An update on the Green synthesis of pyrimidine Scaffold: A Review

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Abstract

Millions of individuals worldwide are affected by the common and deadly condition of hypertension. Despite the availability of several antihypertensive medications, researchers continue to look for new and potent treatments. Because of their eco-friendliness and simplicity of scaling, pyrimidine-based compounds have demonstrated potential antihypertensive efficacy. Recent developments in the green synthesis of pyrimidine compounds and their antihypertensive efficacy are highlighted in this review. The pharmaceutical business and the environment may be significantly impacted by the adoption of sustainable and green chemical methodologies in the synthesis of innovative antihypertensive drugs.

Keywords:-Pyrimidine derivatives, aromatic aldehydes, Antihypertensive agent, calcium channel blockers, green synthesis, animal models**.**

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Introduction

There are millions of people in the globe who have blood pressure (BP) that is judged to cause many serious conditions, such as diabetes, renal failure, and heart disease.[(1,2)] Hypertension is one of the well-known disorders that caused human angiocardiopathy mortality. To manage hypertension and lessen the organ damage it is associated with, several treatment initiatives have been made. For instance, attempts have been made to inhibit the converting enzyme and receptor antagonists (AT1), adrenergic receptor blockers (diuretics) and calcium channel blockers. Strong blood pressure control remains a significant therapeutic challenge despite the

development of antihypertensive drugs, and there has been a consistent interest in novel and more effective therapies.[2] Types of antihypertensive medications derived from plants are a crucial tool for identifying recent chemical structural changes.[1] According to its functional usage as an antihypertensive agent, antiprotozoal, anti-inflammatory, antibacterial, and antifungal, sulphonamides are one of the most well-known pharmacological classes that are used to treat a variety of disorders.[2] There are several effective sulphonamide medications that block carbonic anhydrase.[3] While nerveblockade is used in conjuction to diuretics-sulphonamide when optimum hypertension treatment cannot be achieved with these medications alone, sulphonamide is still the drug of choice for treating neurogenic blocking agents.[4]According to the author, sulphonamide-diuretics are observed in roughly forty percent of individuals with direct or extremely severe essential hypertension as adjuncts to antihypertensive medication. In recent years, it has been clear that the pyrimidine moiety is a crucial pharmacophore, working in tandem with nucleic acid activity and synthesis, such as Thiopental sodium which is an short acting barbiturate[7], the cytostaticum fluorouracil.[5], HIV medication including zidovudine[6] , Pentothal which act as anaesthetics[8] and Stagnant is used as an antiseptic. around large molecules, such as pyrimethamine and aminopyrimidines [9] or trimethoprim[10] are used in conjunction with sulphonamides as antimalarial medications. using minoxidil as an antibiotic[11] antihypertensive such as Sulphadiazine[12]possesses a pyrimidine system and is one of the sulphonamide medicines. As calcium channel blockers and antihypertensive medications, pyrimidines are used.[13-14]

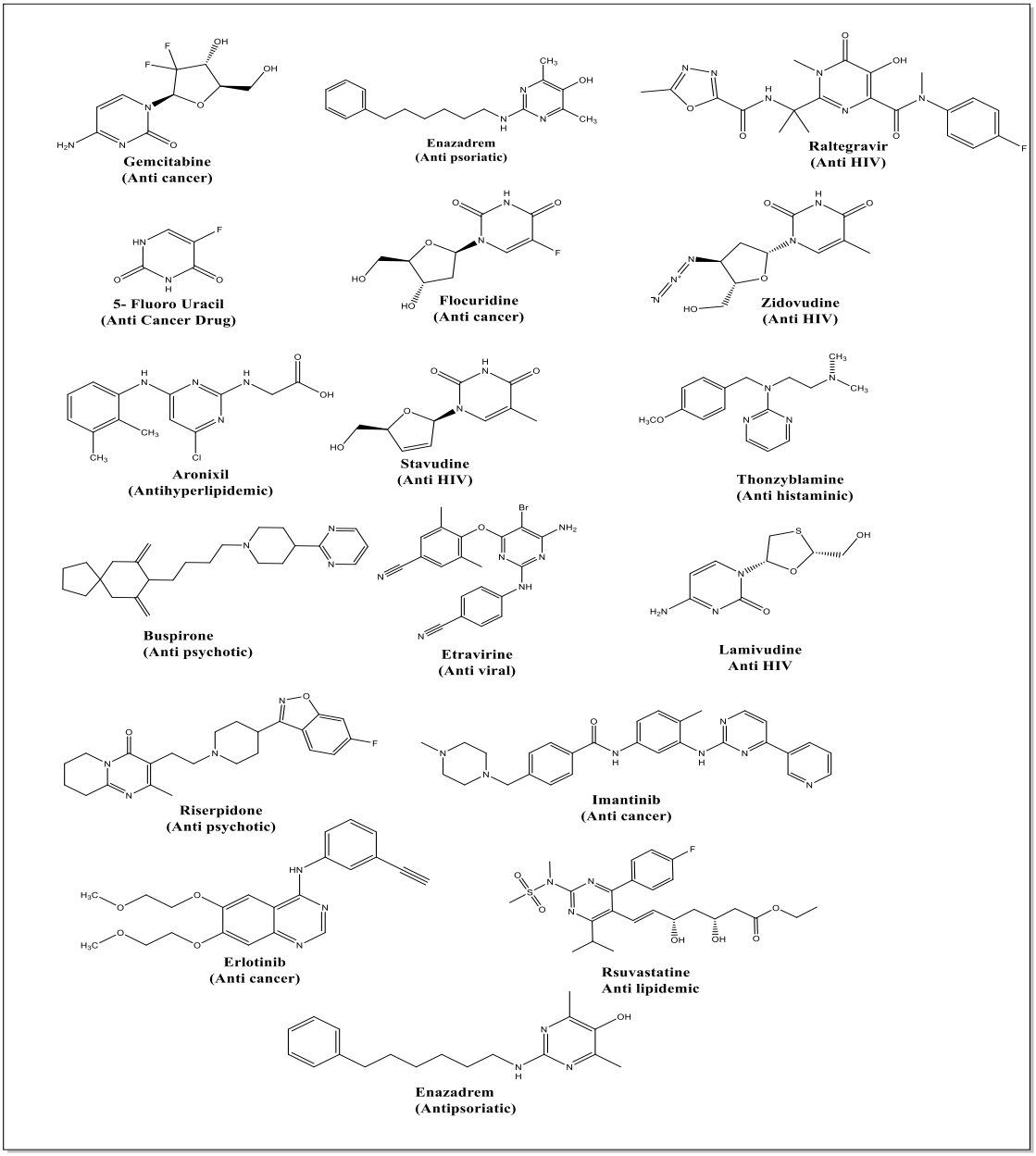


Fig1: Marketed drugs containing pyrimidine ring[45,46]

Pyrimidine scaffold :-

The six-membered nitrogen molecule pyrimidine is well-known in medical chemistry for its medicinal effects[15]. Additionally, pyrimidine nucleoside & nucleotides substituted at the 5th position have been described as analogues of Coenzymes and nucleic acids are made of natural substances [16]. The presence of pyrimidine bases in thymine, cytosine, and uracil, which are major structural constituents of nucleic acids DNA and RNA, is

one possible explanation for their various therapeutic qualities. Pyrimidines are one of the most active chemical groups, having considerable in vitro activity against unrelated RNA and DNA, as well as diuretic, anticancer, anti-HIV, viruses including polioherpes viruses, and cardiovascular activities.[17]. According to the available research, substances containing the pyrimidine nucleus demonstrate a wide spectrum of pharmacological actions. Furthermore, numerous pyrimidine analogues have been shown to exhibit antibacterial properties[18-24], anti-fungal [19-22], antileishmanial [23], anti-inflammatory[24,25], analgesic[26], anti-hypertensive [27,28], anti-pyretic [29], anti-viral [30-31], anti-diabetic [32], antiallerggic [33], anticonvulsant[34], antioxidant [35,36], anti-histaminic [37,38], herbicidal [39], & anti-cancer activities [40-41]& many derivatives of pyrimidines exhibits potential central nervous system (CNS) depressant properties [42,43] as well as calcium channel blockers and chemotherapeutics[44] etc.

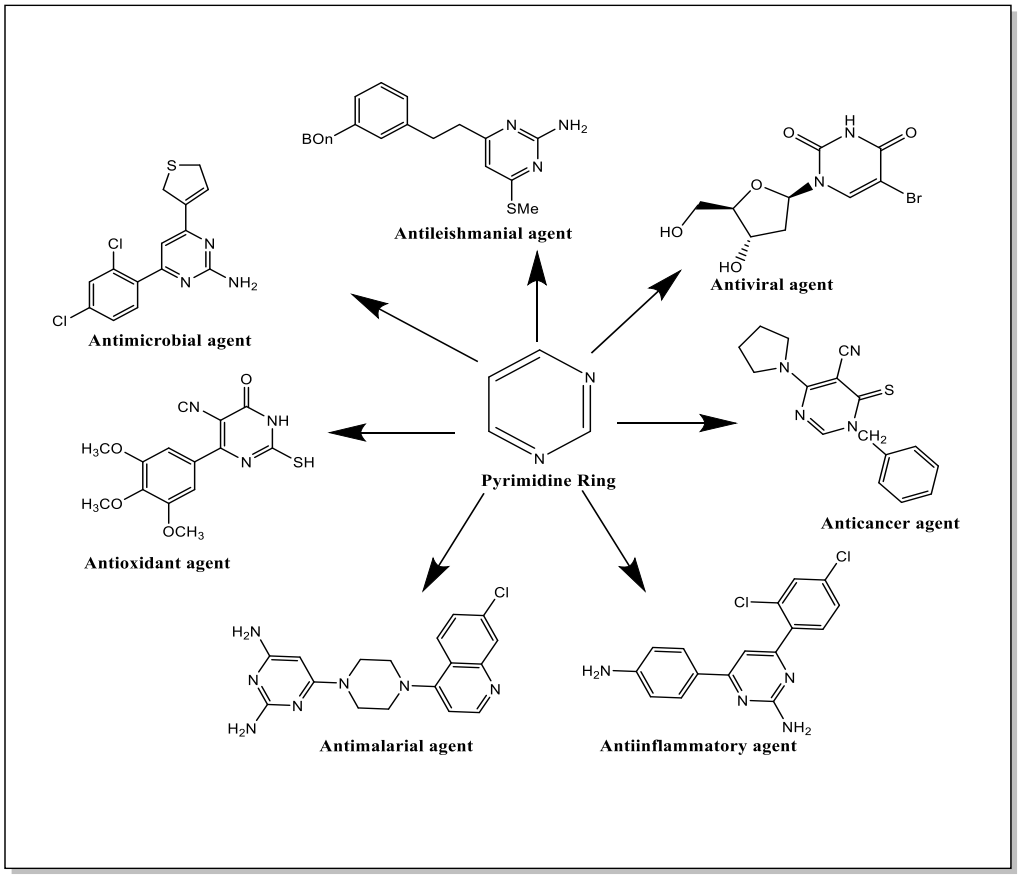


Fig.2:-

Pyrimidine ring exhibiting various biological activity [44]

Structure Activity Relationships (SAR)

Study of SAR provide information on the molecular characteristics that cause receptor affinity and selectivity. The compounds' promising character can be attributable to alterations in the hydrophobic domain. Electron withdrawing and donating groups were discovered at the hydrophobic aryl ring's ortho, meta, and para locations. The changed derivatives were shown to be more active than the other derivatives in general. This might be because the modified derivatives are more suited to the receptor location. All of the pioneering studies identify the existence of hydrogen donor/acceptor unit (HAD), hydrophobic domain (A) (aryl ring substituted/unsubstituted), and electron donor atom (D) (Bruno-Blanch et al. 2003, Estrada and Pena, 2000). This common trait was discovered in the structures of well-known pyrimidine medicines. **(Fig 3)**. [47]

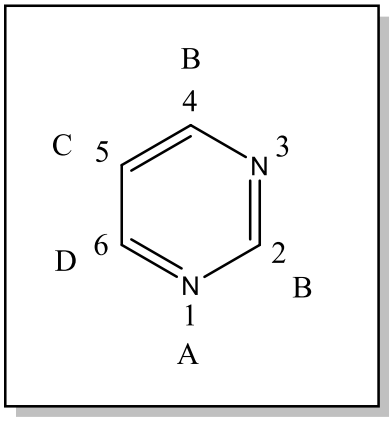


Fig 3:- Nucleus of pyrimidine ring

(a) The substitution of a five-membered saturated heterocyclic ring results in antiviral and anticancer activity.

(b) the second position The substitution of a saturated heterocyclic ring with 6 or 5 members results in antihelmintic and antiparkinsonian properties, as well as expectorant and therapy of GI disturbances and Neuropathies of the extremities.

2. Second and fourth position keto group substitution or amino replacement or combined keto amino group substitution results in anticancer, antiviral, antibacterial, antifungal, and respiratory tract infection and liver problem therapy.

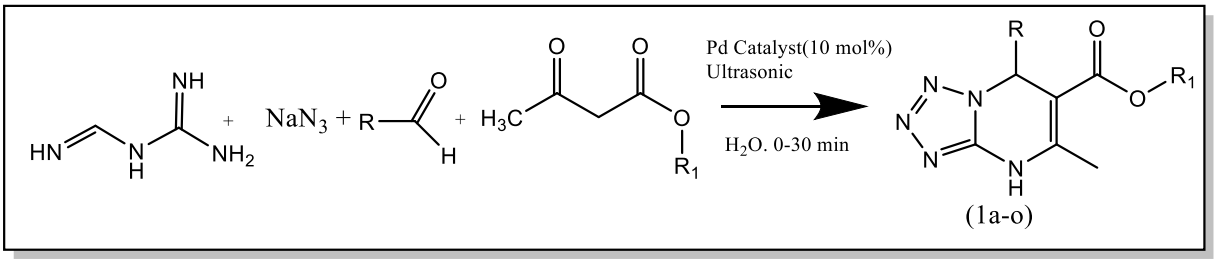
(c) Antibacterial and anticancer action results from fifth position substitution with halogen, substituted amine, or saturated distal heterocyclic ring.

(d). Fusion of the fifth and sixth positions with a heterocyclic ring and an ortho,meta,para substituted distal aryl ring results in anticancer, antiviral, antibacterial, vasodialation, and urinary tract infection treatment.

Ecofriendly synthesis of pyrimidine derivatives

- **Synthesis of dihydrotetrazolo[1,5-a] pyrimidine derivatives**

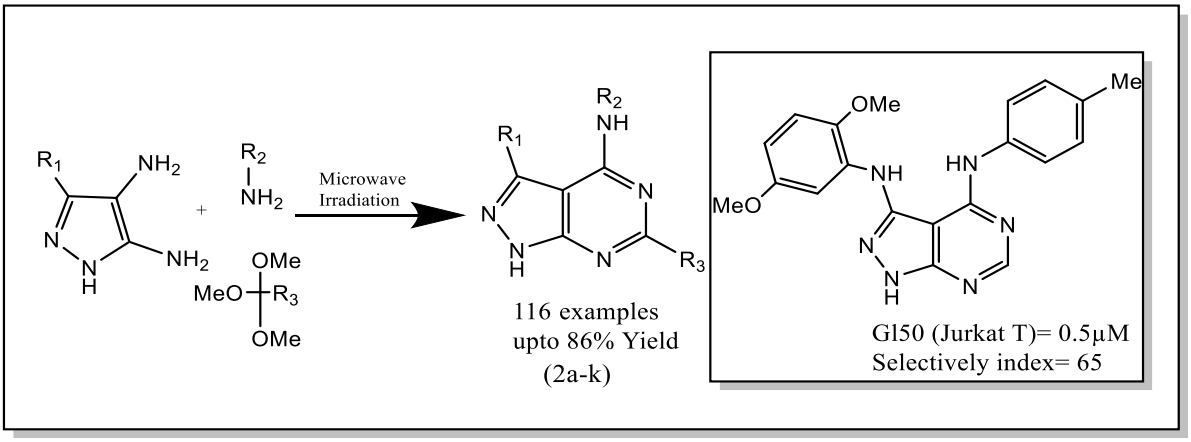
El-Remaily MA et.al had synthesize the series of various di hydrotetrazolo[1,5-a]pyrimidine-6-carboxylic esters (1a-o) by using one pot synthesis which involves four reactants as cyanoguanidine, sodium azide, aromatic aldehyde, & methyl or ethyl acetoacetate, in the presence of water by using ultrasonic irradiation under the mild conditions **(scheme1)**.[48]



Scheme 1: **Synthesis of dihydrotetrazolo[1,5-a] pyrimidine derivatives**

- **Synthesis of N^3,N^4-disubstituted 3,4-diaminopyrazolo[3,4-*d*]pyrimidines**

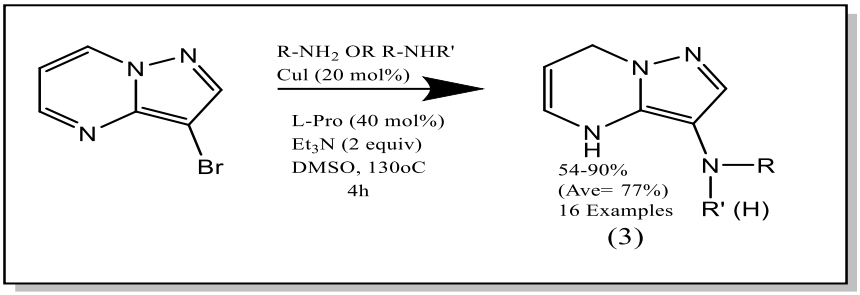
Ng JH et.al had Under microwave irradiation, N3,N4-disubstituted 3,4-diaminopyrazolo[3,4-d]pyrimidines derivatives (2a-k) were synthesised by employing a three-component reaction of 3,5-diaminopyrazole-4-carbonitriles with primary amines and orthoesters. **(scheme2)**.[49]



Scheme2: *Synthesis of* N^3,N^4-disubstituted 3,4-diaminopyrazolo[3,4-*d*]pyrimidines

- **Synthesis of C-3 aminated pyrimidine derivatives**

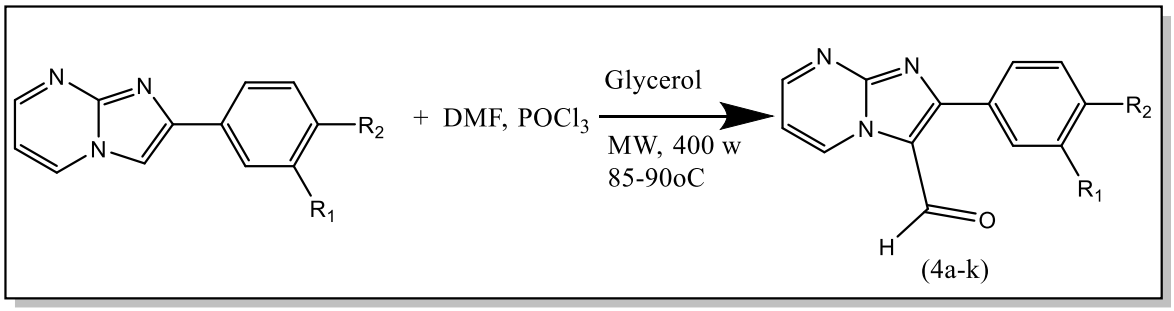
Iorkula TH et al. synthesised C-3 aminated pyrimidine derivatives (3) by reacting 3-bromopyrazolo[1,5-a]pyrimidine with a range of 1° or 2° alkyl amines in DMSO with CuI, L-proline, and Et3N (2 equiv) under microwave heating at 130^0C for 4 hours.**(scheme 3).**[50]



Scheme3: Synthesis of C-3 aminated pyrimidine derivatives

- **Synthesis of 2-Arylimidazo[1,2-a]pyrimidine-3-carbaldehyde**

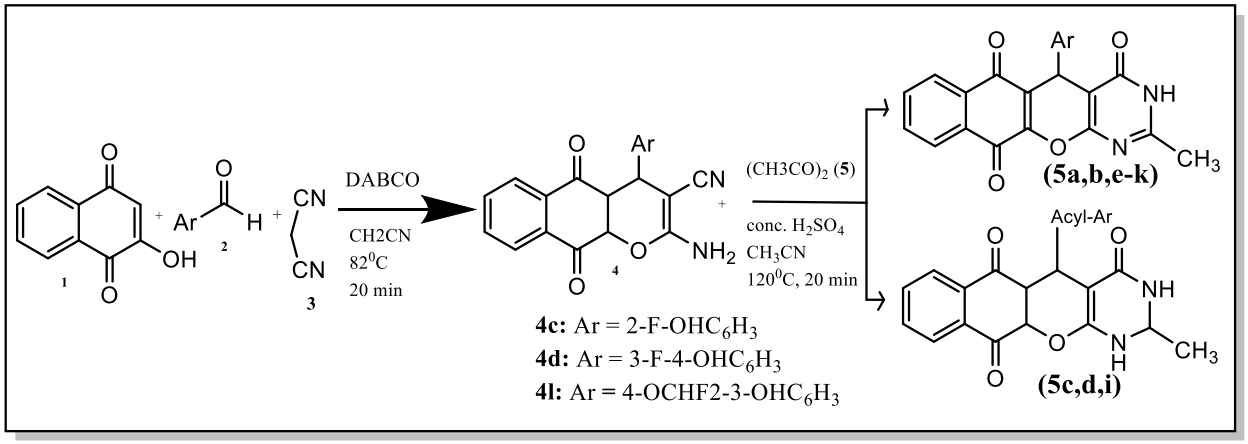
Saeed HY et al. synthesised 2-Arylimidazo[1,2-a]pyrimidine-3-carbaldehyde derivatives (4a-k) by a reaction of 2-phenylimidazo[1,2-a]pyrimidines with (Vilsmeier-Haack reagent) in the presence of glycerol as a green reaction medium under 400 watt microwave irradiation at 90 °C. **(scheme4)**.[51]



Scheme4: Synthesis of 2-Arylimidazo[1,2-a]pyrimidine-3-carbaldehyde

- **Synthesis of chromeno[2,3-*d*]pyrimidines derivatives**

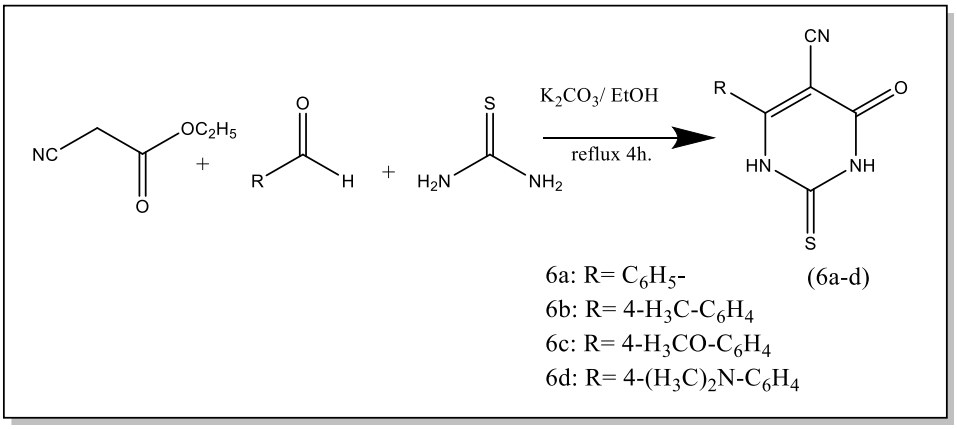
Nguyen HT et.al had synthesized chromeno[2,3-*d*]pyrimidines (5a,b,e-k), (5c,d,I)containing fluorine atoms by using one pot microwave-assisted multicomponent reactions**(scheme5)**.[52]



Scheme5: Synthesis of chromeno[2,3-*d*]pyrimidines derivatives

- **Synthesis of 5-cyano-4-oxo-6-alkyl(aryl)-2-thioxo-1,2,3,4-tetra hydropyrimidine derivatives**

Kambe et al. synthesised 5-cyano-4-oxo-6-alkyl(aryl)-2-thioxo-1,2,3,4-tetra hydropyrimidine derivatives (6a-d) via condensation reaction of ethyl cyanoacetate, aldehydes, and thiourea in the presence of potassium carbonate as a catalyst. **(Scheme 6)**.[53]

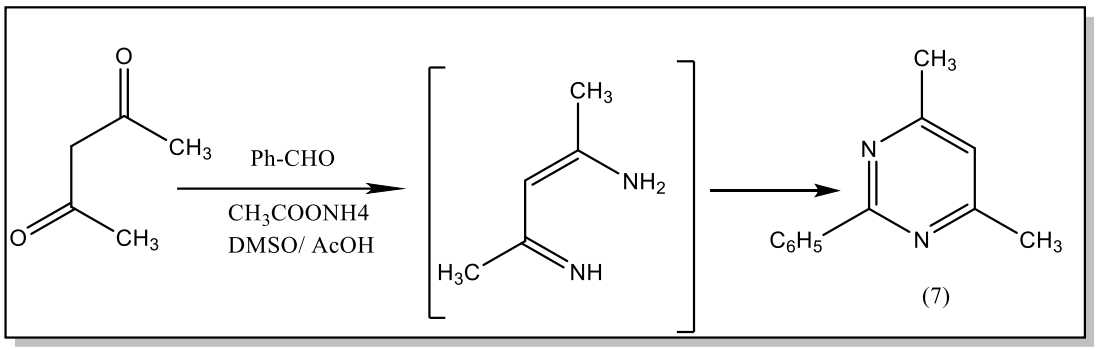


Scheme6: Synthesis of 5-cyano-4-oxo-6-alkyl(aryl)-2-thioxo-1,2,3,4-tetra hydropyrimidine derivatives

- **Synthesis of pyrimidine derivatives**

Lweis et al. synthesised the pyrimidine derivatives (7) by reacting acetyl acetone and benzaldehyde in the presence of two eqs of ammonium acetate to yield (Z)-4-iminopent-2-en-2-amine intermediate, which is subsequently dehydrogenated to yield the pyrimidine

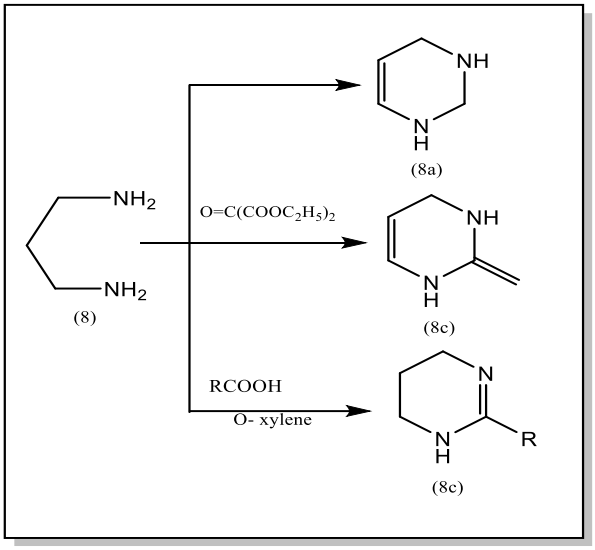
derivative. **(Scheme 7)**.[54]



Scheme7: Synthesis of pyrimidine derivatives

- **Synthesis of tetrahydro pyrimidine derivatives**

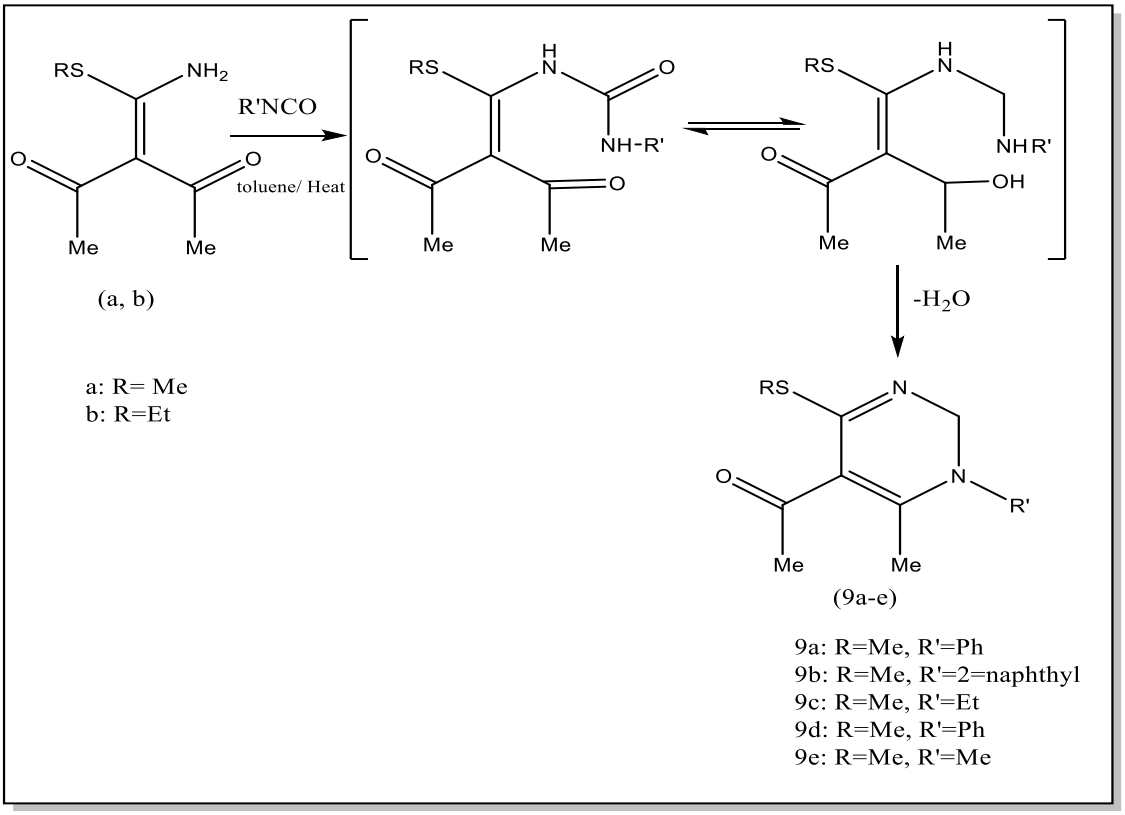
Fischer and Grath P. R. et al. had synthesized tetrahydro pyrimidine derivatives (8a-c) from a reaction of 1,3-diaminopropane with formaldehyde, diethyl carbonate and carboxylic acid**(Scheme8).**[55,56]



Scheme8: Synthesis of tetrahydro pyrimidine derivatives

- **Synthesis of 4-alkylthio-5-acetyl-lalkyl(aryl)-6-methyl-1H-pyrimidin-2-ones derivatives**

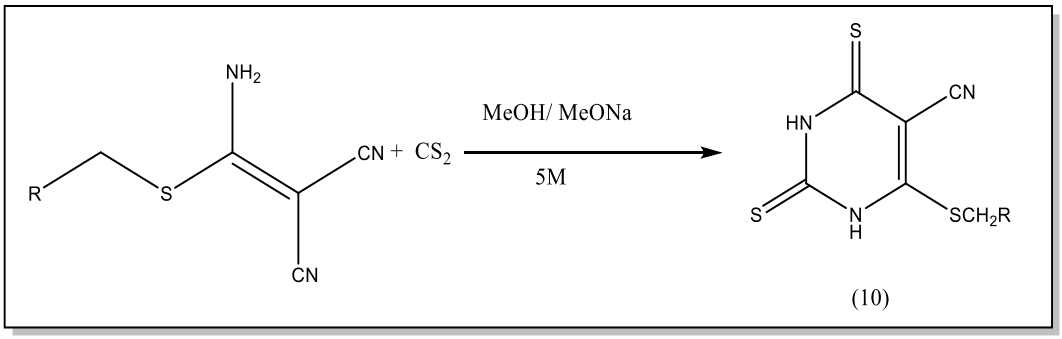
In the absence of bases, Gordeev et al. synthesised 4-alkylthio-5-acetyl-lalkyl(aryl)-6-methyl-1H-pyrimidin-2-one derivatives (9a-e) by reacting 3-(amino(substituted thio)methylene)pentane-2,4-dione with isocyanates. (**Scheme9).**[57]



Scheme 9: Synthesis of 4-alkylthio-5-acetyl-lalkyl(aryl)-6-methyl-1H-pyrimidin-2-ones derivatives

- **Synthesis of pyrimidinethione derivative**

Briel et al. had Synthesized various pyrimidinethione derivative (10) by the reaction of enaminonitrile with CS2 in the presence of sodium methoxide**(scheme10)**.[58]

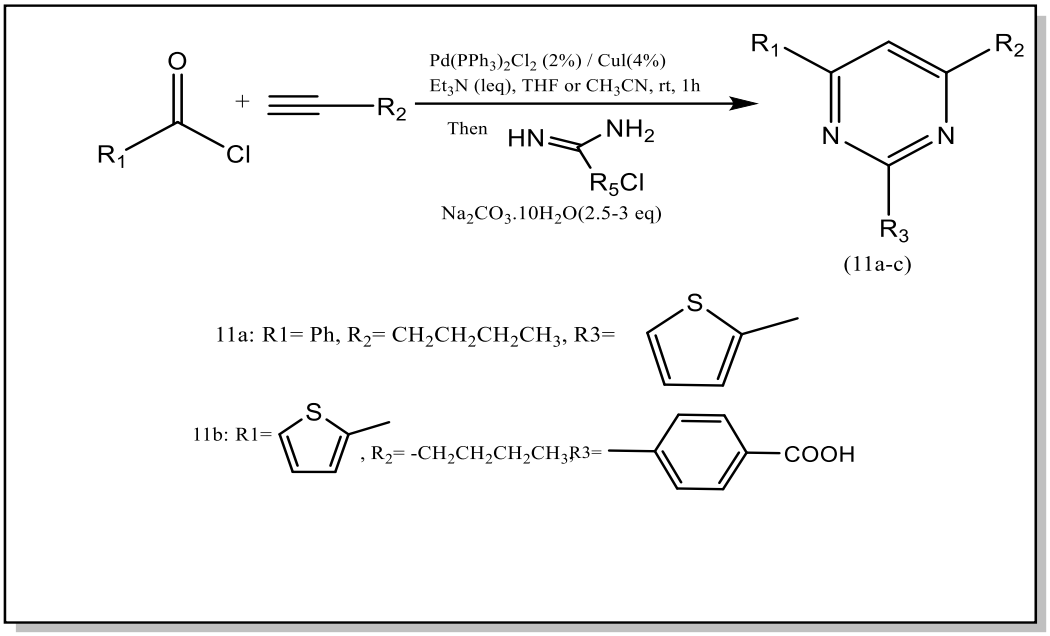


Scheme10: Synthesis of pyrimidinethione derivatives

- **Synthesis of 2,4-diand 2,4,6-trisubstituted pyrimidines**

Under Sonogashira conditions, Karpov A. S et al synthesised 2,4-dianand 2,4,6-

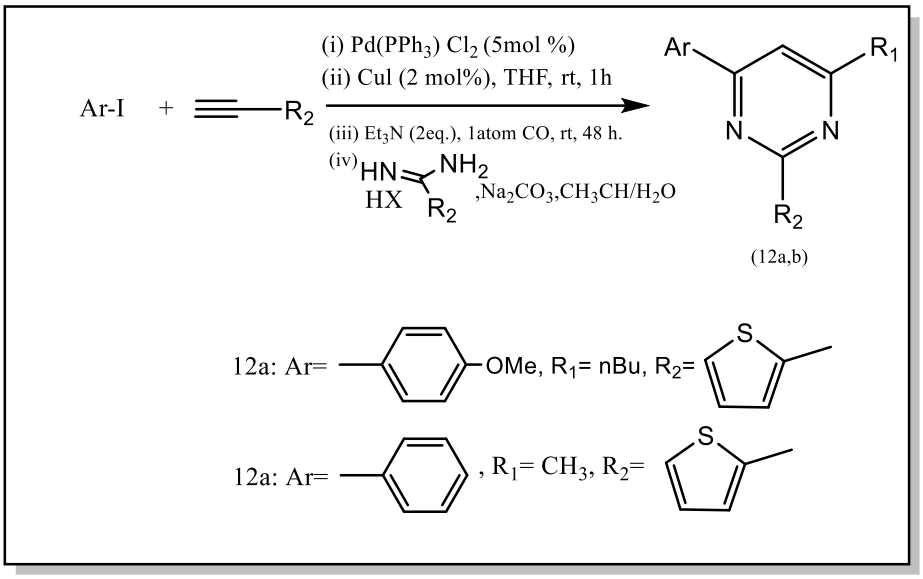
trisubstituted pyrimidines(11a,b) by reacting acid chlorides with terminal alkynes. **(Scheme11).**[59]



Scheme11: Synthesis of 2,4-diand 2,4,6-trisubstituted pyrimidines

- **Synthesis of 2,4,6-tri substituted pyrimidine derivatives**

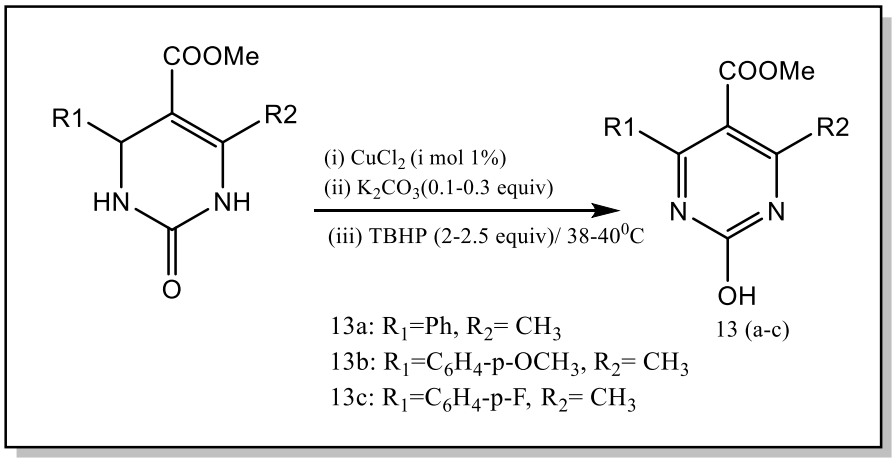
Muller T. J. J. et al. had synthesised 2,4,6-tri substituted pyrimidine derivatives (12a,b) by the reaction of aryl iodides with terminal alkynes in the presence of tetrahydrofuran(THF) at room temperature under 1 atom of carbon monoxide in the presence of 2 eq. of triethylamine and catalytic amounts of [Pd(PPh3)2Cl2 **(Scheme12).**[60]



Scheme12: Synthesis of 2,4,6-tri substituted pyrimidine derivatives

- **Synthesis of Pyrimidine derivatives**

Yamamoto et al. had synthesized few Pyrimidine derivatives (13a-c) by the oxidation of dihydropyrimidinones in the presence of copper(II)chloride, potassium carbonate, dichloromethane the heated at 38^0C then treated with tert-butyl hydroperoxide for 120 m **(Scheme13)**.[61,62]

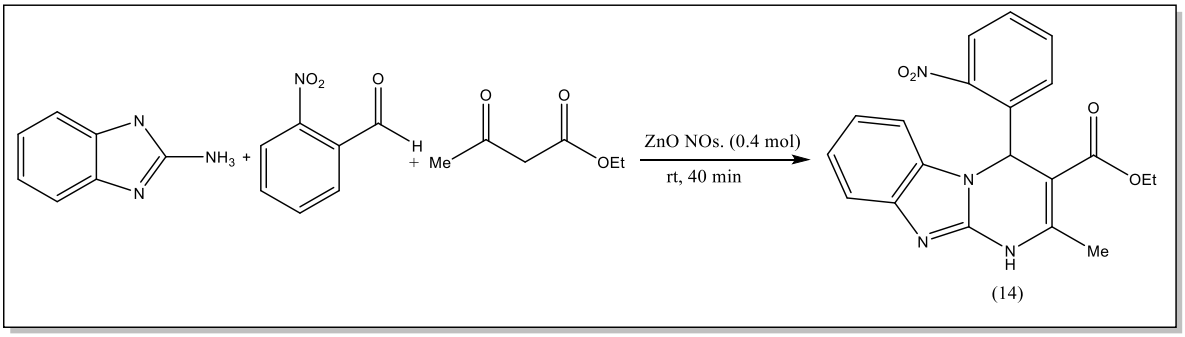


Scheme13:Synthesis of Pyrimidine derivatives

- **Synthesis of ethyl 2-methyl-4-(2-nitrophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2- a]pyrimidine-3-carboxylate derivatives**

Sharma et al. synthesised ethyl 2-methyl-4-(2-nitrophenyl)-1,4-

dihydrobenzo[4,5]imidazo[1,2- a] by synthesising ethyl 2-methyl-4-(2-nitrophenyl)-1,4-dihydrobenzo[4,5pyrimidine-3-carboxylate derivatives(14) were synthesised via a 40-minute reaction of 2-aminobenzimidazole, 2-nitrobenzaldehyde, and ethyl acetoacetate in the presence of ZnONPs as a catalyst. **(Scheme14)**.[63,64]



Scheme14: Synthesis of ethyl 2-methyl-4-(2-nitrophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2- a]pyrimidine-3-carboxylate derivatives

Anti-hypertensive activity of pyrimidine derivatives

Synthesis of pyrimidine derivatives by many research groups as effective and more potent then reference antihypertensive agent were summarized below with their structures: - **Fig3. and Fig4.**

M.F.Ismailmagda et.al (2006) had synthesized various derivatives of substituted pyrimidines and put all these for testing in-vivo and in -vitro antihypertensive activity out of all (**1a and 1c)** showed potent antihypertensive activity then reference[65]**. Alam o. et.al (2010)** had synthesized various derivatives of substituted pyrimidines and put all these for testing invivo and vivo antihypertensive activity all **(2a-2n)** showed better activity then reference [66].**Korany A ali et.al (2011**) had synthesized various derivatives of substituted pyrimidines and put all these for testing invivo and vivo antihypertensive activity (**3a-3d**) shows potent antihypertensive and diuretic activity then standard captopril [67]. **Tae woo kim et.al (2012)** had synthesized various derivatives of substituted pyrimidines and put all these for testing in vivo and vivo antihypertensive activity out of all (**4a**) shows a potent antihypertensive activity then standard losartan [68].**yuanying Fang et.al (2018)** had synthesized various derivatives of substituted pyrimidines and put all these for testing invivo and vivo antihypertensive activity (**5a and 6e)** showed potent activity then reference drug[69]. **Liang li et.al(2019**) had synthesized various derivatives

of substituted pyrimidine and put all these for testing invivo and vivo antihypertensive activity out of all (**7a)**shows a potent antihypertensive activity then standard riociguat[70]. **Yuanying fang et.al (2019)** had synthesized various derivatives of substituted pyrimidines and evaluated as GPR119 agonists out of all, those fused with tetrahydroquinazolines**(8a-8e)** showed greater activity as compared to dihyprocyclopentapyrimidine and tetrahydropyridopyrimidine derivatives then reference [71]. **Hanadi A. katouah et.al (2019**) had synthesized various derivatives of substituted pyrimidines and put all these for testing invivo and vivo antihypertensive activity (**9a-9d)** showed potent antihypertensive then reference [72].**Ahmed M. Farghaly et.al (2019)** had synthesized various derivatives of substituted pyrimidines and put all these for testing invivo and vivo antihypertensive activity out of all (**10b)** showed better activity then reference[73]. **kesarimanoj et.al (2020)** had synthesized various derivatives of substituted pyrimidines and put all these for testing invivo and vivo antihypertensive activity out of all (**10 a)** showed better activity then reference[74]. **Zohny YM et.al (2023)** had synthesized various derivatives of substituted pyrimidines and put all these for testing invivo and vivo antihypertensive activity out of all (**11a, 11b)** showed better activity then reference [75]

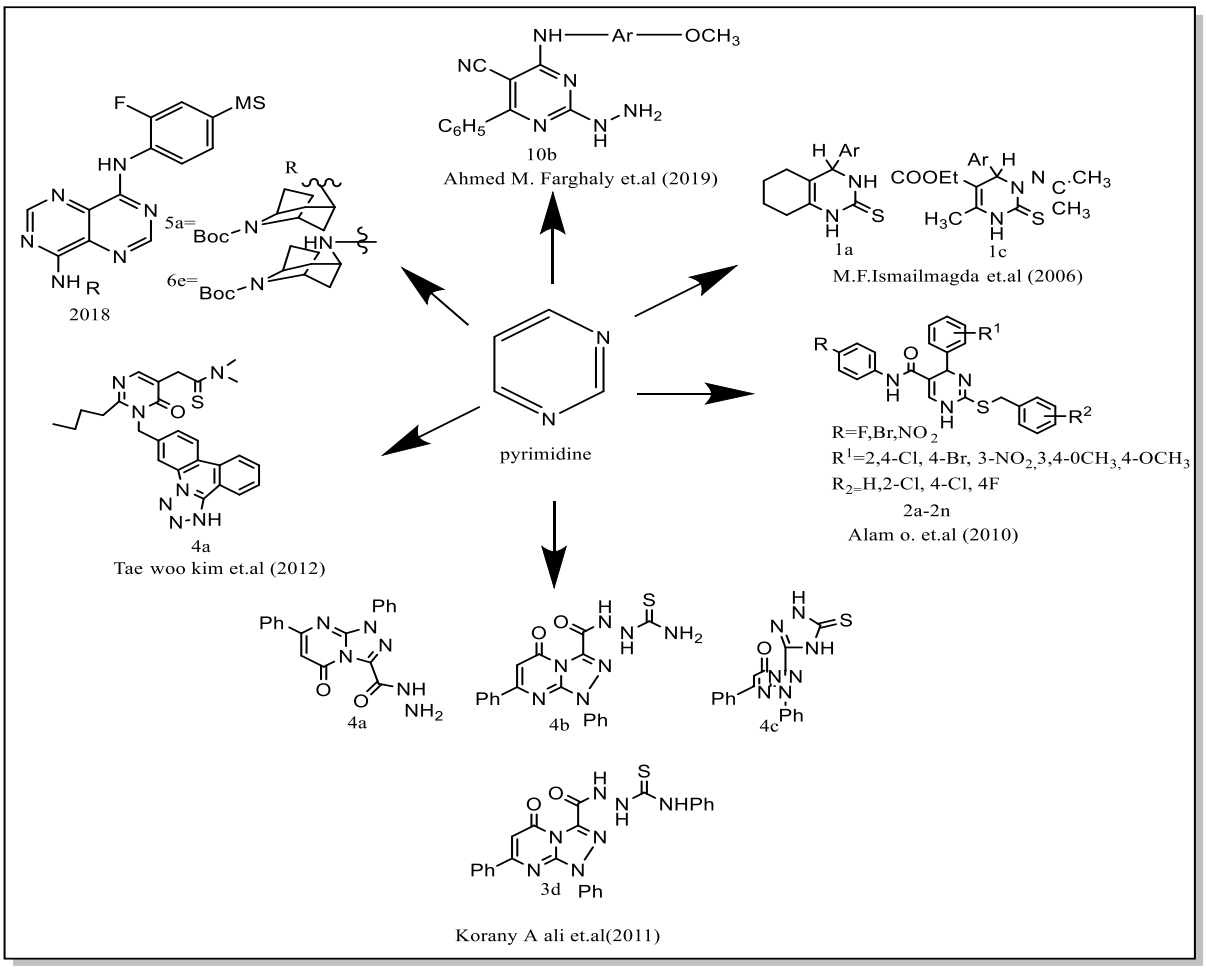


Fig 4:- Various pyrimidine derivatives having antihypertensive activity.

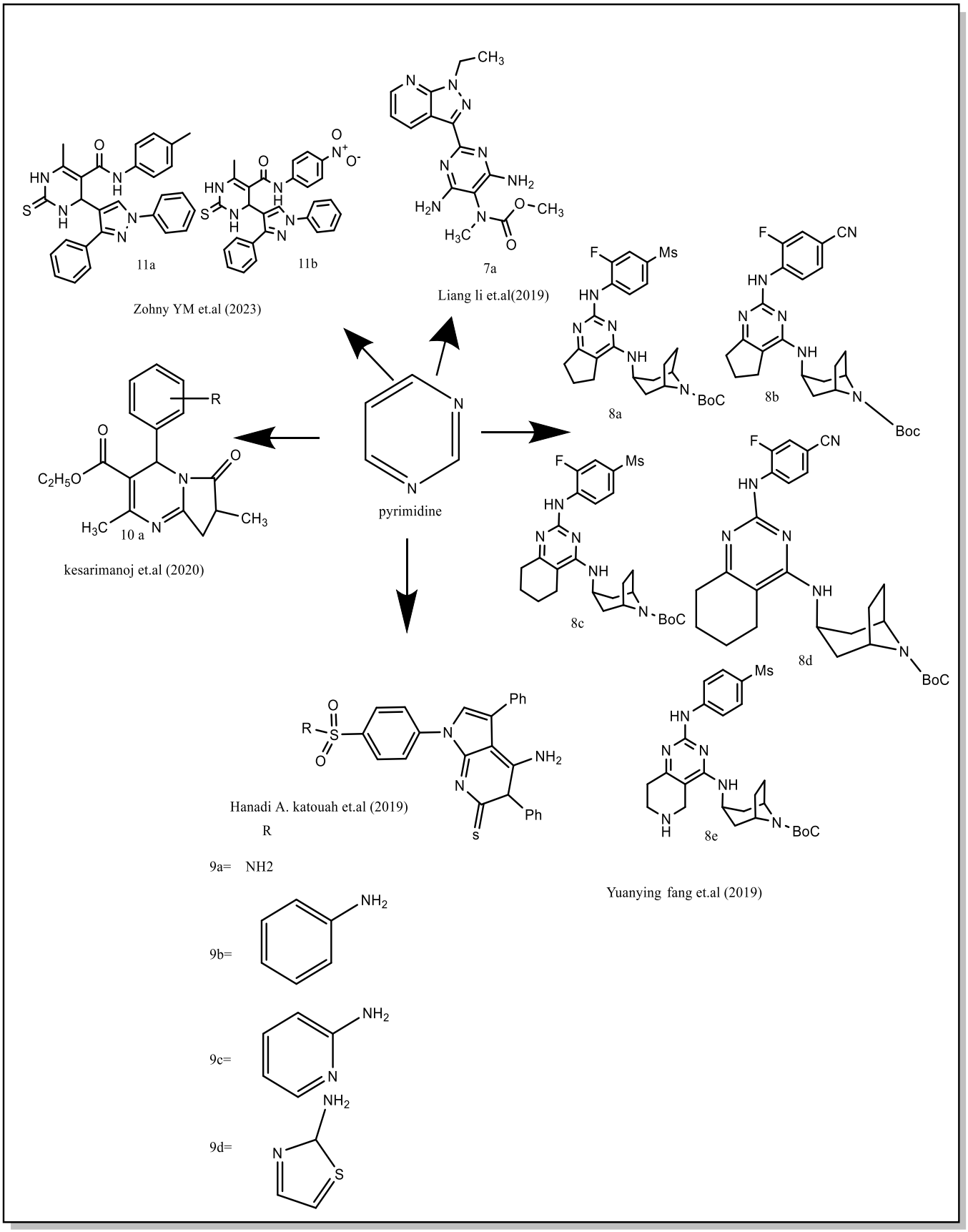
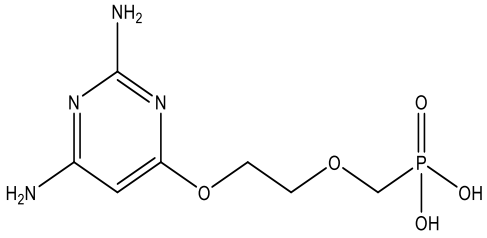
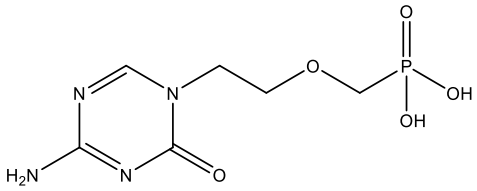
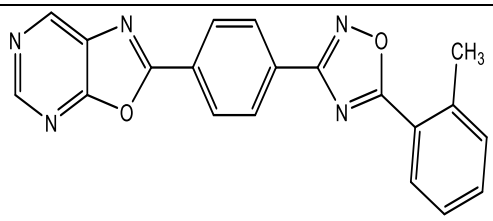
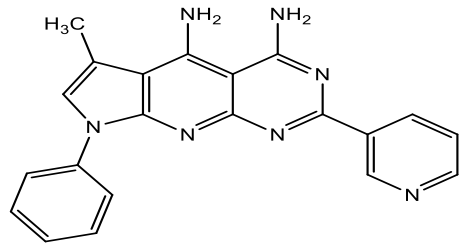
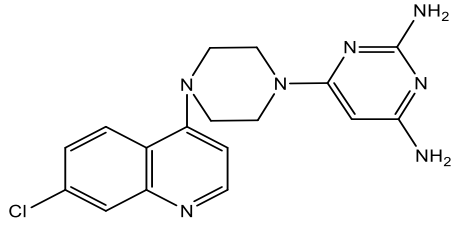
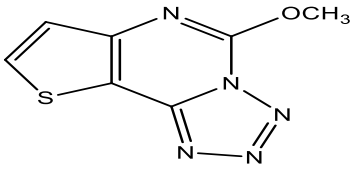
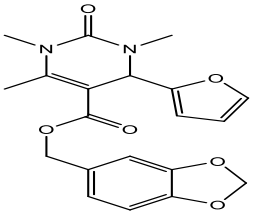
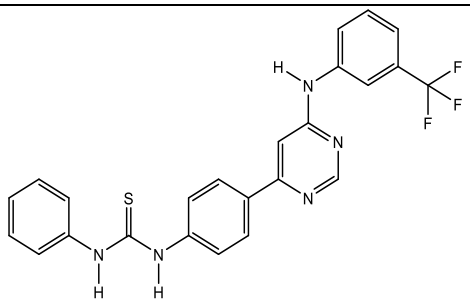
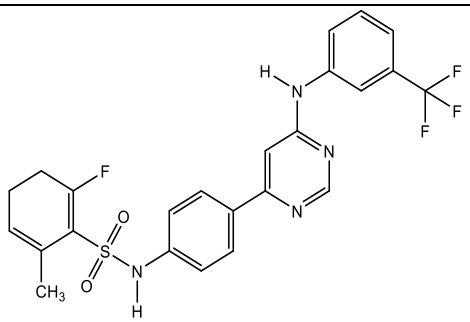
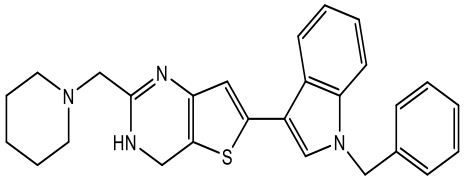
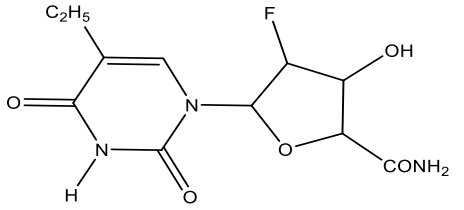

11a
11b
Zohny YM et.al (2023)
7a
Liang li et.al(2019)
pyrimidine
10 a
kesarimanoj et.al (2020)
8a
8b
8c
8d
8e
Yuanying fang et.al (2019)
Hanadi A. katouah et.al (2019)
R
9a= NH2
9b=
9c=
9d=

Fig 5:- Various pyrimidine derivatives having antihypertensive activity.

Table no. 1 List of Pyrimidine and fused pyrimidine marketed drugs

S.No.	Structure	IUPAC Name	Therapeutic Activity
1		2,4-diamino-6-[2-(phosphonomethoxy) ethoxy]pyrimidine	Antiviral activity [76]
2		1-[2(phosphonomethoxy) ethyl]-5-azacytosine	Antiviral activity [76]
3		2-(4-(5-(o-tolyl)-1,2,4-oxadiazol-3-yl) phenyl)oxazolo[5,4-d]pyrimidine	Anticancer Activity [77]
4		6-methyl-8-phenyl-2-(pyridin-3-yl)-8H-pyrrolo[3',2':5,6]pyrido[2,3-d]pyrimidine-4,5-diamine	Antifungal activity [78]
5		6-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)pyrimidine-2,4-diamine	Antimalarial Activity [79]

6		5-methoxytetrazolo[1,5-c]thieno[2,3-e]pyrimidine	Antidepressant, Anticonvulsant Activity[80]
7		benzo[d][1,3]dioxol-5-ylmethyl 4-(furan-2-yl)-1,3,6-trimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	Antithyroid Activity [81]
8		1-phenyl-3-(4-(6-((3-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)phenyl)thiourea	Anti-inflamatory Activity [82]
9		2-fluoro-6-methyl-N-(4-(6-((3-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)phenyl)cyclohexa-1,5-diene-1-sulfonamide	
10		6-(1-benzyl-1H-indol-3-yl)-2-(piperidin-1-ylmethyl)-3,4-dihydrothieno[3,2-d]pyrimidine	Antiangiogenic Activity [83]
11		5-(5-ethyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxytetrahydrofuran-2-carboxamide	Antihepatitis Activity [84,85]

Conclusion

The pyrimidine nucleus has been widely employed in numerous sectors for many years due to its extremely beneficial biological activity for human welfare; as a result, it has

become a significant nucleus for many medications. When pyrimidine derivatives are synthesised using conventional methods, the yield is lower and there is more pollution and environmental damage; however, when pyrimidine derivatives are synthesised using green methods, the yield is higher and there is no environmental damage because there is less byproduct formation. Although green synthesis is vital for the development of other successful techniques of synthesis, the synthesised pyrimidine derivatives will eventually be used in large quantities not only in the pharmaceutical sector but also in other fields. Numerous groups employ the pyrimidine moiety as a pharmacophore for synthesising different derivatives and testing them for invitro and in vivo antihypertensive activity. Some of these demonstrate good and effective antihypertensive activity that will be used for human welfare.

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