ISSN No:-2456-2165

Comprehensive Investigation of Pyrimidine Synthesis, Reactions, and Biological Activity

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Abstract:- Researchers have devoted much attention to the study of the chemistry of pyrimidines due to their broad range of pharmaceutical activities. The important role of pyrimidines in the field of drugs is derived from the fact that they are present in genetic material of cells. In this review, we discuss various synthetic methods for pyrimidine derivatives, as well as their various categories of reactions and biological activities as illustrated by research conducted in recent years.

Keywords:- *Pyrimidine; Pharmaceutical Activities; Drugs.*

I. INTRODUCTION

Pyrimidines **1** (**Figure 1**) are a class of heterocyclic ring compounds characterized by a six-membered structure. These compounds possess two nitrogen atoms located at 1 and 3 positions within the ring. The nomenclature "pyrimidine" was first introduced by Pinner in 1884, who derived it from the amalgamation of the term's "pyridine" and "amidine" due to the structural resemblance shared with both molecules [1].

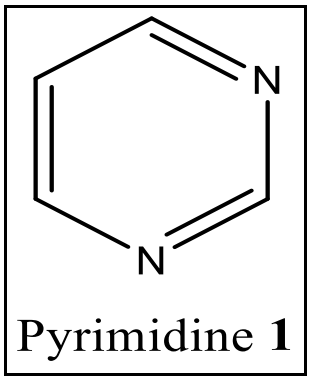

Fig 1 Pyrimidine

Pyrimidines are a fascinating class of heterocyclic compounds with varying pharmaceutical activity because they represent an important class of natural and synthetic products, many of which exhibit beneficial biological activities depending on the nature and position of their substituents [2,3]. The pyrimidine nucleus occurs frequently in numerous naturally occurring compounds. **Figure 2** identifies Uracil **2**, Cytosine **3**, and Thymine **4** as the pyrimidine bases of RNA, and DNA. Cytosine is found in both RNA, and DNA, while uracil and thymine are exclusive to RNA, and DNA, respectively [4].

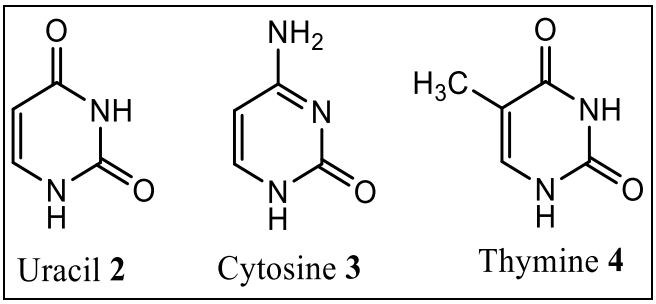

Fig 2 Pyrimidine bases of RNA, and DNA

Also present in the purine bases of RNA and DNA, Adenine **5** and Guanine **6**, is the pyrimidine nucleus (**Figure 3**). **Figure 4** shows the pyrimidine skeleton is present in vitamins such as Thiamine **7** (vitamin B1) and Riboflavin **8** (vitamin B2) [5]. Both coffee beans and tea leaves contain approximately 1.5% caffeine **9** and trace amounts of theophylline **10** [6]. In the cocoa bean pods, Theobromine **11** makes up roughly 1.3%. (**Figure 5)**.

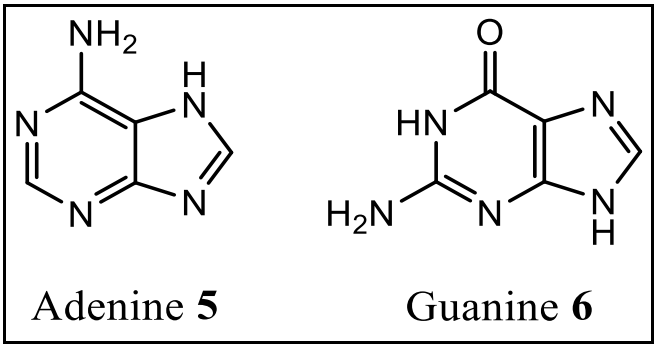

Fig 3 Purine bases Constitute RNA and DNA

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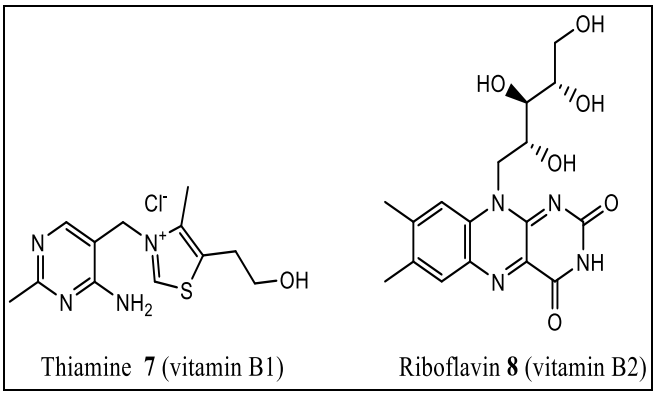


Fig 4 The Presence of the Pyrimidine Skeleton in Vitamins is a Notable Phenomenon.

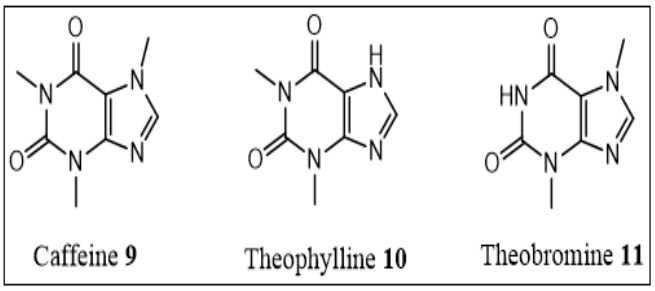
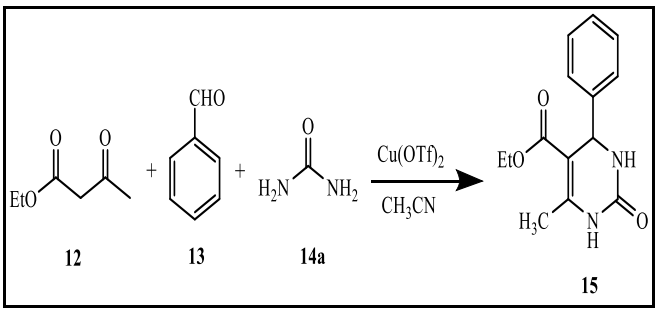


Fig 5 The Chemical Structure of Caffeine, Theophylline, and Theobromine

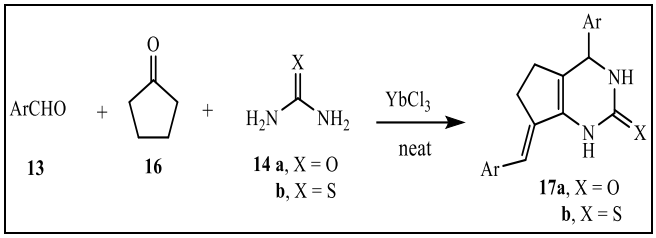
II. SYNTHESIS OF PYRIMIDINE DERIVATIVES

Several methods to produce pyrimidine derivatives have been documented. Biginelli's reaction is the most employed method for synthesizing pyrimidine derivatives, as indicated by its widespread usage [7]. This reaction is illustrated in **Schemes 1-5**. The reaction involving the condensation of ethyl acetoacetate **12**, benzaldehyde **13**, and urea **14** in the presence of copper (II) triflate [$Cu(OTf)_2$] in acetonitrile led to the synthesis of 3,4-dihydropyrimidin-2(1H)-one derivatives **15** with a significant yield (**Scheme 1**).



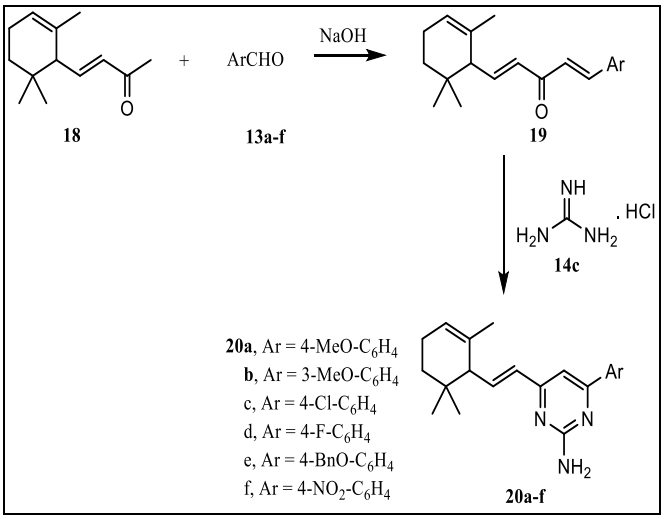
Scheme 1: Synthesis of 3,4-Dihydropyrimidin-2(1H)-One Derivatives 15

A series of arylidene dihydropyrimidinones and thiones **17a,b** were effectively produced using the condensation reaction of aromatic aldehydes **13** with cyclopentanone **16** and urea **14a** or thiourea **14b**, utilizing ytterbium chloride ($YbCl_3$) as a catalyst, under solvent-free conditions [8].



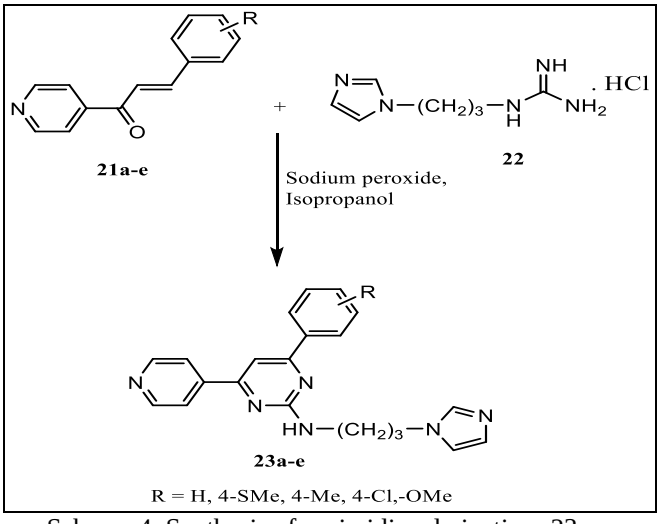
Scheme 2: Synthesis of Arylidene Dihydropyrimidinones and Thiones 17a,b

Condensation of α-ionone with different aldehydes produced chalcones which on reaction with guanidinehydrochloride in the existence of silver oxide afforded the pyrimidine derivatives **20a-f** (**Scheme 3**) [9].



Scheme 3: Synthesis of pyrimidine derivatives 20a-f

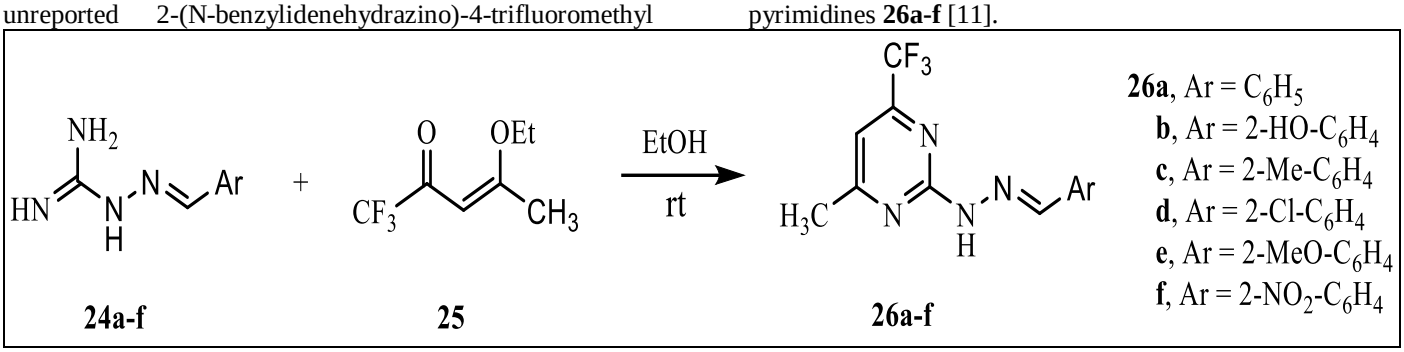
Chalcones **21a-e** were reacted with guanidine derivative **22** in isopropanol and sodium peroxide to produce the pyrimidine derivatives **23a-e** [10].



Scheme 4: Synthesis of pyrimidine derivatives 23a-e

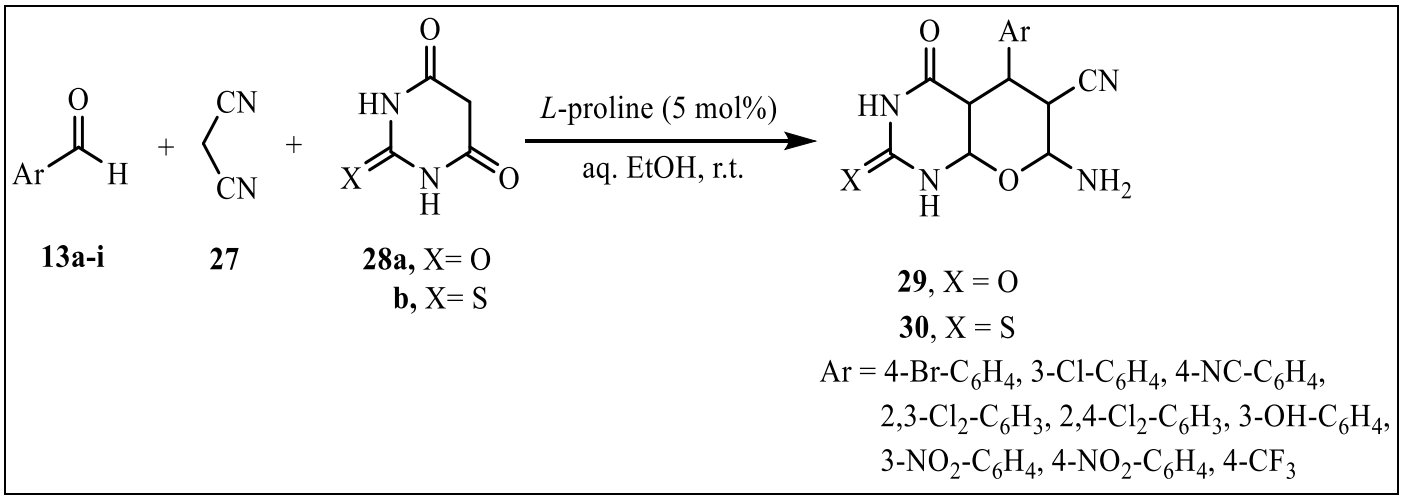
The reaction involving the agitation of N-guanidobenzylimines **24a-f** with enone **25** in ethanol at ambient temperature resulted in the synthesis of previously

unreported 2-(N-benzylidenehydrazino)-4-trifluoromethyl pyrimidines **26a-f** [11].



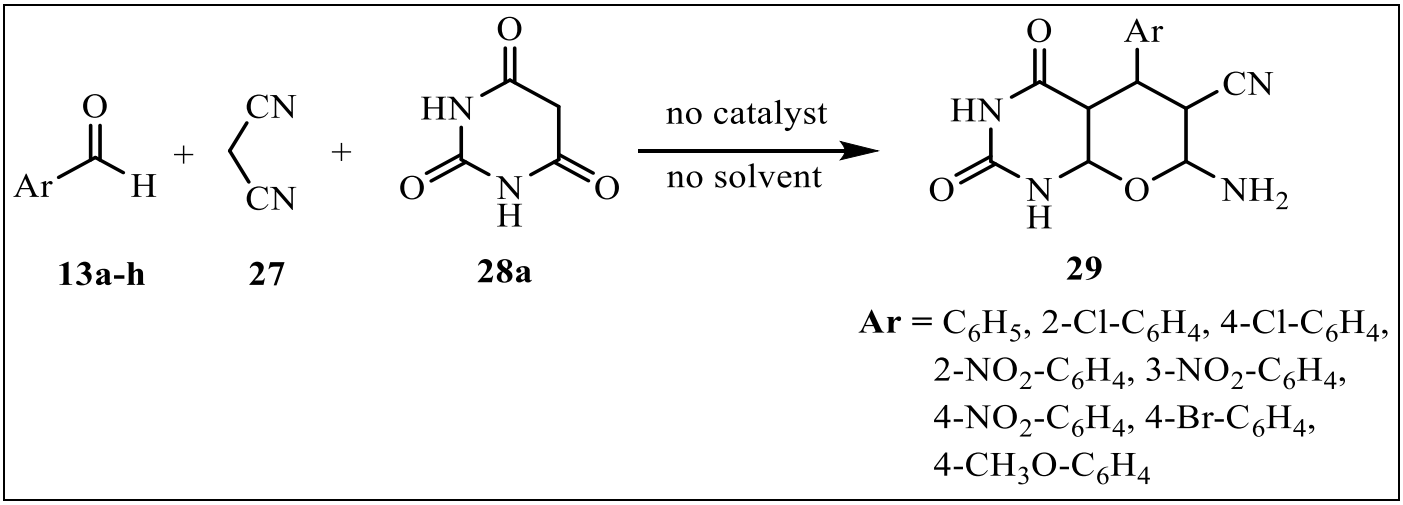
Scheme 5: Synthesis of 2-(N-Benzylidenehydrazino)-4-Trifluoromethylpyrimidines 26a-f

Bararjanian *et al.* [12] have devised a highly effective methodology to produce diverse pyrano[2,3-d]pyrimidinone derivatives **29** and **30** (**Scheme 6**). This involves the condensation of aromatic aldehydes **13a-i**, malononitrile **27a**, and either barbituric **28a** or thiobarbituric acid **28b** in an aqueous ethanol medium, with L-proline serving as the catalyst.



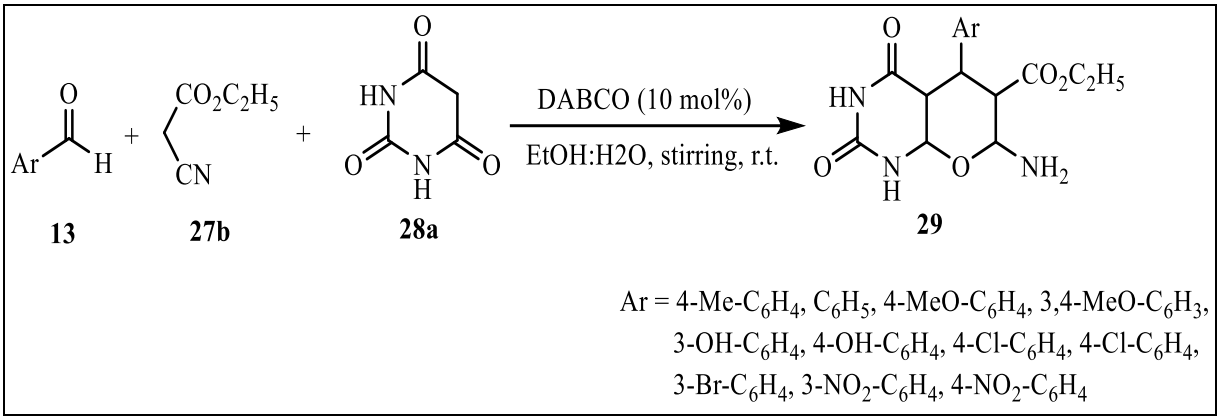
Scheme 6: Synthesis of Pyrano [2,3-d] Pyrimidinone Derivatives 29 and 30

Sara *et al.* [13] described an environmentally friendly technique for producing pyrano[2,3-d].pyrimidine-2,4-(1H,3H)-diones **29** from an aldehyde **13**, malononitrile **27a**, and barbituric acid **28a** mixture without the need of a catalyst or solvent (**Scheme 7**).



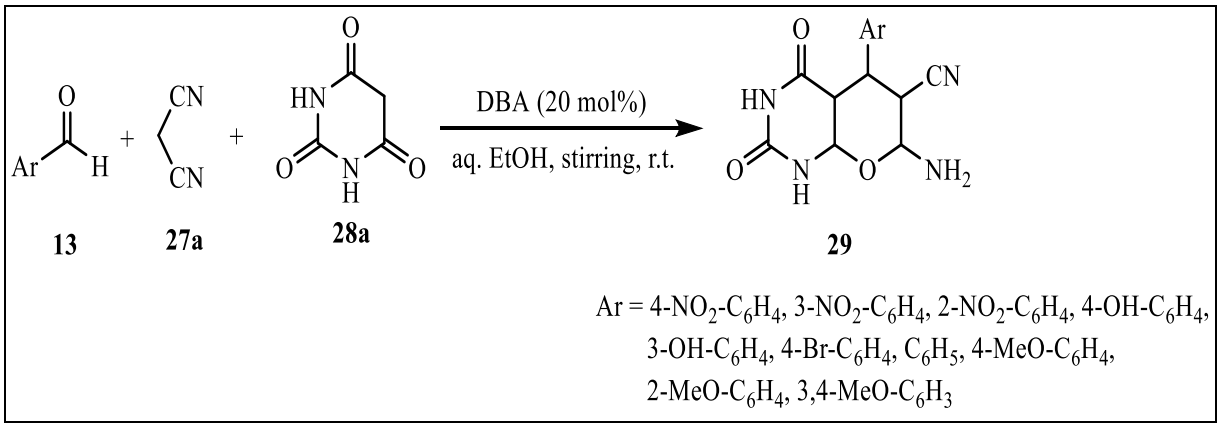
Scheme 7: Synthesis of Pyrano [2,3-d].Pyrimidine-2,4-(1H,3H)-Diones 29

Bhat *et al.* [14] presented a targeted approach for the preparation of pyrano[2,3-d]pyrimidinones **30**. This involved the condensation of different aromatic aldehydes **13a-k**, an active methylene compound, e.g., ethylcyanoacetate **27b**, and barbituric acid **28a** in an aqueous ethanol solution at ambient temperature. The reaction was facilitated by adding 1,4-diazabicyclo[2.2.2]octane (DABCO) as a basic catalyst (**Scheme 8**).



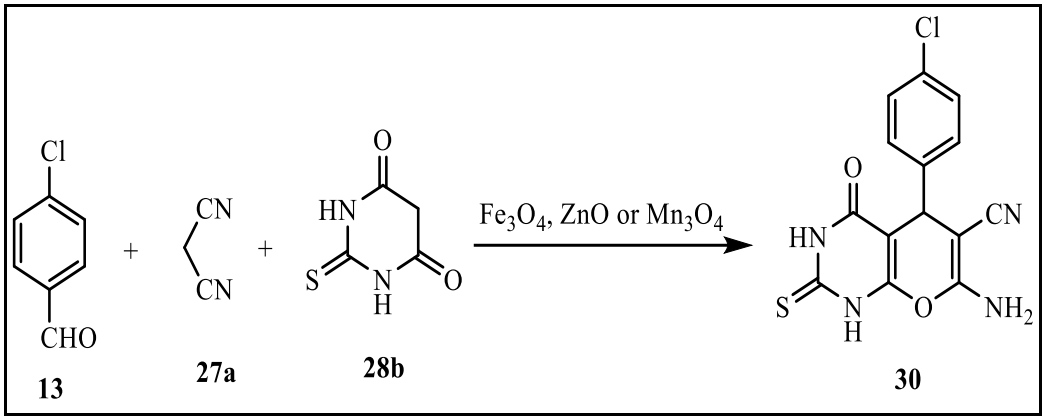
Scheme 8: Synthesis of Pyrano [2,3-d] Pyrimidinones 30

Bhat *et al.* [15] successfully produced annulated pyrano[2,3-d]-pyrimidinone derivatives with high yields. This was achieved through the condensation of aromatic aldehydes, malononitrile, and barbituric acid in an aqueous ethanol solution, with the addition of dibutylamine (DBA) as a catalyst (**Scheme 9**).



Scheme 9: Synthesis of Pyrano[2,3-d]-Pyrimidinone Derivatives with High Yields

AbdEl-Azim *et al.* [16] presented a novel approach for the synthesis of pyrano[2,3-d]pyrimidinones. The method involved the condensation reaction of p-chlorobenzaldehyde, malononitrile, and thiobarbituric acid, utilizing Fe_3O_4, ZnO, or Mn_3O_4 as nanostructure catalysts. The authors noted that their process exhibited high efficiency, cleanliness, and ease of use (**Scheme 10).**



Scheme 10: Synthesis of Pyrano [2,3-d] Pyrimidinones

Ghodsi *et al.* [17] presented a straightforward approach to synthesize tetrahydro[2,3-d]pyrimidine derivatives. This method involved the one-pot condensation of different aromatic aldehydes, malononitrile, and 6-amino uracil under solvent-free conditions at a temperature of 60°C. The reaction was facilitated by the presence of SBA-15-Pr-SO3H, which acted as an active nanoreactor catalyst (**Scheme 11)**.

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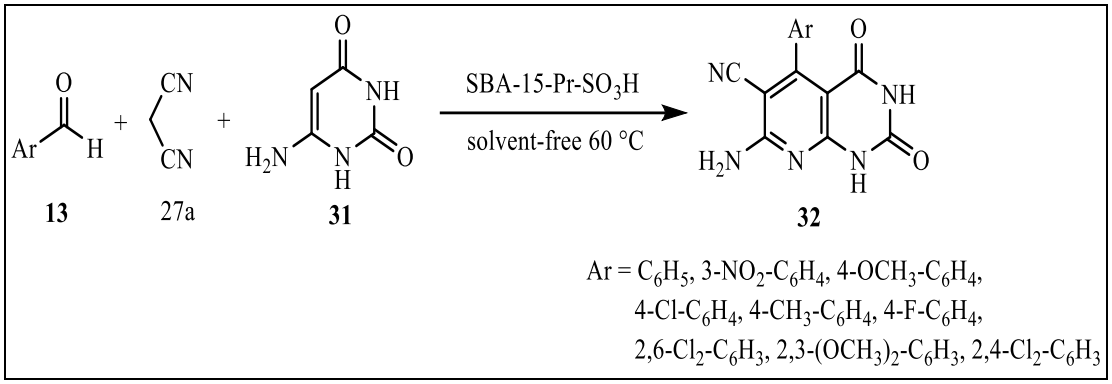
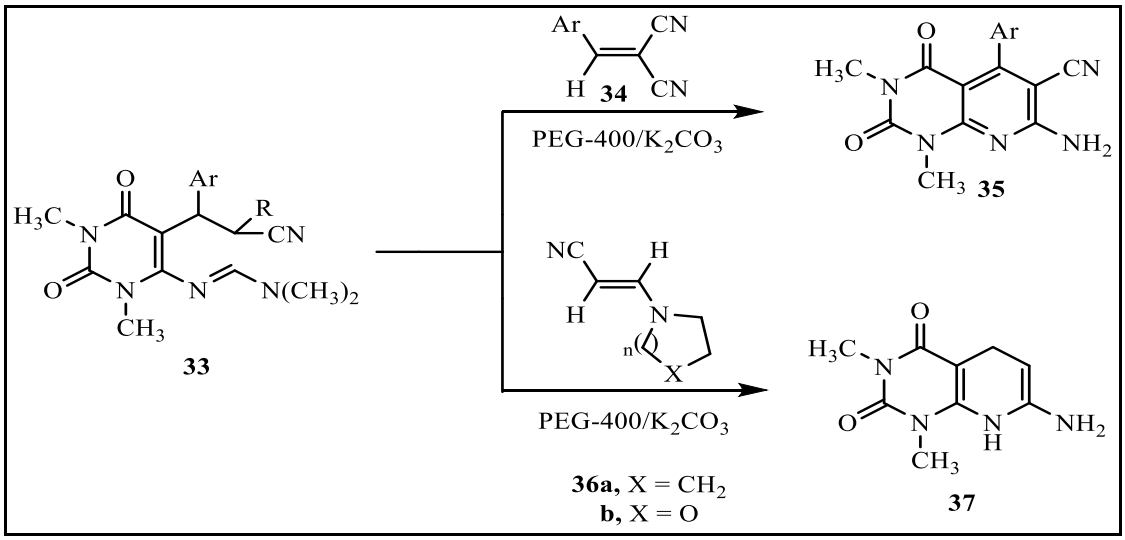


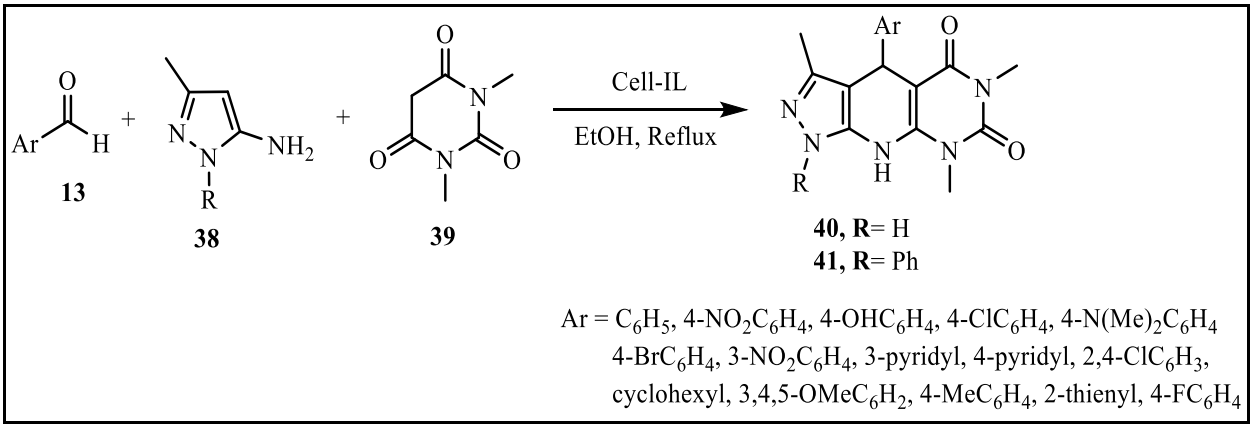
Scheme 11: Synthesis of Tetrahydro [2,3-d] Pyrimidine Derivatives

Rupam *et al.* [18] reported that products derived from the condensation of uracil amidine **33** with polarized alkenes derived from an aromatic aldehyde **34** and an active methylene compound **36** undergo intramolecular cyclization during slow column chromatographic purification to yield pyrido[2,3-d]pyrimidine derivatives **35** and **37** (**Scheme 12**).



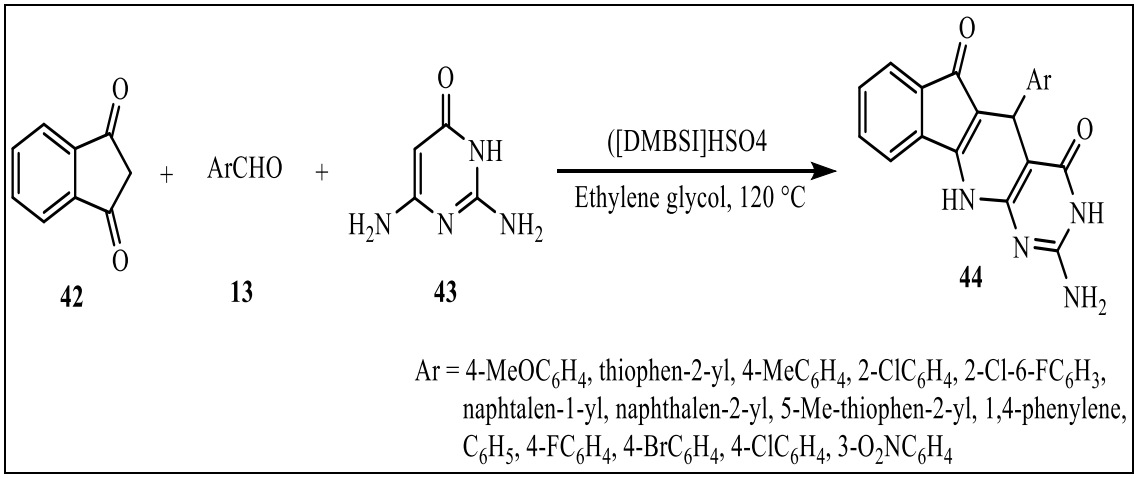
Scheme 12: Synthesis of Pyrido [2,3-d] Pyrimidine Derivatives 35 and 37

Satasia *et al.* [19] documented the synthesis of pyrido[2,3-d]pyrimidine-diones **40** and **41** through the reaction of equimolar quantities of different aldehydes, aminopyrazoles **38**, and 1,3-dimethylbarbituric acid **39**. This reaction was facilitated using cellulose supported ionic liquid (Cell-IL) as a catalyst (**Scheme 13**).



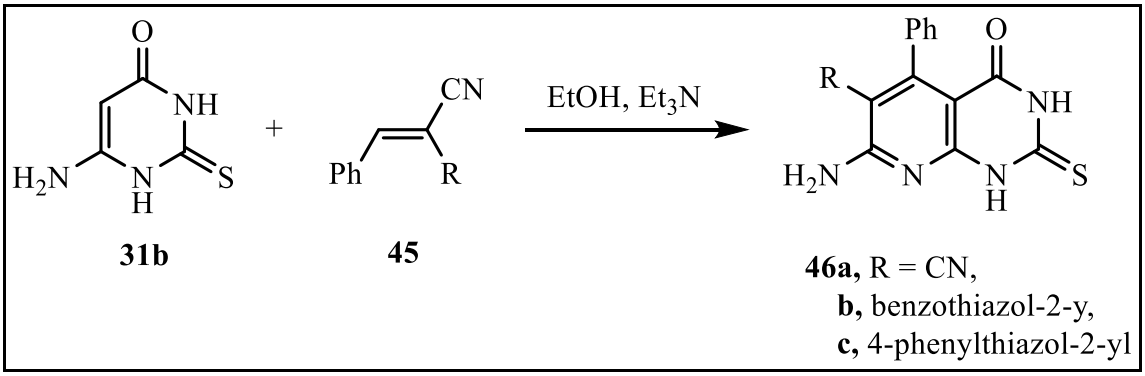
Scheme 13: Synthesis of Pyrido [2,3-d] Pyrimidine-Diones 40 and 41

Mamaghani *et al.* [20] successfully synthesized indeno fused pyrido[2,3-d]pyrimidines through a reaction involving 1,3-indanedione, aromatic aldehydes, and 2,6-diaminopyrimidin-4(3H)-ones. The reaction was facilitated by the use of 1,2-dimethyl-N-butanesulphonic acid imidazolium hydrogen sulphate ([DMBSI]HSO_4) as an effective catalyst in the form of an ionic liquid. This reaction scheme (**Scheme 14**).



Scheme 14: Synthesis of indeno fused pyrido[2,3-d]pyrimidines

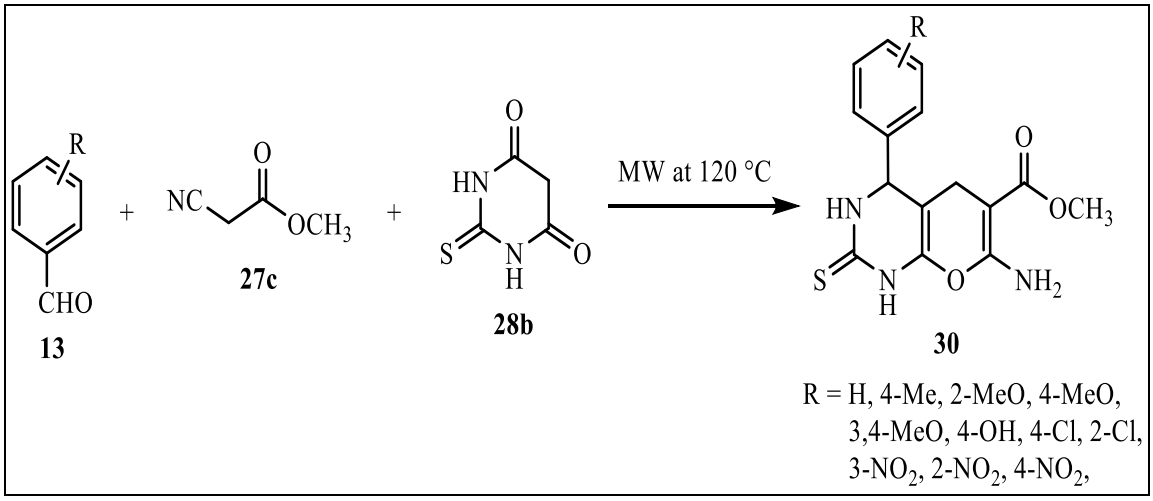
The synthesis of pyrido[2,3-d]pyrimidines was reported by Abdel-Aziem *et al.* [21]. This was achieved by subjecting a mixture of 6-amino-2-thioxo-2,3-dihydro-1H-pyrimidin-4-one and the appropriate 2-benzylidenemalononitrile, 2-(benzo[d]thiazol-2-yl)3-phenylacrylonitrile, and 3-phenyl-2-(4-phenylthiazol-2-yl) acrylonitrile to reflux in absolute ethanol containing triethylamine. This reaction was carried out according to **Scheme 15**.



Scheme 15: Synthesis of pyrido[2,3-d]pyrimidines

➢ *Microwave-Assisted Synthesis of Pyrimidines:*

Bhat *et al.* [22] have documented a method that demonstrates both efficiency and simplicity in synthesizing pyrano[2,3-d]pyrimidinone derivatives. This approach involves the condensation of different aromatic aldehydes, methylcyanoacetate, and thiobarbituric acid in water, which serves as an environmentally friendly solvent. The reaction is facilitated by microwave irradiation at 250 W at 120°C (**Scheme 16**). In a study conducted by Shahrazad et al. [23], a collection of pyrido[2,3-d]pyrimidine derivatives was synthesized by a one-pot three-component reaction involving aromatic aldehydes, malononitrile, and 6-amino uracil. The reaction was facilitated by microwave irradiation, (**Scheme 17**).



Scheme 16: Synthesis of pyrido[2,3-d]pyrimidines derivatives

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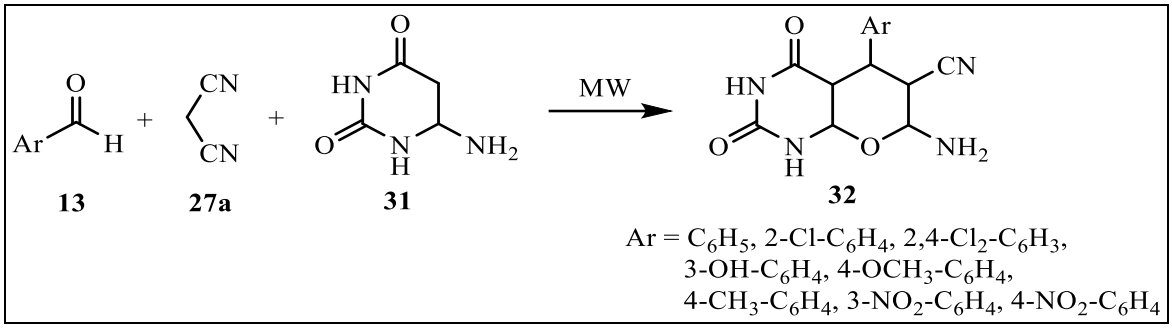
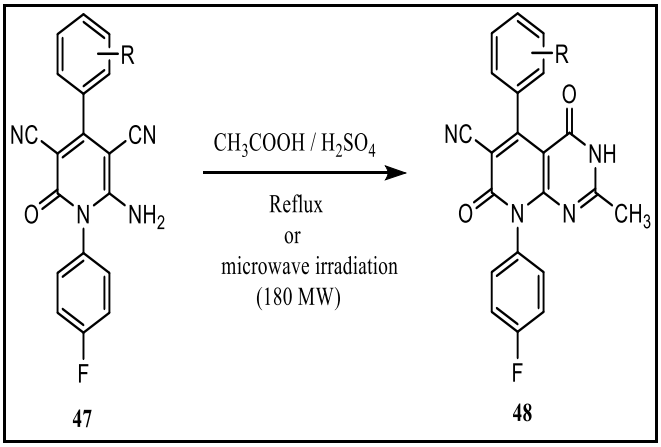


Scheme 17: Synthesis of pyrido[2,3-d]pyrimidine derivatives

Kamlesh *et al.* [24] documented the synthesis of a novel collection of pyrido[2,3-d]pyrimidine derivatives through the process of acidic catalytic cyclization. This was achieved by subjecting 6-amino-1-(4-fuorophenyl)-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbo-nitriles to both conventional heating and microwave irradiation (**Scheme 18**). The substrates were acquired with optimal reaction times and maximized yields using microwave conditions.



Scheme 18: Synthesis of a novel collection of pyrido[2,3-d]pyrimidine derivatives

➢ *Reactions of Pyrimidines:*

This section provides a summary of the various reactions that the pyrimidine ring experiences [25].

➢ *Electrophilic Attack:*

Electrophilic substitution typically takes place in the C-5 position of the pyrimidine ring, which is considered the least electron-deficient site. In order for the reaction to be successful, it is vital to have at least one electron-donating group present.

➢ *Nitration:*

Under somewhat favorable conditions, a minimum of two electron-donating groups is generally required for the process of 5-nitration of a pyrimidine. To illustrate, the synthesis of 6-methyl-5-nitropyrimidine-2,4(1H,3H)-dione **49** necessitates the utilization of nitric acid/sulfuric acid treatment on 6-methylpyrimidine-2,4(1H,3H)-dione at a temperature below 10 °C (**Figure 6**).

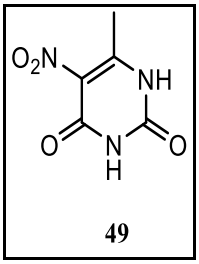


Fig 6 The production of 6-methyl-5-nitropyrimidine-2,4(1H,3H)-dione 49

➢ *Nitrosation:*

Due to its limited stability under harsh conditions, the utilization of nitrous acid is not feasible. Consequently, the nitrosation of pyrimidine substrates necessitates the presence of a minimum of two, and preferably three, electron-donating groups to facilitate the reaction. One possible synthesis route for 5-nitrosopyrimidine-4,6-diamine **50** involves subjecting the corresponding substrate to heated aqueous acid and sodium nitrite. When position C-5 is occupied, it is occasionally feasible to induce 4/6-nitrosation under comparable conditions, as observed in the preparation of 5-hydroxy-6-nitrosopyrimidine-2,4(1H,3H)-dione **51** (**Figure 7**).

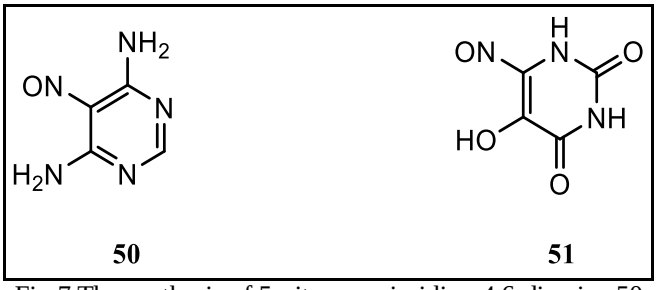


Fig 7 The synthesis of 5-nitrosopyrimidine-4,6-diamine 50 and 5-hydroxy-6-nitrosopyrimidine-2,4(1H,3H)-dione 51.

➢ *Diazo Coupling:*

Under mild circumstances, pyrimidine substrates can be combined with diazotized amines to yield 5-arylazopyrimidine derivatives, exemplified by the synthesis of 6-chloro-5-phenylazopyrimidine-2,4-diamine **52**. Pyrimidines possessing a filled C-5 position and a minimum of two additional electron-donating groups have the capability to conduct 4/6-coupling reactions. As a result of this coupling, a compound known as 5-hydroxy-6-p-sulfophenylazopyrimidine-2,4(1H,3H)-dione **53** is formed (**Figure 8**).

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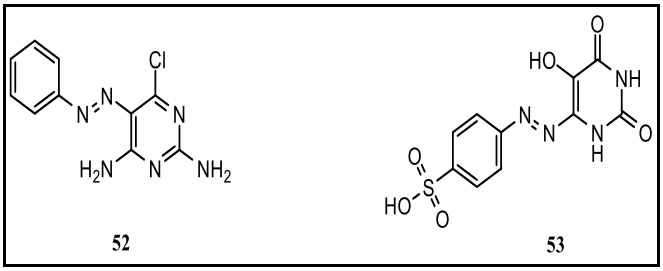

Fig 8 The synthesis of 5-hydroxy-6-p-sulfophenylazopyrimidine-2,4(1H,3H)-dione.

➢ *Halogenation:*

Under certain conditions, pyrimidines without any substitutions can undergo 5-bromination. However, the halogenation of pyrimidines with methyl substitutions at the 2- or 4- positions is less effective due to the higher reactivity of the methyl group compared to the C-5 position. The process of 5-halogenation of pyrimidines, which involves the introduction of halogen atoms at the fifth position, can be readily achieved when pyrimidines include one or more highly electron-donating groups. This can be accomplished using several methods, such as employing elemental halogen in a solvent such aqueous acetic acid, utilizing N-halogenosuccinimide in a suitable solvent, or occasionally employing sulfuryl or thionyl chloride. The pyrimidine-2,4(1H,3H)-dione **54** underwent bromination using aqueous bromine, resulting in forming the 5-bromo derivative **55**. Subsequent addition of hypobromous acid to compound **55** led to the synthesis of 5,5-dibromo-6-hydroxy-5,6-dihydropyrimidine-2,4(1H,3H)-dione **56** (**Figure 9**). Despite its relative stability, the compound underwent a reversion to the monobromo derivative **55** when subjected to extended boiling in a weak acid solution.

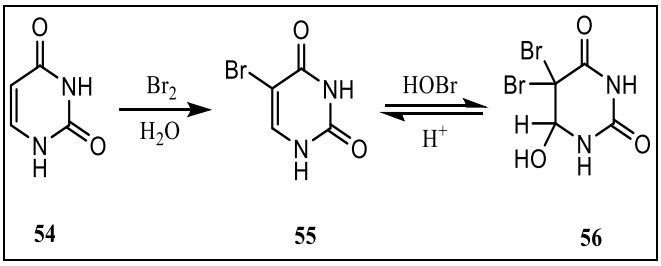

Fig 9 The synthesis of pyrimidine-2,4(1H,3H)-dione 54 and 5,5-dibromo-6-hydroxy-5,6-dihydropyrimidine-2,4(1H,3H)-dione 56

➢ *Sulfonation:*

Pyrimidines that possess at least one electron-donating group have the capability to undergo 5-sulfonation through the utilization of fuming sulfuric acid. Nevertheless, it is more advantageous to employ chlorosulfonic acid for the synthesis of a 5-chlorosulfonyl derivative rather than undergoing the conversion into a sulfonic acid. The process of heating 2-pyrimidinamine under reflux conditions with an excessive quantity of chlorosulfonic acid for a duration of 8 hours resulted in the production of 2-aminopyrimidine-5-sulfonyl chloride **57**. Subsequently, upon treatment with ice, compound **57** was converted to 2-aminopyrimidine-5-sulfonic acid **58** (**Figure 10**).

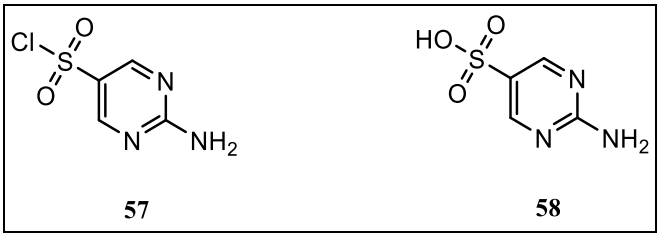

Fig 10 The preparation of 2-aminopyrimidine-5-sulfonyl chloride 57 and 2-aminopyrimidine-5-sulfonic acid 58

➢ *Nucleophilic Attack:*

- *Amination:*

The process of direct amination of the pyrimidine ring is infrequent. However, when 4-methylpyrimidine was subjected to reaction with sodium amide in decalin at a temperature of 150 °C, it resulted in the production of 4-methylpyrimidin-2-amine **59**, 6-methylpyrimidine-2,4-diamine **60**, as well as several additional products. The process of indirect amination, involving the nucleophilic addition of an amine followed by oxidation, is a well-known method. As an illustration, the compound 2-(t-butyl)pyrimidine was subjected to a reaction with sodium amide in liquid ammonia at a temperature of -33 °C. This reaction resulted in the rise of 2-(t-butyl)-3,4-dihydropyrimidin-4-amine **61**. Subsequent oxidation of compound **61** using permanganate led to the formation of 2-(t-butyl)pyrimidin-4-amine **62** (**Figure 11**).

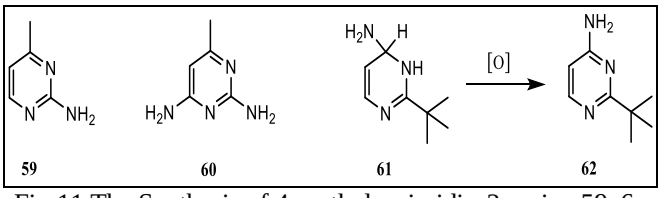

Fig 11 The Synthesis of 4-methylpyrimidin-2-amine 59, 6-methylpyrimidine-2,4-diamine 60, and 2-(t-butyl)pyrimidin-4-amine 62

➢ *C-Alkylation or Arylation*

The pyrimidine molecule has the ability to undergo an indirect process of C-alkylation/arylation. This process involves the nucleophilic addition of phenylmagnesium bromide, which acts as a Grignard reagent. The resulting product is an adduct, referred to as compound **63**. Subsequently, the removal of magnesium through hydrolysis leads to the production of 4-phenyl-3,4-dihydropyrimidine, known as compound **64**. Finally, compound **64** can be oxidized to yield 4-phenylpyrimidine, which is referred to as compound **65** (**Figure 12**).

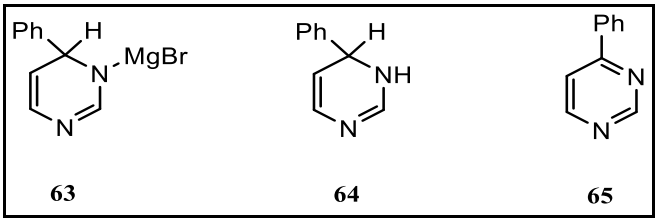

Fig 12 The Synthesis of 4-phenyl-3,4-dihydropyrimidine, and 4-phenylpyrimidine

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➢ *Oxidative Reactions:*

The compound 4,6-dimethylpyrimidin-2(1H)-one **66** was subjected to a reaction with cold alkaline persulfate, resulting in the production of the sulfate ester **67**. Subsequently, this ester was hydrolyzed in warm hydrochloric acid, leading to the preparation of 5-hydroxy-4,6-dimethylpyrimidin-2(1H)-one **68** (**Figure 13**).

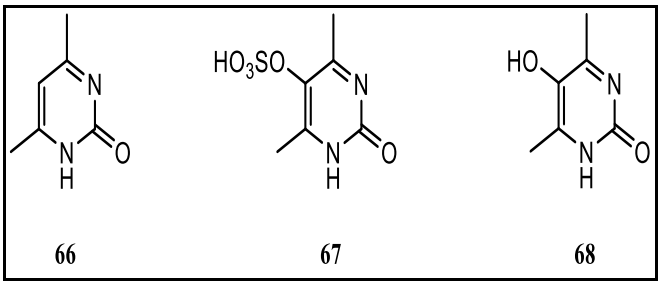

Fig 13 The Synthesis of 5-hydroxy-4,6-dimethylpyrimidin-2(1H)-one 68.

It is possible to elevate the oxidation state in some pyrimidines. For example, 5-hydroxypyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (dialuric acid) **69** was oxidized to pyrimidine-2,4,5,6(1*H*,3*H*)-tetraone (alloxan) **70**, probably *via* alloxantin **71** (**Figure 14**).

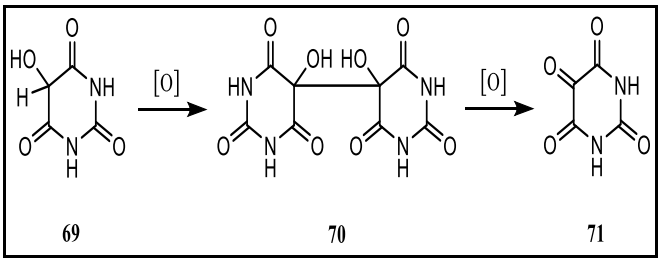

Fig 14 The oxidation of dialuric acid 69 to alloxan 70 and alloxantin 71

➢ *Pharmaceutical Activities of Pyrimidines:*

Polyfunctionalized heterocyclic compounds play a crucial role in the context of drug discovery and development. A diverse array of bioactivities is exhibited by numerous fused pyrimidine systems.

➢ *Anti-Inflammatory Activity:*

Abd El-Salam *et al*. [26] successfully synthesized a series of pyrazolo [3,4-d] pyrimidine derivatives (**Figure 15)**. These derivatives exhibited superior anti-inflammatory properties when compared to the reference drug Diclophenac®, while also demonstrating a high level of selectivity against COX-2.

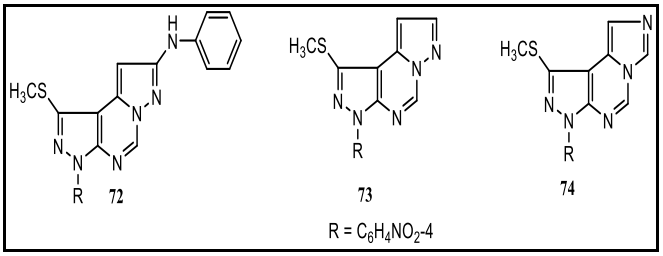

Fig 15 Pyrazolo [3,4-*d*] pyrimidine derivatives

Kota *et al*. [27] conducted the synthesis of a collection of innovative pyrazolo [3,4-d] pyrimidine derivatives **75** (**Figure 16**) and subsequently subjected them to screening for their potential anti-inflammatory properties. Compounds containing electron withdrawing substituents, such as chlorine and fluorine, show significant anti-inflammatory effect when compared to the standard medication indomethacin.

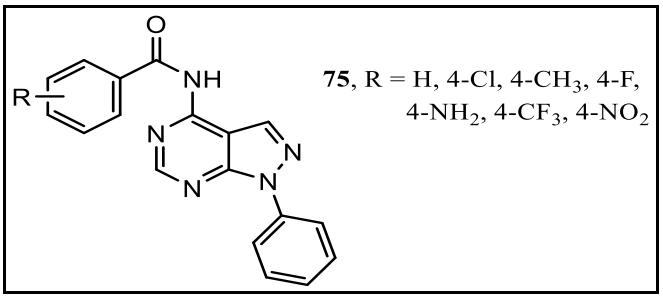

Fig 16 Pyrazolo [3,4-*d*] pyrimidine derivatives 75.

The compound known as afloqualone **76** [28] exhibited effective anti-inflammatory properties in the care of individuals suffering from lower back pain. Epirazole **77** is classified as a selective cyclooxygenase-2 (COX-2) inhibitor, belonging to the class of nonsteroidal anti-inflammatory drugs (NSAIDs) [29]. Proquazone **78** is recognized for its efficacy as a nonsteroidal anti-inflammatory drug (NSAID) (**Figure 17**).

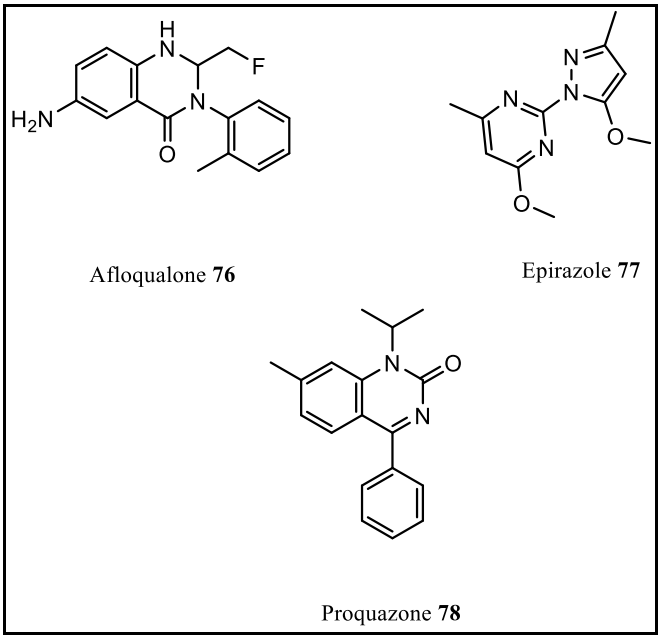

Fig17 Afloqualone, Epirazole and Proquazone Chemical Structure

➢ *Anticancer Activity*

Numerous pyrimidine nucleosides have been synthesized and investigated for their potential as anticancer agents. The use of 5-fluorouracil **79** has been utilized in the treatment of breast cancer and gastrointestinal tract tumors [31, 32]. The compound 5-(phenylthio)acyclouridine **80**, has been found to possess valuable antineoplastic properties [33].

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Also, Raić-Malić *et al.* [34] prepared a series of new pyrimidine derivatives derived from 2,3-*O*,*O*-dibenzyl-6-dideoxy-L-ascorbic acid **81** and 4,5-didehydro-5,6-dideoxy-L-ascorbic acid **82** (**Figure 18**). The recently synthesized compounds showed significant cytostatic effects on murine leukemia (L1210/0), murine mammary carcinoma (FM3A), and human T-lymphocytes (Molt4/C8 and CEM/0) cell lines. 5-Fluorouracil which features a fluoro group substitution at position C-5 of the uracil ring, exhibited notable cytostatic activity, particularly when tested against Molt4/C8 cells.

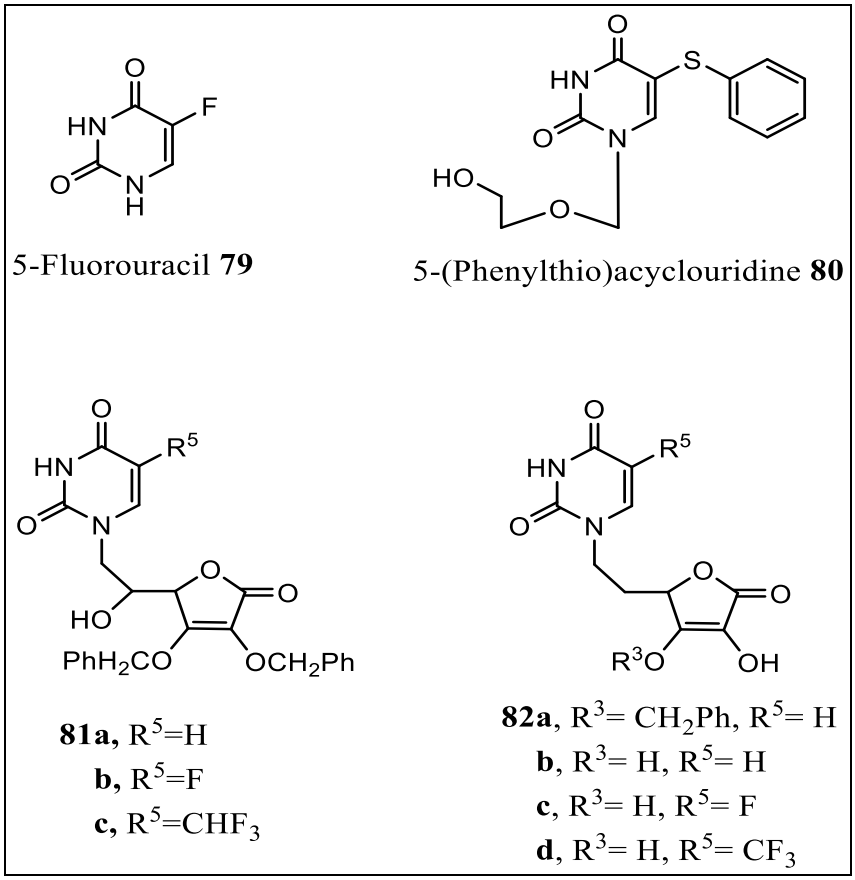


Fig 18 Pyrimidine derivatives of 5-Fluorouracil, 5-(Phenylthio)acyclouridine, 2,3-*O*,*O*-dibenzyl-6-dideoxy-*L*-ascorbic acid and 4,5-didehydro-5,6-dideoxy-*L*-ascorbic acid

Refaat *et al.* [35] conducted the synthesis of multiple series of hexahydrocycloocta [4,5]thieno[2,3-d]pyrimidin-4-ones and hexahydrocyclo-octa[4,5]thieno-[3,2-e]. The compounds (**Figure 19**) are 1,2,4-triazolo [4,3-c]pyrimidine-3(2H)-thiones **83** and 4-substituted hydrazinylhexa-hydrocycloocta [4,5]thieno[2,3-d]pyrimidines **84**. Most of the prepared compounds exhibited *in vitro* antitumor activity against the human colon carcinoma [**HCT 116**] cell line. The following compounds exhibited greater efficacy in inhibiting tumor growth compared to imatinib.

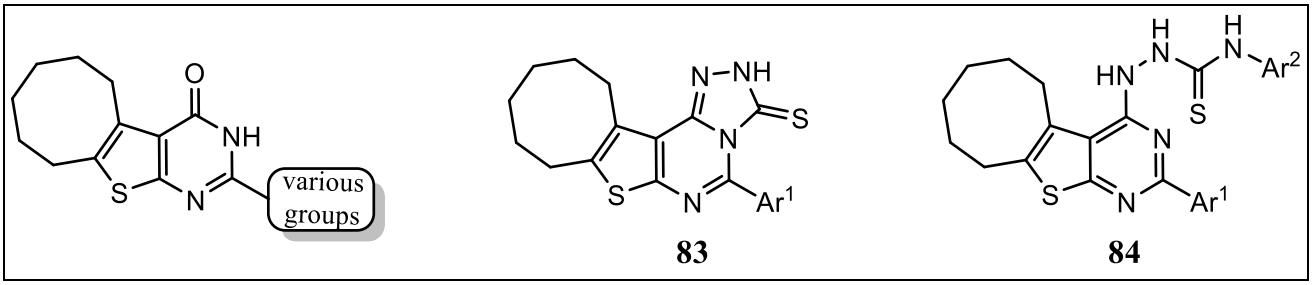


Fig 19 Various Series of Pyrimidine Derivatives

Yousif *et al.* [36] conducted the synthesis of novel pyrimidine and thiazolopyrimidine derivatives **85a-h** as illustrated in **Figure 20**. These derivatives were subsequently evaluated for their potential antitumor activity against hepatocellular carcinoma (**HepG-2**), human prostate adenocarcinoma (**PC-3**), and human colorectal carcinoma (**HCT-116**) cell lines. The assessment of anticancer activity was performed using the 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (**MTT**) assay. The synthesized compounds demonstrated cytotoxic action against **HCT-116** and **PC-3** cell lines, indicating moderate to good levels of activity.

ISSN No:-2456-2165

The preparation of novel 1H,3H-pyrimido[2,1-f]purine-2,4-dione derivatives **86** of arylpiperazine was documented by Jurczyk *et al* [37]. These compounds (**Figure 20**) demonstrated significant binding affinity towards 5-HT1A and α receptors, while exhibiting moderate to low affinity towards 5-HT2A and D2 receptors.

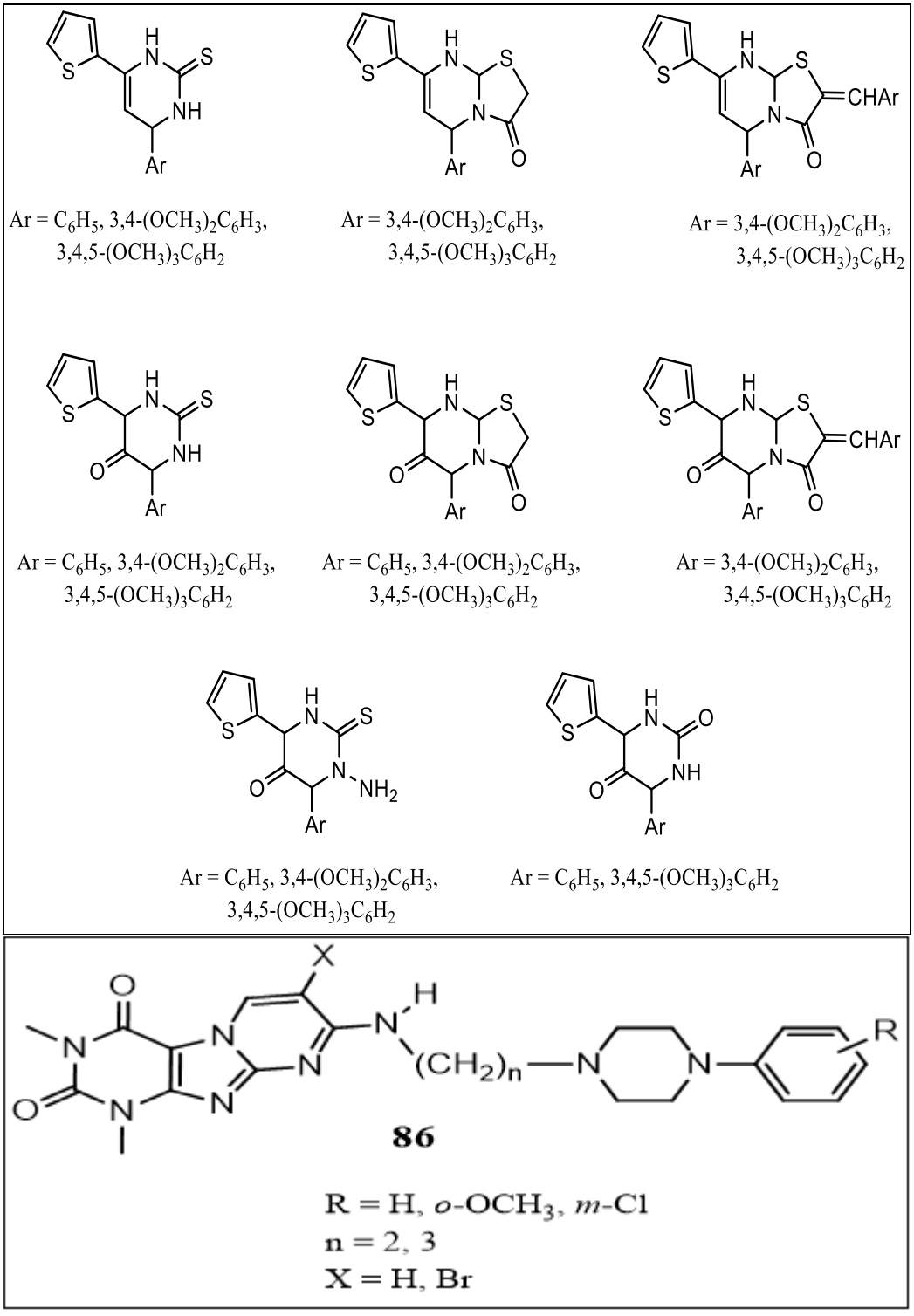


Fig 20 Pyrimidine and Thiazolopyrimidine Derivatives and 1*H*,3*H*-Pyrimido[2,1-f]purine-2,4-Dione Arylpiperazine Derivatives

Matsumoto et al. [38] synthesized some novel 2,8-disubstituted imidazo[1,5-a]pyrimidine derivatives as potential antitumor drugs (**Figure 21**). They were tested for their ability to suppress the growth of the mouse leukemia L1210 and human oral epidermoid KB carcinoma cell lines. These novel compounds include 8-thiocarbamoyl-1,2,3,4-tetrahydroimidazo[1,5-a]pyrimidin-2(1*H*)-thione **88d** and 8-thiocarbamoyl-1,2-dihydroimidazo[1,5-a]pyrimidin-2(1*H*)-thione **88d**.The cytotoxicity of pyrimidin-2(1*H*)-thione **90d** was significant. Compound **88d** was as effective against L1210 and KB cells as 5-fluorouracil. Compound **90d** had the strongest action against L1210, whereas its activity against KB cells was moderate.

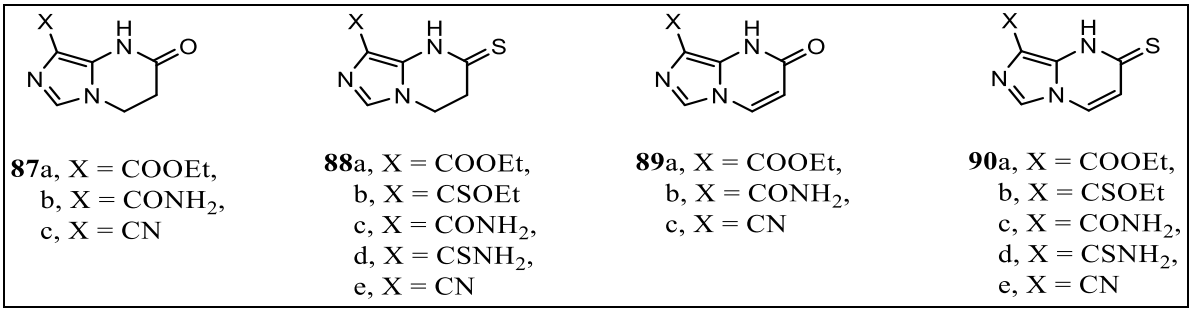


Fig 21 2,8-Disubstituted imidazo[1,5-a]Pyrimidine Derivatives

➢ *Antiviral and anti-HIV Activity:*

Pyrimidine derivatives are antivirals in nature. Many compounds with pyrimidine skeletons have been approved as antiviral medicines. Many compounds containing the pyrimidine moiety have been formally approved for the treatment of human immunodeficiency virus (**HIV**) infections. A combined medicine treatment was discovered to help prevent resistance to any single drug utilized. This was known as extremely active antiretroviral therapy (**HAART**). Zidovudine **91**, zalcitabine **92**, stavudine **93**, lamivudine **94**, and emtricitabine **95** are the most often used pyrimidine-containing HIV infection medications (**Figure 22**) [39].

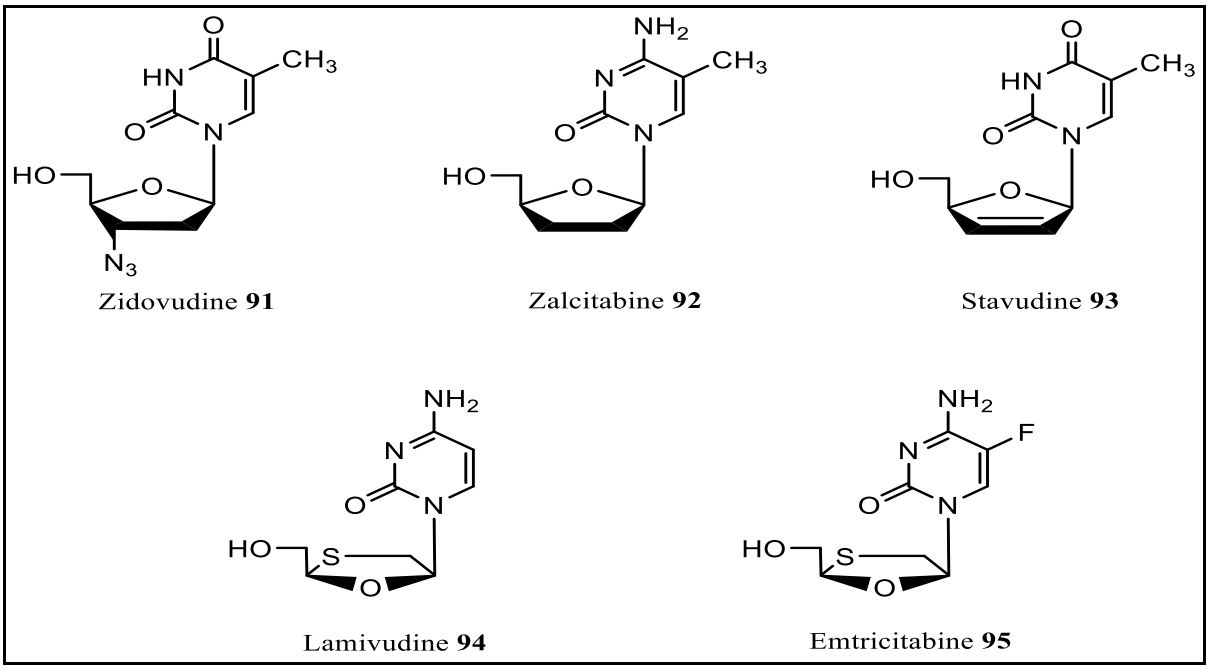


Fig 22 Zidovudine, zalcitabine, stavudine, lamivudine and emtricitabine

Romeo *et al.* [40] developed and evaluated a series of pyrimidine-2,4-diones connected to the isoxazolidine nucleus as potential anti-HIV drugs (**Figure 23**). Compounds **96**, which have an ethereal substituent at position C-3, possess both HIV reverse transcriptase (RT) inhibitory activity and HIV infection inhibiting activity.

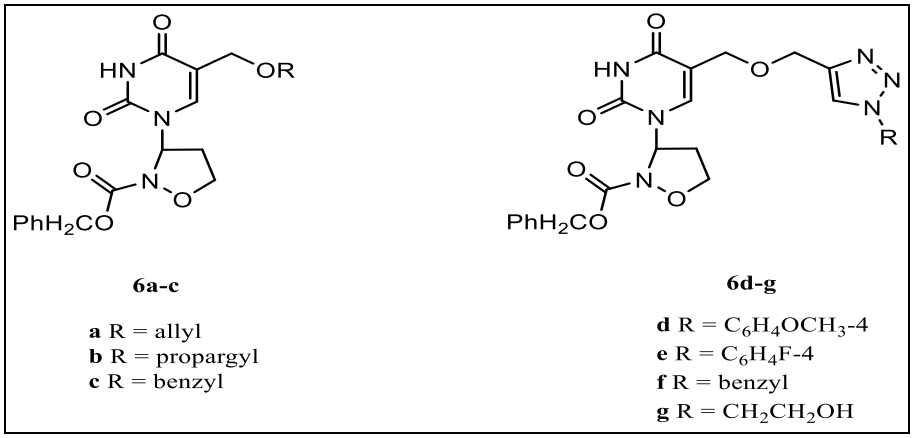


Fig 23 The Linkage of Pyrimidine-2,4-Diones to the Isoxazolidine Nucleus.

The antiviral properties of 3′-azido-3′-deoxythymidine (BW A509U) (zidovudine), (**Figure 22**) have been elucidated by Mitsuya *et al*. [41]. This compound has been shown to block the reverse transcriptase of **HTLV-III/LAV**. The compound **A509U** exhibited minimal or no toxicity even at elevated dosages in experimental models involving rats and dogs. Furthermore, it has been observed that at some doses, it has the ability to effectively impede viral multiplication without causing any significant reduction in several in vitro indicators of T-cell immunological reactivity.

Ultimately, there is a high probability that A509U possesses the capability to be assimilated through oral ingestion, rendering it appropriate for treatment plans that necessitate extended periods of therapy. Collectively, these characteristics are thought to establish a rational foundation for contemplating this medication as a prospective antiviral intervention for individuals afflicted with **HTLV-III/LAV** infection.

Idoxuridine (5-Iodo-2′-deoxyuridine) (**IDU**) and trifluridine (5-trifluoromethyl-2′-deoxyuridine) (**Figure 24**) have been extensively used in the therapeutic management of herpes simplex virus (**HSV**) keratitis. The administration of these substances is typically done topically, either with eye drops or ophthalmic cream [39].

The compound known as Brivudin, chemically referred to as (E)-5-(2-bromovinyl)-2`-deoxyuridine, is an antiviral drug that exhibits selectivity in its activity against the varicella-zoster virus (**VZV**) and herpes simplex virus type 1 (**HSV-1**). This information is depicted in **Figure 24**. Brivudin has obtained licensure for the therapeutic management of herpes zoster in multiple European nations. Cidofovir, chemically known as (S)-1-(3-hydroxy-2-phosphonyl-methoxypropyl)cytosine, is administered to individuals with acquired immunodeficiency syndrome (AIDS) in order to cure cytomegalovirus (CMV) retinitis [39].

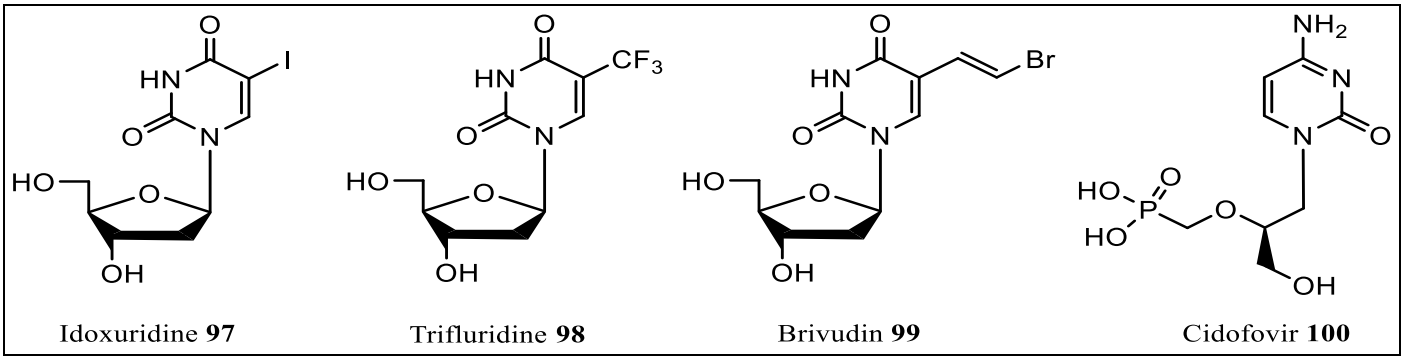


Fig 24 Idoxuridine, Trifluridine, Brivudin, Cidofovir

➢ *Antibacterial and Antifungal Characteristics:*

Siham A. Lahsasni [42] conducted the production of a collection of 1-(3′-chloro-1′,4′-dioxo-1′,4′-dihydronaphthalen-2′-yl-5-substituted-1H-pyrimidine-2,4-diones (**Figure 25**) and investigated their potential as antibacterial agents. The experimental findings indicate that compound **101d**, which includes a fluorine atom, has superior antibacterial activity *in vitro* in comparison to the standard antibiotic gentamicin when tested against *S.* aureus and *B.* subtilis. Compound **101d** had comparable antibacterial efficacy to that of gentamicin when tested against *E.* coli and *P.* aeruginosa.

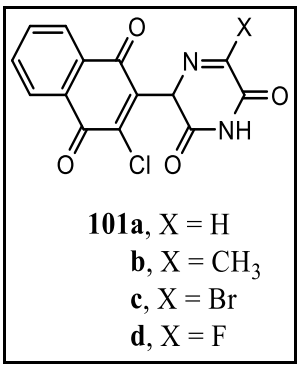


Fig 25 1-(3′-Chloro-1′,4′-Dioxo-1′,4′-Dihydronaphthalen-2′-yl-5-Substituted-1*H*-Pyrimidine-2,4-Diones

Sharma *et al* [43] synthesized and tested many pyrimido[4,5-d]pyrimidine-2,5-diones (**Figure 26**) for antibacterial activity. Antibacterial activity against E. coli, *P.* diminuta, *S.* aureus, and *B.* subtilis was tested in vitro, as was antifungal activity against *A.* niger and *C.* albicans. When compared to the reference antibacterial and antifungal medications utilized (ampicillin trihydrate and clotrimazole, respectively), all the described compounds demonstrated outstanding activity against the tested bacteria and fungi.

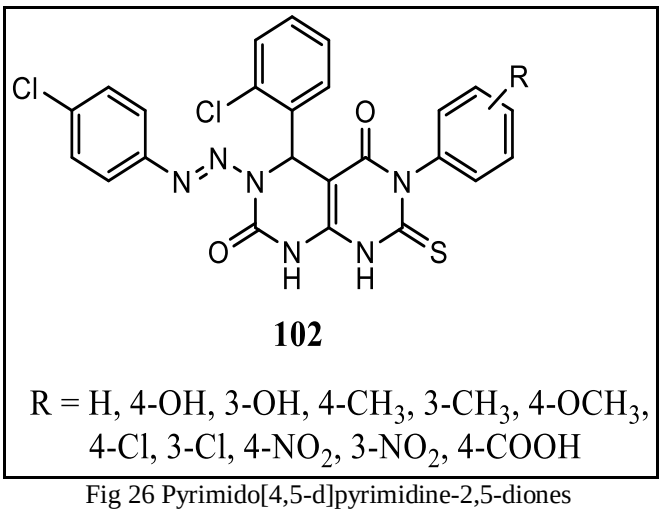
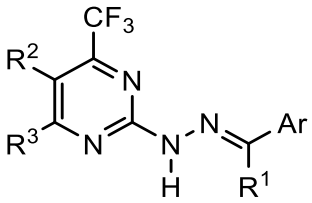


Fig 26 Pyrimido[4,5-d]pyrimidine-2,5-diones

Figure 27 shows the synthesis of a series of 2-(N-benzylidenehydrazino)-4-trifluoromethyl-pyrimidines reported by Zanatta *et al.* [44]. Some of the synthesized chemicals were tested for their ability to inhibit *T.* cruzi cruzain. The studied compounds were active, with 2-(*N*-4-chloro-benzylidenehydrazino)-4-trifluoromethyl-pyrimidine having the highest inhibitory effect (80% at 100 M) and an IC50 value of 85 M.



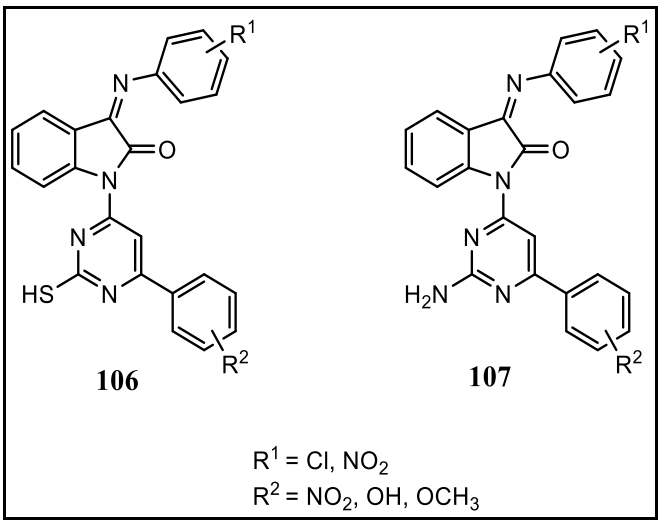
103-105a-i

Compd.	Ar	R^1
103-105a	Ph	H
103-105b	2-Me-Ph	H
103-105c	2-OH-Ph	H
103-105d	2-OMe-Ph	H
103-105e	4-Me-Ph	H
103-105f	4-Cl-Ph	H
103-105g	4-OMe-Ph	H
103-105h	4-NO2-Ph	H
103-105i	Ph	Me

Compd.	R^2	R^3
103	H	H
104	Me	H
105	H	Me

Fig 27 2-(*N´*-Benzylidenehydrazino)-4-Trifluoromethyl-Pyrimidines

Prasenjit Mondal *et al.* [45] synthesized and tested a series of novel mercaptopyrimidine and aminopyrimidine derivatives of indolin-2-one for antimicrobial activity against Gram-positive bacteria *S.* aureus and *B.* subtilis, as well as Gram-negative bacteria *S.* typhi, *S.* dysenteriae, *P.* mirabilis, and E. coli. The compounds were evaluated and shown to have extremely good antibacterial action, comparable to the conventional medication Ampicillin.

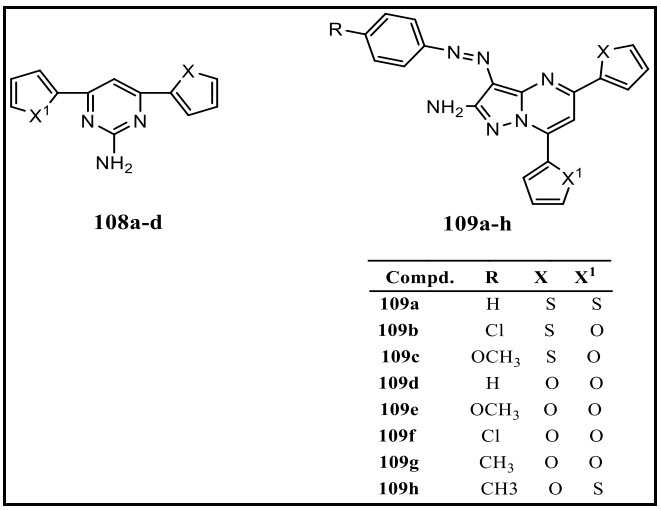


106 **107**

R^1 = Cl, NO_2
R^2 = NO_2, OH, OCH_3

Fig 28 Mercaptopyrimidine and Aminopyrimidine Derivatives of Indolin-2-one

Christina Y. Ishak *et al.* [46] successfully synthesized some pyrimidine and pyrazolo-[1,5-a] pyrimidine derivatives (**Figure 29**) and tested them for antibacterial (against *S.* aureus and *B.* subtilis, *P.* aeruginosa and *E.* coli) and antifungal (against *C.* albicans, *A.* fumigates, *G.* candidum, and *S.* racemosum). All the compounds produced shown promising antibacterial and antifungal properties. The chemical 5,7-di(furan-2-yl)-3-(p-tolydiazenyl)pyrazolo-[1,5-a] pyrimidin-2-amine was discovered to be the most potent against all microbes tested.

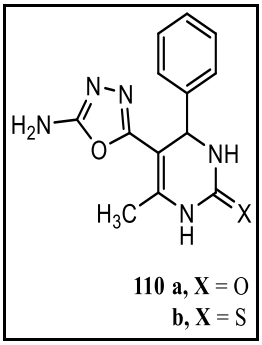


108a-d **109a-h**

Compd.	R	X	X^1
109a	H	S	S
109b	Cl	S	O
109c	OCH_3	S	O
109d	H	O	O
109e	OCH_3	O	O
109f	Cl	O	O
109g	CH_3	O	O
109h	CH3	O	S

Fig 29 Pyrimidine and Pyrazolo-[1,5-a] Pyrimidine Derivatives

Andrews and Mansur [47] developed a series of 1,3,4-oxadiazole-containing pyrimidine derivatives (**Figure 30**). The newly synthesized compounds were tested for antifungal activity against *C.* albicans, *P.* sps, and *A.* niger *in vitro.* Most of the substances examined showed antifungal action, but to a lesser level than the conventional treatment amphotericin-B.



110 a, X = O
b, X = S

Fig 30 Pyrimidine Bearing 1,3,4-Oxadiazole Derivatives.

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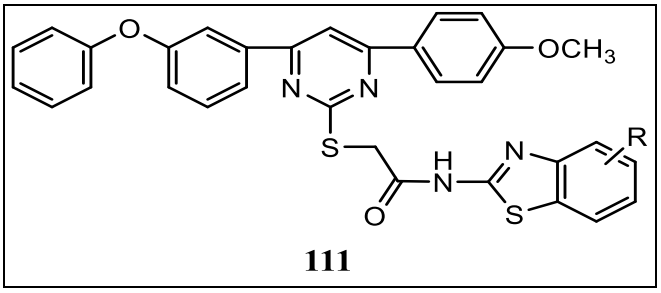
The synthesis and antibacterial activity of several pyrimidine-based benzothiazole derivatives were reported by Gupta *et al.* [48] (**Figure 31**). The synthesized compounds underwent screening to evaluate their antibacterial activity against two Gram-positive bacteria, namely *S.* aureus and *S.* pyogenes, as well as two Gram-negative bacteria, namely *E.* coli and *P.* aeruginosa. The results were compared to those of the conventional medications ampicillin, chloramphenicol, ciprofloxacin, and norfloxacin. The synthesized compounds were subjected to screening for their antifungal activity against *C.* albicans and *A.* niger, in comparison to the conventional medicines' nystatin and griseofulvin. The chemical *N*-(6-methoxybenzo[d]thiazol-2-yl)-2-(4-(4-methoxyphenyl)-6-(3-phenoxy-phenyl) pyramid-in-2-ylthio) acetamide had significant efficacy against both Gram-positive and Gram-negative bacteria. The antifungal screening findings indicated the efficacy of two compounds: 2-(2-(4-(4-methoxyphenyl)-6-(3-phenoxyphenyl)pyrimidin-2-ylthio) acetamido)benzo[d]thiazole-6-sulphonic acid and N-(4,6-dichlorobenzo[d] thiazol-2-yl). The compound -2-(4-(4-methoxyphenyl)-6-(3-phenoxyphenyl)pyrimidin-2-ylthio) acetamide had significant efficacy against Candida albicans. The chemical 2-(4-(4- methoxyphenyl) -6- (3-phenoxyphenyl)-pyrimidin-2-ylthio)-N-(6-nitro-benzo [d] thiazol-2-yl)acetamide had significant efficacy against *A.* niger.



111

Fig 31 Pyrimidine based Benzothiazole Derivatives.

Jat et al [49] developed several novel pyrimidine derivatives **112a-g** (**Figure 32**) and tested them for antibacterial and antifungal activity against E. coli and B. sphaericus, as well as *A.* niger and *P.* funiculosum. According to the screening results, some of the synthesized compounds had high antibacterial and antifungal activity in comparison to ciprofloxacin and ketoconazole, respectively.

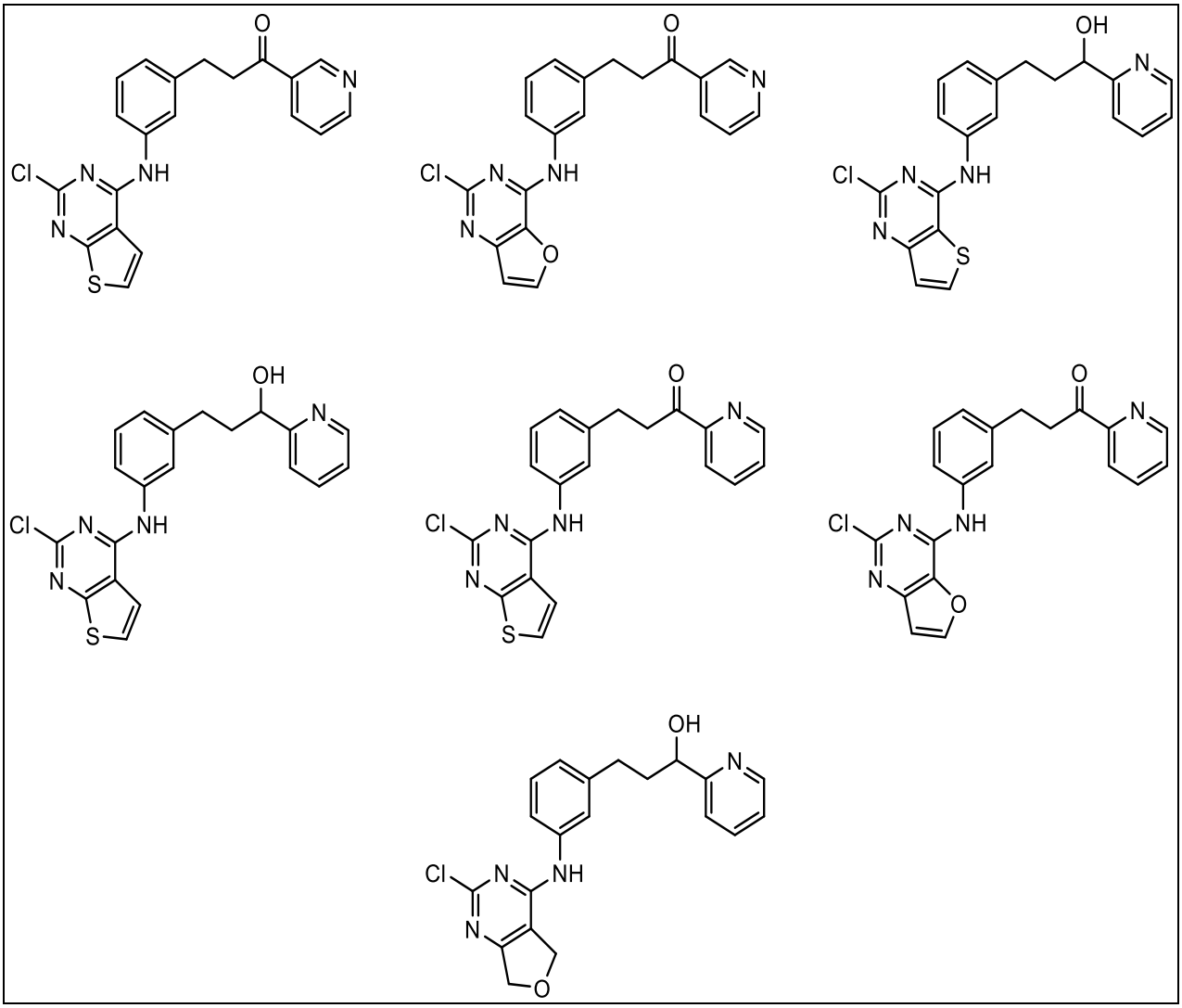


Fig 32 Pyrimidine Derivatives 112a-g

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➢ *Analgesic Activity:*

Goudgaon *et al*. [50] produced and tested analgesic activity of a series of 2-(4-fluorobenzylthio)-N-(substituted phenyl) pyrimidine-4-amines (**Figure 33**). When compared to the standard drug pentazocine, some of the produced compounds had good analgesic effectiveness.

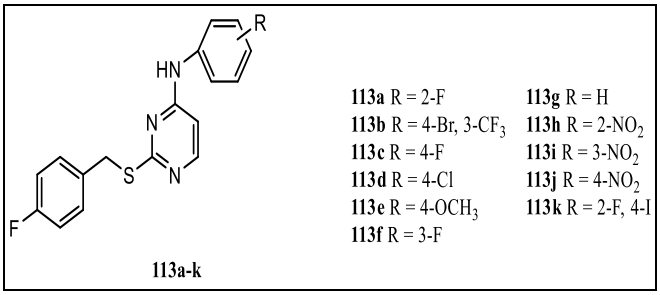

Fig 33 2-(4-Fluorobenzylthio)-*N*-(Substituted Phenyl) Pyrimidine-4-Amines

Vigjaya Raj *et al* [51] reported the synthesis and analgesic activity of some 2-[(1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)oxy]-*N*`-(4-aryl-1,3-thiazol-2-yl)acetohydrazi-de derivatives (**Figure 34**). Among the tested compounds, 2-[(1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)oxy]-*N*`-(4-(4-chlorophenyl)-1,3-thiazol-2-yl)aceto-hydrazide exhibited excellent analgesic effect when compared to the standard drug diclofenac sodium. Some of the remaining compounds also exhibited mild analgesic activity as well.

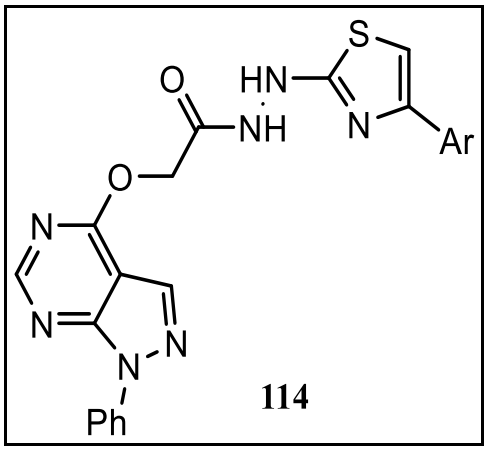

Fig 34 2-[(1-Phenyl-1H-Pyrazolo[3,4-d]Pyrimidin-4-yl)Oxy]-N`-(4-aryl-1,3-Thiazol-2-yl)Acetohydrazide Derivatives

➢ *Anticonvulsant Activity:*

Ali *et al.* [52] reported the synthesis of certain novel 6-oxo-4-aryl-1,6-dihydropyrimidine-5-carbonitrile derivatives (**Figure 35**) and analyzed their anticonvulsant activity in comparison to phenytoin and carbamazepine. The most active compounds were discovered to be **115** and **116**. These two compounds were shown to have anticonvulsant activity comparable to phenytoin and greater than carbamazepine.

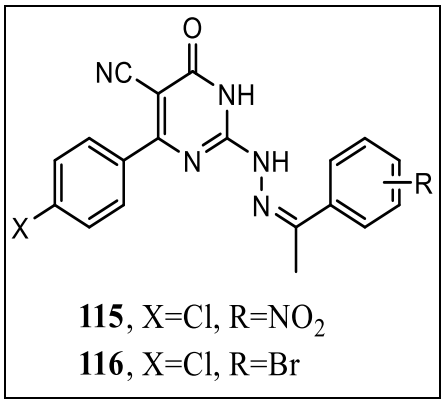

Fig 35 6-Oxo-4-aryl-1,6-dihydropyrimidine-5-carbonitrile derivatives

Vinay *et al.* [53] created a variety of 1,2,4-triazole compounds based on pyrimidines (**Figure 36**) and tested their anticonvulsant effectiveness against the conventional medication phenytoin. The compound 8-bromo-3-(4-bromophenyl)-5-morpholino-[1,2,4]triazolo[4,3,f]pyrimidine was discovered to have the most effective anticonvulsant action while causing no neurotoxicity [54-85].

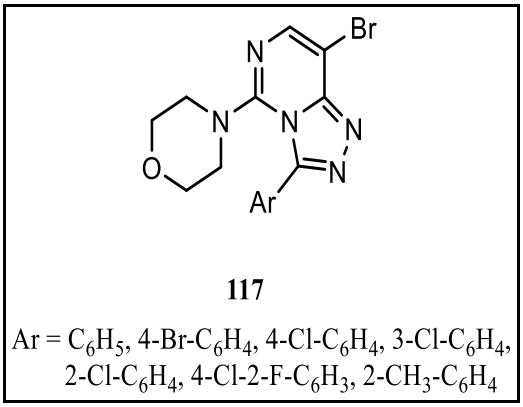

Fig 36 Pyrimidine based 1,2,4-triazole derivatives.

III. CONCLUSION

Pyrimidines have garnered substantial attention within the realm of pharmaceutical research, primarily attributable to their multifaceted pharmacological attributes encompassing anti-inflammatory, anticancer, antiviral, anti-HIV, antibacterial, antifungal, analgesic, and anticonvulsant properties. This comprehensive review aims to elucidate the diverse synthetic approaches employed for the generation of various pyrimidine derivatives, accentuating their pivotal role in medicinal chemistry. Furthermore, this discourse underscores critical reactions associated with pyrimidines, thereby underscoring their strategic importance in the development of pharmaceutical agents. Subsequently, this study underscores the clinical potential and therapeutic significance of pyrimidine derivatives in the domain of pharmacotherapeutics.

ACKNOWLEDGMENTS

The authors would like to thank the Egyptian Cultural Educational Bureau (GM1101) and Faculty of Science at South Valley University for the support allowed this research to accomplished.

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