ejpmr, 2024, 11(8), 149-163

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

EXPLORING THE DYNAMIC CHEMISTRY AND THERAPEUTIC POTENTIAL OF PYRIMIDINE DERIVATIVES

Pooja Patle*, Shweta Dhole, Sakshi Mude, P. P. Katolkar and J. R. Baheti

Department of Pharmaceutical Chemistry, Kamla Nehru College of Pharmacy, Butibori, Nagpur Maharashtra 441108.

***Corresponding Author: Pooja Patle**

Department of Pharmaceutical Chemistry, Kamla Nehru College of Pharmacy, Butibori, Nagpur Maharashtra 441108.

Article Received on 01/06/2024 **Article Revised on 21/06/2024** **Article Accepted on 11/07/2024**

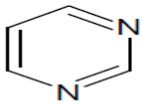
ABSTRACT

Similar to pyridine, pyrimidine is an aromatic heterocyclic chemical molecule. The "Principal Synthesis" method, which involves cyclizing beta-carbonyl molecules with N-C-N compounds, is commonly used to synthesis pyrimidines. Both the Biginelli and Pinner reactions can be used to produce pyrimidine. A class of heterocyclic scaffolds known as pyrimidine and its fused pyrimidine derivatives has a wide range of biological and pharmacological actions, including antibacterial, antiviral, antifungal, anxiolytic, anticancer, and antioxidant properties.

KEYWORDS: Pyrimidine, Heterocyclic, Synthesis, Pharmacological, Anticancer.

INTRODUCTION

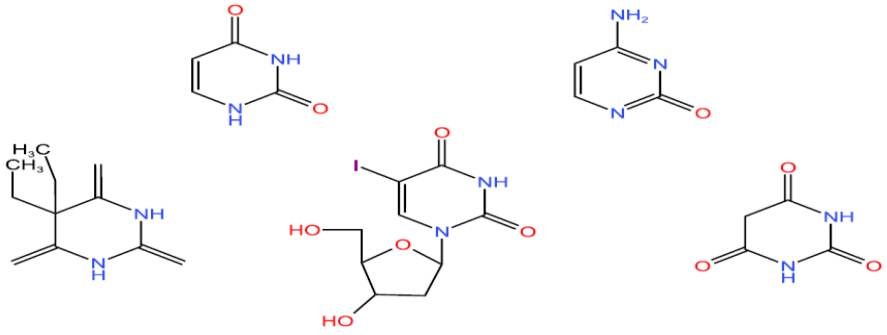
A molecule with a ring composed of more than one type of atom is called heterocyclic.[1] Homocyclic compounds are those in which the rings consist solely of carbon atoms, as in the case of benzene, naphthalene, cyclohexanol, and cyclopentadiene.[2] Similar to pyridine, pyrrimidine is an aromatic heterocyclic chemical molecule. Having two nitrogen atoms in the ring, this compound is one of the three diazines, which are six-membered heterocyclics with the nitrogens located at positions 1 and 3.[3,4]



pyrimidine

Physical properties of Pyrimidine

Molecular formula	C4H4N2
Molar mass	80.088 g mol−1
Density	1.016 g cm−3
Melting point	20 °C (68 °F; 293 K)
Boiling point	123 °C (253 °F; 396 K)
Acidity (pKa)	1.10 (protonated pyrimidine)



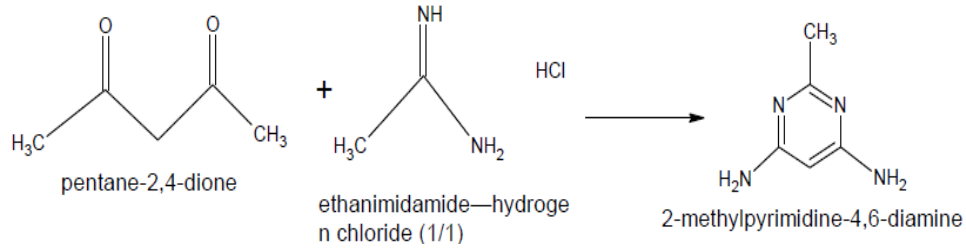
Pyrimidine is a substance without colour. Pinner was the one who originally used the term pyrimidine, which is a mixture of the words pyridine and amidine. It is thought that pyrimidine and its derivatives are crucial for pharmaceuticals and agricultural chemicals. Pyrimidines are highly significant heterocycles in biology and are by far the most common members of the diazine family. They are found in and exhibit a variety of biological activities, with uracil, thymine, and cytosine serving as components of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA).[6] Furthermore, the pyrimidine skeleton can be found in a variety of synthetic and natural goods, including hypnotics like barbituric acid and veranal. Natural items that contain pyrimidines include vitamin B1 (thiamine).[7]

1. Pinner-Type synthesis

The Pinner pyrimidine reaction produces pyrimidines, a class of nitrogenous heterocyclic moiety, by precipitating a beta-keto ester and a number of substituted amidines under the influenceofastrongacid.[8]

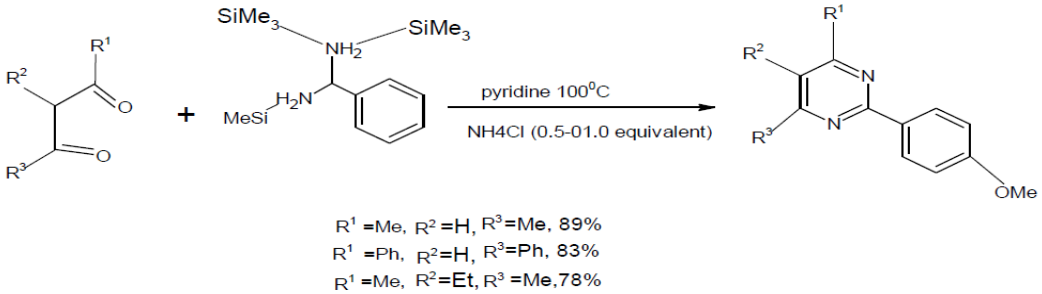
This reaction forms pyrimidine through the cyclization of amidines with beta-diketone molecules in the presence of acid as a catalyst. The most popular method of synthesizing pyrimidines is to combine a 1,3-dicarbonyl molecule with urea, amidine, or guanidine.[9,10] A range of pyrimidine derivatives made from various 1,3 dicarbonyl starting materials, such as acetylated and ethyl acetoacetate, were produced by using the Pinner process.

Synthesis of pyrimidine



Scheme No. 1: Synthesis of pyrimidine.

By using 1,3-dicarbonyl compounds 10 in place of unsubstituted amidines, Ghosh and Katzenellenbogen were able to condense N, N,N'-tris-(trimethylsilyl) amidine[11] and prepare a range of 2,4,6-trisubstituted and 2,4,5,6-tetrasubstituted pyrimidine derivatives.

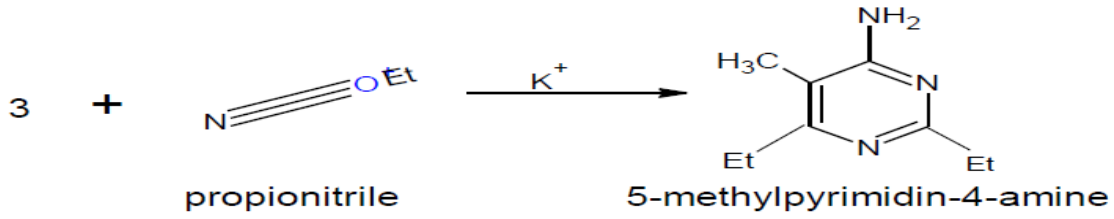


R^1 =Me, R^2 =H, R^3=Me, 89%
R^1 =Ph, R^2=H, R^3=Ph, 83%
R^1 =Me, R^2=Et, R^3 =Me,78%

Scheme No. 2: Synthesis of tetrasubstituted pyrimidine.

2. Frankland and Kolbe synthesis

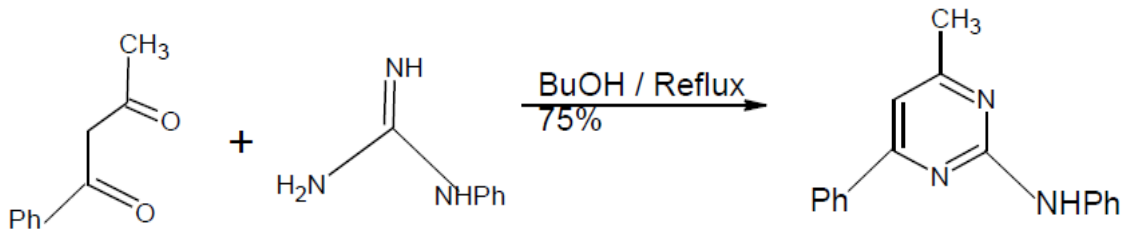
In 1848, described the first synthesis of a pyrimidine cyanalkine (9) by heating propionitrile with potassium metal.[12]



Scheme No. 3: Synthesis of pyrimidine.

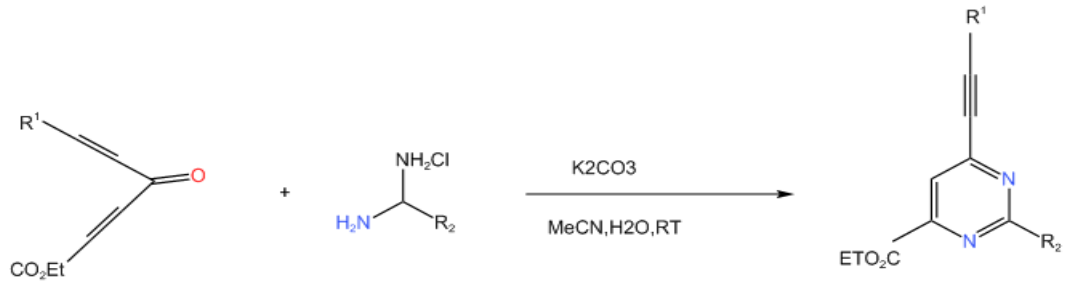
The condensation of N-C-N fragments, most frequently amidines or guanidines, is the basis for several of these widely used tactics (Scheme 4). Following that, N-C-N Fragement, employed amidine or guanidine, is

condensed with the 1,3-dicarbonyl derivatives to generate synthetic pyrimidine derivatives.[13]



Scheme No. 4: A typical pyrimidine synthesis process involves condensation of a diketone and an N-C-N fragment.[14]

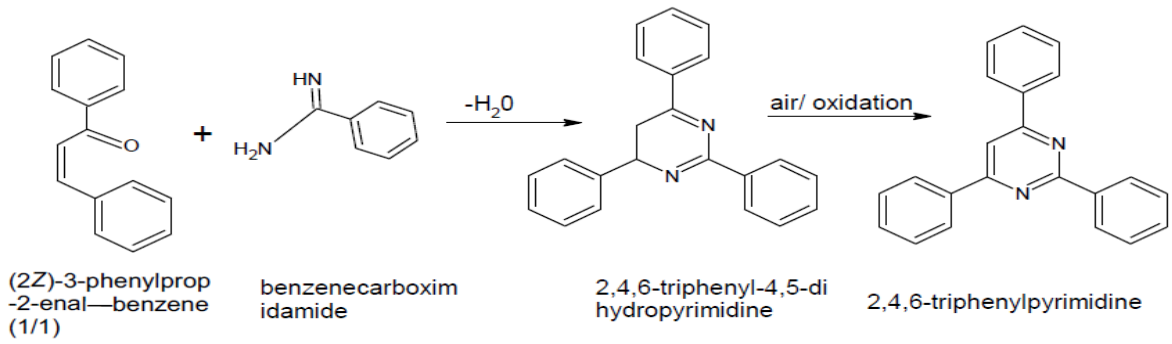
Adamo et al. have created an intriguing pathway utilizing amidinium chlorides 14 and diacetylenic ketoesters to obtain 2,4,6-trisubstituted pyrimidines.[15]



Scheme No. 5: Synthesis of 2,4,6 trisubstituted Pyrimidine.

3. From α –β, unsaturated ketone

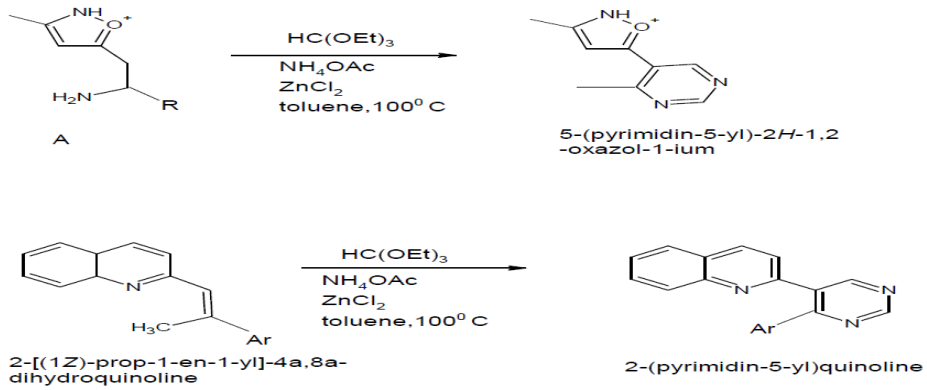
The α–β unsaturated ketone reaction forms 2,4,6-triphenyl-4,5-dihydropyrimidine by reacting 3-phenylprop-2-enal-benzene with benzenecarboximidamide through the loss of a water molecule. additionally, to the product's oxidation to 2,4,6-triphenylpyrimidine.[16]



Scheme no. 6: Synthesis of pyrimidine derivative.

4. From Unsaturated Enamines and Enamides

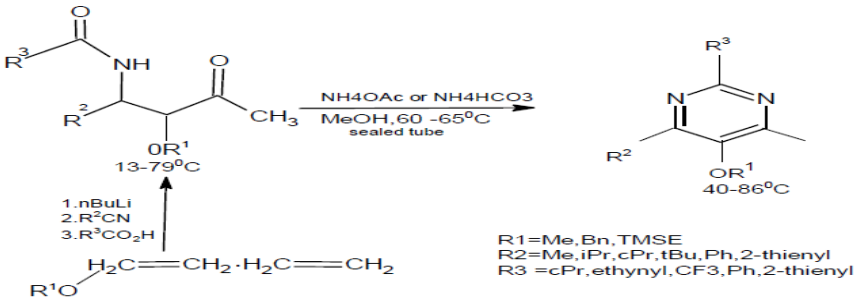
When employed as precursors in the synthesis of pyrimidines, enamines and enamides supply the (N1–C2–) N3–C4–C5 moiety of the resulting skeleton. Because the primary substrates are 5-methylisoxazolyl-, quinolin-2-yl-, and ethoxycarbonyl-substituted enamines A,B respectively, the substitution pattern is highly uncommon. Surprisingly, their counterparts in pyridin-2-yl, thiazolin-2-yl, and (dimethylamino)carbonyl produced mixtures from which the anticipated pyrimidines were only marginally extracted.[17]



Scheme No. 7: Synthesis of pyrimidine from enamides.

5. Creation from β-Enaminones

The process of synthesizing enaminones involves first adding lithiated alkoxy allenes to nitriles, then adding a carboxylic acid and undergoing an internal rearrangement to get the required molecules. Although the reaction is naturally restricted to specific structural characteristics, such as the existence of a 6-methyl and a 5-alkoxy group in the resultant pyrimidine, it can tolerate a wide range of functional groups.[18,19]

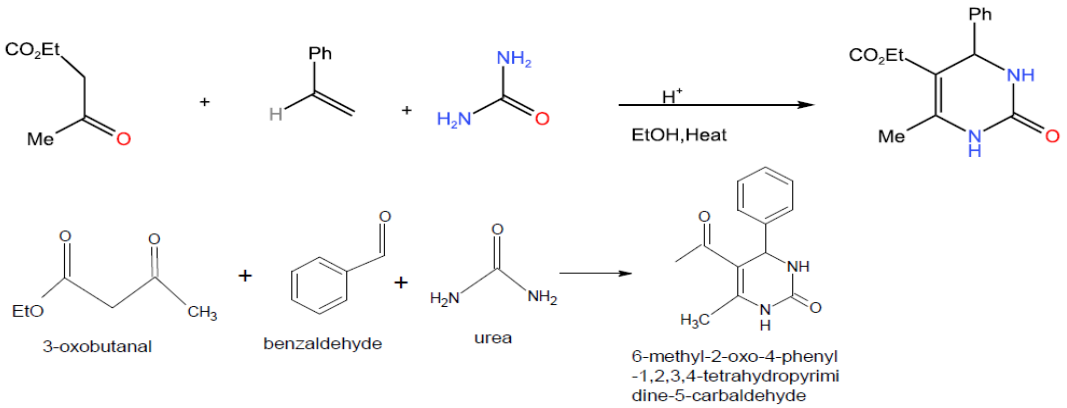


Scheme No. 8: Synthesis of 5-alkoxypyrimidine from β-enaminones.

6. Biginelli reaction

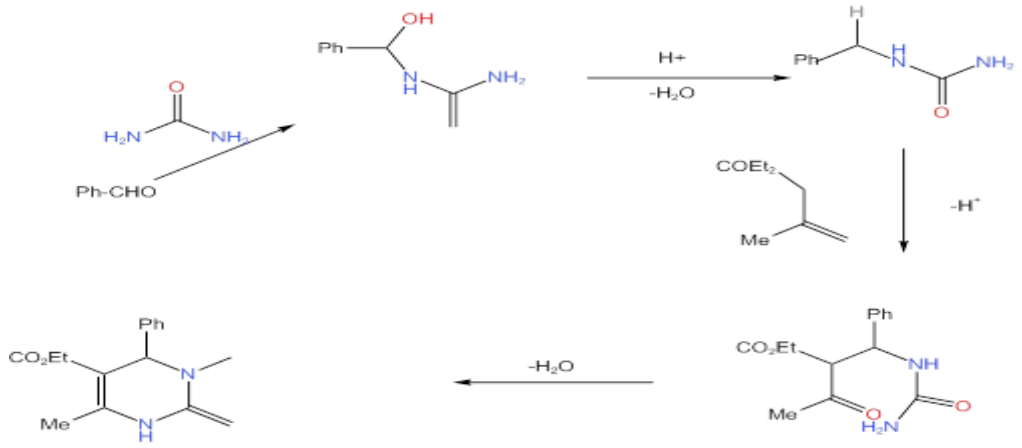
The three-component reaction that an aldehyde, ß-ketoester, and urea catalyzes is a quick and easy way to create dihydropyrimidones, which are intriguing molecules that may find use in medicine.

Example of the Reaction amidines react with to give 2-substituted pyrimidines, with urea to give 2-pyrimidiones, and guanidines to give 2 amino pyrimidines.



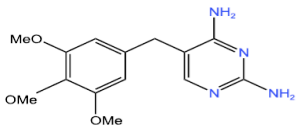
The Biginelli Reaction's Mechanism

The condensation between the aldehyde and urea, which bears some resemblance to the Mannich Condensation, is thought to represent the initial stage in the mechanism. The resulting adduct's ketone carbonyl condenses with urea NH2 to yield the cyclized product, and the iminium intermediate that is formed serves as an electrophile for the nucleophilic addition of the ketoester enol.

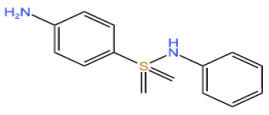


Pyrimidine derivatives

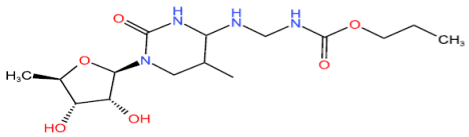
Numerous medications, useful materials, and natural compounds are examples of pyrimidine derivatives. Xeloda (Capecitabine), Gleevec (Imatinib mesilate), trimethoprim, and sulfadiazine are a few examples of pharmaceutically significant chemicals. Pyrimidine derivatives are also present in both artificial and natural polymers.



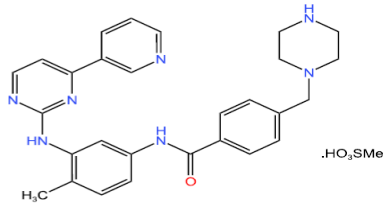
Trimethoprim



Sulfadiazine



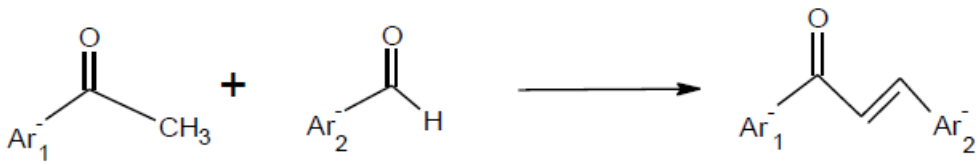
Capecitabine



Imatinib mesilate

Unsaturated ketone (1a–1h) α–β synthesis utilizing EtOH aqueous KOH 40% w/v 00C

With pure ethanol as the starting material, the synthesis of unsaturated ketones (1a1h) was sccessfully completed by ClaisenSchmidt condensation between a suitably substituted ketone nd an appropriately substituted aldehyde.2. Chemistry: Using absolute ethanol and aqueous KH 40% w/v as starting materials, the synthesis of α,βunsaturated ketones (1a1f) was successfulycompleted through ClaisenSchmidt condensation between an appropriately substituted keton and an appropriately substituted aldehyde 34.Pyrimidine derivatives (2a2h) were produced by condensing 4-amino-6-hydroxy-2-mercaptopyrimidine monohydrate in glacial acetic acid 23 with appropriate α,β-unsaturated ketones.



1a. Ar_1 =C_6H_5 Ar_2 =C6H5
1b. Ar_1 =4ClC_6H_4 Ar_2 =C6H5
1c. Ar_1 = C_6H_5, Ar_2 =2-thienyl
1d. Ar_1 =4ClC_6H_4 Ar_2 = 2-thienyl
1e. Ar_1 =C_6H_5 Ar_2 =4ClC6H4
1f. $Ar_{1=}$ 4ClC_6H_4 Ar_2 =4ClC_6H_4s

1. Synthesis of pyrimidine derivatives (2a -2h) using glacial acetic acid ,118^0 C ,96 h[24,25,26]

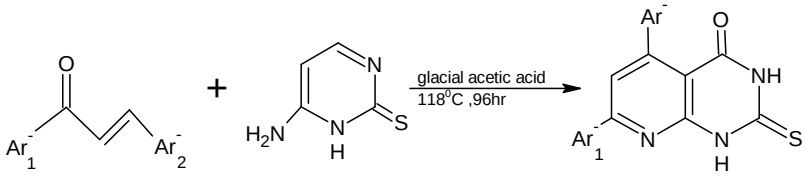
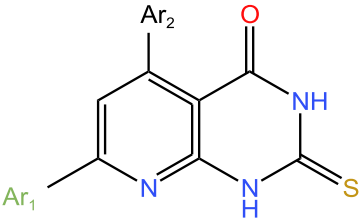
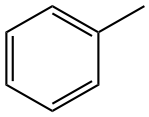
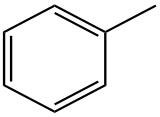
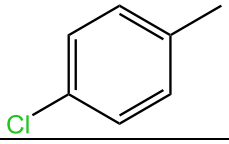
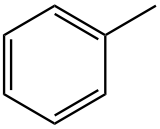
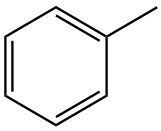
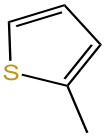
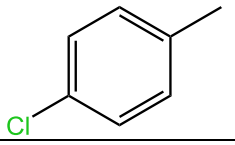
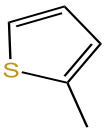
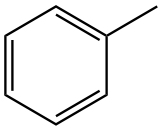
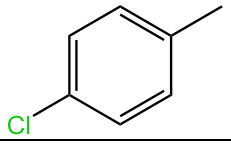
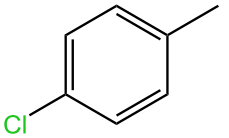
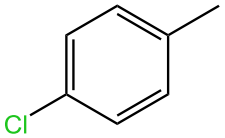
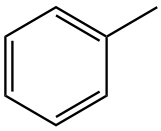
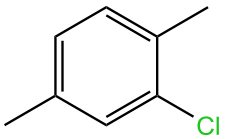
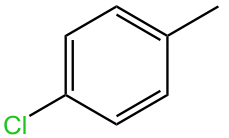
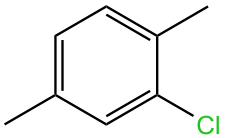
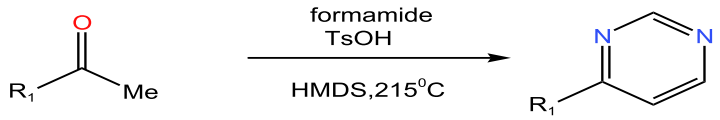


Table 1: Substitutes of pyrimidine derivatives.

Compound	Pyrimidine Scaffold	Ar_1	Ar_2
2a			
2b			
2c			
2d			
2e			
2f			
2g			
2h			

2. Mono substituted pyrimidine derivatives

Synthesis of several 4-monosubstituted pyrimidines by Tyagarajan and Chakravarty.[27] It was advised to use microwave assistance to condense two equivalents of formamide with ketone substrates while adding 1,1,1,3,3,3-hexamethyldisilizane and p-toluenesulfonic acid.

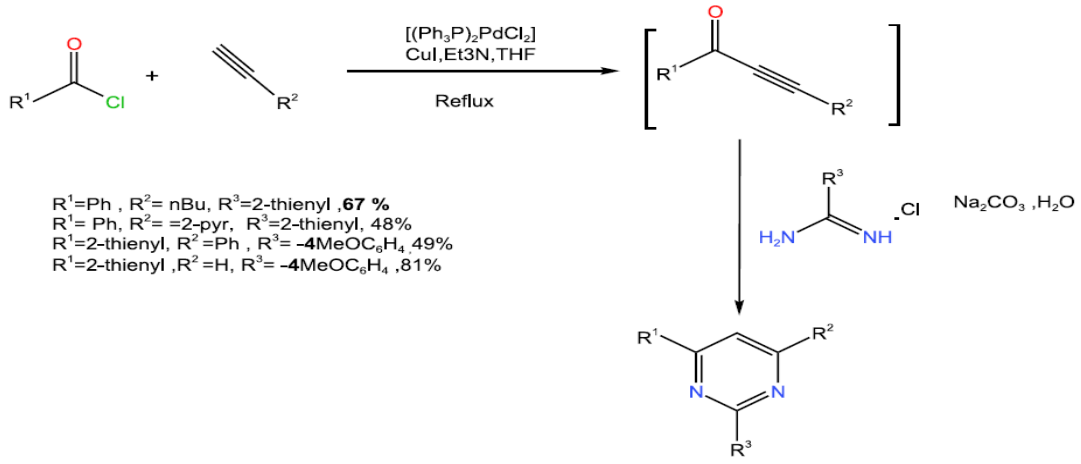


R1 = Ph89%
R1 = 4-BrC6H4,57%
R1 = 4-ClC6H4
R1= cHx, 35%
R1= nBu, 19%
R1 =2- pyr, 27%

Scheme no. 8: Microwave assisted synthesis of pyrimidine derivatives.[25]

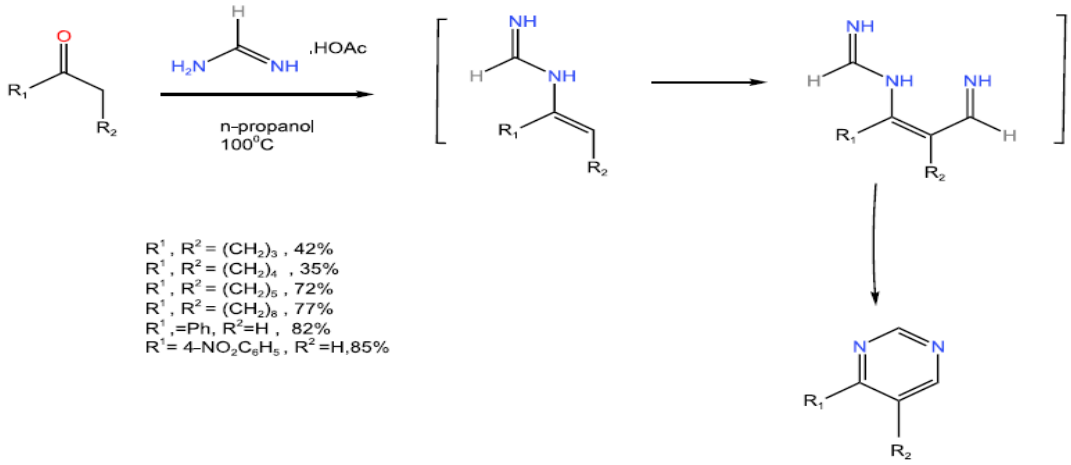
3. Disubstituted pyrimidine derivatives

A cross-coupling/addition/cyclocondensation sequence for the synthesis of 2,4-disubstituted and 2,4,6-trisubstituted pyrimidines[28] was also devised by the Miller group. In order to produce none intermediate, the procedure entails a Sonogashira cross-coupling of acid chloride and alkyne. Amidinium chloride, a base-promoted nucleophilic addition process, can be used to add enone, a highly reactive Michael acceptor, and then cyclocondensate the resulting di- and trisubstituted pyrimidines with heteroatom, alkyl, and aromatic substitution.



Scheme No. 10: One –pot, two step synthesis of pyrimidine derivatives.

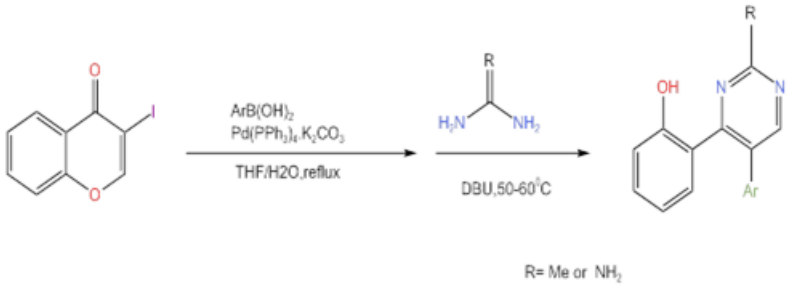
An intriguing one-step synthesis of 4,5-disubstituted and 4-monosubstituted pyrimidines has been reported by the Baran group. The required pyrimidines were obtained by heating two equivalents of formamidine acetate in propanol and condensing them with cycloalkanone and acetophenone derivatives.



Scheme no. 11: Synthesis of pyrimidine derivatives from ketones and formamidine acetate.

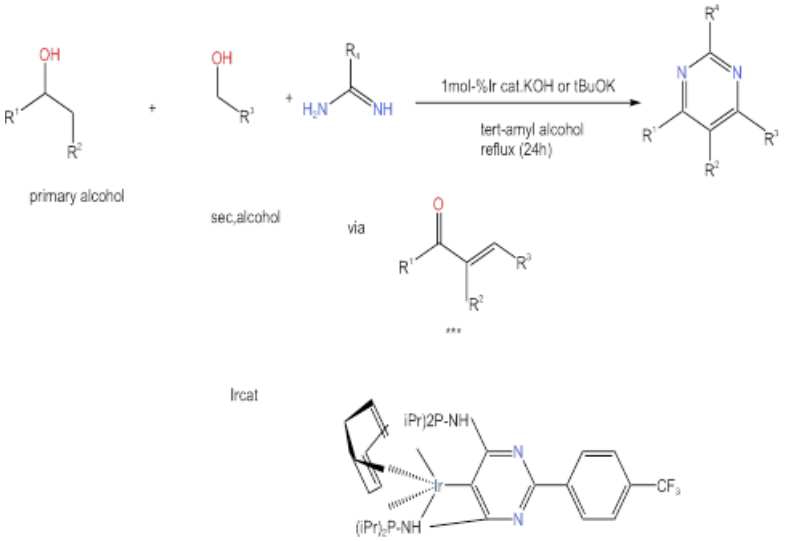
4. Suzuki Coupling/Condensation reaction

3-Iodochromone is, this time, first engaged in Suzuki coupling with various arylboronic acids and then condensed with acetamidine or guanidine to yield the corresponding 2-amino- or 2-methyl 4-(2-hydroxyphenyl)-5-arylpyrimidines 34–85% yields. Hu 30 has reported a related strategy based on sequential condensation/cross coupling functionalization.



5. Kempe's three-component synthesis of pyrimidines

Kempe in 2015 form the three-component condensation procedure with primary alcohols, secondary alcohols, and amidine under iridium catalysis conditions.[31] The reaction proceeds through two successive dehydrogenations of the two alcohols, followed by a base-mediated aldol reaction and by dehydrative amidine condensation onto the resulting enone 14. This methodology presents an impressive scope of reactivity, with 2,4,6-trisubstituted and 2,4,5,6-tetrasubstituted pyrimidines being prepared in good yields and with a remarkable toler ance being shown to many aliphatic and aromatic substituents.

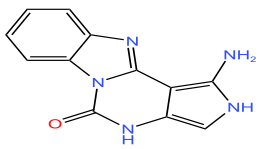


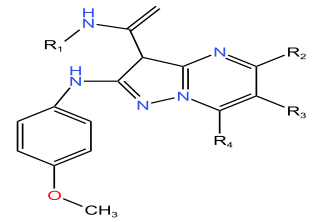
6. Novel pyrimidine derivatives

The derivatives have been designed for the anticancer Activity. The structural activity suggested(SAR) suggests that the presence of two aromatic and an aliphatic chlorine atom linked to the pyrimidine ring gave the compound with maximum potential.

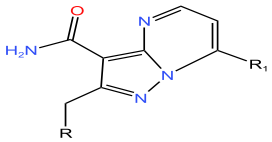
1. Pyrazol pyrimidine derivatives

Some novel fused pyrazolo pyrimidine derivatives were studied for anticancer activity as well as COX-2 inhibition against a 60 cancer cell line panel.

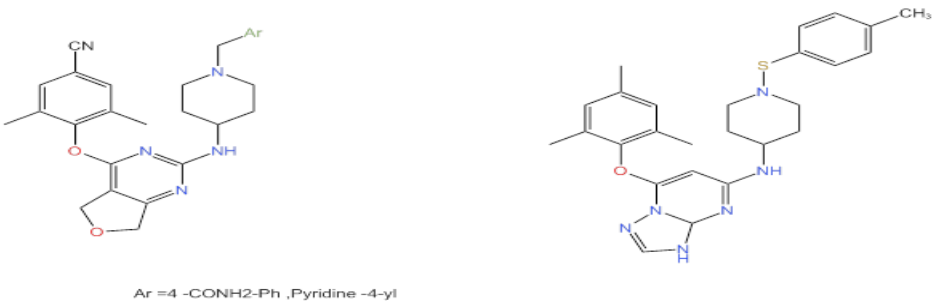




R1= 4-CH_3 -C_6H_5
R_2=NH_2
,R_3=CN
,R_4 =Cl

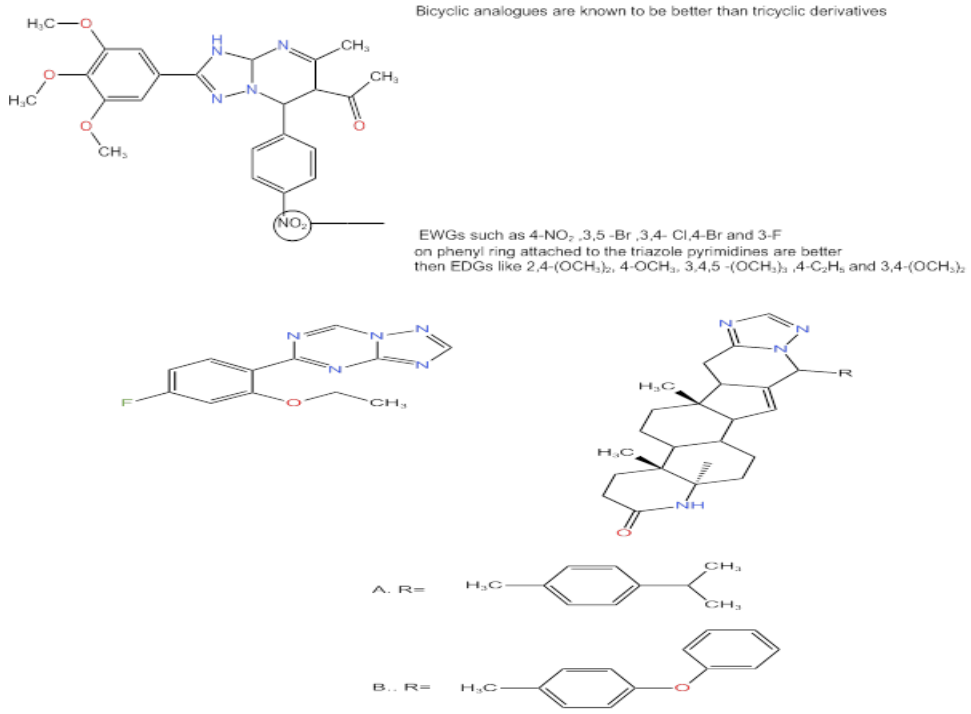


R= C_6H_5 ,R_1=4-ClC_6H_5



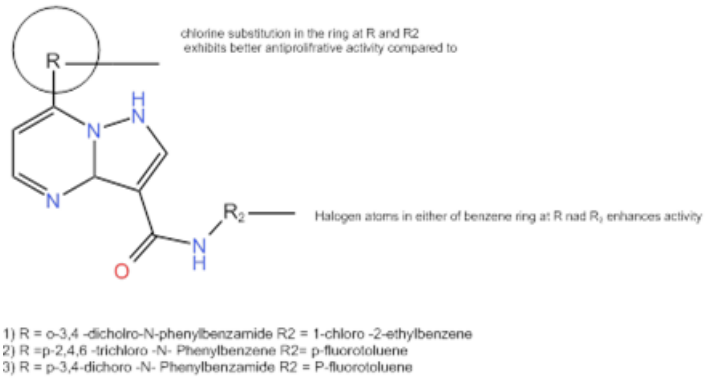
2. Triazole pyrimidine derivatives

[1,2,4] triazolo [1,5-a] pyrimidine derivatives were screened for in vitro antiproliferative activities against HeLa, HCT116, and A549, via MTT assay.[32]



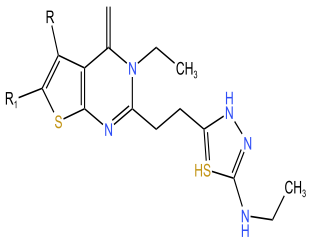
3. Imidazolo pyrimidine derivatives

Antiproliferative activity of N-9- and N-7-1,2,3 tri azole analogs of 2,6-di-substituted purines was reported. They were tested against HCT-1, THP-1, IMR-32, and A 549 cancer cell lines. 75 was the most potent against the THP-1 and A-549 cell lines with the IC50 = 0.08 and 0.4 μM[33] respectively. The activity was mainly due to C6 position substitution with amines like aminoethnol and benzyl amine, and C2 position was substituted with cyclic second aryamines like piperidine and pyrolidine. Earlier, theanticancer activity of newly synthesized imidazo[1,2-a] pyrimidine mannich studied.

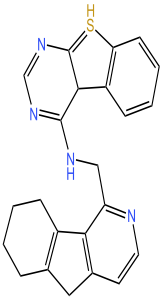


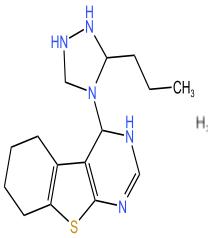
4. Thieno pyrimidine derivatives

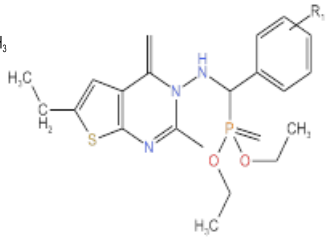
Thieno [2,3-d] pyrimidines Novel 2,3-disubstituted-4-oxo-5,6,7,8-tetrahydrobenzo [4,5] thieno[2,3-d]pyrimidines were studied against breast and liver cancer cell lines with DOX a positive control. 91 showed the best activity in the series with the IC50 = 0.19 µM (breast cancer cell line)



a. R =CH3 , R1 =CH3
b. R = CH3 ,R1 =COOCH3
c. R= R1= $(CH_2)_4$



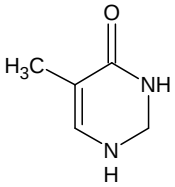




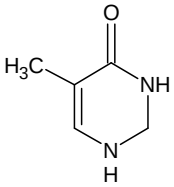
R1 =4-Cl

5. Genetic pyrimidine derivatives

Three nucleobases found in nucleic acid, cytosine (C), thymine (T), and uracil (U), are

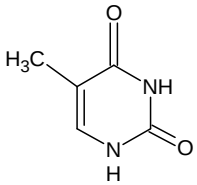


5-methyl-2,3-dihydropyrimidin-4(1*H*)-one



5-methyl-2,3-dihydropyrimidin-4(1*H*)-one

In DNA and RNA, these bases form hydrogen bond with their complementary purines. Thus, in DNA, the purines adenine (A) and guanine (G) pair up with the pyrimidines thymine (T) and cytosine (C), respectively. In RNA, the complement of adenine (A) is uracil (U) instead of thymine (T), so the pairs that form are adenine: uracill and guanine: cytosine very rarely, thymine can appear in RNA, or uracil in DNA. Other than the three major pyrimidine bases presented, some minor pyrimidine bases can also occur in nucleic acid. These minor pyrimidines are usually methylated versions of major ones and are postulated to have regulatory functions.

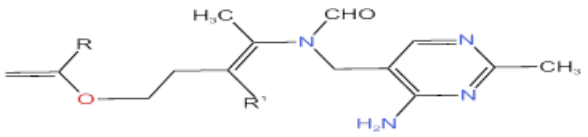


5-methylpyrimidine-2,4(1*H*,3*H*)-dione

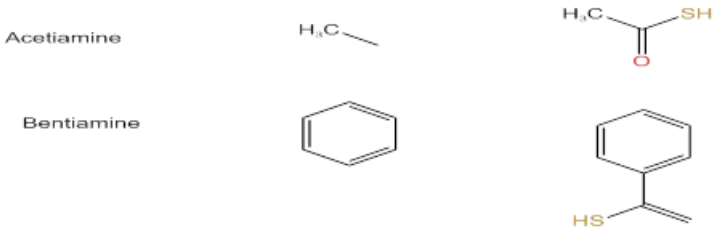
Clinical significance of pyrimidine analogs

1. Analgesic activity

New forms of thiamine are lipidsoluble like acetiamine, Benti-amine etc., having therapeutic use in beriberi, polyneuritis, encephalopathy, pain, malnutrition and alcoholism and especially in the treatment of long-standing insulin-dependent diabetes mellitus.[29]



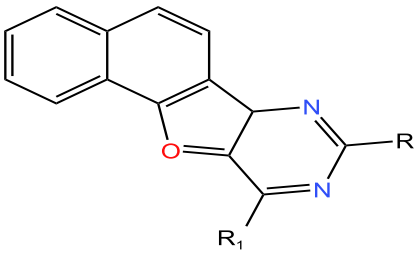
R R1

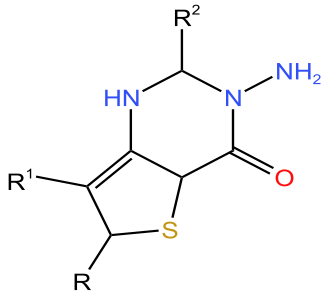


2. Anti-inflammatory drugs

Anti-inflammatory drugs (NSAIDs) have a wide therapeutic benefit that ranges from the treatment of fever, inflammation, and mild pain. Most commonly prescribed drugs like diclofenac, ibuprofen and mefenmic acid, etc.

Pyrimidine has a remarkable pharmacological efficiency and therefore an intensive research has been focused on anti-inflammatory activity of pyrimidine nucleus. Recently two PCT international applications have been filed for 2 thiopyrimidine derivatives possessing potent activity against inflammation and immune disorders. Pyrimidine was reported by Padama shale et al. Carrageen induced rat paw edema method was employed for evaluating the anti- inflammatory activity. The compounds were given at a dose of 80 mg/kg body weight in albino rats weighing between 150 and 200 g. The edema was produced by injecting carrageenan solution at the left hind paw.[30]

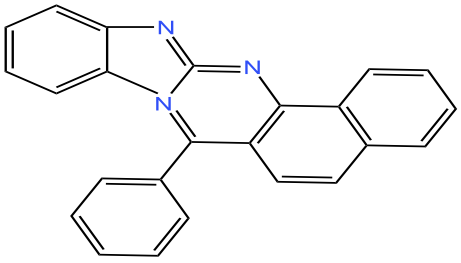




R =CH_3 ,C_6H_5 ; R_1 =OCH_3,OC_2H_5 ,NHC_6H_5 , NHC_2H_5 R1, R2 =$(CH_2)_3$.$(CH_2)_5$, $(CH_2)_4$,R3 =CH_3

3. Antidiabetic activity

Synthesized some novel pyrimidines derivative having thiazolidine dione. These compounds were evaluated for their glucose and lipid lowering activity using pioglitazone and rosiglitazone as reference compound. Synthesized azolopyrimidine derivatives and compounds were evaluated for hypoglycemic activity.[31]



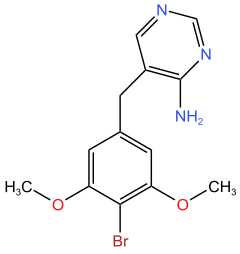
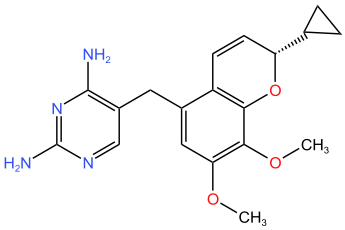
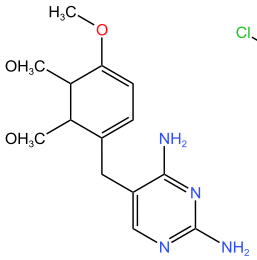
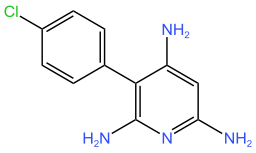
azolopyrimidine

4. Antibacterial activity

created a number of new pyrimidine derivatives with thiazolidine dione. The chemicals pioglitazone and rosiglitazone were used as reference substances to assess these compounds' ability to decrease blood sugar and

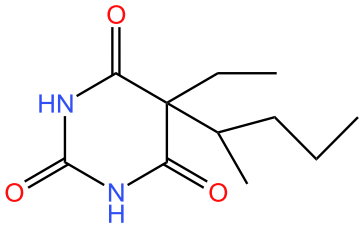
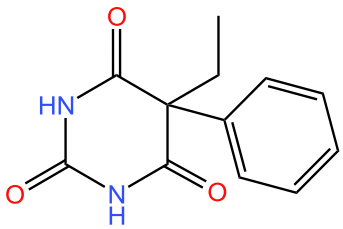
cholesterol.

The hypoglycemic potential of synthesized azolopyrimidine derivatives and compounds was assessed.

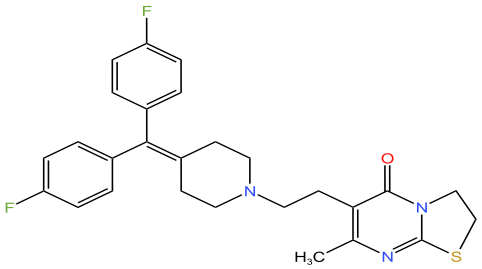
5. Sedatives and Hypnotics

Barbituric acid, the parent nucleus of a broad range of barbiturates, is related to pyrimidine analogues. These analogues, which function as central nervous system depressants and are clinically approved medications, have a wide range of effects, from moderate drowsiness to anesthesia. The central nervous system is unaffected by benituric acid by itself. Barbiturates, however, have been primarily employed for their sedative, hypnotic, and anticonvulsant effects. Additionally, as hypnotics, allobarbital and aprobarbital are employed. Pentobarbital is another barbiturate that is used in emergency situations to reduce convulsions and provide sedation. Moreover, combinations of cyclobarbital or cyclobarbitol and diazepam are utilized to treat insomnia. Propallylonal, sometimes referred to as nostal, ibomal, has hypnotic, anticonvulsant, and sedative effects. Furthermore, a class of medications called phenlobarbial is used to both treat and prevent the symptoms of sedatives and hypnotics.

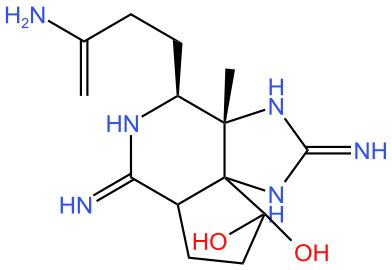
6. As anxiolytic

Piperazine bearing pyrimidine analogs such as buspirone and ritanserin act as anxiolytic agents. In addition to this, fused pyrimidine risperidone is also used as an anxiolytic agent.[32]



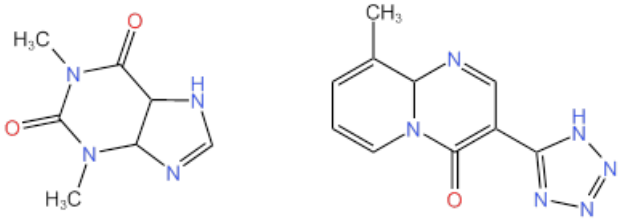
7. As anaesthetics

Biomolecule saxitoxin acts as an anaesthetic drug. Due to its high toxicity, it has been banned. One of the substituted barbiturates, thiamylal, generally prescribed as a short-acting anesthetic drug.[33]



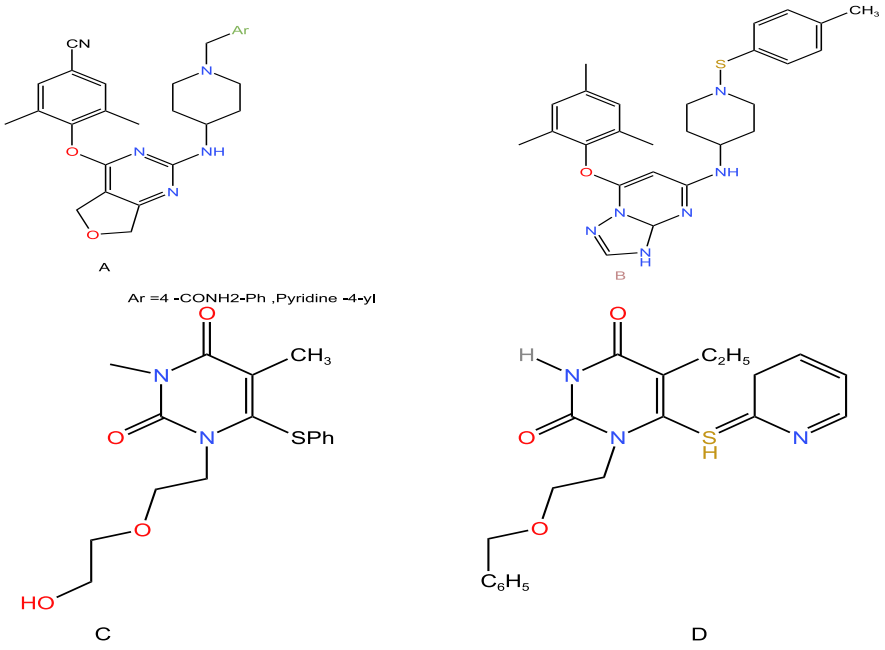
8. As bronchodilator

Theophylline, purine analog, and pemirolast (tetrazole bearing pyrimidine) are two oral nonbronchodilator drugs used for chronic asthma.[34]



9. As an anti- HIV agent

Highly Active Antiretroviral Therapy, or HAART, has demonstrated promising results in the treatment of HIV-1 infection in AIDS patients. We can comprehend the immune system's reaction to HIV infection by using several screening tests for severe human immunodeficiency virus (HIV) infection and by analyzing the outcomes of experimental testing. Medication that slows down or stops the virus's reproduction can be used to treat HIV. Additionally, the body's immunity begins to mend it and prevents additional serious harm. Since HIV can rapidly become resistant to treatment, a different combination of HIV medications is utilized.[35,36,37] 2019 saw the synthesis of new pyrimidine (dihydrofuro) analogs and their anti-HIV screening by Kang D et al. Compound (D) showed promising anti-HIV activity against MT-2 cell lines, with an IC 50 of 24 +0.1 µ M. The action that was seen could taken.

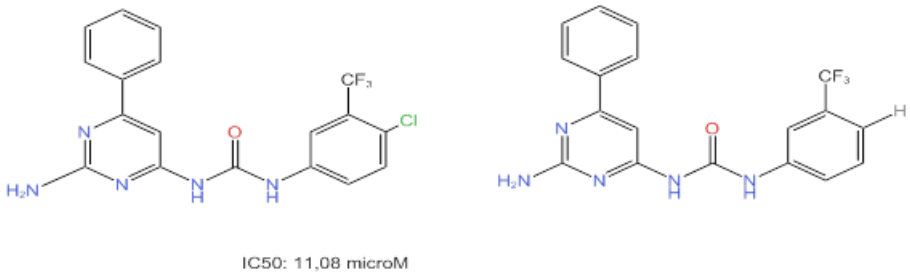


Molecular structure of pyrimidine witha anti -HIV potential.

10. As anti-cancer agent

A considerable contribution to the prevention and treatment of cancer has been made by pyrimidine and its derivatives. Radiation and chemotherapy for cancer have a long history of side effects that negatively impact a person's ability to live a healthy life. In some cases, these side effects have even been linked to major issues. Nine million individuals died from cancer in 2018, mostly as a result of fewer effective treatments, according to a WHO research tht states that eighteen million people are currently afflicted with the disease.[38,39]

Kurt Zuhal Kilic and colleagues (2020) synthesized novel pyrimidines that contain aryl urea analogs and assessed their antitumor potential. Every drug demonstrated adequate anticancer efficacy against cell lines of prostate and colon cancer (IC50: 11.08 µM, SW480). The presence of amino-pyrimidine scaffold, Cl, and CF3 is what causes the increased activity. In 2019, Huang T et al. synthesized.



CONCLUSION

Pyrimidines are bases of DNA that are essential to medicine. The research makes it clear that the majority of medications have fused and pyrimidine structures. Analogs of pyrimidine have demonstrated antimicrobial, antiviral, anti-psychotic, anticancer, and anti-inflammatory properties.[40] However, many of these medications' cytotoxicity and drug resistance have made additional medications necessary. A wealth of knowledge on pyrimidine as a flexible scaffold with prospective uses is offered by this review. Researchers who are willing to produce a range of pyrimidine analogs may become more interested in this review. Moreover, it will be extremely difficult for creative researchers to turn lead compounds into powerful medications free of cytotoxicity and drug resistance.

REFERENCE

1. Al-Mulla, A., A review: biological importance of heterocyclic compounds. Der Pharma Chemica, 2017; 9(13): 141-147.
2. Miller D; Remington- The Science and Practice of Pharmacy; Pennsylvania: MACK Publishing Company, 1995; 19: 425.
3. Amir M, Javed SA and Kumar H; Indian J. Pharm. Sciences, 2007; 69(3): 337-343.
4. Cox RA; Quart. Rev, 1968; 22: 499.
5. Verma V, Joshi CP, Agarwal A, Soni S, Kataria U. A review on pharmacological aspects of pyrimidine derivatives. Journal of Drug Delivery and Therapeutics, 2020; 15, 10(5): 358-61.
6. A. Pinner, Ber. Dtsch. Chem. Ges, 1884; 17: 2519–2520, b) A. Pinner, Ber. Dtsch. Chem. Ges, 1885; 18: 759–763, c) A. Pinner, Ber. Dtsch. Chem. Ges, 1887; 20: 2361–2365.
7. Y. Jiao, S. Ho, C. Cho, Synlett, 2015; 26: 1081–1084.
8. U. Ghosh, J. A. Katzenellenbogen, J. Heterocycl. Chem, 2002; 39: 1101–1104.
9. E. Frankland, H. Kolbe, Justus Liebigs Ann. Chem, 1848; 65: 269-287.
10. W. Wendelin, K. Schermanz, K. Schweiger, A. Fuchsgruber, Mon atsh. Chem, 1983; 114: 1371–1379.
11. 14.M. F. A. Adamo, R.M. Adlington, J. E. Baldwin, G. J. Pritchard, R. E. Rathmell, Tetrahedron, 2003; 59: 2197–2205.
12. Guirado, E. Alarcón, Y. Vicente, R. Andreu, Tetrahedron Lett, 2013; 54: 5115–5117; b) A. Guirado, E. Alarcón, Y. Vicente, R. Andreu, Tetra hedron, 2016; 72: 3922–3929.
13. Detsi, A.; Majdalani, M.; Kontogiorgis, C.A.; Hadjipavlou-Litina, D.; Kefalas, P. Natural and Synthetic 2-Hydroxy-Chalcones and Aurones: Synthesis, Characterization and Evaluation of the Antioxidant and Soybean Lipoxygenase Inhibitory Activity. Bioorg. Med. Chem, 2009; 17: 8073–8085. [CrossRef]
14. Chebanov, V.A.; Saraev, V.E.; Gura, E.A.; Desenko, S.M.; Musatov, V.I. Some Aspects of Reaction of 6-Aminouracil and 6-Amino-2 Thiouracil with,-Unsaturated Ketones. Collect Czechoslov. Chem. Commun, 2005; 70: 350–360. [CrossRef]
15. T. Sasada, F. Kobayashi, N. Sakai, T. Konakahara, Org. Lett, 2009; 11: 2161-2164.
16. M. Bera, H.-U. Reissig, Synthesis, 2010; 2129–2138.
17. M. K. Bera, M. Domínguez, P. Hommes, H.-U. Reissig, Beilstein J. Org. Chem, 2014; 10: 394–404.
18. Detsi, A.; Majdalani, M.; Kontogiorgis, C.A.; Hadjipavlou-Litina, D.; Kefalas, P. Natural and Synthetic 2-Hydroxy-Chalcones and Aurones: Synthesis, Characterization and Evaluation of the Antioxidant and Soybean Lipoxygenase Inhibitory Activity. Bioorg. Med. Chem, 2009; 17: 8073–8085. [CrossRef]
19. Chebanov, V.A.; Saraev, V.E.; Gura, E.A.; Desenko, S.M.; Musatov, V.I. Some Aspects of Reaction of 6-Aminouracil and 6-Amino-2 Thiouracil with,-Unsaturated Ketones. Collect Czechoslov. Chem. Commun, 2005; 70: 350–360. [CrossRef]
20. El-Gazzar, A.B.A.; Gaafar, A.M.; Aly, A.S. Synthesis of Some New Thiazolo[3,2-a]Pyrido[2,3-d]Pyrimidinones and Isoxazolo[5,4:4,5]Thiazolo [3,2-a]Pyrido[2,3-d]Pyrimidinone. Phosphorus Sulfur. Silicon. Relat. Elem, 2002; 177: 45–58. [CrossRef]
21. Quiroga, J.; Insuasty, B.; Sanchez, A.; Nogueras, M.; Meier, H. Synthesis of Pyrido[2,3-d]Pyrimidines in the Reaction of 6-Amino 2,3-Dihydro-2-Thioxo-4(1H)-Pyrimidinone with Chalcones. J. Heterocycl. Chem, 1992; 29: 1045–1048.
22. A. S. Karpov, T. J. J. Mller, Synthesis, 2003; 2815–2826.
23. S. Tyagarajan, P. K. Chakravarty, Tetrahedron Lett, 2005; 46: 7889 7891.
24. P. S. Baran, R. A. Shenvi, S. A. Nguyen, Heterocycles, 2006; 70: 581 586.

25. F. Xie, H. Zhao, L. Zhao, L. Lou, Y. Hu, Bioorg. Med. Chem. Lett, 2009; 19: 275–278.
26. Suzuki coupling N. Deibl, K. Ament, R. Kempe, J. Am. Chem. Soc, 2015; 137: 12804–12807.
27. Hempers Li ZH, Liu XQ, Geng PF, Suo FZ, Ma JL, Yu B, Zhao TQ, Zhou ZQ, Huang CX, Zheng YC, Liu HM Discovery of [1, 2, 3] Triazolo [4, 5-d] pyrimidine derivatives as novel LSD1 inhibitors. ACS Med Chem Lett, 2017; 8(4): 384–389 https://doi.org/10.1021/acsmedchemlett.6b00423
28. Kumar AA, Bodke YD, Lakra PS, Sambasivam G, Bhat KG Design, synthesis and anti-cancer evaluation of a novel series of pyrazolo [1, 5-a] pyrimidine substituted diamide derivatives. Med Chem Res, 2017; 26(4): 714–744 https://doi.org/10.1007/s00044-016-1770-0
29. Ganzevoort W, Rep A, Bonsel G.J, De Vries JI and Wolf H; Hypertension, 2004; 22: 1235–1242.
30. Mery Press B, James Mc Nally J, Joan Keisher A, Steve Offord J, Laurence Katz B, Robert Falotico and Alfonso Tobaia J; Eur. J. Med Chem, 1989; 24: 627.
31. Ronald Russell K, Jeffery Press B, Richard Rampulla A, James Mcnally J, Robert Falotico, Joan Keiser A, David Bright A and Alfonso Tobia; J. Med. Chem, 1988; 31: 1786.
32. A. Jose, M. Sankarganesh, J. Dhaveethu Raja, S. Sukkur Saleem., Pyrimi- dine derivative Schiff base ligand stabilized copper and nickel nanoparticles by two step phase transfer method; in vitro anticancer, antioxidant, anti- microbial and DNA interactions, J. Fluoresc, 2020; 30: 471–482, doi: 10.1007/ s10895-020- 02510- 5.
33. S. Irie, K. Hirai, K. Kano, S. Yanabe, M. Migita, Efficacy and safety of intra- venous thiamylal in pediatric procedural sedation for magnetic resonance imaging, Brain. Dev, 2020; 42: 477–483, doi: 10.1016/j.braindev.2020.04.005.
34. Kurt Zuhal Kilic, et al., Synthesis and anticancer activity of some pyrimidine derivatives with aryl urea moieties as apoptosis-inducing agents, Bioorg. Chem, 2020; 101: 104028, https://doi.org/10.1016/j.bioorg.2020.104028.
35. T. Huang, et al., Synthesis and anticancer activity evaluation of novel oxacalix[2]arene[2]pyrimidine derivatives, Med. Chem. Res, 2019; 28: 580–590.
36. D. Kang, et al., Identification of dihydrofuro[3,4-d]pyrimidine derivatives as novel HIV-1 non-nucleoside reverse transcriptase inhibitors with promising antiviral activities and desirable physicochemical properties, J. Med. Chem, 2019; 62(3): 1484–1501, https://doi.org/10.1021/acs.jmedchem.8b01656.
37. N.M. Goudgaon, et al., Activity of acyclic 6-(phenylselenenyl)pyrimidine nucleosides against human immunodeficiency viruses in primary lymphocytes, J. Med. Chem, 1991; 34: 3305–3309, https://doi.org/10.1021/jm00115a022.
38. Bai-Chuan Pan, et al., Synthesis and anti-HIV-1 activities of 6-arylthio and 6-arylselenoacyclonucleosides, J. Heterocycl. Chem, 1994; 177–185, https://doi.org/10.1002/jhet.5570310130.
39. G.M. Timmis, Antagonists of purine and pyrimidine metabolites and of folic acid, Adv. Cancer Res, 1961; 6: 369–401, doi: 10.1016/s0065-230x(08)60624-7 .
40. Beata Tylinska, et al., Novel pyrimidine derivatives as potential anticancer agents: synthesis, biological evaluation and molecular docking study, Int. J. Mol. Sci, 2021; 22(8): 3825, https://doi.org/10.3390/ijms22083825.