Egypt. J. Chem. **Vol. 68,** No. 7 pp. 71 - 98 (2025)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Pyrimidine as a naturally occurring bioactive ring and its importance in different arenas

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Abstract

The pyrimidine ring is widely known for its biological activity through history, either by itself or attached to other heterocyclic rings. The importance of pyrimidine is due to its presence in the nucleic acid, in addition to its presence in natural and synthetic drugs. Based on the ring significance, that's an overview of the recent pyrimidines synthesis, reactions and its different biological activities over the past three years. It was shown that it has a generous contribution to the pharmaceutical industry. Scientists are still working on its derivatives to get promising results in different areas, especially as anticancer agents.

Keywords: Pyrimidine; anticancer; synthesis; reactions

1. Introduction

With two nitrogen atoms at positions 1 and 3, pyrimidine is a six-membered heterocyclic molecule. Thousands of pyrimidine-containing compounds were discovered, naturally and synthetically, naturally; as it's the core of our Deoxyribonucleic Acids (DNA) and ribonucleic Acids (RNA), either it's present by itself or engaged to diazole ring forming the purines. The term pyrimidine is a combination of pyridine and amidine, and it was initially introduced by Pinner owing to its similarities to both chemicals[1].

Pyrimidine is also present in many naturally occurring goods and vitamins as thiamine and riboflavin. This wide distribution made it an intriguing field of study for scientists, who began modifying it and generating other moieties by binding it to other rings. Pyrimidine derivatives have many biological activities like anticancer, antibacterial, anti-inflammatory, antiviral, and antidiabetic[1,2] (Figure 1). It plays a noteworthy role in the fight against cancer, either on its own or in combination with other substances. It is a crucial component of many commonly used anti-cancer medications, notably 5-fluorouracil, Imatinib, Dasatinib, Ruxolitinib, and Ibrutinib[3] (Figure 2).

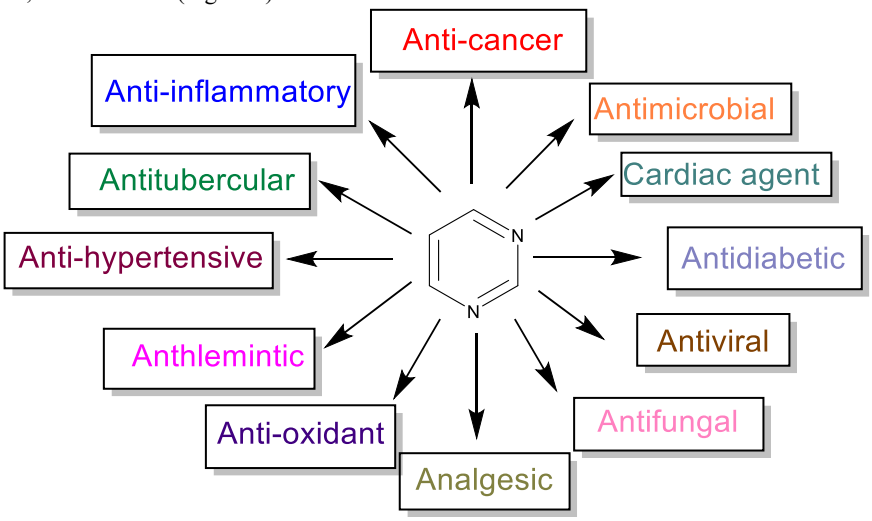

Figure 1: Pyrimidine ring different biological activities

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Receive Date: 24 June 2024, **Revise Date:** 21 August 2024, **Accept Date:** 30 November 2024

DOI: https://doi.org/10.21608/ejchem.2024.299076.9897

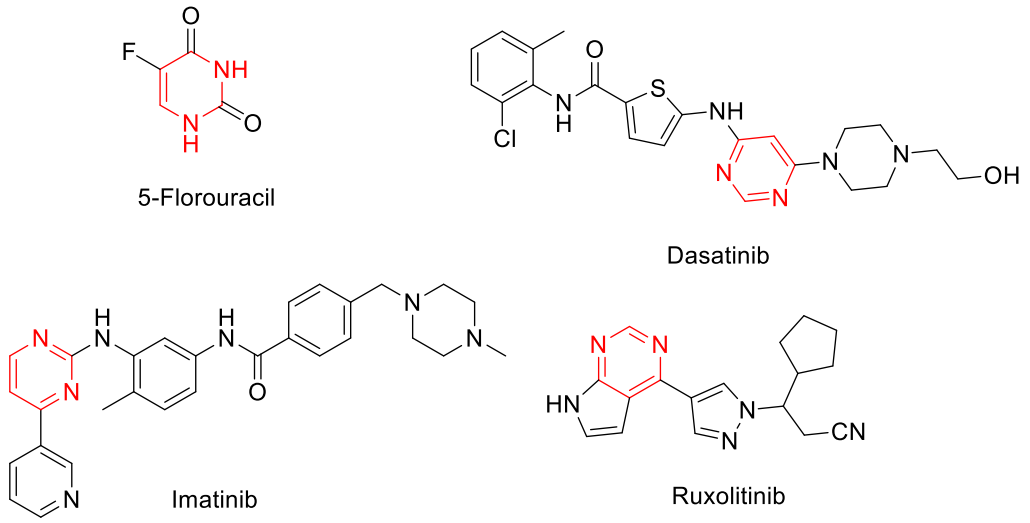


Figure 2: Pyrimidine as widely present anticancer drugs [1]

In order to develop similar moieties with better activity than the existing one, fewer side effect and better selectivity, scientists modified many pyrimidine-bearing drugs. They attempted combining it first with selenophenes or sulphur, which are well-known for their cytotoxic impact against anticancer cells, also, through linking it to fluorine, which improves the compound's lipophilicity and affects it's binding to other molecules. They discovered that its anticancer effects are also based on its similarity to naturally occurring compounds with proven anticancer activity, such as mackinazolinone, a natural alkaloid from the quinazoline family that exhibits promising anticancer activity, Figure 3. Furthermore, it has a propensity to act as kinase inhibitors, which are essential for cancer progression. Despite being typically known for its anticancer properties, it also works wonders against viruses and inflammation. It was also a crucial component of the numerous recent studies conducted in an effort to find a cure for COVID. Consequently, the following review highlights recent processes for the synthesis and reactions of pyrimidine and its derivatives throughout the past three years. (2020–2023)[3]. [4].

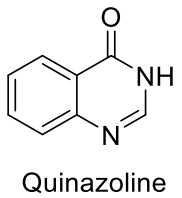


Figure 3 : Naturally occurring quinazoline which act as promising anticancer [3]

2. Chemistry :

2.1 Synthesis of Pyrimidines and its Derivatives

Pyrimidine ring can be synthesized by several pathways which can be summarized in the following figure (Figure 4)

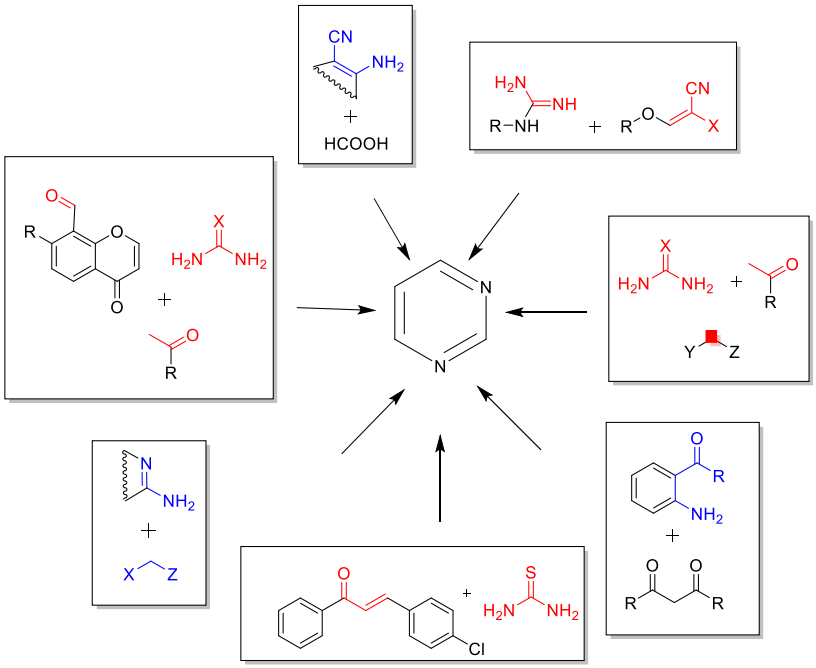


Figure 4: Different Pathways for pyrimidine ring synthesis

2.1.1 Synthesis of pyrimidine ring:

Erdong *et.al.,* 2020 [6] prepared trisubstituted pyrimidine **(1)** through ring formation reaction of thiourea with 4,4,4-trifluoroacetoacetate in basic condition in ethanol.

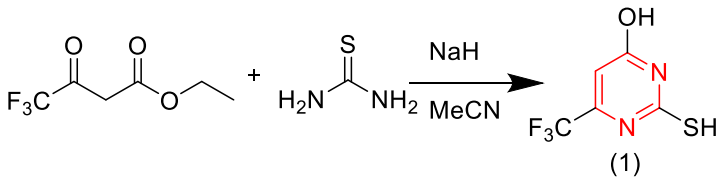


Figure 5: Synthesis of trisubstituted pyrimidine

Boumi *et.al.,* 2021 [7] prepared thiopyrimidine derivative **(2)** *via* the reaction of thiourea with chalcone in presence of potassium hydroxide (KOH).

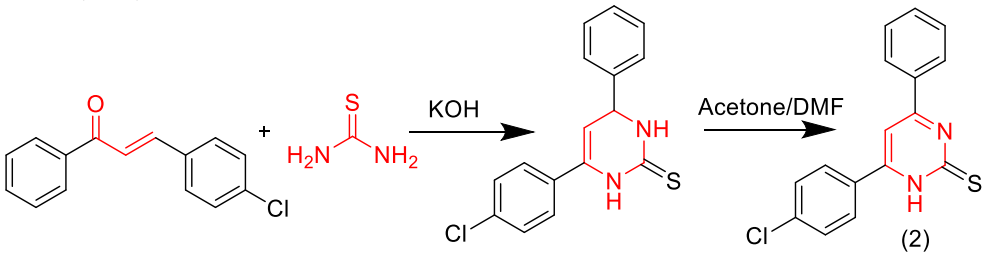
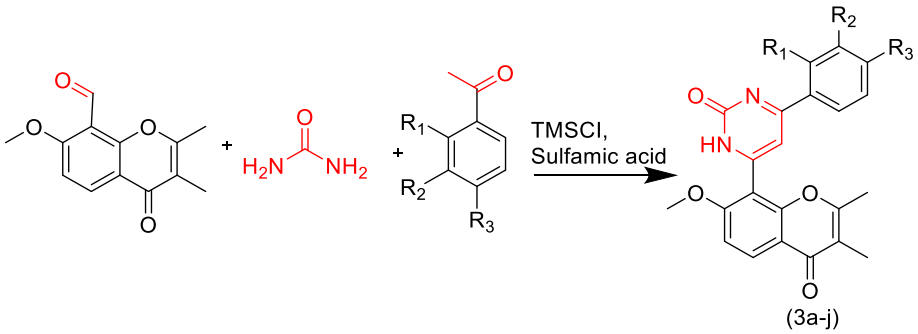


Figure 6: Synthesis of thiopyrimidine derivative

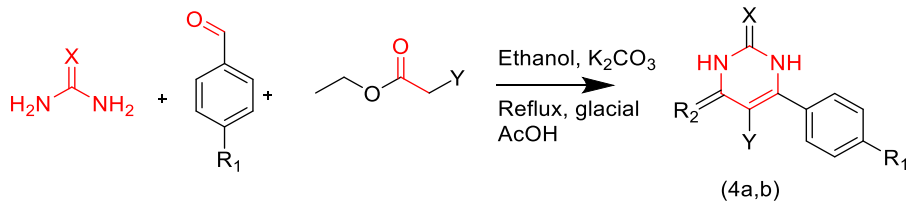
Kantankar e*t.al.,* 2021 [8] introduced an efficient one pot multi-component synthesis of *4-(4-oxo-4H-chromen-8-yl)-6-aryl-3,4-dihydropyrimidin2(1H)-ones* **(3a-e*)***,* by the condensation of acetophenones , 8-formyl chromone and urea in DMF using trimethylsilyl chloride (TMSCl)and sulfamic acid as a catalyst.



Compounds	R_1	R_2	R_3	Compounds	R_1	R_2	R_3
3 a	**H**	**H**	**F**	**3 f**	**H**	**H**	**OCF_3**
3 b	**F**	**H**	**H**	**3 g**	**H**	**H**	**CH_3**
3 c	**H**	**H**	**OCH_3**	**3 h**	**H**	**Br**	**H**
3 d	**H**	**H**	**H**	**3 i**	**H**	**H**	**Br**
3 e	**H**	**OCH_3**	**OCH_3**	**3 j**	**H**	**H**	**Cl**

Figure 7: Synthesis of pyrimidinones

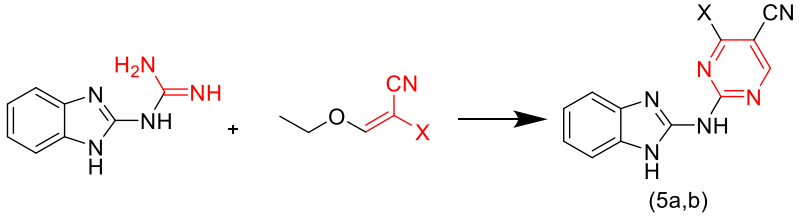
In 2022, scientists prepared [9,10] pyrimidines using Binegelli reaction, by reacting different substituted aldehyde with some active methylenes and urea/thiourea in the presence of ethanol, potassium carbonate and glacial acetic acid to produce the desired Pyrimidine **(4a,b).**



Compounds	X	Y	R_1	R_2
4 a	S	CN	OCH_3	O
4 b	O	$COCH_3$	NO_2	CH_2

Figure 8: Synthesis of pyrimidines using Binegelli reaction

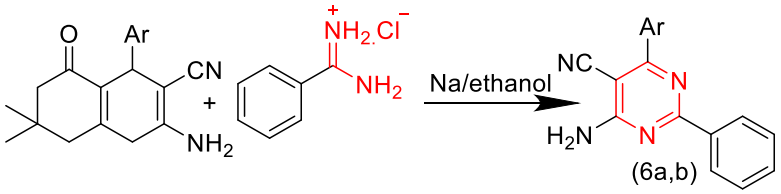
In the same year,. Ismail *et.al.,* 2022 [11] prepared *2- (2-Pyrimidinyl)aminobenzimidazoles* **(5)** *via* the reaction of 2-guanidinobenzimidazole with ethoxymethylenecyanoacetate and ethoxymethylene malononitrile.



Compound	X
5 a	OH
5 b	NH_2

Figure 9: Synthesis of pyrimidinyl aminobenzimidazoles

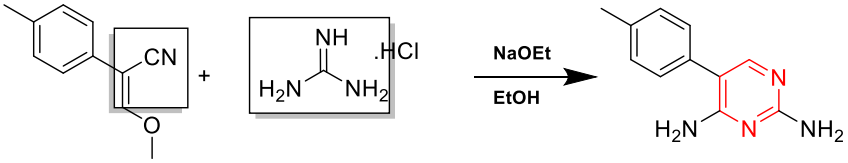
In 2022 ,Ghada S. Masaret prepared [12] pyrimidine derivatives **(6a,b)** *via* refluxing benzamidine HCl with pyran derivative yieldin the desired pyrimidine derivatives.



Compound	Ar
6 a	C_6H_4-CH_3
6 b	C_6H_4-CF_3

Figure 10: Synthesis of pyrimidine derivatives

Brown *et. al*., 2024[13] prepared pyrimidine ring *via* the reaction of phenyl-3-methoxyacrylonitrile with guanidine hydrochloride in presence of ethanol as a solvent and sodium ethoxide



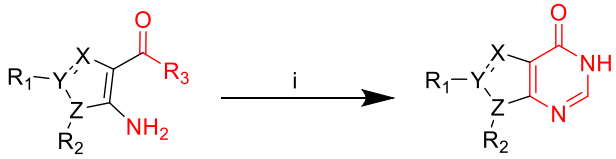
(7)

Figure 11: Synthesis of pyrimidine ring

2.1.2 Synthesis of some Fused pyrimidines:

I)DNA analogues

Various scientists synthesized [5,14–22] fused pyrimidines *via* reaction of ortho amino-carbonyl derivatives(namely; amide, and/or ester), under different conditions, for example triethylorthoformate, anhydrides and/or piperidone , in presence of phosphorul chloride ($POCl_3$) to prepare the the desired fused pyrimidines compound **(8a-g)**



(8a-g)

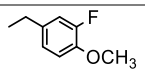
Compounds	I	X	Y	Z	R_1	R_2	R_3
8 a	$HC(OEt)_3$, AcOH , Reflux	Se	C	C	C_4H_8N	CN	NH_2
8 b	$HC(OEt)_3$, 100 C	N	N	N	-		NH_2
8 c	$(CF_3CO)_2O$	S	CS	N	C_2H_5		NH_2
8 d	4-OCH_3 Benzaldehyde, AcOH, Reflux	S	C	C			NH_2
8 e	2-Piperidone, $POCl_3$	O	C	N	C_6H_5	-	OC_2H_5
8 f	$POCl_3$, Dioxane	N	N	C	H	CH_3 / C_6H_5	OC_2H_5
8 g	Ethano , 	S	C	C			OC_2H_5

Figure 12: Synthesis of fused pyrimidines

Huo *et.al.,* 2021 [23] prepared some fused pyrimidines *via* a 2-step reaction. Through the reaction of mercaptotriazole derivative with 4-bromobenzyl chloride, followed by reacting the product with ethyl acetoacetate in acetic acid, leading to the formation of the desired imidazole pyrimidine derivative **(9)**

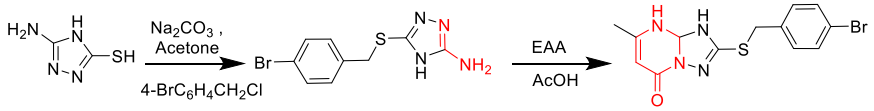


Figure 13: Synthesis of triazolo-pyrimidine

In the same year, El-Metwally *et.al.,* prepared [24] thienopyrimidinone through the well known gewald reaction allowing cyclohexanone and malononitrile to react with elemental sulfur in the presence of morpholine base with continuous stirring for 1 hr at 25 °C. then, the compound was refluxed with formic acid for 10 hr to give the corresponding thienopyrimidinone and by further refluxing in $POCl_3$ and coupling with amine by a multi step reaction producing compound (10)

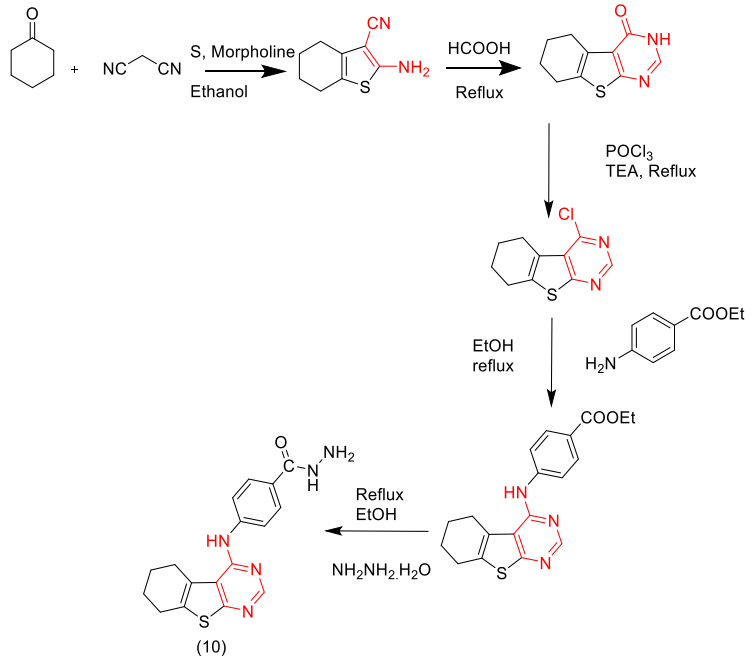
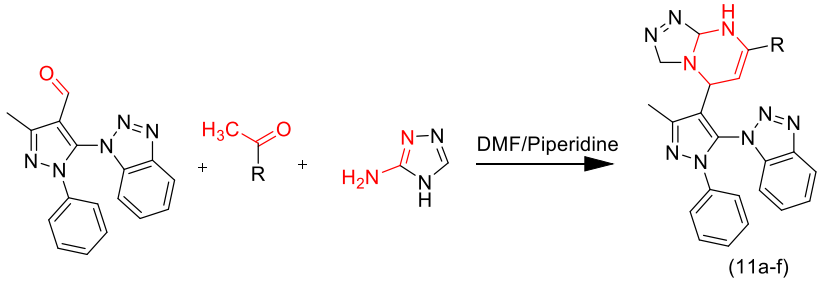


Figure 14: Synthesis of thienopyrimidinone

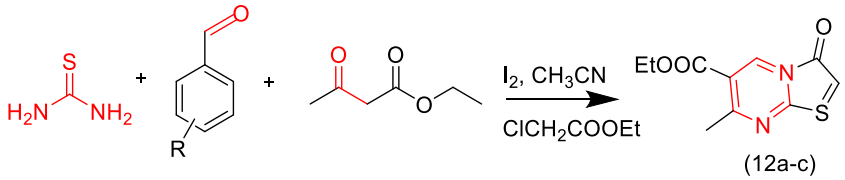
In 2021, the triazolo-pyrimidine derivatives[25] were prepared *via* a multicomponent reaction of *5-(1H-benzo[d][1,2,3]triazol-1-yl)-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde* with various substituted acetophenones and *4H-1,2,4-triazol-3-amine* in DMF in the presence piperidine leading to the formation of the triazolo-pyrimidine derivative **(11a-f)**



Compounds	R
11 a	**C_6H_5**
11 b	**$CH_2C_6H_5$**
11 c	**4-$OCH_3C_6H_5$**
11 d	**4-ClC_6H_5**
11 e	**4-FC_6H_5**
11 f	**4-BrC_6H_5**

Figure 15: Synthesis of triazolo-pyrimidine derivatives

Agarkov *et.al*., 2022[26] prepared thienopyrimidines **(12a-c)** by the three-component Biginelli condensation which is done by the reaction of appropriate aldehyde (benzaldehyde, 2-methoxybenzaldehyde, 4-methoxybenzaldehyde), thiourea and acetoacetic ether in the presence of a catalytic amount of molecular iodine at refluxing in acetonitrile for 10 h.

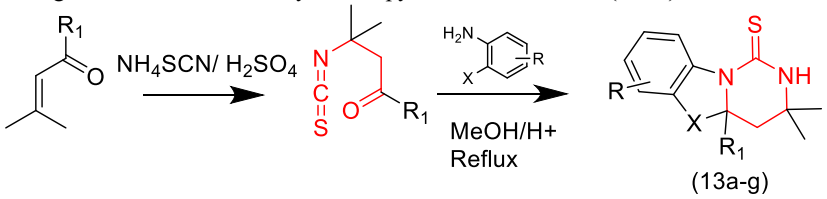


(12a-c)

Compounds	R
12 a	H
12 b	2-OCH_3
12 c	4-OCH_3

Figure 16: Synthesis of thienopyrimidnes

In the same year, Dolly *et.al.,* 2022 [27] prepared thiopyrimidines through the following pathway : the starting material was synthesized by the reaction of aldehyde and acetophenone with ammonium thiocyanate using H_2SO_4 as catalyst and dehydrating agent , Then the resulting product was reacted with various amines in dry methanol in presence of H_2SO_4 to maintain PH 4-5 , resulting in the formation of tricyclic thiopyrimidine derivatives **(13a-f)** .

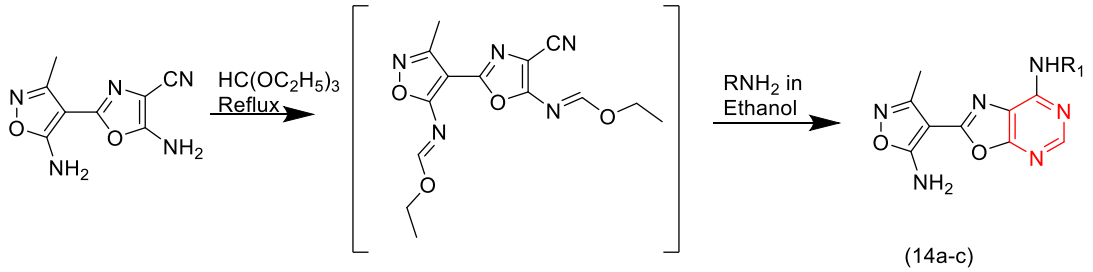


(13a-g)

Compounds	X	R
13 a	NH	H
13 b	NH	CH_3
13 c	O	H
13 d	O	CH_3
13 e	S	H
13 f	S	CH_3

Figure 17: Synthesis of fused thiopyrimidines

Sochacka-Cwikła *et.al.,* 2022 [28] introduced the reaction of oxazole with triethyl orthoformate producing the intermediate imidoester derivative . Then, the ring closure with the ethanol or aqueous solution of methylamine produced *oxazolo[5,4-d]pyrimid*ine .

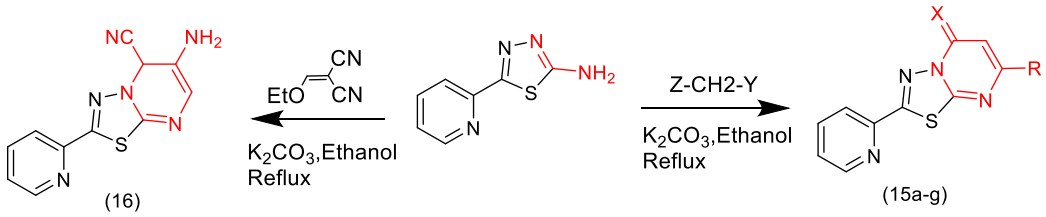


(14a-c)

Compounds	R_1
14 a	CH_3
14 b	C_2H_5
14 c	C_3H_7

Figure 18: Synthesis of oxazolo-pyrimidines

Ibrahima *et.al.,* 2022 [29] introduced Several ways to produce the thiadiazole pyrimidines *via* one-pot reaction , the starting compound *5-(pyridin-2-yl)-1,3,4-thiadiazol-2-ami*ne was reacted with several reagents containing active methylene groups to obtain new condensed moieties **(15a-g)** .



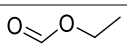
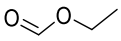
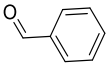
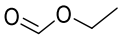
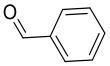
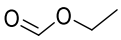
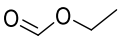
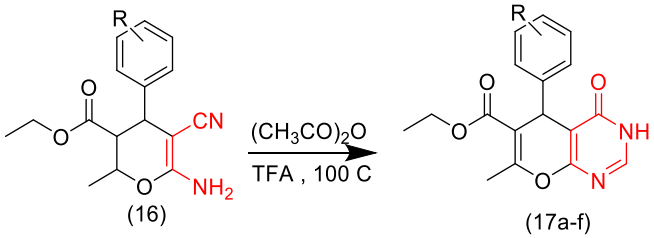
Compounds	Y	Z	R	X
15 a			CH3	O
15 b			C6H5	O
15 c		CN	NH2	O
15 d			CH3	CH3
15 e			CH3	C6H5
15 f		CN	NH2	NH
15 g			O	-

Figure 19: Synthesis of thiadiazole pyrimidines

Thanh *et.al.,* 2023 [30] prepared pyranopyrimidine derivatives **(17a-f)** *via* the reaction of amino-cyano pyran derivative with acetic anhydride in the presence of trifluoroacetic acid (TFA)



Compounds	R
17 a	H
17 b	3-NO_2
17 c	4-NO_2
17 d	3-Cl
17e	4-Cl
17 f	2,3-diCl

Figure 20: Synthesis of pyranopyrimidine derivatives

Qi *et.al.,* 2023 [31] Synthesized piperidopyrimidinedione derivative **(18)** *via* the reaction of piperidine derivative with urea in presence of sodium ethoxide.

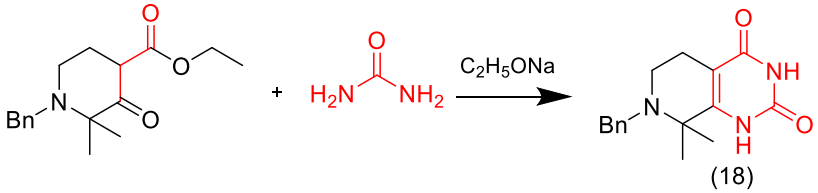


Figure 21: Synthesis of triazole piperidopyrimidinedione

Saiyad *et. al*., 2024[32] prepared fused pyrimidine (19) via one pot reaction of substituted aldehyde , amino benzimidadazole and a di-carbonyl compound in DIPEA .

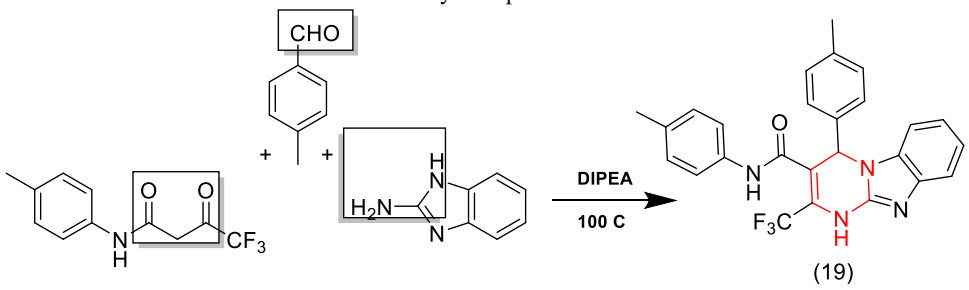


Figure 22: Preparation of fused pyrimidine derivative

2.1.3. Synthesis of Pyrimidine ring through ring transformation from other heterocyclic ring:

In 2020, Deng-Yuan Li prepared [33] pyrimidine via ring rearrangement through multistep reaction to form the desired pyrimidine **(20).**

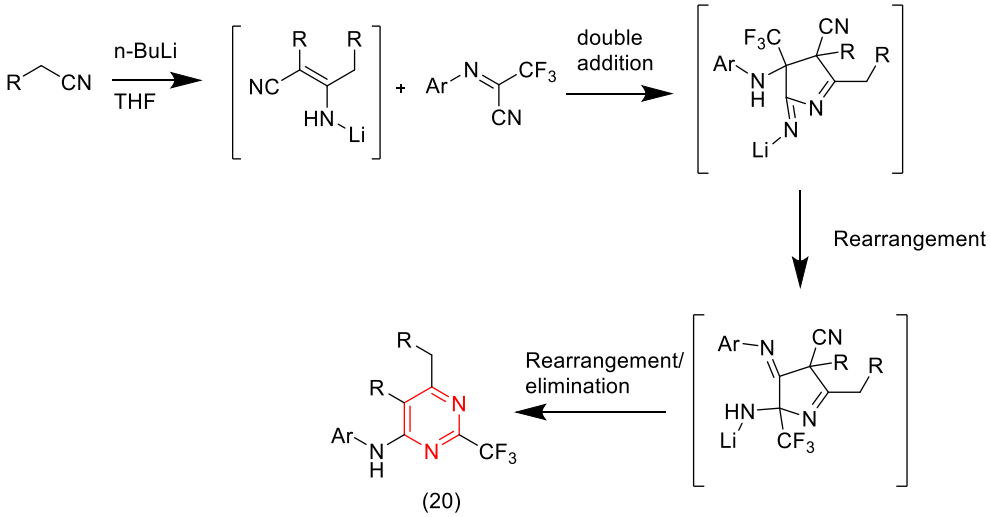


Figure 23: Synthesis of pyrimidine via ring rearrangement

Radini *et.al.,* 2021 [34] prepared pyrazolopyrimidine *via* ring rearrangement method named "Dimorth rearrangement" by reacting *2-(4-imino-6-methyl-1,4-dihydropyrazolo[3,4-d] [1,3]oxazin-3-yl)acetonitrile* with various amines to yield the pyrazolopyrimidines **(21)** .

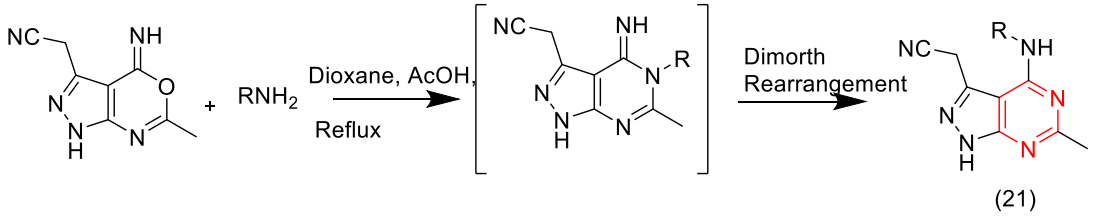


Figure 24: Synthesis of pyrazolopyrimidine

Hyland *et.al.,* 2022 [35] synthesized benzopyrimidines derivatives **(22)** through ring expansion of the pyrazole derivatives .

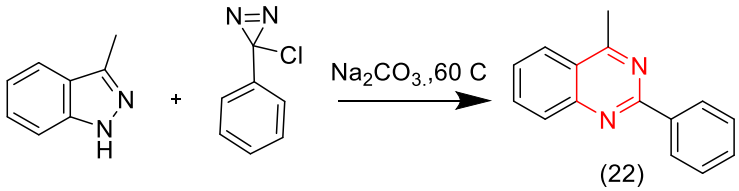
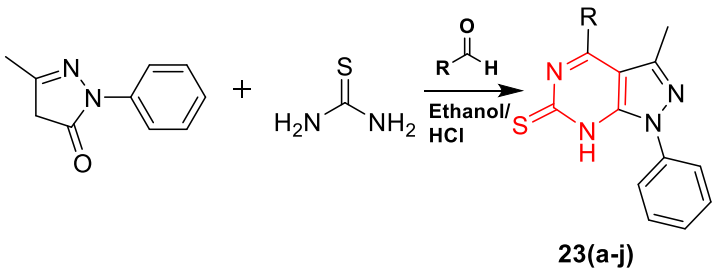


Figure 25: Synthesis of benzopyrimidine

Chavda *et. al.,* 2023[36] prepared pyrazolo-pyrimidine derivatives (23a-j) through the condensation of Disubstituted pyrazolones with different substituted benzaldehydes and thiourea.

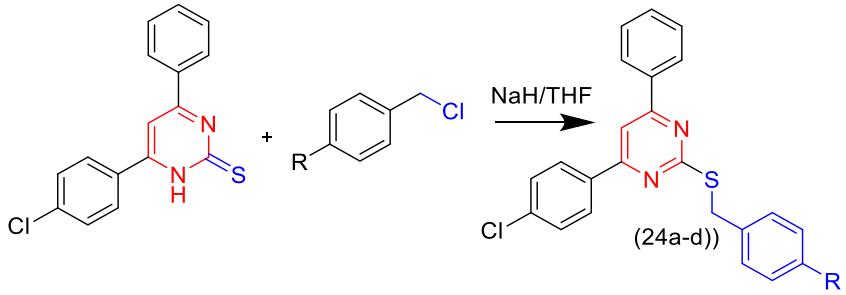


Compound	R
23 a	4-NO2-C6H4
23 b	4-OCH3-C6H4
23 c	4-OH-C6H4
23 d	4-F-C6H4
23 e	4-Cl-C6H4
23 f	3-NO2-C6H4
23 g	3-Cl-C6H4
23 h	2-NO2-C6H4
23 i	2-Cl-C6H4
23 j	2-OH-C6H4

Figure 26 : Synthesis of Pyrazolopyrimidine derivatives

2.2. Different reactions of pyrimidines:

Boumi *et.al.,* 2020 [7] prepared 2-(benzylthio)- pyrimidine derivatives **(24)** by reacting thiopyrimidines with various benzyl halides in presence of sodium hydride (NaH) .



Compound	R
24 a	H
24 b	Cl
24 c	F
24 d	CH_3

Figure 27: benzylthiopyrimidine derivatives preparation

Erdong *et.al.,* 2021 [6] synthesized Compound **(25)** by reacting trisubstituted pyrimidine and 2-chloromethyl benzothiazole under basic conditions .

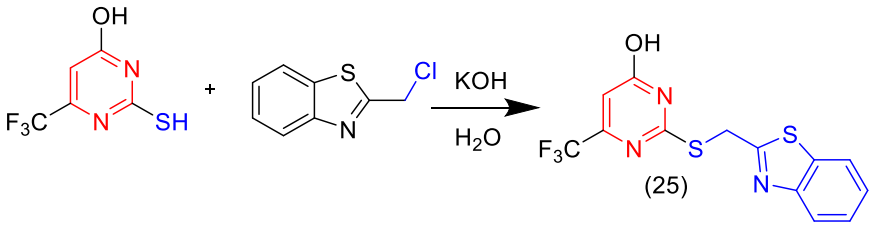
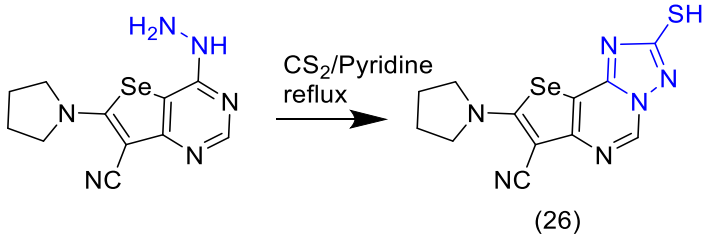


Figure 28: alkylation of thiopyrimidine

In 2021, Omed Kohandel, Seddigheh Sheikhi-Mohammareh prepared [14] new *selenopheno[2,3-e][1,2,4]triazolo[1,5-c]pyrimidine* derivatives**(26)** *via* Dimroth rearrangement by cyclocondensation of *7-cyano-4-hydrazinyl-6-(pyrrolidin-1-*

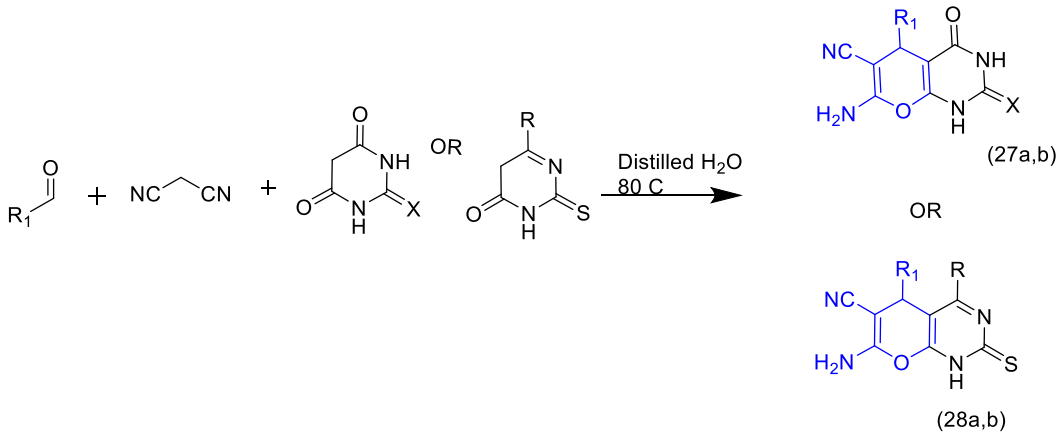
yl)selenopheno[3,2-d]pyrimidine with electrophilic carbons of carbon disulfde in pyridine



(26)

Figure 29: Cyclocondensation of carbondisulfide with pyrimidine derivative

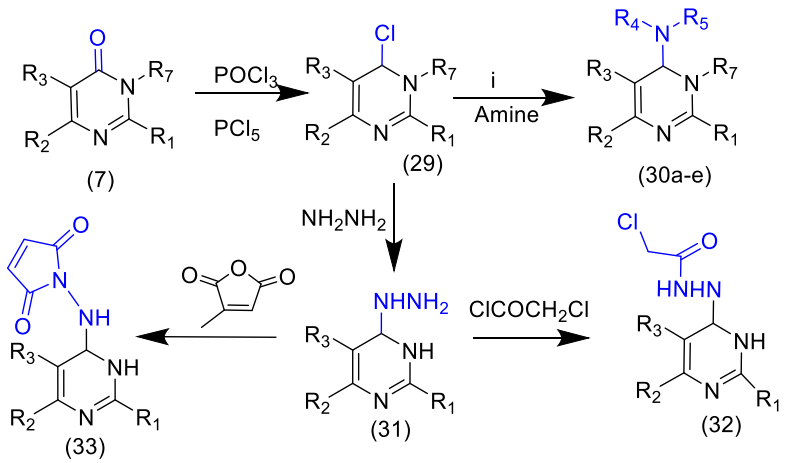
Alia, *et.al.,* 2022 [37] prepared a one-pot, and catalyst-free synthesis of novel ~~*4-5-*~~*(4-oxo-4H-chromen-3-yl)pyrano[2,3-d]pyrimidines* by refluxing a mixture of 4-oxo-4*H*chromene-3-carbaldehyde, malononitrile and cyclic active methylene compound in distilled water .



Compounds	R1	R	X
27 a		H	O
27 b		H	S
28 a		CH_3	-
28 b		C_6H_5	-

Figure 30: preparation of pyranopyrimidine derivatives

The pyrimidine derivative **(7)** was refluxed in $POCl_3$ yielding the corresponding 4-chloropyrimidnes, which was coupled with various amines. The chloro- derivative was also treated with hydrazine monohydrate which was then treated with chloroacetyl chloride yielding the chloroacetamido derivative which underwent Cyclization when heated with 3- methylfuran-2,5-dione [14,15,17,18,23].



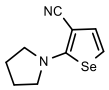
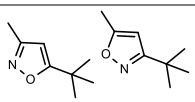
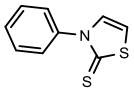
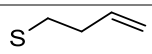
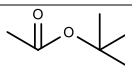
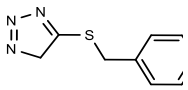
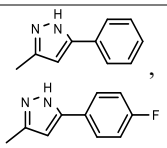
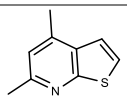
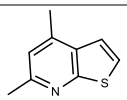
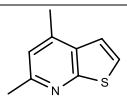
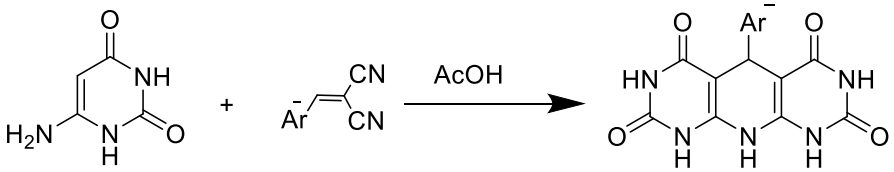
Compounds	R_1	R_2	R_3	R_4	R_5	R_7
29	H			-	-	CH_3, C_2H_5,C_3H_7 C_4H_9
30 a	H				H	H
30 b	CF_3			CH_3,4-$FCH_2C_6H_4$	H	H
30 c		4-OC H_3C $_6H_5$	CN	C_6H_5,2-$CH_3C_6H_4$, 4-$CH_3C_6H_4$	H	H
30 d	S-CH_3	H	CHO	$CH_2C_6H_5$		H
30 e	R1&R7 : 	CH_3	H		H	-
31	4-$OCH_3C_6H_5$, 2-furyl			-	-	H
32	4-$OCH_3C_6H_5$, 2-furyl			-	-	H
33	4-$OCH_3C_6H_5$, 2-furyl			-	-	H

Figure 31: chlorination and amination of pyrimidine derivatives

Farag *et.al.,* 2022 [38] discovered a novel and efficient route towards the synthesis of pyrido[2,3-d:6,5-d'] dipyrimidines as unexpected products through the reaction of 6-aminouracil and arylidenemalononitrile in acetic acid .

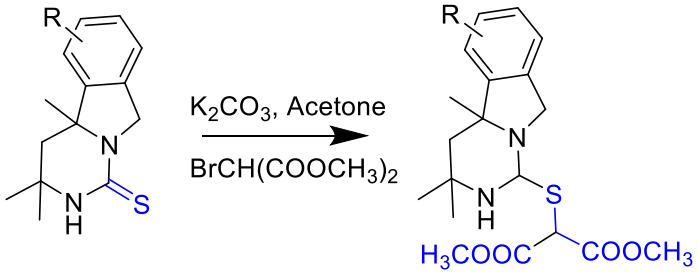


(34a-g)

Compounds	Ar
34a	C_6H_5
34 b	4-$NO_2C_6H_4$
34 c	4-ClC_6H_4
34 d	4-$OCH_3C_6H_4$
34 e	2-OHC_6H_4
34 f	2-$(CH_3)_2N$-C_6H_4

Figure 32: synthesis of dipyrimidnes

Dolly *et.al.,* 2022[27] performed alkylation reaction on the sulphur group of the thiopyrimidine *via* the reaction of tricyclic thiopyrimidine derivatives with dimethyl bromomalonate in presence of anhydrous potassium carbonate with continuous stirring and refluxing at 80ºC



(35a-g)

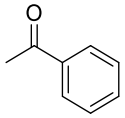
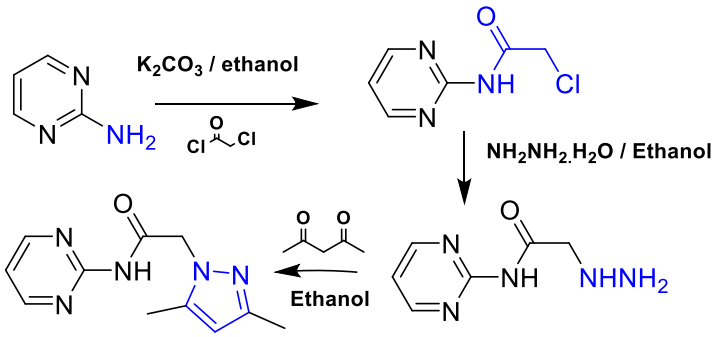
Compounds	R	X
35 a	NO_2	NH
35 b	H	NH
35 c	CH_3	NH
35 d		NH
35 e	OCH_3	NH
35 f	H	S
35 g	H	O

Figure 33: alkylation of thiopyrimidine derivatives

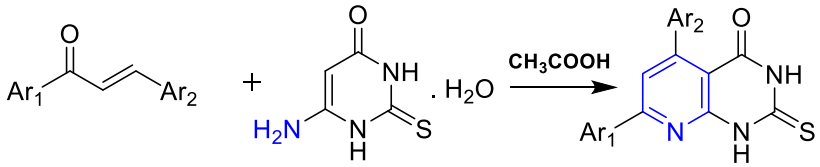
In march 2023, Rana N. Atiya *et. al.,* 2023 [39] reacted pyrimidine-2-amine with chloro-acetyl chloride in basic conditions (K_2CO_3) releasing HCl forming the corresponding acetamide, Performing a multistep reaction to result in formation of pyrazole ring enhancing the antimicrobial activity of the compound producing compound **(36).**



(**36**)

Figure 34: Condensation of pyrimidine derivatives

Myriagkou *et. al.,* 2023[40] prepared fused pyrimidines derivatives **(37a-h)** through reacting α,β-Unsaturated ketone with pyrimidine in presence of glacial acetic acid .



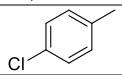
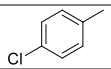
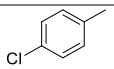
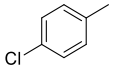
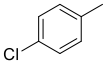
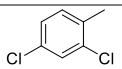
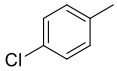
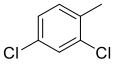
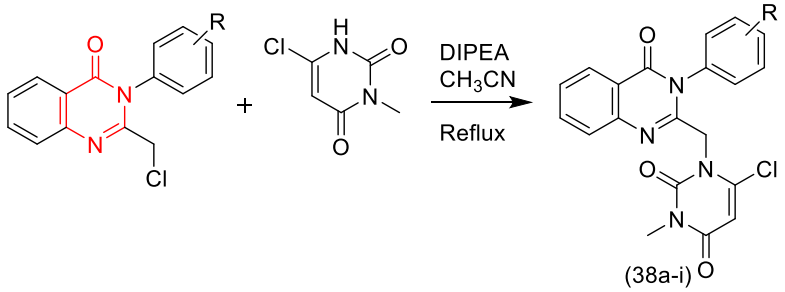
Compound	Ar_1	Ar_2
37 a		
37 b		
37 c		
37 d		
37 e		
37 f		
37 g		
37 h		

Figure 35: Reaction of α,β-Unsaturated ketone with pyrimidine

Ataollahi *et. al.,* 2024[41] prepared fused pyrimidine derivatives *via* the reaction of benzopyrimidinones with 6-chloro-methyl uracil with DIPEA (diisopropylethylamine) as a base in CH_3CN (acetonitrile)



Compound	R	Compound	R
38 a	H	34 f	3-F-4-CH_3
38 b	3-CF_3	34 g	3-Cl-4-F
38 c	4-F	34 h	5-Cl-2-CH_3
38 d	4-OC_6H_5	34 i	5-Cl-2-OCH_3
38 e	2,4-di-OCH_3		

Figure 36 : Reaction of benzopyrimidinone with uracil derivative under basic conditions

Wang *et. al.,* 2024[42] Prepared pyrrolopyrimidine derivative via a multistep reaction , starting by reacting the chloropyrimidine with tert-butyl (3-aminophenyl) carbamate followed by the reaction of the resulting product with propynol , then cyclization occurred resulting in the pyrrole ring formation producing compound **(39).**

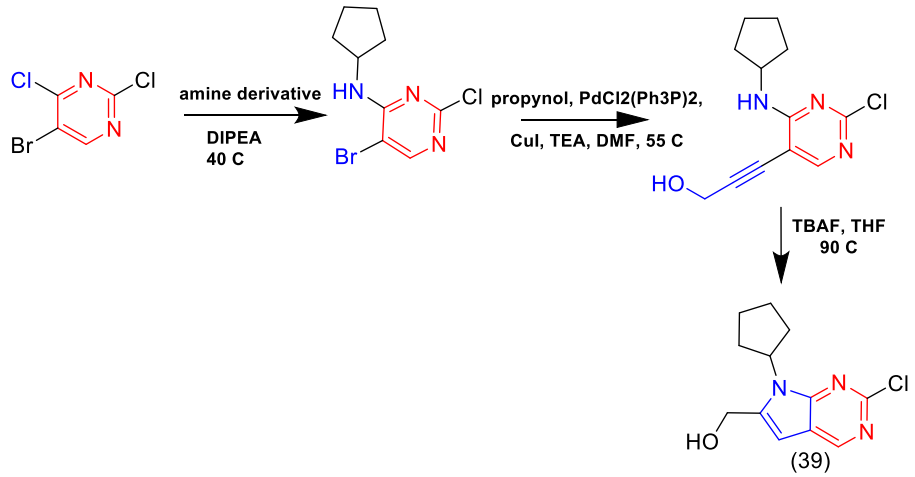


Figure 37: Formation of fused pyrrolopyrimidine derivative

Zeng *et. al.,* 2024[43] prepared pyrimidine derivative via the reaction of trisubstituted aminopyrimidne with ethylypiperazine , then alkylation of amino group on the pyrimidine ring resulting in the formation of the desired compound (40)

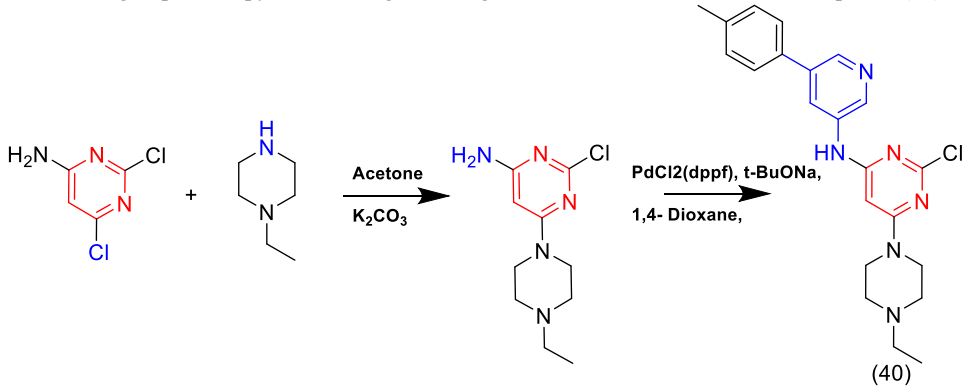


Figure 38 : alkylation of aminopyrimidine

Zhang *et. al.,* 2024[44] preformed coupling reaction of dichloro thienopyrimidine with indole in presence of $AlCl_3$ and dichloroethane resulting in the desired compound (41) .

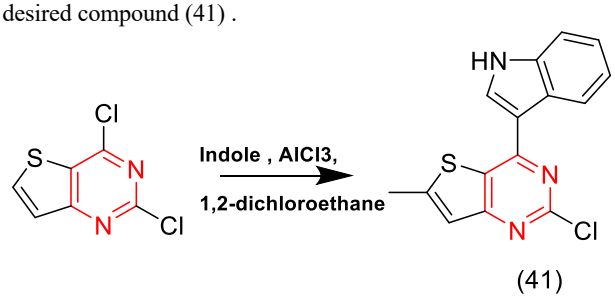


Figure 39: formation of thienopyrimidine derivative

3. Biological Discussion:

Pyrimidines are widely known for their biological activity against a lot of diseases due to their presence in DNA & RNA by itself or in the fused form forming the purines as discussed before , it has an outstanding role in the anticancer area Although it's mainly famous for its anticancer activity ,it also have an excellent antiviral and anti-inflammatory effect as its present in already marketed drugs as broxuridine , Iroxidine as antiviral drugs, Flucytosine as antifungal and tegafur as anticancer (Figure 35). it was also an essential part of the many researches made recently searching for a treatment for covid. So Here are some of the Synthesized pyrimidine derivatives and its Biological activity.

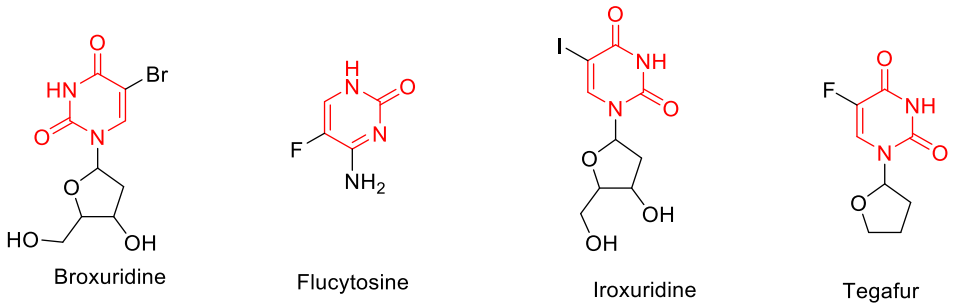


Figure 40: Drugs Containing Pyrimidine ring [45]

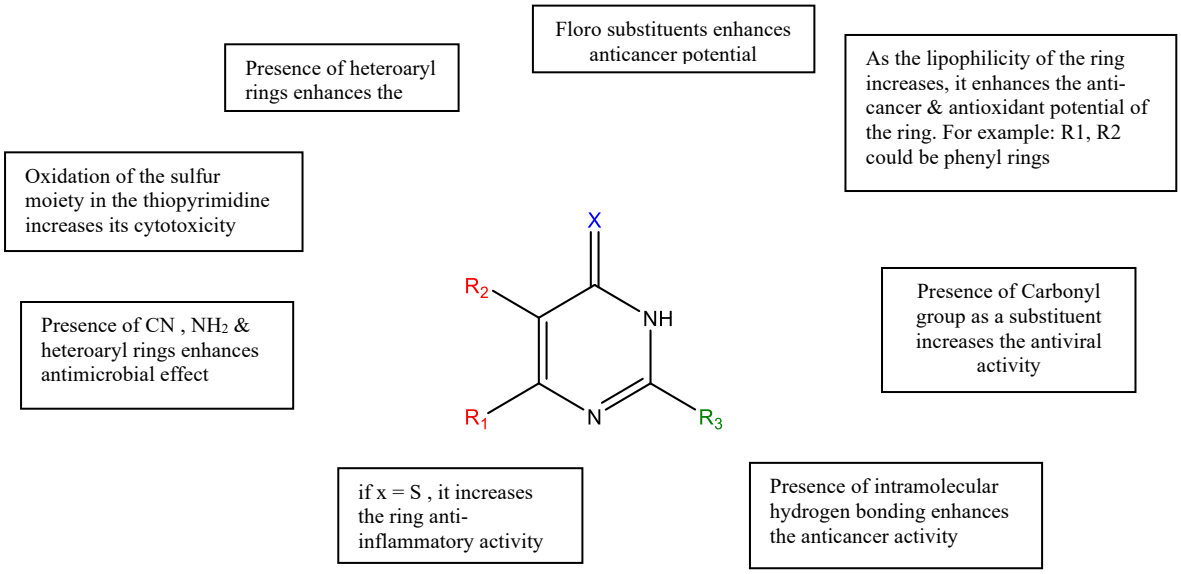


Figure 41: General SAR for Pyrimidine ring

3.1. Pyrimidine as anticancer:

4-substituted amino pyrimidines were reported[9] to have an outstanding anticancer activity. They exhibited excellent effect against human liver cancer "HepG2", lung cancer "A549" and breast cancer "MC F-7" cell lines. The structure activity relationship (SAR) as discussed in the literatutre [9] were summarized in the following figure:

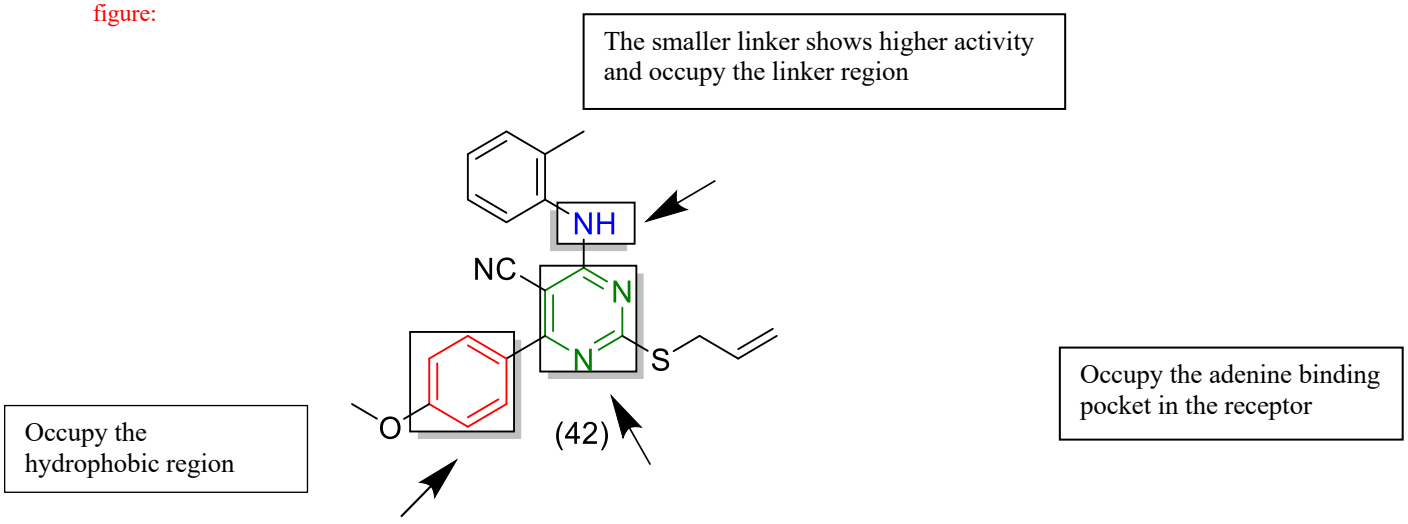
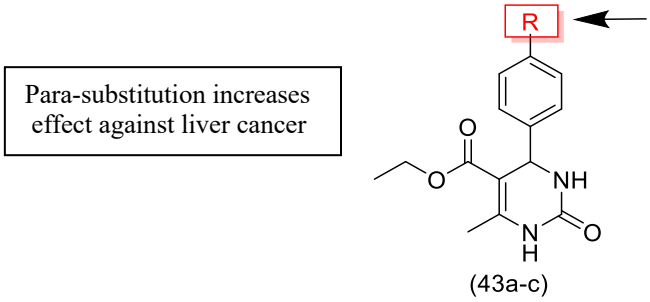


Figure 42: Substituted amino pyrimidines with anticancer activity

Dihydropyrimidines anti-cancer activity was evaluated [10] against certain cell lines which are A549, HT29 "adenocarcinoma", HepG2, those 3 compounds were found the most potent.



Compound	R
43 a	Cl
43 b	OBn
43 c	OCH_3

Figure 43: Dihydropyrimidne with anticancer activity

The *selenopheno[2,3-e] [1,2,4]triazolo[1,5-c]pyrimidine* derivatives were tested against breast carcinoma MCF-7 cell line & L929 cells with doxorubicin as a standard , The S-n-Hexyl derivative showed the highest cytotoxicity next came S-n-Pentyl & S-Ethyl derivatives the presence of the lipophilic chain is essential , as the length of the chain increase on the S-alkyl increases the activity of the compound [14].

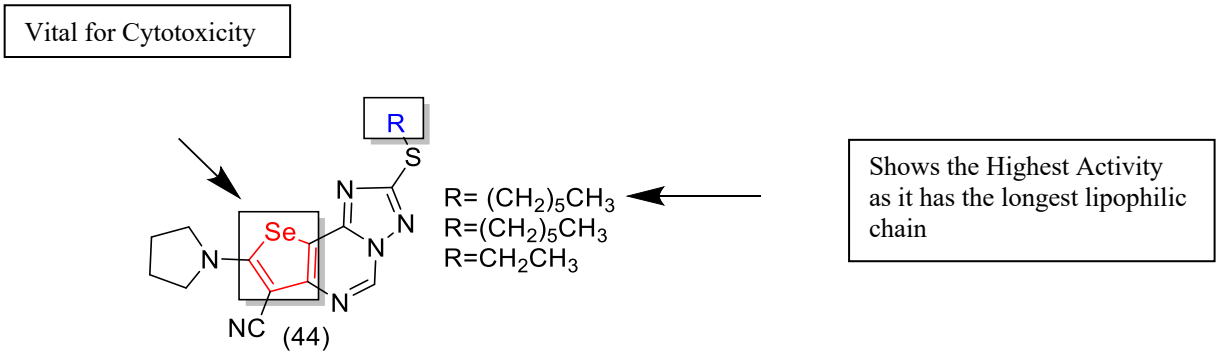


Figure 44: Fused pyrimidines showing antiproliferative activity against breast cancer

The synthesized benzo- and thieno[2,3-d] pyrimidines derivatives were tested [5] against MCF-7 , HeLa "Cervical carcinoma cells" & A549 cell lines ,amongst the tested compound 3,4- Dichlorophenyl derivative gave the highest activity against HeLa while the 3,5-dichlorophenyl showed better effect against MCF-7 and A549 cell lines .

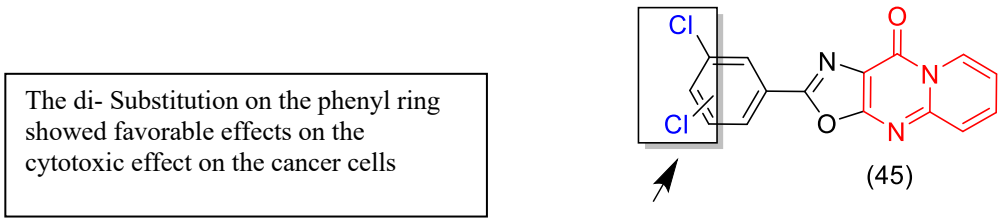


Figure 45: Disubstituted Chloropyrimidines with anti-Hela "cervical carcinoma" effect

A series of thieno[2,3-d] pyrimidines **(46)** were tested for their FLT3 kinase inhibition activity. These 2 derivatives showed the highest activity, the amide derivative showed moderate selectivity for FLT3. While the pyrrole derivative showed inhibitory activity.

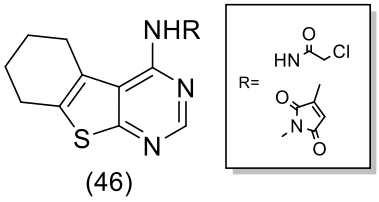


Figure 46: FLT 4 Kinase inhibitors containing thienopyrimidine derivatives

Compound **(47)** was tested against variety of cell lines containing 4 human cancer (A375, C32, DU145, MCF-7)) and two normal cell lines (CHO-K1 and HaCaT), it showed the highest activity with lowest conc tested, it decreased the viability to 20 % for melanotic and amelanotic melanoma cell lines and human keratinocytes [17].

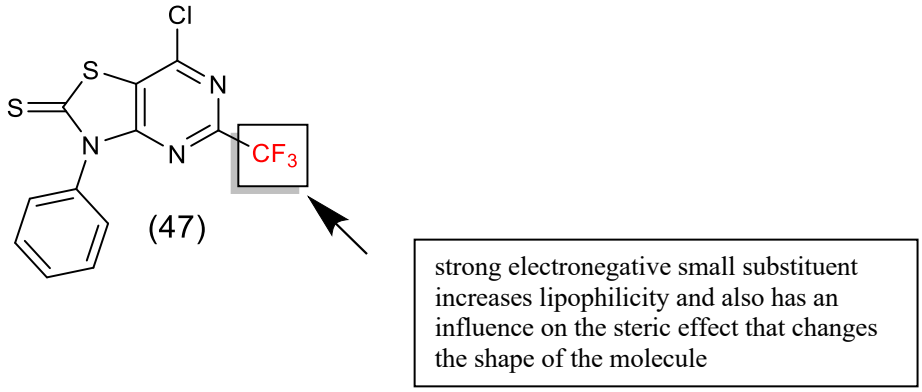


Figure 47: Fused pyrimidines with enhanced anticancer effect due to the presence of floro group

The thienopyrimidne derivatives were tested [18] for their anticancer activity against HepG-2 and MCF-7 cell lines, The 4-aminopyrazolone derivative showed better anticancer activity against both HepG-2 and MCF-7 cell lines.

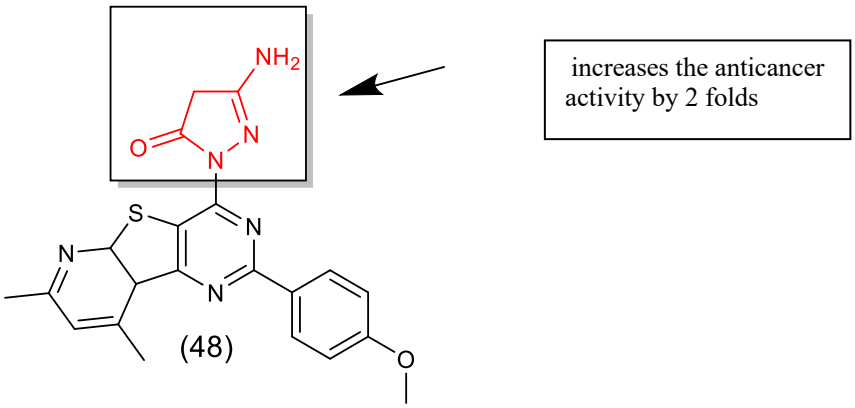


Figure 48: Fused pyrimidine containing aminopyrazolone with anticancer activity

The metallocene-uracil conjugates were evaluated for cytotoxic activity [38], N-1,N-3-disubstituted olefinic uracil derivatives were found having antiproliferative effect, The antiproliferative activity of these compounds was evaluated towards HEPG-2, MCF-7 and HCT116 cell lines.

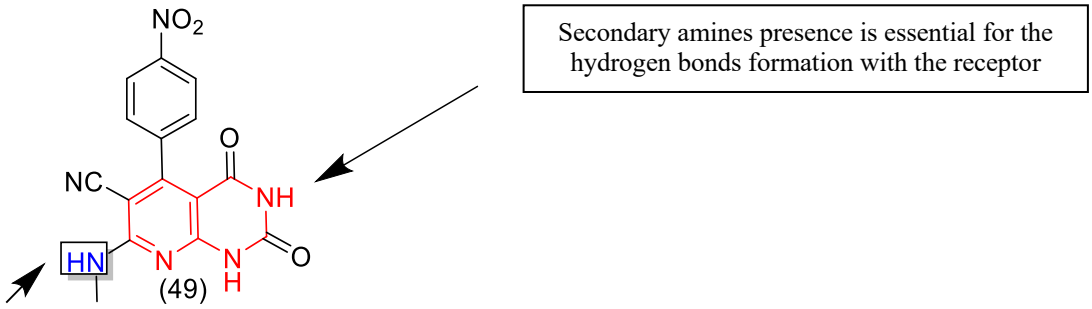


Figure 49: Uracil derivatives with anticancer activity

The thienopyrimidines [20], the compounds inhibitory effect was evaluated and their cytotoxicity was tested against different cancerous cell lines HT-29, HepG-2, and MCF-7. cytotoxic activity of the Compound against the HepG-2 cell line was shown, which exceeded the reference standard activity.

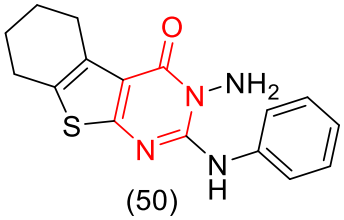
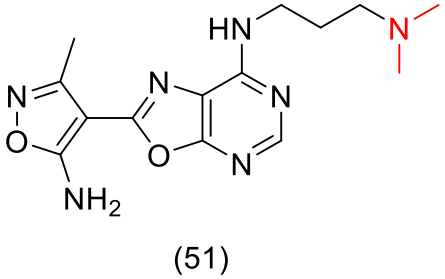


Figure 50: thienopyrimidines with cytotoxic activity

The cytotoxic activity of the isoxazolo-pyrimidine derivative was tested [46] against four human cancer cell lines :lung carcinoma(A549) breast adenocarcinoma (MCF7), metastatic colon adenocarcinoma (LoVo) , primary colon adenocarcinoma (HT29), this compound with a 3-(N,N-dimethylamino)propyl substituent was found to exhibit the highest potency against the HT29 cell line, exceeding the activity of fluorouracil and equal to the effect cisplatin while having lower toxicity to healthy human cells suggesting it is a potentially promising drug for the treatment of primary colorectal cancer .



(51)

Figure 51: Isoxazolo pyrimidine derivatives with anticancer effect

The chloro derivative **(52a)** showed [47] potent anticancer activity against human lung carcinoma "A549"cell line while the ethyl containing derivative **(52b)** showed excellent anticancer activity against human breast cancer "MCF-7" cell line .

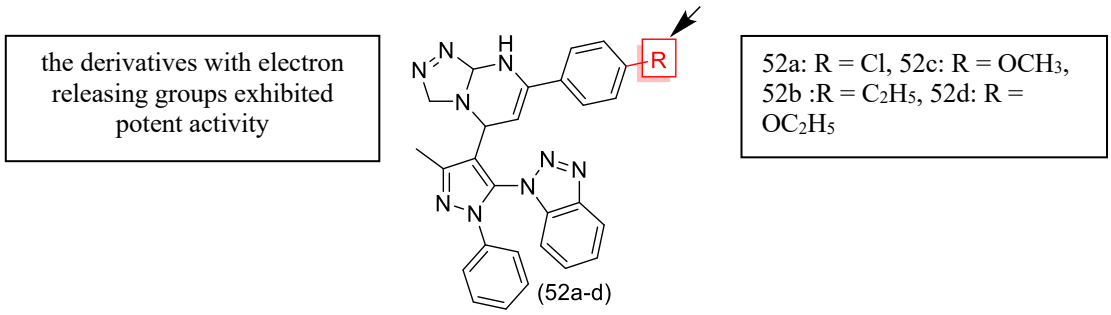
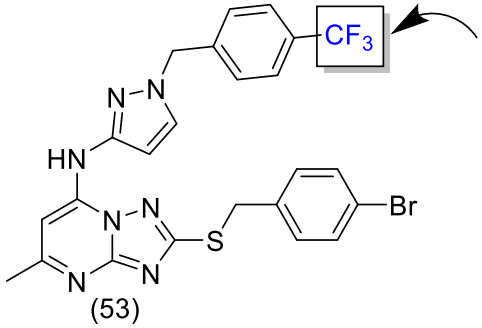


Figure 52: Triazolopyrimidines with anticancer activity

The[1,2,4]triazolo [1,5- a]pyrimidine derivatives **(53)** were tested, against MGC-803, MCF-7, and PC9 "lung adenocarcinoma" cancer cells , and showed the highest activity against MGC-803, MCF-7, and PC9 cell lines.

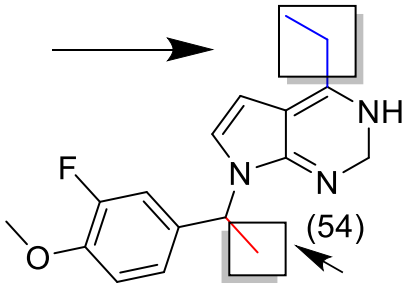


Flourinated Compound have important role in Cytotoxic activity

Figure 53: Fluorinated triazolopyrimidines with cytotoxic effect

Pyrrolopyrimidine derivatives were tested against Hela, MDA-MB-231 , and MDA-MB-426 "human breast cancer cell lines" cancer cells , Compound **(54)** with C-4 ethyl group and a benzylic methyl group exhibited [48] the highest potency in anticancer activity, inhibiting Hela, MDA-MB-231, and MDA-MB-426 cancer cells .

C-4 position should only contain small groups as larger groups will deactivate the compound

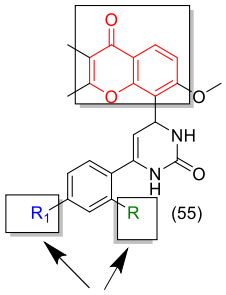


Methyl group at the benzylic position creates steric hindrance and direct the benzyl group to the different positions

Figure 54: Pyrrolopyrimidines showing potent activity against cancer cell lines

The Newly synthesized pyrimidine derivatives **(55)** were tested [8] for their anti-cancer activity against cancer cell lines HeLa, lung A549 & " myelogenous leukaemia" K562 cancer cell lines , the flouro Substituted Compounds showed the highest non-selective anticancer activity against all the cell lines .

Chromone Pharmacophore



R=H, R1=H
R=F, R1=H
R=H, R1=OCF3

floro substituents interestingly showed excellent non-selective anti-cancer activity against all the cell lines. while chloro & bromo substituents have shown moderate activity

Figure 55: Disubstituted pyrimidinones with anticancer activity

The pyrazolopyrimidine derivatives were tested against the MCF-7 cancer cell line and 184B5 (non-malignant mammary epithelial cell) , compound **(56)** showed [34] highest cytotoxicity against MCF-7 cell lines but lower cytotoxicity against the 184B5 normal cell line., which is more active than the reference "Doxorubicin".

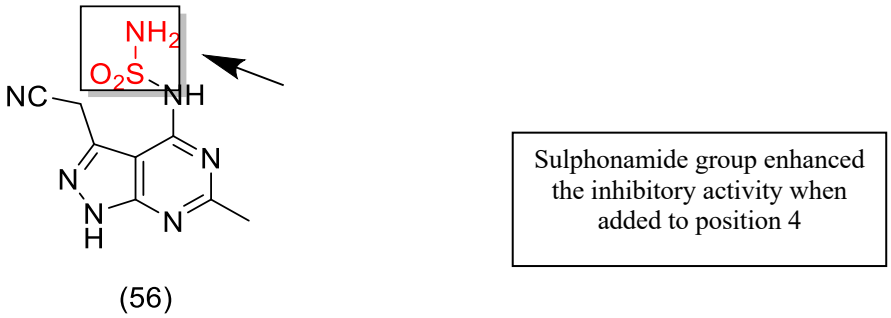


Figure 56: Pyrazolopyrimidnes with enhanced anticancer activity

Derivatives of thieno[2,3-d]pyrimidines were evaluated against human cancer cell lines (HCT-116, HepG2, and MCF-7), compound **(57)** showed [24] the best cytotoxic activities against HCT-116 "colon cancer" and HepG2, and also showed high activity against VEGFR-2 .

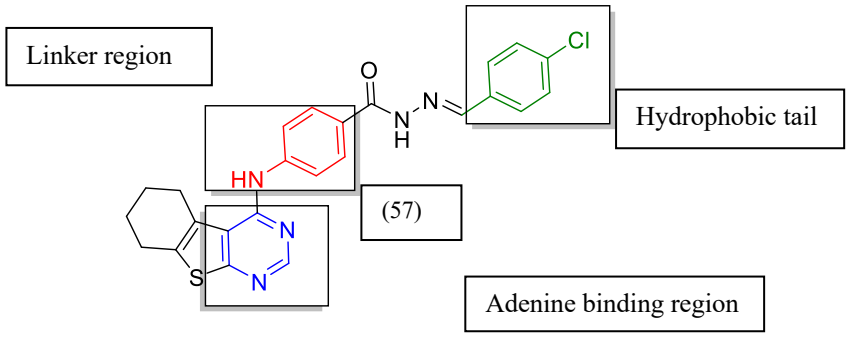
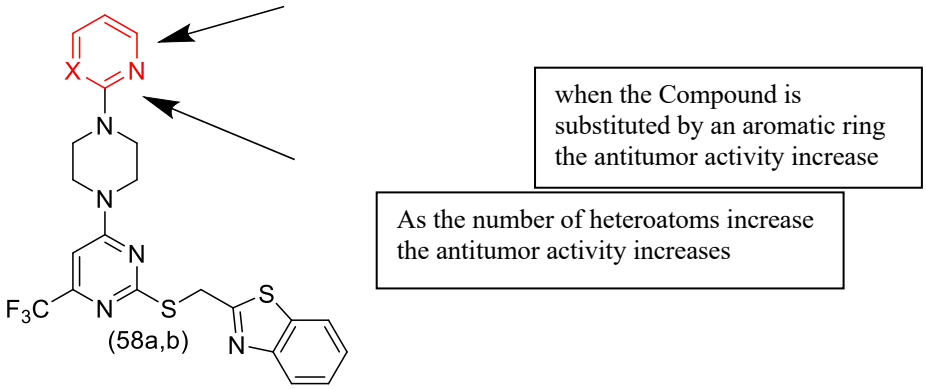


Figure 57: Thienopyrimidines with anticancer activity

Thiopyrimidine derivatives were evaluated [6] for antitumor activities against four cancer cells (EC-109, "human esophageal cancer cells" MGC-803 "human gastric cancer cells" PC-3 "human prostate cancer cells" HepG-2 "human liver cancer cells" GES-1 "human normal gastric mucosal epithelial cells" and HEEC "human normal esophagus cells" , the pyridine and pyrimidine substituted compounds were found the most effective



Compound	X
58a	H
58b	N

Figure 58: Trisubstituted pyrimidines with anticancer activity

The cytotoxic activity of the pyrimidine derivatives were evaluated [7] against 3 different cancerous cell lines (HT-29, MCF-7, T47D and *4-(4-Chlorophenyl)-2-[(4-methylbenzyl)sulfinyl]-6- phenylpyrimidine* **(59)** was found to have the highest cytotoxicity .

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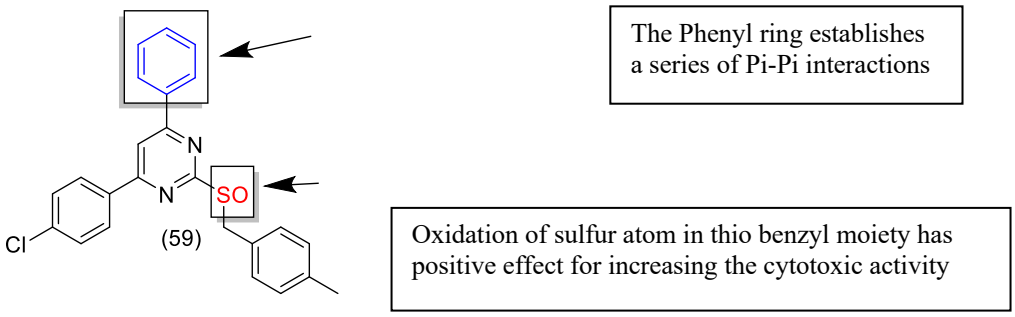


Figure 59: sulfoxide containing pyrimidines

Those Pyrimidine derivatives were tested [12] against three human tumor cell lines HepG2, HCT-116, and mammary MCF-7. Compounds **(56a, b)** were found to have the highest antitumor activity

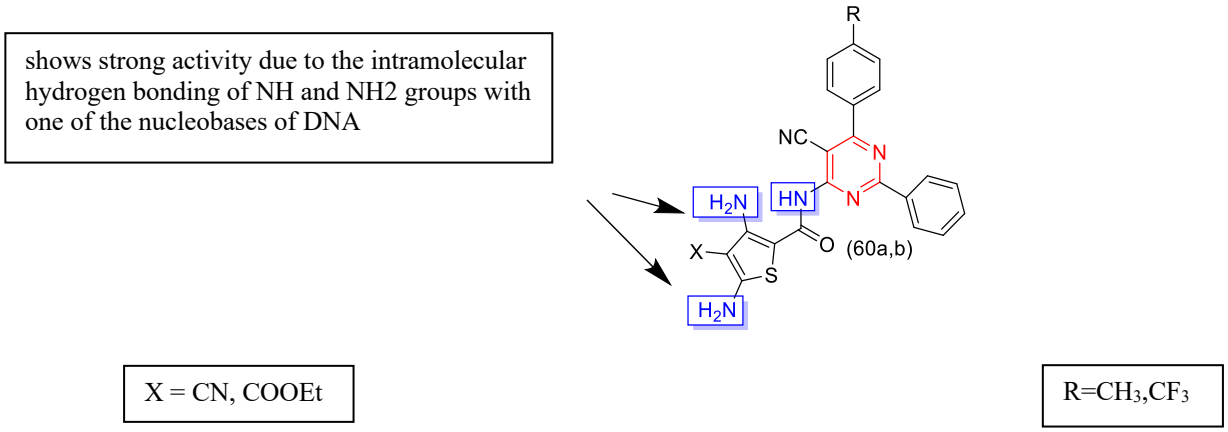


Figure 60: Substituted pyrimidines with high affinity to hydrogen bond formation

The pyrimidine derivatives were tested [11] against 60 human cell lines for primary anticancer screening. Among the tested compounds, Compound (61) was found to have the highest cytotoxic effect.

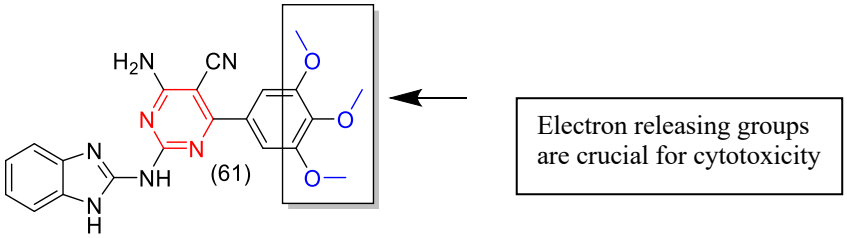
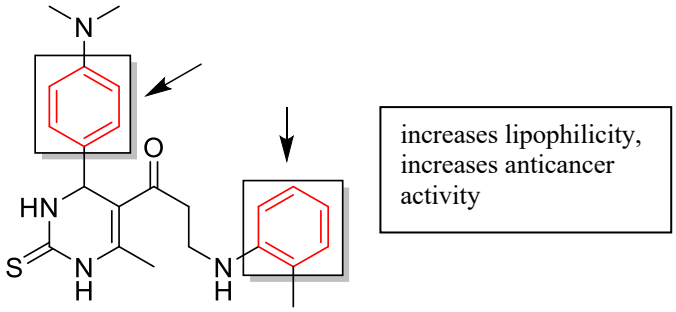


Figure 61: **Substituted pyrimidines with anticancer activity**

In 2021 , indolyl-pyrimidine hybrids were developed [49] & evaluated for anticancer activity , it was found that the compounds that exhibited the best activity was the most lipophilic compounds due to presence of phenyl group on pyrimidine and thiazolidine rings as the following derivative.

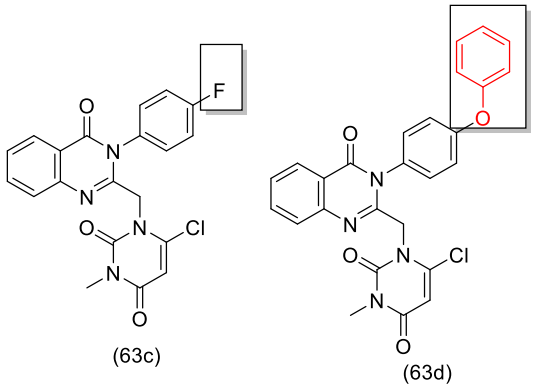


(62)

Figure 62: Thiopyrimidines with high lipophilic groups

In 2024, fused pyrimidinones were synthesized and tested[41] for its anticancer activity, among the prepared products it was found that compounds containing larger groups as phenoxy group in compound (63d) showed enhanced antiproliferative effect by 3-53 folds against MCF-7 and SW-80 cell lines compared to the unsubstituted pyrimidinone (63a) , also introducing a halogen group to the compound as in (63c) improved the activity of the compounds

The floro icreaeses the cytotoxic effect of the compound

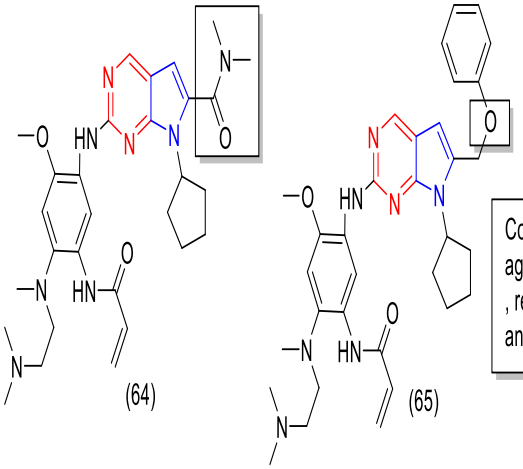


(63c) (63d)

Presence of phenoxy group increases the anticancer activity 3-53 folds

Figure 63: Fused pyrimidinones with anticancer activity

In 2024, Pyrrolopyrimidines were synthesized[42] and evaluated for its EGFR inhibition , it was found that compounds containing oxygen corner (64) showed superior results to the compounds that doesn't (65).

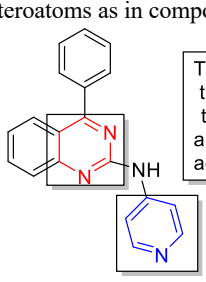


(64) (65)

Compared with 60, the activity of 61 against EGFR was improved significantly , revealing that the oxygen corner may be an important part for binding with kinases

Figure 64 : Pyrrolopyrimidines with anticancer activity

In 2024, quinazoline derivatives were synthesized[50] showing effect against uveal melanoma, it was found that introduction of compounds containing heteroatoms as in compound (66) increased the antiprofilerative activity of the compounds



(66)

The nitrogen atom in quinoline group might affect the activity by forming hydrogen bonds and improving the water solubility, so Pyridine ring was introduced and resulted in improved anti-proliferation activity against MP41 cells

Figure 65: quinazoline derivatives with anticancer effect

In 2024, pyrrolopyrimidine derivatives were synthesized[51] and tested for its kinase inhibition effect , it was found that introducing furan ring , flour group enhanced the activity of compound, also substituent with -I effect on the furan ring elevated the activity of the compound (67).

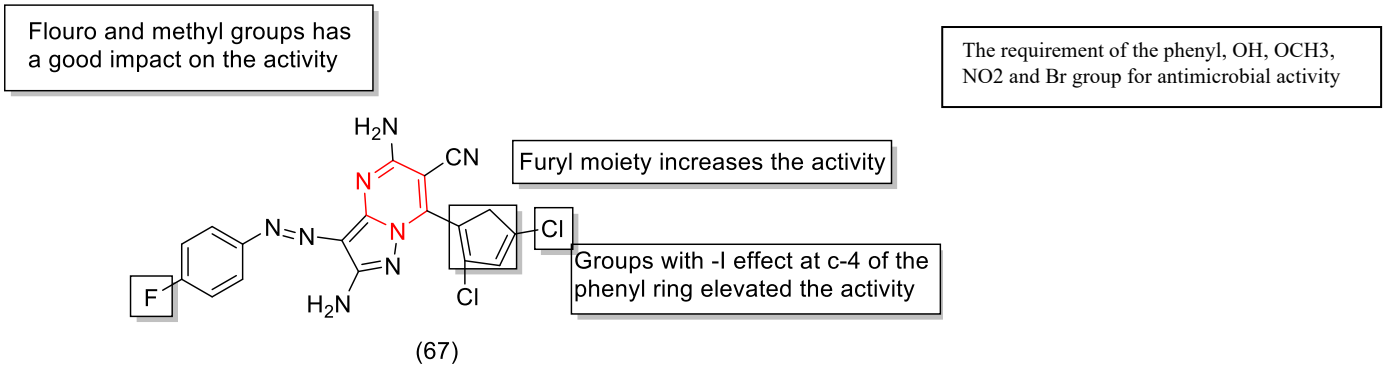


Figure 66: pyrrolopyrimidines with anticancer effect

The anticancer activity of the quinazoline derivative (68) was evaluated[52] against MCF-7 and SW480 cell lines , it was found that the position of the substitution highly affected the effect of the tested compound and that the 3,4 subsitituted phenyl group showed better activity than the other positions .

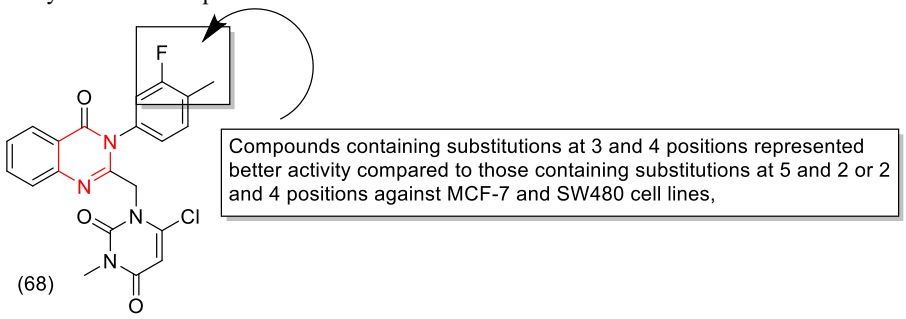


Figure 67: Quinazoline derivatives with anticancer activity

3.2. Pyrimidines as antimicrobial agent:

Pyrano[2,3-d]pyrimidines are an unsaturated heterocyclic as a fusion of pyrimidines and pyrans , These annulated Compounds are considered building blocks, which have an outstanding contribution in the evaluation of antimicrobial activities, , the compounds tested showed different results against different bacteria , compound (65a) showed best broad-spectrum activity against *P. aureus* and *E. coli* bacteria. Compound (65b) exhibited best against *S. aureus* and *K. pneumoniae* bacteria. Compound (65c) exhibited best against *K. pneumonia*. Compound (65d) is best against *S. aureus, P. aureus* and *E. coli* bacteria. Compound (65e) showed the best activity against *B. cereus, S. aureus, P. aureus* and *E. coli*. Compound (65f) exhibited highest activity against S. aureus bacteria and Compound (65g) showed best broad-spectrum activity against *B. cereus* and *E. coli* [53].

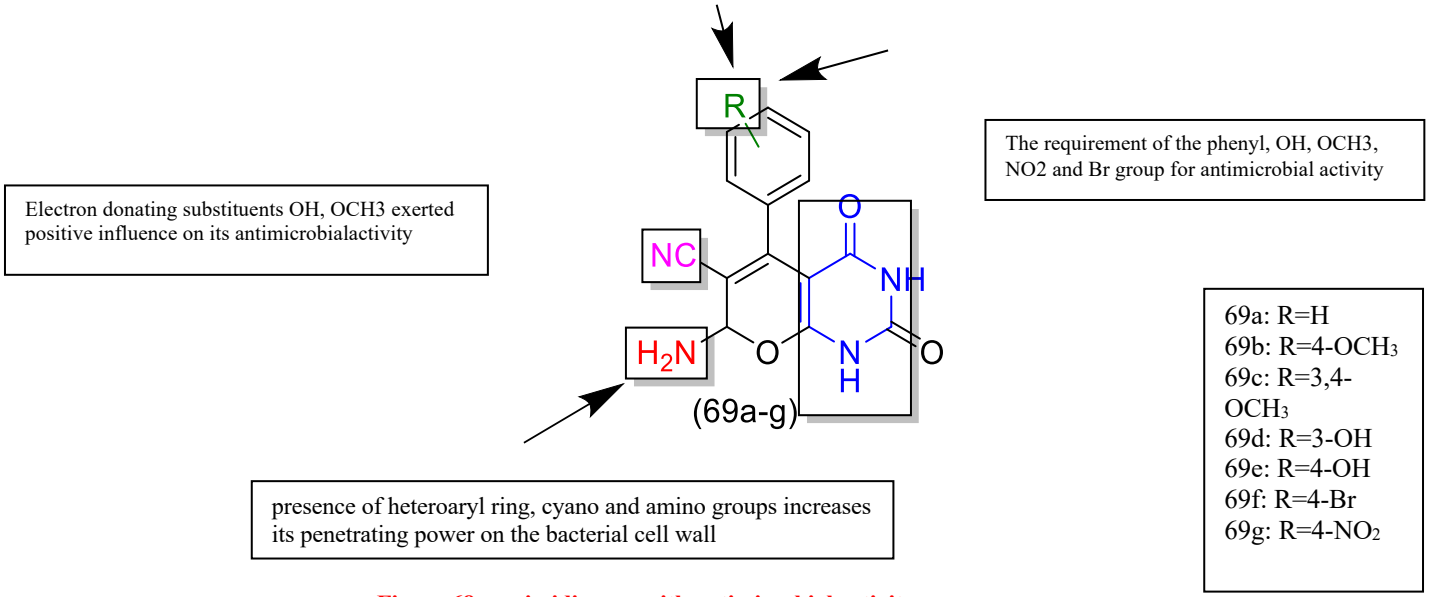
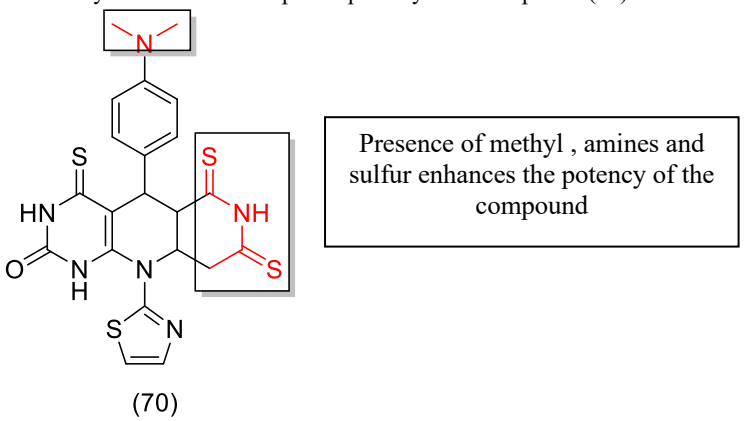


Figure 68: pyrimidinones with antimicrobial activity

Fused pyrimidine analogs were synthesized [49] & evaluated for antimicrobial activity, it was found that the presence of methyl , amines and sulfur substituted pyrimidine moiety increases the compound potency as in compound (70).

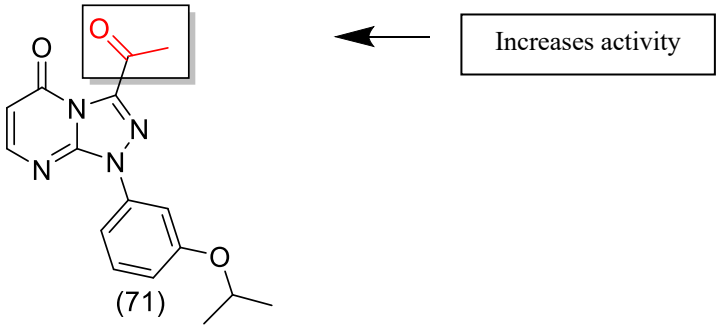


(70)

Figure 69: Fused Pyrimidines with antimicrobial effect

3.3. Pyrimidines as antiviral agents

It was not only tested for its anticancer activity but was also tested for its antiviral effect, it showed [54] the best anti-CHIKV "Chikungunya virus" activity and also cytotoxic effect against breast cancer cell lines MD-AMB-231 and MCF-7.



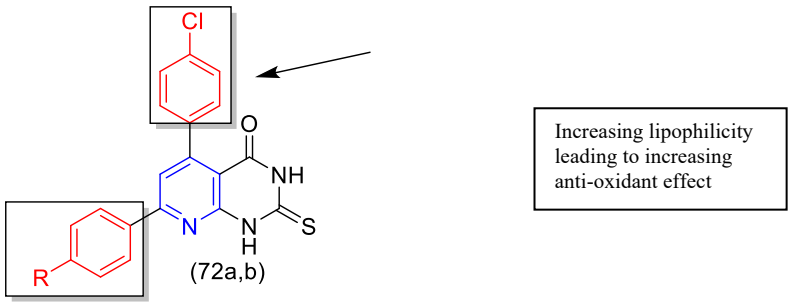
(71)

Figure 70: Pyrimidine derivative with antiviral and anticancer effect

3.4 Pyrimidines as anti-oxidants

It was found that pyrimidine can also act as a powerful anti-oxidant [40] by being a strong reducing agent, after evaluation of its reducing activity, it was proven that as the lipophilicity of the compound increases , its potency increases and those 2 derivatives was found to be the most active in the series tested.

72a	**72b**
R=Cl	R=H



(72a,b)

Figure 71: Fused pyrimidines with antioxidant effect

3.5 pyrimidine as an anti-inflammatory

Analogs of pyrimidine were prepared [49] and tested for anti-inflammatory potential activity, they were tested against ibuprofen , their enhanced activity was found due to the presence of pyrimidine thiol moiety .

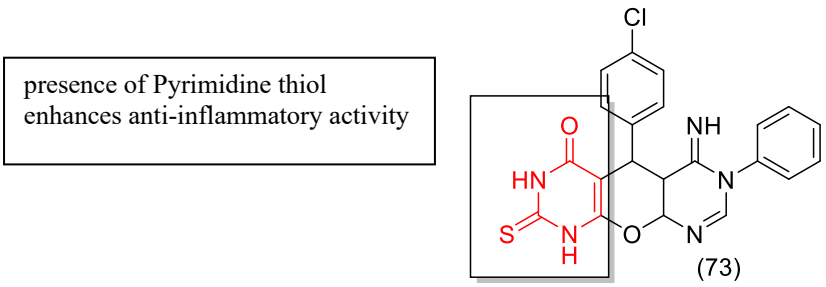


Figure 72: Pyrimidines thiol with anti-inflammatory effect

3.6 Pyrimidine as cardiac agent

Lately pyrimidine derivatives were also evaluated [49] as cardiac agents, it was suggested that its BP lowering effect was due to the presence of substituted pyrimidine scaffold.

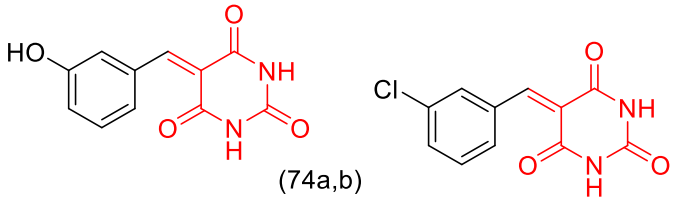


Figure 73: Pyrimidine derivatives with antihypertensive activity

4. Conclusions:

This review highlights the different biological activities of the pyrimidine ring and shows how it has great contribution in the pharmaceutical industry as antimicrobial, antiviral, antidiabetic and its high potential as anticancer, it also shows the different methods and strategies for the synthesis of the pyrimidine ring and its derivatives.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper**.**

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