Current Medicinal Chemistry, 2023, *30*, 1029-1059

REVIEW ARTICLE

Microwave Induced Green Synthesis: Sustainable Technology for Efficient Development of Bioactive Pyrimidine Scaffolds

Biswa Mohan Sahoo[1,*], Bimal Krishna Banik[2], Bera Venkata Varaha Ravi Kumar[1], Krishna Chandra Panda[1], Abhishek Tiwari[3], Varsha Tiwari[3], Sunil Singh[4] and Manish Kumar[5]

[1]*Roland Institute of Pharmaceutical Sciences (Biju Patnaik University of Technology Nodal Centre of Research), Berhampur 760010, Odisha, India;* [2]*Department of Mathematics and Natural Sciences, College of Sciences and Human Studies, Prince Mohammad Bin Fahd University, Al Khobar, Kingdom of Saudi Arabia;* [3]*Faculty of Pharmacy, Pharmacy Academy, IFTM University, Lodhipur Rajput, Moradabad 244102, Uttar Pradesh, India;* [4]*Department of Pharmaceutical Chemistry, Shri Sai College of Pharmacy, Handia, Prayagraj 221503, Uttar Pradesh, India;* [5]*M.M. College of Pharmacy, Maharishi Markandeshwar (Deemed to be University), Mullana, Ambala 133207, Haryana, India*

ARTICLE HISTORY

Received: October 08, 2021
Revised: March 10, 2022
Accepted: April 01, 2022

DOI:
10.2174/0929867329666220622150013

Abstract: Microwave radiation is used as a heating source during the synthesis of heterocyclic compounds. The heating mechanisms involved in microwave-induced synthesis include dipolar polarization and ionic conduction. This heating technology follows the green protocol as it involves the use of recyclable organic solvents during synthesis. The microwave heating approach offers a faster rate of reaction, easier work-up procedure, and higher product yield with purity and also reduces environmental pollution. So, microwave heating is applied as a sustainable technology for the efficient production of pyrimidine compounds as one of the heterocyclic moieties. Pyrimidine is a six-membered nitrogenous heterocyclic compound that plays a significant role due to several therapeutic applications. This moiety acts as an essential building block for generating drug candidates with diverse biological activities, including anti-cancer (capecitabine), anti-thyroid (propylthiouracil), antihistaminic (pemirolast), antimalarial (pyrimethamine), antidiabetic (alloxan), antihypertensive (minoxidil), anti-inflammatory (octotiamine), antifungal (cyprodinil), antibacterial (sulfamethazine), *etc.* This review is focused on the synthesis of pyrimidine analogs under microwave irradiation technique and the study of their therapeutic potentials.

Keywords: Bioactivity, development, green synthesis, microwave, pyrimidine, sustainable.

1. INTRODUCTION

Microwave irradiated organic synthesis is an eco-friendly approach and is regarded as an emerging green or sustainable technology for the rapid production of biologically active heterocyclic compounds [1]. Gedye and Giguere reported the application of microwave (MW) energy in organic synthesis in 1986. Microwave-assisted organic synthesis (MAOS) was used on a large scale due to the development of commercial MW reactors in 1990. Further, Anastas and Warner proposed the twelve principles of Green Chemistry in 1998. The green chemistry approach employs twelve sets of principles that reduce or eliminate the use or generation of hazardous materials during the design and manufacture of chemical products [2]. Microwave irradiation (MWI) is the form of electromagnetic waves with frequencies ranging from 0.3 to 300 GHz [3, 4]. The microwave irradiation of polar molecules at a frequency of 2.45 GHz causes oscillation of ions that orient themselves with the electric or magnetic field, and finally, these movements tend to generate heat due to dielectric polarization and ionic conduction [5].

There are two types of microwave apparatus available for the synthesis of organic compounds such as single-mode and multi-mode. The single-mode microwave heating apparatus is generally used for

*Address correspondence to this author at the Roland Institute of Pharmaceutical Sciences (Biju Patnaik University of Technology Nodal Centre of Research), Berhampur 760010, India;
Tel: 9040442719; E-mail: drbiswamohansahoo@gmail.com

1875-533X/23 $65.00+.00

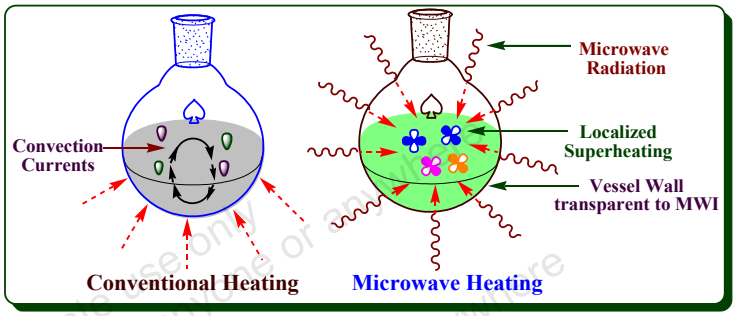


Fig. (1). Mechanism of conventional and microwave heating. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

small-scale preparation in the laboratory. The advantage of single-mode apparatus includes the rapid rate of heating [6]. Whereas the multi-mode microwave is applied for synthesis on a large scale in the pharmaceutical industry. In the case of multi-mode apparatus, the large quantities of the reaction mixture can be processed using either open or closed vessel conditions. But the limitation of multi-mode equipment is that the heating of reacting materials cannot be controlled efficiently due to the lack of uniform temperature in reaction vessels [7].

On the other hand, the conventional synthesis mainly involves the use of a water bath, sand bath, or oil bath as a heating source that heats the walls of the reactors by convection or conduction mechanism [8, 9]. So, the core of the reacting materials takes a long time to attain the target temperature to drive chemical reactions. But in the case of microwave-assisted synthesis, microwave radiation directly penetrates the reacting material without heating the container so that the reaction proceeds faster [10]. The mechanism of heat transfer *via* microwave and conventional heating is illustrated in Fig. (**1**).

MWI technique is found to be more beneficial than the classical heating method in synthetic reactions. Microwave irradiation can develop a cleaner synthetic protocol, accelerate the rate of reaction, provide better product yield, enhance reproducibility of chemical reactions with homogeneity, instantaneous, uniform, and selective heating, *etc.* [11]. The reactions under microwave heating technology are more reproducible as compared to conventional synthetic methods due to uniform heating and proper monitoring of process parameters like temperature and pressure. The microwave accelerated organic reactions (MAORs) provide a cleaner and eco-friendly process than conventional synthesis [12]. With the help of microwave radiation, the components of the reaction mixture are heated directly in which the usage of organic solvents can be reduced or eliminated in the chemical reaction. As compared to conventional synthesis, MAOS enhances the rate of chemical reactions due to its ability to increase the temperature of the reaction medium. Similarly, the synthesis under MWI produces a higher product yield as there is less or no production of waste or by-products. The microwave irradiated synthesis is a highly efficient and energy-saving process. Microwave radiation heats the reaction mixture directly without heating the apparatus or reaction vessels, leading to low energy consumption [13].

Further, the synthesis of heterocyclic compounds *via* multicomponent reactions (MCRs) under microwave irradiation provides various advantages such as ease of work, cost-effectiveness, efficiency, and less generation of waste products as compared to traditional synthetic procedures. Similarly, microwave-assisted solvent-free reactions are recognized as environmentally benign methods that provide improved selectivity, enhanced rate of reaction, and cleaner products (Fig. **2**). So, MWI is applied as an alternative energy source for carrying out the synthesis of pyrimidine derivatives with diverse molecular structures [14].

Pyrimidine is composed of an aromatic ring that contains six atoms, such as two nitrogen atoms and four carbon atoms (Fig. **3**). The pyrimidine ring contains the planar structure and the numbering of the pyrimidine ring start at the hetero atom, *i.e.*, nitrogen, in a clockwise direction [15-17].

Pyrimidine moiety is considered one of the most versatile groups of nitrogen-based heterocyclic compounds with a broad range of therapeutic potentials, including anti-cancer (capecitabine, ibrutinib, folinic acid, monastrol, 5-fluorouracil, floxuridine), anti-thyroid (2-thiouracil, propylthiouracil), antihistaminic (pemirolast, thonzylamine), antimalarial (pyrimethamine), antidiabetic (alloxan), antihypertensive (minoxidil, prazosin, nesapidil), anti-inflammatory (octotiamine), antifungal (cyprodinil, flucytosine, mepanipyrim, pyrimethanil),

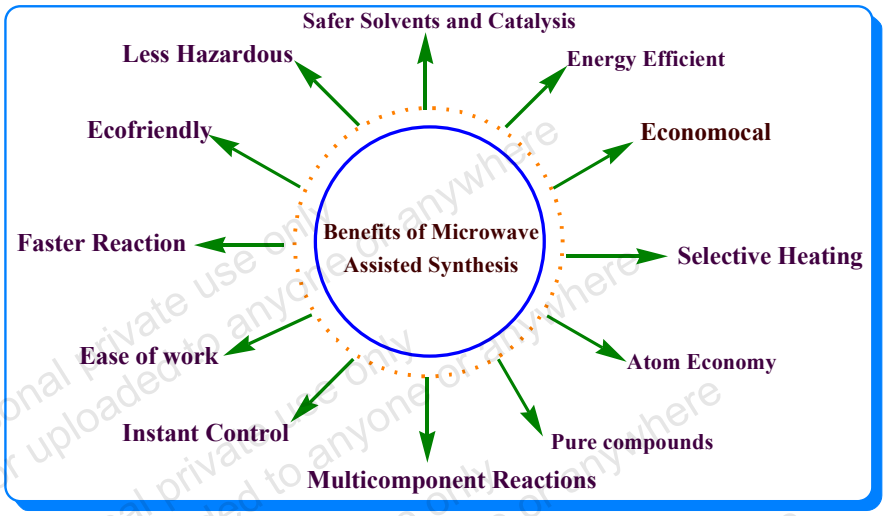


Fig. (2). Benefits of microwave-assisted organic synthesis.

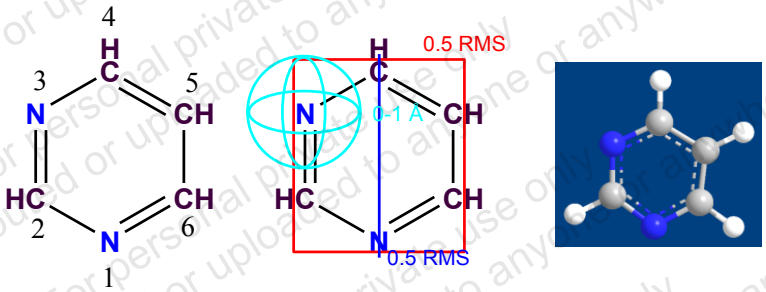


Fig. (3). Structure of pyrimidine and its nomenclature. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

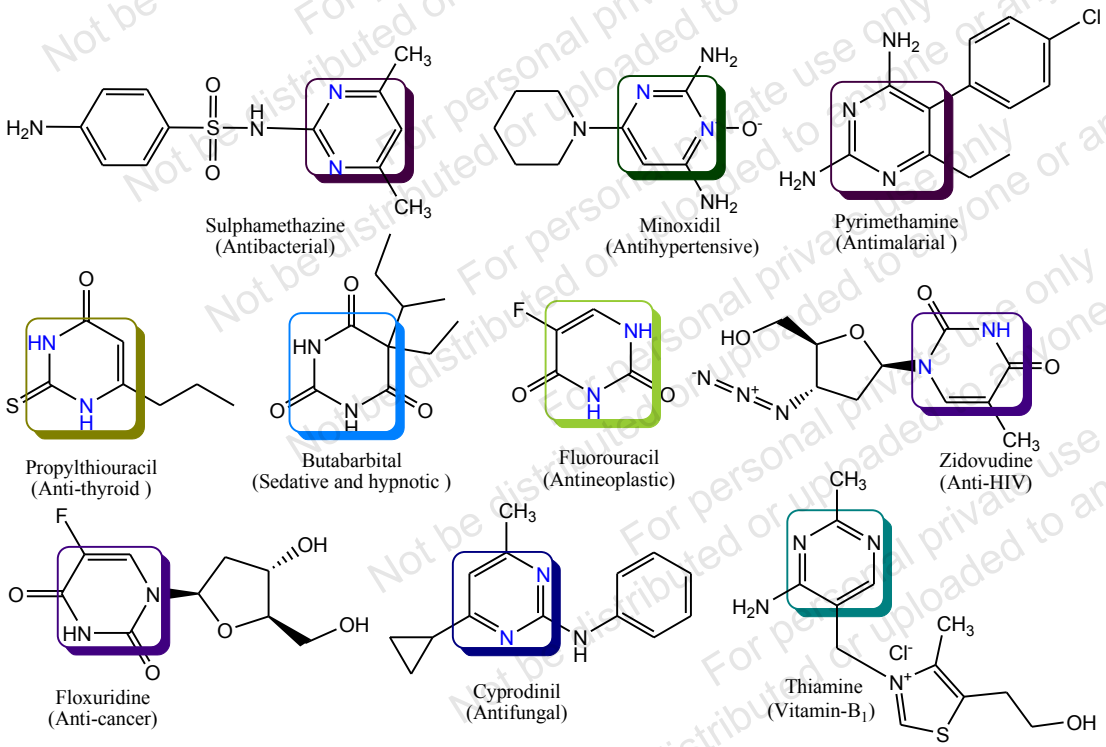
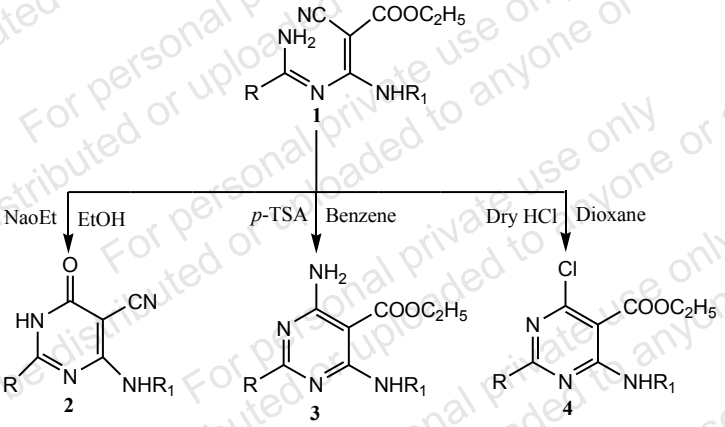


Fig. (4). List of drugs with pyrimidine scaffold.

Table 1. List of drugs with pyrimidine moiety and their mechanism of actions.

Name of Drugs with Pyrimidine Moiety	Mechanism of Action	Biological Activity
Ibrutinib	Bruton's tyrosine kinase inhibitor	Anti-cancer
Monastrol	Kinesin-5 inhibitor	
5-fluorouracil	Thymidylate synthase inhibitor	
Propylthiouracil	Thyroid peroxidase inhibitor	Anti-thyroid
Pemirolast	Histamine H1 antagonist	Antihistaminic
Thonzylamine	Histamine H1 antagonist	
Pyrimethamine	Dihydrofolate reductase inhibitor	Antimalarial
Alloxan	Inhibits glucose-induced insulin secretion through specific inhibition of glucokinase	Antidiabetic
Minoxidil	Vasodilator by opening adenosine triphosphate-sensitive potassium channels in vascular smooth muscle cells	Antihypertensive
Prazosin	Alpha-1 adrenergic receptor antagonist	
Sulfamethazine	Dihydrofolate synthetase inhibitor	Antibacterial
Cidofovir	Adenovirus 5 DNA Polymerase inhibitor	Antiviral
Zidovudine	HIV's reverse transcriptase inhibitor	Anti-HIV



Scheme 1. Synthetic route for one component synthesis of pyrimidines.

antibacterial (sulfamethazine or sulfadimidine, trimethoprim, furamizole), anthelmintic (pyrantel), antiviral (idoxuridine, triflouridine, cidofovir), antiretroviral (Raltegravir), anesthetic (thiopental), anti-HIV (zidovudine), antipsychotic (Mezilamine), antineoplastic (Fluorouracil, Tegafur), vitamin B_1 or thiamine, sedative and hypnotic (butabarbital, thiamylal), *etc.*, as presented in Fig. (**4**) [18, 19]. These drugs with pyrimidine moiety exhibit their pharmacological actions by binding with the target receptors, enzymes, proteins or ion channels involved in the particular disease states [20] (Table **1**).

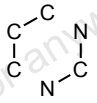
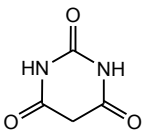
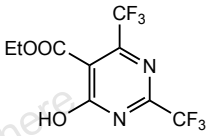
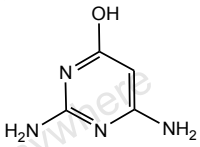
2. GENERAL METHODS FOR SYNTHESIS OF PYRIMIDINE DERIVATIVES

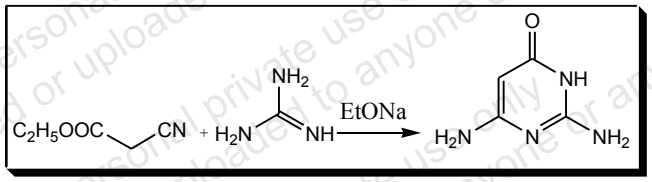
There are various methods involved in synthesizing pyrimidine derivatives that are categorized based on components utilized during the intramolecular cyclization process. These methods include a) one-component system, b) two-component system, c) three-component system, d) multi-component system [21-23].

2.1. One Component Synthesis

The one component synthetic method involves the intramolecular cyclization of intermediates with the open-chain structure to produce corresponding pyrimidine derivatives. For example, the synthesis of pyrimidine involves the condensation reaction between 1,3-dicarbonyl compounds and amidines, which proceeds *via* vinylamidine as an intermediate. The intramolecular cyclization of vinylamidine leads to the formation of a 3,4(1,6)-bond [24]. Further, vinylamidine undergoes cyclization under acidic and basic conditions to

Table 2. Two components synthesis of pyrimidine.

First Component	Second Component	Proposed Structure of Pyrimidine	Structure of Compounds	References
C-C-C	N-C-N			[26]
C-C-C-N	C-N			[27]
C-C-N	C-N-C			[28]



Scheme 2. Synthesis of 2,6-diamino-4-hydroxypyrimidine.

yield corresponding functionalized pyrimidine compounds (Scheme **1**).

2.2. Two Components Synthesis

Two components synthetic method is widely used for the synthesis of pyrimidine analogs. This method involves the condensation of two reacting components. One of these components may contribute three, four, or five atoms of the pyrimidine nucleus, whereas the other part contributes three, two, or one atom, respectively [25-27]. The different types of two components synthesis are presented in Table **2**.

The two components synthesis of pyrimidine involves the reaction between ethyl cyanoacetate and guanidine in the presence of sodium ethoxide to afford 2,6-diamino-4-hydroxypyrimidine (Scheme **2**) [28].

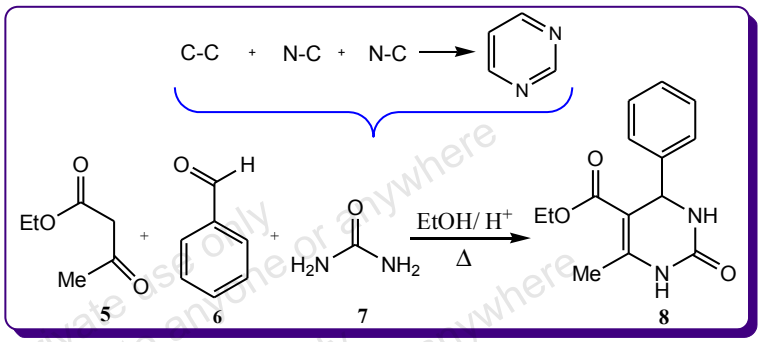
2.3. Three Components Synthesis

In the case of the three components synthesis of pyrimidines, each of the three components contributes two atoms each to carry out a cyclization reaction for generating the corresponding pyrimidine ring (Scheme **3**). Based on this approach, Biginelli reported the synthesis of dihydro-pyrimidines. It involves the cyclocondensation of ethyl acetoacetate, benzaldehyde, and urea catalyzed by acid [29].

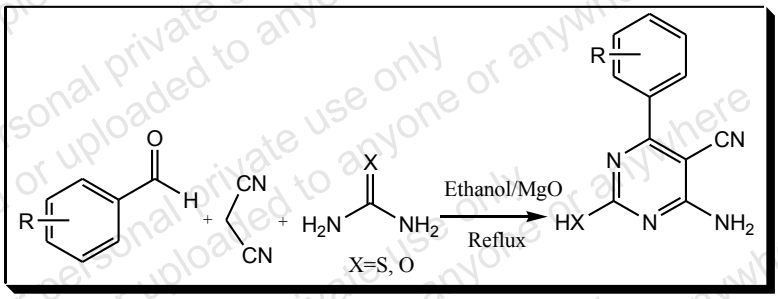
Similarly, the synthesis of pyrimidine derivatives involves a three-component reaction of substituted benzaldehydes, malononitrile and thiourea/urea. The reaction mixtures are refluxed in the presence of ethanol and MgO (Scheme **4**).

3. MICROWAVE-ASSISTED SYNTHESIS OF PYRIMIDINES

MW-assisted organic synthesis is mainly influenced by the ability of the reacting substances to absorb microwave radiation energy, and also it depends on the selection of solvents or medium to accelerate chemical reactions [30]. So, the ability of a specific solvent or material to convert electromagnetic energy to heat is termed a loss tangent (LT). LT is expressed as tan δ to measure the efficiency of a substance to convert microwave energy into thermal energy at a suitable temperature and frequency. If the value of LT is higher, then the solvent is suitable for the absorption of microwave radiation that causes efficient heating [31]. Based on the absorbance level, solvents are categorized into three types; low (tan $\delta < 0.1$), medium (tan δ 0.1-0.5), and high (tan $\delta > 0.5$) microwave absorbing solvent, as summarized in Table **3**.



Scheme 3. Synthesis of pyrimidines *via* three components.



Scheme 4. Synthetic route of pyrimidine derivatives.

Table 3. List of solvents based on their absorbance level.

Absorbance Level	Low (tan δ<0.1)	Medium (tan δ 0.1–0.5)	High (tan δ>0.5)
Name of Solvents	DCM, Chloroform, Carbon tetrachloride, Ethyl acetate, Pyridine, Toluene, Benzene, Chlorobenzene	DMF, water, Butanol, Acetonitrile, Acetone, Acetic acid	DMSO, Ethanol, Methanol, Propanol, Nitrobenzene, Formic acid, Ethylene glycol

The microwave heating technique involves environmentally benign and clean synthetic procedures to synthesize pyrimidine and its derivatives. During the synthesis of these compounds, different reaction mechanisms are involved, including cycloisomerization, cyclization, cycloaddition, condensation, oxidation, reduction, addition, esterification, epoxidation, dehydration, decarboxylation, hydrolysis, coupling reaction, *etc.* (Fig. **5**) [32, 33].

3.1. Synthesis of Pyrimidines *via* Cyclo-condensation Reaction

The cyclo-condensation reaction is a type of chemical reaction in which two or three molecules are combined to form a single cyclic compound. Mobinikhaledi *et al.* performed the synthesis of oxo and thioxopyrimidines (**12**) by using the Biginelli three-component cyclo-condensation reaction of β-diketone (**9**), aryl aldehydes (**10**), and (thio)urea (**11**) under microwave irradiation (Scheme **5**). The reactions are carried out by using a Samsung microwave oven with a power of 900W and an operating frequency of 2450 MHz. This synthetic method leads to the formation of products under mild conditions with increased yields [34].

Quiroga *et al.* explored the regioselective synthesis of novel substituted pyrazolo[1,5-a]pyrimidines under solvent-free microwave irradiation method (Yield: 88-93%) (Scheme **6**). A series of 6-(2-hydroxybenzoyl)-5-methyl-7-phenylpyrazolo[1,5-a]pyrimidine (**15**) was synthesized by cyclo-condensation reaction between 5-amino-1*H*-pyrazoles (**13**) and 3-benzoyl-2-methyl-4*H*-chromen-4-one (**14**). The reactions were performed in a multimode microwave oven at 600 W for 2 min. The reaction mechanism proceeds in a regiospecific fashion by the intramolecular opening of the γ-pyrone ring in a Michael-type reaction followed by cyclization *via* nucleophilic attack of endocyclic pyrazole nitrogen toward the benzoyl group [35].

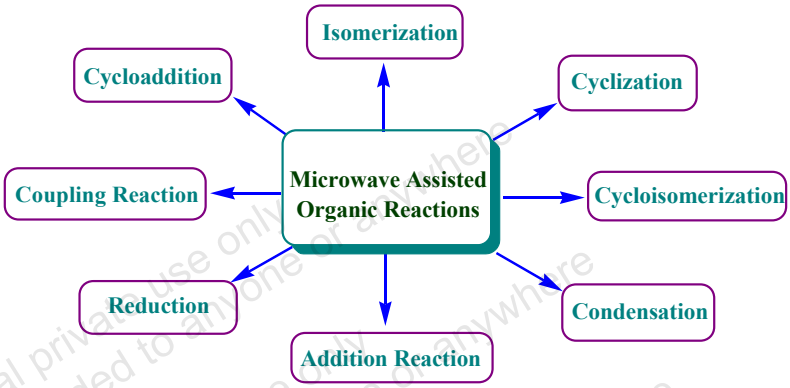
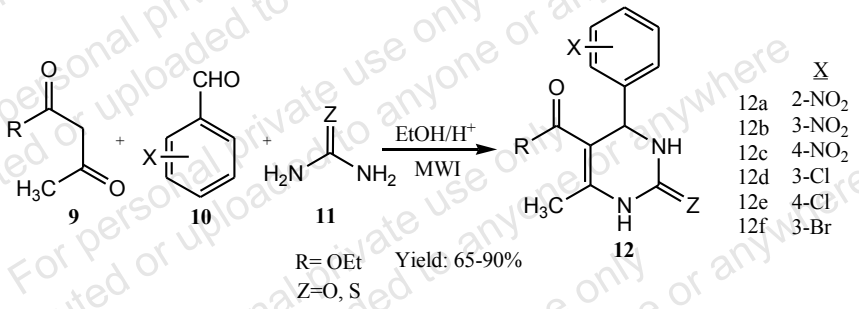
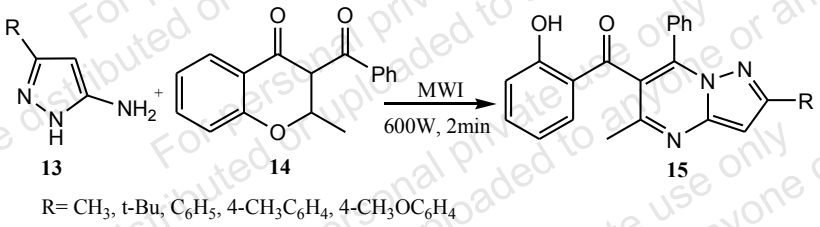


Fig. (5). Chemical reaction involved under MWI.



Scheme 5. Synthetic route for the synthesis of oxo- and thioxopyrimidines.



Scheme 6. Scheme for the synthesis of pyrazolopyrimidine.

Dabiri *et al.* described the novel, efficient, and one-pot synthesis of pyrimido[4,5-d]pyrimidine-2,4,7-trione derivatives (**16**) *via* a three-component cyclo-condensation reaction of 6-amino1,3-dimethyluracil, aromatic aldehydes, and urea under microwave irradiation conditions (Power: 900 W). Similarly, the synthesis of pyrido[2,3-d:6,5-*d*]dipyrimidine-2,4,6,8-tetrone derivatives was carried out by the condensation reaction of 6-amino-1,3-dimethyluracil and aromatic aldehydes in the presence of ionic liquid (Fig. **6** and Table **4**) [36].

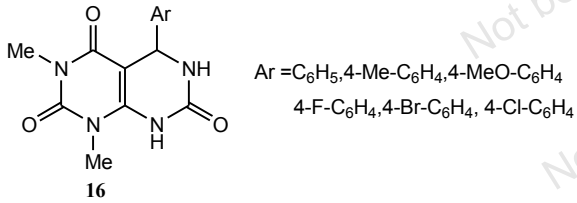
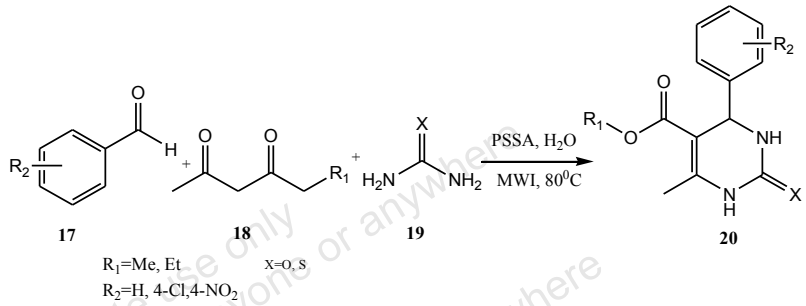


Fig. (6). Synthesis of pyrimido[4,5-d]pyrimidine-2,4,7-trione derivatives under MWI.

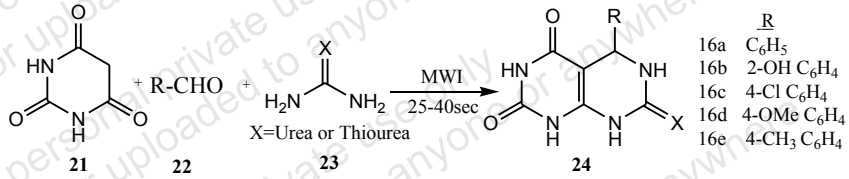
Table 4. Effect of catalysts on the reaction condition.

Entry	Catalyst	Yields (%)
1	CH_3COOH	87
2	CF_3COOH	37
3	4-Me–$C_6H_4SO_3H$	41
4	ZnCl2	<20

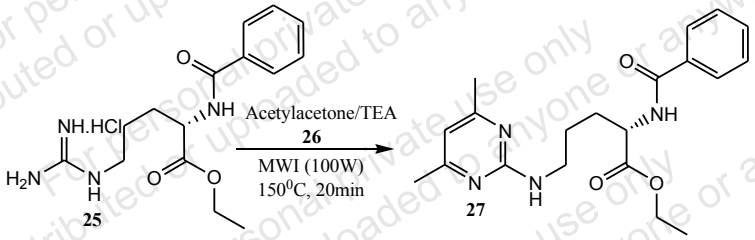
Polshettiwar *et al.* presented an environmentally benign aqueous Biginelli protocol for the synthesis of substituted 3,4-dihydro-pyrimidin-2(1H)-ones (**20**) under MW-irradiation [30]. The synthesis involves the three-component condensation reaction of substituted benzaldehyde (**17**), acetoacetate (**18**), and urea or thiourea (**19**) using polystyrene sulfonic acid (PSSA) as a catalyst (Scheme **7**). The reaction proceeded efficiently in the presence of water without using any organic solvent



Scheme 7. Synthesis of 3,4-dihydro-pyrimidin-2(1H)-ones in aqueous media under MWI.



Scheme 8. Synthesis of pyrimido[4,5-d]pyrimidine derivatives.



Scheme 9. Synthetic route for the synthesis of ethyl(S)-2-benzamido-5-[(4,6-dimethylpyrimidin-2-yl)amino]pentanoate.

(R.T: 20-30min, Yield: 81-90%) in comparison with conventional heating (R.T: 5-6 h, Yield: 50-58%) [37].

3.2. Synthesis of Pyrimidines *via* Cycloaddition Reaction

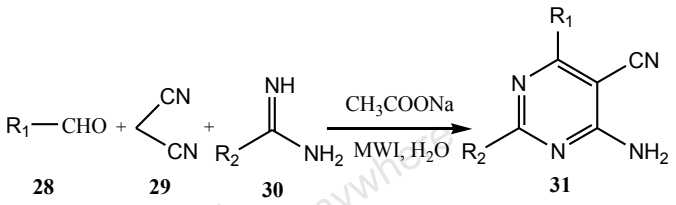
Kategaonkar *et al.* synthesized pyrimido[4,5-*d*]pyrimidine derivatives (**24**) by using a clean, efficient, facile, and solvent-free procedure (Scheme **8**). Here, the synthesis is carried out *via* multi-component reactions that involve cycloaddition of three components such as barbituric acid (0.01 mmol) **21**, aromatic aldehyde (0.01 mmol) **22**, urea or thiourea (0.01 mmol) **23** in the presence of alumina (Al_2O_3) as solid support under microwave irradiation operating at a power level of 150-600 watts for the appropriate period. The advantages of this method include excellent yields (70-98%) in shorter reaction time (25-40sec) with high purity of the products [38].

3.3. Synthesis of Pyrimidines *via* Cyclization Reaction

Mario *et al*. reported the synthesis of ethyl(S)-2-benzamido-5-[(4,6-dimethylpyrimidin-2-yl)amino] pentanoate under microwave irradiation (Yield: 70%) (Scheme **9**). It involves the reaction between (S)-N-α-benzoyl-L-arginine ethyl ester hydrochloride (**25**) and acetylacetone (**26**) to produce a corresponding pyrimidine analog (**27**). The reactions were performed at 150^{0}C for 20 min under the pressure of 150psi [39].

3.4. Synthesis of Pyrimidines *via* Multicomponent Reaction

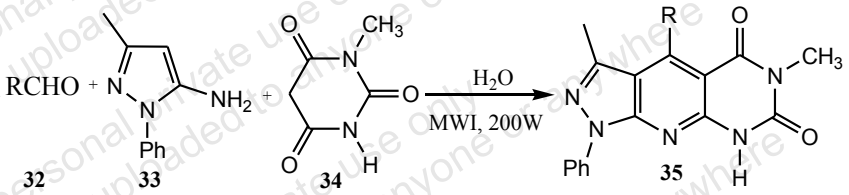
Multicomponent reactions (MCRs) strategies offer significant advantages over conventional linear type synthesis [40]. The combination of three or more reactant molecules in a single operation leads to the formation of combinatorial libraries. So, the 4-amino-5-pyrimidine carbonitrile derivatives (**31**) are produced *via a* one-pot three-component reaction between aldehydes (**28**), malononitrile (**29**), and N-unsubstituted amidines (**30**) (Scheme **10**). The reaction is carried out in the presence of water by conventional (R.T: 3-12h, yield: 60-82%) or under microwave heating (P: 300W, R.T: 25-120sec) method in the presence of sodium acetate. This method provides a new route to produce pyrimidine derivatives in good to excellent yields (75-92%).



R_1= C_6H_5, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4

R_2= Ph, NH_2

Scheme 10. Synthesis of 4-amino-5-pyrimidine-carbonitrile derivatives.



R= 4-FC_6H_4, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, C_6H_5, 4-BrC_6H_4

Scheme 11. Synthesis of polyfunctionalized pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidines.

The synthesis of polyfunctionalized pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidines **35** was carried out by multicomponent reactions of aldehydes (**32**), 3-methyl-1-phenyl-1H-pyrazol-5-amine (**33**), and 1-methylbarbituric acid (**34**) in water without using any catalyst under microwave irradiation at a power level of 200W and 110°C for a given time (Scheme **11**). This synthetic protocol is advantageous in terms of environmental friendliness, short reaction time (5-10min), excellent yields (80-88%), low cost, easy operation, and broad scope of applicability [41].

Jain *et al.* synthesized 2-amino-5-cyano-4,6-disubstituted pyrimidines (**36**) under microwave at 80W for 25-50 minutes (Fig. **7**). The synthesis of pyrimidines involves one-pot synthesis *via* multicomponent reaction of *α*-Cyanoketenes *S*, *S*-acetals, amines, and guanidine carbonate. The reaction was completed in just a few minutes instead of the 18 hrs required under conventional heating. The products were obtained in high yield (76% - 90%) and purity (>95%). A microwave synthesizer with monomode open-vessel was used for this synthesis [42].

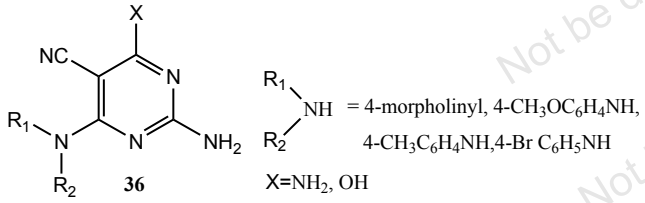


Fig. (7). Synthesis of 2-amino-5-cyano-4,6-disubstituted pyrimidines.

Borisagar *et al.* reported the synthesis of a new class of triazolopyrimidines (**37**). It involves one-pot multicomponent reactions of different acetoacetamides, 4-(phenoxy methyl)benzaldehyde, and 5-amino-1,2,4-triazole by using microwave irradiation within 20-30 minutes with high yield (Fig. **8**) [43].

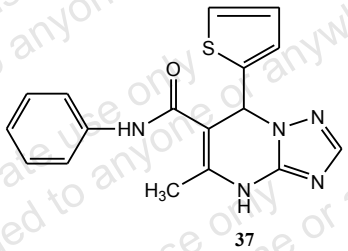
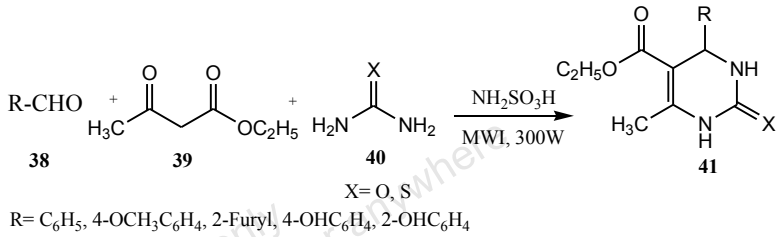


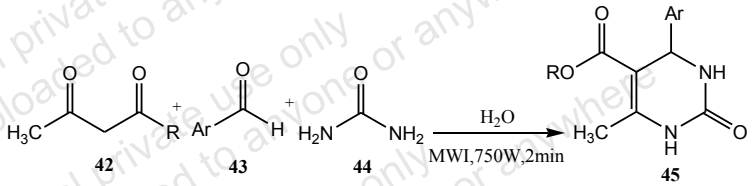
Fig. (8). Synthesis of triazolopyrimidines under MWI.

An efficient synthesis of 3,4-dihydropyrimidinones (DHPMS) **41** using sulfamic acid as a catalyst from aldehydes (**38**), β-keto ester (**39**), urea, or thiourea (**40**) under solvent-free microwave irradiations is depicted in scheme **12**. The solvent-free microwave-assisted green procedure offer advantages such as shorter reaction times (2-3min), simple work-up, and excellent yield (84-93%) over the conventional heating method (R.T:6-7h, Yield: 64-80%). The synthesis was carried out at a power level of 300 watts for 2-3.5 min using a domestic microwave oven (Samsung model) [44].

Singhal *et al.* presented an efficient, simple, and environmentally clean synthesis of 3,4-dihydropyrimidinones (**45**) with excellent yields in the presence of water without using solvents or acid catalysts under the microwave irradiation method. It involves the



Scheme 12. Synthesis of 3,4-dihydropyrimidinones.

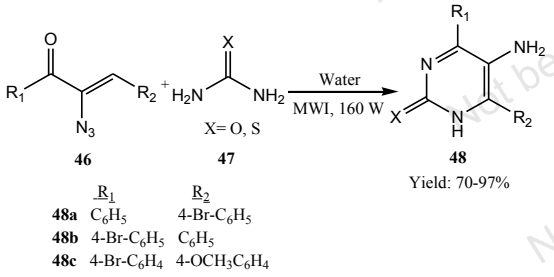


Scheme 13. Synthesis of 3,4-dihydro-pyrimidinones.

reaction between aldehyde (2 mmol) **42**, urea (2 mmol) 4**3**, and *β*-dicarbonyl compound (2 mmol) **44** in the presence of water (3-4 drops) at a power level of 750W for 2 min (Scheme **13**). Synthesis was carried out by using the Milestone START Microwave lab station. The presence of water was found to be vital and the reactions were carried out faster with high product yield (90-98%) under microwave irradiation as compared to the conventional heating method (R.T: 45-75min., Yield: 80-94%) [45].

3.5. Synthesis of Pyrimidines *via* a Coupling Reaction

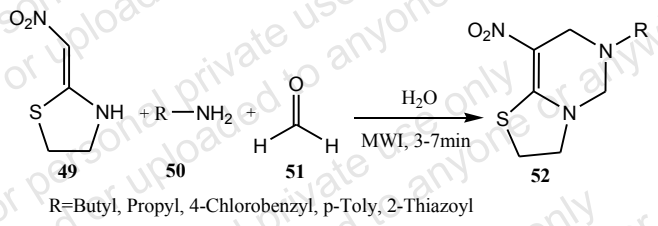
Dehbi *et al.* introduced an efficient and eco-friendly method for the synthesis of disubstituted 5-amino pyrimidines (**48**). It involves the coupling of vinyl azides (**46**) and urea or thiourea (**47**) (Scheme **14**). This reaction was carried out in the presence of water as a solvent under microwave irradiation conditions. The significant features observed in this new protocol were the faster conversion of starting materials to products, shorter reaction times (10min), cleaner reactions, and a simpler work-up procedure [46].



Scheme 14. Synthesis of disubstituted 5-amino pyrimidines under MWI.

3.6. Synthesis of Pyrimidines *via* Mannich Reactions

Yildirim *et al.* developed a green procedure to prepare a new series of thiazolo[3,2-c]pyrimidine derivatives (**52**) through Mannich reactions under MW-irradiation. This synthesis is achieved *via* multicomponent cyclization of 2-(nitromethylene)thiazolidine (**49**), various aliphatic or aromatic amines (**50**), and formaldehyde (**51**) in water (Scheme **15**). The use of MW radiation promoted high product yields (65-100%) and considerably reduced the reaction times (3-7min) concerning conventional heating (R.T: 2-6h, Yield: 58-77%). This green protocol did not require any organic solvents to carry out the reaction or purification of final compounds [47].



Scheme 15. Green synthesis of thiazolo[3,2-c]pyrimidine derivatives.

4. BIOLOGICAL ACTIVITIES OF PYRIMIDINES AND THEIR DERIVATIVES

The pyrimidine base present in thymine, cytosine, and uracil is considered the essential building block of nucleic acids such as DNA and RNA. Pyrimidines scaffold is present in several natural products such as vitamin B_1, bleomycin (antitumor antibiotic), charine (laxative), Gougerotin (antibiotic), Plicacetin (antibiotic), *etc.*

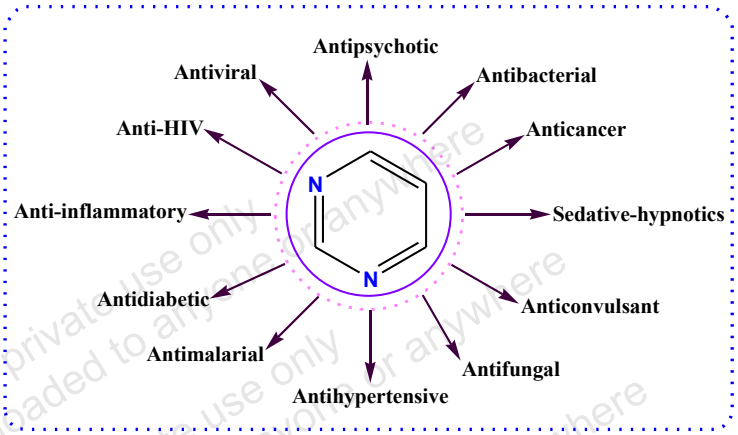


Fig. (9). Biological potentials of pyrimidines and their derivatives.

In addition to this, pyrimidines and their analogs exhibit promising biological activities such as antibacterial, antifungal, antihypertensive, antiviral, antidiabetic, anticonvulsant, antioxidant, anticancer, analgesic, anti-inflammatory, *etc.* (Fig. **9**).

4.1. Pyrimidines as an Analgesic and Anti-inflammatory Agent

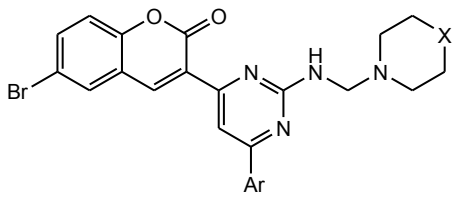
Analgesic and anti-inflammatory agents are the class of drugs that are used for the treatment of swelling, redness, and pain. Analgesia refers to the loss of sensation of pain that results from an interruption in the nervous system pathway between the sense organs and brain. Analgesics are the group of drugs used to relieve pain. Similarly, inflammation is the complex biological response by which the immune system protects the body from harmful pathogens like bacteria and viruses. Inflammation can be categorized into acute or chronic. Acute inflammation is the initial response of the body to harmful stimuli that is achieved by the increased movement of plasma and leukocytes from the blood into the injured tissues. Whereas, chronic inflammation is a prolonged state that causes progressive shifting of cells that are present at the site of inflammation. So, anti-inflammatory agents are used to reduce the redness, swelling, and pain in the inflamed parts of the body. But there are some side effects produced by these agents, including heartburn, stomach pain, ulcers, *etc.* To minimize these problems arising during the administration of anti-inflammatory drugs, investigations are carried out to design novel drug candidates for the treatment of inflammation without causing any ulcerogenic activity [48].

Chaudhary *et al.* performed the synthesis of pyrimidine derivatives **53** (Fig. **10**) under MWI using LG domestic microwave oven (Model No.MC-7148MS). The microwave method offers salient features like a faster rate of reaction, cleaner reaction conditions, and enhancement in product yield (R.T: 2-8 min, 71.9-86.1%) as compared to the conventional heating method (R.T: 8-10h, Yield: 50.4-65.3%). The analgesic and ulcerogenic potential of the title compounds were investigated using the acetic acid-induced writhing model at 20 mg/kg body weights of the animal. For analgesic activity, the first animal group served as control positive that received distilled water orally. Then the second group received the aqueous suspension of test compounds orally at a dose of 20 mg/kg. The last group received a standard drug (Diclofenac sodium) orally at a dose of 20 mg/kg. After 30 minutes, each animal group was administered with 1% aqueous solution of acetic acid (10 ml/kg) and the mice were then kept in transparent boxes for observation. The number of writhes was counted for 15 min after injection of acetic acid at 0.5, 1, and 2 h (Table **5**). The number of writhes in each treated group was compared with the control group and the percentage protection is calculated by the following formula.

$$\% \text{ Protection} = \frac{\text{Control mean} - \text{treated mean}}{\text{Control mean}} \times 100$$

Tested compounds (**53m, 53p**) exhibited better analgesic activity without ulcerogenic effects in comparison with the standard drug Diclofenac sodium [49].

Bhatewara *et al*. reported the one-pot synthesis of 2-amino-dihydropyrimidinone derivatives (**57**) *via* a three-component cycloaddition reaction under solvent-free MWI (power 150 to 750 watts). The reaction proceeds *via* Knoevenagel condensation, followed by the addition and cyclization of aldehydes (**54**), ethyl cyanoacetate (**55**), and guanidine nitrate (**56**) in the presence of piperidine as catalyst (Scheme **16**). This method is advantageous in terms of excellent product yield (79-93%) in a shorter reaction time with high purity.



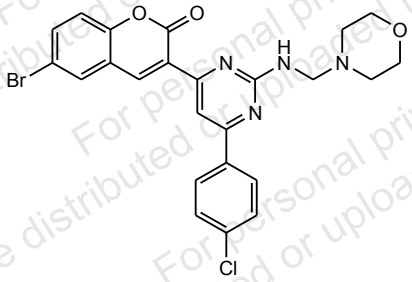
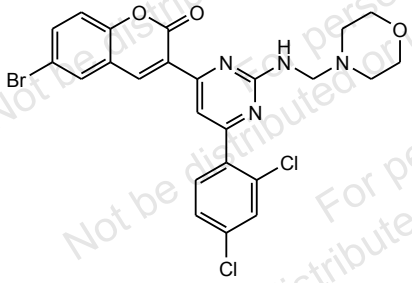
53

Ar =o-chloro benzaldehyde, m-chloro benzaldehyde, p-chloro benzaldehyde, o-bromo benzaldehyde, m-bromobenzaldehyde, p -bromobenzaldehyde o-methoxy benzaldehyde, m-methoxy benzaldehyde 2,4-dichloro benzaldehyde, 2,6-dichloro benzaldehyde

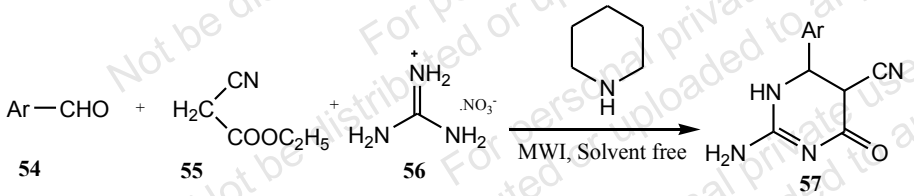
X= CH_2, O

Fig. (10). Structure of pyrimidine derivatives with analgesic activity.

Table 5. Analgesic activity of compounds by acetic acid-induced writhing response model.

Tested Compounds	Percent Protection		
	0.5 h	**1 h**	**2 h**
 **53m**	98.45 ± 0.22***	89.54 ± 0.61***	55.68 ± 1.33
 **53p**	95.34 ± 0.43***	85.36 ± 0.56***	69.60 ± 1.30***
Diclofenac sodium	95.87 ± 0.33	94.25 ± 0.31	84.53 ± 0.37

Values are expressed as Mean ± SEM and *** P≤0.001 indicates the level of statistical significance as compared with control.



54 **55** **56** **57**

Ar= C_6H_5,4-(CH_3O)-C_6H_4, 4-NO_2-C_6H_4

Scheme 16. One-pot synthesis of 2-amino-dihydro-pyrimidinone derivatives.

The *in vivo* anti-inflammatory activity of synthesized compounds was evaluated by using carrageenan induced rat paw edema method. The anti-inflammatory activity of the title compounds was expressed as the percent inhibition of the edema as compared to the control group. The rat paw edema was measured by volume displacement technique using a plethysmometer. The title compound (**57d**) exhibited 32.34%, 27.48%, 26.25%, and 25.25% inhibition of edema with a dose of 20 mg/kg at different time intervals as compared to the standard drugs Indomethacin (Table **6**). The screening results were expressed as the mean ± SEM [50]. The percent of inhibition of the rat paw edema is calculated by the following formula.

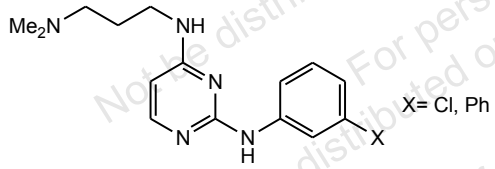
Table 6. Effects of test compounds and indomethacin in inhibition of carrageenan-induced rat paw edema.

Test Compounds	Dose	Percentage (%) Inhibition of Edema			
		1h	2h	3h	4h
Control (Saline water)	10 mL/kg	0.5912± 0.005***	0.5930± 0.002***	0.6102± 0.002***	0.6303 ± 0.002***
Indomethacin (standard)	100 mg/kg	0.2700±0.005** (54.33%)	0.3124±0.005** (47.31%)	0.3133±0.008** (48.65%)	0.3500 ± 0.005** (44.47%)
57d	20 mg/kg	0.4000±0.005*** (32.34%)	0.4300±0.005** (27.48%)	0.4500 ± 0.011*** (26.25%)	0.4711±0.011*** (25.25%)

$$\% \text{ inhibition} = \frac{Vc - Vt}{Vc} \times 100$$

Where *V*-volume, c-control, *t*-test

Patil *et al.* explored the microwave accelerated synthesis of 3,4-dihydro-pyrimidine-2(1H)-one derivative **58**. The synthesized compounds were evaluated for antihypertensive activity by the non-invasive tail-cuff and carotid artery cannulation method for determining the diastolic blood pressure. Hypertension was induced by DOCA-salt. Anti-inflammatory activity was carried out by the carrageenan-induced rat paw edema method. Test compounds (Fig. **11**) exerted comparative antihypertensive activity at a 10 mg/kg dose level compared to nifedipine [51].



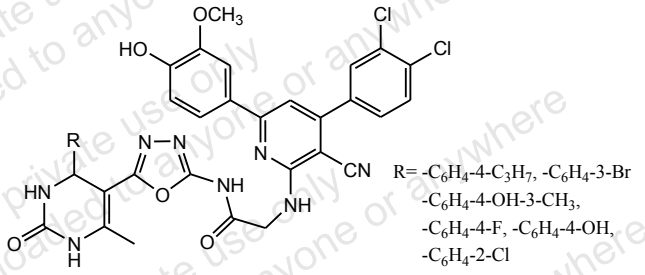
58

Fig. (11). Synthesis of 3,4-dihydro-pyrimidine-2(1H)-one derivative with antihypertensive activity.

4.2. Pyrimidines as Anti-tubercular Agent

Tuberculosis is a contagious infection generally caused by *Mycobacterium tuberculosis*. It mainly affects the lungs and is considered a major killer disease worldwide. Various drugs are available clinically for the treatment of TB, but the use of suitable drugs and length of treatment depends on different factors, including age, overall health condition, possible drug resistance, and infection area in the lungs. So, there is still research going on for the development of novel anti-tubercular agents [52].

Patel *et al.* described the microwave irradiated synthesis of 3,4-dihydro-pyrimidin-2(1H)-one analog **59** using the Biginelli reaction. The synthesized compounds were screened for their *in-vitro* antibacterial activity against *Staphylococcus aureus*, *Staphylococcus Pyogenus*, *Escherichia coli,* and *Pseudomonas aeruginosa* bacterial strains and antifungal activity against *Candida albicans*, *Aspergillus niger,* and *Aspergillus clavatus* by micro-broth dilution method. The *in-vitro* antimycobacterial activity was determined against *Mycobacterium tuberculosis* ($H_{37}Rv$ strain). The synthesized derivatives (Fig. **12**) are found to be active against microorganisms (bacteria and fungi) and *M. tuberculosis* $H_{37}Rv$ as compared to Griseofulvin and Rifampicin as a standard drug [53]



59

Fig. (12). Synthesis of 3,4-dihydropyrimidin-2(1H)-one analog with antimycobacterial activity.

The manifestation of various drug-resistant *Mycobacterium tuberculosis* (Mtb) strains has necessitated the development of new drug candidates to decrease the resistance to existing drug therapies. By screening the Med Chem Express bioactive compound library, Ceritinib was identified as a compound with antimycobacterial activity against Mtb H37Ra. Ceritinib had a MIC value of 9.0μM in vitro and demonstrated *in-vivo* efficacy in a BALB/c mouse model infected with auto luminescent H37Ra. Then, novel ceritinib derivatives were synthesized, and their anti-mycobacterial activities were evaluated in vitro. The antimycobacterial activities of the synthesized compounds were drastically affected by substitutions at position 4 of the pyrimidine nucleus and were enhanced by the presence of 2-isopropoxy-5-methyl-4-(piperidin-4-yl)aniline at position 2 of the pyrimidine nucleus. The *in-vivo* anti-

tubercular activity of the three most potent compounds was evaluated. 5-chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(naphthalen-1-yl)pyrimidine-2,4-diamine (**60**) significantly reduced the Mtb burden of mice. The result suggested that this compound exhibited promising anti-tubercular activity. Further, the *in-silico* modeling reports that dihydrofolate reductase is the potential molecular target for this compound (Fig. **13**) [54].

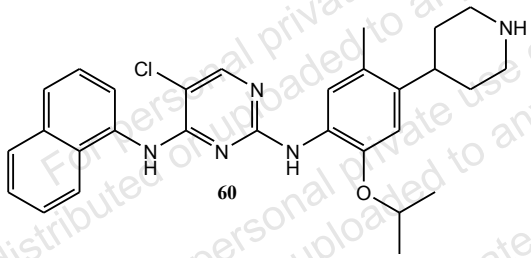


Fig. (13). Structure of 5-chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(naphthalen-1-yl)pyrimidine-2,4-diamine.

A series of 1,2,3,4-tetrahydro-pyrimidine-5-carbonitrile derivatives (**64**) have been synthesized by the multicomponent reaction, which involves one-pot organic reactions using aryl aldehydes (**61**), ethyl cyanoacetate (**62**), and urea/thiourea (**63**) in the presence of ethanolic K_2CO_3 (Scheme **17**). Both conventional and microwave heating methods have been adopted for the synthesis. The latter strategy gave high yields (85.15%) in less than 10 min as compared to long hours (4-6hrs) using the former approach (Table **7**). The titled compounds were also evaluated for anti-tubercular activity *in vitro* against drug-sensitive *M. tuberculosis* H37Rv strain and clinically isolated S, H, R, and E resistant *M. tuberculosis* by luciferase reporter phage (LRP) assay method. The tested compounds were found to be effective as there was more than a 50% reduction in Relative Light Units (RLU) using a luminometer [55]. Among all the test samples, compound 64d showed more effective against *M. tuberculosis* H37Rv and Clinical isolate: S, H, R & E resistant *M. tuberculosis* as compared to the standard drug (Isoniazid) (Table **8**).

A simple and efficient approach toward the single-step synthesis of 6-amino-5-cyano-2-(hydroxy/ mercapto)-4-substituted pyrimidine derivatives (**68**) has been developed by three-component condensation of aromatic aldehydes (**65**), urea or thiourea (**66**), and malononitrile (**67**) using conventional heating and microwave irradiation technique (Scheme **18**). Some of these novel derivatives showed moderate to potent *in-vitro* anti-tubercular activity. Microwave-assisted synthesis is advantageous in terms of simple reaction conditions and easy work-up procedures, less time consuming (2-3.5 min), and eco-friendly, which results in better yields (64-85%) over the conventional method (R.T: 1.5-3h, Yield: 56-81%) [56].

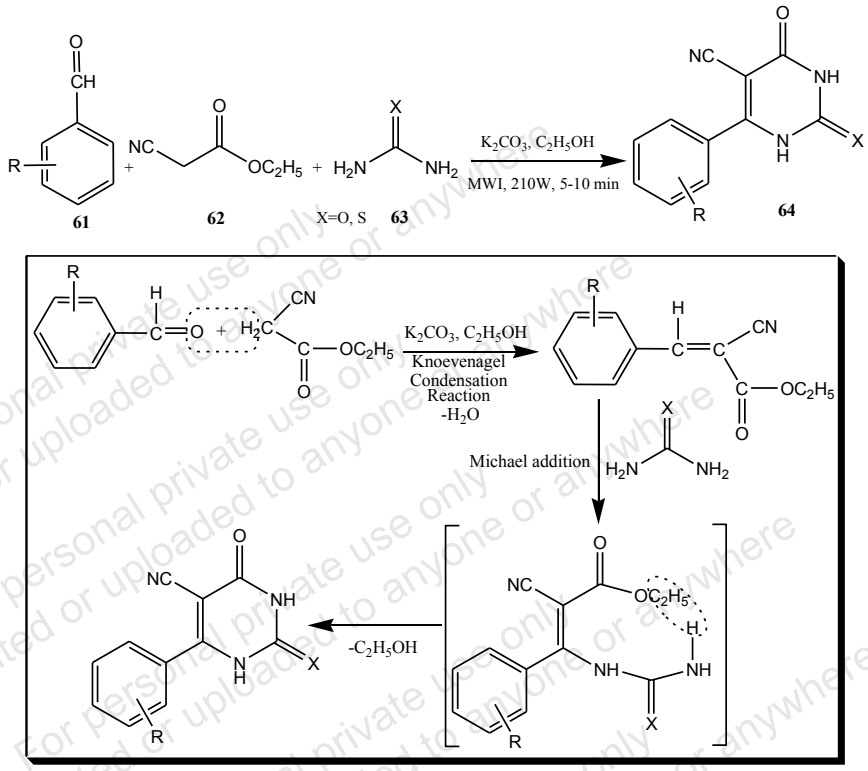
4.3. Pyrimidines as Antimicrobial Agent

Microbial infections are the leading cause of mortality worldwide. Currently, there are different types of antimicrobial drugs available clinically for the treatment of different microbial infections. But, there is still requirement to design and develop potential anti-infective agents with less development of resistance. From the various studies, it is reported that pyrimidine analogs prepared *via* microwave irradiation method are found to be inhibitors of several microbial enzymes and blockers of pathogenesis [57].

Khatri *et al.* explored the microwave-induced synthesis of thieno[2,3-d]pyrimidines (**71**, **73**). These compounds were prepared *via* cyclization of 2-amino-3-cyanothiophenes (**69**) with formamide (**70**) and urea (**72**) under microwave irradiation at a power level of 180 Watts (Scheme **19**). QPro-M microwave synthesizer was used for the synthesis of these compounds. The synthesized compounds were evaluated for their antibacterial and antifungal activities *in-vitro* by using the broth dilution method. The tested compounds exhibited promising antimicrobial activity in comparison to Ampicillin and Griseofulvin (Table **9**) [58].

A series of thiazolopyrimidine derivatives (**77**) have been synthesized *via* multicomponent reaction (Scheme **20**). Both conventional and microwave-assisted irradiation methods (500W, 5-10min) were used to perform the reactions. The reactions were carried out by using Millstone Organic Synthesis Unit (Micro SYNTH) with a continuous focused microwave power delivery system in a pressure glass vessel (10 mL) sealed with a septum under magnetic stirring. All the synthesized compounds were evaluated for their antimicrobial activities. Some compounds displayed moderate antimicrobial activity as compared to standard drugs such as Chloramphenicol and Ampicillin [59].

Sureja *et al.* synthesized a novel series of pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one derivatives **80** (Scheme **21**). It involves the cyclization of an ortho-amino ester of 1-(2,4-dinitrophenyl)pyrazole (**78**) with various aliphatic or aromatic nitriles (**79**) under different reactions conditions such as conventional and microwave-assisted synthesis. The reaction mixture was subjected to irradiation in a microwave oven at the power level of



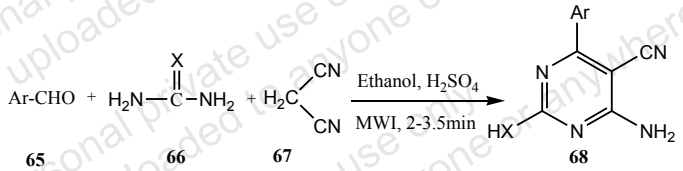
Scheme 17. Synthetic route and reaction mechanism for the preparation of pyrimidine-5-carbonitrile derivatives.

Table 7. Comparison between conventional and microwave-assisted synthesis.

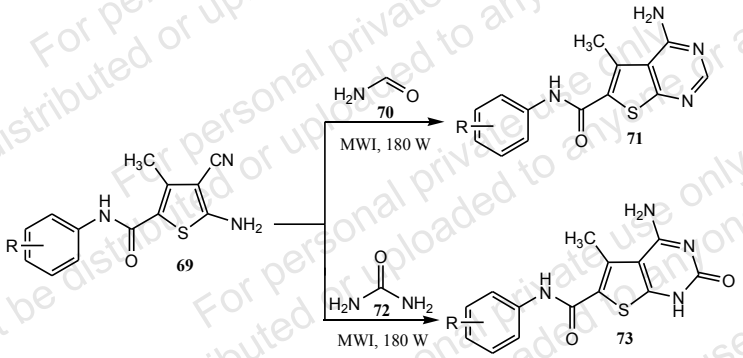
Compounds	R	Conventional Synthesis			Microwave Synthesis		
		Time (hr.)	Energy (Temp. ^{0}C)	Yield (%)	Time (min.)	Energy (Power. Watt)	Yield (%)
64a	H	4	98-100	61.47	5	210	82.67
64b	p-F	6	98-100	60.53	7	210	81.48
64c	o-Cl	5	98-100	59.62	6	210	80.65
64d	m-Cl	7	98-100	58.76	8	210	79.05
64e	p-Cl	6	98-100	61.46	7	210	82.26
64f	m-Br	5	98-100	57.23	7	210	78.40
64g	p-Br	6	98-100	58.37	9	210	79.71
64a	H	4	98-100	66.27	5	210	85.01
64b	p-F	6	98-100	65.31	9	210	85.15
64c	o-Cl	5	98-100	62.59	7	210	82.46
64d	m-Cl	7	98-100	60.53	8	210	79.92
64e	p-Cl	6	98-100	61.46	6	210	82.95
64f	m-Br	5	98-100	57.78	7	210	78.57
64g	p-Br	6	98-100	59.19	8	210	80.61

Table 8. Anti-mycobacterial activity of pyrimidine derivatives.

Compound Code	% Reduction in RLU			
	Test Organisms			
	M. tuberculosis H37Rv		Clinical isolate: S, H, R & E resistant *M. tuberculosis*	
	100 µg/ml	500 µg/ml	100 µg/ml	500 µg/ml
64b	46.49	44.20	38.38	47.86
64d	54.28	61.02	50.10	52.77
64i	33.40	48.72	25.47	33.49
64e	46.21	65.23	61.35	66.65
64g	75.73	82.04	38.03	74.91
Isoniazid (0.5 µg/mL)	98.42		89.6	



Scheme 18. Synthesis of 6-amino-5-cyano-2-(hydroxy/mercapto)-4-substituted-pyrimidine derivatives.

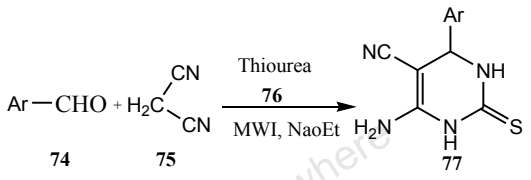


Scheme 19. Synthesis of thieno[2,3-d]pyrimidines under MWI.

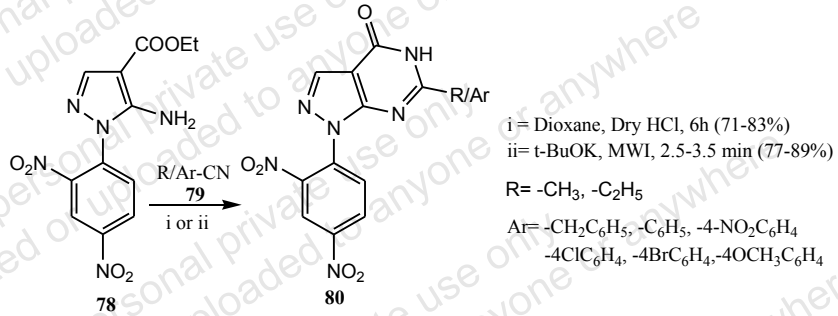
Table 9. Antimicrobial activity of the synthesized compounds.

Compounds Code	R	Minimum Inhibition Concentration (µg mL^{-1})						
		Gram-positive		Gram-negative		Fungal species		
		S.a.	S.p.	E.c.	P.a.	C. a.	A. n.	A.c.
71d	4-Cl	25	100	200	100	1000	500	500
73d	4-Cl	50	125	100	200	>1000	500	>1000
73j	4-F	50	125	250	100	100	1000	500
Amp	-	250	100	100	100	-	-	-
Gri	-	-	-	-	-	500	100	100

Microorganisms selected are as follows: S.a., *Staphylococcus aureus*; S.p., *Streptococcus pyogenes*; E.c. *Escherichia coli*; P.a., *Pseudomonas aeruginosa*; C.a., *Candida albicans*; A.n., *Aspergillus niger*; A.c. *Aspergillus clavatus*. Standards: Amp, Ampicillin; and Gri, Griseofulvin.



Scheme 20. Synthesis of thiazolopyrimidine derivatives.



Scheme 21. Synthetic route to pyrazolo[3,4-d]pyrimidin-4(5*H*)-one derivative.

960 W (CEM, discover microwave lab station operating at 2450 MHz under continuous internal temperature control) for 2.5-3.5 minutes. All the synthesized compounds were evaluated for their *in-vitro* antimicrobial activity against selected bacterial and fungal strains by using the agar well diffusion method. Streptomycin (50 µg/mL) and Fluconazole (50 µg/mL) were used as standard drugs. DMSO was used as a control. The antimicrobial activity was evaluated by measuring the zone of inhibition. Compounds with aryl or heteroaryl substitution at the 6th position exhibited better activity as compared to standard drugs [60].

Panneerselvam *et al.* performed the microwave-assisted synthesis of a series of thiosemicarbazide substituted pyrimidine derivatives (**81**) by using thiosemicarbazide and ethyl-2-((2-amino-5-carbamoyl-6-[substituted benzyl]pyrimidin-4-yl)oxy)acetate and subsequent addition of acetaldehyde and acetone. The experiment was carried out under microwave irradiation at a power level of 400 to 450 W for 3-5 minutes. The synthesized compounds were screened for their antibacterial activity against *S. aureus*, *M. luteus*, *S. epidermidis*, *E. coli*, *B. cereus*, *P. aeruginosa,* and *K. pneumonia* as compared to standard drugs Ciprofloxacin. Similarly, the antifungal activity of these compounds (Fig. **14**) was evaluated against *A. niger* and *A. fumigates* in comparison with Ketoconazole as a standard drug. Among tested compounds, 2-hydroxy and 3-chloro derivatives of thiosemicarbazide substituted pyrimidine exhibited good activity against microorganisms [61].

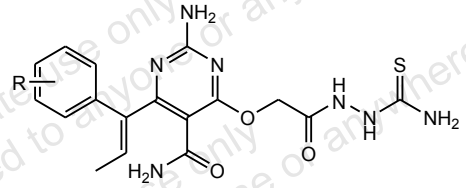
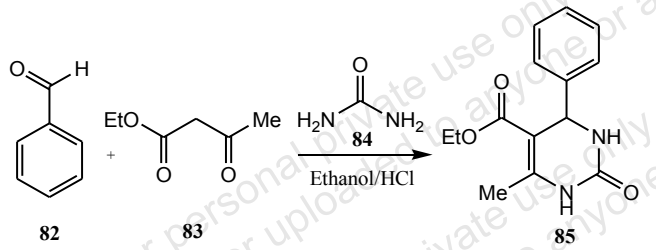


Fig. (14). Synthesis of thiosemicarbazide substituted pyrimidine derivatives.

Various pyrimidine derivatives (**85**) were synthesized by following Biginelli's three-component cyclocondensation reactions of aryl aldehyde (**82**), β -diketone (**83**), and urea (**84**) under microwave irradiation conditions (Scheme **22**). The synthesized compounds were evaluated for their antimicrobial activities against Gram-positive, Gram-negative bacteria, and fungi by using the micro dilution method. The results of this study demonstrated that some compounds were found to be effective and selective for antimicrobial activity against the tested microorganisms [62].

Karthic *et al.* described the synthesis of 5-(5-amino-1,3,4-thiadiazol-2yl)-3,4-dihydro-6-methyl-4-phenyl-pyrimidin-2(1*H*)-thione (**86**) under microwave irradiation at 200W for 2 minutes (Fig. **15**). These pyrimidine derivatives have been evaluated for their possible anti-

fungal activity *in-vitro* against *Candida tropicalis*, *Aspergillus terreus,* and *Penicillium sps* by using the agar well disk diffusion method. Most of the tested compounds exhibited significant antifungal activity in comparison with Amphotericin-B as a standard drug [63].



Scheme 22. Synthesis of pyrimidine derivatives under MWI.

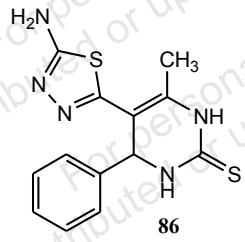


Fig. (15). Structure of pyrimidin-2(1*H*)-thione with antifungal activity.

Chandrasekaran *et al.* reported the microwave-assisted synthesis of some 2-amino-6-aryl-4-(2-thienyl)pyrimidines (**89**) (Scheme **23**). It involves the reaction between 3-aryl-1-thien-2ylprop-2-en-1-ones (**87**) and guanidine hydrochloride (**88**) in the presence of alkali by conventional heating method (R.T: 12-18h, Yield: 25-40%) in alcoholic medium and microwave heating (R.T: 60-70sec, 85-90%) in solvent-free conditions. The reaction mixture was transferred into a beaker and subjected to irradiation in the domestic microwave oven (LG Grill, MG395WA) at 320W. The synthesized compounds were evaluated for *in-vitro* antibacterial activity. The MIC value represents the lowest concentration of test substances required to inhibit the growth of microorganisms. So, the tested compounds (89a, 89b) with lower MIC values exhibit higher effectiveness against bacterial strains as compared to the reference drugs like ciprofloxacin and norfloxacin (Table **10**) [64].

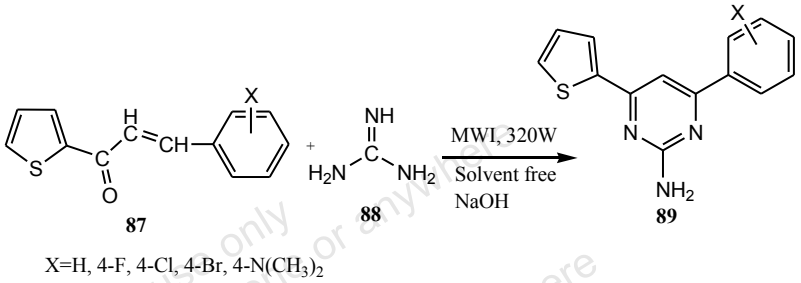
Bakr *et al.* developed the synthesis of newly pyrimidine derivatives (**93**) *via* a facile one-step reaction by treating substituted aldehydes (**90**), active methylene derivatives like diethyl malonate or ethyl cyanoacetate (**91**) and urea or thiourea (**92**) by using 1,4-diazabicyclo[2.2.2]octane (DABCO) as a basic catalyst (Scheme **24**). These derivatives were evaluated for their antibacterial activity against bacteria such as *B. subtilis*, *S. aureus*, *P. aeruginosa,* and *E. coli,* and antifungal activity against fungi such as *A. flavus* and *C. albicans*. All the screened compounds exhibited significant antibacterial and antifungal activity [65].

An efficiently green protocol was developed for the synthesis of methyl-7-amino-4-oxo-5-phenyl-2-thioxo-2,3,4,5-tetrahydro-1*H*-pyrano[2,3-d]pyrimidine-6-carboxylates (**97**) (Scheme **25**). This synthesis was performed through a one-pot three-component condensation reaction between various benzaldehydes (**94**), methyl cyanoacetate (**95**), and barbituric acid (**96**) in the presence of water under microwave irradiation. This methodology offered several advantages, such as high yields (78-94%), short reaction time (3-6 min), safety, and being eco-friendly without using any catalyst (Table **11**). The synthesized compounds demonstrated excellent *in vitro* antimicrobial and antifungal activities against different strains like *S. aureus, B. cereus* (gram-positive bacteria), *E. coli, K. pneumonia, P. aeruginosa* (gram-negative bacteria), *A. niger,* and *P. chrysogenum*. Streptomycin and mycostatin were used as standard drugs for antibacterial and antifungal studies, respectively [66].

Bansal *et al.* presented the microwave-assisted synthesis of pyrimidine derivatives (**102**) (Scheme **26**). The synthesis of pyrimidine derivatives is based on the condensation of chalcones (**100**) with guanidine nitrate (**101**) in the presence of sodium hydroxide and ethanol. Then, the reaction mixture is refluxed under microwave radiation at 180 watts for 2-16 minutes. The titled compounds were screened for their antibacterial activity against *P. aeruginosa* and *E. coli* by using the filter paper disc method. The screening results revealed that some of the tested compounds exhibited significant antibacterial activity at a concentration of 500µg/ml and 1000µg/ml as compared to standard drug amoxicillin [67].

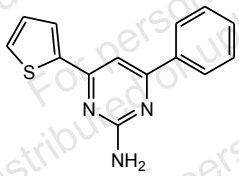
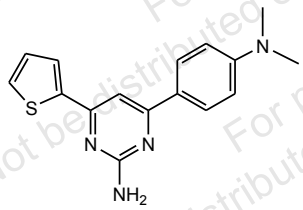
4.4. Pyrimidines as Anti-psychotic Agent

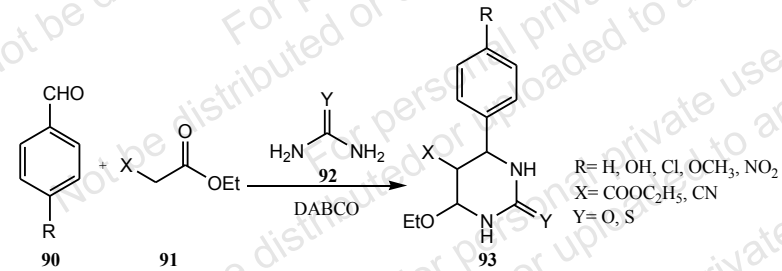
Psychosis is a mental disorder called schizophrenia that causes abnormal thinking and perceptions. The activation of the dopaminergic system is considered the main factor in the etiology of this disorder. So, antipsychotic agents (*e.g.*, clozapine, olanzapine, risperidone) are used clinically for effective treatment of psychosis. But, these drugs are still associated with some extrapyramidal side effects. So, researchers have focused on the development of efficacious therapeutic agents with better bioavailability by minimizing extrapyramidal side effects for the treatment of psychosis [68].



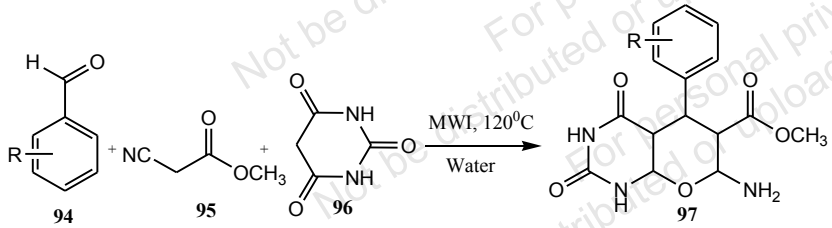
Scheme 23. Synthesis of 2-amino-6-aryl-4-(2-thienyl)pyrimidines with anti-bacterial activity.

Table 10. ***In-vitro*** **antibacterial activity of test compounds.**

Compounds	MIC (µg/ml)				
	S. aureus	***B. subtilis***	***E. coli***	***K. peneumoniae***	***P. aeruginosa***
 **89a**	0.59	0.55	32	>60	>60
 **89b**	0.40	0.47	18	24	42
Ciprofloxacin	0.55	0.03	0.13	0.07	1
Norfloxacin	1	0.05	0.48	0.32	4.5

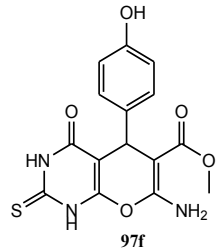


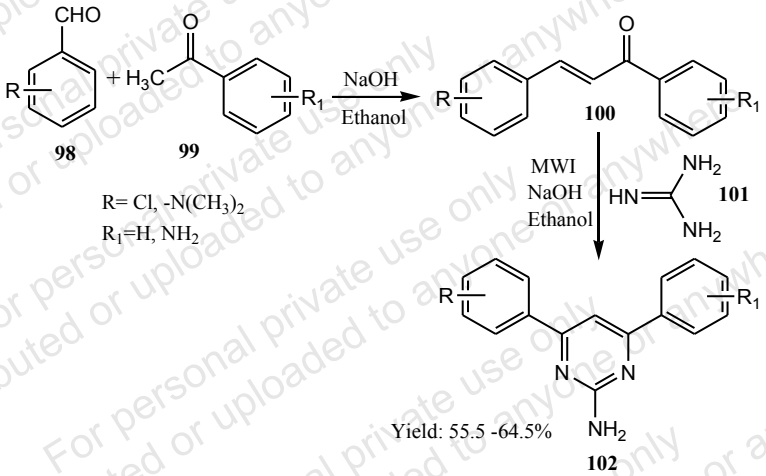
Scheme 24. Synthesis of pyrimidine derivatives with antibacterial and antifungal activity.



Scheme 25. Scheme for the synthesis of pyrimidine derivatives under microwave irradiation.

Table 11. Optimization of catalysts for the synthesis of 97f under microwave irradiation.

Compound	Entry	Catalyst	Mole%	Solvent	Time (min)	Yield (%)
 97f	1	DBU	20 mol	H_2O	15	82
	2	DABCO	20 mol	H_2O	12	71
	3	K_2CO_3	20 mol	H_2O	20	57
	4	Et_3N	2-3 Drops	H_2O	11	64



Scheme 26. Microwave-assisted synthesis of pyrimidine derivatives with antibacterial activity.

Microwave irradiation and classical heating technique were used to synthesize a series of thienopyrimidines (**103**, **104**) and related heterocycles by refluxing related imidoyl chloride with primary and secondary amines (Fig. **16**). Whereas, the imidoyl chlorides are synthesized from corresponding cyclic imides with phosphorus oxychlorides ($POCl_3$) under MWI (R.T; 20 min., power level 4). The titled compounds were screened for their anti-psychotic activity. The tested compounds displayed a significant decrease in locomotor activity at a dose of 20 mg/kg and less cataleptic behavior as compared to the standard drug (Olanzapine) at a dose of 10 mg/kg. The locomotor activity was recorded by using Actophotometer. The locomotor count for each animal was recorded for 5 minutes at 60 minute time intervals for 1 h. The title compounds were found to be safe after oral administration with a dose of 20 mg/kg. There was no mortality observed at this dose up to 24 h. It was also found that there was a decrease in alertness and reactivity by applying stimuli. Further, the experimental animals did not display any loss of righting reflex with normal body position and lacrimation [69].

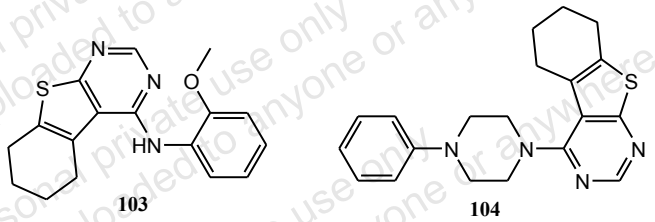


Fig. (16). Structure of thieno-pyrimidines derivatives.

4.5. Pyrimidines as an Anti-cancer Agent

Cancer is a multifactorial disease and is considered the second leading cause of death globally. In the case of cancer, there is an abnormal growth of cells with the potential to invade or spread to other parts of the body. So, anticancer drugs or chemotherapeutic agents (alkylating agents, antibiotics, antimetabolites, and plant alkaloids) are used clinically to destroy, kill or decrease the growth of cancer cells. But the effectiveness of these drugs has been limited due to the development of drug resistance and also side effects on normal cells and tissues. Recently, various drug targets have been identified and there is more development of targeted therapy, such as targeting the proteins with an

Table 12. Comparative study on reaction time and yield of pyrimidine derivatives by conventional and microwave irradiation methods.

Compound No.	Ar	Reaction Time		Yield (%)	
		Conventional (hr)	Microwave (min)	Conventional	Microwave
105a	$-C_6H_5$	4.5	5.5	35	48
105b	$-3Br-C_6H_4$	4.5	4.5	32	47
105c	$4Cl-C_6H_4$	5.5	5.0	42	56
105d	$2,4Cl_2-C_6H_3$	5.0	4.5	49	56
105e	$-4NO_2-C_6H_4$	5.5	6.0	34	43

abnormal expression inside the cancer cells and subsequently designing novel anticancer agents [70].

Ahmad *et al.* performed the synthesis of 2-amino-4,6-diarylpyrimidine derivatives (**105**) (Fig. **17**) by both conventional and microwave-assisted heating techniques (Catalyst Scientific Microwave Oven, Model: CATA 2R, Power: 140-700 W). The prepared compounds were evaluated for their potential cytotoxic and antioxidant activities by using Brine shrimp lethality bioassay and Riboflavin photo-reduction method, respectively. It was demonstrated that the microwave irradiation method is found to be advantageous, with a considerable increase in the rate of reaction with better yield (Table **12**). It was observed that the pyrimidine derivatives were found to possess promising cytotoxic and anti-oxidant activities (Table **13**) [71].

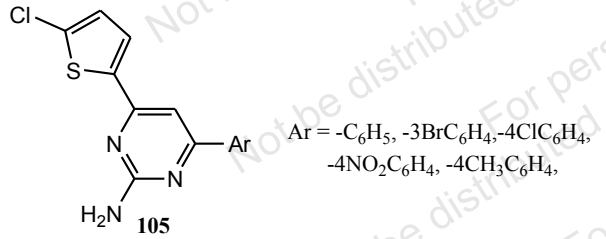


Fig. (17). Synthesis of 2-amino-4,6-diaryl-pyrimidine derivatives.

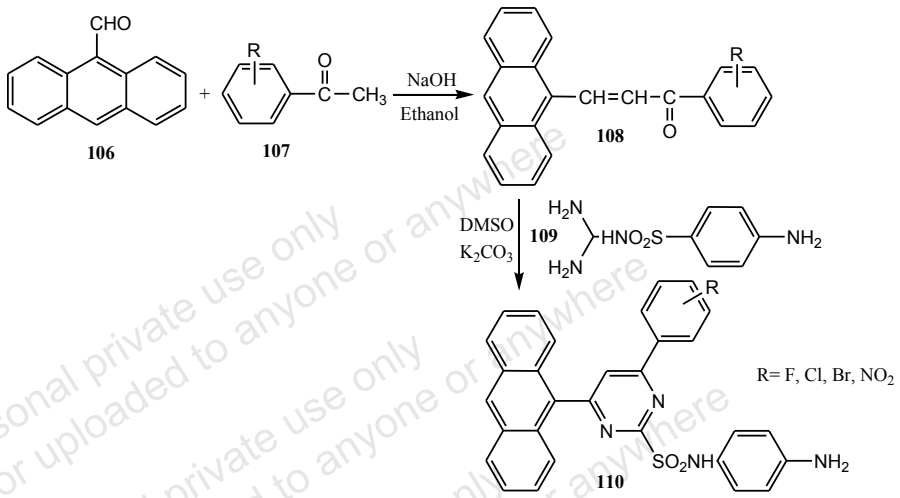
Table 13. Cytotoxic activity of pyrimidine derivatives using Brine shrimp lethality test.

Compound No.	ED_{50} (µg/mL)
105a	4.13
105b	49.47
105c	4.97
105d	43.52
105e	45.39
Standard (Podophyllotoxin)	3.69

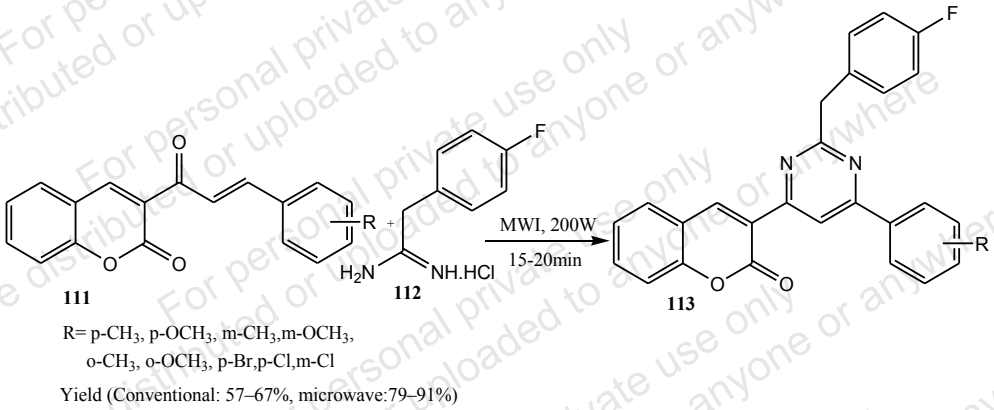
Jainey *et al.* reported the microwave-assisted synthesis of novel pyrimidines bearing benzene sulfonamides (**110**). These pyrimidine derivatives were obtained by the reaction of chalcones (**108**) with sulfaguanidine (**109**) under a microwave-assisted synthetic method (Cata-R, Catalyst Systems 140-700 W) with good product yields (72-84%) (Scheme **27**). The *in-vitro* anticancer activity of these compounds was evaluated based on tryphan blue dye exclusion method. Similarly, the antioxidant activity was performed using DPPH and nitric oxide methods. Some of the tested compounds exhibited significant antitumor and antioxidant activities in comparison to 5-fluorouracil and ascorbic acid as standard drugs, respectively [72].

Microwave-induced heating method was applied for efficient and rapid synthesis of new fluorinated coumarin-pyrimidine hybrids (Yield: 79-91%) (**113**) (Scheme **28**). CEM Discover focused microwave system was used for synthesis of titled compounds at a power level of 200 W for 15-20 min. The newly synthesized compounds were evaluated for their anticancer activity against two human cancer cell lines , including A-549 (human lung carcinoma) and MDA-MB-231 (human adenocarcinoma mammary gland). The activity study revealed that some of the tested compounds exhibit significant cytotoxicity against the two cancer cell lines with $IC_{50} < 10$ µM. Some of the tested compounds exhibited promising activity against the A-549 cell line in comparison with the standard drug cisplatin [73].

Singh *et al.* described the microwave irradiated synthesis of tetrahydro-pyrimidine derivatives (**114**). These compounds were prepared from the condensation reaction of urea and substituted aldehydes under MWI (840W, 3-5min) (Fig. **18**). The titled compounds were evaluated for determining their calcium channel inhibition activity by using nifedipine as a reference [74].



Scheme 27. Synthesis of pyrimidines bearing benzene sulfonamides under MWI.



Scheme 28. Synthesis of fluorinated coumarin-pyrimidine hybrids with anticancer activity.

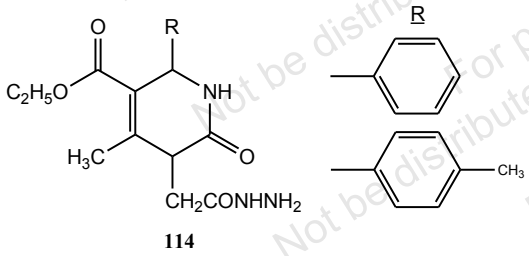


Fig. (18). Structure of 1,2,3,4-tetrahydro-pyrimidine derivatives.

Sandhu *et al.* described the green protocol for the synthesis of 3,4-dihydro-pyrimidine-2-(1*H*)-ones (**115**) under the microwave irradiation method at a power level of 220W for 1.5-3.0 minutes (Synthwave S-402). These types of compounds are synthesized *via* a multi-component reaction of aldehyde, urea or thiourea, and 1,3-dicarbonyl compounds and are catalyzed by $AlCl_3.6H_2O$ under solvent-free conditions (Fig. **19**). Here, it was reported that this catalyst is found to be cheap, safe to handle and the complete process is eco-friendly (Yield: 83-95%) [75].

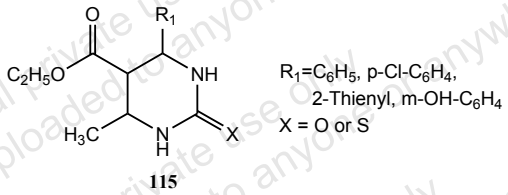


Fig. (19). Structure of 3,4-dihydro-pyrimidine-2-(1*H*)-ones.

4.6. Pyrimidine as Anthelmintics

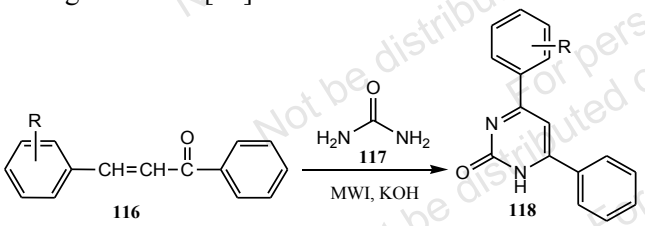
Helminthiasis is a worm infection in which a part of the body is infected with parasitic worms, known as helminths. Anthelmintics are a group of anti-parasitic drugs that expel parasitic worms from the body by paralyzing or killing them without causing any damage to the host cell. Based on this mechanism of action, different pyrimidine derivatives are designed for the effective treatment of helminthiasis [76].

Sahoo *et al.* explored the green protocol for the synthesis of pyrimidine derivatives (**118**) *via* chalcones. These compounds were synthesized by the condensation of chalcones (**116**) with urea (**117**) in an alkaline

Table 14. Comparative study of conventional and microwave synthesis.

Compound Code	R	Conventional			Microwave	
		Time (h)	Energy (Temp. ^{O}C)	Yield (%)	Energy (Power.Watt)	Yield (%)
118a	H	3	98-100	58.67	210	79.48
118b	3-NO_2	4	98-100	60.85	210	82.73
118c	4-NO_2	4	98-100	62.85	210	82.33
118d	2-OH	4	98-100	65.31	210	85.25

medium by using the microwave heating method (Catalyst Scientific microwave oven). Herein, the Claisen-Schmidt condensation reaction mechanism is involved in producing chalcones from acetophenone and different substituted benzaldehydes in the presence of potassium hydroxide solution (Scheme **29**). The synthesis was carried out by using a scientific microwave oven and the reaction temperature was measured by dipping the sensor wire into the reaction medium. This synthetic process by microwave offers a shorter reaction time, environment-friendly procedure, and excellent yields. With the help of microwave synthesis, the product yield was enhanced from 58% up to 85% as compared to a conventional heating method, indicating the utility of the green chemistry approach (Table **14**). The synthesized compounds were evaluated for their anthelmintic activity. Compound with electron-withdrawing substituent was found to be active against helminths among the series [77].



Scheme 29. Synthesis of pyrimidine derivatives *via* chalcones.

4.7. Pyrimidine as Anti-malarial Agent

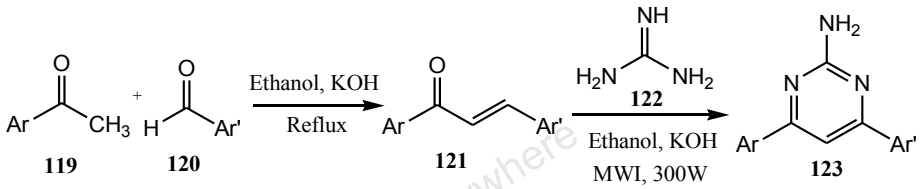
Malaria is an infectious disease caused by protozoan parasites of Plasmodium species that spread to people through the bites of infected female Anopheles mosquitoes. Currently, different classes of anti-malarial drugs are used for the treatment and prevention of malaria, including quinoline derivatives (Chloroquine, hydroxyl chloroquine), antifolates, artemisinin, and antimicrobials. But, these drugs produce gastrointestinal side effects that may lead to a lack of adherence to drug treatment. So, extensive research is carried out to generate potential antimalarial agents with targeted drug delivery [78].

Rathwa *et al.* performed the microwave-assisted synthesis of pyrimidine derivatives (**123**) from chalcones *via* condensation reaction with guanidine hydrochloride in the presence of a basic medium (Scheme **30**). The reaction mixture was irradiated under microwave irradiation (CEM microwave Oven, Model No. 908010) at 300 W for 10-20 minutes. The synthesized compounds were evaluated for their *in-vitro* antimalarial activity against *P. falciparum* strain. The tested compounds displayed promising antimalarial activity with an IC_{50} value of 0.55-0.75µg/mL in comparison with the standard drug pyrimethamine [79].

The microwave irradiation method (340 W, 10-15 min) is utilized efficiently to perform the synthesis of imidazo[1,2-a]pyrimidine derivatives (**124**) with excellent yield (71-93%) in a short reaction time. The microwave-irradiated synthesis is performed in a ‘‘RAGA’s Modified Electromagnetic Microwave System, in which the microwaves are generated by the magnetron at a frequency of 2450 MHz with a power level of 140 to 700 W and a fiber-optic sensor to control the temperature. The sensor is attached to the reflux condenser with constant stirring to avoid any risk of the development of high pressure. It involves a one-pot three-component condensation reaction of pyrazole aldehyde clubbed with imidazole and triazole nuclei and 2-amino benzimidazole in the presence of KOH (Fig. **20**, Table **15**). The synthesized compounds were screened for their preliminary *in-vitro* antimalarial activity against chloroquine, Quinine sensitive strains of *P. falciparum*. Some of the tested compounds displayed excellent antimalarial activity with an IC_{50} value of 0.030-0.079µg/mL in comparison with standard drugs [80].

4.8. Pyrimidine as Antidiabetic

Diabetes mellitus is characterized by high blood glucose levels due to irregular secretion of insulin. So, antidiabetic drugs are developed to stabilize and control the glucose level in the blood. These medications have common side effects like hypoglycemia, weight gain, and gastrointestinal symptoms. To minimize



Scheme 30. Synthesis of pyrimidine derivatives from Chalcones under MWI.

Table 15. Optimization of the reaction conditions for compound 124a.

Entry	Base (equiv.)	Solvent	Yield (%)
1	KOH, 1.5	EtOH :H_2O (1:1)	93
2	KOH, 2.0	EtOH :H_2O (1 : 1)	83
3	NaOH, 1.5	EtOH :H_2O (1 : 1)	71

these side effects, novel pyrimidine analogs are designed with improved pharmacokinetic and pharmacodynamic profiles [81].

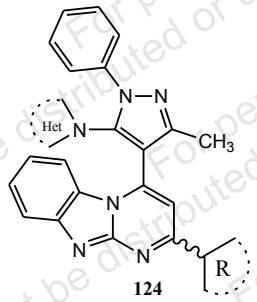
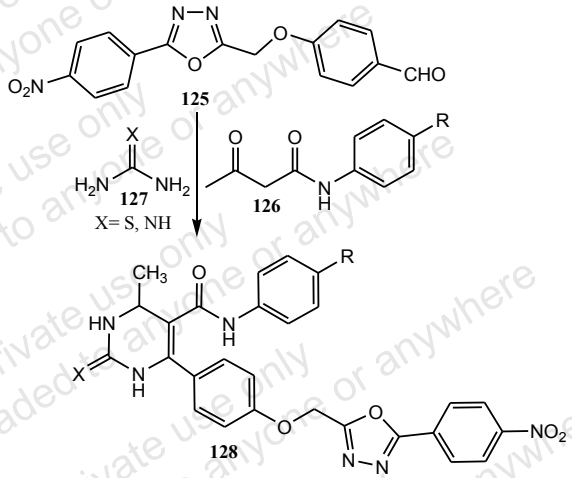


Fig. (20). Structure of imidazo[1,2-a]pyrimidine derivatives.

The syntheses of oxadiazole-based tetrahydropyrimidines (**128**) were carried out efficiently by microwave irradiation at 200W for 25 min. The synthesis of these compounds was performed in an Anton-Paar Monowave 300 Microwave synthesizer using a borosilicate glass G10 vial sealed with PTFE-coated silicone septum. It involves the one-pot multicomponent reaction between aldehydes (**125**), substituted acetoacetanilide (**126**), thiourea, or guanidine (**127**) in ethanol, and a catalytic amount of acidic medium (Scheme **31**). The improved product yield, atom economy, less time consuming, and catalyst-free synthesis was possible due to the microwave irradiation technique (Table **16**). The synthesized compounds were screened for their *in-vitro* anti-diabetic activity based on the α-amylase inhibition strategy (Table **17**). For the determination of OD, the absorbance was measured at a wavelength of 540 nm by using a UV-Visible spectrometer. The screening results revealed that some compounds (**128a, 128b, 128c**) displayed very good potency in comparison with standard drug acarbose [82].



Scheme 31. Synthetic route to 1,3,4-oxadiazole-based tetrahydro-pyrimidine.

The synthesis of tetrahydro-pyrimidine (**132**) is performed based on the Bignelli condensation reaction of benzaldehyde (**129**), ethyl acetoacetate (**130**), and urea (**131**) by using the microwave heating method at 180W for 1-5minutes (Scheme **32**). In-silico screening of the synthesized compounds is performed to predict their anti-diabetic activity. The results of the docking study revealed that tetrahydro-pyrimidine derivatives can bind to insulin receptors and increase the production of insulin [83].

5. SYNTHESIS OF DRUGS WITH PYRIMIDINE SCAFFOLD BY MWI TECHNOLOGY

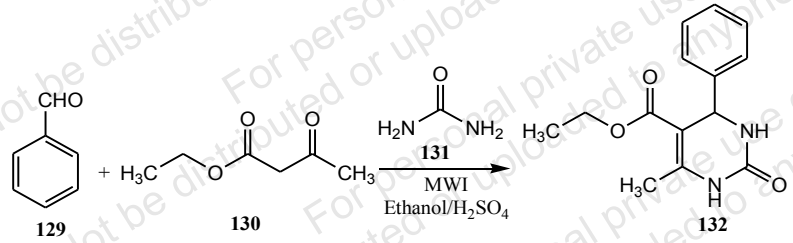
Imatinib (Gleevec) is a blockbuster anticancer drug with tyrosine kinase receptor inhibitory activity. Chemically, it is 4-[(4-methylpiperazin-1-yl)methyl]-*N*-[4-methyl-3-[(4-pyridin-3-ylpyrimidin-2-yl)amino]

Table 16. Optimization and comparative study of conventional and microwave-assisted synthesis of compound 128a.

Entry	Solvent	Catalyst	Conventional			Microwave		
1	EtOH	HCl	Temp (^oC)	Time (hr)	Yield (%)	Temp (^oC)	Time (min.)	Yield (%)
			80	22	56	90	25	92
2	MeOH	PPh_3	70	24	15	90	25	30

Table 17. ***In-vitro*** **anti-diabetic activity of test compounds.**

Compound	R	Concentration (µg/mL)	OD	% Inhibition	IC_{50}
128a	-4-NO_2	50 75 100 125	0.138 0.114 0.0845 0.0414	37.04 ± 1.30 47.79 ± 2.41 61.33 ± 3.69 80.93 ± 4.30	79.23
128b	4-CH_3	50 75 100 125	0.136 0.112 0.0818 0.0421	37.90 ± 3.27 48.83 ± 2.39 62.44 ± 5.45 80.67 ± 2.39	77.21
128c	2-CH_3	50 75 100 125	0.145 0.117 0.0892 0.0456	33.49 ± 2.75 46.65 ± 0.09 59.18 ± 2.61 79.09 ± 2.53	81.46



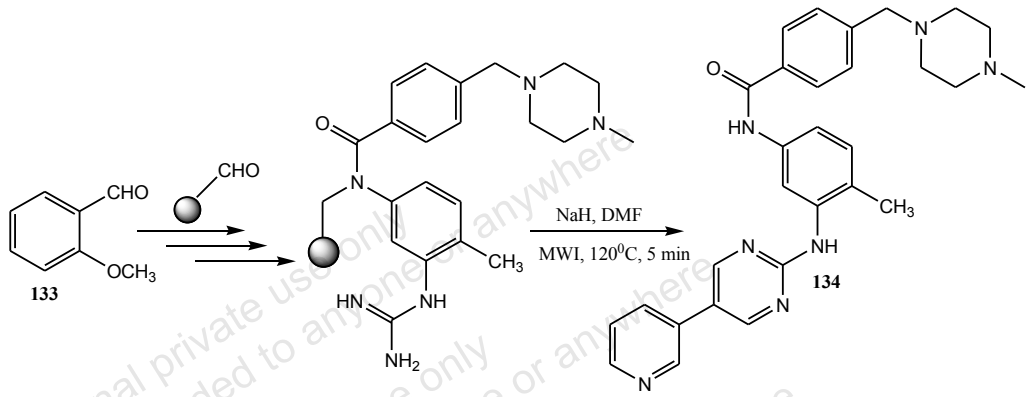
Scheme 32. Synthesis of tetrahydro-pyrimidine with anti-diabetic activity.

phenyl] benzamide. The synthesis of Imatinib is performed by microwave irradiated solid-phase reactions (Scheme **33**). It involves the expeditious, efficient synthesis of Imatinib on an aldehydic, acid-sensitive resin *via* a microwave-induced synthetic strategy. The high versatility of this reaction methodology enabled the production of compound libraries of potential drug candidates with diverse molecular structures [84].

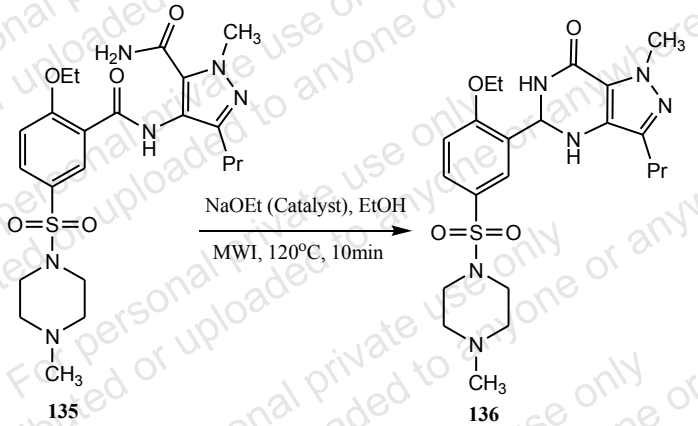
Microwave technology is applied for the convenient synthesis of clinically used drugs like sildenafil (Viagra) (Scheme **34**). Structurally, it is a pyrazolo[4,3-d]pyrimidin-7-one with a methyl substituent at C_1, propyl substituent at C_3, and a 2-ethoxy-5-[(4-methylpiperazin-1-yl)sulfonyl]phenyl group at the C_5 position. Its IUPAC name is 5-[2-ethoxy-5-(4-methylpiperazin-1-yl)sulfonylphenyl]-1-methyl-3-propyl-6*H*-pyrazolo [4,3-*d*]pyrimidin-7-one. Sildenafil is a selective and competitive phospho-diesterases type 5 (PDE5) inhibitor [85].

6. SAR STUDY OF PYRIMIDINES

The structure-activity relationships (SAR) study of pyrimidine scaffolds represents the effect of structural and physicochemical properties on selectivity and



Scheme 33. Solid-phase synthesis of Imatinib (anticancer drug) under MWI.



Scheme 34. Microwave irradiated synthesis of Sildenafil.

binding affinity towards receptors (Fig. **21**). The significant biological activities of the pyrimidine analogs may be attributed to the position (ortho, meta, and para*)* and type of substituents (electron-withdrawing and donating groups) present on the pyrimidine ring. In the case of pyrimidine moiety, the essential core portions are represented by the presence of hydrogen donor or acceptor unit (HAD), hydrophobic domain (A) or aryl ring and electron donor atom (D). In the case of position A on the pyrimidine ring, the presence of five-membered saturated heterocyclic ring substitution leads to anticancer and antiviral activities. Whereas position B, *i.e.*, 2nd position, implies that the presence of five or six-membered saturated heterocyclic ring substitution generates the molecules with anthelmintic, antiparkinsonian, and expectorant. But, in the case of the 4th position, the presence of keto or amino group substitution or mixed keto, amino groups substitution on pyrimidine ring explore the molecules with antibacterial, antifungal, antiviral, and anticancer activities, *etc.* While position C, *i.e.*, 5th position of pyrimidine ring with halogen or substituted amine or saturated distal heterocyclic ring substitution, exhibits antibacterial and anticancer activities. Further, position D, *i.e.*, 6th position fused with heterocyclic ring and *o*, *m*, *p* substituted distal aryl ring substitution exhibits anti-bacterial, antiviral, anticancer, and vasodilator activities [86, 87].

7. FUTURE PROSPECTS

Due to the increased prevalence of infections by viruses and microorganisms, there is a continuous requirement to develop novel therapeutic agents with promising pharmacokinetic and pharmacodynamic properties. For this purpose, researchers are focusing on the synthesis of pyrimidine-containing compounds *via* the microwave irradiation method. The implementation of green chemistry protocols provides an environment-friendly approach for the potential production of pyrimidine analogs [88]. The MW-induced organic reactions have gained popularity because this technique offers features like clean, efficient, faster, and more economical processes for the synthesis of compounds with diverse molecular structures. This heating method facilitates several chemical reactions to be completed under mild reaction conditions in shorter reaction times with higher product yield. In the future, many more

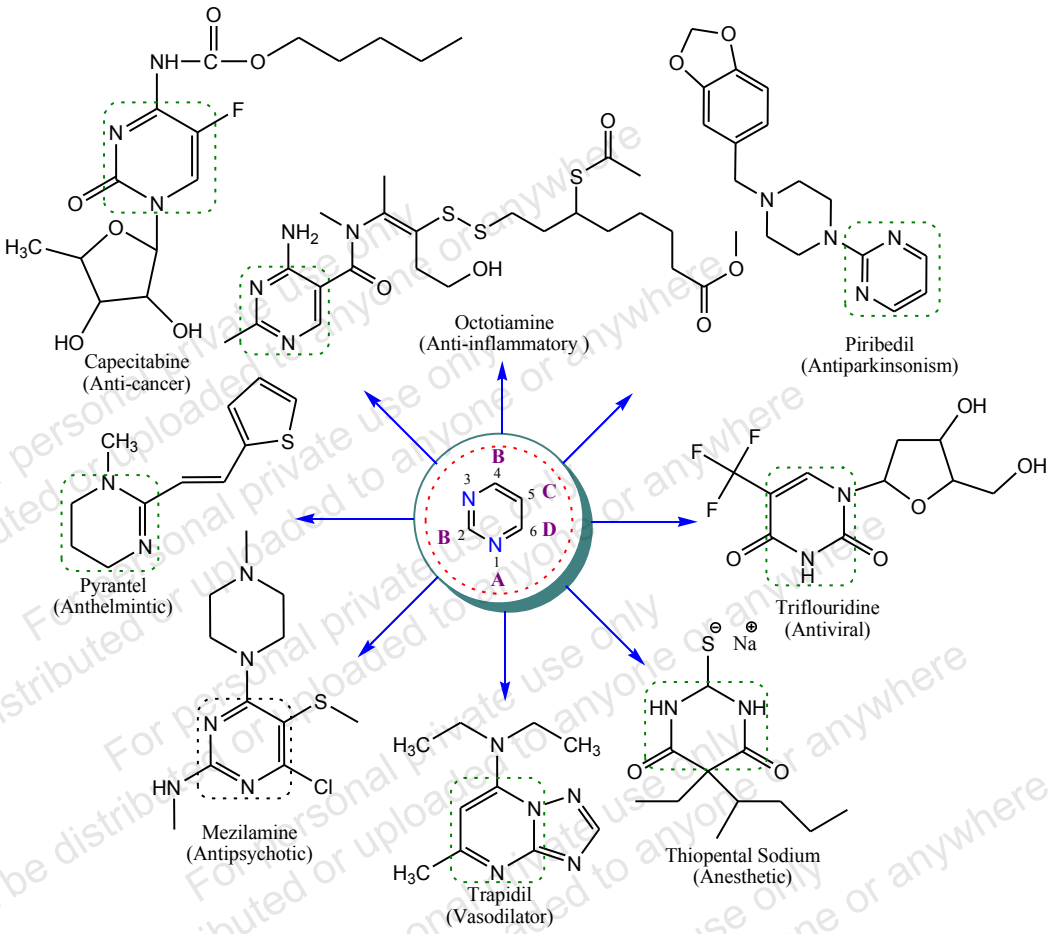


Fig. (21). Structure-Activity Relationships (SAR) study of pyrimidine.

microwave-induced chemical syntheses can be performed on industrial scales to increase the overall efficiency of the processes. So, the application of microwave-assisted drug synthesis looks bright because of its efficiency and potential to generate cleaner products [89-92].

CONCLUSION

The current review focuses on the green synthesis of pyrimidine analogs *via* microwave irradiation technique and the study of their therapeutic potentials. Drugs containing pyrimidine pharmacophore are found to be effective in treating various disease states like cancer, cardiac disease, diabetes, inflammation, malaria, thyroid disorder, bacterial, fungal, and viral infections, *etc.* Microwave-induced reaction is an energy-efficient and eco-friendly approach and has become an emerging tool of the green synthetic method. This heating technology enhances the rate of reaction with selective heating, improves the yield of the product with purity, and reduces the reaction time efficiently from days to hours, hours to minutes compared to the conventional heating method. So, microwave reactors are designed to accelerate the production of drug substances under controlled reaction conditions on a laboratory scale.

LIST OF ABBREVIATIONS

Al_2O_3	=	Alumina
°C	=	Degree celsius
DABCO	=	1,4-diazabicyclo[2.2.2]octane
DBU	=	1,8-Diazabicyclo[5.4.0]undec-7-ene
DHPMS	=	3,4-dihydropyrimidinones
DOCA	=	Deoxycorticosterone acetate
DPPH	=	2,2-diphenyl-1-picrylhydrazyl
Et_3N	=	Triethylamine
GHz	=	Gigahertz
IC_{50}	=	Half-maximal inhibitory concentration
K_2CO_3	=	Potassium carbonate
Kg	=	Kilogram
KOH	=	Potassium hydroxide

LRP = Luciferase reporter phage

MCRs = Multicomponent reactions

Mg = Milligram

MHz = MegaHertZ

Mtb = *Mycobacterium tuberculosis*

MWI = Microwave irradiation

$POCl_3$ = Phosphorus oxychlorides

PSSA = Polystyrene sulfonic acid

RLU = Relative light units

TB = Tuberculosis

W = Watts

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Ravichandran, S.; Karthikeyan, E. Microwave synthesis-A potential tool for green chemistry. *Int. J. Chemtech Res.,* **2011**, *3*(1), 466-470.

[2] Sahoo, B.M.; Banik, B.K.; Panda, J. *Microwave assisted green chemistry approach: A potential tool for drug synthesis in medicinal chemistry,* 2nd ed.; CRC Press, USA, **2018**. http://dx.doi.org/10.1201/9781351240499-12

[3] Krstenansky, J.L.; Cotterill, I. Recent advances in microwave-assisted organic syntheses. *Curr. Opin. Drug Discov. Devel.,* **2000**, *3*(4), 454-461. PMID: 19649876

[4] Sekhon, B.S. Microwave assisted pharmaceutical synthesis: An overview. *Int. J. Pharm. Tech. Res.,* **2010**, *2*(1), 827-833.

[5] Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. Microwave assisted organic synthesis-A review. *Tetrahedron,* **2001**, *57*(45), 9225-9283. http://dx.doi.org/10.1016/S0040-4020(01)00906-1

[6] Varma, R.S. Solvent-free organic syntheses using supported reagents and microwave irradiation. *Green Chem.,* **1999**, *1*(1), 43-55. http://dx.doi.org/10.1039/a808223e

[7] Sahoo, B.M.; Banik, B.K.; Panda, J. *Microwave Synthetic Technology: An eco-friendly approach in organic synthesis,* 2nd ed.; CRC Press, **2018**. http://dx.doi.org/10.1201/9781351240499-11

[8] Varma, R.S. Solvent-free syntheses of heterocycles using microwave irradiation. *J. Heterocycl. Chem.,* **1999**, *36*, 1565-1571. http://dx.doi.org/10.1002/jhet.5570360617

[9] Polshettiwar, V.; Varma, R.S. Microwave-assisted organic synthesis and transformations using benign reaction media. *Acc. Chem. Res.,* **2008**, *41*(5), 629-639. http://dx.doi.org/10.1021/ar700238s PMID: 18419142

[10] Strauss, C.R.; Trainor, R.W. Developments in microwave-assisted organic chemistry. *Aust. J. Chem.,* **1995**, *48*(10), 1665-1692. http://dx.doi.org/10.1071/CH9951665

[11] Giguere, R.J.; Bray, T.L.; Duncan, S.M.; Majetich, G. Application of commercial microwave ovens to organic synthesis. *Tetrahedron Lett.,* **1986**, *27*(41), 4945-4948. http://dx.doi.org/10.1016/S0040-4039(00)85103-5

[12] Varma, R.S. Solvent-free accelerated organic syntheses using microwaves. *Pure Appl. Chem.,* **2001**, *73*(1), 193-198. http://dx.doi.org/10.1351/pac200173010193

[13] Sahoo, B.M.; Panda, J.; Banik, B.K. Thermal and non-thermal effects of microwaves in synthesis. *J. Indian Chem. Soc.,* **2018**, *95*, 1-9.

[14] Mahato, A.K.; Sahoo, B.M.; Banik, B.K. Microwave-assisted synthesis: Paradigm of Green Chemistry. *J. Indian Chem. Soc.,* **2018**, *95*, 1-13.

[15] Agarwal, O.P. Organic chemistry: Reaction and reagents.Krishna Prakashan Media (p) Ltd, **2008**, pp. 735-738.

[16] Verma, A.; Sahu, L.; Chaudhary, N.; Dutta, T.; Dewangan, D.; Tripathi, D.K.A. Review: Pyrimidine their chemistry and pharmacological potentials. *Asian J. Biochem. Pharmaceut. Res.,* **2012**, *1*(2), 1-15.

[17] Arikkatt, S.D.; Baldwin, M.V.; Joseph, J.; Chandran, M.; Bhat, A.R.; Kumar, K. Pyrimidine derivatives and its biological potential-A review. *Int. J. Org. Bio. Org. Chem.,* **2014**, *4*(1), 1-5.

[18] Taylor, A.P.; Robinson, R.P.; Fobian, Y.M.; Blakemore, D.C.; Jones, L.H.; Fadeyi, O. Modern advances in heterocyclic chemistry in drug discovery. *Org. Biomol. Chem.,* **2016**, *14*(28), 6611-6637. http://dx.doi.org/10.1039/C6OB00936K PMID: 27282396

[19] Pratyusha, C.; Poornima, G.; Sandhyarani, K.; Krishnaveni, A.; Brahmaiah, B.; Sreekanth, N. An overview on synthesis and biological activity of pyrimidines. *Int. J. Pharm. Sci. Rev. Res.,* **2013**, *3*(2), 86-90.

[20] Dansena, H.; Dhongade, H.J.; Chandrakar, K. Pharmacological potentials of pyrimidine derivative: A review. *Asian J. Pharm. Clin. Res.,* **2015**, *8*(4), 171-177.

[21] Brown, D.J.; Mason, S.F. Chemistry of heterocyclic compounds: The pyrimidines. **2008**, *6*, 31-81.

[22] Michael, B.S.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure,* 6th ed.; Wiley-Int., **2007**, pp. 102-110.

[23] Kaur, R.; Chaudhary, S.; Kumar, K.; Gupta, M.K.; Rawal, R.K. Recent synthetic and medicinal perspectives of dihydropyrimidinones: A review. *Eur. J. Med. Chem.,* **2017**, *132*, 108-134. http://dx.doi.org/10.1016/j.ejmech.2017.03.025 PMID: 28342939

[24] Mahfoudh, M.; Abderrahim, R.; Leclerc, E.; Campagne, J.M. Recent approaches to the synthesis of pyrimidine derivatives. *Eur. J. Org. Chem.,* **2017**, *20*(20), 2856-2865. http://dx.doi.org/10.1002/ejoc.201700008

[25] Katritzky, A.R.; Rees, C.W. Comprehensive heterocyclic. *Chemistry,* **1984**, *1984*, 106.

[26] Maji, P.K. Recent progress in the synthesis of pyrimidine heterocycles: A review. *Curr. Org. Chem.,* **2020**, *24*(10), 1055-1096. http://dx.doi.org/10.2174/1385272824999200507123843

[27] Gore, R.P.; Rajput, A.P. A review on recent progress in multicomponent reactions of pyrimidine synthesis. *Drug Invent. Today,* **2013**, *5*, 148-152.

[28] Bhat, A.R.; Dongre, R.S.; Naikoo, G.A.; Hassan, I.U.; Ara, T. Proficient synthesis of bioactive annulated pyrimidine derivatives: A review. *J. Taibah Univ. Sci.,* **2017**, *11*(6), 1047-1069. http://dx.doi.org/10.1016/j.jtusci.2017.05.005

[29] Xin, X.; Wang, Y.; Kumar, S.; Liu, X.; Lin, Y.; Dong, D. Efficient one-pot synthesis of substituted pyridines through multicomponent reaction. *Org. Biomol. Chem.,* **2010**, *8*(13), 3078-3082. http://dx.doi.org/10.1039/c001117g PMID: 20480101

[30] Madhvi, A.S.; Jauhar, S.; Desai, K.R. A brief review: Microwave assisted organic reaction. *Arch. Appl. Sci. Res.,* **2012**, *4*(1), 645-661.

[31] Qiya, Z.; Hong, X.H.; Suhui, W. Three-component reaction for the synthesis of 2-amine-4,6-diarylpyrimidine under solvent-free conditions. *Synth. Commun.,* **2009**, *39*(3), 516-522. http://dx.doi.org/10.1080/00397910802399932

[32] Shujian, T.; Shanshan, W.U.; Zhengguo, H.; Wenjuan, H. An efficient microwave-assisted synthesis of pyrido[2,3-d]pyrimidine derivatives. *Chin. J. Chem.,* **2009**, *27*(6), 1148-1152. http://dx.doi.org/10.1002/cjoc.200990192

[33] Caddick, S. Microwave assisted organic reactions. *Tetrahedron,* **1995**, *51*(38), 10403-10432. http://dx.doi.org/10.1016/0040-4020(95)00662-R

[34] Mobinikhaledi, A.; Forughifar, N. Microwave assisted synthesis of some pyrimidine derivatives. *Phosphorus Sulfur Silicon Relat. Elem.,* **2006**, *181*(11), 2653-2658. http://dx.doi.org/10.1080/10426500600862977

[35] Quiroga, J.; Portilla, J.; Abonía, R.; Insuasty, B.; Nogueras, M.; Cobo, J. Regioselective synthesis of novel substituted pyrazolo[1,5-a]pyrimidines under solvent-free conditions. *Tetrahedron Lett.,* **2008**, *49*(43), 6254-6256. http://dx.doi.org/10.1016/j.tetlet.2008.08.044

[36] Dabiri, M.; Arvin-Nezhad, H.; Khavasi, H.R.; Bazgir, A. A novel and efficient synthesis of pyrimido[4,5-d]pyrimidine-2,4,7-trione and pyrido[2,3-d:6,5-d] dipyrimidine-2,4,6,8-tetrone derivatives. *Tetrahedron,* **2007**, *63*(8), 1770-1774. http://dx.doi.org/10.1016/j.tet.2006.12.043

[37] Polshettiwar, V.; Varma, R.S. Biginelli reaction in aqueous medium: A greener and sustainable approach to substituted 3,4-dihydropyrimidin-2(1H)-ones. *Tetrahedron Lett.,* **2007**, *48*(41), 7343-7346. http://dx.doi.org/10.1016/j.tetlet.2007.08.031

[38] Kategaonkar, A.H.; Sadaphal, S.A.; Shelke, K.F.; Shingate, B.B.; Shingare, M.S. Microwave assisted synthesis of pyrimido[4,5-d]pyrimidine derivatives in dry media. *Ukr. Bioorg. Acta,* **2009**, *1*, 1-7.

[39] Mario, L.A.; Vargas, D.; Francisco, L.A.; Julio, G.M.A. Ethyl (S)-2-Benzamido-5-[(4,6-dimethylpyrimidin-2-yl) amino]pentanoate. *Molbank,* **2020**, *4*(M1166), 1-5.

[40] Hassan, S.; Arman, S.S.; Ayoob, B. Three-component process for the synthesis of 4-amino-5-pyrimidinecarbonitriles under thermal aqueous conditions or microwave irradiation. *ARKIVOC,* **2008**, (ii), 115-123.

[41] Shi, F.; Ma, N.; Zhou, D.; Zhang, G.; Chen, R.; Zhang, Y.; Tu, S. Green approach to the Synthesis of polyfunctionalized pyrazolo[4′,3′:5,6] pyrido[2,3-d]pyrimidines *via* microwave-assisted multicomponent reactions in water without catalyst. *Synth. Commun.,* **2010**, *40*(1), 135-143. http://dx.doi.org/10.1080/00397910902962860

[42] Jain, S.K.; Chaudhari, S.K.; More, N.S.; More, K.D.; Wakedkar, S.A.; Kathiravan, M.K. A facile synthesis of 2-amino-5-cyano-4,6-disubstituted-pyrimidines under MWI. *Int. J. Org. Chem. (Irvine),* **2011**, *1*(2), 47-52. http://dx.doi.org/10.4236/ijoc.2011.12009

[43] Borisagar, M.; Joshi, K.; Ram, H.; Vyas, K.; Nimavat, K. A one-pot microwave irradiation synthesis of 1,2,4-triazolo[1,5-a]pyrimidines. *Acta Chim. Pharm. Indica,* **2012**, *2*(2), 101-105.

[44] Nandini, P.; Krishnakant, W.; Dileep, K. Microwave promoted solvent-free Biginelli reaction for the one pot synthesis of dihydropyrimidin-2-(1*H*)-ones catalyzed by sulfamic acid. *Asian J. Chem.,* **2011**, *23*(12), 5217-5219.

[45] Singhal, S.; Joseph, J.K.; Jain, S.L.; Sain, B. Synthesis of 3,4-dihydro-pyrimidinones in the presence of water under solvent free conditions using conventional heating, microwave irradiation/ultrasound. *Green Chem. Lett. Rev.,* **2010**, *3*(1), 23-26. http://dx.doi.org/10.1080/17518250903490126

[46] Dehbi, O.; Ishak, E.A.; Bakht, M.A.; Geesi, M.H.; Alshammari, M.B.; Kaiba, V.C.A.; Lazar, S.; Riadi, Y. Water-mediated synthesis of disubstituted 5-aminopyrimidines from vinyl azides under microwave irradiation. *Green Chem. Lett. Rev.,* **2018**, *11*(2), 62-66. http://dx.doi.org/10.1080/17518253.2018.1437225

[47] Yildirim, M.; Celikel, D.; Durust, Y.; Knight, D.W.; Kariuki, B.M. A rapid and efficient protocol for the synthesis of novel nitrothiazolo[3,2-c]pyrimidines *via* microwave-mediated Mannich cyclisation. *Tetrahedron,* **2014**, *70*(12), 2122-2128. http://dx.doi.org/10.1016/j.tet.2014.02.003

[48] Cudden, C.M. *Analgesics and anti-inflammatory drugs*; Toxicology Cases for the Clinical and Forensic Laboratory, **2020**, pp. 67-74.

[49] Chaudhary, A.; Sharma, P.K.; Verma, P.; Kumar, N.; Dudhe, R. Microwave assisted synthesis of novel pyrimidine derivatives and investigation of their analgesic and ulcerogenic activity. *Med. Chem. Res.,* **2012**, *21*(11), 3629-3645. http://dx.doi.org/10.1007/s00044-011-9907-7

[50] Bhatewara, A.; Jetti, S.R.; Kadre, T.; Paliwal, P.; Jain, S. Microwave assisted synthesis and biological evaluation of dihydropyrimidinone derivatives as anti-inflammatory, antibacterial, and antifungal agents. *Int. J. Med. Chem.,* **2013**, *197612*, 1-5.

[51] Patil, P.A.; Bhole, R.P.; Chikhale, R.V.; Bhusari, K.P. Synthesis of 3,4-dihydropyrimidine-2(1H)-one derivatives using microwave for their biological screening. *Int. J. Chemtech Res.,* **2009**, *1*(2), 373-384.

[52] Inoyama, D.; Paget, S.D.; Russo, R.; Kandasamy, S.; Kumar, P.; Singleton, E.; Occi, J.; Tuckman, M.; Zimmerman, M.D.; Ho, H.P.; Perryman, A.L.; Dartois, V.; Connell, N.; Freundlich, J.S. Novel pyrimidines as antitubercular agents. *Antimicrob. Agents Chemother.,* **2018**, *62*(3), e02063-e17. http://dx.doi.org/10.1128/AAC.02063-17 PMID: 29311070

[53] Patel, N.; Pathan, S.; Soni, H.I. 3,4-dihydropyrimidin-2(1h)-one analogues: Microwave irradiated synthesis with antimicrobial and antituberculosis study. *Curr. Microw. Chem.,* **2019**, *6*(1), 61-70. http://dx.doi.org/10.2174/2213335606666190724093305

[54] Liu, P.; Yang, Y.; Tang, Y.; Yang, T.; Sang, Z.; Liu, Z.; Zhang, T.; Luo, Y. Design and synthesis of novel pyrimidine derivatives as potent antitubercular agents. *Eur. J. Med. Chem.,* **2019**, *163*, 169-182. http://dx.doi.org/10.1016/j.ejmech.2018.11.054 PMID: 30508666

[55] Mohan, S.B.; Ravi Kumar, B.V.V.; Dinda, S.C.; Naik, D.; Prabu Seenivasan, S.; Kumar, V.; Rana, D.N.; Brahmkshatriya, P.S. Microwave-assisted synthesis, molecular docking and antitubercular activity of 1,2,3,4-tetrahydropyrimidine-5-carbonitrile derivatives. *Bioorg. Med. Chem. Lett.,* **2012**, *22*(24), 7539-7542. http://dx.doi.org/10.1016/j.bmcl.2012.10.032 PMID: 23122523

[56] Patil, D.R.; Salunkhe, S.M.; Deshmukh, M.B.; Anbhule, P.V. One step synthesis of 6-amino-5-cyano-4-phenyl-2-mercapto pyrimidine using phosphorus pentoxide. *The Open Cat. J,* **2010**, *3*, 83-86.

[57] Zhuang, J.; Ma, S. Recent development of pyrimidine-containing antimicrobial agents. *ChemMedChem,* **2020**, *15*(20), 1875-1886. http://dx.doi.org/10.1002/cmdc.202000378 PMID: 32797654

[58] Khatri, T.T.; Shah, V.H. Effective microwave synthesis of bioactive thieno[2,3-d]pyrimidines. *J. Chil. Chem. Soc.,* **2017**, *62*(1), 3354-3358. http://dx.doi.org/10.4067/S0717-97072017000100010

[59] Youssef, A.M.S.; Fouda, A.M.; Faty, R.M. Microwave assisted synthesis of some new thiazolopyrimidine and pyrimidothiazolopyrimido-pyrimidine derivatives with potential antimicrobial activity. *Chem. Cent. J.*, **2018**, *2018*, 2-14.

[60] Sureja, D.K.; Dholakia, S.P.; Vadalia, K.R. Synthesis of some novel pyrazolo[3,4-*d*] pyrimidin-4(5*H*)-one derivatives as potential antimicrobial agent. *J. Pharm. Bioallied Sci.,* **2016**, *8*(4), 321-326. http://dx.doi.org/10.4103/0975-7406.199337 PMID: 28216957

[61] Panneerselvam, T.; Reddy, M.J. Microwave assisted synthesis and antimicrobial evaluation of novel substituted thiosemicarbazide derivatives of pyrimidine. *J. Het. Chem.,* **2020**, *2020*, 1-7.

[62] Esvet, A.; Ismet, B.; Inci, A.; Baris, A.; Ela, Y. Microwave assisted synthesis of tetrahydropyrimidines *via* multicomponent reactions and evaluation of biological activities. *Lett. Org. Chem.,* **2011**, *8*(9), 663-667. http://dx.doi.org/10.2174/157017811799304287

[63] Karthic, R.; Andrews, B.; Subramani, K. Microwave assisted synthesis and antifungal studies of 5-amino thiadiazole substituted pyrimidine compounds. *Asian J. Res. Chem,* **2017**, *10*(2), 119-123. http://dx.doi.org/10.5958/0974-4150.2017.00018.9

[64] Chandrasekaran, S.; Nagarajan, S. Microwave-assisted synthesis and anti-bacterial activity of some 2-amino-6-aryl-4-(2-thienyl)pyrimidines. *Farmaco,* **2005**, *60*(4), 279-282. http://dx.doi.org/10.1016/j.farmac.2005.01.012 PMID: 15848201

[65] Elkanzi, N.A.A.; Bakr, R.B. Microwave assisted, antimicrobial activity and molecular modeling of some synthesized newly pyrimidine derivatives using 1,4- diazabicyclo[2.2.2]octane as a catalyst. *Lett. Drug Des. Discov.,* **2020**, *17*(12), 1538-1551. http://dx.doi.org/10.2174/1570180817999200802033351

[66] Bhat, A.R.; Shalla, A.H.; Dongre, R.S. Microwave assisted one-pot catalyst free green synthesis of new methyl-7-amino-4-oxo-5-phenyl-2-thioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carboxylates as potent *in vitro* antibacterial and antifungal activity. *J. Adv. Res.,* **2015**, *6*(6), 941-948. http://dx.doi.org/10.1016/j.jare.2014.10.007 PMID: 26644932

[67] Bansal, S.; Chaudhary, A.N.; Kothiyal, P. Microwave assisted synthesis and antibacterial activity of pyrimidine derivatives. *Int. J. Pharm. Pharm. Sci.,* **2013**, *5*(S1), 346-348.

[68] Stahl, S.M. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications,* 3rd ed; Cambridge University Press: New York, **2008**, pp. 327-451.

[69] Sharma, C.; Yerande, S.; Chavan, R.; Bhosale, A.V. Synthesis of thienopyrimidines and their antipsychotic activity. *E.-J. Chem.,* **2010**, *7*(2), 655-664. http://dx.doi.org/10.1155/2010/369141

[70] Meegan, M.J.; O'Boyle, N.M. Anticancer drugs. *Pharmaceuticals (Basel),* **2019**, *12*(3), 134. http://dx.doi.org/10.3390/ph12030134 PMID: 31527393

[71] Ahmad, M.R.; Sastry, V.G.; Prasad, Y.R.; Khan, M.H.R.; Bano, N.; Anwar, S. Conventional and microwave assisted synthesis of 2-amino-4,6-diarylpyrimidine derivatives and their cytotoxic, anti-oxidant activities. *Eur. J. Chem.,* **2012**, *3*(1), 94-98. http://dx.doi.org/10.5155/eurjchem.3.1.94-98.523

[72] Jainey, P.J.; Ishwar, B.K. Microwave assisted synthesis of novel pyrimidines bearing benzene sulfonamides and evaluation of anticancer and antioxidant activities. *Asian J. Pharm. Clin. Res.,* **2014**, *7*(S1), 111-114.

[73] Hosamani, K.M.; Reddya, D.S.; Devarajegowda, H.C. Microwave-assisted synthesis of new fluorinated coumarin–pyrimidine hybrids as potent anticancer agents, their DNA cleavage and X-ray crystal studies. *RSC Advances,* **2015**, *5*(15), 11261-11271. http://dx.doi.org/10.1039/C4RA12222D

[74] Singh, N.; Kshirsagar, S.S.; Nimje, H.M.; Chaudhari, P.S. Microwave assisted synthesis of 4-substituted 1,2,3,4-tetrahydropyrimidine derivatives. *Int. J. Pharm. Pharm. Sci.,* **2011**, *3*(1), 109-111.

[75] Sandhu, J.S.; Dhruv, K. Microwave enhanced, solvent free green protocol for the production of 3,4-dihydropyrimidine-2-(1*H*)-ones using $AlCl_3.6H_2O$ as a catalyst. *Indian J. Chem.,* **2010**, *49B*, 360-363.

[76] Aceves, J.; Erlij, D.; Martínez-Marañón, R. The mechanism of the paralysing action of tetramisole on Ascaris somatic muscle. *Br. J. Pharmacol.,* **1970**, *38*(3), 602-607. http://dx.doi.org/10.1111/j.1476-5381.1970.tb10601.x PMID: 5445688

[77] Sahoo, B.M.; Rajeswari, M.; Panda, J.; Sahoo, B. Green Expedient Synthesis of Pyrimidine derivatives *via* chalcones and evaluation of their anthelmintic activity. *Ind. J. Pharmac. Edu. Res.,* **2017**, *51*(4S), 136-143. http://dx.doi.org/10.5530/ijper.51.4s.101

[78] Brossi, A.; Venugopalan, B.; Dominguez Gerpe, L.; Yeh, H.J.; Flippen-Anderson, J.L.; Buchs, P.; Luo, X.D.; Milhous, W.; Peters, W. Arteether, a new antimalarial drug: Synthesis and antimalarial properties. *J. Med. Chem.,* **1988**, *31*(3), 645-650. http://dx.doi.org/10.1021/jm00398a026 PMID: 3279208

[79] Rathwa, S.K.; Bhoi, M.N.; Mayuri, A.; Borad, K.D.; Patel, D.P.; Rajani, S.D.; Patel, H.D. Microwave assisted synthesis, biological characterization and docking studies of pyrimidine derivatives. *Curr. Microw. Chem.,* **2016**, *3*(3), 178-186. http://dx.doi.org/10.2174/2213335602666150728205457

[80] Prasad, P.; Kalola, A.G.; Patel, M.P. Microwave assisted one-pot synthetic route to imidazo[1,2-a]pyrimidine derivatives of imidazo/triazole clubbed pyrazole and their pharmacological screening. *New J. Chem.,* **2018**, *42*(15), 12666-12676. http://dx.doi.org/10.1039/C8NJ00670A

[81] Hollander, P. Current and future therapeutic options for treating postprandial glucose. *Curr. Opin. Endocrinol. Diabetes,* **1998**, *5*(4), 268-274. http://dx.doi.org/10.1097/00060793-199811000-00006

[82] Lalpara, J.N.; Hadiyal, S.D.; Radia, A.J.; Dhalani, J.M.; Dubal, G.G. Design and rapid microwave irradiated one-pot synthesis of tetrahydropyrimidine derivatives and their screening *in-vitro* anti-diabetic activity. *Polycycl. Arom. Comp,* **2020**, *2020*, 1-15.

[83] Gejalakshmi, S.; Harikrishnan, N.; Thillai, G.G.E.; Divyasri, A. Microwave assisted synthesis of tetrahydropyrmidine and *in-silico* screening of antidiabetic drug. *Int. J. Curr. Pharm. Res.,* **2020**, *12*(1), 10-13.

[84] Leonetti, F.; Capaldi, C.; Carotti, A. Microwave-assisted solid phase synthesis of Imatinib, A blockbuster anticancer drug. *Tetrahedron Lett.,* **2007**, *48*(19), 3455-3458. http://dx.doi.org/10.1016/j.tetlet.2007.03.033

[85] Baxendale, I.R.; Ley, S.V. Polymer-supported reagents for multi-step organic synthesis: Application to the synthesis of sildenafil. *Bioorg. Med. Chem. Lett.,* **2000**, *10*(17), 1983-1986. http://dx.doi.org/10.1016/S0960-894X(00)00383-8 PMID: 10987432

[86] Xu, L.; Zhang, Y.; Dai, W.; Wang, Y.; Jiang, D.; Wang, L.; Xiao, J.; Yang, X.; Li, S. Design, synthesis and SAR study of novel trisubstituted pyrimidine amide derivatives as CCR4 antagonists. *Molecules,* **2014**, *19*(3), 3539-3551. http://dx.doi.org/10.3390/molecules19033539 PMID: 24662072

[87] Zhou, H.; Che, X.; Bao, G.; Na, W.; Xu, B. Design, synthesis and structure-activity relationship study of pyrimidine-fused diazepine derivatives as L3MBTL3 inhibitors. *Youji Huaxue,* **2016**, *36*(12), 2948-2959. http://dx.doi.org/10.6023/cjoc201607001

[88] Rajeev, K.; Tyagi, M.; Sharma, A.K. Current status and future scenario of pyrimidine derivatives having antimicrobial potential. *Pharm. Chem.,* **2014**, *6*(4), 298-320.

[89] de la Hoz, A.; Díaz-Ortiz, A.; Prieto, P. Microwave assisted green organic synthesis, in alternative energy sources for green chemistry. In: *Alternative Energy Sources for Green Chemistry*; Royal Society of Chemistry: USA, **2016**; pp. 1-33. http://dx.doi.org/10.1039/9781782623632-00001

[90] Then, R.L. History and future of antimicrobial diaminopyrimidines. *J. Chemother.,* **1993**, *5*(6), 361-368. http://dx.doi.org/10.1080/1120009X.1993.11741082 PMID: 8195827

[91] Yadav, P.; Shah, K. An overview on synthetic and pharmaceutical prospective of pyrido[2,3-*d*]pyrimidines scaffold. *Chem. Biol. Drug Des.,* **2021**, *97*(3), 633-648. http://dx.doi.org/10.1111/cbdd.13800 PMID: 32946161

[92] Shilpa, C.; Dipak, S.; Vimukta, S.; Arti, D. Microwave and conventional synthesis of pyrimidine derivatives and their pharmacological activity-A review. *J. Pharm. Biomed. Sci.,* **2012**, *21*(10), 1-11.