of pyrimidine is decreased compared to pyridine therefore N-alkylation and N-oxidation are more difficult.[2] The pyrimidine ring system has wide occurrence in nature as substituted and ring-fused compounds and derivatives, including the nucleotides, thiamine (vitamin B_1), and alloxan. It is also found in many synthetic compounds such as barbiturates and the HIV drug, zidovudine. Pyrimidines have been known since their early days as essential components of nucleic acid to their current usage in the chemotherapy of AIDS. Pyrimidine is the most important member of all the diazines as this ring system occurs widely in living organisms.[3] Furthermore, the prebiotic synthesis of nucleic acid bases is a central issue in the RNA-world hypothesis, one of the main proposals for the origin of life, based on the self-assembly of nucleic acid monomers.

Pyrimidines and its derivatives are integral part of DNA and RNA, it has found to be assosiated with diverse biological activities.[4] Pyrimidine template and its heterofused derivatives exhibit promising anticoagulant, antitubercular, antileukemic, antimicrobial, anti-inflammatory, anti-HIV, analgesic, anticancer, antitumoral, anticonvulsant, antiplatelet, antifungal, antiviral, antibacterial, antimalarial and antinociceptive activities. New thienopyrimido benzothiazole and thieno pyrimidobenzo oxazoles exhibit analgesic and antiinflammatory activity.[5]

The group of pyrido[1,2-*a*]pyrimidin-4-ones is a well-known class of aza-bridgehead fused heterocyclic compounds which have miscellaneous pharmaceutical applications. In view of the occurrence of microorganisms resistance to drugs currently in use and the continuous outbreak of new infectious diseases every time, there is a continuous need for the exploration of new heterocyclic compounds which are pyrimidine-based as potential agents of wide therapeutic implications for effective drug design.[6-8]

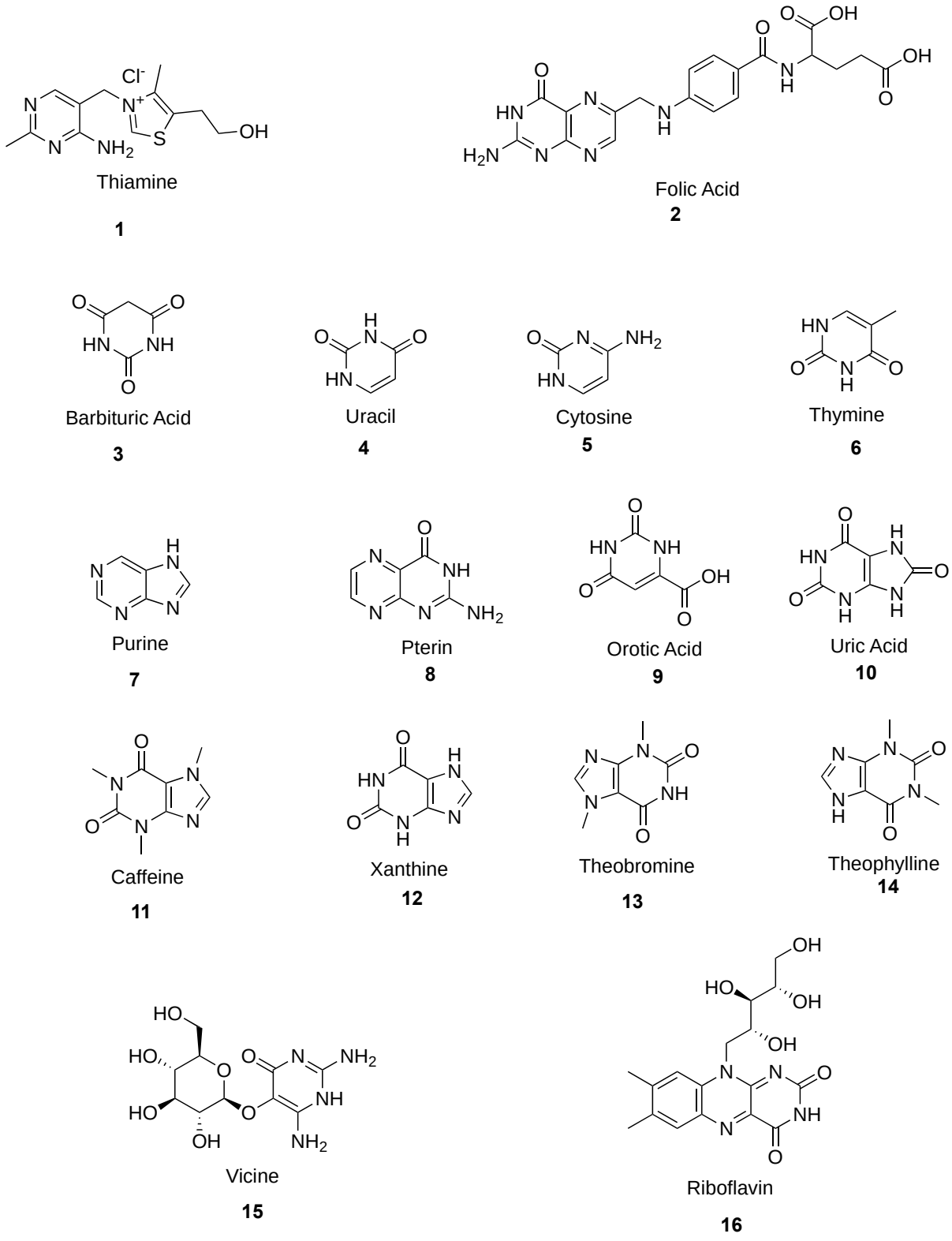


Figure 1. Molecular structures of pyrimidine derivatives

2. SYNTHESIS OF PYRIMIDINE

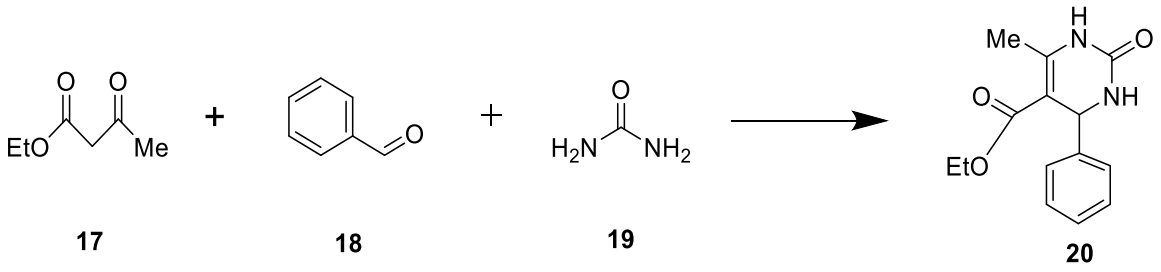
Conventional synthesis refers to the traditional approach of synthesis. A traditional concept in process chemistry has been the optimization of the time-space yield. From our modern perspective, this limited

viewpoint must be enlarged, as for example toxic wastes can destroy natural resources and especially the means of livelihood for future generations. In addition, many feedstocks for the production of chemicals are based on petroleum, which is not a renewable resource. "Sustainability" is a concept that is used to distinguish methods and processes that can ensure the long-term productivity of the environment. As conventional method requires the use of many hazardous chemicals as well as it consumes more energy and time, the green chemistry has come to existence.

Green chemistry is the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances. Green chemistry applies across the life cycle of a chemical product, including its design, manufacture, use, and ultimate disposal. It is also known as sustainable chemistry. It reduces pollution at its source by minimizing or eliminating the hazards of chemical feedstocks, reagents, solvents, and products.Various methods of green synthesis include bioenzymatic process, microwave synthesis, use of sonication, solvent free or solid phase synthesis etc.

2.1 CONVENTIONAL SYNTHESIS OF PYRIMIDINE

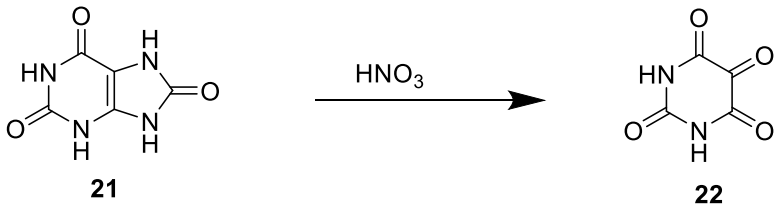
The Biginelli reaction is a multiple-component chemical reaction that creates 3,4-dihydropyrimidin-2(1*H*)-ones **20** from ethyl acetoacetate **17**, an aryl aldehyde such as benzaldehyde **18**, and urea **19**. It is named for the Italian chemist Pietro Biginelli. The reaction can be catalyzed by Brønsted acids and/or by Lewis acids such as copper(II) trifluoroacetate hydrate and boron trifluoride.[9]



17 **18** **19** **20**

Scheme 1. Biginelli multi component reaction

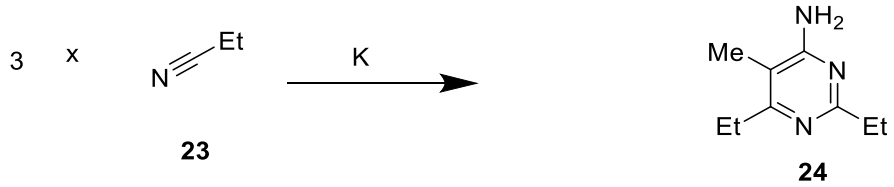
Alloxan **22** was originally prepared in 1818 by Brugnatelli and was named in 1838 by Wöhler and Liebig. The name "alloxan" emerged from an amalgamation of the words "allantoin" and "oxalsäure" (oxalic acid). It was originally obtained by oxidation of uric acid **21** by nitric acid. It is prepared by oxidation of barbituric acid by chromium trioxide. A dimeric derivative alloxantin can be prepared by partial reduction of alloxan with hydrogen sulfide.[10]



21 22

Scheme 2. Brugnatelli alloxan synthesis

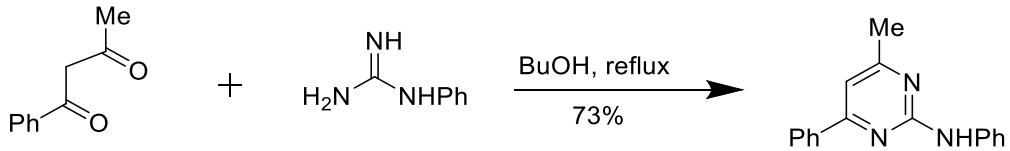
Frankland and Kolbe in 1848, described the first synthesis of a pyrimidine, cyanalkine, by heating propionitrile **23** with potassium metal. This reaction yielded 2,6-diethyl-5-methylpyrimidin-4-amine **24**.[11]



23 24

Scheme 3. Frankland and Kolbe cyanalkine synthesis

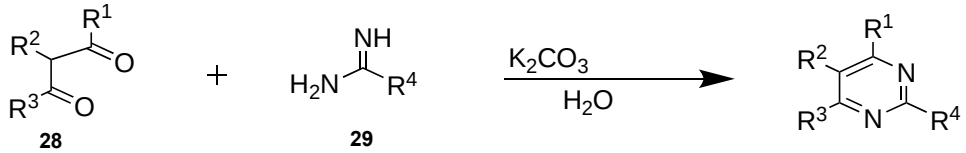
Many of the prevailing strategies for synthesis of pyrimidine rely on condensation of N-C-N fragments, most often guanidines, with 1,3-dicarbonyl derivatives. The reaction of 1-phenylbutane-1,3-dione **25** with phenylguanidine **26** under reflux yielded 4-methyl-*N*,6-diphenylpyrimidin-2-amine **27**. The solvent used was butanol.[12]



25 26 27

Scheme 4. Representative synthesis of pyrimidine by N-C-N fragment and diketone

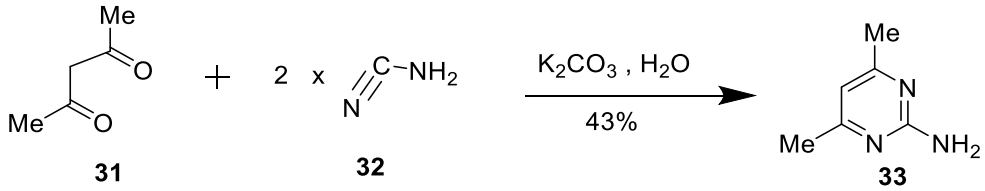
Nitriles are a common N–C source and have been used to form pyrimidines in many syntheses. Cyanamide is a particularly useful nitrile derivative in the synthesis of pyrimidines. The reaction of dicarbonyl compound with urea in the presence of K_2CO_3 was achieved under reflux. H_2O was used as a suitable solvent for this reaction.[13-15]



28 29 30

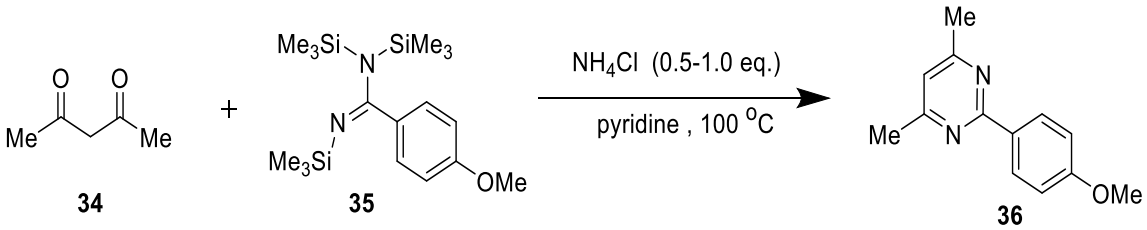
Scheme 5. Pinner pyrimidine synthesis

The reaction is a strong base promoted condensation between a non *N*-substituted amidine-cynamide **32** and a β-keto ester or β-diketone i.e. pentane-2,4-dione **31** to form 4,6-dimethylpyrimidin-2-amine **33**. The reaction was carried under reflux in the presence of K_2CO_3 with H_2O as a solvent.[16]



Scheme 6. Representative use of cyanamide in condensation with acetylacetone for synthesis of pyrimidine

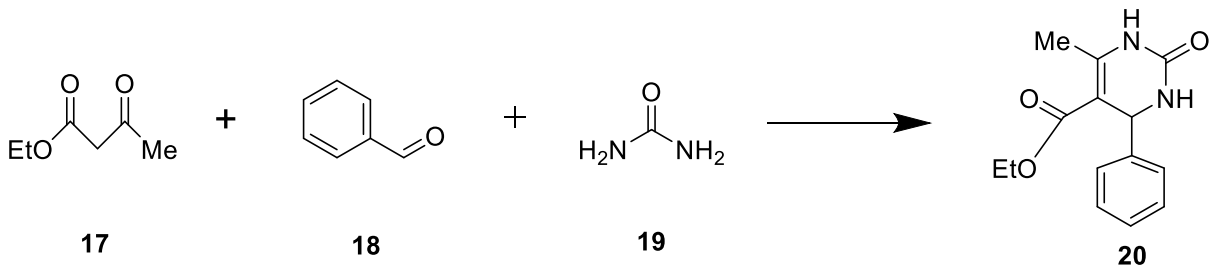
Ghosh and Katzenellenbogen were able to condense *N,N,N'*-tris(trimethylsilyl)amidine **35**, in place of unsubstituted amidines, with 1,3-dicarbonyl compounds and prepare a variety of 2,4,6-trisubstituted and 2,4,5,6-tetrasubstituted pyrimidine derivatives.[16]



Scheme 7. Modified Pinner pyrimidine synthesis

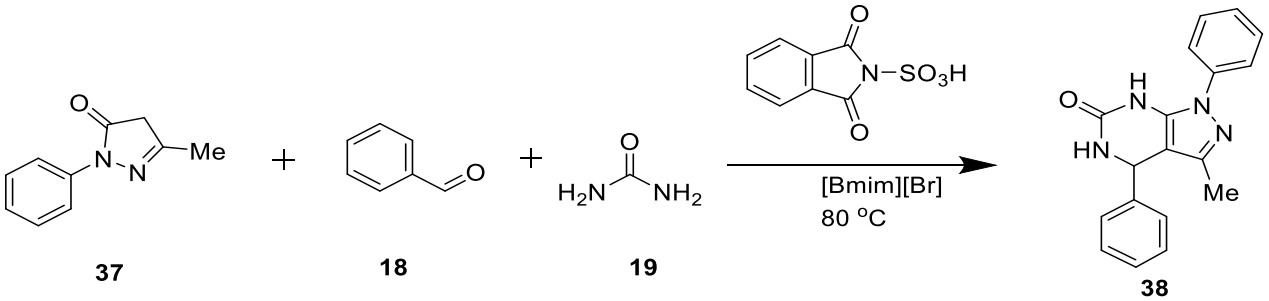
2.2 GREEN SYNTHESIS OF PYRIMIDINE

Baker's yeast and D-glucose were taken in phosphate buffer and stirred overnight. Benzaldehyde **18**, ethyl acetoacetate **17** and urea **19** were added to the fermenting yeast and the reaction mixture stirred for a further 24 h. Next, the reaction was diluted with water and extracted with ethyl acetate. The organic layer was dried over sodium sulphate and concentrated to give a crude product. Pure 3,4-dihydropyrimidin-2-(1*H*)-one **20** derivative was obtained by crystallization of the crude product from methanol in 84% yield.[17]



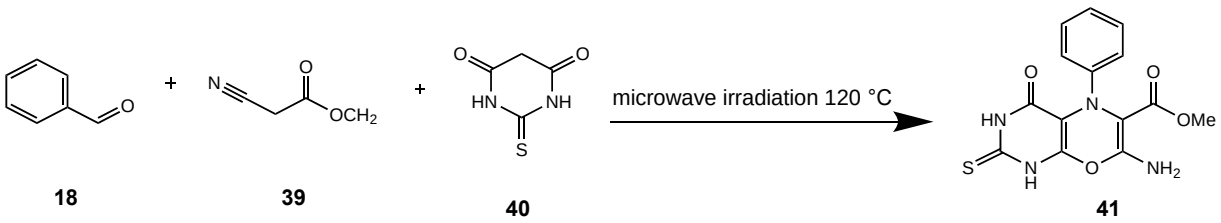
Scheme 8. Baker's yeast mediated synthesis: Reagents and conditions: Baker's yeast, D-glucose, phosphate buffer (pH 7.0), room temperature, 24 h.

A novel and straightforward synthetic pathway to access fused 3-methyl-1,4-diphenyl-1,4,5,7-tetrahydropyrazolo[3,4-*d*]pyrimidin(e)-6-ones/thiones by the three component reaction of 1-phenyl-3-methyl-1*H*-pyrazol-5(4*H*)-one, aromatic aldehyde and urea/thiourea in the presence of catalytic amount of PISA (phthalimide *N*-sulfonic acid) in [Bmim][Br] ionic liquid at 80 °C.[18]



Scheme 9. Synthesis of 3-methyl-1,4- diphenyl-1,4,5,7-tetrahydropyrazolo[3,4-*d*]pyrimidin-6-ones using ionic liquid

A mixture of benzaldehyde **18**, methyl cyanoacetate **39**, thiobarbituric acid **40**, and water was placed into Teflon vessel and subjected to microwave irradiation under catalyst free conditions for a given time at power of 250 W and 120 °C. After completion of the reaction as followed by TLC examination at an interval of 30 seconds using eluent petroleum ether:ethyl acetate (7:3 ratio). The reaction mixture was cooled to room temperature and poured into cold water, causing the precipitation of the product. The solid product was filtered under vacuum, washed with water and subsequently recrystallized from 95% ethanol to yield the pure product in excellent yield (78–94%).[19,20]

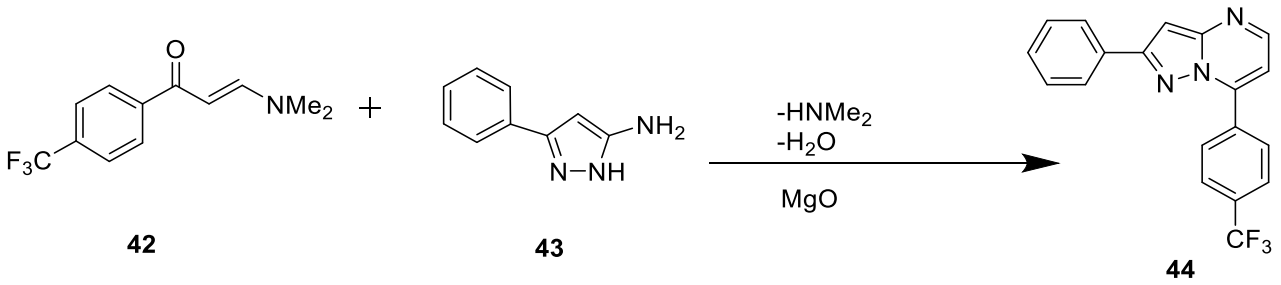


Scheme 10. Microwave assisted one-pot synthesis

In order to address the advantage of utilization of ball-mill technique on the rate of aza-Micheal addition reaction, reaction for synthesis of 4-trifluoromethylphenylpyrazolo[1,5-*a*]pyrimidine derivative **44** was carried out by conventional electrical heating using nano sized MgO catalyst. The solvent-free conventional heating method carried out in oil bath to obtain the product. The obtained results revealed that the reactions required longer reaction time (9 h) to attain considerable yields (71%) under conventional heating methods, which lower than that obtained via ball-mill technique.

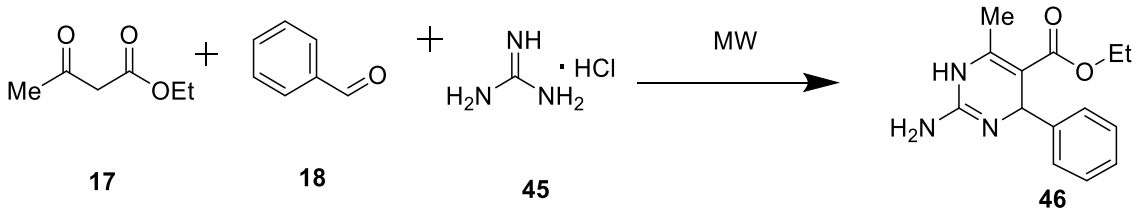
The scope and generality of the above protocol was tested by various derivatives of 5-aminopyrazole **43** for reaction with enaminone using nanosized MgO catalyst under the optimized conditions (0.40 g

catalyst, 30 Hz ball-mill frequency). The corresponding pyrazolo[1,5-*a*]pyrimidine products were obtained in excellent yields (88–97%).[21]



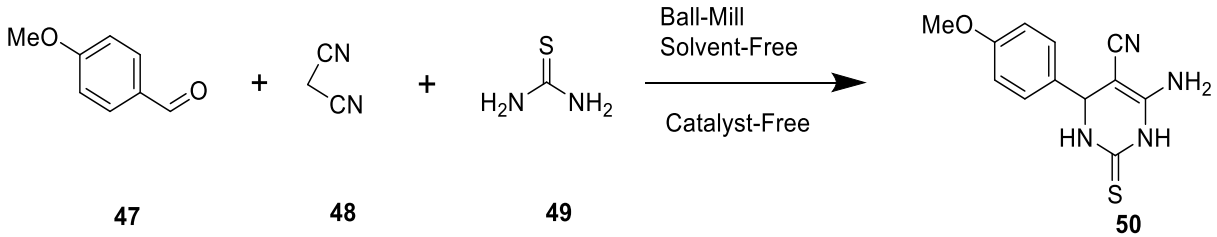
Scheme 11. Synthesis under solvent free mechanochemical condition

The reference reaction of guanidine hydrochloride **45**, benzaldehyde **18**, and ethyl acetoacetate **17** in the presence of $NaHCO_3$ as the base, leading to ethyl 2-amino-6-methyl-4-phenyl-1,4-dihydropyrimidine-5-carboxylate **46**. The best results were obtained with ethanol as solvent and that the best conditions are 120 °C for ten minutes.[22]



Scheme 12. Optimized synthesis under microwave heating

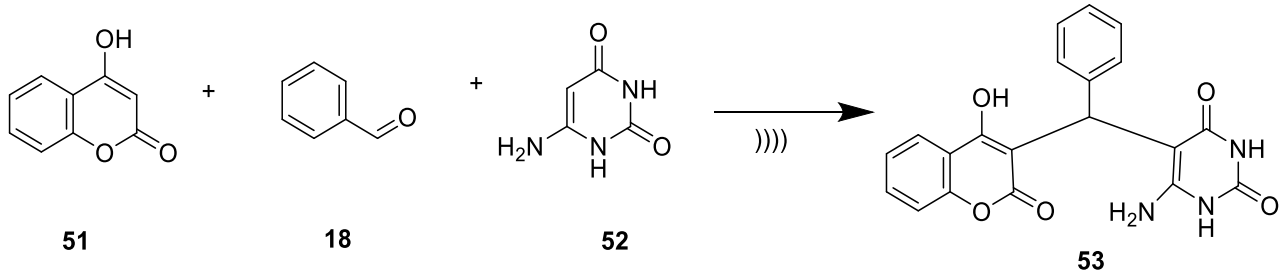
A simple ball-milling procedure for the synthesis of 2-thioxo-pyrimidine-5-carbonitriles **50** by direct condensation of *p*-methoxybenzaldehyde **47**, malononitrile **48**, and thiourea **49** using ball-milling solvent-free, catalyst-free synthesis. In this one-pot synthesis process, only the weight of the balls used in the ball-milling process need to be changed in order to obtain high yield.[23]



Scheme 13. Synthesis of carbonitrile using ball-mill technique

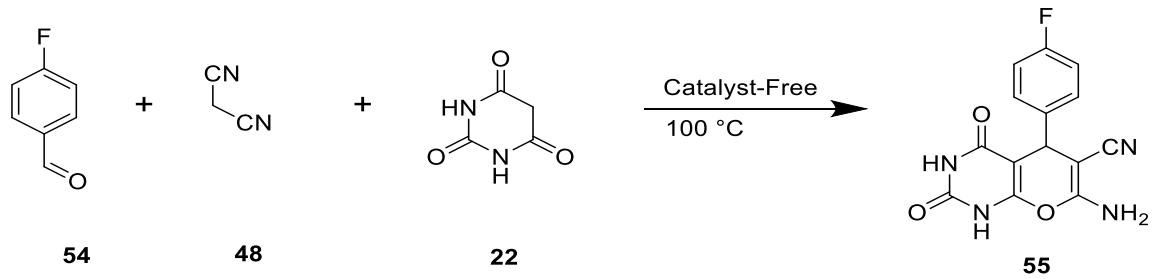
An ultrasound-promoted expedient and green practical method to access functionalized 6-amino-5-((4-hydroxy-2-oxo-2*H*-chromen-3-yl)(aryl)methyl)pyrimidine-2,4(1*H*,3*H*)-diones **53** from the one-pot multi-component reaction between 4-hydroxycoumarin **51**, substituted aromatic aldehydes

and 6-aminouracils, 6-amino-2-thiouracil under sulfamic acid catalysis in aqueous ethanol (1:1) at ambient conditions (28−30 °C) has been developed.[24]



Scheme 14. Ultrasound assisted one-pot synthesis

A catalyst-free, green and highly efficient one-pot strategy for preparation of pyrano[2,3-*d*]pyrimidine scaffolds via three-component Knoevenagel–Michael addition cyclocondensation reaction of aryl aldehyde derivatives, malononitrile with barbituric acid/1,3-dimethylbarbituric acid in ethylene glycol as a green reaction medium.[25]



Scheme 15. Catalyst-Free three component tandem green synthesis

3. MEDICINAL SIGNIFICANCE OF PYRIMIDINES

In medicinal chemistry pyrimidine derivatives have been very well known for their therapeutic applications. During the last two decades, several pyrimidine derivatives have been developed as chemotherapeutic agents and have found wide clinical applications, which are as follows

3.1 PYRIMIDINES AS ANTINEOPLASTIC (ANTICANCER) AGENTS

Cancer is not just one disease, but a large group of almost one hundred diseases. Its two main characteristics are uncontrolled growth of the cells in the human body and the ability of these cells to migrate from the original site and spread to distant sites. If the spread is not controlled, cancer can result in death. The main target of anti-tumor chemotherapies is DNA. Alteration of DNA structure affects its synthesis and function which usually leads to disruption of cell proliferation and can eventually elicit cell death via apoptosis. These effects are currently being exploited to develop novel biologically active drugs with potential applications as anti-proliferative therapies. In addition tegafur and 5-thiouracil are also shown to exhibit some useful antineoplastic activity. Gemitabine a cytosine nucleoside analogue possess

anticancer activity against murine solid tumor. During the last two decades, several pyrimidine derivatives have been developed as chemotherapeutic agents and have found wide clinical applications. Numerous recent reports also highlight the anticancer potential of pyrimidines in fused scaffolds. Apoptosis-inducing activity of thiazolo[5,4-*d*]pyrimidines,[26] thieno[3,2-*d*]pyrimidines as HDAC (histone deacetylase) inhibitors,[27] 4-anilinothieno[2,3-*d*]pyrimidines as irreversible epidermal growth factor receptor inhibitors,[28] pyrazolo[1,5-*a*]pyrimidine-based CHK1 (a serine/threonine-specific protein kinase) inhibitors.[29]

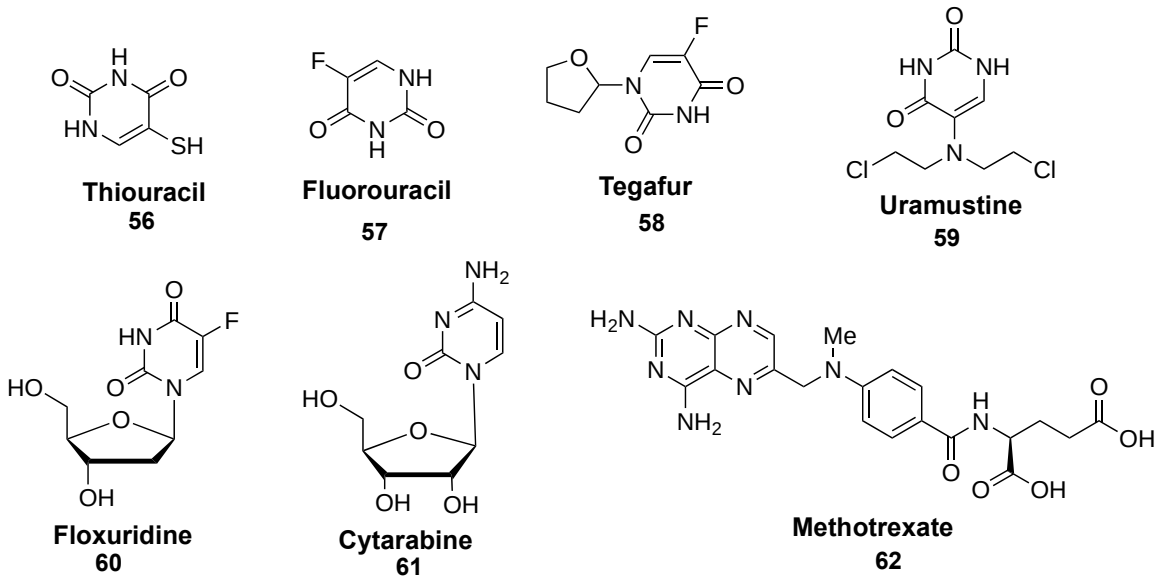


Figure 2. Pyrimidine based antineoplastic agents

3.2 PYRIMIDINE AS ANTI-INFLAMMATORY AND ANALGESIC AGENTS

There are large numbers of pyrimidine derivatives found to exhibit anti-inflammatory and analgesic activity. Some of them are as follows. New lipid soluble forms of thiamine (vitamin B_1) such as Acetamine, Bentamine and Fursultiamine are used for beriberi, polyneuritis, encephalopathy and pain. Nargund *et al.*[30] reported the synthesis of few substituted 2-mercapto-3-(N-alkyl)pyrimido[5,4-*c*]-cinnolin-4-(3*H*)-ones and screened them for anti-inflammatory and antimicrobial activities. Pirisino *et al.*, have studied 2-phenylpyrazolo-4-ethyl-4,7-dihydro[1,5-*a*]pyrimidin-5-one for its analgesic, antipyretic and anti-inflammatory activities. Modica *et al.*[31] synthesized some new thiadiazolothienopyrimidinones and tested them for anti-inflammatory activities and found good results. Cenicola *et al.*[32] evaluated some imidazolo[1,2-*c*]pyrimidines for anti-inflammatory activities.

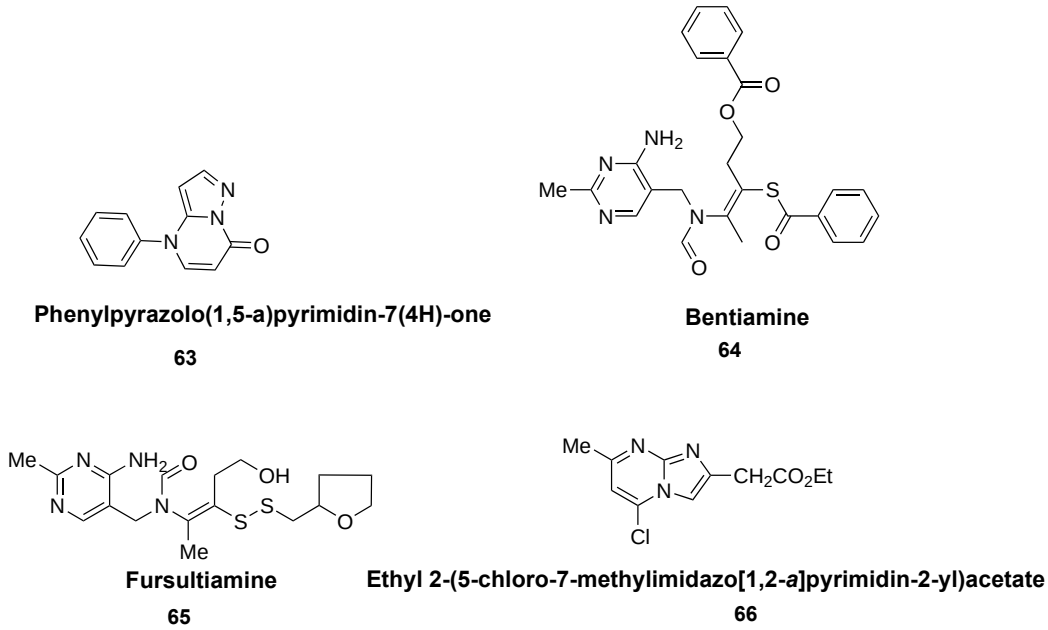


Figure 3. Pyrimidine based anti-inflammatory agents

3.3 PYRIMIDINE ANALOGUES AS ANTIBIOTICS

Pyrimidine derivatives are also known for antibiotic properties. Pyrimidine analogs which act as antibiotic are bacimethrin[33] (5-hydroxymethyl-2-methoxypyrimidin-4-amine) which is found to be effective against several staphylococcal infections. Gourgetin a cytosine derivative is active against mycobacteria as well as several Gram-positive and Gram-negative bacteria. Wide-spectrum antibiotics aminoglycoside antibiotics, phleomycin, bleomycin[34] are some other example of pyrimidine analogues. Further bleomycin is used for the treatment of certain tumors like Hodgkin's lymphoma and disseminated testicular cancer. Nikkomycins were the first nucleoside antibiotics found to inhibit fungal cell wall chitin biosynthesis.

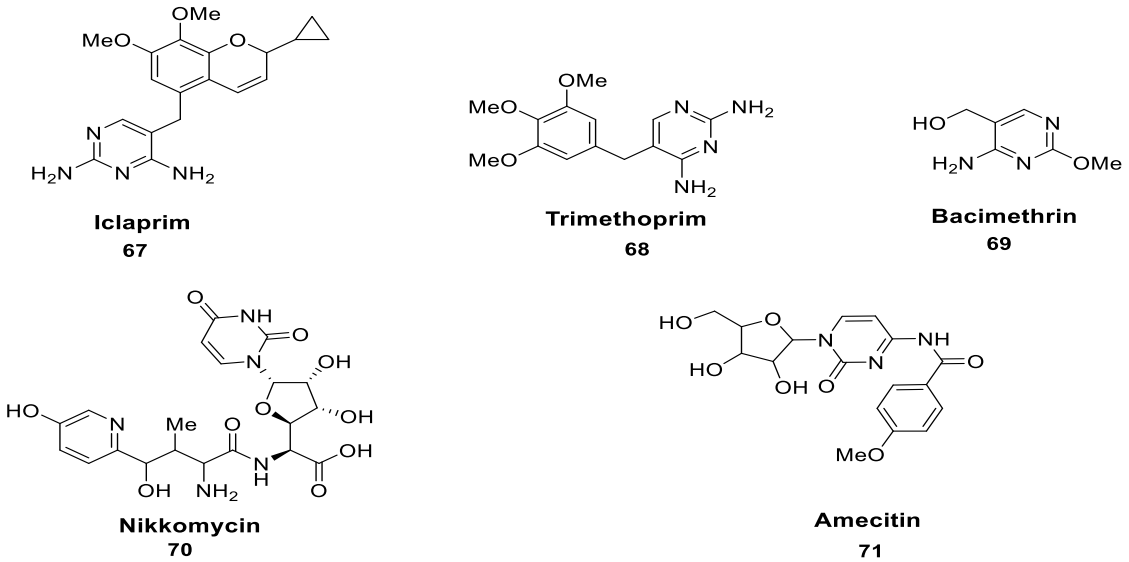


Figure 4. Pyrimidine based antibiotics

3.4 PYRIMIDINE AS ANTI- HIV AGENTS

Human immunodeficiency virus (HIV-1) the causative agent of the acquired immune deficiency syndrome (AIDS), utilizes a reverse transcriptase (RT) that plays a central role in the replicative life cycle of the virus. This enzyme to date has been one of the main chemotherapeutic targets in efforts to control infections. A large number of molecules have been designed and synthesized to target various active sites on this enzyme. Among these chain terminators, the nucleoside analogs, 3'-azidothymidine (AZT), 2', 3'-dideoxycytidine (DDC), and 2', 3'-didehydro-3'-deoxythymidine (d4T) were developed. Although approved for clinical use for patients with AIDS, the toxicity associated with these drugs together with the emergence of resistance strains of the virus has raised the need for molecules with a different mode of action. Cidofovir, an antimetabolite for deoxycytosine triphosphate is used for treatment of cytomegalo virus (CMV) in AIDS patients. Pyrimidine-2,4-diones[35] linked to an isoxazolidine nucleus have been synthesized and tested as nucleoside analogs, endowed with potential anti-HIV activity. In addition, HEPT analogs viz., EPT and BPT having terminal ethoxymethyl and benzyloxymethyl groups respectively are more potent inhibitor of HIV-1 replication than HEPT. HEPT is a potent and selective inhibitor of HIV–1 but not HIV-2. Hence, Goudgaon *et al*.,[36,37] synthesized selenium related analogs of HEPT (6-(phenylselenenyl)pyrimidine nucleoside analogs. These compounds exhibited selective antiviral activity against both HIV-1 and HIV-2 in primary human lymphocytes.

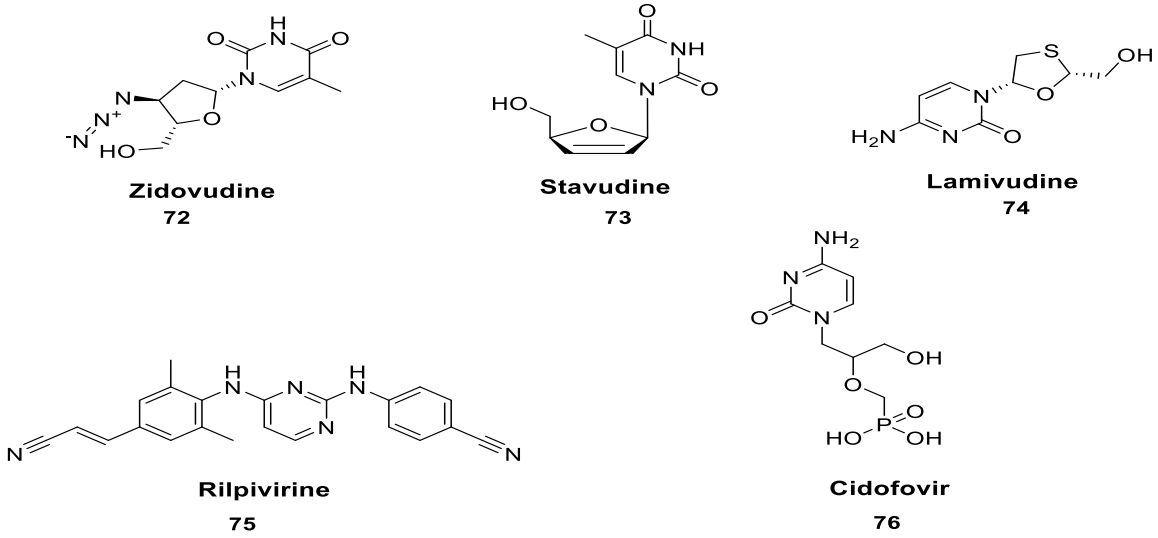


Figure 5. Pyrimidine based anti-HIV agents

4. CONCLUSION

This review has outlined several convergent synthetic approaches that have been reported for pyrimidine, while most of these approaches involves condensation of N-C-N fragments. Recently other approaches have also emerged. Green methodologies are available on a large scale. Pyrimidine scaffold has great

biological and medicinal applications. A vast literature has been accumulated over years for pyrimidine moiety and thus it is an active and important area of research in heterocyclic chemistry.

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