Recent Approaches to the Synthesis of Medicinally Potent Pyrimidine Derivatives using Microwave: A Review

Sinderpal Kabalsingh Tank[ab]

[a]*Department of Chemistry, Sant Baba Bhag Singh University,Jalandhar, India*

[b]*Department of Chemistry, Kanya Maha Vidyalaya, Jalandhar, India*

ABSTRACT:

Syntheses of medicinally potent pyrimidine derivatives are the most significant tasks in N-heterocyclic chemistry because these compounds have proved to be very attractive and useful for the design of new molecular frameworks of potential drugs with varying pharmacological activities.Among the heterocyclic compounds, pyrimidines occupy a central position due to their presence in genetic material of cells. This article aims to review the work reported on the synthesis of pyrimidine derivatives using microwave, the chemistry and the biological activities of pyrimidines(2009 to 2017).

Keywords: Pyrimidines, synthesis, microwave, biological activity.

Introduction

Heterocyclic chemistry is an important branch of organic chemistry accounting for nearly one-third of modern publications [1]. Heterocyclic compounds have vital role in our biological system. They are an integral part of many pharmacologically active molecules, natural products and nucleic acids. The base pair of DNA&RNA (guanine, cytosine, adenine and thymine) are also made up of heterocyclic compounds like purine, pyrimidine etc.Pyrimidine (Fig. 1) is the parent ring system of a variety of substances that play vital roles in biological processes. This structural design also has a subset of a large number of pharmaceutical agents and naturally occurring substances such as vitamins, coenzymes, purines, pterins, nucleotides and nucleic acids. The properties of pyrimidines are governed to a large extent by the electron-attracting properties of the two nitrogen atoms; each of these reinforces the electronic effect of the other in the 2-, 4- and 6-positions.Therefore, electrophilic attack will be strongly hindered at these positions, and nucleophilic attack is stronglyfacilitated. The 5-position is affected only by the inductive effect of the two nitrogen atoms, thereby making this position susceptible to electrophilic attack. Pyrimidine derivatives have various therapeutic applications in medicinal chemistry. One anticipated reason for their activity is presence of a pyrimidine base in thymine, cytosine and uracil, which are essential building blocks of nucleic acids, DNA & RNA [2]. Number of chemical compounds consisting of pyrimidine as core nucleus are reported to be synthesized and evaluated for antihypertensive [3], anticancer [4], antimicrobial [5], antihyperglycemic [6], antiarrhythmic, anti-inflammatory [7], analgesic [8], antibacterial [9], anti-HIV [10] and antitubercular activity [11].

A major challenge of modern synthetic chemistry is to search the ways of developing and applying more efficiently and environmentally benign strategies for future sustainable growth[12]. In this context Green Chemistry has become a research field of great interest due to replacement with greener reagents and solvents instead of hazardous and toxic materials [13].

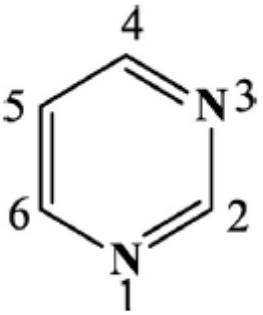
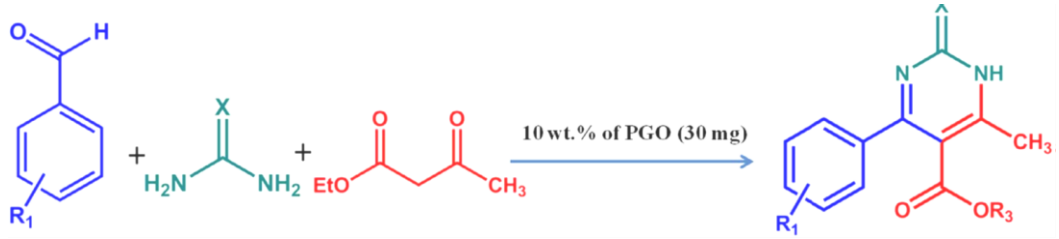


Fig. 1. Pyrimidine.

Now, green chemistry is a new and valuable strategy of looking at organic synthesis and the designing of drug molecules, offering considerable environmental and economic benefits over traditional synthetic processes[14]. The accomplishment of reactions in the presence of green mediums (use of recyclable ionic liquids, greenerand safer alternative solvents) or under solvent-free conditions, microwave and ultrasonic technologies are some of types of green synthetic strategies. In the last few years microwave assisted organic synthesis is gaining popularity as a non-conventional technique for rapid organic synthesis. Some interesting features of this method are the rapid reaction rates, simplicity, solvent-free conditions, the ease of work-up after the reaction, and better selectivity[15−17]. It has increased the safety of organic reactions. There is a rate acceleration of approximately 385 times under microwave conditions. It is said to be an eco- friendly method. Since there is decrease in heating time it effectively reduces the cost of fuel and minimizes environmental pollution [18, 19]. Microwave energy, however, heats the entire samples at once, eliminating hot spots and reducing reaction times, all of which results in larger, purer yields.

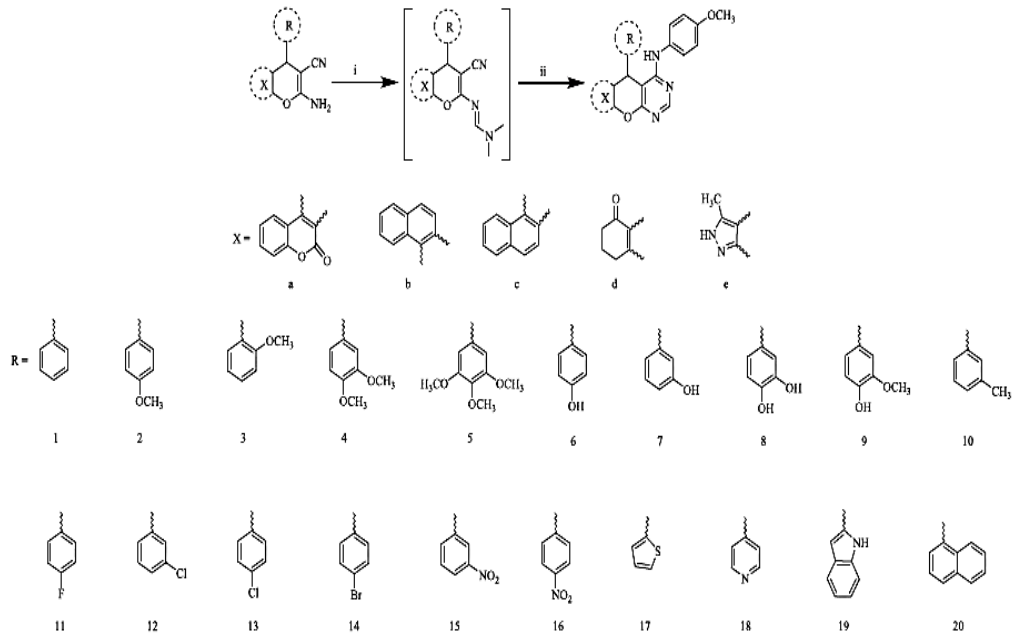
This review paper summarizes the synthesis of pyrimidine derivatives using non conventional microwave techniques,the chemistry and the biological activities of pyrimidines (from 2009 to 2017).

AcharyaL.,et.al[20]reported the microwave assisted synthesis of DHPM andDAPM (3,4-dihydropyrimidin-2(1H)-ones (DHPMs) and 4,6-diarylpyrimidones)(DAPM)molecules using phosphate functionalized GO (PGO) (phosphonated graphene oxide) as an efficient heterogeneous catalyst. The Pyrimidones synthesis was obtained via ternary condensation of urea, aldehydes, and 1, 3-dicarbonyl in the presence of PGO nanocatalyst (Scheme 1)



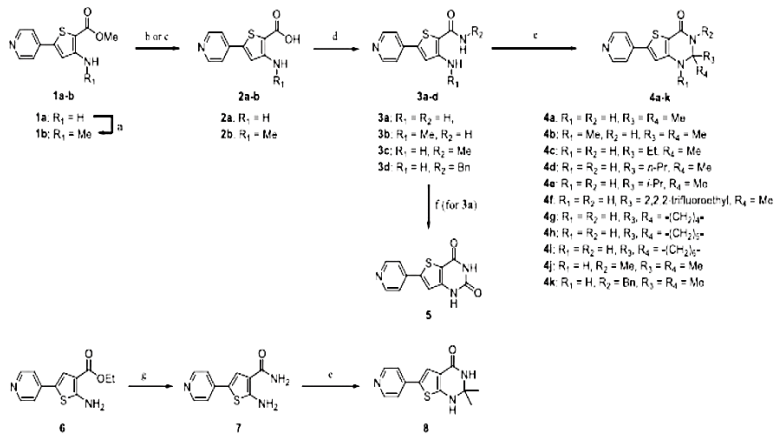
Scheme 1. A model reaction for the synthesis of 3,4-dihydropyrimidin-2(1H)-one.

Kaur Manroopraj et.al[21] reported synthesis ofpyrano[3,2-d]pyrimidines from malononitrile, aryl/heteroaryl aldehyde and CeH activated acidic compound in the presence of catalytic amounts of DMAP under microwave irradiation(Scheme 2).The pyrimidine derivatives were screened for effective xanthine oxidase (XO) enzyme inhibitors.Docking study were performed to investigate the recognition pattern between xanthine oxidase and the most potent XO inhibitor.



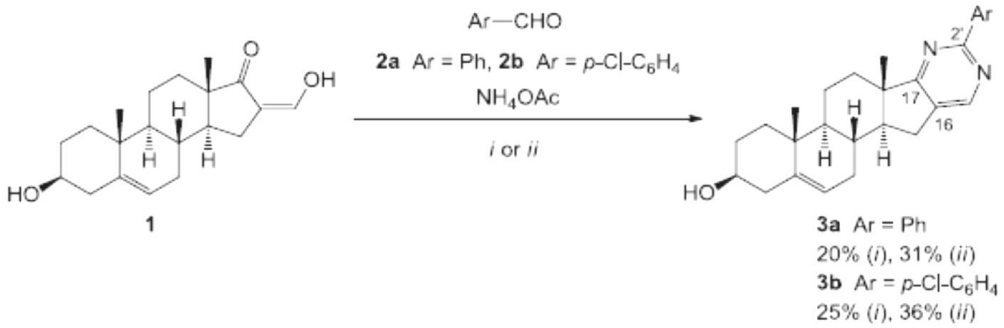
Scheme 2. Synthesis of fused pyrano[3,2-d]pyrimidine derivatives. Reagent and reaction condition: (i) DMF-DMA, stir, rt; (ii) p-anisidine, glacial acetic acid, reflux

Kurasawa Osamu et.al [22]reported synthesis of Dihydrothienopyrimidine derivatives possessing 4-pyridyl group as a hinge binder (4a–k, 5, 8) according to the procedure in Scheme3. After N-methylation of methyl 3- amino-5-(4-pyridyl)thiophene-2-carboxylate 1a, the esters 1a, b were then hydrolyzed under basic conditions to give the carboxylic acids 2a, b. Compounds 2a, b were condensed with appropriate amines to provide the corresponding amides 3a–d. Similarly, ethyl 2-amino-5-(4-pyridyl)thiophene-3-carboxylate 6 was converted to amide 7 in 38% yield by saponification and subsequent amidation. The aminothiophenecarboxamides 3a–d, 7 were reacted with various ketones in the presence of catalytic amount of p-toluenesulfonic acid to afford cyclized products 4a–k, 8 in 11–74% yields. Moreover, the amide 3a was subjected to ring-closure reaction using urea to yield thienopyrimidin-2,4-dione 5.Further structure-activity relationships(SARs), and biological effects of this chemical series was studied. Furthermore, difference in binding modes of a selected compound with Cdc7 and ROCK in docking models is discussed to elucidate high selectivity.

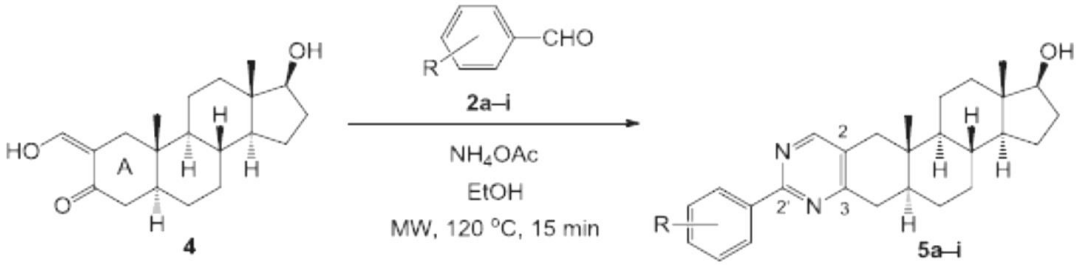


Scheme 3. Reagents and conditions: (a) NaH, MeI, DMF, 0 ?C to rt, 62%; (b) NaOH, MeOH–water, 70^{o}C, 92%; (c) LiOH, MeOH–water, 80^{o}C, quant.; (d) NH_4Cl or R_2NH_2, EDCI,HOBt, Et_3N, DMF, rt, 50–84%; (e) R_3COR_4, p-TsOH, H_2O, toluene or AcOH, 70–110^{o}C, 11–74%; (f) urea, 180^{o}C, 34%; (g) (1) LiOH, EtOH–water, 80^{o}C; (2) NH_4Cl, EDCI, HOBt, Et_3N, DMF, rt, 38%.

BajiÁdám, et.al [23]reported synthesis of novel ring D- and A-fused pyrimidines in the androstane series efficiently within 10-15 min in polar protic solvents under microwave irradiation via two kinds of multicomponent heterocyclization reactions followed by spontaneous or promoted oxidation (Scheme 4a and 4b). The synthesized compounds were tested in vitro on human cancer cell lines as well as on non-cancerous fibroblast cells by the MTT assay in order to investigate their biological effects. As a result of the pharmacological screen, a remarkable structure-function relationship was observed as the acetylated Biginelli products exhibited higher toxicity compared to the deacetylated version of each compound.

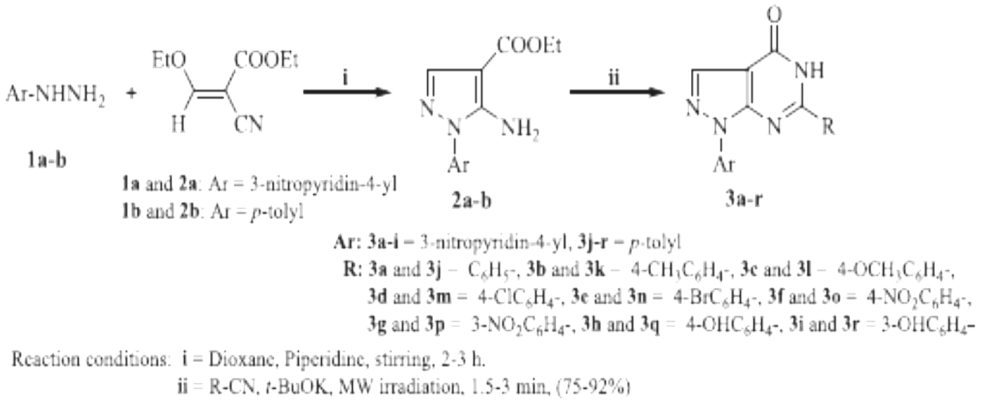


Scheme 4a: MW-assisted synthesis of ring D-fused arylpyrimidines in the androstane series. Reagents and conditions: 1:2:NH_4OAc = 1:2:2 (i) silica gel, MW, 120 °C, 6 min (solvent-free); (ii) EtOH, MW, 120 °C, 15 min.



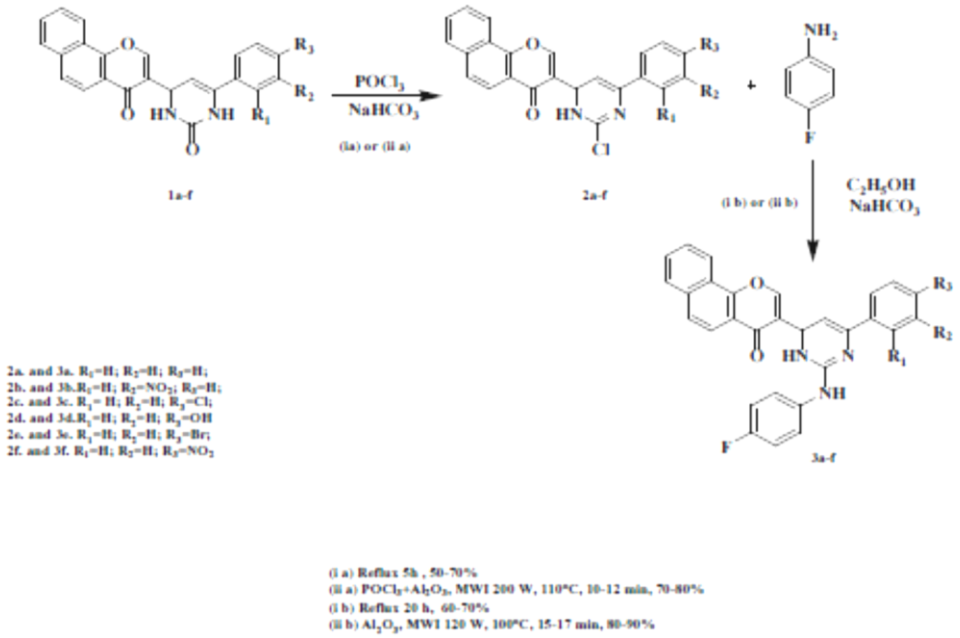
Scheme 4b: MW-assisted synthesis of ring A-fused arylpyrimidines in the androstane series

Sureja Dipen K. et.al [24]reported an efficient and solvent-free synthesis of some novel pyrazolo[3,4-d]pyrimidin-4(5H)-one derivatives under microwave irradiation by the reaction of ortho amino ester of 1-substituted pyrazole with different aromatic nitriles in the presence of potassium tert-butoxide. Furthermore, all the newly synthesized compounds have been screened in-vitro for their antimicrobial activities against S. aureus, B. subtilis, E. coli, P. aeruginosa, A. niger and C. albicans. All the compounds showed weak to good activity against all tested microorganisms.



Scheme 5: Synthetic route of pyrazolo[3,4-d]pyrimidin-4(5H)-one derivatives

LalaKundan, et.al [25]reported the microwave assisted synthesis of some new pyrimidine derivatives with benzochromone pyrimidine nucleus along with substituted phenyl ring. The synthesis of 3-(2-chloro-6-substituted phenyl-3,4-dihydropyrimidin-4-yl)-4H-benzo[h]chromen-4-one 2a-f and 3-(2-(4-fluorophenylamino)-6- substituted phenyl- 3,4-dihydropyrimidin-4-yl)-4H-benzo[h]chromen-4-one 3a-f is discussed. In first step, synthesis of 3-(2-chloro-6-substituted phenyl-3,4- dihydropyrimidin-4-yl)-4H-benzo[h]chromen-4-one 2a-f have been carried out from 4-(4-oxo-4H- benzo[h]chromen-3-yl)-6-substitued phenyl-3,4-dihydropyrimidin-2(1H)-one 1a-f by mixing with phosphoryl chloride($POCl_3$) and irradiating under microwave radiationat 175 W at 110 °C for 10-12 min. In step 2, a mixture of 3-(2-chloro-6- substituted phenyl-3,4-dihydropyrimidin-4-yl)-4H-benzo[h]chromen-4-one 2a-f (1mmol) and alumina and p-fluoro aniline (1 mmol) were irradiated under microwave irradiation at 175 W at 110 °C for 10-12 min (Scheme 6). These new compounds have been evaluated for their biological activities against various species of gram positive and gram negative bacteria and the compounds possessed promising antibacterial properties.

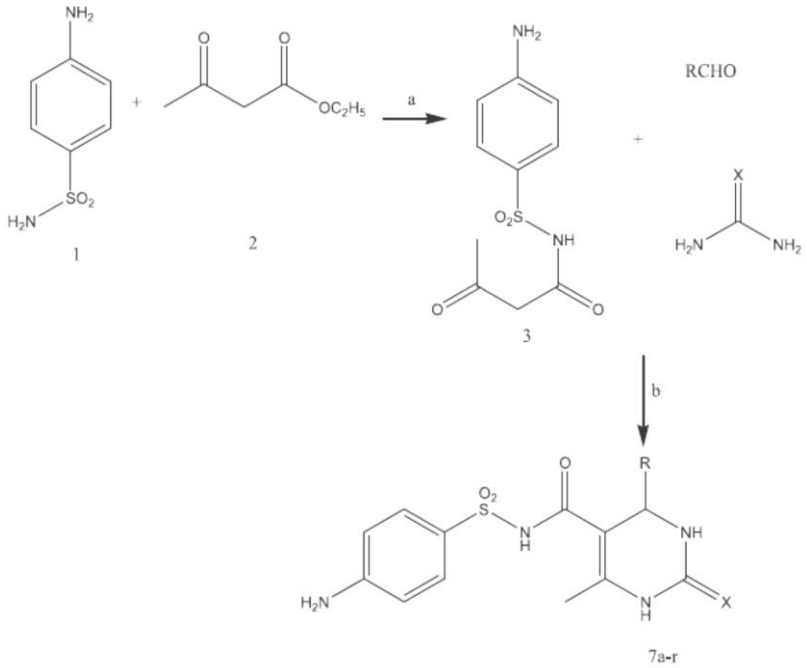


Scheme 6: Synthetic route of 3-(2-chloro-6-substituted phenyl-3,4-dihydropyrimidin-4-yl)-4H benzo[h]chromen-4-one 2a-f and 3-(2-(4-fluorophenylamino)-6- substituted phenyl- 3,4-dihydropyrimidin-4-yl)-4H-benzo[h]chromen-4-one 3a-f.

Moradi Leila et.al [26]reported the synthesis of 3,4- dihydropyridinone/thiones by reacting 0.025 g of Fe_3O_4@MSA (Fe_3O_4@meglumine sulfonic acid) with a homogeneous mixture of aldehyde (1 mmol), b-dicarbonyl (1 mmol) urea or thiourea (1.2 mmol) in a 5 ml of water/ethanol (1:1) under microwave irradiation (400 w, 80^oC)(Scheme 7).

Scheme 7: Synthesis of 3,4-DHPs using Fe_3O_4@MSA. L.

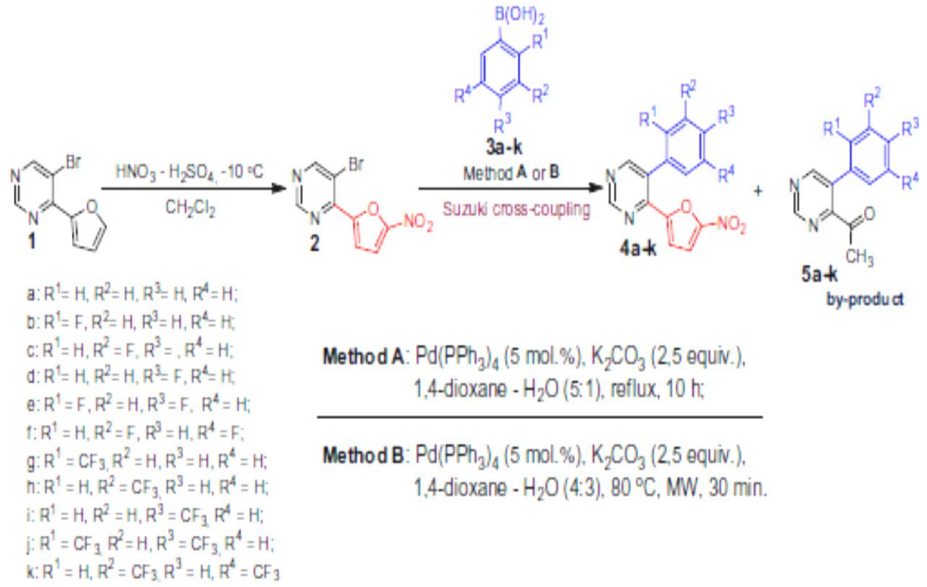
Elumalai Karthikeyan et.al [27]reported synthesis of series of novel sulphanilamide condensed 1,2,3,4-tetrahydropyrimidines by reacting N-[(4-aminophenyl) sulphonyl]-3-oxobutanamide with urea/thiourea and aryl aldehyde in the presence of a catalytic amount of laboratory prepared chlorosulphonic acid as an efficient catalystby reacting mixture of N-[(4-aminophenyl) sulphonyl]-3-oxobutanamide (0.005 M), urea/thiourea (0.0075 M), and aryl aldehyde (0.005 M) with a catalytic amount of chlorosulphonic acid in 10 ml of ethanol and subjecting to microwave irradiation (300 W) for 14 min with 10 s intervals (Scheme 8). The synthesized compounds were evaluated for antimicrobial activity against the Gram-positive bacteria Bacillus subtilis and the Gram- negative bacteria Escherichia coli and for cytotoxicity against Vero cells. These compounds exhibited weak, moderate, or high antimicrobial activities and cytotoxicity.



Scheme 8: Synthesis of compounds (7sa-r). Reagents and conditions: (a) reflux 2.5 h, catalytic amount of anhydrous $K_2CO_3$and 10 ml of ethanol (95%);(b) C_2H_5OH, chloro sulphonic acid, and microwave irradiation (300 W) for 14 min.

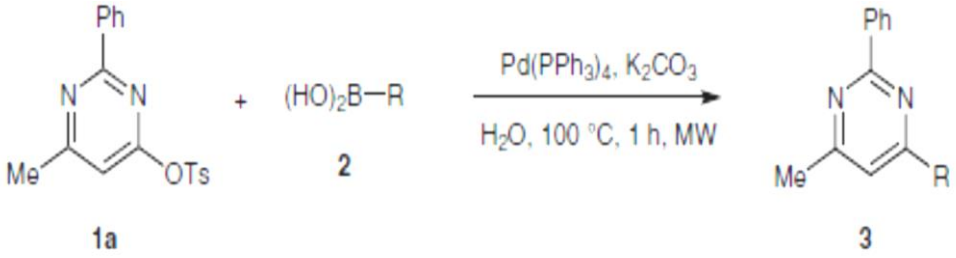
Verbitskiy Egor V. et.al [28]reported synthesis of 5-aryl-4-(5-nitrofuran-2-yl)-pyrimidines by reaction of 5-bromo-4-(5-nitrofu- ran-2-yl)-pyrimidine (2) with the corresponding boronic acid (3a–k) under microwave irradiation in 1,4-dioxane- H_2O (4:3) in the presence of K_2CO_3 and $Pd(PPh_3)_4$, as catalyst (Scheme 9, method B). All synthesized compounds were screened in vitro for their antibacterial activities against twelve various bacterial

strains. It was demonstrated that some of these compounds exhibited significant antibacterial activities against strains Neisseria gonorrhoeae and Staphylococcus aureus, comparable and even higher with that commercial drug Spectinomycin.



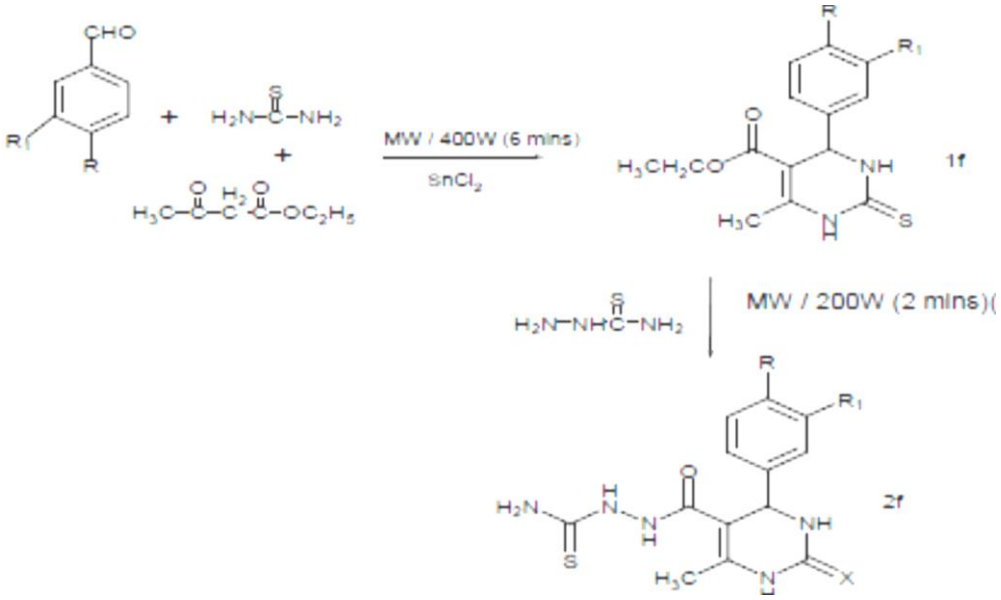
Scheme 9 : Synthesis of 5-aryl-4-(5-nitrofuran-2-yl)-pyrimidines (4a–k)

AguilarRodríguez, et.al [29]reported the palladium catalysed Suzuki–Miyaura coupling reaction of 4-pyrimidyl tosylates with aryl, heteroaryl and alkyl boronic acids. The reaction provided 4-substituted pyrimidines in good-to-excellent yields after one-hour microwave irradiation in water at 100 °C.(Scheme 10)



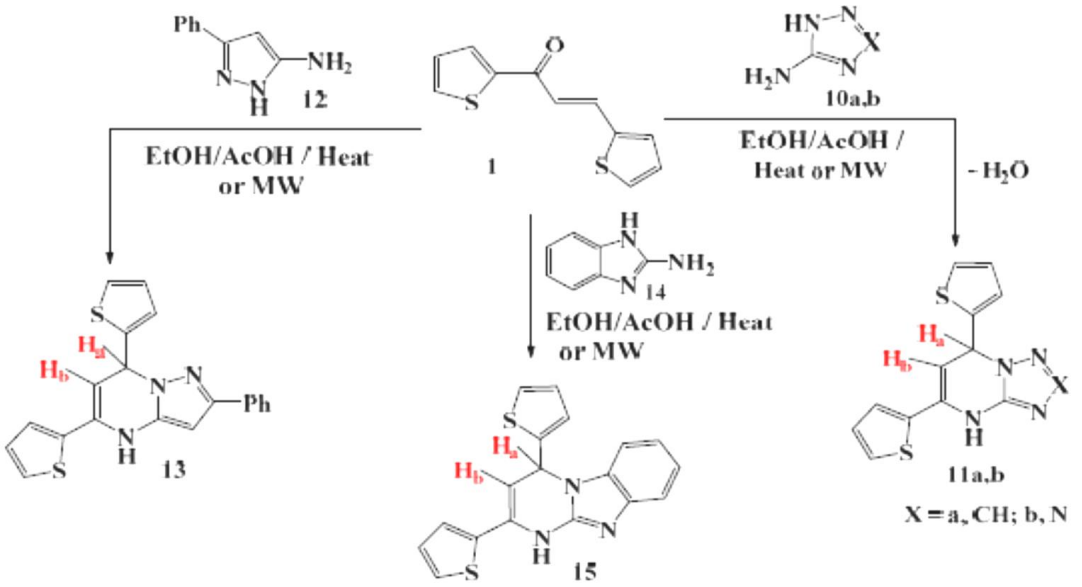
Scheme 10: Suzuki–Miyaura coupling of 4-pyrimidyl tosylate 1 with various aryl and heteroaryl boronic acids

Karthic R, et.al [30]reported synthesis of 5-(5-amino-1,3,4-thiadiazol-2yl)-3,4-dihydro-6-methyl-4-phenylpyrimidin- 2(1H)-thione (3f-j)(Scheme 11). Compound 1 was converted to carbothiamide 2 by reacting compound 1 with thiosemicarbazide in catalytic amount of acetone is irradiated with help of domestic microwave oven (200W) for 2 minutes. The compound 2 was converted to corresponding thiadiazole 3 by treatment with conc.H_2SO_4 and NH_3. Few of these Pyrimidine derivatives had been evaluated for their possible antibacterial activity. Most of the tested compounds showed significant antibacterial activity



Scheme 11: Synthesis of 5-(5-amino-1,3,4-thiadiazole-2-yl)-3,4- dihydro-6-methyl-4-Phenyl pyrimidin-2(1H)-thione (3f-j)

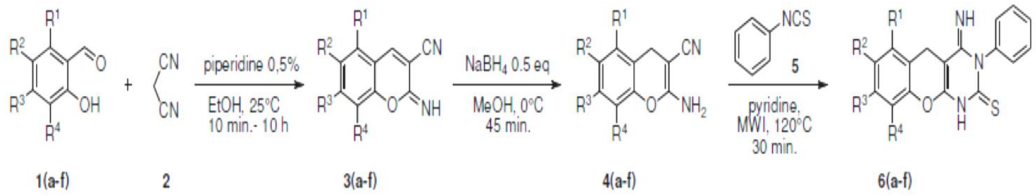
GomhaSobhi M., et.al [31]reported synthesis of Azolopyrimidines 11a,b, 13, and 15 via the reaction of chalcone 1 with heterocyclic amines 10a,b, 12, and 14 in ethanol in the presence of catalytic amount of AcOH using both thermal amines 10a,b, 12, and 14 in ethanol in the presence of catalytic amount of AcOH using both heating and microwave irradiation for comparison (Scheme 12). Their pharmacological activity toward bacteria and fungi inhibition was screened and compared to the references Chloramphenicol and Trimethoprim/sulphamethoxazole. The antimicrobial results of the investigated compounds revealed promising results and some derivatives have activities similar to the references used.



Scheme 12: Synthesis of azolopyrimidine derivatives 11a,b, 13 and 15.

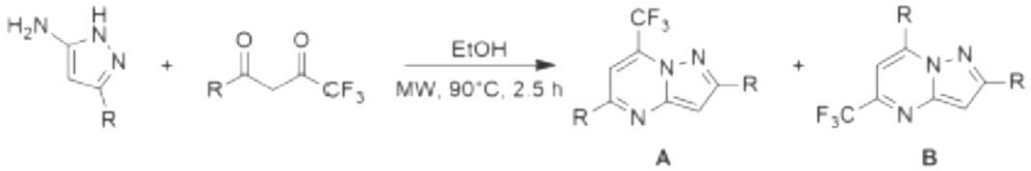
Bouattour Ali et.al [32]reported synthesis of new 4-imino-3,4-dihydro-1H-chromeno[2,3-d]pyrimidine-2(5H)-thiones 6(a-f) without substituent in C-5 position by carrying out reaction between 2-amino- 4H[1]chromene-3-carbonitrile 4 (2.5 mmol.), commercial phenylisothiocyanate 5 (338 mg, 2.5 mmol.) and dry pyridine (5 mL) and irradiating reaction mixture at 120°C for 30 min. under vigorous magnetic stirring.(Scheme 13). The

biological activities of the compounds were explored and found to have impact on protein kinase activity and antiproliferative activity with representative tumoral cell lines.



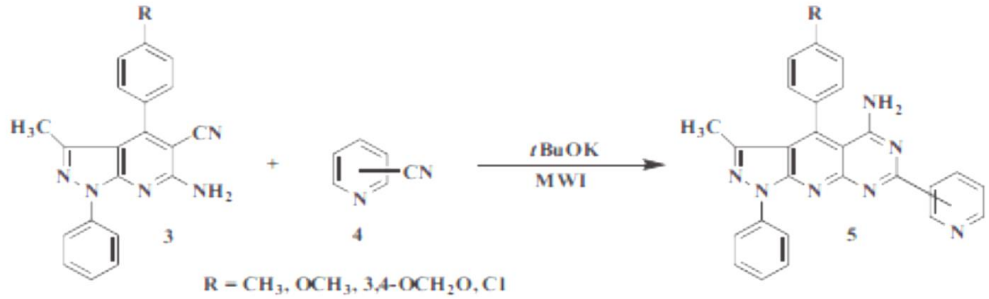
Scheme 13:Synthesis of 2-amino-4H-1-chromene-3-carbonitrile 4(a-f) and 4-imino-3-phenyl-3,4-dihydro-1H- chromeno[2,3-d]pyrimidine-2(5H)-thione 6(a-f) under microwave irradiation

Haucka Stefanie et.al [33]reported synthesis of 7-(trifluoromethyl) pyrazolo[1,5a]pyrimidine by reaction of 1,3-diketone (1 equiv) and the 3-(5)-aminopyrazole (1 equiv) in 3ml ethanol and heating to 90^{o}C via microwave irradiation for 2.5 h.(Scheme 14).Pyrazolo[1,5a]pyrimidine-basedFUBP1 inhibitor derived from medium throughput screening, was found to interfere with the binding of FUBP1 to its single stranded target DNA FUSE.



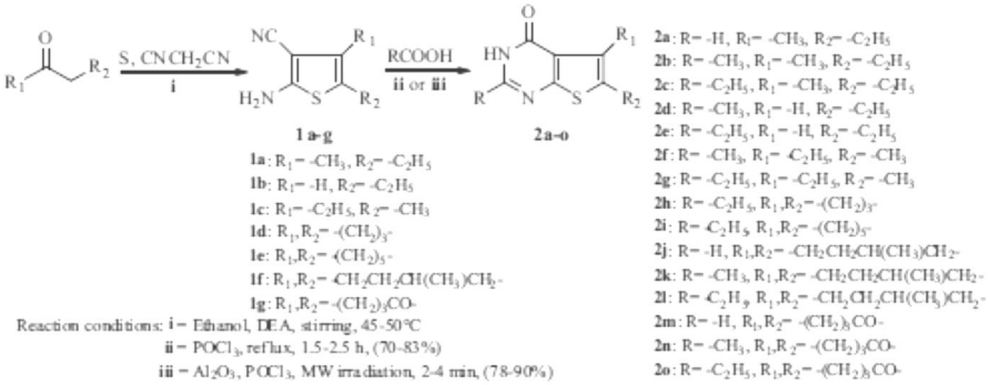
Scheme 14: Synthesis of pyrazolo[1,5a]pyrimidine derivatives

Acosta Paola et.al [34]reported synthesis of novel fused pyrazolo[40,30:5,6]pyrido[2,3-d]pyrimidines by reaction of mixture of ortho-aminonitrile 3(0.3 mmol), cyanopyridine 4(0.4 mmol) and tBuOK (10 mol%),and exposing to microwave irradiation from 1 to 6 min at 100 ^{o}C, a power of 250W and 30 PSI of pressure. (Scheme 15).All compounds were also tested for antifungal properties against two clinically important fungi; Candida albicans and Cryptococcus neoformans. Several compounds showed moderate activity against both fungi.



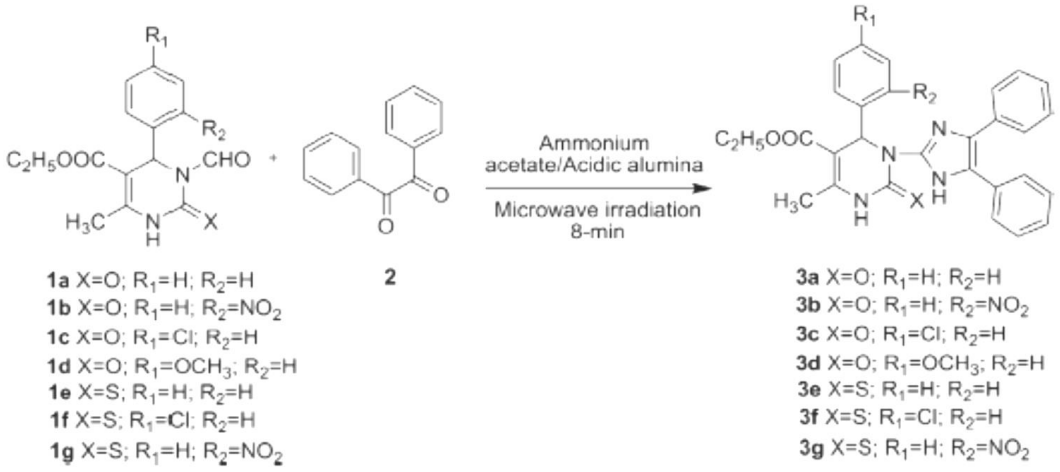
Scheme 15: Synthesis of pyrazolo[40,30:5,6]pyrido[2,3-d]pyrimidine derivatives 5

Sureja Dipen K. et.al [35]reported synthesis of thieno[2,3-d] pyrimidin-4(3H)-one derivatives (2a–o)by finely crushing mixture of 2-amino-4,5-substituted thiophene-3-carbonitrile (1a–g) (1 mM), appropriate aliphatic acid (2 mL) and alumina (0.5 g) and then adding phosphorus oxychloride (0.2 mL). The glass vial was then capped and microwaves were irradiated in a microwave oven at the power of 960W for 2-4 min. (Scheme 16). The compounds were screened in vitro to study their antimicrobial activity, which showed weak to moderate activity against all tested microorganisms.



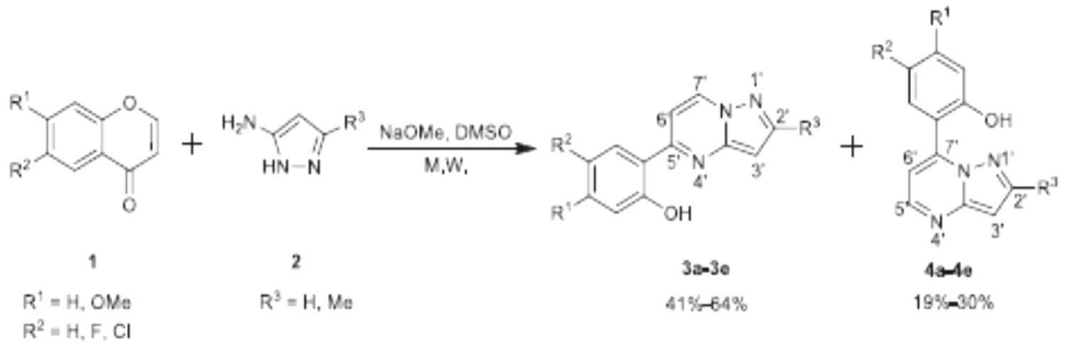
Scheme 16: Synthetic route of thieno[2,3-d] pyrimidin-4(3H)-one derivatives (2a–o)

Pathan Naziyanaz B. et.al [36]reported synthesis of substituted ethyl 1,2,3,6- tetrahydro-4-methyl-2-oxo/thioxo-6-phenyl-1-(4,5-diphenyl-1- H-imidazol-2-yl) pyrimidine-5-carboxylates 3a–g by mixing thoroughly substituted ethyl 1-formyl-1,2,3,6-tetrahydro-4-methyl-6-phe- nyl-2-oxo/thioxopyrimidine-5-carboxylates 1a–g (25 mmol), Benzil 2 (25 mmol, 5.25 g), ammonium acetate (10 g) and acidic alumina (1.0 g) in an agate mortar followed by addition of 2-drops of glacial acetic acid. The beaker was kept in a microwave oven at maximum power level for 8 min with intermittent interval. (Scheme 17).Synthesized compounds were screened for their in vitro antibacterial activity against Staphylococcus aureus, Salmonella typhi, Pseudomonas aurogenosa and Klebsiella pneumonae and also antifungal activity against the oppor- tunistic pathogens Candida albicans.



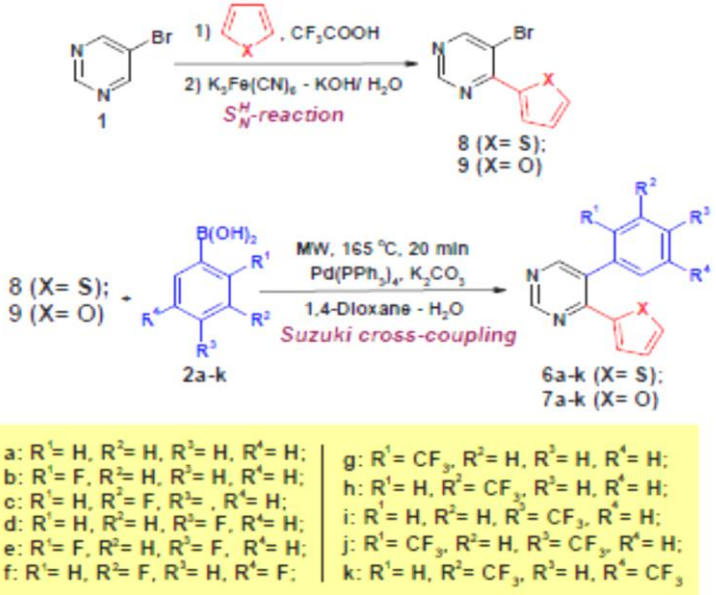
Scheme 17:Synthetic route ofethyl 1,2,3,6- tetrahydro-4-methyl-2-oxo/thioxo-6-phenyl-1-(4,5-diphenyl-1- H-imidazol-2-yl) pyrimidine-5-carboxylates 3a–g

Zhang Jin et.al [37]reported synthesis of 2-(pyrazolo[1,5-a] pyrimidin-5-yl)phenols (3) and 2-(pyrazolo[1,5-a]pyrimidin-5-yl) phenols (4) by dissolving chromone (1; 1 mmol), 3-aminopyrazole (2a; 1.5 mmol) or 3- amino-5-methyl pyrazole (2b; 2 mmol), and CH_3ONa (135 mg, 2.5 mmol) in dried DMSO (15 mL). The resulting mixture was heated under microwave irradiation for 10 min at 100^{o}C. (Scheme 18).The antifungal abilities of the obtained products 3 and 4 were evaluated against five phytopathogenic fungi (Cytospora sp., Colletotrichum gloeosporioides, Botrytis cinerea, Alternaria solani and Fusarium solani and exhibited good antifungal abilities against Colletotrichum gloeosporioides.



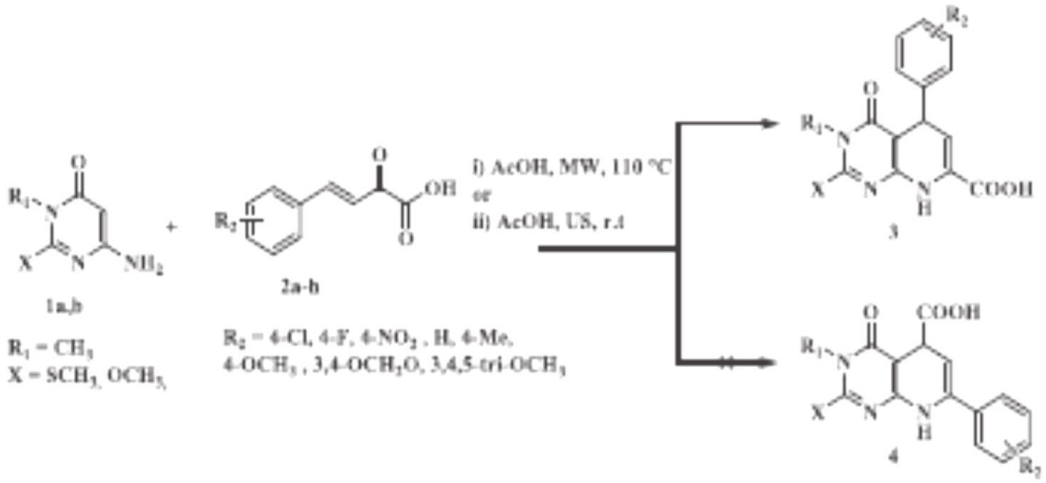
Scheme 18:General synthetic route for compounds 2-(pyrazolo[1,5-a] pyrimidin-5-yl)phenols (3) and 2-(pyrazolo[1,5-a]pyrimidin-5-yl) phenols (4)

VerbitskiyEgor V., et.al [38]reportedsynthesis of 4-(hetero)aryl-5-phenylpyrimidines 6a and 7a 5- (fluoroaryl)-4-(hetero)arylpyrimidines 6b-k and 7b-k by reaction of a solution ofK_2CO_3 (2.5 mmol) in 3 mL H_2O and mixture of 5-bromo-4-(thien-2-yl)pyrimidine (8) [or 5- bromo-4-(furan-2-yl)pyrimidine(9)] (0.5 mmol),the corresponding arylboronic acid (2a-k) (0.6 mmol) and Pd(PPh3)4 (29 mg, 5 mol %) in 1,4-dioxane (4 mL) and irradiating in a microwave apparatus at 165 °C (250 W) for 20 min. (Scheme 19). The antitubercular activity against Mycobacterium tuberculosis H37Rv has been explored. The outcome of the study disclose that, some of the compounds have showed promising activity in micromolar concentration against Mycobacterium tuberculosis H37Rv, Mycobacterium avium, Mycobacterium terrae, and multidrug-resistant strains isolated from tuberculosis patients in Ural region (Russia).



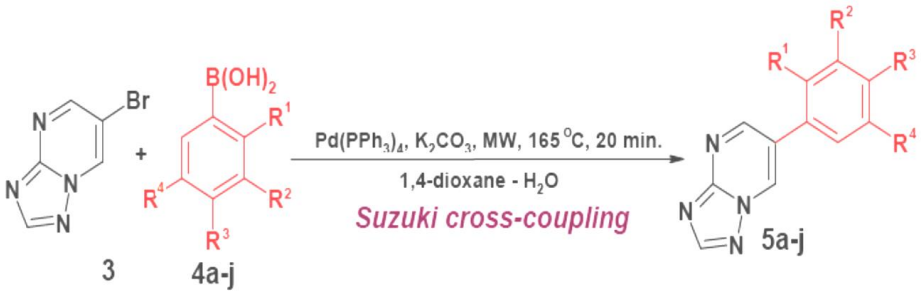
Scheme 19: Synthesis of 4-(hetero)aryl-5-phenylpyrimidines 6a and 7a 5- (fluoroaryl)-4-(hetero)aryl substituted pyrimidines 6b-k and 7b-k through the sequence of SNH and the Suzuki cross-coupling reactions

Quiroga Jairo et.al [39]reported synthesis of 5-aryl-4-oxo-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidine-7-carboxylic acids 3 by reacting the mixture of 6-aminopyrimidines 1 (1 mmol),arylidene pyruvic acid 2 (1 mmol) and AcOH (1 mL) in microwave for 4 min at 110^{o}C, power 100 W and pressure 30 psi (Scheme 20).The antioxidant properties, DPPH free radical scavenging, ORAC, and anodic potential oxidation of the new pyridopyrimidines were studied.



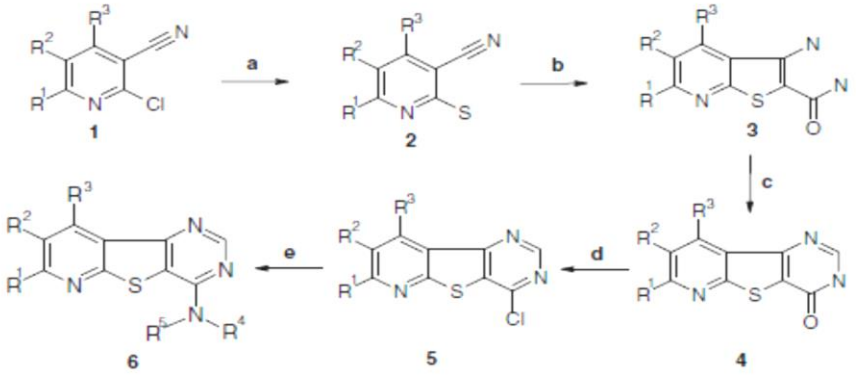
Scheme 20: Synthesis of 5-aryl-4-oxo-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidine-7-carboxylic acids 3.

Verbitskiy Egor V. et.al [40]reported synthesis of novel 6-fluoroaryl-[1,2,4]triazolo[1,5-a]pyrimidines by adding K_2CO_3 (346 mg, 2.5 mmol) in H_2O (3 mL) to a mixture of a 6-bromo-[1,2,4]triazolo[1,5-a]pyrimidine (3) (1.0 mmol), arylboronic (4a-j) acid (1.2 mmol) and $Pd(PPh_3)_4$ (58 mg, 5 mol %) in 1,4-dioxane (4 mL). The resulting mixture was irradiated in a microwave apparatus at 165 °C (250 W) for 20 min. to afford the desired cross-coupling products (5a-j) (Scheme 21). The antimicrobial activity of new compounds was evaluated in vitro against Mycobacterium tuberculosis H37Rv and gram-negative (Neisseria gonorrhoeae ATCC 49226) bacteria.



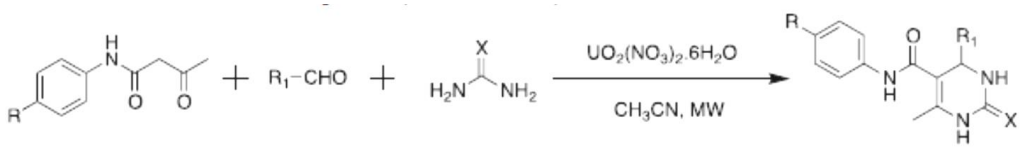
Scheme 21:Synthesis of 6-phenyl- and 6-(fluorophenyl)-[1,2,4]triazolo[1,5-a]pyrimidines (5a-j)

Zhao Chunlinet.al [41] reported synthesis of pyrido-thieno-pyrimidines by treatment of 2-chloro-nicotinonitrile 1 with sodium sulfidegenerated 2-mercapto-nicotinonitrile 2, which was reacted with 2-chloro-acetamide to give 3-amino-thieno-[2,3-b]-pyridine-2- carboxylic acid amide 3. Compound 4 was made by reacting 3 with trimethyl orthoformate with the catalysis of acid. Chlorination of 4 with phosphorus oxychloride followed by substitution of chlorine with amine NHR^4R^5 gave the desired product 6 (Scheme 22).



Scheme 22:Synthesis of pyrido-thieno-pyrimidines. Reagents and conditions: (a) Na_2S, t-Butanol, microwave, 150°C, 20 min; (b) chloroacetamide, K_2CO_3/EtOH, microwave, 120°C, 10 min; (c) $HC(OCH_3)_3$,CH_3COOH, microwave, 150°C, 10 min; (d) $POCl_3$, refluxing; (e) HNR^4R^5 microwave, 120°C, 20 min (when R^4 and R^5 are H, the reaction was run in a sealed tube at 80°C overnight).

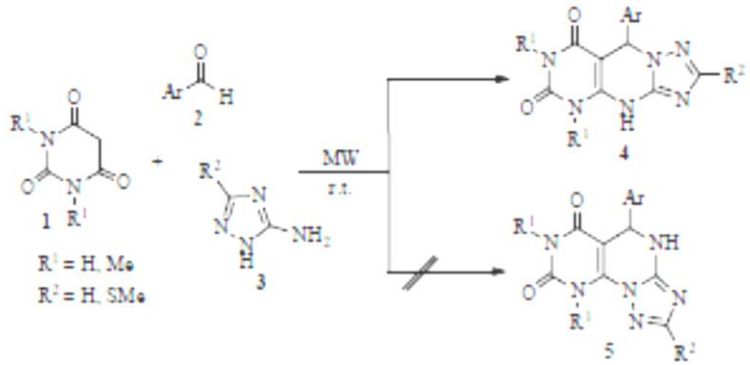
Venkatesan K. et.al [42]reported synthesis of 6-methyl-1,2,3,4-tetrahydro-N-aryl-2-thio/oxo-4-arylpyrimidine-5-carboxamide (4a-o) by reaction of mixture of aldehyde (1 mmol), acetoaetanilide (1 mmol), urea or thiourea (1.2 mmol), $UO_2(NO_3)_2.6H_2O$ (5 mol%) and acetonitrile (5 mL) and subjecting to microwave irradiation at an interval of 3 min at 160 W for about 15-18 min; varying time periods. (Scheme 23).The synthesized compounds 4a-o were screened for their in vitro antioxidant activity using DPPH free radical scavenging method and showed good antioxidant activity.



R = H, Cl, X = O, S; R_1 = 2,4-dichlorophenyl, 4-ethoxyphenyl, 3-ethoxy-4-hydroxylphenyl, 3-methoxy-4-hydroxylphenyl, 2-thiophene

Scheme 23: Facile one pot synthesis of 6-methyl-1,2,3,4-tetrahydro-N-aryl-2-oxo-4-aryl pyrimidine-5-carboxamide derivatives (4a-o) catalyzed by $UO_2(NO_3)_2.6H_2O$

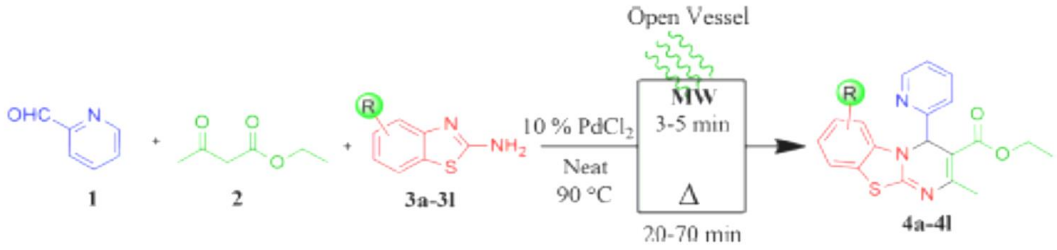
Farahi Mahnaz et.al [43]reported synthesis of 9-aryl-5,9-dihydropyrimido[4,5-d][1,2,4]triazolo[1,5-a]pyrimidine-6,8(4H,7H)-dione 4 by reaction of mixture of barbituric acid derivatives (1 mmol), arylaldehyde (1 mmol) and 3-amino-1H-1,2,4-triazoles (1 mmol) and irradiating at 300 W in a domestic MW oven for 10-15 min(Scheme 24).



Scheme 24: MW-assisted regioselective synthesis of 9-aryl-5,9-dihydropyrimido[4,5-d][1,2,4]triazolo[1,5-a]pyrimidine-6,8(4H,7H)-diones

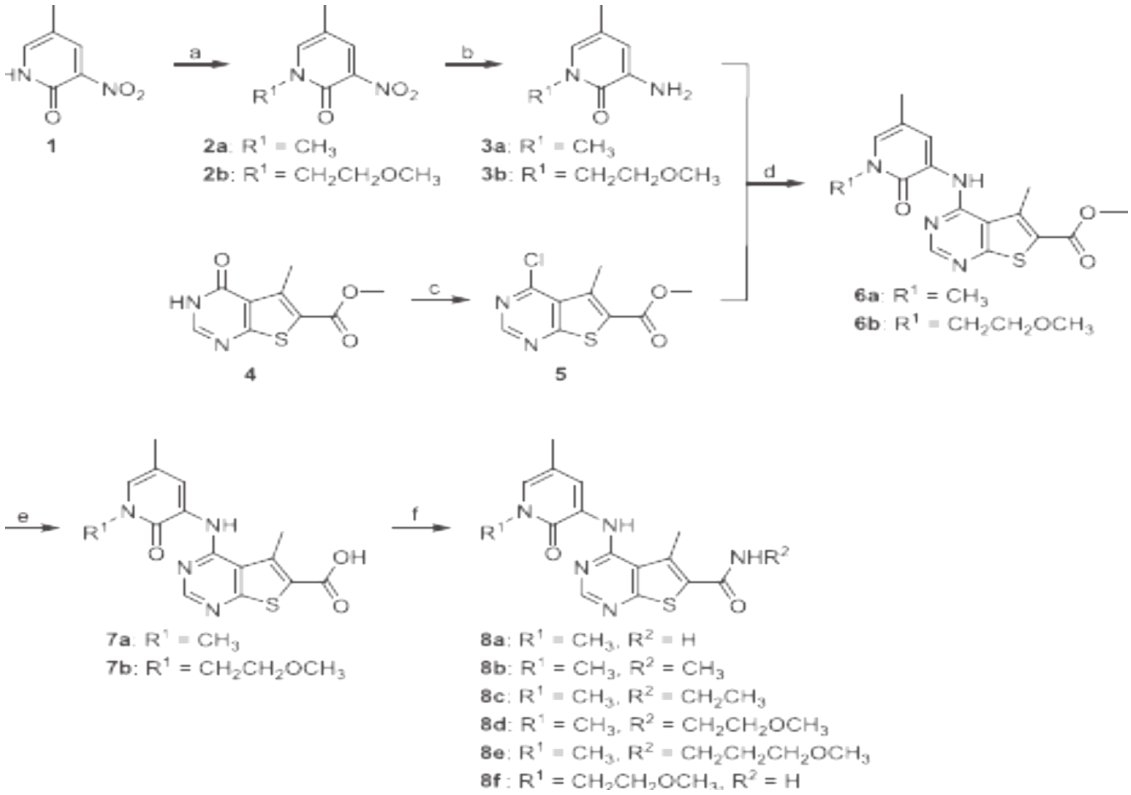
Bhoi Manoj N. et.al [44]reported synthesis of ethyl-(substituted)-2-methyl-4-(pyridin-2-yl)-4H-benzo[4,5]thiazolo[3,2-a] pyrimidine-3-carboxylate (4a–4l) by reacting mixture of

pyridine 2-aldehydes 1 (4.668 mmol), b-diketone like Ethyl acetoacetate 2 (4.668 mmol) and various derivatives of 2-amino benzothiazole 3a–3l (4.668 mmol) in open vessel glass tube in the cavity of a microwave oven (CEM Discover microwave) and irradiating for 2–5 min at 90°C under solvent-free conditions by using $PdCl_2$ (10 mol%)(Scheme 25).The synthesized compounds were evaluated in vitro antibacterial and antioxidant activities. The antibacterial data revealed that the all synthesized compounds proved to be active against the test organism, two gram negative and two gram positive reference strains compared to standard drugs. Moreover, all the synthesized compounds were evaluated as antioxidants according to a DPPH radical scavenging activity, superoxide anion scavenging assay and ABTS+ radical scavenging activity of our synthesized compound. All compounds showed moderate to good antioxidant activity. The compounds were also screened for antitubercular activity against Mycobacterium tuberculosis H37RV strain and compounds showed good antitubercular activity.



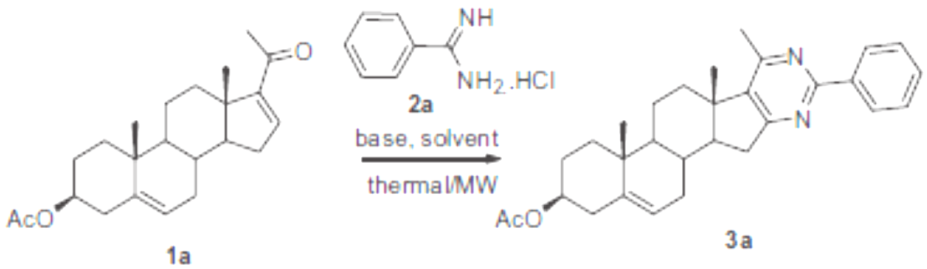
Scheme 25: Synthetic route for ethyl-(substituted)-2-methyl-4-(pyridin-2-yl)- 4H-benzo[4,5]thiazolo[3,2-a] pyrimidine-3-carboxylate (4a–4l) under solvent-free condition reaction

Yu Mingfeng et.al [45]reported the synthesisof methyl 4-((1-alkyl-2-oxo-5-methyl-1,2-dihydropyridin-3-yl)amino)-5-methylthieno [2,3-d]pyrimidine-6-carboxylates (6a and 6b) and their derivatives (7a, 7b and 8a-f).N-Alkylation of 5- methyl-3-nitropyridin-2(1H)-one 1 with iodomethane or 1- bromo-2-methoxyethane in the presence of potassium carbonate gave 1,5-dimethyl-3-nitropyridin-2(1H)-one 2a or 1-(2- methoxyethyl)-5-methyl-3-nitropyridin-2(1H)-one 2b respectively in good yields (2a: 95% and 2b: 60%), which underwent palladium-catalysed hydrogenation to afford the corresponding 3- amino-1,5-dimethylpyridin-2(1H)-one 3a or 3-amino-1-(2- methoxyethyl)-5-methylpyridin-2(1H)-one 3b in excellent yields (3a: 94% and 3b: 100%). Chlorination of methyl 5-methyl-4-oxo- 3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylate 4 with thionyl chloride in the presence of N,N-dimethylformamide (DMF) yielded methyl 4-chloro-5-methylthieno[2,3-d]pyrimidine-6-carboxylate 5 in a yield of 89%. Each of amines 3a and 3bwas individually coupled with chloride 5 in the presence of p-toluenesulfonic acid under microwave irradiation to give the corresponding methyl 4-((1- alkyl-2-oxo-5-methyl-1,2-dihydropyridin-3-yl)amino)-5-methylthieno[2,3-d]pyrimidine-6-carboxylates 6a and 6b in good yields (6a: 86% and 6b: 54%), which were subsequently subjected to saponification in an alkaline methanolic solution to yield the car- boxylic acids 7a and 7b respectively in excellent yields (7a:100% and 7b: 84%). Amination of carboxylic acids 7a and 7b with appropriate amineswas effected in anhydrous DMF in the presence of the coupling reagent 1-[bis(dimethylamino)methylene]-1H- 1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) and N,N-diisopropylethylamine (DIPEA) to give the corre-sponding amides 8a-f in moderate to good yields (36e80%) (Scheme 26).These derivatives are found to be as potent Mnk inhibitors. Phosphorylation of the eukaryotic initiation factor 4E (eIF4E) by mitogen-activated protein kinase (MAPK)-interacting kinases (Mnks) is essential for oncogenesis but unnecessary for normal development, Thus, pharmacological inhibition of Mnks may offer an effective and non-toxic anti-cancer therapeutic strategy.



Scheme 26: Synthesis of methyl 4-((1-alkyl-2-oxo-5-methyl-1,2-dihydropyridin-3-yl)amino)-5-methylthieno[2,3-d]pyrimidine-6-carboxylates (6a-b) and their derivatives (7a-b and 8a-f). Reagents and conditions: (a) appropriate alkyl halide, K_2CO_3, DMF, 0°C to rt for CH_3I, 0°Cto70°C for $BrCH_2CH_2OCH_3$, o/n, 2a: 95%, 2b: 60%; (b) H_2,10% Pd/C, CH_3OH, rt, o/ n, 3a: 94%, 3b: 100%; (c) $SOCl_2$, DMF, reflux, 2 h, 89%; (d) TsOH, H_2O, 1,4-dioxane, microwave 200-300W, 150°C, 30 min, 6a: 86%, 6b: 54%; (e) 2 M NaOH, CH_3OH, reflux, 2 h, 7a: 100%, 7b: 84%; (f) appropriate amine, HATU, DIPEA, DMF, 0°C to rt, o/n, 8a: 80%, 8b: 36%; 8c: 66%, 8d: 58%; 8e: 37%, 8f:66%.

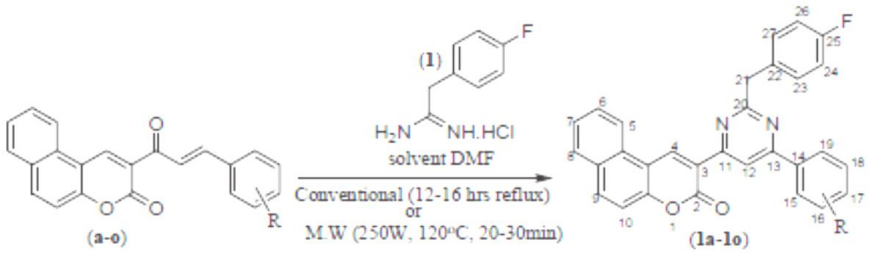
SaikiaPallabi, et.al [46]reported the synthesis of steroidal and nonsteroidal pyrimidines by refluxing 16-DPA (1a, 16-dehydropregnenolone acetate, 1.0 mmol) and benzamidine hydrochloride (2a,1.0 mmol) in isopropanol in the presence of base NaOMe (two equivalents, 2.0 mmol) under microwave irradiation at 110°C/700 W for 10 min to furnish pyrimidine 3a in 26% yield. (Scheme 27).



Scheme 27:Synthetic route for steroidal and nonsteroidal pyrimidines

Reddy Dinesh S. et.al [47]reported the synthesis of 2-(2-(4-fluorobenzyl)-6-(substituted phenyl) pyrimidin-4-yl)-3H-benzo[f]chromen-3-one derivatives (1a-1o) by reaction of mixture of substituted chalconated benzocoumarin (0.01 mol) with 2-(4-fluorophenyl) acetamidine hydrochloride (0.012 mol) and irradiating in a microwave reactor under 250Wpower at 120°C for 20-30 min in 5mL DMF (Scheme 28).Compounds (1a-1o) were evaluated for their in-vitro antitubercular activity while the most active compounds were further subjected for their cytotoxicity and DNA cleavage study. Results revealed that most

of the tested compounds displayed potent antitubercular activity with MIC in the range 0.05-2.81 mg/mL. Among them, compound (1b) possessed excellent activity (MIC 0.05 mg/mL) against M.tb H37Rv strain and exhibited low level of cytotoxicity against Vero cells, which suggested compound (1b) is found to be a promising lead for subsequent investigation in search of new antitubercular agents. DNA cleavage by gel electrophoresis method revealed that compounds (1b, 1g, 1k and 1n) were found to cleave the DNA completely.

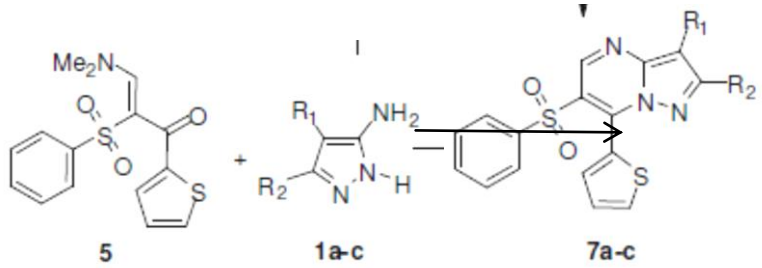


Where,

R= 1a) *p-CH₃*, 1b) *p-OCH₃*, 1c) *m-CH₃*, 1d) *m-OCH₃*, 1e) *o-CH₃* 1f) *o-OCH₃*, 1g) *p-Br*, 1h) *m-Br*, 1i) *o-Br*, 1j) *p-Cl*, 1k) *m-Cl*, 1l) *o-Cl*, 1m) *p-NO₂*, 1n) *m-NO₂*, 1o) *o-NO₂*

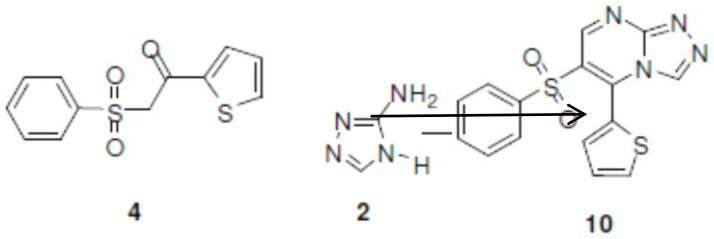
Scheme 28: Synthetic route for the preparation of benzocoumarin-pyrimidine hybrids (1a-1o)

Salema Mostafa E. et.al [48]reported the synthesis of pyrazolo[1,5-a]pyrimidine derivatives (7a-c) and triazolo[1,5-a]pyrimidine derivative (10). Pyrazolo[1,5-a]pyrimidine derivatives (7a-c) was synthesized by reaction of a mixture of the enaminosulfone 5 (3.21 g, 10 mmol) and the appropriate aminopyrazole derivative 1a-c (10 mmol) in pyridine (10 ml) and irradiating with microwaves under pressurized conditions (17.2 bar, 130°C) for 20 min. in 80-87% yield. (Scheme 29a).



Scheme 29a: Synthetic route forpyrazolo[1,5-a]pyrimidine derivatives (7a-c)

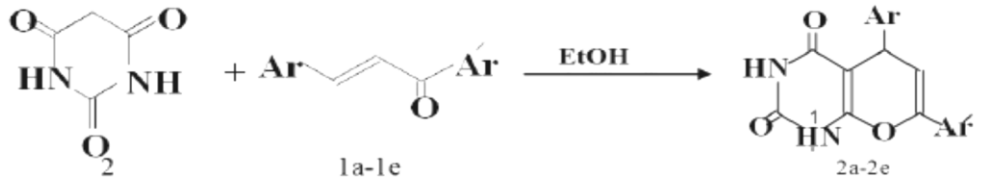
Synthesis of triazolo[1,5-a]pyrimidine derivative (10) was done by reaction of a mixture of the sulfone 4 (3.21g, 10 mmol) and 3-amino-l,2,4-triazole (2) and triethylorthoformate (10 mL) and irradiating with microwaves under pressurized conditions (17.2 bar, 100 °C) for 20 min. (Scheme 29b).



Scheme 29b: Synthetic route fortriazolo[1,5-a]pyrimidine derivative (10).

Sattar M. A. et.al [49]reported the synthesis of Barbituric acid derivatives (2a-2e) by reaction of an equimolar mixture of barbituric acid (2) (0.005 mol) and

arylideneacetphenone (1a-1e) (0.005 mol) in 25 ml rectified spirit and 25 ml water. The mixture was irradiated with microwave at different power level for several minutes. (Scheme 30).The antimicrobial and cytotoxic activities of the synthesized compounds were also investigated. Staphylococcus aureus, Bacillus megaterium, Escherichia coli and Pseudomonas aeruginosa revealed the zone of inhibition were 6-12 mm where sample concentration was 100 µg/disc. However, cytotoxic analysis, the mortality 47-95% were appeared when sample concentration were 0.78-25 (µg/ml) and more than 50 (µg/ml) concentration showed 100% mortality. The presence of a reactive and unsaturated ketone function in synthesized compounds was found to be responsible for their potential antimicrobial and cytotoxic activity.



	Ar	Ar′
2a	C_6H_5	C_6H_5
2b	C_6H_4OH	C_6H_5
2c	C_6H_5	C_6H_4Cl
2d	C_6H_4OH	C_6H_4Cl
2e	C_6H_4Cl	C_6H_5

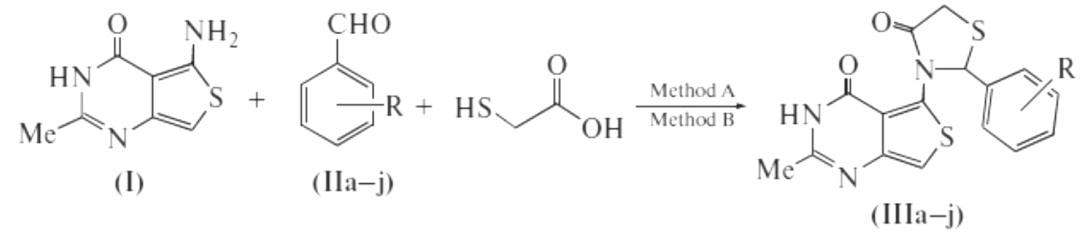
Scheme. 30: Synthetic route for barbituric acid derivatives (2a-2e).

AzabaI. H. El et.al [50]reported the synthesis of new 2-methyl-5-(4-oxo-2-(substituted phenyl)thiazolidin-3-yl)thieno[3,4-d]-pyrimidin-4-one, 5-(2,7-diphenyl-5-thioxo-5,6,7,7a-tetrahydrothiazolo[4,5-d]pyrimidin-3(2H)-yl)-2-methylthieno[3,4-d]pyri- midin-4(3H)-one, and 2-methyl-5-(5-phenyl-thiazolo[5,4-d]isoxazol-6(5H)-yl)thieno[3,4-d]pyrimidin-4(3H)-one derivatives under microwave-assisted conditions. The new compounds were screened for their in vitro antimicrobial activity against two gram-positive bacteria (Bacillus subtilis NCIM-2063 and Staphylococcus aureus NCIM-2901), one Gram-negative bacteria (Escherichia coli NCIM-2256), and three fungal strains (Candida albicans NCIM-3471, Aspergillus flavus NCIM-539, and Aspergillus niger NCIM-1196) and showed promising biological activity.

Synthesis of 2-Methyl-5-(4-Oxo-2- (Substituted Phenyl)-Thiazolidin-3-yl)thieno[3,4-d]pyrimidin-4-one (IIIa–j) was done by reaction of an equimolar amounts of substituted aldehydes (IIa–j) (1 mmol), 5-amino-2-methyl-thieno[3,4-d]pyrimidin-4-one (I) (1 mmol), and thioglycolic acid (1 mmol) in 50 mL dimethylformamide containing 2– 3 drops of glacial acetic acid and irradiating in MW (800 W) at 105°C for 6–9 min (Scheme 31a).

Synthesis of 5-(2,7-Diphenyl-5-Thioxo-5,6,7,7a-Tetrahydro- thiazolo[4,5-d]pyrimidin-3(2H)-yl)-2- Methylthieno[3,4-d]pyrimidin-4(3H)-one (IV) was done by reaction of an equimolar amounts of benzaldehyde (IIa) (1 mmol), 2-methyl- 5-(4-oxo-2-phenylthiazolidin-3-yl)thieno[3,4-d]pyrimidin-4-one (IIIa) (1 mmol), and thiourea (1 mmol) in 50 mL dimethylformamide in presence of 2–3 drops of glacial acetic acid and irradiating in MW (800 W) at 105°C for 9 min(Scheme 31b).

Synthesis of 2-Methyl-5-(5- Phenylthiazolo[5,4-d]isoxazol-6(5H)-yl)thieno[3,4-d]pyrimidin-4(3H)-one (V) was done by reaction of an equimolar amounts of dimethylformamide–dimethylacetal (DMF– DMA) (1 mmol), 2-methyl-5-(4-oxo-2-phenylthiazoli- din-3-yl)thieno[3,4-d]pyrimidin-4-one (IIIa) (1 mmol), and hydroxylamine (1 mmol) in 50 mL dimethylformamide containing 2–3 drops of glacial acetic acid and irradiating in MW (800 W) at 105°C for 10 min (Scheme 31c).

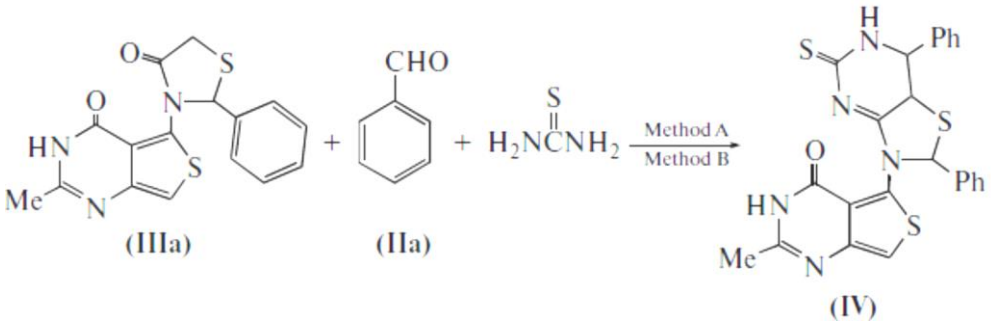


II, III	R	II, III	R
a	H	f	2,4-Methoxy
b	4-Hydroxy	g	2-Chloro
c	2-Nitro	h	4-Chloro
d	4-Nitro	i	4-CN
e	4-Methoxy	j	4-F

Scheme 31a: Synthesis of 2-methyl-5-(4-oxo-2-(substituted phenyl)thiazolidin-3-yl)thieno[3,4-d]pyrimidin-4-one (IIIa–j)

Method A. Microwave-assisted synthesis: AcOH, DMF as a solvent, 110°C, 8–10 min.

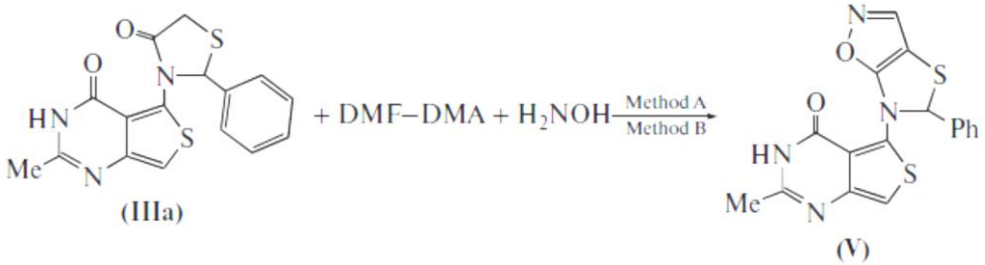
Method B. Conventional synthesis: AcOH, DMF as a solvent, reflux 4–6 h.



Scheme31b: Synthesis of 5-(2,7-diphenyl-5-thioxo-5,6,7,7a-tetrahydrothiazolo[4,5-d]pyrimidin-3(2H)- yl)-2-methylthieno[3,4-d]pyrimidin-4(3H)-one (IV).

Method A. Microwave assisted synthesis: AcOH, DMF as a solvent, 110°C, 9 min.

Method B. Conventional synthesis: dry EtOH, conc. hydrochloric acid as a solvent, reflux 6 h.

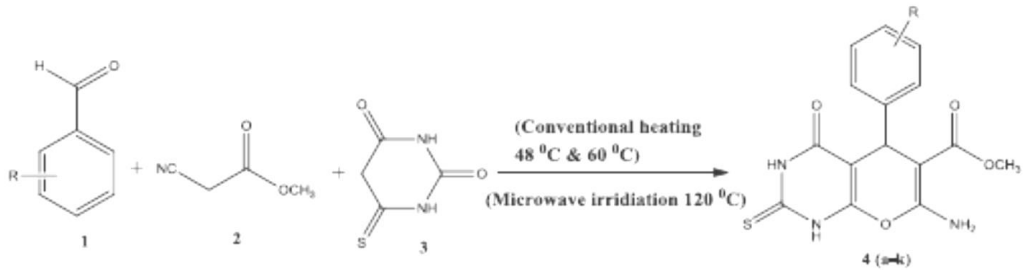


Scheme 31c: Synthesis of 2-methyl-5-(5-phenylthiazolo[5,4-d]isoxazol-6(5H)-yl)thieno[3,4-d]pyrimidin-4(3H)-one (V).

Method A. Microwave assisted synthesis: AcOH, DMF as a solvent, 110°C, 10 min.

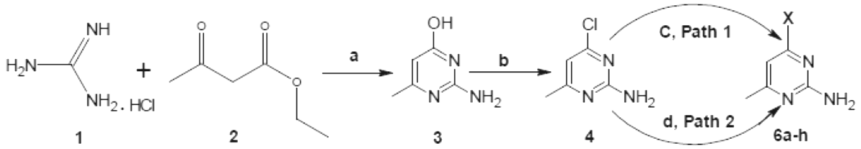
Method B. Conventional synthesis: dry xylene containing anhydrous K_2CO_3 as a solvent, reflux 8 h.

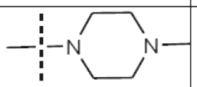
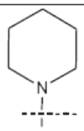
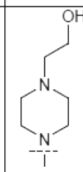
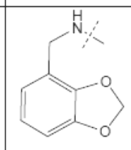
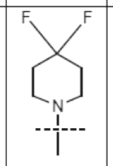
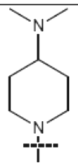
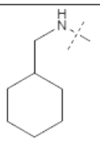
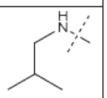
BhatAjmal R., et.al [51]reported synthesis of new methyl 7-amino-4-oxo-5-phenyl-2-thioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d] pyrimidine-6-carboxylate derivatives (4a–k) by reaction of a mixture of benzaldehyde derivatives 1 (1 mmol), methylcyanoacetate 2, (1.2 mmol), thio-barbituric acid 3, (1 mmol) and water (3.0 mL) and subjecting to microwave irradiation under catalyst free conditions for a given time at power of 250W and 120°C.(Scheme 32).The synthesized compounds (4a–4k) showed comparatively good in vitro antimicrobial and antifungal activities against different strains. The Compounds 4a, 4b, 4c, 4d 4e and 4f showed maximum antimicrobial activity against Staphylococcus aureus, Bacillus cereus (gram-positive bacteria), Escherichia coli, Klebshiella pneumonia, Pseudomonas aeruginosa (gram-negative bacteria). The synthesized compound antifungal activity against Aspergillus Niger and Penicillium chrysogenum strains. Streptomycin was used as a standard for bacterial studies and Mycostatin as standards for fungal studies.



Scheme 32: Microwave and conventional synthesis of methyl 7-amino-4-oxo-5-phenyl-2-thioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3- d]pyrimidine-6-carboxylate derivatives (4a–k)

Kumar Manoj et.al [52]reported for the preparation of 2-Amino-6-subsituted-pyrimidine derivatives (6a-h) by reaction of 2-amino-4-chloro-6-methylpyrimidine (4) (1.39 mmol), primary or secondary amines (5a-h) (1.66 mmol), Xantphos (0.027 mmol), $Pd(dba)_2$ (0.055 mmol), Cs_2CO_3(2.085 mmol) and freshly distilled dry acetonitrile(4 mL) dry microwave vial which was sealed and purged with a three cycles of vacuum / nitrogen and irradiated under microwave condition for 30 - 50 min for reaction to complete.(Scheme 33) The compounds were screened for their antimicrobial activity against pathogenic strains such as S.aureus, E.coli, K. aerogenes, A. flavus and C. albicans and anthelmintic activity conducted using P. posthuma (Indian Earthworm). Among the synthesized compounds 6a, 6c & 6f have shown significant antibacterial activity.

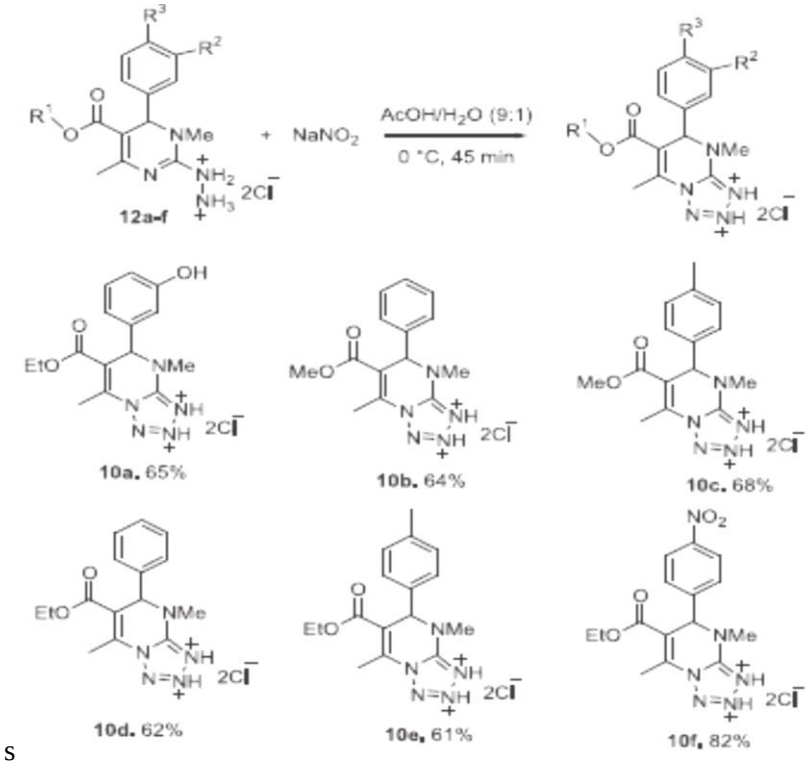


Comp Code	5a/6a	5b/6b	5c/6c	5d/6d	5e/6e	5f/6f	5g/6g	5h/6h
X								

Scheme 33: Reagents and conditions: (a) Neat reaction (b) $POCl_3$, Reflux (c) Path 1: Substituted primary and secondary amines (5a-h), Xantphos, $Pd(dba)_2$, Cs_2CO_3, dry AcCN, Δ 80°C, 10-17 h; (d) Path 2 : Substituted primary and secondary amines (5a-h), Xantphos, $Pd(dba)_2$, Cs_2CO_3,dry AcCN, MW, 30-50 min.

HashimJamshed et.al [53]reported the synthesis of tetrazolo dihydropyrimidines dihydrochloride (10a-f) by stirring reaction of 0.25mmol of the corresponding hydrazinyl dihydropyrimidines dihydrochloride 12a-f and 69 mg (1.0 mmol, 4.0 equiv) of sodium

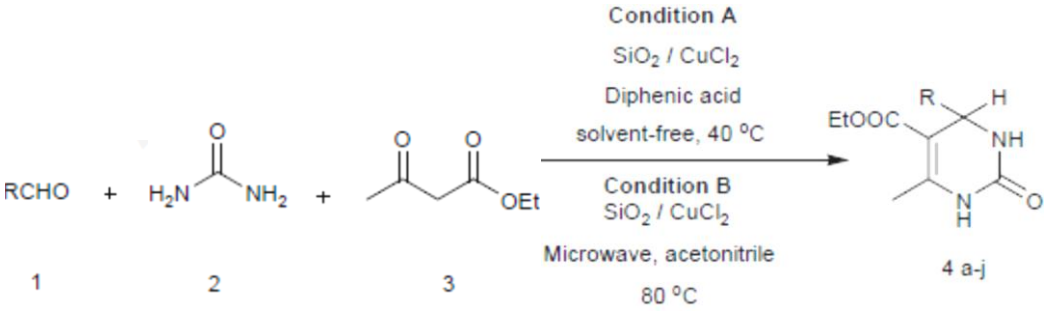
nitrite ($NaNO_2$) in a microwave vial equipped with a magnetic stirrer andkeeping it at 0°Cin a $CaCl_2$ ice bath followed by addition of 6 mL of 90% cold acetic acid in the dark and keeping the reaction mixtureat 0°C for further 45 min under N_2 atmosphere with continuous stirring to provide the desired 2-substituted dihydropyrimidines dihydrochloride (10a-f) as oils. (Scheme 34)



s

Scheme 34: Synthetic route fortetrazolo dihydropyrimidines dihydrochloride (10a-f)

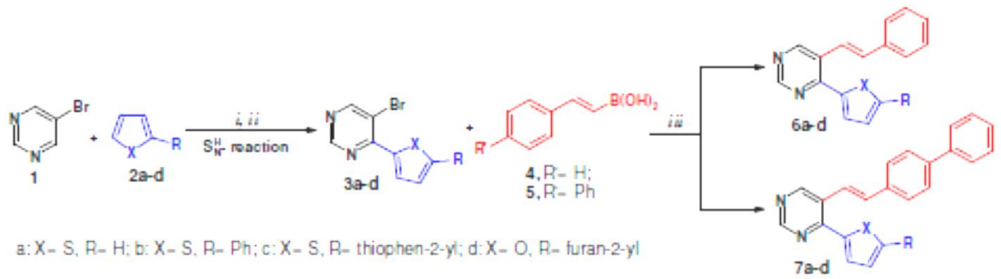
KourGurpreet, et.al [54]reported the synthesis of 3,4-dihydropyrimidin-2(1H)-ones catalyzed by SiO_2 / $CuCl_2$ by reaction of aldehyde (0.5 mmol), ethyl acetoacetate (0.5 mmol), urea (0.5 mmol) and SiO_2/ $CuCl_2$ (0.05g) and stirring at 80°C in acetonitrile for appropriate time in a microwave. (Scheme 35)



Scheme 35: Synthetic route for3,4-dihydropyrimidin-2(1H)-ones

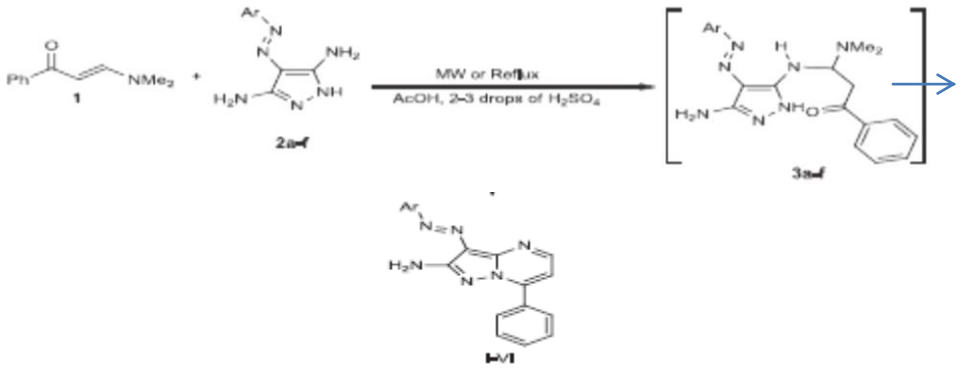
Kravchenko Marionella A. et.al [55]reported the synthesis of 5-styryl-4-(hetero)arylpyrimidines 7a-d by the reaction of 5-bromopyrimidine (1) with thiopene (2a), bithiophene (2b) and 2- phenylthiophene (2c) in CF3COOH to afford the corresponding σH-adducts – 5-bromo-4-(hetero)aryl-3,4-dihydropyrimidinium salts. Further oxidation of these compounds with $K_3Fe(CN)_6$ in an aqueous solution of KOH gave 5-bromo-4-(hetero)arylpyrimidines 3a-c. The reaction 5-bromopyrimidine (1) with (E)-5-arylethenyl-4-(hetero)aryl- furan (2d) under the same conditions leads to the corresponding 5-bromo-4-(furyl-2'l)pyrimidine (3d) in a good yield (64%). Bromo derivatives 3a-d have been involved in the Suzuki reaction with trans-2-styrylboronic acids 4 and 5 under microwave

irradiation (155°C, 20 min). The correspondingcross-coupling products, pyrimidines 6a-d and 7a-d, have been obtained in high yields(Scheme 36).All intermediate 5- bromo-4-(hetero)aryl substituted pyrimidines and also the targeted 5-styryl-4-(hetero)arylpyrimidines were found to be active in micromolar concentrations in vitro against Mycobacterium tuberculosis H37Rv, avium, terrae, and multi-drug-resistant strain isolated from tuberculosis patients in Ural region (Russia). It has been found that some of these compounds possess a low toxicity and have a bacteriostatic effect, comparable and even higher with that of first-line antituberculosis drugs.



Scheme 36: Reagents and conditions: (i) CF_3COOH, r.t., 24 hours; (ii) $K_3Fe(CN)_6$, KOH, H_2O, r.t., 6 hours; (iii) $Pd(PPh_3)_4$, K_2CO_3, H_2O, THF, 155 ºC, MW, 20 min.

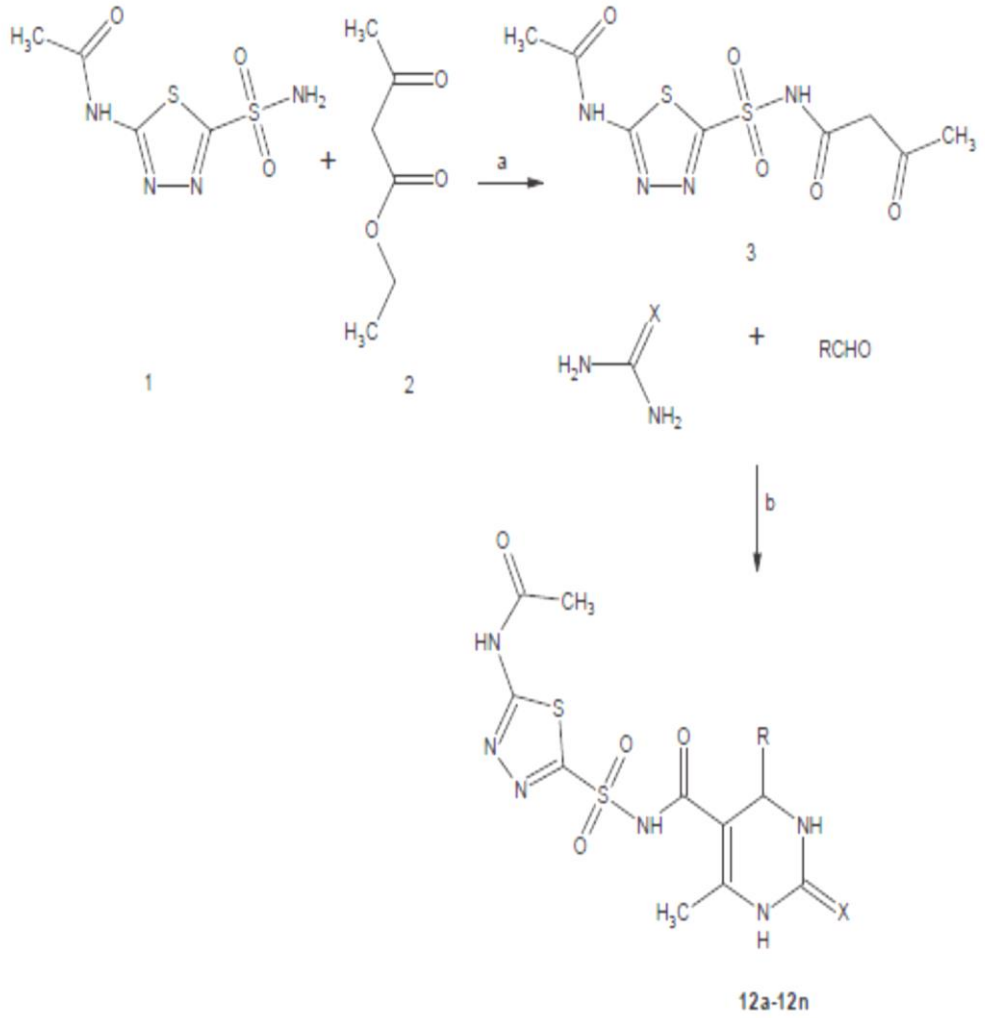
El-Gahami Mohamed A. et.al [56]reported the synthesis of pyrazolo[1,5-a]pyrimidin-2-amine derivatives by reaction of E-3-dimethylamino-1-phenylprop-2-en-1-one (1) (2 mmol) and the appropriate 4-(Aryldiazenyl)-1H- pyrazole-3,5-diamine 2a–f (2 mmol) in glacial acetic acid (25 mL) and adding concentrated sulfuric acid is (0.5 ml) followed bymicrowave irradiation (300 W, 120^{o}C) (Scheme 37). The UV–visible electronic spectra of some azo compounds of pyrazolo[1,5-a]pyrimidin-2-amine have been studied. The solvatochromic behavior of these compounds was investigated by studying their spectra in pure organic solvents of different polarities such as cyclohexane carbon tetrachloride, chloroform, ethanol and DMF. These exhibits a red shift in its kmax with increase relative permittivity of medium changing from cyclohexane-carbon tetrachloride-chloroform-ethanol-DMF. The acid dissociation constants of these compounds were determined in aqueous–organic solvent mixtures such as acetone, methanol, ethanol and DMF. The ionization constants of the dyes in question depended largely on both the proportion and the nature of the organic solvent basicity contribute the major effects on the ionization process. In general, pKa values in all compounds decrease with increase relative permittivity of the medium. The acidity of studied azo compounds increases in the following order: p-NO_2< m-CF_3< p-F < p-Cl < p-H < p-CH_3.



Scheme 37: Synthesis of pyrazolo[1,5-a]pyrimidin-2-amine derivatives.

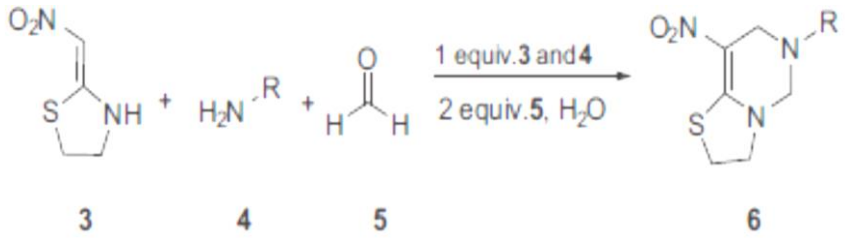
Elumalai Karthikeyan et.al [57]reported the synthesis of 1,2,3,4-tetrahydropyrimidines (12a-n) by the reaction of mixture of N-{[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}-3-oxobutanamide (0.005 M), urea/thiourea (0.0075 M), and appropriate aldehyde (0.005 M) with catalytic amount of p-toluenesulfonic acid in 10 ml of ethanol and subjecting to

microwave irradiation (300 W) for 10 min at the interval of 10s. (Scheme 38). The synthesized compounds were evaluated for in-vitro antimicrobial and cytotoxicity against Bacillus subtilis, Escherichia coli and Vero cells. The titled compounds exhibited weak, moderate, or high in-vitro antimicrobial and cytotoxicity. Compounds 12c, 12d, 12g and 12h, exhibited potential antimicrobial and in-vitro cytotoxicity.



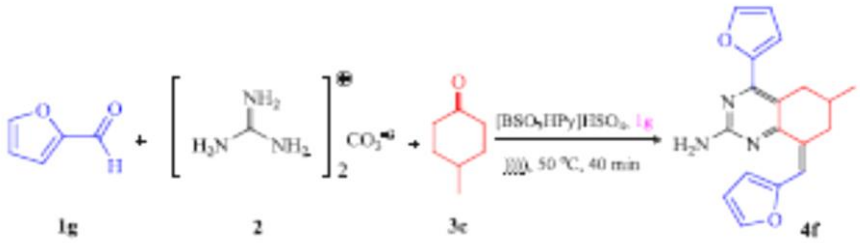
Scheme 38: Synthesis of compounds (12a-12n). R for compounds: 12a: (3-chlorophenyl); 12b: (3chlorophenyl); 12c: (4- chlorophenyl); 12d: (4-chlorophenyl); 12e:(3-nitrophenyl); 12f: (3-nitrophenyl); 12g: (4-flurophenyl); 12h: (4-flurophenyl); 12i: (2-nitorophenyl); 12j: (2-nitorophenyl); 12k: (2-chlorophenyl); 12l: (2-chlorophenyl); 12m: (4-pyridyl); 12n: (4-pyridyl). Reagents and conditions: (a) reflux 4.5 h, CH_3COOH; (b) C_2H_5OH, p-toluenesulfonic acid, and microwave irradiation (300 W) for 10 min.

Yıldırım Muhammet et.al [58]reported the synthesis of thiazolo[3,2-c] pyrimidines (6) by reaction of 2-(Nitromethylene)thiazolidine 3 (0.5 or 0.25 mmol, 1.0 equiv), a primary amine 4 (0.5 or 0.25 mmol,1.0 equiv) and formaldehyde 5 (37% v/v solution in water,1.0 or 0.5 mmol, 2.0 equiv)were mixed in water (2 mL) and the resulting suspension was pre-stirred for 1 min in a microwave reactor prior to reaction. Then the reaction mixture was heated at exactly 90^{o}C in the dynamic mode for 4-6 min. (Scheme 39)



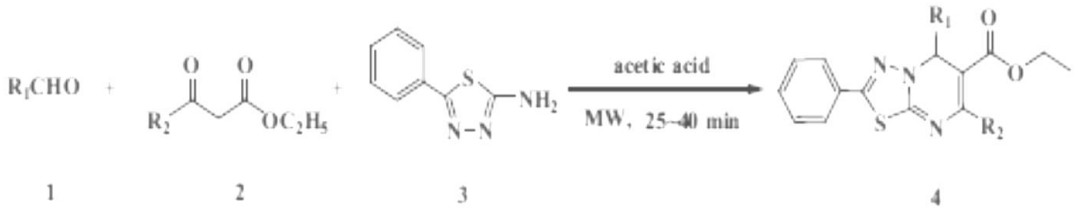
Scheme 39:Synthetic route forthiazolo[3,2-c] pyrimidines (6)

Zakeri Masoumeh et.al [59]reported the synthesis of quinazolin- and pyrimidine-2- amine 4f, by reaction of a mixture of 4-methyl cyclohexanon (2 mmol, 0.224 g), furfural (4 mmol, 0.384 g), guanidine carbonate (2 mmol, 0.180 g) and $[BSO_3HPy]HSO_4$ (15 mol%) in 10 ml microwave reactor and heating to 120 °C. (Scheme 40)



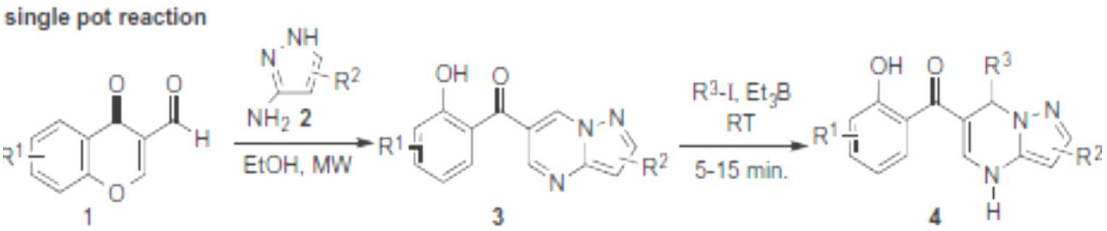
Scheme 40: Synthetic route forquinazolin- and pyrimidine-2- amine 4f

Zhao Bing et.al [60]reported the synthesis of novel 5H-[1,3,4] thiadiazolo[3,2-a]pyrimidine-6-carboxylate derivatives by reaction of mixture of 2-aminothiadiazole (1 mmol), appropriate aldehyde (1 mmol), ethyl acetoacetate (2 mmol) and 1.5 mL acetic acid in a pressurized microwave vial with snap on cap and subjecting to microwave irradiation for appropriate time at 450W at 65°C. (Scheme 41)



Scheme 41: Synthetic route for 5H-[1,3,4] thiadiazolo[3,2-a]pyrimidine-6-carboxylate derivatives

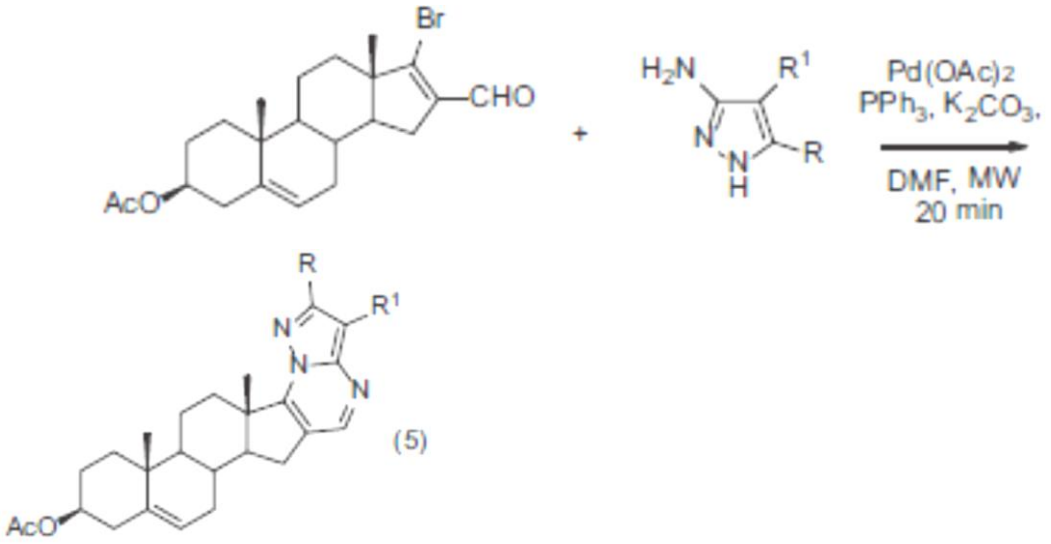
Zimmermana Jake R. et.al [61]reported a two-step, single pot procedure for the synthesis of substituted dihydropyrazolo-pyrimidines starting with a microwave-assisted step to form pyrazolopyrimidine 3 followed by a tin-free radical addition to yield the substituted dihydropyrazolopyrimidine 4.(Scheme 42)



Scheme 42: One-pot synthesis of substituted dihydropyrazolo-pyrimidines.

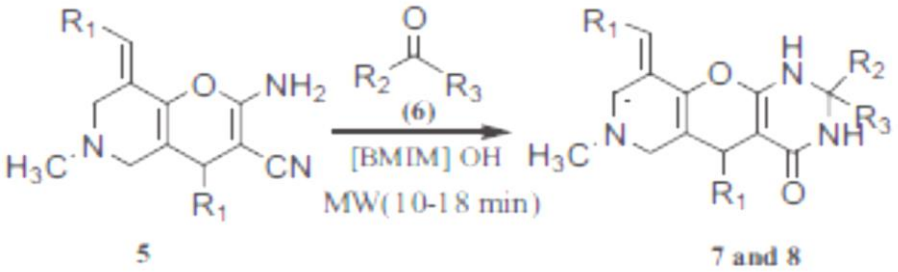
Shekarrao Kommuri et.al [62]reported the synthesis of steroidal D-ring fused pyrazolo[1,5-a]pyrimidines through irradiating a mixture of steroidal b-bromovinyl aldehydes(1.0 mmol)

with pyrazoloamines (1.0 mmol), palladium acetate (10 mol %)catalyst ,triphenylphosphine (10 mol %), and K_2CO_3 (1.2 mmol) in DMF and irradiating in microwave at 700W for 20 min. (Scheme 43)



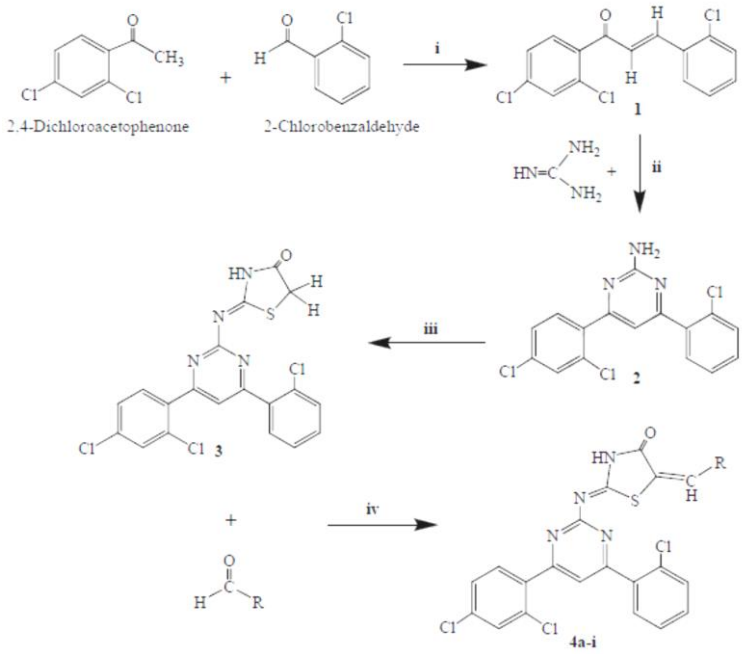
Scheme 43: Synthesis of steroidal pyrazolo[1,5-a]pyrimidines and steroidal pyrimidines.

Siddiqui I.R. et.al [63]reported the synthesis of piperido[3',4':5,6] pyrano[2,3-d] pyrimidinone 7b catalyzed by basic ionic liquid [BMIM]OH by reaction of a solution of corresponding 2-amino-3-cyano-5,6,7,8-tetra- hydro-4H-pyrano[3.2-c]piperidine 5a (1.0 mmol); cyclohexanone 6b (1.3 mmol) and [BMIM]OH (2 mL) in a reaction vial, sealed and irradiated at 90◦C for 10 min (hold time) (Scheme 44).



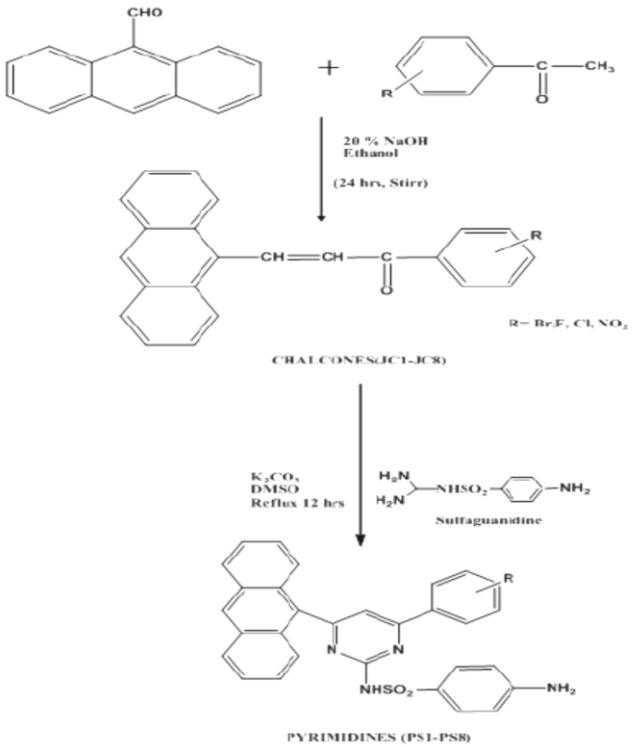
Scheme 44:Synthesis of novel piperido[3';4':5,6]pyrano[2,3-d]pyrimidinone.

Rashid Mohd et.al [64]reported the synthesis of 2-(4-(2-chlorophenyl)-6-(2,4-dichlorophenyl) pyrimidin- 2-yl-imino)-5-(substituted)thiazolidin-4-one (4a-i) by reacting compound 3 (0.01 mol, 4.49 mg) and different types of aromatic aldehydes (0.01 mol) in glacial acetic acid (20 mL) in presence of anhydrous sodium acetate (0.01 mol, 0.82 mg). The reaction mixture was placed into a microwave reaction vessel and kept into the scientific microwave synthesizer (model No. CATA-R, Catalyst systems, India) and then irradiated at a power level of 5 (50%, 350 W) for 10-15 min. The synthesized compounds were screened for their anticancer activities and these compounds were found to be new potential anticancer agents (Scheme 45).



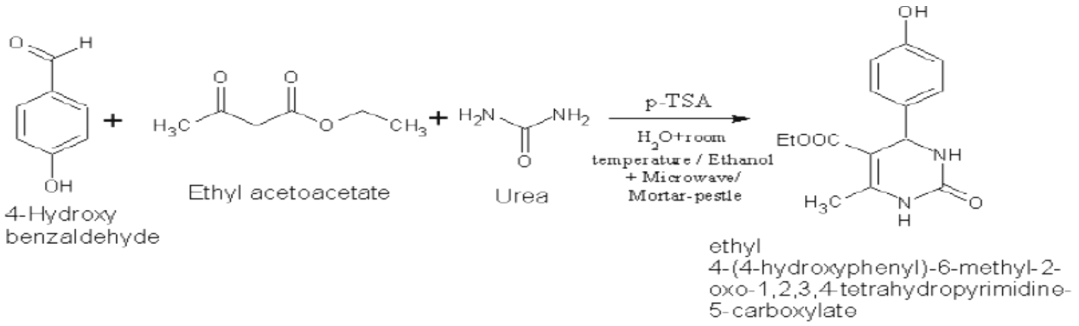
Scheme 45: Synthetic route for 2-(4-(2-chlorophenyl)-6-(2,4-dichlorophenyl) pyrimidin- 2-yl-imino)-5-(substituted)thiazolidin-4-one (4a-i)

Jainey Pj et.al [65]reported the synthesis of 4-amino-N-(4-(anthracen-9-yl)-6-(aryl substituted) pyrimidin 2yl)benzene sulphonamide by reaction of chalcone (0.01 mol), sulfaguanidine (0.01 mol), and 20 ml dimethyl sulfoxide and anhydrous potassium carbonate and subjecting to microwave irradiation for 5-6 min. (Scheme 46). Biological activity studies showed that these compounds exhibited significant antitumor and antioxidant activities and showed good radical scavenging activity.



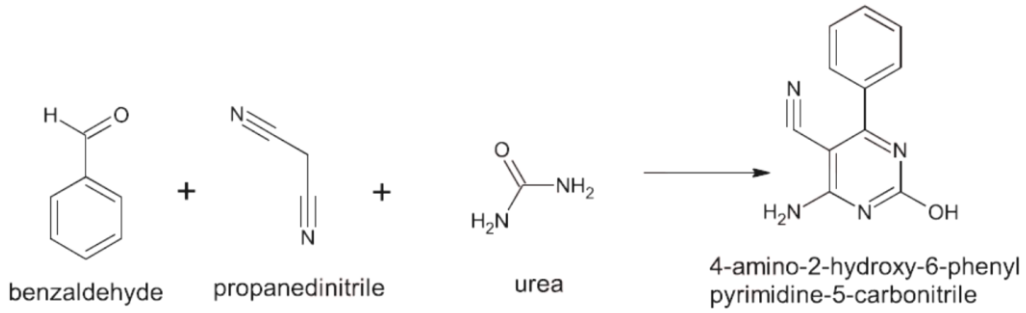
Scheme 46:Synthetic route for 4-amino-N-(4-(anthracen-9-yl)-6-(aryl substituted) pyrimidin 2yl)benzene sulphonamide

Jagwani D. et.al [66]reported the synthesis of 4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester by reaction of 4-Hydroxybenzaldehye (0.122 gm, 0.001 mol), Ethylacetoacetate (0.127 ml, 0.001 mol) and Urea (0.132gm, 0.002 mol, ethanol (5 ml) as a solvent and p- TSA (0.034gm, 0.002mol) were added simultaneously to the above mixture. The mixture was irradiated for 3 minutes (30 second interval @ 20 power level). (Scheme 47)



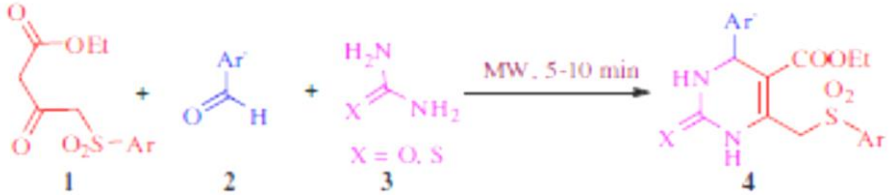
Scheme 47: Synthetic route for 4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester

Marabathuni V.Jhansipriya et.al [67] reported the synthesis of 4-Amino-2-Hydroxy-6-PhenylPyrimidine-5-Carbonitrile by reaction of substituted aldehyde (0.005 mol), malononitrile (0.005 mol), urea or thiourea (0.005mol) and conc. H_2SO_4 (1-2 drops) in absolute ethanol (5 mL) and irradiating in the domestic type microwave oven 900 W with a frequency 2450 MHz (Kenstar OM-25 DCE, India) for 2-4 min (one pulse each of 30 sec) (Scheme 48). The synthesized compound was found to exhibit antibacterial activity.



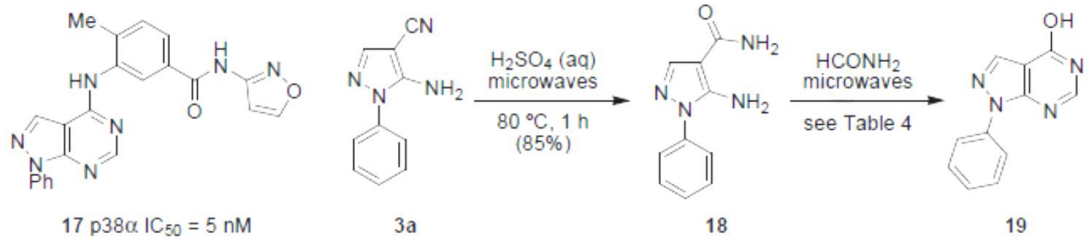
Scheme 48: Synthetic route for4-Amino-2-Hydroxy-6-PhenylPyrimidine-5-Carbonitrile

Harikrishnan Palani Sokkan et.al [68]reported the synthesis of novel ethyl 2-oxo/thio-4-aryl-6-(arylsulfonylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylates by the Biginelli reaction of ethyl 3-oxo-4-(arylsulfonyl)butanoate 1, aromatic aldehyde 2 and diamide (urea/thiourea) 3 under microwave irradiation and solvent- and catalyst-free conditions (Scheme 1). The efficiency of this method has also been compared with reactions carried out in the presence of acid catalysts, viz. acetic acid,aluminium chloride, stannous chloride, cerium(III) chloride-7H_2O, ferric chloride and cupric acetate (Scheme 49).



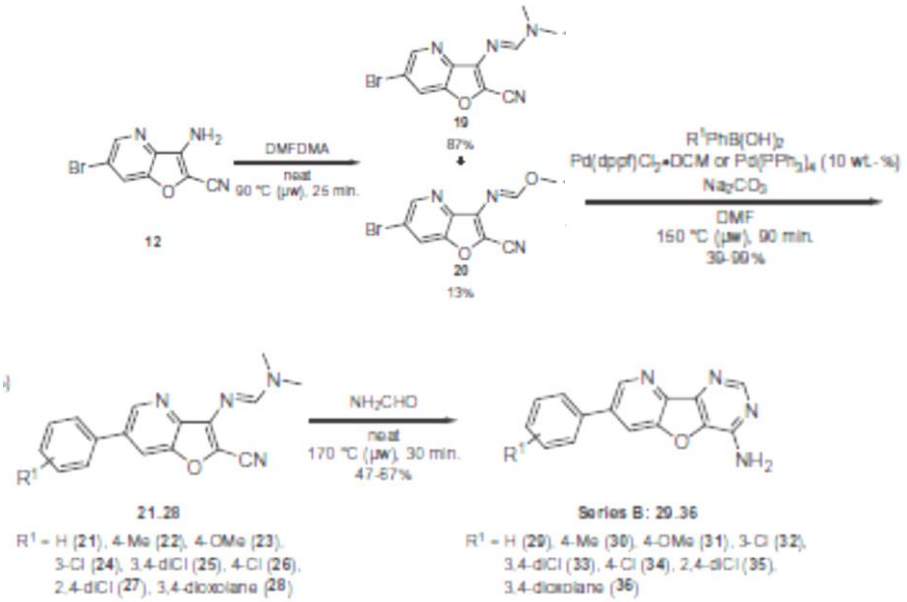
Scheme 49: Synthesis of ethyl 2-oxo/thio-4-aryl-6-(arylsulfonylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylates 4.

Bagley Mark C. et.al [69]reported the synthesis of pyrazolo[3,4-d]pyrimidines(19) by reaction of a mixture of 5-amino-1-phenyl-1H-pyrazole-4-carboxamide (18) (0.15 g, 0.74 mmol) in formamide (0.50 mL, 5.6 mmol) and irradiating at 150 °C for 45 min in a pressure-rated Pyrex tube (10 mL) using a CEM Discover microwave synthesizer by moderating the initial power (150 W). (Scheme 50) The synthesized compound was found to be inhibitor of mitogen activated protein kinase.



Scheme 50: Synthesis of pyrazolo[3,4-*d*]pyrimidine **18** from 5-aminopyrazole **3a**

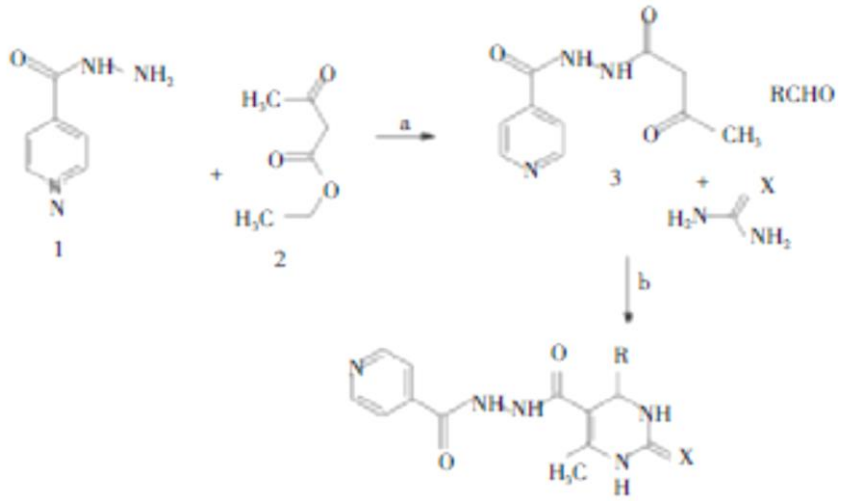
Deau Emmanuel et.al [70]reported the synthesis of 7-substituted pyrido[20,30:4,5]furo[3,2-d]pyrimidin-4-amines and their N-aryl analogues by reaction of precursor 12 with DMFDMA using microwave irradiation at atmospheric pressure, and converted into 6-bromodimethylformimidamide derivative 19 in 87% yield along with traces of the 6-bromoformimidate 20. Functionalization at position 7 of the intermediate 19 into the aryl adducts 21–28 was completed by a microwave-assisted Suzuki–Miyaura cross-coupling in the presence of a catalytic amount of [1,10- bis(diphenylphosphino)ferrocene]-dichloropalladium(II) dichloro methane complex (for cyanoamidines 21–27) or tetrakis(triphen- ylphosphine)palladium(0) (for cyanoamidine 28), the appropriate phenylboronic acid, and sodium carbonate at 150°C (Scheme 51). Cyclisation of cyano-amidine intermediates 21–28 gave the final 7-substituted pyrido[20,30:4,5]furo[3,2-d]pyrimidin-4-amines 29–36, The products were evaluated for their potent inhibition of a series of five Ser/Thr kinases (CDK5/p25, CK1d/ e, CLK1, DYRK1A, GSK3a/b). and the compounds showed the inhibitory activity .



Scheme 51: Microwave-assisted synthesis of cyanoamidine 19 with DMFDMA, aryl adducts 21–28 by palladium-catalyzed Suzuki–Miyaura cross-coupling, and 7-substituted pyrido[20,30:4,5]furo[3,2-d]pyrimidin-4-amines 29–36 by formamide degradation.

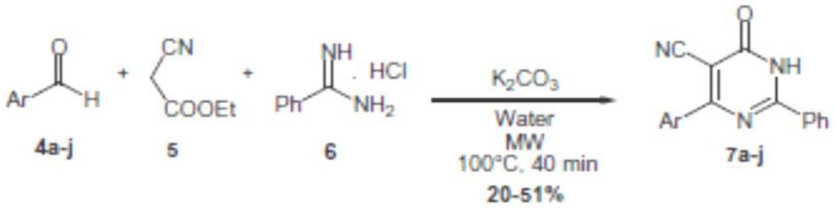
Elumalai Karthikeyan et.al [71]reported the synthesis of 1,2,3,4-tetrahydropyrimidines by microwave irradiation method (4a-n) by reaction of mixture of N' aceto acetyl isonicotino

hydrazide (0.005M), urea/thiourea (0.007 5 M), and appropriate aldehyde (0.005 M) with catalytic amount of benzenesulphonic acid in 10 ml of ethanol and subjecting to microwave irradiation (300 W) for 8 min at the interval of 10 s (Scheme 52). The synthesized compounds were evaluated for in vitro antimicrobial and antimycobacterial activity against Bacillus subtilis (B. subtilis), Escherichia coli (E. coli), Mycobacterium tuberculosis (M. tuberculosis) CIP and H37Rv strain. Results: The titled compounds exhibited weak, moderate, or high antimicrobial and antimycobacterial activity.



Scheme 52: Synthesis of 1,2,3,4-tetrahydropyrimidines (4a – 4n)

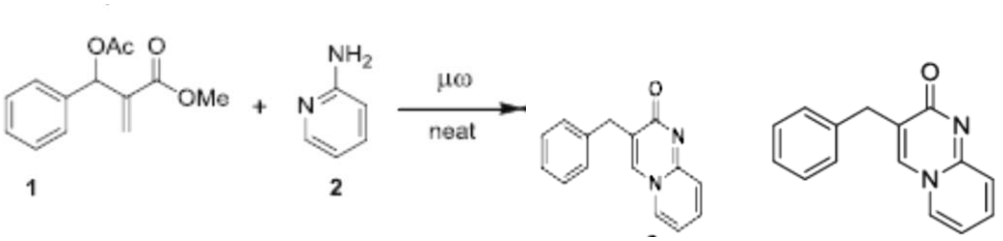
Xavier Augusto L. et.al [72]reported the synthesis of 6-oxo-2,4-diaryl-1,6- dihydro-pyrimidine-5-carbonitriles (7a–j) and 4-amino-2,6-diaryl-pyrimidine-5- carbonitriles (9a–j).by reaction of 1.13 mmol of benzamidine hydrochloride and 1.88 mmol of potassium carbonate dissolved in 10 mL of distilled water and stirring the mixture at room temperature until the neutralization of the benzamidine salt. To the clear basic solution, 0.94 mmol of the corresponding aromatic aldehyde (1.0 equiv) and 1.88 mmol (2.0 equiv) of ethyl cyanoacetate (for the synthesis of 7a–j) or malononitrile (for the synthesis of 9a–j) were added. The mixture was placed in a microwave reactor at temperature 100^{o}C and 300Wof initial power for 40 min. (Scheme 53)



Scheme 53: Three-component reaction of aromatic aldehydes, ethyl cyanoacetate,

and benzamidine.

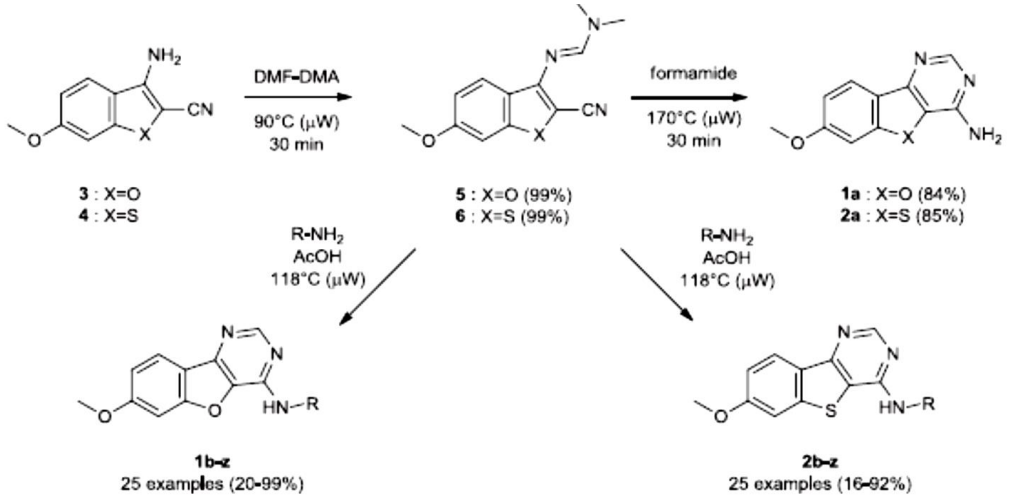
SatyanarayanaS., et.al [73]reported the synthesis of 3- benzyl-2H-pyrido[1,2-a]pyrimidin-2-one derivatives by reaction of mixture of methyl 2-(acetoxy(phenyl)methyl)acrylate (1, 1 mmol), 2-heteroaryl amine (2, 1 mmol) in a 10 mL sealed glass tube followed by irradiation for a specified time as required to complete the reaction at 95 ˚C (temperature was monitored by inbuilt infrared sensor) at 150 W(Scheme 54).



Scheme 54: Synthetic route for 3- benzyl-2H-pyrido[1,2-a]pyrimidin-2-one derivatives

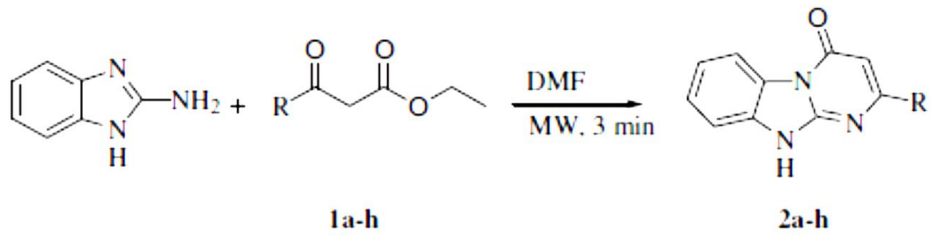
Loidreau Yvonnick et.al [74]reported the synthesis of N-aryl-7-methoxybenzo[b]furo[3,2-d] pyrimidin-4-amines and N-arylbenzo[b]thieno[3,2-d]pyrimidin-4-amine. Synthesis of N-aryl-7-methoxybenzofuro[3,2-d]pyrimidin-4- amines (1b-z) by reaction of a mixture of (E)-N0-(2-cyano-5-methoxybenzofuran-3-yl)-N,N-dimethylformimidamide(5) (0.1 g, 0.38 mmol) and appropriate aniline (1.0 equiv) in acetic acid (2 mL) and irradiating at 118 ^{o}C (400 W) (Scheme 55a).

Synthesis of N-aryl-7-methoxybenzothieno[3,2-d]pyrimidin- 4-amines (2b-z) by reaction of a mixture of (E)-N0-(2-cyano-6- methoxybenzofuran-3-yl)-N,N-dimethylformimidamide (6) (0.1 g, 0.39 mmol) and appropriate aniline (1.0 equiv) in acetic acid (2 mL) and irradiating at 118^{o}C (400 W) (Scheme 55b).The inhibitory potency of the final products against five protein kinases (CDK5/p25, CK1d/ε, GSK3a/b, DYRK1A and CLK1) was estimated. Compounds (2a-z) turned out to be particularly promising for the development of new pharmacological dual inhibitors of CLK1 and DYRK1A kinases.



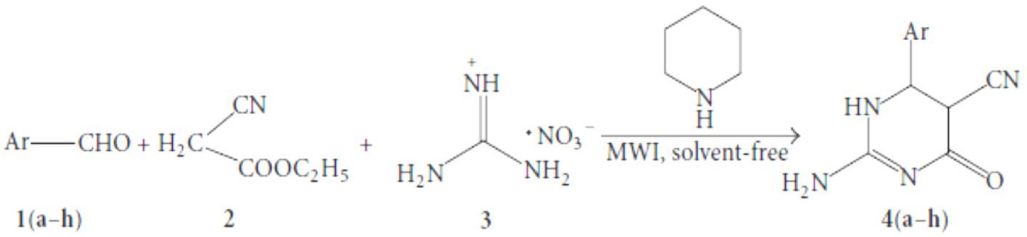
(Scheme 55a) and (Scheme 55b):General synthesis of benzofuro[3,2-d]pyrimidines (1a-z) and benzothieno[3,2-d]pyrimidine (2a-z) derivatives.

Puttaraju Kallimeledoddi B. et.al [75] reported the synthesis of 10H benzo[4,5]imidazo[1,2-a]pyrimidin-4-ones (2a-h) by reaction of an equimolar mixture of 2-aminobenzimadzole (0.5 g,3.75 mmol) and b-ketoesters (1aeh) (3.75 mmol) in DMF (10 mL) in a microwave tube fitted with a reflux condenser and equipped with a magnetic stir bar and irradiating in a microwave reactor at a temperature of 130^{o}C for 3 min at a maximum power of 320 W. The product was screened for their in vitro antibacterial activity against three Gram-positive bacteria viz., Staphylococcus aureus, Enterococcus faecalis, Streptococcus mutans and three Gram-negative bacteria viz., Escherichia coli, Kleb- siella pneumonia, Pseudomonas aeruginosa and antifungal activity against Candida albicans, Aspergillus niger, Aspergillus fumigatus, Aspergillus flavus, Fusarium oxysporum, Penicillium chrysogenum and anti-cancer activity against Dalton's Ascitic Lymphoma (DAL) cell line. In general, all the compounds possessed better antifungal properties than antibacterial properties (Scheme 56).



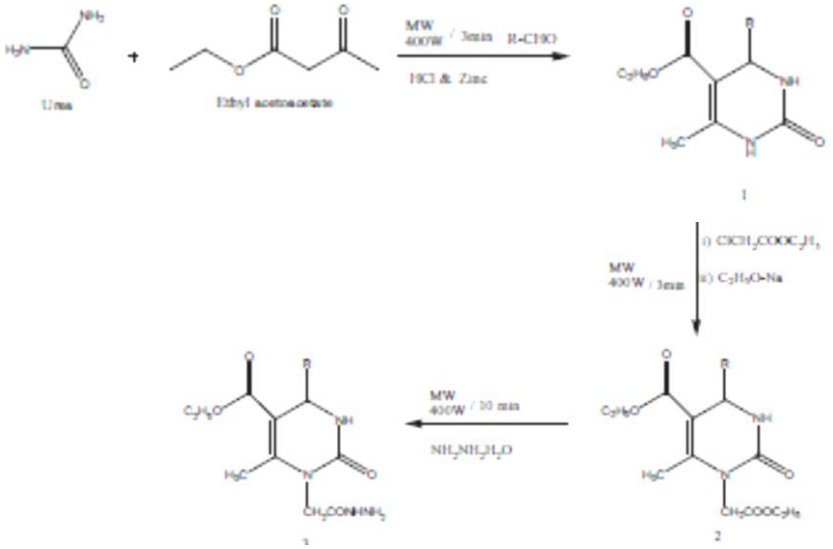
Scheme 56: Synthetic route for10H benzo[4,5]imidazo[1,2-a]pyrimidin-4-ones (2a-h)

BhatewaraAnjna, et.al [76]reported the synthesis of 2-amino Dihy-dropyrimidinoneDerivatives 4(a-h) by reaction of a mixture of aldehyde 1 (1mmol), ethyl cyanoacetate 2 (1.2mmol), guanidine nitrate 3 (1.5mmol), and 2-3 drops of piperidine subjecting to microwave irradiation at 60% power in 600W microwave oven for 5 min. (Scheme 57).The synthesized compounds showed a good anti-inflammatory, antibacterial, and antifungal activity.



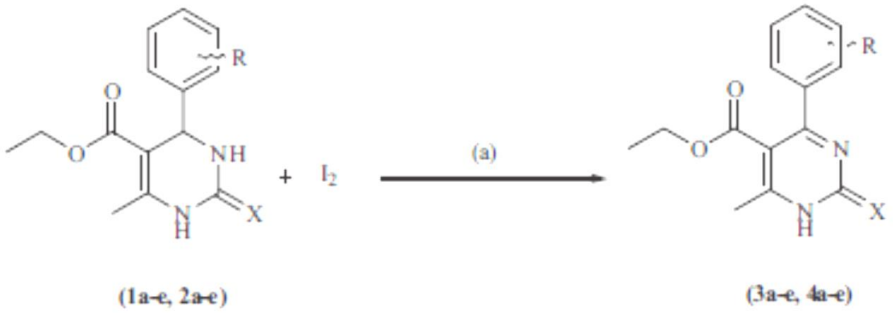
Scheme 57: Synthetic route for2-amino Dihy- dropyrimidinone Derivatives 4(a-h)

Khamgaonkar Vishal D. [77] et.al reported the synthesis of Ethyl 1-[(ethoxycarbonyl) methyl]-1,2,3,4- tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5- carboxylate (2a). The compound 1 (0.1 mol) was dissolved in a solution prepared by reacting Na (0.1 mol) with 200 ml of absolute ethanol. The solution was kept in microwave for 10 min at 200 W. Ethyl chloroacetate (0.1 mol) was then added in three portions over a period of 2 min. (Scheme 58). All compounds were evaluated for antibacterial activity by the broth microdilution assay method and found moderately active.



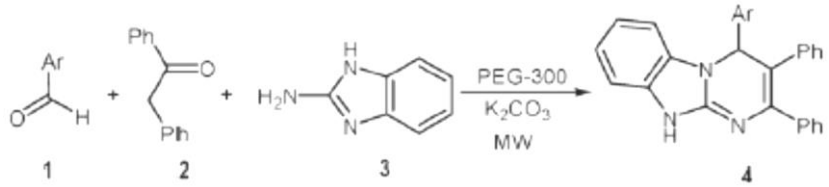
Scheme 58: Synthetic route forEthyl 1-[(ethoxycarbonyl) methyl]-1,2,3,4- tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5- carboxylate (2a).

Kodape Manisha M. et.al [78] reported facile aromatization of 3,4-dihydropyrimidin-2(1H)-ones using iodine in dimethyl sulfoxide under microwave irradiation at 120°C for 5 min(Scheme 59).



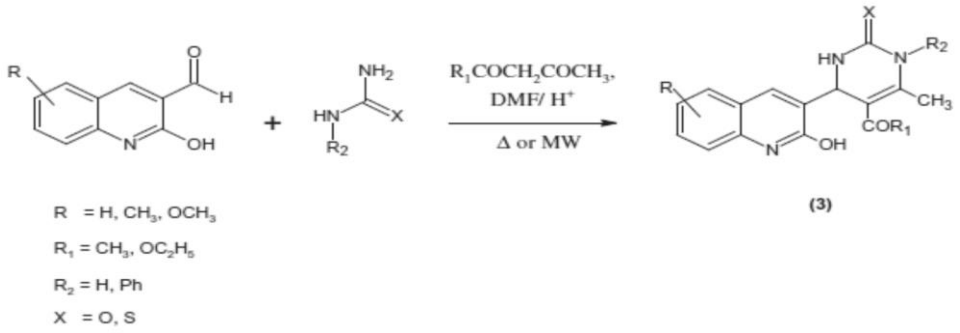
Scheme 59: Synthesis of 3,4-dihydropyrimidin-2(1H)-ones Reagent and condition: (a) I2 (1:1), DMSO, MW, 120°C

WangShu-Liang, et.al [79]reported the one-pot synthesis of benzo[4,5]imidazo[1,2-a]pyrimidine derivatives under microwave irradiation conditions by freaction of aromatic aldehyde 1 (1 mmol), 1,2-diphenyletha- none 2 (1 mmol), 2-aminobenzimidazole 3 (1 mmol), potassium carbonate (0.4 mmol), and PEG-300 (2 mL) and irradiating at 120°C under microwave irradiation (initial power 100 W and maximum power 250 W) (Scheme 60).



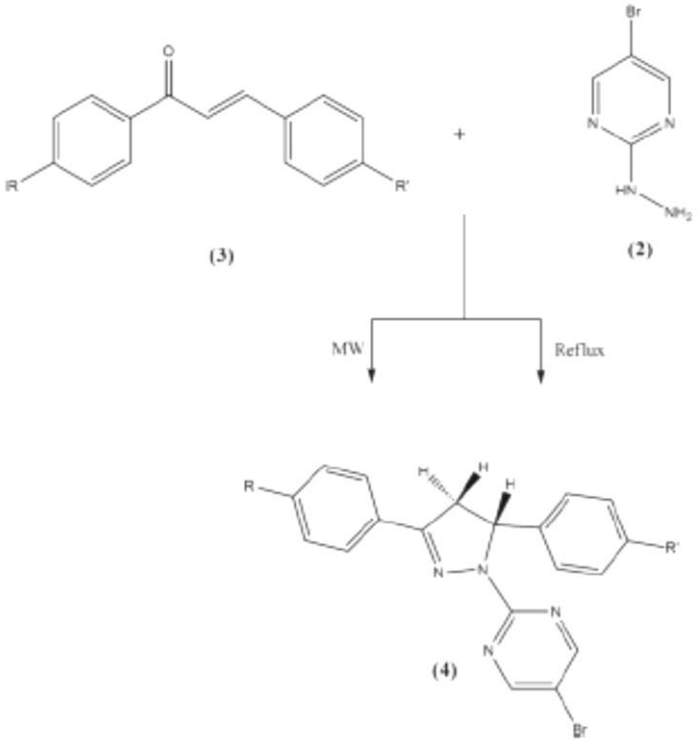
Scheme 60: Synthetic route forbenzo[4,5]imidazo[1,2-a]pyrimidine derivatives

Adhikari Adithya, et.al [80]reported the synthesis of 1-substituted-4-(6- substituted-2-hydroxyquinoline-3-yl)-5-acetyl/carboxyethyl-6-methyl-pyrimidine-2-one/thiones (3a–l) by reaction of 6-Substituted-2-hydroxyquinoline-3-carbaldehyde (0.005 mol), ethyl acetoacetate/ acetylacetone (0.005 mol), urea/thiourea/ phenylthiourea (0.005 mol) and DMF (5 mL) and two drops of conc. H_2SO_4 and subjecting to MW irradiation (160 W) (Scheme 61). Further these compounds were evaluated for their antioxidant, antifungal and antibacterial activities. Most of the compounds showed moderate to good activity when compared with standard.



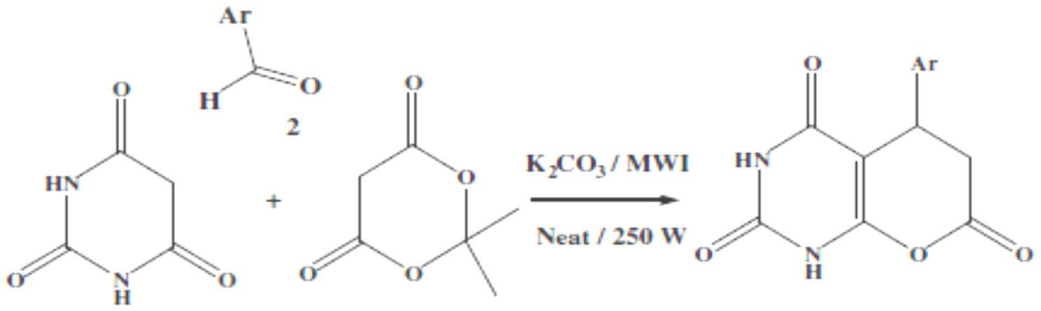
Scheme 61: Synthetic route for1-substituted-4-(6- substituted-2-hydroxyquinoline-3-yl)-5-acetyl/carboxyethyl-6- methyl-pyrimidine-2-one/thiones

Adhikari Adithya et.al [81]reported the synthesis of 5-bromo-2-(3,5-diaryl-4,5-dihydro-1H-pyrazol-1-yl)pyrimidine by grounding substituted chalcones (3) (0.001 mol), 5-bromo-2-hydrazinylpyrimidine (2) (0.001 mol) and 5 drops of glacial acetic acid together in a mortar using a pestle for uniform mixing. This was taken in a 50 mL beaker and subjected to microwave irradiation (90 W) (Scheme 62). These new compounds were screened for their antioxidant, anti-inflammatory and analgesic activities. Some of these compounds exhibited potent biological activities compared to the standard drug.



Scheme 62: Synthetic route for 5-bromo-2-(3,5-diaryl-4,5-dihydro-1H-pyrazol-1-yl)pyrimidine

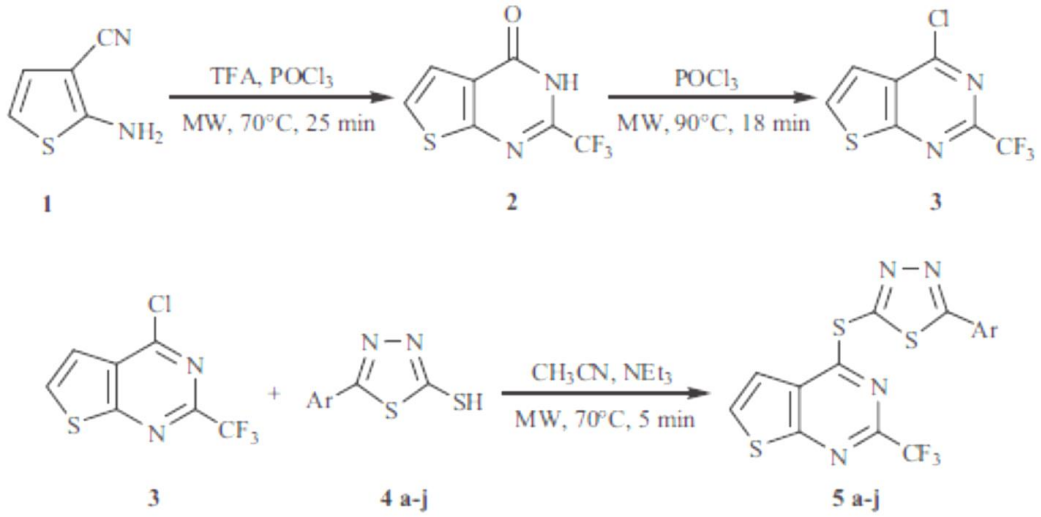
Azzam Sadeq Hamood Saleh et.al [82]reported the synthesis of novel pyrano[2,3-d]pyrimidine-2,4,7-trionesin a pyrex cylindrical tube equipped with a magnetic stir bar, a mixture of aromatic aldehyde (2 mmol), Meldrums acid (2 mmol), barbituric acid (2 mmol), and K_2CO_3 (10 mol %) then irradiating in a microwave reactor for (1 min) at 100^{o}C/250W(Scheme 63).



Scheme 63: Synthesis of 5-aryl-5,6-dihydro-1H-pyrano[2,3-d]pyrimidine-2,4,7-triones.

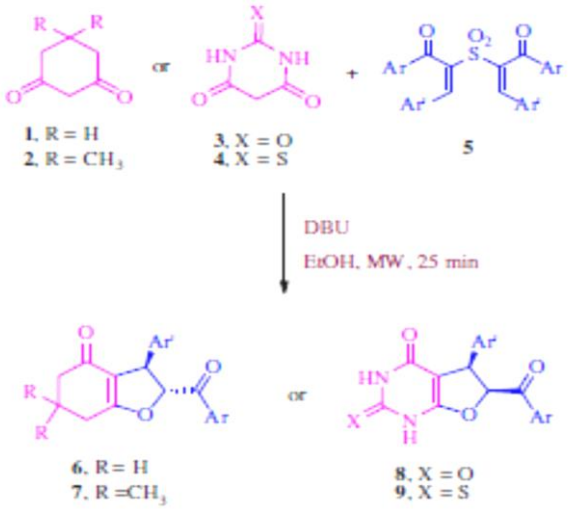
Song Xin Jian et.al [83]reported the synthesis of novel fluorinated thieno[2,3-d]pyrimidine derivatives containing 1,3,4-thiadiazole. Initially a mixture of 2-aminothiophene-3-carbonitrile 1 (10 mmol), trifluoroacetic acid (28 mL) and phosphorus oxychloride (2 mL) was irradiated at 70 ^{o}C for 25 min by microwave to give 2- trifluoromethyl-3H-thieno[2,3-

d]pyrimidin-4-one 2. Then a mixture of 2 (10 mmol) and phosphorus oxychloride (8 mL) was irradiated with microwave at 90°C for 18 min to afford 4-chloro-2-trifluoro-methylthieno[2,3-d]-pyrimidine 3 followed by reaction of solution of 3 (5 mmol) and the appropriate 1,3,4-thiadiazole-2-thiol 4 (5 mmol), triethylamine (0.5 mL) in dried acetonitrile (15 mL) and irradiating to microwave irradiation for 5 min at 70°C to give compounds 5a–j (Scheme 64).



Scheme 64: Synthetic route of fluorinated thieno[2,3-d]pyrimidine derivatives 5a–j.

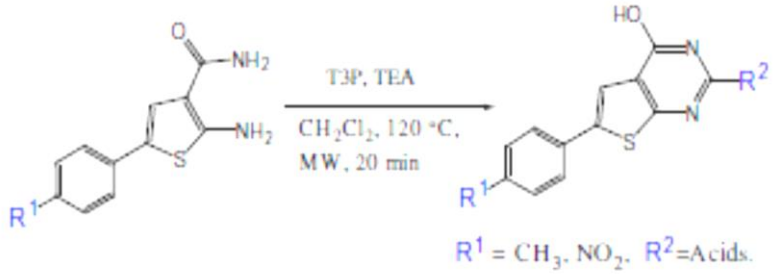
Vinosha Beermohamed et.al [84]reported the synthesis of trans-2,3-dihydrobenzofurans (6 and 7) and cis-5,6- dihydrofuro[2,3-d]pyrimidines (8 and 9) by reaction of a mixture of 2,20- sulfonylbis(1,3-diarylprop-2-en-1-ones) 5 (1 mmol), cyclic 1,3-diketones 1–4 (1 mmol) and DBU (0.5 mmol) in ethanol (5 ml) and subjecting to microwave irradiation microwave oven at 140°C, 50 W, 5 bar pressure and maximum absorption level (Scheme 65). This transformation presumably occured via domino Michael addition-proton exchange-annulation via intramolecular displacement sequence.



Scheme 65: Synthesis of trans-2,3-dihydrobenzofurans (6 and 7) and cis-5,6-dihydrofuro[2,3-d]pyrimidines (8 and 9)

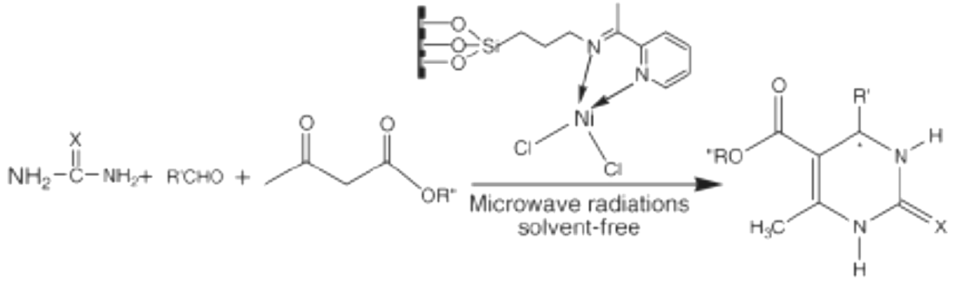
PoojariSubba, et.al [85] reported the synthesis of thieno [2,3-d] pyrimidin-4-ol derivatives mediatedby polyphosphonic anhydride by reaction of a mixture of 2-amino-5-(4-methylphenyl) thiophene-3-carboxamide 1a (0.25 g, 0.107 mol) and 4-benzyloxy benzoic acid 4a (0.319 g, 0.140 mol) in anhydrous chloroform (4 ml) followed by addition of triethylamine (0.32 g, 0.323 mol) and phosphonic acid cyclic anhydride (1.02 g, 0.323 mol).

The reaction mixture was irradiated at 120°C in a microwave initiator for 30 min(Scheme 66).



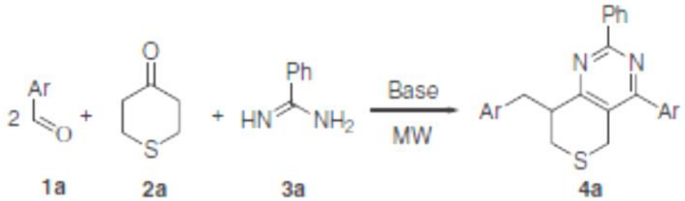
Scheme 66: Synthetic route forthieno [2,3-d] pyrimidin-4-ol derivatives

Sharma R.K. et.al [86]reported the one-pot synthesis of dihydropyrimidinones in presence of covalently anchored nickel complex on silica as catalyst under solvent-free conditions by reaction of a mixture of aldehyde (15 mmol), urea (20 mmol), ethyl acetoacetate (15 mmol), and catalyst (5 mol%) and irradiating in the microwave reactor (100 W) at 80° C for 5 minutes(Scheme 67).



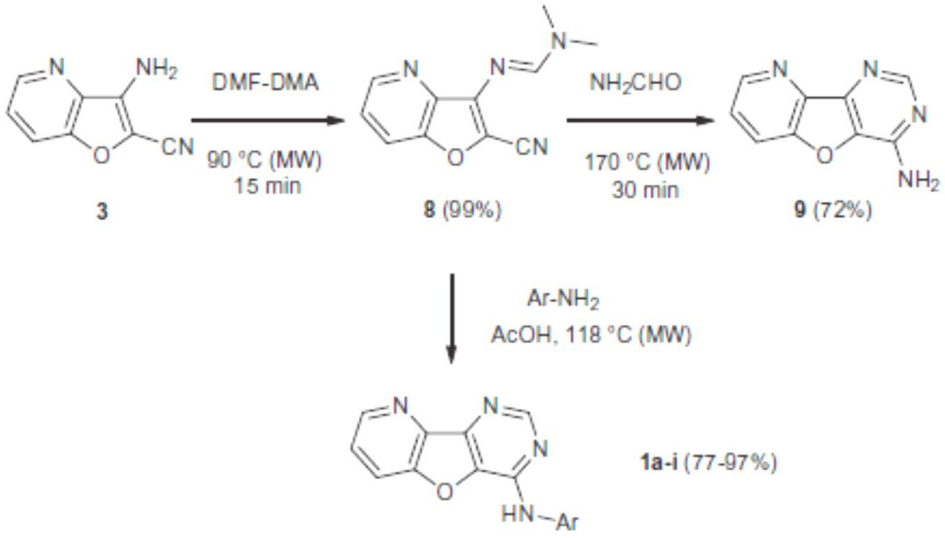
Scheme 67: One-pot synthesis of 3,4-dihydropyrimidinone catalyzed by covalently anchored nickel catalyst under microwave radiation.

Jiang Bo et.al [87]reported the synthesis of a series of new functionalized thiopyrano-, pyrano[4,3-d]pyrimidine derivatives with benzyl group residing in 8-position of fused pyrimidine nucleus were synthesized through multicomponent reactions of aromatic aldehydes, tetrahydrothiopyran-4-one(tetrahydropyran-4-one), and aryl amidines using t-BuOK as a base under microwave heatingby stirring mixture of aromatic aldehyde 1 (2 mmol), tetrahydrothiopyran-4-one or trahydropyran-4-one 2 (1 mmol), t- BuOK (2.0 mmol), t-BuOH (2.0 mL) at room temperature for 10 min. Subsequently aryl amidine 3 (1.1 mmol) was added into the mixture and then capped. The mixture was irradiated for a given time at 140°C.(Scheme 68).



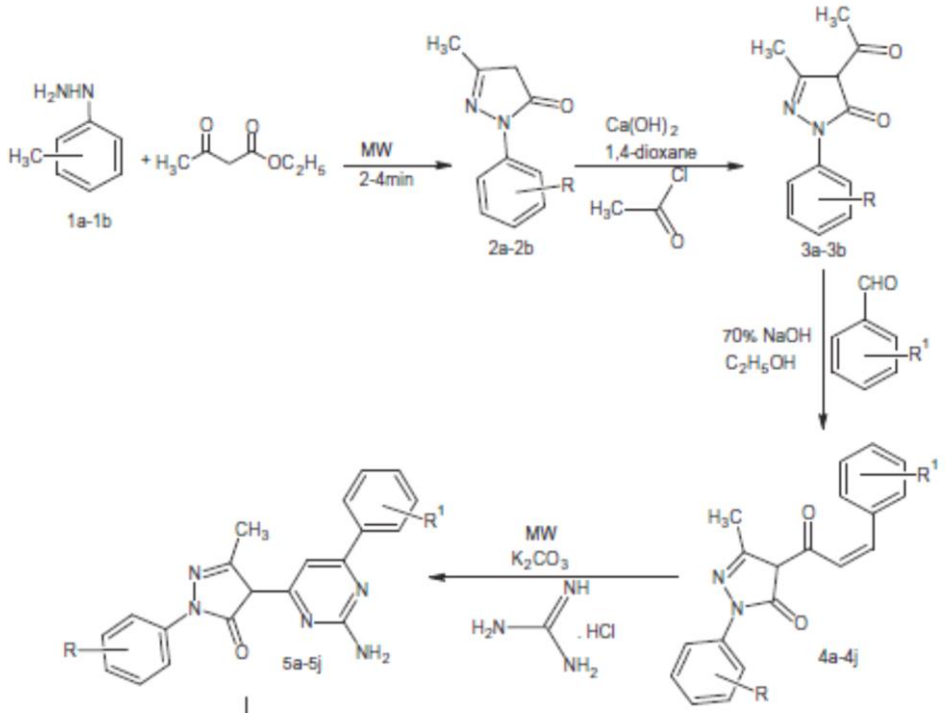
Scheme 68: Synthetic route forthiopyrano-, pyrano[4,3-d]pyrimidine derivatives

Loidreau Yvonnick et.al [88]reported the synthesis of N-arylpyrido[2',3':4,5]furo[3,2-d]pyrimidin-4-amines (1a–i) by reaction of a mixture of N'-(2-cyanofuro[3,2-b]pyridin-3-yl)-N,N-dimethyl formimidamide 8 (0.1 g, 0.47 mmol) and appropriate aniline (1.0 equiv) in acetic acid (2 mL) and irradiating at 118°C (400 W, 3 min ramp) (Scheme 69).



Scheme 69: Synthetic route forN-arylpyrido[2',3':4,5]furo[3,2- d]pyrimidin-4-amines (1a–i)

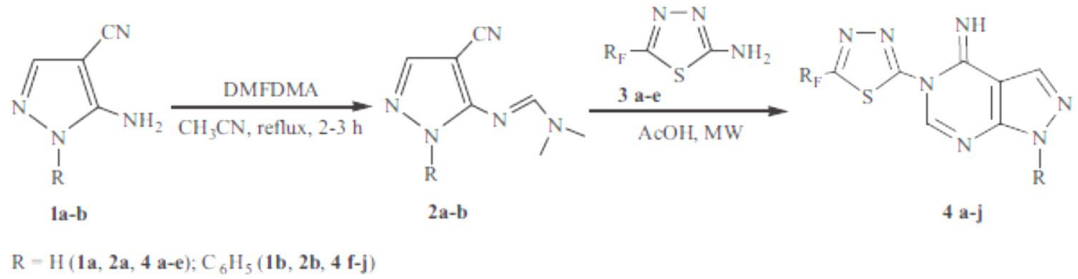
Antre Rishikesh V. et.al [89]reported the synthesis of 4-(2-amino-6-(substituted)pyrimidin-4-yl)-3-methyl-1-(substituted)-1H-pyrazol-5(4H)-one derivatives (5a–5j) by reaction of mixture of the chalcone derivatives (4a–4j) (0.001 mol) and guanidine hydrochloride (0.002 mol) in acetone (5 mL) and ethanol (5 mL), K_2CO_3 and stirring vigorously. After 5 min, solvent was evaporated and the dry powder was irradiated in microwave oven for the appropriate time in between 6–9 min at 50% power output (Scheme 70).The compounds were found to exhibit anti-inflammatory, analgesic and antipyretic activities.



Scheme 70:Synthetic route for 4-(2-amino-6-(substituted)pyrimidin- 4-yl)-3-methyl-1-(substituted)-1H-pyrazol-5(4H)-one derivatives (5a–5j)

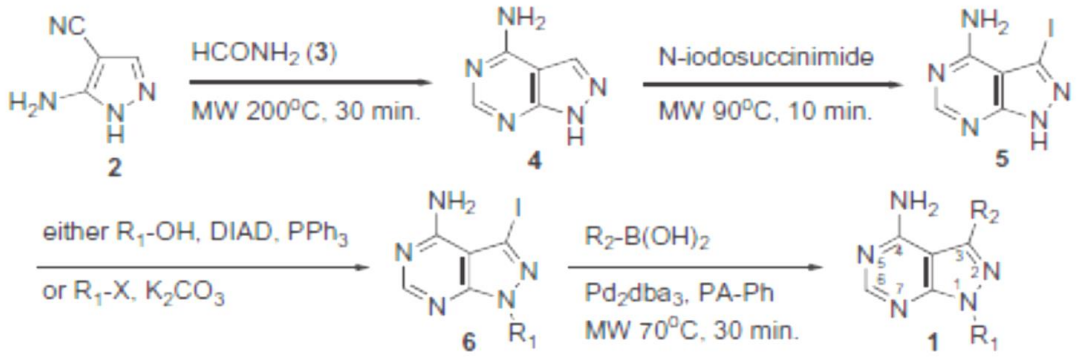
Song Xin Jian et.al [90]reported the synthesis of novel fluorinated pyrazolo[3,4-d]pyrimidine derivatives containing 1,3,4-thiadiazole. The synthesis of 5-(5-substituted-1,3,4-thiadiazol-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-imine (4a–e) was done by reaction of the solution of 1H-4-cyano-5-[(N,N-dimethylaminomethylene)amino]pyrazole 2a (0.33 g, 2 mmol) and the appropriate aminothiadiazoles 3 (2 mmol) in 6 mL glacial acetic

acid and irradiating at 140°C for 18 min by microwave (Scheme 71). Their antitumor activities were evaluated against HL-60 by an MTT assay. The preliminary results indicated that some title compounds exhibit more potent antitumor inhibitory activity than doxorubicin (DOX).

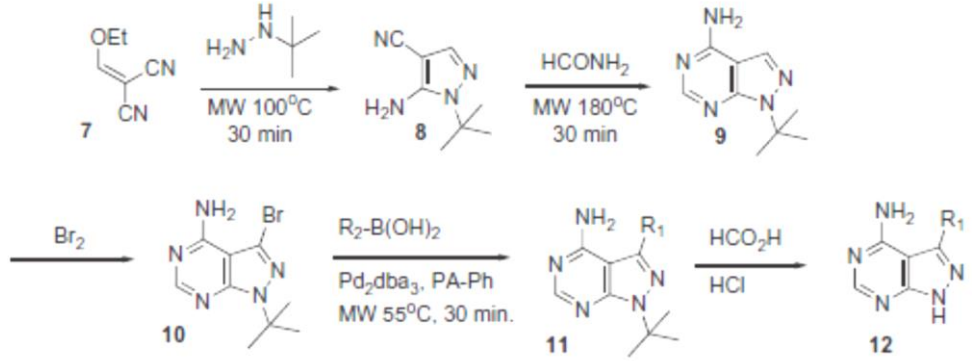


Scheme 71: Synthetic route forfluorinated pyrazolo[3,4-d]pyrimidine derivatives containing 1,3,4-thiadiazole

Todorovic Nick et.al [91]reported synthesis of a library N1- and C3-substituted-pyrazolo[3,4-d]pyrimidines. The microwave-assisted approach involved the de novo generation of the heterocyclic scaffold, facile alkyl- ation at N1 via either a Mitsunobu or a direct alkylation reaction and arylation at C_3 via a Suzuki reaction(Scheme 72a) (Scheme 72b).



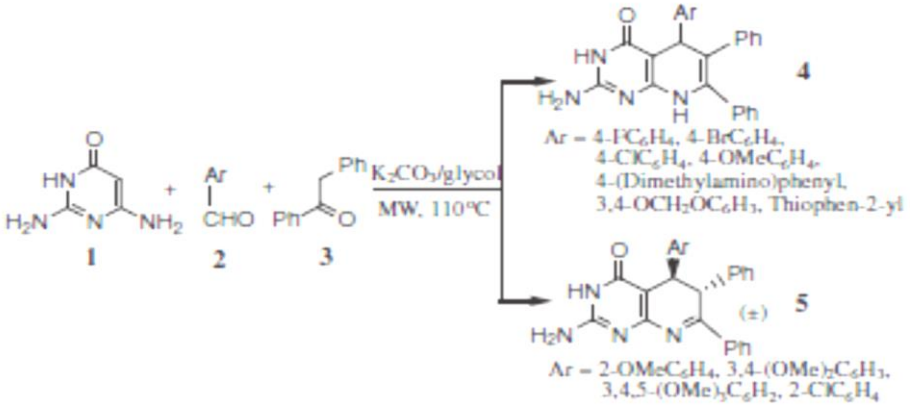
Scheme 72a: Synthetic route to 1-alkyl-3-aryl-1H-pyrazolo[3,4-d]pyrimidin-4-amines



Scheme 72b: Synthetic route to 3-aryl-1H-pyrazolo[3,4-d]pyrimidin-4-amines(12)

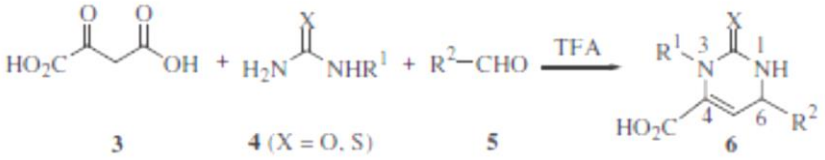
Shi Feng et.al[92] reported the synthesis of novel 5,6,7-triarylpyrido[2,3-d]pyrimidin-4-one derivatives by reaction of 2,6-diaminopyrimidin-4(3H)-one 1(1 mmol), aromatic aldehydes 2 (1 mmol) and 1,2-diphenylethanone 3 (1 mmol) in 2mL of glycol with the presence of K_2CO_3 (0.1 mmol) at 110°C under microwave irradiation (MW) at the initial/maximum power of 100 W/250 W (Scheme 73). The novel compounds were subjected to the test of in

vitro cytotoxicity to carcinoma SW1116 and SGC7901 cells. Most of the tested compounds showed significant cytotoxicity to SW1116 cells.



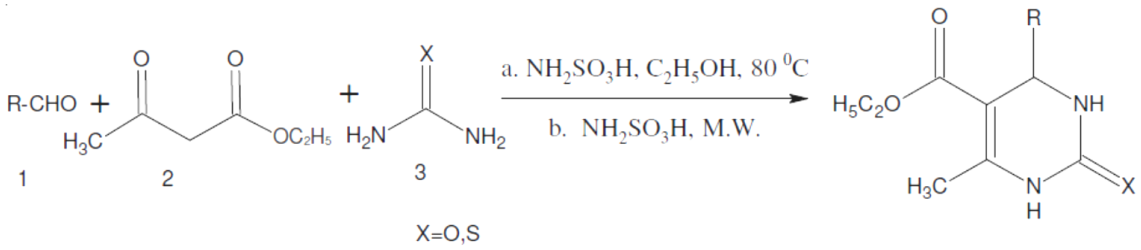
Scheme 73: Chemoselective synthesis of 5,6,7-triarylpyrido[2,3-d]pyrimidin-4-one derivatives 4 and 5.

Fang Zhanxiong et.al [93] reported the synthesis of 5-unsubstituted 3,4-dihydropyrimidin-2-ones and thiones by reaction of a mixture of oxalacetic acid (2.6 mmol), aldehyde (2.0 mmol),and urea/thiourea (2.6 mmol) in THF (3 mL) was added TFA (0.10 mL). The mixture was heated at 95°C for 15 min using microwave irradiation in a sealed tube. (Scheme 74)



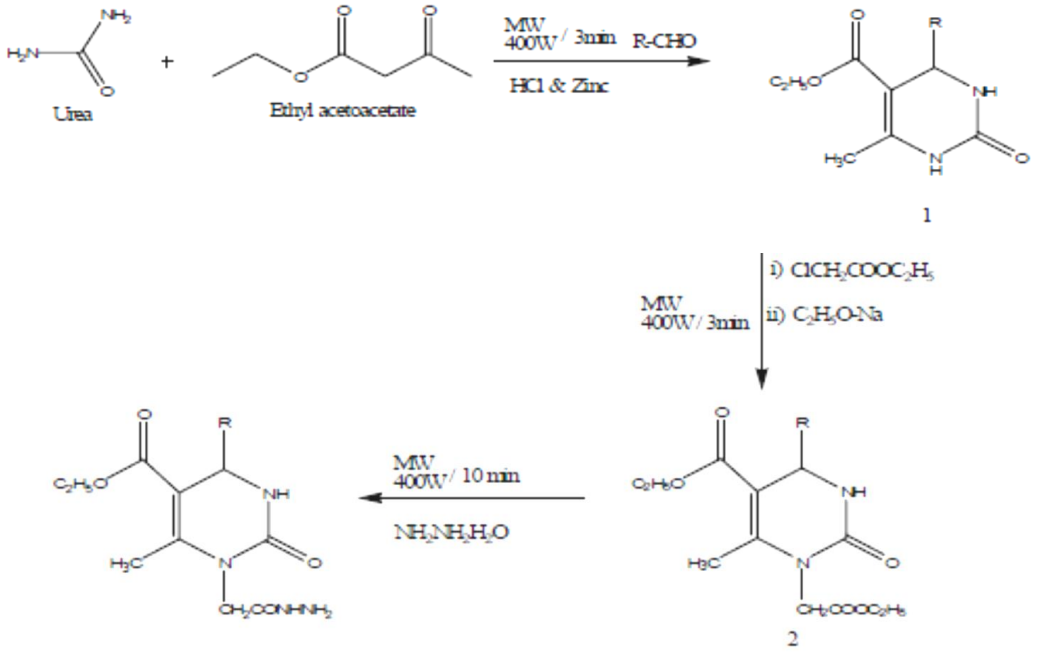
Scheme 74: Synthetic route for 5-unsubstituted 3,4-dihydropyrimidin-2-ones and thiones

Pai Nandini et.al [94]reportedthe synthesis of 3,4-dihydropyrimidinones (DHPMS) using sulfamic acid as catalyst from an aldehyde (1mmol), ethyl acetoacetate (1 mmol), urea or thiourea (1.5 mmol) and sulfamic acid (20 mol %) in a beaker covered with watch glass and irradiating at 300 watt.(Scheme 75)



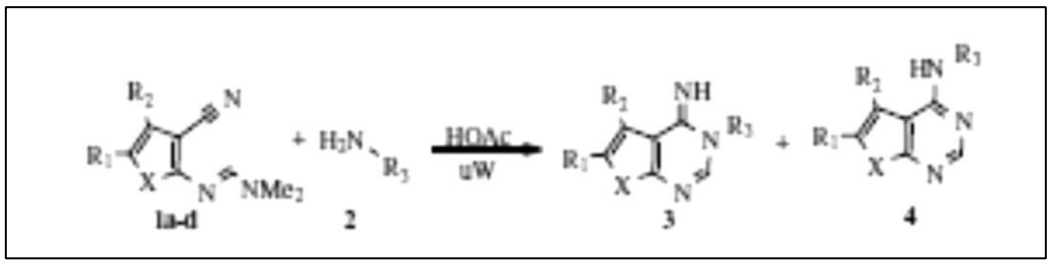
Scheme 75: Synthetic route for 3,4-dihydropyrimidinones (DHPMS)

Singh Niharika I et.al [95] reported the synthesis of Ethyl 1-(2-Hydrazino-2-Oxoethyl)-6-Methyl-2-oxo-4-Phenyl-1, 2, 3, 4-Tetrahydropyrimidine-5-Carboxylate by reaction of a mixture of the appropriate compound (1) (0.1mol), hydrazine hydrate (8 drops), and 10ml of 95% ethanol and refluxing under microwave for 3min at 840 power (Scheme 76).



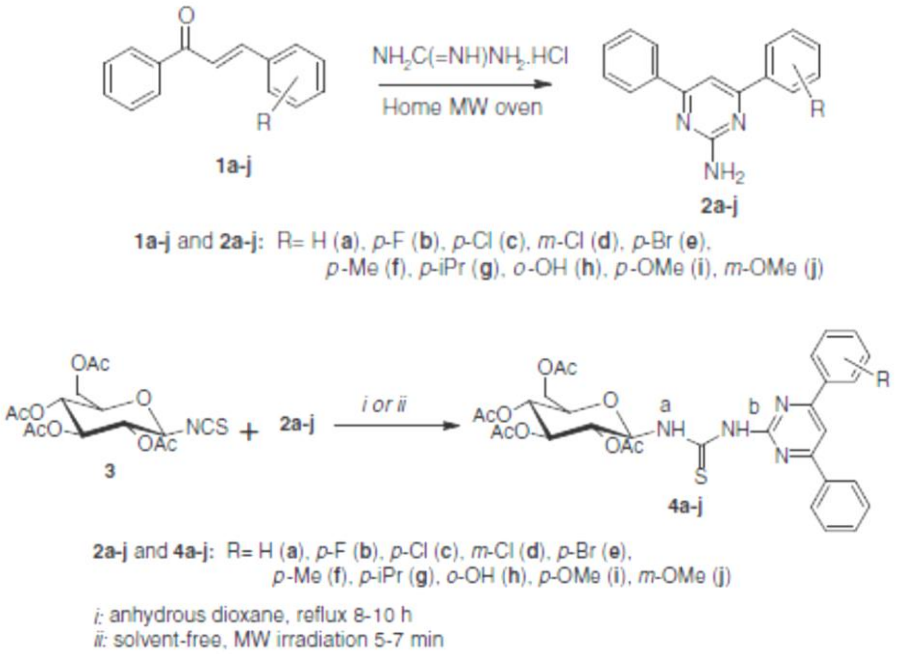
Scheme 76:Synthetic route for Ethyl 1-(2-Hydrazino-2-Oxoethyl)-6-Methyl-2-oxo-4-Phenyl-1, 2, 3, 4-Tetrahydropyrimidine-5-Carboxylate

Han Ying et.al [96]reported the synthesis of furo- and thieno[2,3-d]pyrimidin-4-amine derivatives by microwave irradiation from readily available aminesand substituted 2-aminofuran-3-carbonitrile or 2-aminothiophene-3-carbonitrile (6.2 mmol) and converting into corresponding formamidines(1a) in DMF using benzenesulfonyl chloride (12 mmol).Thenin next step acetic acid (0.8 mL), formimidamide 1a (0.2 mmol), and benzylamine (0.3 mmol) 2a was irradiated in microwave at 180°C for 35 min. (Scheme 77).



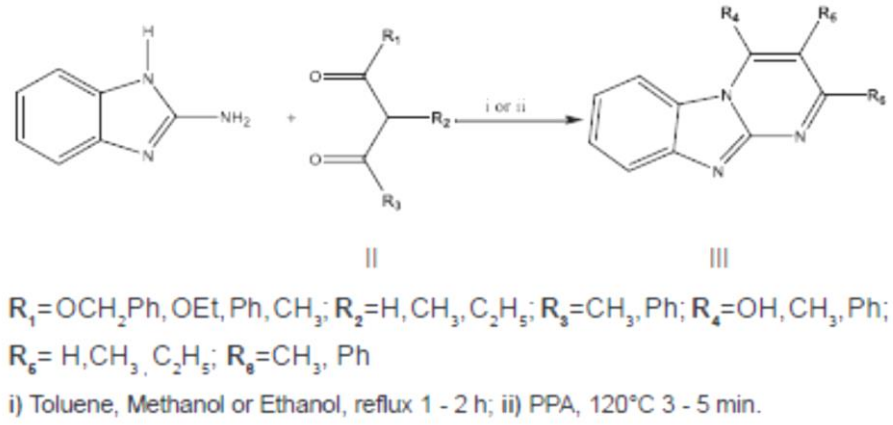
Scheme 77: Synthetic route forfuro- and thieno[2,3-d]pyrimidin-4-amine derivatives

Thanh Nguyen Dinh et.al [97]reported the synthesis of N-(2,3,4,6-tetra-O- acetyl-b-D-glucopyranosyl)-N0-(40,60-diarylpyrimidin-20- yl)thioureas (4a–j) tions) by grinding of a mixture of 2-amino-4,6-diarylpyrimidine 2 (2 mmol) and 2,3,4,6-tetra-O-acetyl-b-D-glucopyranosyl isothiocyanate 3 (2 mmol) in a porcelain beaker. Then the mixture was put into a domestic microwave oven (the power output is 750 W). The adjustor of the microwave oven was set to the proper temperature (about 50°C) (Scheme 78). The compounds were found to exhibit antibacterial and antifungal activities against Staphylococcus epidermidis, Enterobacter aerogenes and Candida albicans.



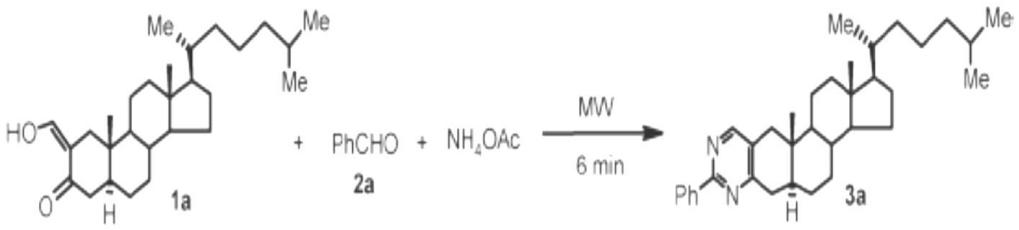
Scheme 78: Synthetic pathway for N-(2,3,4,6-tetra-O-acetyl-b-D-glucopyranosyl)-N0-(4,6-diarylpyrimidin-2-yl)thioureas (4a–j)

Algul Oztekin et.al [98]reported the synthesis of 2,4-di- and 2,3,4-trisubstituted benzimidazo[1,2-a]pyrimidine compounds (IIIa-g) by reaction of 2-Aminobenzimidazole (2.5 mmol), dicarbonyl compounds (2.5 mmol) and 5 g PPA in a microwave oven and irradiating at low power for 3 - 5 min. The compounds were found to exhibit antimicrobial activities. (Scheme 79)



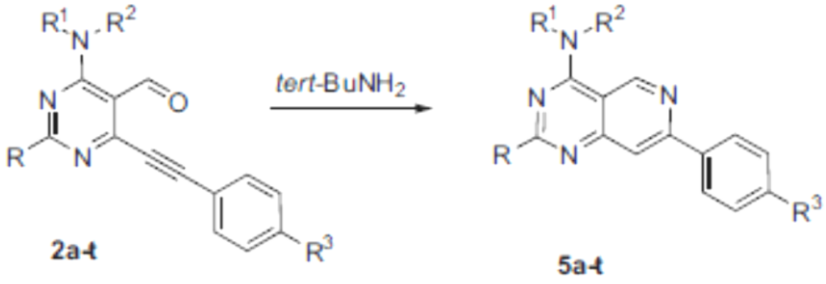
Scheme 79: Synthetic route for 2,4-di- and 2,3,4-trisubstituted benzimidazo[1,2-a]pyrimidine compounds (III)

Barthakur Madan G. et.al [99]reported the synthesis of 2'-Aryl-steroidal[3,2-d]pyrimidine by intimately mixing of 2-Hydroxymethylene-3-ketosteroid (1a, 1mmol), aromatic aldehyde (2a, 2mmol) and ammonium acetate (2mmol) with silica gel (60–120mesh, 2.0 g) in a mortar and irradiating the mixture in microwave reactor for 6min after setting reaction temperature at 120◦C and power at 60% (maximum output 300W) (Scheme 80).



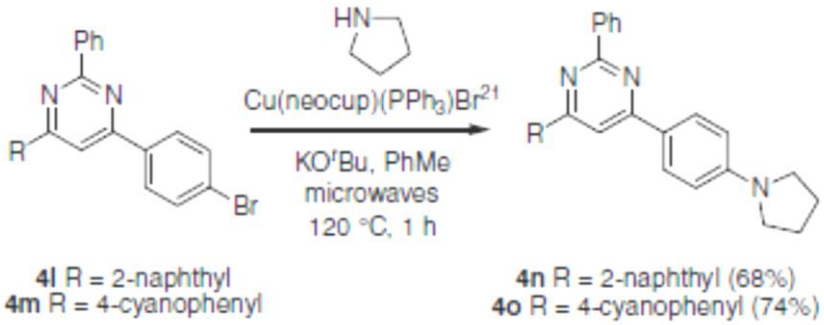
Scheme 80:Synthesis of steroidal pyrimidines 3a from 2-hydroxymethylene-3-ketocholestan 1a.

Cikotiene Inga et.al [100]reported the synthesis of 2,4- disubstituted 7-arylpyrido[4,3-d]pyrimidines 5a–t by reaction of a solution of the corresponding 2,4-disubstituted 6-arylethynylpyrimidine-5-carbaldehydes 2a–t (0.2 mmol) and tert- butylamine (0.15 g, 2 mmol) in DMF (3 mL) and irradiating in a microwave oven at 500W for 10 min to one hour. (Scheme 81)



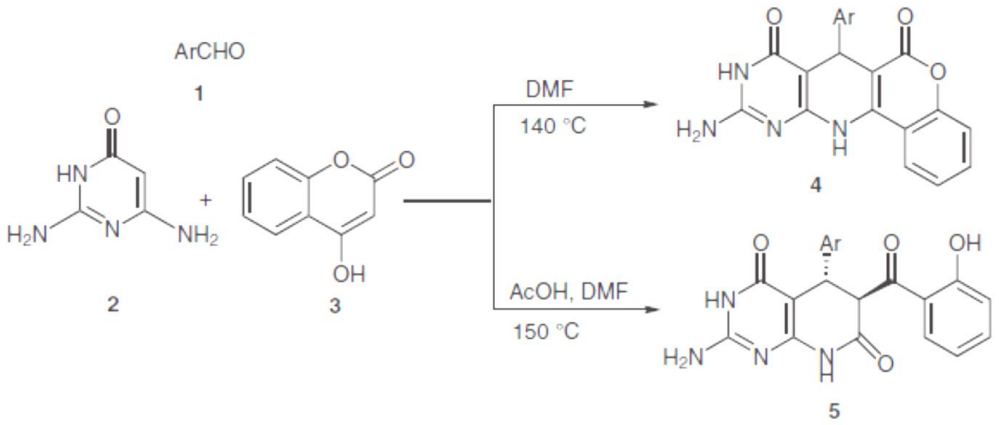
Scheme 81: Synthetic route for2,4- disubstituted 7-arylpyrido[4,3-d]pyrimidines 5a–t

Bagley Mark C. et.al [101]reported the synthesis of 4-{2-phenyl-6-[4-(pyrrolidin-1-yl)phenyl]pyrimidin-4-yl}benzonitril by adding a solution of benzonitrile 4m (0.57 mmol, 1 equiv) in toluene (3 mL) to a stirred solution of pyrrolidine (1.13 mmol, 2 equiv), Cu(neocup)(PPh_3)Br[21] (10 mol %) and potassium tert-butoxide (0.85 mmol, 1.5 equiv) in toluene (3 mL) and irradiating at 120°C, at an initial power of 150 W for 1 h (Scheme 82).



Scheme 82: Synthetic route for 4-{2-phenyl-6-[4-(pyrrolidin-1-yl)phenyl]pyrimidin-4-yl}benzonitril

Tus, et.al [102] reported the synthesis of 2-Amino-5-aryl-6-(2-hydroxybenzoyl)-5,8-dihydropyrido[2,3-d]pyrimidine 4,7 (3H,6H)-dione 5; by reaction of aldehyde 1 (1 mmol), 2,6-diaminopyrimi- din-4(3H)-one (2, 126 mg, 1 mmol), 4-hydroxy-2H-chromen-2-one (3, 162 mg, 1 mmol), AcOH (0.4 mL), and DMF (1.6 mL) and irradiating for 5 min at 100 W (initial power) and 200 W (maximum power) and 150 °C. (Scheme 83)



Scheme 83: Synthetic route for 2-Amino-5-aryl-6-(2-hydroxybenzoyl)-5,8-dihydropyrido[2,3-d]pyrimidine 4,7 (3H,6H)-dione 5

Conclusion:

As described in this paper, pyrimidine derivatives are very important, effective and valuablecompounds in medicine and pharmaceutical industries. Therefore, synthesis of these compounds has received much attention among the organic researchers. During recent years, to synthesize pyrimidine derivatives, prior attention is given to non conventional methods as compared to traditional protocol since in traditional protocols in organic synthesis, unfortunately, most of them have main disadvantage such as unsatisfactory yields, formation of side product, harsh reaction conditions, use of strong bases, and environmentally unfriendly due to use of an hazardous and toxic organic solvent as reaction medium. Green chemistry promotes a modern idea for accomplishing chemical research and productions. With enhancing public concerns on environmental protection, chemistry science researchers are asked to maximize the advantages of chemical products and minimize the side effects that could be harmful to the environment and humans. Organic reactions conducting under nontraditional conditions (green synthetic strategies) are obtaining in popularity, primarily to decrease environmental concerns. The advantages of green synthetic strategies facilitated (assisted) organic transformations, namely the selectivity, simplicity of experimental manipulation, and increased reaction rates, were highlighted. The advantage of these strategies is obvious; it is not only useful for the world economy, but also acts toward making the world more environmentally friendly.

References:

[1] M.M. Karelson, A.R. Katritzky, M. Szafran, M.C. Zerner, Quantitative pre- dictions of tautomeric equilibria for 2-, 3-, and 4-substituted pyridines in both the gas phase and aqueous solution: combination of AM1 with reaction field theory, J. Org. Chem. 54 (1989), 6030-6034.

[2] S.M. Sondhi, R.N. Goyal, A.M. Lahoti, N. Singh, R. Shukla, R. Raghubir, Synthesis and biological evaluation of 2-thiopyrimidine derivatives, Bioorg. Med. Chem. 13 (2005), 3185-3195.

[3] G.C. Rovnyak, K.S. Atwal, A. Hedberg, S.D. Kimball, S. Moreland, J.Z. Gougoutas, B.C. O'Reilly, J. Schwartz, M.F. Malley, Dihydropyrimidine calcium channel blockers. 4. Basic 3-substituted-4-aryl-1, 4-dihydropyrimidine-5-carboxylic acid esters. Potent antihypertensive agents, J. Med. Chem. 35 (1992), 3254-3263.

[4] P.S. Dragovich, B.P. Fauber, L.B. Corson, C.Z. Ding, C. Eigenbrot, H. Ge, A.M. Giannetti, T. Hunsaker, S. Labadie, Y. Liu, Identification of substituted 2- thio-6-oxo-1, 6-dihydropyrimidines as inhibitors of human lactate dehydro- genase, Bioorg. Med. Chem. Lett. 23 (2013), 3186-3194.

[5] N. Agarwal, P. Srivastava, S.K. Raghuwanshi, D. Upadhyay, S. Sinha, P. Shukla, V.J. Ram, Chloropyrimidines as a new class of antimicrobial agents, Bioorg. Med. Chem. 10 (2002), 869-874.

[6] M.R. Bhosle, A.R. Deshmukh, S. Pal, A.K. Srivastava, R.A. Mane, Synthesis of new thiazolylmethoxyphenyl pyrimidines and antihyperglycemic evaluation of the pyrimidines, analogues isoxazolines and pyrazolines, Bioorg. Med. Chem. Lett. 25 (2015), 2442-2446.

[7] G. Lauro, M. Strocchia, S. Terracciano, I. Bruno, K. Fischer, C. Pergola, O. Werz, R. Riccio, G. Bifulco, Exploration of the dihydropyrimidine scaffold for the development of new potential anti-inflammatory agents blocking prosta- glandin E2 synthase-1 enzyme (mPGES-1), Eur. J. Med. Chem. 80 (2014), 407-415.
[8] S.A. Said, A.E.-G.E. Amr, N.M. Sabry, M.M. Abdalla, Analgesic, anticonvulsant and anti-inflammatory activities of some synthesized benzodiazipine, tri- azolopyrimidine and bis-imide derivatives, Eur. J. Med. Chem. 44 (2009), 4787-4792.
[9] R.H. Tale, A.H. Rodge, G.D. Hatnapure, A.P. Keche, The novel 3, 4- dihydropyrimidin-2 (1H)-one urea derivatives of N-aryl urea: synthesis, anti-inflammatory, antibacterial and antifungal activity evaluation, Bioorg. Med. Chem. Lett. 21 (2011), 4648-4651.
[10] B.N. Naidu, M.E. Sorenson, M. Patel, Y. Ueda, J. Banville, F. Beaulieu, S. Bollini, I.B. Dicker, H. Higley, Z. Lin, Synthesis and evaluation of C2-carbon-linked heterocyclic-5-hydroxy-6-oxo-dihydropyrimidine-4-carboxamides as HIV-1 integrase inhibitors, Bioorg. Med. Chem. Lett. 25 (2015), 717-720.
[11] A.R. Trivedi, V.R. Bhuva, B.H. Dholariya, D.K. Dodiya, V.B. Kataria, V.H. Shah, Novel dihydropyrimidines as a potential new class of antitubercular agents, Bioorg. Med. Chem. Lett. 20 (2010), 6100-6102.
[12] Xie, W.; Jin, Y.; Wang, P. G. Chemtech. 1999, 2, 23.
[13] Kazemi M, Kohzadi H, Abdi M., J. Mater. Environ. Sci. 6 (2015), 1451.
[14] Constable D.J.C.C., Dunn P.J.C., Hayler J.D. Green Chem.9 (2007), 411.
[15] S. Caddick, Tetrahedron, 51, 1043 (1995).
[16] R. Laurent, A. Laporterie, J. Dubac, J. Berlan, S. Lefeuvre, and M. Audhuy, J. Org. Chem., 57, 7099 (1992).
[17] D. M. P. Mingos and D. R. Baghurst, Chem. Soc. Rev., 20, 1 (1991).
[18] Angelina Quintero, Araceli Pelcastre and José Dolores Solano (Antitumoral activity of new pyrimidine derivatives of sesquiterpene lactones), J Pharm Pharmaceut Sciences, 2 (3):108-112, 1999.

[19] T.A.Naik and K. H. Chikhalia (Studies on Synthesis of Pyrimidine Derivatives and their Pharmacological Evaluation), E-Journal of Chemistry, Vol. 4, No.1, pp 60-66, January 2007.

[20] Achary, L. S. K., Kumar, A., Rout, L., Kunapuli, S. V. S., Dhaka, R. S., & Dash, P. (2018). Phosphate functionalized graphene oxide with enhanced catalytic activity for Biginelli type reaction under microwave condition. Chemical Engineering Journal, 331(June 2017), 300–310.
[21] Kaur, M., Kaur, A., Mankotia, S., Singh, H., Singh, A., Singh, J. V., … Bedi, P. M. S. (2017). Synthesis, screening and docking of fused pyrano[3,2-d]pyrimidine derivatives as xanthine oxidase inhibitor. European Journal of Medicinal Chemistry, 131, 14–28.
[22] Kurasawa, O., Oguro, Y., Miyazaki, T., Homma, M., Mori, K., Iwai, K., … Cho, N. (2017). Identification of a new class of potent Cdc7 inhibitors designed by putative pharmacophore model: Synthesis and biological evaluation of 2,3-dihydrothieno[3,2-d]pyrimidin-4(1H)-ones. Bioorganic and Medicinal Chemistry, 25(7), 2133–2147.
[23] Baji, Á., Kiss, T., Wölfling, J., Kovács, D., Igaz, N., Gopisetty, M. K., … Frank, É. (2017). Multicomponent access to androstano-arylpyrimidines under microwave conditions and evaluation of their anti-cancer activity in vitro. Journal of Steroid Biochemistry and Molecular Biology, 172, 79–88.
[24] Sureja, D. K., & Vadalia, K. R. (2017). Microwave assisted, solvent-free synthesis and in-vitro antimicrobial screening of some novel pyrazolo[3,4- d]pyrimidin-4(5 H)-one derivatives. Beni-Suef University Journal of Basic and Applied Sciences, 6(1), 33–38.
[25] Lal, K., Paliwal, L. J., & Bagade, M. B. (2017). New Dihydropyrimidines as Antimicrobial Agents. Materials Today: Proceedings, 4(4), 5657–5662.
[26] Moradi, L., & Tadayon, M. (2017). Green synthesis of 3,4-dihydropyrimidinones using nano Fe 3 O 4 @meglumine sulfonic acid as a new efficient solid acid catalyst under microwave irradiation. Journal of Saudi Chemical Society.
[27] Elumalai, K., Ali, M. A., Srinivasan, S., Elumalai, M., & Eluri, K. (2017). Antimicrobial and in vitro cytotoxicity of novel sulphanilamide condensed 1,2,3,4-tetrahydropyrimidines. Journal of Taibah University for Science, 11(1), 46–56.
[28] Verbitskiy, E. V., Baskakova, S. A., Gerasimova, N. A., Evstigneeva, N. P., Zil'berberg, N. V., Kungurov, N. V., … Charushin, V. N. (2017). Synthesis and biological evaluation of novel 5-aryl-4-(5-nitrofuran-2-yl)-pyrimidines as potential anti-bacterial agents. Bioorganic & Medicinal Chemistry Letters, 27(13), 3003–3006.
[29] Rodríguez-Aguilar, J., Ordóñez, B., Vidal, M., Rezende, M., & Domínguez, M. (2017). Microwave-Promoted Synthesis of 4-Arylpyrimidines by Pd-Catalysed Suzuki–Miyaura Coupling of 4-Pyrimidyl Tosylates in Water. SynOpen, 1(1), 0024–0028.
[30] Karthic, R., Andrews, B., & Subramani, K. (2017). Microwave assisted synthesis and antibacterial studies of 5-amino thiadiazole substituted pyrimidine compounds, 5(1), 204–207.
[31] Gomha, S. M., Farghaly, T. A., Mabkhot, Y. N., Zayed, M. E. M., & Mohamed, A. M. G. (2017). Microwave-assisted synthesis of some novel azoles and azolopyrimidines as antimicrobial agents. Molecules, 22(3), 1–10.

[32] Bouattour, A., Fakhfakh, M., Abid, S., Paquin, L., Le Guével, R., Corlu, A., … Bazureau, J. P. (2017). Microwave-assisted practical synthesis of 4-imino-3-phenyl-3,4-dihydro-1H-chromeno[2,3-d]pyrimidine-2(5H)-thione derivatives and exploration of their biological activities. Arkivoc, 2017(4), 291–302.
[33] Hauck, S., Hiesinger, K., Khageh Hosseini, S., Achenbach, J., Biondi, R. M., Proschak, E., … Odadzic, D. (2016). Pyrazolo[1,5a]pyrimidines as a new class of FUSE binding protein 1 (FUBP1) inhibitors. Bioorganic and Medicinal Chemistry, 24(22), 5717–5729.
[34] Acosta, P., Insuasty, B., Ortiz, A., Abonia, R., Sortino, M., Zacchino, S. A., & Quiroga, J. (2016). Solvent-free microwave-assisted synthesis of novel pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidines with potential antifungal activity. Arabian Journal of Chemistry, 9(3), 481–492.
[35] Sureja, D. K., & Vadalia, K. R. (2016). POCl3 catalyzed, one-step, solvent-free synthesis of some novel thieno[2,3-d]pyrimidin-4(3H)-one derivatives as antimicrobial agent. Journal of Saudi Chemical Society, 4, 7–12.
[36] Pathan, N. B., & Rahatgaonkar, A. M. (2016). Solid supported microwave induced synthesis of imidazole–pyrimidine hybrids: Antimicrobial evaluation and docking study as 14DM-CPY51 inhibitors. Arabian Journal of Chemistry, 9, S100–S108.
[37] Zhang, J., Peng, J.-F., Wang, T., Wang, P., & Zhang, Z.-T. (2016). Synthesis, crystal structure, characterization and antifungal activity of pyrazolo[1,5- a]pyrimidines derivatives. Journal of Molecular Structure, 1120, 228–233.
[38] Verbitskiy, E. V., Baskakova, S. A., Kravchenko, M. A., Skornyakov, S. N., Rusinov, G. L., Chupakhin, O. N., & Charushin, V. N. (2016). Synthesis and evaluation of antitubercular activity of fluorinated 5-aryl-4-(hetero)aryl substituted pyrimidines. Bioorganic and Medicinal Chemistry, 24(16), 3771–3780.
[39] Quiroga, J., Romo, P. E., Ortiz, A., Isaza, J. H., Insuasty, B., Abonia, R., … Cobo, J. (2016). Synthesis, structures, electrochemical studies and antioxidant activity of 5-aryl-4-oxo-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidine-7-carboxylic acids. Journal of Molecular Structure, 1120, 294–301.
[40] Verbitskiy, E. V., Baskakova, S. A., Rasputin, N. A., Gerasimova, N. A., Amineva, P. G., Evstigneeva, N. P., … Charushin, V. N. (2016). Microwave-Assisted synthesis and evaluation of antibacterial activity of novel 6-fluoroaryl-[1,2,4]triazolo[1,5-A]pyrimidines. Arkivoc, 2016(5), 268–278.
[41] Zhao, C., Tovar, C., Yin, X., Xu, Q., Todorov, I. T., Vassilev, L. T., & Chen, L. (2009). Synthesis and evaluation of pyrido-thieno-pyrimidines as potent and selective Cdc7 kinase inhibitors.Bioorganic and Medicinal Chemistry Letters, 19(2), 319–323.
[42] Venkatesan K., Satyanarayana V.S.V. and Sivakumar A. Synthesis of pyrimidine carboxamide derivatives catalyzed by uranyl nitrate hexa hydrate with their antibacterial and antioxidant studiesBull. Chem. Soc. Ethiop. 2016, 30(1), 119-128.
[43] Farahi, M., Karami, B., & Banaki, Z. (2015). Improved microwave-assisted catalyst-free synthesis of 9-aryl-5,9-dihydropyrimido[4,5-d][1,2,4]triazolo[1,5-a]pyrimidine-6,8(4H,7H)-dione derivatives. Chinese Chemical Letters, 26(9), 1065–1067. https://doi.org/10.1016/j.cclet.2015.05.035
[44] Bhoi, M. N., Borad, M. A., Pithawala, E. A., & Patel, H. D. (2015). Novel benzothiazole containing 4H-pyrimido[2,1-b]benzothiazoles derivatives: One pot, solvent-free microwave assisted synthesis and their biological evaluation. Arabian Journal of Chemistry.
[45] Yu, M., Li, P., K.c. Basnet, S., Kumarasiri, M., Diab, S., Teo, T., … Wang, S. (2015). Discovery of 4-(dihydropyridinon-3-yl)amino-5-methylthieno[2,3-d[pyrimidine derivatives as potent Mnk inhibitors: Synthesis, structure-activity relationship analysis and biological evaluation. European Journal of Medicinal Chemistry, 95, 116–126.
[46] Saikia, P., Gogoi, S., & Boruah, R. C. (2015). A facile synthesis of steroidal and nonsteroidal pyrimidines under microwave irradiation. Tetrahedron Letters, 56(16), 2106–2109.
[47] Reddy, D. S., Hosamani, K. M., & Devarajegowda, H. C. (2015). Design, synthesis of benzocoumarin-pyrimidine hybrids as novel class of antitubercular agents, their DNA cleavage and X-ray studies. European Journal of Medicinal Chemistry, 101, 705–715.
[48] Salem, M. E., Ahmed, A. A., Shaaban, M. R., Shibl, M. F., & Farag, A. M. (2015). Regioselective synthesis and ab initio calculations of fused heterocycles thermally and under microwave irradiation. Spectrochimica Acta - Part A: Molecular and Biomolecular Spectroscopy, 148, 175–183.
[49] Sattar, M., Khatun, M., Islam, R., Sohrab, M., & Al-Reza, S. (2015). Synthesis of barbituric acid derivatives using microwave irradiation method and in vitro evaluation of antimicrobial and cytotoxic activity. Journal of Applied Pharmaceutical Science, 5(11), 038–042.
[50] El Azab, I. H., & Abdel-Hafez, S. H. (2015). One-Pot Three-Component Microwave-Assisted Synthesis of Novel Thiazolidinone Derivatives Containing Thieno[d]Pyrimidine-4-One Moiety as Potential Antimicrobial Agents. Russian Journal of Bioorganic Chemistry,, 41(3), 357–365.
[51] Bhat, A. R., Shalla, A. H., & Dongre, R. S. (2015). 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. Journal of Advanced Research, 6(6), 941–948.
[52] Kumar, S. V. (2015). Green synthesis and Biological Evaluation of Pyrimidine Derivatives, 4(5), 1462–1468.
[53] Hashim, J., Arshad, N., Khan, I., Nisar, S., Ali, B., & Iqbal Choudhary, M. (2014). Preparation of dihydrotetrazolo[1,5-a]pyrimidine derivatives from Biginelli 3,4-dihydropyrimidine-2-thiones. Tetrahedron, 70(45), 8582–8587. https://doi.org/10.1016/j.tet.2014.09.069

[54] Kour, G., Gupta, M., Paul, S., Rajnikant, & Gupta, V. K. (2014). SiO2-CuCl2: An efficient and recyclable heterogeneous catalyst for one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones. Journal of Molecular Catalysis A: Chemical, 392, 260–269.
[55] Kravchenko, M. A., Verbitskiy, E. V., Medvinskiy, I. D., Rusinov, G. L., & Charushin, V. N. (2014). Synthesis and antituberculosis activity of novel 5-styryl-4-(hetero)aryl- pyrimidines via combination of the Pd-catalyzed Suzuki cross-coupling and S NH reactions. Bioorganic and Medicinal Chemistry Letters, 24(14), 3118–3120.
[56] El-Gahami, M. A., Mekky, A. E. M., Saleh, T. S., & Al-Bogami, A. S. (2014). Acidity constant and solvatochromic behavior of some pyrazolo[1,5-a] pyrimidin-2-amine derivatives. Spectrochimica Acta - Part A: Molecular and Biomolecular Spectroscopy, 129, 209–218.
[57] Elumalai, K., Ali, M. A., Elumalai, M., Eluri, K., Srinivasan, S., & Mohanty, S. K. (2014). Microwave assisted synthesis of some novel acetazolamide cyclocondensed 1,2,3,4-tetrahydropyrimidines as a potent antimicrobial and cytotoxic agents. Beni-Suef University
[58] Yildirim, M., Çelikel, D., Dürüst, Y., Knight, D. W., & Kariuki, B. M. (2014). A rapid and efficient protocol for the synthesis of novel nitrothiazolo[3,2-c]pyrimidines via microwave-mediated Mannich cyclisation. Tetrahedron, 70(12), 2122–2128.
[59] Zakeri, M., Nasef, M. M., & Abouzari-Lotf, E. (2014). Eco-safe and expeditious approaches for synthesis of quinazoline and pyrimidine-2-amine derivatives using ionic liquids aided with ultrasound or microwave irradiation. Journal of Molecular Liquids, 199, 267–274.
[60] Zhao, B., Xu, Y., Deng, Q. G., Liu, Z., Wang, L. Y., &Gao, Y. (2014). One-pot, three component synthesis of novel 5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-carboxylate derivatives by microwave irradiation. Tetrahedron Letters, 55(33), 4521–4524.
[61] Zimmerman, J. R., Myers, B. J., Bouhall, S., McCarthy, A., Johntony, O., & Manpadi, M. (2014). A two-step, single pot procedure for the synthesis of substituted dihydropyrazolo-pyrimidines. Tetrahedron Letters, 55(4), 936–940.
[62] Gogoi, S., Shekarrao, K., Kaishap, P. P., Gogoi, S., & Boruah, R. C. (2014). A facile synthesis of steroidal D-ring fused pyrazolo[1,5-a]pyrimidines. Tetrahedron Letters, 55(38), 5251–5255.
[63] Siddiqui, I. R., Srivastava, A., Shamim, S., Srivastava, A., Waseem, M. A., Shireen, Rai. (2014). Microwave accelerated facile and efficient synthesis ofpiperido[3′,4′:5,6]pyrano[2,3-d] pyrimidinones catalyzed by basic ionic liquid [BMIM]OH. Journal of Molecular Catalysis A: Chemical, 382, 126–135.
[64] Rashid, M., Husain, A., Shaharyar, M., Mishra, R., Hussain, A., & Afzal, O. (2014). Design and synthesis of pyrimidine molecules endowed with thiazolidin-4-one as new anticancer agents. European Journal of Medicinal Chemistry, 83, 630–645. https://doi.org/10.1016/j.ejmech.2014.06.033
[65] Jainey, P. J., & K., I. B. (2014). Microwave Assited Synthesis of Novel Pyrimidines Bearing Benzene Sulfonamindes and Evoluation of Anticancer and Antioxidant Activities. Asian Journal of Pharmaceutical and Clinical Research, 7(1), 112–4.
[66] Jagwani D., Joshi P., A greener chemistry approach for synthesis of 4-(4-hydroxyphenyl)-6- methyl-2-oxo-1,2,3,4 tetrahydropyrimidine-5-carboxylic acid ethyl ester, International Journal of Pharmaceutical Sciences and Research , 2014; Vol. 5(12): 5548-5555.
[67] Marabathuni, V. J., Rehman, P. A., Naidu, N. T. M., Reddy, P. V. K., Manimala, C., & Subbarayudu, P. (2017). International Journal of Trends in Pharmacy and Life Sciences Synthesis Of 4 Amino Hydroxy 6 Phenyl Pyrimidine 5 Carbonitrile And 2 Amino 7 Hydroxy 4 Phenyl 4 Chreone 3 Carbonitrile Using Various Solvents , Catalysts, *3*(2), 50–54.
[68] Harikrishnan, P. S., Rajesh, S. M., Perumal, S., & Almansour, A. I. (2013). A microwave-mediated catalyst- and solvent-free regioselective Biginelli reaction in the synthesis of highly functionalized novel tetrahydropyrimidines. Tetrahedron Letters, 54(9), 1076–1079.
[69] Bagley, M. C., Baashen, M., Paddock, V. L., Kipling, D., & Davis, T. (2013). Regiocontrolled synthesis of 3- and 5-aminopyrazoles, pyrazolo[3,4-d] pyrimidines, pyrazolo[3,4-b]pyridines and pyrazolo[3,4-b]quinolinones as MAPK inhibitors. Tetrahedron, 69(39), 8429–8438.
[70] Deau, E., Loidreau, Y., Marchand, P., Nourrisson, M. R., Loaëc, N., Meijer, L., … Besson, T. (2013). Synthesis of novel 7-substituted pyrido[2′,3′:4,5]furo[3,2-d] pyrimidin-4-amines and their N-aryl analogues and evaluation of their inhibitory activity against Ser/Thr kinases. Bioorganic and Medicinal Chemistry Letters, 23(24), 6784–6788.
[71] Elumalai, K., Ali, M. A., Elumalai, M., Eluri, K., & Srinivasan, S. (2013). Novel isoniazid cyclocondensed 1,2,3,4-tetrahydropyrimidine derivatives for treating infectious disease: a synthesis and in vitro biological evaluation. Journal of Acute Disease, 2(4), 316–321.
[72] Xavier, A. L., Simas, A. M., Falcão, E. P. D. S., & Dos Anjos, J. V. (2013). Antinociceptive pyrimidine derivatives: Aqueous multicomponent microwave assisted synthesis. Tetrahedron Letters, 54(26), 3462–3465.
[73] Satyanarayana, S., Praveen Kumar, K., Lakshmi Reddy, P., Narender, R., Narasimhulu, G., & Subba Reddy, B. V. (2013). Microwave-assisted cyclocondensation: A rapid and solvent-free synthesis of 3-benzyl-2H-pyrido[1,2-a]pyrimidin-2-one derivatives. Tetrahedron Letters, 54(36), 4892–4895.
[74] Loidreau, Y., Marchand, P., Dubouilh-Benard, C., Nourrisson, M. R., Duflos, M., Loaëc, N., … Besson, T. (2013). Synthesis and biological evaluation of N-aryl-7-methoxybenzo[b]furo[3,2-d] pyrimidin-4-amines and their N-arylbenzo[b]thieno[3,2-d]pyrimidin-4-amine analogues as dual inhibitors of CLK1 and DYRK1A kinases. European Journal of Medicinal Chemistry, 59, 283–295.

[75] Puttaraju, K. B., Shivashankar, K., Chandra, Mahendra, M., Rasal, V. P., Venkata Vivek, P. N.,Chanu, M. B. (2013). Microwave assisted synthesis of dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-4-ones; synthesis, in vitro antimicrobial and anticancer activities of novel coumarin substituted dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-4-ones. European Journal of Medicinal Chemistry, 69, 316–322.
[76] Bhatewara, A., Jetti, S. R., Kadre, T., Paliwal, P., & Jain, S. (2013). Microwave-assisted synthesis and biological evaluation of dihydropyrimidinone derivatives as anti-inflammatory, antibacterial, and antifungal agents.Int J Med Chem, 2013, 197612.
[77] Khamgaonkar VD, Kore PV, Game-Patil MM, Kshirsagar SS (2012) Microwave Assisted Synthesis of Novel Ethyl 2-(3,4-Dihydro-6-Methyl- 2-oxo-4-Phenyl-5-Propionylpyrimidin-1(2H)-yl) Acetohydrazide Derivatives. 1:326.
[78] Kodape, M. M., Aswar, A. S., Gawhale, N. D., Humne, V. T., & Mir, B. A. (2012). Facile aromatization of 3,4-dihydropyrimidin-2(1H)-ones (DHPMs) by iodine. Chinese Chemical Letters, 23(12), 1339–1342.
[79] Li, Z., Zhu, A., & Yang, J. (2012). One-Pot Three-Component Mild Synthesis of 2-Aryl-3-(9-alkylcarbazol-3-yl)thiazolin-4-ones. Journal of Heterocyclic Chemistry, 49 (Scheme 1), 1458–1461.
[80] Adhikari, A., Kalluraya, B., Sujith, K. V., Gouthamchandra, & Mahmood, R. (2012).Synthesis, characterization and biological evaluation of dihydropyrimidine derivatives. Saudi Pharmaceutical Journal, 20(1), 75–79.
[81] Adhikari, A., Kalluraya, B., Sujith, K. V., Gouthamchandra, K., Jairam, R., Mahmood, R., & Sankolli, R. (2012). Synthesis, characterization and pharmacological study of 4,5-dihydropyrazolines carrying pyrimidine moiety. European Journal of Medicinal Chemistry, 55, 467–474.
[82] Azzam, S. H. S., & Pasha, M. A. (2012). Microwave-assisted, mild, facile, and rapid one-pot three-component synthesis of some novel pyrano[2,3-d]pyrimidine-2,4,7-triones. Tetrahedron Letters, 53(52), 7056–7059.
[83] Song, X. J., Duan, Z. C., Shao, Y., & Dong, X. G. (2012). Facile synthesis of novel fluorinated thieno[2,3-d]pyrimidine derivatives containing 1,3,4-thiadiazole. Chinese Chemical Letters, 23(5), 549–552.
[84] Vinosha, B., Perumal, S., Renuga, S., & Almansour, A. I. (2012). A facile domino protocol for the stereoselective synthesis of trans-2,3-dihydrobenzofurans and cis-5,6-dihydrofuro[2,3-d]pyrimidines. Tetrahedron Letters, 53(8), 962–966.
[85] Poojari, S., Parameswar Naik, P., & Krishnamurthy, G. (2012). One-pot synthesis of thieno [2,3-d] pyrimidin-4-ol derivatives mediated by polyphosphonic anhydride. Tetrahedron Letters, 53(35), 4639–4643.
[86] Sharma, R. K., & Rawat, D. (2012). Silica immobilized nickel complex: An efficient and reusable catalyst for microwave-assisted one-pot synthesis of dihydropyrimidinones. Inorganic Chemistry Communications, 17, 58–63.
[87] Jiang, B., Xue, L. Y., Wang, X. H., Tu, M. S., Liu, Y. P., & Tu, S. J. (2012). Microwave-assisted multicomponent reaction of aryl amidines: Regiospecific synthesis of new polysubstituted thiopyrano-, and pyrano[4,3-d]pyrimidines. Tetrahedron Letters, 53(10), 1261–1264.
[88] Loidreau, Y., Marchand, P., Dubouilh-Benard, C., Nourrisson, M.-R., Duflos, M., & Besson, T. (2012). First synthesis of 4-aminopyrido[2′,3′:4,5]furo[3,2-d]pyrimidines. Tetrahedron Letters, 53(8), 944–947.
[89] Antre, R. V., Cendilkumar, A., Goli, D., Andhale, G. S., & Oswal, R. J. (2011). Microwave assisted synthesis of novel pyrazolone derivatives attached to a pyrimidine moiety and evaluation of their anti-inflammatory, analgesic and antipyretic activities. Saudi Pharmaceutical Journal, 19(4), 233–243.
[90] Song, X. J., Shao, Y., & Dong, X. G. (2011). Microwave-assisted synthesis of some novel fluorinated pyrazolo[3,4-d]pyrimidine derivatives containing 1,3,4-thiadiazole as potential antitumor agents. Chinese Chemical Letters, 22(9), 1036–1038.
[91] Todorovic, N., Awuah, E., Shakya, T., Wright, G. D., & Capretta, A. (2011). Microwave-assisted synthesis of N1- and C3-substituted pyrazolo[3,4-d]pyrimidine libraries. Tetrahedron Letters, 52(44), 5761–5763.
[92] Shi, F., Ding, J., Zhang, S., Hao, W. J., Cheng, C., & Tu, S. (2011). Substrate-controlled chemoselective synthesis and potent cytotoxic activity of novel 5,6,7-triarylpyrido[2,3-d]pyrimidin-4-one derivatives. Bioorganic and Medicinal Chemistry Letters, 21(5), 1554–1558.
[93] Fang, Z., & Lam, Y. (2011). A rapid and convenient synthesis of 5-unsubstituted 3,4-dihydropyrimidin-2-ones and thiones. Tetrahedron, 67(6), 1294–1297.
[94] Pai, N., Waghmode, K., & Khandekar, D. (2011). Microwave promoted solvent-free biginelli reaction for the one pot synthesis of dihydropyrimidin-2-(1H)-ones catalyzed by Sulfamic Acid. Asian Journal of Chemistry, 23(12), 5217–5219.
[95] Singh, N. I., Kshirsagar, S. S., Nimje, H. M., Chaudhari, P. S. Oswal, R. J., Microwave Assisted Synthesis Of 4-Substituted-1, 2, 3, 4-Tetrahydropyrimidine Derivatives. International J Pharm Pharm Sci, 2011, Vol 3, Issue1, 109-111
[96] Han, Y., Ebinger, K., Vandevier, L. E., Maloney, J. W., Nirschl, D. S., & Weller, H. N. (2010). Efficient and library-friendly synthesis of furo- and thieno[2,3-d] pyrimidin-4-amine derivatives by microwave irradiation. Tetrahedron Letters, 51(4), 629–632.
[97] Thanh, N. D., & Mai, N. T. T. (2009). Synthesis of N-tetra-O-acetyl-β-d-glucopyranosyl-N′-(4′,6′-diarylpyrimidin-2′-yl)thioureas. Carbohydrate Research, 344(17), 2399–2405.
98] Algul, O., Meric, A., Polat, S., Didem Yuksek, N., & Serin, M. S. (2009). Comparative studies on conventional and microwave-assisted synthesis of a series of 2,4-di and 2,3,4-trisubstituted benzimidazo[1,2-a] pyrimidines and their antimicrobial activities. Central European Journal of Chemistry,337–342.

[99] Barthakur, M. G., Gogoi, S., Dutta, M., & Boruah, R. C. (2009). A facile three-component solid phase synthesis of steroidal A-ring fused pyrimidines under microwave irradiation. Steroids, 74(9), 730–734.
[100] Cikotiene, I., Kairys, V., Buksnaitiene, R., Morkunas, M., Rudys, S., Brukstus, A., & Fernandes, M. X. (2009). Study on the cyclization of 6-arylethynylpyrimidine-5-carbaldehydes with tert-butylamine: microwave versus thermal preparation of pyrido[4,3-d]pyrimidines. Tetrahedron, 65(29–30), 5752–5759.
[101] Bagley, M. C., Lin, Z., & Pope, S. J. A. (2009). Barium manganate in microwave-assisted oxidation reactions: synthesis of solvatochromic 2,4,6-triarylpyrimidines. Tetrahedron Letters, 50(49), 6818–6822.
[102] Tu, S., Li, C., Shi, F., Zhou, D., Shao, Q., Cao, L., & Jiang, B. (2008). An Efficient Chemoselective Synthesis of Pyrido[2,3- d]pyrimidine Derivatives under Microwave Irradiation. Synthesis, 2008(3), 369–376.