World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

Check for updates

An overview on synthesis and biological activity of pyrimidines

Mosaad Sayed Mohamed, Samir Mohamed Awad, Neama Abdallah Abd El-tawab * and Naglaa Mohamed Ahmed

Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy, Helwan University, Ain Helwan, Helwan, Egypt.

World Journal of Advanced Research and Reviews, 2022, 15(01), 272–296

Publication history: Received on 05 June 2022; revised on 09 July 2022; accepted on 11 July 2022

Article DOI: https://doi.org/10.30574/wjarr.2022.15.1.0689

Abstract

Pyrimidines represent an important class of heterocycles containing two nitrogen atoms at position 1 and 3 of the six membered ring show wide range of biological activities. Numerous methods for the synthesis of pyrimidine and their diverse reactions offer enormous scope in the field of medicinal chemistry. Pyrimidine possesses wide spectrum of biological activities including antitubercular, antibacterial, antifungal, antiviral, anti-inflammatory, antimalarial, anticancer, and anti-HIV activity. The present review attempts to give brief information about the synthesis and various biological activities of pyrimidines and their derivatives.

Keywords: Pyrimidine; pyrimidine derivatives; Synthesis; Biological activities

1 Introduction

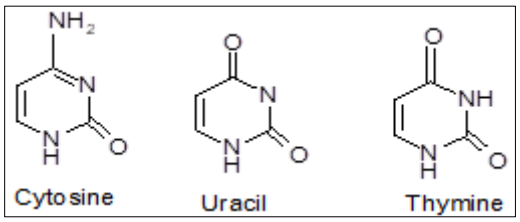


Figure 1 Pyrimidine nucleobases

In medicinal chemistry, the chemist attempts to design and synthesize a medicine or a pharmaceutical agent which will benefit humanity. The practice of medicinal chemistry is devoted to the discovery and development of new agents for treating diseases[1]. The chemistry of heterocyclic compounds is the most important in the discovery of new drugs. The study of these compounds is of great interest both in theoretical as well as practical aspects[2]. Various compounds such as alkaloids, essential amino acids, vitamins, hemoglobin, hormones, large number of synthetic drugs and dyes contain heterocyclic ring systems. There are large number of synthetic heterocyclic compounds like pyrrole, pyrrolidine, furan, thiophene, piperazine, pyridine and thiazole having important application and many are important intermediates in synthesis[3]. Among all heterocyclic compounds, pyrimidines are one of the most important heterocycles exhibiting remarkable pharmacological activities because it is an essential constituent of all cells and thus of all living matter[4]. Pyrimidine is a six-membered heterocyclic ring containing two nitrogen atoms. It contains two nitrogen atoms at positions 1 and 3 of the six-membered ring. Pyrimidine is a much weaker base than pyridine and soluble in water.

* Corresponding author: Neama Abdallah abd El-tawab
Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy, Helwan University, Ain Helwan, Helwan, Egypt.

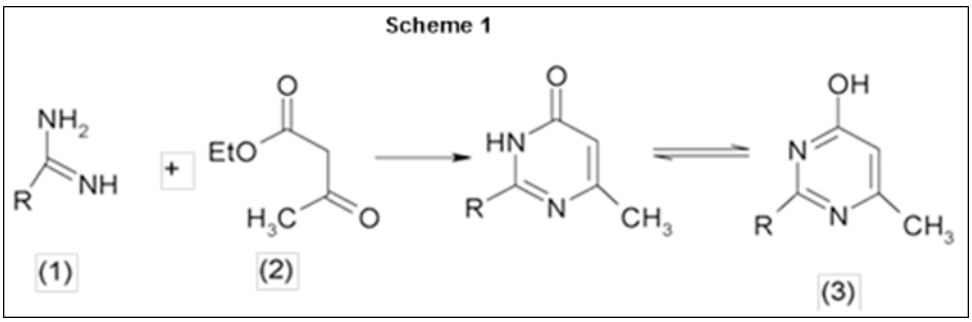
Several pyrimidines have been isolated from the nucleic acid hydrolyses. The metabolism of these pyrimidines is unique and important to understand both biochemical utilization of these compounds and drug metabolism of pyrimidine derivatives[5].

Later, fused pyrimidine chemistry began in 1776, when Scheele isolated uric acid. Pyrimidines are present among the three isomeric diazines. Many simple fused pyrimidines such as purines and pteridines are biologically active by themselves and essential components of very important naturally occurring substances (nucleic acids). Examples of some biologically active pyrimidine derivatives are prazosin, quinethazone, trimethotrexate, folic acid, riboflavin[6].

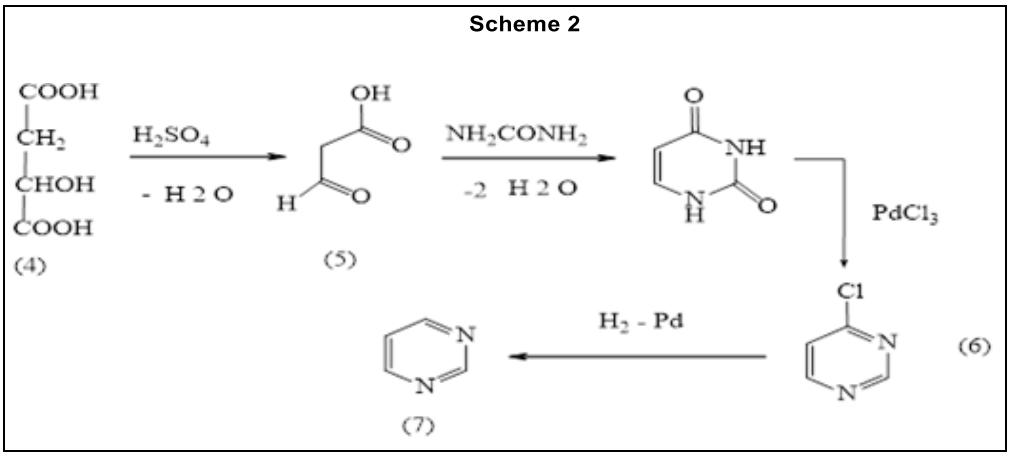
1.1 Synthesis of pyrimidines

Pyrimidines are generally prepared by the condensation between a three carbon compounds and compounds having the amidine structure (**1**) where R= OH (urea), SH or SR (thiourea or its s-derivative) in the presence of catalyst sodium hydroxide or sodium ethoxide. This general reaction may be illustrated by the condensation of acetamidine with ethyl acetoacetate (**2**) to form 4-hydroxy-2,6-dimethylpyrimidine (**3**) [7].

Decarboxylation of malic acid (**4**) with concentrated sulphuric acid forms a ß-ketoacid (**5**) which on reaction with urea produces uracil (**6**). Uracil can be converted to pyrimidine (**7**) in the following step[8].

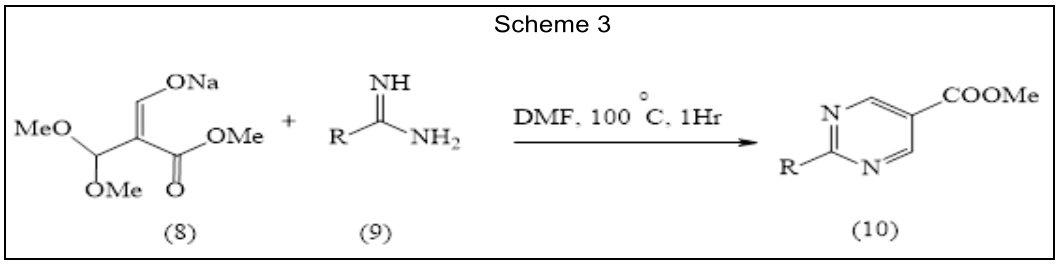


Scheme 1 Synthesis of 4-hydroxy-2,6-dimethylpyrimidine (**3**)



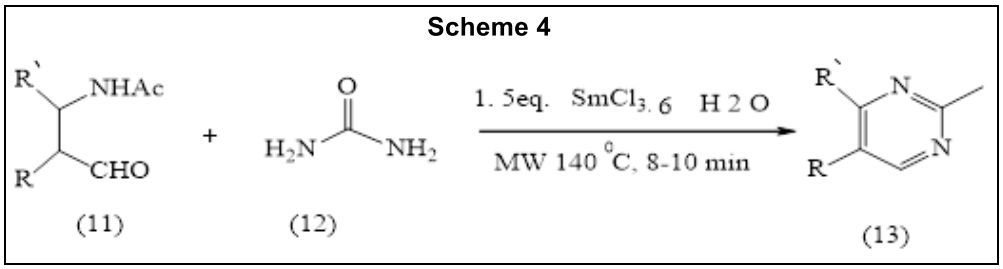
Scheme 2 Synthesis of pyrimidine (**7**) from Uracil

A method for the synthesis of 2-substituted pyrimidine -5-carboxylic esters involves the reaction of sodium salt of 3,3-dimethoxy-2- methoxycarbonylpropen-1-ol (**8**) with a variety of amidinium salts (**9**) to afford the corresponding 2-substituted pyrimidine-5-carboxylic esters (**10**)[9].



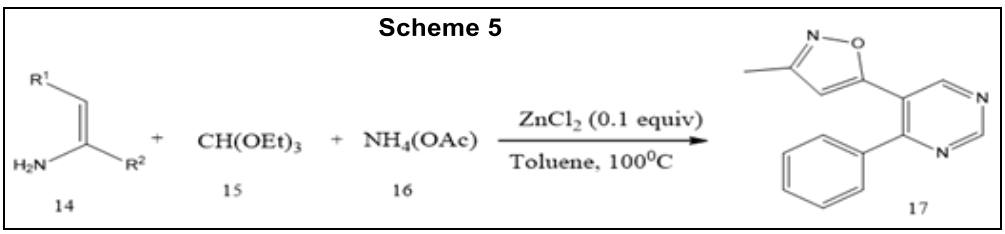
Scheme 3 Synthesis of 2-substituted pyrimidine-5-carboxylic esters (**10**)

Barathkur *et a*l; reported a novel and efficient synthesis of pyrimidine derivatives (**13**) from *ß*-formyl enamide which involves samarium chloride catalyzed cyclisation of *ß*-formyl enamide (**11**) using urea (**12**) as a source of ammonia under microwave irradiation[10].



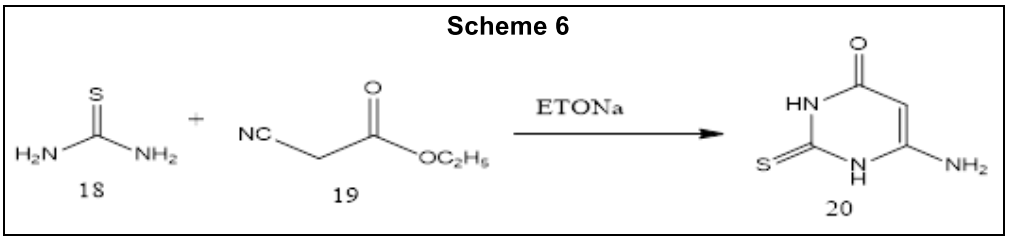
Scheme 4 Synthesis of pyrimidine derivatives (**13**) from *ß*-formyl enamide

Konakahara *et al*. reported the synthesis of 4,5-disubstituted pyrimidine derivatives (**17**) via a $ZnCl_2$-catalyzed three-components coupling reaction involving a variety of functionalized enamines (**14**), triethyl orthoformate (**15**), and ammonium acetate (**16**) [11] .



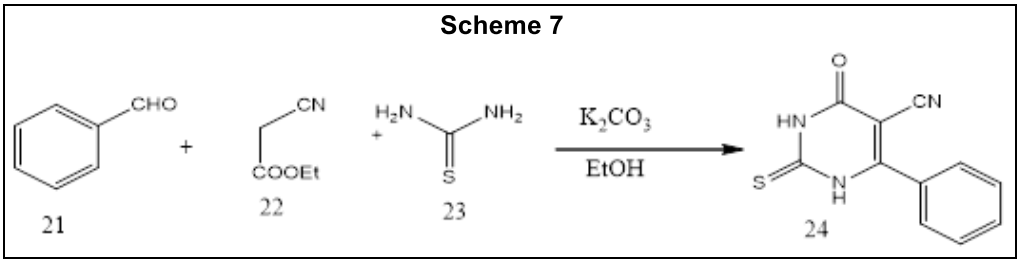
Scheme 5 Synthesis of 4,5-disubstituted pyrimidine derivatives (**17**)

Mosaad *et al*; prepared 6-amino-2-thioxo-2,3-dihydro-1H-pyrimidine-4-one (**20**) by the condensation of thiourea (**18**) with ethyl cyanoacetate (**19**) in sodium ethoxide[12].



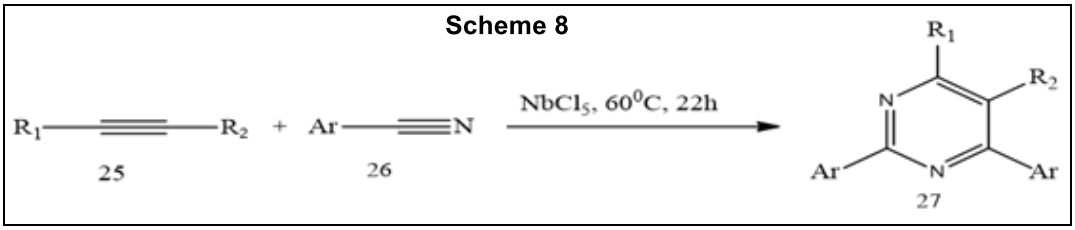
Scheme 6 Synthesis of 6-amino-2-thioxo-2,3-dihydro-1H-pyrimidine-4-one (**20**)

Ebtehal *et al*; reported the synthesis of 6-phenyl-2,4-disubstituted pyrimidine-5-carbonitriles (**24**) via prolonged heating of benzaldehyde (**21**), ethyl cyanoacetate (**22**) and thiourea (**23**) in ethanol, in the presence of potassium carbonate[13].



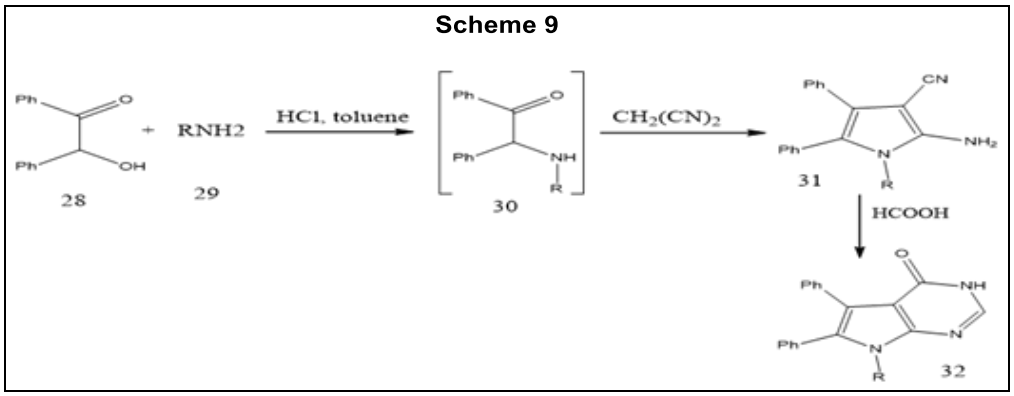
Scheme 7 Synthesis of 6-phenyl-2,4-disubstituted pyrimidine-5-carbonitriles (**24**)

Obora *et al*; reported the preparation of poly substituted pyrimidine derivatives (**27**), in moderate to good yields. By using terminal alkynes with n-octyl, phenyl, and cyclohexyl groups (**25**) and benzonitrile (**26**), in the presence of $NbCl_5$ as a catalyst at 60 ^oC for around 22 h[14].



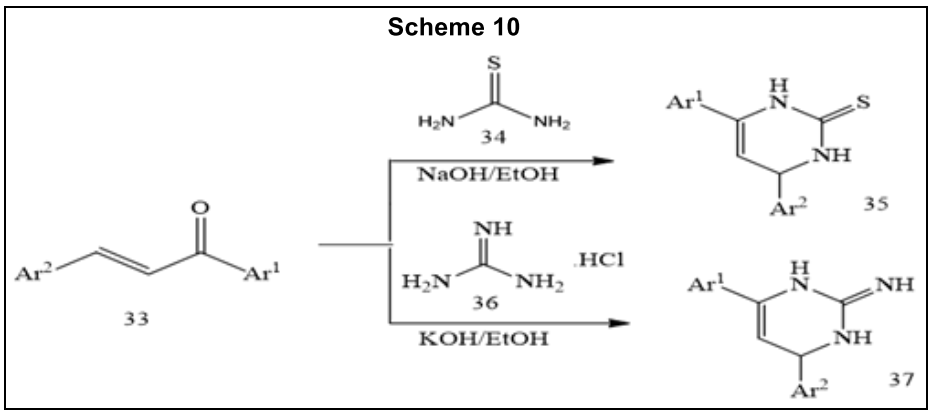
Scheme 8 Synthesis of poly substituted pyrimidine derivatives (**27**)

Mosaad *et al*; prepared pyrrolo[2,3-*d*]pyrimidin-4-ones (**32**) by the Condensation of benzoin (**28**) and primary amines (**29**)in refluxing toluene resulted in the formation of α-aminoketone intermediates (**30**), which were condensed with malononitrile to yield 2-amino-pyrrole-3-carbonitriles (**31**),which were condensed with formic acid to afford the product (**32**)[15].



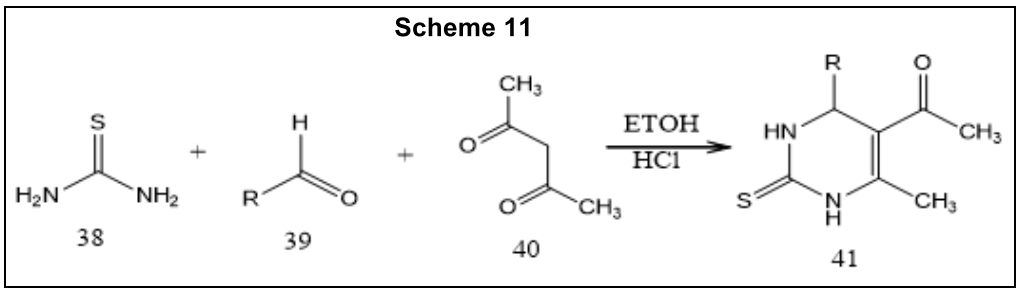
Scheme 9 Synthesis of pyrrolo[2,3-d] pyrimidin-4-ones (**32**)

Yousif *et al*; reported the reaction of α,β-unsaturated ketones (**33**)with thiourea (**34**) in sodium hydroxide to afforded the corresponding thiopyrimidine derivatives (**35**), and with guanidine hydrochloride (**36**) in potassium hydroxide to afford the dihydropyrimidin-2(1H)-imine derivative(**37**)[16].



Scheme 10 Synthesis of thiopyrimidine derivatives (**35**) and dihydropyrimidin-2(1H)-imine derivative (**37**)

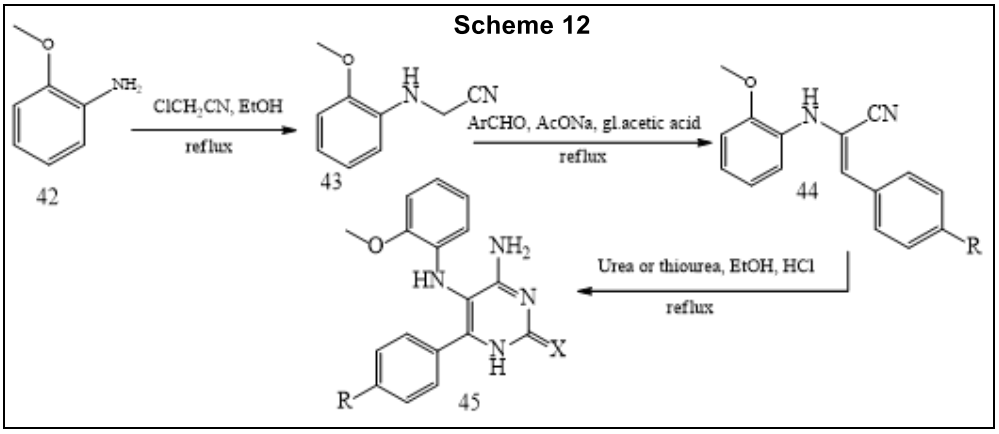
Naglaa *et al*; reported the synthesis of 2-Thioxo-1,2,3,4-tetrahydropyrimidine derivatives (**41**) from condensation of thiourea (**38**), aldehyde (**39**), and ethyl acetoacetate (**40**) in ethanol and few drops of HCl[17].



Scheme 11 Synthesis of 2-Thioxo-1,2,3,4-tetrahydropyrimidine derivatives (**41**)

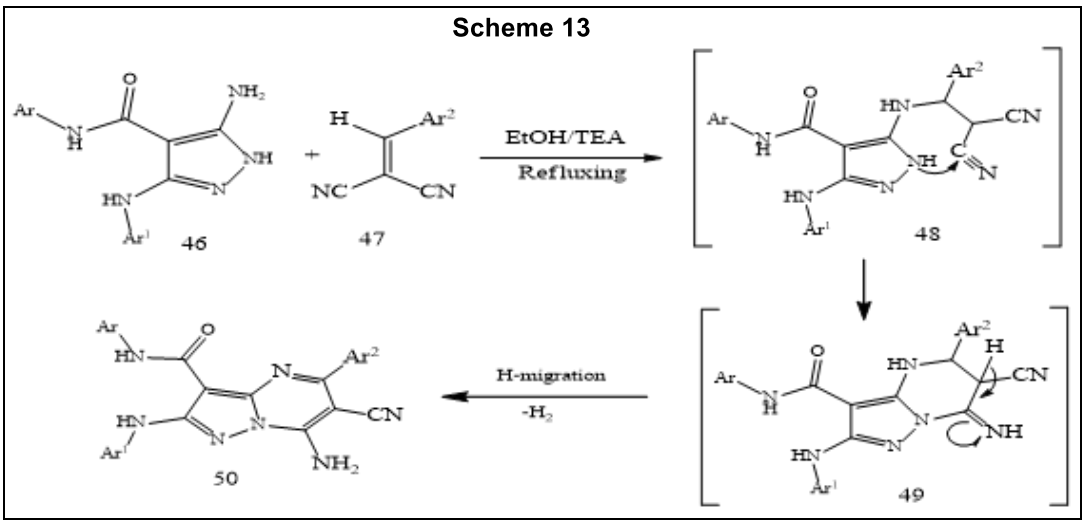
Othman *et al*; reported the reaction of 2-methoxyaniline (**42**) with chloroacetonitrile in ethanol leading to the formation of the key intermediate 2-((2-methoxyphenyl)amino) acetonitrile (**43**), which was treated with different aromatic

aldehydes namely; benzaldehyde and/or 4-methylbenzaldehyde in glacial acetic acid to produce the corresponding acrylonitrile derivatives (**44**), which were subsequently reacted with urea and/or thiourea in refluxing ethanol containing a catalytic amount of HCl to afford the pyrimidine derivatives (**45**)[18].



Scheme 12 Synthesis of pyrimidine derivatives (**45**) from acrylonitrile derivatives

Hassan *et al*; prepared a series of 7-amino-pyrazolo[1,5-a]pyrimidines (**50**) via the reaction of 5-amino-N-aryl-1H-pyrazole-4-carboxamides (**46**) with 2-(arylidene) malononitriles (**47**) in refluxing ethanol to produce the intermediate 5-((2,2-dicyano-1-phenylethyl) amino)-1H-pyrazole derivative (**48**) Furthermore, the cyclic imino group in this intermediate acts as nucleophile to cyano group to obtain 7-imino-pyrazolo[1,5-a]pyrimidine-3-carboxamide derivatives (**49**) that underwent proton shift and oxidation to afford the corresponding 7-amino-pyrazolo[1,5-a]pyrimidine derivatives (**50**)[19].



Scheme 13 Synthesis of a series of 7-amino-pyrazolo[1,5-a] pyrimidines (**50**)

2 Medicinal importance of pyrimidines

The presence of pyrimidine base in thymine, cytosine and uracil, which are the essential building blocks of nucleic acid DNA and RNA, is one possible reason for their widespread therapeutic applications.

Pyrimidine nucleus is present in barbituric acid (**51)** and its several derivatives e.g. Vernal (**52**) which are used as hypnotics[20].

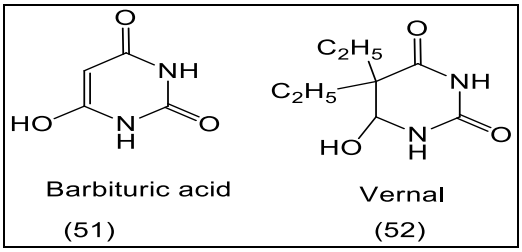


Figure 3 pyrimidine derivatives as hypnotics

In addition to this, pyrimidine nucleus is also found in alloxan (**53**), which is known for its diabetogenic action in a number of animals[21].

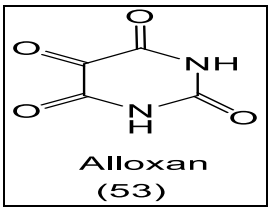


Figure 4 Alloxan as biologically active pyrimidine

2.1 Antimicrobial activity

Drugs which are included in this category are antifolates possessing antagonistic activity against folic acid and sulfa drugs which are Sulphur containing pyrimidine derivative drugs. Examples of folic acid antagonists include Brodiprim (**54**) which is found to be an effective antibacterial compound and Iclaprim (**55**) which is a new selective dihydrofolate inhibitor; it is active against methicillin(22). Trimethoprim (**56**) is an antibacterial drug which selectively inhibits bacterial DHFR[23]. Pyrimethamine (**57**) is a selective inhibitor of the DHFR of malarial plasmodia[24].

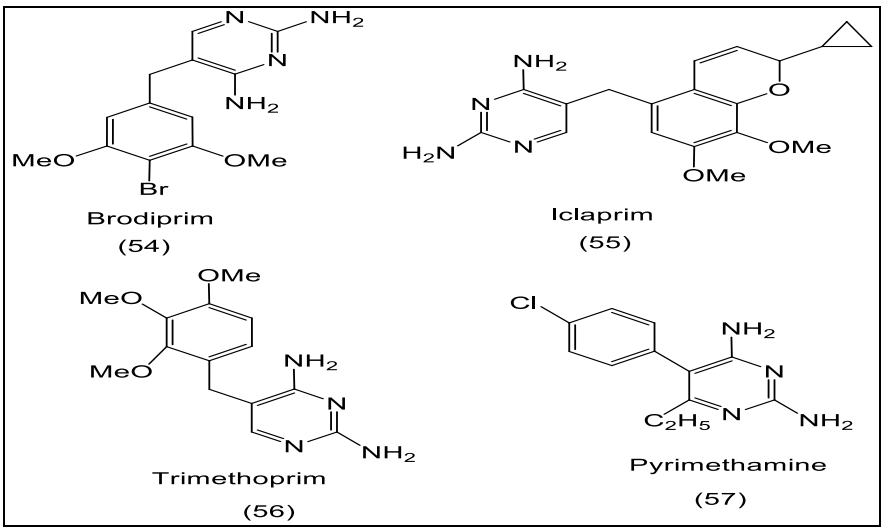


Figure 5 Pyrimidine containing compounds with antimicrobial activity

There are many antibiotics containing pyrimidine moiety such as Amicetine (**58**), Bacimethrin (**59**) and Bleomycin (**60**)[25].

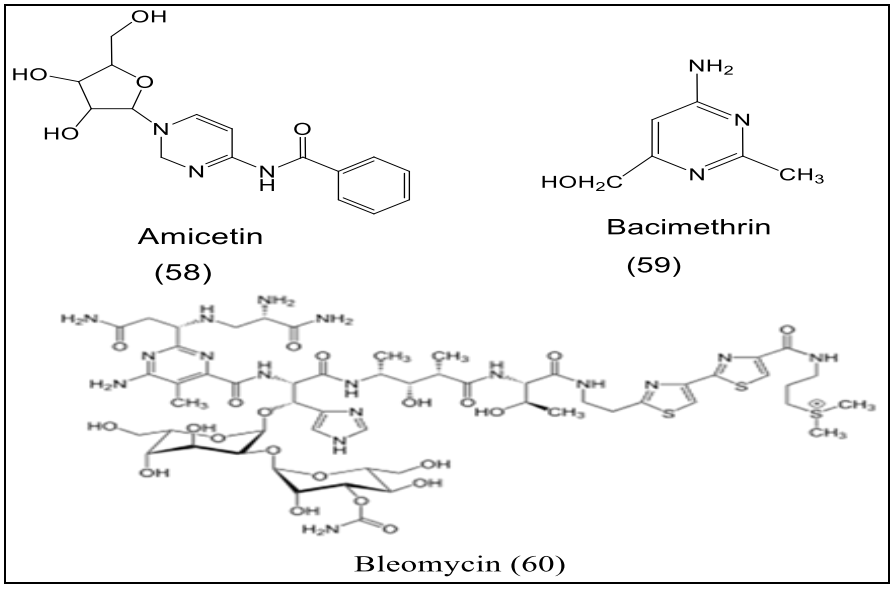


Figure 6 Antibiotics containing pyrimidine

A series of 2, 4, 6-trisubstituted pyrimidines derivatives (**61**) showed significant antibacterial activity when compared with reference standard amikacin and penicillin G against *Bacillus pumilis* and *Escherichia coli*[26].

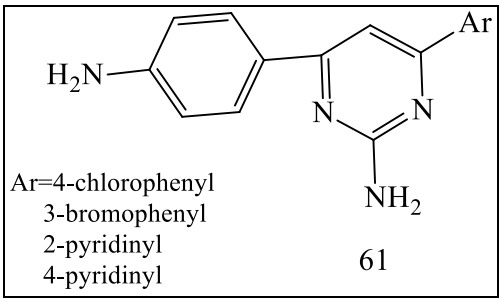


Figure 7: 2, 4, 6-trisubstituted pyrimidines derivatives (**61**) as antibacterial agents

A novel series of indolyl-pyrimidine derivatives (**62- 64**) were synthesized and they showed potent antibacterial activity against *S. aureus, B. cereus, E. coli* compared to the standard drug Penicillin[27].

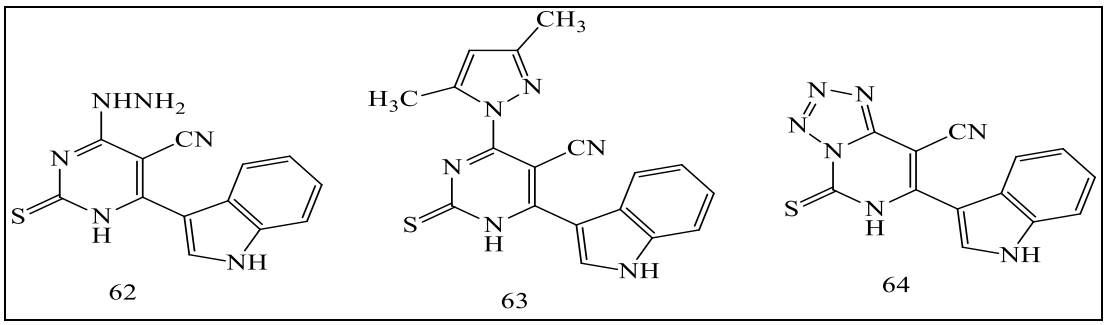


Figure 8 Indolyl-pyrimidine derivatives (**62- 64**) as potent antibacterial agents

Some Novel Substituted Tetrahydro pyrimidine Derivatives (**65- 67**) showed remarkable antimicrobial activity against S. aureus (G+ve) *Pseudomonas aeruginosa* (G-ve), *C. albicans* (yeast), and *A. Niger* (fungus)[28].

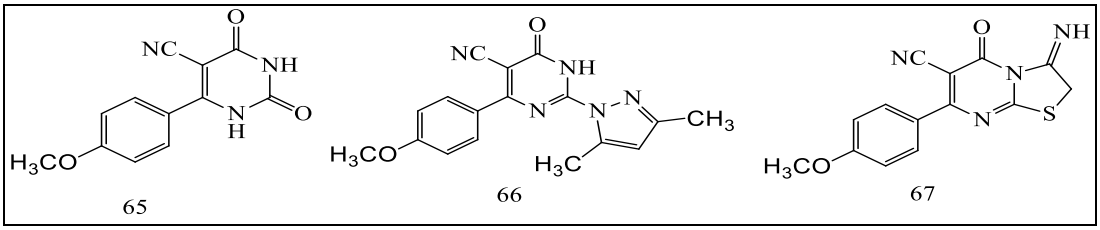


Figure 9 Substituted Tetrahydro pyrimidine Derivatives (**65- 67**) with antimicrobial activity

A series of tetrahydro pyrimidines derivatives (**68**) and (**69**) were synthesized and evaluated for their antibacterial activity and showed high in vitro antibacterial activity against *Escherichia coli, Pseudomonas aeruginosa* and *Staphylococcus aureus*[29].

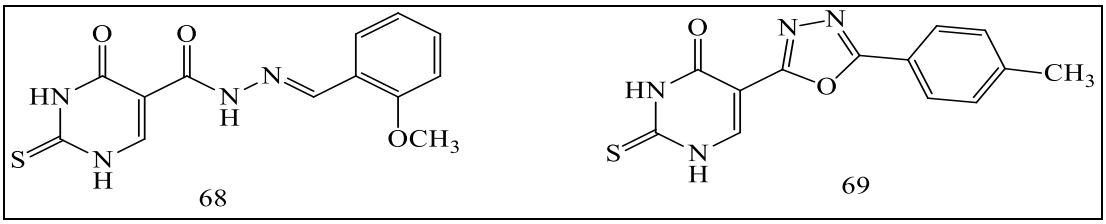


Figure 10 Compound (**68**) and (**69**) as antibacterial agents

A novel series of pyrimidine derivatives were synthesized and evaluated for their antimicrobial activity. Compound (**70**) showed activity against growth of *S. aureus*, and compound (**71**) showed activity against growth of *K. pneumonia*. While compound (**72**) showed activity against growth of both *S. aureus* and *K. pneumonia*[30].

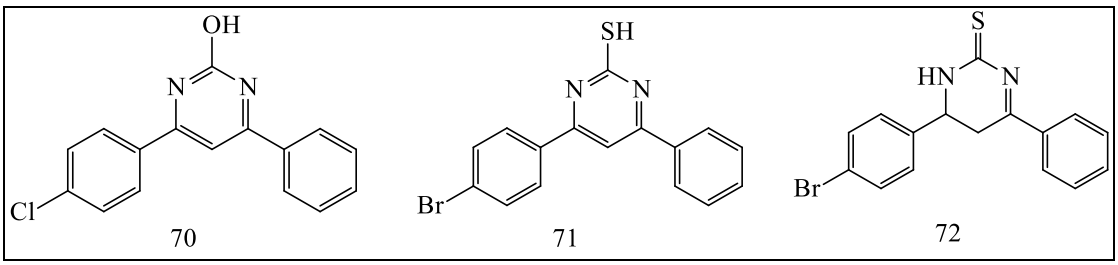


Figure 11 pyrimidine derivatives (**70-72**) with antimicrobial activity against different types of bacteria

2.2 Antiviral activity

Pyrimidines derivatives also possess good antiviral properties; for example, 5-iododeoxyuridine (**73**) .Lamivudine (**74**) is an effective anti-AIDS when used in Combination with Zidovudine also, Zidovudine (**75**) is an analogue of thymidine is active against RNA tumor viruses (retroviruses)[31].

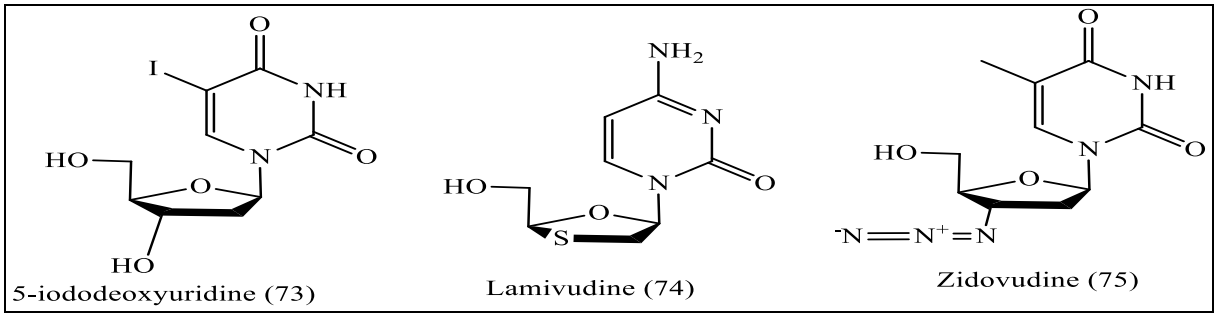


Figure 12 pyrimidine derivatives with antiviral activity

A series of Substituted Pyrimidine glycosides derivatives (**76-78**) were synthesized by Ramiz *et al* and tested for their antiviral activity against HBV using theHepG2.2.2.15-cell line, a human hepatoplastoma cell line producing HBV viral particles, and showed moderate viral replication inhibition and mild cytotoxicity[32].

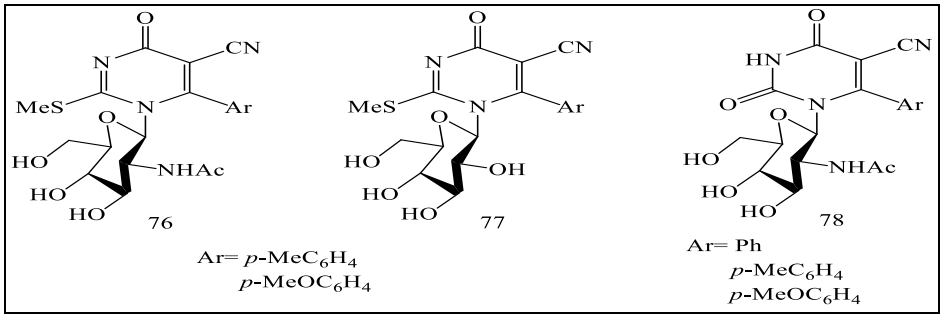


Figure 13 Substituted Pyrimidine glycosides derivatives (**76-78**) with antiviral activity against HBV

Novel chiral amino-pyrimidine derivatives (**79**) and (**80**) were synthesized in economic and straightforward method and showed excellent antiviral activities against tobacco mosaic virus (TMV) superior to the commercial antiviral agent ningnanmycin[33].

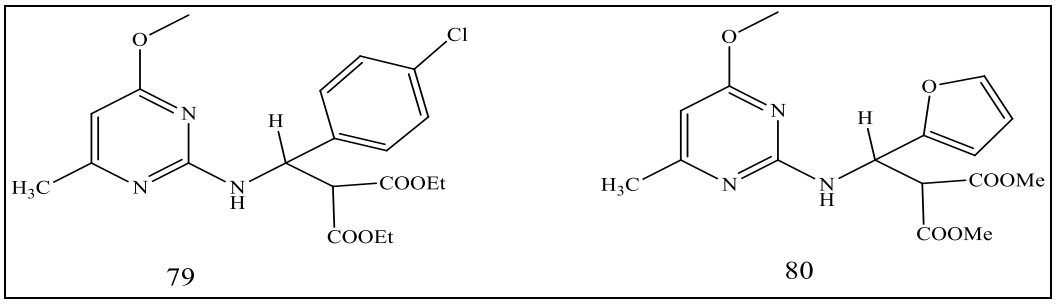


Figure 14 chiral amino-pyrimidine derivatives (**79**) and (**80**) with antiviral activity against (TMV)

A series of novel substituted 2-pyrimidylbenzothiazoles derivatives (**81**) and (**82**) were synthesized and evaluated for its antiviral potency by a plaque reduction assay against HSV-1, CBV4, HAV HM 175, HCV cc genotype 4 viruses and HAdV7, which showed a high level of potency against HSV-1 and a combination of the potent synthesized compounds with acyclovir led to IC50 values lower than that of acyclovir alone[34].

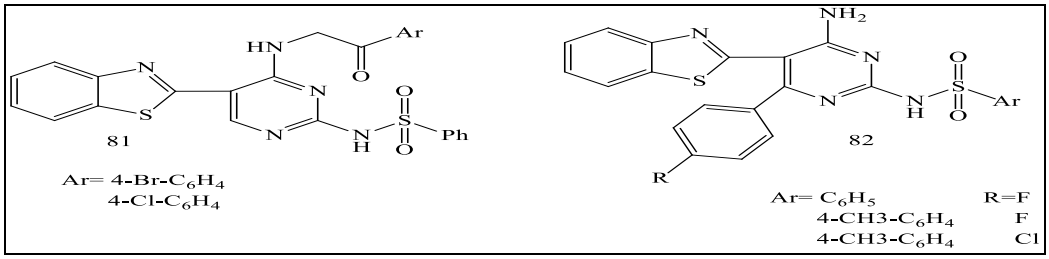


Figure 15 substituted 2-pyrimidylbenzothiazoles derivatives (**81** and **82**) with potent antiviral activity against HSV-1

Some Uracil Nucleosides derivatives (**83**) and (**84**) were synthesized by Awad *et al* and evaluated for their antiviral activity against Herpes Simplex Virus 1. The newly synthesized compounds showed activity against HSV-1 equal to or higher than the standard drug acyclovir[35].

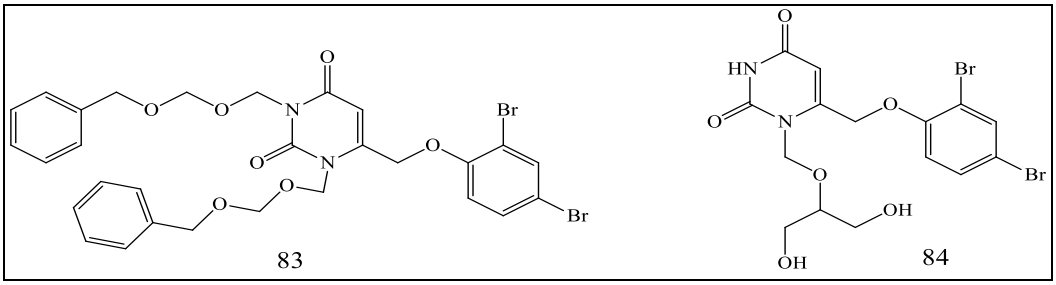


Figure 16 Uracil Nucleosides derivatives (**83**) and (84) with antiviral activity against Herpes Simplex Virus 1

2.3 Antifungal activity

Pyrimidines also exhibit antifungal properties, Flucytosine (**85**) is a fluorinated pyrimidine and is an orally active antifungal agent, which is used for the treatment of serious systemic infections caused by susceptible strains of *Candida Cryptococcus*[36], also Voriconazol (**86**) is a disubstituted drug used a s a broad spectrum antifungal agent[37].

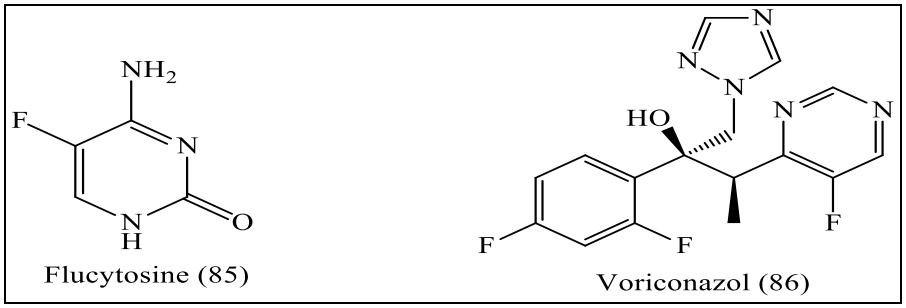


Figure 17 Flucytosine (**85**) and Voriconazole (**86**) as pyrimidine derivatives with antifungal activity

A novel series of 2-thiouracil-5-sulfonamide derivatives were synthesized and investigated for in vitro antibacterial, antifungal and antiviral activities , where substitution at position 5 of 2-thiouracil gave active compounds (**87**) and (**88**)[38].

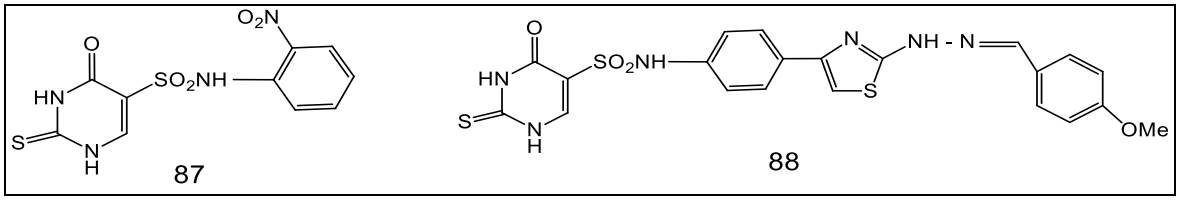


Figure 18 2-thiouracil-5-sulfonamide derivatives (**87** and **88**) with antifungal activity

A series of new pyrimidine derivatives (**89**) and (**90**) were synthesized and their antifungal activities were evaluated in vitro against fourteen phytopathogenic fungi by poisoned food technique, and showed better activity than the lead compound, pyrimehanil to *Gibberella fujikuroi* (GF)[39].

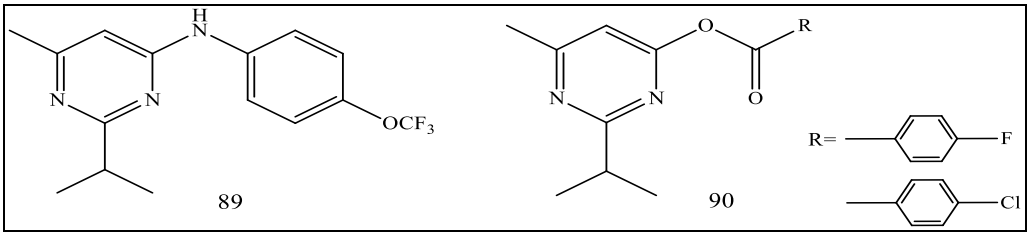


Figure 19 pyrimidine derivatives (**89**) and (**90**) with antifungal activity against *Gibberella fujikuroi*

A novel pyrimidine derivatives (**91**) and (**92**) were screened for their antifungal activity against *Aspergillus Niger* in Sabouraud's dextrose agar , and showed significant antifungal activities compared with that of standard itraconazole[40].

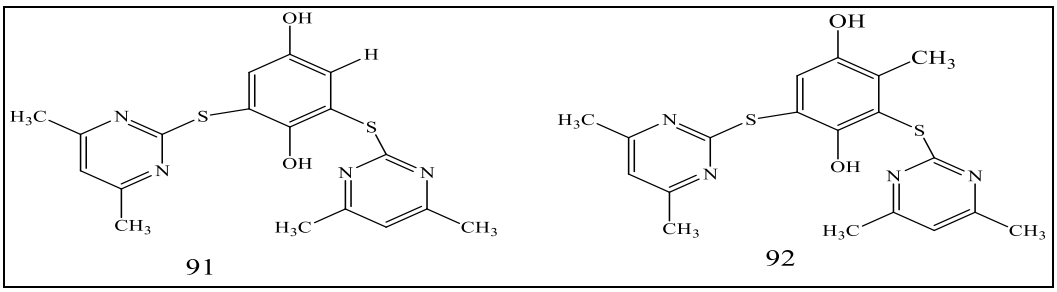


Figure 20 pyrimidine derivatives (**91**) and (**92**) with antifungal activity against *Aspergillus Niger*

The antifungal activities of newly synthesized Pyrimidine derivatives were evaluated for their in vitro antifungal activities against the pathogenic fungi, including *B. dothidea*, *Phompsis sp*., and *B. cinerea* by the poison plate technique. Compound 5-bromo-2-fluoro-N-(3-((2-methyl-6-(trifluoromethyl)pyrimidin-4-yl)oxy)phenyl)benzamide (**93**) exhibited excellent antifungal activity against *Phompsis sp*. with the EC50 value of 10.5 μg /ml, which were even better than that of Pyrimethanil[41].

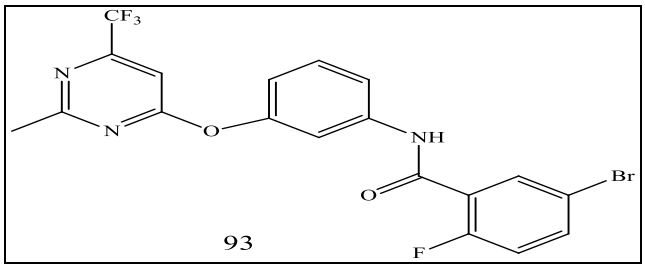


Figure 21 compound (**93**) with antifungal activity against *Phompsis sp.*

2.4 Antineoplastic and anticancer agents

There are many pyrimidine-based antimetabolites. They are usually structurally related to the endogenous substrates that they antagonize. One of the early metabolites prepared was 5-fluorouracil (5-FU) (**94**). 2-Thiouracil (**95**) also exhibits some useful antineoplastic activities[42].

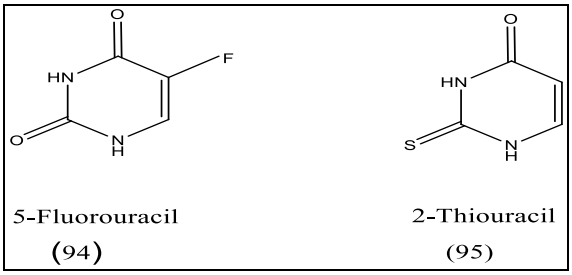


Figure 22 pyrimidine-based antimetabolites with antineoplastic activities

A series of 6-thioxopyrimidines derivatives was synthesized and evaluated for their antitumoral activity against 60 tumoral cell lines, where presence of a benzyl group on N-3 give active compound against all CNS cancer lines. (**96**)[43].

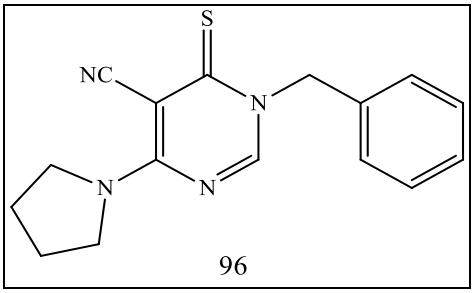


Figure 23 Compound (**96**) with CNS anticancer activity

A novel thiopyrimidine-5-carbonitrile derivative (**97**) was synthesized and its anticancer activity evaluated using three human cell lines of Breast (MCF7), Colon (HCT116) and Liver (HEPG2) cancers, which was highly selective to inhibit three cell lines in comparison with the antitumor agent 5-Flurouracil as a control[44].

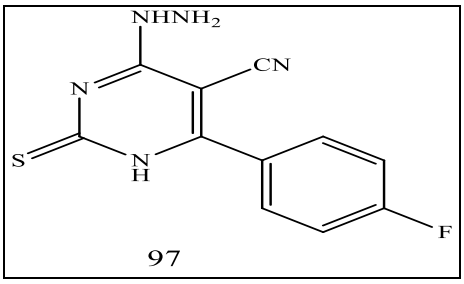


Figure 24 Compound (**97**) with anticancer activity

Recently, some thiopyrimidines (**98**) and (**99**) were prepared and proved to be active against colon and breast cancer[45].

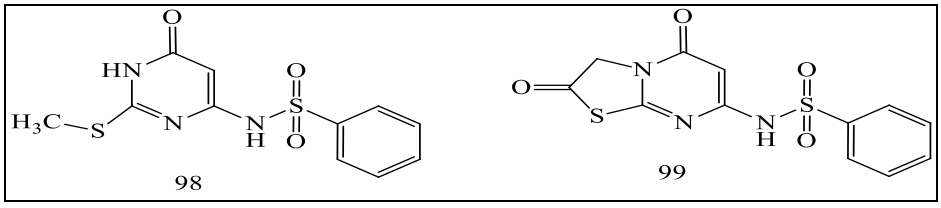


Figure 25 Thiopyrimidines (**98**) and (**99**) with anticancer activity against colon and breast cancer

A series of thiopyrimidines derivatives (**100**) and (**101**) was synthesized and evaluated for their in vitro antiproliferative activities against HePG-2, MCF-7, HCT-116, and PC-3 cell lines, and showed potent anticancer activity with IC50 values between 1.57±0.08 and11.9±0.39μM toward the tested cell lines[46].

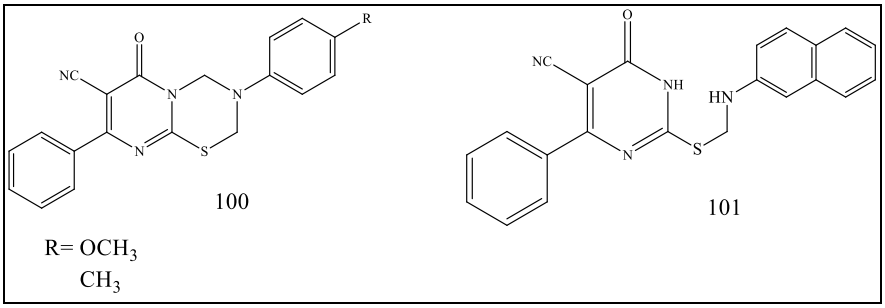


Figure 26 Compound (**100**) and (**101**) with potent anticancer activity

A novel series of pyrimidinone-5-carbonitriles derivatives (**102**) was synthesized and displayed potent cytotoxic activity against MCF-7 and Caco-2 cell lines[47].

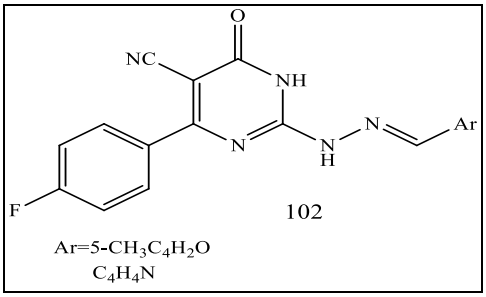


Figure 27 pyrimidinone-5-carbonitriles derivatives (**102**) with cytotoxic activity

A novel series of pyrimidine pyrazoline-anthracene derivative(**103**) was synthesized and screened in vitro against two hepatocellular carcinoma (HCC) cell lines (HepG2 and Huh-7) as well as normal fibroblast cells by resazurin assay, and showed potent anticancer activities against HepG2 and Huh-7 cell lines (IC50=5.34 and 6.13 μg/mL, respectively) comparable to that of doxorubicin (DOX) activities[48].

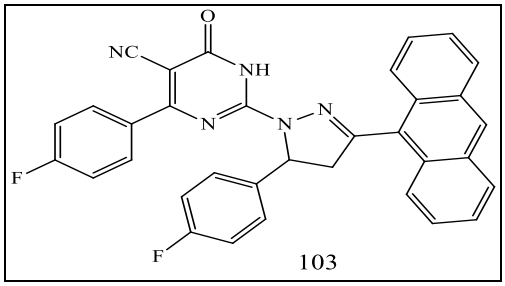


Figure 28 pyrimidine pyrazoline-anthracene derivative (**103**) with anticancer activities

Thiopyrimidine derivative (**104**) was synthesized and In-vitro screened for its potential use as anti-cancer agents, and showed significant and selective antiproliferative activity against MCF-7 cancer cell line with minimal cytotoxic effect[49].

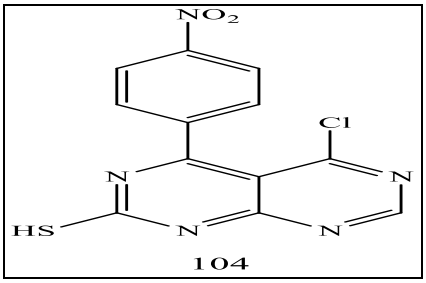


Figure 29 Thiopyrimidine derivative (**104**) with antiproliferative activity against MCF-7 cancer cell line

A novel indolyl-pyrimidine hybrid (**105**) was synthesized and evaluated in vitro and in vivo for its antitumor activity against MCF-7, HepG2, and HCT-116 cancer cell lines, as well as against WI38 normal cells using the resazurin assay, and showed potent antiproliferative activity against these cell lines (IC50 = 5.1, 5.02, and 6.6 μM, respectively) comparable to the standard treatment (5-FU and erlotinib), and showed potent EGFR inhibitory activity equal to that of the reference treatment (erlotinib)[50].

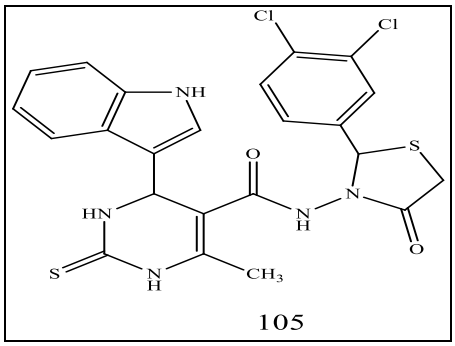


Figure 30 indolyl-pyrimidine hybrid (**105**) with potent EGFR inhibitory activity

A series of Thiazolo[4,5-d] pyrimidine derivatives were synthesized and assessed the antiproliferative properties against human cancer (A375, C32, DU145, MCF-7/WT) and normal (CHO-K1 and HaCaT) cell lines. Compound (**106**) proved to be promising anticancer agent[51].

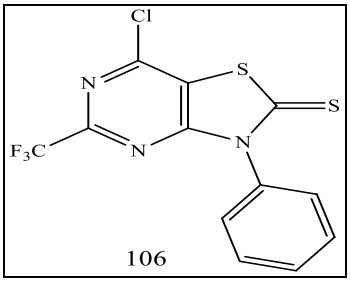


Figure 31 Compound (**106**) as anticancer agent

2.5 Antihyperlipidemic activity

CJ Shishoo *et al*; have prepared some 2-substituted-6-phenyl and 7-phenyl thieno[3,2-d]pyrimidin-4-ones through cyclocondensation of the corresponding thiopheno amino esters with a variety of nitriles in the presence of dry hydrogen chloride gas and reported anti-hyperlipidemic activity in a few thieno pyrimidines (**107**)[52].

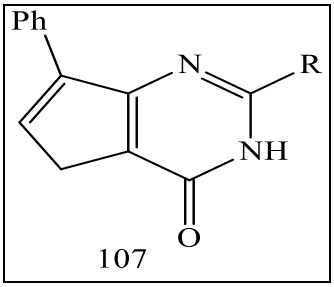


Figure 32 Compound (**107**) with anti-hyperlipidemic activity

Pyrimidine derivatives (**108**) showed antihyperlipidemic action, mediated possibly through HMGCOA inhibition, hepatoprotection, antioxidant, and anti-inflammatory pathways[53].

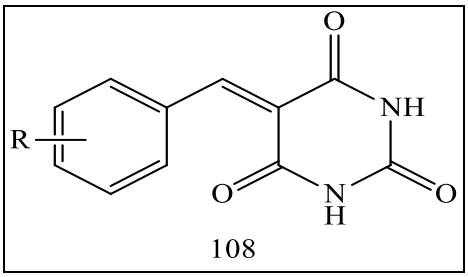


Figure 33 Pyrimidine derivatives (**108**) as antihyperlipidemic agent

2.6 Drugs for hyperthyroidism

2-Thiouracil and its alkyl analogue, thiobarbital are effective drugs against hyperthyroidism. Propylthiouracil (**109**) is used as a drug for hyperthyroidism with minimum side effects[54].

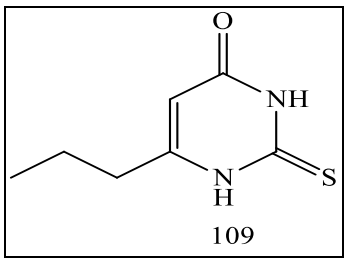


Figure 34 Propylthiouracil (**109**) as a drug for hyperthyroidism

Awad *et al*; prepared series of pyrimidine-5-Sulphonamides derivatives (**110**) and evaluated for their anti-hyperthyroid activity by using a thyroxine-induced hyperthyroid model, and showed a comparable effect in decreasing the mean serum level of T3 to that of PTU[55].

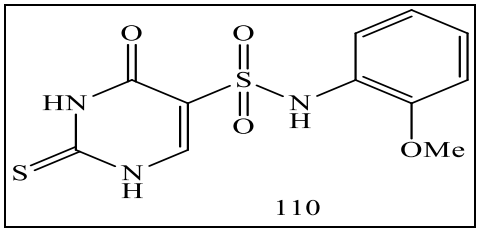


Figure 35 pyrimidine-5-Sulphonamides derivatives (**110**) with anti-hyperthyroid activity

2.7 Anthelmintics

These drugs have the ability of ridding the body of parasitic worms. Pyrantel pamoate (**111**) is a depolarizing neuromuscular blocking agent that causes spastic paralysis in helminths and is employed in the treatment of infestations caused by pinworms and round worms[56].

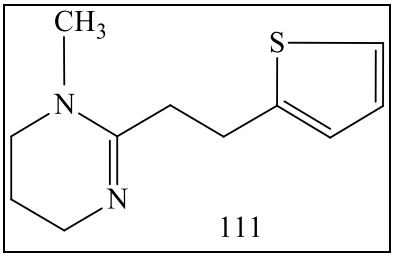


Figure 36 Pyrantel pamoate (**111**) as Anthelmintic agent

Series of pyrimidine derivatives (**112**) were synthesized and investigated for their in vitro anthelmintic properties, and showed comparable anthelmintic activity to that of Albendazole, and could be used as alternative anthelmintic agents to combat the resistance that will certainly follow the use of monotherapy in helminthiasis[57].

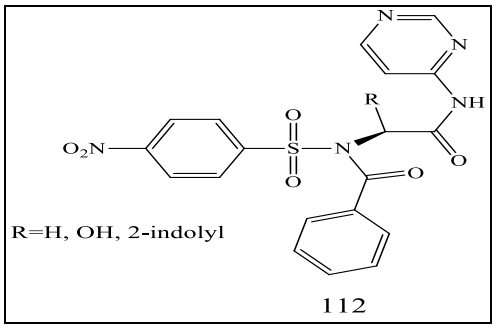


Figure 37 pyrimidine derivatives (**112**) with anthelmintic activity

2.8 Antitubercular activity

Capreomycin (**113**) produced by Streptomyces capreolus is a second line bacteriostatic antitubercular drug containing pyrimidine[58].

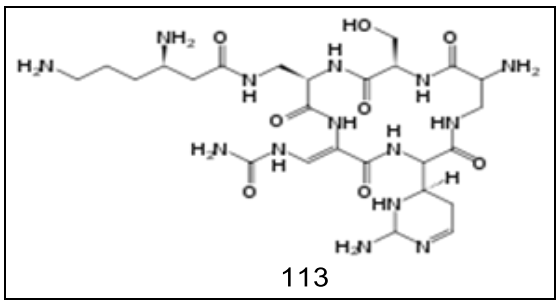


Figure 38 Capreomycin (**113**) as antitubercular drug containing pyrimidine

Viomycin (**114**) is more tuberculostatic than *p*-amino salicylic acid. It is effective in the treatment of experimental tuberculosis[59].

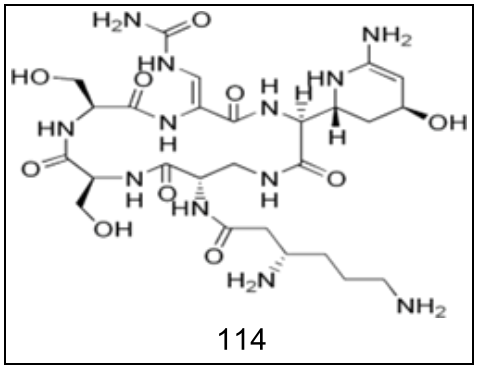


Figure 39 Viomycin (**114**) as antitubercular drug containing pyrimidine

Novel pyrimidine derivatives were synthesized, and their antimycobacterial activities were evaluated. The presence of 2-isopropoxy-5-methyl-4-(piperidin-4-yl)aniline at position 2 of the pyrimidine nucleus give active compound (**115**) against Mycobacterium tuberculosis (Mtb)[60].

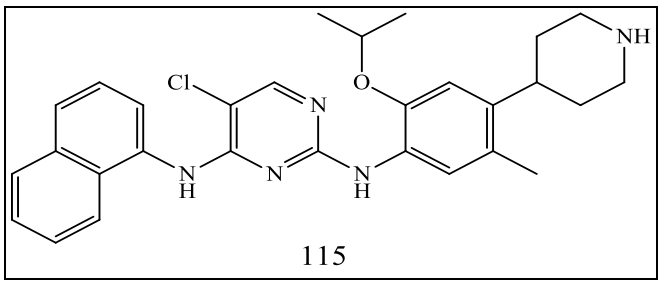


Figure 40 compound (**115**) with activity against Mycobacterium tuberculosis

2.9 Anxiolytic agents

Few of the pyrimidine derivatives are also used as anxiolytics. Most important of these is buspirone, (**116**) indicated in the management of anxiety disorders accompanied with or without depression(61). A simple pyrimidine derivative, mezilamine (**117**) is classified as antipsychotic agent[61].

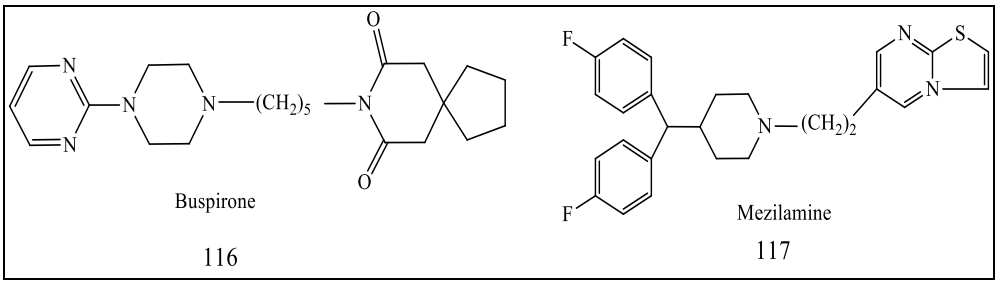


Figure 41 Examples of pyrimidine derivatives used as anxiolytics

A series of pyridofuro[3,2-d] pyrrolo[1,2-a] pyrimidines, pyridofuro[3,2-d] pyrido[1,2-a] pyrimidines and pyridofuro[3′,2′:4,5] pyrimido[1,2-a]azepines were synthesized and The anticonvulsant activity combined by some psychotropic properties of pyrimidine derivatives was evaluated. Compound (**118**) showed good anxiolytic activity[62].

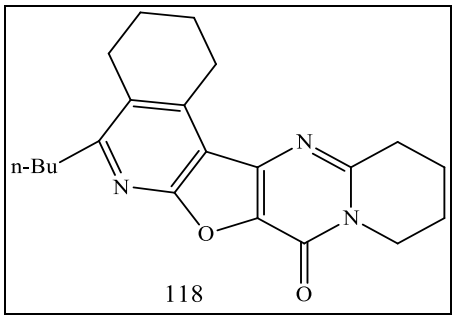


Figure 42 Compound (**118**) with good anxiolytic activity

2.10 Anti-inflammatory activity

The anti-inflammatory activity of novel pyrimidine derivatives (**119**) and (**120**) was investigated in comparison with ibuprofen as standard anti-inflammatory agent, and showed higher activity than ibuprofen[12].

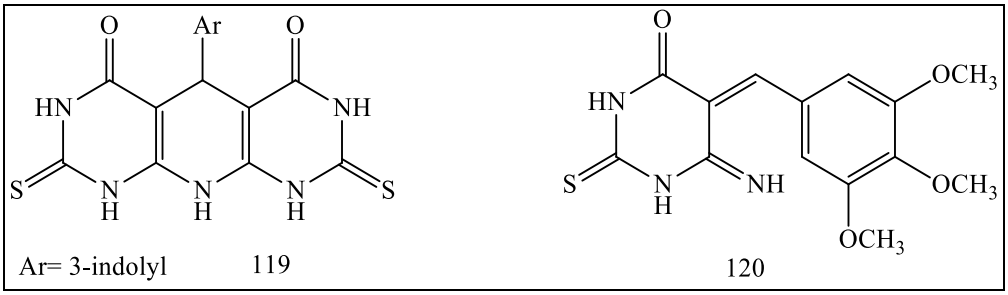


Figure 43 pyrimidine derivatives (**119**) and (**120**) with anti-inflammatory activity

A series of thieno[2,3-d][1,2,4]triazolo[1,5-a]pyrimidine derivatives(**121-123**) were synthesized and evaluated for their anti-inflammatory and analgesic activity using diclofenac Na as a reference standard, and proved to display distinctive anti-inflammatory activity as well as good analgesic profile with a delayed onset of action[63].

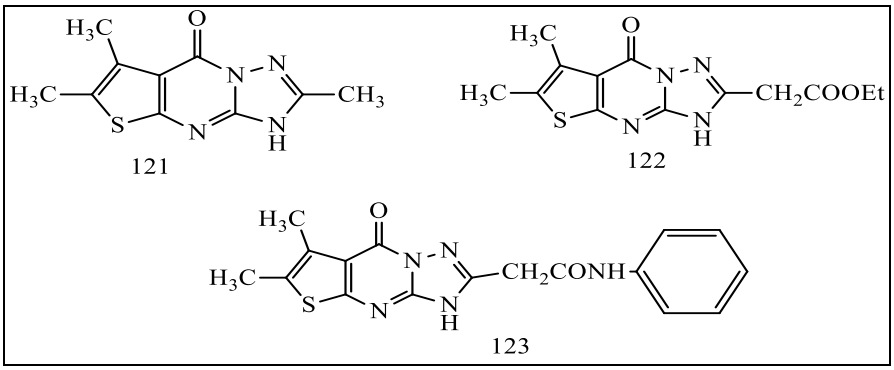


Figure 44 Thieno[2,3-d] [1,2,4] triazolo[1,5-a] pyrimidine derivatives (**121**-**123**) with anti-inflammatory activity

Novel pyrimidin-2-thione derivatives (**124**) and (**125**) were synthesized and examined for their anti-inflammatory activity using the carrageenan-induced rat paw edema assay in comparison to ibuprofen, as a reference drug. The presence of acetyl group at Para-position in the side chain at C-5 gives promising anti-inflammatory activity (78, 86% respectively)[64].

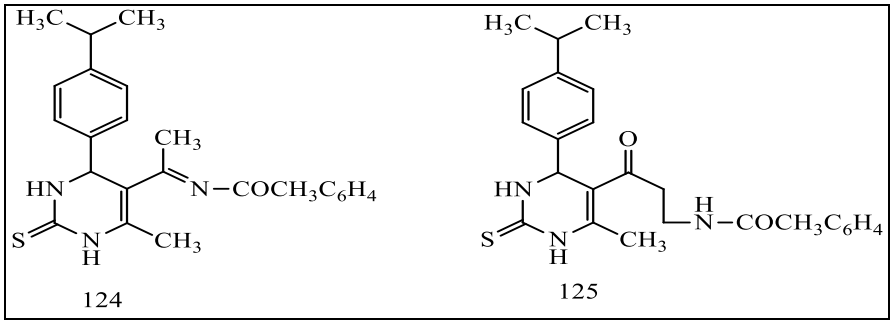


Figure 45 pyrimidin-2-thione derivatives (**124**) and (**125**) with anti-inflammatory activity

Series of pyrimidine-5-carbonitrile derivatives (**126**) were synthesized and evaluated for their ability to inhibit COX-1/COX-2 activity in vitro, and found to be potent and selective COX-2 inhibitors (IC50 = 1.03–1.71 μM, SI = 5.71–8.21) relative to celecoxib (IC50 = 0.88 μM, SI = 8.31)[65].

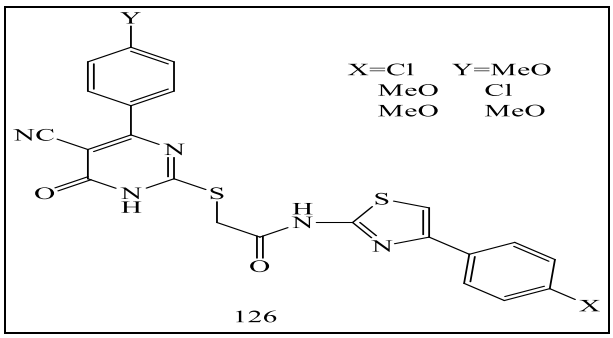


Figure 46 pyrimidine-5-carbonitrile derivatives (**126**) as potent and selective COX-2 inhibitors

2.11 Miscellaneous activity

Novel pyrimidines were synthesized by condensation of chalcones of 4-piperazine acetophenone with guanidine HCl (**127**). The recorded% histamine inhibition showed significant antihistaminic activity when compared to the reference antihistaminic drug mepiramine[66].

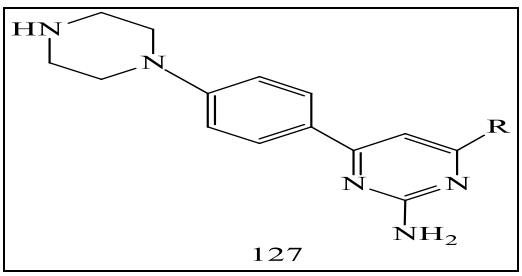


Figure 47 compound (**127**) with antihistaminic activity

Novel Condensed pyrimidine sulfonamides derivatives were synthesized and evaluated for their antiplatelet activity compared with ticlopidine and clopidogrel as standard reference drugs. Thiazolopyrimidine derivative (**128**) with methyl salicylate moiety showed potent thrombolytic effect through inhibition of platelet prostaglandin synthesis[67].

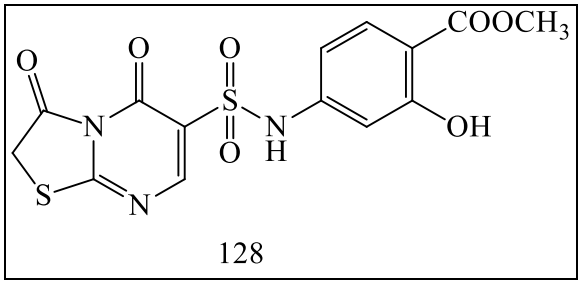


Figure 48 Thiazolopyrimidine derivative (**128**) with thrombolytic effect

3 Conclusion

Pyrimidines occupy a distinct and unique place in our life. This heterocyclic moiety has great biological and medicinal significance. A vast literature has been accumulated over the years and chemistry of pyrimidines constitutes to be a blossoming field. The versatile synthetic applicability and biological activity of these heterocycles will help the medicinal chemists to plan, organize and implement new approaches towards discovery of novel drugs.

Compliance with ethical standards

Acknowledgments

The corresponding author is grateful to authors for their help and support to complete this review.

Disclosure of conflict of interest

The authors declare that they don't have any conflict of interest.

References

[1] Campbell IB, Macdonald SJF, Procopiou PA. Medicinal chemistry in drug discovery in big pharma: past, present and future. Drug Discov Today [Internet]. 2018;23(2):219–34. Available from: http://dx.doi.org/10.1016/j.drudis.2017.10.007

[2] Dinakaran VS, Bomma B, Srinivasan KK. Fused pyrimidines: The heterocycle of diverse biological and pharmacological significance. Der Pharma Chem. 2012;4(1):255–65.

[3] Arora P, Arora V, Lamba HS, Wadhwa D. Importance of Heterocyclic Chemistry: a Review. Ijpsr [Internet]. 2012;3(9):2947–54. Available from: www.ijpsr.com

[4] ZOLLNER N. Purine and pyrimidine metabolism By N. ZOLLNER,. Proc Nuti Soc. 1982;41:329–42.

[5] Parker WB. Enzymology of purine and pyrimidine antimetabolites used in the treatment of cancer. Chem Rev. 2009;109(7):2880–93.

[6] Mishra R, Tomar I. ChemInform Abstract: Pyrimidine: The Molecule of Diverse Biological and Medicinal Importance. ChemInform. 2011;42(40):no-no.

[7] Sharma P, Kumar A, Sharma M. Generation of 4,6-dimethyl-5-[2-(2-methylprop-1-enyl)-1H-benzimidazol-1-yl]pyrimidine-2(5H) -thiones under kinetically controlled phase transfer catalysis conditions. J Mol Catal A Chem. 2005;237(1–2):191–8.

[8] Stockman RA. Heterocyclic chemistry. Annu Reports Sect "B" (Organic Chem [Internet]. 2007;103:107. Available from: http://xlink.rsc.org/?DOI=b614418g

[9] Zhichkin P, Fairfax DJ, Eisenbeis SA. A general procedure for the synthesis of 2-substituted pyrimidine-5-carboxylic esters. Synthesis (Stuttg). 2002;(6):720–2.

[10] Barthakur MG, Borthakur M, Devi P, Saikia CJ, Saikia A, Bora U, et al. A novel and efficient lewis acid catalysed preparation of pyrimidines: Microwave-promoted reaction of urea and β-formyl enamides. Synlett. 2007;(2):223–6.

[11] Sasada T, Kobayashi F, Sakai N, Konakahara T. An unprecedented approach to 4,5-disubstituted pyrimidine derivatives by a ZnCl2-catalyzed three-component coupling reaction. Org Lett. 2009;11(10):2161–4.

[12] Mohamed MS, Awad SM, Sayed AI. Synthesis of certain pyrimidine derivatives as antimicrobial agents and anti-inflammatory agents. Molecules. 2010;15(3):1882–90.

[13] Al-Abdullah ES, Al-Obaid ARM, Al-Deeb OA, Habib EE, El-Emam AA. Synthesis of novel 6-phenyl-2,4-disubstituted pyrimidine-5-carbonitriles as potential antimicrobial agents. Eur J Med Chem [Internet]. 2011;46(9):4642–7. Available from: http://dx.doi.org/10.1016/j.ejmech.2011.08.003

[14] Satoh Y, Yasuda K, Obora Y. Strategy for the synthesis of pyrimidine derivatives: NbCl 5-mediated cycloaddition of alkynes and nitriles. Organometallics. 2012;31(15):5235–8.

[15] Mohamed MS, Abd-El Hameed RH, Sayed AI, Soror SH. Novel antiviral compounds against gastroenteric viral infections. Arch Pharm (Weinheim). 2015;348(3):194–205.

[16] Yousif MNM, El-Sayed WA, Abbas HAS, Awad HM, Yousif NM. Anticancer activity of new substituted pyrimidines, their thioglycosides and thiazolopyrimidine derivatives. J Appl Pharm Sci. 2017;7(11):21–32.

[17] Ahmed NM, Nofal S, Awad SM. Synthesis, Molecular Modelling and Biological Evaluation of Novel Pyrimidine Derivatives as Anti-inflammatory Agents. J Pharm Res Int. 2020;32(22):49–67.

[18] Othman IMM, Alamshany ZM, Tashkandi NY, Gad-Elkareem MAM, Anwar MM, Nossier ES. New pyrimidine and pyrazole-based compounds as potential EGFR inhibitors: Synthesis, anticancer, antimicrobial evaluation and computational studies. Bioorg Chem. 2021 Sep 1;114.

[19] Hassan AS, Morsy NM, Awad HM, Ragab A. Synthesis, molecular docking, and in silico ADME prediction of some fused pyrazolo[1,5-a]pyrimidine and pyrazole derivatives as potential antimicrobial agents. J Iran Chem Soc [Internet]. 2022;19(2):521–45. Available from: https://doi.org/10.1007/s13738-021-02319-4

[20] Shonle HA, Moment A. SOME NEW HYPNOTICS OF THE BARBITURIC ACID SERIES. J Am Chem Soc [Internet]. 1923 Jan 1;45(1):243–9. Available from: https://pubs.acs.org/doi/abs/10.1021/ja01654a033

[21] Rohilla A, Ali S. Alloxan Induced Diabetes : Mechanisms and Effects. Int J Res Pharm Biomed Sci. 2012;3(2):819–23.

[22] Sader HS, Fritsche TR, Jones RN. Potency and bactericidal activity of iclaprim against recent clinical gram-positive isolates. Antimicrob Agents Chemother. 2009;53(5):2171–5.

[23] Hawser S, Lociuro S, Islam K. Dihydrofolate reductase inhibitors as antibacterial agents. Biochem Pharmacol. 2006;71(7):941–8.

[24] Roth B, Cheng CC. 6 Recent Progress in the Medicinal Chemistry of 2,4-Diaminopyrimidines. Prog Med Chem. 1982;19(C):269–331.

[25] Lagoja IM. Pyrimidine as constituent of natural biologically active compounds. Chem Biodivers. 2005;2(1):1–50.

[26] M.KARAARSLAN, P.KOPARIR, A.CANSIZ, C.OREK, O.SAP. Synthesis and Antimicrobial Activity of Some New. Chem Sci Trans. 2012;1(1):226–32.

[27] Mohamed MS, Youns MM, Ahmed NM. Novel indolyl-pyrimidine derivatives: Synthesis, antimicrobial, and antioxidant evaluations. Med Chem Res. 2014;23(7):3374–88.

[28] Mahmoud NFH, Ghareeb EA. Synthesis of Novel Substituted Tetrahydropyrimidine Derivatives and Evaluation of Their Pharmacological and Antimicrobial Activities. J Heterocycl Chem. 2019;56(1):81–91.

[29] El-Etrawy AAS, Sherbiny FF. Design, synthesis, biological assessment and molecular docking studies of some new 2-Thioxo-2,3-dihydropyrimidin-4(1H)-ones as potential anticancer and antibacterial agents. J Mol Struct [Internet]. 2021;1225:129014. Available from: https://doi.org/10.1016/j.molstruc.2020.129014

[30] Atiya RN, Salih NA, Adam RW. Preparation with Biological Study for Pyrimidine Derivatives from Chalcone. Int J Drug Deliv Technol. 2022;12(1):174–9.

[31] Sharma V, Chitranshi N, Agarwal AK. Significance and Biological Importance of Pyrimidine in the Microbial World. Int J Med Chem. 2014;2014:1–31.

[32] Ramiz MMM, El-Sayed WA, Hagag E, Abdel-Rahman AA-H. Synthesis and antiviral activity of new substituted pyrimidine glycosides. J Heterocycl Chem [Internet]. 2011 Sep;48(5):1028–38. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/jhet.686

[33] Bai S, Liu S, Zhu Y, Wu Q. Asymmetric synthesis and antiviral activity of novel chiral amino-pyrimidine derivatives. Tetrahedron Lett [Internet]. 2018;59(33):3179–83. Available from: https://doi.org/10.1016/j.tetlet.2018.07.020

[34] Azzam RA, Osman RR, Elgemeie GH. Efficient Synthesis and Docking Studies of Novel Benzothiazole-Based Pyrimidinesulfonamide Scaffolds as New Antiviral Agents and Hsp90α Inhibitors. ACS Omega. 2020;5(3):1640–55.

[35] Awad SM, Ali SM, Mansour YE, Fatahala SS. Synthesis and evaluation of some uracil nucleosides as promising anti-herpes simplex virus 1 agents. Molecules. 2021;26(10).

[36] Smith J, Andes D. Therapeutic drug monitoring of antifungals: Pharmacokinetic and pharmacodynamic considerations. Ther Drug Monit. 2008;30(2):167–72.

[37] Butters M, Ebbs J, Green SP, MacRae J, Morland MC, Murtiashaw CW, et al. Process development of voriconazole: A novel broad-spectrum triazole antifungal agent. Org Process Res Dev. 2001;5(1):28–36.

[38] Fathalla OA, Awad SM, Mohamed MS. Synthesis of new 2-thiouracil-5-sulphonamide derivatives with antibacterial and antifungal activity. Arch Pharm Res. 2005;28(11):1205–12.

[39] Sun L, Wu J, Zhang L, Luo M, Sun D. Synthesis and antifungal activities of some novel pyrimidine derivatives. Molecules. 2011;16(7):5618–28.

[40] Khan ZUH, Khan AU, Wan P, Chen Y, Kong D, Khan S, et al. In vitro pharmacological screening of three newly synthesised pyrimidine derivatives. Nat Prod Res. 2015;29(10):933–8.

[41] Wu W, Lan W, Wu C, Fei Q. Synthesis and Antifungal Activity of Pyrimidine Derivatives Containing an Amide Moiety. Front Chem. 2021;9(July):1–7.

[42] Longley DB, Harkin DP, Johnston PG. 5-Fluorouracil: Mechanisms of action and clinical strategies. Nat Rev Cancer. 2003;3(5):330–8.

[43] Cocco MT, Congiu C, Onnis V, Piras R. Synthesis and antitumor evaluation of 6-thioxo-, 6-oxo- and 2,4-dioxopyrimidine derivatives. Farmaco. 2001;56(10):741–8.

[44] Mohamed MS, Awad SM, Ahmed NM. Anti-cancer activities of 6-aryl -5-cyano-2-thiouracil derivatives. Pharma Res. 2012;6(2):54–60.

[45] Awad SM, Fathalla OA, Wietrzyk J, Milczarek M, Soliman AM, Mohamed MS. Synthesis of new pyrimidine derivatives and their antiproliferative activity against selected human cancer cell lines. Res Chem Intermed. 2015;41(3):1789–801.

[46] El-Naggar AM, Abou-El-Regal MM, El-Metwally SA, Sherbiny FF, Eissa IH. Synthesis, characterization and molecular docking studies of thiouracil derivatives as potent thymidylate synthase inhibitors and potential anticancer agents. Mol Divers. 2017;21(4):967–83.

[47] Helwa AA, Gedawy EM, Abou-Seri SM, Taher AT, El-Ansary AK. Synthesis and bioactivity evaluation of new pyrimidinone-5-carbonitriles as potential anticancer and antimicrobial agents. Res Chem Intermed [Internet]. 2018;44(4):2685–702. Available from: https://doi.org/10.1007/s11164-018-3254-y

[48] Ahmed NM, Youns M, Soltan MK, Said AM. Design, synthesis, molecular modelling, and biological evaluation of novel substituted pyrimidine derivatives as potential anticancer agents for hepatocellular carcinoma. J Enzyme Inhib Med Chem [Internet]. 2019;34(1):1110–20. Available from: https://doi.org/10.1080/14756366.2019.1612889

[49] Haffez H, Taha H, Rabie MA, Awad SM, Zohny YM. Synthesis, biological evaluation and molecular docking studies of novel thiopyrimidine analogue as apoptotic agent with potential anticancer activity. Bioorg Chem [Internet]. 2020;104(July):104249. Available from: https://doi.org/10.1016/j.bioorg.2020.104249

[50] Ahmed NM, Youns MM, Soltan MK, Said AM. Design, synthesis, molecular modeling and antitumor evaluation of novel indolyl-pyrimidine derivatives with EGFR inhibitory activity. Molecules. 2021;26(7).

[51] Becan L, Pyra A, Rembiałkowska N, Bryndal I. Synthesis, Structural Characterization and Anticancer Activity of New 5-Trifluoromethyl-2-thioxo-thiazolo[4,5-d] pyrimidine Derivatives. Pharmaceuticals. 2022;15(1).

[52] Abdillahi I, Kirsch G. Synthesis of a novel series of thieno[3,2-d]pyrimidin-4-(3H)-ones. Synthesis (Stuttg). 2010;(9):1428–30.

[53] Irshad N, Khan A ullah, Shah FA, Nadeem H, Ashraf Z, Tipu MK, et al. Antihyperlipidemic effect of selected pyrimidine derivatives mediated through multiple pathways. Fundam Clin Pharmacol. 2021;35(6):1119–32.

[54] Manna D, Roy G, Mugesh G. Synthesis , Structure , and Mechanism of Action. 2013;XXX(Xx).

[55] Awad SM, Zohny YM, Ali SA, Mahgoub S, Said AM. Design, synthesis, molecular modeling, and biological evaluation of novel thiouracil derivatives as potential antithyroid agents. Molecules. 2018;23(11).

[56] Magnus PD, Santiago FD, Squires RG, Chemical T, Shiba T. Haynes, g. leclerc,. 1976;427(1972):1109–11.

[57] Ugwu DI, Okoro UC, Mishra NK. Synthesis, characterization and anthelmintic activity evaluation of pyrimidine derivatives bearing carboxamide and sulphonamide moieties. J Serbian Chem Soc. 2018;83(4):401–9.

[58] Stanley RE, Blaha G, Grodzicki RL, Strickler MD, Steitz TA. The structures of the anti-tuberculosis antibiotics viomycin and capreomycin bound to the 70S ribosome. Nat Struct Mol Biol. 2010;17(3):289–93.

[59] da Silva PEA, Palomino JC. Molecular basis and mechanisms of drug resistance in Mycobacterium tuberculosis: Classical and new drugs. J Antimicrob Chemother. 2011;66(7):1417–30.

[60] Liu P, Yang Y, Tang Y, Yang T, Sang Z, Liu Z, et al. Design and synthesis of novel pyrimidine derivatives as potent antitubercular agents. Eur J Med Chem [Internet]. 2019;163:169–82. Available from: https://doi.org/10.1016/j.ejmech.2018.11.054

[61] Becker I. Preparation of pyrimidine derivatives as potential medicinal agents by the reaction of 2-amino-4-chloro-6-methylpyrimidine with primary and secondary amines. J Heterocycl Chem. 2005;42(7):1289–95.

[62] Sirakanyan SN, Spinelli D, Geronikaki A, Kartsev V, Hakobyan EK, Petrou A, et al. Synthesis and Neurotropic Activity of New Heterocyclic Systems: Pyridofuro[3,2-d]pyrrolo[1,2-a]pyrimidines, Pyridofuro[3,2-d]pyrido[1,2-a]pyrimidines and Pyridofuro[3′,2′:4,5]pyrimido[1,2-a]azepines. Molecules [Internet]. 2021 Jun 1;26(11):3320. Available from: https://www.mdpi.com/1420-3049/26/11/3320

[63] Ashour HM, Shaaban OG, Rizk OH, El-Ashmawy IM. Synthesis and biological evaluation of thieno [2′,3′:4,5] pyrimido[1,2-b][1,2,4]triazines and thieno[2,3-d][1,2,4]triazolo[1,5-a] pyrimidines as anti-inflammatory and analgesic agents. Eur J Med Chem. 2013;62:341–51.

[64] Ahmed NM, Nofal S, Awad SM. Synthesis, Molecular Modelling and Biological Evaluation of Novel Pyrimidine Derivatives as Anti-inflammatory Agents. J Pharm Res Int. 2020;32(22):49–67.

[65] Abdel-Aziz SA, Taher ES, Lan P, Asaad GF, Gomaa HAM, El-Koussi NA, et al. Design, synthesis, and biological evaluation of new pyrimidine-5-carbonitrile derivatives bearing 1,3-thiazole moiety as novel anti-inflammatory EGFR inhibitors with cardiac safety profile. Bioorg Chem [Internet]. 2021;111(April):104890. Available from: https://doi.org/10.1016/j.bioorg.2021.104890

[66] Rahaman SA, Rajendra Pasad Y, Kumar P, Kumar B. Synthesis and anti-histaminic activity of some novel pyrimidines. Saudi Pharm J [Internet]. 2009;17(3):255–8. Available from: http://dx.doi.org/10.1016/j.jsps.2009.08.001

[67] Mohsin MM, Jawad MJ, Hassan SM, Awad SM, Hussain YA, Hadi NR. Synthesis and evaluation of the thrombolytic activity of novel condensed pyrimidine sulfonamide derivatives. Eur J Mol Clin Med. 2020;7(2):220–4.